



What's Next for Cancer Immunotherapy?

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Director of the Cancer Immunotherapeutics Center



University of
Pittsburgh



UPMC LIFE
CHANGING
MEDICINE

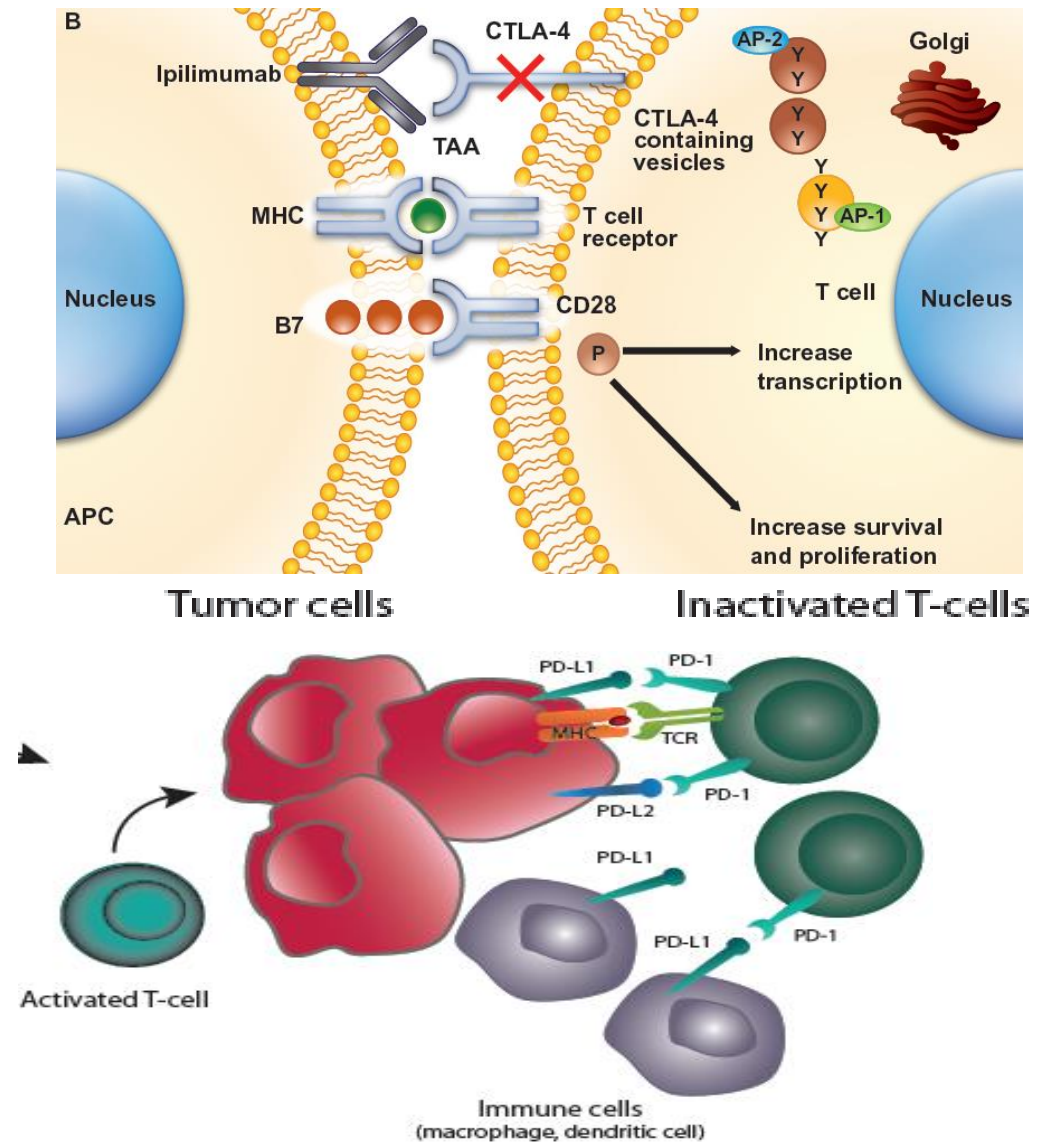
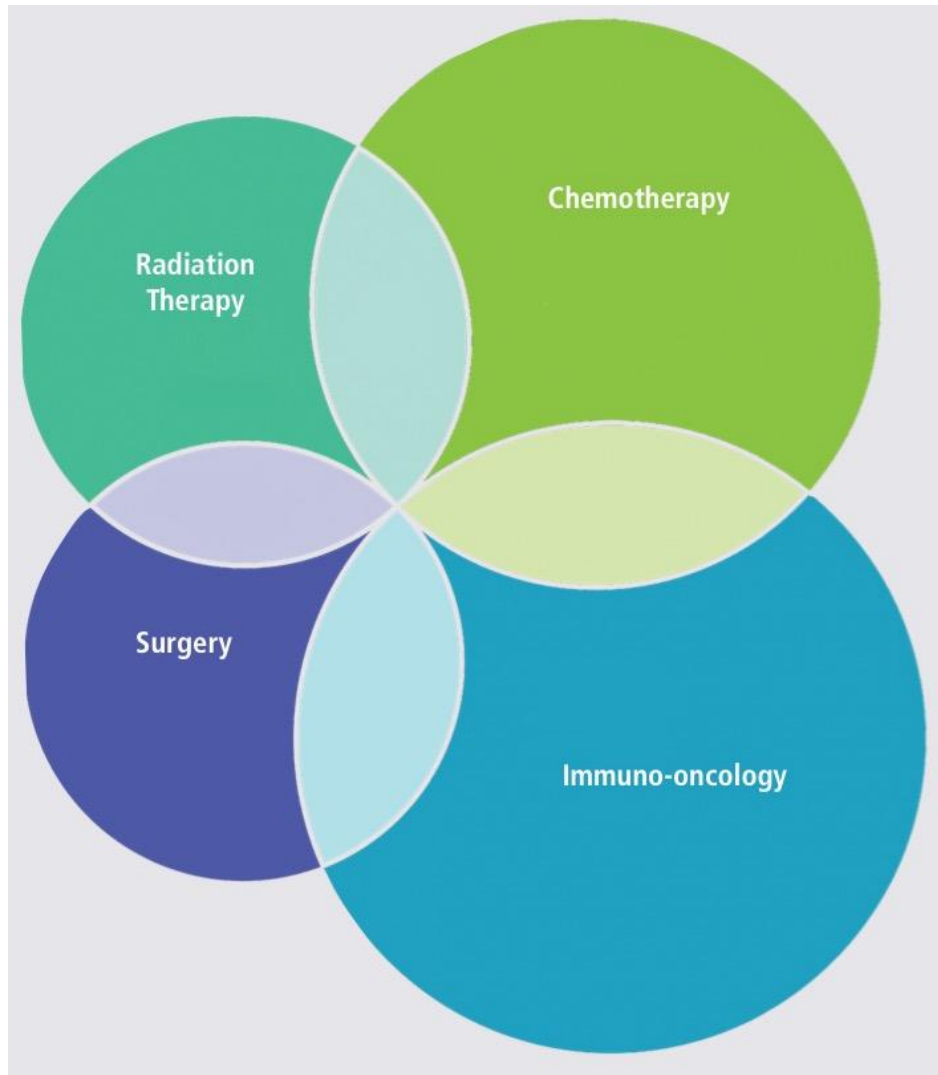
Disclosures

- **Receipt of Intellectual Property Rights/Patent Holder:** Serial #15/612,657 (Cancer Immunotherapy), PCT/US18/36052 (Microbiome Biomarkers for Anti-PD-1/PD-L1 Responsiveness: Diagnostic, Prognostic and Therapeutic Uses Thereof)
- **Consulting Fees:** Abbvie, Alnylam, Array, Bayer, Bristol-Myers Squibb, Checkmate, Cstone, Eisai, EMD Serono, KSQ, Janssen, Inzen, Macrogenics, Merck, Mersana, Nektar, Novartis, Pfizer, Regeneron, Ribon, Rubius, Silicon, Synlogic, TRex, Werewolf, Xilio, Xencor
- **Contracted Research:** AbbVie, Agios (IIT), Array (IIT), Astellas, Bristol-Myers Squibb (IIT & industry), Corvus, EMD Serono, Immatics, Incyte, Kadmon, Macrogenics, Merck, Moderna, Nektar, Numab, Replimmune, Rubius, Spring bank, Synlogic, Takeda, Trishula, Tizona, Xencor
- **Ownership Interest Less than 5%:** Actym, Alphamab Oncology, Arch Oncology, Kanaph, Mavu, Onc.AI, Pyxis, Tempest

Key Points:

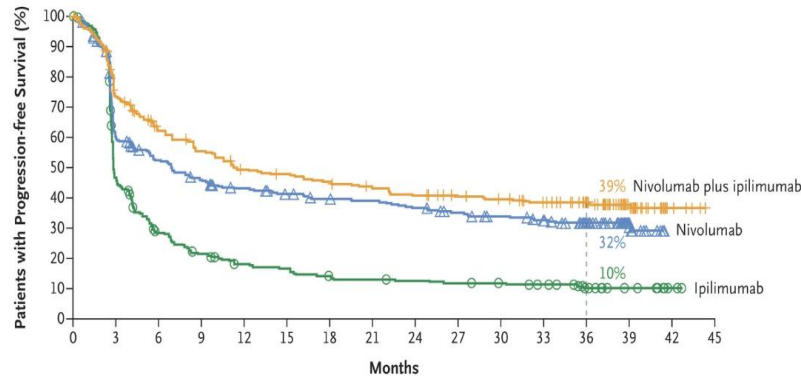
- To identify next generation immune-checkpoints
- To develop understanding of various bispecific approaches
 - CD3-redirection, checkpoints, TME-immune stimulators
- To familiarize with innate immunity/cytokines & IO-metabolism
- To describe truly novel targets and immuno-engineering approaches

