CANCER IMMUNOTHERAPY

Composite Predictors of Efficacy to Checkpoint Inhibitors and Mechanisms of Immune Escape:

Informing Combination Strategies via Personalized Cancer Immunotherapy

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Genentech, Roche

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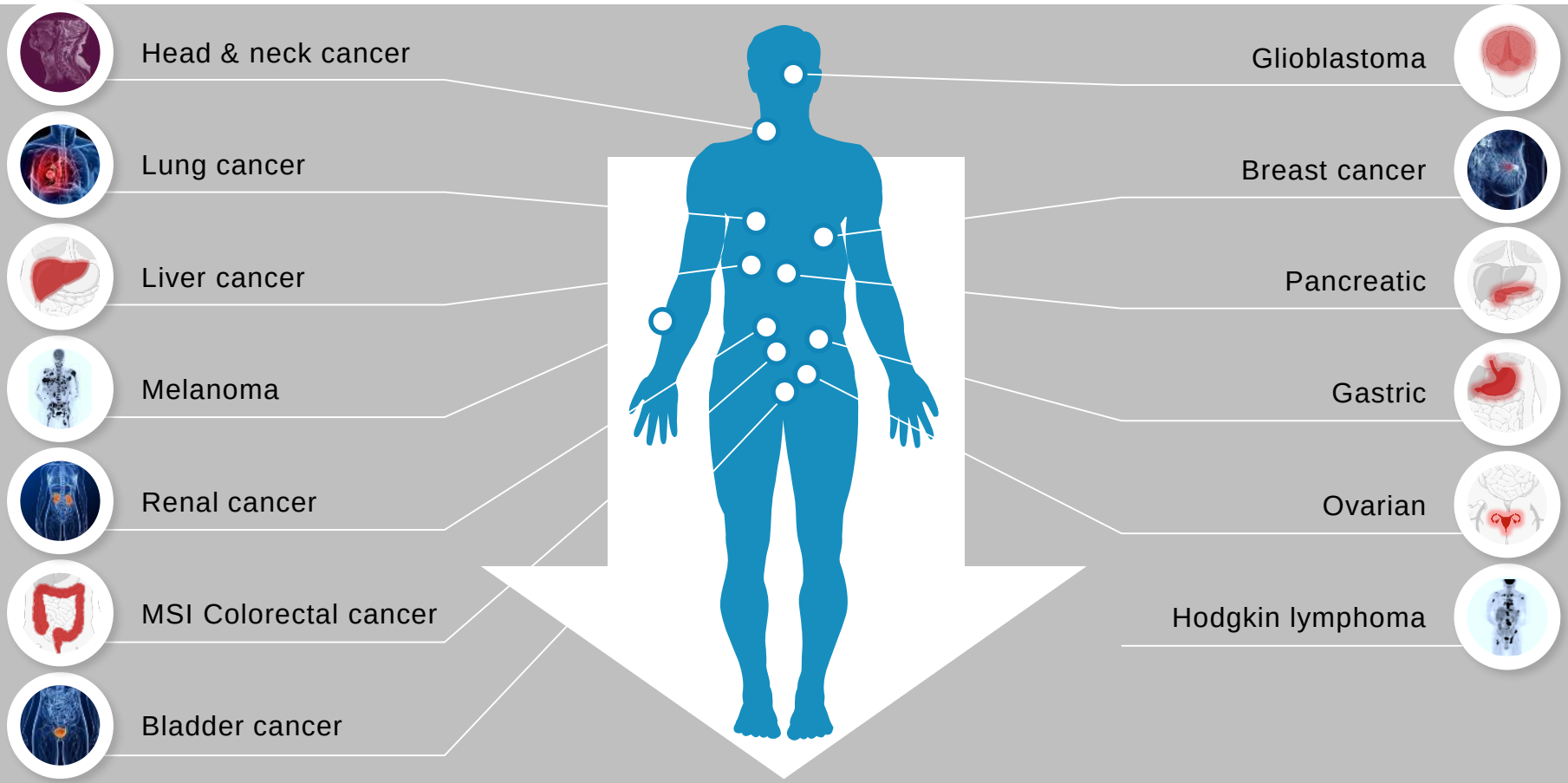
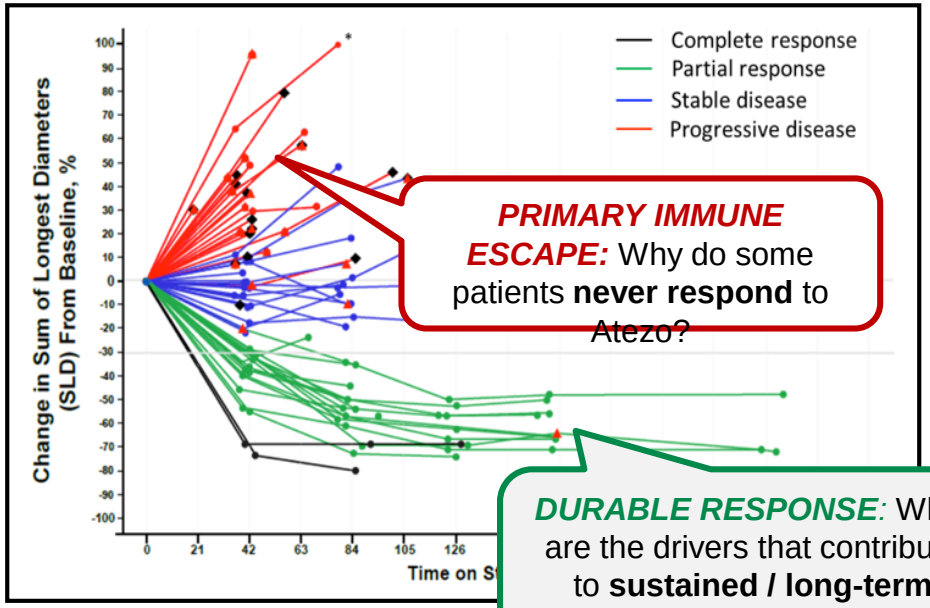
SITC, Washington DC

