CANCER IMMUNOTHERAPY

Predictors of response to Checkpoint inhibitors (CPI): Tumor vs the periphery

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SITC, Washington DC

Disclosures

Employee and share holder at Genentech

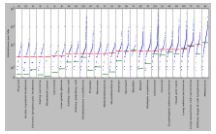
This presentation is not available for CME / CE credit.

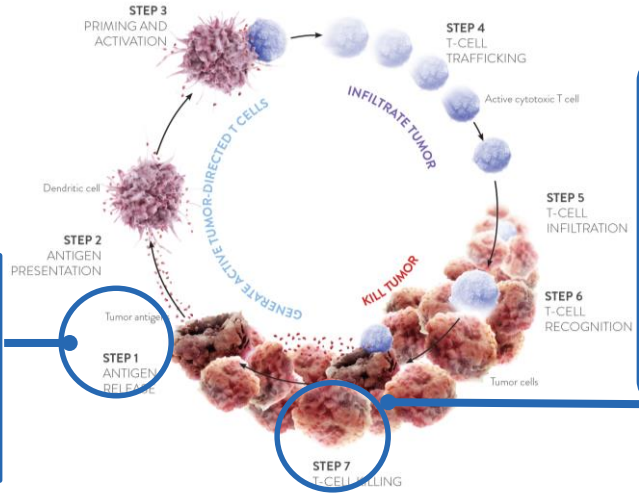
Tumor based predictors of response

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

Tumor Mutation Burden

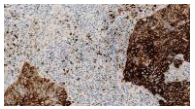
MSI[1], tMB[2]





PD-L1 expression

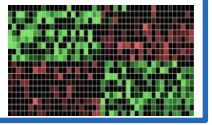
IHC



Tumor Gene Expression

IFNγ signature

NGS



Chen and Mellman, Immunity, 2013

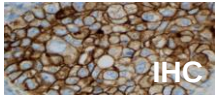
[1]Le et al., NEJM 2015

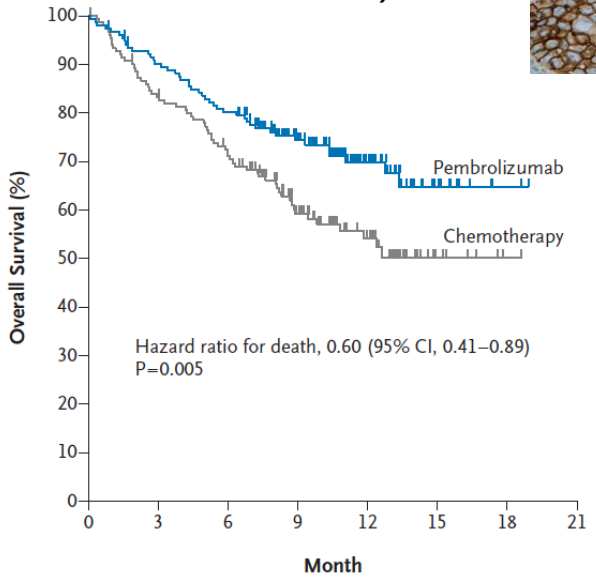
[2] Powles T et al., Lancet 2017

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

Tumor cell PD-L1 by IHC is associated with clinical benefit to CPIs

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

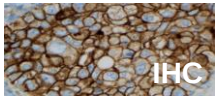


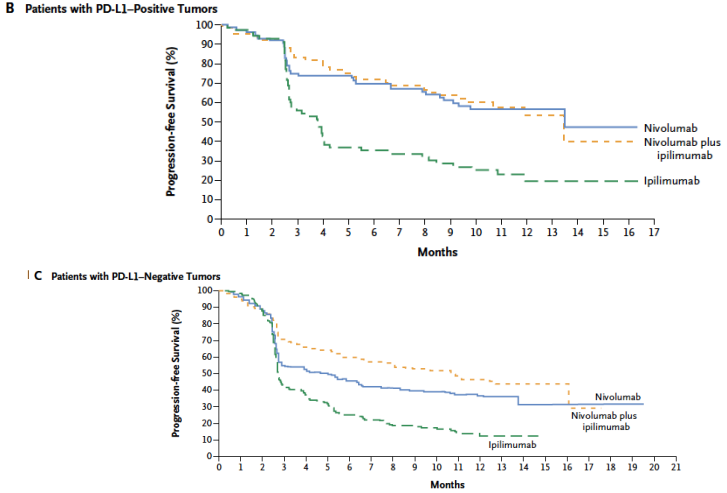


Dx: PD-L1 by IHC: TPS>50%

Brahmer J et al., NEJM 2016

PD-L1 IHC can differentiate monotherapy Nivo vs Ipi/Nivo benefit in Melanoma (CM-067)



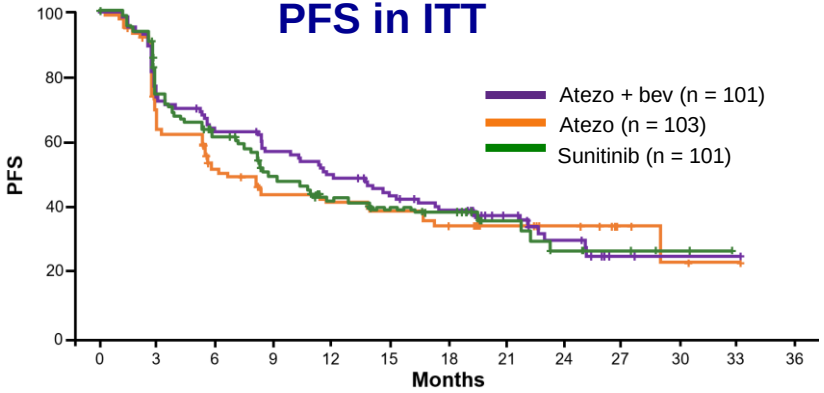


Dx: PD-L1 by IHC: TC>5%

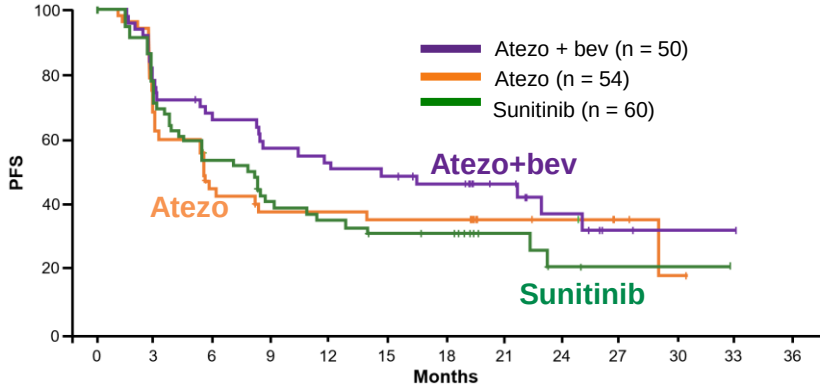
Larkin J et al., NEJM 2015

Atezo+bev vs Sunitinib: improved PFS in PD-L1 immune cell (IC) selected groups: RCC (IMmotion 150)

