Pioneering Novel IO Therapies Focused on Key Mechanisms of Immunosuppression

Targeting TIGIT: Which cell populations are modulated by FcγR engagement?

Characterization of the Multiple MoA of EOS-448

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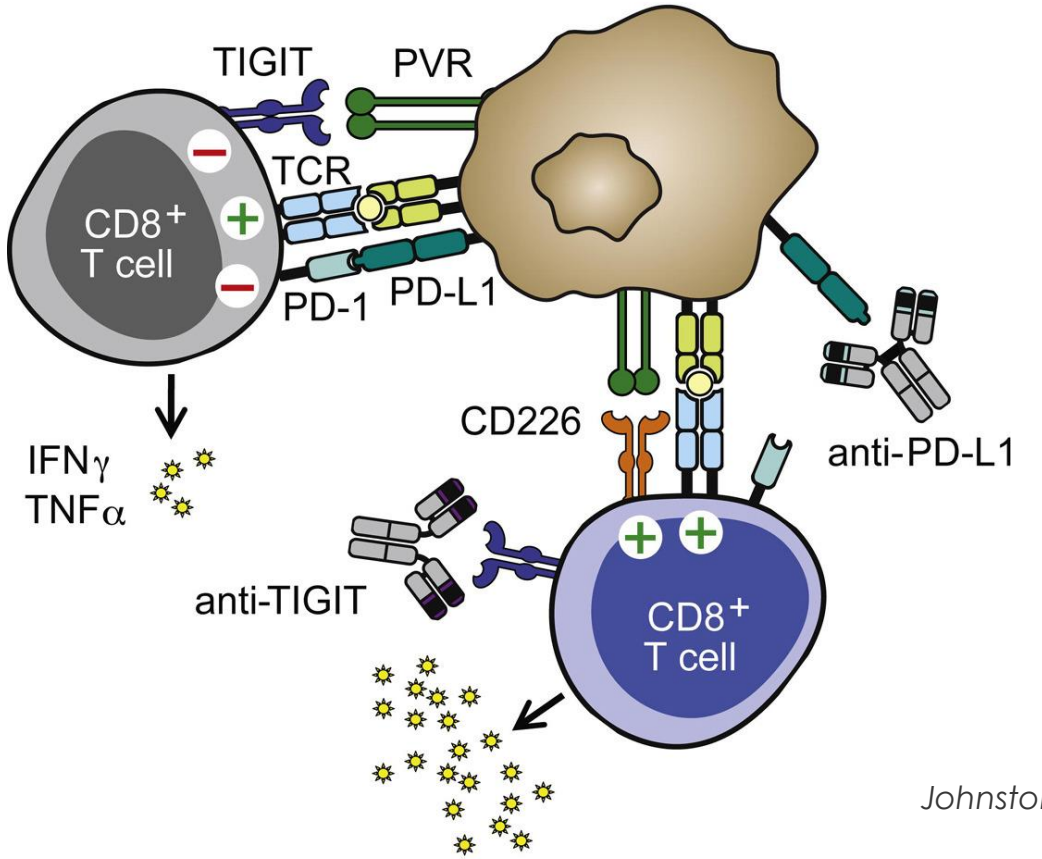
iTeos Therapeutics

Disclosures and Statements

- I am currently a shareholder and employee of iTeos Therapeutics
- Any human biological samples were sourced ethically
- All in vivo experiments were performed in accordance with national and institutional guidelines for animal care and had received the approval of the local Animal Ethics Committee.
- EOS-448 is also named EOS884448 or GSK4428859A

TIGIT/CD226 Axis Is a Key Modulator of NK and T cells Activity



Johnston et al., Cancer Cell, 2014

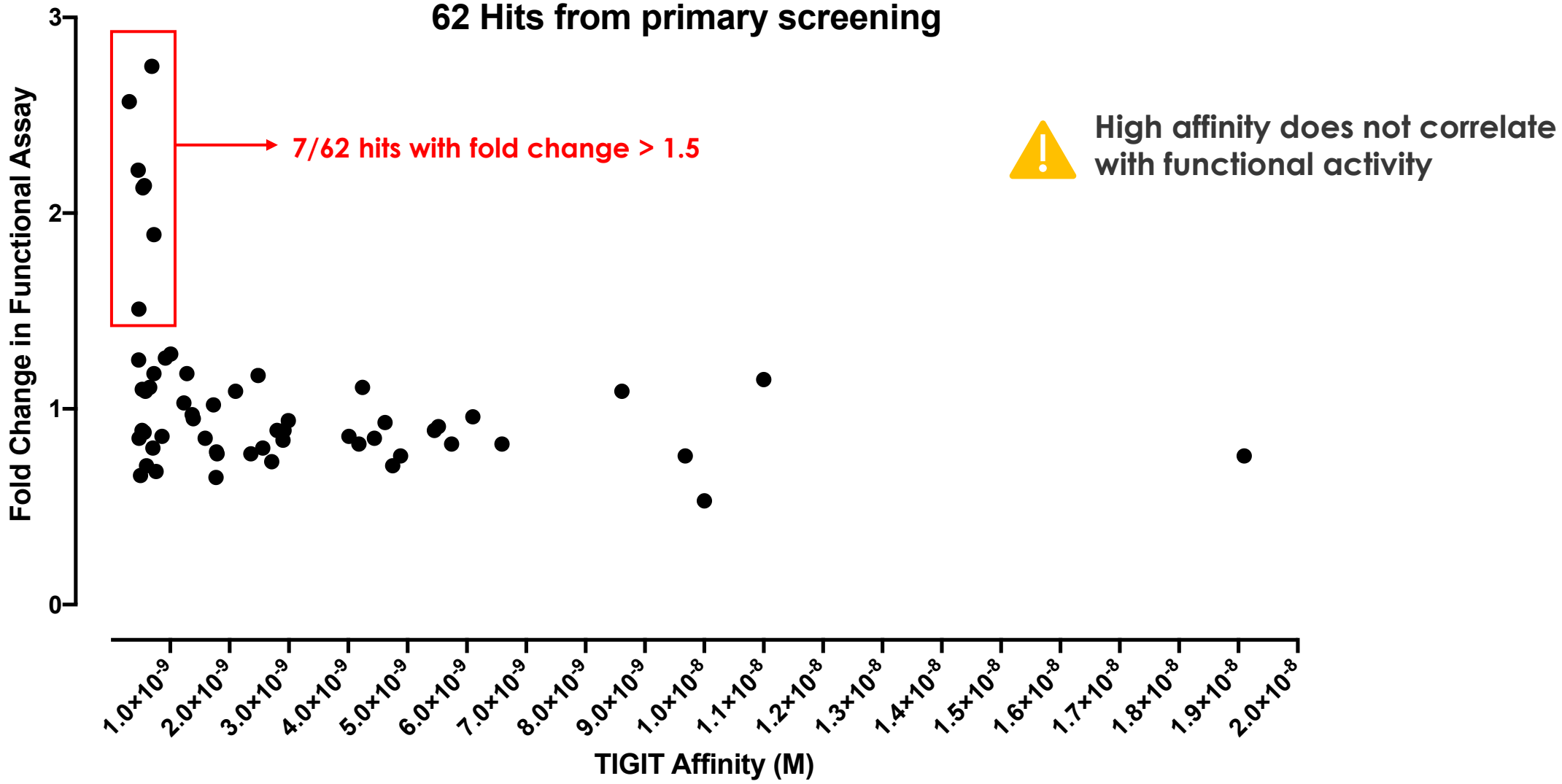
Preclinical Development of EOS-448* and Characterization of its Multiple MoA

