LB189

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Pharmacodynamic Assessment of a-TIGIT mAb EOS-448/GSK4428859A Highlights Multiple FcγR-mediated Mode-of-actions in Blood and Tumor of Patients with Advanced Solid Tumors

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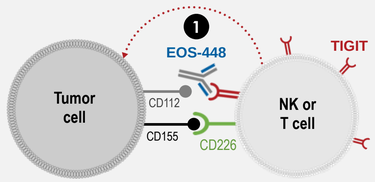
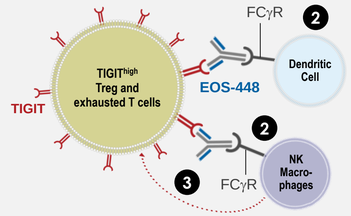




BACKGROUND: EOS-448/GSK4428859A is an anti-TIGIT (a-TIGIT) antibody with a multimodal mechanism of actions (MoAs)

1. Inhibition of TIGIT triggering activation of TIGIT^{LOW} T cells and NK cells
2. Engagement and activation of FcγR-expressing cells
3. FcγR-mediated depletion of immunosuppressive Treg and terminally exhausted TIGIT^{high} T cells

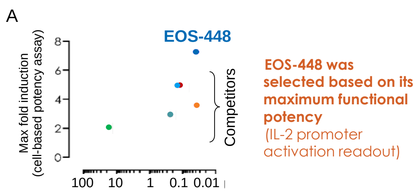
While these multiple MoAs were demonstrated in preclinical models (Preillon J. et al, 2021), an important question was on their translatability into patients, which was explored during Phase 1 dose-escalation trial (NCT04335253)

• Preclinical & Clinical Evidence for Multimodal MoAs of EOS-448 •

Figure1

PRECLINICAL

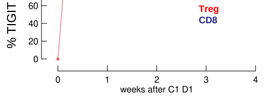
EOS-448 has strong antagonist activity and higher potency than other a-TIGIT mAbs



EOS-448 was selected based on its maximum functional potency (IL-2 promoter activation readout)

CLINICAL

EOS-448 demonstrates full receptor occupancy

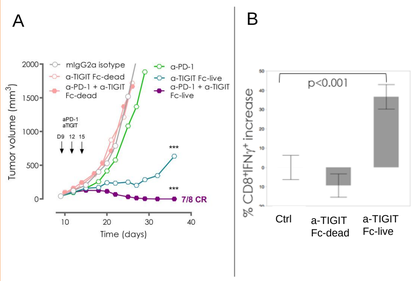


EOS-448 shows full target occupancy in peripheral Tregs and CD8 T cells at all tested doses for full dosing interval (median data at 400 mg Q4W are illustrated)

Figure2

PRECLINICAL

Antitumor activity of a-TIGIT depends on isotype and correlates with T cell activation

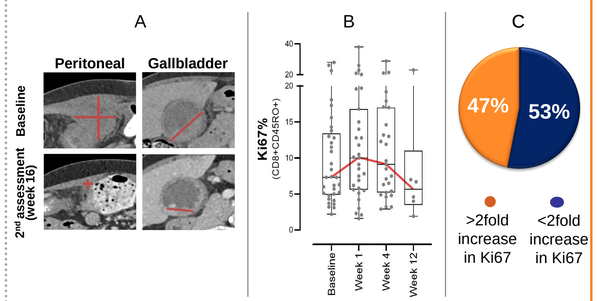


(A) In vivo activity of Fc-live a-TIGIT in CT26 murine model. Antitumor activity depends on FcγR engagement and (B) correlates with the **activation of T cells** within TME. From Preillon J. et al, Mol Cancer Ther 2021

Figure3

CLINICAL

Clinical activity and activation of CD8+ T cells in the periphery of EOS-448 treated patients

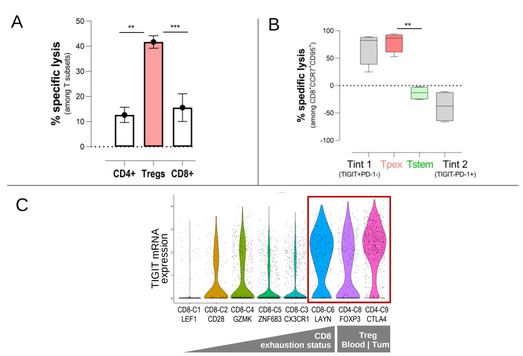


(A) Target lesions showing Partial Response (-58%) at second assessment in a Melanoma Patient enrolled in NCT04335253. **(B,C) EOS-448 induces an increase in proliferation of peripheral CD8+ memory** T cells (>2 fold increase) in ~half of the patients treated with EOS-448 (all doses pooled), between W1-W6 after first infusion.

