Group for Research on Adult Acute Lymphoblastic Leukemia

Multicenter trial for the treatment of
Acute Lymphoblastic Leukemia (ALL) in younger adults (18-59 years)

GRAALL-2014 TRIAL

Comprising 3 sub-studies according to lineage (2 sub-substudies)

GRAALL-2014/B & QUEST substudy	Ph-negative B-lineage ALL
GRAALL-2014/T & ATRIALL substudy	T-ALL
GRAAPH-2014	Ph+ ALL

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Version N° V 5.1 09 April 2018

Research will be conducted according to the protocol, ongoing good medical practice and legislative and regulatory recommendations.

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This research received a favourable advice from the CPP Ile de France IV (Saint Louis) dated 10 mar 2015 and ANSM authorization dated 26 jan 2015 .

PROTOCOL SIGN-OFF PAGE PROTOCOL RELEASE 5.1 FOR THE PRINCIPAL INVESTIGATOR

GRAALL-2014 TRIAL - MULTICENTER TRIAL FOR THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN YOUNGER ADULTS (18-59 YEARS), COMPRISING 3 SUB-STUDIES ACCORDING TO LINEAGE

Principal Investigator in: _____

Having read and understood protocol release 5.1, I agree to conduct the trial as specified in the protocol.

Name: _____ Title: _____

Date: _____ Signature: _____

Abbreviations

6-MP: 6-Mercaptopurin
ALAT: Alanine-Aminotransferase
ALL: Acute Lymphoblastic Leukemia
ANSM: "Agence Nationale de sécurité du médicament et des produits de santé"
ASAT: Aspartate Amino Transferase
AT: Anti Thrombin
ATG: Anti ThymoGlobulin
BID: Twice a day
BM: Bone Marrow
BMI: Body Mass Index
CIR: Cumulative Incidence of Relapse
CIV: ContinuousIntravenous
CML: ChronicMyelogenous Leukemia
CNS: Central Nervous System
CPM: Cyclophosphamide
CPP:"Comité de Protection des Personnes"
CR: Complete Remission
CRA: Clinical Research Assistant
CRF: Case Report Form
CSF: Cerebro Spinal Fluid
DFS: Disease free survival
DIVC: Disseminated Intravascular Coagulation
DMA: Drug Marketing Authorization
DNR: Daunorubicin
DVI: Dexamethasone, Vincristine, ITK
ECG: Electrocardiogram
ECOG: Eastern Cooperative Oncology Group (= PS)
FFD: Form of Functions Delegation
FFP: Fresh Frozen Plasma
FGM: France Greffe de Moelle
FR: Shortening Fraction
GCP: Good Clinical Practice
G-CSF: Granulocyte colony-stimulating factor
GNB: Gram Negative Bacteria
GPB: Gram Positive Bacteria
GVH: Graft *versus* Host
HCR: Hematologic Complete Remission
HD: High Dose
HLA: Human Leukocyte Antigen
HR: High Risk
HSC: Hematopoietic Stem Cells
HSCT: Haematopoietic Stem Cell Transplantation
ISC: Independent Surveillance Committee
IT: Intra-thecal
IUD: Intrauterine Device
IV: Intravenous
IVD: Intravenous Direct
LR: Low Risk
LWH: Low Weight Heparin
MAC: Myelo Ablative Conditioning
MMolR: Major Molecular Response
MRD: Minimal Residual Disease
MRI: Magnetic Resonance Imaging
MTX: Methotrexate
NRM: Non Relapse related Mortality
NYHA: "New York Heart Association"
OS: Overall survival
PB: Peripheral BloodPHRC: "Programme Hospitalier de Recherche Clinique"
ANC: Polymorphonuclears
PO: Per Os
PS: Performans Status (= ECOG)
RBC: Red Blood Cells
RFS: Relapse-Free Survival
RTC: Reduced Toxicity Conditioning
SAE: Serious Adverse Event
SC: SubCutaneous
SGOT: Serum Glutamic OxaloaceticTransferase
SGPT: Serum GlutamopyruvateTransferase
SIV: Slow Intravenous
SPC: Summary of Product Characteristics
SR: Standard Risk
TBI: Total Body Irradiation
TD: Total Dose
TDM: Tomodensitometry
TKI: Tyrosine Kinase Inhibitor
TLP: Traumatic Lumbar Puncture
TUA: Temporary Usage Authorization
ULN: Upper Limit of Normal
VCR: Vincristine
VDS: Vindesine
VEF: Ventricular Ejection Fraction
VHR: Very High Risk
VP-16: Etoposide
WBC: White Blood Cells

SUMMARY

PART I

INTRODUCTION AND GENERAL CONSIDERATIONS

1 SCIENTIFIC JUSTIFICATION OF THE RESEARCH

1.1 Research hypotheses, description of knowledge regarding the pathology considered and summary of pre-clinical experiments and relevant clinical trials

Since 2003, the GRAALL (intergroup gathering 77 hematology centers in France, Belgium and Switzerland) has conducted several studies with the aim to improve treatment results for *de novo* Acute Lymphoblastic Leukemia (ALL) in younger adults aged 15 to 59 years old included.

GRAALL-2003 and GRAAPH-2003 (funded by the French National Cancer Institute PHRC program, ID 0200701, sponsor "Hôpitaux de Toulouse") were phase 2 trials which enrolled 225 and 45 patients respectively[1,2,3].These trials were followed bythe GRAALL-2005 phase 3 study (funded by the French National Cancer Institute PHRC program, ID P040429, sponsor "Hôpital Saint-Louis, Assistance Publique - Hôpitaux de Paris")divided in three randomized sub-studies: 1) GRAALL-2005 for T-ALL and Philadelphia-chromosome (Ph) negative CD20-negative B—ALL (810 patients included), 2) GRAALL-2005/R for Ph-negative CD20-positive B-ALL (220 patients expected) and 3) GRAAPH-2005 for Ph+ ALL (270 patients included). Altogether these 3 sub-studies randomized 1080 patients. GRAALL-2005 yielded the following results (most yet unpublished):

1) marked improvement of the survival in younger adults with Ph-negative ALL with a pediatric-inspired protocol confirming the results of GRAALL-2003 in spite of significant toxicity in patients aged 45 years or above.The general schemes of GRAALL-2003 and GRAALL-2005 are indicated in Figure 1.
2) definition of a new prognostic score, based on the quantitation of minimal residual disease (MRD)by Ig/TCR amplification after the first induction cure (MRD1) and on anomalies of the *NOTCH1*/*FBXW7*, *RAS* and *PTEN* genes for T-lineage or *MLL* and *IKZF1* genes for B-lineage Ph-. In summary:
    a. *MLL* gene rearrangements (including *MLL-AF4* fusion) and *IKZF1* gene deletions are independent bad-prognosis factors in B-ALLPh-,
    b. NOTCH pathway mutations (including *NOTCH1* and *FBXW7* gene mutations) are independent good-prognosis factors in T-ALL,[4] but only in the absence of *N/K -RAS* gene mutation and/or *PTEN* gene deletion, leading to a 4-gene genetic classifier in T-ALL[5],
    c. Poor post-induction Ig-TCR MRD level (MRD1 $\geq 10^{-4}$) is an independent bad-prognosis factor in both lineages.
3) it is possibleto decrease the intensity of chemotherapy in Ph+ ALL patients by combining a first generation tyrosine kinase inhibitor (TKI)and standard chemotherapy
4) the results of two randomizations, namely the interest of a fractionated sequence of cyclophosphamide bolus (Hyper-C) during induction and late intensification, and the interest of adding rituximab for the treatment of CD20+/Ph-negative BB-ALL patients, are still pending.

In spite of these progresses, allowing for a long-term disease free survival increase of 25% to 50% by comparison to historical studies, high risk patients (high risk according to the new score or suffering from Ph+ ALL, which remains of high risk in spite of the introduction of TKI) still present high relapse rates around 30% -35%, justifying for them the introduction of new drugs and/or allogeneic stem cell transplantation (SCT) in first complete remission. Conversely, standard risk patients according to the new score have a favorable evolution, similar to that of large pediatric series rebutting the introduction of potentially toxic drugs for these patients.

[1]Huguet *et al*, J Clin Oncol, 2009; 27:911-918

[2]de Labarthe *et al*, Blood, 2007; 109:1408-1413

[3]Tanguy-Schmidt *et al*, Blood, 2010; 110: abstr. 3080

[4]Asnafi *et al*, Blood, 2009;113:3918-24

[5]Trinquant *et al*, J Clin Oncol, 2013, 31(34): 4333-4342

Figure 1. GRAALL-2003/2005 protocol scheme (Ph-negative ALL)

1.1.1 Results of GRAALL studies in T-ALL and Ph- B-ALL

1.1.1.1 A new prognostic stratification

Like the German GMALL, the Italian NILG and the British-American UKALL/ECOG groups,[6,7,8,9] the GRAALL observed the impact of MRD as a major prognostic factor in adults.[10] Although this criterion was not retained in risk stratification in GRAALL-2005, MRD has been prospectively evaluated in 443 of the 880 CR patients from the GRAALL-2003 and GRAALL-2005 trials (B-ALL Ph- and T-ALL). Through this evaluation, the GRAALL contributed to the STIC ("SoutienTechnologique aux Innovations Coûteuses 2006") program financed by INCa, allowing the evaluation of MRD detection by immunophenotyping versus Ig-TCR molecular analysis.[11]

In the same time, a concomitant genomic evaluation has been done retrospectively in these patients and prognostic genetic subsets were identified.[12] For B-lineage ALL, alterations of the *MLL* gene most frequently represented by t(4;11) (*MLL-AF4* fusion) and *IKZF1* gene (coding for the transcription factor Ikaros) deletions were associated with poor prognosis.[13] In T-lineage ALL, the GRAAL has demonstrated that NOTCH1 pathway gene alterations (*NOTCH1* and *FBXW7* gene mutations) are associated with a good prognosis.[13] This observation has recently been refined in another publication of the GRAALL, showing that this is true only in the absence of

[6]Brüggemann *et al*, Blood, 2006;107:1116-23

[7]Gökbuget *et al*, Blood, 2012; 120:1868-76

[8]Bassan*et al*, Blood, 2009; 113: 4153-62

[9] Patel *et al*, Br J Haematol, 2009; 148: 80-9

[10]Beldjord *et al*, Blood,ASH Meeting 2006 (abstract 577)

[11]Garand *et al*, Leukemia, 2013; Feb;27(2):370-6

[12]Mullighan *et al*, N Engl J Med, 2009; 360:470-80

[13]Beldjord *et al*, Blood, ASH Meeting 2011 (abstract 572)

mutation of *RAS* genes or *PTEN* gene deletion, leading to use a 4-gene oncogenetic classifier (*NOTCH1, FBXW7, RAS* and *PTEN*) in T-lineage ALL.[14]

In multivariate analysis, these oncogenetic alterations and the level of post-induction MRD (MRD1 6 weeks after treatment initiation) are now the only independent risk criteria predictive of relapse.[15] On the basis of these two new factors (MRD1 and oncogenetics), we have identified new subgroups of patients of standard risk (SR) and high risk (HR).

Tables 1A and 1B indicate the results observed in SR and HR groups in T and Ph-negative-B-lineage separately, censored or not at transplantation (unpublished data). Relapse-free survival (RFS) is indicated in Figures 2A and 2B, illustrating the ability of this new risk system to identify two groups of patients with a very different outcome in both lineages. **These observations clearly show that the risk of relapse of new HR patients is high enough to justify the introduction for them of new strategies, even if they are likely to be associated to some tolerable toxicities.**Conversely, the new SR patients have a nearly pediatric outcome which does not support taking such risks.

Table 1A –New HR *versus* SR patients (with SCT censoring).

Ph-negative ALL	5-year CIR	5-year RFS
SR BCP-ALL	16.2%	79.7%
HR* BCP-ALL	50.7%	39.8%
SR T-ALL	15.3%	84.7%
HR** T-ALL	56.4%	43.6%

Tableau 1B –New HR *versus* SR patients (without SCT censoring).

Ph-negative ALL	5-year CIR	5-year RFS
SR BCP-ALL	14.6%	76.0%
HR* BCP-ALL	42.6%	42.1%
SR T-ALL	13.2%	85.1%
HR** T-ALL	46.7%	48.0%

* 60.9% of BCP-ALL cases, defined as$MRD1 \geq 10^{-4}$, and/or*MLL*gene rearrangement, and/or *IKZF1* gene deletion (excluding haplo-insufficiency)

** 60.5% of T-ALL cases, defined as$MRD1 \geq 10^{-4}$ and/or no NOTCH pathway mutation *(NOTCH1-wt* and *FBXW7*–wt genes), and/or *N/K-RAS* genes mutation, and/or *PTEN* gene deletion.

Figure 2A -RFS according to new risk subsets SR/HR (BCP-ALL Ph-negative patients, with SCT censoring).

[14] Trinquant *et al*, J Clin Oncol, 2013, in press

[15]Beldjord *et al*, Manuscript in preparation

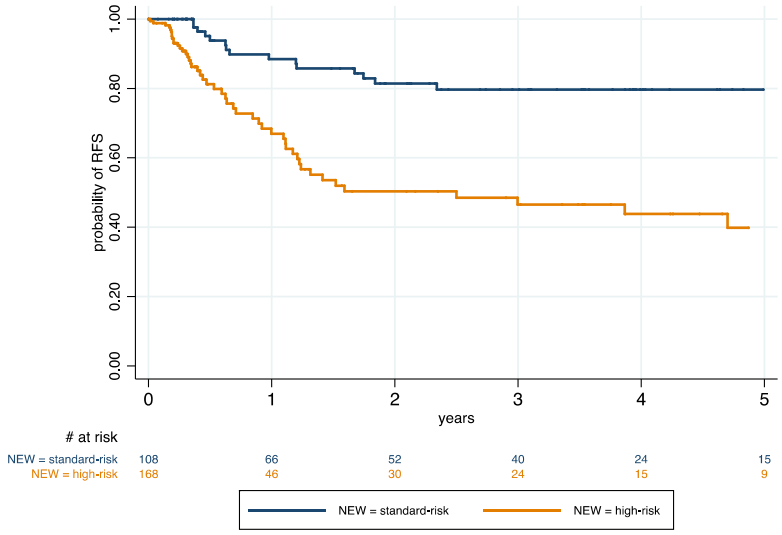
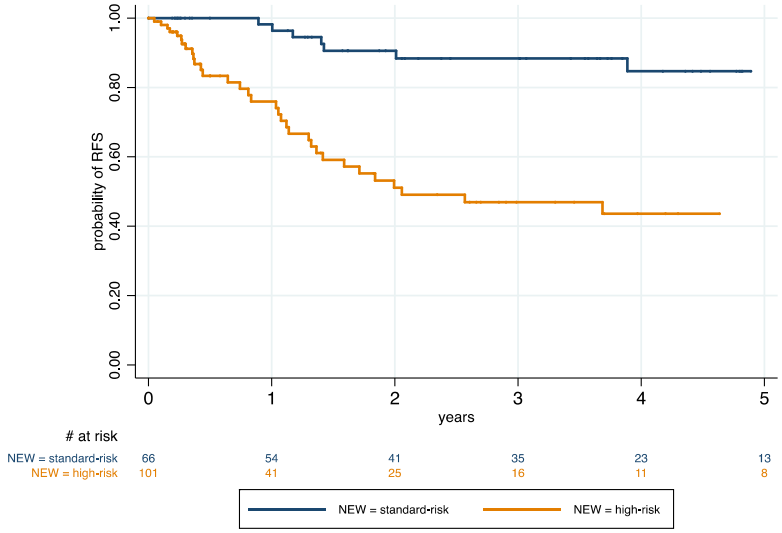


Figure 2B -RFS according to new risk subsets SR/HR (T-ALL patients, with SCT censoring).



When this new risk classification is compared to the former one, which was used in the GRAALL-2003/2005 trials mostly based on historical risk factors (white blood cell count, central nervous system involvement, standard cytogenetics with t(4;11) and t(1;19) translocations, blood sensitivity to steroids at day 1, bone marrow chemosensitivity at day 8, 2 cures for CR) this new classification system: 1) is more simple; 2) integrates MRD to appreciate early response; 3) does not exactly overlap the previous one, meaning that some SR patients become HR patients and conversely (cf. Tables 2A et 2B) ; and 4) is more discriminative as predictive power of relapse (concordance Harrell's *c*-index, 0.671 *versus* 0.581; P=0.003). We need, however, to revalidate this new system prospectively in the GRAALL-2014 trial by including it as one of the major objectives of this study.

Table2A – Ph- B-ALL patient distribution according to the old and new risk subsets (p<0.001)

OLD	NEW standard-risk	high-risk	Total
standard-risk	**47**	**31**	**78**
high-risk	**61**	**137**	**198**
Total	**108**	**168**	**276**

Fisher's exact = **0.000**

Table2B - T-ALL patient distribution according to the old and new risk subsets (p<0.001)

OLD	NEW standard-risk	high-risk	Total
standard-risk	**41**	**27**	**68**
high-risk	**25**	**74**	**99**
Total	**66**	**101**	**167**

Fisher's exact = **0.000**

1.1.1.2 Limits of pediatric-inspired strategies

The GRAALL-2003 study was the first GRAALL study conducted by the GRAALL intergroup. It was developed because of the superiority of a pediatric*versus* adult protocol in adolescentsup to 18-20 years old, (FRALLE-93 vs. LALA-94)[16,17].On the basis of this demonstration for younger adults, we proposed to treat patients up to 60 years of age with a pediatric-inspired chemotherapy, including a steroid pre-phase, an induction favoring non-myelotoxic drugs such as L-asparaginase, a consolidation with several chemotherapy blocks and a late intensification[1]. The good results obtained were confirmed by later studies on smaller patients cohorts[18,19,20].

They were also confirmed by the intermediate analysis of GRAALL-2005, where the patients' outcome is superimposable to that of GRAALL-2003, demonstrating the improvement of progression-free survival and overall survival compared to previous adult trials. In the GRAALL-2003 and GRAALL-2005, age stands as a risk factor. Figure 3 shows that patients between 45 and 59 years old have a lower survival than 18 to 44 years old patients.

This is in fact only due to treatment-related toxicity, with an increased mortality at induction (12,5% *versus* 3,5%) and mortality in CR unrelated to relapse (19% *versus* 8% at 5 years) higher in patients 45 old or higher. Relapse rates (around 30%) do not increase with age in this cohort of 18 - 59 years old patients.

The difference between both trials lays principally in the two questions raised in GRAALL-2005. The first one addressed the best way for endoxan administration at induction (single conventional dose or high

[16]Boissel*et al*, J Clin Oncol, 2003; 21(5):774-80

[17]Huguet*et al*, Education Session, 2009; ASCO Annual Meeting

[18]Rijneveld*et al*, Leukemia, 2011; 25:1697-703

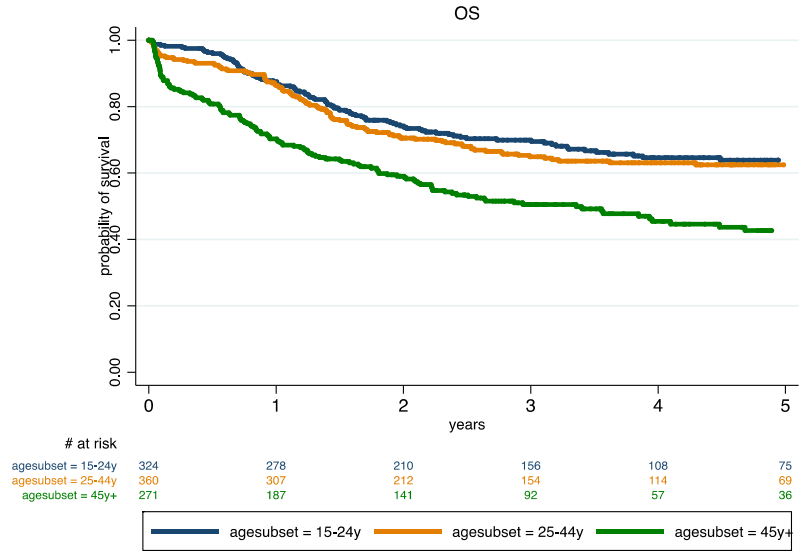
[19] Ruiz Delgado *et al*, LeukLymphoma, 2011; 52:314-6

[20]Haïat*et al*, LeukRes, 2011; 35:66-72

dosebolus twice daily). The second question addressed the addition of rituximab to chemotherapy in CD20+ B-ALL, since CD20 expression had been reported to be of poor prognosis[21].

The current version of the trial is based on this « standard arm ».

Figure 3. OS by age (GRAALL-2003/2005 trials, Ph-negative ALL patients)



1.1.1.3 The allogeneic SCT issue

1.1.1.3.1 Indications

Indications and modalities of allo-SCT in GRAALL-2014 derive from the results observed in GRAALL-2003 and 2005 trials, especially the comparison of transplanted versus non transplanted patients in the various risk groups (manuscript in preparation). In these trials, allo-SCT was indicated for patients less than 56 years old, in CR1, with one poor prognosis factor defined according to historical risk factors as mentioned above and having a familial HLA genoidentical or unrelated HLA 10/10 phenoidentical donor (9/10 related donors were accepted in a risk subgroup).The design of GRAALL-2003 and 2005 thus only allows to evaluate the benefit of allo-SCT in patients previously categorized as high risk and not for the whole cohort. Among the 522 patients with such an indication of allo-SCT, 283 actually were transplanted. Graft vs no graft was compared considering allo-SCT as a time-dependent variable (Mantel-Byar test).

In this population of 522 patients, the RFS of transplanted patients is not better than that of untransplanted patients (p=0.13). This means that the definition of high risk patients according to GRAALL-2003 and2005,did not allow to define the subgroup of patients benefiting from allo-SCT. We thus compared the outcome of transplanted and untransplanted patients according to the newly defined risk groups (SR and HR in Tables 1A and 1B). This analysis was performed for the 317 patients eligible for allo-SCT in CR1 and annotated for MRD1 and oncogenetic features. In the SR population, the outcome of transplanted and untransplanted patients is similar. In the HR population, the RFS of transplanted patients shows a trend towards better outcome (p=0.08; interaction test: p=0.22). The advantage of allo-SCT becomes significant when MRD1 is considered as the only risk factor (Figure 2): the DFS of transplanted patients with MRD1 ≥

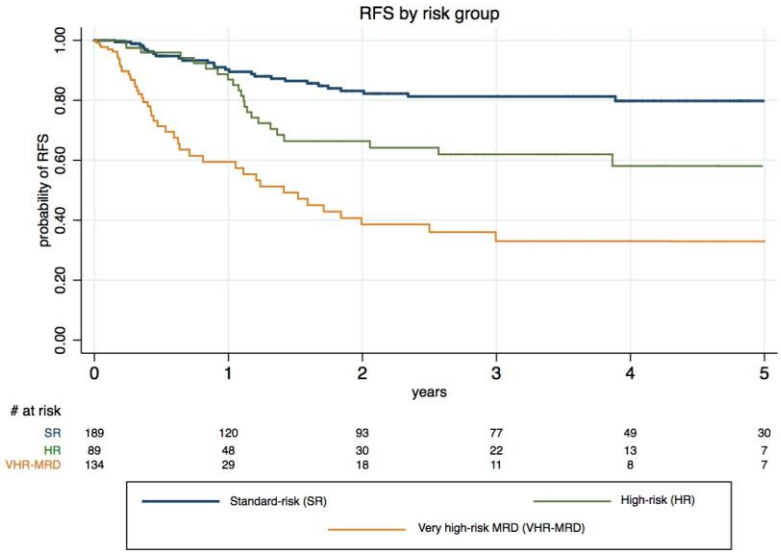
[21] Maury *et al*, Haematologica, 2010; 95:324-8

10^{-4} is better than that of untransplanted patients (p=0.024;interaction test: p=0.04), while allo-SCT provides no advantage to patients with MRD1 $<10^{-4}$.Similar results are obtained considering MRD2 (appreciated after the first 3 consolidation blocks): in the population of patients with MRD2 $\geq 10^{-4}$ (46/166), DFS is significantly better for allo-SCT patients (interaction test: p=0.026).

Thus, the value of MRD1 or MRD2 could allow to better discriminate patients liable to benefit from allo-SCT in CR1. The German group GMALL[7] has also reported that allo-SCT benefited to patients with postinduction MRD $\geq 10^{-4}$.For these reasons, allo-SCT indications in GRAALL-2014 will only depend on the MRD level. We therefore defined a very high risk MRD (VHR-MRD) grouptaking into account MRD1 and MRD2 evaluations. VHR-MRD patients are defined as having MRD1 $\geq 10^{-3}$ (including CR obtained in 2 cures) and/orMRD2 $\geq 10^{-4}$. Figure 4 shows the evolution of RFS comparing SR, HR (without VHR-MRD) and VHR-MRD patients.

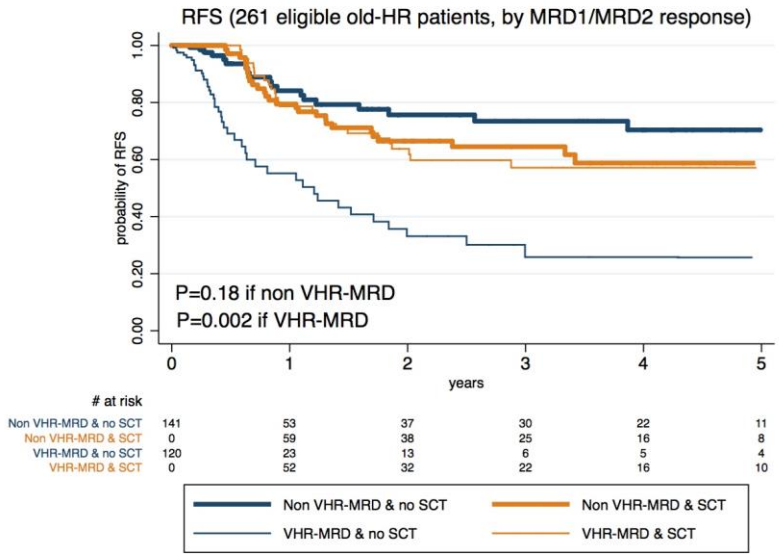
Only VHR-MRD patients (about one third of all patients) will be eligible for allo-SCT in the GRAALL-2014 trial.

Figure 4.RFSaccording to the three SR, HR and VHR-MRD subgroups (with SCT censoring).



According to this definition of VHR-MRD patients, only based on MRD1/MRD2 response levels, Figure 5 shows that VHR-MRD patients significantly benefited from SCT in first CR (p=0.002), while no benefit in RFS was associated with SCT in other patients (p=0.18). The interaction test was strongly positive (p<0.001). This was observed similarly in both B and T-ALL patients (not shown). It is the same when considering new HR patients only (not shown).

Figure 5.RFS according to VHR-MRD status and SCT in GRAALL-2003/2005 patients eligible for SCT in first CR (Mantel-Byar).



1.1.1.3.2 Conditioning in GRAALL-2014

In the GRAALL-2003 and 2005 trials, the SCT conditioning regimen associated total body irradiation (TBI fractionated 12 Gy dose or single 10 Gy dose) and cyclophosphamide (120 mg/kg). This myeloablative conditioning was given until 56 years of age. In the population of allografted patients (median age, 31 years), post-SCT non-relapse-related mortality (NRM) was significantly higher in patients over 45 years old (27% *versus* 14% at 3 years; p=0.012) while age had no impact on the rate of post-allo-SCT relapse (18% at 3 years). For this reason, in the GRAALL-2014 trial, conditioning will be of reduced toxicity in patients aged between 45 and 59 years old. As TBI-including conditioning regimens remain the standard in ALL,[22,23,24,25] younger patients below 45 years of age will still receive TBI (12Gy fractionated dose) and cyclophosphamide (120 mg/kg). Patients 45 years old or older will receive reduced toxicity conditioning (RTC) associating TBI fractionated at 8 Gy and fludarabine (120 mg/m^2), according to the regimen published by Bornhäuser.[26] In this study including AML patients who received allo-SCT, RIC was associated with a lower NRM when compared to a standard TBI 12Gy and cyclophosphamide, without increasing relapse incidence.[23]

1.1.2 Results in Ph+ ALL patients (GRAAPH studies)

1.1.2.1 A major impact of TKIs

The GRAAPH-2003 trial was one of the trials that showed that combining a first-generation tyrosine kinase inhibitor (TKI), imatinib, to standard chemotherapy allowed to clearly improve the outcome of patients with Ph+ ALL[27]. Not only did 96% of the patients reach complete hematological CR, but 56% of them showed a

[22]Bunin*et al*, Bone MarrowTransplant 2003; 32(6):543-8

[23]Ringdén *et al*, Blood, 1994; 83(9):2723-30

[24]Davies *et al*, J Clin Oncol, 2000; 18(2):340-7

[25]Marks*et al*, Blood, 2010; 116(3):366-74

[26]Börnhauser*et al*, Lancet Oncol 2012.

[27]de Labarthe *et al*, Blood, 2007; 109:1408-1413

decrease of BCR-ABL/ABL transcript with a ratio <0,1%. Similar results have been reported by other groups[28,29,30].When compared to pre-imatinib era, the gain in outcome was impressive and still present at long-term.[31] CR rates increased from approximately 60-80% to 80-95%, MRD response ratefrom 30% to 70%, and 3-year OS from approximately 15-40% to 45-75%. Moreover, usage of TKI before allo-SCT improves prognosis with a decrease of relapse incidence after allo-SCT[32].

1.1.2.2 Decreasing conventional chemotherapy intensity

In the subsequent GRAAPH-2005 trial, we addressed the issue of decreasing the intensity of standard chemotherapy in this new imatinib context. Between 2006 and 2011, 268 Ph+ ALL adults aged 18 to 60 years old with Ph+ ALL were randomized to receive a mild chemotherapy imatinib-based induction *versus* an intensive HyperC-VAD/imatinib induction.[33]The aim was to reduce treatment-associated toxicity prior to allogeneic or autologous SCT in these patients, who are usually older than other ALL adult patients (median age, 47 years in this GRAAPH-2005 study). Actually, front-line treatment with imatinib or second-generation TKI dasatinib combined to mild chemotherapy has been reported as highly effective and potentially less toxic. Our group investigated combinations of ITK with vincristine (VCR) and dexamethasone (DEX) with interesting phase 2 results.[34,35]In theGRAAPH-2005 study, the intensive HyperC-VAD/imatinib regimen was prospectively compared to a less intensive DEX-VCR-imatinib regimen. Final results have been recently reported,[36] showing that:

1) a less intensive induction yielded a higher CR rate (98.5% *versus* 92%, p=0.006), due to less induction deaths (1% *versus* 7%, p=0.01);
2) similar *BCR-ABL* MRD response rates (*BCR-ABL*/*ABL* ratio less than 0.1%) were observed in both arms after induction (43% *versus* 45%) or consolidation (66% *versus* 64%);
3) unfortunately, this lower toxicity did not translate into a better outcome. OS, estimated at 52% at 3 years, only confirmed the results of previous phase 2 studies. Notably, non relapse-related mortality after allo-SCT was not different between the light and more intensive arms (29% versus 21% at 3 years, p=0.46) ;
4) finally, good MRD responders in terms of *BCR-ABL*/*ABL* ratio who, in the absence of allogeneic donor received autologous SCT displayed quite a good outcome (66% OS at 3 years).

With respect to the high NRM rate post allo-SCT, another important question can be raised: what is the place of allo-SCT in the TKI era? For instance, pediatric trials do not systematically retain allo-SCT in CR1[37].In adults, even if patient outcome has improved since the introduction of TKI, no plateau suggesting potential cure is observed.[38]For these reasons, we preferred to leave investigators choose in the GRAAPH-2014 trial: patients who have achieved a good MRD response (*BCR-ABL*/*ABL* ratio less than 0.1%), will be proposed allo-SCT or auto-SCT, depending notably on the patient's age, general status and on the origin of identified allogeneic stem cell sources. We have also decided to prolong from 2 cycles to 4 cycles the pre-transplant

[28]Towatari*et al*, Blood, 2004; 104:3507-12

[29] Lee *et al*, Leukemia, 2005; 19:1509-16

[30]Wassmann*et al*, Blood, 2006; 108:1469-77

[31] Tanguy-Schmidt *et al*, BBMT 2013; 19:150-5

[32] Lee *et al*,Blood, 2005; 105(10):3951-5

[33]Thomas *et al*, Blood, 2008; 112: abstr. 2931

[34]Rea *et al*, Leukemia, 2006; 20:400-03

[35]Rousselot *et al*, Blood, 2008; 112: abstr. 2290

[36]Chalandon et al, ASH Meeting 2012 (abstract), manuscript in preparation

[37]Schultz, J Clin Oncol, 2009; 27:5175-80

[38]Ottmann *et al*, Cancer, 2007; 109:2068-76

chemotherapy/TKI period, in order to attempt reaching a higher molecular response rate prior to transplantation. Indeed, obtention of pre-transplant negative MRD allows to predict better post transplantation OS[39]. These 4 cycles will include 2 DEX-VCR-TKI cycles (cycles 1 and 3), while omission of high-dose cytarabine will be evaluated during cycles 2 and 4, which also comprise high-dose methotrexate, pursuing the same idea of a decrease of chemotherapy intensity.

Finally, the GRAAPH-20014 trial will use second-generation TKI, nilotinib, rather than imatinib. Nilotinib (Tasigna®) has demonstrated higher efficacy than imatinib with more rapid and more pronounced responses in patients treated for chronic myelogenous leukemia (CML) or Ph+ ALL.[40,41]As data on nilotinib/chemotherapy combination are relatively spare,[42] we will carefully monitor MRD levels after the first two cycles as compared to historical GRAAPH-2003 results with imatinib. Imatinib will still be used after autologous or allogeneic SCT, for a 24-month maintenance treatment.

1.1.2.3 Allo-SCT in GRAAPH-2014

In the GRAAPH-2005 trial, the SCT conditioning regimen associated TBI (12Gy fractionated) to cyclophosphamide (120 mg/kg). In the population of patients allografted with such a myeloablative conditioning (median age, 40 years), the post-SCT NRM was high but similar (without significant difference) in patients aged 45 years or more and in younger patients (25% *versus* 21%). The relapse rate post allo-SCT was 20% at 3 years without any impact of age. Because of concerns about the risk of increasing relapse incidence with RTC-SCT in Ph+ ALL patients, we will restrict RTC-SCT to patients aged 55 years old or more in the GRAALL-2014 trial, associating TBI fractionated at 8 Gy and fludarabine 120 mg/m² according to Bornhäuser[26]. Younger patients aged 18 to 54 years old will still receive a myeloablativeTBI-Cy regimen.

2 GRAALL-2014 TRIAL: PRINCIPLES AND OBJECTIVES

GRAALL-2014 follows the GRAALL-2003 and 2005 trials.

The GRAALL-2014 trial is subdivided in three sub-studies: GRAALL-2014/B, GRAALL-2014/T and GRAAPH-2014respectively for patients with B-lineage Ph-negative ALL, T-lineage ALL or Ph+ ALL.

France, Switzerland and Belgium will participate to GRAALL-2014.

2.1 GRAALL-2014/B, GRAALL-2014/T, and SUBSTUDIES GRAALL-QUEST & ATRIALL

The general objective of GRAALL-2014 is to improve the results of our pediatric-inspired approach. For this purpose, we will consider the characteristics of ALL (using the new risk classification system) as well as age-related toxicities in order to improve tolerance.

2.1.1 Stratification of disease-related risk

Based on the results of childhood ALL treatment, standard-risk ALL patients according to the new risk classification will receive the standard GRAALL-2014 chemotherapy (including age-related dose modifications) in order to validate our new risk system. The objective is to demonstrate in this risk group that patients can receive chemotherapy only, with an appreciation of DFS high enough in first CR to avoid allo-SCT.

[39]Dombret *et al*,Blood, 2002; 100(7):2357-66

[40]Saglio *et al*, N Engl J Med, 2010; 362:2251

[41]Kantarjian *et al*, N Engl J Med, 2006; 354:2542

[42]Kim *et al*, Blood, 2011; 118:1517

Conversely, all patients with high-risk ALL according to the new risk classification will be eligible for treatment arms testing the addition of new drugs to the standard chemotherapy protocol. We aim here to improve EFS or DFS by adding new drugs in the frame of nested Phase 2 studies (randomized or not).

The phase 2 study designed to test nelarabine in T-ALL patients (ATRIALL substudy), was included in the project submitted for this PHRC.This phase 2 will open during the trial.

A phase 2 study was designed as an amendment of the initial protocol to test blinatumomab in Philadelphia-negative BCP-ALL patients (GRAALL-QUEST substudy). This phase 2 will open during the trial.

All patients with VHR-MRD ALL will be offered allo-SCT in first CR if an available sibling or 10/10 matched MUD donor is identified.

2.1.2 Stratification of patient-related risk

A better tolerance of the trial must be obtained in patients aged ≥ 45 years old. Indeed, toxic deaths essentially of infectious origin currently reach 12% in this age range. Shorter exposure to steroids as well as lower doses of L-asparaginase and anthracycline will be proposed. In younger patients, modifications of the GRAALL-2003 and 2005 schemes will mainly address non myelotoxic drugs: higher doses of methotrexate will be used as in pediatric studies in order to prevent systemic and CNS relapses[43,44]. In consequence, prophylactic CNS irradiation will be abandoned and replaced by a higher total number of prophylactic intrathecal (IT) infusions: from 7 in the GRAALL-2005 (1 simple + 6 triple) to 14 in the GRAALL-2014 (1 simple + 13 triple).

It is also planned to prospectively monitor the appearance of anti-asparaginase antibodies at the end of induction. Indeed, our group has shown that such antibodies develop in more than 50% of the patients, associated with lower asparagine depletion and potential loss of drug efficacy during late intensification.[45]The use of other forms of asparaginase will be proposed to allergic patients, in case of antibodies or poor activity of d'*Escherichia coli* asparaginase.

2.1.3 CNS disease and prophylaxis

CNS relapses occur in less than 5% of the patients. In pediatric reports not including prophylactic CNS irradiation, this incidence is 2.6 to 2.7%.[46,47] In adults, chemotherapy with high dose methotrexate and cytarabine associated to single or triple lumbar punctures (14 to 16 IT without brain irradiation) has shown its efficacy with 2 to 5% of CNS relapse.[48,49,50,51]Patients will be classified asCNS1 (leukocytes below 5/µL and no blasts on cytospin), CNS2 (leukocytes below 5/µL and blasts on cytospin), CNS3 (leukocytes ≥5/µL and blasts on cytospin and/or clinical or X-ray symptoms), TLP- (traumatic IT with ≥ 10 RBC/µL and no blasts on cytospin) or TLP+ (traumatic IT with ≥ 10 RBC/µL and blasts on cytospin) according to the results of the first IT.

It will be possible to omit radiotherapy at least for CNS1 and CNS2 patients. However, by comparison to GRAALL-2005, it will be necessary to increase triple ITs. For CNS3 patients, the specific therapy is unchanged, retaining brain irradiation.

[43]Matloub *et al*, Blood, 2011; 118:243-51

[44]Asselin *et al*, Blood, 2011; 118:874-83

[45]Hunault*et al*, manuscriptin preparation

[46]Veerman *et al*, Lancet Oncol, 2009; 10:957-66

[47]Pui *et al*, N Engl J Med, 2009; 360:2730-41

[48]Sancho *et al*,Eur J Haematol, 2007; 78(2): 102-10

[49]Cortes et al, Blood, 1995; 86(6): 2091-97

[50]Kantarjian *et al*, J Clin Oncol, 2000; 18:547-61

[51]Stock*et al*, Cancer, 2013; 119:90-98

2.2 GRAAPH-2014

In the GRAAPH-2014 study, the GRAALL keeps questioning the balance between TKI and chemotherapy. To achieve this, it has been decided to: 1) use nilotinib, a BCR-ABL inhibitor more potent than imatinib instead of the latter and 2) prolong the duration of chemotherapy + nilotinib exposure prior to SCT (from 2 to 4 monthly cycles). The de-escalating strategy of chemotherapy is moved from the induction phase (as in GRAAPH-2005, DIV being now considered as the appropriate induction therapy) to the consolidation phase. The second intensive cycle, based on high dose methotrexate and cytarabine associated to TKI will be randomized by comparison to methotrexate only associated to TKI.

After this period of 4 cycles combining nilotinib and chemotherapy, all patients in CR with a bone marrow BCR-ABL/ABL MRD ratio lower than 0.1% will receive either autoSCT or allo-SCT (only from genoidentical sibling or 10/10 MUD or 9/10 MUD) according to the investigator's choice.Patients with a bone marrow BCR-ABL/ABL MRD ratio of 0.1% or higher (after cycle 4) will receive an allo-SCT from genoidentical sibling or 10/10 MUD or 9/10 MUD or even from an alternate source of stem cells. They will also be allowed to be discontinued from the study to enter another experimental trial.

The objective of GRAAPH-2014 is thus to appreciate the reduction of chemotherapy intensity combined to a second generation TKI (nilotinib) in order to allow a maximum of patients to receive hematopoietic stem cells transplantation (allogeneic or autologous) with a good molecular response and an good performance index. Evaluation of MRD4 will be the key marker after 4 cycle combining TKI and chemotherapy. In order to further improve patients'outcome, as mentioned below, the following strategy will be adopted: 1) use of a longer combination TKI-chemotherapy period before SCT; 2) introduction of a second generation TKI during this pre-SCT phase; and 3) maintenance therapy by post transplantation TKI (imatinib) with an extended molecular monitoring.

The objectives of GRAAPH-2014 can thus be summarized as follows:

✓Demonstrate the non inferiority of the chemotherapy arm without high dose aracytine: as in GRAAPH-2005, BCR-ABL MRD will be the principal criterion used to calculate the sample size;

✓ Evaluate SCT in good responders: the type of SCT (allogeneic or autologous) will be left to the investigator's choice.

