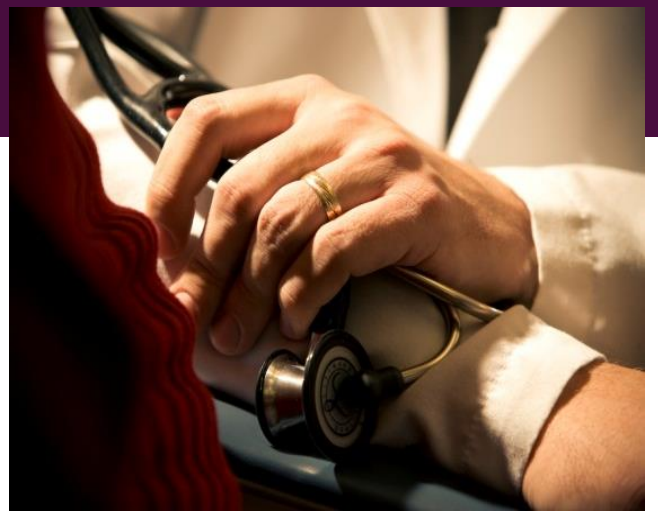


What's Next for Cancer Immunotherapy?

Jason J. Luke, MD, FACP
Associate Professor
Director of the Cancer Immunotherapeutics Center

University of Pittsburgh

NCI Designated Comprehensive Cancer Center

UPMC LIFE CHANGING MEDICINE

Disclosures in past 12 months

- **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:** 7 Hills, Spring bank, Actym, Alphamab Oncology, Arch Oncology, Kanaph, Mavu, Onc.AI, Pyxis, Tempest, Abbvie, Array, Bayer, Bristol-Myers Squibb, Checkmate, Cstone, Eisai, EMD Serono, KSQ, Janssen, Merck, Mersana, Nektar, Novartis, Pfizer, Regeneron, Ribon, Rubius, Silicon, Tesaro, Werewolf, Xilio, Xencor

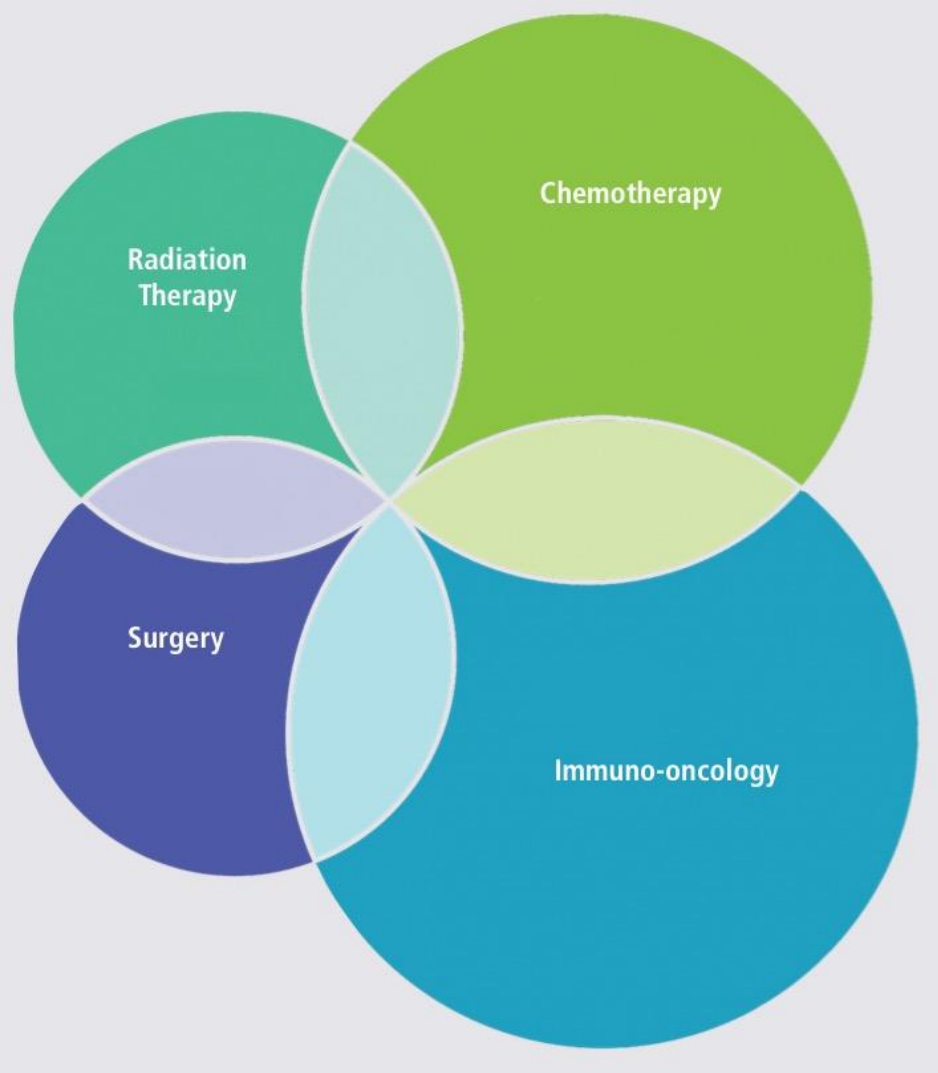
- **Contracted Research:** AbbVie, Agios (IIT), Array (IIT), Astellas, Bristol-Myers Squibb (IIT & industry), Corvus, EMD Serono, Immatics, Incyte, Kadmon, Macrogenics, Merck, Moderna, Nektar, Spring bank, Tizona, Xencor

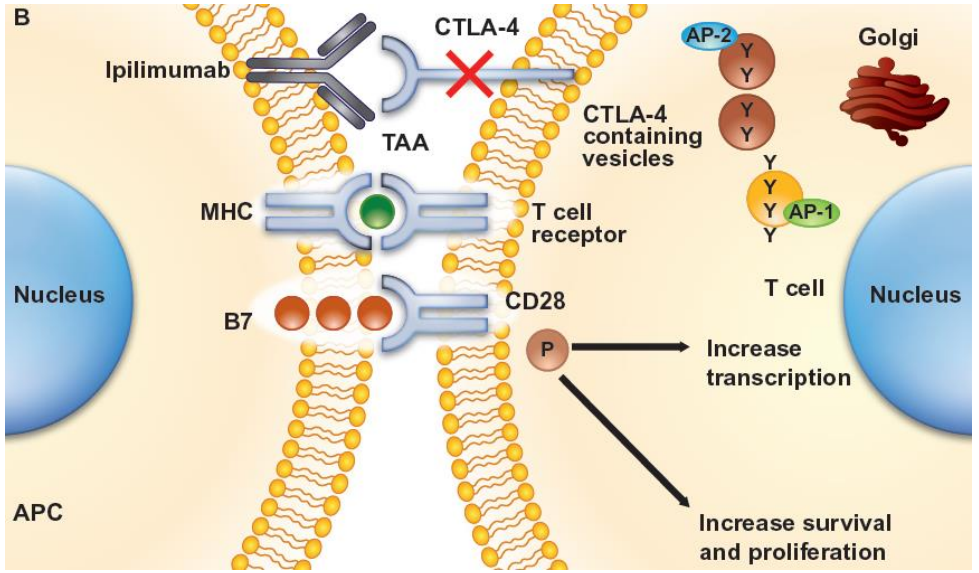
- **Ownership Interest Less than 5%:** Actym, Alphamab Oncology, Arch Oncology, Kanaph, Mavu, Onc.AI, Pyxis, Tempest

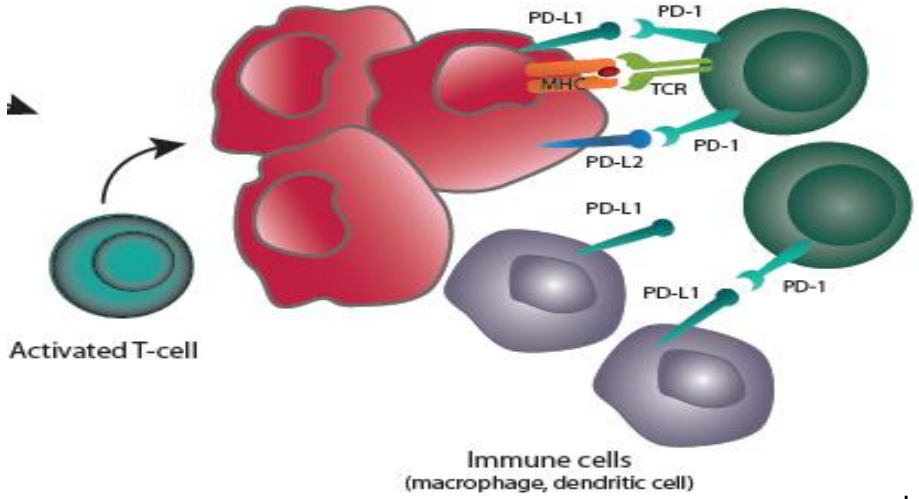
Key Points:

- 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



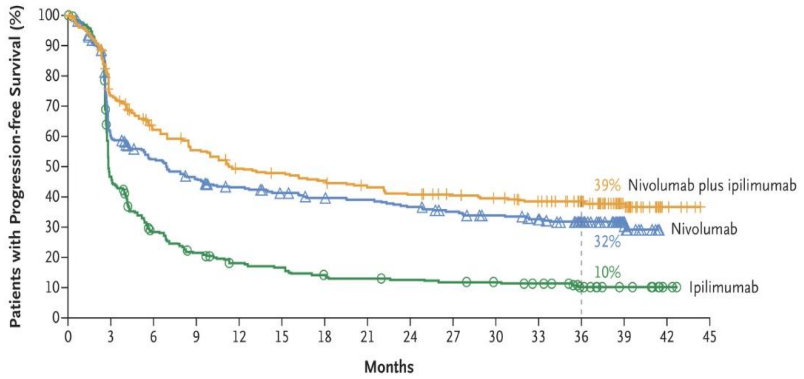




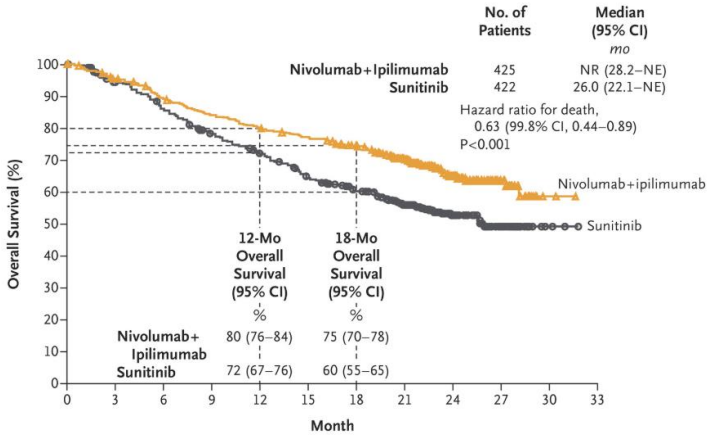
Luke and Hodi. *Oncologist*. 2013
Luke and Ott. *Oncotarget*. 2015