Anti-PDL1/PD-1 is Active Across a Wide Range of Tumor Types



What are the drivers of efficacy and escape from CPI?



Atezolizumab Ph1 mUC data

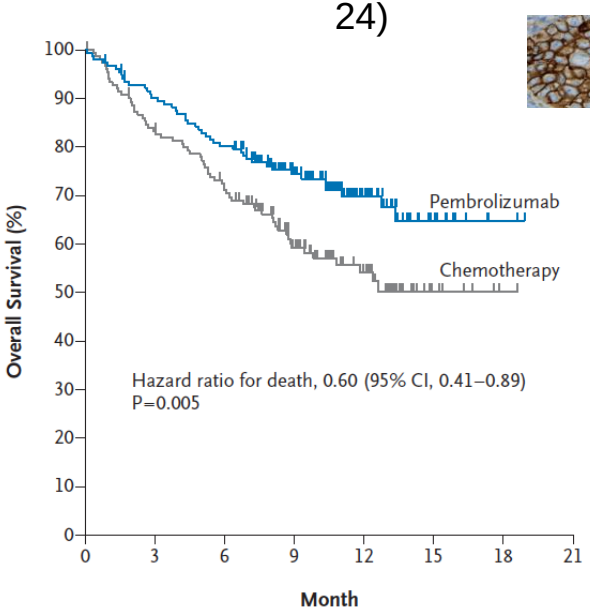
PRIMARY IMMUNE ESCAPE: Why do some patients **never respond** to Atezo?