3 EXPERIMENTAL DRUGS IN THE TRIAL

3.1 Denomination and description

Experimental drugs in the substudy GRAALL-2014/B (Ph- B lineage ALL) are as follows: blinatumomab, cyclophosphamide, methotrexate, vincristine, cytarabine, VP-16, dexamethasone, prednisone, 6-mercaptopurin, daunorubicin, idarubicin, L-Asparaginase and G-CSF.

All these drugs have a MA and will be prescribed according to it within GRAALL-2014/B except blinatumomab which has a MA in relapse/refractory BCP-ALL. Blinatumomab (BLINCYTO®) will therefore be provided by the sponsor in a manner adapted to research (contra-labelling for clinical trials).

The other drugs that will be used in conditions allowing reimbursement by medical insurance in France, as per «article L1121-16-1 of the French Public Health Code». **They will not be provided by the sponsor**.

Experimental drugs in the substudy GRAALL-2014/T (T-lineage ALL) will be the following: **nelarabine**, cyclophosphamide, methotrexate, vincristine, cytarabine, VP-16, dexamethasone, 6-mercaptopurin, daunorubicin, idarubicin, prednisone, L-asparaginase and G-CSF.

All these drugs have a MA and will be prescribed according to it within GRAALL-2014/T except nelarabine which has a MA in T-all only in second intention. Nelarabine (ATRIANCE®) will therefore be provided by the sponsor in a manner adapted to research (contra-labelling for clinical trials). The other drugs will not be provided by the sponsor.

Experimental drugs in the substudy GRAAPH-2014 are as follows: **nilotinib**, imatinib, methotrexate, vincristine, cytarabine, dexamethasone, 6-mercaptopurin, prednisone and G-CSF. All these drugs have a MA and will be prescribed according to it within GRAAPH-2014 except nilotinib which has a MA in CML. Nilotinib (TASIGNA®) will therefore be provided by the sponsor in both treatment arms in a manner adapted to research (contra-labelling for clinical trials). The other experimental drugs will not be provided by the sponsor.

3.2 Description and justification of dosage, administration route and scheme and treatment duration of Blinatumomab, Nelarabine and Nilotinib (prescription outside MA)

3.2.1 Blinatumomab

Blinatumomab (BLINCYTO®) is provided in 4 mL single-use glass injection vials as a sterile, preservation-free, lyophilized powder for reconstitution and administration by IV infusion. Blinatumomab comes with an IV Solution Stabilizer supplied in 10 mL single-use glass injection vials as a sterile, preservative-free, liquid concentrate. It has a specific contra-labelling in 4 languages (French, German, Dutch, Italian) with regulatory mentions for clinical trials.

Blinatumomab and IV Solution Stabilizer are shipped at 2°C to 8°C in a qualified shipper and should be immediately stored in a refrigerator maintained at 5°C +/- 3°C.

The drug's administration is detailed in the relevant substudy.

3.2.2 Nelarabine

Nelarabine (ATRIANCE®) is a solution for perfusion at 5 mg/mL, provided in 50 mL vials, and will be provided by the sponsor through a donation convention with NOVARTIS PHARMA. It has a specific contra-labelling in 4 languages (French, German, Dutch, Italian) with regulatory mentions for clinical trials.

It comes in a form adapted to clinical research and does not require specific conservation conditions.

The drug's administration is detailed in the relevant substudy.

3.2.3 Nilotinib

Nilotinib (TASIGNA® 150 mg and 200 mg) will be provided by the sponsor through a donation convention with the Novartis Company. It has a specific contra-labelling in 4 languages (French, German, Dutch, Italian) with regulatory mentions for clinical trials.

It comes in a form adapted to clinical research and must be stored below or equal to 30°C.

TASIGNA® will be given per os, twice a day, morning and evening at a 12h interval. If the morning dose is delayed of more than 4 hours, it will not be given. Any dose omitted shall not be replaced by a compensatory double dose on the next take. TASIGNA® must be ingested without any food: no food shall be eaten 2 hours before and one hour after TASIGNA® administration. Capsules will be swallowed whole with a large glass of water (250 mL). Grapefruit, carambole, grenade or Seville oranges are prohibited during therapy.

The drug's administration is detailed in the relevant substudy.

3.3 Summary of the benefits and anticipated known risks of Blinatumomab, Nelarabine and Nilotinib for persons involved in research

3.3.1 Blinatumomab

Blinatumomab is a bispecific engager currently approved for the treatment of Philadelphia chromosome-negative (Ph-) relapsed or refractory BCP-ALL. This agent has also been evaluated in MRD positive patients and has shown encouraging results in terms of complete molecular response and disease-free survival. For this reason, the GRAALL-2014 trial plans to introduce 5 cycles of blinatumomab during consolidation and maintenance in patients with the highest risk of relapse.

As a first-in-class non-chemotherapeutic immunotherapy, blinatumomab displays specific side effects. This side effects are mostly due to cytokine release syndrome (CRS) following first administration. The frequency of CRS is lower in patients with positive minimal residual disease (as planed in GRAALL-QUEST study) than in relapsed or refractory setting. Specific neurological events have also been reported and will be cautiously monitored.

Across studies, the most frequently reported (≥ 20% of patients) adverse events were pyrexia, headache, nausea, anemia, hypokalemia, and diarrhea.

Other frequent adverse events expected in patients with minimal residual disease are hypotension, cough, neutropenia, hypokaliemia, neutropenia.

Neurological disorders include headache, tremor, dizziness, aphasia, paraesthesia, encephalopathy, somnolence, ataxia, seizure, insomnia, confusional state, anxiety. These adverse events were rapidly reversible after blinatumomab withdrawal.

Individual benefit can be expected for the patients as blinatumomab appears to decrease the risk of further relapse, even in patients enable that may not proceed to allo-SCT.

Patients who will not agree to take part to this study will receive the therapy usually offered to ALL patients.

3.3.2 Nelarabine

Nelarabine is a chemotherapy currently indicated in case of T-ALL second relapse (MA). The efficacy observed in this indication leaves hope for a decreased risk of relapse if this drug was used earlier in the disease. For this reason the GRAALL-2014 trial plans to propose 5 additional cures of nelarabine in patients with the highest risk of relapse: two cures during consolidation phases and 3 cures during the first year of maintenance therapy.

As a chemotherapy, nelarabine is potentially liable to yield side effects. It can be responsible, as do other chemotherapies, of a decrease of white blood cells, red blood cells and platelets.

The other side effects of nelarabine are mostly neurological. These complications are mostly observed when the drug is associated with radiotherapy or lumbar punctures. For this reason, patients will not receive any lumbar puncture at the same time as nelarabine. Patients will also have a neurological examination in order to detect potential AE related to the drug:

- On D1 of each cure and/or of each block until the initiation of the maintenance period,
- Each month during the first year of maintenance,
- Every three months the second year.

Symptoms most frequently reported upon administration of nelarabine are:

✓ foot and hands itching,

✓ vertigo, balance trouble,

✓ tremor,

✓ walking difficulties,

✓ headaches,

✓ muscle pain,

✓ fuzzy vision,

✓ gastrointestinal troubles: nausea, vomiting, diarrhea, constipation,

✓ limbs edema,

✓ breathing troubles, pleural effusions.

Most of these troubles are usually reversible. Exceptionally, severe peripheral neuropathies (disease of the nerves) have been reported.

Individual benefit can be expected for the patients inasmuch as nelarabine appears to decrease the risk of further relapse.

Patients who will not agree to take part to this study will receive the therapy usually offered to ALL patients.

3.3.3 Nilotinib

TASIGNA® is usually well tolerated. The most frequent side effects are nausea, vomiting, diarrheaor constipation, headaches, fatigue (and insomnia), fever, skin rashes, pruritus, muscle cramps, joint pain, edema, hypertension, cough and night sweats.

TASIGNA® could be responsible for severe troubles of cardiac rhythm. An electrocardiogram will be performed for this reason before treatment initiation and regularly along the whole therapy. Some drugs will be forbidden because their association with TASIGNA® increases the risk of cardiac rhythm troubles. The

biological anomalies which have been noted (and sometimes led to the momentary interruption of TASIGNA® or to dose reduction) are mostly related to toxicity against the liver (increase of serum hepatic enzymes levels), pancreas (increase of serum pancreatic enzymes levels), bone marrow (decreased white blood cells and platelets). These features will be closely monitored and the dosage of TASIGNA® will be adapted to the situation, after potential temporary interruption. Some patients have reported weight gain. The latter will also be closely monitored. Other patients developed pleural effusion and/or ascites. A minority of patients had signs of cardiac failure. More recently, arterial problems have been reported in patients treated with nilotinib without being directly considered as related to the treatment. By precaution, and mostly if the patient already had arterial trouble, diabetes, hypertension or familial lipid dysregulation, a Doppler ultrasound of the neck and limbs arteries will be performed before initiating therapy with nilotinib. This test will be repeated every 4 months during the duration of treatment with nilotinib.

Individual benefit can be expected for the patients inasmuch as the decrease of chemotherapy dosage used in the “lightened strategy based on nilotinib” could be associated to less toxicity.

4 ASSESSMENTS BEFORE TREATMENT

It is preferred to know the lineage of the ALL (before performing the samplings detailed below the results of which will allow inclusion in one of the two substudies), either by a first blood examination or by a diagnostic medullogram.

4.1 Initial assessments at diagnosis

Each patient must have had, before initiation of the prephase, blood and bone marrow samplings allowing to assess the type of ALL and the oncogenetic risk group necessary for inclusion in GRAALL-2014.

4.1.1 Bone marrow

Ideally, all following examinations should be performed on the same aspiration, taking care of avoiding hemodilution (changing trabecula), knowing that only the first two milliliters of an aspiration are representative of the medullary compartment.

4.1.1.1 Locally, on site

- ✓ Bone marrow sternal or iliac aspiration (or bone marrow biopsy if dry tap),
- ✓ Immunophenotype of leukemic lymphoblasts, according to EGIL criteria and including the expression of CD20
- ✓ Karyotype of leukemic lymphoblasts, by conventional cytogenetics and FISH-MLL,
- ✓ Molecular biology* (investigation of BCR-ABL, in case of positivity of sample: *KMT2A-AFF1 (=MLL-AF4), TCF3-PBX1 (=E2A-PBX1))*

*For Switzerland: *KMT2A-AFF1 (=MLL-AF4), TCF3-PBX1 (=E2A-PBX1)* assessment will be performed centrally by Pr Spertini in Lausanne - CHUV – Service d'hématologie/biologie moléculaire - Réception des laboratoires BH/18/100 -1011 Lausanne. Phone: +41 21 314 42 09/10.

- ✓ Examination of the ploidy of leukemic lymphoblasts.

The results of immunophenotype and molecular biology must be anonymized and faxed at the GRAALL secretariat to Véronique LHERITIER (fax: +33 (0)4.72.66.64.40) for central review and validation by the biology coordinators of the GRAALL group.

4.1.1.2 Delocalized

Molecular biology and banking in adult ALL cell banks are performed in 5 reference laboratories, with INCa labelling, in 4 platforms Lille (Pr. Claude Preudhomme), Paris (Necker – Pr. Macintyre and St. Louis – DrCayuela at AP-HP), Rennes (Pr. T. Fest) and Toulouse (Pr E. Delabesse).

- ✓ Oncogenetic anomalies investigation centralized at Paris Necker for T-ALL or at Paris St Louis for B lineage ALL *(2mL on EDTA),*
- ✓ MRD by IGH/TCR: characterization of IgH/TCR targets for MRD follow-up. This sample will be sent to one of the 6 MRD laboratories: Lille, Paris Necker, Paris St Louis, Rennes and Toulouse for France and Belgium. Zurich for Switzerland *(2mL on EDTA),*

✓ Cell bank, centralized in Toulouse GRAALLThèque, for all ALL. Remaining medullary cells of diagnosis samples will be directly sent by the MRD laboratories to the cell bank.

4.1.2 On peripheral blood

4.1.2.1 Locally, on site

✓ Blood cell count with differential by examination of a blood smear

✓ Karyotype of leukemic lymphoblasts, by conventional cytogenetics and FISH-MLL,

✓ Examination of the ploidy of leukemic lymphoblasts

✓ Molecular biology* (investigation of BCR-ABL, in case of positivity of sample: *KMT2A-AFF1 (=MLL-AF4), TCF3-PBX1 (=E2A-PBX1))*

*For Switzerland: *KMT2A-AFF1 (=MLL-AF4), TCF3-PBX1 (=E2A-PBX1)* assessment will be performed centrally by Pr Olivier SPERTINI in Lausanne - CHUV – Service d'hématologie/biologie moléculaire - Réception des laboratoires BH/18/100 -1011 Lausanne. Phone: +41 21 314 42 09/10.

✓ Biochemistry, gamma globulinenia before each consolidation block

✓ Hemostasis with at least TP, TCA, PDF or D-dimers, fibrinogen,

✓ Ferritin assay,

✓ ß-HCG for women in genital activity,

✓ Standard virology (at least VIH, VHB, and VHC serologies),

✓ Parasitology: toxoplasmosis serology,

✓ HLA typing (10 antigens): **typing will be performed systematically for all patients** (whenever possible at inclusion, otherwise after obtention of hematological CR). All siblings will be typed as soon as possible. In the absence of HLA-identical brother or sister, search for an unrelated donor will be systematic for Ph+ ALL. For Ph- patients, it is recommended to look for an unrelated donor in case of chemoresistance (D8 bone marrow).

4.1.2.2 Delocalized

✓ Oncogenetic exploration of T-ALL of B-lineage ALL *(20 mL on EDTA)*.**To be sent mandatorily with the bone marrow,**

✓ MRD by Igh/Tcr *(20 mL on EDTA)*.**To be sent mandatorily with the bone marrow,**

4.1.3 Other assays (locally)

✓ CSF flow cytometry at first lumbar puncture for prospective evaluation (CNS treatment is driven by morphological assessment only).,

✓ Evaluation of myocardial function by ultrasonography or cardiac scintigraphy.

4.1.3.1 Particular case of arteriopathies (GRAAPH)

For patients at vascular risk with one of these conditions:

✓ Known arteriopathy,

✓ Diabetes,

- ✓ Untreated or uncontrolled arterial hypertension (ask for cardiologic opinion when needed),
- ✓ Active smoking,
- ✓ Familial dyslipidemia,

An ultra-sound Doppler of the neck and lower limbs will be performed during the prephase. The medical coordination of the GRAALL must be contacted *via the* secretariat (Véronique LHERITIER: Tel: +33 (0)4 78 86 22 39 Fax: +33 (0)4 72 66 64 40) to confirm or infirm inclusion **in case of anomaly**. For included patients, ultra-sound Doppler will be repeated every 4 months during the period of nilotinib therapy. The investigator will take advice from a cardiologist in order to apply adapted prevention measures for patients at vascular risk.

In case the ultra-sound Doppler could not be performed during the prephase, patients at high cardiovascular risk will not be treated by nilotinib and will receive imatinib.

4.2 Biological Collections

Part of the blood and/or bone marrow samples collected will not be necessary to ensure patient management and could be stored up to 15 years by deep freezing in the laboratories of biological resources centers of the hospitals participating to the biomedical research trial GRAALL-2014 (cf supra).

Some of these samples of blood, serum, plasma as well as blood or bone marrow cells (including leukemic cells) or their content (DNA, RNA, proteins) will be used for research aiming to better understand, for instance, the mechanisms initiating leukemias, to better appreciate their prognosis or favor new therapies.

Annexes 10 and 11 summarize the tests not to forget to perform during the trial.

5 RISK ASSESSMENT AND ALLOGRAFT INDICATIONS

5.1 risk assessment and allograft indication in Ph- B-ALL

5.1.1 High risk Ph- B-ALL patients (HR group)

Risk assessment relies on the 4 following parameters:

- ✓ ***IKZF1* gene deletion,**
- ✓ **Translocation t(4;11)and/or fusion gene *KMT2A-AFF1(=MLL-AF4*) ; or any other rearrangement of *the KMT2A (=MLL)* gene**
- ✓ **Necessity of a salvage cure to reach CR**
- ✓ **Post induction MRD level (MRD1).**

5.1.1.1 Classification of high-risk B-ALL (HR)

***IKZF1* deletions (excluding whole gene deletion or monosomy 7)**
and/or
MLL rearrangement of the *KMT2A (=MLL)* gene, (t(4;11), *KMT2A-AFF1 (=MLL-AF4)* fusion or other)
and/or
MRD1 ≥10^{-4} (including non obtention of CR in 1 cure)

5.1.1.2 Criteria for Allo-SCT in HR patients (VHR group)

All HR patients are not necessarily eligible for allo-SCT in CR1. The decision to perform allo-SCT in CR1 is only based on the MRD answer (MRD1 and MRD2). *IKZF1* deletion or **KMT2A (**=MLL) rearrangements are not per se an indication for allo-SCT.

For this reason a group of very high risk patients (VHR) is defined based on MRD1 and MRD2 results:

MRD1 ≥10^{-3} (including non obtention of CR in 1 cure)
and/or
MRD2 ≥10^{-4}

Only VHR patients will be eligible for allo-SCT in CR1.

Pragmatically, to accelerate the search for a donor in VHR patients, HLA typing of the patient and siblings will be performed at diagnosis. In the absence of an HLA-identical brother or sister, search for an unrelated donor will be initiated for patients chemoresistant on day 8 (local morphological examination). Indeed, medullary chemoresistance on day 8 after chemotherapy initiation is the factor best correlated to VHR.

In all cases, if not already performed, search for a donor will be necessary if MRD1 is ≥ 10^{-3} since all these patients are classified VHR. Yet, a small percentage of patients will be classified VHR only on their MRD2 level (< 5%).

5.2 risk assessment and allograft indication in T-ALL

5.2.1 High risk T-ALL patients (HR group)

Risk assessment relies on 3 parameters:

- ✓ **oncogeneticprofile** (*NOTCH1*, *FBXW7*, *PTEN* and *RAS* mutations)
- ✓ **necessity of a salvage cure to reach CR1**
- ✓ **level of post induction MRD (MRD1).**

5.2.1.1 Classification of high risk T-ALL (HR)

Absence of *NOTCH1* and/or*FBXW7* mutation
or alteration of *RAS* or *PTEN*
and/or
MRD1 ≥10^{-4} (including non obtention of CR in 1 cure)

5.2.1.2 Criteria for Allo-SCT in HR patients (VHR group)

All HR patients are not necessarily eligible for allo-SCT in CR1. The decision of allo-SCT in CR1 is only based on the MRD answer (MRD1 and MRD2). An unfavorable oncogenetic profile is not per se an indication for allo-SCT. Almost all VHR-MRD patients are HR patients and thus eligible for ATRIALL study.

For this reason a group of very high risk patients (VHR) is defined based on MRD1 and MRD2 results:

MRD1 ≥10^{-3} (including non obtention of CR in 1 cure)
and/or
MRD2 ≥10^{-4}

Only VHR patients will be eligible for allo-SCT in CR1.

Pragmatically, to accelerate the search for a donor in VHR patients, HLA typing of the patient and siblings will be performed at diagnosis. In the absence of an HLA-identical brother or sister, search for an unrelated donor will be initiated for patients chemoresistant on day 8 (local morphological examination). Indeed, medullary chemoresistance on day 8 after chemotherapy initiation is the factor best correlated to VHR.

In all cases, if not already performed, search for a donor will be necessary if MRD1 is ≥ 10^{-3} since all these patients are classified VHR. Yet, a small percentage of patients will be classified VHR only on their MRD2 level (< 5%).

NUP-ABL T-ALL patients: NUP ABL is not per se a risk factor. Only oncogenetic criteria and MRD will impact risk classification and will orient patients in a specific group (SR/HR/VHR).

6 EVALUATION AND TREATMENT OF CNS INVOLVEMENT

6.1 Initial evaluation of cnsinvolvement

An initial lumbar puncture explorative with intrathecal (IT) injection (single IT of MTX) must be performed at the latest on D -3 (preferably on D -4 if there is no clinical suspicion of CNS involvement (CNS+), cf infra) of the prephase, **whatever the WBC count.**

The classification shown below will be used to describe potential neuromeningealinvolvement[52,53]. It relies on: clinical examination, morphological examination of CSF and imaging data when available (MTD, MRI). Traumatic lumbar puncture (TLP) is considered when more than 10 red blood cells are seen per microliter.

6.1.1 Non traumatic initial IT (MTX)

CNS-1 to 3 are defined:

CNS-1: leukocytes < 5/µL no lymphoblasts on cytospin,

CNS-2: leukocytes < 5/µL and lymphoblasts on cytospin,

CNS-3: leukocytes ≥ 5/µL and lymphoblasts on cytospin **(or clinical or radiological (e.g. MRI) neurological involvement),**

6.1.2 Traumatic initial IT (MTX) - TLP

TLP -: ≥ 10 RBC /µL and no lymphoblasts on cytospin,

TLP +: ≥ 10 RBC /µL and lymphoblasts on cytospin.

6.1.3 Management of CNS-2 or TLP+ patients.

For patients with initial CNS-2 or TLP+, a new exploratory IT will be performed 4 days later (ex. D -3 if initial IT on D -7). However, this second IT will be combined with a triple IT if performed on D +1, i.e. chemotherapy initiation.

After this second evaluation, patients will be classified**:**

Late CNS-1: CNS-2 at diagnosis and CNS-1 4 days later,

Late CNS-2: CNS-2 at diagnosis and CNS-2 4 days later,

Late CNS-3: CNS-2 at diagnosis and CNS-3 4 days later,

Late TLP+ CNS-1: TLP+ at diagnosis and CNS-1 4 days later,

Late TLP+ CNS-3: TLP+ at diagnosis and CNS-3 4 days later,

It is therefore preferable to perform the first IT on D -4 (if no neuro-meningeal involvement is suspected) because if the patient is classified CNS-2 or TLP+ the next IT (allowing to classify the CNS status) will be that of D +1, sparing an IT to the patient. Rare "late CNS-2 patients" will be treated as "late CNS-3" patients.

[52]Mahmoud *et al,* N Engl J Med, 1993; 329(5):314-319

[53]Pui *et al,* Blood, 1998; 92(2):411-415

6.2 Initial neuro-meningeal involvement (CNS-3 or late CNS-3)

6.2.1 Neuro-meningeal involvement of Ph- B-ALL and T-ALL

6.2.1.1 Intrathecal injections

This part applies to patients classified **CNS-3** at the initial IT, **late CNS-3** (4 days later for CNS-2 or TLP+ patients), or late CNS-2 (4 days later for CNS-2 or TLP+ patients).

Intrathecal treatment: 2 triple IT per week between the pre-phase and D21* (8 IT) then 1 IT per week up to a total of 12 triple IT, then trial-scheduled IT up to CNS irradiation. Patients should not receive IT injections after CNS irradiation during maintenance.

This table represent the triple IT administration scheme for (late) CNS-3 patients

PRE-PHASE	INDUCTION						CONSO: BLOCKS S1/S2/S3			
2 IT between D -7 and D -1 (first IT: single IT with MTX)	D1	D4	D8	D11	D15	D18	D8	D16	D24	D29

* Asparaginase injections of D8, D10 and D12 will not be performed for these patients. For patients ≥ 45 years old, in order to compensate these missed 3 doses of Asparaginase, Asparaginase will be given on D26 and D28 to reach a total of 5 injections of Asparaginase.

Patients with CNS involvement will not be eligible to the phase II – ATRIALL trial.

6.2.1.2 Radiotherapy

- If the patient does not receive Allo-SCT: CNS irradiation before maintenance therapy. This includes two lateral fields encompassing the skull, face (ocular protection), skull base and the first two cervical vertebrae. Doses are of 24 Gy in the median plane in 10 sessions (5 per week for 2 weeks). Patients should not receive IT injections after CNS irradiation during maintenance.
- If the patient receives Allo-SCT: CNS irradiation after blocs S1 to S3. This includes two lateral fields encompassing the skull, face (ocular protection), skull base and the first two cervical vertebrae. Doses are of 15 Gyin the median plane in 10 sessions (5 per week for 2 weeks).

Radiotherapy is associated to the administration of 6-mercaptopurin 60 mg/m²/day PO, with assessment of blood parameters.

6.2.2 Neuro-meningeal involvement of Ph+ ALL

For CNS-3 patients, the scheme below is to be followed (12 triple IT as a whole). Trial-scheduled IT are then resumed.

PRE-PHASE	Cycle1						Cycle 2			
2 triple IT	D1	D4	D8	D11	D15	D18	D2 (C2A ARM)	D9	D15	D22

between D -7 and D -1 (first IT: single IT with MTX)							D1 (C2B ARM)			

7 HEMATOLOGICAL EVALUATION IN GRAALL-2014

7.1 Complete remission or failure of induction therapy

The answer will be established on the basis of the **International Working Group Criteria**, summarized in the table below[54].

Answer	Neutrophils (G/L)	Platelets (G/L)	Bone marrow blasts (%)	Complementary Information
CHR (Complete Hematological Response)	> 1	> 100	< 5	No peripheral blasts, no extramedullary disease
Failure	Persistence of leukemic cells in the blood or bone marrow, or death before treatment response evaluation			

CHR patients at the end of induction initiate consolidation as soon as the criteria of hematologic recovery are reached.

Patients in failure at the end of induction receive either salvage therapy (GRAALL), or cycle 2 (GRAAPH).

A new evaluation will be performed after the second treatment. In case of failure, the patient will be discontinued from the study.

7.2 Relapse

Relapse will be determined on the basis of the **International Working Group Criteria**, summarized in the table below[54].

Relapse	Neutrophils (G/L)	Platelets (G/L)	Bone marrow blasts(%)	Complementary information
Hematological relapse	-	-	> 5	Reappearance of blasts post CR in the blood or bone marrow , the morphology of which is similar to that of the initial pathology
CNS relapse	-	-	-	(Re) appearance of clinical and/or biological (CSF) neurologicalsymptoms, associated or not to a hematological relapse

NB: reappearance of detectable MRD or an increase in MRD (whatever the MRD marker used) is not considered as a relapse.

[54]Cheson et *al*, J Clin Oncol, 2003; 21(24): 4642-49

PART II

GRAALL-2014/B
(PH- B LINEAGE ALL)

SYNOPSIS GRAALL-2014/B AND GRAALL-QUEST SUBSTUDY

Title	**GRAALL-2014/B:** **Multicenter trial risk adapted treatment of Philadelphia chromosome negative (Ph-) B-lineage ALL of young adults (18-59 years).** **GRAALL-QUEST:** **A phase II study to evaluate the safety and the efficacy of a blinatumomab based consolidation and maintenance in patients with high-risk B-cell precursor acute lymphoblastic leukemia (BCP-ALL). GRAALL-QUEST**
Acronym	**GRAALL-2014/B and GRAALL-QUEST**
Coordinator	**Pr. Hervé DOMBRET** **Hématologie, Hôpital Saint Louis, Paris** **Tél: +33 (0)1 57 27 68 47 /(0)1 42 49 96 48** **Email: herve.dombret@aphp.fr**
Sponsor	**Assistance Publique – Hôpitaux de Paris**
Indication	Patients aged 18-59 years old with *de novo* Ph-negative B-lineage-ALL.
Type of study	Multicenter, open, not controlled study (SR patients) Phase II, multicenter, open non controlled (GRAALL-QUEST, HR patients)
Number of selected subjects	500 patients front-line 95 patients for the GRAALL-QUEST study
Number of centers	**About 80 centers expected (Belgium, France, Switzerland)**
Study Duration	Enrollment period, 5 years. Duration of the trial participation (treatment and follow up): 5 years Total duration of the trial: 10 years For GRAALL-QUEST: accrual phase of 2 years + follow-up of 3 years
Experimental drug **Prescription outside MA**	**Blinatumomab (BLINCYTO®) – HR patients enrolled in the GRAALL-QUEST study**
Experimental drugs Prescription according to MA	Cyclophosphamide, Methotrexate, Vincristine, Cytarabine, VP-16, Dexamethasone, 6-mercaptopurin, Daunorubicin, Idarubicin, Prednisone, L-Asparaginase, Granulocyte colony-stimulating factor (G-CSF).
Risk factors definition	• **Standard-risk (SR)** patients not classified as high-risk (HR) nor very high-risk MRD (VHR-MRD) patients. • **High-risk (HR) patients** are defined after induction as having<u>at least one</u> of the following criteria: – *IKZF1* gene deletion, – t[4;11] and/or *KMT2A* (=*MLL*) fusion or other *KMT2A (=MLL)* gene rearrangement – MRD1 level ≥ 10^{-4} (with a sensitivity of at least 10^{-4}), including a salvage cure required to reach hematological CR1. 95 HR patients will be treated in GRAALL—QUEST study and receive blinatumomab as part of the consolidation and maintenance phase. Patients HR, non eligible for the GRAALL-QUEST study will be treated in the SR arm with the same follow up.

	• **Very High-Risk MRD (VHR-MRD) patients** are defined after inductionas having at least one of the following criteria: – MRD1 ≥ 10^{-3} (with a sensitivity of at least 10^{-3}) – MRD2 ≥ 10^{-4} (with a sensitivity of at least 10^{-4}) Almost all VHR-MRD patients are HR patients and thus eligible for GRAALL-QUEST study. All VHR-MRD patients with a donor will receive allo-SCT after consolidation 2.
Objectives	Primary objective: ✓ To prospectively validate the new risk model, based on MRD1 response level and *KMT2A (=MLL*) and *IKZF1* gene status by comparing historical results of GRAALL-2005 with those of GRAALL-2014 in an identical population of patients (Ph- B lineage ALL, aged 18 to 59 years old). ✓ To evaluate the efficacy of blinatumomab-based consolidation and maintenance therapy in term of DFS in HR patients (GRAALL-QUEST substudy) by comparing to historical results of GRAALL-2005 in an identical population of patients with HR features (GRAALL-QUEST study). Secondary objectives: • To appreciate the tolerance of blinatumomab-based consolidation cycles, in bridge to allo-SCT or within further consolidation and maintenance therapy, • To evaluate MRD level, monitored by Ig-TCR, To evaluate cumulative incidence of relapse (CIR) and non-relapse mortality (NRM), disease-free survival (DFS), and overall survival (OS), • To evaluate RFS, CIR, NRM, and OS after censoring at SCT in first CR.
Evaluation criteria	Primary evaluation criterion ✓ Disease free survival (DFS) at 4 years, depending on the status of *KMT2A (=MLL)* and *IKZF1* genes and on MRD1 assessed after the induction cure or on D1 of consolidation 1. ✓ DFS at 3 years in the GRAALL-QUEST study. Secondary evaluation criteria ✓ CIR, NRM, and OS, ✓ DFS, CIR, NRM and OS after censoring at allo-SCT in first CR. ✓ MRD follow-up at different treatment times (cf infra § MRD monitoring). ✓ Adverse events after blinatumomab (GRAALL-QUEST).
Statistical justification of sample size	Each year, approximately 100 patients with Ph-negative BCP-ALL may be recruited front-line in the GRAALL-2014/B trial. After HCR achievement, one may anticipate approximately 40 SR patients/year and 50 HR patients/year (including 30-35 VHR-MRD patients). After consolidation 1 : • All SR patients will be treated by the standard GRAALL protocol, without new agent nor HSCT in first CHR. The objective is here to demonstrate in an uncontrolled study, the non-inferiority in terms of 4-year DFS which must be at least of 60% in the control group (historical reference), with a margin of inferiority of 15%, justifying the absence of allo-SCT in first CR. With a 0.05 unilateral alpha risk and a 0.90 power the calculated sample size is 110 patients. • About 50 HR patients/year will be eligible for GRAALL-QUEST study, with DFS as primary endpoint. DFS will be compared to historical GRAALL-2005 results (50% at 3 years). The objective is here to demonstrate a 50% to 65% DFS improvement. With a 0.05 alpha risk and a 0.90 power in the two-sided setting, the calculated sample size is 91 patients. Considering a drop-out rate of about 5%, 95 patients should be included in the present study (Ref: Sample size tables for clinical studies. Machin D, Campbell M et al. Wiley, 2009).

Identification of subjects	In this trial, subjects will be identified as follows: Center n° (3 digits) – selection order number of the patient in the trial (4 digits) – name initial – surname initial This reference will be unique and retained all along the trial.
GRAALL-2014/B **Inclusion Criteria**	Patient: 1. Whose blood and bone marrow explorations have been completed before the steroids prephase 2. Aged 18 to 59 years old with not previously treated (including intrathecal injection) B-lineage-ALL newly diagnosed according to the WHO 2008 definition with ≥ 20% bone marrow blasts 3. Whose karyotype shows no t(9;22) and/or the absence in molecular biology of BCR-ABL 4. With ECOG ≤3 5. With or without central nervous system (CNS) or testis involvement 6. Without other evolving cancer (except basal cell carcinoma of the skin or "in situ" carcinoma of the cervix) or its radiotherapy or chemotherapy treatment should be finished at least since 6 months 7. Having signed a written informed consent 8. With efficient contraception for women of childbearing age (excluding estrogens and IUD) 9. With health insurance coverage 10. Who have received or being receiving the steroid prephase Secondary ALL (antecedent of chemo- or radio-therapy) can be included.
GRAALL-2014/B **Non inclusion Criteria**	Patient: 1. With lymphoblastic lymphoma and bone marrow blasts < 20%, Burkitt-type ALL, or with antecedents of CML or other myeloproliferative neoplasm 2. With contra-indication to anthracyclines or any other general or visceral contra-indication to intensive therapy except if considered related to the ALL: a. ASAT (SGOT) and/or ALAT (SGPT) > 5 x ULN b. Total bilirubin ≥ 2.5 x ULN c. Creatinine >1.5x ULN or creatinine clearance <50 mL/mn 3. Myocardial infarction within 6 months prior to inclusion in the trial, cardiomyopathy (NYHA grade III or IV), LVEF < 50% and or RF < 30%, 4. HIV, HTLV-I or HCV seropositivity or chronic HBV hepatitis (HbsAg-positive). 5. Pregnant (ß-HCG positive) or nursing woman 6. Not able to bear with the procedures or the frequency of visits planned in the trial 7. Unable to consent, under tutelage or curatorship, or judiciary safeguard. 8. Women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least three months thereafter. Patients not willing to ensure not to beget a child during participation in the study and at least three months thereafter 9. Treated with any other investigational agent or participation in another trial within 30 days prior to entering this study
GRAALL-QUEST **Inclusion criteria**	Patient: 1. Included in GRAALL-2014/B 2. With HR B-ALL 3. ECOG ≤ 3 4. In CR after one or two induction cures and having received the three blocks of consolidation N°1 5. With or without allogeneic donor
GRAALL-QUEST **Non inclusion criteria**	Patient: 1. With ECOG status > 3 after consolidation 1 2. With abnormal laboratory values as defined below after consolidation 1

	a. AST (SGOT) and/or ALT (SGPT) ≥ 5 x ULN b. Total bilirubin ≥ 1.5 x ULN c. Creatinine ≥ 1.5 x ULN or creatinine clearance < 50 ml/min d. Serum amylase and lipase ≥ 1.5 x ULN 3. With active uncontrolled infection, any other concurrent disease or medical condition that is deemed to interfere with the conduct of the study as judged by the investigator 4. NYHA grade 3-4 cardiac disease 5. Infection with human immunodeficiency virus (HIV) or chronic infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive) Primary monitoring of asparaginase activity and of ammoniemia (Annex 5) has to be done **48h after the 3rd injection** (theoretically D14) and. Secondary monitoring has to be done **48 h after the 6th injection** (theoretically D26). For all patients <45 years old, sample collection must be performed immediately before the 7th injection.Not able to bear with the procedures or the frequency of visits planned in the trial
Reference Treatment	**Induction** All patients will receive an induction course. Patients without HCR at the end of induction will receive salvage therapy. The differential diagnosis of Ph+ B-lineage-ALL should be done during the prephase, so that these patients receive GRAAPH-2014 Ig-TCR MRD1 level will be evaluated at the end of the induction cycle orat day 1 of the first consolidation phase. **Consolidation 1** All patients in HCR (after induction eventually followed by salvage) will receive 0, 1 or 2 interim "stand-by" blocks before the first consolidation comprising 3 blocks of chemotherapy (blocks S1, S2, S3). These stand-by blocks will allow to recover from potential toxicities of the induction, notably hepatic, to avoid modifying the order of the following consolidation blocks and to respect the dosage/intensity. HR *versus* SR Patients will be attributed to a risk group during the first consolidation according to MRD1 level, need for salvage to obtain CHR, presence of *IKZF1* gene deletion and *KMT2A* (=*MLL)* gene rearrangements. All HR patients will be proposed the Phase II GRAALL-QUEST study, up to 95 inclusions. After this number has been reached, HR patients who would have been eligible for GRAALL-QUEST will continue to participate to the study and its follow-up planned in GRAALL-2014/B. Ig-TCR MRD2 level will be evaluated at the end of the consolidation 1 or on day one of consolidation 2. **Consolidation 2** After first consolidation, SR patients will continue the standard protocol and receive the consolidation 2 (blocks S4, S5, S6). 95 HR patients will be traited in phase II GRAALL-QUEST study and will receive blinotumomab. Consolidation 2 is composed of 3 blocks: B4 (Blina), B5 (HD-AraC), B6 (HD-MTX). HR *versus* VHR-MRD VHR-MRD is defined by MRD1≥ 10^{-3} or the need of a salvage cure to reach HCR or MRD2≥ 10^{-4} Patients eligible for allo-SCT with a suitable donor will receive blinatumomab continuous infusion until conditioning regimen.. Ig-TCR MRD3 level will be evaluated at day 1 of late intensification (or prior to SCT in allografted patients).