Immuno-oncology: A modern revolution in cancer treatment

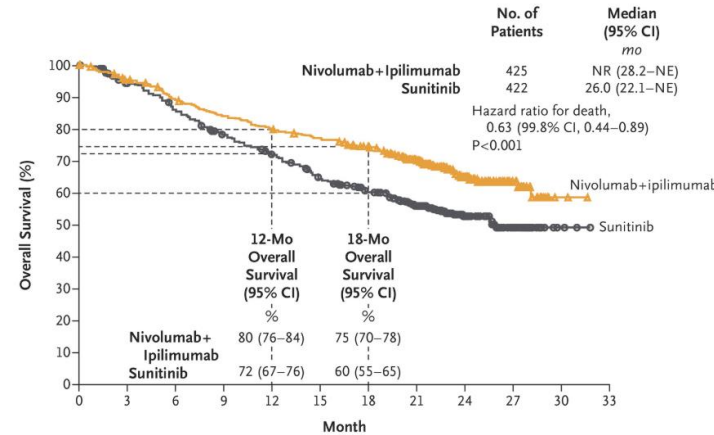


Combination immunotherapy now standard in multiple tumor types

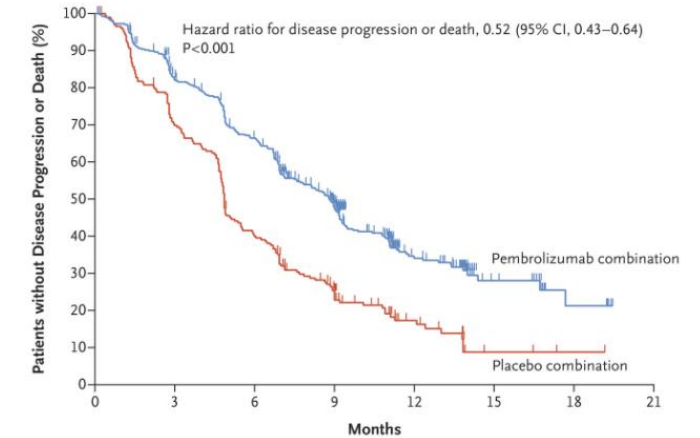
Melanoma: PD1 + CTLA4



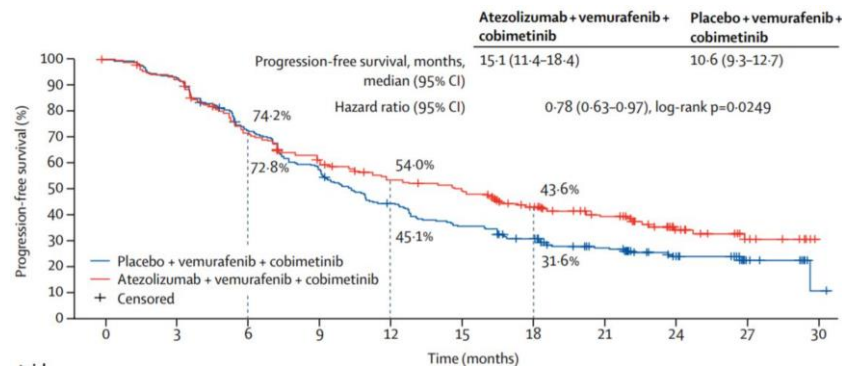
RCC: PD1 + CTLA4



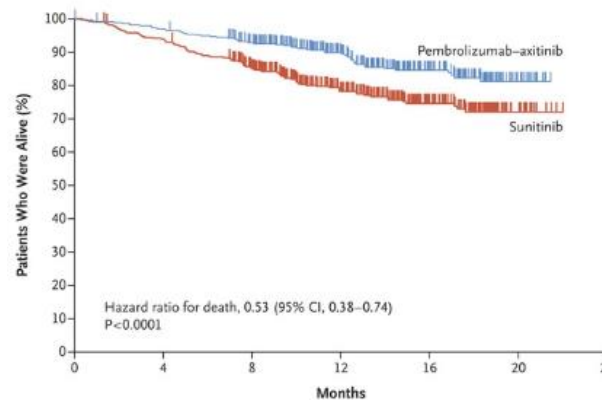
NSCLC: PD1 + chemotherapy



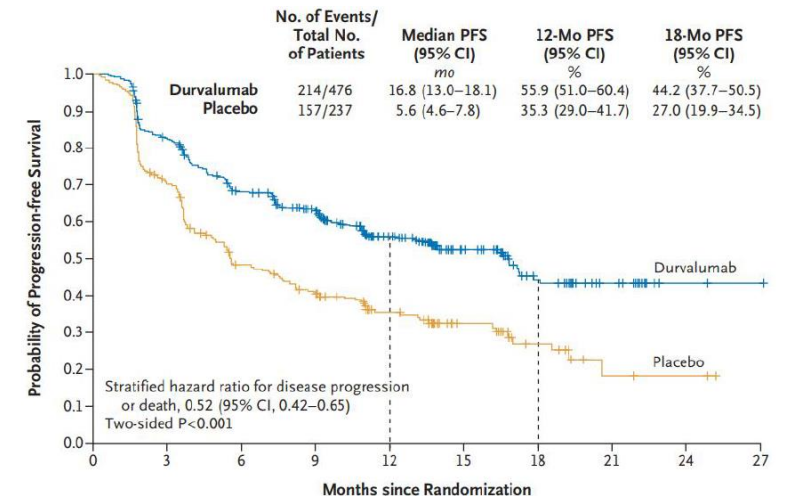
Melanoma: BRAF + MEK + PDL1



RCC: VEGFR2 + PD1/L1

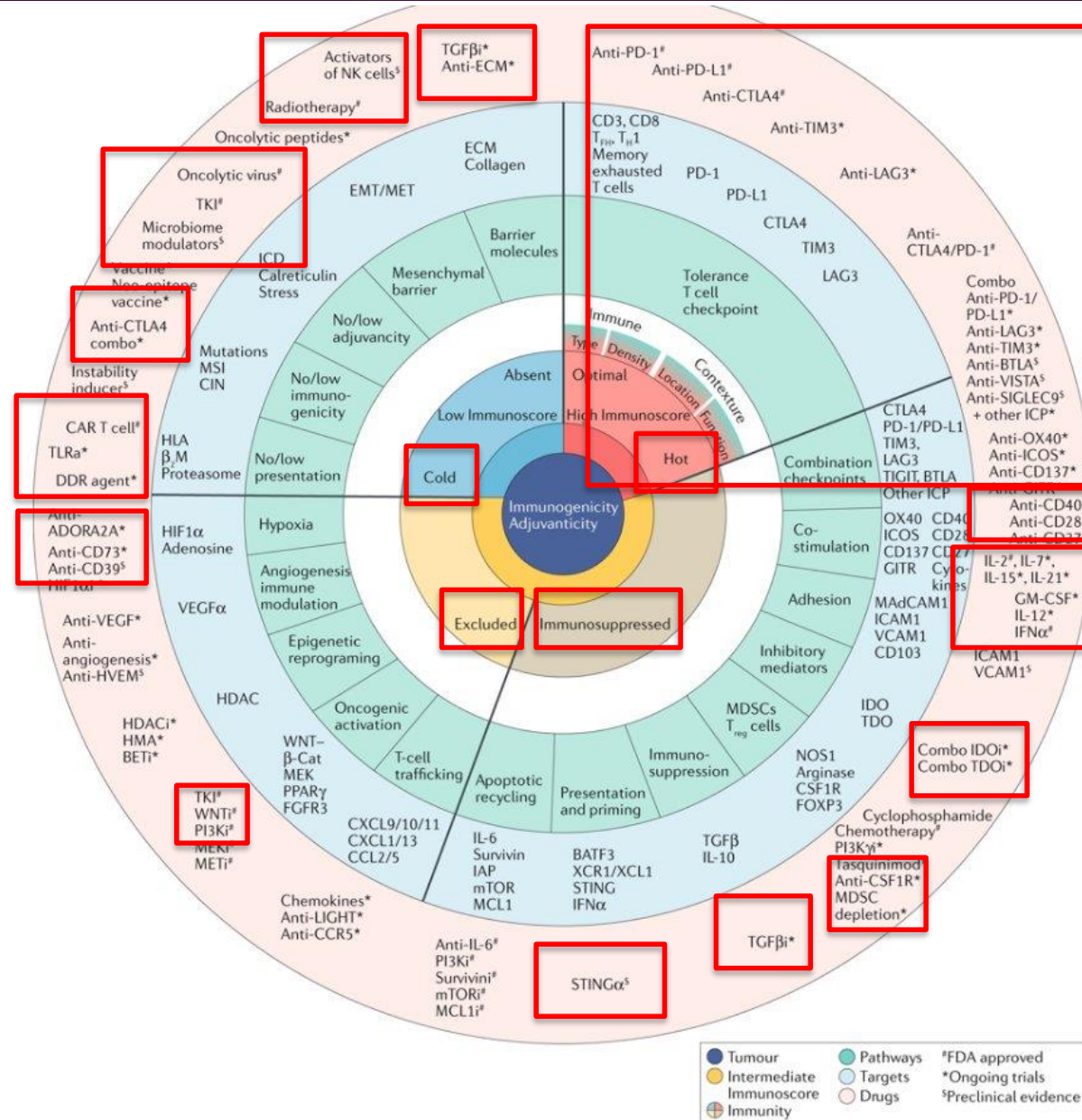


NSCLC: PDL1 following chemoRT



Tumor-immune classification cycle to direct anticancer therapy

Stratify tumors by tumor immune status for early phase trials



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 - LAG3, TIGIT, TIM3

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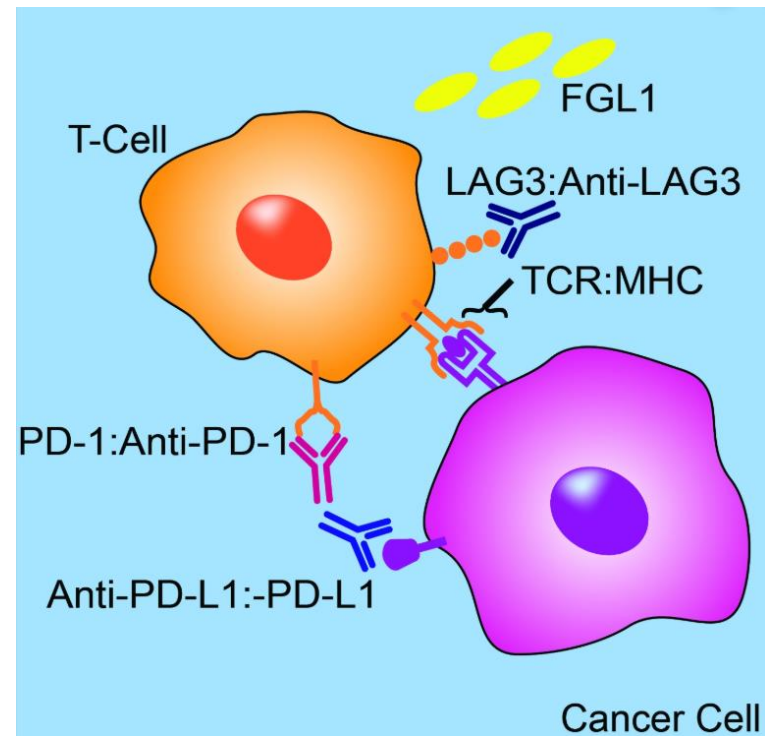
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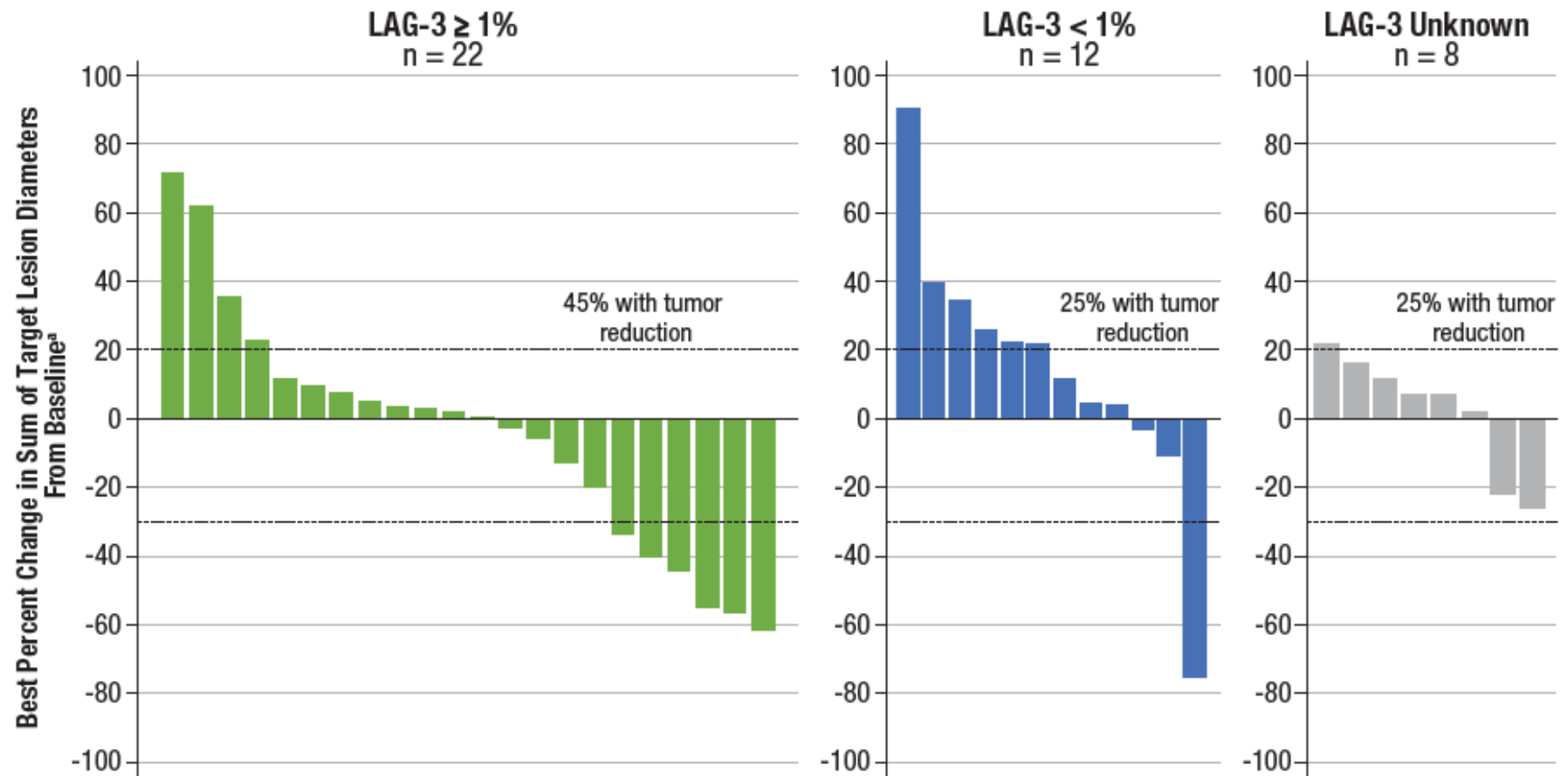
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Rationale for LAG3-PD1 Combination



Melanoma Prior-IO Cohort

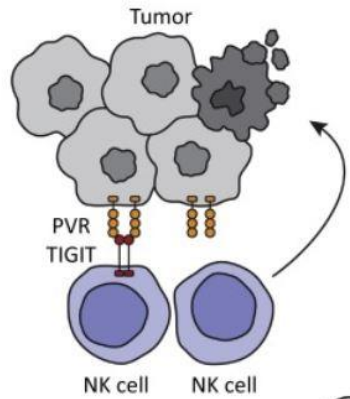


Phase 3 study of nivolumab +/- relatlimab (anti-LAG3) in frontline melanoma

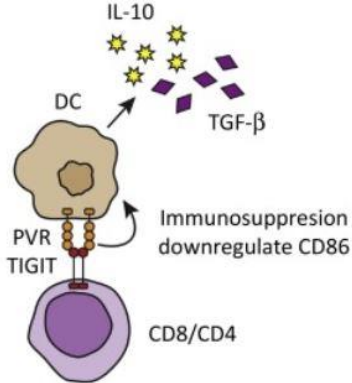
Wang *et al.* Cell 2019; Ascierto *et al.* ASCO 2017

Targeting TIGIT on multiple cell types

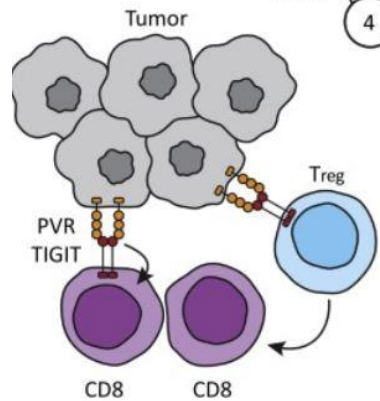
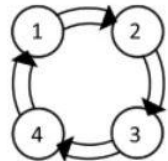
TIGIT can inhibit
NK cell-mediated tumor killing



