ENCOURAGING EFFICACY OBSERVED IN BEXMAB STUDY: A PHASE 1/2 STUDY TO ASSESS SAFETY AND EFFICACY OF BEXMARILIMAB IN COMBINATION WITH STANDARD OF CARE IN MYELOID MALIGNANCIES

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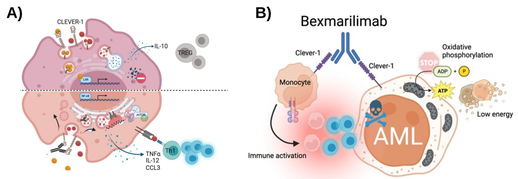
Abstract #2915

INTRODUCTION

Common lymphatic endothelial and vascular endothelial receptor-1 (Clever-1) constitutes a novel macrophage checkpoint. High Clever-1 expression, as observed on malignant blasts and monocytes in AML/MDS, is associated with therapeutic resistance and poor outcome (1, 2).

Bexmarilimab (BEX), a humanized IgG4 monoclonal antibody, binds Clever-1 and alters the function of macrophages. BEX increases antigen presentation, induces secretion of proinflammatory cytokines and increases activation of T cells resulting in immune activation (3). *Ex vivo* treatment of AML bone marrow cells with BEX alone or in combination with azacitidine/venetoclax results in enhanced antigen presentation capacity and increased activation markers on effector T cells (2). BEX may reduce the viability of AML blasts through impairing the cell's metabolism (4).

The ongoing BEXMAB clinical study investigates safety and preliminary efficacy of BEX combined with SoC in patients with AML/MDS (NCT05428969). Phase I data shows good tolerability and promising clinical activity in AML and MDS patients.



A) Clever-1 creates an immunosuppressive environment through scavenging of extracellular components and activation of tolerogenic signaling pathways. By impairing endo-lysosomal acidification, bexmarilimab alters these effects. **B)** In AML, Clever-1 is expressed by blast cells and myeloid immune cells. The antibody activates the immune system and simultaneously may reduce the fitness of AML blasts via impairing the energy production.

RESULTS

Baseline Characteristics

Characteristic	All n=30	1.0mg/kg n=8	3.0mg/kg n=12	6.0mg/kg n=10
Median age years (range)	73 (35;87)	75.5 (52;81)	73 (35;87)	68.5 (51;78)
ECOG PS baseline n (%)				
0	9 (30)	2 (25)	6 (50)	1 (10)
1	16 (53)	3 (37.5)	6 (50)	7 (70)
2	5 (17)	3 (37.5)	0 (0)	2 (20)
MDS r-IPSS n (%)				
Intermediate	1 (3)	0 (0)	0 (0)	1 (10)
High	4 (13)	0 (0)	3 (25)	1 (10)
Very high	5 (17)	2 (25)	1 (8)	2 (20)
AML ELN risk n (%)				
Favorable	2 (7)	1 (12.5)	1 (8)	0 (0)
Intermediate	10 (33)	5 (62.5)	3 (25)	2 (20)
Adverse	8 (27)	0 (0)	4 (30)	4 (40)
# prior therapy n (%)				
0	5 (17)	1 (12.5)	3 (25)	1 (10)
1	12 (40)	3 (37.5)	5 (42)	4 (40)
2	8 (27)	1 (12.5)	3 (25)	4 (40)
≥3	5 (17)	3 (37.5)	1 (8)	1 (1)
Mutation n (%)				
RUNX1	4 (13)	0 (0)	3 (25)	1 (10)
TP53	9 (30)	1 (12.5)	3 (25)	5 (50)
IDH1/2	5 (17)	1 (12.5)	3 (25)	1 (10)
TET2	4 (13)	2 (25)	1 (8)	1 (10)
ASXL1	5 (17)	1 (12.5)	3 (25)	1 (10)

