Precision medicine in the era of comprehensive genomic profiling

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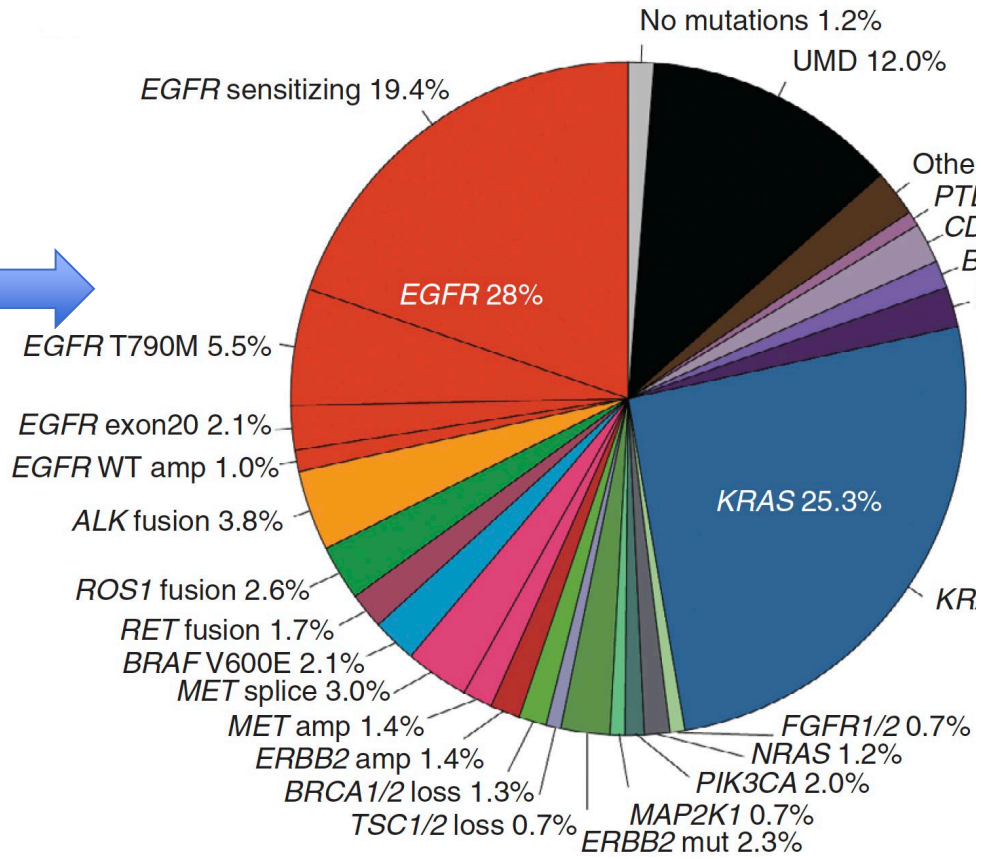
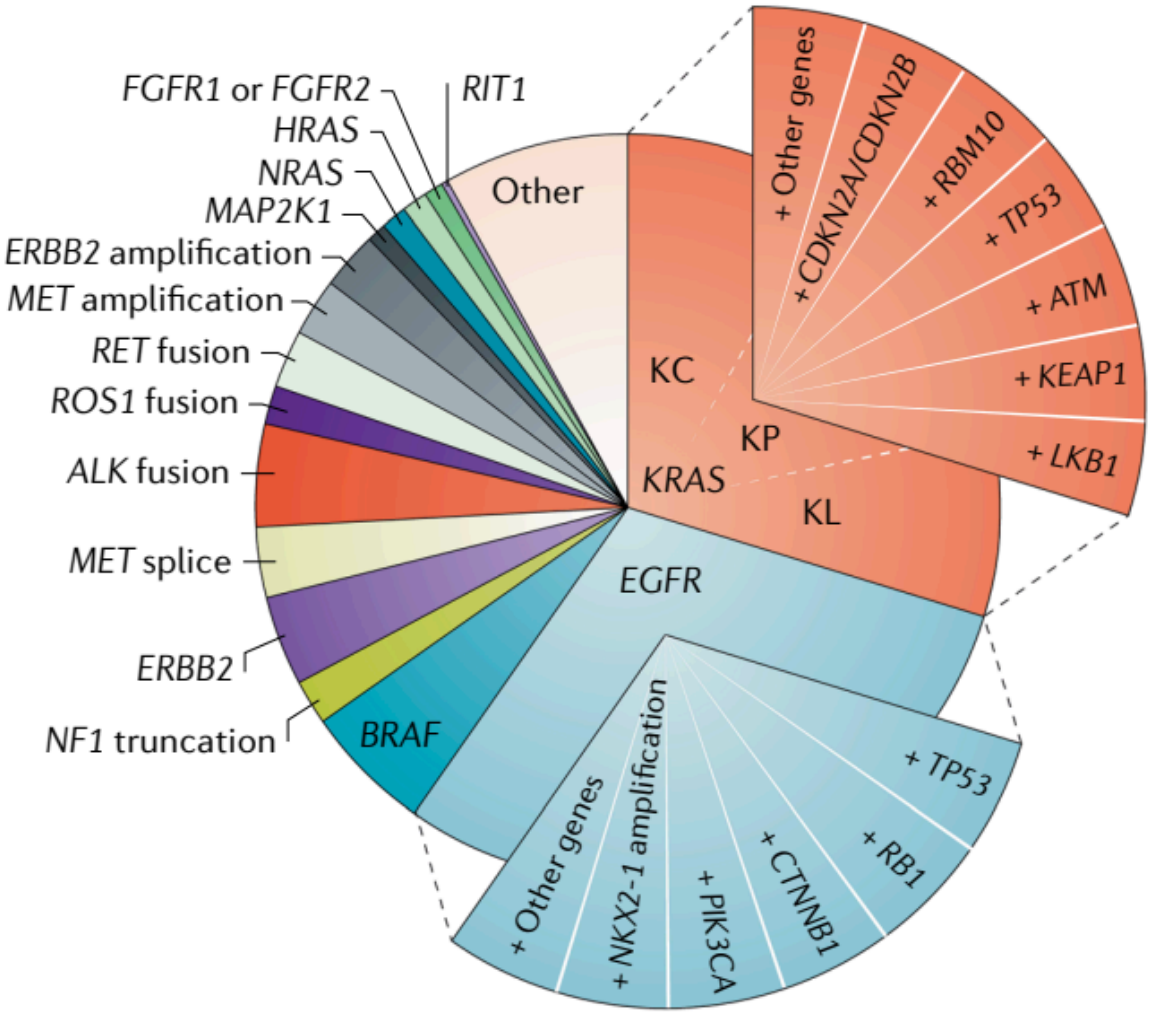
Clinically actionable drivers are on the rise

The number of drivers has risen in lung adenocarcinomas

2000



Jordan et al, *Cancer Discov* 2017

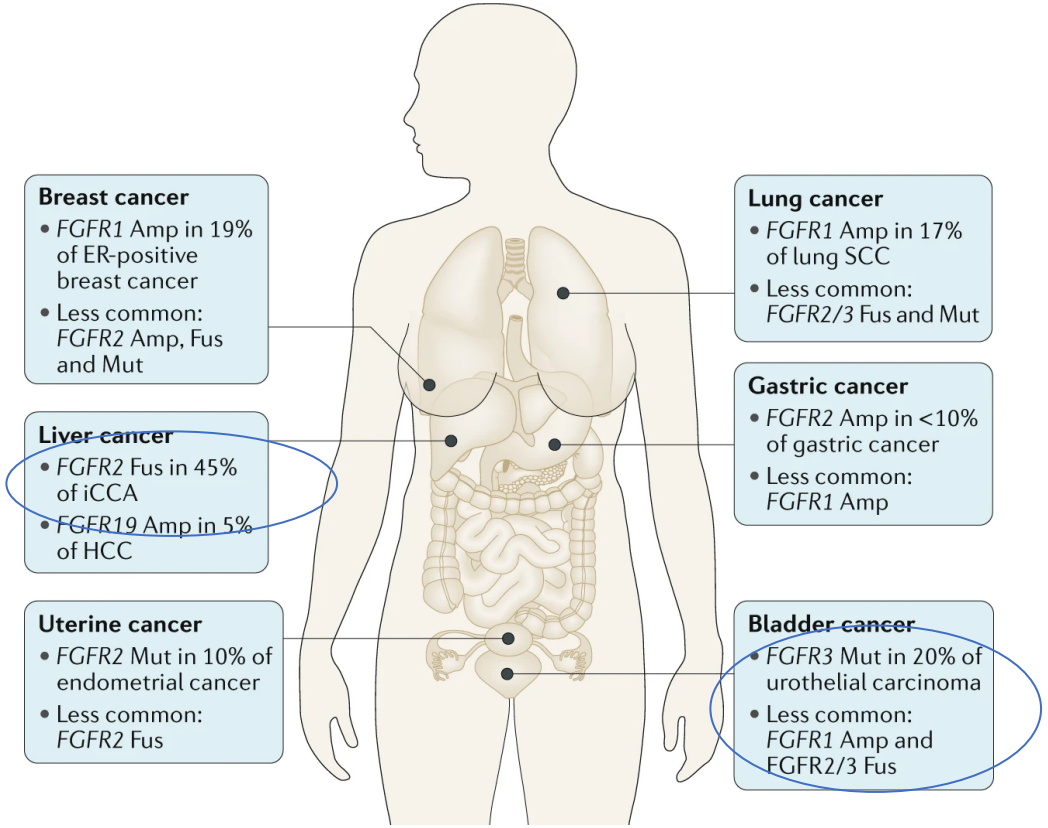


Skoulisdis et al, *Nat Rev Cancer* 2019

A rise in targetable drivers in other cancer types

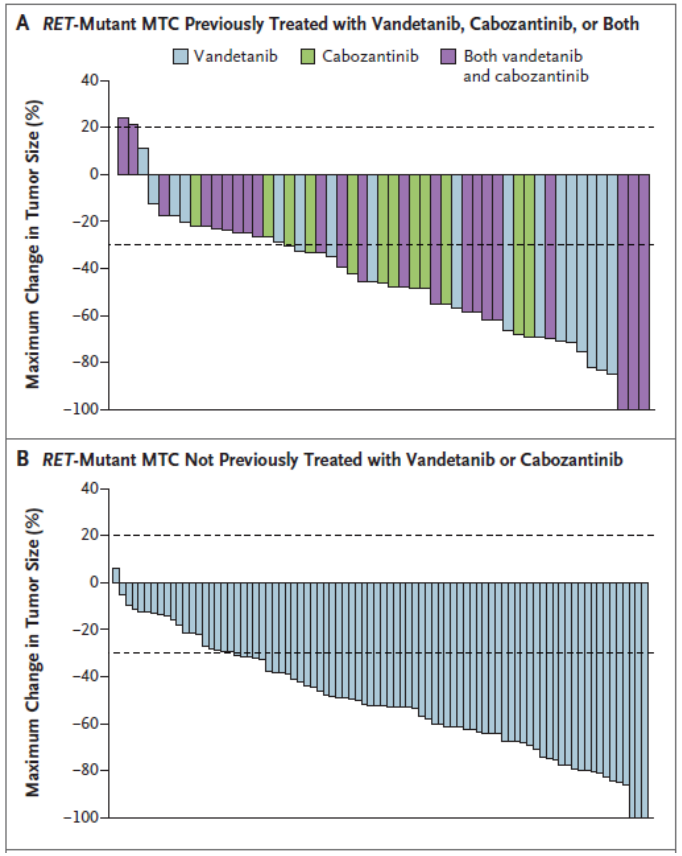
FGFR-dependent cancers

- Erdafitinib (pan-FGFR): urothelial cancers
- Pemigatinib (FGFR1-3): cholangiocarcinoma



RET-dependent cancers

- Selitrectinib: *RET*-mutant medullary thyroid cancers
- Pralsetinib: *RET* fusion-positive lung cancers



Loriot et al, *N Engl J Med* 2019; Abou-Alfa et al, *Lancet Oncol* 2020; Drilon et al, *N Engl J Med* 2020; Wirth et al, *N Engl J Med* 2020

TRK inhibitors approved in a tumor-agnostic fashion for adult and pediatric cancers with *NTRK* fusions

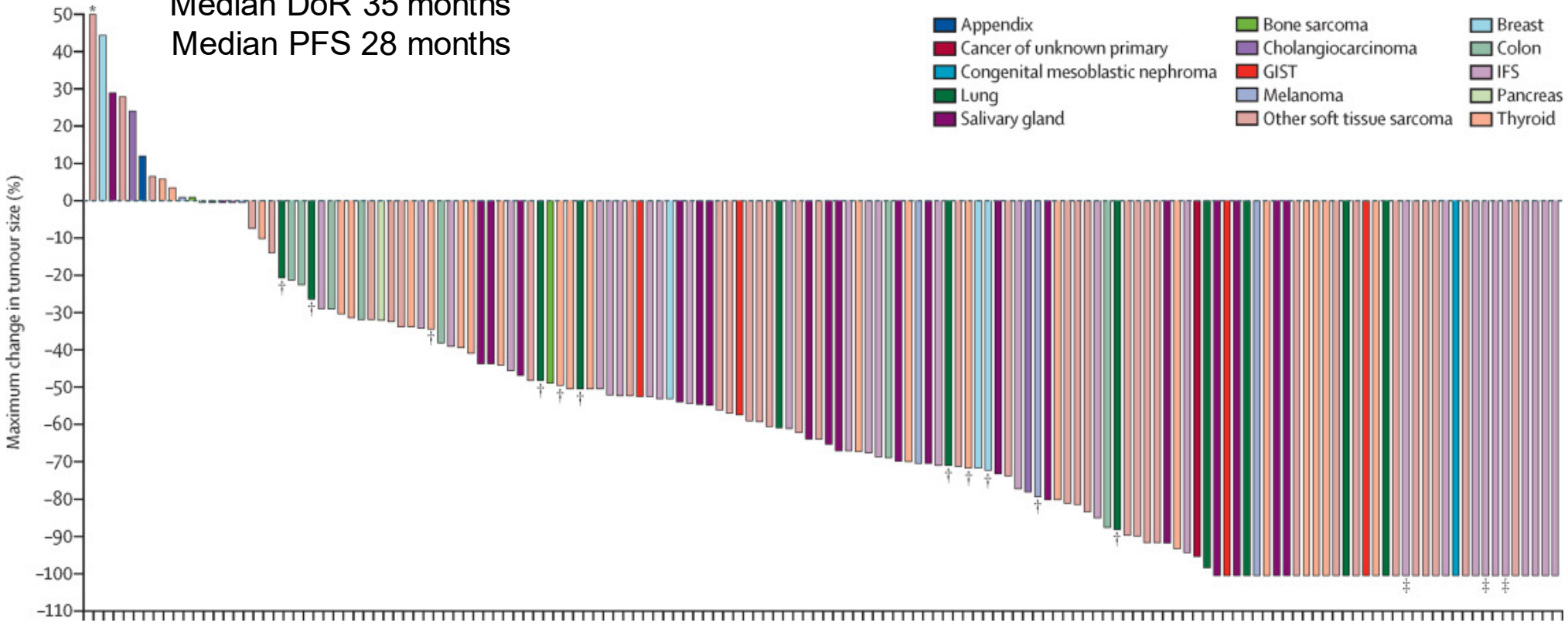
Larotrectinib

ORR 79%

(95% CI 72-85%, n=159)

Median DoR 35 months

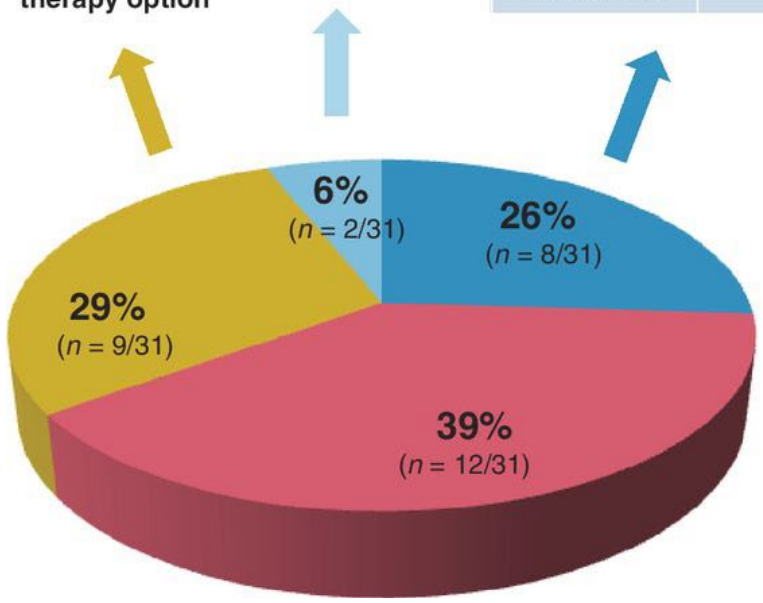
Median PFS 28 months



Hong et al, *Lancet Oncol* 2020

Diagnostic migration toward increasingly comprehensive sequencing approaches

Next-gen sequencing identifies clinically relevant alterations missed by "piecemeal" sequencing



Genomic alteration with targeted therapy in NCCN guidelines	Tumor from same procedure as tumor subjected to non-NGS testing	Patient's clinical course
EGFR G719A	Yes	Recently started erlotinib, response evaluation pending
BRAF V600E	Yes	Subsequently passed away
SOCS5-ALK	Yes	**Disease shrinkage (<30%) with crizotinib**
HIP1-ALK	Yes	**Partial response to crizotinib**
CD74-ROS1	Yes	Recently started crizotinib, response evaluation pending
KIF5B-RET	Yes	**Partial response to cabozantinib**
KIF5B-RET	No	**Disease shrinkage (<30%) with cabozantinib**
CCDC6-RET	Yes	Candidate for cabozantinib after progression on chemotherapy

Genomic alteration with targeted agent available on or off a clinical trial	Targeted therapeutic (clinicaltrials.gov number) with potential activity available at institution
CDKN2A loss	CDK4/6 inhibitor (NCT01237236)
EGFR L747P	erlotinib, afatinib
EGFR exon 18 del (*n* = 2)	pan-ERBB inhibitor (NCT01858389)
EGFR exon 20 ins	pan-ERBB inhibitor (NCT01858389)
ERBB2 L755F	pan-ERBB/mTOR inhibitor (NCT01953926)
FGFR1 T141R	FGFR inhibitor (NCT01948297)
KRAS G12C	ERK inhibitor (NCT01781429)
KRAS Q61H	ERK inhibitor (NCT01781429)
MDM2 amp (*n* = 3)	MDM2 inhibitor (NCT01877382)

Benayed et al, *Clin Cancer Res* 2015

NGS *decreases* care costs compared to smaller panels

- newly diagnosed with mNSCLC → genomic alteration tests compared (*EGFR/ALK/ROS1/BRAF/MET/HER2/RET/NTRK1*)
  - upfront NGS (all alterations tested simultaneously plus *KRAS*)
  - sequential testing (sequence of single-gene tests)
  - exclusionary testing (*KRAS* + sequential testing)
  - hotspot panels (*EGFR/ALK/ROS1/BRAF* tested simultaneously + single-gene tests or NGS for *MET/HER2/RET/NTRK1*

TABLE 3. Total Cost and Cost Difference Versus NGS

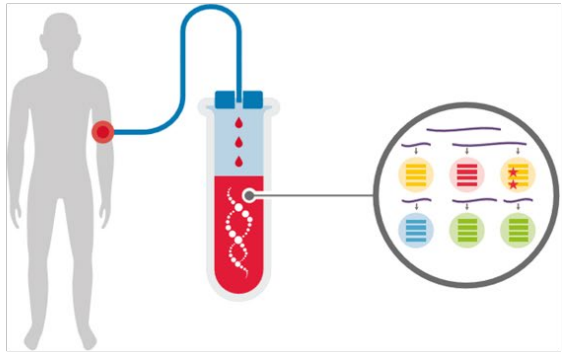
	Medicare-Insured Patients (n = 2,066)		Commercially Insured Patients (n = 156)	
Testing Strategy	**Total Cost**	**Cost Difference *v* NGS**	**Total Cost**	**Cost Difference *v* NGS**
NGS	2,190,499	—	620,369	—
Sequential	3,721,368	1,530,869	747,771	127,402
Exclusionary	3,584,177	1,393,678	624,178	3,809
Hotspot panel	4,331,295	2,140,795	871,211	250,842

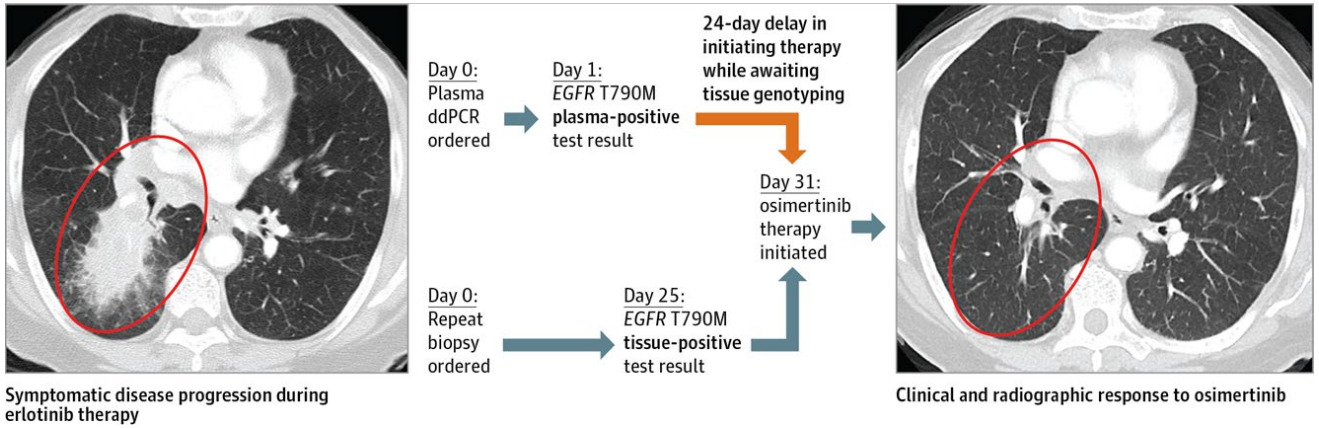
NOTE. Costs are given in 2017 US dollars.

*although **unit cost** of NGS was higher than individual single-gene tests, **overall cost** (included testing and rebiopsy cost) was the lowest for NGS

Pennel et al, *J Clin Oncol Precis Med* 2017

Liquid biopises complement tumor tissue sequencing and can effectively match patients to therapies



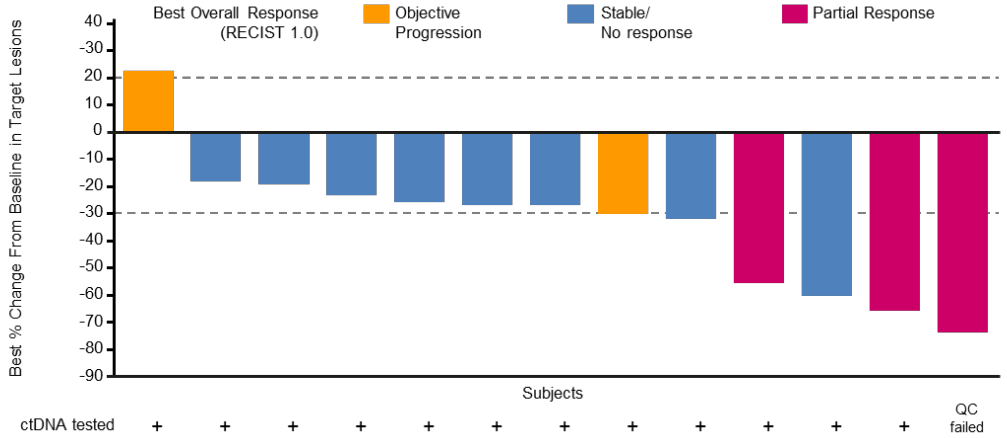


Symptomatic disease progression during erlotinib therapy

Clinical and radiographic response to osimertinib

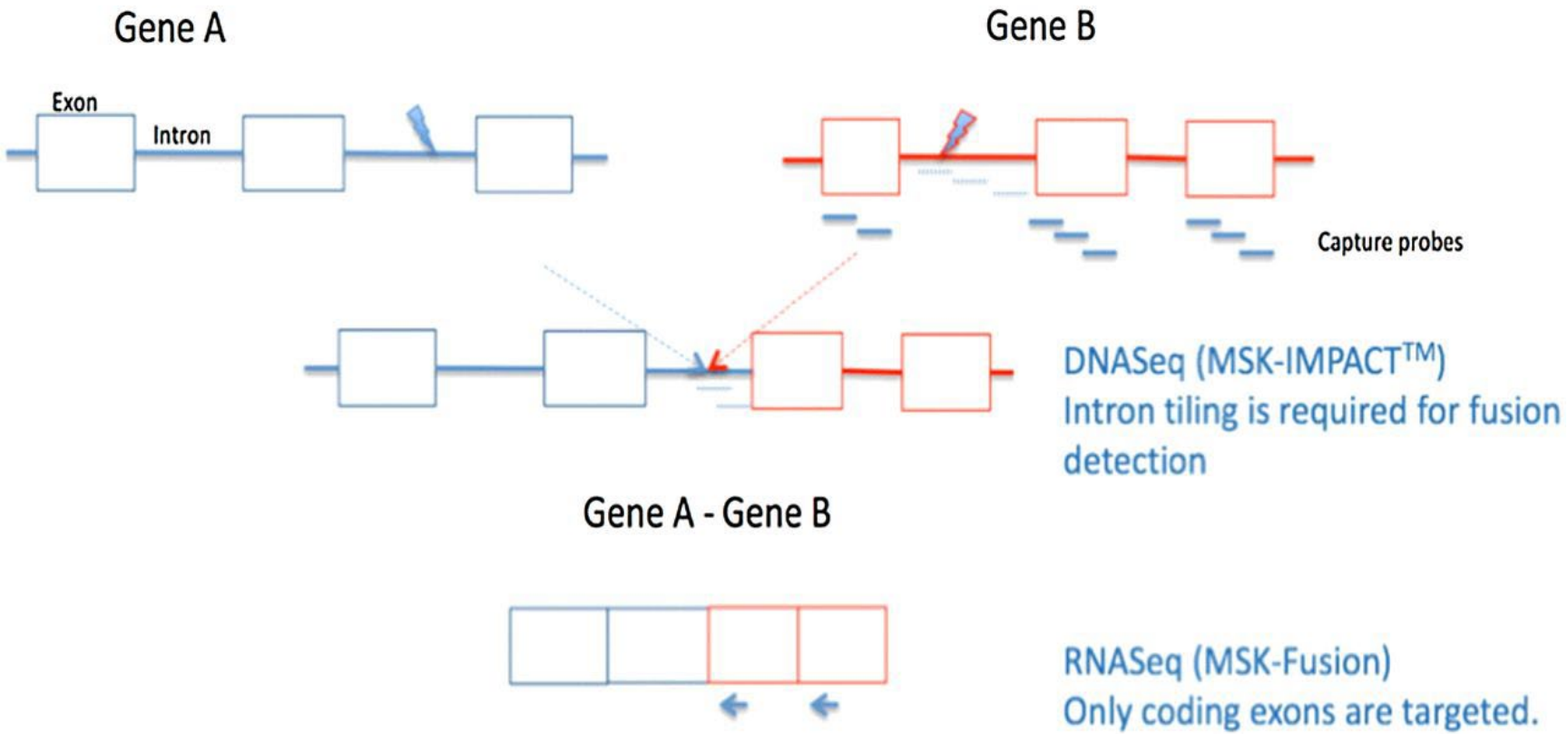
Crizotinib in *MET* exon 14-altered NSCLCs (ctDNA cohort)

Best Percent Change from Baseline in Size of Target Lesions in ctDNA Cohort in Patients with Measurable Disease (n=13)*



Sacher et al, *JAMA Oncol* 2016; Drilon et al, *Nat Med* 2020

Fusion detection by DNA vs. RNA-based NGS

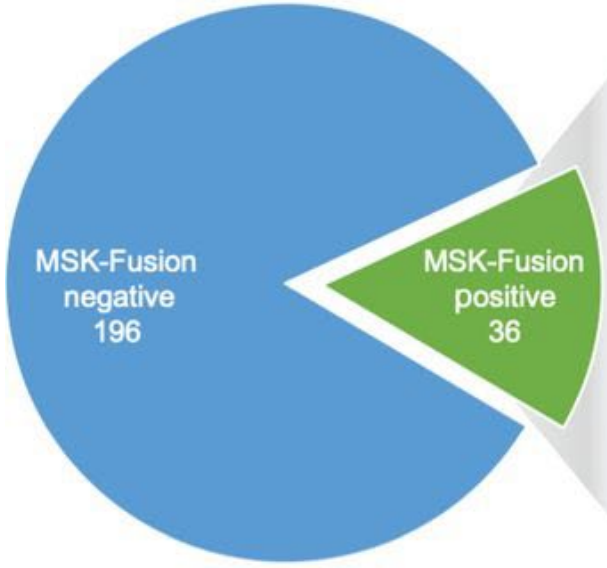


Large intronic regions (e.g. *NTRK2* and *NTRK3*) and **repetitive elements at fusion breakpoints** (e.g. *ROS1*) make even the best DNA-based hybrid capture assays suboptimal at capturing all actionable genomic events.