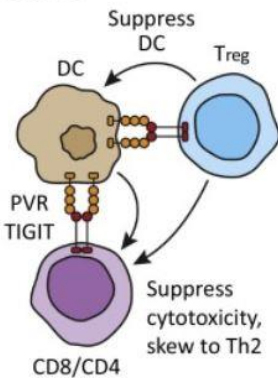
TIGIT can induce
immunosuppressive DCs



Tumor cell
killing

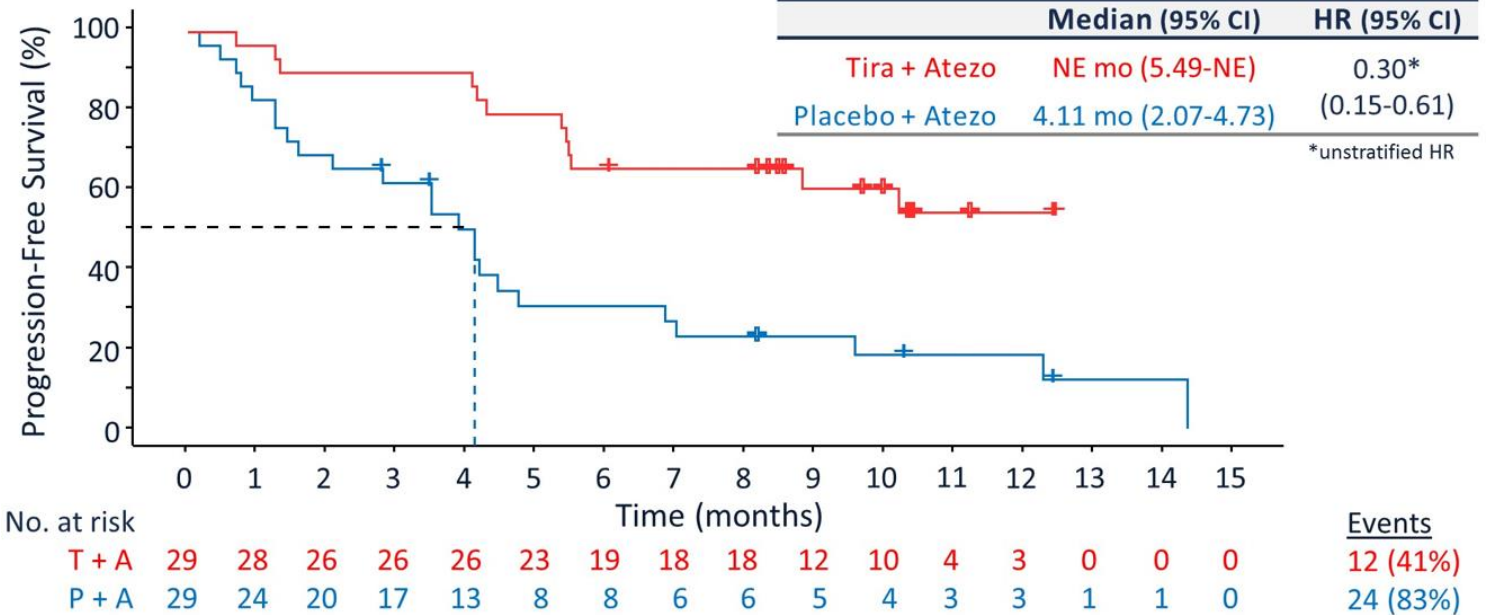


TIGIT can suppress
CD8 T cell-mediated killing



TIGIT can affect
CD8 T cell priming
and differentiation

Updated Investigator-Assessed PFS: PD-L1 TPS $\geq 50\%$



TIM3 checkpoint on multiple cell types

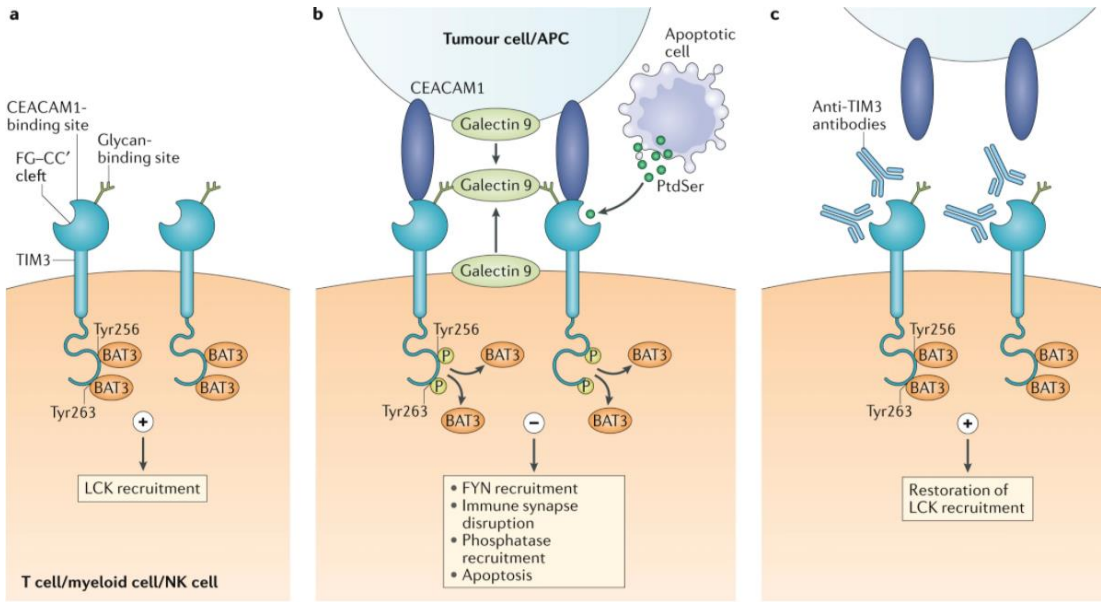
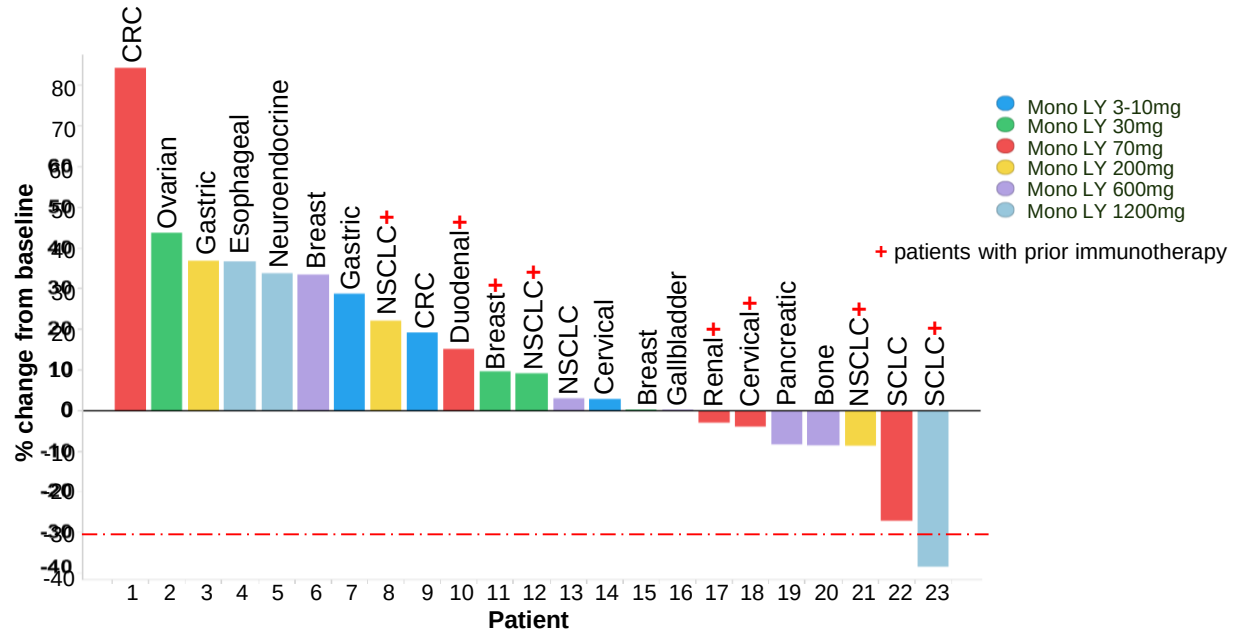
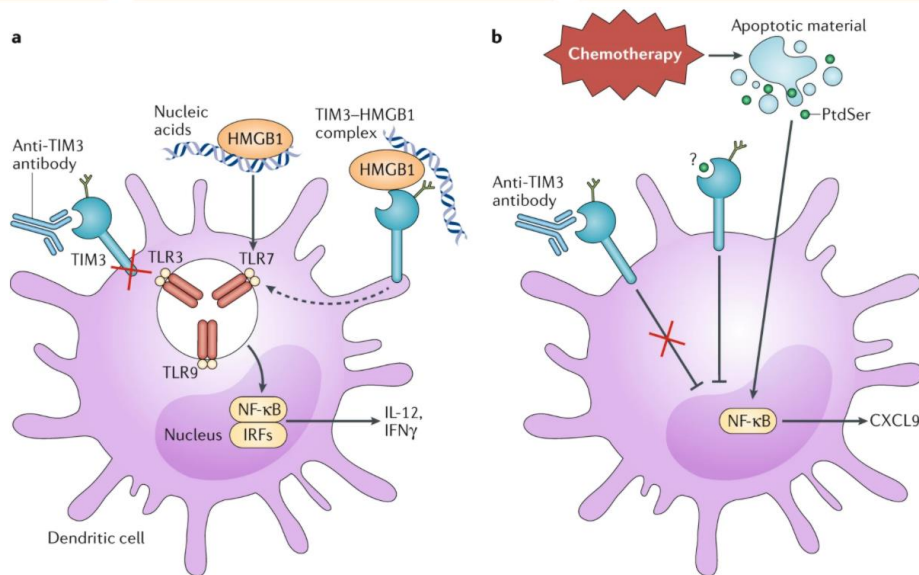
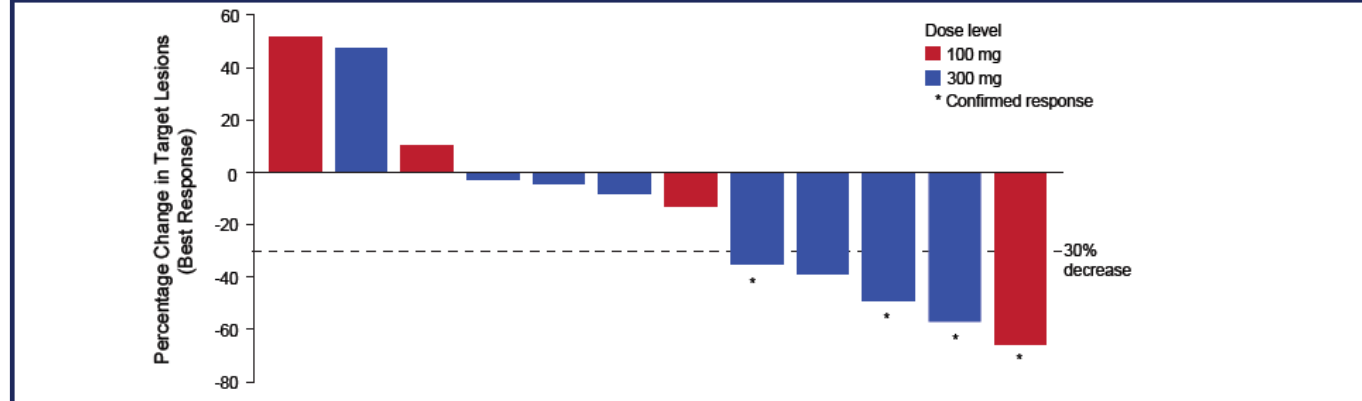


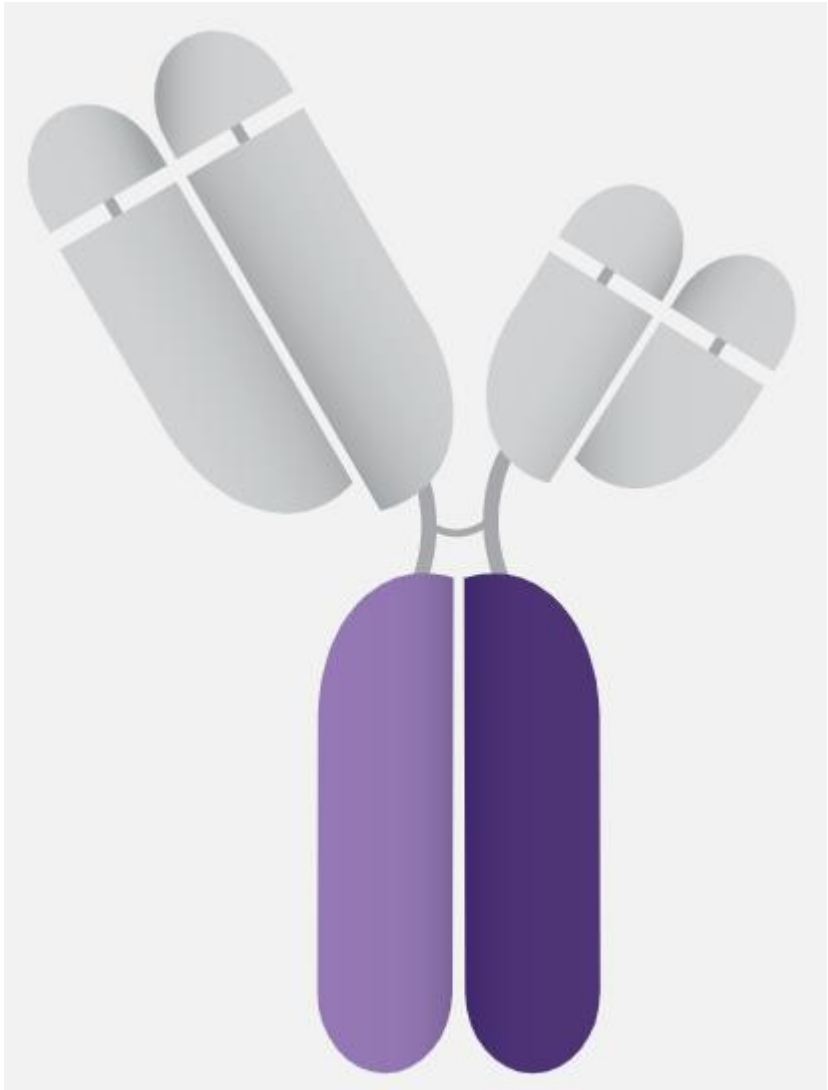
Figure 9. Best Response in PD-L1 Positive (TPS $\geq 1\%$) Patients*