DURABLE RESPONSE: What are the drivers that contribute to **sustained / long-term anti-tumor immunity**

Can we convert non-

Inflamed tumors derive meaningful benefit from CPI

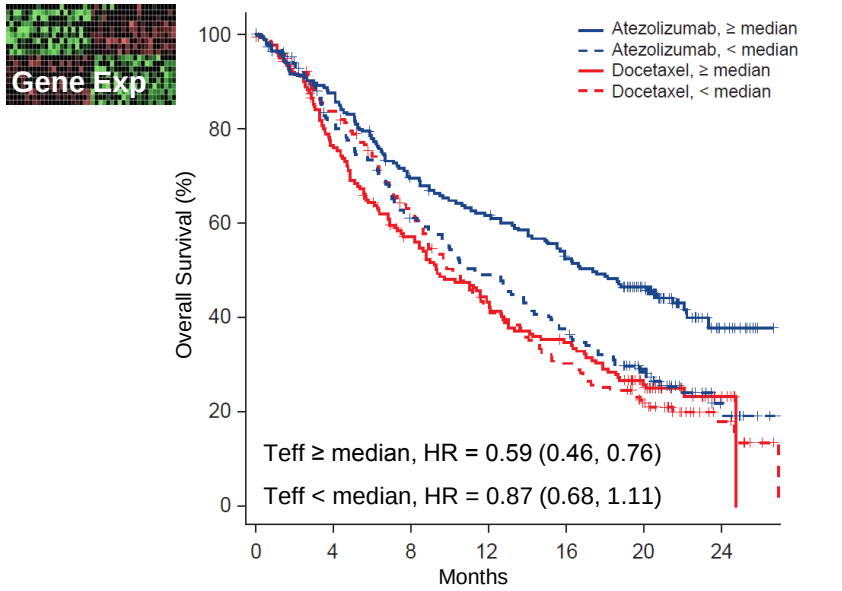
OS benefit observed for Pembrolizumab in PD-L1 (+) patients in front-line NSCLC (KN-24)



Dx: PD-L1 by IHC: TPS>50%

Brahmer J et al., NEJM 2016

OS benefit observed for Atezolizumab in patients with high T_{eff}* gene signature in 2nd line NSCLC (OAK)



Dx: *Effector T-cell (T_{eff}) signature: PD-L1, CXCL9, IFN-γ

Kowanetz et al., WCLC, 2017

Effector-T cell gene signatures may be a more sensitive readout of PFS in inflamed tumors

OAK	PFS	
	PD-L1 IHC* +	T_{eff} Signature +
Prevalence	55%	51%
HR (95% CI)	0.93 (0.76, 1.15)	**0.73** (0.58, 0.91)
HR (95% CI) BEP (N = 753)	0.94 (0.81, 1.10)	

Dx: Effector T-cell (T_{eff}) signature: PD-L1, CXCL9, IFN-γ

T_{eff} gene signature is a more sensitive biomarker of PFS than PD-L1 IHC

- At a similar prevalence, Teff gene expression identified patients who experienced a significant PFS benefit with atezolizumab therapy in 2nd line NSCLC

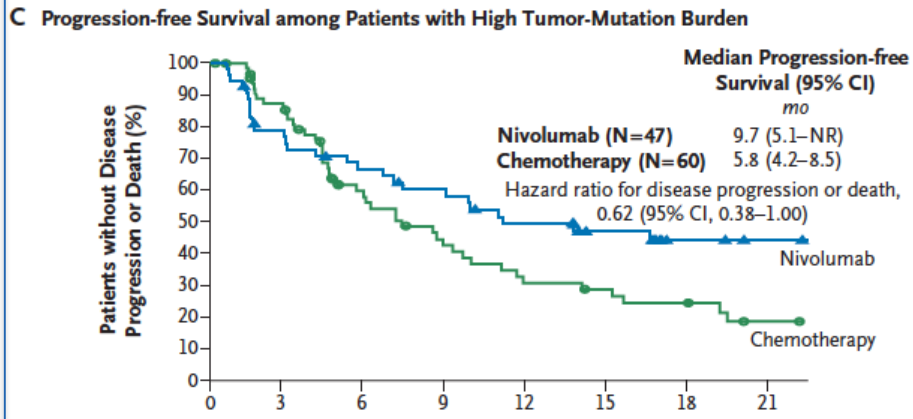
*SP142; TC1 or IC1= TC or IC ≥ 1% PD-L1–expressing cells.

