Clinical Trial Protocol

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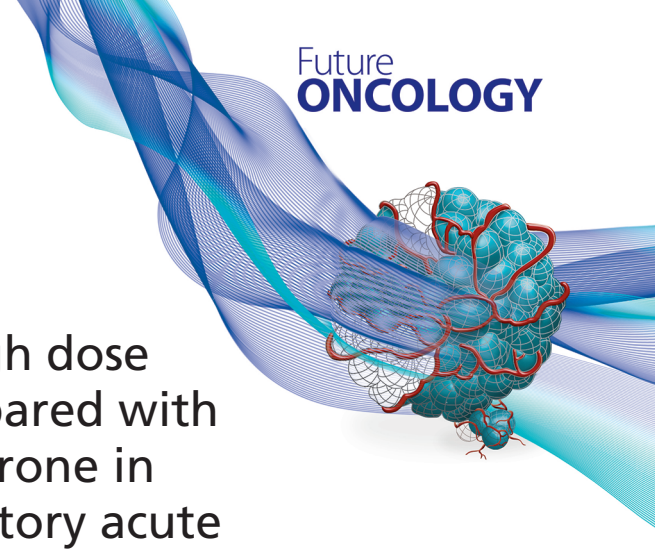

Devimistat in combination with high dose cytarabine and mitoxantrone compared with high dose cytarabine and mitoxantrone in older patients with relapsed/refractory acute myeloid leukemia: ARMADA 2000 Phase III study

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Devimistat (CPI-613®) is an intravenously administered, novel lipoate analog that inhibits two key tricarboxcylic acid (TCA) cycle enzymes, pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase complexes (KGDH). These complexes control TCA cycle entry of glucose and glutamine-derived carbons, respectively. Acute myeloid leukemia (AML) cells upregulate the TCA cycle in response to DNA damaging agents and treatment with devimistat increases sensitivity to them. A Phase I study of devimistat in combination with cytarabine and mitoxantrone produced a complete remission rate of 50% in patients with relapsed or refractory AML. In the combined Phase I/II experience, older patients with R/R AML treated with 2000 mg/m^2 of devimistat had a 52% complete remission/complete remission with incomplete hematologic recovery rate and a median survival of 12.4 months. This report outlines the rationale and design of the ARMADA 2000 study, a Phase III clinical trial of devimistat in combination with high dose cytarabine and mitoxantrone compared with high dose cytarabine and mitoxantrone alone for older patients (≥60 years of age) with relapsed or refractory AML.

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Acute myeloid leukemia (AML) is an aggressive hematologic malignancy characterized by the accumulation of clonal myeloid progenitor cells ('blasts') in the blood or bone marrow. In 2019, an estimated 21,450 individuals will be diagnosed with AML and 10,920 will die of this disease [1]. Outcomes for patients with AML are variable with an approximately 27% 5-year survival rate (SEER database) [2–5]. Older patients with AML have a worse prognosis, especially when treated with traditional cytotoxic chemotherapy [6,7]. A study that looked at the outcome of elderly patients in several clinical trials utilizing front-line cytotoxic chemotherapy found a 5-year survival rate of only 6.6% [6]. This poor prognosis is driven in part from the high prevalence of chromosomal and genetic alterations in older patients with AML that predict a poor response to chemotherapy and a higher probability of relapse [8,9]. Older patients also have a higher incidence of preceding hematological malignancies or prior exposure to chemotherapy and/or radiation. Additionally, genomic instability is a recognized hallmark of aging [10] and AML arising in an older host will have the biological legacy of genomic instability contributing to the higher incidence of poor prognostic

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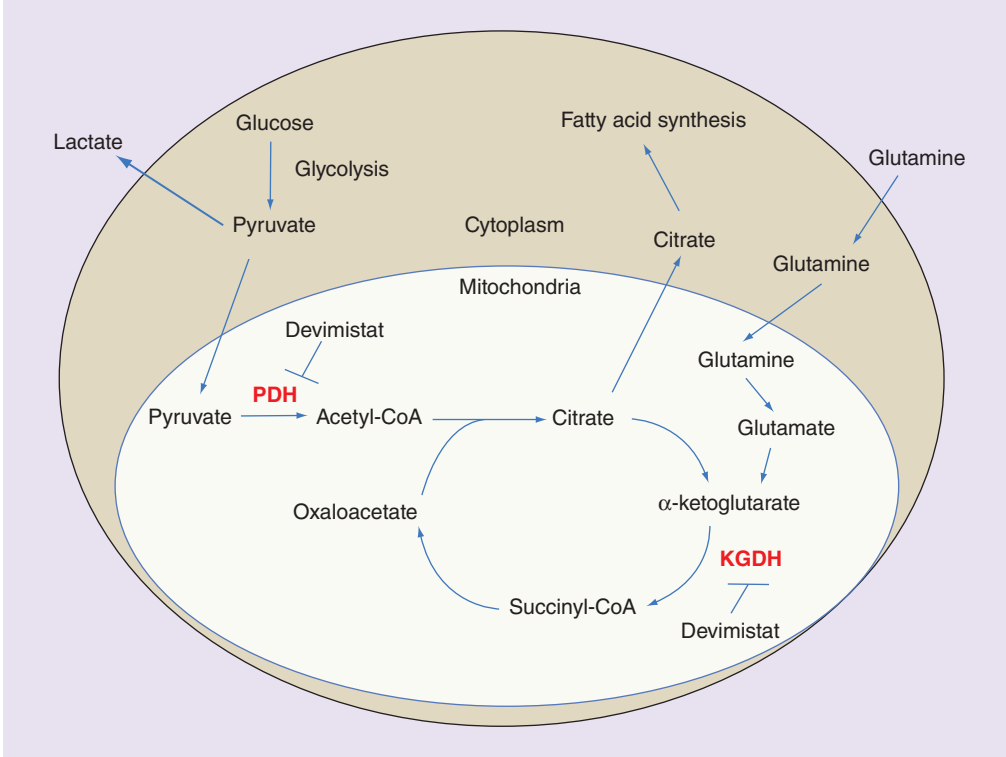

