MIRROS: a randomized, placebo-controlled, Phase III trial of cytarabine ± idasanutlin in relapsed or refractory acute myeloid leukemia

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Patients with refractory or relapsed acute myeloid leukemia (R/R AML) have a poor prognosis, with a high unmet medical need. Idasanutlin is a small-molecule inhibitor of MDM2, a negative regulator of tumor suppressor p53. By preventing the p53–MDM2 interaction, idasanutlin allows for p53 activation, particularly in patients with *TP53* wild-type (WT) status. MIRROS (NCT02545283) is a randomized Phase III trial evaluating idasanutlin + cytarabine versus placebo + cytarabine in R/R AML. The primary end point is overall survival in the *TP53*-WT population. Secondary end points include complete remission rate (cycle 1), overall remission rate (cycle 1) and event-free survival in the *TP53*-WT population. MIRROS has an innovative design that integrates a stringent interim analysis for futility; continuation criteria were met in mid-2017 and accrual is ongoing. **Trial registration number:** NCT02545283

Acute myeloid leukemia (AML) is a malignant and genetically heterogeneous hematologic disease in which uncontrolled clonal expansion of myeloid blast cells occurs in the bone marrow, blood and other tissues [1,2]. The age-adjusted incidence rate of AML in the USA in 2016 was 4.3 per 100,000 person-years, with similar rates in the UK, Australia, Canada and other European countries (e.g., Sweden, Denmark) [3]. The 5-year survival rates for younger (age 18–60 years) and elderly (age >60 years) patients with AML are 40 and 10%, respectively [2]. With
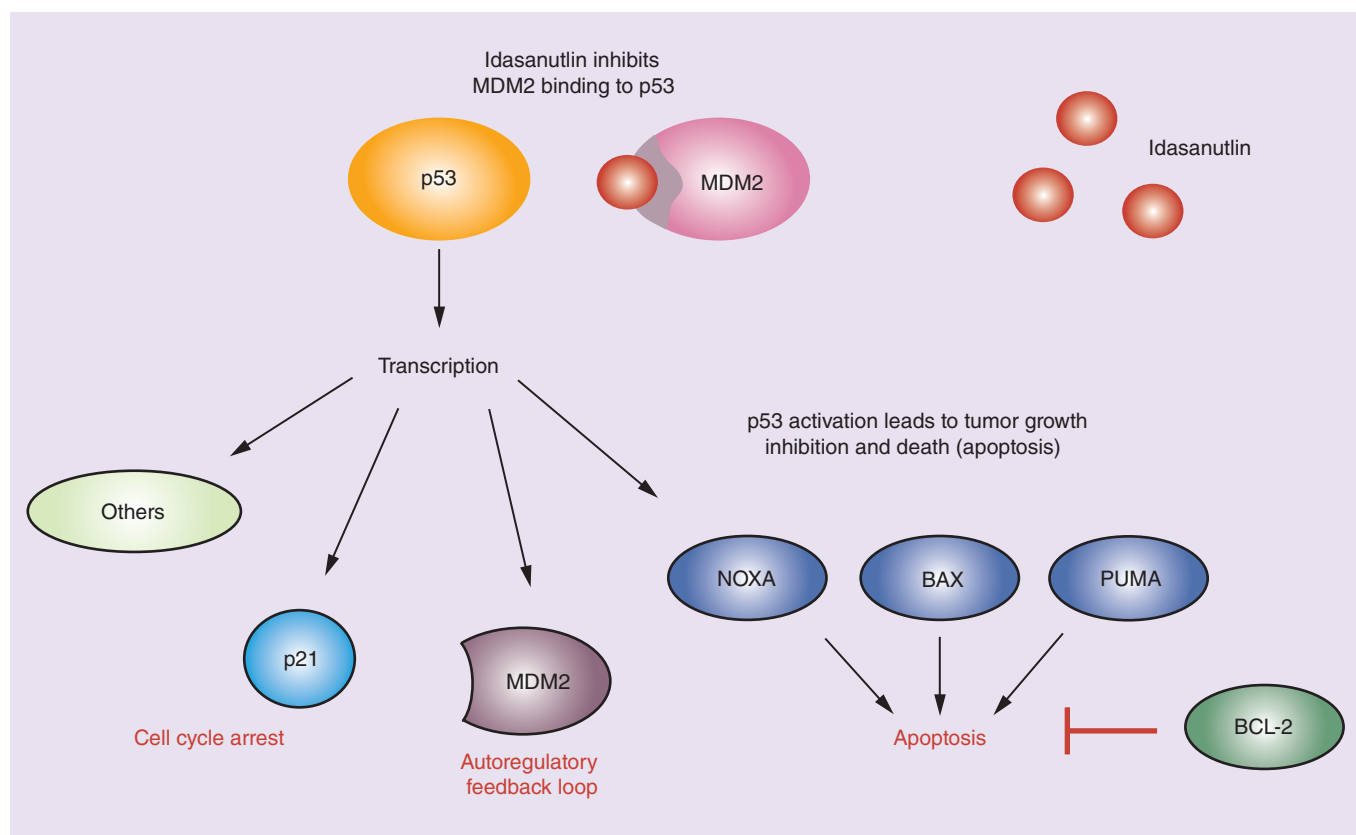
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Figure 1.   Idasanutlin: p53 activation via MDM2 inhibition.

