Phase I/II Clinical Trial Assessing the Combination of Sulfasalazine with Standard of Care Induction Therapy in Newly Diagnosed Acute Myeloid Leukemias (AML) Patients 60 years or older– the SALMA Study

Sulfasalazine in AML treated by intensive chemotherapy: elderly patients-first line treatment

CLINICAL TRIAL A MEDICINAL PRODUCT FOR HUMAN USE

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SIGNATURE page for a research PROTOCOL

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The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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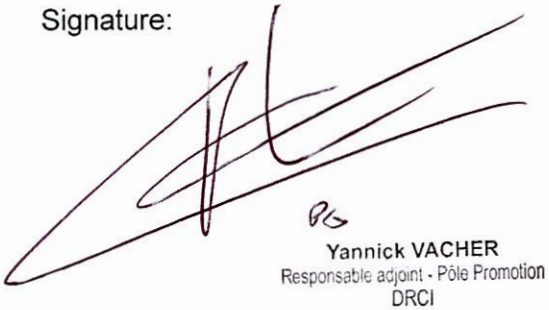

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1) SUMMARY

Full title	**Phase I/II Clinical Trial Assessing the Combination of Sulfasalazine with Standard of Care Induction Therapy in Newly Diagnosed Acute Myeloid Leukemias (AML) Patients 60 years or older – the SALMA Study**
Acronym/reference	SALMA
Coordinating investigator	Prof Raphaël Itzykson
Scientific Director	Dr Alexandre Puissant
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	*Non-Favorable AML in older patients is an unmet medical need.* Acute myeloid leukemia (AML) is a heterogeneous clonal myeloid neoplasm where abnormal proliferation and impaired differentiation of hematopoietic stem and myeloid progenitor cells impedes normal hematopoiesis. Despite the significant progress made in understanding AML oncogenesis over the past decades, this disease remains devastating with about 18,000 new cases every year in Europe and a five-year overall survival of only 17%.[1] The median age at diagnosis of AML is 69 years and the cure rate of patients older than 60 has not improved in the recent decades.[2] The standard of care (SOC) of newly diagnosed AML includes a '7+3' cytarabine-anthracyclin combination followed by repeated courses of high dose cytarabine with or without allogeneic hematopoietic stem cell transplantation (HSCT).[3] Recent advances in this SOC approach include the addition of the multikinase inhibitor midostaurine during induction and consolidation in patients with *FLT3* gene mutations,[4] maintenance with oral azacitidine after completion of induction with or without consolidation in patients ineligible for transplantation,[5] and use of a liposomal formulation of the cytarabine-daunorubicin combination instead of conventional 7+3 in patients with high-risk features.[6] In patients older than 60y with adequate performance status and few comorbidities deemed 'fit' for intensive chemotherapy, a 7+3 induction course combining 3 days of idarubicin (IDA) with a 7-day continuous cytarabine (AraC) infusion can induce complete remission (CR) or CR with incomplete platelet recovery in 64% of cases with non-favorable cytogenetics.[7] Recent advances in the supportive care of these patients, notably progresses in the anti-fungal armementarium, have lowered the toxicity of the 7+3 induction courses, with early date (ED) rates within the 5-10% range.[8] However, despite high CR and low ED rates with 7+3, the median event-free survival (EFS) remains 9.3 months in patients ≥60 years old with non-favorable cytogenetics, owing to frequent relapses.[7] Improving the anti-leukemic efficacy of the 7+3 induction course can contribute to better long-term prognosis in these patients.[9] However,

	modifications of the 7+3 induction course must rely on any additional toxicity to limit the risk of ED, and not to jeopardize post-remission therapy. Repositioning of drugs with excellent safety profiles appears as a promising approach in this regard.[10] As such, non-favorable risk AML in older patients represents an unmet medical need. Novel options to improve the efficacy of the 7+3 induction course are thus necessary. *End of Induction Measurable Residual Disease predicts long-term outcome in older AML patients treated intensively.* Standardization of molecular techniques and development of multiparameter flow cytometry (MFC) assays have made it possible to assess Measurable Residual Disease (MRD) at different time points during the course of AML therapy in virtually all patients.[11] In older patients treated with 7+3, MRD measured at the end of induction course (EOI) time point based on *NPM1c* transcripts in *NPM1*-mutated patients, or with MFC assays (Leukemia Aberrant ImmunoPhenotypes [LAIP] and/or Leukemic Stem Cell [LSC] methods) predict long-term outcome.[12] In *NPM1*-mutated patients younger than 60, the role of EOI MRD assessed by relative *NPM1c* transcript levels is also well established,[13] although data is scarcer in older patients.[14] Altogether, EOI MRD appears a relevant surrogate endpoint to estimate efficacy of alternative induction regimens in older AML patients with non-favorable cytogenetics. *Cystine import is a targetable vulnerability in AML.* The metabolic rewiring of leukemic cells is increasingly recognized as a targetable vulnerability in AML. Leukemic Stem Cells (LSCs) endowed with increased quiescence and chemoresistance,[15] have specific metabolic profiles that may for instance underpin the remarkable efficacy of the azacitidine-venetoclax combination in patients ineligible for 7+3.[16,17] LSCs notably rely on high levels of the cysteine amino acid to fuel glutathione synthesis and maintain low levels of Reactive Oxygen Species (ROS).[18] Chemical depletion of the intracellular pools of cysteine and its precursor cystine have pre-clinical anti-leukemic activity *in vitro*.[19] By querying transcriptional profiles of multiple AML patients' cohorts, we have identified a close correlation between the expression of stemness programs and an active cysteine metabolism pathway. Querying a CrispR screen conducted in 500+ cancer cell lines revealed a specific dependence of AML cell lines on cysteine metabolism. Among genes belonging to this pathway, higher expression of *SLC7A11* was identified to bear poor prognostic relevance in 3 AML cohorts.

	Genetic silencing of *SLC7A11* reduced viability and colony formation of AML cell lines in a cysteine-dependent fashion. *SLC7A11* encodes the xCT neutral amino acid antiporter that imports cystine against glutamate. The xCT antiport is broadly expressed in AML cell lines. Three chemical inhibitors of xCT with different chemical backbones including erastin, S-4-Carboxyphenylglycine (CpG) and sulfasalazine (SSZ) had highly concordant, cystine-dependent, anti-leukemic activity on a panel of 20 AML cell lines. These data suggested that cystine import could represent a targetable vulnerability in AML. *Sulfasalazine can be repurposed to inhibit cystine import in AML.* Sulfasalazine (SSZ) is a broadly available, well tolerated anti-inflammatory medicine approved for the treatment of ulcerative colitis and rheumatoid arthritis.[20] Intact SSZ, but not its metabolites 5-aminosalicylic acid and sulfapyridine, competitively inhibits xCT.[21] SSZ is thus an ideal candidate for drug repurposing in AML. In vitro, SSZ inhibited the viability of 12 primary AML specimens, with a > 10-fold increased sensitivity compared to CD34+ hematopoietic stem and progenitor cells from heathly donors (SSZ IC50 in AML 176µM ± 40µM versus 2.94mM ± 4.21mM in healthy CD34+ cells, p=0.0011). SSZ 250µM, a concentration in the same range as peak plasma concentrations of SSZ in healthy individuals,[22] also significantly reduced the in vitro long-term culture initiating potential of 6 primary AML samples. Finally, twice-daily intraperitoneal administration of single agent SSZ significantly reduced the leukemic burden in two distinct AML patient-derived xenografts (PDX) models. Finally, compassionate administration of oral SSZ at 3-6 g/d over a 20-day period in a patient with advanced refractory AML resulted in a transient, but clinically meaningful cytoreduction. Mechanistic studies found SSZ to induce global metabolic rewiring of the cysteine and one-carbon pathway, resulting in glutathione depletion and ROS-dependent cell death partly corresponding to ferroptosis,[23] Total protein expression of SLC7A11 did not correlate with SSZ activity. Thus, SSZ can be repurposed to inhibit cystine import and impair leukemic viability in AML. *Sulfasalazine improves the efficacy of anthracycline-cytarabine combination chemotherapy in pre-clinical AML models.* In two distinct AML cell lines, the anthracycline daunorubicin (DNR) was identified among a panel of 8 AML drugs as the one with top synergism when combined with SSZ. This observation may be underpinned by the ROS-inducing potential of anthracyclins.[24] In a cohort of 48 primary AML samples,

	addition of SSZ at a low concentration (4 µM) mimicking trough concentrations in healthy donors,[22] significantly increased the anti-leukemic activity of the combination of DNR with araC on both the total leukemic bulk and on GPR56+ LSCs in a niche-like ex vivo drug screening platform combining stromal co-culture, hypoxia and plasma-like medium.[25] Finally, addition of SSZ with a regimen combining 3 days of the anthracycline adriamycin with 5 days of cytarabine (maximally tolerated regimen in immunocompromised NOG-EXL mice) further decreased the leukemic burden in a PDX model and significantly prolonged survival over adriamycin-cytarabine chemotherapy alone (Pardieu et al, manuscript in preparation, data to be presented at the 2021 Annual Meeting of the European Hematology Association). These data support the clinical evaluation of the addition of SSZ with 7+3 in AML. *Addition of sulfasalazine to standard of care chemotherapies is manageable.* Repurposing of SSZ to inhibit xCT has been investigated alone or with standards of care chemotherapies in solid tumors.[26-28] A first study conducted of single-agent SSZ in 10 highly debilitated patients with high grade, progressing glioblastomas was terminated prematurely based on lack of efficacy. In this trial, the toxicity of SSZ at low doses (1.5-6 g/d) was mostly neurological, suggestive of tumor-specific poor tolerability possibly caused by drug-related peri-tumoral edema. [26] Conversely, another dose-escalation study of single-agent SSZ up to 12 g/d for 14 days in 11 patients with advanced gastric cancer identified 12 g/d as MTD with grade 3 anorexia as DLT. Other grade 3 AES included elevated AST (n=1) and bilirubin (n=1), fatigue (n=2), nausea (n=1), vomiting (n=1) and hyponatremia (n=1). There was no grade ≥ 3 hematological or grade 4 non-hematological AE in this trial. The median number of SSZ cycles was 2 (range 1–4) with a mean relative dose intensity of 85% for dose level 1 (8 g/d) and 60% at MTD (12 g/d).[28] Finally, a phase 1 study combining SSZ thrice daily for 21 days with cisplatin and pemetrexed on day 1 of each SSZ cycle was conducted in 15 patients with advanced non-small-cell lung cancers. The MTD was 3 g/day, and the recommended phase 2 dose (RP2D) was 1.5 g/day. DLTs included grade 3 elevations of AST and ALT aminotransferase levels, hypotension, pneumonitis, and anorexia. Overall, the combination appeared manageable, and promising activity was noted in terms of overall response rate progression-free survival compared to historical controls.[27] The anti-tumor activity of SSZ continues to be explored in solid tumors (NCT NCT04205357). Overall,

	addition of SSZ to chemotherapy appears feasible in carefully designed dose escalation phase 1 trials. Collectively, these pre-clinical findings provide a strong rationale for the clinical evaluation of the addition of sulfasalazine to standard of care 7+3 induction regimen in non-favorable AML patients older than 60 years. The purpose of this phase I study is to evaluate the safety and feasibility of such strategy, provide preliminary signals of efficacy, and identify potential biomarkers.
Main objective and primary endpoint	**Primary objectives:** **Phase I** To assess the safety, characterize the dose-limiting toxicities (DLTs), and identify the maximal tolerated dose (MTD), anticipated to be the recommended phase II dose (RP2D) of the combination of Sulfasalazine (SSZ) with idarubicin (IDA) and cytarabine (AraC) in patients with newly diagnosed non-favorable AML. Probability of DLT should not exceed 33% at the end of the induction cycle (EOI) of IDA-AraC + SSZ treatment (up to Day 42). **Phase II** To assess preliminarily the anti-leukemia efficacy of the combination of IDA-AraC + SSZ, mainly in phase II, in newly diagnosed non-favorable AML with reference from historical data on complete remission rate, (as defined in ELN 2022 guidelines) and MRD (by centralized flow cytometry). **Primary endpoints** **Phase I:** Documentation during the dose escalation of dose limiting toxicity (DLT), identification of a maximal tolerated dose (MTD) anticipated to be the recommended phase II dose (RP2D). • **Dose Limiting Toxicity (DLT)** DLT will be defined during a safety observation period corresponding to the induction cycle with IDA-AraC + SSZ (up to Day 42). **Events occurring after the onset of a second treatment cycle (i.e. salvage or consolidation) will not be considered as DLTs.** Any of the following events will be considered a DLT unless the event can be attributed by the investigator to a clearly identifiable cause such as underlying illness or

	disease progression, concurrent other illness, or concomitant medication: o Prolonged myelosuppression defined as Grade ≥ 3 Neutropenia or Thrombocytopenia on Day 42 from start of therapy or later without evidence of leukemia (assessed by bone marrow aspiration and/or biopsy). o Grade ≥3 hemorrhages until day 42. o Grade ≥3 non- hematological toxicity until day 42 with the exception of: ▪ Grade 3 infection, grade 3 fever with neutropenia (NB. grade 4 infections and grade 4 fever with neutropenia are considered as DLTs), ▪ Grade ≥3 nausea, vomiting or diarrhea that can be managed to ≤ Grade 2 within 72 hours of symptomatic treatment, ▪ Grade ≥3 asymptomatic liver enzymes elevation that improves to ≤ Grade 2 within 72 hours of onset, ▪ Grade ≥3 tumor lysis syndrome that resolves within 72 hours of onset with medical treatment. • **Maximal Tolerated Dose (MTD)** MTD is defined by a target DLT rate of 33%, assessed during the dose escalation phase by a continual reassessment method. • **Recommended phase II dose (RP2D)** RP2D is anticipated to be the MTD. However, it could be equal to one dose level lower than the MTD. It will be determined in interaction with the DSMB, insofar that this dose level is validated by PK/PD studies and efficacy preliminary data. **Phase II** MRD-negative Complete Response at EOI (day 28-42) per ELN 2022 Criteria: • Complete response is defined as Complete Remission CR or CRi (CR with incomplete hematologic recovery, meaning CR with platelet count <100,000/µL or absolute neutrophil count <1000/µL) and CRh (CR with partial hematologic recovery, meaning CR not fulfilling CR or CRi

	peripheral blood count criteria but with platelet count >50,000/µL AND absolute neutrophil count >500/µL). • MRD-negativity is defined as an 8-color bone marrow FCM MRD < 0.1% at EOI. • Of note, *NPM1*-transcript based MRD in the BM and PB will be carried as exploratory endpoint in *NPM1*-mutated patients.
Secondary objectives and endpoints	**Secondary objectives** • To characterize the pharmacokinetics (PK) and the pharmacodynamics (PD) of SSZ, IDA and AraC when administered in combination, during the dose escalation phase 1a, and to confirm it during the phase 2 of the trial. • To describe during the phase I of the trial the response of the leukemia to the treatment, the survival of patients up to 12 months after the end of induction (EOI) visit. • To document further during the phase II of the trial the safety profile and confirm the RP2D of the IDA, AraC and SSZ combination. **Secondary endpoints** **1) Assessment of safety** • Safety outcome measures will be assessed continuously during the study. • Monitoring of ECGs and clinical laboratory values are integral to safety assessment. • Adverse events (AE), treatment emergent adverse events (TEAE) and treatment-related TEAEs will be evaluated according to the NCI CTCAE version 5.0. Serious adverse events will be defined per protocol according to EMA/ICH criteria. Causality relationship with the experimental treatment should be assessed by the investigator. • Frequency, duration and maximal severity of each TEAE. Treatment-related TEAEs, TEAEs leading to treatment discontinuation, serious adverse events (SAEs) and deaths should be documented during phase I and II of the trial. • Patients should be followed until all treatment related TEAEs have returned to grade ≤ 1 or baseline or are deemed irreversible by the investigator. **2) Pharmacokinetics** To assess SSZ and its metabolites, IDA (and its metabolite) and AraC. This will allow to determine a PK model for SSZ at an early and late time point and confirm the lack of interaction between SSZ and IDA or AraC. The PK plan is detailed in a section below. Pharmacokinetic (PK) study will be conducted on patients recruited in the phase I part of the trial to assess the

	pharmacokinetics of sulfasalazine, and its main metabolites 5-ASA (mesalazine) and sulfapyridine which is mostly involved in adverse events. PK will be performed at days 0 and 3 and 14. PK profiling of cytarabine and idarubicine (+ idarubicinol) at day 4 will confirm the lack of drug-drug interaction. Following PK parameters will be determined using non-compartmental analysis (WinNonlin Pharsight Corporation: maximum plasma concentration (Cmax), maximum plasma concentration time (Tmax), area under the plasma concentration time curve (AUC), clearance (Cl), mean residence time (MRT), and distribution volume (Vd/F). For pharmacokinetic analysis, the dose of SSZ will be administered orally together with 200 mL water after the patient has fasted overnight, with a meal being permitted after blood sampling at 4 h after the drug is given. Blood samples will be obtained: - on day 0 before (pre-dose) and at 1, 2, 3, 4, 6 and 8h after first SSZ dose; - on day 3 pre-dose and at 5', 10', 20', 40', 1h, 4, 8, 24h of start of IDA injection; - on day 14 before (pre-dose) and at 1, 2, 3, 4 and 6h after first SSZ dose. Blood samples will be collected into heparinized tubes. Immediately after collection, tubes will be inverted several times and kept at approximately 4 °C until centrifugation. The tubes will be centrifuged for 10 min at 1500×g at 4 °C within 60 min of collection to separate plasma. The plasma will be separated into 2 aliquots in polypropylene screw-cap tubes and placed at -80°C until analysis. All samples will be labeled with patient identification, study identification, sample number, and actual date and time at which the sample was collected. The plasma concentration of SSZ and metabolites will be determined by a validated ultraperformance liquid chromatography and tandem mass spectrometry method.[28] **3) Pharmacodynamics** Pharmacodynamic assays aim at demonstrating ROS induction upon SSZ exposure relative to pre-treatment levels. They will be done on peripheral blood, because repeated bone marrow aspiration over a short-time period is unethical. Blood sampling for PD will be done on: - Day 0: effect of SSZ alone - Day 1: combined effect of SSZ, IDA and AraC - PD assays will include: • Plasma levels of malondialdehyde (MDA), glutathione (reduced/oxidized), two robust biomarkers of oxidative stress biomarkers previously involved in ferroptosis and/or SSZ mode of action (our pre-clinical results and [29]) that can be assessed in all patients and at all time points regardless of white blood cell count and percentage of circulating leukemic cells.

	• In patients with circulating leukemic cells, ROS levels of peripheral blood mononuclear cells by flow cytometry (H2DCFDA). **4) Antileukemia activity** • Response at EOI assessment (day 28-42) per ELN 2022 Criteria. o Morphologic leukemia-free state (MLFS): blastic criteria of response on the bone marrow aspirate, absence of extramedullary disease and no requirement of hematologic recovery. o Partial response (PR): absence of circulating blasts; absence of extramedullary disease; decrease of bone marrow blast percentage to 5 to 25% and decrease of pretreatment bone marrow blast percentage by at least 50% o Overall response rate (ORR) being defined as CR, CRi and CRh, MLFS and PR rates. o Primary refractory disease defined as patients lacking criteria for any of the above defined responses (CR, CRi, CRh, MLFS and PR) at EOI assessment, excluding patients with death in aplasia or death due to indeterminate cause as defined per ELN 2022 criteria. o Death in aplasia and death due to indeterminate cause as defined per ELN 2022 criteria. • Survival assessment at 12 months o Event-free survival (EFS); here events are defined as: ▪ Non achievement of hematologic response including CR, CRi, CRh ▪ Hematologic relapse or progressive disease ▪ Initiation of any subsequent anti-leukemic therapy (excluding hydroxyurea) ▪ Deaths prior to one of the events mentioned above. Reasons for subsequent therapy initiation (including intolerance, resistance, hematologic relapse, unsatisfactory MRD evolution), its type (intensive, less-intensive, best supportive care) and its frame (clinical trial, off-label or compassionate use) will be prospectively recorded. o Duration of response (DOR) o Relapse free survival (RFS) o Overall survival (OS)

	○ Incidence of subsequent allogeneic HSCT, overall and in responding patients specifically. Apart from specific mentions, all these hematological endpoints will be defined according to the latest recommendations from the European Leukemia Network (ELN; currently the 2022 ELN recommendations).
Design of the study	Phase I-II, open label, multicenter clinical trial with 2 subsequent phases: ● Phase I: dose-escalation with a design using a survival continual reassessment method to identify the maximal tolerated dose (MTD) and recommended phase II dose (RP2D). ● Phase II: extension at the RP2D chosen by the data and safety monitoring board (DSMB), to confirm the safety of RP2D and preliminarily documents its clinical efficacy.
Category	Cat 1/2 : Phase 1/2
Population of study participants	Patients ≥ 60 years with a recently diagnosed non favorable AML and eligible for intensive chemotherapy
Inclusion criteria	- Patients aged 60 years or older - With newly diagnosed AML (short course treatment with hydroxyurea and or steroids is acceptable). Patients with AML secondary to an antecedent Myelodysplastic Syndrome (MDS) or Myeloproliferative Neoplasm (MPN) are eligible, as those with therapy-related AML. - Eligible for an intensive chemotherapy according to the investigator's opinion - Multiparameter Flow Cytometry at screening compatible with MFC-based MRD monitoring according to ELN criteria (Phase II only). - ECOG performance status ≤2 - AST and ALT ≤3.0 x upper the limit of normal (ULN) and total and direct serum bilirubin ≤ 1.5 x ULN unless considered due to leukemia. - Estimated glomerular filtration rate (GFR) ≥ 50 mL/min according to the MDRD equation. - Written informed consent obtained prior to any screening procedures. - Eligible for National Health Insurance in France.
Exclusion criteria	- Myeloid Sarcoma with < 20% bone marrow blasts - Patient who has received a vaccine injection with live-attenuated virus in the last three weeks - Proven central nervous system leukemic involvement. - Favorable risk cytogenetics: t(15;17), t(8;21), inv(16) or t(16;16) or *PML-RARA*, *RUNX1-RUNX1T1*, *CBFB-MYH11* fusion transcript. - Presence of FLT3-ITD or TKD mandating treatment with midostaurin. - Concurrent therapy with any cytotoxic drug within 3 weeks before the first study dose. Only hydroxyurea for the control of blood counts is permitted. - Patients planned to received CPX-351 for myelodysplasia-related changes or therapy-related AML. - Previous treatment with sulfasalazine in the last 5 years or ongoing treatment with sulfasalazine or 5-aminosalicylic acid (5-ASA) for ulcerative colitis or inflammatory rheumatisms. - History of allergic reaction to sulfonylarylamines

	sulfonamides, salicylates, or sulfasalazine excipients. - History of allergic reaction to idarubicin or idarubicin excipients - History of allergic reaction to cytarabine or cytarabine excipients - Known glucose 6-phosphate dehydrogenase deficiency - Known acute intermittent porphyria or porphyria variegata. - Uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate treatment) - Other uncontrolled or active malignant disease within prior 12 months (excluding myelodysplastic syndrome; cutaneous basal cell carcinoma, “in-situ” carcinoma of the cervix or breast, or other local malignancy excised) - Known human immunodeficiency virus (HIV) infection or HIV-related malignancy. - Clinically active hepatitis B or hepatitis C infection. - Inability to swallow. - Known malabsorption syndrome or other condition that may significantly impair absorption of oral study medications. - Participation in another therapeutic interventional clinical study within 30 days of enrolment. - Administration of any therapy that is considered investigational (i.e., used for non-approved indications(s) or in the context of a research investigation) within 5 drug half-lives (whichever is longer) prior to the first dose of study drug. - Previous treatment by anthracyclines - Any contraindication to use anthracyclines including uncontrolled coronary disease, severe renal failure, severe hepatic failure, recent myocardial infarction, symptomatic congestive heart failure, severe cardiomyopathy, significant arrhythmia as estimated by the investigator or LVEF <53% as assessed by echocardiography or MUGA, anterior treatment by idarubicin and/or anthracyclines and anthracenediones beyond the maximum cumulative dose. - Any contraindication to use cytarabine including degenerative and toxic encephalopathy. - Any condition requiring treatment with digoxin. - Any of concurrent severe and/or uncontrolled medical condition, which could compromise participation in the study. - Females who are pregnant or breastfeeding. - In a man whose sexual partner is a woman of childbearing potential, unwillingness or inability of the man or woman to use a highly effective contraceptive method for the entire treatment period and for at least 6 months after completion of protocol treatment. Highly effective contraception methods include: combined (estrogen and progestogen containing) hormonal methods associated with inhibition of ovulation, intra-uterine device; surgical sterilization (including bilateral tubal occlusion, partner’s

	vasectomy) or sexual abstinence if this is the preferred and usual lifestyle of the patient. Male patients must not freeze or donate sperm starting at screening and throughout the treatment period and 3 months after the administration of the final dose of study medication. - In a heterosexually active woman of childbearing potential, unwillingness or inability to use a highly effective contraceptive method (as described above) for the entire treatment period and for at least 6 months after the administration of the final dose of study medication. Women are not regarded as of childbearing potential if they are post-menopausal (at least 2 years without menses) or are surgically sterile (at least 1 month before enrollment). Female patients must not donate or retrieve, for their own use, ova from the time of screening and throughout the treatment period, and for 12 weeks after the administration of the final dose of study medication. Female patients must agree not to breastfeed from the time of screening and throughout the protocol period, and for (5 1/2 lives) days after the administration of the final dose of study medication. - Adults subjects to a legal protection order or unable to give their consent - Persons deprived of their freedom by judicial or administrative decision, person hospitalized without their consent by virtues of articles L 3212-1 and L3213-1 and who are not subject to the provisions of article L 1121-8.
Investigational medicinal product and auxiliairy medicinal products	Investigational medicinal product: Sulfasalazine, approved and marketed for years as treatment of inflammatory diseases Tablets dosed at 500 mg Oral route with water at the following dose levels (DL) tested during the phase I: DL-2: 0.5 g, bid hence 1.0 g/d, days 0-7 DL-1: 0.5 g, tid hence 1.5 g/d, days 0-7 DL1: 0.5 g, tid hence 1.5 g/d, days 0-14 DL2: 1.0 g, tid hence 3.0 g/d, days 0-14 DL3: 1.5 g, tid hence 4.5 g/d, days 0-14 DL4: 2.0 g, tid hence 6.0 g/d, days 0-14 DL5: 2.0 g, four times per day hence 8.0 g/d, days 0-14 At all dose levels, patients will receive the standard of care IDA-AraC backbone, considered as auxiliary medicinal products in this clinical trial,[7] consisting of:

	<table><tr><th>Drug</th><th>doses</th><th>Administration</th><th>Days</th><th>Time</th></tr><tr><td>Idarubicin*,**</td><td>12 mg/m²</td><td>IV, 30mn</td><td>3 days</td><td>Day 1 to 3</td></tr><tr><td>Cytarabine*</td><td>200 mg/m²</td><td>CIV over 24h</td><td>7 days</td><td>Day 1 to 7</td></tr></table> **for these two drugs the body area should not be capped to 2 m²* Dose escalation will be conducted according to the survival continual reassessment method, the number of patients assessed at each dose level depending on the safety observations. Patients should be hospitalized during the induction course at least until day 21 and/or achievement of a neutrophil count > 500/µL. Thereafter they can be discharged if, according to the judgment of the investigator, their medical condition allows it and when all non-hematological treatment-emergent AEs resolve to Grade ≤ 2. Patients should have adequate IV hydration during SSZ exposure. Following the EOI visit, patients will continue to be followed for treatment related TEAEs for 30 days following the end of SSZ exposure, and for post-induction therapy, relapse and survival for 12 months after the EOI visit. Treatments beyond EOI are left to the clinicians' choice and may include consolidation chemotherapy, oral maintenance and/or allogeneic stem cell transplantation. ALFA guidelines for post-remission therapy in AML patients 60 years or older treated intensively are provided in the protocol Appendices. A minimal follow-up for transplantation, relapse and death for an additional 5 years after study exit will be undertaken.
Comparator treatment	None
Interventions added for the study	Interventions added by the studies are limited to the following procedures: - Systematic assessment of troponin in serum at D0, D3, D14 and EOI, - Additional ECG at D3, D14 and EOI, - PK and PD exams from peripheral blood samples (plasma, serum and cells), - Centralized MRD on peripheral blood and bone marrow aspirate by FCM.
Expected benefits for the participants and for society	Foreseeable benefits, whose demonstration is the primary objective of the current study, is an improvement of the complete response with undetectable minimal residual disease (MRD), which predicts an improvement of long-term outcome.
Number of participants included	Total: 64 patients phase I: 20 patients phase II: 44 patients
Number of centers	• 8 centers in phase I • 13 centers in phase II Conducted only in France, in hematology centers
Duration of the study	• Inclusion period: 56 months • Treatment period: 2 months • Follow-up period: 12 months • Total duration: 70 months

Number of enrolments expected per site and per month	0.07 to 0.1
Statistical analysis	**Phase I** A Bayesian adaptive dose escalation design will be used for the trial objectives. It allows sequential monitoring of data during the trial, using all current evidence for straightforward inference on safety and efficacy and decision making to select and evaluate an optimal dose. The design will rely on the Bayesian continual reassessment method (CRM) for the phase I, with cohorts of size 1 and a maximum sample size of 20 patients.[30] The target DLT rate for the definition of the MTD will be 33% within the EOI observation window. The time-to-event extension of the CRM (survCRM) design will be used depending on the anticipated accrual rate compared to the DLT observation window [31]; this will allow accounting for right-censored toxicity observation in sequential MTD estimation and dose assignment process. **Phase II** Once phase I has been completed providing the estimated MTD, the RP2D will be determined based on DSMB recommendations according to safety data and efficacy signals from Phase I. Inclusion criteria will be the same as in Phase I with the addition of an additional inclusion criteria (LAIP detected at baseline FCM assessment) related to the primary endpoint of complete response with negative MRD. Based on historical data, the rate of MRD-negative complete response in the study population is estimated at ~50% (British AML16 data, [12] Spanish PETHEMA data,[32] British AML17 data [S. Freeman, pers. comm.]). A Simon minimax two-stage design will be used for this phase (Simon R. Optimal Two-Stage Designs for Phase II Clinical Trials. Controlled Clinical Trials 1989;10: 1-10). This phase II assessment will require a maximum total of 44 subjects to decide whether the proportion responding, P, is less than or equal to 0.50 or greater than or equal to 0.70. At the first stage (that is among the first 22 included patients), if the number of responses is lower than or equal to r1=11, the phase II will stopped early, for futility. Otherwise, if r1 ≥ 12, enrollment will continue up to a maximum of 44 patients. Overall, if the number of responses R becomes 28 or more, the hypothesis that P ≤ 0.50 is rejected with a target type I error rate of 0.05. If the total number of responses is R=27 or less, the hypothesis that P ≥ 0.70 is rejected with a target type II error rate of 0.15. Of note, phase I patients treated at the RP2D of choice will be included in this analysis if they are assessable by FCM MRD (presence of a LAIP).
Funding sources	Fondation ARC
Study will have a Data Safety Monitoring Board	Yes

2) SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

The study hypotheses that addition of sulfasalazine to a conventional 7+3 regimen of cytarabine and idarubicine is safe in newly diagnosed AML patients 60 years or older, and that sulfasalazine will improve the response rate to this intensive chemotherapy combination in the study population.

