Immune Checkpoint Receptors Targeting to Enhance Cetuximab Therapy

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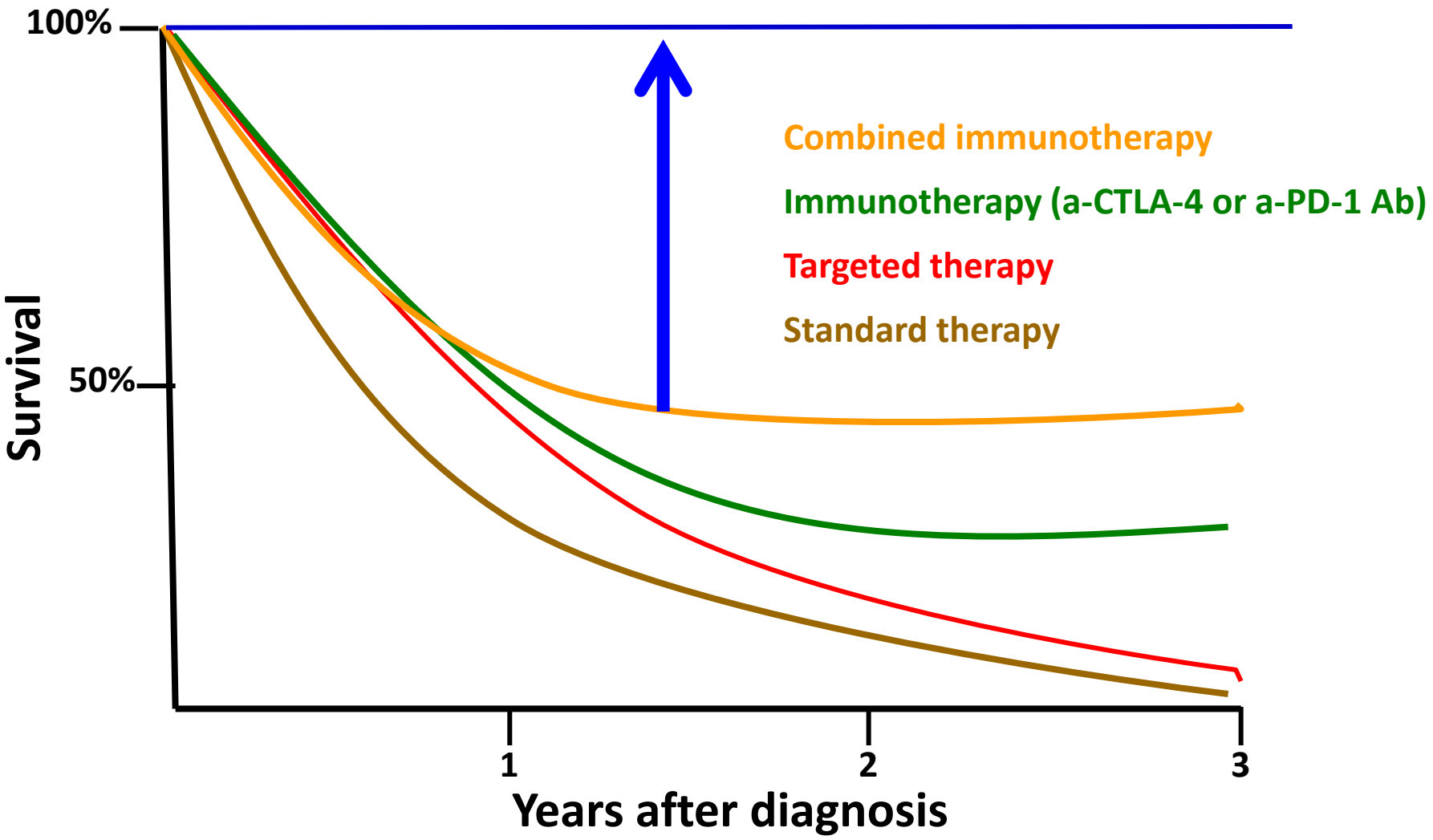
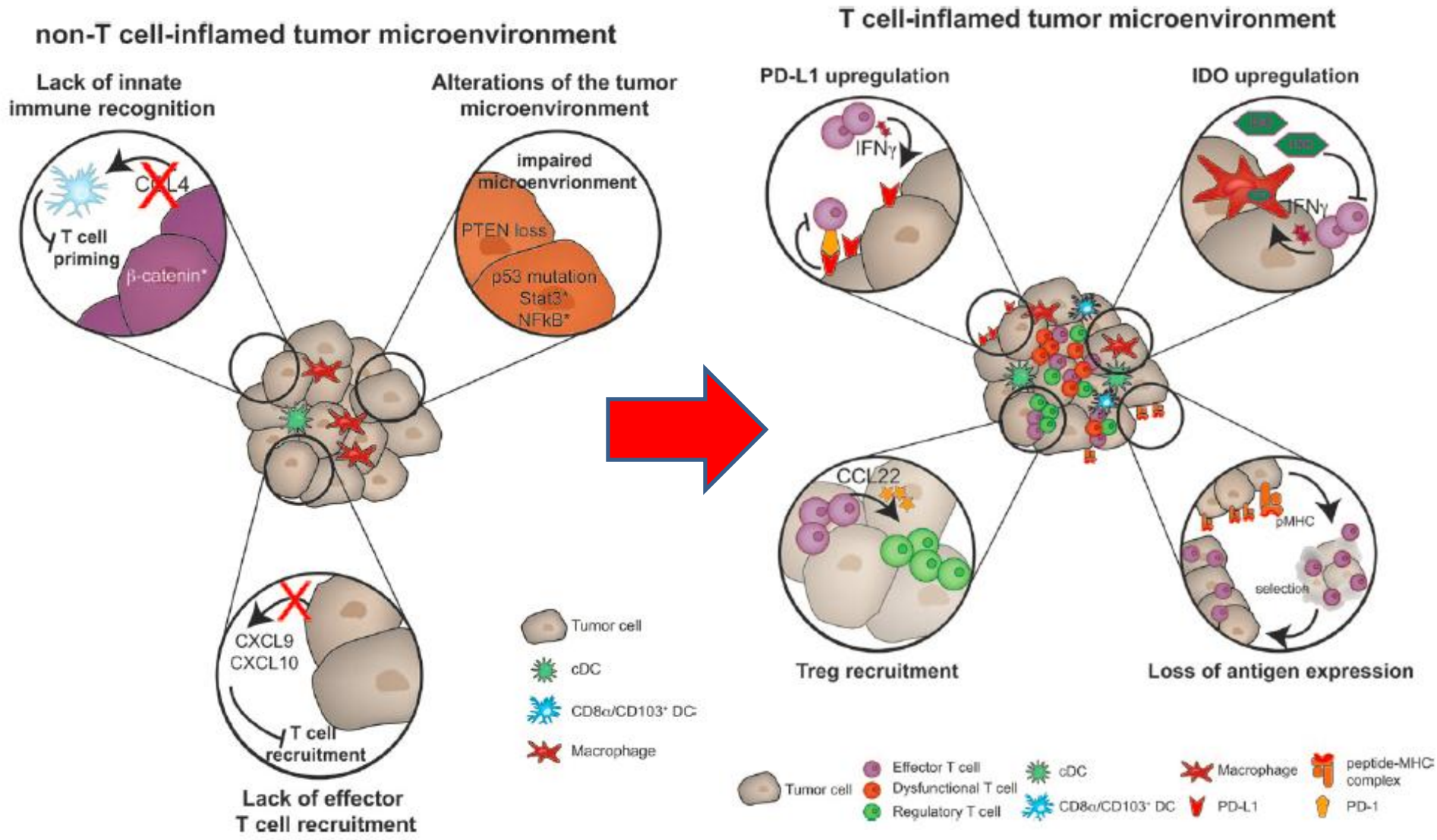
The perfect blend:
Next frontier in cancer immunotherapy

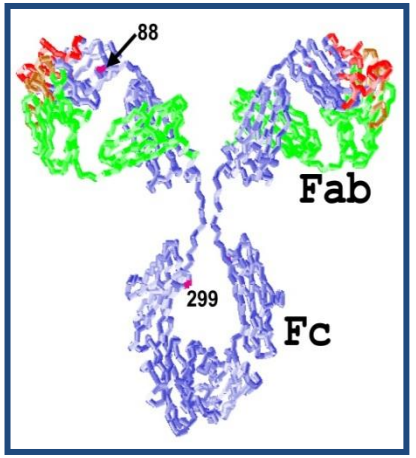


Non-T cell-inflamed vs T cell-inflamed tumor microenvironment



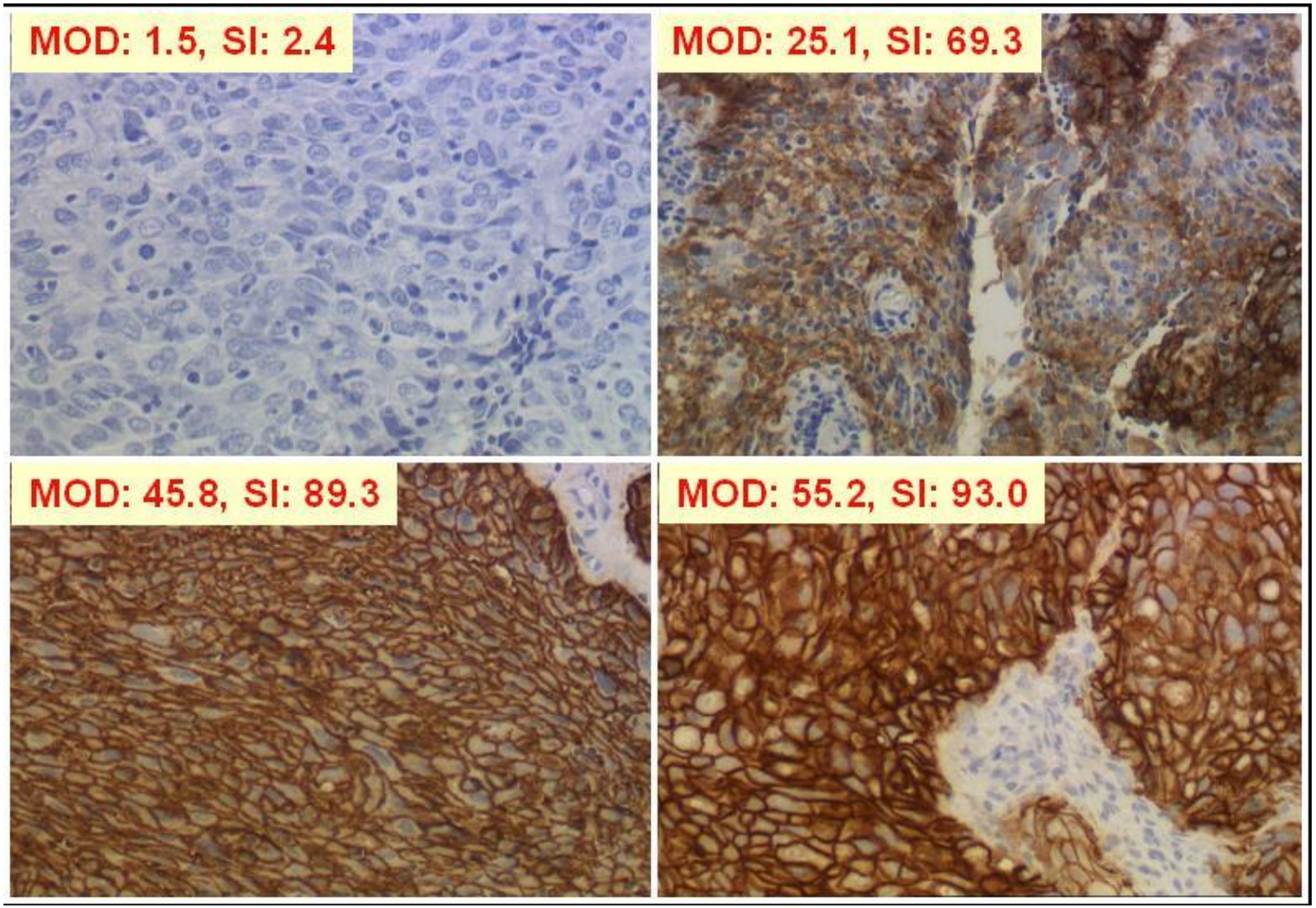
International Immunology 2016, March 17

EGFR-specific Ab (Cetuximab, Erbitux^{TM}) therapy



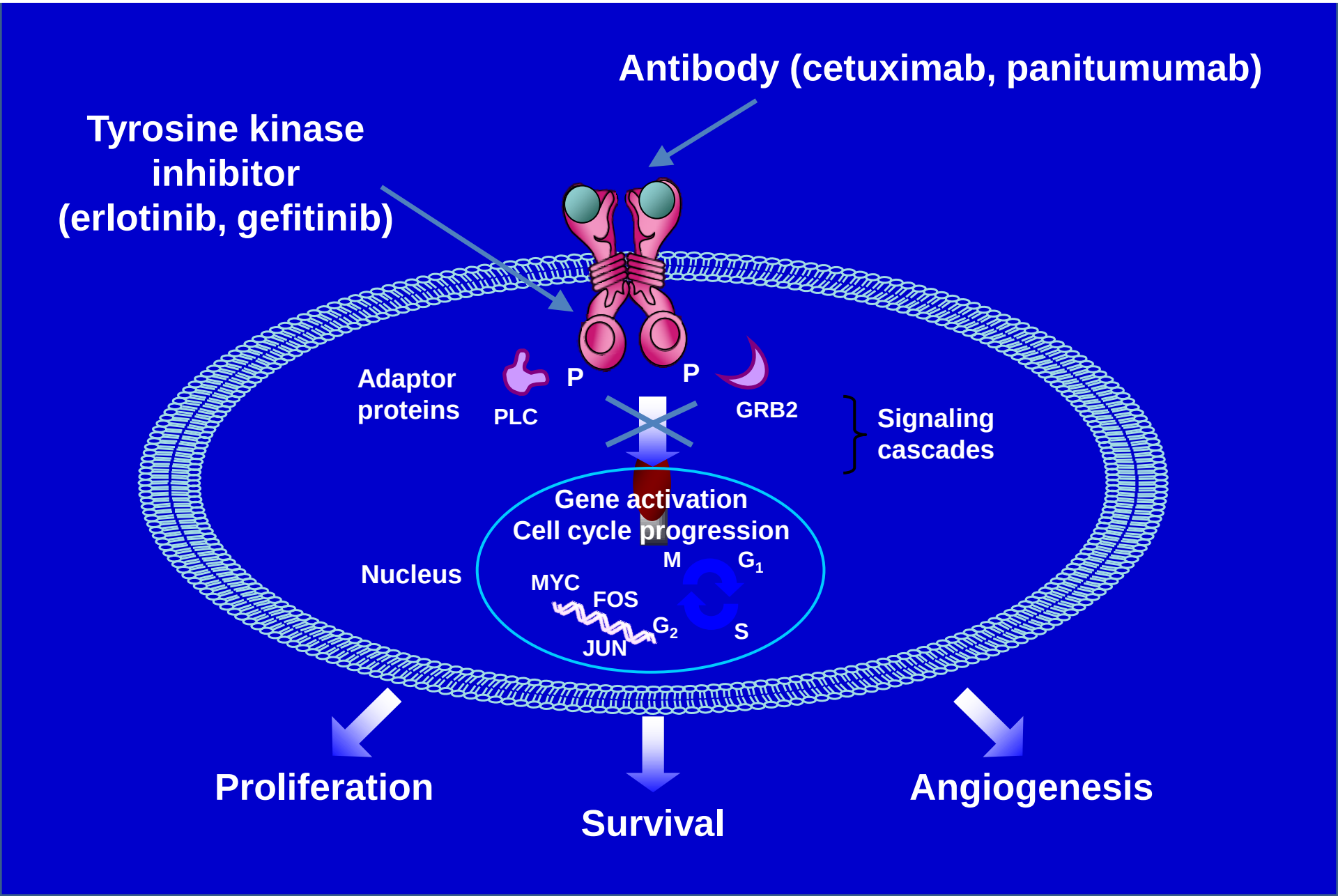
1. Cetuximab therapy is effective in the treatment of several kinds of cancer patients including head and neck cancer (HNC) patients (Ferris JCO 2010, Argiris Lancet 2008).
2. However, the response rate for cetuximab therapy in HNC patients is low (15 ~ 20%) and might be improved as its mechanism of action is elucidated.
3. Cetuximab (human IgG1, chimeric mAb) can induce Ab-dependent cell-mediated cytotoxicity (ADCC) of NK cells and cross-presentation for inducing tumor antigen specific CTL (Lopez-Albaitero et al 2007, Lee et al 2010).

