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POSTER ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Phase 1/2 First-in-Human Study of the Menin-MLL Inhibitor DSP-5336 in Patients with Relapsed or Refractory Acute Leukemia

Naval Daver, MD[1], Joshua F. Zeidner, MD[2], Junichiro Yuda, MD PhD[3], Justin M. Watts, MD[4], Mark J. Levis, MD PhD[5], Kentaro Fukushima, MDPhD[6], Takayuki Ikezoe, MDPhD[7], Yoshiaki Ogawa, MD PhD[8], Joseph Brandwein, MD[9], Eunice S. Wang, MD[10], Yasushi Miyazaki, MDPhD[11], Timothy Pardee, MD PhD[12], Naoko Hosono, MD[13], Takahiro Shima, MDPhD[14], Hisayuki Yokoyama[15], Noboru Asada, MDPhD[16], Joseph Jurcic, MD[17], Hongliang Cai, PhD[18], Akinobu Watanabe[18], Matthew Hitron, MD[18], Emily Brooks, PhD[18], Bo Xu, PhD[18], Jatin Shah, MD[18], Hagop M. Kantarjian, MD[1], Harry P. Erba, MDPhD[19]

[1] Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
[2] University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC
[3] National Cancer Center Hospital East, Kashiwa, Japan
[4] Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, MIAMI, FL
[5] Division of Hematologic Malignancies, Johns Hopkins University, Baltimore, MD
[6] Osaka University Graduate School of Medicine, Suita, Japan
[7] Fukushima Medical University, Fukushima, Japan
[8] Tokai University School of Medicine, Kanagawa, Japan
[9] University of Alberta, Edmonton, CAN
[10] Roswell Park Cancer Institute, Buffalo, NY
[11] Nagasaki University, Nagasaki, Japan
[12] Comprehensive Cancer Center of Atrium Health Wake Forest Baptist, Winston-Salem, NC
[13] Department of Hematology and Oncology, University of Fukui, Fukui, Japan
[14] Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medicine, Fukuoka, Japan
[15] Department of Hematology, Tohoku University Graduate School of Medicine, Sendai, Japan
[16] Department of Hematology and Oncology, Okayama University Hospital, Okayama, Japan
[17] Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY
[18] Sumitomo Pharma America, Inc., Marlborough, MA
[19] Duke Cancer Institute, Durham, NC

Introduction: Menin inhibitors are an exciting new class of agents in development for patients (pts) with acute leukemia who overexpress HOXA9 and MEIS1 genes. Although there is a growing list of fusion genes in acute leukemia that appear to be dependent on homeobox-related gene activity, menin inhibition has been shown to be particularly active in pts with *NPM1* mutations (NPM1c) and *KMT2A* rearrangements (MLLr). DSP-5336 is an investigational, oral small molecule designed to inhibit the menin and MLL protein interaction.

Methods: A Phase 1/2 study of DSP-5336 is being conducted in pts with relapsed or refractory (R/R) acute leukemia. The dose escalation portion of the study consists of two parallel arms (Arm A: without concomitant anti-fungal azole therapy; Arm B: with concomitant azole therapy). Pts were eligible with R/R AML, ALL or acute leukemia of ambiguous lineage without a limit on number of prior therapies, with a focus on those with MLLr and NPM1c.

Results: Accrual is ongoing with 24 pts enrolled as of April 2023; 14 pts in Arm A at doses of 40 mg BID (n=2), 80 mg BID (n=4), 100 mg BID (n=2) and 120 mg BID (n=6), and 10 pts in Arm B at doses of 40 mg BID (n=4) and 60 mg BID (n=6). The median age was 67.0 years (range 20 - 85) and 62.5% were male. All pts had AML except for 1 pt with acute leukemia of ambiguous lineage. Pts had received a median of 3 (range 1 to 9) prior treatments, and 6 (25%) had received prior alloSCT. MLLr or NPM1c were present in 6 (25%) and 4 (17%) patients, respectively.

No dose-limiting toxicities have been observed thus far. Most treatment-emergent adverse events (TEAEs) were grade 1/2. TEAEs assessed as related to DSP-5336 in ≥ 3 pts were nausea (Grade 1 or 2, n = 3 pts) and vomiting (Grade 1 or 2, n = 4

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pts). Grade >3 TEAEs occurring in ≥ 3 pts included anemia (6 pts), pneumonia (5 pts), sepsis (3 pts) and hypokalemia (3 pts), all unrelated to study drug. A possible Grade 4 differentiation syndrome (DS) was observed in 1 pt with a TP53 mutation in Arm A receiving 80 mg BID although concurrent pneumonia and sepsis made a clear attribution difficult. No other DS events of any grade have been reported to date. No cardiac toxicities, and no QTc prolongation of any grade related to DSP-5336 have been observed.

Out of the 6 pts enrolled with MLLr, 4 were treated at dose levels projected to be active based on preclinical modeling (≥ 60 mg BID with azoles, or ≥ 120 mg BID without azoles). Of these 4 pts, all had received prior intensive induction chemotherapy as well as a venetoclax-based regimen, and 3 had received prior allo-transplant. Of these 4 pts, 1 achieved CRi with a duration of therapy of 5.1 months, 1 achieved MLFS with a duration of therapy of 6.2 months (ongoing), and 1 achieved SD with clearance of peripheral blasts, recovery of peripheral counts, resolution of leukemic gingival infiltration, and reduction in bone marrow (BM) blasts from 85% to 31%.

Of the 4 enrolled pts with NPM1c, 2 were treated at doses projected to be effective. Stable disease with complete clearance of peripheral blasts were observed in both pts, and BM blasts were reduced by 66% and 83% respectively.

