ENCOURAGING EFFICACY OF BEXMARILIMAB WITH AZACITIDINE IN RELAPSED OR REFRACTORY MDS IN BEXMAB PH1/2 STUDY

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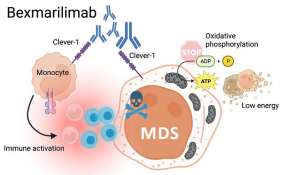
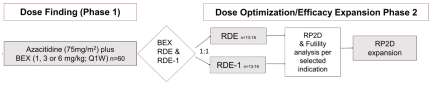
INTRODUCTION

Bexmarilimab (BEX), a humanized IgG4 monoclonal antibody, blocks Common lymphatic and vascular endothelial receptor-1 (Clever-1) to enhance antigen presentation and T cell activation (1). Clever-1 is also abundant on myeloid blasts (2,3) where BEX hampers the malignant cells' energy production, allowing enhanced efficacy of cytotoxic agents, such as hypomethylating agents (HMAs) (4). The ongoing BEXMAB study investigates safety and preliminary efficacy of BEX combined with SoC in patients with MDS or AML (NCT05428969). Phase I/II data shows good tolerability and promising clinical activity especially in MDS patients relapsed or refractory (r/r) to HMA or HMA-containing regimen. Here, we present also translational data supporting the unique dual mechanism of action in MDS.



Clever-1 is expressed by blast cells and myeloid immune cells. The antibody activates the immune system and simultaneously may reduce the fitness of myeloid blasts via impairing the energy production.

STUDY DESIGN



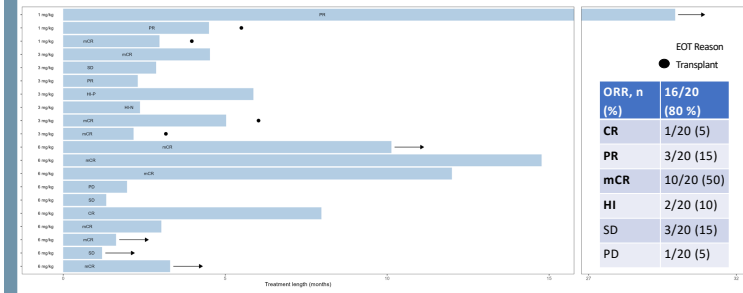
Phase I based on BOIN design, 1, 3 and 6mg/kg BEX (FPFV 07Jun2022). Indications: Higher risk MDS (IPSS-R) with indication for azacitidine treatment, CMML with 10-19% marrow blasts, MDS and CMML post-HMA therapy, r/r AML after ≥1 therapy line with indication for azacitidine treatment.
Phase II initiated in r/r MDS Dec2023, at dose optimization phase with patients randomized to RDE (6mg/kg) or RDE-1 (3mg/kg) BEX, based on Simon's 2-stage design. Study sites: 4 in Finland and 4 in US, UK opening 2024.

Updated efficacy and safety data from 20 consecutive r/r MDS patients are presented.

Patient baseline characteristics		r/r MDS; n (%)
Age (years); median (range)		72.5 (52-84)
ECOG PS	0	7 (35)
	1	13 (65)
IPSS-R	Intermediate (>3– ≤4.5 points)	2 (10)
	High (>4.5 - ≤6 points)	8 (40)
	Very high (> 6 points)	10 (50)
Mutations	TP53	9 (45)
	RUNX1	4 (20)
N and type of previous therapy lines	1	10 (50)
	2	7 (35)
	≥3	3 (15)
	Venetoclax + HMA	8 (40)
	Immunotherapy + AZA	3 (15)

RESULTS

Efficacy – objective response in 80 % of r/r MDS patients



ORR, n (%)	16/20 (80 %)
CR	1/20 (5)
PR	3/20 (15)
mCR	10/20 (50)
HI	2/20 (10)
SD	3/20 (15)
PD	1/20 (5)

Remission (CR/PR/mCR) achieved in 14/20 (70%) patients.

mTP53: ORR 56% (5/9 patients)

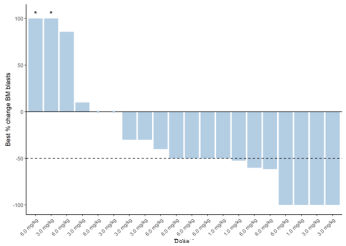
Ven + HMA pre-treated: ORR 63% (5/8 patients; all CR/mCR)

Transplant as end-of-treatment reason in 4/20 (20%) patients.

Current median overall survival estimate 13.4 months.

