Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

New Directions and Immunotherapy Resistance: How to Treat Patients Progressing on Therapy

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#LearnACI

Disclosures

- Consultant for: Genentech, Bristol-Myers Squibb, Merck, AstraZeneca, Maverick, Blueprint Medicine, Syndax, Ariad, Nektar, ArcherDX, Mirati, NextCure, Novartis, EMD Serono
- Research funding (to institute): AstraZeneca, Lilly, Genentech, Bristol-Myers Squibb
- I will be discussing non-FDA approved indications during my presentation.

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NSCLC: Advances in precision genomic medicine

Actionable genomic mutation by NGS?

↓

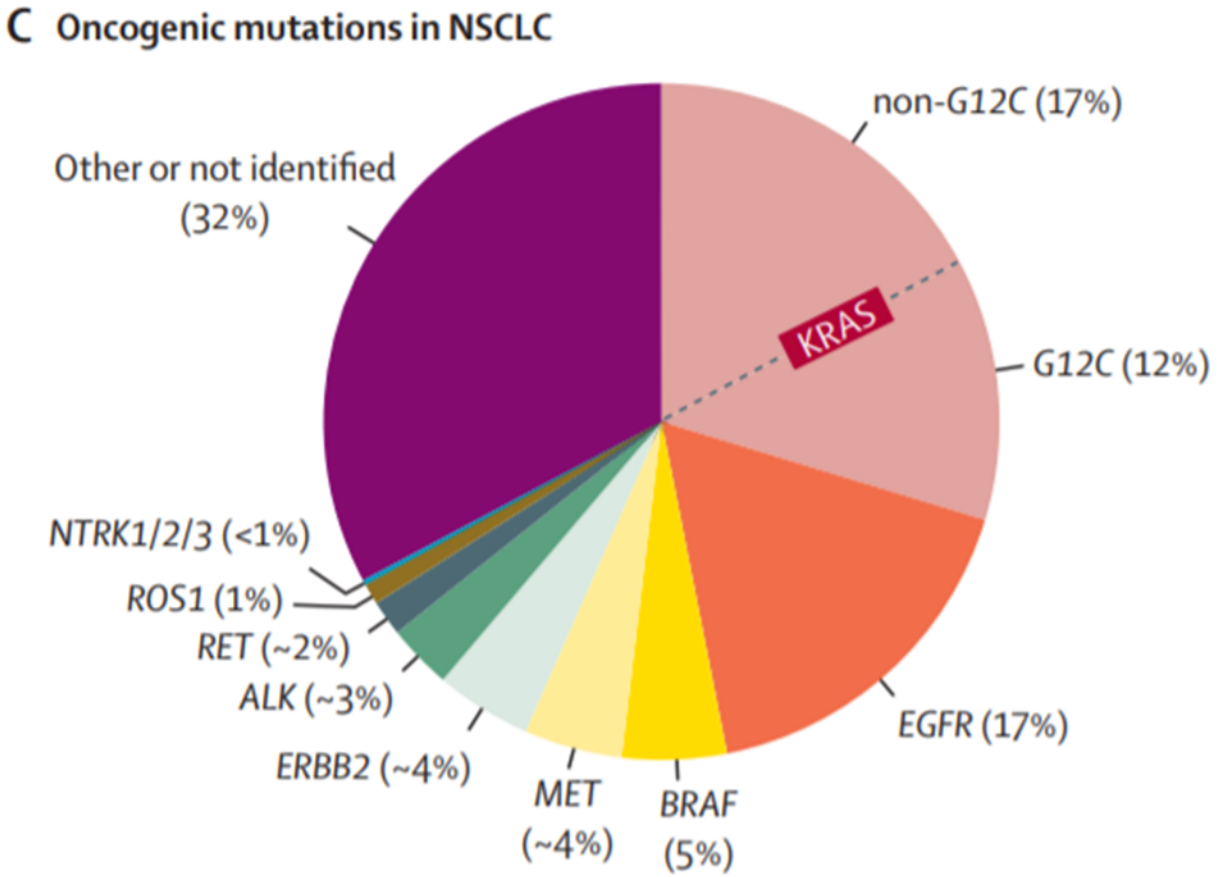
Treat with targeted therapy

↓ *Upon development of acquired resistance*

Repeat biopsy & ctDNA analysis

↓

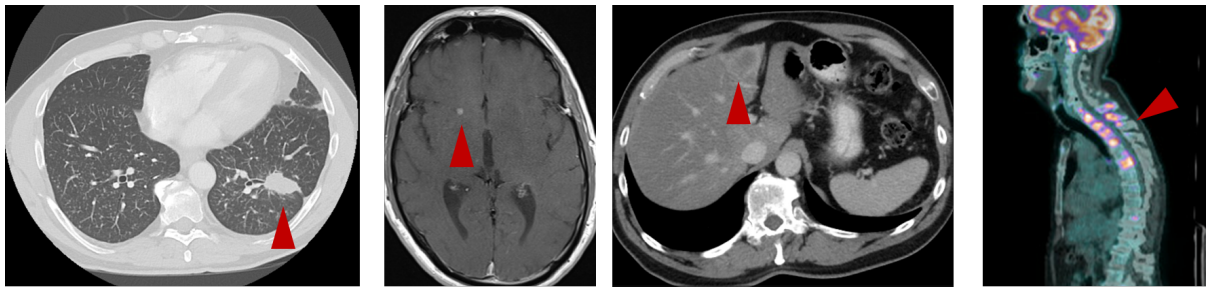
Treat resistance mutations if possible



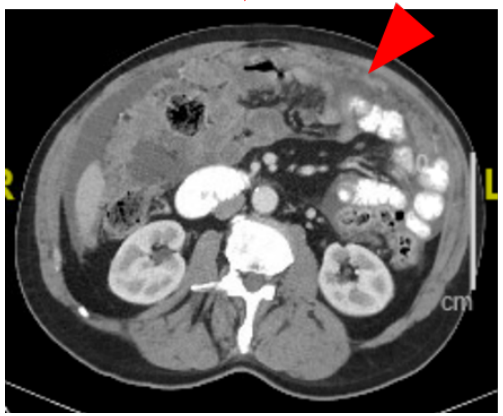
Thai AA, et al, *Lancet* 2021; 398: 535–54

NSCLC: Advances in precision genomic medicine

62yoM with stage IV NSCLC & EGFR exon 19 deletion

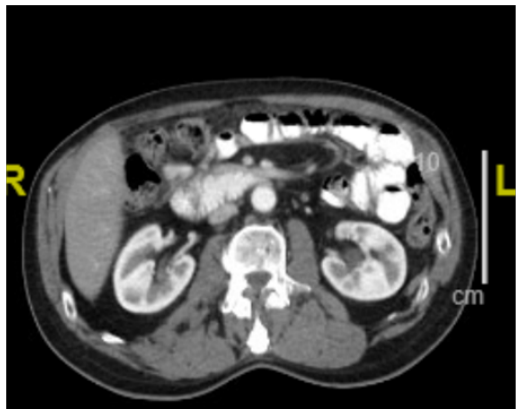


Responded to osimertinib (EGFR TKI), developed resistance at 20 months, new peritoneal carcinomatosis and ascites

