Preliminary data from Phase I first-in-human study of EOS884448, a novel potent anti-TIGIT antibody, monotherapy shows favorable tolerability profile and early signs of clinical activity in immune-resistant advanced cancers

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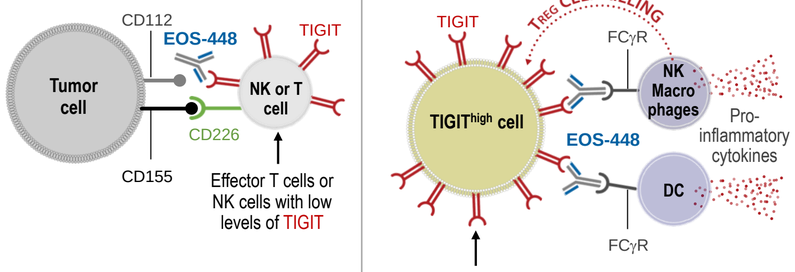
EOS-448 Has Multiple Mechanisms of Action (MoA)

1. **Inhibition of TIGIT triggering activation of TIGIT^{LOW} T cells and NK cells**
2. **Depletion of immunosuppressive Treg and exhausted TIGIT^{HIGH} T cells**
   — *and* —
3. **Reverse activation via FCγR engagement**



Background

- EOS-448 is a fully human a-TIGIT Ab with multiple MoA
- EOS-448 demonstrated good safety profile and strong anti-tumor activity in preclinical development

Objective of the Ph1 Study

- To evaluate the safety and tolerability, PK, PD, and antitumor activity of EOS-448 as single agent in participants with advanced cancers.

Method

Study design and Patients

- First-in-human, open-label dose-escalation, phase 1 trial (NCT04335253) enrolled adult participants with advanced solid tumors for whom no standard treatment was further available.
- All patients received EOS-448 intravenously (IV) on day 1 of each Q2W or Q4W cycle according to their dose and schedule allocation. Doses of 20, 70, 200, 700 mg Q2W and 1400 mg Q4W were evaluated.

Assessments and Statistical Analyses

- Primary end points were safety and tolerability
- Secondary and exploratory end points included objective response rate (ORR), based on investigator review per RECIST v1.1, Pharmacokinetics and Pharmacodynamic assessments
- Safety was analyzed in all patients who received at least one dose of study medication
- Efficacy was analyzed in all patients with measurable disease at baseline who received at least one dose of study medication
- PK/PD were analyzed by using validated methods. For PD, whole blood samples were analyzed fresh by flow cytometry to monitor receptor occupancy and changes in immune cell subsets. Treg were stained as CD4$^+$ CD25$^+$ CD127^{low}.
- Database cutoff date was December 31, 2020

TABLE 1 | Baseline Characteristics in Patients Treated with EOS-448

Characteristic	All Subjects (N=22)
Median age (range)	58 (28-79)
Male/Female n(%)	7 (32%)/15 (68%)
Primary Diagnosis, n(%)	
Ovarian	4 (18%)
Cervical	3 (14%)
Head & Neck	3 (14%)
Colorectal	3 (14%)
other solid tumors n=1 each	9 (40%)
Time Since Initial Diagnosis, months	
Median (range)	48 (5-269)
Number of Lines of Prior Metastatic Therapy Median (range)	3 (1-4)

TABLE 2 | Adverse Event Summary in Patients Treated with EOS-448

A. Overall Summary of EOS-448 Related Treatment-Emergent Adverse Events, Number (%) of Patients	All Subjects (N=22)
Patients with At Least One [n (%)]	
Treatment Emergent Adverse Event (TEAE)	21 (95)
Treatment-Related TEAE	18 (82)
Grade 3+ TEAE	11 (50)
Grade 3+ Related TEAE[1]	1 (5)
Serious TEAE	8 (36)
Treatment-Related Serious TEAE[2]	1 (5)
Related TEAE Leading to Treatment Discontinuation	0 (0)
Any related TEAE Leading Death	0 (0)

1. One Grade 3 Rash maculo-papular,
2. One Grade 2 Systemic inflammatory response syndrome

B. TEAE Related to EOS-448 Occurring in at Least 2 Patients by Preferred Term, Number (%) of Patients	All Subjects (N=22)
Patients with At Least One [n (%)]	
TEAE Related to EOS-448	18 (82)
Pruritus	7 (32)
Infusion related reaction	4 (18)
Fatigue	4 (18)
Pyrexia	3 (14)
Rash maculo-papular	2 (9)
Eczema	2 (9)
Hypothyroidism	2 (9)
Blood Creatinine increased	2 (9)

TABLE 3 | Response Summary Based on Investigator Assessment per RECIST v1.1

Overall summary of response per Recist v1.1	All Subjects (n=22)
Response Evaluable Patients [n]	**20**
Best Overall Response [n (%)]	
Complete Response (CR)	0 (0%)
Partial Response (PR)	1 (5%)
Stable Disease (SD)	9 (45%)
Progressive Disease (PD)	10 (50%)