BEP, biomarker-evaluable population. Data cutoff: July 7, 2016

Kowanetz et al. OAK Teff biomarker. WCLC 2017.

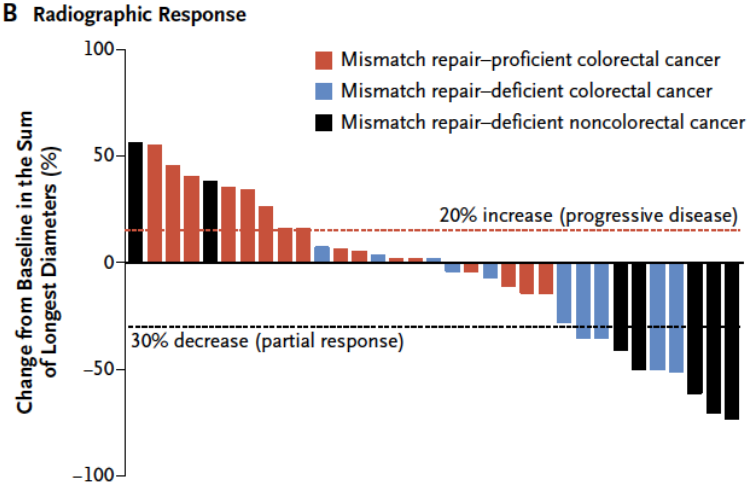
Tumor types with a high mutation load (TMB) may derive benefit from monotherapy CPI

Patients with high tumor mutation load derive PFS benefit from Nivolumab in front-line NSCLC (CM-026)



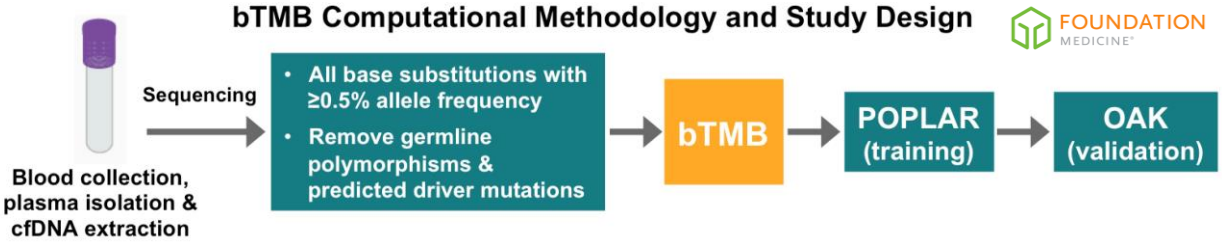
Carbone DP et al., NEJM 2017

MMR deficiency is associated with response to Pembrolizumab

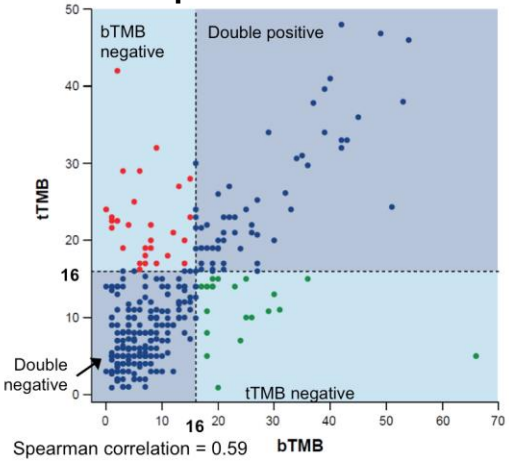


Le et al., NEJM 2015

Exploring the utility of blood as a sensor for actionable tumor markers – eg. blood based TMB



