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Full efficacy analysis of phase I/II trial investigating Bexmarilimab, a novel macrophage-guided immunotherapy in refractory solid tumors

Petri Bono[1,*], Loic Verlingue[2], Maria de Miguel[3], Annika Pasanen[4], Debbie Robbrecht[5], Tanja Skyttä[6], Sanna Iivanainen[7], Shishir Shetty[8], Yuk Ting Ma[8], Donna M. Graham[9], Sukeshi P. Arora[10], Panu Jaakkola[11], Christina Yap[12], Jenna H. Rannikko[13], Yujuan Xiang[14], Sinem Karaman[14] Maija Hollmén[13,15], Jussi Koivunen[15], Anna Minchom[16]

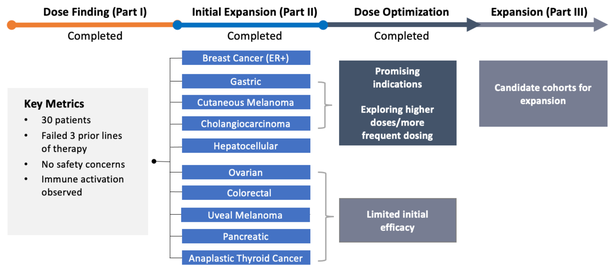
[1]Terveystalo Finland and University of Helsinki, Helsinki, Finland; [2]Institut Gustave Roussy, Paris and Centre Leon Berard in Lyon, France; [3]START-CIOCC HM Sanchinarro, Madrid, Spain; [4]Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; [5]Erasmus Medical Center/Cancer Institute, Rotterdam, Netherlands; [6]Tampere University Hospital, Tampere, Finland; [7]Oulu University Hospital, University of Oulu, Oulu, Finland; [8]University of Birmingham/University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; [9]The Christie NHS Foundation Trust, Manchester, UK; [10]Mays Cancer Center, UT Health San Antonio, San Antonio, Texas, USA; [11]Turku University Hospital, Turku, Finland; [12]The Institute of Cancer Research, ICR-CTSU, London, United Kingdom; [13]University of Turku, Turku, Finland; [14]University of Helsinki, Helsinki, Finland; [15]Faron Pharmaceuticals Ltd, Turku, Finland; [16]Drug Development Unit, Royal Marsden Hospital/Institute of Cancer Research, Sutton, United Kingdom

Background

- CLEVER-1 is an immunosuppressive scavenger receptor expressed on tumor associated macrophages[1,2]. High levels of CLEVER-1 are associated with poor survival, T-cell exclusion and dysfunction, and immunotherapy resistance[3-7].
- Bexmarilimab (Bex) is a novel humanized anti-CLEVER-1 IgG4-antibody capable of promoting an immune switch, potentially leading to intratumoral proinflammatory responses in patients[8].
- The aim of this first-in-human trial was to study the safety and tolerability of Bex in patients with treatment-refractory solid tumors and to assess preliminarily antitumor efficacy, pharmacodynamics, and immunologic correlates.

Methods

- Patients with refractory advanced solid tumors were enrolled in the first-in-human phase I/II MATINS (Macrophage Antibody To INhibit immune Suppression) study (NCT03733990).
- In dose escalation part I, 30 patients received Bex intravenously at 0.1, 0.3, 1, 3, or 10mg/kg Q3W to determine the maximal tolerated dose (MTD).
- In part II, 118 patients from selected tumor types received Bex at 0.3, 1, 3mg/kg Q3W.
- In the dose optimalization cohorts of part II, 66 patients were exposed to Bex with 1-3mg/kg Q1W, 1-3mg/kg Q2W, or 3-30mg/kg Q3W dosing.
- Pre- and on-treatment tumor and blood samples were analyzed for potential predictive biomarkers



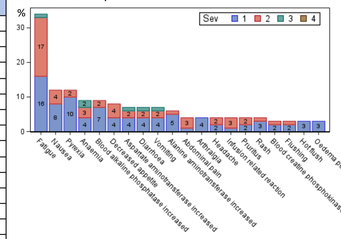
Results

- As of Apr 2023, a total of 214 patients have been enrolled to the study (**Table 1**).
- Bexmarilimab was well tolerated with no observed DLTs and MTD was not determined.
- No additional safety signals were detected in part II and fatigue and pyrexia were the most common treatment related adverse events (TREA) (**Figure 1**).
- Alternative doses or dosing frequency resulted in similar safety profile (**Table 2**).