FIGS. 1&2 | Best Change from Baseline and Response Duration in Target Lesions on Investigator Assessment per Recist v1.1

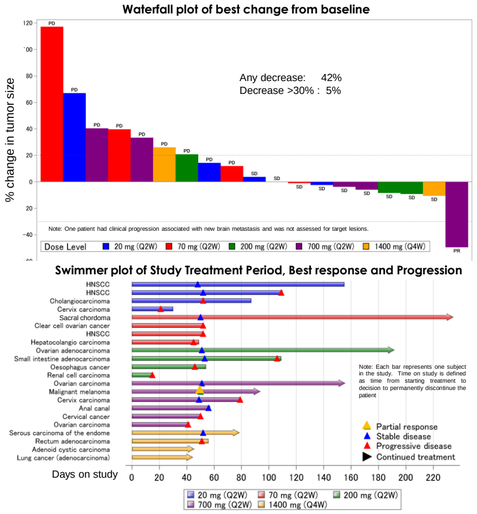
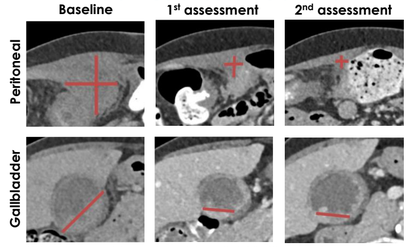


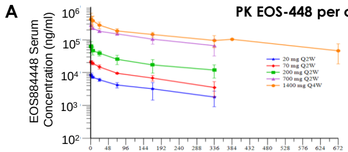
FIG. 3 | Partial response in a 65-year-old female with BRAF mutant Cutaneous Melanoma



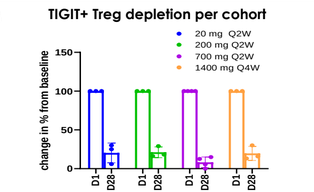
Note: images were taken on different days with slightly different angle

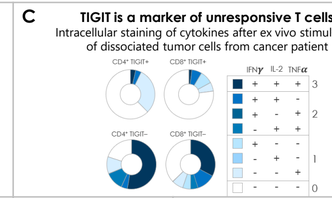
- 2 prior lines of therapy with BRAF-MEK inhibitor followed by pembrolizumab with documented PD
- Received EOS884448 700 mg Q2W
- PR per RECIST with 49% and 58% reduction in size of intra-abdominal target lesions, at 8 and 16 weeks, respectively
- Therapy ongoing at 24 Weeks

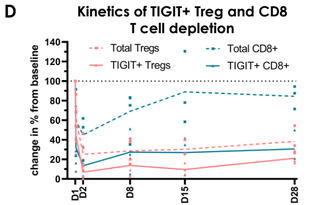
FIG. 4 | PharmacoKinetic and Dynamic Assessments in Blood Confirm Strong Potential for Depletion of Suppressive Treg and Exhausted T cells by EOS-448

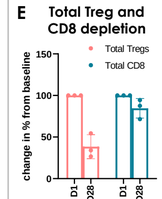


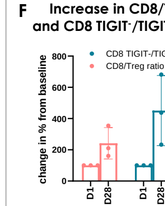
- Linear PK with dose proportionality.
- No immunogenicity observed.
- PK profile is compatible with dosing interval of Q3W or Q4W
- Receptor Occupancy Assay shows high target engagement at all tested doses and at all time during dosing interval











- Strong depletion of Total and TIGIT$^+$ suppressive Treg is observed at all doses and maintained during dosing interval
- Strong reduction of TIGIT$^+$ CD8 T cells, considered to be exhausted and not responsive to immune stimulation
- Total CD8 T cells are minorly impacted, as shown in panel C for the 200mg Q2W cohort
- Ratio of CD8 T cells / Treg as well as CD8 TIGIT$^-$ / CD8 TIGIT$^+$ T cells is shifted towards effector cells by a factor 2 and 4, respectively for cohort at 200mg Q2W, shown as example. This effect is seen at all doses
- Biomarker results in blood show a reduction of suppressive and exhausted immune populations shifting the balance towards a more functional antitumor immune response

Conclusions

- EOS-448 was generally well tolerated to date, at all tested doses in patients with advanced cancer
- Preliminary data on 20 evaluable patients show promising antitumor activity of EOS-448 as single agent, with confirmed partial response in PD1-resistant patient and multiple patients experiencing disease stabilization
- PK and PD assessment indicate a linear and dose-proportional PK with complete target engagement that correlates with strong depletion of Treg and TIGIT$^+$ T cell populations, known to be exhausted. Total T cells have been minorly impacted resulting in a shift towards a more functional antitumor immune response
- Preliminary FIH data support further evaluation of EOS-448 as monotherapy and in combination with approved and investigational therapies which is planned in both immune checkpoint-naïve and -refractory patients

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