# Evorpacept, a CD47-Blocking Myeloid Checkpoint Inhibitor, in Combination with Azacitidine and Venetoclax in Patients with Acute Myeloid Leukemia (ASPEN-05): Results from Phase 1a Dose Escalation Part

Guillermo Garcia-Manero[1*], Amanda Przespolewski[2*], Yasmin Abaza[3], Michael Byrne[4], Abraham Fong[5], Shanhong Guan[5], Feng Jin[5], Alison Forgie[5], Athanasios C. Tsiatis[5], Harry Erba[6]

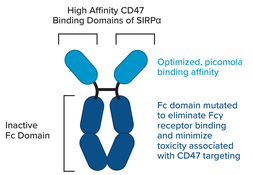
[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [3]Robert H Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; [4]Vanderbilt-Ingram Cancer Center, Nashville, TN; [5]ALX Oncology Inc., South San Francisco, CA; [6]Duke Cancer Institute, Durham, NC

*Co-First Authors

## Background

- Evorpacept (ALX148) is a high affinity CD47-blocking fusion protein with an inactivated human IgG1 Fc region[1] (Figure 1) that is designed to enhance phagocytosis of tumor cells in combination with other anti-neoplastic therapies, with minimal additional toxicity (Figure 2).
- Here, we present results from the phase 1a dose escalation part of the ASPEN-05 study evaluating the safety and tolerability of evorpacept administered in combination with standard dosing of venetoclax (VEN) and azacitidine (AZA) in subjects with acute myeloid leukemia (AML).

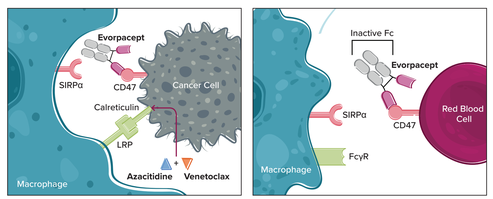
**Figure 1.** Evorpacept is Designed as a Potent and Selective CD47-Blocker




- Fc domain enables antibody-like PK profile.
- Molecular weight is half the size of typical antibody.

- Treatment with VEN and AZA induces cell-surface expression of calreticulin, a potent pro-phagocytic signal, on AML cells.[2,3]
- Concurrent blockade of the CD47 myeloid checkpoint with evorpacept augments the phagocytosis of leukemia cells by macrophages, resulting in an increase in both the depth and duration of response in preclinical AML models.[2]
- Toxicity on normal hematopoietic cells is spared due to evorpacept's inactivated Fc region.

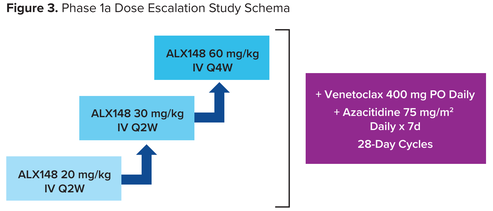
**Figure 2.** Evorpacept Blocks the CD47 Myeloid Checkpoint While Sparing Toxicity to Normal Hematopoietic Cells




## Methods

- ASPEN-05 (NCT04755244) is a phase 1/2 open-label, multicenter study.
- The phase 1a dose escalation part (Figure 3) is designed to evaluate the safety and tolerability and establish the maximum tolerated dose (MTD) of intravenous (IV) evorpacept in combination with VEN and AZA.
- Adult subjects with relapsed/refractory (R/R) AML or newly diagnosed (ND) AML with adverse risk genetics and considered ineligible for intensive induction therapy were enrolled into cohorts of escalating doses of evorpacept combined with VEN and AZA in a 28-day treatment cycle.
- The primary endpoint is the frequency of first cycle dose-limiting toxicities (DLTs).
- Key secondary endpoints are to characterize the pharmacokinetic (PK) profile of evorpacept in combination with VEN and AZA, and to assess anti-leukemic activity using the ELN 2017 response criteria.

**Figure 3.** Phase 1a Dose Escalation Study Schema




**Q2W** – Every 2 weeks; **Q4W** – Every 4 weeks.

## Results

- As of October 3, 2022, 14 subjects were treated at evorpacept doses of:
  - 20 mg/kg Q2W (N=4)
  - 30 mg/kg Q2W (N=4)
  - 60 mg/kg Q4W (N=6)
- 11 subjects had R/R AML with a median of 1 prior line of therapy (range 1-2), including:
  - 9 with prior VEN
  - 5 with a prior hypomethylating agent
- 3 subjects had ND AML, including:
  - 2 with therapy-related AML
  - 3 with TP53 mutation
- Patient median baseline laboratory values included:
  - Creatinine 0.92 mg/dL (range 0.54-3.31)
  - Total bilirubin 0.7 mg/dL (0.3-1.7)
  - Platelets 31.5 x $10^9$/L (range 13-117) and WBC 2 x $10^9$/L (range 0.4-12.3)
- Bone marrow studies at screening demonstrated:
  - Median blast percentage of 27% (range 5-84)
  - 13 subjects with adverse risk and 1 with intermediate risk cytogenetics
  - Mutations in TP53 (N=11), DNMT3A (N=3), ASXL1, and RUNX1 (N=2 each)