FcγR-engaging Anti-TIGIT Antibody

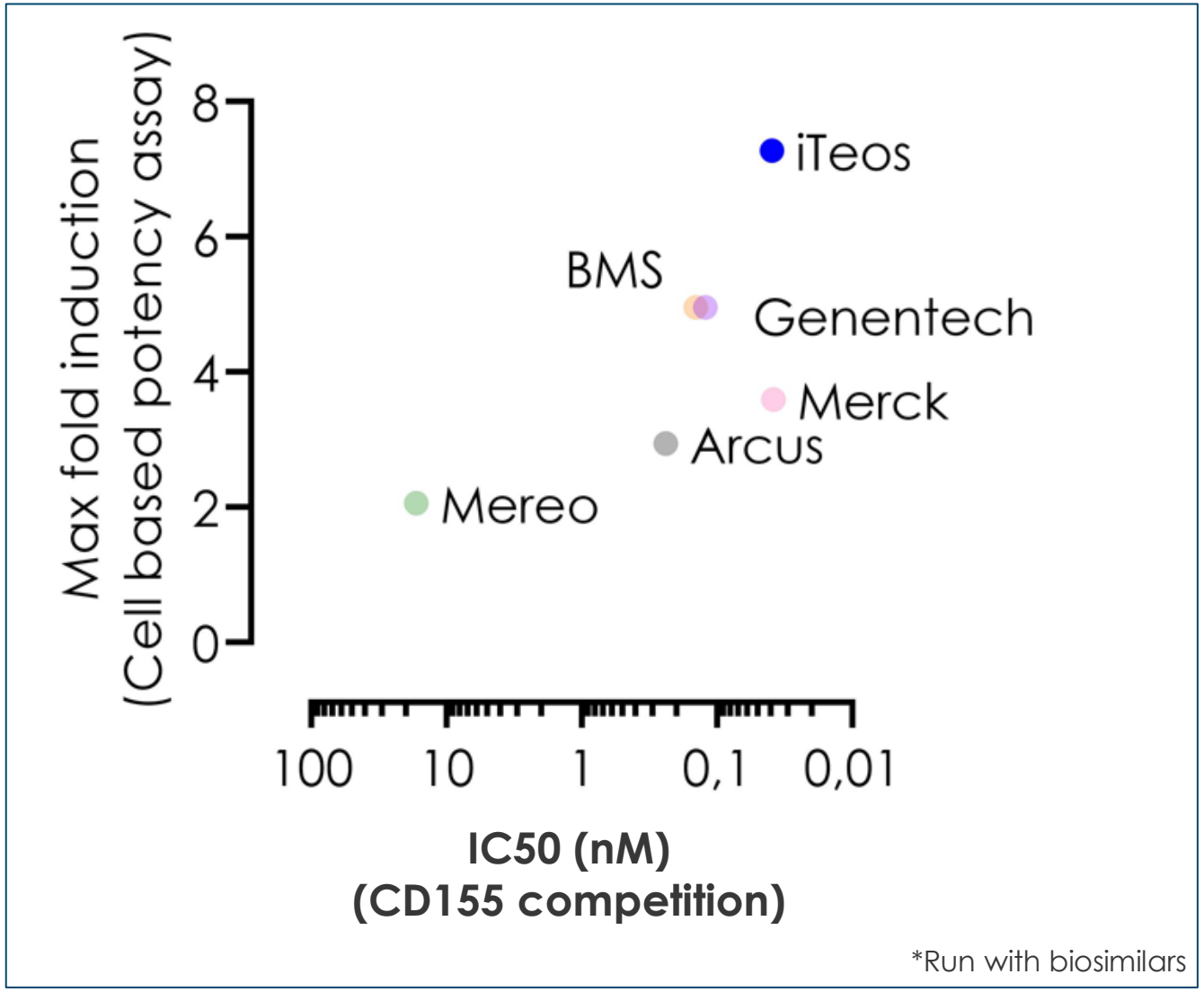
*also named GSK4428859A

iTeos Therapeutics

EOS-448 Was Selected from a Small Panel of High Affinity Binders with High Potency



EOS-448 Displays a Unique Combination of High Potency and Affinity*

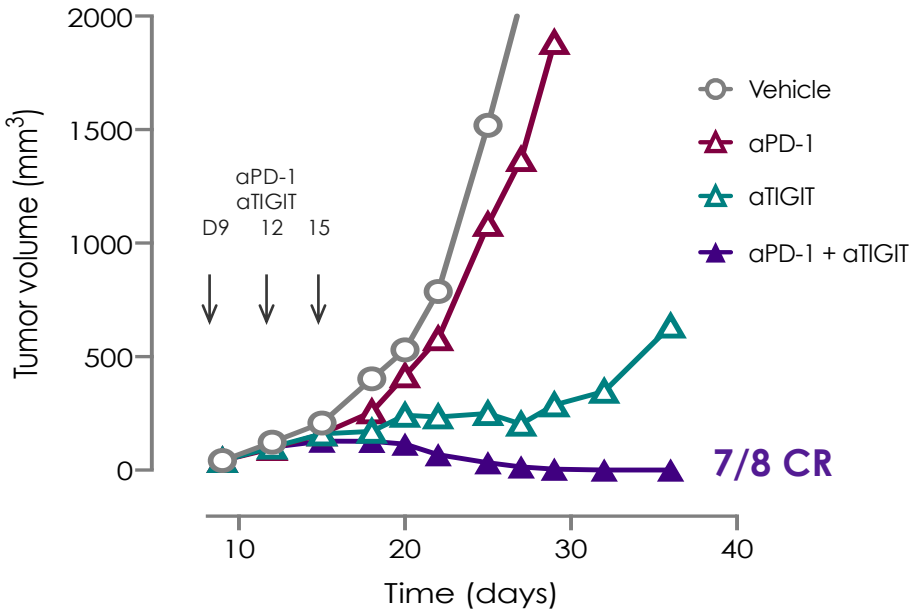


*Run with biosimilars

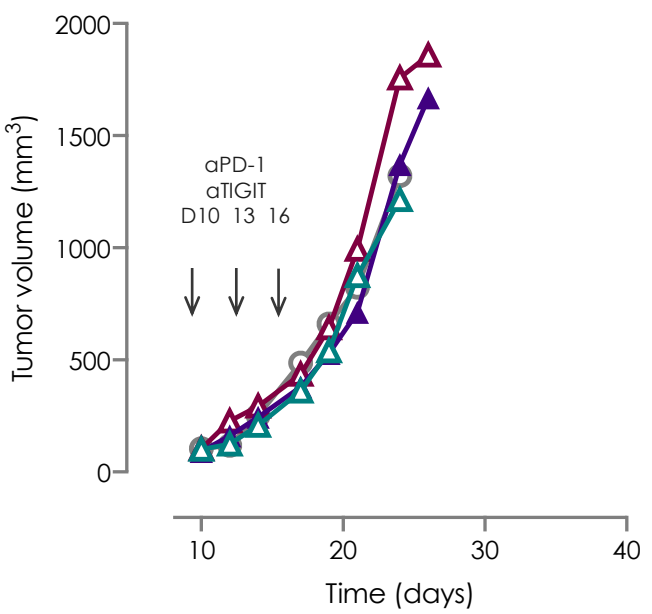
FcγR Engagement Is a Key Feature for Antitumor Activity in Preclinical Models

CT26 Colon Cancer Tumor Model

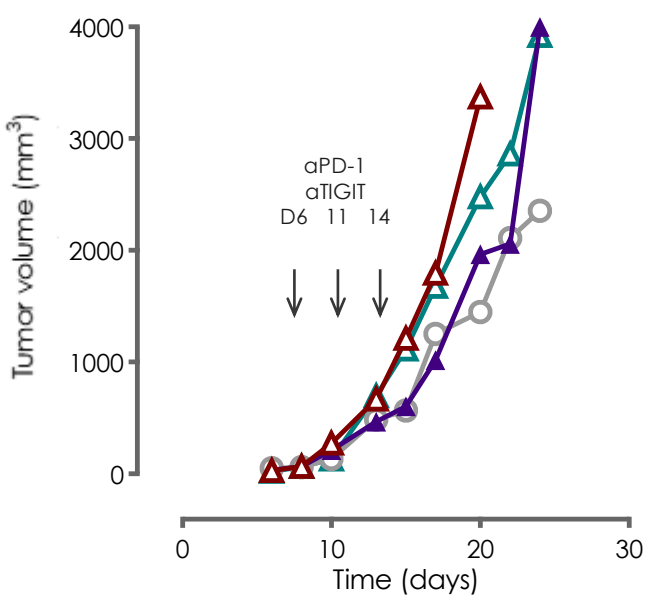
***High* FcγR-engaging isotype in WT mice**



***Low* FcγR-engaging isotype in WT mice**



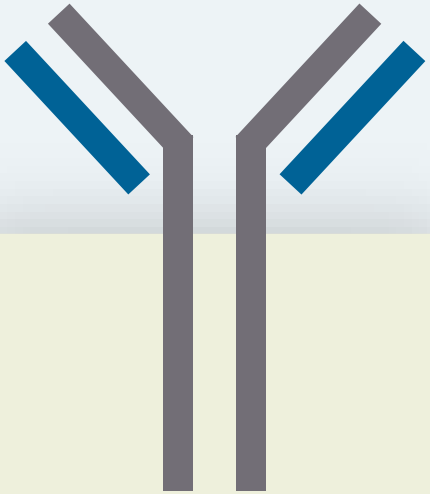
***High* FcγR-engaging isotype in *FcγR KO* mice**