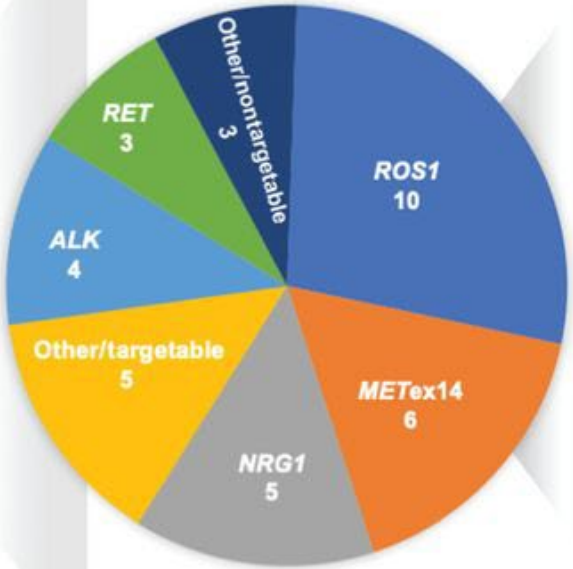
Benayed et al, *Clin Cancer Res* 2019

Patients with drivers identified by RNA matched to therapy

MSK-IMPACT negative
(*n* = 232)



MSK-Fusion positive
(*n* = 36)



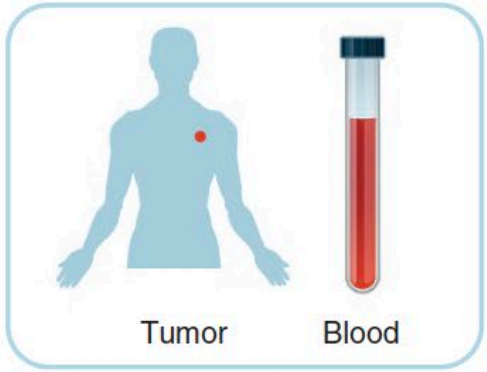
Clinical benefit of matched targeted therapy
(*n* = 10)

Rearrangement	Matched therapy	Best response*
EML4-ALK	Alectinib	SD
CD74-ROS1	Entrectinib	SD
SQSTM1-NTRK3	Larotrectinib	PR**
STRN-NTRK2	Larotrectinib	SD
CD74-ROS1	Entrectinib	PR**
CD74-NRG1	Afatanib	SD
MET Exon14 Skipping	Crizotinib	SD
SLC34A2-ROS1	Crizotinib	PD
SLC34A2-ROS1	Crizotinib	SD
SDC4-NRG1	Afatinib	PD

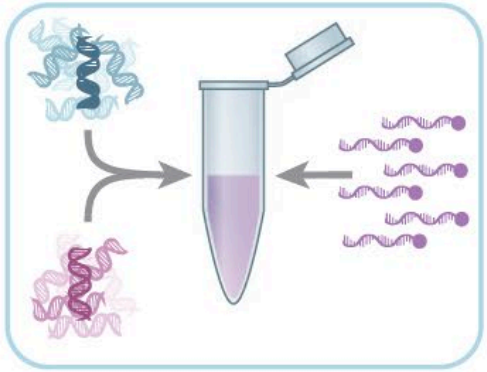
Benayed et al, *Clin Cancer Res* 2019

Clinical workflow at MSKCC

1. Patient consent

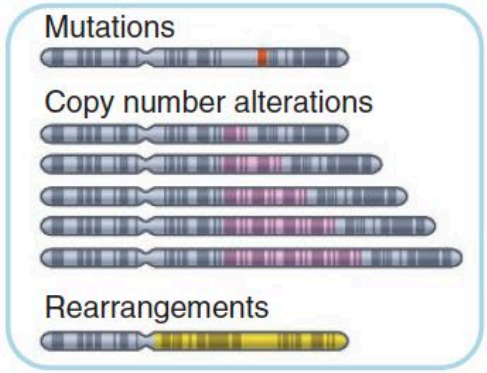


2. Sample accessioning



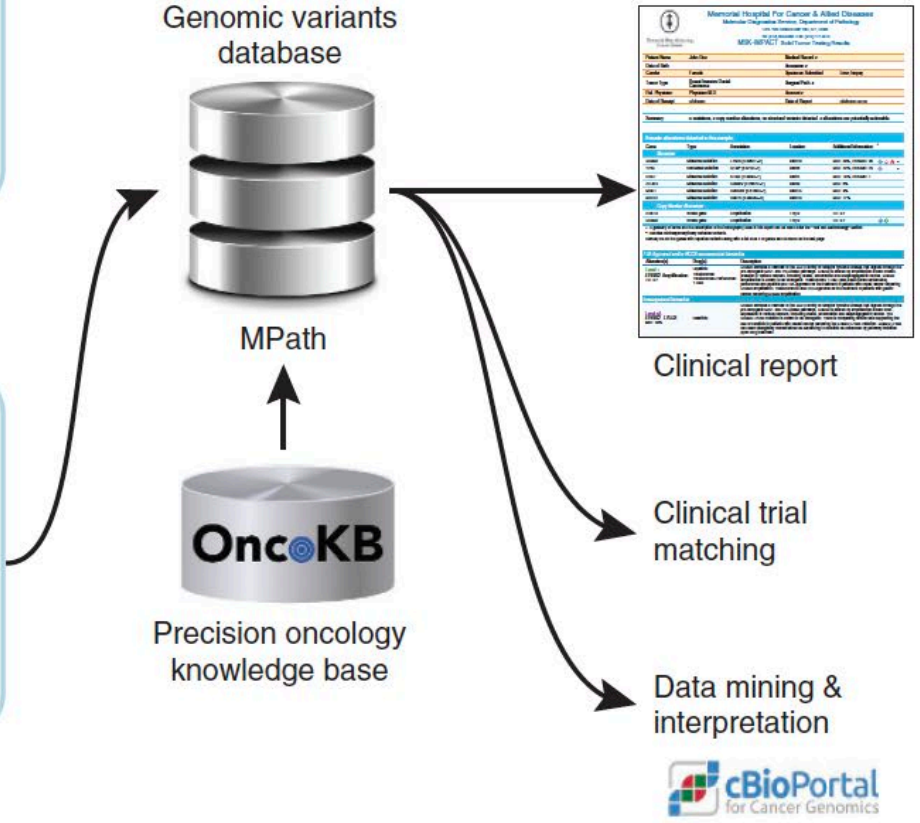
3. Sample preparation

4. Sequencing



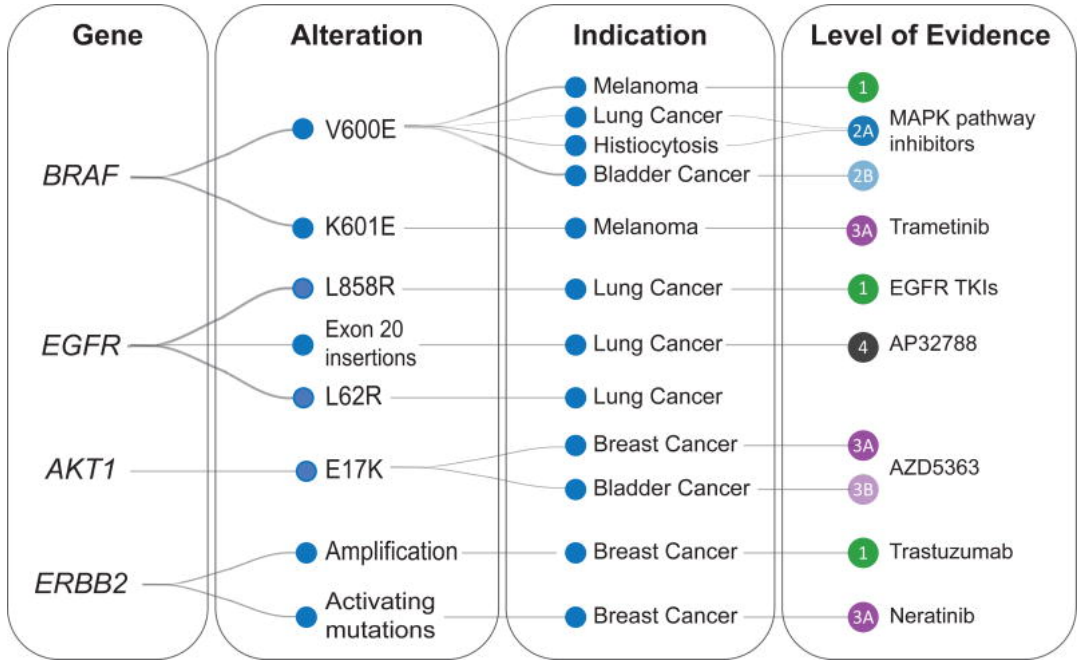
5. Bioinformatics analysis

6. Case review and sign out



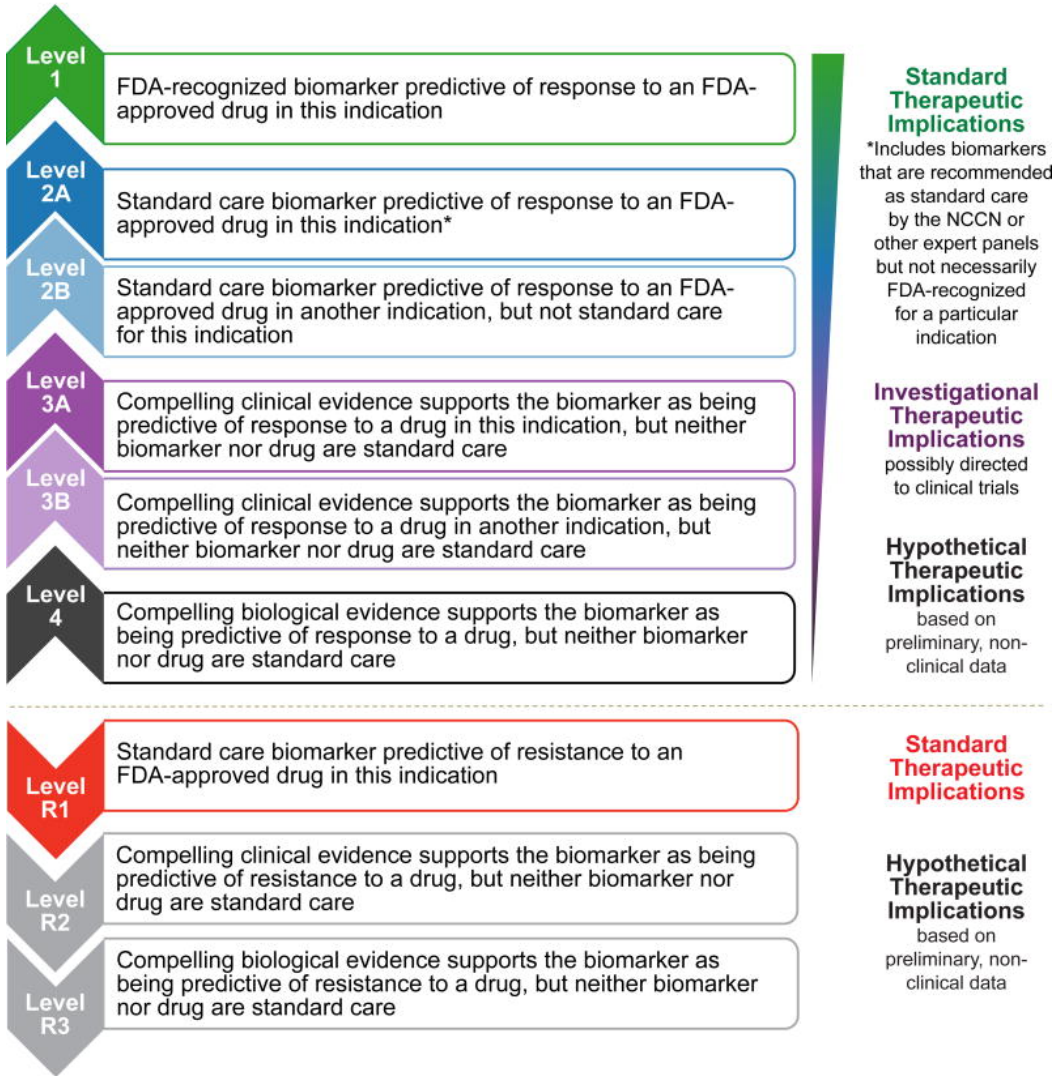
Over 125,000 served!!!

Alterations filtered through curated database of actionability



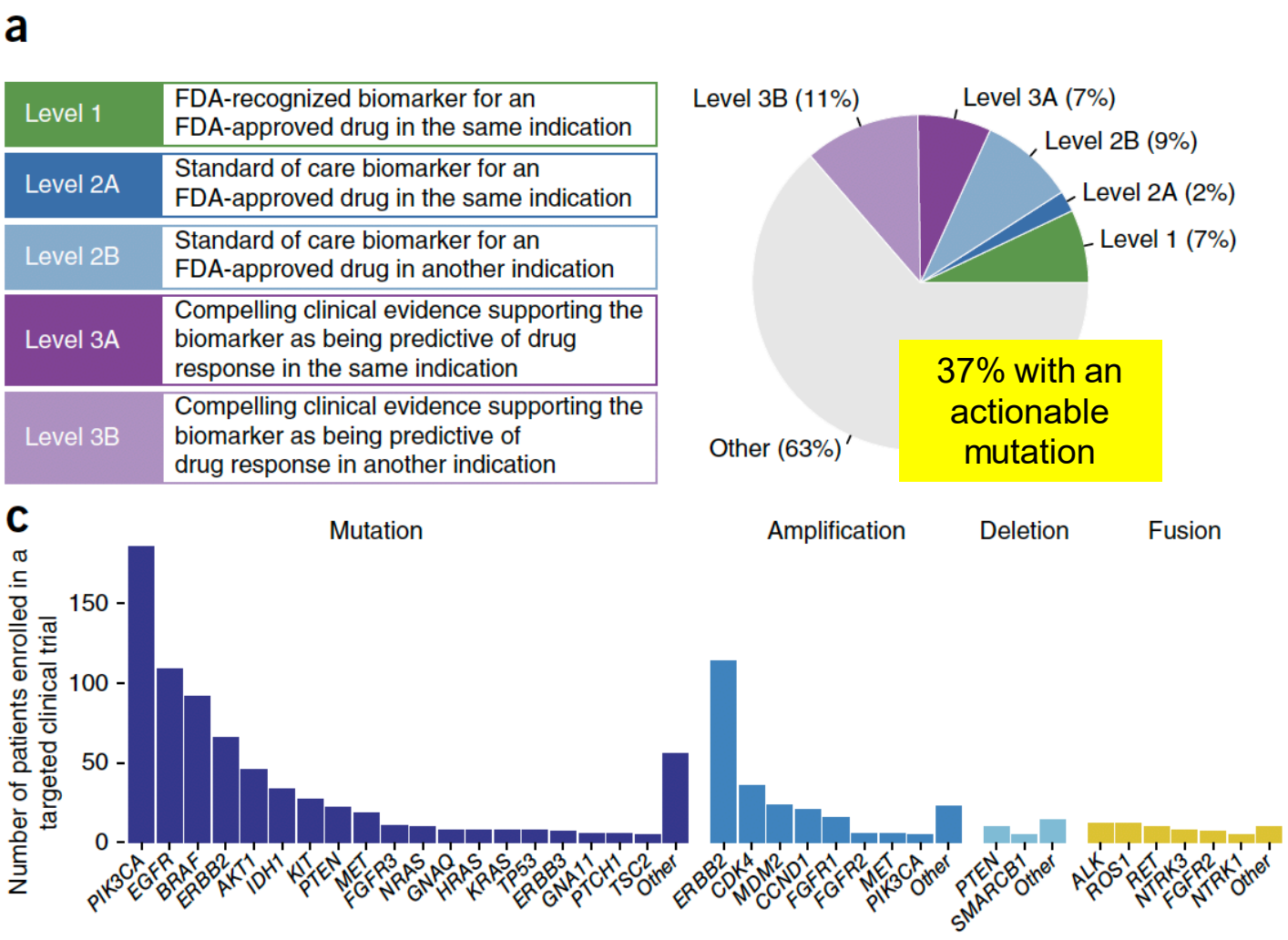
Data sources for clinical genomics annotation committee: variant databases, treatment guidelines, scientific literature, recurrence

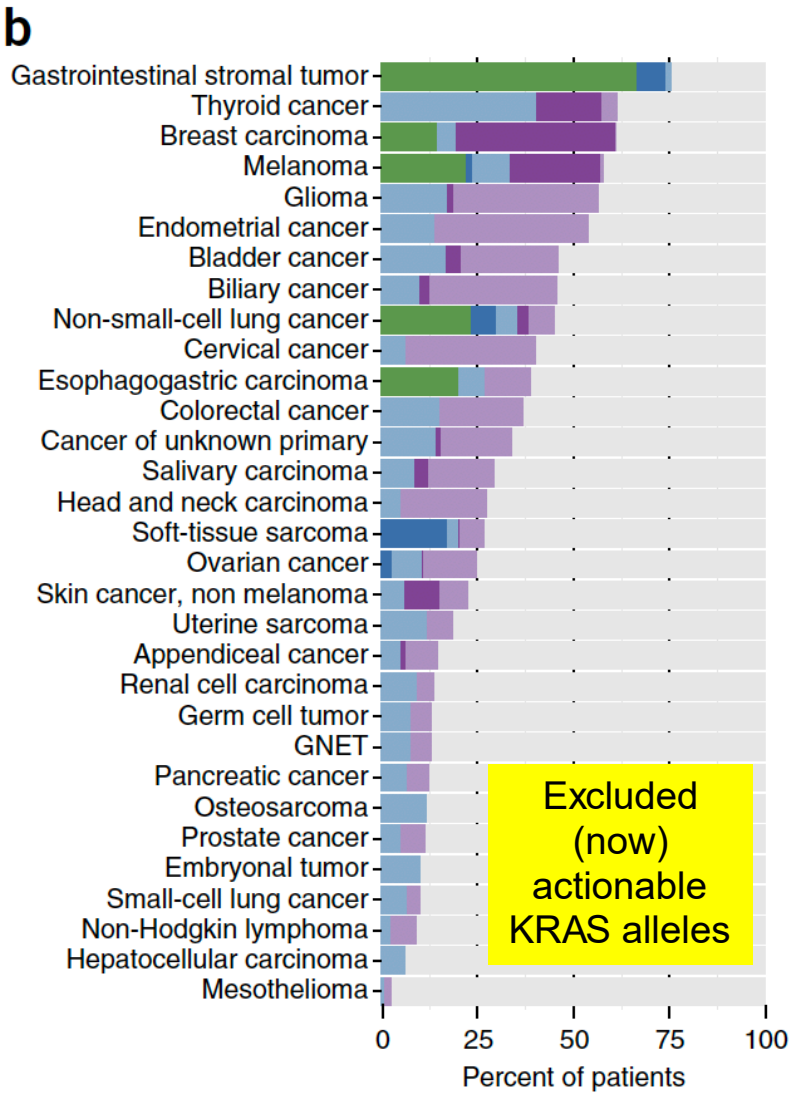
Posts to: oncokb.org website, cBioPortal, clinical reports



Chakravarty et al, *J Clin Oncol Precis Oncol* 2017

How has this impacted clinical research and clinical practice?