Combination immunotherapy now standard in multiple tumor types

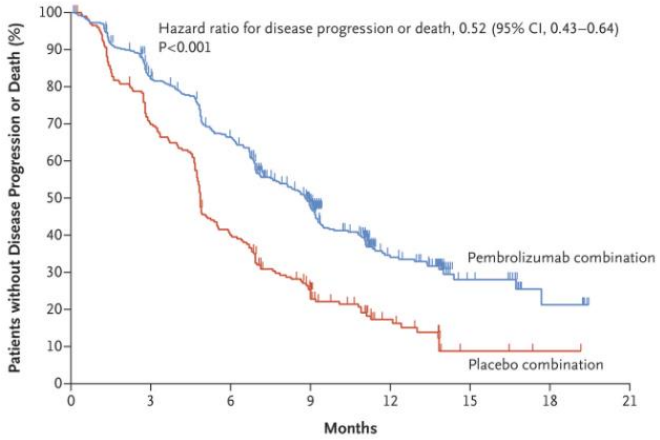
Melanoma: PD1 + CTLA4



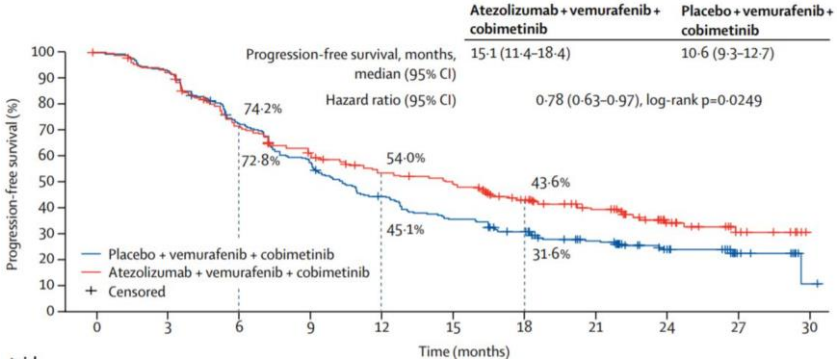
RCC: PD1 + CTLA4



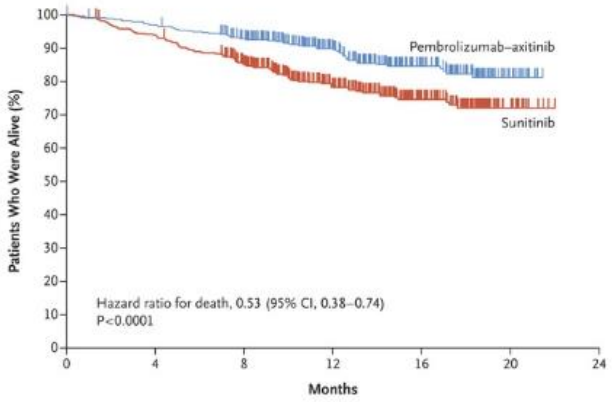
NSCLC: PD1 + chemotherapy



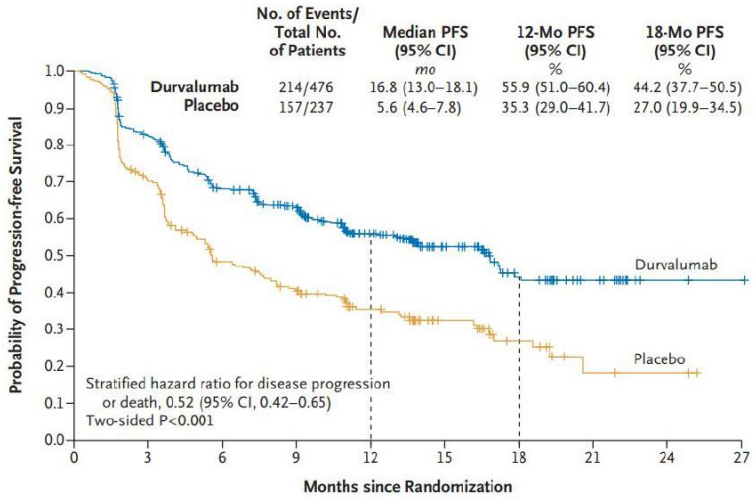
Melanoma: BRAF + MEK + PDL1



RCC: VEGFR2 + PD1/L1



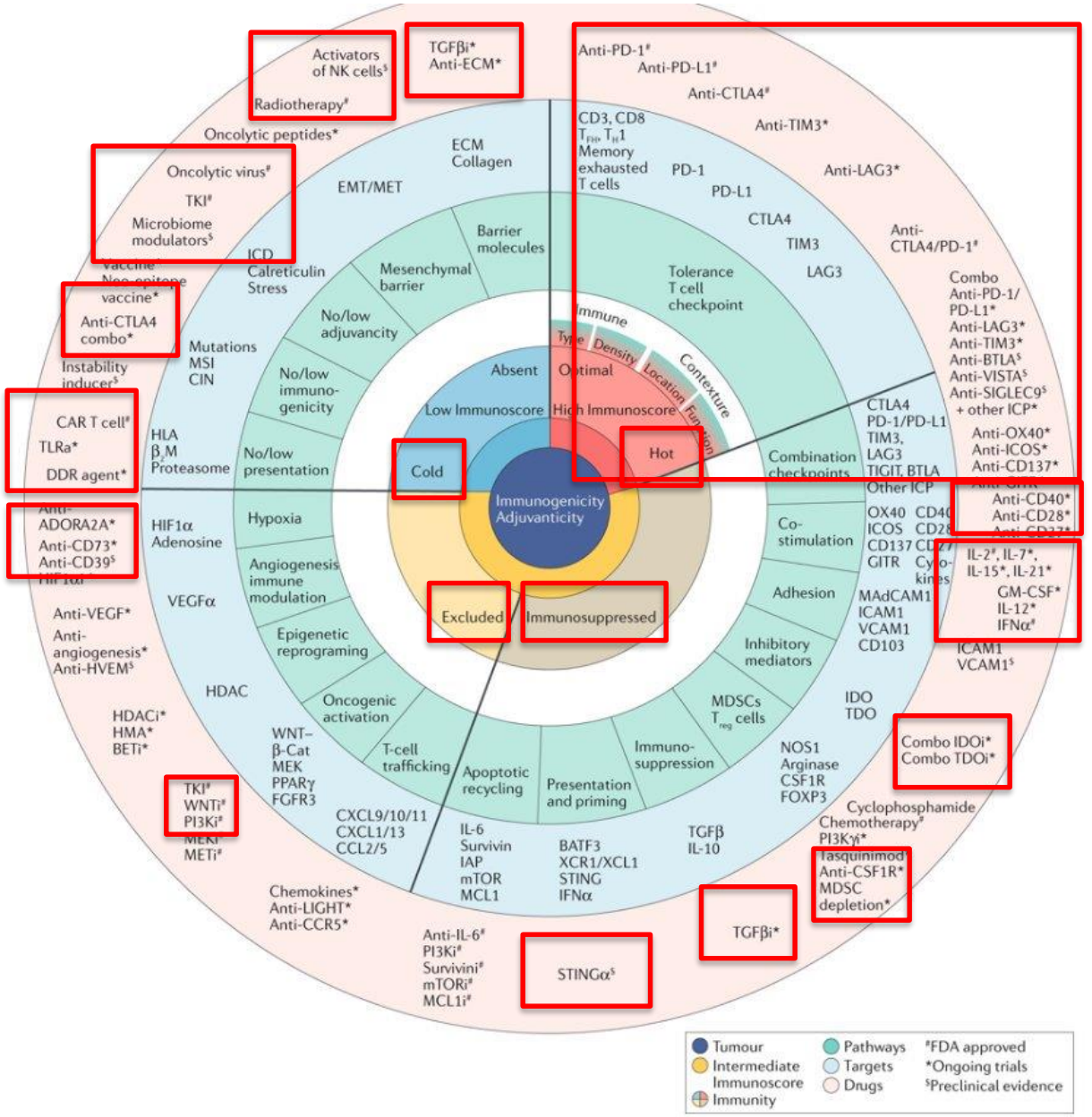
NSCLC: PDL1 following chemoRT



Wolchok *et al*. NEJM 2017; Gutzmer *et al*. *Lancet*. 2020; Motzer *et al*. NEJM 2018; Rini *et al*. NEJM 2019; Ghandi *et al*. NEJM 2018; Antonia *et al*. NEJM 2017

Tumor–immune classification cycle to direct anticancer therapy

Stratify tumors by tumor immune status for early phase trials



Galon and Bruni, Nat Rev Drug Disc 2019

Drug Development in Immuno-Oncology

- **Next gen immune-checkpoints**
  - LAG3, TIGIT, TIM3

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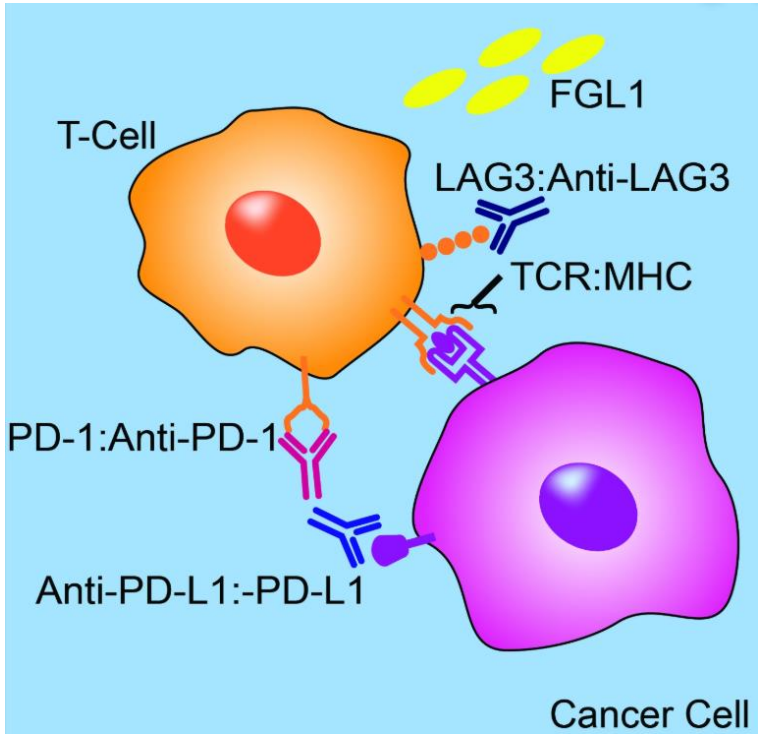
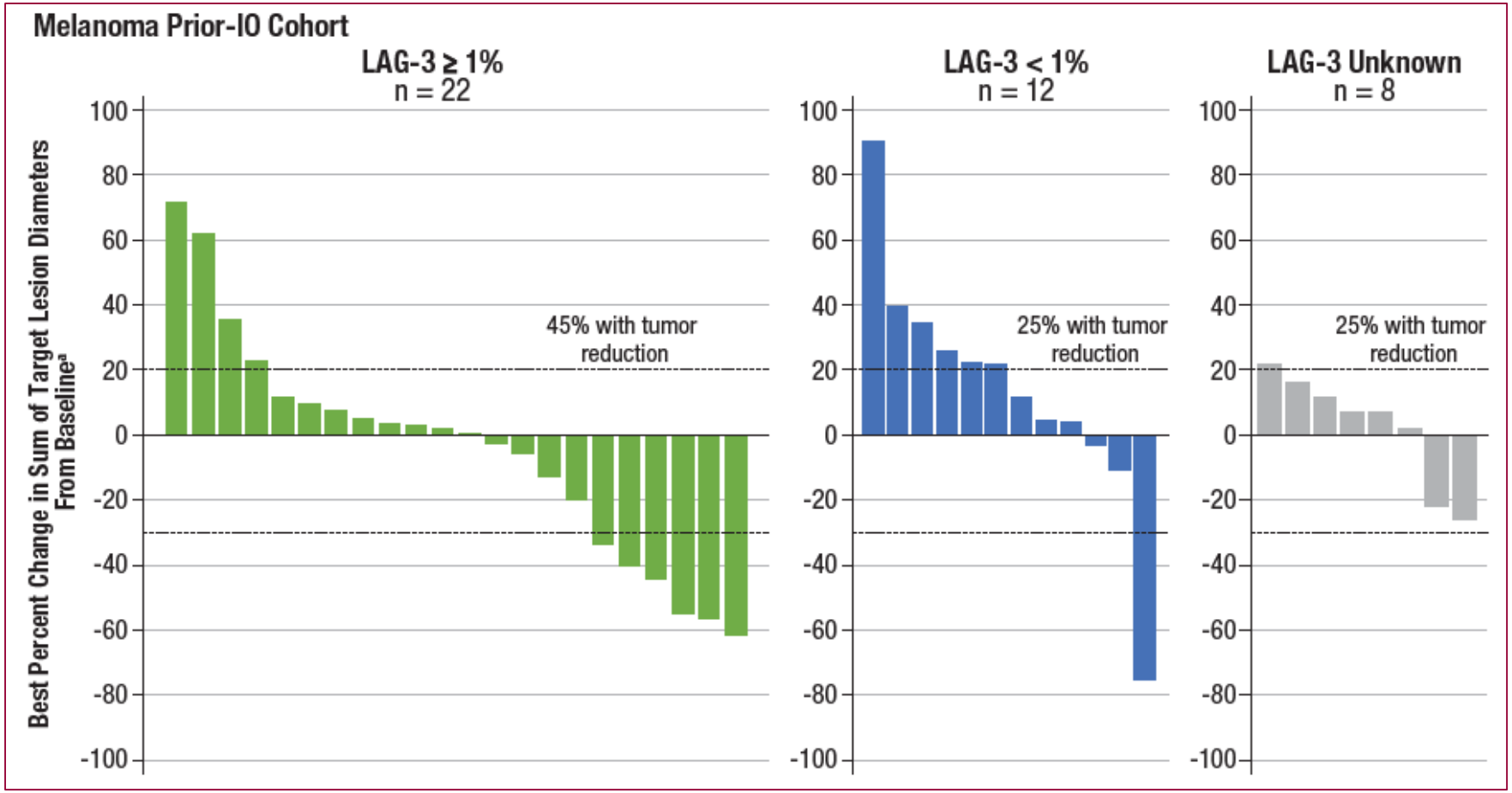
Rationale for LAG3-PD1 Combination





