Targeting GITR enhances tumour-infiltrating T cell functionality in mismatch-repair proficient primary colorectal carcinoma and liver metastases

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SITC Annual Meeting
12th of November, 2020

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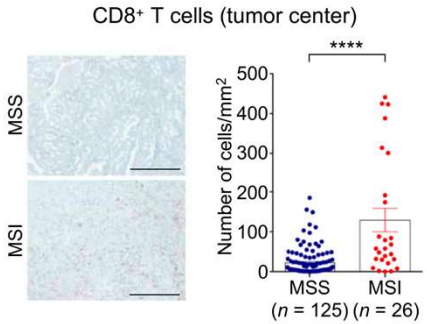
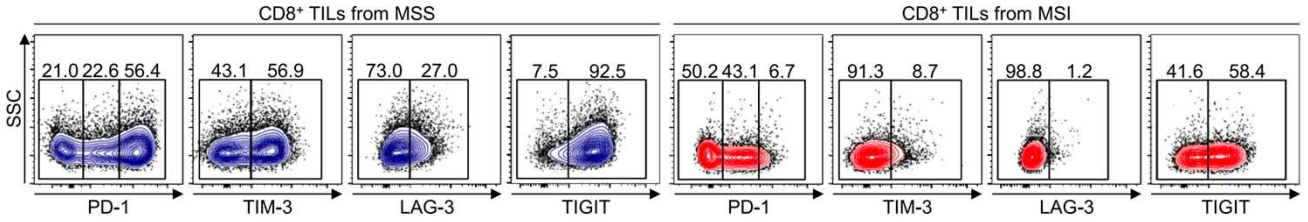
Disclosures

I have NO financial disclosure nor conflicts of interest with the presented material

Response rates to immune checkpoint blockade in CRC are limited

- 3rd most common type of cancer (25% M1)
- 4th most common type of cancer-related death
- Stage 4 disease 5-yr survival of 12.6%
- Immune Therapy promising (in MMR- CRC)





Erasmus MC

Shin, et al. Science Immunology, 2019

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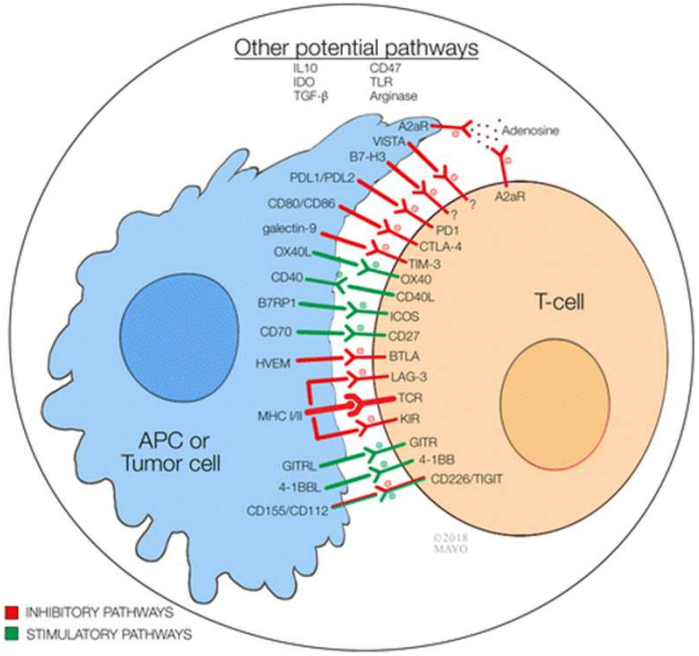
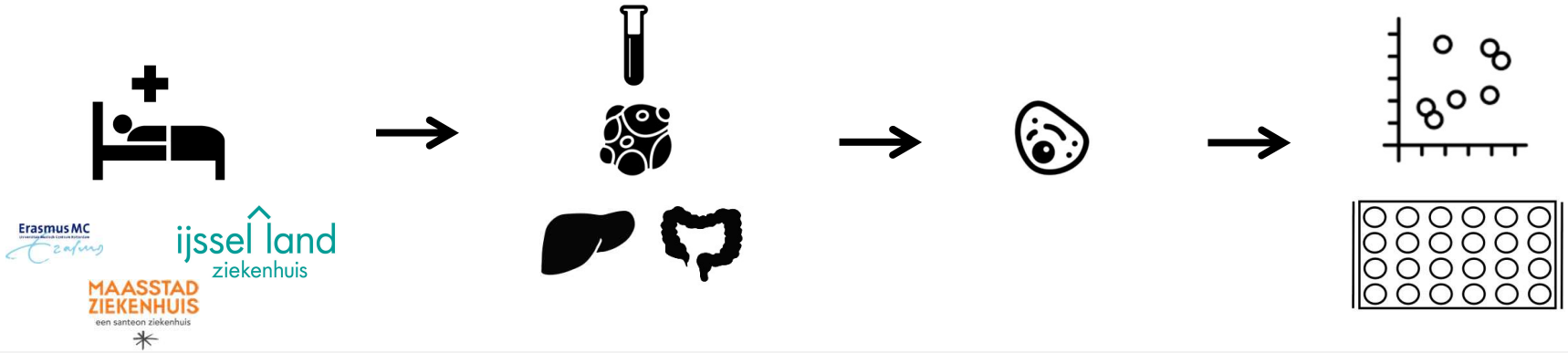


