Phase 1/2, open-label, dose-escalation, dose-expansion study of menin inhibitor DSP-5336 in adult patients with acute leukemia with and without *mixed-lineage leukemia* (*MLL*)–rearrangement (r) or *nucleophosmin 1* (*NPM1*) mutation (*m*)

TPS7066

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Introduction

- Acute leukemias, such as acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), are difficult to treat and are associated with poor outcomes[1,2]
- Patients with acute leukemia with rearrangements of the *MLL* gene or a mutation in the *NPM1* gene (with concomitant *FLT3*-internal tandem duplication mutations) have a worsened prognosis[3-5]
  - These genetic risk factors have been linked to upregulation of homeobox A9 (HOXA9) and myeloid ecotropic viral integration site 1 (MEIS1), which further promote leukemia pathogenesis and cell proliferation (**Figure 1**)[6,7]
- DSP-5336 is a menin-MLL interaction inhibitor that has demonstrated antitumor activity in the following models[8]:
  - *In vitro*, utilizing human acute leukemia cell lines with *MLL*–r or *NPM1m*
  - *In vivo*, utilizing AML xenograft models with *MLL*–r or *NPM1m*
- Herein, we describe the design of an ongoing phase 1/2 study of DSP-5336 in patients with relapsed/refractory (R/R) AML or acute ALL

Figure 1. Mechanism of action of DSP-5336

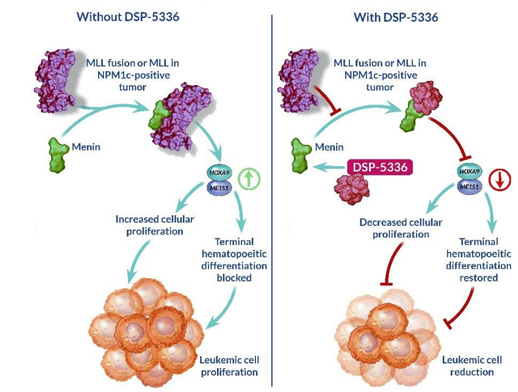


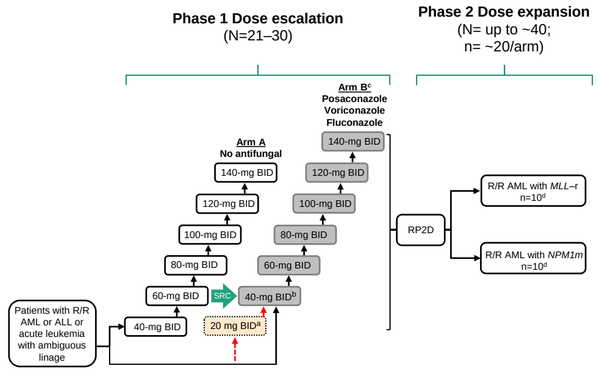
Figure from: Sumitomo Pharma Oncology, Inc., Available at: https://www.sdponcology.com/pipeline/?gclid=EAIaIQobChMIlfeEsqPd9gIV1O2zCh20uQETEAAYASABEgLT4_D_BwE#DSP-5336_background. Accessed March 23, 2022.
HOXA9, homeobox A9; MEIS1, myeloid ecotropic viral integration site 1; MLL, mixed-lineage leukemia; NPM1c, nucleophosmin 1 mutation.

Methods

- NCT04988555 is an open-label, single-arm, phase 1/2 study of oral DSP-5336 (**Figure 2**):
  - In phase 1, there will be 2 parallel escalation arms: patients who do not receive concomitant azole antifungal medication (Arm A) and patients who receive antifungal azoles (ie, posaconazole, voriconazole, or fluconazole) (Arm B) (**Table 1**)
    - Patients in the first cohort of Arm A will be administered DSP-5336 40 mg twice daily (BID)
    - After Arm A has cleared the dose level of 60 mg BID or above, dose escalation in Arm B may begin at 40 mg BID
    - If adverse events or pharmacokinetic (PK) data observed in Arm A suggest a lower starting dose for Arm B, then patients in the first cohort of Arm B will be administered DSP-5336 20 mg BID
  - In phase 2, there will be 2 arms: R/R AML with *MLL*–r and R/R AML with *NPM1m*
    - Patients will be treated at the recommended phase 2 dose (RP2D), established in phase 1, to evaluate clinical activity and safety

Study Design

Figure 2. Study design



[a]If a patient presents on azole and Arm A has not started enrolling, or if patients treated in Arm A at 40 mg BID have not yet been evaluated by the SRC, patients may be enrolled in Arm B at a reduced dose as shown, provided the investigator consults with the medical monitor, who agrees.
[b]If unexpected AEs are seen in Arm A at dose level 1 or 2, consider starting Arm B at <40 mg BID.
[c]Arm B starts after SRC clearance of dose level (60 mg BID cohort) in Arm A.
[d]Clinical activity will be monitored using the Bayesian posterior probability to optimize enrollment and to handle the recommended target response rate with Bayesian stopping rules.
AE, adverse event; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia, BID, twice daily, MLLr, mixed-lineage leukemia rearrangement; NPM1m, nucleophosmin 1 mutation; RP2D, recommended phase 2 dose; SRC, safety review committee.

