Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Patient Selection, Efficacy and Biomarkers

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Disclosures

- Consultant for Sanofi, Oncocyte, and Lilly; research funding from Oncocyte.
- I will not be discussing non-FDA approved indications during my presentation.

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Outline

- Existing ICI biomarkers and their role/limitations
- Landscape of novel genomic and molecular biomarkers
- Emerging challenges: treatment synergy and selecting combination therapies

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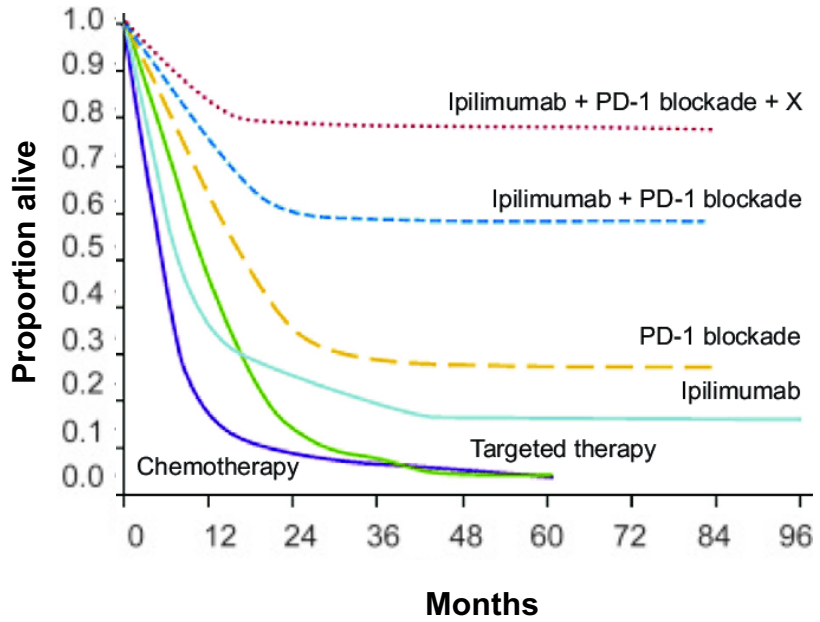
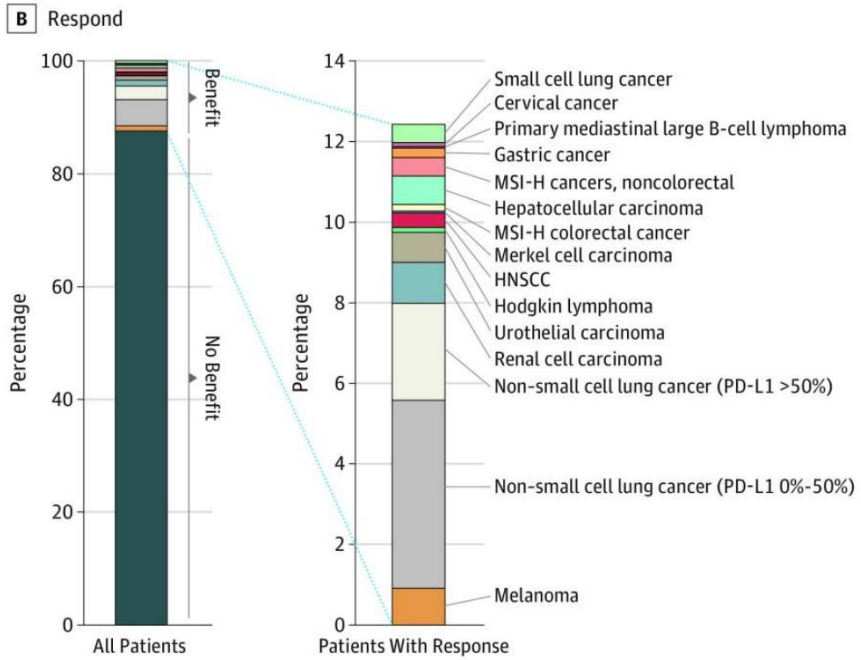
Challenge: immune checkpoint inhibitors provide durable long-term response – to a *minority* of patients





PD-L1, MSI status, and TMB are the only FDA-approved biomarkers to date

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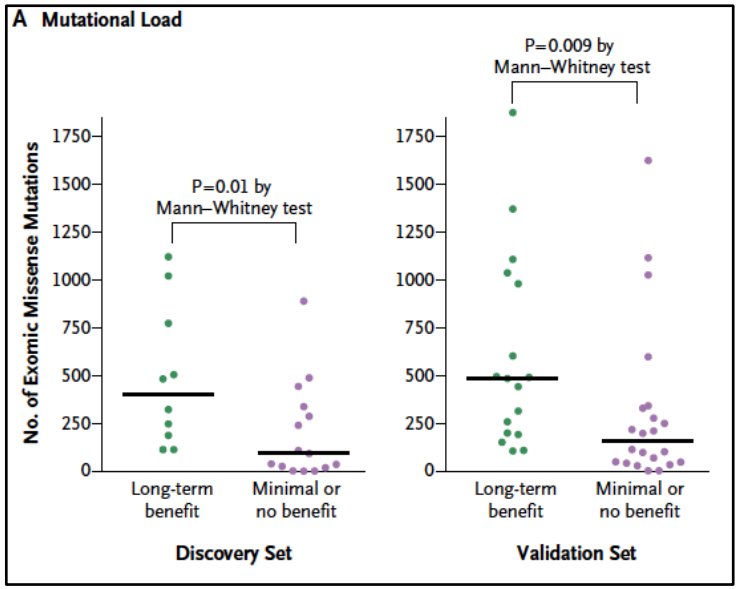
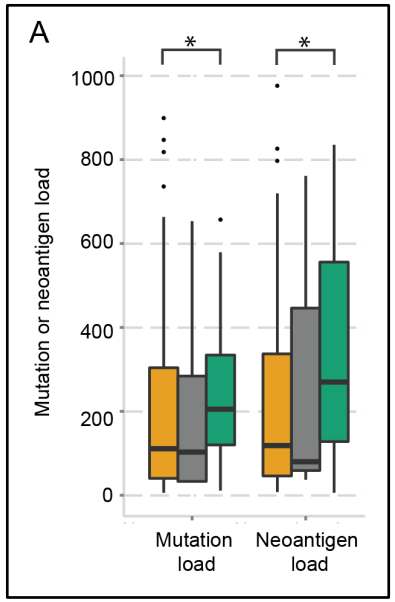
Emens et al., *Eur J Cancer* 2017
Haslam & Prasad, *JAMA Network Open* 2019

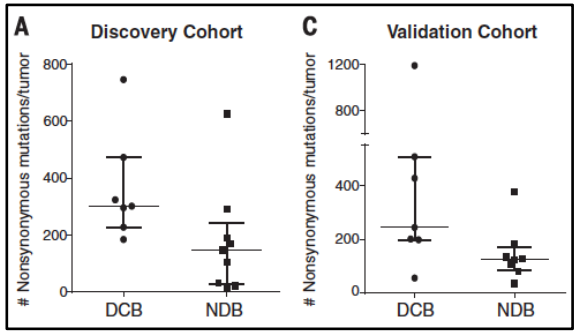
Tumor mutation burden (TMB) and immune checkpoint inhibitor (ICI) outcomes



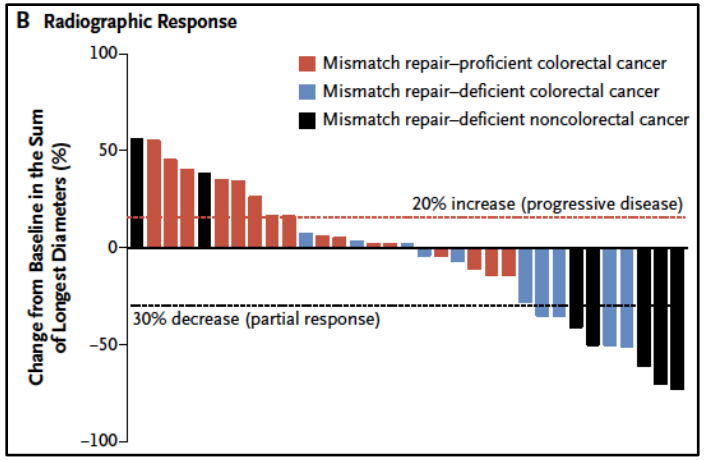
CTLA4 Ab
and melanoma



CTLA4 Ab
and melanoma



PD-1 Ab
and NSCLC



PD-1 Ab and
MSI-high tumors

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Snyder et al *NEJM* 2014
Rizvi et al *Science* 2015
Van Allen et al *Science* 2015
Le et al *NEJM* 2015

Slide courtesy of Eli Van Allen

Challenge: selecting optimal TMB threshold for patient stratification

Tumor type	Study and therapy	Sequencing Methodology	Reporting	Cutoff for high TMB
NSCLC	KEYNOTE-001 Pembrolizumab	WES	Nonsynonymous mutations	≥178 mutations
NSCLC	POPLAR, FIR, and BIRCH Atezolizumab	FoundationOne (315 genes)	SNVs (synonymous and nonsynonymous) and indels	≥13.5 mut/Mb (1st line); ≥17.1 or ≥15.8 mut/Mb (2nd line) (≥75th %ile)
NSCLC	CheckMate 026 Nivolumab	WES	Missense mutations per sample (tumor and blood)	≥243 mutations (upper tertile)
NSCLC	Real-world MSKCC population Pembrolizumab or nivolumab	MSK-IMPACT	Nonsynonymous mutations	≥7.4 mut/Mb (median)
Multiple (solid tumors)	KEYNOTE-012 & -028 Pembrolizumab	WES	Nonsynonymous mutations	≥102 mutations
Urothelial carcinoma	IMvigor 210 Atezolizumab	FoundationOne (315 genes)	SNVs (synonymous and nonsynonymous) and indels	>16 mut/Mb
NSCLC	POPLAR and OAK Atezolizumab	bTMB assay (FoundationOne, 394 genes)	SNVs (synonymous and nonsynonymous)	≥14 mut/Mb
SCLC	CheckMate 032 Nivolumab ± ipilimumab	WES	Missense mutations	≥248 mutations (upper tertile)
NSCLC	CheckMate 012 Nivolumab + ipilimumab	WES	Nonsynonymous mutations (SNVs or indels)	>158 (median), or ≥307 mutations (upper quartile)
Melanoma	CheckMate 038 Nivolumab ± ipilimumab	WES	Nonsynonymous mutations (SNVs or indels)	≥100 mutations
Urothelial carcinoma	CheckMate 275 Nivolumab	WES	Missense mutations	≥167 mutations (upper tertile)
NSCLC	CheckMate 227 & 568 Nivolumab and ipilimumab	FoundationOne CDx (324 genes)	SNVs (synonymous and nonsynonymous) and indels	≥10 mut/Mb
NSCLC	B-F1RST Atezolizumab	bTMB assay (FoundationOne, 394 genes)	SNVs (synonymous and nonsynonymous)	≥14 mut/Mb

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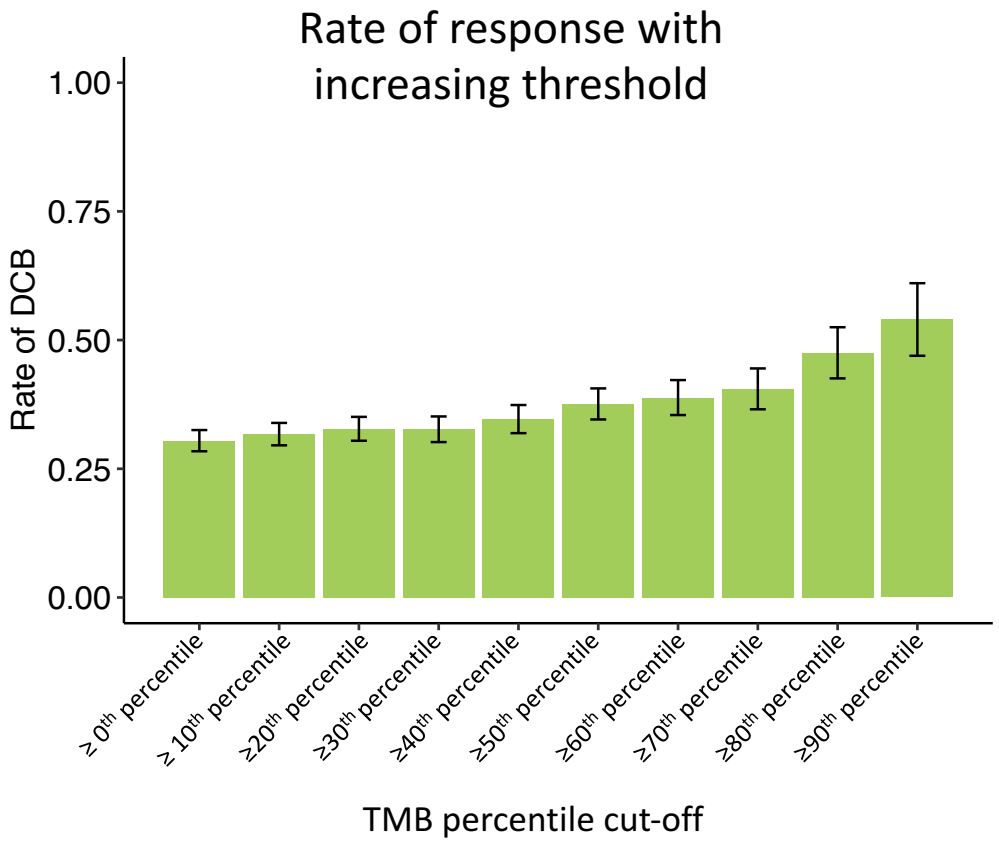
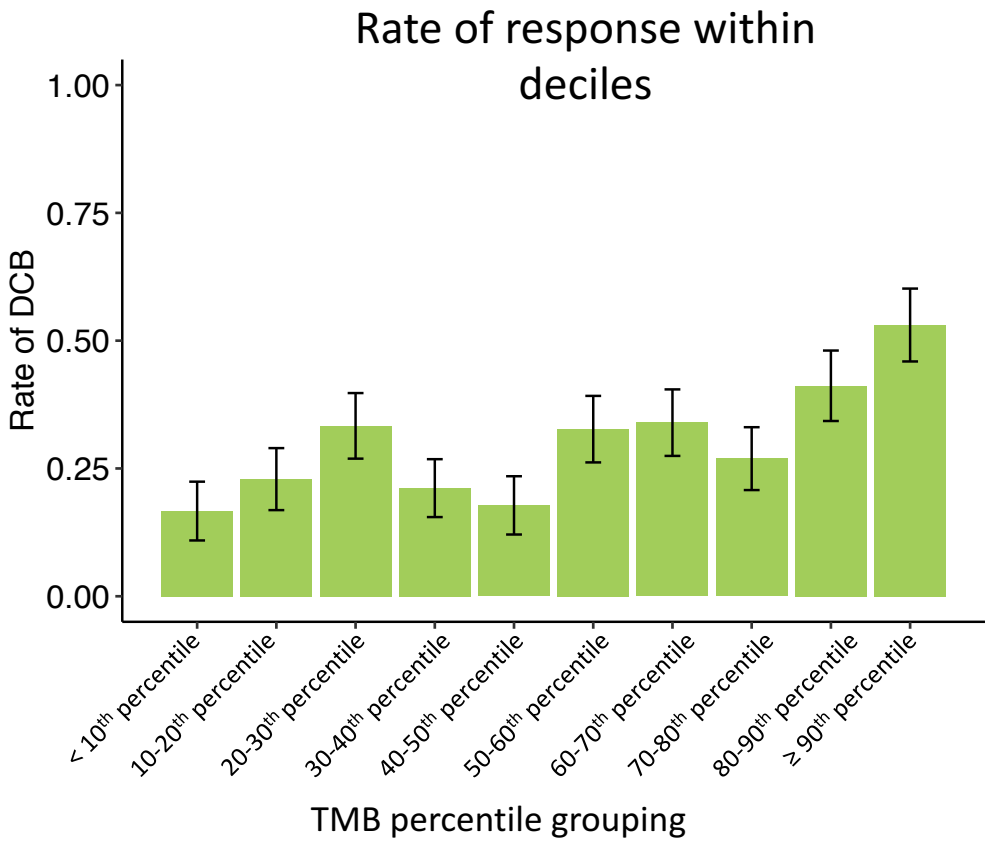
Stenzinger et al, Genes Chromosomes Cancer 2019

TMB imperfectly segregates patients who benefit from ICIs





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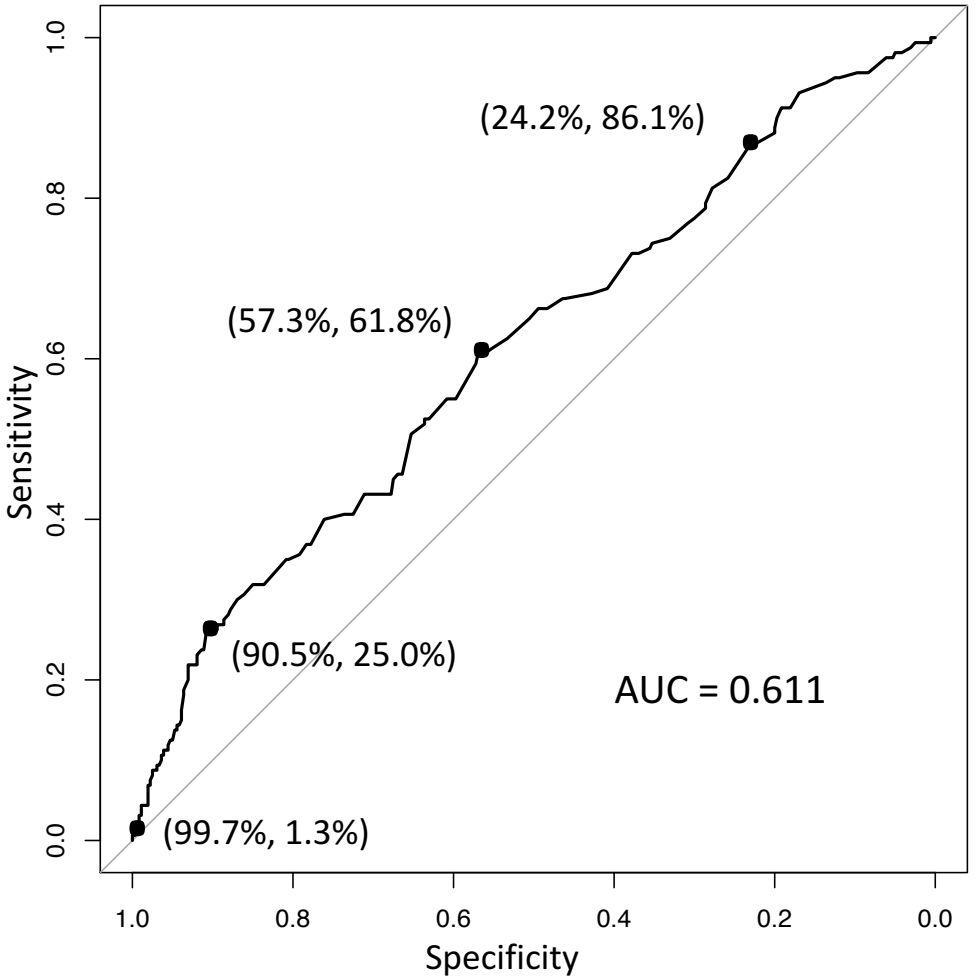
Vokes N et al, *JCO PO*, 2019