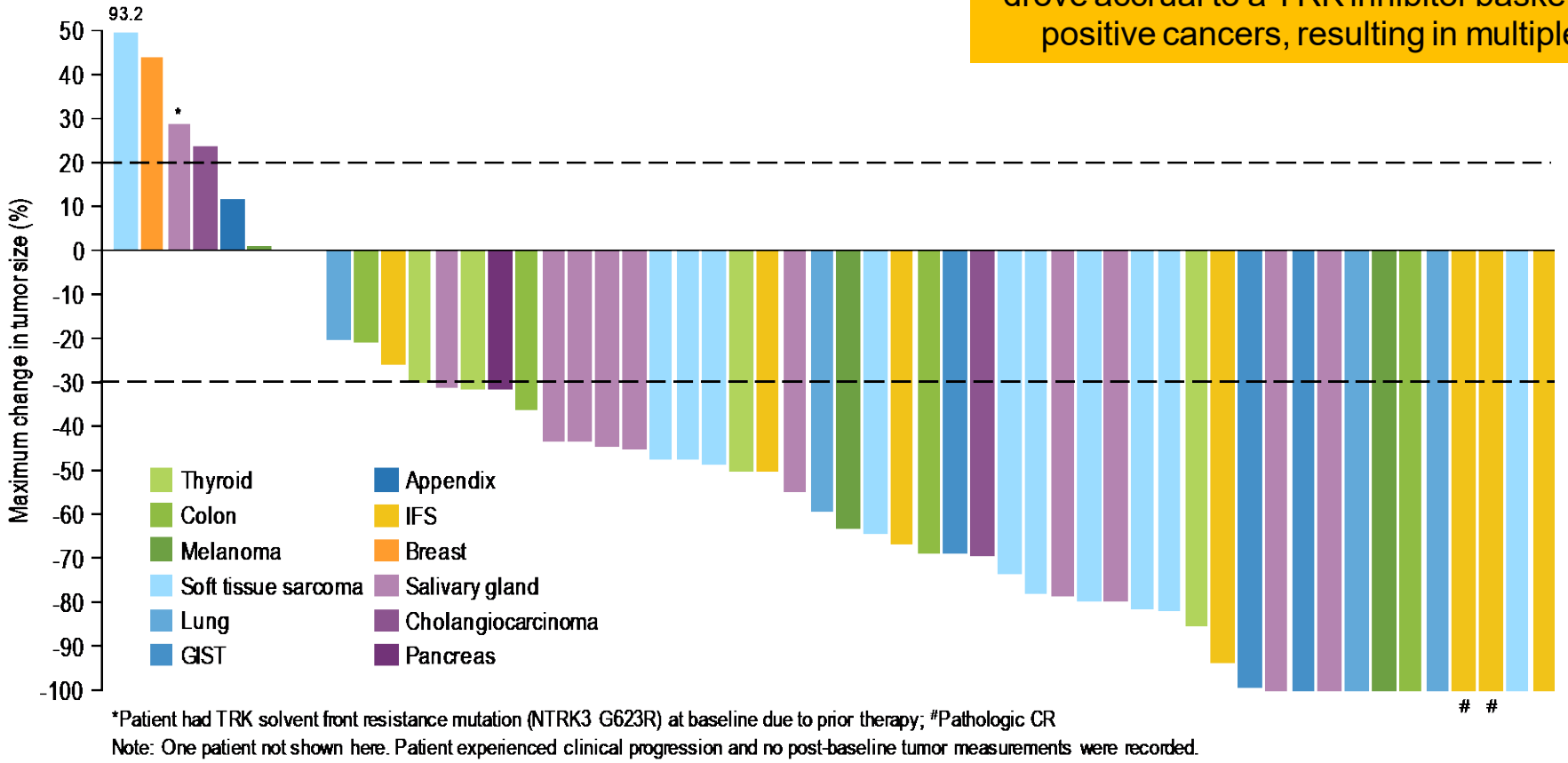




Zehir et al, *Nat Med* 2017

Enterprise-scale NGS drives basket trial accrual

MSK-IMPACT and **Darwin Cohort Management System** drove accrual to a TRK inhibitor basket trial for TRK fusion-positive cancers, resulting in multiple global approvals



*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

Drilon et al, *N Engl J Med* 2018

Contemporary comprehensive sequencing platforms offer advantages over limited panels

NGS detects germline alterations across multiple cancer types

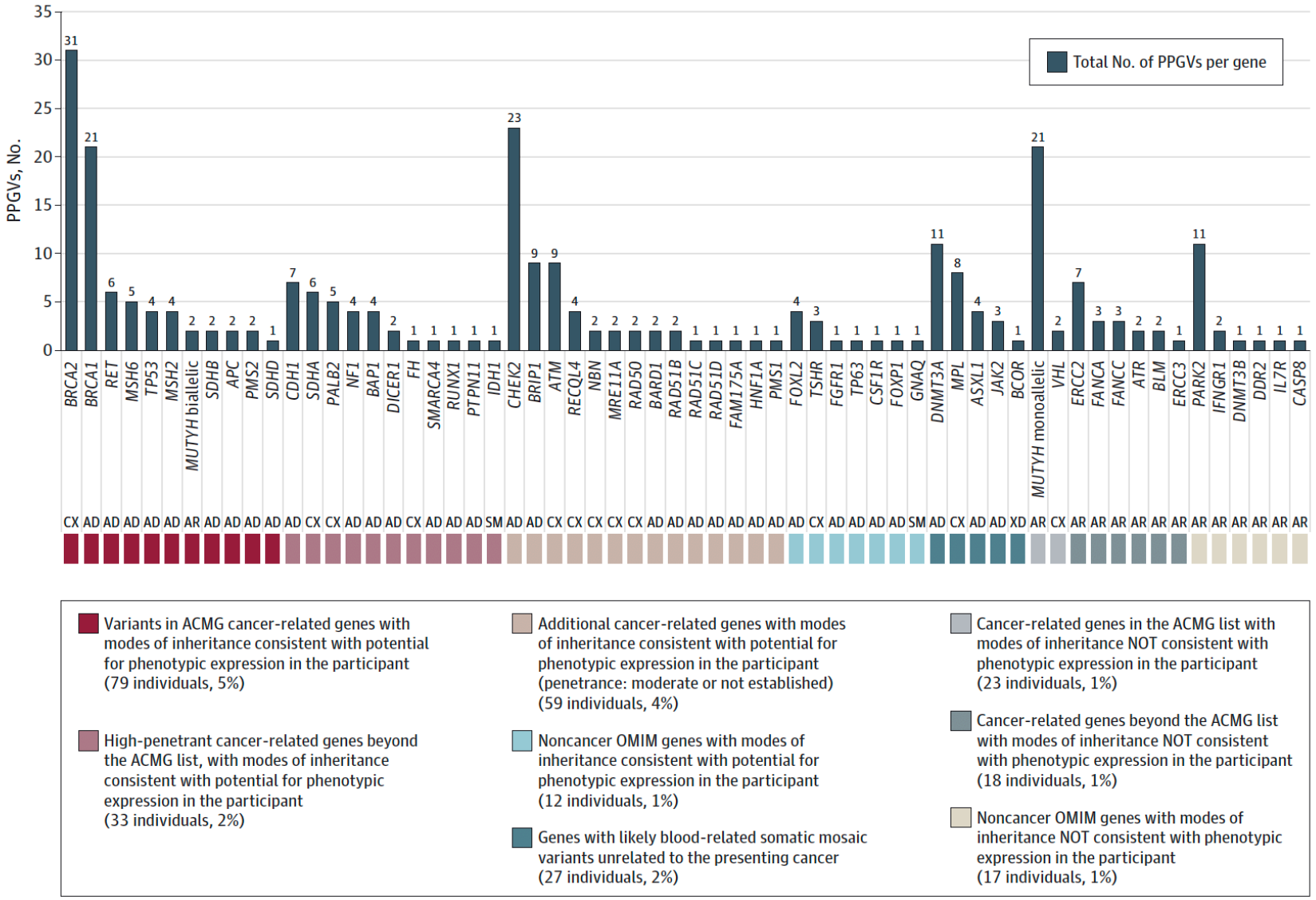
1566 patients with MSK-IMPACT germline sequencing

16% with potentially pathogenic germline variant

92% retained in tumor

80% in cancer susceptibility genes

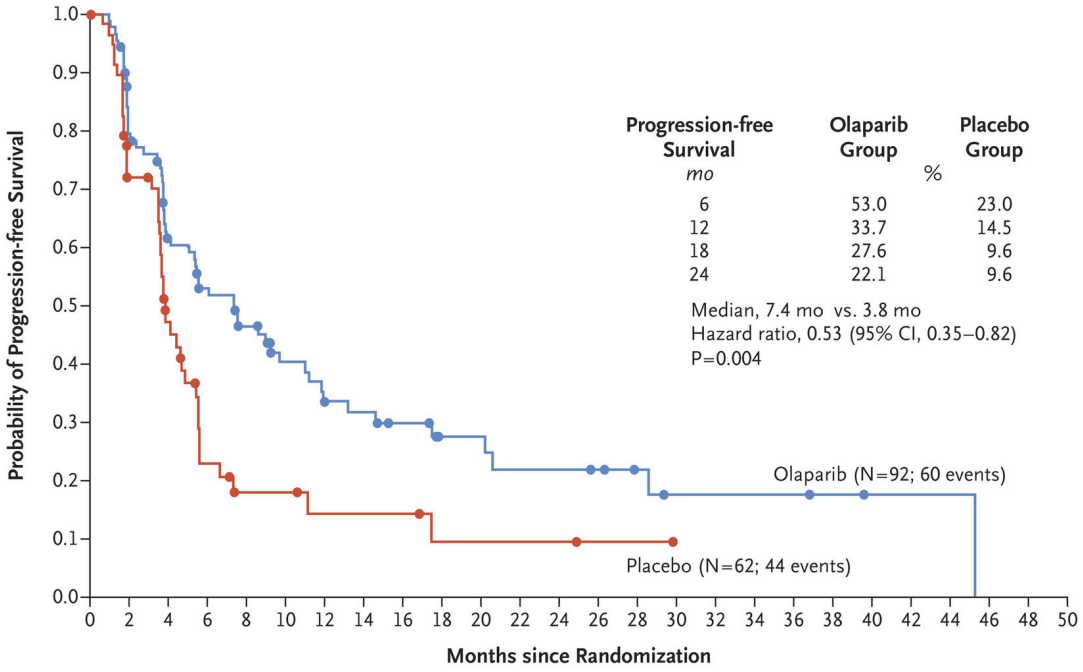
5% actionable (e.g. BRCA)



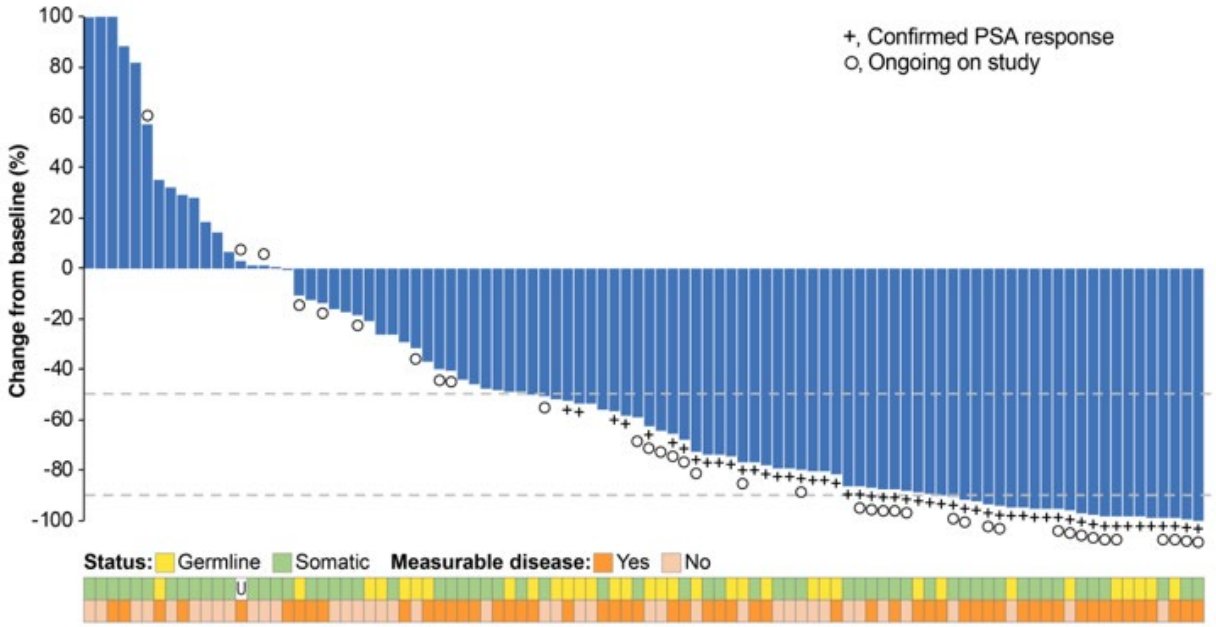
Schrader et al, *JAMA Oncol* 2016

PARP inhibition in cancers with *BRCA1/2* mutations including germline alterations

POLO trial
olaparib in pancreatic CA



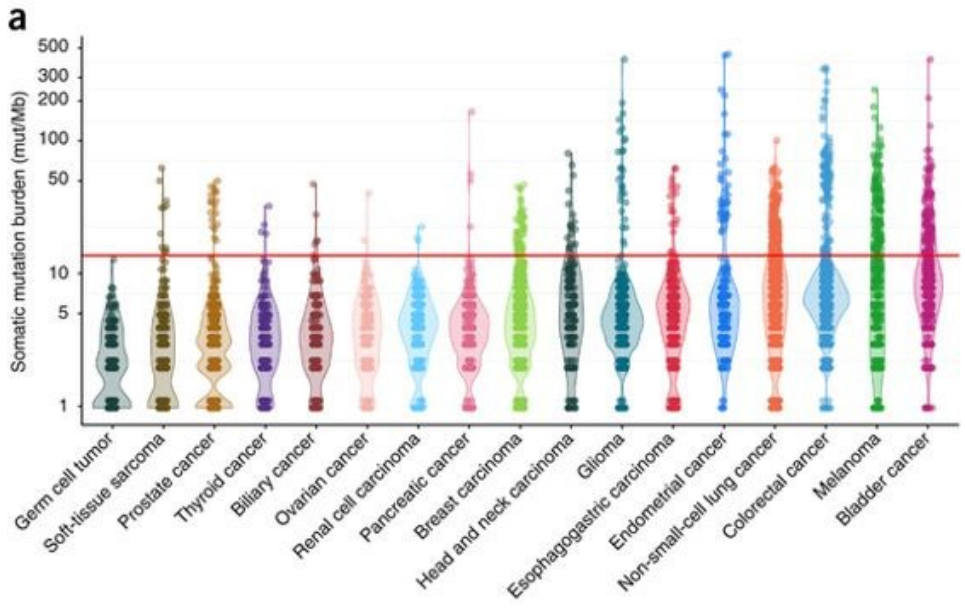
TRITON2 trial
rucaparib in prostate cancer



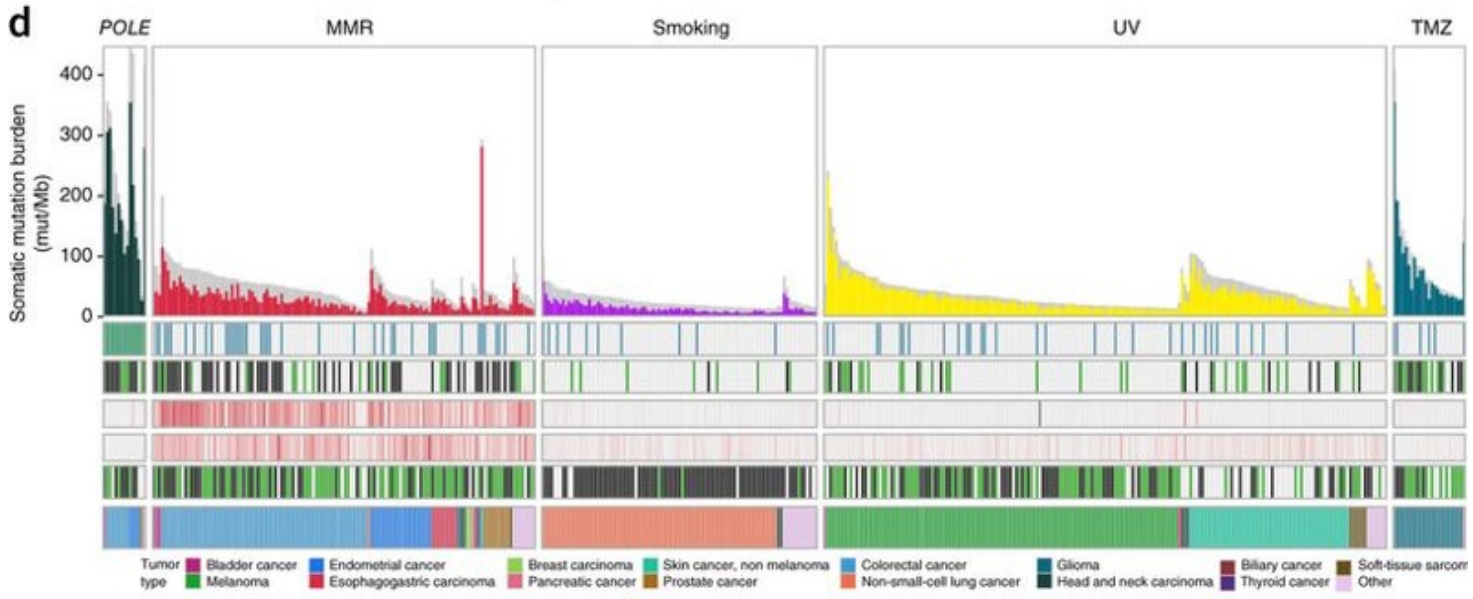
Goilan et al, *N Engl J Med* 2019; Abida et al, *Clin Cancer Res* 2020

Genomic signatures of response to immunotherapy can be identified by NGS

Tumor mutational burden calculated across cancer types.



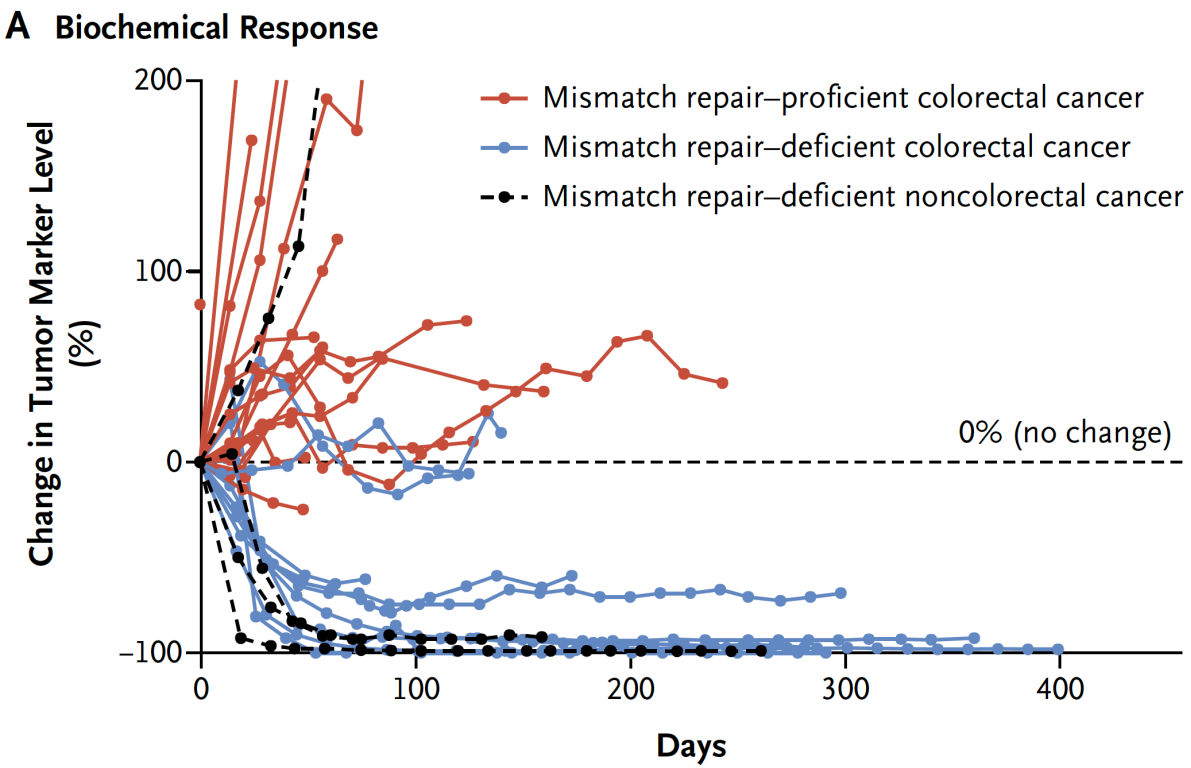
Exogenous mutagen signatures may inform disease etiology

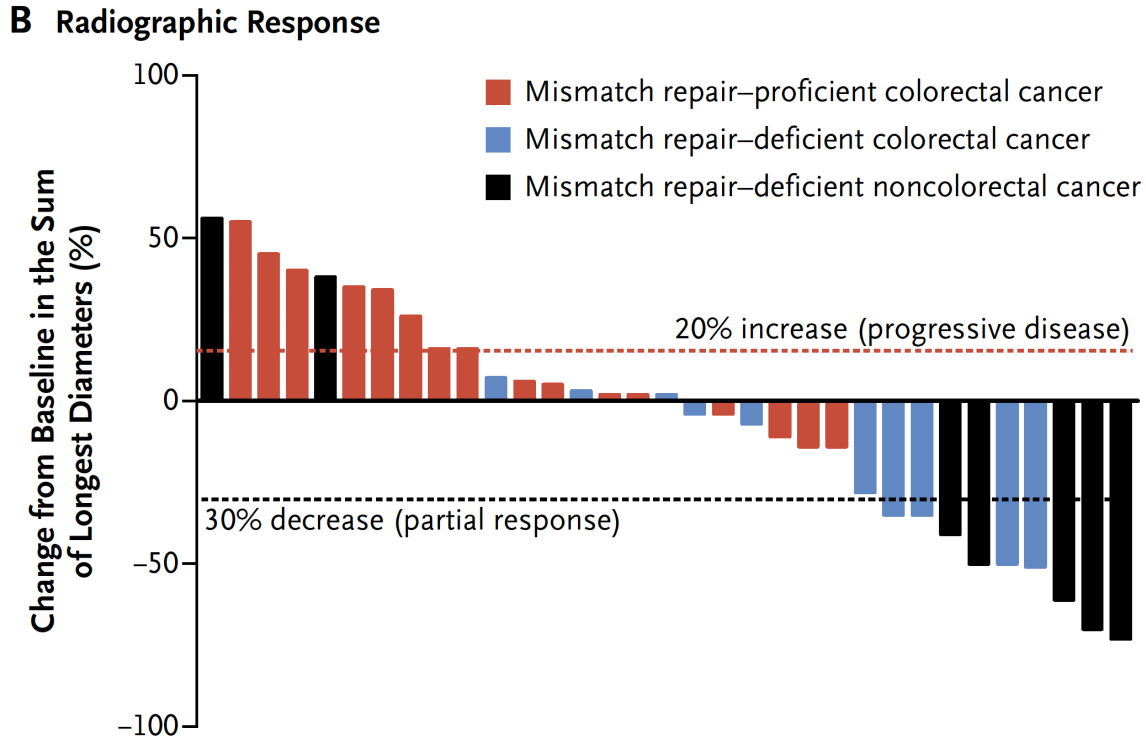


Can detect MSI status, matching MSI-high patients of any cancer type to immunotherapy

Zehir et al, *Nat Med* 2017

MSI as a predictor of response to immunotherapy





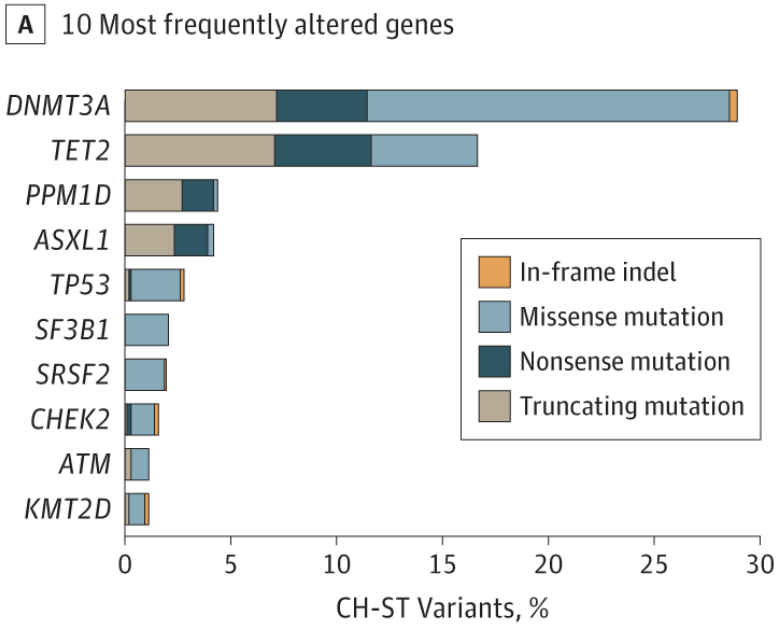
Le et al, *N Engl J Med* 2015

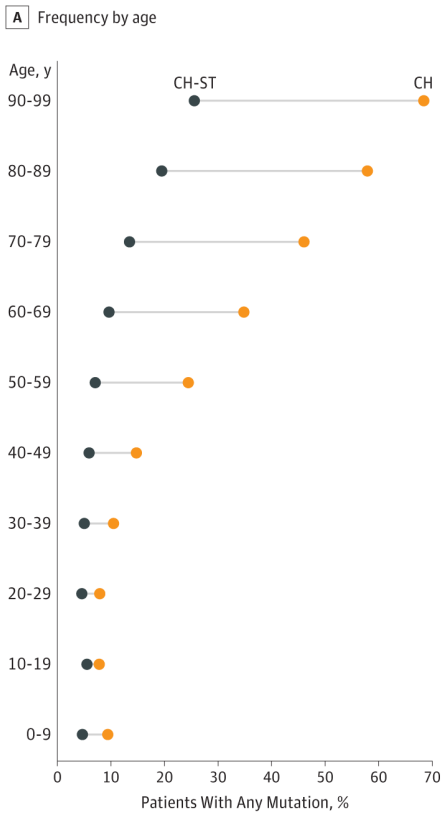
Clonal hematopoiesis identified in MSK-IMPACT sequencing

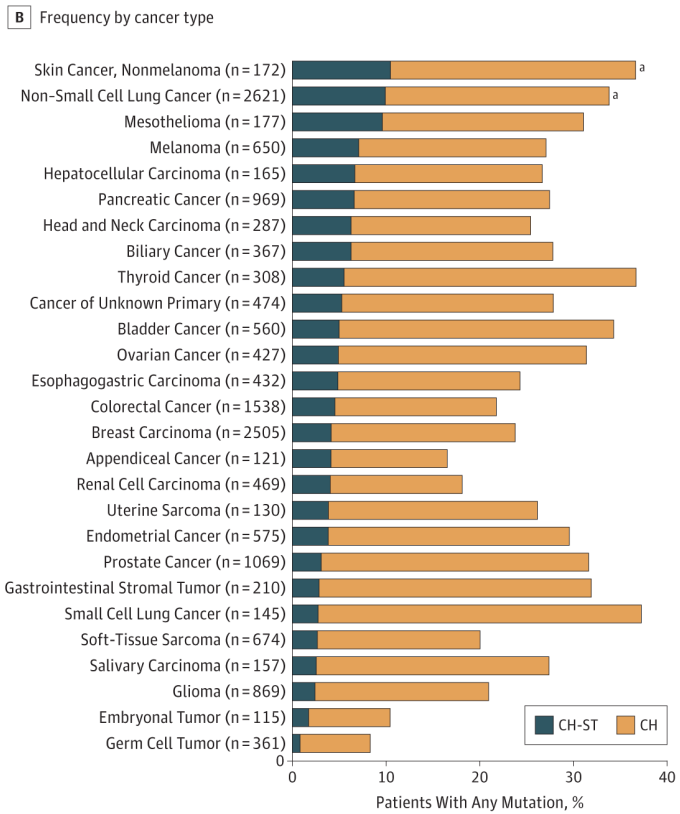
17,469 patients: clonal hematopoiesis (CH) interrogated in peripheral blood leukocytes by MSK-IMPACT

- **26% had CH mutations in blood**

CH mutations increased with age
Most commonly found in skin cancer and NSCLC.







