ABSTRACT: 5198

A dose optimization phase 1b/2 study evaluating mipletamig (formerly APVO436), a novel bispecific CD123 x CD3 ADAPTIR™ molecule in combination therapy for the treatment of frontline acute myeloid leukemia (AML) in patients unfit for intensive chemotherapy

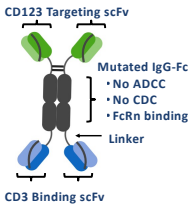
J. Watts[1], G. Borthakur[2], T. L. Lin[3], N. Gabrail[4], K. Patel[5], Y. F. Madanat[6], J. F. Zeidner[7], N. Khaskhely[8], L. Bonham[8], M. H. Nelson[8], J. Kumer[8], D. Taylor[8], C. Taromino[8], M. W. Miller[8], D. Huebner[8], and M. Maris[9]

[1]Sylvester Comprehensive Cancer Center, University of Miami, Coral Gables, FL; [2]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]University of Kansas, Westwood, KS; [4]Gabrail Cancer Center, Canton, OH; [5]Oncology Hematology Care, Cincinnati, OH; [6]UT Southwestern Medical Center, Dallas TX ; [7]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; [8]Aptevo Therapeutics, Seattle, WA; [9]Colorodo Blood Cancer Institutes, Denver, CO.

BACKGROUND

- While many elderly patients with acute myeloid leukemia (AML) achieve complete remission (CR) with azacitidine and venetoclax (AZA/VEN), relapse rates and subsequent mortality remain high.[1]
- Immunotherapy offers the promise of a new paradigm in a variety of settings for patients with AML and myelodysplastic syndromes (MDS).[2]
- Mipletamig, formerly APVO436 (**Figure 1**), **a novel bispecific anti-CD123 x anti-CD3 ADAPTIR™** molecule, has shown pre-clinical proof of concept[3] and been evaluated as monotherapy in a dose escalation study[4] and a dose expansion in combination[5] with various standard of care. Responses, CRs, and clinical activity have been previously reported in AML and MDS.
- The RAINIER Study (APVO436-5201, NCT06634394) is an ongoing 2-part, phase 1b/2 dose optimization.[6] The aim is to evaluate safety and tolerability of mipletamig when used as an adjunct to the AZA/VEN standard of care and to assess the anti-leukemia activity of this regimen.
- Herein, we report preliminary data through cohort 3 from the phase 1b dose optimization phase of this study.

Figure 1. Mipletamig



STUDY DESIGN

- The dose optimization phase will enroll a total of up to 51 frontline patients (aged ≥18 years) with AML who are not eligible or unfit for intensive induction due to age or other factors across seven escalating dose level cohorts. Patient had to have received at least 1 dose of mipletamig at the target dose level (C1D15) to be evaluable for target dose limiting toxicity (DLT) assessment. Patients withdrawn prior to C1D15 were evaluable for safety and priming dose DLT assessment. Patients were evaluable for response, if they had at least one post treatment bone marrow assessment. Patients were evaluable for DLT assessment if they completed at least the first cycle.

Figure 2. Study design

	Cohort 1	Cohort 2	Cohort 3
Mipletamig	9 mcg QW	18 mcg QW	27 mcg QW

In cycle 1, each cohort receives 4 priming doses, administered by 4-hour intravenous (IV) infusion of mipletamig (1, 2, 4, and 8 mcg) on days 1, 3, 5, and 8, respectively, followed by the cohort assigned weekly dose on days 15 and 22, which continued weekly during cycle 2 and beyond. Priming and target dose levels are subject to modification based on safety observations, using a Bayesian optimal interval (BOIN) design

Combination: Mipletamig/AZA/VEN triplet therapy starts on cycle 1 day 1 (C1D1) in a 28-day cycle. VEN duration is 21 days/cycle and AZA (75 mg/m^2) 7 days/cycle

C, cycle; D, day; mcg, microgram; QW, weekly

STUDY ENDPOINTS

- **Primary:** Safety & Tolerability: Grade 3–4 treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), TEAEs of interest (Grade ≥2: cytokine release syndrome [CRS], infusion-related reactions [IRRs], cardiac TEAEs and neurotoxicity). Assess maximum tolerated dose (MTD) and determine the recommended phase 2 dose (RP2D)
- **Secondary:** Efficacy: Incidence of complete remission rate (CR)

PATIENTS

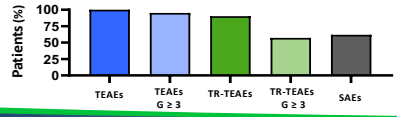
- Through Oct 6, 2025, 15 evaluable frontline AML patients were enrolled in cohorts 1, 2, and 3 and treated with mipletamig in combination with AZA/VEN.
- Overall, patients had a median age of 75 years (range 58–87).
- 40% of patients had an ECOG PS of 1, and 33.33% had an ECOG PS of 2.
- All patients were newly diagnosed AML and were VEN and AZA naive.