Patients

Table 1. Key eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • ECOG PS ≤2 • WBC <30,000/μL • Adequate renal and hepatic function • Life expectancy ≥3 months **Phase 1 only** • Refractory[a] or relapsed[b] AML, ALL, or acute leukemia of ambiguous lineage[c] **Phase 2 only** • Refractory[a] or relapsed[b] AML[d] • KMT2A (*MLL*)-fusion *or NPM1* mutation, which includes those with coexisting *FLT3* genomic alterations and/or *IDH1/2* mutations	• Prior menin-MLL inhibitors • Acute promyelocytic leukemia • Immediately life-threatening or severe complications of leukemia • Active central nervous system leukemia • Received high cumulative doses of anthracycline[e] • Abnormal ECGs that are clinically significant[f] • LVEF <45% • History of Torsades de Pointes

For a comprehensive list of eligibility criteria, please refer to Clinicaltrials.gov (NCT04988555).
[a]Did not achieve CR or CRi, defined by the 2017 ELN guideline under initial intensive therapy, or did not achieve CR, CRi, or partial remission after an initial sufficient time course of treatment with HMA or LDAC, with "sufficient time course" defined as at least 4 cycles of HMA or LDAC therapy, or at least 2 cycles of combination therapy (ie, HMA or LDAC in combination with venetoclax or glasdegib). [b]Diagnosed by bone marrow assessment or by the appearance of peripheral blasts after the achievement of CR or CRi defined by 2017 ELN guideline with or without consolidation or maintenance, and with or without HSCT.
[c]According to WHO classification, as determined by pathology review at the treating institution, and who failed available standard therapies known to be active for their AML or ALL; participants who are candidates for stem cell transplantation must have been offered this therapeutic option. [d]According to WHO classification, as determined by pathology review at the treating institution, and who failed available standard therapies known to be active for their AML; participants who are candidates for stem cell transplantation must have been offered this therapeutic option. [e]Cumulative doses exceeded the upper limit per the label approved in each country or investigator discretion (if there is no label restriction, investigator must state the cumulative dose received for each patient and sign to indicate that, in his/her medical opinion, stated prior dose of the agent does not put patient at undue risk of anthracycline-related cardiotoxicity. [f]Such as QT prolongation (QTc >450 msec for males and >470 msec for females), with QTc corrected according to Fridericia's formula.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CAR-T, chimeric antigen receptor T-cell; CR, complete remission, CRi, complete remission with incomplete hematologic recovery; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European Leukemia Net; *FLT3*, fms-like tyrosine kinase 3; GVHD, graft versus host disease; HMA, hypomethylating agents; HSCT, hematopoietic stem cell transplantation; *IDH1/2*, isocitrate dehydrogenase isoforms 1 and 2; KMT2A, lysine (K)-specific methyltransferase 2A; LDAC, low-dose cytarabine; LVEF, left ventricular ejection fraction; *MLL*, *mixed-lineage leukemia*; *NPM1m*, *nucleophosmin 1* mutation; WBC, white blood cell; WHO, World Health Organization.

Objectives

- The primary objectives of the phase 1, dose-escalation part of this study are:
  - Safety and tolerability
  - RP2D
- The primary objective of the phase 2, dose-expansion part of this study is:
  - Clinical activity

Endpoints

- All study endpoints are summarized in **Table 2**

Table 2. Endpoints

	Phase 1 (R/R AML, ALL or acute leukemia with ambiguous lineage)	Phase 2 (R/R AML with *MLL*–r or *NPM1m*)
Primary	**Safety** • DLTs; TEAEs; SAEs; changes in vital signs, PEs, clinical lab values, ECG parameters, and ECHO parameters **Tolerability** • Dose interruptions, reductions, and/or discontinuations	**Clinical responses** • Response endpoints CR (MRD−), CR, CRh, CRi, PR, MLFS • Composite response endpoints CR + CRh OR (CR [MRD−] + CR + CRh + CRi + MLFS + PR) • Time to response endpoints DOR, TTR, time to CR • Other time to event endpoints TI, EFS, RFS, OS
Secondary	**Pharmacokinetics** • Plasma DSP-5336 concentration-time profiles and PK parameters as a single agent and with selected azoles **Clinical responses** • Response endpoints CR (MRD−), CR, CRh, CRi, PR MLFS • Composite response endpoints (=CR [MRD−] + CR + CRh + CRi + MLFS + PR) • Time to response endpoints time to CR, DOR, TTR • Other time to event endpoints TI, EFS, RFS, OS **Cardiac Safety** • QT interval changes and morphology	**Safety** • DLTs; TEAEs; SAEs; changes in vital signs, PEs, clinical lab values, and ECG parameters **Tolerability** • Dose interruptions, reductions, and/or discontinuations
Exploratory	**PD, PK and biomarkers** • DSP-5336-induced changes in gene expression levels • PK exposure-response relationship endpoints (such as: PD markers and hematologic response; PD markers and dose/AUC) • Detection DSP-5336 metabolites • Analysis of other genomic alteration and genes that may be found to be relevant in the control of acute leukemias, as needed	**PD and biomarkers** • DSP-5336-induced changes in gene expression levels • Analyses of other genomic alterations and genes that may be found relevant in the control of acute leukemias, as needed

