Emerging Biomarkers

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Genentech

SITC Cancer Immunotherapy Winter School
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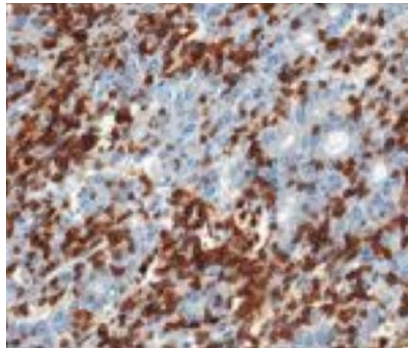
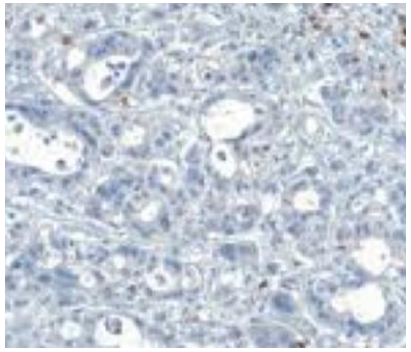
Inflamed vs non-inflamed tumors

Inflamed



TILs
PD-L1 expression
CD8+ T cells
Pre-existing immunity

Non-inflamed



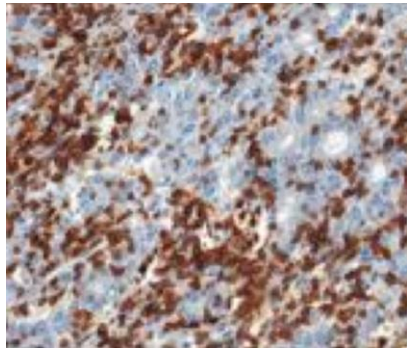
Checkpoint inhibitors are Standard of Care

What is the next line of therapy option?

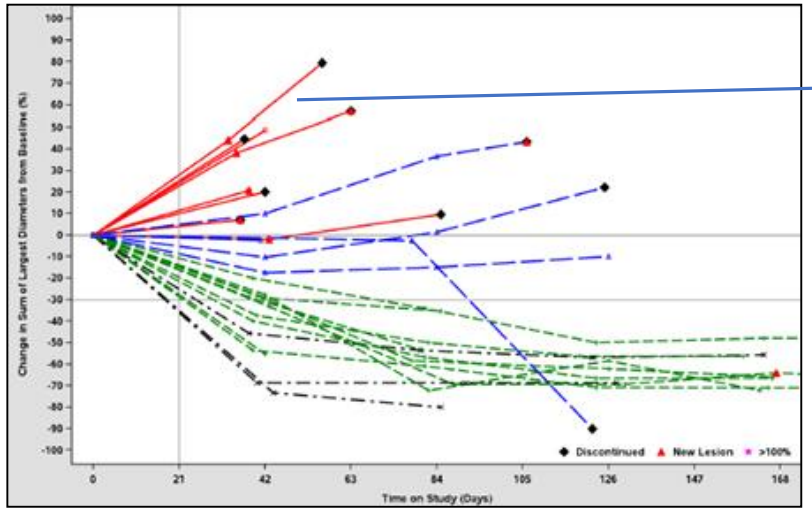
How to inflame these tumors?

What are the mechanisms of acquired escape?

Inflamed

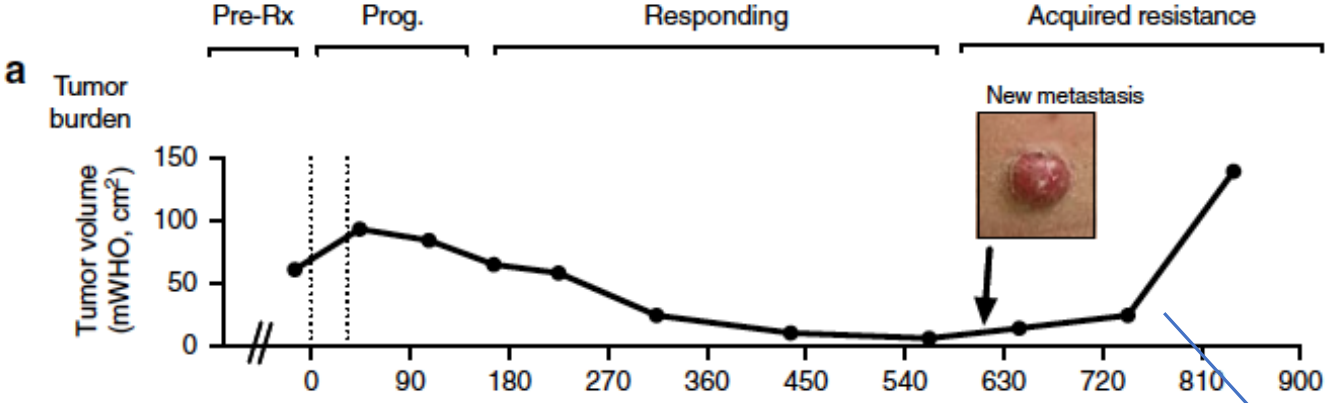


Checkpoint inhibitors are Standard of Care



Patients who progress without a response to CPI

Primary escape or innate escape

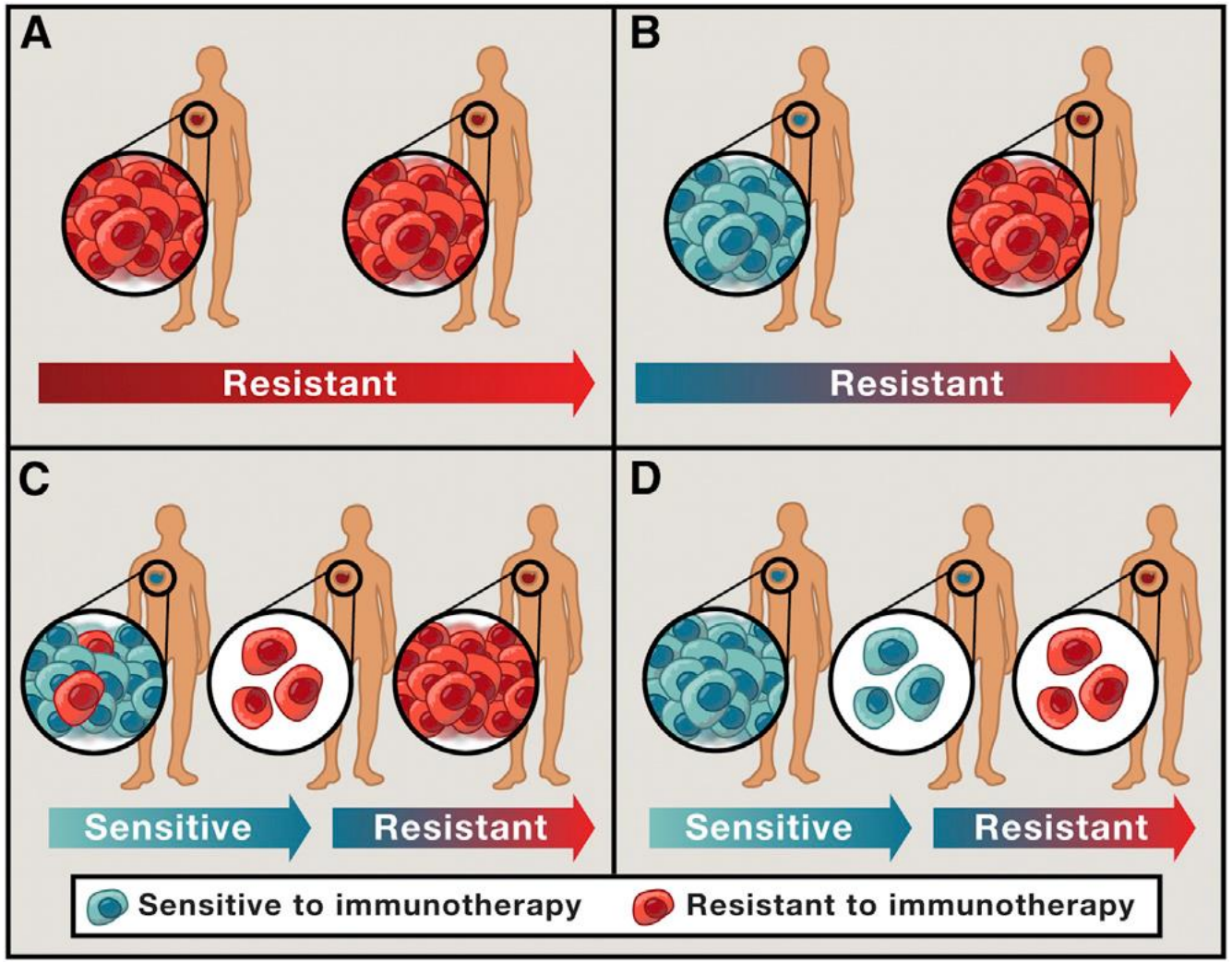


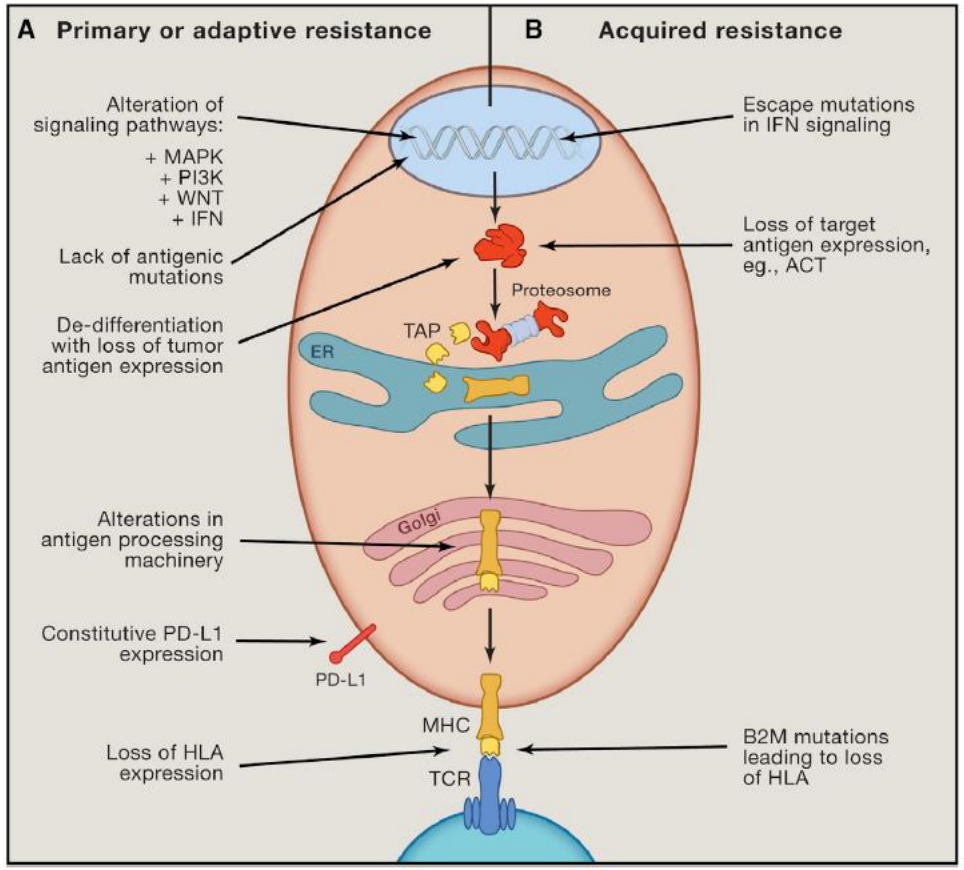
Paulson KG et al., Nat Comms 2018

Patients who respond and then progress on CPI

Acquired escape

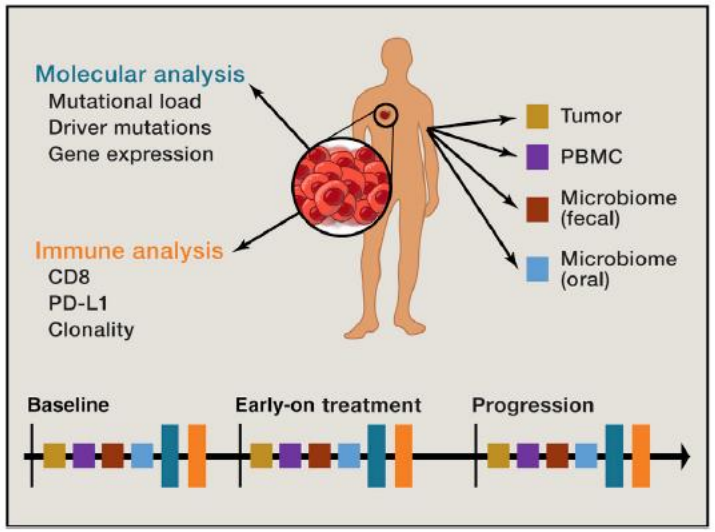
Primary, Adaptive and Acquired Immune Escape