Figure 1. Simplified overview of the tricarboxcylic acid cycle and carbon metabolism. Shown is a simplified schematic of carbon metabolism with the devimistat targets PDH and KGDH shown in red.
KGDH: α-ketoglutarate dehydrogenase complexes; PDH: Pyruvate dehydrogenase.

features [5]. Because of this constellation of circumstances, AML in older patients is not optimally treated with DNA damaging agents alone [11].

Altered metabolism is seen across many tumor types including AML [12]. AML cells that are resistant to chemotherapy have higher mitochondrial mass, consume more oxygen and have a gene expression signature consistent with a more oxidative metabolic phenotype [13]. There is growing evidence that the tricarboxcylic acid (TCA) is a critical element of cancer cell survival and resistance to chemotherapy. Consistent with this when PDH is genetically deleted, AML cells are unable to become more oxidative and have a significant increase in sensitivity to chemotherapy *in vitro* and *in vivo* [14]. Diminished mitochondrial quality is a hallmark of aging and older adults have diminished mitochondrial content and quality in muscle as well as hematopoietic cells and this correlated strongly with physical function [10,15,16]. This suggests that leukemias arising in an older host will contain impaired mitochondrial function and strategies that inhibit mitochondrial function have the potential to preferentially benefit older patients.

Devimistat (CPI-613®) is a nonredox active analog of lipoic acid, a required cofactor of PDH and KGDH, two key enzymes of the TCA cycle [17,18]. PDH is responsible for the entry of glucose derived carbons and KGDH is responsible for the entry of glutamine-derived carbons into the TCA cycle (Figure 1). Devimistat inhibits these complexes resulting in decreased oxygen consumption in AML cells and sensitization to chemotherapy [14,19]. Devimistat is being evaluated in over 14 completed or ongoing Phase I–III clinical trials either as a single agent or in combination with chemotherapy (Table 1). In AML, devimistat has been studied in combination with high dose cytarabine and mitoxantrone (CHAM) for patients with relapsed and refractory AML. In an analysis of the combined Phase I and II data, a significant dose response was seen in patients 60 years of age or older but not in younger patients [20]. When treated with 2000 mg/m^2 of devimistat in CHAM, patients 60 years of age or older with relapsed or refractory AML had a complete remission (CR)/complete remission with incomplete hematologic recovery (CRi) rate of 52% with a median overall survival (OS) of 12.4 months [20]. This compares favorably with the historical data for high dose cytarabine and mitoxantrone (HAM) and asparaginase, which had a CR rate

Table 1. Ongoing and completed clinical trials with devimistat.