Ptashkin et al, *JAMA Oncol* 2018

Clonal hematopoiesis mutations can be categorized as "actionable" and lead to erroneous treatment recommendations

Table. Clonal Hematopoiesis in Solid Tumor Mutations With Treatment Implications Based on OncoKB Database

Sex/Age at Blood Sampling, y	Gene	Amino Acid Change	VAF		Cancer Type	Highest OncoKB Level[a]
			Blood	Tumor		
M/84	*BRCA2*	Q3156*	0.344	0.118	Melanoma	2B
M/74	*IDH2*	R140Q	0.405	0.082	Pancreatic	2B
F/72	*IDH2*	R140Q	0.298	0.063	NSCLC	2B
M/68	*IDH2*	R140Q	0.162	0.048	NSCLC	2B
M/76	*IDH2*	R140Q	0.270	0.039	NSCLC	2B
F/59	*BRCA1*	E1836Q	0.332	0.036	Endometrial	2B
F/74	*NRAS*	G12R	0.442	0.119	NSCLC	3B
F/80	*NRAS*	G12V	0.081	0.037	Uterine sarcoma	3B
F/83	*IDH1*	R132H	0.077	0.033	Melanoma	3B
F/70	*IDH1*	R132C	0.048	0.022	Melanoma	3B
M/43	*PTEN*	D24G	0.348	0.174	Colorectal	4
F/50	*NF1*	R2616*	0.237	0.095	Breast carcinoma	4
M/68	*KRAS*	G60D	0.297	0.094	Prostate	4
M/55	*NF1*	X1554_splice	0.105	0.049	Melanoma	4
M/79	*NF1*	F256Lfs*	0.141	0.043	Prostate	4
M/78	*KRAS*	A146P	0.132	0.035	Skin cancer, nonmelanoma	4
F/77	*KRAS*	G12R	0.087	0.041	Colorectal	R1

Ptashkin et al, *JAMA Oncol* 2018

Next gen sequencing drives discovery science

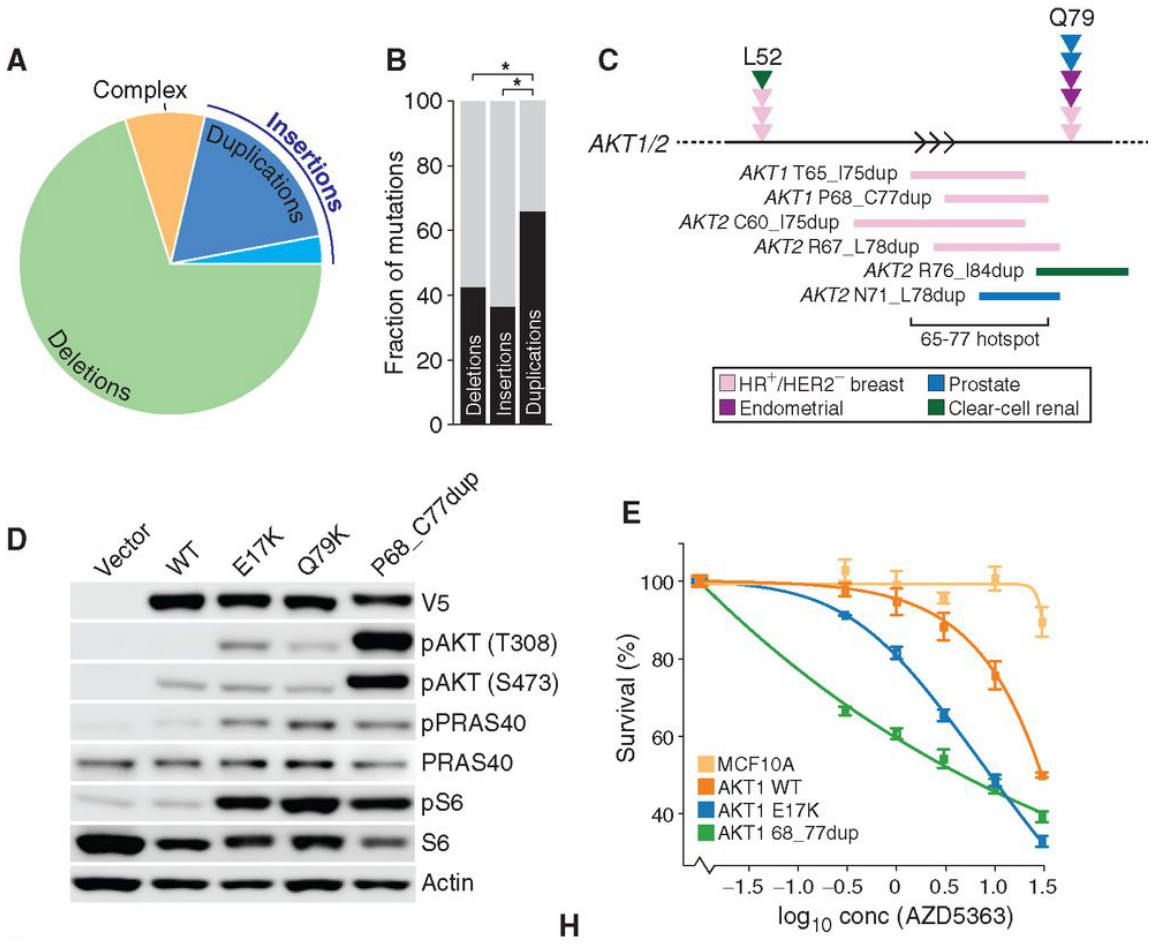
Comprehensive NGS assays drive discovery

Unbiased discovery of recurrent oncogenic indels from population-scale data

Variants of unknown significance (VUS)

- Some may be clinically actionable.
- Laboratory validation can take years.

- Computational weight of evidence can be used to identify potentially oncogenic variants.



- Duplications more commonly occurred in oncogenes

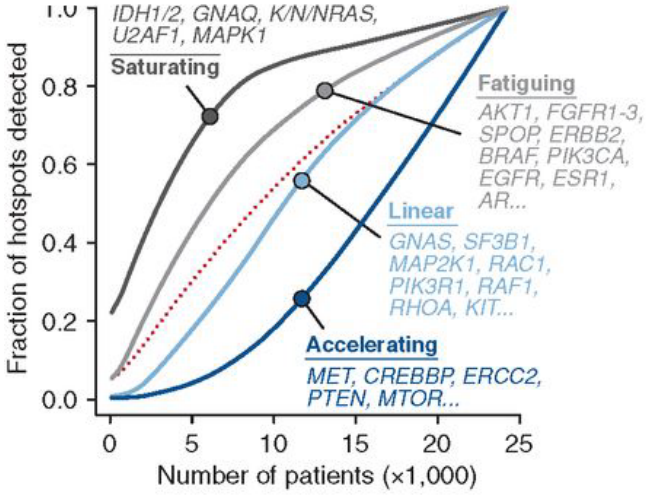
- Paralogous AKT1/2 hotspot duplications identified.

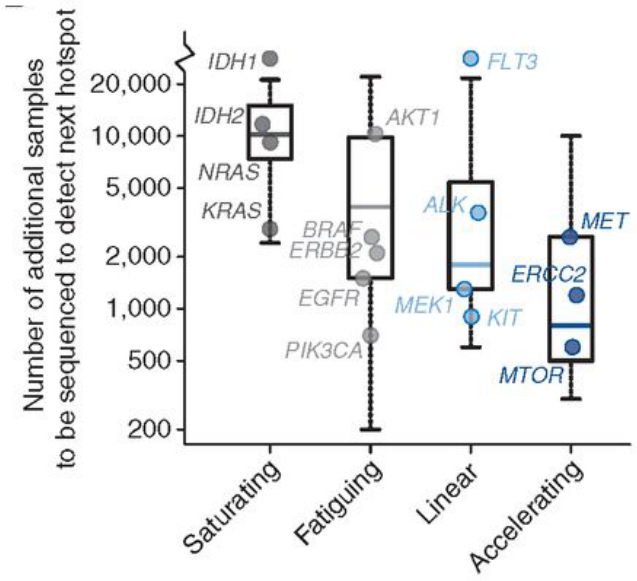
- ***AKT1/2* duplications found to be oncogenic**
  - downstream signaling more active
  - increased sensitivity to AKT inhibitor
  - used to select patients for AKT inhibitor basket trial

Chang et al, *Cancer Discov* 2017

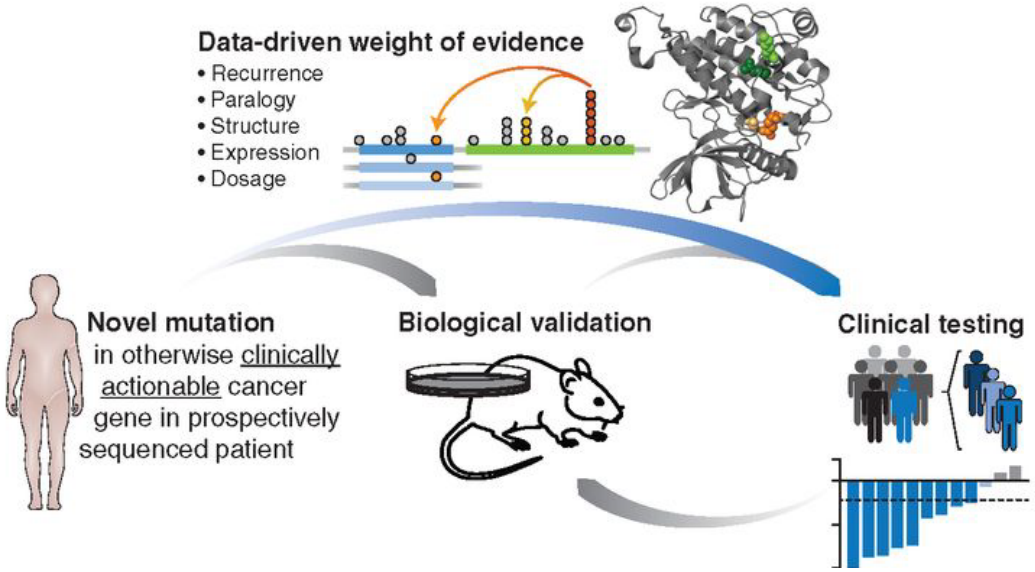
Computational vetting can identify potentially actionable variants

Increased likelihood of hotspot identification the more patient samples are sequenced and analyzed



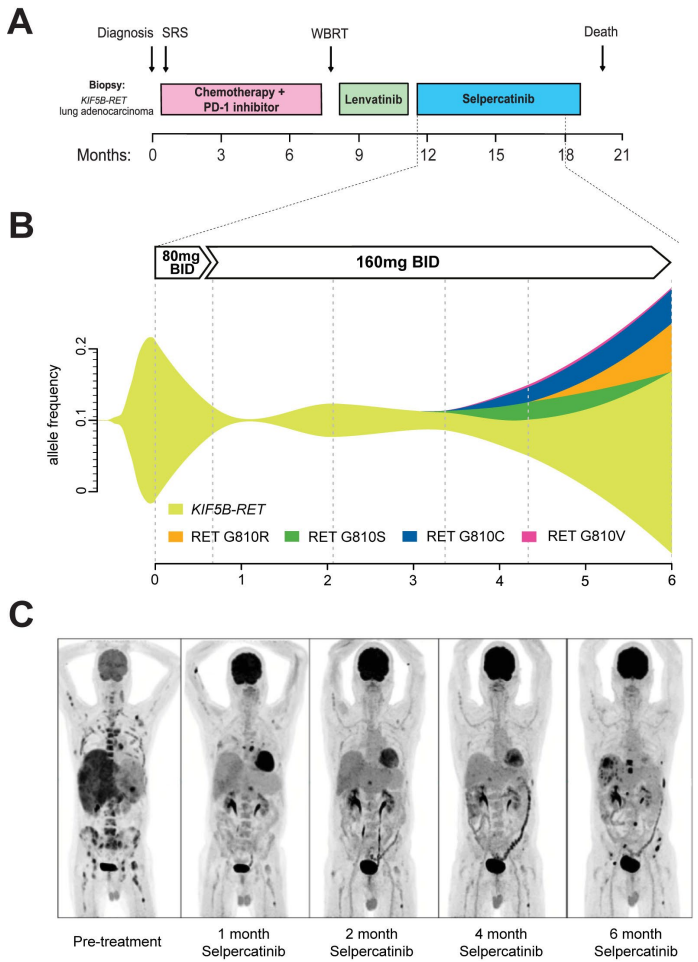


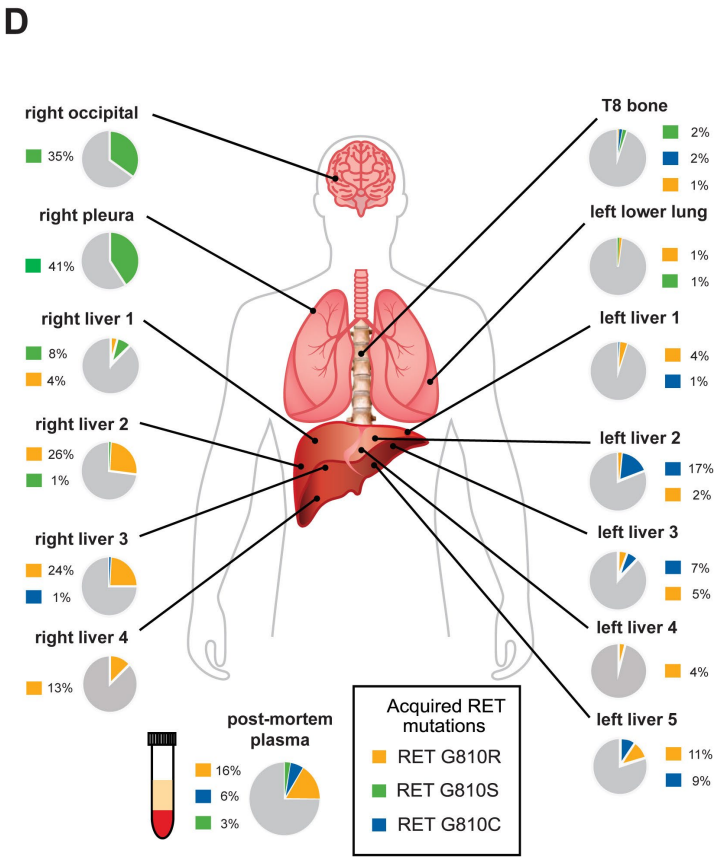
Using prospective sequencing, computational analyses can nominate select variants for exploration both in the clinic and in the laboratory.

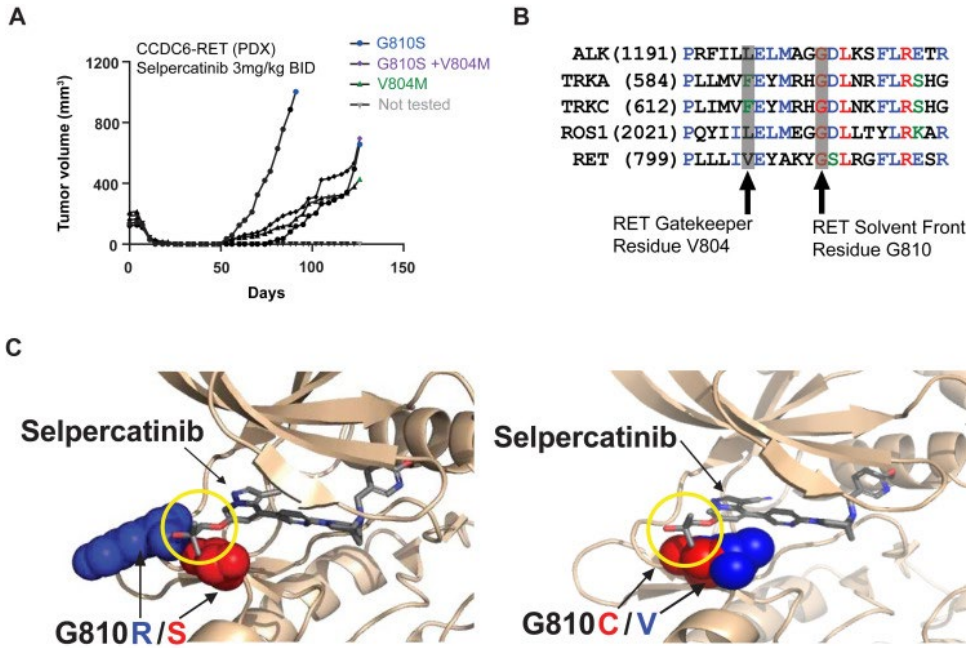


Chang et al, *Cancer Discov* 2017

Sequencing identifies mechanisms of therapeutic resistance

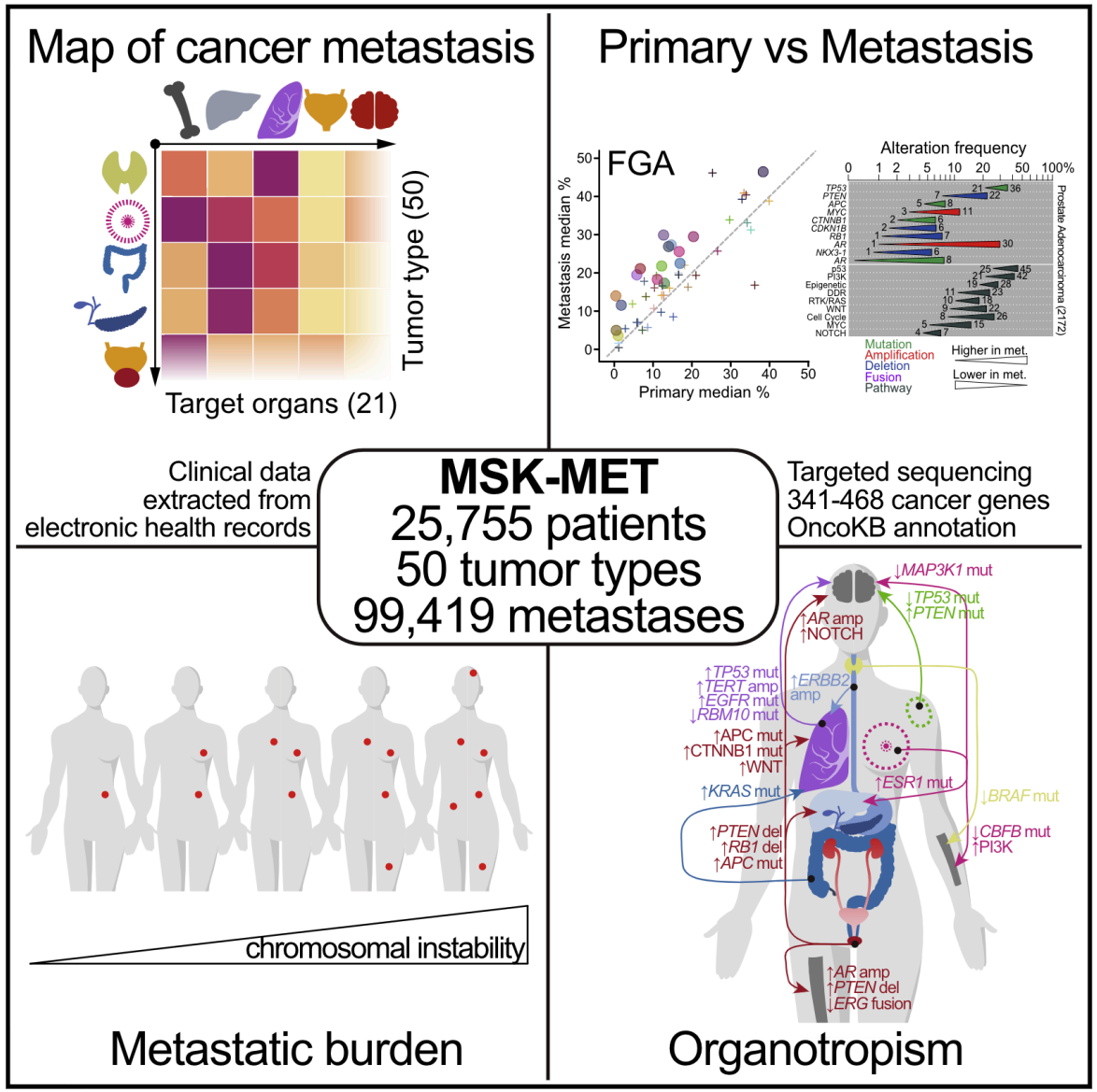






Solomon et al, *J Thor Oncol* 2020

Genomic profiles of metastatic tropisms



Nguyen et al, *Cell* 2022

Summary

- The list of actionable molecular drivers with approved targeted therapies continues to grow

- Comprehensive DNA/RNA-based cancer sequencing
  - improves the detection of clinically actionable drivers vs older strategies
  - is potentially cost-saving

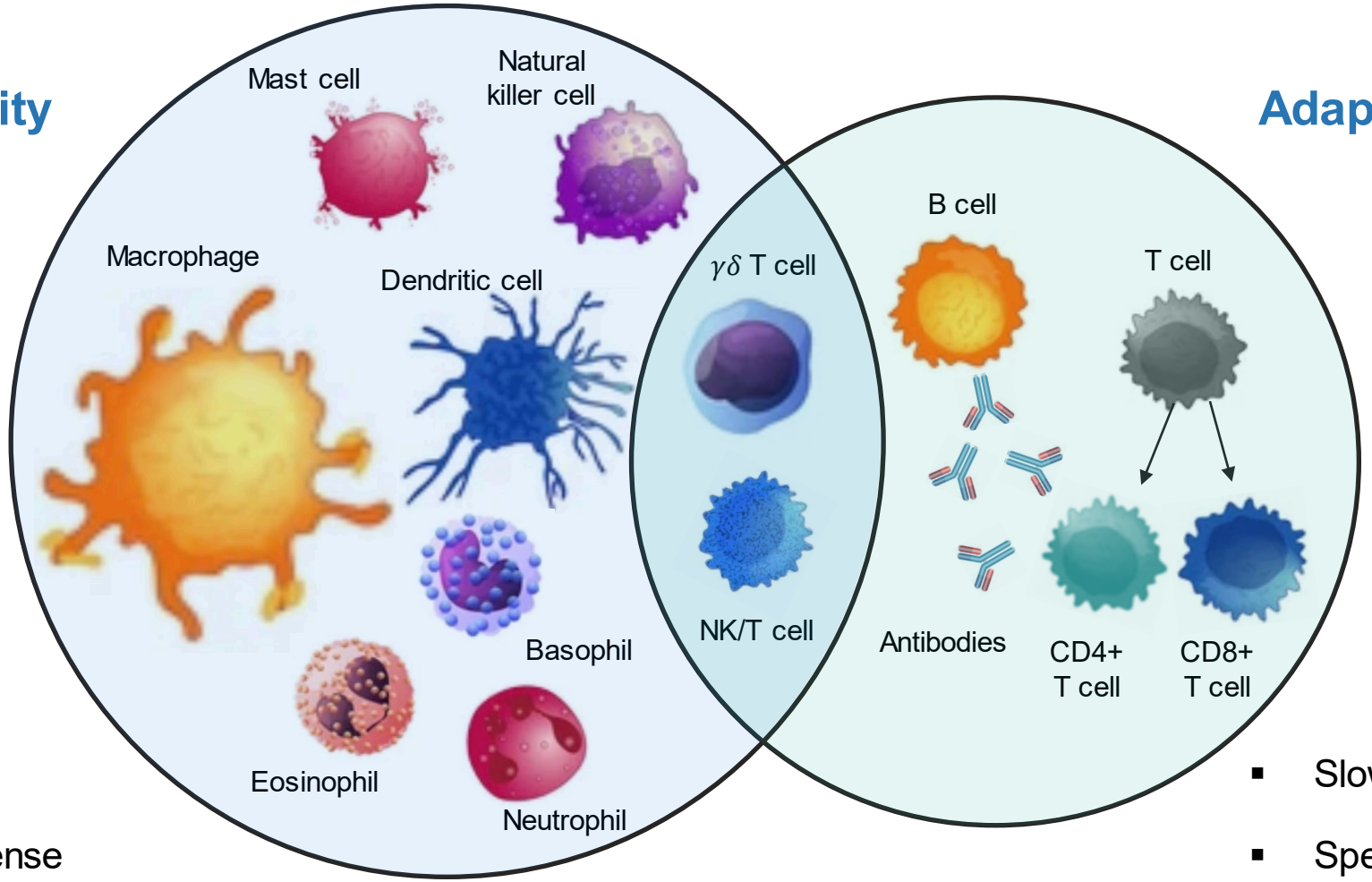
- NGS assays can also detect
  - potentially pathogenic germline variants
  - clonal hematopoiesis mutations in solid tumors
  - potential immunotherapy biomarkers and other mutational signatures

- NGS assay data can be leveraged to
  - aid driver discovery, capitalizing on computational analyses
  - develop prospectively monitored cohorts that aid therapy matching

Next gen sequencing and applications to improving immunotherapy

A broad look at anti-cancer immune effectors

Innate Immunity



Adaptive Immunity

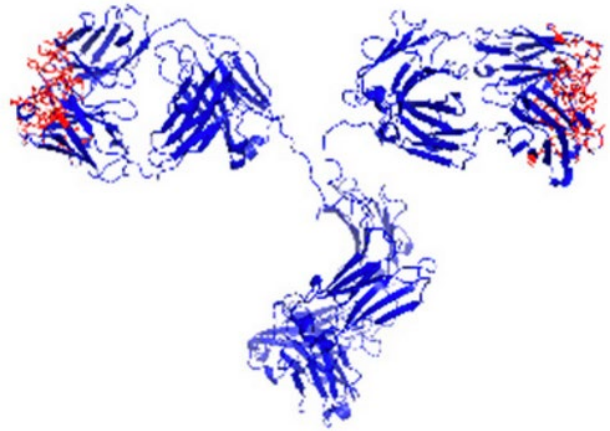
- Nonspecific
- First line of defense
- Can prime activation of adaptive immunity

- Slower to develop
- Specific target recognition
- Memory functions
  - Faster, stronger subsequent responses

Anti-cancer applications of adaptive immunity

Naked antibodies (or antibody fragments)