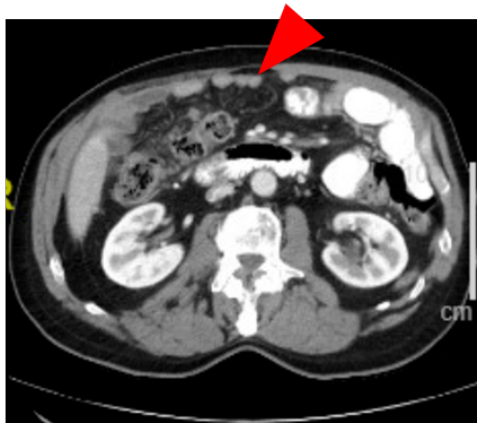


Acquired RET Fusion

Added selpercatinib (RET TKI) to osimertinib



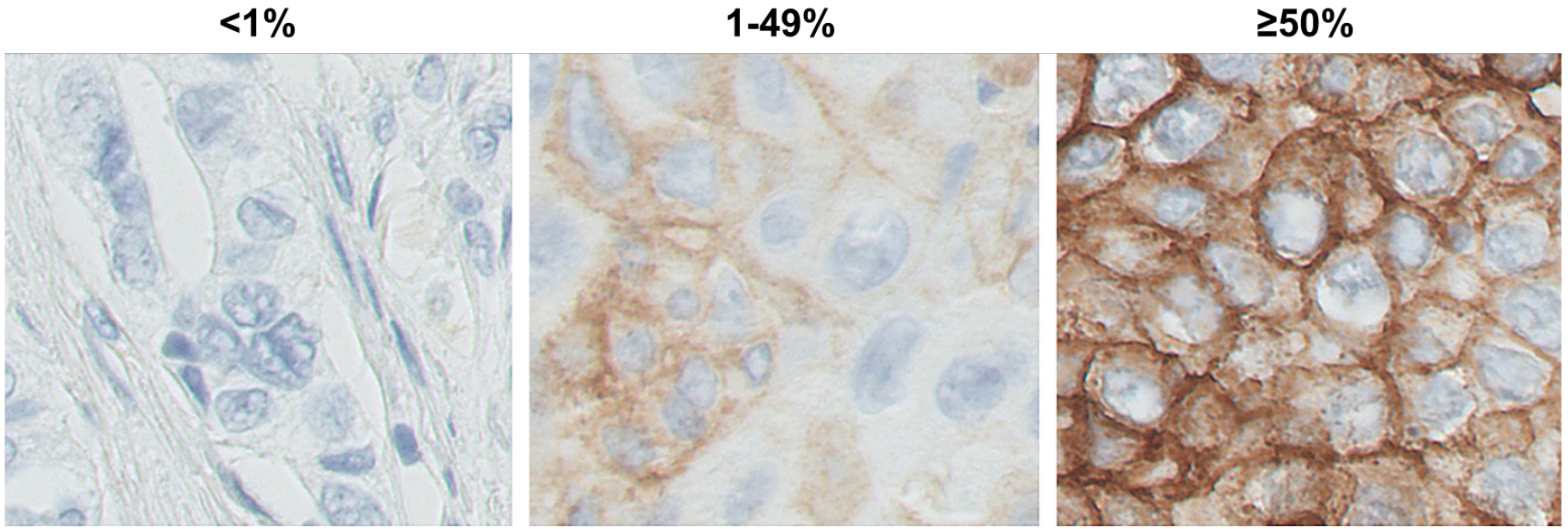
Acquired Resistance



EGFR C797S + RET G810S

Chemotherapy

Biomarkers for Immunotherapy Selection



PD-L1 Tumor Proportion Score (TPS)

Garon EB et al. *N Engl J Med* 2015;372:2018-2028.

Developing Precision Medicine for Immunotherapy

If no targetable mutation, check PD-L1

PD-L1 TPS ≥50%

PD-L1 TPS <50%

Pembrolizumab Monotherapy

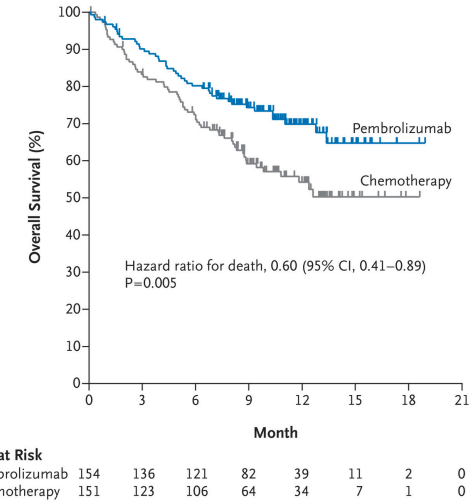
Pembrolizumab + Chemotherapy

Upon development of resistance

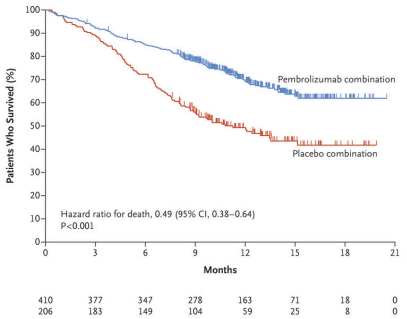
?

Limited understanding of resistance

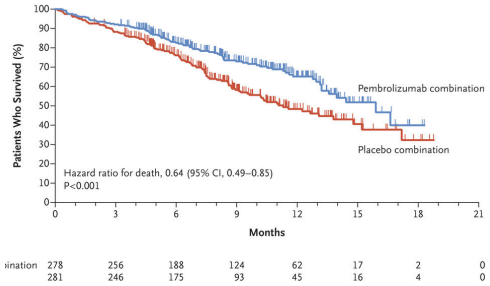
KEYNOTE 024
Pembro vs Chemo
in NSCLC
with PD-L1 TPS ≥50%



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%



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

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

What are the known mechanisms of primary and acquired resistance to immunotherapy in lung cancer?

