ASPEN-02: A Phase 1 Study of Azacitidine in Combination with Evorpacept for Higher-Risk Myelodysplastic Syndrome (MDS)

ALX ONCOLOGY

Guillermo Garcia-Manero[1], Bart L. Scott[2], Ashwin Kishtagari[3], Srinivasa R. Sanikommu[4], Aref Al-Kali[5], Je-Hwan Lee[6], Juan Miguel Bergua-Burgues[7], Maria Diez-Campelo[8], Harry P. Erba[9], Carmen Garcia-Hernandez[10], Guillermo Sanz Santillana[11], Casey O'Connell[12], Jun Ho Jang[13], Dong-Yeop Shin[14], Hamid Sayar[15], Mayank Rao[16], Richard S. Schwartz[16], Xuebei An[16], Feng Jin[16], Alison J. Forgie[16], Athanasios C. Tsiatis[16], Jessica K. Altman[17]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [3]Vanderbilt University Medical Center, Nashville, TN, USA; [4]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [5]Mayo Clinic, Rochester, MN, USA; [6]University of Ulsan College of Medicine, Seoul, Korea, Republic of (South); [7]Hospital San Pedro de Alcántara, Caceres, Spain; [8]Hospital Universitario de Salamanca, Salamanca, Spain; [9]Duke University, Durham, NC, USA; [10]Hospital General Universitario de Alicante, Alicante, Spain; [11]Hospital Universitario y Politécnico La Fe, Valencia, Spain; [12]University of Southern California - Keck School of Medicine, Los Angeles, CA, USA; [13]Samsung Medical Center, Seoul, Korea, Republic of (South); [14]Seoul National University Hospital, Seoul, Korea, Republic of (South); [15]Indiana University Cancer Center, Indianapolis, IN, USA; [16]ALX Oncology Inc., South San Francisco, CA, USA; [17]Northwestern University Feinberg School of Medicine, Chicago, IL, USA.

Background

- CD47, a marker of self, engages signal regulatory protein alpha (SIRPα) and signals macrophages to ignore the cell on which CD47 is expressed.[1] Tumors upregulate CD47 to evade immunologic attack.
- Evorpacept (EVO) is a high affinity CD47-blocking fusion protein with an inactivated human immunoglobulin Fc region[1] (Figure 1) that has the potential to enhance the anti-neoplastic activity of azacitidine with minimal additional toxicity (Figure 2).
- Final results are presented from the Phase 1 part of the ASPEN-02 study which is assessing the safety and initial activity of evorpacept (EVO) in combination with azacitidine (AZA) in the treatment of patients with higher-risk myelodysplastic syndrome (MDS).

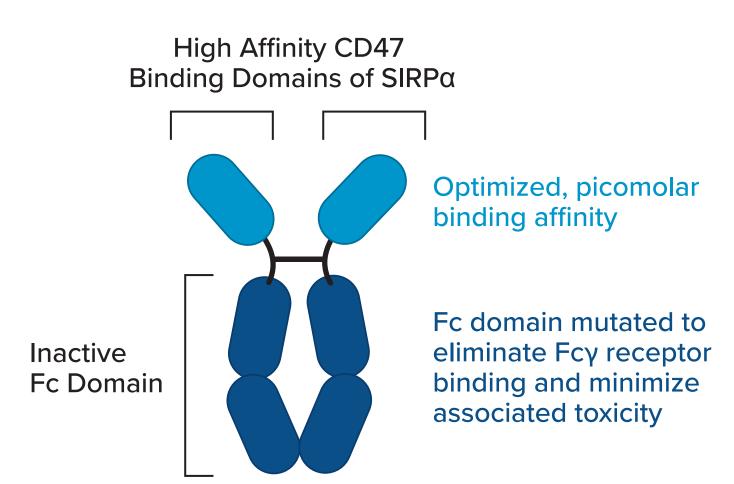**Figure 1.** Evorpacept Potently and Selectively Blocks CD47 Binding to SIRPα