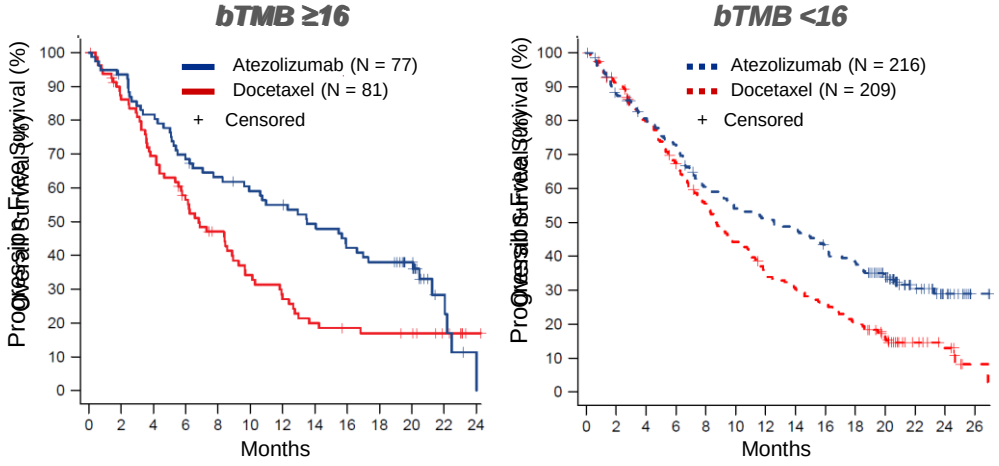
Comparison of b vs t TMB



(PPA: 64%; NPA: 88%)

Atezolizumab PFS benefit in bTMB subgroups

OS in bTMB subgroups



Interaction *P* = 0.75

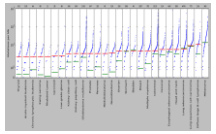
Gandara DL., et al., ESMO 2017; Manuscript in review

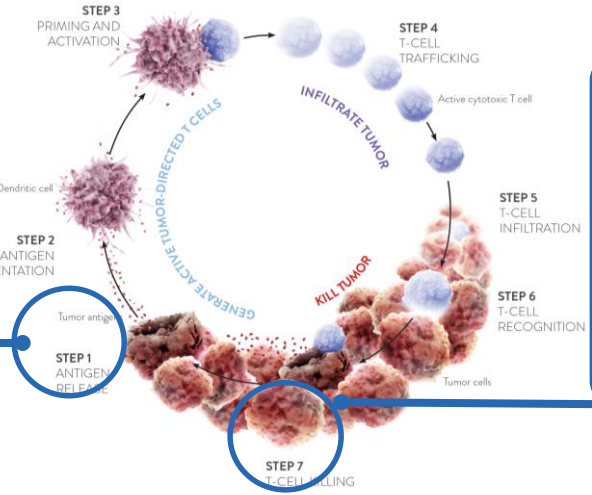
BFAST: Prospective trial to validate the biomarker

Where are we today with predictors for PD-L1/PD-1 targeted agents?

Tumor Mutation Burden

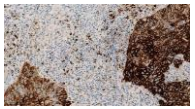
MSI[1], tMB[2]