Biomarkers of Immunotherapy Efficacy

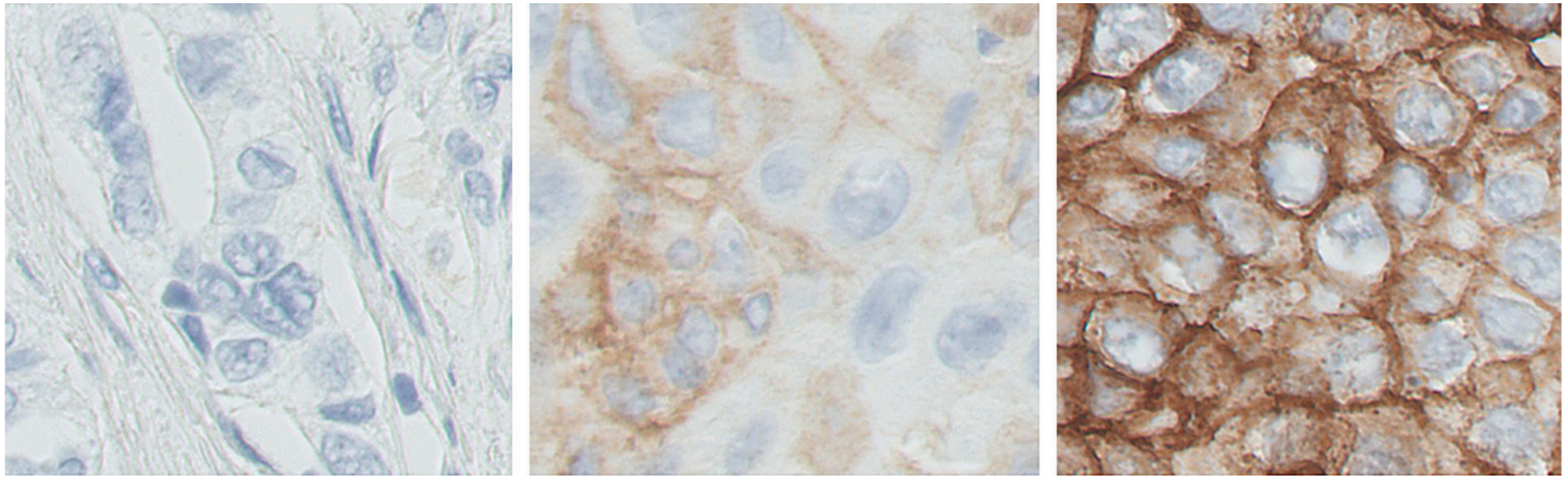
- Pathologic Factors
  - PD-L1 expression
- Genomic Factors
  - Tumor mutational burden, specific genomic subtypes
- Circulating Factors
  - Neutrophil-lymphocyte ratio (NLR)
- Immunologic Factors
  - Gene expression signatures
  - Immune cell subsets

PD-L1 Expression

PD-L1 as a predictive biomarker

PD-L1 Tumor Proportion Score (TPS)

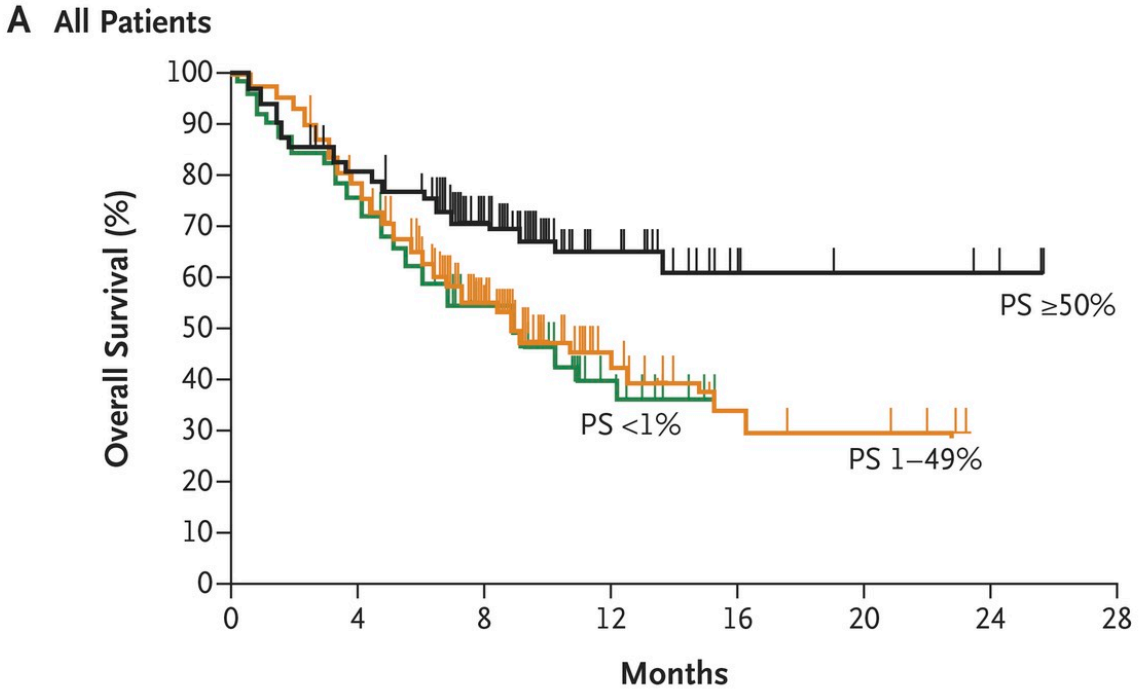
<1% **1-49%** **≥50%**



Garon EB et al. *N Engl J Med* 2015;372:2018-2028.

PD-L1 as a predictive biomarker

KEYNOTE 001



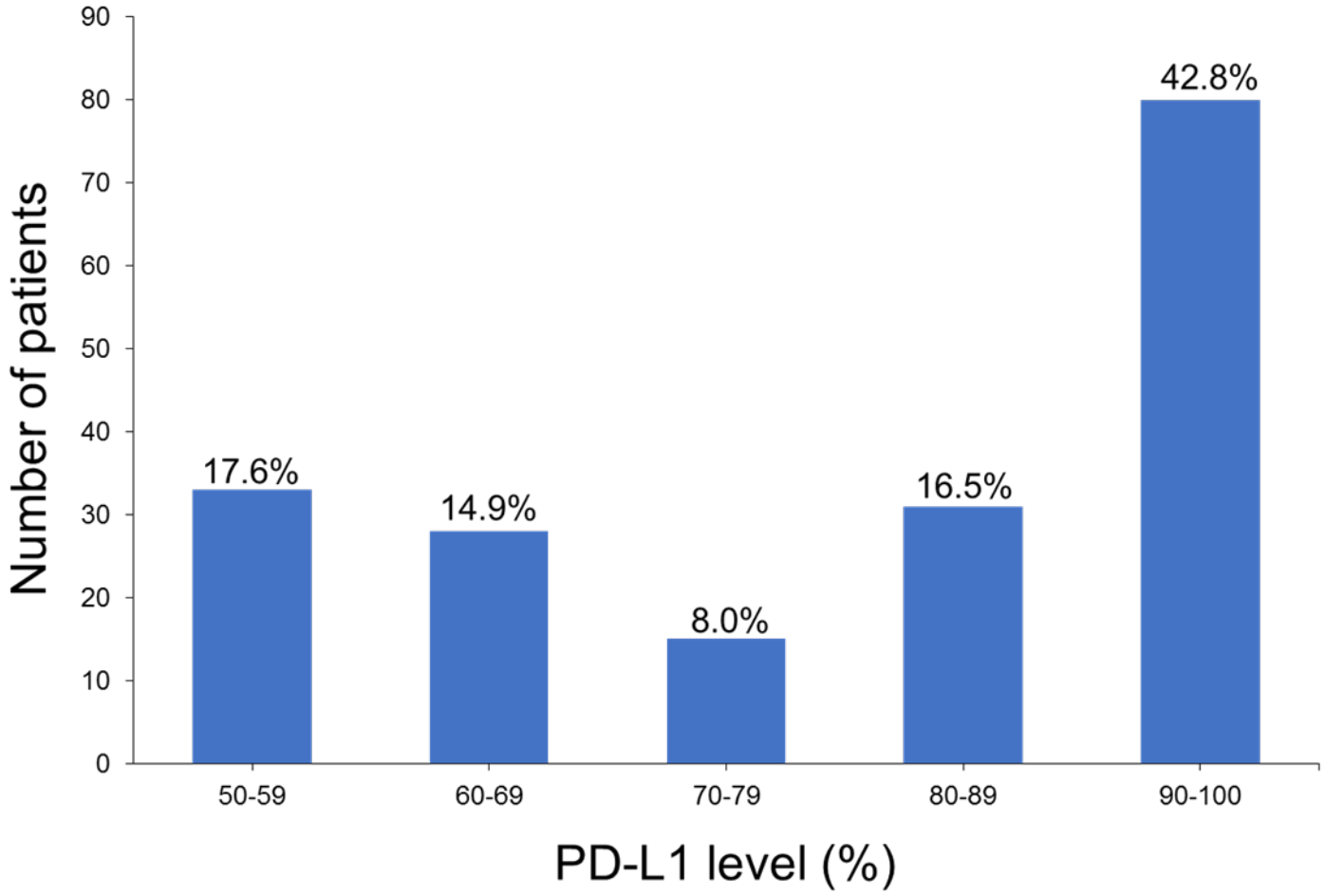
No. at Risk								
PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