Erasmus MC

Wykes, et al. Nature Reviews Immunology, 2017

From bed to benchside

I. Patient Selection	II. Tissue Processing	III. Single Cell Suspension	IV. In vitro analysis



Primary Colorectal Carcinoma ***CRC***
Liver metastasis CRC ***CRLM***

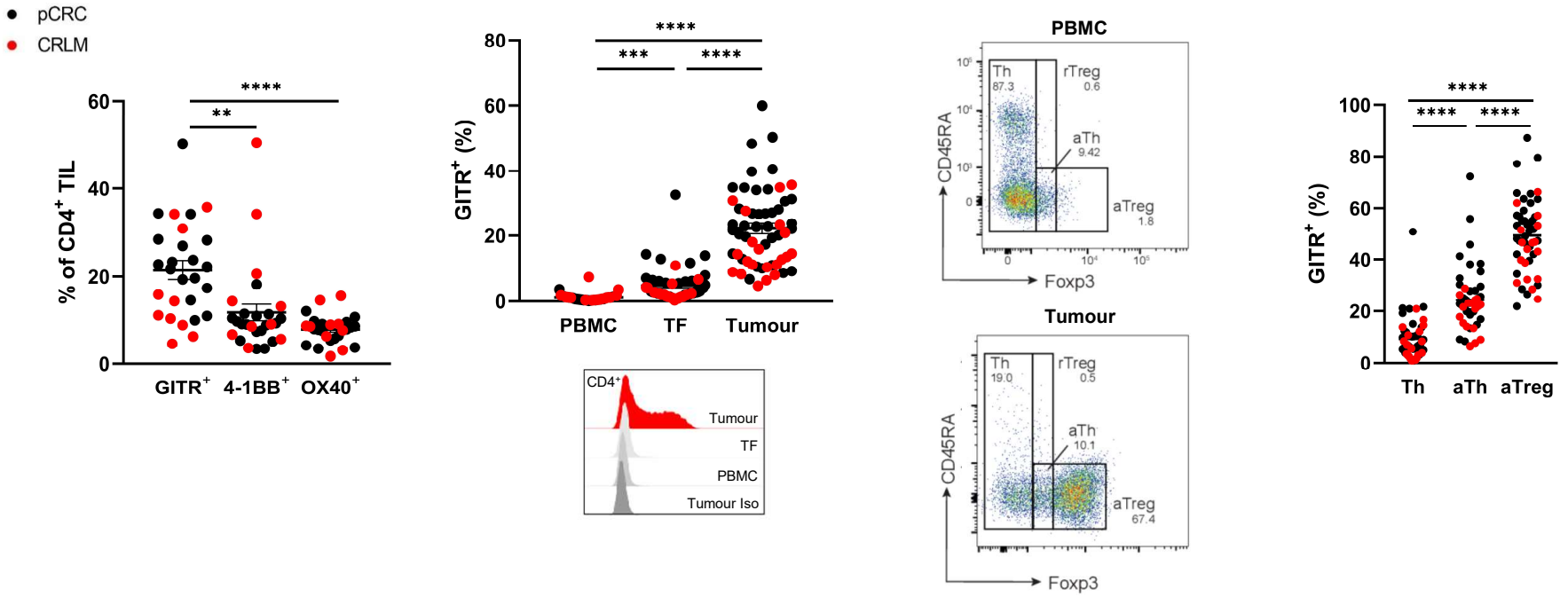
Mismatch Repair Proficient

Blood (during surgery)
Tumor tissue
Tumor-free liver/colon (resp. TFL/TFC)

