Biomarker basics and current biomarkers in cancer immunotherapy

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Genentech

SITC Cancer Immunotherapy Winter School

Phoenix, AZ

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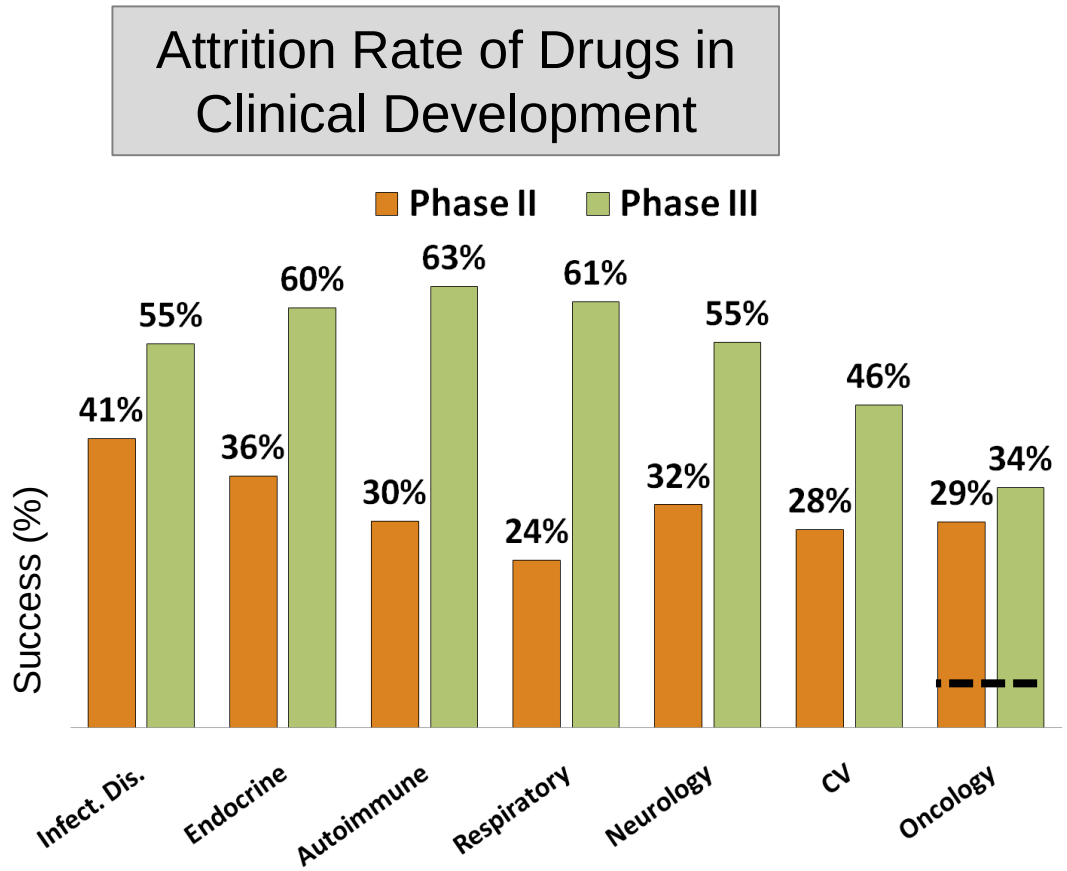
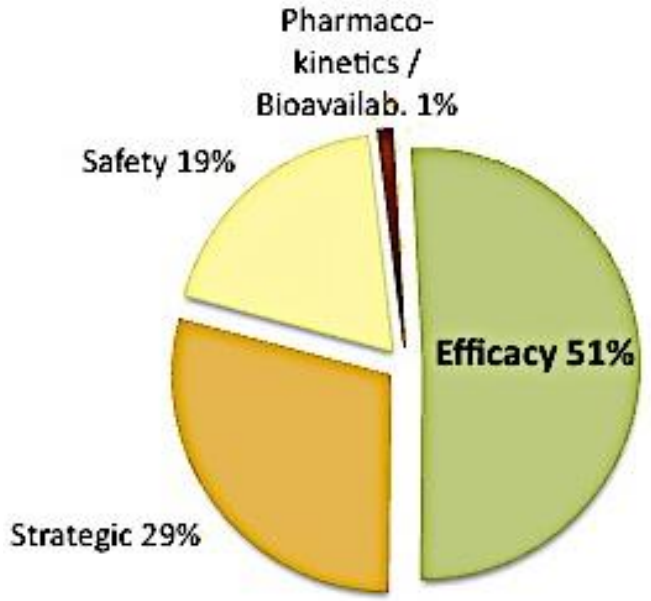
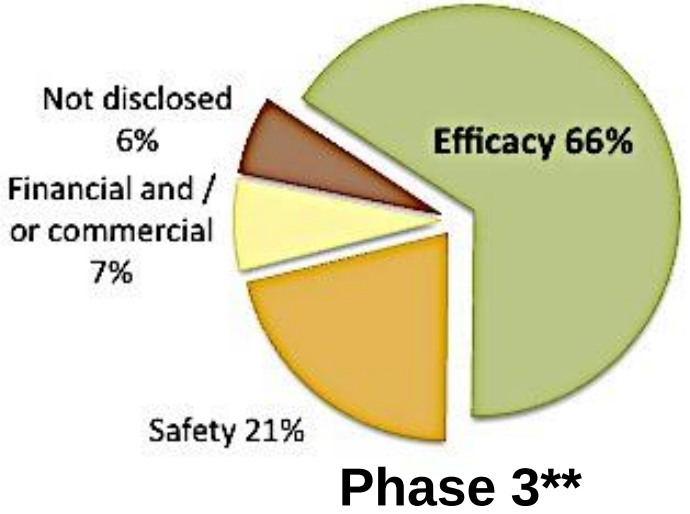
Agenda

- Biomarkers and types of Biomarkers
- Biomarkers in cancer immunotherapy
- Implications of personalized healthcare for patients, industry and economy

Getting the Right Drug to the Patient



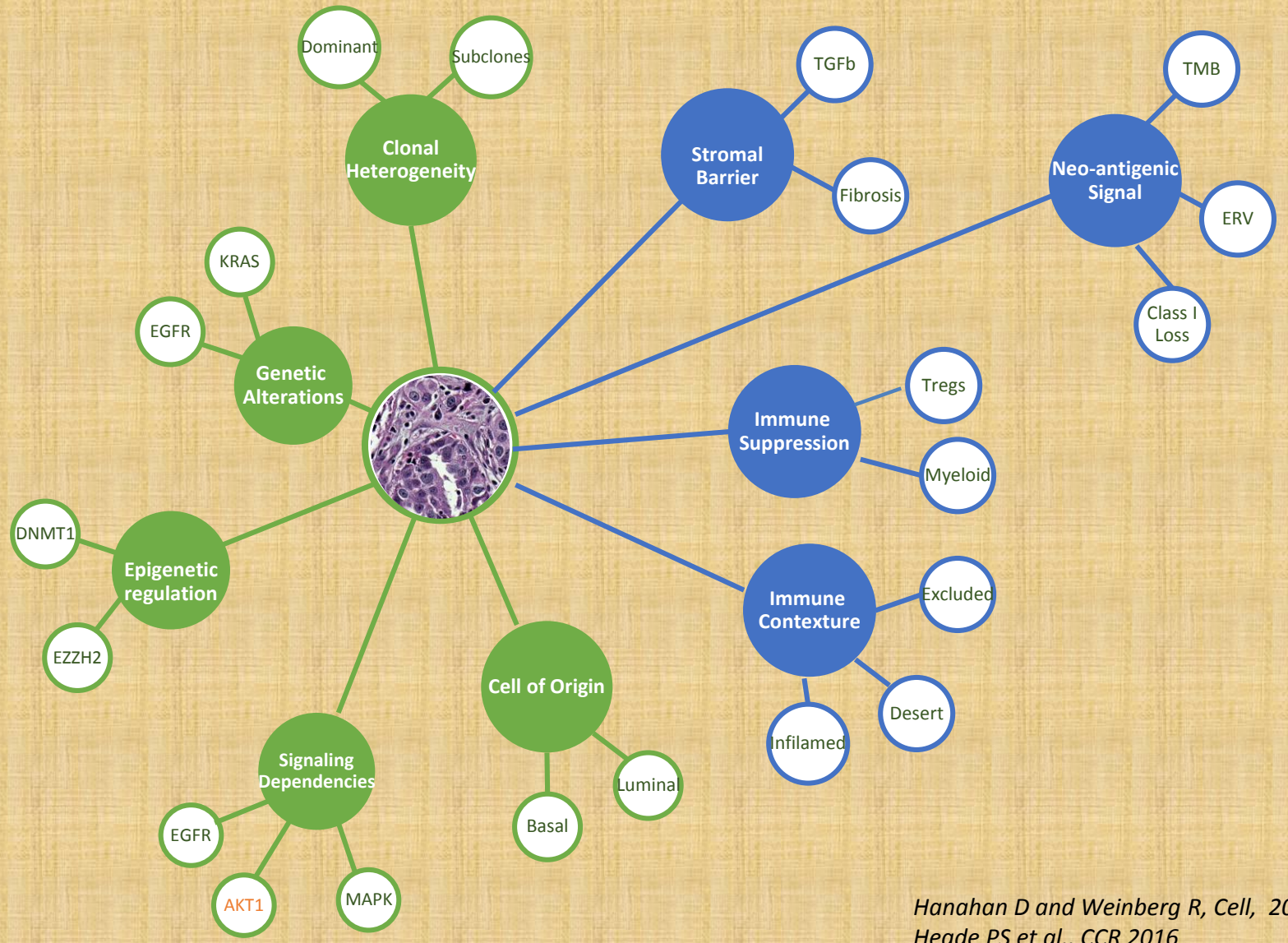




Oct 2003 to 2010: Source—BIO CEO and Investor Conference, Feb 15, 2011

Cancer is a heterogenous disease

Treatment options need to account for heterogeneity



Tumor cell intrinsic

Tumor microenvironment

Hanahan D and Weinberg R, Cell, 2011
Hegde PS et al., CCR 2016
Chen D and Mellman I, Nature 2017

Definition

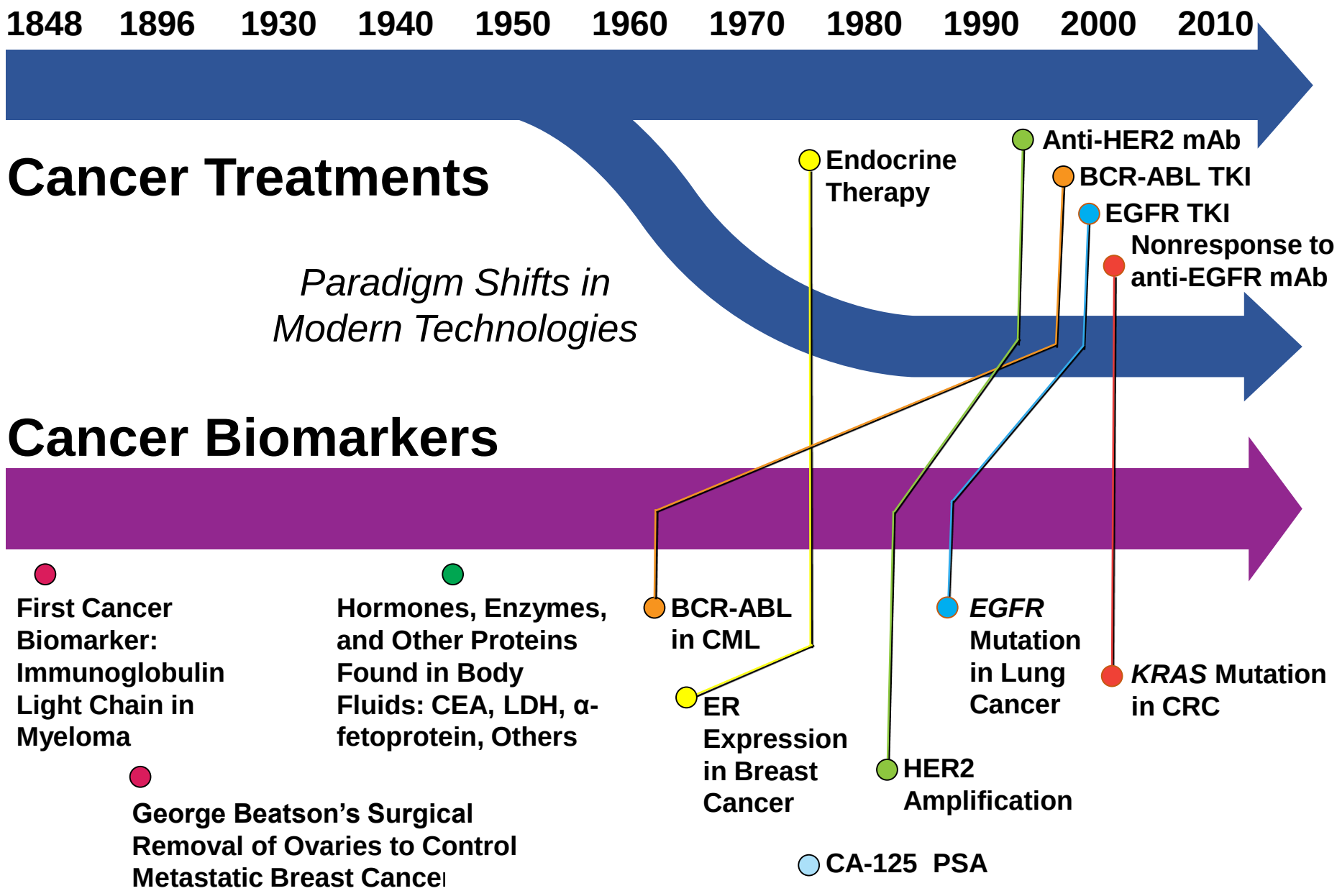
"A characteristic that is objectively measured and evaluated as an indicator of:

Normal Biological Processes,
Pathogenic Processes, or
Pharmacologic Responses

…to a therapeutic intervention."