No.	Trial ID, NCT ID, US FDA IND No.	Phase	Indication	Treatment detail	#Dosed	#Evaluated for efficacy	#Evaluated for safety	Efficacy summary	Recruitment status	Result (interim/final)	
										Efficacy	Safety
1	CCCWFU 22215; NCT02484391; 114372	II	Relapsed or refractory AML; granulocytic sarcoma	CPI-613 + Cytarabine + Mitoxantrone hydrochloride	47	47	39	CR: 32% CRi: 13%	Closed (active, not recruiting)	Interim (11 October 2018)	Interim (27 March 2018)
2	CCCWFU 22112; NCT01768897; 114372	I	Relapsed or refractory AML	CPI-613 + Cytara-bine + Mitoxantrone hydrochloride	67	62	66	CR: 42% CRi: 8%	Closed (completed)	Final (7 March 2017)	Final (29 September 2016)
3	CCCWFU 57112; NCT01835041; 74530	I	Metastatic pancreatic cancer	CPI-613 + mFOLFIRINOX	20	18	20	Median OS: 19.9 months Median PFS: 9.9 months CR: 17% PR: 44%	Closed (active, not recruiting)	Interim (10 August 2018)	Final (4 October 2018)
4	CCCWFU 57113; NCT01839981; 74530	I	Locally advanced or metastatic pancreatic cancer	CPI-613	9	5	9	PD: 100%	Closed (completed)	Final (December 2016)	Final (26 January 2018)
5	CCCWFU 28314; NCT02168140; 114372	I	Relapsed or refractory T-cell lymphoma or hodgkin lymphoma	CPI-613 + Bendamustine hydrochloride	10	7	10	CR: 38% PR: 38%	Open (recruiting)	Interim (29 November 2017)	Interim (14 September 2018)
6	CCCWFU 29113; NCT01902381; 114372	II	Relapsed or refractory MDS	CPI-613	12	11	12	Marrow CR: 10% SD: 80%	Open (recruiting)	Interim (28 July 2017)	Interim (14 September 2018)
7	CCCWFU 29109; NCT01034475; 114372	I	Advanced hematological malignancies	CPI-613	26	20	26	CR: 5% MLFS: 5% PR: 10%	Closed (completed)	Final (21 April 2015)	Final (1 March 2015)
8	CCCWFU 59212; NCT01766219; 74530	I/II	Cholangiocarcinoma; liver cancer; bile duct cancer	CPI-613	17	10	17	PD: 100%	Open (recruiting)	Interim (December 2017)	Interim (14 September 2018)
9	CCCWFU 59314; NCT02232152; 74530	I	Metastatic colorectal cancer	CPI-613 + Fluorouracil	10	6	14	MR: 17%	Open (recruiting)	Interim (December 2017)	Interim (1 October 2018)
10	CCCWFU 62113; NCT01931787; 74530	I	Relapsed or refractory small cell lung cancer	CPI-613	14	13	8	PD: 100%	Closed (completed)	Final (December 2016)	Final (1 March 2015)
11	CCCWFU 28114; NCT02168907; 114372	I	Relapsed or refractory B-cell nonhodgkin lymphoma	CPI-613 + Bendamustine hydrochloride + Ritux-imab	1	1	1	PD: 100%	Closed (terminated)	Final (December 2016)	Final (July 2016)
12	CL-CPI-613-002; NCT00741403; 74530	I	Advanced cancer	CPI-613	41	41	39	SD: 61%	Closed (completed)	Final (21 April 2015)	Final
13	CL-CPI-613-004; NCT00907166; 74530	I/II	Cancer; pancreatic cancer	CPI-613 + Gemcitabine	38	31	33	SD: 68%	Closed (terminated)	Final (21 April 2015)	Final
14	CL-CPI-613-023; NCT01832857; 74530	II	Cancer	CPI-613	7	5	7	SD: 40%	Closed (terminated)	Final (2 June 2015)	Final

AML: Acute myeloid leukemia; CR: Complete remission; CRi: Complete remission with incomplete hematologic recovery; MDS: Myelodysplastic syndrome; OS: Overall survival; PFS: Progression free survival; SD: Standard deviation.

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of 26% and a median survival of 5.2 months [21]. Given these encouraging data, this regimen was selected for a randomized Phase III clinical trial in older patients (≥60 years of age) with relapsed or refractory AML.

Phase III trial

The Armada 2000 study is a multicenter open-label, international, Phase III randomized trial (NCT#03504410) evaluating the efficacy and safety of devimistat in CHAM compared with HAM alone in patients 60 years or older with relapsed or refractory AML. The study is being conducted consistent with good clinical practice standards and in accordance with the declaration of Helsinki. All participating sites will have the protocol reviewed and approved by an institutional review board and will sign an institutional review board-approved informed consent document prior to enrollment.

Objectives

The primary objective of this study is to determine efficacy of CHAM compared with HAM, with the primary end point being the rate of CR. CR will be determined as per standard international working group response criteria for AML [22]. Secondary objectives include OS and the rate of CR with partial hematologic recovery (CRh), safety, pharmacokinetics (PK) and patient-reported outcomes as determined by EORTC QLQ-C30. Exploratory objectives include examining the correlation of AML-associated mutations and/or genetic alterations with response. Additionally, the correlation of baseline pyruvate dehydrogenase kinases (PDKs), PDH, KGDH, superoxide dismutase 2 (SOD2) and a B cell immunophenotypic marker (CD79a) in the bone marrow, as assessed by immunohistochemistry (IHC) staining, will be correlated with response and OS. Finally, gene expression analysis by RNA sequencing from baseline bone marrow aspirate/biopsy samples will be used to validate previously described response signature from the Phase I study [14].