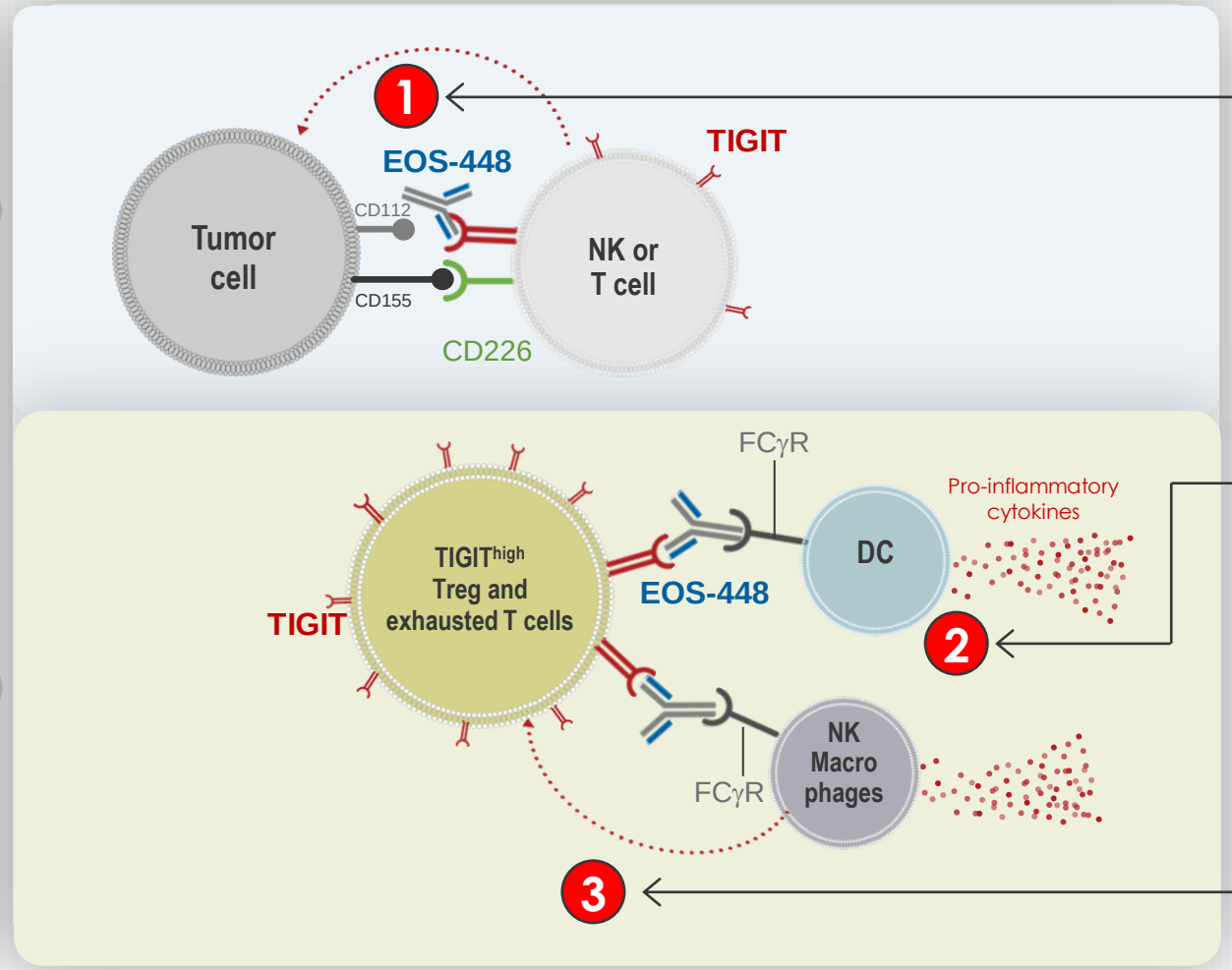
- Changing the isotype or deleting the FcγR binding potential suppressed anti-tumor effect
- Supports the selection of IgG1 isotype for clinical development

Can We Show Evidence of the Multiple MoA of EOS-448?

High affinity TIGIT-binding domain



Functional Fc domain

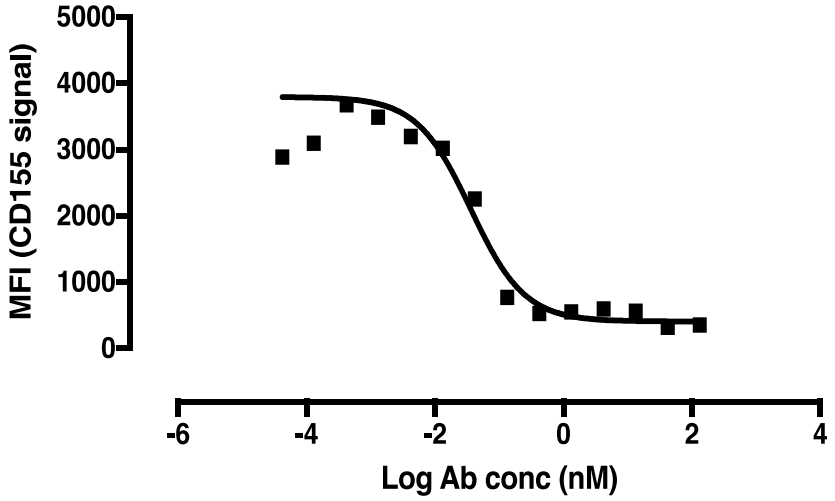


1. Antagonist activity to increase T cell and NK cell killing of tumor cells
2. Pro-inflammatory cytokine release and activation of APCs
3. Depletion of Tregs and exhausted T cells

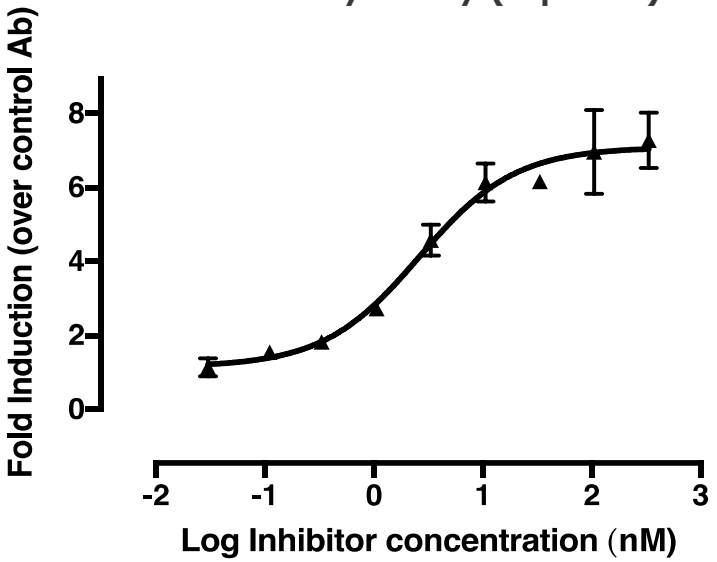
Does EOS-448 Compete with TIGIT Ligands to Activate T Cells? **Yes**

EOS-448 competes with TIGIT ligands and induces secretion of pro-inflammatory cytokines in functional assay

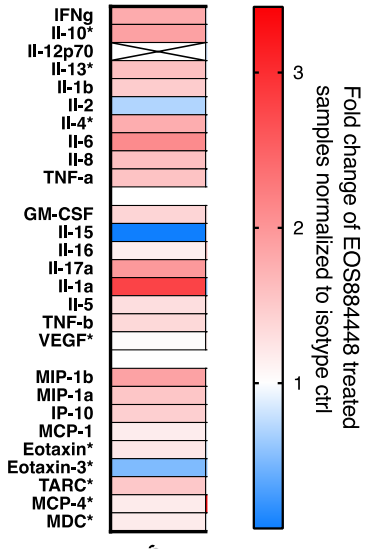
CD155 competition assay



Potency assay (reporter)

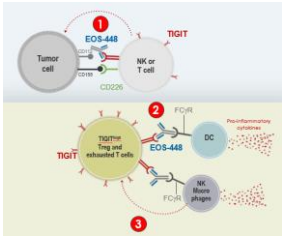


Potency assay (1ary T cells)



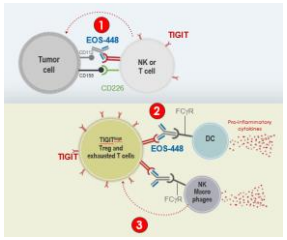
Preillon J et al,
Mol Cancer Ther 2021

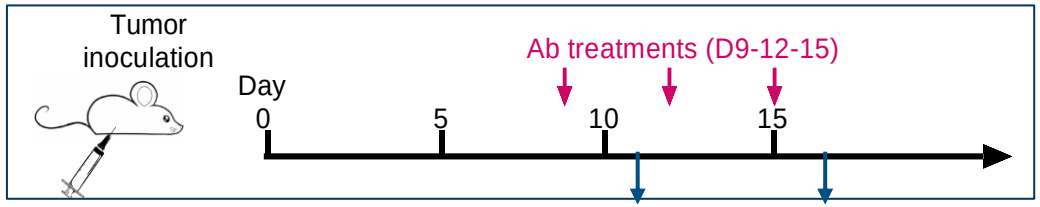
MoA 1



Does a-TIGIT Fc-live Ab Modulate APCs in Tumor? - **Yes**

MoA 2



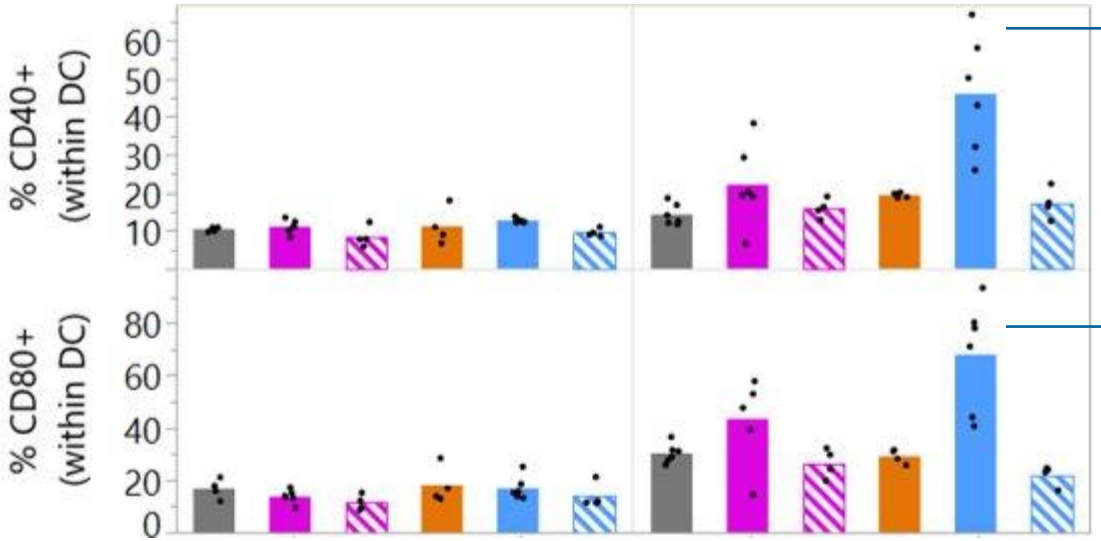


After 1 dose tumor sampling (D11)