- Fc domain enables antibody-like PK.
- Molecular weight is half the size of typical antibody.
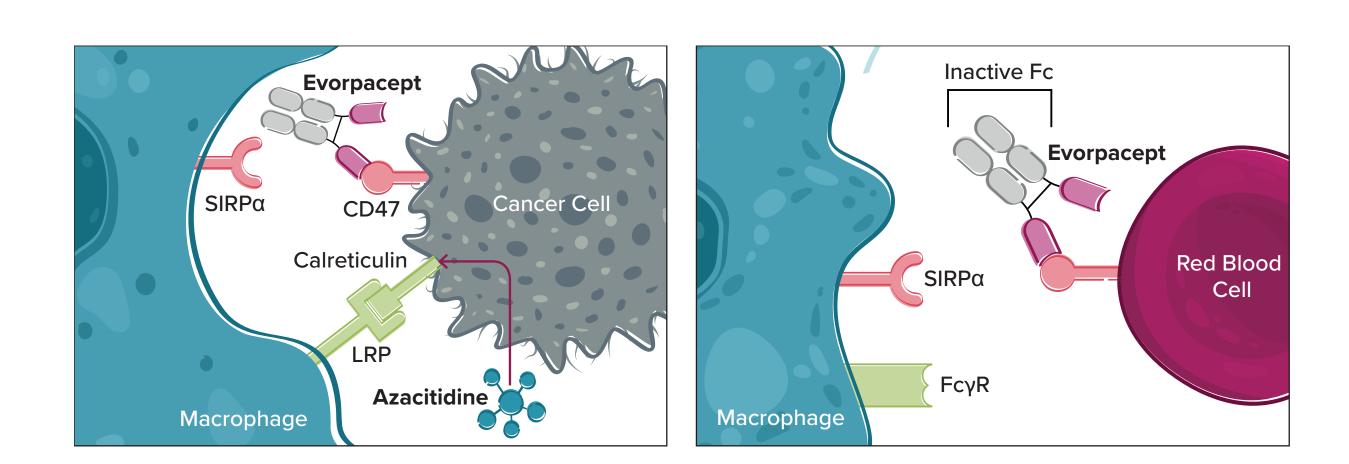
Figure 2. Evorpacept Blocks the CD47 Myeloid Checkpoint While Sparing Normal Hematopoietic Cells from Destruction

- *In vitro* models suggest that evorpacept enhances phagocytosis in combination with azacitidine.
- Treatment with azacitidine induces cell-surface expression of calreticulin, a pro-phagocytic signal. Concurrent blockade of the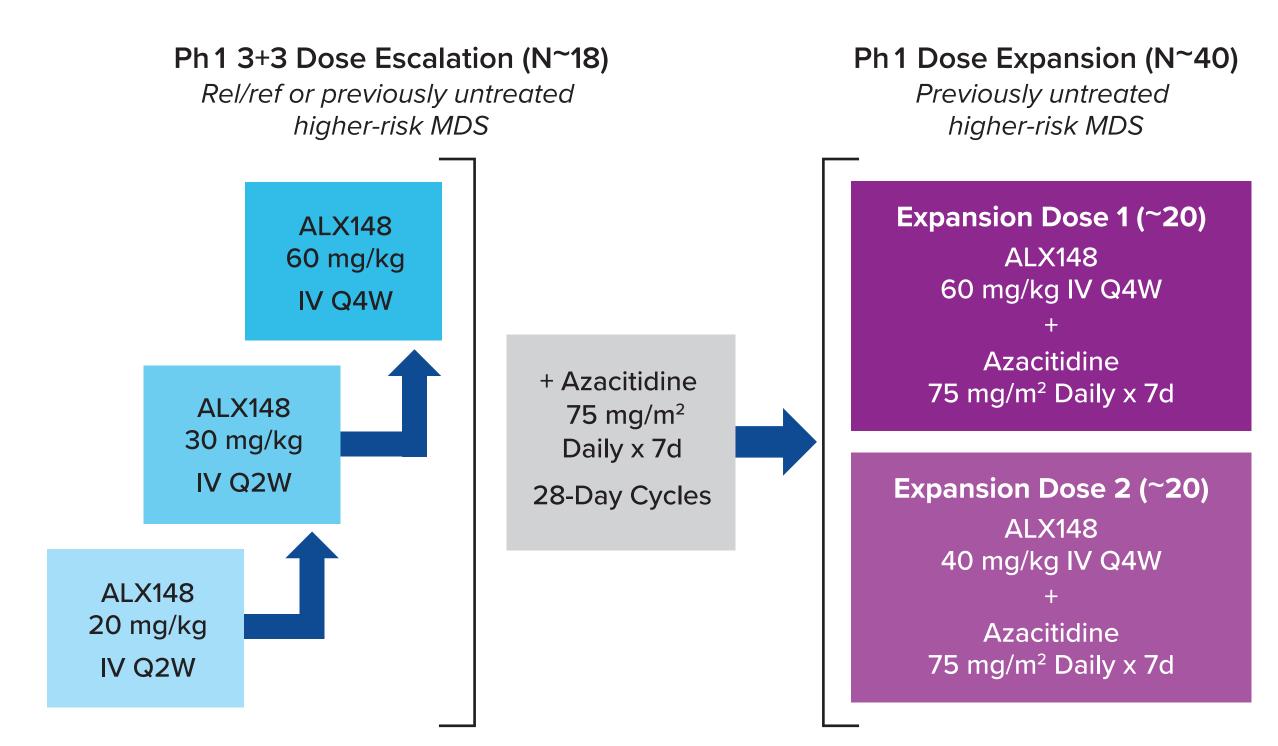 CD47 myeloid checkpoint with EVO may augment the phagocytosis of leukemia cells by macrophages, in preclinical models.[2]
- Toxicity from CD47-targeted antibody dependent cellular phagocytosis (ADCP) on normal hematopoietic cells is spared due to evorpacept's inactivated Fc region.