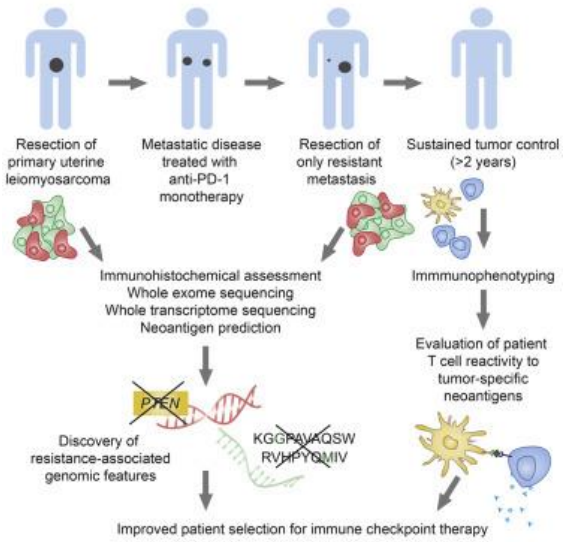


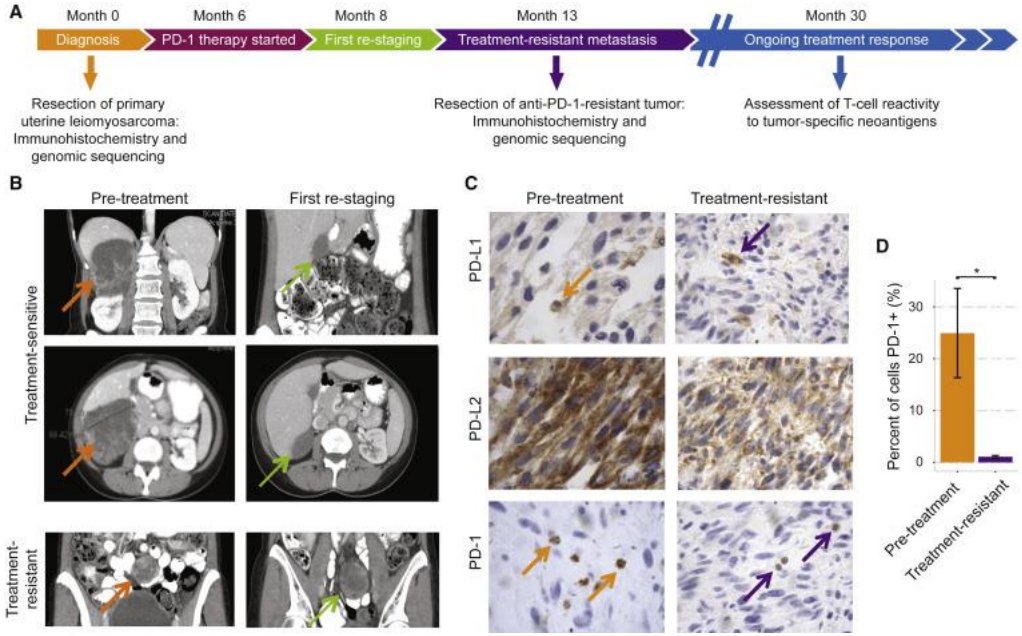


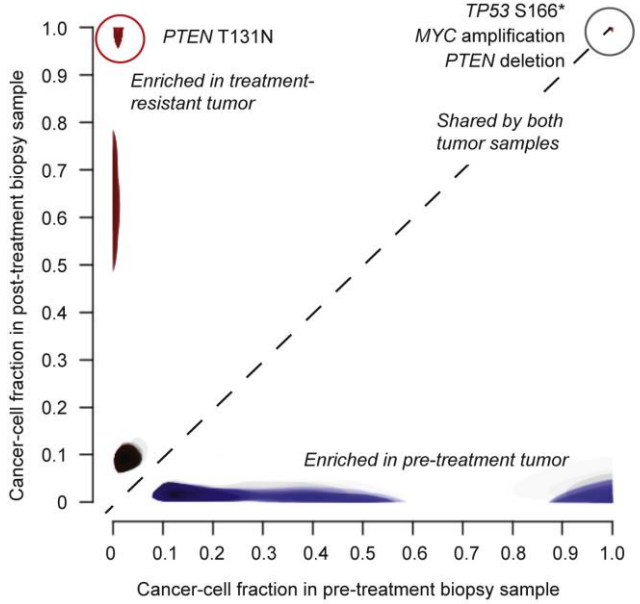
Sharma P et al, Cell 2017

Biomarkers of acquired escape





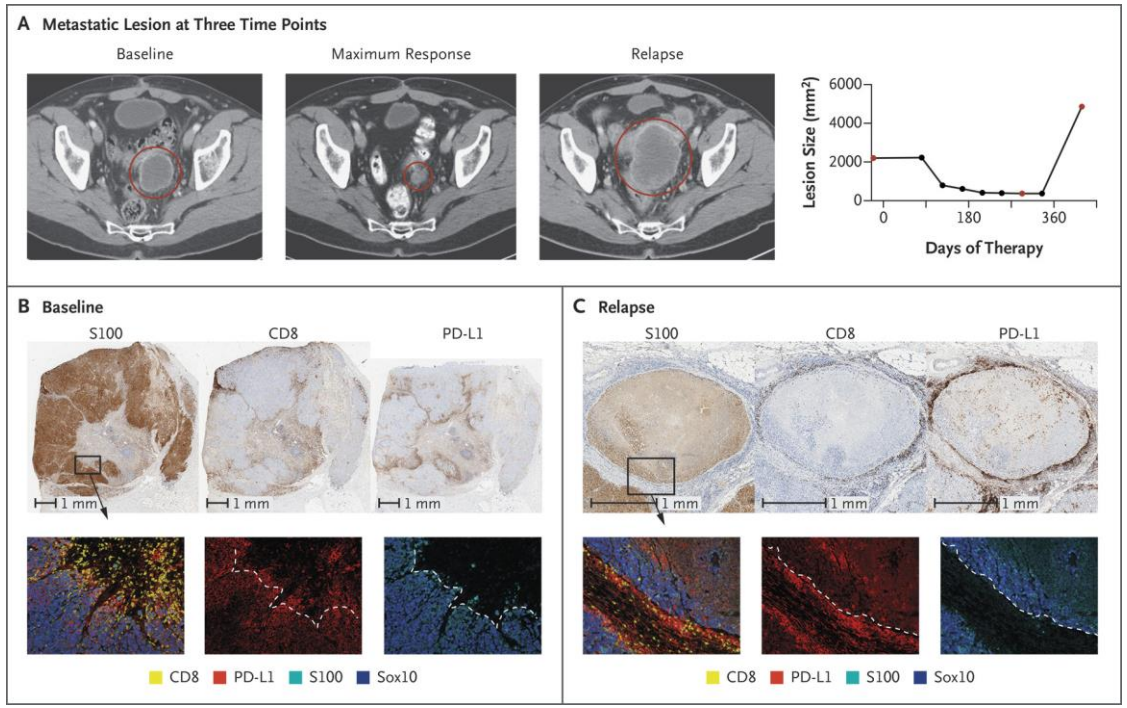




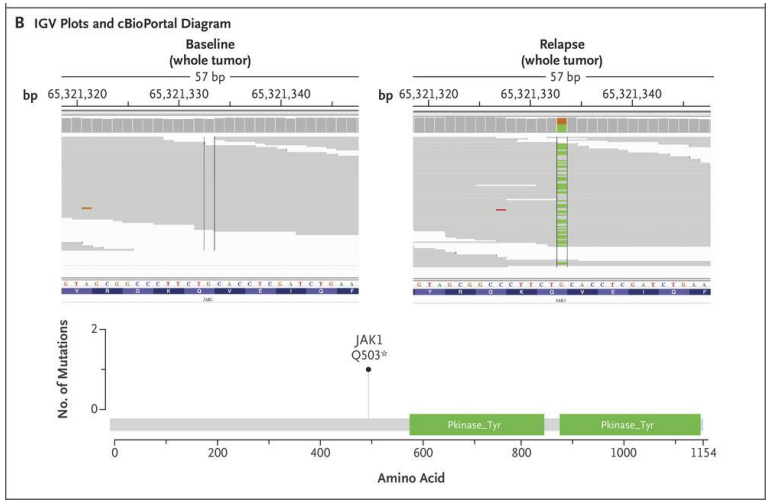
George S et al., Cell 2017

Biomarkers of acquired resistance

Tumor PD-L1 and inflammation maintained



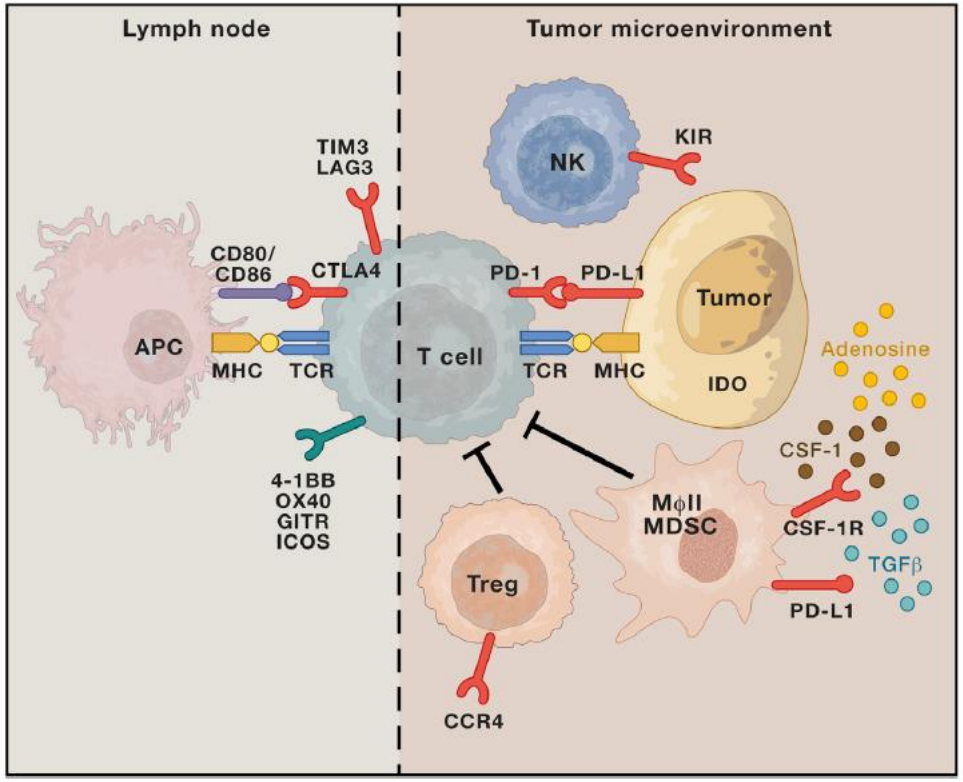
Acquired LOF mutation in JAK1



Anecdotal evidence for loss of B2M, JAK1, JAK2 mutations in Melanoma (N=4)

Zaretsky et al., NEJM 2016

Biomarkers of acquired resistance

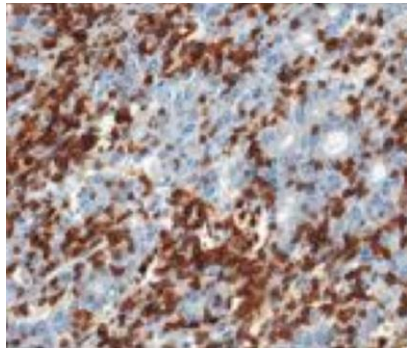


Sharma P et al, Cell 2017

Unclear if immunosuppressive factors eg Tregs, myeloid cells etc lead to acquired escape

Inflamed vs non-inflamed tumors

Inflamed



TILs
PD-L1 expression
CD8+ T cells
Pre-existing immunity

Checkpoint inhibitors are Standard of Care

What is the next line of therapy option?