After 3 doses tumor sampling (D17)

1 dose | 3 doses

vehicle
a-TIGIT-Fc-live
a-TIGIT-Fc-dead
a-PD-1 + a-TIGIT-Fc-live
a-PD-1 + a-TIGIT-Fc-dead
a-PD-1



p<0.01 vs all other groups

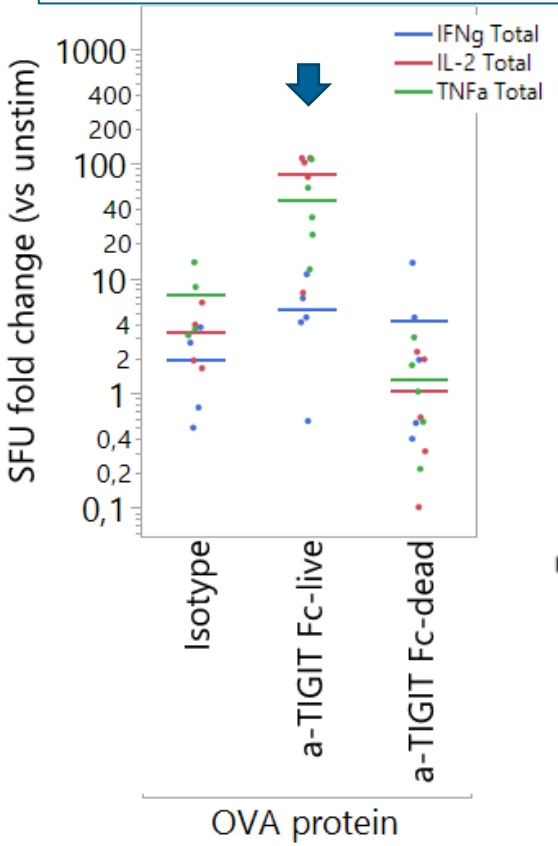
p<0.05 vs all other groups

- a-TIGIT Fc-live treatment increases activation in DC, reflected by CD40 and CD80 expression
- This activity is further enhanced by combination with a-PD-1 treatment
- a-TIGIT Fc-dead has no activity as single agent or in combination with a-PD1

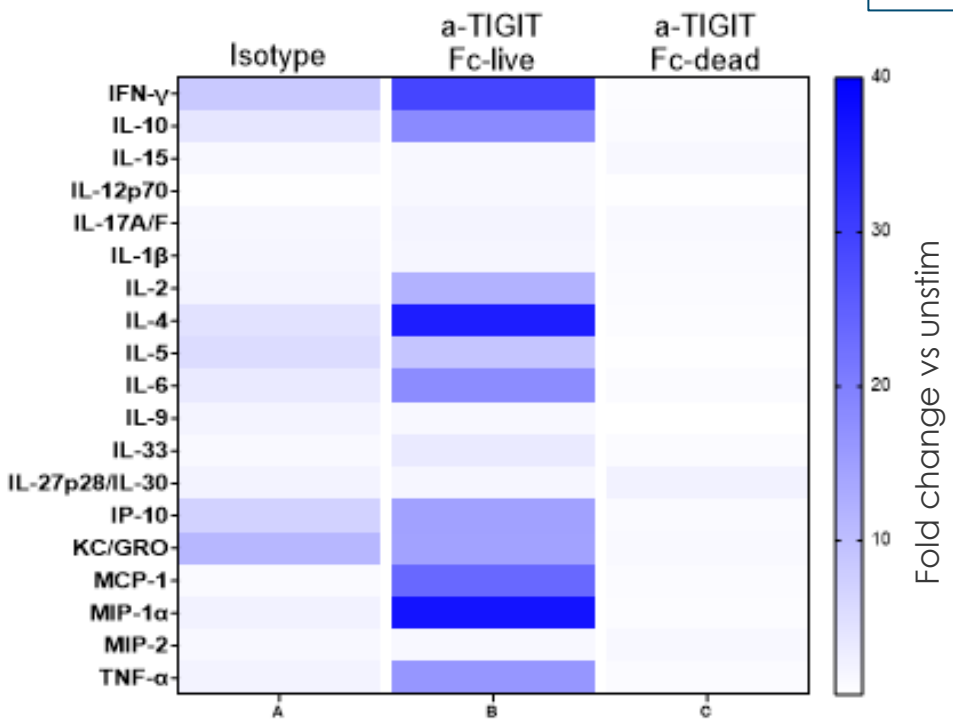
Does a-TIGIT Fc-live Increase Ag-specific Activation in TDLN? - **Yes**