Methods

ASPEN-02 Phase 1 Design

- Using a 3+3 dose escalation, patients with relapsed/refractory (R/R) or with higher risk (HR) and newly diagnosed (ND) MDS were administered escalating doses of intravenous EVO (20 mg/kg Q2W, 30 mg/kg Q2W, or 60 mg/kg Q4W) combined with AZA (75 mg/m² IV/SC x 7d) in a 28-day treatment cycle. Subsequently patients with ND HR-MDS were randomized to receive EVO 40mg/kg Q4W or 60 mg/kg Q4W in combination with standard AZA in expansion cohorts.
- The primary Phase 1 objective is to characterize the safety and tolerability of EVO administered in combination with AZA.
- The primary Phase 1 endpoint is the frequency of first cycle dose-limiting toxicities (DLTs) and adverse events as characterized by type, frequency, severity, timing, seriousness and relationship to study treatment.
- Key eligibility requirements include patients with R/R or ND HR-MDS (IPSS-R score >3.5) and a baseline ECOG status of 0-2. For patients with R/R MDS, prior exposure to hypomethylating agents (HMA) is allowed (Dose escalation). Patients with ND HR-MDS must have had no prior exposure to HMA or cytotoxic chemotherapy for higher-risk MDS (prior use of single agent lenalidomide for low or intermediate-1 risk MDS with deletion 5q abnormality is allowed) and must be appropriate candidates for single-agent AZA treatment.
- Response assessments were performed by the investigator per modified International Working Group (IWG) criteria.[3]
- The Phase 1 will enroll approximately up to 18 patients over 3 planned dose levels in the dose escalation part, and approximately 40 patients over 2 dose levels in the dose expansion part (Figure 3).

Figure 3. Phase 1 Study Schema

Results

Patient Baseline Characteristics

- As of January 3, 2024, 65 subjects were treated in the phase 1 portion, including 13 subjects with R/R MDS (EVO doses of 20 mg/kg Q2W [n=1] or 60 mg/kg Q4W [n=12]), and 52 subjects with ND HR-MDS (EVO doses of 40 mg/kg Q4W [n=23] and 60 mg/kg Q4W [n=29]).
- For all 65 patients, median age was 70 (range 24 – 88) years, and baseline ECOG scores were 0 (n=27, 41.5%), 1 (n=31, 47.7%), or 2 (n=7, 10.8%).
- 3/13 (23.1%) R/R MDS and 9/52 (17.3%) ND HR-MDS patients, 12/65 (18.5%) patients overall, had therapy-related MDS.
- TP53 mutations were present at baseline in 5/13 (38.5%) R/R MDS and 17/52 (32.7%) ND HR-MDS patients, 22/65 (33.8%) overall.
- Very poor cytogenetic risk (Complex: >3 abnormalities) was present in 4/13 (30.8%) R/R MDS and in 15/52 (28.8%) ND HR-MDS, 19/65 (29.2%) overall.
- 13/13 (100%) R/R MDS patients had received prior hypomethylating agents (HMA) or cytotoxic chemotherapy.