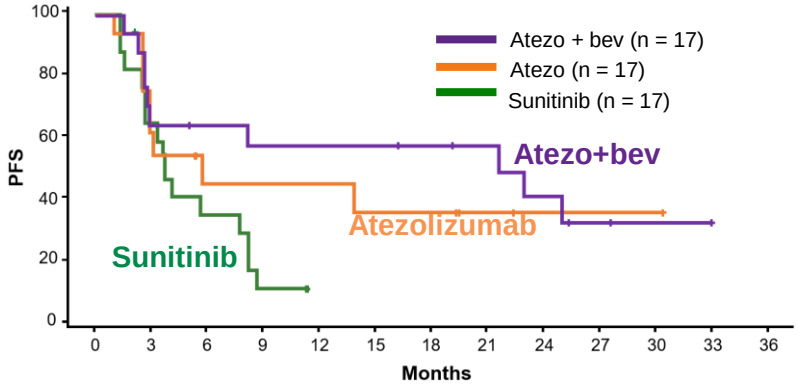
PFS in ITT



PFS in ≥ 1% PD-L1 IC



PFS in ≥ 5% PD-L1 IC



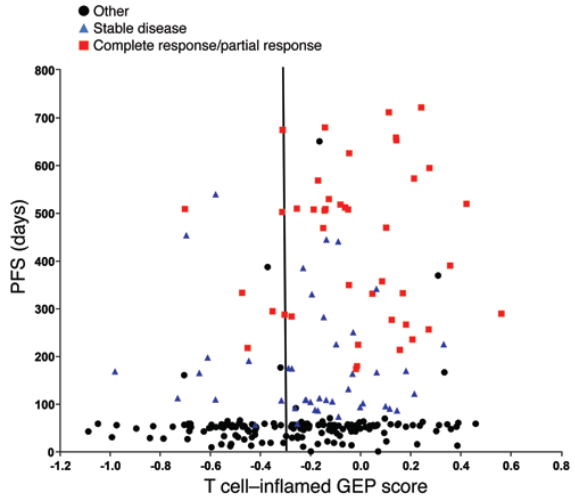
Stratified HR (95% CI)			
	ITT	≥ 1% PD-L1	≥ 5% PD-L1
Atezo + bev vs sunitinib	1.00 (0.69, 1.45)	0.64 (0.38, 1.08)	0.34 (0.13, 0.91)
Atezo vs sunitinib	1.19 (0.82, 1.71)	1.03 (0.63, 1.67)	0.64 (0.27, 1.54)

3-arm Phase II Front line RCC; IMmotion 150; N=100 in each arm

McDermott D, AACR 2017; McDermott D, Huseni M et al., manuscript in review

Gene expression based functional readouts of pre-existing immunity associated with benefit to CPIs

18-gene IFNγ signature associated with PFS benefit to Pembrolizumab (KN-012, KN-028)

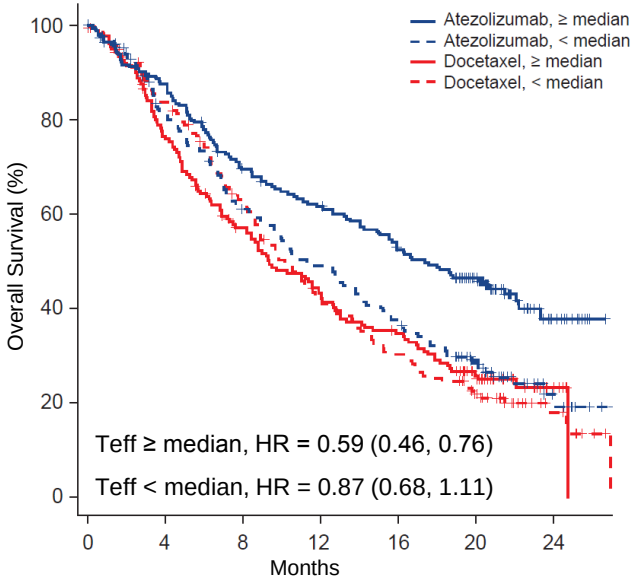


PFS time versus T cell–inflamed GEP score in 244 patients from KEYNOTE-012 and KEYNOTE-028 for the 9 cancer cohorts used to determine the T cell–inflamed GEP.

18 gene signature, Nanostring: TIGT, CD27, CD8A, PD-L2, LAG3, PD-L1, CXCR6, CMKLR1, NIKG7, CCL5, PSMB10, IDO1, CXCL9, HLA.DQA1, CD276, STAT1, HLA.DRB1, HLA.E

Ayers M et al., JCI 2017

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



PCR: *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

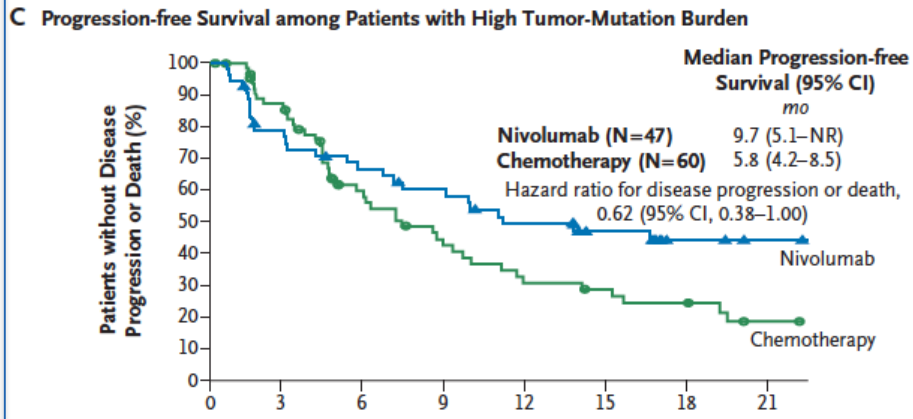
*SP142; TC1 or IC1= TC or IC ≥ 1% PD-L1–expressing cells.

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

Kowanetz et al. OAK Teff biomarker. WCLC 2017.

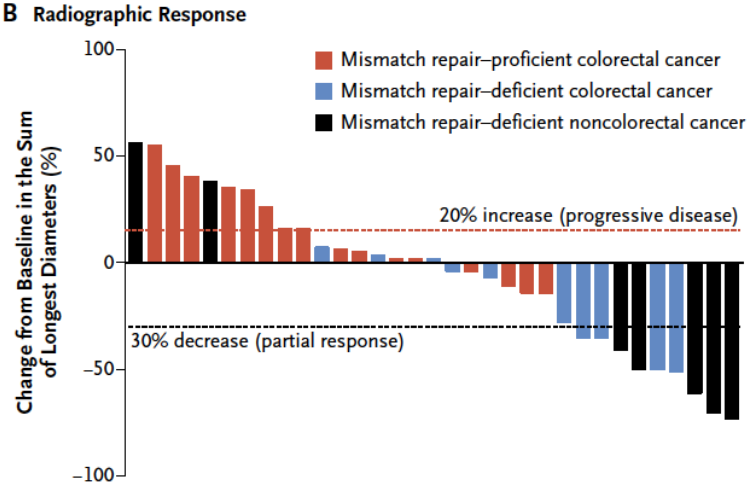
Tumor types with a high mutation load (TMB) may derive benefit from monotherapy CPI

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



Carbone DP et al., NEJM 2017

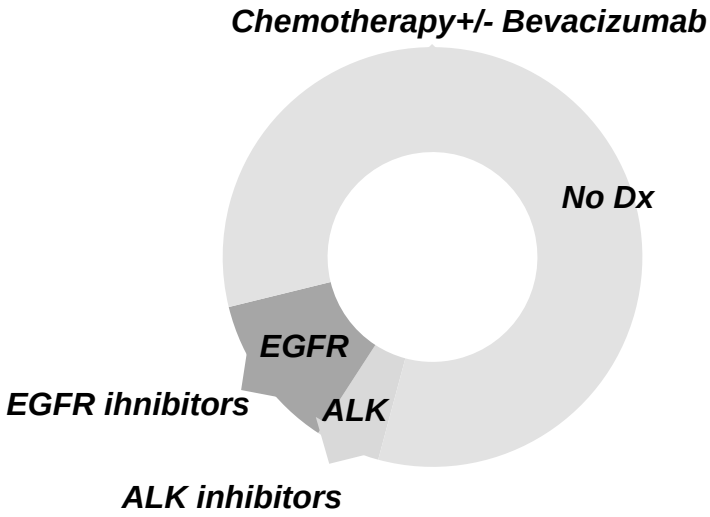
MMR deficiency is associated with response to Pembrolizumab