Cut-point analysis demonstrates trade-off in over- vs under-treatment



Z-score cut-off	DFCI TMB	MSKCC TMB	Sens (%)	Spec (%)	DCB rate (%)	OR (p-value)	# ≥ cut-off	# not treated	# treated w/o response
-0.44	7.34	3.77	86.1	24.2	33	1.99 (<0.01)	394	21 (4%)	263 (53%)
0.28	11.9	7.18	61.8	57.3	39	2.18 (< 0.01)	242	58 (12%)	148 (30%)
1.16	20.6	15.1	25.0	90.5	54	3.16 (< 0.01)	71	114 (23%)	33 (7%)
3.10	61.4	68.2	1.3	99.7	67	4.59 (0.22)	3	150 (30%)	1 (0.2%)

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Vokes N et al, *JCO PO*, 2019

Limited evidence underlying FDA approval of TMB

- June, 2020: pembrolizumab approved in second-line in patients with TMB ≥ 10
- Approval based on Keynote-158 in a prospectively planned, retrospective analysis of 10 cohorts of patients

Table 58: Efficacy Results for Patients with TMB-H Cancer in KEYNOTE-158

Endpoint	KEYTRUDA 200 mg every 3 weeks	
	TMB ≥10 mut/Mb n=102*	TMB ≥13 mut/Mb n=70
Objective Response Rate		
ORR (95% CI)	29% (21, 39)	37% (26, 50)
Complete response rate	4%	3%
Partial response rate	25%	34%
Duration of Response	n=30	n=26
Median in months (range)†	NR (2.2+, 34.8+)	NR (2.2+, 34.8+)
% with duration ≥12 months	57%	58%
% with duration ≥24 months	50%	50%

ORR in (32) pts with TMB ≥ 10 & < 13: 13%

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FDA Pembrolizumab prescribing information

Limitations to FDA approval

- Approval based on response, not on overall survival
- 'Tumor agnostic' approval
  - Only ten subtypes studied – e.g. breast and prostate cancers not included
  - Adds little efficacy data to tumor types without pre-existing FDA approvals
- TMB cut-off remains problematic – no evidence that 10 is the best cut-off, within or across tumor types

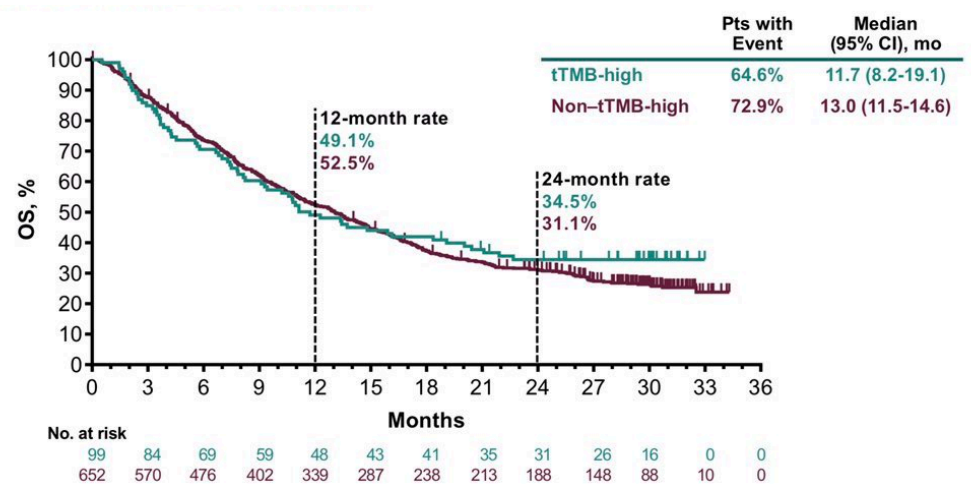

Table 59: Response by Tumor Type (TMB ≥10 mut/Mb)

	N	Objective Response Rate n (%)	95% CI	Duration of Response range (months)
Overall*	102	30 (29%)	(21%, 39%)	(2.2+, 34.8+)
Small cell lung cancer	34	10 (29%)	(15%, 47%)	(4.1, 32.5+)
Cervical cancer	16	5 (31%)	(11%, 59%)	(3.7+, 34.8+)
Endometrial cancer	15	7 (47%)	(21%, 73%)	(8.4+, 33.9+)
Anal cancer	14	1 (7%)	(0.2%, 34%)	18.8+
Vulvar cancer	12	2 (17%)	(2%, 48%)	(8.8, 11.0)
Neuroendocrine cancer	5	2 (40%)	(5%, 85%)	(2.2+, 32.6+)
Salivary cancer	3	PR, SD, PD		31.3+
Thyroid cancer	2	CR, CR		(8.2, 33.2+)
Mesothelioma cancer	1	PD		

* No TMB-H patients were identified in the cholangiocarcinoma cohort

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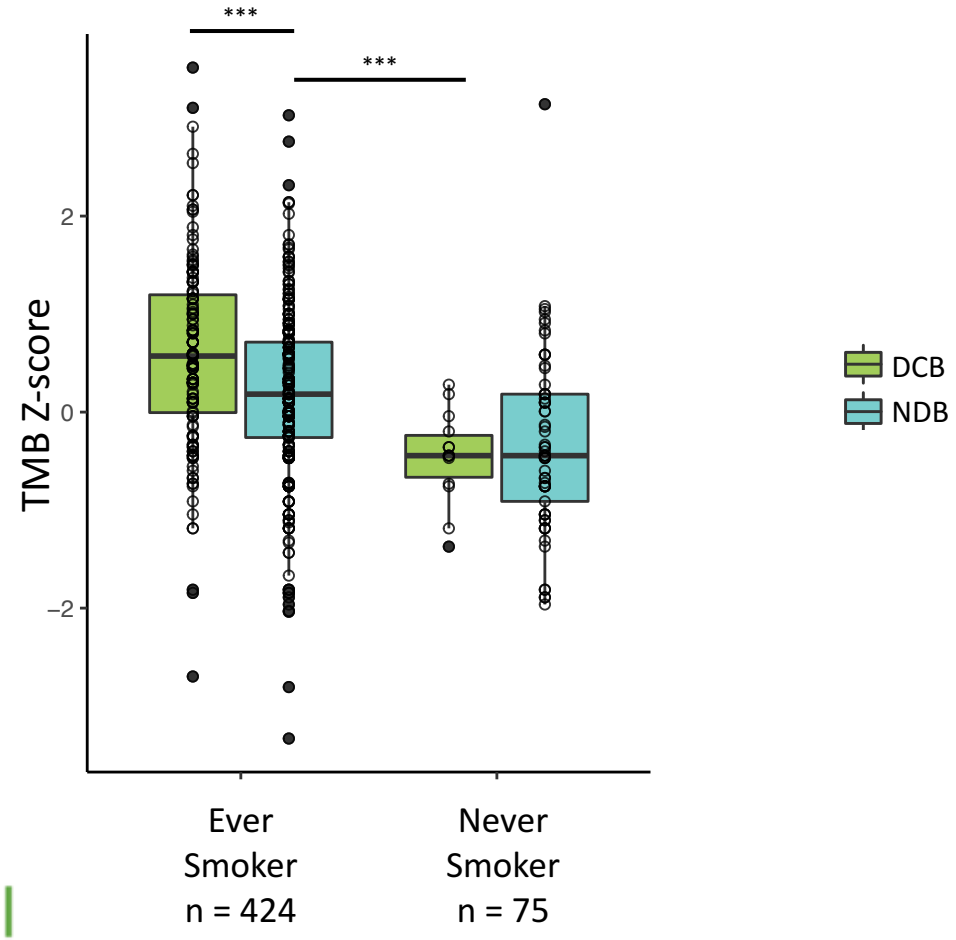
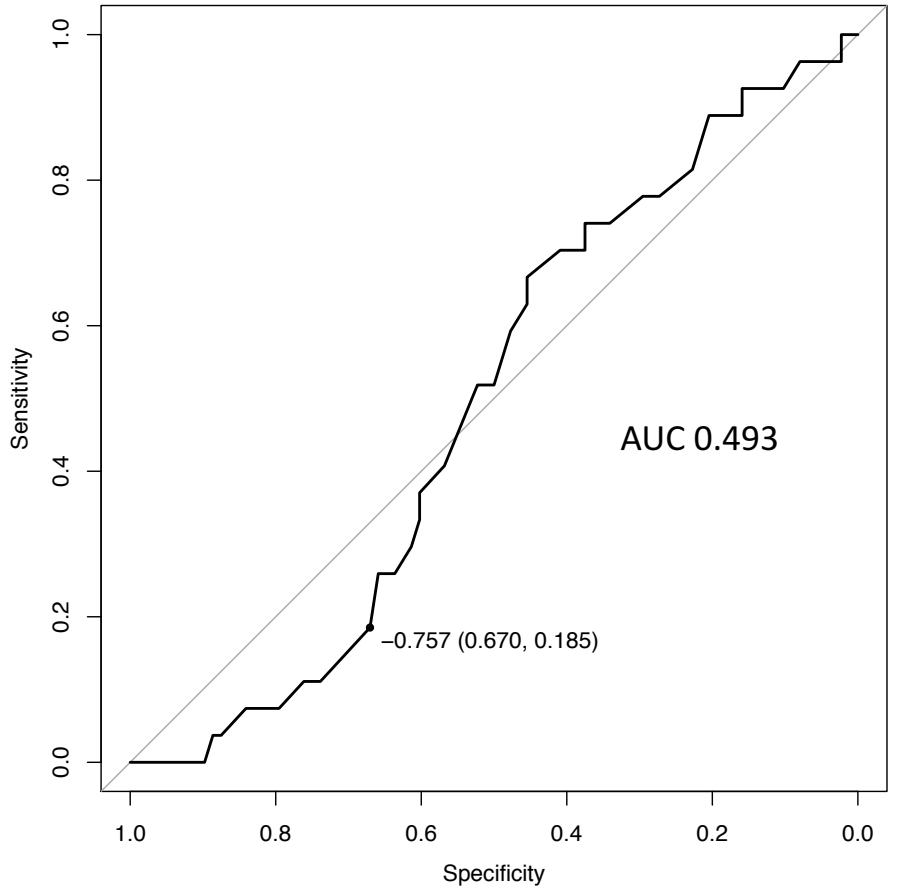
FDA Pembrolizumab prescribing information

TMB does not associate with response in never smokers



ROC curve of TMB in never smokers



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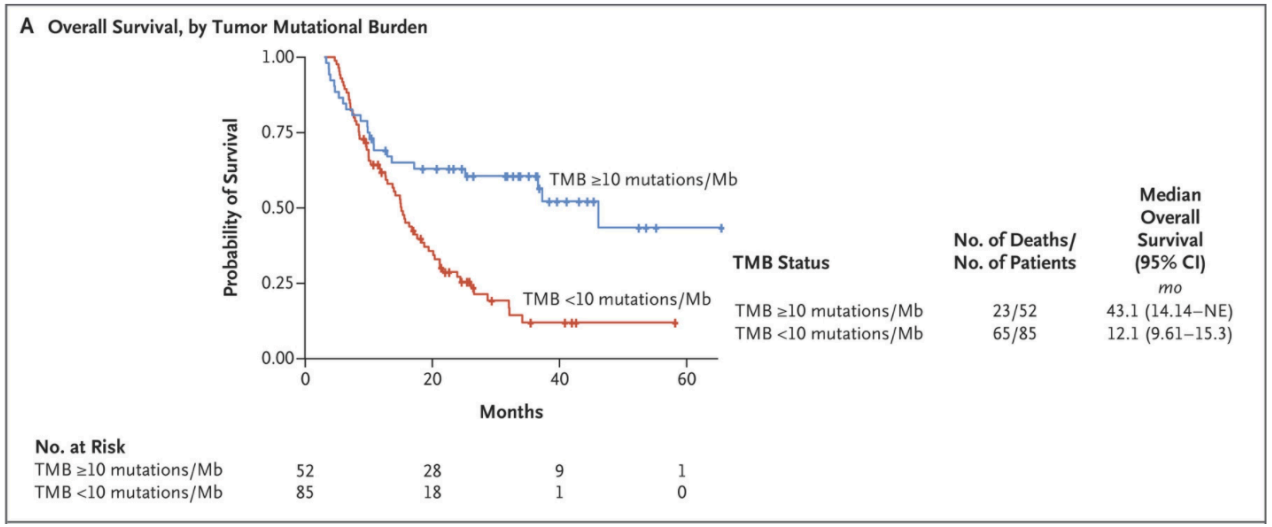
Vokes N et al, *JCO PO*, 2019

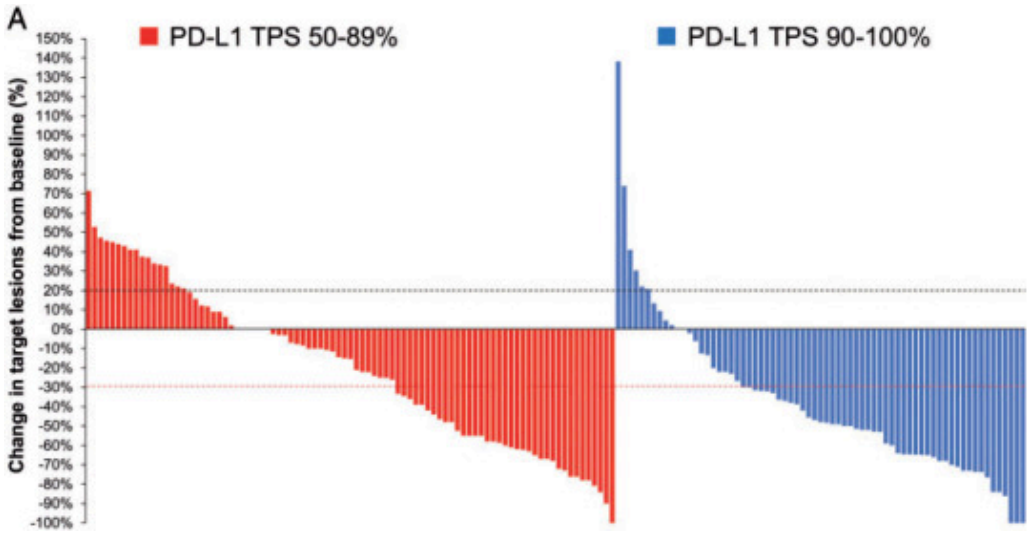
Not all TMB, and not TMB contexts, are the same

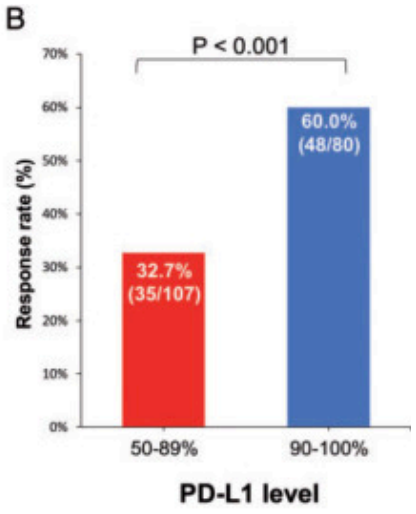


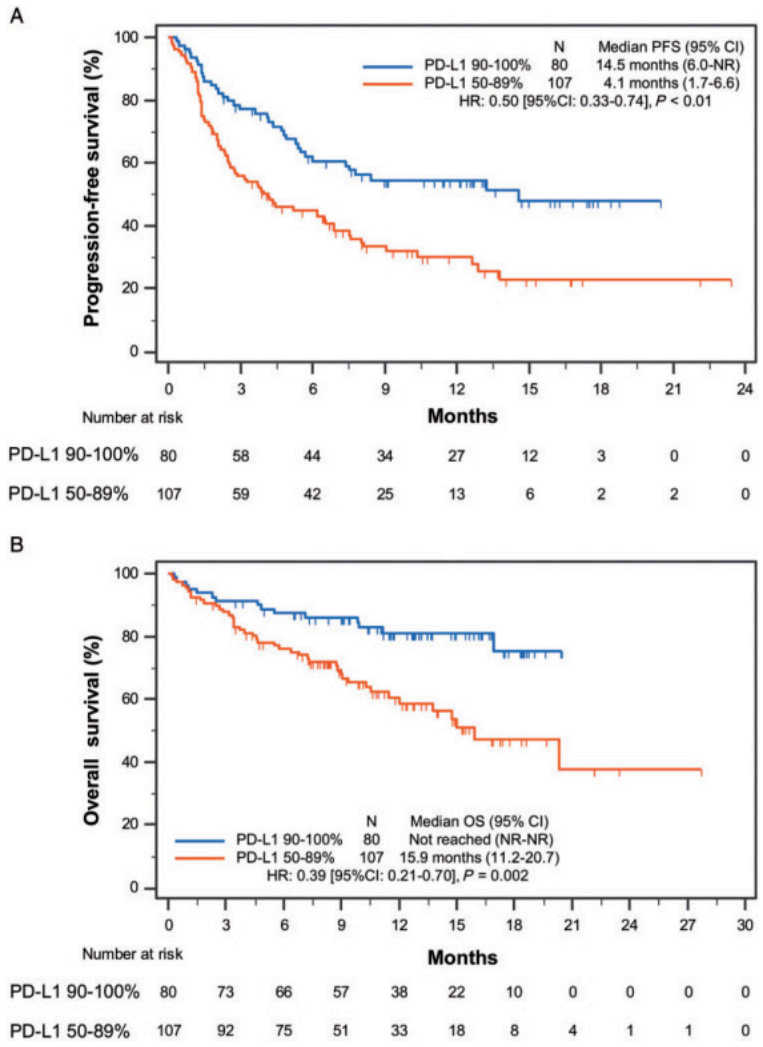
TMB Status	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
TMB ≥10 mutations/Mb	23/52	43.1 (14.14–NE)
TMB <10 mutations/Mb	65/85	12.1 (9.61–15.3)