- Blocking
- Activating

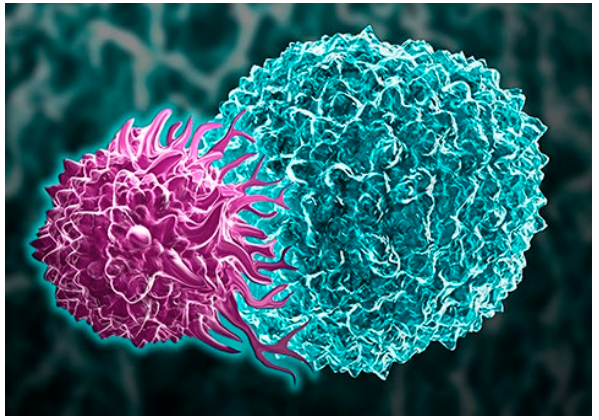


Trojan horse strategies

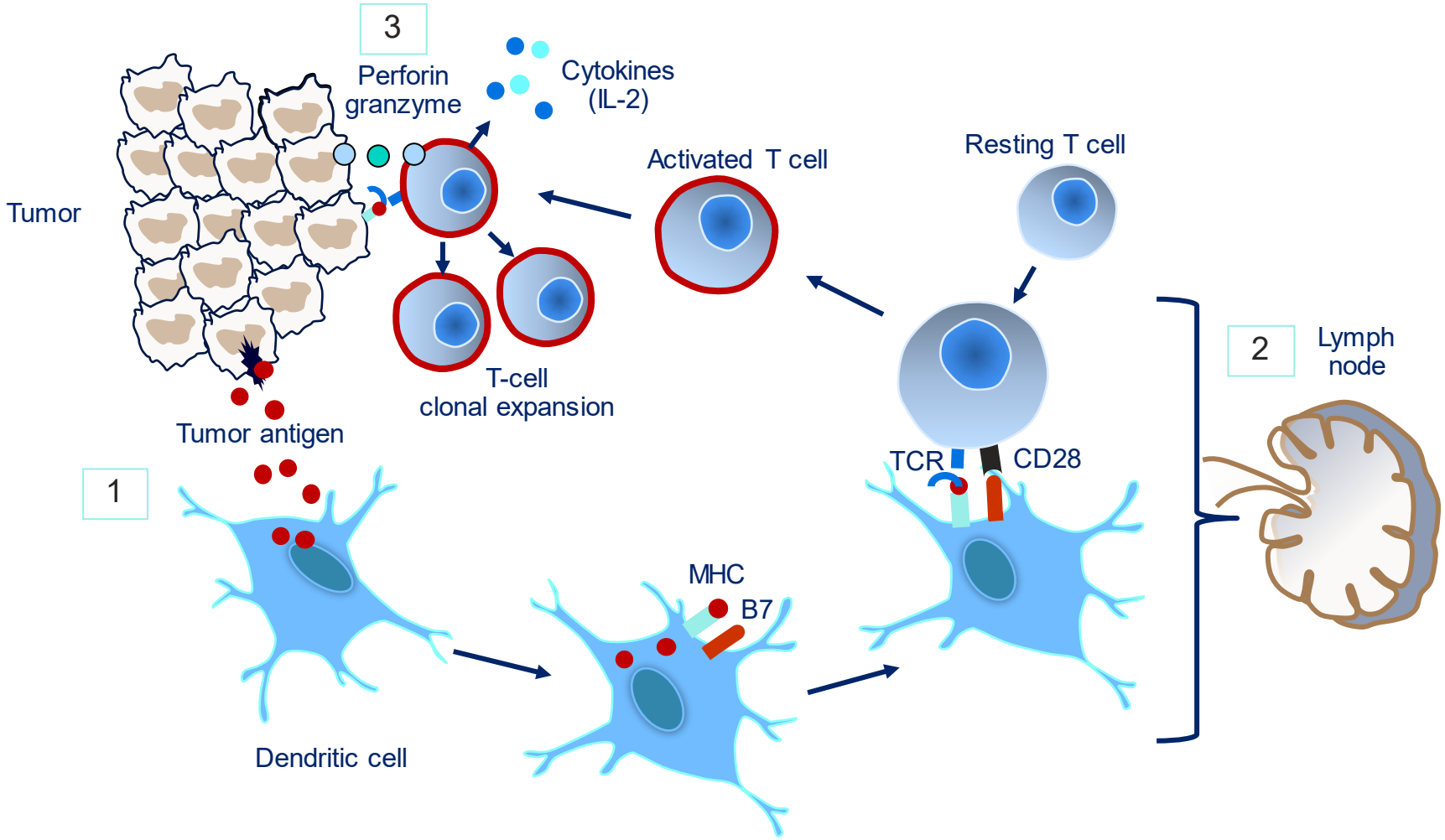
- Antibody-drug conjugates
- Radioimmunoconjugates

Cell therapies

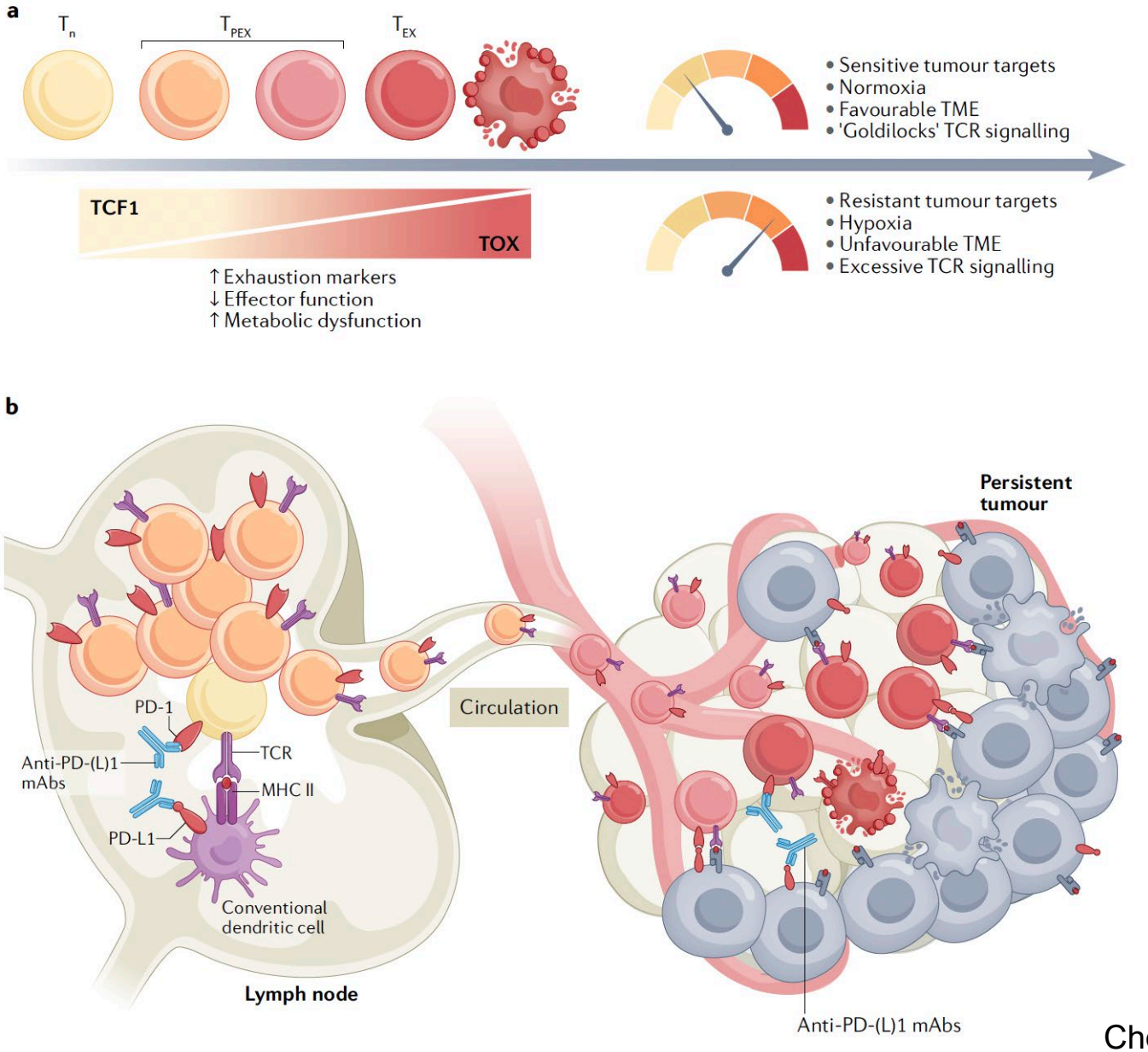
- TIL
- TCR and TCR-like structures
- CAR-Ts



T cell activation in anti-tumor immunity: an overview

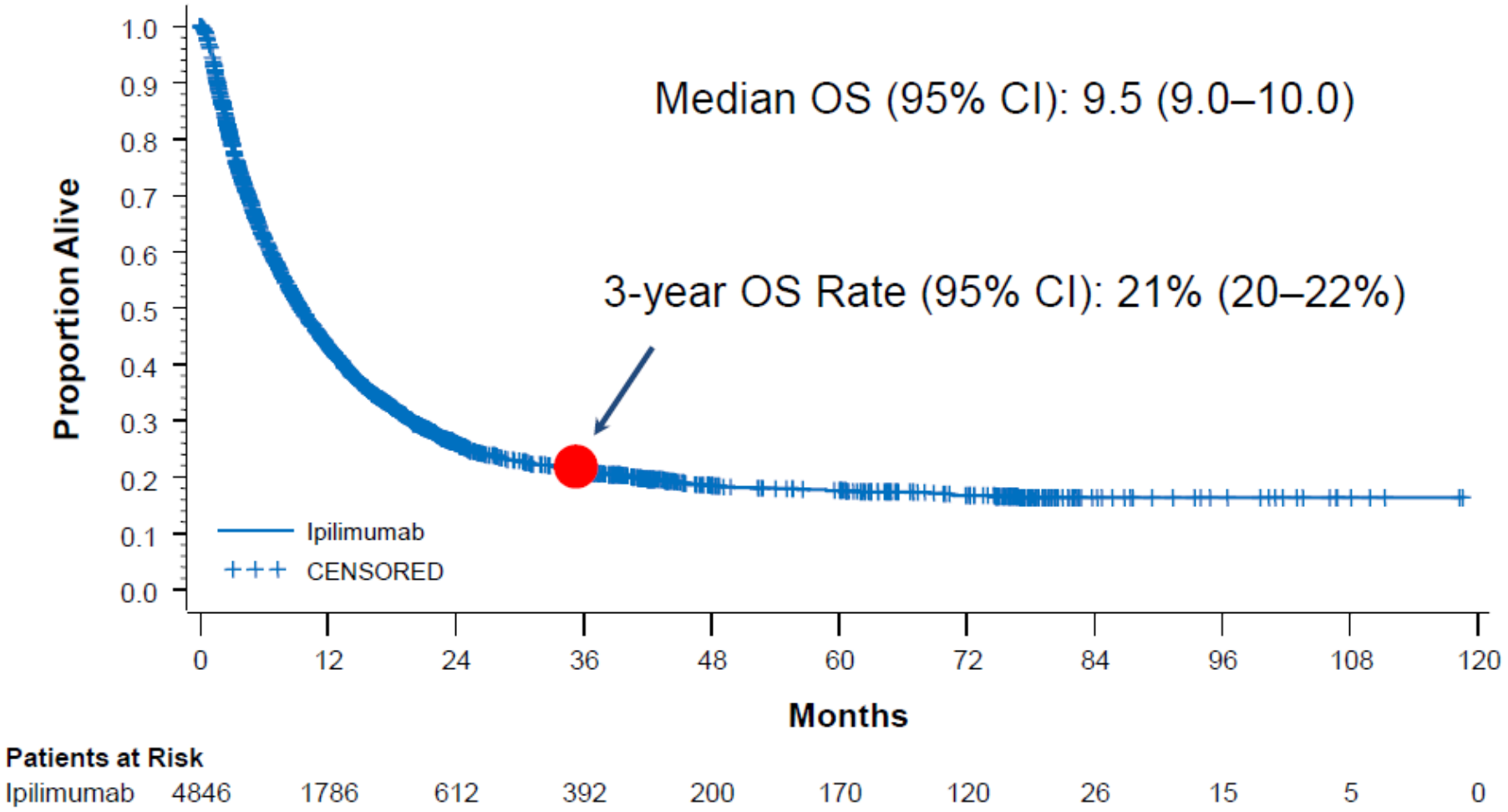


But is that right? A more nuanced, view



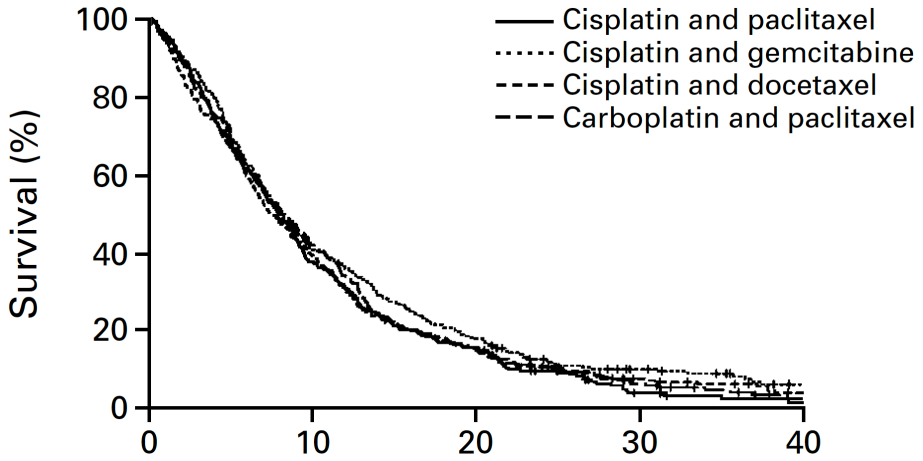
Chow et al, *Nat Rev Clin Oncol* 2022

Metastatic melanoma – ipilimumab



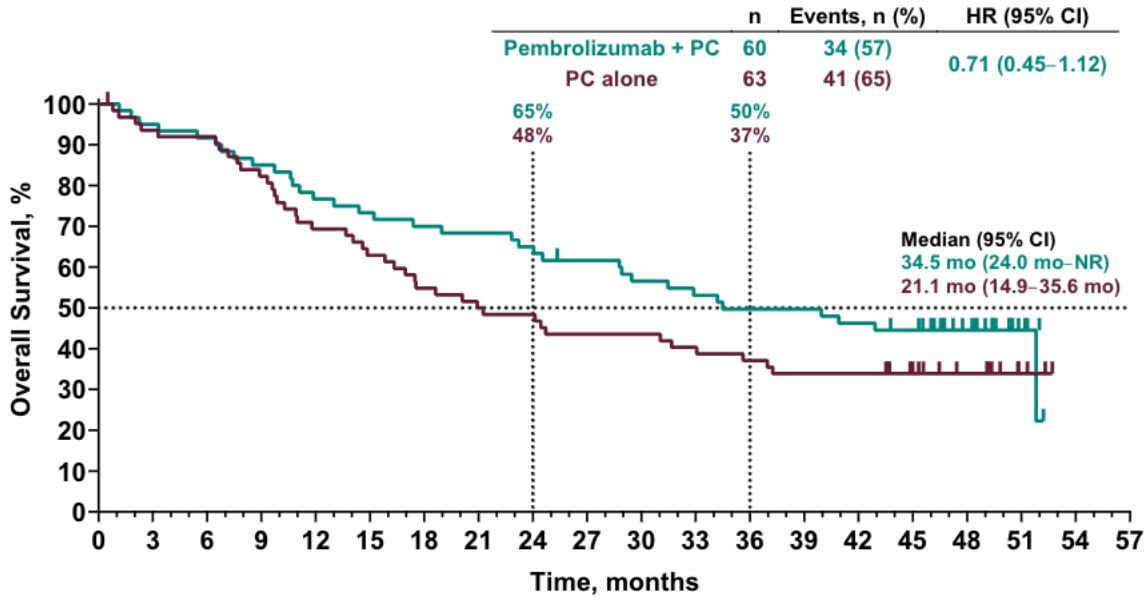
Schadendorf et al., *J Clin Oncol* 2015

Non-small cell lung cancer: where we were, where we are



2001
Comparison of 4 platinum doublet regimens

Median survival for all 4, about 10 months
Three-year survival under 10%



2021
Comparison of platinum doublet with or without IO

Median survival for chemoIO is 3 years
Long-term survival is about 40% (curves flatten out)

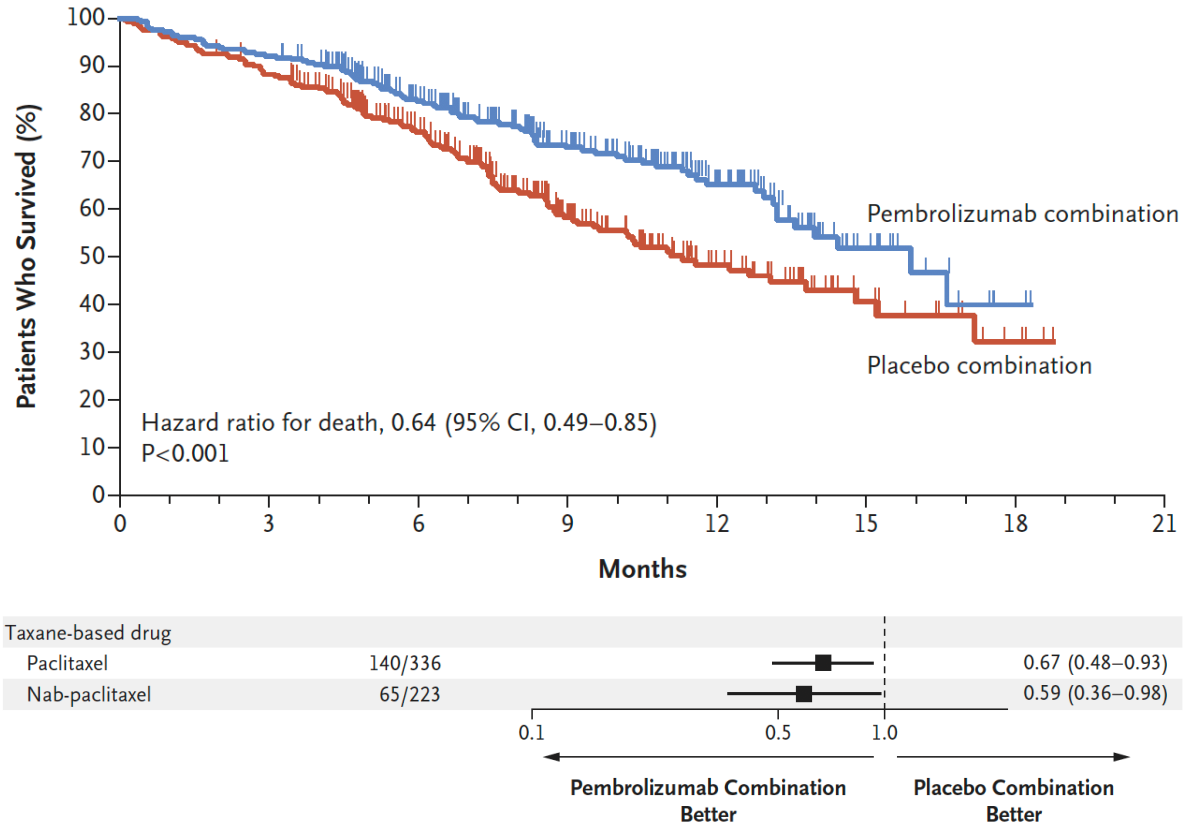
Note the group randomized to chemo alone gets IO later – even of these some can be rescued

Schiller et al., *N Engl J Med* 2001 Awad et al., *J Thor Oncol* 2021

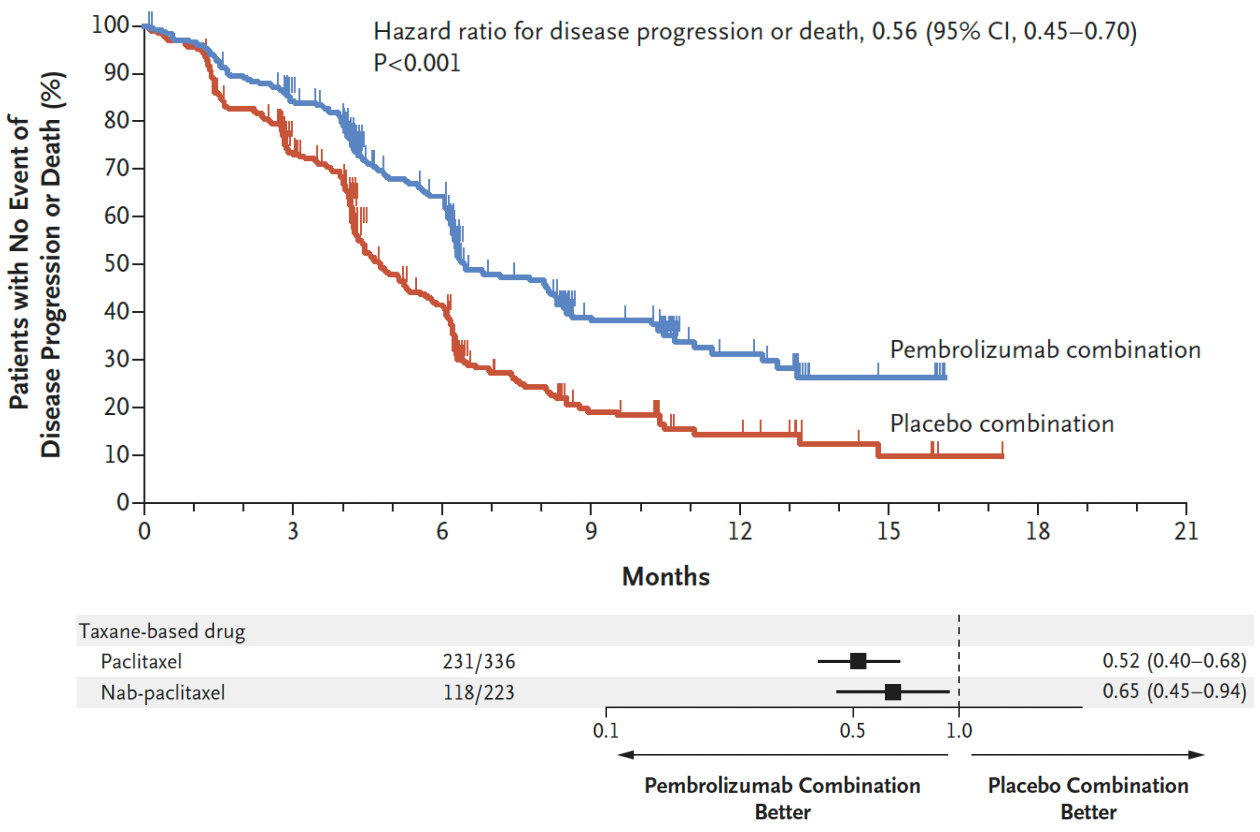
Chemoimmunotherapy for squamous cell carcinoma