Key eligibility criteria

Patients aged ≥60 years with a histologically documented AML that is relapsed from, or refractory to, prior standard therapies will be eligible. Refractory disease is defined as failure to achieve CR or CRi following: one or two standard dose cytarabine-based induction cycles or one HiDAC-based cycle, no decrease in marrow blast percentage from diagnosis on day 14 marrow following either HiDAC or standard dose cytarabine, or no response after a minimum of three cycles of a hypomethylating agent (azacytidine or decitabine)-based therapy. Relapsed disease is defined as the development of recurrent AML after CR or CRi has been achieved with a prior therapy. Patients must have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–2 and an expected survival >3 months. No radiotherapy, treatment with other cytotoxic chemotherapy, treatment with biologic agents or any anticancer therapy within the 2 weeks prior to treatment with devimistat is allowed, except for hydroxyurea, oral FLT3 inhibitors or isocitrate dehydrogenase 1 and 2 inhibitors, which can be used until the day prior to starting study therapy provided there is no grade 3 toxicity. Previous exposure to a hypomethylating agent either alone or in combination with venetoclax is allowed. No marked baseline prolongation of electrocardiogram QT/QTc (corrected QT interval) interval (confirmed QTc interval >450 ms for male and >470 ms for female patients) is allowed. Patients meeting any of the following exclusion criteria are not eligible to participate: receipt of previous cytotoxic chemotherapy treatment for relapsed or refractory AML; history or evidence of any other clinically significant disorder, condition or disease (e.g., symptomatic congestive heart failure, unstable angina pectoris, symptomatic myocardial infection, uncontrolled cardiac arrhythmia, pericardial disease or heart failure New York Heart Association Class III or IV) or severe debilitating pulmonary disease, that would potentially increase patients' risk for toxicity and in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures or completion; active CNS involvement (leukemic infiltration, blast in the spinal fluid); any active uncontrolled bleeding, and any patients with a bleeding diathesis (e.g., active peptic ulcer disease); known sensitivity to any of the CHAM or HAM medications to be administered; history of other malignancy within the past 5 years, with the following exception(s): adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of recurrent or residual disease, or adequately treated cervical carcinoma *in situ* without evidence of disease or limited stage prostate cancer. Patients who received immunotherapy of any type within the past 2 weeks prior to initiation of devimistat treatment or who previously received an allogenic stem cell transplant are not eligible.

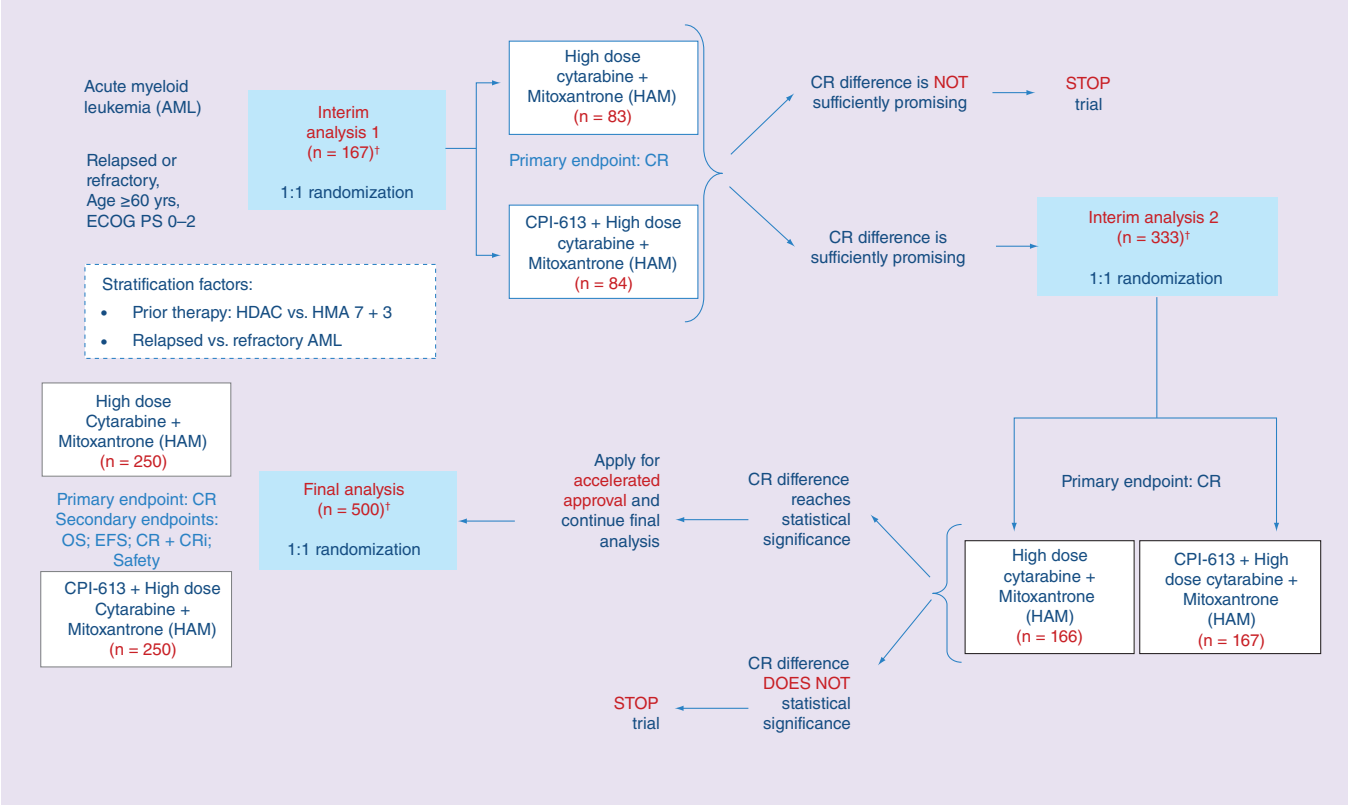

Figure 2. Armada 2000 trial schematic.
†When these number of patients are evaluable for response.