intensive chemotherapy, approximately 60–80% of patients achieve complete remission; however, nearly a quarter will have primary refractory disease and more than half will relapse, typically within 3 years from initial response [4–6]. For patients with refractory or relapsed (R/R) AML, there is no standard treatment regimen. Recommended therapies in R/R AML include intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation (HSCT) in patients fit enough to tolerate aggressive treatment, hypomethylating agents or best supportive care in the unfit patient population [7,8]. Targeted therapies for select patients with certain genetic profiles such as *FLT3*-, *IDH1*- or *IDH2*-mutated AML have also become available [8]. Despite these novel therapeutic approaches to R/R AML, the prognosis in this population is poor [4] and a high unmet medical need remains.

TP53 is a tumor suppressor gene, which is frequently mutated or deleted in human cancers, leading to a dysfunctional p53 tumor suppressor protein and facilitating uncontrolled cell proliferation [9]. In addition, p53 can be inactivated through protein degradation, which is triggered by binding to the E3 ligase MDM2, the main negative regulator of p53 [10–12]. Indeed, overexpression of *MDM2* has been observed in human tumors [13]. Therefore, in cancers with wild-type *TP53* (*TP53*-WT), which includes a large proportion of patients with AML (≈80%) [14–16], targeting MDM2 may be a promising therapeutic strategy to stabilize p53 levels and activate p53 tumor suppressor function and downstream apoptotic pathways (Figure 1).