Keynote 407: carboplatin (nab)-paclitaxel +/- pembrolizumab

Overall survival



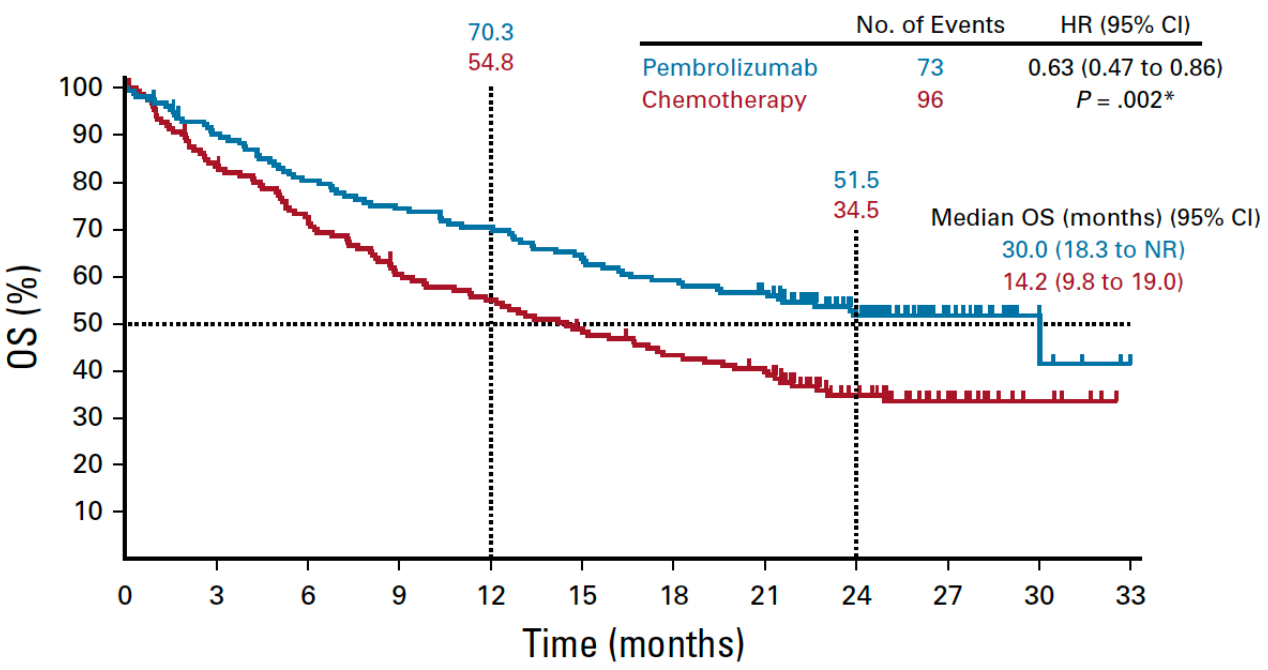
Progression-free survival



Paz-Ares et al., *N Engl J Med* 2018

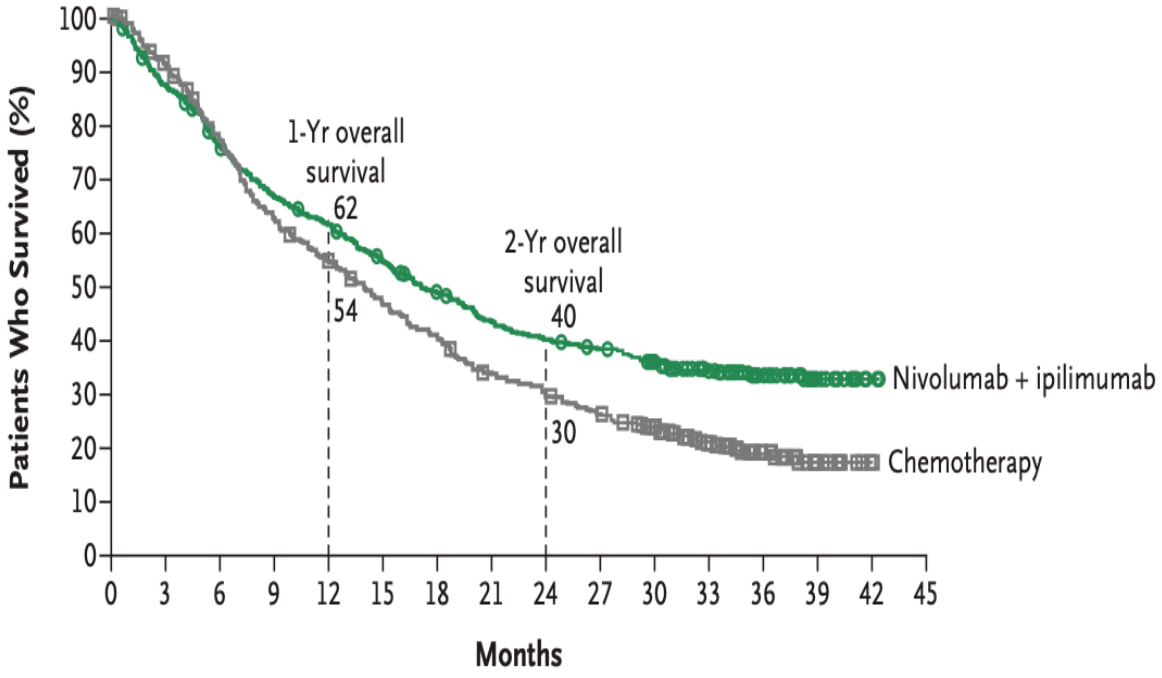
“Chemo-free” options

Keynote 604: PD-L1 ≥ 50%



Reck et al., *J Clin Oncol* 2019

CheckMate 227: nivolumab and ipilimumab



Hellmann et al, *N Engl J Med* 2019

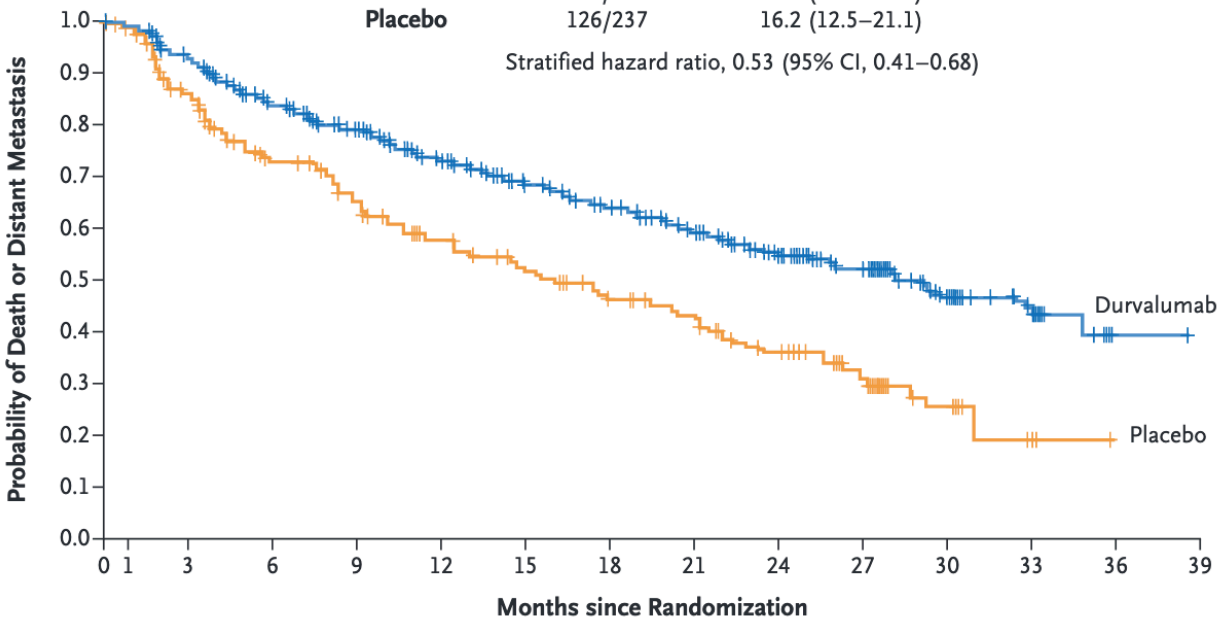
Bringing immunotherapy to early stage disease: Durvalumab after chemoRT for stage III NSCLC

PACIFIC

Metastasis-free survival

	No. of Events/ Total No. of Patients	Median Time to Death or Distant Metastasis (95% CI)
		mo
Durvalumab	182/476	28.3 (24.0–34.9)
Placebo	126/237	16.2 (12.5–21.1)

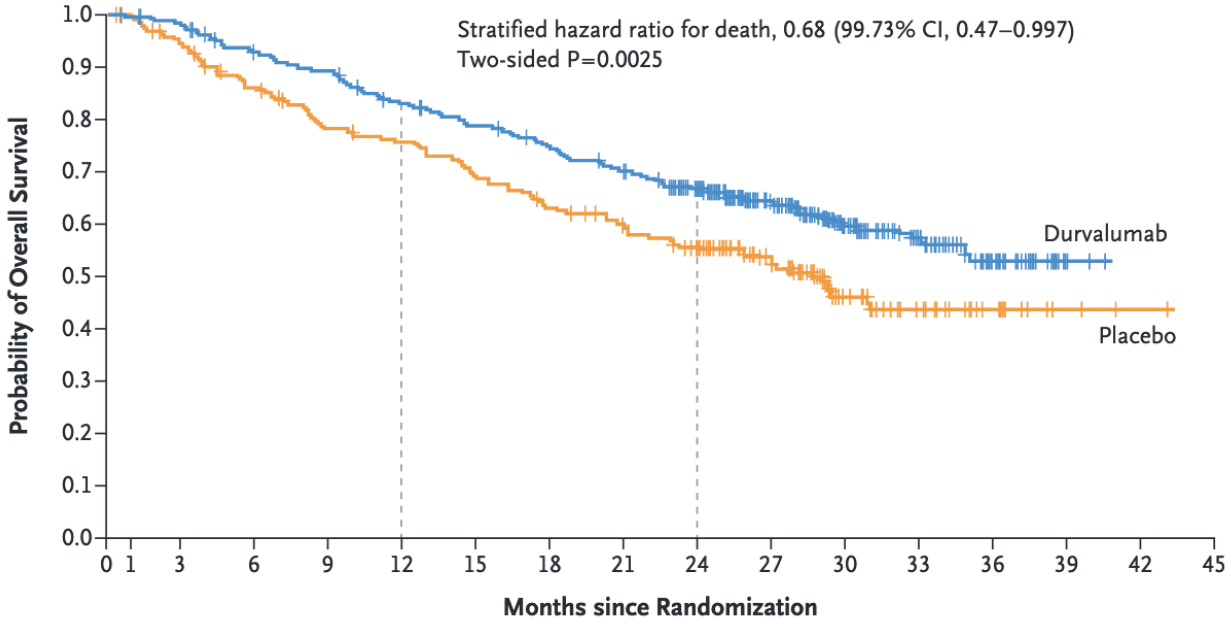
Stratified hazard ratio, 0.53 (95% CI, 0.41–0.68)



Overall survival

	No. of Events/ Total No. of Patients	Median Overall Survival (95% CI)	12-Mo Overall Survival Rate (95% CI)	24-Mo Overall Survival Rate (95% CI)
		mo	%	%
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)

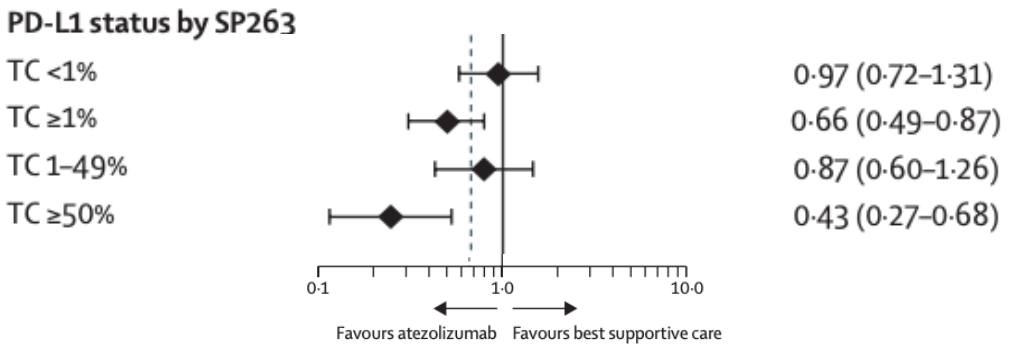
Stratified hazard ratio for death, 0.68 (99.73% CI, 0.47–0.997)
Two-sided P=0.0025



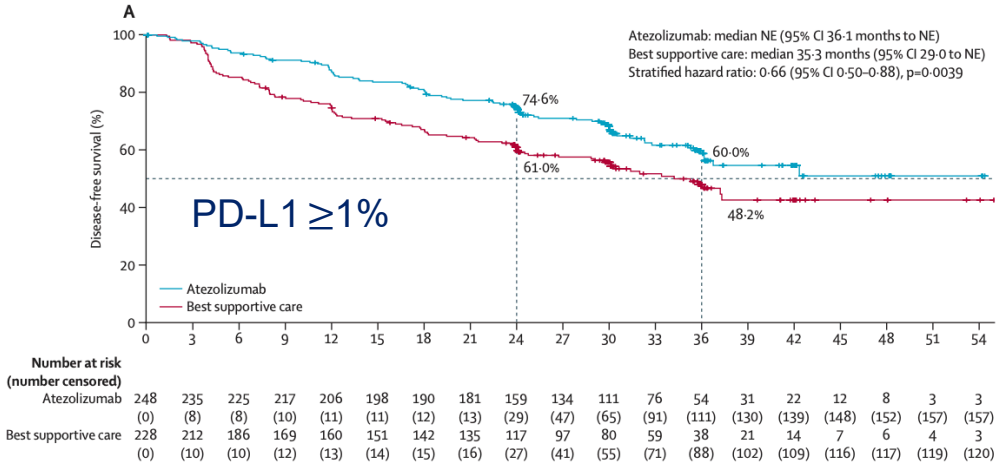
Antonia et al, *N Engl J Med* 2018

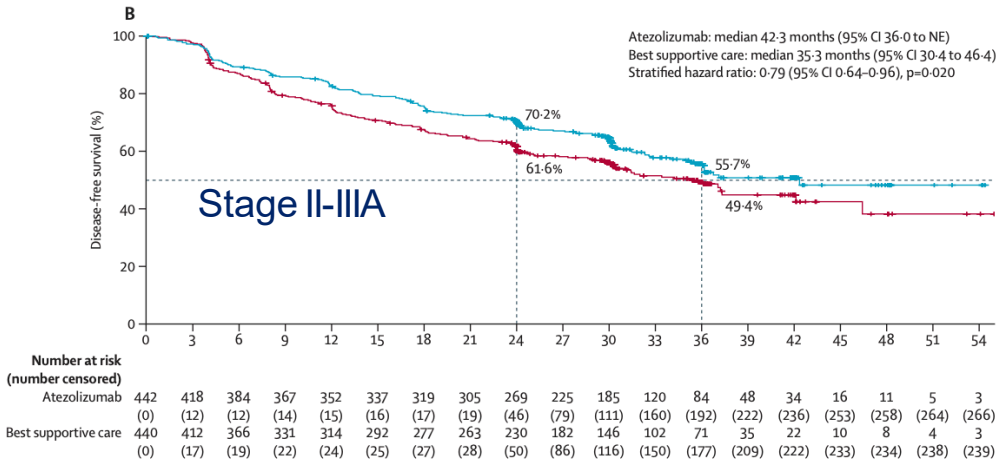
Adjuvant (post-surgical) immunotherapy

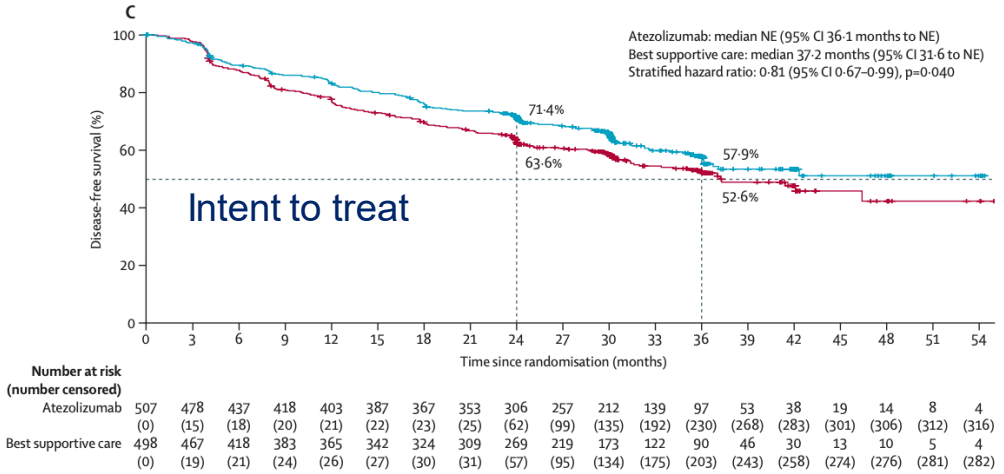
IMpower010:
Adjuvant atezolizumab for stage IB– IIIA NSCLC



Felip et al, *Lancet* 2021



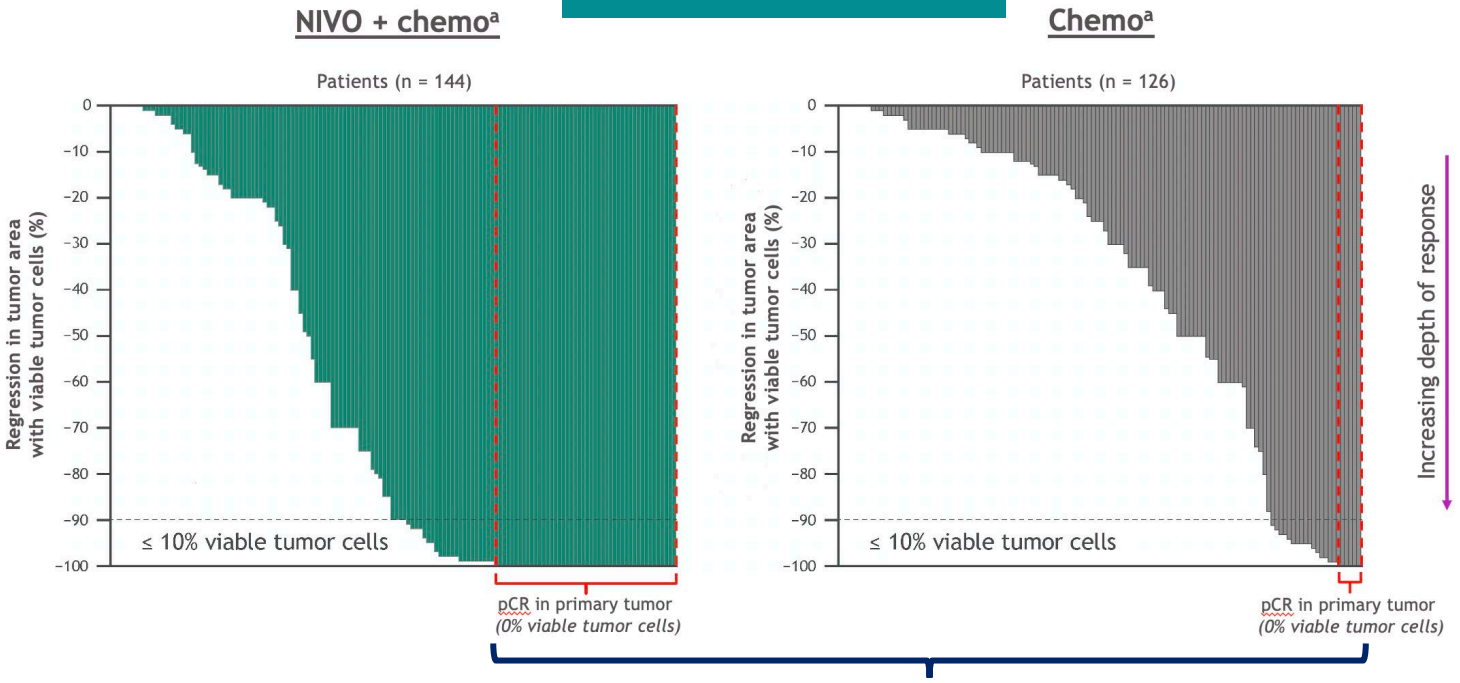




Bringing immunotherapy before surgery: Neoadjuvant chemoIO for NSCLC

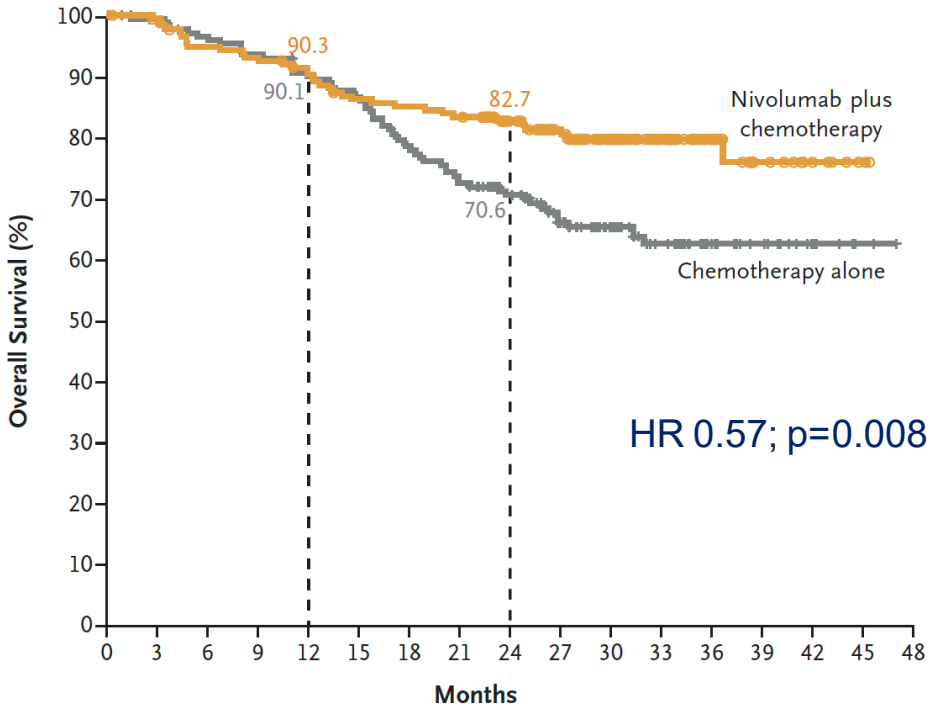
CheckMate 816: Neoadjuvant platinum doublet +/- nivolumab

Tumor reduction



Path CR 24% vs. 2.2%; OR 13.94, p < 0.0001

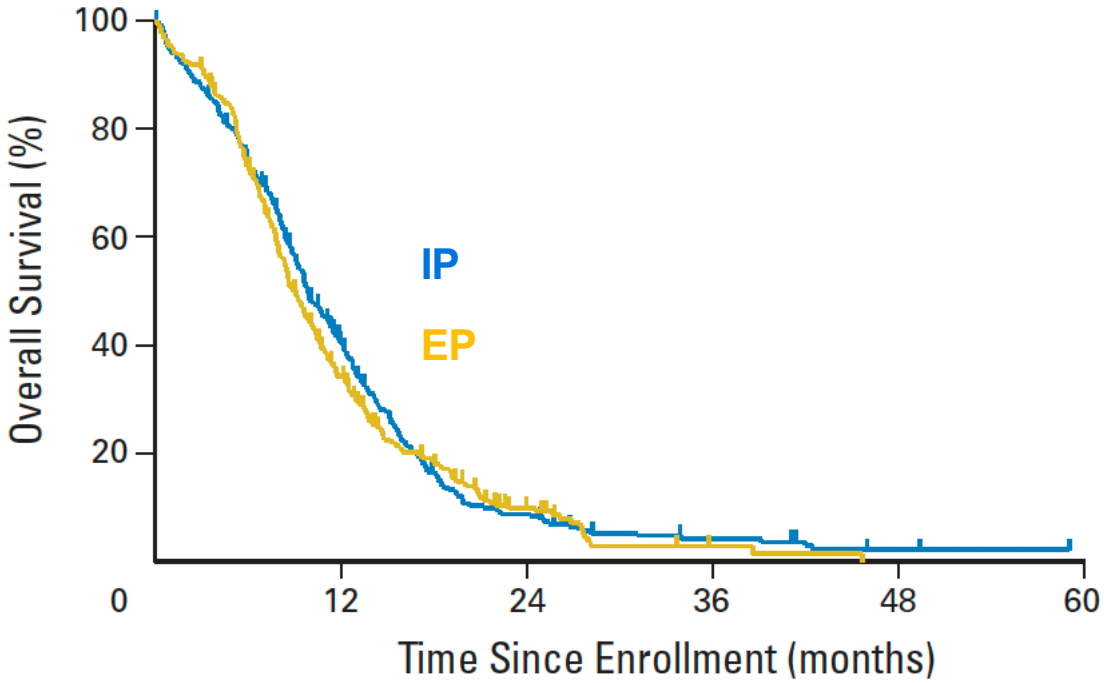
Overall survival



HR 0.57; p=0.008

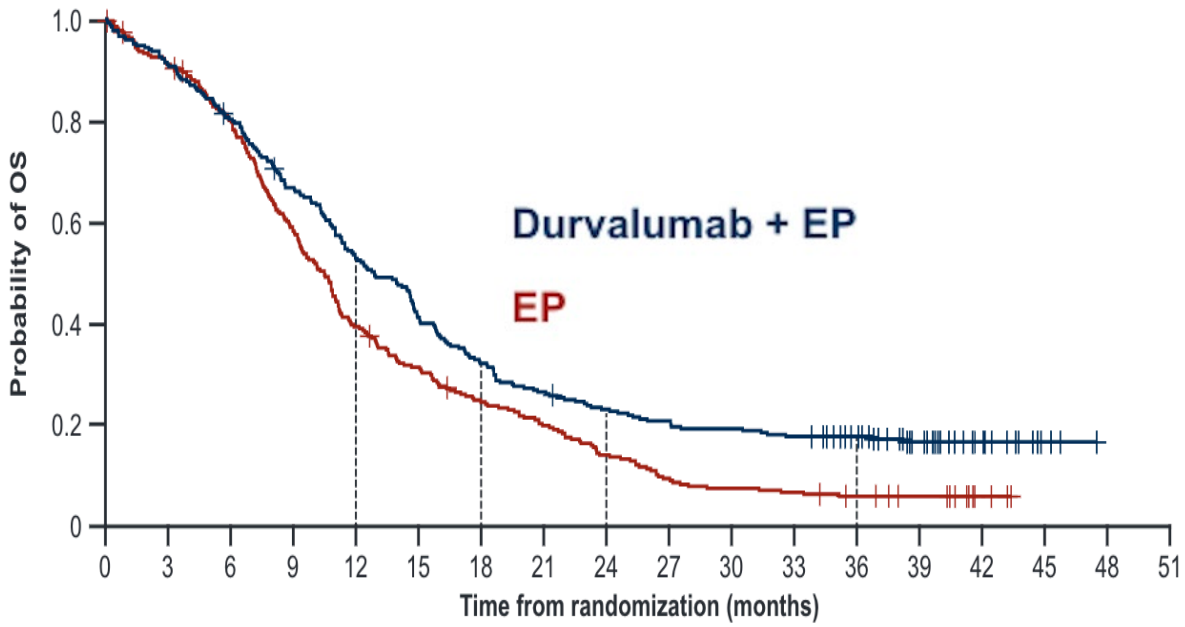
Forde et al, *N Engl J Med 2022*

Small cell lung cancer: where we were, where we are



2009
Comparison of 2 platinum doublet regimens

Two-year survival under 10%
Essentially no long-term survivors



2021
Comparison of platinum doublet with or without IO

Two-year survival approximately 20%
Curves flatten out – 3-year survival will be similar to 2

Again evidence of salvage in the control arm – later IO

Lara et al., *J Clin Oncol* 2009; Goldman et al., *Lancet Oncol* 2021

Summary: first-line indications for immunotherapy in lung cancer

Non-small cell lung cancer

Surgically resectable
- Neoadjuvant ✓
- Adjuvant ✓

Locally advanced
- Post-chemoRT ✓
- *with* chemoRT X?