2.2 Description of knowledge relating to the condition involved

Acute myeloid leukemia (AML) is a heterogeneous clonal myeloid neoplasm where abnormal proliferation and impaired differentiation of hematopoietic stem and myeloid progenitor cells impedes normal hematopoiesis. Despite the significant progress made in understanding AML oncogenesis over the past decades, this disease remains devastating with about 18,000 new cases every year in Europe and a five-year overall survival of only 17%.[1]

The median age at diagnosis of AML is 69 years and the cure rate of patients older than 60 has not improved in the recent decades.[2] The standard of care (SOC) of newly diagnosed AML includes a '7+3' cytarabine-anthracyclin combination followed by repeated courses of high dose cytarabine with or without allogeneic hematopoietic stem cell transplantation (HSCT).[3] Recent advances in this SOC approach include the addition of the multikinase inhibitor midostaurine during induction and consolidation in patients with *FLT3* gene mutations,[4] maintenance with oral azacitidine after completion of induction with or without consolidation in patients ineligible for transplantation,[5] and use of a liposomal formulation of the cytarabine-daunorubicin combination instead of conventional 7+3 in patients with high-risk features.[6]

In patients older than 60y with adequate performance status and few comorbidities deemed 'fit' for intensive chemotherapy, a 7+3 induction course combining 3 days of idarubicin (IDA) with a 7-day continuous cytarabine (AraC) infusion can induce complete remission (CR) or CR with incomplete platelet recovery in 64% of cases with non-favorable cytogenetics.[7] Recent advances in the supportive care of these patients, notably progresses in the anti-fungal armementarium, have lowered the toxicity of the 7+3 induction courses, with early date (ED) rates within the 5-10% range.[8] However, despite high CR and low ED rates with 7+3, the median event-free survival (EFS) remains 9.3 months in patients ≥60 years old with non-favorable cytogenetics, owing to frequent relapses.[7] Improving the anti-leukemic efficacy of the 7+3 induction course can contribute to better long-term prognosis in these patients.[9] However, modifications of the 7+3 induction course must rely on any additional toxicity to limit the risk of ED, and not to jeopardize post-remission therapy. Repositioning of drugs with excellent safety profiles appears as a promising approach in this regard.[10]

As such, non-favorable risk AML in older patients represents an unmet medical need. Novel options to improve the efficacy of the 7+3 induction course are thus necessary.

2.3 Summary of relevant pre-clinical experiments and clinical trials

Cystine import is a targetable vulnerability in AML

The metabolic rewiring of leukemic cells is increasingly recognized as a targetable vulnerability in AML. Leukemic Stem Cells (LSCs) endowed with increased quiescence and chemoresistance,[15] have specific metabolic profiles that may for instance underpin the *in vitro*.[19]

By querying transcriptional profiles of multiple AML patients' cohorts, we have identified a close correlation between the expression of stemness programs and an active cysteine metabolism

pathway. Querying a CrispR screen conducted in 500+ cancer cell lines revealed a specific dependence of AML cell lines on cysteine metabolism. Among genes belonging to this pathway, higher expression of *SLC7A11* was identified to bear poor prognostic relevance in 3 AML cohorts.

Genetic silencing of *SLC7A11* reduced viability and colony formation of AML cell lines in a cysteine-dependent fashion. *SLC7A11* encodes the xCT neutral amino acid antiporter that imports cystine against glutamate. The xCT antiport is broadly expressed in AML cell lines. Three chemical inhibitors of xCT with different chemical backbones including erastin, S-4-Carboxyphenylglycine (CpG) and sulfasalazine (SSZ) had highly concordant, cystine-dependent, anti-leukemic activity on a panel of 20 AML cell lines. These data suggested that cystine import could represent a targetable vulnerability in AML.

remarkable efficacy of the azacitidine-venetoclax combination in patients ineligible for 7+3.[16,17] LSCs notably rely on high levels of the cysteine amino acid to fuel glutathione synthesis and maintain low levels of Reactive Oxygen Species (ROS).[18] Chemical depletion of the intracellular pools of cysteine and its precursor cystine have pre-clinical anti-leukemic activity.

Sulfasalazine can be repurposed to inhibit cystine import in AML

Sulfasalazine (SSZ) is a broadly available, well tolerated anti-inflammatory medicine approved for the treatment of ulcerative colitis and rheumatoid arthritis.[20] Intact SSZ, but not its metabolites 5-aminosalicylic acid and sulfapyridine, competitively inhibits xCT.[21] SSZ is thus an ideal candidate for drug repurposing in AML. In vitro, SSZ inhibited the viability of 12 primary AML specimens, with a > 10-fold increased sensitivity compared to CD34+ hematopoietic stem and progenitor cells from heathly donors (SSZ IC50 in AML 176µM ± 40µM versus 2.94mM ± 4.21mM in healthy CD34+ cells, p=0.0011). SSZ 250µM, a concentration in the same range as peak plasma concentrations of SSZ in healthy individuals,[22] also significantly reduced the in vitro long-term culture initiating potential of 6 primary AML samples. Finally, twice-daily intraperitoneal administration of single agent SSZ significantly reduced the leukemic burden in two distinct AML patient-derived xenografts (PDX) models. Finally, compassionate administration of oral SSZ at 3-6 g/d over a 20-day period in a patient with advanced refractory AML resulted in a transient, but clinically meaningful cytoreduction. Mechanistic studies found SSZ to induce global metabolic rewiring of the cysteine and one-carbon pathway, resulting in glutathione depletion and ROS-dependent cell death partly corresponding to ferroptosis,[23] Total protein expression of SLC7A11 did not correlate with SSZ activity. Thus, SSZ can be repurposed to inhibit cystine import and impair leukemic viability in AML.

Sulfasalazine improves the efficacy of anthracycline-cytarabine combination chemotherapy in pre-clinical AML models.

In two distinct AML cell lines, the anthracycline daunorubicin (DNR) was identified among a panel of 8 AML drugs as the one with top synergism when combined with SSZ. This observation may be underpinned by the ROS-inducing potential of anthracyclins.[24] In a cohort of 48 primary AML samples, addition of SSZ at a low concentration (4 µM) mimicking trough concentrations in healthy donors,[22] significantly increased the anti-leukemic activity of the combination of DNR with araC on both the total leukemic bulk and on GPR56+ LSCs in a niche-like ex vivo drug screening platform combining stromal co-culture, hypoxia and plasma-like medium.[25] Finally, addition of SSZ with a regimen combining 3 days of the anthracycline adriamycin with 5 days of cytarabine (maximally tolerated regimen in immunocompromised NOG-EXL mice) further decreased the leukemic burden in a PDX model and significantly prolonged survival over adriamycin-cytarabine chemotherapy alone (Pardieu et al, manuscript

in preparation, data to be presented at the 2021 Annual Meeting of the European Hematology Association).

These data support the clinical evaluation of the addition of SSZ with 7+3 in AML.

Sulsalazine is approved for years as treatment of inflammatory diseases

SSZ consists of 5-aminosalicylic acid (5 ASA also called mesalamine) linked to a sulfonamide, sulfapyridine, by an azo bond. 5-Asa is regarded as the anti-inflammatory moiety with little, if any, contribution by sulfapyridine. Although 5-ASA is a salicylate, its therapeutic effect does not appear to be mainly related to cyclooxygenase inhibition and is not precisely elucidated

Around 30% of SSZ is absorbed in the small intestine, as a whole molecule. Most of orally administered SSZ reaches the colon where it is cleaved by bacterial enzymes. Most of 5-ASA is excreted in stool while most of sulfapyridine reaching it is rapidly absorbed.

Side effects of SSZ would be mainly although not exclusively related to the sulphonamide moiety:

- The most usual reactions are dose- related and include headache, dizziness, fatigue, anorexia, nausea and vomiting. They resolve with dose reduction.
- Hypersensitivity reactions occur rarely but irrespective of the dose. The less infrequent are limited to a skin rash. Sometimes this rash can combine with fever, hepatitis, adenopathies and eosinophilia defining a DRESS syndrome. Severe reactions have been observed, although rarely: the Stevens Johnson syndrome, hemolytic anaemia, bone marrow failure, interstitial nephritis, peripheral neuropathy, pancreatitis or pneumonitis.
- SSZ affects reversibly spermatogenesis but does not impair female fertility. Rarely SSZ can induce crystalluria with intra-tubular precipitation of SSZ metabolites and subsequent acute kidney injury. Adequate hydration and monitoring of renal function are warranted.
- Some but not all haemolytic anaemia complicating SSZ treatment could be related to a glutathione deficiency fosterzs by an inherited glucose 6-phosphate dehydrogenase deficiency.

SSZ absorbed in small intestine is taken up by the liver and excreted unchanged in the urine.

Sulfapyridine undergoes extensive hepatic metabolism including acetylation, hydroxylation, conjugation with glucuronic acid and excretion in the urine.

In heathy adults, half-life of SSZ was short reaching approximately 10 hours. Cmax reached around 100 µM with a Tmax of approximately 4 hours. Pharmacokinetics of sulfapyridine actually depends one genetic polymorphism of proteins involved in its hepatic metabolism: Acetylation of sulfapyridine depends on N acetyltransferase-2 (*NAT2*) polymorphism. The plasma levels of sulfapyridine and the probability of adverse reactions are higher in low acetylators. The polymorphism of an efflux ABC transporter, the breast cancer resistance protein (BRCP, *ABCG2* gene) also impacts SSZ and sulfapyridine clearance[21].

Metabolites of SSZ can interfere with hepatic metabolism of digoxin (reducing digoxinemia of around 50%) or azathioprine and mercaptopurine (increasing the rate of their active metabolites and thus their adverse myelo-suppressive effect).

In IBD, doses of 6 to 8g/ day (e.g. 2g tid or qid) and 2 g/ day (e.g. 1 g bid) are usually used as initial therapy (during several weeks) and maintenance therapy, respectively.

Addition of sulfasalazine to standard of care chemotherapies is manageable.

Repurposing of SSZ to inhibit xCT has been investigated alone or with standards of care chemotherapies in solid tumors.[26-28]

A first study conducted of single-agent SSZ in 10 highly debilitated patients with high grade,

progressing glioblastomas was terminated prematurely based on lack of efficacy. In this trial, the toxicity of SSZ at low doses (1.5-6 g/d) was mostly neurological, suggestive of tumor-specific poor tolerability possibly caused by drug-related peri-tumoral edema. [26]

Conversely, another dose-escalation study of single-agent SSZ up to 12 g/d for 14 days in 11 patients with advanced gastric cancer identified 12 g/d as MTD with grade 3 anorexia as DLT. Other grade 3 AES included elevated AST (n=1) and bilirubin (n=1), fatigue (n=2), nausea (n=1), vomiting (n=1) and hyponatremia (n=1). There was no grade ≥ 3 hematological or grade 4 non-hematological AE in this trial. The median number of SSZ cycles was 2 (range 1–4) with a mean relative dose intensity of 85% for dose level 1 (8 g/d) and 60% at MTD (12 g/d).[28]

Finally, a phase 1 study combining SSZ thrice daily for 21 days with cisplatin and pemetrexed on day 1 of each SSZ cycle was conducted in 15 patients with advanced non-small-cell lung cancers.

The MTD was 3 g/day, and the recommended phase 2 dose (RP2D) was 1.5 g/day. DLTs included grade 3 elevations of AST and ALT aminotransferase levels, hypotension, pneumonitis and anorexia. Overall, the combination appeared manageable, and promising activity was noted in terms of overall response rate progression-free survival compared to historical controls. [27] The anti-tumor activity of SSZ continues to be explored in solid tumors (NCT NCT04205357). Overall, addition of SSZ to chemotherapy appears feasible in carefully designed dose escalation phase 1 trials.

Collectively, these pre-clinical findings provide a strong rationale for the clinical evaluation of the addition of sulfasalazine to standard of care 7+3 induction regimen in non-favorable AML patients older than 60 years. The purpose of this phase I study is to evaluate the safety and feasibility of such strategy, provide preliminary signals of efficacy, and identify potential biomarkers.

2.4 Description of the population to be studied and justification for this choice of participants

- *Criteria related to the disease*
    - Favorable cytogenetic lesions include t(15;17) defining acute promyelocytic leukemias with chemo-free standard of care,[33] and t(8;21) and inv(16), which are associated with excellent CR rates after 7+3 induction chemotherapy, including in older patients,[34] Patients with these rare favorable cytogenetic lesions are excluded from the study. Presence of isolated *NPM1* mutations (i.e. without *FLT3* mutation) also defines a favorable risk subset in patients younger than 60 years of age. However, there outcome is less favorable in patients older than 60 treated intensively due to frequent co-occurrence of adverse co-mutations.[35] These patients are thus eligible for the present study.
    - AML with central nervous system involvement are excluded as they require additional CNS-directed therapy (intrathecal chemotherapy), and because SSZ diffusion in CNS is unlikely.
    - Myeloid sarcomas are excluded because evaluation of response requires different methods compared to AML. Notably, achievement of bone marrow MRD negativity may have different value in the context of myeloid sarcoma.

- *Criteria related to the use of SSZ:*
    - Patients with G6PD deficiency, porphyria variegata or acute intermittent porphyria are excluded because exposure to SSZ can trigger acute manifestation of their condition.
    - Patients with previous history of hypersensitivity to SSZ, one of its metabolites (5-aminosalicylic acid, 5-ASA or mesalazine), sulfonylarylamines sulfonamides, salicylates or SSZ excipients are obviously excluded.Patients with a previous

history of allergy to non-sulfonylarylamines (furosemide, hydrochlorothiazide, glibenclamide or celecoxib) sulfonamides may be accrued with cauting because there is no data supporting a risk of cross-reactivity between these drugs and SSZ.[36,37]

- Finally, patients previously treated with SSZ for an inflammatory disease are excluded due to the risk of acquisition of resistance by the leukemia before trial inclusion, which may obscure the interpretation of efficacy signals.

- *Organ failures and functional insufficiency*

  - Other selection criteria are usual and intended to exclude patients ineligible for a 7+3-based intensive chemotherapy or more susceptible to develop well documented adverse reactions to SSZ (abnormalities of liver functional tests, renal failure).

- *Combination with other drugs*

  - Patients with a *FLT3* mutation (ITD or TKD) benefit from the addition of midostaurin to 7+3.[4] They are excluded from the study to facilitate safety assessment of SSZ addition to intensive chemotherapy.

2.5 Identification and description of the investigational medication or medications

The investigational medication is sulfasalazine (SSZ). Further details are provided in Section 7 below.

2.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

SSZ is administered *per os* by tablets, *bid* to *qid*, because of its fast hepatic metabolic and short half-life.

Ex vivo, as a standalone or combined with anthracycline, activity of SSZ as inhibitor of cystine import by leukemic cells appeared to be dose dependent. Correspondence between orally administered doses and circulating levels has been documented in healthy volunteers. Doses deserving to be tested because of their potential activity as inhibitors of cysteine import by leukemic cells, should lead to plasma levels in the 10-100 µM range, corresponding to the IC_{50} of SSZ on primary AML cells (~100 µM) and the concentration of SSZ potentiating daunorubicin-cytarabine combination in short-term ex vivo cultures of primary cells from 45 AML patients.[25]

Such doses are included in the therapeutic range of SSZ usually used to treat inflammatory diseases, as single therapy or combined with other anti-inflammatory drugs.

However, tolerance of SSZ is mainly dose-dependent, and MTD identified in patients with metastatic non-small cell lung carcinoma, was low (3g/day) when SSZ was combined with other chemotherapies used in this disease. These considerations should lead to a cautious dose escalation.

- The starting dose, DL1 = 1.5 g/day (0.5g TID from D0 to D14) is the regimen used at the start of attack-treatment of inflammatory bowel disease (IBD) and can be used as maintenance therapy in the same disease. This SSZ regimen is well tolerated. Furthermore,

this first dose level could have some anti-leukemic activity, although likely suboptimal, by reaching peak plasma concentrations n the range of SSZ IC_{50} on primary AML cells. if MTD was reached at DL1, lower exposure of 8 instead of 15 consecutive days will first be explored (DL-1) then reducing the daily dose of SSZ to 0.5g BID for 8 days (DL-2).

- The highest tested dose, DL5 = 8 g/day (2g QID) from D0 to D14 is used as attack dose of IBD. Such dose should enable to achieve a continuous inhibition of cystin import by reaching trough plasma concentrations in the range of SSZ IC_{50} on primary AML cells. Such dose may also induce some discomfort with moderate fatigue and gastrointestinal (GI) adverse effects in a substantial proportion of patients.

- The pace of the dose-escalation does not exceed 100% at the first step, thereafter, at the second step, 50%, and eventually 33%.

This 2-week treatment is administered in hospitalized patients and would not interfere with the hematopoietic recovery which does not begin, before the 3rd of fourth week following the 3+7.

Further information about the administration of the product is given in **section 7**.

2.7 Summary of the known and foreseeable benefits and risks for the Clinical Trial participants

Foreseeable benefits

Forseeable benefits, whose demonstration is the primary objective of the current study, is an improvement of the rate of complete remission (CR) with undetectable Measurable Residual Disease (MRD), which is a surrogate for long-term survival in older AML patients treated intensively.

CR and MRD are easy to measure from peripheral blood and bone marrow aspirates routinely sampled during the follow-up of these AML patients. Furthermore, MRD-negative CR with MRD predicts long term outcome in older AML patients treated intensively. Standardization of molecular techniques and development of multiparameter flow cytometry (MFC) assays have made it possible to assess MRD at different time points during the course of AML therapy in virtually all patients.[11] In older patients treated with 7+3, MRD measured at the end of induction course (EOI) time point based on *NPM1c* transcripts in *NPM1*-mutated patients, or with MFC assays (Leukemia Aberrant ImmunoPhenotypes [LAIP] and/or Leukemic Stem Cell [LSC) methods) predict long-term outcome.[12] In *NPM1*-mutated patients younger than 60, the role of EOI MRD assessed by relative *NPM1c* transcript levels is also well established,[13] although data is scarcer in older patients.[14] Altogether, EOI MRD appears a relevant surrogate endpoint to estimate efficacy of alternative induction regimens in older AML patients with non-favorable cytogenetics.

Long term outcome will be documented in all the patients through the standard assessment of the duration of response (DOR), relapse free survival (RFS), overall survival (OS).

Though the limited sample size and non-comparable design of this early phase clinical trial will not enable to demonstrate an improvement of these efficacy endpoints, it has to be considered that the assessment of both benefits and risks will be facilitated by the homogeneous management of AML patients, as defined by the ALFA group in its previous ALFA1200 study,[7,35] and, more its ongoing ALFA PPP non interventional study (IDRCB no.: 2020-A03290-39):

- Overlapping study populations. ALFA PPP prospective registry will include patients fulfilling all the eligibility criteria of the present study.

- Identical induction chemotherapy regimen in the study population.

- Identical MRD assessment at EOI by multi-center flow cytometry and by molecular biology in central laboratories.

Thus, ALFA PPP prospective registry will provide a highly relevant 'historical' control.

Foreseeable risks

Foreseeable risks are related to the potential toxicity of SSZ. Safety profile of this old drug is however perfectly documented and mainly dose dependent. It is easy to assess by clinical examinations and usual laboratory tests frequently performed in these patients.

However, a hypothetical risk might be related to a potentiation of anthracycline cardiotoxicity (here, idarubicin, administered as part of the induction therapy) by SSZ. Cardiotoxicity of anthracyclines is at least partly mediated by ferroptosis of cardiomyocytes which is susceptible to be enhanced by an inhibition of cystine import into these cells.

The cautious dose-escalation design described in the **section 2.3.2** and the Bayesian approach, with a continuous reassessment of safety endpoints enables to limit the risks related to the introduction of this drug.

A specific management of this risk is planned in the study:

- Adverse events induced by idarubicin and cytarabin will be managed according to SmPC.
- Homogeneous 7+3 backbone induction therapy with a single anthracycline (idarubicin) and dosing regimen allowed per protocol. Although post-remission therapy is at the investigator's discretion, none of the currently used post-remission consolidation regimens will lead to cumulative doses of anthracyclines at risk of cardiotoxicity.38
- A strengthened monitoring of idarubicin cardiac toxicity (notably through ECG and troponin level monitoring) coordinated by a central onco-cardiologist.
- Inpatient management during the first month of intensive chemotherapy, far beyond the clearance of SSZ, which administration will be limited to the first 2 weeks of this first treatment cycle.

Various measures routinely taken with 7+3 induction including anti-emetic prophylaxis will prevent the most frequently observed adverse events related to SSZ administration.

After the completion of induction course, the participation of the patient to SALMA study does not impact the management considered as adequate for the patient, including consolidation courses, allogeneic stem cell transplantation or maintenance therapy.

Finally, the trial does not impose any additional medical procedures in besides those which are indicated for the efficacy and safety monitoring of 7+3 induction therapy.

3) OBJECTIVES

3.1 Primary objective

Phase I

To assess the safety, characterize the dose-limiting toxicities (DLTs), and identify the maximal tolerated dose (MTD), and recommended phase II dose (RP2D) of the combination of Sulfasalazine (SSZ) with Idarubicin (IDA) and Cytarabine (AraC) in patients with newly diagnosed non-favorable AML.

Probability of DLT should not exceed 33% at the end of the induction cycle (EOI) of IDA-AraC + SSZ treatment (up to Day 42).

Phase II

To assess preliminarily the anti-leukemia efficacy of the combination of IDA-AraC + SSZ, mainly in phase II, in newly diagnosed non-favorable AML with reference from historical data on complete remission rate,[7] and MRD.[39]

3.2 Secondary objectives

- To characterize the pharmacokinetics (PK) of SSZ, IDA and AraC when administered in combination, during phase I.
- To characterize the pharmacodynamics (PD) of SSZ, IDA and AraC when administered in combination, during phase I, and to confirm it during the phase II of the trial.
- To describe during the phase I of the trial the response of the leukemia to the treatment, the survival of patients up to 12 months after the EOI visit.
- To document further during the phase II of the trial the safety profile and confirm the RP2D of SSZ in combination with IDA and AraC.

4) STUDY DESIGN

4.1 Study endpoints

4.1.1 Primary endpoint Phase I

Documentation during the dose escalation of dose limiting toxicity (DLT), identification of a maximal tolerated dose (MTD) if any and selection of the recommended phase II dose (RP2D)

- **Dose Limiting Toxicity (DLT)**

DLT will be defined during a safety observation period corresponding to the induction cycle with IDA-AraC + SSZ (up to Day 42). **Events occurring after the onset of a second treatment cycle (i.e. salvage or consolidation) will not be considered as DLTs.**

Any of the following events will be considered a DLT unless the event can be attributed by the investigator to a clearly identifiable cause such as underlying illness or disease progression, concurrent other illness, or concomitant medication.

- Prolonged myelosuppression defined as Grade ≥ 3 Neutropenia or Thrombocytopenia until Day 42 from start of therapy or later without evidence of leukemia (assessed by bone marrow aspiration and/or biopsy).
- Grade ≥3 hemorrhages until day 42.
- Grade ≥3 non- hematological toxicity until day 42 with the exception of:
  - Grade 3 infection, grade 3 fever with neutropenia (NB. grade 4 infections and grade 4 fever with neutropenia are considered as DLTs),
  - Grade ≥3 nausea, vomiting or diarrhea that can be managed to ≤ Grade 2 within 72 hours of symptomatic treatment,
  - Grade ≥3 asymptomatic liver enzymes elevation that improves to ≤ Grade 2 within 72 hours of onset,
  - Grade ≥3 tumor lysis syndrome that resolves within 72 hours of onset with medical treatment.

