



## CAALL-F01: a French protocol for the treatment of acute lymphoblastic leukemia (ALL) in children and adolescents

INTERVENTIONAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

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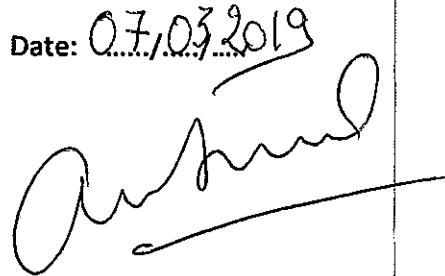
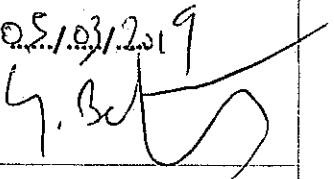
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**List of abbreviations**

ALL	: Acute Lymphoblastic Leukemia
API	:Active Pharmaceutical Ingredient
Ara-C	: cytarabine
CMO	: Contract Manufacturing Organization
CNS	: Central Nervous System
CR	: complete remission
DFS	: disease-free survival
DNR	: daunorubicine
DEX	: dexamethasone
EFS	: event-free survival
EIG	: événement indésirable grave (voir SAE)
G/L	: Giga /liter
GMP	: Good Manufacturing Practices
HD-MTX	: high-dose methotrexate
HR	: High Risk
HSCT	: Hematopoietic Stem Cell Transplantation
IM	: intramuscular
IMP	: Investigational Medicinal Product
IT	: intrathecal injection
IV	: intravenous infusion
MR	: Medium Risk
MRD	: minimal residual disease
MTX	: methotrexate
NCI	: National Cancer Institute
NCI-CTCAE	: National Cancer Institute Common Terminology Criteria for Adverse Events
OS	: overall survival
PEG	: pegaspargase
PNN	: neutrophils
PRED	: prednisone
SAE	: severe adverse event
6-MP	: 6-mercaptopurine
SR	: Standard Risk
6-TG	: 6-thioguanine
TP	: Time Point
TLP	: Traumatic lumbar puncture
VCR	: vincristine
VHR	: Very High Risk
WBC	: White Blood Cell Count

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## Protocol Summary and Overview

Name of the study	<b>CAALL-F01: a French protocol for the treatment of acute lymphoblastic leukemia (ALL) in children and adolescents</b>																								
Study committee representatives	<b>Coordinating investigator:</b> Pr André BARUCHEL <b>Co-coordinating Investigator:</b> Pr Yves BERTRAND Methodologist/Biostatistics: Pr Sylvie CHEVRET Leukemia Biology Coordination: Pr Hélène CAVE Asparaginase Studies Dr Jean-François BENOIST Dr Christine SABAN																								
Study Sponsor	Assistance Publique-Hôpitaux de Paris																								
Main backgrounds	<p><b>1. ALL is now a curable disease in 80-90% of children and 70-80% of the adolescents. Nevertheless numerous problems remain</b></p> <p>These good results are obtained with intensive and prolonged treatments which include risk of toxic death, sequelae, and secondary malignancies.</p> <p>Results are still insufficient for high-risk forms, particularly those exhibiting an early resistance to chemotherapy</p> <p>Early bone marrow relapses (less than 30 months after diagnosis) still have a dismal prognosis which renders their prevention mandatory</p> <p>ALL is an extremely heterogeneous disease in terms of biology and response to treatment. To envisage targeted treatments in the future renders key to decipher this heterogeneity.</p> <p>The two cooperative groups FRALLE and the French centers of the EORTC-CLCG have decided to elaborate a common protocol for the treatment of childhood and adolescent ALL: Childhood and Adolescent ALL-France- 01(CAALL-F01).</p> <p>The two previous studies from these groups have comparable results:</p> <table border="1"> <thead> <tr> <th></th> <th colspan="2"><b>Event-Free Survival</b></th> <th colspan="2"><b>Overall Survival</b></th> </tr> <tr> <th></th> <th>5 years</th> <th>8 years</th> <th>5 years</th> <th>8 years</th> </tr> </thead> <tbody> <tr> <td><b>FRALLE 2000</b> (2146 pts)</td> <td>84.0%</td> <td>82%</td> <td>91%</td> <td>89%</td> </tr> <tr> <td><b>EORTC 58951</b> (1947pts)</td> <td>82.6%,</td> <td>81.3%</td> <td>89.7%</td> <td>88.1%</td> </tr> </tbody> </table> <p><b>2. A still major question in the field of ALL is the optimal use of L-asparaginase (ASNase)</b></p> <p>It is known that administering ASNase results in the depletion of asparagine circulating in the blood, which starves the leukemic cells and results in their death. But indeed the use of ASNase varies between protocols considering the different brands, the dose and the administration modalities (rythm, route-IM or IV). Three major forms of ASNase are currently available: <i>E. coli</i> asparaginase (Kidrolase® in France), <i>Erwinia</i> asparaginase (Erwinase®, for patients with allergy) and a pegylated form of <i>E.coli</i> Asparaginase (Oncaspar® in USA and in Europe).</p> <p><u><b>2.1.Oncaspar® in the USA</b></u></p> <p>Oncaspar® (PEGylated <i>E. coli</i> asparaginase or pegaspargase manufactured initially by ENZON and now SHIRE/Servier) was developed with the goal of reducing the immunogenicity of the native ASNase. In addition, Oncaspar®, because of its prolonged serum terminal half-life (<math>t_{1/2}</math>), can be dosed less frequently than native ASNase with achievement of similar PD.</p> <p>In the USA, CCG-1962 was the pivotal clinical trial supporting first-line use of Oncaspar®. Children with standard risk ALL (n=118) were randomized to receive native or PEGylated <i>E. coli</i> asparaginase (API from Merck) as part of induction and 2 delayed intensifications (DI) phases. Oncaspar® was administered intramuscularly</p>						<b>Event-Free Survival</b>		<b>Overall Survival</b>			5 years	8 years	5 years	8 years	<b>FRALLE 2000</b> (2146 pts)	84.0%	82%	91%	89%	<b>EORTC 58951</b> (1947pts)	82.6%,	81.3%	89.7%	88.1%
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(IM) at a dose of 2,500 IU/m<sup>2</sup> once during the 4-week induction phase and once during each of two 8-week DI phases. Native E. coli asparaginase from Merck (Elspar<sup>®</sup>) was administered IM at a dose of 6,000 IU/m<sup>2</sup> three times weekly for 9 doses during induction and for 6 doses during each DI phase. Children treated with Oncaspar<sup>®</sup> had a more rapid clearance of lymphoblasts from Day 7 and Day 14 bone marrow aspirates and a more prolonged asparaginase activity than those treated with the native form. In the first DI phase, 26% of native asparaginase patients had high-titer antibodies compared to 2% of those patients receiving Oncaspar<sup>®</sup>. High titer antibodies were associated with low asparaginase activity in the native arm, but not the Oncaspar<sup>®</sup> arm. The rate of infections, hospitalizations and the safety profile were similar between the arms (Avramis et al., 2002). Oncaspar<sup>®</sup> is approved for the treatment of ALL as a component of multi-agent chemotherapy in the USA since 1994, including for first-line use since 2006. This first line use has been transferred to a “new” Oncaspar<sup>®</sup> manufactured by Sigma-tau (pegaspargase; asparaginase from Lonza) in 2011, and now by SHIRE.

### 2.2. Oncaspar<sup>®</sup> in Europe

Until now, Oncaspar<sup>®</sup>, currently available in Europe differed from the Oncaspar<sup>®</sup> marketed in the USA in terms of the asparaginase origin (Kyowa-Hakko v. Lonza), although both products are pegylated by Sigma-Tau in the USA.

In Germany and Poland, Oncaspar KH (Kyowa-Hakko) is registered as a component of antineoplastic combination therapy for reinduction in patients with a known hypersensitivity to native L-asparaginase (second-line).

Oncaspar KH has been used as the first line asparaginase preparation in at least three European ALL protocols: UK MRC protocols for ALL since 2003 (UK), BFM-AIEOP protocol for ALL since 2010 (Germany, Italy, Austria, Switzerland; Czech Republic, Israel), INTERFANT (a protocol dedicated to infants with ALL) since 2006 (many countries).

Since January 2016, the European Commission has granted Marketing Authorization for use of ONCASPAR as a combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients. With this approval, Baxalta is authorized to market ONCASPAR in the 28 member countries of the European Union (EU), as well as Iceland, Liechtenstein and Norway. This authorization is related to the Onacaspar incorporating the API manufactured by Lonza

### 2.3 Current status of asparaginase preparations in France

Until January 2016, only Kidrolase<sup>®</sup> was registered for first line use.

Erwinase<sup>®</sup> is available for patients that are allergic to native or pegylated asparaginase (MAA in France: 30.03.2015).

Oncaspar<sup>®</sup> (Oncaspar KH) was available under a named patient program (ATUOn 19 November 2015, ) until Oncaspar<sup>®</sup> received a marketing authorization on january 2016.

### **3. Different dosing and schedules using ONCASPAR<sup>®</sup> during induction therapy are currently proposed according to first-line ALL protocols**

- 2500 IU/m<sup>2</sup> one infusion: COG and DFCI protocols(US) (using ONCASPAR LONZA)
- 3500 IU/m<sup>2</sup> one infusion: St Jude protocol(US) (ONCASPAR LONZA)
- 2500 IU/m<sup>2</sup> two infusions: AIEOP-BFM protocol (Europe)(ONCASPAR KH)
- 2500 IU/ m<sup>2</sup> two infusions: EORTC protocol(Belgium) (ONCASPAR KH)
- 2500 IU/ m<sup>2</sup> one infusion: Interfant 06 protocol (mainly Europe)(ONCASPAR KH)
- 1000 IU/m<sup>2</sup> two infusions: UKALL protocol (UK)(ONCASPAR KH)
- 1500 IU/m<sup>2</sup> two infusions: DCOG protocol (NL)(ONCASPAR KH)

**4. The results of the 2003 Protocol UKALL are interesting:** EFS 86% at 5 years, overall survival at 5 years 92% (Vora A et al, Lancet Oncol 2013 and 2014). They have been obtained by using a low dosage per infusion of Oncaspar KH (1000 IU/m<sup>2</sup> IM) but repeated at 15 day intervals for induction.

	In a subgroup of 482 patients treated in UKALL 2003, CYK Fong et al (ASH 2011) show that the dose that provides adequate asparaginase activity (> 100 IU/L) in 86% of samples studied after the 1st and second injection.
<b>Questions asked in the CAALL-F01 protocol</b>	<p>This French protocol will be the first in Europe to use the ONCASPAR® LONZA used in the USA since 2012 (first approval in 1994 was for another “ONCASPAR® manufactured with a Merck API).</p> <p><u>Randomized question:</u> what is the best way to administer pegaspargase? A cohort of children and adolescents with standard or medium risk ALL will be randomized to receive during induction either one infusion of ONCASPAR® (LONZA) 2500 IU/m<sup>2</sup> at D12 or two infusions of ONCASPAR® (LONZA) at 1250 IU/m<sup>2</sup> each at D12 and D26. Patients will then receive 2500 IU/m<sup>2</sup> or 1250 IU/m<sup>2</sup> per dose during consolidation and delayed intensification according to the initial arm of randomization.</p> <p><u>Non randomized question:</u> In the High/Very High Risk groups, a non randomized intensification of the scheme of asparaginase administration is proposed during induction therapy: 2 infusions of 2500 IU/m<sup>2</sup>/day (D12 and D26) will be administered. All patients will receive 2500 IU/m<sup>2</sup> per dose during consolidation and delayed intensifications.</p>
<b>Primary objectives</b>	<ol style="list-style-type: none"> <li>For children and adolescents with standard or medium risk ALL, the study has two primary objectives: 1) to assess the superiority in terms of PK at D33 of the fractionated scheme; 2) to assess the equivalence in the tolerance of the 2 schemes (from D12 of induction to D49)</li> <li>In the High/Very High Risk group two primary objectives have been defined: 1) to assess the PK at D33; 2) to assess the toxicity of the intensified scheme from D12 of induction to D49</li> </ol>
<b>Main end-points</b>	<ul style="list-style-type: none"> <li>○ <b>Adequate asparaginase activity</b> (&gt;100 IU/L) at D33 of induction</li> <li>○ <b>Toxicity:</b> Incidence of severe toxicities (Grade ≥ 3) directly asparaginase-related (CNS thrombosis, pancreatitis, anaphylaxis, and hyperbilirubinemia) between D12 and D49 of treatment and anyway before D8 of consolidation</li> </ul>
<b>Secondary end-points</b>	<p><b>1. Linked to the study Drug</b></p> <p><b>PHARMACOKINETICS/ PHARMACODYNAMICS /IMMUNOGENICITY:</b></p> <p>A comparison of the 2 arms will be made for the patients with Standard-Risk or Medium-Risk ALL. A non comparative assessment will be made for patients belonging to the High-Risk/Very High Risk-groups.</p> <p>The criteria will include:</p> <ul style="list-style-type: none"> <li>– Asparaginase activity and asparagine levels at defined time-points</li> <li>– Incidence of asparaginase antibodies</li> <li>– Incidence of silent inactivation in both arms during induction, consolidation and intensification phase(s)</li> <li>– Allergic reaction rate in both arms during induction, consolidation and intensification phase(s)</li> <li>– Percentage of patients without switch to Erwinia asparaginase</li> <li>– Percentage of patients receiving more than 95% of the intended dose of asparaginase</li> </ul> <p><b>EFFICACY</b></p> <p>A comparison of the 2 arms will be made for the patients with Standard-Risk or Medium-Risk ALL. A non comparative assessment will be made for patients belonging to the High-Risk/Very High Risk-groups.</p> <p>The criteria for efficacy will include:</p> <ul style="list-style-type: none"> <li>– Morphological CR rates assessed on the whole population or on subgroups (B-Lineage ALL, T-cell ALL).</li> <li>– Minimal Residual Disease (MRD) at the end of induction (TP1) and at the later time-point (TP2)(TP3 for a subgroup of patients) assessed by Ig/TCR-based RQ-PCR. This evaluation will be made in the whole population and within subgroups</li> <li>– Cumulative Incidence of relapses overall.</li> </ul>

	<ul style="list-style-type: none"> <li>– Cumulative Incidence of BM relapses, CNS relapses, gonadal relapses, combined relapses</li> </ul> <p><b>TOXICITY</b></p> <p>A comparison of the 2 arms will be undertaken for the patients with Standard-Risk or Medium-Risk ALL. A non comparative assessment will be made for patients belonging to the High-Risk/Very High Risk-groups.</p> <ul style="list-style-type: none"> <li>– All other adverse events (AE) related to asparaginase occurring within the first 7 weeks (D49) of treatment and anyway before D8 of consolidation: <ul style="list-style-type: none"> <li>○ Hyperglycemia / induced diabetes, coagulopathy, allergy, hyperlipidemia (hypertriglyceridemia and/or hypercholesterolemia)</li> <li>○ Non CNS thrombosis</li> <li>○ Grade 1-2 AE: pancreatitis, hyperbilirubinemia,</li> </ul> </li> <li>– Adverse events related to asparaginase but occurring after D49 of induction or anyway at D8 of consolidation or after</li> <li>– Incidence of all grade 3-4 adverse events, whatever their imputability.</li> </ul> <p><b>SURVIVAL TIME-POINTS</b></p> <p>5-year event-free survival, disease-free survival and overall survival are classical outcome measures for the evaluation of survival in children with ALL.</p> <p>Event-free survival is the survival time free of treatment failure, relapse or secondary malignancy from Day 1 of treatment or after randomization (in randomized arms); disease-free survival is the event-free survival in responders measured from the time of complete remission following induction. Treatment failure is defined after induction at day 35-day 42, by at least 5% blasts and MRD <math>\geq 5 \times 10^{-2}</math>. In case of no available MRD, only the <math>\geq 5\%</math> blasts criterion will be required.</p> <p><b>2-other secondary objectives</b></p> <ul style="list-style-type: none"> <li>– to evaluate the incidence of rare subgroups of ALL and their prognostic value e.g. so-called “B-other” subgroup: BCR-ABL like (including EBF1-PDGFRB), MEF2D-X, ZNF384-X, TCF3-HLF...</li> <li>– 5 year EFS, DFS and OS of the rare patients with suboptimal response to therapy (induction failure or MRDTP1 <math>\geq 10^{-3}</math>) and ABL-class fusions ALLs treated with imatinib</li> <li>– Imatinib related adverse events (immediate and long term, cf appendix 9) in the rare patients with suboptimal response to therapy (induction failure or MRDTP1 <math>\geq 10^{-3}</math>) and ABL-class fusions ALLs treated with imatinib</li> </ul>
<b>Definitions</b>	<p><u>NCI Standard-risk ALL (all criteria)</u></p> <ul style="list-style-type: none"> <li>• B-cell precursor ALL</li> <li>• 365 days &lt; age &lt;10 years</li> <li>• WBC &lt; 50 G/L</li> </ul> <p><u>NCI High-risk ALL</u></p> <ul style="list-style-type: none"> <li>• B-cell precursor ALL</li> <li>• age <math>\geq 10</math> years or WBC <math>\geq 50</math> G/L</li> </ul> <p><u>T-cell ALL</u></p> <p>ALL of the T-cell lineage</p> <p><u>CNS involvement:</u> CNS3 status, according to current standard definitions for CNS1, CNS2, CNS3, and traumatic lumbar puncture (TLP)</p> <p><u>Testis involvement:</u> clinical enlargement of one or both testes confirmed by ultrasonography</p> <p><u>Prednisone response</u> (measured at D8 of induction therapy):</p> <ul style="list-style-type: none"> <li>• Good prednisone response (GPR): less than 1000 blast cells/mm<sup>3</sup> after 7 days of Prednisone 60 mg/m<sup>2</sup>/day and one intrathecal injection of methotrexate</li> <li>• Poor Prednisone response (PPR): no good prednisone response</li> </ul>

	<p><u>Minimal residual disease (MRD)</u> (measured after induction and during or after consolidation): evaluation by Real time -Quantitative PCR after search for two Ig/TCR markers if possible or at least one with a minimum sensitivity of <math>10^{-4}</math>, according to the ESG-MRD recommendations. No detectable MRD means no signal with at least one marker at the <math>10^{-4}</math> sensitivity level.</p> <p>In case of failure (less than 10% of the cases) a Flow Cytometry evaluation of MRD will be done in a reference centre.</p>
<b>Stratification of the patients:</b> B-Lineage and T-cell lineage ALL are considered separately	<p><b>1) B-cell Precursor ALL (3 subgroups)</b>  <b>For patients pretreated with corticosteroids, refer to protocol (table 7 section 3-5-1)</b></p> <p><b>Standard-Risk (B-SR)</b></p> <hr/> <ul style="list-style-type: none"> <li>. patients NCI-SR  <b>AND</b></li> <li>. no CNS or gonadal involvement  <b>AND</b></li> <li>. no hypodiploidy (&lt;44 chromosomes), no monosomy 7, no t(17,19)/TCF3-HLF, no t(1,19)/TCF3-PBX1, no iAMP21, no MLL rearrangement,  <b>AND</b></li> <li>. D8 good prednisone response</li> </ul> <p><b>Randomized Questions</b></p> <p>pegaspargase 2500 IU/m<sup>2</sup> in one infusion during induction, consolidation and delayed intensification  vs  pegaspargase 2 infusions of 1250 IU/m<sup>2</sup> during induction, then 1 infusion of 1250 IU/m<sup>2</sup> during consolidation and delayed intensification</p> <p><b>Medium-Risk (B-MR)</b></p> <hr/> <ul style="list-style-type: none"> <li>. patients NCI-SR with D8 poor prednisone response and/or</li> <li>. patients NCI-HR with D8 good prednisone response and/or</li> <li>. patients with t(1,19)/ TCF3-PBX1 with no B-HR or VHR criterion and/or</li> <li>. patients with monosomy 7 and/or</li> <li>. patients with gonadal involvement with no B-HR or VHR criterion  <b>AND</b></li> <li>. no MLL rearrangement</li> <li>. no iAMP 21</li> <li>. no hypodiploidy (&lt;44 chromosomes) and/or DNA index &lt; 0.8</li> <li>. no t(17,19)/TCF3-HLF  <b>AND</b></li> <li>. no CNS involvement (CNS3)</li> </ul> <p><b>Randomized Question</b></p> <p><b>Arm 1:</b> pegaspargase 2500 IU/m<sup>2</sup> in one infusion during induction, consolidation and delayed intensification  vs  <b>Arm 2:</b> pegaspargase 2 infusions of 1250 IU/m<sup>2</sup> each during induction, then 1 infusion of 1250 IU/m<sup>2</sup> during consolidation and delayed intensification</p> <p><b>High Risk (B-HR)/Very High-risk (B-VHR)</b></p> <hr/> <p>pts NCI-HR with D8 poor prednisone response  <b>AND/OR</b></p> <p>pts with at least one of the following features:</p> <ul style="list-style-type: none"> <li>. MLL rearrangement</li> <li>. hypodiploidy (&lt;44 chromosomes) and/or DNA index &lt; 0.8</li> <li>. translocation t(17;19)/TCF3-HLF</li> </ul>

	<p>. iAMP 21  <b>AND/OR</b>          pts with CNS3 status</p> <p><b>■ Uncontrolled Question</b>          Two infusions of pegaspargase 2500 IU/m<sup>2</sup> each during induction          Pegaspargase 2500 IU/m<sup>2</sup> during consolidation and subsequent phases of treatment          HSCT strategy for a subgroup of non responders (B-VHR patients)  <b>Stratification switches can occur either after induction (induction failure) or after D42-50 assessment (IKZF1 status, MRD-TP1 result) or later (MRD-TP2 result) : refer to protocol for switches (table3 section 3-2-3)</b></p> <p><b>2) T-cell ALL (2 subgroups)</b></p> <p><b>For patients pretreated with corticosteroids, refer to protocol (table8 section3-5-2)</b></p> <hr/> <p><b>Standard risk (T-SR)</b></p> <p>patients with D8 good prednisone response  <b>AND</b>  <b>No CNS3</b>  <b>AND</b>          MRD &lt; 10<sup>-4</sup> at TP2</p> <p><b>■ Randomized Question</b>  <b>Arm 1:</b> pegaspargase 2500 IU/m<sup>2</sup> in one infusion during induction and delayed intensification  <b>Arm 2:</b> pegaspargase 2 infusions of 1250 IU/m<sup>2</sup> each during induction and 1 infusion of 1250 IU/m<sup>2</sup> during delayed intensification</p> <hr/> <p><b>High risk (T-HR) /Very High-risk (T-VHR)</b></p> <p>patients with D8 poor prednisone response  <b>AND/OR</b>          CNS 3  <b>AND/OR</b>          MRD ≥ 10<sup>-4</sup> at TP2</p> <p><b>■ Uncontrolled Question</b>          Two infusions of pegaspargase 2500 IU/m<sup>2</sup> each during induction          Pegaspargase 2500 IU/m<sup>2</sup> during consolidation and subsequent phases          HSCT strategy for a subgroup of non responders (T-VHR patients)</p> <p><b>Stratification switches can occur either after induction (induction failure) or after MRD evaluations (TP2 and TP3- for a subgroup of patients-): refer to protocol for switches (table 5 section 3-3-2)</b></p>
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Children and adolescents</li> <li>Age &gt; 12 months but &lt; 18 years</li> <li>B-lineage or T- lineage ALL</li> <li>• Written informed consent obtained before day 8 of treatment</li> </ul> <p><i>NB: patients with Down syndrome can be included but not randomized (see details in the protocol section 5-3-2)</i></p>
<b>Non inclusion criteria</b>	<ul style="list-style-type: none"> <li>• L3 (Burkitt's leukemia) (LMB type protocols)</li> <li>• Mixed Phenotype Acute Leukemia (WHO criteria).</li> <li>• Infant ALL (age ≤ 365 days (Interfant 06 protocol)</li> <li>• Secondary leukemia</li> </ul>

	<ul style="list-style-type: none"> <li>Patients previously treated with chemotherapy (steroid exposed pts can be included and stratified according to Section 3.5) Known allergy to pegylated products</li> <li>Pregnancy. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant must have a negative serum pregnancy before inclusion and a reliable contraception except oral contraceptives. The contraception should be maintained throughout the study and for 3 months after treatment discontinuation.</li> <li>Known HIV positivity</li> <li>CNS thrombosis during Prophase</li> </ul>
<b>Exclusion criterion</b>	<ul style="list-style-type: none"> <li>Ph+/BCR-ABL ALL (ESPhALL protocol)</li> <li>CNS thrombosis before D12</li> </ul>

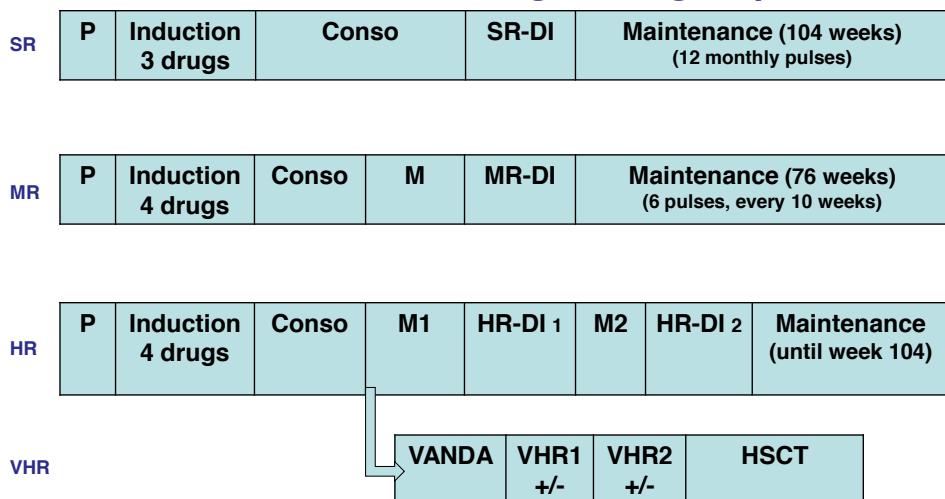
<b>Study Design</b>	<p>This is a <b>French prospective multicentric cohort study</b> of children and adolescents with ALL, <b>stratified on (i) the type of ALL (B vs T) and (ii) the anticipated risk</b> (stratified in 3 groups for BCP-ALL and 2 groups for T-cell ALL)</p> <p><b>A randomized clinical trial will be performed in the population of patients composed of the B-SR/B-MR/T-SR</b>, after checking the eligibility criteria, using a two-parallel arm randomization design. Patients will be allocated either to receive one infusion of Oncaspar® 2500 IU/m² vs. or 2 infusions of 1250 IU/m² during induction therapy. The dose per infusion after induction therapy is the dose per infusion attributed by the initial randomization</p> <p><b>No randomized question will be asked in the high/very high risk groups of the B and T lineage</b>, these patients receiving 2 infusions of Oncaspar® 2500 IU/m² during induction and 2500 IU/m²/infusion afterwards. Nevertheless, these patients will be submitted to the same evaluation in terms of PK/PD, toxicity and efficacy.</p> <p><b>All patients will be included in the CAALL-F01 study before Day 8 of induction treatment.</b></p> <p><b>Randomization will take place between D8 and D11, i.e. 1-4 days before the first infusion of pegaspargase (D12), for patients belonging to the B-SR/B-MR/T-SR groups.</b></p>
<b>Investigational drug</b>	Oncaspar®(pegaspargase;) is supplied as a sterile solution at the beginning of the trial and replaced by a powder for solution for injection. Both are packaged in Type I single-use vials containing 3,750 International Units of Native asparaginase per 5 mL solution. Oncaspar® is to be stored under refrigeration at 2°C to 8°C. Product must not be shaken or frozen and must be protected from light.
<b>Treatment schedules</b>	Refer to protocol
<b>Leukemia-oriented biological assessments</b>	<p><b>Morphology</b> on blood and bone marrow (according standard procedures)</p> <p><b>Immunophenotyping</b> (according standard procedures)</p> <p><b>Cytogenetics</b> (standard procedures + FISH TEL-AML1 (detects TEL-AML1/ETV6-RUNX1 translocation, iAMP21 and confirms indirectly hyperdiploidy) + FISH for MLL rearrangements).</p> <p><b>Molecular cytogenetics and genetics</b></p> <p>B-lineage: TEL-AML1/ETV6-RUNX1, MLL-AF4, BCR-ABL, TCF3-PBX1. E2A-HLF if B-Lineage ALL with DIC and/or hypercalcemia. IKZF1 (MLPA and/or multiplex PCR and/or CGH &amp;). Satellite Biology (non mandatory for protocol): <i>CRLF2 hyperexpression, CRLF2 lesions: IGH@-CRLF2, P2RY8-CRLF2, CRLF2 F232C. Ph like ALL; new druggable fusion transcript entities.</i></p> <p>T-lineage: Satellite biology (non mandatory for protocol): <i>HOX11, HOX11L2, SIL-TAL, CALM-AF10, NUP214-ABL1. Notch/FXBW7/FLASH, RA, PTEN.</i></p> <p><b>Minimal residual disease:</b> Evaluation by Real time Quantitative PCR after search for two Ig/TCR markers if possible or at least one with a minimum sensitivity of <math>10^{-4}</math>, according to the ESG-MRD recommendations, at 2 time points (TP1,TP2) (TP3 for a subgroup of patients). <b>Ig/TCR MRD evaluation of MRD is centralized in 6 centres</b></p>

	<p><b>(Lille, Paris- Robert Debré, Paris- Necker, Paris-St Louis, Toulouse, Rennes).</b> In case of failure (less than 10% of the cases) a Flow Cytometry evaluation of MRD will be done in a reference centre.</p>
<b>ASPARAGINASE-Oriented assays</b>	Asparaginase activity (all centers, whole duration of study) Asparagine depletion (limited number of centers, 2 years of inclusion) Antibodies against asparaginase and against PEG (all centers, first 2 years of the study. <b>For sampling time points refer to protocol (appendix 6)</b>

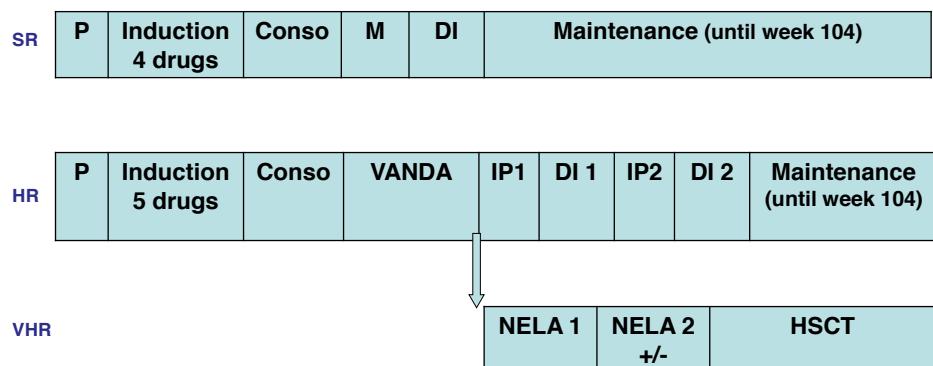
<b>Add-on studies</b>	A comprehensive bio-banking connected to the database is performed to enable subsequent research studies. These may include: - Array CGH / SNP array: this new technology measures the gains and losses of chromosomal regions, even when subtle. It is necessary to assess its impact in terms of diagnosis and prognosis prospectively - <b>Patients with Induction failure or with high levels of MRD will be screened by all necessary techniques (FISH, CGH, DNA or RNA sequencing) in search of molecular abnormalities allowing the use of targeted drugs, particularly tyrosine kinase inhibitors in combination with chemotherapy for ABL-class fusions.</b> - Genetic polymorphisms of the host (pharmacogenomics): in particular receptors and enzymes regulating the metabolism of 6-mercaptopurine, methotrexate and glucocorticoids.		
<b>Centres: 28</b>	Amiens Angers Besançon Bordeaux Brest Caen Clermont-Ferrand Dijon Grenoble Lille Limoges Lyon Marseille Montpellier Nancy	Nantes Nice Paris : Armand Trousseau, Robert Debré Saint-Louis Poitiers Reims Rennes Rouen Saint-Etienne Strasbourg Toulouse Tours	See list on p
<b>Number of subjects chosen</b>	2000 patients could be enrolled to obtain: B-SR, B-MR, T-SR: 1578 evaluable patients B-HR, T-HR :250-300 evaluable patients		
<b>Research period</b>	Duration of inclusions: 60 months Duration of participation of each patient: 60 months Total duration of the study: 120 months		
<b>First interim analysis</b>	Will be performed based on all patients randomized before January, 1, 2018, as requested by the DSMB of the study on November 2017		

## OVERVIEW

### CAALL-F01: B-lineage ALL groups



### CAALL-F01:T-cell ALL groups



## 1 Background

### 1.1 Overview of acute lymphoblastic leukemia (ALL)

#### 1.1.1 ALL: characteristics of the disease

Acute lymphoblastic leukemia (ALL) is defined as a proliferation of monoclonal lymphoblasts that infiltrate at least 20% of the bone marrow ([OMS 2008](#)). The consequences are bone marrow insufficiency and tumoral syndrome leading to death without treatment.

ALL is the most common cancer diagnosed in children (23% of cancers) and its incidence is may be slightly increasing. A peak of incidence is observed at the age of 2 to 3 years. Few factors associated with an increased risk of ALL have been identified: there are mainly prenatal exposure to x-rays, postnatal exposure to high dose of radiation, Down syndrome and other genetic conditions and inherited genetic polymorphisms.

Dramatic improvements in the treatment of ALL were seen during the last 25 years, resulting in an 80 to 85% survival rate, 5 years after diagnosis, in developed countries. Between 1975 and 2002, the 5-year survival rate raised from 60% to 89% for children younger than 15 years, and from 28% to 50% for those aged from 15 to 19 years ([Smith 2010](#)).

Children with ALL are usually treated according to risk groups defined by both clinical and laboratory features. With a worse prognostic than the children under 10 years, the adolescents and young adults seem to benefit from a treatment copied on those of the children but with a higher risk of therapy-related complications.

#### 1.1.1.1 Clinical characteristics

Clinical prognostic characteristics used for the elaboration of risk groups are age at diagnosis, CNS, and testicular involvement at diagnosis.

- **Age** has the strong prognostic significance; young children (aged from 1 to 9 years) have a better outcome than infants or older children or adolescents ([Möricke 2005](#)). This applies nevertheless essentially to B-lineage ALL. The prognosis of adolescents has significantly increased since their inclusion in pediatric protocols compared to adult ones ([Boissel 2003](#)).
- Clinical features qualifying for **CNS involvement** (CNS3 status, see [Appendix 5](#)) include one or more cranial palsies; a mass or masses on brain imaging compatible with specific localizations of ALL.
- Overt **testicular involvement** at the time of diagnosis occurs in approximately 2% of males, most commonly in T-cells ALL and is commonly treated in high-risk groups ([Sirvent 2007](#)).
- **Down syndrome** has been reported to be associated with a worse prognosis due to a diminished tolerance to chemotherapy (especially methotrexate) and an increased rate of severe infections. Down syndrome children represent 2% of the population of children with ALL. An international retrospective study evaluated the fate of 653 patients treated from 1995 to 2004. The EFS to 8 years is  $64 \pm 2\%$ , the OS at 8 years was  $74 \pm 2\%$  ([Buytenkamp 2014](#)). See next section for biological considerations –IKZF1/CRLF2/JAK- and section 5.3.2 for special guidelines and care of children with Down syndrome in this protocol.

#### 1.1.1.2 Biological characteristics

Leukemic cell characteristics at diagnosis are of prognostic significance. The World Health Organization (WHO) classifies ALL as either B or T lymphoblastic leukemia.

- WHO B lymphoblastic leukemia, also called Precursor B-cell ALL (80% to 85% of childhood ALL) is defined by the expression of cytoplasmic CD79a, CD19, HLA-DR, and other B cell-associated antigens. The CD10 surface antigen is expressed in around 90% of cases. Absence of CD10 is associated with MLL translocations and to a poorer outcome.

***There are 3 major subtypes of precursor B-cell ALL:***

- Pro-B ALL-CD10 negative and no surface or cytoplasmic antigen (<5% of non-infant patients)
- Common precursor B-cell ALL-CD10 positive and no surface or cytoplasmic Ig (around 75% of patients)
- Pre-B ALL: presence of cytoplasmic Ig

An additional rare subtype, still to be treated as an ALL, is the transitional Pre-B ALL (< 3% of patients). Transitional pre-B ALL is defined by lymphoblasts expressing cytoplasmic and surface mu heavy chains without kappa or lambda light chains. Patients with transitional pre-B ALL lack FAB L3 morphology, bulky extramedullary disease and the t(8;14), t(8;22), and t(2;8) translocations, features that characterize B-cell ALLs.

Mature B-cell leukemias (Burkitt's leukemia) (around 2% of patients) need to receive a treatment based on therapy for Burkitt's lymphomas and are not to be included in the CAALL-F01 protocol.

- T-cell ALL is defined by the expression of the T cell-associated antigens (cytoplasmic CD3 with CD7 plus CD2 or CD5) on leukemic blasts and is frequently associated with male gender, older age, leucocytosis, and mediastinal mass.

A distinct subset of childhood T-cell ALL termed early precursor T-cell ALL is identified in ~13% of T-cell ALL children and is characterized by CD1a and CD8 negativity, with expression of stem cell or myeloid markers and weak expression of CD5. Its prognostic impact remains controversial. A recent COG report links ETP to a higher risk of induction failure in T-ALL but no final inferior outcome (Wood BL, ASH 2014)

**Cytogenetics and genetics**

A number of recurrent chromosomal abnormalities have been shown to have prognostic significance especially in B-precursor ALL.

**A. B-lineage ALL**

***Chromosomes number***

High hyperdiploidy defined as 51 to 65 chromosomes per cell or a DNA index greater than 1.16 occurs in 20% to 25% of cases of precursor B-cell ALL but very rarely in T-cell ALL. It generally occurs in cases with clinically favorable prognostic factors and is itself an independent favorable prognostic factor ([Paulsson 2009](#)). Patients with trisomies 4, 10 and 17 (triple trisomies) have a particular favorable outcome and trisomies 4 and 10 classified in NCI standard-risk group have also a very good prognosis ([Sutcliffe 2005](#), [Harris 1992](#)). Patients with high hyperdiploidy (> 58 chromosomes) have an excellent prognosis ([Dastugue 2013](#)).

Certain patients with hyperdiploid ALL may have a hypodiploid clone that has doubled (masked hypodiploidy). These cases may be interpretable based on the pattern of gains and losses of specific chromosomes. DNA index profile can be of great help here. These patients have an unfavorable outcome, similar to those with hypodiploidy.

Forms with hypodiploidy (<44 chromosomes) have a bad prognosis but represent less than 2% of childhood B-Lineage ALL ([Nachman 2007](#)). The lowest is the chromosome number (towards near haploidy), the worse the outcome. Recently genomic profiling of 124 hypodiploid ALL cases identified two subtypes that differ in the severity of aneuploidy, transcriptional profiles and submicroscopic genetic alterations. *Near-haploid ALL with 24–31 chromosomes* harbor alterations targeting receptor tyrosine kinase signaling and Ras signaling (71%) and the lymphoid transcription factor gene *IKZF3* (13%). In contrast, *low-hypodiploid ALL with 32–39 chromosomes* are characterized by alterations in *TP53* (91.2%) that are commonly present in nontumor cells, *IKZF2* (53%) and *RB1* (41%). Both near-haploid and low-hypodiploid leukemic cells show activation of Ras-signaling and phosphoinositide 3-kinase (PI3K)-signaling pathways and are sensitive to PI3K inhibitors, indicating that these drugs should be explored as a new therapeutic strategy for this aggressive form of leukemia. The fact that the *TP53* alterations observed in low-hypodiploid ALL are also present in nontumor cells in approximately 40% of cases, suggest that these mutations are germline and that low-hypodiploid ALL represents, in some cases, a manifestation of Li-Fraumeni syndrome ([Holmfeldt 2013](#)).

***Chromosome translocations***

The fusion between the ETV6 gene on chromosome 12 with the RUNX1 gene on chromosome 21 (ETV6-RUNX1 t(12;21) (formerly known as TEL-AML1) is detected in 20-25% of B-precursor ALL but rarely in T-cell ALL. It is observed mainly in children from 2 to 9 years and has an excellent prognosis. Late and very late relapses can nevertheless be observed ([Rubnitz 2008](#), [Kanerva 2004](#), [Gandemer 2012](#)).

The Philadelphia chromosome, t(9;22) fusion of BCR-ABL genes leading to the production of a protein with tyrosine kinase activity, is present in approximately 3% of ALL, had historically a bad prognosis but recent studies with intensive

therapy and tyrosine kinase inhibitors showed an increase of the 3-year Event Free Survival (EFS) rate ([Schultz 2009](#)). These patients will not be included in the CAALL-F01 study.

Translocations involving the MLL (11q23) gene occur in up to 5% of childhood ALL but around 1-2% over one year of age. The prognostic of non-infant MLL- ALLs has progressed but is still associated with a higher risk of failure, particularly if corresponding to the high-risk NCI category.

The translocation t(1;19)/TCF3-PBX1 occurs in around 5% of childhood ALL and involves the fusion of the E2A/TCF3 gene on chromosome 19 to the PBX1 gene on chromosome 1. Its adverse prognosis is negated by aggressive therapies but it is associated with a higher risk of CNS relapse ([Uckun 1998, Pui 2009](#)).

#### ***Intrachromosomal amplification of chromosome 21 (iAMP21)***

iAMP21 with multiple extra copies of the RUNX1 (AML1) gene occurs in 1% to 2% of precursor B-cell ALL and may be associated with inferior outcome ([Moorman 2007](#)). These forms should be recognized (through the systematic use of the ETV6-RUNX1 FISH probe) and treated in the high-risk group ([Harrison 2014](#))

#### ***IGH@ translocations***

Rearrangements of the immunoglobulin heavy chain locus (*IGH@*) on chromosome 14q32 are rare in B-ALL, occurring in <5% of cases. *IGH@* rearrangements occur more frequently in adolescents and appear to be associated to a poorer clinical outcome. It is not considered as an independent prognostic factor in children and adolescents in the MRD era. The most common *IGH@* partners include *CRLF2* (*cytokine receptor-like factor 2*) at the pseudoautosomal region 1 (PAR1) of Xp22.3/Yp11.3 (resulting in overexpression of *CRLF2*), *ID4* (*inhibitor of DNA binding 4*) at 6p22, and members of the *CEBP* (*CCAAT/enhancer binding protein*) family. Translocations between *IGH@* and *EPOR* (*erythropoietin receptor*) at 19p13 have also been reported, with other remaining translocations appearing sporadic.

#### ***Recently described abnormalities***

- The *IKAROS* transcription factor, encoded by *IKZF1*, was recently associated with an unfavorable prognosis in childhood B-cell precursor (BCP) ALL. A monoallelic (often partial) deletion in *IKZF1* results in a loss of its tumor suppressor function. Ten percent to 15% of BCP-ALL cases have an *IKZF1* deletion, which therefore represents the most frequently observed genetic marker for an unfavorable outcome identified in children. Moreover its prognostic value seems independent of MRD. Pathogenic mutations have also been described and would be considered as equivalent to a deletion since they are associated to the loss of the tumor suppressor function. ***It has thus been chosen in the CAALLF01 protocol to exclude patients with deletions/mutations from the standard risk group (50-60% of all children with B-Lineage ALL), their final assessment (medium, high or very high risk) being decided after MRD evaluation at 2 time points.***

***IKZF1 deletions also worsen the prognosis of Down syndrome ALL patients. It has been decided to increase the intensity of treatment for children with DS and IKZF1 deletions/mutations. They will thus receive the MR group treatment instead of the SR one, limiting the use of HD-MTX nevertheless.***

- The *BCR-ABL1-like* gene expression signature is a second recently identified unfavorable prognostic marker in childhood BCP-ALL. *BCR-ABL1-like* ALL was identified based on a gene expression signature of its leukemic cells, which is similar to that of *BCR-ABL1*-positive ALL, although these leukemic cells do not harbor the *BCR-ABL1* translocation. Approximately 15% of BCP-ALL cases have *BCR-ABL1-like* ALL, which is associated with a 5-year EFS of <60%. More than 80% of *BCR-ABL1-like* ALL cases have abnormalities in genes involved in B-cell development, including *IKZF1* deletions in ~40%. Transcriptome and whole-genome sequencing of *BCR-ABL1*-like ALL has also identified other genetic alterations involved in the activation of kinase signaling, including *EBF1-PDGFRB*, comprised of the transcription factor *EBF1* (early B-cell factor 1) and the receptor tyrosine kinase *PDGFRB* (platelet-derived growth factor receptor β), resulting from 5q33q33 microdeletion. Some reports suggest that the use of TKIs to treat B-ALL harboring the *EBF1-PDGFRB* rearrangement may be of clinical benefit ([Weston 2013, Lengline 2013](#)).

***As no easy tool allows to detect BCR-ABL like ALL, There is now a consensus to identify this group by evidencing specific gene fusions. using a panel of techniques such as FISH, SNP/CGH array, RT-PCR, NGS and RNAseq. It has been decided to concentrate the efforts on patients with induction failure or high MRD and belonging to the B-other subgroup (no classical classifying abnormality e.g. TEL-AML1, TCF3-PBX1 etc)..***

***The present amendment authorizes TKI (imatinib) to be added on top of the B-HR/VHR group chemotherapy in patients with ABL-class fusions. Indeed experience of imatinib added to intensive chemotherapy exists in classical Philadelphia positive childhood ALL (COG and ESPHALL protocols, Schultz 2009, Biondi 2012). Moreover case reports showing the feasibility and early effectiveness of TKI plus chemotherapy in so-called BCR-ABL like ALL have been published*** ([Lengline 2013, Weston 2013, Schwab 2015](#)).

- ***JAK mutations and CRLF2 rearrangements***

The role of cytokine receptors and JAK family members are playing increasingly larger roles in B-ALL studies. The JAK family encodes four nonreceptor tyrosine kinases (*JAK1, JAK2, JAK3, TYK2*) involved in cytokine-mediated signaling (JAK-STAT pathway). Mutations occur in about 10% of high-risk childhood B-ALL cases. In the setting of *BCR-ABL1*-like B-ALL, JAK mutations are also associated with concomitant *IKZF1* (*Ikars*)

and *CDKN2A/B* alterations, and correlate with worse outcomes. *JAK2* mutations are also associated with *CRLF2* rearrangements (as described above), and are described in 60% of Down syndrome (Trisomy 21)-associated ALL. Approximately 40% of *CRLF2*-rearranged cases can harbor *JAK2* mutations.

Cytokine receptor-like factor 2 (*CRLF2*) or thymic stromal-derived lymphopoietin receptor is a protein encoded by the *CRLF2* gene. This gene encodes for a cytokine receptor chain related to  $\gamma$ c/IL2R $\alpha$ . Deregulated expression of *CRLF2* results from either a cryptic chromosomal translocation [t(X;14)(p22;q32)/t(Y;14)(p11;q32)] or interstitial deletion within the pseudoautosomal region [PAR1; del(X)(p22.33p22.33)/del(Y)(p11.32p11.32)]. Overexpression of *CRLF2* is driven by its juxtaposition to either the IGH@ enhancer (IGH@-*CRLF2*) or the P2RY8 promoter (P2RY8-*CRLF2*). This phenomenon has recently been found in B-cell precursor acute lymphoblastic leukemia (BCP-ALL), including Down syndrome patients, lacking recurring chromosomal translocations. *CRLF2* deregulation occurs in 5%-7% of childhood ALL but is more frequent among Down syndrome patients (50%-60% of the cases). Overexpression of *CRLF2* is associated with activation of the JAK-STAT pathway in cell lines and transduced primary B-cell progenitors, sustaining their proliferation and indicating a causal role of *CRLF2* overexpression in lymphoid transformation. Increased *CRLF2* expression is in most of the cases associated with a *JAK2* mutation, suggesting that mutant *JAK2* and *CRLF2* may cooperate to contribute to BCP-ALL genesis. *CRLF2* overexpression is not considered as an independent risk factor since conflicting results are available.

The *JAK2* inhibitor, ruxolitinib, has been shown to reduce tumor burden in xenograft mouse models harboring *BCR-JAK2* [t(9;22)(p24;q11.2)], and has demonstrated promising results in the treatment of *CRLF2*-rearranged, *JAK2*-mutated leukemic cells in vitro.

## B. T-cell ALL

No prognostic factor based on cytogenetics or genetics has been universally accepted in T-cell ALL.

Nevertheless, very interesting data recently emerged concerning:

- a) The prognostic value of the NOTCH1/FBXW7 mutations in T-cell lymphoblastic lymphoma in children ([Callens 2012](#))
  - A good prognosis is associated to the mutated status with an independent value in multivariate analysis.
- b) The combined use of NOTCH1/FBXW7/RAS/PTEN mutational status in adult T-cell ALL ([Trinquand 2013](#)).
  - The good prognostic group is constituted by the patients having a mutated status for NOTCH1/FBXW7 and no mutation of RAS or PTEN

### 1.1.1.3 Response to initial treatment

Along with clinical and biological characteristics, response to initial treatment is of major prognostic significance.

#### Peripheral blood response to steroid prophase

Patients with a reduction in peripheral blast count to less than 1 000/ $\mu$ L after a 7-day induction prophase with prednisone and one dose of intrathecal methotrexate (a good prednisone response) have a more favorable prognosis than do patients whose peripheral blast counts remain above 1 000/ $\mu$ L (poor prednisone response). The latter is observed in fewer 10% of patients. Moreover, patients with no circulating blasts on Day 7 have a better outcome than those patients whose circulating blast count is between 1 and 999/ $\mu$ L ([Möricker 2008; Lauten 2001, Manabe 2008](#)).

#### Induction failure

The presence of greater than 5% lymphoblasts at the end of the induction phase is observed in up to 5% of children with ALL. Patients at risk are those with T-cell disease and B-cell precursors ALL with very high presenting leukocyte counts and/or Philadelphia chromosome and/or ABL-class fusion transcript (Lengline 2013, Weston 2013, Schwab 2015). Induction failure leads to a very poor outcome. The French FRALLE 93 study found a 5-year overall survival (OS) rate of 30% for patients with initial induction failure. The Ponte di Legno international study on 1041 patients led to the conclusion that pediatric ALL with induction failure is highly heterogeneous. Patients who have T-cell leukemia appear to have a better outcome with allogeneic stem-cell transplantation than with chemotherapy, whereas patients who have precursor B-cell leukemia without other adverse features appear to have a better outcome with chemotherapy ([Silverman 1999, Oudot 2008, Schrappe 2012](#)).

#### MRD determination

Multiple studies have demonstrated that end-induction MRD is an important, independent predictor of outcome in children and adolescents with ALL. Patients with higher levels of end-induction MRD have a poorer prognosis than those with lower or undetectable levels ([Cavé 1998, Borowitz 2008, Zhou 2007, Conter 2010, Schrappe 2011](#)). Recently, in the AIEOP-BFM-ALL 2000 study evaluating treatments of BCP-ALL and T-cell ALL in childhood, was proposed a double MRD evaluation (Day 33 and Day 78) with a cut-off of  $\leq 10^{-4}$  and  $\geq 10^{-3}$  to define the prognostic groups ([Conter 2010, Schrappe 2011](#)).

### 1.1.1.4 Prognostic groups

The NCI risk groups are defined as standard risk group which includes patients with B precursor ALL aged from 1 to <10 years with less than  $50 \times 10^9$  WBC/ $\mu\text{L}$ . All other children with ALL are considered to belong to the high-risk group ([Smith 1996](#)).

This classification was refined and some groups split the standard risk group in low, average, and very high standard risk according to other criteria as cytogenetics, Day 8 peripheral blood MRD and Day 35 bone marrow MRD, presence or absence of CNS disease...

***CAAL-F01 stratification algorithm will associate upfront features (B vs T immunophenotype, NCI grouping with cytogenetics/genetics for B-lineage LL), early response to treatment (Day 8 prednisone response) and kinetics of MRD for adequate and dynamic grouping of the patients (possible switch at some check-points for upgraded treatment intensity)***

### 1.1.2 General features of ALL treatment

Treatment of childhood ALL typically involves chemotherapy given for 2 years. It generally includes a phase to induce complete remission (induction therapy, with steroid prophase in most European protocols), post-induction therapy including consolidation/intensification and maintenance/continuation therapy. Hematopoietic stem cell transplantation is reserved to very-high risk (VHR) patients (~ 5% of the patients): VHR being defined either by cytogenetic/genetics and/or response.

#### 1.1.2.1 Induction prophase

Early response has a strong prognostic significance. The BFM type prophase consists in 7 days of  $60 \text{ mg/m}^2/\text{day}$  of prednisone with one dose of intrathecal methotrexate. It has also been used in EORTC Protocols (58881, 58951) and FRALLE protocols (93, 2000).

#### 1.1.2.2 Remission induction for newly diagnosed ALL

For B-ALL, three-drug induction therapy using vincristine, corticosteroid (prednisone or dexamethasone) and L-asparaginase in conjunction with intrathecal (IT) therapy, results in complete remission (CR) rates of greater than 95%. For patients presenting with high-risk features and T-cell ALL, addition of an anthracycline (e.g. daunorubicin) allows improvement of the EFS. Many current regimens utilize dexamethasone instead of prednisone during remission induction and later phases of therapy. While dexamethasone may be more effective than prednisone, data also suggest that dexamethasone may also be more toxic, especially in the context of more intensive regimens and in adolescents (higher risk of osteonecrosis). Teuffel et al reported the results of a meta-analysis of 8 studies comparing the efficacy and the safety of dexamethasone versus prednisone for induction in childhood ALL. The results showed that dexamethasone reduced events like death from any cause, refractory or relapse or second malignancy but did not alter the bone marrow relapse and the overall mortality. There was clear evidence that dexamethasone was protective against CNS relapse, probably due to its better CNS penetration. There were no statistically difference between the 2 drugs for osteonecrosis, sepsis, fungal infection, diabetes and pancreatitis but a higher risk of mortality at induction, neuro-psychiatric events and myopathy were detected with dexamethasone. Moreover, patients who received dexamethasone were at significant higher risk to be withdrawn from the study after randomization because of adverse events ([Teuffel 2011](#)).

In the recent randomized study EORTC 58951, no difference was found between  $6 \text{ mg/m}^2/\text{day}$  of dexamethasone and  $60 \text{ mg/m}^2/\text{day}$  of Prednisone during induction, patients of both arms receiving dexamethasone during delayed intensification (protocol II) ([Domenech 2014](#))

***It has been decided to use for induction in the CAALL-F01 protocol:***

- ***3 drugs with dexamethasone  $6 \text{ mg/m}^2/\text{day}$  in the B-lineage SR group***
- ***4 drugs with prednisone in the B-lineage MR and HR group***
- ***4 drugs with dexamethasone  $10 \text{ mg/m}^2/\text{day}$  in the T-lineage SR group***
- ***5 drugs with prednisone in the T-lineage HR group***

#### 1.1.2.3 Post-induction treatment

##### Consolidation/intensification therapy

Once remission has been achieved, systemic treatment in conjunction with CNS sanctuary therapy follows. The intensity of the chemotherapy varies considerably depending on risk group assignment.

For standard risk ALL, clinical trials demonstrated the improvement of outcome with a 3- or 4-week reinduction treatment (including anthracycline) and a reconsolidation treatment with cyclophosphamide, cytarabine, and 6-thioguanine given approximately 3 months after remission is achieved ([Gaynon 2010, Riehm 1990](#)).

In high-risk patients, a number of different approaches have been used with comparable efficacy. The treatment is generally more intensive and typically includes higher cumulative doses of multiple agents, including anthracyclines and/or alkylating agents as in the "augmented BFM" protocol ([Nachman 1998; Seibel 2008](#)).

In very high-risk ALL, the treatment consist on multiple cycles of intensive chemotherapy during the consolidation phase, often including high-dose cytarabine, alkylating agents and etoposide.

***It has been decided to use for consolidation in the CAALL-F01 protocol:***

- ***A standard consolidation (FRALLE2000-A type) but reinforced with pegaspargase in the B-lineage SR group***
- ***An intensive consolidation (classical BFM Ib reinforced with Vincristine and pegaspargase) in the B-lineage MR and HR group***
- ***A classical consolidation (Ib) in the T-lineage SR group (where the objective is to reproduce the excellent BFM group results).***
- ***An intensive consolidation (classical BFM Ib reinforced with Vincristine and pegaspargase) in the T-lineage HR group***

**CNS Prophylaxis and treatment (see Appendix 5 for definitions and treatment details)**

The presence of CNS involvement at the time of diagnosis is uncommon (about 3% to 7%), but a substantial proportion of patients (> 50%) will eventually develop CNS-leukemia in the absence of CNS-directed therapy. CNS-leukemia is defined by the presence of white blood cell in the cerebrospinal fluid with presence of lymphoblasts. In children with ALL, CNS leukemia at diagnosis was associated with significantly decreased EFS rates. Factors associated with increased risks for CNS leukemia in children include T-cell immunophenotype, high presenting white blood cell counts, Ph-positive disease, t(4;11) translocation, and presence of leukemic cells in the cerebro-spinal fluid.

CNS-directed therapy is therefore an indispensable component of the successful treatment of childhood acute lymphoblastic leukemia. Historically, pre-symptomatic cranial or crano-spinal irradiation was a standard component of treatment for all patients, but was associated with serious adverse events such as neuro-cognitive dysfunctions, secondary malignancies, and other long term complications. As concerns about the long-term consequences of radiation increased, irradiation was first limited to the brain, then decreased in dose, and finally largely replaced by effective intrathecal (IT) chemotherapy (e.g., methotrexate alone, or with cytarabine and corticosteroids, which constitutes the triple IT regimen) and/or high-dose systemic chemotherapy (e.g. methotrexate, cytarabine, L-asparaginase), but retained for patients with high-risk disease or leukemic blasts identifiable in the cerebro-spinal fluid at diagnosis.

A successful CNS prophylaxis is achieved in the vast majority of the patients with intra-thechal therapy. Variations between protocols include the nature of the first IT (mainly cytarabine in the US, versus methotrexate in Europe), simple (methotrexate) versus triple IT for continuation of the therapy directed at the CNS, total number of ITs (ranging from 12 to 25 ITs), and administration or not of ITs during maintenance treatment. A randomized study has compared simple versus triple IT in children with standard risk ALL. It was found paradoxically, that if a reduction of CNS relapse was shown, an increase of bone marrow and testis relapses was documented. Because the salvage rate after bone marrow relapse is inferior to that after CNS relapse, the 6-year overall survival rate for children assigned to receive ITs was 90.3% versus 94.4% for ITs methotrexate ([Matloub 2006](#)).

In studies of children with ALL who only received intrathecal and/or intensive systemic chemotherapy regimens for CNS prophylaxis, the 5-year cumulative incidence of isolated CNS-relapse or any CNS-relapse was 3%-4% and 4%-5%, respectively. Historically, the incorporation of adequate systemic chemotherapy and intra-thechal chemotherapy regimens made possible to restrict the use of upfront cranial irradiation to the patients envisaged to be at higher risk of CNS relapse. Moreover, some contemporary clinical trials have reported very interesting results while completely omitting CNS prophylactic or curative irradiation, for all patients ([Pui 2009](#)). Moreover, a BFM-based study in Israel suggests that extended intrathecal therapy may allow the replacement of radiotherapy without apparent damage in the population of patients with T-cell ALL and good early response to prednisone, whatever the white blood cell count. Finally, patients with isolated relapse in the CNS who have not received prophylactic irradiation seem eminently curable, especially if there is no involvement of the bone marrow, as assessed by determination of minimal residual disease. Thus, omission of prophylactic or curative cranial therapy in childhood and adolescent ALL is a feasible goal to achieve, even in fully exhaustive mid-term and long-term studies focusing on the impact of replacement therapy are still lacking.

***It has been decided to use no preventive or curative cranial irradiation in the CAALL-F01 protocol.***

**Continuation / Maintenance therapy (see section 5 and appendix 11 )**

The backbone of maintenance therapy in most protocols includes daily oral mercaptopurine and weekly oral or parenteral methotrexate. Intrathecal chemotherapy is continued during maintenance therapy.

Pulses of vincristine and corticosteroid are often added to the standard maintenance backbone for a possible but controversial benefit ([Conter 2010, De Moerloose 2010](#)). Maintenance therapy generally continues until 2 to 3 years from treatment initiation.

***It has been decided to use for maintenance in the CAALL-F01 protocol:***

- ***12 monthly pulses (VCR DEX) in the B-lineage SR group ( idem FRALLE 2000-A)***
- ***6 pulses (VCR DEX) administered every 10 weeks in the B-lineage MR (idem EORTC 58951)***
- ***No pulses in the B-lineage HR group***
- ***No pulses in the T-lineage SR and HR groups***

**Hematopoietic stem cell transplantation (HSCT)**

Transplantation in first complete remission is indicated overall in less than 10% of the patients with ALL. In previous trials (Fralle 2000 and EORTC 58951) VHR criteria were used for indication to allogeneic HSCT, except for patients with poor prednisone response only. Essentially very high risk criteria now include high-risk cytogenetics (hypodiploidy < 44 chromosomes, t(17;19), MLL rearrangement with HR NCI criteria) and/or inadequate response criteria (induction failure, MRD > 10<sup>-3</sup> after consolidation therapy) ([Nachman 2007, Schrappe 2012, Conter 2010, Schrappe 2011](#))

***Indications for HSCT in the CAALL-F01 protocol will then be:***

- ***patients with no CR at the end of induction***
- ***patients with high MRD levels at the end of the consolidation phase***
- ***patients with poor prognosis cytogenetic abnormalities (hypodiploidy < 40 chromosomes, t(17;19)/TCF3-HLF, MLL rearrangement with HR NCI criteria)***

HSCT will be performed according to international guidelines (IBFM-HSCT) or ongoing protocol after CAAL-F01 opening (FORUM trial).

## 1.2 Introduction to investigational treatment(s) and other study treatment(s)

### 1.2.1 Overview of PEG-asparaginase

The investigational product, pegaspargase (Oncaspar®), is marketed in the USA as a component of a multi-agent chemotherapeutic regimen for the first-line treatment of patients with ALL. On 19 November 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a MA for the medicinal product Oncaspar, intended for the treatment of acute lymphoblastic leukaemia. Pegaspargase (Oncaspar®) is a PEGylated form of E. Coli L-asparaginase. The L-asparaginase (L-asparagine amidohydrolase, type EC-2, EC 3.5.1.1) used in the manufacture of Oncaspar® is derived from Escherichia coli (E. Coli) and is supplied by LONZA.

The E. Coli L-asparaginase is composed of four identical subunits with one active site per tetramer. Monomethoxypolyethylene glycol (m-PEG) with a molecule weight of approximately 5,000 daltons is covalently attached to the lysine residues of the L-asparaginase enzyme through a succinimidyl succinate (SS) linker.

L-asparaginase is an enzyme that hydrolyses asparagine to aspartic acid and ammonia. Asparagine is a nonessential amino acid synthesized from aspartic acid and glutamine by the enzyme asparagine synthetase. Certain malignant cells, such as ALL cells, are not capable of synthesizing asparagine because they lack asparagine synthetase, and they can obtain it only by diffusion from the environment outside the cell membrane. In such cells, L-asparaginase will decrease protein, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) synthesis in tumor cells, thereby exerting its cytotoxic effect while sparing most normal cells. Tumor cells can develop resistance to L-asparaginase by producing asparagine synthetase, which then enables them to produce their own asparagine. Alternative mechanisms of resistance include the production of asparagine by mesenchymal cells.

#### 1.2.1.1 Non-clinical experience

Preclinical single-dose pharmacokinetic (PK) and pharmacodynamic (PD) studies in rats and dogs were performed. The results showed that after single-dose intramuscular (i.m.) or intravenous (i.v.) administration at doses between 26 and 260 IU/kg, the maximum observed drug concentration (Cmax) and area under the time-concentration curve (AUC) for the period of 0 to infinity (AUC<sub>0-∞</sub>) values of pegaspargase proportionally increased with the increase of dose over the 10-fold dose range in both rats and dogs. The elimination half-lives with i.m. administration (79 hours at 260 IU/kg) are comparable to those by i.v. administration (67 hours at 260 IU/kg) in rats. In dogs, the elimination half-life with i.m. injection is 154 hours at 260 IU/kg as compared with 161 hours with i.v. injection. In the high-dose group, plasma asparagine levels were completely depleted throughout the 20-day study in rats; similar results were observed in the dog study.

The pharmacokinetics and the depletion of L-asparagine from the plasma and cerebrospinal fluid (CSF) following an i.m. dose of 2500 IU/m<sup>2</sup> PEG-L-asparaginase was studied in rhesus monkeys. PEG-L-asparaginase activity in plasma was

detectable by 1 h after injection and maintained a plateau of approximately 4 IU/ml for more than 5 days. Subsequent elimination from plasma was monoexponential with a half-life of  $6 \pm 1$  days. Plasma L-asparagine concentrations fell from pretreatment levels of 14-47  $\mu\text{M}$  to < 2  $\mu\text{M}$  by 24 h after injection in all animals and remained undetectable for the duration of the 25-day observation period in four of six animals. In two animals, plasma L-asparagine became detectable when the PEG-L-asparaginase plasma concentration dropped below 0.1 IU/ml. Pretreatment CSF L-asparagine levels ranged from 4.7 to 13.6  $\mu\text{M}$  and fell to < 0.25  $\mu\text{M}$  by 48 h in five of six animals. CSF L-asparagine concentrations remained below 0.25  $\mu\text{M}$  for 10-14 days in four animals. One animal had detectable CSF L-asparagine concentrations within 24 h and another had detectable concentrations within 1 week of drug administration despite a plasma PEG-L-asparaginase activity profile that did not differ from that of the other animals ([Berg 1993](#)).

No long-term carcinogenicity studies in animals have been performed. Oncaspar<sup>®</sup> did not exhibit a mutagenic effect when tested against *salmonella Typhimurium* strains in the Ames assay.

### 1.2.1.2 Clinical experience

#### 1.2.1.2.1 Clinical experience with ONCASPAR<sup>®</sup>

##### Pharmacokinetics/ Pharmacodynamics (PD)

PEG-asparaginase shows one-compartment distribution, a monophasic half-life, and a single elimination phase.