Metastatic ✓

Small cell lung cancer

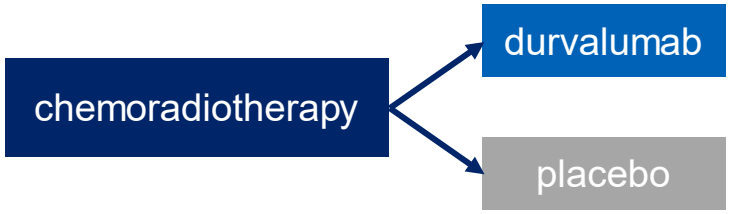
Extensive stage ✓

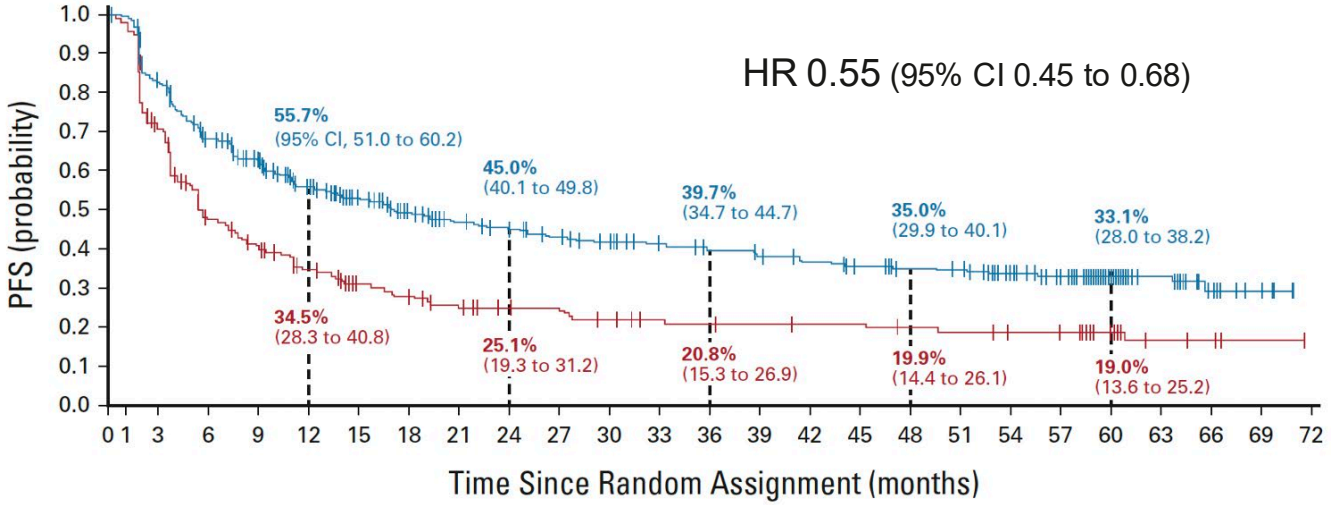
Limited stage
- Post-chemoRT ✓?
- *with* chemoRT ?

Press reports only

Combining IO with radiation – negative interaction?

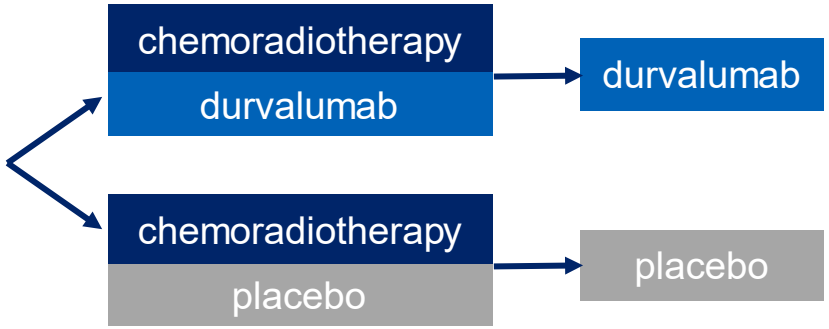
PACIFIC





Spiegel et al., ***J Clin Oncol*** 2022

PACIFIC-2



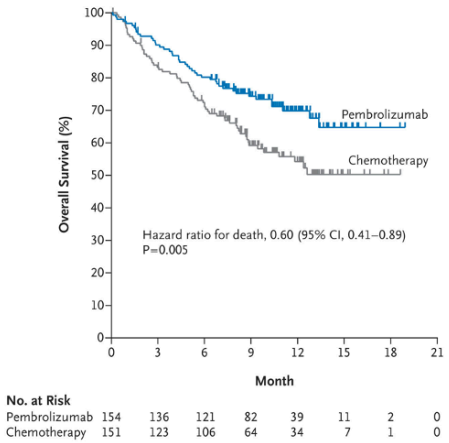
Uh-oh…

Update on PACIFIC-2 Phase III trial of Imfinzi concurrently administered with platinum-based chemoradiotherapy in unresectable, Stage III non-small cell lung cancer

PUBLISHED
14 November 2023

Developing precision medicine for immunotherapy

KEYNOTE 024
Pembro vs Chemo
in NSCLC
with PD-L1 TPS ≥50%



Reck M et al. *N Engl J Med* 2016;375:1823-1833.

If no targetable mutation, check PD-L1

PD-L1 TPS ≥50%

Pembrolizumab Monotherapy

PD-L1 TPS <50%

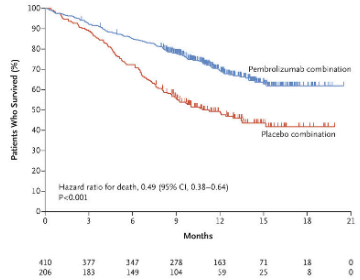
Pembrolizumab + Chemotherapy

Upon development of resistance

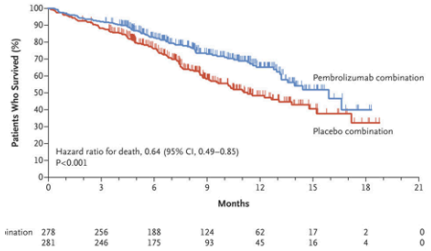
?

Limited understanding of resistance

KEYNOTE 189
Chemo +/- Pembro
in Nonsquamous NSCLC
with PD-L1 TPS 0-100%

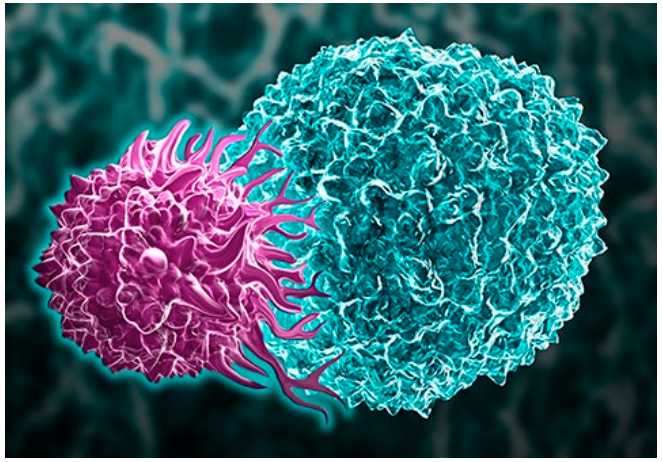


KEYNOTE 407
Chemo +/- Pembro
in Squamous NSCLC with
PD-L1 TPS 0-100%

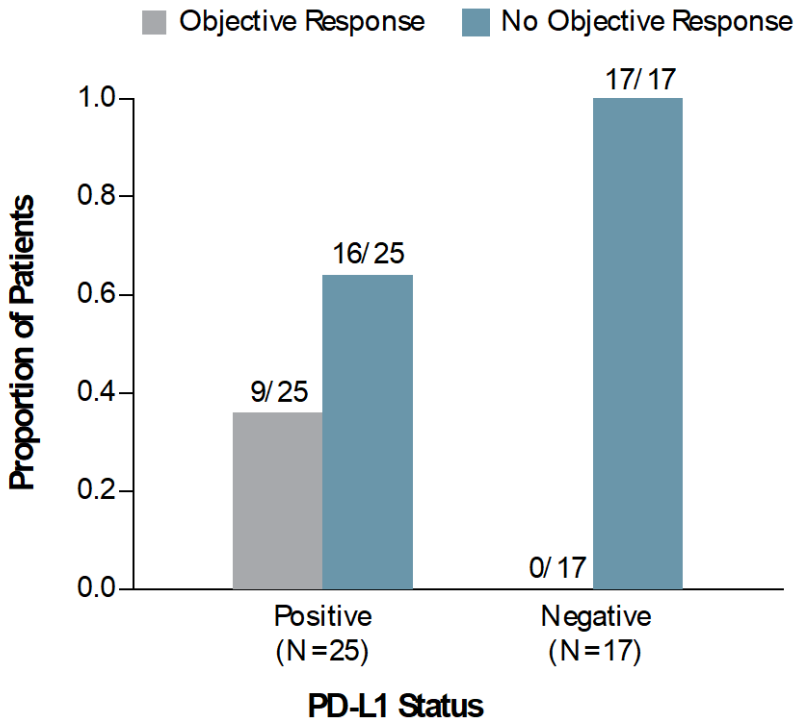


Gandhi L, et al. *N Engl J Med* 2018;378:2078-2092.
Paz-Ares L, et al. *N Engl J Med* 2018;379:2040-2051.

The search for predictive biomarkers



Biomarker 1.0: the target, PD-L1!



Association between Pretreatment Tumor PD-L1 Expression and Clinical Response

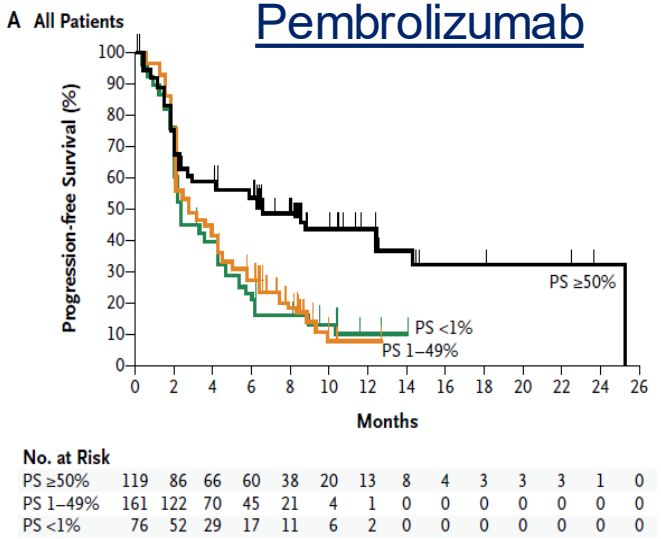
Response Status	PD-L1–Positive	PD-L1–Negative	Total
		number (percent)	
Objective response	9 (36)	0	9 (21)
No objective response	16 (64)	17 (100)	33 (79)
All	25	17	42

P=0.006 for association by Fisher's exact test

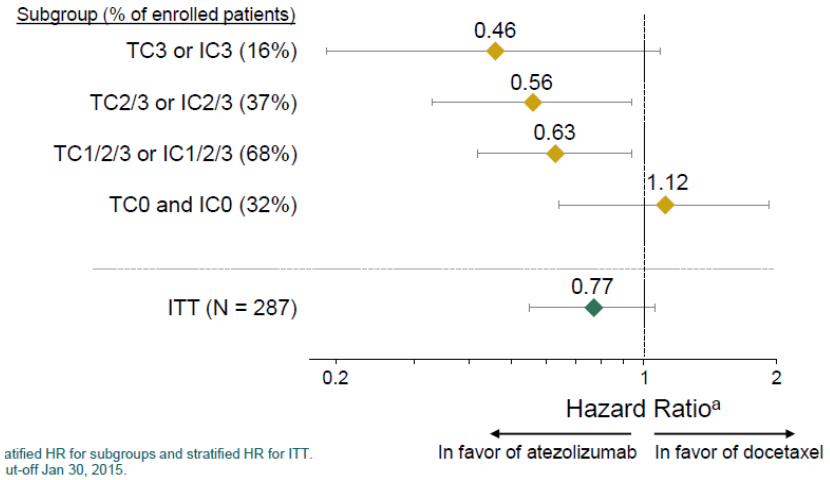
Topalian et al. *NEJM* 2012

PD-L1 positivity is associated with improved responses

Pembrolizumab



Atezolizumab in NSCLC



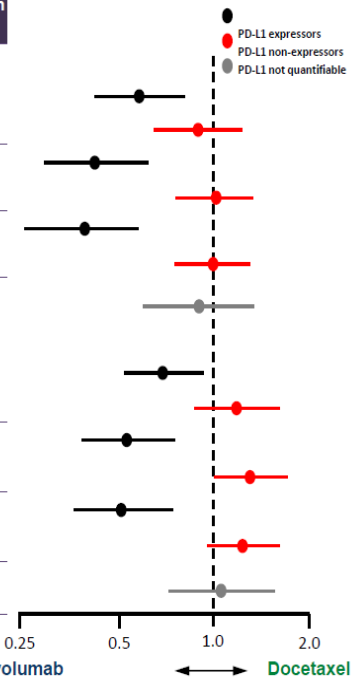
atified HR for subgroups and stratified HR for ITT.
ut-off Jan 30, 2015.

Nivolumab in Non-Squamous NSCLC

OS and PFS Hazard Ratios by Baseline PD-L1 Expression

PD-L1expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction *P*-value[a]
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.0646
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	0.0004
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	0.0002
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable	61	66	0.91 (0.61, 1.35)	
PFS				
≥1%	123	123	0.70 (0.53, 0.94)	0.0227
<1%	108	101	1.19 (0.88, 1.61)	
≥5%	95	86	0.54 (0.39, 0.76)	<0.0001
<5%	136	138	1.31 (1.01, 1.71)	
≥10%	86	79	0.52 (0.37, 0.75)	0.0002
<10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable	61	66	1.06 (0.73, 1.56)	

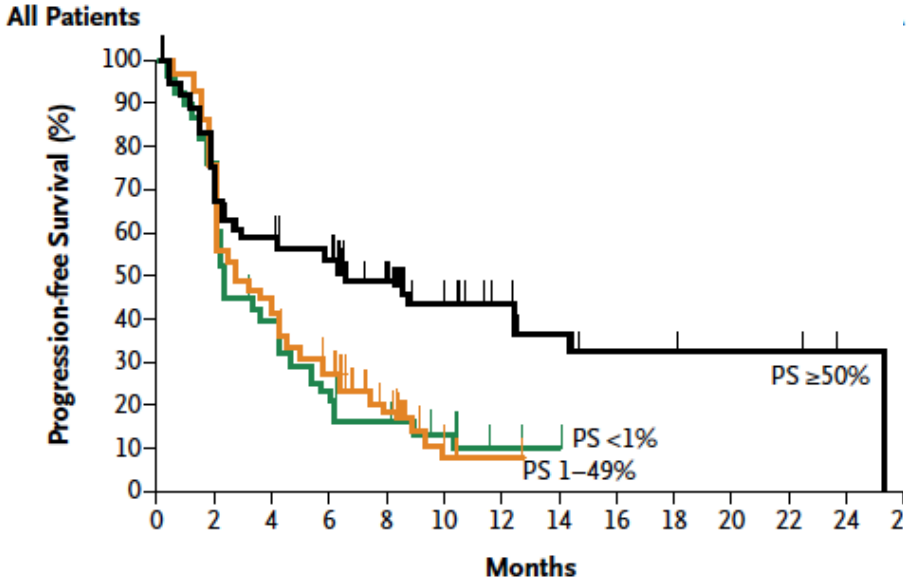
[a] Interaction p-value from Cox proportional hazard model with treatment, PD-L1 expression and treatment by PD-L1 expression interaction.



Garon et al, *NEJM* 2015
Paz Ares, *ASCO* 2015
Spira, *ASCO* 2015

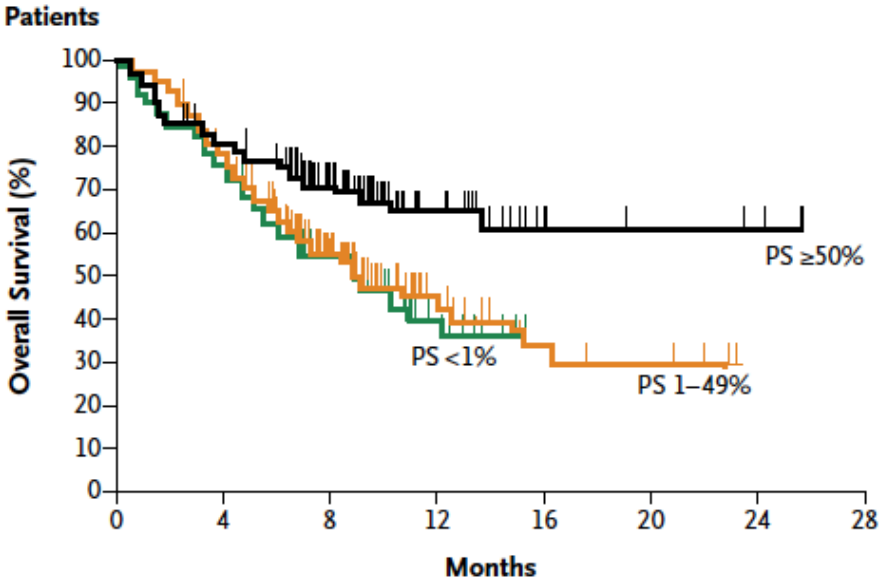
Pembrolizumab in NSCLC – importance of PD-L1?

Progression-free survival



No. at Risk													
PS ≥50%	119	86	66	60	38	20	13	8	4	3	3	3	1
PS 1–49%	161	122	70	45	21	4	1	0	0	0	0	0	0
PS <1%	76	52	29	17	11	6	2	0	0	0	0	0	0

Overall survival

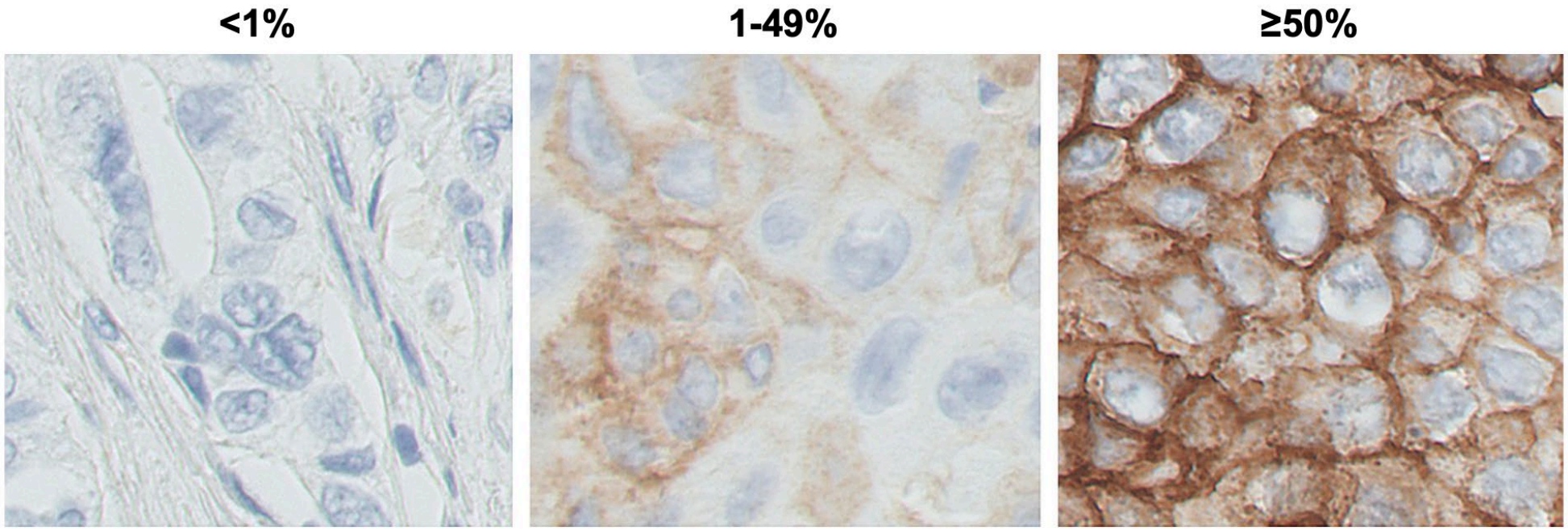


No. at Risk								
PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

Garon et al, *N Engl J Med* 2015

PD-L1 as a predictive biomarker

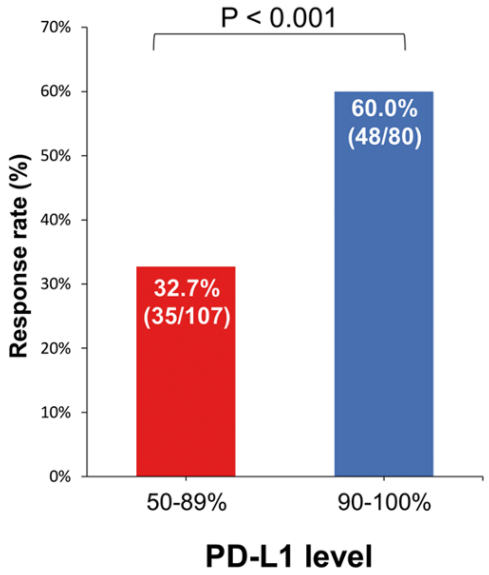
PD-L1 Tumor Proportion Score (TPS)

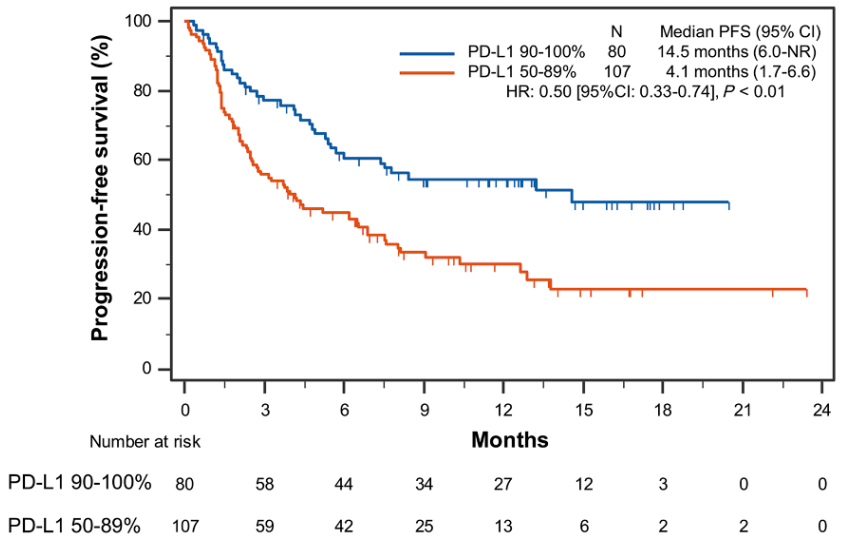


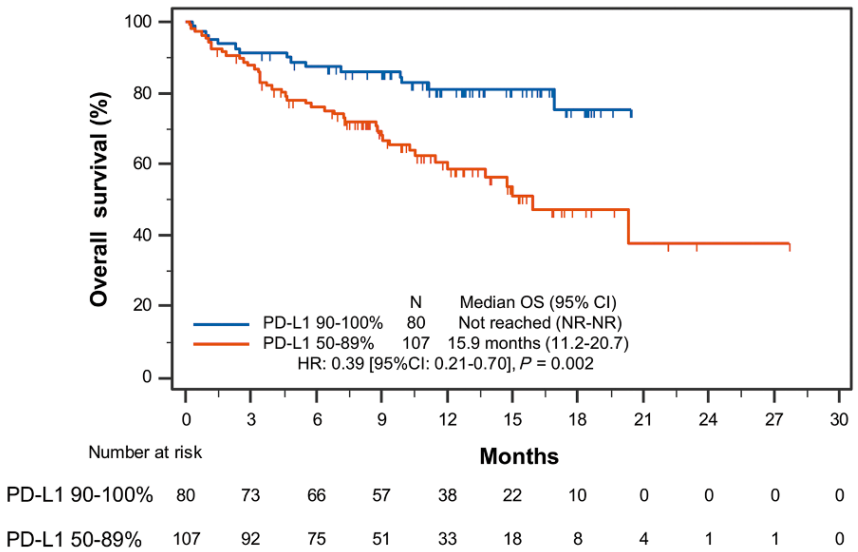
When the PD-L1 TPS is above 50%, are higher levels even better?

Garon et al., *N Engl J Med* 2015

PD-L1 TPS 50-89% vs ≥ 90%







Aguilar et al., *Ann Oncol* 2019

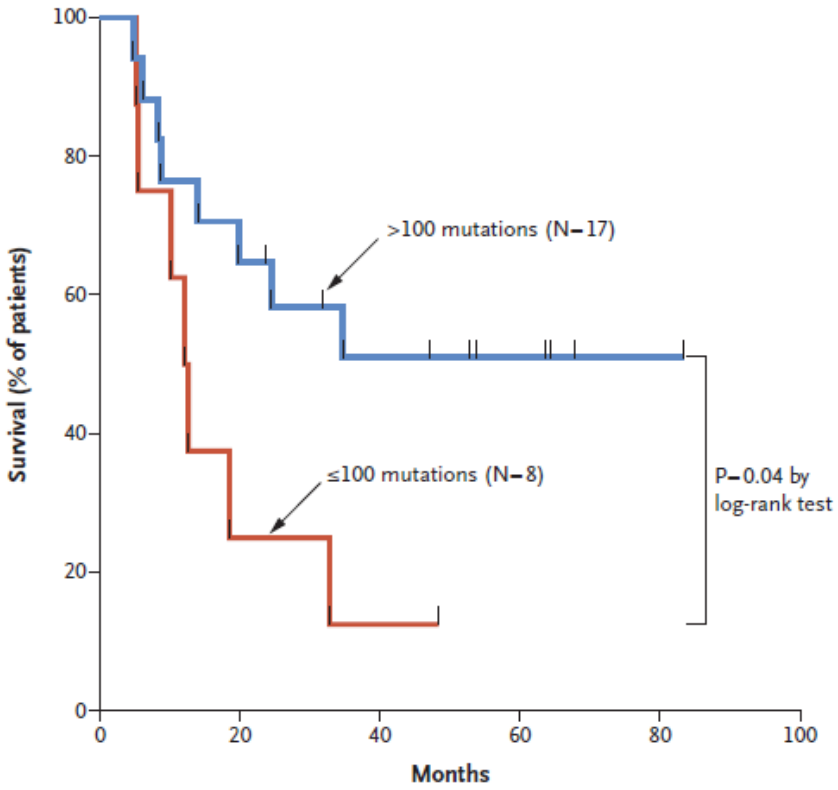
What is the clinical application of PD-L1 testing?