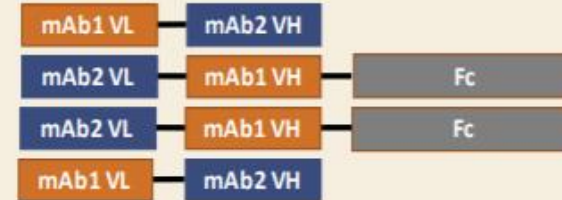
Novel bispecific checkpoint antibodies

Some of the bispecific checkpoints under investigation

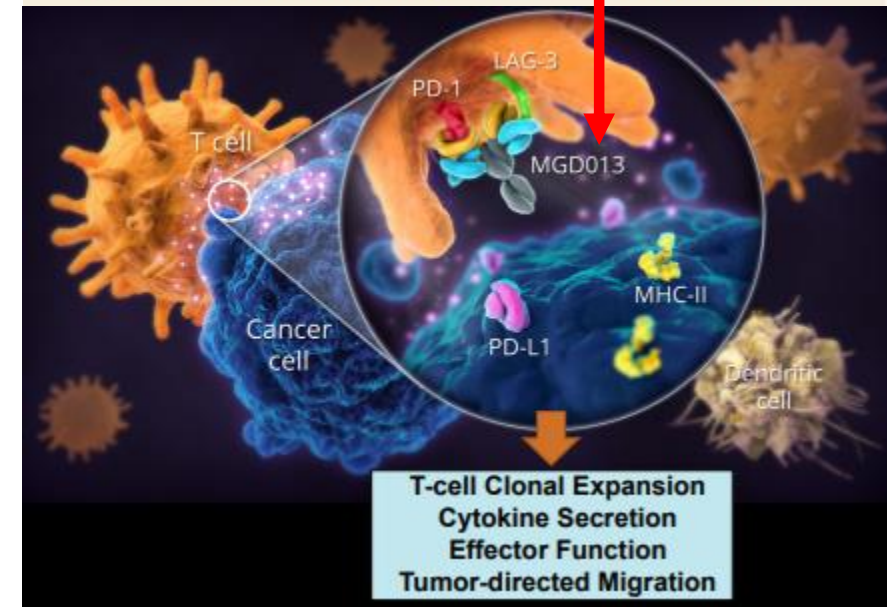
PD1-CTLA4
PD1-LAG3
PD1-ICOS
CTLA4-LAG3



General Structure

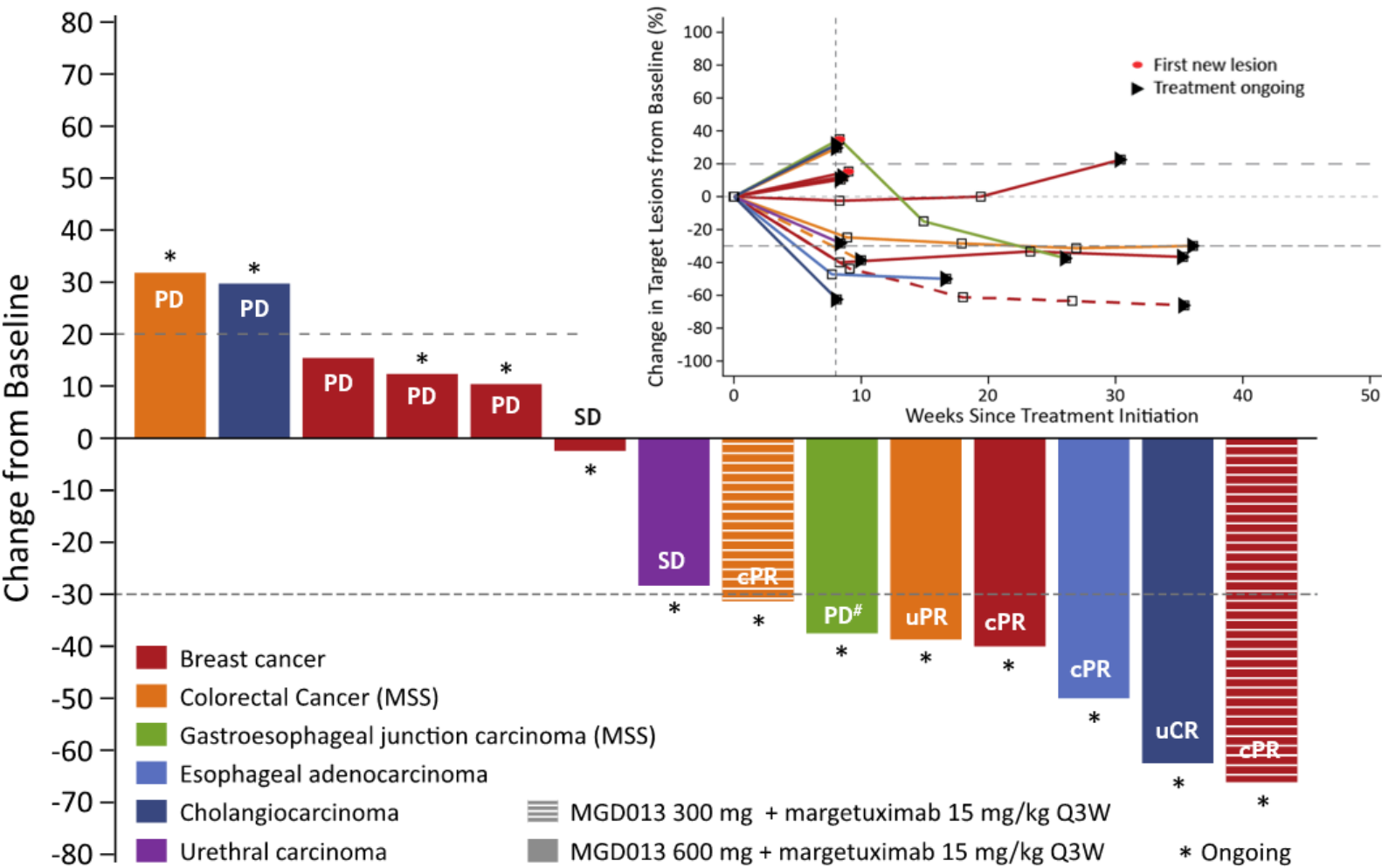


MGD013 (PD1 x LAG3) hinge stabilized
IgG4 tetravalent, bispecific DART molecule



Fc-engineered α HER2 + PD-1 $\times$ LAG-3 DART (Margetuximab plus MGD013)

Preliminary results in patients with relapsed/refractory HER2+ solid tumors



- ORR = 42.9% (6/14 evaluable pts)
- Includes unconfirmed objective responses
- Well-tolerated
- Responding patients remain on therapy

Baseline PD-L1 & LAG-3 in # of Responding Patients (N = 6)			
PD-L1 CPS:	< 1	1	TBD
N	4	1	1

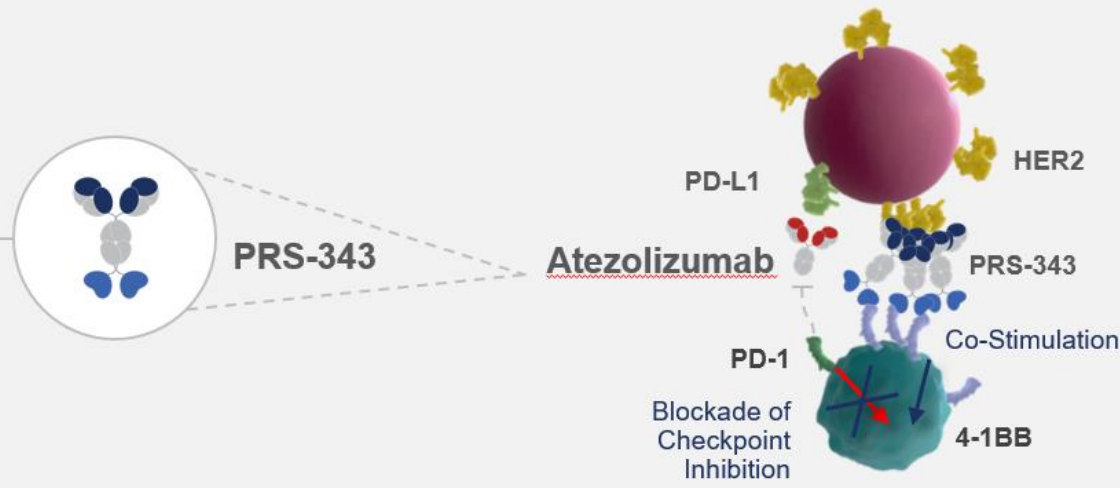
LAG-3 Score:	< 5	5-15	TBD/NE
N	3	1	2

GEJ pt with apparent pseudo-progression (PD per RECIST), now with 37.5% reduction in target lesions (iPR per iRECIST).

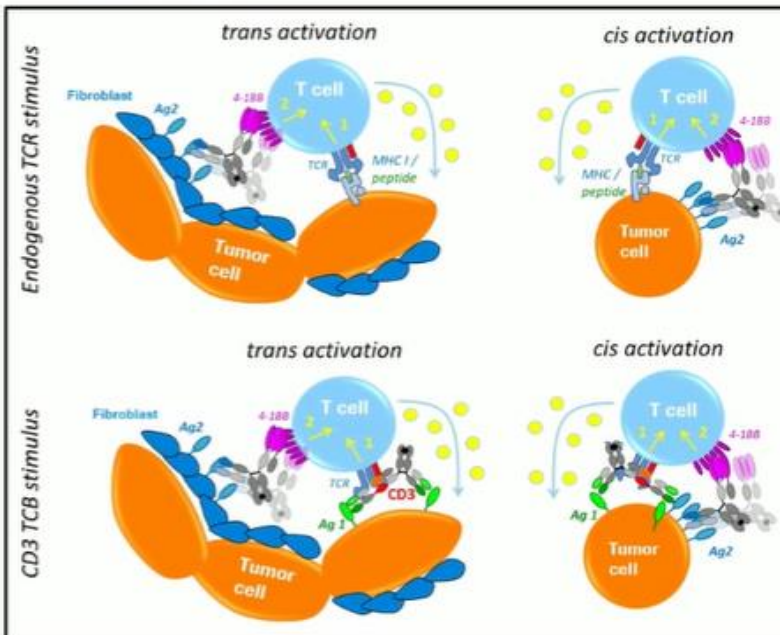
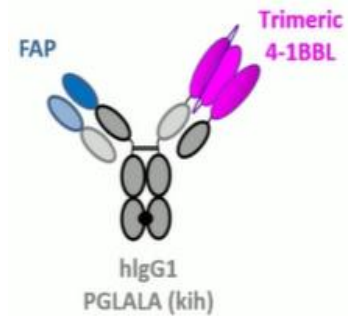
Bispecific tumor microenvironment targeting