Still unclear as to what next line of therapy should be for patients who progress upon an initial response to CPI

Second course of CPI may be effective in promoting a durable response

Figure 5. Treatment Duration and Time to Response in Patients Who Completed 35 Cycles or 2 Years of Pembrolizumab[a]

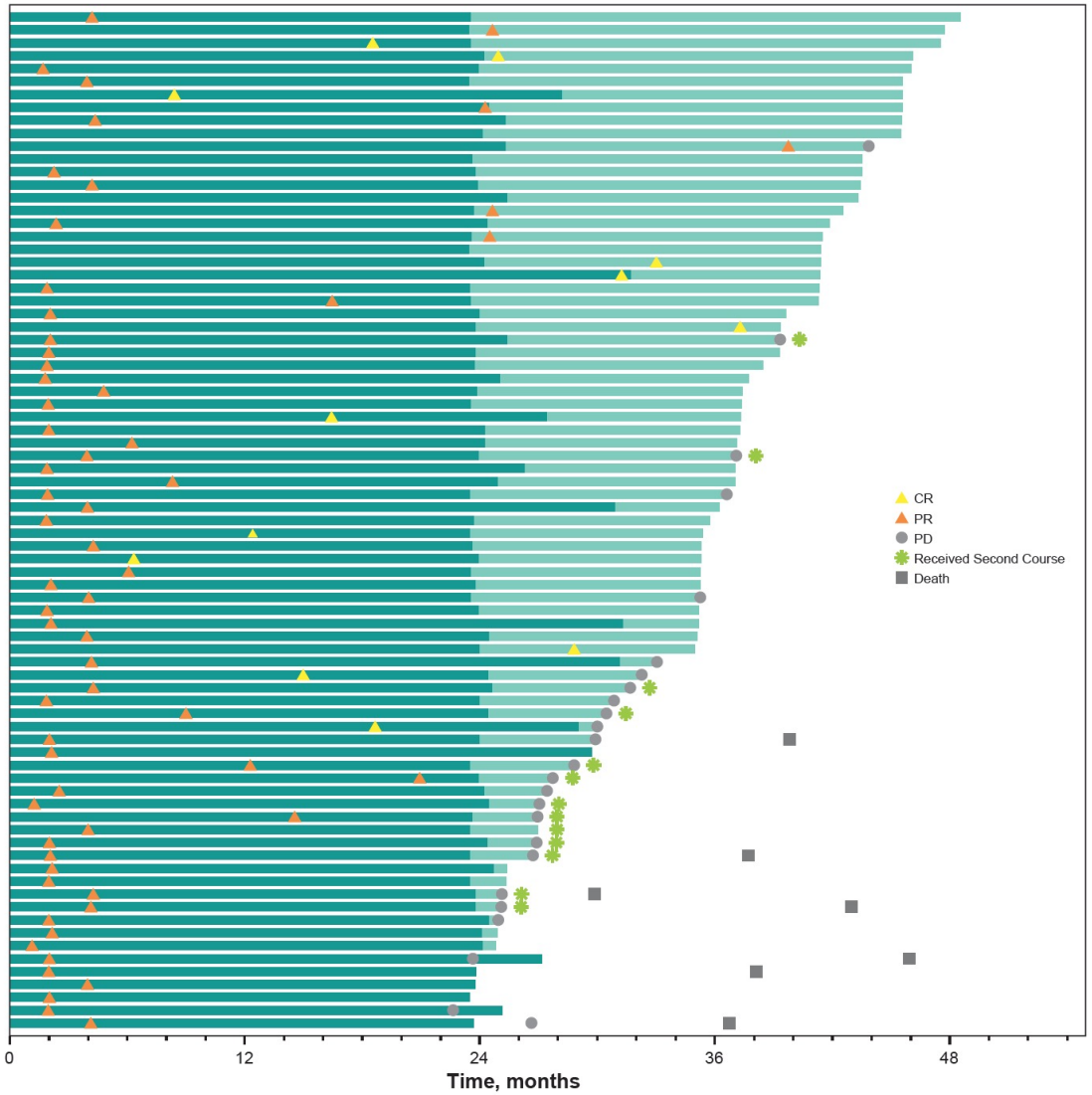
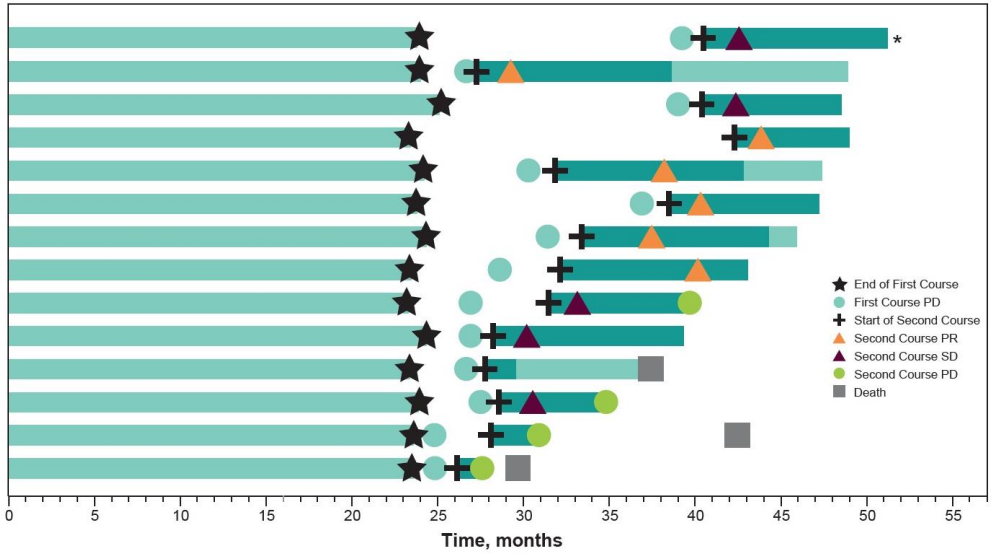


Figure 6. Treatment Duration and Time to Response in Patients Who Received a Second Course of Pembrolizumab[a]



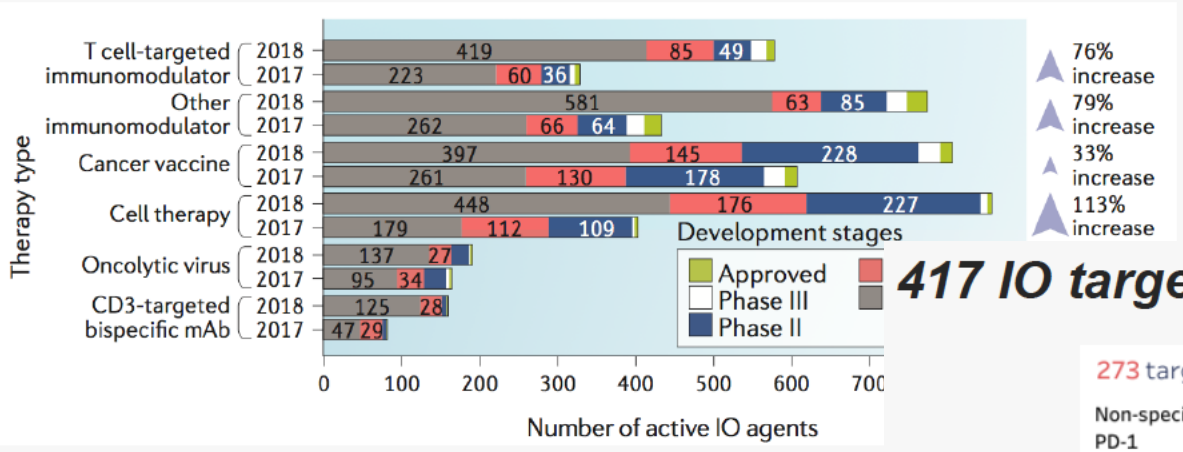
~50% of the progressing patients achieved a PR at treatment re-initiation

NSCLC patients treated with pembrolizumab for 2 years

Herbst et al,., ESMO 2018

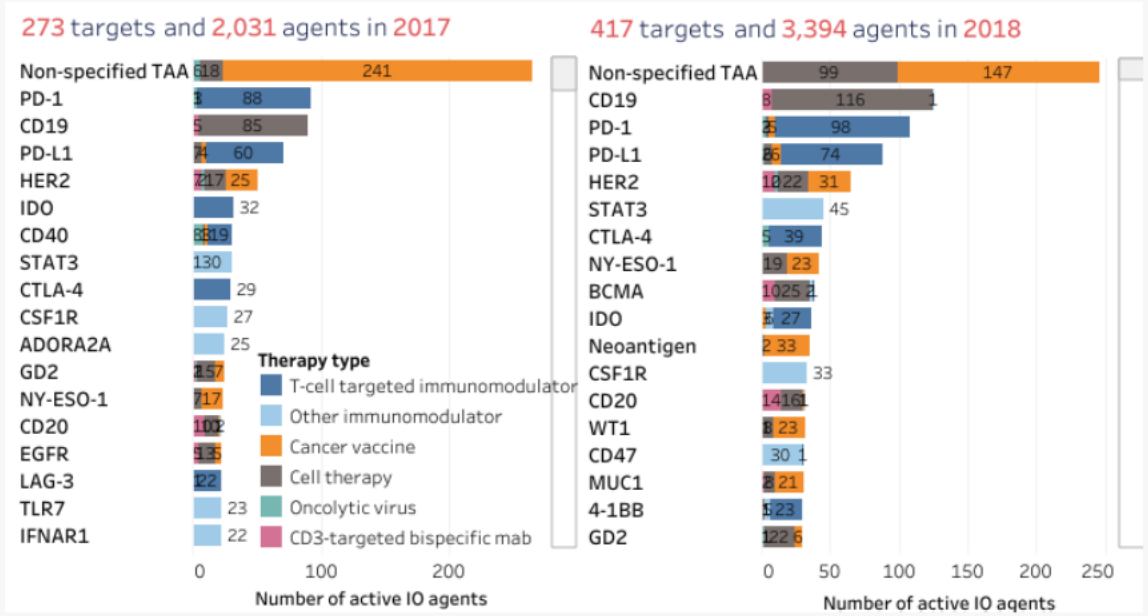
Most clinical combinations with CPIs are in inflamed cancers

3,394 IO agents in the current pipeline, a 67% increase in a year



Credit: Cancer Research Institute. T

417 IO targets in development, compared with 273 a year ago

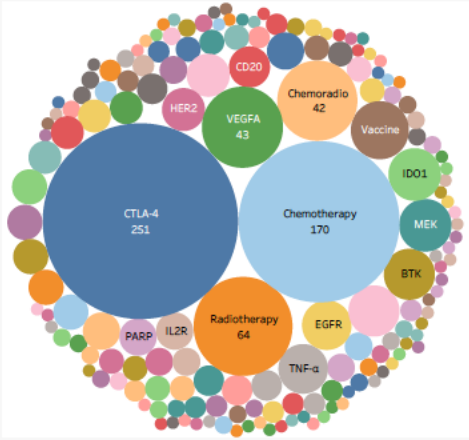


Credit: Cancer Research Institute. Tang et al, *Nat Rev Drug Discover*, Oct 19, 2018