	Late intensification will be administered to all **non-allografted** patients, whatever their risk group. **Consolidation 3** After late intensification, patients SR will receive a third consolidation (blocks S7, S8, S9). HR patients will receive a second investigational blinatumomab-based consolidation composed of 3 blocks: B7 (Blina), B8 (HD-AraC), B9 (HD-MTX). Ig-TCR MRD4 level will be evaluated at day 1 of maintenance therapy (or day 100 after SCT). **Maintenance therapy** The whole duration will be two years It is a classical maintenance therapy for all patients, based on the association of 6-mercaptopurin + methotrexate, with monthly reinductions associating vincristine and prednisone during the first year.. Patients HR: patients will receive 3 blinatumomab courses instead of vincristine pulses at month 1, 3, and 5 **Allogeneic stem cell transplantation (SCT)** Allogeneic SCT in first CR will be offered to all VHR-MRD patients with a genoidentical familial or unrelated donor (10/10 or 9/10). Allo-SCT has to be done as early as possible after the second consolidation phase. In patients < 45 years old, conditioning will be myeloablative: TBI 12 Gy fractionated; and cyclophophamide, 120 mg/kg (+ ATG in case of unrelated Allo-SCT). Patients aged >45 years old or with co-morbidity criteria will benefit from a reduced intensity conditioning with TBI, fractionated 8 Gy dose and fludarabine, 120 mg/m^2 (+ ATG in case of unrelated Allo-SCT). Patients HR: becarfull, SCT has to be done not earlier than end of the first blinatumomab cycle. **Central nervous system involvement** Patients with CNS+ disease at diagnosis will receive intensified IT therapy by lumbar puncture during induction and CNS irradiation will be performed after consolidation 3. No IT after CNS irradiation during maintenance.
Chemotherapy	**Induction (GRAALL2014/B)** **Prednisone** **60 mg/m^2/d** (PO) : D1-14 * **Vincristine** **2 mg/d** (IVD) : D1, D8, D15, D22 **Daunorubicin** **50 mg/m^2/d** (IV 30 min) ** : D1,D2,D3 **30 mg/m^2/d** (IV 30 min) : D15, D16 **Cyclophosphamide** **750mg/m^2/d** (IV 3h) : D1, D15 **L-Asparaginase#** **6000 UI/m^2/d** (SIV 1h) : D8, D10, D12, D20, D22, D24, D26, D28 *** **G-CSF** **5 µg/kg/d** (SC or IV) : D18 until neutrophil >1G/L **IT** **MTX + Ara-C + Depomedrol** : D1, D8 *: only from D1 to D7 if age ≥45y **: reduced to 30 mg/m^2/d if age ≥45y ***: at D8, D10, D12, D20, D22, D24 if age ≥45y . #: substituted by Erwinase® if immunization to *E coli* L-asparaginase. **Salvage** **Idarubicin** **12 mg/m^2/d** (IV 1h) : D1, D2, D3

	Aracytine	**2000 mg/m²/12h** (IV 3h)	: D1, D2, D3, D4
	G-CSF	**5 µg/kg/d** (SC or IV)	: D8 until neutrophil >1G/L
	Standard consolidation (SR patients)		
	Weekly stand-by block (0, 1 or 2 if needed)		
	VP-16	**150 mg/m²/d** (IV 1h)	: D1
	Aracytine	**30 mg/m²/12h** (SC)	: D1,D2
	Blocks S1/S4/S7 (D1-D14)		
	Aracytine	**2000 mg/m²/12h** (IV 2h)	: D1, D2
	Dexamethasone	**10 mg/12h** (IV)	: D1, D2
	G-CSF	**5 µg/kg/d** (SC or IV)	: D8 toD12
	Blocks S2/S5/S8 (D15-D28)		
	Methotrexate	**5000 mg/m²/d** (CIV 24h) *	: D15
	Vincristine	**2 mg/d** (IVD)	: D15
	6-mercaptopurin	**60 mg/m²/d** (PO)	: D15 to 21
	G-CSF	**5 µg/kg/d** (SC or IV)	: D22 to 26
	IT	**MTX + Ara-C + Depomedrol**	: D16 (H24 after start MTX)
	*: 500 mg/m² over 30 minutes, then over 23 hours and 30 minutes followed by folinic acid rescue; reduced to 3000 mg/m²/d if age ≥45y		
	Block S3/S6/S9 (D29-D35)		
	Cyclophosphamide	**500 mg/m²/d** (IV 3h)	: D29, D30
	VP-16	**75 mg/m²/d** (IV 1h)	: D29, D30
	Methotrexate	**25 mg/m²/d** (IV)	: D29
	G-CSF	**5 µg/kg/d** (SC or IV)	: D31 until neutrophil >1G/L
	IT	**MTX + Ara-C + Depomedrol**	: D29
	Late intensification (for patients who did not receive salvage after induction)		
	Prednisone	**60 mg/m²/d** (PO)	: D1 to D 14 *
	Vincristine	**2 mg/d** (IVD)	: D1, D8, D15, D22
	Daunorubicin	**30 mg/m²/d** (IV 30 min)	: D1, D2, D3, D15**, D16 **
	Cyclophosphamide	**750mg/m²/d** (IV 3h)	: D1, D15
	L-Asparaginase[##]	**6000 UI/m²/d** (SIV 1h)	: D8, D10, D12, D20, D22, D24, D26, D28 ***
	G-CSF	**5 µg/kg/d** (SC or IV)	: D18 until neutrophil >1G/L
	IT	**MTX + Ara-C + Depomedrol**	: D1, D8
	*: only D1 to D7 if age ≥45y **: D15-16 only if age <45y ***: at D8, D10, D12, D20, D22, D24 if age ≥45y [#]: substitution by Erwinase if immunization to *E coli* L-asparaginase		
	Late intensification (for patients who received salvage after induction)		
	Idarubicin	**9 mg/m²/d** (IV 1h)	: D1, D2, D3
	Aracytine	**2000 mg/m²/12h** (IV 3h)	: D1, D2, D3, D4
	G-CSF	**5 µg/kg/d** (SC or IV)	: D8 until neutrophil >1G/L
	IT	**MTX + Ara-C + Depomedrol**	: D8, D15

Maintenance therapy (2 years)

Vincristine	**2 mg** (IVD)	: D1, Month 1 to 12
Prednisone	**40 mg/m^2/d** (PO)	: D1 to D7 Month1 to 12
MTX	**25 mg/m^2/wk** (PO)	: 24 months
6-mercaptopurin	**60 mg/m^2/d** (PO)	: 24 months
IT	**MTX + Ara-C + Depomedrol**	: D1 Month 1,3,5

Blinatumomab – consolidation (HR), patients not proceeding to ASCT

begins after block S3

Blocks B4/B7 (D1-D34)

Dexamethasone	**40 mg**	**: D1, 1 h before Blina**
Blinatumomab	**28 µg/d (IVC)**	**: D1 to D28**
IT	**MTX + Ara-C + Depomedrol**	**: D1**

Blocks B5/B8 (D35-D49)

Aracytine	**2000 mg/m^2/12h** (IV 2h)	: D1, D2
Dexamethasone	**10 mg/12h** (IV)	: D1, D2
G-CSF	**5 µg/kg/d** (SC or IV)	: D8 toD12

Blocks B6/B9 (D50-D65 max)

Methotrexate	**5000 mg/m^2/d** (CIV 24h) *	: D1
Vincristine	**2 mg/d** (IVD)	: D15
6-mercaptopurin	**60 mg/m^2/d** (PO)	: D1 to D7
G-CSF	**5 µg/kg/d** (SC or IV)	: D8 to 12
IT	**MTX + Ara-C + Depomedrol**	: D2 (H24 after start MTX)

*: 500 mg/m^2 over 30 minutes, then over 23 hours and 30 minutes followed by folinic acid rescue; reduced to 3000 mg/m^2/d if age ≥45y

Late intensification (for patients who did not receive salvage after induction)

Prednisone	**60 mg/m^2/d** (PO)	: D1 to D 14 *
Vincristine	**2 mg/d** (IVD)	: D1, D8, D15, D22
Daunorubicin	**30 mg/m^2/d** (IV 30 min)	: D1, D2, D3, D15**, D16 **
Cyclophosphamide	**750mg/m^2/d** (IV 3h)	: D1, D15
L-Asparaginase$^{\#\#}$	**6000 UI/m^2/d** (SIV 1h)	: D8, D10, D12, D20, D22, D24, D26, D28 ***
G-CSF	**5 µg/kg/d** (SC or IV)	: D18 until neutrophil >1G/L
IT	**MTX + Ara-C + Depomedrol**	: D1, D8

*: only D1 to D7 if age ≥45y

**: D15-16 only if age <45y

***: at D8, D10, D12, D20, D22, D24 if age ≥45y

$^{\#}$: substitution by Erwinase if immunization to *E coli* L-asparaginase

Late intensification (for patients who received salvage after induction)

Idarubicin	**9 mg/m^2/d** (IV 1h)	: D1, D2, D3
Aracytine	**2000 mg/m^2/12h** (IV 3h)	: D1, D2, D3, D4
G-CSF	**5 µg/kg/d** (SC or IV)	: D8 until neutrophil >1G/L
IT	**MTX + Ara-C + Depomedrol**	: D8, D15

Blinatumomab-based maintenance therapy (2 years, n=24)

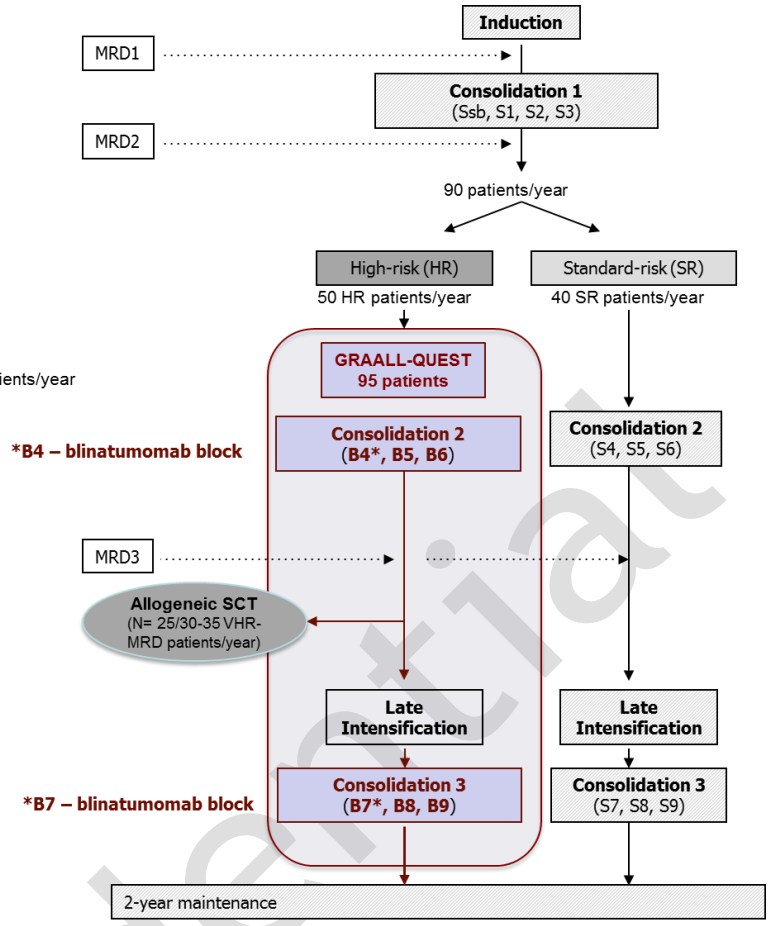
	Dexamethasone **40 mg** : D1, 1h before blinatumomab **Blinatumomab** **28 µg/d (IVC)** : D1 to D28, Month 1, 3 and 5 **Vincristine** **2 mg** (IVD) : D1, Month 2, 4, 6 to 12 **Prednisone** **40 mg/m^2/d** (PO) : D1 to D7 Month 2, 4, 6 to 12 **MTX** **25 mg/m^2/wk** (PO) : 24 months* **6-mercaptopurin** **60 mg/m^2/d** (PO) : 24 months* **IT** **MTX + Ara-C + Depomedrol** : D1 Month 1,3, 5 * except during the 4-week blinatumomab (month 1,3 and 5) **Blinatumomab – consolidation (HR), patients proceeding to ASCT** begins after block S3 **Dexamethasone** **40 mg** **: D1, 1 h before Blina** **Blinatumomab** **28 µg/d (IVC)** **: D1 to D28** **IT** **MTX + Ara-C + Depomedrol** **: D1** VHR patients with a suitable donor will receive blinatumomab continuously until allo-SCT conditioning regimen (stop 7 days before).
MRD monitoring	MRD evaluation will be performed on bone marrow aspirates at the following time-points: • MRD1: after induction or on day 1 of first consolidation • MRD2: on day 1 of second consolidation • MRD3: on day 1 of late intensification(or at pre Allo-SCT evaluation) • MRD4: on day 1 of maintenance phase (or at day 100 after Allo-SCT)
SAEs	Serious adverse events (SAEs) must be reported on the SAE page of the eCRF and declared to the sponsor immediately for each patient (Annex 9) in each participating country whatever their causality to the research.
Added risks of the research	D
Financing	PHRC
Independent surveillance committee planned	Yes

GRAALL-2014/B study
Ph-neg ALL
Front-line
18-59y

INDUCTION
CONSOLIDATION
LATE INTENSIFICATION

100 Ph-neg BCP-ALL patients per year front-line

After CR achievement:
1) 50 HR patients/year, including 30-35 VHR-MRD patients/year
2) 40 SR patients/year

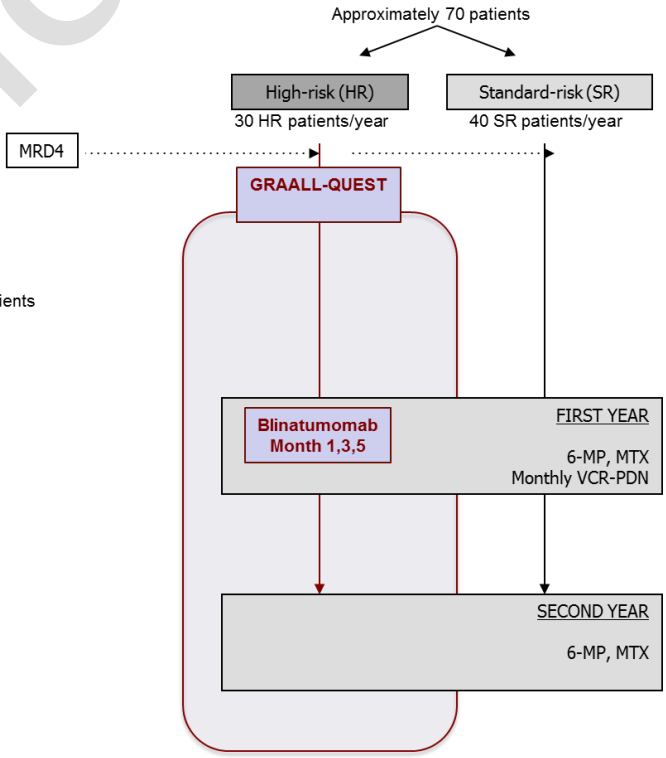


GRAALL-2014/B study
Ph-neg ALL
Front-line
18-59y

MAINTENANCE

Approximately 70 Ph-neg BCP-ALL patients per year will receive maintenance therapy

Including:
1) 30 HR patients/year, including non-transplanted VHR-MRD patients
2) 40 SR patients/year



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1 OBJECTIVES OF GRAALL-2014/B

1.1 Primary objective

- ✓ To prospectively validate the new risk model, based on MRD1 response level and KMT2A (=MLL) and IKZF1 gene status by comparing historical results of GRAALL-2005 with those of GRAALL-2014 in an identical population of patients (Ph- B lineage ALL, aged 18 to 59 years old).
- ✓ To evaluate the efficacy of blinatumomab-based consolidation and maintenance therapy in term of DFS in HR patients (GRAALL-QUEST substudy) by comparing to historical results of GRAALL-2005 in an identical population of patients with HR features (GRAALL-QUEST study).

1.2 Secondary objectives

- ✓ To appreciate the tolerance of blinatumomab-based consolidation cycles, in bridge to allo-SCT or within further consolidation and maintenance therapy,
- ✓ To evaluate MRD level, monitored by Ig-TCR,
- ✓ To evaluate cumulative incidence of relapse (CIR) and non-relapse mortality (NRM), disease-free survival (DFS), and overall survival (OS),
- ✓ To evaluate RFS, CIR, NRM, and OS after censoring at SCT in first CR.

The hypothesis is to demonstrate the non inferiority of DFS at 4 years by comparison to the historical group (<60%).

2 EVALUATION CRITERIA

2.1 Primary evaluation criterion

- ✓ Disease free survival (DFS) at 4 years, depending on the status of KMT2A (=*MLL)* and *IKZF1* genes and on MRD1 assessed after the induction cure or on D1 of consolidation 1.
- ✓ Disease-free survival (DFS) at 3 years in the GRAALL-QUEST study.

2.2 Secondaryevaluationcriteria

Secondary evaluation criteria will be as follows:

- ✓ CIR, NRM, and OS,
- ✓ DFS, CIR, NRM and OS after censoring at allo-SCT in first CR.
- ✓ MRD follow-up at different treatment times (cf infra § MRD monitoring).
- ✓ Adverse events after blinatumomab (GRAALL-QUEST).

3 DESCRIPTION OF RESEARCH METHODOLOGY

3.1 Experimental plan

GRAALL-2014/B is a multicenter open study (76 centers in France, Belgium and Switzerland). 500 patients will be included, over a previsional period of 5 years.

Each year, about 100 patients with Ph- B-lineage ALL will be able to be treated in first line in this trial. Upon achievement of complete hematologic remission (CHR) about 40 patients will be SR and 50 patients HR (including 30-35 patients VHR-MRD).

Patients will be recruited in hospital hematology departments.

3.2 Type of research

In the GRAALL-2014/B trial, the management of patients for treatment application and follow-up of the disease is as usual besides the 4 samples planned to assay anti-asparaginase antibodies, performed before induction and on day 1 of consolidation blocks S1, S3 and S4. In the hypothesis that a patient would not receive allo-SCT, a 5th sample will be collected before maintenance.

4 MODALITIES OF RECRUITMENT AND INCLUSION OF PATIENTS

Results of the various explorations performed at the time of the initial medullogram will condition the participation of patients to the GRAALL-2014/B trial.

4.1 Inclusion of patients

During the prephase and up to D1 maximum, **if needed**, investigation centers will contact the medical GRAALL coordination *via* the secretariat (Véronique LHERITIER: Tel: +33 (0)4 78 86 22 39 Fax: +33(0)4 72 66 64 40) to confirm or infirm the eligibility of the patient for the study.

Each inclusion will be performed in a centralized fashion, on line *via* the e-CRF, by secure internet connexion (CleanwebTélémédecine). During the prephase and at most on D1, each patient must be included on the trial.

As soon as the trial is implemented in a center and when the form of functions delegation (FFD) is filled and signed by all investigator team participants to the trial in the center, the monitoring CRA will forward the request for center opening to Télémédecine.Télémédecine will send by e-mail only, a login and password to each participant (according to their profile) in the center. This e-mail will also contain the internet link allowing to login into the e-CRF.

4.2 Identification of patients for on line data collection

Within this research, subjects will be identified for data collection as follows:

Center n° (3 digits) – selection order number of the patient in the trial (4 digits) – name initial – surname initial ➔|__|__|__|-|__|__|__|__|-|__|-|__|.

This reference will be unique and retained all along the trial.

As the Swiss regulations don't allow the disclosure of the patients' initials, all Swiss patients will have the following dummy initials: "X" for the name initial and "X" for the surname initial.

4.3 Identification of patients for samples shipping

Centralized research samples (*GRAALLThèque and anti-asparaginase antibodies assay)* will be identified as for one line data collection.

Centralized samples, collected within the usual follow-up of patients (*oncogenetic evaluation at diagnosis, MRD…)* will be identified by the patient's name without any mention relative to this biomedical research, according to the center's habits.

According to Swiss regulations the disclosure of the patient's name even for usual follow up assessments which have to be done outside of Switzerland according to the protocol (oncogenetic evaluation at diagnosis, asparaginase activity assessments,…) is nevertheless not allowed. Therefore all Swiss sites will code their patients' data before receiving the selection order number by AP-HP as follows:

- Center number
- Selection order number of the patient in the trial (if applicable)
- Hospital chart identifier,

- Birth year

An adequate liaison form will be used to accompany the shipping of tube(s) (see Annexes 1 and 5).

5 INCLUSION CRITERIA

Patient:

1. Whose blood and bone marrow explorations have been completed before the steroids prephase
2. Aged 18 to 59 years old with not previously treated B-lineage-ALL (including intrathecal injections) newly diagnosed according to the WHO 2008 definition with $\geq$ 20% bone marrow blasts
3. Whose karyotype shows no t(9;22) and/or the absence in molecular biology of BCR-ABL marker
4. With ECOG $\leq$ 3
5. With or without central nervous system (CNS) or testis involvement
6. Without other evolving cancer (except basal cell carcinoma of the skin or "in situ" carcinoma of the cervix) or its treatment should be finished at least since 6 months
7. Having signed a written informed consent
8. With efficient contraception for women of childbearing age (excluding estrogens and IUS)
9. With health insurance coverage
10. Who have received or being receiving the steroid prephase

Secondary ALL (antecedent of chemo- or radio-therapy) can be included.

6 NON INCLUSION CRITERIA

Patient:

1. With lymphoblastic lymphoma and bone marrow blasts < 20%, Burkitt-type ALL or with antecedents of CML or other myeloproliferative neoplasm
2. With contra-indication of anthracyclines or any other general or visceral contra-indication to intensive therapy except if considered related to the ALL:
   a. AST (SGOT) or ALT (SGPT) > 5 x ULN
   b. Total bilirubin ≥ 2.5 x ULN
   c. Creatinine > 1.5 x ULN or creatinine clearance <50 mL/mn
3. Myocardial infarction within 6 months prior to inclusion in the trial, cardiomyopathy (NYHA grade III or IV), LEVF < 50% and or RF < 30%,
4. HIV, HTLV-I or HCV seropositivity or chronic HBV hepatitis (HbsAg-positive).
5. Pregnant (β-HCG positive) or nursing woman
6. Not able to bear with the procedures or the frequency of visits planned in the trial
7. Unable to consent, under tutelage or curatorship, or judiciary safeguard.

8. Women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least three months thereafter. Patients not willing to ensure not to beget a child during participation in the study and at least three months there after

9. Treated with any other investigational agent or participation in another trial within 30 days prior to entering this study

7 GENERAL RULES FOR THE WHOLE TREATMENT

✓ Have a central venous access

✓ Counsel on the mode of contraception an on the necessity of protected sexual intercourse in order to prevent any toxic exposure for the partner. Birth control methods acceptable during the treatment GRAALL are progestogen-only contraception (progestogen pills or subdermal implant) and mechanical contraceptives (condoms, diaphragm…). Continuous progestogen contraception is frequently proposed to avoid the risk of bleeding during intensive chemotherapy phases. The use of estrogen is contraindicated until the onset of maintenance phase, because of the increased risk of venous thrombosis.

✓ It is recommended to use full weight-based chemotherapy doses in the treatment of obese patients (without capping body-surface area at $2m^2$)[55, 56, 57] However, vincristine is capped at a maximum dose of 2.0 mg.

✓ Prevent *Pneumocystis* infection with monthly Bactrim® or Pentacarinat® (do not prescribe folinic acid in association with Bactrim® during maintenance in order not to decrease the efficacy of methotrexate).

About chemotherapy

✓ In case of neuropathy ≥ 3 or severe ileus related to vincristine, replace by vindesine (4 mg TD/injection) or other treatment according to investigator judgment.

✓ Administration of Purinethol® (6-MP) at bedtime, at distance from dairy products consumption

✓ Intrathecal injections: total volume at least 6 mL; ventral decubitus 30 min (Annex 3)

About corticosteroids

✓ Antibioprophylaxis as soon as neutropenia becomes < 0.5 G/L in patients receiving or having received corticotherapy (broad spectrum antibiotherapy active on GNB germs, including *Pseudomonas aeruginosa*, and GPB germs according to each center's policy). Fluoroquinolones should not be given alone because of the inconstant sensitivity of *P aeruginosa* and of the reduced efficacy of Endoxan[58].

Fungal prophylaxis

✓ This is left toeach center's policy.It is suggested to avoid azoles associated to VCR (neurological toxicity) and L-Asparaginase (liver toxicity).

About L-Asparaginase

[55]Griggs, *et al,* J Clin Oncol, 2012; 30(13):1553-61

[56]Gurney*et al,* J Clin Oncol, 2007; 25(30):4703-4

[57]Sparreboom*et al,* J Clin Oncol, 2007; 25(30):4707-13

[58]Carlens*et al*,Clin Transplant, 1998; 12(2):84-92

✓ It is recommended to stop estroprogestatives for female patients and replace them by continuous progestatives,

✓ Anaphylactoid reaction (grade ≥ 2) **must be reported as SAE**,

✓ Prevention of thromboembolic events:

- Anti-thrombin (AT) levels should be assayed daily or every second day, from D8 up to 48h after the end of induction or late intensification, without interrupting between D12 and D20, in order to maintain AT levels over 60% constantly, since the median date of occurrence of brain thrombosis was D17 in the GRAALL-2005 trial,
- Substitutive AT treatment (not FFP) is detailed in Annex 4 and Annex 6 ; substitution with fibrinogen is not recommended,
- Prophylactic heparin is recommended.

Specific attention should be given to several issues differing from GRAALL-2005 (Annex 6):

✓ Age-adapted chemotherapy for each cure

✓ Monitoring of anti-asparaginase antibodies and of asparaginase activity,

✓ More regular monitoring of AT,

✓ CSF analyses modalities.

8 PREPHASE

From D-7 to D-1, maximum D-10 to D-1

PREDNISONE 60 mg/m², PO **(or methylprednisolone IV 48 mg/m²)**	D-7 to D-1 (maximum D-10)
SIMPLE IT (N°0) only with MTX IT 15 mg total dose	During the first 3 prephase days **whatever the peripheral blast cells count.**

Note: CNS lesions are detailed in § 6.2 PART I.

CAREFUL !

Nor cytarabine nor steroids in this IT

This prephase is common to all ALL patients and belongs to the usual management of this disease. It is performed as soon as the diagnosis is obtained and the initial examinations have been performed.

8.1 Definition of corticosensitivity

Whatever the day of corticotherapy onset, corticosensitivity assessment should be performed seven days after the initiation of corticotherapy.

Corticosensitivity assessment requires a detailed blood differential before prephase onset and on D1. It is reminded that corticosensitivity is always assessable **whatever the level of peripheral blasts since it is defined by a value of less than 1 G/L blast cells.**

In case of extramedullary location, especially in lymph nodes, a significant decrease of the tumor burden must be associated to biological criteria. Corticosensitivity includes ≥75% decrease of extra-medullary locations.

8.2 corticoprogression

8.2.1 Definition of corticoprogression

For patients whose peripheral blast count increases during the prephase, the following rules apply:

- ✓ corticoprogression must be concluded after at least 48h of Prednisone and IT MTX
- ✓ if WBC < 100 G/L at diagnosis: at least 50% WBC increase compared to diagnosis and > 100 G/L
- ✓ if WBC > 100 G/L at diagnosis: any WBC increase after at least 48h prephase
- ✓ in case of tumor syndrome, any tumor size progression after 48h of prephase is corticoprogression.

8.2.2 Management of corticoprogression

✓ Chemotherapy is initiated,

✓ The patient remains in the trial,

✓ The patient is scored as corticoresistant.

TREATMENT GIVEN TO PATIENTS ENROLLED IN RESEARCH

9 INDUCTION

The investigator collects, at the latest before initiating induction, the free informed written consent of the person enrolled in research. The results of immunophenotype and molecular biology must be anonymized and faxed at the GRAALL secretariat to Véronique LHERITIER (fax: +33 (0)4.72.66.64.40) for central review and validation by the biology coordinators of the GRAALL group.

Induction can only start if the patient has been enrolled in GRAALL-2014/B (cf § 4 PART I).

Induction begins after evaluating corticosensitivity on D1

This phase must be initiated immediately after the prephase, whatever the hematologic situation (D1 follows D-1; there is no D0).

A simple medullogram must be performed on D8. Search for a donor can be initiated for all patients with medullary infiltration at this stage. Indeed, many of them will end up classified as VHR.

	18 – 44 years old	**45 - 59 years old**
PREDNISONE 60 mg/m^2, PO (or methylprednisolone IV 48 mg/m^2)	D1 to D14	D1 to D7
DAUNORUBICIN, over 30 mn	50 mg/m^2, slow IV D1 to D3 30 mg/m^2, slow IV D15 to D16	30 mg/m^2, slow IV D1 to D3 30 mg/m^2 , slow IV D15 to D16
VINCRISTINE 2 mg total dose slow IV	D1, D8, D15 and D22	
CYCLOPHOSPHAMIDE** 750 mg/m^2, IV, over 3h	D1 and D15	
L-ASPARAGINASE 6000 UI/m^2, IV, over1 h (Annex 4)	D8, D10, D12* D20, D22, D24, D26 and D28	D8, D10, D12* D20, D22 and D24
G-CSF 5 µg/kg/d, SC or IV	J18 until ANC > 1G/L	
TRIPLE IT(N°1 and 2) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®*** IT 40 mg total dose*	D1 and D8	

* D8, D10 and D12 L-Asparaginase injections must not be performed for CNS+ patients in order to allow for curative IT. Moreover, 2 injections (D26 and D28) must be added for patients ≥ 45 years old to obtain a total of 5 injections of L-Asparaginase.

** Use of mesna (Uromitexan®) to prevent cyclophosphamide toxicity is allowed (dosage according to investigator discretion).).

*** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence

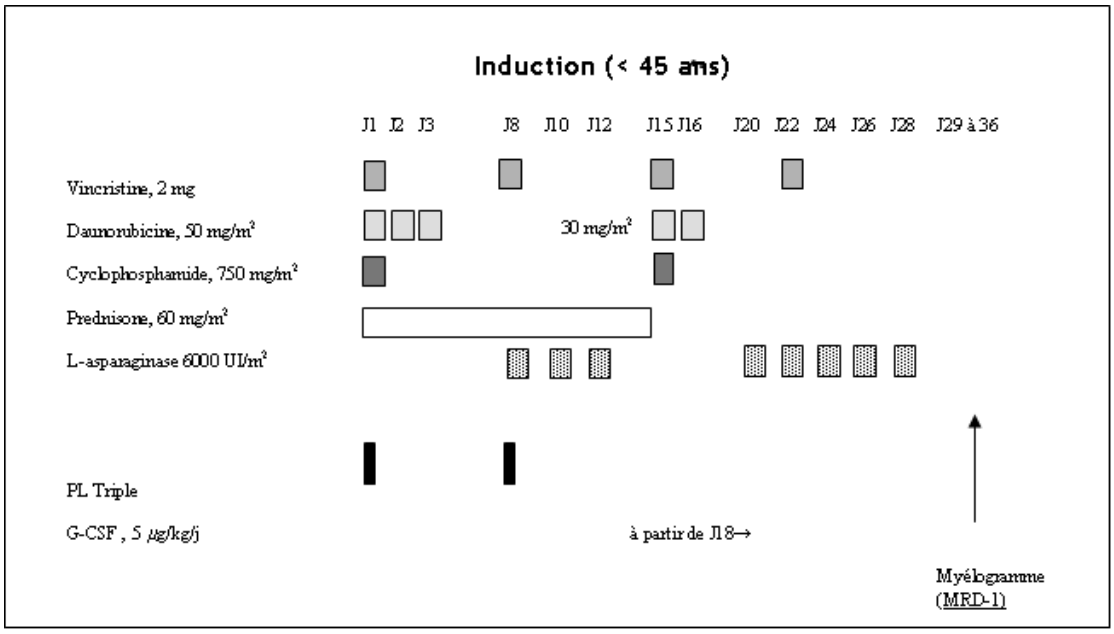
Of note, CNS lesions are detailed in § 6.2 PART I.

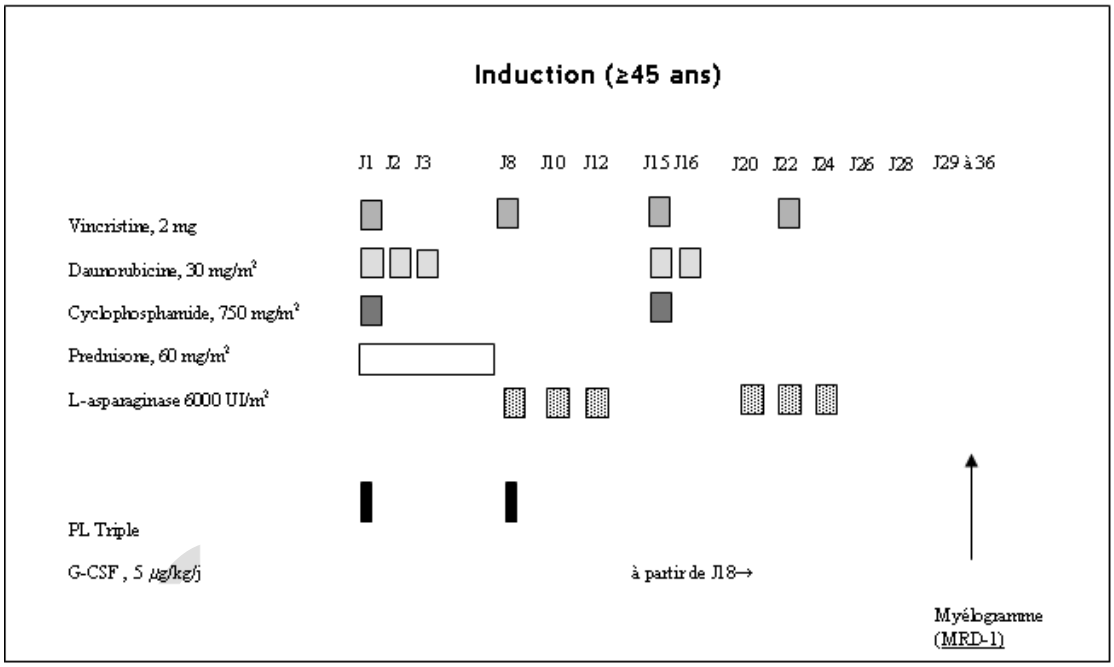
ⓘ **Age-adaptation of induction**. The duration of prednisone administration, doses of daunorubicin and L-asparaginase injections numbers are age-adapted (18-44 years old *vs* 45-59 years old).

Monitoring of asparaginase:

1. Assay of anti-asparaginase antibodies: a reference sample must be collected at latest on D1 of chemotherapy (cf. Annex 5).
2. Primary monitoring of asparaginase activity and of ammoniemia (Annex 5) has to be done **48h after the 3rd injection** (theoretically D14) and. Secondary monitoring has to be done **48 h after the 6th injection** (theoretically D26). For all patients <45 years old, sample collection must be performed immediately before the 7th injection.
3. Anti-thrombin (AT) levels should be assayed daily or every second day, from D8 up to 48h after the end of induction or late intensification, without interrupting between D12 and D20, in order to maintain AT levels over 60% constantly, since the median date of occurrence of brain thrombosis was D17 in the GRAALL-2005 trial

NB: Rules for kidrolase/erwinase switch are in annex 4





9.1 Hematological evaluation of the induction

9.1.1 Bone marrow

- ✓ Post-induction bone marrow examination must be performed as soon as the level of ANC reaches 1 G/L **AND** that of platelets 100 G/L. **If by D35** these levels have not been reached, bone marrow then becomes **MANDATORY**.
- ✓ **The evaluation of post-induction MRD (MRD1) is performed at that time, on BONE MARROW, before initiation of the first consolidation block.**

The response to induction therapy will be assessed according to **International Working Group Criteria**, summarized in part I paragraph 7.

9.1.2 Other sample

- ✓ A blood sample (5mL on EDTA) must be shipped to the GRAALLThèque.

9.2 Salvage

In case of induction failure, a salvage cure is proposed, whatever the patient's age. It can be initiated immediately after the bone marrow evaluation of induction completion.

Patients who failed induction are considered High Risk (HR) and become candidates for other biomedical research. Only survival will be collected for this trial. VHR patients will be liable to receive allo-SCT in first complete remission.

IDARUBICIN 12 mg/m²/d, IV (1h)	D1 to D3
CYTARABINE 2000 mg/m²/12h, IV (3h)	D1 to D4 (or 8 perfusions over 4 days)
G-CSF 5 µg/kg/d, SC or IV (or pegylated G-CSF 6 mg, SC on D8)	D8 until ANC > 1G/L

Although salvaged patients are de facto considered high risk, MRD1 will be evaluated after salvage (MRD1 Bis), before consolidation.

9.3 Reminder- classification of high risk (HR) B-lineage ALL

After induction, HR patients are identified as having:

IKZF1 gene deletion (except whole gene deletion or monosomy 7)

and/or

***KMT2A (=MLL*) gene rearrangement, (t(4;11) *KMT2A-AFF1* (= *MLL-AF4*) fusion or other**

and/or

MRD1 ≥ 10^{-4} (including non obtention of CR in 1 cure)

10 CONSOLIDATION N°1

Consolidation has to be initiated between D29 and D35 **AT THE LATEST** (and 24h after the last administration of G-CSF). Depending on the patient's condition, it begins by one or two stand-by blocks or by the S1 block.

10.1 Stand-by blocks

Once CR is reached, 1 or 2 stand-by blocks may be prescribed, depending on patient condition. The objectives are to allow recovery from potential toxicities of induction, notably affecting the liver, not to modify the order of consolidation blocks, and to respect dose/intensity.

ETOPOSIDE (VP16) 150 mg/m²/d, IV (over 1h)	D1

CYTARABINE 30 mg/m^2/12h, SC	D1 to D2 (or 4 injections over 2 days)

ⓘ **If stand-by blocks are decided upon, it is recommended to initiate the first one as soon as CR is reached.** The second one begins on D8 of the first.

10.2 Consolidation scheme n°1

Consolidation scheme n°1 is ongoing with three « standard » blocks of cytarabine (S1), methotrexate (S2) and cyclophosphamide (S3). **Of note, compared to GRAALL-2003 and 2005 trials** (Annex 6)**:**

✓ **L-Asparaginase will no longer be given during those blocks in order to minimize the risk of immunization,**

✓ **Methotrexate dose is increased to 5000 mg/m² in patients less than 45 years old,**

✓ **An additional IT occurs during the S2 block.**

ⓘ Between blocks intervals. The S1 block is initiated on D8 of stand-by block n°1 or n°2 if the latter were deemed necessary. Planned intervals between each block are strictly of two weeks, whatever the blood parameters.

ⓘ **Biological criteria to fulfill before S1 and S2 blocks:**

✓ ALAT (SGPT or TGP) < 5 x ULN,

✓ Creatinine clearance ≥ 60 mL/mn.

Whenever these biological criteria are not met before each block, the order of blocks is not modified and it is postponed until all criteria are met.

From S1 block on, patients are monitored for the investigation of anti-Asparaginase antibodies on D1 of blocks S1, S3 and S4 (Annex 5)

S1 Block – AraC

Block S1 – AraC (D1 to D14)	Whatever the patient's age
CYTARABINE 2000 mg/m^2/12h, IV (2h)	D1 and D2 (or 4 perfusions over 2 days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (or 40 mg over 2 days)
G-CSF 5 µg/kg/d, SC or IV	D8 to D12
ⓘ Remember to assay anti-Asparaginase antibodies on D1 (Annex 5)	

S2 Block – MTX

Block S2 – MTX (D15 to D28)	18 - 44 years old	45- 59 years old
VINCRISTINE 2 mg total dose slow IV	D1	D1
METHOTREXATE, IV continuous over 24 h	5000 mg/m² on D1	3000 mg/m² on D1
500 mg/m² CIV over 30 minutes then remaining dose (4500 mg/m² or 2500 mg/m²) CIV over 23h30	Rescue by folinic acid (Annex 7)	
6 – MERCAPTOPURIN* 60 mg/m², PO	D1 to D7	D1 to D7
G-CSF 5 µg/kg/d, SC or IV	D8 to D12	D8 to D12
TRIPLE IT (N°3) including *Methotrexate IT 15 mg total dose* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D2, H24 of methotrexate initiation	

* at bedtime, at distance from dairy products consumption

**Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

S3 block – CPM

Block S3 –CPM (D29 to D35)	Whatever the patient's age
METHOTREXATE 25 mg/m^2/IV (30 mn)	D1
CYCLOPHOSPHAMIDE 500 mg/m², IV (3h **mandatory**)	D1 and D2
ETOPOSIDE (VP16) 75 mg/m², IV (1h)	D1 and D2
G-CSF 5 µg/kg/d, SC or IV	D3 until ANC > 1 G/L
TRIPLE IT (N°4) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D1
ⓘ Remember to assay anti-Asparaginase antibodies on D1 (Annex 5)	

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

11 « STANDARD » CONSOLIDATION N°2

For standard risk (SR) patients or HR patients unable to be included in other biomedical research, consolidation n°2 (second series of 3 blocks) is initiated after hematologic recovery defined by ANC > 1 G/L and platelets > 100 G/L.

Consolidation n°2 includes the same 3 « standard » blocks as consolidation n°1: cytarabine (S4 identical to S1), methotrexate (S5 identical to S2) and cyclophosphamide (S6 identical to S3).

The medullogram for evaluation of MRD2 post-consolidation n°1 must be performed before initiating **D1 of block S4**. It is essential for patient stratification in the VHR group which determines the indication of allograft.

Evaluation of post-consolidation n°1 MRD (MRD2) is performed at this time, on BONE MARROW, before initiating S4 consolidation block.

ⓘ Planned intervals between each block are of strictly 2 weeks, whatever the blood parameters.

ⓘ **Biological criteria to fulfill before S4 and S5 blocks:**

✓ ALAT (SGPT or TGP) < 5 x ULN,

✓ Creatinine clearance ≥ 60 mL/mn.

Whenever these biological criteria are not met, the order of blocks is not modified and it is postponed until all criteria are met.

S4 block- AraC

Block S4 – AraC (D1 to D14)	**Whatever the patient's age**
CYTARABINE 2000 mg/m^2/12h, IV (2h)	D1 and D2 (or 4 perfusions over 2 days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (or 40 mg over 2 days)
G-CSF 5 µg/kg/d, SC or IV	D8 to D12
ⓘ Remember to assay anti-Asparaginase antibodies on D1 of S4 block (Annex 5)	

S5 block – MTX

Block S5 – MTX(D15 to D28)	18 - 44 years old	45- 59 years old
VINCRISTINE 2 mg total dose SIV	D1	D1
METHOTREXATE, IV continuous over 24h	5000 mg/m² on D1	3000 mg/m² on D1
500 mg/m² CIV over 30 minutes then the remaining (4500 mg/m² or 2500 mg/m² CIV) over 23h30	Salvage with folinic acid (Annex 7)	
6 – MERCAPTOPURIN* 60 mg/m², PO	D1 to D7	D1 to D7
G-CSF 5 µg/kg/d, SC or IV	D8 to D12	D8 to D12
TRIPLE IT(N°5) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol® IT** 40 mg total dose*	D2, H24 of methotrexate initiation	

* at bedtime, at distance from dairy products consumption

** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

S6 block – CPM

Block S6 –CPM(D29 toD35)	Whatever the patient's age
METHOTREXATE 25 mg/m²/IV (30 mn)	D1
CYCLOPHOSPHAMIDE 500 mg/m², IV (**3h mandatory**)	D1 and D2
ETOPOSIDE (VP16) 75 mg/m², IV (1h)	D1 and D2
G-CSF 5 µg/kg/d, SC or IV	D3 until ANC > 1 G/L
TRIPLE IT (N°6) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D1

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

12 LATE INTENSIFICATION

12.1 ALL not requiring salvage cure

This applies to all patients without an indication of allo-SCT in CR1 who did not require salvage therapy to reach CR1. Late intensification begins one week after hematological reconstitution following the S6 block of consolidation n°2 (ANC >1 G/L and platelets >100 G/L) providing ALAT are < 2.5 x ULN and creatinine clearance ≥ 60 mL/mn.

Pre-intensification MRD3 is performed on BONE MARROW just before late intensification.

It is has no decisional value.

Late intensification follows the same regimen as induction except:

✓ **daily DNR dose of D1-D3 is 30 mg/m²/d instead of 50 mg/m²/d for patients <45 years old**

✓**age-related dose adaptation at and over 45 years of age,**

✓**Introduction of an alternative to *E Coli* Asparaginase for immunized patients (or clinically allergic without antibodies assessment)*.**

* In case of immunization to L-Asparaginase, substitution by *Erwiniachrysanthemi* (ERWINASE®) **Asparaginase** will be performed at a dosage of 25000 UI/m^2 (IV 1h) according to Annex 4.

	18 - 44 years old	**45 - 59 years old**
PREDNISONE 60 mg/m^2, PO (or Methylprednisolone IV 48 mg/m^2)	D1 to D14	D1 to D7
DAUNORUBICIN, 30 mg/m^2,SIV over 30 mn	D1 to D3 D15 and D16	D1 to D3
VINCRISTINE 2 mg total dose SIV	D1, D8, D15 and D22	
CYCLOPHOSPHAMIDE* 750 mg/m^2, IV over 3h	D1 and D15	
L-ASPARAGINASE 6000 UI/m^2, IV, over 1 h (Annex 4) Or, if allergic reaction or positive anti-asparaginase antibodies: ERWINASE 25000 UI/m^2, IV over 1h at the same dates as Asparaginase	D8, D10, D12, D20, D22, D24, D26 and D28	D8, D10, D12, D20, D22 and D24
G-CSF 5 µg/kg/d, SC or IV	D18 until ANC > 1G/L	
TRIPLE IT(N°7 and 8) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D1 and D8	

* Use of mesna (Uromitexan®) to prevent cyclophosphamide toxicity is allowed (dosage according to investigator discretion).
** Other corticoids can be used instead of Depo-Medrol® (dosage according tothe sites).

ⓘ **Age-related adaptation.** Prednisone administration time, doses of daunorubicin and L-Asparaginase injections numbers are age-adapted. Of note, daunorubicin will be given on days 15 and 16 only for patients < 45 years of age.