Rousseau et al, NEJM 2021

PD-L1 may be a continuous biomarker without a clear cut-point







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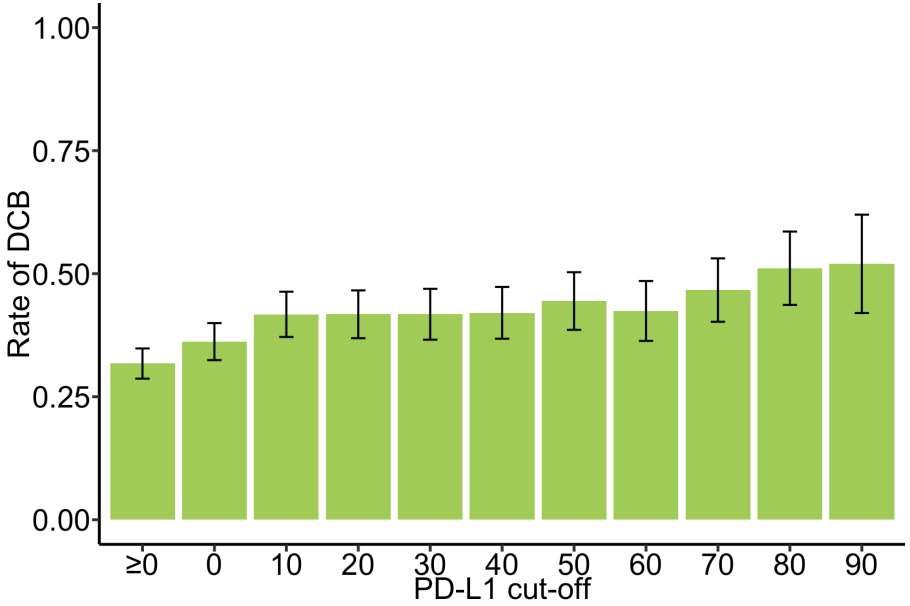
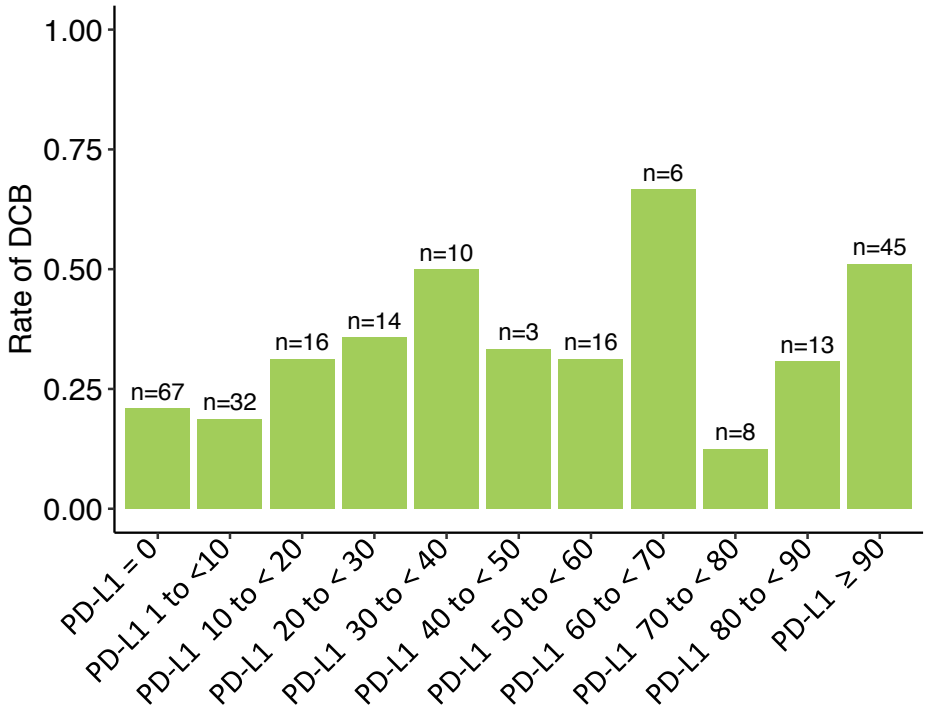
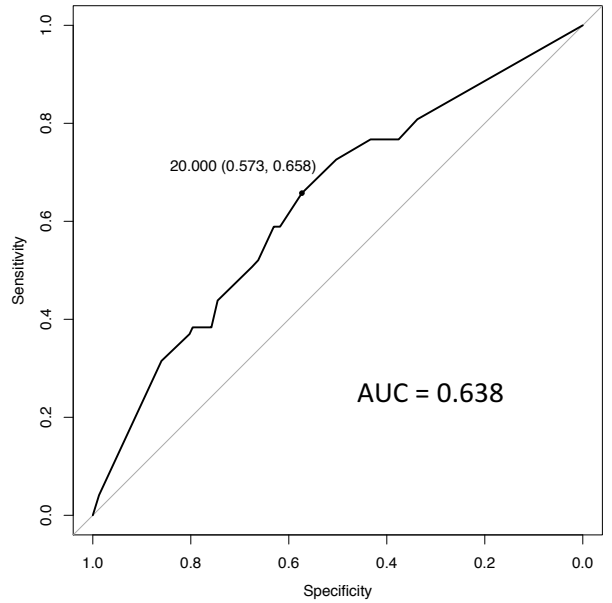
Alguilar et al, Annals of Oncol, 2019

PD-L1 may have similar limitations as TMB as a biomarker







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Take away

- Current FDA-approved biomarkers can help predict the likelihood of ICI-response, but they are imperfect and should not be used to exclude patients from an otherwise appropriate trial of ICIs.

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Outline

- Existing ICI biomarkers and their role/limitations
- Landscape of novel genomic and molecular biomarkers
- Emerging challenges: treatment synergy and selecting combination therapies

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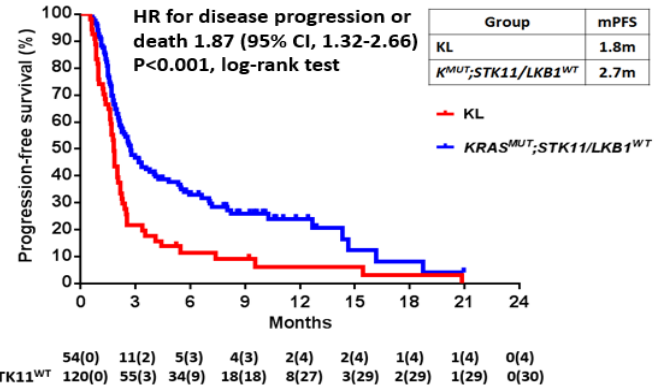
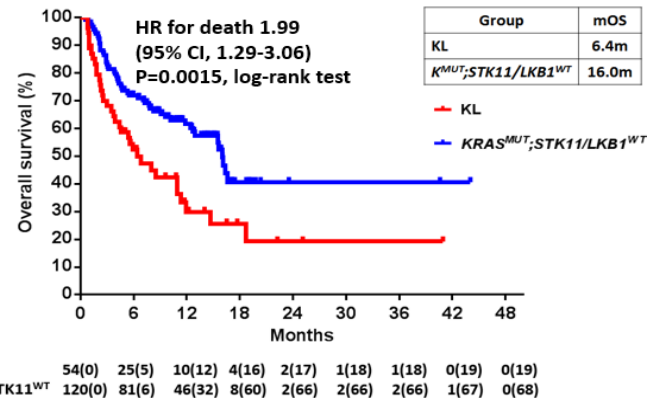
STK11 and *KEAP1* alterations associate with inferior outcomes to ICIs

ICI monotherapy





ICI plus chemotherapy

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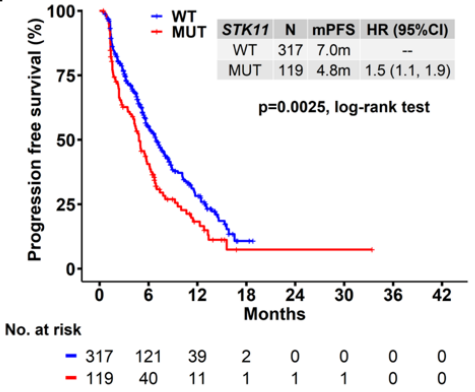

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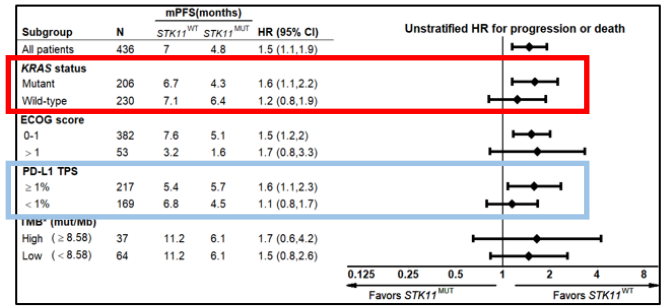

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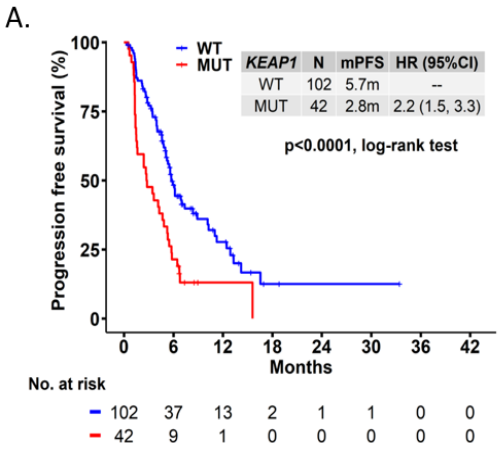

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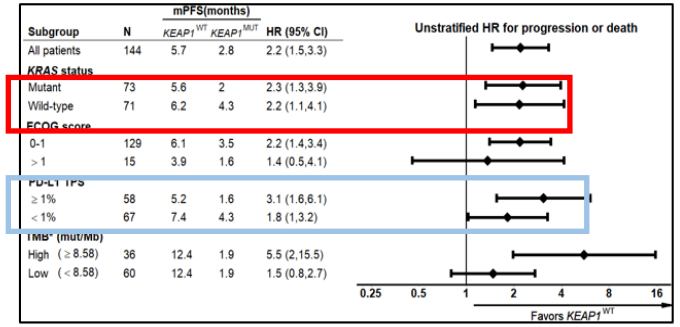

Skoulidis F et al., *Cancer Discov*, 2018
Skoulidis F et al, in preparation
Slide courtesy of Dr F. Skoulidis

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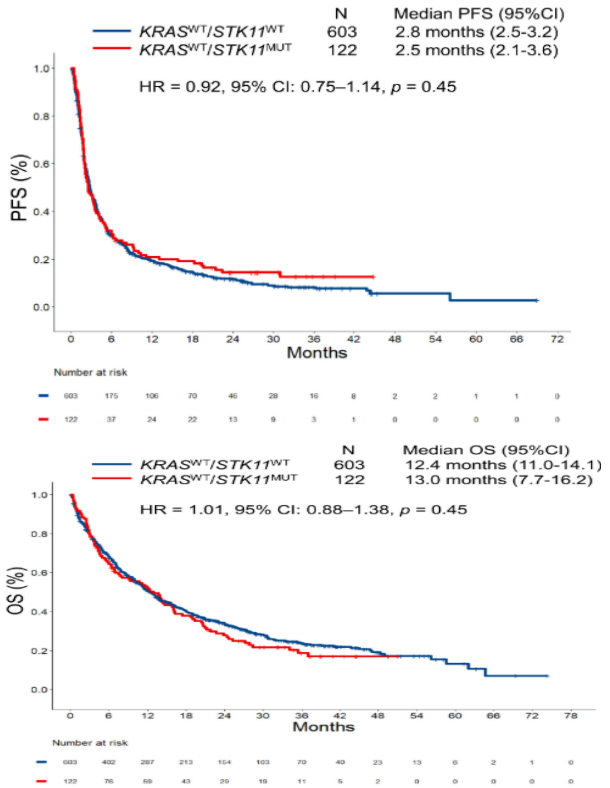
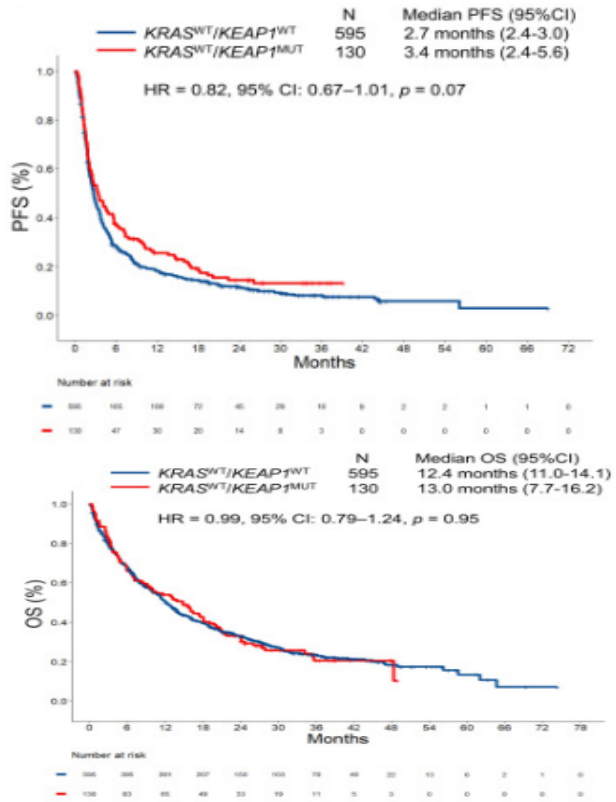
However, co-mutations may modulate this association

$KRAS^{WT}/STK11^{WT}$ vs $KRAS^{WT}/STK11^{MUT}$



$KRAS^{WT}/KEAP1^{WT}$ vs $KRAS^{WT}/KEAP1^{MUT}$



Onco-genotype	mPFS	mOS
$KRAS^{MUT};STK11^{WT}$	4.8m	17.3m
$KRAS^{MUT};STK11^{MUT}$	2.0m	6.2m
$KRAS^{WT};STK11^{WT}$	2.8m	12.4m
$KRAS^{WT};STK11^{MUT}$	2.5m	13.0m
$KRAS^{MUT};KEAP1^{WT}$	4.6m	18.4m
$KRAS^{MUT};KEAP1^{MUT}$	1.8m	4.8m
$KRAS^{WT};KEAP1^{WT}$	2.7m	12.4m
$KRAS^{WT};KEAP1^{MUT}$	3.4m	13.0m

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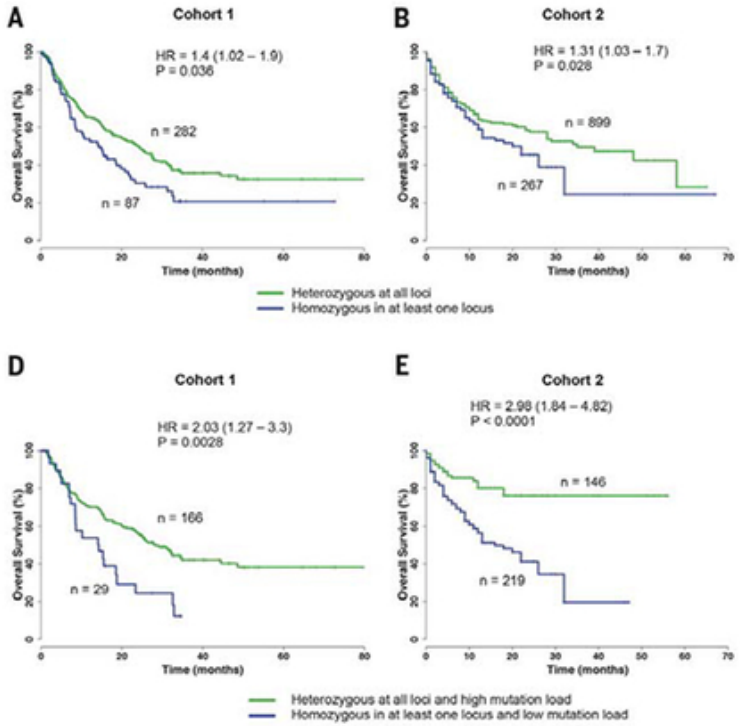
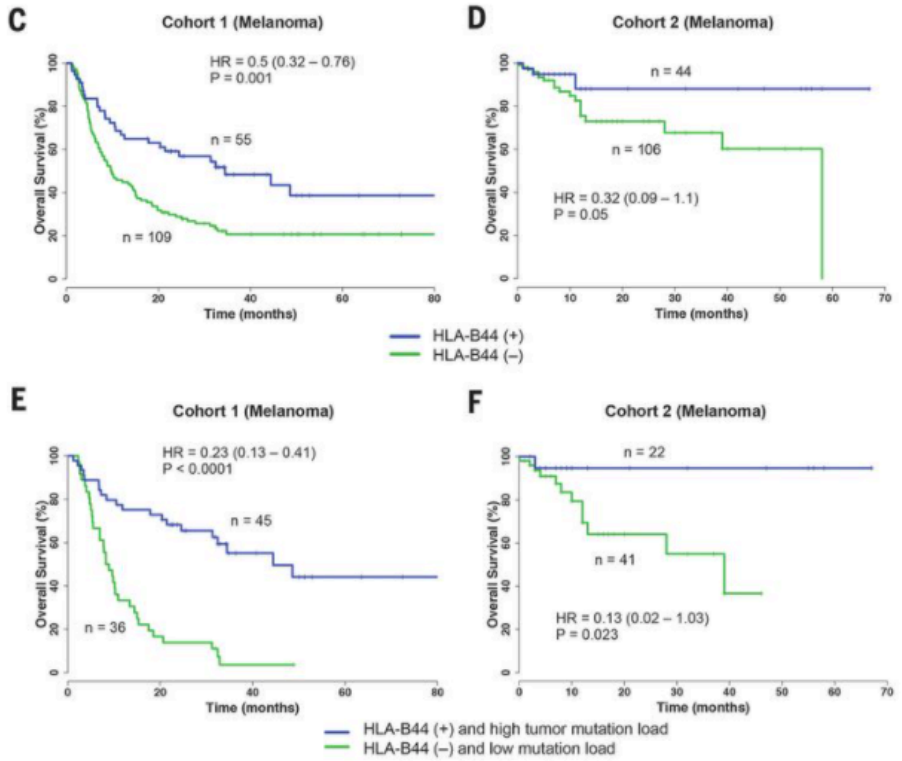
Ricciuti B et al., *JTO,* 2021