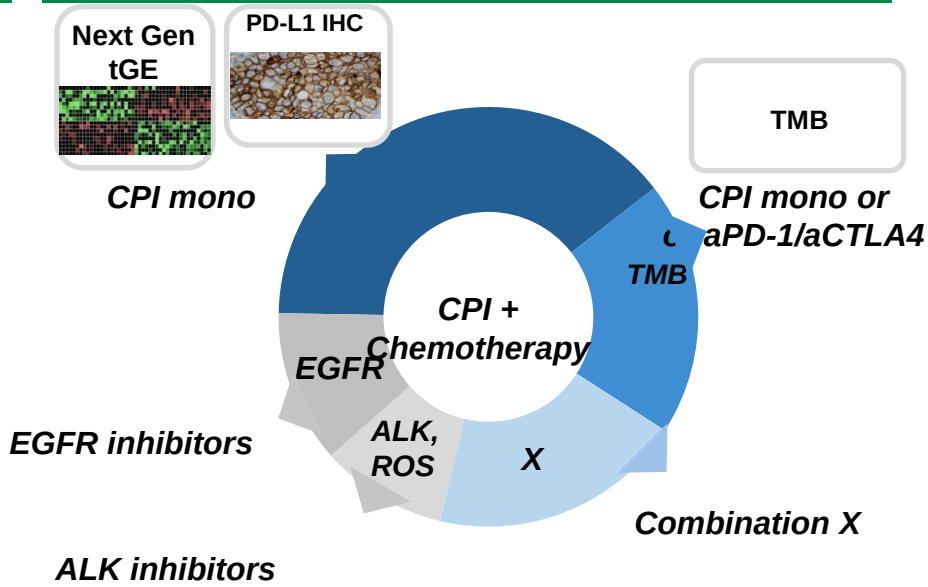
Le et al., NEJM 2015

Rapidly evolving landscape for treatment decisions: Eg front-line NSCLC

2015 Front-line NSCLC Dx landscape

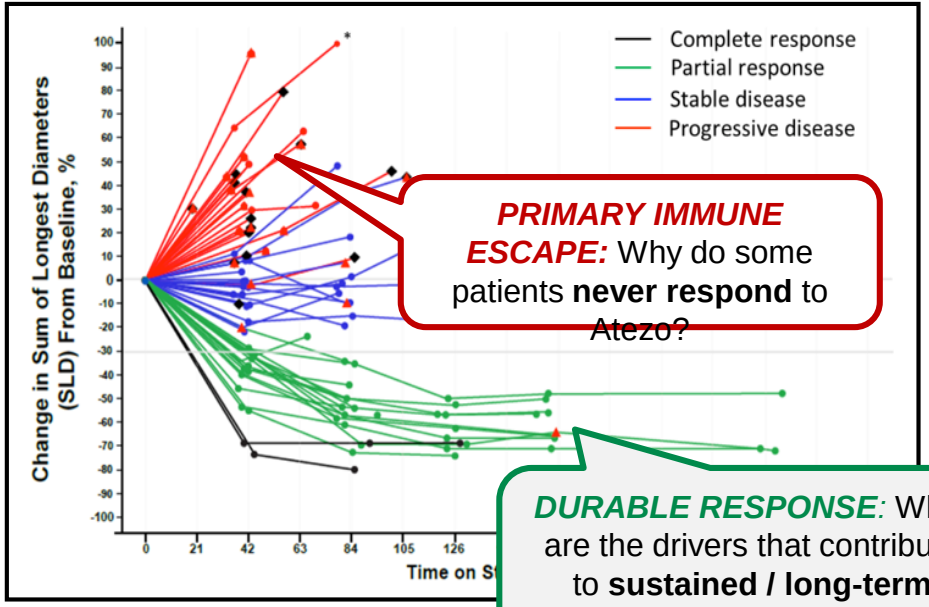


Future NSCLC Dx landscape



Illustrative purposes only

What are the drivers of escape from CPI?



Atezolizumab Ph1 mUC data

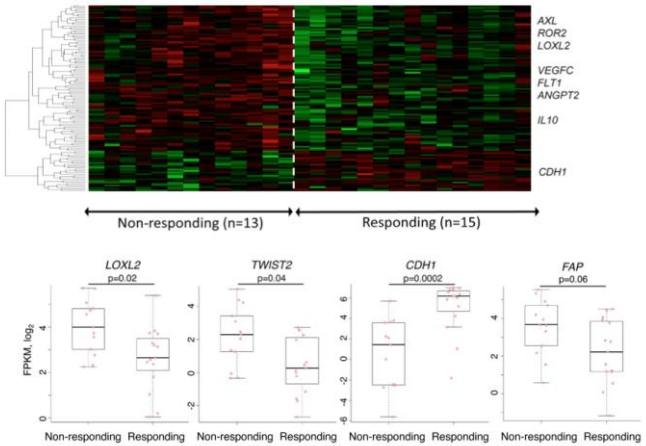
PRIMARY IMMUNE ESCAPE: Why do some patients **never respond** to Atezo?

Can we convert non-

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

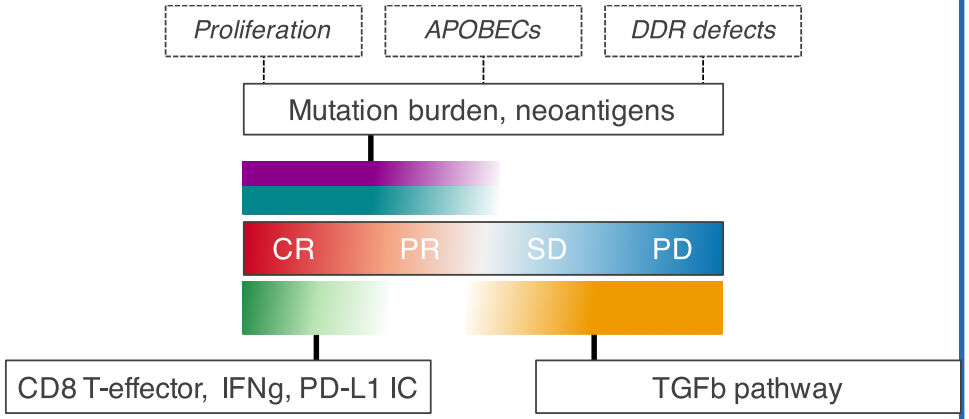
Reactive Stromal biology may present an immune escape mechanism

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



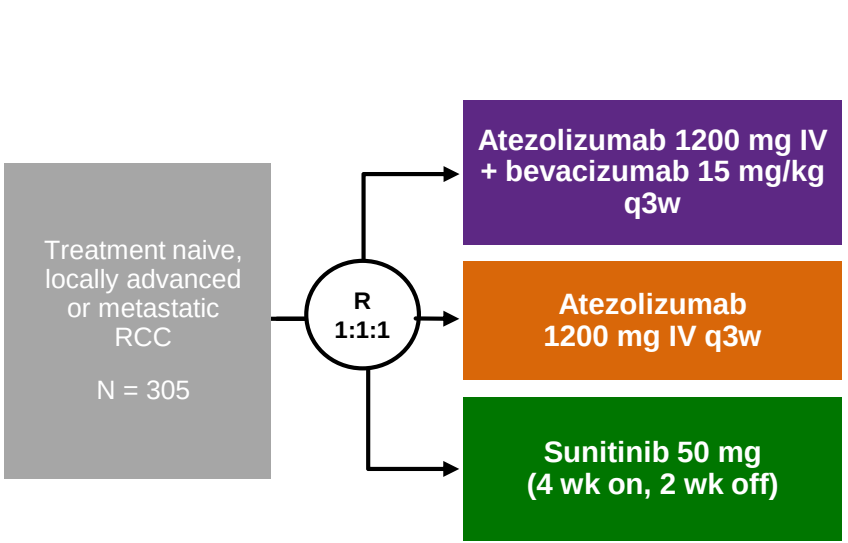
Willy et al., Cell (2016)

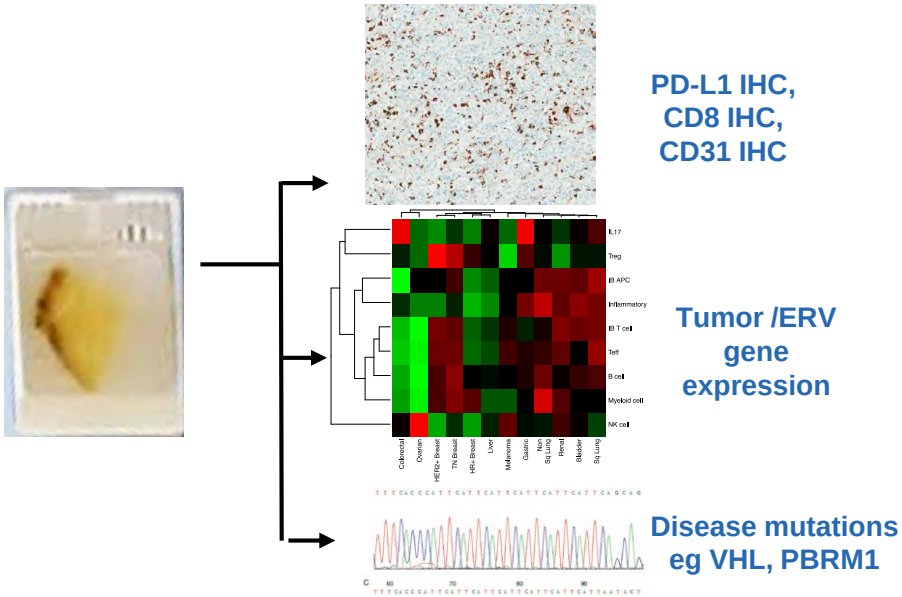
Bladder Cancer: Atezolizumab (IMvigor210)



