AOU Città della Salute e della Scienza di Torino – PO Molinette

Titolo:	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:	Leucemia acuta
Tipo di Studio:	monotherapy
Fase:	2
Principali criteri di inclusione:	Have a confirmed diagnosis of refractory or relapsed AML or ALL according to WHO 2022 classification, as determined by pathology review at the treating institution, and who have ≥5% blasts by morphologic assessment in the bone marrow. Patients with extramedullary disease or peripheral blasts as the only manifestation of relapse are not eligible. Patients must have received clinically applicable standard therapies with confirmed survival benefit. a. Refractory is defined as: patient did not achieve marrow remission under previous intensive therapies, or after a sufficient time course of treatment with 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) (Döhner, 2017).* *In rare circumstances, patients may be enrolled after only one cycle of HMA or LDAC in combination with venetoclax or glasdegib if there is clear evidence of disease progression despite optimal dosing and compliance such that a second cycle of the combination regimen would be unethical and would put the patient at risk for disease-associated complications. b. Relapse is defined as: morphologic relapse (ie, ≥5% blasts in marrow) diagnosed by bone marrow assessment after the achievement of marrow remission by prior antileukemia therapies c. Patients must not have had prior exposure to a menin inhibitor

	Have a documented KMT2A (MLL)-fusion or NPM1 mutation assessed at relapse or immediately prior to the determination of refractory status. KMT2A genetic alterations other than fusions (eg, KMT2A-PTD, amplification, point mutation) are not permitted Be ≥18 years of age (or other age criteria of adult if required by local/country law or regulation. For South Korea, be ≥19 years of age). For countries and sites where permitted, for DSP-5336 monotherapy, acute leukemia patients ≥12 years of age who weigh ≥40 kg may be enrolled. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. For DSP-5336 monotherapy, white blood cell (WBC) count must be below 30,000/μL at the time of enrollment and prior to starting study treatment. For the combination arms, WBC count must be below 25,000/μL at the time of enrollment and prior to starting study treatment. (Hydroxyurea and steroid for cytoreduction purpose will be allowed prior to enrollment and during study treatment) Any prior treatment-related toxicities resolved to ≤Grade 1 prior to enrollment, with the exception of ≤Grade 2 alopecia or neuropathy 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 Be willing to attend study visits as required by the protocol Have an estimated life expectancy ≥3 months, based on the investigator's assessment Females of childbearing potential must have a negative serum or urine pregnancy test. Females of childbearing/child-producing potential are defined as women who have (1) experienced menarche and have not undergone sterilization procedures (hysterectomy or bilateral oophorectomy), or (2) have not experienced menopause, as defined in Section 10.3.3. Must agree to use one highly effective contraception method or 2 acceptable methods of birth control (each partner must use one method) or use prevention of pregnancy measures (ie, sexual abstinence, when this is the usual and preferred lifestyle of the patient) during the study and for 6 months (for females and males alike) after the last dose of study drug, if the male or female patient is of child-producing potential. Refer to Section 10.3.3 for complete information on contraception guidelines. For sites in UK: All men and all women of childbearing potential and male patients' partners who are women of childbearing

	potential are required to use a highly effective method of contraception. Have AML/ALL/MDS/MM bone marrow material suitable for genomic analysis (eg, MLLr or NPM1 mutations) of AML, ALL, MDS, or MM genetic alterations. Note: if a bone marrow material is insufficient, an alternative suitable tissue (eg, peripheral blood) must be provided.
Principali criteri di esclusione:	Have a history of Torsades de Pointes 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 21.2); 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 Have an active and uncontrolled bacterial, viral, or fungal infection requiring parenteral therapy Note: Patients must be afebrile with negative blood cultures at least 72 hours prior to Cycle 1 Day 1. 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 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/assent process, protocol, or protocol-required visits and procedures 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, ≥14 days for isavuconazole), that patient could be allowed on study (Arm B). 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. Have any history or complication of interstitial lung disease (for sites in Japan, in Phase 1 dose escalation). For clinical sites in the EU, have a history of Grade ≥ 2 drug-induced interstitial lung disease or Grade ≥ 2 non-infectious pneumonitis within 6 months of starting study treatment. Have plasma cell leukemia (>2.0 x 109 /L plasma cells in blood by standard differential) (for patients with MM) For patients intending to enroll into the combination cohort with gilteritinib: patients must be gilteritnib-naïve or -sensitive and have not received a FLT3 inhibitor in the relapsed or refractory setting (prior FLT3 inhibitor in front line therapy is allowed) Have a known intolerance or hypersensitivity reaction to components of any of the investigational medicinal products
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