A phase 2/3 trial of oral azacitidine in patients with low- or intermediate-risk myelodysplastic syndromes

MDS-367

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Introduction

- Myelodysplastic syndromes (MDS) are a heterogeneous group of bone-marrow disorders characterized by ineffective erythropoiesis resulting in peripheral blood cytopenias and an increased risk for progression to acute myeloid leukemia (AML). MDS are broadly classified into lower- or higher-risk disease per the Revised International Prognostic Scoring System (IPSS-R)[1-3]
- Current treatments for symptomatic lower-risk MDS (LR-MDS) include erythropoiesis stimulating agents, red blood cell (RBC)/platelet transfusions, luspatercept (for MDS with ring sideroblasts [RS]), and lenalidomide (for MDS with deletion of 5q [MDS-del(5q)])[2]
  - However, unmet needs remain for LR-MDS as limited options are available for patients who are unresponsive to or have failed treatment, or become transfusion dependent[1]
- A phase 3, placebo-controlled, AZA-MDS-003 study evaluated oral azacitidine (Oral-AZA) 300 mg QD for 21 days/28-day (28d) cycle in patients with LR-MDS with RBC transfusion dependent anemia and thrombocytopenia[4]
  - Oral-AZA treatment resulted in improvements in transfusion independence and blood values
  - Gastrointestinal and hematologic adverse events were more common in the Oral-AZA arm versus placebo arm. More early deaths (days 1-56) were reported in the Oral-AZA arm versus placebo arm (n = 16 vs. 6); however, these patients had severe neutropenia and thrombocytopenia at baseline, and early deaths did not impact overall survival which remained similar between the two arms
- A new phase 2/3 trial is ongoing to evaluate the 14-day (14d) Oral-AZA regimens in patients with IPSS-R-defined low- or intermediate-risk MDS

Methods

Study design

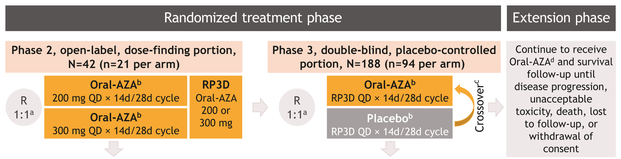
- CA055-026 (NCT05469737)[5] is an ongoing, multicenter, randomized, phase 2/3 trial designed to evaluate the safety and efficacy of Oral-AZA plus best supportive care in patients with IPSS-R-defined low- or intermediate-risk MDS **(Figure 1, Table 1, Table 2)**

Table 1. CA055-026 trial key inclusion and exclusion criteria

Screening	
Key inclusion criteria	**Key exclusion criteria**
• ≥ 18 years of age • WHO 2016 MDS diagnosis with low or intermediate risk disease per IPSS-R (score 1.5-4.5) — MDS-SLD, MDS-MLD, MDS-RS (SLD or MLD), MDS-U, MDS-EB1, MDS-del(5q), t-MN • ≥ 1 cytopenia (anemia, thrombocytopenia, or neutropenia; **Table 2**) • Eastern Cooperative Oncology Group Performance Status of 0-2	• Prior malignancies and 1) anticipated median life expectancy of < 12 months and/or have had 2) active treatment within 24 weeks prior to randomization • Hypoplastic MDS with ≤ 10% marrow cellularity, MDS with grade 2/3 marrow fibrosis, MDS-EB2, overlapping syndrome (MDS/MPN), CMML, atypical CML, or unclassified MPD • History of significant cardiac disease (≤ 6 months), HIV, HCV, or active HBV • Low absolute neutrophil count (< 0.5 × 10^9/L) or abnormal liver or kidney function • Prior treatment: hypomethylating agent (any time); chemotherapeutic, investigational, steroid, or hematopoietic agents, luspatercept, or lenalidomide (≤ 1-8 weeks of randomization depending on the agent)

CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS-EB1, MDS with excess blasts-1; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MDS-EB2, MDS with excess blasts-2; MDS-MLD, MDS with multilineage dysplasia; MDSSLD, MDS with single lineage dysplasia; MDS-U, MDS unclassifiable; MPD, myeloproliferative disorder; MPN, myeloproliferative neoplasms; t-MN, therapy-related myeloid neoplasms; WHO, World Health Organization.