(From the NIH Biomarker Definitions Working Group)

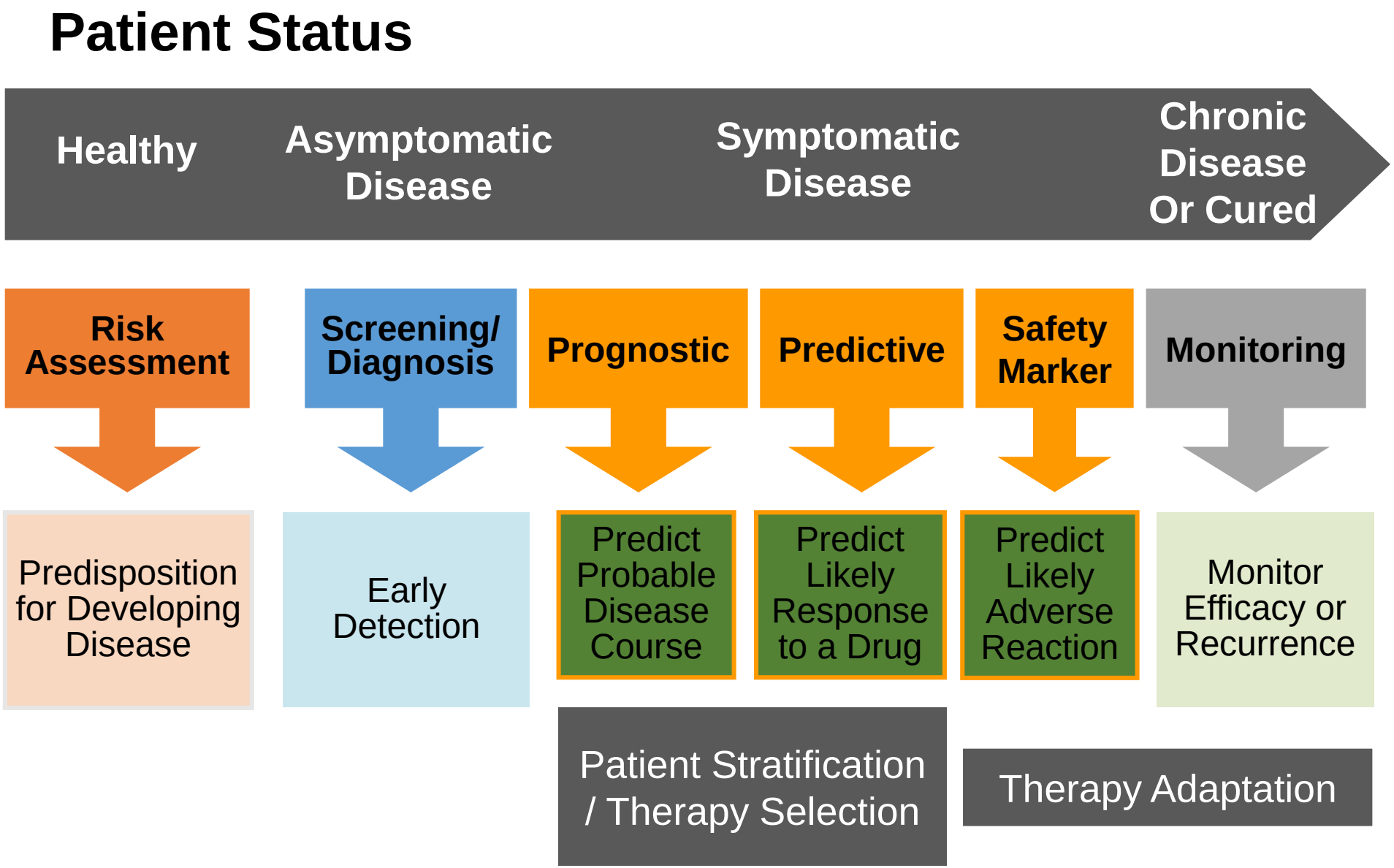
Biomarker Milestones



Biomarker Terminology

Diagnostic Biomarker	Used for disease diagnosis (typically for screening)
Predictive Biomarker	Provides information about the response or outcome of a specific treatment in an individual (typically pre-treatment)
Prognostic Biomarker	Provides information about a patient's overall outcome, regardless of therapy
Pharmacodynamic Biomarkers	On-treatment biomarkers to confirm drug activity at the right dose
Pharmaco-genomics	Correlates gene expression (or somatic mutations in tumoral DNA) with a drug's efficacy

Biomarker Categories



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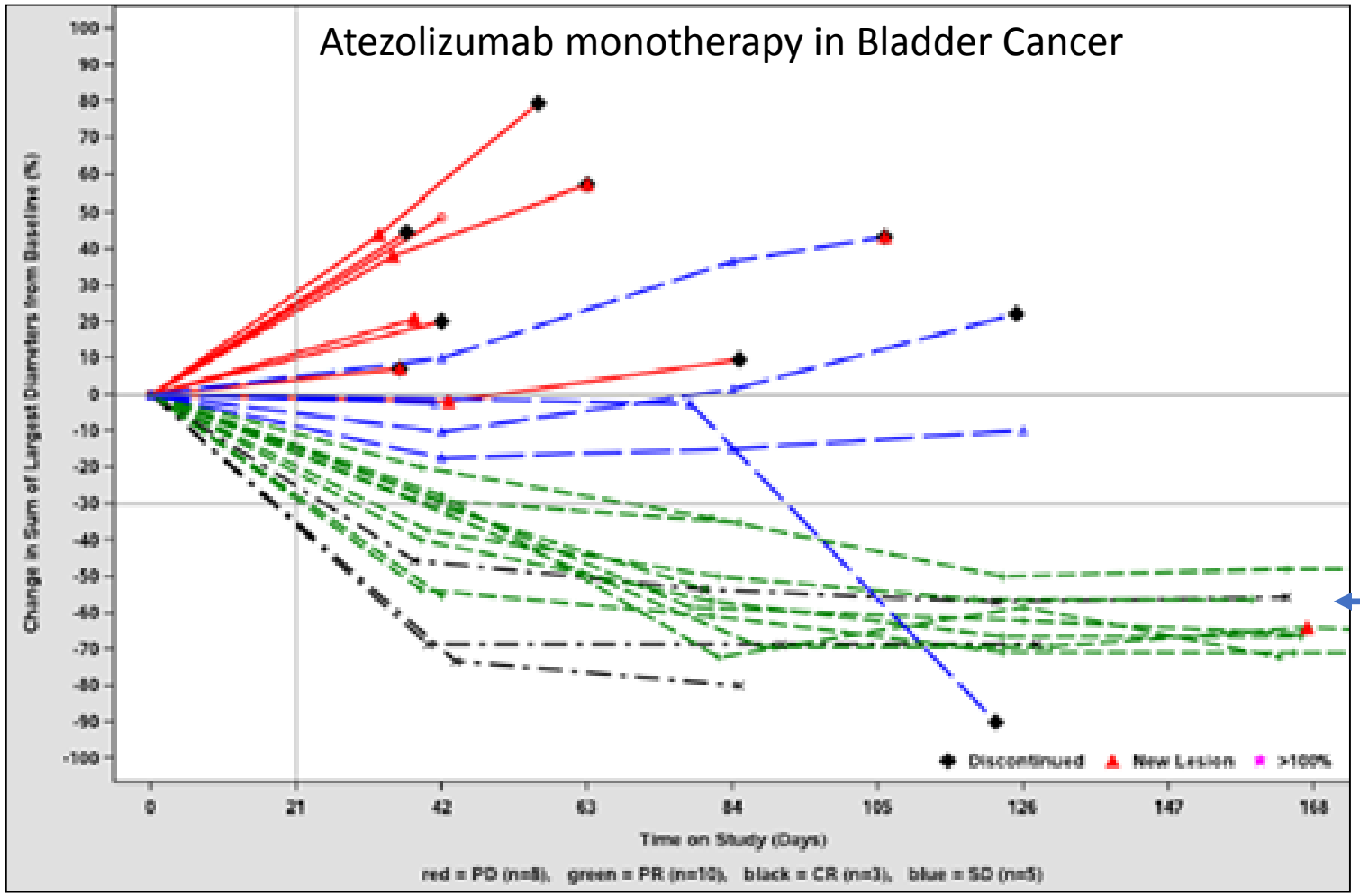
Predictive Biomarker

Provides information about the response or outcome of a specific treatment in an individual (typically pre-treatment)



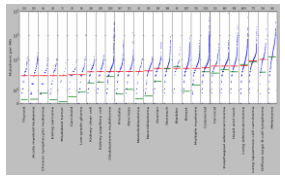
What is the tumor profile associated with these patients?

These are the markers that can become companion diagnostics Included on the drug label

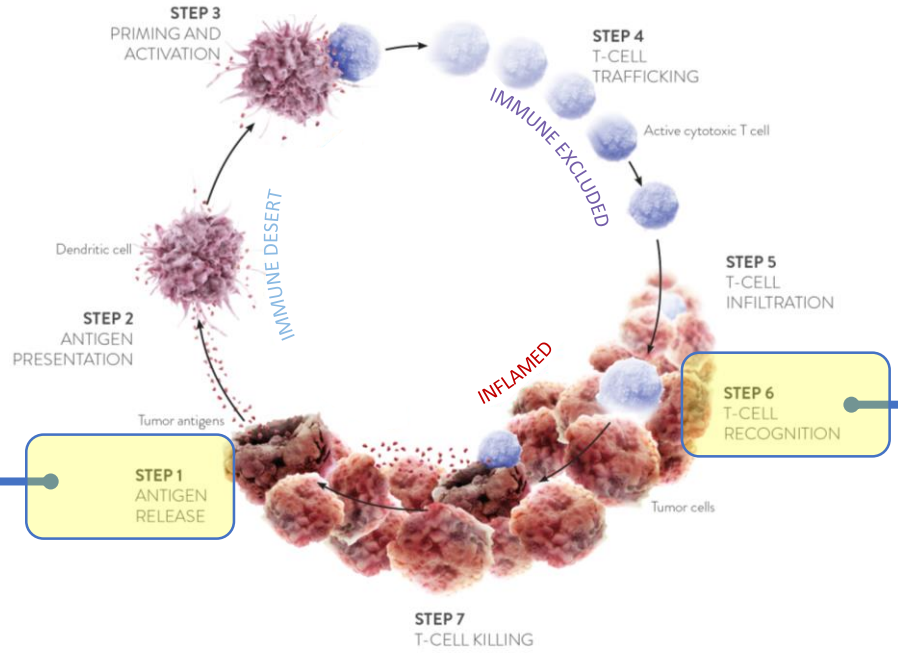
Presence of neo-antigenic signal IR + pre-existing immune activation signal IA = anti-tumor immune response

Immune Recognition (IR)

Tumor Mutation Burden

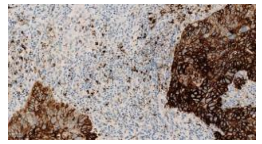


MSI[1], tMB[2]



PD-L1 expression

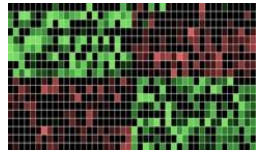
IHC



Tumor Gene Expression

IFNg/ T effector signature

NGS

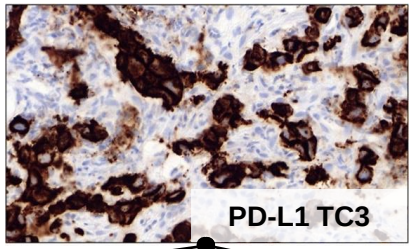


Immune Activation (IA)

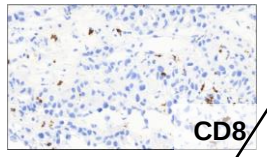
Chen and Mellman, Immunity, 2013
[1]Le et al., NEJM 2015
[2] Powles T et al., Lancet 2017

Distinct biology of PD-L1 on tumor cells and immune cells in NSCLC

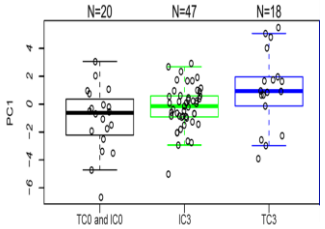
Tumor intrinsic PDL1 expression



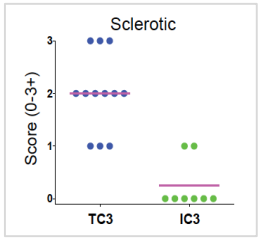
Poor immune infiltration



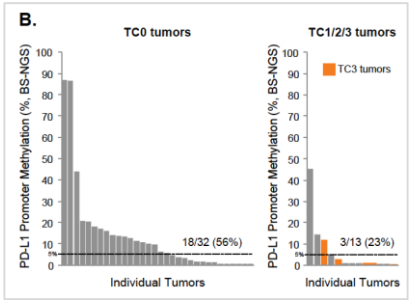
Associated with EMT

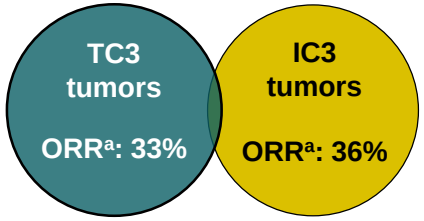


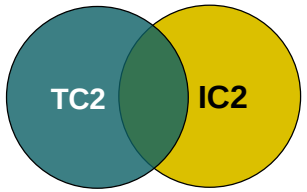
Sclerotic / desmoplastic

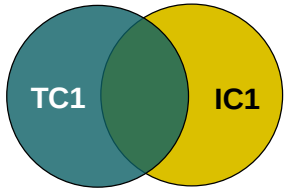


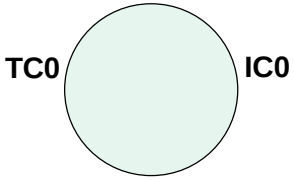
PD-L1 promoter de-methylation



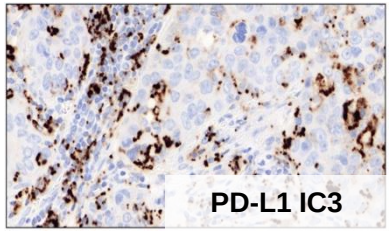


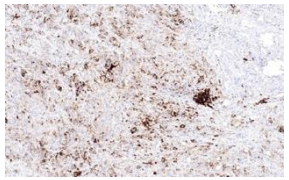


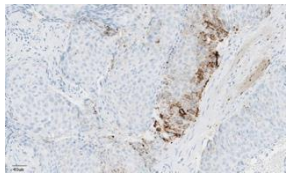


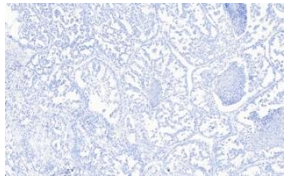


Adaptive PDL1 expression

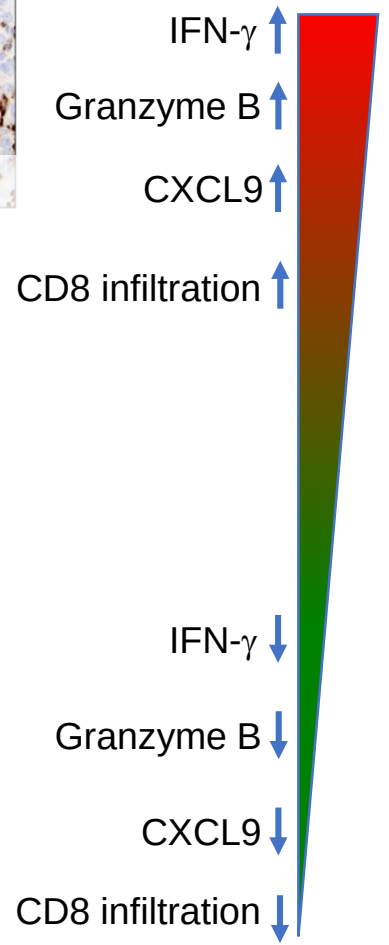








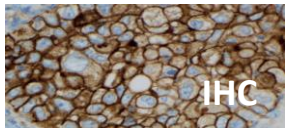
T_{eff} signature and immune cell infiltration