EGFR - Human SCCHN (+ in 80-100%)

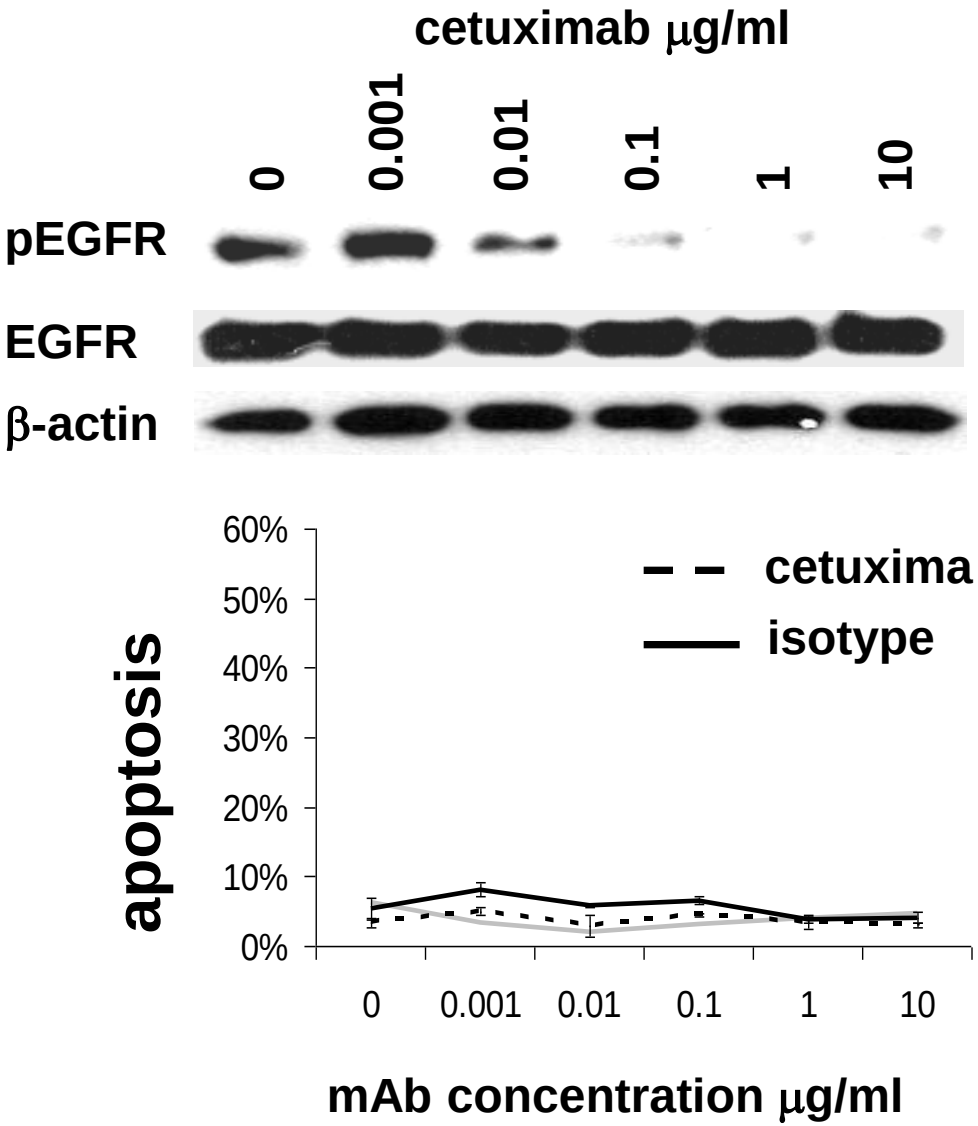


Ang et al. Cancer Research 2002
Grandis, et al. JNCI 1998

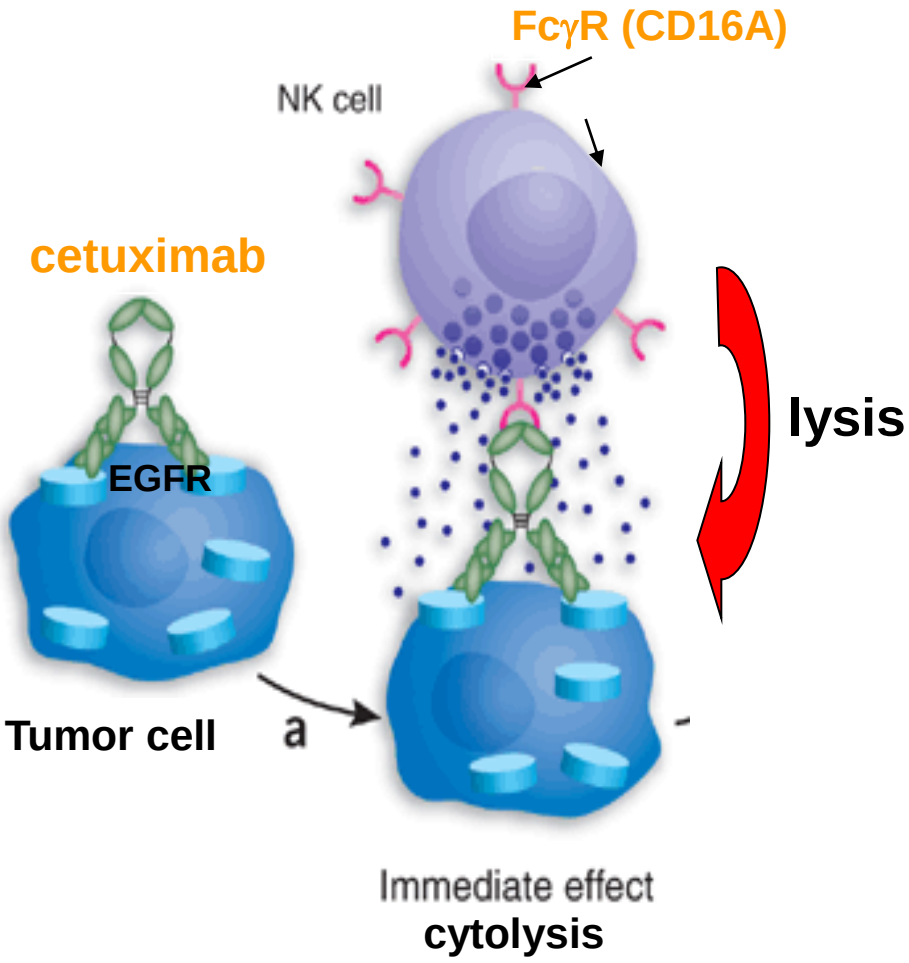
EGFR Inhibition – immune mechanism of action?

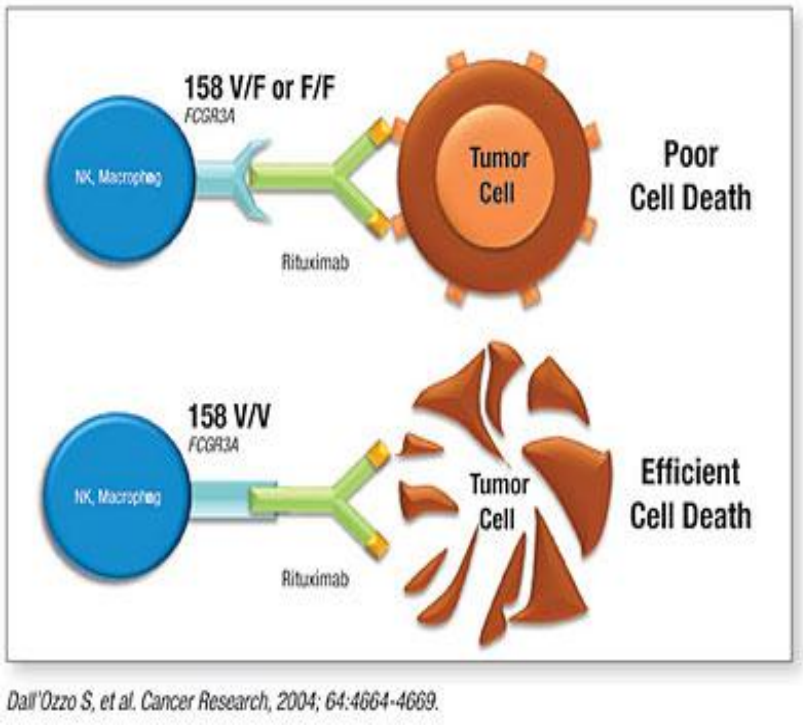


Cetuximab blocks EGFR activation but does not kill HNC cells



Potential immune effect of cetuximab for cancer therapy – explanation for variability in responses

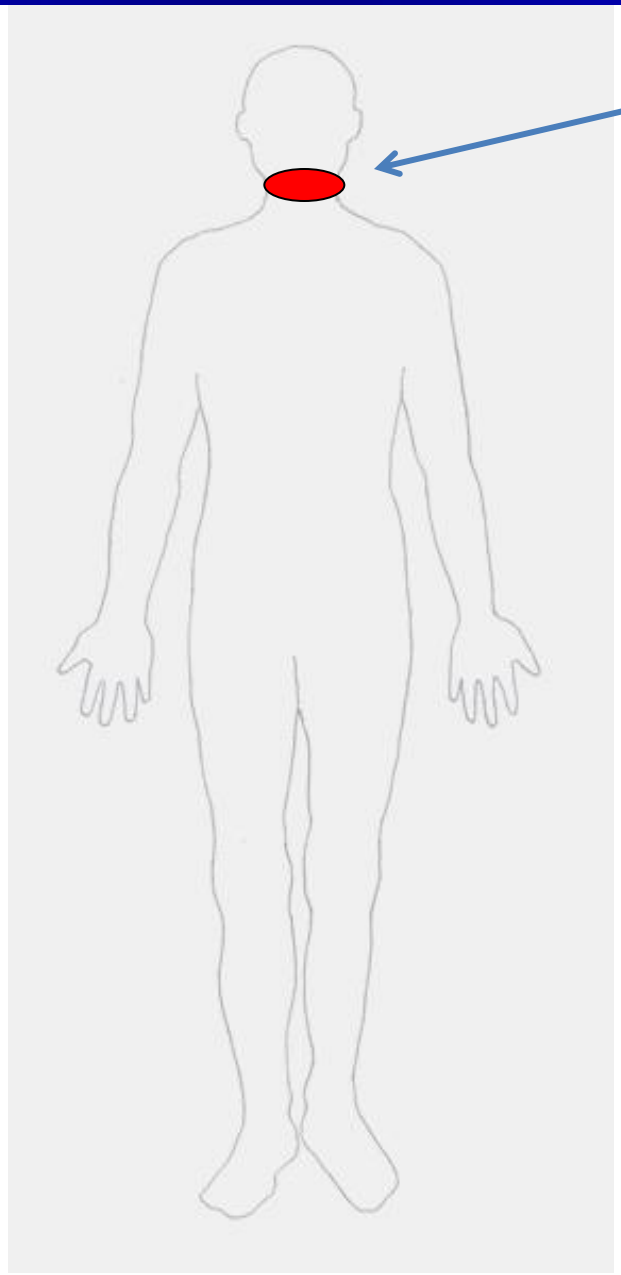




Dall'Ozzo S, et al. Cancer Research, 2004; 64:4664-4669.

Modified from Adams et al *Nature Biotechnology* **23**, 1147 - 1157 (2005)

