DSP-5336-101

Studio di fase 1/2, in aperto, di incremento della dose, di espansione della dose di DSP-5336 in pazienti adulti affetti da leucemia acuta con e senza riarrangiamento del gene della leucemia a linea cellulare mista (MLL) o mutazione del gene della nucleofosmina 1 (NPM1)

Patologia: Pazienti adulti con leucemie acute che abbiano già ricevuto la terapia standard, ma la cui leucemia si sia ripresentata. Altri requisiti per la partecipazione includono la presenza di cambiamenti o mutazioni a carico di uno o più geni (per esempio, riarrangiamento di MLL o mutazione di NPM1)

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Inclusion Criteria

For patients in the Phase 1 dose-escalation portion of the study:

1. Have a confirmed diagnosis of refractory or relapsed AML, ALL, or acute leukemia of ambiguous lineage according to World Health Organization (WHO) 2022 classification, as determined by pathology review at the treating institution, and who failed available standard therapies known to be active for their AML, ALL, or acute leukemia of ambiguous lineage.* Participants must have a documented KMT2A (MLL) fusion or NPM1 mutation, which includes those with coexisting FLT3 genomic alterations and/or IDH1/2 mutation, and those who are candidates for stem cell transplantation must have been offered this therapeutic option.

a. Refractory is defined as: patient did not achieve complete remission (CR) or complete remission with incomplete hematologic recovery (CRi), defined by the 2017 European LeukemiaNet (ELN) guideline under initial intensive therapy, or did not achieve CR, CRi, morphologic leukemia-free state (MLFS) or partial remission (PR) after an initial sufficient time course of treatment with hypomethylating agents (HMA) or low-dose cytarabine
(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) (Hartmut et al 2017)

b. Relapse is defined as: relapse 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

*Examples of standard therapies include, but are not limited to: high dose cytarabine with/without anthracycline, FLAG (fludarabine, cytarabine, idarubicin, G-CSF), or targeted therapy based on the defining genetic anomaly or cell surface marker as follows: AML with IDH1 mutation: ivosidenib or olutasidenib, AML with IDH2 mutation: enasidenib, AML with FLT3 mutation: gilteritinib, AML with CD33+: gemtuzumab ozogamicin, ALL with
CD22+: inotuzumab ozogamicin, ALL with CD19+: blinatumomab, and ALL Phi+: ponatinib

For patients in the Phase 2 dose-expansion portion of the study:

2. Have a confirmed diagnosis of refractory or relapsed AML according to WHO 2022 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. See Criterion 1 for definitions of refractory and relapsed.
3. Have documented KMT2A (MLL)-fusion or NPM1 mutation, which includes those with coexisting FLT3 genomic alterations and/or IDH1/2 mutations

For all patients:

4. Be ≥18 years of age
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2
6. White blood cell (WBC) count must be below 30,000/μL at the time of enrollment and prior to starting study treatment (Hydroxyurea will be allowed prior to enrollment and during study treatment)
7. Have any prior treatment-related toxicities resolved to ≤Grade 1 prior to enrollment, with the exception of ≤Grade 2 alopecia or neuropathy
8. Have adequate renal and hepatic function at Screening as determined by:
a. Clearance of creatinine (CLcr) level ≥50 ml/min, assessed by the Cockcroft-Gault formula
b. Total bilirubin ≤1.5 times the upper limit of normal (ULN) (or ≤2.0 times ULN for patients with known Gilbert's syndrome)
c. Aspartate aminotransferase (AST) ≤3.0 times ULN
d. Alanine aminotransferase (ALT) ≤3.0 times ULN
9. Be willing to attend study visits as required by the protocol
10. Have an estimated life expectancy ≥3 months, based on the investigator's assessment
11. Have a negative serum or urine pregnancy test, if female patient of childbearing potential. Females of childbearing/child-producing potential are defined as women who have (1) experienced menarche and have not undergone sterilization procedures (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or (2) have not experienced menopause (defined as having amenorrhea continuously for more than 12 months that is not
determined to be drug induced, or who are taking hormone replacement therapy with serum follicle stimulating hormone >35 mIU/mL).
12. Must agree to use a combination of 2 or more different contraception methods (oral contraceptives/ implantable hormonal contraceptives*, and a barrier method*) or use prevention of pregnancy measures (ie, agreement to
refrain completely from heterosexual intercourse) during the study and for 6 months (for females and males alike) after the last dose of study drug, if male or female patient of child-producing potential
*For sites in Japan only: Implantable hormonal contraceptives, a diaphragm with spermicide, cervical cap with spermicide and contraceptive sponge (spermicide is already in the contraceptive sponge) included in the barrier contraceptive method are not approved and cannot be used in Japan.
13. Have AML/ALL material (eg, bone marrow or peripheral blood) suitable for genomic analysis (eg, MLLr or NPM1 mutations) of AML or ALL genetic alterations