In 1993, Asselin and coworkers reported work that compared the PK of native *E. Coli* asparaginase, *Erwinia* derived asparaginase, and PEG-L-asparaginase (derived from *E. Coli* asparaginase) in patients undergoing treatment for ALL. Asparaginase activity was measured using a spectrophotometric assay. Although most of the work focused on *E. Coli* asparaginase, some comparative data were presented. The half-lives of the 3 preparations differed from each other: *E. Coli* (1.24 days), *Erwinia* asparaginase (0.65 days), and PEG-L asparaginase (5.73 days) following the induction dose. Pharmacokinetic parameters did not change during subsequent administrations of the same preparation. The t½ of *E. Coli*-derived asparaginase activity correlated with protein levels. In 4 patients who experienced an anaphylactic reaction to *E. Coli* asparaginase, enzyme activity was undetectable in their sera in the week following the allergic event. In 5 patients with a history of allergic reaction to the *E. Coli* formulation, the t½ of the PEG-L-asparaginase was also shortened to 1.8 days ([Asselin 1993](#)).

##### ***Relapsed pediatric patients with ALL***

Hawkins has published work on the kinetics of PEG-L-asparaginase in 28 pediatric patients with relapsed ALL undergoing intensive asparaginase therapy. Patients had been previously exposed to either native *E. Coli* asparaginase (n=22) or to PEG-L-asparaginase (n=3) or to both (n=3), and 4 patients had recognized hypersensitivity to L-asparaginase before entry into the study. PEG-L-asparaginase determinations were obtained 5 days after dosing, near the peak typically observed after an i.m. injection. The authors claim that trough levels are unlikely to be dramatically lower, since the half-life of PEG-L-asparaginase is estimated to be 5-6 days. In this study, PEG-L-asparaginase was administered at a dose of 2,500 IU/m<sup>2</sup> i.m. for induction on Days 2, 9, 16, and 23 and for intensification on Day 7. Satisfactory asparaginase activity was observed throughout the induction period in more than 90% of patients, although 25% of patients did not receive all of the protocol-dictated doses of PEG-L-asparaginase due to adverse events (n=6) and lack of PEG-L-asparaginase supply (n=1). Asparaginase activity >0.1 IU/mL was maintained in 94% and 80% of patients at Day 14 and Day 21, after starting intensification, respectively. Serum and cerebrospinal fluid (CSF) asparagines levels were depleted throughout induction and intensification in most samples. Overall, in this patient population with relapsed ALL, intensive treatment with PEG-L-asparaginase produced satisfactory enzymatic activity during induction, and antibody development was observed in only 3 patients ([Hawkins 2004](#)).

##### ***Newly diagnosed pediatric patients with ALL***

The PK/PD of PEG asparaginase results of the phase III study comparing native *E-coli* asparaginase versus PEG-asparaginase in induction treatment in children with newly diagnosed ALL showed a mean PEG-asparaginase activity in serum peaked on Day 5 after 2500 IU/m<sup>2</sup> i.m. The mean half-life of absorption from the i.m. site was 1.7 days and the elimination half-life was 5.5 days. The one-compartment population analysis showed an apparent volume of distribution for the central compartment of 1.5 L/m<sup>2</sup>. Asparagine levels fell rapidly by 4 days after the first asparagine dose and remained low for about 3 weeks. Serum glutamine concentration also declined during the first 2 weeks of induction therapy. CSF asparagine fell from a median pretreatment level of 2.3  $\mu\text{M}$  to 1.1  $\mu\text{M}$  on Day 7 and 0.6  $\mu\text{M}$  on day 28 of induction in patients treated with PEG-asparaginase ([Avramis 2002](#)).

Recently, Silverman et al reported results of a clinical study in 197 children newly diagnosed with lymphoblastic leukemia and treated with PEG-asparaginase including in a combination chemotherapy protocol. The patients received a dose of PEG-asparaginase 2500 IU/m<sup>2</sup> intravenously over 1 hour. Serum samples were collected before and on Day 4, 11, 18 and 25 after PEG asparaginase administration. The results showed that measurable serum asparaginase activity (limit of quantification

of 0.025 IU/mL) was observed in 96% of patients 18 days after the infusion. With a threshold of 0.1 IU/mL, 88% had serum asparaginase activity but only 7% maintained this level after Day 25 ([Silverman 2010](#)).

Modeling of the PK/PD data collected in study CCG-1962 led to the conclusions that PEG-asparaginase has superior PK parameters (peak and AUC) in induction and subsequent treatment phase (delayed consolidation 1) compared with 9 doses of native L-asparaginase ([Avramis 2007](#)).

***In the UKALL 2003, patients were treated with intramuscular PEG-asparaginase at 1 000 IU/m<sup>2</sup> on Day 4 and Day 18 at induction and at least one post-induction. Trough asparaginase activity during therapy was analyzed. Overall, 86% of samples had adequate activity during induction time points with a large range (44% had activity >3 times the therapeutic threshold of 100 IU/L). In the other hand, 51% of samples with inadequate activity had no detectable activity. Inadequate asparaginase activity correlated with high MRD (≥10-4) in SR patients (p=0.045), mainly those with good risk cytogenetics (p=0.012) and hyperdiploidy particularly (p=0.03). NCI HR patients had a higher incidence of inadequate asparaginase activity (p=0.002) in this study (Fong 2011).***

### **Clinical efficacy in second-Line ALL**

In 2000, Abshire et al designed a phase III study for patients under 22 years old with B-precursor ALL, in first marrow and/or extramedullary relapse. Reinduction included doxorubicin on day 1, prednisone from D1 to D29, vincristine weekly for 4 weeks, and PEG-L asparaginase at a dose of 2500 IU/m<sup>2</sup>intramuscularly, either weekly for 4 doses (D1, D8, D15, D22) or biweekly for 2 doses (D1 and D15) by randomization. Asparaginase concentrations were measured weekly on day 8, 15, 22 and 29 as trough levels. E coli asparaginase and PEG-L asparaginase antibodies were measured weekly on day 8, 15, 22 and 29 just before each asparaginase dose. Overall, 129 of 144 evaluable patients (90%) achieved a complete remission (CR). There was a highly significant difference in CR rates between weekly (69/71; 97%) and biweekly (60/73; 82%) PEG-L asparaginase dosing (p=0.003). Grade 3 or 4 infectious toxicity was common (50%), but only 4 patients died of sepsis during induction. Other toxicities were infrequent and hypersensitivity was rare (6/144; 4%). Low asparaginase levels (<0.03 U/mL) were associated with high antibody titers to either native (p=0.024) or PEG asp (p=0.0013). The CR rate was significantly associated with higher levels of asparaginase (0.75 U/ML vs 0.45 U/mL, p=0.012). Patients with ALL in first relapse receiving weekly PEG-Asp (4 infusions) had a higher rate of second remission compared with biweekly dosing (2 infusions). Low levels of asparaginase were associated with high antibody titers. Increased asparaginase levels may correlate with an improved CR rate. The conclusion was that the use of intensive PEG-Asp should be further explored in the treatment of ALL ([Abshire 2000](#)).

### **Clinical efficacy in first-Line ALL**

The safety and effectiveness of Oncaspar® was evaluated in 2 phase III clinical trials including 495 patients and compared PEG-ASP to native ASP in induction regimens for newly diagnosed pediatric ALL (DFCI 91-01 and CCG-1962 studies).. In the CCG-1962 study, 118 pediatric patients aged 1 to 9 years with previously untreated standard-risk ALL were randomized 1:1 to Oncaspar® or native E. Coli L-asparaginase as part of combination therapy. Oncaspar® was administered i.m. at a dose of 2 500 IU/m<sup>2</sup> on Day 3 of the 4-week induction phase and on Day 3 of each of two 8-week delayed intensification phases. Native E. Coli L asparaginase was administered i.m. at a dose of 6 000 IU/m<sup>2</sup> three times weekly for 9 doses during induction and for 6 doses during each delayed intensification phase. In all phases of treatment, serum asparagine concentrations decreased within 4 days of the first dose of asparaginase in the treatment phase and remained low for approximately 3 weeks for both Oncaspar® and native E. Coli L-asparaginase arms. The patterns of serum asparagine depletion in the two delayed intensification phases are similar to the pattern of serum asparagine depletion in the induction phase. There was more rapid clearance of blasts on Day 7 (p=0.05) and Day 14 (p=0.015) and a more prolonged asparaginase activity than those treated with the native form.in the PEG-asparaginase arm than in the native asparaginase arm. Twice as many patients in the native asparaginase arm had M3 bone marrow on Day 7 than in the PEG-asparaginase arm. In the first DI phase, 26% of patients treated with the native asparaginase had high-titer antibodies compared with 2% of patients receiving Oncaspar®. High-titer antibodies were associated with low asparaginase activity in the native arm, but not the Oncaspar® arm. The rate of infections, hospitalizations and the safety profile were similar between the arms. The 3-year EFS rates for PEG-asparaginase and native asparaginase were 85% and 78% respectively (NS) ([Avramis 2002](#)).

In the DFCI 91-01 study, 377 patients aged 0 to 18 years were enrolled. Asparaginase was included in the intensification phase and patients were randomized between PEG-asparaginase 2500 IU/m<sup>2</sup> i.m. every 2 weeks for 15 doses or native E. coli asparaginase 25000 IU/m<sup>2</sup> i.m. every week for 30 doses. A total of 137 patients were considered standard risk and 240 patients were high risk. With a median follow up of 5.0 years, the estimated 5-year EFS was 83% There was no significant difference in 5-year EFS based upon risk group. Conversely, age at diagnosis was a significant prognostic factor (severe outcome in infants and children ≥9 years) along with asparaginase tolerance. Patients who tolerated 25 or fewer weeks of asparaginase had a significantly worse outcome than those who received at least 26 weeks of asparaginase (p<0.01) ([Silverman 2001](#)).

### **Safety of PEG-asparaginase**

A total of 197 patients aged 1 to 17 years were enrolled onto the Protocol 05-01 and received a single dose of PEG-asparaginase 2500 IU/m<sup>2</sup> i.v. The most asparaginase-related toxicity was pancreatitis (4.5%) developing in a median of 13 days after dosing. Others related toxicities were thrombosis (2%), hypersensitivity (1.5%) and 1 case of grade 4 hypertriglyceridemia ([Silverman 2010](#)). In the CCG-1962 study, the incidence and type of toxic events were similar between the PEG-asparaginase and the native E. Coli asparaginase. In the DFCI 91-01 study, there was no difference between the asparaginases used. Asparaginase-related toxicities occurred in 29% of the 377 patients and were mainly allergic reactions (15%), pancreatitis (7%), and coagulopathy (4.5%). Patients aged 9-18 years were more likely to experience an asparaginase-related toxicity compared with those less than 9 years (48% vs 24%, p<0.01). Since the security use is comparable between both forms of asparaginase for non-allergic events, the lower risk of antibodies formation and allergy gives an advantage to the PEG-form ([Avramis 2002](#)).

### **Antibody Formation**

The formation of anti-asparaginase antibodies is an important determinant of the persistence of asparaginase activity in the plasma of treated patients. Wetzler et al reported a rate of 9.5% of anti-asparaginase antibodies in the 63 patients who achieved asparagine depletion at some point as compared with 31.8% of the 22 patients who did not (p=0.012) ([Wetzler 2007](#)). Antibodies anti-asparaginase has been reported in 4% to 15% after PEG-asparaginase in asparaginase naive patients whereas a higher rate was noticed with native E.Coli asparaginase administration in adults (79%) and in children (60-70%) ([Zeidan 2009](#)). The PEG- asparaginase has a reduced potential to provoke antibodies and thus has an increased likelihood of enabling a full course of effective therapy. Similarly, it is associated with a reduced incidence of clinically overt allergic phenomena. In the CCG-1962, Avramis found that 26% of native asparaginase patients had high-titer antibodies whereas 2% of patients treated with PEG-asparaginase had those levels during the first delayed intensification (p=0.001). He also reported that the antibody levels tended to decrease between Day 7 and Day 28 of each asparaginase-containing phase and were lower in dose intensification (DI) 2 than in DI 1 ([Avramis 2002](#)). In 2004, Panosyan and coworkers have reported the results of antibody development in patients entered into CCG-1961, a study of pediatric patients with high-risk ALL. In brief, 61% of 1001 patients developed antibodies during CCG-1961, in which all patients initially received 9 doses of E. Coli asparaginase during induction. In contrast, the authors report that only 2 of 59 patients in CCG-1962 developed antibodies after a second exposure to PEG-L-asparaginase. In CCG-1961, anti-asparaginase antibody was associated with undetectable asparaginase activity. The use of PEG-L-asparaginase would appear to offer the prospect of improved outcome by virtue of its apparently diminished immunogenicity ([Panosyan 2004](#)). Wang and associates evaluated the cross-reactivity of antibodies identified in a cohort of 24 pediatric patients with newly diagnosed ALL (n=22) or lymphoma (n=2). Patients were treated with E. Coli asparaginase 10000 IU/m<sup>2</sup> i.m. three times weekly for nine doses as part of induction and re-induction multi-agent chemotherapy and subsequently received monthly doses during the first 7 months of continuation treatment. Six of the 24 patients had no clinical reactions to the asparaginase and received only the E. Coli preparation. The remaining 18 who had allergic reactions were switched to Erwinia asparaginase, and all of these had an anaphylactoid reaction to the Erwinia formulation and were switched to PEG-L-asparaginase. Anti-E.Coli antibodies correlated with anti-PEG antibodies but not with anti-Erwinia antibodies. The result is not surprising since PEG-L-asparaginase is derived from an E. Coli asparaginase preparation. The authors did not correlate the presence of antibody with serum asparaginase or ASN levels ([Wang 2003](#)).

### 1.2.1.2.2 Clinical experience with ONCASPAR KH

#### Introduction

In Europe ONCASPAR is registered for second line use in Germany and Poland. The brand of asparaginase used is differing from the one originally used in the ONCASPAR used in the USA. Indeed the API comes from Kyowa-Hakko; the pegylation was done historically by ENZON and now SHIRE/Servier. It is thus slightly differing from ONCASPAR KH. **Nevertheless the currently FDA-approved ONCASPAR uses a form of asparaginase (Lonza API) with exactly the same amino-acid sequence than the one from Kyowa Hakko.**

#### Published data

In 2000, Muller reported the results of a multicenter study of re-induction therapy in 70 children (68 ALL; 2 NHL) to determine the suitability of using PEG-L-asparaginase from Medac for treatment following initial exposure to E. Coli ASNase. The study included 66 patients who received 8 infusions of native E. Coli asparaginase without signs of hypersensitivity and 4 other patients who exhibited signs of hypersensitivity. For re-induction on Day 8, patients received a single infusion of 1,000 IU/m<sup>2</sup> PEG-L-asparaginase i.v. over 2 hours as a substitute for 4 doses of 10,000 IU/m<sup>2</sup> E. Coli asparaginase on Days 8, 11, 15, and 18. According to the authors, no hypersensitivity phenomena were observed with PEG-L-asparaginase, in contrast to the expected rate of approximately 30% with E. Coli enzyme; however, 22 (33%, 22/66) patients had a rapid decline in asparaginase activity, with asparaginase activity at Day 14 below the therapeutic target (<100 U/L). Note the doses of PEG-L-asparaginase used in the study (1,000 IU/m<sup>2</sup>) were lower than those recommended in current labeling (2,500 IU/m<sup>2</sup>) and the doses were administered i.v. rather than i.m. These conditions might have contributed to the rapid decline in asparaginase activity observed in 30% of patients ([Muller 2000](#)).

A follow-up study conducted by the same group in 2001 examined a dose of 2500 IU/m<sup>2</sup> i.v. in an effort to see if this larger dose would yield higher and more persistent activity of asparaginase in patient serum following treatment. A total of 39 patients were administered re-induction treatment, and 20 were treated for relapse. The authors state that the threshold for adequacy of asparaginase levels is 100 U/L 14 days following treatment. Approximately one third of patients treated with the original dose of PEG-L-asparaginase (1000 IU/m<sup>2</sup>), and a similar fraction treated with 2500 IU/m<sup>2</sup> failed to achieve this level of asparaginase activity ([Muller 2002](#)).

In 2005, Vieira Pinheiro et al reported results of a PK study of serum asparaginase activities and asparagine concentrations in the CSF after a single infusion of 2500 IU/m<sup>2</sup> PEG asparaginase in children with LR and HR ALL. A total of 70 patients treated according to the CALL-06-07 protocol were included in the PK study. During the induction therapy, they received 3 (LR) or 4 (HR) doses of native asparaginase and a single dose of 2500 IU/m<sup>2</sup> i.v. of pegylated asparaginase KH® on Day 80 (LR) or 108 (HR). Blood samples were collected before the application and weekly for 8 weeks after PEG-asparaginase had been given. CSF samples were obtained when IT chemotherapy treatment was scheduled. The PK measurements showed baseline serum asparaginase activity values in a range considered ineffective. After infusion of asparaginase, activity values range above 100 UI/L over a period of 3 to 4 weeks. Concerning the CSF asparagine, the results showed pretreatment concentrations below the reference values of 3-8μM established for children that was most likely due to a residual effect from the asparaginase given 21 days before according to the authors. Due to no lumbar puncture within the first 2 weeks following PEG-asparaginase administration, the CSF asparagine data were limited. CSF asparagine recovery was observed from the second week. Asparagine concentrations comparable with the baseline values were found after about 3 weeks and those similar to reference values after 5 weeks. When relating the CSF asparagine results to same-day serum asparaginase activity values, higher serum asparaginase values were associated with lower CSF asparagine concentrations. Since asparaginase, native, or pegylated does not cross the blood-brain barrier, decrease of asparagine concentration in CSF could be explained by equilibration with the serum following asparagine depletion. Moreover, the correlation also showed that serum enzyme activity values clearly ranging above 100 U/L were not always combined with complete CSF asparagine depletion ([Vieira Pinheiro 2006](#)).

In 2008, Appel and coworkers reported results from 57 patients in whom the use of PEG-L-asparaginase (pegaspargase MEDAC, 1,000 IU/m<sup>2</sup> i.v. at Day -5 before induction chemotherapy). The median serum level of asparagine decreased below the limit of detection (0.2μM) after the administration of PEG-asparaginase and remained below until Day 21 in all patients but 2, so for at least 26 days. The serum asparaginase activity was >100 IU/L for at least 15 days and the level of aspartic acid and glutamic acid increased rapidly after the infusion and remained increased at Day 0 ([Appel 2008](#)).

#### Antibody Formation

Armstrong et al analyzed retrospectively antibody against polyethylene glycol in serum samples of 44 pediatric patients included in the ALL-BFM 2000 and ALL-BFM REZ 2002 protocols. In this protocol, 28 patients received PEG-asparaginase and 16 received native E. Coli asparaginase. The mean serum asparaginase activity for all samples tested were 240 IU/L for the PEG-asparaginase and 84 IU/L for the native asparaginase groups. A total of 9 of 28 sera (32%) from patients with PEG-asparaginase treatment contained IgG and IgM anti-PEG and the asparaginase activity in all 9 patients was below the detection (<5 IU/L). To be noted, 12 patients were not previously exposed to PEG-asparaginase and 7 (58%) had undetectable asparaginase activity and 4 (33%) of which were positive for anti-PEG. No relation was observed between anti-PEG and serum asparaginase activity for patients treated with native asparaginase. The authors concluded that the presence of anti-PEG was very closely associated with rapid clearance of PEG-asparaginase for a subgroup of pediatric patients treated

for ALL without any clinical manifestation of an allergy or hypersensitivity ([Armstrong 2007](#)). In the retrospective analysis of Willer et al , an inversely correlation was found between asparaginase activity and anti-asparaginase antibody levels with native E. Coli and pegylated asparaginase ( $p<0.0001$ ): no antibodies was detectable in 96.2% and 97.3% of samples with an asparaginase activity above 50 U/L, respectively. Conversely, when the samples were tested negative for antibodies, the asparaginase activity was above 50 U/L or 100 U/L in 96.7% and 94.2%, respectively. Switching to pegylated E. Coli asparaginase increased the rate of samples with sufficient activity only when antibodies levels were <200 AU/mL. No significant correlation was found between the asparaginase activity and the antibody levels after the administration of Erwinia asparaginase ([Willer 2011](#)).

Fong et al reported a rate of 22% (18/81) of patients with antibodies: all had anti-PEG and 7 had also anti-asparaginase antibodies. All had inadequate activity after antibody detection but 17 had activity prior to antibody detection. Moreover, 14/15 patients who had inadequate activity at first exposure, had no antibodies detected ([Fong 2011](#)).

### 1.2.2 Other drugs used in the different combinations of treatment

Dexamethasone, vincristine, daunorubicin, doxorubicin, cyclophosphamide, ifosfamide, etoposide, mitoxantrone, 6-mercaptopurine, methotrexate, cytarabine, 6-thioguanine are all registered and marketed for several decades and are included in different combinations of pediatric ALL treatments. Their efficacy/safety profiles are well known. Only Nelarabine has been more recently introduced in first and a second line ([Commander 2010](#), [Dunsmore 2012](#), [Winter 2015](#)) but has been considered safe in a randomized COG study AALL 0434, conducted until its end without any toxicity concern raised by the Data Monitoring Committee ([Winter 2015](#)). Please, refer to [Appendix 9](#) for synthesis of expected adverse events. See Summary of product Characteristics for full prescribing information on each compound.

## 1.3 Study Rationale and Purposes

### 1.3.1 Current results

Although great progresses had been made during the last tens of years in the treatment of pediatric patients with ALL, 10 to 20% of children and 20 to 30% of adolescents are going to die from the disease. ALL is an extremely heterogeneous disease in terms of biology and response to treatment. To envisage targeted treatments in the future means to decipher this heterogeneity. Moreover, insufficient results are observed in high-risk groups, particularly in those experiencing an early resistance to chemotherapy.

The cooperative group FRALLE and the French centres of EORTC-CLG have decided to elaborate a protocol for the treatment of children and adolescent with ALL. The two previous studies from these groups have comparable results:

**Table 1: Estimates of outcomes from previous trials**

	N	Event-Free Survival		Overall Survival	
		5 years	8 years	5 years	8 years
FRALLE 2000	2146	84.0%	82%	91%	89%
EORTC 58951	1947	82.6%	81.3%	89.7%	88.1%

The re-analysis of these studies with common criteria, compared with the available literature and the unpublished data of cooperative groups led to a new potential stratification with therapeutic implications:

- *A Standard-Risk group exists and is candidate to de-escalation (B-SR group). The projected 5-year EFS is  $\geq 95\%$  for this population. This group will obviously exclude High-risk or Very-high risk cytogenetics but also patients with IKZF1 deletion/mutation, and bad responders to induction/ consolidation (MRD TP1 and TP2)*
- *Patients with B-Lineage ALL not belonging to the Standard risk group will be treated in the Medium risk and High risk according to cytogenetics/genetics and response to treatment (D8, MRD TP1 and TP2)*
- *Patients with T-cell ALL will be treated in the Standard-Risk group or High-Risk according to response to treatment (D8, MRD TP1 and TP2)*
- *Patients initially included in the B- and T- High Risk groups are candidate to further treatment intensification including HSCT if no adequate MRD kinetics.*

### 1.3.2 A pending major question in the field of ALL is the optimal use of asparaginase.

It is known that administering asparaginase results in the depletion of asparagine circulating in the blood, which starves the leukemic cells and results in their death.

Actually, the use of asparaginase varies between protocols considering the different brands, the dose and the administration modalities (rhythm, route-IM or IV).

***Three major forms of asparaginase are currently available: E. coli asparaginase (Kidrolase<sup>®</sup>), Erwinia asparaginase (Erwinase<sup>®</sup>, for patients with hypersensitivity) and a pegylated form of E.coli Asparaginase (Oncaspar<sup>®</sup> in USA (API: Lonza), Oncaspar<sup>®</sup> in Europe (API: Kyowa-Hakko), to be substituted in 2016-2017 by Oncaspar including the Lonza API .***

### **1.3.2.1 Oncaspar<sup>®</sup>**

In 1994, the FDA approved the PEGylated formulation of asparaginase (Oncaspar<sup>®</sup> from ENZON-API from Merck) which has the unique therapeutic advantages of sustained duration and prolonged effect over the native asparaginase, resulting in enhanced convenience for patients and providers. Oncaspar<sup>®</sup> was updated to first-line indication in 2006. CCG-1962 was the pivotal clinical trial supporting first-line use of Oncaspar<sup>®</sup>. (See Section 1.2.1.2 for more details.)

### **1.3.2.2 Oncaspar<sup>®</sup> KH in Europe**

Oncaspar<sup>®</sup>, which is currently available in Europe differs from the Oncaspar<sup>®</sup> marketed in the USA because the asparaginase manufacturer is different (Kyowa-Hakko, KH), even if the pegylation is also performed by Sigma-Tau. Of note, Oncaspar<sup>®</sup> KH is used in first line in at least three major protocols: UK MRC protocols for ALL since 2003 (UK), BFM-AIEOP protocol for ALL since 2010 (Germany, Italy, Austria, Switzerland; Czech Republic, Israel), INTERFANT (a protocol dedicated to infants with ALL) since 2006 (many countries).

This first-line use is observed despite the fact that KH API including Oncaspar KH is not registered for first line use in patients with ALL. In Europe, Oncaspar<sup>®</sup> was only registered in second-line in Germany and Poland.

### **1.3.2.3 Products registered in France**

Until January 2016, only Kidrolase<sup>®</sup> was registered for first-line use. If hypersensitivity occurs, Erwinase<sup>®</sup> should be administered in second line. Oncaspar Medac<sup>®</sup> could only be obtained on a patient-named basis after hypersensitivity reactions to the two other forms.

### **1.3.2.4 A “new” Oncaspar<sup>®</sup>**

A new form of Oncaspar<sup>®</sup> has been approved in the USA (2011) and is registered in Europe, since January 2016. Sigma-Tau Pharmaceuticals, Inc. announced on April 18, 2011 that it has received approval from the U.S. Food and Drug Administration (FDA) to manufacture Native asparaginase, the primary ingredient in the oncology medicine Oncaspar<sup>®</sup> (pegaspargase). The attempt to secure approval to manufacture Native asparaginase came after the previous supplier decided to cease production, leading to a three-year development effort to create a comparable active ingredient. This ingredient, provided by Lonza, has the same amino-acid sequence than the ingredient provided by Kyowa-Hakko, which is used in the pegylated form of asparaginase available in Europe. Since January 2016, the European Commission has granted MA for use of ONCASPAR as a combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients. With this approval, the MA holder is authorized to market ONCASPAR in the 28 member countries of the European Union (EU), as well as Iceland, Liechtenstein and Norway. This authorization is related to the Oncaspar incorporating the API manufactured by Lonza

### **1.3.2.5 Study purposes**

The primary aims of the study are two-fold:

- 1. To determine what is the best schedule of administration (2500 IU x1/m<sup>2</sup> or 1250 IU x2/m<sup>2</sup>) of pegaspargase in children with Standard-risk (SR) B- and T-cell ALL and medium-risk (MR) B -ALL.**
- 2. To determine the safety and efficacy of intensification of pegaspargase dosage during induction treatment in children with High-risk (HR)/Very High Risk (VHR) B- ALL and T-ALL.**

Patients with IKZF1 deleted ALL will be excluded from the SR group. The indirect question being: is intensification of the treatment of this subtype of disease is able to reverse the worse prognosis of these patients?

Add-on studies will focus on helping to further refine the classification of ALL by newer techniques (CGH/SNP arrays in particular) and will help to confirm prospectively the prognostic value of newly described cytogenetical/molecular aberrations in B-lineage and T-lineage ALL. Patients with induction failure or high MRD will be screened for new druggable molecular abnormalities allowing the potential use of TKI or other new targeted agents (e.g. ruxolitinib) in association to chemotherapy. Exhaustive banking correlated to the protocol data base is thus of paramount importance. Add-on studies will also take into account the role of host variability (pharmacogenomics).

## 1.4 Rationale for dose and regimen selection

### 1.4.1 Pegasparagase

Several studies demonstrated the efficacy on asparagine depletion, clinical efficacy and the good tolerance of one dose of 2 500 IU/m<sup>2</sup> of pegasparagase in pediatric patients administered i.m. ([Avramis 2002, Silverman 2001](#)) or i.v. ([Vieira Pinheiro 2006, Silverman 2010](#)).

Less immunogenicity, due to shielding of antigenic epitopes by the large covalently bound polyethylene glycol chains, is expected with the use of pegasparagase instead of native E. Coli L-asparaginase.

Different schedules of ONCASPAR® administration are currently evaluated in first-line ALL protocols during induction therapy:

- 1000 IU/m<sup>2</sup> two infusions: UKALL protocol (ONCASPAR KH)
- 1500 IU/m<sup>2</sup> two infusions : DCOG protocol (ONCASPAR KH)
- 2500 IU/m<sup>2</sup> one infusion: COG and DFCI protocols (ONCASPAR LONZA)
- 2500 IU/m<sup>2</sup> one infusion: Interfant 06 protocol (ONCASPAR KH)
- 2500 IU/m<sup>2</sup> one infusion: EORTC protocol (ONCASPAR KH)
- 2500 IU/m<sup>2</sup> two infusions: AIEOP-BFM protocol (ONCASPAR KH)
- 3500 IU/m<sup>2</sup> one infusion: St Jude protocol (ONCASPAR LONZA)

A fortnightly administration of a pegylated form of asparaginase has been used during induction therapy in the UKALL MRC 2003 protocol (Oncaspar® Medac: 1 000 IU/m<sup>2</sup> x 2 infusions) ([Vora 2010 and 2014](#)). It is currently used in the UKALL 2011 (same scheme than previously) and in the AIEOP-BFM 2010 protocol (2 500 IU/m<sup>2</sup> x 2 infusions) (refer to protocols). As a reassuring note, Abshire et al treated 73 children with weekly Oncaspar® 2 500 IU/m<sup>2</sup> (4 infusions) and 74 children with biweekly Oncaspar® 2 500 IU/m<sup>2</sup> (2 infusions) in the context of a 4-drug reinduction therapy without excessive toxicity ([Abshire 2000](#)).

The i.v administration of asparaginase is an easier way and showed comparable efficacy and safety as the i.m one ([Silverman L Blood 2010](#)).

#### **Choices and questions in CAALL-F01:**

1. *The choice of testing the total dose at induction (2 500 IU/m<sup>2</sup>) equally divided into 2 doses administered 2 weeks apart was led by the hypothesis that 1 250 IU/m<sup>2</sup> could be a sufficient dose to obtain an asparagine depletion and that a second administration would prolong this depletion. This will be tested in a randomized way, in the non-high risk patients of the B ad T lineage.*
2. *Since more induction failures and more early relapses occur in the very high-risk groups leading to a poorer 5-year EFS, we propose to increase the number of pegasparagase administration to 2 infusions of 2 500 IU/m<sup>2</sup> with the aim to prolong the asparagine depletion. No randomization is planned for these high-risk patients because of the heterogeneity of the population in a context of small numbers.*

### 1.4.2 Corticosteroids

All patients will receive a classical prophase of prednisolone 60 mg/m<sup>2</sup>/day or equivalent from Day 1 to Day 7

After Day 7, 3 modalities of steroid will be administered during induction and further phases according to the risk group the patient is allocated to:

- *Dexamethasone 6 mg/m<sup>2</sup>/day for the induction phase of B-SR group:* this dosing was used in the FRALLE and in the EORTC protocols; 6 mg/m<sup>2</sup> was better than 40 mg/m<sup>2</sup> in the CCG-1922 ([Bostrom 2003](#)) and 6 mg/m<sup>2</sup> showed comparable results as 60 mg/m<sup>2</sup> of prednisolone (EORTC-58951) ([Domenech 2014](#)).
- *Dexamethasone 10 mg/m<sup>2</sup>/day for the induction and delayed intensifications of T-SR and the delayed intensifications of B-SR, B-MR B-H/VHR and T-H/VHR groups:* This dosing demonstrated superiority over prednisone 60 mg/m<sup>2</sup> and better crosses the blood-brain barrier. Improvement of EFS is expected with this higher dosing ([Schrappe 2008](#)).
- *Prednisolone 60 mg/m<sup>2</sup>/day in the induction phases of B-MR and B-H/VHR groups and T-H/VHR groups:* comparable results were observed between prednisone 60 mg/m<sup>2</sup> and dexamethasone ([Domenech 2014; Schrappe 2008](#)). The use of prednisone will avoid the toxicity of the dexamethasone, particularly in older children and adolescents.

## 1.5 Other drugs used in combination

**All the drugs used in this protocol are included in various regimens for more than thirty years for treating childhood ALL.** The combinations of the drugs were modified with time, leading to a progressive improvement of EFS. The backbones of these combinations are:

- at induction: vincristine - asparaginase - corticoids ± anthracyclines ± cyclophosphamide
- CNS-directed treatment: methotrexate IT/triple IT/high-dose Methotrexate/ Asparaginase/ dexamethasone
- at delayed intensification: vincristine - asparaginase - corticoids + anthracyclines + Cyclophosphamide +6-thioguanine and cytarabine
- at maintenance/consolidation: 6-mercaptopurine/ methotrexate / pulses (vincristine-steroids)
- A subgroup of patients will receive block therapy (VANDA, VHR1 block, VHR2 block) leading to combine asparaginase according to protocol to mitoxantrone, etoposide, ifosfamide, high-dose methotrexate, on top of classical drugs).

First exception is Nelarabine which will be used in a very small subset of patients: patients with non responding T-cell ALL and candidate to HSCT:

- Nelarabine was added to a BFM 86-backbone in children with newly diagnosed T-ALL and poor early response (SER). Nelarabine was first added at a dosage of 400mg/m<sup>2</sup> for 6 courses and then patients received 650 mg/m<sup>2</sup> (5 day course) 6 times (70 patients were treated); Nelarabine was well tolerated ([Dunsmore 2012](#)). Administration of Nelarabine has been randomized in the large ALLO434 COG trial ([Winter 2015](#)). This intensive protocol has been conducted until its programmed end without stopping for toxicity. In adult patients, Nelarabine was combined to hyperCVAD treatment : it was safe and active in 40 pts at the dose of 650mg/m<sup>2</sup> for five days (2 cycles) ([Jain 2014](#))
- Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. In particular Nelarabine could offer the patient the possibility to receive allogeneic stem cell transplantation after suboptimal MRD response (non responding disease).

Second exception: since V5 of the protocol, a subgroup of patients, i.e. those with induction failure and/or MRD TP1  $\geq 10^{-3}$  and blast harbouring an ABL-class fusion will receive imatinib on top of chemotherapy (see B-HR consolidation and further courses). Of note, Imatinib is already used since 2004 in Europe for Ph+ ALL in the frame of intensive polychemotherapy (EsPhALL studies)([Biondi 2012](#))

See Section 5 and Appendix 9 for more information.

## 1.6 Rationale for evaluation timelines

### 1.6.1 Efficacy time-points

- a) Asparaginase activity sampled 21 days after one pegaspargase infusion or 7 days after the second infusion in case of 2 infusions ( $\pm$  Day 33) is **the main time-point** for the evaluation of the primary objective of the study.
- b) The treatment to be administered depends on the leukemia response at different time-points, i.e.:
  - **Day 8 prednisone response** for stratification in SR, MR, or HR/VHR groups
    - Good prednisone response (GPR): less than 1 000 blast cells/mm<sup>3</sup> after 7 days of prednisone 60 mg/m<sup>2</sup>/day and one intrathecal injection of methotrexate
    - Poor prednisone response (PPR): no good prednisone response
  - **Day 35 for the evaluation of complete remission by morphology**
  - **Evaluation of Minimal Residual Disease at end of induction (Time Point1-TP1), during or post consolidation (TP2) and for some patients post VANDA course (TP3).** See Section 3.4, Table 6, for a summary of MRD time points according to groups.

### 1.6.2 Safety time-points

- For main end-point: incidence of severe toxicities (Grade  $\geq 3$ ) directly asparaginase-related (CNS thrombosis, pancreatitis, anaphylaxia, and hyperbilirubinemia) will be measured within the first 7 weeks (D49) of treatment and anyway before D8 of consolidation.

Within these time intervals, all patients will receive a homogenous treatment with no expected reduction of dosage leading to homogenous populations to be compared.

- For secondary end-points: a comparison of the 2 arms will be undertaken for the patients with Standard-Risk or Medium-Risk ALL. A non comparative assessment will be made for patients belonging to the High-Risk/Very High Risk-groups.
  - All other adverse events (AE) related to asparaginase occurring within the first 7 weeks (D49) of treatment and anyway before D8 of consolidation:
    - Hyperglycemia / induced diabetes, coagulopathy, allergy, hyperlipidemia (hypertriglyceridemia and/or hypercholesterolemia)
      - Non CNS thrombosis
      - All Grades pancreatitis, hyperbilirubinemia
    - Adverse events related to asparaginase but occurring after D49 of induction or anyway at D8 of consolidation or after
    - Incidence of all grade 3-4 adverse events, whatever their imputability.
  - Other end points not directly related to study drug
    - Imatinib related adverse events (immediate and long term, cf appendix 9) in the rare patients with suboptimal response to therapy (induction failure or MRDTP1  $\geq 10^{-3}$ ) and ABL-class fusions ALLs treated with imatinib

### **1.6.3 Survival time-points**

5-year event-free survival, disease-free survival and overall survival are classical outcome measures for the evaluation of survival in children with ALL.

Event-free survival is the survival time free of treatment failure, relapse or secondary malignancy from Day 1 of treatment or after randomization (in randomized arms); disease-free survival is the event-free survival in responders measured from the time of complete remission following induction. Treatment failure is defined after induction at day 35-day 42, by at least 5% blasts and MRD  $\geq 5 \times 10^{-2}$ . In case of no available MRD, only the  $\geq 5\%$  blasts criterion will be required.

## 2 Objectives and Endpoints

### 2.1 Primary objectives

The primary objectives are a) to compare, within the non-high risk patients, the group of patients treated with 1 250 IU/m<sup>2</sup> x 2 pegaspargase and the group of patients treated with 2 500 IU/m<sup>2</sup> x 1 pegaspargase, and b) to evaluate within the group of high-risk patients receiving 2 500 IU/m<sup>2</sup> /day x 2 pegaspargase during the induction phase:

- The incidence of **adequate** (>100 IU/L) **asparaginase activity at the induction phase**: 21 days after one pegaspargase infusion or 7 days after the second infusion in case of 2 infusions ( $\pm$  Day 33)
- The incidence of **severe** (Grade  $\geq 3$ ) **toxicities directly asparaginase-related** (e.g. CNS thrombosis, pancreatitis, anaphylaxia, and bilirubine) within the first 7 weeks (D49) and anyway **before D8 of consolidation**

### 2.2 Secondary objectives linked to study drug

The secondary objectives are a) to compare between the group of patients treated with of 1250 IU/m<sup>2</sup> /day x 2 infusions of pegaspargase and the group of patients treated with 2 500 IU/m<sup>2</sup> x 1 infusion of pegaspargase and b) to evaluate in the group of patients receiving 2 500 IU/m<sup>2</sup>/day x 2 pegaspargase in terms of pharmacokinetics/pharmacodynamics/immunogenicity, efficacy and safety.

#### 2.2.1 Pharmacokinetics/ Pharmacodynamics /Immunogenicity

The criteria will include:

- Asparaginase activity and asparagine levels at defined time-points
- Incidence of asparaginase antibodies
- Incidence of silent inactivation in both arms during induction, consolidation and intensification phase(s)
- Allergic reaction rate in both arms during induction, consolidation and intensification phase(s)
- Percentage of patients without switch to Erwinia asparaginase
- Percentage of patients receiving more than 95% of the intended dose of asparaginase

#### 2.2.2 Efficacy

The criteria for efficacy will include:

- Morphological CR rates (M1 marrow at the end of induction, see **Section 6** for response criteria), assessed on the whole population or on subgroups (B-Lineage ALL, T-cell ALL).
- Minimal Residual Disease (MRD) at the end of induction (TP1) and at the later time-point (TP2) (TP3 for a subgroup of patients) assessed by Ig/TCR-based RQ-PCR. This evaluation will be made in the whole population and within subgroups
- Cumulative Incidence of relapses overall.
- Cumulative Incidence of BM relapses, CNS relapses, gonadal relapses, combined relapses
- Event Free Survival, defined as the survival time free of treatment failure (see section 1.6.3), relapse or secondary malignancy

#### 2.2.3 Safety

- All other adverse events (AE) related to asparaginase occurring within the first 7 weeks (D49) of treatment and anyway before D8 of consolidation:
  - Hyperglycemia / induced diabetes, coagulopathy, allergy, hyperlipidemia (hypertriglyceridemia and/or hypercholesterolemia)
  - Non CNS thrombosis
  - Grade 1-2 AE: pancreatitis, hyperbilirubinemia
- Adverse events related to asparaginase but occurring after D49 of induction or anyway at D8 of consolidation or after
- Incidence of all grade 3-4 adverse events, whatever their imputability.

**NB: Grading of adverse events (AE) will be performed using the NCI-CTC scale version 4.03.**

**2.3. other secondary objectives****2.3.1. to evaluate the incidence of rare subgroups of ALL and their prognostic value**

e.g. so-called “B-other” subgroup : BCR-ABL like (including EBF1-PDGFRB), MEF2D-X, ZNF384-X, TCF3-HLF...

**2.3.2** 5 year EFS, DFS and OS of the rare patients with suboptimal reponse to therapy (induction failure or MRDTP1  $\geq 10^{-3}$ ) and ABL-class fusions ALLs treated with imatinib

**2.3.3** Imatinib related adverse events (immediate and long term, cf appendix 9) in the rare patients with suboptimal reponse to therapy (induction failure or MRDTP1  $\geq 10^{-3}$ ) and ABL-class fusions ALLs treated with imatinib

### 3 Study design

#### 3.1 Description of the study design

This is a prospective, French, multicenter, open-label, design, stratified on the immunophenotypic characterization (B- or T- lineage) and the patient risk group, that aims at evaluating the efficacy and the tolerance of different schedules of pegaspargase in **patients from 12 months to less than 18 years newly diagnosed with standard/medium-risk ALL**. Moreover, in the **high/very high-risk group**, an intensification of the scheme of pegaspargase administration will be proposed and evaluated during induction therapy.

When diagnosed, the patients will enter a prophase including a 7-day of prednisone treatment and a Day 1 methotrexate IT.

Then, according to the prednisone response (cf. **Section 1.6.1** and **Section 6**) and the cytogenetic/molecular genetics results, the presence or absence of CNS and/or gonadal involvement, the patients will be stratified in 5 groups related to the immunophenotypic characterization (B- or T- lineage) and risk factors: 3 groups for the B-cell ALL and 2 groups for the T-cell ALL (see below). **All patients will be included in the CAALL-F01 study before Day 8 of induction treatment.**

**Randomization will take place between D8 and D11 of induction treatment, i.e. 1 to 4 days before first infusion of pegaspargase (D12), for patients belonging to the B-SR/B-MR/T-SR groups.**

In B-Standard-risk (SR) and B-medium-risk (MR) and T-SR groups, a two-parallel randomized arms design will allocate patients between the two following arms:

- **Arm 1**
  - **during induction**  
Oncaspar® 2 500 IU/m<sup>2</sup> x 1 on Day 12
  - **during consolidation and delayed intensification**  
Oncaspar® 2 500 IU/m<sup>2</sup> per infusion
- **Arm 2**
  - **during induction**  
Oncaspar® 1 250 IU/m<sup>2</sup>/day x 2 (1 on Day 12 and 1 on Day 26)
  - **during consolidation and delayed intensification**  
Oncaspar® 1250 IU/m<sup>2</sup> per infusion

#### WARNINGS

1. **In case of refusal of randomization, patients will be excluded from the study. They will be treated according to previously established EORTC or FRALLE protocols using native E.coli asparaginase (Kidrolase®).**
2. **If Oncaspar infusion is not done at day 12 of induction for clinical or biological reasons:**
  - a. **pharmacokinetics samples should be delayed of the same number of days so that the main PK endpoint occurs 21 days after infusion.**
  - b. **patients randomized in Arm 2 should receive the second infusion 14 days after the first one**
3. **If, for any reason, randomization cannot be done before day 12, both randomization and Oncaspar infusion are to be delayed. Pharmacokinetics samples should be delayed of the same number of days.**
4. **For patients who are to receive 2 infusions of Oncaspar during induction:**  
**if the second infusion of Oncaspar (D26) cannot be performed because of toxicity (e.g. hypofibrinogenemia), a maximum delay of Oncaspar of 3 days is accepted (D29). After D29, Oncaspar n°2 is to be cancelled.**

In B-High-risk (HR) and B-very-high risk (VHR) and T-H/VHR groups, an uncontrolled design will be used to assess the following treatment schedule:

- **during induction**
  - Oncaspar® 2 500 IU/m<sup>2</sup> x 2 (1 on Day 12 and 1 on Day 26)

- ***during consolidation and delayed intensification***
  - Oncaspar® 2 500 IU/m<sup>2</sup> per infusion

**Warnings: If Oncaspar infusion is not done at day 12 of induction for clinical or biological reasons:**

- a. **pharmacokinetics samples should be delayed of the same number of days so that the main PK endpoint occurs 21 days after infusion.**
- b. **patients should receive the second infusion 14 days after the first one**

**Patients with Down syndrome are not randomized. They are treated according to the control arm of the B-SR group. Their treatment is upgraded to B-MR in case of IKZF1 deletion/mutation and/or high MRD after induction (see section 5.3.2)**

### 3.2 Description of risk groups for B lineage (Table 2)

#### 3.2.1 Definitions

- ❖ **NCI Standard-Risk B-cell precursor (BCP) ALL**
  - 365 days < age < 10 years
  - WBC < 50 G/L
- ❖ **NCI High-Risk B-cell precursor (BCP) ALL**
  - age >10 years or WBC ≥50 G/L

**Table 2: Prognostic group definitions in B-cell ALL:**

**Warning: In case of preexposure to steroids, refer to table 7 (section 3.5) for risk stratification at admission**

### **B-Standard-risk : inclusion criteria**

- **NCI standard-risk ALL (SR)**
  - BCP-ALL
  - 365d <age< 10y AND WBC < 50 G/L
  - Without
    - Ph1/BCR-ABL, iAMP21, MLL rearrangement, hypodiploidy<44 chr, monosomy 7, t(1;19)/TCF3-PBX1, t(17;19)/TCF3-HLF \*

#### **AND**

- No CNS-3 or testis involvement
- D8 Good Prednisone response

\* : For B-SR and MR patients without hypercalcemia and/or DIC , this translocation/fusion transcript will be considered as absent (very low incidence < 1/1000). This search will be done secondarily if no other classifying abnormality is found

## B-Medium-risk : inclusion criteria

- NCI SR with D8 Poor Prednisone response
  - NCI HR with D8 Good Prednisone Response
  - t(1;19)/TCF3-PBX1
  - monosomy 7
  - testis involvement
- } if no HR criteria

**AND**

- No CNS-3

## B-High and Very High risk: inclusion criteria

- NCI HR and D8 poor prednisone response

**AND/OR**

- MLL gene rearrangement
- hypodiploidy (<44 chr) and/or DNA index<0,8
- iAMP21
- t(17;19)(q22;p13) / TCF3-HLF\*

**AND/OR**

- CNS-3

### 3.2.2 Stratification switches after induction related to induction failure

All the patients who failed to respond after induction will be treated in the VHR group.

*Exception: ABL-class fusion forms*

- 1) Imatinib will be added to B-HR chemotherapy.
- 2) MRD TP2 will be decisional for final stratification and treatment strategy:  
refer to table 3 bis for final stratification
  - a. HR if MRD-TP2 <  $10^{-3}$
  - b. VHR if MRD-TP2  $\geq 10^{-3}$

### 3.2.3 Stratification switches after induction related to IKZF1 status and response to treatment

These switches are detailed in the Table 3.

**Table 3: Stratification switches linked to IKZF1 and MRD in B-lineage ALL**

	TP1		TP2
	IKZF1 No del /No mutation	IKZF1 Del / mutation	
B-SR	< 10 <sup>-3</sup> : SR	< 10 <sup>-3</sup> : MR	< 10 <sup>-4</sup> : stay in group defined after TP1
	≥10 <sup>-3</sup> <10 <sup>-2</sup> : MR *	≥10 <sup>-3</sup> <10 <sup>-2</sup> : HR	≥ 10 <sup>-4</sup> <10 <sup>-3</sup> : HR
	≥ 10 <sup>-2</sup> : HR	≥ 10 <sup>-2</sup> : HR	≥ 10 <sup>-3</sup> : VHR
B-MR	< 10 <sup>-3</sup> : MR	< 10 <sup>-3</sup> : MR	< 10 <sup>-4</sup> : stay MR ≥ 10 <sup>-4</sup> <10 <sup>-3</sup> : HR ≥ 10 <sup>-3</sup> : VHR
	≥ 10 <sup>-3</sup> : HR	≥ 10 <sup>-3</sup> HR	< 10 <sup>-3</sup> : stay HR ≥ 10 <sup>-3</sup> : VHR
B-HR/VHR	HR/VHR	HR/VHR	< 10 <sup>-3</sup> : HR ≥ 10 <sup>-3</sup> : VHR

SR,HR,VHR: standard, high, very high risk groups; TP: Time Point  
HSCT: hematopoietic stem cell transplantation (only VHR pts go to HSCT)

NB: MR/HR pts presenting an induction failure confirmed by a MRD-TP1 ≥ 5 x 10<sup>-2</sup> go to VHR

\* Patients switch to HR Group if MRD TP1 ≥10<sup>-3</sup> and ABL class fusion transcript (e.g. EBF1-PDGFRB)

For a description of MRD Time Points see Table 6 (Section 3.4) and Appendix 3

**Table 3 bis: stratifications switches for B ALL with ABL-class fusion linked to MRD and Exposure to Imatinib**

Exposure to Imatinib during HR Consolidation	TP2	TP3	
<14 Days HR + Imatinib	< 10 <sup>-3</sup> M1 PHASE HR + IMATINIB	TP3 Day 35 M1 Phase	
	≥10 <sup>-3</sup> VANDA + IMATINIB	< 10 <sup>-4</sup> HR+ IMATINIB	≥10 <sup>-4</sup> VHR Stop IMATINIB Start VANDA (TP4 before HSCT)
>14 Days HR + Imatinib	< 10 <sup>-3</sup> M1 PHASE HR + IMATINIB	TP3 Post VANDA	
	≥ 10 <sup>-3</sup> VHR VANDA – STOP IMATINIB	<10 <sup>-4</sup> M1 PHASE + IMATINIB	≥10 <sup>-4</sup> VHR Stop IMATINIB (TP4 before HSCT)
>14 Days HR + Imatinib	< 10 <sup>-3</sup> M1 PHASE HR + IMATINIB	TP3 Day 35 M1 Phase	
	≥ 10 <sup>-3</sup> VHR VANDA – STOP IMATINIB	<10 <sup>-4</sup> HR+ IMATINIB	≥10 <sup>-4</sup> VHR Stop IMATINIB (TP4 before HSCT)
	≥ 10 <sup>-3</sup> VHR VANDA – STOP IMATINIB	TP3 post VANDA	
		VHR (TP4 before HSCT)	

### 3.3 Description of risk groups of T lineage (Table 4)

#### 3.3.1. Definitions

**Table 4: Prognostic group definitions in T-cell ALL:**

**Warning: In case of preexposure to steroids, refer to table 8 (section 3.5) for risk stratification at the end of the prophase**

#### **Standard risk T-cell : inclusion criteria**

- 
- T-cell ALL
  - AND D8 good prednisone response  
AND no CNS3  
AND D35 Complete remission  
AND MRD TP2 < 10<sup>-4</sup>

#### **High risk/VHR T-cell ALL : inclusion criteria**

---

T-cell ALL and D8 poor prednisone response

**AND/OR**

CNS 3

**AND/OR**

No Complete Remission at D35

**AND/OR**

T-SR and MRD TP2 ≥ 10<sup>-4</sup>

#### **3.3.2. Stratification switches after induction related to inadequate response to treatment**

MRD evaluation on Day 35 (Time Point 1- TP1) is not decisional. Stratification switches related to MRD evaluation on TP2 and for some patients TP3, are displayed in Table 5.

**Table 5: Stratification switches linked to MRD in patients with T-ALL**

	<b>TP1</b>	<b>TP2</b> (post consolidation)	<b>TP3</b> (post VANDA course i.e. HR or VHR pts)
<b>T-SR</b>	not decisional	<10 <sup>-4</sup> : stay SR	NA
		10 <sup>-4</sup> ≤ MRD <10 <sup>-3</sup> : HR	<10 <sup>-4</sup> : stay HR ≥10 <sup>-4</sup> : T-VHR
		≥10 <sup>-3</sup> : VHR	to be done for HSCT timing
<b>T-HR</b>	<10 <sup>-2</sup> : stay HR	<10 <sup>-3</sup> : stay HR	<10 <sup>-4</sup> : stay HR ≥10 <sup>-4</sup> : VHR
	≥10 <sup>-2</sup> & D8 PPR: VHR	≥10 <sup>-3</sup> : VHR	to be done for HSCT timing

SR,HR,VHR: standard, high, very high risk groups

PPR: Poor Prednisone Response

TP: Time Point; HSCT: hematopoietic stem cell transplantation (only VHR pts got o HSCT)

For a description of MRD Time Points see Table 6 (Section 3.4) and Appendix 3.

### 3.4 MRD time points according to risk groups (Table 6)

Table 6: MRD time points according to risk groups

	TP1 (post induction)	TP2 (post consolidation)	TP3*
B-SR	D35-42	D65-75	NA
B-MR	D35-42	D95-105	NA
B-HR/VHR	D35-42	D95-105	D125-135
T-SR	D35-42	D85-95	NA
T-HR/VHR	D35-42	D95-105	D125-135

MRD samplings are to be performed after sufficient hematological recovery (at least PNN &gt;0,5 G/L &amp; platelets &gt; 50 G/L)

- \* Only if indicated:
- B-lineage: patients with TP2 ≥ 10<sup>-3</sup> or patients with Imatinib (Refer to Table 3 bis)
  - T-lineage: patients with TP2 ≥ 10<sup>-4</sup>

### 3.5 Stratification adaptation for patients with steroid exposure before ALL diagnosis

#### 3.5.1 In case of steroid pre-treatment for B-lineage ALL

*Patients can be included in the CAALL-F01 protocol* but stratification will be adapted to 3 parameters according to the Table 7.

Final stratification nevertheless will also rely on cytogenetics/genetics and MRD assessments.

**Table 7: Conditions for inclusion of B-ALL pts previously treated with corticosteroids**

<b>AGE</b>	<b>WBC post steroid but at admission</b>	<b>Duration of exposure to steroids within 15 days preceding the diagnosis</b>
< 10 years	< 50G/L	≤48h: SR group >48h: MR group
	≥ 50G/L	≤ 7 days of exposure: MR group > 7 days of exposure: HR group
≥ 10 years	Whatever the WBC count	≤ 7 days of exposure: MR group
	Whatever the WBC count	> 7 days of exposure: HR group

### 3.5.2 In case of steroid pre-treatment for T-cell ALL

**Patients can be included in the CAALL-F01 protocol** but stratification will be adapted to 3 parameters according to the Table 8.

Final stratification nevertheless will also rely on MRD assessments.

**Table 8: Assessment of prednisone response in T-ALL pts previously treated with corticosteroids**

<b>Duration of exposure to steroids within 15 days preceding the diagnosis</b>	<b>Peripheral Blast count post steroid but at admission</b>	<b>Peripheral Blast count at D8 post protocolar prednisone prephase</b>	<b>Final assessment of prednisone response</b>
≤ 48h	Whatever the count	< 1000/mm3	D8 good prednisone response
	Whatever the count	≥ 1000/mm3	D8 poor prednisone response
> 48h	< 1000/mm3 + M3 bone marrow	< 1000/mm3	D8 good prednisone response
		≥ 1000/mm3	D8 poor prednisone response
	≥ 1000/mm3 + M3 bone marrow	Whatever the D8 count	D8 poor prednisone response

## 3.6 Randomization/Inclusion

When diagnosed, the patient eligibility will be evaluated from inclusion and non-inclusion criteria. Once the consent will be signed by the patient and parents, the patient will be included by connecting the eCRF. The patient identification number will be allocated (see below, **Section 3.6.2**). The treatment prophase will start.

### 3.6.1 Randomization of B-SR and MR, and T-SR patients

The randomization lists **stratified by center, cell-lineage T or B) and risk-groups (2B-SR/MR, and T-SR)** will be established by the Clinical and Biostatistics research unit of Saint-Louis Hospital before the beginning of the study according to a method based on permutation blocks whose size will be kept confidential.

Randomization of patients will be **centralized** and carried out using a computerized system in the eCRF website.

Distribution in the two arms (arm 1 versus arm 2) will be made in a 1/1 ratio. All inclusion and exclusion criteria will be checked before randomization.

***Randomization is to be performed between D8 and D11 of induction treatment :***

***As prednisone prephase result is only available at Day 8 and first pegaspargase administration takes place at D12.***

***As molecular biology markers and cytogenetics results for risk stratification must be available before day12***

***As patient is B-SR or B-MR or T-SR at day 8 of prephase***

In **B-SR** patients, randomization arm will be allocated between:

- **Arm 1 : pegaspargase 2500 IU/m<sup>2</sup> per infusion** : at induction (**D12**), consolidation that begins at D35-D42 (**D8, D36, D64**) and delayed intensification (**D4**)
- **Arm 2 : pegaspargase 1250 IU/m<sup>2</sup> per infusion** at induction (**D12 and D26**), consolidation that begins at D35-D42 (**D8, D36, D64**) and delayed intensification (**D4**)

**B-MR** patients: randomization arm will be allocated between:

- **Arm 1 : pegaspargase 2500 IU/m<sup>2</sup> per infusion** : at induction (**D12**), consolidation that begins at D35-D42 (**D15 and D43**) and delayed intensification (**D4**)
- **Arm 2 : pegaspargase 1250 IU/m<sup>2</sup> per infusion** at induction (**D12 and D26**), consolidation that begins at D35-D42 (**D15 and D43**) and delayed intensification (**D4**)

For the **T-SR** group, the allocation will be between the two arms:

- **Arm 1: pegaspargase 2500 IU/m<sup>2</sup> per infusion** at induction (**D12**) and delayed intensification (**D4**)
- **Arm 2: pegaspargase 2 infusions of 1250 IU/m<sup>2</sup> per infusion** at induction (**D12 and D26**) and 1 infusion of 1250 IU/m<sup>2</sup> during the delayed intensification (**D4**)

### **3.6.2 Inclusion of B- and T- HR/VHR patients**

These patients will be included but not randomized, using the same eCRF web site, once the eligibility criteria have been checked, including the signed consent forms.

No randomization will thus be done, and they will all received the following

- Infusions of pegaspargase **2500 IU/m<sup>2</sup>** during induction (**D12 and D26**), consolidation (**D15 and D43**), delayed intensification 1 (**D4 and D43**), delayed intensification 2 (**D4 and D43**). For patients going to HSCT, pegaspargase **2500 IU/m<sup>2</sup>** will be infused during the VANDA course (**D6**) and during optional pretransplant blocks (**D6**)

***For Down syndrome patients, see Section 5.3.2.***

### 3.6.3 Patient identification

For this research, the subjects will be identified as follows:

Centre No. (3 numerical positions) – Inclusion No. of the patient (4 numerical positions) - surname initial - first name initial (2 digits)

|\_|\_|\_| / |\_|\_|\_| / |\_|\_|

*Center      Inclusion      Initials*

***This reference is unique and will be retained for the entire research period. It will constitute the unique randomization or enrolment number of the patient for the whole research.***

### 3.6.4 Recruitment methods

Participating centers will be pediatric/hematological pediatric/oncology departments of public hospitals located in France belonging to the SCFE (Société Française de lutte contre les Cancers et Leucémies de l'Enfant et de l'adolescent) and/or to the SFH (French Society of Hematology).

A total of 1578 pts (B-SR, B-MR and T-SR) will be randomized and about 250-300 pts from B- and T-HR will be enrolled (Table 9) (see **Section 10.2** for details).

**Table 9: Number of patients to be enrolled in the study**

<b>Number of subjects</b>	
B-SR, B-MR, T-SR	1578
B-HR, T-HR	250-300
<b>Number of centres</b>	28
Inclusion period (months)	60

### 3.7 Starting of treatment

***Before starting and during the treatment, the accuracy of sampling and result acquisition of the decisional/investigational analyses should be regularly checked (cf Appendix 2 to 4).***

Following a 7-day prophase treatment period, the treatment will be organized according to usual ALL phases: induction, consolidation(s), delayed intensification(s) and maintenance therapy.

***Between D8 and D11 of induction treatment,*** the patient will be randomly assigned to one of the arms of treatment according to his/her stratification group.

***Only patients with Down syndrome (see section 5.4.2) or patients belonging to the HR/VHR groups (B or T-lineage ALL) will not be randomized.***

### 3.8 Monitoring

Patients will continue on treatment until disease progression or until pre-defined discontinuation criteria are met. Patients will be monitored at least at each visit for treatment administration.

### 3.9 Follow-up

The safety follow-up period will continue for at least 5 years for each patient.

The efficacy and survival follow-up period will continue for at least 5 years for each patient.

### **3.10 Definition of end of the study**

The study will end after a 5-year follow-up of the last patient included or if and when the study is terminated early.

### **3.11 Early study termination**

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely terminate all or part of the research, temporarily or permanently, upon the recommendation of a data and safety monitoring board in the following situations:

- ✓ first of all, if suspected unexpected serious adverse reactions (SUSARs) are seen in an arm being treated or if there is a discrepancy in the serious adverse reactions between the 2 arms being treated, and which require a reassessment of the benefit-risk ratio for the research
- ✓ in the case of interim analysis: stopping treatment to demonstrate the efficacy of one of the arms being treated or on the other hand stopping due to futility
- ✓ likewise, unexpected facts, new information about the product, in light of which the objectives of the research or of the clinical programme are unlikely to be achieved, can lead AP-HP as sponsor or the Competent Authority (ANSM) to prematurely halt the research

AP-HP as sponsor reserves the right to suspend permanently inclusions at any time if it appears that the inclusion objectives are not met.

If the research is terminated prematurely, the decision and justification will be given by the sponsor, AP-HP, to the Competent Authority (ANSM) and to the CPP within 15 days, along with recommendations from the Data and Safety Monitoring Committee.

## 4 Population

### 4.1 Patient population

The patient population consists of children/adolescents from >365 days to <18 years old with newly diagnosed acute lymphoblastic leukemia.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered enrollment in the study.

### 4.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet all of the following criteria:

- Acute lymphoblastic leukemia (ALL)
- B-or T-lineage
  - *NB: Children with Down syndrome are not eligible to randomization. See Section 5.3.2*
- from >12 months to < 18 years old
- Written informed consent obtained before day 8 of treatment

### 4.3 Non-inclusion criteria

Patients eligible for this study must not meet any of the following criteria:

- L3 (Burkitt leukemia) as defined by the French-American-British (FAB) morphology classification
- Secondary leukemia
- Mixed Phenotype Acute Leukemia (MPAL according to WHO)
- Patients previously treated with chemotherapy (steroid exposed pts can be included and stratified according to **Section 3.5**)
- Known allergy to pegylated products
- Pregnancy. - Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant must have a negative serum pregnancy before inclusion and a reliable contraception except oral contraceptives. The contraception should be maintained throughout the study and for 3 months after treatment discontinuation.
- Known HIV positivity
- CNS thrombosis during Prophase

### 4.4 Exclusion criteria

- Philadelphia positive/BCR-ABL acute lymphoblastic leukemia
- CNS thrombosis before D12

## 5 Treatment

**As a general rule, before starting and during the treatment:**

1. All leukemia-related decisional and investigational analyses should be regularly checked (cf appendix 2 to 4)
2. Main local and systemic toxicities of each drug should be anticipated (see Appendix 9 for overview)
3. Dosage of chemotherapy according to weight / height variations during treatment
  - a. for induction and consolidation cycles: take into account Weight and Size at Day1 of Induction for induction; apply the same measures to consolidation except if weight loss is higher than 10%; in this last case, body surface area must be reevaluated .
  - b. after consolidation, for M phase(s) or Delayed Intensification (s) or VANDA or any other cycle of treatment, body surface area must be reevaluated according to weight and size at D1 of each cycle of chemotherapy.

### 5.1 Treatment for B-lineage ALL

The general schedule for all stratification groups will be as following:

- an induction phase
- a consolidation phase
- one or 2 delayed intensification phases
- a continuation “maintenance” phase

All these sequences are going to follow each other without any free interval. The total duration of the treatment will vary between 24 and 30 months according to groups. The treatments in each phase will depend on the stratification groups. Details are given below.

**Warning: In case of preexposure to steroids, refer to table 7 (section 3.5.1) for risk stratification at the end of the prophase**

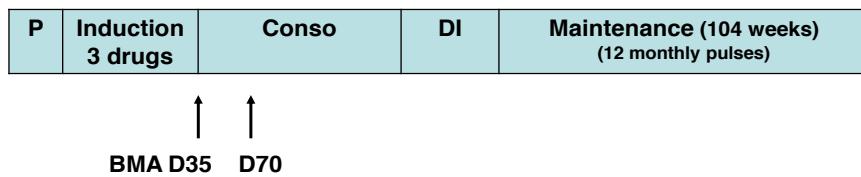
#### 5.1.1 B-Standard Risk (SR) Group

Treatment overview of the SR group is displayed in Figure 1.