Figure4

PRECLINICAL

***Ex-vivo*, EOS-448 preferentially depletes Treg and progenitors of exhausted T cells (Tpex)**

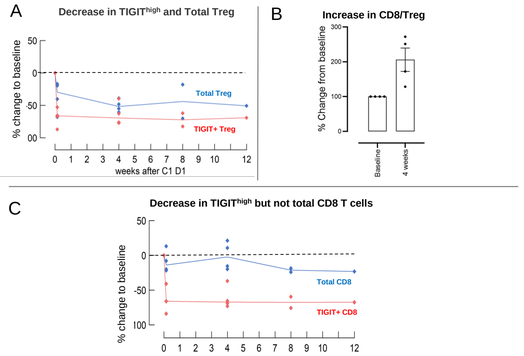


(A) EOS-448 mediates preferential depletion of Treg and **(B) progenitors of exhausted T cells** (Tpex) but not stem-like T cells (Tstem), in human PBMCs. **(C) TIGIT is highly expressed in CD8 exhausted T cells and Tregs:** violin plot generated using dataset from *Guo et al., Nat Med, 2018.*

Figure5

CLINICAL

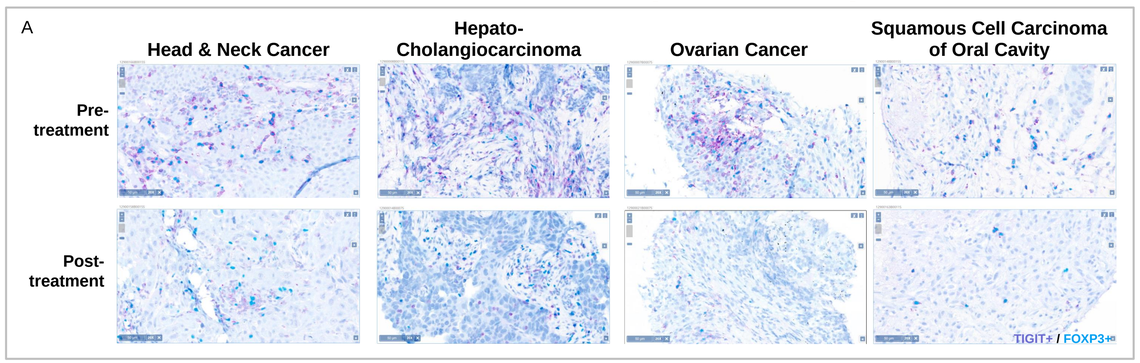
In patients, EOS-448 depletes Treg and TIGIT^{high} CD8+ T cells, enriched for exhausted T cells

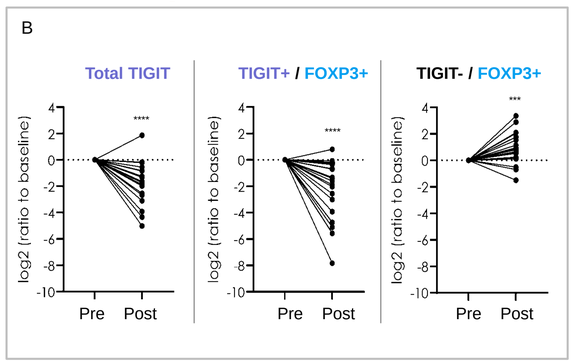


(A) EOS-448 mediates Treg depletion and (C), a sustained decreased of TIGIT^{high} CD8+ T cells described to be terminally exhausted. This results in an increase of the CD8:Treg ratio (B). Data show 400mg Q4W regimen.

Figure6

• Reduction of TIGIT in paired biopsies of EOS-448 treated patients •





Exposure to EOS-448 results in decreased detection of TIGIT in patient tumor biopsies. (A) Examples of IHC images of dual TIGIT (Purple) FOXP3 (Blue) staining by IHC in pre- and post-treatment (day 17-24) biopsies. (B) Comparative quantification in 22 paired biopsies shows significant decrease of TIGIT detection (One sample t-test, ****p<0.0001, ***p=0.0004) and suggests replacement of TIGIT^{+} Tregs by TIGIT^{-}, described to be less immunosuppressive Tregs (Joller et al, Immunity, 2014; Fourcade et al, JCI Insight, 2019).

Conclusions

- EOS448 **multimodal activity is observed** both in preclinical models and in patients with advanced cancer
- **Strong depletion of Total and TIGIT^{high} suppressive Treg** in the periphery that is maintained during dosing interval
- >50% **reduction of TIGIT^{high} CD8 T cells**, described to be terminally exhausted, while **total CD8+ T cells are less impacted** (in the periphery)
- Peripheral assessment in treated patients shows a **reduction of suppressive and exhausted immune populations,** shifting the balance toward a more functional antitumor immune response
- **Target engagement** demonstrated in paired tumor biopsies
- Decreased TIGIT detection in tumor suggests replacement of TIGIT^{pos} Tregs with TIGIT^{neg} known to be **less immunosuppressive Tregs**
- **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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