**Table 1.** Patient Baseline Characteristics

| | | Phase 1 (N=14) |
|---|---|---|
| **Age, Years (median, range)** | | 71 (50-82) |
| **Sex, n** | **Male**<br>**Female** | 10<br>4 |
| **Race, n** | **White**<br>**Black or African American**<br>**Native Hawaiian or Other Pacific Islander**<br>**Asian** | 8<br>2<br>1<br>3 |
| **AML status, n** | **Relapsed or Refractory**<br>**Number of Prior Treatment Regimens (median, range)**<br>**Prior Venetoclax, n**<br>**Venetoclax-Naïve, n**<br>**Prior Hypomethylating Agents, n**<br>**Newly Diagnosed** | 11<br>1 (1-2)<br>9<br>2<br>5<br>3 |
| **WHO AML Classification at Screening, n** | **AML with Myelodysplasia-Related Changes**<br>**Therapy-Related Myeloid Neoplasms**<br>**AML, NOS**<br>**Unknown/Missing** | 5<br>2<br>4<br>3 |
| **Cytogenetic Risk at Screening, n** | **Intermediate**<br>**Adverse** | 1<br>13 |
| **Bone Marrow Myeloblast Percentage at Baseline (median, range)** | | 27 (5-84) |
| **Mutation Status, n (%)** | **DNMT3A**<br>**RUNX1**<br>**ASXL1**<br>**TP53 Mutation**<br>**Other** | 3 (21)<br>2 (14)<br>2 (14)<br>11 (79)<br>8 (57) |

## Safety

- An MTD of evorpacept was not reached. The maximum administered dose was 60 mg/kg Q4W.
- All subjects experienced an adverse event (AE).
- Evorpacept-related AEs of vomiting (n=2; 14%), nausea, cytokine release syndrome, and metabolic acidosis (n=1 each; 7%) were observed among 3 subjects.
- Grade ≥3 AEs of any causality occurring in ≥4 subjects were febrile neutropenia (n=6; 43%), anemia (n=5; 36%), AST increased (n=5; 36%), and pneumonia (n=4; 29%). There was 1 Grade 3 evorpacept-related AE of cytokine release syndrome that resolved and met criteria for DLT in the 60 mg/kg Q4W cohort.
- There were 3 Grade 5 AEs (1 in each dosing cohort) of pneumonia (n=2, both considered related to disease) and disease progression (n=1), all unrelated to evorpacept treatment.

### Most Common Treatment-Emergent and All Evorpacept-Related Adverse Events

**Table 2a:** Evorpacept-Related AEs

| | 20 mg/kg Q2W (N=4) | | 30 mg/kg Q2W (N=4) | | 60 mg/kg Q4W (N=6) | | Total (N=14) |
|---|---|---|---|---|---|---|---|
| **Adverse Event, n** | **Grade 1/2** | **Grade ≥3** | **Grade 1/2** | **Grade ≥3** | **Grade 1/2** | **Grade ≥3** | **All Grades (%)** |
| **Vomiting** | 1 | – | 1 | – | – | – | 2 (14) |
| **Nausea** | 1 | – | – | – | – | – | 1 (7) |
| **Cytokine Release Syndrome** | – | – | – | – | – | 1 | 1 (7) |
| **Metabolic Acidosis** | – | – | – | – | 1 | – | 1 (7) |

Safety population includes all enrolled subjects who received at least one dose of study treatment.