**Figure 1: Treatment flow chart of the B-SR group**

## CAALL-F01: B-SR (BCP ALL standard-risk)

### General design

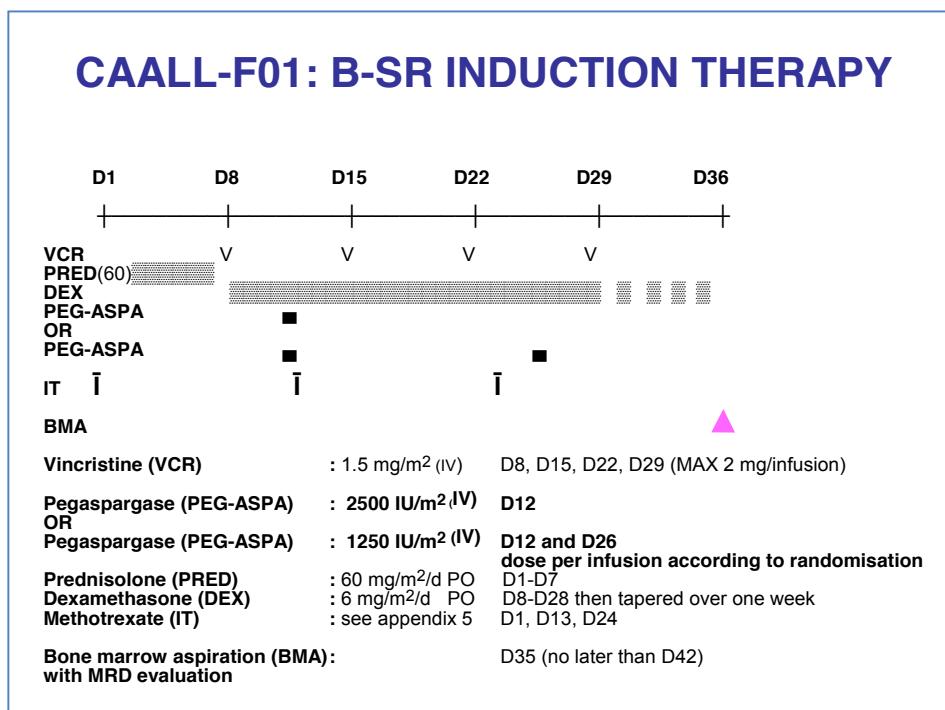


*P: Prednisone prephase; Conso: consolidation, DI: delayed intensification  
BMA: bone marrow aspiration with MRD evaluation (TP1, TP2)*

**Warning: there is no emergency in this group to begin the prephase quickly (except if pains refractory to opioids). Start only when sure that the whole stratification biology is analyzable (e.g. sufficient sampling for molecular biology and culture for caryotype) and will be available at D8**

### B-SR group: Induction phase (Figure 2)

Figure 2: Flow scheme of B-SR induction treatment



*Ancillary treatments including trimethoprim-sulfamethoxazole are to be found in appendix 10*

The treatment will be administered as follows:

#### Prephase

- **Prednisolone: 30 mg/m<sup>2</sup> every 12 hours per os from Day 1 to Day 7 (total 14 doses). IV methyl prednisolone at the same dose can be an alternative**
- **Methotrexate IT: Day 1**

The dosage depends on the age of the patient. Guidelines for methotrexate for intrathecal administration are available in **Appendix 5. In case of initial Traumatic Lumbar Puncture or CNS2 status, intensified CNS prophylaxis during induction phase is mandatory according to guidelines in Appendix 5.**

**On Day 8, the prednisone response is to be evaluated on a blood-smear. A good response is defined as less than 1000 blast cells per mm<sup>3</sup> in the peripheral blood.**

### Induction therapy from Day 8

- Dexamethasone: 3 mg/m<sup>2</sup> x 2/day per os from Day 8 to Day 28 (total 42 doses), then tapered over one week.
- Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 8, 15, 22 and 29.

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

A neurological examination will be performed before every administration.

– **Pegaspargase**

Oncaspar® will be administered intravenously over 60 min.

The schedule to be administered during induction therapy is determined by randomization:

➤ **Arm 1/B-SR: ONCASPAR®:2 500 IU/m<sup>2</sup> on Day 12**

OR

➤ **Arm 2/B-SR: ONCASPAR®:1 250 IU/m<sup>2</sup> /day on Day 12 and Day 26**

Guidelines for ONCASPAR® use are available in **Appendix 7**

**If Pegaspargase infusion is not performed at Day 12 or Day 26 see warning at Section 3.1**

In case of allergy and/or clinical reaction during Oncaspar infusion, refer to Appendix 7

– **IT methotrexate D13 and D24**

The dosage depends on the age of the patient. Guidelines for methotrexate for intrathecal administration are available in **Appendix 5. In case of initial Traumatic Lumbar Puncture or CNS2 status, intensified CNS prophylaxis during induction phase is mandatory according to guidelines in Appendix 5.**

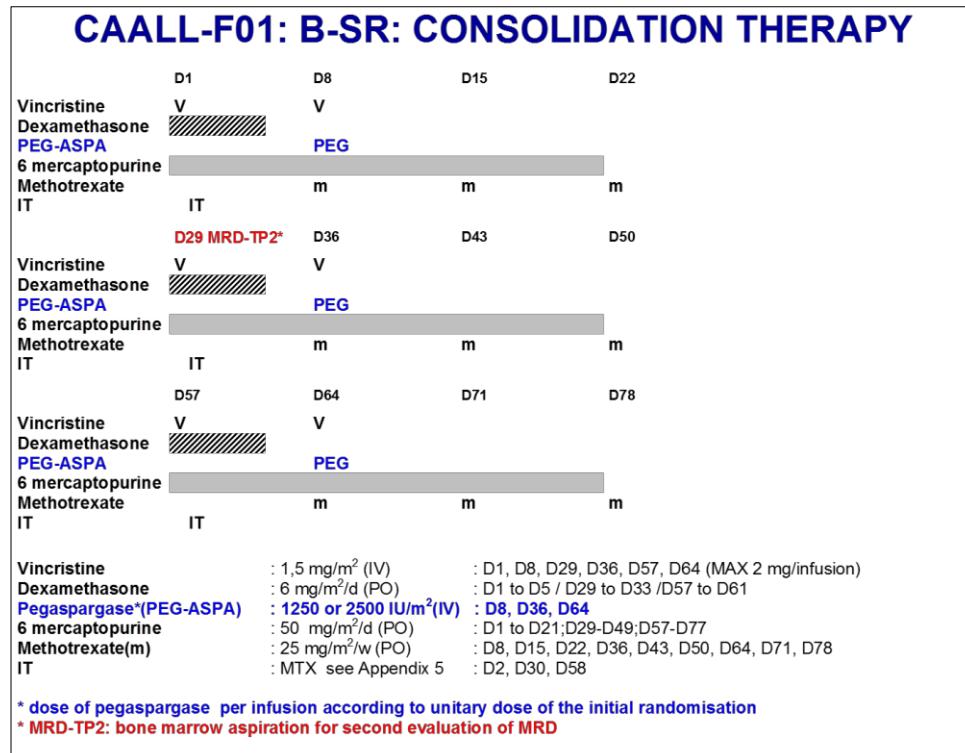
**Warning: a switch to the MR group is to be done if the following toxicities are observed during induction:**

1. **CNS thrombosis:** B-MR consolidation is to be performed without any asparaginase; reserve Oncaspar for delayed intensification
2. **Grade 3-4 pancreatitis:** follow MR group courses without any asparaginase
3. **Allergy to Oncaspar:** refer to appendix7

### B-SR group: Consolidation (Figure 3)

**Criteria to begin the course:** D35-42 Bone marrow showing complete remission AND  $\geq 1000$  PNN/mm<sup>3</sup> and Platelets  $\geq 100.000/\text{mm}^3$ . *In case of induction failure* at D35-42 begins HR consolidation, whatever the blood count if clinical condition is adequate.

**Criteria to begin D29 and D57:  $\geq 1000$  PNN/mm<sup>3</sup> and Platelets  $\geq 100.000/\text{mm}^3$**

**Figure 3: Flow scheme of B-SR consolidation treatment**

The treatment will be administered as follows:

- **Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 1, 8, 29, 36, 57 and 64.**  
Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.
- **Dexamethasone: 6 mg/m<sup>2</sup>/day per os (divided in 3 takes a day) from Day 1 to Day 5, Day 29 to Day 33 and Day 57 to Day 61**

#### – **Pegasparagase**

Oncaspar® will be administered intravenously over 60 min.

The schedule to be administered during induction therapy is determined by randomization:

- **Arm 1/B-SR: ONCASPAR®:2 500 IU/m<sup>2</sup> /day on Day 8, Day 36 and day 64**
- OR
- **Arm 2/B-SR: ONCASPAR®:1 250 IU/m<sup>2</sup>/day on Day 8, Day 36 and day 64**

Guidelines for ONCASPAR® use are available in **Appendix 7**

In case of allergy and/or clinical reaction during Oncaspar infusion, refer to Appendix 7

- **6-mercaptopurine: 50 mg/m<sup>2</sup>/day per os from Day 1 to 21, Day 29 to 49 and Day 57 to 77**

1- Patients homozygous for TPMT deficiency give: only 7.5 mg/m<sup>2</sup>/day of 6-mercaptopurine.

2- Patients heterozygous for TPMT deficiency:

- Do not adapt and give full dose of 6-mercaptopurine
- Monitor: if next phase of chemotherapy is delayed diminish the dose by 50% and reevaluate

- **Methotrexate: 25 mg/m<sup>2</sup> once a week per os on Day 8, 15, 22, 36, 43, 50, 64, 71 and 78**

- **Methotrexate IT: Day 2, 30 and 58**

The dosage depends on the age of the patient. Guidelines for methotrexate for intrathecal administration are available in **Appendix 5**.

**Warning: Risk Stratification must be reevaluated at MRD TP1 and MRD TP2**

**1: D42-50 assessment: according to IKZF1 status, MRD TP1**

- if no deletion/mutation of IKZF1 and MRD TP1  $<10^{-3}$ : patient stays in SR-Group
- if deletion/mutation of IKZF1 and/or MRD TP1  $\geq 10^{-3}$ (\*): patient switches to MR/HR Group

1: stop SR consolidation (before D15 of consolidation)

2: begin MR/HR consolidation

3: final group assessment depends on MRD TP1 and TP2 (see Table 3)

(\*) if MRD TP1  $\geq 10^{-3}$  and/or induction failure and ABL-class Fusion transcript (e.g. EBF1-PDGFRB):

Patient switches to HR Group but with imatininib on top of chemotherapy:

- stop SR consolidation
- begin HR consolidation from Day 1 with Imatinib as soon as diagnosis of ABL-class fusion obtained
- final group assessment (HR or VHR) depends on MRD TP2 and TP3 (**refer to table 3bis page 45**)

**2: D65-75 assessment according to MRD TP2**

Patients stay in SR-Group if MRD TP2  $<10^{-4}$

Patients switch to HR group if MRD TP2  $\geq 10^{-4}$

1: stop SR consolidation (before D43 of consolidation)

2: begin HR consolidation from Day 1

3: final group assessment: HR or VHR (only if MRD TP2  $\geq 10^{-3}$ )

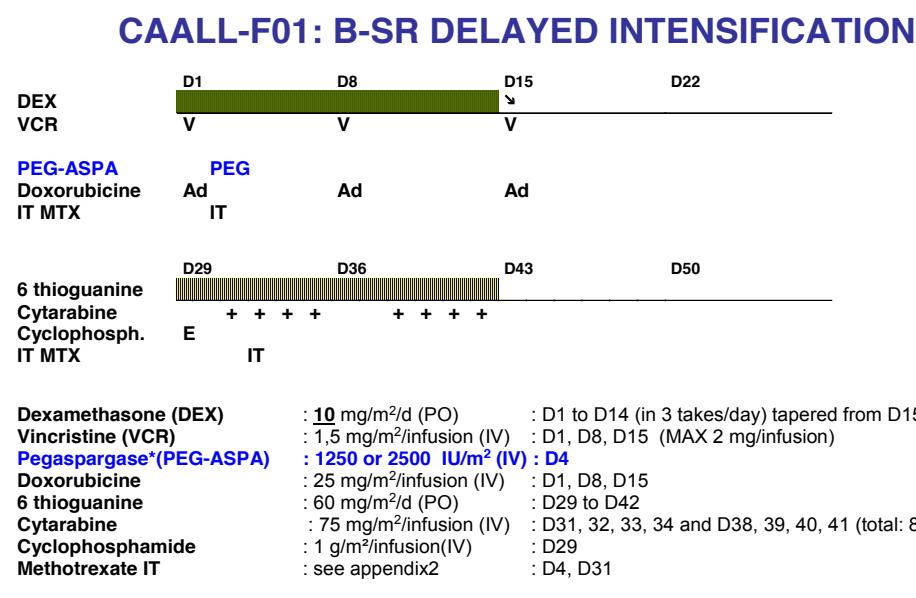
Warning: if patients switch to the HR group, Oncaspar will be given at 2500UI/m<sup>2</sup> whatever the initial group of randomisation

### **B-SR group: Delayed intensification (Figure 4)**

**Criteria to begin each phase of the course (D1 and D29): PNN  $\geq$ 1000/mm<sup>3</sup> and Platelets  $\geq$  100.000/mm<sup>3</sup>**

**Warning: Infectious complications often occur during this phase particularly between D15 and D28 and D43-D57**

**Figure 4: Flow scheme of B-SR delayed intensification treatment**



\* dose of pegasparagase per infusion according to unitary dose of the initial randomisation

The treatment will be administered as follows:

- Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 1, 8, and 15.**  
Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.
- Dexamethasone: 10 mg/m<sup>2</sup>/day per os (divided in 3 intakes) from Day 1 to Day 14 ; , then tapered from Day 15**

- Pegasparagase**

Oncaspar® will be administered intravenously over 60 min.

The schedule to be administered during induction therapy is determined by randomization:

- Arm 1/B-SR: ONCASPAR®:2 500 IU/m<sup>2</sup> on Day 4**

OR

- Arm 2/B-SR: ONCASPAR®:1 250 IU/m<sup>2</sup> on Day 4**

Guidelines for ONCASPAR® use are available in **Appendix 7**

- Doxorubicin: 25 mg/m<sup>2</sup>/infusion on Day 1, 8 and 15**

Doxorubicin will be administered intravenously over 60 min.

- 6-Thioguanine: 60 mg/m<sup>2</sup>/day per os from Day 29 to Day 42**

1- Patients homozygous for TPMT deficiency: give only 10 mg/m<sup>2</sup>/day of 6-Thioguanine.

2- Patients heterozygous for TPMT deficiency:

- Do not adapt and give full dose of 6-Thioguanine
- Monitor: if next phase of chemotherapy is delayed diminish the dose by 50% and reevaluate

- **Cytarabine: 75 mg/m<sup>2</sup>/infusion as push i.v. on Day 31, 32, 33, 34 and Day 38, 39, 40 and 41**
- **Cyclophosphamide: 1g/m<sup>2</sup>, intravenously over 60 min on Day 29**
  - Give **Mesna** (400 mg/m<sub>2</sub>/dose) before and at hour 4 and 8 after start of cyclophosphamide infusion
  - During these 8 hours, hyperhydratation (1 liter/m<sup>2</sup> / 8h) followed by oral hyperhydratation for the remaining 16 hours.
- **Methotrexate IT: Day 4 and Day 31**

The dosage depends on the age of the patient. Guidelines for methotrexate for intrathecal administration are available in **Appendix 5**.

#### **B-SR group: Maintenance (Figure 5): not earlier than Day 57 of previous phase**

***The total duration of the maintenance phase will be 104 weeks.***

**Criteria to begin the course:** PNN ≥1000/mm<sup>3</sup> and Platelets ≥ 100.000/mm<sup>3</sup>

Figure 5: Flow scheme of B-SR maintenance treatment

### **CAALL-F01: B-SR Continuation therapy «maintenance»**

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- 104 weeks (i.e. total duration of ALL treatment: ~30 months)
- 12 pulses: one cycle every 4 weeks during the first year of maintenance
  - VCR: 1.5 mg/m<sup>2</sup>/infusion: D1 (MAX 2mg per infusion)
  - DEX: 6 mg/m<sup>2</sup>/day: D1 to D5
  - IT MTX: D15 (see appendix 5)
- 6MP: 50 mg/m<sup>2</sup>/day
- MTX: 25 mg/m<sup>2</sup>/week

***NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX***

**Since D1 of maintenance, patients will receive oral maintenance treatment combining:**

- 6-mercaptopurine: 50 mg/m<sup>2</sup>/day per os for 104 weeks
- Methotrexate: 25 mg/m<sup>2</sup> once a week per os for 104 weeks

***See Appendix 11 for dose modification/adaptation of 6MP/MTX***

***NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX***

**In addition, one pulse of the following combination will be administered every 4 weeks for a total of 12 administrations.**

- **Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 1**  
Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.
- **Dexamethasone: 6 mg/m<sup>2</sup>/day (divided in 2 intakes) per os from Day 1 to Day 5**

**Finally, 8 intrathecal injections of methotrexate will be given:**

- **Methotrexate IT: Day 15 at month 1 (M1), M3, M5, M7, M9, M11, M13, M15**

The dosage depends on the age of the patient. Guidelines for methotrexate for intrathecal administration are available in **Appendix 5**.

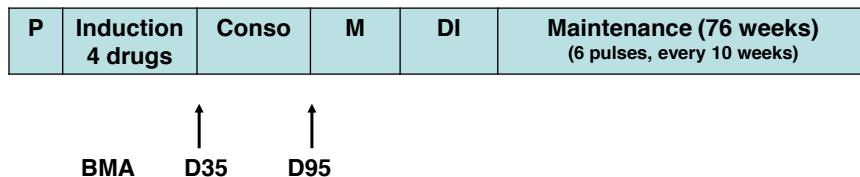
### 5.1.2 B-Medium Risk (B-MR) Group

Treatment overview of the MR group is displayed in Figure 6.

**Figure 6: Treatment flow chart of the B-MR group**

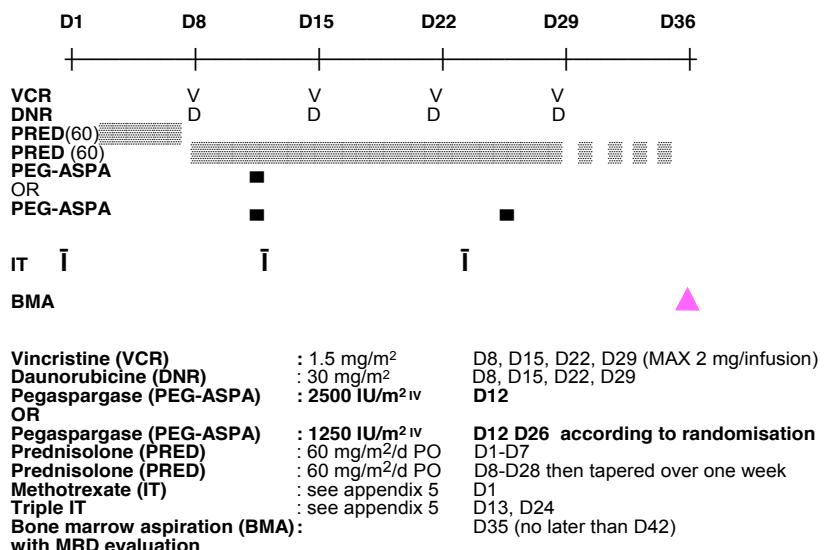
## CAALL-F01: B-MR (BCP-ALL medium risk)

General design



*Conso: consolidation course; M: high dose MTX cycle; DI: delayed intensification*

*BMA: bone marrow aspiration with MRD evaluation (TP1, TP2)*

**B-MR group: Induction phase (Figure 7)****Figure 7: Flow scheme of B-MR induction treatment****CAALL-F01: B-MR INDUCTION THERAPY**

The treatment will be administered as follows:

**Prephase**

- **Prednisolone: 30 mg/m<sup>2</sup> every 12 hours per os from Day 1 to Day 7 (total 14 doses). IV methyl prednisolone at the same dose can be an alternative**
- **Methotrexate IT: Day 1**

The dosage depends on the age of the patient. Guidelines for methotrexate for intrathecal administration are available in **Appendix 5. In case of initial Traumatic Lumbar Puncture or CNS2 status, intensified CNS prophylaxis during induction phase is mandatory according to guidelines in Appendix 5.**

**NB: if WBC ≥ 100 000/mm<sup>3</sup> refer to appendix 10**

**On Day 8, the prednisone response is to be evaluated on a blood-smear. A good response is defined as less than 1000 blast cells per mm<sup>3</sup> in the peripheral blood.**

**Induction therapy from Day 8**

- **Prednisolone: 30 mg/m<sup>2</sup> x 2/day per os from Day 8 to Day 28 (total 42 doses), then tapered over one week.** IV methyl prednisolone at the same dose can be an alternative.
- **Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 8, 15, 22 and 29.**

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

**A neurological examination will be performed before every administration.**

- **Daunorubicin 30 mg/m<sup>2</sup> on Day 8, 15, 22 and 29**

Daunorubicin will be administered strictly intravenously over 60 min.

- **Pegasparagase**

Oncaspar® will be administered intravenously over 60 min.

The schedule to be administered during induction therapy is determined by randomization:

- **Arm 1/B-MR: ONCASPAR®:2 500 IU/m<sup>2</sup> on Day 12**

**OR**

- **Arm 2/B-MR:** ONCASPAR®:1 250 IU/m<sup>2</sup> /day on Day 12 and Day 26  
Guidelines for ONCASPAR® use are available in **Appendix 7.**

**If Pegaspargase infusion is not performed at Day 12 or Day 26 see warning at Section 3.1**

In case of allergy and/or clinical reaction during Oncaspar infusion, refer to Appendix 7

- **Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine): Day 13 and Day 24**
- The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5. In case of initial Traumatic Lumbar Puncture or CNS2 status, intensified CNS prophylaxis during induction phase is mandatory, according to guidelines in Appendix 5.**

**B-MR group: Consolidation (figure 8)**

**Criteria to begin the course:** D35-42 bone marrow showing complete remission AND  $\geq 1000$  PNN/mm<sup>3</sup> and Platelets  $\geq 100.000$ /mm<sup>3</sup>. *In case of induction failure* at D35-42 begin HR consolidation whatever the blood count if clinical condition is adequate.

**Warning: Risk stratification at D42-50 according to MRD TP1: table 3 (section 3.2.3)**

- Patients stay in MR-Group if MRD TP1 <10<sup>-3</sup>: begin B-MR Consolidation
- Patients switch to HR Group if MRD TP1  $\geq 10^{-3}$  and/or induction failure

Search for ABL-class fusion on frozen initial material must be undertaken: if positive (e.g. EBF1-PDGFRB transcript) imatinib should be added to the HR chemotherapy: **\_Warning, refer to Table 3bis page 44 for final stratification according to TP2 and TP3 and duration of exposure to imatinib**

- Do not forget: final group assessment will depend on MRD TP1 and TP2 (see Table 3)

The treatment will be administered as follows (Figure 8):

- **6-mercaptopurine: 60 mg/m<sup>2</sup>/day per os from Day 1 to Day 14, Day 29 to Day 42**
  - 1- Patients homozygous for TPMT deficiency: give only 10 mg/m<sup>2</sup>/day of 6-mercaptopurine.
  - 2- Patients heterozygous for TPMT deficiency:
    - Do not adapt and give full dose of 6-mercaptopurine
    - Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate
- **Cyclophosphamide: 1g/m<sup>2</sup>, intravenously over 60 min on Day 1 and Day 29**
  - Give Mesna (400 mg/m<sup>2</sup>/dose) before and at hour 4 and 8 after start of cyclophosphamide infusion
  - During these 8 hours, hyperhydratation (1 liter/m<sup>2</sup> / 8h) followed by oral hyperhydratation for the remaining 16 hours.

**Pegaspargase**

Oncaspar® will be administered intravenously over 60 min.

The schedule to be administered during induction therapy is determined by randomization:

- **Arm 1: ONCASPAR®:2 500 IU/m<sup>2</sup> /day on Day 15 and Day 43**

OR

- **Arm 2: ONCASPAR®:1 250 IU/m<sup>2</sup> /day on Day 15 and Day 43**

Guidelines for ONCASPAR® use are available in **Appendix 7**

In case of allergy and/or clinical reaction during Oncaspar infusion, refer to Appendix 7

- **Vincristine: 1.5 mg/m<sup>2</sup> (max total dose: 2 mg) on Day 15, 22, 43 and 50**

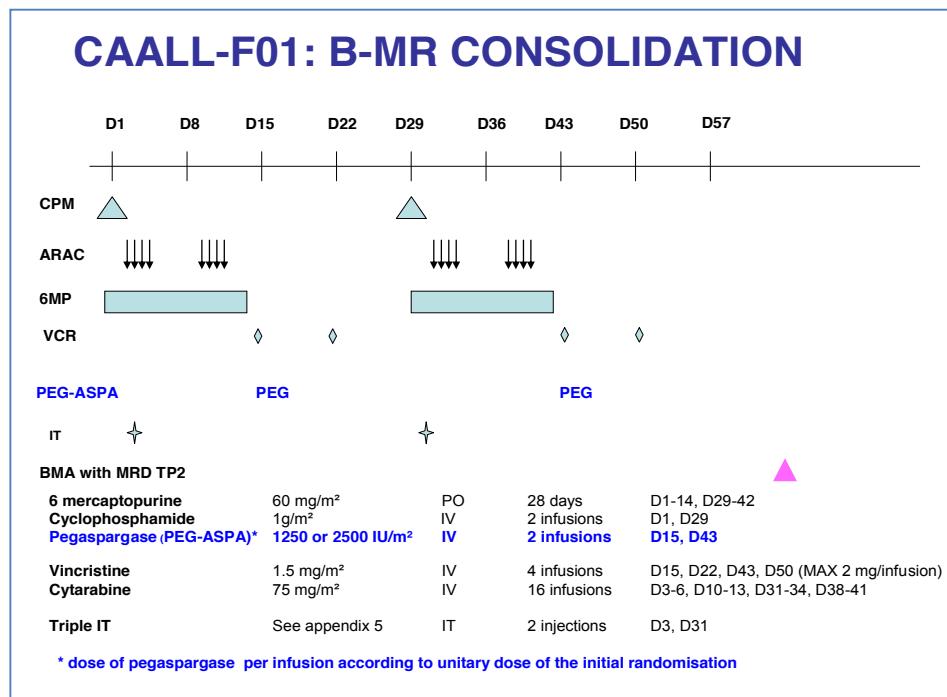
Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

- Cytarabine: 75 mg/m<sup>2</sup>/infusion as push i.v. on Day 3 to Day 6, Day 10 to Day 13, Day 31 to Day 34 and Day 38 to Day 41**
- Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine) on Day 3 and Day 31**

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

**NB: Administration of the second part of the cycle (from D29) should begin only if good clinical status and WBC over 1 G/L**

**Figure 8: Flow scheme of B-MR consolidation treatment**



### **B-MR: Phase M (Figure 9)**

**Criteria to begin the M Phase:** PNN  $\geq$ 1000/mm<sup>3</sup> and Platelets  $\geq$  100.000/mm<sup>3</sup>

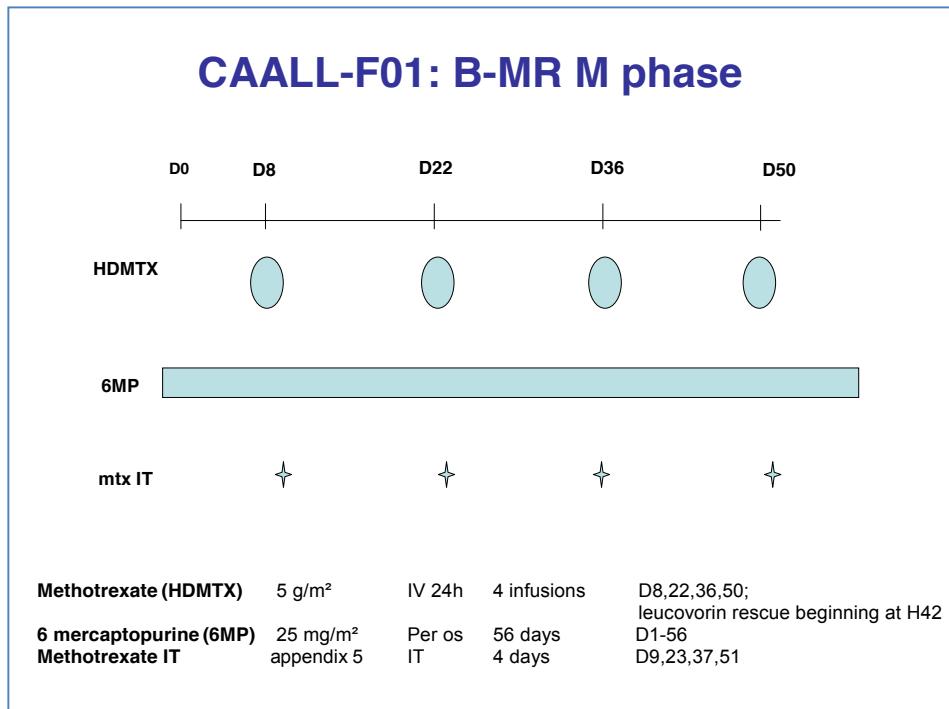
Criteria for each course of HD methotrexate: PNN  $\geq$  500/mm<sup>3</sup> and Platelets  $\geq$  50.000/mm<sup>3</sup>.

If these criteria are not met = stop 6-Mercaptopurine which is to be reintroduced after the beginning of HD methotrexate

**Figure 9: Flow scheme of B-MR Phase M**

### **Warning: Risk stratification at D95 assessment according to MRD TP2**

- Patients stay in MR-Group if MRD TP2  $< 10^{-4}$ : begin B-MR Phase M
- Patients switch to HR group if MRD TP2  $\geq 10^{-4}$  and  $< 10^{-3}$  : B-HR Phase M1
- Patients switch to VHR group final only if MRD TP2  $\geq 10^{-3}$ : Stop phase M and begin B- VHR VANDA



The treatment will be administered as follows:

- **HD methotrexate: 5 g/m<sup>2</sup> i.v. over 24 hours with leucovorin rescue beginning at H42 on Day 8, 22, 36 and 50.**

Guidelines for HD methotrexate administration and leucovorin rescue are available in **Appendix 8**.

- **6-mercaptopurine: 25 mg/m<sup>2</sup>/day per os from Day 1 to Day 56**

1- Patients homozygous for TPMT deficiency: give only 4 mg/m<sup>2</sup>/day of 6-mercaptopurine.

2- Patients heterozygous for TPMT deficiency:

- Do not adapt and give full dose of 6-mercaptopurine
- Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate

- **Methotrexate IT on Day 9, 23, 37 and 51**

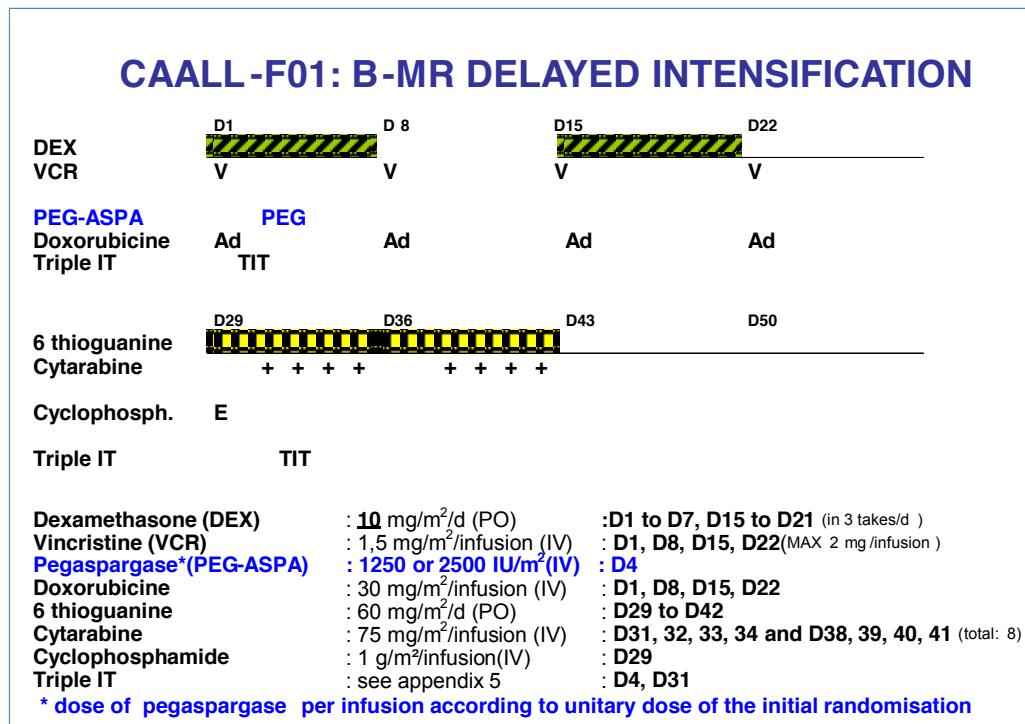
The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

#### **B-MR group: Delayed intensification (Figure 10)( not earlier than D70 of previous phase)**

**Criteria to begin each phase of the course (D1 and D29):** PNN ≥1000/mm<sup>3</sup> and Platelets ≥ 100.000/mm<sup>3</sup>

**Warning: Infectious complications often occur during this phase particularly between D15 and D28 and D43-D57**

**Figure 10: Flow scheme of B-MR delayed intensification treatment**



The treatment will be administered as follows:

- Dexamethasone: 10 mg/m<sup>2</sup>/day per os (divided in 3 intakes) from Day 1 to Day 7 and from Day 15 to Day 21
  - Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 1, 8, 15, 22

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

### **Pegaspargase**

Oncaspar® will be administered intravenously over 60 min.

The schedule to be administered during induction therapy is determined by randomization:

- = Arm 1/B-MB: ONCASPAR®: 2 500 IU/m<sup>2</sup> on Day 4

OR

- = Arm 2/B-MB: ONCASPAN®:1 250 IU/m² on Day 4

Guidelines for ONCASPAR® use are available in Appendix 7.

- **Doxorubicin: 30 mg/m<sup>2</sup>/infusion on Day 1, 8, 15, 22**
  - **Doxorubicin will be administered strictly intravenously over 60 min.**
  - **6-Thioguanine: 60 mg/m<sup>2</sup>/day per os from Day 29 to Day 42**

- 1- Patients homozygous for TPMT deficiency: give only 10 mg/m<sup>2</sup>/day of 6-Thioguanine.

- ### 2- Patients heterozygous for TPMT deficiency:

- Do not adapt and give full dose of 6-Thioguanine.

- Monitor if next phase of chemotherapy is delayed, discontinue the drug by 50% and evaluate.

- Cytarabine: 75 mg/m<sup>2</sup>/infusion as push i.v. on Day 31 to Day 34 and Day 38 to Day 41.

- 6 clusters with  $1/\mu^3$  interactions up to 60 microns. **Fig. 2c**

- Give Mesna (400 mg/m<sup>2</sup>/dose) before and at hour 4 and 8 after start of cyclophosphamide infusion.

- During these 8 hours, hyperhydratation (1 liter/m<sup>2</sup> / 8h) followed by oral hyperhydratation for the remaining 16 hours.
- **Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine) on Day 4 and Day 31**

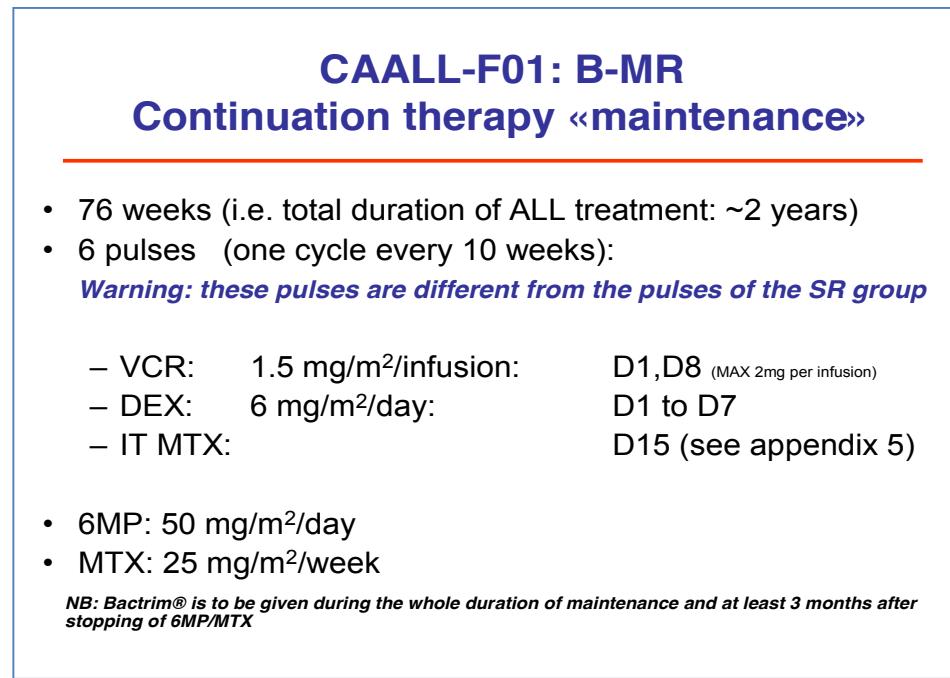
The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

#### **B-MR group: Maintenance (Figure 11) not earlier than Day 57 of previous phase**

***The total duration of the maintenance phase will be 76 weeks of treatment.***

**Criteria to begin the course:** PNN ≥ 1000/mm<sup>3</sup> and Platelets ≥ 100.000/mm<sup>3</sup>

**Figure 11: Flow scheme of B-MR maintenance treatment**



**Since D1 of maintenance, patients will receive oral maintenance treatment combining:**

- 6-mercaptopurine: 50 mg/m<sup>2</sup>/day per os for 76 weeks
- Methotrexate: 25 mg/m<sup>2</sup> once a week per os for 76 weeks

***See Appendix 11 for dose modification/adaptation of 6MP/MTX***

***NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX***

**In addition, one pulse of the following combination will be administered every 10 weeks for a total of 6 administrations.**

- **Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 1 and Day 8**  
Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.
- **Dexamethasone: 6 mg/m<sup>2</sup>/day (divided in 2 intakes) per os from Day 1 to Day 7**

**Finally, 6 intrathecal injections of methotrexate will be given:**

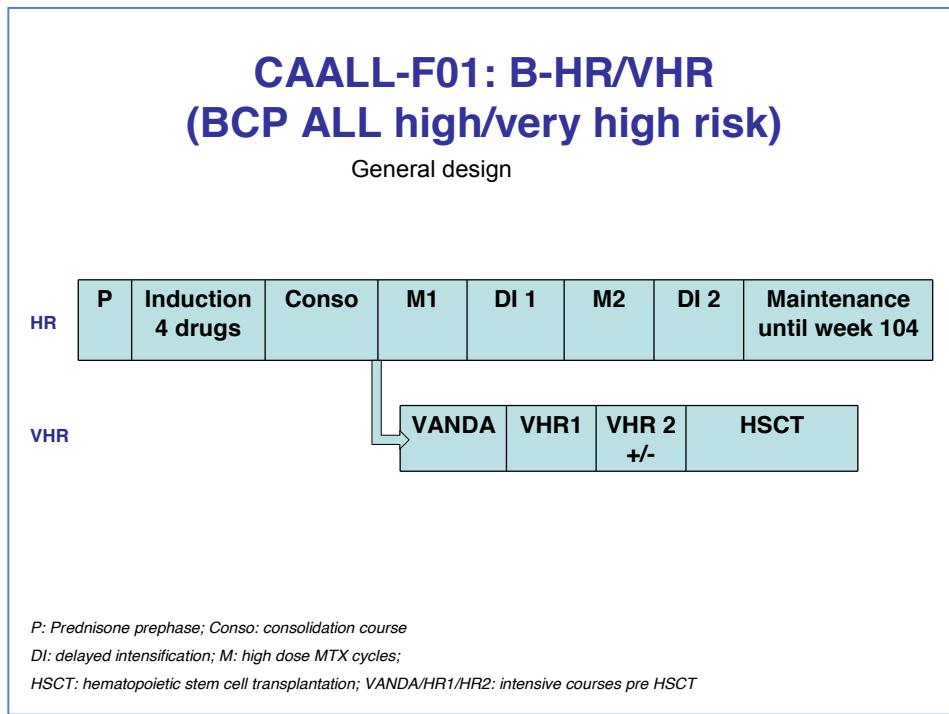
- **Methotrexate IT: Day 15 of each cycle.**

The dosage depends on the age of the patient. Guidelines for methotrexate for intrathecal administration are available in **Appendix 5**.

### 5.1.3 B-High/Very High Risk (B-H/VHR) Group

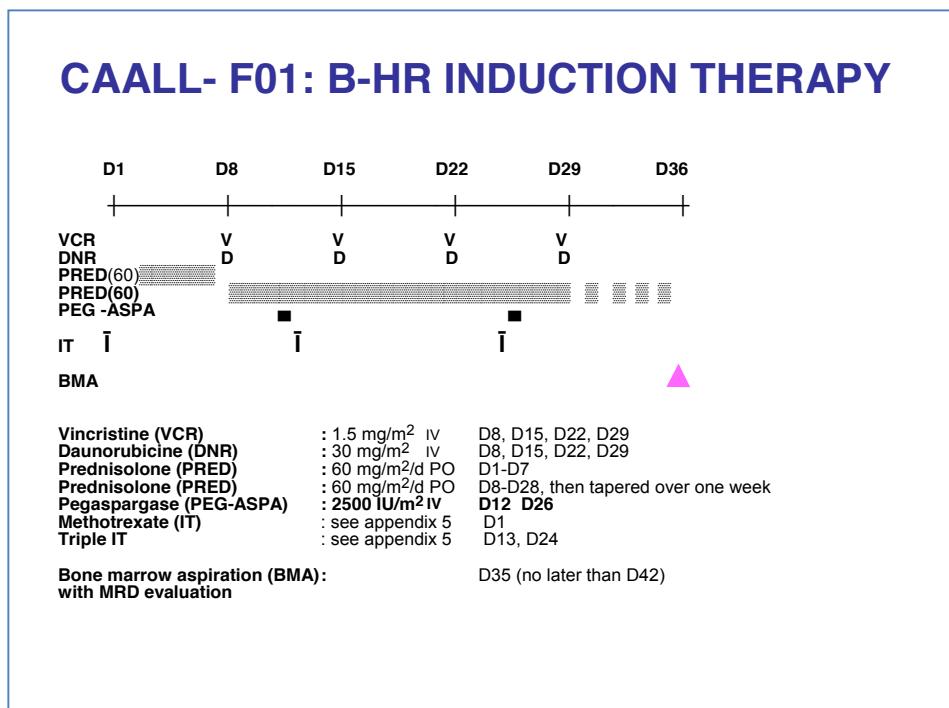
Treatment overview of the B-H/VHR group is displayed in Figure 12.

**Figure 12: Treatment flow chart of the B-H/VHR group**



### B-HR group: Induction phase (Figure 13)

Figure 13: Flow scheme of B-HR induction treatment



The treatment will be administered as follows:

#### Prephase

- **Prednisolone: 30 mg/m<sup>2</sup> every 12 hours per os from Day 1 to Day 7 (total 14 doses).** IV methyl prednisolone at the same dose can be an alternative.
- **Methotrexate IT: Day 1**

The dosage depends on the age of the patient. Guidelines for methotrexate for intrathecal administration are available in **Appendix 8. In case of initial Traumatic Lumbar Puncture or CNS2 status, intensified CNS prophylaxis during induction phase is mandatory according to guidelines in Appendix 5.**

**NB : if WBC ≥ 100 000/mm<sup>3</sup> refer to appendix 10**

*On Day 8, the prednisone response is to be evaluated on a blood-smear. A good response is defined as less than 1000 blast cells per mm<sup>3</sup> in the peripheral blood.*

### Induction therapy from Day 8

- **Prednisolone: 30 mg/m<sup>2</sup> x 2/day per os from Day 8 to Day 28 (total 42 doses), then tapered over one week**
- **Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 8, 15, 22 and 29.**

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

A neurological examination will be performed before every administration.

- **Daunorubicin 30 mg/m<sup>2</sup> on Day 8, 15, 22 and 29**

Daunorubicin will be administered strictly intravenously over 60 min.

– **Pegaspargase**

Oncaspar® will be administered intravenously over 60 min.

- **ONCASPAR®:2 500 IU/m<sup>2</sup> /day on Day 12 and Day 26**

Guidelines for ONCASPAR® use are available in **Appendix 7**

**If Pegaspargase infusion is not performed at Day 12 or Day 26 see warning at Section 3.1**

In case of allergy and/or clinical reaction during Oncaspar infusion, refer to Appendix 7

- **Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine): Day 13 and 24.**

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5. In case of initial Traumatic Lumbar Puncture or CNS2 status, intensified CNS prophylaxis during induction phase is mandatory, according to guidelines in Appendix 5.**

- **For patients with CNS3 status, supplementary triple ITs are to be given on Day 4 and Day 9, for a total of 5 during induction therapy (Day 1, 4, 9, 13, 24) (see Appendix 5)**

### B-HR group: Consolidation (Figure 14)

**Criteria to begin the course:** D35-42 Bone marrow showing complete remission (M1 marrow) AND ≥1000 PNN/mm<sup>3</sup> and Platelets ≥ 100.000/mm<sup>3</sup>. *In case of induction failure (M2 ou M3 marrow) at D35-42 begin HR consolidation whatever the blood count if clinical condition is adequate.*

The treatment will be administered as follows:

- **6-mercaptopurine: 60 mg/m<sup>2</sup>/day per os from Day 1 to Day 14, Day 29 to Day 42**

1- Patients homozygous for TPMT deficiency: give only 10 mg/m<sup>2</sup>/day of 6-mercaptopurine.

2- Patients heterozygous for TPMT deficiency:

- Do not adapt and give full dose of 6-mercaptopurine

– Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate

- **Cyclophosphamide: 1g/m<sup>2</sup>, intravenously over 60 min on Day 1 and Day 29**

– Give **Mesna** (400 mg/m<sup>2</sup>/dose) before and at hour 4 and 8 after start of cyclophosphamide infusion

- During these 8 hours, hyperhydratation (1 liter/m<sup>2</sup> / 8h) followed by oral hyperhydratation for the remaining 16 hours.

**– Pegaspargase**

Oncaspar® will be administered intravenously over 60 min.

➤ **ONCASPAR®: 2 500 IU/m<sup>2</sup> /day on Day 15 and Day 43**

Guidelines for ONCASPAR® use are available in **Appendix 7**

In case of allergy and/or clinical reaction during Oncaspar infusion, refer to Appendix 7

**– Vincristine: 1.5 mg/m<sup>2</sup> (max total dose: 2 mg) on Day 15, 22, 43 and 50**

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

**– Cytarabine: 75 mg/m<sup>2</sup>/infusion as push i.v. on Day 3 to Day 6, Day 10 to Day 13, Day 31 to Day 34 and Day 38 to Day 41**

**– Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine) on Day 3 and Day 31. *For patients with CNS3 status, supplementary triple ITs are to be given on Day 16 and Day 46 (see Appendix 5)***

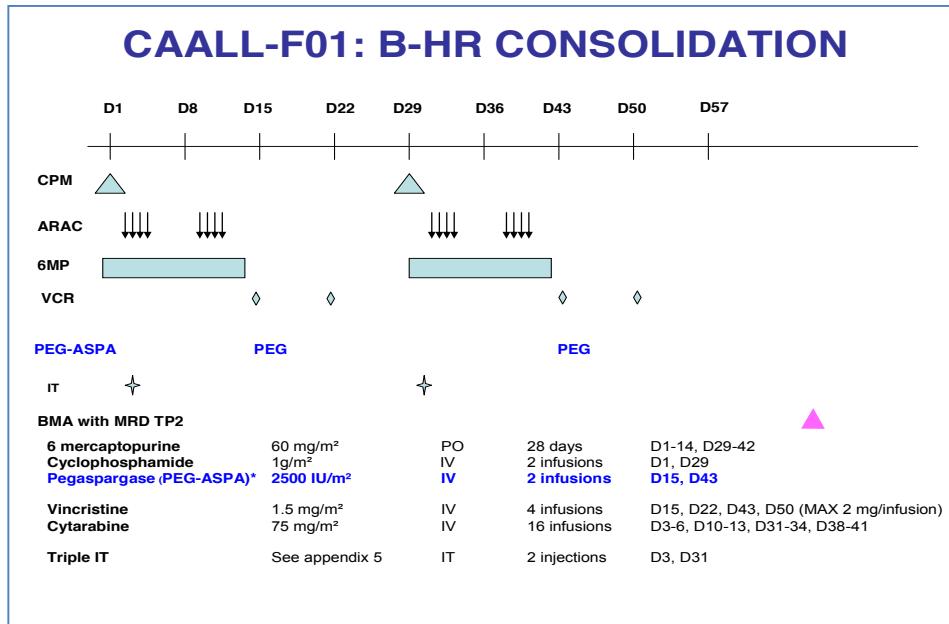
The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

**– NB: Administration of the second part of the cycle (from D29) should begin only if good clinical status and WBC over 1 G/L**

**Warning:** patients with ABL-class fusion transcripts (e.g. EBF1-PDFGRB) experiencing an induction failure and/or a MRD TP1  $\geq 10^{-3}$ , join this HR group at consolidation, as soon as possible, whatever their initial group. Imatinib 340 mg/m<sup>2</sup>/day is to be given from D1 of this phase and for the whole ALL treatment duration (exceptions are detailed in the concerned courses).

**NB 1** a very cautious approach of these situations is mandatory since toxicity, especially infection and prolonged aplasia could be increased. Stopping imatinib should then be considered

**NB2** refer to Table 3bis page 44 for final stratification of these patients with ABL-class fusion transcripts according to TP2 and TP3 and duration of exposure to Imatinib

**Figure 14: Flow scheme of B-HR consolidation treatment****Warning:**

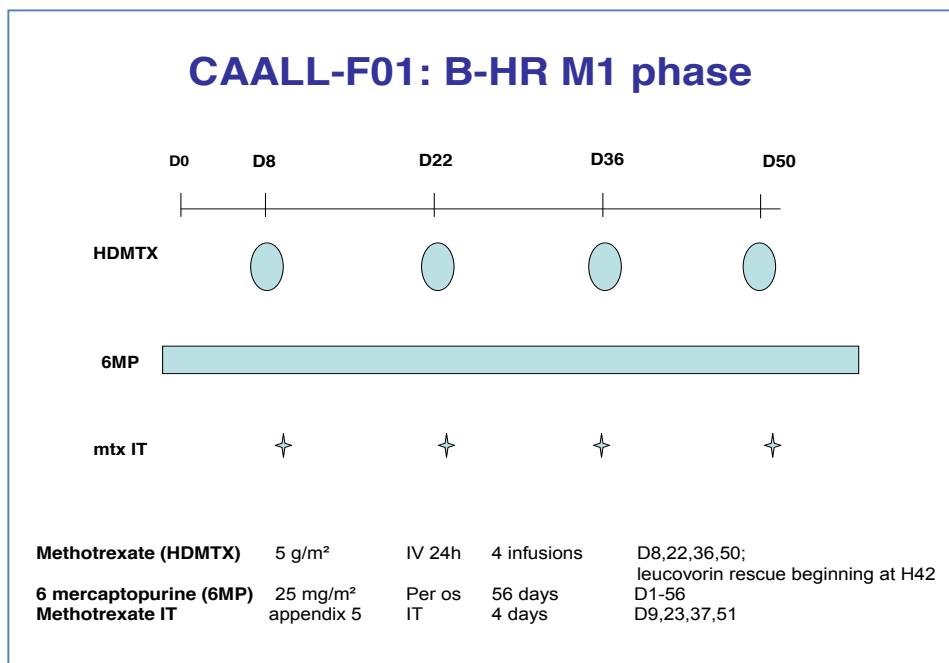
- **Risk stratification at D65-75 assessment: according to MRD TP2: table 3 (section 3.2.3)**
  - Patient stay in B-HR if MRD TP2 <10<sup>-3</sup>: Begin B-HR phase M1
  - All Patients switch to the B-VHR if MRD TP2 ≥10<sup>-3</sup>:** Stop Phase M and begin VANDA
- **For patients with ABL-class fusion transcripts (e.g. EBF1-PDFGRB) Imatinib 340 mg/m<sup>2</sup>/day is to be added from D1 of this phase.**
  - **Warning, refer to Table 3bis page 44 for final stratification according to TP2 and TP3 and duration of exposure to Imatinib.**
  - **For the subgroup of patients having both an ABL class fusion, an imatinib exposure of less than 14 days during consolidation and a MRD TP2≥10<sup>-3</sup> : begin VANDA (cf B-VHR group) plus imatinib (340 mg/m<sup>2</sup>/day). Same caution to infection and/or prolonged aplasia is to be applied; reevaluate MRD (MRDTP3) refer to Table 3bis page 44**

**B-HR: Phase M1 (Figure 15)**

**Criteria to begin the M Phase:** PNN ≥1000/mm<sup>3</sup> and Platelets ≥ 100.000/mm<sup>3</sup>

**Criteria for each course of HD methotrexate:** PNN ≥ 500/mm<sup>3</sup> and Platelets ≥ 50.000/mm<sup>3</sup>. If these criteria are not met = stop 6-Mercaptopurine which is to be reintroduced after the beginning of HD methotrexate

Figure 15: Flow scheme of B-HR phase M1 treatment



The treatment will be administered as follows:

- **HD methotrexate: 5 g/m<sup>2</sup> i.v. over 24 hours with leucovorin rescue at H42 on Day 8, 22, 36 and 50.**

Guidelines for HD methotrexate administration and leucovorin rescue are available in the **Appendix 8**.

- **6-mercaptopurine: 25 mg/m<sup>2</sup>/day per os from Day 1 to Day 56**

- 1- Patients homozygous for TPMT deficiency: give only 4 mg/m<sup>2</sup>/day of 6-mercaptopurine.
- 2- Patients heterozygous for TPMT deficiency:
  - Do not adapt and give full dose of 6-mercaptopurine
  - Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate

- **Methotrexate IT on Day 9, 23, 37 and 51**

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

*For patients with ABL-class fusion transcripts (e.g. EBF1-PDFGRB) Imatinib 340 mg/m<sup>2</sup>/day is to be added from D1 of this phase. **Warning, refer to Table 3bis page 44 for final stratification according to TP2 and TP3 and duration of exposure to Imatinib.** Of note a very cautious approach of these situations is mandatory since toxicity, especially infection and prolonged aplasia could be increased. Stopping imatinib should then be considered*

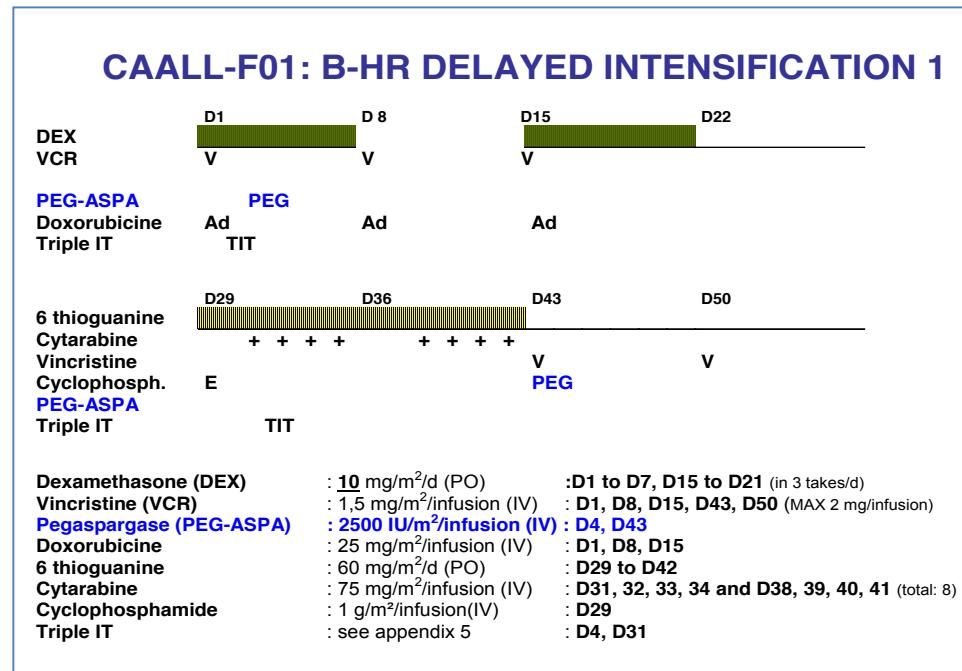
**Warning:** a possible interaction between high dose methotrexate and imatinib is to be monitored through methotrexate levels and renal function monitoring. In case of documented interaction (delayed elimination of methotrexate and/or renal insufficiency), stop imatinib until normalization. Resume imatinib then. Stop again imatinib at day-3 until day +3 of the next course of high dose methotrexate

#### **B-HR group: Delayed intensification 1 (Figure 16) (not earlier than D70 of previous phase)**

**Criteria to begin each phase of the course (D1 and D29):** PNN  $\geq$ 1000/mm<sup>3</sup> and Platelets  $\geq$  100.000/mm<sup>3</sup>

**Warning: Infectious complications often occur during this phase particularly between D15 and D28 and D43-D57**

**Figure 16: Flow scheme of B-HR delayed intensification 1 treatment**



The treatment will be administered as follows:

- Dexamethasone: 10 mg/m<sup>2</sup>/day per os (divided in 3 intakes) from Day 1 to Day 7 and from Day 15 to Day 21
  - Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 1, 8, 15, 43 and 50

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

#### **– Pegaspargase**

Oncaspar® will be administered intravenously over 60 min.

➤ ONCASPAN® 2 500 IU/m<sup>2</sup> /day on Day 4 and Day 43

Guidelines for ONCASP<sup>®</sup> use are available in **Appendix 7**.

- Doxorubicin: 25 mg/m<sup>2</sup>/infusion on Day 1, 8 and 15

Doxorubicin will be administered intravenously over 60 min.

- 6-Thioguanine: 60 mg/m<sup>2</sup>/day per os from Day 29 to Day 42

- 1- Patients homozygous for TPMT deficiency: give only 10 mg/m<sup>2</sup>/day of 6-Thioguanine.
  - 2- Patients heterozygous for TPMT deficiency:
    - Do not adapt and give full dose of 6-Thioguanine
    - Monitor: if next phase of chemotherapy is delayed diminish the dose by 50% and reevaluate

- Cytarabine: 75 mg/m<sup>2</sup>/infusion as push i.v. on Day 31 to Day 34 and Day 38 to Day 41**

- = Cyclophosphamide: 1g/m<sup>2</sup>, intravenously over 60 min on Day 29

- Give **Mesna** (400 mg/m<sup>2</sup>/dose) before and at hour 4 and 8 after start of cyclophosphamide infusion
  - During these 8 hours, hyperhydratation (1 liter/m<sup>2</sup> / 8h) followed by oral hyperhydratation for the remaining 16 hours.

- Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine) on Day 4 and Day 31

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

*For patients with ABL-class fusion transcripts (e.g. EBF1-PDFGRB) Imatinib 340 mg/m<sup>2</sup>/day is to be added from D1 of this phase.*

*NB a very cautious approach of these patients is mandatory since toxicity, especially infection and prolonged aplasia, could be increased. Stopping imatinib should then be considered*

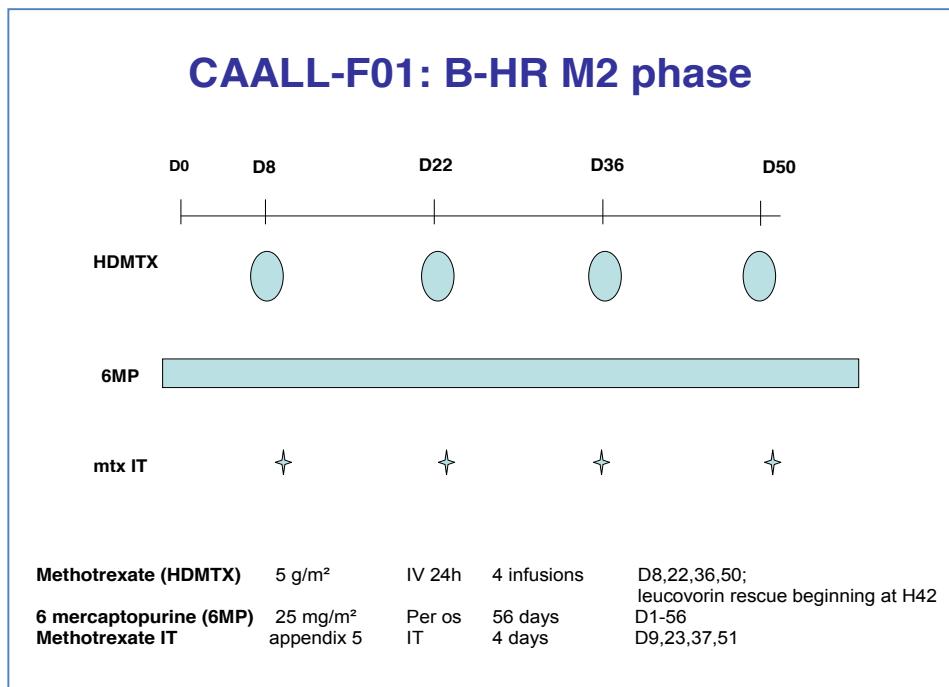
#### **B-HR: Phase M2 (Figure 17) not earlier than Day 57 of previous phase**

**Criteria to begin the M Phase:** PNN  $\geq$ 1000/mm<sup>3</sup> and Platelets  $\geq$  100.000/mm<sup>3</sup>

Criteria for each course of HD methotrexate: PNN  $\geq$  500/mm<sup>3</sup> and Platelets  $\geq$  50.000/mm<sup>3</sup>.

If these criteria are not met = stop 6-Mercaptopurine which is to be reintroduced after the beginning of HD methotrexate

**Figure 17: Flow scheme of B-HR Phase M2 treatment**



The treatment will be administered as follows:

- **HD methotrexate: 5 g/m<sup>2</sup> i.v. over 24 hours with leucovorin rescue at H42 on Day 8, 22, 36 and 50.**

Guidelines for HD methotrexate administration and leucovorin rescue are available in **Appendix 8**.

- **6-mercaptopurine: 25 mg/m<sup>2</sup>/day per os from Day 1 to Day 56**

1- Patients homozygous for TPMT deficiency: give only 4 mg/m<sup>2</sup>/day of 6-mercaptopurine.

2- Patients heterozygous for TPMT deficiency:

- Do not adapt and give full dose of 6-mercaptopurine

- Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate

- **methotrexate IT on Day 9, 23, 37 and 51**

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

*For patients with ABL-class fusion transcripts (e.g. EBF1-PDFGRB) Imatinib 340 mg/m<sup>2</sup>/day is to be added from D1 of this phase.*

*Of note a very cautious approach of these situations is mandatory since toxicity, especially infection and prolonged aplasia, could be increased. Stopping imatinib should then be considered*

**Warning:** a possible interaction between high dose methotrexate and imatinib is to be monitored through methotrexate levels and renal function monitoring. In case of documented interaction (delayed elimination of methotrexate and/or renal insufficiency), stop imatinib until normalization. Resume imatinib then. Stop again imatinib at day-3 until day +3 of the next course of high dose methotrexate

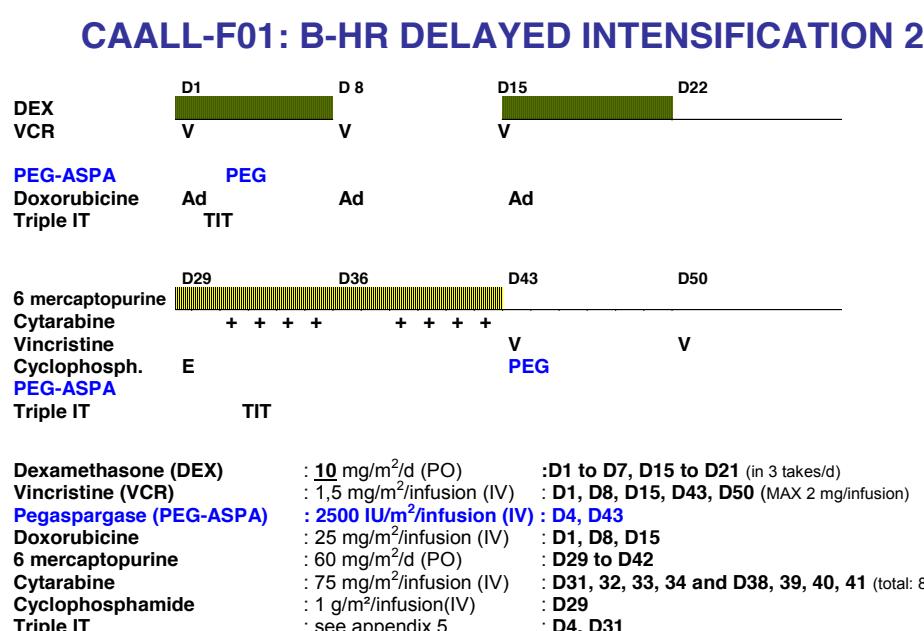
#### **B-HR group: Delayed intensification 2 (Figure 18) (not earlier than D70 of previous phase)**

**Criteria to begin each phase of the course (D1 and D29):** PNN  $\geq$ 1000/mm<sup>3</sup> and Platelets  $\geq$  100.000/mm<sup>3</sup>

**Warning:** infectious complications often occur during this phase particularly between D15 and D28 and D43-D57

***Warning: 6-mercaptopurine (and not 6-thioguanine) is used here (VOD risk reduction)***

**Figure 18: Flow scheme of B-HR delayed intensification 2 treatment**



The treatment will be administered as follows:

- **Dexamethasone: 10 mg/m<sup>2</sup>/day per os (divided in 3 intakes) from Day 1 to Day 7 and from Day 15 to Day 21**
- **Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 1, 8, 15, 43 and 50**

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

– **Pegasparagase**

Oncaspar® will be administered intravenously over 60 min.

➤ **ONCASPAR® 2 500 IU/m<sup>2</sup> /day on Day 4 and Day 43**

Guidelines for ONCASPAR® use are available in **Appendix 7**

- **Doxorubicin: 25 mg/m<sup>2</sup>/infusion on Day 1, 8 and 15**

Doxorubicin will be administered intravenously over 60 min.

- **6-Mercaptopurine: 60 mg/m<sup>2</sup>/day per os from Day 29 to Day 42**

1- Patients homozygous for TPMT deficiency: give only 10 mg/m<sup>2</sup>/day of 6-mercaptopurine.

**2- Patients heterozygous for TPMT deficiency:**

- Do not adapt and give full dose of 6-mercaptopurine
- Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate
- **Cytarabine: 75 mg/m<sup>2</sup>/infusion as push i.v. on Day 31 to Day 34 and Day 38 to Day 41**
- **Cyclophosphamide: 1g/m<sup>2</sup>, intravenously over 60 min on Day 29**
  - Give **Mesna** (400 mg/m<sub>2</sub>/dose) before and at hour 4 and 8 after start of cyclophosphamide infusion
  - During these 8 hours, hyperhydratation (1 liter/m<sup>2</sup> / 8h) followed by oral hyperhydratation for the remaining 16 hours.
- **Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine) on Day 4 and Day 31**

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5.**

*For patients with ABL-class fusion transcripts (e.g. EBF1-PDFGRB) Imatinib 340 mg/m<sup>2</sup>/day is to be added from D1 of this phase.*

*Of note a very cautious approach of these situations is mandatory since toxicity, especially infection and prolonged aplasia, could be increased. Stopping imatinib should then be considered*

**B-HR group: Maintenance (Figure 19) not earlier than Day 57 of previous phase**

The maintenance phase will last at week 104 overall.