HLA type and zygosity are proposed biomarkers…

HLA zygosity



HLA-B44 type



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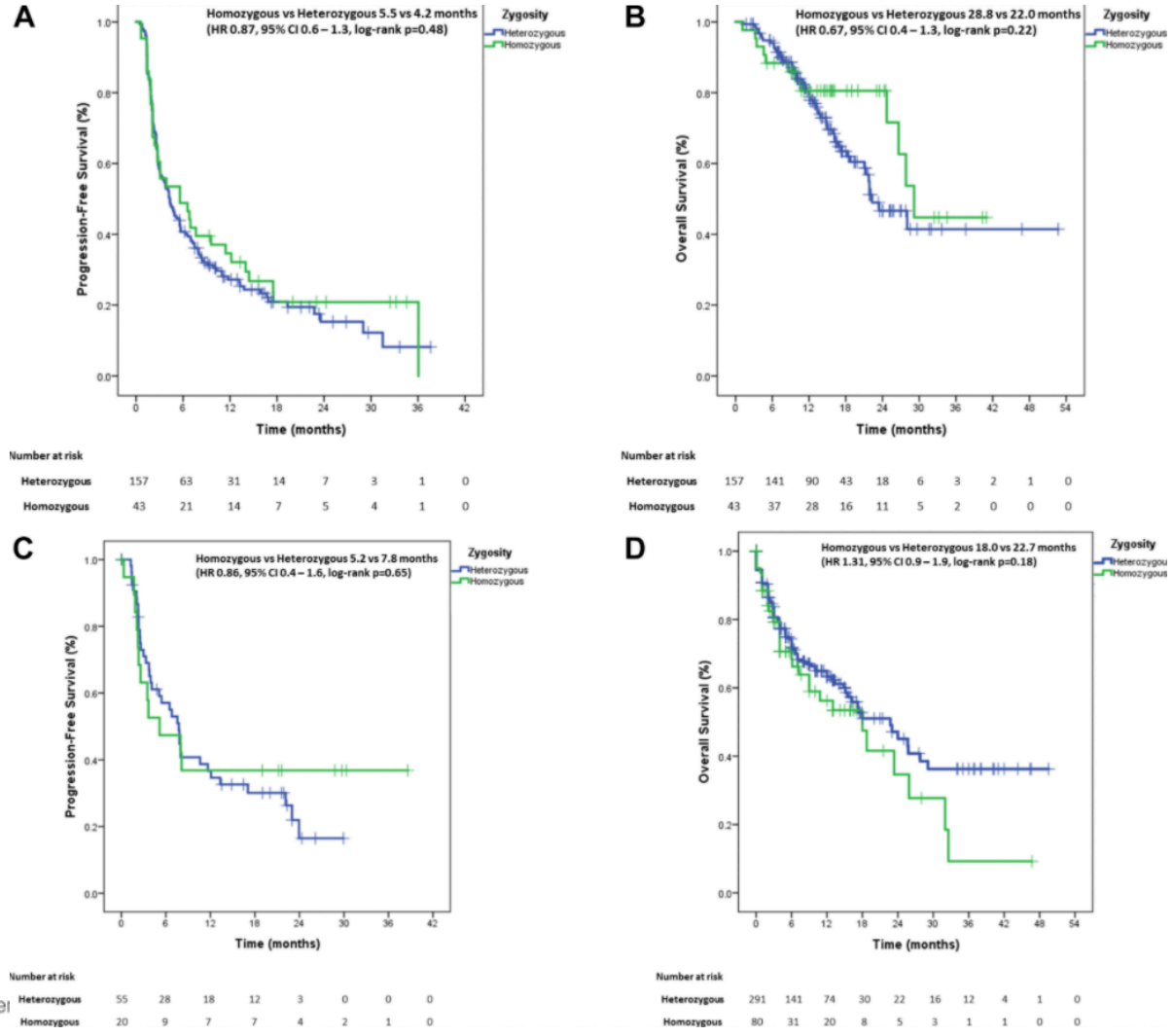
Chowell et al, Science 2018

But HLA heterozygosity doesn't validate



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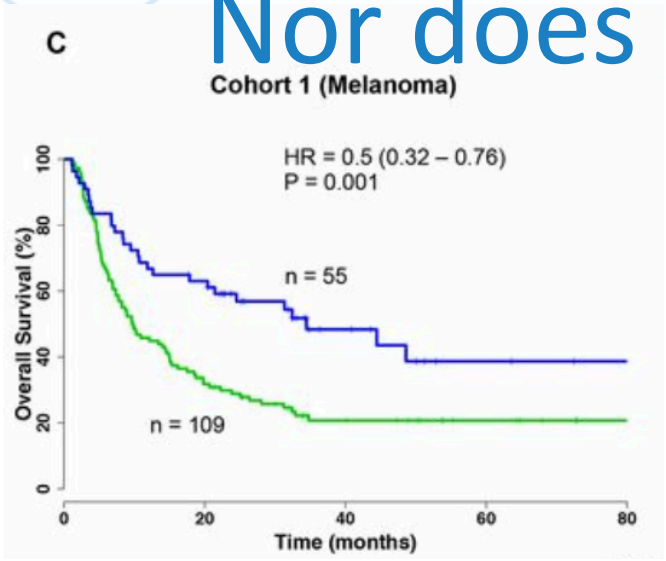
Negrao et al, *JTO* 2019

Nor does HLA-B44



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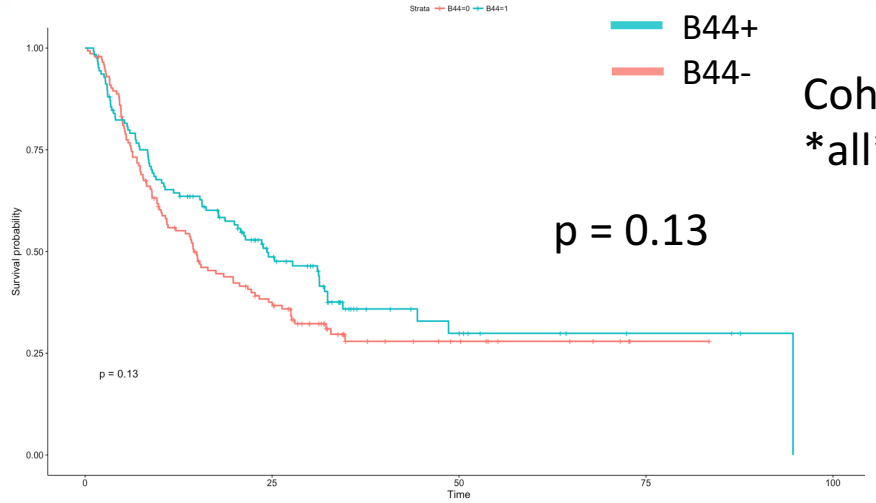
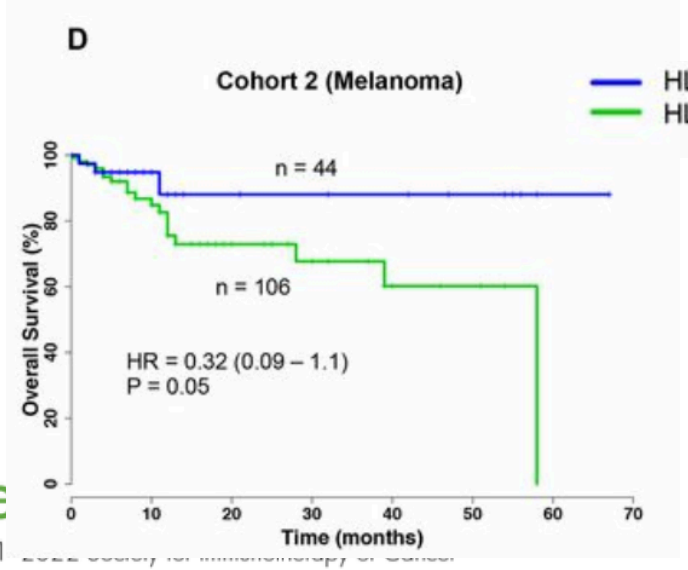


Cohort 1: *all* patients, *all* HLA-B44 subtypes



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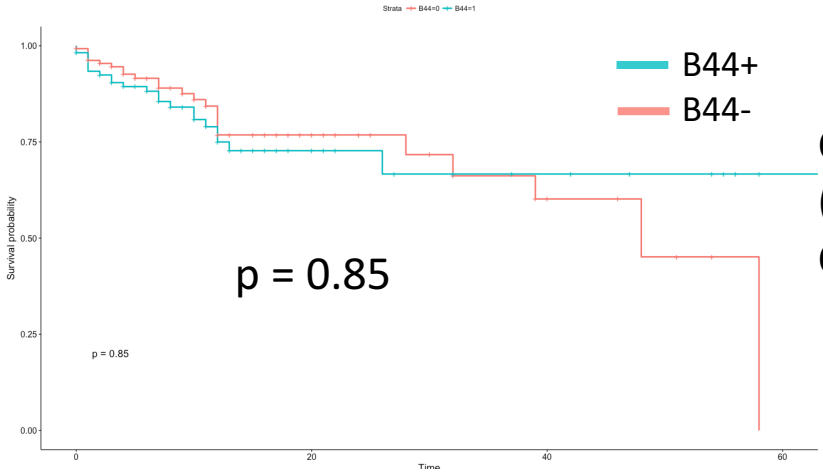

Cohort 2: all patients (including combination CTLA4 + PD-1)

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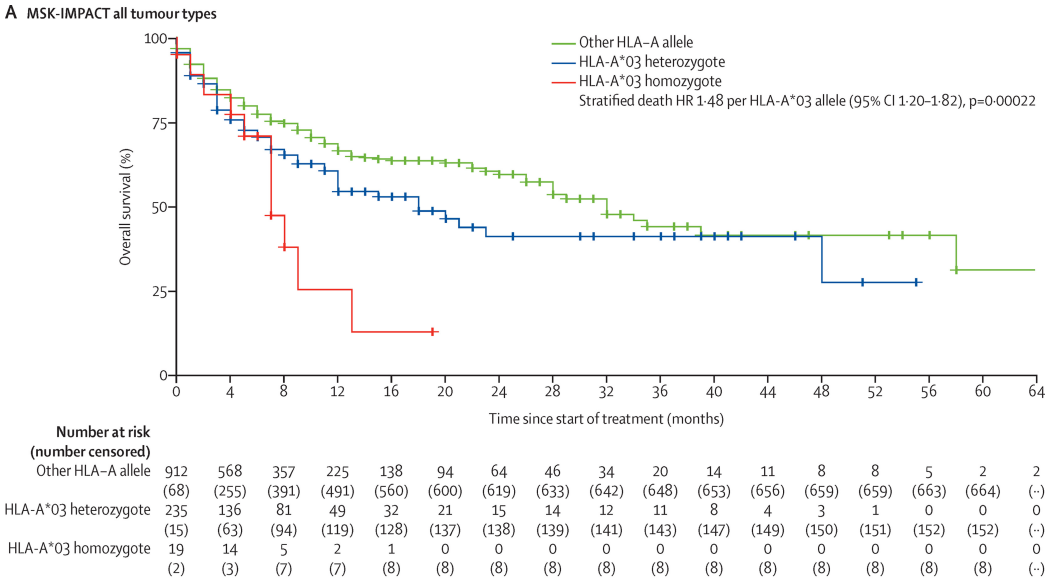
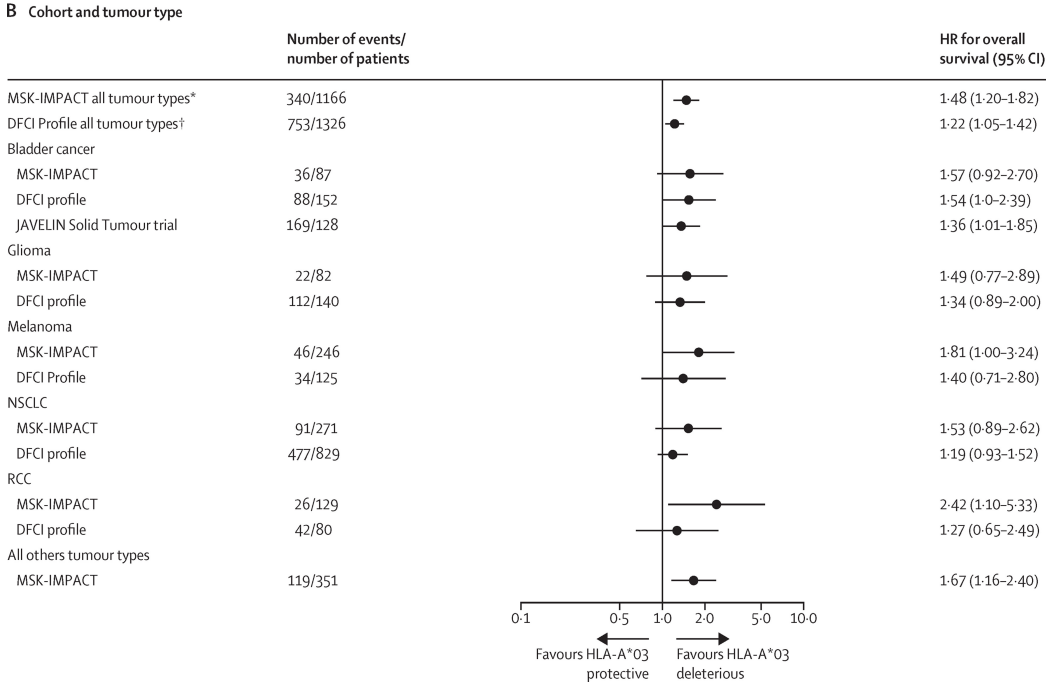
However, work is ongoing and novel analyses may implicate new biology





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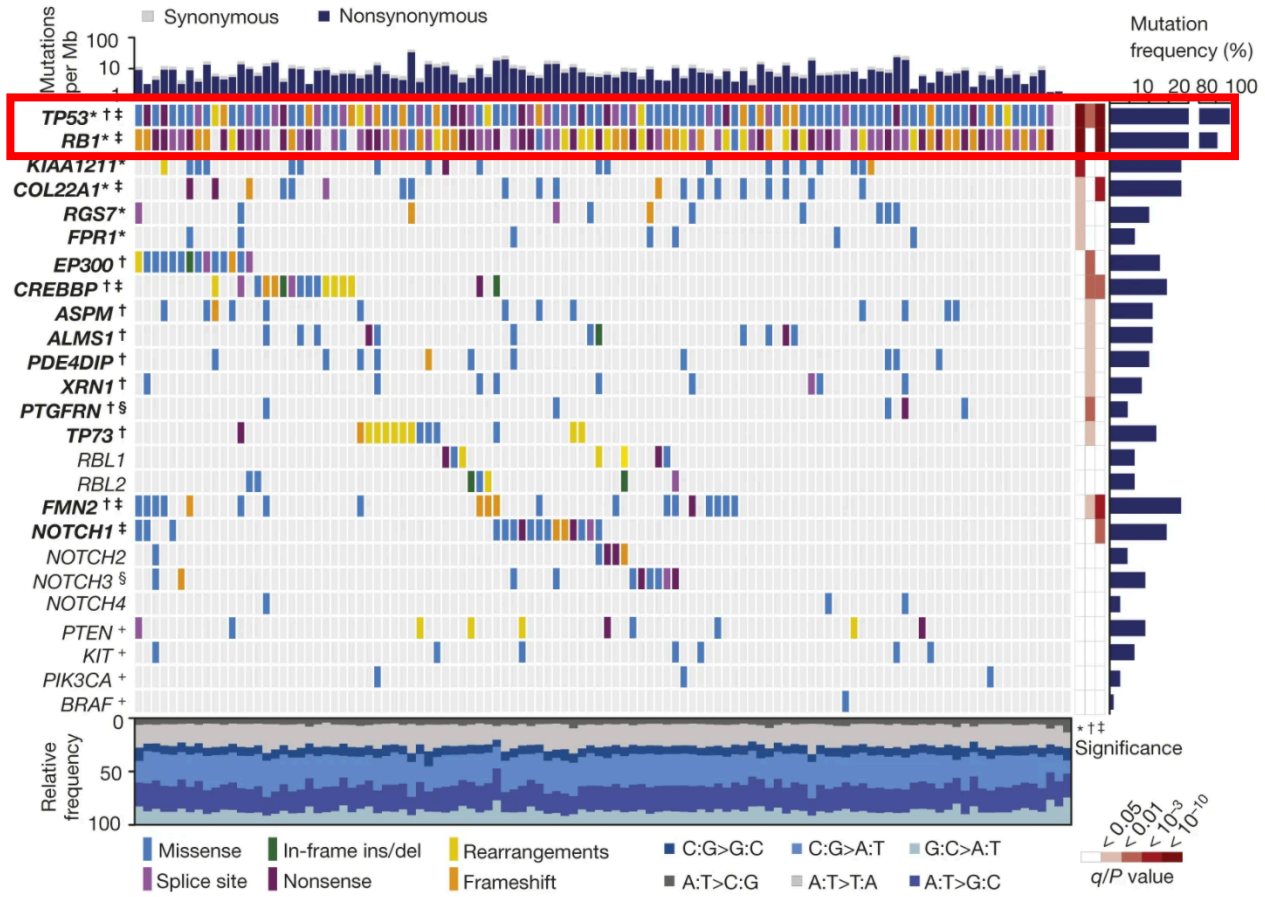
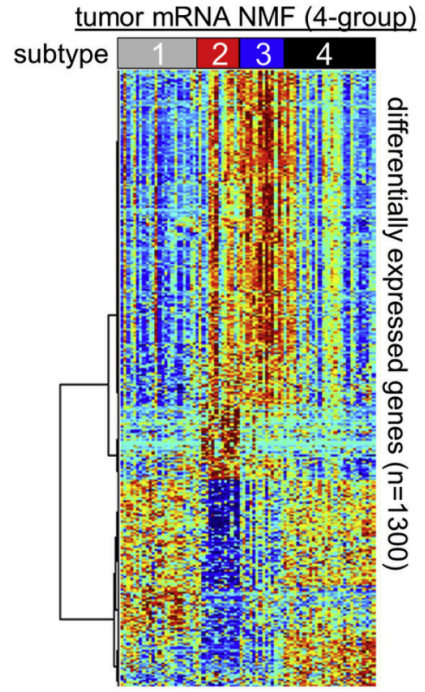
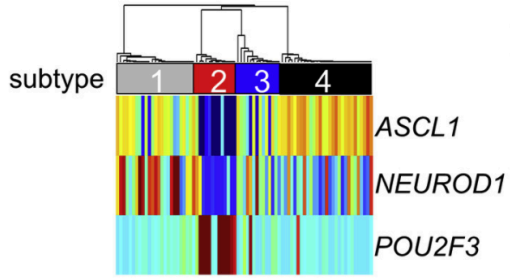
Naranbai et al, *Lancet Oncology* 2022