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

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

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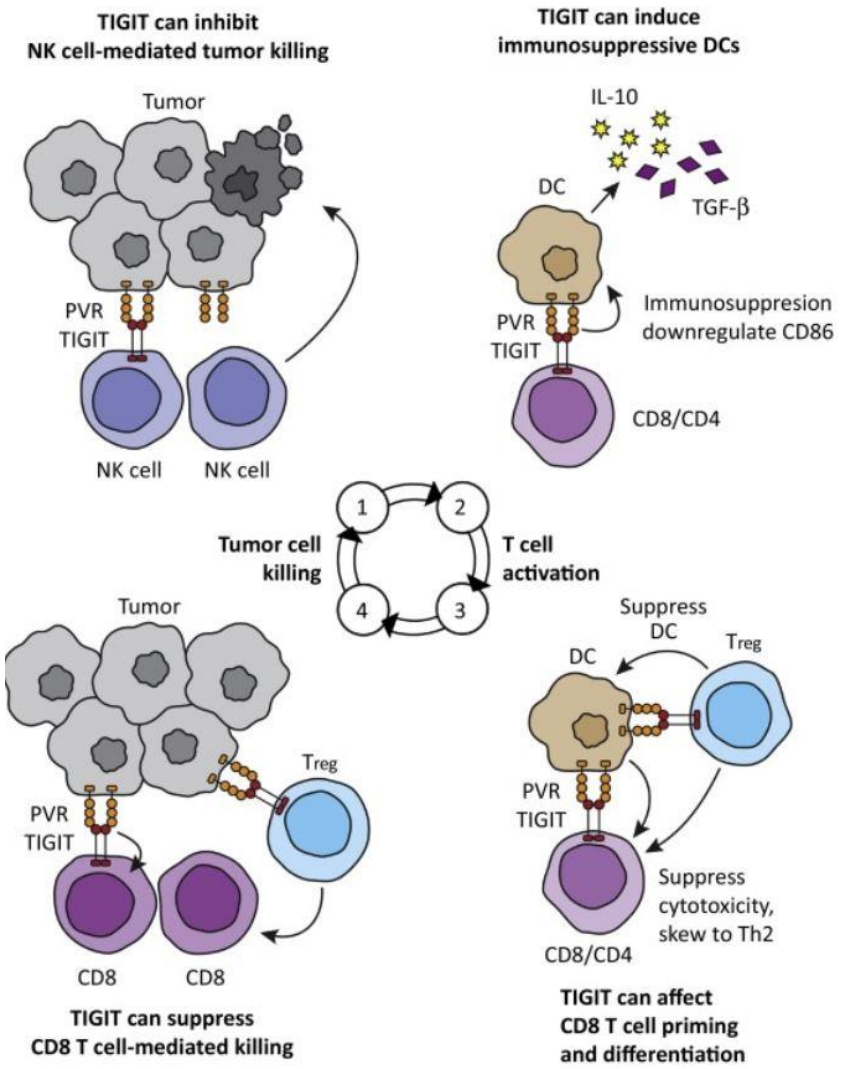
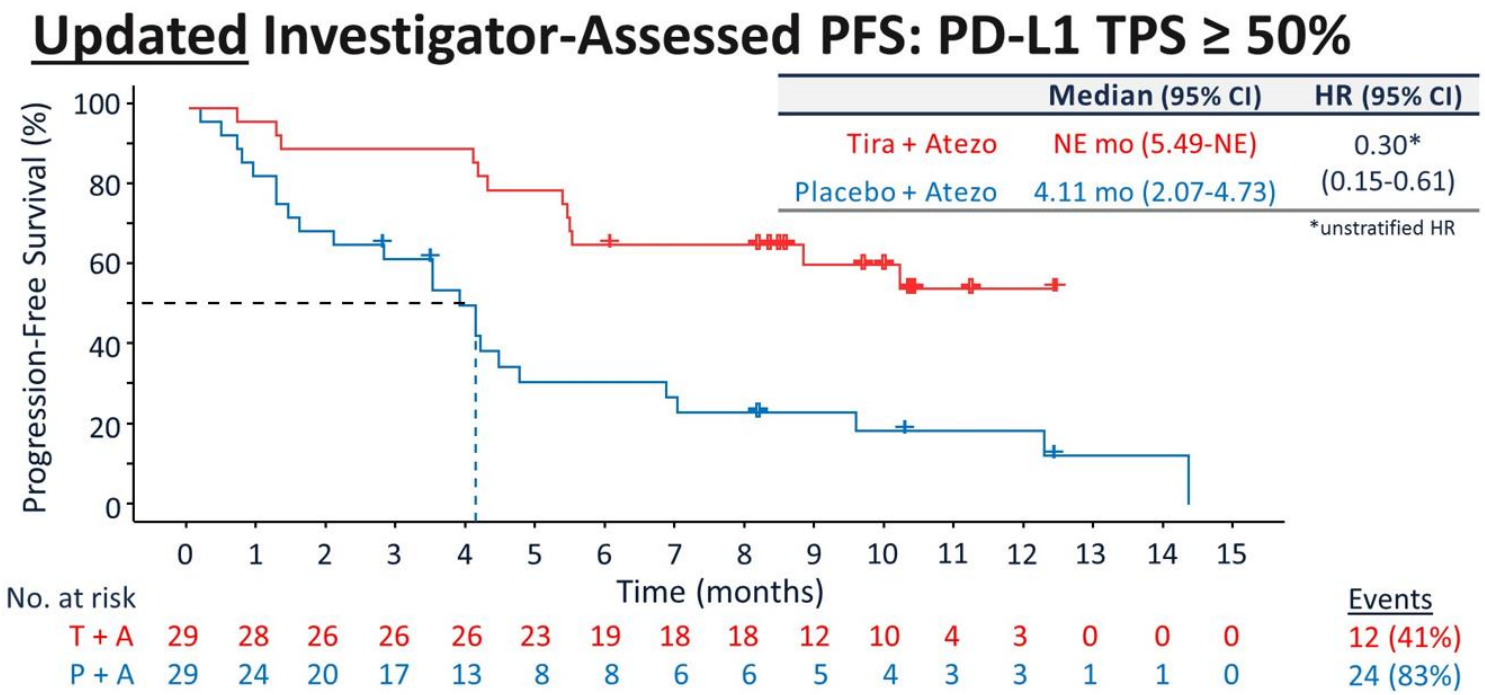
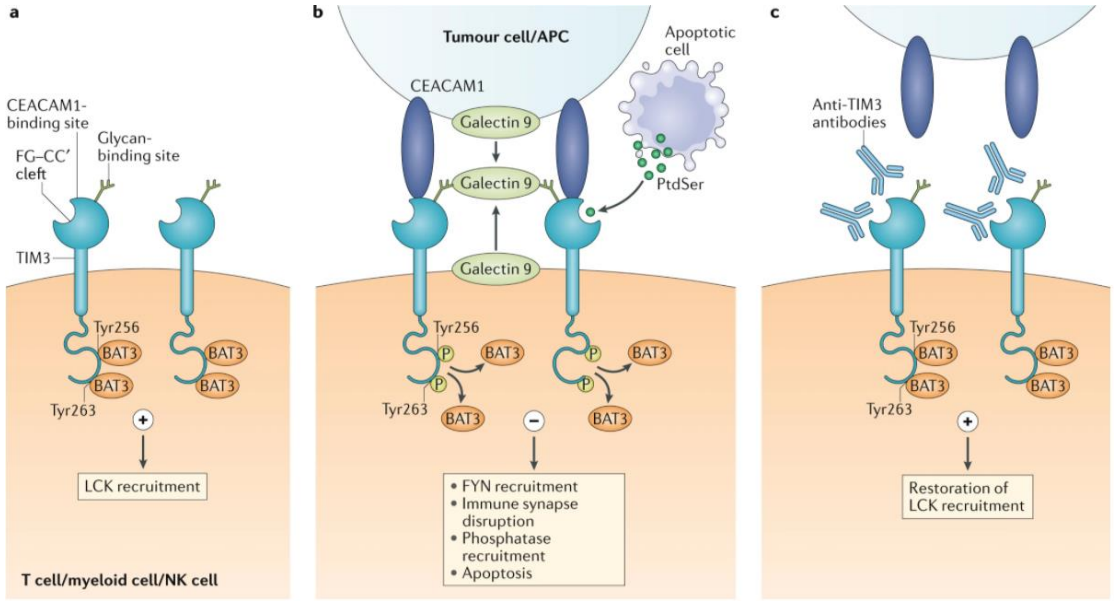
Targeting TIGIT on multiple cell types

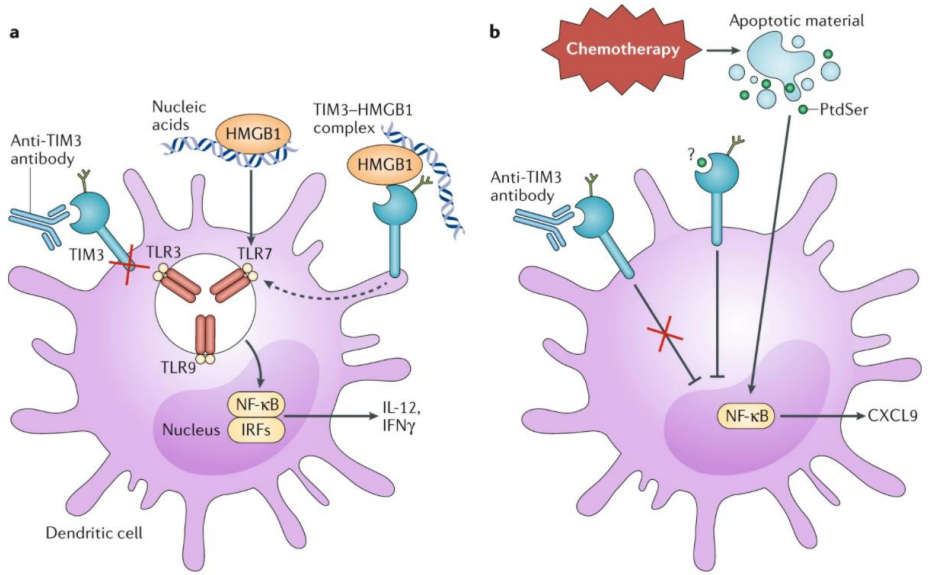


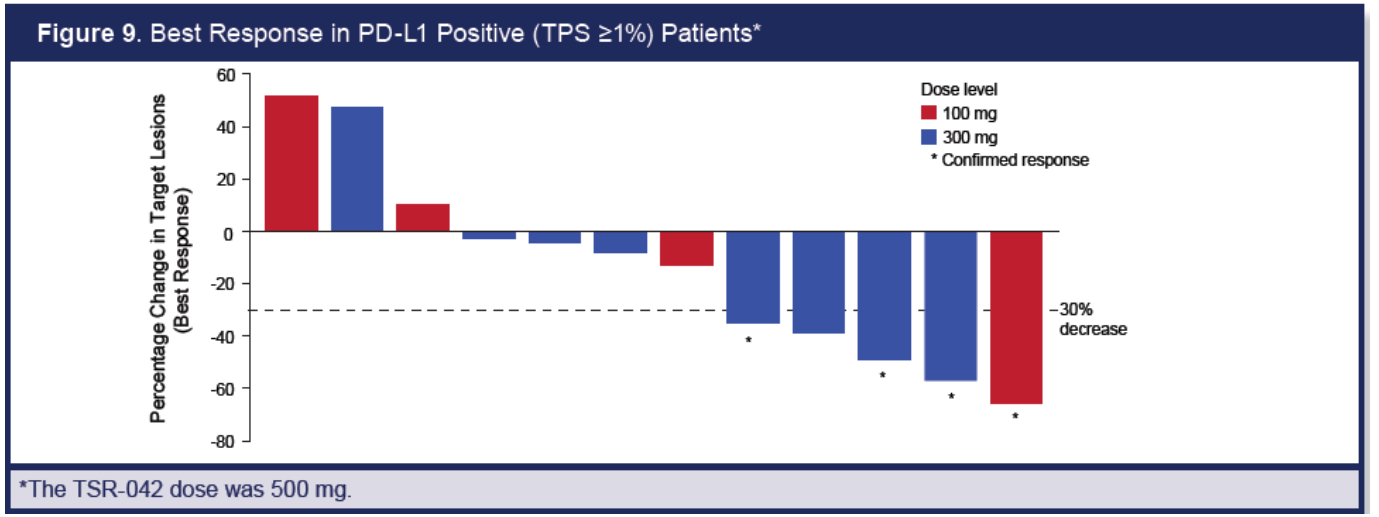


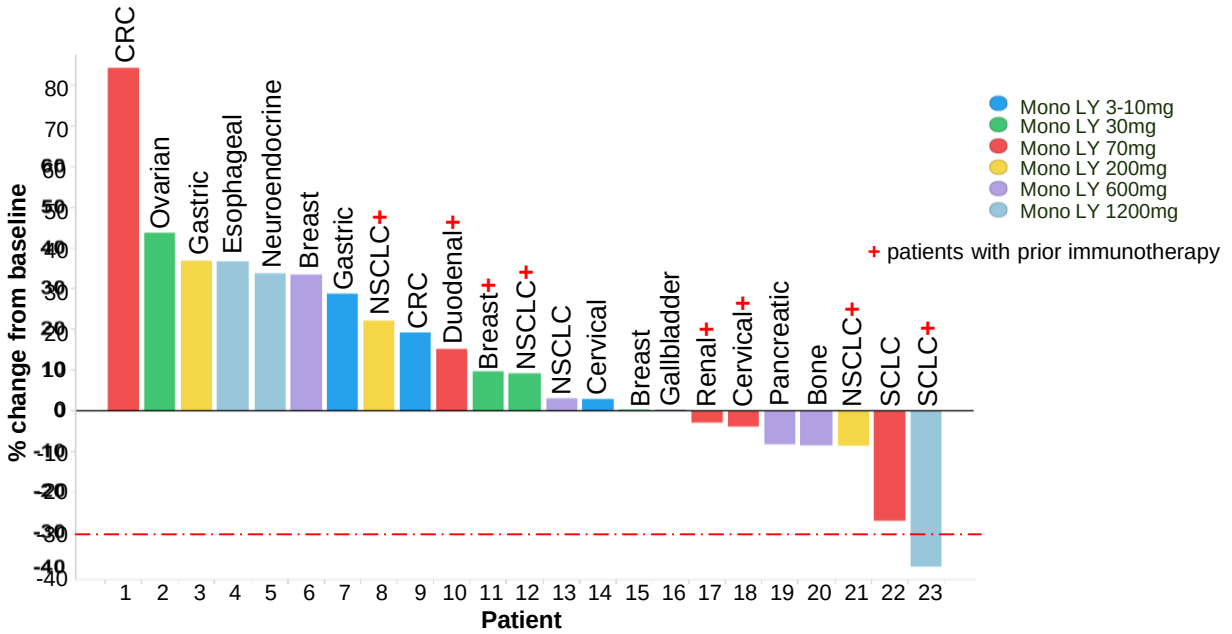
Manieri *et al*. *Trends in Immuno* 2017; Rodriguez-Abreu *et al*. ASCO 2020