**Criteria to begin the course:** PNN ≥1000/mm<sup>3</sup> and Platelets ≥ 100.000/mm<sup>3</sup>

**Figure 19: Flow scheme of B-HR maintenance treatment**

**CAALL-F01: B-HR  
Continuation therapy « maintenance »**

- Total duration: until week 104
- No pulses
- No ITs (*except for CNS3 pts see annex 5*)
- 6-MP: 50 mg/m<sup>2</sup>/day
- MTX : 25 mg/m<sup>2</sup>/week

*NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX*

**Since D1 of maintenance, patients will receive oral maintenance treatment combining:**

- 6-mercaptopurine: 50 mg/m<sup>2</sup>/day per os up to week 104
- Methotrexate: 25 mg/m<sup>2</sup> once a week per os up to week 104

*See Appendix 11 for dose modification/adaptation of 6MP/MTX*

**NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX**

- **For patients with CNS3 status, 4 supplementary triple ITs are to be given during maintenance (M1, M4, M7, M10) (see Appendix 5)**
- **For patients with ABL-class fusion transcripts (e.g. EBF1-PDFGRB) Imatinib 340 mg/m<sup>2</sup>/day is to be added from D1 of this phase until end of maintenance therapy.**

**NB: a very cautious approach of these situations is mandatory since toxicity, especially infection and unexpected cytopenias/prolonged aplasia, could be increased. Stopping imatinib should then be considered. Advice from PIs is available for these very rare patients**

#### 5.1.4 Patients with B-lineage ALL eligible for Hematopoietic Stem Cell Transplantation

- **Population: Patients with B-lineage ALL and/or**
  - **High-risk Cytogenetics**
    - MLL and NCI-HR
    - hypodiploidy < 40
    - t(17;19)/ TCF3-HLF
  - **Induction failure MR/HR and D35 TP1 MRD ≥ 5.10<sup>-2</sup>**
  - **TP2 MRD ≥ 10<sup>-3</sup> (Day 95)**
- **These patients are candidate to HSCT**
- These patients receive **one course of VANDA** (fig 20) followed by one or two blocks of chemotherapy (VHR1+/-VHR2).
  - The intent is to reduce the MRD as much as possible before HSCT.
  - Thus a control of MRD should be performed at least after the VANDA course (TP3) and before HSCT.
- **Criteria to begin the VANDA course: PNN ≥ 1000/mm<sup>3</sup> and Platelets ≥ 100.000/mm<sup>3</sup>**

**Warning: Severe infectious complications often occur during this phase.**

**Figure 20: Flow scheme of VANDA**

	D1	D2	D3	D4	D5	D6
Dexamethasone						
Cytarabine						
Mitoxantrone						
Etoposide						
Pegaspargase						PEG
Triple IT						
Dexamethasone	20 mg/m <sup>2</sup> in 2 takes	PO	5 days		D1-D5	
Dexamethasone	10 mg/m <sup>2</sup> in 2 takes	PO	1 day		D6	
Cytarabine	2 g/m <sup>2</sup> every 12 hours	IV (3h)	2 days		D1 D2	
Mitoxantrone	8 mg/m <sup>2</sup>	IV (1h)	2 days		D3 D4	
Etoposide	150 mg/m <sup>2</sup>				D3 D4 D5	
Pegaspargase	2500 IU/m <sup>2</sup>	IV (1h)	1 day		D6	
Triple IT	see appendix 5	intrathecal	1 day		D5	

The treatment will be administered as follows:

- Dexamethasone: 20 mg/m<sup>2</sup>/day *per os* (divided in 2 intakes) from Day 1 to Day 5 and 10 mg/m<sup>2</sup> on Day 6.
- Cytarabine: 2 g/m<sup>2</sup>/infusion over 3 hours x 2, 12 hours apart, on Day 1, and Day 2
- Mitoxantrone: 8 mg/m<sup>2</sup>/infusion over 1 hour on Day 3 and on Day 4
- VP16: 150 mg/m<sup>2</sup>/infusion over 1 hour on Day 3, Day 4 and Day 5

– **Pegaspargase**

Oncaspar® will be administered intravenously over 60 min.

➤ **ONCASPAR® 2 500 IU/m<sup>2</sup> on Day 6**

Guidelines for ONCASPAR® use are available in **Appendix 7**

- **Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine) on Day 5**

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

▪ **After VANDA and before HSCT**

After the VANDA course VHR1 and/or VHR2 blocks could be administered.

- **The VHR1 block is optional (Figure 21).** Its realization will depend on MRD levels, donor availability and organizational issues.

**Criteria to begin the VHR1 course:** PNN ≥1000/mm<sup>3</sup> and Platelets ≥ 100.000/mm<sup>3</sup>

**Warning: Severe infectious complications often occur during this phase.**

The treatment will be administered as follows:

- Dexamethasone: 20 mg/m<sup>2</sup>/day *per os* (divided in 2 intakes) from Day 1 to Day 5 and 10 mg/m<sup>2</sup> on Day 6.
- Cytarabine: 2 g/m<sup>2</sup>/infusion over 3 hours x 2, 12 hours apart, on Day 5

- **Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 1, 6**

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

- **Methotrexate: 5g/ m<sup>2</sup> over 24 hours on D1 with folinic acid rescue beginning at H42 (cf appendix 8).**

- **6-mercaptopurine: 100 mg/m<sup>2</sup> per os (one take/day) D1 to D5 (total 5 takes)**

1- Patients homozygous for TPMT deficiency: give only 15 mg/m<sup>2</sup>/day of 6-mercaptopurine.

2- Patients heterozygous for TPMT deficiency:

- Do not adapt and give full dose of 6-mercaptopurine

- Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate

- **Pegaspargase**

Oncaspar® will be administered intravenously over 60 min.

- **ONCASPAR® 2 500 IU/m<sup>2</sup> on Day 6**

Guidelines for ONCASPAR® use are available in **Appendix 7**

- **Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine) on Day 2**

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

Figure 21: Flow scheme of VHR1

<b>VHR1 Block</b>						
	<b>D1</b>	<b>D2</b>	<b>D3</b>	<b>D4</b>	<b>D5</b>	<b>D6</b>
<b>Dexamethasone</b>						
<b>6 Mercaptopurine</b>						
<b>Vincristine</b>						
<b>Methotrexate</b>						
<b>Cytarabine</b>						
<b>Pegaspargase</b>						<b>PEG</b>
<b>Triple IT</b>			<b>pink</b>			
Dexamethasone	20 mg/m <sup>2</sup> in 2 takes	PO	5 days		D1-D5	
Dexamethasone	10 mg/m <sup>2</sup> in 2 takes	PO	1 day		D6	
6 mercaptopurine	100 mg/m <sup>2</sup> in 1 take	PO	5 days		D1-D5	
Vincristine	1.5 mg/m <sup>2</sup> (MAX 2mg)	IV direct	2 days		D1 and D6	
Methotrexate	5g/m <sup>2</sup>	IV (24h)	1 day		D1	
Cytarabine	2 g/m <sup>2</sup> every 12 hours	IV (3h)	1 day		D5	
<b>Pegaspargase</b>	<b>2500 IU/m<sup>2</sup></b>	<b>IV (1h)</b>	<b>1 day</b>		<b>D6</b>	
Triple IT	see appendix 5	intrathecal	1 day		D2	

- **The VHR2 block is optional (fig 22).**

Its realization will depend on MRD levels, donor availability and organizational issues.

**Criteria to begin the VHR2 course:** PNN ≥1000/mm<sup>3</sup> and Platelets ≥ 100.000/mm<sup>3</sup>

**Warning: Severe infectious complications often occur during this phase.**

Figure 22: Flow scheme of R2

	D1	D2	D3	D4	D5	D6
<b>Dexamethasone</b>						
<b>6 mercaptopurine</b>						
<b>Vindesine</b>						
<b>Methotrexate</b>						
<b>Ifosfamide</b>						
<b>Daunorubicine</b>						
<b>Pegasparagase</b>						<b>PEG</b>
<b>Triple IT</b>						
Dexamethasone	20 mg/m <sup>2</sup> in 2 takes	PO	5 days	D1-D5		
Dexamethasone	10 mg/m <sup>2</sup> in 2 takes	PO	1 day	D6		
6 mercaptopurine	100 mg/m <sup>2</sup> in 1 take	PO	5 days	D1-D5		
Vindesine	3 mg/m <sup>2</sup>	IV push	2 days	D1 and D6		
Methotrexate	5g/m <sup>2</sup>	IV (24h)	1 day	D1		
Ifosfamide	400 mg/m <sup>2</sup>	IV (1h)	5 days	D1-D5		
Daunorubicine	35 mg/m <sup>2</sup>	IV (1h)	1 day	D5		
Pegasparagase	<b>2500 IU/m<sup>2</sup></b>	<b>IV (1h)</b>	<b>1 day</b>	<b>D6</b>		
Triple IT	see appendix 5	intrathecal	1 day	D2		

The treatment will be administered as follows:

- **Dexamethasone: 20 mg/m<sup>2</sup>/day per os (divided in 2 intakes) from Day 1 to Day 5 and 10 mg/m<sup>2</sup> on Day 6.**
- **Ifosfamide: 400 mg/m<sup>2</sup>/infusion over 1 hours from Day 1 to Day 5 (total dose 2 g/m<sup>2</sup>)**
- **Vindesine: 3 mg/m<sup>2</sup> (maximum total dose: 4 mg) on Day 1, 6**  
Vindesine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.
- **Methotrexate: 5g/ m<sup>2</sup> over 24 hours on D1 with folinic acid rescue beginning at H42 (cf Appendix 8).**
- **Daunorubicin: 35 mg/m<sup>2</sup> (IV infusion over 1 hour) on Day 5**
- **6-mercaptopurine: 100 mg/m<sup>2</sup> per os (one take/day) D1 to D5 (total 5 takes )**

1- Patients homozygous for TPMT deficiency: give only 15 mg/m<sup>2</sup>/day of 6-mercaptopurine.

2- Patients heterozygous for TPMT deficiency:

- Do not adapt and give full dose of 6-mercaptopurine
- Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate

#### – **Pegasparagase**

Oncaspar® will be administered intravenously over 60 min.

➤ **ONCASPAR® 2 500 IU/m<sup>2</sup> on Day 6**

Guidelines for ONCASPAR® use are available in **Appendix 7**

- **Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine) on Day 2.** The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

## 5.2 Treatment for T-lineage ALL

The general schedule for all stratification groups will be as follows:

- an induction phase
- a consolidation phase
- one or 2 delayed intensification phases
- a continuation “maintenance” phase

All these sequences are going to follow each other without any free interval. The total duration of the treatment will be 24 months. The treatments in each phase will depend on the stratification groups. Details are given below.

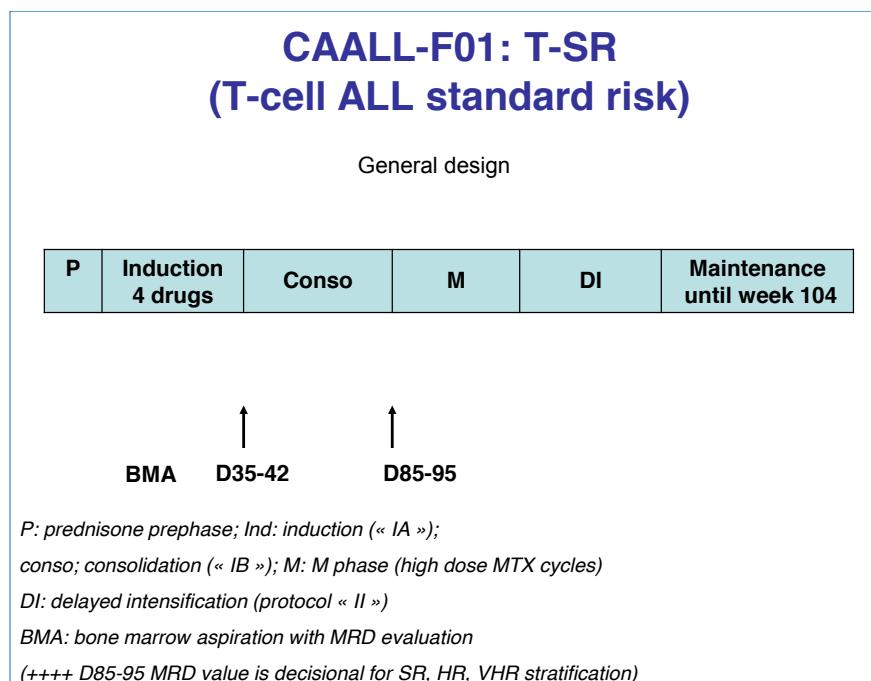
**Warning: In case of preexposure to steroids, refer to table 8 (section 3.5.2) for risk stratification at the end of the prednisone phase**

- Only a minority of patients will be submitted to an HSCT (see section 5.2.3)

### 5.2.1 T-Standard Risk (SR) Group

Treatment overview of the T-SR group is displayed in Figure 23.

**Figure 23: Treatment flow chart of the T-SR group**

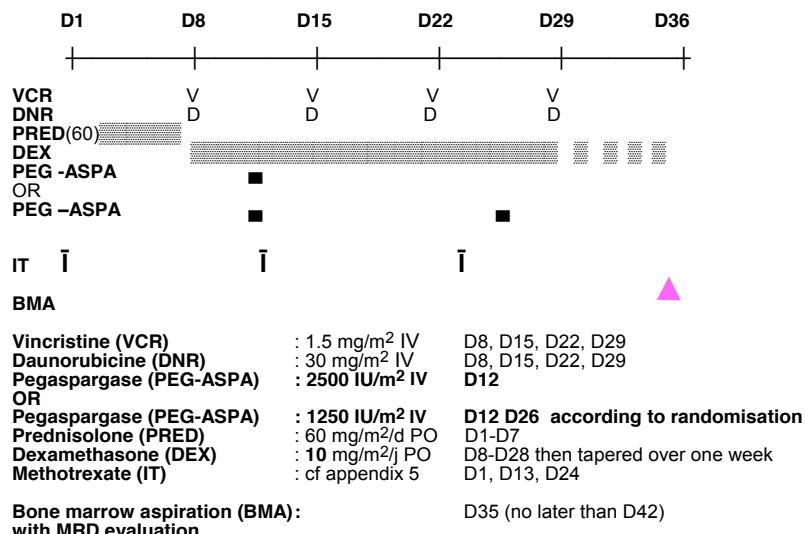


### **T-SR group: Induction phase (Figure 24)**

Before administering each dose of each drug, contraindications must be checked. Please refer to the SPC of each drug.

Figure 24: Flow scheme of T-SR induction treatment

## **CAALL-F01: T-SR INDUCTION THERAPY**



The treatment will be administered as follows:

### **Prephase**

- **Prednisolone: 30 mg/m<sup>2</sup> every 12 hours per os from Day 1 to Day 7 (total 14 doses).** IV methyl prednisolone at the same dose can be an alternative.
- **Methotrexate IT: Day 1**

The dosage depends on the age of the patient. Guidelines for methotrexate for intrathecal administration are available in **Appendix 5. In case of initial Traumatic Lumbar Puncture or CNS2 status, intensified CNS prophylaxis during induction phase is mandatory according to guidelines in Appendix 5.**

**NB : if WBC ≥ 100 000/mm<sup>3</sup> refer to appendix 10**

*On Day 8, the prednisone response is to be evaluated on a blood-smear. A good response is defined as less than 1000 blast cells per mm<sup>3</sup> in the peripheral blood.*

**Warning: Risk stratification at the end of prephase:**

- If Poor prednisone response, patient switch in T-HR for induction
- Assessment of prednisone response in T-ALL patients in case of preexposure to steroids: refer to table 8 (section 3.5.2):

### **Induction therapy from Day 8**

- **Dexamethasone: 5 mg/m<sup>2</sup> x 2/day per os from Day 8 to Day 28 (total 42 doses), then tapered over one week**

**Warning: The daily dose of 10 mg/m<sup>2</sup> of dexamethasone has been linked to an increased incidence of infectious complications (bacteria and fungi). Prevention and empirical treatment of fungal infections are to be considered avoiding azoles due to the concomitant use of vincristine**

**Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 8, 15, 22 and 29.**

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

A neurological examination will be performed before every administration.

- **Daunorubicin 30 mg/m<sup>2</sup> on Day 8, 15, 22 and 29**

Daunorubicin will be administered strictly intravenously over 60 min.

- **Pegaspargase**

Oncaspar® will be administered intravenously over 60 min.

The schedule to be administered during induction therapy is determined by randomization:

- **Arm 1/T-SR: ONCASPAR®:2 500 IU/m<sup>2</sup> on Day 12**

OR

- **Arm 2/T-SR: ONCASPAR®:1 250 IU/m<sup>2</sup> /day on Day 12 and Day 26**

Guidelines for ONCASPAR® use are available in **Appendix 7**

**If Pegaspargase infusion is not performed at Day 12 or Day 26 see warning at Section 3.1**

In case of allergy and/or clinical reaction during Oncaspar infusion, refer to Appendix 7

- **IT Methotrexate: Day 13 and Day 24**

The dosage depends on the age of the patient. Guidelines for intrathecal administration of methotrexate are available in **Appendix 5**. *In case of initial Traumatic Lumbar Puncture or CNS2 status, intensified CNS prophylaxis during induction phase is mandatory, according to guidelines in Appendix 5.*

**T-SR group: Consolidation (Figure 25)**

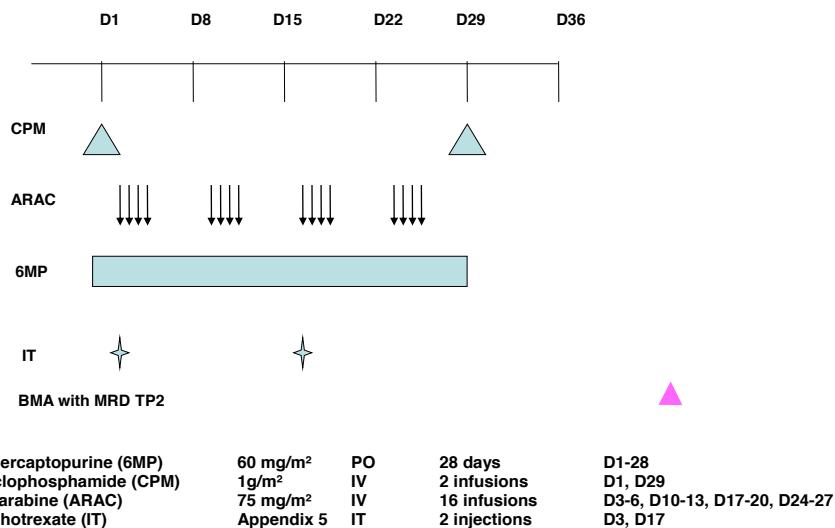
**Warning : Risk stratification according to MRD TP1 : refer to table 5 (section 3.3.2)**

**Criteria to begin the course:** D35-42 Bone marrow showing complete remission (M1 marrow) AND  $\geq 1.000$  PNN/mm<sup>3</sup> and Platelets  $\geq 100.000/\text{mm}^3$ . *In case of induction failure (M2 ou M3 marrow) at D35-42 begin T-HR consolidation whatever the blood count if clinical condition is adequate.*

**Criteria for D29 cyclophosphamide administration:** WBC $\geq 1000/\text{mm}^3$

**Figure 25: Flow scheme of T-SR consolidation treatment**

## CAALL-F01: T-SR CONSOLIDATION



The treatment will be administered as follows:

– **6-mercaptopurine: 60 mg/m<sup>2</sup>/day per os from Day 1 to Day 28**

- 1- Patients homozygous for TPMT deficiency: give only 10 mg/m<sup>2</sup>/day of 6-mercaptopurine.
- 2- Patients heterozygous for TPMT deficiency:
  - Do not adapt and give full dose of 6-mercaptopurine
  - Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate

– **Cyclophosphamide: 1g/m<sup>2</sup>, intravenously over 60 min on Day 1 and Day 29**

- Give Mesna (400 mg/m<sup>2</sup>/dose) before and at hour 4 and 8 after start of cyclophosphamide infusion
- During these 8 hours, hyperhydration (1 liter/m<sup>2</sup> / 8h) followed by oral hyperhydration for the remaining 16 hours.

– **Cytarabine: 75 mg/m<sup>2</sup>/infusion as push i.v. from Day 3 to Day 6, Day 10 to Day 13, Day 17 to Day 20 and from Day 24 to Day 27**

– **Methotrexate IT: on Day 3 and Day 17**

The dosage depends on the age of the patient. Guidelines for intrathecal administration of methotrexate are available in **Appendix 5**.

**T-SR: Phase M (Figure 26) :**

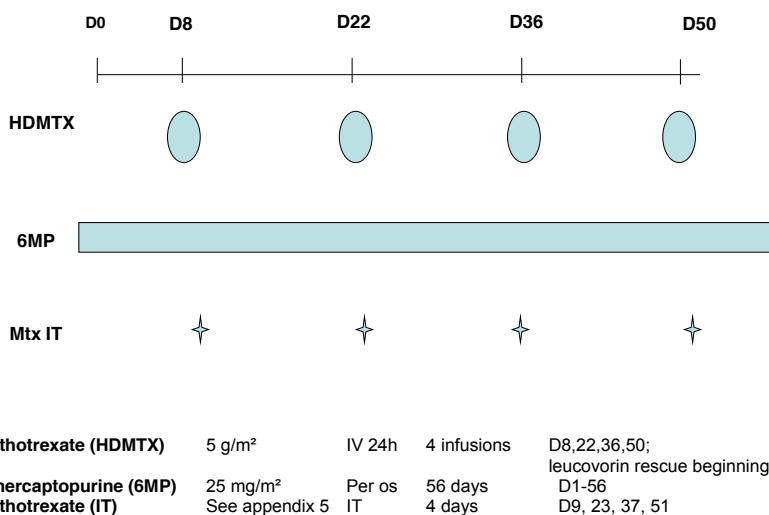
**Warning : Risk stratification according to MRD TP2 : refer to table 5 (section 3.3.2)**

**Criteria to begin the M Phase:** PNN  $\geq$ 1000/mm<sup>3</sup> and Platelets  $\geq$  100.000/mm<sup>3</sup>

Criteria for each course of HD methotrexate: PNN  $\geq$  500/mm<sup>3</sup> and Platelets  $\geq$  50.000/mm<sup>3</sup>. If these criteria are not met = stop 6-Mercaptopurine which is to be reintroduced after the beginning of HD methotrexate

**Figure 26: Flow scheme of T-SR Phase M treatment**

## CAALL-F01: T-SR M phase



The treatment will be administered as follows:

**HD methotrexate: 5 g/m<sup>2</sup> i.v. over 24 hours with leucovorin rescue beginning at H42, on Day 8, 22, 36 and 50.** Guidelines for HD methotrexate administration and leucovorin rescue are available in **Appendix 8**.

– **6-MercaptoPurine: 25 mg/m<sup>2</sup>/day per os from Day 1 to Day 56**

- 1- Patients homozygous for TPMT deficiency: give only 4 mg/m<sup>2</sup>/day of 6-mercaptopurine.
- 2- Patients heterozygous for TPMT deficiency:
  - Do not adapt and give full dose of 6-mercaptopurine
  - Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate

– **Methotrexate IT: on Day 9, 23, 37 and 51**

The dosage depends on the age of the patient. Guidelines for intrathecal administration of methotrexate are available in **Appendix 5**.

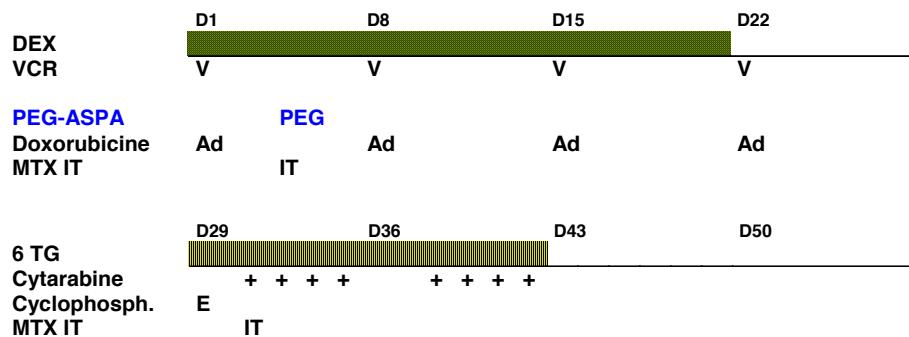
**T-SR group: Delayed intensification 1 “protocol II” (Figure 27)**

Criteria to begin each phase of the course (D1 and D29): PNN ≥1000 /mm<sup>3</sup> and Platelets ≥ 100.000/mm<sup>3</sup> and no earlier than D70 of previous phase.

**Warning: Infectious complications often occur during this phase particularly between D15 and D28 and D43-D57**

**Figure 27: Flow scheme of T-SR delayed intensification n°1 “protocol II” treatment**

## CAALL-F01: T-SR Delayed intensification n°1 “protocol II”



<b>Dexamethasone (DEX)</b>	: <b>10 mg/m<sup>2</sup>/d (PO)</b>	: <b>D1 to D21 (in 3 takes)</b>
<b>Vincristine(VCR)</b>	: <b>1.5 mg/m<sup>2</sup>/infusion (IV)</b>	: <b>D1, D8, D15, D22 (MAX 2mg/infusion)</b>
<b>Pegaspargase*(PEG-ASPA)</b> : <b>1250 or 2500 IU/m<sup>2</sup> (IV)</b>	: <b>D4</b>	
<b>Doxorubicin</b>	: <b>30 mg/m<sup>2</sup>/infusion (IV)</b>	: <b>D1, D8, D15, D22,</b>
<b>6 thioguanine (6TG)</b>	: <b>60 mg/m<sup>2</sup>/d (PO)</b>	: <b>D29 to D42</b>
<b>Cytarabine</b>	: <b>75 mg/m<sup>2</sup>/infusion (IV)</b>	: <b>D31, D32, D33, D34 and D38, 39, 40, 41</b>
<b>Cyclophosphamide</b>	: <b>1 g/m<sup>2</sup> (IV)</b>	: <b>D29</b>
<b>MTX IT</b>	: see appendix 5	: <b>D4, D31</b>

\* dose of pegaspargase per infusion according to unitary dose of the initial randomisation

The treatment will be administered as follows:

- **Dexamethasone: 10 mg/m<sup>2</sup>/day per os (divided in 3 intakes) from Day 1 to Day 21, tapered from Day 22**
- **Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 1, 8, 15 and 22**

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

– **Pegaspargase**

Oncaspar® will be administered intravenously over 60 min.

– **Arm 1/T-SR: ONCASPAR®: 2 500 IU/m<sup>2</sup> on Day 4**

**OR Arm 2/T-SR: ONCASPAR®: 1 250 IU/m<sup>2</sup> on Day 4**

Guidelines for ONCASPAR® use are available in **Appendix 7**

– **Doxorubicin: 30 mg/m<sup>2</sup>/infusion on Day 1, 8, 15 and 22**

Doxorubicin will be administered intravenously over 60 min.

– **6-Thioguanine: 60 mg/m<sup>2</sup>/day per os from Day 29 to Day 42 (14 takes)**

1- Patients homozygous for TPMT deficiency: give only 10 mg/m<sup>2</sup>/day of 6-Thioguanine.

2- Patients heterozygous for TPMT deficiency:

– Do not adapt and give full dose of 6-Thioguanine

– Monitor: if next phase of chemotherapy is delayed diminish the dose by 50% and reevaluate

– **Cytarabine: 75 mg/m<sup>2</sup>/infusion as push i.v. from Day 31 to Day 34 and from Day 38 to Day 41 (total 8 doses)**

– **Cyclophosphamide: 1g/m<sup>2</sup>, intravenously over 60 min on Day 29**

○ Give Mesna (400 mg/m<sup>2</sup>/dose) before and at hour 4 and 8 after start of cyclophosphamide infusion

○ During these 8 hours, hyperhydratation (1 liter/m<sup>2</sup> / 8h) followed by oral hyperhydratation for the remaining 16 hours.

– **Methotrexate IT: on Day 4 and Day 31**

The dosage depends on the age of the patient. Guidelines for intrathecal administration of methotrexate are available in **Appendix 5**.

**T-SR group: Maintenance (Figure 28) not earlier than Day 57 of previous phase**

The total duration of the maintenance phase will be around 76 weeks. Maintenance is to be stopped at week 104 from D1 of ALL treatment.

**Criteria to begin the maintenance: PNN/mm<sup>3</sup> ≥1.000 PNN/mm<sup>3</sup> and Platelets ≥ 100.000/mm<sup>3</sup>**

**Figure 28: Flow scheme of T-SR maintenance treatment**

## **CAALL-F01:T-SR Continuation therapy « maintenance »**

- Up to week 104.
- No pulses
- 6MP 50 mg/m<sup>2</sup>/day
- MTX 25 mg/m<sup>2</sup>/week

Indications of cranial Radiotherapy (RT): **NO**

**Patients with initial WBC <100 G/L:**

6 ITmtx: every 6 weeks beginning week 2 of maintenance

**Patients with initial WBC ≥100 G/L:**

6 HD-MTX + 6 ITmtx: every 6 weeks beginning week 2 of maintenance. *See annex 5*

*NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX*

- **No pulses will be administered neither cranial radiotherapy.**

**All patients will receive oral maintenance treatment combining**

- 6-mercaptopurine: 50 mg/m<sup>2</sup>/day per os up to week 104
- Methotrexate: 25 mg/m<sup>2</sup> once a week per os up to week 104

***See Appendix 11 for dose modification/adaptation of 6MP/MTX***

***NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX***

**In addition, for patients with WBC < 100 G/L at diagnosis**

- **Methotrexate IT:** 1 administration every 6 weeks to be started on week 2 of the maintenance phase for 6 administrations (week 2, week 8, week 14, week 20, week 26, week 32)  
The dosage depends on the age of the patient. Guidelines for intrathecal administration of methotrexate are available in **Appendix 5**.

**In addition, for patients with WBC≥ 100 G/L at diagnosis**

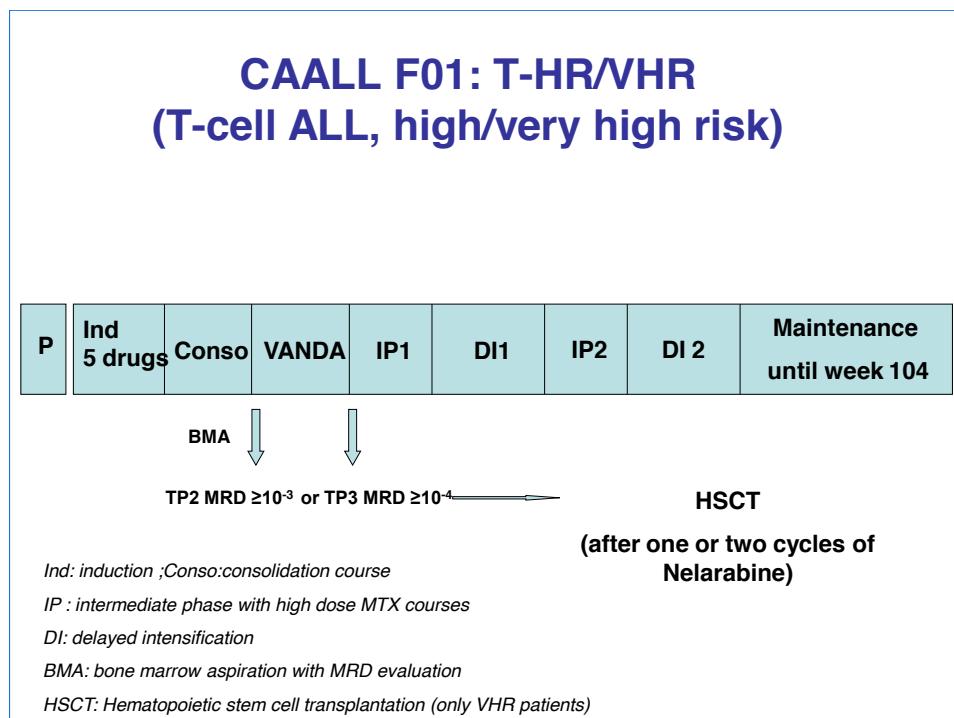
- **HD methotrexate** (5 g/m<sup>2</sup> i.v. over 24 hours with leucovorin rescue beginning at **H42**): 1 administration every 6 weeks beginning on week 2 of the maintenance phase for 6 administrations (week 2, week 8, week 14, week 20, week 26, week 32).  
Guidelines for HD methotrexate administration and leucovorin rescue are available in **Appendix 8**.  
**No oral methotrexate is to be given the week of HD-MTX course**
- **Methotrexate IT:** at H24 of each course of HD-MTX (total 6 ITs).

The dosage depends on the age of the patient. Guidelines for intrathecal administration of methotrexate are available in **Appendix 5**.

### 5.2.2 T-High Risk/very high (T-H/VHR) Group

Treatment overview of the T-H/VHR group is displayed in Figure 29.

**Figure 29: Treatment flow chart of the T-H/VHR group**



### **If CNS3 status**

**Add Triple IT on Day 4 and Day 9 for a total of 5 IT during induction (D1, D4, D9, D13, D24) and add Triple IT on Day 16 and Day 46 during consolidation (D3, 16, 31, 46) & refer to Appendix 5.**

These patients will also receive 6 courses of HD methotrexate during the maintenance phase (refer to **Appendix 8**)

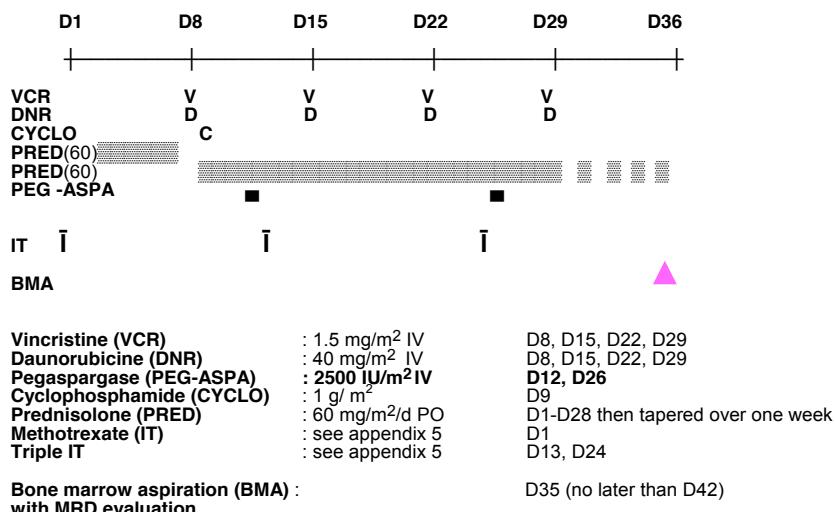
### **If WBC >100 G/L**

These patients will also receive 6 courses of HD methotrexate during the maintenance phase (refer to **Appendix 8**)

### **T-HR group: Induction phase (Figure 30)**

**Figure 30: Flow scheme of T-HR induction treatment**

## **CAALL-F01: T-HR INDUCTION THERAPY**



The treatment will be administered as follows:

### **Prephase**

- **Prednisolone: 30 mg/m<sup>2</sup> every 12 hours per os from Day 1 to Day 7 (total 14 doses).** IV methyl prednisolone at the same dose can be an alternative.
- **Methotrexate IT: Day 1**

The dosage depends on the age of the patient. Guidelines for methotrexate for intrathecal administration are available in **Appendix 5. In case of initial Traumatic Lumbar Puncture or CNS2 status, intensified CNS prophylaxis during induction phase is mandatory according to guidelines in Appendix 5.**

**NB: if WBC ≥ 100 000/mm<sup>3</sup> refer to appendix 10**

**On Day 8, the prednisone response is to be evaluated on a blood-smear. A good response is defined as less than 1000 blast cells per mm<sup>3</sup> in the peripheral blood.**

### **Induction therapy from Day 8**

- **Prednisolone: 30 mg/m<sup>2</sup> x 2/day per os from Day 8 to Day 28 (total 42 doses), then tapered over one week**
- **Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 8, 15, 22 and 29.**

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

A neurological examination will be performed before every administration.

- **Daunorubicin 40 mg/m<sup>2</sup> on Day 8, 15, 22 and 29**

Daunorubicin will be administered intravenously over 60 min.

– **Pegaspargase**

Oncaspar® will be administered intravenously over 60 min.

➤ **ONCASPAR®:2 500 IU/m<sup>2</sup> /day on Day 12 and Day 26**

Guidelines for ONCASPAR® use are available in **Appendix 7**

**If Pegaspargase infusion is not performed at Day 12 or Day 26 see warning at Section 3.1**

In case of allergy and/or clinical reaction during Oncaspar infusion, refer to Appendix 7

- **Cyclophosphamide: 1g/m<sup>2</sup>, intravenously over 60 min on Day 9**
  - Give Mesna (400 mg/m<sub>2</sub>/dose) before and at hour 4 and 8 after start of cyclophosphamide infusion
  - Hyperhydratation (3 liters/m<sup>2</sup> /24h) for prevention of Tumor Lysis Syndrome (appendix 10) and prevention of hematuric cystitis
- **Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine): Day 13 and 24.**

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5. In case of initial Traumatic Lumbar Puncture or CNS2 status, intensified CNS prophylaxis during induction phase is mandatory, according to guidelines in Appendix 5.**
- **For patients with initial CNS3 status, supplementary triple ITs are mandatory on Day 4 and Day 9, for a total of 5 ITs during induction therapy (Day 1, 4, 9, 13, 24).**

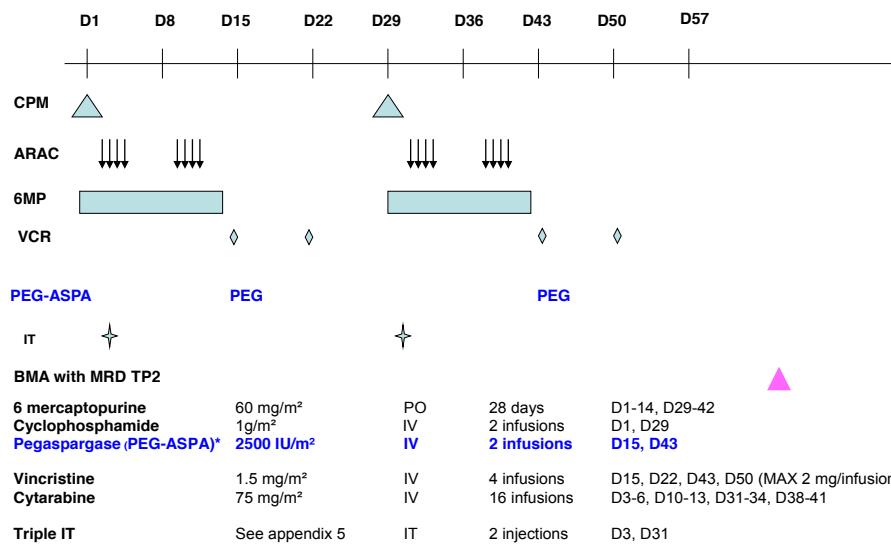
**Warning: Intensified inductions (5 drugs) have been linked to an increased incidence of infectious complications (bacteria and fungi). Prevention and empirical treatment of fungal infections are to be considered avoiding azoles due to the concomitant use of vincristine.**

### **T-HR group: Consolidation (Figure 31)**

**Criteria to begin the course:** D35-42 bone marrow showing complete remission (M1 marrow) AND  $\geq 1000$  PNN/mm $^3$  and Platelets  $\geq 100.000/\text{mm}^3$ . *In case of induction failure (M2 ou M3 marrow) at D35-42 begin consolidation whatever the blood count if clinical condition is adequate.*

**Figure 31: Flow scheme of T-HR consolidation treatment**

## **CAALL-F01: T-HR CONSOLIDATION**



The treatment will be administered as follows:

- **Cyclophosphamide: 1g/m $^2$ , intravenously over 60 min on D1 and D29**
  - Give Mesna (400 mg/m $^2$ /dose) before and at hour 4 and 8 after start of cyclophosphamide infusion
  - During these 8 hours, hyperhydratation (1 liter/m $^2$  / 8h) followed by oral hyperhydratation for the remaining 16 hours.
- **Cytarabine: 75 mg/m $^2$ /infusion as push i.v. on D3 to D6, D10 to D13, D31 to D34 and Day 38 to Day 41 (total 16 doses)**
- **6-mercaptopurine: 60 mg/m $^2$ /day per os from Day 1 to Day 14 and Day 29 to D42 (total 28 doses)**

- 1- Patients homozygous for TPMT deficiency: give only 10 mg/m $^2$ /day of 6-mercaptopurine.
  - 2- Patients heterozygous for TPMT deficiency:
    - Do not adapt and give full dose of 6-mercaptopurine
    - Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate
- **Vincristine: 1.5 mg/m $^2$  (max total dose: 2 mg) on Day 15 and Day 22, D43 and D50**

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.
- **Pegasparagase: ONCASPAR® 2 500 IU/m $^2$  /day on Day 15 and D43 (over 60 mn IV)**
  - Guidelines for ONCASPAR® use are available in **Appendix 7**
  - In case of allergy and/or clinical reaction during Oncaspar infusion, refer to Appendix 7r
- **Triple IT (hydrocortisone-methotrexate-cytarabine) on Day 3 and Day 31.**

**For patients with CNS3 status, supplementary triple ITs are to be given on Day 16 and Day 46) (see Appendix 5)**

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

**NB: Administration of the second part of the cycle (from D29) should begin only if good clinical status and WBC over 1 G/L**

**After recovery from consolidation, the VANDA protocol will be administrated:**

NB: Do not forget the TP2 MRD evaluation before VANDA.

**Criteria to begin the VANDA:** no ongoing infection, PNN  $\geq 1.000/\text{mm}^3$  and Platelets  $\geq 100.000/\text{mm}^3$

**Warning: Severe infectious complications often occur during this phase.**

The treatment will be administered as follows (Figure 32).

**Figure 32: Flow scheme of VANDA**

	D1	D2	D3	D4	D5	D6
<b>Dexamethasone</b>						
<b>Cytarabine</b>						
<b>Mitoxantrone</b>						
<b>Etoposide</b>						
<b>Pegasparagase</b>						<b>PEG</b>
<b>Triple IT</b>						
<b>Dexamethasone</b>	20 mg/m <sup>2</sup> in 2 takes	PO	5 days		<b>D1-D5</b>	
<b>Dexamethasone</b>	10 mg/m <sup>2</sup> in 2 takes	PO	1 day		<b>D6</b>	
<b>Cytarabine</b>	2 g/m <sup>2</sup> every 12 hours	IV (3h)	2 days		<b>D1 D2</b>	
<b>Mitoxantrone</b>	8 mg/m <sup>2</sup>	IV (1h)	2 days		<b>D3 D4</b>	
<b>Etoposide</b>	150 mg/m <sup>2</sup>				<b>D3 D4 D5</b>	
<b>Pegasparagase</b>	<b>2500 IU/m<sup>2</sup></b>	<b>IV (1h)</b>	<b>1 day</b>		<b>D6</b>	
<b>Triple IT</b>	see Appendix 5	intrathecal	1 day		<b>D5</b>	

- **Dexamethasone: 20 mg/m<sup>2</sup>/day per os (divided in 2 intakes) from Day 1 to Day 5 and 10 mg/m<sup>2</sup> on Day 6.**
- **Cytarabine: 2 g/m<sup>2</sup>/infusion over 3 hours x 2, 12 hours apart, on Day 1, and Day 2**
- **Mitoxantrone: 8 mg/m<sup>2</sup>/infusion over 1 hour on Day 3 and on Day 4**
- **Etoposide (VP16): 150 mg/m<sup>2</sup>/infusion over 1 hour on Day 3, Day 4 and Day 5**

– **Pegasparagase**

Oncaspar® will be administered intravenously over 60 min.

➤ **ONCASPAR® 2 500 IU/m<sup>2</sup> on Day 6**

Guidelines for ONCASPAR® use are available in **Appendix 7**.

- **Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine) on Day 5**

- The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

### **T-HR: Interim Phase 1 (Figure 33)**

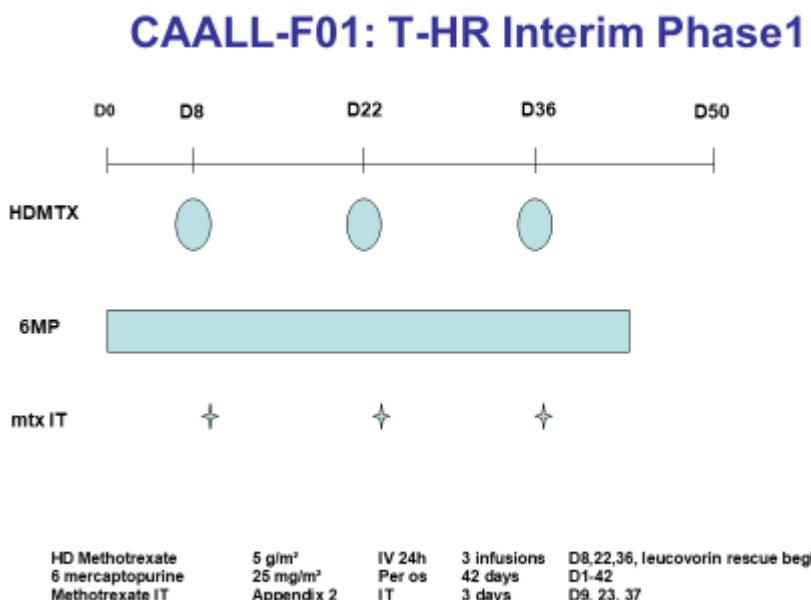
Criteria to begin the M phase: MRD TP2 <  $10^{-3}$  AND PNN  $\geq 1000/\text{mm}^3$  and Platelets  $\geq 100.000/\text{mm}^3$

Criteria for each course of HD methotrexate: PNN  $\geq 500/\text{mm}^3$  and Platelets  $\geq 50.000/\text{mm}^3$ . If these criteria are not met = stop 6-Mercaptopurine which is to be reintroduced after the beginning of HD methotrexate

#### **Warning for Risk stratification:**

- 1. MRD TP3 is to be performed before Interim Phase 1 if MRD TP2 is detectable (whatever the value)**
- 2. If MRD TP3  $\geq 10^{-4}$** 
  - Stop interim phase
  - Begin a Nelarabine course (see Section 5.2.3), no earlier than D15 of interim course, i.e. 7 days after HD MTX, for concerns of potential added neurotoxicity
  - Program HSCT

**Figure 33: Flow scheme of T-HR interim phase 1 treatment**



The treatment will be administered as follows:

**HD methotrexate: 5 g/m<sup>2</sup> i.v. over 24 hours with leucovorin rescue beginning at H42, on Day 8, 22\*, and 36.** \*As a recall HDMTX at D22 is to be performed only if TP3 < 10<sup>-4</sup>. If not see above how to proceed to HSCT programming

Guidelines for HD methotrexate administration and leucovorin rescue are available in **Appendix 8**.

- **6-mercaptopurine: 25 mg/m<sup>2</sup>/day per os from Day 1 to Day 42**

- 1- Patients homozygous for TPMT deficiency: give only 4 mg/m<sup>2</sup>/day of 6-mercaptopurine.
- 2- Patients heterozygous for TPMT deficiency:
  - Do not adapt and give full dose of 6-mercaptopurine
  - Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate

- **Methotrexate IT on Day 9, 23 and 37**

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

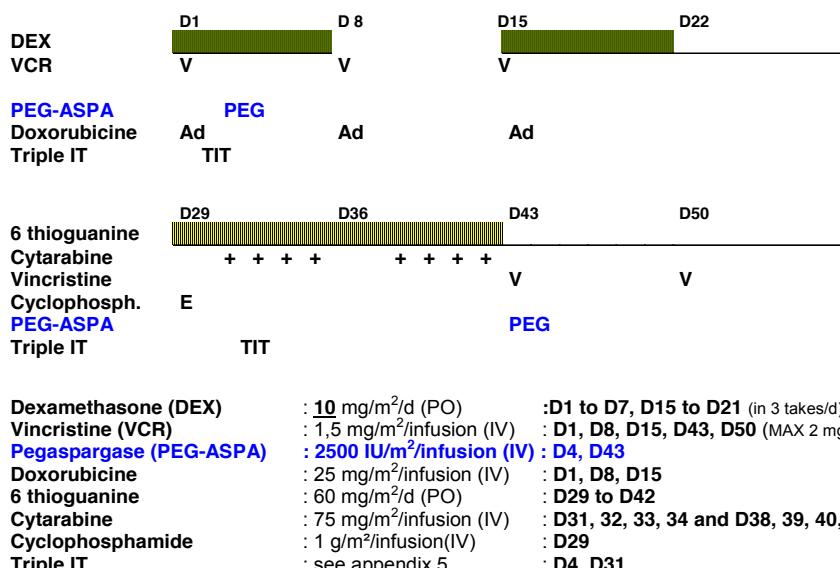
**T-HR group: Delayed intensification 1 (Figure 34) (not earlier than D56 of previous phase)**

Criteria to begin each phase of the course (D1 and D29): PNN/mm<sup>3</sup> ≥ 1000 and Platelets ≥ 100.000/mm<sup>3</sup>

**Warning: infectious complications often occur during this phase particularly between D15 and D28 and D43-D57**

**Figure 34: Flow scheme of T-HR delayed intensification 1 treatment**

### **CAALL-F01: T-HR DELAYED INTENSIFICATION 1**



The treatment will be administered as follows:

- **Dexamethasone: 10 mg/m<sup>2</sup>/day per os (divided in 3 intakes) from Day 1 to Day 7 and from Day 15 to Day 21**
- **Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 1, 8, 15, 43 and 50**

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

- **PEG-L-asparaginase**

Oncaspar® will be administered intravenously over 60 min.

- **ONCASPAR®: 2 500 IU/m<sup>2</sup> /day on Day 4 and Day 43**

Guidelines for ONCASPAR® use are available in **Appendix 7**

- **Doxorubicin: 25 mg/m<sup>2</sup>/infusion on Day 1, 8 and 15**

Doxorubicin will be administered intravenously over 60 min.

- **6-Thioguanine: 60 mg/m<sup>2</sup>/day per os from Day 29 to Day 42**

- 1- Patients homozygous for TPMT deficiency: give only 10 mg/m<sup>2</sup>/day of 6-Thioguanine.
- 2- Patients heterozygous for TPMT deficiency:
  - Do not adapt and give full dose of 6-Thioguanine
  - Monitor: if next phase of chemotherapy is delayed diminish the dose by 50% and reevaluate

- **Cytarabine: 75 mg/m<sup>2</sup>/infusion as push i.v. on Day 31 to Day 34 and Day 38 to Day 41**

- **Cyclophosphamide: 1g/m<sup>2</sup>, intravenously over 60 min on Day 29**

- Give **Mesna** (400 mg/m<sup>2</sup>/dose) before and at hour 4 and 8 after start of cyclophosphamide infusion
- During these 8 hours, hyperhydratation (1 liter/m<sup>2</sup>/ 8h) followed by oral hyperhydratation for the remaining 16 hours.

- **Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine) on Day 4 and Day 31**

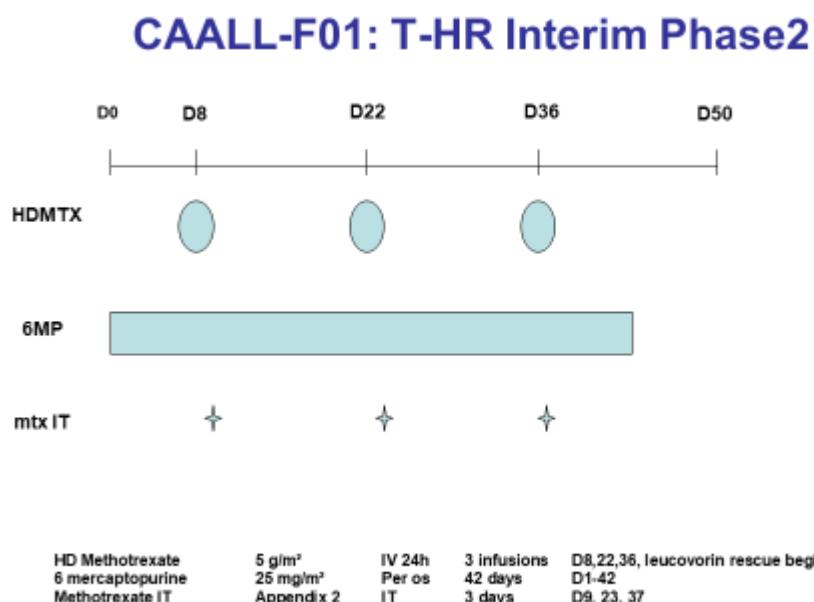
The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

**T-HR: Interim Phase 2 (Figure 35) not earlier than Day 57 of previous phase**

**Criteria to begin the M Phase:** PNN  $\geq 1000/\text{mm}^3$  and Platelets  $\geq 100.000/\text{mm}^3$

Criteria for each course of HD methotrexate: PNN  $\geq 500/\text{mm}^3$  and Platelets  $\geq 50.000/\text{mm}^3$ . If these criteria are not met = stop 6-Mercaptopurine which is to be reintroduced after the beginning of HD methotrexate

**Figure 35: Flow scheme of T-HR interim phase 2 treatment**



The treatment will be administered as follows:

- **HD methotrexate: 5 g/m<sup>2</sup> i.v. over 24 hours with leucovorin rescue beginning at H42, on Day 8, 22, and 36.**

Guidelines for HD methotrexate administration and leucovorin rescue are available in **Appendix 8**.

- **6-mercaptopurine: 25 mg/m<sup>2</sup>/day per os from Day 1 to Day 42**

- |   |
|---|
| 1- Patients homozygous for TPMT deficiency: give only 4 mg/m <sup>2</sup> /day of 6-mercaptopurine. |
| 2- Patients heterozygous for TPMT deficiency:   |
| – Do not adapt and give full dose of 6-mercaptopurine   |
| – Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate            |
- **Methotrexate IT on Day 9, 23 and 37**

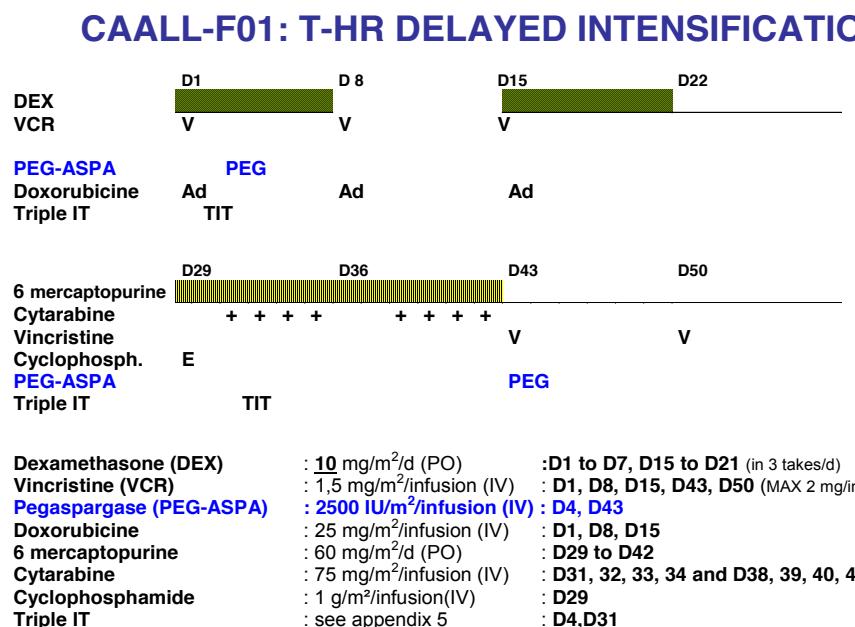
The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

**T-HR group: Delayed intensification 2 (Figure 36) (not earlier than D56 of previous phase)**

**Criteria to begin each phase of the course (D1 and D29): PNN/mm<sup>3</sup>  $\geq 1000$  and Platelets  $\geq 100.000/\text{mm}^3$**

**Warning 1: Infectious complications often occur during this phase particularly between D15 and D28 and D43-D57**

**Warning 2: The 6 mercaptopurine and not the 6 thioguanine is used (VOD risk reduction)**

**Figure 36: Flow scheme of T-HR delayed intensification 2 treatment**

The treatment will be administered as follows:

- **Dexamethasone: 10 mg/m<sup>2</sup>/day per os (divided in 3 intakes) from Day 1 to Day 7 and from Day 15 to Day 21**
- **Vincristine: 1.5 mg/m<sup>2</sup> (maximum total dose: 2 mg) on Day 1, 8, 15, 43 and 50**

Vincristine should be administered IV over 5 to 10 min. It is extremely important to be sure that the injection is strictly intravenous.

– **PEG-L-asparaginase**

Oncaspar® will be administered intravenously over 60 min.

➤ **ONCASPAR®: 2 500 IU/m<sup>2</sup> /day on Day 4 and Day 43**

Guidelines for ONCASPAR® use are available in **Appendix 7**

- **Doxorubicin: 25 mg/m<sup>2</sup>/infusion on Day 1, 8 and 15** (intravenously over 60 min).
- **6-mercaptopurine: 60 mg/m<sup>2</sup>/day per os from Day 29 to Day 42**

1- Patients homozygous for TPMT deficiency: give only 10 mg/m<sup>2</sup>/day of 6-mercaptopurine.

2- Patients heterozygous for TPMT deficiency:

- Do not adapt and give full dose of 6-mercaptopurine
- Monitor: if delayed next phase of chemotherapy diminish the dose by 50% and reevaluate

**Cytarabine: 75 mg/m<sup>2</sup>/infusion as push i.v. on Day 31 to Day 34 and Day 38 to Day 41**

– **Cyclophosphamide: 1g/m<sup>2</sup>, intravenously over 60 min on Day 29**

- Give Mesna (400 mg/m<sup>2</sup>/dose) before and at hour 4 and 8 after start of cyclophosphamide infusion
- During these 8 hours, hyperhydratation (1 liter/m<sup>2</sup> / 8h) followed by oral hyperhydratation for the remaining 16 hours.

– **Triple IT (hydrocortisone hemisuccinate-methotrexate-cytarabine) on Day 4 and Day 31**

The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

**T-HR group: Maintenance (Figure 37) not earlier than Day 57 of previous phase****Criteria to begin the course: PNN/mm<sup>3</sup> ≥1000 and Platelets ≥ 100.000/mm<sup>3</sup>**

Figure 37: Flow scheme of T-HR maintenance treatment

## **CAALL-F01:T-HR Continuation therapy « maintenance »**

- 52 weeks (total duration of the treatment: 104 weeks)
- No pulses
- 6MP 50 mg/m<sup>2</sup>/day
- MTX 25 mg/m<sup>2</sup>/week

Indications of cranial Radiotherapy (RT): **NO**

**Patients with initial WBC <100 G/L:**

6 ITmtx: every 6 weeks from beginning week 2 of maintenance

**Patients with initial WBC ≥100 G/L:**

6 HD-MTX + 6 ITmtx : every 6 weeks beginning week 2 of maintenance

*See Appendix 5*

**NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX**

The maintenance will be stopped at week 104 (total duration of ALL treatment: 2 years)

*No pulses will be administered neither cranial radiotherapy.*

**All patients will receive oral maintenance treatment combining**

- 6-mercaptopurine: 50 mg/m<sup>2</sup>/day per os up to week 104
- Methotrexate: 25 mg/m<sup>2</sup> once a week per os up to week 104

*See Appendix 11 for dose modification/adaptation of 6MP/MTX*

**NB: Bactrim® is to be given during the whole duration of maintenance and at least 3 months after stopping of 6MP/MTX**

**In addition, for patients with initial WBC/mm<sup>3</sup> < 100 G/L**

- **IT Methotrexate:** 1 administration every 6 weeks beginning on week 2 of the maintenance phase for 6 administrations (week 2, week 8, week 14, week 20, week 26, week 32).  
The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5.**

**In addition, for patients with initial WBC/mm<sup>3</sup> ≥100 G/L and for patients with initial CNS3 status**

- **HD methotrexate** (5 g/m<sup>2</sup> i.v. over 24 hours with leucovorin rescue beginning at H42): 1 administration every 6 weeks beginning on week 2 of the maintenance phase for 6 administrations (week 2, week 8, week 14, week 20, week 26, week 32).

Guidelines for HD methotrexate administration and leucovorin rescue are available in **Appendix 8.**

**No oral methotrexate is to be given the week of HD-MTX course**

**IT methotrexate:** at **H24** of each course of HD-MTX (total 6 ITs). The dosages depend on the age of the patient. Guidelines for intrathecal administration are available in **Appendix 5**.

### 5.2.3 Patients with T-lineage ALL eligible for Hematopoietic stem cell transplantation

- **Criteria**
  1. **T-lineage with minimum residual disease  $\geq 10^{-3}$  on Time Point 2 (SR pts: Day 80; HR: Day 95)**
  2. **T-lineage with minimum residual disease  $\geq 10^{-4}$  on Time Point 3 (after the VANDA course)**
  3. **T-lineage with D8 PPR and TP1 minimum residual disease  $\geq 10^{-2}$  (i.e. after induction therapy)**
- These patients are candidate to HSCT and have already received one course of VANDA.
- One or 2 courses of Nelarabine are to be given before HSCT to reduce the MRD as much as possible before HSCT. Thus a control of MRD should be performed at least after the VANDA course (TP3) and before HSCT.
- **Criteria to begin the Nelarabine course: PNN  $\geq 1000/\text{mm}^3$  and Platelets  $\geq 100.000/\text{mm}^3$**

The treatment will be administered as follows (Figure 38):

- **Nelarabine:  $650 \text{ mg/m}^2/\text{day}$  intravenously over 60 min from Day 1 to Day 5**

**Warnings: Potential neurotoxicity (see Appendix 9).**

- **no IT between D-7 and D15 of each cycle of Nelarabine**

Figure 38: Flow scheme of the Nelarabine course

## CAALL-F01:T-VHR (T-cell ALL/Very High Risk)

### NELARABINE consolidation course

	D1	D2	D3	D4	D5
Nelarabine					

Nelarabine       $650 \text{ mg/m}^2/\text{day}$       IV (1h)      5 days      D1-D5

*NB: no IT is to be given during any nelarabine cycle from D-7 to D+15*

- According to transplant availability one or two courses can be given.
- If a second course is given, it should begin at D21 after the first day of course 1

### 5.3 Synthesis for special situations

#### 5.3.1 CNS involvement: Issues, definitions and treatment

Please refer to **Appendix 5**.

#### 5.3.2 Down syndrome

The expected rate of patients with Down syndrome is around 2%.

Due to the risk of infection and worse tolerance to chemotherapy, particularly methotrexate, the following measures apply to these children:

- inclusion in CALL-F01: possible

- **randomization: no**
- **initial group of treatment** (whatever age, leucocytosis, phenotype, cytogenetics): **B-lineage Standard Risk group**
- **initial dose of pegaspargase 2500 IU/m<sup>2</sup>, one dose at D12 during induction**
- **second dose and further doses of pegaspargase: 1250 IU/m<sup>2</sup> during consolidation (D8, D36 and D64) and delayed intensification (D4)**
- **secondary assessment (D42-50)**
  - if no IKZF1 deletion / mutation, no CNS3 status, and MRD-TP1 < 10<sup>-3</sup>: stay in B-SR group
  - if IKZF1 deletion/mutation and/or CNS3 and/or MRD-TP1 ≥ 10<sup>-3</sup>: go to B-MR group and/or T-cell phenotype. M phase to be performed with 4 cycles of 0.5 g/m<sup>2</sup> with leucovorin rescue beginning at H42.
- intrathecal injections
  - Simple IT for all patients whatever SR group or MR group.
  - only the exceptional CNS+ pts will be candidate to receive triple IT except during M phase and maintenance (simple ITs)
  - In case of mucositis associated to ITs, consider to add leucovorin rescue 15mg/m<sup>2</sup> at H24 and H36 post IT

### 5.3.3 Hematopoietic stem cell transplantation (HSCT)

**Indications of HSCT are related either to very high-risk cytogenetics and/or response.**

- ***Indications according to genetics:***
  - B-lineage:
    - Hypodiploidy < 40 chromosomes
    - t(17;19)/E2A-HLF
    - MLL rearrangement and NCI-HR
  - T-lineage:
    - no indication
- ***Indications according to response :***
  - B lineage :
    - MR/HR induction failure with MRD-TP1 ≥ 5 × 10<sup>-2</sup>
    - MRD-TP2 ≥ 10<sup>-3</sup>
  - T-lineage :
    - D8 PPR and MRD-TP1 ≥ 10<sup>-2</sup>
    - MRD-TP2 ≥ 10<sup>-3</sup>
    - MRD-TP3 \*≥ 10<sup>-4</sup> (\*TP3: performed if TP2 ≥ 10<sup>-4</sup>)

***HSCT will be performed according to international guidelines (I-BFM-HSCT) or ongoing protocol at CAALL-F01 opening (FORUM trial).***

### 5.3.4 Allergy

Modification for allergy to Oncaspar is detailed in **Appendix 7**

### 5.4 Ancillary treatments

Guidelines for the treatments of nausea-vomiting, hyperhydration, prevention of tumoral lysis syndrome, transfusions, care of an out-patient with infection, are available in **Appendix 10**.

## 5.5 Study /Treatment : modifications, interruptions, discontinuation, duration

- For patients who do not tolerate the protocol-specified dosing schedule, dose delays are permitted in order to allow the patient to continue the study treatment but should be limited. Except if justified, no intensive chemotherapy dose reductions are recommended.

**In case of prolonged SAE precluding the beginning of the next phase of protocole, a waiting chemotherapy should be undertaken for a limited period of time (< 2 weeks) until resolution of the SAE, the main idea being the non interruption of the leukemia treatment. The nature of this chemotherapy depends of the nature of the SAE and could be discussed with the Coordinators**

All these changes must be recorded on the eCRF.

- Dose modification for maintenance treatment are detailed in **Appendix 11**
- Modification for allergy to Oncaspar is detailed in **Appendix 7**
- Study discontinuation for a given patient will occur if:
  - No CR is reached, as defined in **Section 6**, at the end of the consolidation phase
  - A persistent severe toxicity (non-hematological) occurs. Withdrawing from the study should be done only after discussion with the study coordinators
  - Patient and/or parents withdraw his/their consent- No further follow-up will be provided.

***In all these cases, overall follow up is to be provided (status -alive/dead-, CR/no CR, relapse).***

## 5.6 Concomitant medications

Oral contraceptives are prohibited during the intensive phases of the treatment containing pegaspargase. They should be used with caution during maintenance treatment. Alternative contraception methods are to be used anyway throughout the treatment and at least 3 months days after the end of treatment. Progestins can be used to limit hemorrhagic menstrua during intensive therapy but not as a reliable contraceptive because of drug interactions.

