ABSTRACT: 2760

# Updated Results from a Phase 1 Study of APVO436, a Novel Bispecific Anti-CD123 x Anti-CD3 ADAPTIR™ Molecule, in Relapsed/Refractory Acute Myeloid Leukemia and Myelodysplastic Syndrome

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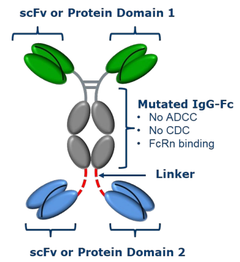
## BACKGROUND

- While many patients with acute myeloid leukemia (AML) achieve complete remission (CR) with chemotherapy, 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).[1,2]
- APVO436 (**Figure 1**), a **novel bispecific anti-CD123 x anti-CD3 ADAPTIR™** molecule, has shown pre-clinical proof of concept.[3]
- APVO436-5001 (NCT03647800) is an ongoing 2-part, phase 1a/b dose-escalation and -expansion study.[4]
- The aim is to evaluate safety and tolerability of APVO436 when used as an adjunct to standard of care and to assess the anti-leukemia activity of APVO436-containing experimental monotherapy and combination therapy modalities.
- Responses, CRs, and clinical activity have been previously reported in AML and MDS.[5]
- Here, we report preliminary data from the phase 1b dose-expansion phase of the study at the RP2D in patients with de novo and secondary AML.

## STUDY DESIGN

- The expansion phase will enroll a total of up to 90 patients (aged ≥18 years) with AML at different disease stages into five different cohorts of 18 patients each (**Figure 2**).

### Figure 1. APVO436




### Figure 2. Study design

| | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 | Cohort 5 |
|---|---|---|---|---|---|
| Patients | 1st or 2nd early relapse or primary refractory disease | Frontline or 1st relapse or primary refractory disease | Consolidation after frontline or 2nd line or primary refractory disease | MRD+: 1st remission | MRD+: 2nd remission |
| Combination agent | IDAC D1–5 4 cycles **or** MEC D1–6 2 cycles | Venetoclax (Ven) D1–21 4 cycles **+** Azacitidine (Aza) D1–7 4 cycles | None | Azacitidine (oral) D1–14 4 cycles | None |
| APVO436 | 18 µg QW 4 cycles* | 18 µg QW 4 cycles* | 18 µg QW 4 cycles* | 18 µg QW 4 cycles | 18 µg BIW 4 cycles* |

APVO436 dose was ramped from 6 µg to 18 µg during Cycle 1 (Cohorts 1, 3, 4, 5) or Cycles 1–2 (Cohort 2); *Optional APVO436 monotherapy after Cycle 4 for ≤4 additional cycles
BIW, twice weekly; D, day; IDAC, intermediate dose cytarabine; MEC, mitoxantrone, etoposide, cytarabine; MRD, minimal residual disease; QW, weekly.

## STUDY ENDPOINTS

- **Primary:** Safety: 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).
- **Secondary:** Efficacy: Incidence of composite CR (CR + CRi [CR with incomplete hematologic recovery] + morphologic leukemic-free state [MLFS])

## PATIENTS

- Through Oct 6, 2022, 42 de novo/secondary AML patients were enrolled on cohorts 1, 2, 3, and 5 and treated with APVO436.
  - No patients have been enrolled in Cohort 4.
- Overall, patients had a median age of 63.5 years (range 25–84).
- 19% of patients had an ECOG PS of 2.
- Most patients were diagnosed with de novo AML and had received a median of 2 prior lines of therapy (range 1–7; **Table 1**).

### Table 1. Patient demographics and disease characteristics

| | Cohort 1 (n=16) | Cohort 2 (n=17) | Cohort 3 (n=7) | Cohort 5 (n=2) |
|---|---|---|---|---|
| **Median age, years (range)** | 59 (25–81) | 64 (29–78) | 71 (50–77) | 74.5 (65–84) |
| **Sex, n (%)** | | | | |
| **Male / Female** | 8 (50) / 8 (50) | 11 (65) / 6 (35) | 2 (29) / 5 (71) | 1 (50) / 1 (50) |
| **Race, %** | | | | |
| **White / Black / Other** | 63 / 6 / 31 | 88 / 0 / 12 | 71 / 14 / 14 | 100 / 0 / 0 |
| **ECOG PS, %** | | | | |
| **0 / 1 / 2** | 19 / 50 / 25 | 12 / 65 / 24 | 43 / 43 / 0 | 50 / 50 / 0 |
| **Diagnosis, n (%)** | | | | |
| **De novo AML** | 10 (63) | 12 (71) | 5 (71) | 2 (100) |
| **t-AML** | 2 (13) | 1 (6) | 0 | 0 |
| **Secondary AML with prior MDS** | 2 (13) | 0 | 0 | 0 |
| **Other*** | 2 (13) | 4 (24) | 2 (29) | 0 |
| **Median LOT (range)** | n=11<br>2 (1–5) | n=10<br>2 (1–7) | n=2<br>1.5 (1–2) | n=1<br>4 (4–4) |

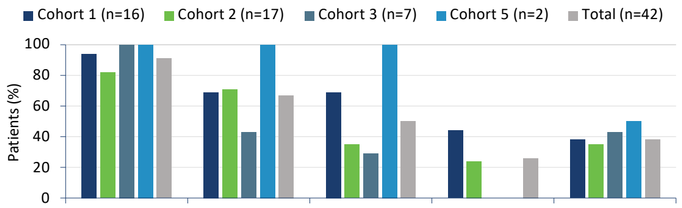
*Includes a variety of secondary AML transformed from myeloproliferative neoplasms.

AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LOT, line of therapy; MDS, myelodysplastic syndrome; t-AML, therapy-related AML.