- **Maximal Tolerated Dose (MTD)**

MTD is defined by a target DLT rate of 33%, assessed during the dose escalation phase by a continual reassessment method.

- **Recommended phase 2 dose (RP2D)**

RP2D is anticipated to be the MTD. However, it could be equal to one dose level lower than the MTD. It will be determined in interaction with the DSMB, insofar that this dose level is validated by PK/PD studies and efficacy preliminary data.

Phase II

MRD-negative Complete Response at EOI (day 28-42) per ELN 2022 Criteria[40] :

- Complete response is defined as Complete Remission CR or CRi (CR with incomplete hematologic recovery, meaning CR with platelet count <100,000/µL or absolute neutrophil count <1000/µL) and CRh (CR with partial hematologic recovery, meaning CR not fulfilling CR or CRi peripheral blood count criteria but with platelet count >50,000/µL AND absolute neutrophil count >500/µL).
- MRD-negativity is defined as an 8-color bone marrow FCM MRD < 0.1% at EOI.

4.1.2 Secondary endpoints

4.1.2.1 Assessment of safety

- Safety outcome measures will be assessed continuously during the trial.
- Monitoring of ECGs and clinical laboratory values are integral to safety assessment.
- Adverse events (AE), treatment emergent adverse events (TEAE) and treatment related TEAEs will be evaluated according to the NCI CTCAE version 5.0. Serious adverse events will be defined per protocol according to EMA/ICH criteria. Causality relationship with the experimental treatment should be assessed by the investigator.
- Frequency, duration and maximal severity of each TEAE. Treatment-related TEAEs, TEAEs leading to treatment discontinuation, serious adverse events (SAEs) and deaths should be documented during phase 1a and 1b of the trial.
- Patients should be followed until all treatment related TEAEs have returned to grade ≤ 1 or baseline or are deemed irreversible by the investigator.

4.1.2.2 Pharmacokinetics

A pharmacokinetics (PK) study will be done during the Phase I part of the trial to assess SSZ and its metabolites (5-ASA [mesalazine] and sulfapyridine), IDA (and its metabolite idarubicinol) and AraC. This will allow to determine a PK model for SSZ at early (days 0 and 3) and late (day 14) time points, and to confirm the lack of interaction between SSZ and IDA or AraC.

The following PK parameters will be determined using non-compartmental analysis (WinNonlin Pharsight Corporation: maximum plasma concentration (Cmax), maximum plasma concentration time (Tmax), area under the plasma concentration time curve (AUC), clearance (Cl), mean residence time (MRT), and distribution volume (Vd/F).

For pharmacokinetic analysis, the dose of SSZ will be administered orally together with 200 mL water after the patient has fasted overnight, with a meal being permitted after blood sampling at 4 h after the drug is given.

Blood samples will be obtained:

- on day 0 before (pre-dose) and at 1, 2, 3, 4, 6 and 8h after first SSZ dose;
- on day 3 pre-dose and at 5', 10', 20', 40', 1h, 4, 8, 24h of start of IDA injection,
- on day 14 before (pre-dose) and at 1, 2, 3, 4 and 6h after first SSZ dose.

Blood samples will be collected into heparinized tubes. Immediately after collection, tubes will be inverted several times and kept at approximately 4 °C until centrifugation. The tubes will be centrifuged for 10 min at 1500×g at 4°C within 60 min of collection to separate plasma. The plasma will be separated into 2 aliquots in polypropylene screw-cap tubes and placed at -80°C until analysis.

All samples will be labeled with patient identification, trial identification, sample number, and actual date and time at which the sample was collected. The plasma concentration of SSZ and metabolites will be determined by a validated ultraperformance liquid chromatography and tandem mass spectrometry method.[28]

4.1.2.3 Pharmacodynamics

Pharmacodynamic (PD) assays aim at demonstrating ROS induction upon SSZ exposure relative to pre-treatment levels. They will be done on peripheral blood, because repeated bone marrow aspiration over a short-time period is unethical. Blood sampling for PD will be done on:
- Day 0: effect of SSZ alone
- Day 1: combined effect of SSZ, IDA and AraC

PD assays will include:

- Plasma levels of malondialdehyde (MDA), glutathione (reduced/oxidized), two robust biomarkers of oxidative stress biomarkers previously involved in ferroptosis and/or SSZ mode of action (our pre-clinical results and [29]) that can be assessed in all patients and at all time points regardless of white blood cell count and percentage of circulating leukemic cells.
- In patients with circulating leukemic cells, ROS levels of peripheral blood mononuclear cells by flow cytometry (H2DCFDA).

4.1.2.4 Antileukemia activity

- Response at EOI assessment (day 28-42) per ELN 2022 Criteria.[40]
    - Morphologic leukemia-free state (MLFS): blastic criteria of response on the bone marrow aspirate, absence of extramedullary disease and no requirement of hematologic recovery
    - Partial response (PR): absence of circulating blasts; absence of extramedullary disease; decrease of bone marrow blast percentage to 5 to 25% and decrease of pretreatment bone marrow blast percentage by at least 50%
    - Overall response rate (ORR) being defined as CR, CRi and CRh, MLFS and PR rates.
    - Primary refractory disease defined as patients lacking criteria for any of the above defined responses (CR, CRi, CRh, MLFS and PR) at EOI assessment, excluding patients with death in aplasia or death due to indeterminate cause as defined per ELN 2022 criteria.
    - Death in aplasia and death due to indeterminate cause as defined per ELN 2022 criteria.
- *NPM1*-transcript based MRD in the BM and PB in *NPM1*-mutated patients
- NGS-based MRD.
- Survival assessment at 12 months.
    - Event-free survival (EFS); here events are defined as:
        - Non achievement of hematologic response including CR, CRi, CRh
        - Hematologic relapse or progressive disease

- Initiation of any subsequent anti-leukemic therapy (excluding hydroxyurea
- Deaths prior to one of the events mentioned above.

Reasons for subsequent therapy initiation (including intolerance, resistance, hematologic relapse, unsatisfactory MRD evolution), its type (intensive, less-intensive, best supportive care) and its frame (clinical trial, off-label, or compassionate use) will be prospectively recorded.

- Duration of response (DOR)
- Relapse free survival (RFS)
- Overall survival (OS)
- Incidence of subsequent allogeneic HSCT, overall and in responding patients specifically.

Apart from specific mentions, all these hematological endpoints will be defined according to the latest recommendations from the European Leukemia Network (ELN; currently the 2022 ELN recommendations).[40]

Patients from the Phase I part of the trial receiving SSZ at a DL equal to the RP2D will be included in the assessment of efficacy plan.

4.1.2.5 Biomarkers

Biomarkers are intended for the description of the cohort and comparison with historical cohorts, and for exploratory correlation with depth of response or event-free survival. They will be studied on bone marrow and peripheral blood samples collected at screening (and repeated at EOI visit as internal control):

- Targeted sequencing of a panel of genes recurrently mutated in AML will be done at inclusion according to published methods.[7] Samples collected at EOI visit will be used for NGS-based MRD (exploratory analysis).

- SLC7A11 expression by flow cytometry (FCM) and/or western blot (WB)

- Genotyping of *ABCG2* rs2231142 polymorphisms and *NAT2* genotype (NAT2*4, NAT2*5B, NAT2*6A, NAT2*7B) known to impact SSZ bioavailability will be done in patients having signed the specific genetic consent form.[27,28]

- The RNA-based antioxidogram and antioxidant score, a biomarker of oxidative stress with prognostic relevance in AML[41] and expression of *NRF2* target genes (*NRF2* score) will be determined on baseline and EOI bone marrow samples.

4.2 Description of research methodology

4.2.1 Design of the trial

Phase I/II open label (non-comparative, non-randomized and not controlled) clinical trial with two consecutive parts:

- Phase I: dose escalation with a survival continual reassessment method design, using cohorts of 1 patient for dose assignments, to identify the maximal tolerated dose anticipated to be the recommended phase II dose (RP2D). Additional safety rules are implemented, notably escalation to a new dose level *i* is allowed only if at least 3 patients have been treated at dose level *i-1* among all included patients so far.

- Phase II: extension at the MTD or at the RP2D chosen by the data safety monitoring board (DSMB) to confirm the safety of RP2D and preliminarily documents its clinical efficacy.

4.2.2 Number of participating sites

This French multicenter study will involve a total of 9 and 13 centers in phase I and II respectively.

- **Recruitment centers**

Patients will be recruited in hospitals by hematologists expert in AML management.

All patients will be hospitalized before the initiation of the induction therapy including the experimental treatment. They will stay in the hospital until neutrophil recovery, no sooner than day 21.

- **Centralized biology centers**

Flow-based MRD (and molecular biology in patients with *NPM1* mutations) will be carried in the hematology laboratory of Hôpital Saint-Louis (Dr Stéphanie Mathis).

Analysis of PK samples will be done by the clinical pharmacology laboratory of Hôpital Saint-Louis (Dr Lauriane Goldwirt).

Samples for PD analyses will be collected at INSERM U944 under the supervision of Pr Raphael Itzykson for use by INSERM U944 (Pr Raphael Itzykson) and CNRS/Université de Tours ERL 7001 (Pr Olivier Hérault).

4.2.3 Identification of participants

The participants in this Clinical Trial will be identified as follows:
Site number (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial.
This reference number is unique and will be used for the entire duration of the trial.

5) IMPLEMENTATION OF THE STUDY

Before any examination or intervention related to the study may be carried out, the investigator must obtain the *freely given, informed and written consent of the participant, or of his/her legal representative* where applicable.

Individuals liable to participate in studies benefit from a preliminary medical examination adapted to the study.

The visits will be conducted by an investigator expert in acute myeloid leukemia management.

Patients will most often be hospitalized at screening visit and will always hospitalized at the beginning of the induction course.

The start of the clinical trial is the inclusion of the first patient.

'Start of a clinical trial' means the first act of recruitment of a potential subject for a specific clinical trial, unless defined differently in the protocol. In most cases, we will considerer that start of the CT = Start of recruitement = First inclusion but it can be adapted if necessary

5.1 Screening visit

The screening visit takes place between 1 day and no later than 14 days before the day 0 visit and is intended to collect the patient informed consent and to assess eligibility criteria. Specifically, the visit will record:

- Signed informed consent form (ICF)
- Medical and disease history and demographics
- Physical examination
- Height and weight
- Vital signs determination
- ECOG performance status evaluation
- HCT-CI
- Assessment of prior and concomitant medications, including medications received within 14 days prior to screening.
- 12-lead ECG
- Echocardiography for LVEF.
- Clinical laboratory tests: complete blood count, peripheral blood smear, glucose, sodium, potassium, calcium, phosphorus, magnesium, serum albumin, uric acid, blood urea nitrogen (BUN), creatinine level, troponin, AST, ALT, alkaline phosphatases, γGT, bilirubin, LDH, lipase, fibrinogen, partial thromboplastin time and prothrombin time [PT]/international normalized ratio [INR].
    - NB: Patients with a troponin level ≥99% percentile and/or an increase in troponin level ≥30% relative to baseline will trigger a cardio-oncology visit (coordinator: Dr Mathilde Baudet, Hôpital Saint-Louis, Paris).
- Creatinine clearance according to MDRD
- Viral Serology: HIV, HVC, HVB, CMV, EBV, HTLV1
- Hematological specialized assessment:
    - Bone marrow aspiration and peripheral blood for confirmation of diagnosis and baseline characteristics of the AML. A bone marrow biopsy will be performed only if aspiration inadequate. Bone marrow cytogenetic and routine molecular biology can be performed in local laboratories.
    - Bone marrow aspiration and peripheral blood for determination of LAIP (baseline for flow MRD) and *NPM1* transcript quantification (baseline for *NPM1* MRD in *NPM1*-mutated patients), sent to the central hematology lab of Saint-Louis hospital.
- Biomarkers
    - Targeted sequencing of a panel of genes recurrently mutated in AML.
    - Genotyping of ABCG2 rs2231142 polymorphisms and NAT2 genotype (NAT2*4, NAT2*5B, NAT2*6A, NAT2*7B).
    - RNA-based antioxidogram and antioxidant score and expression of *NRF2* target genes (NRF2 score).

Whose consent must be obtained	Who informs the individuals and collects their consent	At what point the individuals are informed	At what point the consent is obtained

• *the individual participating in the study;*	• *the principal investigator or collaborating physician declared and trained in the study (hematology)*	• *screening visit ;*	• *after a reflection period of at least 24 hours at the time a specific procedure for the study is implemented*

Enrollment Procedure

After checking the inclusion and exclusion criteria, a patient enrolment request can be faxed at 01 42 38 53 25.

Upon approval by the Coordinating Investigator, the patient will be enrolled by the Investigator through the eCRF.

The investigational team will inform in advance the statistical team of each scheduled enrolment; an on-call statistician will be identified to perform the upcoming dose assignment computation. Moreover, on the day of inclusion, the statistical team will be informed by an automated mailing from the eCRF tool of the actual inclusion of the new patient. Upon receiving this inclusion email, the on-call statistician will compute the dose level assigned to a new patient using the dose-finding surv-CRM algorithm based on updated DLT data extracted from the eCRF (see statistical details in **Section 12**).

Thus, **the DL of the study drug assigned to the patient being enrolled will be provided to the investigator via email** upon completing the enrolment procedure on the eCRF.

Details and outputs of the dose-assignment computations will be recorded for each included patient for traceability.

5.2 Baseline visit or randomization visit

Not applicable

5.3 Follow-up visits

5.3.1 Induction course

Visits during the induction course will take place at D0, D1, D2, D3, D7 and D14 of the cycle and report:

- Physical examination
- Vital signs determination
- ECOG performance status evaluation (at D0)
- Assessment of prior and concomitant medications
- 12-lead ECG (at D0, D3 and D14)
- Clinical laboratory results
    - At each visit: complete blood count, peripheral blood smear, glucose, sodium, potassium, calcium, phosphorus, magnesium, uric acid, blood urea nitrogen (BUN),

creatinine level, AST, ALT, alkaline phosphatases, γGT, bilirubin, LDH, lipase, fibrinogen, partial thromboplastin time and prothrombin time (PT)/international normalized ratio (INR).
    - At D0, D3 and D14: troponin
- PK (<u>only during phase I</u>)
    - at D0, at pre-dose, 1h, 2h, 3h, 4h, 6h and 8h of first SSZ dose
    - at D3 on pre-dose, 5',10' 20', 40', 1h, 4h, 8h, 24h of start of IDA injection
    - at D14 on pre-dose, 1h, 2h, 3h, 4h, and 6h of first SSZ dose
- AE/SAE evaluation
- PD
    - At D0 pre-dose and 6h of first SSZ dose
    - At D1 pre-dose and 6h of start of IDA injection

  Plasma levels of malondialdehyde (MDA), glutathione (reduced/oxidized), in all patients. In patients with circulating leukemic cells, ROS levels of peripheral blood mononuclear cells by flow cytometry (H2DCFDA).

5.3.2 End of induction visit (D28 to D42)

- Physical examination
- Vital signs determination
- ECOG performance status evaluation
- Assessment of prior and concomitant medications.
- 12-lead ECG
- Clinical laboratory results: complete blood count, peripheral blood smear, glucose, sodium, potassium, calcium, phosphorus, magnesium, serum albumin, uric acid, blood urea nitrogen (BUN), creatinine level, troponin, AST, ALT, alkaline phosphatases, γGT, bilirubin, LDH, lipase, fibrinogen, partial thromboplastin time and prothrombin time (PT)/international normalized ratio (INR).
- Specialized hematological assessment:
    - Bone marrow aspiration for assessment of response according to ELN 2022 criteria. A bone marrow biopsy will be performed only if aspirate is inadequate.
    - Bone marrow aspiration for flow based MRD (sent to the central hematology lab of Saint-Louis hospital).
    - Bone marrow aspiration and peripheral blood for *NPM1* transcript MRD in *NPM1* mutated patients (sent to the central hematology lab of Saint-Louis hospital.
- Biomarkers: bone marrow aspiration for biomarkers (targeted sequencing, antioxydogram and *NRF2* score).

5.3.3 Post induction visits

They will take place at the end of each consolidation cycle, before allogeneic stem transplantation (HSCT, 3 months after the last chemotherapy course (consolidation or HSCT conditioning regimen) and every 3 months until the end of study visit:

- Physical examination
- Vital signs determination
- Assessment of prior and concomitant medications
    - Consolidation chemotherapy will be documented.

- In transplanted patients, the origin of the donor, stem cell source and intensity of conditioning regimen will be documented.

- Clinical laboratory results: complete blood count, peripheral blood smear, glucose, sodium, potassium, calcium, phosphorus, magnesium, serum albumin, uric acid, blood urea nitrogen (BUN), creatinine level, AST, ALT, alkaline phosphatases, γGT, bilirubin, LDH, lipase, fibrinogen, partial thromboplastin time and prothrombin time (PT)/international normalized ratio (INR).
- If performed, results from bone marrow aspiration/biopsy will be recorded.
- If performed, results from local bone marrow or peripheral blood MRD will be recorded.

5.3.4 Relapse

- Physical examination
- Vital signs determination
- ECOG performance status
- Assessment of prior and concomitant medications
- Clinical laboratory results: complete blood count, peripheral blood smear, glucose, sodium, potassium, calcium, phosphorus, magnesium, serum albumin, uric acid, blood urea nitrogen (BUN), creatinine level, AST, ALT, alkaline phosphatases, γGT, bilirubin, LDH, lipase, fibrinogen, partial thromboplastin time and prothrombin time (PT)/international normalized ratio (INR).
- Hematological specialized assessment with its date, enabling to specify the date of the relapse:
    - Bone marrow aspiration and peripheral blood. A bone marrow biopsy will be performed only if aspiration inadequate. Bone marrow cytogenetic and routine molecular biology can be performed in local laboratories.
    - Pathology report in case of extramedullary relapse.

5.4 Last study visit

- Physical examination
- Vital signs determinations
- ECOG performance status evaluation
- Assessment of prior and concomitant medications,
- 12-lead ECG
- Clinical laboratory results: complete blood count, peripheral blood smear, glucose, sodium, potassium, calcium, phosphorus, magnesium, serum albumin, uric acid, blood urea nitrogen (BUN), creatinine level, AST, ALT, alkaline phosphatases, γGT, bilirubin, LDH, lipase, fibrinogen, partial thromboplastin time and prothrombin time (PT)/international normalized ratio (INR).
- Echocardiography for LVEF triggered during the induction period, notably by a troponin level ≥99% percentile and/or an increase in troponin level ≥30% relative to baseline will be recorded in this visit.
- Results from any bone marrow aspiration/biopsy performed since the last post induction visit will be recorded.
- Results from any local bone marrow or peripheral blood MRD assessment performed since the last post induction visit will be recorded.

Post-study follow-up

Within 5 years of trial completion, investigators may be periodically asked to the following information:

- The vital status of the patient, and if he deceased, the date of his death
- The status of the AML, and, if any, the date of its relapse
- The receipt of allogeneic stem cell transplantation and if any, the date of transplantation.

The patient will be informed and should not oppose this, as stated in the information note/consent form.

Patients enrolled in an ALFA center will be invited to join the ALFA PPP prospective registry and its long-term follow-up cohort. They will have received a separate oral and written information and signed a separate consent form.

5.5 Early termination visit

Patients are allowed to withdraw their participation in the Clinical Trial at any time and for any reason. The investigator can temporarily or permanently withdraw a participant from the trial for any safety reason or if it is in the participant's best interests.

If a participant wishes to withdraw their consent from the trial, we will use the following strategies to minimize the impact on the validity of the trial meanwhile respecting the participant's right to withdraw. We will seek a better understanding of the patient's wishes and offer the following alternatives to complete withdrawal:

1) Discontinue in-person follow-up but allow telephone follow-up;
2) Discontinue in person and by telephone follow-up but allow access to medical records and to use personal data to be able to get life status from the national centre of epidemiology of deaths (Centre d'épidémiologie sur les causes de décès - CépiDc).

In any case, all the data that would have been collected before the patient's consent withdrawal will be kept in. The early termination visit will be similar to the last study visit (see **section 5.4**).

5.6 Expected length of participation and description of the chronology and duration of the study.

- Maximum period between screening and enrolment: 14 days
- Duration of enrolment period: 56 months
- Duration of participation for each participant:
    - Treatment period: 2 months
    - Follow-up period: 12 months
- Total study duration*: 70 months

*End of trial is defined as the last visit of the last patient.

5.7 Table or diagram summarising the chronology of the study

Study Visit	Baseline Screening	Induction Cycle							Post induction[9]	Relapse	Study Exit
		D0	D1	D2	D3	D7	D14	EOI (D28-42)			
Informed Consent	x										
Baseline medical history	x										
Physical exam	x	x	x	x	x	x	x	x	x	x	x
Height, Weight	x										
ECOG PS	x	x						x			x
BM aspirate	x							x	(x)	x	(x)
Cytogenetics	x								x	x	x
Targeted sequencing	x								x	x	x
Biomarkers[1]	x							x			
PD[2]		x	x								
Response Assessment								x	(x)	x	(x)
Hematology[3]	x	x	x	x	x	x	x	x	x	x	x
Chemistry[4]	x	x	x	x	x	x	x	x	x	x	x
Serum albumin	x							x	x	x	x
Pregnancy test[5]	x										
Central MRD[6]	x							x			
Local MRD[6]									(x)	(x)	
ECG & troponin[7]	x	x			x		x	x			(x)[7]
Echocardiography[7]	x										(x)[7]
PK[8]		(x)			(x)		(x)				
AE	x	x	x	x	x	x	x	x	X[10]	x[10]	x[10]

[1] Targeted gene sequencing, genotyping of *ABCG2* and *NAT2* (screening only), RNA-based antioxidogram and antioxidant score, and expression of *NRF2* target genes.
[2] PD assays at H0 and H6 of first SSZ dosing (day 0) and start of IDA injection (day 1): plasma levels of malondialdehyde (MDA), glutathione (reduced/oxidized), and, in patients with circulating leukemic cells, ROS levels of peripheral blood mononuclear cells by flow cytometry (H2DCFDA).
[3] Including full CBC, fibrinogen, aPTT and PT/INR.
[4] Including glucose, sodium, potassium, calcium, phosphorus, magnesium, uric acid, BUN, creatinine, AST, ALT, alkaline phosphatases, γGT, bilirubin, LDH, lipase, and albumin (screening visit only)
[5] Restricted to women of childbearing potential.
[6] FCM on BM samples in all patients, and RQ-PCR for *NPM1* patients on BM and PB samples.
[7] 2D echocardiography for LVEF. A troponin level ≥99% percentile and/or an increase in troponin level ≥30% relative to baseline will trigger a cardio-oncology referral (coordinator: Dr Mathilde Baudet, Hopital Saint-Louis, Paris) including a control ECG and echocardiography that will be captured in the study exit visit.
[8] Only in the phase I part of the study.
[9] At the end of each consolidation cycle, before HSCT if performed more than one month after the last consolidation cycle, 3 months after the last chemotherapy course (consolidation or HCT conditioning regimen) and every 3 months until the end of study visit. Bone marrow and MRD assessments done locally will be collected.
[10] Only Adverse events of special interest (cf. 10.3.2.2.1).

5.8 Distinction between standard care and study

Most of the above-mentioned management correspond to standard care of these patients. Interventions added by the studies are limited to the following procedures:

- SSZ administration,
- Idarubicin and cytarabine administration,
- Systematic assessment of troponin in serum at D0, D3, D14 and EOI,
- Additional ECG at D3, D14 and EOI,
- PK and PD exams from peripheral blood samples (plasma, serum or cells),
- Centralization of EOI MRD.

Interventions carried out for the Clinical Trial purposes	**Interventions, procedures and treatments associated with standard care**	**Interventions, procedures added for <u>Clinical Trial</u> purposes**
Visits	Standard care	Study exit visit
Treatments	Idarubicin-Cytarabine induction chemotherapy and standard supportive care (anti-emetics, prevention of tumor lysis syndrome, transfusion support, antibiotics, antifungal prophylaxis	Administration of SSZ during the induction cycle.
Procedures	Echocardiography Central IV line	ECG at D3, D14 and EOI.
Blood samples	Monitoring of hematology and chemistry tests. PB MRD for *NPM1* transcripts in *NPM1* mutated patients	Troponin level at D0, D3, D14 and EOI visit. PK monitoring at D0 (35 mL), D3 (40 mL) and D14 (30 mL) for patients in the phase I portion of the study. PD monitoring at D0 (10 mL) and D1 (10 mL).
Bone Marrow	Aspiration at screening (diagnosis) for cytology smears, cytogenetics (1 mL), flow cytometry (1 mL) and molecular genetics (1 mL). Aspiration at EOI evaluation for cytology smears, flow cytometry (1 mL) and molecular genetics (1 mL).	Additional volume (2 mL EDTA) at screening and EOI evaluation aspirations for biomarkers.

5.9 Biological samples collection

Serum, plasma, nucleic acids, proteins and cells from bone marrow and peripheral blood samples taken at protocol specified visits will be stored in a biological sample collection.

During the study the sample collection(s) will be stored at INSERM U944 under the supervision

of Pr Raphael Itzykson for no more than 20 years. The collection is intended to perform the biomarker and PD analyses of the study.

At the end of the study, remaining samples will be kept and may be used for further analyses not described in the initial protocol, but which may be useful for investigation of acute myeloid leukemia in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the informed consent form.

The sample collection will be declared to the ministry of research and to the director of the competent regional healthcare authority - (Article L. 1243-3 of the *Code de la Santé Publique* [French Public Health Code]).

6) ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Patients aged 60 years or older
- With newly diagnosed AML (short course treatment with hydroxyurea and or steroids is acceptable). Patients with AML secondary to an antecedent Myelodysplastic Syndromes (MDS) or Myeloproliferative Neoplasms (MPN) are eligible, as those with therapy-related AML.
- Eligible for intensive chemotherapy in the investigator's opinion
- Multiparameter Flow Cytometry detected at screening allowing and / or compatible with MFCM-based MRD monitoring defined according to ELN criteria (Phase II only).[11]
- ECOG performance status ≤2
- AST and ALT ≤3.0 x upper the limit of normal (ULN) and total and direct serum bilirubin ≤ 1.5 x ULN unless considered due to leukemia
- Estimated glomerular filtration rate (GFR) ≥ 50 mL/min according to the MDRD equation
- Written informed consent obtained prior to any screening procedures
- Eligible for National Health Insurance in France.

6.2 Exclusion criteria

- Myeloid Sarcoma with < 20% bone marrow blasts
- Patient who has received a vaccine injection with live-attenuated virus in the last three weeks
- Proven central nervous system leukemic involvement
- Favorable risk cytogenetics: t(15;17), t(8;21), inv(16) or t(16;16) or presence of *PML-RARA*, *RUNX1-RUNX1T1* or *CBFB-MYH11* fusion transcript.
- Presence of *FLT3*-ITD or TKD mandating treatment with midostaurin.
- Concurrent therapy with any cytotoxic drug within 3 weeks before the first study dose. Only hydroxyurea for the control of blood counts is permitted.
- Patients planned to received CPX-351 for myelodysplasia-related changes or therapy-related AML.

