Evorpacept (ALX148), a CD47-Blocking Myeloid Checkpoint Inhibitor, in Combination with Azacitidine: A Phase 1/2 Study in Patients with Myelodysplastic Syndrome (ASPEN-02)

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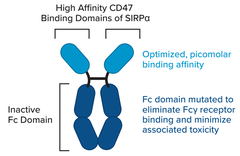
Background

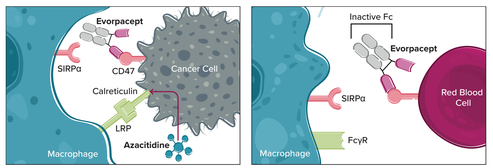
- CD47, a marker of self, engages signal regulatory protein alpha (SIRPα) and signals macrophages to ignore the cell on which CD47 is expressed.[1] Tumors upregulate CD47 to evade immunologic attack.
- Evorpacept (ALX148) is a high affinity CD47-blocking fusion protein with an inactivated human immunoglobulin Fc region[2] (Figure 1) that is designed to enhance the activity of other anti-neoplastic therapies, such as azacitidine, with minimal additional toxicity (Figure 2).
- Here, we present preliminary results from the Phase 1 part of the ASPEN-02 study which demonstrate the safety of combining evorpacept with azacitidine and promising initial activity in patients with 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



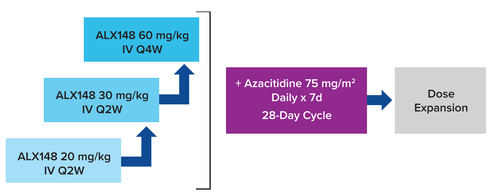
- Evorpacept enhances phagocytosis in combination with azacitidine.
- Treatment with azacitidine induces cell-surface expression of calreticulin, a potent pro-phagocytic signal. Concurrent blockade of the CD47 myeloid checkpoint with evorpacept augments the phagocytosis of leukemia cells by macrophages, leading to enhanced depth and durability of response in preclinical models.[3]
- Toxicity from CD47-targeted 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, subjects were administered escalating doses of intravenous evorpacept (20 mg/kg Q2W, 30 mg/kg Q2W, or 60 mg/kg Q4W) combined with azacitidine (75 mg/m^2 IV/SC x 7d) in a 28-day treatment cycle.
- The primary Phase 1 objective is to characterize the safety and tolerability of evorpacept administered in combination with azacitidine.
- The primary Phase 1 endpoint is the frequency of first cycle dose-limiting toxicities (DLTs).
- Eligible patients include adults with a documented diagnosis of relapsed/refractory (R/R) MDS or higher risk (HR) previously untreated 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. Patients with previously untreated HR-MDS must have had no prior exposure to HMA or cytotoxic chemotherapy for the treatment of 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 azacitidine treatment.
- Response assessments were performed by the investigator per IWG criteria.[4]

Figure 3. Phase 1 Study Schema



Results

Patient Baseline Characteristics

- 22 patients with R/R or previously untreated HR-MDS have been enrolled in the Phase 1 (Table 1) as of the data cutoff date of 25-Oct-2021.
- 6 of 9 patients with previously untreated HR-MDS had therapy related disease.
- All patients with R/R MDS had failed 1 or more prior HMA regimen.
- Among the 9 patients enrolled with previously untreated HR-MDS, 7 (78%) had a TP53 mutation together with complex (>3) cytogenetic abnormalities.

Table 1. Patient Baseline Characteristics

		Phase 1 n=22
Median Age, Years (range)		70.5 (56-81)
Sex, n	F	8
	M	14
Race, n	White	17
	Black	4
	Unknown	1
ECOG PS, n	0	6
	1	16
	2	0
MDS Status, n	Previously Untreated HR-MDS	9
	• Therapy Related	6
	Rel/Ref MDS	13
	• Prior HMA Treatment	13
IPSS-R Score	Mean	6.0
	Median	5.8
	Min-Max	1.0 - 10.0
Mutation Status, n (%)	TP53	8 (36)
	ASXL1	4 (18)
	TET2	3 (14)
	DNMT3A	2 (9)
	SF3B1	1 (4.5)
	SRSF2	1 (4.5)
	RUNX1	1 (4.5)
Cytogenetic Risk at Diagnosis, n (%)	Very Good	0
	Good	2 (9)
	Intermediate	0
	Poor	2 (9)
	Very Poor	8 (36)
	N/A	10 (45)