## SAFETY

- The median number (range) of APVO436 cycles were 1.0 (1–4), 2.0 (1–4), 2.0 (1–4), and 3.0 (3–3) for cohorts 1, 2, 3, and 5, respectively.
- Overall, patients received 1–24 doses of APVO436 (median: 4 doses) and the primary reason for dose modification was adverse event (AE; 24%).
- A summary of treatment-emergent AEs (TEAEs) is presented in **Figure 3**.

### Figure 3. Summary of TEAEs




SAE, serious adverse event; TEAE, treatment-emergent adverse event; TR, treatment-related.

- The most common TEAEs (reported in ≥20%) were fatigue (33%), pyrexia (31%), hypokalemia (29%), nausea (24%), and anemia (21%).
- TEAEs of special interest are presented in **Table 2**.
- There was 1 death from CRS (cohort 1) which was considered treatment-related, however, this case was confounded by sepsis and pneumonia. There were 3 non-treatment-related deaths from TEAEs, 1 in cohort 1 (septic shock) and 2 in cohort 2 (sudden death and dis ease progression ).

### Table 2. TEAEs of s pecial interes t

| | Cohort 1 (n=16) | Cohort 2 (n=17) | Cohort 3 (n=7) | Cohort 5 (n=2) |
|---|---|---|---|---|
| **CRS, n (%)** | 5 (31) | 4 (24) | 0 | 1 (50) |
| **Grade ≥2, Grade ≥3** | 4 (25), 1 (6) | 4 (24), 0 | 0, 0 | 1 (50), 0 |
| **IRR, n (%)** | 0 | 1 (6) | 1 (14) | 0 |
| **Grade ≥2, Grade ≥3** | 0, 0 | 0, 0 | 0, 0 | 0, 0 |
| **Cardiac TEAEs, n (%)** | 6 (38) | 3 (18) | 1 (14) | 1 (50) |
| **Grade ≥2, Grade ≥3** | 4 (25), 1 (6) | 0, 0 | 0, 0 | 1 (50), 0 |
| **Neurotoxicity, n (%)** | 1 (6) | 0 | 0 | 0 |
| **Grade ≥2, Grade ≥3** | 0, 0 | 0, 0 | 0, 0 | 0, 0 |

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

## EFFICACY

- Response was based on Investigator assessment using European LeukemiaNet 2017 criteria[6] for the efficacy evaluable population, defined as patients who received APVO436 and had a post-baseline response assessment.
- Response rates for cohorts 1, 2, and 3 are shown in **Table 3**.
- In Cohort 5, one patient was treated with 3 cycles (28 days each) of APVO436 before a relapse occurred. The second patient in this cohort was not yet evaluable.
- The overall median time to response was 1.1 months (range 0.3–2.1).
- The highest response rate of 80% (composite CR) and 70% (CR/CRi) was seen in cohort 2 in Venetoclax naïve patients.

### Table 3. Response rates

| | Cohort 1 | Cohort 2 | Cohort 2 (Ven pretreatment excluded) | Cohort 3 |
|---|---|---|---|---|
| **Cohort description** | APVO436 + MEC | APVO436 + Ven/Aza | APVO436 + Ven/Aza | APVO436 only after CT induction |
| **Patients enrolled, n** | 16 | 17 | 12 | 7 |
| **Patients evaluable, n** | 10* | 14† | 10‡ | 4¶ |
| **CR, n** | 4 | 3 | 3 | 0 |
| **CRi, n** | 0 | 4 | 4 | 0 |
| **MLFS, n** | 0 | 1 | 1 | 1 |
| **SD, n** | 4 | 3 | 2 | 2 |
| **CBR§, %** | **80** | **79** | **100** | **75** |
| **Composite CR§, %** | **40** | **57** | **80** | **25** |
| **CR/CRi, %** | **40** | **50** | **70** | **0** |

*Discontinued before response assessment, n=6 (clinical progression [2], AE [3], Investigator's decision [1]).
†Discontinued before response assessment, n=3 (clinical progression [1], AE [1], still on treatment - no BMBx results available for response assessment [1]);
‡Still on treatment - no BMBx results available for response assessment [1], Venetoclax history unavailable [1], n=2;
¶Discontinued before response assessment, n=3 (clinical progression [1], Investigator's decision [2]);
§CBR=CR+CRi+MLFS+SD; Composite CR=CR+CRi+MLFS.
AE, adverse event; Aza, Azacitidine; BMBx, bone marrow biopsy; CBR, clinical benefit rate; CR, complete remission; CRi, CR with incomplete hematologic recovery; CT, chemotherapy; MEC, mitoxantrone, etoposide, cytarabine; MLFS, morphologic leukemia-free state; SD, stable disease; Ven, Venetoclax.

## CONCLUSIONS

- **Preliminary results from the dose-expansion phase indicate that APVO436 is well tolerated and safe as a single agent and in combination with induction regimens (MEC & Ven/Aza) across cohorts with different underlying leukemic conditions.**
- **Single agent activity in this expansion phase has been demonstrated and extends observations of safety and activity from the dose escalation portion of the study, reported previously.**
- **The combination of Ven/Aza plus APVO436 shows compelling potential, especially in the Venetoclax naïve population.**
- **Encouraging efficacy supports moving APVO436 to the next development stage of a Phase 2 program.**

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**References:** 1. Isidori A, et al. Front Oncol 2021;11:656218; 2. Linder K & Lulla P. Hum Vaccin Immunother 2021;17:2602–16; 3. Comeau MR, et al. Cancer Res 2017;77 (13_Supplement):597; 4. https://clinicaltrials.gov/ct2/show/NCT03647202; 5. Uckun FM, et al. Cancers 2021;13:4113; 6. Döhner H, et al. Blood 2017;129:424–47.
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