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

IMmotion 150:
Atezolizumab ± Bevacizumab vs Sunitinib in 1L mRCC

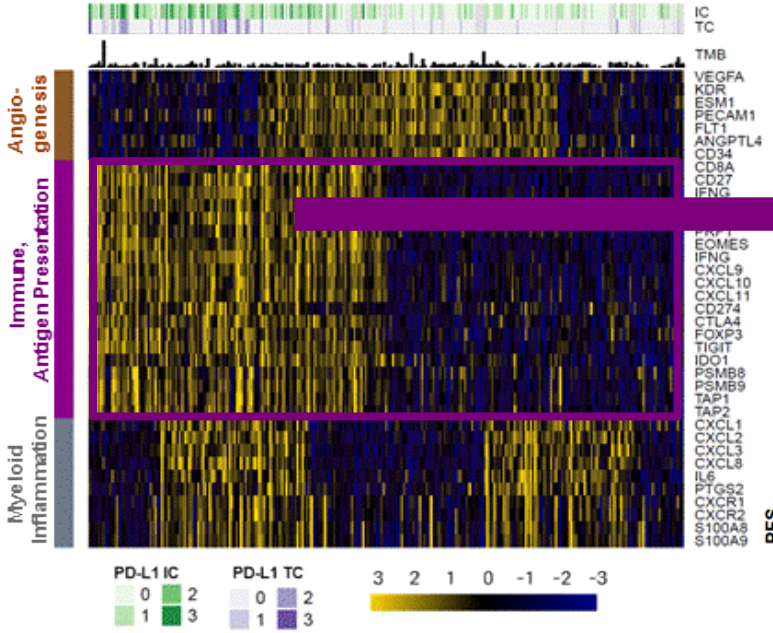


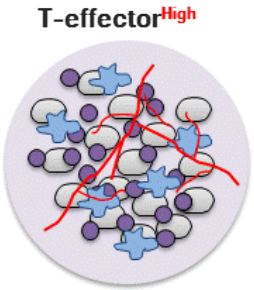


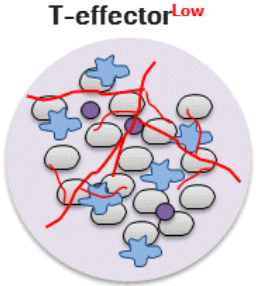
- IMmotion150 was designed to be hypothesis generating and inform the Phase III study IMmotion151
- Co-primary endpoints were PFS (RECIST v1.1 by IRF) in ITT patients and patients with ≥ 1% of IC expressing PD-L1
- Exploratory endpoints included interrogation of the association between outcome and TME gene signatures

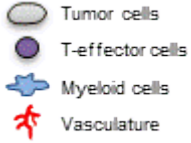
McDermott D, AACR 2017; McDermott D, Huseni M et al., manuscript in review

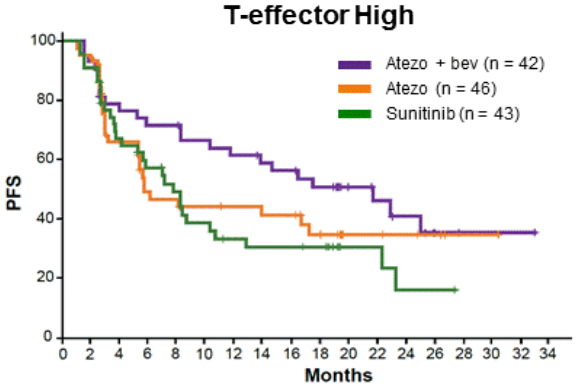
Atezolizumab and Bevacizumab Demonstrated Improved PFS vs Sunitinib in the T-Effector^{High} Subset

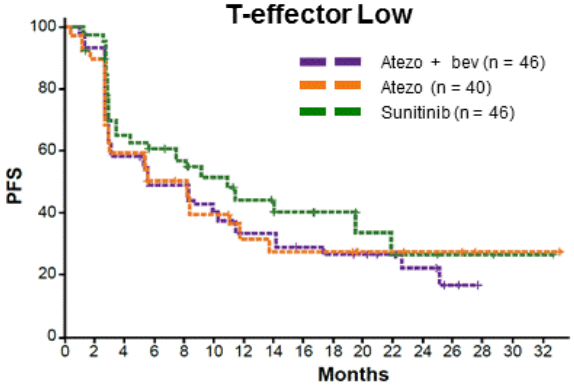








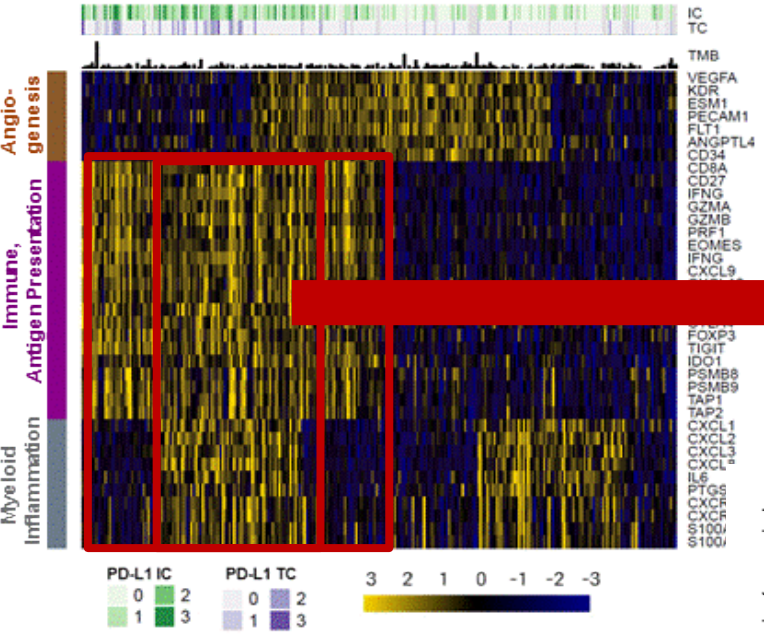


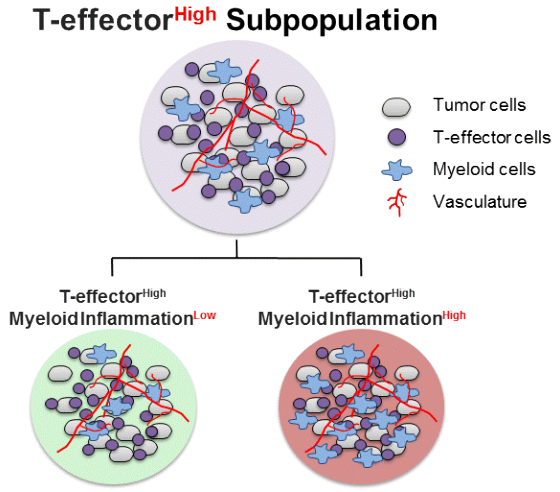


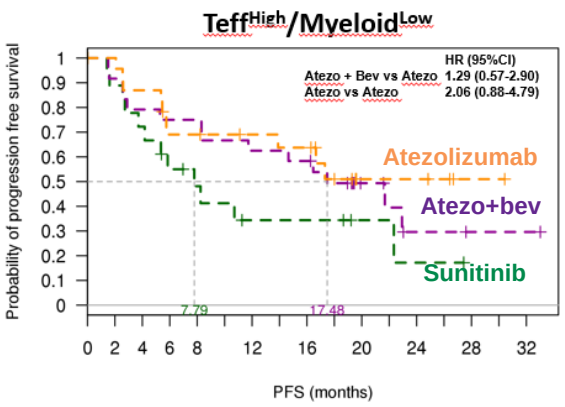
HR (95% CI)		
	T-effector High	**T-effector Low**
Atezo + bev vs sunitinib	**0.55 (0.32, 0.95)**	1.41 (0.84, 2.36)
Atezo vs sunitinib	0.85 (0.50, 1.43)	1.33 (0.76, 2.33)