Table 1. Patient Baseline Characteristics

		R/R MDS N=13	ND HR-MDS N=52	Total N=65
Median Age, Years (range)		70.0 (62-81)	70.5 (24-88)	70.0 (24-88)
Sex, n	M	8	31	39
	F	5	21	26
Race, n	White	10	41	51
	Black	2	3	5
	Asian	0	6	6
	Other	0	1	1
	Unknown	1	1	2
ECOG PS, n	0	3	24	27
	1	10	21	31
	2	0	7	7
MDS Status, n (%)	Therapy Related	3 (23.1%)	9 (17.3%)	12 (18.5%)
	Prior HMA Treatment	13 (100%)	0	13 (20.0%)
IPSS-R Score at Initial Diagnosis, n (%)	<4	2 (15.4%)	1 (1.9%)	3 (4.6%)
	4-4.5	2 (15.4%)	16 (30.8%)	18 (27.7%)
	>4.5-6	5 (38.5%)	14 (26.9%)	19 (29.2%)
	>6	4 (30.8%)	21 (40.4%)	25 (38.5%)
Mutation Status, n (%)	TP53	5 (38.5%)	17 (32.7%)	22 (33.8%)
	ASXL1	5 (38.5%)	11 (21.2%)	16 (24.6%)
	TET2	5 (38.5%)	6 (11.5%)	11 (16.9%)
	DNMT3A	2 (15.4%)	10 (19.2%)	12 (18.5%)
	SF3B1	2 (15.4%)	3 (5.8%)	5 (7.7%)
	SRSF2	0	8 (15.4%)	8 (12.3%)
	RUNX1	1 (7.7%)	8 (15.4%)	9 (13.8%)
Cytogenetic Risk at Screening, n (%)	Very Good	0	1 (1.9%)	1 (1.5%)
	Good	4 (30.8%)	17 (32.7%)	21 (32.3%)
	Intermediate	4 (30.8%)	10 (19.2%)	14 (21.5%)
	Poor	1 (7.7%)	6 (11.5%)	7 (10.8%)
	Very Poor	4 (30.8%)	15 (28.8%)	19 (29.2%)
	Not Evaluable	0	2 (3.8%)	2 (3.1%)
	Missing	0	1 (1.9%)	1 (1.5%)

Safety

- EVO in combination with azacitidine was well tolerated. No dose-limiting toxicity was observed, and a maximum tolerated dose (MTD) was not reached.[2]
- Treatment-emergent AEs (TEAEs) were reported in 65/65 (100%) subjects. TEAEs considered possibly related to EVO were reported in 36/65 (55.4%) subjects and were generally low grade (Table 2).
- Discontinuation of EVO was infrequent, with 3/52 (5.8%) ND-HR, and 0/13 (0%) R/R MDS subjects discontinuing EVO due to a regimen-related TEAE.
- No subjects discontinued EVO due to an EVO-related TEAE.
- 19/65 (29.2%) subjects experienced any TEAE ≥Grade 3 in severity related to EVO.
- 40/65 (61.5%) subjects experienced a serious adverse event (SAE), however, only 8/65 (12.3%) and 7/65 (10.8%) subjects experienced an SAE related to AZA and EVO respectively.
- There were no EVO-related deaths on study.

Table 2: Most Common Evorpacept Related Adverse Events*

	AZA + EVO								
	R/R MDS				ND HR-MDS				
	20 mg/kg Q2W (N=1)		60 mg/kg Q4W (N=12)		40 mg/kg Q4W (N=23)		60 mg/kg Q4W (N=29)		(N=65)
Adverse Event, n	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	All Grades n (%)
Diarrhea	–	–	–	–	6	–	3	–	9 (13.8%)
Nausea	–	–	–	–	3	–	5	–	8 (12.3%)
Vomiting	–	–	–	–	3	–	5	–	8 (12.3%)
Neutrophil Decreased	–	–	1	1	–	3	–	3	8 (12.3%)
Infusion Related Reaction	–	–	2	–	3	–	3	–	8 (12.3%)
Platelet Count Decreased	–	–	–	1	1	2	–	1	5 (7.7%)
Fatigue	–	–	1	–	3	–	1	–	5 (7.7%)
Constipation	–	–	1	–	3	–	–	–	4 (6.2%)
White Blood Cell Count Decreased	–	–	–	1	–	2	1	–	4 (6.2%)
Chills	–	–	–	–	1	–	3	–	4 (6.2%)
Febrile Neutropenia	–	–	–	–	–	3	1	–	4 (6.2%)
Anemia	–	–	–	–	–	3	–	–	3 (4.6%)
Neutropenia	–	–	–	–	–	1	–	2	3 (4.6%)

* Data Cutoff 03January 2024; Safety population (n=65); Table includes evorpacept related adverse events in ≥5% of patients and all Grade 3 and Grade 4 evorpacept-related adverse events occurring in ≥2 subjects.