Tumor antigen-specific antibody therapy

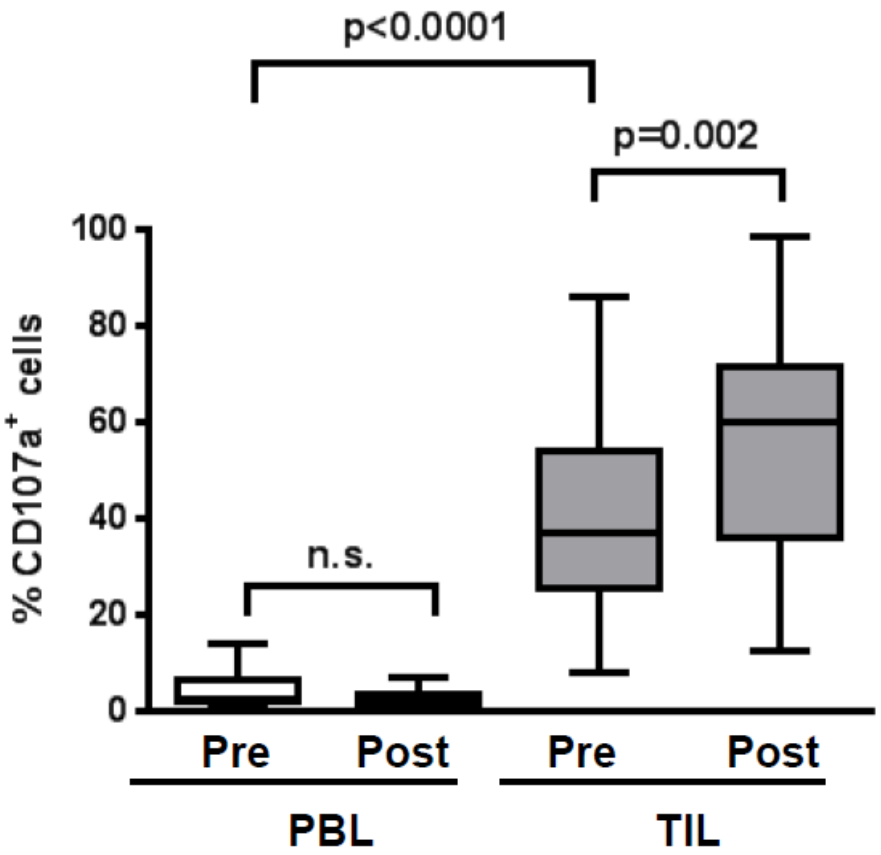


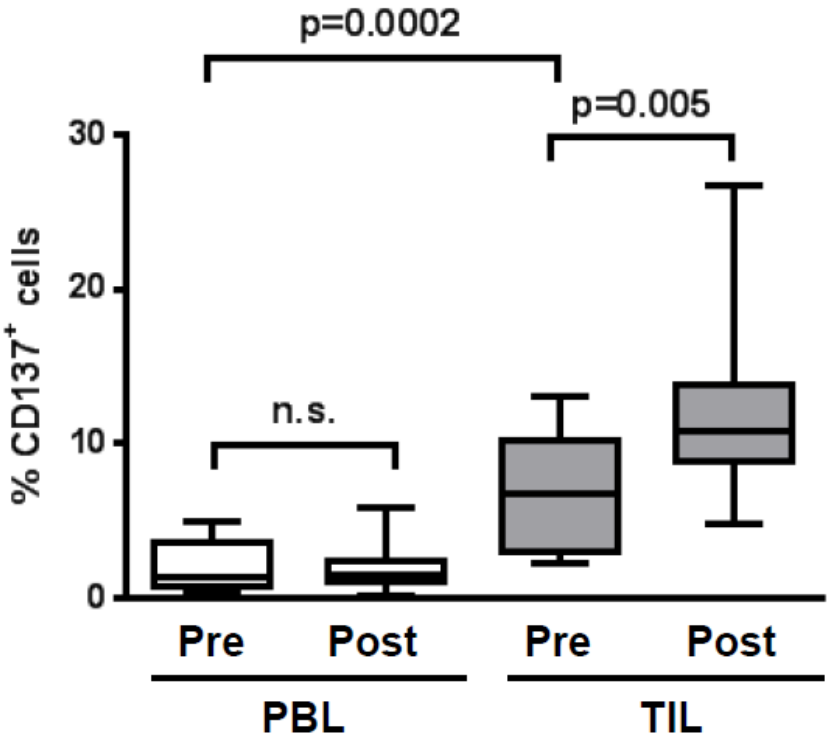
antibody

NK

Intratumoral NK cells are activated by cetuximab therapy

Gated on $CD3^{-}CD56^{hi}$ NK cells

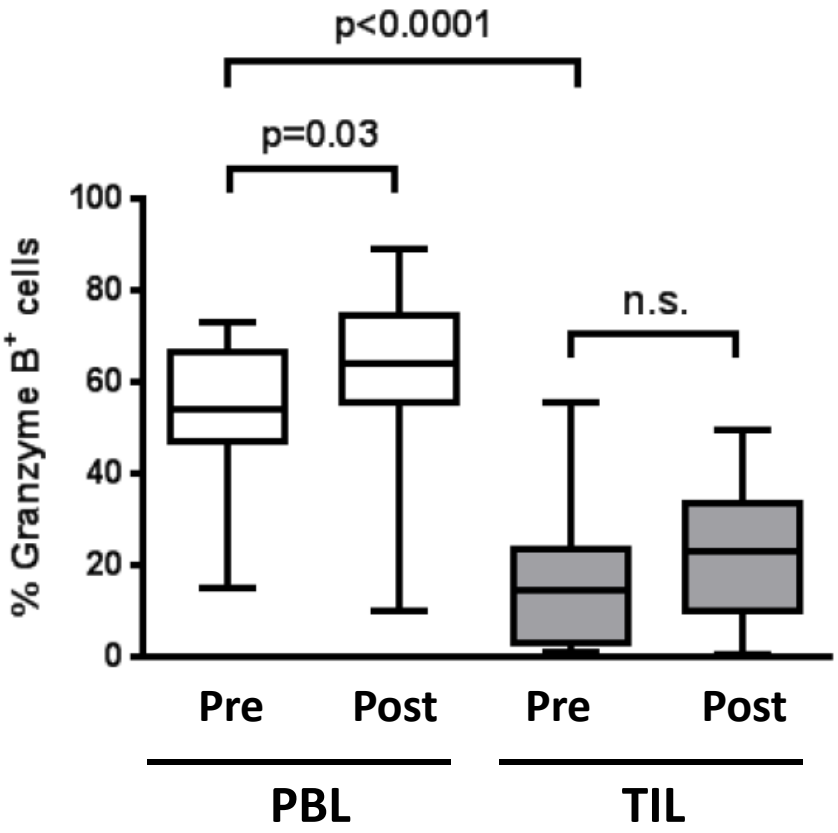


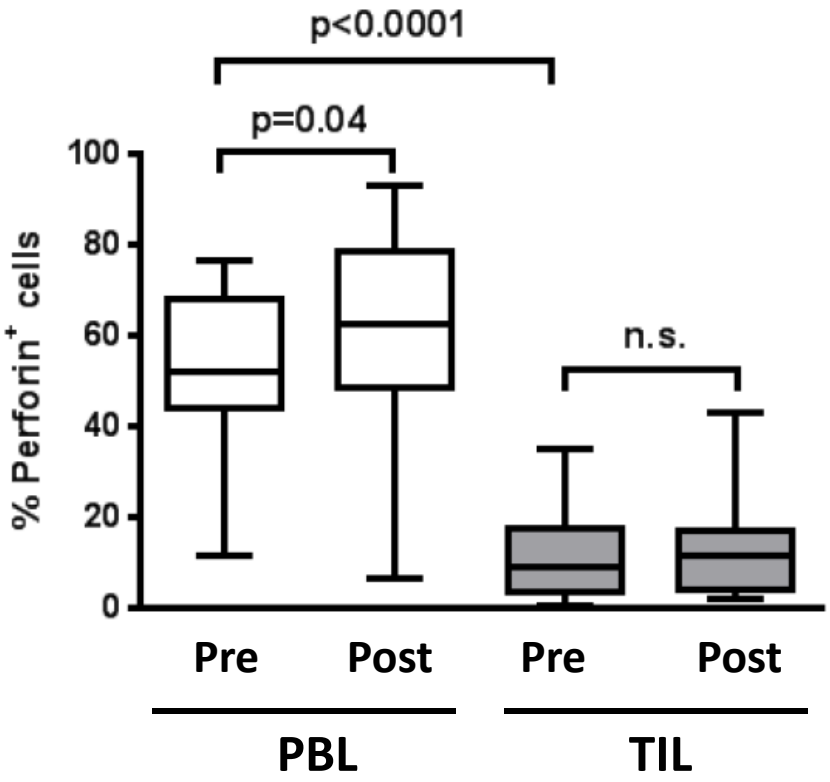


CD107a: degranulation marker, CD137: activation marker, a member of TNF receptor superfamily

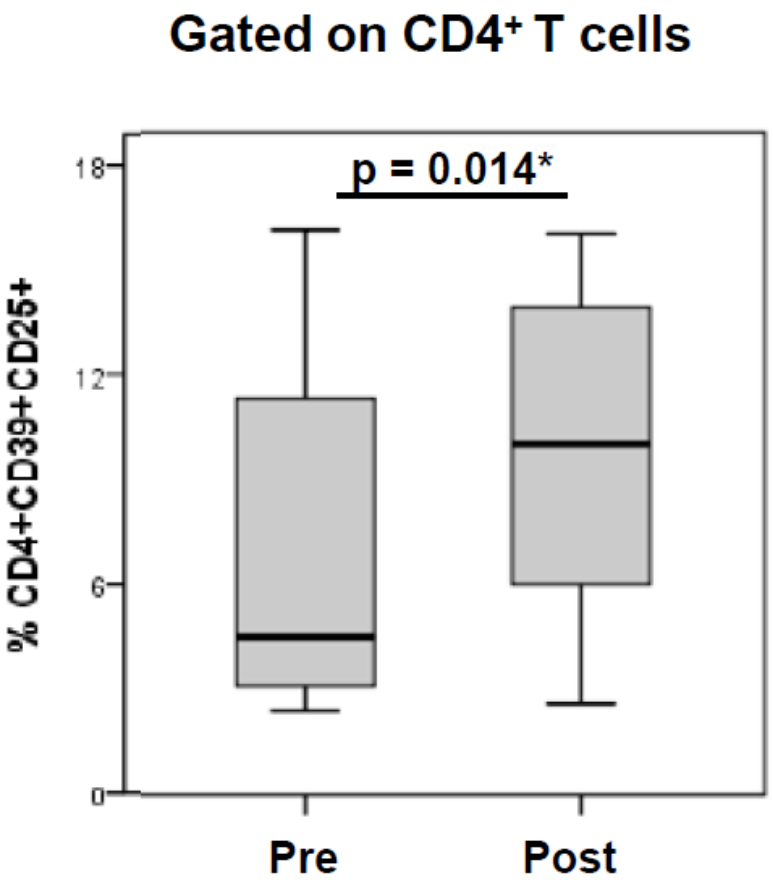
Intratumoral NK cells are significantly impaired for granzyme B and perforin expression

Gated on $CD3^{-}CD56^{hi}$ NK cells

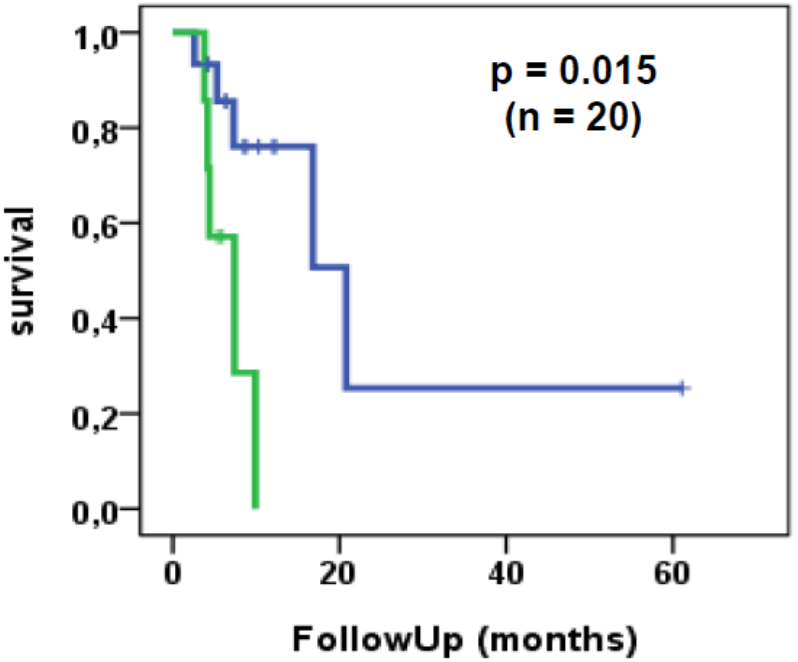




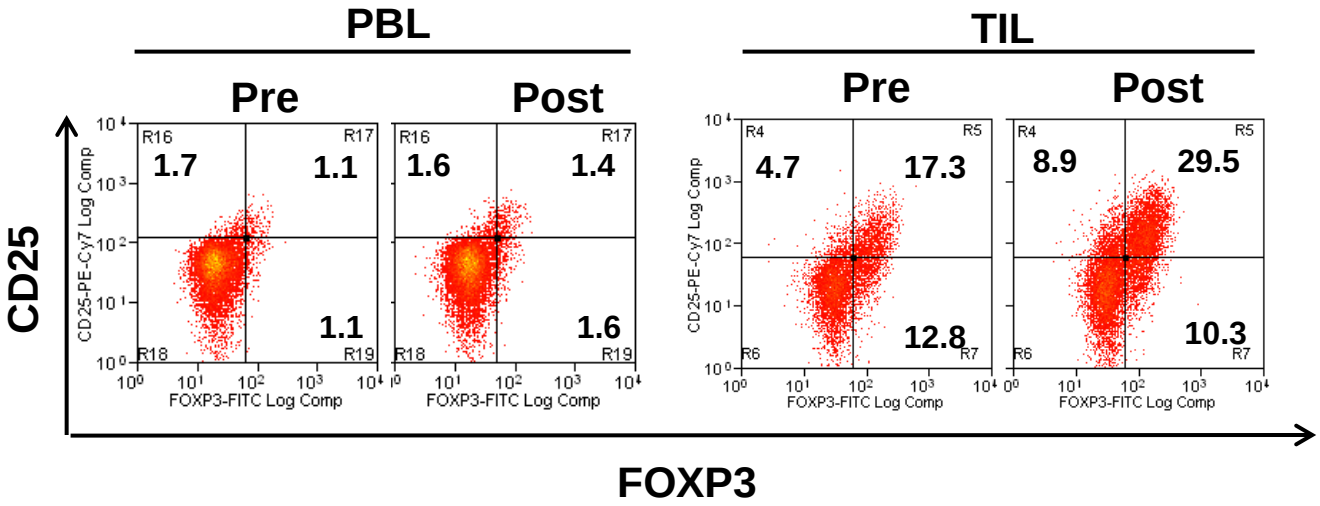
Cetuximab-based therapy increases $CD4^+CD39^+CD25^{hi}$ Treg in HNC patients' peripheral blood and correlated with clinical outcome.

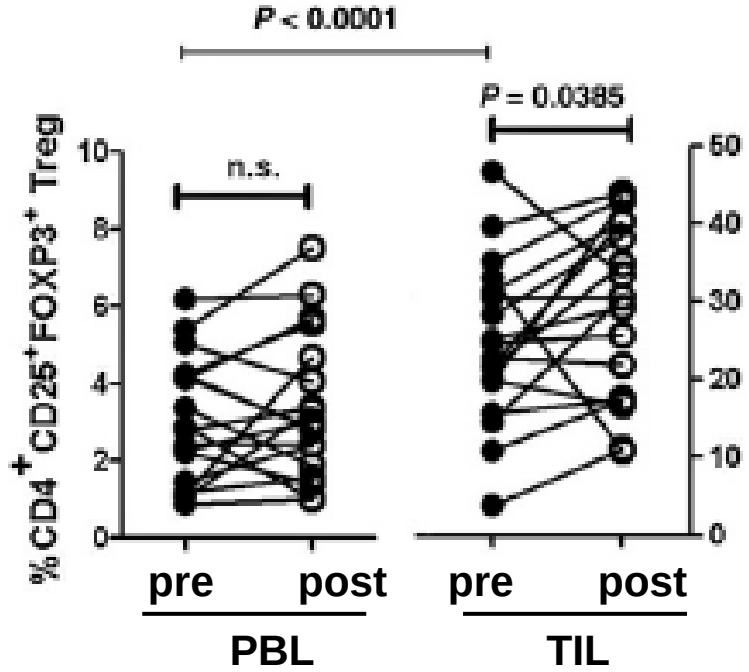


(n=22)

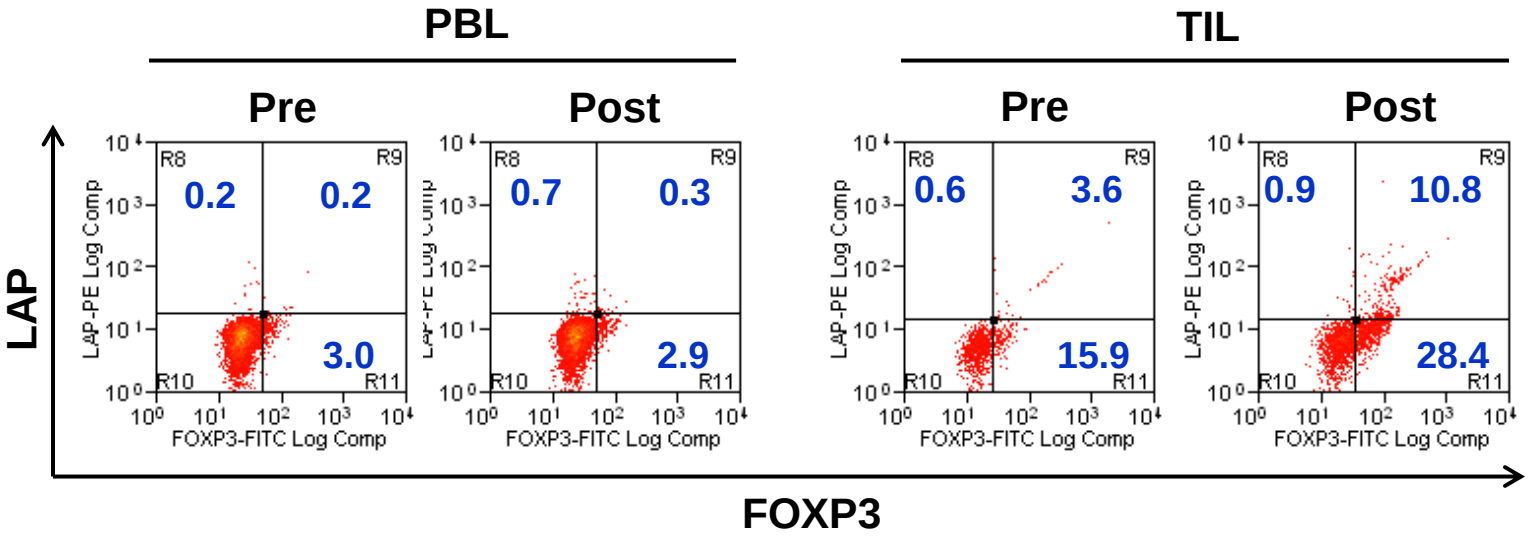


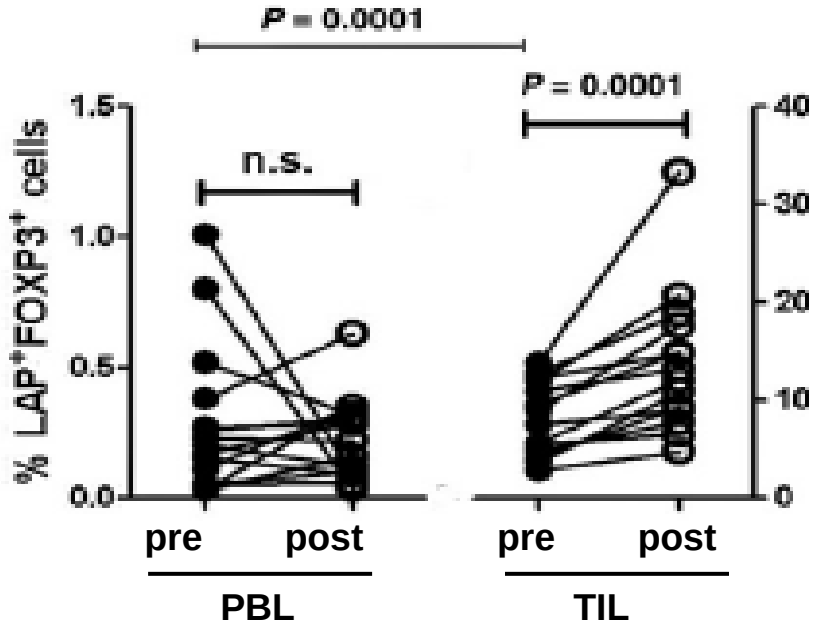
Cetuximab monotherapy increases $CD4^+CD25^+FOXP3^+$ Treg in HNC patients