Study design & methodology

This is a prospective, multicenter, open label, randomized Phase III study of CHAM compared with HAM in older patients (≥60 years) with relapsed/refractory AML. Patients will be randomized in a 1:1 fashion between arm 1: CHAM (devimistat + HAM) and Arm 2: HAM as outlined in Figure 2. The randomization will be implemented using a minimization procedure to balance the following prognostic factors at baseline: prior therapy (HiDAC based vs hypomethylator [azacytidine or decitabine]), hypomethylating agent (HMA)-based versus 7+3 (high dose cytarabine+ mitoxantrone + asparaginase), relapsed versus refractory AML, cytogenetic risk category, age (60–69 vs ≥70 years old), performance status (0–1 vs 2) and treating institution (this latter factor will subsume any regional effects, since the trial will be conducted in North America, Europe and Asia–Pacific). Patients in arm 1 (CHAM) will undergo induction cycle 1, with devimistat given at a dose of 2,000 mg/m^2 administered over 2 h via a central line infusion once daily from day 1 through day 5 for a total of five doses. Immediately following devimistat high dose cytarabine will be given at a dose of 1 g/m^2 every 12 hours starting on day 3 and continuing through day 5, for a total of five doses. The time between completion of devimistat infusion and the start of cytarabine infusion should be ≤10 min. Mitoxantrone at dose of 6 mg/m^2, will be administered following completion of high dose cytarabine, over 15 min as an IV infusion after the first, third and fifth doses of cytarabine on day 3 through day 5 (total of three doses). Mitoxantrone should be given as soon as possible, but no later than 30 min, after completion of each cytarabine infusion. On day 6 through day 14, no therapy is administered. A nadir bone marrow biopsy is obtained on day 14 of the first cycle and the results will guide whether, and of what duration, a second cycle of induction therapy is given. If a given site opts not to obtain a nadir marrow biopsy on day 14 then no second induction cycle is given. If the nadir marrow result shows <5% myeloblasts, no induction cycle 2 therapy is to be administered. If the nadir marrow result shows ≥5% but <30% myeloblasts and cellularity ≤20%, an abbreviated induction Cycle 2 (3-day duration, three daily doses of devimistat, three doses of cytarabine every 12 h starting on day 2 and two doses of mitoxantrone after the first and third cytarabine doses) will be administered. If neither of the above criteria are met, a full induction cycle 2 (repeat of cycle 1 described above) is given. Patients who obtain

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a CR or CRi can proceed to consolidation therapy. Up to two cycles of consolidation therapy are allowed, each one consisting of an abbreviated induction course (3-day duration, three daily doses of devimistat, three doses of cytarabine every 12 h starting on day 2 and two doses of mitoxantrone after the first and third cytarabine doses). Patients randomized to CHAM (Arm 1) who achieve CR or CRi according to standard response criteria for AML and who have completed all planned induction and consolidation therapy (0, 1 or 2 cycles) but are not eligible for or refuse HSCT; or for whom it is anticipated that there will be a delay prior to HSCT of ≥6 weeks, will receive maintenance therapy. Maintenance therapy is to commence within 3 weeks from count recovery and following completion of induction/consolidation therapy. Devimistat maintenance will be administered via a central line IV infusion at a dose of 2500 mg/m^2 given on day 1 through day 5 of the cycle every 28 days. No treatment will be administered on day 6 through day 28. This therapy can be delivered in the inpatient or outpatient setting. There is no maximum number of cycles allowed and patients will continue maintenance therapy until disease recurrence, availability of stem cell transplant, the advent of intolerable side effects or patient withdrawal of consent. Patients randomized to arm 2 (HAM) will be treated identically except that there will be no devimistat administered and after completion of all planned induction and consolidation therapy, patients will be observed only. Given the myeloablative nature of the chemotherapy regimen, prophylactic antimicrobials and tumor lysis prophylaxis are allowed per site guidelines. Additionally, myeloid growth factors for patients with severe neutropenia and concurrent sepsis are also allowed per site guidelines.

Efficacy evaluations

The 2010 European LeukemiaNet response criteria are currently used to determine response (to be updated in future amendment to 2017 version). During induction therapy, bone marrow biopsies will be obtained at baseline, day 14 of cycle 1 of induction and at time of count recovery or day 42 from most recent therapy. Bone marrow aspiration will also be obtained at completion of all planned consolidation therapy and then every fourth cycle of maintenance therapy for patients on arm 1 or at any time recurrence of disease is suspected. EORTC-QLQ-C30 will be collected at baseline, at time of recovery bone marrow, at completion of all planned consolidation therapy and thereafter every 3 months and at time of study discontinuation.