  Previous treatment with sulfasalazine in the last 5 years or ongoing treatment with sulfasalazine or 5-aminosalicylic acid (5-ASA) for ulcerative colitis or inflammatory rheumatisms.
- History of allergy SSZ, one of its metabolites (5-aminosalicylic acid, 5-ASA) or mesalazine, other sulfonylarylamines sulfonamides or salicylates, or sulfasalazine

excipients (list in **section 18.5**).

- History of allergic reaction to idarubicin or idarubicin excipients
- History of allergic reaction to cytarabine or cytarabine excipients
- Known glucose 6-phosphate dehydrogenase deficiency.
- Known acute intermittent porphyria or porphyria variegata.
- Uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate treatment).
- Other uncontrolled or active malignant disease within prior 12 months (excluding myelodysplastic syndrome; cutaneous basal cell carcinoma, “in-situ” carcinoma of the cervix or breast, or other local malignancy excised).
- Known human immunodeficiency virus (HIV) infection or HIV-related malignancy.
- Clinically active hepatitis B or hepatitis C infection.
- Inability to swallow.
- Known malabsorption syndrome or other condition that may significantly impair absorption of oral study medications.
- Participation in another therapeutic interventional clinical study within 30 days of enrolment.
- Administration of any therapy considered investigational (i.e., used for non-approved indications(s) or in the context of a research investigation) within 5 drug half-lives (whichever is longer) prior to the first dose of study drug.
- Previous treatment by anthracyclines
- Any contraindication to use anthracyclines including uncontrolled coronary disease, severe renal failure, severe hepatic failure, recent myocardial infarction, symptomatic congestive heart failure, severe cardiomyopathy, significant arrhythmia as estimated by the investigator or LVEF <53% as assessed by echocardiography or MUGA, anterior treatment by idarubicin and/or anthracyclines and anthracènediones beyond the maximum cumulative dose.
- Any contraindication to use cytarabine including degenerative and toxic encephalopathy.
- Any condition requiring treatment with digoxin.
- Any of concurrent severe and/or uncontrolled medical condition, which could compromise participation in the study.
- Females who are pregnant or breastfeeding.
- In a man whose sexual partner is a woman of childbearing potential, unwillingness or inability of the man or woman to use a highly effective contraceptive method for the entire treatment period and for at least 6 months after completion of protocol treatment.

  Highly effective contraception methods include: combined (estrogen and progestogen containing) hormonal methods associated with inhibition of ovulation, intra-uterine device; surgical sterilization (including bilateral tubal occlusion, partner’s vasectomy) or sexual abstinence if this is the preferred and usual lifestyle of the patient.

  Male patients must not freeze or donate sperm starting at screening and throughout the treatment period and 3 months after the administration of the final dose of study medication.
- In a heterosexually active woman of childbearing potential, unwillingness or inability to use a highly effective contraceptive method (as described above) for the entire treatment period and for at least 6 months after the administration of the final dose of

study medication.

Women are not regarded as of childbearing potential if they are post-menopausal (at least 2 years without menses) or are surgically sterile (at least 1 month before enrollment).

Female patients must not donate or retrieve, for their own use, ova from the time of screening and throughout the treatment period, and for 12 weeks after the administration of the final dose of study medication.

Female patients must agree not to breastfeed from the time of screening and throughout the protocol period, and for (5 1/2 lives) days after the administration of the final dose of study medication.

- Adults subjects to a legal protection order or unable to give their consent
- Persons deprived of their freedom by judicial or administrative decision, person hospitalized without their consent by virtues of articles L 3212-1 and L3213-1 and who are not subject to the provisions of article L 1121-8.

6.3 Recruitment procedure

	Number of participants
Total number of participants to be included	A maximum of 64 20 in phase I 44 in phase II
Number of centers	8 in phase I 13 in phase II
Enrolment period (months)	56 months
Number of participants/center	4 to 8
Number of participants/center/month	0.07-0.1 center/ month

6.4 Termination rules

6.4.1 Criteria and procedures for prematurely terminating the study treatment

Several situations are possible.

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF).
- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation.
- Premature discontinuation of treatment and withdrawal from the study.

The investigator must:

- Document the reason(s),
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees,
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In the case of severe adverse events (hypersensitivity to investigational medicinal product), the investigator must notify the sponsor and follow up the participant for 1 month following the premature discontinuation of treatment or until the adverse resolution if it occurred before.

Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

- If, during the course of his/her participation in the study, the participant presents one non hematological grade ≥ 3 AE that is attributable to the study product in the investigator's opinion, then the study product must be interrupted until toxicity resolves or improve to grade 1, and the participant will continue to be monitored for the study.

6.4.2 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead.

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

- In case of serious adverse events, see the corresponding section on vigilance.

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up.

6.4.3 Follow-up of participants following premature withdrawal from the study

If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section **6.4.1**.

6.4.4 Procedures for replacing participants

Participants in the phase I part of the study who have withdrawn their consent before the end of the evaluation window for reasons other than death or DLT will not be replaced. The dose finding design used allows accounting for incomplete observations due to patients' discontinuation.

Participants in the phase II part of the study who have prematurely discontinued the study before the EOI visit for reasons other than death, lack of efficacy or adverse reaction will be replaced.

6.4.5 Full or partial discontinuation of the study

Early and temporary or definitive discontinuation of the study, early and temporary discontinuation of inclusions can be decided based on DSMB recommendations, and whether or not participants are allowed to complete their treatment or should immediately discontinue study drugs will all be based on DSMB recommendations. Moreover, in the phase I of the trial, probability of DLT at dose level 1 (DL1) within the EOI observation window becomes greater than 95%. In the phase II of the study, which relies on a Simon's two-stage design, safety will be assessed as part of the secondary objectives. The DSMB will examine all safety data throughout the trial, notably at the interim analysis of the phase II part.

AP-HP as sponsor or the Competent Authority can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:

- first of all, if any suspected unexpected serious adverse reactions (SUSARs) are observed, requiring a reassessment of the benefit-risk ratio for the study.
- if an interim analysis confirms the efficacy of the treatment or, alternatively, the lack of efficacy

Similarly, AP-HP, as the sponsor, or the Competent Authority may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical program are unlikely to be achieved.

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

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority and to the Ethics Committee without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

7) TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 Description of the investigational medicinal product: sulfasalazine SSZ

7.1.1 Investigational medicinal product: sulfasalazine

SSZ which belongs to the family of disease modifying anti-rheumatic drug (DMARD) and has been approved and used in France as treatment of inflammatory bowel diseases and rheumatoid arthritis for several decades.

Tablets are film coated gastro-resistant and contain 500mg of SSZ each. SSZ is available commercially under the name of salazopyrine® (Pfizer) or as generic drugs. The latter can be used in this clinical study as long as tablets contain 500mg of SSZ.

Given that the elimination half-life of SSZ is ~10 h in human blood, we anticipate that administration of the drug three times daily will ensure a sufficient blood concentration.[22]

Sulfasalazine (SSZ) will be administered orally with water at the following dose levels (DL):

DL-2: 0.5 g, twice a day hence 1.0 g/d, days 0-7
DL-1: 0.5 g, three times a day hence 1.5 g/d, days 0-7
DL1: 0.5 g, three times a day hence 1.5 g/d, days 0-14
DL2: 1 g, three times a day hence 3.0 g/d, days 0-14
DL3: 1.5 g, three times a day hence 4.5 g/d, days 0-14
DL4: 2.0 g, three times a day hence 6.0 g/d, days 0-14
DL5: 2.0 g, four times per day hence 8.0 g/d, days 0-14

Dose escalation will be conducted according to a time-to-event continual reassessment method design with cohorts of size 1, the number of patients assessed at each dose level depending on the safety observations. Additional safety rules are implemented, notably escalation to a new dose level *i* is allowed only if at least 3 patients have been treated at dose level *i-1* among all included patients so far.

Adverse reactions triggered by SSZ are detailed in the product SmPC (provided as Appendix in **section 18.4**).

Dosing should be interrupted, or doses should be reduced as follows:

Adverse events & reactions	Recommended action
Hematological AE grade 4	Continue cycle.
Non hematological grade ≥3 TEAE	Interrupt SSZ until toxicity resolves or improve to grade 1. Resume SSZ at the next lower dose level except if the event qualifies as DLT.

Management of Drug rash with eosinophilia and systemic symptoms (DRESS)

Severe, potentially life-threatening, systemic hypersensitivity drug reactions have rarely been reported with SSZ. Patients with fever, rash, enlarged lymph nodes should be monitored closely. SSZ must be withheld if the manifestations cannot be attributed to another cause

Management of Severe Skin reactions

Severe, potentially life-threatening, skin reactions including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) have exceptionally been reported with SSZ. SSZ should be immediately withheld in patients presenting with skin rash compatible with these entities during SSZ exposure, enlarged lymph nodes should be monitored closely. SSZ must be definitely interrupted if the manifestations cannot be attributed to another cause.

Management of cardiac events

Severe, potentially life-threatening, myocardial infarction have rarely been reported with SSZ.

Severe, potentially life-threatening, acute cardiac failures have exceptionally been reported with anthracyclin utilization. To mitigate cardiac toxicity, all patients will have an echocardiography for LVEF at screening visit with a troponin dosage and an ECG.. During study, systematic assessment of troponin in serum at D0, D3, D14 and EOI will be performed. Patients with a troponin level ≥99% percentile and/or an increase in troponin level ≥30% relative to baseline will trigger a local cardio-oncology visit and the investigator will notify the coordinating cardio-oncologist (Dr Mathilde Baudet, Hôpital Saint-Louis, Paris) and study coordinator. Any time during the treatment evaluation period (i.e. from inclusion to end of follow-up period), should the patient present with clinical signs compatible with a- heart failure b- myocardial ischemia or c- with sepsis requiring admission to an intensive care unit, , an ECG, a troponin assay and an echocardiography for LVEF evaluation will be performed and will trigger a cardio-oncology visit (coordinator: Dr Mathilde Baudet, Hôpital Saint-Louis, Paris).

SSZ must be withheld if the manifestations cannot be attributed to another cause.

Cardiac AESI must be notified without delay by the investigator to the sponsor but must be also notified to the PI (Pr Raphael Itzykson) and to the cardio-oncology coordinator (Dr Mathilde Baudet).

7.2 Description of Auxiliary medicinal products (treatments required to conduct the study)

According to the Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014, an auxiliary medicinal product is a medicinal product used in the context of a clinical trial but not as investigational medicinal product.

SSZ is combined with the intensive chemotherapy recommended by the ALFA group as standard of care for patients ≥ 60 years old with previously untreated AML.

Induction by idarubicin and cytarabine (IDA-AraC) backbone. Such a treatment (also called 7+3) combines 3 days of idarubicin, an anthracvcline, administered as short IV infusions, and 7 days of continuous IV infusions of cytarabine.[7]

Drug	doses	Administration	Days	Time
Idarubicin*,**	12 mg/m^2	IV, 30mn	3 days	Day 1 to 3
Cytarabine*	200 mg/m^2	CVI over 24h	7 days	Day 1 to 7

**for these two drugs the body area should not be capped to 2 m^2;*

Patients should be hospitalized during the induction course at least until day 21 and/or achievement of a neutrophil count > 500/µL. Thereafter they can be discharged if, according to the judgment of the investigator, their medical condition allows it and when all non-hematological treatment-emergent AEs resolve to Grade ≤ 2.

Patients should have adequate IV hydration during SSZ exposure.

Following the EOI visit, patients will continue to be followed for treatment related TEAEs for 30 days following the end of SSZ exposure.

Treatments beyond EOI are left to the clinicians' choice and may include consolidation chemotherapy, oral maintenance and/or allogeneic stem cell transplantation. Recommendations from the ALFA collaborative groups are indicated in Appendix (**section 18.6).**

Patients will have regular post-inductions visit until relapse or study exit after 12 months of

follow-up beyond the EOI visit. Minimal follow-up information on relapse, transplantation and death may be obtained up to 5 years after study exit.

7.2.1 Idarubicin

Expected site effects of IDA are hematological toxicities. The most common non-hematological side effects include: cardiotoxicity, nausea, vomiting, oral mucositis, esophagitis and diarrhea, fever, chills, skin rash, alopecia, rise of hepatic enzymes and bilirubin.

Extravasation

Extravasation of IDA during intravenous injection may cause local pain, severe tissue lesions (vesication, severe cellulitis), and necrosis. If signs or symptoms of extravasation occur during intravenous administration of IDA, the drug infusion should be immediately stopped. In cases of extravasation, dexrazoxane can be used to prevent or reduce tissue injury.

Tumour Lysis Syndrome

IDA may induce hyperuricemia as a consequence of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells ('tumour lysis syndrome'). Blood uric acid levels, potassium, calcium, phosphate, and creatinine should be evaluated after initial treatment. Hydration with isotonic fluids and prophylaxis with allopurinol/rasburicase are recommanded to prevent hyperuricemia may minimize potential complications of tumour lysis syndrome.

Adverse events induced by idarubicin will be managed according to SmPC.Cytarabine

Cytarabine (AraC) is commonly used for treatment of acute myeloid leukemia and is part of the standard treatment including the induction course.

The most common adverse reactions reported with AraC dosage used during the induction cours e.g., ≤ 200 mg/m^2/day) include hematologic, gastrointestinal, dermatologic, and hepatic reactions. Myelosuppression includes neutropenia, thrombocytopenia and anemia. AraC is considered highly emetogenic. In addition to nausea and vomiting, diarrhea and mucositis are reported in >10% of patients receiving the drug. Alopecia is common. Rash, including hand-foot syndrome, is reported also. Mild jaundice, and elevated transaminase levels also are reported in >10% of patients. Fever (non-infectious) is also reported among the most common adverse reactions associated with AraC. Less commonly, a “cytarabine syndrome” or “AraC syndrome” has been reported. The syndrome may be characterized by fever, myalgia, bone pain, rash, malaise, and chest pain.

The most common adverse reaction reported with AraC high dose, in addition to those already described above, is neurologic toxicity cerebellar toxicity and polyneuropathy.
For neurotoxicity > grade 2 due to cytarabine during salvage or consolidation therapy, discontinue cytarabine for the remainder of the cycle.

Adverse events induced by cytarabin will be managed according to SmPC.

7.3 Authorized and prohibited treatments

7.3.1 Recommended treatments

- Patients should receive adequate IV and/or oral hydration during treatment with SSZ.
- Patients should receive adequate anti-emetic prophylaxis during treatment with SSZ, including setrons, anti-emetic neuroleptics, and/or substance P antagonists.

- Use of G-CSF after SSZ discontinuation is authorized.
- Use of posaconazole as antifungal prophylaxis is allowed after discontinuation of both idarubicin and cytarabine.
- Intrathecal chemotherapy (steroids, cytarabine, and/or methotrexate) for the prophylaxis of central nervous system leukemic involvement should be delivered at the investigator's discretion.

7.3.2 Prohibited medications and medications with precautions for use

- Use of other anti-leukemic agents during the induction course, including other chemotherapy agents, midostaurine or other kinase inhibitors, is prohibited.
- Use of erythropoiesis stimulating agents and thrombopoietin analogs is prohibited.
- Following concomitant medications are prohibited except if they are considered by the investigator as absolutely essential for the care of the patient:
    - Purine analogs, notably azathioprine
    - Digoxin
    - Anion-exchange resins.Phenytoin and fosphenytoin
- Additive toxicities in case of radiotherapy concomitant in the last three weeks can be observed.
- Close monitoring is required for patients treated with immunosuppressors (such as cyclosporine and tacrolimus).

7.4 Methods for monitoring compliance with the treatment

SSZ will be administered in hospitalized patients, enabling to document perfectly the compliance of the treatment by nurses and clinical research assistants.

8) EFFICACY ASSESSMENT

8.1 Description of efficacy endpoints assessment parameters

The primary endpoint of phase II, MRD negative complete response combines 2 definitions:

- The ELN 2022 definition of CR or CRi or CRh[40]:
    - CR is defined as bone marrow blasts < 5% and blasts with Auer rods, absence of circulating blasts; absence of extramedullary disease, ANC ≥ 1.0 x10^9/L and platelets ≥ 100 x x10^9/L
    - CRi (CR with incomplete hematologic recovery, is defined as CR with platelet count <100,000/µL or absolute neutrophil count <1000/µL
    - CRh (CR with partial haematological recovery) is defined as CR not fulfilling CR or CRi peripheral blood criteria but with platelet count >50,000/µL AND absolute neutrophil count >500/µuL.
- MRD negativity is defined as a centralized 8-color bone marrow flow cytometry MRD < 0.1% at EOI.

- Secondary endpoints of efficacy include the following criteria of response and outcome

measures which are also defined in ELN 2022 guidelines:

- Response criteria at EOI:
  - Morphologic leukemia-free state (MLFS): blastic criteria of response on the bone marrow aspirate, absence of extramedullary disease and no requirement of hematologic recovery.
  - Partial response (PR): absence of circulating blasts; absence of extramedullary disease; decrease of bone marrow blast percentage to 5 to 25% and decrease of pretreatment bone marrow blast percentage by at least 50%
  - Overall response rate (ORR) being defined as CR, CRi and CRh, MLFS and PR rates.
  - Primary refractory disease defined as patients lacking criteria for any of the above defined responses (CR, CRi, CRh, MLFS and PR) at EOI assessment, excluding patients with death in aplasia or death due to indeterminate cause as defined per ELN 2022 criteria.
  - Death in aplasia defines as death occurring ≥ 7 days following completion of initial treatment while cytopenic with an aplastic or hypoplastic bone marrow obtained within 7 days of death without evidence of persistent leukemia.
  - Death due to indeterminate cause defined as death occurring before completion of therapy or <7 days following its completion or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood but no bone marrow available
- Outcomes measures
  - Overall survival
  - Event free survival measured from the date of entry into the study. Here events are defined as:
    - Non achievement of hematologic response including CR, CRi, CRh
    - Hematologic relapse or progressive disease
    - Initiation of any subsequent anti-leukemic therapy (excluding hydroxyurea)
    - Deaths prior to one of the events mentioned above.
  - Relapse free survival defined only for patients achieving CR, CRh or CRi and measured from the date of achievement of a remission
  - Duration of response
- Incidence of subsequent allogeneic HSCT, overall and in responding patients specifically

8.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy data

The primary endpoint of efficacy will be assessed at EOI, between D28 and D42 at the latest and in any case before the beginning of the first consolidation course or the initiation of a conditioning regimen for allogeneic HSCT.

Criteria of response are assessed from peripheral blood count and bone marrow aspirates performed according to this timeline.

- Morphological examination, will be performed in local hematology laboratories

- Eight color FCM MRD will be performed centrally in Saint Louis Hospital on peripheral blood and bone marrow aspirates sampled according to the same timeline.

In *NPM1* mutated patients, standard PCR-based MRD will also be conducted on the bone marrow and peripheral blood to guide post-remission therapies. However, its results will not be used to define the primary endpoint of the phase II portion of the trial.

Samples for MRD, biomarkers and PD (30 ml of blood and 3 ml of bone marrow aspirates in EDTA tubes) should be sent at room temperature within 24 hours to the *Laboratoire d'Hématologie Hôpital Saint Louis 1 avenue Claude Vellefaux 75010 Paris* for MRD assessment.

PK samples (5 mL of blood) will be collected into heparinized tubes. Immediately after collection, tubes will be inverted several times and kept at approximately 4 °C until centrifugation. The tubes will be centrifuged for 10 min at 1500×g at 4 °C within 60 min of collection to separate plasma. The plasma will be separated into 2 aliquots in polypropylene screw-cap tubes and placed at -80°C until analysis.

9) SPECIFIC STUDY COMMITTEES

Two committees will govern the study.

English name	French name	Description
Data Safety Monitoring Board (DSMB)	Comité de surveillance indépendant (CSI)	Members independent from the investigator
Steering Committee	Comité de Pilotage	Investigators, sponsor

9.1 Steering Committee

9.1.1 Role

The role of the steering committee is manifold:

- To oversee the progression of the study
- Propose procedures to be followed during the study, acknowledging any recommendations from the DSMB. The DRCI sponsor retains decision-making authority.
- At the end of the phase 1, determine in interaction with the DSMB the recommended phase II dose (RP2D).
- Review and validate the analysis plan of the data.
- Review and validate the draft of the publications.

9.1.2 Composition

The steering committee should meet the main players of the study:

- The coordinator investigator (Prof Raphaël Itzykson)
- The biostatistician in charge of the project (Dr Lucie Biard, Saint-Louis, Unité de Recherche Clinique biostatistics department)
- The referral cardio-oncologist of the study (Dr Mathilde Baudet, Saint Louis Hospital, Paris)

- The pharmacologist (Dr Lauriane Goldwirt, Saint Louis pharmacology department, Paris)
- The principal investigators of each participating centres
- The scientific director of the study (Dr Alexandre Puissant)
- A representative of the sponsor (APHP DRCI)
- The coordination team of THEMA (Karine Celli-Lebras, Dr Renaud Buffet, Dr Laure Gilles).

9.2 DSMB

See the section 10.4.4.

10) SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

10.1 Description of Safety endpoints assessment parameters

Safety endpoints including DLT definition are described in section **4.1** of the protocol. Identification and grading of AEs is entirely based on NCI CTCAE version 5.0 of the NCI.

10.2 Recommendation in case of cardiac toxicity

Patients with a troponin level ≥99% percentile and/or an increase in troponin level ≥30% relative to baseline will trigger a local cardio-oncology visit and the investigator will notify the coordinating cardio-oncologist (Dr Mathilde Baudet, Hôpital Saint-Louis, Paris) and study coordinator. Any time during the treatment evaluation period (i.e. from inclusion to end of follow-up period), should the patient present with clinical signs compatible with a- heart failure b- myocardial ischemia or c- with sepsis requiring admission to an intensive care unit, , an ECG, a troponin assay and an echocardiography for LVEF evaluation will be performed and will trigger a cardio-oncology visit (coordinator: Dr Mathilde Baudet, Hôpital Saint-Louis, Paris).

SSZ must be withheld if the manifestations cannot be attributed to another cause.

Cardiac AESI must be notified without delay by the investigator to the sponsor (see paragraph 10.4.2.2.1) but must be also notified to the PI (Pr Raphael Itzykson) and to the cardio-oncology coordinator (Dr Mathilde Baudet).

10.3 Anticipated methods and timetable for measuring, collecting and analyzing the safety endpoints

Safety endpoints are easily monitored through clinical examination, usual laboratory tests, ECG and echocardiography.

During the phase I portion of the trial, **the eCRF should be filled in nearly real time** and monitored as soon as possible after the EOI visit. Real-time assessment of DLTs is central to the Bayesian continual reassessment method (CRM). All monitored DLTs will inform the modelling of the DL allocated to the next enrolled patient (see details on enrollment procedure in **Section 5.1.2** and on the CRM model in **Section 12**).

10.4 Recording and reporting adverse events

10.4.1 Definitions

According to Article 2 of the Regulation (EU) N° 536/2014:

- **Adverse event**

Any untoward medical occurrence in a subject, to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

- **Serious adverse event**

Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

- **Unexpected serious adverse reaction**

A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

According to Article 53 of the Regulation (EU) No 536/2014:

- **Unexpected event**

An unexpected event which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 42. That notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

According to Article 54 of the Regulation (EU) No 536/2014:

- **Urgent safety measure**

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects. The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken.
That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

10.4.2 The role of the investigator

The investigator must **assess the seriousness 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.

The investigator must **assess the intensity** of the adverse events: by using the' Common Terminology Criteria for Adverse Events' (CTCAE of the National Cancer Institute), version 5.0 of November 2017.

The investigator must **assess the causal relationship** between serious adverse events and sulfasalazine (investigational medicinal product added by the study), and between serious adverse events and idarubicin and cytarabine (auxiliary medicinal products).

The method used by the investigator is based on the following 2 causality terms:

- Related
- Not related

10.4.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

The investigator notifies the sponsor without undue delay but not later than within 24 hours on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in article 41 of Regulation (EU) N°536/2014, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening to the participant enrolled in the study
3- requires hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, require the investigator to notify the sponsor without delay.

10.4.2.2 Specific features of the protocol

10.4.2.2.1 Other events that require the investigator to notify without delay the sponsor

- Adverse events deemed "medically significant"
    - Any grade ≥ 3 non hematological adverse events fitting with DLT criteria.

      The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).
- Adverse events of special interest
    - Emerging cardiopathy including any decrease ≥ grade 2 of ejection fraction or elevation of troponin serum levels ≥ grade 2 during the induction course.

      The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).
- In utero exposure

  The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.

  If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.
- Exposure while breastfeeding

  Exposure while breastfeeding occurs if an infant or a child may have been exposed to a medicinal product *via* the breast milk of a mother being treated with an investigational medicinal product.

  Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day the investigator becomes aware of the exposure while breastfeeding.

10.4.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the case report forms. A data retrieval of the case report forms will be implemented for serious adverse events at EOI at the latest.

- Hospitalization for the induction treatment of AML.
- Hematological toxicities except if persisting at grade ≥3 after day 42 in the absence of proven disease persistence by bone marrow aspiration and/or biopsy. This rule is justified by the fact that conventional induction chemotherapy with 7+3 results in grade 4 neutropenia in all patients, resolving in median at day 22, with 17% of patients still having grade 4 neutropenia by day 28 (Gardin et al., Blood 2007 [38] and ALFA9803 data on file).

- *Special circumstances*
- Hospitalisation for a pre-existing illness or condition
- Hospitalisation for a medical or surgical treatment scheduled prior to the study
- Admission for social or administrative reasons

10.4.2.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:
- from the date on which the participant begins treatment with sulfasalazine,
- until 4 weeks after the end of sulfasalazine treatment for all SAEs defined in sections 10.4.2.1 and 10.4.2.2.1,
- or throughout the whole follow-up period required for the trial for the AESI of emerging cardiopathy defined in section 10.4.2.2.1,
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

10.4.2.2.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilization at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

For studies which use e-CRFs
- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

10.4.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of each investigational medicinal product throughout the study.

10.4.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:
- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medicinal product and any other treatments,
  All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expected or unexpected nature** 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, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

- For serious adverse events likely to be related to investigational medicinal product (sulfasalazine): refer to the SmPC for sulfasalazine enclosed in CTIS platform.

❖ For serious adverse events that may be related to the auxiliairy medicinal products (idarubicin and cytarabine): refer to the SmPC for idarubicin and cytarabine enclosed in CTIS platform.
❖ The expected serious adverse events potentially related to the interventions, procedures or examinations specific to the study are:
- For blood samples: hematoma, pain, vagal malaise, mild bleeding
- For ECG: mild cutaneous eruption, mild irritation
- For bone marrow aspiration: bleeding, pain, hematoma

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs) via Eudravigilance, within the regulatory time frame, to the competent authority:
- in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction;
- in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;
- in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening
- in the uncompleted case of fatal or life-threatening suspected unexpected serious adverse reactions, all additional information to complete this case have to be reported as soon as possible and in any event not later than eight days after the initial report
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 15 days starting from when the sponsor had this information.

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

Specific case of serious adverse events of special interest:
The sponsor may be required to declare serious adverse events of special interest, in accordance with the same procedures and deadlines as for SUSARs.

10.4.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

During Phase 2, only medically significant or grade ≥3 AEs (including investigations) will be recorded in the eCRF.

The sponsor will report in CTIS platform and to ANSM without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

10.4.3.3 Annual safety report

Once a year for the duration of the clinical trial, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- a safety analysis for the Clinical Trial participants,
- a description of the patients included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- summary tables of all the serious adverse events that have occurred since the start of the trial,

The sponsor produces one annual safety report (Development Safety Update Report - DSUR) for one clinical trial.