HER2
targeting
Antibody

4-1BB
targeting
Anticalin®
Proteins

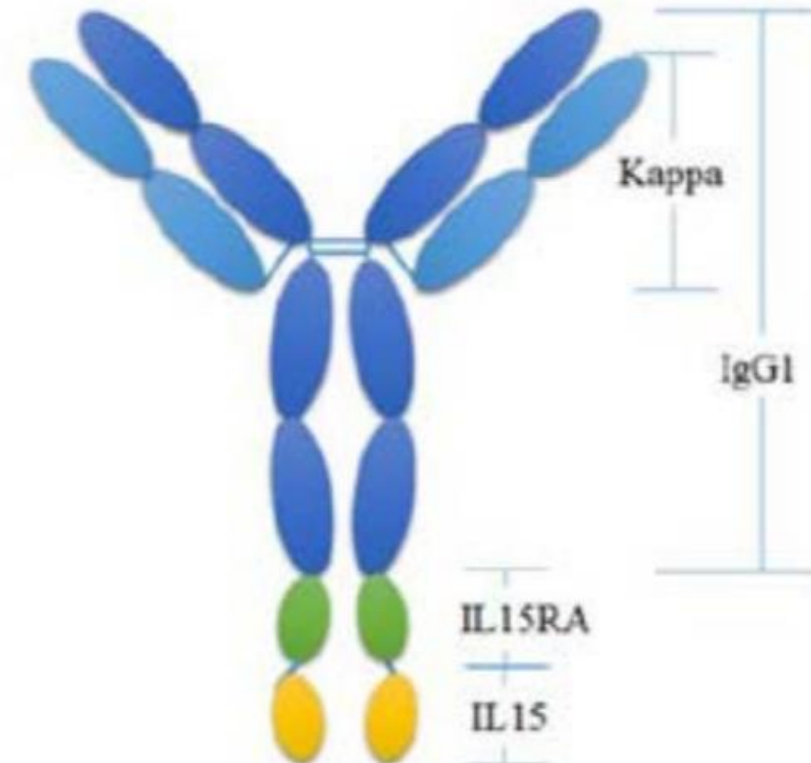


Mode of action

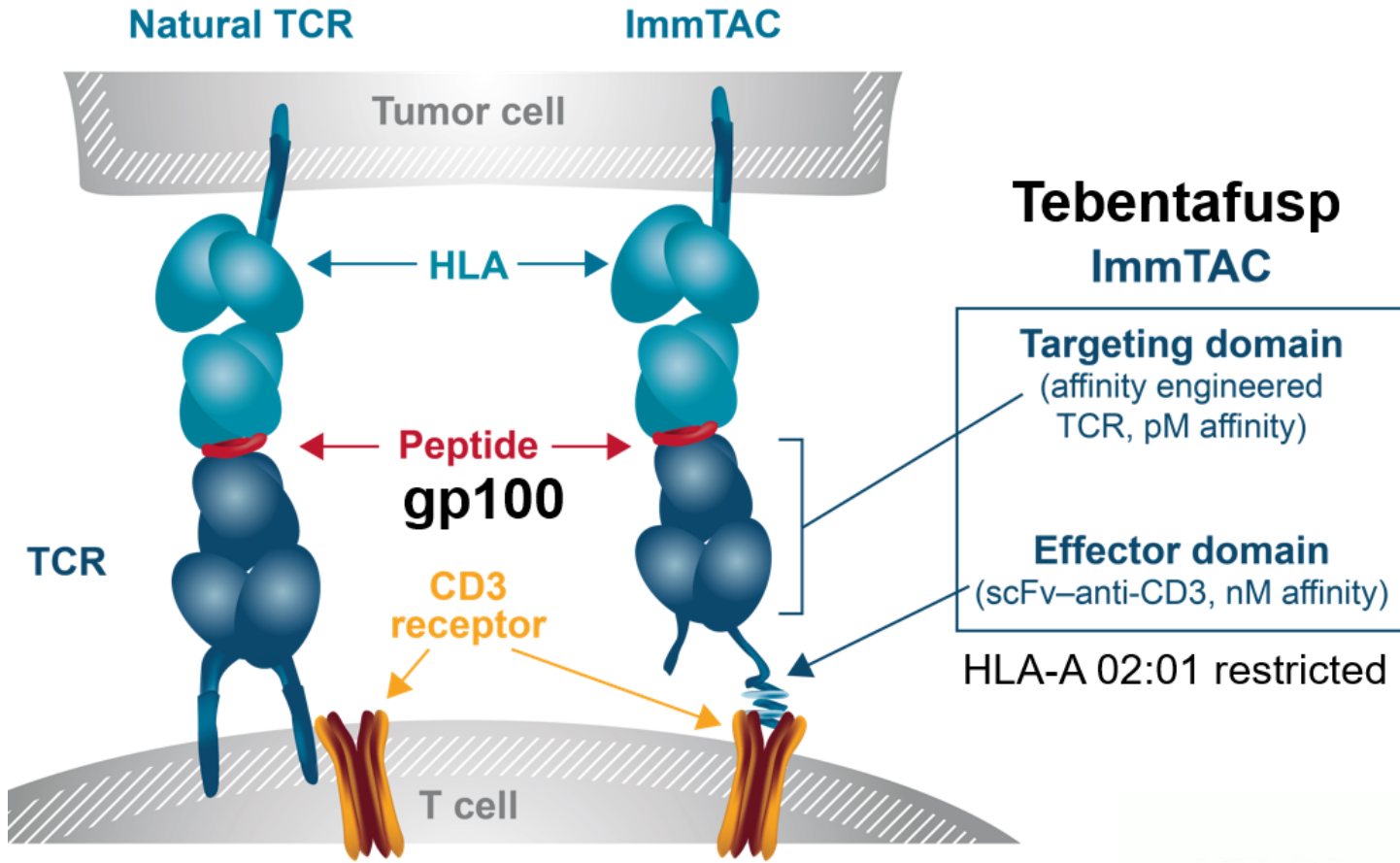


**aPD-L1
antibody**

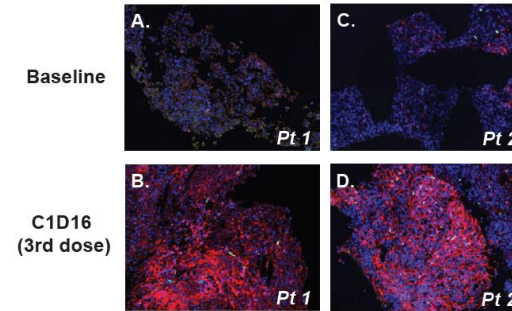
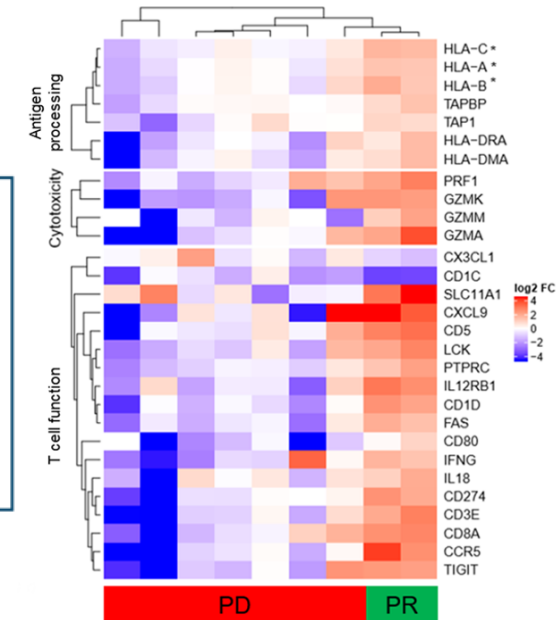
**IL-15/IL15Rα
sushi domain
is fused to the
C-terminal of
CH3 of PD-L1
antibody**



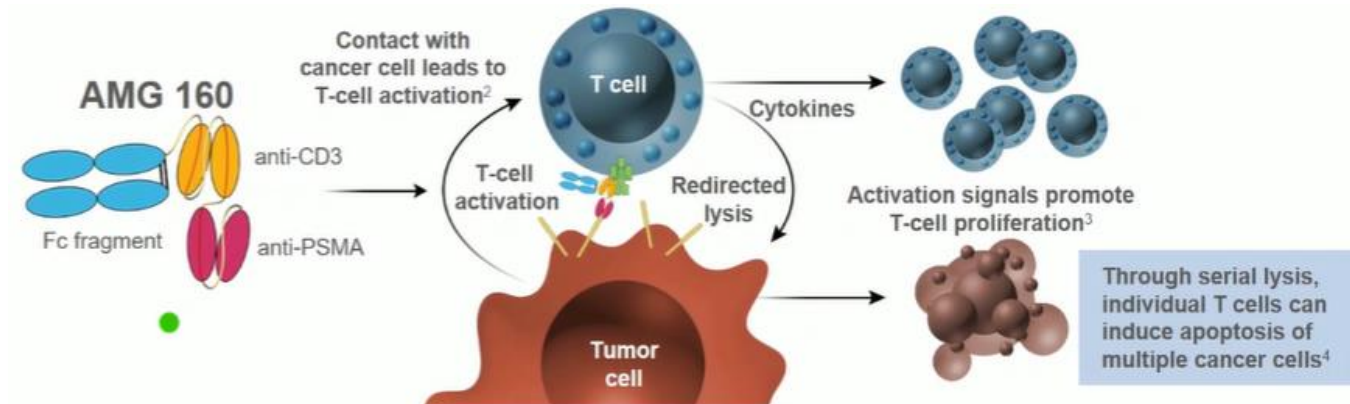
T cell redirection Activate T Cells Against Cancer



Induction of inflammatory genes and inflamed TME in PR vs PD patients



(A-D) Two patients with Baseline and C1D16 biopsies with IMF with CD8 (green), PD-L1 (red) and PD-1 (magenta).



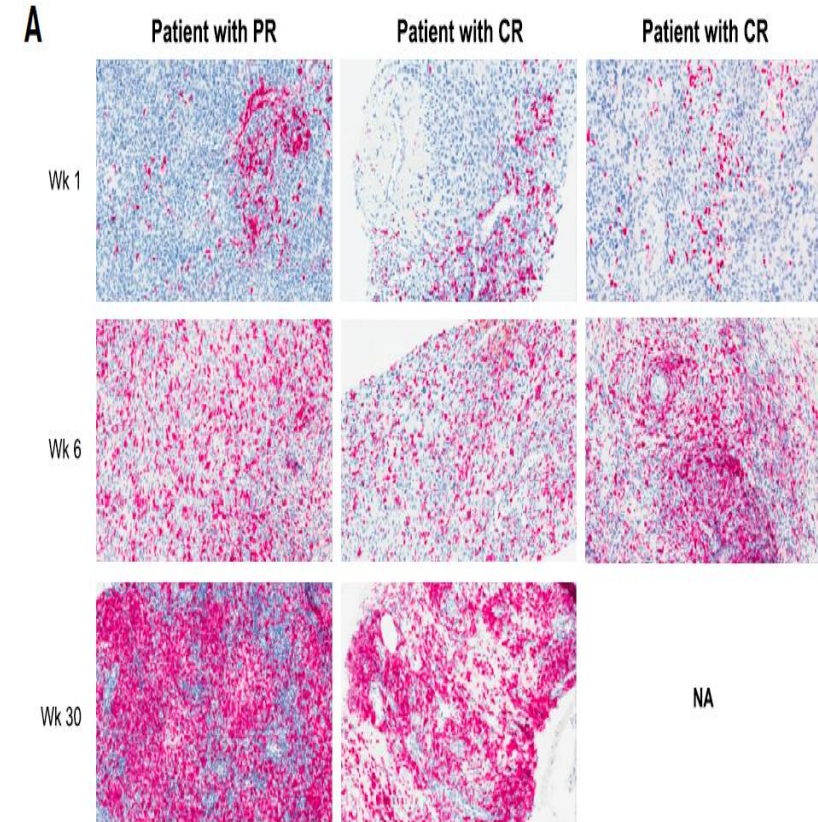
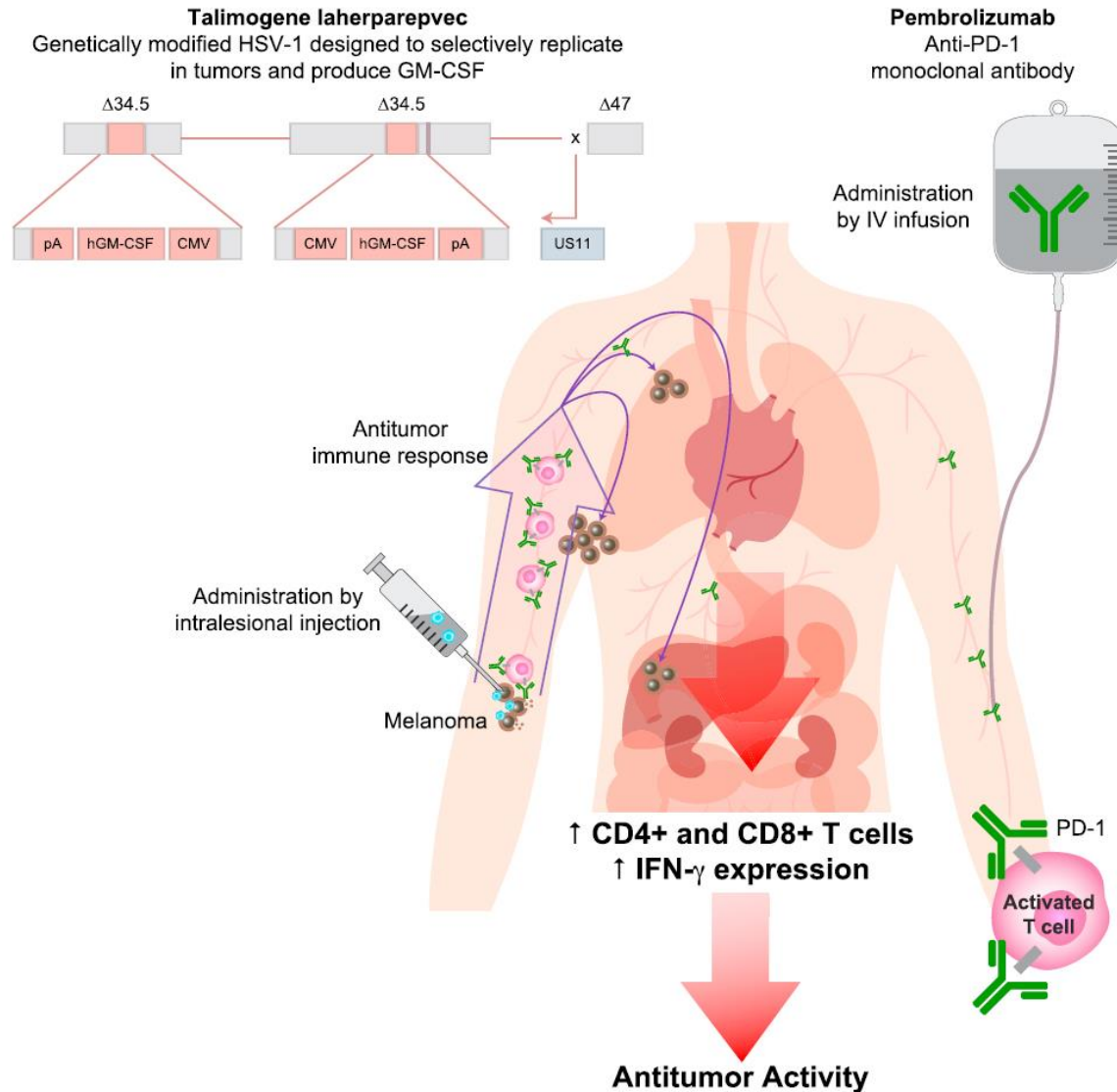
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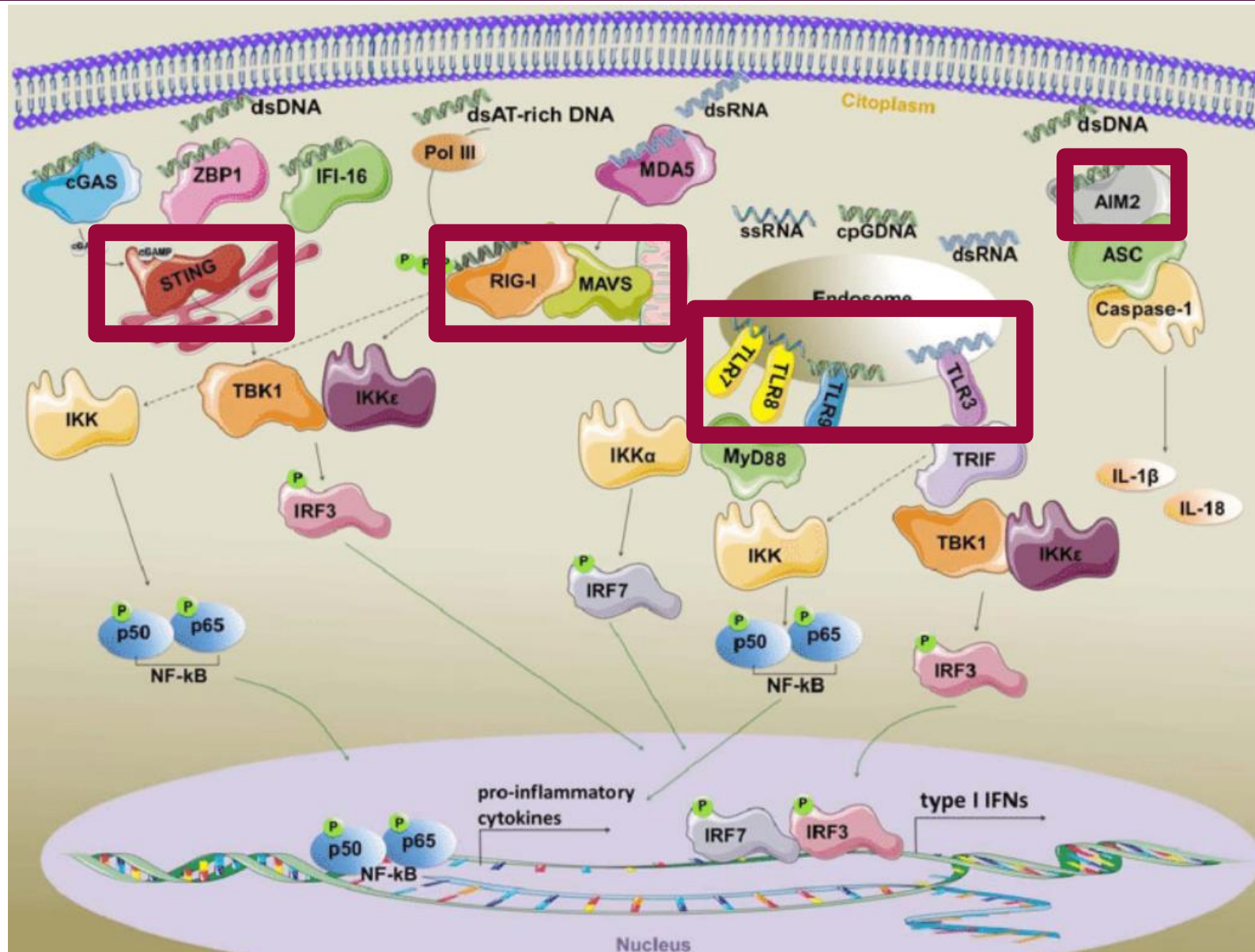
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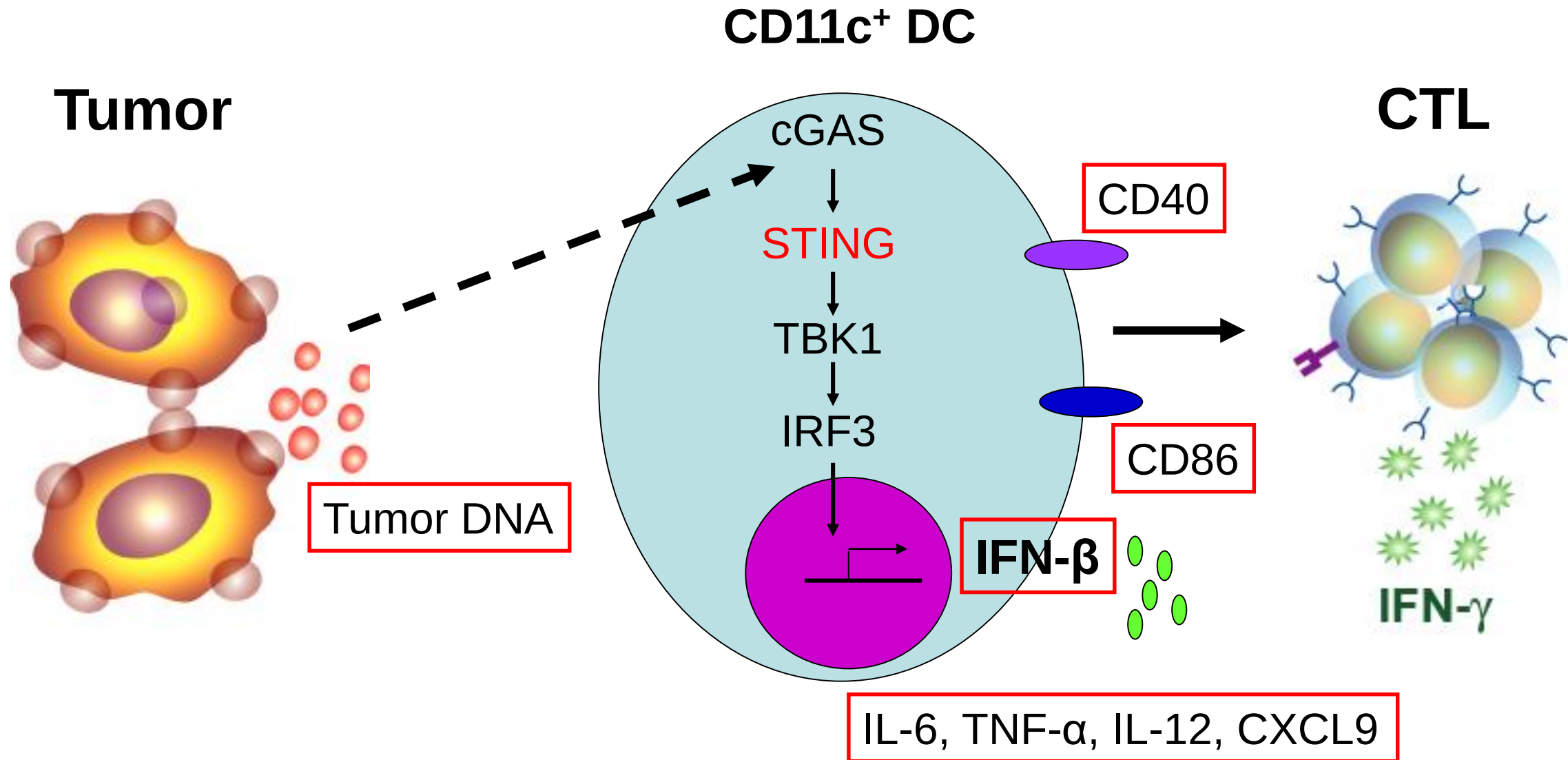
Oncolytic virotherapy promotes intra-tumoral T cell infiltration and improves anti-PD1 immunotherapy