Safety

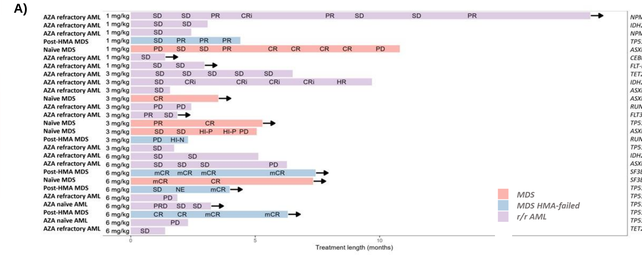
The addition of BEX is well tolerated across dose levels

	AEs n (% of all AEs)	1.0 mg/kg (n=7)	3.0 mg/kg (n=11)	6 mg/kg (n=10)
Any grade	244 (100)	61 (25)	79 (32)	104 (43)
≥ Grade 3	81 (33)	19 (24)	38 (47)	24 (29)
SAEs	37 (15)	11 (31)	18 (47)	8 (22)
Related AEs				
Any Grade	24 (10)	4 (20)	8 (30)	12 (50)
≥ Grade 3	9 (4)	0	7 (78)	2 (22)

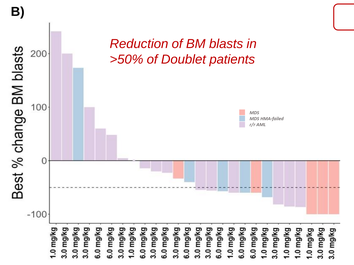
- No dose limiting toxicities (DLT)
- SAEs related to BEX:
  - n=3 at 3mg/kg: Capillary leak syndrome (Gr 3); Hemophagocytic lymphohistiocytosis (Gr 5); Cryptogenic organizing pneumonia (Gr 3)
- Discontinuation in 2 patients due to BEX related AEs
- Immune-related AEs reported at 3.0 and 6.0mg/kg across indications

Efficacy and Pharmacokinetics

Objective responses in ~50% of patients across indications



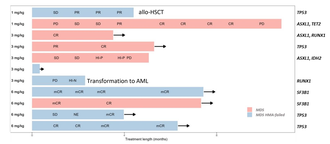
Swimmer plot of Doublet BEX combined with azacitidine (n=27) showing responses across doses and indications



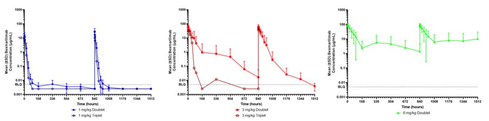
Reduction of BM blasts in >50% of Doublet patients

Response rate and response duration in MDS patients

	Number n	CR	mCR	PR/HI-P
All MDS	10	5 (50%)	2 (20%)	3 (30%)
MDS untreated	5	4 (80%)		1 (20%)
MDS HMA-failed	5	1 (20%)	2 (40%)	2 (40%)



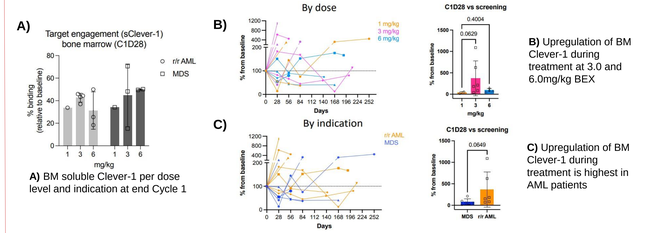
Increased exposure with higher BEX doses



- C_{max} *increases nearly dose-proportional*
- *AUC increased more than dose-proportional at 3 and 6 mg/kg (highest exposure)*
- $T_{1/2}$ *between 17 – 19 h*

Biomarker & Pharmacodynamics

Clever-1 target engagement and expression across doses and indications



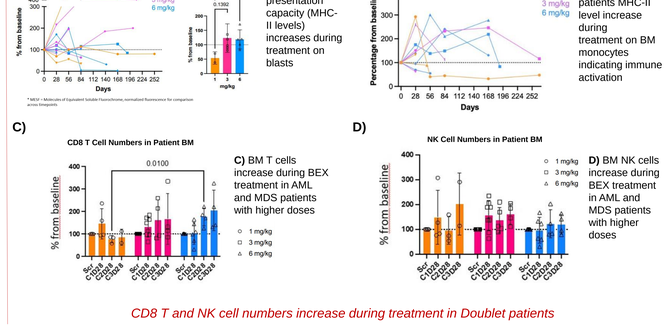
A) BM soluble Clever-1 per dose level and indication at end Cycle 1