Table 1. Patient characteristics

Characteristic	n (%)
Overall	214 (100)
Age, median	61
Gender	
Male	111 (51.9)
Female	103 (48.1)
ECOG	
0	83 (38.8)
1	131 (61.2)
Cancer type	
Colorectal cancer	56 (26.2)
Gastric adenocarcinoma	29 (13.6)
Bile duct cancer	28 (13.1)
Cutaneous Melanoma	23 (10.8)
Pancreatic cancer	18 (8.4)
Ovarian cancer	17 (7.9)
ER+ breast cancer	12 (5.6)
Hepatocellular carcinoma	11 (5.1)
Uveal melanoma	10 (4.7)
Anaplastic thyroid cancer	10 (4.7)
Number of previous line therapies, median	3

Figure 1. Treatment related adverse events (frequency) and their severity



*Included are treatment related adverse events with NCI-CTCAE version 5.0 that occurred in ≥3 patients. Data cut-off Jan 2023.

Table 2. Treatment related adverse events by dose and dosing frequency of Bex

Dose mg/kg	0.1 (N = 5) n (%)		0.3 (N = 13) n (%)		1.0 (N = 126) n (%)		3.0 (N = 38) n (%)		10 (N = 18) n (%)		30 (N = 9) n (%)		Overall (N = 209) n (%)	
SOC and PT	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**
Overall	3 (60.0)	1 (20.0)	8 (61.5)	0 (0.0)	56 (44.4)	10 (7.9)	15 (39.5)	2 (5.3)	8 (44.4)	1 (5.6)	4 (44.4)	0 (0.0)	94 (45.0)	14 (6.7)
General disorders and administration site conditions	2 (40.0)	0 (0.0)	6 (46.2)	0 (0.0)	28 (22.2)	1 (0.8)	6 (15.8)	0 (0.0)	3 (16.7)	0 (0.0)	1 (11.1)	0 (0.0)	46 (22.0)	1 (0.5)
Fatigue	1 (20.0)	0 (0.0)	5 (38.5)	0 (0.0)	21 (16.7)	1 (0.8)	5 (13.2)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	34 (16.3)	1 (0.5)
Pyrexia	1 (20.0)	0 (0.0)	2 (15.4)	0 (0.0)	6 (4.8)	0 (0.0)	2 (5.3)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	12 (5.7)	0 (0.0)

Dose Frequency	Q1W (N = 14) n (%)		Q2W (N = 14) n (%)		Q3W (N = 181) n (%)		Overall (N = 209) n (%)	
SOC and PT	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Overall	11 (78.6)	1 (7.1)	3 (21.4)	1 (7.1)	80 (44.2)	12 (6.6)	94 (45.0)	14 (6.7)
General disorders and administration site conditions	3 (21.4)	0 (0.0)	0 (0.0)	0 (0.0)	43 (23.8)	1 (0.6)	46 (22.0)	1 (0.5)
Fatigue	3 (21.4)	0 (0.0)	0 (0.0)	0 (0.0)	31 (17.1)	1 (0.6)	34 (16.3)	1 (0.5)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (6.6)	0 (0.0)	12 (5.7)	0 (0.0)

*Included are treatment related adverse events with NCI-CTCAE version 5.0 that occurred in ≥ 5%. Data cut-off Jan 2023.

Conclusions

- Bexmarilimab continues to demonstrate good tolerability and promising anti-tumor activity as a monotherapy in several refractory solid tumors.
- Safety is not dose or frequency dependent and the highest disease control rates are achieved with 1mg/kg Q3W.
- Immune activation with bexmarilimab is observed in a proportion of patients, which then leads to disease control and longer survival.
- Preliminary biomarker analysis suggests a possibility for patient selection based on tumor Clever-1 expression.

Correspondence: Dr. P Bono (Petri.Bono@terveystalo.com)

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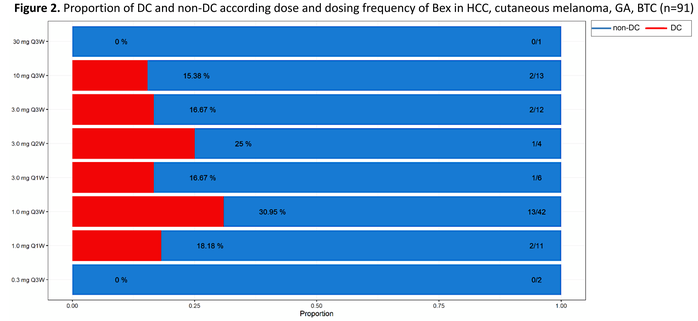
Results

- The highest disease control (DC) rates (36-21%) were observed in hepatocellular cancer, estrogen receptor (ER)+ breast cancer, cutaneous melanoma, bile duct, and gastric cancers (**Table 3**).
- There is no correlation between DC and dose or dosing frequency of Bex (**Figure 2**).