**Table 2b:** Most Common (>4 Subjects) Treatment Emergent AEs (All Causality)

| | 20 mg/kg Q2W (N=4) | | 30 mg/kg Q2W (N=4) | | 60 mg/kg Q4W (N=6) | | Total (N=14) |
|---|---|---|---|---|---|---|---|
| **Adverse Event, n** | **Grade 1/2** | **Grade ≥3** | **Grade 1/2** | **Grade ≥3** | **Grade 1/2** | **Grade ≥3** | **All Grades (%)** |
| **Pneumonia** | 1 | 1 | 1 | 2 | 1 | 1 | 7 (50) |
| **Diarrhea** | 2 | – | 1 | – | 3 | – | 6 (43) |
| **Nausea** | 3 | – | 2 | – | 1 | – | 6 (43) |
| **Hypokalaemia** | 2 | 1 | 1 | 1 | 1 | – | 6 (43) |
| **Fatigue** | 1 | 1 | 1 | – | 3 | – | 6 (43) |
| **Aspartate Aminotransferase Increased** | 1 | 1 | – | 3 | – | 1 | 6 (43) |
| **Febrile Neutropenia** | – | 2 | – | 1 | – | 3 | 6 (43) |
| **Constipation** | 2 | – | 1 | – | 2 | – | 5 (36) |
| **Peripheral Edema** | 1 | – | 2 | – | 2 | – | 5 (36) |
| **Pyrexia** | 1 | – | 2 | – | 2 | – | 5 (36) |
| **Blood Creatinine Increased** | 1 | – | 3 | – | 1 | – | 5 (36) |
| **Muscular Weakness** | 1 | 1 | 2 | 1 | – | – | 5 (36) |
| **Anemia** | – | 2 | – | 1 | – | 2 | 5 (36) |
| **Hypotension** | 1 | – | 2 | – | 1 | 1 | 5 (36) |
| **Confusional State** | 1 | – | 2 | – | 1 | 1 | 5 (36) |

Safety population includes all enrolled subjects who received at least one dose of study treatment.

## Efficacy

- Among 13 response evaluable subjects:
  - 3/3 subjects with ND AML achieved a response (1 CR, 1 CRi, 1 MLFS).
  - 2/2 subjects with R/R VEN-naïve AML achieved a response (2 CRi).
  - 2/8 with R/R VEN-exposed AML achieved a response (2 MLFS).
- A reduction in bone marrow blasts was observed across all dose cohorts, including in all R/R VEN-exposed subjects (Figure 4) and those refractory to their last cycle of VEN-containing therapy.
- The median overall survival (OS) for the entire Phase 1 cohort was 6.3 months (IQR 4.1-10.7 months), with a median follow up time of 4.2 months.

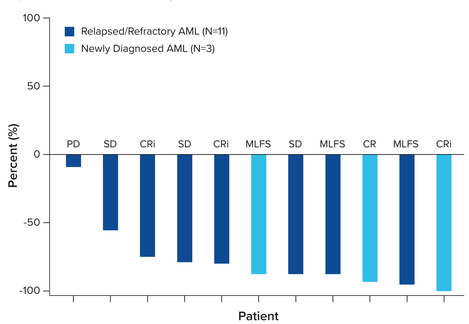
**IQR** – Interquartile Range.

**Table 3:** Objective Responses per Modified ELN Criteria[#]

| | Newly Diagnosed (N=3) | Rel/Ref (N=10) | | Overall (N=13) n (%) |
|---|---|---|---|---|
| | | VEN-Naïve (N=2) | Prior VEN (N=8) | |
| **ORR** | 3 | 2 | 2 | 7 (54) |
| **CR** | 1 | 0 | 0 | 1 (8) |
| **CRi** | 1 | 2 | 0 | 3 (23) |
| **PR** | 0 | 0 | 0 | 0 |
| **MLFS** | 1 | 0 | 2 | 3 (23) |
| **SD** | 0 | 0 | 4 | 4 (31) |
| **PD** | 0 | 0 | 1 | 1 (8) |
| **Death** | 0 | 0 | 1 | 1 (8)* |

Response evaluable population includes all enrolled patients who received at least one dose of study treatment and had at least one post-baseline disease assessment or died before the first post-baseline disease assessment. One patient not included due to DLT and no post-baseline disease assessment; [#]Per Döhner H et al. *Blood*. 2017 Jan 26;129(4):424-447, with addition of CRh; *Grade 5 pneumonia prior to first post-baseline disease assessment, considered related to disease.

**Figure 4.** Best Percent Change in Bone Marrow Blast % from Baseline




Note: One subject with missing data, two subjects with no post-baseline disease assessment (1 DLT, 1 death).

**Figure 5a.** Responses Over Time – Relapsed/Refractory AML Patients

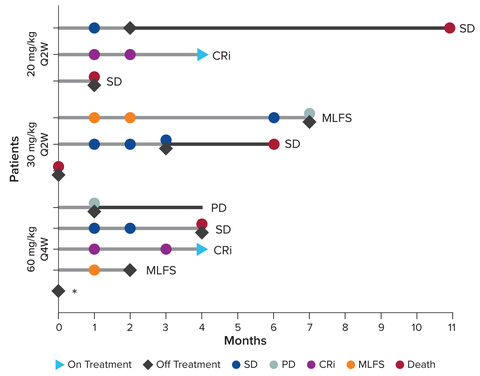
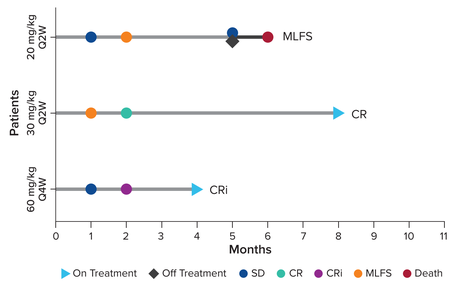