Integrating across data types reveals new biology

SCLC as a 'homogeneous disease'







Gay et al, *Cell Reports*, 2021

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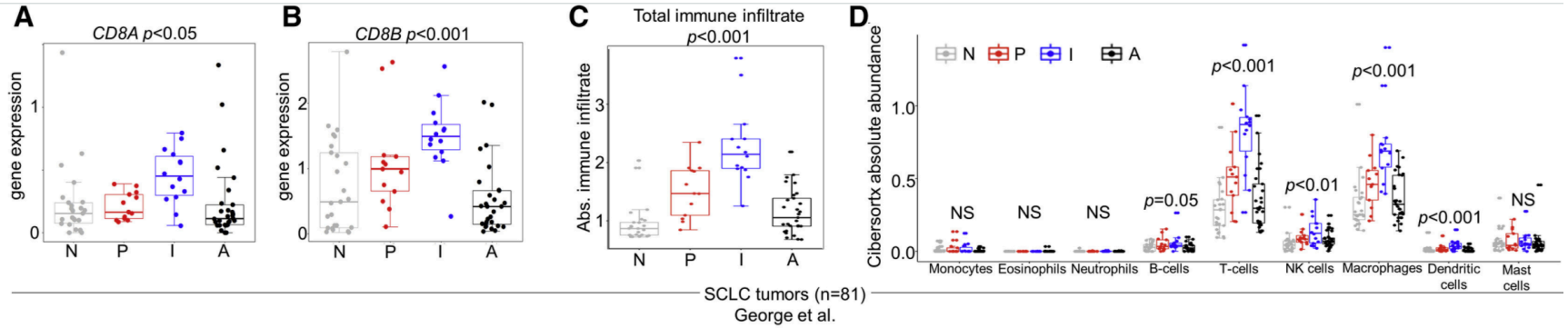
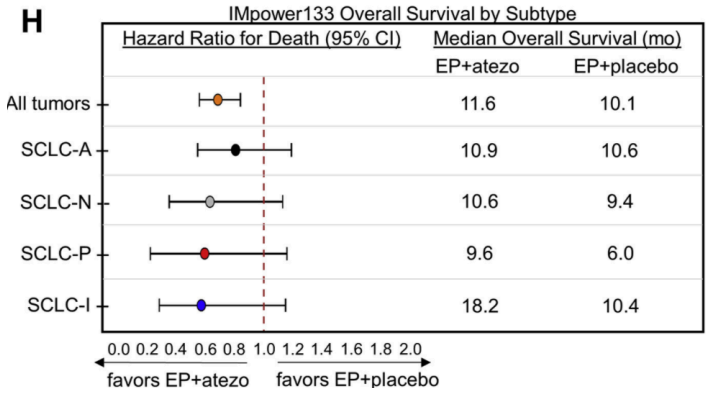
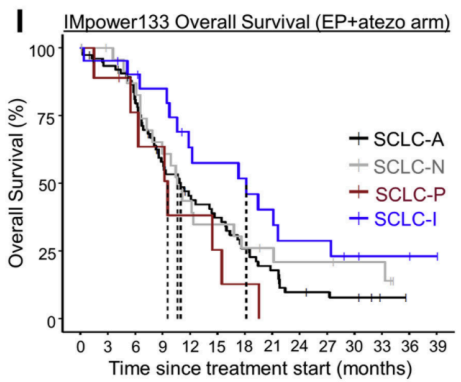
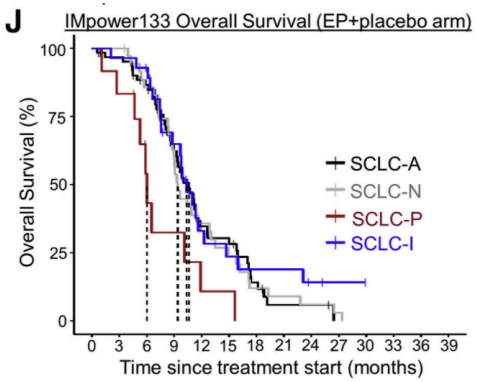
SCLC transcriptomic signatures associate with ICI response









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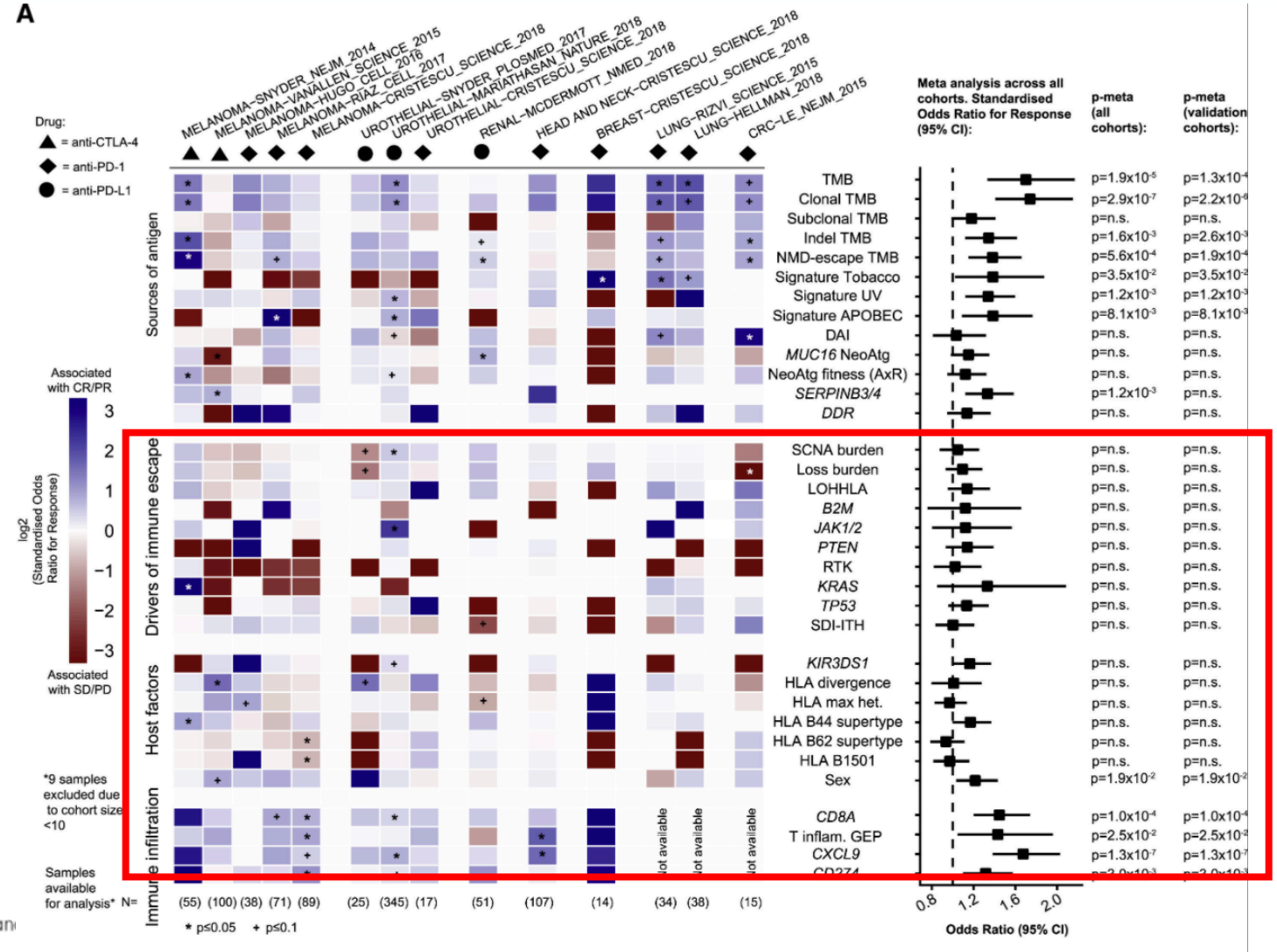
Gay et al, *Cell Reports*, 2021

More work is needed to identify consistent genomic response correlates



Litchfield et al, *Cell* 2021

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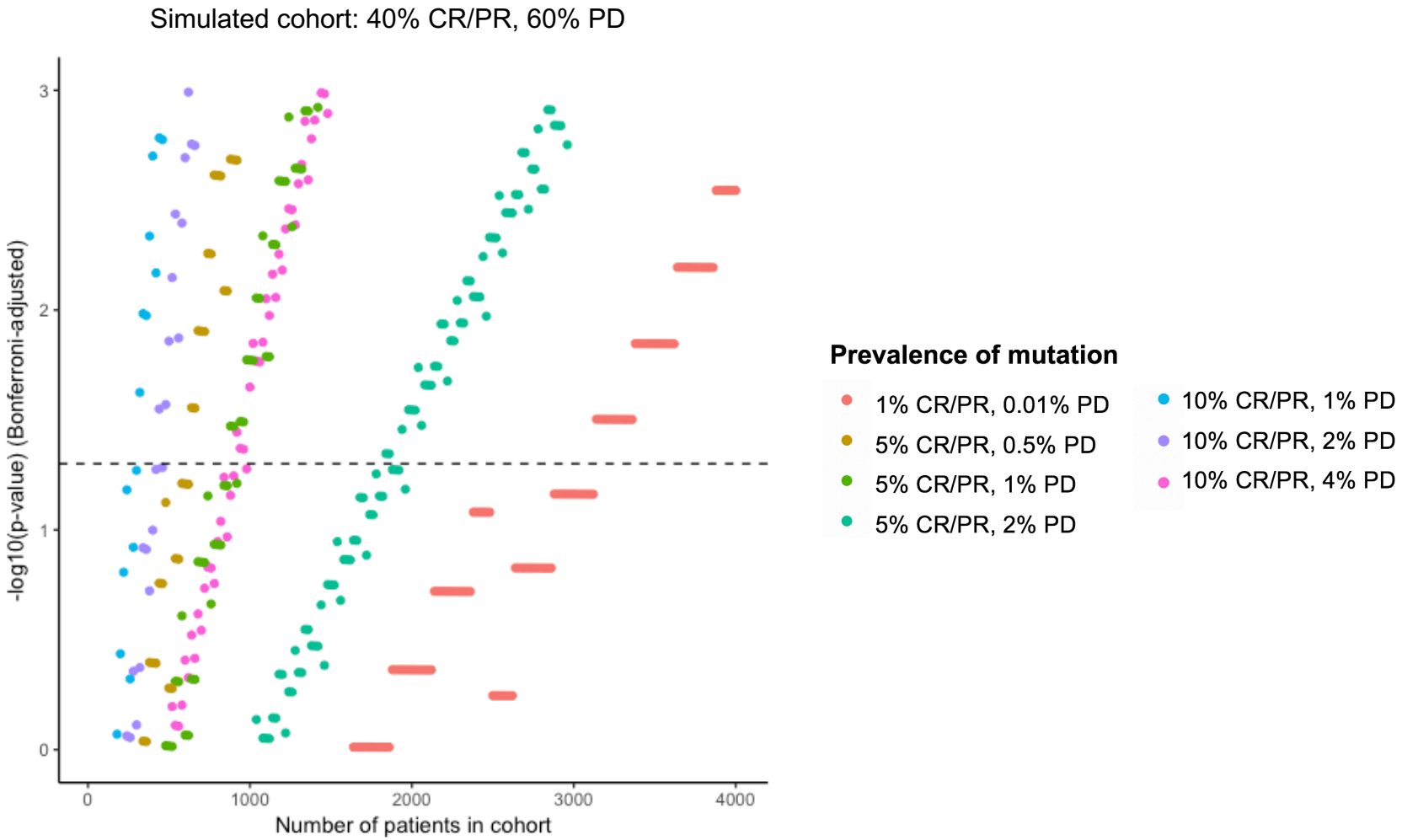
Larger, better annotated cohorts are needed

All of the models shown need validation in external datasets!



Miao, Margolis, Vokes et al *Nature Genetics* 2018

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Outline

- Existing ICI biomarkers and their role/limitations
- Landscape of novel genomic and molecular biomarkers
- Emerging challenges: treatment synergy and selecting combination therapies

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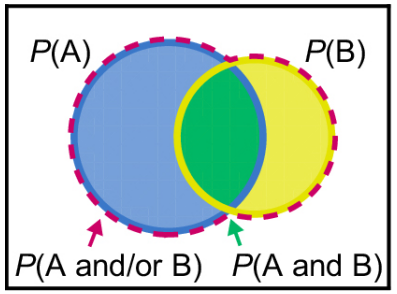
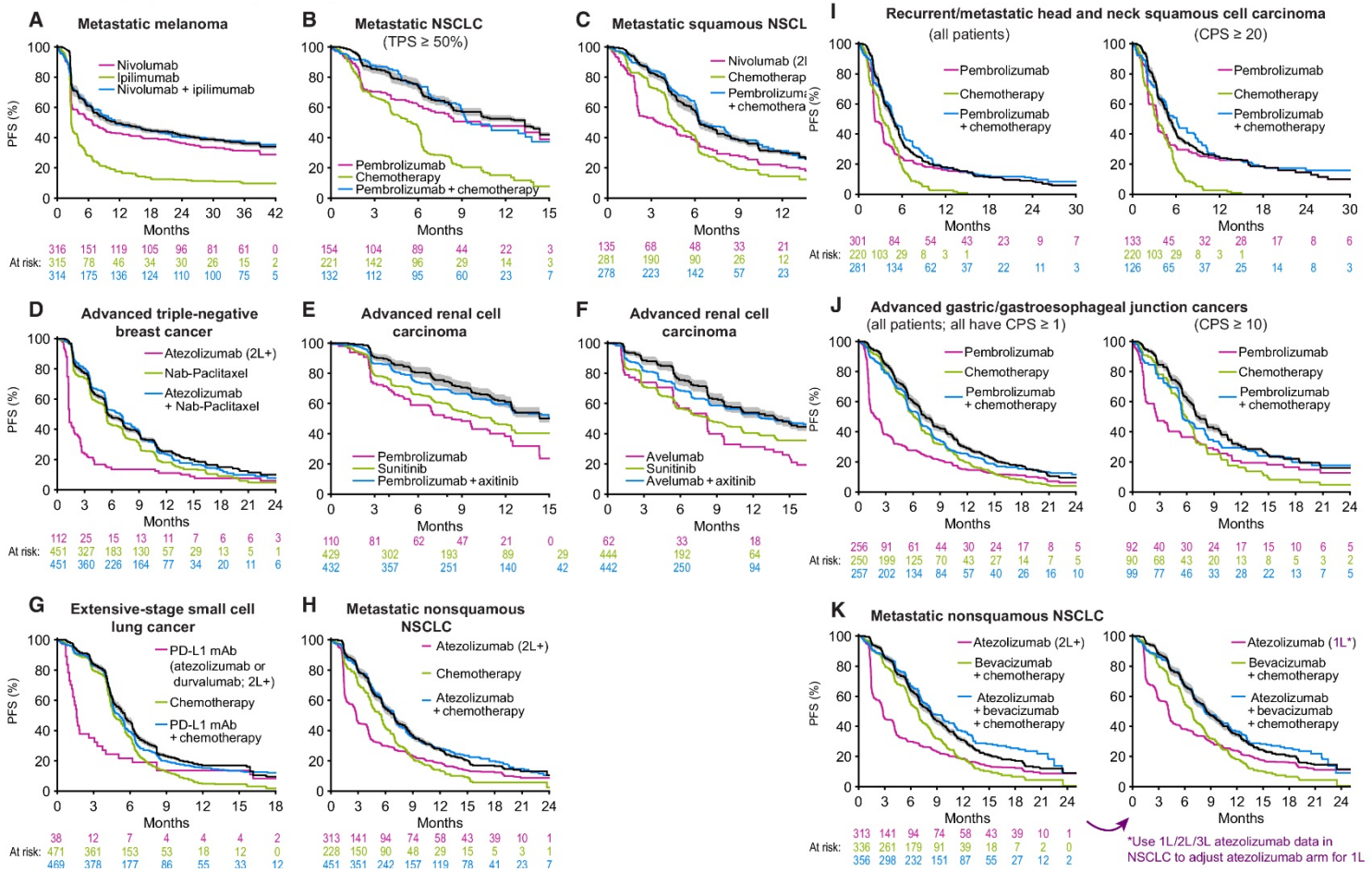
Understanding the role of combination therapy and identifying features to guide patient selection



If $P(B) > P(A \text{ and } B)$

$\Rightarrow P(A \text{ and/or } B) > P(A)$

$\Rightarrow$ Combination therapy can be superior to monotherapy via independent drug action [where combining A and B does not increase $P(A)$, $P(B)$]