Idasanutlin

Idasanutlin is a novel, potent and selective small-molecule MDM2 antagonist with a pyrrolidine structure [17,18]. It has an identical cellular mechanism to other Nutlin family molecules; however, enhanced potency, selectivity and bioavailability have been observed with the novel chemistry of idasanutlin [17]. Preclinical evaluations showed induction of cell cycle arrest and/or apoptosis with idasanutlin in tumor cell lines [18]. In addition, antitumor activity was observed with both idasanutlin monotherapy and combination therapy with cytarabine in xenograft models [18].
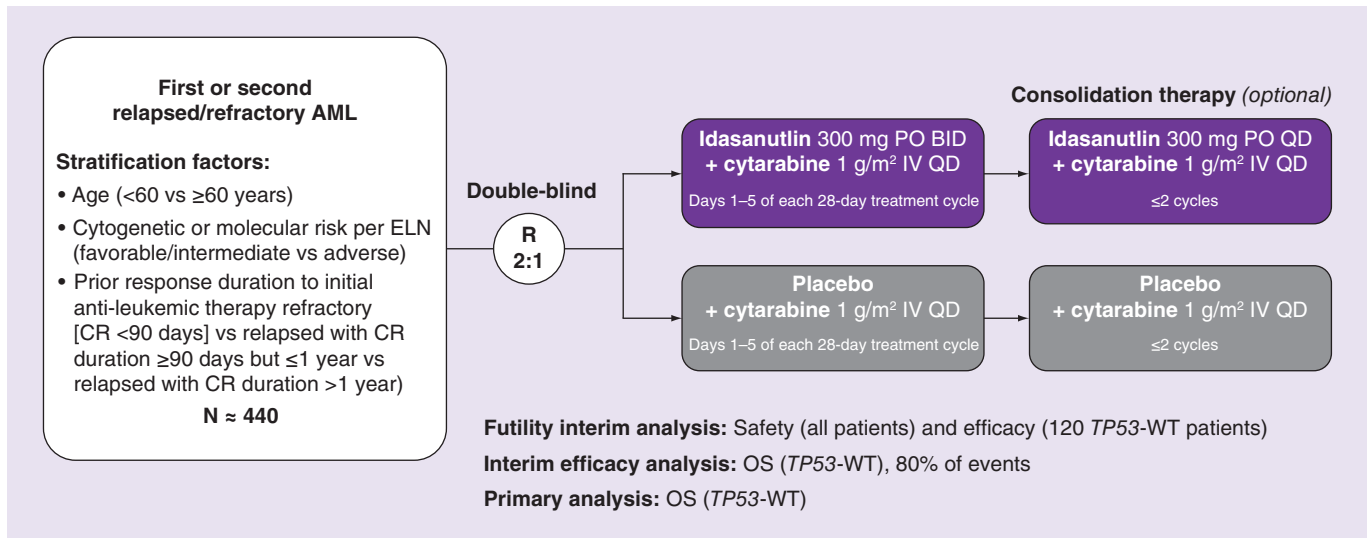
Figure 2. MIRROS study design.
AML: Acute myeloid leukemia; CR: Complete remission; ELN: European LeukemiaNet; HSCT: Hematopoietic stem cell transplant; IV: Intravenously; OS: Overall survival; PO: Orally; QD: Once daily; R: Randomized; WT: Wild-type.

In a multicenter, open-label, Phase I/Ib trial in patients with AML (NCT01773408), idasanutlin (400–1600 mg daily for 5 days) demonstrated tolerable safety and encouraging clinical activity alone and in combination with cytarabine (1 g/m² iv. for 6 days) [16,19]. This study enrolled patients regardless of *TP53* mutation status, as some mutations in *TP53* allow p53 functionality to be retained [20,21]. Adverse events (AEs) reported across treatment cohorts included gastrointestinal events, hematologic events or events related to infections or infestations [16,19]. Grade ≥3 AEs included hypokalemia, diarrhea, nausea and febrile aplasia or neutropenia [16,19]. No unexpected toxicities were reported with the combination regimen compared with other relapse regimens containing cytarabine [16,22,23]. Overall response rate (ORR) (complete remission [CR] + CR with incomplete platelet recovery [CRp] + CR with incomplete blood count recovery [CRi] + morphologic leukemia free state) in the monotherapy cohorts was 15% (n = 7/46) [19]. In the combination cohorts, ORR was 33% (n = 25/75) [16]. The majority of responses were achieved after one cycle of treatment [16,19]. In the combination cohorts, median duration of response for patients with CR/CRp/CRi followed up to 1 year was >8 months [16].

Preliminary findings from this study led to the continuing evaluation of idasanutlin in combination with cytarabine in R/R AML in the Phase III MDM2 Inhibitor in R/R AML for Overall Survival (MIRROS) trial (NCT02545283).

