A PHASE I/II STUDY TO ASSESS SAFETY, TOLERABILITY AND PRELIMINARY EFFICACY OF BEXMARILIMAB IN COMBINATION WITH STANDARD OF CARE AZACITIDINE (DOUBLET) IN PATIENTS WITH MYELOID MALIGNANCIES (BEXMAB)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

FARON

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M. Kontro[1], T. Siitonen[2], J. Rimpiläinen[3], M. Pyörälä[4], M. Hollmén[5], S. Aakko[5], I. Pawlitzky[5], M.-L. Fjällskog[5], N. Daver[6]

[1] Department of Hematology, Helsinki University Hospital Comprehensive Cancer Centre, Helsinki, Finland; [2] Department of Medicine, Oulu University Hospital, Oulu, Finland; [3] Department of Internal Medicine, Tampere University Hospital, Tampere, Finland; [4] Kuopio University Hospital, Kuopio, Finland ; [5] FARON Pharmaceuticals, Turku, Finland; [6] Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

OVERVIEW

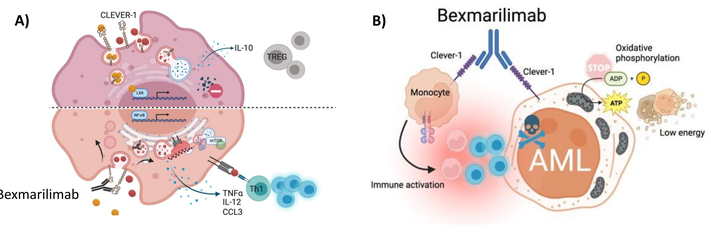
Common lymphatic endothelial and vascular endothelial receptor-1 (Clever-1) constitutes a novel macrophage checkpoint. High Clever-1 expression, as observed on malignant blasts and monocytes in AML/MDS, is associated with therapeutic resistance and poor outcome (1, 2).

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 also reduces the viability of AML blasts through impairing the cell's metabolism (4).

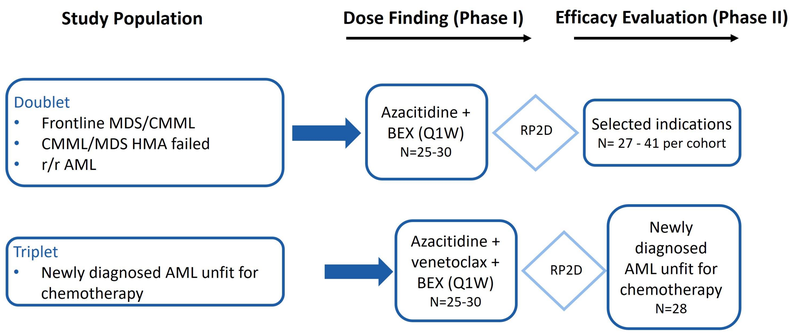
The ongoing BEXMAB clinical study investigates safety and preliminary efficacy of BEX combined with SoC in patients with AML/MDS (NCT05428969).

Clever-1 function (left) and BEX activity (right) on myeloid and leukemia cells



A) Expression of Clever-1 on tumor-associated macrophages creates an immunosuppressive environment through scavenging of extracellular components leading to the 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 adjacent myeloid immune cells. The antibody can activate the immune system in the bone marrow and simultaneously reduce the fitness of AML blasts through impairing cells' energy production.

STUDY DESIGN AND STATUS



Study Design & Sites

- Dose escalation Phase I using BOIN design
- Simon 2-Stage design in Phase II
- 8 sites (4 in Finland/4 in U.S)
- FPFV: 07Jun2022

Study Status

- Clinical data cut-off 11 APR 2023
- Total number treated n=18 (Doublet n=13; Triplet n=5)
- Doublet cohorts 1/3/6 mg/kg filled
- Ongoing: Triplet cohort 1 mg/kg

RESULTS

Baseline Characteristics

Characteristic	All n=10	1.0 mg/kg n=5	3.0 mg/kg n=5
Female/male	4/6	4/1	0/5
Median age years (range)	69 (52-81)	69 (52-81)	68 (62-74)
ECOG PS at baseline n (%)			
0	4 (40)	2 (40)	2 (40)
1	4 (40)	1 (20)	3 (60)
2	2 (20)	2 (40)	0
MDS IPSS-r n (%)			
Intermediate	0	0	0
High	1 (10)	0	1 (20)
Very high	2 (20)	2 (40)	0
AML ELN risk n (%)			
Favorable	1 (10)	1 (20)	0
Intermediate	4 (40)	2 (40)	2 (40)
Adverse	2 (20)	0	2 (40)
# Prior therapy n (%)			
1	1 (10)	1 (20)	0
2	4 (40)	1 (20)	3 (60)
≥3	3 (30)	2 (40)	1 (20)

Patient demographics BEXMAB (data cut-off 11Apr2023)

Safety

Addition of BEX to Azacitidine Well Tolerated

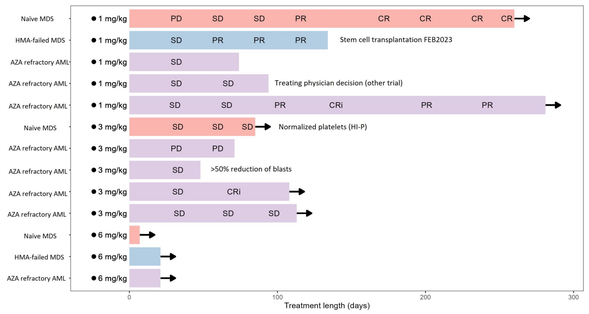
- No dose limiting toxicities (DLT)
- No serious adverse events (AE) related to BEX
- No Grade ≥ 3 AEs related to BEX
- No discontinuation due to BEX related AEs