TIL cell suspension
CD45 purity 5-80%

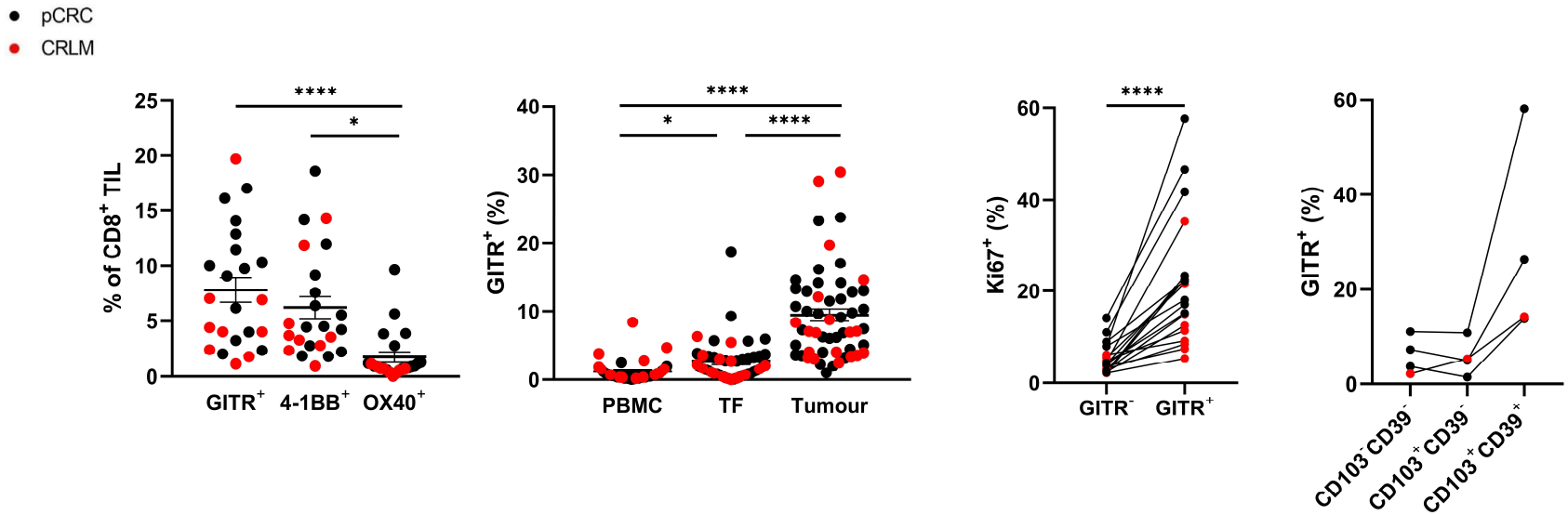
Phenotyping immune infiltrates
In vitro functional stimulation assays