MIRROS trial
Study design
MIRROS is a multicenter, randomized, double-blind, Phase III trial evaluating idasanutlin in combination with cytarabine versus placebo in combination with cytarabine in patients with R/R AML (Figure 2). Approximately 440 patients will be enrolled across 80 centers and 18 countries in the Americas, Europe and Asia-Pacific region. Patients are being randomized 2:1 to receive idasanutlin 300 mg orally twice daily and cytarabine 1 g/m² iv. once daily on days 1–5 of each 28-day treatment cycle versus placebo and cytarabine 1 g/m² iv. once daily on days 1–5 of each 28-day treatment cycle; this dosing regimen is based on results of the Phase Ib study that investigated tolerability and clinical activity [16,19]. The initial induction cycle is 28 days and a maximum of two additional cycles of consolidation therapy with idasanutlin/placebo 300 mg orally once daily and cytarabine iv. may be administered to patients who respond to treatment. Antibiotic, antifungal, antidiarrheal and anti-emetic prophylaxis during treatment cycles is required. Stratification factors are age (<60 vs ≥60 years), cytogenetic/molecular risk per 2010 European LeukemiaNet recommendations [24] (favorable/intermediate vs adverse), prior HSCT (yes or no) and prior response duration to initial antileukemic therapy (refractory [CR <90 days] vs relapsed with CR duration ≥90 days but ≤1 year vs relapsed with CR duration >1 year). For eligibility and response assessments, AML disease is confirmed locally based on bone marrow aspirate or biopsy review. Following randomization screening bone

Table 1. Futility interim analysis criteria.

Results	GO	STOP
Efficacy (futility; 120 *TP53*-WT patients)	• CR[†] odds ratio ≥2.5 or • CR[†] odds ratio ≥2.0 and EFS HR ≤1	• CR[†] odds ratio <2.0 or • CR[†] odds ratio ≥2.0 and <2.5 and EFS HR >1 Probability (stop if drug does not work) = 90%
Safety (all patients)	• GI toxicity[‡]: grade 3 ≤40%; grade 4 ≤15% and • <10% difference in early death rate (≤day 30) in treatment vs control (≤20% early death rate)	• GI toxicity[‡]: grade 3 >40%; grade 4 >15% or • ≥10% difference in early death rate (≤day 30) in treatment vs control (>20% early death rate)

[†]Defined as CR or CR with incomplete platelet recovery with a duration of ≥28 days.
[‡]Defined as nausea, vomiting and diarrhea.
CR: Complete remission; EFS: Event-free survival; GI: Gastrointestinal; HR: Hazard ratio; WT: Wild-type.

marrow samples are tested centrally using a next-generation sequencing diagnostic platform to identify populations for study objectives (e.g., *TP53*, *IDH1* and *IDH2* mutational status). Post-treatment bone marrow specimens are centrally evaluated for minimal residual disease using flow cytometry and polymerase chain reaction technology.

An interim efficacy analysis on overall survival (OS) is planned to be conducted by the independent data monitoring committee (iDMC) after 80% of death events have been observed in the *TP53*-WT population to allow for early testing of OS and data unblinding, if relevant efficacy is achieved.

MIRROS is unique in that it integrates Phase II safety and efficacy criteria into a Phase III study via a blinded interim analysis for futility. This study design feature mitigates the risk of moving directly from a Phase Ib to a Phase III trial [25,26].

During the design phase, an important challenge of the interim futility analysis was assessing the magnitude of efficacy benefit because infection-related death in patients with AML and transplant-related mortality increase the risk of death without clear causality to study treatment after randomization. Thus, if the observation period for OS was not long enough, the treatment-effect comparison between the arms would be weighted toward early death events. Therefore, MIRROS was designed with durable CR (defined as CR or CRp with a duration of ≥28 days) as an intermediate efficacy end point in the interim futility analysis. Though not fully recognized as a surrogate end point, CR as an intermediate end point is associated with the primary end point of OS [27].

The interim futility analysis utilized a high bar on the odds ratio for durable CR and event-free survival (EFS), supporting the association between CR and OS to increase the quality of the futility assessment and included gating criteria to evaluate safety (Table 1). The futility analysis was performed by an iDMC after 120 patients with *TP53*-WT were enrolled, received ≥80% of the first treatment cycle and had a confirmatory response assessment available or who had withdrawn before response/confirmation; patients with *TP53*-WT were assessed for efficacy and all patients were assessed for safety. The prespecified number of 120 patients was chosen because it was considered sufficient for an interim decision and mirrored the sample size of a randomized Phase II trial [26]. Both the trial sponsors and investigators were blinded to the iDMC-reviewed data, thus maintaining trial integrity and avoiding the introduction of bias.