Figure 1. CA055-026 trial design and endpoints



	Phase 2	Phase 3
Primary endpoints	• Adverse events per NCI CTCAE v.5.0 • Rate of CR per IWG 2006 ≤ 6 cycles • RP3D per safety, efficacy, available PK/PD data	• Rate of CR per IWG 2006 ≤ 6 cycles
Secondary endpoints	• ORR[e] and duration ≤ 6 cycles, best response • CR duration • Rate and duration of 84-day pRBC-TI ≤ 6 cycles • Rate and duration of 84-day PLT-TI ≤ 6 cycles	• Rate and duration of 84-day pRBC-TI ≤ 6 cycles • Rate and duration of 84-day PLT-TI ≤ 6 cycles • Rate and duration of pRBC transfusion reduction • CR duration • ORR[e] and duration ≤ 6 cycles, best response • Overall survival and event-free survival,[f] time to AML transformation, and time to subsequent therapy • Iron parameters • Adverse events per NCI CTCAE v.5.0 • Change from baseline: FACT-An, QUALMS, and EQ-5D-5L • Healthcare resource use
Exploratory endpoints	• PK/PD • Assessment of DNA methylation and biomarkers[g] • Rate and duration of 84-day pRBC-TI per IWG 2018	• PK/PD • Assessment of DNA methylation and biomarkers[g] • Rate and duration of 84-day pRBC-TI per IWG 2018 • Safety/efficacy of participants who crossed over from placebo to the Oral-AZA arm

[a]Stratified by IPSS-R classification (low vs. intermediate) and pRBC-TD (transfusion independent vs. low transfusion burden vs. high transfusion burden); [b]Dose modifications are permitted for managing treatment-related toxicity; [c]Patients receiving placebo with stable disease at treatment cycle 6 disease assessment or with documented disease progression after ≥ 3 treatment cycles will have the option to cross over into the Oral-AZA arm; [d]Patients benefiting from treatment with Oral-AZA may continue to receive it; [e]ORR includes CR, PR, mCR, HI-E, HI-P, and HI-N (IWG 2006); [f]Event defined as death, AML, or MDS-EB2; [g]Molecular and/or cellular markers in bone marrow and/or peripheral blood.

AML, acute myeloid leukemia; CR, complete remission; DNA, deoxyribonucleic acid; EQ-5D-5L, Five-level EuroQol five-dimensional questionnaire; FACT-An, Functional Assessment of Cancer Therapy-Anemia; HI-E, hematologic improvement-erythroid; HI-N, HI-neutrophil; HI-P, HI-platelet; IWG, International Working Group; mCR, marrow complete remission; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; PLT, platelet; PR, partial remission; pRBC, packed red blood cells; pRBC-TD, pRBC transfusion dependence; QD, once daily; QUALMS, Quality of Life in Myelodysplasia Scale; R, randomization; RP3D, recommended phase 3 dose; TI, transfusion independence.

Table 2. Criteria for cytopenias

Cytopenia	Definitions
Anemia: (1 or 2) and 3 and (4 or 5, if applicable)	1. pRBC transfusion dependent anemia: average > 1 unit of pRBC transfused in participants with ≤ 9 g/dL hemoglobin over 56 days prior to randomization 2. Non-transfusion dependent anemia: 0-1 units of pRBC transfused in participants with ≤ 9 g/dL hemoglobin on ≥ 3 readings ≥ 2 weeks apart over 56 days prior to randomization plus the presence of MDS-EB1 or IPSS-R-defined intermediate-risk MDS 3. Refractory/relapsing after prior ESA treatment or ineligible to receive ESA treatment[a] 4. MDS-RS only: refractory/relapsing after prior luspatercept treatment, ineligible to receive luspatercept, or have no access to luspatercept[b] 5. MDS-del5q only: refractory/relapsing after prior lenalidomide treatment, ineligible to receive lenalidomide, or have not access to lenalidomide[b]
Thrombocytopenia plus ≥ 1 high-risk features: 1 or 2	1. Presence of MDS-EB1 or IPSS-R-defined intermediate-risk MDS and platelet count < LLN on ≥ 3 readings ≥ 2 weeks apart over 56 days prior to randomization 2. Presence of a chronic thrombocytopenia with a PLT count of < 50 × 10^9/L on ≥ 3 readings ≥ 2 weeks apart over 56 days prior to randomization
Neutropenia (isolated)	Presence of MDS-EB1 or IPSS-R intermediate and ANC of 0.5-1.5 × 10^9/L on ≥ 3 readings ≥ 2 weeks apart and no G-CSF or GM-CSF treatment over 56 days prior to randomization