TIM3 checkpoint on multiple cell types







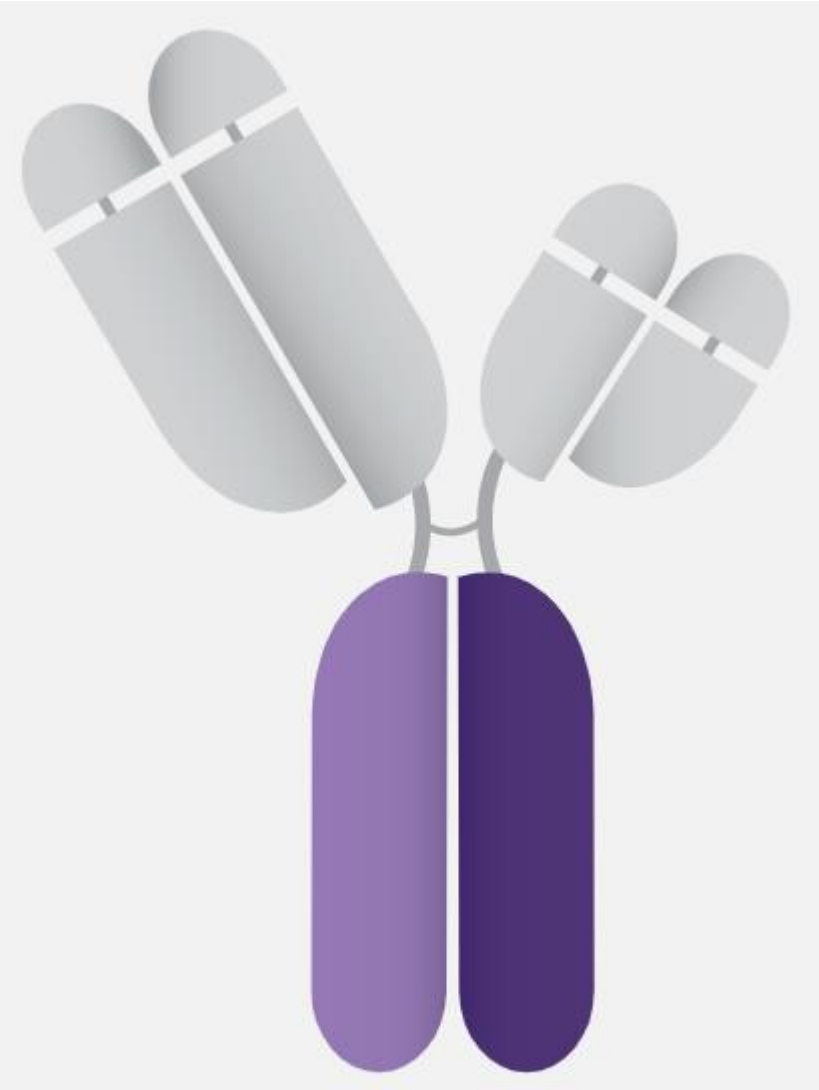


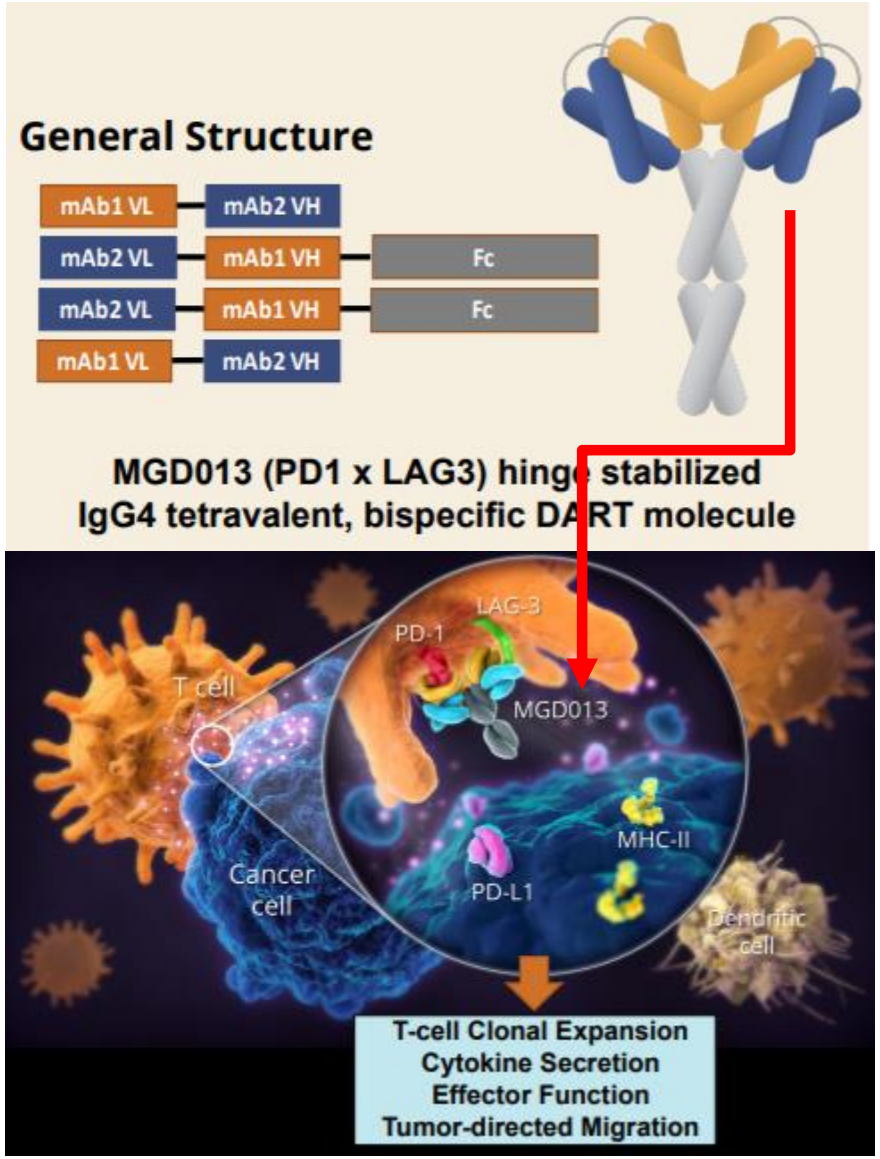
Wolf *et al*. *Nat Rev Immuno* 2019; Davar *et al.* SITC 2018; Harding *et al*. ASCO-SITC 2019

Novel bispecific checkpoint antibodies

Some of the bispecific checkpoints under investigation

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

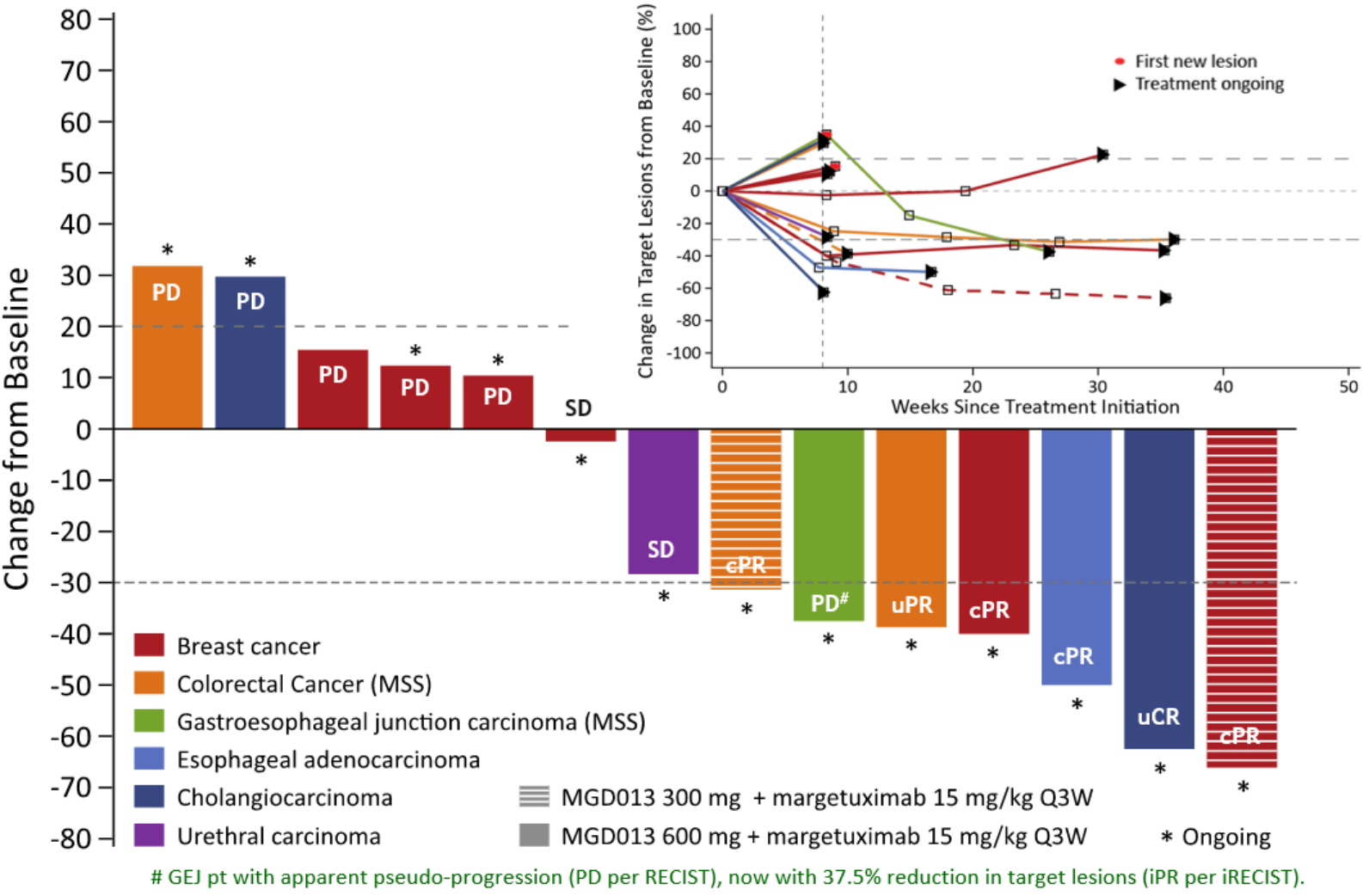




Hickingbottom et al. ASCO 2020 abst e15001; Motte-Mohs et al. SITC 2017

Fc-engineered αHER2 + PD-1×LAG-3 DART (Margetuximab plus MGD013)

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



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

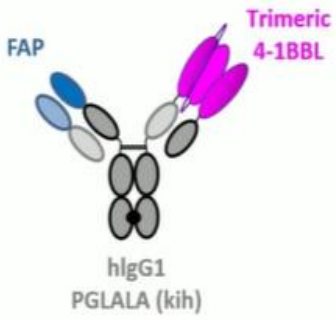
- ORR = 42.9% (6/14 evaluable pts)
  - Includes unconfirmed objective responses
- Well-tolerated
  - Responding patients remain on therapy

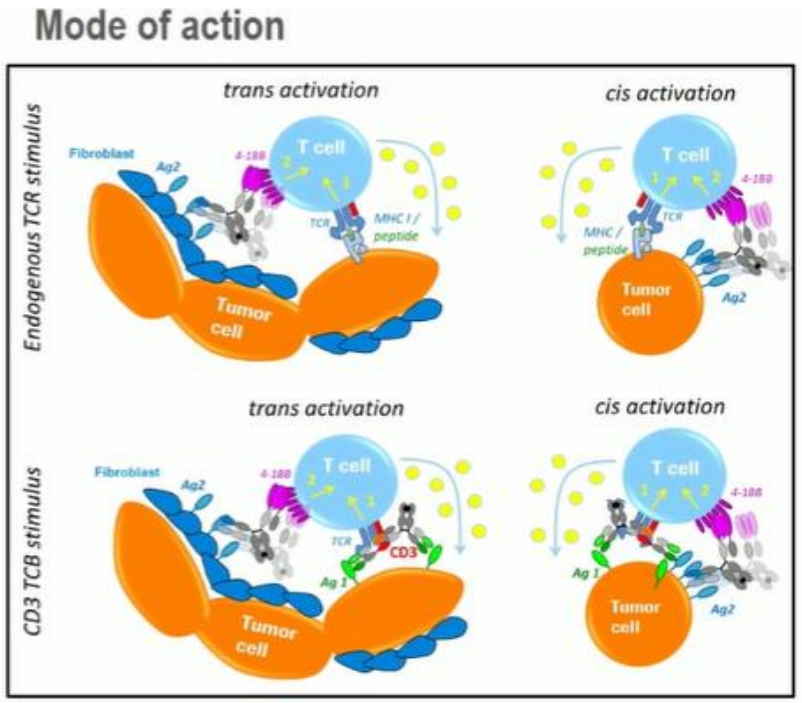
Baseline PD-L1 & LAG-3 in # of Responding Patients (N = 6)