PD-L1 ≠ EGFR

- PD-L1 is a dynamic marker
- PD-L1 is heterogeneously expressed in tumor tissue
- PD-L1 negative tumors can respond to checkpoint blockade
- Would not use PD-L1 status to exclude a patient from checkpoint blockade therapy, however, in the setting of multiple immunotherapeutic agents, this information may be used to shape clinical decisions

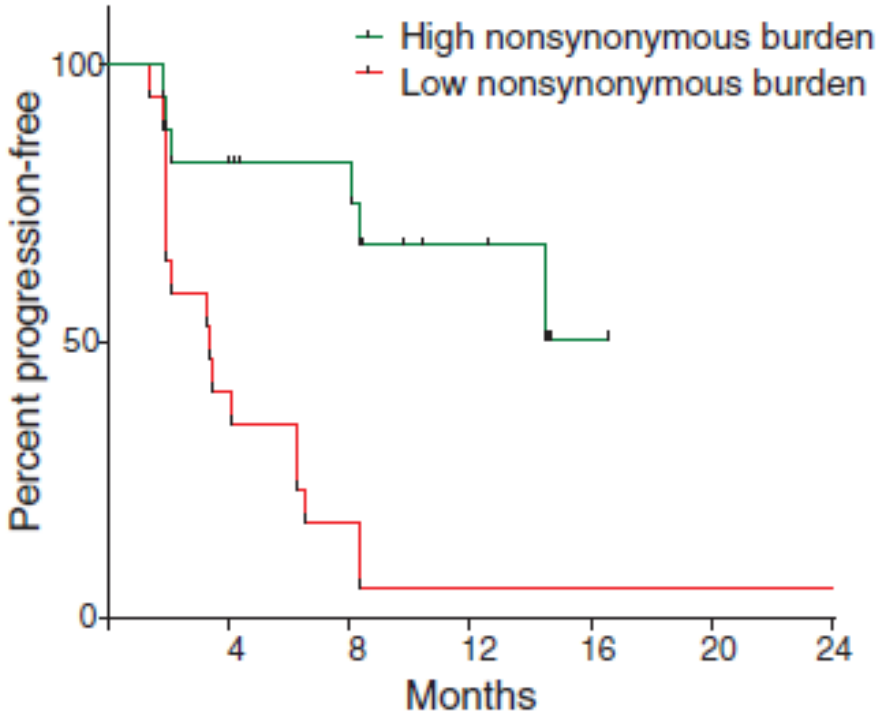
Mutational burden as a predictive biomarker

Melanoma: ipilimumab



Snyder et al, *N Engl J Med* 2015

Lung CA: pembrolizumab



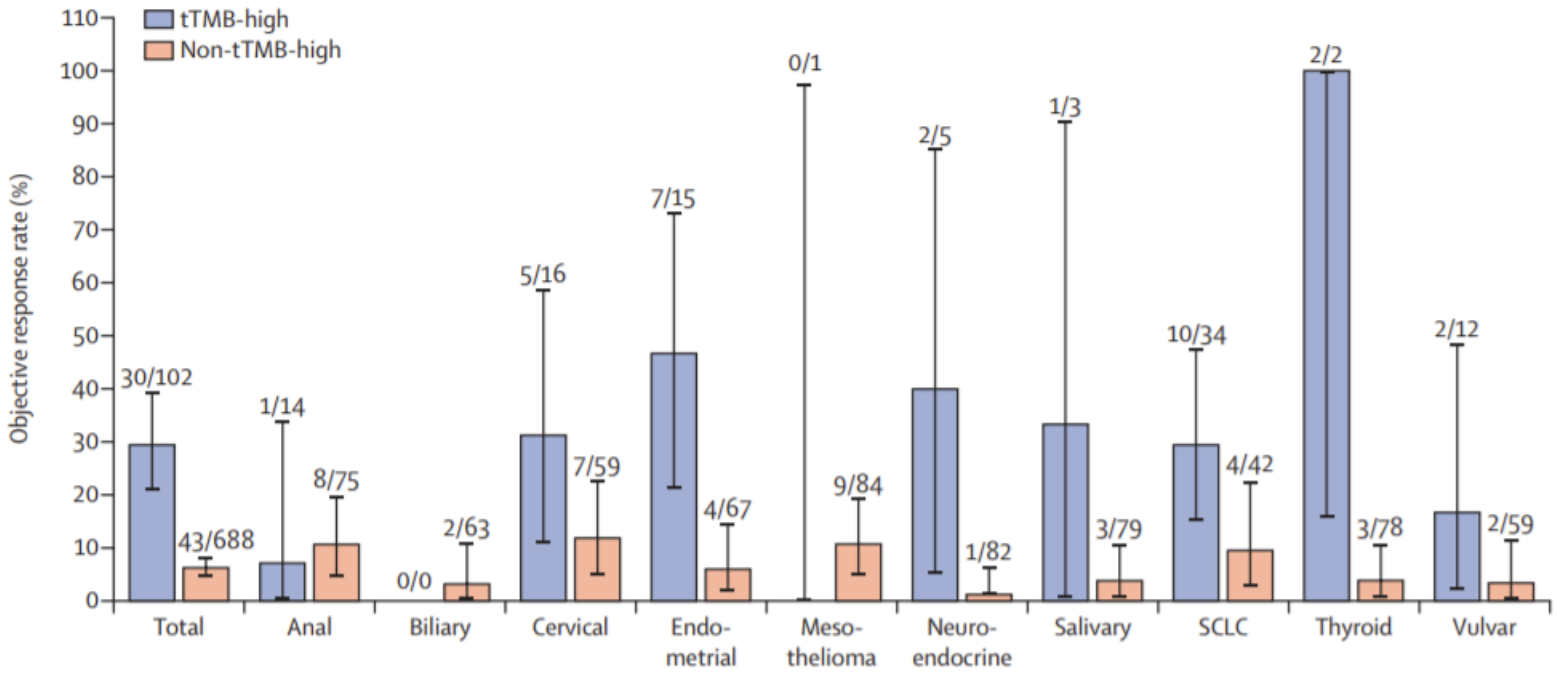
Rizvi et al, *Science* 2015

Pembrolizumab in TMB-high cancers

	tTMB-high (n=102)	tTMB-high (excluding MSI-H; n=81)*	Non-tTMB-high (n=688)
Best response			
Complete response	4 (4%)	3 (4%)	11 (2%)
Partial response	26 (25%)	20 (25%)	32 (5%)
Stable disease	14 (14%)	11 (14%)	227 (33%)
Non-complete response or non-progressive disease†	0	0	3 (<1%)
Progressive disease	48 (47%)	38 (47%)	349 (51%)
Not evaluable‡	1 (1%)	1 (1%)	13 (2%)
Not assessed§	9 (9%)	8 (10%)	53 (8%)
Objective response rate	29% (21–39)	28% (19–40)	6% (5–8)

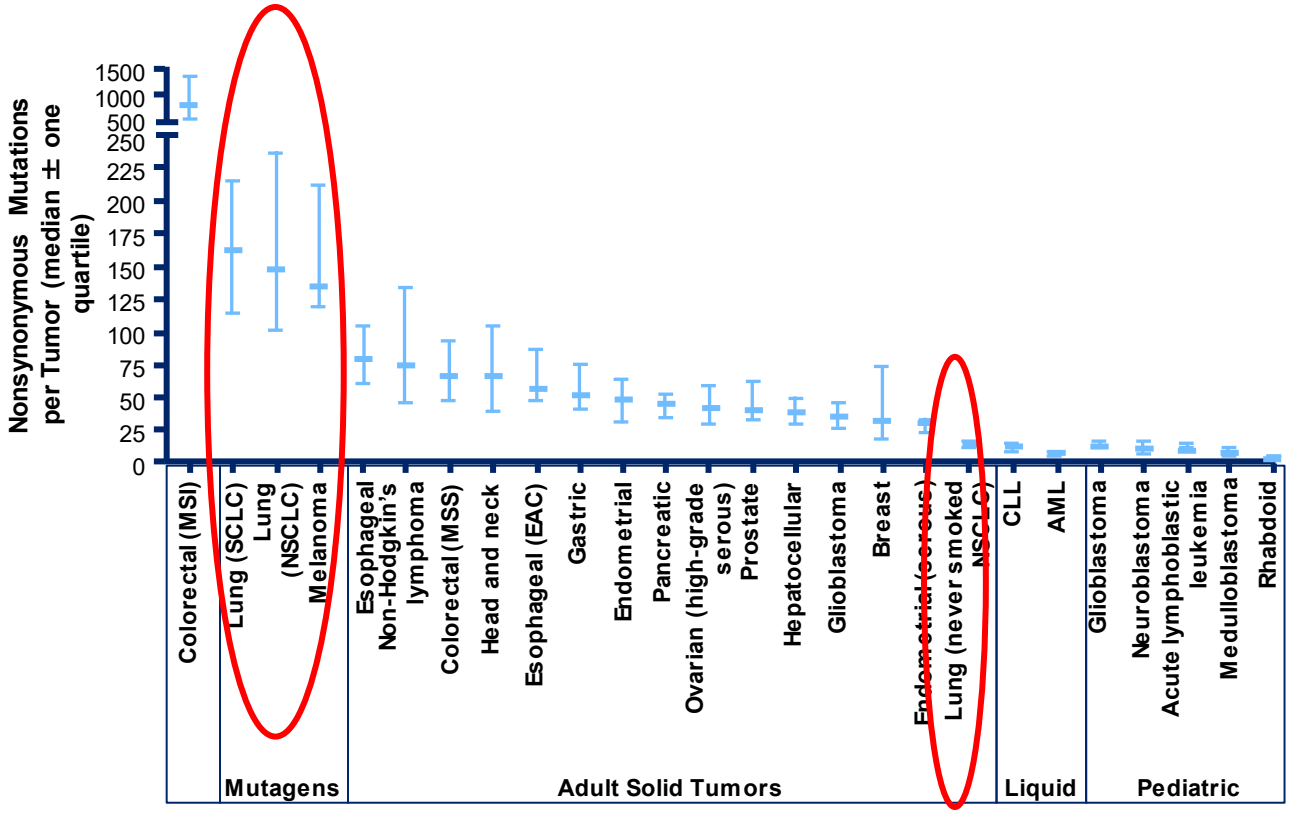
Data are n (%) or % (95% CI). MSI-H=high microsatellite instability. RECIST=Response Evaluation Criteria in Solid Tumors. tTMB-high=high tissue tumour mutational burden. *Excludes 14 patients who were MSI-high and seven additional patients who had missing MSI status. †Patients without measurable disease per central review at baseline who did not have a complete response or progressive disease. ‡Patients who did not have a post-baseline imaging assessment evaluable for response. §Patients who did not have post-baseline imaging.

Table 2: **Objective response (per RECIST version 1.1), assessed by independent central review in the efficacy population**



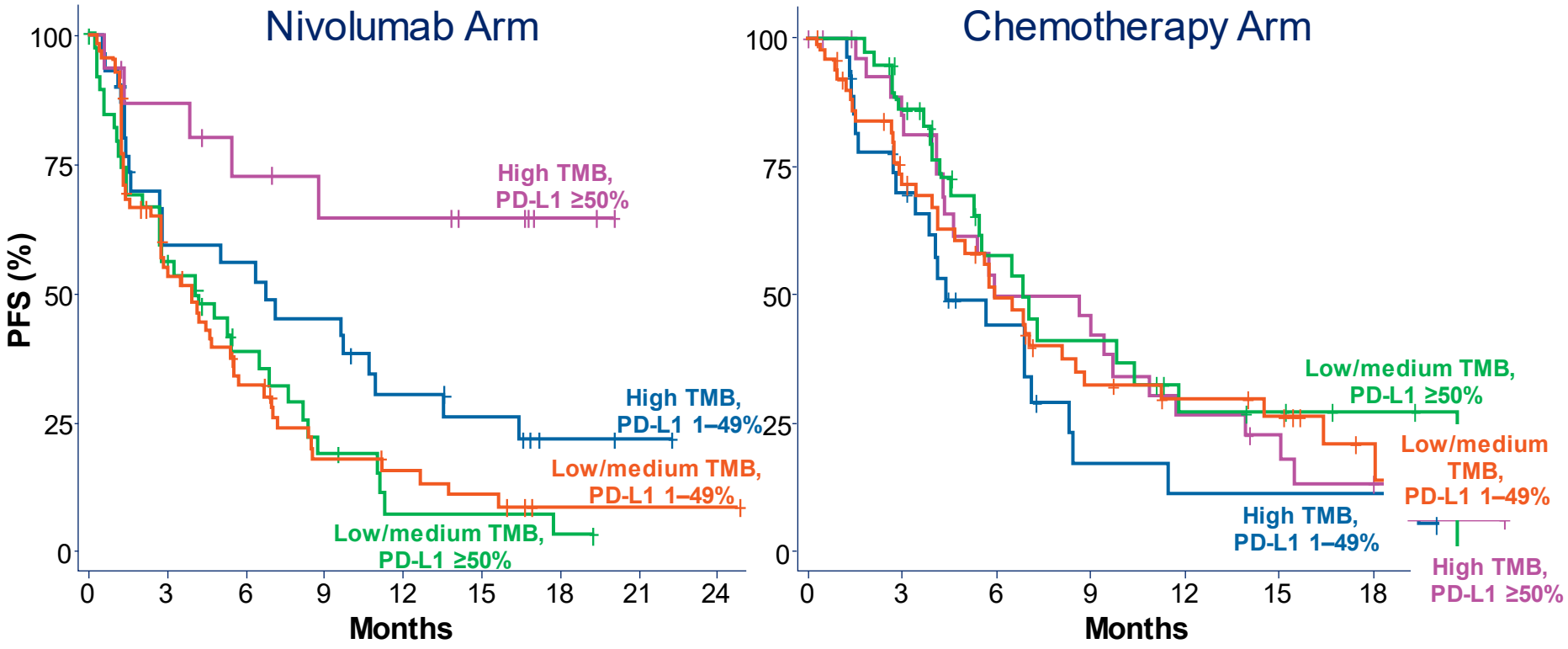
Marabelle et al, *Lancet Oncol* 2020

PD-(L)1 blockade is more active in tumors with high mutation burden



Vogelstein B, et al. *Science*. 2013

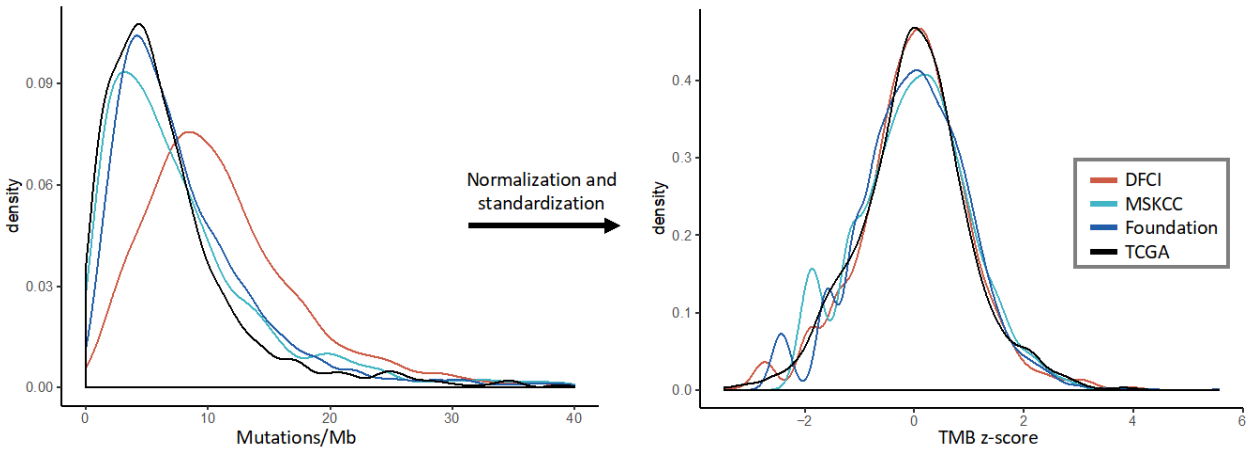
Both PD-L1 and TMB influence response to checkpoint blockade



Peters et al., *AACR* 2017

Challenges with TMB

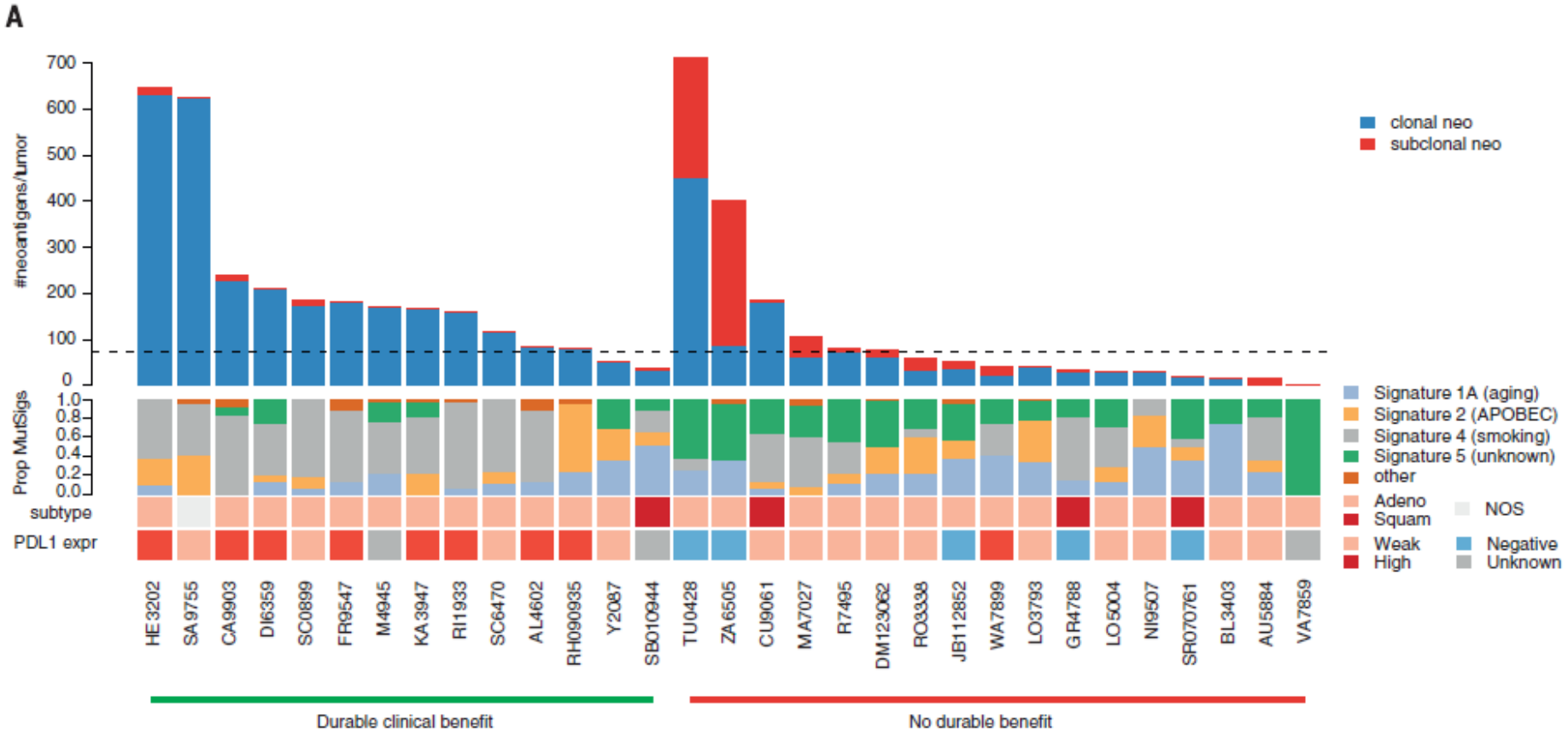
- Still not used routinely for treatment selection in NSCLC
- Limited access to published trial data
- Cohort sizes at any individual institution are relatively small
- Differences across platforms make it difficult to compare and combine data



Percentile	TMB z-score	DFCI TMB	MSKCC TMB	Foundation TMB	TCGA TMB (mutation count)
10th	-1.04	4.81	2.27	2.83	1.84 (55)
20th	-0.47	7.22	3.89	4.45	3.35 (101)
30th	-0.24	8.42	4.78	5.30	4.18 (125)
40th	0.00	9.87	5.90	6.36	5.25 (158)
50th	0.17	11.07	6.89	7.27	6.10 (183)
60th	0.45	13.24	8.76	8.97	7.58 (228)
70th	0.70	15.47	10.82	10.80	9.41 (282)
80th	0.95	18.05	13.34	13.00	11.31 (339)
90th	1.38	23.49	19.10	17.90	15.43 (463)

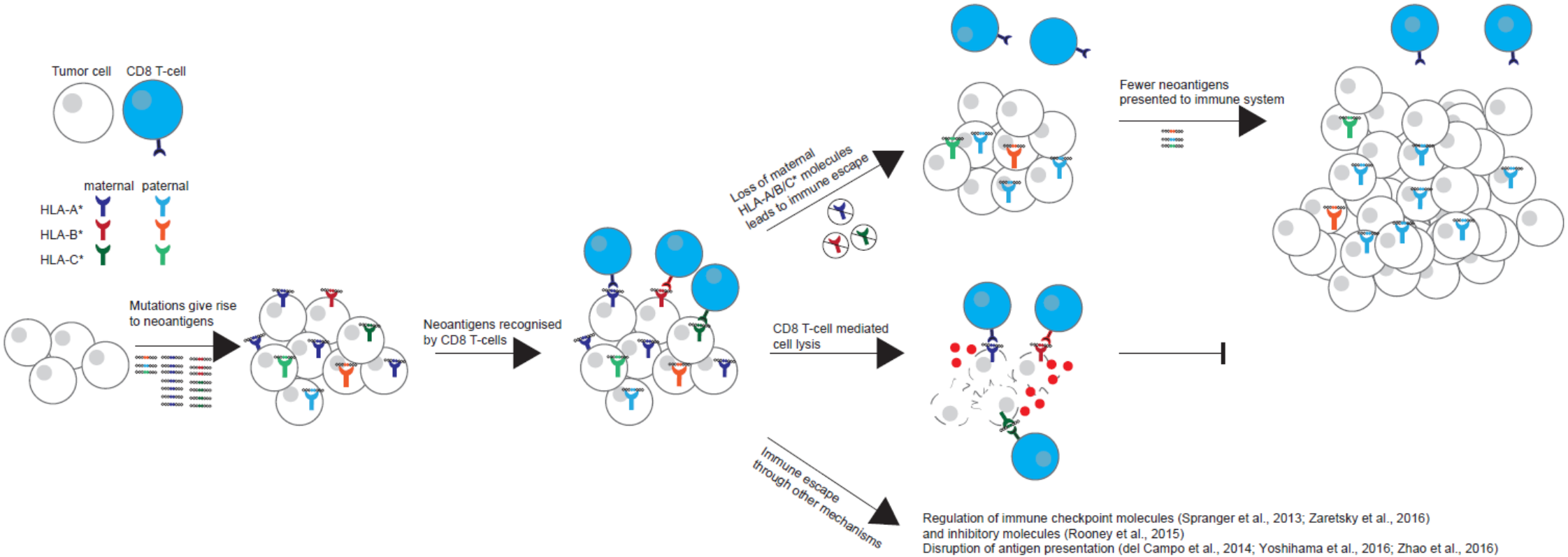
Vokes et al. *JCO Precis Oncol*, 2019

Importance of mutational clonality



McGranahan et al, *Science* 2015

Immune editing through HLA loss of heterozygosity



McGranahan et al, *Cell* 2017

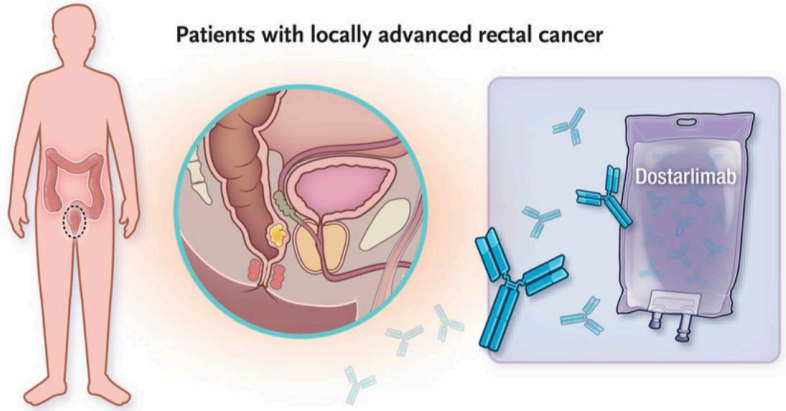
At the extreme end of TMB… MRD rectal cancer

The NEW ENGLAND JOURNAL of MEDICINE

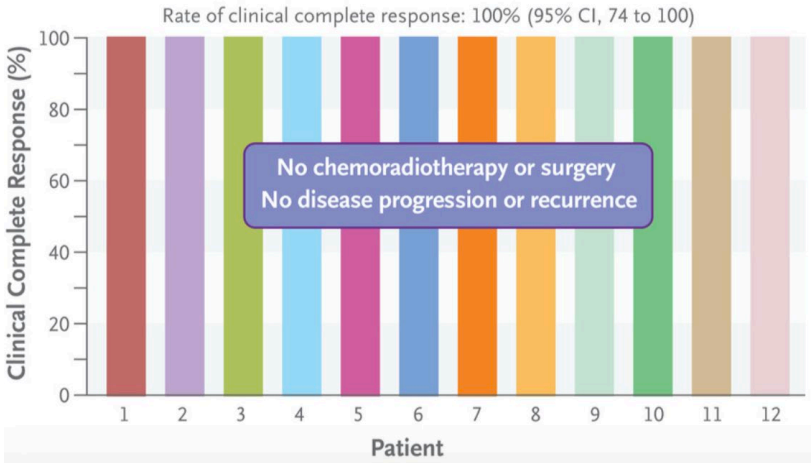
RESEARCH SUMMARY

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Cercek A et al. DOI: 10.1056/NEJMoa2201445



Overall Response to Dostarlimab in 12 Patients



Summary

CTLA-4 blockade is an effective treatment that confers a benefit in overall survival in patients with advanced melanoma

PD-1 (or PD-L1) blockade appears to have activity in melanoma, lung cancer, renal cancer, bladder cancer, head and neck cancer, ovarian cancer, and many other solid tumors

Unique kinetics of response, including delayed responses and long-term durability of responses are characteristic

Unique toxicities are managed with algorithms that employ immunosuppressive agents such as steroids

Further studies are needed to develop biomarkers for these agents and to understand which combinations are most promising

Memorial Sloan Kettering
Cancer Center