PD-L1 expression

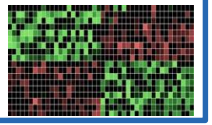
IHC



Tumor Gene Expression

IFNγ signature

NGS

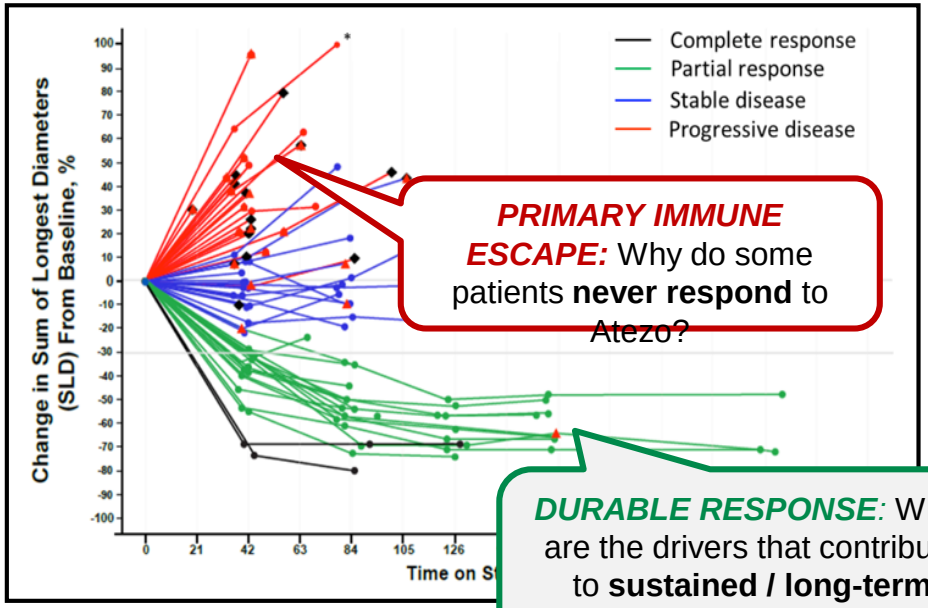


Chen and Mellman, Immunity, 2013
[1]Le et al., NEJM 2015
[2] Powles T et al., Lancet 2017

No single biomarker fully describes patients who derive benefit from monotherapy CPIs

..More on systemic predictors of response in tomorrow at session III at 1:00pm

What are the drivers of escape from CPI?



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Can we convert non-

The Tumor Immunity Continuum- framework for combinations

Inflamed — Non-inflamed

INFLAMED

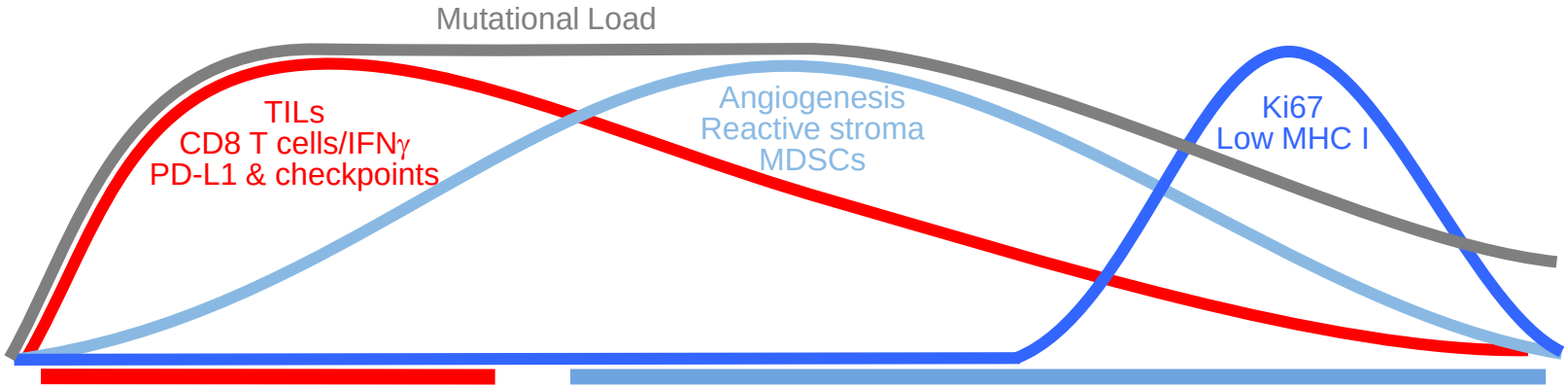
CD8+ T cells infiltrated, but non-functional