Any comedication during chemotherapy should be administered after cautious checking of known interactions. See **Appendix 7, 8 and 9** for drug summaries including drug interactions.

## 5.7 Study drug :

### 5.7.1 Study drug presentation

The IMPs called **Oncaspar®** (pegaspargase), E.U. License No. EU/1/15/1070/001 and EU/1/15/1070/002..

From opening of the study until an estimated date as end of February 2019, this IMP is a **sterile solution for injection**, in a single-use vial, containing **3,750 International Units** of L-asparaginase **in 5 mL**. From an estimated date as of beginning of March 2019, the IMP as a solution will be progressively replaced by a powder for solution for injection (lyophilisate), also in a single-use vial, containing **3,750 International Units** of L-asparaginase. Each vial should be reconstituted with 5.2 mL of water for injection to obtain a solution at 750 UI/mL. The final concentration is the same for the two formulations.

From an estimated period ranging from March to October 2019, the 2 forms will be available. During this period:

- patients already treated with the ONCASPAR solution will continue with the solution
- any new treatment (from inclusion) will start with the ONCASPAR lyophilisate

The purpose is to avoid, as much as possible, the switch from one form to the other. However, from an estimated date as of November 2019, the solution will not be available any more. A few patients may not have ended their treatment yet and should then switch from solution to lyophilisate.

### 5.7.2 Study drug importation, labeling and shipping

After importation and European batch release, the manufacturer will provide the ONCASPAR® batches to the sponsor's GMP certified European CMO.

This CMO will be in charge of:

- French labelling according to regulatory requirements and certification of the units for the CAALL F01 trial
- Shipping to the hospital pharmacies.

A patient card will be supplied to subjects at entry, indicating names of study, sponsor, investigational site, and telephone contacts.

#### **5.7.3 Study drug supply and storage**

Each local pharmacy initial stock will be adapted to the predictable inclusion rate of the center.

***Due to the very short shelf life of the drug in solution (less than 6 months at receipt), the local stock will be exchanged regularly.***

The re-supply will be automatically triggered every other month on receipt of a new lot from the manufacturer.

From an estimated date as of March 2019, Oncaspar® is also provided as a new freeze dried presentation. This powder for solution for injection has a longer shelf life (2 years).

Oncaspar® is to be stored under refrigeration at 2°C to 8°C. Product must not be shaken or frozen.

#### **5.7.4 Study drug preparation and dispensation**

A prescription specifically designed for the trial will be available in the eCRF.

***\*Doses vary according to stratification group and/or randomization and are specified in the protocol and on the prescription.***

✓ Preparation

In this trial, Oncaspar® is administered IV over 1 hour.

Each hospital pharmacy will be in charge of the preparation by dilution of **of the required dose in sodium chloride or 5% dextrose solution for injection**.

According to stability data obtained for Oncaspar, final concentration should be between 11.25 and 62.5 UI/ml. Final volume will depend on total dose (ie body surface and posology): 25, 50 or 100 ml.

The administration has to be performed through an infusion that is already running.

✓ Dispensing

The treatment will be dispensed by the hospital pharmacy on the basis of the prescription signed by one of the study investigators.

#### **5.7.5 Study drug compliance and accountability**

Reception of Oncaspar® vials into each center pharmacy will be recorded on a pharmaceutical logbook. The temperatures and storage conditions will be registered by the pharmacist responsible for the CAALL-F01 study in each center. Controls of these conditions and temperature will be monitored regularly throughout the study. The pharmacist will also record in the pharmaceutical logbook each receipt, dispensing and return of treatment.

✓ Treatment administration.

Each treatment administration will be recorded in the e-CRF.

#### **5.7.6 Disposal and destruction**

The delivered, used and recovered quantities of product will be recorded, reconciled and verified by the sponsor in each trial site.

Destruction of unused investigational medicinal products will be carried out for a given trial site only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted.

Recording of destruction operations will be carried out in such a manner that all operations may be accounted for. The records should be kept by the Sponsor.

## 5.8 Imatinib

After induction, the rare patients (< 5% of patients) with suboptimal response to therapy (induction failure or MRDTP1  $\geq 10^{-3}$ ) and ABL-class fusions ALLs will receive imatinib in addition to chemotherapy.

Imatinib will be prescribed according to posology for treatment of Ph+ ALL in children: 340 mg/m<sup>2</sup>/d, not to exceed 600 mg/d. Treatment will be stopped during HD-MTX courses.

Imatinib is available as 100 mg and 400 mg tablets, from different manufacturers. It won't be provided by sponsor. Instead, in accordance with article D. 5125-45-1 of the French "Code de la Santé Publique", a prescription will be made to patients who will get the drug at their usual pharmacies.

Center will also provide a dedicated form to trace dispensation by local pharmacist as the same time as the imatinib prescription. Patients will be asked to give this form to their pharmacists along with the prescription. Pharmacists will fill the form with the requested information including: lot number, quantity and dispensation date. Completed forms will be kept by the patient representatives and regularly collected by investigational centers and joined to patient file to ensure sufficient traceability of the treatment

## 6 Response criteria

### 6.1 Response to prephase

Determination of the number of leukemic blasts in peripheral blood at D8 i.e. the end of the prephase after systemic therapy with corticosteroids and one dose of intrathecal methotrexate on day 1

- Prephase good responders: patients with < 1000 leukemic blasts/mm<sup>3</sup> at the end of the prephase (D8)
- Prephase poor responders: patients with ≥1000 leukemic blasts/mm<sup>3</sup> at the end of the prephase (D8)

### 6.2 Response criteria after induction (D35-42: TP1) and consolidation (TP2)

#### 6.2.1 Hematological response

The hematological response depends on the internationally accepted bone marrow status (M1-M3) assessed by classical cytomorphologic methods.

- M1 (< 5% leukemic cells) \*: hematological CR
- M2 ( ≥ 5% and ≤ 25% leukemic cells : non hematological CR
- M3 ( > 25% leukemic cells): non hematological CR

\*The cytomorphologic analysis is reinforced by the first MRD Time Point which should be < 5.10<sup>-2</sup>; the cellularity should be normal or moderately reduced with signs of recovering myelopoiesis and thrombopoiesis. In case of hypoplastic bone marrow with cytopenia in the peripheral blood, the bone marrow sampling has to be repeated after one week.

#### 6.2.2 Minimal Residual Disease (MRD)

- Adequate MRD reponse definition varies according to groups and time-points
  - see tables 3,3bis, 5 and 6 +++

#### 6.2.3 Extra-hematological remission status

The extra-hematological remission status depends on:

- The absence or presence of blasts in the CSF
- The absence or persistence of a residual mass with Good partial response if the residual mass is < 30% of the initial diameter in one tumor site and No extra-hematological CR if the residual mass is ≥ 30% of the initial diameter (the real nature of the mass has to be determined (biopsy if possible, PET scan)

#### 6.2.4 Treatment failure

Treatment failure is defined after induction at day 35-day 42, by at least 5% blasts and MRD >= 5x10<sup>-2</sup>. In case of no available MRD, only the >=5% blasts criterion will be required.

### 6.3 Definition of relapse

#### 6.3.1 Isolated bone marrow relapse is defined as

- Reappearance of 5% or more leukemic blasts cells in the bone marrow, assessed by morphology and confirmed by immunophenotyping and molecular MRD (mandatory for blast content ranging from 5% to 20%  
AND
- Absence of leukemic infiltration out of the bone marrow and blood

**6.3.2 Isolated extramedullary relapse is defined as**

- Presence of leukemic infiltration out of the bone marrow or blood, preferably confirmed by immunophenotyping of an uncontested leukemic clone and/or genotyping (PCR quantitation of a clonal marker)  
AND
- < 5% leukemic blasts in the bone marrow assessed by morphology and confirmed by immunophenotyping and/or genotyping (PCR quantitation of a clonal marker)

**6.3.3 Combined relapse is defined as**

- ≥ 5% or more leukemic blasts cells in the bone marrow, assessed by morphology and confirmed by immunophenotyping and molecular MRD (PCR quantitation of a clonal marker)
- Presence of leukemic infiltration elsewhere, preferably confirmed by immunophenotyping and molecular MRD (PCR quantitation of a clonal marker)

## 7 Visit Schedule and Assessments

### 7.1 Patient demographics and other baseline characteristics

The investigator must not start any study related procedure before the Informed Consent Form is signed and dated by both the patient (or both parents/legal representative, if applicable) and the investigator. Upon signature of the Informed Consent Form, the investigator will confirm the registration of the patient for study participation sending the Enrolment Confirmation form to the Clinical Research Unit (see **Section 3.6**).

The investigator or designee must ensure that only patients who meet all of the eligibility criteria are offered enrollment in the study. All data for the Inclusion/Exclusion criteria must be verifiable in the patient's source document.

**The data that will be collected on patient characteristics at baseline include:**

- Demography (date of birth and initials, gender)
- Relevant medical history, including
  - Family history including cancer and genetic diseases
  - Personal history including cancer and genetic disease
  - Date of diagnosis of ALL, Type of ALL
  - Assessment of any current ongoing medical conditions
- All medications and significant non-drug therapies taken within 14 days before the first dose of steroids (D1 of treatment protocol) is administered. They must be recorded on the CRF and updated on a continual basis if there are any new changes to the medications.
- Physical examination including
  - Height, weight, Body Surface Area (calculated)
  - Vital signs
  - Search for tumoral syndrome signs
  - Neurological examination
  - Annual Tanner stage
  - Annual Bone Age assessment during peripubertal period for patients treated with imatinib
- Hematological and biochemistry evaluations
  - Complete ionogram, calcemia, phosphoremia, Uric acid, creatinin, urea, glycemia, liver function tests, LDH.
  - Coagulation tests with D-Dimers
  - Appropriate tests if fever (CRP, Blood culture, cytobacteriological examination of urine)
  - Pregnancy test as appropriate
  - Complete blood grouping
  - **TPMT status**
- Viral serologies including CMV, EBV, VZV, HBV, HIV, HCV
- ECG if patient at risk of tumor lysis syndrome (frequent) or hypercalcemia (rare)
- Cardiac imaging (cardiac ultrasound or MUGA scan) before any anthracycline administration
- Bone marrow aspiration for analyses listed below (see **Appendices 2 and 3**):
  - Cytology and cytochemistry (myeloperoxidases)
  - Immunophenotyping ; DNA index
  - Caryotype with FISH (probes for TEL-AML1 and MLL rearrangement)
  - Molecular biology (see **Appendices 2-3** for details):
    - Ig-TCR status for MRD probe definition
    - fusion transcripts analysis

- IKZF1 status
- Others
- Biobanking
  - CSF evaluation with cytopspin to be systematically realized (**Appendix 4**)

## 7.2 Treatment period

The treatment period will last 24 to 30 months, depending on subgroups, and is divided in different phases: prephase, induction, consolidation, delayed intensification (1 or 2) maintenance and depending on the stratification group are added a consolidation phase and 1 or 2 interim phases.

For the small subset of patients undergoing HSCT, protocol treatment period is considered until HSCT. Outcome measures (OS, EFS, cumulated incidence of relapse) will nevertheless be recorded, taking into account patient information obtained after HSCT.

## 7.3 End of treatment, including premature withdrawal and study discontinuation

Patients who discontinue study treatment should be considered withdrawn from the study only after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the eCRF.

***If a subject leaves the research prematurely, data related to the subject can be used unless an objection was recorded when the subject signed the consent form.***

If consent is withdrawn, no data about the subject may be used unless the subject states in writing that he/she does not object. In practice, the subject is excluded from the research.

Ending a subject's participation does not affect the normal management of the subject's illness in any way. If there are serious adverse events, the investigator must notify the sponsor and monitor the patient following the premature termination of treatment for the next 30 days.

***If treatment is stopped prematurely due to a serious adverse event, a serious adverse event notification form will be sent by fax (01 44 84 17 99) to the sponsor. The serious adverse event will be monitored until it is resolved (see Section 8.3).***

### Criteria for premature patient withdrawal

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if intolerable serious adverse event that prevent the continuation of the treatment as planned in the protocol

**To be noted:** The occurrence of a pregnancy on therapy will lead to withdrawal of the patient. This complex situation will be discussed between hematologist and obstetrician. Section 7.4.1.4.6

## 7.4 Follow-up period

All the examinations are similar to those of the usual care of such patients including developmental items (growth and puberty).

All patients must have safety evaluations for 30 days after the last dose of study treatment.

Patients lost to follow up should be recorded as such on the eCRF.

Given the main analysis is based on the intent-to-treat principle, all end points should be monitored, whatever treatment discontinuation or not.

Patients discontinued prematurely from treatment will still be followed every year (except in case of explicit consent withdrawal) according to the center's policy until the end of the planned duration of participation to the research.

#### 7.4.1 Laboratory Assessments

##### 7.4.1.1 Evaluation of response in blood (D8) and bone marrow: see Section 6 and table 3,5 and 6

##### 7.4.1.2 Cerebrospinal Fluid (CSF)

A CSF analysis will be performed:

- At each IT injection
- See **Appendix 4 and 5** for a synthesis

##### 7.4.1.3 Pharmacokinetics linked to pegaspargase: blood collection and handling

###### 7.4.1.3.1 Blood collection plan for asparaginase activity and antibodies

There is no sampling in M, interim and maintenance phases.

Pharmacokinetic plasma samples will be collected from every patient (Table 10)

**Table 10: Collections for pharmacokinetic according to patient groups**

Blood Sample handling is detailed in **Appendix 6**.

#### Sampling for CAALL-F01 (all centers)

	Induction*	Consolidation	M phase	Delayed Intensification	M phase	Delayed intensification n°2	Total sampling
<b>ALL B-SR 1000 pts</b>	D12 D19 D26 D33 D40	D8 D8 D15 D43 D71		D4 D8 D15			Ase: 10  AB: 3
<b>ALL B-MR 480 pts</b>	D12 D19 D26 D33 D40	D15 D22 D50		D4 D8 D15			Ase: 8  AB: 3
<b>ALL B-HR 230 pts</b>	D12 D19 D26 D33 D40	D15 D22 D50		D4 D8 D15 D50		D4 D8 D15 D50	Ase: 12  AB: 4
<b>ALL T-SR 150 pts</b>	D12 D19 D26 D33 D40			D4 D8 D15			Ase: 6  AB: 2
<b>ALL T-HR 110 pts</b>	D12 D19 D26 D33 D40	D15 D22 D50		D4 D8 D15 D50		D4 D8 D15 D50	Ase: 11  AB: 4

Dxx: antibodies (AB) (first 2 years only)

Dxx: asparaginase activity (Ase)(whole study duration)

###### 7.4.1.3.2 Asparagine level in blood and CSF (4 centers only)

All samples must be labeled with labels available in the investigator's file (Table 11).

**Table 11: Extended sampling for CAALL-F01**

## Extended Sampling for CAALL-F01: 4 centers

	Induction*	Consolidation	M phase	Delayed Intensification	M phase	Delayed intensification n°2	Total sampling
<b>ALL B-SR</b>	D12 D12 D19 D26 <b>D33</b> D40	D8 D8 D15 D43 D71		D4 D8 D15			Ase: 10 ASN: 7 AB: 3
<b>ALL B-MR</b>	D12 D12 D19 D26 <b>D33</b> D40	D15 D22 D50		D4 D8 D15			Ase: 8 ASN: 7 AB: 3
<b>ALL B-HR</b>	D12 D12 D19 D26 <b>D33</b> D40	D15 D22 D50		D4 D8 D15 D50		D4 D8 D15 D50	Ase: 12 ASN: 7 AB: 4
<b>ALL T-SR</b>	D12 D12 D19 D26 <b>D33</b> D40			D4 D8 D15			Ase: 6 ASN: 7 AB: 2
<b>ALL T-HR</b>	D12 D12 D19 D26 <b>D33</b> D40	D15 D22 D50		D4 D8 D15 D50		D4 D8 D15 D50	Ase: 12 ASN: 7 AB: 4

\*Asparagine (ASN) in CNS:

Dxx: antibodies    Dxx: activity plus asparagine    Dxx: activity only    Dx: asparagine only    only at D13 & D24 of induction

### 7.4.1.4 Laboratory evaluations

The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance. At any time during the study, abnormal laboratory parameters that are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the eCRF.

Examinations may be performed more frequently at the investigator's discretion if medically indicated; those results should be recorded on the CRF.

**Laboratory data will be summarized using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.**

#### 7.4.1.4.1 Complete blood count (CBC)

The hematological work-up includes the following parameters: complete blood count consisting of a red blood cell (RBC) count, white blood cell (WBC) count with differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils), hemoglobin (Hgb), hematocrit (Hct), and platelet counts.

A CBC should be **performed at least:**

- On Day 1, 8, 12, 15, 19, 22, 26, 29, 33 and ±40 of the induction phase
- On Day 1 of every phase of treatment from induction to delayed intensification
- Every 2-4 weeks during maintenance phase

#### **7.4.1.4.2 Clinical chemistry includes the following parameters:**

- Potassium, sodium, calcium, magnesium, chloride, phosphorus
- ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, Gamma GT
- Creatinine, urea, uric acid, lipase, albumin, total protein
- Fasting plasma glucose. if abnormal on at least 2 measurements 2 weeks apart and after diet ± insulin are started, C-peptide and HbA1c have to be performed

Clinical chemistry should be performed (all analysis are not mandatory):

- On Day 1, 8, 12, 15, 19, 22, 26, 29, 33 and ±40 of the induction phase
- On Day 1 of every phase of treatment from induction to delayed intensification
- As required during maintenance phase

#### **7.4.1.4.3 Coagulation**

The coagulation profile including partial thromboplastin time (PTT), prothrombin time (PT), fibrinogenemia, antithrombin III and when necessary, fibrin degradation products, should be performed :

- On Day 1, 8, 12, 15, 19, 24, 26, 29, 33 and ±40 of the induction phase
- On Day 1 of every phase of treatment from induction to delayed intensification
- As required during maintenance phase

#### **7.4.1.4.4 Bacteriology**

The bacteriology assessment including hemoculture, cytobacteriological examination of the urine, throat culture, stool investigation, and samples of all suspected infectious areas should be performed according to the clinical status during the different phases of the treatment.

#### **7.4.1.4.5 Viral assessment**

Serology of hepatitis B and C, Human Immunodeficiency Virus, Cytomegalovirus, Epstein Barr Virus and Varicella-Zona Virus have to be performed according to the clinical status during the different phases of the treatment.

#### **7.4.1.4.6 Pregnancy and assessments of fertility**

*All females of child-bearing potential, defined as all women physiologically capable of becoming pregnant must have a negative serum pregnancy test before inclusion and at the end of the treatment and a reliable contraception except oral contraceptives. The contraception should be maintained throughout the study and for 3 months after treatment discontinuation. Additional pregnancy test should be performed as soon as indicated in case the patient is suspected to be pregnant.*

In case of pregnancy, the patient will be withdrawn from study treatment. The woman will be carefully followed up for her pregnancy with a close collaboration between the hematologist and the obstetrician.

**Pegaspargase Pregnancy Warnings: This drug should be used during pregnancy only if clearly needed (US FDA pregnancy category: C). Animal reproduction studies have not been conducted. There are no controlled data in human pregnancy. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.**

**Each pregnancy in a patient on study drug must be reported to the sponsor within 24 hours of learning of its occurrence. See Section 8.3.2.6 for detailed reporting and follow up procedures.**

#### **7.4.2 Radiological examinations**

A chest X-ray is to be done at diagnosis and will be then performed according to the clinical status during the different phases of the treatment.

Abdominal ultrasonography is recommended at diagnosis in patients with high tumor burden (high WBC, high LDH levels, T-cell ALL). It helps to determine if a kidney involvement is present.

It is also helpful in any case of suspicion of acute pancreatitis.

***A cranial MRI will be performed at the end of the treatment if:***

- ***CNS3 status at diagnosis***
- ***T-cell ALL and initial WBC > 100 G/L***
- ***Any neurological complication during treatment (CNS thrombosis, stroke like syndrome, seizures etc)***

An annual radiography for bone age assessment will be performed during peripubertal period until end of puberty for patients treated with imatinib

#### **7.4.3 Cardiac assessments**

##### **7.4.3.1 Electrocardiogram (ECG)**

A standard 12 lead ECG will be performed in cases of tumor lysis syndrome (risk of hyperkaliemia) and in the rare cases with hypercalcemia.

##### **7.4.3.2 Echocardiogram or cardiac imaging-MUGA (multiple gated acquisition) scan**

*It is mandatory to perform an echocardiography before each phase including an anthracycline (daunorubicin, doxorubicin, mitoxantrone), at the end of treatment and at least 5 years and 10 years after diagnosis.*

#### **7.4.4 Safety and tolerability assessments**

**Safety will be monitored** by assessing general condition (weight, vital signs), laboratory tests, concomitant medications, as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to **Section 8**.

The allergic reactions during the induction and the intensification phases will be assessed by clinical monitoring during the administration of asparaginase, and also by assessment of antibodies against pegaspargase (cf. **Appendix 6**).

***The safety and tolerability and in particular pancreatitis and thrombosis will be assessed by the analysis of the frequency and the severity of the adverse events graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.***

**Main examinations are reported below.**

<b>Phase of treatment</b>	<b>Induction</b>	<b>Consolidation(s)</b>	<b>Delayed intensification(s)</b>	<b>Maintenance</b>			
<b>Laboratory Assessments</b>							
Evaluation of response in blood (D8) and bone marrow	cf table 6	cf table 6					
Cerebrospinal Fluid (CSF) analysis	at each IT injection at each IT injection at each IT injection at each IT injection						
<b>Laboratory evaluations*1</b>							
<b>Hematology</b> : Blood count (RBC;WBC) count with differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils), hemoglobin (Hgb), hematocrit (Hct), and platelet counts.	<b>On Day 1, 8, 12,15, 19, 22, 26,29, 33 and ±40</b>	<b>Day 1</b>	<b>Day 1</b>	Every 2-4 weeks during maintenance			
<b>Clinical chemistry</b> : (Potassium, sodium, calcium, magnesium, chloride, phosphorus); (ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, Gamma GT); (Creatinine, urea, uric acid, lipase, albumin, total protein) and <i>Fasting plasma glucose</i> .	<b>On Day 1, 8, 12,15, 19, 22, 26,29, 33 and ±40</b>	<b>Day 1</b>	<b>Day 1</b>	As required during maintenance			
Lipid profile	<b>On Day 12, 19, 26, 33±40</b>						
<b>Coagulation</b> : Partial thromboplastin time (PTT), prothrombin time (PT), fibrinogenemia, antithrombin III and when necessary the fibrin degradation products	<b>On Day 1, 8, 12,15, 19, 22, 26,29, 33 and ±40</b>	<b>Day 1</b>	<b>Day 1</b>	As required during maintenance			
<b>Bacteriology</b> : Hemocultures, cytobacteriological examination of the urine (ECBU), throat culture, stool investigation, and samples of all suspected infectious areas	should be performed according to the clinical status during the different phases of the treatment.						
<b>Viral assessment</b> : Serology of hepatitis B and C, Human Immunodeficiency Virus, Cytomegalovirus, Epstein Barr Virus and Varicella-Zona Virus	Should be performed according to the clinical status during the different phases of the treatment.						
<b>Pregnancy and assessments of fertility</b> : serum pregnancy test ( $\beta$ -HCG)	All females of childbearing potential should have a serum pregnancy test ( $\beta$ -HCG) at screening and at the end of the treatment*2.						
<b>Radiological examinations :</b>							
- Chest X-ray (face and profile)	Should be performed at diagnosis and then according to the clinical status during the different phases of the treatment.						
- Cranial MRI scan	At the end of the treatment if...*3						
<b>Cardiac assessments</b>							
Electrocardiogram (ECG)	Standard 12 lead ECG in cases of tumor lysis syndrome (risk of hyperkalemia) and in the rare cases with hypercalcemia						
Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram	Before each phase including an anthracycline (daunorubicin, doxorubicin, mitoxantrone), at the end of treatment and at least 5 years						

\*1 The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

At any time during the study, abnormal laboratory parameters that are clinically relevant (e.g., require dose modification and/or interruption of study drug,

lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the CRF.

*Examinations may be performed more frequently at the investigator's discretion if medically indicated; those results should be recorded on the CRF.*

*Laboratory data will be summarized using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03*

\*2      *Additional pregnancy test should be performed as soon as indicated in case the patient is suspected to be pregnant*

\*3      *Cranial MRI scan will be performed at the end of the treatment if:*

- CNS3 status at diagnosis
- T-cell ALL and initial WBC > 100 G/L
- Any neurological complication during treatment (CNS thrombosis, stroke like syndrome, seizures etc)

***NB for patients treated with imatinib: an annual radiography for bone age assessment will be performed during peripubertal period until end of puberty***

## 8 Safety Monitoring and Reporting

### 8.1 Adverse events

#### 8.1.1 Definitions and reporting

According to Article R1123-46 of the French Public Health Code.

##### **Adverse event**

Any untoward medical occurrence in trial subject which does not necessarily have a causal relationship or with the investigational product.

- **Adverse reaction to an investigational medicinal product**

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal product response to a medicinal product which is noxious and unintended.

- **Serious adverse event or reaction**

Any adverse event or reaction that at any dose of medication results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

- **Unexpected adverse reaction to an investigational medicinal product**

An adverse reaction to the product, whose nature, severity, frequency or outcome is not consistent with the safety information described in the Reference Safety Information (summary of product characteristics (SmPC) for an authorised product or the investigator's brochure for an unauthorised investigational product).

According to article R.1123-46 of the Code de la Santé Publique and the notice to sponsors of clinical trials for medications (ANSM).

- **Emerging safety issue**

- Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.
- For the clinical trials involving the first administration or use of an investigational medicinal product in healthy volunteers, any serious adverse reaction.
- Examples:
  - a) any clinically significant increase in the frequency of an expected serious adverse reaction
  - b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports
  - c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product, that may impact the safety of the trial subjects.
- Examples:
  - - a serious adverse event likely to be related to the interventions and the trial's diagnostic procedures and which may impact the conduct of the clinical trial,
  - - a significant risk on the trial subjects such as ineffectiveness of the investigational medicinal product in treating a life-threatening illness under investigation,
  - - significant safety results from a recently completed non-clinical study (such as a carcinogenicity study),
  - - the premature termination, or temporary suspension, of a trial conducted on the same investigational medicinal product in another country, for safety reasons,

- - an unexpected serious adverse reaction associated with a non-experimental medication required for the conduct of the clinical trial, (e.g. challenge agents, rescue treatment)
- d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, that may affect the safety of the trial subjects
- e) any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the **Common Terminology Criteria for Adverse Events (CTCAE) version 4.03**. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 to 4, will be used. CTCAE Grade 5 (death) will not be used in this study.

*As far as possible, each adverse event should be evaluated to determine:*

1. *The severity grade (CTCAE Grade 1-4)*
2. *Its duration (Start and end dates)*
3. *Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)*
4. *Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)*
5. *Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)*
6. *Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)*
7. *Whether it is serious, as defined in Section 8.1.1*

If a concomitant medication or non-drug therapy is given, this action should be recorded on the eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

## 8.1.2 Laboratory test abnormalities

### 8.1.2.1 Definitions and reporting

Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below (cf section 8.3.1.1) and/or as per investigator's discretion.

## 8.2 Special protocol requirements

### 8.2.1 All serious and non-serious adverse events must be reported in the CRF.

### 8.2.2 Serious adverse events that do not require the investigator to immediately notify the sponsor

These serious adverse events are only recorded in the "adverse event" section of the case report form.

- **Normal and natural evolution of the pathology**

- Hospitalizations for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition do not require immediate notification to the sponsor
- Progression of leukemia (including relapses or fatal outcomes), documented by the use of appropriate methods do not require immediate notification to the sponsor
- SAE related to standard chemotherapy\*, occurring during chemotherapy phase with no administration of Oncaspar® (e.g. prephase, M or IP phases, maintenance) do not require immediate notification to the sponsor

The following common adverse events occurring during Oncaspar® treatment phases (induction, consolidation, delayed intensification) do not require immediate notification to the sponsor :

- mucositis, nausea, vomiting, alopecia : these adverse events (if < grade 4 CTCAE) do not require immediate notification to the sponsor
- Hospitalisation for Anemia, neutropenia (including febrile neutropenia), leucopenia, thrombocytopenia, aplasia without clinical complication : these adverse events do not require immediate notification to the sponsor
- SAE related to catheter implantation (infections, thrombosis) do not require immediate notification to the sponsor
- Hypofibrinogenemia < grade 4 do not require immediate notification to the sponsor
- Hepatic laboratory abnormalities < grade 4 without clinical complication do not require immediate notification to the sponsor. A CRF extraction of these serious adverse events will be realized every 3 months by clinical research unit and transmitted to vigilance department at [expertisecsi.drc@aphp.fr](mailto:expertisecsi.drc@aphp.fr).

\* Standard chemotherapy: vincristine, daunorubicine, doxorubicine, mitoxantrone, prednisone, dexamethasone, hydrocortisone hemisuccinate, methotrexate, 6-mercaptopurine, 6-thioguanine cytarabine, nelarabine, cyclophosphamide, ifosfamide, VP16

- **Hospitalizations for special circumstances**

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent do not require immediate notification to the sponsor
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission do not require immediate notification to the sponsor
- Social reasons and respite care in the absence of any deterioration in the patient's general condition do not require immediate notification to the sponsor
- **Adverse events likely to be associated with the treatments prescribed as part of the patient's care during the monitoring of the research** do not require immediate notification to the sponsor. The investigator as health care professional must notify these events to the appropriate health surveillance institution according to the situation. Examples: Agence Régionale de Santé, quality department of your hospital, Centre Régional de Pharmacovigilance, local correspondent of the materiovigilance unit (ANSM), etc.

## 8.3 Reporting

### 8.3.1 Regulatory obligations of the investigator (Art R1123-54 of the French Public Health Code)

#### 8.3.1.1 Obligations of the investigator

The investigator must notify the sponsor all Serious Adverse Events, except those that are listed in the protocol (see **Section 8.2.2**).

All SAE occurring during Oncaspar® treatment phase (induction, consolidation, delayed intensification (s)) must be notified immediately to the sponsor **except those listed in 8.2.2**.

The investigator must report all adverse events that meet one of the seriousness criteria below, **except for events listed in Section 8.2.2** as not requiring immediate notification:

- 1- Death
- 2- Life threatening situation
- 3- Requiring hospitalisation or prolonging hospitalisation
- 4- Persistent or significant disability or incapacity
- 5- Congenital abnormality or birth defect
- 6- Or any other adverse event considered "medically significant"

#### *Serious adverse events of special interest*

*Severe toxicities directly asparaginase-related (e.g. CNS thrombosis, pancreatitis, anaphylaxis, and bilirubine) within the first 7 weeks (D49) following induction therapy onset unless at or after day 7 post-consolidation, will be recorded as defining the main toxicity end point of the study, and must be notified immediately to the sponsor :*

*Pancreatitis ≥ grade 3 of NCI-CTCAE*

*CNS Thrombosis*

*Anaphylaxis ≥ grade 3 of NCI-CTCAE*

*Bilirubin increase ≥ grade 3 of NCI-CTCAE (> 3 ULN)*

*SAE occurring within the month following nelarabine administration must be notified immediately to the sponsor, in particular neurotoxicity, as it is one of the most frequent adverse event related to nelarabine*  
*All secondary malignancies and pregnancies (see Section 8.3.2) must be notified immediately to the sponsor.*

These serious adverse events are recorded in the "adverse event" section of the case report form and the investigator must notify the sponsor's Vigilance division (see below in the **Section 8.3.3**) immediately.

#### 8.3.1.2 Adverse events of special interest (included in the evaluation criteria)

#### 8.3.1.3 Pancreatitis

Acute Pancreatitis is a well-known complication of the treatment of childhood ALL and occurred in 7 to 18% of patients. Protocol 05-01 of the DFCI has included 197 patients aged 1 to 17 years who received a single dose of PEG-asparaginase 2500 IU/m<sup>2</sup> i.v. The most common asparaginase-related toxicity was pancreatitis (4.5%) developing in a median of 13 days after dosing in the pegaspargase ([Silverman 2010](#)).

Pancreatitis is associated with significant complications, such as multiorgan failure and pseudocysts.

Pancreatic lipase levels should be tested before each asparaginase infusion.

In case of abdominal pain associated or not with pancreatic enzymes increase, a pancreatitis should be evoked and an abdominal ultrasound should be performed

**The NCI-CTCAE V3 describes 2 relevant pancreatic disorders:**

- **Pancreatic necrosis: a disorder characterized by a necrotic process occurring in the pancreas**
  - **the following gradings are defined (no grade 1 or 2):**
  - **grade 3: tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated**
  - **grade 4: life-threatening consequences; urgent operative intervention indicated**
  - **grade 5: death**
- **Pancreatitis: a disorder characterized by inflammation of the pancreas**
  - **the following gradings are defined (no grade 1):**
  - **grade 2: enzyme elevation or radiologic findings only**
  - **grade 3: severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)**
  - **grade 4: life-threatening consequences; urgent operative intervention indicated**
  - **grade 5: death**

A suspicion of acute pancreatitis should lead to withhold the treatment with asparaginase, if possible, at least temporarily.

An established diagnosis of acute pancreatitis could lead to a definitive withdrawal of the asparaginase

An isolated increase of pancreatic enzymes possibly associated with abdominal pain that resolves (abdominal pain-hyperamylasemia syndrome) does not contraindicate the quick re-start of the asparaginase after discussion with the investigator and with a close monitoring.

#### 8.3.1.4 Thrombosis

The risk of thrombosis is increased in ALL children and the occurrence was evaluated between 1% and 37% depending on inclusion or not of asymptomatic events. Asparaginase administration during induction is one of the risk factor along with concomitant administration of corticosteroids, inherited thrombophilia, compressive tumoral mass and early insertion of indwelling central venous catheter. Sites of thrombotic events are classified as central nervous system and non-central nervous system.

The meta-analysis of Caruso et al ([Caruso 2006](#)) in 1752 pediatric patients with ALL drew some interesting conclusions:

- Globally, the incidence rate of symptomatic thrombosis was 5.2% (95% CI: 4.2-6.4)
- The event occurred mainly during the induction phase: 4.8% (95% CI: 3.7-6.0)
- Out of 91 thrombotic events, 54% were located in CNS and 27.5% were deep venous thrombosis of upper limbs and associated with central venous line (CVL).
- Thrombotic events were more frequent with the lower dose of asparaginase ( $\leq 6\ 000\text{ IU/m}^2$  versus  $10\ 000$  or  $25\ 000\text{ IU/m}^2$ )
- Patients who received more than 9 days of asparaginase had a higher incidence of thrombosis
- Use of dexamethasone instead of prednisone was reportedly associated with a lower incidence of thrombotic events (but non-significant due to the low number of patients and non-randomized data)
- The thrombotic risk in ALL patients with thrombophilia increased approximately 8-fold (relative risk: 8.5; 95% CI: 4.4-17.4)

The PARKAA study (Prophylactic Antithrombin Replacement in Kids with ALL treated with Asparaginase) ([Mitchell 2003](#)) showed that the risk of CVL thrombosis was higher with left-sided catheter (OR 2.5; 95% CI: 1.0-6.4, p=0.048) and sub-clavian insertion (OR 3.5; 95%CI: 1.3-9.2, p=0.011).

Retrospective analysis of patients with SR-ALL treated in the POG 9201 trial showed that the risk of thrombosis was lower with fully implantable CVLs (port-a –cath) (OR 3.9; 95% CI: 1.5-10.3, p=0.006) ([McLean 2005](#)).

Thrombosis developed in 2% of patients in the Protocol 05-01 that included 197 patients aged 1 to 17 years who received a single dose of PEG-asparaginase  $2500\text{ IU/m}^2$  i.v. ([Silverman 2010](#)).

**The NCI-CTCAE V3 describes thrombo-embolic events according to the following gradings:**

- grade 1: venous thrombosis (e.g.superficial thrombosis)
- grade 2: venous thrombosis (e.g.,uncomplicated deep vein thrombosis), medical intervention indicated
- grade 3: thrombosis (e.g.,uncomplicated pulmonaryembolism [venous], nonembolic cardiac mural[arterial] thrombus), medical intervention indicated
- grade 4: life-threatening (e.g.pulmonary embolism,cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability;urgent intervention indicated
- grade 5: death

CNS thrombosis, is thus classified as a grade 4 event.

### 8.3.1.5 Hypersensitivity reactions / anaphylaxis

Hypersensitivity to native E.coli asparaginase is common (around 30% of patients at reexposure during the delayed intensification). PEG-L-asparaginase is less allergenic than the native form of asparaginase. Hypersensitivity was experienced by 1.5% of the 197 patients aged 1 to 17 years enrolled onto the Protocol 05-01 and who received a single dose of PEG-asparaginase 2500 IU/m<sup>2</sup> i.v. (Silverman 2010).The rate of hypersensitivity to pegaspargase at reexposure (delayed intensification) is probably less than 10% (oral communications , IBFM meeting 2015).

**The NCI-CTCAE V3 describes hypersensitivity/anaphylaxis events according to the following gradings:**

Adverse Event	1	2	3	4	5
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					

### 8.3.1.6 Bilirubin grade 3-4

Hyper bilirubinemia (grade 1-4) have been recently reported in the control arm of COG AALL07P4 ([Angiolillo 2014](#)) during induction therapy in 20 out 54 children with High-risk NCI ALL (37%) and in 4 out of 38 during delayed intensification (10.5%). It is known that the incidence of grade 3-4 bilirubin increases with age. **The incidence of increased Bilirubin will be looked for in the CAALF01 protocol, particularly of the NCI grade 3-4 alterations.**

**The NCI-CTCAE V3 describes bilirubin abnormalities according to the following gradings:**

Adverse Event	1	2	3	4	5
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					

### 8.3.3. other SAE of interest

#### 8.3.1.1. Secondary malignancies

All secondary malignancies must be reported to the sponsor via a specific SAE form.

#### 8.3.1.2. In utero exposure

**The sponsor must be notified immediately** about any pregnancy during which the foetus (from the pre-embryonic stage up to birth) could have been exposed at a given time to an experimental medication, even if the pregnancy is not associated with an adverse event.

The investigator had to complete the "form for monitoring a pregnancy that developed during an interventional research", found in **Appendix 16** and sends it by fax to the Vigilance Division at **01 44 84 17 99**.

The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy, using this form.

If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAE.

If the exposure involves the father, the investigator must obtain the mother's permission before collecting information about the pregnancy.

#### 8.3.1.3. Exposure while breastfeeding

Exposure while breastfeeding occurs if an infant or child could have been exposed to a medication *via* the breast milk of a mother being treated with an experimental medication.

Even if such exposure is not associated with an adverse event, the investigator must always notify the sponsor about exposure while breastfeeding as soon as the investigator becomes aware.

#### The investigator's other roles

The investigator must document the serious adverse event as thoroughly as possible and provide the medical diagnosis, if possible.

The investigator assesses the severity of the adverse events:

- either by using the NCI-CTCAE scale, attached to the protocol
- or by using more general terms:
  - *Mild: tolerated by the patient, does not interfere with daily activities*
  - *Moderate: sufficiently uncomfortable to affect daily activities*
  - *Serious: preventing daily activities*

Notification of an SAE must initially be provided in a written report using the special form for reporting SAE (see **Appendix 15**). The investigator completes the SAE notification form in the e-CRF, validates, prints and signs the form before sending it via fax.

For all questions relating to the notification of an adverse event, the Vigilance Division of the DRCDDRCI can be contacted via email: [vigilance.drcd@drc.aphp.fr](mailto:vigilance.drcd@drc.aphp.fr).

The reception of the SAE form to the vigilance department is **centralized** to allow immediate processing of SAE as soon as they are received. The initial SAE notification, the SAE monitoring reports and any other document will be sent to the sponsor represented by its Vigilance department by fax (+33 1 44 84 17 99). It is possible to transmit the SAE form to the Vigilance department by e-mail ([eig-vigilance.drc@aphp.fr](mailto:eig-vigilance.drc@aphp.fr)) **only in case** of unsuccessful attempt to send the SAE form by fax.

**NB: Do not transmit by e-mail the documents initially successfully transmitted by fax to avoid duplication.**

**If it is not possible to connect to the e-CRF, the investigator will complete, sign and send the SAE notification form found in Appendix 15. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.**

Each item in the form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

This initial notification must be followed by one or more detailed follow-up report(s), in writing and signed, within a maximum of 8 days in the case of a fatal or life-threatening event and within 15 days for all other cases.

The investigator assesses the causal relationship between the serious adverse events and the experimental medication(s) and/or the procedures added by the research.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results of additional exams, etc.). These documents must be made anonymous. In addition, the documents must include the following: research acronym, number, and initials of the subject, nature, and date of the serious adverse event.

Any adverse event will be monitored until fully resolved (stabilization at a level considered acceptable by the investigator, or return to the previous state) even if the subject has left the trial.

The investigator must comply with all requests from the sponsor for additional information.

#### **8.3.1.4. Period for notifying the sponsor**

The investigator must report all SAE that occur in research subjects:

- after the date on which treatment with an experimental medication began/the date of the first procedure specific to the research
- throughout the period during which the participant is monitored, as determined by the research
- with no time limit, if the SAE is likely to be due to the experimental medication or to the research procedures (for example, serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

### **8.4. The sponsor's roles**

The sponsor, represented by its Vigilance Division, continuously assesses the safety of each experimental medication throughout the research.

#### **1. Analysis and declaration of serious adverse events**

The sponsor assesses:

- the seriousness of all adverse events reported
- the causal relationship of these events with each experimental medication and/or specific medical procedures/exams added by the research and with other possible treatments
- the expected or unexpected nature of these adverse reactions

All serious adverse events which the investigator and/or the sponsor believe could reasonably have a causal relationship with the experimental medication are considered as suspected adverse reactions. Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, or in the protocol for this research is considered unexpected.

The sponsor, acting through its safety Department, assesses the expectedness of the serious adverse reaction based on the information described below.

SAEs related to Oncaspar® and/or to the standard chemotherapy (including corticosteroids) association and/or Imatinib and which are expected (and will not be considered as SUSAR) are:

All SAE mentioned in last updated SmPC and,

SAE ≤ grade 4 : diarrhea, nausea, vomiting, mucositis, hand-foot syndrome, aplasia, febrile aplasia, neutropenia, febrile neutropenia, leukopenia, thrombopenia, anemia, hyperuricemia and CIVD associated with tumor lysis syndrome, post lumbar puncture syndrome, anxiety and depression syndrome, peripheral neuropathy and paresthesia, ileus and intestinal obstruction, catheter-related incidents (catheter rupture...) , extravasation,

hypofibrinogenemia, antithrombin III decreased, fever, asthenia, altered general state, weightloss, malnutrition, anorexia, abdominal pain, hepatotoxicity, cytosis, cholestasis, icterus, hepatic enzyme increased, hyperbilirubinemia, GGT and PAL increased, hyperammonemia, acute hepatitis, pancreatitis, hyperglycemia, diabetes mellitus, hypertriglyceridemia, hyperlipidemia, cholangitis, hemorrhage, thromboembolic disorders ; sepsis and fungal and viral infection, renal failure.

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency)).

- The sponsor must send the initial report without delay upon receipt of the unexpected serious adverse reaction if it is fatal or life-threatening, or otherwise within 15 days from receipt of any other type of unexpected serious adverse reaction;
- The sponsor must provide all relevant additional information by sending follow-up reports, within 8 calendar days following receipt.

Any suspected unexpected serious adverse reaction must also be declared electronically in the Eudravigilance European database for adverse events due to medications, established by the European Medicines Agency (EMA).

The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the research subjects.

Specific cases of serious adverse events of special interest:

At the request of ANSM, the sponsor may be asked to declare serious adverse events of special interest, in accordance with the same procedures and deadlines as SUSARs.

## **2. Analysis and declaration of other safety data**

This relates to any new safety data that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.

The sponsor will inform the competent authority and the Ethics committee without delay after becoming aware of the emerging safety issue and, if applicable, describe which measures have been taken.

Following the initial declaration of emerging safety issue, the sponsor will declare to ANSM any additional relevant information about the new safety issues in the form of a follow-up report, which must be sent no later than 8 days after becoming aware of the information.

## **3. Annual safety report**

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:

- An analysis of the safety of the research subjects
- A description of the patients included in the trial (demographic characteristics, etc.)
- A line listing of suspected serious adverse reactions that occurred during the period covered by the report
- A cumulative summary tabulation of serious adverse events that have occurred since the start of the research

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorised the trial.

### **8.5. Data Safety Monitoring Committee**

The Data and Safety Monitoring Committee (DSMC) will be established by the sponsor. Its primary mission is to serve as a committee for monitoring safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).

The sponsor is responsible for justifying the creation or absence of a supervisory committee to the Competent Authority (ANSM) and to the CPP.

The DSMC will hold its preliminary meeting before the first inclusion of the first subject. All missions as well as the precise operating methods of the DSMC are described in the charter for the research's DSMC.

#### General information about the DSMC

The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of:
  - safety data: serious adverse reactions
  - efficacy data: proven futility or efficacy

The DSMC is appointed by the sponsor and is made up of at least 3 people with no connection to the research, including at least one clinician specialising in the pathology being studied and one specialist in the medication being studied (or a pharmacologist/pharmacovigilance specialist), and possibly a methodologist/biostatistician, particularly in the case of interim analysis.

The DSMC has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research.

The DSMC must hold its preliminary meeting before the first inclusions of the first subject and ideally before the protocol is submitted to the competent authority and the CPP. The committee's agenda will be as follows:

#### Definition of the DSMC's missions

- Validation of tolerance monitoring methods
  - nature of the evaluated parameters
  - frequency of the evaluations, consultation schedule
- Validation of termination criteria
  - criteria for terminating a subject's participation for tolerance reasons
  - criteria for the temporary or permanent termination of the research (leading to the establishment of certain recommendations ("stopping rules"))
- Modification of the protocol and recommendations:

In light of the analysis of tolerance data for the research, the DSMB can propose substantial modifications in order to modify certain data, in particular relating to the protocol (inclusion and non-inclusion criteria, monitoring, additional exams, etc.).

Likewise the DSMC can issue any recommendations it deems useful in order to best ensure the safety of the research subjects and to maintain a favourable benefit-risk balance throughout the research.

**Definition of the DSMC's operating methods**

- meeting types (open session, then closed sessions) and schedule
- desired methods and format of SAE notification from the sponsor to the DSMB

**The DSMC appoints its chairman at the first meeting.**

The sponsor retains decision-making authority. When applicable, the sponsor delivers its decision, with justification, and DSMC reports to the Competent Authority (ANSM) and the CPP.

## 9. Data Management

### 9.1. Data collection

#### 1. Source documents

Source documents, defined as any original document or object through which the existence or accuracy of a data or fact recorded during the research can be proven, shall be kept by the investigator or the hospital, if it concerns a hospital medical record, for 15 years

#### 2. Data confidentiality

The persons responsible for the quality control of an interventional research (article L.1121-3 of the Public Health Code) shall take all the necessary precautions to ensure the confidentiality of the information related to the experimental medicines, the research and the trial subjects, notably in relation to their identity as well as the results obtained.

Like the investigators themselves, these persons are bound by professional secrecy (according to the conditions defined in articles 226-13 and 226-14 of the Criminal Code).

During the interventional research or at its conclusion, the data collected concerning the trial subjects and transmitted to the sponsor by the investigators (or any other specialised intervening party) shall be depersonalised.

Under no circumstances should the names or addresses or any information allowing identification of the persons be visible.

Only the initials of the first name and surname shall be recorded, accompanied by a coded research number indicating patients' order of inclusion.

The sponsor shall ensure that each trial subject gives written consent for access to his/her personal data concerning which is strictly necessary for quality control of the research.

### 9.2. Right to access source data and documents:

In accordance with GCPs:

- the sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor
- the investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

#### 1. Data processing and storage of documents and data

##### 9.2.1.1. Data entry

Data entry will be carried out on electronic media via a web browser.

##### 9.2.1.2. Data processing (CNIL, the French Data Protection Authority) in France

This research falls under the "Méthodologie de référence" (MR-001, amended) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978 relating to information technology, data files and privacy. This change was approved in a decision made on 5 January 2006. AP-HP, the research sponsor, has signed a commitment to comply with this "Méthodologie de référence".

### **9.2.1.3. Archival**

The specific documents of the interventional research on a medicinal product for use in humans shall be archived by the investigator and the sponsor for a period of 15 years after the conclusion of the research.

This indexed archiving includes notably:

- A sealed envelope containing the original copies of all the information forms and signed consent forms of all persons from the centre who participated in the research, for the investigator;
- A copy of all the information forms and signed consent forms of all the persons from the centre who participated in the research, for the sponsor;
- The "research" binders for the investigator and the sponsor with:
  - the successive versions of the protocol (identified by the n° and date of the version) and their appendices
  - the ANSM (French National Medicinal and Healthcare Products Safety Bureau) authorisations and the CPP (French Institutional Review Board) opinions
  - the letters,
  - the inclusion list or register,
  - the research-specific appendices
  - the final research report.
- The data recording documents

### **9.2.1.4. Ownership of the data**

AP-HP is the owner of the data, which cannot be used or disclosed to a third party without its prior approval.

## 10. Statistical aspects

### 10.1. Description of statistical methods to be used including the timetable for the interim analyses

The analysis will be performed based on an intent-to-treat principle; once patients are randomized, all will be analyzed. This policy, known as the intent-to-treat (ITT) analysis principle, is a cornerstone of good clinical trial practice. All participants randomized and entered into the trial should be included in the analysis of the group to which they were assigned including loss of follow-up, regardless of whether they completed the trial or switched to receive different treatment. Similar principle will surround the analysis of the uncontrolled part of the trial.

The study's primary aims in the randomized part of the study provide two hypotheses testing. Therefore, the sample size has been computed to reach adequate statistical power for detecting the effects if present (see below, **Section 10.2**). As stated below, those numbers of patients to be included will be adjusted according to the results of the interim analysis. For the uncontrolled design, the sample size has been computed on the basis of expected prevalence of such patients during the enrolment of those to be randomized, that allow precision around the estimates that appeared satisfactory (see below, **Section 10.2**).

**Actually, given the uncertainties in estimates, one interim analysis will be performed based on all patients randomized before January, 1, 2018, as requested by the DSMB of the study on November 2017.** It will have two main goals: (i) estimating the treatment effect on the EFS, and (ii) assessing the validity in estimates on which the sample sizes have been computed, with possible re-adjustment as described below.

The statistical report will be based on the Consolidated Standards of Reporting Trials (CONSORT).

### 10.2. Calculation hypotheses for the number of subjects required and the result

#### 1. Randomized trial

For the Randomized Clinical Trial (RCT), the scheme will be divided into three steps:

1. **Initial calculation of a provisional sample size**,  $2n_0$ , from an initial estimation of the proportion of response within the control arm
  - First, considering that the response rate in the control arms will be 75% of the patients, and assuming a 10% absolute increase in the response rate in the experimental arm (from 75% to 85%), 826 patients are required to be enrolled, based on a balanced allocation across randomized groups (413 patients in each arm), a two-sided test chi-square test, and given a type I error of 0.05 and a statistical power of 95%.
  - Secondly, based on the aim of demonstrating equivalence of the two arms in terms of severe toxicity directly asparaginase-related (e.g. CNS thrombosis, pancreatitis, anaphylaxia, and bilirubine) within the first 7 weeks (D49) or anyway before Day 8 of consolidation (see definition in section 3) of 8%, and a maximal difference of 4.5%, it was computed that 1578 patients should be enrolled based on a two-sided chi-square test, and given a type I error of 0.05 and a statistical power of 80%.
  - Thus, overall the sample size of the trial will be fixed at  $n_0=1578$  patients (that is, 789 in each arm).
2. **Re-estimation of the size of the sample size** to include in each arm,  $\hat{N}$ , after observation of the responses of a sample of size  $n_1=n_0/2$  first included patients. This re-estimation will be based upon the estimated overall proportion of response, obtained by substituting this rate by its estimate  $p = \frac{x_C+x_T}{n_1}$  where  $x_C + x_T$  is the total number of observed responses in these  $n_1$  patients, while other quantities are unchanged (Gould 1997). The re-estimated sample size can then be expressed as a function of the initial sample size  $n_0$ :  $\hat{N} = n_0 \frac{p(1-p)}{\pi(1-\pi)}$ . This formula shows that such a computation is independent from the type I and II error rates (Friede 2006). This re-estimated sample size to be further included in each arm is given by  $n_2=\max(n_1, \hat{N})-n_1$  (« unrestricted design ») (Birkett 1994). Of note, this sample size may be limited by the independent trial committee due to budget or recruitment constraints (Friede 2006).
3. **Interim analysis** of the EFS across randomized arms. To avoid any inflation of the type I error, we will use the Haybittle-Peto approach. Thus, a p-value of 0.002 or less will be required to conclude against the null hypothesis.

4. **Terminal analysis** on the  $n=n_1+n_2$  observations, based on the chi-square test, similarly to a fixed design (Proschan 2007). Even if there is a theoretical possibility of inflated type I error rate using this re-estimation process based on the reevaluation of the overall proportion of response, blinded to treatment arm, this approach has been shown asymptotically valid without any substantial inflation of the type I error rate I (Gould 1992, 2001; Proschan 2006).

**Note that two analyses will be performed, one once the last patient has been terminated Asparaginase treatment), and one after all patients have 5 years of follow-up.**

## 2. Uncontrolled trial

For the uncontrolled trial, it is expected that while the total sample size of 1578 patients (B-SR/MR and T-SR) have been enrolled, about 250-300 patients (B/T-HR) will have been enrolled. Such a sample size would allow the estimation of the main endpoints with a 95% confidence interval, the width of which is below 5% for the proportion of asparaginase activity above 100 (expected rate of 95%), and below 7.5% for the toxicity rate (expected rate of 10%).

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### 10.3. Statistical methods

The baseline (i.e., at randomization) characteristics of the randomized groups will be compared roughly, based on estimations, with 95% confidence intervals and without any statistical tests of significance. Randomization is the best means for creating balanced groups.

The right-censored endpoints (event-free survival and overall survival) will be estimated by the nonparametric Kaplan-Meier method and compared between randomized groups by the log-rank test after checking for the proportionality of hazard functions. The treatment comparisons will be adjusted for imbalances or prognostic covariates using a multivariable Cox model, stratified on the lineage and risk group. The models will be evaluated based on the testing assumptions of the proportionality of hazard functions and log-linear relationships between the predictors and hazard.

Competing risks endpoints (relapse incidence, etc) will be analysed using competing risks methods. Specifically, the cumulative incidences of these events will be estimated considering deaths prior to the event of interest as competing risk outcomes and compared using the Gray test. The adjustments for potential confounders will be based on the cause-specific Cox model.

All tests will be two-sided, with p-values of 0.05 or less denoting statistical significance. All analyses will be performed using the SAS (SAS Inc., Cary, NC) and R (<http://www.R-project.org/>) software packages.

### 10.4. Methods for taking into account missing, unused or invalid data

Multiple imputation, which is a popular approach for handling the pervasive problem of missing data in biostatistics, will be used. It is usually performed under a missing at random (MAR) assumption. Multiple

imputation by chained equation (MICE) is to our knowledge the most flexible approach to handle complex patterns of missing data (including categorical data, quantitative data, and survival data).

#### **10.5. Management of modifications made to the analysis plan for the initial strategy**

All modifications will be submitted for approval to the CPP.

#### **10.6. Selection of populations**

Primary analyses will be performed on an intent-to-treat basis.

Secondary exploratory analyses will consider the population of compliers, that is, those who completed the treatment according to the scheduled protocol.

## **11. Quality Control and assurance**

Each interventional research project managed by AP-HP is ranked from A to D according to the projected risk incurred by research subjects using the classification of interventional research sponsored by AP-HP.

### **11.1. General organisation**

The sponsor must be responsible for the safety and respect of those subjects who have agreed to participate in the research. The sponsor must implement a quality assurance system to best monitor the conduct of the research in the investigation centres.

For this purpose, the sponsor shall delegate Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the research locations, after having carried out initial visits.

The objectives of monitoring the research, as defined in the French Good Clinical Practices (BPC), are to verify that:

- the rights, safety and protection of the research subjects are met
- the data reported is exact, complete and consistent with the source documents
- the research is carried out in accordance with the protocol in force, with the French GCPs and with the legislative and regulatory provisions in force

#### **1. Strategy for opening the centres**

The strategy for opening the centres established for this research will be determined using the appropriate monitoring plan.

#### **2. Level of centre monitoring**

In the case of this research, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the research. Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a research monitoring level to be implemented: level D

### **11.2. Quality control**

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper conduct of the research, for collecting and documenting, recording and reporting the data generated in writing, in accordance with the Standard Operating Procedures applied within the DRCI and in accordance with the French Good Clinical Practices as well as with the legislative and regulatory provisions in force.

The investigator and the members of the investigator's team agree to make themselves available during Quality Control visits carried out at regular intervals by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the research protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

### **11.3. Case Report Form**

All information required according to the protocol will be entered in the electronic case report form (eCRF). The data will be collected as and when they are obtained, and clearly recorded.

This eCRF form will be implemented in each of the centres thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool.

When the investigators complete the case report via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be subject to an audit trail. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

#### **11.4. Management of non-compliance**

Any events that occur as a result of non-compliance, by the investigator or any other individual involved in conducting the research, with the protocol, with the standard operating procedures, with the good clinical practices or with the legislative and regulatory provisions in force must be noted in a declaration of non-compliance addressed to the sponsor.

The sponsor has its own procedures for managing these non-compliances.

#### **11.5. Audits/inspections**

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. Medical secrecy cannot be invoked in opposition to these audits and inspections.

An audit can be carried out at any time by individuals appointed by the sponsor and who are not associated with the research directors. The objective of the audit is to ensure the quality of the research, the validity of the results and compliance with the legislation and regulations in force.

The individuals who lead and monitor the research agree to comply with the sponsor's requirements and with the competent authority regarding research audits or inspections.

The audit may be applicable to all stages of the research, from the development of the protocol to the publication of the results and the organization of the data used or produced as part of the research.

#### **11.6. Primary investigator's commitment to assume responsibility**

Before starting the research, each investigator will give the sponsor's representative a copy of his/her personal curriculum vitae, signed and dated, with his/her number in the RPPS (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.

The primary investigator at each participating centre will sign a responsibility commitment (standard DRCI document) which will be sent to the sponsor's representative.

The investigators and their employees will sign a delegation of duties form specifying each person's role.

## 12. Ethical and Legal Considerations

### 12.1. Methods for obtaining information and consent from research participants

#### 1. Information and consent of parents or legal guardians in the case of a research protocol relating to a minor

In accordance with Article L1122-2 of the French Public Health Code, when interventional research is carried out on a dependent minor, authorization is given by those responsible for exercising parental authority.

The parents or legal guardians will be granted a fair period of reflection before signing the consent form after getting informed about disease and study.

The free and informed consent, in writing, of those responsible for exercising parental authority is obtained by the investigator, or by a doctor representing the investigator, before the definitive inclusion of the minor in the research. [

However, in accordance with Article L1122-2 of the French Public Health Code, authorization may be given by the only individual responsible for exercising parental authority who is present, subject to the following conditions:

- the research only includes negligible risks and restrictions and has no effect on the medical treatment of the minor participating in the research
- the research is carried out at the same time as medical care is provided
- the other individual responsible for exercising parental authority cannot give permission within the time period required by the specific methodology of the research, given the purpose of the research

If only one parent is present, the investigator should arrange to discuss the study with the absent parent (telephone, skype or others) and to send consent forms for his/her signature. The absent parent may receive the forms by mail or fax, and may mail or fax a signed consent form back to the investigator. The child may not be enrolled until the absent parent has returned the signed consent form to the investigator.

#### 2. Information for minors participating in the research

Minors receive the information specified in Article L. 1122-1 of the French Public Health Code appropriate for their level of understanding, both from the investigator and from those responsible for exercising parental authority.

Minors are asked for a personal commitment regarding their participation in the interventional research. In all cases, the investigator must accept a minor's refusal to participate or a withdrawal of their agreement.

A copy of the signed and dated consent form is given to the parents or legal guardians as well as to the investigator or the doctor representing the investigator. The investigator will retain the original.

At the end of the research, a copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

Minors who reach the age of majority during their participation in the research will be given new, relevant information at that time. After they have been given the information, they will be asked to confirm their consent.

### 12.2. Legal obligations

#### 1. The sponsor's role

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this research and by delegation, the Delegation of Clinical Research and Innovation (DRCI) carries out the research's missions in accordance with Article L.1121-1 of the French Public Health Code. Assistance Publique - Hôpitaux de Paris reserves the right to halt the research at any time for medical or administrative reasons. In this case, notification will be sent to the investigator

**2. Request for an opinion from the Comité de Protection des Personnes (CPP, ethical review board)**

AP-HP, as sponsor, obtains for this interventional research relating to a medication for human use and prior to starting the research, the favourable opinion of the appropriate CPP, within the scope of its authority and in accordance with the legislative and regulatory provisions.

**3. Request for authorization to ANSM**

AP-HP, as sponsor, obtains for this interventional research relating to a medication for human use and prior to starting the research, authorization from the ANSM, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

**4. Commitment to compliance with the MR 001 "Méthodologie de Référence"**

AP-HP has signed a commitment to comply with this "Méthodologie de référence".

**5. Modifications to the research**

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to starting the research, a favourable opinion from the CPP and authorization from the ANSM within the scope of their respective authorities. The information sheet and the consent form can be revised if necessary, in particular if there is a substantial modification to the research.

**6. Final research report**

The final interventional research report referred to in Article R1123-67 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the report written according to the competent authority's reference plan will need to be sent to the competent authority and ethical review board within one year after the end of the research, meaning the end of the participation of the last research subject.

### **13. Publication rules**

*"The research was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2010 (Ministère de la Santé)*

**This research has been registered on the website <http://clinicaltrials.gov/> under NCT02716233 registration number.**

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## **15. Appendices**

### **Appendix 1: Patient Information - Informed consent**

These documents are available as separate documents.

## Appendix 2: Decisional Leukemia Biology at diagnosis

The diagnosis is based on morphological and immunological analysis of bone marrow; cytogenetic and molecular analyses are mandatory for further risk assessment and stratification

### 1. Criteria for ALL diagnosis

#### - Morphologic criteria for ALL

- o > 20% blasts in a representative bone marrow aspirate or otherwise in a bone marrow biopsy
- o Myeloperoxidase (MPO) or Sudan Black positivity of the blasts < 3% (cytochemistry and/or immunophenotype)

#### - Classification of ALL according to immuno-phenotype

ALL will be classified as B-Lineage ALL or T-cell ALL according to surface and intracytoplasmic markers as detailed respectively in the next paragraphs 2.2.2. and 2.2.3.

### 2. Criteria for initial risk assessment and stratification

#### 2.1. CNS cytomorphological evaluation (cf appendix 4)

#### 2.2. Immunophenotyping

Immunophenotyping of blood and bone marrow by flow cytometry will be performed at diagnosis in all patients.

##### 2.2.1. Panel of markers to be used

To be considered as **positive**, an immunological marker needs to be detected on **at least 20%** of blasts for surface markers and **at least 10%** of blasts for the following intra-cytoplasmic markers (anti MPO, CD3, CD79a, TdT), when assessed by flow cytometry.

- **First line recommended panel, for lineage identification**

**CD2 CD5 CD7 s/cCD3 :** CD3 is mandatory (cytoplasmic –c- or surface –s-).  
if sCD3 was negative, cCD3 is mandatory

At least 2 of the 3 other markers must be tested

**CD19 s/cCD22 cCD79a CD10 :** (CD19 is mandatory)  
all of the 3 other markers need to be tested  
(if sCD22 was negative, cCD22 is mandatory)

**CD13 CD33 CD117 MPO :** (MPO is mandatory or need to be tested in cytochemistry)  
at least 2 of the 3 other markers must be tested

**CD34 CD45 TdT HLA-DR :** all of these

- **Second line recommended panel, for evaluation of maturation**

B-lineage: cμ chain, CD10, sIgK, sIgL, sIgM

T-lineage: CD1a CD4 CD8. If sCD3 positive, sTCRA/B, sTCRG/D are recommended

*NOTE: Additional markers will be used, including CD123, CD20, CD24, CD58 for B lineage, CD99, CD56 for T lineage and CD38.*

- **LAP (Leukemia Associated Phenotype) for flow-MRD assessment (see also specific recommendations in MRD section)**

A standardized back-bone, including at least CD45, CD10, CD38 and CD19 for BCP-ALL and CD45, cCD3 and sCD3 for T-ALL, is recommended for MRD panel to be performed both at diagnosis and on MRD samples (see Garand et al/Leukemia. 2013 Feb;27(2):370-6.)

LAP markers should include CD34, CD58, CD123 and CD20 for BCP-ALL and TdT, CD99, CD5, CD7, CD2 for T-ALL. This list is not exhaustive and may include other markers. Conversely all markers are not required during follow-up as most informative LAP will be selected according to the observed phenotype at diagnosis.

### **2.2.2. B-cell lineage**

#### **Definition**

- CD19 expression is required with at least 1 (if CD19 is strongly expressed) or 2 (if CD19 is weakly expressed) positive markers out of the following: CD10 cCD22 cCD79a
- and c or s CD3 shall be negative,
- and MPO (flow cytometry or cytochemistry) shall be negative
- and no evidence of monocytic differentiation shall be done.

#### **Subclassification of B-cell lineage**

Pro B (early-B):	CD10 cμ chain s/clgK and s/clgL negative
Common ALL:	CD10: positive cμ chain s/clgK and s/clgL negative
Pre-B:	cμchain: positive s/clgK and s/clgL negative
Mature B:	s/clgKor s/clgL positive

#### **The conclusion report should be:**

**Acute lymphoblastic leukemia of (B-I,B-II,B-III,B-IV) subtype whose immunological profile is as follows: cCD79a +/-, CD19+/-, CD22+/-, CD10 +/-, chaîne μ-cytoplasmique +/-, sIg +/-**

### **2.2.3. T-cell lineage**

#### **Definition**

- Either cCD3 or sCD3 positivity suffices for classification as T-cell lineage
- and CD19 being negative or in case of its strong expression no marker being positive out of the following
- and in case of its weak expression less than 2 markers being positive out of the following : CD10, cCD22,cCD79a
- and myeloperoxidase (MPO by flow cytometry or cytochemistry) shall be negative and no evidence of monocytic differentiation shall be done.