The report must be submitted in CTIS no later than 60 days after the anniversary of the date on which the competent authority authorised the trial.

10.4.4 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the Competent Authority and the Ethics Committee.

The DSMB members are (To be confirmed):
- Two experts in AML
    - One national expert : Dr Sylvain Garciaz, Marseille
    - One international expert : Prof Pau Montesinos, Valencia
- One expert in the experimental drug, SSZ
    - Dr Anne-Laure Pelletier, Hôpital Bichat
- One methodologist
    - Dr Monia Ezzalfani, Institut Curie

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

11 DATA MANAGEMENT

11.1 Data access

In accordance with GCPs and appendix 1 of the European Regulation N°536-2014:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the Sponsor declares that investigators and participating institution will ensure the persons in charge of monitoring, quality control and auditing or inspecting the clinical trial have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force

11.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a

hospital medical file.

In the context of the study source document are medical files, original biological examination results, summary from imaging examinations.

11.3 Data confidentiality

The persons responsible for the quality control of clinical trials will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy.
During and after the clinical trial, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.

The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of research documents and data

11.4.1 Identification of the data processing manager and location(s)

Dr. Lucie BIARD from the Clinical Research Unit (URC, an INCa labeled Data Center) and Service Biostatistique et Informatique Médicale (SBIM) of Hôpital Saint Louis, AP-HP, Paris will be responsible for data entry and the relevant procedures. The same goes for conducting the statistical analysis.

11.4.2 Data entry

Non-identifying data will be entered electronically via a web browser.

11.5 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

Phase I

A Bayesian adaptive dose escalation design will be used for the trial objectives. It allows sequential monitoring of data during the trial, using all current evidence for straightforward inference on safety and efficacy and decision making to select and evaluate an optimal dose.

The design will rely on the Bayesian continual reassessment method (CRM) for the phase I, with cohorts of size 1 and a maximum sample size of 20 patients.[30] The target DLT rate for the definition of the MTD will be 33% within the EOI observation window. The time-to-event extension of the CRM for right censored data (survCRM) design will be used depending on the anticipated accrual rate compared to the DLT observation window.[31] This will allow accounting for right-censored toxicity observation in sequential MTD estimation and dose assignment

process, and accounting for potential incomplete observations due to unplanned patient discontinuation while avoiding patient replacement.

Safety rules will be implemented:

- No dose skipping will be allowed during dose escalation;
- For each newly escalated dose level, at least three patients must have been treated at this level prior to escalating to the next above dose level;
- For each newly escalated dose level, the first three patients treated at this dose level will be included at least one week apart;
- The trial will be terminated if the posterior probability of DLT within the EOI observation window at dose level 1 (DL1) is greater than 95%.

The design will be calibrated to obtain desirable operating characteristics (notably, probability of correct MTD selection, probability of overdose selection).[42] Specifically, the dose skeleton will be defined using the indifference interval approach and a least informative prior variance will be used for the working model parameter.

Simulation study

The working model for the dose-toxicity relationship is $Pr_{toxicity} = 1\text{-}exp\{t^* exp(d^* exp(beta)\}$ where doses *d* are given by the skeleton and parameter *beta* is estimated by its posterior mean assuming a normal prior with mean 0 and variance=1.34.

Dose skeletons were calibrated using the indifference interval approach (Lee and Cheung 2009).
We implemented the algorithm described by Lee and Cheung (2009) with the working model described above, a target toxicity probability of 0.33, 7 dose levels and dose level 6 as anticipated MTD. Based on 2,000 simulations, on a set of scenarios defined following Lee and Cheung (2009), we set the halfwidth of the indifference interval for toxicity at 0.05, as providing the highest percent of correct selection corresponding to the following skeleton described in the table below.

Dose level		**Assumed Pr DLT**
DL-2	0.5 g, twice a day hence 1.0 g/d, days 0-7	0.04
DL-1	0.5 g, three times a day hence 1.5 g/d, days 0-7;	0.07
DL1	0.5 g, three times a day hence 1.5 g/d, days 0-14	0.11
DL2	1 g, three times a day hence 3.0 g/d, days 0-14	0.16
DL3	1.5 g, three times a day hence 4.5 g/d, days 0-14	0.24
DL4	2.0 g, three times a day hence 6.0 g/d, days 0-14	0.33
DL5	2.0 g, four times a day hence 8.0 g/d, days 0-14	0.44

The simulated trials were generated using the Surv -CRM design, starting at dose level 3 with cohort size of 1 patient, and implementing the above listed safety rules. We performed 5000 simulations, with a maximum sample size of 20 patients, target DLT rate of 0.33 for the MTD and patient arrival generated from a Poisson process, with rate 4 patients per 42 days ([0,t*]:observation window). Simulation results are reported in the table below.

	%Stopped	DL-2	DL-1	DL1	DL2	DL3	DL4	DL5
Scenario 1 True DLT rate		**0.04**	**0.06**	**0.10**	**0.16**	**0.24**	**0.33**	**0.44**
% Selected	2	0	0	1	8	23	31	36
N pts allocated		0	0	4	4	5	4	3
Scenario 2 True DLT rate		0.20	0.22	0.25	0.28	0.30	0.32	0.35
% Selected	12	1	5	11	16	18	17	20
N pts allocated		1	2	5	5	4	2	2
Scenario 3 True DLT rate		**0.33**	**0.35**	**0.37**	**0.39**	**0.41**	**0.43**	**0.45**
% Selected	36	3	13	15	13	10	6	4
N pts allocated		1	3	6	5	3	1	1
Scenario 4 True DLT rate		**0.40**	**0.43**	**0.45**	**0.48**	**0.50**	**0.52**	**0.55**
% Selected	57	6	13	12	8	3	1	0
N pts allocated		2	4	6	5	2	1	0

Reference
Lee, SM and Cheung YK (2009). Model calibration in the continual reassessment method. Clinical Trials 6, 227-238.[43]

Phase II

The RP2D is anticipated as the MTD dose identified in the phase I part of the study. The final choice of the RP2D for Phase II will depend on DSMB recommendations based on safety data, PK/PD and efficacy signals from Phase I and could eventually be one dose level below the estimated MTD. Inclusion criteria will be the same as in Phase I with the addition of an additional inclusion criteria (LAIP detected at baseline FCM assessment) related to the primary endpoint of complete response with negative MRD.

The rate of MRD-negative complete response in the study population is estimated at ~50% based on British AML16 data,[12] Spanish PETHEMA data, [32] and British AML17 data (S. Freeman, *pers. comm.*).

A Simon minimax two-stage design will be used for this phase.[44] This phase II assessment will require a maximum total of 44 subjects to decide whether the proportion responding, P, is less than or equal to 0.50 or greater than or equal to 0.70. At the first stage (that is among the first 22 included patients), if the number of responses is lower than or equal to r1=11, the phase 2 will stopped early, for futility. Otherwise, if r1 ≥ 12, enrolment will continue up to a maximum of 44 patients. Overall, if the number of responses R becomes 28 or more, the hypothesis that P ≤ 0.50 is rejected with a target type I error rate of 0.05. If the total number of responses is R=27 or less, the hypothesis that P ≥ 0.70 is rejected with a target type II error rate of 0.15. Of note, phase I patients treated at the RP2D of choice will be included in this analysis if they are assessable by FCM MRD (presence of a LAIP).

13 QUALITY CONTROL AND ASSURANCE

Every clinical trial sponsored by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored clinical trial.

13.1 General organization

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centers.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

13.1.1 Strategy for center opening

The strategy for opening the centers established for this study is determined using the appropriate monitoring plan.

13.1.2 Scope of center monitoring

In the case of this level D risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level D.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent,
- compliance with the study protocol and with the procedures defined therein,
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.),
- management of the treatments used.

13.3 Case report forms

All information required by 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. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form 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. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

13.5 Audits/inspections

The investigators agree to consent to 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. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the Clinical Trial. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.
The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.
The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

13.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of

Health Professionals, for France). The CV must include any previous involvement in clinical research and related training.
Any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki. Each investigator will give the sponsor's representative a GCP certificate dated fewer than three years ago.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

13.7 Suitability of the facilities

Before starting the study, each clinical trial sites will give the sponsor's representative a duly justified written statement on the suitability adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise.

13.8 Pharmacist's commitment of responsibility

Production problems must be recorded according to the Manufacturing unit (LTCG) procedures.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing research participants and obtaining their consent

According to article 29 of European regulation N°536/2014, No clinical trials on medicinal products for human use can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in article 29.2 of the European Regulation.
A minimum reflection period of ***24 hours*** is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study.

A copy of the information note and consent form, signed and dated by the Clinical Trial participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent by article European regulation

N°536/2014 (art. 29 and following))] as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

14.2 Compensation for participants

No compensation for participants is planned.

14.3 Authorization for the research location

In France, the study will be carried out in treatment units on individuals presenting a clinical condition for which the units are specialized and who require interventions that are routinely performed at those units. Therefore, the research location does not require specific authorization.

14.4 Legal obligations

14.4.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and all national Laws. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.4.2 Request for authorisation

Prior to starting the study, AP-HP, as sponsor, must obtain authorisation from the Competent Authority and the Research Committee for this clinical trial on medicinal product for human use within the scope of its authority and in accordance with in force legislation and regulatory requirements.

14.4.3 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended “Informatique et Libertés” law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

The Clinical Trial is governed by the “Reference Methodology” (MR-001)

For France:

- Commitment to comply with “Reference Methodology” MR-001

This Clinical Trial is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001). AP-HP, as sponsor of the Clinical Trial, has signed a declaration of compliance with this “Reference Methodology”.

14.4.4 Start of the Clinical Trial

The sponsor shall notify each Member State concerned of the start of a clinical trial and the start of the recruitment through the EU portal. That notification shall be made within 15 days from the start of the clinical trial.

14.4.5 Amendments to the Clinical Trial

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, approval from the Ethics Committee and authorization from the competent authority within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.4.6 End of the Clinical Trial

The end of the Clinical Trial corresponds to the end of the participation of the last person who participate to the Clinical Investigation.
The end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified in CTIS. That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.
Summary of the results of the clinical trial
According to article 37.4 of the European regulation n°536/2014, irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the CTIS a summary of the results of the clinical trial. This summary shall be accompanied by a summary written in a manner that is understandable to laypersons.

14.4.7 Archiving

Specific documents for a clinical trial on medicinal product for human use will be archived by the investigator and the sponsor for 25 years after the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the center who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the center who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list):
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - the competent authority authorizations and Ethics Committee decisions
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - final study report
- The data collection documents

15 FUNDING AND INSURANCE

15.1 Funding sources

The study is funded by the Fondation ARC under the reference

ARCPGA12021020003259_3569). The study is developed in the THEMA program (ANR IHU-B-2018) and the resources of the THEMA program (study coordination) will contribute to the study conduction.

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article 76(1) of regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

16 PUBLICATION RULES

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and must name the sponsor AP-HP (DRCI) and the source of funding.

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

- "The sponsor was Assistance Publique – Hôpitaux de Paris (Direction de la Recherche Clinique et de l'Innovation)"

16.3 Mention of the financial backer in the acknowledgements of the text

This study has been registered on the website http://clinicaltrials.gov/ under number 2022-001269-11.

17 BIBLIOGRAPHY

1. Visser O, Trama A, Maynadie M, et al: Incidence, survival and prevalence of myeloid malignancies in Europe. Eur J Cancer 48:3257-66, 2012
2. Juliusson G, Lazarevic V, Horstedt AS, et al: Acute myeloid leukemia in the real world: why population-based registries are needed. Blood 119:3890-9, 2012
3. Dombret H, Gardin C: An update of current treatments for adult acute myeloid leukemia. Blood 127:53-61, 2016
4. Stone RM, Mandrekar SJ, Sanford BL, et al: Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med 377:454-464, 2017
5. Wei AH, Dohner H, Pocock C, et al: Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission. N Engl J Med 383:2526-2537, 2020
6. Lancet JE, Uy GL, Cortes JE, et al: CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia. J Clin Oncol 36:2684-2692, 2018
7. Gardin C, Pautas C, Fournier E, et al: Added prognostic value of secondary AML-like gene mutations in ELN intermediate-risk older AML: ALFA-1200 study results. Blood Adv 4:1942-1949, 2020
8. Dombret H, Itzykson R: How and when to decide between epigenetic therapy and chemotherapy in patients with AML. Hematology Am Soc Hematol Educ Program 2017:45-53, 2017
9. Lowenberg B, Ossenkoppele GJ, van Putten W, et al: High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 361:1235-48, 2009
10. Schlenk RF, Lubbert M, Benner A, et al: All-trans retinoic acid as adjunct to intensive treatment in younger adult patients with acute myeloid leukemia: results of the randomized AMLSG 07-04 study. Ann Hematol 95:1931-1942, 2016
11. Schuurhuis GJ, Heuser M, Freeman S, et al: Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood 131:1275-1291, 2018
12. Freeman SD, Virgo P, Couzens S, et al: Prognostic relevance of treatment response measured by flow cytometric residual disease detection in older patients with acute myeloid leukemia. J Clin Oncol 31:4123-31, 2013
13. Balsat M, Renneville A, Thomas X, et al: Postinduction Minimal Residual Disease Predicts Outcome and Benefit From Allogeneic Stem Cell Transplantation in Acute Myeloid Leukemia With NPM1 Mutation: A Study by the Acute Leukemia French Association Group. J Clin Oncol 35:185-193, 2017
14. Lachowiez CA, Loghavi S, Kadia TM, et al: Outcomes of older patients with NPM1-mutated AML: current treatments and the promise of venetoclax-based regimens. Blood Adv 4:1311-1320, 2020
15. Saito Y, Kitamura H, Hijikata A, et al: Identification of therapeutic targets for quiescent, chemotherapy-resistant human leukemia stem cells. Sci Transl Med 2:17ra9, 2010
16. Pollyea DA, Stevens BM, Jones CL, et al: Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. Nat Med 24:1859-1866, 2018

17. DiNardo CD, Jonas BA, Pullarkat V, et al: Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med 383:617-629, 2020
18. Jones CL, Stevens BM, D'Alessandro A, et al: Inhibition of Amino Acid Metabolism Selectively Targets Human Leukemia Stem Cells. Cancer Cell 34:724-740 e4, 2018
19. Jones CL, Stevens BM, D'Alessandro A, et al: Cysteine depletion targets leukemia stem cells through inhibition of electron transport complex II. Blood 134:389-394, 2019
20. Chen J, Lin S, Liu C: Sulfasalazine for ankylosing spondylitis. Cochrane Database Syst Rev:CD004800, 2014
21. Gout PW, Buckley AR, Simms CR, et al: Sulfasalazine, a potent suppressor of lymphoma growth by inhibition of the x(c)- cystine transporter: a new action for an old drug. Leukemia 15:1633-40, 2001
22. Yamasaki Y, Ieiri I, Kusuhara H, et al: Pharmacogenetic characterization of sulfasalazine disposition based on NAT2 and ABCG2 (BCRP) gene polymorphisms in humans. Clin Pharmacol Ther 84:95-103, 2008
23. Stockwell BR, Friedmann Angeli JP, Bayir H, et al: Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease. Cell 171:273-285, 2017
24. Gewirtz DA: A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics adriamycin and daunorubicin. Biochem Pharmacol 57:727-41, 1999
25. Figueiras RDB, Pasanisi J, Joudinaud R, et al: Niche-like Ex Vivo High Throughput (NEXT) Drug Screening Platform in Acute Myeloid Leukemia. Blood 136:12-13, 2020
26. Robe PA, Martin DH, Nguyen-Khac MT, et al: Early termination of ISRCTN45828668, a phase 1/2 prospective, randomized study of Sulfasalazine for the treatment of progressing malignant gliomas in adults. BMC Cancer 9:372, 2009
27. Otsubo K, Nosaki K, Imamura CK, et al: Phase I study of salazosulfapyridine in combination with cisplatin and pemetrexed for advanced non-small-cell lung cancer. Cancer Sci. 108:1843-1849, 2017
28. Shitara K, Doi T, Nagano O, et al: Dose-escalation study for the targeting of CD44v+ cancer stem cells by sulfasalazine in patients with advanced gastric cancer (EPOC1205). Gastric Cancer 20:341-349, 2017
29. Lei P, Bai T, Sun Y: Mechanisms of Ferroptosis and Relations With Regulated Cell Death: A Review. Front Physiol 10:139, 2019
30. O'Quigley J, Pepe M, Fisher L: Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics 46:33-48, 1990
31. Andrillon A, Chevret S, Lee SM, et al: Dose-finding design and benchmark for a right censored endpoint. J Biopharm Stat 30:948-963, 2020
32. Vidriales MB, Perez-Lopez E, Pegenaute C, et al: Minimal residual disease evaluation by flow cytometry is a complementary tool to cytogenetics for treatment decisions in acute myeloid leukaemia. Leuk Res 40:1-9, 2016
33. Lo-Coco F, Avvisati G, Vignetti M, et al: Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 369:111-21, 2013
34. Prebet T, Boissel N, Reutenauer S, et al: Acute myeloid leukemia with translocation (8;21) or inversion (16) in elderly patients treated with conventional chemotherapy: a collaborative study of the French CBF-AML intergroup. J Clin Oncol

27:4747-53, 2009
35. Itzykson R, Fournier E, Berthon C, et al: Genetic identification of patients with AML older than 60 years achieving long-term survival with intensive chemotherapy. Blood 138:507-519, 2021
36. Strom BL, Schinnar R, Apter AJ, et al: Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. N Engl J Med 349:1628-35, 2003
37. Zawodniak A, Lochmatter P, Beeler A, et al: Cross-reactivity in drug hypersensitivity reactions to sulfasalazine and sulfamethoxazole. Int Arch Allergy Immunol 153:152-6, 2010
38. Gardin C, Turlure P, Fagot T, et al: Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. Blood 109:5129-35, 2007
39. Freeman SD, Hills RK, Virgo P, et al: Measurable Residual Disease at Induction Redefines Partial Response in Acute Myeloid Leukemia and Stratifies Outcomes in Patients at Standard Risk Without NPM1 Mutations. J Clin Oncol 36:1486-1497, 2018
40. Dohner H, Wei AH, Appelbaum FR, et al: Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood 140:1345-1377, 2022
41. Picou F, Vignon C, Debeissat C, et al: Bone marrow oxidative stress and specific antioxidant signatures in myelodysplastic syndromes. Blood Adv 3:4271- 4279, 2019
42. Lee SM, Cheung YK: Calibration of prior variance in the Bayesian continual reassessment method. Stat Med 30:2081-9, 2011
43. Lee SM, Ying Kuen C: Model calibration in the continual reassessment method. Clin Trials 6:227-38, 2009
44. Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1-10, 1989

18 LIST OF ADDENDA

a. List of investigators
b. Serious Adverse Events notification form
c. Pregnancy notification form
d. Therapy-related malignancy notification form
e. SmPC or Investigator's Brochure
f. List of Sulfa agents and salicylates
g. Recommended post-induction therapy
h. Description of the Clinical Trial in the AP-HP Trials Register
i. Statistical article (Andrillon, Chevret, Lee, Briard, 2020)

18.1 List of investigators

Address of the study location	Title	First name Surname	Telephone/E-mail/Fax
Hôpital Saint-Louis, Paris	Pr	Raphael Itzykson	Tel. +33142499643 Fax. +33142494010 raphael.itzykson@aphp.fr
Hôpital Avicenne, Bobigny	Pr	Thorsten Braun	Tel. Fax Thorsten.braun@aphp.fr
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CHU Henri Mondor, Créteil	Dr	Mathieu LECLERC	Tel. +33149812057 Fax. mathieu.leclerc@aphp.fr
Hôpital de la Conception, AP-HM	Dr	Geoffroy VENTON	Tel. Fax. GEOFFROY.VENTON@ap-hm.fr

18.2 Serious Adverse Events notification form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par télécopie au +33 (0)1 44 84 17 99

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche

Acronyme : **SALMA**

Code de la Recherche :
APHP211176
Eudract: 2022-001269-11

Risque : D

Essai portant sur la 1ère administration du médicament chez des personnes qui ne présentent aucune affection (à ajouter ou à supprimer selon la recherche)

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de l'EIG par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la recherche :
Phase I/II Clinical Trial Assessing the Combination of Sulfasalazine with Standard of Care Induction Therapy in Newly Diagnosed Acute Myeloid Leukemias (AML) Patients 60 years or older– the SALMA Study.

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : ..... Fax : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
(n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance : |__|__| |__|__| |__|__|__|__|
(jj mm aaaa)

Age : |__|__|__|ans

Date de signature du consentement : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de randomisation : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
.....
.....
.....
.....
.....
.....
.....

☐ Groupe (à compléter*) ☐ Groupe (à compléter*)
*préciser de manière explicite si les personnes concernées ne présentent aucune affection
N° randomisation (si nécessaire) : N° traitement (si nécessaire) :

4. Médicament(s) expérimental(aux) (ME) ou produit(s) assimilé(s) [préciser le(s)quel(s)] avant la survenue de l'EIG
(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
.....	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
.....	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

5. Procédures et actes ajoutés par la recherche *(ex. : biopsies, IRM …)* ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG

.....	|__|__|__|_2_|_0_|__|__|	☐	☐
.....	|__|__|__|_2_|_0_|__|__|	☐	☐

Acronyme : **SALMA**

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

6. Médicament(s) concomitant(s) au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable ***(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)***

Annexe jointe au présent formulaire : ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours (2)	Indication	***Action prise*** *0 : poursuite sans modification de la posologie 1 : arrêt 2 : diminution de la posologie 3 : augmentation de la posologie 4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament 1 : lié au médicament 2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

7. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire
.....
.....
.....

Organe(s) concerné(s) :
.....
.....
.....
.....
.....
.....

Date de survenue des premiers symptômes : |__|__| |__|__| |_2_|_0_|__|__|
Préciser lesquels :
.....

Date d'apparition de l'EIG :
|__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
Heure de survenue : |__||__| hh |__||__| min
☐ *donnée manquante*

Délai entre la date de la dernière administration du ME/produit assimilé ou la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG :
|__||__| / |__||__| |__||__|
jj hh min

Critères de gravité :

☐ Nécessite ou prolonge l'hospitalisation :
du |__|__| |__|__| |_2_|_0_|__|__|
au |__|__| |__|__| |_2_|_0_|__|__| ☐ *en cours*

☐ Décès
☐ Mise en jeu du pronostic vital
☐ Incapacité ou handicap important ou durable
☐ Anomalie ou malformation congénitale
☐ Autre(s) critère(s) médicalement significatif(s), préciser :
.....
.....

L'évènement a-t-il conduit à :
☐ aucune mesure prise concernant le ME
☐ diminution de la posologie du ME ☐ augmentation de la posologie du ME
☐ arrêt définitif du ME
☐ arrêt transitoire du ME, date de reprise : |__|__| |__|__| |_2_|_0_|__|__|
☐ ne sais pas

Récidive de l'EIG après ré-administration : ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
☐ Non applicable

Des mesures symptomatiques ont-elles été prises ?
☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__| Préciser : .....

L'évènement a-t-il conduit à une levée d'insu ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__| ☐ Non applicable **L'évènement fait-il suite à :** - une erreur médicamenteuse ? ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__| - un surdosage ? ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__| - un mésusage ? ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__| - autre (préciser) : ..... ☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|	**<u>Degré de sévérité</u>** ***(à adapter à la recherche) :*** ☐ Léger ☐ Modéré ☐ Sévère

Acronyme : **SALMA**

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Evolution de l'événement

☐ **Décès** Date : |__|__| |__|__| |2|0|__|__|
☐ sans relation avec l'EIG jj mm aaaa
☐ en relation avec l'EIG

☐ **Sujet non encore rétabli**, préciser :
☐ Etat stable ☐ Amélioration ☐ Aggravation

☐ **Résolu :** Date : |__|__| |__|__| |2|0|__|__|
☐ sans séquelles jj mm aaaa
☐ avec séquelles, préciser lesquelles: |__|__| |__|__|
hh min

☐ **Evolution inconnue**

8. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : .....
.....
.....

9. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés].....
.....
.....

10. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

Lié à la recherche : ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**
Lequel : ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**
☐ **à la (aux) procédure(s)/acte(s) de la recherche : la/le(s)quel(les) ?**
La/lequel(le) : ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**
La/lequel(le) : ☐ **Relation certaine** ☐ **Relation probable** ☐ **Relation possible** ☐ **Relation improbable (non exclue)**

☐ **Non :** ☐ **à la progression de la maladie faisant l'objet de la recherche : (à compléter)**
☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) :** .....
☐ **à une maladie intercurrente, laquelle :** .....
☐ **autre, préciser :** .....

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature	Nom : Signature	

18.3 Pregnancy notification form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Notification et suivi d'une grossesse apparue au cours d'une recherche portant sur un Médicament ou produit assimilé***	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE INTERNE :** Référence GED : REC-DTYP-0185

Ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par télécopie au +33 (0)1 44 84 17 99

1. Identification de la recherche

Acronyme : **SALMA**
Code de la recherche :
APHP211176
Eudract: 2022-001269-11

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

Date de notification : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Date de prise de connaissance de la grossesse l'investigateur : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Titre complet de la Recherche : Phase I/II Clinical Trial Assessing the Combination of Sulfasalazine with Standard of Care Induction Therapy in Newly Diagnosed Acute Myeloid Leukemias (AML) Patients 60 years or older– the SALMA Study.

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : Fax :

3. Identification de la personne présentant une grossesse

Référence de la personne : |__|__|__| - |__|__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Date de naissance : |__|__| |__|__| |__|__|__|__|
Date d'inclusion : |_|_| |_|_| |2|0|_|_| Date
de randomisation : |__|__| |__|__| |2|0|__|__|

Groupe de randomisation : ☐ (à compléter) ☐ (à compléter)
Date des dernières règles : |__|__| |__|__| |2|0|__|__|
Et/ou date début de grossesse : |__|__| |__|__| |2|0|__|__|

Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Référence de la personne : |__|__|__| - |__|__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Date de naissance : |__|__| |__|__| |__|__|__|__|
Date d'inclusion : |_|_| |_|_| |2|0|_|_| Date
de randomisation : |__|__| |__|__| |2|0|__|__|
Groupe de randomisation : ☐ (à compléter) ☐ (à compléter)

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux :	**Chirurgicaux :**

Obstétricaux : |__|__| geste |__|__| pare

Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable).*

5. Médicament(s) expérimental (aux) administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	_____ _____ |2|0|_____ ☐ Non administré	_____ _____ |2|0|_____ ☐ En cours		
	_____ _____ |2|0|_____ ☐ Non administré	_____ _____ |2|0|_____ ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

6. Procédures et actes ajoutés par la recherche ***(Barrez l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
	|__|__| |__|__| |_2_|_0_|__|__|		
	|__|__| |__|__| |_2_|_0_|__|__|		

Acronyme : ***SALMA***

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :
REC-DTYP-0192

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre – n° ordre de sélection – initiale nom – initiale prénom

7. Médicament(s) concomitants administré(s) dans le cadre du soin
(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ ***Oui*** ☐ ***Non applicable)***

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_| __|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_| __|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_| __|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

8. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

9. Grossesse en cours ou issue de la grossesse
☐ (faxer un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale)
☐ (compléter ci-dessous)

Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J

☐ Fausse couche
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Grossesse extra-utérine
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Interruption de grossesse → Raison :
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :
Souffrance fœtale : ☐ Non ☐ Oui, précisez :
Mort-né : ☐ Non ☐ Oui, précisez :
Placenta normal : ☐ Oui ☐ Non, précisez :
Liquide amniotique : ☐ Clair ☐ Autre, précisez :
Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

10. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et le faxer)

Sexe : ☐ Masculin ☐ Féminin

Poids : |__| | | | grammes Taille : | | | | cm Périmètre crânien : | | | | cm

APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____		
Malformation(s) congénitale(s) : ☐ Non ☐ Oui, précisez :		
Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :		
Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez : ☐ Non applicable		
Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature :	Nom : Signature :	

18.4 Therapy-related malignancy notification form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) *Direction de la Recherche Clinique et de l'Innovation (DRCI)*	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Formulaire de notification des cancers secondaires/myélodysplasies survenant au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé***	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0191

Ce formulaire doit être dûment complété (4 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.frmailto:)

Il est possible de transmettre les formulaires de notification de cancers secondaires/myélodysplasies au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons.