Per the nonbinding efficacy futility criteria, the trial would continue if the confirmed CR odds ratio was ≥2.5 or ≥2.0 with an EFS hazard ratio of ≤1 (Table 1). With regard to safety, the trial would continue if the proportion of gastrointestinal toxicity (nausea, vomiting or diarrhea) in the idasanutlin plus cytarabine arm was ≤40% of grade 3 or ≤15% of grade 4 events, there was <10% difference in the proportions of early deaths (≤30 days from randomization) between treatment arms or ≤20% of early deaths occurred in the idasanutlin plus cytarabine arm (Table 1). A relatively high false-negative error probability was considered in the interim boundary selection; thus, setting a high bar for futility and providing increased confidence in the experimental arm should the trial pass the thresholds [26].

Comparator arm

Cytarabine is an analog of cytosine, which may impede DNA synthesis, cause cellular damage and may thus enhance the antitumor activity of MDM2 inhibitors [24,28]. In the R/R setting, cytarabine is effective and generally used in combinations at doses ranging from 1–2 g/m^2 [6,8,29]. In MIRROS, cytarabine 1 g/m^2 once daily (over 1–3 h) was chosen in combination with idasanutlin based on findings from a Phase Ib study that evaluated the combination of cytarabine at low (20 mg/m^2 subcutaneous) and intermediate (1 g/m^2 once daily × days 1–6) doses with MDM2-antagonist, RG7112 [30]. Doses of cytarabine greater than 1 g/m^2 daily were considered too toxic and unlikely to provide substantial benefit in the expected patient population [31,32].

Table 2. Key eligibility criteria.

Inclusion criteria
• Age ≥18 years
• Confirmed primary or secondary refractory[†] or relapsed AML per WHO classification, except APL
• ≤2 prior induction regimens (excluding prior HSCT) in first-line treatment, including cytarabine with an anthracycline (or anthracenedione)
• ECOG PS 0–2

Exclusion criteria
• First relapsed patients aged <60 years with a first CR duration of >1 year
• Prior documented AHD, including myelodysplastic syndromes, myeloproliferative disease (i.e., CMML, PV, primary MF, ET) and aplastic anemia
• AML secondary to any prior chemotherapy unrelated to leukemia
• Refractory to or has relapsed within 90 days of receiving a regimen containing a cumulative dose of cytarabine ≥18 g/m^2
• Allogeneic HSCT ≤90 days prior to randomization
• Prior treatment with an MDM2 antagonist
• Infection considered by the investigator to be clinically uncontrolled (e.g., patients who are or should be on antimicrobial agents for treatment of active infection)

[†]Primary refractory: lack of response after 1–2 induction cycles in front line; secondary refractory: lack of response after one line of treatment for relapsed/refractory AML.
AHD: Antecedent hematological disorder; AML: Acute myeloid leukemia; APL: Acute promyelocytic leukemia; CMML: Chronic myelomonocytic leukemia; CR: Complete remission; ECOG PS: Eastern Cooperative Oncology Group performance status; ET: Essential thrombocythemia; HSCT: Hematopoietic stem cell transplantation; MF: Myelofibrosis; PV: Polycythemia vera.

There is no global standard treatment regimen for R/R AML and prior studies did not show significant difference in OS between chemotherapy regimens including a 1 g/m^2 comparator [33]. Choice of a placebo in combination with the cytarabine comparator was therefore considered ethical and acceptable for the blinded study design and facilitated establishing the toxicity profile of the experimental arm.

To have fewer patients assigned to placebo, the randomization ratio is 2:1 in favor of the experimental arm. Eligibility criteria were also introduced to exclude patients who are refractory to or who have relapsed within 90 days of receiving a cumulative dose of >18 g/m^2 cytarabine, as they were unlikely to benefit from treatment with the comparator. Young patients with a first CR of >1 year as higher intensity chemotherapy rather than single-agent cytarabine dose was considered a more appropriate treatment option for those patients.