IMMUNE EXCLUDED

CD8+ T cells accumulated but have not efficiently infiltrated

IMMUNE DESERT

CD8+ T cells are absent from tumour and its periphery



Modified from Hegde PS et al., Clin Canc Res 2016

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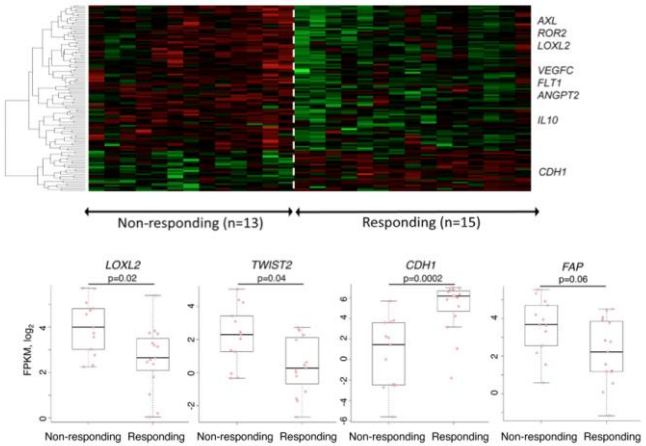
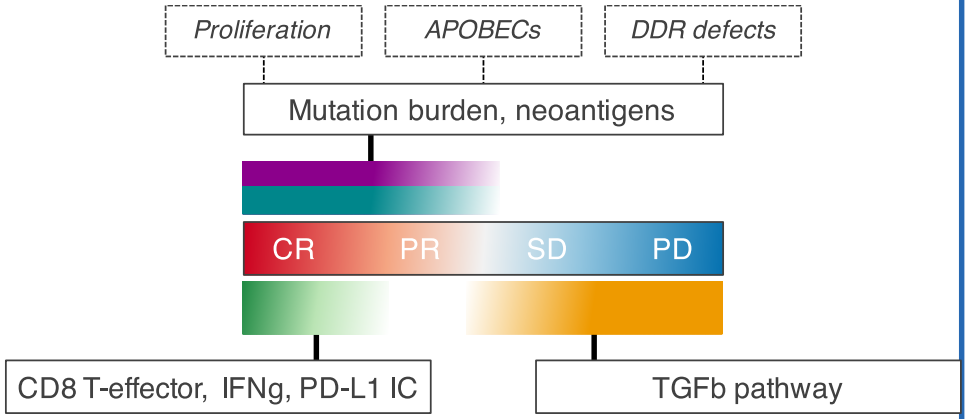
Reactive Stromal biology may present an immune escape mechanism

Mesenchymal biology associated with resistance to PD-1 blockade in melanoma



Willy et al., Cell (2016)

Bladder Cancer: Atezolizumab (IMvigor210)



Mariathasan S., et al., manuscript accepted, Nature
*Mariathasan S et al., poster **p13** Friday 12:30pm Nov 10 SITC2017*

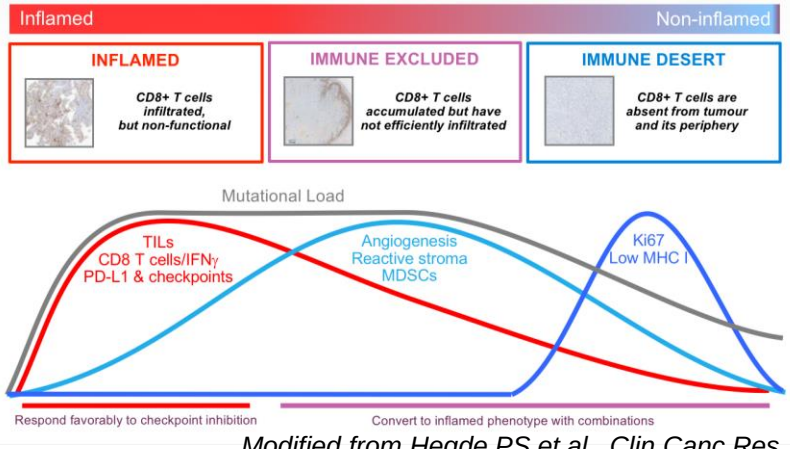
..More on predictors of escape in tomorrow at Session III 1:00pm