#### **Subclassification of T-cell lineage**

Pro-T (early-T):	cCD3 CD7: positive all other T markers negative
Pre-T:	cCD3 CD7: positive CD2 CD5 CD8: at least one of these positive CD1a sCD3: negative
Cortical T (intermediate-T):	CD1a: positive sCD3: positive or negative
Mature T:	sCD3: positive CD1a: negative Group a: TCRA/B positive Group b: TCRG/D positive

#### **The conclusion report should be:**

**Acute lymphoblastic leukemia of (T-I,T-II,T-III,T-IV) subtype whose immunological profile is as follows: cCD3+/-, CD7 +/-, CD2+/-, CD5+/-, CD8+/-, CD1a +/-, sCD3+/-, TCR +/-**

**2.2.4. New definition of acute leukemias of ambiguous lineage (WHO classification 2008)**

*MPAL (Mixed Phenotype Acute Leukemias including bilineal and biphenotypic acute leukemias) is partitioned in:*

- B/myeloid or T/myeloid according to the lineage mix they display

These acute leukemias meet the diagnostic criteria for assignment to both B and myeloid or T and myeloid lineage, and blasts lack genetic abnormalities involving BCR-ABL or MLL (as these entities are respectively separated in MPAL with t(9;22) and MPAL with MLL rearrangement).

- Rare types including T/B coexpression and trilineage T/B/myeloid

These acute leukemias meet the diagnostic criteria for assignment to both B and T lineage.

### 2.3. Cytogenetics/Oncogenetics

**Decisional tests:** Bone marrow cells (or blood if more than 10% peripheral blasts) will be investigated at diagnosis for the presence of oncogenic markers defined by cytogenetics/molecular biology that are mandatory for risk-assessment and/or targeted therapy.

**Mandatory annotations:** More specialised biomarkers such as additional classifying oncogenetic markers are to be comprehensively assessed, providing useful annotations for further analysis of the protocol. Although mandatory as well, the characterization of these latter markers can be postponed and centralized since results will not lead to clinical decision.

Decisional tests and mandatory annotations that are not performed locally will have to be performed by the MRD center and or a central lab if appropriate.

#### 2.3.1. BCP-ALL

Biomarker	Decision making (required delivery time, in days)	Technique A <sup>§</sup>	Technique B	Technique C	Remark
iAMP21	D8	FISH	SNP/CGH array	MLPA	
Ploidy	D8	SNP/CGH array	Karyotype	DNA index	
MLL	D8	FISH	RT-PCR	Karyotype	Genomic fusion can be used as a MRD target
BCR-ABL*	D8	RT-PCR	FISH	Karyotype	
E2A-PBX1/TCF3-PBX1	D8	RT-PCR (quantitative)	FISH	Karyotype	
E2A-HLF/TCF3-HLF	D8	RT-PCR (quantitative)	FISH		
<i>IKZF1</i> <sup>del</sup> or pathogenic variant	D50	SNP/CGH array	MLPA	PCR/Fragment analysis	Technique C more sensitive but only detects recurring intragenic deletions. Variants can also be detected by sequencing;
TKI targets (ABL-class fusion)	(D50)	FISH, RT-PCR, Séquençage ADN et ARN			"B-other" ALL only** These analyses will be centralised in Robert Debré/ St Louis University hospital, Paris
<i>MEF2D</i> fusions	Annotation	RT-PCR/RT-MLPA	RNAseq	FISH	
<i>ZNF384</i> fusions	Annotation	RT-PCR/RT-MLPA	RNAseq	FISH	
<i>PAX5</i> amp	Annotation	CGH	MLPA		
<i>PAX5</i> -fusion	Annotation	RT-PCR/RT-MLPA	RNAseq	FISH	
<i>TEL-AML1/ETV6-RUNX1</i>	Annotation	RT-PCR	FISH		
<i>ERG</i> <sup>del</sup> / <i>ERG</i> <sup>alt</sup> / <i>DUX4</i>	Annotation	PCR/Fragment analysis			
<i>CRLF2</i> overexpression	Annotation	RT-QPCR			
<i>P2RY8-CRLF2</i>	Annotation	RT-QPCR	MLPA		
<i>IGH@-CRLF2</i>	Annotation	FISH			If CRLF2 overexpression and no PAR1 deletion
<i>CRLF2</i> F232C	Annotation	sequence			PAR1 deleted patients only
<i>JAK2</i> <sup>mut</sup>	Annotation	sequence			PAR1 deleted patients only

\*In case of BCR/ABL positivity, patients will be shifted towards a specific treatment protocol based on TKI.

Patients with iamp21, hypodiploidy < 44 chromosomes, E2A-HLF translocation or MLL rearrangement will be treated in the B-HR group

\*\*"B-other" ALL are ALL lacking known classifying genetic abnormalities (i.e.iAMP21, Hyperdiploidy >50 chromosomes, hypodiploidy <44 chromosomes, BCR-ABL, E2A-PBX1, E2A-HLF, TEL-AML1, and ERG<sup>del</sup>).

Patients with E2A-PBX1 rearrangement are excluded from the B-SR group.

IKZF deletion status will be known at D50. Patients with IKZF deletion will be treated in the B-MR or B-HR/VHR group according to the results of MRD (cf table 3).

§Technical choice has to consider both the quality of the results and the time required to obtain them.

MLPA: multiplex ligation probe analysis

FISH: Fluorescent in situ hybridization

RT-PCR : Reverse transcription – Polymerase chain reaction

*RT-QPCR: Reverse transcription – Quantitative polymerase chain reaction*

*SNP: single nucleotide polymorphism*

*CGH array: competitive genomic hybridization*

*N/A: not applicable*

### 2.3.2. T-ALL

Biomarker	Decision making (required delivery time, in days)	Technique A	Technique B	Technique C	Remark
<b>SIL-TAL</b>	Annotation	RT-PCR (quantitative)	CGH	FISH	Genomic fusion can be used as a MRD target
<b>TLX1/HOX11</b>	Annotation	RT-QPCR	karyotype		
<b>TLX3/HOX11L2</b>	Annotation	RT-QPCR	FISH		
<b>CALM-AF10</b>	Annotation	RT-PCR	karyotype	FISH	
<b>NUP214-ABL1</b>	Annotation	RT-PCR	SNP/CGH array	FISH	
<b>SET-NUP214</b>	Annotation	RT-PCR	SNP/CGH array		
<b>PTEN<sup>del</sup></b>	Annotation	SNP/CGH array	MLPA		
<b>NOTCH1<sup>mut</sup></b>	Annotation	Sequence			Centralised in Necker hospital
<b>FBXW7<sup>mut</sup></b>	Annotation	Sequence			id
<b>PTEN<sup>mut</sup></b>	Annotation	Sequence			id
<b>N/KRAS<sup>mut</sup></b>	Annotation	Sequence			id

See **Appendix 3** for further details.

## Appendix 3: MRD analysis and biobanking

### 1. Minimal residual disease monitoring

MRD is measured by quantitative PCR (ASO-PCR or Genescan) of a specific DNA marker. The DNA marker used can be clono-specific rearrangements of the immunoglobulin and T-cell receptor genes (IG/TCR), or oncogenic DNA markers (*MLL* genomic breakpoint, TALd, ...). ASO-PCR is performed and interpreted as described in up-to date EuroMRD guidelines [[van der Velden et al., Leukemia. 2007 Apr;21\(4\):604-11](#)]. In case MRD is not possible or failed by these technics, flow cytometry-based MRD can be accepted [[Garand et al., Leukemia 2013 Feb;27\(2\):370-6](#)]

### 2. MRD diagnostics via PCR analysis of rearranged Ig/TCR genes

#### - Principle of the analysis

Rearrangements of variable (V), diversity (D) and joining (J) gene segments in the Ig and TCR genes occurs early during B-and T-cell differentiation and aims at creating a broad repertoire of antigen-specific receptors, i.e. the Ig and TCR molecules. This diversity in Ig/TCR genes is in part based on the potential of many different combinations of the available V, D, and J gene segments and particularly on the unique composition of the coupling sites of the gene segments, the so-called junctional regions. These junctional regions are characterized by the random deletion and insertion of nucleotides during the rearrangement process, which results in unique segments that can serve as clone-specific markers. Consequently, the junctional regions of rearranged Ig/TCR genes can be regarded as unique “DNA fingerprints” for ALL and therefore as PCR target for MRD diagnostics.

The Ig/TCR based MRD technique requires that for each individual ALL patient, the Ig/TCR gene rearrangement pattern of the leukemia cells has to be determined, the junctional regions have to be sequenced, junctional regions-specific primers have to be designed for TaqMan-based RQ-PCR analysis, and sensitivity testing has to be performed for each set of TaqMan probe/primers.

#### - Technical and laboratory aspects

- The diagnosis samples will be used for assessment of the complete Ig/TCR gene rearrangement status : *IGH* (VH-JH and DH-JH), *IGK* (V $\kappa$ -J $\kappa$ , V $\kappa$ -Kde, and intron RSS-Kde), *TCRD* (D $\delta$ 2-D $\delta$ 3, V $\delta$ 2-D $\delta$ 3, D $\delta$ 2-J $\delta$ 1, V $\delta$ J $\delta$ ), *TCRG*, *TCRB* (V $\beta$ -J $\beta$  and D $\beta$ -J $\beta$ ), and V $\delta$ 2-J $\alpha$ . Germline TaqMan probe/primer sets are available for all indicated Ig/TCR gene rearrangements. Junctional region-specific primers will be designed for three selected MRD-PCR targets (if available) and tested for sensitivity in TaqMan-based RQ-PCR assays.
- Follow-up samples of the patient will be analyzed and results delivered within 15 days after arrival.

Analysis of the RQ-PCR data will be performed according to the guidelines of the European Study

Group on MRD detection in ALL (ESG-MRD-ALL), a European Consortium of 35 Ig/TCR-MRD

laboratories. Based on the results of the sensitivity testing, at least two MRD PCR targets are selected, which reach a sensitivity of  $\leq 10^{-4}$ , including at least one target with a quantitative and interpretation range of  $\leq 10^{-4}$ .

- If a patient relapses, the Ig/TCR gene rearrangement pattern of the diagnosis and relapse samples will be compared to investigate the stability of the rearrangements.

### 3. MRD diagnostics via flow cytometry

#### - Principle of the analysis

Flow cytometry (FC), based on the detection of leukemia-associated immunophenotypic (LAIP) abnormalities at diagnosis, is a more recently introduced alternative MRD technique in ALL, the specificity, sensitivity and feasibility of which has increased with the development of multiparameter analysis.

Leukemic lymphoblasts differ from physiological lymphoid precursors in qualitative (for example, presence of myeloid markers or asynchronous antigenic expression) and quantitative antigen expression patterns. In addition, ectopic detection of immature phenotypes outside their normal tissues (e.g. detection of immature T-cells outside the thymus) can be used for MRD detection in particular in T-ALL. Such leukemia-associated immunophenotypes are present in the vast majority of ALLs, if a panel of at least 6–8 relevant markers in strategic combinations is used for assessment. This approach currently reaches sensitivities of 10–4, which is slightly less than that of molecular methods, because positivity of flow-MRD relies on detection of populations rather than single cells.

To be unambiguous, it needs to demonstrate a certain amount (10 to 20) of cells with similar (leukemia associated) characteristics ('cluster'). Leukemic cells identified within a complex mixture of

normal cells are then directly quantified as a ratio with other cells in the specimen without a need for external calibrators. The implementation of more than four-color (8–10 colors) techniques increased the applicability and sensitivity/specificity of the method, and allowed for simultaneous determination of extensive phenotypic patterns at the single-cell level. Further improvements in multicolor FC, standardization of instruments, new antibody panels, innovative fluorochromes, upgraded computerization and new software tools allowing for optimized data acquisition and automated pattern recognition are currently evolving.

A potential pitfall of the method results from similarities between leukemic lymphoblasts and nonmalignant lymphoid precursors in various phases of regeneration during and after chemotherapy that may lead to false positivity. So far, time-point-matched cross-leukemia-lineage BM samples can be used as adequate background controls. In addition, phenotypic shifts frequently occur in MRD cells during induction (compared with patterns at diagnosis) among others because of steroid-induced gene expression modulation. Nowadays, **expert knowledge** of typical time-point-related non malignant background and experience with patterns of phenotypic shifts of leukemic cells are essential to identify MRD properly and bypass these potential pitfalls.

In order to join therapeutic trials, several groups have shown that standardization of FC-MRD evaluation is feasible in a multi-center setting. In a recent study (Garand et al), a French standardization effort (within the STIC-06 network), including similar antibody panels and clones, fixed backbone, agreement on gating strategies for MRD determination and bi-annual workshops organization to collectively reviewed and re-analyzed results, allowed the establishment of a robust network of 8 laboratories capable of carrying out the evaluation of the MRD by flow cytometry.

#### - Technical and laboratory aspects

##### **Sample preparation**

- Both gradient separation and erythrocyte lysis are used as preparation methods.

Expression of homogeneous results can be achieved as Ficoll preparation can be mimicked by gating out high side-scatter cells when analyzing data files based originally on total nucleated cell preparations.

- A minimum of  $1-3 \times 10^6$  nucleated cells should be available for initial marker characterization and for follow-up analysis.

**- Initial diagnostic material for identification of the leukemic immunophenotype is highly recommended** and can be omitted only on very rare occasions (for example, availability of an early follow-up sample with high-level MRD without diagnostic sample available for flow-analysis).

**- Shipment should be performed within 24h for an acquisition within 48h after sample collection**

Shipment time is an important issue when analyzing vital cells and should optimally not exceed 24 h; however, dead cells should only be excluded from analysis if scatter properties are severely changed and autofluorescence is present.

**- Flow-MRD assessment should be performed on fresh samples**

Flow MRD relies on analysis viable cells. Leukemic cells viability is highly variable between samples but generally blast cells are fragile and die quickly. This prompts to perform MRD analysis on a fresh sample within 48h and avoid any assessment on thawed samples. Similarly, antigenic expression may also be affected by the thawing process meaning that the selection of LAPs should be based on analysis of a fresh leukemic sample.

**- Sample analysis**

- A minimum of 6–8 relevant markers in strategic combinations are recommended, that is, a constant backbone of 2–4 lineage markers, which allow tracking of the cells of interest in similar ways in all staining combinations, plus additional aberration markers.

Antibodies should be carefully selected for optimal performance and the choice of fluorochromes should be based on avoiding fluorochrome interactions and the type of marker (or aberration), to allow the best discrimination between normal and malignant cells. Controls for staining should be in accordance with standard FC procedures.

Selection of LAP at the diagnosis time point : a minimum of 2 LAP will be selected whenever possible from the diagnosis analysis. Selection will be performed based on known patterns of normal B-cell development / regeneration through chemotherapy courses and informative markers will be used during follow-up.

- The target sensitivity for Flow-MRD is 10<sup>-4</sup>

The detection limit of an FC MRD assay is partly determined by the minimum number of events that can reliably be used to define a population of neoplastic cells ('cluster'). It has been shown that under certain circumstances, accurate identification of a population using up to 4-color FCM requires at least 20 events. Final consensus on number of events required to identify positive MRD was not reached. Most MRD groups require a cluster of 20 events to define a significant population. To reach a sensitivity of 10E-4, number of cells that need to be acquired is thus of at least 200 000. In order to reach such a number of acquired events, a minimum of 1,000,000 cells should be stained.

#### Standardization and harmonized procedures

Instrument setup should be performed according to updated procedures to respect PMT minimum and ensure detection of low antigen-expressions. Monitoring of the instrument should be performed to check stability of the instrument and reproducibility over time of antigenic intensities.

Standardization based on written guidelines, along with suitable QC schemes, is a prerequisite for optimal usage of FC for MRD assessment in the clinical setting. Within the STIC-06 consortium, the 8 laboratories collaborate, bringing about and maintaining a high degree of similarity in MRD results with continued exchange of experience and external QC.

- In case of relapse, new phenotypic assessment will be performed as at the diagnosis time point to investigate an eventual phenotypic shift related to emergence of a subclone, or occurrence of a new leukemia or phenotypic modulation. Subsequent MRD assessment will then be based on the newly defined LAP in case of phenotypic changes.

#### **Time points for Flow-MRD analysis**

- Flow-MRD analysis should be concomitant to the molecular-MRD time points
- An additional time point could be considered depending on the center with the analysis of a day 8 and /or day 15 blood sample for early treatment response evaluation.

#### **4. Biobanking**

Sampling of patient's biological material will be performed at some of the sampling time points foreseen for the standard monitoring of the disease. Biobanking refers to the collection and storage of biological material or residual biological material or derivates in compliance with ethical and technical requirements as specified by the french regulation and/or legislation.

The biobank will be established by the MRD center with the remaining bone marrow material from routine tests at diagnosis and relapse.

An additional (5 ml) blood sample will be drawn at TP2 or later during molecular complete remission for constitutional DNA biobanking. The clinical centers for which Robert Debré is the MRD center will send this one with the TP2. For the others, blood samples will be sent in the suitability of the MRD centers .

The constitutional DNA biobanking will be established at Robert Debré Hospital – Laboratoire de Génétique Moléculaire – under the responsibility of Pr Hélène Cavé.

#### *In case of relapse*

If applicable, other biological material (tissues, cerebro-spinal fluid (CSF) or other), depending on the site of relapse will be biobanked at relapse, unless the patient is included in a second line protocol (see protocol IntReALL). In which case, it will be necessary to follow the rules of shipment according to the protocol of relapse.

#### **5. Timepoints for MRD assessment and biobanking**

##### **5.1 Timepoints**

Samples (peripheral blood, bone marrow, cerebrospinal fluid - CSF - and/or solid tissue) will be collected:

- At diagnosis, before starting treatment
- At the end of induction (TP1)
- At the end of consolidation (TP2)
- At relapse, before starting second line treatment, if applicable

Timepoint for sample collection	Type of samples	BCP-ALL	Threshold	T-ALL	Threshold	Remarks
<b>Diagnosis (before starting treatment)</b>	BM (+/-PB if blasts≥70%)	D0		D0		Biobanking of the remainder
<b>TP1</b>	BM	D35-42	10 <sup>-3</sup>	D35-42	10 <sup>-3</sup>	
<b>TP2</b>	BM	D65-75 (SR) or D95-105 (MR/HR/VHR)	10 <sup>-4</sup>	D85-95 (SR) or D95-105 (HR/VHR)	10 <sup>-3</sup> /10 <sup>-4</sup>	
		x		x		
	PB <sup>a</sup>		N/A		N/A	Constitutional DNA Biobanking
<b>Other timepoints (depending on result of MRD at TP2<sup>b</sup>)</b>	BM	D125-135 (HR/VHR)		D125-135 (HR/VHR)		
<b>At relapse (if applicable)<sup>c</sup></b>		x		x		Biobanking of the remainder

BM: bone marrow - PB: peripheral blood

<sup>a</sup> This blood sample is dedicated to constitutional DNA biobanking. In case this sample is not available (missing sample or positive MRD result at TP2), another sample will be collected later, at complete remission for constitutional DNA biobank.

<sup>b</sup> if MRD at TP2≥10<sup>-3</sup> (BCP-ALL) et MRD at TP2≥10<sup>-4</sup> (T-ALL)

<sup>c</sup> See on previous page, point 4 "Biobanking" - "In case of relapse"

Detailed description of the MRD network is indicated in appendix 18.

## 5.2. Logistics

Logistics of MRD diagnosis (samples collection and shipment) and biobanking are described in a separate technical form written in French and called « CAALL-F01 - Gestion des échantillons biologiques – MRD et BIOBANKING – Fiche technique »

## Appendix 4: CerebroSpinal Fluid (CSF) cytocentrifugation technique

### **Preanalytical phase**

Cerebrospinal fluid (CSF) is collected on sterile tube and order collection tube must be respected: the third tube is reserved for the microscopic examination of cellular components. If only a small amount of CSF is obtained and a single collection tube must be used, the ordering physician must prioritize cytological examination and record this priority on the requisitions.

Specimens must be delivered as soon as possible to the laboratory : it should be transported at room temperature within 1H after lumbar puncture and not more than 2H. If transport is delayed, specimens should be refrigerated and transported at 4°C.

### **Analytical phase**

The cytological examination requires a minimum of 500 µL of CSF. After reception, the specimen should be analyzed as soon as possible. The CSF sample should be homogenized by gentle inversion at least 10 times. Erythrocytes and leukocytes are counted by manual method. Undiluted fluid sample is introduced in a counting chamber of a conventional hematocytometer (Nageotte, Malassez) or a C-CHIP plastic disposable hematocytometer. Before manual counting erythrocytes and leucocytes, cells must be allowed to settle for about a few minutes in a humid room.

Direct cytocentrifugation method should be performed, using preferably Shandon Cytospin apparatus. Before cytocentrifugation 30 µL of hyperproteinated serum (serum albumin 30% or fetal calf serum) must be added. These serums add a protein concentration that will aid in cell to slide adhesion and decrease cellular distortion due to the centrifugal force. The volume of CSF to be centrifuged depends on cell count (Table 13).

**Table 12: Volume of CSF to be centrifuged**

Number of nucleated cells per mm <sup>3</sup>	Volume of CSF sample (µL)	Volume of hyperproteinated serum (µL)	Volume of saline solution 9% (µL)
If erythrocytes or leucocytes are <500/mm <sup>3</sup>	350 µL	30 µL	0 µL
If leukocytes are > 500/mm <sup>3</sup> : make a 1:2 dilution	175 µL	30 µL	175 µL
If erythrocytes are > 500/mm <sup>3</sup> : partitioned in at least 2 tubes and make a dilution*	Ex: 1:10 dilution 35 µL	30 µL	315 µL

\* A suitable dilution should be chosen to minimize erythrocyte contamination. The final volume of each diluted tube should be of 350 µL.

Specimens are spun at 800 RPM during 8 to 15 minutes (70 g for Shandon Cytospin apparatus) mode LOW.

Slides need to be air-dried at room temperature during 5 minutes before classical staining with May-Grünwald Giemsa or Wright.

### **PostAnalytical phase**

After microscopic examination, CSF samples should be stored during 24 hours at +4°C.

## Appendix 5: Central Nervous System

### Some issues, involvement definitions, intrathecal (IT) injections (nature of drugs and dose), summary of IT injections according to group

#### SOME IMPORTANT ISSUES

- Any lumbar puncture (and particularly the diagnostic lumbar puncture) must be done under a stable hemostatic condition. This means that the level of platelets shortly before lumbar puncture must be at least  $> 50\,000/\text{mm}^3$ .
- Because it is important to avoid blood contamination in the first lumbar puncture:
  - this procedure should be done by an experienced doctor;
  - the level of white blood cells must be  $< 100\,000/\text{mm}^3$  and the procedure not delayed after Day 4.
- The volume of medication must be  $\geq 6 \text{ ml}$  (this is the same volume that is redrawn during the puncture).
- The use of the smallest needle possible is recommended to decrease the leak of CSF and prevent post-puncture headache.
- Just after the lumbar puncture the patient must be brought or stays in prone position during at least 1hour (to increase the intra-ventricular concentration of chemotherapy).

#### DEFINITIONS

##### 1. Non-traumatic initial lumbar puncture

The patients having a **non-traumatic initial lumbar puncture** ( $< 10 \text{ erythrocytes}/\mu\text{L}$ ) must be classified in one of the three following categories, according to the number of elements (white blood cells)  $/\mu\text{L} = \text{mm}^3$ , and the presence or the absence of blasts on the smear read after cyt centrifugation (cytospin cf **Appendix 4**):

- **CNS1:** CSF without blasts on the smear read after cyt centrifugation
- **CNS2:** CSF with less than 5 elements/ $\text{mm}^3$  and presence of blasts on the smear read after cyt centrifugation.
- **CNS3:** CSF with 5 or more elements/ $\text{mm}^3$  and presence of blasts on the smear read after cyt centrifugation

##### 2. Traumatic initial lumbar puncture

The patients having a **traumatic initial lumbar puncture** ( $\geq 10 \text{ erythrocytes}/\mu\text{L}$ ) must be classified in one of the two following categories:

- **Traumatic lumbar puncture with blasts (TLP +):**  $\geq 10 \text{ erythrocytes}/\mu\text{L}$  and blasts in the smear obtained after cytospin
- **Traumatic lumbar puncture without blasts (TLP -):**  $\geq 10 \text{ erythrocytes}/\mu\text{L}$  and no blasts in the smear obtained after cytospin: patient is treated as CNS1

To determine if a patient who had a traumatic lumbar puncture with blasts must be considered as having a meningeal involvement (CNS3), the algorithm of the Children Oncology Group (COG) should be used. It is based on the relative concentrations of the white blood cells and the red blood cells, in the CSF and in the blood:

*If the white blood cells/red blood cells ratio in the CSF is  $\geq 2$  upper to the white blood cells/red blood cells ratio in the peripheral blood, the patient is considered as having a *meningeal involvement* and considered CNS3.*

*If the white blood cell/red blood cell ratio in the CSF is  $< 2$  to the white blood cells/red blood cells ratio, the patient is considered CNS2*

##### 3. Are also considered as CNS3, whatever the result of the CSF analysis, the patients presenting with:

- Paralysis of one or more cranial pairs (irrespective of CSF or imaging findings)

- Intra-cerebral or meningeal leukemic mass/infiltration seen on the MRI or CT scans compatible with the diagnosis of specific involvement due to ALL.

## **INTRATHECAL INJECTIONS: NATURE AND DOSE**

### **1. Simple intrathecal injections**

<b>Age (years)</b>	<b>MTX methotrexate for IT</b>
1 ≤ age <2	8 mg
2 ≤ age < 3	10 mg
3 ≤ age <10	12 mg
≥10	15 mg

### **2. Triple intrathecal injections:**

<b>Age (years)</b>	<b>MTX methotrexate for IT</b>	<b>Ara-C cytarabine</b>	<b>Hydro-Cortisone HemiSuccinate</b>
1 ≤ age <2	8 mg	20 mg	10.0 mg
2 ≤ age < 3	10 mg	25 mg	12.5 mg
3 ≤ age <10	12 mg	30 mg	15.0 mg
≥10	15 mg	30 mg	15.0 mg

## SUMMARY OF INTRATHECAL INJECTIONS (ITs) ACCORDING TO GROUP

NB : *In case of extremely delayed first IT (D8), the total number of ITs expected according to group stratification and CNS status, must be performed during induction therapy.*

*For example: 5 ITs to be spread during induction of CNS3 patients, if no IT has been given prior to D8.*

### 1. Patients with a CNS1 status: see table below

NB: this is the more frequent situation. *Recall that IT n°1(D1) is with methotrexate only in all groups*

**Summary of Intrathecal injections for CNS1 patients**

	Induction	Consolidation		M phase	Delayed Intensification	M phase n 2	Delayed intensification n 2	Maintenance	Total ITs
<b>ALL B-SR</b>	<b>D1</b> D13 D24	<b>D2</b> D30 D58			<b>D4</b> D31			<b>M1, M3, M5, M7, M9, M11, M13, M15</b>	<b>16</b>
<b>ALL B-MR</b>	<b>D1</b> D13 D24	<b>D3</b> D31		<b>D9</b> D23 D37 D51	<b>D4</b> D31			<b>M1, M3, M5, M7, M9, M11</b>	<b>17</b>
<b>ALL B-HR</b>	<b>D1</b> D13 D24	<b>D3</b> D31		<b>D9</b> D23 D37 D51	<b>D4</b> D31	<b>D9</b> D23 D37 D51	<b>D4</b> D31	<b>NO</b>	<b>17</b>
<b>ALL T-SR</b>	<b>D1</b> D13 D24	<b>D3</b> D17		<b>D9</b> D23 D37 D51	<b>D4</b> D31			<b>If WBC &lt;100 G/L W2,W8,W14, W20,W26,W32</b>	<b>17</b>
								<b>If WBC ≥100 G/L MTX HD +IT W2,W8,W14, W20,W26,W32</b>	<b>17</b>
<b>ALL T-HR</b>	<b>D1</b> D13 D24	<b>D3</b> D31	<b>VANDA D5</b>	<b>D9</b> D23 D37	<b>D4</b> D31	<b>D9</b> D23 D37	<b>D4</b> D31	<b>If WBC &lt;100 G/L W2,W8,W14, W20,W26,W32</b>	<b>22</b>
								<b>If WBC ≥100 G/L MTX HD +IT W2,W8,W14, W20,W26,W32</b>	<b>22</b>

### 2. Patients with initial CNS2 or TLP+ status

NB1: patients with CNS-2 or TLP + status are to be included in the same stratification group than CNS-1 patients but with a **reinforced intrathecal treatment during induction** therapy .

NB2: due to the higher frequency of CNS2 status observed in many cooperative groups and centers after modified techniques prior to cytopsin reading (as high as 40% of the patients), it is not recommended to perform an early IT n°2 which is a potential cause of bias in evaluation of D8 response to prednisone prophase.

#### 2.1. Composition of intrathecal injections

Patients will receive during induction:

- on day 1: intrathecal injection with **MTX only**
- on day 9 and after: intrathecal injection with one drug (MTX) or 3 drugs (TIT): MTX, cytarabine, hydroxy-cortisone hemi-succinate) **according to initial group stratification**

#### 2.2. Schedule of IT administrations

**5 IT injections** will be performed during induction (in red supplementary injections):

- D1, **D9**, D13, **D18**, D24

### **3. Patients with initial CNS3 status**

NB1: patients with CNS involvement are allocated to the High Risk group (B or T)

NB2: ***no CNS irradiation will be given during the CAALF01 therapy, except for the few patients who will be eligible for a total body irradiation prior to a stem cell transplantation.***

#### **3.1. CNS3+ patients with B-Lineage leukemia**

##### **3.1.1. Composition of intrathecal injections**

Patients will receive during induction:

- on day 1: intrathecal injection with MTX only
- on day 4 and after: intrathecal injection with 3 drugs (TIT): MTX, cytarabine, hydroxy-cortisone hemi-succinate) *except for M phases (Simple IT: MTX only)*

##### **3.1.2. Schedule of IT administrations (in red supplementary injections):**

###### **a) B-HR CNS3 without indication for HSCT**

- induction : D1, **D4, D9**, D13, D24
- consolidation: D3, **D16**, D31, **D46**
- M phase: D9, D23, D37, D51
- delayed intensification N°1 : D4; D31
- M phase: D9, D23, D37, D51
- delayed intensification N°2 : D4, D31
- maintenance: **4** supplementary TIT (M1, M4, M7, M10)

*Total number of I.T. injections in case of initial CNS-involvement: 25*

*Total number of HD-MTX: 8*

###### **b) B -HR CNS3 but with indication for HSCT**

- induction : D1, **D4, D9**, D13, D24
- consolidation: D3, **D16**, D31, **D46**
- +/- M phase D9
- VANDA: D5,
- +/- modified R1 (HD-MTX 5g/m<sup>2</sup> over 24h) : D2
- +/- modified R2 (HD-MTX 5g/m<sup>2</sup> over 24h) : D2
- one IT within 15 days before D1 of conditioning regimen is allowed if more than 21 days have been elapsed since D1 of last course R1/R2.

#### **3.2. CNS3+ patients with T-cell ALL**

##### **3.2.1. Composition of intrathecal injections**

Patients will receive during induction:

- on day 1: intrathecal injection with MTX only
- on day 4 and after: intrathecal injection with 3 drugs (TIT): MTX, cytarabine, hydroxy-cortisone hemi-succinate) *except for M phases and maintenance (Simple IT: MTX only)*

### 3.2.2. Schedule of IT administrations

I.T. injections will be performed during (in red supplementary injections):

#### a) T-HR CNS3 without indication for HSCT

- induction : D1, **D4, D9**, D13, D24
- consolidation: D3, **D16**, D31, **D46**
- VANDA: D5,
- M phase: D9, D23, D37
- delayed intensification n°1 : D4; D31
- M phase: D9, D23, D37
- delayed intensification n°2 : D4, D31
- maintenance:
  - patients will receive High dose MTX ( $5\text{g}/\text{m}^2$ ) courses : one every six weeks: at week 2, 8, 14, 20, 26, 32 (total: 6 courses, including then 6 IT)

*Total number of I.T. injections in case of initial CNS-involvement: 26*

*Total number of HD-MTX: 12*

#### b) T-HR CNS3 with indication for HSCT

- induction : D1, **D4, D9**, D13, D24
- consolidation: D3, **D16**, D31, **D46**
- VANDA: D5,
- +/- M phase D9
- No intrathecal therapy during the nelarabine course
- One IT within 15 days before D1 of conditioning regimen is allowed if more than 21 days have been elapsed since D1 of nelarabine course

## Appendix 6: Asparaginase-related studies

### Overview of asparaginase-related studies

3 determinations related to the experimental drug will be applied:

**a. Asparaginase activity will be monitored as follows:**

- i. in all the patients included in all the centers for the whole duration of the study (5 years)
- ii. in plasma by collection of peripheral blood on heparin at defined sampling times
- iii. centralized and assayed in Robert Debré Hospital (Dr Benoist): ~20,000 samples

**b. Asparagine depletion will be monitored as follows:**

- i. In a subgroup of patients included in only 4 centers (Paris Armand Trousseau, Paris Robert Debré, Paris Saint-Louis and Lyon) during the 2 first years of the trial
- ii. In CNS sampled on tubes without any anticoagulant and in plasma by collection of peripheral blood on heparin at defined sampling times
- iii. CNS and blood samples will be centralized in Lyon (Dr Saban): ~ 1500 samples

**c. Antibodies directed against asparaginase and against PEG will be monitored as follows:**

- i. in all the patients included in all the centers for a limited period (first 2 years of inclusion)
- ii. In serum obtained from peripheral blood collected in tubes without any anticoagulant at defined sampling times
- iii. Samples will be centralized and analysed in US (BioAgilytix) : ~2000-2500 samples

**Sampling calendar****Sampling for CAALL-F01 (all centers)**

	Induction*	Consolidation	M phase	Delayed Intensification	M phase	Delayed intensification n°2	Total sampling
<b>ALL B-SR 1000 pts</b>	D12 D19 D26 D33 D40	D8 D8 D15 D43 D71		D4 D8 D15			Ase: 10  AB: 3
<b>ALL B-MR 480 pts</b>	D12 D19 D26 D33 D40	D15 D22 D50		D4 D8 D15			Ase: 8  AB: 3
<b>ALL B-HR 230 pts</b>	D12 D19 D26 D33 D40	D15 D22 D50		D4 D8 D15 D50		D4 D8 D15 D50	Ase: 12  AB: 4
<b>ALL T-SR 150 pts</b>	D12 D19 D26 D33 D40			D4 D8 D15			Ase: 6  AB: 2
<b>ALL T-HR 110 pts</b>	D12 D19 D26 D33 D40	D15 D22 D50		D4 D8 D15 D50		D4 D8 D15 D50	Ase: 11  AB: 4

Dxx: antibodies (AB) (first 2 years only)

Dxx: asparaginase activity (Ase)(whole study duration)

**Extended Sampling for CAALL-F01: 4 centers**

	Induction*	Consolidation	M phase	Delayed Intensification	M phase	Delayed intensification n°2	Total sampling
<b>ALL B-SR</b>	D12 D12 D19 D26 D33 D40	D8 D8 D15 D43 D71		D4 D8 D15			Ase: 10  ASN: 7  AB: 3
<b>ALL B-MR</b>	D12 D12 D19 D26 D33 D40	D15 D22 D50		D4 D8 D15			Ase: 8  ASN: 7  AB: 3
<b>ALL B-HR</b>	D12 D12 D19 D26 D33 D40	D15 D22 D50		D4 D8 D15 D50		D4 D8 D15 D50	Ase: 12  ASN: 7  AB: 4
<b>ALL T-SR</b>	D12 D12 D19 D26 D33 D40			D4 D8 D15			Ase: 6  ASN: 7  AB: 2
<b>ALL T-HR</b>	D12 D12 D19 D26 D33 D40	D15 D22 D50		D4 D8 D15 D50		D4 D8 D15 D50	Ase: 12  ASN: 7  AB: 4

\*Asparagine (ASN) in CNS:

Dxx: antibodies    Dxx: activity plus asparagine    Dxx: activity only    Dx: asparagine only    only at D13 &amp; D24 of induction

## Asparaginase activity measurement

### 1. Summary of the technique

Asparaginase activity in plasma is followed by measurement of the ammonium production catalyzed by the enzyme from its natural substrate the asparagine. Asparaginase catalyzes the hydrolysis of asparagine into aspartate and ammonium. The ammonium release is measured using a secondary reaction catalyzed by the glutamate dehydrogenase. The later enzyme combined ammonium together with  $\alpha$ -ketoglutarate and NADPH to produce glutamate. The NADPH consumed by the reaction absorbs at 340 nm (Molar Coefficient of Absorption  $\epsilon = 3200 \text{ L.mol}^{-1}.\text{cm}^{-1}$ ). Hence, the reaction is monitored by the decrease of the absorbance at 340 nm. Results are expressed in Units per liter (U/L, quantity of enzyme that catalyzed the transformation of 1 micromole of asparagine per minute and per liter of plasma). The lower limit of quantification is 2 U/L.

### 2. Sampling for asparaginase activity: practical considerations

All samples for asparaginase activity measurement must be labeled with labels available in the investigator's file. Example of the label for the asparaginase activity analysis:

CAALL-F01 – Date : _ / _ / _	J I I
ID° Patient: I I I I I I I I I I I I	
X Activité <input type="checkbox"/> Déplétion <input type="checkbox"/> Anticorps	

- 1.2 to 5 ml of peripheral whole blood is to be collected in a heparine tube (EDTA tolerated) with separator gel (specific gel tube ++++ BD Vacutainer® PST™).
- Immediately after blood sampling, do not shake the tube but homogenize by gentle reversal.
- The tube is then transferred to the laboratory where it must be centrifuged:
  - room temperature or 4°C
  - 2000 g (around 3000 rpm for classical laboratory centrifuge)
  - 5 to 10 minutes
- The tube is then directly frozen and stored at -20 °C in boxes
- At D33 the shipment of the complete pack of induction samples (SHIPMENTn°1 of the protocol) is to be done. This shipment can be done at room temperature as thawing will occur during transportation without having an impact on the test. The asparaginase lab in Robert Debré Hospital (Dr J.F. Benoist : 01 40 03 33 65 ; [jean-francois.benoist@rdb.aphp.fr](mailto:jean-francois.benoist@rdb.aphp.fr)) is to be contacted prior to the shipment for checking for reception.
- From D40 to last asparaginase activity sampling delayed intensification n°1 or 2, samples are collected and stored at -20°C as described above. After the last sampling, SHIPMENT n°2 (package of all tubes since D40) is to be done in the same way as SHIPMENT n°1 was performed.

## Asparagine depletion measurement

### 1. Summary of the technique

Asparagine measurement is performed using reverse phase liquid chromatography combined with electrospray ionisation by tandem mass spectrometry (LC-ESI-MS/MS). Selectivity is given by LC separation followed by quantification with MRM mode monitoring using specific transitions for Asn and its stable isotope  $^{13}\text{C} - ^{15}\text{N}$  used as internal standard. Plasma asparagine concentration is expressed in  $\mu\text{mol}/\text{L}$ . The LOQ is 0.4  $\mu\text{mol}/\text{L}$ .

### 2. Blood sampling for asparagine measurement: practical considerations

All samples for asparagine measurement must be labeled with labels available in the investigator's file.

Example of the label for the asparagine depletion analysis:

CAALL-F01 – Date : _ _ / _ _ / _ _	J I I
ID° Patient: I I I I I I I I I I I I	
<input type="checkbox"/> Activité X Déplétion <input type="checkbox"/> Anticorps	

- 1.2 to 5 ml of peripheral whole blood is to be collected in a heparine (EDTA tolerated) tube with separator gel (specific gel tube ++++ BD Vacutainer® PST™).
- Immediately after blood sampling, do not shake the tube but homogenize by gentle stirring.
- Then put it immediately in an ice containing bag or bowl.
- The tube is then quickly transferred to the laboratory where it must be centrifuged within 30 minutes after the sampling as follows:
  - 4°C
  - 2000 g (around 3000 rpm for classical laboratory centrifuge)
  - 5 to 10 minutes
- The tube is then directly frozen and stored at -80 °C in boxes

### **3. CSF sampling and treatment**

- The sample must be collected in a 5 ml conical-bottomed plastic tube (Specific tube).  
The minimum volume to be collected is 0.5 mL (10 drops).
- Immediately after collection put the tube in an ice containing bag or bowl.
- Centrifuge within 30 minutes after taking as follows:
  - 4°C
  - 2000 g (around 3000 rpm for classical laboratory centrifuge)
  - 5 to 10 minutes
- The supernatant is transferred in a new labelled cryotube and immediately frozen to be stored at -80°C in the same boxes as blood samples.

### **4. Common shipment for blood and CNS liquor**

Shipment of the samples to Lyon (Bron hospital) is scheduled as soon as all samples for five patients are obtained (35 tubes) .

When prepared for shipment, the samples must be carefully packed in suitable material containing sufficient dry ice to keep them frozen during shipment. A list of samples, including the date, subject number, and the time of sampling should be included in the shipment, and simultaneously sent by e-mail (christine.saban@chu-lyon.fr; cecile.acquaviva-bourdain@chu-lyon.fr ). Any missing samples should be notified on the list.

At D40 the shipment of the complete pack of induction samples (SHIPMENT ASPARAGINE of the protocol) is to be done. This shipment must be done in dry ice. The asparagine lab in Lyon (Bron): **Dr Saban and Dr Acquaviva (téléphone : 0472129694 or 0472129691 or 0472129632; e-mail: christine.saban@chu-lyon.fr ; cecile.acquaviva-bourdain@chu-lyon.fr )** is to be contacted prior to the shipment for checking for reception.

#### **Antibodies against asparaginase:**

##### **1: Summary of the technique:**

All samples for antibodies must be labeled with labels available in the investigator's file. Example of the label for the Antibodies analysis:

CAALL-F01 – Date : _ _ / _ _ / _ _
ID° Patient:
I _ I _ I - I _ I _ I _ I - I _ I
J I _ I
<input checked="" type="checkbox"/> Anticorps <input type="checkbox"/> Depletion LCR

- 3 to 5 ml of peripheral whole blood is to be collected in a heparine tube with separator gel (specific gel tube +++++ BD Vacutainer® PST™ ).
- Immediately after blood sampling, do not shake the tube but homogenize by gentle reversal.
- The tube is then transferred to the laboratory where it must be centrifuged:
  - room temperature or 4°C
  - 2000 g (around 3000 rpm for classical laboratory centrifuge)
  - 5 to 10 minutes
  - The supernatant is transferred in 2 new labelled cryotubes and immediately frozen to be stored at -20°C in the same boxes as blood samples. At least 0.6ml in each cryotube is needed

## 2: Shipment of the samples:

- Twice a year, in May and November, each laboratory will send all his antibodies samples to Robert Debre Hospital to Dr J.F benoist (**Dr J.F. Benoist : 01 40 03 33 65 ; [jean-francois.benoist@rdb.aphp.fr](mailto:jean-francois.benoist@rdb.aphp.fr)**) He is to be contacted prior to the shipment for checking for reception. All antibodies samples are centralized by Dr benoist before shipment to the US to BioAgilytix for Clinical test in June and December.

## 3: Assay Of the Clinical test samples:

Laboratory Contact: BioAgilityx

### 3.1 : Assay of the clinical test samples.

#### 3.1.1 Sample Accessioning

BioAgilytix will receive samples in batches from the clinical sites. Each case will be accessioned individually into BioAgilytix's secure database and will be assigned an internal tracking number.

#### 3.1.2 Immunogenicity Assay

Each sample is subjected to 1st Tier immunogenicity assay in which the sample is deemed positive or negative with regard to the presence of anti-Oncaspar (or EZN 2285) antibodies. Samples which test positive in the 1st Tier are subjected to "2nd Tier" analysis in which the titer of the reactive antibody is determined. Samples which test positive in the 1st Tier are also subjected to neutralizing activity assay.

At present, a total of about 2000-2500 samples are anticipated for immunogenicity assay. Of these, probably no more than 20% (400 or so samples) will test positive in the 1st Tier assay.

#### 3.1.3 Neutralization Assay

Samples which test positive in the 1st Tier immunogenicity assay are also subjected to asparaginase neutralizing activity assay to assess the presence of neutralizing antibodies.

#### 3.1.4 Anti-PEG Antibody Assay

The presence of antibodies to PEG in the test plasma samples is done by ELISA per company SOP IMMUNO00033 "Detection of Anti-PEG Antibodies in Human Plasma

## 3.2: Sample retention.

All test samples received from the clinical test sites will be stored under appropriate condition (assumed to be frozen at <-65 C) for the requisite period of time specified by the Sigma Tau. BioAgilytix has deep freezers, and

refrigerators, frost-free freezers, and frost freezers in a separate area accessible by magnetic card reader to authorized personnel only for use in storing customer samples.

### **3.3: Sample Handling**

It is anticipated that the clinical sites will send a minimum of TWO tubes of each sample. The plasma in one tube will be used for the 1st Tier assay and for the PEG assay; the plasma in the 2nd Tube will be used for the 2nd Tier and neutralization assays. Any unused sample will be archived at <-65C for the period of time specified by Sigma Tau.

Each sample tube should contain a minimum of 0.3 mL plasma which will be sufficient for conduct of the assays. Each plasma sample should be frozen at the collection site and then sent by overnight express mail delivery on dry ice to **BioAgilytix**.

Samples will be assayed on arrival at **BioAgilytix**. AAU review is done on completion of the assay work. The results summary will be provided to Sigma Tau on a monthly basis.

### **3.4: Electronic Reporting of the Results.**

Unless instructed otherwise, **BioAgilytix** will provide the results in the form of locked spread sheets transmitted to the contact person at Sigma Tau as specified by Sigma tau.

## Appendix 7: Asparaginase administration guidelines

### The asparaginases used in CAALF01

- a) **Oncaspar®** (pegylated E.coli L-asparaginase or pegaspargase) is supplied either as a sterile solution or as a lyophilisate, both in Type I single-use vials containing 3,750 International Units of L-asparaginase per 5 mL solution. Oncaspar® is to be stored under refrigeration at 2°C to 8°C. Product must not be shaken or frozen.
- Oncaspar® is administered IV in this protocol over 1 hour.
- Doses vary according to stratification group and/or randomization and are specified in the main protocol.
- The Oncaspar® is obtained through the protocol. Each patient will receive Oncaspar® from labelled vials.
- b) In case of allergy: **Erwinase®** Crisantaspase (Erwinia chrysanthemi L-asparaginase or Crisantaspase, JAZZ Pharmaceuticals) is supplied as a powder in vial containing 10,000 International Units of L-asparaginase. When reconstituted with 1 mL, the resultant concentration is 10,000 IU/mL. When reconstituted with 2 mL, the resultant concentration is 5,000 IU/mL. Dissolve contents by gentle mixing or swirling. Do not shake or invert vial. Withdraw the volume containing the calculated dose from the vial into a polypropylene syringe within 15 minutes of reconstitution. Do not freeze or refrigerate reconstituted solution; administer within 4 hours or discard.

Erwinase can be administered IV over one hour.

Due to its shorter half-life, ASP Erwinia chrysanthemi must be administered at higher doses and/or more frequently than PEG-ASP or native E coli ASP in order to maintain consistent asparagine depletion. Results of the Children's Oncology Group (COG) ALL07P2 trial showed that 25,000 IU/m<sup>2</sup> ASP Erwinia chrysanthemi administered IM 3 times a week achieved ASP activity >0.1 IU/mL in 92.7% of evaluable patients at 48-hours and 88.4% of evaluable patients at 72-hours postdose. Based on these results, the substitution dose of ASP Erwinia chrysanthemi recommended by the FDA in patients with hypersensitivity to E coli-derived ASP is 25,000 IU/m<sup>2</sup> administered IM for each scheduled dose of native E coli asparaginase or 3 times a week (Monday/Wednesday/Friday) for 6 doses for each planned dose of PEG-ASP. The current AIEOP-BFM ALL 2009 trial recommends the following: substitution of a single administration of PEG-ASP by seven doses of 20,000 IU/m<sup>2</sup> ASP Erwinia chrysanthemi administered IV every other day for two weeks. The UKALL protocols substitute one dose of 1000 IU/m<sup>2</sup> by a total of six doses of 20,000 IU/m<sup>2</sup> ASP Erwinia chrysanthemi administered IV 3 times a week (Monday, Wednesday, Friday).

**As dose/peak does not seem to influence the length of depletion, the choice in CAALL F01, where asparaginases are to be infused IV, is to recommend that**

- a) a single administration of 2500 IU/m<sup>2</sup> of pegaspargase is to be substituted by seven doses of 20,000 IU/ m<sup>2</sup> crisantaspase administered IV every other day for two weeks.
- b) a single dose of 1250 IU/ m<sup>2</sup> is also to be substituted by seven doses of 20,000 IU/ m<sup>2</sup> crisantaspase administered IV every other day for two weeks.

### Expected adverse events linked to asparaginase administration

#### 1. Hypersensitivity

The asparaginase administration should be performed under medical supervision considering the risk of hypersensitivity reaction. The patient must be supervised at least one hour after administration. The risk of hypersensitivity is more important when the L-asparaginase is reintroduced.

In case of hypersensitivity reaction ≥grade 1, the pegaspargase infusion must be stopped immediately and investigator must follow the recommendations below the patient should receive crisantaspase (Erwinase) as mentioned above.

Facilities and equipment for resuscitation have to be immediately available: antihistamine (e.g. dexchlorpheniramine), steroids, adrenaline will be administered according to the event severity.

***BELOW ARE THE RECOMMENDATIONS IN CASE OF ALLERGIC REACTIONS TO ONCASPAR******In case of any doubt please contact national coordinators for advice******I/ Allergy and/or clinical reaction linked to Oncaspar at D12 or D26 during induction******A) FOR ALL GROUPS, IF CLINICAL REACTION AT FIRST PEGASPARGASE INFUSION (D12): This event is rare (< 5%) but not mandatory linked to the asparaginase moiety. Thus these reactions need***

1. precise evaluation of the infused volume

2.send a sample for REAL-TIME monitoring of asparaginase activity (H48or H72).

*Those 2 elements will be taken into account by the Asparaginase Lab (Paris Robert Debré) and PIs to give one the following advices**- adequate activity: use pegaspargase with premedication (antihistaminic +/- dexamethasone)**- non adequate activity: switch to Erwinia for only one course (whatever the randomization) of 7 infusions administered every other day ( see above)****B) FOR ALL GROUPS, IF CLINICAL REACTION AT ONCASPAR INFUSION AT DAY26 OF INDUCTION (HR AND SR/MR ARM 2)***

1.Precise evaluation of the infused volume

2.send immediately D19 and D26 samples for Real time monitoring of Asparaginase activity

- o If adequate Asparaginase activity ( $\geq 100\text{UI/L}$  at both time points): Do not administrate Erwinia for induction.
- o If non adequate Asparaginase activity at one time point: ***switch to Erwinia for only one course of 7 infusions administered every other day ( see above)***

3.Patients are to finish induction according to the initial stratification group

4.For consolidation and If non adequate Asparaginase activity at least one time point (D19 and/or D26)

- o For B-SR group: follow the same recommendations as early allergy at day 8 of consolidation; switch in B-MR group (consolidation w/o Erwinia; administer Erwinia during delayed intensification (7 infusions)
- o For MR and HR groups: No group switching. Consolidation w/o any asparaginase; Erwinia will be used during intensification (7 Erwinia infusions for each infusion of oncaspar to be replaced)

5. For consolidation and adequate Asparaginase activity at all time points D19, D26, D33) : reintroduction of pegaspargase with premedication (antihistaminic +/- dexamethasone) can be discussed

***II: Allergy and/or clinical reaction linked to Oncaspar during consolidation******A: For the B-SR group:******- Early allergy occurring at D8 of consolidation:***

- do not give the replacement doses with Erwinia from D10,
- treat according to the MR group from D1 of MR group consolidation but perform the consolidation w/o Erwinia. Reserve Erwinia for delayed intensification (7 infusions)

***- Early allergy occurring at D36 of Consolidation and SR status confirmed (MRD TP1 and TP2 OK, IKZF1 germline)***

- do not give the replacement doses with Erwinia from D38.
- further treatment will depend on the previous asparaginase activities:
  - o Adequate asparaginase activities measured at D33IND & D15CONSO OK (Activity  $\geq 100\text{ IU / l}$  for the 2 points): leave the pt in the SR group. Do not give Erwinia at D64 but reserve it for delayed intensification (7 infusions).

- asparaginase activity measured at D33IND or D15CONSO unsatisfactory (at least one point <100 IU / L): switch the pt to the MR group: resume from the D29 MR consolidation but do not give Erwinia. Reserve Erwinia for delayed intensification (7 infusions).
- Early allergy occurring at D64 of Consolidation and confirmed SR status (MRDTP1 and TP2 OK, IKZF1 germline)
  - do not give Erwinia replacement from D66.
  - further treatment will depend on previous asparaginase activities
    - Adequate asparaginase activities measured at D33IND & D15CONSO & D43CONSO OK (Activity ≥ 100 IU / L for the 3 points): patients stay in the SR group. Reserve Erwinia for delayed intensification (7 infusions).
    - asparaginase activity measured at D33IND or D15CONSO or D43CONSO unsatisfactory (at least one point <100 IU / L): asparaginase activity measured J33IND OK, J15CONSO J43CONSO or unsatisf: switch to the MR group from D1 of the M Phase. Administer Erwinia during delayed intensification (7 injections )

**B) For the B-MR or HR or T-HR groups :**

- early allergy at D15 or D43 of consolidation: no longer give Oncaspar during consolidation. During the delayed intensification, administration of Erwinia (7 infusions)

**C) FOR ALL PATIENTS WITH ALLERGIC REACTION TO ONCASPAR, ALL AVAILABLE PK SAMPLES MUST BE SENT IN EMERGENCY TO Dr JF BENOIST (BIOCHEMISTRY, Robert Debré Hospital, Paris) FOR REAL TIME DETERMINATION OF ASPARAGINASE ACTIVITY (pre-allergic reaction samples and H48 post allergy; secondarily send a D7 Sample)**

## 2. Coagulopathy and thrombosis

### (a) In case of hypofibrinogenemia (<0.5 g/L)

– Postpone the asparaginase infusion,

**To be noted:** The main risk is the occurrence of a thrombosis; therefore, fibrinogen and plasma cannot be recommended because they were reported as being responsible for possible appearance of thrombosis.

### (b) Antithrombin level should be monitored at the same time:

- A low antithrombin level does not contraindicate the administration of the asparaginase
- Intravenous infusion of antithrombin (ACLOTINE®) could be performed to improve the level. One IU/Kg is necessary to increase the level of 2%. The target could be a level of 80 to 100%. The maximal infusion rate should not exceed 400 IU/min.
- The monitoring of the antithrombin level should be continued until the week after the last dose of asparaginase and afterwards if necessary.

### (c) Thrombosis

**To be noted: no oral contraception is allowed in the CAALF01 protocol since it increases the risk of thrombosis** already augmented by:

- Thrombophilia due to the disease
- Asparaginase
- Compression of vascular axes
- Central lines

(Progestins use can be proposed but only to limit menometrorrhagia and not as a contraception method)

Central nervous system (CNS) thrombosis involving the cerebral venous sinuses is a unique feature of asparaginase-related thrombosis and is reported to occur in 1–3% of patients. Headaches during induction should be interpreted with caution. If other classic causes are not found (e.g. hypertension, drug-induced headache, hypoglycemia) a CNS imaging should be performed, particularly when platelets are increasing at the end of induction. Seizures are also a classic symptom revealing a CNS thrombosis.

**In case of CNS thrombosis and other sever thrombosis:** Asparaginase should be withdrawn if possible.

- Anticoagulation should be undertaken with Low Molecular Weight Heparin (LMWH).
- Reintroduction of asparaginase for the next phase with LMWH is only possible if clinical, radiological features have improved and timing should be discussed with the study coordinators.
- In case of other sever thrombosis (e.g. Pulmonary embolism) : some recommendation for Reintroduction of asparaginase should be followed-up

### **3. Diabetes**

- When stabilized, the diabetes should not be a contraindication of the administration of asparaginase.

### **4. Pancreatitis**

- pancreatic lipase and amylase levels should be tested before each asparaginase infusion
- In case of abdominal pain associated with pancreatic enzymes increase, a pancreatitis should be evoked and an abdominal ultrasound should be performed. A CT scan is more interesting after few days for a full evaluation of intra thoracic and intra-abdominal damages.
- A suspicion of acute pancreatitis should lead to withhold the treatment with asparaginase, at least temporarily.
- A established diagnosis of acute pancreatitis NCI Grade 4 leads to a definitive withdrawal of the asparaginase
- An increase of pancreatic enzymes associated with abdominal pain (transient abdominal pain-hyperamylasemia syndrome) does not contraindicate the re-use of the asparaginase after discussion with the study coordinator and with a close monitoring.

### **5. Liver toxicity / bilirubin**

- a) **Some abnormalities of liver test results occur in almost all patients treated with asparaginase.** Most typical is a decrease in serum albumin and clotting factors (including II, V, VII, VIII, IX, prothrombin and fibrinogen) due to inhibition of hepatic protein synthesis. *Most patients also have a rise in alkaline phosphatase levels and a lower proportion have increases in serum aminotransferase levels and bilirubin.* Symptoms of fatigue and anorexia may be present. The inhibition of clotting factor and thrombolytic activity rarely results in excess bleeding, but paradoxically can also cause excessive clotting and a hypercoagulable state. Serum aminotransferase elevations during asparaginase therapy are mild-to-moderate in severity (2 to 10 times the upper limit of normal) and self-limiting. The abnormalities typically arise after 2 to 3 weeks of therapy and resolve within 2 to 4 weeks of stopping. *The hepatic dysfunction is accompanied by hepatic steatosis which can be severe and accompanied by jaundice, hepatomegaly and evidence of hepatic failure (somnolence, coma, ascites).* Deaths due to asparaginase hepatotoxicity have been reported but are exceptional. The clinical features of hepatic injury due to asparaginase are often overshadowed by its other systemic toxicities, including severe nausea and vomiting, weakness, edema, pancreatitis and encephalopathy.
- b) **Bilirubin:** hyper bilirubinemia (grade 1-4) have been recently reported in the control arm of COG AALL07P4 (Angiolillo A et al, J Clin Oncol 2014 1;32(34):3874-82). during induction therapy in 20 out 54 children with High-risk NCI ALL (37%) and in 4 out of 38 during delayed intensification (10.5%). It is known that the incidence of grade 3-4 bilirubin increases with age.

The incidence of increased Bilirubin will be looked for in the CAALF01 protocol, particularly of the NCI grade 3-4 alterations.

### **Summary of potential toxicities**

	<b>Common</b> 21-100 children out of every 100	<b>Occasional</b> 5-20 children out of every 100	<b>Rare</b> < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	<ul style="list-style-type: none"> <li>• Allergic reactions (total likelihood of local, and or systemic reaction especially if previous hypersensitivity reaction to native asparaginase)</li> <li>• pain at injection site,</li> <li>• weakness, fatigue, diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>• Allergic reactions (total likelihood of local, and or systemic reaction if no previous hypersensitivity reaction to native asparaginase)</li> </ul>	<ul style="list-style-type: none"> <li>• Anaphylaxis, hyper/hypotension, tachycardia,</li> <li>• periorbital edema, chills, fever, dizziness, dyspnea, bronchospasm, lipedema,</li> <li>• arthralgia, myalgia, urticaria, mild nausea/vomiting, abdominal pain, flatulence, somnolence, lethargy, headache, seizures</li> </ul>
Prompt: Within 2-3 weeks, prior to the next course	<ul style="list-style-type: none"> <li>• Hyperammonemia</li> <li>• coagulation abnormalities with prolonged PTT, PT and bleeding times (secondary to decreased synthesis of fibrinogen, AT-III &amp; other clotting factors) (L)</li> </ul>	<ul style="list-style-type: none"> <li>• Hyperglycemia</li> <li>• abnormal liver function tests</li> <li>• pancreatitis, increased serum lipase/amylase</li> </ul>	<ul style="list-style-type: none"> <li>• thrombosis, CNS ischemic attacks,</li> <li>• mild leukopenia, granulocytopenia, thrombocytopenia, pancytopenia,</li> <li>• infections (sepsis with/without septic shock)</li> <li>• CNS changes including irritability, depression, confusion, EEG changes, hallucinations, coma and stupor, paresthesias, hyperammonemia</li> <li>• hypertriglyceridemia, hyperlipidemia</li> <li>• hyperbilirubinemia</li> </ul>
Delayed: Any time later during therapy			<ul style="list-style-type: none"> <li>• liver failure</li> </ul>

## Appendix 8: High dose Methotrexate- Practical guidelines

- **CAUTION:** due to interactions of Methotrexate with these substances, do not combine HD-MTX with: trimethoprim-sulfamethoxazole (Bactrim), penicillins, vancomycin, ciprofloxacin, omeprazole, imatinib, amiodarone, macrolides, azoles (voriconazole, fluconazole, itraconazole).
- Biological criteria to begin a course: ALAT < 10 x ULN, Creatinine < 1.5 ULN
- MTX is administered as a 24-hour intravenous infusion. One tenth of the dose ( $500 \text{ mg/m}^2$ ) is given over the first hour. The remaining of the dose ( $4.500 \text{ mg/m}^2$ ) is infused over the subsequent 23 hours at a constant rate.
- Prior to the MTX infusion alcaline hyperhydration is achieved. Urinary pH must be > 7 before starting i.v. MTX. Alkalisation is achieved through administration of sodium bicarbonate, 1 meq/kg, in 20 to 50 ml (according to age) of 5 % glucose solute over 15 minutes (1 ml of NaCO<sub>3</sub>H 4.2 % contains 1 mEq).
- Hyperhydration is started with the MTX infusion and is pursued during 72 h, at a rate of  $3 \text{ L/m}^2/24 \text{ h}$ .
- On Day 1, hyperhydration is implemented intravenously with the following solute mixture :
  - glucose 5 % : 2/3 of the total volume
  - NaHCO<sub>3</sub>(14%) : 1/3 of the total volume
  - KCL 30 mEq/L
  - MTX can be mixed with this solution.
- On Day 2 and Day 3, in the absence of emesis, hyperhydration and alkalinisation can be continued orally. During 72 hours starting from the beginning of MTX infusion, hyperhydration and alkalinisation must be pursued in order for the diuresis to be maintained  $> 1.600 \text{ ml/m}^2/24 \text{ h}$  and urinary pH  $> 7$ . Urinary pH must be measured on fresh urine immediately after each voiding. Whenever it becomes  $< 7$ , a booster alkalinisation is to be given through the administration of NaHCO<sub>3</sub> 1 mEq/kg in 50 ml of glucose 5 % over 15 minutes. Urinary pH tends to fall during the night and monitoring should be particularly stringent at that time.
- Monitoring :
  - blood electrolytes and creatinine : H24, H48, +/-H72
  - minimum monitoring of MTX levels: H48 and H72 after the start of MTX infusion
- The intrathecal chemotherapy (cf Appendix 5) is to be given around H24. A too much delayed IT administration can result in a delay of MTX elimination.
- Leucovorin rescue : the first dose of Leucovorin is given 42 hours after the start of the MTX-infusion. Following doses of  $15 \text{ mg/m}^2$  each are given at 6-hour interval until hour 72 (i.e. H42, H48, H54, H60, H66, H72) or until MTX serum level has fallen to  $< 2 \times 10^{-7} \text{ M}$ . If MTX levels are closely monitored, Leucovorin can often be stopped after 4 administrations. Alternatively if H48 MTX is  $< 6 \times 10^{-7} \text{ M}$ , current experience favors stopping after H60 (4 doses) as this threshold correlates with absence of delayed elimination of MTX at H72. Leucovorin should preferentially be given orally. If the oral route cannot be used because of emesis, the drug is given through i.v. bolus every 6-hours in the same dose. If Levofolinic acid is used, only  $7,5 \text{ mg/m}^2/\text{dose}$  is to be given.
- The dose of Leucovorin may have to be adjusted in case of protracted high serum MTX levels according to the guidelines of table 14.

**Table 13: Adjustments of Leucovorin doses to MTX serum levels and timing**

<b>MTX/T</b>	<b>48 H</b>	<b>72 H</b>	<b>96 H</b>	<b>&gt; 96 H</b>
$> 1 \times 10^{-5}$	$4 \times 50 \text{ mg/m}^2$	$4 \times 200 \text{ mg/m}^2$	$4 \times 200 \text{ mg/m}^2$	$4 \times 200 \text{ mg/m}^2$
$> 5 \times 10^{-6}$	$4 \times 15 \text{ mg/m}^2$	$4 \times 100 \text{ mg/m}^2$	$4 \times 200 \text{ mg/m}^2$	$4 \times 200 \text{ mg/m}^2$
$> 1 \times 10^{-6}$	$4 \times 15 \text{ mg/m}^2$	$4 \times 50 \text{ mg/m}^2$	$4 \times 100 \text{ mg/m}^2$	$4 \times 200 \text{ mg/m}^2$
$> 5 \times 10^{-7}$	$4 \times 15 \text{ mg/m}^2$	$4 \times 15 \text{ mg/m}^2$	$4 \times 50 \text{ mg/m}^2$	$4 \times 100 \text{ mg/m}^2$
$> 2 \times 10^{-7}$	$4 \times 15 \text{ mg/m}^2$	$4 \times 15 \text{ mg/m}^2$	$4 \times 15 \text{ mg/m}^2$	$4 \times 50 \text{ mg/m}^2$
$\leq 2 \times 10^{-7}$	0 mg	0 mg	0 mg	0 mg

T = time since the start of MTX infusion

MTX = MTX serum level in moles/l (M)

### **Glucarpidase (formerly Carboxypeptidase) = Voraxaze®**

Glucarpidase (formerly known as carboxypeptidase-G2 (CPDG2) and marketed as Voraxaze®) is a **recombinant bacterial enzyme** that rapidly hydrolyses MTX to an inactive metabolite, DAMPA (2, 4-diamino-N10-methypteroic acid). It may be used as a rescue agent for methotrexate-induced nephrotoxicity (*S. Demirdjian, S. Laghouati, G. Vassal. Glucarpidase: a method of rescue from HD MTX, European Journal of Oncology Pharmacy. 2008: 20-22.*)

MTX is hydrolysed to 7-OH MTX and is cleared primarily by renal excretion. High doses of MTX cause acute renal dysfunction: MTX and its metabolites precipitate in the renal tubules. The results of this lead to delayed MTX elimination and life-threatening toxicity. An elevation of plasma MTX concentrations increases other MTX-related side effects such as myelosuppression, hepatitis, dermatitis, and orointestinal mucositis.

Nephrotoxicity is prevented by alkaline hydration. If overexposure is found by monitoring MTX serum levels, the dose of leucovorin is increased over a prolonged period of time, but it does not completely reverse the toxicity of MTX. Leucovorin (LV) rescue prevents the nephrotoxicity due to HD-MTX but has no effect on delayed MTX excretion.