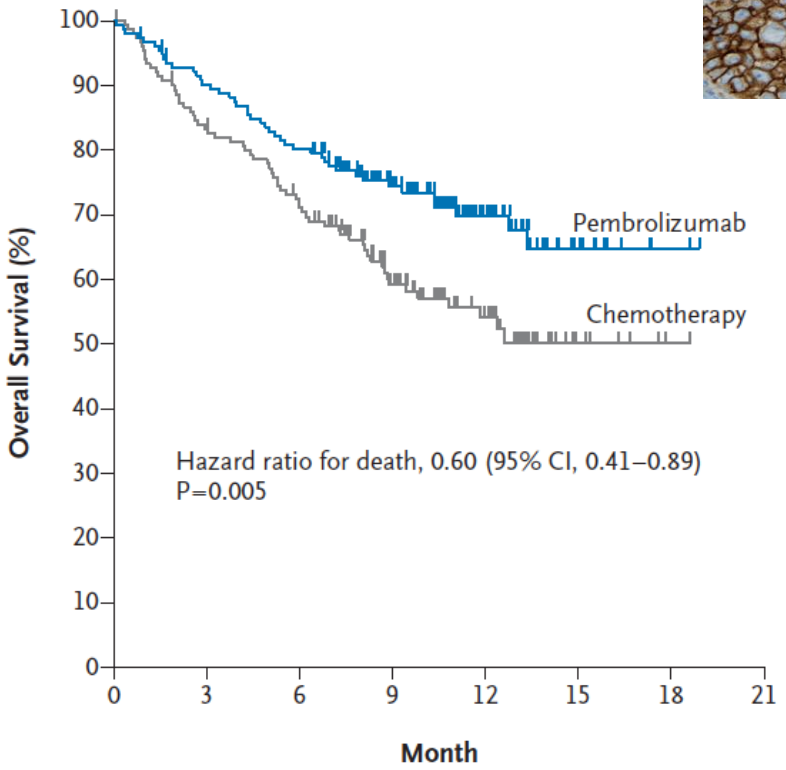


Kowanetz M et al., PNAS 2018

Inflamed tumors derive meaningful benefit from CPI

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

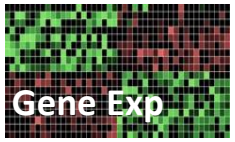


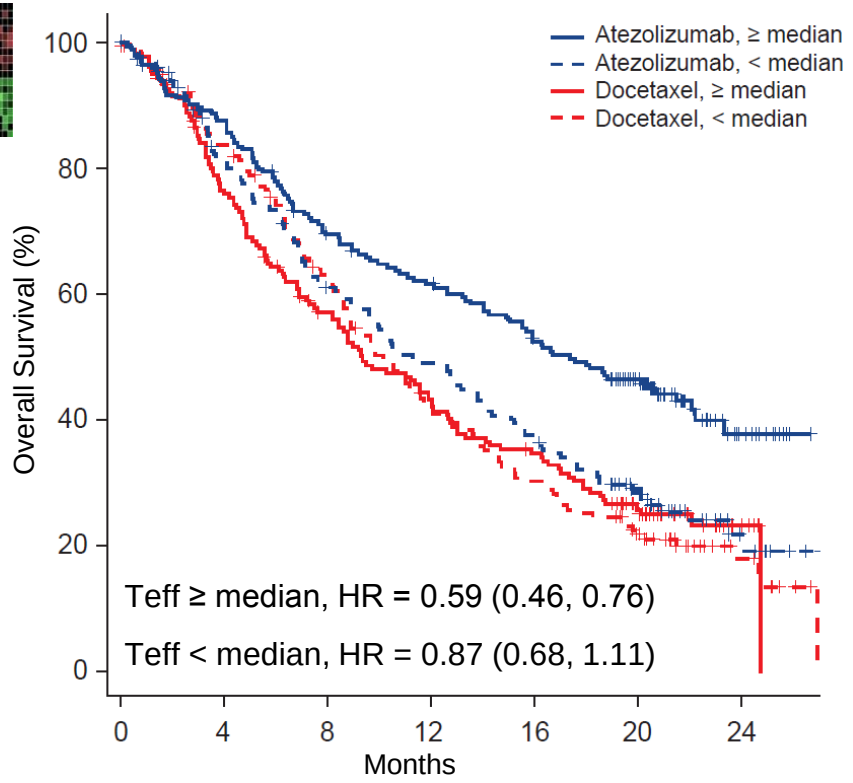


Dx: PD-L1 by IHC: TPS>50%

Brahmer J et al., NEJM 2016

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

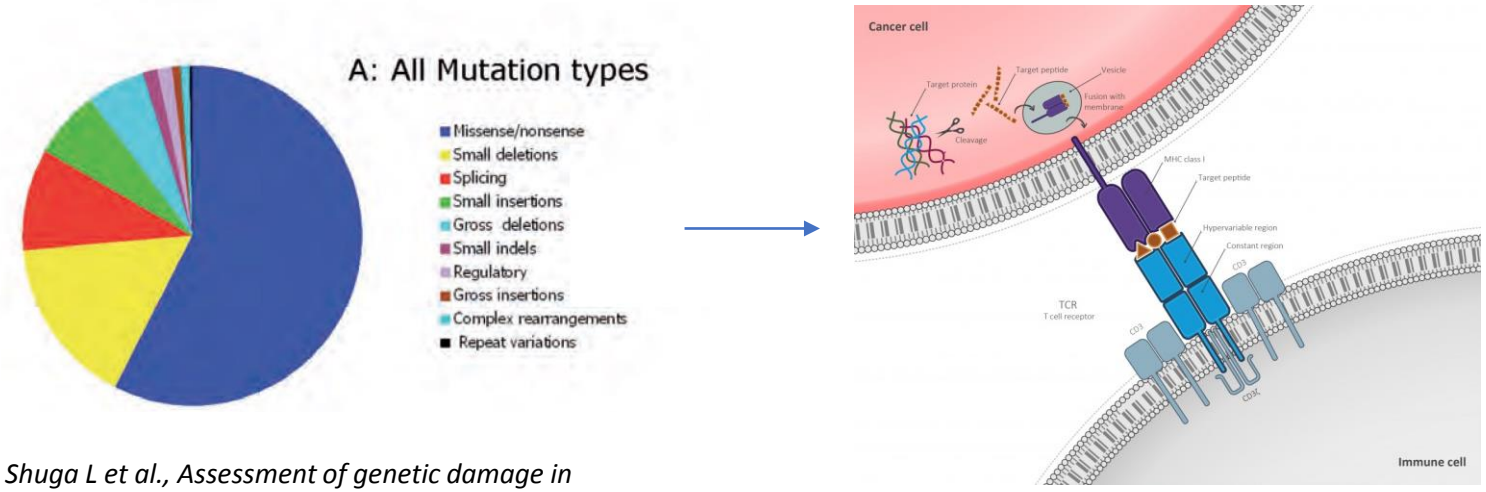




Dx: *Effector T-cell (T_{eff}) signature: PD-L1, CXCL9, IFN-γ

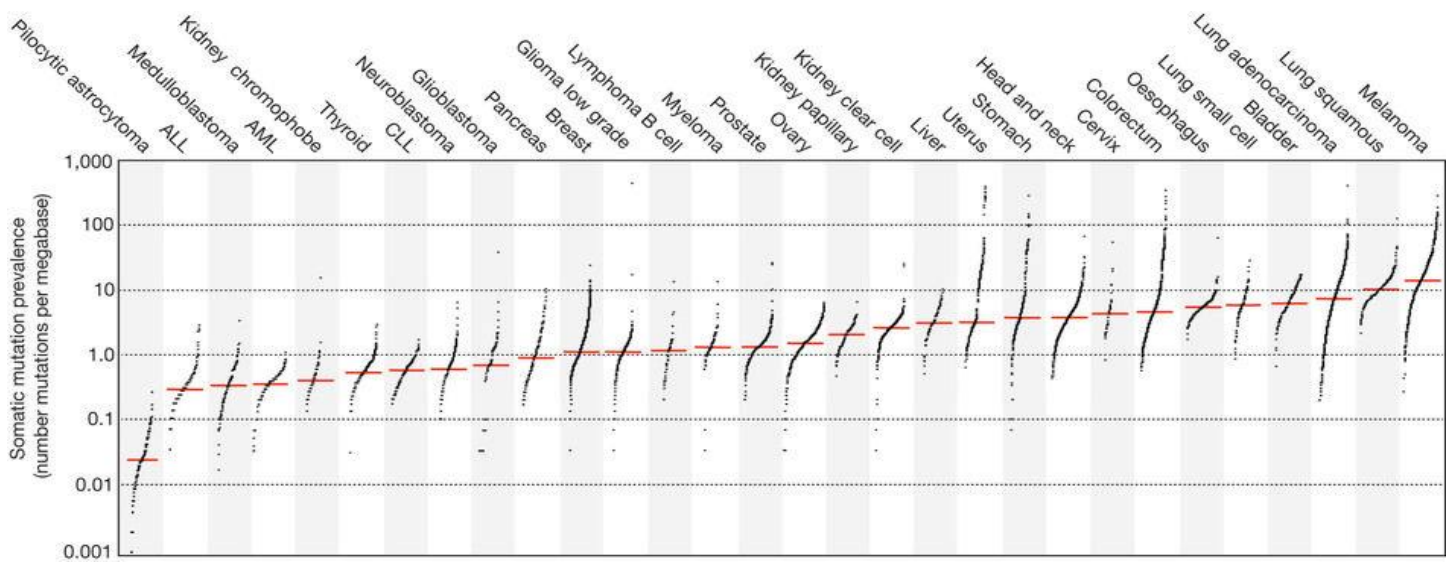
Kowanetz et al., WCLC, 2017

TMB is a surrogate for predicted neo-antigens

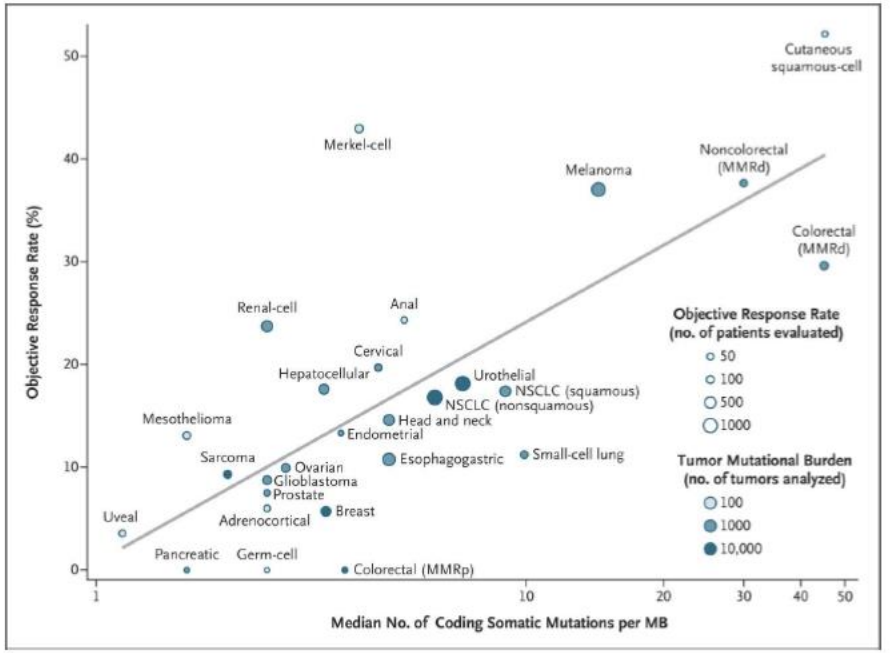


Shuga L et al., Assessment of genetic damage in healthy and diseased tissues (Book, chapter 2)