Palmer et al, Clin Cancer Res. 2022

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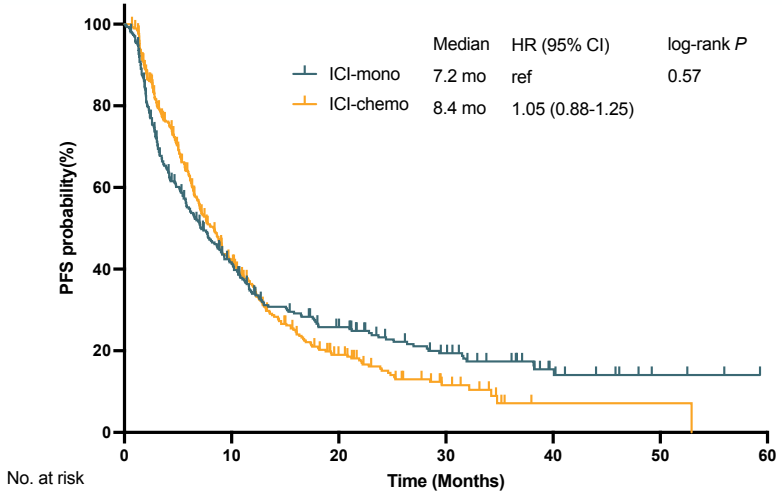
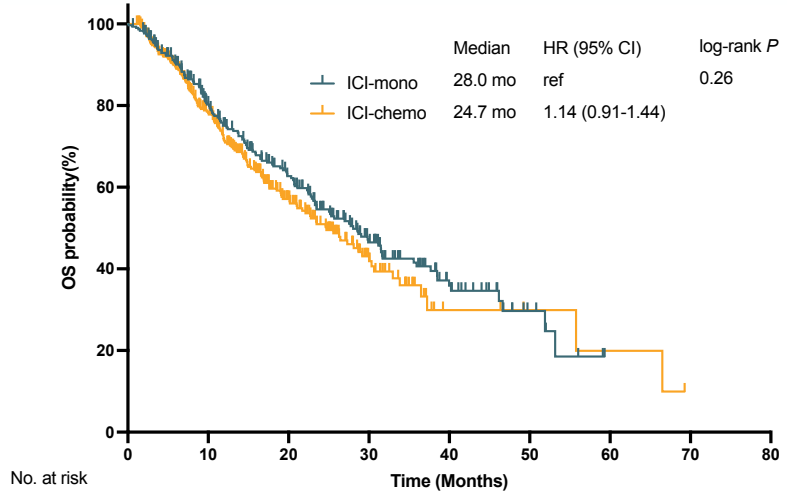
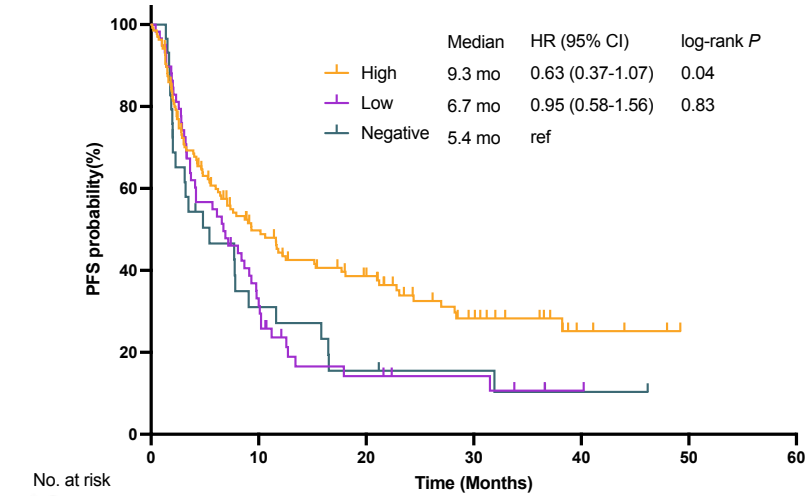
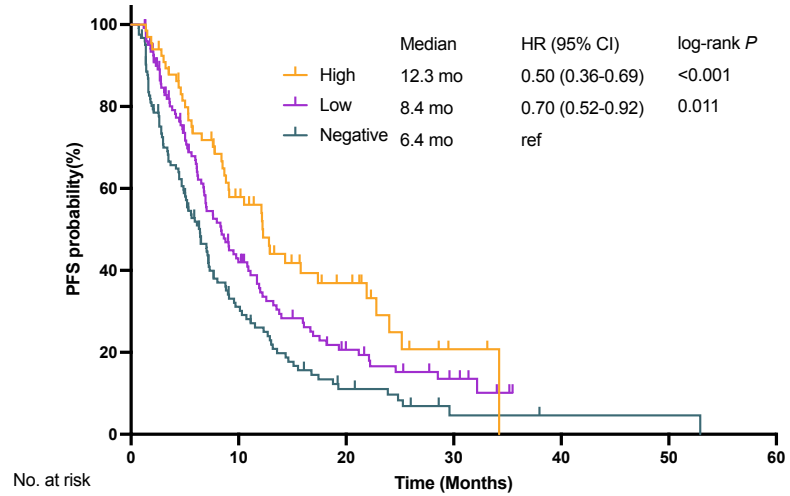
Minimal empiric evidence for long-term synergy









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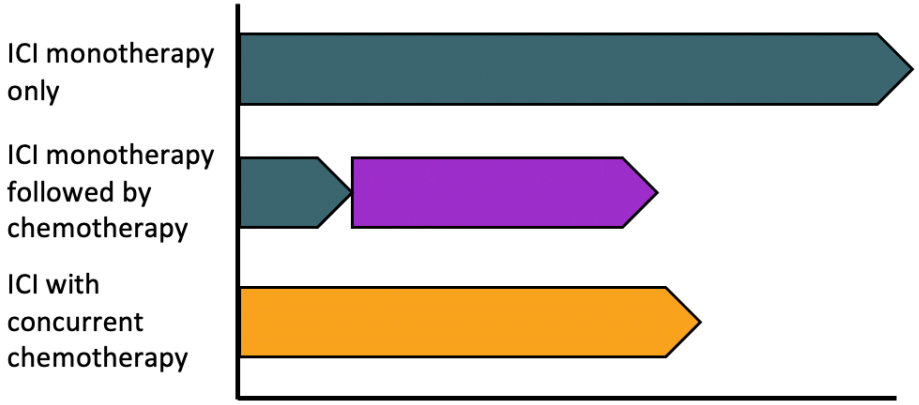
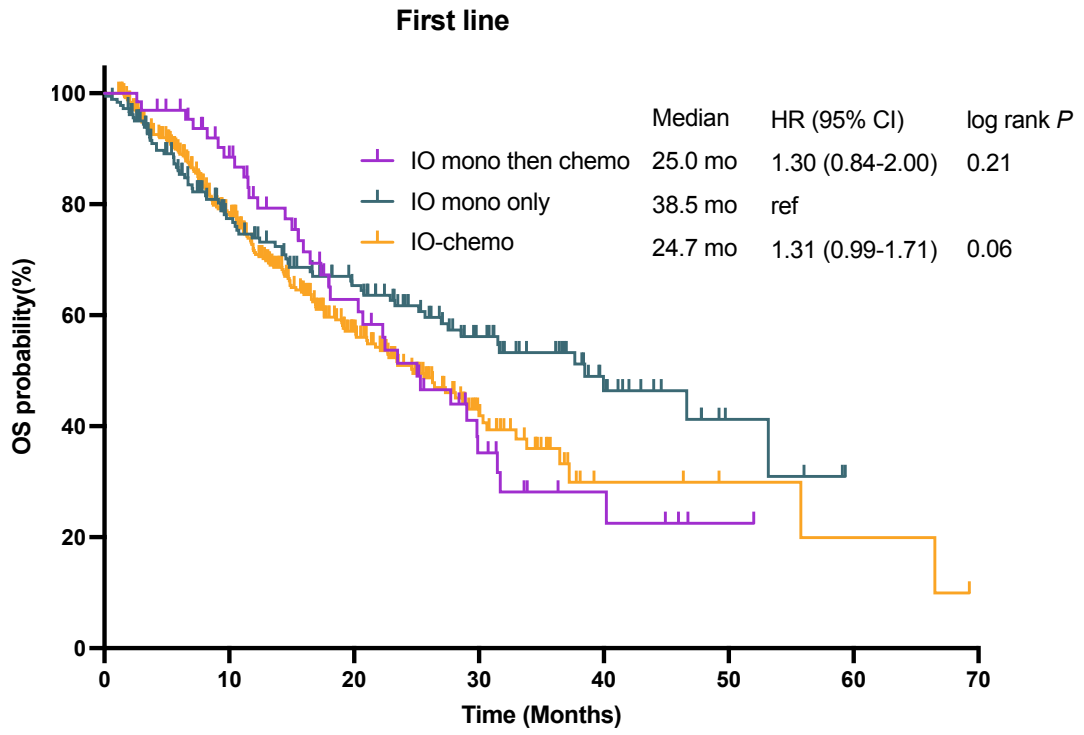
Hong et al, *under review*

Minimal empiric evidence for long-term synergy



A



No. at risk							
IO mono then chemo	65	51	29	13	5	2	0
IO mono only	183	111	78	44	18	5	0
IO-chemo	376	230	104	36	7	4	2

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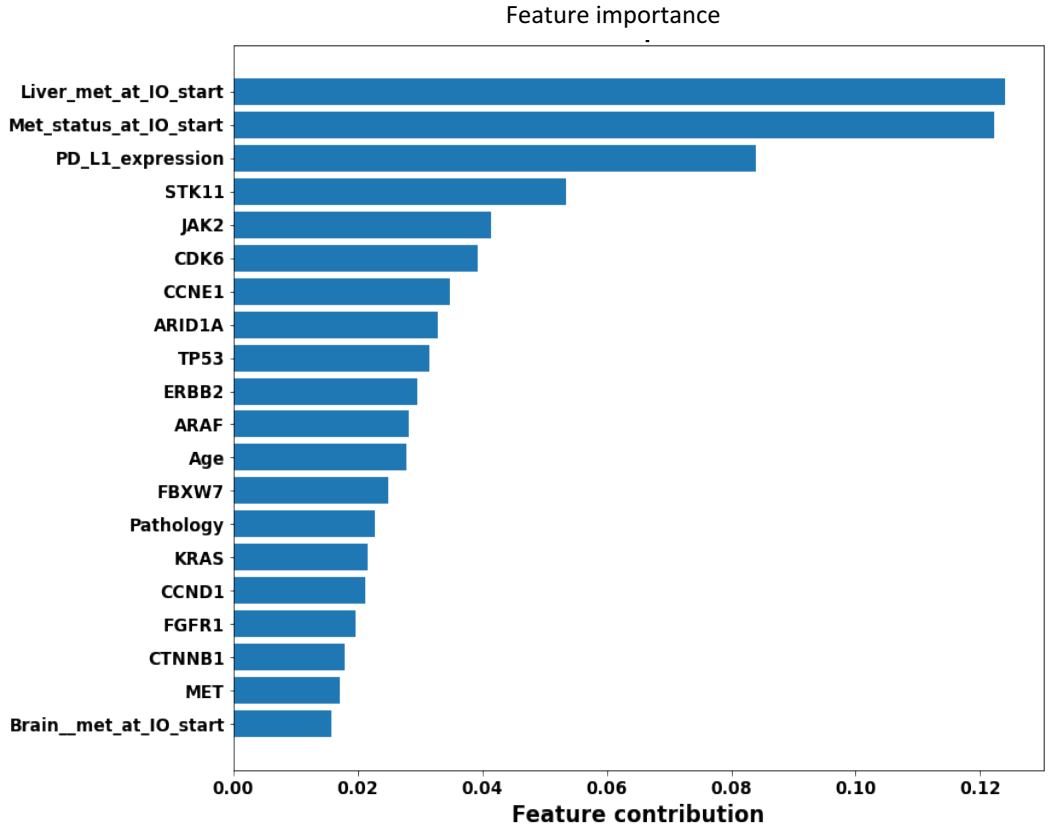
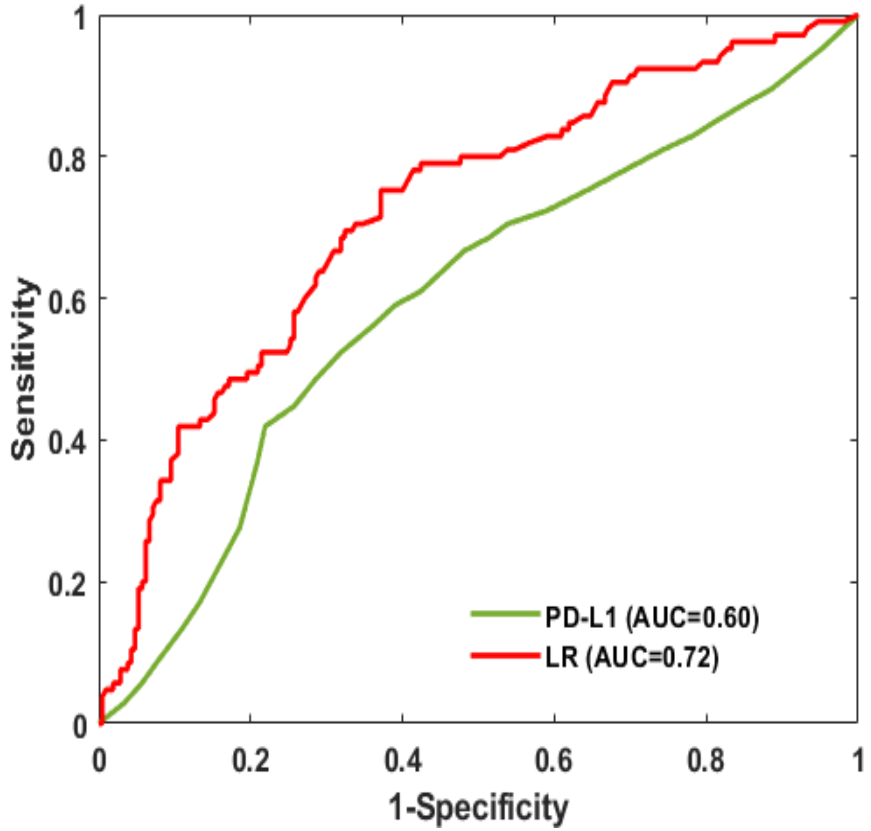
Identifying features to help select monotherapy vs combination therapy





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Conclusions

- TMB and other FDA-approved biomarkers have some but limited utility.
- Further investigations to identify new biomarkers and validate their clinical application will help advance precision immuno-oncology.
- Combination therapeutic approaches make is more challenging to disentangle the underlying biology, and careful analyses are needed to determine whether synergy or independent drug action is at play.
- Advanced computational approaches can help integrate multiple features into more sophisticated models, identify relevant biology, and ultimately may improve therapy

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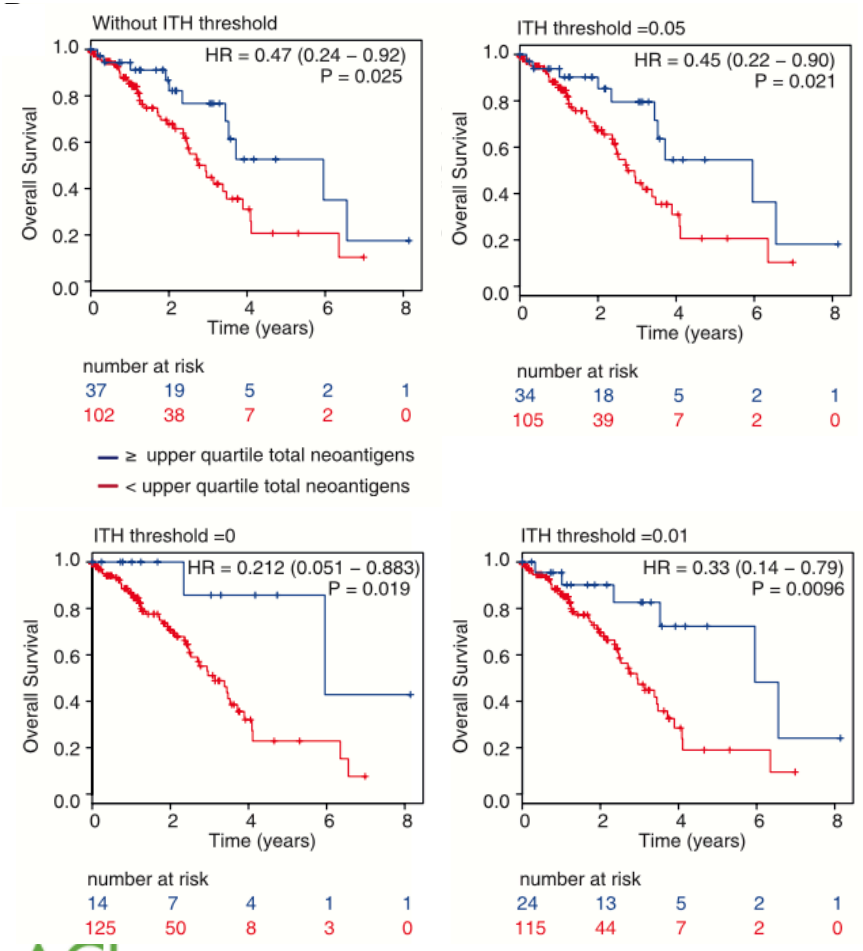
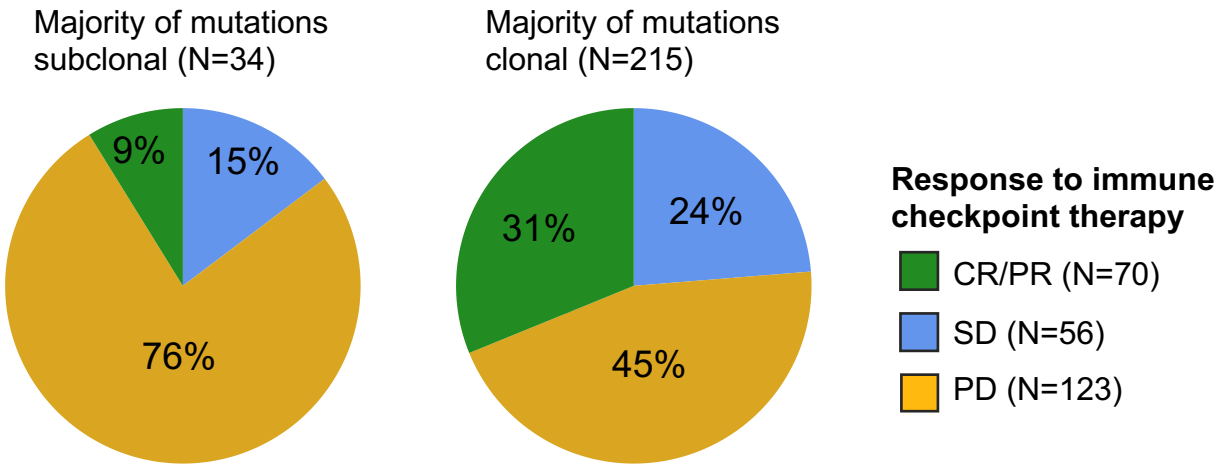
Mutation clonality modulates TMB response association





p-value = 0.0014

McGranahan et al, *Science* 2016
Miao, Margolis, Vokes et al *Nature Genetics* 2018