Garon EB et al. *N Engl J Med* 2015;372:2018-2028.

PD-L1 TPS ≥50%: Is higher even better?

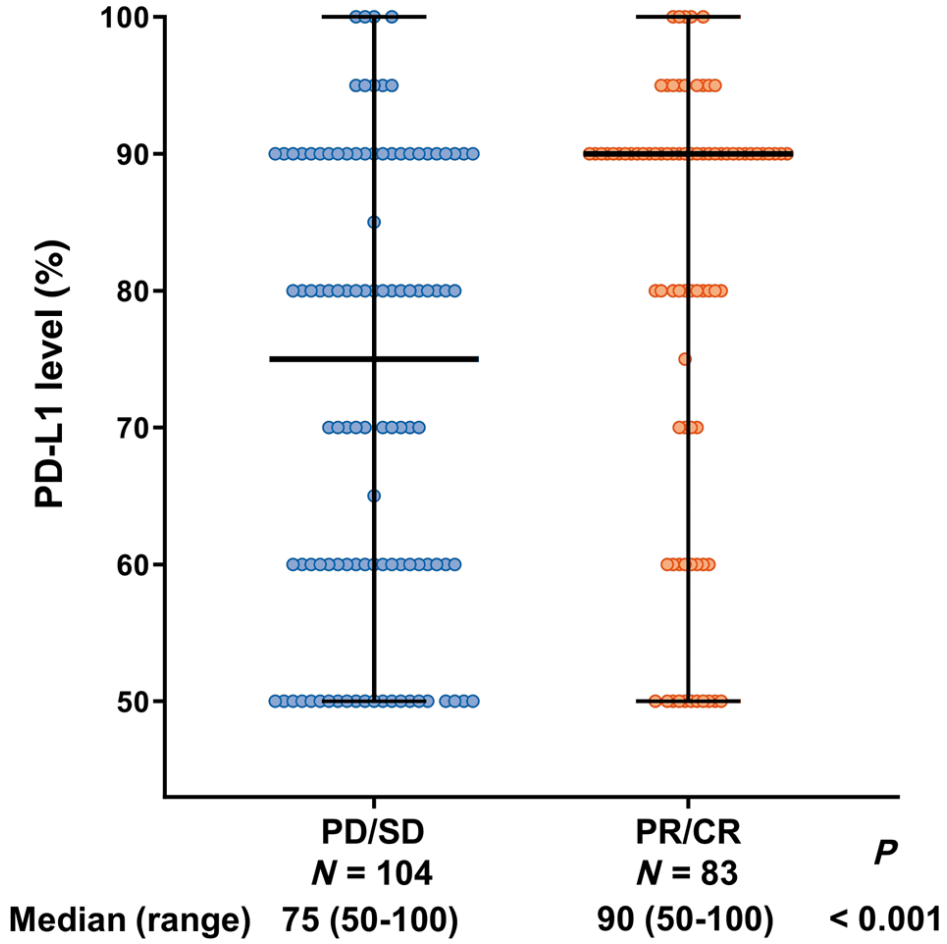
Retrospective analysis:

- 4 academic institutions
- 187 patients with NSCLC
- 1st-line commercial pembrolizumab
- PD-L1 TPS ≥50%
- EGFR/ALK excluded