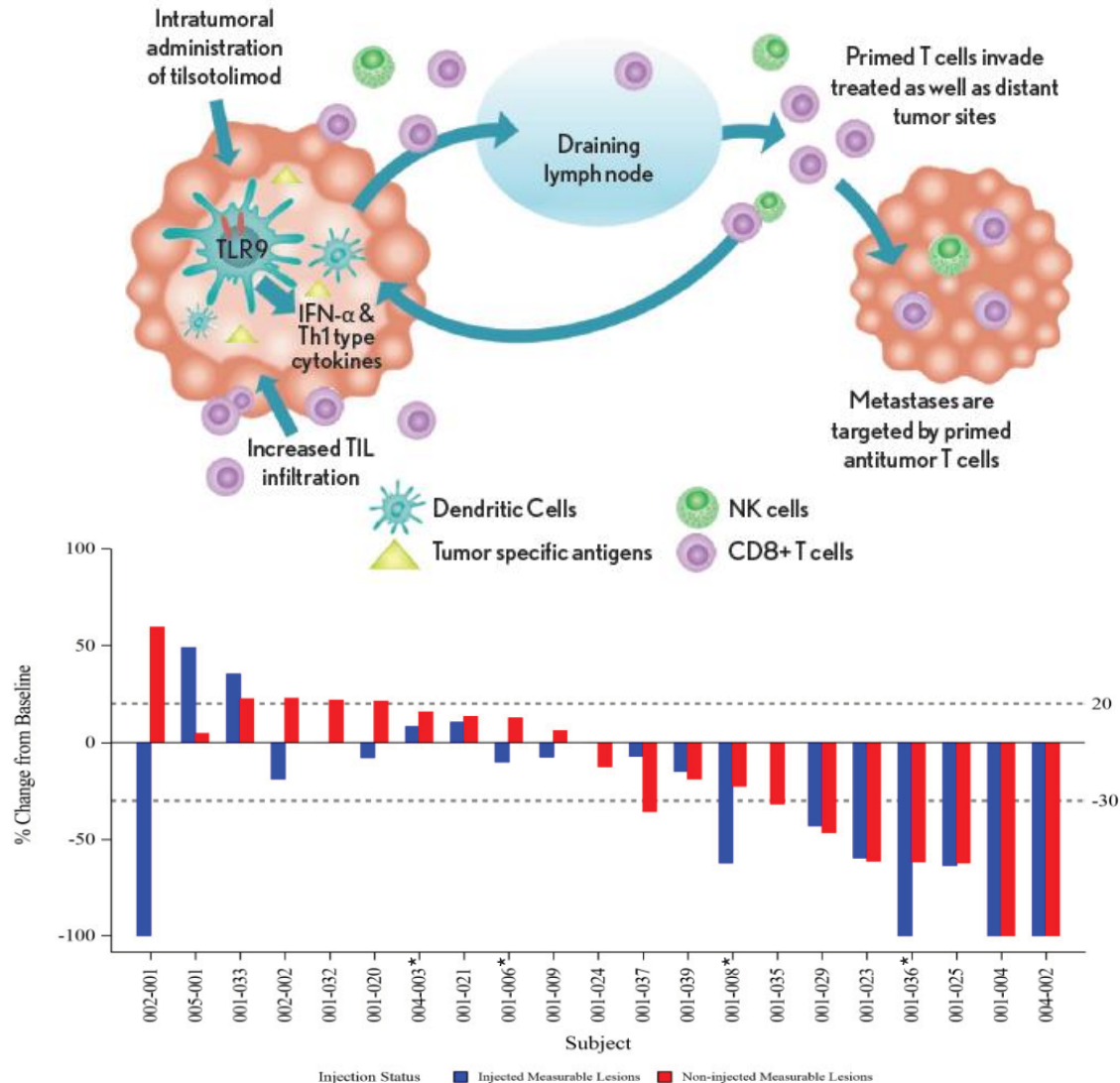
Pathways of danger (nucleic acid) sensing machinery active DCs



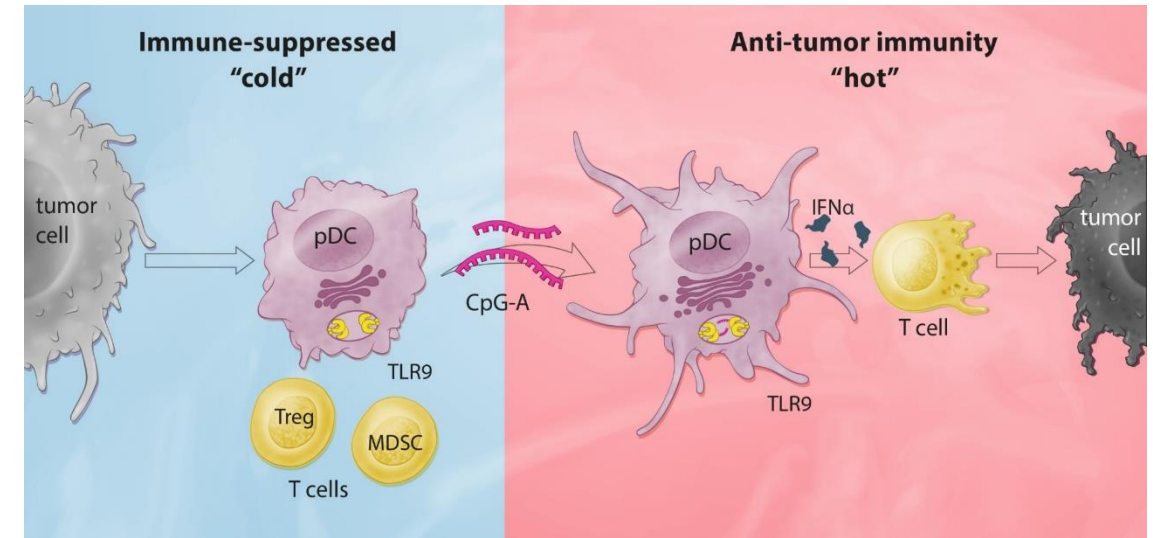
Model for innate immune sensing of tumors through the host STING pathway and tumor-derived DNA



Innate activation of viral sensing via TLR9 agonism may overcome checkpoint inhibitor resistance

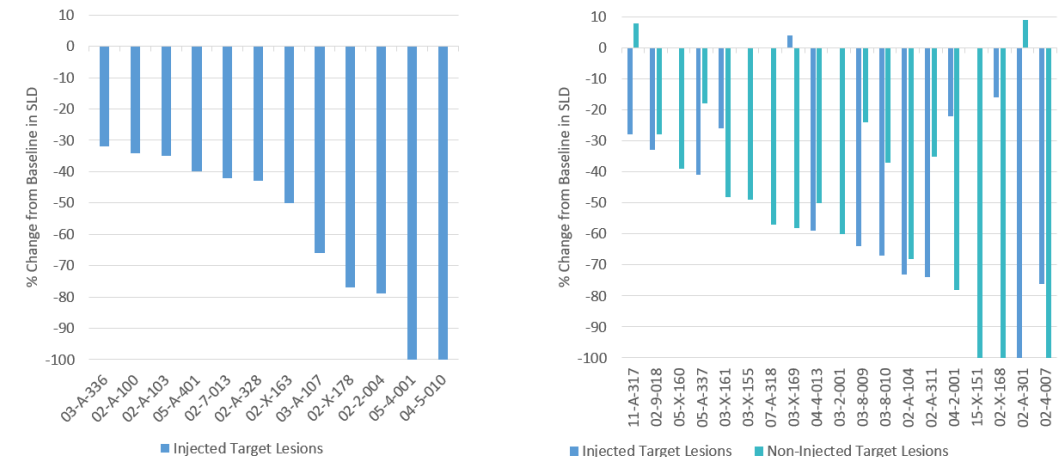


*Subjects were previously treated with ipilimumab in the metastatic setting.