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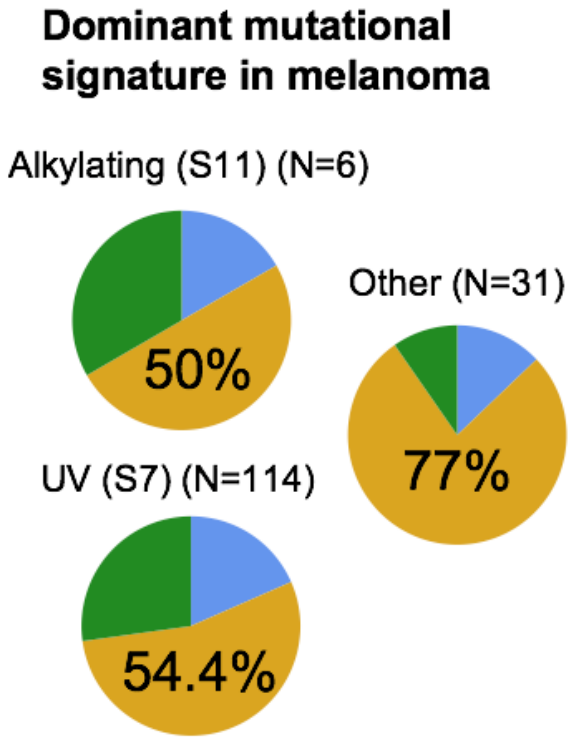
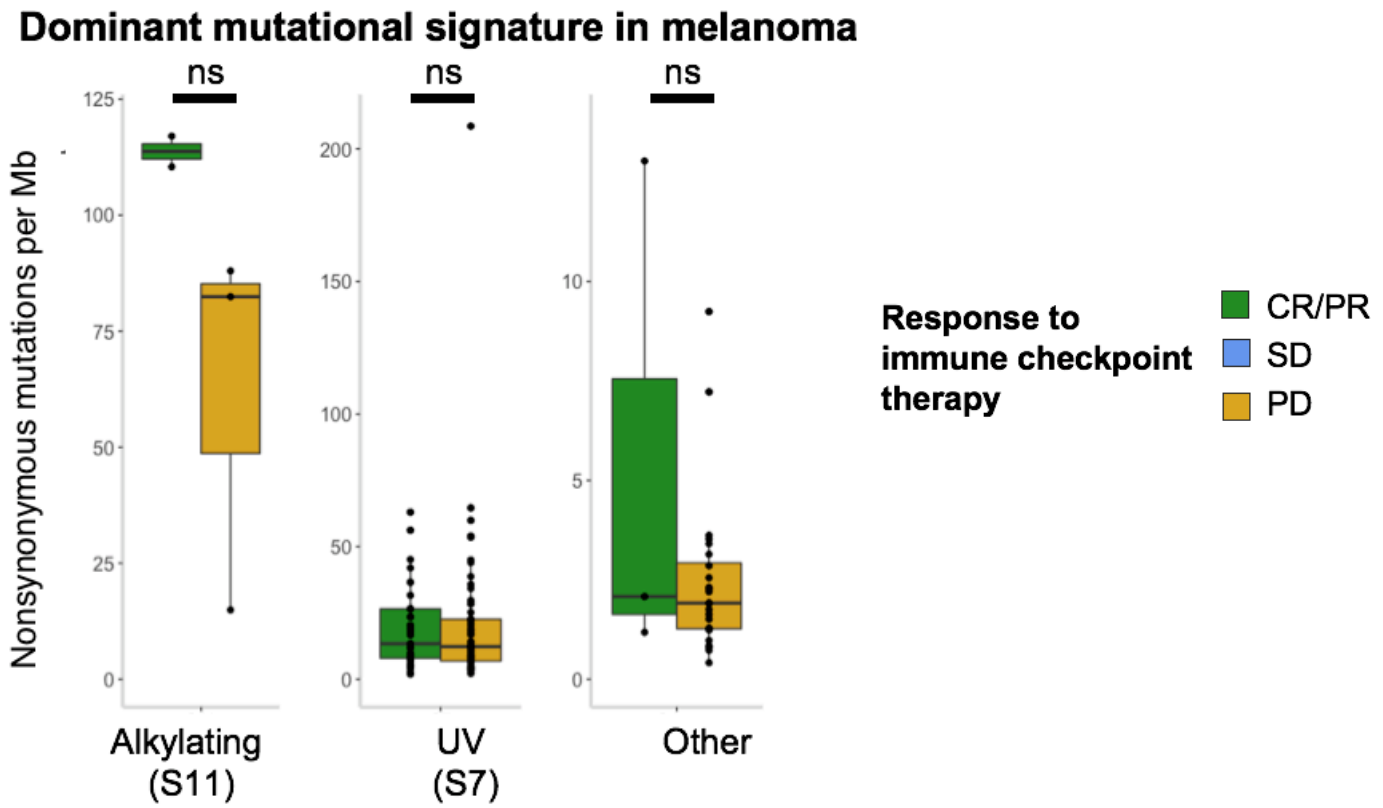
Mutational signature may also modulate TMB response association (in melanoma)





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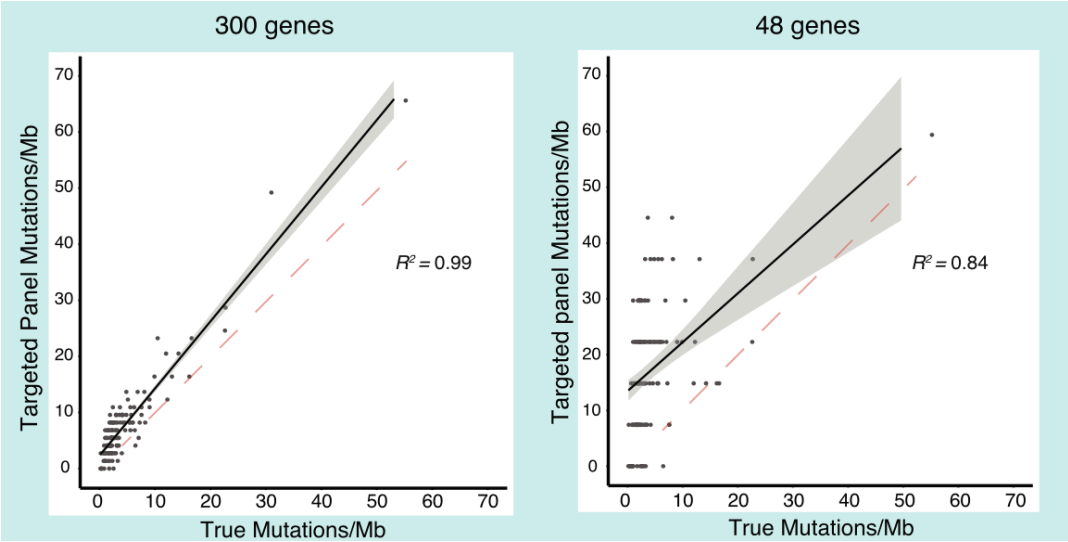
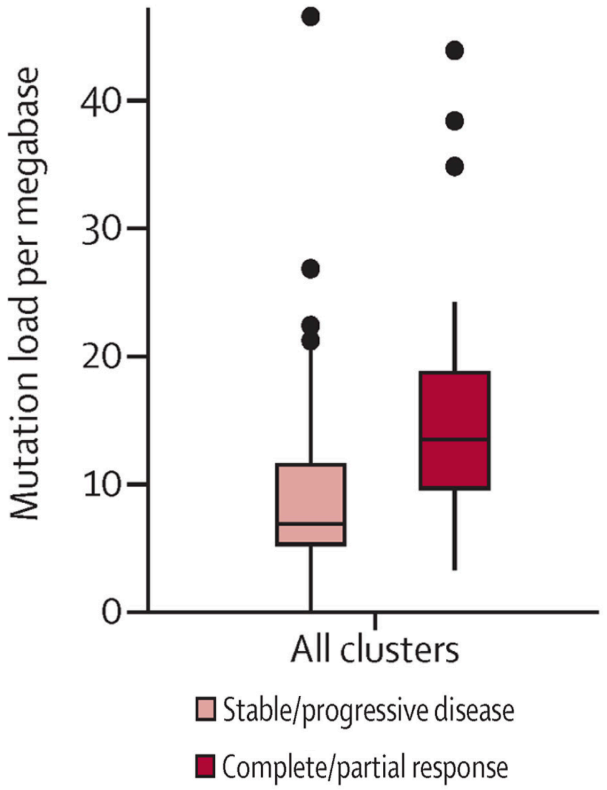
Miao, Margolis, Vokes et al *Nature Genetics* 2018

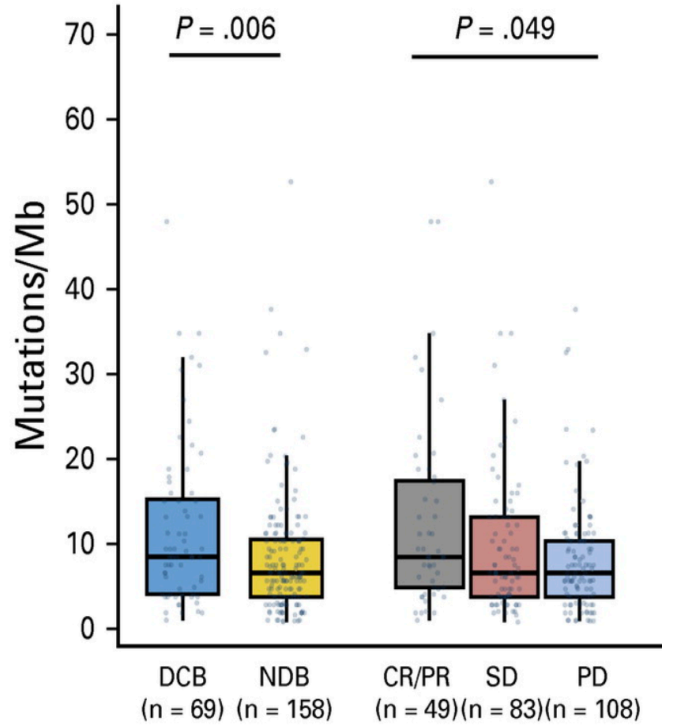
TMB calculated from NGS panels associates with response



TMB from NGS panels ≥ 300 genes correlates with WES



PD-L1 Ab bladder cancer sequenced via FoundationOne



PD-(L)1 Ab NSCLC sequenced via MSK-IMPACT

Garofalo et al, Genome Med 2016
Rosenberg et al, Lancet 2016
Rizvi et al, JCO 2018

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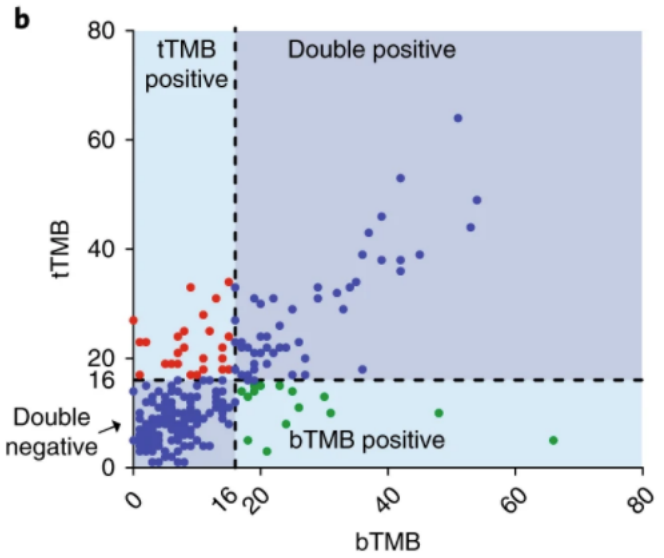
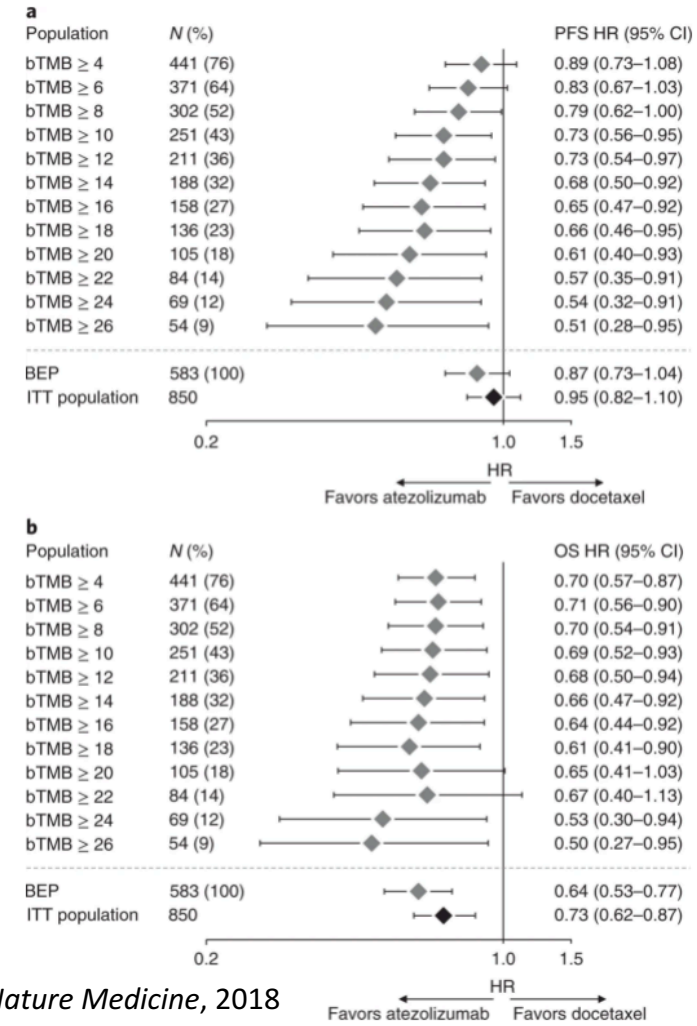
ctDNA-based assays – bTMB similar to tTMB

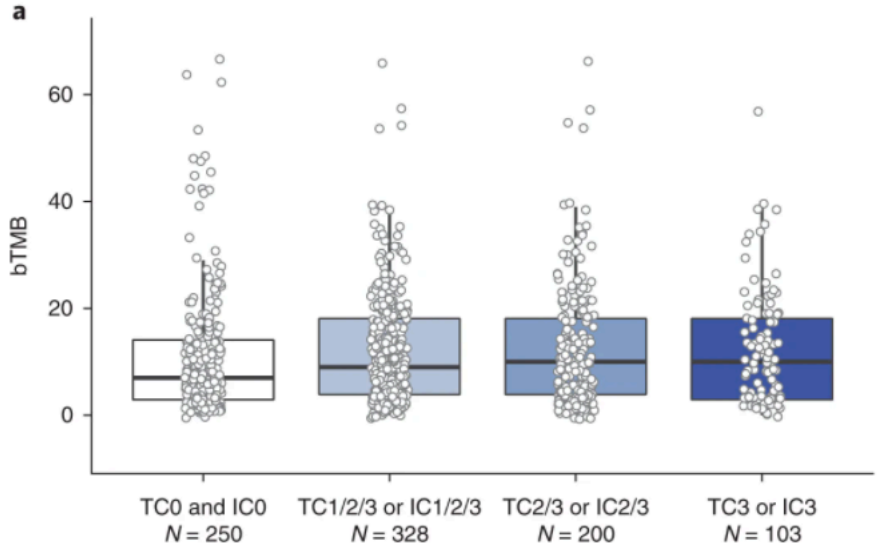
bTMB correlates with tTMB



Increasing bTMB cut-offs associate with improved outcomes



bTMB and PD-L1 are orthogonal



Gandera et al, *Nature Medicine*, 2018

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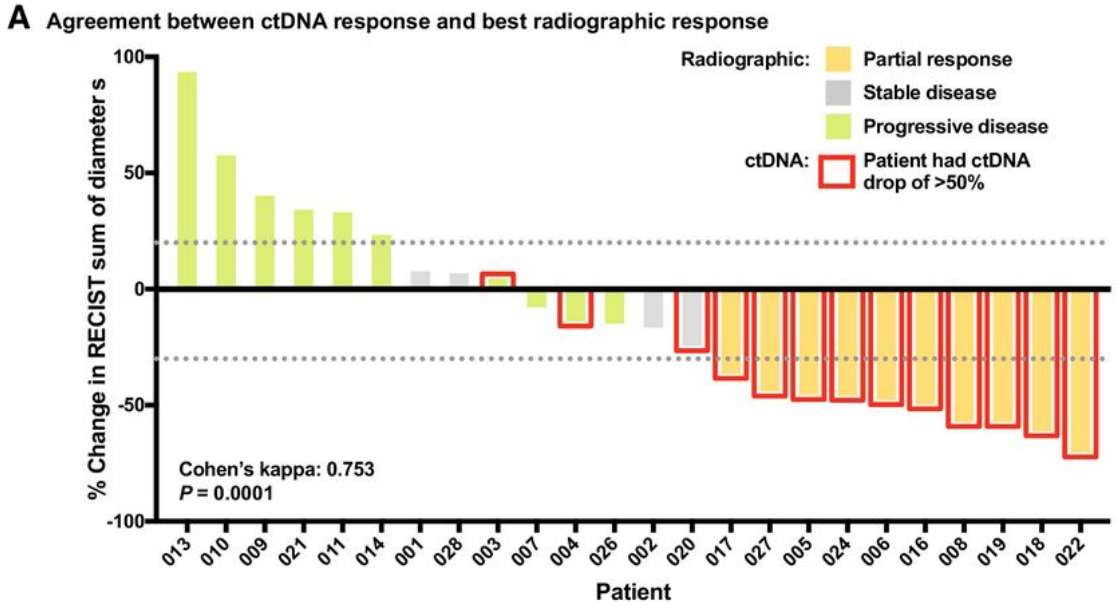
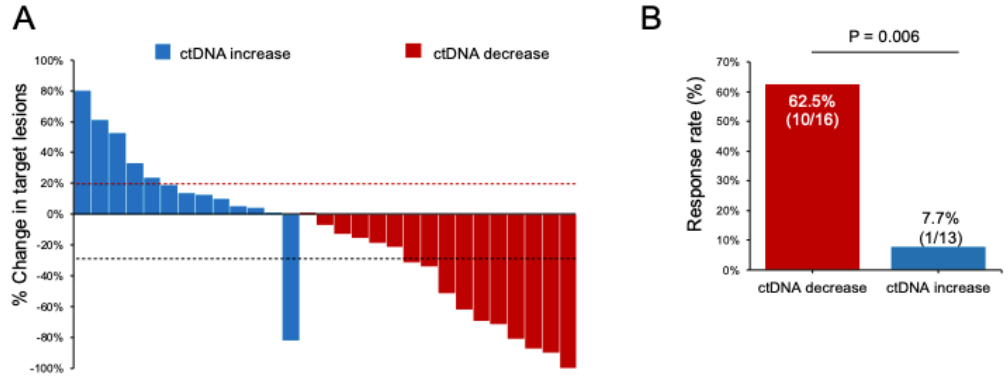
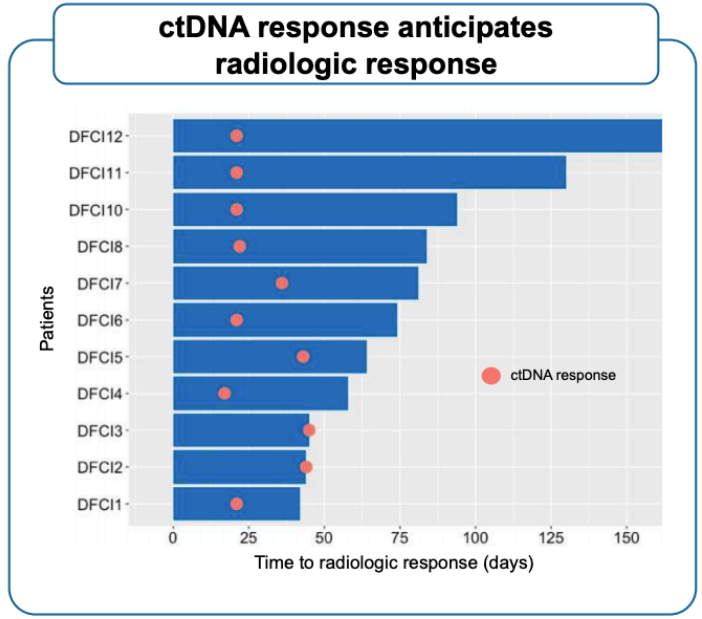
ctDNA-based assays – response dynamics