Initial Activity of EVO + AZA

- Among subjects evaluable for response:
  - 21 out of 52 (40.4%) subjects with ND HR-MDS achieved a response, including 8 with CR, 1 with PR, 10 marrow CR, 2 with HI-E and HI-P, 21 SD and 3 PD.
  - 2 out of 13 (15.4%) subjects with R/R MDS achieved a response, including 2 marrow CR, 8 SD and 2 PD.
- The median duration of treatment is 4.6 months (range: 0.9-22.1 months) for ND HR-MDS and 3.7 months (range: 0.9-17.1 months) for R/R MDS. The median duration of treatment for all patients is 4.4 months (range: 0.9-22.1).
- Decrease in bone marrow blasts was observed in subjects with both ND HR-MDS and R/R MDS (Figure 4).
- Median duration of response (DOR) was 8.5 months (95% CI 5.8 months, NA) and 3.5 months (95% CI NA, NA) for ND HR-MDS, and R/R MDS, respectively.
- Median overall survival (OS) was 16.6 months (95% CI 12.6, 17.9 months) and 11.9 months (95% CI 5.7, 19.4 months) for ND HR-MDS and R/R MDS, respectively.

Table 3: Best Overall Response by Modified IWG Criteria[3]

	R/R MDS (N=13)	ND HR-MDS (N=52)	Total (N=65)
ORR	2 (15.4%)	21 (40.4%)	23 (35.4%)
CR	0	8 (15.4%)	8 (12.3%)
PR	0	1 (1.9%)	1 (1.5%)
Marrow CR	2 (15.4%)	10 (19.2%)	12 (18.5%)
HI		2 (3.8%)	2 (3.1%)
with HI-E		2 (3.8%)	2 (3.1%)
with HI-P	0	2 (3.8%)	2 (3.1%)
with HI-N		1 (1.9%)	1 (1.5%)
SD	8 (61.5%)	21 (40.4%)	29 (44.6%)
PD	2 (15.4%)	3 (5.8%)	5 (7.7%)
Not Evaluable	0	3 (5.8%)	3 (4.6%)
No Post-Baseline Assessment	1 (7.7%)	4 (7.7%)	5 (7.7%)

Note: Only Best Overall Responses lasting at least 4 weeks for CR, PR, mCR, CyR and at least 8 weeks for HI are included; The best overall response is determined over the first 6 cycles of treatment; Data are pooled between dose escalation and expansion. ORR – Objective response rate = CR + PR + mCR + HI; CR – Complete remission; PR – Partial remission; SD – Stable disease; HI – Hematologic improvement; E – Erythroid; P – Platelet; N – Neutrophil.