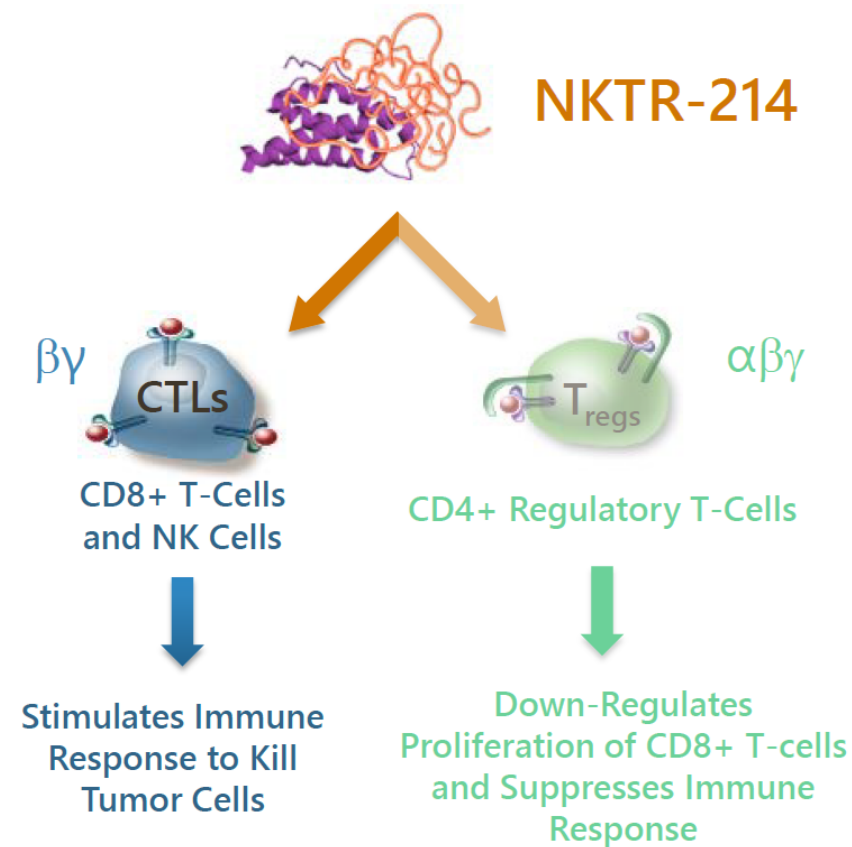
CMP-001 + Pembrolizumab in Anti-PD-1 Refractory Melanoma

Similar Responses in Injected vs. Non-Injected Lesions of Responders (N= 31)

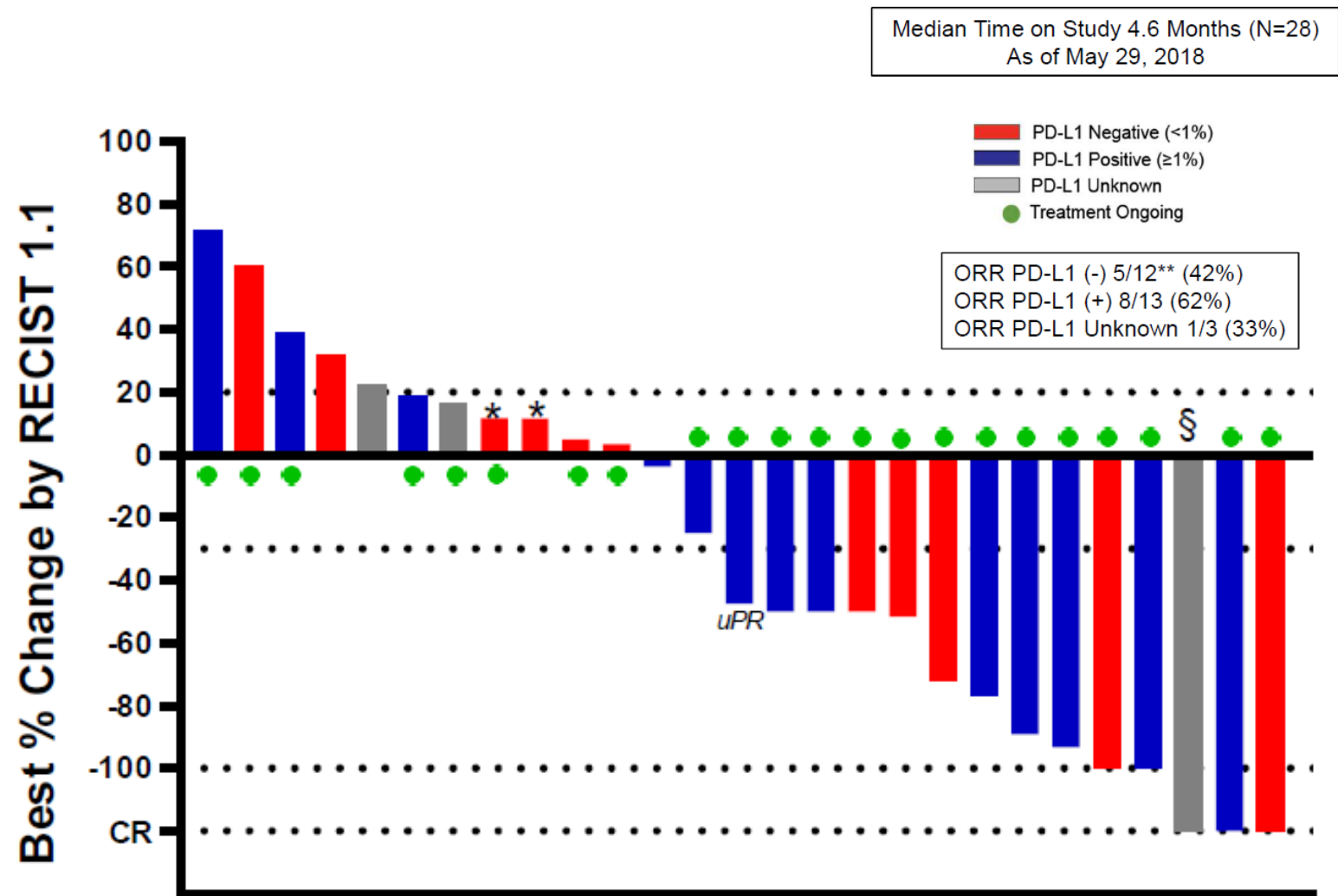


Diab *et al.* ESMO 2018; Kirkwood *et al.* SITC. 2019

Pegylated CD122 (IL-2R $\beta\gamma$) agonist may synergize with anti-PD1

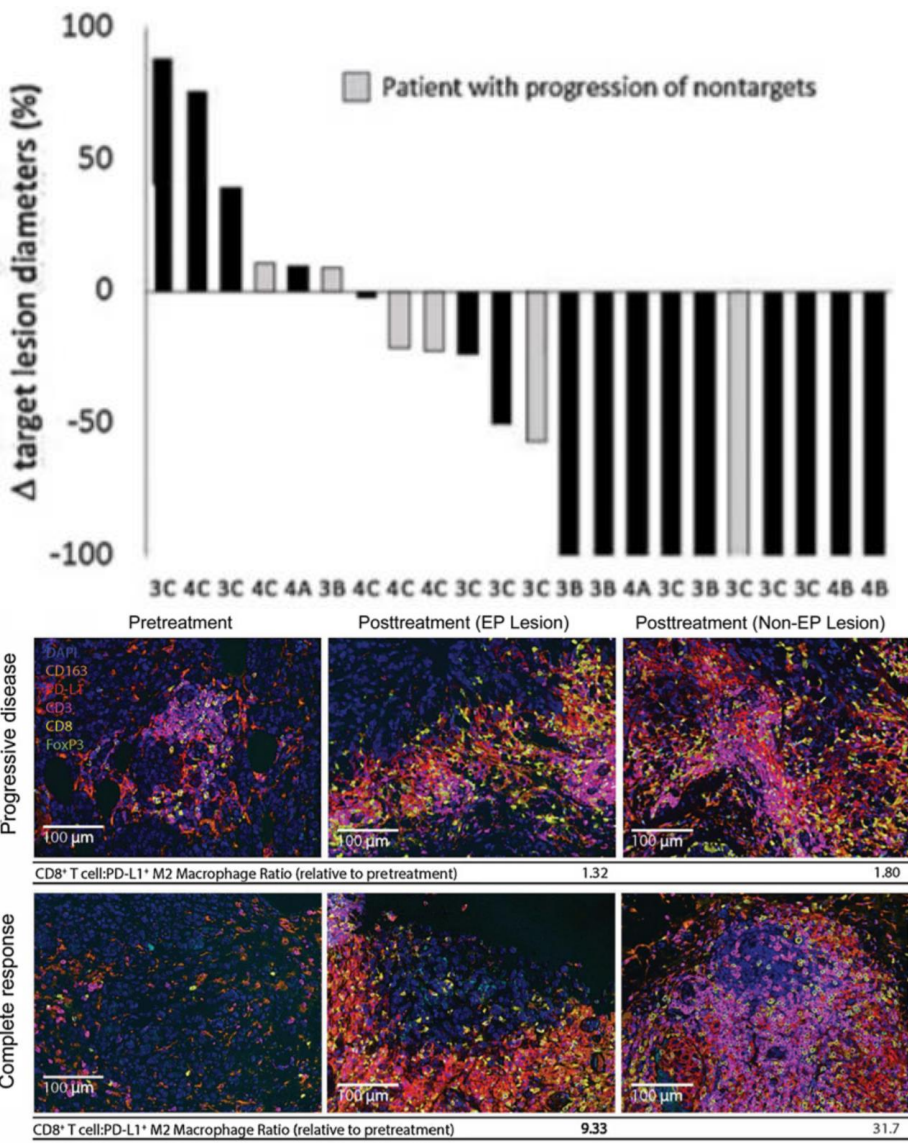
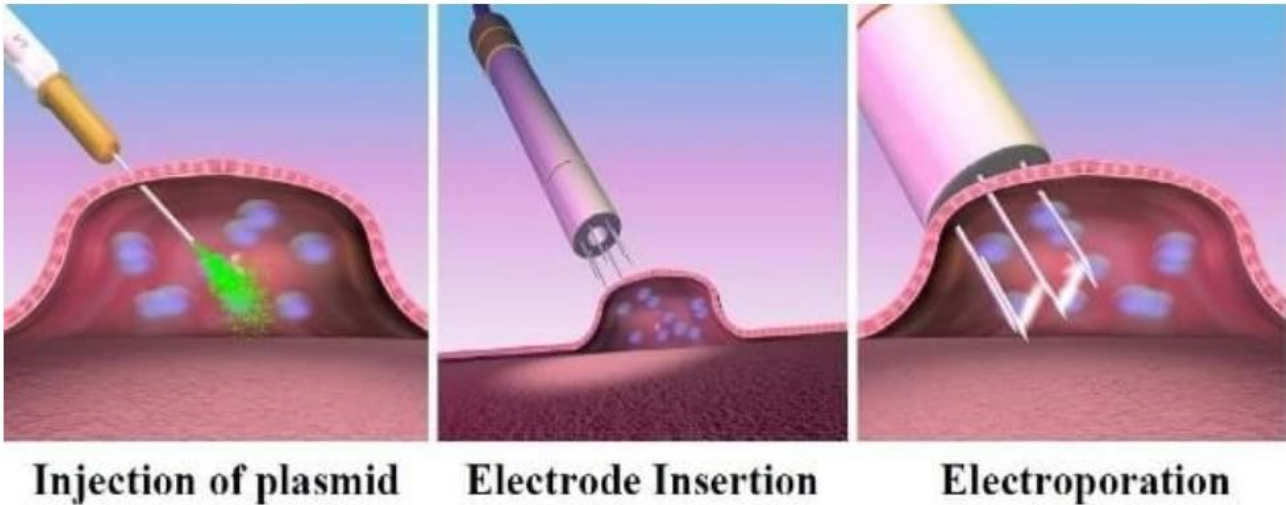
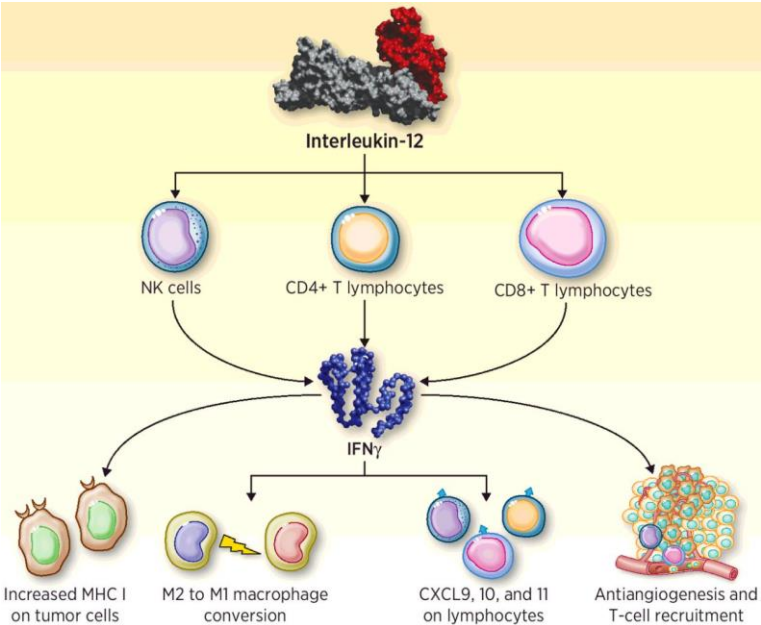


A Phase 3 Study of NKTR-214 Plus Nivolumab Vs Nivolumab in Untreated Metastatic Melanoma



**One PD-L1(-) patient did not have target lesions assessed at first scan due to PD of non-target lesions, therefore only 27 patients included in waterfall plot.