Glucarpidase decreases extracellular MTX concentrations. A slow process leads to an efflux of intracellular MTX back into the serum and MTX concentrations rise again some hours after infusion of glucarpidase. For this reason LV is always administered in combination, before or after glucarpidase.

Glucarpidase rapidly hydrolyses MTX into DAMPA. This is less soluble than MTX in acidic pH but is eliminated by an extra-renal route. This is the reason why with glucarpidase, patients continue to need hydration and alkalinisation.

Haemofiltration or haemodialysis might be used when the patients are oliguric or anuric.

#### **1. Mechanism of action**

Glucarpidase hydrolyses MTX and 7-OH MTX into DAMPA, a non-toxic metabolite. Glucarpidase is restricted to the extracellular compartment due to its molecular size and does not hydrolyse intracellular MTX.

This hydrolysis results in the plasma MTX concentration decreasing by 99% within 15 minutes

#### **2. Indications**

Plasma MTX concentration > 10 µM more than 42 hours after start of HD-MTX infusion

- **or**

3 µM > plasma MTX concentration > 10 µM AND preexisting renal insufficiency [serum creatinine 1.5 x basal values or creatinine clearance < 60 ml/mn/m<sup>2</sup>] with delayed elimination of MTX [plasma levels > mean +2 standard deviations 12 hours after the MTX administration, i.e. at least H36]

- **and**

Availability to infuse glucarpidase within 96 hours of starting HD-MTX infusion

### **3. Posology and administration**

Glucarpidase is given at 50 Units/Kg in an intravenous (IV) infusion over 5 min (maximum 4000 units).

It is presented in a lyophilised form. The lyophilised powder is reconstituted with 1 ml of NaCl 0,9%.

The solution obtained contains 1000 units of glucarpidase [7].

Hyperhydration (3L/m<sup>2</sup>), alkalinisation and leucovorin rescue are required when using glucarpidase

As LV is a competitive substrate of glucarpidase, a study of the interaction between Voraxaze® and LV has shown that glucarpidase increases the clearance of LV and reduce its efficacy.

Thus LV should be administered at least 2 hours prior or 2 hours after Glucarpidase infusion, to replete intracellular reduce folate pools.

### **4. Undesirable effects**

Glucarpidase is well tolerated. Anaphylactic reactions could theoretically occur. As with all therapeutic proteins, there is potential for immunogenicity.

Side effects are infrequent, reversible and minor: paraesthesia, feeling of warmth, tingling in the fingers, flushing, shaking, and headache.

### **5. Special warnings and special precautions for use**

The patients must be evaluated for signs and symptoms toxicity: complete blood counts, liver function and serum creatinine level.

To evaluate the efficacy of glucarpidase, plasma MTX concentrations are measured, but using High- Pressure Liquid Chromatography (HPLC) because this technique can quantify bothMTX and its metabolite DAMPA. The commercially available immunoassays as Fluorescence PolarisationImmunoassay (FPIA with TDX) is not appropriate to determine MTX concentrations after glucarpidase administration because DAMPA, the metabolite of MTX, cross-reacts with MTX. The concentrations of MTX are thus overestimated.

The samples for determination of MTX concentrations are obtained before and 30 minutes, 24 hours after glucarpidase is given: the blood samples are placed on ice and rapidly centrifuged. To inactivate glucarpidase, the serum samples are heated to above 80°C for 5 min in a water bath or treated with 1N HCl to obtain a final concentration of 0.1N of HCl.

The results of this monitoring show that glucarpidase leads to decrease the plasma MTX concentrations of 99%. A second dose may be necessary in some patients.

### **6. Pharmaceutical problems for the management of glucarpidase**

The number of glucarpidase infusions depends on the concentration of MTX

***Voraxaze® is supplied in packs of 1 vial. Each vial contains 1000 Units and each vial costs 13975 euros (march 2015)***

### **7. How to obtain glucarpidase in Europe**

The manufacturer of Voraxaze® is Protherics/BTG. For France, supply is under the responsibility of Clinigen Healthcare which is normally able to deliver Voraxaze® within 24 hours of receipt of the order, with a shipment the next day.

- ***The investigator fills in a “named patient basis” form (ATU)*** and an access form.
- The pharmacist faxes the ATU to the national competent authority (Here ANSM)
- When the competent authority authorises the request for the product, the hospital pharmacy can order Voraxaze® from Clinigen Healthcare with the access form.

## Appendix 9: Main adverse effects of antileukemic drugs used in CAALL F01

In French for a more easy reading in France but:

- see *Summary of Product Characteristics forms for full prescribing information and expected adverse events*
- see *Appendix 7 for more details on pegaspargase*
- see *Appendix 8 for more details on high-dose methotrexate*

### **CORTICOIDES**

*METHYL-PREDNISOLONE (SOLUMEDROL<sup>R</sup>),  
PREDNISONE (CORTANCYL<sup>R</sup>), PREDNISOLONE (SOLUPRED<sup>R</sup>)  
DEXAMETHASONE (DECTANCYL<sup>R</sup> ou SOLUDECADRON<sup>R</sup>)*

- Syndrome Cushingoïde
- Trouble de la glycérégulation (surtout si associé à l'Asparaginase)
- Pancréatite (surtout si associé à l'Asparaginase)
- Troubles du comportement, agitation (surtout avec la DEXAMETHASONE)
- Hypertension artérielle
- Immunosuppression
- Osteonecrose

### **CRISANTASPASE (ERWINASE<sup>R</sup>)**

voir Appendix 14

### **CYCLOPHOSPHAMIDE (ENDOXAN<sup>R</sup>)**

*Flacons de 100 et 500 mg.*

- Nausées et vomissements.
- Alopécie.
- Myélosuppression.
- Cystite hémorragique (si utilisation à fortes doses : > 500 mg/m<sup>2</sup>) : prévention par l'uromitexan (MESNA<sup>R</sup>).
- Toxicité cardiaque si utilisation à fortes doses et association aux anthracyclines.
- SIADH
- Leucémie secondaire
- Aménorrhée / azoospermie

### **CYTARABINE (ARACYTINE<sup>R</sup>, CYTARBEL<sup>R</sup> et formes génériques)**

*Ampoules à 40, 100, 500, 1 000, 2 000 mg.*

- Nausées, vomissements, ulcérations buccales, mucite.
- Myélosuppression.
- Cytolyse hépatique
- Fièvre médicamenteuse.
- Toxidermie (éruption)

**En cas d'administration à haute-dose** (supérieure à 1 g/m<sup>2</sup> par bolus) :

- Myélosuppression profonde mais de durée brève.
- Toxicité digestive cutanée, hépatique plus marquées.
- Conjonctivite, kératite : **prescription de larmes artificielles + Chibrocadron<sup>R</sup>.**
- Risque de toxicité neurologique, en particulier cérébelleuse (rare chez l'enfant).

### **DAUNORUBICINE (CERUBIDINE<sup>R</sup>)**

*Ampoules à 20 mg.*

- myélosuppression (3 lignées)
- nausées et vomissements
- douleurs locales et phlébites. **Nécrose locale si extravasation (surveillance +++ en cas de perfusion périphérique)**
- toxicité cardiaque

- immédiate à type de trouble du rythme (**surtout en cas d'hypokaliémie : vérifier que la kaliémie est > 3 mEq/l au ionogramme avant d'autoriser l'injection**).
- tardive, à type de myocardiopathie.

**Faire pratiquer une échographie cardiaque avant chaque phase comportant une anthracycline (Daunorubicine, Doxorubicine, Mitoxantrone), à l'arrêt du traitement, puis au minimum à 5 ans et 10 ans du diagnostic**

- alopecie.
- ulcérations buccales
- coloration rouge des urines

#### **DOXORUBICINE (ADRIBLASTINE<sup>R</sup>, Doxorubicine Gé.)**

*Ampoules à 10, 20 et 50 mg.*

Mêmes effets indésirables que la daunorubicine (cf ci-dessus **Section 15.9.5**).

#### **ETOPOSIDE (VEPESIDE<sup>R</sup>)**

*Flacons à 100 mg*

- Leucopénie et thrombopénie
- Nausées et vomissements
- Alopecie
- Neuropathie périphérique
- Hypotension artérielle et bronchospasme lors de la perfusion, d'où la nécessité d'une perfusion lente.  
NB : l'ETOPOPHOS<sup>R</sup>, mieux toléré et d'administration plus rapide, peut être utilisé aux mêmes posologies que le VP-16.

#### **IFOSFAMIDE**

*40 mg/ml sol p perf*

- Myélosuppression
- Affections rénales et urinaires : insuffisances rénales aiguës et chroniques ont été signalées plus particulièrement chez l'enfant après administration de posologies élevées. Une atteinte principalement tubulaire proximale est possible et plus rarement glomérulaire. Des syndromes de Fanconi ont été signalés. Des cas d'hypokaliémie ont été rapportés.
- Risque de cystite hématurique : prévention par l'uromitexan (MESNA<sup>R</sup>) a priori non nécessaire aux doses retenues dans le protocole CAALL-F01
- Affections psychiatriques / Troubles du système nerveux central :
- Toxicité neurologique :
  - Somnolence, confusion, mutisme, mais aussi désorientation, agitation, troubles du comportement et symptômes cérébelleux.
  - Plus rarement sévère : convulsions, cliniques ou seulement électriques hallucinations, encéphalopathie, coma. Les facteurs de risque évoqués sont une administration intraveineuse rapide, une insuffisance rénale ou un taux faible d'albumine sérique. Cette symptomatologie est le plus souvent réversible à la diminution des posologies ou à l'arrêt du traitement.
  - Cette toxicité neurologique débute en moyenne entre 25 et 50 heures après le début de la perfusion difosfamide. Les troubles sont plus fréquents et plus intenses chez les patients présentant une insuffisance rénale.
- SIADH
- Leucémies secondaires
- Aménorrhée / azoospermie possibles

#### **IMATINIB (Glivec<sup>R</sup> et Génériques- attention à la galénique-volume des comprimés- qui doit être adaptée à l'enfant)**

*Comprimés à 100 mg et Comprimés à 400 mg*

- Asthénie
- Nausées, vomissements, diarrhée
- Crampes, myalgies, douleurs articulaires
- Oedèmes, en particulier péri-orbitaires

- CYTOPENIES PROLONGEES ET RISQUE INFECTIEUX MAJORE ++++
  - LORS DE L' ASSOCIATION A LA CHIMIOTHERAPIE INTENSIVE COMME ICI
- Retard pubertaire après administration prolongée : Si patient traité avec Imatinib, réaliser un Age Osseux annuel en période péripubertaire jusqu'à la fin de la puberté est conseillé.
- Retard de croissance après administration prolongée

### **METHOTREXATE**

*METHOTREXATE ROGER BELLON<sup>R</sup>, LEDERTREXATE<sup>R</sup>, METHOTREXATE Gé.*

*Comprimés à 2,5 mg. Flacons à 5, 20, 25, 50, 500 et 5.000 mg.*

*(Voir modalités d'administration en Annexe 8)*

- Myélosuppression
- Mucite, diarrhée, vomissements
- Cytolyse hépatique (ALAT)

#### **En cas d'utilisation à haute dose**

- Mucite +++, avec parfois rectorragies
- Toxicité hépatique : augmentation, parfois importante, des transaminases avec normalisation en quelques jours.  
En cas d'intoxication, possibilité d'ictère associé.
- Néphrotoxicité : la toxicité rénale est en partie expliquée par la précipitation du Méthotrexate ou de ses métabolites dans le tubule rénal. Le méthotrexate et ses métabolites sont bien plus solubles en solution alcaline. L'alcalinisation des urines est donc indispensable.
- Myélotoxicité
- Toxidermie (lobster syndrome)
- Neurotoxicité (stroke-like syndrome)

**NB1 : Les manifestations toxiques, en dehors de la cytolyse pratiquement constante, peuvent correspondre à un surdosage, soit accidentel, soit corrélé à une interaction médicamenteuse (BACTRIM<sup>R</sup>, KETOCONAZOLE<sup>R</sup>), soit à un retard d'élimination à un rebond avec sauvetage insuffisant par l'acide folinique**

**NB2 : Un retard majeur d'élimination doit conduire à proposer un traitement par glucarpidase cf annexe 8**

### **MERCAPTOPURINE (PURINETHOL<sup>R</sup>)**

*Comprimés à 50 mg*

- Toxicité hépatique (cytolyse)
- Nausées et vomissements
- Myélosuppression et lymphopénie
- Attention chez les sujets ayant un déficit génétique en TPMT :
  - Pendant les phases intensives (induction, consolidation, phase M, intensification décalée(s) :
    - 1- Patients homozygotes ayant un déficit génétique en TPMT : Adapter la posologie selon les recommandations protocolaires (faîtes pour chaque cure)
    - 2- Patients hétérozygotes ayant un déficit génétique en TPMT: Ne pas adapter et donner la dose complète de 6-mercaptopurine
  - A surveiller: si la prochaine phase de chimiothérapie est retardée, diminuez la dose de 50% et réévaluez
  - Pendant la phase d'entretien cf appendix 11

## MERCAPTOPURINE (XALUPRINE<sup>R</sup>)

*Suspension orale à 20 mg/ml (flacon de 100 ml)*

Il faut noter la non-disponibilité d'études pédiatriques, en particulier dans les LAL. Ce médicament a une AMM européenne dans les LAL de l'adulte et de l'enfant. Il est utilisé depuis plusieurs années dans les protocoles du Royaume Uni (UKALL 2003 et successeur) et du Danemark (NOPHO 2008) en particulier.

Le laboratoire n'a en effet fourni à l'EMA que les résultats d'une étude de bioéquivalence qui a comparé la suspension orale et la forme comprimé de la mercaptourine chez des volontaires adultes sains. Celle-ci a montré que la suspension orale à 50 mg de XALUPRINE, par rapport à la forme comprimé de la mercaptourine à 50 mg, donne une aire sous la courbe (ASC) supérieure de 13% (ce qui entre dans la limite de la bioéquivalence) et donne une concentration maximale (Cmax) supérieure de 39% (IC 90% 22% à 58%) malgré une variabilité inter-individuelle (coefficient de variation « CV » en %) plus faible (46% vs 69 %).

Il a été convenu pour le CAALL F01 de l'utiliser dans son AMM.

***Il a également été convenu de repérer son utilisation dans le CRF.***

***En raison de la vitesse d'absorption plus rapide (ce qui correspond à une Cmax plus élevée des ajustements de dose pourront être nécessaires en cas de switch d'une formulation à l'autre.***

Les effets secondaires attendus sont les mêmes que pour le Purinethol. Les précautions d'emploi en cas de déficit homozygote ou hétérozygote en TPMT également (cf **Appendix 11 et pour les cures intensives, suivre les recommandations protocolaires données pour chaque cure**).

## MITOXANTRONE (NOVANTRONE<sup>R</sup> ; génériques)

La mitoxantrone est une anthracène-dione produite par synthèse.

Il s'agit d'une molécule apparentée aux anthracyclines.

Elle partage la toxicité locale (danger de nécrose en cas d'extravasation) et la toxicité systémique (mucite, myélosuppression) et cardiaque (même si la mitoxantrone est considérée par certains comme moins cardiotoxique à équi-efficacité anti-leucémique)

## NELARABINE (ATRIANCE<sup>R</sup>)

*Ampoules de 250 mg.*

La nélarabine est une prodrogue de l'analoge désoxyguanosine : ara-G

## EFFETS INDESIRABLES NEUROLOGIQUES +++

- altération de l'état mental incluant somnolence importante et confusion
- convulsions
- neuropathie périphérique pouvant aller d'un engourdissement et de paresthésies jusqu'à une faiblesse musculaire et une paralysie.
- Exceptionnellement toxicité neurologique sévère : coma, état de mal épileptique, démyélinisation ou neuropathie ascendante d'apparence similaire à un syndrome de Guillain-Barré

***\*\*\*surveillance neurologique attentive des patients (examen neurologique pré, per et post cycle ++)***

***\*\*\* pas d'injection intrathécale de J-7 à J15 d'une cure***

Myélosuppression

Immuno-suppression

## PEGASPARAGASE (ONCASPAR<sup>®</sup>)

Voir **Appendix 7**

**Il a été convenu de repérer dans le CRF la forme utilisée (liquide ou lyophilisée) de Pegasparagase à chaque administration.**

### **THIOGUANINE (LANVIS®)**

*Comprimés à 40 mg*

Même toxicité que le 6-MP;

Risque de Maladie Veino-occlusive ++ et à plus long-terme d'hypertension portale révélée par thrombopénie +/- splénomégalie

**Suivre les mêmes recommandations que pour la 6-mercaptopurine: en cas de Déficit Homozygote ou Hétérozygote en TPMT , les posologies sont à adapter selon les recommandations protocolaires faites dans les cures d'intensifications retardées n°1.**

### **VINCRISTINE (ONCOVIN® et formes génériques)**

*Flacons à 1 mg.*

- **Toxicité neurologique périphérique** +++: abolition des R.O.T., paresthésies, myalgies, paralysies des nerfs crâniens (ptosis ++), convulsions, iléus paralytique, constipation, douleurs des maxillaires, douleurs mal systématisées
- Alopécie modérée
- Hyponatrémie par sécrétion inappropriée d'ADH.
- Leucopénie modérée
- Nécrose locale si extravasation: avis en urgence auprès d'un chirurgien plasticien pour aspiration / lavage +++.

**NB1 : certains médicaments sont susceptibles d'interagir avec le métabolisme de la vincristine. La diminution de la clairance de celle ci peut auquel cas être responsable d'une toxicité sévère. Ces médicaments, dont l'utilisation concomitante à la vincristine est donc contre-indiquée, sont :**

- *les azolés : itraconazole surtout, mais aussi ketoconazole ou fluconazole.*
- *la ciclosporine.*
- *les macrolides (érythromycine surtout).*
- *les inhibiteurs calciques.*

**NB2 : L'administration intrathécale de la vincristine conduit à une neurotoxicité fatale. Selon le protocole, l'administration de vincristine n'est pas effectuée le même jour que l'injection intrathécale.**

### **VINDESINE (ELDISINE®)**

*Flacons à 1 mg.*

- Mêmes effets indésirables que la **Vincristine**.
- Mêmes médicaments contre-indiqués en association.

## Appendix 10: Ancillary treatments - Recommendations

### Nausea/vomiting

The choice of the treatments for nausea/vomiting is left to the investigator's discretion. Nevertheless, the investigator should follow updated and validated guidelines at the time of administration.

### Hydration, hyperhydration and prevention of the tumoral lysis syndrome (TLS)

- **No hyperleucocytosis and low tumor burden (WBC count < 100 G/L)**

A non-alkaline hydration is sufficient.

Rasburicase: FASTURTEC® 0.2 mg/kg x 1 intravenous administration/24 hours

- **Hyperleucocytosis (> 100G/L) and/or high tumor burden**

a) An alkaline hyperhydration is necessary and should be interrupted as soon as kaliemia is normal

– Volume of infusion: 3 L/m<sup>2</sup>/day of Dextrose 5% with electrolytes.

– Electrolytes per liter of Dextrose 5%:

- NaCl: 2g,

- KCl: none at starting. To be adapted secondarily to kaliemia.

- Calcium: justified especially in case of TLS.

Initial dosing of 500 mg/m<sup>2</sup>/day to be adapted according to the calcemia and phosphoremia tests.

- Magnesium: supplementation according to tests.

– Rasburicase: FASTURTEC®

The treatment is mandatory for all patients with a risk of TLS. The contraindications are hypersensitivity to uricase or at one of its components, G6PD deficiency and other metabolic disorders known to give hemolytic anemia.

FASTURTEC®: 0.2 mg/kg x 1 intravenous administration/24 hours. In case of severe TLS, 2 administrations per day are allowed. See the package insert.

– b) Guidelines for steroid prophase: The first 30 mg/m<sup>2</sup> dose of steroid prephase can be divided in 2 doses, according to investigator's choice. If yes, the total dose of steroids during prophase should nevertheless be equal to 420 mg/m<sup>2</sup> administrate in first 7 days (= 168 hours). The idea is to have day 8 count of blast fully interpretable

– In case of increasing leucocyte count or life threatening situation during steroid prephase, according to investigator's choice, an early beginning of multiagent chemotherapy is possible. In that case, D8 is arbitrarily fixed as the day of the first Vincristine infusion.

### Disseminated intravascular coagulation (DIC)

A DIC could be present at the time of diagnosis or can occur after initiation of treatment.

- platelets transfusions, 2 to 3 times a day in order to maintain platelets rate above 50 000/mm<sup>3</sup>
- Heparin: could be discussed

## Monitoring

### At the initial phase, every 4 hours:

- Pulse rate, respiratory rate, blood pressure and temperature every 4 hours
- Diuresis every 4 hours with assessment of fluid balance.
- Furosemide: 1 to 1.5 mg/Kg/injection if necessary to maintain an effective diuresis
- Once a day (at least):
  - Complete Blood Count, hemostasis, D-dimers, electrolytes, creatinine, calcium, phosphorus and uricemia.
  - In case of lysis syndrome, the biological assessments should be done more often.

### Following the acute phase

- Adapt the electrolyte intakes (Na, K, Ca, Mg) according to the type of infusion, the clinical physical exam and the biological assessments:
  - Stop the bicarbonates as soon as possible
  - Pay attention of hypokalemia secondary to insufficient intake, recovery of lysis and the treatment with furosemide
  - Pay attention to hyponatremia secondarily to furosemide, insufficient intake, mainly after bicarbonate stop.
- Stop FASTURTEC® as soon as the risk of hyperuricemia has disappeared.

## Transfusions

***Mandatory: A briefing paper on transfusions should be given to parents before the first transfusion.***

- **Transfusion of red blood cells**
  - Transfusion if Hb <8 g/dL (consider the clinical tolerance, the therapeutic phase and the risk of the planned worsening depending on the chemotherapeutic therapy administered).
  - Use of phenotyped red blood cells leucocyte reduced "CMV undifferentiated" can be used since they are leucocyte reduced.
  - The volume of transfusion can be calculated by the following formula:  

$$Q \text{ (volume in mL)} = \text{weight (Kg)} \times (\text{target of the Hb rate variation}) \times (3 \text{ or } 4)$$
- **Transfusion of platelets**
  - Transfusion if platelets < 20 000/mm<sup>3</sup>.
  - During the thrombocytopenia phase: monitoring of the CBC (take into account the therapeutic stage and the planned worsening risk according to the chemotherapy administered).
  - Use platelets and leucocyte reduced from apheresis.
- **Transfusions of granulocytes**
  - To be discussed when occurs a severe infection non-controlled with antibiotics, in a patient with predictable long-lasting severe neutropenia (<200/mm<sup>3</sup>).
  - Best indication is **cellulitis**.

## Care of an out-patient with infection

### a) Fever

In case of fever ( $>38^{\circ}\text{C}$ ) in an out-patient with less than 500 neutrophils /mm $^3$ , there is a major risk of the occurrence of a septic shock: an hospitalization is mandatory without delay.

- A broad-spectrum, parenteral antibiotherapy targeting the gram negative bacilli including *Pseudomonas Aeruginosa* should be started as soon as possible, ideally before the 6th hour of fever.
- A combination of beta-lactam antimicrobial and an aminoglycoside should be used.
- The use of a glycopeptide as vancomycin or teicoplanin is indicated when a central catheter is present and if a streptococcus or staphylococcus infection is suspected and/or in case of hemodynamic disorder (triple antibiotherapy from the beginning).
- Hemodynamic disorders, respiratory distress, metabolic acidosis (lactate to be dosed) should lead to consider a transfer in Intensive Care Unit.
- An antifungal treatment should be considered in case of a persistent fever beyond 48 hours after the beginning of antibiotherapy and in case of secondary fever.

If the patient is non-neutropenic (neutrophils  $>1000/\text{mm}^3$ ), the treatment will depend on the clinical status, the stage of treatment and the initial assessment.

### b) Interstitial lung disease

- The patients with an ALL are at risk of interstitial lung disease, especially during the maintenance therapy when the lymphopenia could be deep. This justifies a prophylaxis treatment with trimethoprim-sulfamethoxazole (BACTRIM®) to prevent a pneumocystis jiroveci/carinii infection.
- A chest X-ray should be done as soon as the slightest pulmonary sign appears.
- A hospitalization and a broncho-alveolar lavage should be considered in case of confirmed diagnosis of interstitial lung disease.

### c) Varicella-zoster virus infection

- In case of contagious contact, polyvalent immunoglobulins (200 to 400 mg/Kg once) should be administered, if possible, within 72 hours of the contagious contact. During maintenance therapy a per os treatment with aciclovir can be used at the dose of 80 mg/kg/d in four doses for 10 days
- In case of infection by varicella-zoster virus, the treatment is intravenous acyclovir **through a central catheter** (possible necrosis in case of extravasation) at the dose of 500mg/m $^2$ /day fractionated in 3 doses for 7 days minimum.

A hospitalization in a specialized unit is to be considered according to the patient age, to the clinical assessment (level of fever, eruption characteristics, visceral or neurologic signs), on-going treatment with corticoids, cell blood count (deep lymphopenia) and social and family context.

In the best favorable cases, a per os treatment with acyclovir 800 mg x 5 per day (every 4 hours without a dose during the night) could be discussed.

In case of zoster, a treatment with acyclovir per os at a dose of 800 mg x 5/day will be prescribed.

### d) Other viral infections

The maintenance therapy is sometimes responsible for deep lymphopenia ( $<500/\text{mm}^3$ ) with severe immunosuppression leading to life-threatening viral infections.

**Patients with CMV-negative serology at inclusion should be monitored closely.**

**e) G-CSF**

The indication of G-CSF is severe infection in a neutropenic patient at the dose of 5µg/Kg/day subcutaneously or intravenously over 30 minutes if the patient is hospitalized and has thrombocytopenia.

**f) Trimethoprim-sulfametoxazole (BACTRIM®)**

Treatment administered during all the treatment and until 3 months after the end of chemotherapy.

- dosage of 25 mg/kg/d sulfamethoxazole, 3 days a week (max daily dose 800 mg).

**g) Oral Contraception:**

***No oral contraception is recommended in the CAALL-F01 protocol since it increases the risk of thrombosis.***

## Appendix 11: Continuation/maintenance therapy guidelines

### 1. General objective of maintenance/ continuation treatment

**Continuation therapy with 6 mercaptopurine (6-MP) and methotrexate (MTX) is an essential component of the treatment of childhood ALL.**

**The objective is to maintain the total leucocyte count between 2000 and 3000/mm<sup>3</sup>. But this should be associated to neutrophils above 500/mm<sup>3</sup> and lymphocytes above 300/mm<sup>3</sup> and platelets above 50.000 mm<sup>3</sup>**

Liver function tests will not be decisional except if ALAT ≥ 10N and /or bilirubin ≥ 3N (Arico M et al, Leukemia 2005). In such cases other causes such as viral hepatitis or Gilbert syndrome should also be considered.

### 2. Monitoring frequency

CBC should be evaluated every 2 weeks for the first 3 months and then monthly

CBC should be evaluated in case of fever or clinical problem.

### 3. Dose adaptation

**Table 14: Dose adaptation**

Leucocyte/neutrophils (PN) /mm <sup>3</sup>	% dose	6-Mercaptopurine	Methotrexate dose
< 1000 and/or PN < 500	0		0
1000-1999	66%		66%
2000-2999	100%**		100%***
3000-4000*	125%		125%
> 4000 *	150%		150%

- (\*) consider compliance problems, particularly if no increase in ALAT is observed. Not to be evaluated / adapted at D8 after pulses since dexamethasone will increase the counts
- (\*\*) initial dose of 6-MP: 50 mg/m<sup>2</sup>/day
- (\*\*\*) initial dose of MTX: 25 mg/m<sup>2</sup>/day
- Lymphocytopenia occurs frequently during maintenance treatment. A severe lymphocytopenia (< 300/mm<sup>3</sup>) should lead to a 25-33% reduction of 6-MP without MTX modification.
- Any increase of the dose should lead to a control CBC not earlier than one month after.
- ALAT impact on conduct of maintenance treatment
  - If ALAT ≥ 10N and neutrophils ≤ 800/mm<sup>3</sup>: Stop 6-MP/MTX for one week.
  - If ALAT ≥ 10N and neutrophils > 800/mm<sup>3</sup>: Stop MTX only for one week
- Any stopping of the treatment should not exceed one week and lead to at least weekly control of CBC count. If recovery is not observed within 2 weeks after stopping of the treatment, a bone marrow evaluation should be discussed.
- Patients homozygous for TPMT deficiency: begin 6-MP at 7.5 mg/m<sup>2</sup>/day. Patients heterozygous for TPMT deficiency: begin 6-MP at 30 mg/m<sup>2</sup>/day and control as for other patients the CBC after 15 days. Of note a deficiency in NUDT15 can be found in patients with Hispanic or East Asia ancestry.

## **Appendix 12: NCI-CTC version 4.03**

This document is available as a separate document.

**Appendix 13: SUMMARY OF PRODUCT CARACTERISTICS ONCASPAR (EMEA)**

Last updated : 27/03/2018 Consult EMEA's website for last version

▼ Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Les professionnels de la santé déclarent tout effet indésirable suspecté. Voir rubrique 4.8 pour les modalités de déclaration des effets indésirables.

## **9 DÉNOMINATION DU MÉDICAMENT**

Oncaspar 750 U/ml, poudre pour solution injectable/pour perfusion.

## **10 COMPOSITION QUALITATIVE ET QUANTITATIVE**

Chaque flacon contient 3 750 unités (U)\*\* de pégaspargase\*.

Après reconstitution, 1 ml de solution contient 750 U de pégaspargase (750 U/ml).

\* La substance active est un conjugué covalent de L-asparaginase dérivée d'*Escherichia coli* et de monométhoxypolyéthylène glycol.

\*\* Une unité se définit comme la quantité d'enzymes nécessaire pour libérer 1 µmol d'ammoniaque par minute à un pH de 7,3 et à 37 °C.

L'activité de ce médicament ne doit pas être comparée à celle d'une autre protéine pégylée ou non pégylée de la même classe thérapeutique. Pour plus d'informations, voir rubrique 5.1.

Pour la liste complète des excipients, voir rubrique 6.1.

## **11 FORME PHARMACEUTIQUE**

Poudre pour solution injectable/pour perfusion.

Poudre blanche à blanc cassé.

## **12 DONNÉES CLINIQUES**

### **12.1 Indications thérapeutiques**

Oncaspar est utilisé en association à d'autres agents antinéoplasiques pour le traitement de la leucémie lymphoblastique aiguë (LLA) en pédiatrie de la naissance jusqu'à 18 ans et chez les adultes.

## 12.2 Posologie et mode d'administration

Oncaspar doit être prescrit et administré par des médecins et des professionnels de santé expérimentés dans l'utilisation des médicaments antinéoplasiques. Il ne doit être administré qu'en milieu hospitalier où du matériel de réanimation adapté est disponible.

### Posologie

Oncaspar est généralement utilisé dans des protocoles de chimiothérapie, en association avec d'autres agents antinéoplasiques (voir aussi rubrique 4.5).

#### Population pédiatrique et adultes ≤ 21 ans

La dose recommandée chez les patients âgés de moins de 21 ans et dont la surface corporelle est supérieure ou égale à  $0,6 \text{ m}^2$  est de 2 500 U de pégaspargase (équivalent à 3,3 ml d'Oncaspar)/ $\text{m}^2$  de surface corporelle tous les 14 jours.

Chez les enfants dont la surface corporelle est inférieure à  $0,6 \text{ m}^2$ , la dose recommandée est de 82,5 U de pégaspargase (équivalent à 0,1 ml d'Oncaspar)/kg de poids corporel tous les 14 jours.

#### Adultes > 21 ans

Sauf indication contraire, la posologie recommandée chez les adultes âgés de plus de 21 ans est de 2 000 U/ $\text{m}^2$  tous les 14 jours.

Le traitement peut être surveillé en se basant sur l'activité sérique minimale de l'asparaginase, mesurée avant la prochaine administration de pégaspargase. Si les valeurs de l'activité de l'asparaginase n'atteignent pas les taux cibles, le remplacement par une autre préparation à base d'asparaginase peut être envisagé (voir rubrique 4.4).

#### Populations particulières Insuffisants rénaux

Étant donné que la pégaspargase est une protéine de haut poids moléculaire, elle n'est pas excrétée par les reins ; aucun ajustement posologique n'est nécessaire chez les patients ayant une insuffisance rénale.

#### Insuffisants hépatiques

Aucun ajustement posologique n'est nécessaire chez les patients ayant une insuffisance hépatique.

#### Sujets âgés

Les données disponibles pour les patients âgés de plus de 65 ans sont limitées.

#### Mode d'administration

Oncaspar peut être administré par injection intramusculaire ou par perfusion intraveineuse.

Pour les plus petits volumes, il est préférable d'administrer par voie intramusculaire. Lorsqu'Oncaspar est administré par injection intramusculaire, le volume injecté à un même endroit ne doit pas dépasser 2 ml chez l'enfant et l'adolescent, et 3 ml chez l'adulte. En cas d'administration de volumes plus importants, la dose doit être divisée et administrée en plusieurs sites d'injection.

La perfusion intraveineuse d'Oncaspar est généralement administrée sur une période de 1 à 2 heures, dans 100 ml de solution injectable de chlorure de sodium à 9 mg/ml (0,9 %) ou dans une solution de glucose à 5 %.

La solution diluée peut être administrée avec une perfusion déjà en cours de chlorure de sodium à 9 mg/ml ou de glucose à 5 %. Ne pas perfuser d'autres médicaments par la même ligne intraveineuse en même temps qu'Oncaspar.

Pour les instructions concernant la reconstitution et la dilution de ce médicament avant administration, voir la rubrique 6.6.

### **12.3 Contre-indications**

Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1. Déficience hépatique sévère (bilirubine > 3 fois la limite supérieure de la normale [LSN] ; transaminases > 10 x LSN).

Antécédents de thrombose grave lors d'un précédent traitement par L-asparaginase.

Antécédents de pancréatite (voir rubrique 4.4).

Antécédents d'événements hémorragiques graves lors d'un précédent traitement par L-asparaginase (voir rubrique 4.4).

### **12.4 Mises en garde spéciales et précautions d'emploi**

L'activité sérique ou plasmatique de l'asparaginase peut être mesurée afin d'exclure toute réduction accélérée de l'activité de l'asparaginase.

Des anticorps anti-asparaginase peuvent être associés à de faibles taux d'activité de l'asparaginase étant donné l'activité neutralisante possible de ces anticorps. Dans ce cas, le remplacement par une autre préparation à base d'asparaginase doit être envisagé.

Des réactions d'hypersensibilité à la pégaspargase, y compris une anaphylaxie potentiellement mortelle, peuvent survenir pendant le traitement. Par mesure de précaution, le patient doit être surveillé pendant une heure après l'administration, et du matériel de réanimation et autres traitements de l'anaphylaxie (épinéphrine, oxygène, stéroïdes par voie intraveineuse, etc.) doivent être disponibles. Oncaspar doit être arrêté chez les patients présentant des réactions allergiques graves (voir rubriques 4.3 et 4.8). En fonction de la sévérité des symptômes, il peut être nécessaire d'administrer des antihistaminiques, des corticoïdes et des vasopresseurs.

Des événements thrombotiques graves, y compris une thrombose du sinus sagittal, peuvent se produire chez les patients recevant de la pégaspargase. Oncaspar doit être arrêté chez les patients présentant des événements thrombotiques graves.

Un allongement du temps de prothrombine (TP), un allongement du temps de thromboplastine partiel (TTP) et une hypofibrinogénémie peuvent se produire chez les patients recevant de la pégaspargase. Les paramètres de coagulation doivent être surveillés avant le traitement et régulièrement pendant et après le traitement, particulièrement lorsque d'autres médicaments ayant des propriétés anticoagulantes tels que l'acide acétylsalicylique et des anti-inflammatoires non stéroïdiens sont utilisés en même temps (voir rubrique 4.5).

Un contrôle régulier du profil de coagulation est nécessaire. Le fibrinogène peut être considéré comme un paramètre des systèmes procoagulant et anticoagulant. En cas de chute importante du fibrinogène ou d'un déficit en antithrombine III (ATIII), il faut envisager un produit de substitution (par exemple, du plasma frais congelé).

La pégaspargase peut présenter des propriétés immunsuppressives. Il est donc possible que l'utilisation de ce médicament favorise les infections chez certains patients.

Un traitement combiné à base d'Oncaspar peut engendrer une toxicité hépatique sévère et une toxicité du système nerveux central.

Il convient d'être vigilant lorsqu'Oncaspar est administré en association avec d'autres substances hépatotoxiques, surtout en cas d'insuffisance hépatique préexistante. Dans ce cas, l'apparition d'une éventuelle insuffisance hépatique doit être surveillée.

En présence de symptômes d'hyperammoniémie (par exemple, nausées, vomissement, léthargie, irritation), les taux d'ammoniaque doivent être étroitement surveillés.

Une augmentation du risque d'hépatotoxicité est possible lors d'un traitement combinant Lasparaginase et inhibiteurs de la tyrosine kinase pour le traitement de la LLA chez les patients porteurs du chromosome de Philadelphie ; par conséquent, il convient d'être prudent lors de l'utilisation d'Oncaspar dans cette population de patients.

La diminution du nombre de lymphoblastes circulants est souvent assez marquée, et des numérations normales ou trop basses des leucocytes sont souvent constatées les premiers jours qui suivent le début du traitement. Cela peut être associé à une augmentation marquée du taux sérique d'acide urique. Une néphropathie urique peut se développer. Afin de surveiller l'effet thérapeutique, il faut surveiller de près l'hémogramme ainsi que la moelle osseuse du patient.

Des cas de pancréatite ont été rapportés. Les patients doivent être informés des symptômes caractéristiques de la pancréatite qui, si elle n'est pas traitée, peut être mortelle : douleur abdominale persistante pouvant être sévère et pouvant s'étendre vers le dos. En cas de suspicion de pancréatite, le traitement par Oncaspar doit être interrompu. Si la pancréatite est confirmée, le traitement par Oncaspar ne doit pas être repris. Des examens appropriés doivent donc être réalisés après la fin du traitement par pégaspargase. Étant donné que la pathogenèse exacte n'est pas connue, seules des mesures de soutien sont recommandées.

Des mesures de l'amylase sérique doivent être réalisées fréquemment afin d'identifier les premiers signes d'inflammation du pancréas.

Dans des cas isolés, une pancréatite nécrosante ou hémorragique avec une issue fatale a été signalée. Le taux de glucose urinaire et la glycémie doivent être surveillés pendant le traitement par Oncaspar, car ils peuvent être augmentés.

Une contraception non orale efficace doit être utilisée pendant le traitement par Oncaspar et pendant au moins 6 mois après son arrêt. Une interaction indirecte entre les contraceptifs oraux et la pégaspargase ne pouvant être exclue, les contraceptifs oraux ne sont pas considérés comme une méthode de contraception acceptable (voir rubriques 4.5 et 4.6).

Ce médicament contient moins de 1 mmol de sodium (23 mg) par dose, c.-à-d. qu'il est essentiellement « sans sodium ».

## **12.5 Interactions avec d'autres médicaments et autres formes d'interactions**

La diminution des protéines sériques causée par la pégaspargase peut augmenter la toxicité d'autres médicaments qui se lient aux protéines.

En outre, en inhibant la synthèse des protéines et la division cellulaire, la pégaspargase peut perturber le mécanisme d'action d'autres substances qui nécessitent une division cellulaire pour être efficaces, par exemple le méthotrexate.

Le méthotrexate et la cytarabine peuvent interférer différemment : une administration antérieure de ces substances peut augmenter l'action d'Oncaspar par synergie. Si ces substances sont administrées l'une après l'autre, l'effet de la pégaspargase peut être réduit par antagonisme.

La pégaspargase peut interférer avec le métabolisme enzymatique d'autres médicaments, particulièrement dans le foie.

L'utilisation d'Oncaspar peut engendrer une fluctuation des facteurs de coagulation. Cela peut favoriser la tendance aux saignements et/ou les thromboses. La prudence est donc recommandée lors de l'administration concomitante d'anticoagulants tels que la coumarine, l'héparine, le dipyridamole, l'acide acétylsalicylique ou d'anti-inflammatoires non stéroïdiens.

Lors de l'administration concomitante de glucocorticoïdes (par exemple, prednisone) et de pégaspargase, les altérations des paramètres de coagulation (par exemple, diminution du fibrinogène et déficit en antithrombine III [ATIII]) peuvent être plus prononcées.

Un traitement par vincristine administré simultanément ou juste avant peut augmenter la toxicité de la pégaspargase et augmente le risque de réactions anaphylactiques. L'administration d'Oncaspar avant la vincristine peut augmenter la neurotoxicité de la vincristine. Par conséquent, la vincristine doit être administrée au moins 12 heures avant l'administration d'Oncaspar afin de limiter la toxicité.

Une interaction indirecte entre la pégaspargase et les contraceptifs oraux ne peut être exclue en raison de l'hépatotoxicité de la pégaspargase qui peut altérer la clairance hépatique des contraceptifs oraux. Par conséquent, l'association d'Oncaspar et de contraceptifs oraux n'est pas recommandée. Les femmes en âge de procréer doivent utiliser un autre moyen de contraception (voir rubriques 4.4 et 4.6).

La vaccination simultanée avec des vaccins vivants entraîne une augmentation du risque d'infections sévères attribuable à l'activité immunosuppressive de la pégaspargase et à la présence de la maladie sous-jacente et de la chimiothérapie associée (voir rubrique 4.4). Par conséquent, la vaccination avec des vaccins vivants ne doit pas être effectuée dans les 3 mois qui suivent la fin de l'intégralité du traitement anti-leucémique.

## **12.6 Fertilité, grossesse et allaitement**

### Femmes en âge de procréer/Contraception masculine et féminine

Les hommes et les femmes doivent utiliser une contraception efficace pendant le traitement par Oncaspar et pendant au moins 6 mois après son arrêt. Une interaction indirecte entre les contraceptifs oraux et la pégaspargase ne pouvant être exclue, les contraceptifs oraux ne sont pas considérés comme suffisamment sûrs dans cette situation clinique. Les femmes en âge de procréer doivent utiliser un autre moyen de contraception (voir rubriques 4.4 et 4.5).

### Grossesse

Il existe des données limitées sur l'utilisation de la L-asparaginase et il n'existe pas de données sur l'utilisation d'Oncaspar chez la femme enceinte. Aucune étude de reproduction n'a été réalisée avec la pégaspargase chez l'animal, mais des études menées chez l'animal avec la L-asparaginase ont mis en évidence une tératogénicité (voir

rubrique 5.3). Par conséquent, et en raison de ses propriétés pharmacologiques, Oncaspar ne doit pas être utilisé pendant la grossesse à moins que la situation clinique de la patiente ne justifie un traitement par pégaspargase.

#### Allaitement

On ne sait pas si la pégaspargase est excrétée dans le lait maternel. Compte tenu de ses propriétés pharmacologiques, un risque pour les nouveau-nés/nourrissons allaités ne peut être exclu. Par mesure de précaution, l'allaitement doit être interrompu au cours du traitement avec Oncaspar et ne doit pas être repris après l'arrêt du traitement.

#### Fertilité

Aucune étude évaluant l'effet de la pégaspargase sur la fertilité n'a été réalisée.

### **12.7 Effets sur l'aptitude à conduire des véhicules et à utiliser des machines**

Oncaspar a une influence importante sur l'aptitude à conduire des véhicules et à utiliser des machines, car il altère la capacité de réaction.

Il doit être conseillé aux patients de ne pas conduire de véhicules ni d'utiliser de machines en cas de confusion mentale, de somnolence ou d'autres effets indésirables qui pourraient réduire leur capacité à conduire des véhicules ou à utiliser des machines.

### **12.8 Effets indésirables**

#### Résumé du profil de sécurité

Les effets indésirables décrits dans cette rubrique ont été collectés à partir des données des essais cliniques menés sur Oncaspar et de pharmacovigilance chez des patients atteints de LLA. Les analyses de sécurité ont été réalisées en tenant compte des effets indésirables observés lors de l'étude clinique 1 [CCG-1962] et de l'étude 2 [AALL07P4] (voir rubrique 5.1).

#### Liste tabulée des effets indésirables

Les effets indésirables et leur fréquence sont présentés dans le Tableau 1. Les fréquences sont définies par la convention suivante : très fréquent ( $\geq 1/10$ ), fréquent ( $\geq 1/100, < 1/10$ ), peu fréquent ( $\geq 1/1\,000, < 1/100$ ), rare ( $\geq 1/10\,000, < 1/1\,000$ ), très rare ( $< 1/10\,000$ ), et fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Au sein de chaque groupe de fréquence, les effets indésirables sont présentés suivant un ordre décroissant de gravité.

**Tableau 1 : Effets indésirables rapportés lors du traitement par Oncaspar**

<b>Classe de systèmes d'organes MedDRA</b>	<b>Effets indésirables</b>
Affections hématologiques et du système lymphatique	Fréquent : neutropénie fébrile, anémie, coagulopathie Fréquence indéterminée : insuffisance de la moelle osseuse
Affections endocriniennes	Très fréquent : hyperglycémie
<b>Classe de systèmes d'organes MedDRA</b>	<b>Effets indésirables</b>
Affections gastrointestinales	Très fréquent : pancréatite, diarrhée, douleur abdominale, nausées Fréquent : vomissement, stomatite Rare : pancréatite nécrosante, pancréatite hémorragique Fréquence indéterminée : pseudokyste pancréatique, parotidite*
Troubles généraux et anomalies au site d'administration	Fréquence indéterminée : pyrexie
Affections hépatobiliaires	Fréquent : hépatotoxicité, stéatose hépatique Rare : nécrose hépatique, ictere, cholestase, insuffisance hépatique
Affections du système immunitaire	Très fréquent : hypersensibilité, urticaire, réaction anaphylactique Fréquence indéterminée : nécrolyse épidermique toxique*
Infections et infestations	Fréquent : infections, septicémie
Investigations	Très fréquent : poids diminué Fréquent : amylase augmentée, alanine aminotransférase augmentée, bilirubinémie augmentée, albumine sanguine diminuée, neutrophiles diminués, numération plaquettaires diminuée, temps de céphaline activée allongé, hypofibrinogénémie Fréquence indéterminée : urée sanguine augmentée, anticorps antipégasparegase
Troubles du métabolisme et de la nutrition	Très fréquent : appétit diminué Fréquent : hypertriglycéridémie, hyperlipidémie, hypercholestérolémie Fréquence indéterminée : acidocétose diabétique
Affections musculosquelettiques et systémiques	Fréquent : extrémités douloureuses
Affections du rein et des voies urinaires	Fréquence indéterminée : insuffisance rénale aiguë*
Affections du système nerveux	Fréquent : convulsion, neuropathie motrice périphérique, syncope Rare : syndrome de leucoencéphalopathie postérieure réversible Fréquence indéterminée : somnolence, tremblement*
Affections psychiatriques	Fréquence indéterminée : état confusionnel

Affections respiratoires, thoraciques et médiastinales	Fréquent : hypoxie
Affections de la peau et du tissu sous-cutané	Très fréquent : rash
Affections vasculaires	Fréquent : thrombose** Fréquence indéterminée : accident cérébrovasculaire

\*Effets indésirables observés avec d'autres médicaments à base d'asparaginase de la même classe

\*\*Légende : thrombose du SNC

#### Description de certains effets indésirables

Les effets indésirables suivants ont été observés lors d'un traitement concomitant par asparaginase. Bien qu'ils n'aient pas été associés spécifiquement à l'utilisation de la pegaspargase, ils peuvent se produire avec Oncaspar :

#### *Affections hématologiques et du système lymphatique*

Oncaspar peut provoquer une myélosuppression légère à modérée et les trois lignées cellulaires sanguines peuvent être affectées.

Environ la moitié des hémorragies et thromboses graves affectent les vaisseaux cérébraux et peuvent induire par exemple un accident vasculaire cérébral, des convulsions, des céphalées ou une perte de conscience.

#### *Affections du système nerveux*

Oncaspar peut provoquer des dysfonctionnements du système nerveux central qui se manifestent par des convulsions, et moins souvent par un état confusionnel et de la somnolence (état de conscience légèrement altéré).

Dans de rares cas, un syndrome de leucoencéphalopathie postérieure réversible (SLPR) peut se produire.

De très rares cas de légers tremblements des doigts ont été rapportés.

#### *Affections gastro-intestinales*

Environ la moitié des patients présentent des réactions gastro-intestinales légères à modérées telles qu'une perte d'appétit, des nausées, des vomissements, des crampes abdominales, de la diarrhée et une perte de poids.

Les pancréatites aiguës sont fréquentes. Des cas isolés de formation de pseudo-kystes ont été rapportés (jusqu'à 4 mois après la dernière administration).

Les pancréatites hémorragiques ou nécrosantes sont rares. Un cas de pancréatite avec parotidite aiguë simultanée a été décrit avec le traitement par L-asparaginase. Un seul cas de pancréatite nécrosante ou hémorragique d'issue fatale a été signalé.

L'amylase sérique peut augmenter pendant le traitement par Oncaspar et également après son arrêt.

#### *Affections du rein et des voies urinaires*

Une insuffisance rénale aiguë peut se développer dans de rares cas pendant un traitement avec des produits contenant de la L-asparaginase.

#### *Affections de la peau et du tissu sous-cutané*

Des réactions allergiques cutanées peuvent se manifester. Un cas de nécrolyse épidermique toxique (syndrome de Lyell) associé à la L-asparaginase a été rapporté.

### *Affections endocrinien*nes

Des altérations de la fonction endocrine du pancréas sont fréquemment observées et se manifestent principalement sous la forme d'un métabolisme anormal du glucose. Des cas d'acidocétose diabétique et d'hyperglycémie hyperosmolaire, répondant généralement bien à l'administration d'insuline, ont été rapportés.

### *Troubles du métabolisme et de la nutrition*

Une altération des taux lipidiques sériques a été observée ; des modifications des valeurs lipidiques sériques, dans la plupart des cas sans symptômes cliniques, sont très fréquentes.

Une augmentation de l'urée sérique s'observe régulièrement ; elle n'est pas liée à la dose et est presque toujours le signe avant-coureur d'un déséquilibre du métabolisme rénal.

### *Troubles généraux et anomalies au site d'administration*

De la fièvre peut apparaître après l'injection, mais elle disparaît généralement spontanément.

### *Affections du système immunitaire*

L'apparition d'anticorps spécifiques dirigés contre la pégaspargase a été détectée. Dans de rares cas, ils ont été associés à des réactions d'hypersensibilité. L'apparition d'anticorps neutralisants entraînant une baisse de l'efficacité clinique a également été signalée.

### *Affections hépatobiliaires*

Des altérations des paramètres hépatiques sont fréquentes. Une augmentation des transaminases sériques et de la bilirubine sérique, non liée à la dose, est fréquemment observée.

Une infiltration graisseuse du foie est très fréquemment observée. De rares cas de cholestase, de jaunissement, de nécrose des cellules hépatiques et d'insuffisance hépatique d'issue fatale ont été rapportés.

Une altération de la synthèse protéique peut conduire à une diminution des protéines sériques. Chez la majorité des patients, on constate une diminution de la sérum-albumine pendant le traitement, non liée à la dose.

Les types d'effets indésirables d'Oncaspar sont semblables à ceux de la L-asparaginase non pégylée native (c.-à-d. l'asparaginase native dérivée d'*E. coli*).

### Déclaration des effets indésirables suspectés

La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : Agence nationale de sécurité du médicament et des produits de santé (Ansm) et réseau des Centres Régionaux de Pharmacovigilance - Site internet: [www.ansm.sante.fr](http://www.ansm.sante.fr).

## **12.9 Surdosage**

Quelques cas de surdosages d'Oncaspar dus à des administrations accidentelles ont été rapportés. Après le surdosage, une augmentation des enzymes hépatiques, un rash et une hyperbilirubinémie ont été observés. Il n'existe pas de traitement pharmacologique spécifique des surdosages. En cas de surdosage, les patients doivent être minutieusement surveillés afin de détecter tout signe et symptôme d'effets indésirables, et doivent être pris en charge de manière adéquate par un traitement symptomatique et de soutien.

## 13 PROPRIÉTÉS PHARMACOLOGIQUES

### 13.1 Propriétés pharmacodynamiques

Classe pharmacothérapeutique : agents antinéoplasiques et immunomodulateurs, autres agents antinéoplasiques

Code ATC : L01XX24

#### Mécanisme d'action

Le mécanisme d'action de la L-asparaginase est dû au clivage enzymatique de l'acide aminé Lasparagine en acide aspartique et ammoniaque. La déplétion de la L-asparagine dans le serum sanguin entraîne une inhibition de la synthèse des protéines, de l'ADN et de l'ARN, particulièrement dans les blastes leucémiques qui ne peuvent plus synthétiser la L-asparagine, et subissent donc une apoptose.

À l'inverse, les cellules normales sont capables de synthétiser la L-asparagine et sont moins affectées par sa suppression rapide pendant le traitement par l'enzyme L-asparaginase. La PEGylation ne modifie pas les propriétés enzymatiques de la L-asparaginase, mais elle influence la pharmacocinétique et l'immunogénicité de l'enzyme.

#### Effets pharmacodynamiques

L'effet anti-leucémique de la L-asparaginase est lié à une déplétion prolongée en L-asparagine. Dans l'étude 1, la pharmacodynamique a été évaluée chez 57 patients pédiatriques présentant une LLA à risque standard nouvellement diagnostiquée, qui ont reçu trois doses d'Oncaspar (2 500 unités/m<sup>2</sup>) par voie intramusculaire (une dose lors de la phase d'induction et une dose lors des deux phases d'intensification retardée). L'activité pharmacodynamique a été évaluée à travers différentes mesures de l'asparagine dans le serum (n = 57) et dans le liquide céphalo-rachidien (LCR) (n = 50).

#### Efficacité et sécurité cliniques

L'efficacité et la sécurité d'Oncaspar ont été évaluées sur la base de deux études cliniques utilisant Oncaspar, solution injectable/pour perfusion comme traitement de première intention dans la LLA : l'étude 1 menée chez des patients atteints d'une LLA à risque standard et l'étude 2 menée chez des patients atteints de LLA à haut risque.

L'efficacité d'Oncaspar chez les patients atteints de LLA présentant une maladie en récidive/réfractaire et des antécédents de réaction allergique clinique à la L-asparaginase native dérivée d'*E. coli* repose sur un groupe de 94 patients inclus dans six études en ouvert [ASP-001, ASP-201A, ASP-302, ASP304, ASP-400 et ASP-001C/003C].

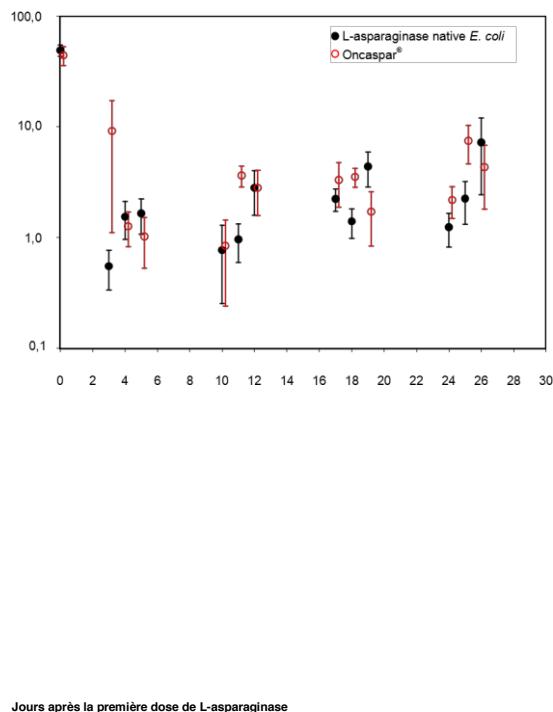
#### Traitement de première intention (patients atteints de LLA non hypersensibles à la L-asparaginase native dérivée d'*E. coli*)

La sécurité et l'efficacité d'Oncaspar ont été évaluées au cours d'une étude randomisée, multicentrique, ouverte, contrôlée versus traitement actif (étude 1). Dans cette étude, 118 patients pédiatriques âgés de 1 à 9 ans atteints de LLA à risque standard non précédemment traitée ont été randomisés selon un rapport de 1:1 pour recevoir Oncaspar ou de la L-asparaginase native dérivée d'*E. coli* dans le cadre d'un traitement combiné. Oncaspar était administré par voie intramusculaire à une dose de 2 500 unités/m<sup>2</sup> le jour 3 de la phase d'induction de 4 semaines et le jour 3 de chacune des deux phases d'intensification retardée (IR) de 8 semaines. La L-asparaginase native dérivée d'*E. coli* était administrée par voie intramusculaire à une dose de 6 000 unités/m<sup>2</sup> trois fois par semaine, soit 9 doses au total pendant la phase d'induction et 6 doses au total pendant chaque phase d'intensification retardée.

La détermination principale de l'efficacité reposait sur la preuve d'une déplétion en asparagine similaire (amplitude et durée) dans les bras Oncaspar et L-asparaginase native dérivée d'*E. coli*. L'objectif fixé par le protocole était

l'obtention d'une déplétion en asparagine à une concentration sérique  $\leq 1 \mu\text{M}$ . La proportion de patients ayant atteint ce niveau de déplétion était similaire dans les deux bras pendant les 3 phases de traitement, aux points de mesure indiqués dans le protocole.

Dans toutes les phases de traitement, les concentrations sériques d'asparagine ont diminué dans les 4 jours qui ont suivi la première administration d'asparaginase, et sont restées faibles pendant environ 3 semaines aussi bien dans le bras recevant Oncaspar que dans celui recevant la L-asparaginase native dérivée d'*E. coli*. Les concentrations sériques d'asparagine obtenues pendant la phase d'induction sont présentées en figure 1. Les profils de déplétion en asparagine sérique dans les deux phases d'intensification retardée sont comparables à ceux observés lors de la phase d'induction.

**Figure 1 : Asparagine sérique moyenne ( $\pm$  erreur standard) pendant la phase d'induction de l'étude 1**

Remarque : Oncaspar (2 500 unités/m<sup>2</sup> en intramusculaire) était administré le jour 3 de la phase d'induction de 4 semaines. La L-asparaginase native dérivée d'*E. coli* (6 000 unités/m<sup>2</sup> en intramusculaire) était administrée 3 fois par semaine, soit 9 doses pendant la phase d'induction.

Les concentrations en asparagine dans le LCR ont été mesurées chez 50 patients pendant la phase d'induction. Ces concentrations ont diminué, passant d'une concentration moyenne avant traitement de 3,1  $\mu\text{M}$  à une concentration de 1,7  $\mu\text{M}$  le jour 4  $\pm$  1 et de 1,5  $\mu\text{M}$  au jour 25  $\pm$  1 après l'administration d'Oncaspar. Ces résultats étaient comparables à ceux observés dans le bras recevant la L-asparaginase native dérivée d'*E. coli*.

Les données relatives à la survie sans événement (SSE) pour les bras Oncaspar et L-asparaginase native dérivée d'*E. coli* sont résumées dans le tableau 2 ; l'étude 1 n'avait pas pour objectif d'évaluer les différences en termes de taux de SSE.

**Tableau 2 : Taux de survie sans événement à 3, 5 et 7 ans (étude 1)**

	Oncaspar	L-asparaginase native dérivée d' <i>E. coli</i>
Taux de SSE à 3 ans, % (IC à 95 %)	83 (73, 93)	79 (68, 90)
Taux de SSE à 5 ans, % (IC à 95 %)	78 (67, 88)	73 (61, 85)
Taux de SSE à 7 ans, % (IC à 95 %)	75 (63, 87)	66 (52, 80)

Dans l'étude 1, les effets indésirables les plus fréquents étaient des infections, dont deux infections potentiellement mortelles (1 patient dans chaque bras). En général, l'incidence et le type d'effets indésirables de grades 3 et 4 étaient similaires dans les deux groupes de traitement. Deux patients dans le bras Oncaspar ont eu des réactions allergiques pendant la phase d'intensification retardée (IR) n° 1 (réaction allergique de grade 1 et éruptions urticariennes de grade 3).

Une étude pilote a été menée chez des patients âgés de 1 à 30 ans ayant une LLA à précurseurs B à haut risque nouvellement diagnostiquée (étude 2). Il s'agissait d'une étude randomisée, contrôlée comparant Oncaspar à une autre asparaginase pégylée en association avec une chimiothérapie à agents multiples en traitement de première intention. Concernant la numération leucocytaire, les critères étaient les suivants : a) âge compris entre 1 et 10 ans : numération  $\geq 50\,000/\mu\text{l}$ ; b) âge compris entre 10 et 30 ans : numération indifférente ; c) corticothérapie antérieure : numération indifférente. Les patients ne devaient pas avoir reçu de chimiothérapie cytotoxique préalable, à l'exception des corticoïdes et de cytarabine par voie intrathécale. Au total, 166 patients ont participé à cette étude : 54 patients ont été randomisés pour recevoir 2 500 U/m<sup>2</sup> d'Oncaspar et 111 patients ont été randomisés pour recevoir une autre asparaginase pégylée. Oncaspar était administré par voie intraveineuse à la dose de 2 500 unités/m<sup>2</sup> pendant les phases d'induction, de consolidation, d'IR et d'entretien provisoire à des patients ayant une LLA à haut risque recevant un traitement BerlinFrankfurt-Munster augmenté. À 3 ans, les taux de SSE et de survie globale (SG) dans le bras Oncaspar étaient de 85,1 % [IC à 95 % : 72 % à 92 %] et de 92,4 % [IC à 95 % : 81 % à 97 %], respectivement. Globalement, dans le groupe Oncaspar, le taux d'hypersensibilité tous grades confondus était de 9,8 %, celui des réactions anaphylactiques de 19,6 % et celui des pancréatites de 5,9 %. Le taux de neutropénie fébrile de grade 3 ou plus était de 37,9 %.

***Patients atteints de LLA hypersensibles à la L-asparaginase native dérivée d'E. coli*** Six études en ouvert ont évalué Oncaspar dans le traitement de maladies hématologiques en récidive/réfractaires. Lors de ces études, un total de 94 patients ayant une LLA et des antécédents de réaction allergique clinique à la L-asparaginase native dérivée d'*E. coli* ont été exposés à Oncaspar. Un patient a reçu des doses d'Oncaspar de 250 et 500 unités/m<sup>2</sup> par voie intraveineuse. Les autres patients ont reçu 2 000 ou 2 500 U/m<sup>2</sup> par voie intramusculaire ou intraveineuse. Les patients ont reçu Oncaspar seul ou en association avec une chimiothérapie à agents multiples. De manière générale, dans les cinq études analysées, parmi les 65 patients atteints de LLA exposés à Oncaspar et en tenant compte de la réponse thérapeutique la plus élevée pendant toute l'étude, une rémission complète a été observée chez 30 patients (46 %), une rémission partielle chez 7 patients (11 %) et une amélioration hématologique chez 1 patient (2 %). Dans l'étude restante, la réponse au traitement pendant la phase d'induction a été évaluée chez 11 des 29 patients atteints de LLA et hypersensibles exposés à Oncaspar. Parmi eux, 3 ont présenté une rémission complète (27 %), 1 une rémission partielle (9 %), 1 une amélioration hématologique (9 %) et 2 une efficacité thérapeutique (18 %). L'efficacité thérapeutique se définissait comme une amélioration clinique ne répondant pas aux critères des autres résultats positifs. Pendant la phase d'entretien, 19 patients ont été évalués : 17 patients ont présenté une rémission complète (89 %) et un patient une efficacité thérapeutique (5 %).

### 13.2 Propriétés pharmacocinétiques

Les évaluations pharmacocinétiques d'Oncaspar reposent sur un test enzymatique mesurant l'activité de l'asparaginase.

Chez les adultes ayant une leucémie, l'activité enzymatique initiale après administration intraveineuse d'Oncaspar était proportionnelle à la dose. La demi-vie d'élimination plasmatique était comprise entre 1 et 6 jours et ne semblait pas être liée à la dose reçue.

Elle était également indépendante de l'âge, du sexe, de la surface corporelle, des fonctions rénale et hépatique, du diagnostic et de la sévérité de la maladie. Cependant, la demi-vie terminale était plus courte chez les patients hypersensibles que chez les patients non-hypersensibles ; ceci est peut-être dû à la formation d'un nombre élevé d'anticorps anti-pegaspargase.

Le volume de distribution était compris dans l'intervalle du volume plasmatique estimé. Après une perfusion intraveineuse d'une heure, l'activité de l'asparaginase a été détectée pendant au moins 15 jours après la première administration d'Oncaspar.

Les patients présentant une LLA nouvellement diagnostiquée ont reçu une seule injection intramusculaire d'Oncaspar (2 500 U/m<sup>2</sup> de surface corporelle) ou de l'asparaginase native dérivée d'*E. coli* (25 000 U/m<sup>2</sup> de surface corporelle) ou d'*Erwinia* (25 000 U/m<sup>2</sup> de surface corporelle). La demi-vie d'élimination plasmatique d'Oncaspar était significativement plus longue d'un point de vue statistique (5,7 jours) que celle des asparaginases natives dérivées d'*E. coli* (1,3 jour) et d'*Erwinia* (0,65 jour). L'apoptose immédiate des cellules leucémiques *in vivo*, mesurée par fluorescence avec rhodamine, était identique pour les trois préparations à base de L-asparaginase.

Les patients dont la LLA avait rechuté plusieurs fois ont reçu soit Oncaspar, soit de l'asparaginase native dérivée d'*E. coli* lors de la phase d'induction. Oncaspar était administré par voie intramusculaire à la dose de 2 500 U/m<sup>2</sup> de surface corporelle les jours 1 et 15 de la phase d'induction. La demi-vie plasmatique moyenne d'Oncaspar était de 8 jours chez les patients non hypersensibles (ASC de 10,35 U/ml/jour), et de 2,7 jours chez les patients hypersensibles (ASC de 3,52 U/ml/jour).

Étant donné que la pegaspargase est une protéine de haut poids moléculaire, elle n'est pas excrétée par les reins ; aucune modification de la pharmacocinétique d'Oncaspar n'est attendue chez les patients atteints d'insuffisance rénale.

Compte tenu de la distribution tissulaire ubiquitaire des enzymes protéolytiques responsables du métabolisme d'Oncaspar, le rôle exact du foie n'est pas connu. Cependant, une atteinte de la fonction hépatique ne devrait pas poser de problèmes cliniques majeurs en cas d'utilisation d'Oncaspar.

Il n'existe pas de données disponibles pour les patients âgés.