PD-L1 CPS:	< 1	1	TBD
N	4	1	1

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

Bispecific tumor microenvironment targeting

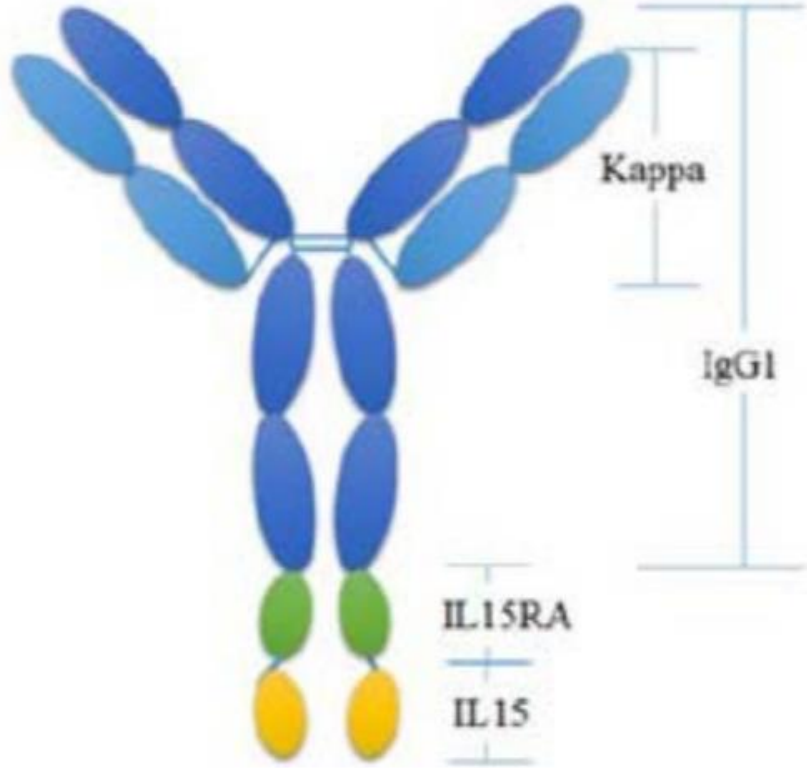




Claus et al. *Sci. Transl. Med*, 2019

aPD-L1 antibody

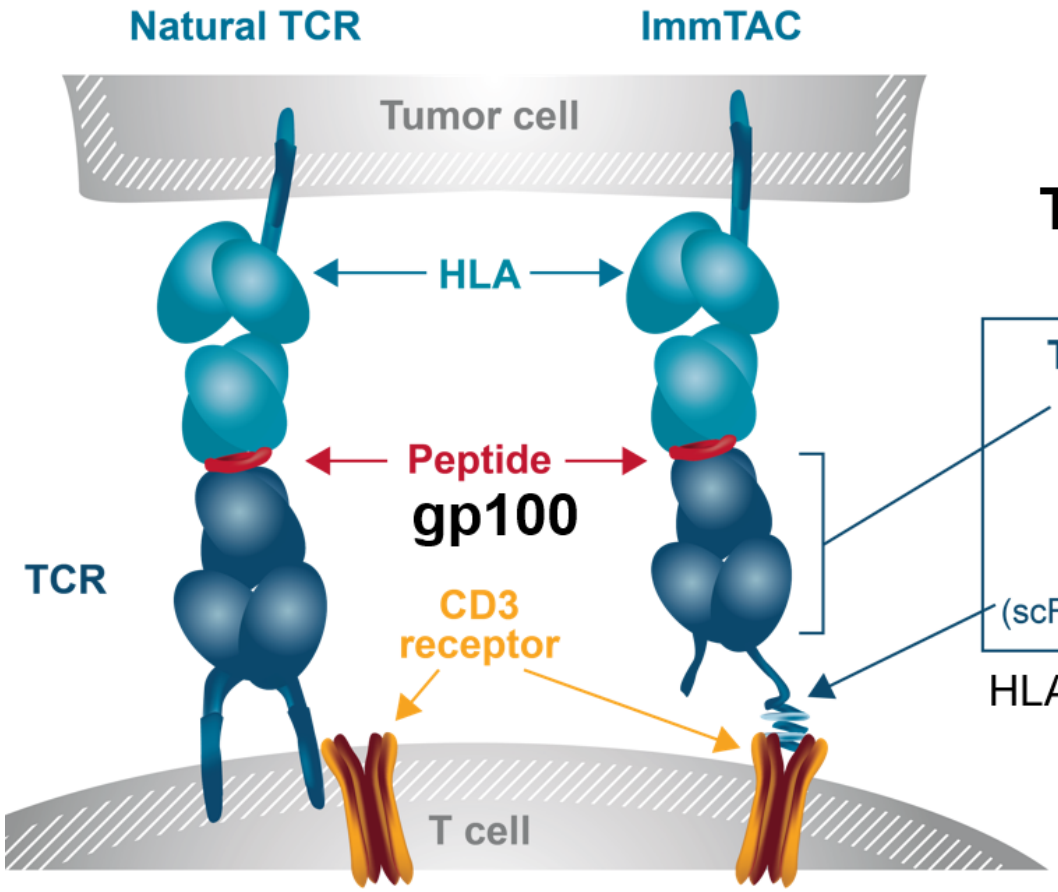
IL-15/IL15Rα sushi domain is fused to the C-terminal of CH3 of PD-L1 antibody



@jasonlukemd

Piha-Paul *et al*. ESMO 2020; Melero *et al*. ESMO 2020

T cell redirection Activate T Cells Against Cancer



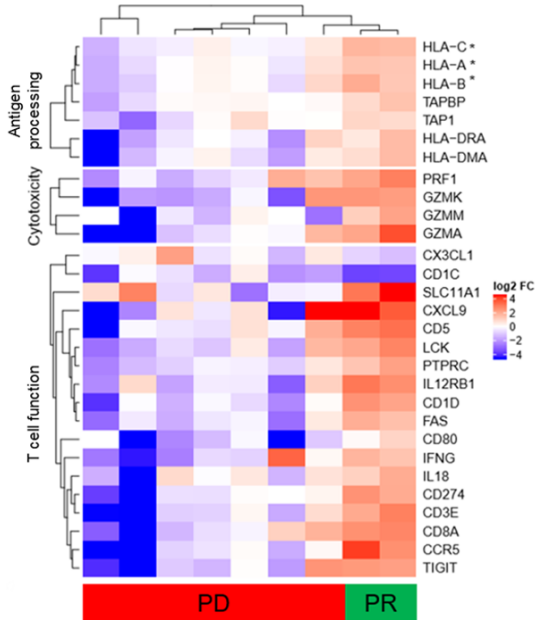
Tebentafusp
ImmTAC

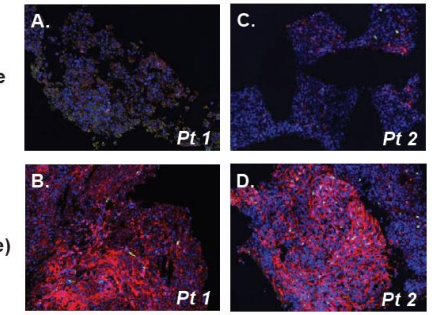
Targeting domain
(affinity engineered TCR, pM affinity)

Effector domain
(scFv–anti-CD3, nM affinity)

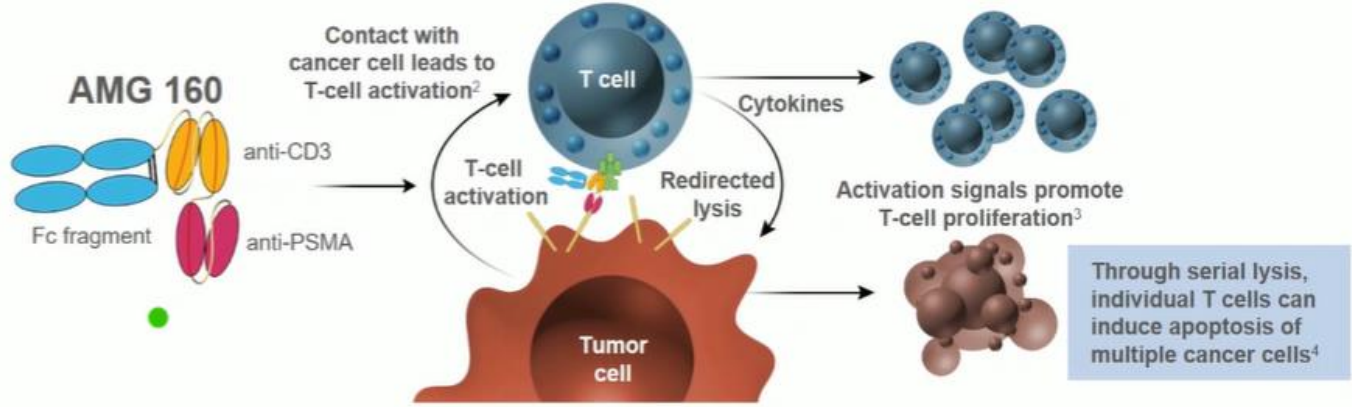
HLA-A 02:01 restricted

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**).*



Jason J. Luke @jasonlukemd

Presented by Shoushtari on behalf of Middleton et al. SMR 2019; Tran *et al*. ESMO 2020

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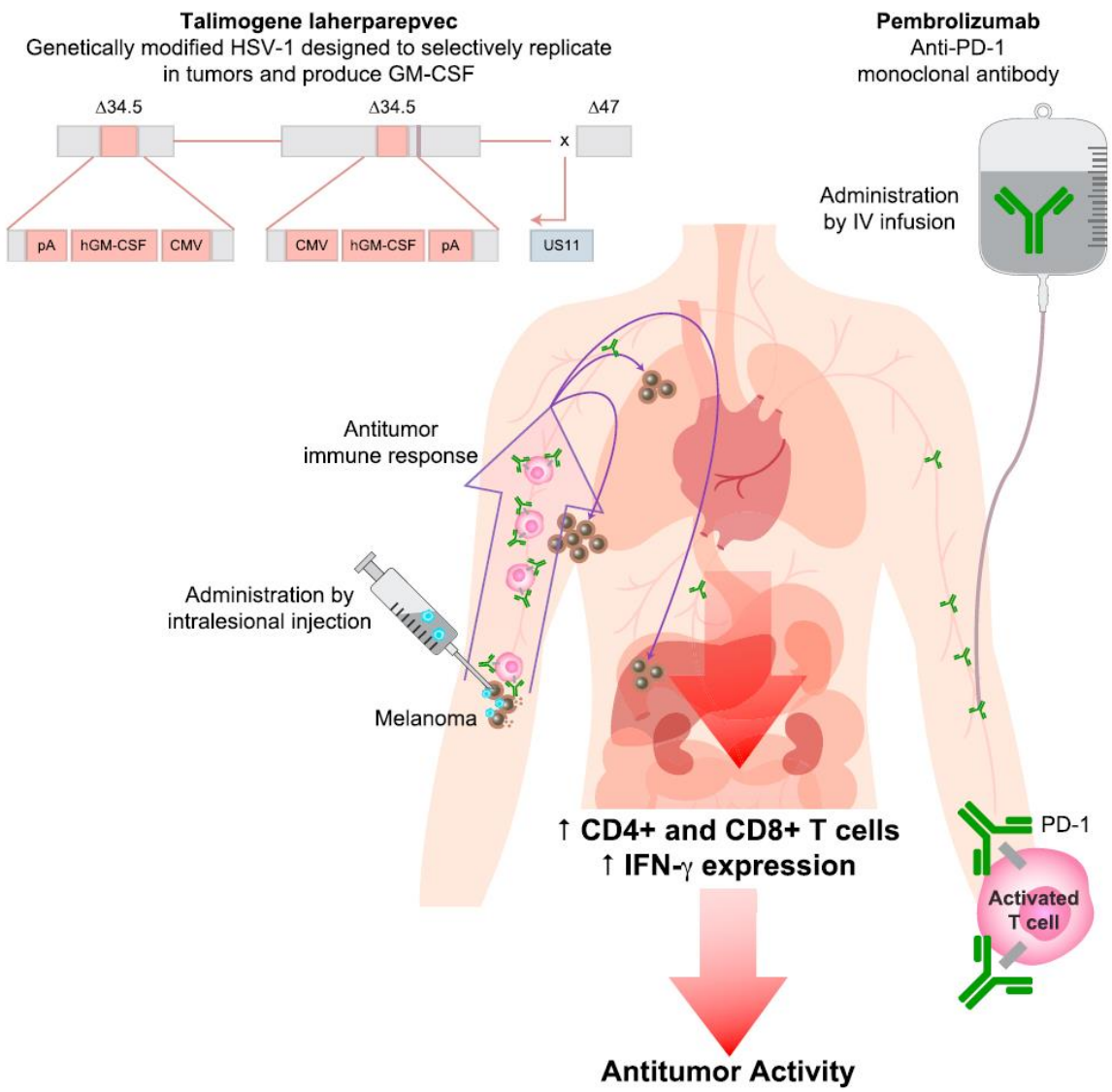
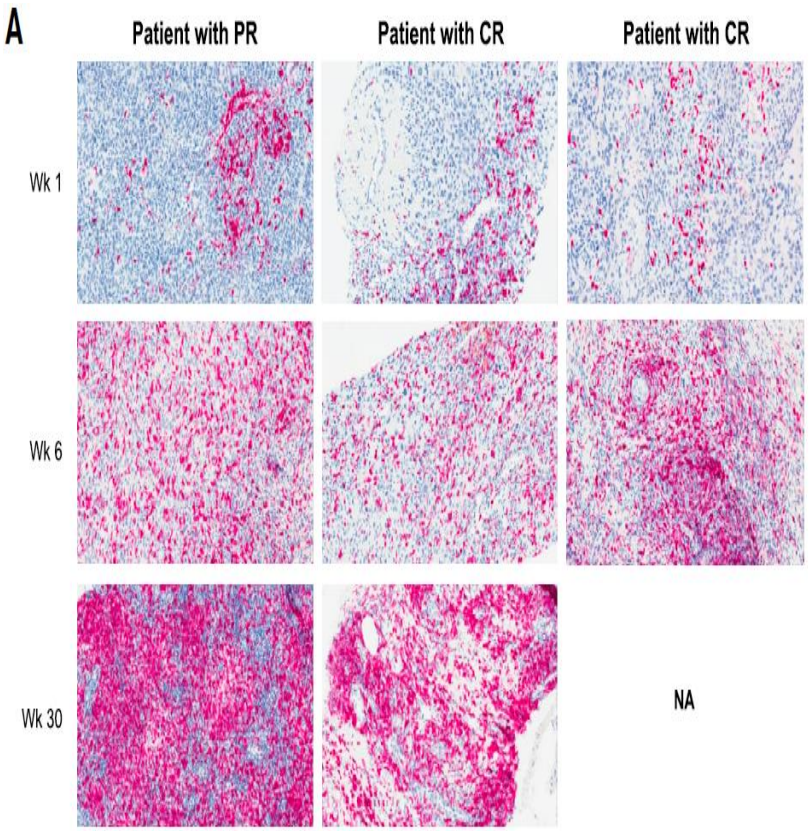
Oncolytic virotherapy promotes intra-tumoral T cell infiltration and improves anti-PD1 immunotherapy