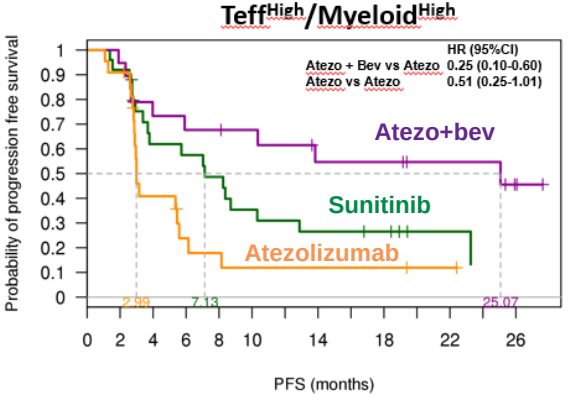
McDermott D, Huseni M et al., manuscript in review

Myeloid inflammation may be associated with lack of clinical benefit to CPI- αVEGF may overcome this escape mechanism





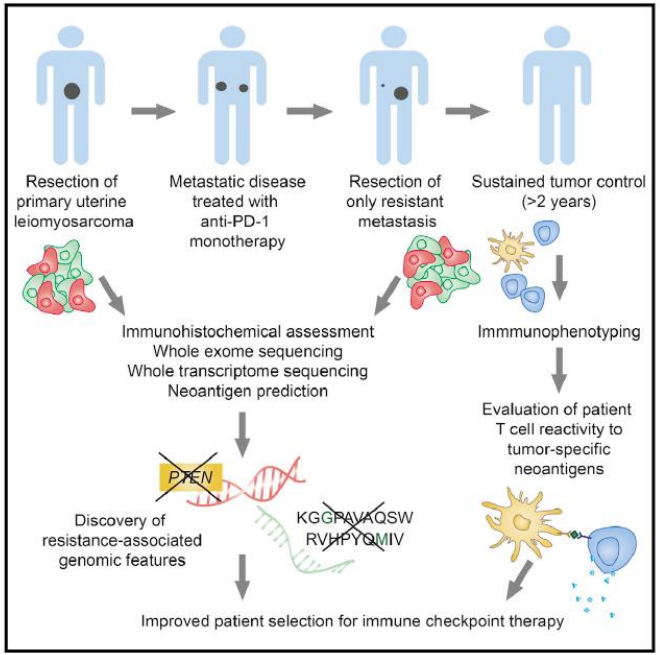




McDermott D, Huseni M et al., manuscript in review

Single patient case reports can be highly informative

Bi-allelic PTEN loss associated with immunosuppressive TME and resistance to αPD-1 in a Lipsarcoma case study



George S et al., Immunity 2017

Evolution of disease molecular subtypes, genomic landscape and TME over 3 years of chemo and 4 years of atezolizumab in a TNBC case study

*Molinero L…Emens L , Friday Poster p**68** , SITC 2017*

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

Mutational Load

TILs
CD8 T cells/IFNγ
PD-L1 & checkpoints

Angiogenesis
Reactive stroma
MDSCs

Ki67
Low MHC I

Viral Load?

Microbiome?

Genetic Predisposition?

Respond favorably to checkpoint inhibition

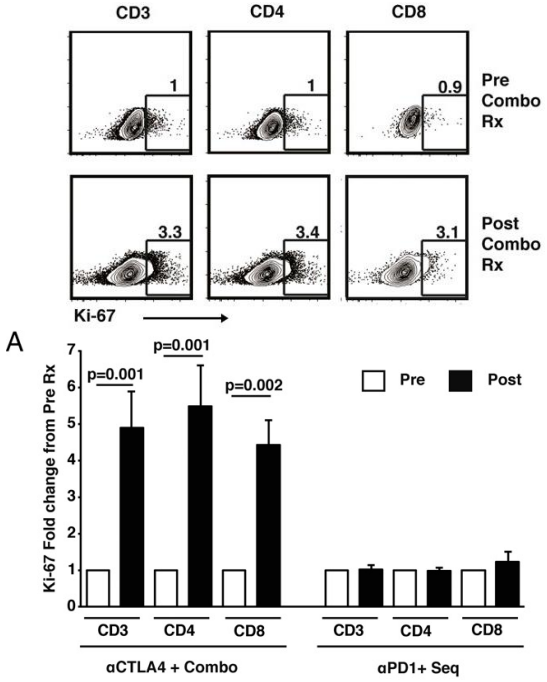
Convert to inflamed phenotype with combinations

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

Predictors of response in the periphery

Circulating proliferating CD8+ T-cells represent a pharmacodynamic biomarker to CPI

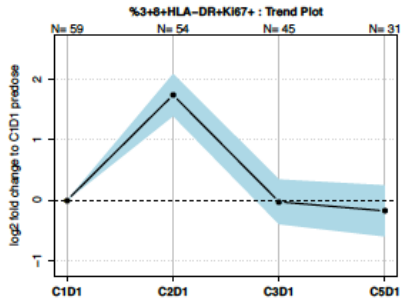
Increase in Ki-67+/CD3+ T cells Upon aCTLA4 tx in Melanoma

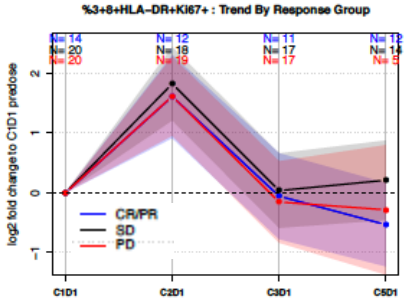


Das R et al., J Immunol 2015

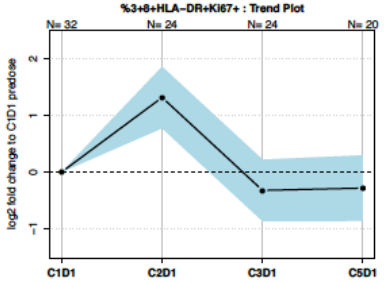
Systemic increase in CD3/CD8/HLA-DR/Ki-67+ T cells not associated with outcomes to atezolizumab