GITR is predominantly expressed on CD4⁺ activated Th and Treg TIL



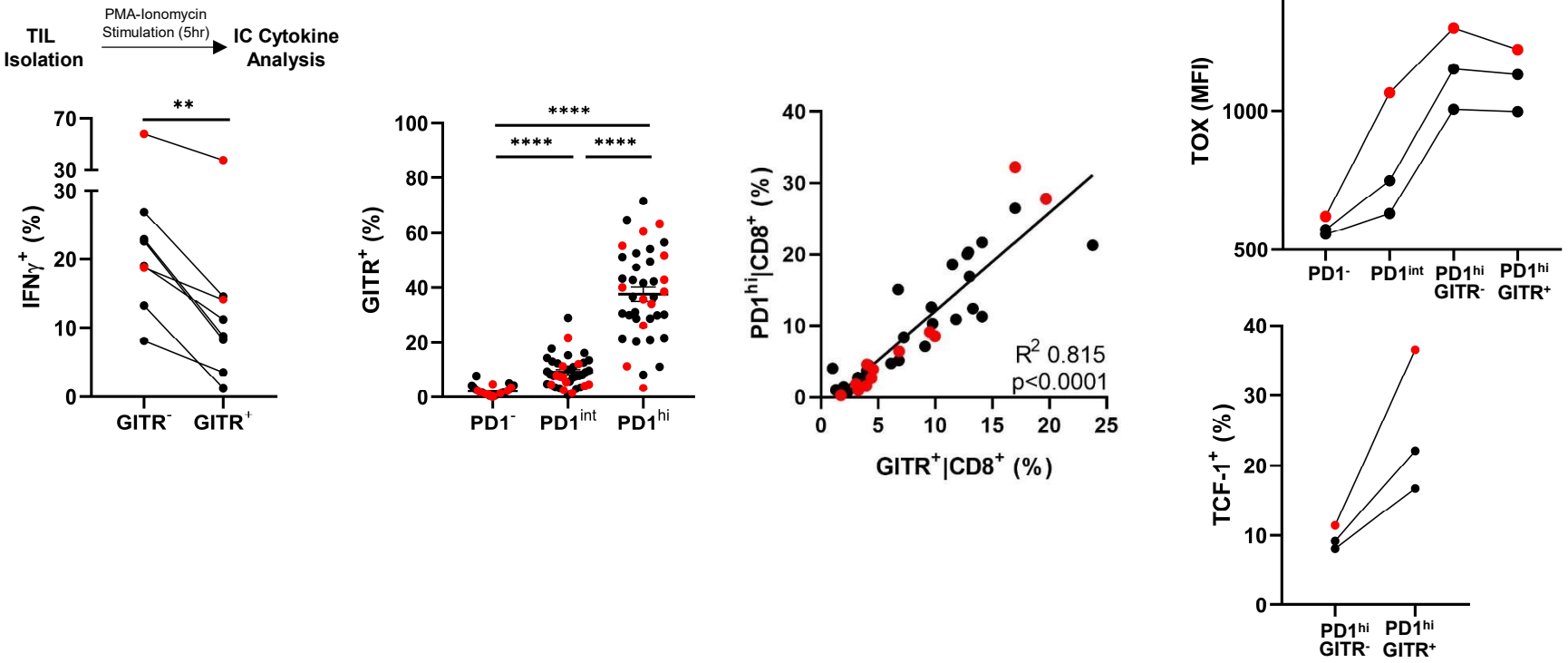
TIL: tumour-infiltrating lymphocytes
PBMC: peripheral blood mononuclear cells
TF: tumour-free surrounding tissues
(a)Th: (activated) helper T cells
aTreg: activated regulatory T cells

GITR is predominantly expressed on activated CD103$^+$CD39$^+$CD8$^+$ TIL



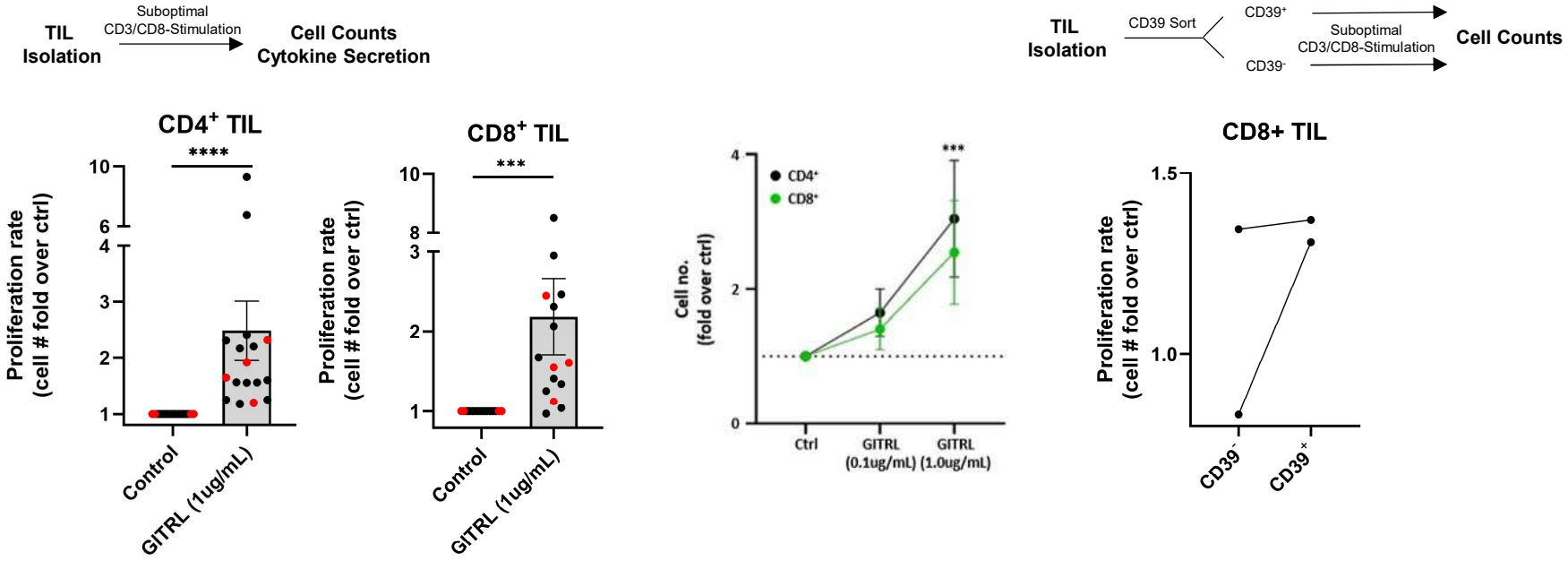
TIL: tumour-infiltrating lymphocytes
PBMC: peripheral blood mononuclear cells
TF: tumour-free surrounding tissues