1. Primary monitoring of asparaginase activity and of ammoniemia (Annex 5) has to be done **48h after the 3rd injection** (theoretically D14) and. Secondary monitoring has to be done **48 h after the 6th injection** (theoretically D26). For all patients <45 years old, sample collection must be performed immediately before the 7th injection.
2. AT levels should be assayed daily or every second day, from D8 up to 48h after the end of induction or late intensification, without interrupting between D12 and D20, in order to maintain AT levels over 60% constantly, since the median date of occurrence of brain thrombosis was D17 in the GRAALL-2005 trialNB: Rules for kidrolase/erwinase switch are in Annex 4

12.2 ALL with salvage cure

Patients who reached CR1 after salvage therapy with idarubicin + aracytine will receive the same late intensification.

Pre-intensification molecular evaluation (MRD3) will be performed on the BONE MARROW just before late intensification. It has no decisional value.

IDARUBICIN 9 mg/m², IV (1h)	D1 to D3
CYTARABINE 2000 mg/m²/12h, IV (2h)	D1 to D4 (or 8 perfusions over 4 days)
G-CSF 5 µg/kg/d, SC or IV (or Neulasta)	D8 until ANC > 1G/L
TRIPLE IT (N°7 and 8) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D8 and D15

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

13 CONSOLIDATION N°3

Late intensification, whether or not patients required salvage therapy to reach CR1, is followed by consolidation n°3 including again 3 blocks. The latter repeat the AraC, MTX and CPM blocks of consolidations 1 and 2 (S7 identical to S1 and S4, S8 identical to S2 and S5, S9 identical to S3 and S6).**These blocks are not followed by prophylactic CNS irradiation.**

This sequence is to be initiated as soon as hematologic recovery is reached after late intensification (ANC >1G/L and platelets>100 G/L).

ⓘ Planned intervals between each block are strictly of two weeks, whatever the blood parameters.

ⓘ **Biological criteria to fulfill before S7 and S8 blocks:**

✓ ALAT (SGPT or TGP) < 5 x ULN,

✓Creatinine clearance ≥ 60 mL/mn.

Whenever these biological criteria are not met, the order of blocks is not modified and it is postponed until all criteria are met.

S7 block – AraC

Block S7 – AraC(D1 to D14)	**Whatever the patient's age**
CYTARABINE 2000 mg/m^2/12h, IV (2h)	D1 and D2 (or 4 perfusions over 2 days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (or 40 mg over 2 days)
G-CSF 5 µg/kg/d, SC or IV	D8 to D12

S8 block – MTX

Block S8 – MTX(D15 to D28)	**18 - 44 years old**	**45 - 59 years old**
VINCRISTINE 2 mg total dose SIV	D1	D1
METHOTREXATE, IV continuous over 24h **500 mg/m² CIV over 30 minutes then the remaining (4500 mg/m² or 2500 mg/m² CIV) over 23h30**	5000 mg/m² on D1	3000 mg/m²on D1
	Rescue by folinic acid (Annex 7)	
6 – MERCAPTOPURIN* 60 mg/m², PO	D1 to D7	D1 to D7
G-CSF 5 µg/kg/d, SC or IV	D8 to D12	D8 to D12
TRIPLE IT(N°9) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D2, 24h after methotrexate initiation	

* at bedtime, at distance from dairy products consumption

** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence)

S9 block – CPM

Block S9 –CPM(D29 to D35)	Whatever the patient's age
METHOTREXATE 25 mg/m²/IV (30 mn)	D1
CYCLOPHOSPHAMIDE 500 mg/m², IV (3h **mandatory**)	D1 and D2
ETOPOSIDE (VP16) 75 mg/m², IV (1h**)**	D1 and D2
G-CSF 5 µg/kg/D, SC or IV	D3 until ANC > 1 G/L
TRIPLE IT(N°10) including *Methotrexate IT 15 mg total dose ,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D1 **Do not administer to patients with CNS involvement and no SCT (irradiation to follow)**

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

14 MAINTENANCE

The whole duration of maintenance therapy is 24 months. Maintenance therapy is initiated after recovering from consolidation n°3 (ANC >1 G/L and platelets > 100 G/L).

Assessment of MRD4 is performed on BONE MARROW before initiating maintenance therapy. It has no decisional value.

A search for anti-Asparaginase antibodies on D1 of month 1 must be performed (Annex 5)

It is a classical maintenance regimen based on the association of 6-mercaptopurin + MTX, with monthly reinductions of vincristine and prednisone during the first year.

No G-CSF is given during this phase.

KEEP IN MIND RECOMMENDATIONS ENTITLED

«GENERAL RULES FOR THE WHOLE TREATMENT ».

(§ 7 of part II)

14.1 First maintenance year: 12 monthly reinductions

Total duration of maintenance is 2 years. During the first year, 12 reinductions should be given, each cycle duration being approximatively 4 weeks.

	Month 1 to Month 12
PREDNISONE 40 mg/m²/d, PO	D1 to D7
VINCRISTINE 2 mg total dose, IVD	D1
6-MERCAPTOPURIN 60 mg/m², PO at bedtime at distance from dairy products consumptionat distance from dairy products consumption	Every day, no interruption while reinduction Scrupulous dose adaptation (Annex 2).
METHOTREXATE 25 mg/m², PO	Once per week Scrupulous dose adaptation (Annex 2).
TRIPLE IT (N°11, 12, 13) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D1 of Month 1, 3, 5 only in CNS1/2

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence)

These monthly reinductions apply up to a total of **12 Vincristine injections**. They can be rescheduled if toxicity criteria recommend transient interruption of therapy (Annex 2).

Monthly administration of Bactrim® or Pentacarinat® is strongly recommended during maintenance (no folinic acid together with Bactrim® in order not to lessen MTX efficacy).

CNS-3 patients should not receive IT injections after CNS irradiation during maintenance.

14.2 Second maintenance year

Maintenance therapy is given until second anniversary of maintenance starting date.

	Month 13 to Month 24
6-MERCAPTOPURIN 60 mg/m², PO at bedtime at distance from dairy products consumption	Daily Scrupulous dose adaptation (Annex 2).
METHOTREXATE 25 mg/m², PO	Weekly Scrupulous dose adaptation (Annex 2).

Monthly administration of Bactrim® or Pentacarinat® is strongly recommended during maintenance (no folinic acid together with Bactrim® in order not to lessen MTX efficacy).

15 CNS PROPHYLAXIS FOR UNTRANSPLANTED PATIENTS

CNS prophylaxis includes 13 triple IT + 1 simple IT, and high dose MTX.

No prophylactic CNS irradiation is proposed.

Note: in case of initial testis involvement, the medical GRAALL coordination *via* the secretariat (Véronique LHERITIER: Tel: +33 (0)4 78 86 22 39 Fax: +33(0)4 72 66 64 40) should be contacted to decide on the local irradiation or irradiation complement to prescribe.

16 MANAGEMENT OF CNS INVOLVEMENT

In case of initial CNS involvement (CNS-3 and late CNS-2/3, § 6.2), patients will receive 1 simple IT and 12 triple IT between the prephase, induction and first consolidation.

Patients without Allo-SCT will moreover receive 6 triple IT between consolidation N°2, late intensification and consolidation N°3, then CNS irradiation (24 Gy).

CNS-3 patients should not receive IT injections after CNS irradiation during maintenance.

Patients with Allo-SCT will receive CNS irradiation (15 Gy) at the end of consolidation n°1.

17 ALLO-SCT IN CR-1

17.1 Criteria leading HR patients to allo-SCT (VHR group)

All patients classified as HR (High Risk) are not necessarily eligible for allo-SCT in CR1. The decision of allo-SCT in CR1 is only based on the MRD response (MRD1 and MRD2). IKZF1 gene deletion or KMT2A (=MLL) gene rearrangement are not by themselves allo-SCT indications.

For this, a very high risk (VHR) group is defined according to MRD1 and MRD2:

MRD1 ≥ 10^{-3} (including non-obtention of CR in 1 cure)
and/or
MRD2 ≥ 10^{-4}

Only VHR will be eligible to allo-SCT in CR1.

Patients will receive Allo-SCT, after age-adapted conditioning, with a geno-identical unrelated donor 10/10 or 9/10. Allo-SCT will be performed at the end of consolidation n°2. Allo-SCT indication being possibly identified at a later stage (MRD2), it is recommended to initiate early the search for a donor. As mentioned previously, the results of D8 medullogram may be used to initiate this search.

17.2 Allo-sct in patients < 45 years old

✓ TBI: 12 Gy in 6 fractions with pulmonary protection above 8 Gy
✓ Cyclophosphamide: 60 mg/kg per day for 2 days

✓+/- ATG in case of unrelated 10/10 or 9/10 graft (thymoglobuline or ATG Frésenius) according to centers' habits.

GVH prophylaxis will associate ciclosporine A and MTX on D1, D3, D6 (+/- D11). A bone marrow graft will be preferred.

Patients with Allo-SCT will receive CNS irradiation (15 Gy) at the end of consolidation n°1 before TBI.

Assessment of MRD4 is performed on BONE MARROW at D100 post Allo-SCT.

It has no decisional value.

17.3 Allo-sct in patients aged from 45 to 59 years old

Allo-SCT after RTC associating TBI 8 Gy + Fluda according to Bornhäuser Lancet Oncology 2012.

✓ TBI: 8 Gy in 4 fractions (D-3 and D-2) or 6 Gy in one fraction.

✓ Fludarabine: 30 mg/m^2/d x 4d from D-6 to D-3

✓ +/- ATG in case of unrelated 10/10 or 9/10 graft (thymoglobuline or ATG Frésenius) according to centers' habits.

GVH prophylaxis will associate ciclosporine A and MTX on D1, D3, D6, D11). A graft of peripheral stem cells will be preferred.

Patients with Allo-SCT will receive CNS irradiation (15 Gy) at the end of consolidation n°1 before TBI.

Assessment of MRD4 is performed on BONE MARROW at D100 post Allo-SCT.

It has no decisional value.

17.4 Pre-allo-sct interphase blocks (optional)

Alternating blocks as delivered during consolidations 1 and 2 should not be retained.

If needed, it is possible to perform interphase waiting blocks between consolidation n°2 and allo-SCT. These blocks rely on alternating cytarabine/dexamethasone and Vincristine/6MP + Methotrexate according to the scheme below, for up to 4 interphase blocks. Hematological recovery should be waited upon between each of these blocks.

Waiting blocks 1 and 3

Block S7 – AraC (D1 toD14)	**Whatever the patient's age**
CYTARABINE 1000 mg/m^2/12h, IV (2h)	D1 andD2 (4 perfusions over 2 days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (40 mg over 2 days)
G-CSF 5 µg/kg/d, SC or IV	D8 toD12

Waiting blocks 2 and 4

Block S8 – MTX(D15 toD28)	Whatever the patient's age
VINCRISTINE 2 mg dose totale SIV	D1
METHOTREXATE, IV continuous over 24 hours	1500 mg/m² at D1
	Salvage by folinic acid (Annex 7)
6 – MERCAPTOPURIN* 60 mg/m², PO	D1 to D7
G-CSF 5 µg/kg/d, SC or IV	D8 to D12

* at bedtime, at distance from dairy products consumption

HIGH RISK PATIENTS

GRAALL-QUEST SUBSTUDY

Patients with high risk B-ALL will be included as early as at second consolidation, in a phase II study appreciating the interest of blinatumomab.

Inclusion in GRAALL-QUEST requires that the patient fulfills specific additional inclusion and non-inclusion criteria listed below

Inclusion must occur at the end of consolidation n°1 as soon as informations about MRD1 and of the oncogenetic profile (*IKZF1*, *MLL*) are available.

Patients included in GRAALL-QUEST will retain the identification provided at inclusion in GRAALL-2014/B.

Patients having besides an indication of Allo-SCT will receive continuous blinatumomab infusion until transplantation.

18 EXPERIMENTAL DRUG PRESCRIBED OUTSIDE MA AND PROVIDED BY THE SPONSOR

Blinatumomab (BLINCYTO®) is provided in 4 mL single-use glass injection vials as a sterile, preservation-free, lyophilized powder for reconstitution and administration by IV infusion. Blinatumomab comes with an IV Solution Stabilizer supplied in 10 mL single-use glass injection vials as a sterile, preservative-free, liquid concentrate. It has a specific contra-labelling in 4 languages (French, German, Dutch, Italian) with regulatory mentions for clinical trials.

Blinatumomab and IV Solution Stabilizer are shipped at 2°C to 8°C in a qualified shipper and should be immediately stored in a refrigerator maintained at 5°C +/- 3°C.

The drug's administration is detailed in the relevant substudy.

19 INCLUSION AND NON INCLUSION CRITERIA

19.1 Inclusion criteria

Following criteria should all be checked:

Patient

1. Included in GRAALL-2014/B
2. With HR B-ALL (cf infra)
3. ECOG ≤ 3
4. In CR after one or two induction cures and having received the three blocks of consolidation 1
5. Without documented CNS involvement at diagnosis
6. With or without allogeneic donor

19.2 Non Inclusion criteria

The following criteria should all be checked:

Patient

1. With ECOG status > 3 after consolidation 1
2. With abnormal laboratory values as defined below after consolidation 1:
    a. ASAT (SGOT) and/or ALAT (SGPT) ≥ 5 x ULN
    b. Total bilirubin ≥ 1.5 x ULN
    c. Creatinine ≥ 1.5 x ULN or creatinine clearance < 50 ml/min
    d. Serum amylase and lipase ≥ 1.5 x ULN
3. With active uncontrolled infection, any other concurrent disease or medical condition that is deemed to interfere with the conduct of the study as judged by the investigator
4. Infection with human immunodeficiency virus (HIV) or chronic infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive
5. Women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least three months thereafter. Patients not willing to ensure not to beget a child during participation in the study and at least three months thereafter
6. Not able to bear with the procedures or the frequency of visits planned in the trial

19.3 Reminder- classification of high risk (HR) B-lineage ALL

After induction, HR patients are identified as having:

IKZF1 gene deletion (except whole gene deletion or monosomy 7)

and/or

***KMT2A (=MLL*) gene rearrangement, (t(4;11) *KMT2A-AFF1* (= *MLL-AF4*) fusion or other**

and/or

MRD1 ≥ 10^{-4} (including non obtention of CR in 1 cure)

19.4 Criteria leading HR patients to allo-SCT (VHR group)

All HR patients are not necessarily eligible for allo-SCT in CR1. The decision of allo-SCT in CR1 is only based on the MRD answer (MRD1 and MRD2). An unfavorable oncogenetic profile is not *per se* an indication for allo-SCT. Almost all VHR-MRD patients are HR patients and thus eligible for GRAALL-Quest study.

For this reason a group of very high risk patients (VHR) is defined based on MRD1 and MRD2 results:

MRD1 ≥ 10^{-3} (including non-obtention of CR in 1 cure)

and/or

MRD2 ≥ 10^{-4}

Only VHR will be eligible to allo-SCT in CR1.

Patients will receive Allo-SCT, after age-adapted conditioning, with a geno-identical unrelated donor 10/10 or 9/10. Allo-SCT will be performed at the end of consolidation n°2. Allo-SCT indication being possibly identified at a later stage (MRD2), it is recommended to initiate early the search for a donor. As mentioned previously, the results of D8 medullogram may be used to initiate this search.

Pragmatically, to accelerate the search for a donor in patients who will be VHR, a simple bone marrow aspiration (with local morphologic analysis) is planned on day D8 of induction chemotherapy. HLA typing of the patient and siblings will be performed at diagnosis. In the absence of HLA-identical brother or sister, search for an unrelated donor will be initiated for patients chemoresistant on D8 (local morphological assessment). Indeed, chemoresistance on D8 is the factor best correlated to the VHR criterion.

In all cases, if not already performed, search for a donor will be necessary if MRD1 is ≥10^{-3} since all these patients are classified VHR. Yet, a small percentage of patients will be classified VHR only on their MRD2 level (< 5%).

20 TREATMENT

20.1 Patient HR only (but not VHR)

This course concerns patients who will not proceed to allo-SCT.

Consolidation n°2 includes 3 blocks. The first one will be composed of 1 blinatumomab cycle. The two following blocks are consecutively a cytarabine block (B5 identical to S1) and a MTX block (B6 identical to S2).

Blinatumomab block (begins after haematological recovery from block S3).

Evaluation of MRD2 is performed at that time, on BONE MARROW, before initiating the Blinatumomab block

ⓘ **Biological criteria to fulfill before B5 and B6 blocks:**

✓ ALAT (SGPT or TGP) < 5 x ULN,

✓ Creatinine clearance ≥ 60 mL/mn.

Whenever these biological criteria are not met, the order of blocks is not modified and it is postponed until all criteria are met.

B4 block – Blina

Block 4 - Blinatumomab (D1 to D28)	**Whatever patient's age**
Dexaméthasone 40 mg IV	D1, 1 h before blinatumomab
Blinatumomab 28µg/D (IVC)	D1 to D28
TRIPLE IT(N°5) including* *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol® IT 40 mg total dose*	D1
ⓘ Remember to assay anti-Asparaginase antibodies on D1 of B4 block (Annex 5)	

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

B5 block – AraC

Begin at D36

Block B5 – AraC (D36 to D49)	**Whatever the patient's age**
CYTARABINE 2000 mg/m^2/12h, IV (2h)	D1 and D2 (4 perfusions over days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (or 40 mg over 2 days)
G-CSF 5 µg/kg/D, SC or IV	D8 to D12

B6 block – MTX

Block B6 – MTX (D50 to D63)	18 - 44 years old	45- 59 years old
VINCRISTINE 2 mg total dose SIV	D1	D1
METHOTREXATE, IV continuous over 24h	5000 mg/m² on D1	3000 mg/m² on D1
500 mg/m² CIV over 30 minutes then the remaining (4500 mg/m² or 2500 mg/m² CIV) over 23h30	Salvage with folinic acid (Annex 7)	
6 – MERCAPTOPURIN* 60 mg/m², PO	D1 to D7	D1 to D7
G-CSF 5 µg/kg/d, SC or IV	D8 to D12	D8 to D12
TRIPLE IT(N°6) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol® IT** 40 mg total dose*	D2, H24 of methotrexate initiation	

* at bedtime, at distance from dairy products consumption

** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

20.1.1 Late Intensification

20.1.1.1 ALL not requiring salvage cure

This applies to all patients without an indication of allo-SCT in CR1 who did not require salvage therapy to reach CR1. It begins no earlier than ~~D14 of B6 Block (~~D64 of consolidation 2~~)~~,after hematological reconstitution following the S6 block of consolidation n°2 (ANC >1 G/L and platelets >100 G/L) providing ALAT are < 2.5 x ULN and creatinine clearance ≥ 60 mL/mn.

Pre-intensification MRD3 is performed on BONE MARROW just before late intensification.

It is has no decisional value.

Late intensification follows the same regimen as induction except:

✓ daily DNR dose of D1-D3 is 30 mg/m²/d instead of 50 mg/m²/d for patients <45 years old

✓age-related dose adaptation at and over 45 years of age,

✓Introduction of an alternative to *E Coli* Asparaginase for immunized patients (or clinically allergic without antibodies assessment)*.

* In case of immunization to L-Asparaginase, substitution by *Erwiniachrysanthemi* (ERWINASE®) A**sparaginase** will be performed at a dosage of 25000 UI/m² (IV 1h) according to Annex 4.

	18 - 44 years old	45 – 59 years old
PREDNISONE 60 mg/m^2, PO (or Methylprednisolone IV 48 mg/m^2)	D1 to D14	D1 to D7
DAUNORUBICIN, 30 mg/m^2,SIV over 30 mn	D1 to D3 D15 and D16	D1 to D3
VINCRISTINE 2 mg total dose SIV	D1, D8, D15 and D22	
CYCLOPHOSPHAMIDE* 750 mg/m^2, IV over 3h	D1 and D15	
L-ASPARAGINASE 6000 UI/m^2, IV, over 1 h (Annex 4) Or, if allergic reaction or positive anti-asparaginase antibodies: ERWINASE 25000 UI/m^2, IV over 1h at the same dates as Asparaginase	D8, D10, D12, D20, D22, D24, D26 and D28	D8, D10, D12, D20, D22 and D24
G-CSF 5 µg/kg/d, SC or IV	D18 until ANC > 1G/L	
TRIPLE IT(N°7 and 8) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D1 and D8	

* Use of mesna (Uromitexan®) to prevent cyclophosphamide toxicity is allowed (dosage according to investigator discretion).
** Other corticoids can be used instead of Depo-Medrol® (dosage according tothe sites).

ⓘ **Age-related adaptation.** Prednisone administration time, doses of daunorubicin and L-Asparaginase injections numbers are age-adapted. Of note, daunorubicin will be given on days 15 and 16 only for patients < 45 years of age.

3. Primary monitoring of asparaginase activity and of ammoniemia (Annex 5) has to be done **48h after the 3rd injection** (theoretically D14) and. Secondary monitoring has to be done **48 h after the 6th injection** (theoretically D26). For all patients <45 years old, sample collection must be performed immediately before the 7th injection.
4. AT levels should be assayed daily or every second day, from D8 up to 48h after the end of induction or late intensification, without interrupting between D12 and D20, in order to maintain AT levels over 60% constantly, since the median date of occurrence of brain thrombosis was D17 in the GRAALL-2005 trialNB: Rules for kidrolase/erwinase switch are in Annex 4

20.1.1.2 ALL with salvage cure

Patients who reached CR1 after salvage therapy with idarubicin + aracytine will receive the same late intensification.

Pre-intensification molecular evaluation (MRD3) will be performed on the BONE MARROW just before late intensification. It has no decisional value.

IDARUBICIN 9 mg/m², IV (1h)	D1 to D3
CYTARABINE 2000 mg/m²/12h, IV (2h)	D1 to D4 (or 8 perfusions over 4 days)
G-CSF 5 µg/kg/d, SC or IV (or Neulasta)	D8 until ANC > 1G/L
TRIPLE IT (N°7 and 8) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D8 and D15

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

20.1.2 Consolidation n°3

Late intensification, whether or not patients required salvage therapy to reach CR1, is followed by consolidation n°3 including again 3 blocks which repeat the blinatumomab, AraC and MTX blocks of consolidation 2 (B7 = B4, B8 = B5, B9 = B6).

This sequence is to be initiated as soon as hematologic recovery is reached after late intensification (ANC >1G/L and platelets>100 G/L).

Biological criteria to fulfill before B8 and B9 blocks:

✓ ALAT (SGPT or TGP) < 5 x ULN,

✓ Creatinine clearance ≥ 60 mL/mn.

Whenever these biological criteria are not met, the order of blocks is not modified and it is postponed until all criteria are met.

B7 block – Blina

Block 7 – Blinatumomab (D1 to D28)	Whatever patient's age
Dexaméthasone 40 mg IV	D1, 1h before blinatomumab
Blinatumomab 28µg/D (IVC)	D1 to D28
TRIPLE IT(N°9) including* *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol® IT 40 mg total dose*	D1

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

B8 block – AraC

Begin at D36

Block B8 – AraC (D36 to D49)	Whatever the patient's age
CYTARABINE 2000 mg/m^2/12h, IV (2h)	D1 and D2 (4 perfusions over days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (or 40 mg over 2 days)
G-CSF 5 µg/kg/D, SC or IV	D8 to D12

B9 block – MTX

Block B9 – MTX (D50 to D63)	18 - 44 years old	45- 59 years old
VINCRISTINE 2 mg total dose SIV	D1	D1
METHOTREXATE, IV continuous over 24h	5000 mg/m² on D1	3000 mg/m² on D1
500 mg/m² CIV over 30 minutes then the remaining (4500 mg/m² or 2500 mg/m² CIV) over 23h30	Salvage with folinic acid (Annex 7)	
6 – MERCAPTOPURIN* 60 mg/m², PO	D1 to D7	D1 to D7
G-CSF 5 µg/kg/d, SC or IV	D8 to D12	D8 to D12
TRIPLE IT(N°10) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol® IT** 40 mg total dose*	D2, H24 of methotrexate initiation	

* at bedtime, at distance from dairy products consumption

** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

ⓘ **Patients with initial CNS involvement should receive CNS irradiation before maintenance therapy.**

20.1.3 Maintenance

The whole duration of maintenance therapy is 24 months. Maintenance therapy is initiated after recovering from consolidation n°3 (ANC >1 G/L and platelets > 100 G/L).

Assessment of MRD4 is performed on BONE MARROW before initiating maintenance therapy. It has no decisional value.

A search for anti-Asparaginase antibodies on D1 of month 1 must be performed (Annex 5)

It is a classical maintenance regimen based on the association of 6-mercaptopurin + MTX, with monthly reinductions of vincristine and prednisone during the first year. Blinatumomab will substitute vincristine and prednisone at months 1, 3, and 5 (3 cycles.)

No G-CSF is given during this phase.

KEEP IN MIND RECOMMENDATIONS ENTITLED

«GENERAL RULES FOR THE WHOLE TREATMENT ».

(§ 7 of part II)

20.1.3.1 First maintenance year: 12 monthly reinductions (3 blinatumomab and 9 vincristine)

Total duration of maintenance is 2 years. During the first year, 12 reinductions should be given, each cycle duration being approximatively 4 weeks.

	Month 2, 4, 6 to 12	Month 1, 3, 5
	PREDNISONE 40 mg/m²/day PO from D1 to D7	**DEXAMETHASONE** 40 mg IV, 1 h before **Blina**
	VINCRISTINE 2 mg total dose IVD on D1	
	6-MERCAPTOPURIN* 60 mg/m², PO at bedtime at distance from dairy products consumption	**BLINATUMOMAB** 28 µg/d From D1 to D28
	METHOTREXATE* 25 mg/m², PO, weekly	
TRIPLE IT(N°11, 12, 13) including *Methotrexate IT 15 mg total dose, Cytarabine IT 40 mg total dose, Depo-medrol®** IT 40 mg total dose*		D1 of Month 1, 3, 5

* Scrupulous dose adaptation (Annex 2)
*** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

Reinductions can be rescheduled if toxicity criteria recommend transient interruption of therapy (Annex 2).

Monthly administration of Bactrim® or Pentacarinat® is strongly recommended during maintenance (no folinic acid together with Bactrim® in order not to lessen MTX efficacy).

20.1.3.2 Second maintenance year

1 month = 4 weeks (5 if needed)

	Month 13 to 24
6-MERCAPTOPURIN 60 mg/m^2, PO at bedtime at distance from dairy products consumption	Daily Scrupulous dose adaptation (Annex 2).
METHOTREXATE 25 mg/m^2, PO	Weekly Scrupulous dose adaptation (Annex 2).

Monthly administration of Bactrim® or Pentacarinat® is strongly recommended during maintenance (no folinic acid together with Bactrim® in order not to lessen MTX efficacy).

20.2 Patient VHR proceeding to ASCT

Consolidation will be composed only of blinatumomab block (begins after hematological recovery from block S3).

Evaluation of MRD2 is performed at that time, on BONE MARROW, before initiating the Blinatumomab block

B4 block – Blina

Block 4 - Blinatumomab (D1 to D28)	**Whatever the patient's age**
Dexaméthasone 40 mg IV	D1, 1h before blinatomumab
Blinatumomab 28µg/D (IVC)	D1 to D28
TRIPLE IT including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol® IT 40 mg total dose*	D1

ⓘ Blinatumomab blocks will be repeated (including IT) every 28 days until ASCT.

Blinatumomab will be stop 1 week before conditioning regimen start.

Evaluation of MRD3 is performed at that time, on BONE MARROW, before Allo-SCT

21 ALLO-SCT IN CR1

Eligible patients will receive Allo-SCT, after age-adapted conditioning, with a geno-identical or unrelated 10/10 or 9/10 donor. Allo-SCT will be performed at the end of consolidation n°2 after inclusion in phase II trials (GRAALL QUEST) if MRD1 $>10^{-4}$.

Allo-SCT indication being possibly identified at a later stage (MRD2), it is recommended to initiate early the search for a donor. Results of D8 bone marrow examination can be used to help as mentioned above.

22 ALLO-SCT IN PATIENTS < 45 YEARS OLD

✓TBI: 12 Gy in 6 fractions with lung protection above 8 Gy

✓Cyclophosphamide: 60 mg/kg per day for 2 days

✓+/- ATG in case of unrelated 10/10 or 9/10 graft (according to each center's habits)

GVH prophylaxis will associate ciclosporine A and MTX on D1, D3, D6 (+/- D11). A bone marrow graft will be preferred.

Assessment of MRD4 is performed on BONE MARROW (medullogram) at D100 post Allo-SCT.

It has no decisional value.

23 ALLO-SCT IN PATIENTS AGED FROM 45 TO 59 YEARS OLD

Allo-SCT after RTC associating TBI 8 Gy + Fluda according to Bornhäuser Lancet Oncology 2012

✓TBI: 8Gy in fractions (D-3 and D-2) or unfractionated 6 Gy

✓Fludarabine: 30mg/m^2/d x 4 d from D-6 to D-3

✓+/- ATG in case of unrelated 10/10 or 9/10 graft according to centers'habits (thymoglobuline or ATG Fresenius) according to each center's habits.

GVH prophylaxis will associate ciclosporine A and MTX on D1, D3, D6 and D11. A mobilized peripheral graft will be preferred.

Assessment of MRD4 is performed on BONE MARROW (medullogram) at D100 post Allo-SCT.

It has no decisional value.

PART III
GRAALL-2014/T

SYNOPSIS GRAALL-2014/T AND ATRIALL (T-ALL) SUBSTUDY

Title	**GRAALL-2014/T:** **Multicenter study of risk-adapted treatment for T-lineage ALL of young adults (18-59 years old).** **ATRIALL (delayed opening):** **A phase II study to treat patients with T-cell acute lymphoblastic leukemia (T-ALL) and evaluate the efficacy of a nelarabine based consolidation and maintenance in high-risk patients. GRAALL-2014/T and ATRIALL studies.**
Acronym	**GRAALL-2014/T and ATRIALL**
Coordinator	**Pr. Hervé DOMBRET** **Hématologie, Hôpital Saint Louis, Paris** **Tél: +33 (0)1 57 27 68 47 /(0)1 42 49 96 48** **Email:** herve.dombret@aphp.fr
Sponsor	**Assistance Publique – Hôpitaux de Paris**
Indication	Patients aged 18-59 years old with *de novo* T-ALL.
Type of study	Multicenter, open non controlled study (SR patients) Phase II, multicenter, open non controlled (HR patients)
Number of subjects enrolled	275 patients 120 patients for the ATRIALL study **(delayed opening)**
Study Duration	Enrollment period, 5 years Trial participation duration (treatment + follow-up): 5 years Total study duration: 10 years
Centers number	**About 80 centers expected (Belgium, France, Switzerland)**
Experimental drug Prescription outside MA	Nelarabine (HR patients enrolled in the ATRIALL substudy)
Experimental drugs Prescription according to MA	Cyclophosphamide, Methotrexate, Vincristine, Cytarabine, VP-16, Dexamethasone, 6-mercaptopurin, Daunorubicin,Idarubicin, Prednisone, L-Asparaginase, Granulocyte colony-stimulating factor (G-CSF).
Risk factors Definition	• **Standard-risk (SR)** patients not classified as high-risk (HR) or very high-risk MRD (VHR-MRD). • **High-risk (HR) patients** defined after induction as having at least one of the following criteria: – Absence of*NOTCH1* or *FBXW7* gene mutation whatever the RAS/PTEN genotype – Or *RAS* mutation or *PTEN* gene alteration – Or MRD1 level ≥ 10^{-4} (with a sensitivity of at least 10^{-4}), including notably the need for as salvage cure to reach CHR). 120 HR patients will be treated within the ATRIALL study **(delayed opening)**, and receive nelarabine. • **Very High-Risk MRD (VHR-MRD) patients** defined after induction as having: – MRD1 level ≥ 10^{-3} (with a sensitivity of at least 10^{-3}) – MRD2 level ≥ 10^{-4} (with a sensitivity of at least 10^{-4}) The large majority of VHR-MRD patients are HR patients and thus eligible for the ATRIALL

	study. All VHR-MRD patients (but not other HR patients) with a donor receive allo-SCT after the second consolidation phase in the frame of the ATRIALL study.
Objectives	Primary objective: • To prospectively validate the new risk factors based on MRD1 response level and *NOTCH1/FBXW7/RAS/PTEN* gene status. • To evaluate the efficacy of nelarabine-based consolidation and maintenance therapy in term of RFS in HR patients (ATRIALL substudy). Secondary objectives: • Appreciate the toxicity of nelarabine-based consolidation cycles, followed by allo-SCT or further consolidation and maintenance therapy, • Evaluate MRD level, monitored by Ig-TCR, • Cumulative incidence of relapse (CIR) and non-relapse mortality (NRM), • Relapse-free survival (RFS) and overall survival (OS), • RFS, CIR, NRM and OS after censoring at SCT in first CR.
Evaluation criteria	Primary evaluation criteria • Analysis of the new risk factors based on MRD1 response level and *NOTCH1/FBXW7/RAS/PTEN* gene status by comparing the historical results of GRAALL-2005 with those of GRAALL-2014 in an identical population (T-lineage ALL aged 18 to 59 years old), • DFS at 4 years in SR patients, according to the status of *NOTCH1/FBXW7/RAS/PTEN* and of MRD1 evaluated at the end of the induction cure or on D1 or consolidation cure 1 • RFS at 4 years, in the ATRIALL substudy. Secondary evaluation criteria • OS, • Cumulative incidence of relapse (CIR) and non-relapse mortality (NRM), • DFS, CIR, NRM and OS after censoring at allo-SCT in first CR. • Evaluation of nelarabine toxicity • Proportion of patients having received the 5 cycles of nelarabine, • MRD follow-up at various times of treatment (cf infra § MRD monitoring).
Statistical justification of sample size	Each year, approximately 55 patients with T-ALL will enter the GRAALL-2014/T study. Among 50 HCR patients/year, approximately 20 will be SR and 30 will be HR (including approximately 15 VHR-MRD patients). After consolidation 1 • All SR patients (about 100 in 5 years) will be treated by the standard GRAALL-2014 protocol, with no new agent norallo-SCT in first CR. The objective is here to demonstrate that, in a single arm non-inferiority study, 4-year DFS for these patients is at least of 60%, justifying the absence of allo-SCT in first CR. With a 0.05 alpha risk and a 0.80 power and a security margin of 15%, the calculated sample size is 82 patients. Given a certain ratio of patients who will be eventually non evaluable, the planned number of enrolled patients is 85. • All HR patients (expected, 150 in 5 years) will be eligible for the phase II ATRIALL study (delayed opening) evaluating nelarabine in consolidation. DFS will be compared to historical results (50% at 4 years). The objective is here to demonstrate a 50% to 65% DFS improvement. With a 0.05 alpha risk and a 0.90 power in the two-sided setting, the calculated sample size is 113 patients. Given a certain ratio of patients who will be eventually non evaluable, the planned number

	of enrolled patients is 120. Upon reaching the 120 patients enrolled, inclusions will stop in the ATRIALL study. Other HR patients who would have been eligible for ATRIALL will continue to participate to the study and its follow-up planned in GRAALL-2014/T.
GRAALL-2014/T Inclusion Criteria	Patient: 1. Whose blood and bone marrow explorations have been completed before the steroids prephase 2. aged 18-59 years old with a not previously treated (including IT injection) T-ALL newly-diagnosed according to the WHO 2008 definition with $\geq$ 20% bone marrow blasts 3. With ECOG $\leq$ 3 4. With or without central nervous system (CNS) involvement or testis 5. Without other evolving cancer (except basal cell carcinoma of the skin and "in situ" carcinoma of the cervix) or its chemo or radio-therapy treatment finished at least since 6 months 6. Having signed a written informed consent 7. With efficient contraception for women of childbearing age (excluding estrogens and IUD) 8. Having received or being receivingsteroid prephase 9. With health insurance coverage Secondary ALL (antecedent of chemo- or radio-therapy) can be included
GRAALL-2014/T Non inclusion Criteria	Patients: 1. With lymphoblastic lymphoma and bone marrow blasts < 20%, Burkitt-type ALL or with antecedents of CML or other myeloproliferative neoplasm 2. With contra-indication to anthracyclines or any other general or visceral contra-indication to intensive therapy except if considered related to the ALL: • ASAT (SGOT) and/or ALAT (SGPT) > 5 x ULN • Total bilirubin $\geq$ 2.5 x ULN • Creatinine > 1.5 x ULN or creatinine clearance <50 mL/mn 3. Myocardial infarction within 6 months prior to inclusion in the trial, cardiomyopathy (NYHA grade III or IV), LEVF < 50% and or RF < 30%, 4. Active severe infection or known seropositivity for HIV or HTLV-1 or chronic hepatitis B (HbsAg-positive) or C 5. Other active malignancy 6. Pregnant (β-HCG positive) or nursing woman 7. Women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least three months thereafter. Patients not willing to ensure not to beget a child during participation in the study and at least three months thereafter 8. Treated with any other investigational agent or participation in another trial within 30 days prior to entering this study 9. Not able to bear with the procedures or the frequency of visits planned in the trial 10. Unable to consent, under tutelage or curatorship, or judiciary safeguard.
ATRIALL Inclusion Criteria (HR patients)	Patient 1. Included in GRAALL-2014/T 2. With HR T-ALL 3. ECOG $\leq$ 2 4. In CR after one or two induction cures and having received the three blocks of consolidation N°1 5. Without documented CNS involvement at diagnosis 6. With or without allogeneic donor

ATRIALL **Non Inclusion Criteria** **(HR patients)**	Patients 1. With ECOG status ≥ 3 after consolidation 1 2. With CNS disease at diagnosis, or symptomatic CNS disease , or uncontrolled epilepsy 3. With peripheral neuropathy grade ≥ 2 after consolidation 1 4. With abnormal laboratory values as defined below after consolidation 1 a. AST (SGOT) and/or ALT (SGPT) ≥ 5 x ULN b. Total bilirubin ≥ 1.5 x ULN c. Creatinine ≥ 1.5 x ULN or creatinine clearance < 50 ml/min d. Serum amylase and lipase ≥ 1.5 x ULN 5. With active uncontrolled infection, any other concurrent disease or medical conditionthat is deemed to interfere with the conduct of the study as judged by the investigator 6. With childbearing potential not willing to use an effective form of contraception during participation in the study and at least three months thereafter. Patients not willing to ensure not to beget a child during participation in the study and at least three months thereafter 7. With known hypersensitivity to nelarabine 8. Not able to bear with the procedures or the frequency of visits planned in the trial
Treatment	**Induction** All patients will receive induction. Patients not reaching HCR after induction will be proposed a salvage induction course. Ig-TCR MRD1will be evaluated after the induction course or on D1 of consolidation 1 **Consolidation 1** All patients in HCR (after induction eventually followed by salvage) will receive 0, 1 or 2 interim "stand-by" blocks before the first consolidation comprising 3 blocks of chemotherapy (blocks S1, S2, S3). These stand-by blocks will allow to recover from potential toxicities of the induction, notably hepatic, to avoid modifying the order of the following consolidation blocks and to respect the dosage/intensity. Ig-TCR MRD2 will be evaluated after consolidation 1 or on D1 of consolidation 2. HR *versus* SR Patients will be attributed to a risk group during the first consolidation according to MRD1 level, need for salvage to obtain CHR, and NOTCH/FBXW7 and RAS/PTEN gene status. At that point, all HR patients will be proposed the Phase II ATRIALL study, up to 120 inclusions. After this number has been reached, HR patients who would have been eligible for ATRIALL will continue to participate to the study and its follow-up planned in GRAALL-2014/T. **Consolidation 2** 120 HR patients will be included in phase II ATRIALL study and will receive nelarabine.Consolidation 2 is composed of 3 blocks (T4, T5, T6). SR patients will continue with standard protocol and receive consolidation 2 (blocks S4, S5, S6). HR *versus* VHR-MRD VHR-MRD is defined by MRD1≥ 10^{-3} or the need or a salvage cure to reach HCR or MRD2≥ 10^{-4}. Almost all VHR-MRD patients are HR patients and thus eligible for ATRIALL study. After consolidation 2, VHR-MRD patients will be proposed allo-SCT in first CR if there is no contra-indication.

	Ig-TCR MRD3 will be evaluated on D1 of late intensification (or during pretransplantationevaluation). **Late intensification**will be given to all non-transplanted patients, whatever their risk group. **Consolidation 3** HR patients will receive a new consolidation with nelarabine, composed of 3 blocks (T7, T8, T9). SR patients will receive a third standard consolidation (blocks S7, S8, S9). Ig-TCR MRD4 will be evaluated on D1 of maintenance (or day 100 post allo-SCT) **Maintenance therapy** The total duration is 2 years. SR patients will receive a standard maintenance therapy based on the association of 6-mercaptopurin + methotrexate, with monthly reinductions associating vincristine and prednisone during the first year. HR patients will receive will receive a standard maintenance therapy based on the association of 6-mercaptopurin + methotrexate, and reinduction by nelarabine (Month 2, 4 and 6) or by vincristine and prednisone (Month 1, 3, 5 and 7 to 12) during the first year.Reinductions will be monthly. **Allogeneic stem cell transplantation (SCT)** Allogeneic SCT in first CR will be offered to all VHR-MRD patients with a genoidentical or unrelated donor (10/10 or 9/10). Allo-SCT has to be done as early as possible after the second consolidation phase. In patients aged <45 years old, conditioning will be myeloablative: TBI 12 Gy fractionated and cyclophophamide,120 mg/kg (+/- ATG in case of unrelated Allo-SCT). Patients aged ≥ 45 years old or with co-morbidity criteria will benefit from a reduced toxicity conditioning with TBI-Fludarabine (TBI, fractionated 8 Gy dose or non-fractionated 6 Gy, and fludarabine 120 mg/m^2+ATG in case of unrelated Allo-SCT 10/10). **Central nervous system involvement** Patients with CNS+ disease at diagnosis will not be eligible for an inclusion in the phase II ATRIALL trial.
Chemotherapy<	Induction **Prednisone** **60 mg/m^2/d** (PO) : D1 to D14 * **Vincristine** **2 mg/d** (IVD) : D1, D8, D15, D22 **Daunorubicin** **50 mg/m^2/d** (IV 30 min) ** : D1,D2,D3 **30 mg/m^2/d** (IV 30 min) : D15, D16 **Cyclophosphamide** **750mg/m^2/d** (IV 3h) : D1, D15 **L-Asparaginase#** **6000 UI/m^2/d** (SIV 1h) : D8, D10, D12, D20, D22, D24, D26, D28 *** **G-CSF** **5 µg/kg/d** (SC or IV) : D18 until neutrophil >1G/L **IT** **MTX + Ara-C + Depomedrol** : D1, D8 *: only from D1 toD7 if age ≥45y **: reduced to 30 mg/m^2/d if age ≥45y ***: at D8, D10, D12, D20, D22, D24 if age ≥45y #substituted by Erwinase® if immunization to *E coli* L-Asparaginase.