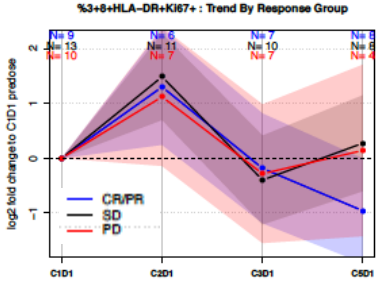
Bladder Cancer





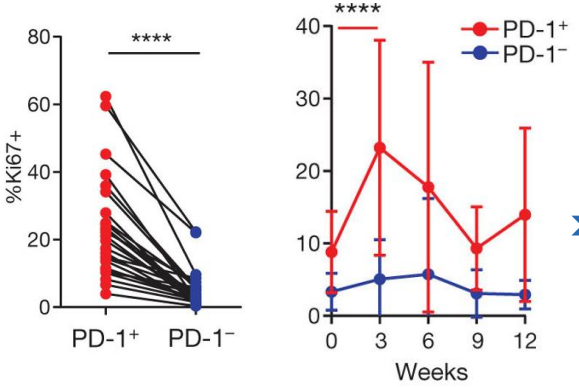
NSCLC



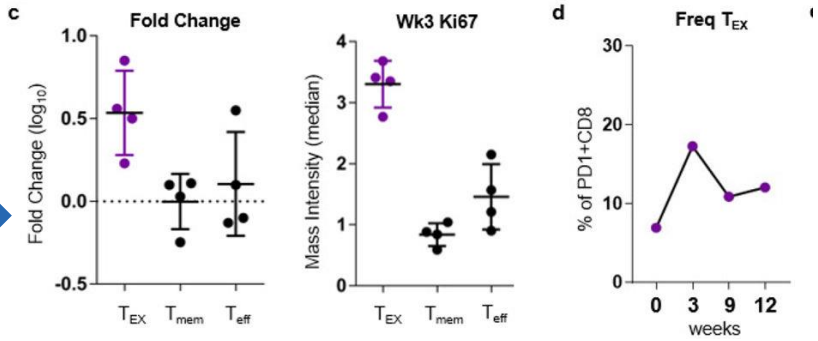


T-cell invigoration to tumor burden ratio associated with anti-PD1 response

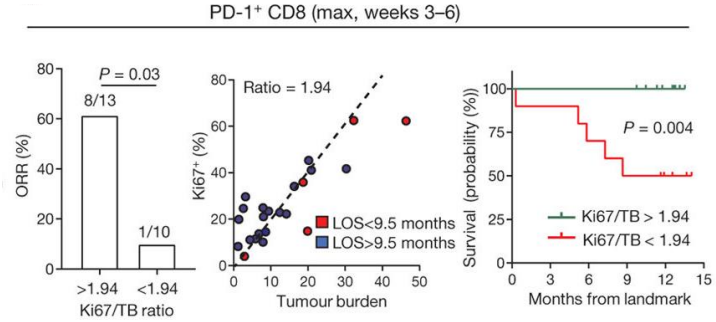
Proliferating CD8+ T-cells represent an exhausted phenotype



aPD-1 reinvigorates exhausted T-cells



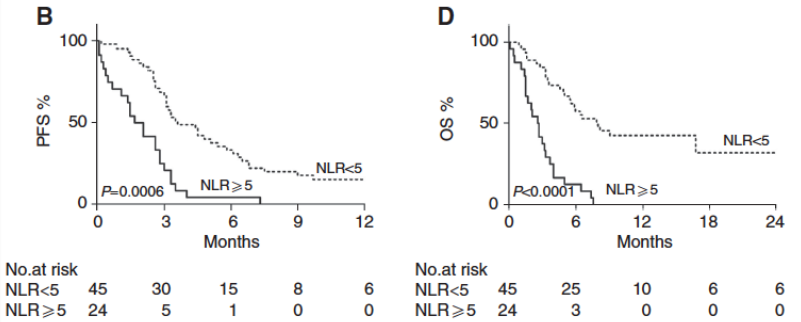
Ratio of T-cell invigoration to tumor burden predicts response to CPI



Huang AC et al., Nature 2017

Is high Neutrophil-to-Lymphocyte ratio (NLR) a systemic marker of poor outcomes to CPIs?

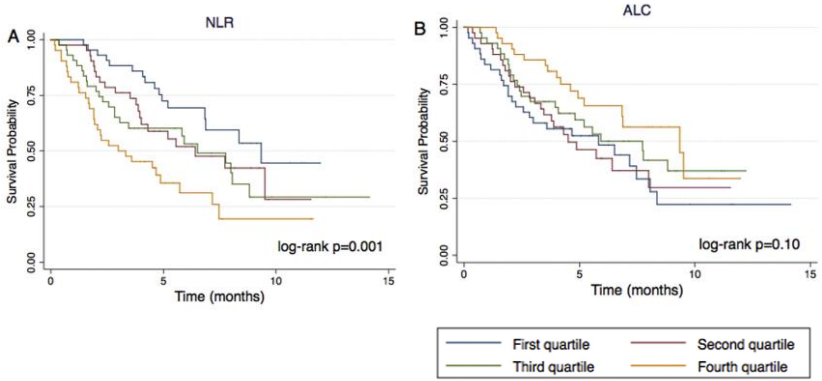
High NLR associated with poor outcomes to Ipilimumab in Melanoma



Independently validated in a cohort of 115 patients

Ferrucci PF et al., BJC 2015

High NLR associated with poor outcomes to Nivolumab in NSCLC (N=175)



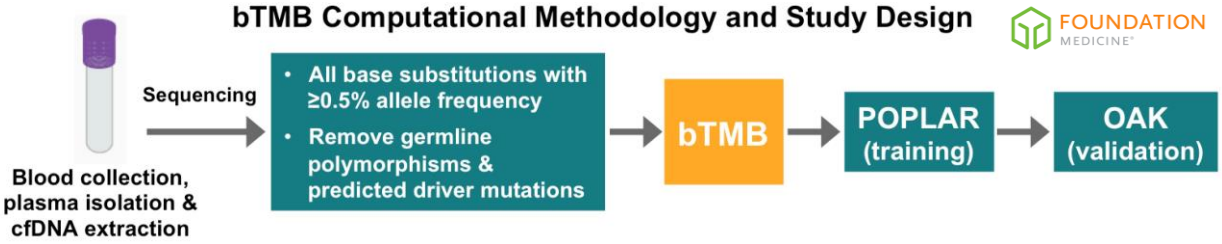
Bagley SJ et al., Lung Cancer 2017

Is systemic immune health an important factor?

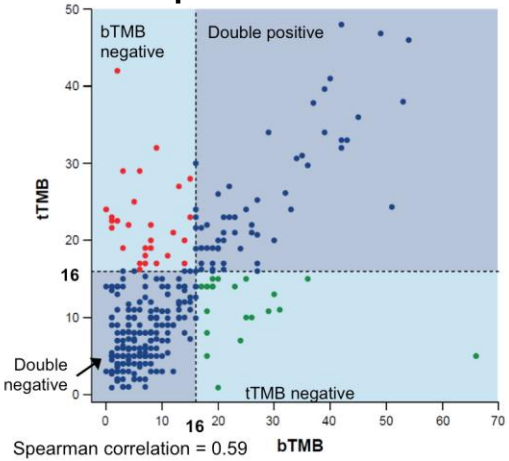
Single arm studies, hard to delineate prognostic from predictive association.

Worth further interrogation in randomized trials

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



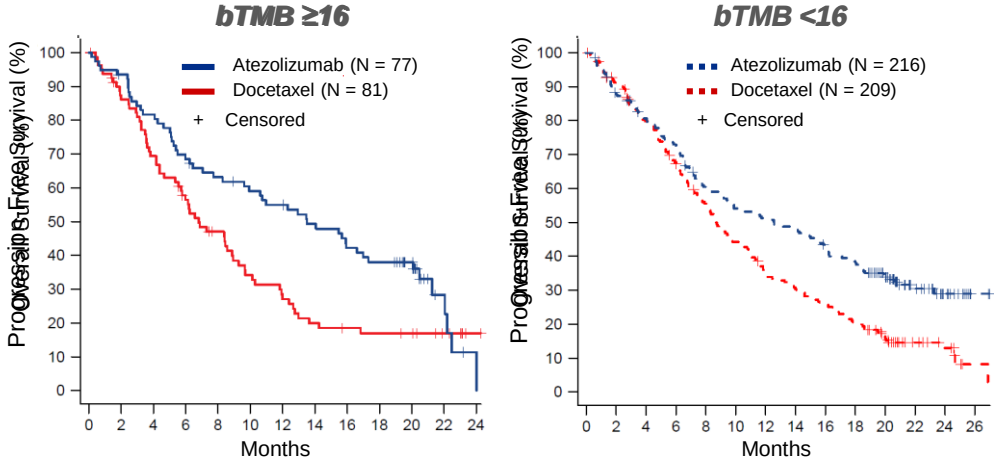
Comparison of b vs t TMB



(PPA: 64%; NPA: 88%)

Atezolizumab PFS benefit in bTMB subgroups

OS in bTMB subgroups



Interaction *P* = 0.75

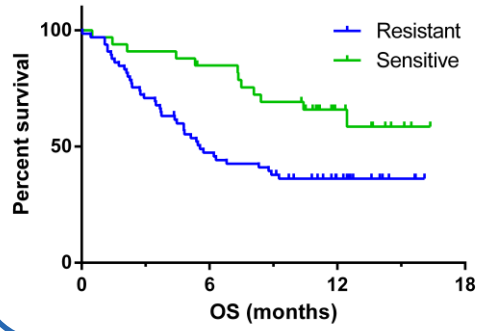
Gandara DL., et al., ESMO 2017; Manuscript in review