GITR expressing CD8 TIL demonstrate a (pre-)exhausted phenotype



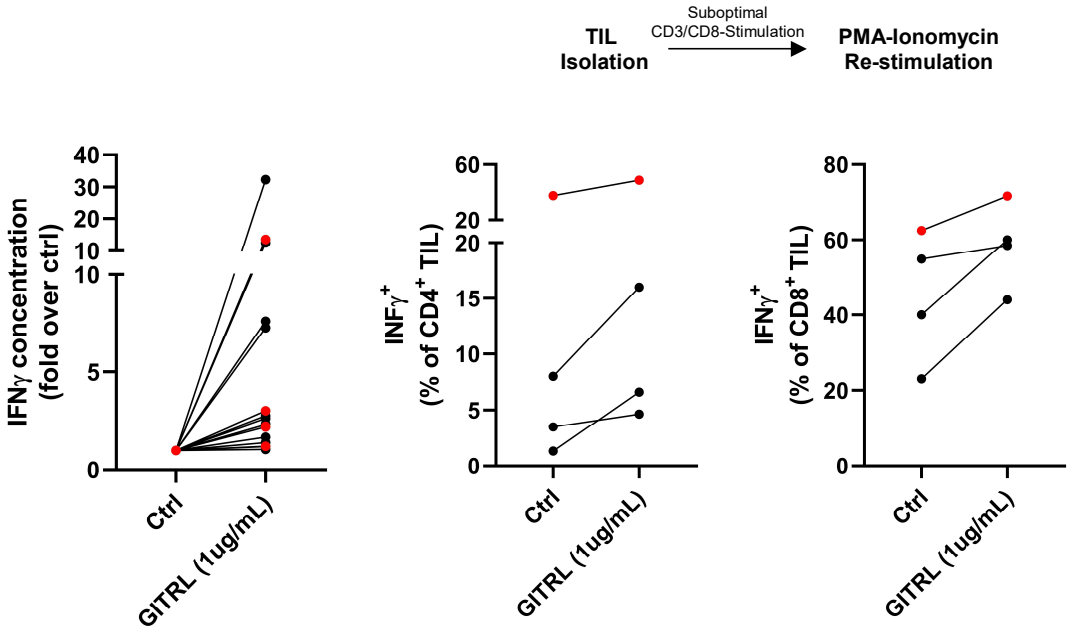
TIL: tumour-infiltrating lymphocytes
IC: intra-cellular