Table 3. ORR and DCR rates by tumor type.

	n (%)
Overall	214 (100)
ORR	1 (0.5)
CR	0 (0)
PR	1 (0.5)
SD	27 (13)
PD	186 (86.9)
DCR	
Colorectal cancer	2 (3.6)
Gastric adenocarcinoma	6 (20.7)
Bile duct cancer	6 (21.4)
Cutaneous melanoma	5 (21.7)
Pancreatic cancer	0 (0)
Ovarian cancer	1 (5.9)
ER+ breast cancer	4 (33.3)
Hepatocellular carcinoma	4 (36.4)
Uveal melanoma	0 (0)
Anaplastic thyroid cancer	0 (0)

Figure 2. Proportion of DC and non-DC according dose and dosing frequency of Bex in HCC, cutaneous melanoma, GA, BTC (n=91)



- High pre-treatment intratumoral Clever-1 staining is associated with DC (p=0.038) (**Table 4**).
- Activation of interferon signaling and M1-like gene expression is seen in tumor macrophages of DC patients (**Figure 3**).
- Serum IFNg elevation is observed in DC patients (**Figure 4**).

Table 4. Clexver-1 and PD-L1 expression in pre-treatment tumors

	n (%)	median (range)	p-value
Clever-1	78 (100)		
Whole tumor	78 (100)	15 (1-55)	
non-DC	71 (91)	15 (1-55)	ns
DC	7 (9)	20 (13-35)	
Stroma	78 (100)	20 (0-75)	
non-DC	71 (91)	20 (0-75)	ns
DC	7 (9)	20 (5-40)	
Intratumoral	78 (100)	5 (0-85)	
non-DC	71 (91)	3 (0-85)	0.038
DC	7 (9)	15 (0-25)	
PD-L1 CPS	43 (100)	2 (0-100)	
non-DC	39 (91)	5 (0-100)	ns
DC	4 (9)	1 (0-2)	

Figure 3. GeoMx digital spatial profiling of CD68+ tumor macrophages in pre- and on-treatment tumors

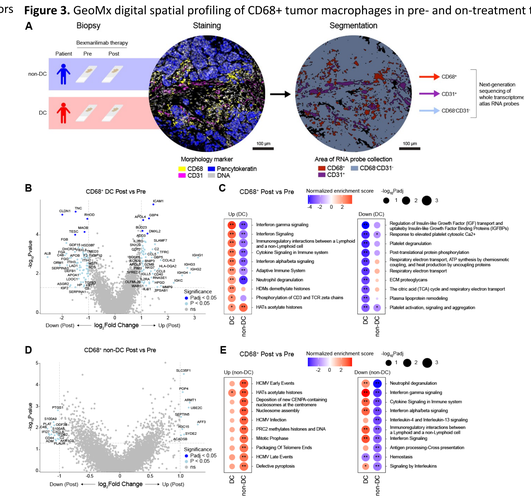
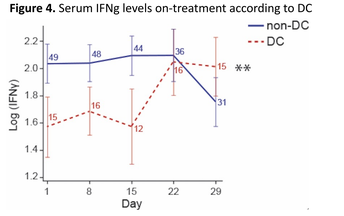


Figure 4. Serum IFNg levels on-treatment according to DC



- DC was associated with improved survival in landmark analysis (HR 0.34, 95% CI 0.20-0.59) while there was no difference in previous line treatment duration (**Figure 5B-C**).

Figure 5. Survival analysis of the patients treated in part I and II of the study
(A) K-M analysis for PFS and OS.
(B) K-M analysis (landmark) for OS from cycle four on according to the DCR or non-DCR response with bexmarilimab at 9 weeks.
(C) K-M analysis for previous therapy line treatment duration according to DCR or non-DCR response with bexmarilimab.

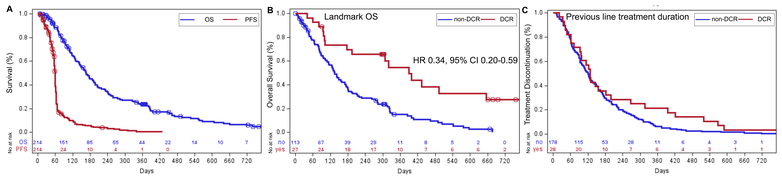


Table 5. PFS2/1 ratio of ≥ 1.3x

	n (%)	p-value
All	206 (100)	
Yes	30 (14.6)	
No	176 (85.4)	
non-DC	178 (86.4)	
Yes	17 (9.6)	
No	161 (90.5)	
DC	28 (13.6)	0.0001
Yes	13 (46.4)	
No	15 (53.6)	