Preliminary pharmacokinetic (PK) analysis has demonstrated generally higher mean exposures at higher dose levels. Across all the dose levels, plasma $t_{1/2}$ ranged from 2-6 hours in Arm A and from 2-10 hours in Arm B, with T_{max} reached within 2 hours. Little to no drug accumulation was observed with repeat dosing in both arms. Data to date suggests that azoles may not have a significant effect on DSP-5336 exposure, but enrollment and comparative analyses are ongoing.

Target pharmacodynamic changes have been achieved in pts who have MLLr or NPM1m, including rapid decreases in HOXA9, MEIS1, and PBX3 with treatment and, conversely, increases in CD11b compared to pretreatment.

Conclusion: DSP-5336 has been well tolerated with no DLTs to date in heavily pretreated R/R AML patients with NPM1c and MLLr AML. Importantly, no cardiac signals (including no QTcF prolongation) have been observed. PK studies have not identified a significant drug-drug interaction with azoles. Although there are early signs of clinical activity and pharmacodynamic changes during administration of DSP-5336, the study is ongoing to determine a recommended Phase 2 dose for single-agent expansion and potential combination regimens. Updated safety and efficacy data will be presented at the meeting.

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Baseline chracterstics	Arm A (n=14)	Arm B (n=10)	Overall (n=24)
Age (years)			
Median	64.0	75.5	67.0
Min, Max	24, 84	20, 85	20, 85
< 65 years	7 (50.0)	3 (30.0)	10 (41.7)
>= 65 years	7 (50.0)	7 (70.0)	14 (58.3)
Sex, n (%)			
Female	6 (42.9)	3 (30.0)	9 (37.5)
Male	8 (57.1)	7 (70.0)	15 (62.5)
Diagnosis, n (%)			
AML	13 (92.9)	10 (100.0)	23 (95.8)
ALL	0	0	0
MPAL	1 (7.1)	0	1 (4.2)
Clinical setting of Leukemia, n (%)			
De novo	4 (28.6)	4 (40.0)	8 (33.3)
Secondary (Treatment-related)	2 (14.3)	3 (30.0)	5 (20.8)
Secondary (Transformation from prior heme malignancy)	5 (35.7)	2 (20.0)	7 (29.2)
Unknown	1 (7.1)	0	1 (4.2)
ELN2017 risk stratification by genetics, n (%)			
Favorable	0	1 (10.0)	1 (4.2)
Intermediate	2 (14.3)	1 (10.0)	3 (12.5)
Adverse	9 (64.3)	5 (50.0)	14 (58.3)
Unknown	1 (7.1)	1 (10.0)	2 (8.3)
Prior treatments, #			
Median	3.0	2.5	3.0
Min, Max	1, 9	1, 6	1, 9
Prior Transplant, n(%)			
Yes	3 (21.4)	3 (30.0)	6 (25.0)
No	11 (78.6)	7 (70.0)	18 (75.0)
Prior Venetoclax, n(%)			
Yes	11 (78.6)	10 (100.0)	21 (87.5)
No	3 (21.4)	0	3 (12.5)
Prior other Menin inhibitors, n(%)			
Yes	0	0	0
No	14 (100.0)	10 (100.0)	24 (100.0)
Genetics, n (%)			
NPM1c	2 (14.3)	2 (20.0)	4 (16.7)
MLLr	2 (14.3)	4 (40.0)	6 (25.0)
other documented mutations			
ASXL1	4 (28.6)	2 (20.0)	6 (25.0)
CEBPA	0	1 (10.0)	1 (4.2)
FLT3	1 (7.1)	1 (10.0)	2 (8.3)
NUP98	1 (7.1)	1 (10.0)	2 (8.3)
RUNX1	4 (28.6)	2 (20.0)	6 (25.0)
SETBP1	0	1 (10.0)	1 (4.2)
TP53	1 (7.1)	1 (10.0)	2 (8.3)
Bone marrow blast (%) at baseline			
Median	54.0	75.0	64.0
Min, Max	5.0, 98.0	16.0, 90.0	5.0, 98.0

Treatment-Emergent Adverse Events Related to DSP-5336						
	Overall (n =24)		Arm A (n =14)		Arm B (n =10)	
	Any Grade n (%)	≥ Grade 3 n (%)	Any Grade n (%)	≥ Grade 3 n (%)	Any Grade n (%)	≥ Grade 3 n (%)
Vomiting	4 (16.7)	0	2 (14.3)	0	2 (20.0)	0
Nausea	3 (12.5)	0	2 (14.3)	0	1 (10.0)	0
Decreased appetite	2 (8.3)	0	2 (14.3)	0	0	0
Hypertriglyceridaemia	1 (4.2)	1 (4.2)	0	0	1 (10.0)	1 (10.0)
Hyperuricaemia	1 (4.2)	0	1 (7.1)	0	0	0
AST increased	1 (4.2)	1 (4.2)	0	0	1 (10.0)	1 (10.0)
Increased appetite	1 (4.2)	0	1 (7.1)	0	0	0
Leukocytosis	1 (4.2)	1 (4.2)	0	0	1 (10.0)	1 (10.0)
Differentiation syndrome	1 (4.2)	1 (4.2)	1 (7.1)	1 (7.1)	0	0
Photophobia	1 (4.2)	0	1 (7.1)	0	0	0
Thirst	1 (4.2)	0	1 (7.1)	0	0	0
Headache	1 (4.2)	0	1 (7.1)	0	0	0

Figure 1

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