Development of Combinations

From a disease-centric to a biology-centric model

Diagnostic and treatment options in Oncology have traditionally been disease centric

In the era of CIT, treatment strategies will become disease agnostic and biology centric



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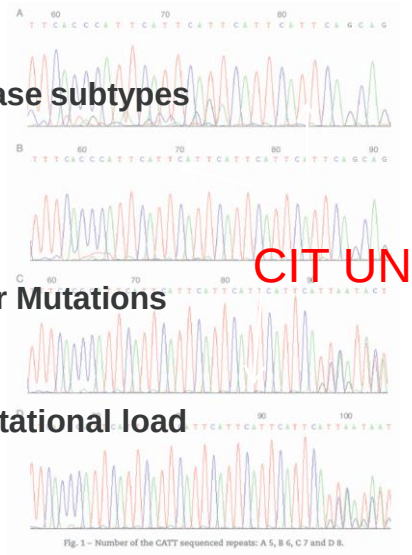
Need for a composite testing platform



Disease subtypes (tGE)

Driver Mutations

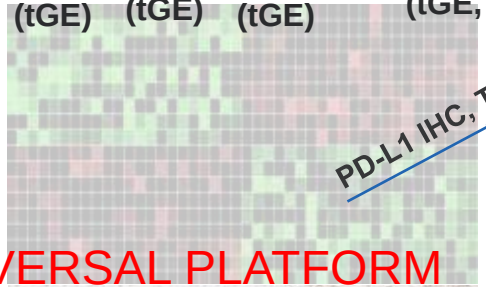
Mutational load

Reactive Stroma (tGE)

TGFβ (tGE)

BRCA (tGE)

DNA repair/proliferation (tGE, mutations)

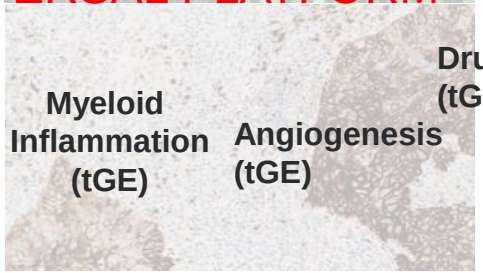


PD-L1 IHC, T eff

CPI mono Algorithm 1

CPI chemo combo Algorithm 2

CIT UNIVERSAL PLATFORM



Myeloid Inflammation (tGE)

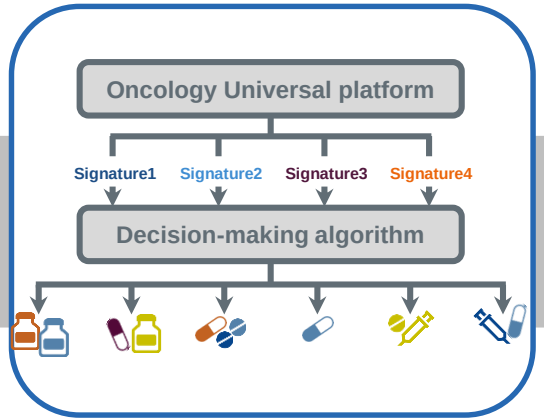
Angiogenesis (tGE)

Drug Targets (tGE, IHC)

Treatment Decision Algorithms

Over 1500 trials ongoing with ~300,000 patients

Incorporate validated platform across all trials
Develop treatment decision algorithms



Patients receive best-in-disease tailored treatment

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Rich Price
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