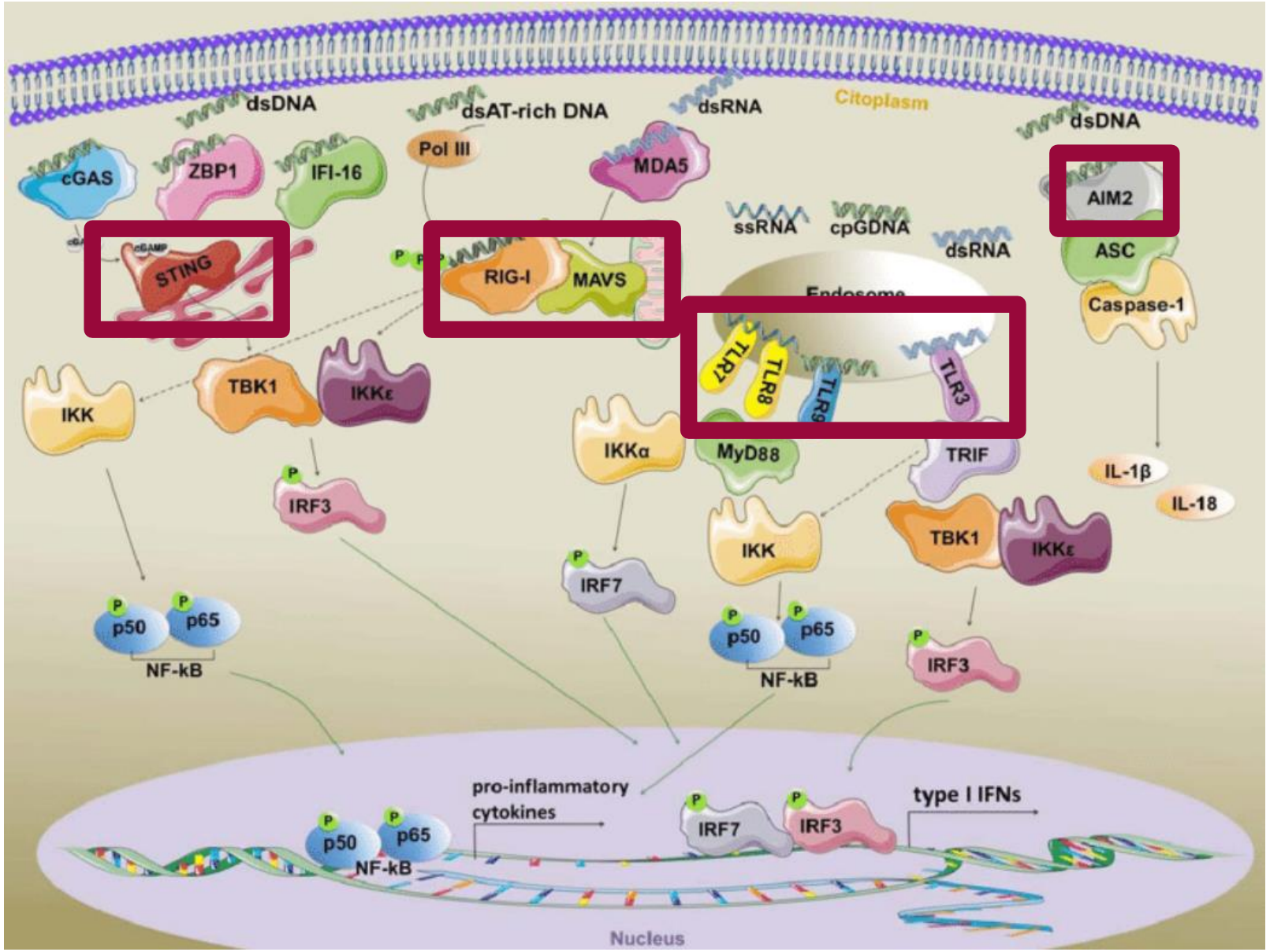




@jasonlukemd

Ribas *et al*. *Cell* 2017

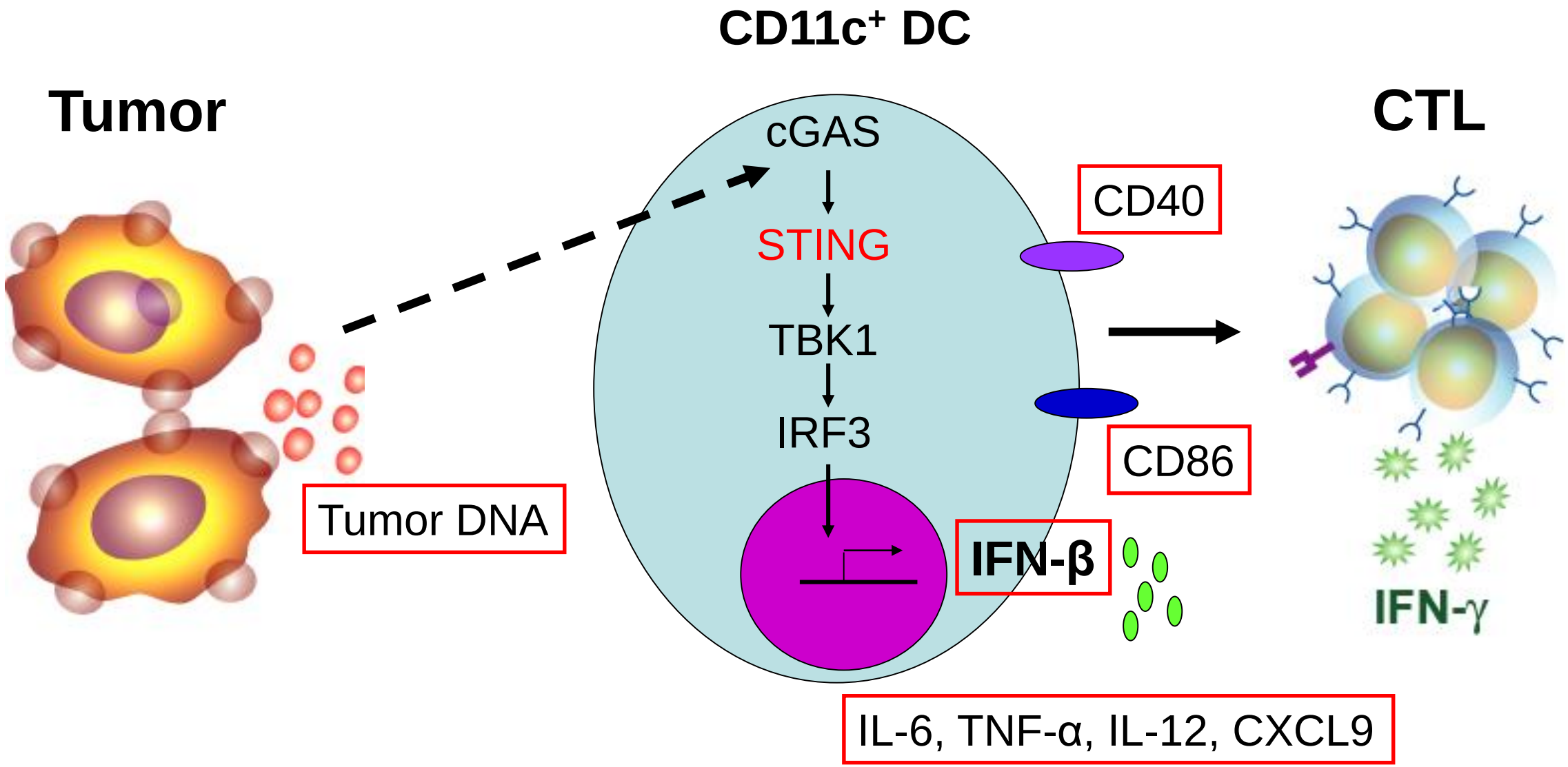
Pathways of danger (nucleic acid) sensing machinery active DCs



@jasonlukemd

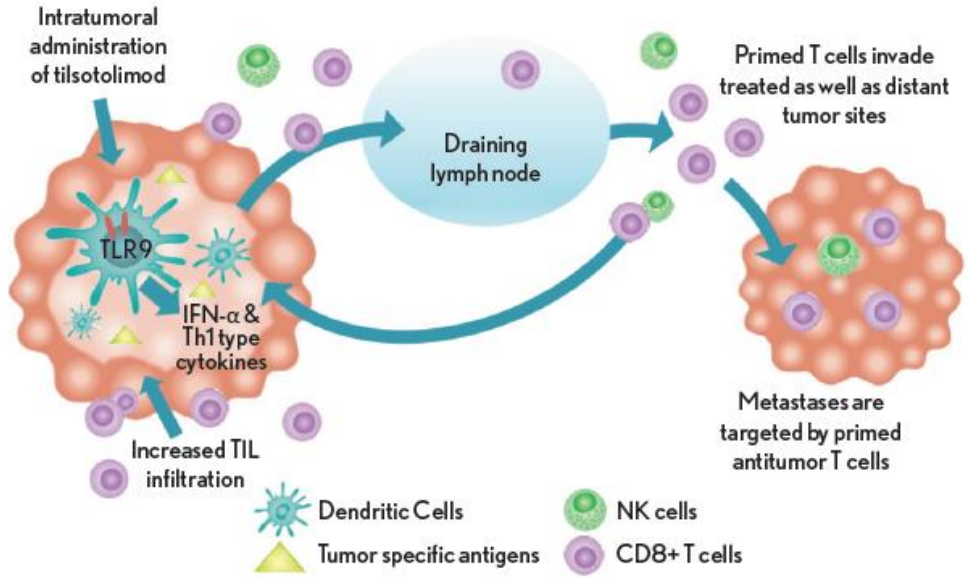
Iurescia *et al*. Recent Patents on Anti-Cancer Drug Discovery 2017

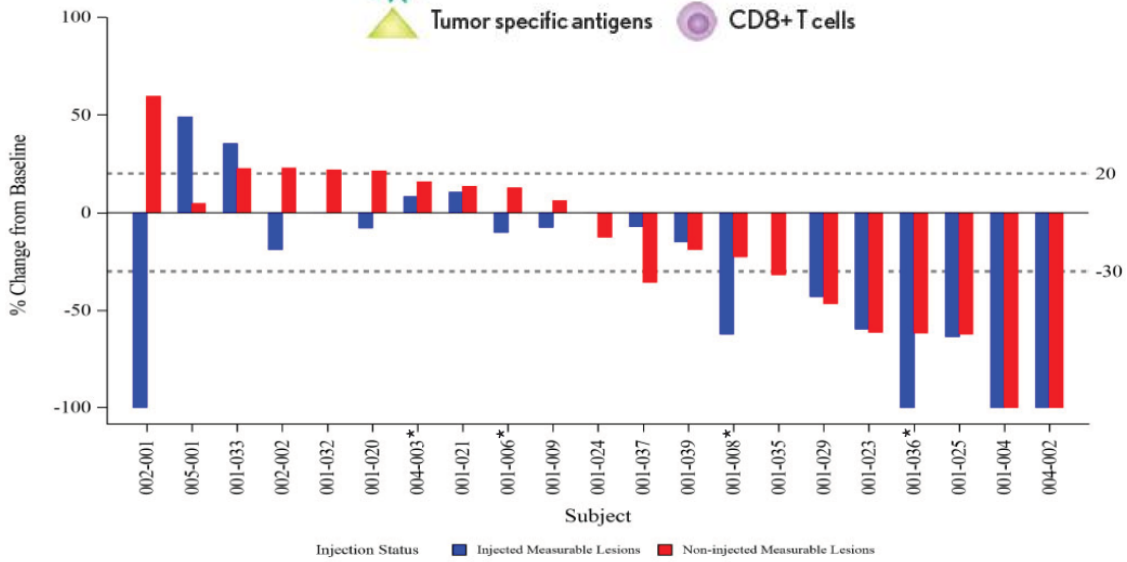
Model for innate immune sensing of tumors through the host STING pathway and tumor-derived DNA



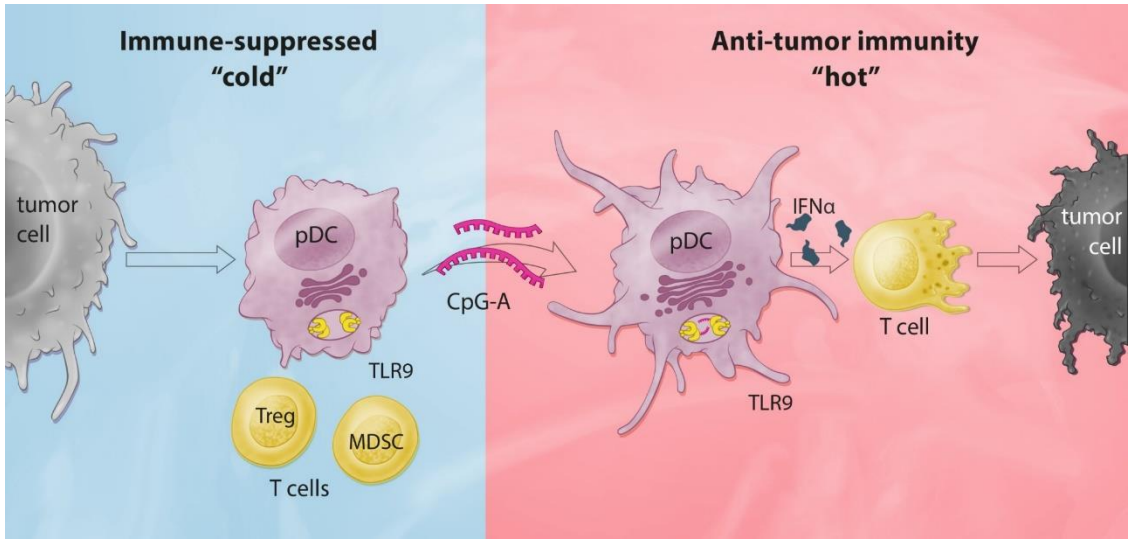
Woo *et al*. Immunity. 2014

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



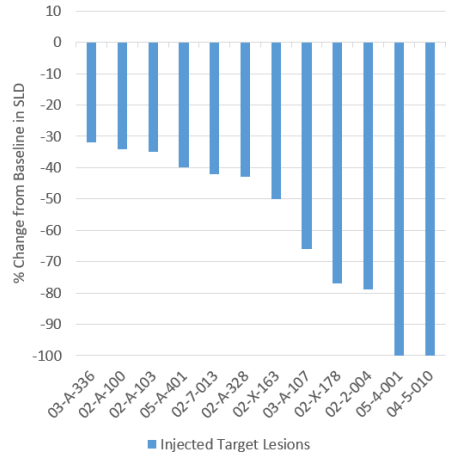


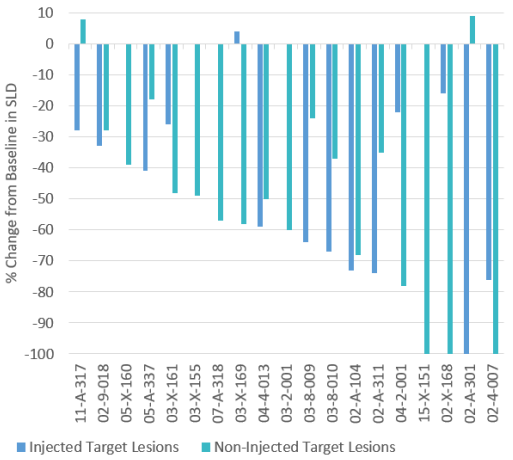
*Subjects were previously treated with ipilimumab in the metastatic setting.