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

1. Identification de la recherche

Acronyme : SALMA

Code de la Recherche :
APHP211176
Eudract: 2022-001269-11

Titre complet de la Recherche : Phase I/II Clinical Trial Assessing the Combination of Sulfasalazine with Standard of Care Induction Therapy in Newly Diagnosed Acute Myeloid Leukemias (AML) Patients 60 years or older– the SALMA Study.

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance du des cancer secondaire/myélodysplasie par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Risque : ☐ A ☐ B ☐ C ☒ D

Plan expérimental : ☐ Essai non comparatif ☐ Essai comparatif ☐ Double aveugle ☐ Simple aveugle ☐ Ouvert ☐ Randomisé ☐ Non randomisé

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) :
.....
.....
Tél : ..... Fax : .....
Mail : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance : |__|__| |__|__|__|__| (m m a a a a)

Age : |__|__|__|ans

Date de signature du consentement : |__|__| |__|__| |2|0|__|__| (j j m m a a a a)

Date d'inclusion : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
.....
.....
.....
.....
.....
.....
.....
.....
.....

4. Diagnostic du cancer secondaire/de la myélodysplasie

4.1 Diagnostic clinique :

Date du diagnostic : |__|__| |__|__| |2|0|__|__| (j j m m a a a a)

Confirmation histologique : ☐ **Non** ☐ **Oui**

Confirmation cytologique : ☐ **Non** ☐ **Oui**

Diagnostic final retenu :
.....

4.2 Grade : (précisez l'échelle de classification ex : TNM) ☐ Grade 0 ☐ Grade I ☐ Grade II ☐ Grade III ☐ Grade IV
.....

4.3 Grade histologique ☐ Grade 0 ☐ Grade I ☐ Grade II ☐ Grade III ☐ Grade IV

4.4 Si autre classification, précisez :

4.5 Antécédents médicaux pertinents : ☐ Non ☐ Oui, précisez :

Acronyme : **SALMA**

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale - initiale

5. Médicaments/procédures de la recherche

5.1 Médicament expérimental (ME) ou produit assimilé avant la survenue de l'EIG

(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
Sulfasalazine.....	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
.....	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

5.2 Médicaments auxiliaires nécessaires à la réalisation de la recherche : si applicable avant la survenue de l'EIG

(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
Idarubicine.....	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Cytarabine.....	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

5.3 Procédures et actes ajoutés par la recherche *(ex. : biopsies, IRM …)* ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
Prélèvements sanguins.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
ECG.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
Ponction de moelle osseusse.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

6. Précision de l'imputabilité de l'investigateur

6.1 Selon l'investigateur, l'événement indésirable grave (cancer secondaire/myélodysplasie) est (plusieurs cases possibles)

Lié à la recherche :

☐ **Oui :**
- ☐ **au médicament/produit assimilé de la recherche : sulfasalazine**
- ☐ **aux médicaments auxiliaires nécessaires à la réalisation de la recherche :**
  - ☐ **Idarubicine**
  - ☐ **Cytarabine**
- ☐ **à la (aux) procédure(s)/acte(s) de la recherche : la/le(s)quel(les) ?**
  - ☐ **Prélèvements sanguins**
  - ☐ **ECG**
  - ☐ **Ponction de moelle osseuse**

☐ **Non :**
- ☐ **à la progression de la maladie faisant l'objet de la recherche : LAM**
- ☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : .....**
- ☐ **à une maladie intercurrente, laquelle : .....**
- ☐ **autre, préciser : .....**

6.2 La survenue de cet EIG est-elle susceptible d'être liée à un manque d'efficacité du ME ? ☐ **Non** ☐ **Oui**

7. Détails de la chimiothérapie administrée pour traiter la pathologie initiale (phase)

☐ Induction |__|__| |__|__| |_2_|_0_|__|__|	☐ Consolidation |__|__| |__|__| |_2_|_0_|__|__|
j j m m a a a a	j j m m a a a a

☐ Post greffe : renseignez la partie 6.2	☐ Maintenance |__|__| |__|__| |_2_|_0_|__|__| jj mm aaaa
☐ Autre :	☐ Interphase

7.1 Médicament(s) ou produit(s) assimilé(s) de chimiothérapie anticancéreuse ou de thérapie ciblée avant la survenue du cancer secondaire/de la myélodysplasie *(barrez l'encadré si aucun traitement débuté) :*

Nom commercial ou Dénomination Commune International	Date de première administration Ou non administré	Date de dernière administration Ou en cours (2)	Voie d'administration(1)	Posologie / 24h	Lien de causalité avec l'EIG *(Relation selon méthode OMS)*
	|__|__| |__|__||_2_|_0_|__|__| jj mm aaaa ☐ Non administré	|__|__| |__|__||_2_|_0_|__|__| jj mm aaaa ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
	|__|__| |__|__||_2_|_0_|__|__| jj mm aaaa ☐ Non administré	|__|__| |__|__||_2_|_0_|__|__| jj mm aaaa ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)
(2) En cours au moment de la survenue de l'EIG

7.2 Greffe de cellules souches hématopoïétiques (CSH) pour le traitement de la pathologie initiale :

☐ Non ☐ Oui, précisez ci-dessous :

Date de la greffe : le |__|__| |__|__| |_2_|_0_|__|__| jj mm aaaa ☐ autogreffe ☐ allogreffe	Si allogreffe : Donneur : ☐ apparenté ☐ fichier volontaires / banque
Origine CSH : ☐ CSP ☐ Moelle osseuse ☐ Sang de cordon	
Date de sortie d'aplasie : |__|__| |__|__| |_2_|_0_|__|__| jj mm aaaa	

7.3 Traitements de conditionnement de la greffe (immunosuppresseurs, irradiation corporelle, etc.) :

☐ Non applicable ☐ Applicable, précisez ci-dessous le schéma thérapeutique :

Nom commercial ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|		

Acronyme : **SALMA**

Référence de la personne se prêtant à la recherche : \|__\|__\|__\| - \|__\|__\|__\|__\| - \|__\| - \|__\|
n°centre - n° ordre de sélection - initiale - initiale

8. Statut de la pathologie initiale à la date de survenue du cancer secondaire/de la myélodysplasie
(Joindre si possible les résultats du dernier myélogramme le cas échéant) **:**

☐ Rémission complète le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|
☐ Rémission avec séquelles le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|, précisez les séquelles :
☐ Rémission partielle le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|, précisez :
☐ Stable depuis le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|
☐ Maladie en progression
☐ Rechute depuis le\|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

9. Traitement du cancer secondaire/de la myélodysplasie

9.1 Hospitalisation(s) :

Hospitalisation (1) du \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\| au \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|
Hospitalisation (2) du \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\| au \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

Hospitalisation (3) du |__|__| |__|__| |_2_|_0_|__|__| au |__|__| |__|__| |_2_|_0_|__|__|

9.2 Intervention chirurgicale : ☐ Non ☐ Oui, précisez ci-dessous :

Type d'intervention chirurgicale :	Date de l'intervention chirurgicale : |__|__| |__|__| |_2_|_0_|__|__|

9.3 Chimiothérapie : ☐ Non ☐ Oui, précisez ci-dessous :

Précisez le schéma thérapeutique, date(s) de début, les posologies et dates de fin si applicable :

9.4 Radiothérapie : ☐ Non ☐ Oui, précisez ci-dessous :

Précisez le schéma thérapeutique et les doses :	Date de début : |__|__| |__|__| |_2_|_0_|__|__|	Date de fin : |__|__| |__|__| |_2_|_0_|__|__|

9.5 Traitement(s) adjuvant(s) : ☐ Non ☐ Oui, précisez ci-dessous :

9.6 Une greffe de CSH a été réalisée pour le traitement du cancer secondaire/de la myélodysplasie : ☐ Non ☐ Oui, précisez ci-dessous :

Date de la greffe : le |__|__| |__|__| |_2_|_0_| __| __| ☐ autogreffe ☐ allogreffe	Si allogreffe : Donneur : ☐ apparenté ☐ fichier volontaires / banque

Origine CSH : ☐ CSP ☐ Moelle osseuse ☐ Sang de cordon

Date de sortie d'aplasie : |__|__| |__|__| |_2_|_0_|__|__|

10. Evolution du cancer secondaire/de la myélodysplasie

10.1 Etat actuel (hors décès)

☐ Rémission complète le |__|__| |__|__| |_2_|_0_|__|__|
☐ Rémission avec séquelles le |__|__| |__|__| |_2_|_0_|__|__|, précisez les séquelles :
☐ Rémission partielle le |__|__| |__|__| |_2_|_0_|__|__|, précisez :
☐ Stable depuis le |__|__| |__|__| |_2_|_0_|__|__|
☐ Maladie en progression
☐ Rechute depuis le|__|__| |__|__| |_2_|_0_|__|__|

10.2 Evolution fatale

Date du décès : |__|__| |__|__| |_2_|_0_|__|__|

Autopsie effectuée : ☐ Non ☐ Oui (joindre le compte-rendu)

Veuillez spécifier la « cause du décès » rapportée dans le certificat de décès / le rapport d'autopsie :

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction :	Nom :	

18.5 SmPC or Investigator's Brochure

SmPC for sulfasalazine, idarubicin and cytarabin available on: http://agence-prd.ansm.sante.fr/php/ecodex/index.php

18.6 List of Sulfa agents and salicylates

Known history of allergy to any drug or exception from the list below excludes the patient from the present trial, as it may favor allergy to SSZ.

Sulfonylarylamines sulfonamides:

- sulfanilamide,
- sulfamethoxazole,
- dapsone,
- amprénavir
- fosamprénavir.

Salicylates:

- acetylsalicylic acid (aspirin),
- 5-aminosalicylic acid (mesalazine).

SSZ excipients:

- Pegylated starch,
- magnesium stearate,
- colloidal silica.

There is no data supporting a risk of cross-reactivity between non-sulfonylarylamines (furosemide, hydrochlorothiazide, glibenclamide or celecoxib) and SSZ.[36,37] Inclusion of patients with previous history of allergic reaction to these non-sulfonylarylamines sulfamides should be discussed with the *Coordinating Investigator*.

18.7 Recommended post-induction therapy

Salvage/induction2

For an eventual salvage/induction2 course, intermediate dose of cytarabine (IDAC) should be generally used and adapted to patient's age (60-70 years and >70 years old), comorbidities and residual toxicities.

Drug	Doses	Administration	Days	Time
Cytarabine*, **	60-69 years: 1500 mg/m^2/12h ≥70 years: 1000 mg/m^2/12h	IV, 2 h	3 days	Days 1, 2, 3

** Patients with a glomerular filtration rate (GFR) 30-59 ml/min should have a 50% dose reduction. Cytarabine is not recommended in patients with a GFR < 30 ml/min.*

***The body area should not be capped to 2 m^2. Cytarabine dosage must be reduced to 1000 mg/m²/12h in patients 70 years or older.*

Patients in CR/CRp after the 1 (respectively 2) courses of chemotherapy should receive 2 (respectively 1) consolidation cycles.

Consolidation cycles

These cycles should be administered every 30-45 days, according to recovery from cytopenias (neutrophils > 1.5 x10^9/L and platelets > 100 x10^9/L) and resolved toxicities (≤ CTCAE 5.0 grade 2).

Drug	Doses	Administration	Days	Time
Cytarabine*, **	60-69 years: 1500 mg/m^2/12h ≥70 years: 1000 mg/m^2/12h	IV, 2 h	3 days	Days 1, 2, 3

** Patients with a glomerular filtration rate (GFR) 30-59 ml/min should have a 50% dose reduction. Cytarabine is not recommended in patients with a GFR < 30 ml/min.*

***The body area should not be capped to 2 m^2. Cytarabine dosage must be reduced to 1000 mg/m²/12h in patients 70 years or older.*

Patients should receive **2 consolidation cycles** (or 1 salvage + 1 consolidation), even those who will proceed to allogeneic stem cell transplantation (HSCT).

Allogeneic Stem Cell Transplantation (HSCT)

HSCT indication, timing and procedure are left at the investigator's decision.

Oral azacitidine (Onureg®) maintenance

Patients achieving CR or CRi and not eligible for HSCT should receive maintenance with oral azacitidine (Onureg®) per SmPC. Maintenance should be initiated after completion of the 2 consolidation (or 1 salvage + 1 consolidation) cycles and after recovery from cytopenias (neutrophils > 1.5 x10^9/L and platelets > 100 x10^9/L) and resolved toxicities (≤ CTCAE 5.0 grade 2).

18.8 Description of the Clinical Trial in the AP-HP Trials Register

Vous êtes potentiellement éligible à cette étude parce que vous avez 60 ans ou plus et venez récemment d'être diagnostiqué d'une leucémie aigüe myéloïde (LAM) traitable par une chimiothérapie intensive standard.

L'étude de vos cellules leucémiques a montré qu'elles n'étaient pas porteuses d'anomalies de gènes qui vous aurait rendu éligible à des médicaments particuliers en plus de la chimiothérapie.

Vous devez recevoir une chimiothérapie intensive standard. Celle-ci débute par une cure dite « d'induction » selon un schéma « 3+7 », c'est-à-dire combinant 3 jours de traitement par des perfusions brèves d'une chimiothérapie appelée idarubicine et 7 jours de traitements par une perfusion continue de cytarabine (aussi appelée aracytine).

La cure d'induction vise à obtenir la rémission complète, c'est-à-dire l'absence de cellules leucémiques visibles lors de l'examen de votre moelle osseuse au microscope et le fonctionnement à nouveau normal de votre moelle osseuse. Même lorsqu'elles ne sont plus détectables au microscope, de rares cellules leucémiques résiduelles peuvent persister dans le sang et dans la moelle osseuse. Il faut alors des examens de laboratoire plus élaborés (cytométrie en flux, biologie moléculaire) pour les énumérer. Ces rares cellules leucémiques persistantes forment ce que l'on appelle la « maladie résiduelle ». Leur élimination nécessite la poursuite des traitements après la cure de chimiothérapie d'induction.

La recherche à laquelle nous vous proposons de participer porte sur l'ajout à la chimiothérapie d'induction standard « 3+7 » d'un médicament appelé sulfasalazine. La recherche vise à évaluer chez des patients de 60 ans ou plus et récemment diagnostiqués d'une LAM si l'ajout de ce médicament (sulfasalazine) est sans danger, et s'il augmente le taux de rémission complète profonde, c'est-à-dire d'une rémission complète associée à une maladie résiduelle dite « négative » (cellules leucémiques indétectables ou inférieures à 0,1% des cellules analysées par cytométrie en flux).

L'obtention d'une rémission complète avec maladie résiduelle négative présage souvent d'une rémission prolongée.

La sulfasalazine n'est pas une nouvelle molécule. Ce médicament est utilisé (et dispose d'un enregistrement) depuis plus de 40 ans dans le traitement d'autres pathologies (certains rhumatismes inflammatoires et des maladies inflammatoires chroniques de l'intestin). Dans le cadre de la recherche qui vous est proposée, la sulfasalazine s'administre par voie orale, sous forme de comprimés qui doivent être pris 2 à 4 fois par jour pendant 8 à 15 jours.

De récents travaux de recherche ont montré que la sulfasalazine provoquait la mort des cellules de LAM et, en outre, augmentait l'effet anti-leucémique de chimiothérapies de type 3+7, notamment de la classe des anthracyclines (comme l'idarubicine). Le mécanisme d'action de la sulfasalazine a pu en être caractérisé avec précision. Ces travaux ont été présentés dans des congrès médicaux internationaux et font l'objet d'une publication dans un journal scientifique. Si vous avez des connaissances en biologie cellulaire n'hésitez pas à poser des questions sur ces travaux au médecin qui vous propose cette étude.

La recherche à laquelle nous vous proposons de participer comporte successivement deux phases :

- La première (phase 1) est une recherche de dose : elle porte sur la tolérance, l'évaluation de la dose maximale tolérée, et l'identification de la dose recommandable devant être administrée à la phase suivante (phase 2) du médicament sulfasalazine lorsqu'il est combiné avec la chimiothérapie standard d'induction « 3+7 », associant perfusion d'idarubicine

et cytarabine comme indiqué ci-dessus ;

- La seconde (phase 2) permet de confirmer la bonne tolérance de la sulfasalazine à la dose recommandée pour la phase 2 lorsqu'elle est combinée à la chimiothérapie « 3+7 », et d'évaluer de façon préliminaire l'efficacité de l'ajout de la sulfasalazine avec la chimiothérapie standard d'induction « 3+7 ».

Si vous participez à la phase 1 de cette étude, la dose de sulfasalazine qui vous sera administrée dépendra de votre ordre d'entrée dans l'étude et de la tolérance de ce médicament en combinaison avec la chimiothérapie « 3+7 » chez les patients atteints de LAM précédemment traités dans le cadre de cette recherche.
Si vous participez à la phase 2, la dose de sulfasalazine qui vous sera administrée en combinaison avec la chimiothérapie « 3+7 » aura été identifiée à la fin de la première phase de cette étude.
Pour répondre à la question posée dans la recherche, il est prévu d'inclure au total un maximum de 64 personnes présentant une LAM récemment diagnostiquée traités dans une dizaine de services d'hématologie différents, tous localisés en France
Vous trouverez ci-dessous quelques explications sur votre maladie susceptibles d'éclairer l'objectif de cette étude :

La leucémie aigüe myéloïde est l'accumulation dans la moelle osseuse et parfois dans le sang de cellules cancéreuses leucémiques. Les autres cellules du sang normalement fabriquées par la moelle osseuse ne sont plus produites, et la leucémie est responsable de la baisse des globules rouges (anémie) de la baisse des plaquettes (thrombopénie, avec un risque de saignement) et de la baisse des globules blancs normaux responsables d'un déficit immunitaire à l'origine d'infections souvent bactériennes qui peuvent être sévères. La leucémie aigüe myéloïde est une maladie grave qui en l'absence de traitement est d'évolution défavorable en quelques mois.

La chimiothérapie standard d'induction (« 3+7 ») conduit, indépendamment de l'effet de la sulfasalazine, à une aplasie transitoire qui correspond à l'arrêt de la production des globules du sang par la moelle osseuse, pendant laquelle une hospitalisation en chambre seule est requise. Pendant cette période, des transfusions de globules rouges et de plaquettes sont nécessaires et il est fréquent d'avoir recours à des antibiotiques. Ces contraintes et ces soins sont liés à la cure d'induction standard et ne sont pas imposées par la recherche.

Comme vous l'avez compris, cette cure d'induction permet souvent d'obtenir une rémission complète de votre maladie.

Après votre cure d'induction, même si la rémission induite est comme expliqué plus haut, « complète et profonde » vous devrez recevoir des cycles supplémentaires de chimiothérapie (dite alors de consolidation) pour éviter que la LAM ne revienne (ne « rechute »). Ces cures de consolidation peuvent induire elles aussi des aplasies transitoires, le plus souvent plus courtes que celle qui fait suite à la cure d'induction. Il est aussi possible que l'on vous propose de recevoir une greffe de moelle le plus souvent après un premier cycle de consolidation. Il s'agit de la transfusion de cellules issues du sang ou de la moelle osseuse d'un donneur en bonne santé, cellules capables de fabriquer tous les éléments du sang (on parle en langage médical de « greffe allogénique de cellules souches hématopoïétiques »). Le donneur peut appartenir à votre famille, ou ne pas être apparenté mais être un volontaire pour le don des cellules issues de la moelle osseuse. Dans tous les cas ces cellules greffées devront être génétiquement suffisamment semblables aux vôtres. En l'absence de greffe, il est également possible que votre médecin vous propose de recevoir un traitement dit « d'entretien » (ou « de maintenance ») par des comprimés d'Onureg®, 14 jours par mois. A chaque début de cycle de chimiothérapie de consolidation ou avant la greffe de moelle, puis tous les 3 mois pendant l'année suivant la fin de la cure d'induction, une visite médicale aura lieu dans le cadre de la recherche pour recueillir des informations sur votre état de santé (examen clinique, examens biologiques de routine). Aucune procédure supplémentaire ne

sera imposée par la recherche (notamment prélèvement de moelle osseuse) pendant cette période.

La sulfasalazine ne sera ajoutée qu'à la chimiothérapie d'induction (« 3+7 »). En outre, même si, au terme de cette étude, ce médicament s'avérait efficace et bien toléré, il ne dispenserait pas des traitements complémentaires par chimiothérapie de consolidation, éventuellement greffe de moelle, et/ou traitement d'entretien par Onureg®.

Un an après la fin de votre chimiothérapie d'induction, une visite médicale sera organisée à l'occasion de votre sortie d'étude. Après votre sortie d'étude, des informations sur le statut de votre maladie (rémission ou rechute) et votre devenir seront cependant ponctuellement demandés par les organisateurs de la recherche à votre médecin pendant les 5 ans suivant la fin de la recherche, sans que vous ne soyez personnellement dérangé.

Vous pouvez retrouver des informations concernant la LAM et ses traitements sur les sites des groupes coopérateurs français ALFA (www.alfa.leukemia.org) et FILO (FILO- leucémie.org).

18.9 Statistical article (Andrillon, Chevret, Lee, Briard, 2020)

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Dose-finding design and benchmark for a right censored endpoint

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ABSTRACT

Dose-finding trials aim to determine a safe dose to be tested in larger trials for efficacy. In oncology, designs generally assume conventional monotonic increasing dose-toxicity relationships, mostly with binary outcomes (e.g., dose-limiting toxicity or not), measured in the first cycle of therapy or for a fixed number of cycles. However, with new anti-cancer agents such as molecularly targeted therapies and immunotherapies, late-onset toxicities have become more frequent. Designs with prolonged observation windows and censored endpoints analyzed using survival models, appear particularly suited to these settings. Moreover, in this setting, the observation of the late-onset toxicity endpoint could be precluded by trial discontinuation due to death, progression, patient withdrawal, or physician discretion, defining a competing event to toxicity. We propose extensions of the Continual Reassessment Method (CRM) dose-finding design using survival working models for right-censored endpoints and for handling treatment discontinuation in the toxicity observation window, namely the Survival-CRM (Surv-CRM) and the informative survival-CRM (iSurv-CRM). We also developed a benchmark approach for its evaluation. In a simulation study, we compared the performance of the Surv-CRM and iSurv-CRM, to those of the Time-to-event (TITE)-CRM and the nonparametric benchmark. The performance of the proposed methods was consistent with the complexity of scenarios as assessed by the nonparametric benchmark. Without treatment discontinuations, the Surv-CRM provides proportions of correct dose selection close to those of the TITE-CRM with fewer observed toxicities and patients assigned to overtoxic dose levels. In the presence of treatment discontinuation, the iSurv-CRM outperforms the TITE-CRM in identifying the correct dose level.

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Dose-finding; survival data; late-onset toxicity; competing risks; treatment discontinuation; benchmark

1. Introduction

The general goal of a phase I cancer clinical trial is to define an "acceptable," usually safe, dose level among several candidates. Toxicity is generally assessed in the first cycle of treatment, based on the observation of dose limiting toxicities (DLT), assuming a monotonic increasing dose-DLT relationship. This optimal paradigm does not work when considering the new classes of anti-cancer agents, such as molecularly-targeted therapies (MTAs) and immunotherapies drugs. Indeed, their modes of action, often targeting the immune system or cancer-cell specific pathways, differ from those of cytotoxic chemotherapies. In particular, new agents may confer late-onset toxicities, related to their specific pharmacology or to prolonged administration, contrary to cytotoxic chemotherapies, that are mainly associated with acute severe toxicities and interval administration (Mathijssen et al. 2014; Postel-Vinay et al. 2011; Wages et al. 2018). Thus, new agents require the use of specific designs with prolonged observation windows (Postel-Vinay et al. 2014) and dose optimization for drugs in later phases of development (Lee et al. 2016,

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2019). Furthermore, with longer observation windows, treatment discontinuations during the trial, due to death, progression, patient withdrawal or physician discretion may occur. Toxicity assessment may be precluded by termination of the patient's exposure to the drug.

Some designs have been adapted for continuous accrual and incomplete observations during trials, such as the Time-to-Event Continual Reassessment Method (Cheung and Chappell 2000; Wheeler et al. 2018; Yuan and Yin 2009). The TITE-CRM design addresses the issue of late-onset toxicity by allowing staggered patient accrual relaxing the need for complete DLT follow-up of previously included patients. By allowing the enrollment of new patients when previous patients are still under observation, it is suitable for long observation windows and late-onset toxicities. Moreover, it can shorten the duration of a trial compared to the standard CRM. Although the TITE-CRM handles incomplete observations it relies on binary endpoints for toxicity and does not take into account the time to occurrence of toxicity. Furthermore, even if some practical strategies address treatment discontinuation, operating characteristics of the design may be impacted (Biard et al. 2020). To handle late-onset toxicities while allowing for continuous accrual, we propose new dose-finding designs, the survival-CRM (Surv-CRM) and the informative survival CRM (iSurv-CRM), that formally include the information of time to toxicity using a survival working model for right-censored endpoints, thus allowing the toxicity outcomes to be delayed or unobserved due to competing events within the trial observation window.

As for any clinical trial design, it is crucial to have diagnostic tools to evaluate the performance of a newly proposed design in term of false/correct trial conclusion. O'Quigley et al. (2002) first introduced the nonparametric optimal benchmark to provide an upper bound estimate on the performance of a dose-finding design in the setting of binary toxicity endpoints, under a given scenario, and at a fixed sample size. These benchmark values for dose selection provide meaningful information on the complexity of scenario in terms of maximum tolerated dose (MTD) identification and provide a reference for the performance of a dose-finding algorithm with complete potential information, that is, as if outcomes could be observed at all dose levels for all patients. It contrasts with real clinical trials, in which patients are allocated to receive only one dose level, thus resulting in *incomplete information* due to non observation of patient outcomes at all other dose levels. Cheung (2014) developed the benchmark for phase I/II clinical trials simultaneously evaluating binary toxicity and efficacy endpoints, or for phase I trials with multiple toxicity endpoints. Similarly, Mozgunov et al. (2020) generalized a benchmark for dose finding designs to various settings with several discrete and continuous outcomes. To our knowledge, no specific benchmark approaches for survival dose-finding models has been implemented.

In this work, we propose the survival-CRM (Surv-CRM) design building on the CRM dose-finding design, but using survival models for right-censored DLT endpoints allowing the outcomes to be delayed. To handle possible informative censoring, we also propose the informative survival-CRM (iSurv-CRM), that extends the Surv-CRM by considering a competing-risk model. In addition, we develop a nonparametric benchmark approach for evaluation of dose-finding designs with right censored time-to-event endpoints.