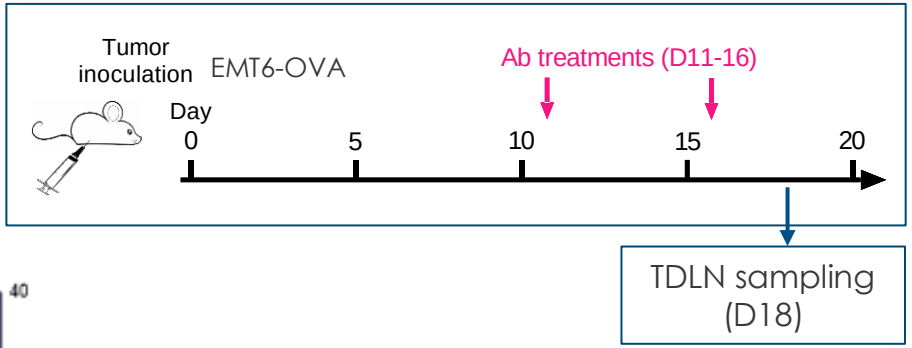
Collection: Day 18

Intracellular analysis

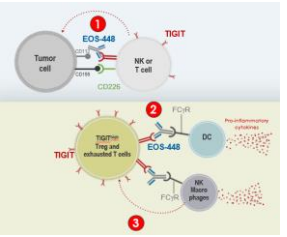


Supernatant analysis





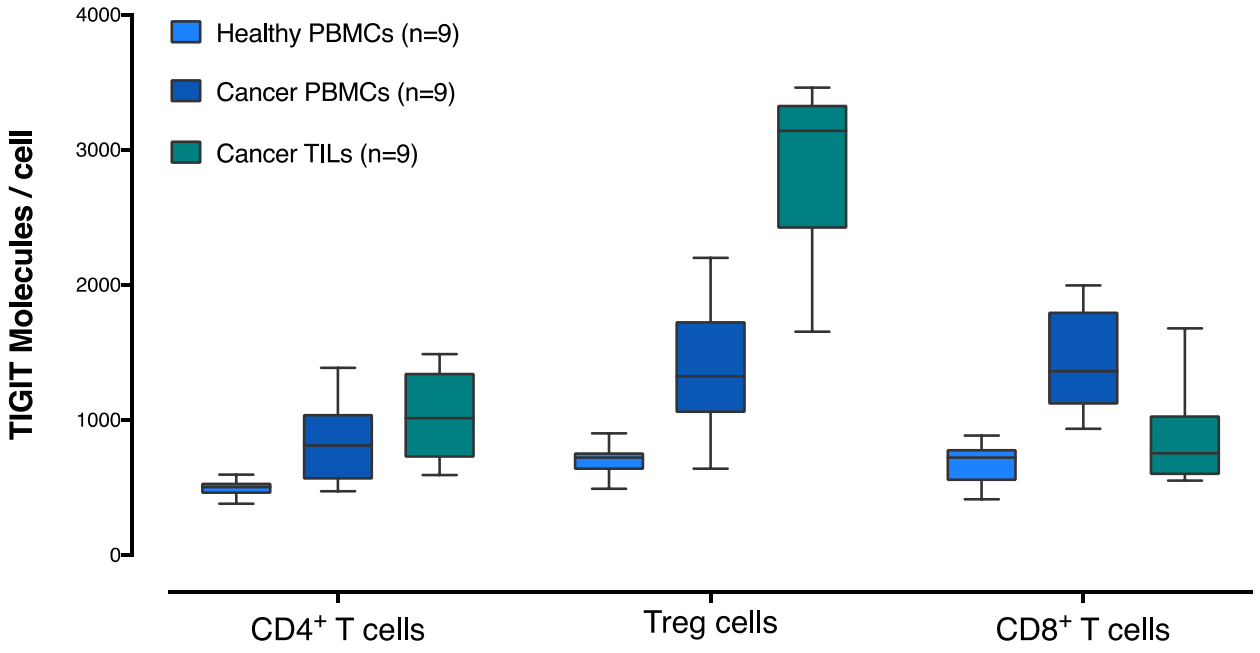
MoA 2

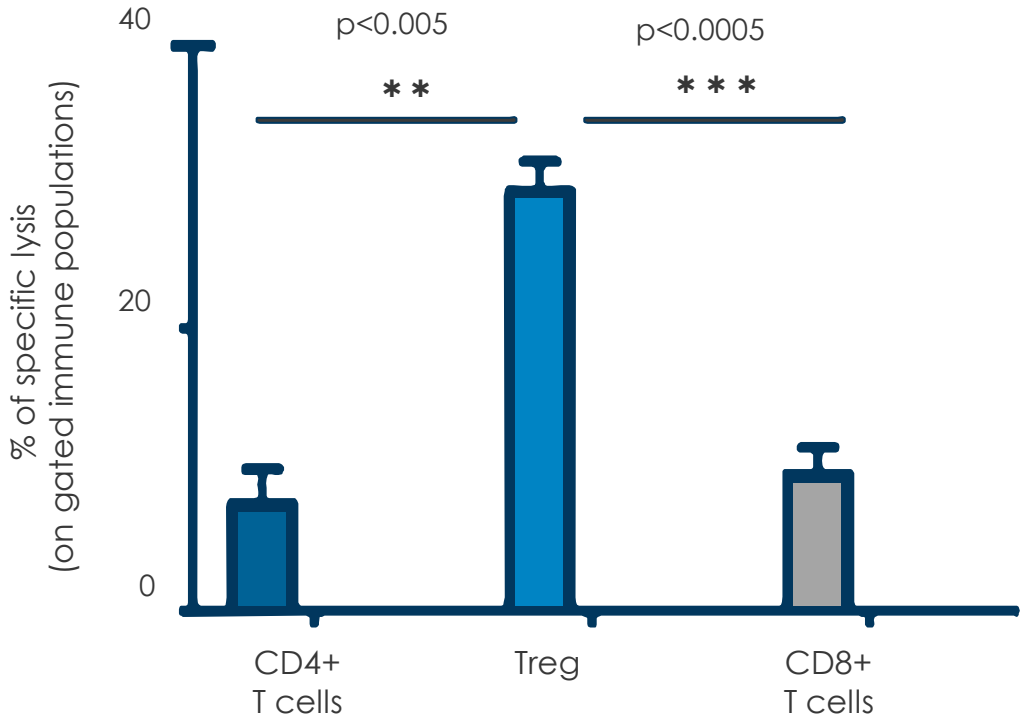


- a-TIGIT Fc-live treatment increases Ag specific T cells stimulation by APCs
- a-TIGIT Fc-dead has no activity

Does EOS-448 Deplete Tregs? - **Yes**

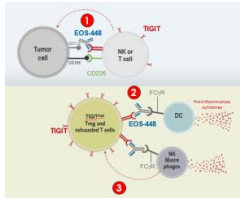
EOS-448 preferentially depletes Tregs that express highest level of TIGIT, sparing effector T cells





Preillon J et al,
Mol Cancer Ther 2021

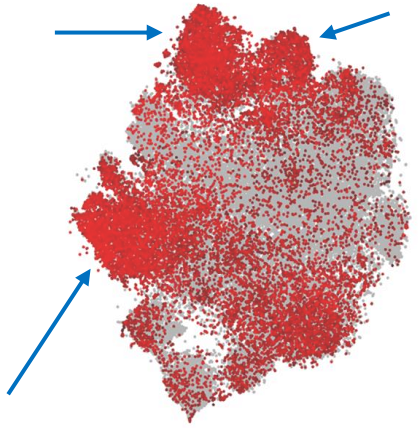
MoA 3



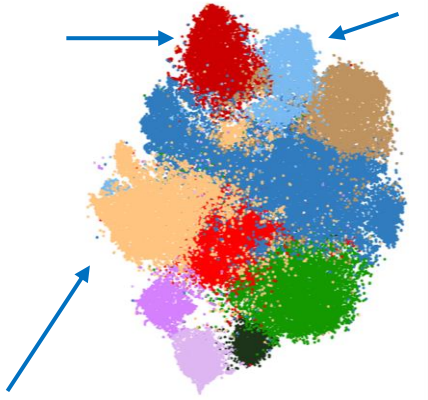
➢ **Does EOS-448 deplete other TIGIT-high cells?**

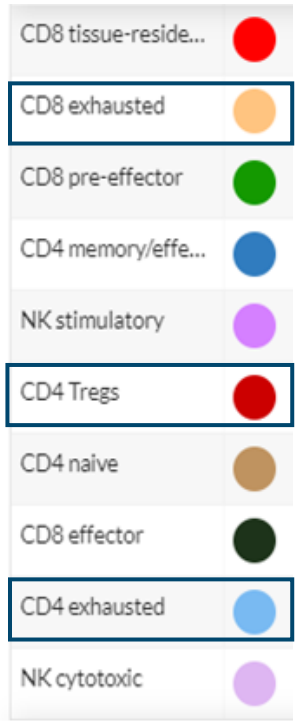
Terminally Exhausted T Cells Express High Level of TIGIT, Similar to Tregs

TIGIT RNA Expression in TME

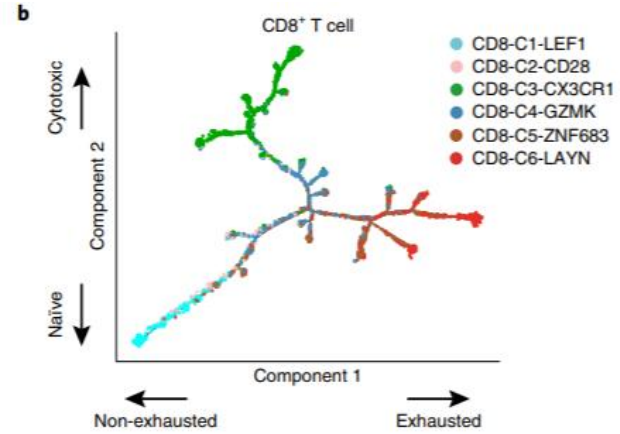


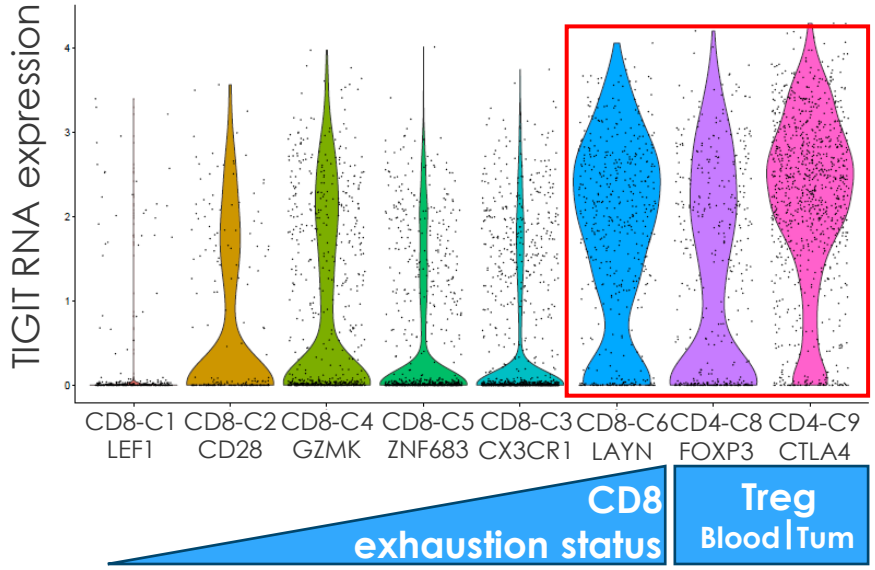
Immune populations





From Qian et al, Cell Research, 2020





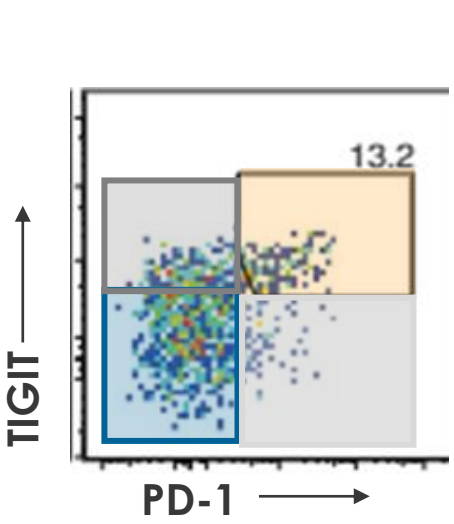
From Guo et al., Nat Med, 2018

TIGIT is mainly expressed on terminally exhausted T cells and Treg

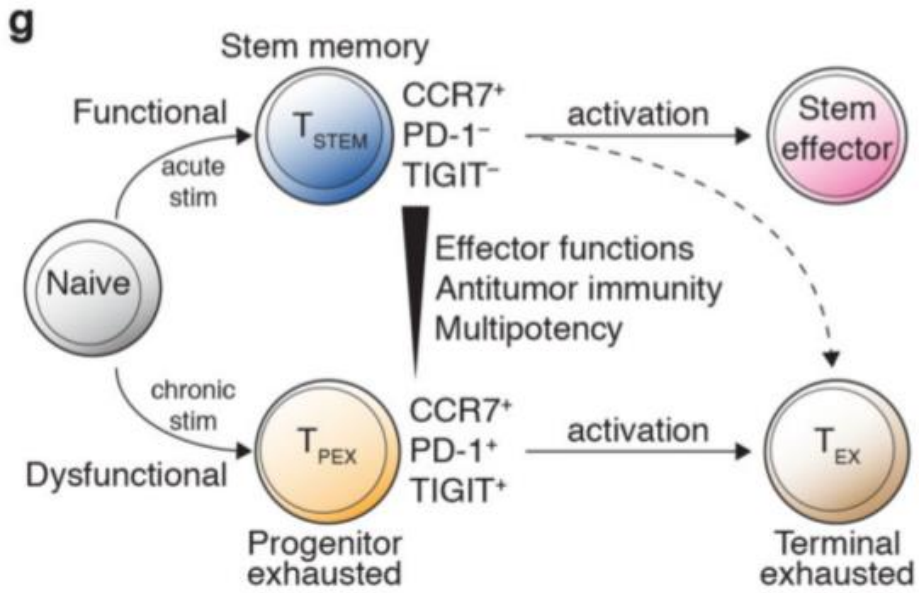
Does EOS-448 deplete Tstem and/or Tpex?