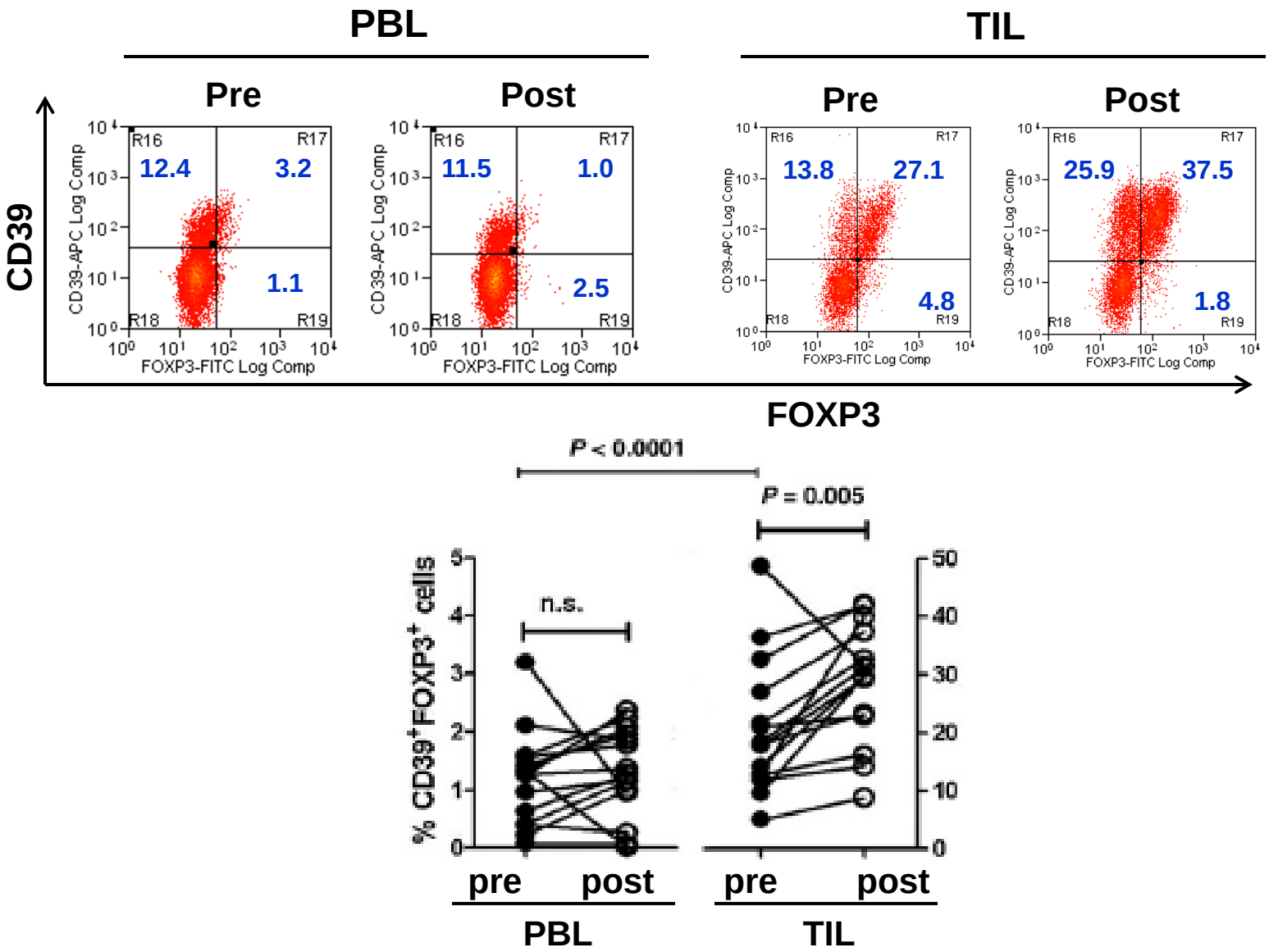


LAP (TGF-β) is upregulated on intratumoral Treg isolated from cetuximab treated HNC patients

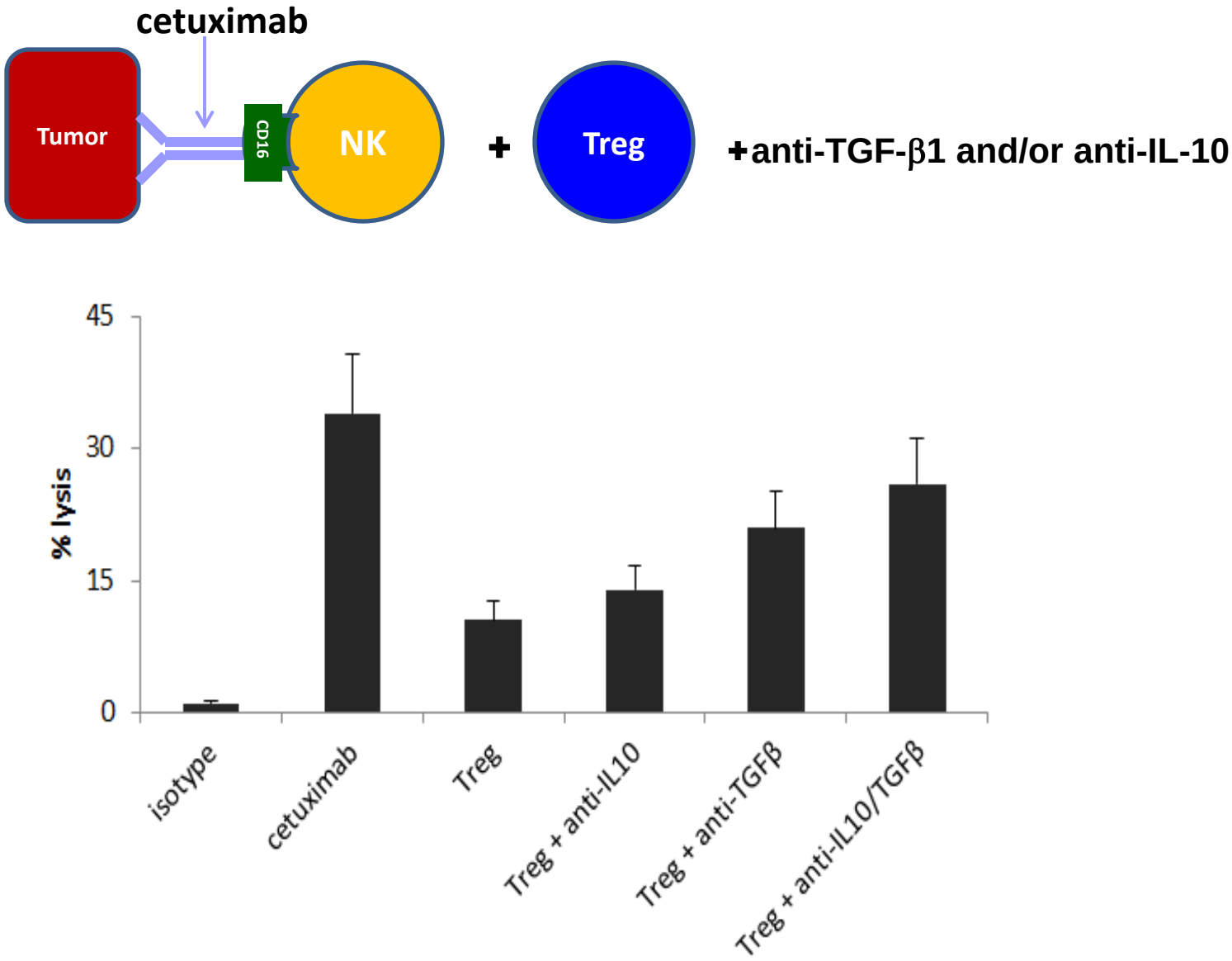




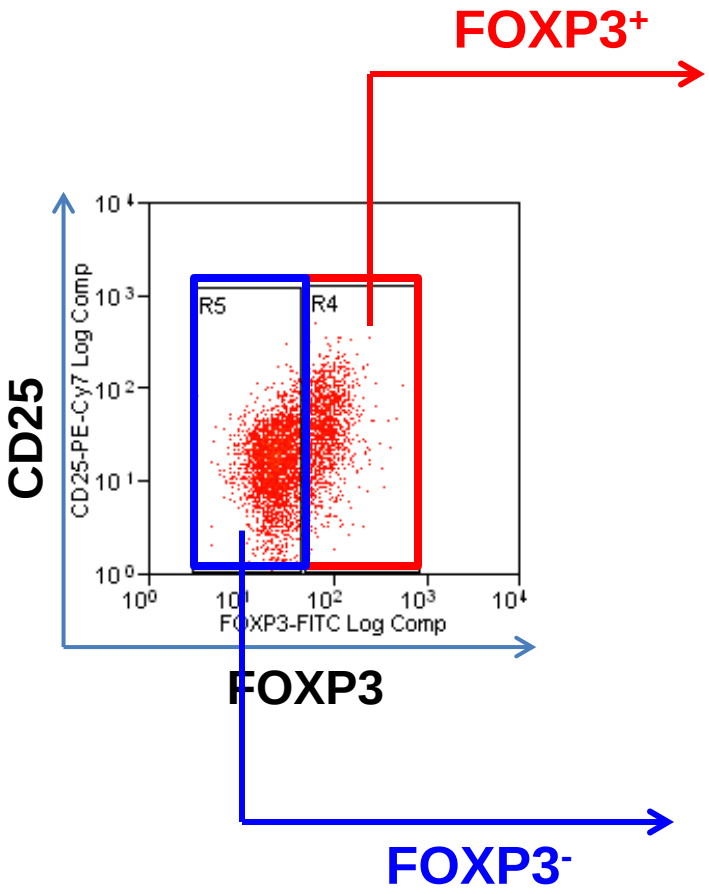
CD39 is upregulated on intratumoral Treg isolated from cetuximab treated HNC patients

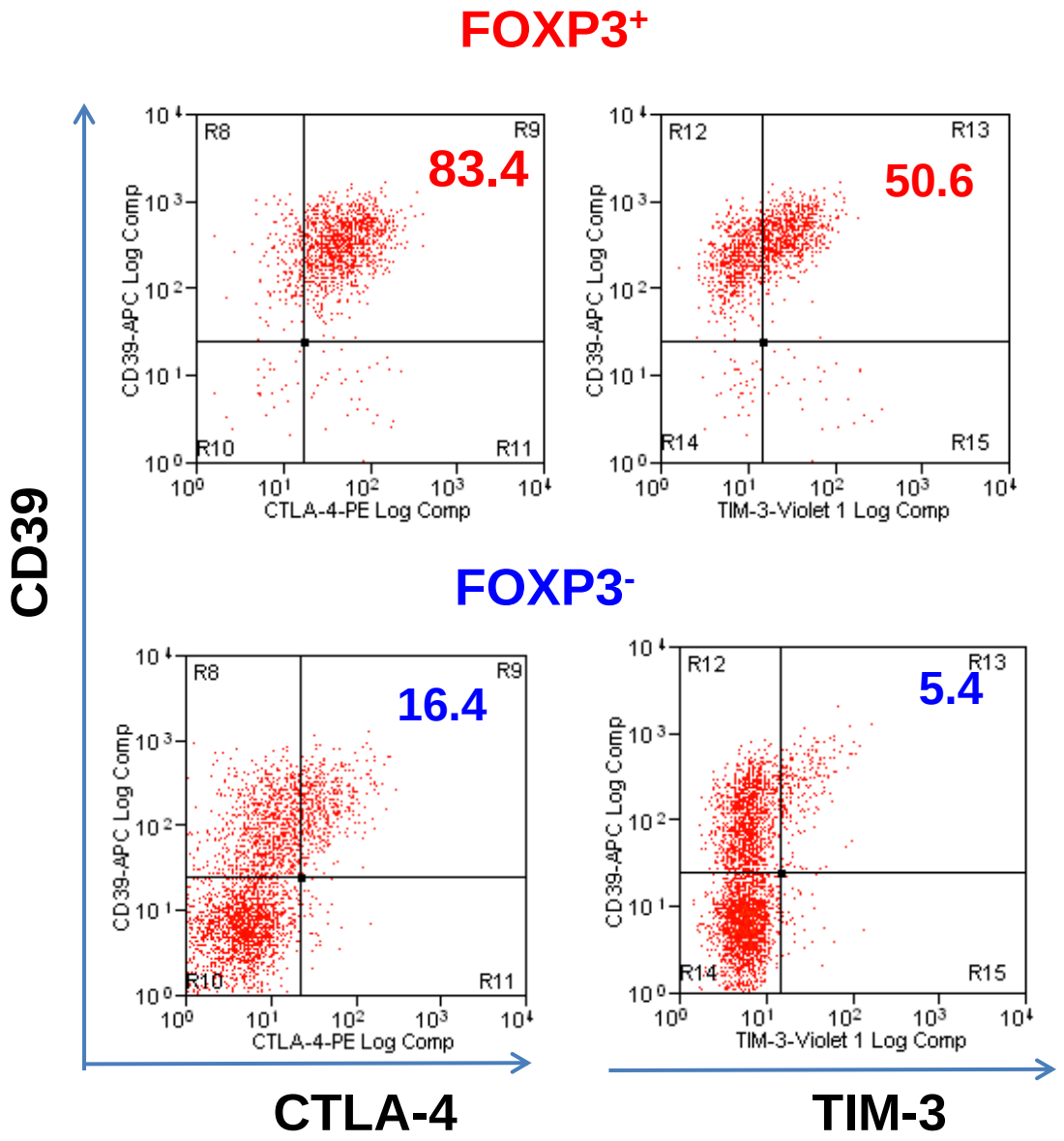


Treg inhibit cetuximab-mediated ADCC mainly by TGF-β1

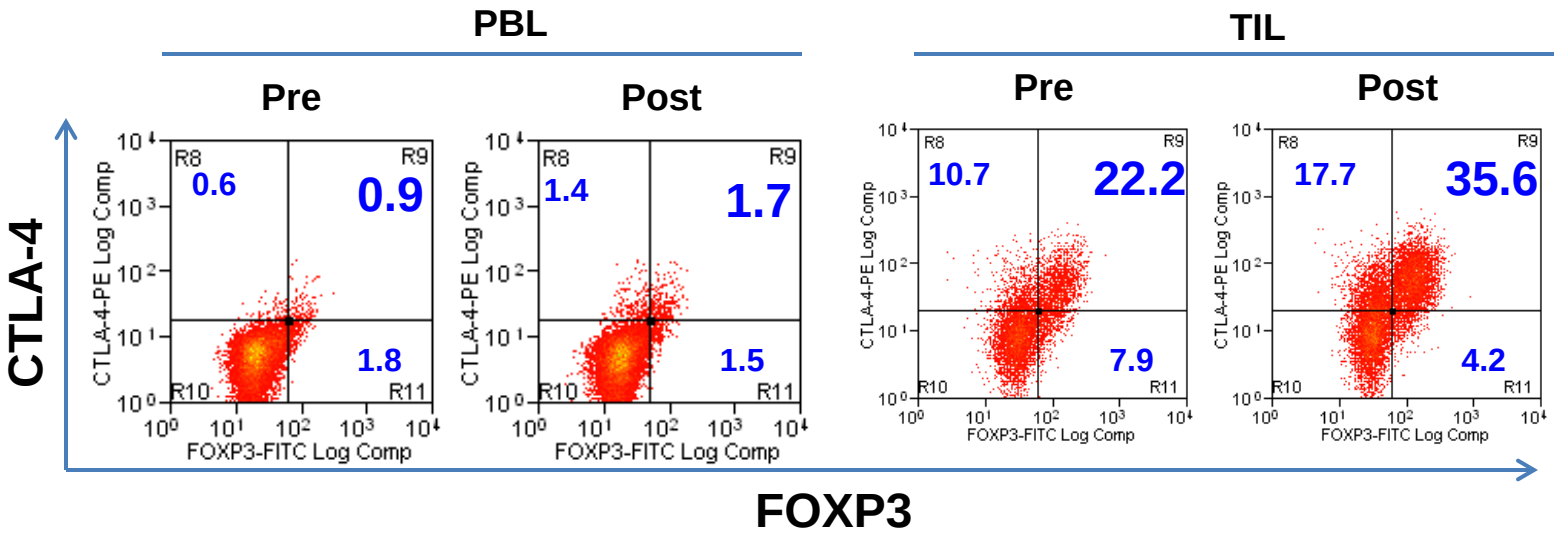


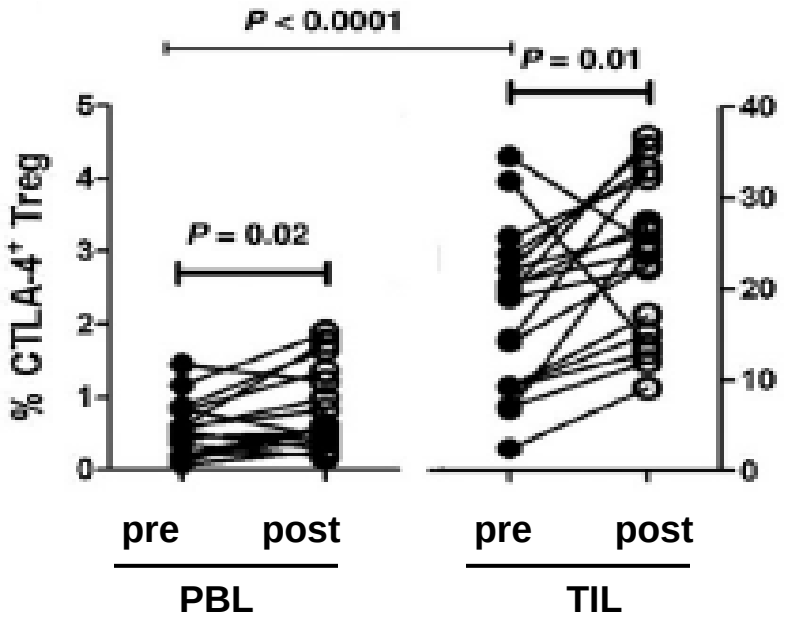
CTLA-4 and CD39 are predominantly expressed on $CD4^{+}FOXP3^{+}$ Treg in the microenvionment