[a]**Failure of ESA (1 or 2 or 3): 1.** Serum erythropoietin level of > 500 mU/mL in ESA-naive participants. **2.** Persistent transfusion-dependence or no improvement in hemoglobin level (IWG 2006 criteria) despite a minimum ESA dose of > 40,000 U/week r-HuEPO × 8 weeks or equivalent dose of darbepoetin or other erythropoietin agent. ESA + G-CSF for an additional 8 weeks can be considered based on local guidelines before declaring refractory to ESA (optional). **3.** Prior ESA responders with a new episode of transfusion-dependency (≥ 1 unit of pRBC given for a hemoglobin ≤ 9 g/dL) despite continuous ESA treatment, absent of secondary causes (eg, bleeding events, surgery); or any ESA-related severe AE leading to permanent discontinuation of ESA; [b]**Failure of luspatercept or lenalidomide (1 or 2 or 3): 1.** Persistent transfusion-dependence or no improvement in hemoglobin level (IWG 2006 criteria) despite adequate treatment of luspatercept at MTD for ≥ 9 weeks (i.e. ≥ 3 cycles at full dose), or lenalidomide treatment at MTD for ≥ 4 months. **2.** Prior luspatercept/lenalidomide responders with a new episode of transfusion dependency (≥ 1 unit of pRBC given for a hemoglobin of ≤ 9 g/dL) despite continuous treatment and/or retreatment with luspatercept/lenalidomide at MTD, absent of secondary causes (eg, bleeding events, surgery). **3.** Any severe drug-related AE leading to a permanent treatment discontinuation.

AE, adverse event; ANC, absolute neutrophil count; ESA, erythropoiesis stimulating agents; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-marcrophage colony-stimulating factor; LLN, lower limit of normal; MTD, maximum tolerated dose; r-HuEPO, recombinant human erythropoietin

Statistical analysis

Sample size

- The study is planned to enroll ~230 participants
  - Phase 2: sample size (N = 42 total; n = 21 per arm) was based on clinical judgement considering 4% drop-out
  - Phase 3: sample size (N = 188 considering 4% drop-out) was based on the participants needed to provide:
    - 97% power (one-sided alpha, 0.025) to detect 20% difference in complete remission (CR) rate between treatment arms (25% Oral-AZA vs. 5% placebo)
    - 93% power (assuming 75% of 188 participants; one-sided alpha, 0.025) to detect 22% difference in 84-day pRBC-TI rate between arms (28% Oral-AZA vs. 6% placebo)

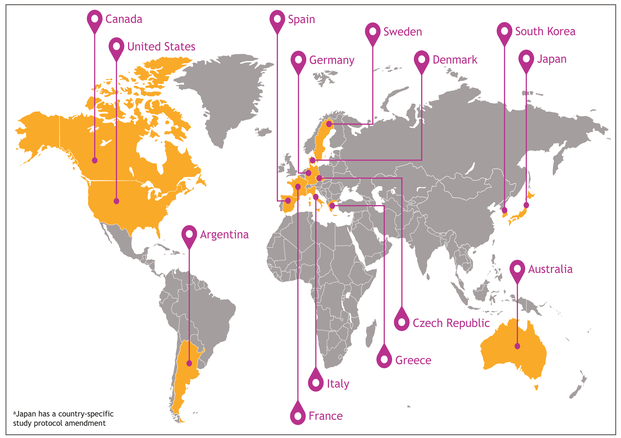
Efficacy and safety analyses (conducted using SAS® Version 9.4 or higher)

- Adverse events will be summarized by system organ class and preferred term, and by grade
- The rate difference between the two treatment arms will be tested using stratified Miettinen and Nurminen (M&N) test along with 95% confidence intervals using M&N approach. Gate-keeping approach will be used to control overall type I error on primary endpoint (CR) and key secondary endpoint (84-day pRBC-TI)

Enrollment

- The study began in December 2022 and is currently recruiting patients for Phase 2 part of the study (**Figure 2**)

Figure 2. Countries with active study sites as of July 2023[a]



[a]Japan has a country-specific study protocol amendment

References

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