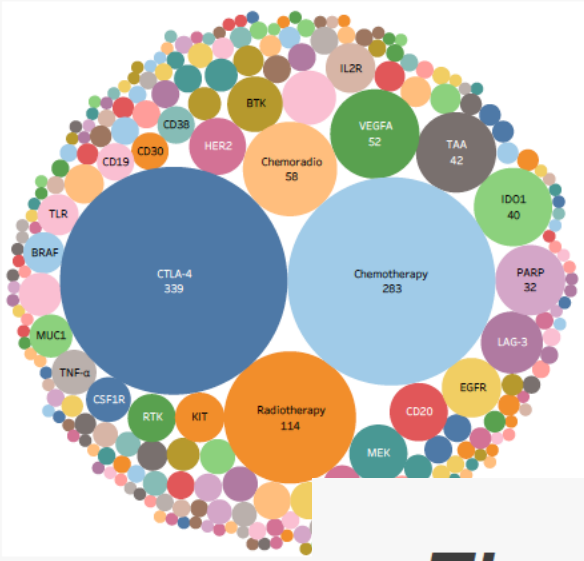
John Carrol, IO360, 2019

614 more PD-1/L1 combination trials added to this space in a year

In 2017, **1,102** trials testing **165** targets

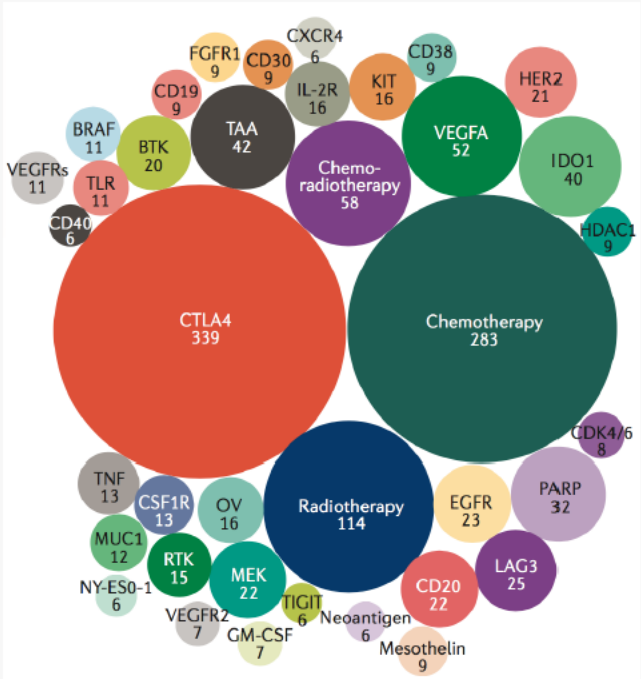


In 2018, **1,716** trials testing **240** targets



Credit: Cancer Research Institute. Tan

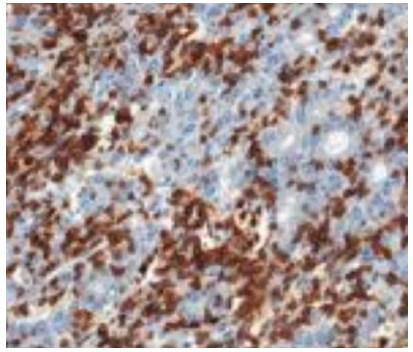
The top 38 targets in the current PD-1/L1 combination trial space



Credit: Cancer Research Institute. Tang et al, *Nat Rev Drug Discover*, Oct 19, 2018

Inflamed vs non-inflamed tumors

Inflamed



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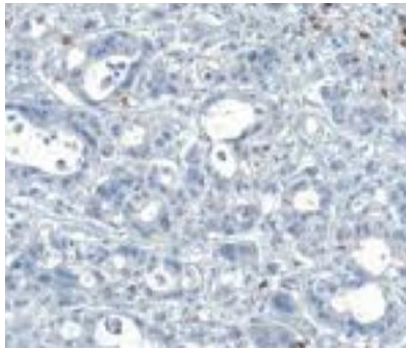
Non-inflamed

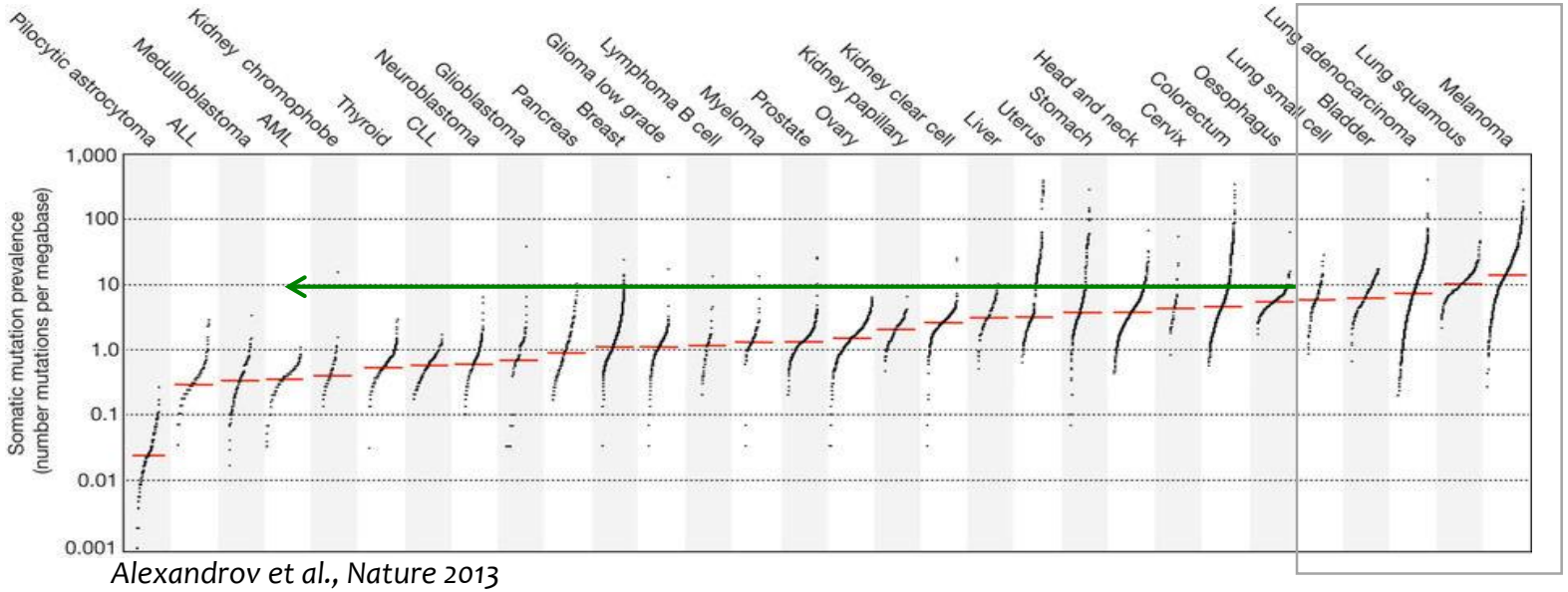


Checkpoint inhibitors are Standard of Care

What is the next line of therapy option?

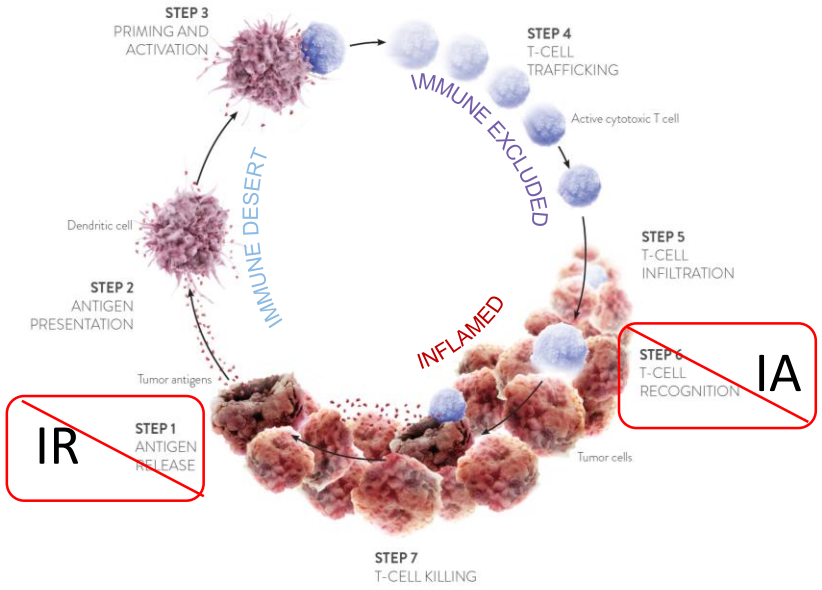
How to inflame these tumors?

How can we generate an immune recognition signal in non-inflamed tumors?



Alexandrov et al., Nature 2013

CI Cycle propagation via CPIs



Most non-inflamed cancers do not achieve the TMB threshold

Two Potential Options:

1 **Adaptive Immunity:** Neo-antigen vaccine delivery (PCV), engineered T-cells

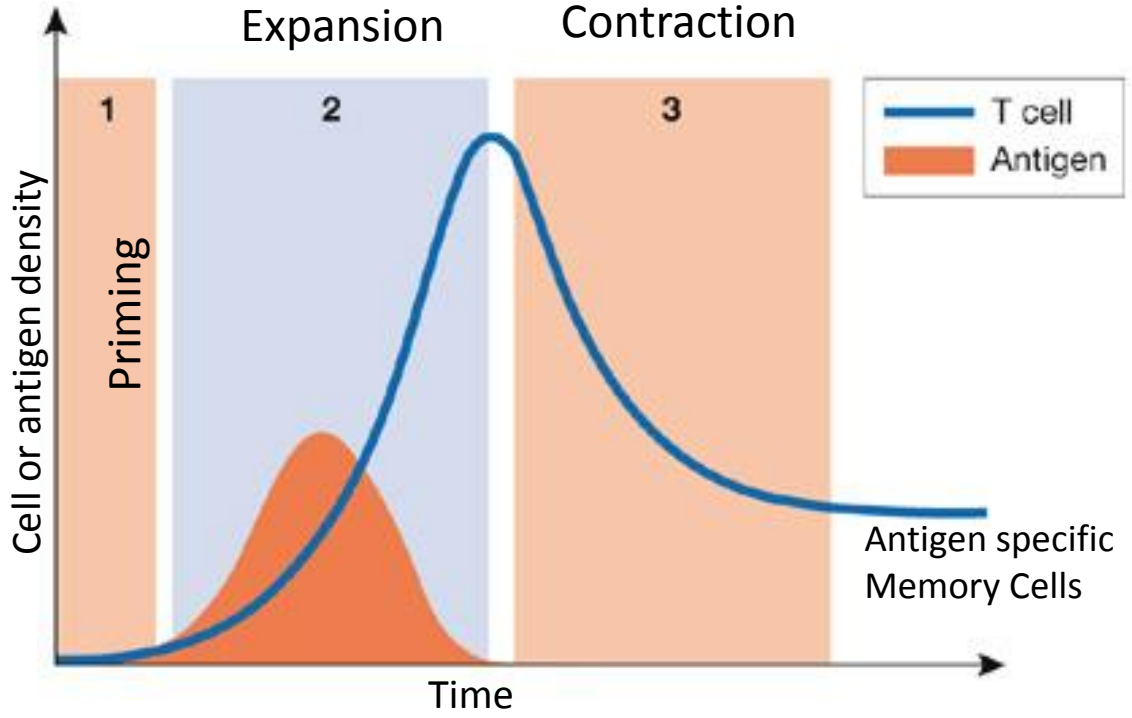
Will improving step 1 drive all steps of the CI cycle?

2 **Synthetic Immunity:** T-cell engagers (TDBs, CAR-Ts etc)

Will efficacy be sustained when synthetic immunity is engaged?

Adaptive vs Synthetic Immunity

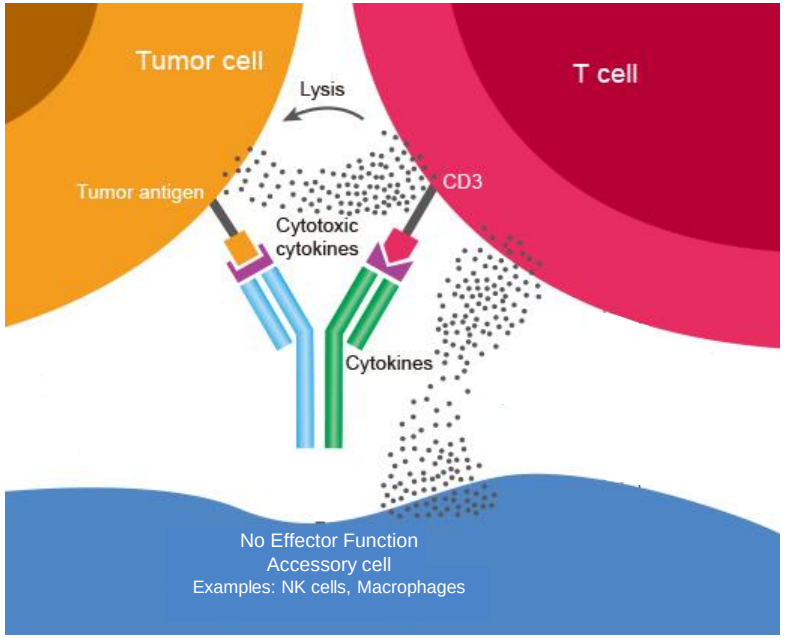
1 Adaptive Immunity: Potential to drive Memory Response