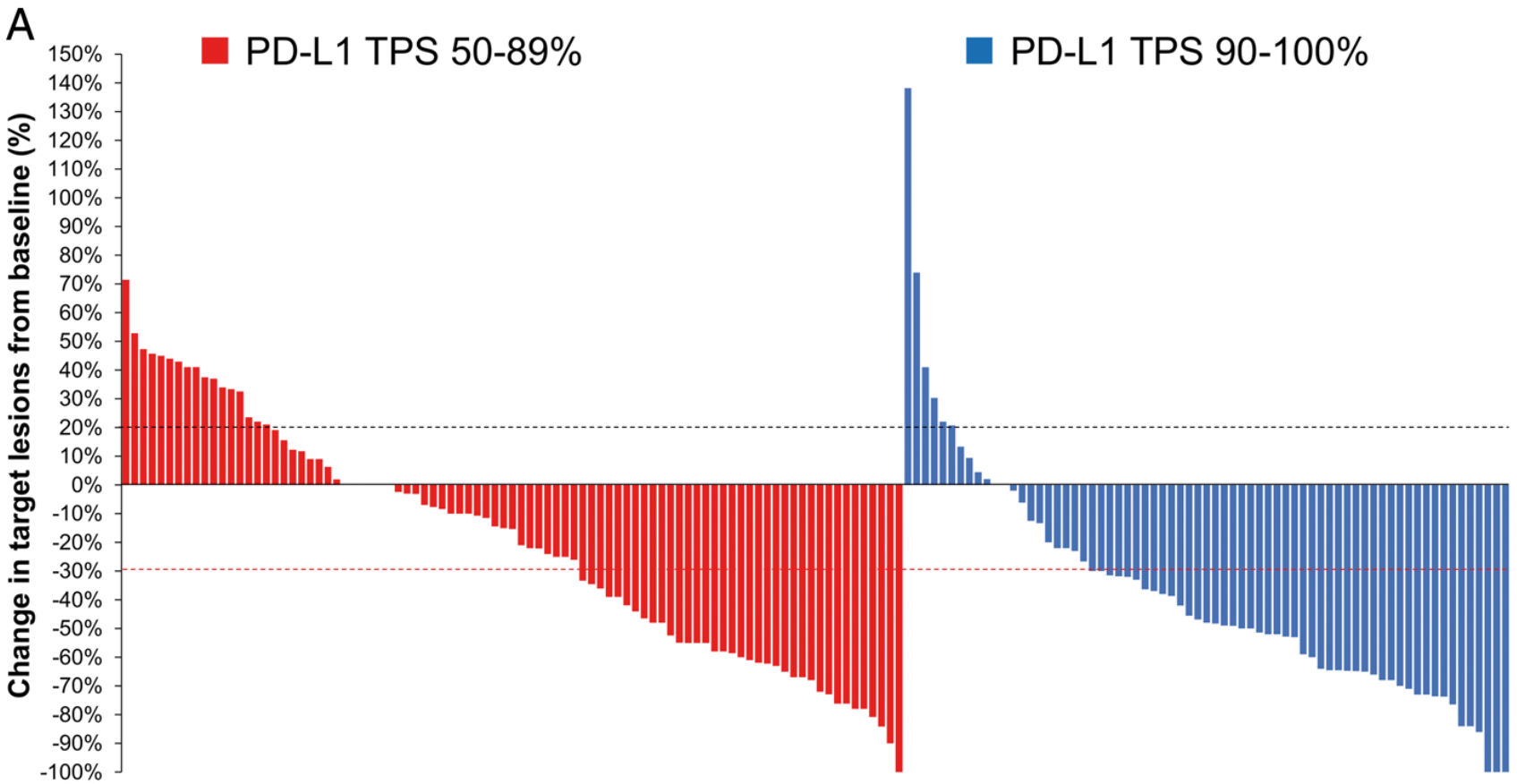
Aguilar, EJ, Ricciuti, B, et al, *Ann Oncol*, 2019, 30 (10), 1653-1659.

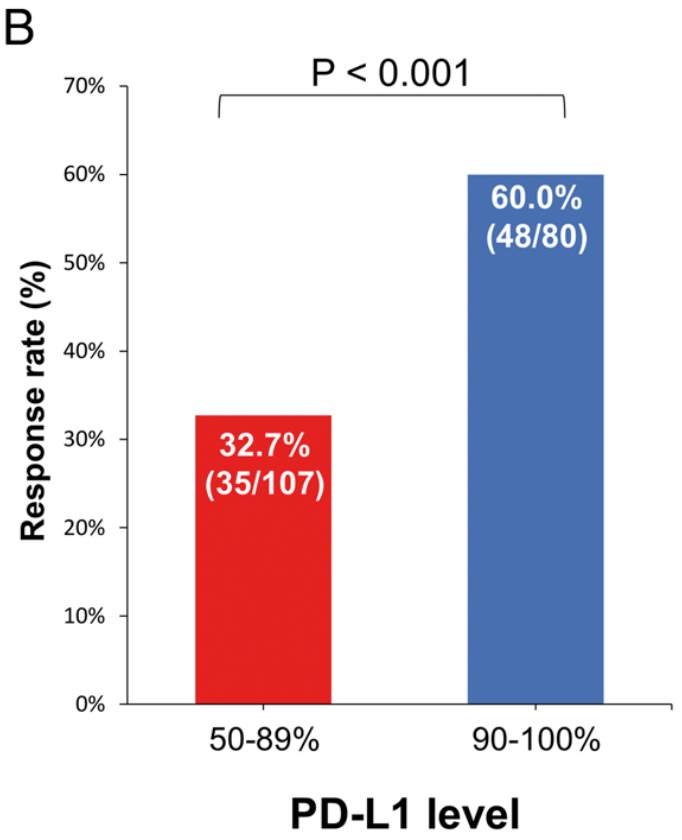
PD-L1 TPS in responders vs nonresponders



Aguilar, EJ, Ricciuti, B, et al, *Ann Oncol*, 2019, 30 (10), 1653-1659.

PD-L1 TPS 50-89% vs ≥90%





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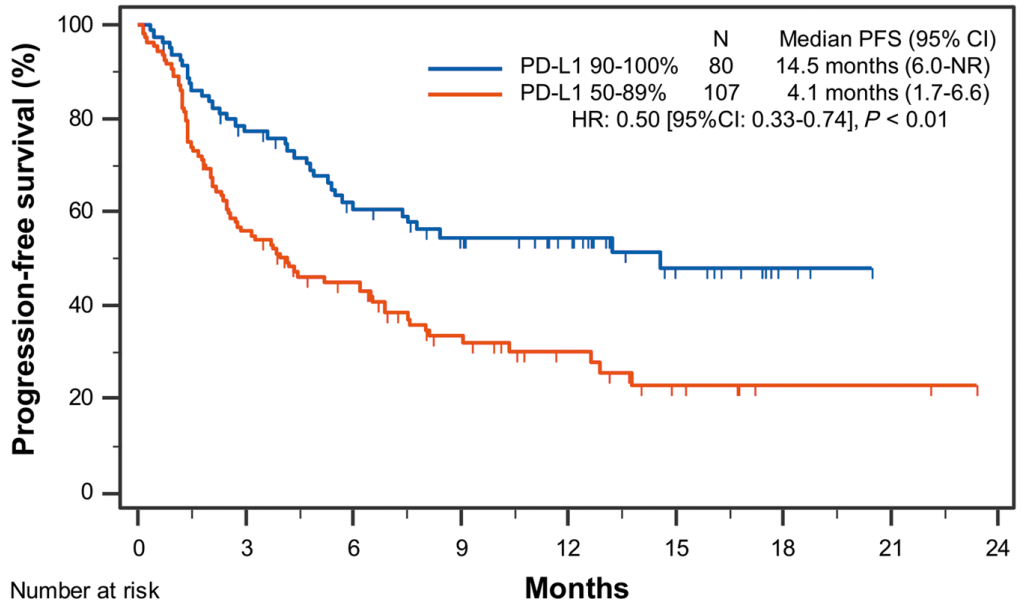
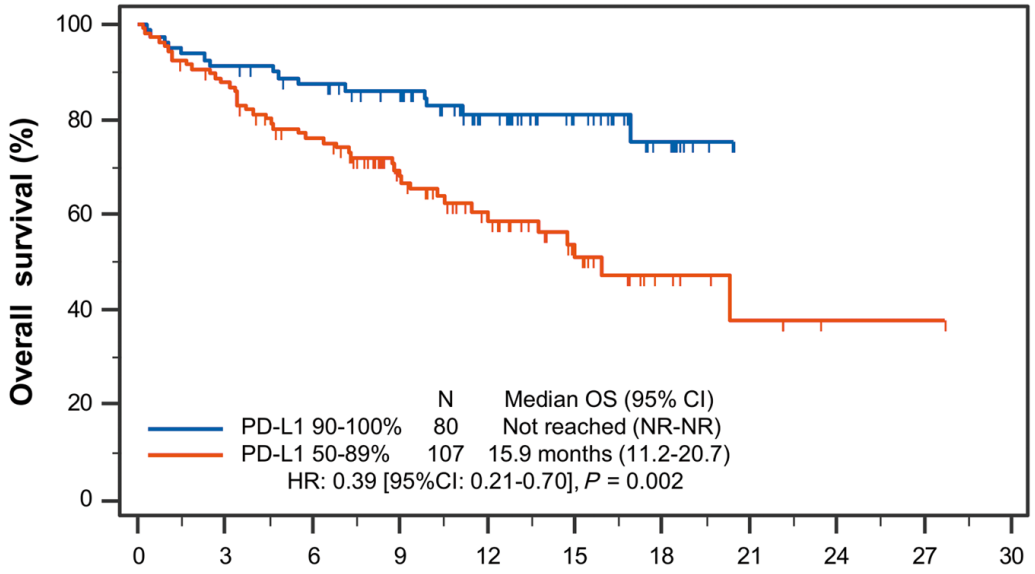
PD-L1 TPS 50-89% vs ≥90%