AE, adverse event; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DLT, dose-limiting toxicity; DOR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; EFS, event-free survival; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; OR, objective response; PD, pharmacodynamics; PE, physical examination; PK, pharmacokinetics; PR, partial response; RFS, relapse-free survival; SAE, serious AE; TEAE, treatment-emergent AE; TI, transfusion independence; TTR, time to response.

Statistical Design and Analysis (Phase 1)

- Approximately 21–30 patients will be enrolled in the phase 1, dose escalation portion of the study:
  - Dose-escalation will start in Arm A at a dose level of 40 mg BID and will escalate after Arm A clears the DLT (defined in **Table 3**) period
    - Dose escalation will follow a Bayesian logistic regression model along with PK and pharmacodynamic assessments along with dose-escalation with overdose control principle
  - Each dose level will be evaluated in a cohort of 1 to 6 DLT-evaluable patients
    - In each dose cohort, the second and subsequent patients will be dosed after all safety assessments for cycle 1 day 8 have been completed for the first patient
    - A dose level will be considered safe if the probability of excessive toxicity, ie, the probability of a DLT rate >33% is ≤25%
    - If a DLT is observed, at least 3 DLT-evaluable patients will need to be treated in that specific cohort
    - If, during the DLT period, a patient in Arm A (no azole-class antifungals at enrollment) at any given dose must start on an azole-class antifungal for medical necessity, the patient would be considered DLT-evaluable if they received ≥75% of the planned first 28-day dose of DSP-5336 without concomitant azole therapy
- Data will be summarized primarily using descriptive statistics

Table 3. Definition of MTD and DLT

	Definition
MTD	• Highest drug dosage that is unlikely (<25% posterior probability) to cause DLT in >33% of the treated patients in the first cycle of DSP-5336 treatment
DLT	• Grade ≥3 non-hematologic events, except the following: – Grade 3 fatigue that resolves to grade ≤2 within 7 days – Grade 3 anorexia, diarrhea, nausea, or not requiring tube feeding, total parenteral nutrition, or hospitalization – Blood chemistry abnormalities without clinically significant symptoms that resolve to grade ≤2 ≤72 hours – Infections that are direct complications of leukemia-related cytopenia • Myelosuppression with the persistence of grade 4 neutropenia or thrombocytopenia in the absence of leukemia assessed ≥28 days after treatment initiation • Grade 3 febrile neutropenia lasting more than 28 days • New onset cardiac failure or worsening symptomatic cardiac failure based on the New York Heart Association Functional Classification • Reduction of ejection fraction ≥10%, as assessed by ECHO, with clinical symptoms • Hepatic injury consistent with Hy's Law, defined as AST or ALT ≥3 times the ULN in the setting of total bilirubin ≥2 times the ULN, without findings of cholestasis or other reason to explain the combination of increased AST and ALT and total bilirubin • Treatment-related death

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; ECHO, echocardiogram; MTD, maximum tolerated dose; ULN, upper limit of normal.

Statistical Design and Analysis (Phase 2)

- Up to approximately 40 patients will be enrolled in the phase 2, dose-expansion portion of the study:
  - A Bayesian approach will be used to continuously assess clinical activity (posterior probability of achieving complete remission [CR] + complete remission with partial hematologic recovery [CRh] rate above pre-specified threshold)
  - The posterior probability will be updated continuously for patients with *MLL*–r and with *NPM1m* as more patients are enrolled into each cohort and later become response-evaluable
  - Enrollment may be stopped early due to lack of efficacy based on pre-specified posterior probability parameters
- Data will be summarized primarily using descriptive statistics
- Duration of response, event-free survival, relapse-free survival, and overall survival will be summarized via the Kaplan–Meier method

Conclusions

- This phase 1/2 study of oral DSP-5336 in patients with acute leukemia is currently recruiting in the United States, Canada, and Japan
- For further information, please refer to ClinicalTrials.gov (NCT04988555)

References

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