B) Upregulation of BM Clever-1 during treatment at 3.0 and 6.0mg/kg BEX

C) Upregulation of BM Clever-1 during treatment is highest in AML patients

Soluble Clever-1 and Clever-1 expression measured from patient BM per dose level and indication during treatment

Increased immune activation in BM of AML/MDS patients in doublet



A) Antigen presentation capacity (MHC-II levels) increases during treatment on blasts

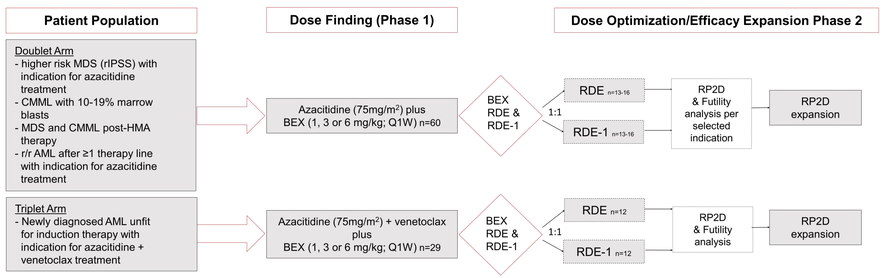
B) In MDS patients MHC-II level increase during treatment on BM monocytes indicating immune activation

C) BM T cells increase during BEX treatment in AML and MDS patients with higher doses

D) BM NK cells increase during BEX treatment in AML and MDS patients with higher doses

CD8 T and NK cell numbers increase during treatment in Doublet patients

STUDY DESIGN



- Phase 1 set-up based on BOIN design (20% toxicity rate)
- Phase 2 set-up as randomized parallel arm, dose response part (planned Dec2023)
- Total enrollment (30Oct2023): n=30 (28 treated + 2 in screening):
  - r/r AML n=19; MDS frontline n=5; MDS HMA-failed n=6
  - Sites in Finland n=4; sites in the US n=2
  - Phase 1 FPFV 07Jun2022

CONCLUSIONS

- *The combination of BEX and azacitidine remains well tolerated with immune-related AEs observed at higher dose levels*
- *Durable target engagement of Clever-1 in the bone marrow with an increase in antigen presentation capacity and CD8 T and NK cells seen supporting BEX mode of action on AML/MDS*
- *Clinical activity with 13/28 objective responses observed across indications*
- *5/5 (100%) MDS patients and 5/5 (100%) MDS patients with HMA-failure show objective responses across risk-groups*
- *Phase 2 to initiate with 6.0mg/kg as BEX recommended dose for expansion (RDE) in MDS patients having failed prior HMA-therapy (FPFV planned for Dec2023)*

REFERENCES

1. **Lin, S. Y. et al.** Identification of STAB1 in Multiple Datasets as a Prognostic Factor for Cytogenetically Normal AML: Mechanism and Drug Indications. *Mol Ther Nucleic Acids 2019; 18*; 476-484
2. **Aakko, S. et al.** Therapeutic targeting of myeloid cell checkpoint CLEVER-1 induces ex vivo immune activation in myeloid malignancies. *submitted*
3. **Viitala, M. et al.** Immunotherapeutic Blockade of Macrophage Clever-1 Reactivates the CD8(+) T-cell Response against Immunosuppressive Tumors. *Clin Cancer Res 2019; 25*(11); 3289-3303
4. **Ylitalo, A. et al.** Ex vivo immune activation with the macrophage-targeting immunotherapy, anti-Clever-1 antibody bexmarilimab, in acute myeloid leukemia and myelodysplastic syndrome. *Abstract #14.Presented at the American Association of Cancer Research Special Conference: Acute Myeloid Leukemia and Myelodysplastic Syndrome; January 23-25, 2023; Austin, Texas.*

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