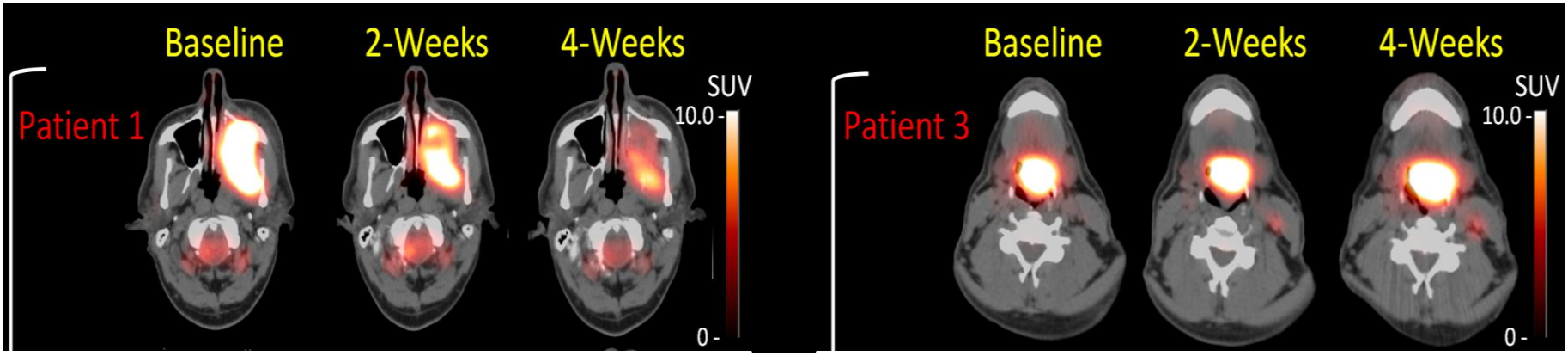
CTLA-4 is upregulated on intratumoral Treg isolated from cetuximab treated HNC patients



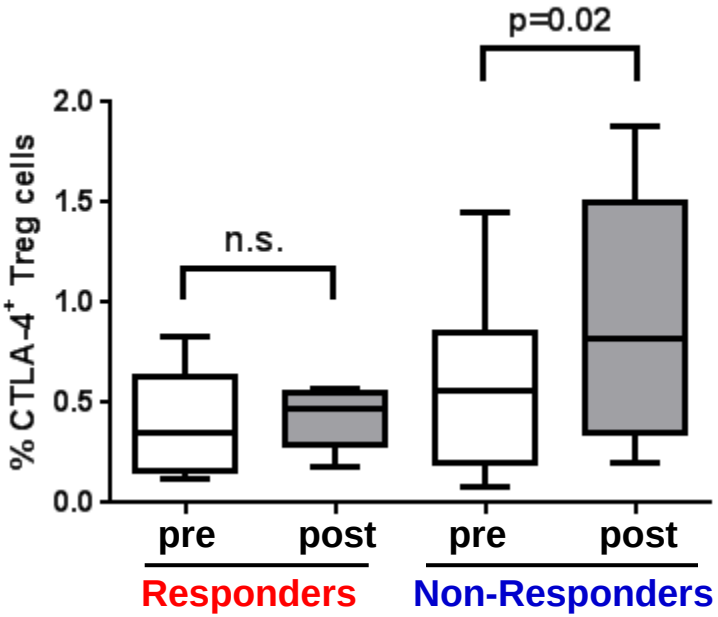


CTLA-4^{+} Treg expansion during cetuximab therapy (responder vs non-responder)

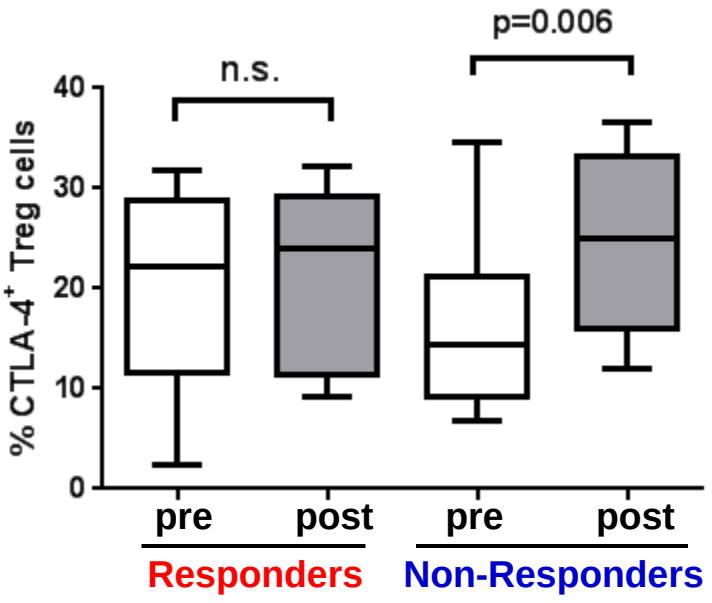
Responder | **Non-responder**



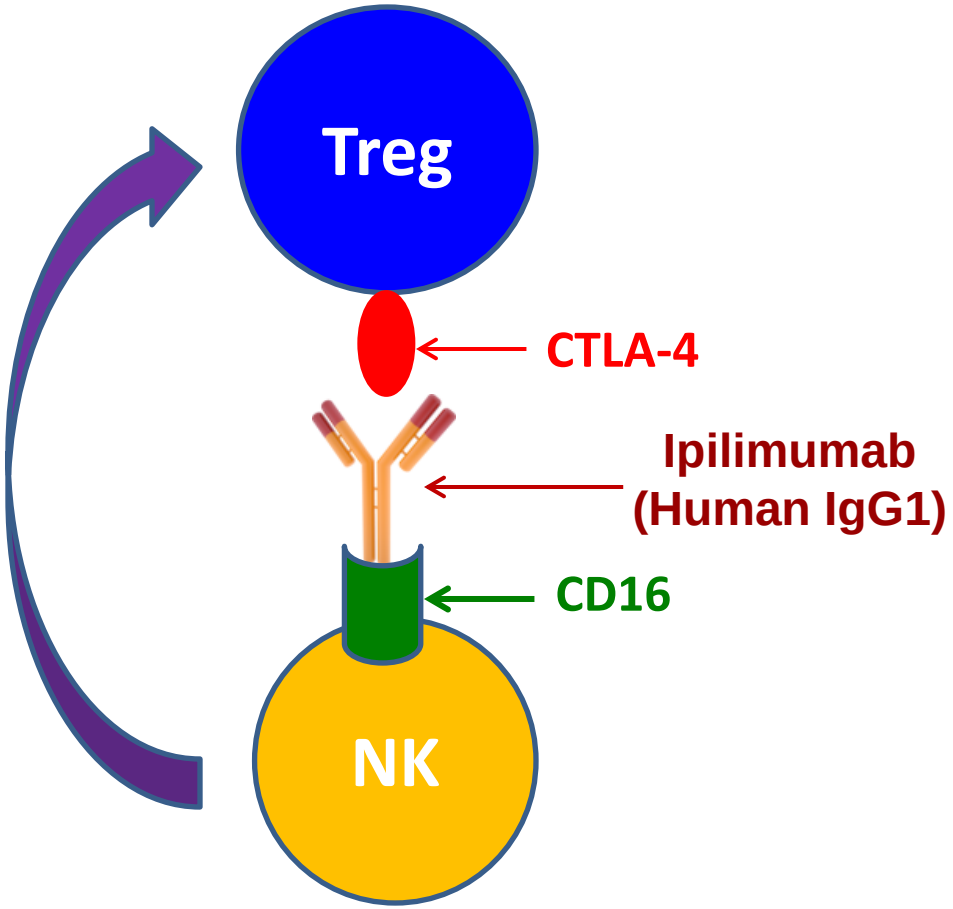
Gated on CD4^{+} PBL



Gated on TIL CD4 $^{+}$ TIL

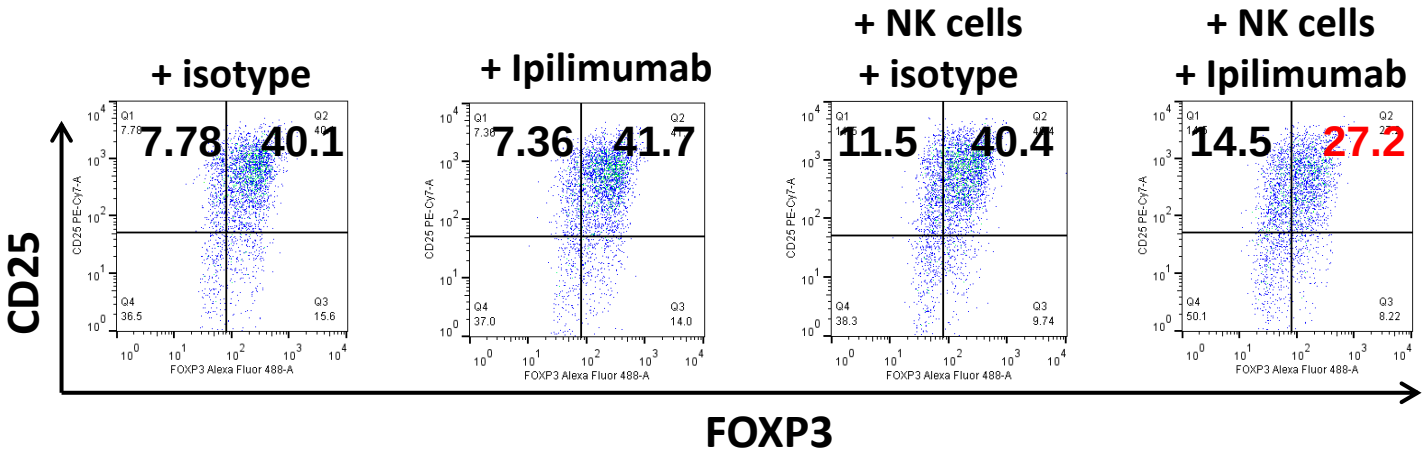


Model: NK cells selectively eliminate intratumoral Treg in the presence of Ipilimumab

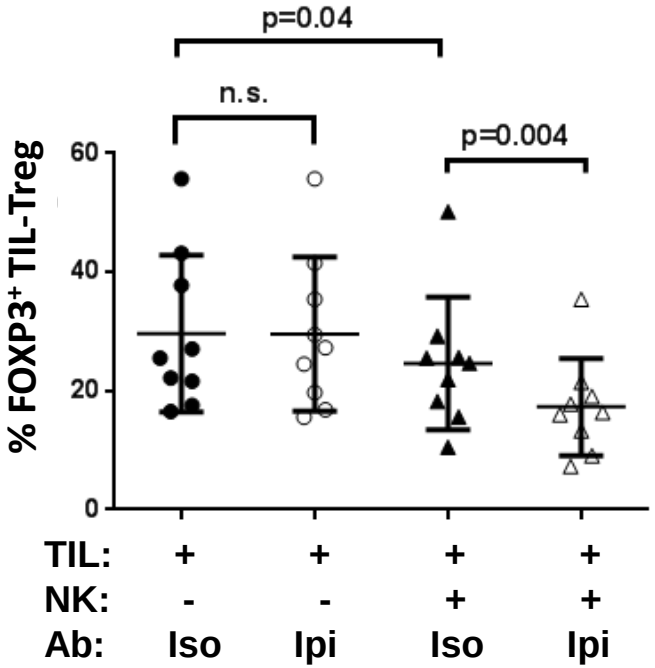


1. *Cancer Immunol Res 2013;1:32-42.*
"Anti-CTLA-4 Antibodies of IgG2a Isotype Enhance Antitumor Activity through Reduction of Intratumoral Regulatory T Cells"
2. J Exp Med. 2013 Aug 26;210(9):1685-93.
"Activating Fc γ receptors contribute to the antitumor activities of immunoregulatory receptor- targeting antibodies."
3. J Exp Med. 2013 Aug 26;210(9):1695-710.
"Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma."

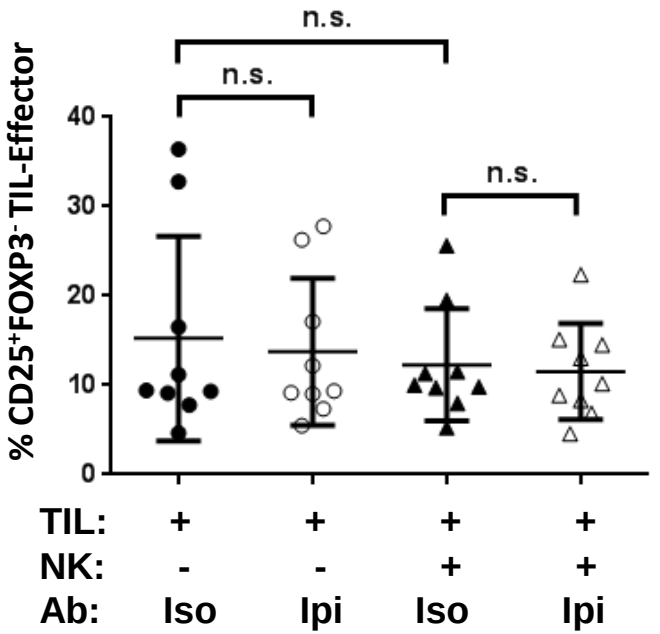
NK cells selectively eliminate intratumoral Treg in the presence of Ipilimumab