PK evaluations

PK samples will be collected from patients randomized to arm 1 only. There will be two different schedules of PK samples: a full schedule for 24 patients and a sparse schedule for all remaining patients. The full PK sample schedule will collect a sample at the time points outlined in Table 2. The sparse PK sample schedule is outlined in Table 3.

Pharmacodynamic/exploratory samples

Optional blood and serum samples will be collected from consenting patients just prior to initiation of therapy and at 2, 4 and 6 h after start of therapy on day 1 through day 5 of induction, and days 1–3 of consolidation. A bone marrow aspirate sample will be obtained from consenting patients at the time of trial entry and when possible at the time of progression. These samples will be separated into plasma and cells. Cells will be frozen in DMSO-containing media to preserve viability. Buccal mucosal swabs will be obtained as a source of germline DNA. Samples will be used for exploratory biomarker analysis and correlation between inhibition of PDH and KGDH and response. The biomarker exploratory analysis is composed of a cellular and a metabolite approach. Specifically, in a retrospective fashion, the top and bottom 10% of patients in terms of response and survival enrolled on the study arm will have their aspirate samples analyzed. In the cellular approach, samples will be CD34 selected and analyzed by RNA sequencing to assess expression and/or mutational patterns that predict response or resistance. Special attention will be paid to the genes identified in the Phase I study [14]. Should the previously identified expression signature be confirmed or a novel one identified, the remaining samples will be analyzed using the NanoString assay. Should a mutational pattern be identified, the remaining samples will be analyzed by targeted exome sequencing. In the metabolite approach, aspirate derived plasma will be analyzed in an unbiased fashion by liquid-chromatography high resolution mass spectrometry (LC-HRMS) metabolite profiling. Should this analysis identify predictive metabolites, the remaining samples will be analyzed in a targeted fashion. Additionally, data on the cytogenetic and mutational profile of patients obtained at the time of enrollment is being collected when available and will be correlated with response and survival. Finally, unstained slides from baseline bone marrow

Table 2. Full pharmacokinetics schedule.

Phase, Cycle #, Day #	Time points	Comment
Induction, Cycle 1, Day 1	0 h (predose) 0.5 h ± 10 min 1 h ± 15 min 2 h ± 15 min 2.5 h ± 15 min 3 h ± 30 min 4 h ± 30 min 8 h ± 1 h	Pre-CPI-613 infusion During CPI-613 infusion During CPI-613 infusion During CPI-613 infusion End of CPI-613 infusion
Induction, Cycle 1, Day 2	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Induction, Cycle 1, Day 3	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Induction, Cycle 1, Day 4	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Induction, Cycle 1, Day 5	0 h (predose) 0.5 h ± 10 min 1 h ± 15 min 2 h ± 15 min 2.5 h ± 15 min 3 h ± 30 min 4 h ± 30 min 8 h ± 1 h	Pre-infusion During CPI-613 infusion During CPI-613 infusion End of CPI-613 infusion
Induction, Cycle 1, Day 6	24 h ± 1 h	Day 6
Induction, Cycle 1, Day 7	48 h ± 1 h	Day 7
Induction, Cycle 2, Day 1	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Induction, Cycle 2, Day 5 (or Day 3)†	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Consolidation, Cycle 1, Day 1	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Consolidation, Cycle 1, Day 3	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Consolidation, Cycle 2, Day 1	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Consolidation, Cycle 2, Day 3	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Maintenance, Cycle 1, Day 1	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Maintenance, Cycle 1, Day 5	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Maintenance, Cycle 2, Day 1	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion
Maintenance, Cycle 2, Day 5	0 h (predose) 2 h ± 15 min	Pre-CPI-613 infusion End of CPI-613 infusion

†Day 5 if 5 days of treatment or Day 3 if 3 days of treatment in Induction Cycle 2.

Table 3. Sparse pharmacokinetics schedule.

Sample #	Phase, Cycle #, Day #	Time point window
1	Induction, Cycle 1, Day 1	0–24 h
2	Induction, Cycle 2, Day 5 (or Day 3)†	0–24 h
3	Consolidation, Cycle 1, Day 1	0–24 h
4	Consolidation, Cycle 2, Day 3	0–24 h
5	Maintenance, Cycle 1, Day 1	0–24 h
6	Maintenance, Cycle 2, Day 5	0–24 h

†Day 5 if 5 days of treatment or day 3 if 3 days of treatment in induction cycle 2.

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biopsies are being collected and PDKs, PDH, KGDH, SOD2 and CD79a expression will be assessed by IHC staining and correlated with response and OS.

Safety evaluations

The Cancer Therapy Evaluation Program Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE Version 5 or later) will be utilized for adverse event (AE) evaluation and reporting. Patients will be monitored for adverse events at each study visit. All patients who receive at least one dose of study-mandated drug on either arm will be included in the safety analysis. All AEs and serious adverse events (SAEs) will be reported per protocol to appropriate regulatory bodies. SAEs will be reported within 24 h of site awareness. Rates of AEs and SAEs will be compared between the two arms as part of the safety secondary objective.