Cell Medica



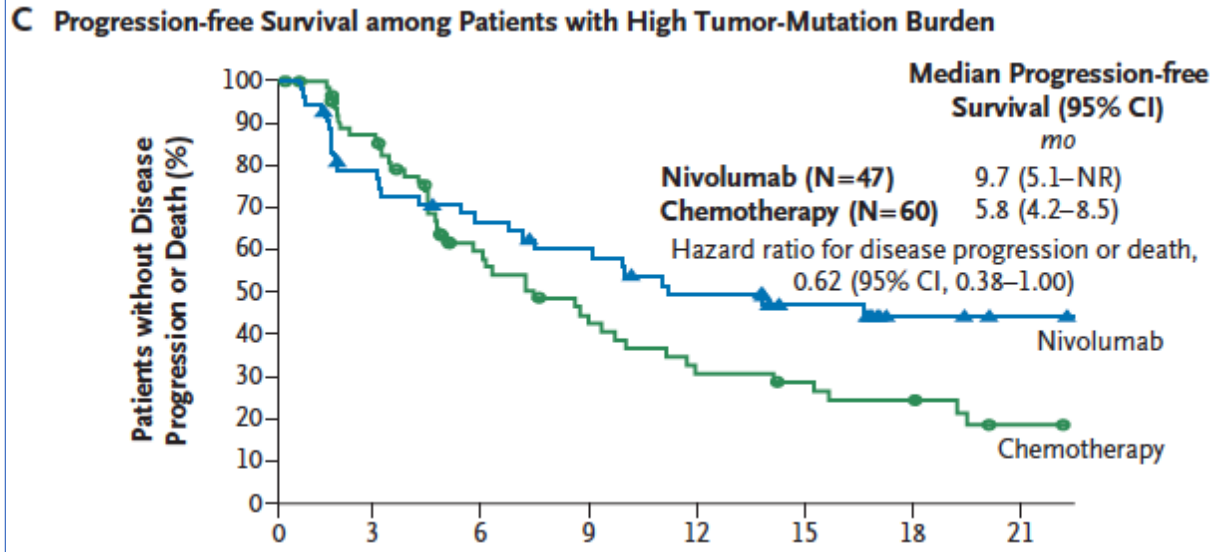
Alexandrov et al., Nature 2013



Yarchoan et al., NEJM 2017

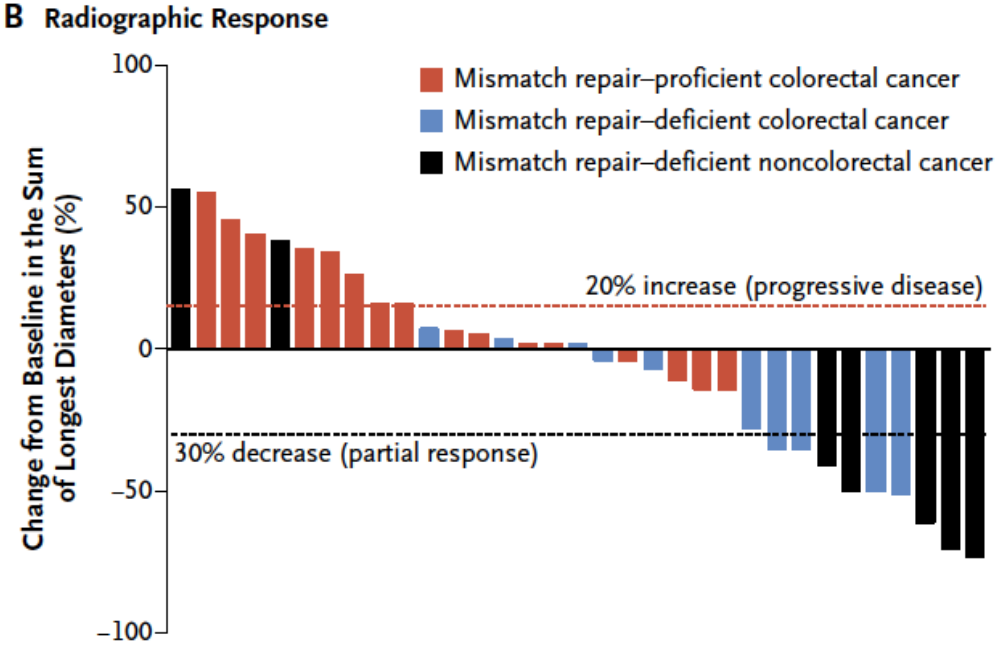
Tumor types with a high mutation load (TMB) may derive benefit from monotherapy CPI

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

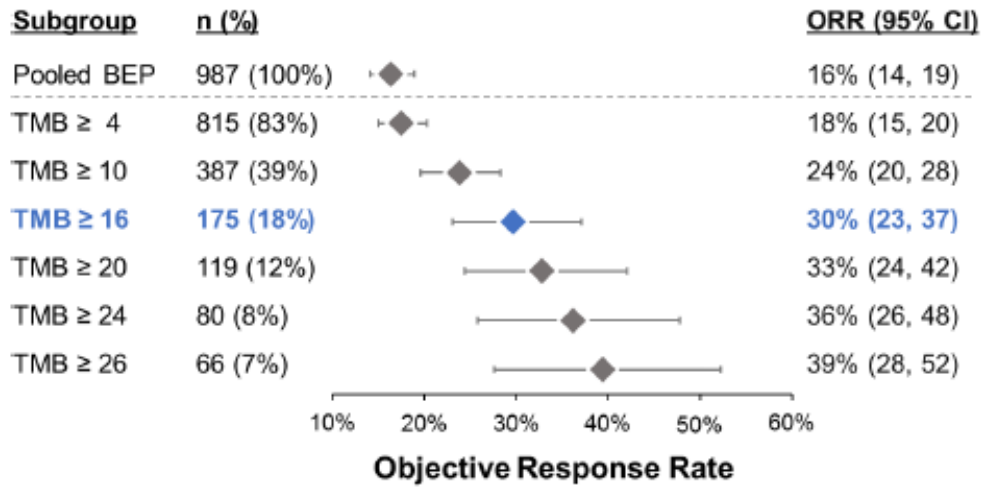


Le et al., NEJM 2015

Tissue-based TMB (tTMB) is associated with efficacy across tumor types and lines of therapy

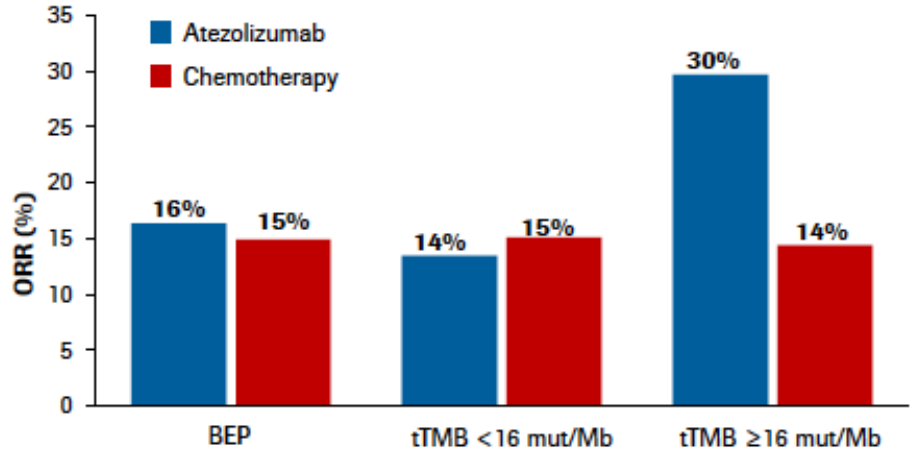
Enabling pan-tumor based strategies for Tecentriq monotherapy

ORR by tTMB cut-offs[a]



ASCO 2018, Legrand FA et al
Oral presentation on Tuesday, Jun 5th

ORR and DOR in tTMB* ≥16 vs <16 subgroups



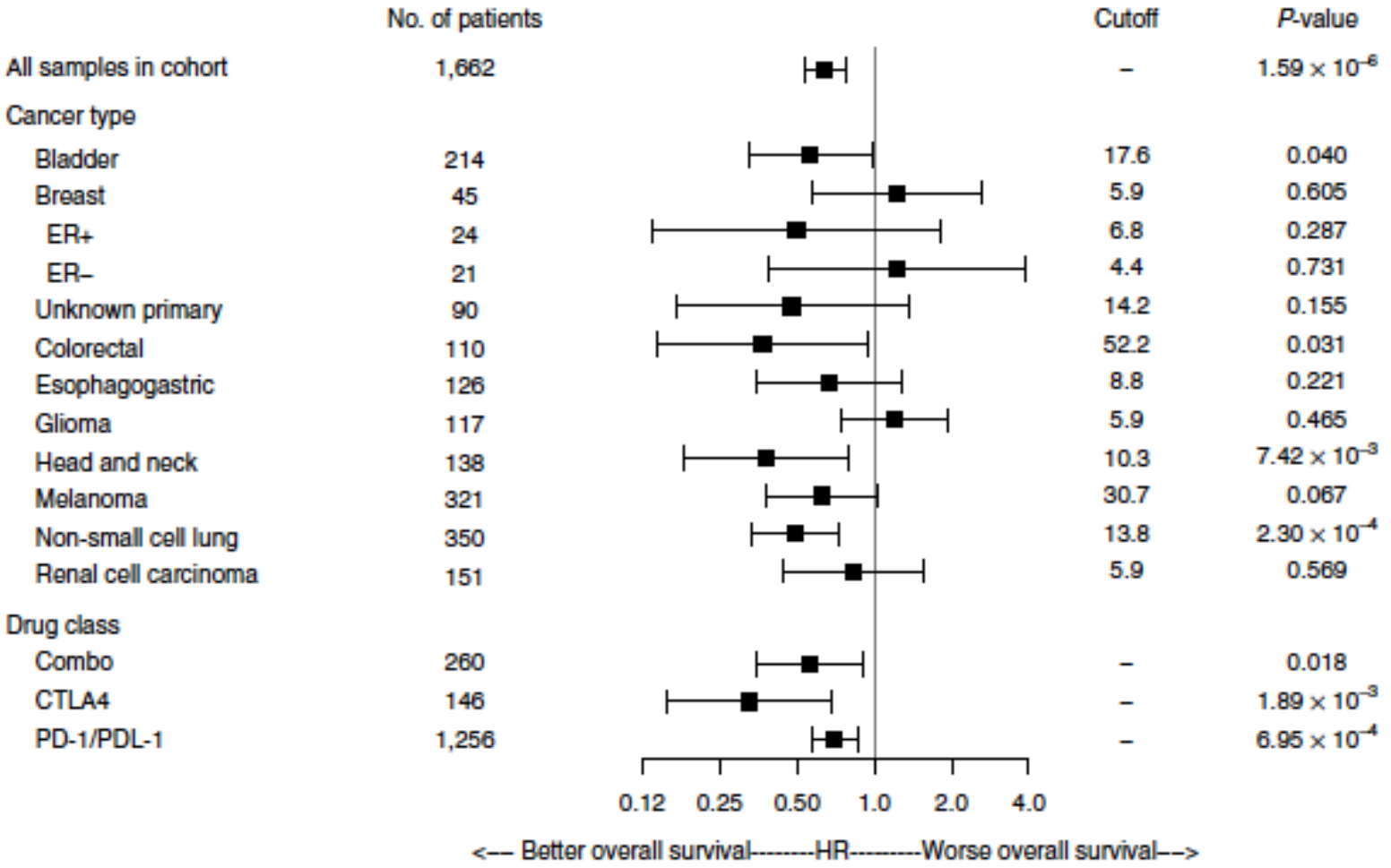
	BEP		tTMB <16 mut/Mb		tTMB ≥16 mut/Mb	
Median DOR (95% CI), mo	16.6 (13.8, 23.1)	6.2 (5.5, 6.7)	13.8 (12.5, 17.4)	6.2 (5.6, 6.9)	29.0 (18.6, NE)	6.2 (4.6, 8.3)

The ≥16 mut/Mb TMB cutoff balances a high ORR and reasonable prevalence across numerous tumor types

ASCO 2018, Legrand FA; [a]TMB cutoffs shown are measured in mut/Mb (date of analysis: November 1, 2017); *Balar AV et al., Lancet. 2017 Jan 7;389(10064):67-76.
tTMB was evaluated by the FoundationOne (F1) assay across 7 Tecentriq monotherapy studies: NSCLC n=342 (FIR, BIRCH, POPLAR, OAK), metastatic urothelial carcinoma (mUC) n=400 (IMvigor210, 211), and other advanced solid tumors n=245 (PCD4989g).

nature genetics
LETTERS
https://doi.org/10.1038/s41588-018-0312-8

Tumor mutational load predicts survival after immunotherapy across multiple cancer types

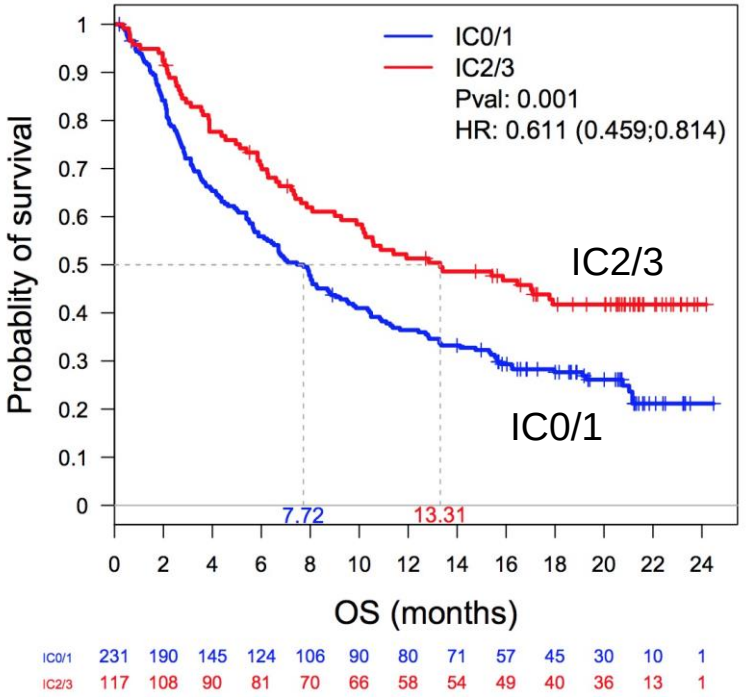


Samstein et al., Nat Gen 2019

Improved overall survival (OS) benefit to atezolizumab was observed in patients with both high tumor mutation burden (TMB) and high PD-L1 IC scores (mUC)