Table 1. Patient demographics and disease characteristics

	Cohort 1 (n=3)	Cohort 2 (n=6)	Cohort 3 (n=6)
Median age, years (range)	73 (77-85)	73 (68-87)	76 (67-79)
Sex, n (%) Male / Female	2 (67) / 1 (33)	5 (83) / 1 (17)	5 (83) / 1 (17)
Race, % White / Black / Other	2 / 0 / 1	3 / 0 / 3	3 / 1 / 2
ECOG PS, % 0 / 1 / 2	1 / 2 / 0	1 / 2 / 3	2 / 3 / 1
Discontinuations, n AE / PD NT / NR / Death	0 / 2 1 / 0 / 0	0 / 0 4 / 0 / 2	0 / 0 1 / 0 / 1

AE, adverse event; ECOG PS, Easter Cooperative Oncology Group Performance Status; NR, no response; NT, new therapy; PD, progressive disease

Figure 3. Summary of TEAEs



SAFETY

- The median number (range) of mipletamig cycles administered were 6.0 (3– 9), 3.0 (1– 4), and 4.0 (1- 5) for cohorts 1, 2, and 3, respectively.
- Overall, patients received 1–38 doses of mipletamig (median: 14 doses) and the primary reason for dose modification was adverse events
- Six additional patients came off study and were not DLT evaluable for the cohort dose level due to: withdrew consent (1), suicide (1), treating physician decision (2), priming dose limiting toxicity AE (1), Death not related to study drug (1).
- No patients experienced cytokine release syndrome (CRS)
- The most common TEAEs (reported in ≥25%) were IRR (71%) constipation (62%), thrombocytopenia (62%), increased ALT (47%), increased AST (47%), nausea (43%), fatigue (43%), febrile neutropenia (43%), anemia (38%), cough (38%), hypokalemia (33%), hypotension (33%), neutropenia (33%), hypoxia (33%), anorexia (28%), diarrhea (28%), dizziness (28%), oedema peripheral (28%), headache (28%), vascular access complications (28%)

Table 2. TEAEs of special interest

	Cohort 1 (n=3)	Cohort 2 (n=6)	Cohort 3 (n=6)
CRS, n (%) Grade ≥3	0 0	0 0	0 0
IRR, n (%) Grade ≥3	2 (66.7) 0	5 (83.3) 0	5 (83.3) 2
Cardiac TEAEs, n (%) Grade ≥3	2 (66.7) 0	2 (33.3) 0	3 (50.0) 1
Neurotoxicity, n (%) Grade ≥3	3 (100.0) 1	4 (66.7) 0	3 (50.0) 0

CRS, cytokine release syndrome; IRR, infusion-related reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TR-TEAE, treatment-related adverse event

EFFICACY

- Response was based on Investigator assessment using European LeukemiaNet 2022 criteria[7] for the efficacy evaluable population, defined as patients who received mipletamig and had a post-baseline response assessment.
- 12 of 15 response evaluable patients achieved CR/CRi after the first cycle and 1 patient achieved a PR after the first cycle and then achieved a CRi after the second cycle (Total 13 of 15; 87%). ORR was 14 of 15 evaluable patients (93%).
- 6 of 10 MRD evaluable CR/CRi patients achieved an MRD negative status.

Table 3. Best Overall Response

	Cohort 1	Cohort 2	Cohort 3
Cohort description	9 mcg	18 mcg	27 mcg
Patients enrolled, n	3	10*	8*
Patients evaluable, n	3	6	6
CR, n	3	4	4
CRi, n	0	0	2
PR, n	0	1	0
ORR, %	100.0	83.3	100.0
CR, %	100.0	66.7	66.7
CR/CRi, %	100.0	66.7	100.0

ORR, clinical benefit rate; CR, complete remission; CRi, CR with incomplete hematologic recovery; PR, partial response
*Six patients came off study before the end of the first cycle and did not have an evaluable bone marrow biopsy.

Table 4. MRD & TP53 status; ELN Risk Category

Best Response	MRD* Status	TP53 Status	ELN Risk Category
Cohort 1 – 9mcg			
CR	Negative	Wild Type	Intermediate
CR	Negative	Mutated	Adverse
CR	Negative	Wild Type	Favorable
Cohort 2 – 18 mcg			
CR	Negative	Wild Type	Adverse
CR	Positive	Mutated	Adverse
Refractory	NA	Mutated**	Adverse
CR	Pos	Wild Type	Adverse
PR	NA	Mutated	Adverse
CR	Negative	Wild Type	Adverse
Cohort 3 – 27mcg			
CRi	NA	Wild Type	NA
CR	NA	Wild Type	NA
CR	Positive	Mutated	Adverse
CR	Negative	Wild Type	Intermediate
CRi	NA	Mutated	NA
CR	Positive	Mutated	Adverse

*MRD and ELN status was assessed by participating clinical institutions **One allele mutated

CONCLUSIONS

- **Preliminary results from the dose-expansion phase indicate that mipletamig is well tolerated and safe in combination with AZA/VEN regimens, through 3 cohorts tested. No CRS has been observed.**
- **The combination of AZA/VEN plus mipletamig shows compelling potential, where 93% of patients experienced ORR, 87% achieved CR/CRi and 73% achieved CR.**

References:
1. DiNardo et al. N Engl J Med 2020;383:617-29
2. Linder K & Lulla P. Hum Vaccin Immunotherapy 2021;17:2602–16
3. Comeau MR, et al. Cancer Res 2017;77 (13_Supplement):597
4. Watts et al. Blood;140 (Supplement 1):6204-6205
5. Uckun FM, et al. Cancers 2021;13:4113
6. https://clinicaltrials.gov/study/NCT06634394
7. Döhner H, et al. Blood 2022; 140:1345-1377

Acknowledgments: We thank all patients and investigators involved in this study.