Planned sample size

The sample size calculation is based on an improvement in CR from 26% in the control arm to 39% in the experimental arm (a 13% absolute increase, or a 50% relative increase). For a power of 80%, 500 patients need to be evaluated for response. This number allows for two interim analyses to be performed. The study is also powered to detect a clinically meaningful difference in OS defined as the duration from the date of randomization to the date of death from any cause. For the primary analysis, subjects will not be censored at the time of transplant. The study is powered to detect a difference in survival with an expected median OS equal to 5.2 months in the control arm versus 6.9 months in the experimental arm, in other words, a hazard ratio equal to 0.75 assuming exponential survival distributions. For a power of 80%, 394 events need to be observed. This number allows for one interim analysis but is merely added to protect the type I error as no interim analysis for OS is planned. Assuming an accrual rate of 15 patients per month and a common dropout rate of 10% at 3 years, a sample size of 500 patients will provide a power of 80% for the OS analysis 36 months after the first randomization. Note that all secondary end points will be analyzed after 394 deaths are observed. Finally, the study has more than 86% power to detect a clinically meaningful difference in CR+CRh rate at the final analysis, with an expected rate equal to 33% in the control arm versus 47% in the experimental arm. Similar to the OS analysis, this sample size allows for one interim analysis for response although there is no intent to analyze CR+CRh at interim.

Planned study period

Patients randomized to the control arm (HAM, Arm 2) will continue to receive planned treatment until completion of all required induction/consolidation therapy cycles and then observed as part of the long-term follow-up. Patients randomized to the study arm (CHAM, Arm 1) following completion of all planned induction and/or consolidation therapy cycles will continue to receive devimistat during maintenance until disease recurrence, availability of stem cell transplant, the advent of intolerable side effects or patient withdrawal of consent.

Statistical plan

One-sided tests will be used at a significance level equal to 0.025. Two-sided CIs will be computed for a coverage probability of 0.95.

Time to event outcomes ('survival times') will be described by treatment arm using the Kaplan–Meier method. Patients who have not had the event of interest at the time of the analysis will be censored at the time of the last follow-up. Summary statistics will be provided by treatment arm in terms of the number of events, median and 95% CI and survival probabilities at specific time points (such as 1 year, 2 years, etc.). Survival curves will be plotted by treatment arm and compared with a log-rank test stratified by performance status, age and refractory versus relapsed disease. A stratified Cox regression model will be used to estimate the hazard ratio and its 95% CI, as well as to adjust the comparison for baseline covariates.

The primary end point is CR. The CR rate will be compared between the experimental arm and the control arm. The primary analysis will be a rerandomization test based on the CMH test-statistic, stratified by performance status, age and refractory versus relapsed disease. The rerandomization approach fixes all data except the treatment assignment at their observed values, regenerates the randomization sequence using the minimization algorithm and computes the test statistic corresponding to those reshuffled assignments. This process is repeated a large number of times, and a p-value is calculated as the proportion of rerandomized trials whose test statistic is at least as extreme as the observed one from the original assignments.

The trial design includes two interim analyses, and one final analysis. Both interim analyses are only performed for the primary end point CR rate with the intent to stop the trial if the difference in CR between arms is not sufficiently promising; there is no intention to stop the study early if efficacy is shown. The futility boundaries are nonbinding, allowing the DMC to decide independently at the timing of the interim analysis, taking all available data into account, whether the study should continue or stop.

The secondary end points are OS, defined as the duration from the date of randomization to the date of death from any cause, CRh and safety.

The primary analysis of all secondary efficacy end points will be a rerandomization test that calculates the p-value by rerandomizing patients to treatments as explained above. For OS, the rerandomization will use a stratified Cox proportional hazard test-statistic. For CRh, the CMH test-statistic will be used. The secondary end points will only be analyzed at the final analysis. Note that by design an interim analysis has been foreseen for OS, using an O'Brien-Fleming type Lan-DeMets boundary for efficacy. When the number of required deaths is observed, all secondary end points will be analyzed. The number of required deaths for a final analysis of OS is 394.

Interim analysis

The first interim analysis will be performed when 167 patients are evaluable for response. This analysis will take place approximately 14 months after the first randomization. The only end point analyzed at this interim analysis will be CR. The significance level to be used for this interim analysis will be determined using an O'Brien-Fleming type Lan-DeMets boundary for efficacy, and a Pocock type Lan-DeMets boundary for futility. Assuming an information fraction of 33% for CR at this interim analysis, the significance level for efficacy will be 0.0001 and it will be reached if the difference in CR is larger than 26.7%. The significance level for futility is 0.32 and it will be reached if the difference in CR is smaller than 3.3%. If, based on this interim analysis, the CR difference is not sufficiently promising, consideration will be given to stopping the trial; otherwise, the trial will proceed. There is however no intention to stop the trial for efficacy with only 167 patients.