Number at risk

PD-L1 90-100%	80	58	44	34	27	12	3	0	0
PD-L1 50-89%	107	59	42	25	13	6	2	2	0



Number at risk

PD-L1 90-100%	80	73	66	57	38	22	10	0	0	0	0
PD-L1 50-89%	107	92	75	51	33	18	8	4	1	1	0

Aguilar, EJ, Ricciuti, B, et al, *Ann Oncol*, 2019, 30 (10), 1653-1659.

Cemiplimab in Very High PD-L1 Expressing NSCLC

EMPOWER-Lung 1

	PD-L1 ≥90%	PD-L1 >60 to <90%	PD-L1 ≥50 to ≤60%	PD-L1 <50% or unknown
Number of patients	98 *vs* 94	89 *vs* 90	96 *vs* 96	73 *vs* 74
Overall survival				
Median, months (95% CI)	NR (17·3–NE) *vs* 15·1 (11·1–NE)	22·1 (17·9–NE) *vs* 12·0 (9·6–19·2)	21·9 (13·2–NE) *vs* 14·0 (9·4–19·3)	16·5 (11·6–NE) *vs* 15·2 (10·2–NE)
Hazard ratio (95% CI)	0·46 (0·25–0·85)	0·47 (0·27–0·80)	0·77 (0·49–1·23)	1·082 (0·68–1·72)
Progression-free survival				
Median, months (95% CI)	15·3 (10·4–18·7) *vs* 5·9 (4·3–6·2)	6·2 (4·2–8·4) *vs* 4·2 (4·1–5·7)	4·3 (2·8–6·3) *vs* 6·2 (5·0–6·2)	4·1 (2·6–6·1) *vs* 5·0 (4·2–6·2)
Hazard ratio (95% CI)	0·28 (0·17–0·46)	0·55 (0·38–0·80)	0·79 (0·56–1·12)	0·82 (0·56–1·18)
Tumour response				
Objective response rate, % (95% CI)	46 (36–56) *vs* 18 (11–27)	39 (29–50) *vs* 20 (12–30)	32 (23–43) *vs* 23 (15–33)	26 (17–38) *vs* 22 (13–33)

Data are median (95% CI), hazard ratio (95% CI), and objective response rate % (95% CI). NE=not evaluable. NR=not reached. PD-L1=programmed cell death ligand 1.

***Table 3*: Correlation of survival and objective response with baseline PD-L1 proportion scores for cemiplimab versus chemotherapy**

Sezer A, et al, *Lancet*, 2021 Feb 13;397(10274):592-604.

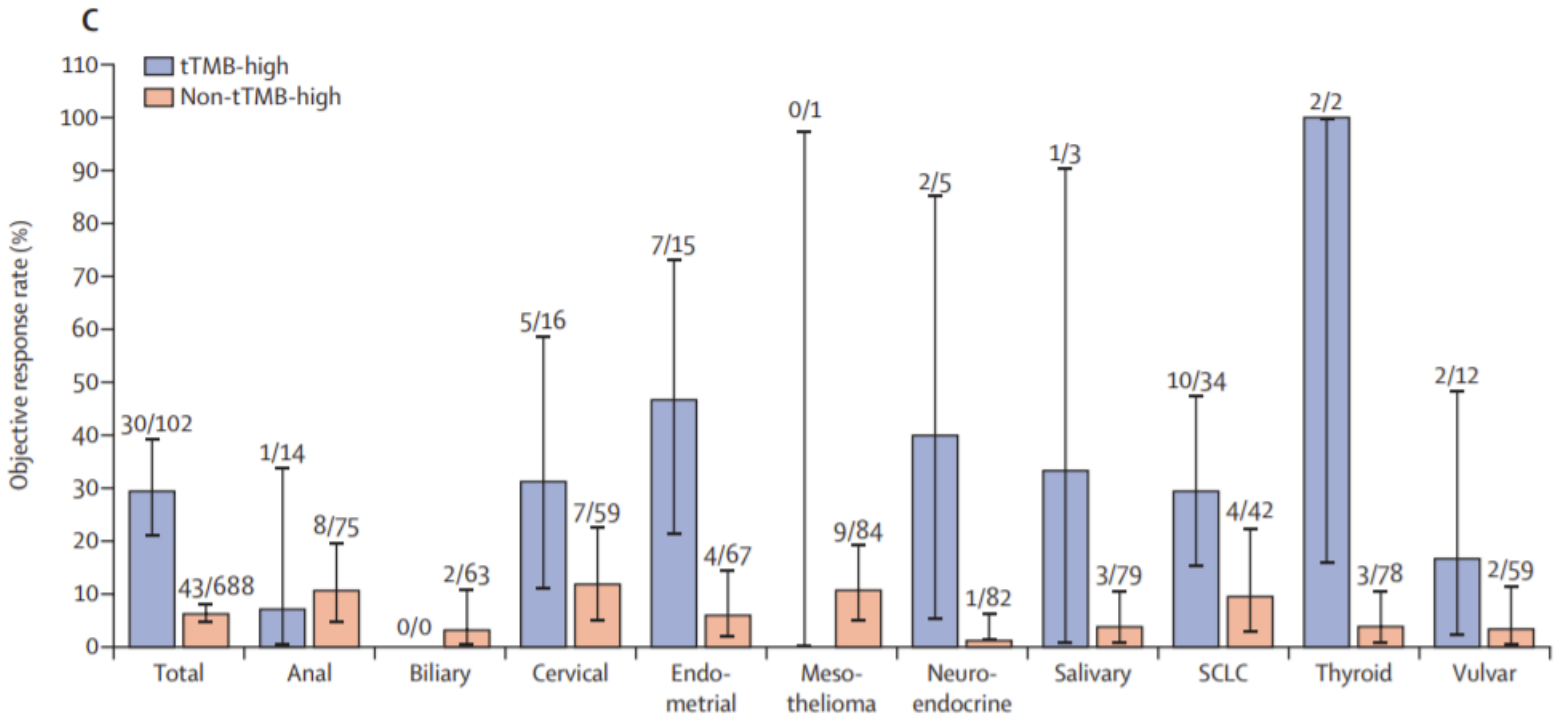
Tumor Mutational Burden

KEYNOTE-158: 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.