Treatment-Related Adverse Events	Patients (%) n=10
Any grade	5 (50)
Grade 3	0 (0)
Grade 4	0 (0)

Treatment-Related Adverse Events	Grade 1/2	Grade 3/4
Constipation	2 (20)	0 (0)
Nausea	1 (10)	0 (0)
Pyrexia	1 (10)	0 (0)
Vomiting	1 (10)	0 (0)

Efficacy & Pharmacokinetics

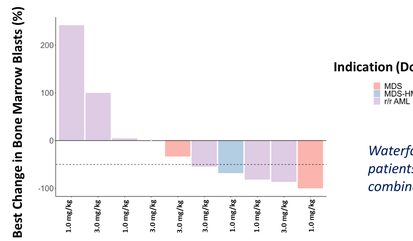
Objective Responses Observed in 5 of 10 Patients* Across Indications



Swimmer plot of doublet patients at 1 and 3 mg/kg BEX combined with azacitidine.

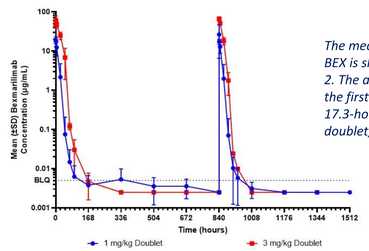
(*6 mg/kg read-out Jul2023)

Reduction of Bone Marrow Blasts Observed in >50% of Patients

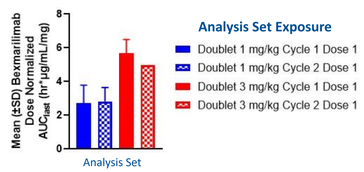


Waterfall plot of Doublet patients at 1 and 3 mg/kg BEX combined with azacitidine.

Dose Proportional Increase of BEX C_{max}, $AUC_{0\text{-}48h}$ and AUC_{last} Observed in Doublet



The mean concentration of BEX is shown for Cycles 1 and 2. The average half-life after the first dose was 19.8 and 17.3-hours for 1 and 3 mg/kg doublet, respectively

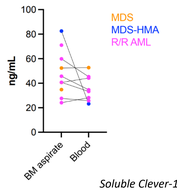


Dose normalized exposure comparison shows proportional increase in AUC_{last} for BEX at 1 and 3 mg/kg doublet.

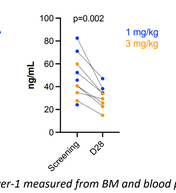
Biomarkers & Pharmacodynamics

Clever-1 Target Engagement in Patient Bone Marrow

Higher Clever-1 levels in BM compared to blood at baseline

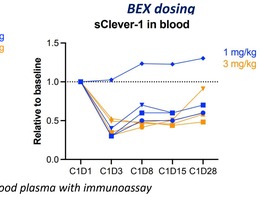


Target engagement of Clever-1 in BM after treatment with BEX



Sustained *target engagement of Clever-1 in blood with Q1W BEX dosing*

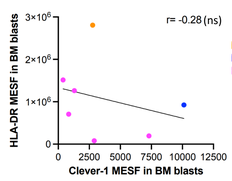
sClever-1 in blood



Soluble Clever-1 measured from BM and blood plasma with immunoassay

Increase in Antigen Presentation and T Cell Activity Observed

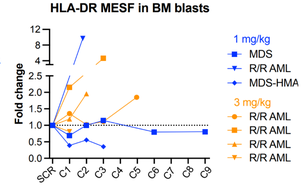
High Clever-1 is associated with low antigen presentation capacity across indications



Correlation analysis of Clever-1 levels and HLA-DR expression at baseline

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

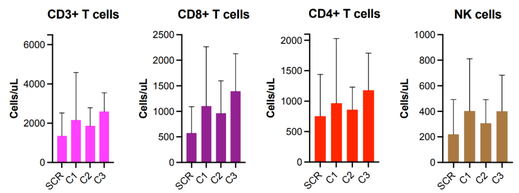
HLA-DR MESF in BM blasts



HLA-DR change from baseline

* MESF = Molecules of Equivalent Soluble Fluorochrome, normalized fluorescence for comparison across timepoints

Up to 2-3-fold increase of CD8 T and NK cells in the BM of bexmarilimab treated patients



T and NK cell numbers of Doublet patients from screening and up to Cycle 3.

CONCLUSION

- The combination of BEX and azacitidine is well tolerated
- Durable target engagement of Clever-1 in the bone marrow with an increase in antigen presentation capacity and CD8 T cells supporting BEX mode of action on AML/MDS
- Clinical activity with 5/10 objective responses observed across indications
- Dose escalation ongoing - Phase II anticipated in Q4 2023

References:

1. Lin et al. Mol Ther 2019; 2. Aakko et al. 2022 EHA P380; 3. Viitala et. al. Clin Cancer Res 2019; 4. Ylitalo et al. 2023 AACR poster

Correspondence: *Dr. Mika Kontro (mika.kontro@helsinki.fi)*

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