BFAST: Prospective trial to validate the biomarker

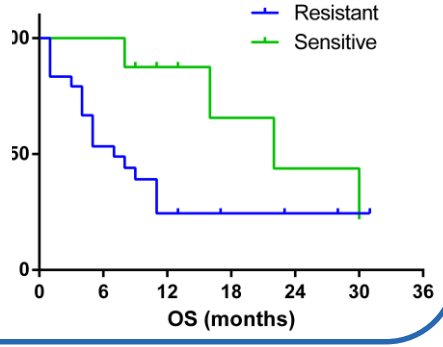
Deep MALDI ToF MS of Serum in NSCLC

Biodesix platform

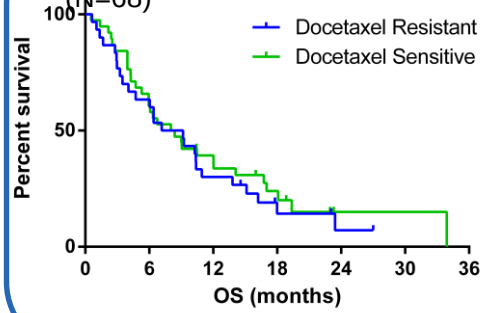
Development (nivolumab) [1]



Validation (nivolumab)[1] (N=32)



Evaluation (chemotherapy) (N=68)



Patients who do poorly on CPI have elevated acute phase reactant, complement and wound healing signaling

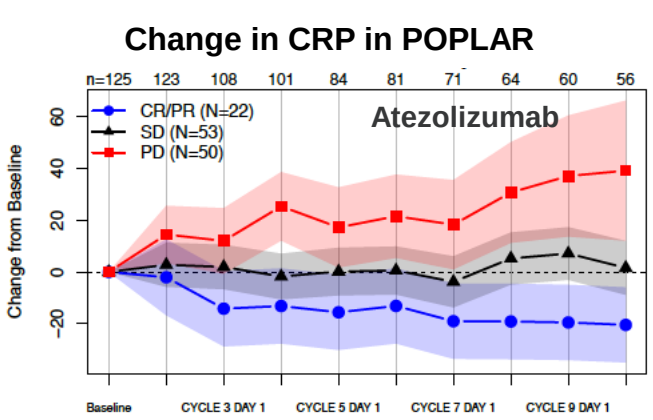
Biological factors associated with sensitivity/resistance to CPI

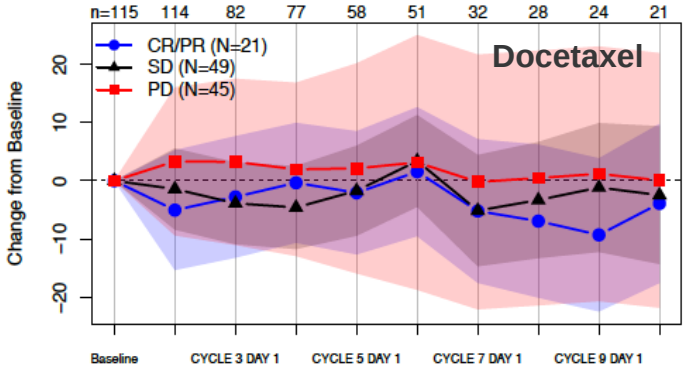
Signaling process	Checkpoint test
Acute inflammatory response	NS
Activation of innate immune response	NS
Regulation of adaptive immune response	NS
Positive regulation of glycolytic process	NS
Immune T-cells	NS
Immune B-cells	NS
Cell cycle regulation	NS
Natural killer regulation	NS
Complement system	p < 0.05
Acute response	NS
Cytokine activity	NS
Wound healing	p < 0.01
Interferon	NS
Interleukin-10	NS
Growth factor receptor signaling	NS
Immune Response Type 1	NS
Immune Response Type 2	NS
Acute phase	p < 0.01
Hypoxia	NS
Cancer	NS