2. Methods

We consider dose-finding clinical trials where patients are followed-up for an observation window $[0, t^*]$ defined for DLT observation and safety assessment. By time t^*, a patient may have two different outcomes: DLT under treatment or not. In the case of novel agents, the need for prolonged observation windows leads us to consider a time-to-event working model which allows for right-censored observations.

Denote n the maximum sample size of the trial. Let $\mathbb{D} = \{d_1, d_2, \ldots, d_m\}$ be the set of numerical labels for the m doses investigated in the trial. We assumed no censoring due to lost to follow-up.

Given our framework of oncology phase I dose-finding trials, where patients are usually in advanced stage of their disease, such an assumption is likely valid.

2.1. Problem formulation

2.1.1. Survival-CRM design (Surv-CRM)

We first considered censoring occurs during trial accrual only, at the time a dose assignment computation, when a fraction of the toxicity window has been observed for some patients and they have not developed any DLT yet. In this setting, censored observations are administrative, and thus independent from the time-to-toxicity endpoint, and could be considered as noninformative.

Let T, be the time to first DLT and define $\lambda(t)$ the instantaneous hazard function, and $\Lambda(t)$ the cumulative hazard function:

$$\Lambda(t) = \int_0^t \lambda(s)\,\mathrm{d}s. \tag{1}$$

The survival function $S(t)$, that is the probability of being free of DLT at time t, is given by:

$$S(t) = exp(-\Lambda(t)). \tag{2}$$

and the cumulative incidence function, $F(t) = Prob(T \leq t) = 1 - S(t)$, can be expressed as:

$$F(t) = \int_0^t f(s)\,ds \;=\; \int_0^t \lambda(s)\,S(s)\,ds \tag{3}$$

where $f(\cdot)$ is the density function of the time to DLT, T.

At the end of a dose-finding trial, given an observation window $[0, t^\star]$, for each included patient , $i, i = 1, \ldots, n$, observations consist in pairs $(X_i^\star, Y_i^\star)$, where $X_i{}^\star = min(T_i, t^*)$ and $Y_i = \mathbb{I}\,(T_i \leq t^*)$, with $I(\cdot)$ the indicator function ($Y_i = 1$ if the patient experienced a DLT before t^*, or $Y_i{}^* = 0$ otherwise).

During the trial, at the time of the dose assignment for a new patient, DLT observations of previously included patients may be right-censored, if only a fraction of the observation window has passed and the patient has not developed any DLT yet. For the MTD estimation during the trial at date τ, we therefore updated data on patient i such as: (X_i^τ, Y_i^τ) where $X_i{}^\tau = min(T_i, \tau - \tau_1^0)$ and $Y_i{}^\tau = \mathbb{I}\,(T_i \leq \tau - \tau_i^0)$, where τ_i^0 is the date of arrival of patient i.

The proposed survival-CRM is an extension of the CRM with an exponential working model for the cumulative incidence of DLT. Specifically, we assumed T to be exponentially distributed and we assumed the instantaneous hazard of toxicity as an increasing function of the dose:

$$\lambda_j(\beta, d_j) = exp(d_j \times exp(\beta)),\;\; \text{for } j \in \{1, \ldots, m\} \tag{4}$$

where β is the unknown model parameter considered a random variable with a prior distribution $\Phi(\beta)$ assumed. Given our setting of right-censored data, the exponential distribution was chosen to model failure times. The cumulative incidence of toxicity at the end of observation window t^* for dose $d_j \in \mathbb{D}$ is then defined as follows:

$$F(t^*, \beta, d_j) \;=\; 1 - exp(t^* \times \exp\,(d_j \times \exp(\beta))) \tag{5}$$

The survival likelihood on n patients can be expressed as follows:

$$L_n(X, Y|\beta) = \prod_{i=1}^{n} f(X_i, \beta, d_i)^{Y_i} S\big(X_j, \beta, d_i\big)^{1-Y_i} \tag{6}$$

with $d_i \in \mathbb{D}$, the dose allocated to patient i, X_i the right-censored time-to-toxicity and Y_i the toxicity outcome.

Given the prior distribution of β, $\Phi(\beta)$, the posterior distribution for β is estimated using Bayes formula:

$$\Phi(\beta|\,(X,Y)) \;=\; \frac{L_n(X,Y|\,\beta)\Phi(\beta)d\beta}{\int_{-\infty}^{\infty} L_n(X,Y|\beta)\Phi(\beta)d\beta} \tag{7}$$

and the posterior mean $\hat{\beta}_n$ can be plugged in equation (5) to obtain estimates of the DLT cumulative incidence at each dose level:

$$\hat{\beta}_n \;=\; \frac{\int_{-\infty}^{\infty} \beta\, L_n(X,Y|\,\beta)\Phi(\beta)d\beta}{\int_{-\infty}^{\infty} L_n(X,Y|\beta)\Phi(\beta)d\beta} \tag{8}$$

2.1.2. Informative survival-CRM design (iSurv-CRM)

We then considered non negligible occurrences of treatment discontinuation in the observation window $[0, t^*]$ due to disease progression, death, withdrawal, and physician discretion, that preclude complete or reliable DLT assessment. In this setting, DLT and discontinuation of treatment are mutually exclusive events within $[0, t^*]$. We thus extended the survival-CRM (Surv-CRM) to the informative survival-CRM (iSurv-CRM) by considering a competing-risk working model in the dose-finding setting.

In a competing risks framework (Putter et al. 2006), let $k = 1$ denote the occurrence of DLT and $k = 2$ that of treatment discontinuation. Let $\lambda_{jk}(t)$ be the cause-specific hazard and $\Lambda_{jk}(t)$ the cause-specific cumulative hazard of cause k at dose d_j. The cause-specific hazard for toxicity $\lambda_{j1}(\cdot)$ was defined according to equation (4) and the cause-specific hazard of discontinuation $\lambda_{j2}(\cdot)$ as follows:

$$\lambda_{2j}(\beta_2,\, d_j) \;=\; \exp(-d_j \times \exp(\beta_2)), for\, j \in \{1, ..., m\} \tag{9}$$

resulting in a decreasing function of the dose. The cumulative incidence of DLT, at time t^* for dose level j, corresponding to a subdistribution function, depends on cause 2 through:

$$F_1(t^*, \lambda_{1j},\, \lambda_{2j}) \int_0^{t*} \lambda_{1j} \,\times\, S(s)ds \;=\; \frac{\lambda_{1j} \,\times\, (1 - exp(-(\lambda_{1j} + \lambda_{2j}) \times t^*))}{\lambda_{1j} + \lambda_{2j}} \tag{10}$$

where the event-free survival at time t is defined by:

$$S(t) \;=\; exp(-(\Lambda_1(t) + \,\Lambda_2(t))) \tag{11}$$

Inference on cause–specific hazards may then be performed separately for toxicity and treatment discontinuation, since the log-likelihood factors into two pieces, one involving λ_1 and the other involving λ_2 (Jeong and Fine 2006).

2.2. Dose-finding algorithm

The objective of the dose-finding trial is to identify the maximum tolerated dose (MTD), d^*, defined as the dose which has the estimated cumulative incidence of toxicity at time t^* closest to a pre-specified target π_{DLT} among the set $\mathbb{D}$ of candidate dose levels $d_j, j = 1 \ldots, m$:

$$d^* \;=\; \arg\min_{d_j \in\, \mathbb{D}} |\,\hat{F}\,(t^*, \beta, d_j) - \pi_{\,DLT}| \tag{12}$$

In the setting of competing risks, it becomes

$$d^* = \arg\min_{d_j \in \mathbb{D}} |\hat{F}_1(t^*, \lambda_{1j}, \lambda_{2j}) - \pi_{DLT}| \quad (13)$$

2.2.1. Trial design implementation

In the Surv-CRM and iSurv-CRM designs presented above, dose assignments of new patients are performed from the sequentially updated probabilities of DLT, based on available data at the time of analysis. Sequential estimates of the cumulative incidences of DLT were used to assign the estimated dose $\hat{d}^*$ to the next patient cohort. We used a one-stage CRM design, with a Bayesian estimation of the posterior distribution of parameter β (equation (7)), with a normal prior for β, with mean 0 and standard deviation $\sqrt{1.34}$ (O'Quigley and Shen 1996). This prior allowed a reasonable compromise between flexibility and severity for the skeleton, though sensitivity analyses to this choice were also performed. Then, for patient i's dose assignment, initiating a new cohort, we computed the posterior mean $\hat{\beta}_i$ of the model parameter (equation (7)) based on data history $H_i = (X_{i-1}, Y_{i-1})$, and used it as plug-in estimate to obtain estimated cumulative incidences of DLT for each dose level j. The new cohort, starting with patient i, was allocated to the MTD estimate, defined using (13), given H_i. The assignment continued in a sequential fashion until the prespecified sample size n was reached.

2.2.2. Benchmark implementation

For the benchmark, we assumed the whole information about a patient's toxicity outcomes could be summarized in a tolerance profile drawn from a uniform distribution $U(1, 0)$. Precisely, for patient i, with profile u_i, the quantile transformation $T_{ij} = F^1(u_i, \lambda_j)$ was applied to obtain the time to DLT outcome that this patient would have had at each dose level j, with F the assumed cumulative distribution function of time-to-toxicity, in our case an exponential distribution. Independent administrative censoring was then applied at time t^* to obtain trial observations. Basically, for a given patient i, this results in a set of outcomes at each of the m candidate dose levels, $(X^*_{i1}, Y^*_{i1}), \ldots, (X^*_{im}, Y^*_{im})$, $i = 1, \ldots, n$, also called the *complete information* about patient i.

Given our setting of right-censored data and in the absence of informative censoring, the non parametric Kaplan Meier estimator was used to estimate the cumulative incidences of DLT at each dose j, $\hat{F}(t^*, \lambda_j)$. In the presence of informative censoring, cumulative incidences were estimated as described by Gray (1988). Non parametric estimators for the benchmark were chosen, similarly to the original benchmark proposal for binary endpoints (O'Quigley et al. 2002). In case of a limited sample size n, there might be no DLTs at a given dose level; in these cases, $\hat{F}(t^*, \lambda_j)$ was set to 0. Last, the MTD, d^*, was estimated from the complete dataset as the dose level associated with the estimated probability of toxicity at time t^*, $\hat{F}(t^*, \lambda_j)$ closest to π_{DLT} (equation (13)).

The algorithm presented in Table 1 (Supplementary materials) provides step-by-step guidance on how the benchmark can be constructed based on simulated patient data.

2.3. Simulation study

We simulated trials to assess the performance of our proposed Surv-CRM and iSurv-CRM designs, in comparison to the TITE-CRM and the proposed benchmark.

2.3.1. Data generation

Assuming that the set of probabilities of DLT at time t^* at each dose level is known, complete trial data were generated according to the tolerance profile procedure presented for the benchmark. Inverse transform sampling was applied on the time to DLT cumulative distribution function. We considered time-constant and time-varying toxicity hazards of DLT, using Weibull distributions. Values of 1, 0.5, and 3 were used for the shape parameter to obtain time-constant, decreasing or increasing hazards respectively, given a standardized timeframe for observation $t^* = 1$ (Figure 1), Supplementary

materials). In case of time-varying hazard, Weibull scale parameters were computed from the cumulative incidence of toxicity at time t^* for each scenario, and according to the desired shape value.

Independent administrative censoring was applied at time t^* to mimic the trial observation window and obtain $X_i = min(T_i, t^*)$ and $Y_i = \mathbb{I}(T_i \leq t^*)$. While the trial design only uses the observed outcomes with the doses assigned following the trial algorithm, the performance of the benchmark is obtained using the *complete information* on patient outcomes at each dose level, hence providing the best performance for the dose-finding objective.

Competing risks data were simulated following Beyersmann et al. (2009). Observations were sampled from an exponential model for the time to first event T (event-free-survival), with all-cause hazard $(\lambda_1 + \lambda_2)$ and the cause of failure at the sampled time T_i determined by a random draw from a Bernoulli distribution with probability $\frac{\lambda_1}{\lambda_1+\lambda_2}$ for toxicity (otherwise treatment discontinuation).

2.3.2. Simulation setting

Without loss of generality, we set the observation window t^* to 1 (one time unit). We considered $m = 5$ candidate dose levels, and, within the time window t^*, a target toxicity probability of DLT at $\pi_{DLT} = 0.25$. The sample size was set at $n = 25$, with cohort size of 1.

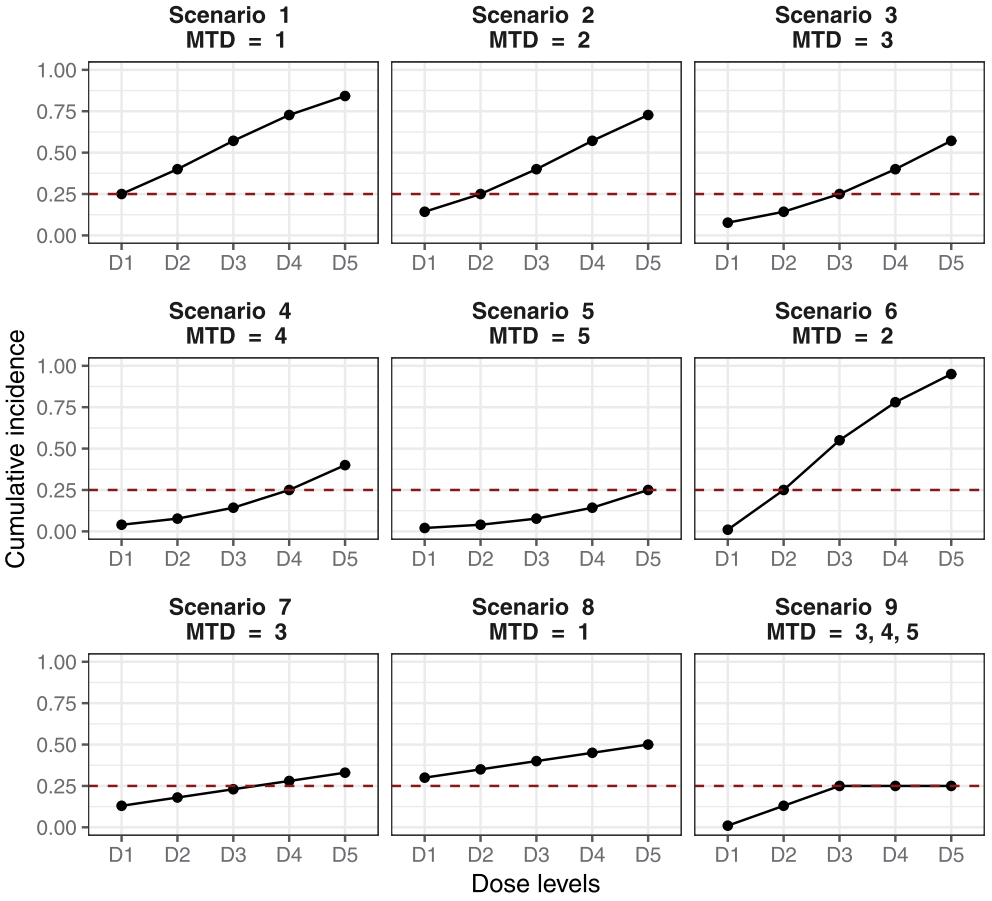

Figure 1. Simulation scenarios: cumulative incidence of DLT at time t^* by dose. Simulated trials included $m = 5$ candidate dose levels.

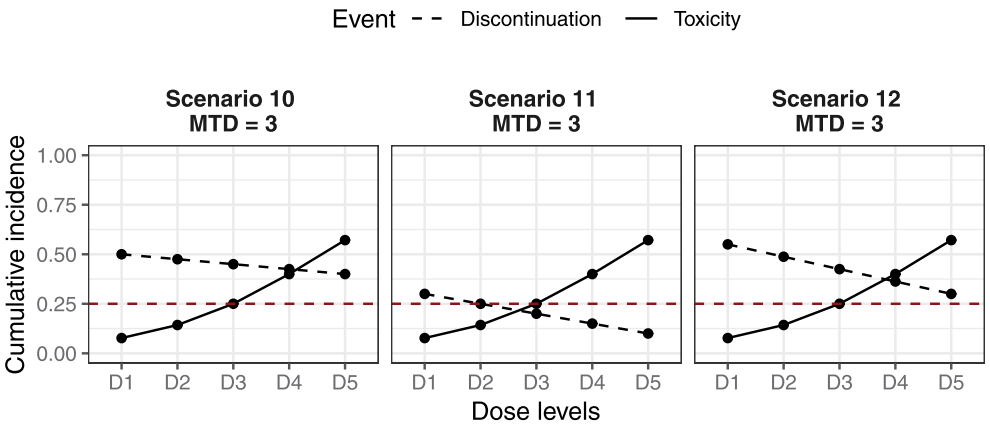

Figure 2. Simulation scenarios: cumulative incidence of DLT (solid line) and discontinuation (dashed line) at time t^* by dose. Simulated trials included $m = 5$ candidate dose levels.

Different non-parametric scenarios of dose-toxicity relationships were examined (Figure 1). They were defined based on the cumulative incidence of DLT at time t^* by dose level and they encompass different shapes of dose-DLT relationships, including monotone increasing (Sc1–Sc8, cytotoxicity scenarios) and plateau (Sc9). For the first five scenarios (Sc1–Sc5), the same interval in DLT probability was chosen between dose levels, with the MTD shifted from dose 1 to dose 5, respectively. The remaining four scenarios were sensitivity scenarios. For scenarios 6 (Sc6), a steeper dose-toxicity curve around the MTD was considered. Scenarios 7 and 8 are similar to scenarios 3 and 1, respectively, but with a less steep slope. Simulations with competing events were performed under three additional scenarios, Sc10 to 12 illustrated in Figure 2. We examined three different dose-discontinuation relationships, combined with toxicity scenario Sc3, previously presented. We considered high and moderate risks of discontinuation with cumulative incidence at t^* decreasing from 0.5 to 0.4 respectively for scenario 10, and from 0.3 to 0.1 for scenario 11. In scenario 12, the cumulative incidence ranges from 0.55 to 0.30.

For a comparison purpose, we also applied a TITE-CRM design to the simulated data. We used the Bayesian framework with an empirical dose-toxicity model and a linear weighting scheme. We applied the TITE-CRM design to all scenarios, without (Sc1–9) and with (Sc10–12) competing discontinuation. For Sc10–12, we handled incomplete toxicity observations caused by competing discontinuation by assigning and maintaining weights throughout the trial to patients without DLT who discontinued the trial during the observation window.

Designs skeletons were calibrated using the indifference interval approach (Lee and Cheung 2009; Wheeler et al. 2019), applied on the toxicity working model estimating the cumulative incidence of toxicity at the end of the observation window defined in equation (5) for Surv-CRM, and based on the empirical model for the TITE-CRM. For the Surv-CRM, we implemented the algorithm described by Lee and Cheung (2009) with target toxicity probability $\pi_{DLT} = 0.25$, $m = 5$ dose levels and dose level 3 as anticipated MTD. Based on 2,000 simulations, on a set of scenarios defined following Lee and Cheung (2009), we set the halfwidth of the indifference interval at 0.05, as providing the highest PCS corresponding to the following skeleton {0.069, 0.151, 0.250, 0.346, 0.426}. For the iSurv-CRM, we calibrated the toxicity skeleton using the best guess prior proposed by Polley (2011), i.e. {0.05, 0.10, 0.25, 0.35, 0.50} and we set the prior estimates of the treatment discontinuation probabilities to {0.50, 0.45, 0.40, 0.35, 0.35} based on clinical considerations. For the TITE-CRM, the halfwidth of the indifference interval was set at 0.07, based on the recommendations of Lee and Cheung (2009), corresponding to the following skeleton: {0.043; 0.124; 0.250; 0.398; 0.542}.

Simulated trials were initiated with the first dose level, d_1. The cohort size was one patient and no dose skipping was allowed during dose escalation. The trial was terminated either when the maximum sample size was reached, or for safety decisions, i.e. if the posterior probability of $F(t^\star|d_1)$ being above the target π_{DLT} was at least 0.95. In the latter, we considered all doses over-toxic and terminated the trial. A modified Surv-CRM with adaptive wait time between two consecutive patients was also examined following the rule proposed by Polley (2011). As a sensitivity analysis, we considered time-constant and time-varying toxicity hazards of DLT and examined different patient accrual schemes by varying the expected number of arrivals per observation window from 1 to 8. Varying the patient-to-window ratio allowed us to simulate short or long observation windows.

2.3.3. Performance measures

A total of $N = 10,000$ independent replications of each scenario were run, using either the survival-CRM or the TITE-CRM design, while benchmark performances were obtained from complete data. Based on those N replicates, for each design, we computed the probability of correct selection (PCS) of the true MTD and safety indexes such as the probability of overdose selection (POS), the average number of patients who experienced a DLT during the trial, and the overdose (OD) number, defined as the average number of patients treated at a dose above the true MTD during the trial (Cheung 2011). We also computed the percentage of early trial stopping for safety decisions, (P_{stop}).

Finally, we calculated the accuracy index, proposed by Cheung (2011), that incorporates information at all dose levels into a single summary measure:

$$\mathcal{A}_n = 1 - m \times \frac{\sum_{j=1}^{m} |p_j - \pi_{DLT}| \times PS_j}{\sum_{j=1}^{m} |p_j - \pi_{DLT}|}$$

where p_j is the true probability of DLT for dose level j and PS_j is the probability of selecting dose level j at the end of the trial. The index summarizes the distribution of the selected doses through a weighted average, accounting for the discrepancy of the scenario around the target, π_{DLT}. It ranges from $1 - m$ to 1, reached when the probability of selecting the MTD is equal to 1 and the true probability predefined associated to the MTD is equal to the target. This measure penalizes selecting doses distant from the true MTD: A_n could be negative when the probability of selecting wrong doses is higher than or equal to $1/m$.

3. Results

Tables 1 and 2 summarize the performance of both trial designs and the benchmark, for respectively the five main scenarios (Sc1–Sc5) and the four sensitivity scenarios (Sc6–Sc9), when patient accrual is set at four patients per time window, in the absence of competing discontinuations.

First, as expected, the performance of the methods depended on the scenario. In the case of constant hazards of toxicity over time, the highest benchmark accuracy index, 0.97, was reached for the steepest scenario (Sc6), while the lowest, 0.13, was observed with the flatest one (Sc7); corresponding benchmark PCS were 96% and 24%, respectively. The performance of the proposed Surv-CRM design were in line with these findings, with accuracy index of 0.81 for Sc6 and 0.19 for Sc7. Indeed, in case of a flat dose-toxicity relationship with dose level 3 being the MTD (Sc7), the proposed design failed to identify the right dose the majority of time (PCS of 30%), in line with the benchmark (PCS of 24%). However, in scenario 7, d_3 and d_4 have DLT probability of 0.23 and 0.28 respectively, so that both are reasonable MTD candidates. Indeed, the proportion of correct selection within a 5%-acceptable region, which captures dose candidates lying closely to the true MTD, is 53% (result not shown). In the case of a true plateau relationship (Sc9), the PCS was 83% for the Surv-CRM versus 80% for the benchmark. For scenarios 2 to 4, with the MTD shifted from dose 2 to 4, PCS was 52% for Sc2,

Table 1. Simulation results for Sc1 to Sc5 of the survival-CRM, TITE-CRM and benchmark: percent of correct selection (PCS); accuracy index (A_{25}); percent of overdose selection (POS); percent of stopped trials for safety (P_{stop}); relative bias (R. bias in estimated probability of DLT at the true MTD); average overdose number (OD); number of observed DLT (No. DLT) and number of patients treated with the true MTD (No. MTD) during the trial. N=10,000 simulated trials with with n=25 and $\pi_{DLT} = 25\%$. Accrual rate of four patients per observation window. (n/a: not applicable).

Method	Hazard	PCS	A_{25}	POS	P_{stop}	R. Bias	OD	No. DLT	No. MTD
S1: 0.25; 0.40; 0.57; 0.73; 0.84									
Surv-CRM	decreasing	79	0.89	21	18	0.044	7.52	7.28	17.48
	constant	79	0.89	21	12	0.032	8.57	7.78	16.43
	increasing	76	0.88	24	4	0.004	10.88	8.79	14.12
TITE-CRM	decreasing	74	0.87	26	14	−0.083	9.07	7.70	15.93
	constant	75	0.87	25	12	−0.073	9.97	8.05	15.03
	increasing	76	0.88	24	9	−0.053	11.56	8.78	13.44
Benchmark		80	0.90	20	.	0.000	.	.	.
S2: 0.14; **0.25**; 0.40; 0.57; 0.73									
Surv-CRM	decreasing	50	0.71	18	2	0.073	5.81	6.29	8.95
	constant	52	0.71	19	1	0.054	6.90	6.73	9.07
	increasing	54	0.71	22	0	0.015	9.20	7.64	9.09
TITE-CRM	decreasing	57	0.73	21	1	0.018	6.85	6.71	10.06
	constant	57	0.73	21	1	0.021	7.71	7.04	9.90
	increasing	57	0.74	20	1	0.027	9.35	7.71	9.49
Benchmark		57	0.74	19	.	0.000	.	.	.
S3: 0.08; 0.14; **0.25**; 0.40; 0.57									
Surv-CRM	decreasing	49	0.56	16	0	0.090	4.99	5.62	8.20
	constant	50	0.57	18	0	0.070	5.98	6.02	8.45
	increasing	53	0.59	20	0	0.031	8.06	6.80	8.59
TITE-CRM	decreasing	53	0.59	19	0	0.072	5.74	5.99	9.04
	constant	54	0.60	18	0	0.070	6.50	6.28	9.08
	increasing	55	0.61	18	0	0.067	8.03	6.84	8.91
Benchmark		57	0.63	19	.	0.000	.	.	.
S4: 0.04; 0.08; 0.14; **0.25**; 0.40									
Surv-CRM	decreasing	47	0.48	15	0	0.106	3.94	4.98	7.91
	constant	49	0.50	16	0	0.084	4.76	5.29	8.26
	increasing	51	0.51	20	0	0.046	6.47	5.84	8.59
TITE-CRM	decreasing	50	0.51	17	0	0.118	4.25	5.22	8.76
	constant	51	0.52	17	0	0.113	4.90	5.44	8.88
	increasing	52	0.53	17	0	0.105	6.20	5.82	8.92
Benchmark		57	0.57	19	.	0.000	.	.	.
S5: 0.02; 0.04; 0.08; 0.14; **0.25**									
Surv-CRM	decreasing	61	0.67	n/a	0	0.105	n/a	4.02	10.13
	constant	63	0.70	n/a	0	0.084	n/a	4.19	11.14
	increasing	69	0.75	n/a	0	0.049	n/a	4.47	12.89
TITE-CRM	decreasing	63	0.70	n/a	0	0.164	n/a	4.13	10.70
	constant	64	0.71	n/a	0	0.158	n/a	4.25	11.39
	increasing	65	0.71	n/a	0	0.148	n/a	4.45	12.64
Benchmark		75	0.80	n/a	.	0.000	.	.	.

50% for Sc3 and 49% for Sc4 compared to 57% with the benchmark. Of note, with flat scenarios, Sc7 and Sc9, the Surv-CRM design slightly outperformed the benchmark.