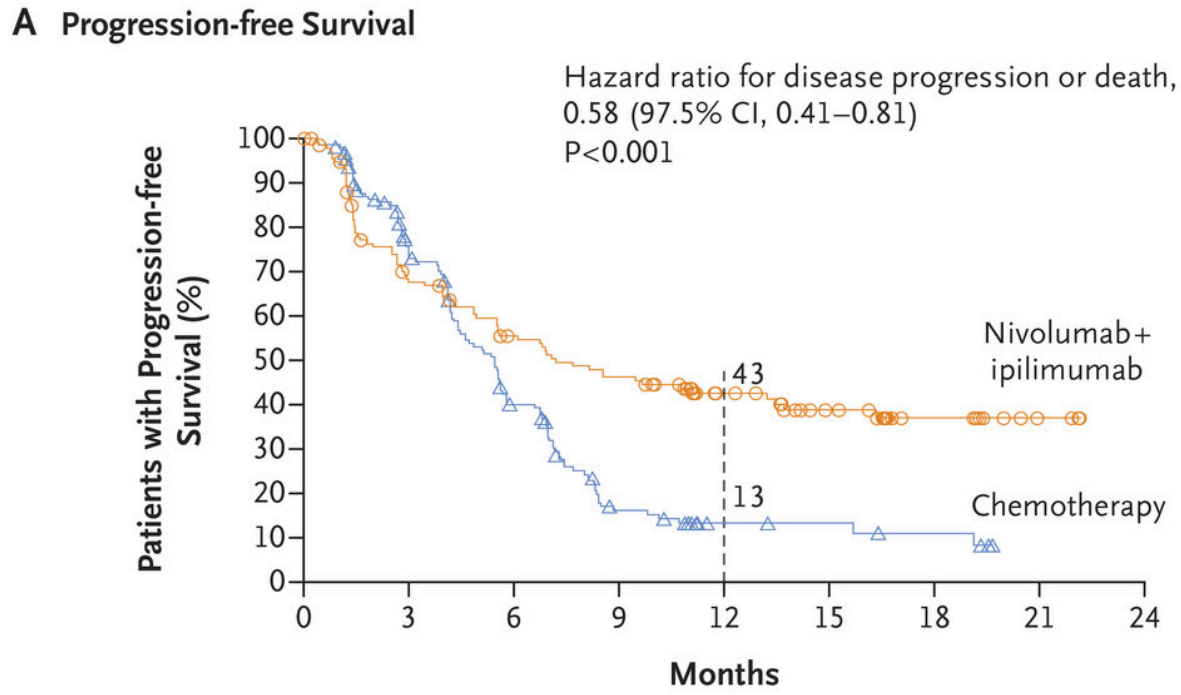
Table 2: **Objective response (per RECIST version 1.1), assessed by independent central review in the efficacy population**



Marabelle A et al. *Lancet Oncol* 2020; 21: 1353–65

Tumor mutational burden (TMB)

CheckMate 227
High TMB: ≥10 mutations/megabase



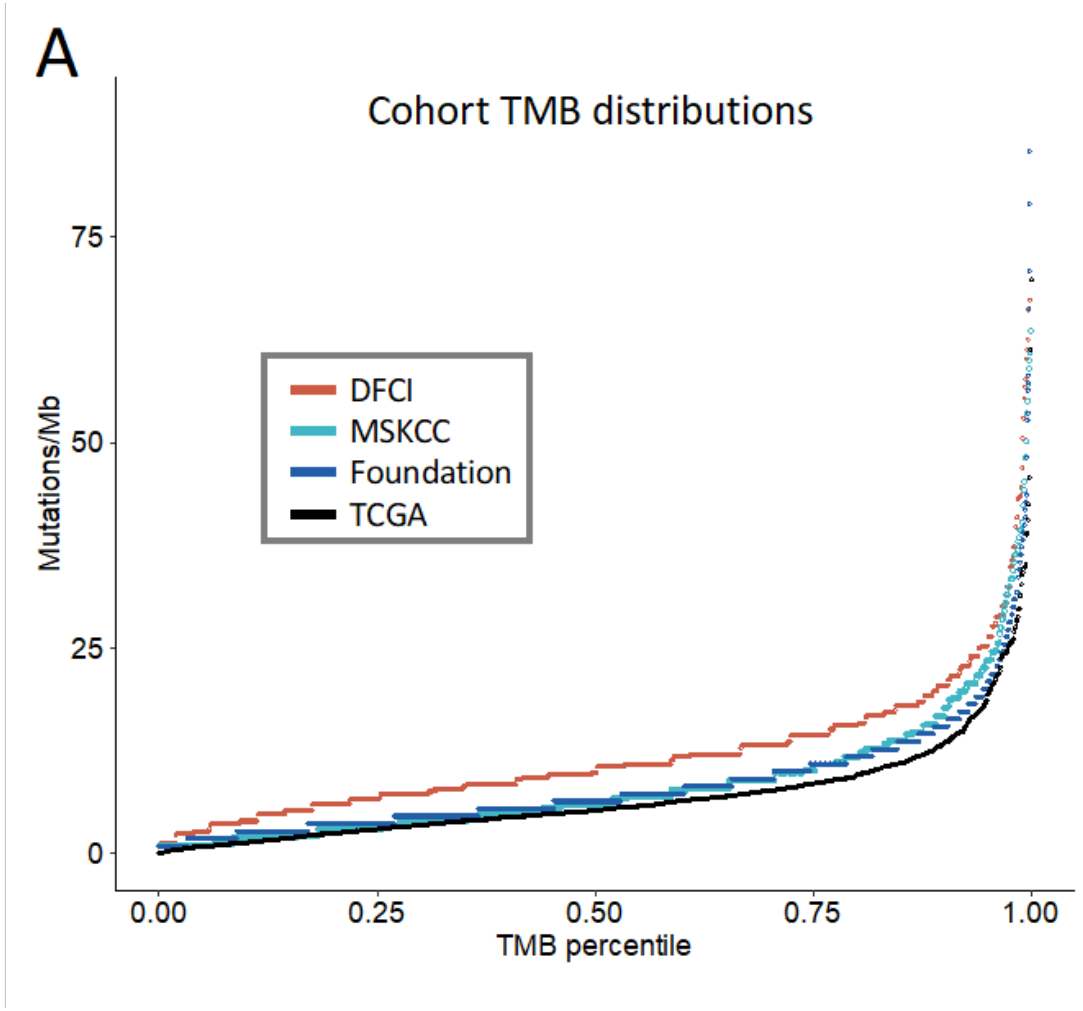
No. at Risk									
Nivolumab + ipilimumab	139	85	66	55	36	24	11	3	0
Chemotherapy	160	103	51	17	7	6	4	0	0

Hellmann MD et al. *N Engl J Med* 2018;378:2093-2104.