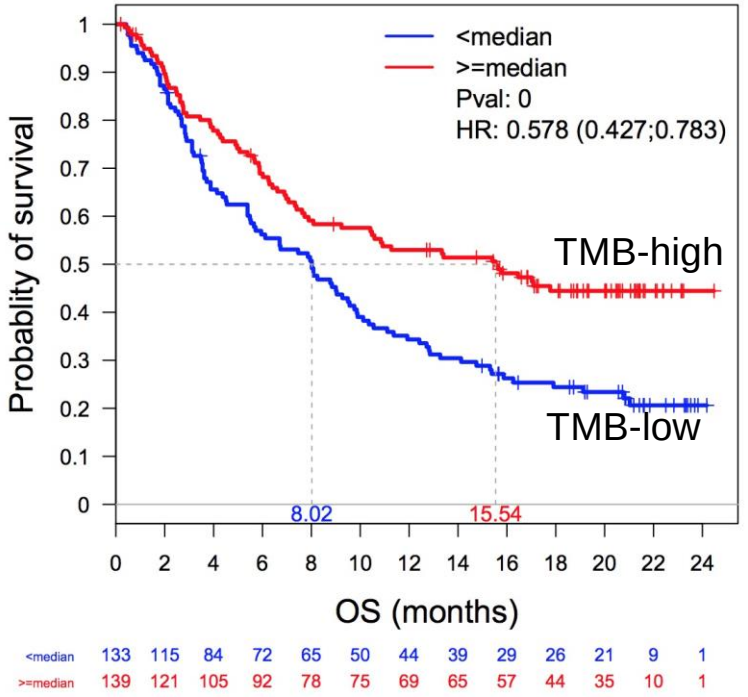
SIGNAL IA

OS by PD-L1 IC status



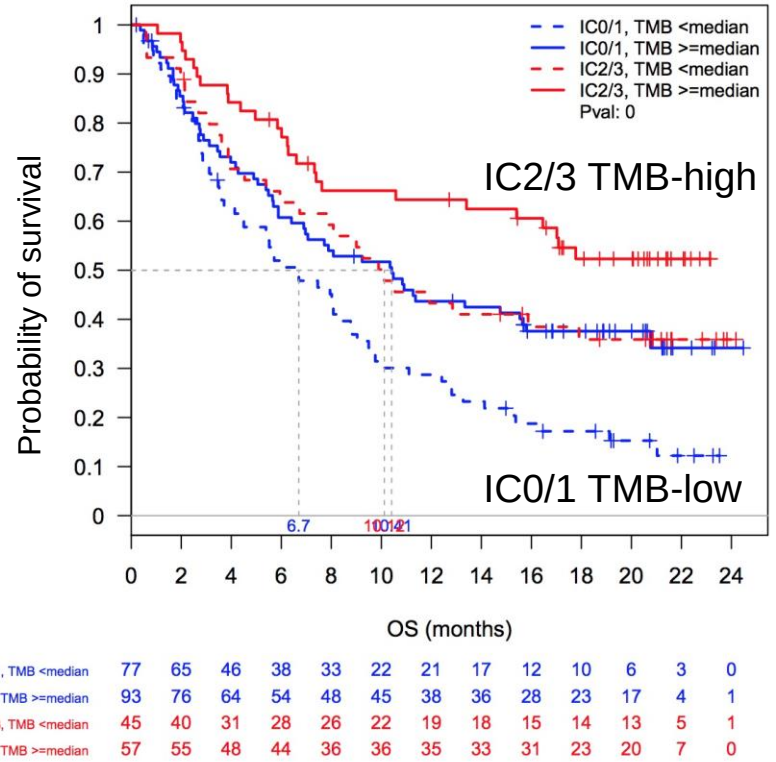
SIGNAL IR

OS by TMB status



SIGNAL IA+ SIGNAL IR

OS by combined PD-L1 IC and TMB status



IMvigor 210

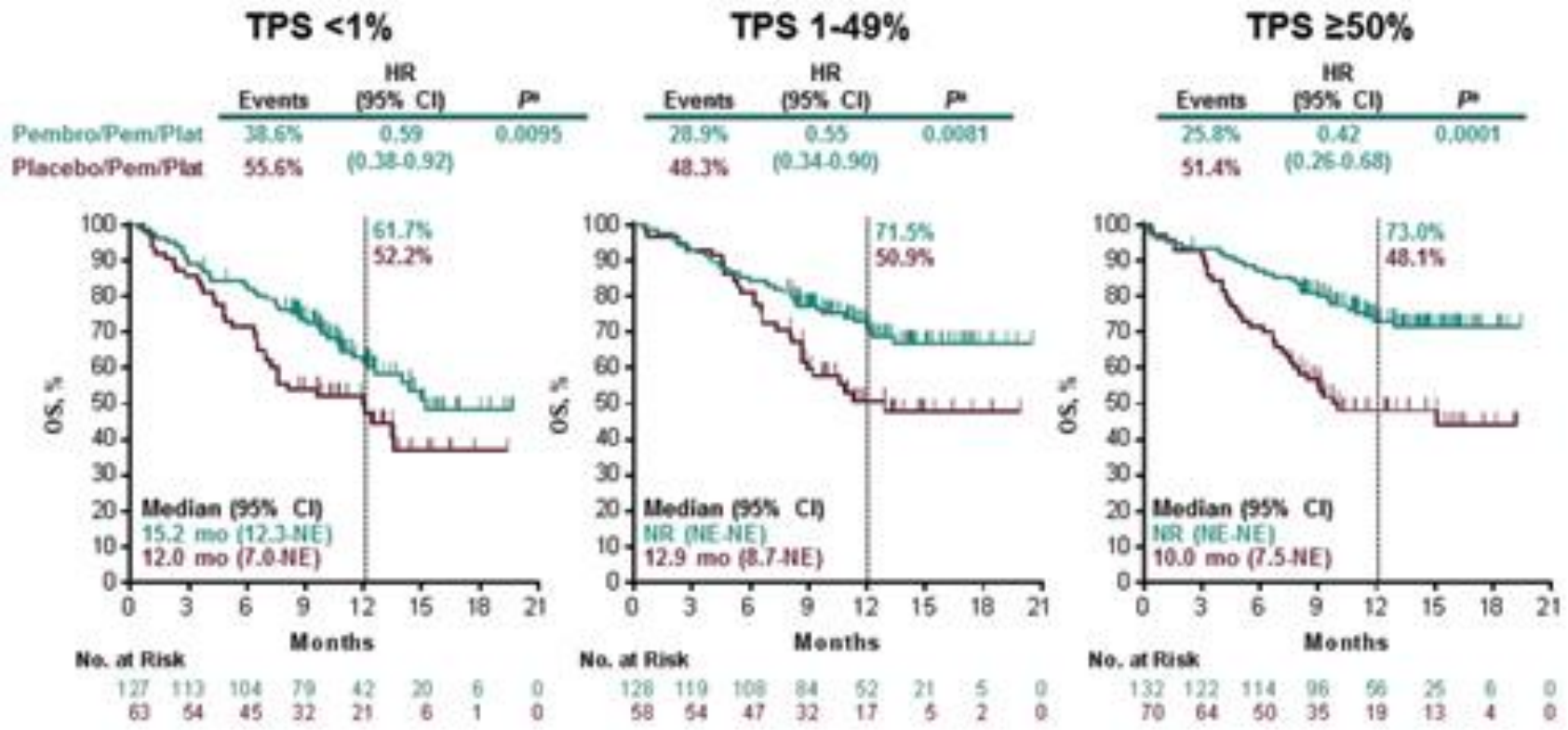
Combination of biomarkers help better predict responses to immunotherapy

IC, tumor-infiltrating immune cells

Mariathasan S et al., AACR 2018

Predictors of benefit to Checkpoint Inhibitors in combination with chemotherapy

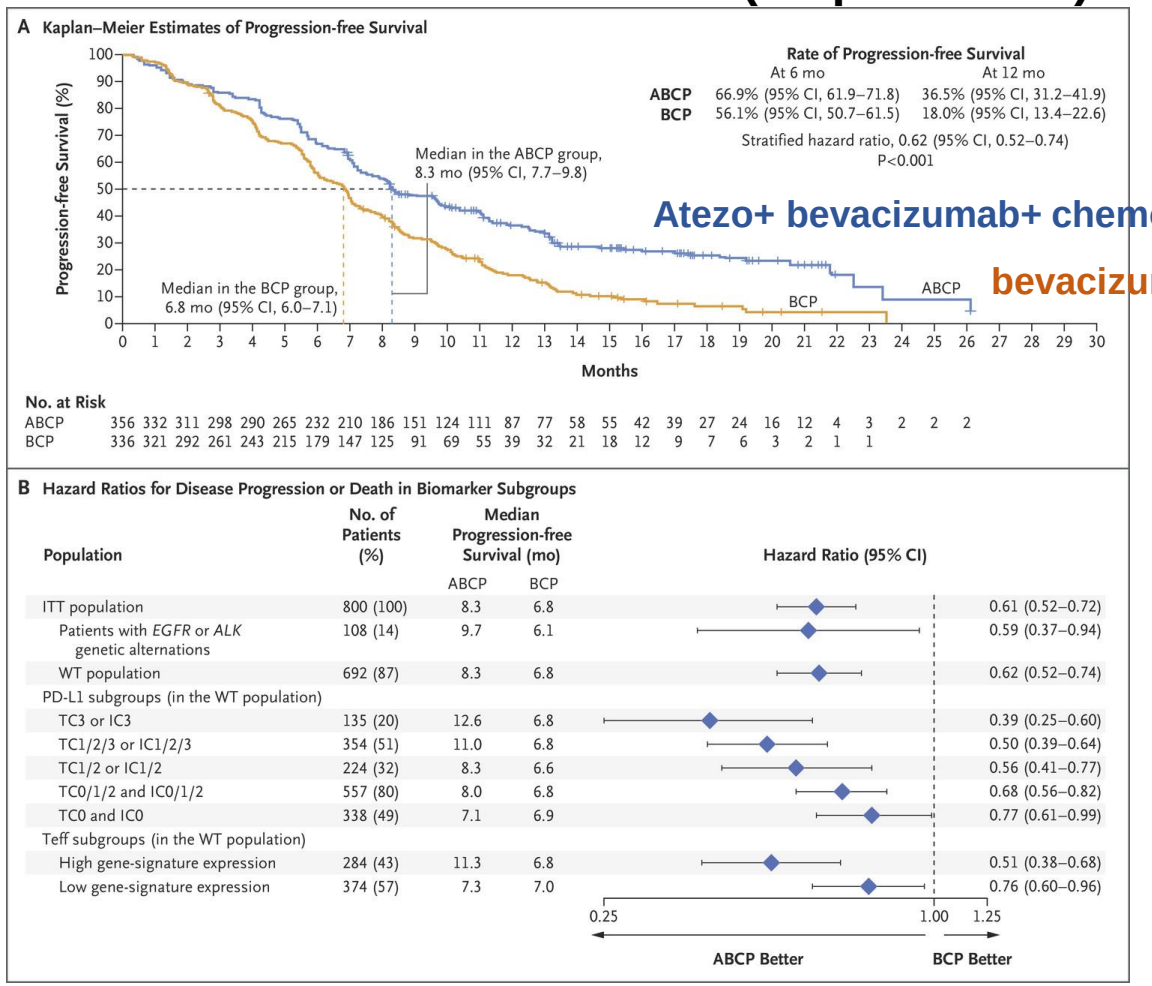
Efficacy to CPI observed across PD-L1 subgroups in NSCLC
Keynote-189 (Pembrolizumab+carbo/pem)



Gandhi et al., NEJM, 2018

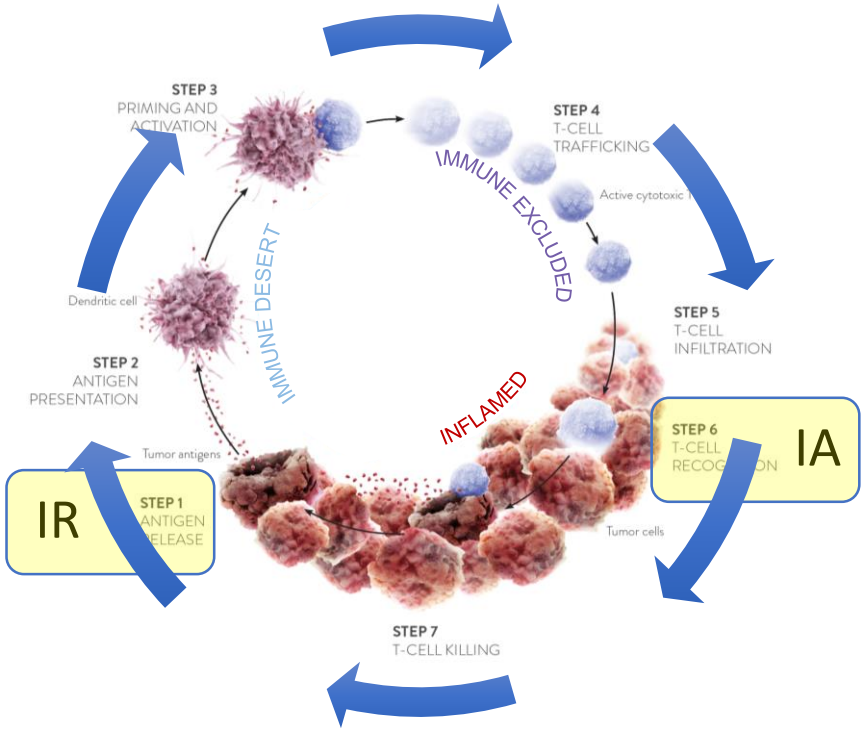
Broad efficacy observed when both signals IR and IA present

ITT benefit observed in NSCLC for Atezolizumab + SOC chemo ([1]IMpower 150)



Atezo+ bevacizumab+ chemo

bevacizumab+ chemo



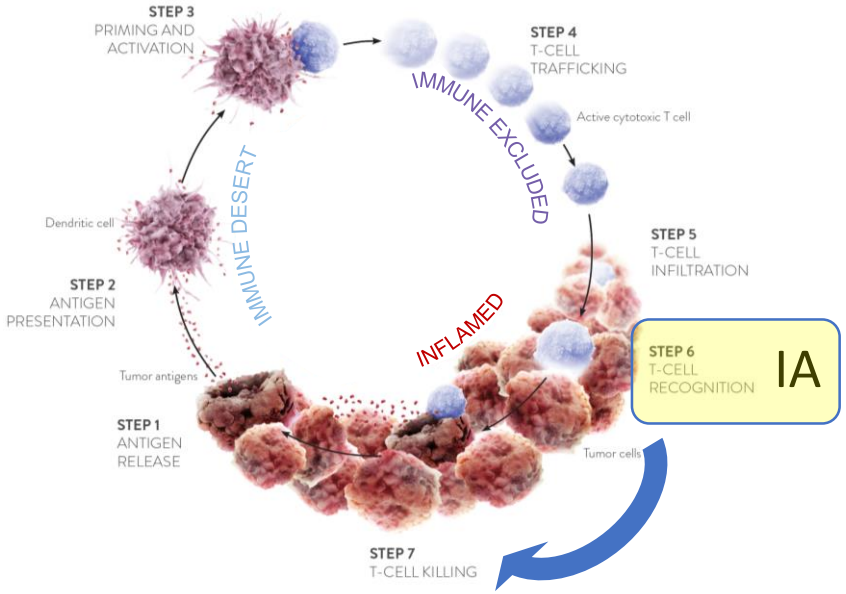
When both signals in place, broad efficacy observed

How to address CPI refractory space?