Bachman and Oxenius, EMBO Reports, 2007

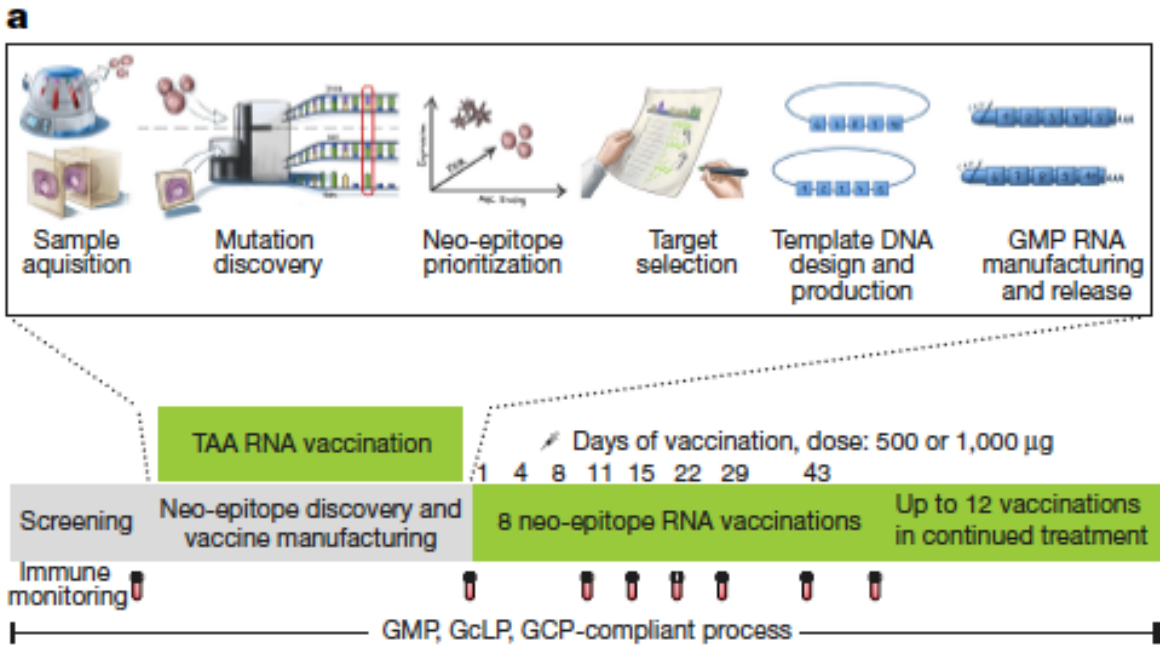
- Antigen specific T-cell expansion
- Ability to generate Tem cells
- Promote propagation of the CI cycle

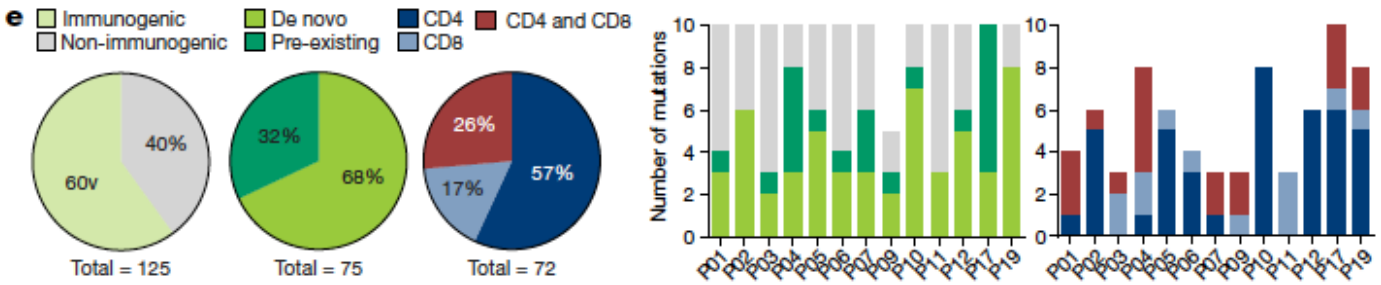
2 Synthetic Immunity: Potential to drive Log Kill



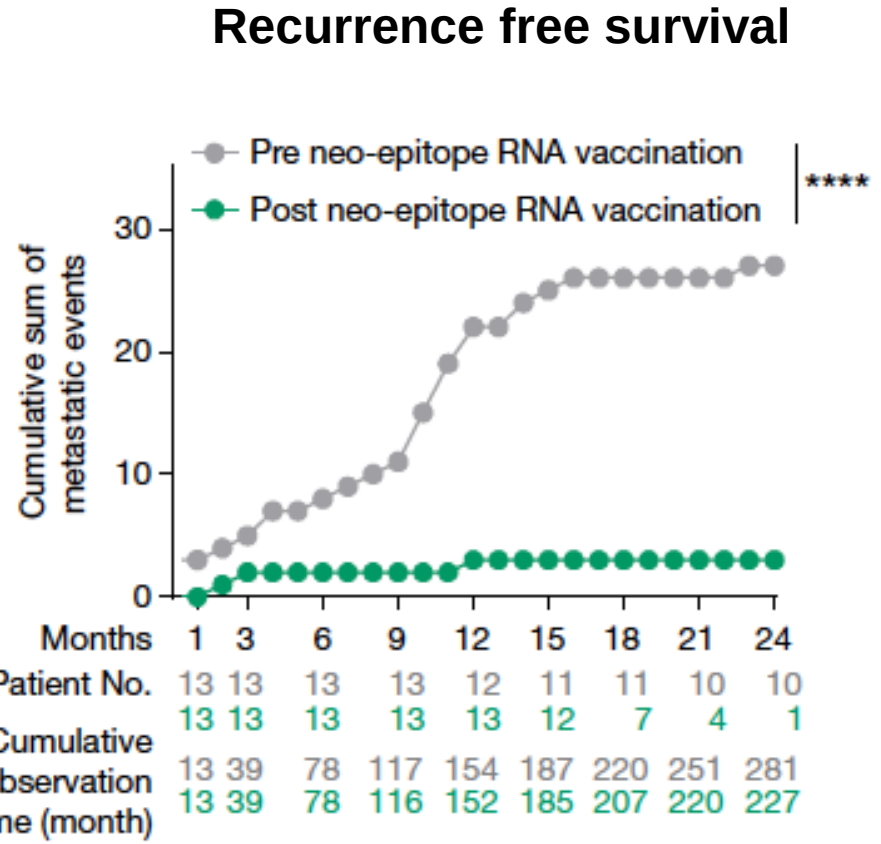
- Promotes proliferation of tumor resident and non-specific T-cells recruited to tumor
- Co-stimulation may be required to drive memory cells
- Promotes Log kill of Tumor Cells

1 Tumor mutanome vaccine and disease control in melanoma patients at high risk of relapse





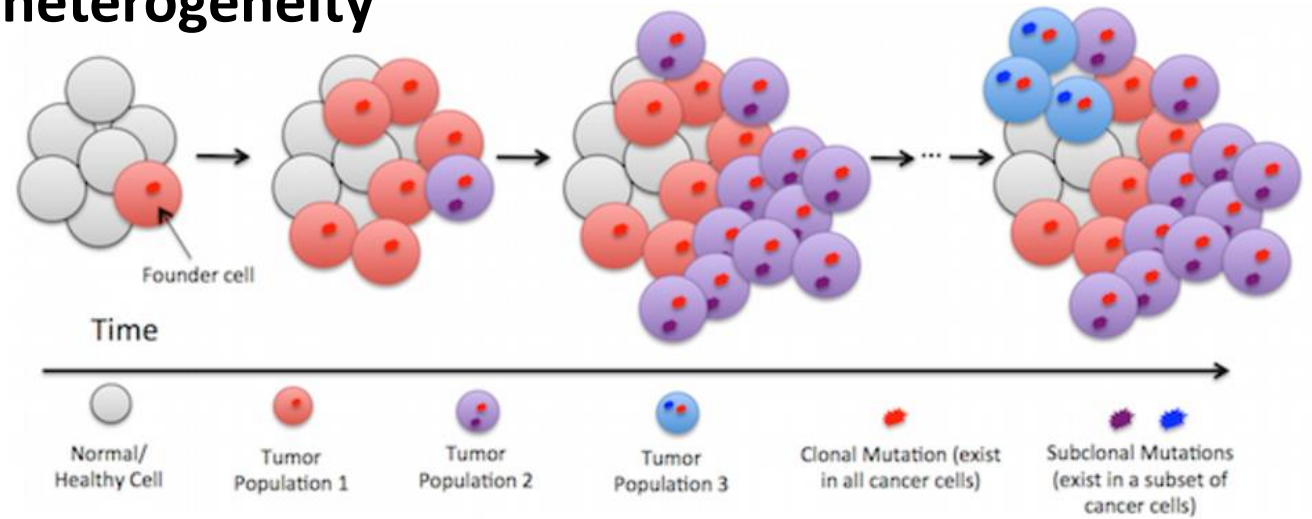
Hegde PS SITC 2018



Sahin U et al., Nature 2017

Emerging biomarkers in the era of personalized vaccines

Leverage cancer heterogeneity



Prediction algorithms to prioritize presented peptides

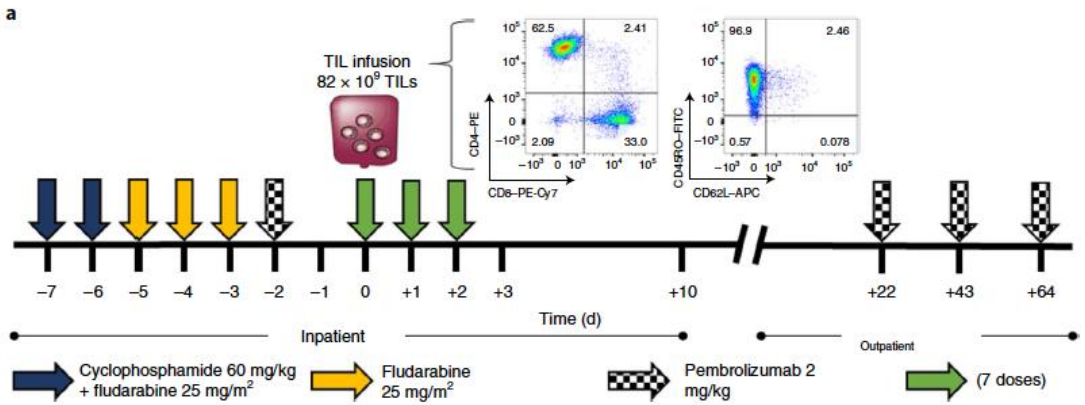
Ground truth is unknown (TCR sequencing to get to this question)

Neo-antigens against different HLA haplotypes

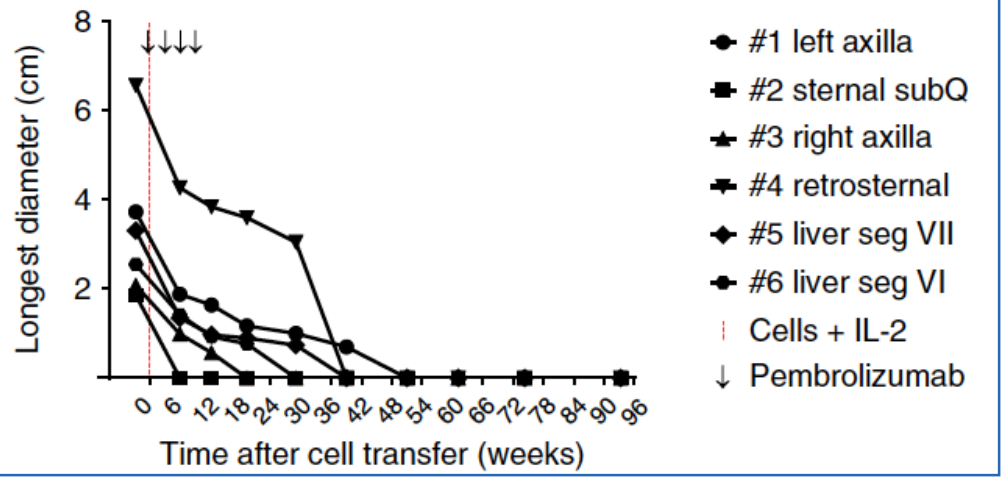
Tumor heterogeneity is truly unknown

1 Neo-antigen reactive TIL therapy leading to complete durable regression in HR+Her2- metastatic breast cancer

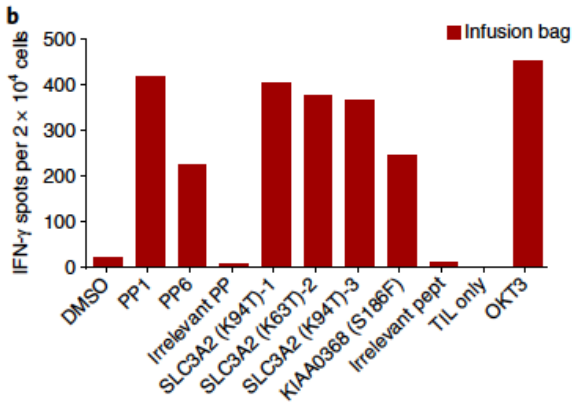
Adoptive transfer of mutant neo-antigen specific TILs