Eligibility criteria

Key inclusion and exclusion criteria are listed in Table 2. Overall, eligible patients are aged ≥18 years and have confirmed first or second R/R AML per WHO classification [34]. An Eastern Cooperative Oncology Group performance status ≤2, acceptable hepatic/renal function and ≤2 prior induction regimens (excluding HSCT) for first-line therapy, including cytarabine with an anthracycline or anthracenedione, are also required. The exclusion of first-relapsed patients aged <60 years with a first CR duration of >1 year from enrollment omits patients in whom standard practice would be to use intensive chemotherapy. Patients treated with >2 prior induction regimens as first-line therapy or who had documented refractory disease or relapse(s) within 90 days of receiving a regimen including a cumulative dose of cytarabine ≥18 g/m^2 are excluded to limit the study population to patients with the potential to respond to the 1 g/m^2 intermediate once daily iv. (over 1–3 h) dose of cytarabine. Patients with secondary AML were also excluded from this study. As not every *TP53* mutation negatively affects p53 functionality [35], patients are being enrolled regardless of *TP53* mutation status.

Study end points & outcome measures

The primary end point of this study is OS in the *TP53*-WT population. Secondary efficacy end points in the *TP53*-WT population include CR rates per investigator during the induction cycle, EFS, overall remission rates (CR, CRp and CRi) during the induction cycle, duration of CR, the proportions of allogeneic HSCT following CR and OS and CR in the subpopulation with clinically actionable mutations (i.e., *FLT3*, *IDH1* and *IDH2*). Additional study end points are safety, pharmacokinetics (PK) and patient-reported outcomes (PROs) using the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EuroQol 5 Dimension 5-Level Questionnaire (EQ-5D-5L). Exploratory end points include pharmacodynamic (PD)/biomarkers, CR$_{MRD}$ rate in all patients and the *TP53*-WT population, OS in the intention-to-treat (ITT) population, secondary efficacy end points in the ITT population, CR during treatment, proportion of allogeneic HSCT regardless of response and leukemia-free survival.

Safety measures include the incidence, severity, nature and seriousness of AEs and the incidence of clinically significant laboratory abnormalities. PK measures include apparent clearance and apparent volume of distribution, maximum concentration, steady-state concentration at the end of a dosing interval, area under the concentration–time curve (AUC) during one dosing interval, AUC$_{0-24 h}$ and the half-life of idasanutlin, as well as the total

clearance and volume of distribution of cytarabine and the effect each agent has on the PK of the other. Related to PD/biomarkers, mutational analysis in *TP53*, *FLT3*, *IDH1*, *IDH2* and other tumor-associated genes is being conducted and serum macrophage inhibitory cytokine-1 profiles, MDM2 expression, gene signatures and minimal residual disease are being assessed.

Statistical analysis

A mechanistic simulation model, incorporating cure proportion [26], was used to determine sample size, with a total of 275 OS events in patients with *TP53*-WT required to provide 82% power for the primary analysis to detect an OS hazard ratio of 0.67 corresponding to an improvement in median OS from 6 to 9 months in favor of the experimental arm. All patients are randomized to this study regardless of *TP53* mutation status. Based on the assumption that 85% of patients will have *TP53*-WT disease and 15% will have *TP53*-mutant disease, 440 patients are being enrolled in this study.

All randomized patients will be included in the ITT population. Patients will be assessed per the treatment arm to which they were randomized. The *TP53*-WT population, which will be assessed for the primary end point, includes all randomized patients with *TP53*-WT as determined by a central laboratory test. OS in the primary end point is defined as the time from randomization to death due to any cause. Kaplan–Meier methodology will be used to estimate survival curves in each treatment arm. The treatment effect of idasanutlin combined with cytarabine versus placebo combined with cytarabine will be described as a hazard ratio using a stratified Cox proportional-hazard regression, including a 95% CI. To adjust for multiple statistical testing of the primary and key secondary efficacy end points, thus controlling the overall type I error at a two-sided significance level of 5%, the fixed sequence testing procedure will be utilized. Treatment responses will be assessed at the end of each cycle and summarized by study arm along with the two-sided 95% CI by the Pearson–Clopper method. Secondary end points such as CR, EFS, overall remission, duration of response, proportion of HSCT following a CR and OS and CR in *FLT3*, *IDH1* and *IDH2* populations are part of this analysis. PD/biomarker analyses will be presented using listings and descriptive summary statistics.