[1]*Socinski M et al., NEJM 2018*

When IA signal present, efficacy predominantly observed in PD-L1+ cases

TNBC



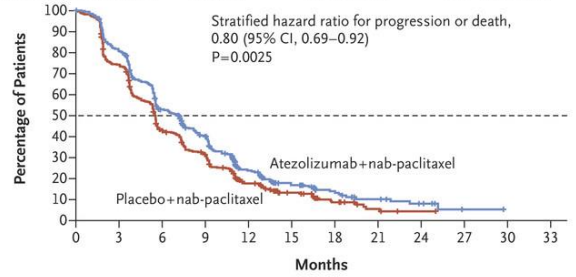
Efficacy observed in PD-L1 (+) patients when only IA signal present

How to address steps 1-5?

Atezolizumab+ Abraxane in TNBC(IMpassion 130)

A Progression-free Survival in the Intention-to-Treat Population

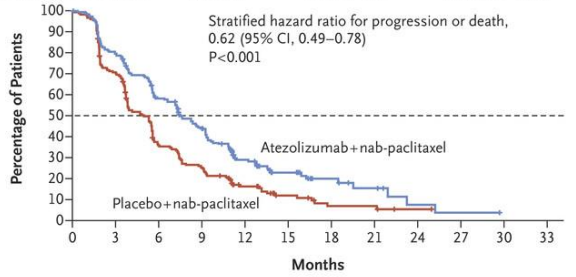
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	358/451	7.2 (5.6–7.5)	23.7 (19.6–27.9)
Placebo+Nab-Paclitaxel	378/451	5.5 (5.3–5.6)	17.7 (14.0–21.4)



No. at Risk												
Atezolizumab+ nab-paclitaxel	451	360	226	164	77	34	20	11	6	1	NE	NE
Placebo+ nab-paclitaxel	451	327	183	130	57	29	13	5	1	NE	NE	NE

B Progression-free Survival in the PD-L1–Positive Subgroup

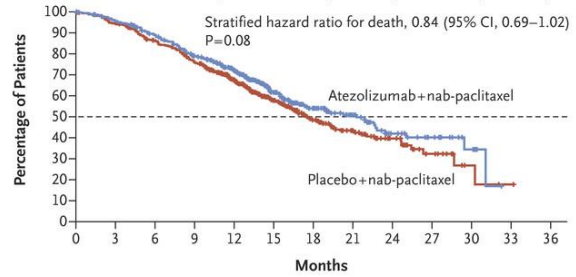
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



No. at Risk												
Atezolizumab+ nab-paclitaxel	185	146	104	75	38	19	10	6	2	1	NE	NE
Placebo+ nab-paclitaxel	184	127	62	44	22	11	5	5	1	NE	NE	NE

C Overall Survival in the Intention-to-Treat Population

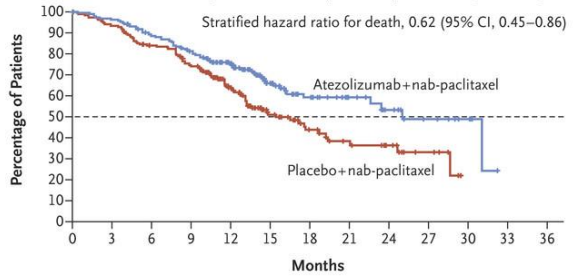
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	181/451	21.3 (17.3–23.4)	42.1 (34.3–49.9)
Placebo+Nab-Paclitaxel	208/451	17.6 (15.9–20.0)	39.7 (33.2–46.3)



No. at Risk												
Atezolizumab+ nab-paclitaxel	451	426	389	337	271	146	82	48	26	15	6	NE	NE
Placebo+ nab-paclitaxel	451	419	375	328	246	145	89	52	27	12	3	1	NE

D Overall Survival in the PD-L1–Positive Subgroup

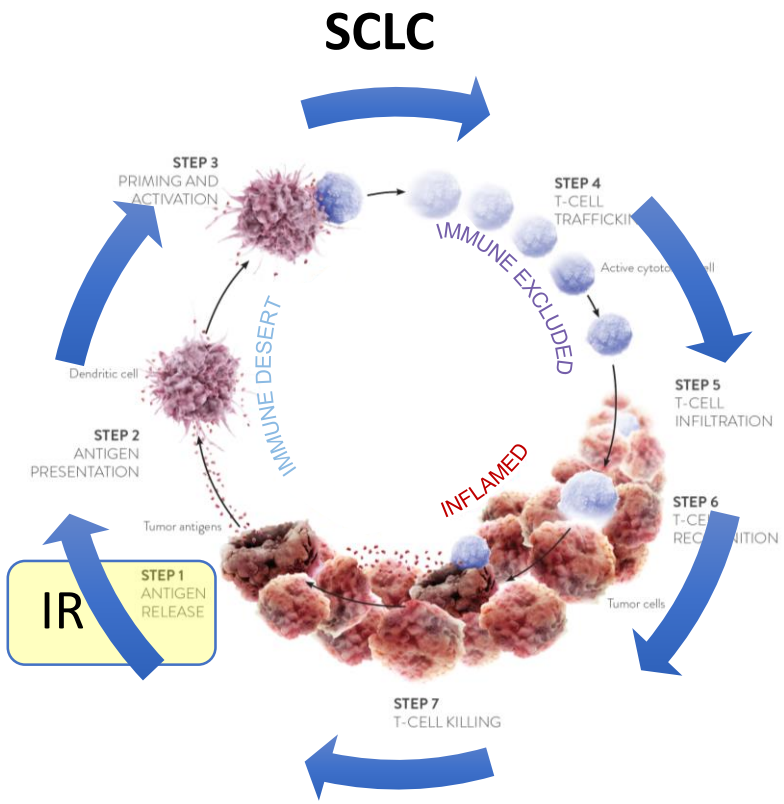
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	64/185	25.0 (22.6–NE)	53.5 (42.3–64.6)
Placebo+Nab-Paclitaxel	88/184	15.5 (13.1–19.4)	36.6 (26.4–46.7)



No. at Risk												
Atezolizumab+ nab-paclitaxel	185	177	160	142	113	61	36	22	15	9	5	NE	NE
Placebo+ nab-paclitaxel	184	170	147	129	89	44	27	19	13	6	NE	NE	NE

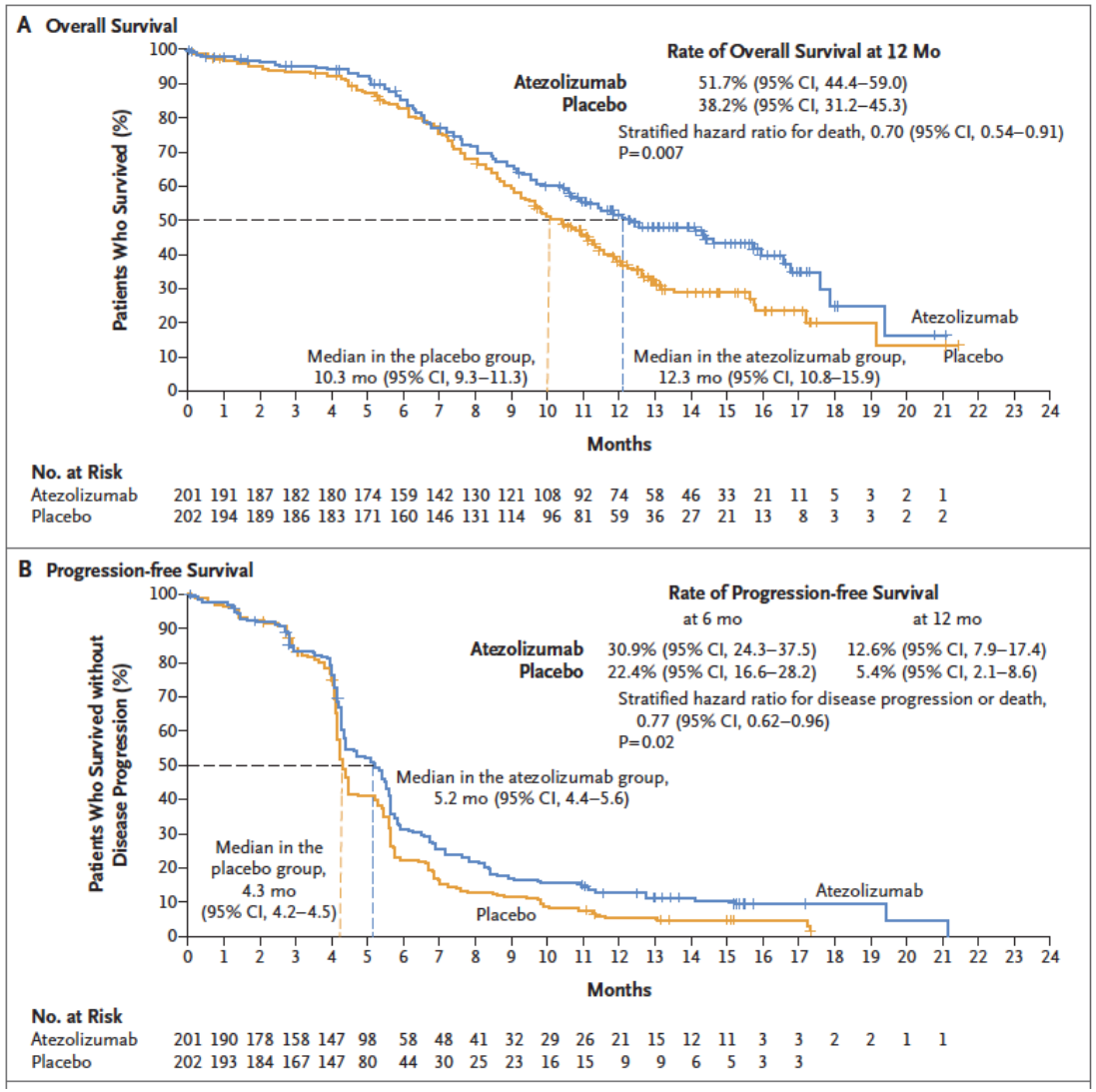
Schmid P et al., NEJM 2018

When IR signal present, efficacy observed in all patients



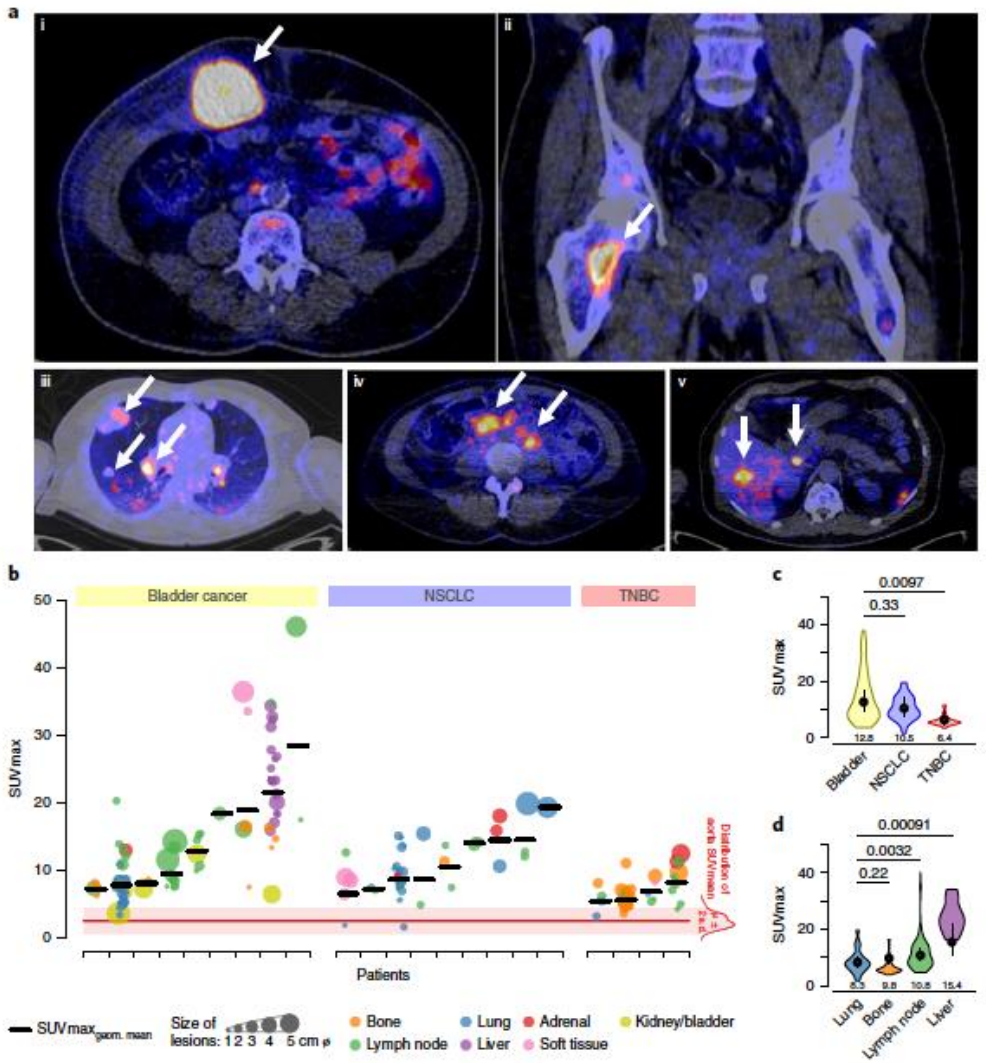
Broad efficacy observed when only IR signal present