Additionally, with constant hazards, the probability of overdose selection (POS) with the survival-CRM was slightly lower to that of the TITE-CRM for most of scenarios. In particular, for Sc1 and Sc8, with MTD at the first dose level, the POS was 21% and 32% with Surv-CRM respectively, versus 25% and 43% with the TITE-CRM. In terms of patient safety during the trials, the average number of patients assigned to a dose above the MTD (OD) during the trial ranged from 4.79 to 11.29 using the survival-CRM versus 4.90 to 13.19 using the TITE-CRM. Finally, the average number of patients who experienced a DLT during the trial (No. DLT) was slightly lower with the Surv-CRM compared to the TITE-CRM for all scenarios. All selection performance measures were not markedly modified when the proportion of right-censored observations decreased, due to a slower accrual rate (Table 2, Supplementary material).

Table 2. Simulation results for Sc6 to Sc9 of the survival-CRM, TITE-CRM and benchmark: percent of correct selection (PCS); accuracy index (A_{25}); percent of overdose selection (POS); percent of stopped trials for safety (P_{stop}); relative bias (R. bias in estimated probability of DLT at the true MTD); average overdose number (OD); number of observed DLT (No. DLT) and number of patients treated with the true MTD (No. MTD) during the trial. N=10,000 simulated trials with with n=25 and $\pi_{DLT} = 25\%$. Accrual rate of 4 patients per observation window. (n/a: not applicable).

Method	Hazard	PCS	A_{25}	POS	P_{stop}	R. Bias	OD	No. DLT	No. MTD
S6: 0.01; **0.25**; 0.55; 0.78; 0.95									
Surv-CRM	decreasing	75	0.81	14	0	−0.003	4.72	6.22	13.27
	constant	76	0.81	13	0	0.001	5.60	6.75	12.95
	increasing	76	0.82	12	0	0.006	7.24	7.85	12.42
TITE-CRM	decreasing	82	0.86	12	0	−0.021	4.91	6.67	14.66
	constant	82	0.86	10	0	−0.001	5.51	6.99	14.12
	increasing	80	0.85	7	0	0.033	6.64	7.67	13.01
Benchmark		96	0.97	3	.	0.000	.	.	.
S7: 0.13; 0.18; **0.23**; 0.28; 0.33									
Surv-CRM	decreasing	29	0.15	32	1	0.116	7.46	5.36	5.64
	constant	30	0.19	36	0	0.061	8.58	5.57	5.80
	increasing	30	0.23	44	0	−0.036	10.72	5.95	5.84
TITE-CRM	decreasing	30	0.21	37	1	0.077	8.41	5.55	5.92
	constant	31	0.22	39	1	0.042	9.26	5.71	6.03
	increasing	31	0.25	43	0	−0.021	10.90	5.99	6.03
Benchmark		24	0.13	47	.	0.001	.	.	.
S8: 0.30; 0.35; 0.40; 0.45; 0.50									
Surv-CRM	decreasing	71	0.53	29	27	−0.158	10.20	7.47	14.80
	constant	68	0.51	32	18	−0.184	11.29	7.86	13.71
	increasing	61	0.47	39	6	−0.249	13.76	8.54	11.24
TITE-CRM	decreasing	59	0.47	41	20	−0.316	12.08	7.87	12.92
	constant	57	0.46	43	16	−0.327	13.19	8.10	11.81
	increasing	53	0.43	47	10	−0.354	15.29	8.55	9.71
Benchmark		69	0.51	31	.	−0.002	.	.	.
S9: 0.01; 0.13: **0.25; 0.25; 0.25**									
Surv-CRM	decreasing	81	0.67	n/a	0	0.148	n/a	4.93	16.58
	constant	83	0.71	n/a	0	0.105	n/a	5.12	17.77
	increasing	88	0.79	n/a	0	0.027	n/a	5.42	19.51
TITE-CRM	decreasing	85	0.75	n/a	0	0.231	n/a	5.12	17.64
	constant	86	0.76	n/a	0	0.199	n/a	5.25	18.49
	increasing	87	0.79	n/a	0	0.143	n/a	5.46	19.78
Benchmark		80	0.66	n/a	.	0.000	.	.	.

Compared to constant hazard, the performance of the Surv-CRM in terms of correct selection slightly improved in case of an increasing hazard of DLT (late-onset toxicities), for Sc2–Sc5 (Table 1). However, late-onset toxicities resulted in an increased overdose selection, whereas early-onset toxicities (decreasing hazard) resulted in improved (smaller) POS. In case of an increasing hazard of DLT, though the survival-CRM had a somewhat lower PCS compared to the TITE-CRM, it outperformed the later in terms of estimation (with smaller relative biases) for all scenarios. In terms of patients' safety during the trial, consistently across scenarios, late-onset toxicities increased the average number of patients assigned to toxic doses and the average number of observed DLTs and decreased the average number of patients assigned to the MTD; this was even more obvious as the accrual rate increased (Figures 3, 4 and 5). In line with these safety results, the Surv-CRM favored stopping trials for safety more often when all dose levels were considered over-toxic. In particular, in scenarios 1 and 8 with dose level 1 as MTD, and early toxicities (time-decreasing hazard of DLT), the percentage of early trial stopping for safety was 18% and 27% with Surv-CRM, respectively versus 14% and 20% with the TITE-CRM (Tables 1 and 2). Finally, in most scenarios, with time-varying hazards and varying accrual rate, Surv-CRM was slightly safer than the TITE-CRM during the trial.

The performance of all three methods improved with larger sample sizes (Figure 2, Supplementary material). The PCS was 100% with the benchmark in all scenarios but Sc7,

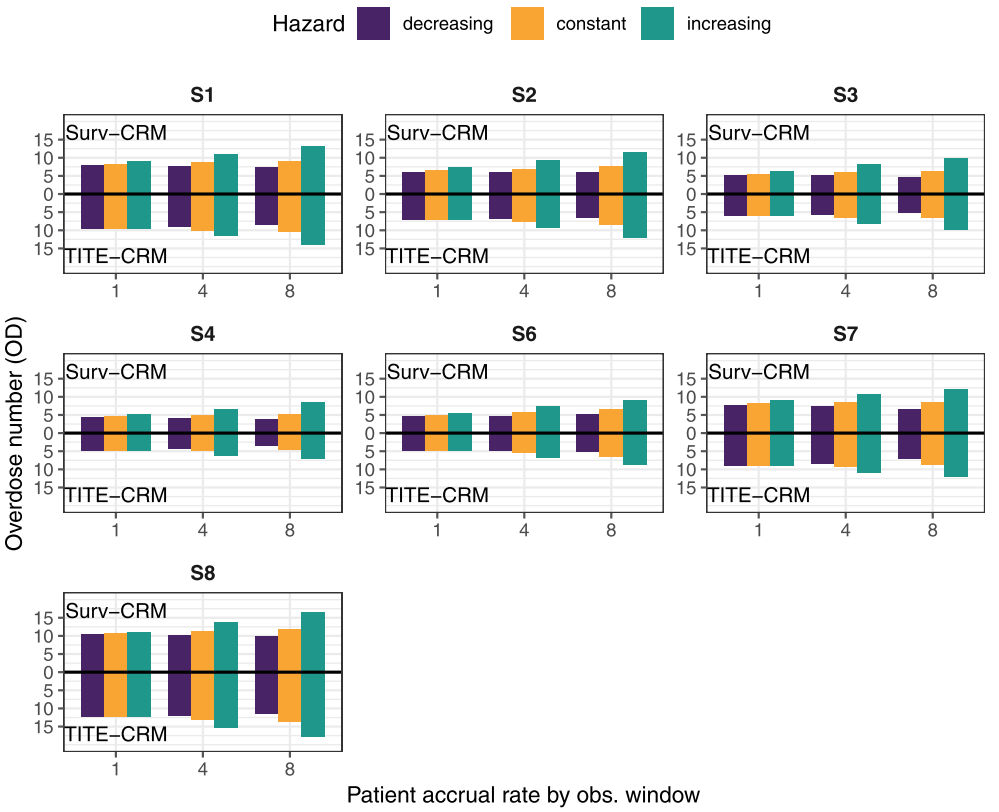

Figure 3. Number of patients administered with a dose above the MTD (OD) during the trial with the survival-CRM (barplots above the x-axis) and TITE-CRM (below) designs according to the patient accrual rate by observation window and the shape of hazard. N=10,000, n=25, and $\pi_{DLT} = 0.25$.

with a minimal sample size varying according to the scenario: from 100 (Sc6) to 300 (Sc4). Consistently, in Scenario 7, using the Surv-CRM and the TITE-CRM, PCS remained low (56% and 58%, respectively), even with $n = 200$.

In the presence of treatment discontinuation precluding complete observation of the toxicity outcomes, simulation results indicated a clear contrast between the informative Surv-CRM and the TITE-CRM (Table 3). The greater the risk of discontinuation, the better the performance of selection with iSurv-CRM compared to TITE-CRM. Indeed, for Sc10 and Sc11 with high and moderate risk of treatment discontinuation, PCS was 60% and 57% with the iSurv-CRM respectively versus 32% and 47% with the TITE-CRM, respectively. For Sc12, the steepest scenario, the iSurv-CRM also outperformed the TITE-CRM (PCS 59% *vs.* 33%). However, the probability of overdose selection ranged from 10% to 18% with the iSurv-CRM, and 3% to 11% with the TITE-CRM. Last, the iSurv-CRM allocated patients to the MTD more frequently than the TITE-CRM.

4. Discussion

In this paper, we propose an extension of the CRM that uses a survival working model to handle right-censored outcomes, the survival-CRM design, and the informative survival-CRM design for trials with a non negligible risk of competing event related to treatment discontinuation during the desired observation window, as well as a benchmark for its evaluation. This work was motivated by the need

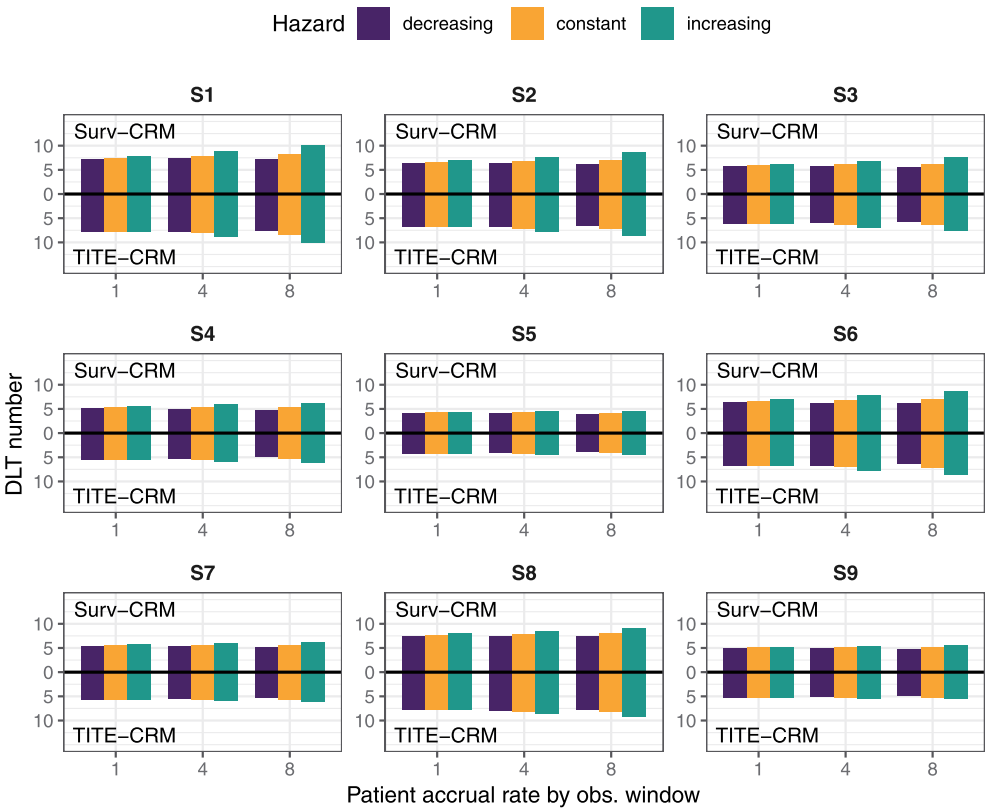

Figure 4. Number of observed DLTs during the trial with the survival-CRM (barplots above the x-axis) and TITE-CRM (below) designs according to the patient accrual rate by observation window and the shape of hazard. N=10,000, n=25, and $\pi_{DLT} = 0.25$.

for specific methods for dose finding with novel anti-cancer agents, such as targeted therapies or immunotherapies, which often require prolonged observation windows and result in some patients who do not experience a DLT but have not yet reached the end of the window. Survival inference relies of survival functions, assuming all patients will developed the event under treatment, with valid inference under independent or noninformative censoring. In our setting when the endpoint of interest is the DLT within some observation window of interest, the survival working models can provide unbiased estimates of cumulative incidence of DLT at the end of the observation window, given the choice of this window is likely independent of the toxicity process. Otherwise, when the rhythm of inclusion is short relatively to the observation window, and the observation of toxicity could be incomplete in patients already included, these data could be also considered administratively, i.e., noninformatively right-censored. Survival models have recently gained interest in dose finding due to the need for prolonged observation window with new anti-cancer therapies. Nevertheless, they have been mostly used in settings with complex endpoints, combining toxicity and efficacy endpoints or multiple response endpoints (Guo et al. 2018, 2019; Yuan and Yin 2009). For instance, Yuan and Yin (2009) proposed to jointly model toxicity and efficacy as time-to-event outcomes using a Weibull distribution for the hazard of toxicity, resulting in three model parameters to estimate, potentially less suited to our setting of Phase I clinical with small sample sizes. Thus, we proposed the Surv-CRM phase I dose-finding design using a one-parameter exponential working model for the dose-toxicity relationship, allowing for the use of those censored observations in the sequential process of MTD estimation during the trial. Nevertheless, when the observation window is long relatively to the underlying disease process, the observation of toxicity may be precluded by trial discontinuation

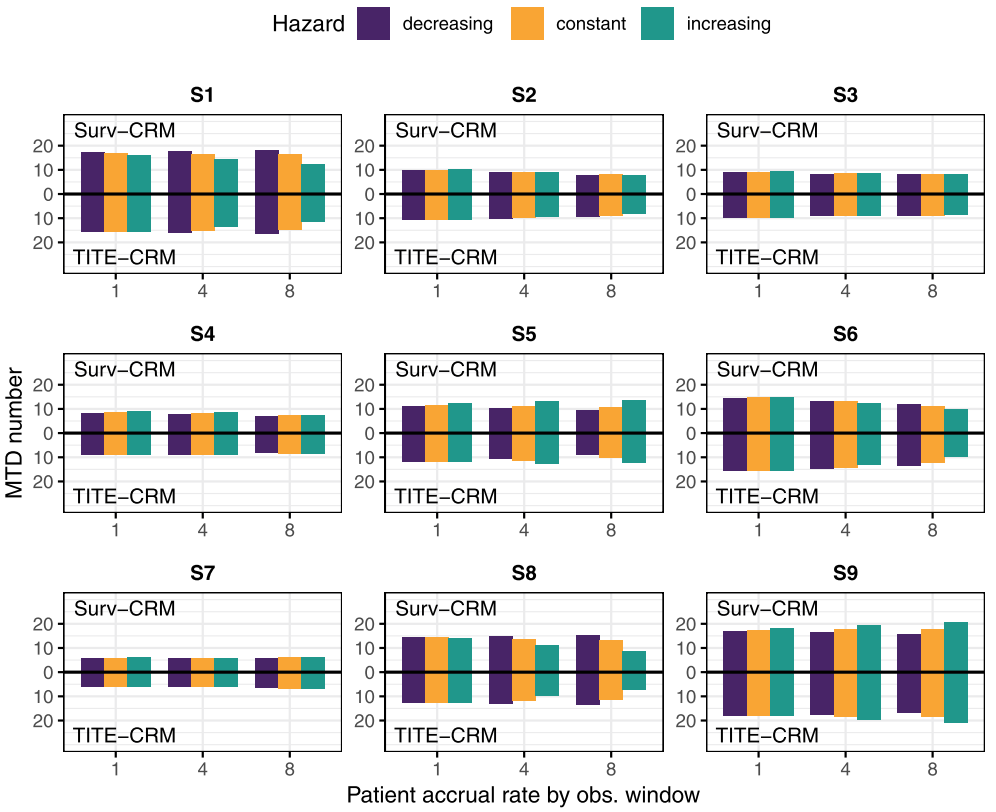

Figure 5. Number of patients treated with the true MTD (correct dose number) during the trial with the survival-CRM (barplots above the x-axis) and TITE-CRM (below) designs according to the patient arrival rate by observation window and the shape of hazard. N=10,000, n=25, and $\pi_{DLT} = 0.25$.

Table 3. Simulation results for Sc10–Sc12 of the informative survival-CRM (iSurv-CRM), TITE-CRM and benchmark: percent of correct selection (PCS); accuracy index (A_{25}); percent of overdose selection (POS); percent of stopped trials for safety (P_{stop}); relative bias (R. bias in estimated probability of DLT at the true MTD); average overdose number (OD); number of observed DLT (No. DLT) and number of patients treated with the true MTD (No. MTD) during the trial. N=10,000 simulated trials with with n=25 and $\pi_{DLT} = 25\%$. Accrual rate of four patients per observation window; time-constant toxicity hazards. (n/a: not applicable).

Method	PCS	A_{25}	POS	P_{stop}	R. Bias	OD	No. DLT	No. MTD
S10: F_1: 0.08; 0.14; **0.25**; 0.40; 0.57 F_2: 0.50; 0.48; 0.45; 0.43; 0.40								
iSurv-CRM	60	0.68	10	0.28	0.133	4.14	28.54	11.51
TITE-CRM	32	0.44	3	0.48	0.447	3.51	28.17	6.80
Benchmark	57	0.62	17	.	−0.004	.	.	.
S11: F_1: 0.08; 0.14; **0.25**; 0.40; 0.57 F_2: 0.30; 0.25; 0.20; 0.15; 0.10								
iSurv-CRM	57	0.63	18	0.08	0.110	5.75	16.56	10.49
TITE-CRM	47	0.57	11	0.15	0.214	5.42	16.65	8.16
Benchmark	56	0.62	17	.	0.000	.	.	.
S12: F_1: 0.08; 0.14; **0.25**; 0.40; 0.57 F_2: 0.55; 0.49; 0.43; 0.36; 0.30								
iSurv-CRM	59	0.66	12	0.27	0.124	4.32	27.84	11.34
TITE-CRM	33	0.44	4	0.54	0.437	3.81	28.18	6.80
Benchmark	57	0.62	16	.	−0.003	.	.	.

related to lack of efficacy of the drug (due to death, progression, withdrawal, etc.). To accommodate

this particular setting, we proposed the iSurv-CRM that uses estimation of the sub-distribution function of toxicity, to define the MTD, rather than that of the survival function.

Although Surv-CRM and TITE-CRM working models are different, the designs performed closely in most simulations in terms of correct dose selection at the end of the trial. Both designs were mostly robust to the rate of right-censored observations, either due to increased patient accrual or to time-varying hazards of DLT (that is, in case of either early or late-onset toxicities). Furthermore, the proposed design outperformed the TITE-CRM in measures of patient safety during the trial; notably, it allowed a reduced number of patients treated at an overtoxic dose level during the trial, and of those experiencing a DLT. Although the main objective of a dose-finding trial is to identify the MTD at the end of the trial, safety for patients enrolled in the trial is a matter of concern, for obvious ethical reasons, in these early phase trials. As we observed in the simulation study, inclusion of an adaptive wait time during the trial as proposed by Polley (2011) in our designs further reduces toxic doses selection without compromising the performances in correctly selecting the true MTD and keeping the trial length within a reasonable constraint. In the presence of competing discontinuations precluding complete observation of the toxicity outcomes, iSurv-CRM clearly outperformed the TITE-CRM for selecting the correct dose, expectedly when informative censoring was high. Additional performance comparisons with designs other than the TITE-CRM also assuming a time-to-event endpoint such as the PoD-TPI recently developed by Zhou et al. (2020) could also be considered in further studies.

To assess the operating characteristics of our proposed survival-CRM design, we developed a non-parametric benchmark approach (O'Quigley et al. 2002), adapted to a working model for censored data using the cumulative incidence of toxicity as the dose-finding endpoint, relying on Kaplan-Meier estimator. This provides an useful tool in assessing the design performance in various toxicity scenarios given a pre-specified sample size. The surv-CRM, as well as the TITE-CRM, outperformed the benchmark in scenarios with flat dose-toxicity relationship, illustrating how parametric methods might, in complex scenarios, combined with small samples sizes, outperform the nonparametric benchmark (Cheung 2011).

In summary, we proposed extensions of the CRM using survival working models for dose finding trials, which fit the natural censoring of data collected in these early clinical trials, and can handle an underlying competing risks framework, together with the corresponding benchmark assessment method. The Surv-CRM design, which provides the flexibility of a survival framework, showed desirable operating characteristics, close to those of the TITE-CRM, while providing a slightly safer profile for patients enrolled in these trials. When trial discontinuations within the observation window are likely to preclude the observation of DLTs in a non-negligible proportion of patients, the iSurv-CRM achieved the best performance in selecting the correct dose and allocating patients to the MTD. It should be considered when designing dose-findings trials of targeted therapies with long observation window in advanced cancer patients where treatment discontinuations are likely to occur.

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Declaration of interest statement

The authors declare that they have no competing interests.

Data availability statement

R code for the use of the Surv-CRM, the iSurv-CRM and the associated benchmark is freely available on GitHub (https://github.com/SurvivalCRM).

References

Beyersmann, J., A. Latouche, A. Buchholz, and M. Schumacher. 2009. Simulating competing risks data in survival analysis. *Statistics in Medicine* 28 (6):0 956–971. doi:10.1002/sim.3516.

Biard, L., B. Cheng, G. A. Manji, and S. M. Lee. 2020. A simulation study of methods for handling disease progression in dose-finding clinical trials. *Journal of Biopharmaceutical Statistics*1–12. doi:10.1080/10543406.2020.1814796.

Cheung, Y. K. 2011. *Dose finding by the continual reassessment method*. Chapman & Hall/CRC Biostatistics Series. New York.

Cheung, Y. K. 2014. Simple benchmark for complex dose finding studies. *Biometrics* 70 (2):0 389–397. doi:10.1111/biom.12158.

Cheung, Y. K., and R. Chappell. 2000. Sequential designs for phase I clinical trials with late–onset toxicities. *Biometrics* 56 (4):82–1177. doi:10.1111/j.0006-341x.2000.01177.x.

Gray, R. 1988. A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Annals of Statistics* 16 (3):0 1141–1154. doi:10.1214/aos/1176350951.

Guo, B., D. Li, and Y. Yuan. 2018. SPIRIT: A seamless phase I/II randomized design for immunotherapy trials. *Pharmaceutical Statistics* 170 (5):0 527–540. doi:10.1002/pst.1869.

Guo, B., Y. Park, and S. Liu. 2019. A utility-based bayesian phase i–ii design for immunotherapy trials with progression-free survival end point. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 68 (2):0 411–425. doi:10.1111/rssc.12288.

Jeong, J.-H., and J. Fine. 2006. Direct parametric inference for the cumulative incidence function. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 55 (2):0 187–200. doi:10.1111/j.1467-9876.2006.00532.x.

Lee, S. M., D. Backenroth, Y. K. Cheung, D. L. Hershman, D. Vulih, B. Anderson, P. Ivy, and L. Minasian. 2016. Case example of dose optimization using data from bortezomib dose-finding clinical trials. *Journal of Clinical Oncology* 34 (12):0 1395–1401. doi:10.1200/JCO.2015.66.0662.

Lee, S. M., M. Ursino, Y. K. Cheung, and S. Zohar. 2019. Dose-finding designs for cumulative toxicities using multiple constraints. *Biostatistics* 20 (1):0 17–29. doi:10.1093/biostatistics/kxx059.

Lee, S. M., and Y. K. Cheung. 2009. Model calibration in the continual reassessment method. *Clinical Trials* 6 (3):38–227. doi:10.1177/1740774509105076.

Mathijssen, R. H. J., A. Sparreboom, and J. Verweij. 2014. Determining the optimal dose in the development of anticancer agents. *Nature Reviews Clinical Oncology* 11 (5):0 272–281. doi:10.1038/nrclinonc.2014.40.

Mozgunov, P., T. Jaki, and X. Paoletti. 2020. A benchmark for dose finding studies with continuous outcomes. *Biostatistics* 210 (2):0 189–201. doi:10.1093/biostatistics/kxy045.

O'Quigley, J., and L. Z. Shen. 1996. Continual reassessment method: A likelihood approach. *Biometrics* 52 (2):0 673–84. doi:10.2307/2532905.

O'Quigley, J., X. Paoletti, and J. Maccario. 2002. Non-parametric optimal design in dose finding studies. *Biostatistics* 3 (1):0 51–56. doi:10.1093/biostatistics/3.1.51.

Polley, M.-Y. 2011. Practical modifications to the time-to-event continual reassessment method for phase I cancer trials with fast patient accrual and late-onset toxicities. *Statistics in Medicine* 30 (17):0 2130–2143. doi:10.1002/sim.4255.

Postel-Vinay, S., C. Gomez-Roca, L. R. Molife, B. Anghan, A. Levy, I. Judson, J. De Bono, J.-C. Soria, S. Kaye, and X. Paoletti. 2011. Phase I trials of molecularly targeted agents: Should we pay more attention to late toxicities? *Journal of Clinical Oncology* 29 (13):01728–1735. doi:10.1200/JCO.2010.31.9236.

Postel-Vinay, S., L. Collette, X. Paoletti, E. Rizzo, C. Massard, D. Olmos, C. Fowst, B. Levy, P. Mancini, P. Lacombe, et al. 2014. Towards new methods for the determination of dose limiting toxicities and the assessment of the recommended dose for further studies of molecularly targeted agents–dose-limiting toxicity and toxicity assessment recommendation group for early trials of targeted therapies, an European organisation for research and treatment of cancer-led study. *Eur J Cancer* 500 (12):0 2040–9. doi:10.1016/j.ejca.2014.04.031.

Putter, H., M. Fiocco, and R. B. Geskus. 2006. Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* 260 (11):0 2389–2430. doi:10.1002/sim.2712.

Wages, N. A., C. Chiuzan, and K. S. Panageas. 2018. Design considerations for early-phase clinical trials of immune-oncology agents. *Journal for ImmunoTherapy of Cancer* 60 (8). doi: 10.1186/s40425-018-0389-8.

Wheeler, G. M., A. P. Mander, A. Bedding, K. Brock, V. Cornelius, A. P. Grieve, T. Jaki, S. B. Love, L. Odondi, C. J. Weir, et al. 2019. How to design a dose-finding study using the continual reassessment method. *BMC Medical Research Methodology* 190 (1):0 1–15. doi:10.1186/s12874-018-0638-z.

Wheeler, G. M., M. J. Sweeting, and A. P. Mander. 2018. A Bayesian model-free approach to combination therapy phase I trials using censored time-to-toxicity data. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 680 (2):0 309–329. doi:10.1111/rssc.12323.

Yuan, Y., and G. Yin. 2009. Bayesian dose finding by jointly modelling toxicity and efficacy as time-to-event outcomes. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 58 (5):0 719–736. doi:10.1111/j.1467-9876.2009.00674.x.

Zhou, T., W. Guo, and Y. Ji. 2020. Pod-tpi: Probability-of-decision toxicity probability interval design to accelerate phase I trials. *Statistics in Biosciences* 120 (1):0 1–22. doi:10.1007/s12561-019-09264-0.