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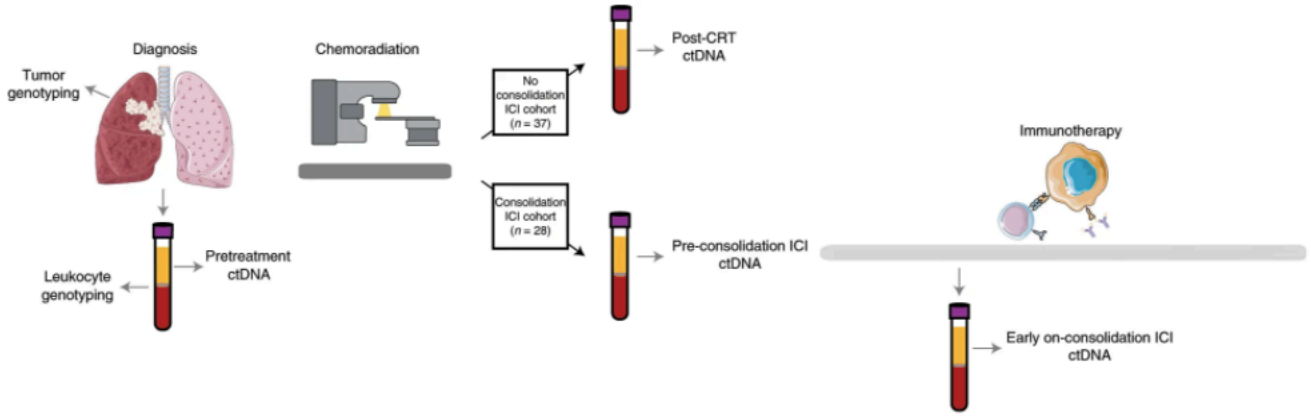
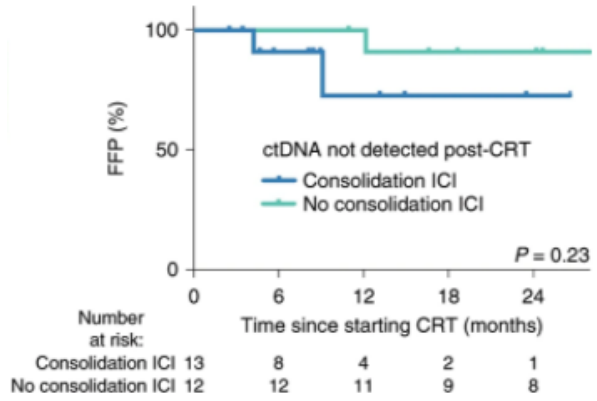
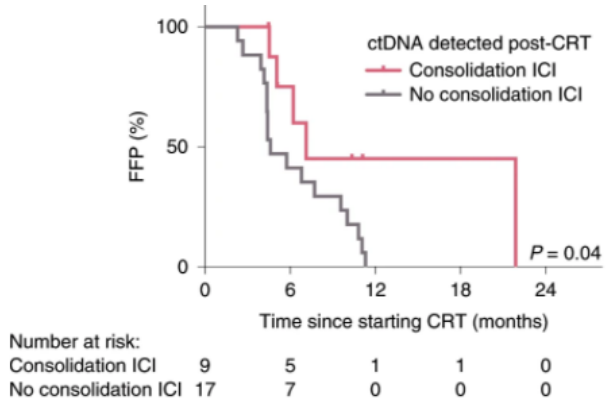
Goldberg et al, *Clin Cancer Research*, 2018
Ricciuti et al, *JCO suppl*, 2020

ctDNA for treatment intensification – proof of principal in locally advanced NSCLC

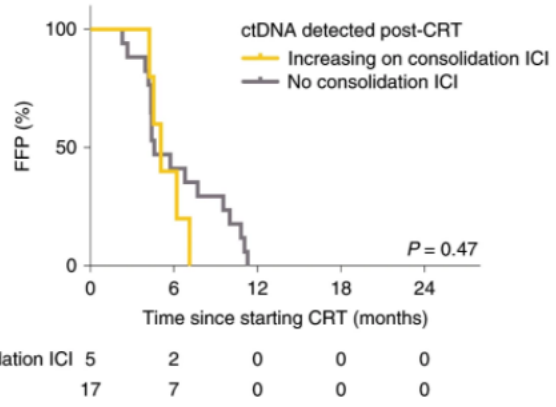




Minimal/negative benefit from consolidation in ctDNA negative samples



Consolidation ICI improves outcome in ctDNA positive samples



Pts with increased ctDNA on adjuvant ICI do as badly as those who do not receive adjuvant therapy

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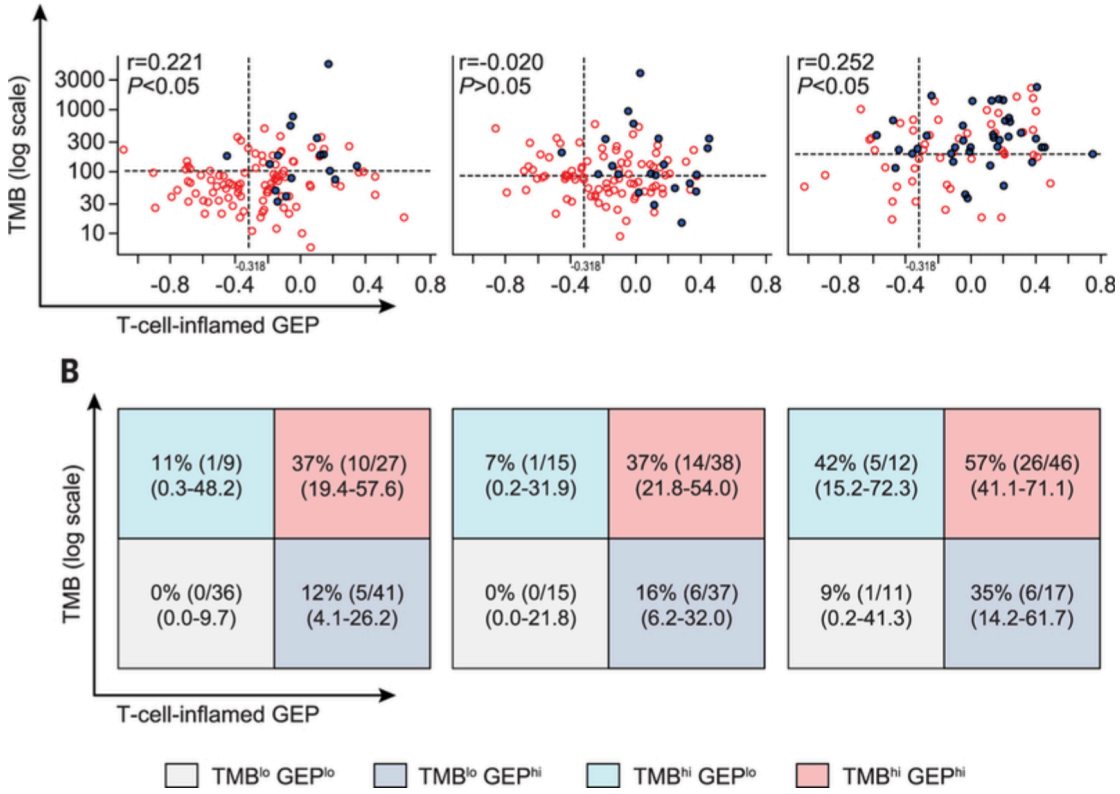
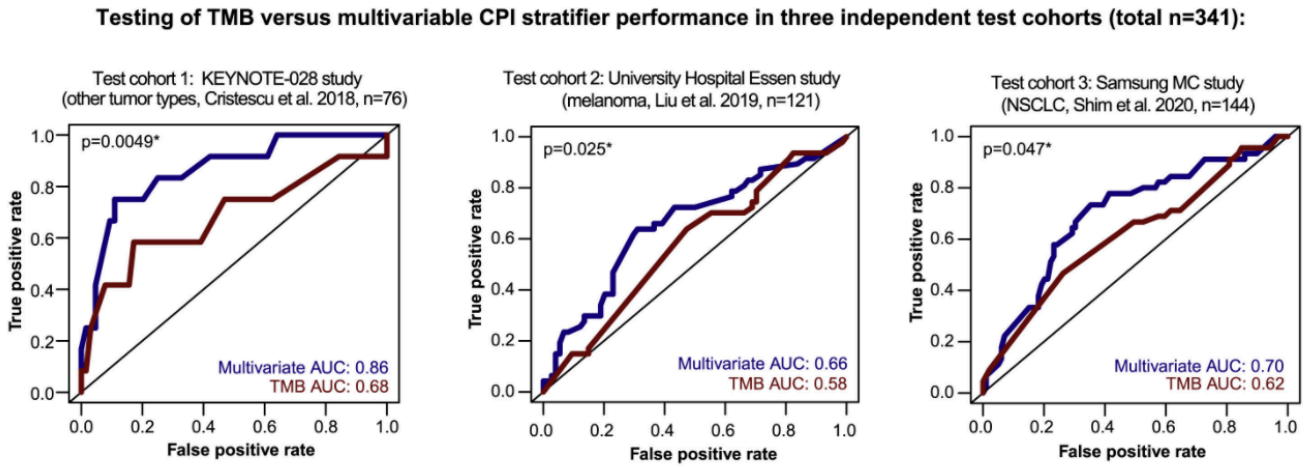
Moding et al, *Nature Cancer* 2020

Genomic + transcriptomic signatures may integrate orthogonal biologies





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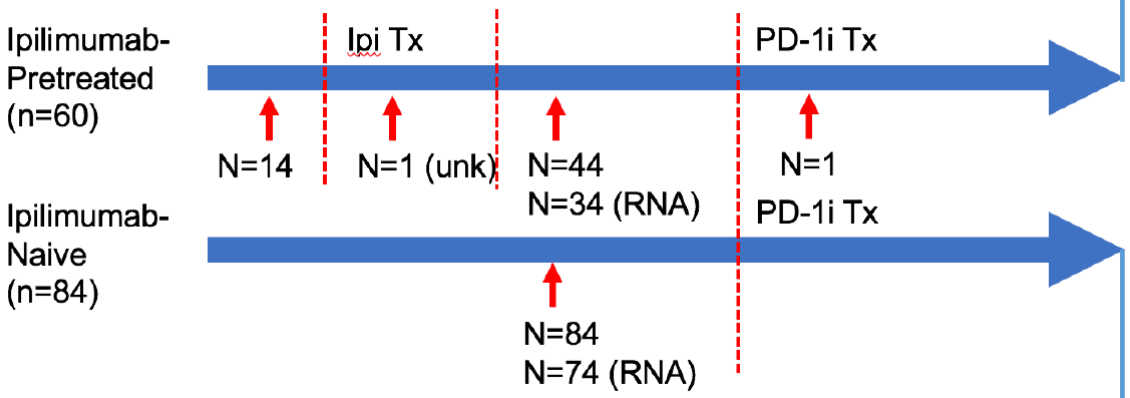
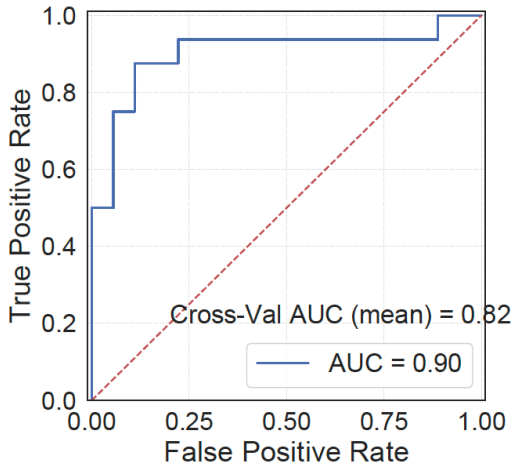
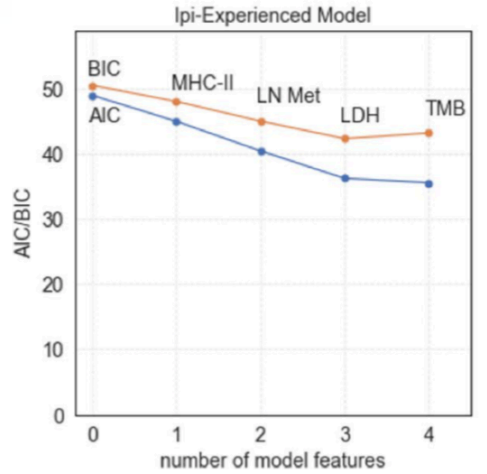
Cristescu et al, *Science* 2018
Litchfield et al, *Cell*, 2021

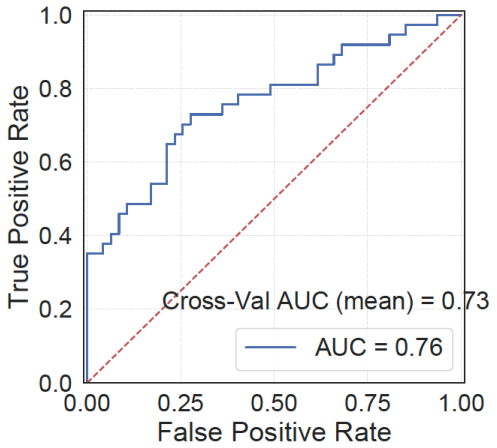
From biology to prediction using context sensitive, multi-modal features



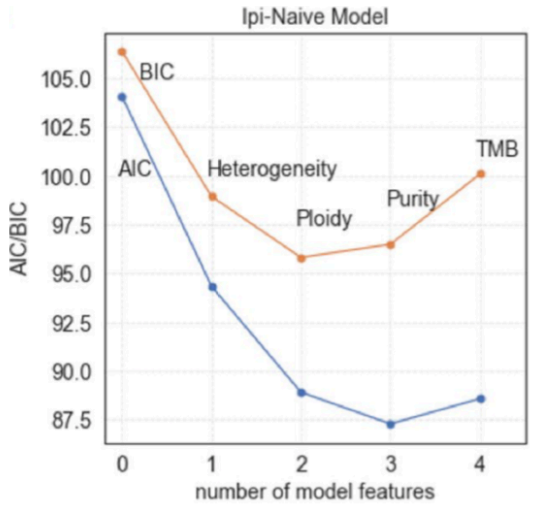


(MHC-II, LN Met, LDH)





(heterogeneity, ploidy, purity)



Liu et al, *Nature Medicine*, 2019

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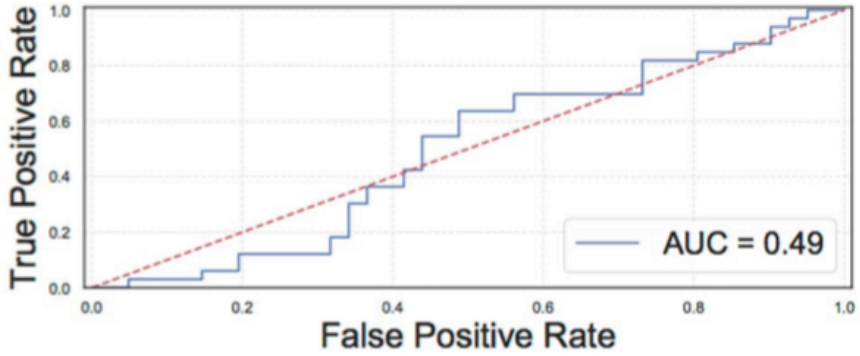
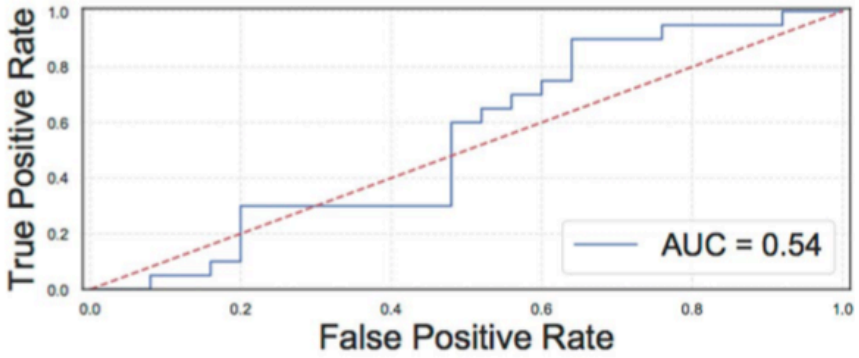
Observations

- TMB did not emerge as a feature of interest in either model (genetic features minimally useful)
- Clinical features may be important but are often unavailable
- Cohorts are limited (few clinically and molecularly characterized cohorts) and more validation is needed
- Models still need to be informed by biology

Ipi-treated model applied to ipi-naïve group



Ipi-naïve model applied to ipi-treated group



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Liu et al, *Nat Medicine*, 2019