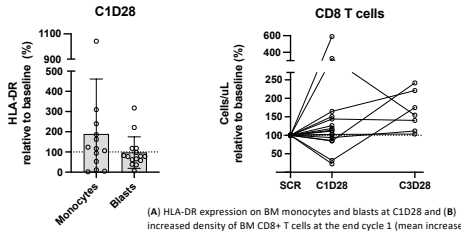
Swimmer plot showing best response to BEX + AZA (IWG2018 criteria) and treatment duration in r/r MDS patients. Datacut 25Nov2024.

≥50% reduction of BM blasts in 55% of patients



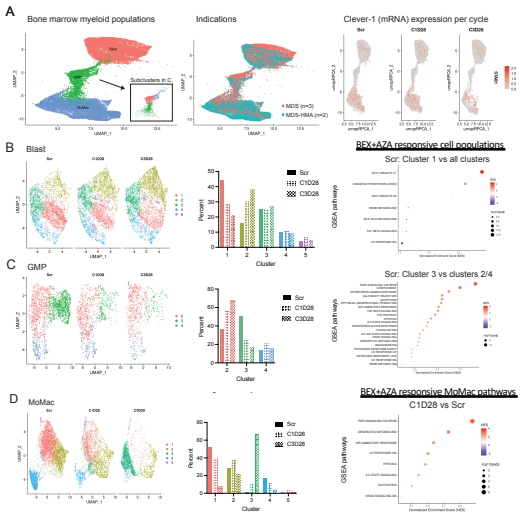
Waterfall plot showing best change in BM blast % vs baseline. Datacut 25Nov2024.
>5% BM blasts at baseline in 12/20 patients. *actual change 250% (left) and 107% (right).

BEX + AZA increases immune activity in BM



(**A**) HLA-DR expression on BM monocytes and blasts at C1D28 and (**B**) increased density of BM CD8+ T cells at the end cycle 1 (mean increase 48%) and cycle 3 (mean increase 63%), relative to baseline, in r/r MDS patients patients treated with BEX+AZA.

BEX + AZA targets MDS blasts dependent on MYC, Nf-κB and OXPHOS



(**A**) UMAP (Uniform Manifold Approximation and Projection) plot of myeloid cell populations in BM aspirates of BEXMAB trial patients, grouped by (left) major cluster or (middle) clinical indication. (right) Feature plot of *STAB1* mRNA expression in myeloid populations, split by treatment cycle. (**B**) (left) UMAP plot of subclustered Blast cluster. (middle) Percentage of blast cells in each subcluster at each treatment cycle. (right) Significantly (padj < 0.05) enriched GSEA (Gene Set Enrichment Analysis) hallmark pathways in blast subcluster 1 compared to subclusters 2-5 at screening. (**C**) (left) UMAP plot of subclustered GMP (granulocyte-monocyte progenitor) cluster. (middle) Percentage of GMP cells in each subcluster at each treatment cycle. (right) Significantly enriched GSEA hallmark pathways in GMP subcluster 3 compared to subclusters 2 and 4 at screening. (**D**) (left) UMAP plot of subclustered MoMac (monocyte/macrophage) cluster. (middle) Percentage of MoMac cells in each subcluster at each treatment cycle (right) Significantly enriched GSEA hallmark pathways in the MoMac cluster at C1D28 compared to screening.

SAFETY

BEX + AZA is well tolerated

	Event count n	Subject count n (%*)
TEAEs, total	184	19 (95)
Grade ≥3	58	14 (70)
BEX-related AEs, total	25	7 (35)
Grade ≥3	0	0

*% of r/r MDS patients, n=20 . Datacut 25Nov2024.

- Most common TEAEs: febrile neutropenia, nausea and neutrophil count decreased.
- Most common BEX-related AEs: nausea, peripheral oedema and infusion-related reactions. No accumulation of TRAEs with higher doses.
- Two immune-related AEs (Gr 1-2) at 3mg/kg BEX.
- One BEX-related SAE at 3mg/kg, acute febrile neutrophilic dermatosis (immune-related; Gr 2; recovered).
- No discontinuations due to BEX related AEs, 4 discontinuations due to TEAEs.

CONCLUSIONS

- Combination of BEX with azacitidine is well tolerated.
- Clinical activity in 80% of MDS patients with HMA refractory or relapsed disease.
- CR/PR/mCR rate 70%, in ven+HMA pre-treated subgroup 63%.
- Current estimate of mOS 13.4 months.
- BEX+AZA targets blasts with high MYC, OXPHOS and NF-κB signalling.
- Increased BM macrophage proinflammatory phenotype supports BEX mechanism-of-action.

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CONTACT INFORMATION

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