Tstem do not co-express TIGIT nor PD-1 and show differential proliferative and cytokine secretion capacity than Tpex

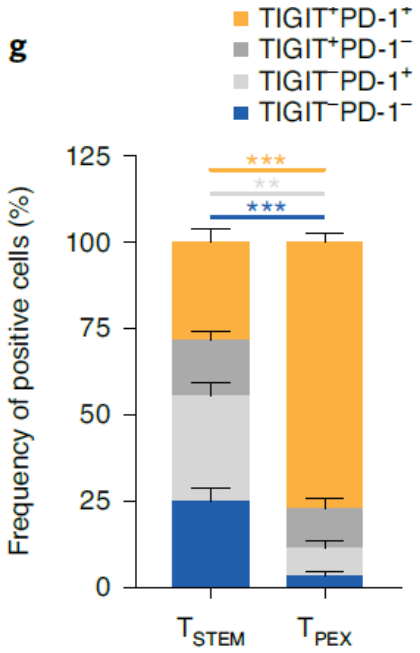
% TIGIT/PD-1 among Tscm CD8



Tpex
Tint1
Tint2
Tstem



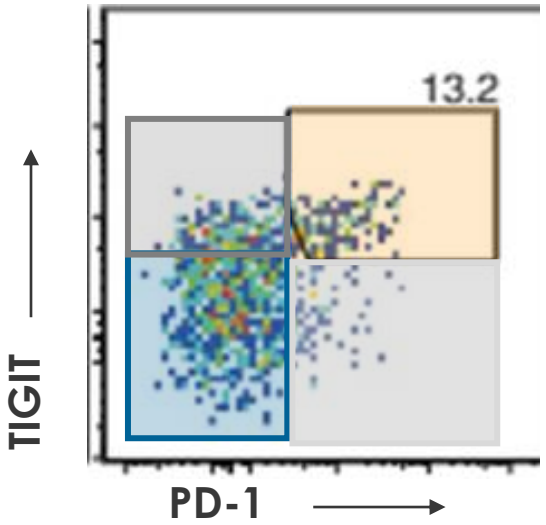
Activation of Tstem vs Tpex



Galletti et al, Nat Immunol, 2020

Does EOS-448 deplete Tstem and/or Tpex ? – **Tpex but not Tstem**

EOS-448 targets CD8 cells expressing TIGIT among CD8 exhausted progenitors, either co-expressing PD-1 (Tpex) or not (Tint1)

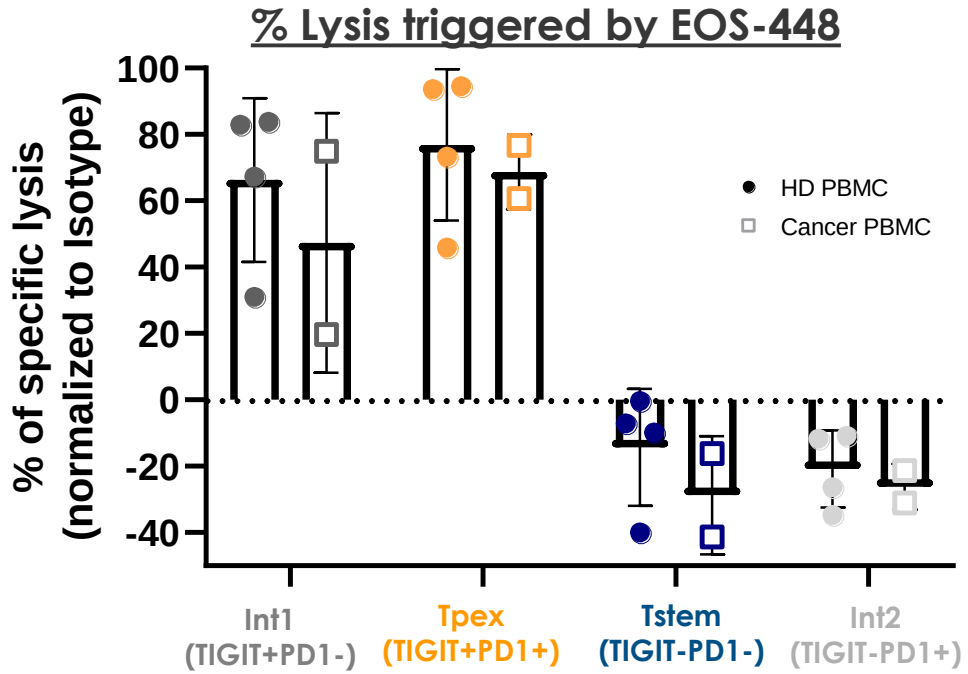


Tpex

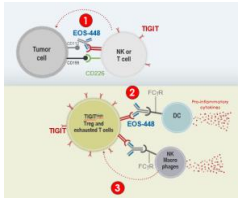
Tint1

Tint2

Tstem

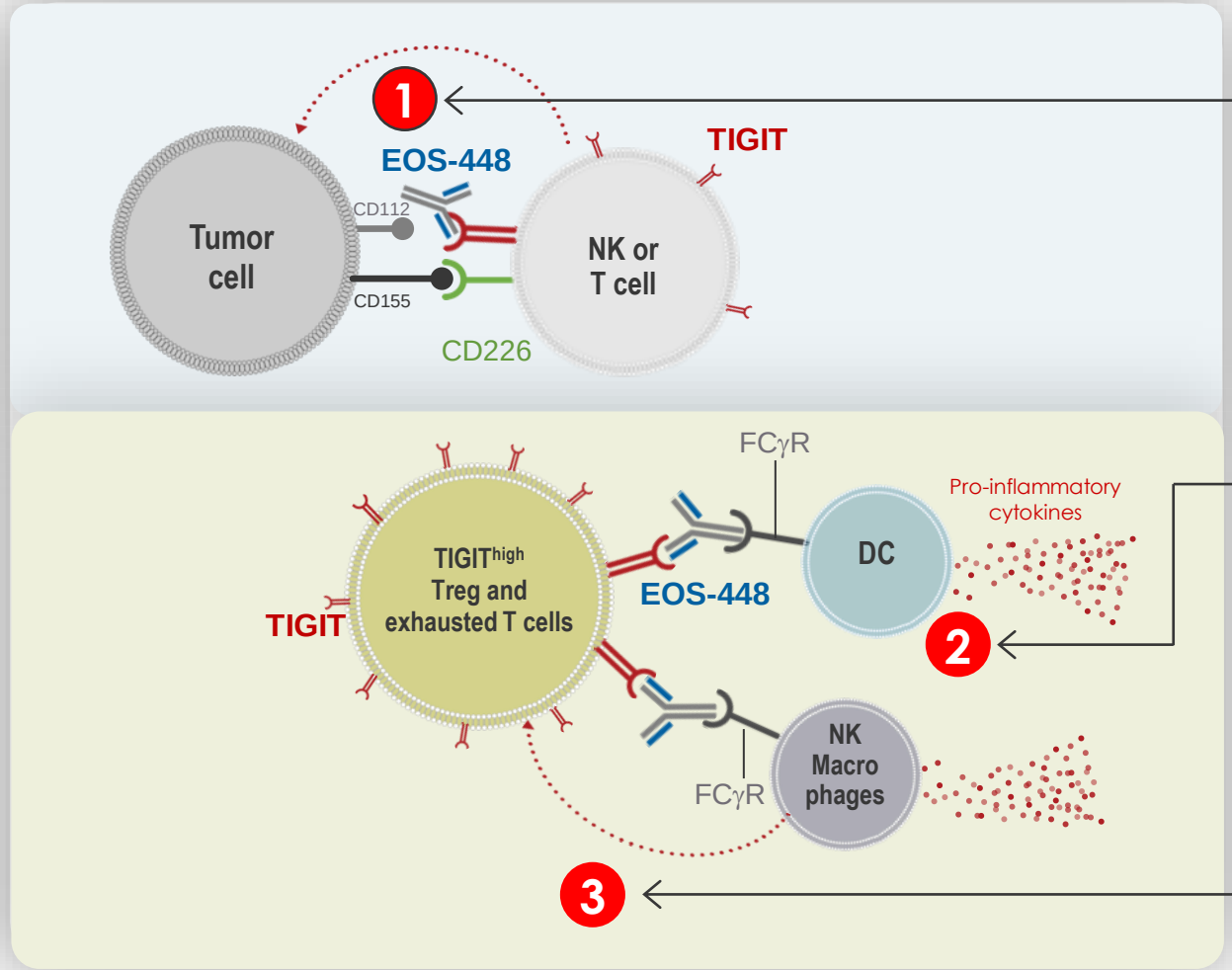


MoA 3



- EOS448 depletes Tpex and TIGIT+ cells lacking PD-1 co-expression (Tint1)
- PD-1 single positive cells (Tint2) are not targeted by EOS448, and can be reactivated by a-PD-1 therapy