Change in Bone Marrow Blast Percentage from Baseline
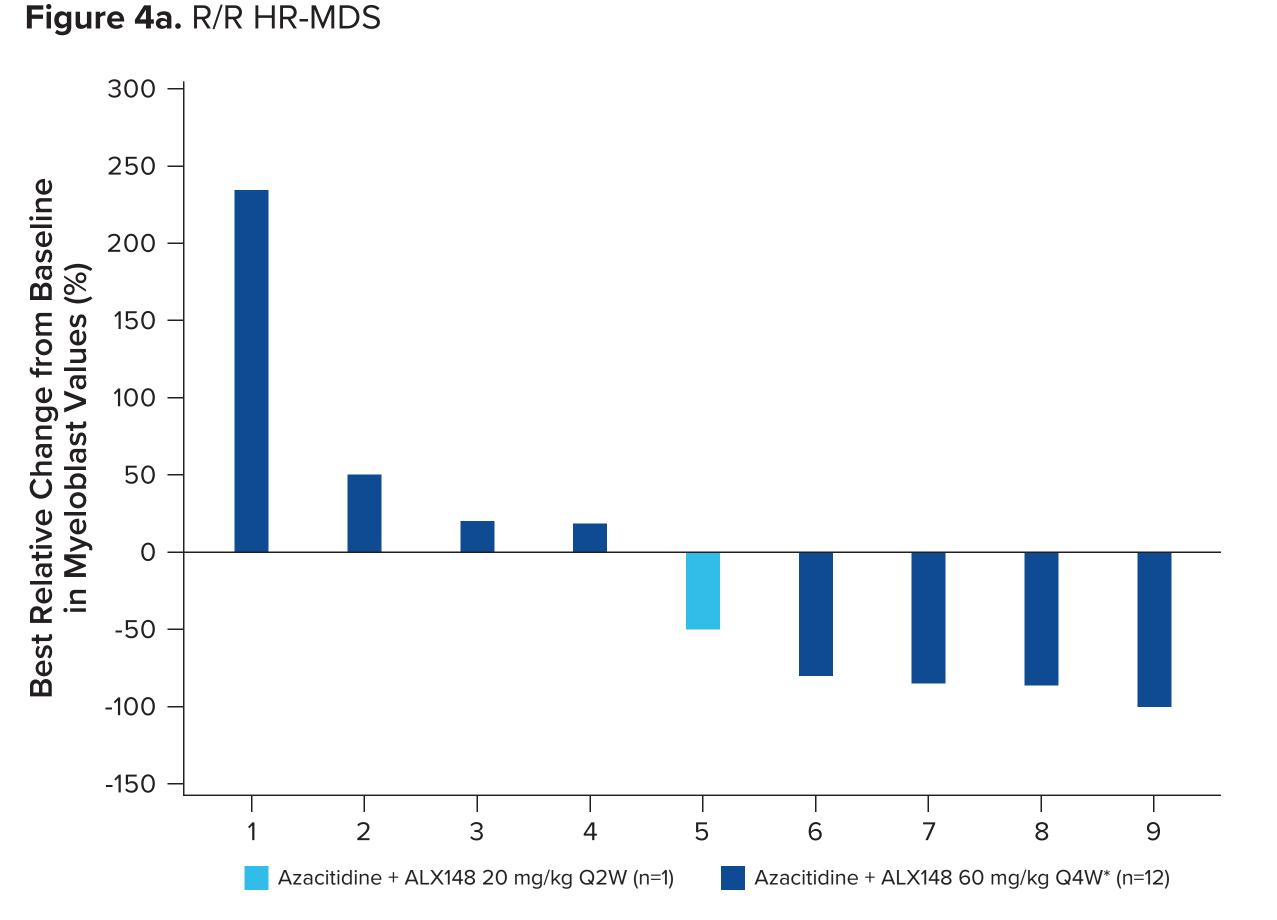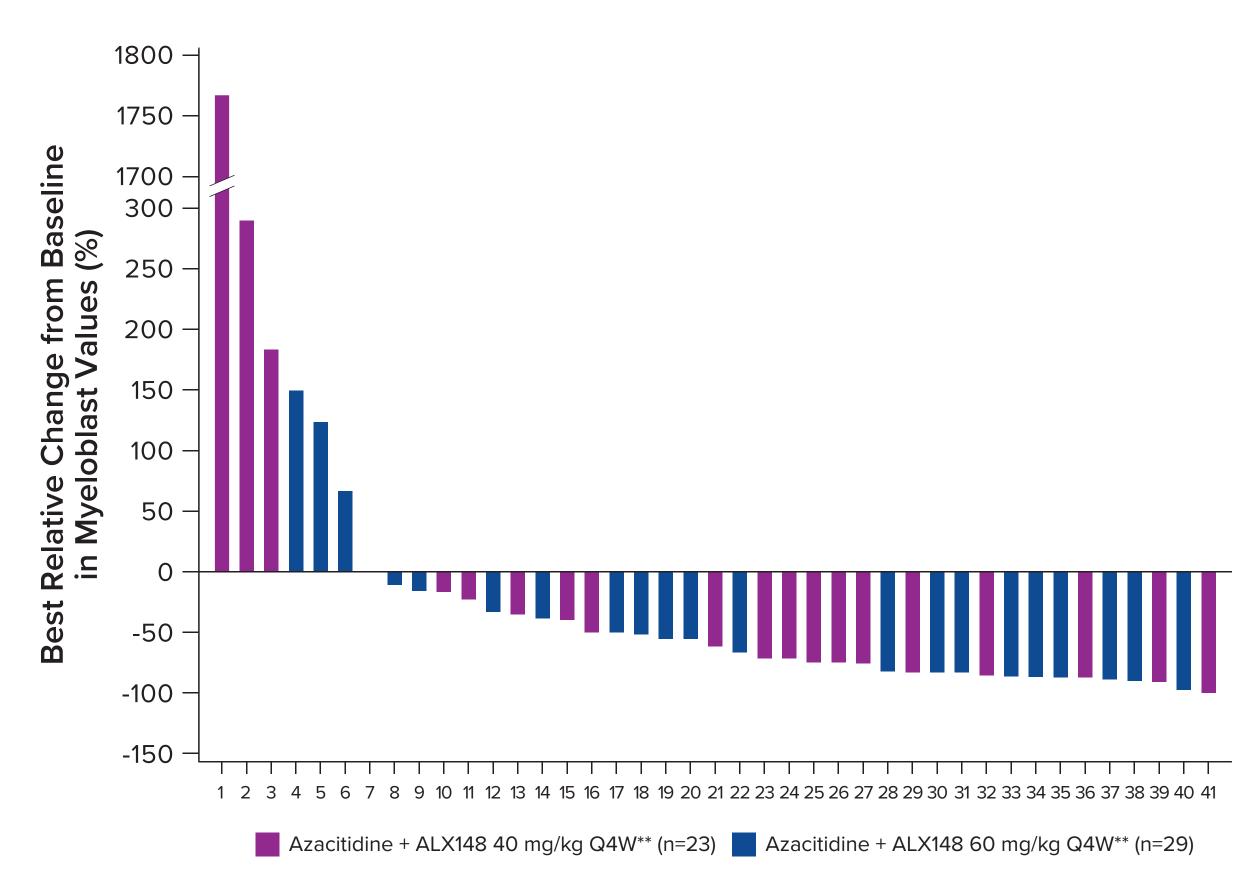
Figure 4a. R/R HR-MDS