GITR ligation enhances CD4 and CD8 TIL expansion



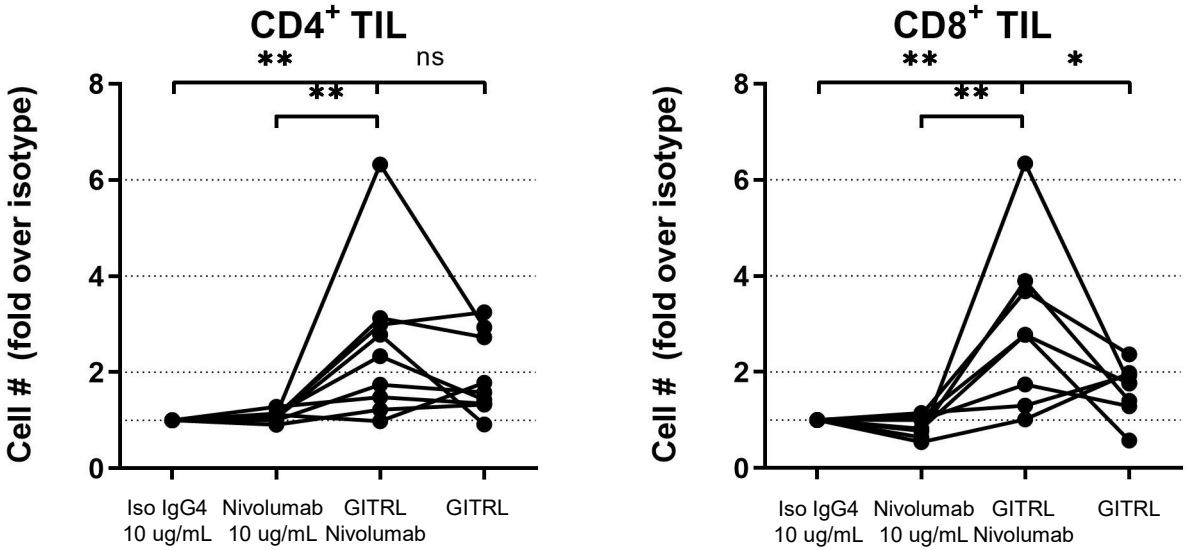
TIL: tumour-infiltrating lymphocytes

GITR ligation enhances CD4 and CD8 effector cytokine secretion



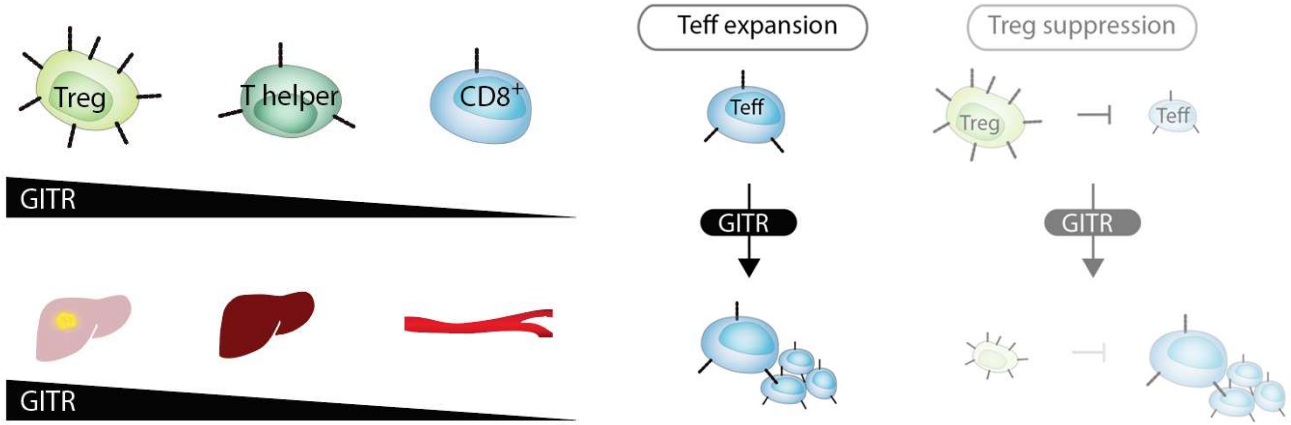
TIL: tumour-infiltrating lymphocytes
IFN: interferon

GITRL and anti-PD1 combination therapy enhance TIL expansion



Take home messages

- GITR is overexpressed on $CD4^+$ (aTh/aTreg) and (activated) $CD8^+$ TIL in MMR+ CRC/CRLM
- $GITR^+$ CD8 TIL demonstrate a pre-exhaustive phenotype
- GITR ligation enhances TIL expansion and effector cytokine secretion
- GITR ligation can reinforce anti-PD-1 activity



Acknowledgements

Erasmus MC Cancer Institute
Jaap Kwekkeboom (GE)
Dave Sprengers (GE)
Jan IJzermans (Surgery)
Lucia Campos Carrascosa (GE)
Adriaan van Beek (GE)
Valeska de Ruiter (GE)
Michael Doukas (Pathology)
Cees Verhoef (Surgery)
Dirk Grünhagen (Surgery)

Pascal Doornebosch (Surgery)
Maarten Vermaas (Surgery)

Erwin van der Harst (Surgery)
Peter Paul Coene (Surgery)

Special thanks to all patients that were included in this study