Salvage

Idarubicin	**12 mg/m²/d** (IV 1h)	: D1, D2, D3
Aracytine	**2000 mg/m²/12h** (IV 3h)	: D1 to D4
G-CSF	**5 µg/kg/d** (SC or IV)	: D8 until neutrophil >1G/L

Standard consolidation (SR)

Weekly stand-by block (0, 1 or 2 if needed)

VP-16	**150 mg/m²/d** (IV 1h)	: D1
Aracytine	**30 mg/m²/12h** (SC)	: D1,D2

Blocks S1/S4/S7 (D1-D14)

Aracytine	**2000 mg/m²/12h** (IV 2h)	: D1, D2
Dexamethasone	**10 mg/12h** (IV)	: D1, D2
G-CSF	**5 µg/kg/d** (SC or IV)	: D8 to D12

Blocks S2/S5/S8 (D15-D28)

Methotrexate	**5000 mg/m²/d** (CIV 24h) *: D15	
Vincristine	**2 mg/d** (IVD)	: D15
6-mercaptopurin	**60 mg/m²/d** (PO)	: D15-to D21
G-CSF	**5 µg/kg/d** (SC or IV)	: D22 to D26
IT	**MTX + Ara-C + Depomedrol**	: D16 (H24 after start MTX)

*: 500 mg/m² over 30 minutes, then over 23 hours and 30 minutes,followed by folinic acid rescue; reduced to 3000 mg/m²/d if age ≥45y

Block S3/S6/S9 (D29-D35)

Cyclophosphamide[#]	**500 mg/m²/d** (IV 3h)	: D29, D30
VP-16	**75 mg/m²/d** (IV 1h)	: D29, D30
Methotrexate	**25 mg/m²/d** (IV)	: D29
G-CSF	**5 µg/kg/d** (SC or IV)	: D31 until neutrophil >1G/L
IT	**MTX + Ara-C + Depomedrol**	: D29

Maintenance therapy (SR)

Vincristine	**2 mg** (IVD)	: D1, Month 1 to 12
Prednisone	**40 mg/m²/d** (PO)	: D1 to D7 Month1 to 12
MTX	**25 mg/m²/wk** (PO)	: 24 months
6-mercaptopurin	**60 mg/m²/d** (PO)	: 24 months
IT	**MTX + Ara-C + Depomedrol**	: D1 Month 1,3,5 (only CNS1/2)

Nelarabine- consolidation (HR):

Blocks T4/T7 (D1-D21)

Nelarabine	**1500 mg/m²/d** (IV 2h)	: D1, D3, D5
Cyclophosphamide	**150 mg/m²/d** (IV 3h)	: D1, D3
VP-16	**75 mg/m²/d** (IV 1h)	: D1, D3
G-CSF	**5 µg/kg/d** (SC)	: D7 until neutrophil >1G/L

No IT during blocs T4/T7

Blocks T5/T8 (D22-D35)

Aracytine	**2000 mg/m²/12h** (IV 2h)	: D22, D23
Dexamethasone	**10 mg/12h** (IV)	: D22, D23

	G-CSF **5 µg/kg/d** (SC) : D29 to D33 *Blocks T6/T9 (D36-D49)* **Vincristine** **2 mg/d** (SIV) : D36 **Methotrexate** **3000 mg/m²/d** (CIV 24h) : D36 **6-mercaptopurin** **60 mg/m²/d** (PO) : D36 to D42 **G-CSF** **5 µg/kg/d** (SC) : D43 to D47 **IT** **MTX + Ara-C + Depomedrol** : D37(H24 after start MTX) <u>**Late intensification (for patients who did not receive salvage after induction):**</u> **Prednisone** **60 mg/m²/d** (PO) : D1 to D14 * **Vincristine** **2 mg/d** (IVD) : D1, D8, D15, D22 **Daunorubicin** **30 mg/m²/d** (IV 30 MIN) : D1, D2, D3, D15, D16 ** **Cyclophosphamide** **750mg/m²/d** (IV 3h) : D1, D15 **L-Asparaginase#** **6000 UI/m²/d** (SIV 1h) : D8, D10, D12, D20, D22, D24, D26, D28 *** **G-CSF** **5 µg/kg/d** (SC or IV) : D18 until neutrophil >1G/L **IT** **MTX + Ara-C + Depomedrol** : D1, D8 *: only form D1 to D7 if age ≥45y **: D15 and D16 only if age <45y ***: at D8, D10, D12, D20, D22, D24 if age ≥45y #: substitution by Erwinase® if immunization to *E coli* L-Asparaginase <u>**Late intensification (for patients who received salvage after induction):**</u> **Idarubicin** **9 mg/m²/d** (IV 1h) : D1, D2, D3 **Aracytine** **2000 mg/m²/12h** (IV 3h) : D1 to D4 **G-CSF** **5 µg/kg/d** (SC or IV) : D8 until neutrophil >1G/L **IT** **MTX + Ara-C + Depomedrol** : D8, D15 <u>**Nelarabine-based maintenance therapy:**</u> **Vincristine** **2 mg** (IVD) : D1, Month 1,3,5,7 to 12 **Prednisone** **40 mg/m²**(PO) : D1 to D7, Month 1,3,5,7 to 12 **Nelarabine** **1500 mg/m²/d** (IV 2h) : D1, D3, D5, Month 2,4,6 **MTX** **25 mg/m²/wk** (PO) : 24 months* **6-mercaptopurin** **60 mg/m²/d** (PO) : 24 months* **IT** **MTX + Ara-C + Depomedrol** : D1,Month 1,3,5 * except during the 4-week nelarabine cycles (month 2,4 and 6)
MRD monitoring	MRD evaluation will be performed on bone marrow aspirates at the following time-points: • MRD1: after induction or on day 1 of first consolidation • MRD2: on day 1 of second consolidation • MRD3: on day 1 of late intensification (or at pre Allo-SCT evaluation) • MRD4: on day 1 of maintenance phase (or at day 100 after Allo-SCT)
SAEs	Serious adverse events (SAEs) must be reported on the SAE page of the eCRF and declared to the sponsor immediately for each patient (Annex 9) in each participating country whatever their causality to the research.
Added risks of the research	D
Financing	PHRC
Independent	Yes

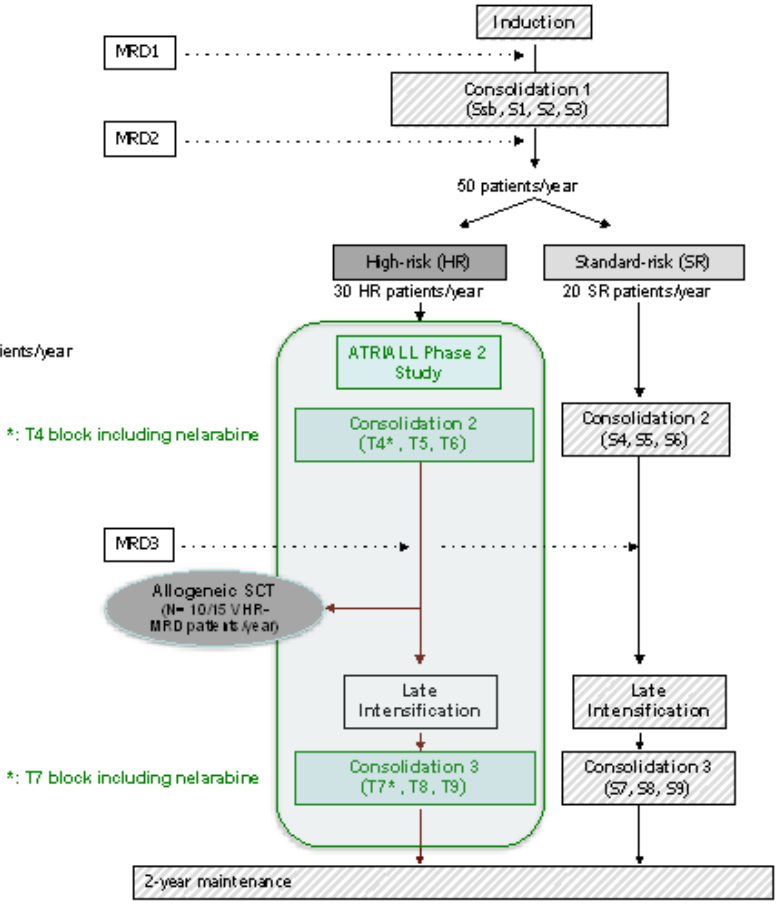
surveillance committee planned	

GRAALL-2014/T study
T-ALL
Front-line
18-59y

INDUCTION
CONSOLIDATION
LATE INTENSIFICATION

55 T-ALL patients per year front-line

After CR achievement:
1) 30 HR patients/year, including 15 VHR-MRD patients/year
2) 20 SR patients/year

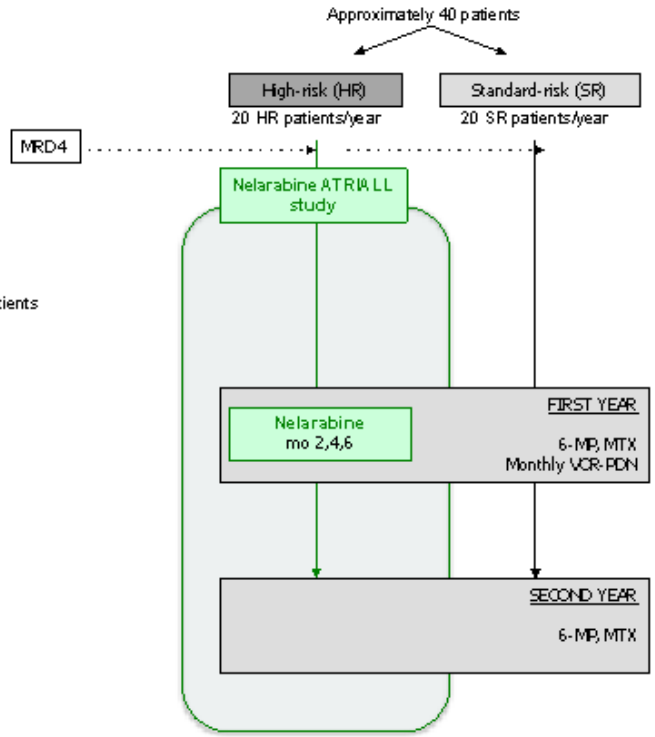


GRAALL-2014/T study
T-ALL
Front-line
18-59y

MAINTENANCE

Approximately 40 T-ALL patients per year
will receive maintenance therapy

Including:
1) 20 HR patients/year, including non-transplanted VHR-MRD patients
2) 20 SR patients/year



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1 OBJECTIVES OF GRAALL/T-2014

1.1 PRIMARY OBJECTIVE

- To prospectively validate the new risk factors based on MRD1 response level and NOTCH1/FBXW7/RAS/PTEN gene status.
- To evaluate the efficacy of nelarabine-based consolidation and maintenance therapy in term of RFS in HR patients (ATRIALL substudy).

1.2 Secondary objectives

- Appreciate the toxicity of nelarabine-in consolidation, followed by allo-SCT or further consolidation and maintenance therapy,
- Evaluate MRD level, monitored by Ig-TCR,
- Cumulative incidence of relapse (CIR) and non-relapse mortality (NRM),
- Relapse-free survival (RFS) and overall survival (OS),
- RFS, CIR, NRM and OS after censoring at SCT in first CR.

2 EVALUATION CRITERIA

2.1 Primary evaluation criteria

- Analysis of the new risk factors based on MRD1 response level and *NOTCH1/FBXW7/RAS/PTEN* gene status by comparing the historical results of GRAALL-2005 with those of GRAALL-2014 in an identical population (T-lineage ALL aged 18 to 59 years old),
- DFS at 4 years in SR patients, according to the status of *NOTCH1/FBXW7/RAS/PTEN* and of MRD1 evaluated at the end of the induction cure or on D1 or consolidation cure 1
- RFS at 4 years, in the ATRIALL substudy.

2.2 Secondary evaluation criteria

- Overall survival
- Cumulative incidence of relapse (CIR) and non-relapse mortality (NRM),
- DFS, CIR, NRM and OS after censoring at SCT in first CR.
- Evaluation of nelarabine toxicity
- Proportion of patients having received the 5 cycles of nelarabine,
- MRD follow-up at various times of treatment (cf infra § MRD monitoring).

3 DESCRIPTION OF RESEARCH METHODOLOGY

3.1 Experimental plan

GRAALL-2014/T is a multicenter (76 centers in France, Belgium and Switzerland) open uncontrolled study for patients of the SR group and a substudy (ATRIALL), phase II, uncontrolled for patients of the HR group.

Each year, approximately 55 patients with T-ALL will enter the GRAALL-2014/T study. Among 50 HCR patients/year, approximately 20 will be SR and 30 will be HR (including approximately 15 VHR-MRD patients). 275 patients will be included over 5 years.

3.2 Type of research

In the GRAALL-2014/T trial, the management of patients for treatment application and follow-up of the disease is as usual besides the 4 samples planned to assay anti-asparaginase antibodies, performed before induction and on day 1 of consolidation blocks S1, S3 and S4. In the hypothesis that a patient would not receive allo-SCT, a 5th sample will be collected before maintenance.

4 MODALITIES OF RECRUITMENT AND INCLUSION OF PATIENTS

Patients will be recruited in hospital hematology departments.

Each year, approximately 55 patients with T-ALL will enter the GRAALL-2014/T study. Among 50 HCR patients/year, approximately 20 will be SR and 30 will be HR (including approximately 15 VHR-MRD patients). After consolidation 1, all SR patients (about 100 in 5 years) will be treated in the standard arm of the GRAALL-2014 trial and all HR patients (about 150 in 5 years) will be eligible for the phase II ATRIALL trial (delayed opening), the expected number of enrolled patients is 120. Above this number, HR patients eligible for ATRIALL will not participate to ATRIALL and will continue to participate to the follow up planned in GRAALL-2014/T.

4.1 Inclusion of patients

During the prephase and up to D1 maximum, **if needed**, investigation centers will contact the medical GRAALL coordination *via* the secretariat (Véronique LHERITIER: Tel: +33 (0)4 78 86 22 39 Fax: +33(0)4 72 66 64 40) to confirm or infirm the eligibility of the patient for the study.

Each inclusion will be performed in a centralized fashion, on line via the e-CRF, by secure internet connexion (CleanwebTélémédecine). During the prephase and at most on D1, each patient must be included on the trial.

As soon as the trial is implemented in a center and when the form of functions delegation (FFD) is filled and signed by all investigator team participants to the trial in the center, the monitoring CRA will forward the request for center opening to Télémédecine.Télémédecine will send by e-mail only, a login and password to each participant (according to their profile) in the center. This e-mail will also contain the internet link allowing to login into the e-CRF.

4.2 Identification of patients for on line data collection

Within this research, subjects will be identified for data collection as follows:

Center n° (3 digits) – selection order number of the patient in the trial (4 digits) – name initial – surname initial ➔|__|__|__|-|__|__|__|__|-|__|-|__|.

This reference will be unique and retained all along the trial.

As the Swiss regulations don't allow the disclosure of the patients' initials, all Swiss patients will have the following dummy initials: "X" for the name initial and "X" for the surname initial.

4.3 Identification of patients for samples shipping

Centralized research samples (*GRAALLThèque and anti-asparaginase antibodies assay)* will be identified as for one line data collection.

Centralized samples, collected within the usual follow-up of patients (*oncogenetic evaluation at diagnosis, MRD…)* will be identified by the patient's name without any mention relative to this biomedical research, according to the center's habits.

According to Swiss regulations the disclosure of the patient's name even for usual follow up assessments which have to be done outside of Switzerland according to the protocol (oncogenetic evaluation at diagnosis,

asparaginase activity assessments,…) is nevertheless not allowed. Therefore all Swiss sites will code their patients' data before receiving the selection order number by AP-HP as follows :• Center number

- Selection order number of the patient in the trial (if applicable)
- Hospital chart identifier,
- birth year

An adequate liaison form will be used to accompany the shipping of tube(s) (see Annexes 1 and 5).

5 INCLUSION CRITERIA

Patient:

1. Whose blood and bone marrow explorations have been completed before the steroids prephase
2. aged from 18 to59 years old with a not previously treated (including IT injection) T-ALL newly-diagnosed according to the WHO 2008 definition with $\geq$ 20% bone marrow blasts
3. With ECOG $\leq$ 3
4. With or without central nervous system (CNS) involvement or testis
5. Without other evolving cancer (except basal cell carcinoma of the skin and "in situ" carcinoma of the cervix) or its treatment should be finished at least since 6 months
6. Having signed a written informed consent
7. With efficient contraception for women of childbearing age (excluding estrogens and IUD)
8. Having received or being receiving the recommended steroid prephase
9. With health insurance coverage

Secondary ALL (antecedent of chemo- or radio-therapy) can be included

6 NON INCLUSION CRITERIA

Patients:

1. With lymphoblastic lymphoma and bone marrow blasts < 20%, Burkitt-type ALL or with antecedents of CML or other myeloproliferative neoplasm

2. With contra-indication to anthracyclines or any other general or visceral contra-indication to intensive therapy except if considered related to the ALL:
    - ASAT (SGOT) and/or ALAT (SGPT) > 5 x ULN
    - Total bilirubin ≥ 2.5 x ULN
    - Creatinine > 1.5 x ULN or creatinine clearance <50 mL/mn
3. Myocardial infarction within 6 months prior to inclusion in the trial, cardiomyopathy (NYHA grade III or IV), LEVF < 50% and or RF < 30%,
4. Active severe infection or known seropositivity for HIV or HTLV-1 or chronic hepatitis B (HbsAg-positive) or C
5. Other active malignancy
6. Pregnant (β-HCG positive) or nursing woman
7. Women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least three months thereafter. Patients not willing to ensure not to beget a child during participation in the study and at least three months thereafter
8. Treated with any other investigational agent or participation in another trial within 30 days prior to entering this study
9. Not able to bear with the procedures or the frequency of visits planned in the trial
10. Unable to consent, under tutelage or curatorship, or judiciary safeguard.

7 GENERAL RULES FOR THE WHOLE TREATMENT

✓ Have a central venous access

✓ Counsel on the mode of contraception an on the necessity of protected sexual intercourse in order to prevent any toxic exposure for the partner. Birth control methods acceptable during the treatment GRAALL are progestogen-only contraception (progestogen pills or subdermal implant) and mechanical contraceptives (condoms, diaphragm…). Continuous progestogen contraception is frequently proposed to avoid the risk of bleeding during intensive chemotherapy phases. The use of estrogen is contraindicated until the onset of maintenance phase, because of the increased risk of venous thrombosis.

✓ It is recommended to use full weight-based chemotherapy doses in the treatment of obese patients (without capping body-surface area at $2m^2$)[59, 60, 61] However, vincristine is capped at a maximum dose of 2.0 mg.

✓ Prevent *Pneumocystis* infection with monthly Bactrim® or Pentacarinat® (do not prescribe folinic acid in association with Bactrim® during maintenance in order not to decrease the efficacy of methotrexate).

About chemotherapy

✓ In case of neuropathy ≥ 3 or severe ileus related to vincristine, replace by vindesine (4 mg TD/injection) or other treatment according to investigator judgment.

✓ Administration of Purinethol® (6-MP) at bedtime, at distance from dairy products consumption

✓ Intrathecal injections: total volume at least 6 mL; ventral decubitus 30 min (Annex 3)

About corticosteroids

✓ Antibioprophylaxis as soon as neutropenia becomes < à 0.5 G/L in patients receiving or having received corticotherapy (broad spectrum antibiotherapy active on GNB germs, including *Pseudomonas aeruginosa*, and GPB germs according to each center's policy). Fluoroquinolones should not be given alone because of the inconstant sensitivity of *P aeruginosa* and of the reduced efficacy of Endoxan[62].

Fungal prophylaxis

✓ This is left to each center's policy. It is suggested to avoid azoles associated to VCR (neurological toxicity) and L-Asparaginase (liver toxicity).

About Nelarabine (ATRIALL)

- ✓ Labile blood products will be irradiated (ASH recommendation)
- ✓ Patients will have a neurological examination in order to assess a possible AE related to the drug:
  - on D1 of each block until the beginning of maintenance
  - every month during the first year of maintenance
  - every 3 months on the second year.

[59]Griggs, *et al,* J Clin Oncol, 2012; 30(13):1553-61

[60]Gurney*et al,* J Clin Oncol, 2007; 25(30):4703-4

[61]Sparreboom*et al,* J Clin Oncol, 2007; 25(30):4707-13

[62]Carlens*et al*,Clin Transplant, 1998; 12(2):84-92

About L-Asparaginase (annexe 5)

✓ It is recommended to stop estroprogestatives for female patients and replace them by continuous progestatives,

✓ Anaphylactoid reaction (grade ≥ 2) **must be reported as SAE**,

✓ Prevention of thromboembolic events:

- AT levels should be assayed daily or every second day, from D8 up to 48h after the end of induction or late intensification, without interrupting between D12 and D20, in order to maintain AT levels over 60% constantly, since the median date of occurrence of brain thrombosis was D17 in the GRAALL-2005 trialSubstitutive AT treatment (not FFP) is detailed in Annex 4 ; substitution with fibrinogen is not recommended,
- Prophylactic heparin is recommended.

Specific attention should be given to several issues from GRAALL-2005 (Annex 6):

✓ Age-adapted chemotherapy according to cures

✓ Monitoring of anti-asparaginase antibodies and of asparaginase activity,

✓ More regular monitoring of AT,

✓ CSF analyses modalities.

8 PREPHASE

From D -7 to D -1, maximum D -10 to D -1

PREDNISONE 60 mg/m2, PO **(or methylprednisolone IV 48 mg/m²)**	D-7 to D-1 (maximum D-10)
SIMPLE IT (N°0) only with **MTX IT 15 mg full dose**	During the first 3 prephase days whatever the peripheral blast cells count.

Note: CNS lesions are detailed in § 5.2.

CAREFUL!

Nor cytarabine, nor steroids in this IT

This prephase is common to all ALL patients and belongs to the usual management of this disease. It is performed as soon as the diagnosis is obtained and the initial examinations have been performed.

8.1 Definition of corticosensitivity

Whatever the day of corticotherapy onset, corticosensitivity assessment should be performed seven days after the initiation of corticotherapy.

Corticosensitivity assessment requires a detailed blood differential before prephase onset and on D1. It is reminded that corticosensitivity is always assessable **whatever the level of peripheral blasts since it is defined by a value of less than 1 G/L blast cells.**

In case of extramedullary location, especially in lymph nodes, a significant decrease of the tumor burden must be associated to biological criteria. Corticosensitivity includes ≥75% decrease of extra-medullary locations.

8.2 corticoprogression

Management of corticoprogressionFor patients whose peripheral blast count increases during the prephase, the following rules apply:

- ✓ corticoprogression must be concluded after at least 48h of Prednisone and IT MTX
- ✓ if WBC <100 G/L at diagnosis: at least 50% WBC increase compared to diagnosis and > 100 G/L
- ✓ if WBC > 100 G/L at diagnosis: any WBC increase after at least 48h prephase
- ✓ in case of tumor syndrome: any tumor size progression after 48h of prephase is corticoprogression.

8.3 Management of corticoprogression

✓ Chemotherapy is initiated,

✓ The patient remains in the trial,

✓The patient is scored as corticoresistant.

TREATMENT GIVEN TO PATIENTS ENROLLED IN RESEARCH

9 INDUCTION

The investigator collects, at the latest before initiating induction, the free informed written consent of the person enrolled in research.

The results of immunophenotype and molecular biology must be anonymized and faxed at the GRAALL secretariat to Véronique LHERITIER (fax: +33 (0)4.72.66.64.40) for central review and validation by the biology coordinators of the GRAALL group.

Induction can only start if the patient has been enrolled in GRAALL-2014/B (cf § 4).

Induction begins after evaluating corticosensitivity on D1

This phase must be initiated immediately after the prephase, whatever the hematologic situation (D1 follows D-1; there is no D0).

A simple medullogram must be performed on D8. Search for a donor can be initiated for all patients with medullary infiltration at this stage. Indeed, many of them will end up classified as VHR.

	18 – 44 years old	**45 - 59 years old**
PREDNISONE 60 mg/m^2, PO (or methylprednisolone IV 48 mg/m^2)	D1 to D14	D1 to D7
DAUNORUBICIN, over 30 mn	50 mg/m^2, slow IV D1 to D3 30 mg/m^2, slow IV D15 to D16	30 mg/m^2, slow IV D1 to D3 30 mg/m^2 , slow IV D15 to D16
VINCRISTINE 2 mg total dose slow SIV	D1, D8, D15 and D22	
**CYCLOPHOSPHAMIDE ****750 mg/m^2, IV, over 3h	D1 and D15	
L-ASPARAGINASE 6000 UI/m^2, IV, over1 h (Annex 4)	D8, D10, D12* D20, D22, D24, D26 and D28	D8, D10, D12* D20, D22 and D24
G-CSF 5 µg/kg/d, SC or IV	J18 until ANC > 1G/L	
TRIPLE IT(N°1 and 2) including *Methotrexate IT 15 mg total dose, Cytarabine IT 40 mg total dose, Depo-medrol®*** IT 40 mg total dose*	D1 and D8	

* D8, D10 and D12 L-Asparaginase injections must not be performed for CNS+ patients in order to allow for curative IT. Moreover, 2 injections (D26 and D28) must be added for patients ≥ 45 years old to obtain a total of 5 injections of L-Asparaginase.

** Use of mesna (Uromitexan®) to prevent cyclophosphamide toxicity is allowed (dosage according to investigator discretion).

*** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

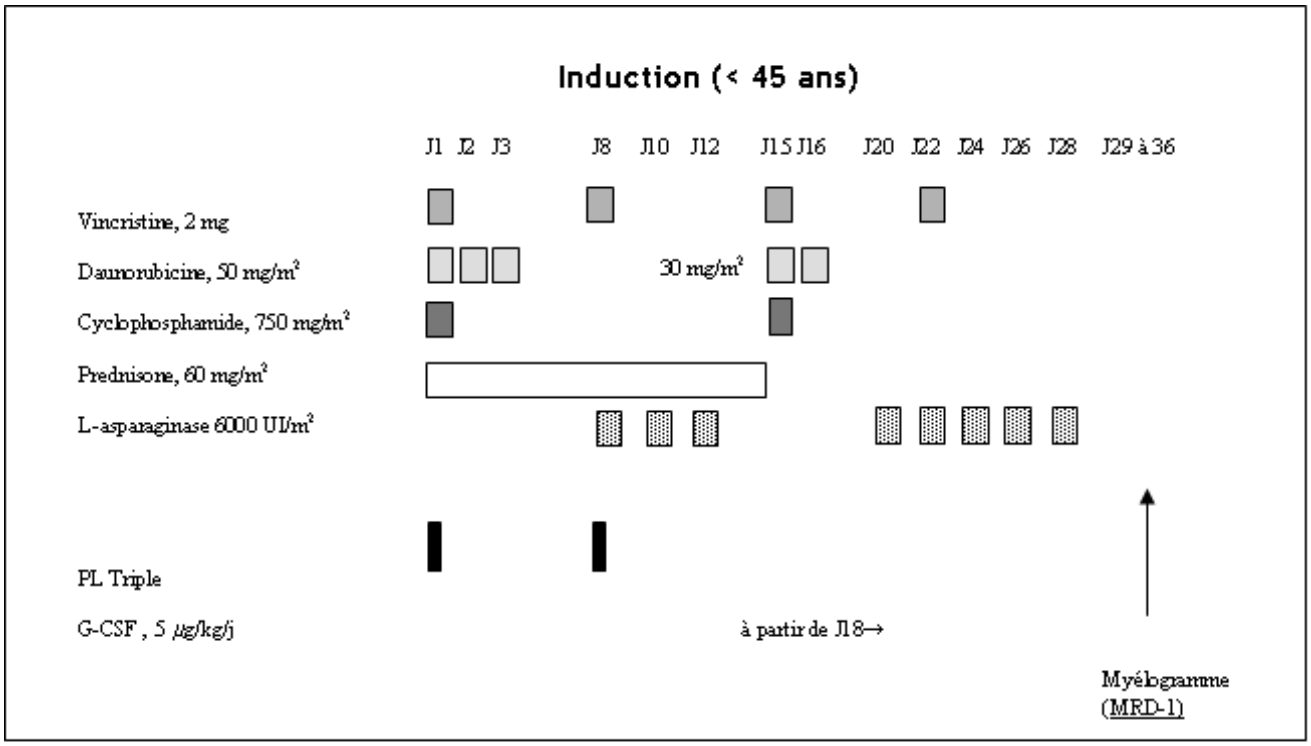
Of note, CNS lesions are detailed in § 6.2.

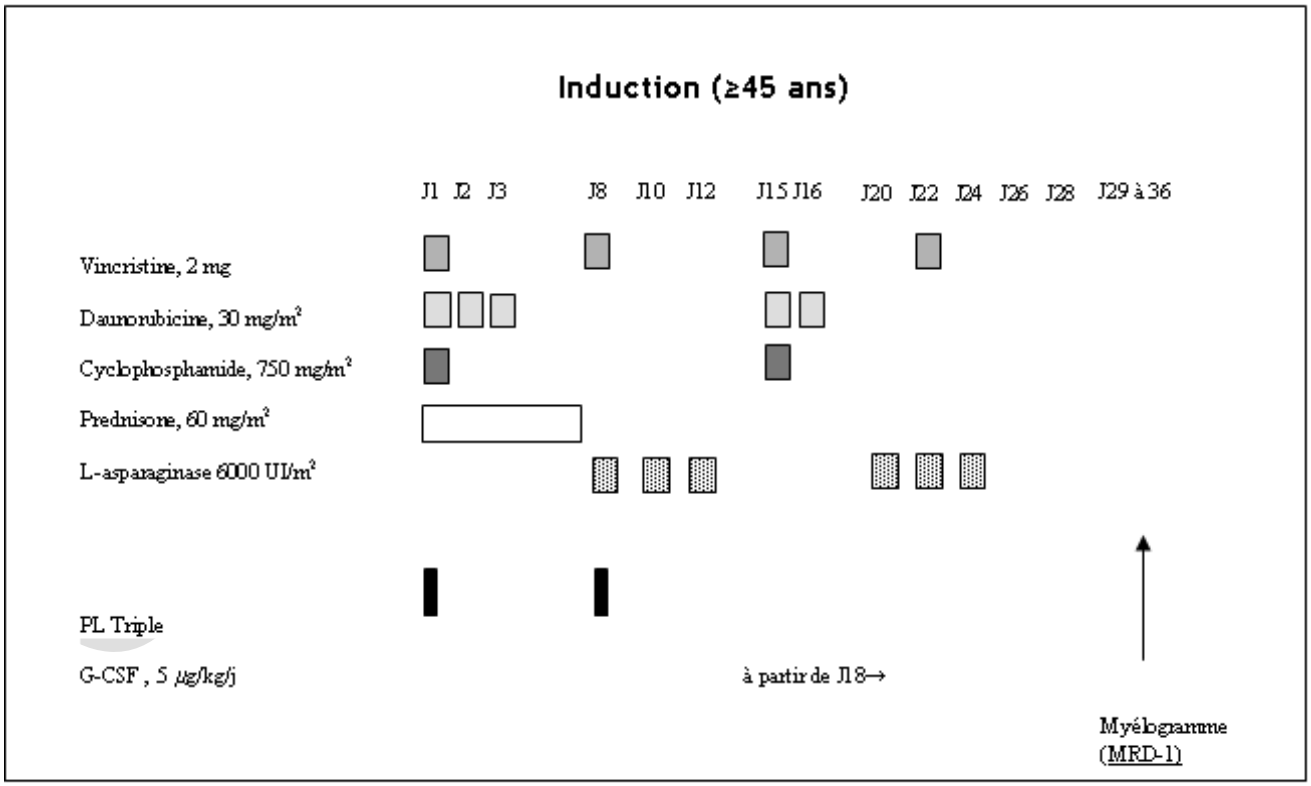
ⓘ **Age-adaptation of induction**. The duration of prednisone administration, doses of daunorubicin and L-Asparaginase injections numbers are age-adapted (18-44 years old *vs* 45-59 years old).

ⓘ **Monitoring of asparaginase**

1. Assay of anti-asparaginase antibodies: a reference sample must be collected at latest on D1 of chemotherapy (cf. Annex 5).
2. Primary monitoring of asparaginase activity and of ammoniemia (Annex 5) has to be done **48h after the 3rd injection** (theoretically D14) and. Secondary monitoring has to be done **48 h after the 6th injection** (theoretically D26). For all patients <45 years old, sample collection must be performed immediately before the 7th injection.
3. AT levels should be assayed daily or every second day, from D8 up to 48h after the end of induction or late intensification, without interrupting between D12 and D20, in order to maintain AT levels over 60% constantly, since the median date of occurrence of brain thrombosis was D17 in the GRAALL-2005 trial.

NB: Rules for kidrolase/erwinase switch are in annex 4


Induction (< 45 ans)
J1 J2 J3 J8 J10 J12 J15 J16 J20 J22 J24 J26 J28 J29 à 36
Vincristine, 2 mg
Daunorubicine, 50 mg/m²
30 mg/m²
Cyclophosphamide, 750 mg/m²
Prednisone, 60 mg/m²
L-asparaginase 6000 UI/m²
PL Triple
G-CSF , 5 µg/kg/j
à partir de J18→
Myélogramme
(MRD-1)


Induction (≥45 ans)
J1 J2 J3 J8 J10 J12 J15 J16 J20 J22 J24 J26 J28 J29 à 36
Vincristine, 2 mg
Daunorubicine, 30 mg/m²
Cyclophosphamide, 750 mg/m²
Prednisone, 60 mg/m²
L-asparaginase 6000 UI/m²
PL Triple
G-CSF , 5 µg/kg/j
à partir de J18→
Myélogramme
(MRD-1)

9.1 Evaluation of complete remission (and MRD1)

Post-induction bone marrow examination must be performed as soon as the level of ANC reaches 1 G/L AND that of platelets 100 G/L. **If by D35** these levels have not been reached, bone marrow then becomes MANDATORY.

The evaluation of post-induction MRD (MRD1) is performed at that time, on BONE MARROW, before initiation of the first consolidation block.

A blood sample (5 mL on EDTA) must be forwarded in parallel to the GRAALLThèque.

The response to induction therapy will be assessed according to **International Working Group Criteria**, summarized in part I paragraph 7.

9.2 Salvage

In case of induction failure, a salvage cure is proposed, whatever the patient's age. It can be initiated immediately after the bone marrow evaluation of induction completion.

Patients who failed induction are considered High Risk (HR) and become candidates for the ATRIALL substudy. VHR patients will be liable to receive allo-SCT in first complete remission.

IDARUBICIN 12 mg/m²/d, IV (1h)	D1 to D3
CYTARABINE 2000 mg/m²/12h, IV (3h)	D1 to D4 (or 8 perfusions over 4 days)
G-CSF 5 µg/kg/d, SC or IV (or pegylated GCSF 6 mg, SC on D8)	D8 until ANC > 1G/L

Although salvaged patients are de facto considered high risk, MRD1 will be evaluated after salvage (MRD1 Bis), before consolidation.

9.3 Reminder- classification of high risk (HR) T-lineage ALL

After induction, HR patients are identified as having:

Absence of NOTCH1 and/or FBXW7 mutation
or alteration of RAS or PTEN

and/or

MRD1 ≥ 10^{-4} (including non obtention of CR in 1 cure)

10 CONSOLIDATION N°1

Consolidation should be initiated between **D29 and D35 AT THE LATEST** (and 24 h after the last administration of G-CSF). Depending on the patient's condition, it begins by one or two stand-by blocks or by the S1 block.

10.1 Stand by blocks

Once CR is reached, 1 or 2 stand-by blocks may be prescribed, depending on patient condition. The objectives are to allow recovery from potential toxicities of induction, notably affecting the liver, not to modify the order of consolidation blocks, and to respect dose/intensity.

ETOPOSIDE (VP16) 150 mg/m²/d, IV (over 1h)	D1
CYTARABINE 30 mg/m²/12h, SC	D1 to D2 (or 4 injections over 2 days)

ⓘ **If stand-by blocks are decided upon, it is recommended to initiate the first one as soon as CR is reached.** The second one begins on D8 of the first.

10.2 Consolidation scheme n°1

Consolidation scheme n°1 is ongoing with three « standard » blocks of cytarabine (S1), methotrexate (S2) and cyclophosphamide (S3). **Of note, compared to GRAALL-2003 and 2005 trials** (Annex 6)**:**

✓ **L-Asparaginase will no longer be given during those blocks in order to minimize the risk of immunization,**

✓ **Methotrexate dose is increased to 5000 mg/m² in patients less than 45 years old,**

✓ **An additional IT occurs during the S2 block.**

ⓘ Between blocks intervals. The S1 block is initiated on D8 of stand-by block n°1 or n°2 if the latter were deemed necessary. Planned intervals between each block are strictly of two weeks, whatever the blood parameters.

ⓘ **Biological criteria to fulfill before S1 and S2 blocks:**

✓ ALAT (SGPT or TGP) < 5 x ULN,

✓ Creatinine clearance ≥ 60 mL/mn.

Whenever these biological criteria are not met before each block, the order of blocks is not modified and it is postponed until all criteria are met.

From S1 block on, patients are monitored for the investigation of anti-Asparaginase antibodies on D1 of blocks S1, S3 and S4 (Annex 5)

S1 Block – AraC

Block S1 – AraC (D1 to D14)	Whatever the patient's age
CYTARABINE 2000 mg/m^2/12h, IV (2h)	D1 and D2 (or 4 perfusions over 2 days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (or 40 mg over 2 days)
G-CSF 5 µg/kg/d, SC or IV	D8 to D12
ⓘ Remember to assay anti-Asparaginase antibodies on D1 (Annex 5)	

S2 Block – MTX

Block S2 – MTX (D15 to D28)	18 - 44 years old	45- 59 years old
VINCRISTINE 2 mg total dose slow IV	D1	D1
METHOTREXATE, IV continuous over 24 h	5000 mg/m² on D1	3000 mg/m² on D1
500 mg/m² CIV over 30 minutes then remaining dose (4500 mg/m² or 2500 mg/m²) CIV over 23h30	Rescue by folinic acid (Annex 7)	
6 – MERCAPTOPURIN* 60 mg/m², PO	D1 to D7	D1 to D7
G-CSF 5 µg/kg/d, SC or IV	D8 to D12	D8 to D12
TRIPLE IT (N°3) including *Methotrexate IT 15 mg total dose* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D2, H24 of methotrexate initiation	

* at bedtime, at distance from dairy products consumption
** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

S3 block – CPM

Block S3 –CPM (D29 to D35)	Whatever the patient's age
METHOTREXATE 25 mg/m^2/IV (30 mn)	D1
CYCLOPHOSPHAMIDE 500 mg/m², IV (3h **mandatory**)	D1 and D2
ETOPOSIDE (VP16) 75 mg/m², IV (1h**)**	D1 and D2
G-CSF 5 µg/kg/d, SC or IV	D3 until ANC > 1 G/L
TRIPLE IT (N°4) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D1
ⓘ remember assessing anti-Asparaginase antibodies on D1 (Annex 5)	

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

STANDARD RISK PATIENTS OR HIGH RISK PATIENTS NON ELIGIBLE FOR THE ATRIALL SUBSTUDY OR HIGH RISK PATIENTS ELIGIBLE FOR ATRIALL BEFORE ITS OPENING OR AFTER INCLUSION CLOSED (120 PATIENTS INCLUDED)

11 «STANDARD» CONSOLIDATION N°2

For standard risk (SR) patients or HR patients unable ineligible for being included in ATRIALL, consolidation n°2 (second series of 3 blocks) is initiated after hematologic recovery defined by ANC > 1 G/L and platelets > 100 G/L.

Consolidation n°2 includes the same 3 « standard » blocks as consolidation n°1: cytarabine (S4 identical to S1), methotrexate (S5 identical to S2) and cyclophosphamide (S6 identical to S3).

The medulogram evaluating MRD2 after consolidation n°1 must be performed before initiating D1 of block S4. It is essential for the stratification of patients in the VHR group which also conditions allo-SCT indication.

Evaluation of post-consolidation n°1 MRD (MRD2) is performed at this time, on BONE MARROW, before initiating S4 consolidation block.

ⓘ Planned intervals between each block are of strictly 2 weeks, whatever the blood parameters.

ⓘ **Biological criteria to fulfill before each block:**

✓ ALAT (SGPT or TGP) < 5 x ULN,

✓Creatinine clearance ≥ 60 mL/mn.

Whenever these biological criteria are not met, the order of blocks is not modified and it is postponed until all criteria are met.