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

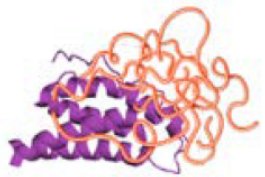
Similar Responses in Injected vs. Non-Injected Lesions of Responders (N= 31)





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

Pegylated CD122 (IL-2Rβγ) agonist may synergize with anti-PD1



NKTR-214

βγ

CTLs

CD8+ T-Cells and NK Cells

Stimulates Immune Response to Kill Tumor Cells

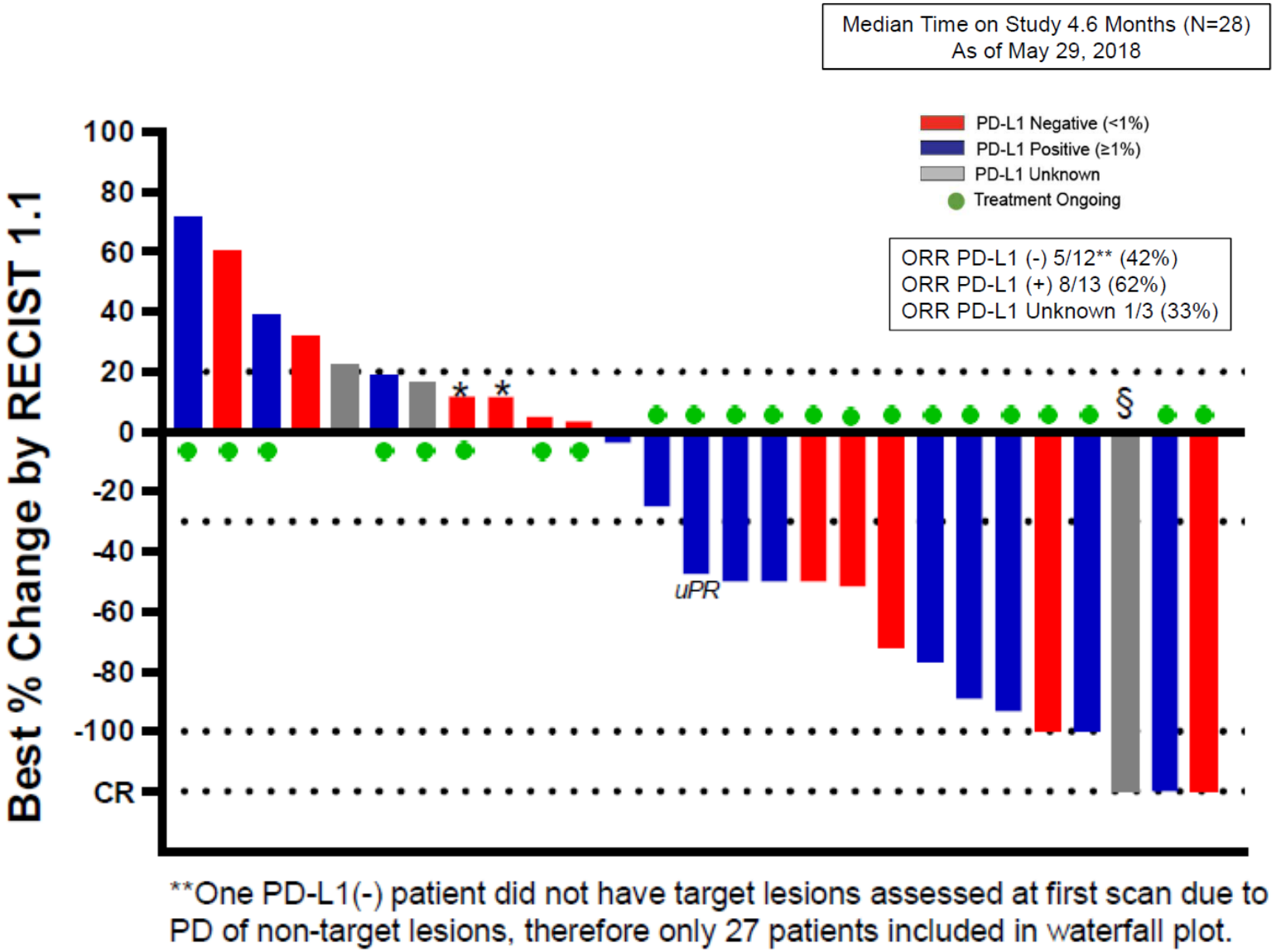
αβγ

Tregs

CD4+ Regulatory T-Cells

Down-Regulates Proliferation of CD8+ T-cells and Suppresses Immune Response

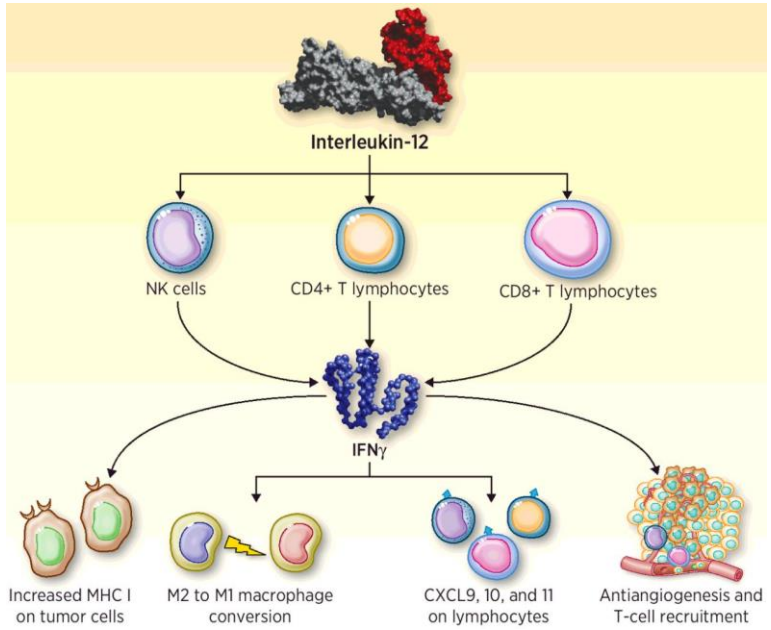
A Phase 3 Study of NKTR-214 Plus Nivolumab Vs Nivolumab in Untreated Metastatic Melanoma

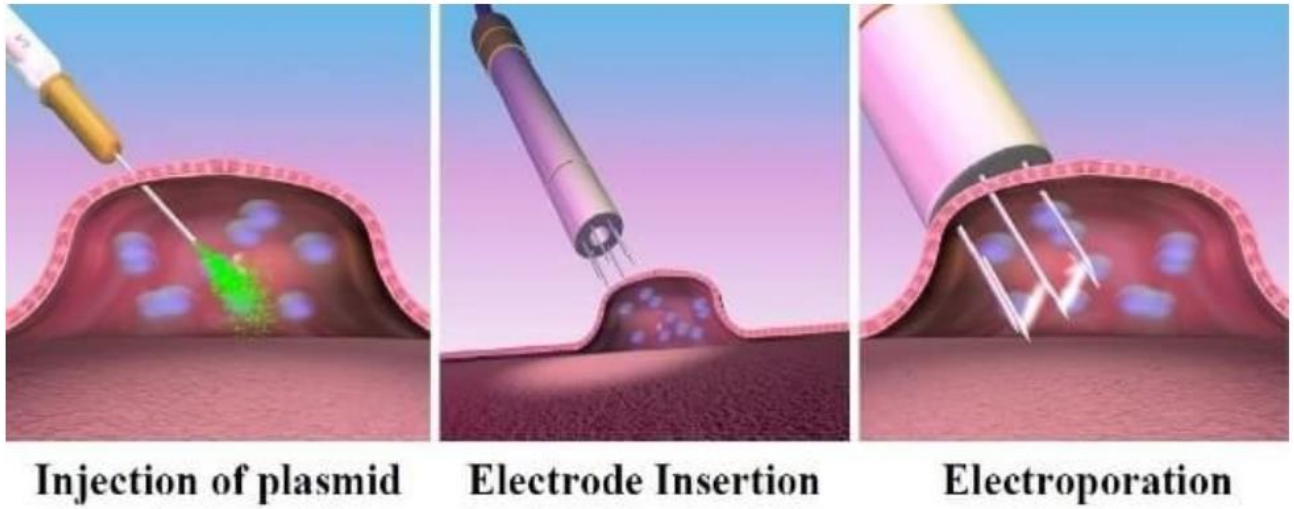


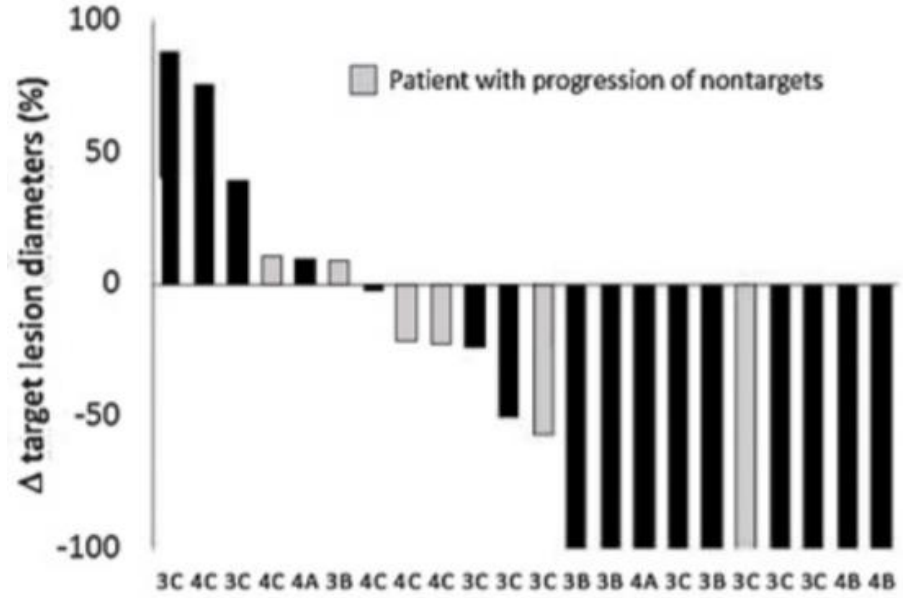
**One PD-L1(-) patient did not have target lesions assessed at first scan due to PD of non-target lesions, therefore only 27 patients included in waterfall plot.

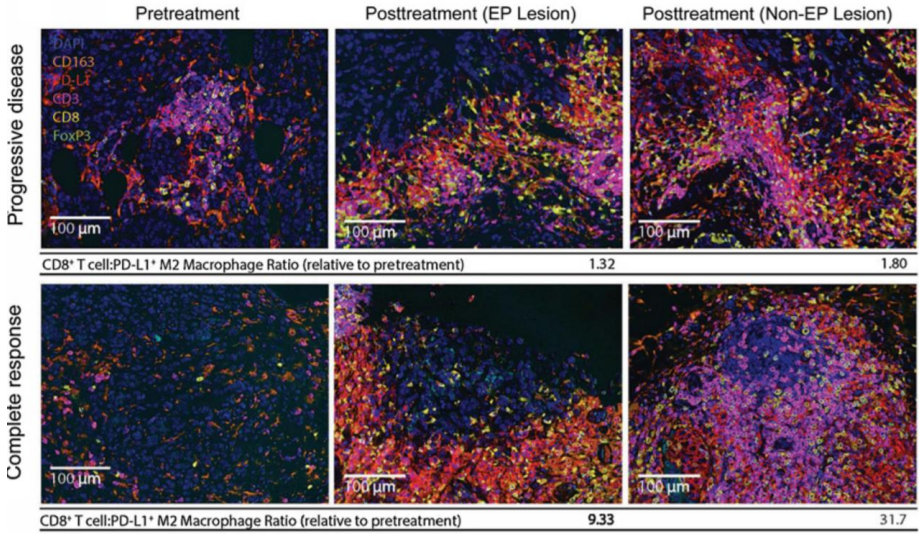
Diab *et al*. ASCO 2018

Electroporation of plasmid IL-12 may overcome resistance









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Berraondo *et al*. *Clin Can Res* 2020; Algazi *et al*. *Clin Can Res* 2020

Drug Development in Immuno-Oncology

- **Next gen immune-checkpoints**
  - LAG3, TIGIT, TIM3
- **Bispecific antibodies: CD3-, checkpoints, TME agonists**
  - PD1-CTLA4, PD1-LAG3, PD1-ICOS, CTLA4-LAG3,
  - T cell-redirection gp100, PSMA; TME agonist HER2-41bb, FAP-41bbL, PDL1-IL15
- **Innate immune modifiers**
  - Oncolytic virus, STING, TLRs, p38, NLRP3
- **Immuno-metabolism**
  - CD39, CD73, A2aR, Aryl-hydrocarbon receptor (AHR), IDO, PPARα
- **Novel targets and immuno-engineering**
  - Dual signaling molecules (CD47-CD137), Glycan biology, Red cell therapeutics