Electroporation of plasmid IL-12 may overcome resistance



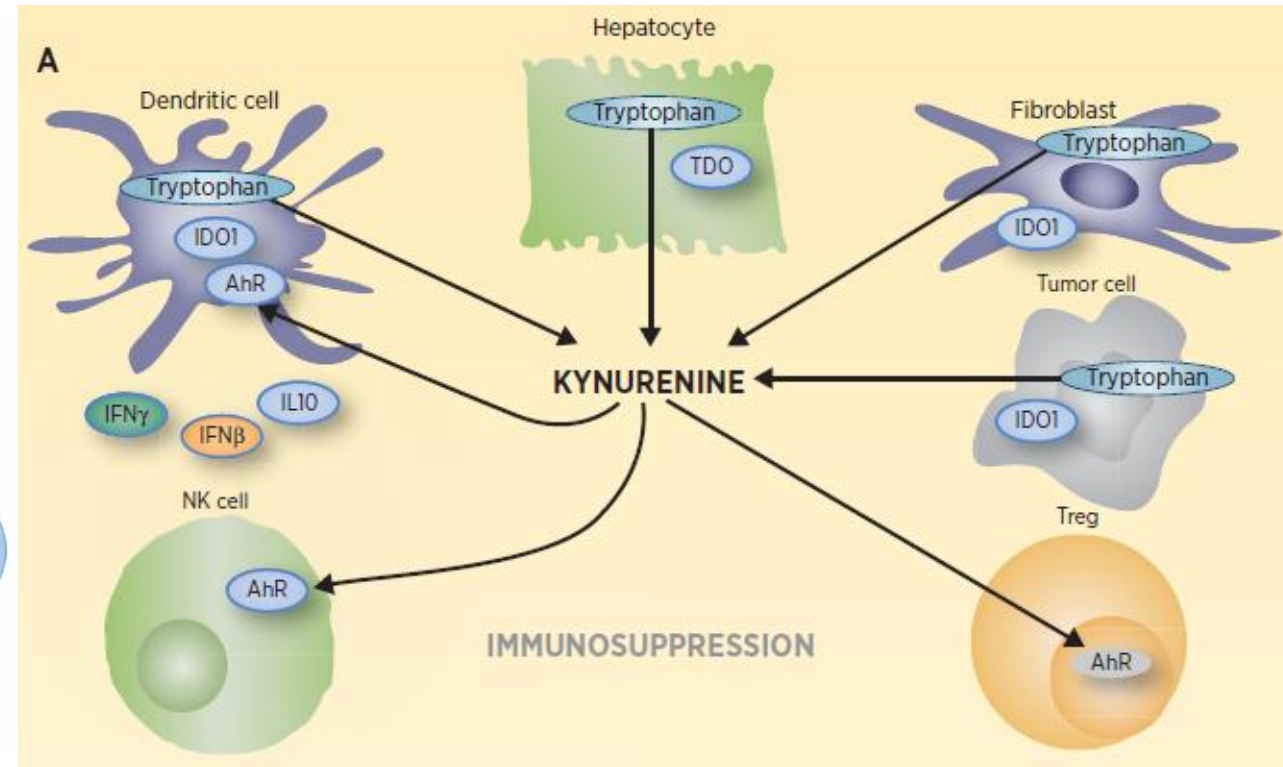
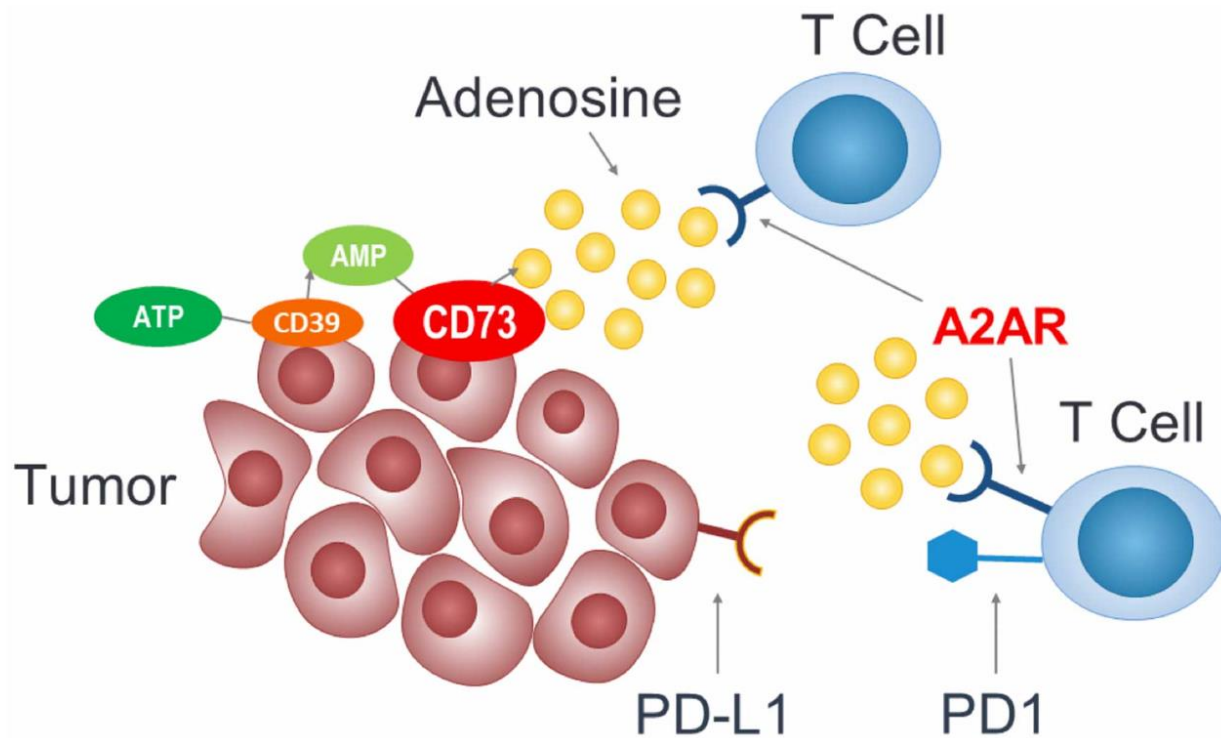
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Targeting immuno-metabolism



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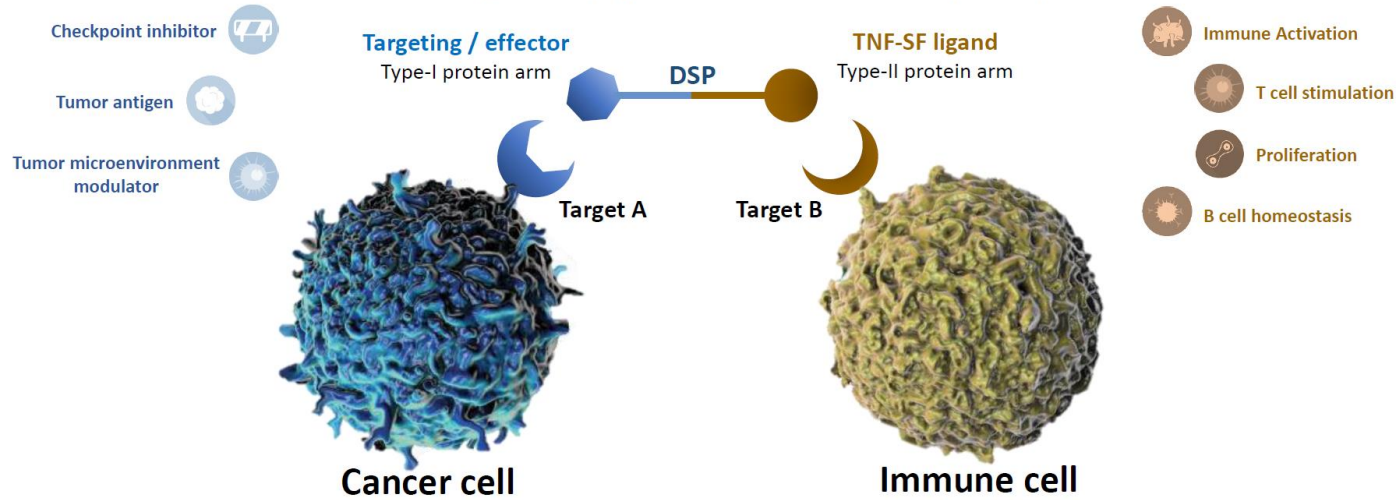
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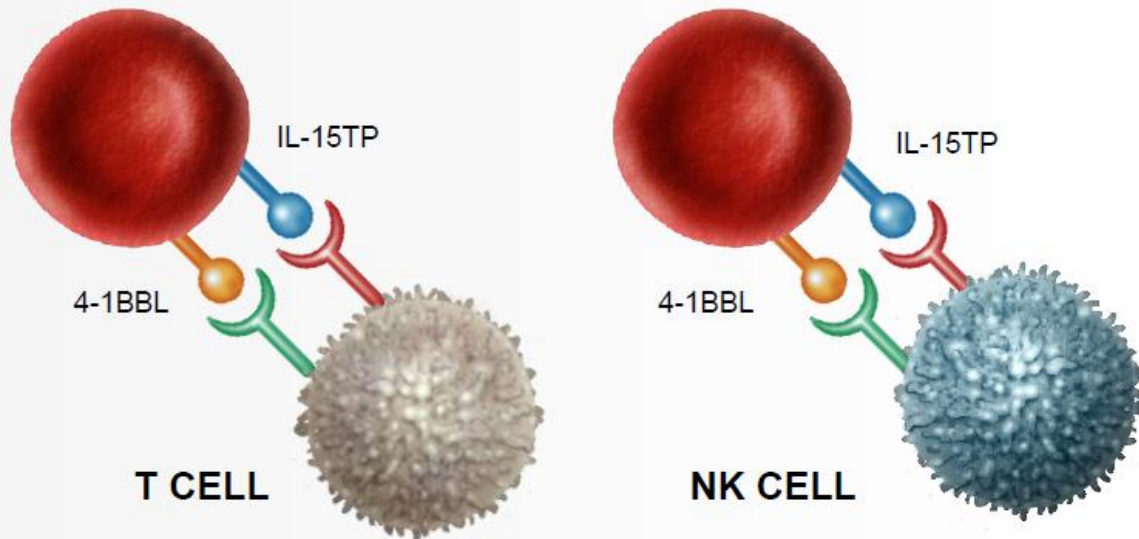
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Novel targets and immuno-engineering

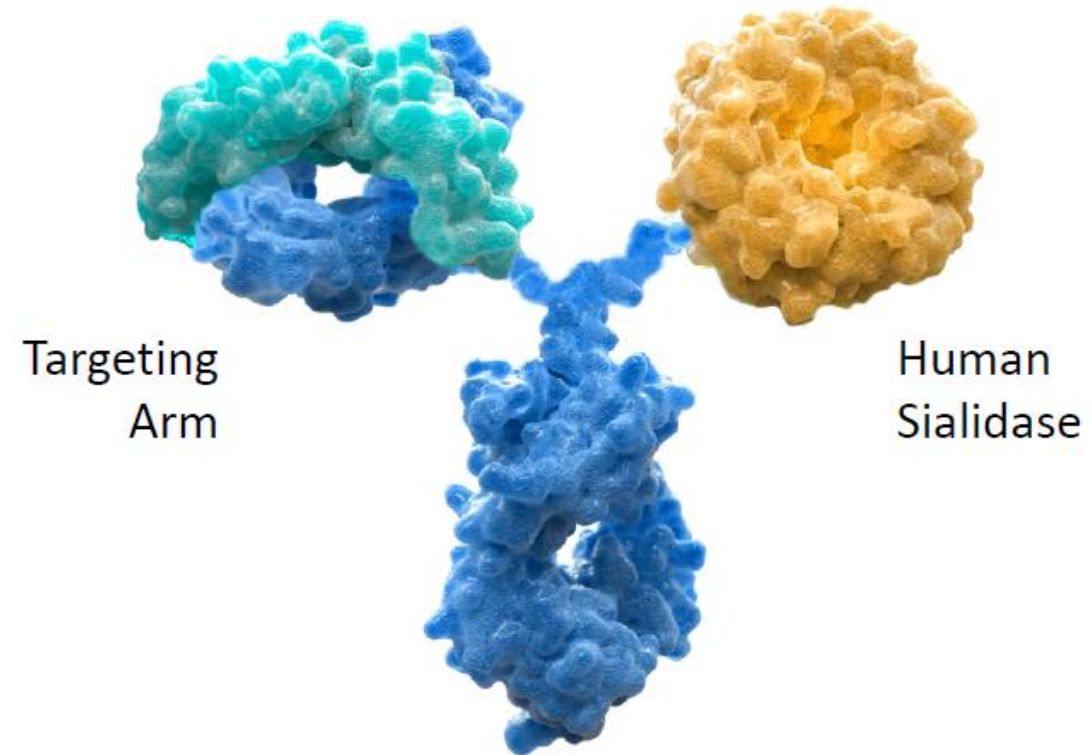
DSPs are generated by fusion of sequences from extracellular domains of type-I membrane protein and TNF superfamily ligand to form a trimeric bi-specific protein



RTX-240 | (4-1BBL + IL-15TP)



Enzyme-Antibody Glyco-Ligand Eediting



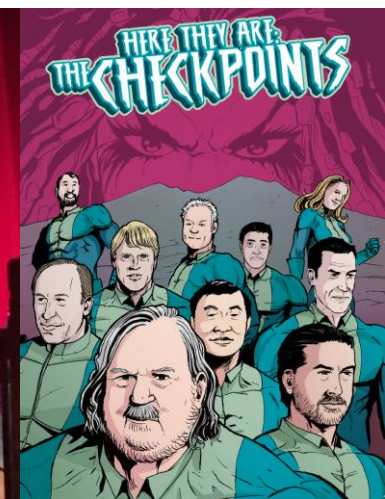
Conclusions

- **Combination immunotherapy is the future of cancer therapy**
- **The T cell-inflamed tumor microenvironment is a biological guide to IO drug development**
- **Many novel IO approaches being developed including but not limited to**
 - Next gen checkpoints and bispecific approaches
 - Innate immune modifiers, cytokines and immuno-metabolism
 - Novel targets and immuno-engineering
- **Exciting time in cancer drug development!**

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