S4 block- AraC

Block S4 – AraC (D1 to D14)	**Whatever the patient's age**
CYTARABINE 2000 mg/m^2/12h, IV (2h)	D1 and D2 (or 4 perfusions over 2 days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (or 40 mg over 2 days)
G-CSF 5 µg/kg/d, SC or IV	D8 to D12
ⓘ Remind of assessing anti-Asparaginase antibodies on D1 of S4 block (Annex 5)	

S5 block – MTX

Block S5 – MTX(D15 to D28)	18 - 44 years old	45- 59 years old
VINCRISTINE 2 mg total dose SIV	D1	D1
METHOTREXATE, IV continuous over 24h	5000 mg/m² on D1	3000 mg/m² on D1
500 mg/m² CIV over 30 minutes then the remaining (4500 mg/m² or 2500 mg/m² CIV) over 23h30	Salvage with folinic acid (Annex 7)	
6 – MERCAPTOPURIN* 60 mg/m², PO	D1 to D7	D1 to D7
G-CSF 5 µg/kg/d, SC or IV	D8 to D12	D8 to D12
TRIPLE IT(N°5) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D2, H24 of methotrexate initiation	

* at bedtime, at distance from dairy products consumption
** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

S6 block – CPM

Block S6 –CPM(D29 to D35)	Whatever the patient's age
METHOTREXATE 25 mg/m²/IV (30 mn)	D1
CYCLOPHOSPHAMIDE 500 mg/m², IV (3h **mandatory**)	D1 and D2
ETOPOSIDE (VP16) 75 mg/m², IV (1h)	D1 and D2
-CSF 5 µg/kg/d, SC or IV	D3 until ANC > 1 G/L
TRIPLE IT (N°6) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D1

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

12 LATE INTENSIFICATION

12.1 ALL not requiring salvage cure

Late intensification begins one week after hematological reconstitution following the S6 block of consolidation n°2 (ANC >1 G/L and platelets >100 G/L) providing ALAT are < 2.5 x ULN and creatinine clearance ≥ 60 mL/mn.

Pre-intensification MRD3 is performed on BONE MARROW just before late intensification.

It is has no decisional value.

Late intensification follows the same regimen as induction except:

✓ **daily DNR dose of D1 to D3 is 30 mg/m²/d instead of 50 mg/m²/d** for patients <45 years old

✓**age-related dose adaptation at on over 45 years of age,**

✓**Introduction of an alternative to *E Coli* Asparaginase for immunized patients (or clinically allergic without antibodies assessment)*.**

* In case of immunization to L-Asparaginase, substitution by *Erwiniachrysanthemi* (ERWINASE®) Asparaginase will be performed at a dosage of 25000 UI/m² (IV 1h) according to Annex 4.

	18 - 44 years old	45 - 59 years old
PREDNISONE 60 mg/m², PO (or Methylprednisolone IV 48 mg/m²)	D1 to D14	D1 to D7
DAUNORUBICIN, 30 mg/m²,SIV over 30 mn	D1 to D3 D15 and D16	D1 to D3
VINCRISTINE 2 mg total dose slow IV	D1, D8, D15 and D22	
CYCLOPHOSPHAMIDE* 750 mg/m², IV over 3h	D1 and D15	
L-ASPARAGINASE 6000 UI/m², IV, over 1 h (Annex 4) Or, if allergic reaction or positive anti-asparaginase antibodies: ERWINASE 25000 UI/m², IV over 1h at the same dates as Asparaginase,	D8, D10, D12, D20, D22, D24, D26 and D28	D8, D10, D12, D20, D22 and D24
G-CSF 5 µg/kg/D, SC or IV	D18 until ANC > 1G/L	
TRIPLE IT(N°7 and 8) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D1 and D8	

* Use of mesna (Uromitexan®) to prevent cyclophosphamide toxicity is allowed (dosage according to investigator discretion).

** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

Age-related adaptation. Prednisone administration time, doses of daunorubicin and L-Asparaginase injections numbers are age-adapted (< 45 ans vs ≥ 45 ans). Of note, daunorubicin will be given on days 15 and 16 only for patients < 45 years of age.

Monitoring of asparaginase

1. Primary monitoring of asparaginase activity and of ammoniemia (Annex 5) has to be done **48h after the 3rd injection** (theoretically D14) and. Secondary monitoring has to be done **48 h after the 6th injection** (theoretically D26). For all patients <45 years old, sample collection must be performed immediately before the 7th injection.
2. AT levels should be assayed daily or every second day, from D8 up to 48h after the end of induction or late intensification, without interrupting between D12 and D20, in order to maintain AT levels over 60% constantly, since the median date of occurrence of brain thrombosis was D17 in the GRAALL-2005 trial.

NB: Rules for kidrolase/erwinase switch are in annex 4

12.2 ALL with salvage cure

Patients who reached CR1 after salvage therapy with idarubicin + aracytine will receive the same late intensification.

Pre-intensification molecular evaluation(MRD3) is performed on the BONE MARROW just before late intensification. It has no decisional value.

IDARUBICIN 9 mg/m², IV (1h)	D1 to D3
CYTARABINE 2000 mg/m²/12h, IV (2h)	D1 to D4 (or 8 perfusions over 4 days)
G-CSF 5 µg/kg/d, SC or IV (or Neulasta)	D8 until ANC > 1G/L
TRIPLE IT (N°7 and 8) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D8 and D15

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

13 CONSOLIDATION N°3

Late intensification, whether or not patients required salvage therapy to reach CR1, is followed by consolidation n°3 including again 3 blocks. The latter repeat the AraC, MTX and CPM blocks of consolidations 1 and 2 (S7 identical to S1 and S4, S8 identical to S2 and S5, S9 identical to S3 and S6).**These blocks are not followed by prophylactic CNS irradiation.**

This sequence is to be initiated as soon as hematologic recovery is reached after late intensification (ANC >1G/L and platelets>100 G/L).

Planned intervals between each block are strictly of two weeks, whatever the blood parameters.

Biological criteria to fulfill before each block:

✓ ALAT (SGPT or TGP) < 5 x ULN,

✓Creatinine clearance ≥ 60 mL/mn.

Whenever these biological criteria are not met, the order of blocks is not modified and it is postponed until all criteria are met.

S7 block – AraC

Block S7 – AraC (D1 to D14)	**Whatever the patient's age**
CYTARABINE 2000 mg/m²/12h, IV (2h)	D1 and D2 (or 4 perfusions over 2 days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (or 40 mg over 2 days)
G-CSF 5 µg/kg/d, SC or IV	D8 to D12

S8 block – MTX

Block S8 – MTX (D15 to D28)	**18 - 44 years old**	**45- 59 years old**
VINCRISTINE 2 mg total dose SIV	D1	D1
METHOTREXATE, IV continuous over 24h **500 mg/m² CIV over 30 minutes then the remaining (4500 mg/m² or 2500 mg/m² CIV) over 23h30**	5000 mg/m² on D1 Rescue by folinic acid (Annex 7)	3000 mg/m²on D1
6 – MERCAPTOPURIN* 60 mg/m², PO	D1 to D7	D1 to D7
G-CSF 5 µg/kg/d, SC or IV	D8 to D12	D8 to D12
TRIPLE IT(N°9) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D2, 24h after methotrexate initiation	

* at bedtime, at distance from dairy products consumption

** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

S9 block – CPM

Block S9 –CPM (D29 to D35)	Whatever the patient's age
METHOTREXATE 25 mg/m²/IV (30 mn)	D1
CYCLOPHOSPHAMIDE 500 mg/m², IV (3h **mandatory**)	D1 and D2
ETOPOSIDE (VP16) 75 mg/m², IV (1h**)**	D1 and D2
G-CSF 5 µg/kg/D, SC or IV	D3 until ANC > 1 G/L
TRIPLE IT (N°10) including *Methotrexate IT 15 mg total dose ,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D1 **Do not administer to patients with CNS involvement and no SCT (irradiation to follow)**

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

14 MAINTENANCE

The whole duration of maintenance therapy is 24 months. Maintenance therapy is initiated after recovering from consolidation n°3 (ANC >1 G/L and platelets > 100 G/L).

Assessment of MRD4 is performed on BONE MARROW before initiating maintenance therapy. It has no decisional value.

A search for anti-Asparaginase antibodies on D1 of month 1 must be performed (Annex 5)

It is a classical maintenance regimen based on the association of 6-mercaptopurin + MTX, with monthly reinductions of vincristine and prednisone during the first year.

No G-CSF is given during this phase.

KEEP IN MIND

«GENERAL RULES FOR THE WHOLE TREATMENT »

(§ 7 of part III)

14.1 First maintenance year: 12 monthly reinductions

Total duration of maintenance is 2 years. During the first year, 12 reinductions should be given, each cycle duration being approximatively 4 weeks.

	Month 1 to Month 12
PREDNISONE 40 mg/m²/d, PO	D1 to D7
VINCRISTINE 2 mg total dose, IVD	D1
6-MERCAPTOPURIN 60 mg/m², PO at bedtime at distance from dairy products consumption	Every day, no interruption while reinduction Scrupulous dose adaptation (Annex 2).
METHOTREXATE 25 mg/m², PO	Once per week Scrupulous dose adaptation (Annex 2).
TRIPLE IT (N°11, 12, 13) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D1 of Month 1, 3, 5 (only CNS 1/2)

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

These monthly reinductions apply up to a total of **12 Vincristine injections**. They can be rescheduled if toxicity criteria recommend transient interruption of therapy (Annex 2).

Monthly administration of Bactrim® or Pentacarinat® is strongly recommended during maintenance (no folinic acid together with Bactrim® in order not to lessen MTX efficacy).

CNS-3 patients should not receive IT injections after CNS irradiation during maintenance.

14.2 Second maintenance year

Maintenance therapy is given until second anniversary of maintenance starting date.

	Month 13 to Month 24
6-MERCAPTOPURIN 60 mg/m², PO at bedtime at distance from dairy products consumption	Daily Scrupulous dose adaptation (Annex 2).
METHOTREXATE 25 mg/m², PO	Weekly Scrupulous dose adaptation (Annex 2).

Monthly administration of Bactrim® or Pentacarinat® is recommended during maintenance (no folinic acid together with Bactrim® in order not to lessen MTX efficacy).

15 CNSPROPHYLAXIS FOR PATIENTS NOT TRANSPLANTED

CNS prophylaxis includes 13 triple IT + 1 simple IT, and high dose MTX

No prophylactic CNS irradiation is proposed.

Note: in case of initial testis involvement, medical GRAALL coordination *via* the secretariat (Véronique LHERITIER: Tel: +33 (0)4 78 86 22 39 Fax: +33(0)4 72 66 64 40) should be contacted to decide on the local irradiation or irradiation complement to prescribe.

16 MANAGEMENT OF CNS INVOLVEMENT

In case of initial CNS involvement (CNS-3 and late CNS-2/3, § 6.2), patients will receive 1 simple IT and 12 triple IT between the prephase, induction and first consolidation.

Patients without Allo-SCT will moreover receive 6 triple IT between consolidation n°2, late intensification and consolidation n°3, then CNS irradiation (24 Gy).

CNS-3 patients should not receive IT injections after CNS irradiation during maintenance.

Patients with Allo-SCT will receive CNS irradiation (15 Gy) at the end of consolidation n°1.

HIGH RISK PATIENTS / ATRIALL SUBSTUDY

Patients with high risk T-ALL will be included as early as at second consolidation, in a phase II study appreciating the interest of nelarabine.

Inclusion in ATRIALL requires that the patient fulfills specific additional inclusion and non-inclusion criteria listed below (paragraph 18). Inclusion must occur at the end of consolidation n°1 as soon as information about MRD1 and of the oncogenetic profile (NOTCH1, FBXW7, PTEN, RAS) are available. Patients included in ATRIALL will retain the identification provided at inclusion in GRAALL-2014/T.

Patients having besides an indication of Allo-SCT will receive consolidation n°2, including nelarabineblock T4 before transplantation.

17 EXPERIMENTAL DRUG PRESCRIBED OUTSIDE MA AND PROVIDED BY THE SPONSOR

Nelarabine (ATRIANCE®) is a solution for perfusion at 5 mg/mL, provided in 50 mL vials, and will be provided by the sponsor through a donation convention with the GSK company. It has a specific contra-labelling in 4 languages (French, German, Dutch, Italian) with regulatory mentions for clinical trials.

It comes in a form adapted to clinical research.

It does not require specific conservation conditions.

18 INCLUSION AND NON INCLUSIONCRITERIA

18.1 Inclusion criteria

Following criteria should all be checked:

Patient

7. Included in GRAALL-2014/T
8. With HR T-ALL
9. ECOG ≤ 2
10. In CR after one or two induction cures and having received the three blocks of consolidation 1
11. Without documented CNS involvement at diagnosis
12. With or without allogeneic donor

18.2 Non Inclusion criteria

The following criteria should all be checked:

Patient

7. With ECOG status ≥ 3 after consolidation 1
8. With CNS involvement at diagnosis, or symptomatic CNS disease, or uncontrolled epilepsy
9. With peripheral neuropathy grade ≥ 2 after consolidation 1
10. With abnormal laboratory values as defined below after consolidation 1:
    a. ASAT (SGOT) and/or ALAT (SGPT) ≥ 5 x ULN
    b. Total bilirubin ≥ 1.5 x ULN
    c. Creatinine ≥ 1.5 x ULN or creatinine clearance < 50 ml/min
    d. Serum amylase and lipase ≥ 1.5 x ULN
11. With active uncontrolled infection, any other concurrent disease or medical condition that is deemed to interfere with the conduct of the study as judged by the investigator
12. Women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least three months thereafter. Patients not willing to ensure not to beget a child during participation in the study and at least three months thereafter
13. With known hypersensitivity to nelarabine
14. Not able to bear with the procedures or the frequency of visits planned in the trial

19 HIGH RISK "T" CONSOLIDATION N°2

19.1 reminder: Classification of high risk T-ALL (HR)

Absence of *NOTCH1* and/or *FBXW7* mutation
or alteration of *RAS* or *PTEN*
and/or
MRD1 ≥10^{-4} (including non obtention of CR in 1 cure)

19.2 Criteria for Allo-SCT in HR patients (VHR group)

All HR patients are not necessarily eligible for allo-SCT in CR1. The decision of allo-SCT in CR1 is only based on the MRD answer (MRD1 and MRD2). An unfavorable oncogenetic profile is not *per se* an indication for allo-SCT.

For this reason a group of very high risk patients (VHR) is defined based on MRD1 and MRD2 results:

MRD1 ≥10^{-3} (including non obtention of CR in 1 cure)
and/or
MRD2 ≥10^{-4}

Only VHR patients will be eligible for allo-SCT in CR1. Almost all VHR-MRD patients are HR patients and thus eligible for ATRIALL study.

Pragmatically, to accelerate the search for a donor in patients who will be VHR, a simple medullogram (with local morphologic analysis) is planned on day D8 of induction chemotherapy. HLA typing of the patient and siblings will be performed at diagnosis. In the absence of HLA-identical brother or sister, search for an unrelated donor will be initiated for patient's chemoresistanton D8 (local morphological assessment). Indeed, chemoresistance on D8 is the factor best correlated to the VHR criterion.

In all cases, if not already performed, search for a donor will be necessary if MRD1 is ≥10^{-3} since all these patients are classified VHR. Yet, a small percentage of patients will be classified VHR only on their MRD2 level(< 5%).

19.3 Treatment

Consolidation n°2 includes 3 blocks. The first one is a block associating nelarabine to cyclophosphamide and VP-16 (T4, NELA). The two following blocks are consecutively an AraC block (T5 identical to S1) and an MTX block (T6 identical to S2 with methotrexate capped at 3000 mg/m² whatever the age).

Evaluation of MRD2 is performed at that time, on BONE MARROW, before initiating the first consolidation block (T4).

ⓘ Planned intervals between each block are **3 weeks** between block **T4 (NELA) and block T5** (AraC) and strictly **2 weeks** before block **T5 and T6** (MTX), whatever blood count results.

ⓘ Biological criteria to fulfill before initiating blocks T5 and T6:

✓ ALAT (SGPT or TGP) < 5 x ULN,

✓Creatinine clearance ≥ 60 mL/mn.

For toxicity reasons, the blocks' order must not be modified, for any reason.

T4 block- Nela

Block T4 – Nelarabine(D1 to D21)	**Whatever the patient's age**
NELARABINE 1500 mg/m^2, IV (2h)	D1, D3 and D5
CYCLOPHOSPHAMIDE 150 mg/m^2, IV (3h **mandatory**)	D1 and D3
ETOPOSIDE (VP16) 75 mg/m^2, IV (1h**)**	D1 and D3
G-CSF 5 µg/kg/D, SC or IV	D7 until ANC > 1 G/L
ⓘ **no IT during nelarabine block** ⓘ anti-Asparaginase antibodies assay on D1 (Annex 5) ⓘ Neurological examination before administration of nelarabine	

T5 block – AraC

Block T5 – AraC(D22 to D35)	**Whatever the patient's age**
CYTARABINE 2000 mg/m^2/12h, IV (2h)	D1 and D2 (4 perfusions over days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (or 40 mg over 2 days)
G-CSF 5 µg/kg/D, SC or IV	D8 to D12
ⓘ Neurological examination must be performed at D1 of this cure	

T6 block – MTX

Block T6 – MTX(D36 to D49)	**Whatever the patient's age**
VINCRISTINE 2 mg total dose SIV	D1
METHOTREXATE*, IV continuous over 24 h 500 mg/m² CIV over 30 minutes then 2500 mg/m² CIV over 23h30	3000 mg/m² on D1 Rescue with folinic acid (Annex 7)
6 – MERCAPTOPURIN** 60 mg/m², PO	D1 to D7
G-CSF 5 µg/kg/D, SC or IV	D8 to D12
TRIPLE IT(N°9) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®*** IT 40 mg total dose*	D2, 24h after methotrexate initiation
ⓘ Neurological examination must be performed at D1 of this cure	

* no age adaptation; ** at bedtime at distance from dairy products consumption

*** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

20 LATE INTENSIFICATION

20.1 all not having required rescue CURE

Late intensification applies to all patients without an indication of Allo-SCT in CR1 and who did not require salvage therapy to reach CR1. It begins one week after hematological recovery following the T6 block of consolidation n°2 (ANC >1 G/L and platelets >100 G/L) providing ALAT are < 2.5 x ULN and creatinine clearance ≥ 60 mL/mn.

Pre-intensification MRD3 is performed on BONE MARROW just before late intensification. It has no decisional value.

Late intensification follows the same regimen as induction except:

✓daily DNR dose of D1 to D3: 30 mg/m²/d instead of 50 mg/m²/d for patients <45 years old

✓age-related dose adaptation at on over 45 years old of age,

✓introduction of an alternative to *E Coli* Asparaginase for immunized patients (or clinically allergic without antibodies assessment)*.

* In case of immunization to L-Asparaginase, substitution by *Erwiniachrysanthemi* (ERWINIA®) **Asparaginase** will be performed at a dosage of 25000 UI/m² (IV 1h) according to Annex 4.

	18 - 44 years old	45 – 59 years old
PREDNISONE 60 mg/m², PO (or Methylprednisolone IV 48 mg/m²)	D1 to D14	D1 to D7
DAUNORUBICIN, 30 mg/m²,SIV over 30 mn	D1 to D3 D15 and D16	D1 to D3
VINCRISTINE 2 mg total dose slow IV	D1, D8, D15 and D22	
CYCLOPHOSPHAMIDE* 750 mg/m², IV over 3h	D1 and D15	
L-ASPARAGINASE 6000 UI/m², IV, over 1 h (Annex 4) Or, if allergic reaction or positive anti-asparaginase antibodies: ERWINASE 25000 UI/m², IV over 1h at the same dates as Asparaginase,	D8, D10, D12, D20, D22, D24, D26 and D28	D8, D10, D12, D20, D22 and D24
G-CSF 5 µg/kg/D, SC or IV	D18 until ANC > 1G/L	
TRIPLE IT(N°7 and 8) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D1 and D8	

* Use of mesna (Uromitexan®) to prevent cyclophosphamide toxicity is allowed (dosage according to investigator discretion).

** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

ⓘ Neurological evaluation must be performed on D1 of this cure

Age-related adaptation. Prednisone administration time, doses of daunorubicin and L-Asparaginase injections numbers depend whether the patient is less or more than 45 years old. Of note, daunorubicin will be given on D15 and D16 only for patients < 45 years of age.

Monitoring of asparaginase

1. Primary monitoring of asparaginase activity and of ammoniemia (Annex 5) has to be done **48h after the 3rd injection** (theoretically D14) and. Secondary monitoring has to be done **48 h after the 6th injection** (theoretically D26). For all patients <45 years old, sample collection must be performed immediately before the 7th injection.
2. AT levels should be assayed daily or every second day, from D8 up to 48h after the end of induction or late intensification, without interrupting between D12 and D20, in order to maintain AT levels over 60% constantly, since the median date of occurrence of brain thrombosis was D17 in the GRAALL-2005 trial.

NB: Rules for kidrolase/erwinase switch are in annex 4

20.2 ALL with rescue CURE

Patients who reached CR1 after salvage therapy with idarubicin + aracytine will receive the same late intensification.

Pre-intensification molecular evaluation (MRD3) will be performed on the BONE MARROW just before late intensification. It has no decisional value.

IDARUBICIN 9 mg/m², IV (1h)	D1 to D3
CYTARABINE 2000 mg/m²/12h, IV (2h)	D1 to D4 (8 perfusions over 4 days)
G-CSF 5 µg/kg/D, SC or IV (or Neulastaon D8)	D8 until ANC > 1G/L
TRIPLE IT(N°7 and 8) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D8 and D15
Neurological evaluation must be performed on D1 of this cure	

*Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

21 CONSOLIDATION N°3

Late intensification is followed by consolidation n°3 including again 3 blocks, which repeat the NELA, AraC and MTX blocks of consolidation 2 (T7 = T4, T8 = T5, T9 = T6). These blocks are not followed by prophylactic CNS irradiation.

This sequence is to be initiated as soon as hematologic recovery is reached after late intensification (ANC >1G/L and platelets>100 G/L).

ⓘ Planned intervals between each block are strictly of **three weeks** between **T7 block (NELA) and T8 block (AraC**) and strictly **two weeks** between **T8 and T9** (MTX) blocks, whatever the blood parameters.

ⓘ Biological criteria to record before each block:

✓ ALAT (SGPT oy TGP) < 5 x ULN,

✓Creatinine clearance ≥ 60 mL/mn.

Because of potential toxicity, the blocks order must not be modified, for any reason.

T7 block- Nela

Block T7 – Nelarabine(D1 to D21)	**Whatever the patient's age**
NELARABINE 1500 mg/m^2, IV (2h)	D1, D3 and D5
CYCLOPHOSPHAMIDE 150 mg/m^2, IV (3h **mandatory**)	D1 and D3
ETOPOSIDE (VP16) 75 mg/m^2, IV (1h**)**	D1 and D3
G-CSF 5 µg/kg/D, SC or IV	D7 until ANC > 1 G/L
ⓘ **No IT during nelarabine block** ⓘ Neurological evaluation must be performed before nelarabine administration	

T8 block – AraC

Block T8 – AraC(D22 toD35)	**Whatever the patient's age**
CYTARABINE 2000 mg/m^2/12h, IV (2h)	D1 and D2 (or 4 perfusions over 2 days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (or 40 mg over 2 days)
G-CSF 5 µg/kg/D, SC or IV	D8 to D12
ⓘ Neurological evaluation must be performed on D1 of this cure	

T9 block – MTX

Block T9 – MTX(D36 to D49)	**Whatever the patient's age**
VINCRISTINE 2 mg total dose SIV	D1
METHOTREXATE*, IV continuous over 24 h 500 mg/m² CIV over 30 minutes then 2500 mg/m² CIV over 23h30	3000 mg/m² on D1
	Folinic acid rescue (Annex 7)
6 – MERCAPTOPURIN** 60 mg/m², PO	D1 to D7
G-CSF 5 µg/kg/D, SC or IV	D8 to D12
TRIPLE IT (N°9) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®*** IT 40 mg total dose*	D2, 24h after methotrexate initiation
ⓘ Neurological evaluation must be performed on D1 of this cure	

* no age adaptation ** at bedtime without dairy productsat distance from dairy products consumption
*** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

22 MAINTENANCE

The whole duration of maintenance is 24 months. Maintenance therapy is initiated after recovering from consolidation n°3 (ANC >1 G/L and platelets > 100 G/L (Annex 2)).

Assessment of MRD4 is performed on BONE MARROW before initiating maintenance therapy. It has no decisional value.

Search for anti Asparaginase antibodies must be performed on D1 of month 1 (Annex 5)

It is a classical maintenance regimen based on the association of 6-mercaptopurin + MTX, with reinductions either by nelarabine (Month 2, 4 and 6) or by vincristine and prednisone (Month 1, 3, 5, and 7 to 12) for the first year. Reinductions are monthly.

No G-CSF is given during this phase.

KEEP IN MIND RECOMMANDATIONS ENTITLED « GENERAL RULES FOR THE WHOLE TREATMENT » (§ 7 of part III)

22.1 First maintenance year: 12 monthly reinductions (3 nela and 9 vcr)

Total duration of maintenance is 2 years. During the first year, 12 reinductions should be given, each cycle duration being approximatively 4 weeks.

<table>
<tr><th></th><th>Month 1, 3, 5, and 7 to 12</th><th>Month 2, 4, 6</th></tr>
<tr><td></td><td>PREDNISONE 40 mg/m²/day PO from D1 to D7</td><td rowspan="3">NELARABINE 1500 mg/m²/IV (2h) on D1, D3 and D5</td></tr>
<tr><td></td><td>VINCRISTINE 2 mg total dose IVD on D1</td></tr>
<tr><td></td><td>6-MERCAPTOPURIN 60 mg/m²/day, PO
at bedtime at distance from dairy products consumption
Scrupulous dose adaptation (Annex 2).</td></tr>
<tr><td></td><td>METHOTREXATE 25 mg/m², PO
Weekly
Scrupulous dose adaptation (Annex 2).</td><td rowspan="2">No IT during nelarabine</td></tr>
<tr><td>TRIPLE IT(N°11, 12, 13) including
Methotrexate IT 15 mg total dose,
Cytarabine IT 40 mg total dose,
*Depo-medrol® * IT 40 mg total dose</td><td>D1 of Month 1, 3, 5</td></tr>
<tr><td colspan="3">Neurological evaluation must be performed on D1 of each month</td></tr>
</table>

Reinductions can be rescheduled if toxicity criteria recommend transient interruption of therapy (Annex 2).

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

Monthly administration of Bactrim® or Pentacarinat® is strongly recommended during maintenance (no folinic acid together with Bactrim® in order not to lessen MTX efficacy).

22.2 Second maintenance year

Maintenance therapy is given until second anniversary of maintenance starting date.

<table>
<tr><th></th><th>Month 13 to 24</th></tr>
<tr><td>6-MERCAPTOPURIN 60 mg/m², PO
at bedtime at distance from dairy products consumption</td><td>Daily
Scrupulous dose adaptation (Annex 2).</td></tr>
<tr><td>METHOTREXATE 25 mg/m², PO</td><td>Weekly
Scrupulous dose adaptation (Annex 2).</td></tr>
<tr><td colspan="2">Neurological evaluation must be performed every 3 months</td></tr>
</table>

Monthly administration of Bactrim® or Pentacarinat® is strongly recommended during maintenance (no folinic acid together with Bactrim® in order not to lessen MTX efficacy).

23 ALLO-SCT IN CR1

Eligible patients will receive Allo-SCT, after age-adapted conditioning, with a geno-identical or unrelated 10/10 or 9/10 donor. Allo-SCT will be performed at the end of consolidation n°2 after inclusion in GRAALL-2014/T or phase II trials (ATRIALL) if MRD1 $>10^{-4}$.

Allo-SCT indication being possibly identified at a later stage (MRD2), it is recommended to initiate early the search for a donor. Results of D8 bone marrow examination can be used to help as mentioned above.

23.1 Allo-sct in patients < 45 years old

✓ TBI: 12 Gy in 6 fractions with lung protection above 8 Gy

✓ Cyclophosphamide: 60 mg/kg per day for 2 days

✓ +/- ATG in case of unrelated 10/10 or 9/10 graft (thymoglobuline or ATG Frésenius) (according to each center's habits)

GVH prophylaxis will associate ciclosporine A and MTX on D1, D3, D6 (+/- D11). A bone marrow graft will be preferred.

Patients with Allo-SCT will receive CNS irradiation (15 Gy) at the end of consolidation n°1 before TBI.

Assessment of MRD4 is performed on BONE MARROW (medullogram) at D100 post Allo-SCT. It has no decisional value.

23.2 Allo-sct in patients aged from 45 to 59 years old

Allo-SCT after RTC associating TBI 8 Gy + Fluda according to Bornhäuser Lancet Oncology 2012

✓ TBI: 8Gy in 4 fractions (D-3 and D-2) or 6 Gy in one fraction

✓ Fludarabine: 30mg/m^2/d x 4 d from D-6 to D-3

✓ +/- ATG in case of unrelated 10/10 or 9/10 graft according to centers'habits (thymoglobuline or ATG Fresenius) according to each center's habits.

GVH prophylaxis will associate ciclosporine A and MTX on D1, D3, D6 and D11. A mobilized peripheral graft will be preferred.

Assessment of MRD4 is performed on BONE MARROW (medullogram) at D100 post Allo-SCT. It has no decisional value.

23.3 Pre-SCT interphase blocks (optional)

The alternance of blocks administrated during consolidations 1 and 2 should not be performed.

If needed, it is possible to perform interphase waitingblocks between the end of consolidation n°2 and allo-SCT. These blocks rely on an alternance of cytarabine/dexamethasone and Vincristine/6MP + Methotrexate according to the schema below, for at most 4 interphase blocks.

Hematological recovery should be waited upon between each of these blocks.

STAND BY BLOCKS 1 AND 3

Block S7 – AraC (D1 to D14)	**Whatever the patient's age**
CYTARABINE 1000 mg/m^2/12h, IV (2h)	D1 and D2 (or 4 perfusions over 2 days)
DEXAMETHASONE 10 mg/12h, total dose, IV	D1 and D2 (or 40 mg over 2 days)
G-CSF 5 µg/kg/d, SC or IV	D8 to D12

STAND BY BLOCKS 2 AND 4

Bloc S8 – MTX(D15 to D28)	**Whatever the patient's age**
VINCRISTINE 2 mg total dose SIV	D1
METHOTREXATE, IV continuous over 24 hours	1500 mg/m² à D1
	Folinic acid rescue (Annex 7)
6 – MERCAPTOPURIN* 60 mg/m², PO	D1 to D7
G-CSF 5 µg/kg/d, SC or IV	D8 to DJ12

* at bedtime at distance from dairy products consumption

PART IV
GRAAPH-2014
(PHILADELPHIA CHROMOSOME ALL)

SYNOPSIS GRAAPH-2014 (ALL PH+)

Title	**A phase III study, randomized, to evaluate the reduction of chemotherapy intensity in association with nilotinib (Tasigna®) in Philadelphia chromosome-positive (Ph+) ALL of young adults (18-59 years old).**
Acronym	**GRAAPH-2014**
Coordinator	**Pr. Hervé DOMBRET** **Hématologie, Hôpital Saint Louis, Paris** **Tél: +33 (0)1 57 27 68 47 /(0)1 42 49 96 48** **Email: herve.dombret@ aphp.fr**
Sponsor	**Assistance Publique – Hôpitaux de Paris**
Experimental drug Prescription outside MA	**Nilotinib (Tasigna®)**
Experimental drugs Prescription according to MA	Imatinib (IM), Prednisone (PDN), Dexamethasone (DEX), Vincristine (VCR), Methotrexate (MTX), Cytarabine (ARA-C), 6-Mercaptopurin (6MP), Granulocyte colony-stimulating factor (G-CSF).
Indication	Patients aged 18-59 years old with *de novo*Ph+ ALL.
Type of study	Multicenter, open-label, randomized,phase III
Number of subjects selected	265 patients
Study duration	Enrollment period: 5 years. Participation according to trial (treatment + follow-up): 5 years Total duration of the study: 10 years
Number of centers	About 80 centers expected (Belgium, France, Switzerland)
Objectives	Primary objective: Non-inferiority of the experimental arm (arm B) compared to the control arm (arm A) in terms of Major Molecular Response (MMolR**)** after the 4th cycle (MRD4). Secondary objectives: Comparison of the experimental arm and of the control arm in terms of tolerance, CIR, EFS and OS.
Evaluation criteria	Primary evaluation criterion • Major Molecular Response (MMolR**)** defined as a BCR-ABL/ABL ratio < 0.1% in the bone marrow sample of MRD4 Secondary evaluation criteria • Tolerance • Complete remission after cycle 1 • Cumulative incidence of treatment- and transplantation-related mortality • Cumulative incidence of relapse • Relapse free survival • Event free survival • Overall survival • Investigation of T315I mutation and of resistance (mutations will be assessed by RQ-PCR sequencing in case of progression or relapse).
Statistical justification of sample size	It is planned to include 265 patients with Ph+ ALL in the GRAAPH-2014 trial over 5 years. With an anticipated rate of 80% MRD4 MMolR expected in the control arm, accepting a 15% delta, with a 0.05 alpha risk and a 0.90 power 125 patients will be randomized in each arm in order to demonstrate the non inferiority of the experimental arm in terms of MRD4 MMolR.

	Moreover, an intermediate analysis of MRD2 MMolR will be planned for the first patients in order to estimate the global rate of MMolR with a confidence interval of 95%. If this rate was found lower than that observed in the GRAAPH-2005 (which used imatinib), an amendment allowing to replace nilotinib by imatinib (or even dasatinib) for the whole 4 pre-SCT cycles will be discussed by the independent committee of the trial. In order to have an interval of 0.2 width (or 0.1 precision), assuming an MRD2 rate of 80%, this intermediate analysis should be performed on the 60 first patients included(about ¼ of the global cohort). A total of 265 patients will therefore be included, in order to be able to reach the objective of 250 evaluable patients.
GRAAPH-2014 **Inclusion Criteria**	Patient 1. Whose blood and bone marrow explorations have been completed before the steroids prephase 2. Aged 18-59 years old with newly-diagnosed non previously treated Ph+ ALL according to WHO 2008 criteria (confirmed diagnosis of the Philadelphia chromosome defined by the reciprocal translocation of chromosomes 9 and 22, t(9;22) and/or presence of the BCR-ABL molecular maker) 3. With ≥ 20% bone marrow blasts 4. With ECOG ≤ 3 5. With or without central nervous system (CNS) or testis involvement 6. Without evolving cancer (except basal cell carcinoma of the skin or "in situ" carcinoma of the cervix) or its chemo- or radio-therapy should be finished at least since 6 months. 7. Having received no previous treatment for this hematological disease (including IT injection) 8. Having signed written informed consent 9. With efficient contraception for women of childbearing age (excluding estrogens and IUD) 10. With health insurance coverage 11. Who have received (or being receiving) the recommended steroid prephase. Note 1: Secondary ALL (antecedent of chemo- or radio-therapy) can be included Note 2: Incase of high vascular risk (seesection "study management") the patient will not be able to receive nilotinib unless an ultra sound Doppler of the neck and lower limbs has been performed during the pre-phase and treatment validated by the medical coordinators of the GRAALL *via* the secretariat.
GRAAPH-2014 **non inclusion Criteria**	Patient: 1. Previously treated with Tyrosine Kinase Inhibitor (TKI) 2. With another active malignancy 3. With general or visceral contra-indication to intensive therapy (except if considered related to the ALL): a. ASAT (SGOT) and/or ALAT (SGPT) > 2.5 x ULN b. Total bilirubin > 1.5 x ULN c. Creatinine > 1.5 x ULN or creatinine clearance <50 mL/mn d. Serum amylase or lipase ≥ 1.5 x ULN or antecedents of acute pancreatitis 4. With heart failure, including at least one of the following criteria: a. left ventricular ejection fraction (LVEF) <50% or below the lowest normal threshold, as determined by ECG or heart failure (NYHA grade III or IV) b. impossibility to measure the QT interval on ECG c. complete left bundle branch block d. pacemaker e. congenital long QT syndrome of known familial antecedents of long QT syndrome f. antecedents or current ventricular or atrial tachyarrhythmia, clinically significant g. baseline bradycardia (<50 bpm) clinically significant

h. QTc> 450 msec established on the mean of 3 baseline ECG
i. Antecedents of myocardial infarct in the past 6 months
j. Instable angor within the past 12 months
k. Any heart condition clinically significant (i.e. congestive heart failure, uncontrolled hypertension)

5. active uncontrolled infection, any other concurrent disease deemed to interfere with the conduct of the study as judged by the investigator
6. with severe evolving infection, or known HIV or HTLV1 seropositivity, or chronic hepatitis B (HbsAg-positive) or C
7. Pregnant (β-HCG) or nursing woman
8. Women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least three months thereafter. Patient not willing to ensure not to beget a child during participation in the study and at least three months thereafter.
9. Having received an investigational treatment or participation in another trial within 30 days prior to entering this study.
10. Not able to bear with the procedures or the frequency of visits planned in the trial.
11. Unable to consent, under tutelage or curatorship, or judiciary safeguard

Treatment

During the prephase, all patients will be randomized between Arm A (control arm) and Arm B (experimental arm).

4 treatment cycles will be administered before HSCT (evaluation of the primary objective at MRD4). Odd cycles (1 and 3) will be identical between both arms. Cycles 2 and 4will differ. MRD will be monitored after each cycle.

Chemotherapy

Cycle 1 (D1-D28) identical in both arms

Nilotinib	**400 mg/12h**	**D1 to D28**
Dexamethasone	**40 mg, PO or IV**	**D1, D2, D8, D9, D15, D16, D22, D23**
Vincristine	**2 mg total dose IV**	**D1, D8, D15, D22**
IT	**MTX + Ara-C + Depomedrol**	**D1, D8, D15**
G-CSF	**5 µg/kg/d (SC)**	**D15 until neutrophils> 1G/L**

Cycle 2A - Arm A

Nilotinib	**400 mg/12h**	**D1 to D28**
MTX	**1 g/m²CIV**	**D1**
AraC	**3 g/m²/12h***	**D2, D3**
G-CSF	**5µg/kg/d** (SC)	D6 until ANC > 1 G/L
IT	**MTX + Ara-C + Depomedrol**	**D9**

* dose decreased to 1.5 g/m²/12h if ≥ 45 y

Cycle 2B - Arm B

Nilotinib	**400 mg/12h**	**D1 to D28**
MTX	**1 g/m²CIV**	**D1**
	No AraC	
G-CSF	**5µg/kg/d** (SC)	D6 until ANC > 1 G/L
IT	**MTX + Ara-C + Depomedrol**	**D9**

Cycle 3 (D1-D28) identical in both arms

Nilotinib	**400 mg/12h**	**D1 to D28**
Dexamethasone	**40 mg, PO or IV**	**D1, D2, D8, D9, D15, D16,D22, D23**
Vincristine	**2 mg total dose IV**	**D1, D8, D15, D22**
IT	**MTX + Ara-C + Depomedrol**	**D1**
G-CSF	**5 µg/kg/d (SC)**	**D15 until ANC >1G/L**

Cycle 4A - Arm A

Cycle 4B - Arm B

Nilotinib	**400 mg/12h**	**D1 to D28**		**Nilotinib**	**400 mg/12h**	**D1 to D28**
MTX	**1 g/m²CIV**	**D1**		**MTX**	**1 g/m²CIV**	**D1**
AraC	**3 g/m²/12h***	**D2, D3**			**No AraC**	
G-CSF	**5µg/kg/d** (SC)	D6 until ANC > 1 G/L		**G-CSF**	**5µg/kg/d** (SC)	D6 until ANC > 1 G/L
IT	**MTX + Ara-C + Depomedrol**	**D9**		**IT**	**MTX + Ara-C + Depomedrol**	**D9**
* dose decreased to 1.5 g/m²/12h if ≥ 45 y						

<u>Interphase</u> (2 cycles) **<u>identical in both arms</u>**

Nilotinib	**300 mg/12h**	**D1 to D14**
MTX	**25 mg/m², PO**	**D1, D8**
6MP	**60 mg/m², PO**	**D1 to D14**

MRD4 level should be available during the first interphase cycle.

- Patients with a BCR-ABL/ABL ratio lower than 0.1% will receive either auto-SCT or allo-SCT (from sibling or MUD 10/10 or 9/10 MUD) according to the investigator's choice. Autologous peripheral blood SC (PBSC) harvest will be achieved between the two interphase cures, in a stable state.
- Patients with a BCR-ABL/ABL ratio of 0.1% or higher will receive an allo-SCT (from sibling or MUD 10/10 or 9/10)or even from an alternate source of stem cells (cord blood, haploidentical SCT) or will go off-study to enter another experimental trial.

<u>Hematopoietic Stem Cell Transplantation</u> <u>(after 4 cycles + interphase)</u>

Evaluation of MRD5 on Bone marrow and peripheral blood BCR-ABL during pre-SCTassessment

Allogeneic SCT:

Conditioning will be myeloablative (TBI-Cy) for patients up to 55 years old (TBI, fractionated 12 Gy and cyclophosphamide, 120 mg/kg <u>+</u> ATG if phenoidentical allo-SCT 10/10 and + ATG if 9/10 graft). Patients ≥ 55 years old or with a contra-indication for the myeloablative conditioning will receive a RTC with TBI-fludarabine (TBI, fractionated 8 Gy dose or unfractionated 6 Gy; and fludarabine, 120 mg/m²+ ATG if phenoidentical SCT 10/10 or 9/10 graft).

Autologous SCT:

Conditioning will be myeloablative (TBI-Cy) depending on the age and status of the patient (TBI 8-10-12 Gy in 5-6 fractions; and cyclophosphamide 120mg/kg).

<u>Post-SCT Maintenance</u>

MRD6 evaluation on bone marrow and peripheral blood BCR-ABL at day 100 after SCT

Maintenance treatment will start as soon as ANC ≥ 1G/L, platelets ≥ 80G/L and at the latest on D100, in the absence of other contra-indications.

Maintenance therapy will be Imatinib 300 mg/12h for during at least 2 years.

If MRD is undetectable (with a sensitivity of at least 0.01%) for 2 years then imatinib Mesylatecould be discontinued.