EOS-448 Shows Experimental Evidence for Multiple MoA



1. **EOS-448 antagonize TIGIT ligands and activates T cells**

2. **EOS-448 modulates APCs and increases the production of pro-inflammatory cytokines**

3. **EOS-448 depletes preferentially Tregs and terminally exhausted T cells**

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Clinical Development of EOS-448

EOS-448 Is Well Tolerated in Single Agent Dose-Escalation Study

Dose Escalation single Agent

All Advanced Solid Tumors

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)

Van den Mooter et al, AACR 2021
(DCO, Dec 31st 2020)

EOS-448 Monotherapy Shows Early Signs of Efficacy

Best Change from Baseline in Target Lesions Based on Investigator Assessment per Recist v1.1

Waterfall plot of best change from baseline

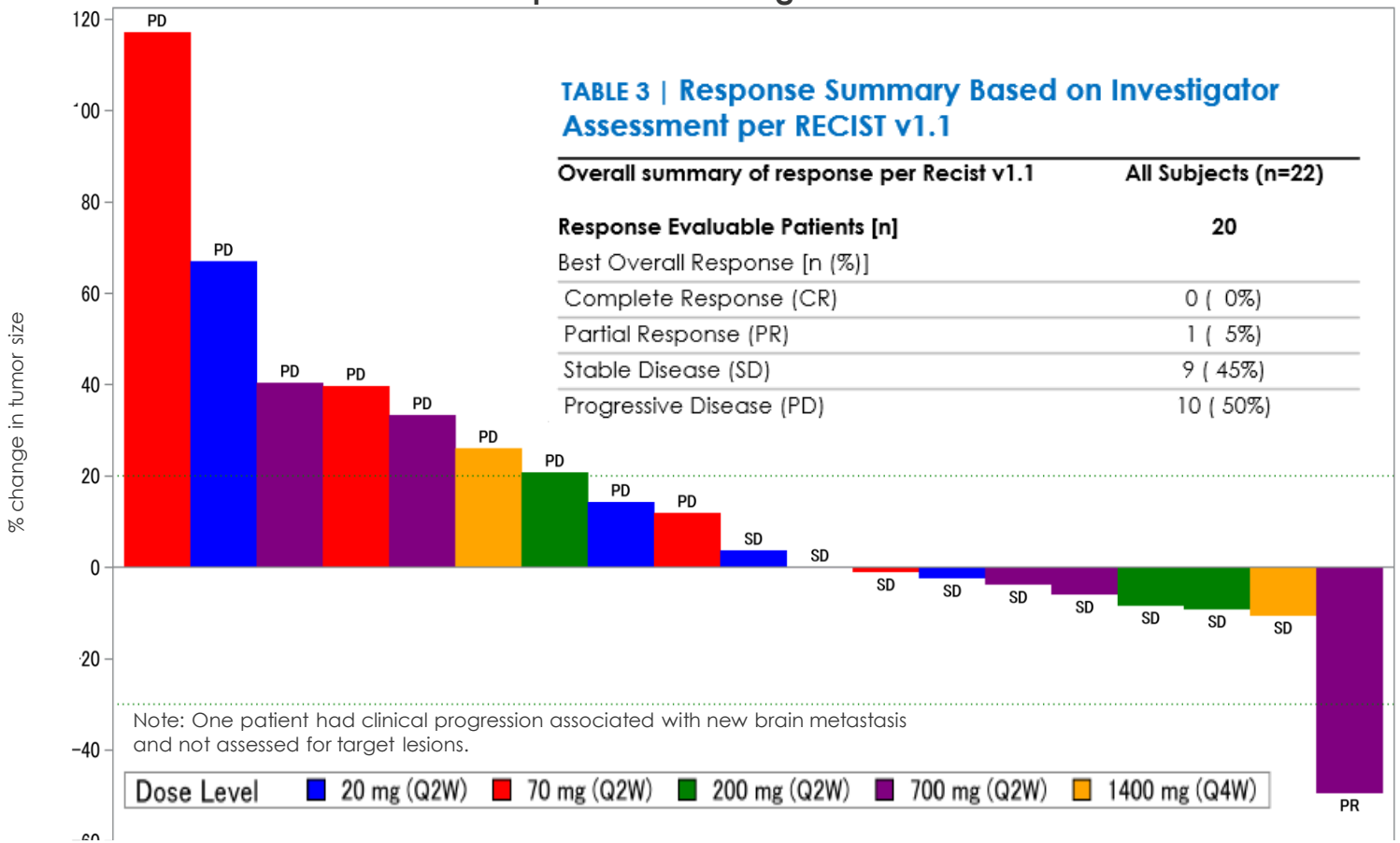


TABLE 3 | Response Summary Based on Investigator Assessment per RECIST v1.1

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%)

Van den Mooter et al, AACR 2021

Partial response in CPB-refractory Metastatic Melanoma

BRAF Mutated Melanoma
Diagnosed in 2017

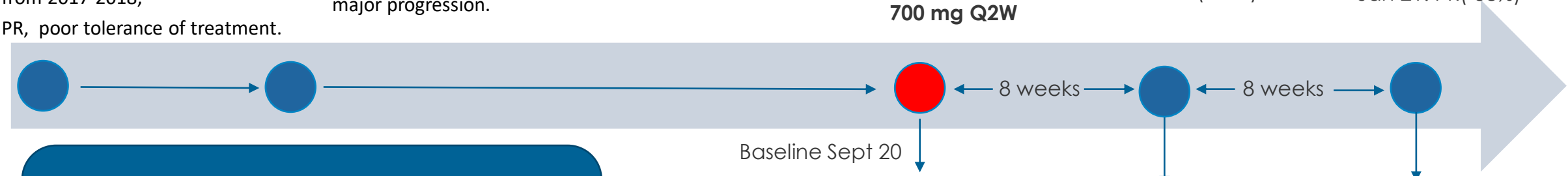
1st line BRAF MEK inhibitor
from 2017-2018,
PR, poor tolerance of treatment.

2nd line pembrolizumab from Dec2018 until Aug2020, slow progression quite early in the treatment, recent major progression.

EOS-448 started
29-Sep-2020
700 mg Q2W

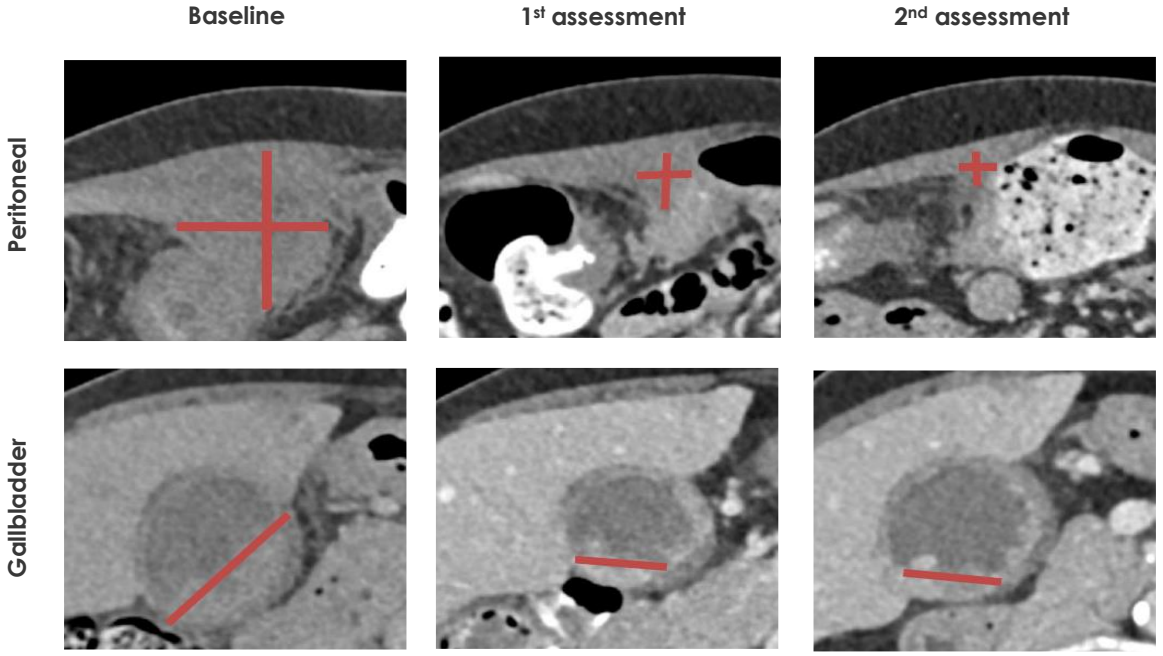
First assessment
Nov20: PR(-49%)