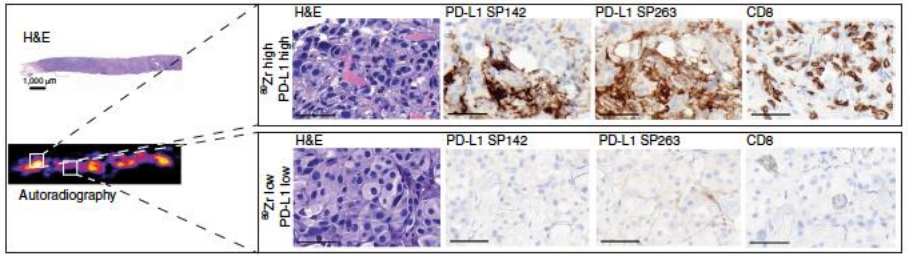
Etoposide+ Carboplatin ± Atezolizumab (IMpower 133)

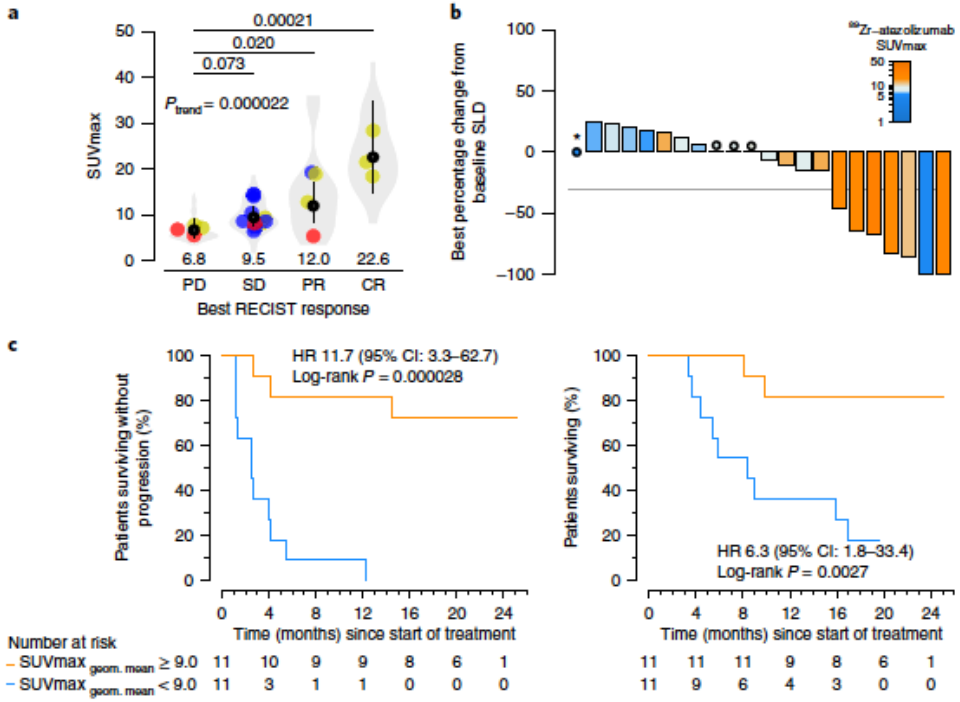


Horn L et al., NEJM 2018

PD-L1 Imaging using ^{89}Zr—Atezolizumab as a non-invasive biomarker







Bensch F et al., Nat Med 2018

Biomarker Terminology

Diagnostic Biomarker	Used for disease diagnosis (typically for screening)
Predictive Biomarker	Provides information about the response or outcome of a specific treatment in an individual (typically pre-treatment)
Prognostic Biomarker	Provides information about a patient's overall outcome, regardless of therapy
Pharmacodynamic Biomarkers	On-treatment biomarkers to confirm drug activity at the right dose
Pharmaco-genomics	Correlates gene expression (or somatic mutations in tumoral DNA) with a drug's efficacy

New Drug Clinical Trials

Downward Trend: Only 16 out of every 100 drugs that enter Phase 1 will make it to FDA approval.

20-100 volunteers
1st state of testing in humans

100 - 500 patients
How well does the drug work?

1,000 – 5,000 patients
- Drug MUST be safe
- Comparison with current 'gold standard' treatment

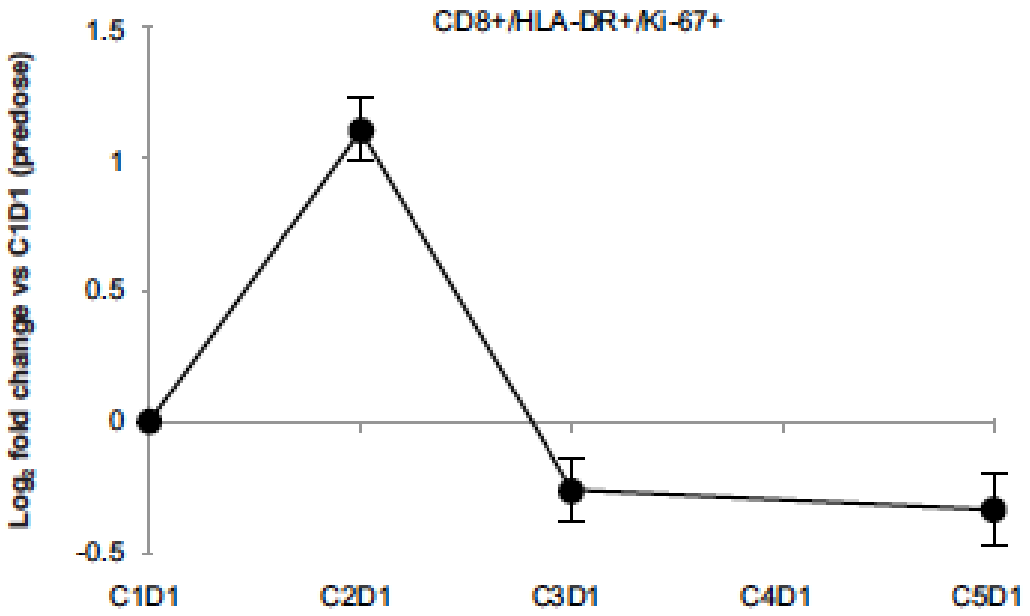
Safety surveillance in *'Real-life'* patients

Given the number of combinations, confirming biological activity has become a central Paradigm for new drugs in Phase I studies

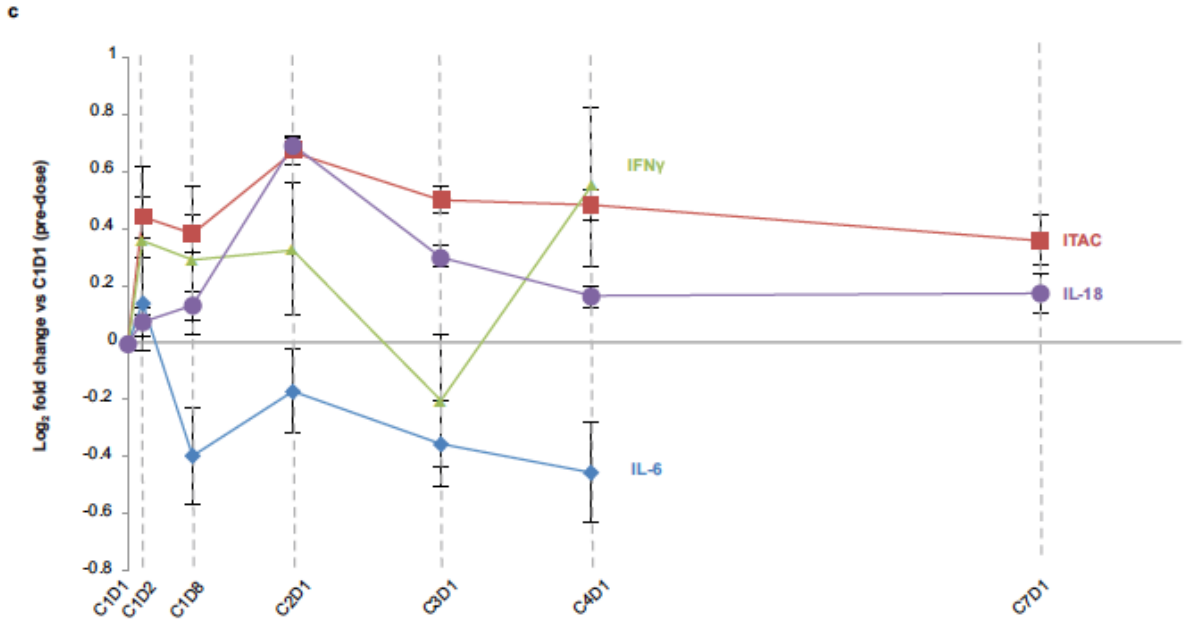
Pharmacodynamic Biomarkers

Peripheral markers of checkpoint inhibition

Transient cycle 1 rise in circulating activated CD8+ T-cells



Transient cycle 1 rise in circulating plasma markers



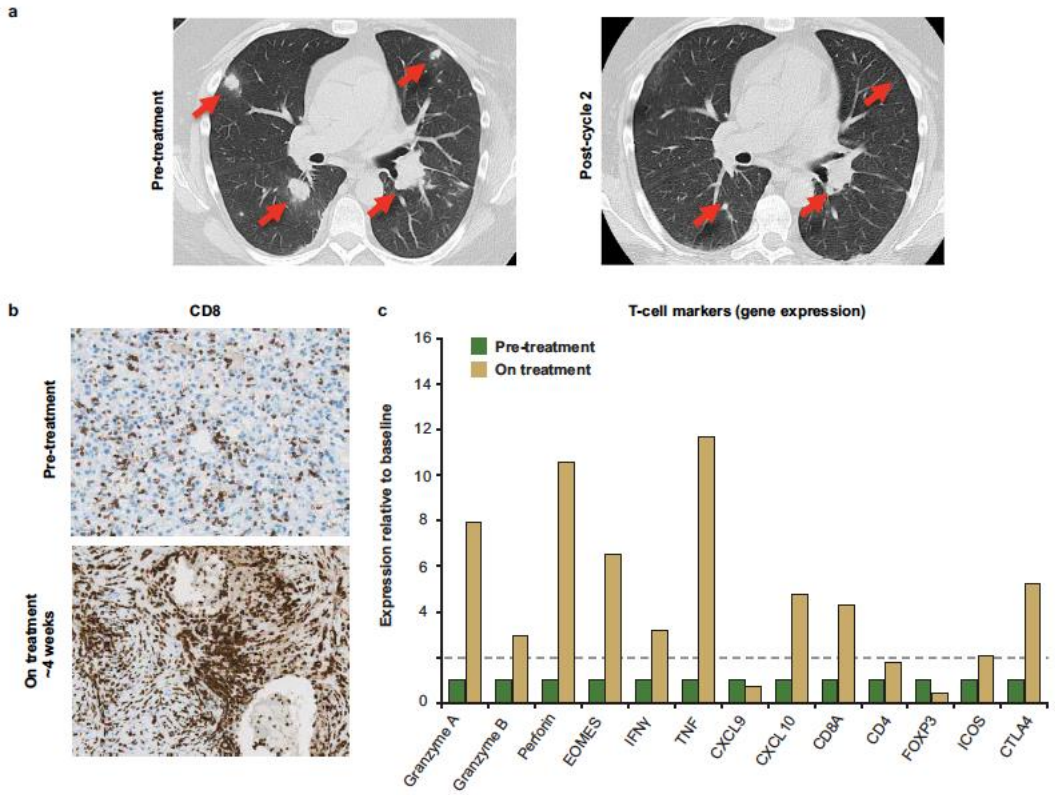
Circulating markers identified to date are Pharmacodynamic and observed in all patients.
No association observed with efficacy.

Herbst et al., Nature 2014

Pharmacodynamic Biomarkers

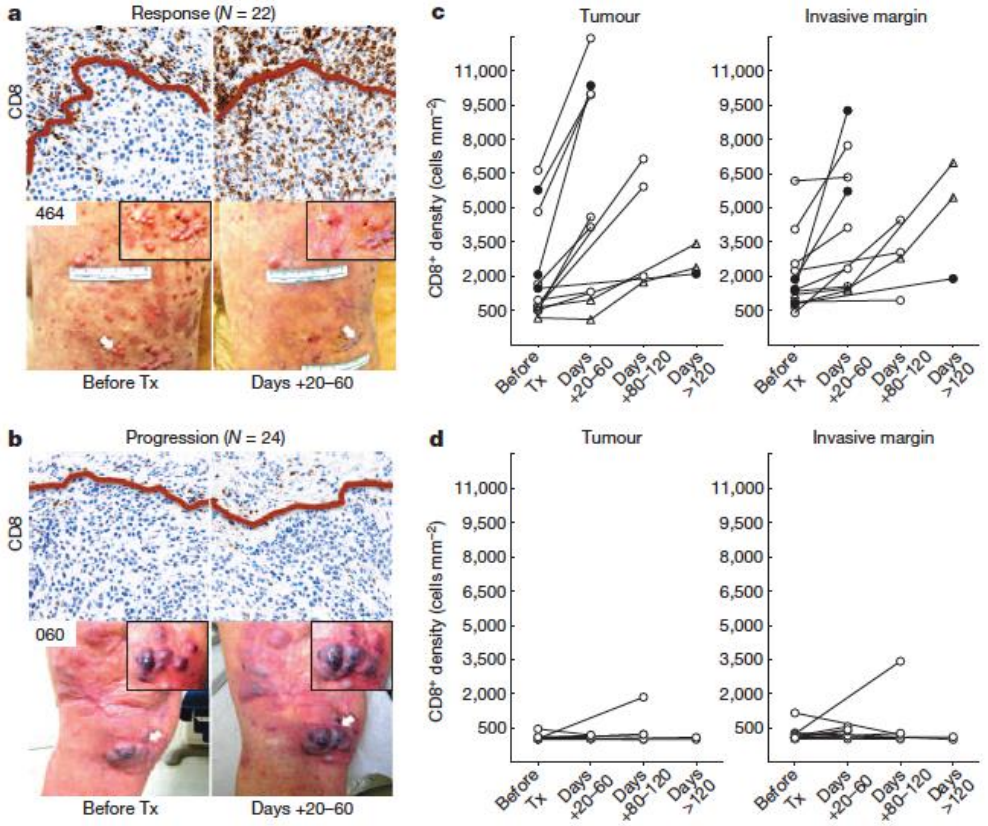
Tumor associated Pharmacodynamic Biomarkers