N/A –Not available

Safety

- Evorpacept in combination with azacitidine was well tolerated with no dose-limiting toxicities observed, and most adverse events (AE) were of low grade and frequency.
- 21 (95.5%) patients administered ALX148 + azacitidine experienced any treatment emergent AE (TEAE), with 10 (45.5%) patients experiencing any AE considered possibly related to ALX148 treatment.
- The most common treatment related AEs (TRAE) observed with evorpacept + azacitidine were Grade 1-2 infusion related reactions (IRR) (n=4; 18%) (Table 2b). All patients experiencing IRRs were able to complete evorpacept infusions and did not experience recurrence of IRRs with subsequent cycles.
- 13 (59%) patients experienced any TEAE ≥Grade 3 in severity, with a total of 2 (9%) patients experiencing any ≥Grade 3 TRAE (both with transient neutropenia/neutrophil count decreased); there was 1 (4.5%) G5 TEAE of sepsis unrelated to study treatment.
- No patients (0%) experienced any serious adverse event (SAE) considered related to evorpacept treatment.

Table 2a: Most Common (>2 Subjects) Treatment Emergent AEs (All Causality)

	20 mg/kg Q2W (N=3)		30 mg/kg Q2W (N=3)		60 mg/kg Q4W (N=16)		Total (N=22)
Adverse Event, n	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	All Grades (%)
Blood Creatinine Increased	2	–	1	–	2	–	5 (23)
Constipation	1	–	1	–	2	1	5 (23)
Diarrhea	1	–	1	–	3	–	5 (23)
Fatigue	–	–	–	–	4	1	5 (23)
Neutropenia/Neutrophil Count Decreased	–	–	–	1	1	3	5 (23)
Anemia	1	1	1	–	–	1	4 (18)
Dizziness	–	–	1	–	3	–	4 (18)
Dyspnoea	1	–	–	–	2	1	4 (18)
Febrile Neutropenia	–	2	–	–	–	2	4 (18)
Infusion Related Reaction	–	–	–	–	4	–	4 (18)
Nausea	–	–	1	–	3	–	4 (18)
Abdominal Pain	1	–	1	–	1	–	3 (14)
Contusion	1	–	1	–	1	–	3 (14)
Platelet Count Decreased	–	2	–	1	–	–	3 (14)
Pneumonia	–	1	–	–	–	2	3 (14)
Transfusion Reaction	2	–	–	–	1	–	3 (14)
Vomiting	1	–	–	–	2	–	3 (14)

Data Cutoff 25Oct2021; Safety population (n=22).

Table 2b: Most Common (>1 Subject) Evorpacept-Related AEs

	20 mg/kg Q2W (N=3)		30 mg/kg Q2W (N=3)		60 mg/kg Q4W (N=16)		Total (N=22)
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	All Grades (%)
Infusion Related Reaction	–	–	–	–	4	–	4 (18)
Constipation	1	–	–	–	2	–	3 (14)
Neutropenia/ Neutrophil Count Decreased	–	–	–	–	1	2	3 (14)
Nausea	–	–	1	–	1	–	2 (9)
Vomiting	1	–	–	–	1	–	2 (9)

Data Cutoff 25Oct2021; Safety population (n=22); Table includes all ≥G3 evorpacept-related AEs.

Efficacy

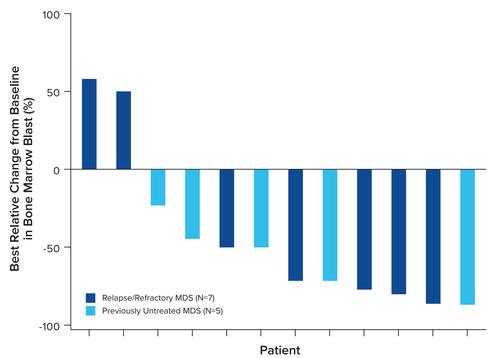
- Among subjects evaluable for IWG response:
  - 3 out of 6 subjects with previously untreated HR-MDS achieved a response, including 2 with CR ([n=1 at 20 mg/kg Q2W, n=1 at 60 mg/kg Q4W] both subjects also achieved cytogenetic response), 1 marrow CR with HI-E and HI-P (20 mg/kg Q2W), 2 SD (n=2 at 60 mg/kg Q4W) and 1 PD (30 mg/kg Q2W).
  - 5 out of 8 subjects with R/R MDS achieved a response, including 5 marrow CR (n=1 at 20 mg/kg Q2W, n=4 at 60 mg/kg Q4W), 2 SD (n=2 at 30 mg/kg Q2W) and 1 PD (60 mg/kg Q4W). One subject had a G5 event unrelated to study treatment and was not evaluable for IWG response.
  - Among the 2 patients with CR, 1 proceeded to stem cell transplant and 1 has ongoing CR with full count recovery and remains on treatment and transfusion independent.
  - Overall, 3 patients have been able to proceed to stem cell transplant.
  - The median follow up time on study is 3.4 months.
- Decrease in bone marrow blasts was observed in subjects with both previously untreated HR-MDS and R/R MDS (Figure 4).