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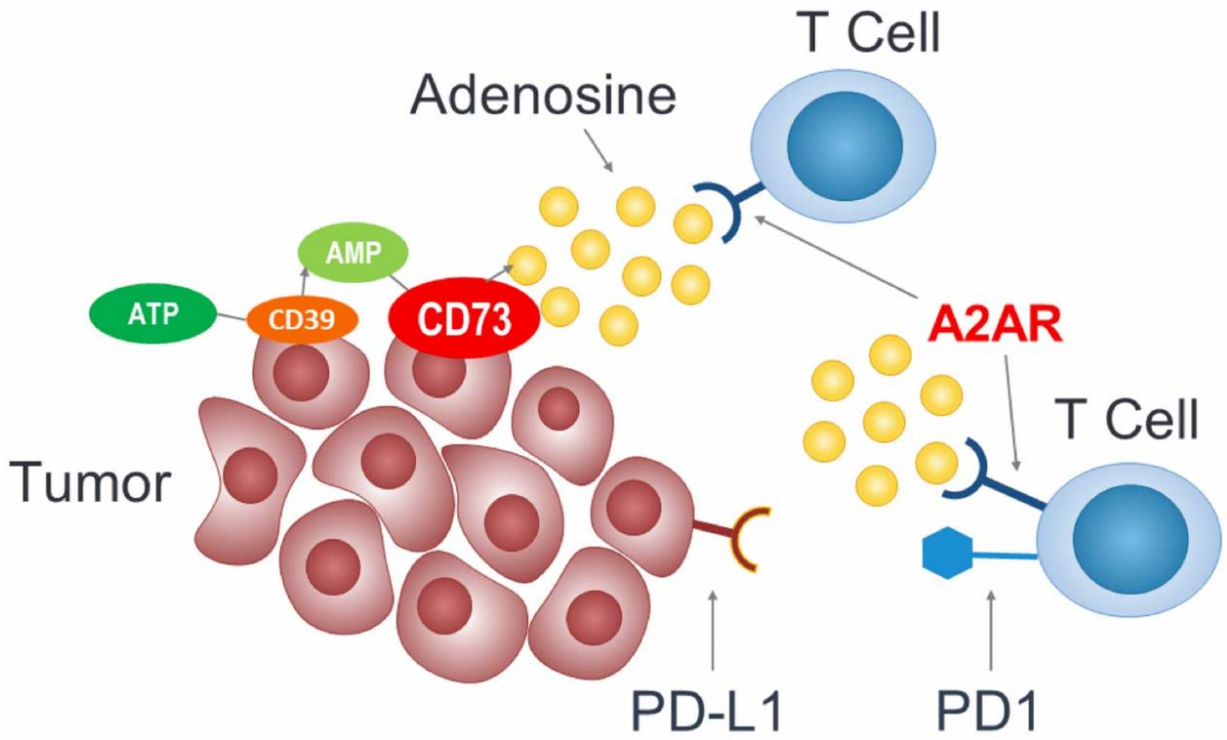
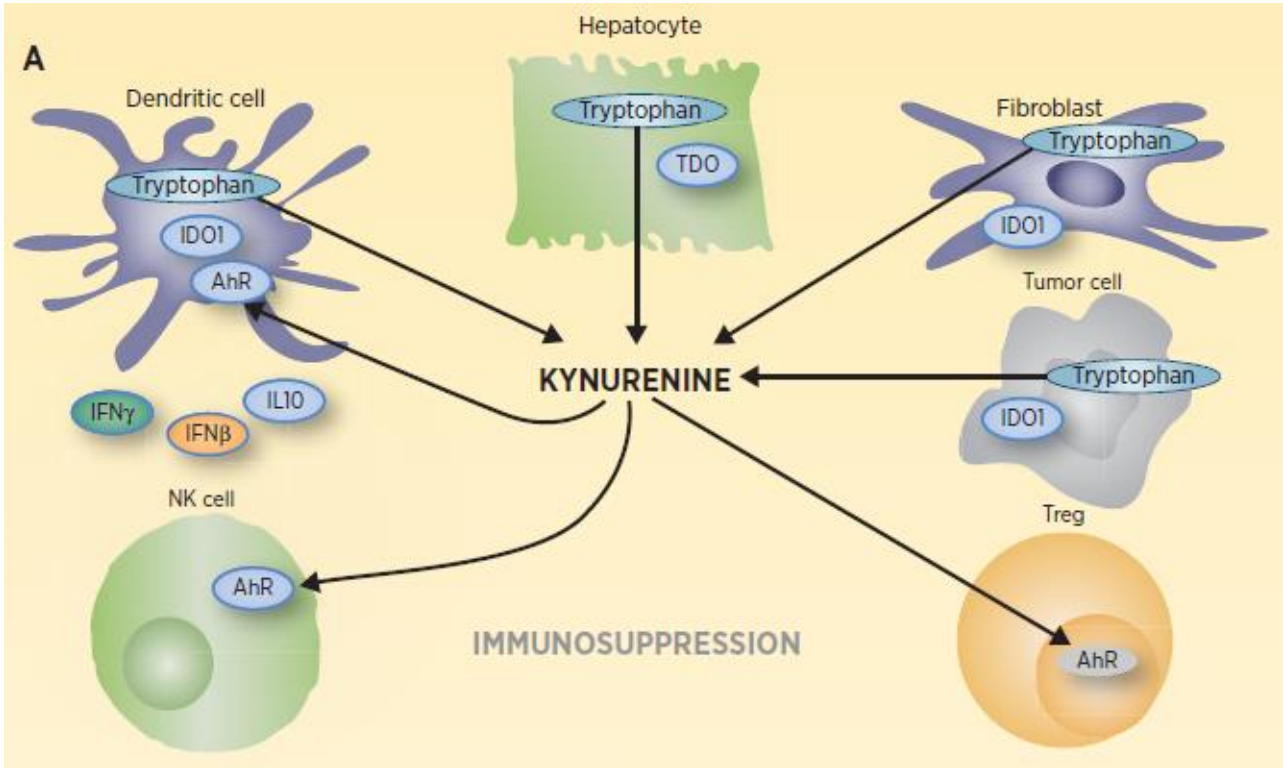
Targeting immuno-metabolism





Luke *et al*. ASCO. 2019
Labadie, Bao and Luke. Clinical Cancer Research 2018

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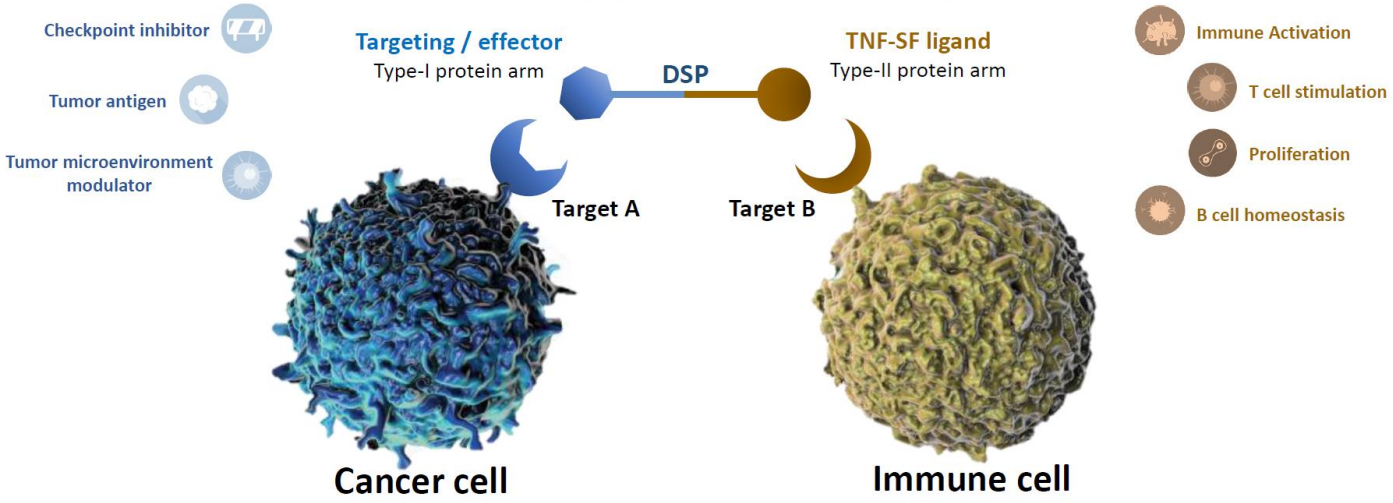
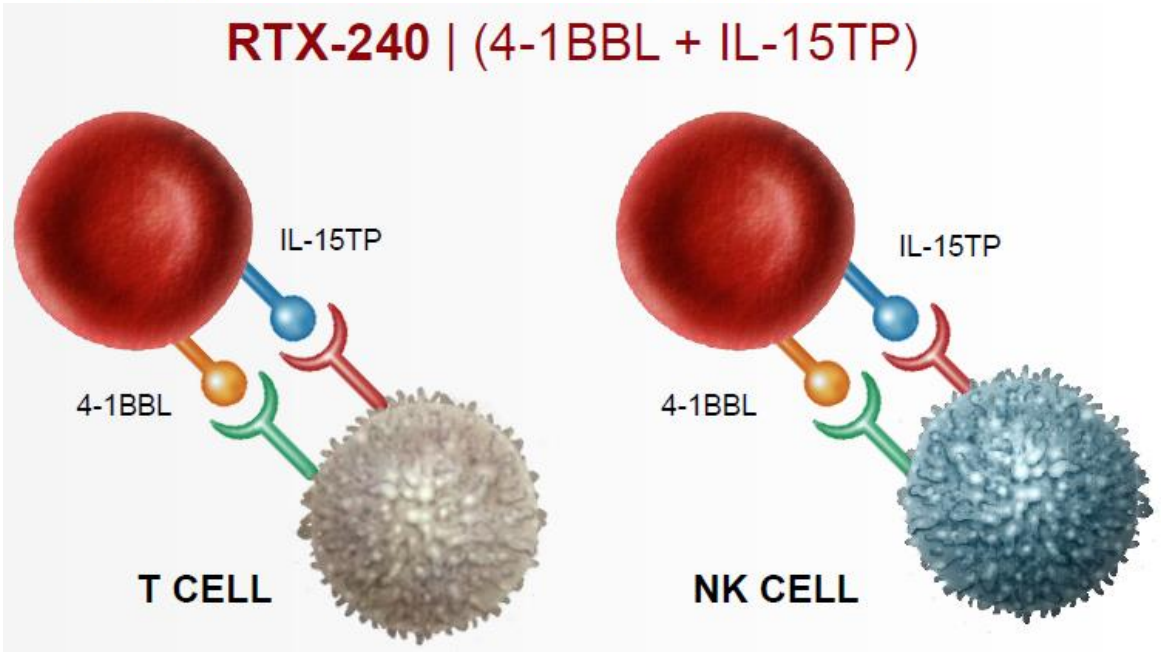
Novel targets and immuno-engineering

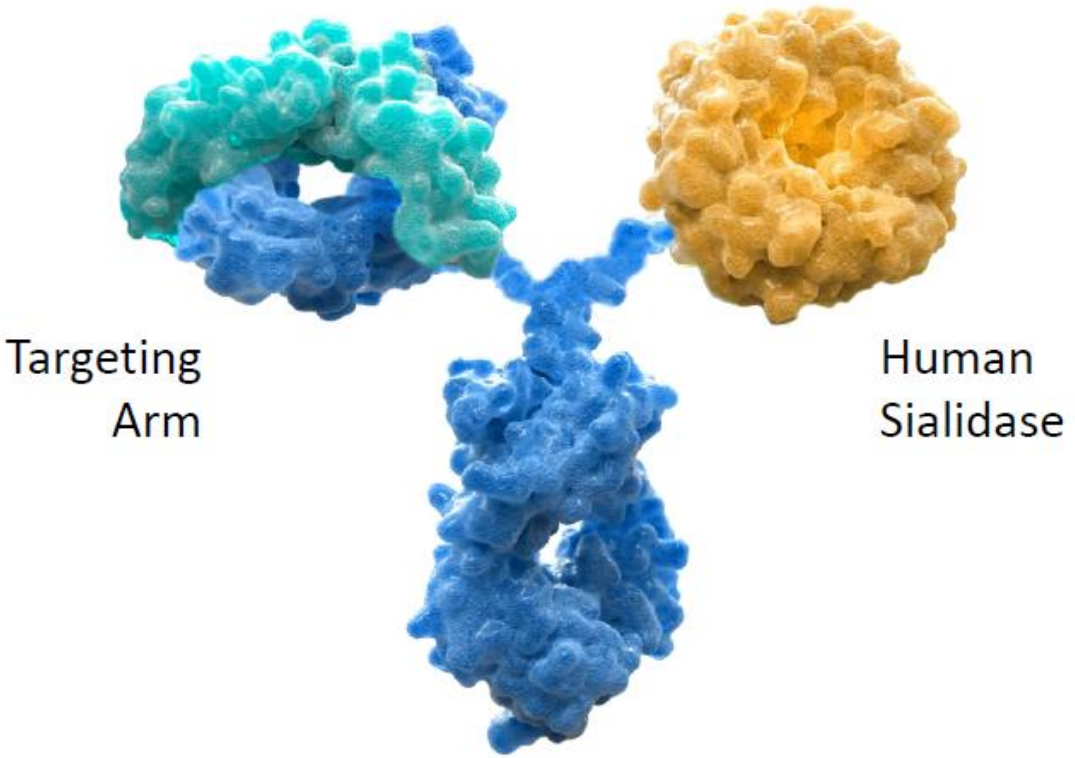
DSPs are generated by fusion of sequences from extracellular domains of type-I membrane protein and TNF superfamily ligand to form a trimeric bi-specific protein





EAGLE

Enzyme-Antibody Glyco-Ligand Editing



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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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