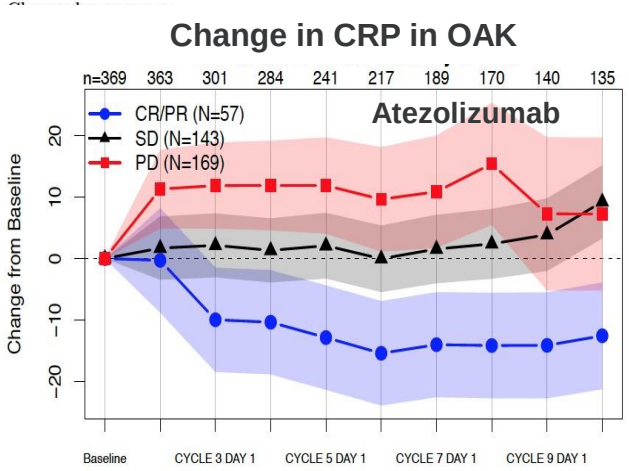
[1]S. Goldberg et al, SITC2017, P30

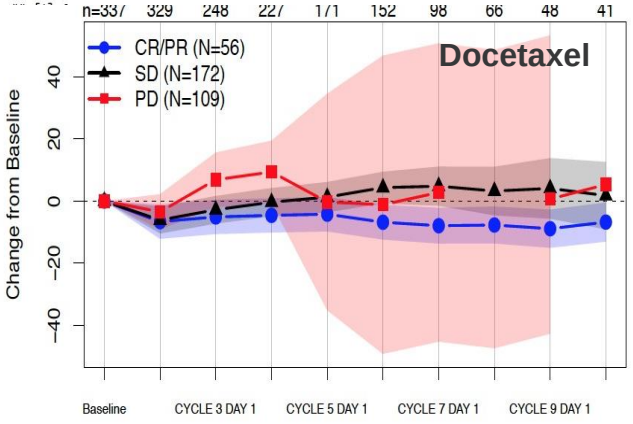
Courtesy: Heinrich Roder, Biodesix

Systemic inflammation marker like CRP may provide a good surrogate for OS









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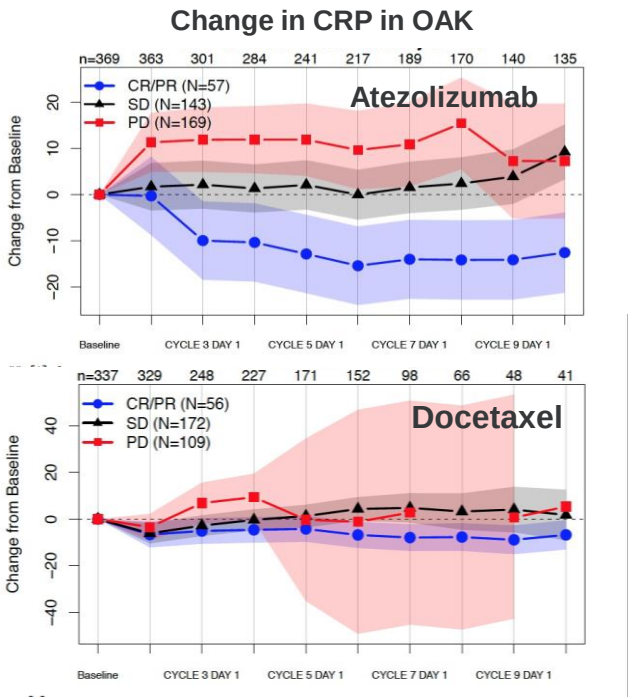
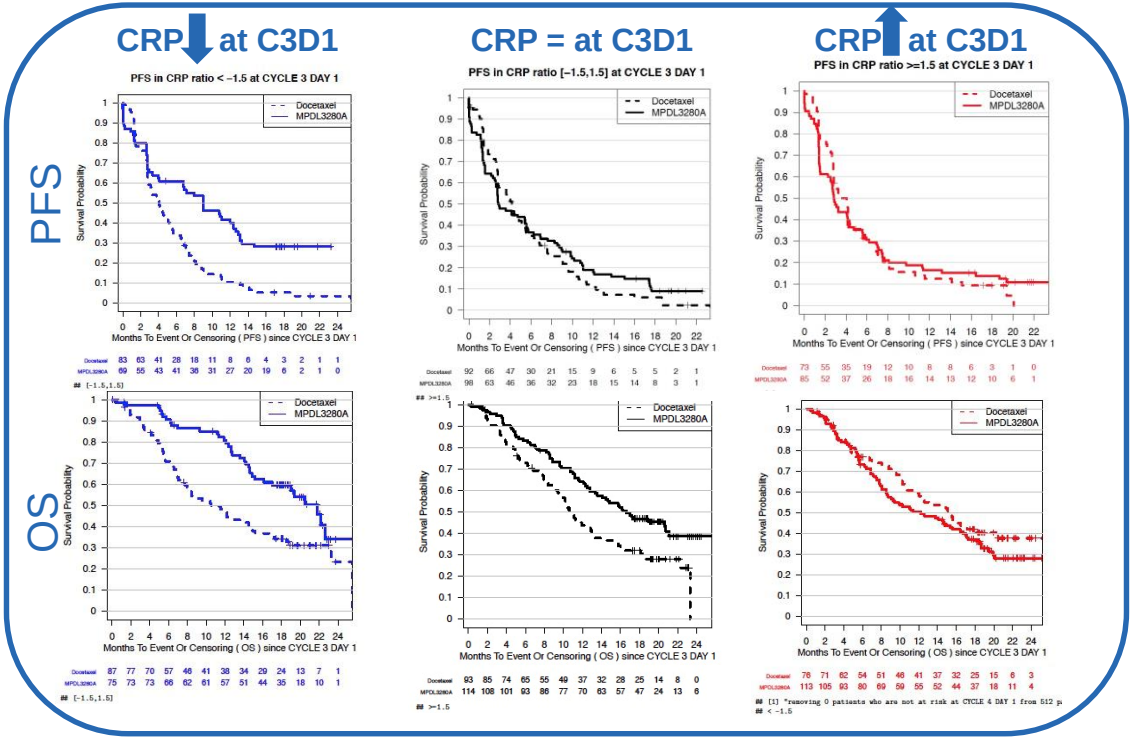
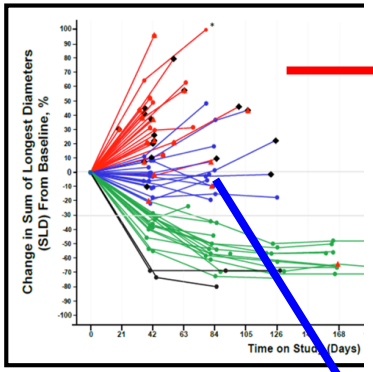
Change in CRP and association with OS NSCLC



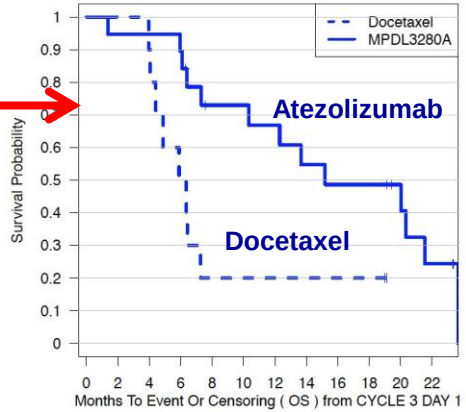


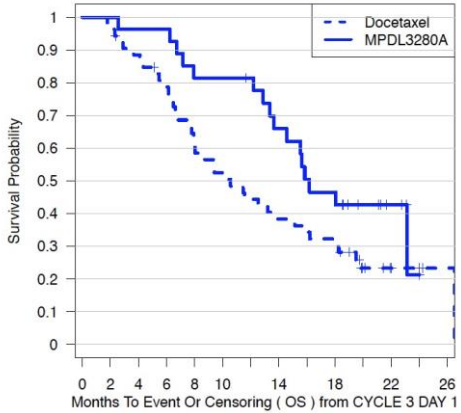
Zou W, Kowanetz M, Patil N

Decrease in CRP associated with improved OS in patients with RECIST 1.1 SD/PD

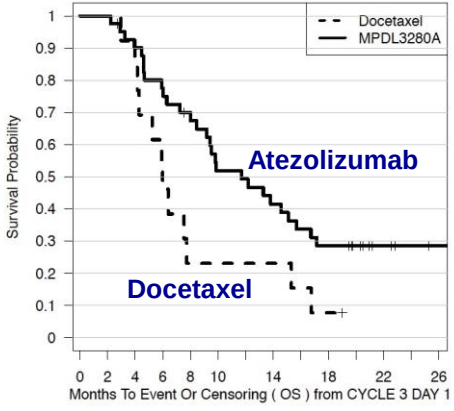


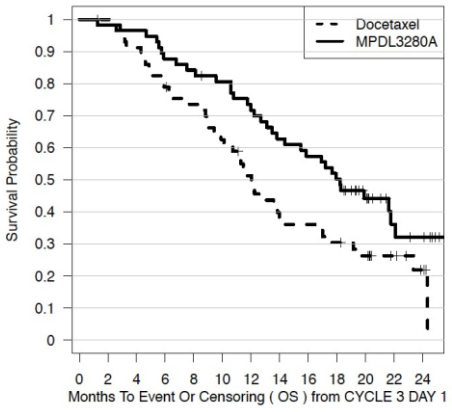
Decrease in CRP at C3



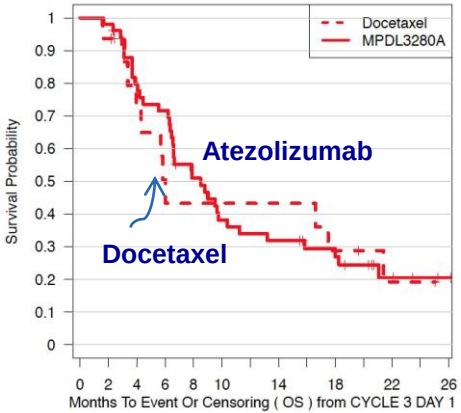


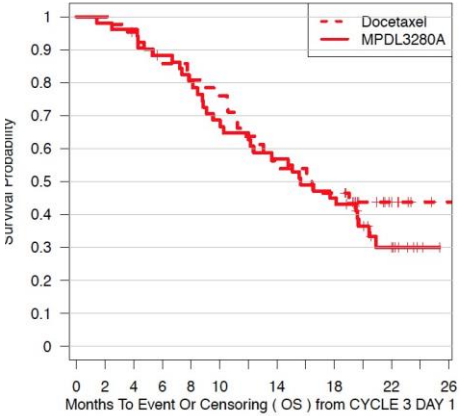
No Change in CRP at C3





Increase in CRP at C3





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Registration trials of CDK4/6 inhibitors

First line AI sensitive – with AI		HR	(95% CI)
PALOMA2	Palbociclib	**0.58**	(0.46, 0.72)
MONALEESA2	Ribociclib	**0.58**	(0.46, 0.70)
MONARCH3	Abemaciclib	**0.54**	(0.41, 0.72)
Endocrine pre-treated – with fulvestrant			
PALOMA3	Palbociclib	**0.50**	(0.40, 0.62)
MONARCH2	Abemaciclib	**0.55**	(0.45, 0.68)

Hazard ratios for PFS primary endpoint

Courtesy: Nick Turner, Discussant for MONARCH 3, ESMO 2017

Finn RS, *et al.* NEJM 2016, Turner NC, *et al.* NEJM 2015 updated SABCS 2016, Hortobagyi GN, et al. NEJM 2016 updated ASCO 2017, Sledge, *et al* JCO 2017

Randomized trials with monotherapy Checkpoint inhibitors

POS / NEG	Melanoma	Adj Melanoma	2nd line NSLC	1st line NSCLC	Early NSCLC	mUC	H&N
Atezolizumab			OAK			IMvigor211	
Nivolumab	CM-067	CM-238	CM-057/017	CM-026			CM-141
Pembrolizumab	KN-006		KN-010	KN-024		KN-045	KN-040
Durvalumab					PACIFIC		

Deluge of data over the next 2-5 years with 1500 trials ongoing today…~ 300,000 patients in trials

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Sami Mahrus
Mahesh Yadav
Dustin Smith
Yulei Wang
Kwame Okrah
Mark McLeland
Eka Kortkhonjia
Richard Bourgon
Ron Mazumdar
Rich Price
Katja Schulze
Yan Li
Christophe Mancao
Craig Cummings
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Patients who participate in trials