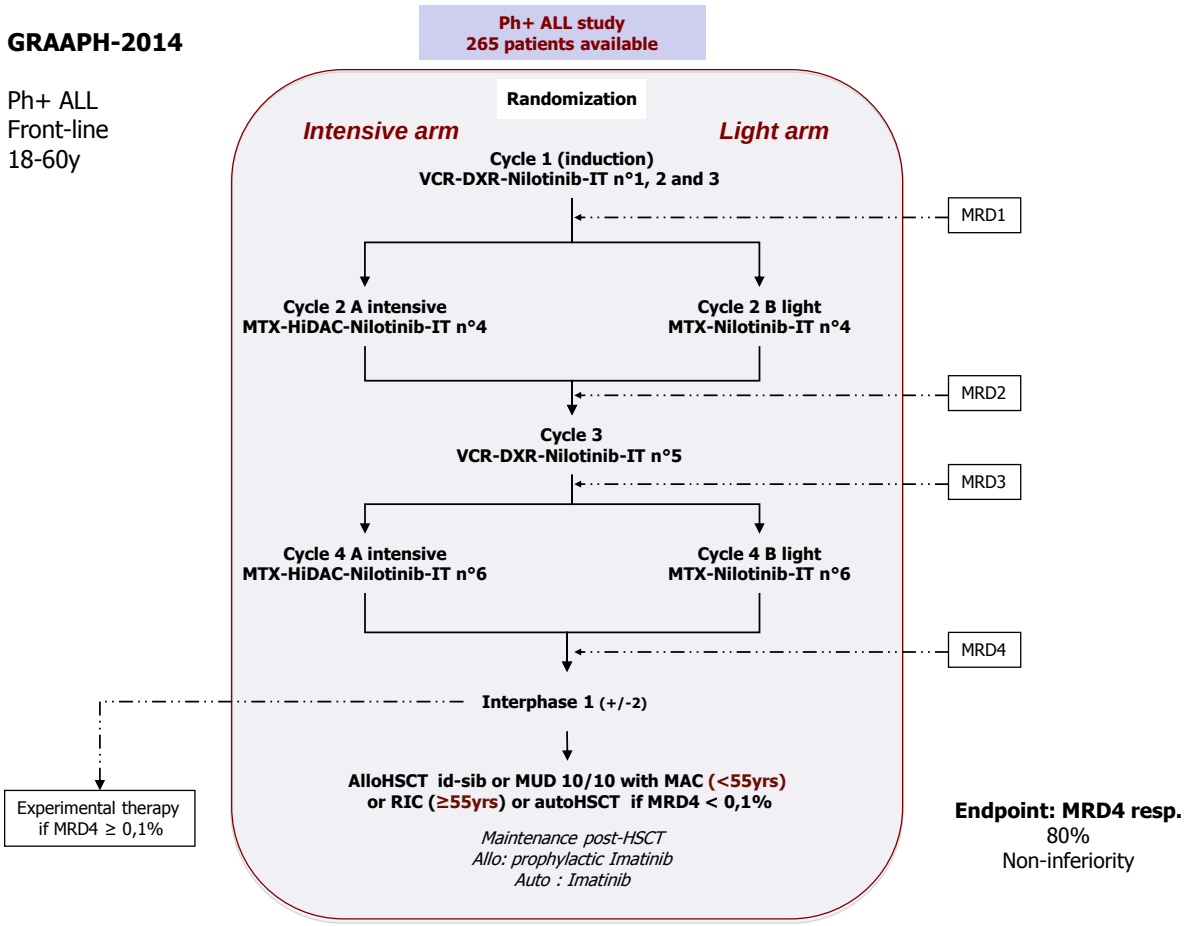
If MRD is still detectable after 2 years of maintenance, the choice to continue will be as per the investigator's preference.

ITK switch	Patients with non hematological toxicity due to nilotinib (grade ≥ 3 AE) during first cycle will be proposed to receive dasatinib (<u>140 mg/day tapered to 100 mg/day at cycle 2</u>) or by imatinib 600 mg/day, up to 800 mg/day if well tolerated.

	Patients with any toxicity due to nilotinib (grade ≥ 3 AE) during cycles 2-4 will be proposed to receive dasatinib (induction 140 mg/day during induction and 100 mg/day during consolidation courses) or by imatinib 600 mg/day, up to 800 mg/day if well tolerated.
Biological study	Mutations and MRD (1-4) will be performed for all patients in a centralized laboratory according to their country of origin and their reference laboratory (Annex 1).
MRD monitoring & BCR-ABL mutations	MRD evaluation is planned at the following time-points: • MRD1: after cycle 1 (PB + BM) • MRD2: after cycle 2 (PB + BM) • MRD3: after cycle 3 (PB) • MRD4: Primary endpoint after cycle 4 (PB + BM) • MRD5: before SCT (PB + BM) • MRD6: at Day 100 after SCT (PB + BM) It is then recommended to follow PB MRD level monthly for 2 years, every 3 months until 5 years, and then twice a year. Mutation screening will be performed when the BCR-ABL/ABL ratio is ≥ 0.1% or in case of significant increase. MRD1 to MRD4 assessments will be sent to centralized lab seven if they may be performed locally (Jean-Michel Cayuela, Paris Saint-Louis, for France and Belgium; Pr Olivier Spertini, Lausanne, for Switzerland). It will be mandatory to send a diagnosis sample to these central laboratories.
SAEs	Serious adverse events (SAEs) must be reported on the SAE page of the eCRF and will be **immediately**declared to the sponsor for each patient (Annex 9) in each participating country, whatever their relationship with the trial's treatment or the research.
Added risks of the research	D
Financing	PHRC
Independent surveillance committee planned	Yes

GRAAPH-2014

Ph+ ALL
Front-line
18-60y



Endpoint: MRD4 resp.
80%
Non-inferiority

ASSOCIATED GRAALL COORDINATORS

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GRAAPH-2014 – LALB Ph+

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1 OBJECTIVES OF GRAAPH-2014

1.1 Primary objective

- ✓ Non-inferiority of the experimental arm (arm B) compared to the control arm (arm A) in terms of Major Molecular Response (MMolR) after the 4th cycle (MRD4).

1.2 Secondary objectives

- ✓ Comparison of the experimental arm and of the control arm in terms of tolerance, CIR, EFS and OS.

2 EVALUATION CRITERIA

2.1 Primary evaluation criterion

- ✓ Major Molecular Response (MMolR) defined as a BCR-ABL/ABL ratio < 0.1% in the bone marrow sample of MRD4.

2.2 Secondary evaluation criteria

- ✓ Tolerance
- ✓ Complete remission after cycle 1
- ✓ Cumulative incidence of treatment- and transplantation-related mortality
- ✓ Cumulative incidence of relapse
- ✓ Relapse free survival
- ✓ Event free survival
- ✓ Overall survival
- ✓ Investigation of T315I mutation and of resistance (mutations will be assessed by RQ-PCR sequencing in case of progression or relapse).

3 DESCRIPTION OF THE RESEARCH METHODOLOGY

3.1 Experimental plan

GRAAPH-2014 is a multicenter phase III opened randomized study. The 265 patients to be included will be recruited in 76 centers in France, Belgium and Switzerland. The period of inclusion will be 5 years.

3.2 Type of research

Within GRAAPH-2014, procedures added by the research only relate to patients with vascular risk (i.e. known arteriopathy, diabetes, untreated or uncontrolled hypertension, active smoking, familial dyslipidemia) for whom an ultra sound Doppler of the neck and lower limbs shall be repeated every 4 months during the whole duration of nilotinib treatment.The investigator will take advice from a cardiologist in order to apply adapted prevention measures for patients at vascular risk.

Besides this, no supplemental research-related act is performed in GRAAPH-2014 outside usual samples taken for the follow-up of treatments or disease.

4 MODALITIES OF RECRUITMENT AND RANDOMIZATION OF PATIENTS

Patients will be recruited in hospital hematology departments.

It is planned to include 265 patients with Ph+ ALL in the GRAAPH-14 trial over 5 years.

4.1 Patients randomization

During the prephase and up to D1 maximum, **if needed**, investigation centers will contact the medical GRAALL coordination *via* the secretariat (Véronique LHERITIER: Tel: +33 (0)4 78 86 22 39 Fax: +33 (0)4 72 66 64 40) to confirm or infirm the eligibility of the patient for the study.

Randomization will be performed in a centralized fashion, on line via the e-CRF, by secure internet connexion (CleanwebTélémédecine). During the prephase and at most on D1, each patient must be randomized on the trial.

The randomization between the two parallel arms (intensive versus light arm) will be

- **centralized, carried out using a computerized system, CleanWeb®/CMTS**
- **stratified studywide according to**
    - **Age (≤40 versus > 40 years old)**
    - **Transcript (m-bcr, M-bcr, nd)**

This will result in 6 distinct randomization lists. Each will be based on permutation blocks to insure equilibrium, the size of which will be kept unknown to the investigators. They 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 block whose size will be kept confidential

As soon as the trial is implemented in a center and when the form of functions delegation (FFD) is filled and signed by all investigator team participants to the trial in the center, the monitoring CRA will forward the request for center opening to Télémédecine.Télémédecine will send by e-mail only, a login and password to each participant (according to their profile) in the center. This e-mail will also contain the internet link allowing to login into the e-CRF.

Experimental treatment numbers will be generated automatically by Cleanweb.

4.2 Randomization criteria

Randomization should be done before D1 of cycle n°1. After the prephase, all patients will be randomized between Arm A (control arm) and Arm B (experimental arm).

A total of 4 treatment cycles combining nilotinib and chemotherapy will be administered before primary objective assessment and HSCT procedure.

Cycles n°1 and n°3 are identical between both arms (1A = 1B, 3A = 3B).

Cyclesn°2 and n°4 will differ between the two randomization arms. MRD will be monitored after each of these 4 cycles: the BCR-ABL/ABL ratio will be expressed as percentage.

Due to the administration of nilotinib, inclusion criteria about liver function are stricter in the GRAAPH-2014 trial than in the GRAALL-2014 trial (cf. non inclusion criteria).

4.3 Identification of patients for on line data collection

Within this research, subjects will be identified for data collection as follows:

Center n° (3 digits) – selection order number of the patient in the trial (4 digits) – name initial – surname initial ➔|__|__|__|-|__|__|__|__|-|__|-|__|.

This reference will be unique and retained all along the trial.

As the Swiss regulations don't allow the disclosure of the patients' initials, all Swiss patients will have the following dummy initials: "X" for the name initial and "X" for the surname initial.

4.4 Identification of patients for samples shipping

Centralized research samples (*GRAALLThèque)* will be identified as for on line data collection.

Centralized samples, collected within the usual follow-up of patients (*MRD)* will be identified by the patient's name without any mention relative to this biomedical research, according to the center's habits.

According to Swiss regulations the disclosure of the patient's name even for usual follow up assessments which have to be done outside of Switzerland according to the protocol (oncogenetic evaluation at diagnosis, asparaginase activity assessments,…) is nevertheless not allowed. Therefore all Swiss sites will code their patients' data before receiving the selection order number by AP-HP as follows ::

- Center number
- Selection order number of the patient in the trial (if applicable)
- Hospital chart identifier,
- birth year

An adequate liaison form will be used to accompany the shipping of tube(s) (see Annexes 1 and 5).

5 INCLUSION CRITERIA

Patient:

- Whose blood and bone marrow explorations have been completed before the steroids prephase
- Aged 18-59 years old with newly-diagnosed non previously treated Ph+ ALL according to WHO 2008 criteria (confirmed diagnosis of the Philadelphia chromosome defined by the reciprocal translocation of chromosomes 9 and 22, t(9;22) and/or presence of the BCR-ABL molecular maker)
- With ≥ 20% bone marrow blasts
- With ECOG ≤3
- With or without central nervous system (CNS) or testis involvement
- Without evolving cancer (except basal cell carcinoma of the skin or "in situ" carcinoma of the cervix) or its chemo- or radio-therapy finished at least more than 6 months.
- Having received no previous treatment for this hemopathy (including IT injection)
- Having signed written informed consent
- With efficient contraception for women of childbearing age (excluding estrogens and IUD)
- With health insurance coverage
- Who having received or beingreceiving the recommended steroid prephase.

Note 1: Secondary ALL (antecedent of chemo- or radio-therapy) can be included.

Note 2: In case of high vascular risk (see section "study management") the patient will not be able to receive nilotinib unless an ultra sound Doppler of the neck and lower limbs has been performed during the pre-phase and his treatment validated by the medical coordinators of the GRAALL *via* the secretariat.

6 NON INCLUSION CRITERIA

Patient:

1. Previously treated with Tyrosine Kinase Inhibitor (TKI)
2. With another active malignancy
3. With general or visceral contra-indication to intensive therapy (except if considered related to the ALL):
   a. ASAT (SGOT) and/or ALAT (SGPT) > 2.5 x ULN
   b. Total bilirubin > 1.5 x ULN
   c. Creatinine > 1.5 x ULN or creatinine clearance <50 mL/min
   d. Serum amylase or lipase $\geq$ 1.5 x ULN or antecedents of acute pancreatitis
4. With heart failure, including at least one of the following criteria:
   a. left ventricular ejection fraction (LVEF) <50% or below the lowest normal threshold, as determined by ECG or heart failure (NYHA grade III or IV)
   b. impossibility to measure the QT interval on ECG
   c. complete left bundle branch block
   d. pacemaker
   e. congenital long QT syndrome of known familial antecedents of long QT syndrome
   f. antecedents or current ventricular or atrial tachyarrhythmia, clinically significant
   g. baseline bradycardia (<50 bpm) clinically significant
   h. QTc> 450 msec established on the mean of 3 baseline ECG (by using the QTCF formula)
   i. Antecedents of myocardial infarct in the past 6 months
   j. Instable angor within the past 12 months
   k. Any heart condition clinically significant (i.e. congestive heart failure, uncontrolled hypertension)
5. active uncontrolled infection, any other concurrent disease deemed to interfere with the conduct of the study as judged by the investigator
6. with severe evolving infection, or known HIV or HTLV1 seropositivity, or chronic hepatitis B (HbsAg-positive) or C
7. Pregnant (β-HCG) or nursing woman
8. Women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least three months thereafter. Patient not willing to ensure not to beget a child during participation in the study and at least three months thereafter.
9. Having received another investigational agent or participation in another trial within 30 days prior to entering this study
10. Not able to bear with the procedures or the frequency of visits planned in the trial.

11. Unable to consent, under tutelage or curatorship, or judiciary safeguard.

7 GENERAL RULES FOR THE WHOLE TREATMENT

✓ Have a central venous access

✓ Counsel on the mode of contraception and on the necessity of protected sexual intercourse in order to prevent any toxic exposure for the partner. Birth control methods acceptable during the treatment GRAALL are progestogen-only contraception (progestogen pills or subdermal implant) and mechanical contraceptives (condoms, diaphragm…). Continuous progestogen contraception is frequently proposed to avoid the risk of bleeding during intensive chemotherapy phases. The use of estrogen is contraindicated until the onset of maintenance phase, because of the increased risk of venous thrombosis.

✓ It is recommended to use full weight-based chemotherapy doses in the treatment of obese patients (without capping body-surface area at $2m^2$), However, vincristine is capped at a maximum dose of 2.0 mg.

✓ Prevent *Pneumocystis* infection with monthly Bactrim® or Pentacarinat® (do not prescribe folinic acid in association with Bactrim® during maintenance in order not to decrease the efficacy of methotrexate).

About chemotherapy and ITK

✓ Nilotinib (or any other ITK) should be continuously given throughout the 4 cycles.

✓ In case of neuropathy ≥ 3 or severe ileus related to vincristine, replace by vindesine (4 mg TD/injection) or other treatment according to investigator judgment.

✓ Administration of Purinethol® (6-MP) at bedtime, at distance from dairy products consumption

✓ Intrathecal injections: total volume at least 6 mL; ventral decubitus 30 min (Annex 3)

About corticosteroids

✓Antibioprophylaxis as soon as neutropenia becomes < à 0.5 G/L in patients receiving or having received corticotherapy (broad spectrum antibiotherapy active on GNB germs, including *Pseudomonas aeruginosa*, and GPB germs according to each center's policy). Fluoroquinolones should not be given alone because of the inconstant sensitivity of *P aeruginosa*and of the reduced efficacy of Endoxan[63].

Fungal prophylaxis

✓This is left toeach center's policy.It is suggested to avoid azoles associated to VCR (neurological toxicity).

Patients at vascular risk

✓ Known arteriopathy,

✓ Diabetes,

✓ Untreated or uncontrolled arterial hypertension (ask for cardiologic opinion when needed),

✓ Active smoking,

✓ Familial dyslipidemia,

[63]Carlens*et al*,Clin Transplant, 1998; 12(2):84-92

An ultra-sound Doppler of the neck and lower limbs will be performed every 4 months during the period of nilotnib therapy. The investigator will take advice from a cardiologist in order to apply adapted prevention measures for patients at vascular risk.

ITK switch

✓ Patients with non hematological toxicity due to nilotinib (grade ≥ 3 AE) during first cycle will be proposed to receive dasatinib (140 mg/day tapered to 100 mg/day at cycle 2) or by imatinib 600 mg/day, up to 800 mg/day if well tolerated.

Patients with any toxicity due to nilotinib (grade ≥ 3 AE) during cycles 2-4 will be proposed to receive dasatinib (induction 140 mg/day during induction and 100 mg/day during consolidation courses) or by imatinib 600 mg/day, up to 800 mg/day if well tolerated. As haematological toxicity is anticipated to be unfrequent after cycle 1, such toxicity should be acertained (i.e. recurrence after rechallenge).

8 PREPHASE

From D -7 to D -1, maximum D -10 to D -1

PREDNISONE 60 mg/m², PO (or methylprednisolone IV 48 mg/m²)	D-7 to D-1 (maximum D-10)
SIMPLE IT (N°0) only with MTX IT 15 mg full dose	During the first 3 prephase days **whatever the peripheral blast cells count.**

Note: CNS lesions are detailed in § 6.2.

CAREFUL !

Nor cytarabine nor corticosteroids in this IT

This prephase is common to all ALL patients and belongs to the usual management of this disease. It is performed as soon as the diagnosis is obtained and the initial examinations have been performed.

8.1 Definition of corticosensitivity

Whatever the day of corticotherapy onset, corticosensitivity assessment should be performed 7days after the initiation of corticotherapy.

Corticosensitivity assessment requires a detailed blood differential before prephase onset and on D1. It is reminded that corticosensitivity is always assessable **whatever the level of peripheral blasts since it is defined by a value of less than 1 G/L blast cells.**

In case of extramedullary location, especially in lymph nodes, a significant decrease of the tumor burden must be associated to biological criteria. Corticosensitivity includes ≥75% decrease of extra-medullary locations.

8.2 corticoprogression

8.2.1 Definition of corticoprogression

For patients whose peripheral blast count increases during the prephase, the following rules apply:

✓ corticoprogression must be concluded after at least 48h of Prednisone and IT MTX

✓ if WBC <100 G/L at diagnosis: at least 50% WBC increase compared to diagnosis AND/OR WBC becoming> 100 G/L

✓ if WBC > 100 G/L at diagnosis: any WBC increase after at least 48h prephase

✓ in case of tumor syndrome, any tumor size progression after 48h of prephase is corticoprogression.

8.2.2 Management of corticoprogression

✓ Chemotherapy is initiated,

✓ The patient remains in the trial,

✓The patient is scored as corticoresistant.

TREATMENT GIVEN TO PATIENTS ENROLLED IN RESEARCH

The results of immunophenotype and molecular biology must be anonymized and faxed at the GRAALL secretariat to Véronique LHERITIER (fax: +33 (0)4.72.66.64.40) for central review and validation by the biology coordinators of the GRAALL group.

The investigator collects, at the latest before initiating induction, the free informed written consent of the person enrolled in research.

9 EXPERIMENTAL DRUG, PRESCRIBED OUT OF MA AND PROVIDED BY THE SPONSOR

9.1 Presentation of nilotinib.

Nilotinib (TASIGNA® 150 mg and 200 mg) is provided by the sponsor through a donation convention with the Novartis Company. It has a specific contra-labelling in 4 languages (French, German, Dutch, Italian) with regulatory mentions for clinical trials.

It comes in a form adapted to clinical research.

It must be stored below 30°C.

9.2 Administration modalities

During the 4 first cycles of treatment, patients will receive an association of nilotinib and standard chemotherapy.

Nilotinib will be given *per os*. The patients will be treated by a dose of 400 mg nilotinib two times a day *per os* (morning and evening with an interval of about 12h between the two takes). Capsules are dosed at 200 mg. They will be swallowed whole with water. No food shall be eaten 2 hours before and one hour after the administration.

In order to avoid overdoses, in case of delay of omission of a dose of more than 4 hours, nilotinib will not be given and the next dose will be taken at the planned time.

The patients should avoid eating some fruits during the study: grapefruit, carambole, grenade or sour Seville oranges. Juices and other products containing these fruits will also be avoided. In case of vomiting, the drug dose should not be repeated.

10 CHEMOTHERAPY (CYCLES 1 TO 4)

All patients must be randomized before initiating the first cycle (1A or 1B) (cf § 3). This part should follow immediately the prephase, whatever the hematologic situation (D1 follows D-1; D0 does not exist).

10.1 Cycle 1: 1A or 1B

10.1.1 Cycles 1A and 1B are identical.

Cycle 1A / 1B	Whatever the patient's age
VINCRISTINE 2 mg TD, in IVD	D1, D8, D15, and D22
DEXAMETHASONE 40 mg TD, PO or IV	D1, D2,D8, D9,D15, D16,D22, and D23
NILOTINIB 400 mg /12h, PO (400 mg in the morning and 400 mg in the evening)	D1 to D28
G-CSF 5 µg/kg/D, SC or IV	D15 until ANC > 1 G/L
TRIPLE IT(N°1,2, and 3) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®* IT 40 mg total dose*	D1, D8 and D15

* Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

10.1.2 Evaluation of the response after cycle 1 (MRD1)

Evaluation of minimal residual disease (MRD1) by assessment of the BCR-ABL/ABL ratio will be performed on D29 of cycle 1, on peripheral blood and bone marrow, before starting cycle 2.

Centralized monitoring in molecular biology is mandatory since molecular response is the principal evaluation criterion of GRAAPH-2014.

These laboratories will also investigate mutations in case of resistance to nilotinib.

A blood sample (5 mL on EDTA) must be sent in parallel to the GRAALLThèque.

The response to induction therapy will be assessed on the basis of the International Working Group Criteria, summarized in a table, part I paragraph 7. **Patients not reaching HCR after cycle 1 will nonetheless receive cycle 2.**

10.2 Cycle 2: 2A or 2B

For this second cycle, the treatment differs between randomization arms. The standard arm (2A) associates MTX and aracytine (AraC) to nilotinib while the experimental arm (2B) only comprises MTX and nilotinib.

Cycle 2 (2A or 2B) is initiated just after the evaluation of cycle 1, in the absence of contra-indication to immediate continuation. Depending on creatinine clearance, methotrexate and cytarabine doses will be adapted. Depending on the results of MTX blood levels, the dose of AraC given at D2 H12 and D3 H0 and H12 may be modified (Annex 8).

10.2.1 Cycle 2A

Cycle 2A	Patient < 45 years old	Patient ≥45 years old
METHOTREXATE 1000 mg/m² in continuous perfusion over 24 h	D1 Folinic acid rescue (Annex 7)	
ARACYTINE IV adapted to renal function, over 2h in perfusion	3000 mg/m²/12h on D2 and D3 (or 4 bolus)	1500 mg/m²/12h on D2 and D3 (or 4 bolus)
NILOTINIB 400 mg /12h, PO (400 mg in the morning and 400 mg in the evening)*	D1 to D28	
NEULASTA 6mg, SC (or G-CSF from D9 on until ANC>1G/L)	D6	
TRIPLE IT (N°4) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D9	

* Can be stopped in case of toxicity (annex 8)
** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

10.2.2 Cycle 2B

Cycle 2B	Whatever the patient's age
METHOTREXATE 1000 mg/m² in continuous perfusion over 24 h	D1 Folinic acid rescue (Annex 7)
NILOTINIB 400 mg /12h, PO (400 mg in the morning and 400 mg in the evening)*	D1 to D28
NEULASTA 6mg, SC (or G-CSF from D9 on until ANC>1G/L)	D6
TRIPLE IT (N°4) including *Methotrexate IT 15 mg total dose ,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D9

* Can be stopped in case of toxicity (Annex 8)
** Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

10.2.3 Evaluation of the response after cycle 2 (MRD2)

Evaluation of minimal residual disease (MRD2) by assessment of the BCR-ABL/ABL ratio will be performed on D29 of cycle 2 on peripheral blood and bone marrow.

Centralized monitoring in molecular biology is <u>mandatory</u> since molecular response is the principal evaluation criterion of GRAAPH-2014.

Patients not in complete hematological remission after cycle 2 (according to standard bone marrow criteria of the National Cancer Institute) will be discontinued from the study and stop the trial's TKI.

NB: Patients in failure after cycle 1 but reaching HCR after cycle 2 will continue treatment and receive cycle 3.

10.3 Cycle 3: 3A or 3B

The third cycle of chemotherapy is identical in both randomization arms and is almost identical to cycle 1.

This cycle is initiated on D29 of cycle 2, after evaluation of the response post cycle 2.

10.3.1 Cycle 3

Cycle 3 (3A and 3B)	Whatever the patient's age
VINCRISTINE 2 mg TD, IVD	D1, D8, D15 and D22
DEXAMETHASONE 40 mg TD, PO or IV	D1, D2,D8, D9,D15, D16, D22, and D23
NILOTINIB 400 mg /12h, PO (400 mg in the morning and 400 mg in the evening) *	D1 to D28
G-CSF 5 µg/kg/D SC or IV	D15 until ANC > 1 G/L
TRIPLE IT (N°5) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D1

* Can be stopped in case of toxicity (Annex 8)
**Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

10.3.2 Evaluation of the response after cycle 3 (MRD3)

Evaluation of minimal residual disease (MRD3) by assessment of the BCR-ABL/ABL ratio will be performed on D29 on peripheral blood and bone marrow.

Centralized monitoring in molecular biology is mandatory since molecular response is the principal evaluation criterion of GRAAPH-2014.

10.4 Cycle 4: 4A or 4B

This fourth cure is identical to cycle 2, depending on the randomization arm.

The standard arm (4A) associates MTX, aracytine and nilotinib while the experimental arm (4B) only comprises MTX and nilotinib.

This cycle is initiated just after post cycle 3 evaluation. Depending on creatinine clearance, methotrexate and aracytine doses will be adapted (Annex 8). The dosage of AraC given will depend on the results of MTX blood levels.

10.4.1 Cycle 4A

Cycle 4A	Patient <45 years old	Patient ≥45 years old
METHOTREXATE 1000 mg/m² in continuous perfusion over 24 h	D1 Folinic acid rescue(Annex 7)	
ARACYTINE IV adapted to renal function; by perfusion over 2h	3000 mg/m²/12h on D2 and D3 (or 4 bolus)	1500 mg/m²/12h on D2 and D3 (or 4 bolus)
NILOTINIB 400 mg /12h, PO (400 mg in the morning and 400 mg in the evening)*	D1 to D28	
NEULASTA 6mg, SC (or G-CSF from D9 on until ANC>1G/L)	D6	
TRIPLE IT(N°6) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D9	

* Can be stopped in case of toxicity (Annex 8)
**Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

10.4.2 Cycle 4B

Cycle 4B	Whatever the patient's age
METHOTREXATE 1000 mg/m² in continuous perfusion over 24 h	D1 Folinic acid rescue (Annex 7)
NILOTINIB 400 mg /12h, PO (400 mg in the morning and 400 mg in the evening)*	D1 to D28
NEULASTA 6mg,SC (or G-CSF from D9 on until ANC>1G/L)	D6
TRIPLE IT(N°6) including *Methotrexate IT 15 mg total dose,* *Cytarabine IT 40 mg total dose,* *Depo-medrol®** IT 40 mg total dose*	D9

* Can be stopped in case of toxicity (Annex 8)
**Other corticosteroids may be used instead of Depo-Medrol® (dosing should respect steroid equivalence).

10.4.3 Evaluation of the response after cycle 4 (MRD4)

Evaluation of minimal residual disease (MRD4) by assessment of the BCR-ABL/ABL ratio will be performed from D29 as soon as ANC>1G/L and platelets >100G/L, on peripheral blood and bone marrow.

Centralized monitoring in molecular biology is mandatory since molecular response is the principal evaluation criterion of GRAAPH-2014.

MRD4 is also essential to orient toward a possible auto-HSCT if MRD4 ratio is <0.1%

All patients will then receive an interphase allowing to wait for MRD4 results, organize hematopoietic stem cell transplant and the collection of hematopoietic stem cells in case of auto-SCT for eligible patients.

This interphase comprises 1 or 2 identical cures (MTX + 6MP) provided in association with nilotinib 300 mg/d, twice a day.

10.5 Interphase n°1 and interphase n°2

The interval between D1 of the first interphase and D1 of the second should not exceed 1 month.

Interphasesn°1 and n°2	
METHOTREXATE 25 mg/m², PO	D1 and D8 of each interphase
6 MP 60 mg/m², PO	D1 to D14 of each interphase
NILOTINIB 300 mg, PO/*12h* (300 mg in the morning and 300 mg in the evening, 150 mg pills)*	D1 to D14

* Can be stopped in case of toxicity (see Annex 8)

10.5.1 Patients eligible to an auto-SCT in CR1 (MRD4 < 0.1%)

For patients eligible to an auto-SCT in CR1 (these patients must have MRD4<0.1%), the harvest of peripheral stem cells will be performed between the 2 cures of interphase, when stable, after mobilization of peripheral stem cells by G-CSF at 10 µg/kg/D,SC. The patient will not receive nilotinib during mobilization and harvest.

In case of harvest failure, a bone marrow harvest may be done.

The second cure of interphase can or not be given to the patients, depending on the organization of HSCT.

10.6 Allogeneic or autologous hematopoietic stem cell transplantation

Patients with a bone marrow MRD4 BCR-ABL/ABL ratio lower than 0.1% will receive either an allo-SCT (only from a genoidentical or unrelated 10/10 or 10/9 donor) or auto-SCT at the investigator's choice.

Patients with a bone marrow MRD4 BCR-ABL/ABL ratio ≥ 0.1% will receive an allo-SCT from a sibling or 10/10 MUD or 9/10 MUD or even from an alternate source of stem cells (cord blood, haploidentical SCT) or will be discontinued from the study to enter another experimental trial.

Bone marrow evaluation pre-HSCT (MRD5) will be performed
on bone marrow and peripheral blood
just before HSCT conditioning (or during pre-transplant check-up).
MRD5 has no decisional value.

10.6.1 Allo-HSCT

10.6.1.1 Myeloablative Allo-SCT

Patients below 55 years of age and without co-morbidities factors precluding a standard conditioning regimen will receive the following:

- ✓ TBI : fractionated dose: 12 Gy in 6 fractions (limited to 8 or 10 Gy near the lungs)
- ✓ Cyclophosphamide 60 mg/kg/d for 2 consecutive days.
- ✓ ± ATG in case of 10/10 graft (according to the center's habits) or + ATG in case of 9/10.

GVH disease prophylaxis is classical: association of ciclosporine A and methotrexate on D1, D3, D6, +/- D11.

In order to accelerate post-transplant hematological recovery, G-CSF use SC or IV is allowed.

10.6.1.2 Reduced toxicity conditioning

This conditioning is for Ph+ ALL patients aged 55 to 59 years of age or patients with a contra-indication to standard conditioning:

- ✓ Patients ≥ 55 years old in CR1,
- ✓ Patients < 55 years old with comorbidities factors precluding the use of standard therapy before Allo-SCT.

Allo-SCT after RTC associates TBI 8 Gy + Fludarabin according to Bornhäuser Lancet Oncology 2012:

- ✓ TBI: 8 Gyin 4 fractions (D-3 and D-2),
- ✓ Fludarabine: 30 mg/m²/d x 4 from D-6 to D-3,
- ✓+ ATG in case of phenoidentical allo-SCT 9/10 or 10/10 (Thymoglobuline or ATG Frésenius) according to the center's habits.

GVH prophylaxis will associate ciclosporine A and methotrexate on D1, D3, D6, and D11.

Stem cell sources: preferably peripheral stem cells but bone marrow is allowed.

10.6.1.3 Post Allo-SCT maintenance therapy

Maintenance therapy is initiated when:

✓ ANC ≥ 1 G/L and

✓ Platelets ≥ 80 G/L

at the latest on D100 in the absence of other contra-indications.

Maintenance therapy relies on imatinib mesylate (and not nilotinib) given as prophylaxis at a dosage of 300 mg twice daily *per os*.

10.6.1.3.1 Duration of maintenance therapy

For at least two years.

If MRD is undetectable (sensitivity 10^{-4} or 0.01%) for 2 years, imatinib mesylate might be stopped.

If MRD is still positive after 2 years of maintenance therapy, the choice of continuing will be left to the investigator.

In case of grade 3 or 4 hematological and/or liver toxicity the dosage of imatinib mesylate will be adapted (Annex 8).

10.6.1.3.2 Hematological toxicity

In case of grade $\geq$3 hematological toxicity imatinib mesylate will be decreased to 400 mg then upgraded to 600 mg TD as soon as the toxicity will have disappeared.

If hematological toxicity lasts at least 15 days, imatinib mesylate can be stopped and resumed as soon as WBC ≥ 4 G/L, ANC ≥ 1 G/L and platelets ≥ 80 G/L.

10.6.1.3.3 Liver toxicity

If bilirubin is > 3 x ULN or ASAT/ALAT > 5 x ULN, imatinib mesylate will be stopped until bilirubin returns to < 1.5 x ULN or ASAT/ALAT to < 2.5 x ULN.

Imatinib mesylate will be resumed at a dosage of 400 mg/d, *per os*.

In case of toxicity during dosage reduction of imatinib mesylate, the latter will be interrupted until obtention of aforementioned criteria and resumed only when the liver function will have returned to normal.

10.6.1.3.4 Injection of donor lymphocytes

For patients receivieng Allo-SCT with reduced intensity conditioning only, after 3 months of complete molecular CR with imatinib mesylate, without any sign of graft versus host disease and for patients without immunosuppressive therapy, increasing injections of donor lymphocytes (DLI) will be allowed, with dosage increment every 6 to 8 weeks (after evaluation and in the absence of graft versus host disease) starting at 10^6 CD3/kg then 5.10^6 CD3/kg then 10^7 CD3/kg.

The first injection of lymphocytes will be allowed by Week 8.

10.6.2 Autologous hematopoietic stem cell transplantation

Patients with MRD4 and a BCR-ABL/ABL ratio <0.1% will be eligible for autologous hematopoietic stem cell transplantation.

Conditioning is based on the association of cyclophosphamide and TBI.

✓ **TBI**: 8 or 10 Gy in a single dose (with decreased dose for the lungs over 8 Gy)

or

8 or 10 or 12 Gy in 4-6 fractions (with lung protection over 8 Gy) depending on the patient's age and status.

✓ Cyclophosphamide 60 mg/kg/d, IV for 2 consecutive days.

10.6.2.1 Maintenance after autologous hematopoietic stem cell transplantation

Maintenance therapy is initiated when:

✓ ANC ≥ 1 G/L and

✓ Platelets ≥ 80 G/L

at the latest on D100 in the absence of other contra-indications.

Maintenance therapy relies on imatinib mesylate (and not nilotinib) given as prophylaxis at a dosage of 300 mg twice daily *per os*.

10.6.2.1.1 Duration of maintenance therapy

For at least two years.

If MRD is undetectable (sensitivity 10^{-4} or 0.01%) for 2 years, imatinib mesylate might be stopped.

If MRD is still positive after 2 years of maintenance therapy, the choice of continuing will be left to the investigator.

In case of grade 3 or 4 hematological and/or liver toxicity the dosage of imatinib mesylate will be adapted (Annex 8)

10.6.2.1.2 Hematological toxicity

In case of grade ≥3 hematological toxicity imatinib mesylate will be decreased to 400 mg TD then upgraded to 600 mg as soon as the toxicity will have disappeared.

If hematological toxicity lasts at least 15 days, imatinib mesylate can be stopped and resumed as soon as WBC ≥ 4 G/L, ANC ≥ 1 G/L and platelets ≥ 80 G/L.

10.6.2.1.3 Liver toxicity

If bilirubin is > 3 x ULN or ASAT/ALAT > 5 x ULN, imatinib mesylatewill be stopped until bilirubin returns to < 1.5 x ULN or ASAT/ALAT to < 2.5 x ULN.

Imatinib mesylate will be resumed at a dosage of 400 mg/d, *per os*.

In case of toxicity during dosage reduction of imatinib mesylate, the latter will be interrupted until obtention of aforementioned criteria and resumed only when the liver function will have recovered.

10.6.3 Molecular monitoring after transplantation

BCR-ABL/ABL ratiomonitoring will be performed on D100 post-transplant on bone marrow and peripheral blood (MRD6).

MRD will be monitored every 2/3 months for the first 2 years post-transplant, then according to the investigator's choice.

At 3 Month, 1 year and 2 year post-transplant, bone marrow MRD will be mandatory, because, at variance with chronic myeloid leukemia, there is no necessary correlation between bone marrow and peripheral blood.

Bone marrow evaluation will also be performed on Month 12 and 24 post-SCT.

10.6.4 Relapse or progression of the disease

Karyotypic and molecular analyses together with a search for mutations leading to resistance to imatinib mesylate and other TKI will be systematically performed in case of relapse.

Relapse therapy will be left to the choice of the investigator.

10.7 Patients without donor and MRD4 > 0.1%

These patients will be discontinued from protocol but information on relapse and survival will continue being collected.

Choice of the next therapy will be left to the investigator's appreciation.

PART V

STUDY MANAGEMENT

1 PATIENTS' FOLLOW-UP

1.1 Explorations during treatment

Complementary tests to be performed during therapy are indicated all along the schedule. They are classical tests to be performed in each participating center without specific recommendations. Their type and frequency will be adapted to possible intercurrent events.

Of note, it will be necessary to repeat anti-thrombin assays daily during all treatment phases including L-Asparaginase administrationfor patients included in GRAALL-2014/B and GRAALL-2014/T.

1.2 Response assessment

Treatment response assessment is standardized as follows:

✓ Evaluation of corticosensitivity on D1 by a blood count with differential on blood smears. This differential is performed before prephase and on D1. D1 result will be used to assess corticosensitivity

✓ Evaluation of hematological remission after recovery from chemo-induced cytopenias after induction ± salvage, by a blood count with differential on blood smear and medullogram (except if peripheral blasts remain at that time) 48 h after the end of growth factors injections and on the latest at D35.

✓ Bone marrow and/or peripheral blood evaluation of minimal residual disease (Annex 1)

- Non Ph+ patients: Post-induction (MRD1), mid-consolidation (MRD2), before SCT or before late intensification (MRD3) and on D100 post-transplant or D1 of maintenance (MRD4),
- Ph+ patients: MRD1 after cyce 1 (PB+BM), MRD2 after cycle 2 (PB+BM), MRD3 after cycle 3 (PB), MRD4, principalcriterion, after cycle 4 (PB+BM).

1.3 Criteria and modalities of premature discontinuation from the research.

In case of premature discontinuationof the research for a patient, his/her data will be used except in case of consent withdrawal with opposition to data usage (this should be documented in the source file).

The eCRF must list the reasons why participation to the research was discontinued:

- ✓ Inefficacy
- ✓ Severe adverse event, poor tolerance,
- ✓ Other medical problem,
- ✓ Personal reasons of the patient,
- ✓ Explicit consent withdrawal.

In case of patient lost to follow-up, (what happened to the patient is unknown), the investigator will try by all means to resume contact with the person (and documented this in the source file) in order to at least know whether the patient is alive of deceased.

Follow-up will be asked for all patients discontinued from the study. Only the patients refusing any follow-up (withdrawal of informed consent) and enrollement in the research will not be analyzed, their data being destroyed in the database.

1.3.1 Definitive premature discontinuation of the trial treatment

✓ Non obtention of HCR after 2 cures,

✓ Relapse,

✓ Severe toxicity impairing treatment continuation

✓ Pregnancy.

Patients discontinued prematurelyfrom treatment will still be followed, according to the center's policy until the end of the planned duration of participation to the research, and will be included in the analysis of the trial in intention to treat. Only data relative to relapse and survival will be collected.

1.3.1.1 Other situations of premature discontinuation from the treatment and from participation to the study.

Any individual may stop his/her participation to the research, at any time and whatever the reason. The investigator may interrupt temporarily or definitely the participation of a patient to a trial for any reason impacting the patient's safety or that would serve the individual's interests at best.

Participation to this trial can be interrupted without the patient's consent for the following reasons:

- ✓ presence of adverse events considered dangerous
- ✓ refusal of the patient to respecttherapeutic recommendations or comply with follow-up visits prescribed by the physician,
- ✓ refusal of the patient to comply to the necessary examinations allowing to appreciate treatment efficacy and tolerance,
- ✓ removal from the market of the drug studied,
- ✓ decision of the sponsor to interrupt the trial,
- ✓ decision of health authorities to interrupt the trial.

Discontinuation of nelarabine treatment:

As indicated in the SPC, nelarabine treatment must be interrupted at the first appearance of neurological signs of adverse event, of grade 2 or more, defined according to the NCI - CTCAE classification ("National Cancer Institute Common Terminology Criteria Adverse Event").

The investigator must:

- ✓ Documentthe reason(s) of trial participation or treatment cessation and its possible resuming into the patient's source file, and report it/them in the e-CRF,
- ✓ Collect evaluation criteria at the time of discontinuation from the research, if the patient agrees,
- ✓ Plan follow-up for the patient, especially in case of severe adverse event.

1.3.1.2 Patient's follow-up after premature discontinuation of the treatment.

Discontinuation will not change the patient's management as usually carried out for this disease. Severe adverse events must be notified by the investigator to the sponsor and monitored until resolution or stabilization of the event.

In case of premature discontinuation from treatment for toxicity, a notification of severe adverse event will be faxed (+33 (0)1 44 84 17 99) to the sponsor. The adverse event will be monitored until resolved.

The independent surveillance committee might be required to precise and/or validate the modalities of monitoring.

2 SAFETY EVALUATION – RISKS AND ADDITIONAL OBLIGATIONS RELATED TO THE TRIAL

2.1 Definitions

According to Article R1123-46 of the French Public Health Code:

- **Adverse event**

Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial 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

- **Serious adverse event or reaction**

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalisation or prolongs hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product, whose nature, severity, frequency or outcome is inconsistent with the safety information described in the Reference Safety Information (summary of product characteristics, or the investigator's brochure if the product is not authorised).