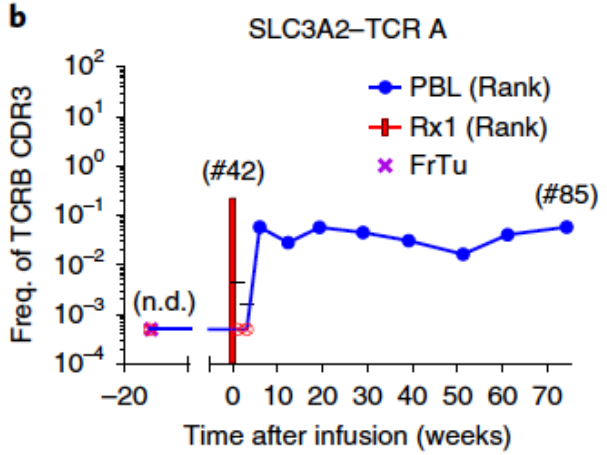
Regression of multiple metastatic lesions



TIL reactivity to mutant antigens



Persistence of mutant reactive TCR clonotypes



Zacharakis N et al., Nat Med 2018

1 Proof of concept that neo-antigen specific T-cell therapies can promote adaptive immunity in non-inflamed tumors

Limited but encouraging data:

Neo-antigen reactive TIL therapy in HR+HER2- BC

[1]Adoptive TIL therapy in KRAS ^{G12D} CRC

Early signals of neo-antigen specific immune responses with PCVs

- ***Personalized approach*** *may require longer manufacturing time lines*
- *Efficacy may be superior is earlier lines of therapy*
- *May require patients to exhibit good performance status (lymphodepletion + IL-2 therapy required for TIL protocols)*
- *Will these be curative in solid tumors?*

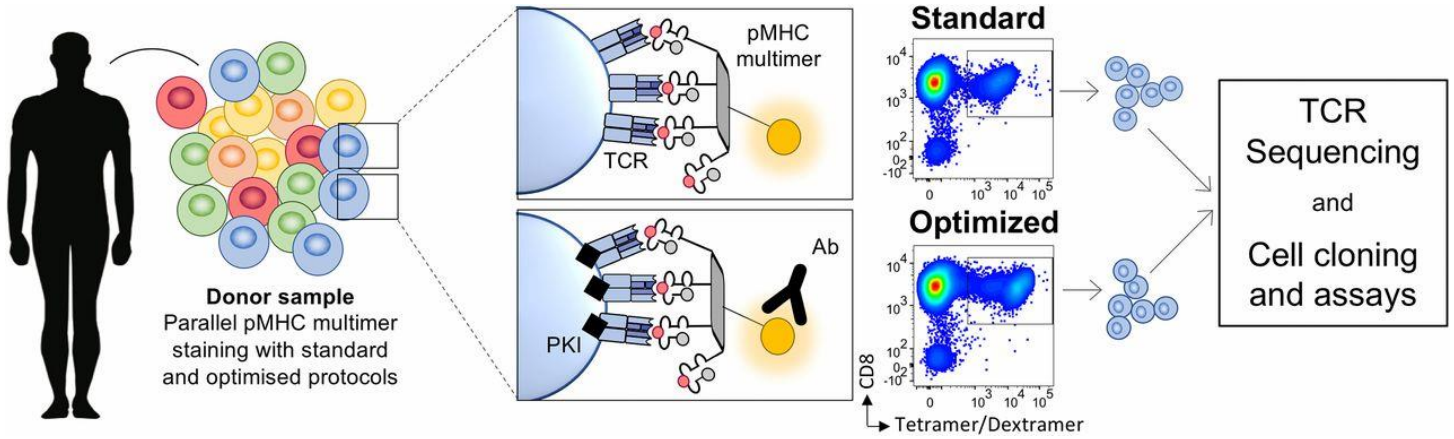
[2]Evidence in Melanoma for durable CRs. Loss of [3]functional b2-microglobulin, [1]HLA haplotype associated with progression

[1]Tran et al., NEJM 2016; [3]Rosenberg SA et al., CCR 2011; [3]Restifo N et al., JNCI 1996

Monitoring patients on personalized T-cell therapies

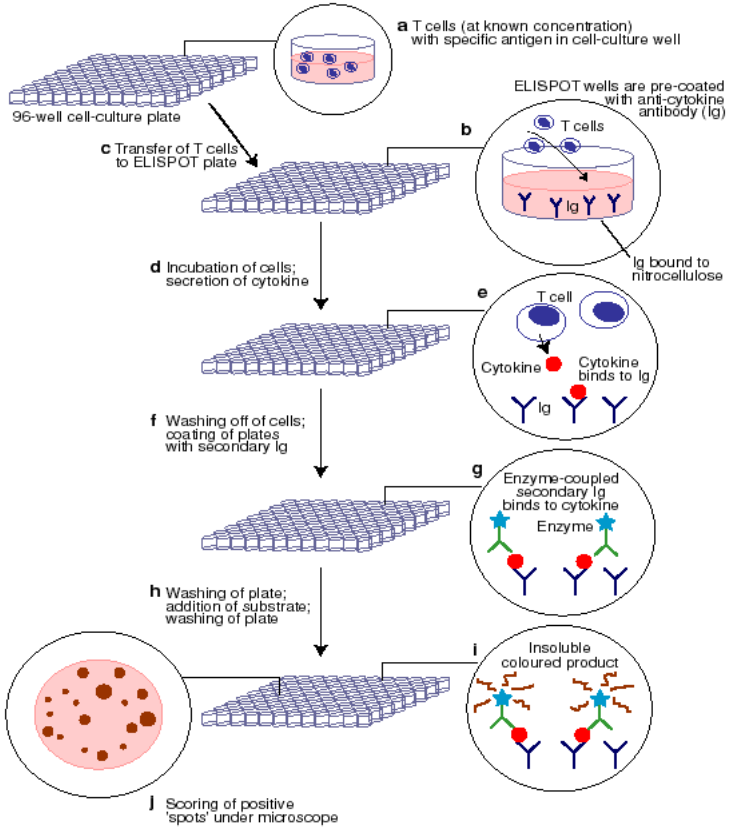
Are T-cell responses observed to antigens through the course of therapy?
Tetramer positive immune cells, ELISPOT

Antigen specificity- Tetramers



Rius, et al., J Immunol, 2018

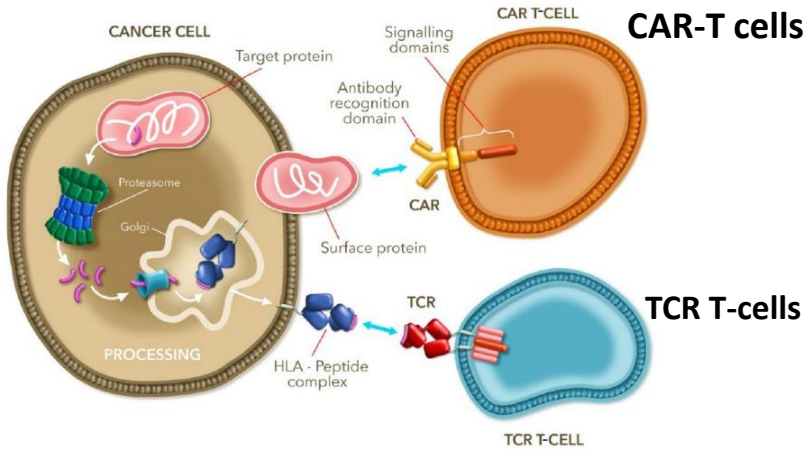
ELISPOT- General sense for immune reactivity



Synthetic Immunity Approaches

Engineered T-cells

Target cell surface antigens



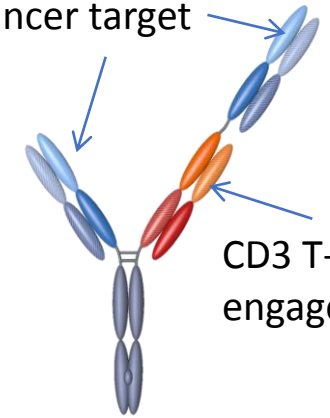
Can target intracellular antigens

Adaptimmune

Engineered antibodies

T-cell directed bi-specific

Cancer target

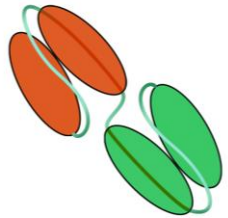


CD3 T-cell engager

Bi-specific T-sell engager

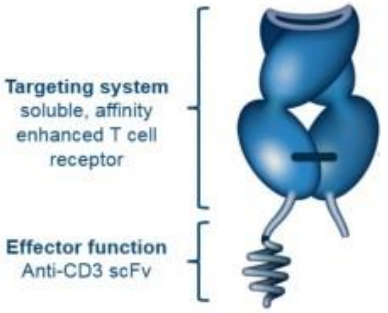
A BITE® antibody construct

Anti-CD3 scFv



Anti-EGFR scFv

ImmTAC

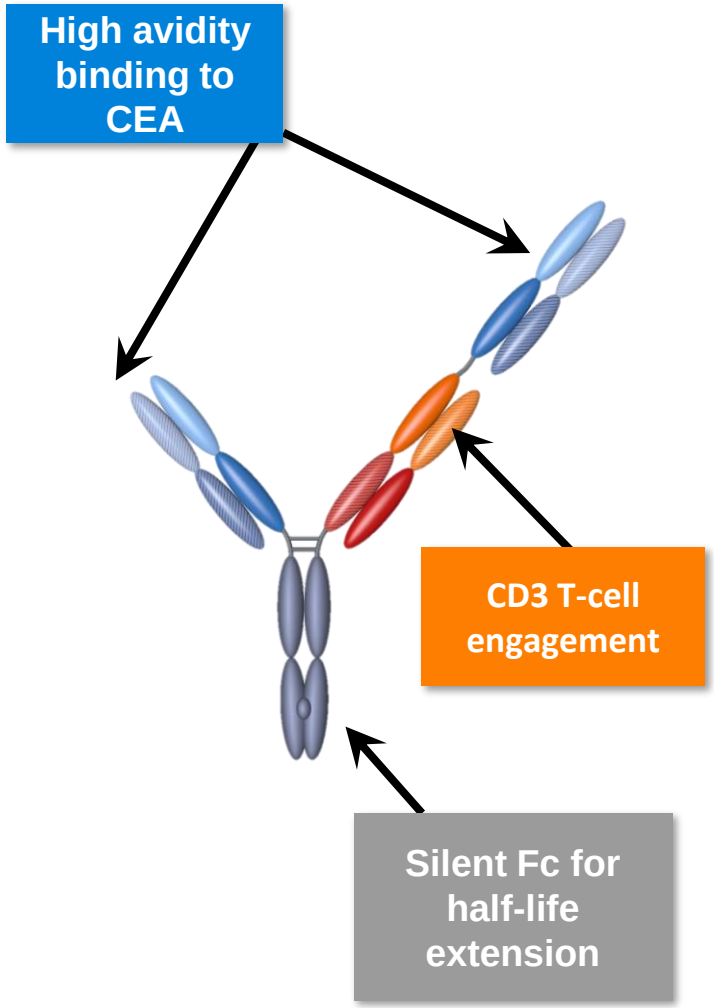


Images of molecules obtained from drug developer brochures

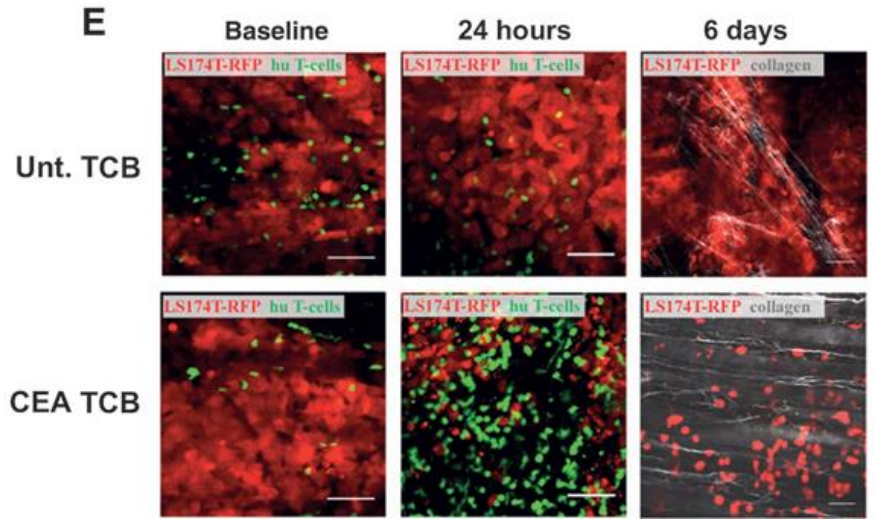
Similar mechanism:

- T-cell mediated tumor cell killing independent of pre-existing immunity
- T-cell proliferation at site of activity
- Cell surface target expression (or HLA-peptide presentation) required

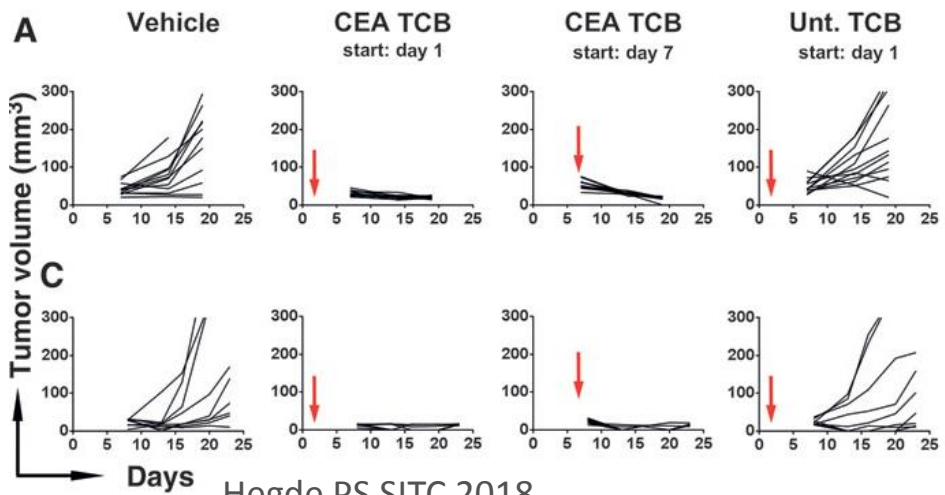
2 T-cell directed bi-specifics can inflame non-inflamed tumors



Infiltration and proliferation of T-cells

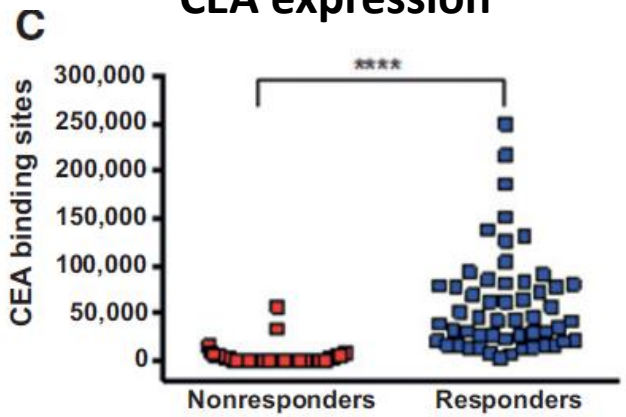


Tumor regression post CEA-TCB tx



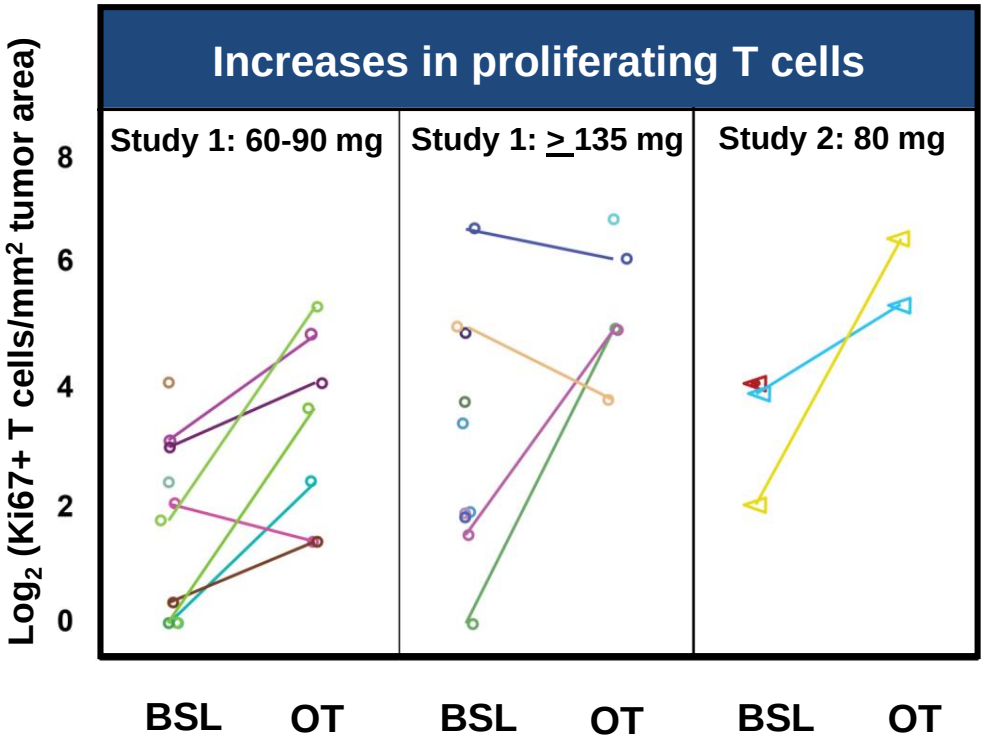
Hegde PS SITC 2018

Response associated with CEA expression

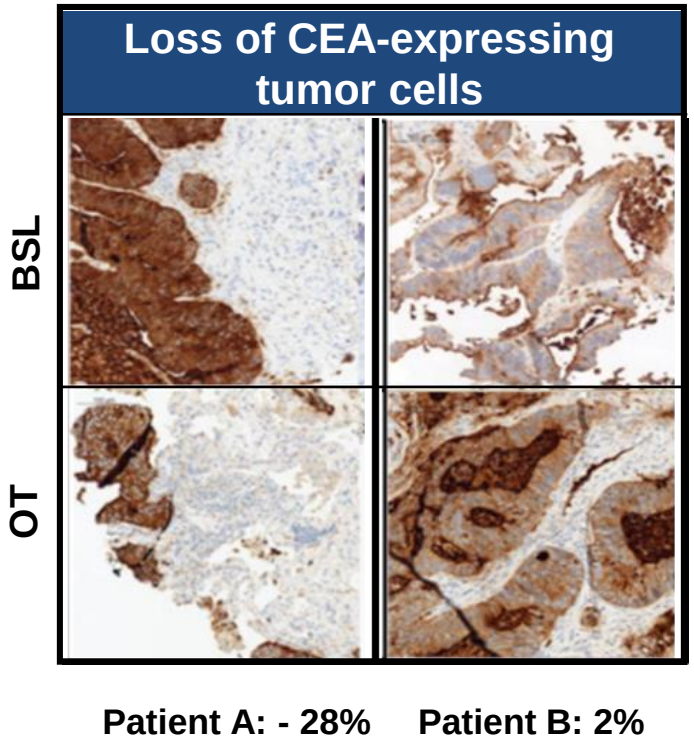


Bacac M et al., CCR 2016

Clinical translation of pre-clinical MOA-CRC Phase I experience for CEA-TCB



Increase in proliferating tumor resident T-cells upon CEA-TCB treatment



Loss of CEA+ tumor cells in responding tumors

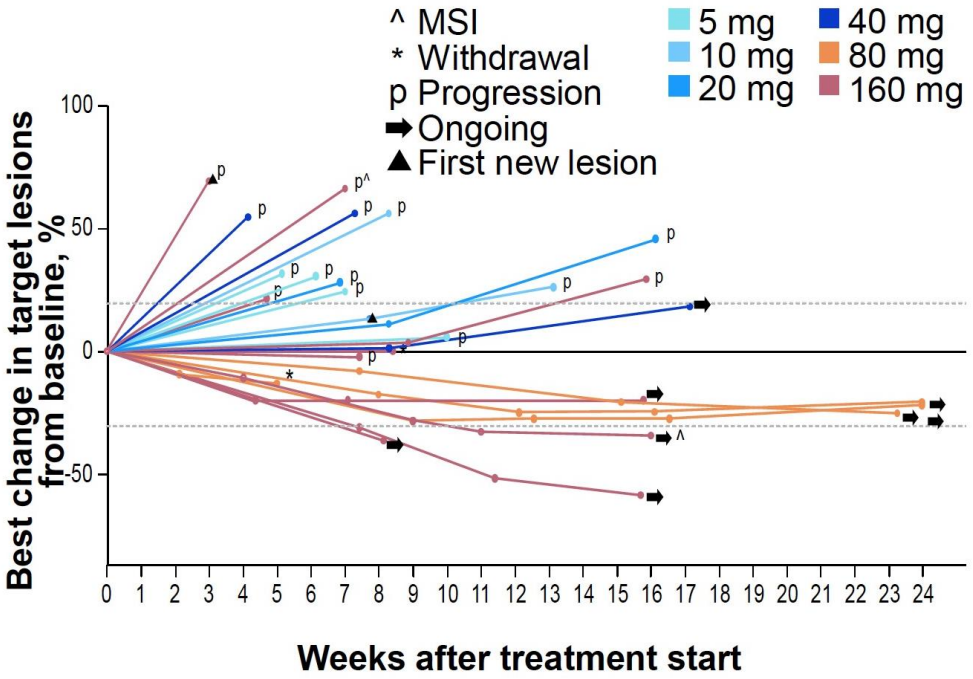
Hegde PS SITC 2018

Argiles G et al., ESMO GI 2017

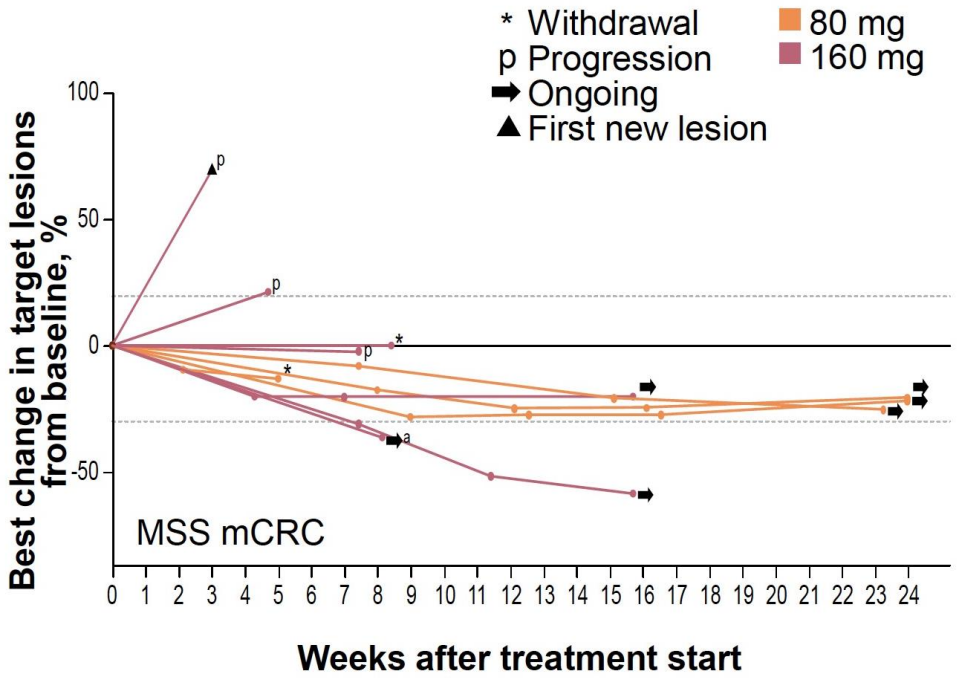
2

Promising activity of CEA-TCB in 3rd line MSS CRC - Low TMB, Low PD-L1 tumors

CEA-TCB + atezolizumab (n = 25, 5-160 mg of CEA-TCB)



CEA-TCB + atezolizumab (n = 11, 80 and 160 mg of CEA-TCB)