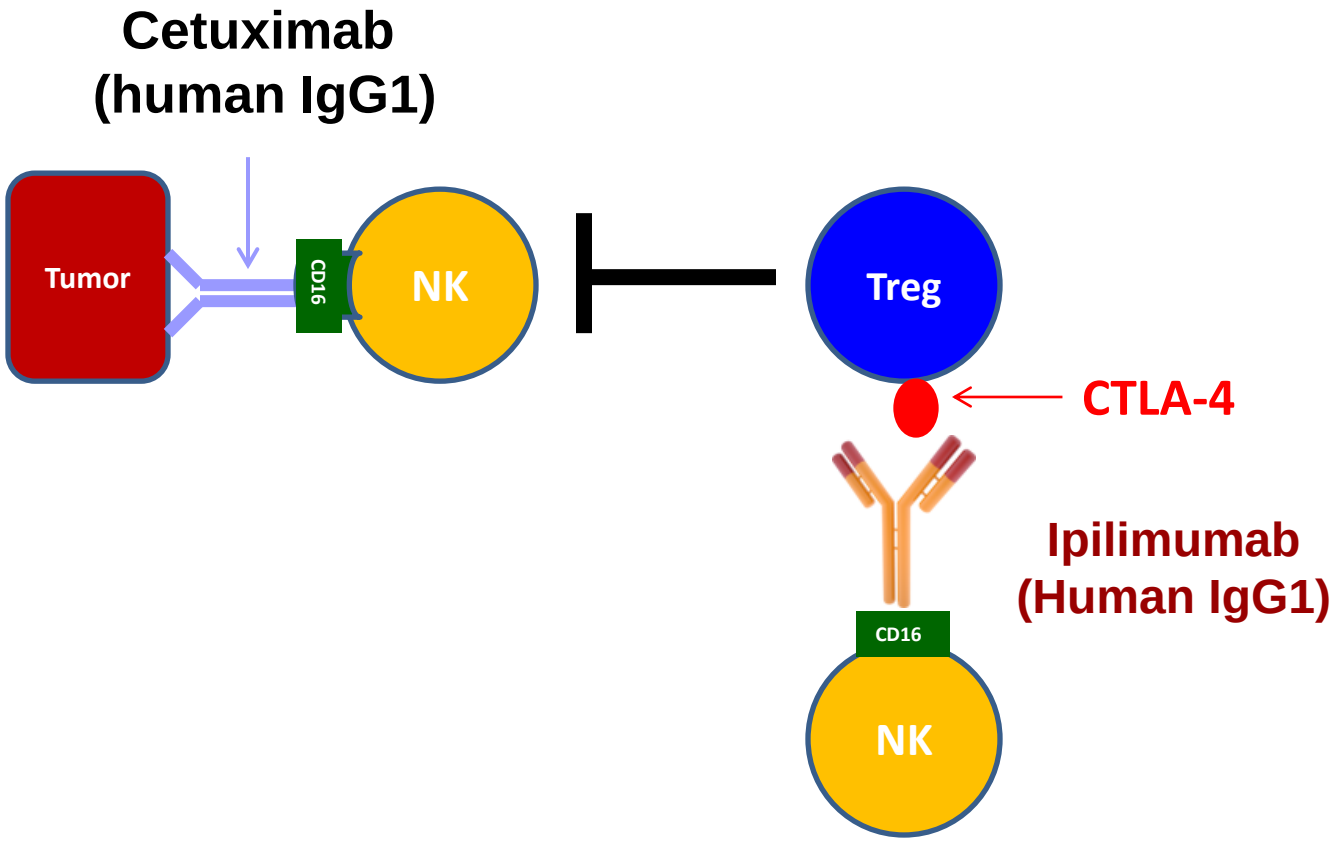
Gated on CD25⁺FOXP3⁺ cells



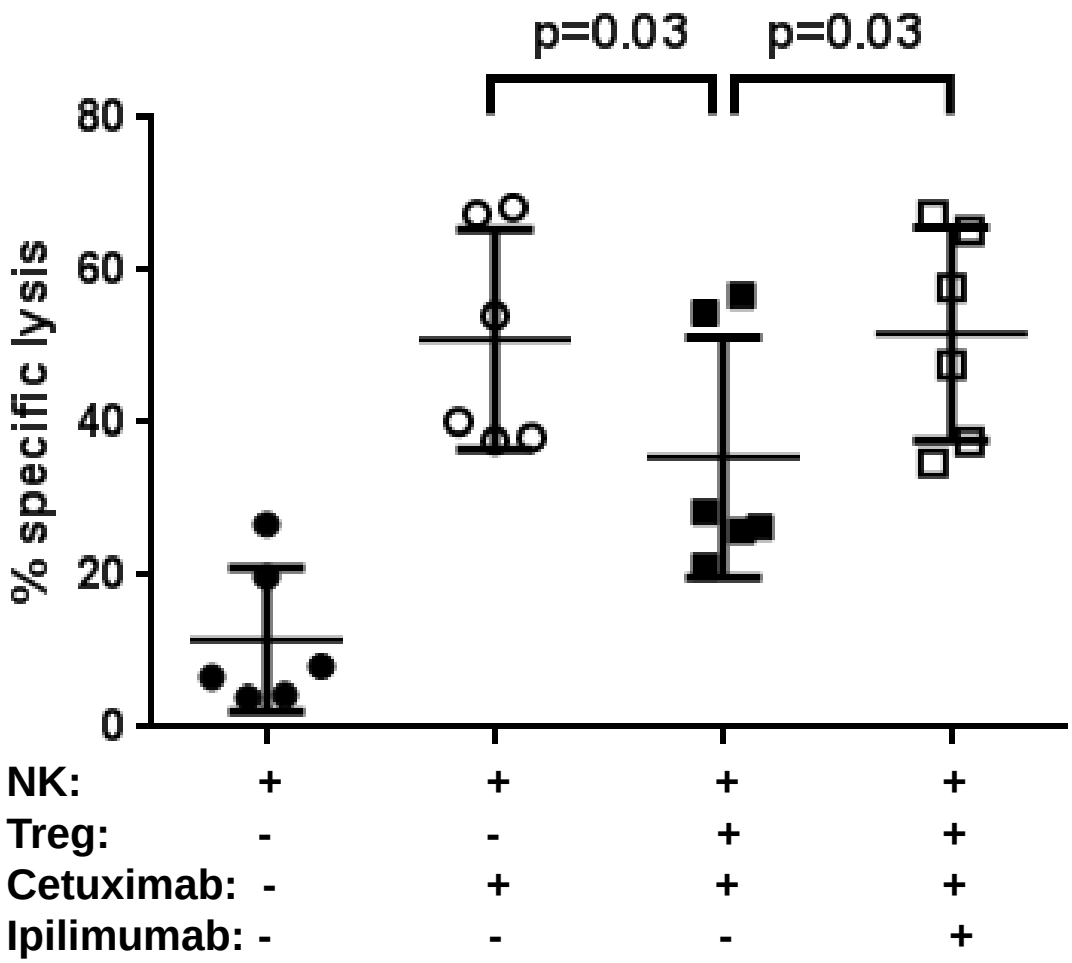
Gated on CD25⁺FOXP3⁻ cells



Model: Ipilimumab enhances cetuximab-mediated ADCC by eliminating Treg

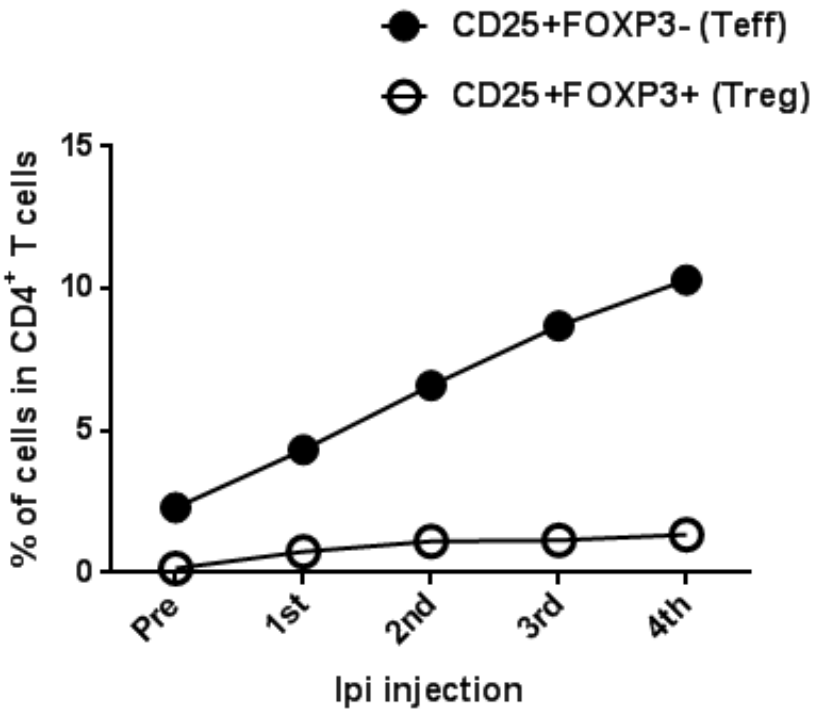


Ipilimumab enhances cetuximab-mediated ADCC by eliminating Treg

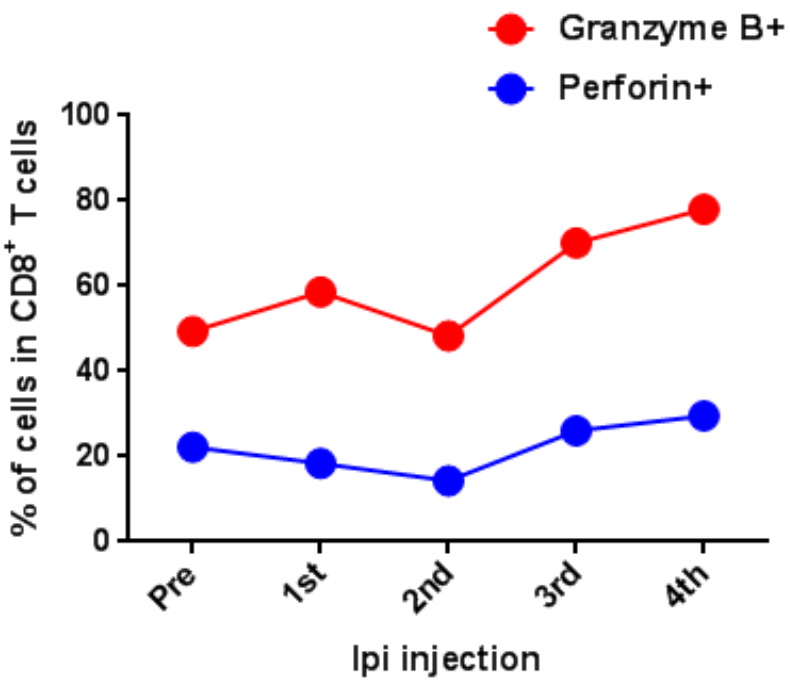


Combination therapy using cetuximab and ipilimumab clinical trial

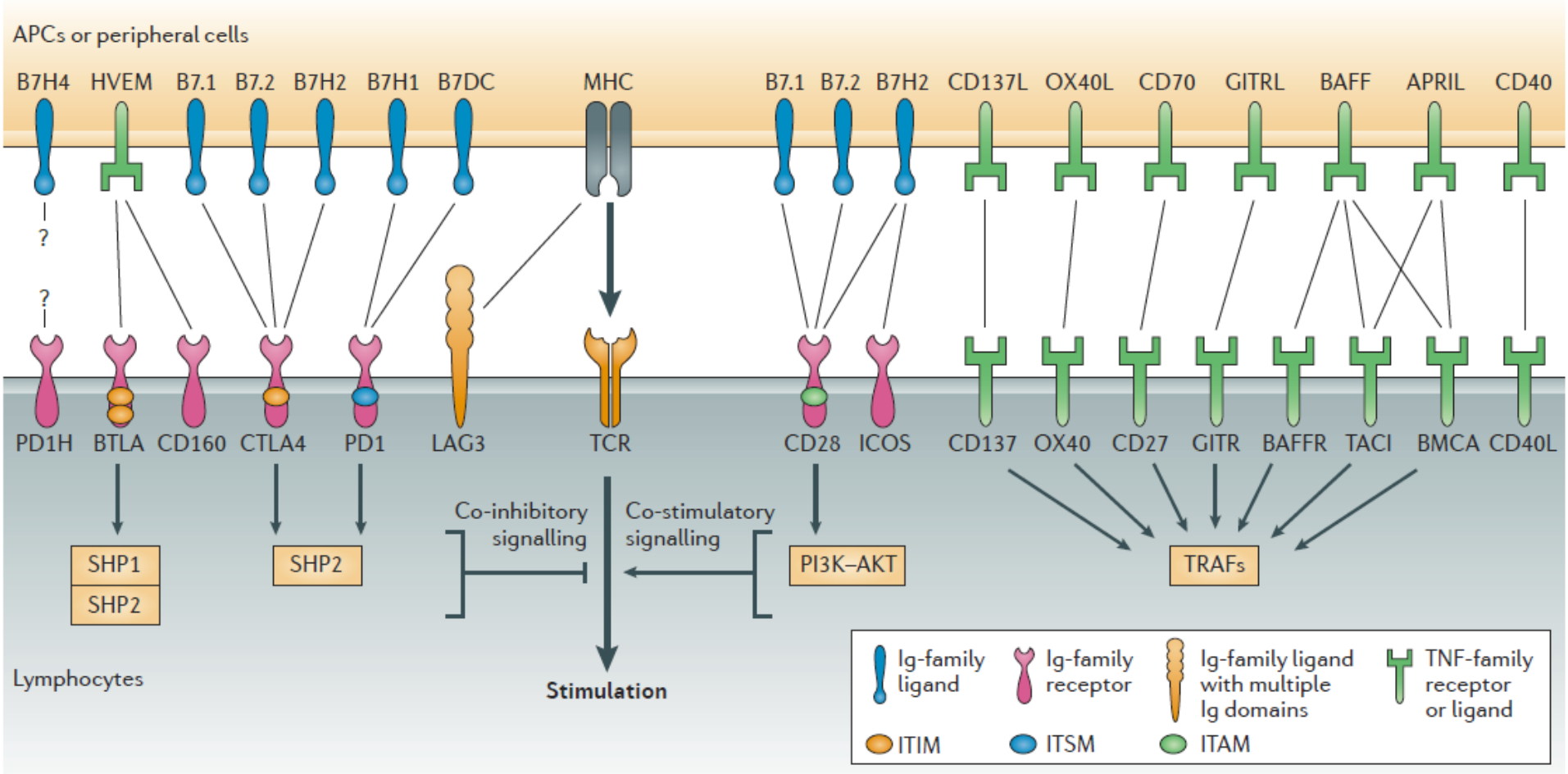
Gated on CD4$^+$ T cells



Gated on CD8$^+$ T cells



Immune checkpoint receptors & TNF receptor superfamily

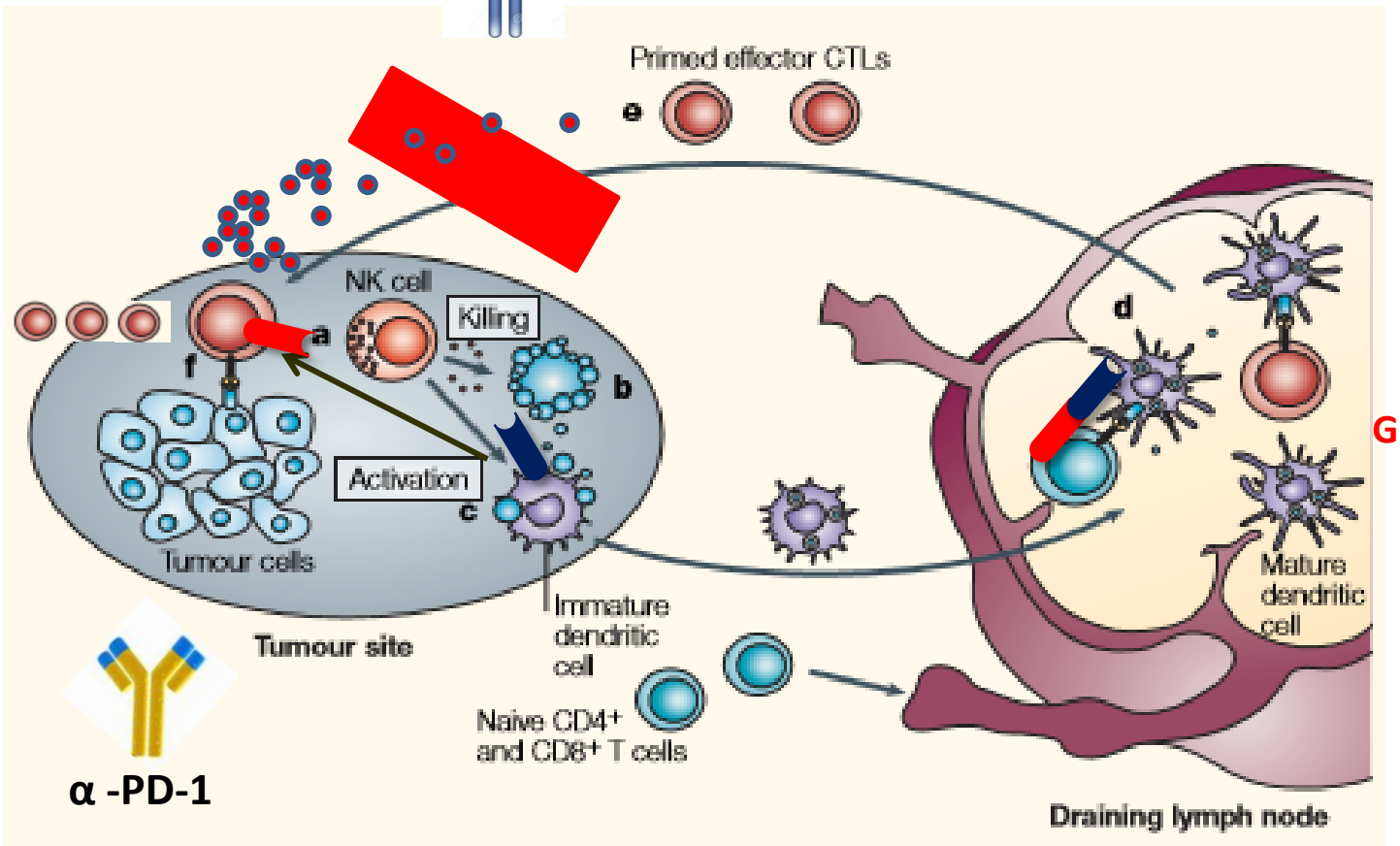


Nature Reviews of Drug Discovery (2013, 12:130)

Immune checkpoint receptors & TNF receptor superfamily

J.I. 2010, 185:7133, Frey AB et al.
Science,2015, 348:56, Allison jp et al.
NRD, 2013, 12:130, Chen l et al.