The second interim analysis will be performed when 333 patients are evaluable for response. This analysis will take place approximately 25 months after the first randomization. The only end point analyzed at this interim analysis will be CR. As with the first interim analysis, the significance level to be used for this interim analysis will be determined using an O'Brien-Fleming type Lan-DeMets boundary for efficacy, and a Pocock type Lan-DeMets boundary for futility. Assuming an information fraction of 67% for CR at this interim analysis, the significance level for efficacy will be 0.006 and it will be reached if the difference in CR is larger than 12.8%. The significance level for futility is 0.094 and it will be reached if the difference in CR is smaller than 6.7%. If, based on this interim analysis, the CR difference is not sufficiently promising, consideration will be given to stopping the trial; otherwise, the trial will proceed.

The final analysis will be performed when 500 patients are evaluable for response. This analysis will take place approximately 36 months after the first randomization. At that time, the primary end point of CR will be analyzed first, with a significance level determined using an O'Brien-Fleming type Lan-DeMets boundary for efficacy equal to 0.023, which will be reached if the difference in CR is larger than 8.3%. In case efficacy is declared for CR, the Sponsor may consider filing for accelerated approval based on CR, while patients are further followed to collect OS data.

Discussion

Relapsed or refractory AML remains a significant challenge especially in older patients with low response rates and short median survivals [23]. Recently, several novel therapies were approved for AML in the relapsed setting including the *IDH1* and two inhibitors as well as the *FLT3* inhibitor gilteritinib. While these agents are a significant step forward, many issues remain. Patients treated with these agents achieve a composite remission (CR+CRi) only 20–30 % of the time, median response duration is less than a year and all patients eventually relapse [24–26]. Novel approaches are desperately needed. Devimistat is a novel folate analog that simultaneously inhibits two key TCA cycle enzymes, blocking the entry of either glucose or glutamine-derived carbons entry [17,18]. The Armada 2000 trial seeks to leverage the unique mechanism of action of this agent to improve the outcomes for older patients suffering from relapsed or refractory AML. This is based on preclinical and clinical data suggesting synergy between chemotherapy and devimistat [14]. An interesting and somewhat unexpected finding of the combined data from the Phase I and Phase II trials was that the outcomes of patients younger than 60 and those 60 years of age or older were not different [20] The possible beneficial effect in older patients was further suggested by the dose–response

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relationship seen in older but not younger patients [20]. The beneficial effect of devimistat seen in older patients may be a reflection of the fact that mitochondrial quality declines with age [27]. Some studies have suggested that mitochondrial quality in muscle fibers is lower in elderly populations and correlates well with physical function [28]. This correlation was also seen when the mitochondria from peripheral blood cells was analyzed, suggesting that there is a decline in mitochondrial quality throughout all tissues as a function of aging [29]. This suggests that cells in the hematopoietic compartment are affected by the hallmarks of aging and since AML arises from this compartment, it follows that AML in an older host would have impaired mitochondrial function. Targeting mitochondrial function in elderly AML represents a promising approach and leverages an age-associated vulnerability. The Armada 2000 trial will provide important data on the validity of this approach and further our understanding of the role of mitochondrial metabolism in therapy response in elderly AML patients. The trial is designed to detect worthwhile benefits on all relevant clinical outcomes, including OS, while at the same time having early stopping rules in case interim analyses look less promising than anticipated.

Executive summary

Background

- Mitochondrial metabolism is altered in cancer cells including acute myeloid leukemia (AML) cells.
- The tricarboxcylic acid cycle is a source of resistance to DNA-damaging agents in AML.
- Mitochondrial quality declines with age and targeting mitochondria metabolism may leverage an age-related vulnerability in AML in the elderly.

Devimistat

- Novel lipoate analog that inhibits two key tricarboxcylic acid cycle enzymes, PDH and KGDH.
- Devimistat impairs AML cell mitochondrial metabolism and sensitizes cells to DNA damaging agents.
- Devimistat has shown promising results when combined with cytarabine and mitoxantrone in Phase I and II studies.

Phase III trial

- Armada 2000 is a randomized, international, Phase III study.
- The primary objective is to compare the efficacy of high dose cytarabine and mitoxantrone (HAM) with devimistat combined with high dose cytarabine and mitoxantrone in terms of complete remission rate.
- Secondary objectives include comparisons of overall survival and rates of complete remission with incomplete hematologic recovery.

Key eligibility criteria

- Patients $\geq$60 years of age with relapsed or refractory AML.
- ECOG PS of 0–2.
- No previous cytotoxic therapy for relapsed or refractory disease.

Study design

- Eligible patients are randomized 1:1 to devimistat plus HAM or to HAM alone.

Efficacy and pharmacokinetics evaluations

- Response criteria from the 2010 European LeukemiaNet will be used for all bone marrow biopsies.
- Pharmacokinetics samples will be collected on either a full (intensive) or sparse schedule at defined time points following administration of devimistat.

Discussion

- Outcomes in elderly patients with relapse or refractory AML are poor and novel approaches are needed.
- Several lines of evidence suggest mitochondrial metabolism is a source of resistance to therapy in AML.
- The Armada 2000 trial will provide important new insights into the activity of an approach that combines DNA damaging agents with mitochondrial metabolism inhibition.

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