All patients who received any amount of idasanutlin, placebo or cytarabine will comprise the all-patient safety population. Patients with *TP53*-WT who received any amount of study drug will comprise the *TP53*-WT safety population. All AEs will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Event version 4.03 grading system.

For PROs, the evaluable patients will include the randomized population with baseline and ≥1 post-baseline PRO assessment(s). PRO evaluable patients will be included in descriptive analyses of visit summaries and change from baseline as well as responder assessments. All PRO analyses will be conducted based on the assigned treatment arm at randomization.

Discussion & future perspective

The assessment of futility based on an intermediate end point of confirmed CR corresponded to an integrated Phase II step, which allowed continuous patient enrollment while preserving trial integrity and minimizing bias, since the sponsor and investigators were blinded to the data. Although accelerating development in the AML disease setting was desired at the time of study design, as only later new drugs in targetable subpopulations were approved, skipping Phase II altogether was considered unsound. Integrating a Phase II step with an intermediate end point was therefore considered preferable as risk mitigation to reduce development time, compared with traditional Phase II and III trials, as well as patient exposure, while allowing early stopping for less than expected treatment performance. Absence of an accepted standard of care in R/R AML made the choice of a comparator arm a challenge for this study. While several chemotherapeutic combination therapies are used globally, none has proven superior in clinical trials. Prior example and study design consideration led to selection of a placebo-controlled study design.

The specific design of the MIRROS study with its acceleration of development and reduction of patient exposure made establishment of a clear safety profile a necessity. The benefit of allowing clear assessment of the experimental arm safety profile as well as the possibility to operationalize a randomized blinded study favored selection of a placebo-controlled design. In line with this conclusion, the eligibility criteria limited study enrollment to patients who could also expect benefit from treatment in the control arm.

In mid-2017, MIRROS successfully met the safety and efficacy criteria for continuation without modification, as evaluated during the assessment of the interim futility analysis. As of April 2019, approximately 90% of the projected patient population was recruited and accrual is still ongoing. An interim efficacy analysis is planned to

occur when approximately 80% of the death events have been observed in the *TP53*-WT population, leading to a potential readout of the data in early 2020. Alternatively, if data are still not mature, the study will proceed to final analysis.

Conclusion

MIRROS investigates whether idasanutlin in combination with cytarabine may improve OS in patients with R/R AML compared with placebo in combination with cytarabine. The results of this study may lead to the availability of a novel treatment option for patients with R/R AML.

Executive summary

Background
- For patients with acute myeloid leukemia (AML), the risk of relapse is high and a substantial proportion will have primary refractory disease.
- In relapsed or refractory AML, there is no standard treatment regimen. The prognosis in this population is poor and an unmet medical need remains despite advances in therapeutic approaches.
- Idasanutlin, is a potent small molecule MDM2 inhibitor that disrupts the p53–MDM2 interaction, leading to activation of p53.
- Idasanutlin in combination with cytarabine demonstrated acceptable safety and promising clinical activity in a Phase I/Ib study in patients with AML. The recommended dose for Phase III evaluation of idasanutlin was also identified in this study.

MIRROS
- The global, randomized, double-blind, Phase III MIRROS trial is evaluating idasanutlin in combination with cytarabine versus placebo in combination with cytarabine in patients with relapsed or refractory AML.
- MIRROS includes a futility interim analysis that serves as an integrated Phase II step, thus allowing for continuous enrollment of patients and accelerated development.
- The futility interim analysis used a high bar on the odds ratio for durable complete remission and event-free survival and stop/go gating criteria for safety; MIRROS met its continuation criteria in mid-2017.
- Enrollment is ongoing in the Americas, Europe and Asia-Pacific region; 90% of the projected patient population has been recruited as of April 2019.
- The primary end point is overall survival in the *TP53* wild-type population.
- The interim overall survival analysis will allow for treatment benefit to be assessed earlier in this aggressive disease.

Ethical conduct of research

All patients provided written informed consent by signing and dating the consent forms prior to study participation. The study protocol, informed consent documents, patient information and other study-related materials were approved by the Institutional Review Board or Ethics Committee at each study site.

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