Table 3: Best Overall Response by IWG Criteria[4]

	Previously Untreated HR-MDS (N=6)	Previously Untreated HR-MDS with TP53 Mutation (N=5)	Relapsed/Refractory MDS (N=9)[#]
ORR	3 (50%)	3 (60%)	5 (56%)*
CR	2 (33%)	2 (40%)	0
PR	0	0	0
Marrow CR	1 (17%) with HI	1 (20%) with HI	5 (56%)*
HI	0	0	0
SD	2 (33%)	1 (20%)	2 (22%)
PD	1 (17%)	1 (20%)	1 (11%)

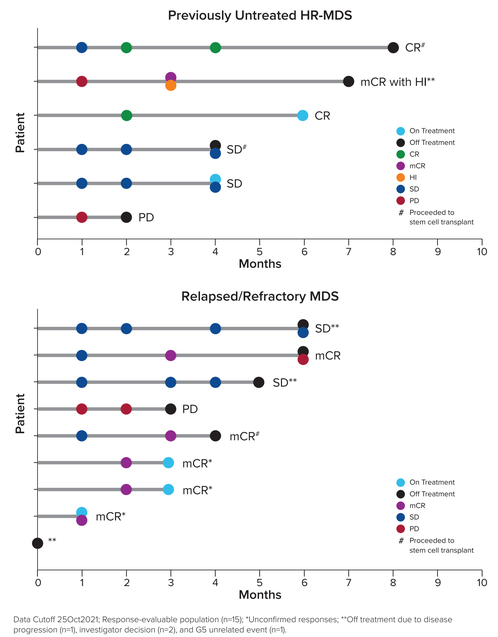
Data Cutoff 25Oct2021; Response evaluable population (n=15); *includes 3 unconfirmed responses; [#]1 subject had G5 event unrelated to treatment prior to first disease assessment; **ORR** – Objective response rate; **CR** – Complete response; **PR** – Partial response; **HI** – Hematologic improvement; **E** – Erythroid; **P** – Platelet; **SD** – Stable disease; **PD** – Disease progression; **IWG** – international working group.

Figure 4. Change in Bone Marrow Blast Percentage from Baseline



Data Cutoff 25Oct2021; Response-evaluable population (n=15); 2 subjects (1 Relapsed/Refractory and 1 Previously Untreated) with missing data and 1 subject with G5 unrelated event not represented on graph.

Figure 5. Duration of Response

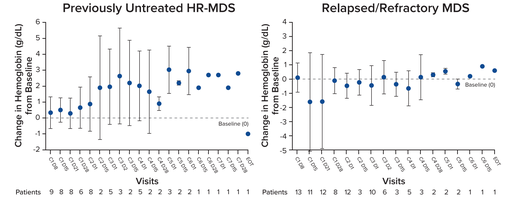


Data Cutoff 25Oct2021; Response-evaluable population (n=15); *Unconfirmed responses; **Off treatment due to disease progression (n=1), investigator decision (n=2), and G5 unrelated event (n=1).

Changes in Hemoglobin Level and RBC Transfusion Frequency

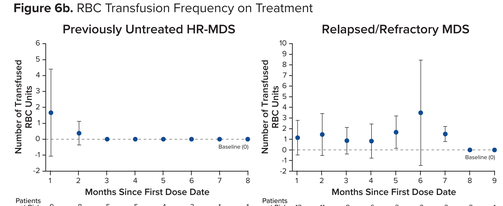
- Preliminary data indicate a trend towards improvement in hemoglobin levels and decrease in RBC transfusion frequency in patients with previously untreated HR-MDS treated with evorpacept + azacitidine, but no clear change from baseline in patients with R/R MDS.