Exclusion Criteria

1. [Criterion removed with protocol amendment]
2. Have a histologic diagnosis of acute promyelocytic leukemia
3. [Criterion removed with protocol amendment]
4. Underwent HSCT or chimeric antigen receptor cell (CAR-T) therapy or other modified T-cell therapy within 60 days prior to the first dose of DSP-5336

5. Received a donor lymphocyte infusion within 28 days prior to the first dose of DSP 5336, or receiving immunosuppressive therapy post-HSCT at the time of Screening, or with clinically active GVHD or GVHD requiring active medical intervention other than the use of topical steroids for ongoing cutaneous GVHD
6. Received antineoplastic agents (except hormonal therapies as adjuvant maintenance for breast or prostate cancers if a patient is taking before starting study treatment, and hydroxyurea given for controlling blast cells) within
14 days prior to the first dose of DSP-5336
7. Received systemic calcineurin inhibitors within 4 weeks prior to the first dose of DSP 5336
8. Received immunotherapy, including tumor vaccines and checkpoint inhibitors, within 42 days or 5 half-lives, whichever is shortest, prior to the first dose of DSP-5336
9. Have been on other investigational treatment within the previous 4 weeks prior to the first dose of DSP-5336
10. Had major surgery within 28 days prior to the first dose of DSP-5336
11. Have active central nervous system leukemia
12. [Criterion removed with protocol amendment]
13. Have abnormal ECGs at screening that are clinically significant, such as QT prolongation (QTc >450 msec for males and >470 msec for females, with QTc corrected according to Fridericia's formula [QTcF])
14. Have a left ventricular ejection fraction (LVEF) <50%, as determined by ECHO
15. Have a history of Torsades de Pointes
16. In the opinion of the treating investigator, have any concurrent conditions that could pose an undue medical hazard or interfere with interpretation of study results; these conditions include, but are not limited to: clinically significant non-healing or healing wounds; concurrent congestive heart failure (New York Heart Association Functional Classification Class III or IV; see Section 21.7); concurrent unstable angina; concurrent cardiac arrhythmia requiring treatment (excluding asymptomatic atrial fibrillation); recent (within the prior 6 months) myocardial infarction; acute coronary syndrome within the previous 6 months; significant pulmonary disease (shortness of breath at rest or on mild exertion), eg, due to concurrent severe obstructive pulmonary disease, concurrent hypertension not controlled with concomitant medication, or diabetes mellitus with more than 2 episodes of ketoacidosis in the prior 6 months
17. Have a known detectable viral load for human immunodeficiency virus or hepatitis C, or evidence of a hepatitis B surface antigen, all being indicative of active infection For sites in Japan only: Hepatitis B core (HBc) antibody or hepatitis B surface (HBs) antibody test should be performed if HBsAg is negative. If HBc antibody or HBs antibody test is positive, HBV DNA quantification test should be performed to confirm that HBV DNA is negative.
18. Have an active, uncontrolled, bacterial, viral, or fungal infection requiring systemic therapy
19. [Criterion removed with protocol amendment]
20. [Criterion removed with protocol amendment]
21. [Criterion removed with protocol amendment]
22. Have known severe dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally, including the inability to swallow oral medication
23. Have a cognitive, psychologic, or psychosocial impediment that would impair the ability of the patient to receive therapy according to the protocol, or adversely affect the ability of the patient to comply with the informed consent process, protocol, or protocol-required visits and procedures

24. Receive concurrent sensitive substrates with a narrow safety window or strong inhibitors or inducers of CYP3A4/5, including specifically: ketoconazole, itraconazole, and isavuconazole. Other antifungals that are used as standard of care to prevent or treat infections are permitted
Note: If a patient is on one of the excluded azole class antifungals and can be switched to a permitted azole 7 or more days prior to study (≥7 days for ketoconazole and itraconazole, ≥21 days for isavuconazole), that patient could be allowed on study (Arm B) with approval of the medical monitor
25. Are pregnant or breastfeeding or planning to become pregnant
Note: Patients who are breastfeeding may be enrolled if they interrupt breastfeeding prior to the first dose of any study drugs and do not feed the baby with breast milk expressed after receiving the first dose of any study drugs. Breastfeeding should not be resumed for at least 6 months after the last dose of study drug.
26. Have any history or complication of interstitial lung disease (for sites in Japan only) and, for clinical sites operating under the European Medicines Agencies, a history of Grade ≥ 2 drug-induced interstitial lung disease or Grade ≥ 2 non-infectious pneumonitis within 6 months of starting study treatment
27. Have a known intolerance or hypersensitivity reaction to components of investigational medicinal product