α -TIGIT



α -PD-1

α-CTLA-4

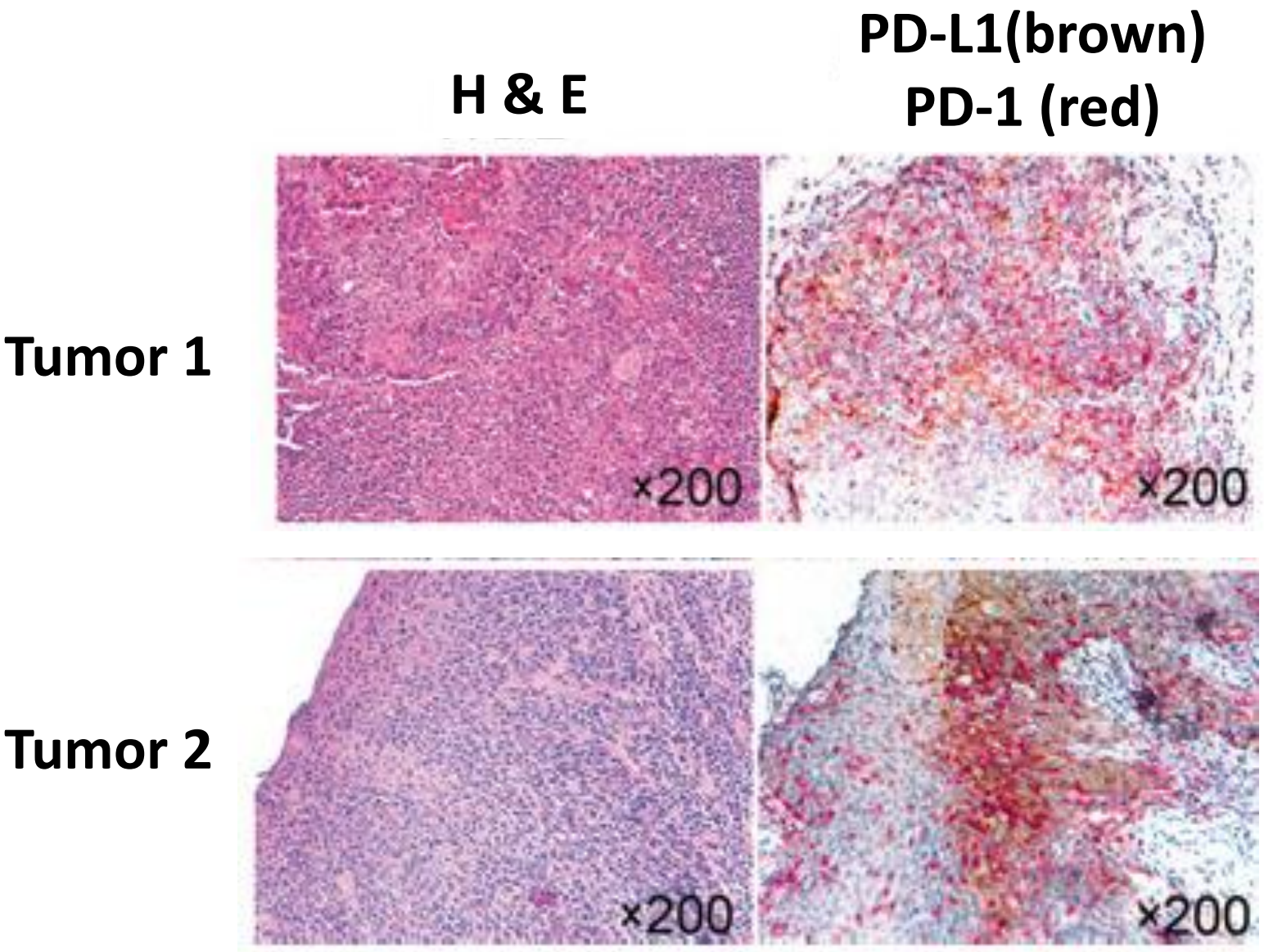
GranzymesB and Perforin

Cell survival
(Effector & memory)

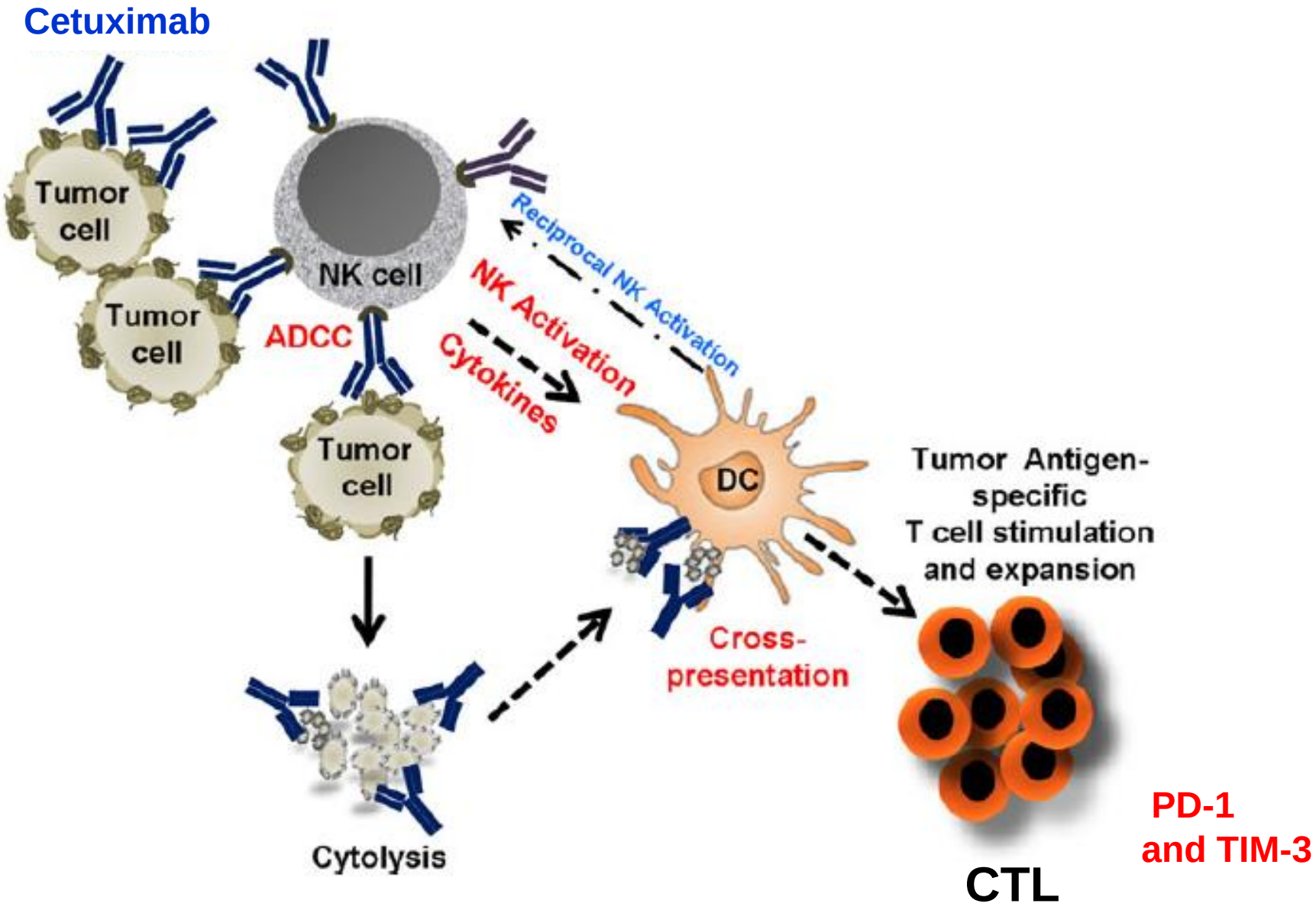
Tumor infiltration
(Cell migration)

TNFRS TNFRS-L

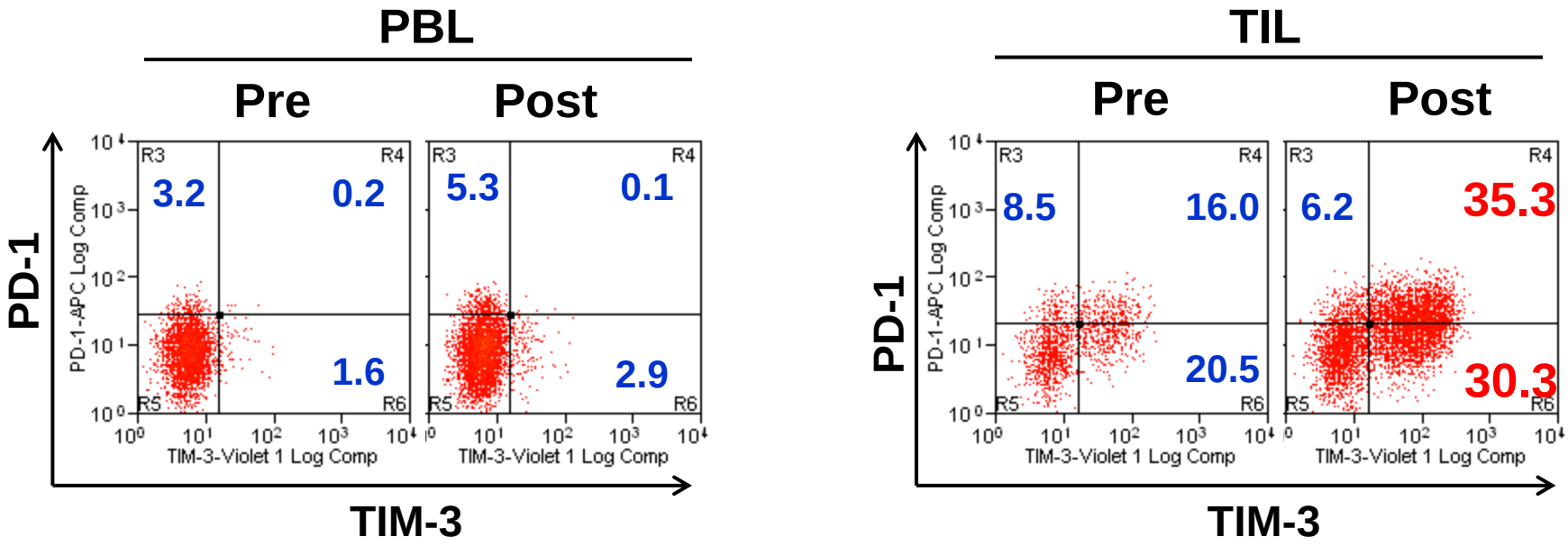
PD-1^{+} TILs colocalize with PD-L1^{+} HNSCC cells in the tumor microenvironment.



CTL responses induced by cetuximab treatment



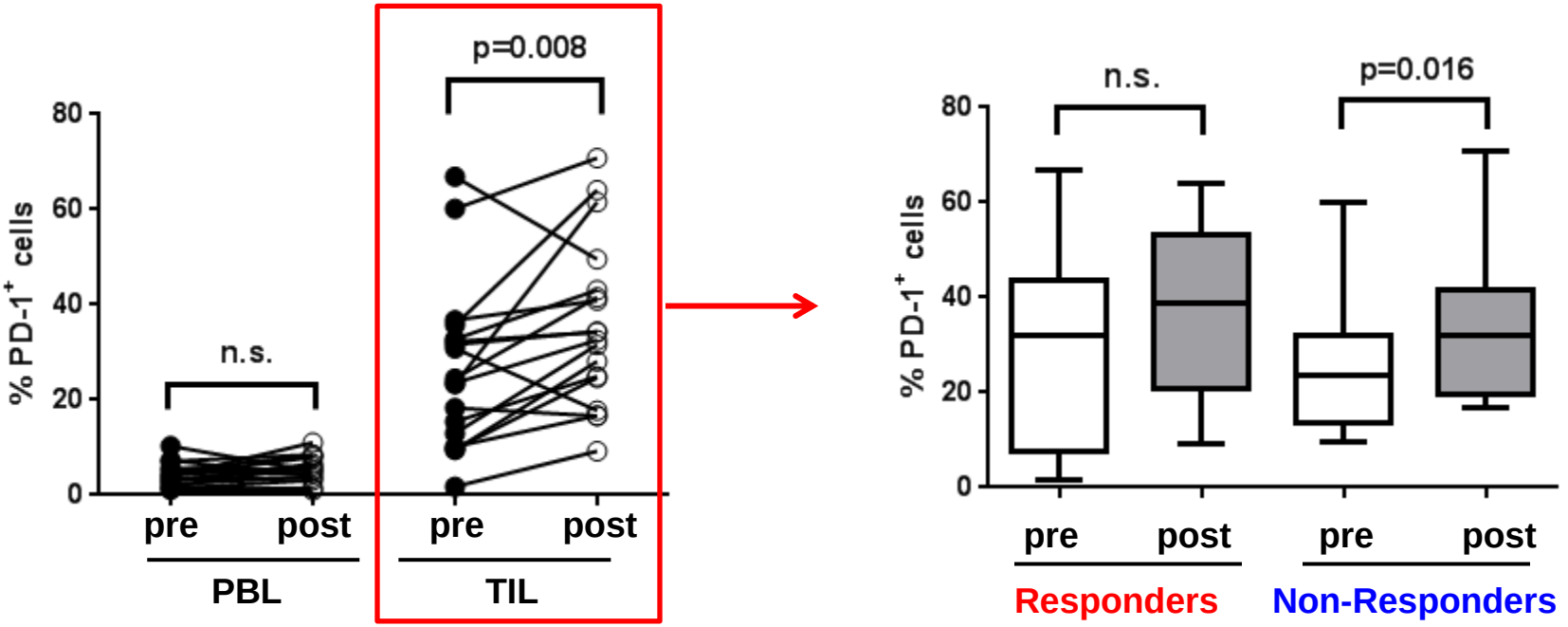
Cetuximab therapy upregulates PD-1and TIM-3 only on intratumoral CTL



PD-1 expression on CD8 + T cells during cetuximab therapy (responder vs non-responder)