2nd assessment
Jan 21: PR(-58%)



58% total size tumor reduction
Symptomatic improvement with reduced abdominal pain after the first infusion

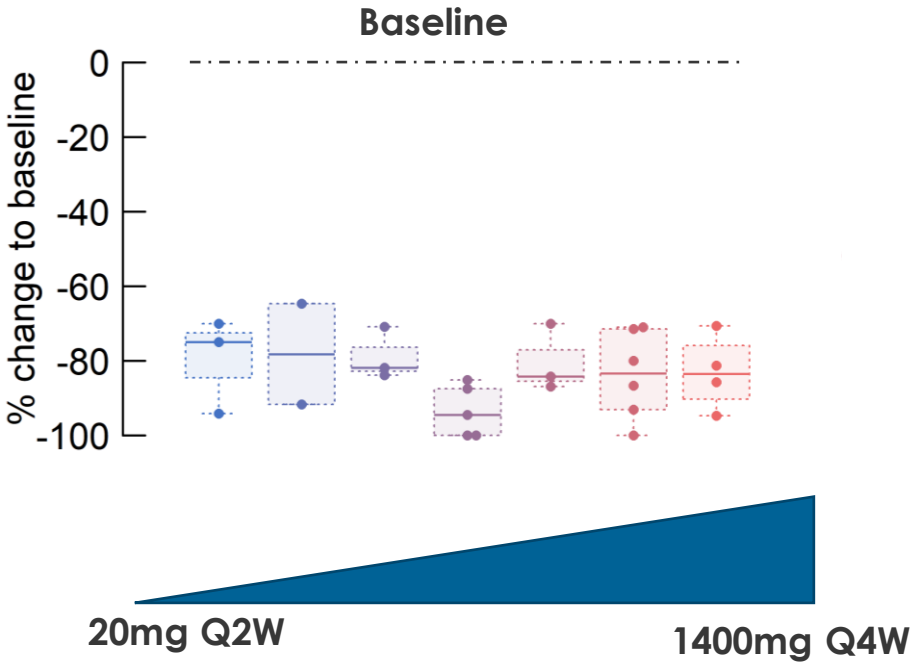
- 2 prior lines of therapy with BRAF-MEK inhibitor followed by pembrolizumab with documented PD
- Received EOS884448 700 mg Q2W
- PR per RECIST with 49% and 58% reduction in size of intra-abdominal target lesions, at 8 and 16 weeks, respectively
- Therapy ongoing at 24 Weeks



Van den Mooter et al, AACR 2021

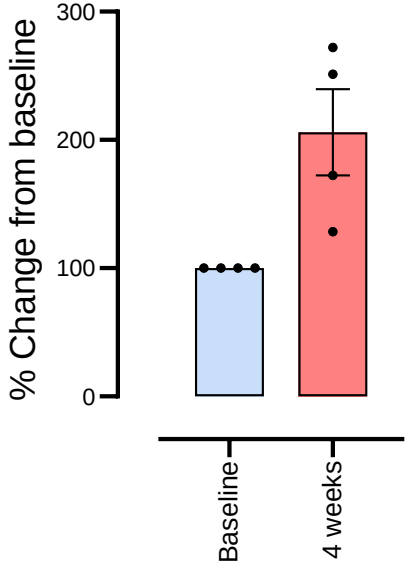
EOS-448 Demonstrates Strong Pharmacodynamic Effect in Periphery

TIGIT+ Treg Depletion at D28

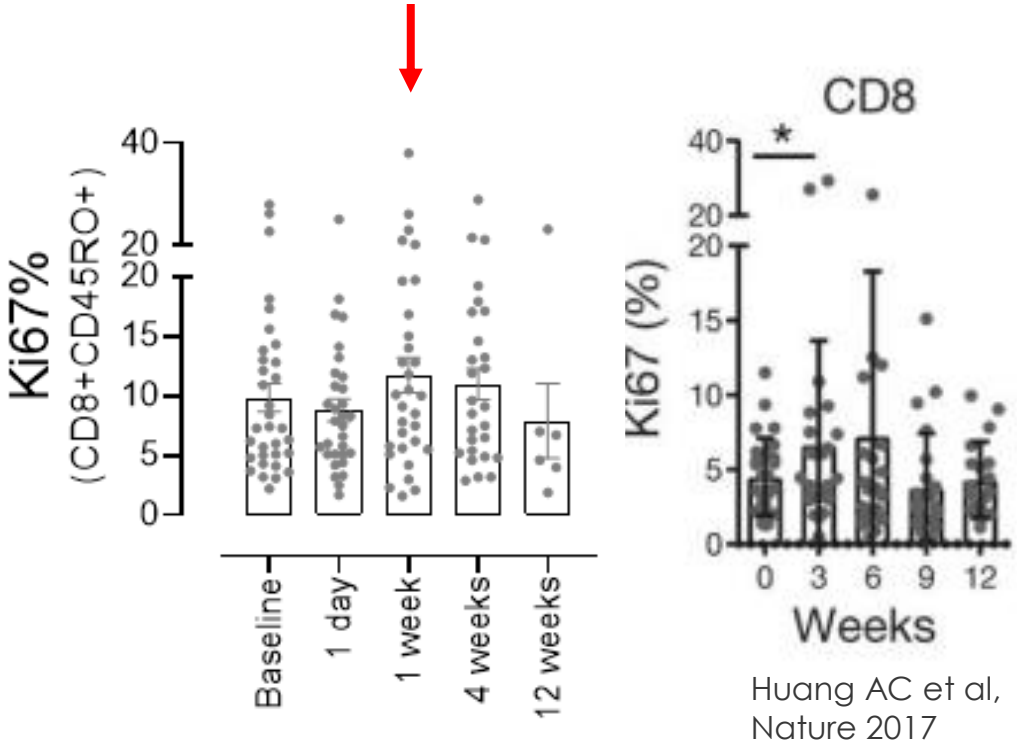


Increase in CD8/Treg ratio

Example at 400mg Q4W



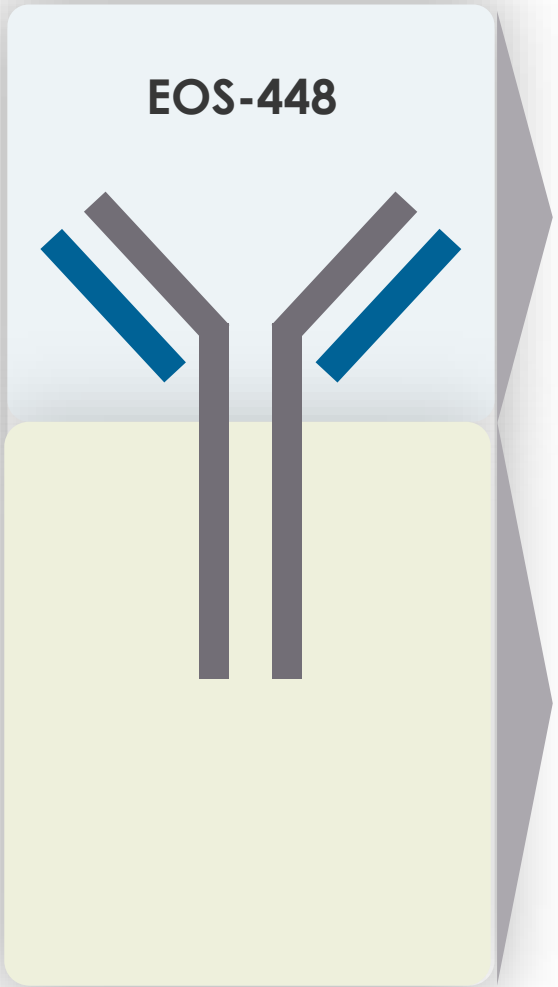
Transient increase of Ki67 in memory CD8 T cells Similar to data observed with pembrolizumab



Huang AC et al, Nature 2017

- PD assessment suggests complete target engagement in the periphery that correlates with depletion of Treg and TIGIT+ T cells known to be exhausted and restoration of CD8/Treg balance

Ongoing Development of EOS-448 in Multiple Indications and Combination to Diversify Risks and Opportunities



- **EOS-448 demonstrates strong preclinical evidence for antitumor activity that involves multiple mechanisms of actions**
- **Ph1 clinical data show a tolerable profile that correlates with strong pharmacodynamic activity as single agent and early signs of activity**
- **Ongoing development in multiple indications including NSCLC, HNSCC, Melanoma and Multiple Myeloma**
- **Ongoing development in multiple combinations including pembrolizumab, dostarlimab, inupadenant, iberdomide**
- **Launch multiple randomized trials in 2022**

Acknowledgments

- iTeos preclinical TIGIT team
- iTeos clinical TIGIT team
- GSK team for the great partnership
- PI and clinical centers involved in current in studies
- Patients and their families
- Public financial support from Walloon region and EU FEDER fund