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for sponsors of clinical trials conducted on investigational medicinal product (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.

2.2 Investigator's roles

2.2.1 Regulatory obligations for investigators (Art R1123-54 of the French Public Health Code)

The investigator must notify the sponsor **with no delay as of the day he/she is becomes aware** of any seriousadverse event, except for those listedin the protocol (please refer to section 2.3.2) asnot requiring immediate notification.

The serious adverse events are collected in the « adverse events» section of the e-CRF and require mandatory immediate notification from the investigator to the sponsor through its Vigilance department (please refer to section 2.4).

2.2.2 Other roles of the investigator

The investigator must **assess the seriousness criteria of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).

The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

- ✓ In case of the occurrence of neurological troubles during treatment with nelarabine, the investigator must complete, along with the SAE notification form, the « nelarabine-related neurotoxicity » form (please refer to appendix 9.4), during the whole duration of the trial, starting from the first nelarabine dose administration to the patient.
- ✓ In case of the occurrence of a secondary cancer or myelodysplasia, the investigator must complete the «notification of secondary cancers/myelodysplasia » form (please refer to appendix 9.3) during the whole duration of the trial, with no time limit if there is a causal relationship with the investigational drugs.
- ✓ The investigator assesses the severity of adverse event by using the CTCAE, *Common Terminology Criteria for Averse Events (current version at SAE notification's time) [National Cancer Institute]*

  CTCAE specify grades 1 to 5, with specific clinical description of severity for each AE according to the below procedure:
  - Grade 1: mild AE, asymptomatic or with mild symptoms, only detected on clinical examination, not requiring therapy

- Grade 2: moderate AE, requiring minimal treatment, local or non-invasive, interfering with any daily life activities
- Grade 3: severe or clinically significant AE with no life-threatening condition, indication of hospitalization, invalidating, interfering with any daily life activities
- Grade 4: life-threatening AE requiring emergency treatment
- Grade 5: AE-related death.

✓ Causal relationship:

The investigator must assess the **causal relationship** between the serious adverse events and the investigational medicinal product(s) or the study procedure(s).

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not ruled out).

These terms are defined as follows (extracted from the WHO-UMC causality categories, version dated 17/04/2012).

WHO-UMC causality categories (extract)

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake **

Causality term	Assessment criteria*
	· that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with

** Or study procedures

2.3 Trial specific features

2.3.1 Serious adverse events (SAE) requiring immediate notification by the investigator to the sponsor.

According to Article R.1123-49 of the French Public Health Code (CSP), the investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any serious adverse event which occurs during a trial as described in Article L.1121-1(1) CSP, except those which are listed in the protocol and, if applicable, in the investigator's brochure as not requiring a notification without delay.

As a rule, the investigator must report all adverse events that fulfill at least one of the following seriousness criteria, except for those events listed in the protocol section as not requiring immediate report:

1. Death
2. Life threatening event
3. Event requiring hospitalization or prolonging hospitalization
4. Event leading to handicap persistent or significant disability or incapacity
5. Congenital anomaly or birth defect
6. Any other adverse event considered as medically significant

2.3.2 OTHER events requiring immediate notification from the investigator to the sponsor.

✓ Other adverse events and abnormal test results which affect the patients' safety assessment require immediate notification.

These events must be reported by the investigator to the sponsor in accordance with the same procedures and deadlines of a serious adverse event.

❖ Special case (hepatotoxicity should only be reported as serious adverse events in patients included in GRAAPH 2014 and ATRIALL):
Abnormal liver test results such as ALAT ≥ 3 x ULN and bilirubin ≥ 2 x ULN (>35% direct bilirubin) also known as "Hy's Law" must be considered as serious adverse events.

✓ *In utero* exposure

Any pregnancy during which the foetus (from the pre-embryonic stage up tobirth) may have been exposed for some time to one of investigational drugs administered during the trial, even if the pregnancy is not associated to an adverse event, **must be reported to the sponsor immediately**.

Notification is required in case of:

- Maternal exposure,
- Paternal exposure if the experimental drug is genotoxic.

✓ Exposure during breast-feeding

Exposure during breast-feeding occurs when an infant or a child may have been exposed to a drug *via*breastfeeding of a mother receiving an experimental drug.

Even if it is not associated to an adverse event, exposure during breast-feeding must always be reported to the sponsor by the investigator as soon as she/he becomes aware.

2.3.3 adverse events not requiring notification by the investigator to the sponsor.

These AE are only collected in the « adverse event » section of the case report form :

✓ 2 ≤ Adverse event grade ≤ 3

✓ **Natural and usual progression of the disease:**

- Medullary and/or meningeal relapse (disease progression)
- Planned hospitalization for the follow-up of the disease, such as a non complicated febrile neutropenia.
- Hospitalization for aplasia after transplantation not complicated (prolonged aplasia must be reported to the sponsor in accordance with the investigator's appreciation)
- Hospitalization for treatment or surveillance of the disease, not associated to patient health status deterioration
- AE related to classical chemotherapy i.e.: isolated grade < 4 neutropenia without fever, non complicated febrile neutropenia (according to the ongoing CTCAE classification at the time of AE notification).
- Hospitalisation for transfusions, febrile aplasia without complications
- AE related to L-Asparaginase and more specifically the allergic reactions of grade 1 and/or grade 2.
- Anaemia, thrombocytopenia (like blood or platelet transfusions in outpatients), leukopenia.

✓ **Special circumstances**

- Hospitalization for a pre-existing condition
- Hospitalization for a medical or surgical intervention planned before the enrolment in the trial
- Admission for social or regulatory reasons
- Visit to emergency room (<12 heures).

2.3.4 Adverse event documentation in the database

Following AEs are collected in the « adverse event » section of the case report form :

✓ Adverse Events ≥ grade 2

✓

✓ **Note:** As a SAE is by definition also an AE, please document the occurring SAE also in the AE section of the CRF.

These AEs do NOT need to be collected in the « adverse event » section of the case report form:

- Adverse Events < grade 2
- The alopecia, vomiting, diarrhea, mucositis, hand-foot syndromes < grade 4,
- The microbiological documentation not leading therapeutic decision (i.e positive sputum culture, blood culture positive staphylococcus ...)

2.4 procedures and deadlines for notifying the sponsor

Investigators must notify the sponsor **immediately on the day when she/he becomes aware** of any serious adverse events requiring immediate notification to the sponsor.

Notification of an SAE must initially be provided in a written report using the special form for reporting SAE (see Appendix 9.1). Thisform must be signed by the investigator.

Each item of this form must be completed by the investigator in order to allow the sponsor to perform the event analysis and assessment.

This initial notification must be followed, by one or more detailed follow-up report(s), signed by the investigator, 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 will also provide the sponsor, where possible, with any document that might be useful (medical reports, laboratory tests results, results of additional investigations, and so on). These documents must be made anonymous. In addition, they should include the following data: research's acronym, trialidentification number and initials of the subject (except for Switzerland for which initials will be "X-X"), nature and date of occurrence of the serious adverse event.

Any adverse event occurring during treatment/maintenance phase have to be documented in the CRF and will be monitored until its complete resolution (stabilization at an acceptable level for the investigator, or return to the previous status) even if the patient is discontinued from the study. (for SAEs see section 2.5).

Initial notification, SAE follow-up reports and any other document should be faxed to the sponsor Vigilance department at the at following number**+33(1) 44 84 17 99**.

The investigator should complete the SAE notification form in the e-CRF and after validation, the investigator should print it out, sign it and fax it to Vigilance department.

If it is not possible to connect to the e-CRF, the investigator will complete, sign and fax the SAE notification form found in Appendix. As soon as the connection is restored, the SAE notification form in the e-CRF must be completed. .

The investigator must comply with all requests for additional information from the sponsor.

For all questions relating to an adverse event report, the Safety Department can be contacted via email at eig.vigilance@aphp.fr.

Important informationto be provided to the sponsor:

The following information must be completed in the SAE notification form:

- patient's identification
- reporter's identification
- seriousness and severity of the adverse event
- SAE onset date and SAE resolution date
- SAE description (diagnosis, symptoms, chronology, actions taken and results obtained, evolution)
- ongoing diseasesor patient's medical history
- treatments administered to the patient (investigational drug(s), concomitant medication(s))
- Causal relationship between the SAE and the investigational drug(s), trial act(s), procedure(s) or test(s).
    - ❖ The investigator must complete:
        - in addition tothe SAE notification form, thenelarabine-related neurotoxicity form (please refer to appendix 9.4) if a neurological disorder will occur in a patient receiving nelarabine (Atriance®)
        - a specific form to notify secondary cancers /myelosysplasia (please refer to appendix 9.3) in case of secondary malignancy.

If the investigator considers that the seriousadverse event is related to the research or to the investigationaldrug(s), he/she will provide the sponsor, where possible, with any additional document useful for the case's assessment (medical reports, biological tests results, additional tests results, and so on.). These documents must be made anonymous. In addition, they should include the following data: research's acronym, trialidentification number and initials of the subject, nature and date of occurrence of the serious adverse event.. The investigator should answer to any additional queriesfrom the sponsor.

For any question related to the notification of an adverse event, the investigator can contact the Vigilancedepartment by e-mailat the following address: vigilance.drcd@aphp.fr

***In utero*exposure**

The investigator completes and returns by fax to the Vigilance department at the following number **+33(1) 44 84 17 99**. **"Follow-up form for reporting a pregnancy occurring in a clinical trial".**

The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated and must notify the sponsor about its outcome usingthe above mentioned form.

If the pregnancy outcomefulfills one of the serious adverse eventscriteria (miscarriage, pregnancy interruption, foetal death, congenital **anomaly**…...), the investigator must follow the procedure of SAE notification.

In case of paternal exposure, the investigator must obtain the pregnant woman consent to collect information about the pregnancy.

Exposure during breast-feeding

Breast-feeding exposure occurs when a breastfed infant may have been exposed through the mother's milk to the investigational drug.

Exposure during breast-feeding must always be reported to the sponsor by the investigator as soon as possible even if it is not associated to an adverse event.

Initial notification of pregnancy, SAE follow-up reports and any other document should be sentto the sponsor to the Vigilance department only by fax at the following number:**+33(1) 44 84 17 99**.

2.5 Sponsor's notification period

Any SAE occurred in a trial participant must be reported by the investigator to the sponsor:

- starting from the date of the participant informed consent form signature
- throughout the whole trial follow-up period
- with no time limit, if the SAE is likely to be related to the investigational drug or to any trial procedures (for instance the serious reactions that might appear long after the exposure to the drug, such as cancers congenital abnormalities).

Once a year throughout the clinical trial, the sponsor should provide Member States where the clinical trial is conducted and the ethical committee with a line listing of all SAEs that have occurred during that period, along with a report about the trial participants' safety.

2.6 Sponsor's role

The sponsor represented by its Vigilance department continuously assesses the safety of each investigational drug and trial's procedures throughout the trial.

2.6.1 Analysis and declaration of seriousadverse events

The sponsor assesses:

- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and investigational medicinal product *and/or study procedures* and any other treatments,

  All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal product are considered as suspected serious adverse reactions.
- the **expectedness assessment** of the serious 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, is considered unexpected.

  The sponsor, acting through its Safety Department, assesses the expectedness of the serious adverse reaction based on the information described below.

For serious adverse events likely to be related to the investigational medicinal product(s):

Please refer to the investigator's brochure of Tasigna® (nilotinib), the SmPC of Nelarabine (Atriance®), the SmPC of Blinatumomab (Blincyto®) and to the following SmPC:

- **Cyclophosphamide (Endoxan®)**
- **Methotrexate (Ledetrexate®)**
- **Vincristine (Oncovin®)**
- **Cytarabine (Aracytine®)**
- **VP16/Etoposide (EtoposideTeva®)**
- **Dexamethasone (Neofordex®)**
- **Prednisone (Cortancyl®)**
- **6-mercaptopurin (Purinethol®)**
- **Daunorubicine (Cerubidine®)**
- **Idarubicine (Zavedos®)**

- **L-asparaginase (Kidrolase®)**
- **G-CSF (Granocyte®)**
- **Imatinib**
- **Methylprednisolone (Solumedrol®)**
- **Mesna (Uromitexan®)**
- **Methylprednisolone acetate (Depomedrol®)**

The following SAEs (except from the grade 5 or death) are related to the classical chemotherapy and are expected:

- Thrombocytopenia, hemorrhage, Hemorrhagic Cystitis, subdural hematoma in a context of thrombocytopenia
- Sepsis, septic shock, septicemia, bacterial, viral, fungal infections, catheter related infections,
- Hepatotoxicity, cytolysis, cholestasis, icterus, acute hepatitis, pancreatitis, cholangitis
- Arterial and venous thrombosis including cerebral thrombosis, thrombophlebitis, embolism catheter thrombosis
- Diarrhea, vomiting, nausea, mucositis , hand-foot syndrome
- - Bone marrow aplasia, febrile bone marrow aplasia
- Neutropenia, febrile neutropenia, leukopenia, anemia
- Tumor lysis syndrome
- Post-lumbar-puncture syndrome
- Lumbar pain after lumbar puncture
- Renal insufficiency
- Peripheral neuropathy, paresthesia
- Digestive perforation, paralytic ileus, intestinal obstruction, sub-occlusive syndrome
- Anaphylactoid and anaphylactic reactions
- Diabetes steroid-induced, hypokalemia, glucocorticoid-induced osteoporosis,
- Hypertriglyceridemia, hyperlipidemia
- Delay in MTX elimination (MTX > 1 g / m^2)
- Extravasation
- Arrhythmia, long QT syndrome, cardiomyopathy, heart failure
- Hemorrhage following liver biopsy performed to explore liver toxicity
- Anxiety syndrome, depression syndrome, suicide attempt
- Incident on the catheter
- Anorexia, weight loss, asthenia, abdominal pain, Alopecia

Complications of hematopoietic stem cell allogeneic or autologous transplantation and conditioning graft (chemotherapies and TBI): the following SAEs (except from the grade 5 or death) are expected:

- Acute or chronic GVHD
- Veino-occlusive disease
- Transplant rejection
- Bronchiolitis obliterans organizing pneumonia
- Bone marrow aplasia, febrile bone marrow aplasia
- Sepsis, septic shock, septicemia, bacterial, viral, fungal infections, catheter related infections
- Hemorrhage, thrombocytopenia
- Neutropenia, febrile neutropenia, leukopenia, anemia
- Nausea, vomiting, nausea, loss of appetite, weight loss, diarrhea
- Capillary leak syndrome: weight gain, ascites, pulmonary edema
- Restrictive respiratory syndrome, obstructive pulmonary disease
- Renal insufficiency
- Peripheral neuropathy, paresthesia
- Somnolence, confusion, disorientation, Insomnia
- Pericarditis
- Cataract
- Hypothyroidism
- Hemorrhagic Cystitis
- Fertility disorders, infertility, gonadal insufficiency
- Anorexia, asthenia, pain, Alopecia
- Secondary cancers

- Skin reactions
- Anxiety or depression syndrome

Classical chemotherapy includes the following investigational drugs (administered in accordance with their MA):

- **- GRAALL-2014/B: cyclophosphamide, methotrexate, vincristine, cytarabine, VP-16, dexamethasone, prednisone, 6-mercaptopurin, daunorubicine, idarubicine, L-Asparaginase, G-CSF, methylprednisolone, Methylprednisolone acetate, blinatumomab.**
- **- GRAALL-2014/T: cyclophosphamide, methotrexate, vincristine, cytarabine, VP-16, dexamethasone, prednisone, 6-mercaptopurin, daunorubicine, idarubicine, L-Asparaginase, methylprednisolone, Methylprednisolone acetate.**
- **- GRAAPH-2014: imatinib, methotrexate, vincristine, cytarabine, dexamethasone, 6-mercaptopurine, methylprednisolone, Methylprednisolone acetate and prednisone.**

Nelarabine (substudy GRAALL-2014/T) and nilotinib (substudy GRAAPH-2014) are not used in accordance with their MA and are not considered as "classical" chemotherapy then.

Reporting to EMA:

Any suspected unexpected serious adverse reaction must also be declared electronically in the European database for adverse reactions, Eudravigilance, established by the European Medicine Agency (EMA) by the sponsor.

SAE reporting in France:

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.

SAE reporting in Switzerland and in Belgium:

SAE are reported by the local sponsor representative to the national regulatory authority, according to the local regulation and within the legal timeframe

The sponsor should inform all the investigators aboutany data that might affect the trial participants' safety.

2.6.1.1 Special case of serious adverse events

The following events must have a special follow-up from the sponsor:

- ❖ nelarabine-related neurotoxicity
- ❖ secondary malignancy
- ❖ Pregnancy
- ❖ Tumor Lysis Syndrome with a fatal outcome
- ❖ Completed Suicide

. Although these events are expected and listed in the Investigator Brochure, tumor lysis with a fatal outcome and completed suicide must be reported to the competent authorities as "serious adverse reactions of special interest" within the same timeframe as SUSAR declaration.

2.6.2 Analysis and declaration of other safety data

This relates to any safety data or any new fact that could significantly modify the benefit-risk ratio assessment of an investigational drug, or of the trial, or which could lead the sponsor to modify either the drug administration or the conduct of the trial.

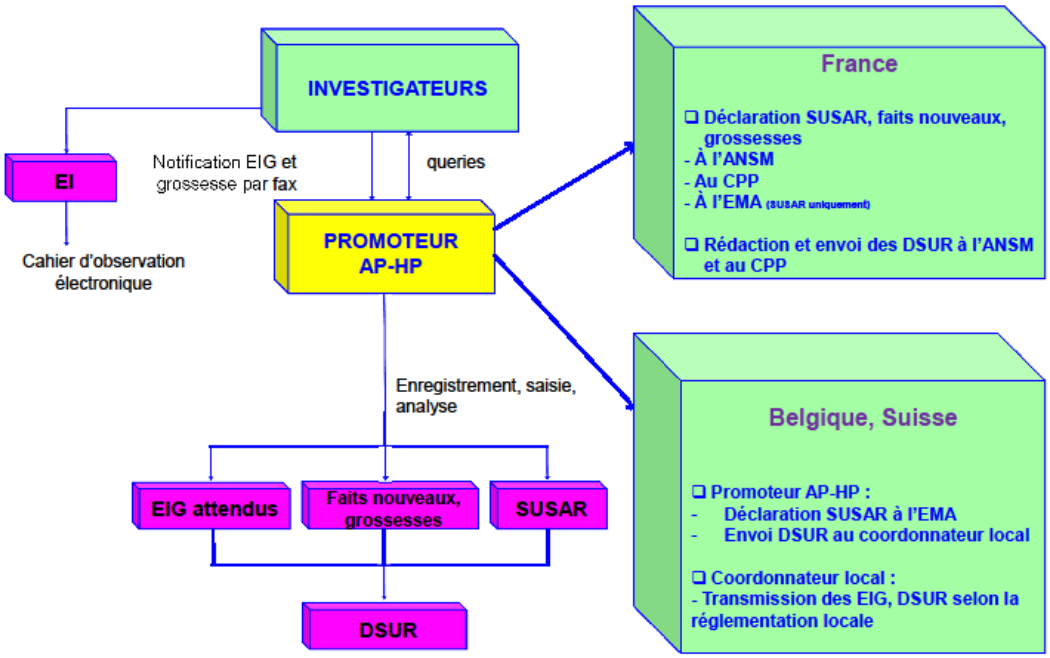
The declaration of new facts to competent authorities must be performed as soon as the sponsor is informed. Additional relevant data must be provided, within 8 additional days.

2.6.3 Annual safety report

Once ayear, during the whole trial duration, the sponsor must prepare a safety report (Development Safety Update Report - DSUR) which includes in particular the following items:

- ✓ an analysis of the trial participants safety,
- ✓ adescription of the patients includedin the trial (demographic characteristics, etc.),
- ✓ aline listingof allseriousadverse reactionsoccurred during the DSUR reporting period,
- ✓ acumulative summary tabulation of all serious adverse events occurred since the beginningof the trial.

A single DSUR will be realized for France, Belgium and Switzerland. The DSUR should be provided annually to the competent authorities within 60 days of the birth date of the ANSM trial authorisation.



2.7 data safety monitoring board (DSMB)

The DSMB is mentioned in article L. 1123-7 of the French Public Health Code.

An DSMB is planned for this biomedical research. A preliminary meeting of the DSMB is planned before the first inclusion of the first patient. The missions and precise functioning modalities of the DSMB will be described in its charter, at the latest before inclusion of the first patient. The DSMB will be, among other things, consulted for the results of the intermediate analysis of GRAAPH-2014.

2.7.1 Generalities about the DSMB

The DSMB proposed recommendations to the sponsor on the continuation, modification or discontinuation of the research. Such recommendations emanating from an DSMB may be:

- ✓ continuation of the research without modification,
- ✓ continuation of the research with modification of the trial and/or of the patients' surveillance,
- ✓ temporary halt of inclusions,
- ✓ definitive discontinuation of the research upon examination of
- ✓ safety data: severe adverse events
- ✓ Efficacy: futility or demonstrated efficacy.

The DSMB is designated by the sponsorand comprises at least three individuals not involved in the research including at least a clinician specialist to the disease studied and a specialist of the drug studied (or a pharmacologist pharmacovigilant), and possibly a methodologist/biostatistician especially in case of interim analysis.

The DSMB has a consulting function when the sponsor requires its advice on security issues such as tolerance or re-evaluation of the benefit/risk ratio during the research.

2.7.1.1 Definition of DSMB'S MISSIONS

- ✓ Validation of the research's methodology
- ✓ The methodology proposed for the clinical trial must be validated by the DSMB so that it does not impair the security of the patients, especially concerning inclusion and randomization modalities
- ✓ Validation of tolerance follow-up modalities
- ✓ Nature of evaluated parameters
- ✓ Frequency of evaluations, visits' planning
- ✓ Validation of discontinuation criteria
- ✓ Discontinuation criteria for a subject of tolerance reasons
- ✓ Temporary or definitive discontinuation criteria (leading to the definition of certain recommendations (« stopping rules »)
- ✓ Modification of the trial and recommendations
- ✓ Regarding the analysis of the trial's tolerance, the DSMB will be able to: propose substantial modifications to modify some data of the protocol (inclusion and non-inclusion criteria, follow-up, additional tests …) as well as itwill be liable to propose any recommendation deemed useful to guarantee at best the security of the subjects participating to the research and preserve the most favorable risk/benefit balance along the study.

2.7.1.2 Definition of DSMB functioning modalities:

- ✓ Meetings modalities (open session, then by closed doors) and frequency will be detailed in the DSMB charter at the latest before inclusion of the first patient,
- ✓ Modalities and format expected for the transmission of SAE from the sponsor to the DSMB will be detailed in the DSMB charter at the latest before inclusion of the first patient,
- ✓ During the first meeting, the ISC elects its president.

The sponsor takes the decisions. If needed argumented decisions are forwarded, together with DSMB reports to the ANSM and relevant CPP.

At the express request of the ANSM, the DSMB will sit after 10 treated patients by the blinatumomab. A synthesis and analysis of the tolerance data will be sent to the ANSM.

3 DATA MANAGEMENT

3.1 Access rights to data and sourcedocuments

3.1.1 Access to data

According to GCP:

- ✓ 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)

3.1.2 Source documents

Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during theresearch. These documents will be kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.

3.1.3 Data confidentiality

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects and in particular the identity of the subjects and the results obtained.

These individuals, as well as the investigators themselves, are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).

During or after the biomedical research, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialized parties) will be made non-identifying.

Under no circumstances should the names and addresses of the subjects involved be shown.

Only initials of the name and surname will be recorded, accompanied by a coded number specific to the research and including the inclusion order of each individual. As the Swiss regulations don't allow the disclosure of the patients' initials, all Swiss patients will have the following dummy initials: "X" for the name initial and "X" for the surname initial.

The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her which is strictly necessary for the quality control of the research.

3.2 Data processing and storage of documents and data.

3.2.1 Identification of the person responsible for and the location(s) of data processing

Data processing will be performed by Pr. Sylvie Chevretin the « Service de Biostatistique et Information Médicale (SBIM), hôpital Saint-Louis, Paris ».

3.2.2 Data capture

Data will be entered on a web-based electronic support.

3.2.3 Data processing (CNIL, the French Data Protection Authority) in France

This research falls under the "Méthodologie de référence" (MR-001) 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 " The same level of personal data processing is required for other countries involved in the study.

3.2.4 Archival

Specific documents for biomedical research relating to a medication for human use will be archived by the investigator and the sponsor for a period of 15 yearsafter the end of the research.

However, documents must be archived for a longer period if required by applicable local rules.

This indexed archival includes, in particular:

- ✓ One or more sealed envelope for the investigator : containing the original copies of all information notes and consent forms signed for all individuals at the centre that participated in the research
- ✓ One or more sealed envelope(s) for the sponsor : containing a copy of all the information notes and consent forms signed for all subjects at the centre that participated in the research
- ✓ "Research" binders for the Investigator and the sponsor, including:
  - the successive versions of the protocol (identified by the version no. and date), and the appendices
  - the ANSM authorizations and CPP favorable opinions
  - letters of correspondence
  - the inclusion list or register
  - the appendices specific to the research
  - the final research report
- ✓ The data collection documents

3.2.5 Ownership of theData

AP-HP is the owner of the data, which cannot be used or disclosed to a third party without its prior approval.

3.2.5.1 Patients included in GRAALL-2014

The GRAALL will be allowed to conduct retrospective studies not relative to the primary endpoint criteria of GRAALL-2014 studyn or experimental drugs prescribed outside the Main trial, only for itself, with the understanding that such studies do not imply the transfer of data to a non-member of the GRAALL and not participating to GRAALL-2014. In case such retrospective studies would be performed in collaboration with industrials and/or academic partners, they will be submitted to the approval of AP-HP and a contract will be established and signed between AP-HP, GRAALL and the partner involved. The GRAALL commits itself to notinjure to the sponsor AP-HP.

3.2.5.2 Trans-protocol studies

The GRAALL will be allowed to conduct transversal retrospective studies about patients involved in studies performed with the AP-HP being sponsor, only for itself, with the understanding that such studies do not imply the transfer of data to a non-member of the GRAALL and not participating to GRAALL-2014. In case such retrospective studies would beperformed in collaboration with industrial and/or academic partners they will be submitted to the approval of AP-HP and a contract will be established and signed between AP-HP, GRAALL and the partner involved. The GRAALL commits itself to not injure the sponsor AP-HP.

4 STATISTICAL ASPECTS

4.1 Description of planned statistical methods including the agenda of interim analyses

Primary analyses of the 3 trials will be performed on the whole population of included patients, i.e. in intention to treat (ITT), independently from the treatment received, whatever the treatments received and whatever the objective of superiority or non-inferiority demonstration[64].

In order to address non inferiority questions, confidence intervals at 95% of principal judgment criteria (DFS at 4 years for GRAALL-2014/B ; percentage of major molecular response for GRAAPH-2014 AAL Ph+) will be calculated and their lower threshold compared to the margin of non-inferiority (15%) planned in each trial.

For superiority questions or for secondary criteria, effect sizes will be appreciated one-shot and with a confidence interval of 95%, using statistical tests adapted to each criterion (log-rank test with non-informative data censored on the right, and Gray test in case of competition). Effects measured on censored criteria will be the ratio of instant risk functions, the effect on proportions will be measured by the relative risk and the difference between risks. These estimations will be adjusted on prognostic factors and if necessary risk-stratified (SR, HR, VHR).

Besides, an interim analysis is planned on the Ph+ ALL study (GRAAPH-2014), after inclusion of the 60 first patients, on MRD2 molecular response: one-shot estimation by exact binomial confidence interval at 95% will be calculated, with a binomial test of the null hypothesis for equality of this response probability at 80%. Results will be transmitted to the ISC which will decide on a possible replacement of nilotinib by imatinib (or dasatinib) for all 4 cycles pre-transplant. Of note, this interim analysis is not investigating the comparison between treatment arms and a global adjustment of the trial population is not required.

4.2 Hypotheses for the calculation of the sample size required and the result

4.2.1 GRAALL-2014/B

The objectiveis here to demonstrate through a non-controlled study, the non-inferiority in terms of DFS at 4 years which must be at least 60% in standard risk patients (historical reference for this SR group), with a 15% inferiority margin, justifying the absence of Allo-SCT in first remission. With a unilateral alpha risk of 0.05 and a power of 0.90, the calculated sample size is **110 standard risk patients** (SR)**.**

Over 5 years, 500 Ph- B-ALL patients should be included. This size population allows to anticipate 150 standard risk (SR) patients in remission after consolidation 1 (cf. trial schema). Taking into account the likely number of non-evaluable patients, the necessary population of 110 SR patients should be reached.

If a biomedical research trial for HR patients would be developed during the GRAALL-2014, investigators might privilege this new research for the interest of the patient. Only survival data would keep being collected.If not, HR patients will remain in the GRAALL-2014 study.

[64]Wiens BL et *al*, ClinTrials, 2007; 4(3): 286-9

4.2.1.1 GRAALL-QUEST substudy

The objective, in these B-ALL HR patients, is to demonstrate an improvement of DFS at 3 years from 50% (historical level) to 65%. With a unilateral alpha risk of 0.05 and a power of 0.90 (bilateral formation), the minimal calculated sample size is 91 patients. To account for dropouts 95 patients should be included.

Over 5 years, 500 Ph- B-ALL patients should be included. This size population allows to anticipate 250 high risk (HR) patients alive and in remission after consolidation 1 (cf. trial schema). Taking into account the likely number of non-evaluable patients or patients not consenting to participate to this substudy, the necessary population of 95 HR patients should be easily reached within probably 2 years.

Once these 95 patients will have been included, enrollment in ATRIALL will be closed. Further HR patients eligible for the GRAALL-QUEST substudy will not take part to it but will continue the participation and follow-up anticipated in GRAALL-2014/B.

4.2.2 GRAALL-2014/T trial

The objective is here to demonstrate through a non-controlled study, the non-inferiority in terms of DFS at 4 years which must be at least 60% in standard risk patients (historical reference for this SR group), with a 15% inferiority margin, justifying the absence of Allo-SCT in first remission. With a unilateral alpha risk of 0.05 and a power of 0.90, the calculated sample size is 82 **standard risk patients.** To account for dropouts 85 patients should be included.

Over 5 years, 275 T-ALL patients should be included. This size population allows to anticipate 100 standard risk (SR) patients in remission after consolidation 1 (cf. trial schema). Taking into account the likely number of non-evaluable patients, the necessary population of 85 SR patients should be reached.

Patients qualified as high risk (HR), about 150 over 5 years, will be eligible for the substudy ATRIALL, beginning after consolidation 1 and appreciating the addition of nelarabine in the subsequent treatment phases, with RFS as principal objective (cf. paragraphs about this study).

4.2.2.1 ATRIALL substudy

The objective, in these HR patients, is to demonstrate an improvement of DFS at 4 years from 50% (historical level) to 65%. With a unilateral alpha risk of 0.05 and a power of 0.90 (bilateral formation), the minimal calculated sample size is 113patients. To account for dropouts 120 patients should be included.

Over 5 years, 275 T-ALL patients should be included. This size population allows to anticipate 150 high risk (HR) patients alive and in remission after consolidation 1 (cf. trial schema). Taking into account the likely number of non-evaluable patients or patients not consenting to participate to this substudy, the necessary population of 120 SR patients should be easily reached.

Once these 120 patients will have been included, enrollment in ATRIALL will be closed. Further HR patients eligible for the ATRIALL substudy will not take part to it but will continue the participation and follow-up anticipated in GRAALL-2014/T.

4.2.3 GRAAPH-2014 trial

With a MMolR of 80% at MRD4 expected in the control arm, accepting a non-inferiority margin of 15%, with an alpha risk of 0.05 and a power of 0.90 125 patients should be randomized in each arm to demonstrate a non-inferiority of the experimental arm in terms of MMolR at MRD4. A total number of 250 patients will therefore be included to reach this goal.

Over 5 years, 265 Ph+ ALL patients should be included. Taking into account the likely number of non-evaluable patients, the necessary population of 250 randomized patients should be easily reached.

4.3 Statistical significance retained

The 0.05 threshold is retained.

4.4 Statistical criteria of study cessation.

The Ph+ ALL (GRAAPH-2014) trial is the only one planning an interim analysis after inclusion of the first 60 patients, with the objective of verifying the level of MRD2. No statistical criterion for stopping inclusions in the other 4 studies is planned.

4.5 Methodology to deal with missing, unused or invalid data

Missing data on covariablesof interest will be attributed by multiple imputation using chained equations (Multiple Imputation by Chained Equation: MICE).

Data analysis methods of censored information (on the right) are adapted to the presence of patients with different follow-up, assuming that follow-up interruption is independent from the studied process (which cannot be verified); for MRD4 measurements, a study of sensibility to missing data will be possible, comparing obtained results in complete cases, by imputation of the last value (MRD2 ; « *last observation carried forward* ») and by the Hackman method.

4.6 Gestionof modifications brought to the initial strategyof the statistical analysis plan

An amendment will be filed in case of modification of the initialstatistical analysis plan.

4.7 Populations selection

Final analyses of the three substudies including ATRIALL will be performed on the whole population of included patients, i.a. in intention to treat (ITT), independently from the treatments received and whatever the objective of demonstration of superiority or non-inferiority[64].

5 QUALITY CONTROL AND INSURANCE

Each biomedical 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 biomedical research sponsored by AP-HP.

5.1 General organization

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 centers.

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 section5.18.1), 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

A visit is organized at the onset of the study, one or several others occur during the study and there is a closing visit.

5.1.1 Strategy for opening the centers

The strategy for opening the centres established for this research is determined using the appropriate monitoring plan. Each pharmacy is visited at the opening of participating centers in order to present the trial.

5.1.2 Level of center monitoring

In the case of this research, which is considered **"high risk D"**, 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 according to internal procedures. The monitoring in Switzerland will be done according to the SOPs of the sponsor representative in Switzerland (named SAKK) and to the local monitoring plan approved by AP-HP.

5.2 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 DRCD 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:

- ✓ 100% Consents ;
- ✓ 100% SAE(s)/Tolerance ;
- ✓ 100% Eligibility criteria;
- ✓ 100% Evaluation criteria ;
- ✓ 100% Trial therapy ;
- ✓ 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.).

5.3 CASE REPORT FORM

All information required according to the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Each missing data item must be coded.

This digital case report 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 theresearch. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

5.4 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. As a first step, major or critical non-compliances will be reviewed and processed by the DRCD's medical coordinator in order to implement the necessary corrective or preventive actions. Next, the non-compliances will be sent to the Quality - Risk Management Division of the DRCD for verification and analysis. These verifications could result in the investigator in charge of the research location in question being asked for information or could lead to compliance or audit visits.

5.5 Audit / 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.

5.6 principal investigator’s commitment to assume responsibilities.

Before starting the research, each investigator will give the sponsor’s representative a copy of his/her personal curriculum vitæ, signed and dated, mentioning he/she obtained a medical degree and, for French investigators, his/her number in the RPPS (RépertoirePartagé 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, and GCP ICH6, adhering to the Declaration of Helsinki terms in force.

The principal investigator at each participating centre will sign a responsibility commitment (standard DRCD document) which will be sent to the sponsor's representative.

The investigators and their team will sign a delegation of duties form specifying each person's role.

6 ETHICAL AND LEGAL CONSIDERATIONS

6.1 Modalities for the information and collection of consent from persons involved in the research

In accordance with “article L1122-1-1 of theFrench Public Health Code” , no biomedical research can be practiced on a person without obtaining his/her free and informed consent, in writing, after receiving the information specified in “article L. 1122-1 of the French Public Health Code”.

Free, informed and written consent of the person is collected by the investigator, or a medical doctor representing the investigatorbefore inclusion of the patient in the research, i.e. at the latest before D1 of

chemotherapy, as soon as the diagnostic examinations have been performed. **This must occur before any procedure related to the research the patient will accept to enter.**

The information notice and a copy of the informed consent form, dated and signed by the person participating to research as well as by the investigator or the medical doctor representing him/her are given to the patient before his/her participation to the research.

Moreover, the investigator will notify in the medical file of the person his/her participation to the research, the modalities for obtaining his/her consent, and the modalities of information delivery in view of obtaining this consent. The original of the dated and signed consent form is retained by the investigator.

Special case: If it is physically impossible for the subject being recruited to consent in writing, his or her consent will be confirmed by a third party. This third party must have no association with the investigator or with the sponsor.

6.2 Interdiction for the person to take part to another research or exclusion period after the research if applicable.

No exclusion period is defined in the frame of this research.

Patients can participate to other non-interventional research programs.

NB: if a biomedical research trial for HR patients occurred during the GRAALL-2014 trial, the investigators could privilege this new research, in the interest of the patient.

6.3 Patients compensation

No compensation is planned for the patients as a compensation for the constraints related to the research.

6.4 Legal obligations

6.4.1 Sponsor role

« Assistance publiquehôpitaux de Paris (AP-HP) »is the sponsor of this research and, by delegation the « Département de la recherche Clinique et du Développement (DRCD) »carries these missions on, in conformity with article « L.1121-1 of the French Public Health Code». AP-HP retains the right to discontinue the research at any time for medical or administrative reasons; in such a case, a notification will be provided to the investigator.

6.5 Regulatory authorizations

6.5.1 In France

6.5.1.1 Request for an opinion of the « comité de protection des personnes CPP » (French ethical review board)

AP-HP, as sponsor, obtains for the biomedical research involving drugs for human use, before its initiation, a favorable opinionfrom the relevant CPP, according to its competence and in conformity with ongoing legal and regulatory dispositions.

6.5.1.2 Request for ANSM authorization (French health authority)

AP-HP, as sponsor, obtains for the biomedical research involving drugs for human use, before its initiation, an authorization from the ANSM, according to its competence and in conformity with ongoing legal and regulatory dispositions.

6.5.2 Other countries

Authorizations from the competent authorities (health authority and Ethic Committee) must be obtained before initiation of the research in the county involved, in conformity with local ongoing legal and regulatory dispositions.

6.6 Conformity engagement to « Méthodologie de référence » MR 001

AP-HP, as sponsor of this research, has signed a conformity engagement to this « Méthodologie de Référence ».

6.7 Research modifications

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 favorable opinion from the CPP and authorization from the ANSM within the scope of their respective authorities.

The information notice and the consent form can be revised if necessary, in particular if there is a substantial modification to the research or if adverse reactions occur.

6.8 Final report of the research

The final biomedical research report referred to in Article R1123-60 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the report or the full report (depending of the local regulation) 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.

7 FINANCING AND INSURANCE

7.1 Financing source

This study was financed in the frame of the call for projects: **"Programme Hospitalier de Recherche Clinique Cancer 2012"** by the French Ministry of Health.

7.2 Insurance

The sponsor purchases, for the whole duration of the research, an insurance covering its own civil responsibility as well as that of any medical doctor involved in performing the research. An integral compensation of damages consecutive to the research for persons engaged in it and their relatives is also covered by this insurance, unless proof (at the discretion of the sponsor) that the damage is not imputable to the sponsor's or any other participant's fault, without accepting that may be opposed the doing of a third party or a voluntary retraction of the person who initially agreed to participate in the research.

AP-HP has contracted an insurance by HDI-GERLING through BIOMEDIC-INSURE for the whole duration of the research, covering its own civil responsibility as well as that of any person involved in performing the research

in France (medical doctor of personnel involved in the research), in conformity with "article L.1121-10 of French Public Health Code". For other countries, local insurance will be contracted according to local regulation. An insurance for Swiss patients will be purchased by the sponsor representative in Switzerland (named SAKK).

8 PUBLICATION RULES

Writers of manuscripts liable to result from this study must vouch that:

1. the three first positions will be occupied by investigators having taken an active part to the achievement, analysis and /or redaction. It is not mandatory that the last position(s) is(are) systematically occupied by the "chairmen"or"presidents" of the cooperative groups united in the GRAALL. For instance, the last position can be attributed to the principal investigator of a study, if it is felt necessary to leave the first positions to younger investigators who performed a significant part in data analysis and manuscript writing,
2. the two founder groups of the Intergroup (LALA and GOELAMS) must be represented by at least one coauthor at one of the 4 best positions (first, second, penultimate or last signature),
3. eachgroup (LALA, GOELAMS) must be represented by a total number of authors as representative as possible of the partition of the numbers of patients included in the study. The choice of authors' names representing each constitutive group will then be left at the discretion of discussions conducted within each group,
4. each country within the Intergroup GRAALL-(France, Belgium, Switzerland) must be represented by at least one co-author,
5. each authors list must be followed by the mention: "on behalf of the GRAALL.

8.1 Mention of the affiliation of AP-HP for projects sponsored or managed by AP-HP

- ✓ If an author has several affiliations, the order used to mention the institutions (AP-HP, Université, INSERM…) only bears importance if the latter authors belongs to AP-HP and in such a case, AP-HP must appear as the first affiliation.
- ✓ Each affiliationmust be identified by a separate address using a semi-colon (;).
- ✓ AP-HP must appear as « **AP-HP** » in first position in the address as follows: **AP-HP**, hospital, department, city, post code, France.

8.2 Mention of AP-HP manager (DRCD) and supports, notably of the industry in the "acknowledgments" of the text

« The sponsor was Assistance Publique – Hôpitaux de Paris (Département de la Recherche Clinique et du Développement) ».

« This research was supported by EUSA PHARMA ».

« This research was supported by NOVARTIS ».

This mention is used as needed for any industrial or academic partner wishing that such support is mentioned.

8.3 Mention of financing, in « acknowledgments » of the text

« The study was funded by a grant from Programme Hospitalier de Recherche Clinique Cancer 2012 – PHRC Cancer 2012 (Ministère de la Santé) ».

This research is registered by http://clinicaltrials.gov/ as

GRAALLT : NCT02619630

GRAAPH : NCT02611492

GRAALLB : NCT02617004

PART VI

ANNEXE