Gated on CD8 + T cells

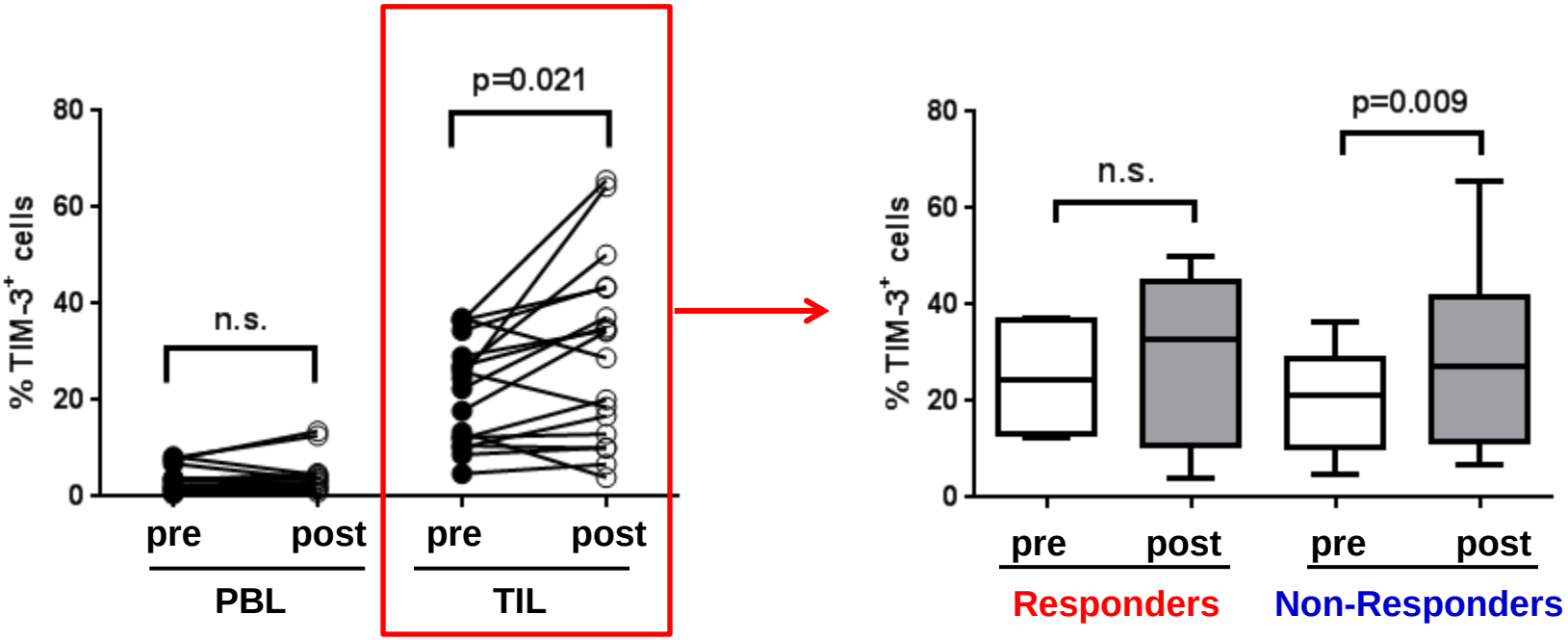
Gated on CD8 + TIL only



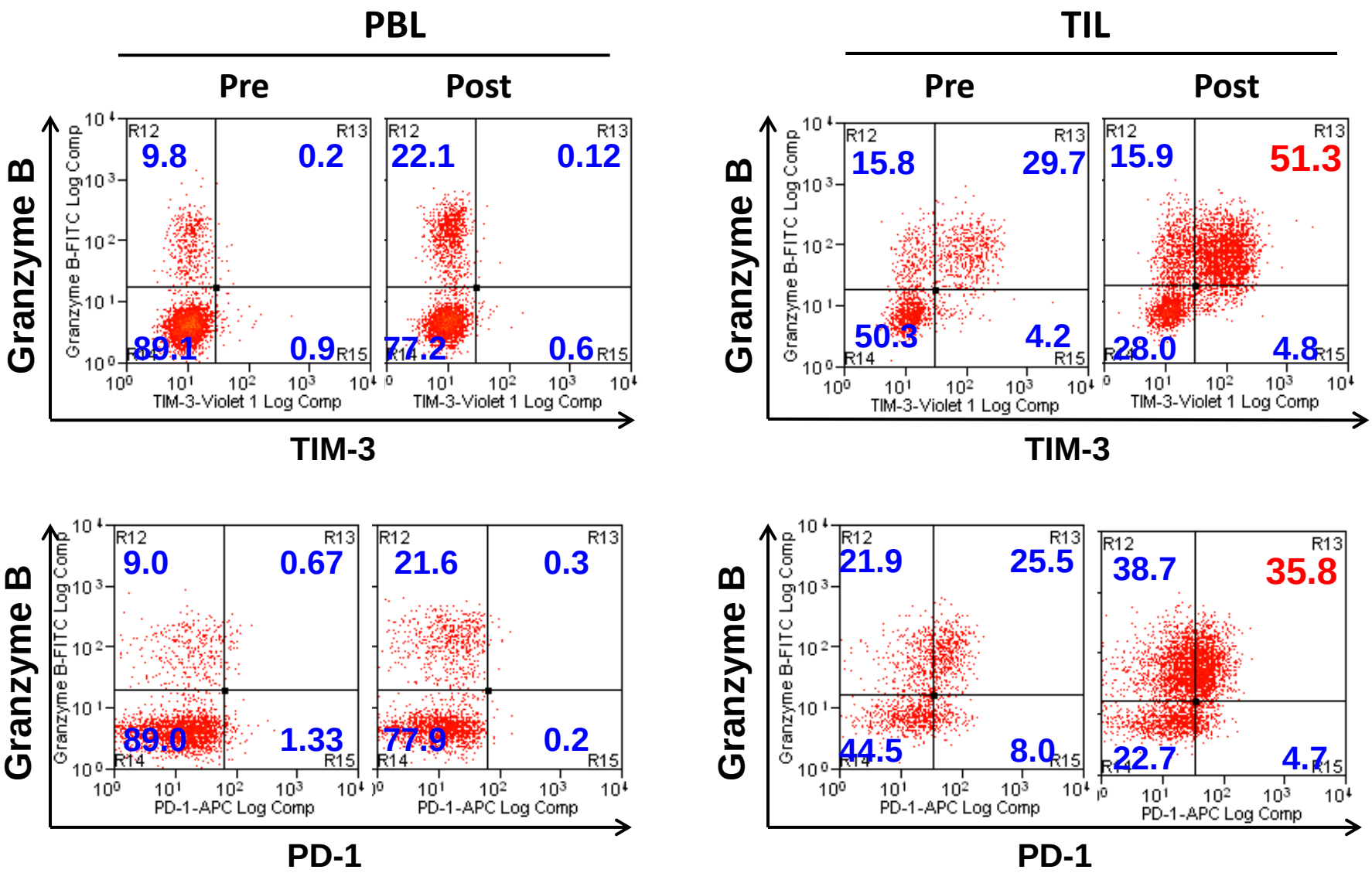
TIM-3 expression on CD8 + T cells during cetuximab therapy (responder vs non-responder)

Gated on CD8 + T cells

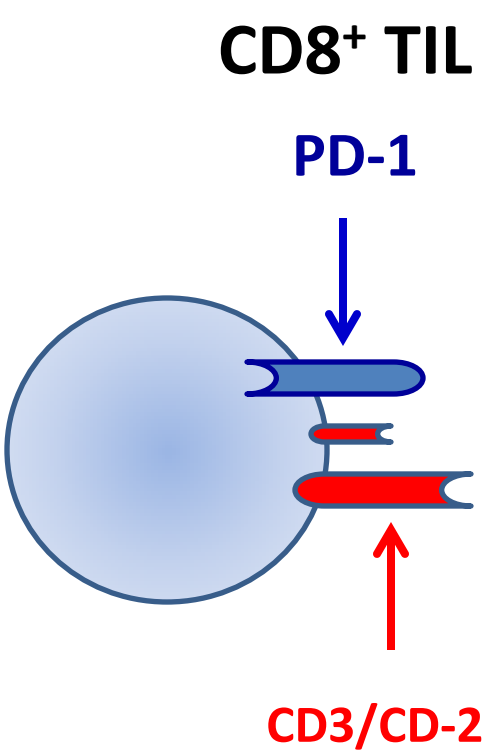
Gated on CD8 + TIL only



Granzyme B and PD-1/TIM-3 are co-expressed on CD8$^+$ T cells during cetuximab therapy



The effect of PD-1 blockade on TCR signaling and cytokine production in tumor infiltrating lymphocytes



1) anti-CD3/28 + IgG1 + IgG4

2) anti-CD3/28 + IgG1 + anti-PD-1

3) anti-CD3/28 + PD-L1 + IgG4

4) anti-CD3/28 + PD-L1 + anti-PD-1

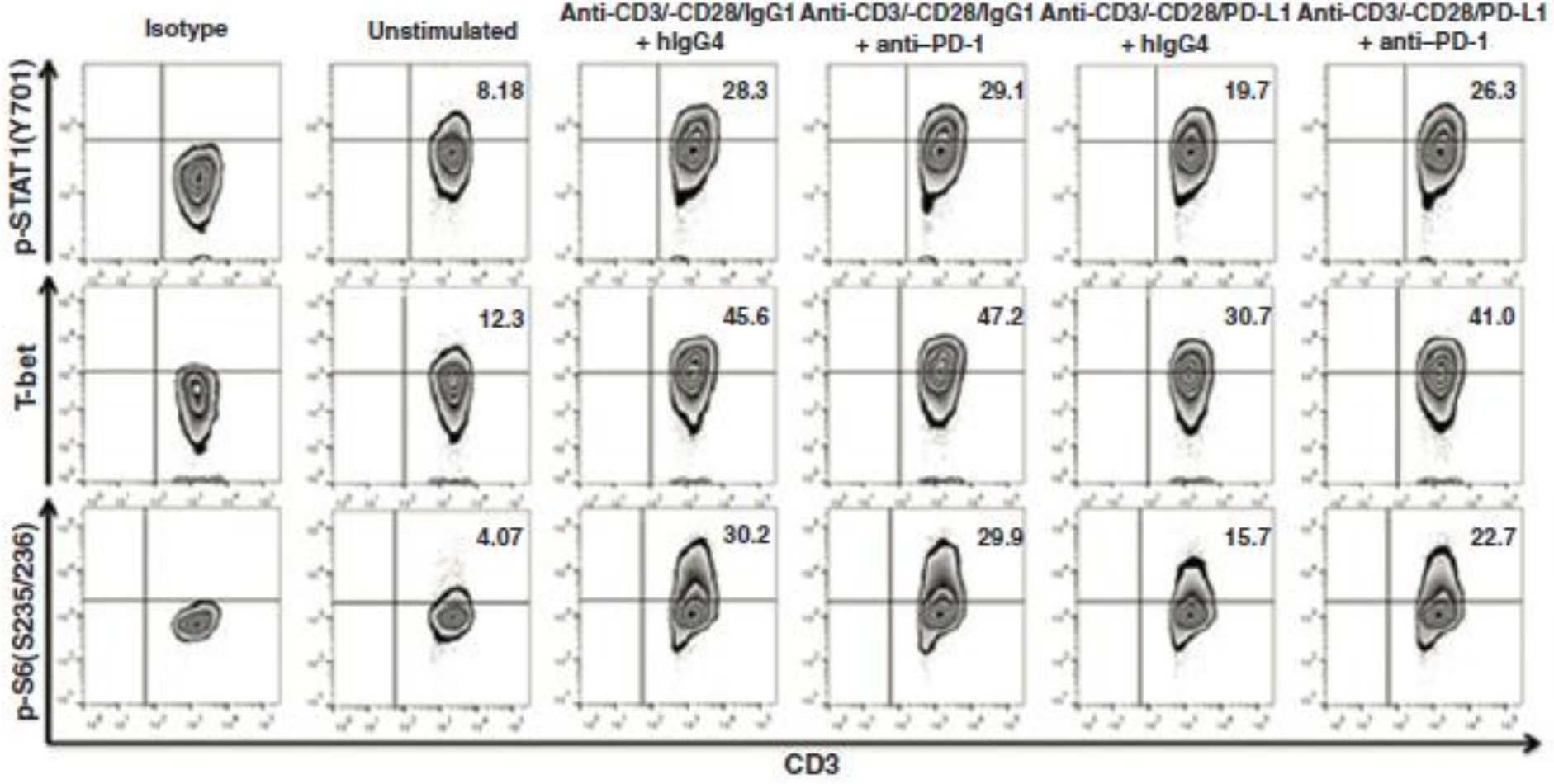
Endpoints:

1. p-STAT-1
2. T-bet
3. p-S6
4. Cytokines

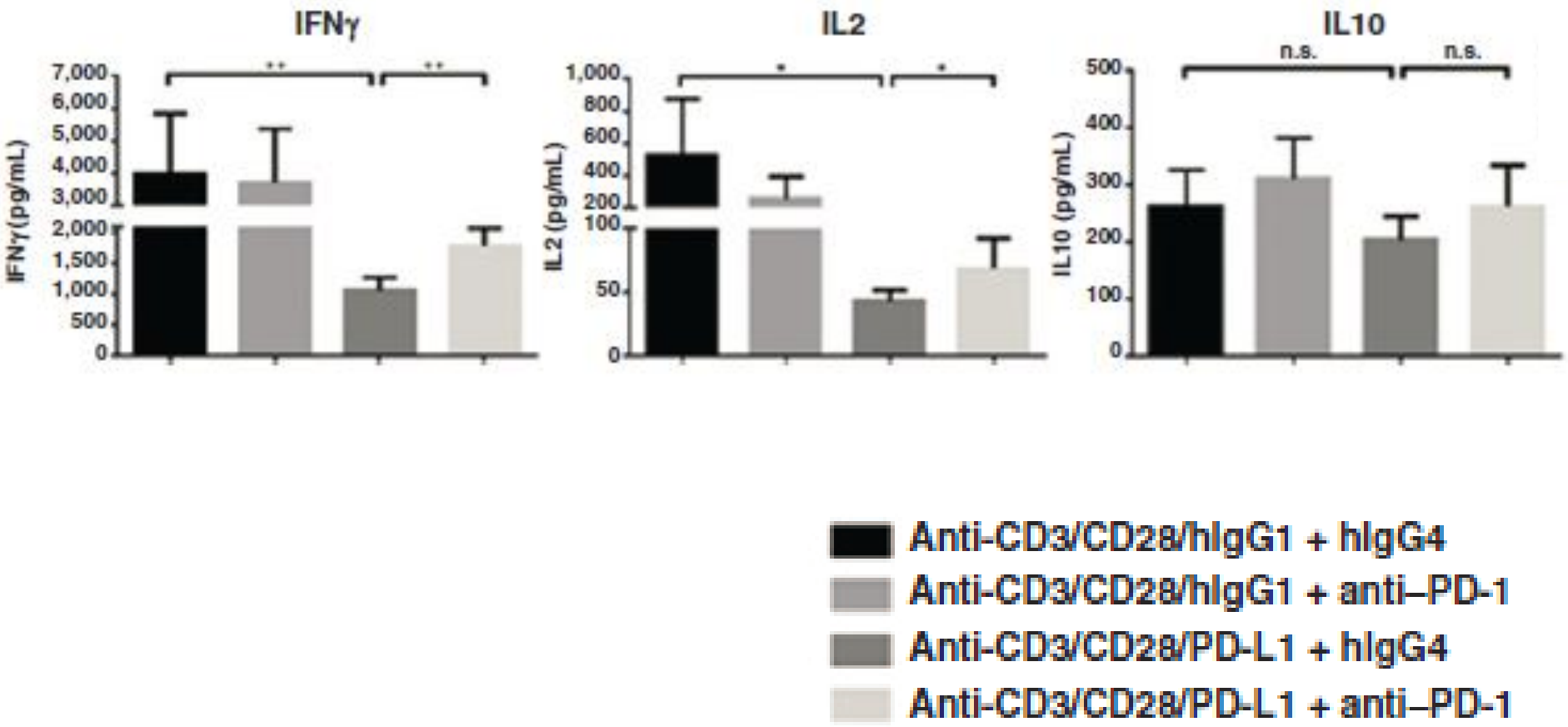
(IFN-g, IL-2, IL-10)

The effect of PD-1 blockade on TCR signaling in tumor infiltrating lymphocytes

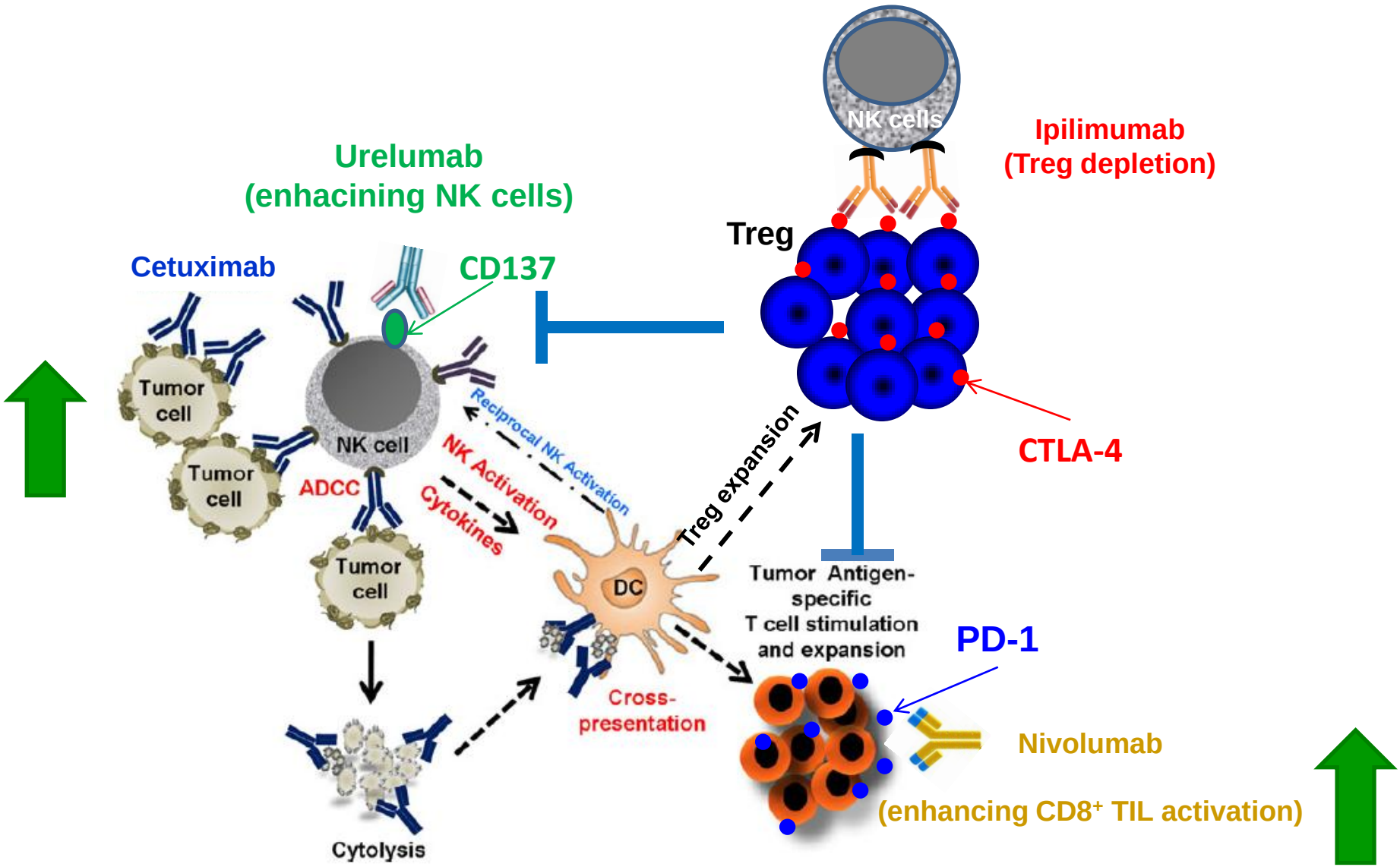
$CD8^+$ TIL



The effect of PD-1 blockade on cytokine production in tumor infiltrating lymphocytes



Strategy for combined cancer immunotherapy using cetuximab and immune checkpoint mAbs



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Neil Gildener-leapman
Jing Li

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Cancer Therapy & Research Center

Athanassios Argiris

*Theresa L. Whiteside Lab

#Patrick J. Schuler

Massachusetts General Hospital

Soldano Ferrone