Figure 6a. Changes in Hemoglobin Level on Treatment



Data Cutoff 25Oct2021; Parameters presented as mean ± SD; Safety population (n=22).

Figure 6b. RBC Transfusion Frequency on Treatment



Data Cutoff 25Oct2021; Parameters presented as mean ± SD; Safety population (n=22).

Preliminary Phase 1 PK and 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 three dose levels evaluated.

Figure 7. Evorpacept Concentration-Time Profiles Following IV Infusion at 20 mg/kg Q2W, 30 mg/kg Q2W, and 60 mg/kg Q4W (Cycle 1, Day 1)

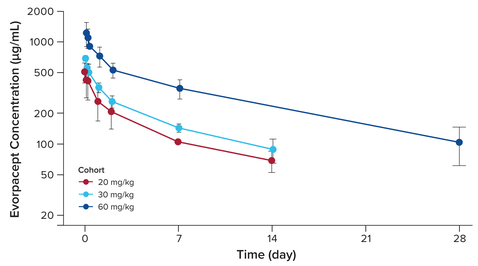
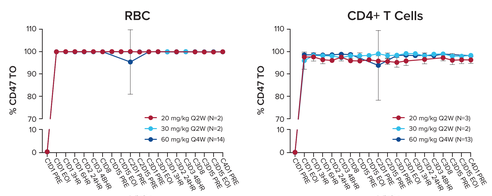


Table 4: Evorpacept PK Parameters Following IV Infusion at 20 mg/kg Q2W, 30 mg/kg Q2W, and 60 mg/kg Q4W (Cycle 1, Day 1)

Parameters	20 mg/kg Q2W (N=3)	30 mg/kg Q2W (N=3)	60 mg/kg Q4W (N=6)
C_{max} (µg/mL)	446 ± 137	628 ± 113	1250 ± 319
AUC_{inf} (µg*h/mL)	66200 ± 16000	81200 ± 16500	222000 ± 70800
CL (mL/h/kg)	0.313 ± 0.068	0.379 ± 0.069	0.296 ± 0.101
Vss (mL/kg)	78.2 ± 21.3	83.9 ± 16.2	94.0 ± 15.9

Data Cutoff 18Jun2021; Parameters presented as mean ± SD.

Figure 8. Preliminary CD47 Target Occupancy in Peripheral Blood



Data Cutoff 25Oct2021; One subject in the 60 mg/kg Q4W cohort had reduced CD47 TO due to dose delay prior to C2D1; Parameters presented as mean +/- SD; **PRE** – pre-infusion; **EOI** – end of infusion.

Conclusions

Initial data suggest that the CD47 myeloid checkpoint blocker evorpacept was well tolerated in combination with azacitidine and demonstrates promising preliminary activity in patients with MDS.

- The combination displays a favorable initial safety profile across the evaluated exposure range that is similar to azacitidine monotherapy.
- No dose limiting toxicities have been observed and no maximum tolerated dose has been reached in the Phase 1. The maximum administered dose was 60 mg/kg Q4W.
- Preliminary biomarker analysis indicates full CD47 occupancy in peripheral blood at all evaluated doses of evorpacept, including at 4 weeks post-dosing.
- Evorpacept + azacitidine demonstrates objective responses in multiple subgroups of MDS associated with poor prognosis, including: TP53 mutation associated with complex cytogenetic abnormalities, therapy-related MDS, and prior HMA failure.
- Complete remissions with cytogenetic responses, hematologic improvement, and transfusion independence were observed in patients with previously untreated HR-MDS. Evidence of activity was also observed in patients that had failed 1 or more prior HMA regimen(s).
- Enrollment in the Phase 1 dose expansion is ongoing to determine the optimal dose of evorpacept in combination with azacitidine for the randomized Phase 2 portion of this study (NCT0441751).

References: 1. Weiskopf, K., *Eur J Cancer*. 2017 May;76:100-109; 2. Kauder, S.E. et al., *PLoS ONE*. 2018 August;13(8): e0201832; 3. Chen et al. ASH 2020. Poster #1965; 4. Cheson et al. *Blood*. 2006

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