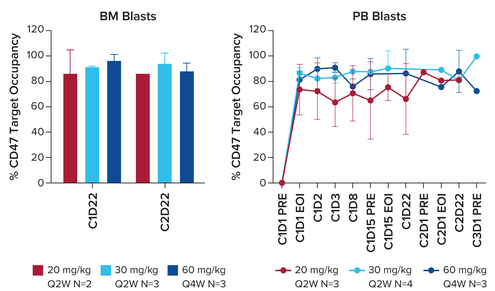

**Figure 5b.** Responses Over Time – Newly Diagnosed AML Patients




**SD** – Stable Disease; **CR** – Complete Remission; **CRi** – Complete Remission with Incomplete Hematologic Recovery; **MLFS** – Morphologic Leukemia-Free State; **PD** – Progressive Disease; *Patient not response evaluable.

## Biomarker

**Figure 6.** CD47 Occupancy in Bone Marrow (left) and Peripheral Blood (right) Blasts




**Pre** – Predose; **EOI** – End of Infusion.

- Preliminary data indicate robust CD47 occupancy in both peripheral blood and bone marrow blasts across all dose levels throughout the dosing interval.

## Pharmacokinetics

**Figure 7.** ALX148 Concentration-Time Profiles Following First ALX148 IV Infusion at 20 mg/kg Q2W, 30 mg/kg Q2W, and 60 mg/kg Q4W

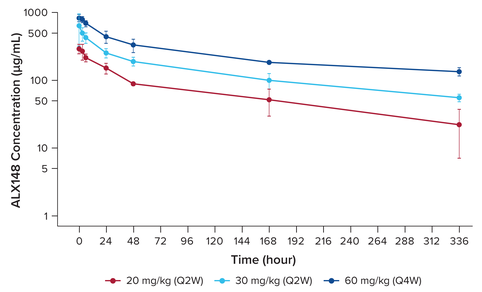



**Table 4:** ALX148 PK Parameters Following First ALX148 IV Infusion at 20 mg/kg Q2W, 30 kg/mg Q2W, and 60 kg/mg Q4W

| Parameters | 20 mg/kg Q2W (N=3) | 30 mg/kg Q2W (N=4) | 60 mg/kg Q4W (N=3) |
|---|---|---|---|
| $C_{max}$ (µg/mL) | 296 ± 50.5 | 648 ± 317 | 836 ± 104 |
| $AUC_{inf}$ (µg*h/mL) | 27400 ± 9729 | 53800 ± 14800 | 125000 ± 12300 |
| **CL** (mL/h/kg) | 0.798 ± 0.298 | 0.599 ± 0.202 | 0.483 ± 0.046 |
| $V_{ss}$ (mL/kg) | 127 ± 15.3 | 97.5 ± 13.4 | 155 ± 22.7 |

Parameters presented as mean ± SD.

- Preliminary PK data indicate dose-proportional pharmacokinetics that are consistent with results from prior studies.

## Conclusions

- Evorpacept is a next generation CD47-blocker designed to activate both the innate and adaptive immune response against cancer cells.
- The addition of evorpacept to standard dose VEN and AZA for AML was well tolerated with no MTD reached.
- The maximum administered evorpacept dose was 60 mg/kg Q4W, and preliminary dose-proportional pharmacokinetics was seen along with robust CD47 occupancy in both peripheral blood and bone marrow blasts across all dose levels evaluated.
- Consistent with preclinical data demonstrating enhancement of antileukemic activity with the addition of evorpacept to VEN+AZA[2], initial anti-leukemic activity was observed in a cohort of subjects with poor risk AML, including R/R AML both after prior VEN treatment and VEN-naïve, and ND AML with TP53 mutation.
- These encouraging results along with prior results[5] support further evaluation of evorpacept in hematologic malignancies, including in combination with VEN and AZA for AML (NCT04755244) and in combination with AZA for MDS (NCT04417517), as well as in solid tumors with other combination partners (NCT04675294, NCT04675333, NCT05002127).

### References

1. Kauder SE et al. *PLoS One*. 2018;13(8):e0201832.
2. Chen A et al. 2020 ASH Annual Meeting & Exposition. Abstract #1965.
3. Boasman K et al. *J Blood Disord Transfus* 2018; 10:1000413.
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