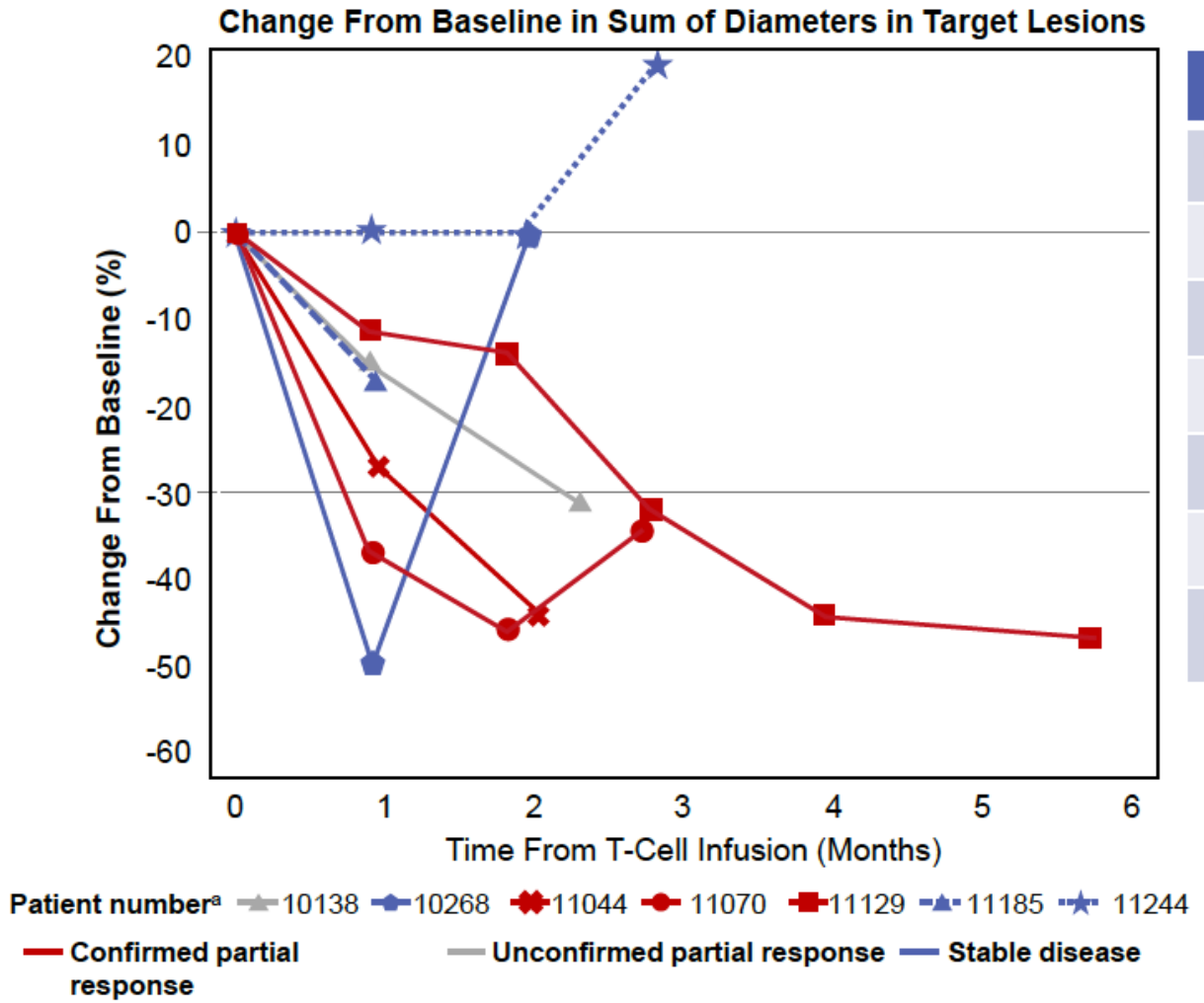
Data reported by investigators, cutoff: March 3, 2017.

[a] Radiological signs of tumor inflammation seen at ≥ 60 mg (safety data cutoff is ≥ 40 mg).

Argiles G et al., ESMO GI 2017

Responses in two distinct solid tumors with NY-ESO

Data from ongoing MRCLS study



Best overall response	N=8
Confirmed CR	0
Confirmed PR	3
Unconfirmed PR	1
Stable disease	3
Progressive disease [a]	0
Not assessed [b]	1
Overall unconfirmed response	4

[a] Three patients have progressed

[b] Patient 11832 recently treated and post-infusion disease assessment is not yet available

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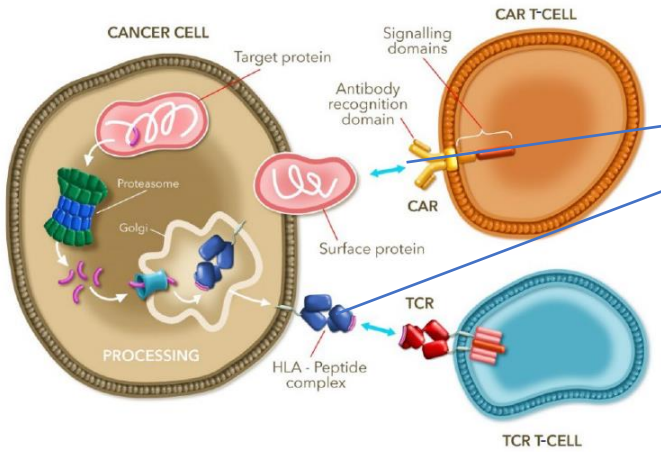
Emerging Biomarkers for Synthetic Immunity

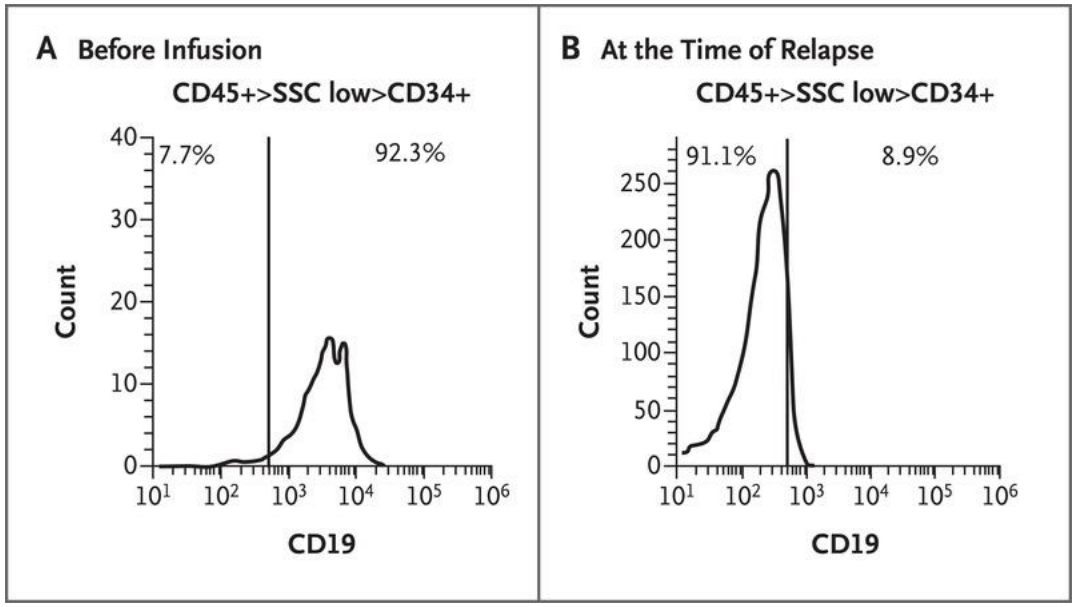


Target Expression

Prior to start of therapy

At progression

Loss of target expression (CD19) in a ALL patient relapsing from CD19+ CAR-T



Grupp S et al., NEJM 2013

Observed in ~ 28% of patients with ALL

2 Proof of concept that synthetic immunity approaches are feasible in solid tumors and CIT refractory heme malignancies

CEA T-cell directed bi-specifics
Clinical activity to both monotherapy and Atezolizumab combinations in MSS CRC (High CEA expression)

NY-ESO SPEAR T cells
Myxoid Liposarcoma, Synovial Sarcoma
(diseases with high NY ESO expression)

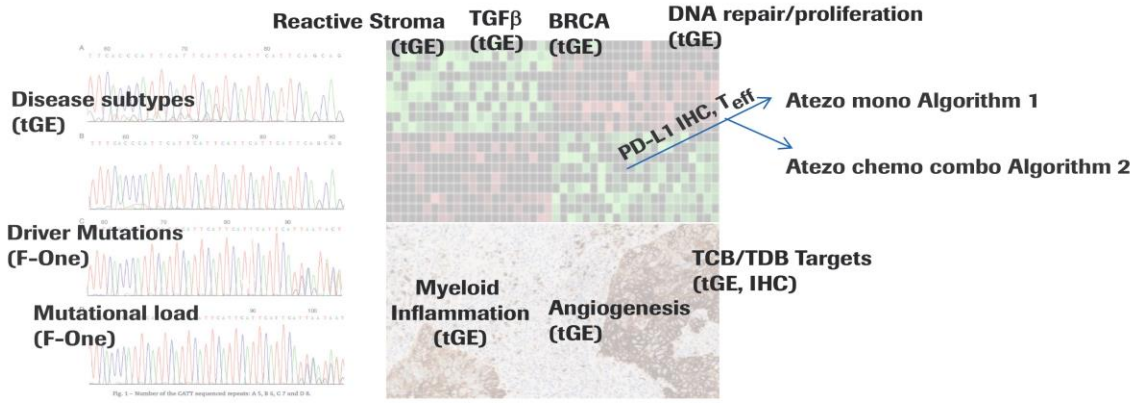
[1]BCMA CAR-T cells
Activity observed in Multiple Myeloma

Many molecules in early drug development: CD20, CD22, Her2, FcRH5, MAGE-A4, A10
[2]Antigen loss observed as a potential mechanism of escape
On-target off tumor toxicity is a watch out for these therapies
Durability of response in solid tumors is unknown

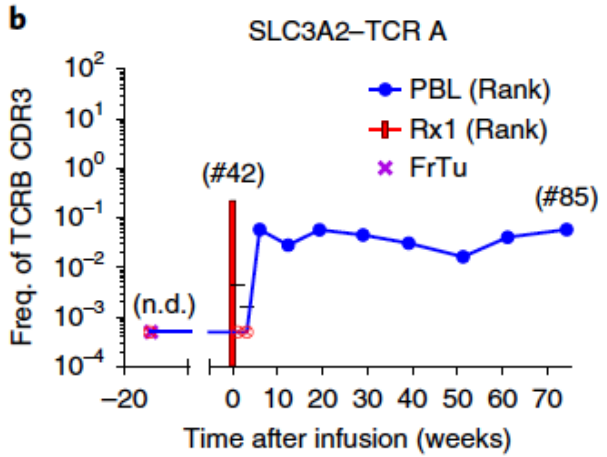
[1]Ali SA, BLOOD, 2016; [3]O'Rourke DM, et al., STM 2017

Patient profiling in the era of Personalized cancer immunotherapy

WES (proposed neo-antigens, driver mutations)
RNAseq (target expression for Synthetic immunity)
IHC (disease specific)



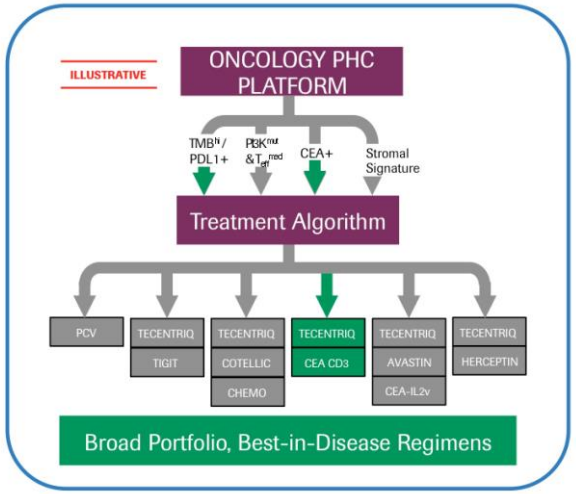
WES (proposed neo-antigens)
ELISPOT/Tetramer assays for immune monitoring
ctDNA, disease burden for tumor monitoring



Treatment decision algorithms

Drug Developers and Physicians face a complex, fragmented treatment landscape

Incorporate validated platform across all trials
Develop treatment decision algorithms
Implement innovative statistical/regulatory strategies for filing



Patients receive best-in-disease tailored treatment

An informed patient

Imagine a world where a patients “actionable” tumor molecular fingerprint is at their fingertips…