### 13.3 Données de sécurité préclinique

La comparabilité non clinique des paramètres pharmacocinétiques/pharmacodynamiques entre les deux formes pharmaceutiques d'Oncaspar, solution injectable/pour perfusion, et poudre pour solution, a été démontrée chez les chiens après une dose unique et des doses répétées (500 U/kg), par voie intraveineuse. Les études mentionnées ci-dessous ont été réalisées avec la formulation « solution injectable/pour perfusion ».

Seules des doses très élevées (25 000 à 100 000 U/kg de poids corporel) de pégaspargase administrées en une injection intrapéritonéale unique ont provoqué le décès de 14 % de toutes les souris traitées. Une légère hépatotoxicité a été observée avec les mêmes dosages. Les effets indésirables étaient les suivants : perte de poids, horripilation et activité réduite. Une diminution du poids de la rate pourrait être le signe de potentielles propriétés immunosuppressives du traitement.

La pégaspargase a été bien tolérée aussi bien par les rats que par les chiens qui ont reçu une dose unique allant jusqu'à 500 U/kg, par voie intraveineuse.

#### Toxicité à doses répétées

Une étude de 4 semaines menée sur des rats ayant reçu 400 U/kg/jour de pégaspargase par voie intrapéritonéale a montré une diminution de la prise alimentaire et du poids corporel par rapport au groupe témoin.

Une étude de 3 mois portant sur l'administration de pégaspargase par voie intrapéritonéale ou intramusculaire à des souris à des doses allant jusqu'à 500 U/kg a montré de légers changements hépatocellulaires, uniquement à la dose la plus élevée administrée par voie intrapéritonéale.

Une diminution temporaire de la prise de poids corporel et une légère diminution temporaire de la numération totale des leucocytes ont été observées chez les chiens qui avaient reçu 1 200 U/kg de pégaspargase par semaine pendant 2 semaines. Une augmentation de l'activité de la transaminase glutamique pyruvique sérique a également été constatée chez l'un des quatre chiens.

#### Immunogénicité

Aucune réponse immunitaire n'a été détectée au cours d'une étude de 12 semaines sur des souris auxquelles de la pégaspargase était administrée chaque semaine à la dose de 10,5 U/souris, par voie intramusculaire ou intrapéritonéale.

#### Toxicité sur la reproduction

Aucune étude de toxicité sur la reproduction n'a été menée avec la pégaspargase.

Des études sur l'embryotoxicité de la L-asparaginase ont montré un potentiel tératogène chez les rates traitées du 6<sup>e</sup> au 15<sup>e</sup> jour de gestation, la dose sans effet observable (DSEO) pour les effets tératogènes s'élevant à 300 U/kg en administration intraveineuse. Chez les lapines, des doses de 50 ou 100 U/kg administrées par voie intraveineuse aux jours 8 et 9 de gestation ont engendré des fœtus viables, mais présentant des malformations congénitales : aucune DSEO n'a été déterminée. Plusieurs malformations et effets embryolétaux ont été observés avec des doses comprises dans la plage thérapeutique. Aucune investigation concernant l'effet sur la fertilité et le développement péri et postnatal n'a été menée.

#### Carcinogénicité, mutagénicité, fertilité

Aucune investigation de carcinogénicité ou étude à long terme de l'effet sur la fertilité chez les animaux n'a été menée avec la pégaspargase.

La pégaspargase ne s'est pas avérée mutagène lors du test d'Ames avec des souches de *Salmonella typhimurium*.

#### **14.1 Liste des excipients**

Phosphate disodique heptahydraté  
Phosphate monosodique monohydraté  
Chlorure de sodium  
Saccharose  
Hydroxyde de sodium (pour l'ajustement du pH)  
Acide chlorhydrique (pour l'ajustement du pH)

#### **14.2 Incompatibilités**

Ce médicament ne doit pas être mélangé avec d'autres médicaments à l'exception de ceux mentionnés dans la rubrique 6.6.

#### **14.3 Durée de conservation**

2 ans.

##### Solution reconstituée

La stabilité physico-chimique de la solution après reconstitution a été démontrée pendant 24 heures à une température ne dépassant pas 25 °C. D'un point de vue microbiologique, à moins que la méthode de reconstitution n'exclue tout risque de contamination microbienne, le produit doit être utilisé immédiatement. S'il n'est pas utilisé immédiatement, sa durée et ses conditions de conservation relèvent de la responsabilité de l'utilisateur.

##### Solution diluée

La stabilité physico-chimique de la solution après reconstitution a été démontrée pendant 48 heures à une température comprise entre 2 °C et 8 °C. D'un point de vue microbiologique, le produit doit être utilisé immédiatement. En cas d'utilisation non immédiate, les durées et conditions de conservation avant utilisation relèvent de la responsabilité de l'utilisateur et ne devraient normalement pas dépasser 24 heures entre 2 °C et 8 °C, sauf si la reconstitution/dilution a été réalisée dans des conditions aseptiques contrôlées et validées.

#### **14.4 Précautions particulières de conservation**

À conserver au réfrigérateur (entre 2 °C et 8 °C).

Ne pas congeler.

Pour les conditions de conservation du médicament reconstitué et dilué, voir la rubrique 6.3.

#### **14.5 Nature et contenu de l'emballage extérieur**

Flacon en verre flint de type I muni d'un bouchon en élastomère chlorobutyle recouvert d'une capsule amovible (en aluminium de 20 mm) contenant 3 750 U de pégaspargase.

## 14.6 Précautions particulières d'élimination et manipulation

Le contact avec ce médicament peut provoquer des irritations. La poudre doit donc être manipulée et administrée avec beaucoup de précautions. L'inhalation de la vapeur et le contact avec la peau et les muqueuses, particulièrement les yeux, doivent être évités. Si le médicament entre en contact avec les yeux, la peau ou les muqueuses, rincer immédiatement avec beaucoup d'eau pendant au moins 15 minutes.

Oncaspar doit être administré par voie intraveineuse ou intramusculaire après reconstitution du produit. La poudre doit être reconstituée avec 5,2 ml d'eau pour préparations injectables avant l'administration (voir rubrique 4.2).

### Instructions de manipulation

1. Le personnel doit être formé sur la manière de manipuler et de transférer le médicament (les femmes enceintes ne peuvent pas travailler avec ce médicament).
2. Procéder de manière aseptique.
3. Respecter les procédures de manipulation des agents antinéoplasiques.
4. Il est recommandé de porter des gants et des vêtements de protection jetables lors de la manipulation d'Oncaspar.
5. Tous les objets ayant servi à l'administration ou au nettoyage, y compris les gants, doivent être jetés dans des sacs pour déchets à haut risque qui seront incinérés à haute température.

### Reconstitution

1. Injecter 5,2 ml d'eau pour préparations injectables dans le flacon à l'aide d'une seringue et d'une aiguille de calibre 21.
2. Agiter doucement le flacon jusqu'à reconstitution de la poudre.
3. Après la reconstitution, la solution doit être limpide, incolore et exempte de particules visibles. Ne pas utiliser si la solution reconstituée est trouble ou si un précipité s'est formé. Ne pas secouer.
4. Utiliser immédiatement la solution dans les 24 heures suivant la reconstitution, si le produit est conservé à moins de 25 °C.

### Administration

1. Inspecter les produits parentéraux pour vérifier l'absence de particules avant l'administration ; seule une solution limpide, incolore et exempte de particules visibles peut être utilisée.
2. Administrer le médicament par voie intraveineuse ou intramusculaire. La solution doit être administrée lentement.

En cas d'injection intramusculaire, le volume injecté ne doit pas dépasser 2 ml chez l'enfant et l'adolescent et 3 ml chez l'adulte.

En cas d'administration intraveineuse, la solution doit être diluée dans 100 ml de solution injectable de chlorure de sodium à 9 mg/ml (0,9 %) ou de solution de glucose à 5 %. La solution diluée peut être administrée pendant 1 à 2 heures avec une perfusion déjà en cours de chlorure de sodium à 9 mg/ml ou de glucose à 5 %. Ne pas perfuser d'autres médicaments par la même ligne intraveineuse en même temps qu'Oncaspar (voir rubrique 4.2).

Après dilution, la solution doit être utilisée immédiatement. S'il n'est pas possible d'utiliser la solution diluée immédiatement, elle doit être conservée à une température comprise entre 2 °C et 8 °C pendant maximum 48 heures (voir rubrique 6.3).

### Élimination

Oncaspar est réservé à un usage unique. Tout médicament non utilisé ou déchet doit être éliminé conformément à la réglementation en vigueur.

**15 TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ**

Baxalta Innovations GmbH  
Industriestrasse 67  
A-1221 Vienne  
Autriche

**16 NUMÉRO(S) D'AUTORISATION DE MISE SUR LE MARCHÉ**

EU/1/15/1070/001/002

**17 DATE DE PREMIÈRE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION**

Date de première autorisation : 8 décembre 2017

**18 DATE DE MISE À JOUR DU TEXTE**

27 mars 2018

Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments <http://www.ema.europa.eu>.

## Appendix 14: ERWINASE - RESUME DES CARACTERISTIQUES DU PRODUIT

(à noter que la posologie retenue dans le protocole CAALL F01 diffère de celle proposée dans le RCP)

### 1. DÉNOMINATION DU MÉDICAMENT

**ERWINASE 10000 UI/flacon, poudre pour solution pour injection.**

### 2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Crisantaspase (asparaginase d'*Erwinia chrysanthemi* : L-asparaginase d'*Erwinia*), 10 000 UI/flacon.

Après reconstitution avec 2 ml de solution injectable de chlorure de sodium à 0,9 %, un ml de solution prête à l'emploi contient 5 000 UI de crisantaspase, et après reconstitution avec 1 ml de solution injectable de chlorure de sodium à 0,9 %, un ml de solution prête à l'emploi contient 10 000 UI de crisantaspase.

*Excipients* : Glucose monohydraté, Chlorure de sodium , Hydroxyde de sodium, Acide acétique.

### 3. FORME PHARMACEUTIQUE

Poudre pour solution injectable.

### 4. DONNÉES CLINIQUES

#### 4.1. Indications thérapeutiques

Erwinase est utilisé en association à d'autres agents chimiothérapeutiques pour le traitement des patients, principalement pédiatriques, atteints de leucémie aiguë lymphoblastique chez qui une hypersensibilité (allergie clinique ou inactivation silencieuse) à l'asparaginase native ou pégylée dérivée d'*E. coli* est apparue.

#### 4.2. Posologie et mode d'administration

*Posologie* : La posologie recommandée est de 25 000 UI/m IM ou IV trois fois par semaine (lundi, mercredi et vendredi) pendant deux semaines pour remplacer chaque dose de pegaspargase ou chaque cycle de traitement par asparaginase. Le traitement peut être adapté selon le protocole local. La dose optimale d'Erwinase peut varier selon les patients en raison de la forte variabilité interindividuelle de l'activité moyenne de l'asparaginase observée en pédiatrie. Il peut donc être conseillé de surveiller la concentration de l'asparaginase dans le but d'individualiser la posologie.

*Population pédiatrique* : La posologie est la même chez l'adulte et chez l'enfant.

*Mode d'administration* : La solution d'Erwinase peut être administrée par injection intraveineuse ou intramusculaire. Pour des instructions sur la reconstitution du médicament avant son administration, voir rubrique 6.6.

#### 4.3. Contre-indications

Antécédents de réaction allergique à la crisantaspase ou à l'un des excipients mentionnés dans la rubrique Composition. Anomalies de la fonction hépatique. Pancréatite, y compris antécédents d'épisodes de pancréatite aiguë liés à un traitement par L-asparaginase.

#### 4.4. Mises en garde spéciales et précautions d'emploi

Erwinase doit être uniquement utilisé par un médecin expérimenté dans l'utilisation des traitements des hémopathies malignes. Même si la survenue d'une réaction anaphylactique est rare, les moyens de traitement d'une réaction de ce type (par exemple adrénaline, glucocorticoïde IV et oxygène) doivent être disponibles. En cas de survenue d'une réaction d'hypersensibilité, le traitement par Erwinase doit être arrêté. Le risque de

réaction d'hypersensibilité augmente lorsque le traitement est répété (voir rubrique 4.8.). En cas de survenue d'une pancréatite le traitement doit être interrompu. Une activité immunosuppressive de la L-asparaginase a été décrite dans des modèles animaux. L'administration de ce médicament chez l'homme peut favoriser l'apparition d'une infection. Une surveillance attentive est nécessaire avant et pendant le traitement : - Le bilan hépatique doit être surveillé régulièrement durant le traitement. - afin d'éviter la survenue d'une hyperglycémie et d'une pancréatite sévère, l'amylasémie, la lipasémie et/ou l'insulinémie doivent être surveillés. Une hyperglycémie peut être traitée par insuline si nécessaire. - Un bilan de la coagulation, incluant temps de prothrombine, temps de céphaline activé, taux de fibrinogène et d'antithrombine III (AT III), peut être effectué avant l'instauration du traitement et doit être réalisé à intervalles réguliers. En cas de survenue d'une coagulopathie symptomatique, le traitement par L-asparaginase doit être interrompu jusqu'à la disparition des troubles, puis réinstauré conformément au protocole. - La fonction rénale et l'uricémie doivent être surveillées. Il est fortement recommandé de manipuler la poudre ou la solution avec prudence, car Erwinase peut être sensibilisant (voir rubrique 6.6.).

#### **4.5. Interactions avec d'autres médicaments et autres formes d'interactions**

Aucune étude d'interaction n'a été réalisée. L'asparaginase ne doit pas être mélangée à tout autre médicament avant son administration. La possibilité d'interactions entre la crisantaspase et des médicaments dont la pharmacocinétique est affectée par des modifications de la fonction hépatique ou de la protéinémie doit être prise en compte. L'administration concomitante de crisantaspase et d'un médicament affectant la fonction hépatique peut accroître le risque de modification de paramètres hépatiques (par exemple augmentation du taux d'ASAT et d'ALAT et de la bilirubinémie). Un effet antagoniste ou synergique peut apparaître quelle que soit la dose si la crisantaspase est administrée immédiatement avant ou après le méthotrexate (un antimétabolite). La crisantaspase peut diminuer ou abolir l'effet du méthotrexate sur les cellules malignes, et ce tant que la concentration plasmatique de l'asparagine demeure faible. La crisantaspase agit également comme un « facteur de secours » si elle est administrée dans les 24 heures suivant l'administration d'une forte dose de méthotrexate. Le méthotrexate ne doit donc pas être administré avec la crisantaspase ou à la suite de celle-ci, tant que la concentration plasmatique d'asparagine n'est pas revenue à la normale. L'administration de crisantaspase en association à un traitement par prednisone ou immédiatement avant celui-ci, peut être associée à une augmentation de sa toxicité (possibles modifications des paramètres de la coagulation telle qu'une diminution du taux de fibrinogène et d'AT III). L'administration de crisantaspase en association à un traitement par vincristine ou immédiatement avant celui-ci, peut être associée à une augmentation de la toxicité et du risque de réaction anaphylactique. La crisantaspase peut influencer l'interprétation des tests de la fonction thyroïdienne en raison d'une diminution sévère du taux sérique de globuline liant la thyroxine (TBG) (voir également la rubrique 4.8.). L'administration d'allopurinol est indiquée en cas de néphropathie uratique, dans le but de réduire l'hyperuricémie. Un accroissement de l'hépatotoxicité a été rapporté lors de l'administration concomitante d'imatinib et de L-asparaginase. Son utilisation en association avec l'imatinib nécessite donc des précautions particulières.

#### **4.6. Grossesse et allaitement**

##### **Grossesse**

Il n'existe pas de données suffisantes sur l'utilisation de la crisantaspase chez la femme enceinte. Les publications limitées ayant trait à l'administration de L-asparaginase en association à d'autres agents antinéoplasiques chez des femmes enceintes ne fournissent pas de données suffisantes pour pouvoir parvenir à une conclusion quelconque. Des études menées chez l'animal ont montré des effets nocifs sur le développement embryofœtal (voir rubrique 5.3.). Erwinase ne doit pas être utilisé au cours de la grossesse sauf en cas d'absolue nécessité.

##### **Allaitement**

On ne sait pas si la crisantaspase est excrétée dans le lait humain. L'excrétion de la crisantaspase dans le lait n'a pas été étudiée chez l'animal. Un risque pour les nouveau-nés ou les nourrissons ne peut être exclu. Erwinase ne doit pas être utilisé durant l'allaitement.

## Fertilité

Aucune donnée sur l'effet de la crisantaspase sur la fertilité n'est disponible. Des données cliniques limitées indiquent que la L-asparaginase n'entraîne pas une infertilité.

## **4.7. Effets sur l'aptitude à conduire des véhicules et à utiliser des machines**

Aucune donnée n'est disponible. La possibilité d'un effet dépresseur sur le système nerveux central, de nausées et de vomissements doit être prise en compte en cas de conduite de véhicules et d'utilisation de machines.

## **4.8. Effets indésirables**

a) *Résumé du profil de tolérance* : Les effets indésirables les plus fréquents sont les suivants : - Hypersensibilité, y compris éruption urticarienne, fièvre, bronchospasme, arthralgie, œdème laryngé, hypotension, autre réaction allergique ou choc anaphylactique. En cas de réaction d'hypersensibilité systémique, le traitement doit être immédiatement et définitivement arrêté. Des anticorps neutralisants anti-L-asparaginase peuvent apparaître chez certains patients sans manifestation clinique d'hypersensibilité. Ces anticorps peuvent entraîner une inactivation et une élimination plus rapide de la L-asparaginase (« hypersensibilité silencieuse »), et certaines données indiquent que leur apparition peut être associée à une perte de l'efficacité antileucémique. Une mesure du taux d'asparaginase peut donc être justifiée. (Pour des informations relatives aux précautions d'emploi, voir rubrique 4.4.). Des anomalies de la coagulation dues à une altération de la synthèse des protéines sont les deuxièmes effets indésirables les plus fréquemment rapportés. Des troubles de la coagulation dus à la diminution du taux de certains facteurs de la coagulation et d'inhibiteurs de la coagulation (tels que l'antithrombine III et les protéines S et C), à une hypofibrinogénémie, à une prolongation du temps de prothrombine et du temps de céphaline activée et à une diminution du taux de plasminogène peuvent entraîner des complications thromboemboliques et hémorragiques. Des cas de thromboses de vaisseaux sanguins périphériques, pulmonaires ou du système nerveux central ont été rapportés, ayant engagé le pronostic vital ou ayant été associés à des effets résiduels retardés selon la localisation de l'occlusion. D'autres facteurs de risque contribuant à des anomalies de la coagulation sont la maladie elle-même, une corticothérapie concomitante et la présence d'un cathéter veineux central. (Pour des informations relatives aux précautions d'emploi, voir rubrique 4.4.). Les effets indésirables sont généralement transitoires.

b) *Tableau des effets indésirables* : Le tableau ci-dessous présente les effets indésirables notifiés spontanément et décrits dans la littérature survenus chez des patients traités par Erwinase dans le cadre d'un protocole de chimiothérapie. Les effets indésirables sont classés par classe de système d'organe et fréquence. Définitions de la fréquence : très fréquent ( $\geq 1/10$ ), fréquent ( $\geq 1/100$  à  $< 1/10$ ), peu fréquent ( $\geq 1/1\,000$  à  $< 1/100$ ), rare ( $\geq 1/10\,000$  à  $< 1/1\,000$ ), très rare ( $< 1/10\,000$ ) et fréquence indéterminée (ne peut être estimée sur la base des données disponibles).

### **Infections et infestations<sup>(5)</sup> :**

Rare : Sepsis ou choc septique (y compris engageant le pronostic vital), pneumopathie, hépatite adénovirale, candidose systémique, autres infections.

### **Affections hématologiques et du système lymphatique :**

Très fréquent : Coagulopathies<sup>(5)</sup> – anomalie du taux de facteurs de la coagulation, diminution du taux d'antithrombine III, de protéine C et de protéine S ou de la fibrinogénémie<sup>(1)</sup>.

Fréquent : Coagulopathies<sup>(5)</sup> associées à un saignement ou à des complications thrombotiques, état d'hypocoagulation, coagulopathie asymptomatique, neutropénie fébrile, leucopénie (y compris neutropénie).

Peu fréquent : Anémie, thrombocytopénie, pancytopenie.

Fréquence indéterminée : Anémie hémolytique, dépression médullaire.

### **Affections du système immunitaire :**

Fréquent : Hypersensibilité<sup>(5)</sup>.

Peu fréquent : Réaction anaphylactique<sup>(5)</sup>.

### **Troubles du métabolisme et de la nutrition :**

Fréquent : Augmentation de l'amylasémie ou de la lipasémie<sup>(5)</sup>.

<u>Peu fréquent :</u>	Hyperlipidémie <sup>(1)</sup> , hyperglycémie <sup>(5)</sup> .
<u>Rare :</u>	Acidocétose diabétique.
<u>Fréquence indéterminée :</u>	Hyperammoniémie <sup>(3)</sup> , hypothyroïdie secondaire, diminution du taux de globuline liant la thyroxine (TBG), anorexie.
<b>Affections psychiatriques :</b>	
<u>Fréquence indéterminée :</u>	Agitation, hallucinations.
<b>Affections du système nerveux :</b>	
<u>Fréquent :</u>	Léthargie, somnolence, état confusionnel, sensations vertigineuses, neurotoxicité *, crises comitiales de type grand mal <sup>(2)</sup> , crises comitiales partielles <sup>(2)</sup> , céphalées.
<u>Rare :</u>	Parésie, encéphalopathie <sup>(3)</sup> , altération de l'état de conscience, coma, dysphasie.
<b>Affections cardiaques :</b>	
<u>Rare :</u>	Infarctus du myocarde - secondaire à d'autres effets indésirables (par exemple, thrombose, pancréatite <sup>(5)</sup> ).
<b>Affections vasculaires :</b>	
<u>Fréquent :</u>	Thrombose pulmonaire, veineuse, périphérique ou cérébrale, pâleur.
<u>Fréquence indéterminée :</u>	Hémorragie, hypertension, bouffées vasomotrices <sup>(4)</sup> et hypotension <sup>(4)</sup> .
<b>Affections respiratoires, thoraciques et médiastinales :</b>	
<u>Fréquent :</u>	Dyspnée <sup>(4)</sup>
<u>Peu fréquent :</u>	Œdème laryngé <sup>(4)</sup> , arrêt respiratoire, hypoxie, rhinite, bronchospasme <sup>(4)</sup> .
<b>Affections gastro-intestinales :</b>	
<u>Fréquent :</u>	Diarrhée, pancréatite aiguë *(5), nausées, vomissements, douleurs abdominales.
<u>Rare :</u>	Pancréatite hémorragique ou nécrosante <sup>(5)</sup> .
<u>Très rare :</u>	Dysphagie.
<b>Affections hépatobiliaires(5) :</b>	
<u>Fréquent :</u>	Augmentations de la bilirubine, des transaminases et de la phosphatase alcaline, hépatotoxicité, hypercholestérolémie.
<u>Rare :</u>	Insuffisance hépatique.
<u>Fréquence indéterminée :</u>	Hépatomégalie, ictere cholestatique, hypoprotéinémie, hypoalbuminémie, augmentation de la rétention de la BSP, stéatose hépatique.
<b>Affections de la peau et du tissu sous-cutané :</b>	
<u>Fréquent :</u>	Éruption cutanée, urticaire, prurit, érythème, œdème facial, gonflement des lèvres <sup>(4)</sup> .
<u>Fréquence indéterminée :</u>	Nécrolyse épidermique toxique.
<b>Affections musculo-squelettiques et systémiques :</b>	
<u>Très rare :</u>	Myalgie, arthrite réactionnelle.
<u>Fréquence indéterminée :</u>	Douleurs dans les membres, arthralgies.
<b>Affections rénales et urinaires :</b>	
<u>Fréquence indéterminée :</u>	Protéinurie, insuffisance rénale aiguë, néphropathie uratique, altération de la fonction rénale, insuffisance rénale.
<b>Troubles généraux :</b>	
<u>Fréquent :</u>	Pyrexie, frissons, œdème périphérique, réaction au site d'injection (y compris douleurs, érythème, hématome, ou œdème), douleur.
<u>Fréquence indéterminée :</u>	Asthénie, malaise.

\* Voir rubrique c).

<sup>1</sup> À titre de conséquence de l'inhibition de la synthèse des protéines.

<sup>2</sup> Des convulsions peuvent être associées à des cas de thrombose ou d'encéphalopathie métabolique

<sup>3</sup> À titre de conséquence d'une production excessive d'ammoniaque induite par l'action de la L-asparaginase sur l'asparaginase et la glutamine endogènes.

<sup>4</sup> Ces symptômes sont fréquemment associés à des réactions d'hypersensibilité.

<sup>5</sup> Voir également rubrique 4.4.

*c) Description d'effets indésirables sélectionnés :* Troubles pancréatiques (voir également rubrique 4.4.) – une pancréatite aiguë est survenue dans moins de 10 % des cas, et des cas isolés de formation de pseudokystes jusqu'à quatre mois après le dernier traitement ont été décrits. Une pancréatite hémorragique ou nécrosante à issue fatale est survenue dans de très rares cas. La L-asparaginase peut affecter la fonction du pancréas endocrine. Une hyperglycémie (voir également rubrique 4.4.) est l'effet indésirable le plus souvent rapporté, et est facilement contrôlée au moyen d'agents hypoglycémiants, dont l'insuline. De rares cas d'acidocétose diabétique ont été rapportés. Des troubles du système nerveux ou cardiaques sont souvent secondaires à d'autres effets indésirables (par exemple thromboembolie) ou synergiques aux effets d'autres médicaments de chimiothérapie (par exemple élimination retardée du méthotrexate).

*d) Population pédiatrique :* La fréquence, le type et la sévérité des effets indésirables devraient être identiques chez l'enfant et chez l'adulte. *e) Autres populations particulières :* Aucune population particulière de patients dans laquelle le profil de tolérance aurait différé de celui décrit ci-dessus n'a été identifiée. *Déclaration des effets indésirables suspectés :* La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : Agence nationale de sécurité du médicament et des produits de santé (ANSM) et réseau des Centres Régionaux de Pharmacovigilance - Site internet: www.ansm.sante.fr.

#### 4.9. Surdosage

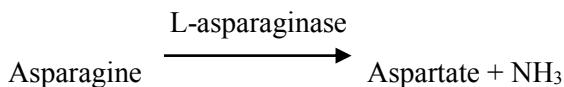
Un surdosage en L-asparaginase peut provoquer une intoxication chronique caractérisée par une altération de la fonction hépatique ou rénale, ainsi qu'une réaction allergique aiguë ou un choc anaphylactique. L'administration de L-asparaginase doit être arrêtée immédiatement, et un traitement symptomatique doit être administré sans délai.

### 5. PROPRIÉTÉS PHARMACOLOGIQUES

#### 5.1. Propriétés pharmacodynamiques

Classe pharmacothérapeutique : Autres agents antinéoplasiques. Code ATC : L01XX02.

La L-asparaginase catalyse la désamination de l'asparaginase exogène en acide aspartique et ammoniaque. La réaction biochimique peut être schématiquement décrite comme suit :



L'asparagine est incorporée dans la plupart des protéines, et la protéosynthèse s'arrête en son absence, ce qui inhibe la synthèse de l'ARN et de l'ADN et bloque ainsi la prolifération cellulaire.

L'activité antitumorale de la L-asparaginase est due à une déplétion persistante de l'asparagine exogène.

#### 5.2. Propriétés pharmacocinétiques

La demi-vie d'Erwinase après perfusion intraveineuse est de  $6,4 \pm 0,5$  heures. La demi-vie d'Erwinase après injection intramusculaire est d'environ 16 heures. La L-asparaginase passe dans le liquide céphalorachidien, et à un moindre degré dans la lymphe. Les concentrations sériques minimales de crisantaspase ont été déterminées

chez 48 patients atteints de leucémie aiguë lymphoblastique âgés de  $\geq 2$  ans à  $\leq 18$  ans inclus dans une étude clinique multicentrique menée en ouvert en un seul groupe évaluant la tolérance et la pharmacologie clinique (étude AALL07P2). Le critère principal d'évaluation était la proportion de patients présentant une concentration sérique minimale d'asparaginase supérieure ou égale à 0,1 UI/ml. Une activité sérique minimale de l'asparaginase  $\geq 0,1$  UI/ml a été corrélée à la déplétion en asparagine (asparagine  $< 0,4$  mcg/ml ou 3  $\mu$ M) et aux concentrations sériques prédictives de l'efficacité clinique. À la suite de l'administration d'une dose de 25 000 UI/m<sup>2</sup> pour le premier cycle de traitement, l'activité sérique de l'asparaginase a été maintenue au-dessus de 0,1 UI/ml 48 heures après la dose chez 92,5 % des patients, et au moins à 0,1 UI/ml après 72 heures chez 88,5 % des patients. Avec des administrations répétées, le médicament peut se lier à des anticorps spécifiques et être éliminé.

### **5.3. Données de sécurité préclinique**

Des études de toxicologie de la reproduction ont montré un transfert placentaire de la L-asparaginase chez le lapin. Des effets tératogènes ont été observés chez le lapin, le rat et la souris à des doses inférieures ou égales à celles cliniquement pertinentes. Des malformations des poumons, des reins et du squelette (spina bifida, extrusion abdominale, queue manquante) ont été observées chez le lapin. Le traitement de rates et de souris gestantes a produit une exencéphalie et des anomalies du squelette

## **6. DONNÉES PHARMACEUTIQUES**

### **6.1. Liste des excipients**

Glucose monohydraté  
Chlorure de sodium  
Hydroxyde de sodium  
Acide acétique

### **6.2. Incompatibilités**

En l'absence d'étude de compatibilité, ce médicament ne doit pas être mélangé avec d'autres médicaments. Voir la rubrique 4.5. Aucun diluant autre que ceux recommandés dans la rubrique 6.6. ne doit être utilisé.

### **6.3. Durée de conservation**

a) Durée de conservation du produit dans son emballage : 3 ans.

b) Durée de conservation à la suite de la reconstitution conformément aux instructions : 15 minutes dans le récipient d'origine, 4 heures dans une seringue stérile en verre ou en polypropylène (voir rubrique 6.6.), et à conserver à une température ne dépassant pas 25 °C.

### **6.4. Précautions particulières de conservation.**

À Conserver au réfrigérateur (entre +2 °C et +8 °C).

### **6.5. Nature et contenu de l'emballage extérieur**

Boîte contenant cinq flacons chacun avec une capacité nominale de 3 ml, en verre neutre transparent de type 1, fermé au moyen d'un bouchon de 13 mm en halobutyle pour lyophilisation et d'un sceau externe en aluminium. Chaque flacon contient une substance lyophilisée solide de couleur blanche.

### **6.6. Précautions particulières d'élimination et de manipulation**

Le contenu de chaque flacon doit être reconstitué au moyen de 1 à 2 ml de solution injectable de chlorure de sodium à 0,9 %. Ajouter lentement la solution à reconstituer en la faisant couler le long de la paroi interne du flacon afin qu'elle n'atteigne pas directement la poudre. Laisser le contenu se dissoudre en agitant ou en faisant tourner délicatement le flacon tout en le maintenant en position verticale. Ne pas agiter vigoureusement afin d'éviter la formation de mousse. La solution doit être limpide sans aucune particule visible. Des agrégats cristallins ou filiformes de protéines peuvent être visibles si le flacon a été trop agité. La solution reconstituée doit être jetée en cas de présence de particules visibles ou d'agrégats de protéines. La solution doit être administrée dans les 15 minutes suivant sa reconstitution. Si un délai de plus de 15 minutes entre la reconstitution et l'administration ne peut être évité, la solution doit être aspirée en utilisant une technique d'asepsie dans une seringue stérile en verre ou en polypropylène pendant la période précédant l'administration. La solution doit être administrée dans les quatre heures et conservée à une température ne dépassant pas 25° C. Erwinase n'est pas un médicament cytotoxique et ne nécessite pas les précautions particulières nécessaires pour la manipulation des agents de ce type. Le potentiel sensibilisant d'Erwinase doit cependant être pris en compte lors de sa préparation et de son administration. Toute inhalation de la poudre ou de la solution doit être évitée. En cas de contact du produit avec la peau ou des muqueuses, notamment en cas de contact avec les yeux, rincer abondamment la zone atteinte avec de l'eau pendant au moins 15 minutes. Tout médicament non utilisé ou déchet doit être éliminé conformément à la réglementation en vigueur.

## DONNÉES ADMINISTRATIVES

### **EXPLOITANT :**

JAZZ Pharmaceuticals France - 84 quai Charles de Gaulle - 69006 Lyon

### **NUMÉRO D'AUTORISATION DE MISE SUR LE MARCHÉ**

34009 550 041 6 5 : 10000 UI de poudre en flacon verre avec bouchon en halobutyle. Boite de 5.

### **DATE DE PREMIÈRE AUTORISATION :** Avril 2016.

### **CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE :**

Liste I. Médicament réservé à l'usage hospitalier. Prescription réservée aux spécialistes en hématologie ou aux médecins compétents en maladies du sang. Médicament nécessitant une surveillance particulière pendant le traitement.

### **DATE DE MISE À JOUR DU TEXTE :** Avril 2016.

Agréé aux Collectivités.

Non remboursé sec soc.

Pour une information complète, se référer au Résumé des Caractéristiques du Produit, sur : <http://base-donnees-publique.medicaments.gouv.fr>.

Pour toutes informations complémentaires, merci de contacter le service d'information médicale :  
+33 176 728 925 / [medinfo-fr@jazzpharma.com](mailto:medinfo-fr@jazzpharma.com) .

Pour toute question et/ou observation relative à la qualité de la visite médicale, merci de contacter :  
[qualityeurope@jazzpharma.com](mailto:qualityeurope@jazzpharma.com) / 04 37 49 85 85

## **Appendix 15: Severe Adverse Event Declaration**

**CAALL-F01 :**

Référence de la personne se prêtant à la recherche : |\_\_\_\_\_| - |\_\_\_\_\_| - |\_\_\_\_\_| - |\_\_\_\_\_|  
 n°centre - n° d'inclusion - initiale nom - initiale prénom

**PARTIE RESERVEE AU PROMOTEUR**  
**REFERENCE VIGILANCE :**

<input type="checkbox"/> intensification retardée 2 (si applicable)  _____   _____   _____   _____   _____	<input type="checkbox"/> Autre :  _____   _____   _____   _____   _____
Interruption prématuée du traitement de la recherche : <input type="checkbox"/> Non <input type="checkbox"/> Oui  _____   _____   _____   _____   _____	
Si oui, préciser la(les) raison(s) :	

<b>4. Médicament expérimental (Oncaspar®) avant la survenue de l'EIG (barrer l'encadré si traitement non débuté ou n'ayant pas lieu d'être administré) :</b>								
Nom commercial (de préférence) ou Dénomination Commune Internationale	Phase de traitement (induction, consolidation...)	Voie <sup>(1)</sup>	Posologie / jour	Date de début (jj/mm/aaaa)	En cours <sup>(2)</sup>	Date de fin (jj/mm/aaaa)	Date d'administration ( par exemple J1 à J28 ou J1, J7, J14...)	
Oncaspar®	.....	.....	.....UI	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
Oncaspar®	.....	.....	.....UI	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
Oncaspar®	.....	.....	.....UI	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
Oncaspar®	.....	.....	.....UI	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
Oncaspar®	.....	.....	.....UI	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
<b>4.1 Procédures de la recherche (chimiothérapie associée au médicament expérimental ex : nelarabine, aracytine, idarubicine..., corticoïdes) – Précisez le nom de la spécialité utilisée de préférence (ou la DCI à défaut)</b>								
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____		

Lien de Causalité entre le médicament administré et l'EIG (selon la méthode OMS) : (1=non lié), (2=relation certaine), (3=relation probable), (4=relation possible), (5=improbable)

**5. Médicament(s) concomitant(s) au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable (compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ➔ Annexe jointe au présent formulaire :  Oui  Non ou barrer l'encadré si non applicable) :**

Nom commercial (de préférence) ou Dénomination Commune Internationale y compris forme pharmaceutique et dosage	Indication	Voie <sup>(1)</sup>	Posologie / jour	Date de début (jj/mm/aaaa)	En cours <sup>(2)</sup>	Date de fin (jj/mm/aaaa)
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____
.....	.....	.....	.....	_____   _____   _____   _____   _____	<input type="checkbox"/>	_____   _____   _____   _____   _____

CAALL-F01 :

**PARTIE RESERVEE AU PROMOTEUR**  
**REFERENCE VIGILANCE :**

Référence de la personne se prêtant à la recherche :                  -                  -                  -                   
n°centre - n° d'inclusion - initiale nom - initiale prénom

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

## **6. Evènement indésirable grave [EIG]**

<input type="checkbox"/> Non : <input type="radio"/> à la progression de la maladie faisant l'objet de la recherche : Leucémie aiguë lymphoïde <input type="radio"/> à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : ..... <input type="radio"/> à une maladie intercurrente, laquelle : ..... <input type="radio"/> autre, préciser (ex : complications liées au cathéter veineux central) : .....		
Notificateur	Investigateur	Tampon du service :
Nom et fonction :	Nom :	
Signature :	Signature :	

*DIRECTION DE L'ORGANISATION  
MÉDICALE ET DES RELATIONS  
AVEC LES  
UNIVERSITÉS (DOMU)*

**ASSISTANCE  
PUBLIQUE**  **HÔPITAUX  
DE PARIS**

**Liste relative aux médicaments concomitants  
utilisés dans le cadre d'une recherche biomédicale : Annexe au formulaire de notification  
d'un Evènement Indésirable Grave (EIG)**

**PARTIE RESERVÉE AU PROMOTEUR  
REFERENCE VIGILANCE :**

**Dès la prise de connaissance de l'EIG par l'investigateur, ce document doit être dûment complété, signé et retourné sans délai au pôle Vigilance du DRCD-Siège par télecopie au +33 (0)1 44 84 17 99 avec le formulaire de notification d'EIG complété**

## Notification initiale

**Suivi d'EIG**  **N° du suivi** | | |

<b>Acronyme :</b> CAALL-F01	<b>Investigateur (nom/prénom) :</b>					
Référence de la personne se prêtant à la recherche :     _____  -  _____  -  __  -  __	..... .....					
n° centre	-	n° d'inclusion	-	initialle nom	-	initialle prénom
<b>Service :</b>				<b>Tél. :</b>		<b>Fax :</b>
.....				.....		.....

**REPORTER TOUS LES MEDICAMENTS CONCOMITANTS AU MOMENT DE L'EIG, A L'EXCLUSION DE CEUX UTILISES POUR TRAITER L'EVENEMENT INDESSIRABLE :**

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIGG

Notificateur	Investigateur	Tampon du service :
Nom et fonction :	Nom :	
Signature :	Signature :	

## **Appendix 16: Declaration of pregnancy**

<p>DIRECTION DE L'ORGANISATION MÉDICALE ET DES RELATIONS AVEC LES UNIVERSITÉS (DOMU)</p> <p>DÉPARTEMENT DE LA RECHERCHE CLINIQUE ET DU DÉVELOPPEMENT (DRCD)</p>	<p>ASSISTANCE PUBLIQUE</p>  <p>HÔPITAUX DE PARIS</p>	<p>Formulaire</p> <p>Suivi d'une grossesse apparue au cours d'une recherche biomédicale</p> <p>Version n°1</p>
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**Ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au pôle Vigilance du DRCD-Siège par télécopie au +33 (0)1 44 84 17 99**

**DRRC 20** \_\_\_\_\_  
(N° unique interne au DRCD)

<b>1. Identification de la recherche</b>		<b>Notification initiale</b> <input type="checkbox"/>	<b>Suivi de notification</b> <input type="checkbox"/> N° du suivi  _____   _____   _____   2 0 _____  jj mm aaaa
Acronyme : CAALL-F01 Code de la Recherche : P091205		Date de notification :	_____   _____   2 0 _____  jj mm aaaa
		Date de prise de connaissance de la grossesse par l'investigateur :	_____   _____   2 0 _____  jj mm aaaa
<b>Titre complet de la Recherche Biomédicale : «Protocole français pour le traitement de la leucémie aiguë lymphoblastique (LAL) chez les enfants et les adolescents»</b>			
<b>2. Identification du centre Investigateur</b>			
Nom de l'établissement : .....		Investigateur (nom/prénom) : .....	
Ville et code postal : .....		Tél : .....	
Service : .....		Fax : .....	
<b>3. Identification de la personne présentant une grossesse</b>			
Référence de la personne :  _____  -  _____  -  _____  -  _____  n°centre - n° ordre de sélection - initiale - initiale nom - prénom		<b>Cas particulier d'une exposition paternelle</b> : <input type="checkbox"/> Non <input type="checkbox"/> Oui	
Date de naissance :  _____   _____   2 0 _____		Référence de la personne :  _____  -  _____  -  _____  -  _____  n° centre - n° d'inclusion - initiale - initiale nom - prénom	
Date de signature du consentement :  _____   _____   2 0 _____		Date de naissance :  _____   _____   2 0 _____	
Date d'inclusion :  _____   _____   2 0 _____		Date de signature du consentement :  _____   _____   2 0 _____	
Date de randomisation (si applicable) :  _____   _____   2 0 _____		Date d'inclusion :  _____   _____   2 0 _____	
Date des dernières règles :  _____   _____   2 0 _____		Date de randomisation (si applicable) :  _____   _____   2 0 _____	
Et/ou date début de grossesse :  _____   _____   2 0 _____			
<b>Expositions</b> : Préciser si exposition au tabac (paquets/année), à l'alcool (unités OH), à des drogues et autres expositions. Préciser si l'exposition est antérieure à la grossesse, poursuivie ou arrêtée (mentionner la date d'arrêt le cas échéant).			
<b>4. Antécédents maternels</b>			
Médicaux :		Chirurgicaux :	
<b>Obstétricaux</b> :  _____  geste  _____  pare Préciser si fausse couche spontanée, grossesse extra-utérine, interruption de grossesse, mort <i>in utero</i> , malformation néonatale, pathologie néonatale non malformatrice ... (nombre, date et nature/raison si applicable).			
<b>5. Médicament expérimental administré pendant la grossesse ou s'il s'agit une exposition paternelle</b> ( <i>barrer la mention inutile</i> )			

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non Administré	Date de dernière administration Ou en cours	Voie d'administration <sup>(1)</sup>	Posologie / 24h
Oncaspar®	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> Non administré	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> En cours		
Oncaspar®	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> Non administré	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

<b>6. Procédures et actes ajoutés par la recherche (Barrez l'encadré si procédures et actes non réalisés) – Chimothérapie associée, corticothérapie</b>				
Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non Administré	Date de dernière administration Ou en cours	Voie d'administration <sup>(1)</sup>	Posologie / 24h
	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> Non administré	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> En cours		
	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> Non administré	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> En cours		
	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> Non administré	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> En cours		
	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> Non administré	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> En cours		
	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> Non administré	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

**7. Médicament(s) concomitants administré(s) dans le cadre du soin**

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration <sup>(1)</sup>	Posologie / 24h
	_ _ _ _ _  _2_ _0_ _ _	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> En cours		
	_ _ _ _ _  _2_ _0_ _ _	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> En cours		
	_ _ _ _ _  _2_ _0_ _ _	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> En cours		
	_ _ _ _ _  _2_ _0_ _ _	_ _ _ _ _  _2_ _0_ _ _  <input type="checkbox"/> En cours		

**8. Suivi de la grossesse** Echographiques. Date(s) et résultats à préciser : Autres examens. Date(s) et résultats à préciser (joindre les CR) :

<b>9. Grossesse en cours</b> <input type="checkbox"/> (faxer un nouveau formulaire complété à l'issue de la grossesse) <b>ou Issue de la grossesse</b> <input type="checkbox"/> (compléter ci-dessous)	
<input type="checkbox"/> Fausse couche spontanée → Examen anatomo-pathologique disponible : <input type="checkbox"/> Non <input type="checkbox"/> Oui, précisez le résultat :	Date :  _ _ _ _ _  _2_ _0_ _ _  Terme :  _ _  SA  _ _ _J
<input type="checkbox"/> Grossesse extra-utérine	Date :  _ _ _ _ _  _2_ _0_ _ _  Terme :  _ _  SA  _ _ _J
<input type="checkbox"/> Interruption de grossesse → Raison : → Examen anatomo-pathologique disponible : <input type="checkbox"/> Non <input type="checkbox"/> Oui, précisez le résultat :	Date :  _ _ _ _ _  _2_ _0_ _ _  Terme :  _ _  SA  _ _ _J
<input type="checkbox"/> Accouchement <input type="checkbox"/> Spontané <input type="checkbox"/> Provoqué <input type="checkbox"/> Voie basse <input type="checkbox"/> Césarienne	Date :  _ _ _ _ _  _2_ _0_ _ _  Terme :  _ _  SA  _ _ _J

Naissance multiple :	<input type="checkbox"/> Non	<input type="checkbox"/> Oui, précisez le nombre :		
Souffrance fœtale :	<input type="checkbox"/> Non	<input type="checkbox"/> Oui, précisez :		
Placenta normal :	<input type="checkbox"/> Oui	<input type="checkbox"/> Non, précisez :		
Liquide amniotique :	<input type="checkbox"/> clair	<input type="checkbox"/> autre, précisez :		
Anesthésie :	<input type="checkbox"/> Générale	<input type="checkbox"/> Péridurale	<input type="checkbox"/> Rachianesthésie	<input type="checkbox"/> Aucune

**10. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et le faxer)**

Sexe : <input type="checkbox"/> Masculin	<input type="checkbox"/> Féminin	
Poids :  _____  g	Taille :  _____  cm	Périmètre crânien :  _____  cm
APGAR : 1 minute : _____	5 minutes : _____	10 minutes : _____
Malformation(s) néonatale(s) : <input type="checkbox"/> Non		
Pathologie néonatale non malformatrice : <input type="checkbox"/> Non		
Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : <input type="checkbox"/> Non		
<b>Notificateur</b>		
Nom et fonction :	<b>Investigateur</b>	Tampon du service :
Signature :	Signature :	

## **Appendix 17: Declaration of secondary malignancies**

<i>DIRECTION DE L'ORGANISATION MÉDICALE ET DES RELATIONS AVEC LES UNIVERSITÉS (DOMU)</i>	<b>ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS</b>	Formulaire
<i>DÉPARTEMENT DE LA RECHERCHE CLINIQUE ET DU DÉVELOPPEMENT (DRCD)</i>	<b>Formulaire de notification des cancers secondaires/myélodysplasies</b>	Version n°1

**Ce formulaire doit être dûment complété, signé et retourné au pôle Vigilance du DRCD-Siège par télécopie au +33 (0)1 44 84 17 99**

**DRRC 20** \_ \_ -  
(Numéro unique interne au DRCD)

<b>1. Identification de la recherche</b>		Date de notification : <u>                        </u> jj mm aaaa
Acronyme : CAALL-F01		
Code de la Recherche : P091205		Date de prise de connaissance de l'EIG par l'investigateur : <u>                     </u> jj mm aaaa
Titre complet de la Recherche Biomédicale : «Protocole français pour le traitement de la leucémie aiguë lymphoblastique (LAL) chez les enfants et les adolescents»	Risque : <input type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C <input checked="" type="checkbox"/> D	
	Plan expérimental : <input type="checkbox"/> LAL de type B et T HR/ VHR / Trisomie21: <input checked="" type="checkbox"/> Essai non comparatif <input type="checkbox"/> LAL de type BSR/ MR et T-SR: <input checked="" type="checkbox"/> Ouvert <input type="checkbox"/> Essai comparatif <input type="checkbox"/> Randomisé	
<b>2. Identification du centre Investigateur</b>		
Nom de l'établissement : .....	Investigateur (nom/prénom) : .....	
Ville et code postal : .....	Tél : ..... Fax : .....	
Service : .....		
<b>3. Identification et antécédents de la personne se prêtant à la recherche</b>		
Référence de la personne : <u>         </u> - <u>            </u> - <u>      </u> - <u>      </u> n°centre - n° ordre de sélection - initiale - initiale nom prénom		Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
Sexe : <input type="checkbox"/> M <input type="checkbox"/> F	Date de naissance : <u>                     </u> jj mm aaaa	
Poids : <u>            </u> kg	Age : <u>            </u> ans	
Taille : <u>            </u> cm		
Date de signature du consentement : <u>                     </u> jj mm aaaa		
Date d'inclusion : <u>                     </u>		
Date de randomisation : <u>                     </u> (si applicable) jj mm aaaa		
Strat : <input type="checkbox"/> LAL B-SR <input type="checkbox"/> LAL B-MR <input type="checkbox"/> LAL T-SR		Start : <input type="checkbox"/> LAL B- HR <input type="checkbox"/> LAL B- VHR <input type="checkbox"/> LAL de type B et Trisomie21
Bras :	<input type="checkbox"/> 1250 IU/m2 par jour d'Oncaspar® <input type="checkbox"/> 2500 IU/m2 par jour d'Oncaspar®	
	<input type="checkbox"/> LAL T -HR <input type="checkbox"/> LAL T-VHR <input type="checkbox"/> LAL de typeT et Trisomie21	

#### **4.1 Diagnostic clinique :**

Date du diagnostic :  __ _ _  __ _ _  _2_ _0_ __ _	Diagnostic final retenu : .....
Confirmation histologique : <input type="checkbox"/> Non <input type="checkbox"/> Oui	
Confirmation cytologique : <input type="checkbox"/> Non <input type="checkbox"/> Oui	

<b>4.2 Grade :</b> (précisez l'échelle de classification ex : TNM)	<input type="checkbox"/> Grade 0 <input type="checkbox"/> Grade I <input type="checkbox"/> Grade II <input type="checkbox"/> Grade III <input type="checkbox"/> Grade IV .....				
<b>4.3 Grade histologique :</b>	<input type="checkbox"/> Grade 0 <input type="checkbox"/> Grade I <input type="checkbox"/> Grade II <input type="checkbox"/> Grade III <input type="checkbox"/> Grade IV				
<b>4.4 Si autre classification, précisez :</b>					
<b>4.5 Antécédents médicaux pertinents :</b> <input type="checkbox"/> Non <input type="checkbox"/> Oui, précisez					

<b>5. Précision de l'imputabilité de l'investigateur</b>					
<b>5.1 Lien de causalité entre l'EIG (cancer secondaire/myélodysplasie) et la recherche (selon la méthode OMS)</b>					
<b>L'EIG semble plutôt :</b>	<input type="checkbox"/> lié au(x) médicament(s) expérimental (aux) [ME] (précisez) : Oncaspar®	<input type="checkbox"/> Relation certaine		<input type="checkbox"/> Relation probable	
		<input type="checkbox"/> Relation possible		<input type="checkbox"/> Relation improbable (non exclu)	
	<input type="checkbox"/> lié à une/des procédure(s) de la recherche :	<input type="checkbox"/> Chimiothérapie(s) associée(s), renseigner le <b>tableau 6.1</b>			
		<input type="checkbox"/> Traitement de conditionnement de la greffe <i>Relation :</i> <input type="checkbox"/> <i>certaine</i> <input type="checkbox"/> <i>probable</i> <input type="checkbox"/> <i>possible</i> <input type="checkbox"/> <i>improbable</i>			
		<input type="checkbox"/> Autre, précisez : <i>Relation :</i> <input type="checkbox"/> <i>certaine</i> <input type="checkbox"/> <i>probable</i> <input type="checkbox"/> <i>possible</i> <input type="checkbox"/> <i>improbable</i>			
	<input type="checkbox"/> non lié à la recherche	<input type="checkbox"/> Maladie intercurrente			
		<input type="checkbox"/> Progression de la maladie			
<input type="checkbox"/> Autre, précisez :					

<b>5.2 La survenue de cet EIG est-elle susceptible d'être liée à une pathologie sous-jacente ?</b>					
<input type="checkbox"/> Non <input type="checkbox"/> Oui, précisez :					
<b>5.3 La survenue de cet EIG est-elle susceptible d'être liée à un manque d'efficacité du ME ?</b>					<input type="checkbox"/> Non <input type="checkbox"/> Oui
.....					
<b>6. Détails de la chimiothérapie administrée pour traiter la pathologie initiale (phase)</b>					
<input type="checkbox"/> Induction  __ __   __ __   _2_ _0_ __ __			<input type="checkbox"/> Consolidation n° __ :  __ __   __ __   _2_ _0_ __ __		
<input type="checkbox"/> Post greffe : renseigner la partie 6.2			<input type="checkbox"/> Maintenance  __ __   __ __   _2_ _0_ __ __		
<input type="checkbox"/> Autre :  __ __   __ __   _2_ _0_ __ __			<input type="checkbox"/> Interphase  __ __   __ __   _2_ _0_ __ __		
<b>6.1 Médicament(s) ou produit(s) assimilé(s) de chimiothérapie anticancéreuse ou de thérapie ciblée administrés avant la survenue du cancer secondaire/de la myélodysplasie (barrez l'encadré si aucun traitement débuté) :</b>					

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie <sup>(*)</sup>	Posologie / jour	Date de début (jj/mm/aaaa)	En cours (**)	Date de fin (jj/mm/aaaa)	Lien de causalité avec l'EIG (1, 2, 3, 4, 5)
Oncaspar®	.....	.....	_____2_0_____	<input type="checkbox"/>		Cf. 5.1
	.....	.....	_____2_0_____	<input type="checkbox"/>		Cf. 5.1
<b>Chimiothérapies anticancéreuses associées au(x) médicament(s) expérimental(aux) (ex : aracytine, idarubicine, kidrolase..., corticoïdes...) ou autres thérapies cibles administrées avant la date de survenue du cancer secondaire/myélodysplasie</b>						
	.....	.....	_____2_0_____	<input type="checkbox"/>		
	.....	.....	_____2_0_____	<input type="checkbox"/>		
	.....	.....	_____2_0_____	<input type="checkbox"/>		
	.....	.....	_____2_0_____	<input type="checkbox"/>		
	.....	.....	_____2_0_____	<input type="checkbox"/>		
	.....	.....	_____2_0_____	<input type="checkbox"/>		
	.....	.....	_____2_0_____	<input type="checkbox"/>		
	.....	.....	_____2_0_____	<input type="checkbox"/>		
	.....	.....	_____2_0_____	<input type="checkbox"/>		
	.....	.....	_____2_0_____	<input type="checkbox"/>		
	.....	.....	_____2_0_____	<input type="checkbox"/>		
<b>Lien de Causalité entre le médicament administré et l'EIG (selon la méthode OMS) : (1=non lié), (2=relation certaine), (3=relation probable), (4=relation possible), (5=improbable)</b>						
(*) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)						
(**) En cours au moment de la survenue du cancer secondaire/de la myélodysplasie						
<b>6.2 Greffe de cellules souches hématopoïétiques (CSH) pour le traitement de la pathologie initiale :</b>						
<input type="checkbox"/> Non <input type="checkbox"/> Oui, précisez ci-dessous :						
Date de la greffe : le  __   __   __   __   2 0 _ _				Si allogreffe : Donneur : <input type="checkbox"/> apparenté <input type="checkbox"/> fichier volontaires / banque		
Origine CSH : <input type="checkbox"/> CSP <input type="checkbox"/> Moelle osseuse <input type="checkbox"/> Sang de cordon						
Date de sortie d'aplasie :  __   __   __   __   2 0 _ _						
<b>6.3 Traitements de conditionnement de la greffe (immunosuppresseurs, irradiation corporelle, etc.) :</b>						
<input type="checkbox"/> Non applicable <input type="checkbox"/> Applicable, précisez ci-dessous le schéma thérapeutique :						
Nom commercial ou Dénomination Commune Internationale	Date de première administration		Date de dernière administration		Voie d'administration <sup>(1)</sup>	Posologie / 24h
	__   __   __   __   2 0 _ _		__   __   __   __   2 0 _ _			
	__   __   __   __   2 0 _ _		__   __   __   __   2 0 _ _			
	__   __   __   __   2 0 _ _		__   __   __   __   2 0 _ _			
	__   __   __   __   2 0 _ _		__   __   __   __   2 0 _ _			
<b>7. Statut de la pathologie initiale (LAL) à la date de survenue du cancer secondaire/de la myélodysplasie (joindre si possible les résultats du dernier myélogramme le cas échéant) :</b>						
<input type="checkbox"/> Rémission complète le  __   __   __   __   2 0 _ _						
<input type="checkbox"/> Stable depuis le  __   __   __   __   2 0 _ _						
<input type="checkbox"/> Maladie en progression						
<input type="checkbox"/> Rechute le  __   __   __   __   2 0 _ _						
<b>8. Traitement du cancer secondaire/de la myélodysplasie</b>						
<b>8.1 Hospitalisation(s) :</b>						
Hospitalisation (1) du  __   __   __   __   2 0 _ _  au  __   __   __   2 0 _ _						
Hospitalisation (2) du  __   __   __   __   2 0 _ _  au  __   __   __   2 0 _ _						
Hospitalisation (3) du  __   __   __   __   2 0 _ _  au  __   __   __   2 0 _ _						
<b>8.2 Intervention chirurgicale :</b> <input type="checkbox"/> Non <input type="checkbox"/> Oui, précisez ci-dessous :						
Type d'intervention chirurgicale :	Date de l'intervention chirurgicale :  __   __   __   __   2 0 _ _					
<b>8.3 Chimiothérapie :</b> <input type="checkbox"/> Non <input type="checkbox"/> Oui, précisez ci-dessous :						
Précisez le schéma thérapeutique, date(s) de début, les posologies et dates de fin si applicable :						

<b>8.4 Radiothérapie :</b> <input type="checkbox"/> Non <input type="checkbox"/> Oui, précisez ci-dessous :		
Précisez le schéma thérapeutique et les doses :	Date de début :  _ _ _ _ _2_ _0_ _ _	Date de fin :  _ _ _ _ _2_ _0_ _ _
<b>8.5 Traitement(s) adjuvant(s) :</b> <input type="checkbox"/> Non <input type="checkbox"/> Oui, précisez ci-dessous :		
<b>8.6 Une greffe de CSH a été réalisée pour le traitement du cancer secondaire/de la myélodysplasie :</b> <input type="checkbox"/> Non <input type="checkbox"/> Oui, précisez ci-dessous :		
Date de la greffe : le  _ _ _ _ _2_ _0_ _ _  <input type="checkbox"/> autogreffe <input type="checkbox"/> allogreffe	Si allogreffe : Donneur : <input type="checkbox"/> apparenté <input type="checkbox"/> fichier volontaires / banque	
Origine CSH : <input type="checkbox"/> CSP <input type="checkbox"/> Moelle osseuse <input type="checkbox"/> Sang de cordon		
Date de sortie d'aplasie :  _ _ _ _ _2_ _0_ _ _		
<b>9. Evolution du cancer secondaire/de la myélodysplasie</b>		
<b>9.1 Etat actuel (hors décès)</b>		
<input type="checkbox"/> Rémission complète le  _ _ _ _ _2_ _0_ _ _  <input type="checkbox"/> Rémission avec séquelles le  _ _ _ _ _2_ _0_ _ _ , précisez les séquelles : <input type="checkbox"/> Rémission partielle (si applicable) le  _ _ _ _ _2_ _0_ _ _ , précisez : <input type="checkbox"/> Stable <input type="checkbox"/> Maladie en progression <input type="checkbox"/> Rechute		
<b>9.2 Evolution fatale</b>		
Date du décès :  _ _ _ _ _2_ _0_ _ _		
Autopsie effectuée : <input type="checkbox"/> Non <input type="checkbox"/> Oui (joindre le compte-rendu)		
Veuillez spécifier la « cause du décès » rapportée dans le certificat de décès / le rapport d'autopsie :		
<b>Notificateur</b> Nom et fonction : Signature :	<b>Investigateur</b> Nom : Signature :	Tampon du service :

**Appendix 18: Coordonnées des centres MRD**

MRD CENTERS	CLINICAL CENTERS	LOCAL REFERENT BIOLOGIST			PHYSICIANS		OTHER LOCAL CONTACTS		(responsible for sample and information sending)
<p><b>Pr Hélène CAVE</b> sec : 01.40.03.57.11 UF de Génétique Moléculaire 48 bd Séurier Bâtiment Ecran + 2 75935 PARIS Cedex 19 secretariat.genetique-moleculaire@aphp.fr</p>	Besançon	Dr Francine GARNACHE OTTOU	Immunologie	francine.garnache@efs.sante.fr	Dr Pauline SIMON Dr Nathalie CHEIKH Dr Sébastien KLEIN	p_simon@chu-besancon.fr ncheikh@chu-besancon.fr s_klein@chu-besancon.fr	Stéphanie CLERC GUAY Marie Agnès COLLONGE-RAME	ARC Cytogénétique	sclercguay@chu-besancon.fr macollongerame@chu-besancon.fr
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	Dijon	Pr Patrick CALLIER	Cytogénétique	patrick.callier@chu-dijon.fr	Dr Elodie BOTTOILLER COLOMB Dr Claire BRIANDET	elodie.bottoiller-lemaillaz@chu-dijon.fr claire.briandet@chu-dijon.fr	Frédérique DEBOMY	ARC	Frederique.debomy@chu-dijon.fr
	Grenoble	Dr Christine LEFEBVRE	Cytogénétique	clefebvre@chu-grenoble.fr	Pr Dominique PLANTAZ Dr Corinne ARMARI-ALLA Dr Dalila ADJAOUD Dr Cécile PERRET Dr Anne PAGNIER	dplantaz@chu-grenoble.fr carmarilla@chu-grenoble.fr dadjaoud@chu-grenoble.fr cperret@chu-grenoble.fr apagnier@chu-grenoble.fr	Sandrine BILLET Martine CHAUVENT	ARC Attachée scientifique	SBillet@chu-grenoble.fr MChauvet@chu-grenoble.fr
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	Nice	Dr Michel TICCHIONI Dr Alessandra Maria ROSENTHAL	Immunologie Immunologie	michel.ticchioni@unice.fr roenthal.m@chu-nice.fr	Pr Pierre Simon ROHRICH Dr Maryline POIREE Dr Anne DEVILLE Dr Joy BENADIBA Dr Marion LEMEIGNEN DIOP Dr Karima SOLER	rohrich.p@chu-nice.fr poiree.m@chu-nice.fr deville.ad@pediatric-chulerval-nice.fr benadiba.j@chu-nice.fr lemeignen-dop.m@chu-nice.fr soler.c@chu-nice.fr	Isabelle CHAMPOENOIS Chokri HATHROUBI	ARC REFERENT ARC BACK-UP	champenois.i@chu-nice.fr hathroubi.c@chu-nice.fr
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	Strasbourg	Dr Anne SCHNEIDER	Biologie moléculaire	anne.schneider@chru-strasbourg.fr	Pr Patrick LUTZ Pr Catherine PAILLARD Dr Alexandra SPIEGEL	patrick.lutz@chru-strasbourg.fr catherine.pallard@chru-strasbourg.fr alexandra.spiegel@chru-strasbourg.fr	Françoise UETWILLER	ARC	Francoise.Uettwiller@chru-strasbourg.fr
<p><b>Pr Eric DELABESSE</b> sec : 05 61 77 76 67 LD : 05.61.77.76.67 ED : 05 61 77 76 94 Hôpital PURPAN Pavillon Lefebvre TSA 40031 31059 TOULOUSE Cedex 10 delabesse.e@chu-toulouse.fr</p>	Toulouse	Pr Eric DELABESSE	Biologie moléculaire	delabesse.eric@iuct-oncopole.fr	Dr Geneviève PLAT Dr Marline PASQUET Dr Marion GAMBART Dr Anne Isabelle BERTOZZI Dr Marie Pierre CASTEX Dr Cécile BOULANGER	plat.g@chu-toulouse.fr pasquet.m@chu-toulouse.fr gambart.m@chu-toulouse.fr bertozzi.ai@chu-toulouse.fr castex.mp@chu-toulouse.fr boulanger.c@chu-toulouse.fr	Nathalie COUTEAU	ARC	couteau.n@chu-toulouse.fr
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MRD CENTERS	CLINICAL CENTERS	LOCAL REFERENT BIOLOGIST			PHYSICIANS		OTHER LOCAL CONTACTS			(responsible for sample and information sending)
<b>Dr Nathalie GRARDEL</b>  03.20.44.48.08 CHRU de Lille Centre de Biologie Pathologique Laboratoire d'Hématologie Secteur Analyses Spécialisées Biologie moléculaire Niveau 1 Rue du Pr. Jules Leclercq 59037 Lille Cedex  <a href="mailto:Nathalie.GRARDEL@chu-lille.fr">Nathalie.GRARDEL@chu-lille.fr</a>	Lyon	Dr Adriana PLESA Dr Sandrine GIRARD	Immunologie Hématologie	adriana.plesa@chu-lyon.fr sandrine.girard@chu-lyon.fr	Pr Yves BERTRAND Dr Nathalie GARNIER Dr Cécile RENARD Dr HALLON-DOMENECH Carine	Yves.BERTRAND@i.hope.fr Nathalie.GARNIER@i.hope.fr cecile.renard@i.hope.fr <b>DE RETOUR EN SEPTEMBRE 2016</b>	Caroline PETIT	ARC	caroline.petit@lyon.unicancer.fr	
	Lille	Dr Nathalie GRARDEL	Biologie moléculaire	nathalie.grardel@chu-lille.fr	Dr Françoise MAZINGUE Dr Brigitte NELKEN Dr Wadil ABOU CHAHLA Dr Anne LAMBILOTE Dr Eva DEBERANGER Dr Bénédicte BRUNO	francoise.mazingue@chu-lille.fr brigitte.nelken@chu-lille.fr wadil.abouchahla@chu-lille.fr anne.lambilote@chu-lille.fr eva.deberanger@chu-lille.fr benedicte.bruno@chu-lille.fr	Cécile VERON Aurélie TESSIER Céline RODRIGUEZ (assistante N. GRARDEL)	ARC REFERENT ARC BACK-UP Ingénieur hospitalier	cecile.veron@chu-lille.fr aurelie.fernandez@chu-lille.fr celine.rodriguez@chu-lille.fr	
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	Rouen	Dr Pascaline ETANCELIN	Biologie moléculaire	<a href="mailto:pascaline.etancelin@chb.unicancer.fr">pascaline.etancelin@chb.unicancer.fr</a>	Pr Jean Pierre VANNIER Dr Aude MARIE-CARDINE Dr Bruno FILHON Dr Cécile DUMESNIL Pr Pascale SCHNEIDER	jean-pierre.vannier@chu-rouen.fr aude.marie-cardine@chu-rouen.fr bruno.filhon@chu-rouen.fr cecile.dumesnil@chu-rouen.fr pascale.schneider@chu-rouen.fr	Solenn LE GALIC-CATHERINE	ARC	<a href="mailto:Solenn.Le-Galic@chu-rouen.fr">Solenn.Le-Galic@chu-rouen.fr</a>	
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