Increased infiltration of activated intra-tumoral T-cells In biopsies upon treatment with a CPI



Herbst R et al., Nature 2014

Increased infiltration of intra-tumoral T-cells may be associated with response to CPI



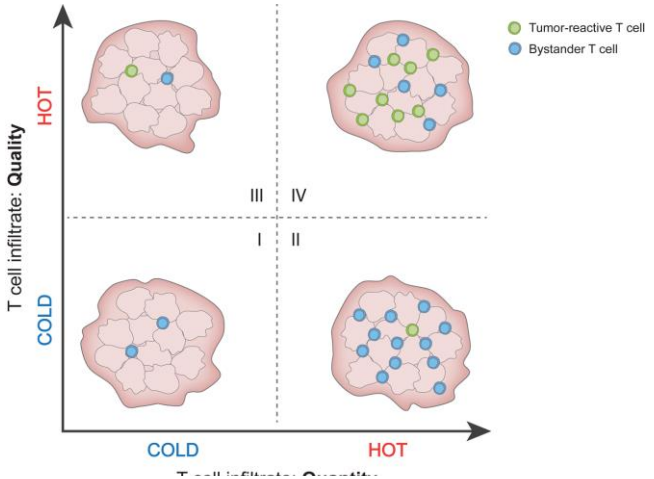
Tumeh P et al., Nature 2014

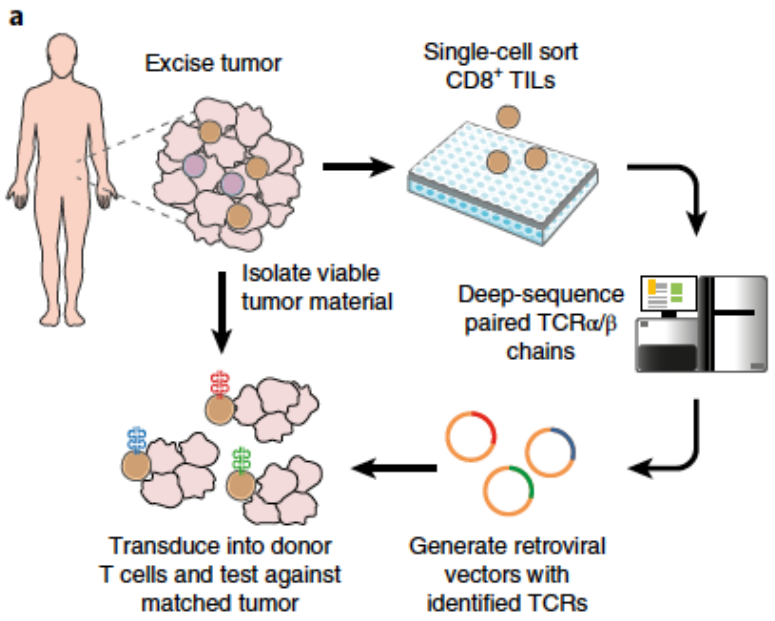
As low as 10% of infiltrating T-cells are tumor reactive

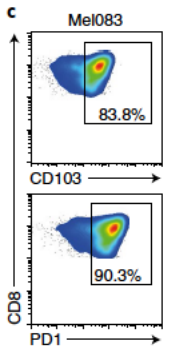
nature medicine
LETTERS
https://doi.org/10.1038/s41591-018-0266-5

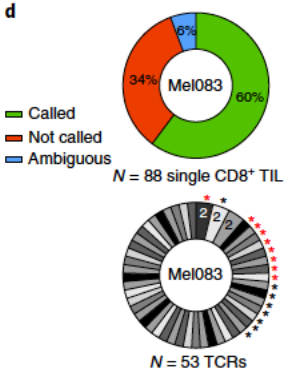
Low and variable tumor reactivity of the intratumoral TCR repertoire in human cancers

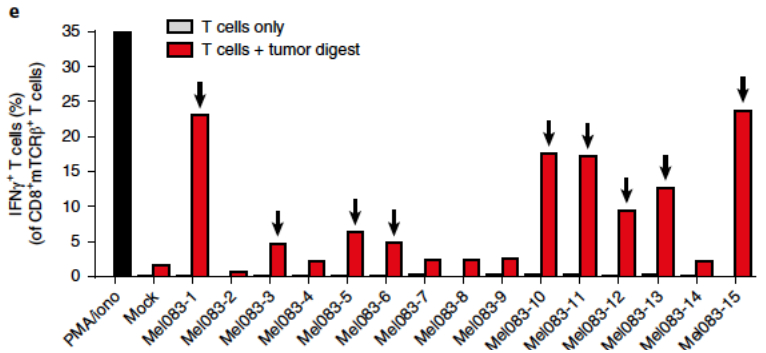
Wouter Scheper[1,10], Sander Kelderman[2,10], Lorenzo F. Fanchi[1], Carsten Linnemann[2], Gavin Bendle[2], Marije A. J. de Rooij[2], Christian Hirt[3], Riccardo Mezzadra[1], Maarten Slagter[1,4], Krijn Dijkstra[2], Roelof J. C. Kluin[5], Petur Snaebjornsson[6], Katy Milne[7], Brad H. Nelson[7], Henry Zijlmans[8], Gemma Kenter[8], Emile E. Voest[2,9], John B. A. G. Haanen[2,9] and Ton N. Schumacher[1*]

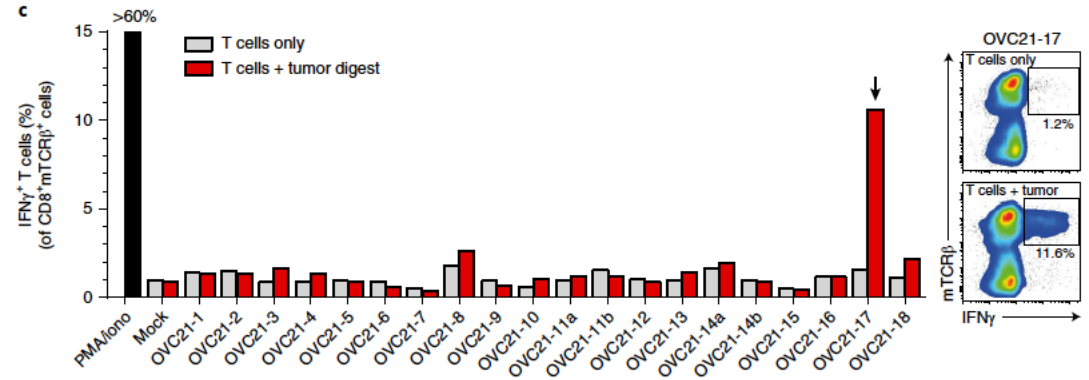










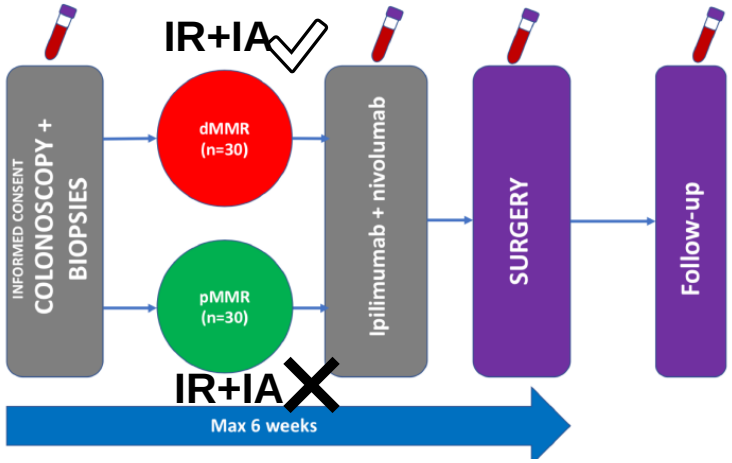


Scheper et al., Nat Med 2019

Neoadjuvant Ipilimumab plus Nivolumab in Early Stage Colon Cancer

Chalabi M, ESMO 2018

- first results of the NICHE study

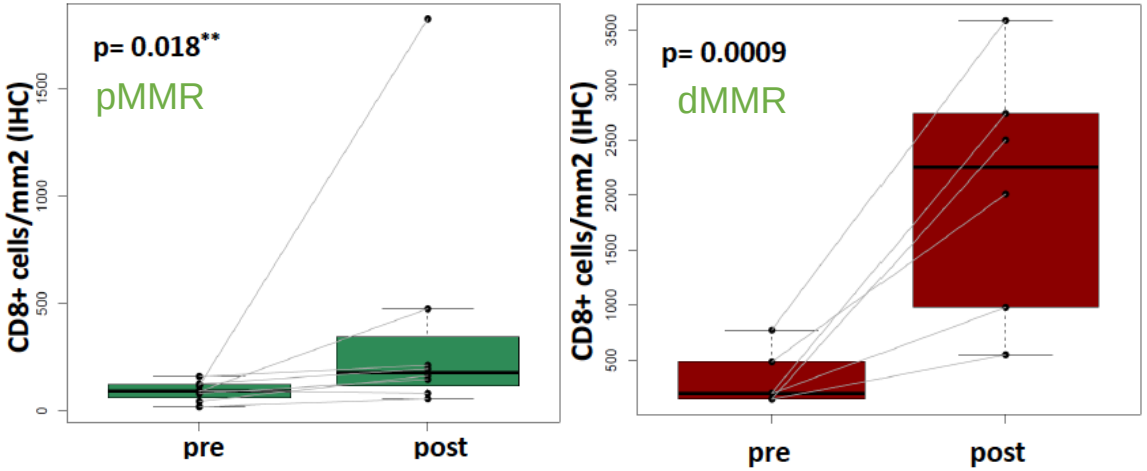


Major response observed in 100% of dMMR tumors

dMMR (n=7)		
Pre-treatment clinical stage	**Pathological stage at resection**	**Residual vital tumor**
cT2N2a	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT3N0	ypT0N0	0 %
cT3N2a	ypT1N0	1 %
cT4aN2a	ypT2N0	2 %
cT4aN1a	ypT3N1	2 %

pMMR (n=8)		
Pre-treatment clinical stage	**Pathological stage at resection**	**Residual vital tumor**
cT3N1a	ypT3N2	85 %
cT3N0	ypT3N0	90 %
cT2N0	ypT3N1	90 %
cT2N0	ypT3N0	90 %
cT3N1b	ypT3N1	90 %
cT3N1b	ypT3N2	95 %
cT3N0	ypT3N0	100%
cT2N0	ypT2N0	100 %

Increase in CD8+T-cells in dMMR tumors

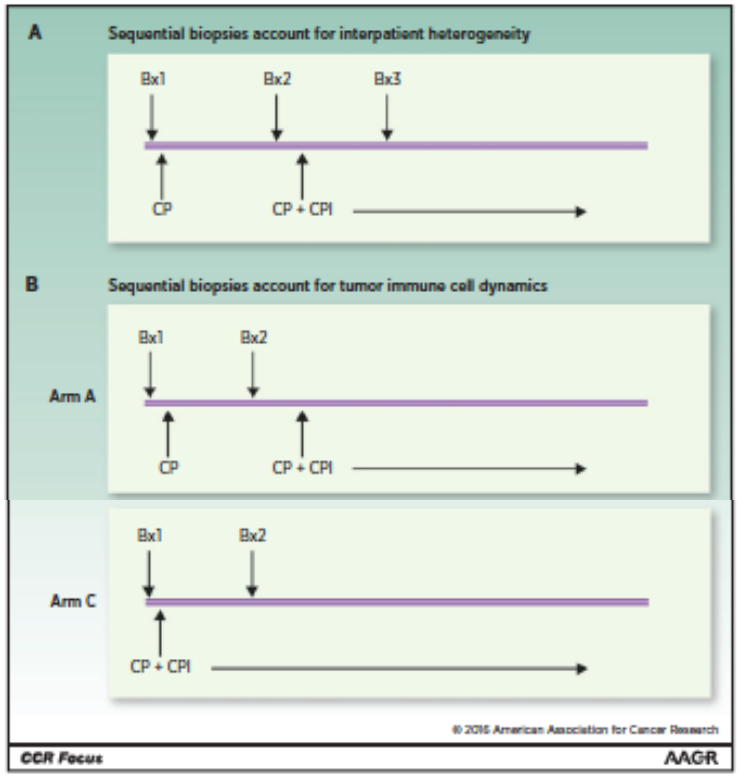


Pharmacodynamic Biomarkers

Tumor associated Pharmacodynamic Biomarkers - Combinations

What is the proposed mechanism of action?
Is the biology measurable in the tumor?

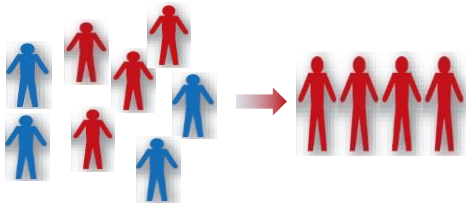
Quantity: Infiltration of CD8+ T-cells
Quality: Tumor specificity of tumor infiltrating T-cells



Hegde PS et al., CCR 2016

Implications of personalized healthcare for patients, industry and healthcare providers

Patients



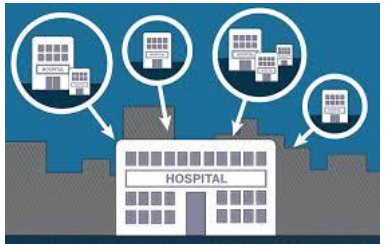
Informed treatment decisions, greater clinical benefit, avoid unnecessary toxicity, impact on quality of life

Drug Developer

© Can Stock Photo

Increased probability of success, smaller focused trials faster drug development, address unmet need

Healthcare providers



Reduced inpatient time, better pricing, informed patient management, better health economics