Figure 4b. ND HR-MDS

*AZA + EVO 60 mg/kg Q4W group includes subjects treated with 30 mg/kg Q2W and 60 mg/kg Q4W in the dose escalation Phase 1; **AZA + EVO 40 mg/kg Q4W group includes previously untreated subjects in the Phase 1 treated with 20 mg/kg Q2W (dose escalation) and 40 mg/kg Q4W (dose expansion). AZA + EVO 60 mg/kg Q4W group includes previously untreated subjects in the Phase 1 treated with 30 mg/kg Q2W and 60 mg/kg Q4W in both dose escalation and dose expansion; Note: Only subjects who had bone marrow blasts at both baseline and post-baseline assessed with the same sample collection method and a non-zero bone marrow blast count at baseline are included.

Summary of Red Blood Cell (RBC) Transfusion Dependence

RBC Transfusions

- At baseline, 26 of 52 (50.0%) subjects with ND HR-MDS were RBC transfusion-dependent, 10 (38.5%) of whom achieved RBC transfusion-independence, starting at median 14.6 (range 8.0-43.0) weeks after commencing treatment with AZA + EVO.
  - The median of the longest RBC transfusion independence interval is 22.4 (range 8.1-48.3) weeks.
- At baseline, 26 of 52 (50.0%) subjects with ND HR-MDS were RBC transfusion-independent, 17 (65.4%) of whom maintained RBC transfusion-independence, and 9 (34.6%) of whom became RBC transfusion-dependent on study.
- At baseline, 9 of 13 (69.2%) subjects with R/R HR-MDS were RBC transfusion-dependent, 1 (11.1%) of whom achieved RBC transfusion-independence, starting at 14.6 weeks after commencing treatment with AZA + EVO.
  - The longest RBC transfusion independence interval is 15.0 weeks.
- Of 4 subjects with R/R HR-MDS who were RBC transfusion-independent at baseline, 2 (50%) maintained RBC transfusion-independence, and 2 (50%) became RBC transfusion-dependent on study.

Note: **Transfusion dependence at baseline** – Any RBC transfusion in 8 weeks prior to starting treatment; **Transfusion independence** – No transfusion over an 8-week period on study; The time to achieving RBC transfusion independence is the time from first dose to the first time that an 8-week transfusion-free interval is achieved.

Preliminary Phase 1 Pharmacokinetic (PK) and Pharmodynamic (PD) Results

- Overall, evorpacept exhibited dose-proportional PK, consistent with results from prior studies.
- Full CD47 target occupancy (TO) was observed on peripheral blood RBCs and CD4+ T cells throughout the dosing interval, including at both peak and trough concentrations of evorpacept, across the four dose levels evaluated.

Figure 5. Evorpacept Concentration-Time Profiles Following IV Infusion at 20 mg/kg Q2W, 30 mg/kg Q2W, 40 mg/kg Q4W, and 60 mg/kg Q4W (Cycle 1, Day 1)
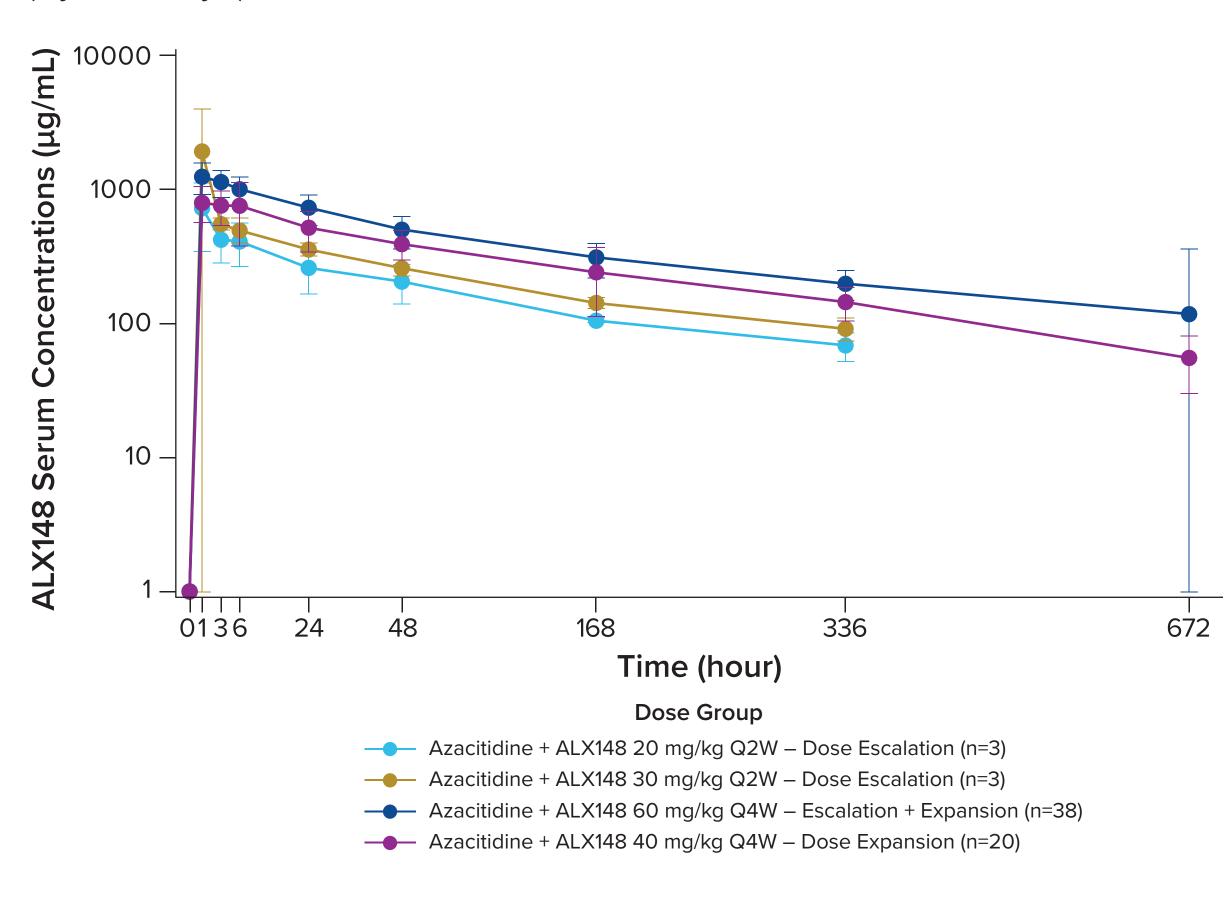

Table 4: Evorpacept PK Parameters Following IV Infusion at 20 mg/kg Q2W, 30 mg/kg Q2W, 40 mg/kg Q4W and 60 mg/kg Q4W (Cycle 1, Day 1)

Parameters	20 mg/kg Q2W (N=3)	30 mg/kg Q2W (N=3)	40 mg/kg Q4W (N=19)	60 mg/kg Q4W (N=36)
C_{max} (µg/mL)	730 ± 389	1911 ± 2113	888 ± 378	1255 ± 283
AUC_{inf} (µg*h/mL)	66833 ± 15312	90633 ±10553	151156 ± 39955	209628 ± 63867
CL (mL/h/kg)	0.309 ± 0.062	0.334 ± 0.041	0.282 ± 0.072	0.322 ± 0.145
Vss (mL/kg)	76.6 ± 19.0	86.7 ± 11.0	95.4 ± 23.0	104 ± 25.2

Data Cutoff 05Feb2024; Parameters presented as mean ± SD.

Conclusion

Evorpacept was well tolerated in combination with azacitidine, for treatment of patients with R/R and ND HR-MDS.

- The combination displays a favorable safety profile across the evaluated exposure range and is similar to azacitidine monotherapy.
- No maximum tolerated dose was reached, and there were no treatment-related deaths on study. The maximum administered dose was 60 mg/kg.
- Overall, Evorpacept demonstrated dose-proportional PK consistent with prior data.
- Evorpacept + azacitidine demonstrates initial activity with 40.4% ORR in ND HR-MDS.

References

1. Kauder, Steven E et al. ALX148 blocks CD47 and enhances innate and adaptive antitumor immunity with a favorable safety profile." *PloS one* vol. 13,8 22 Aug. 2018
2. Garcia-Manero G et al. Evorpacept (ALX148), a CD47-Blocking Myeloid Checkpoint Inhibitor, in Combination with Azacitidine: A Phase 1/2 Study in Patients with Myelodysplastic Syndrome (ASPEN-02), Blood 2021; 138 (Supplement 1); 2601.
3. Cheson BD et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood* 2006; 108 (2); 419–425.