Tumor mutational burden (TMB)

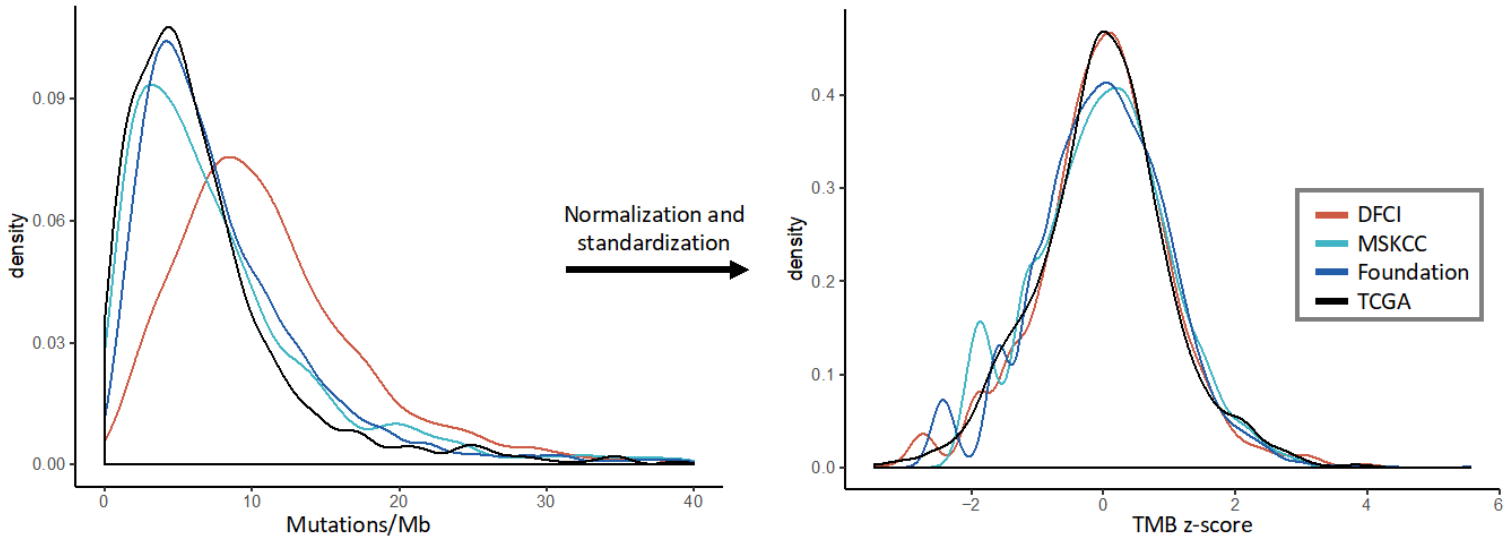
- Challenges with TMB
  - Still not used routinely for treatment selection in NSCLC
  - Limited access to published trial data
  - Cohort sizes at any individual institution are relatively small
  - Differences across platforms make it difficult to compare and combine data

Tumor mutational burden (TMB)



Vokes NI, et al. *JCO Precis Oncol*, 2019;3:PO.19.00171

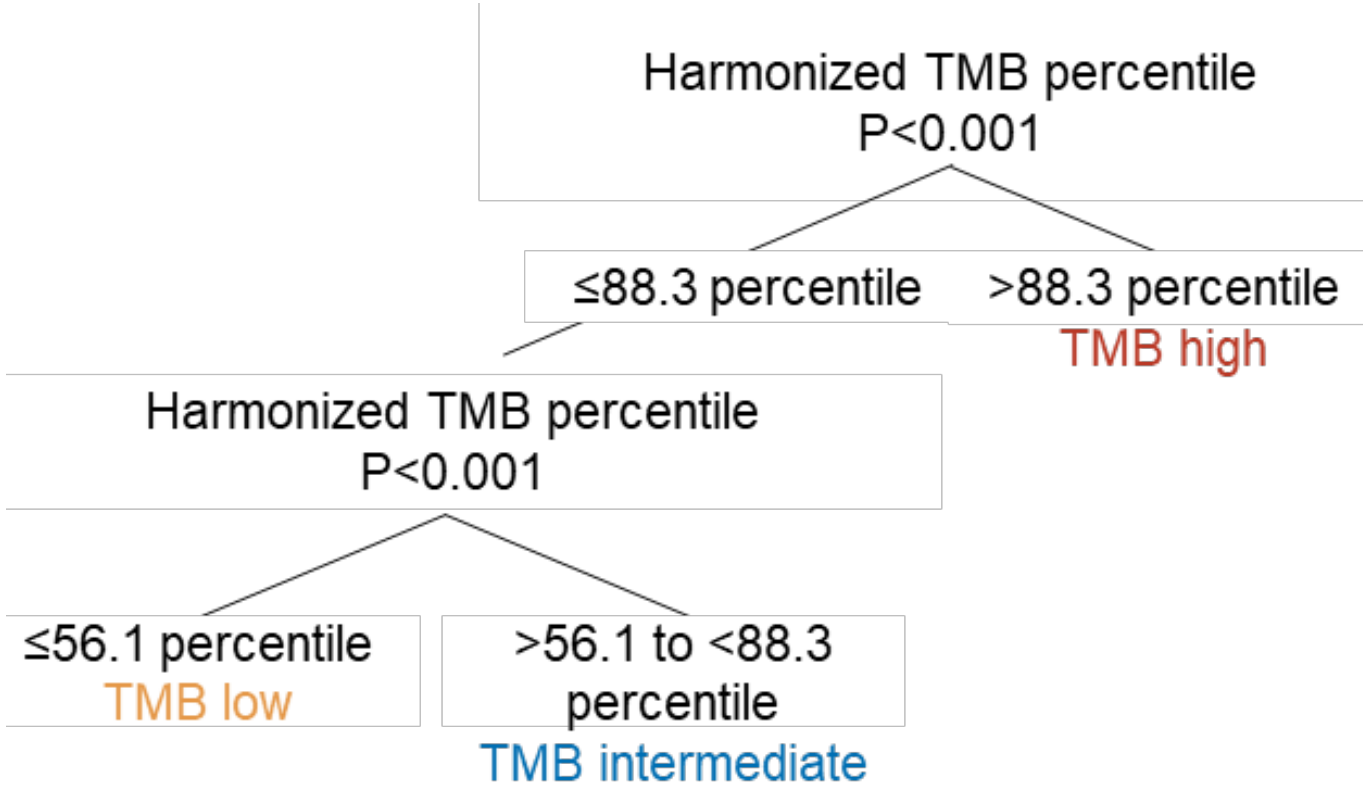
TMB Harmonization

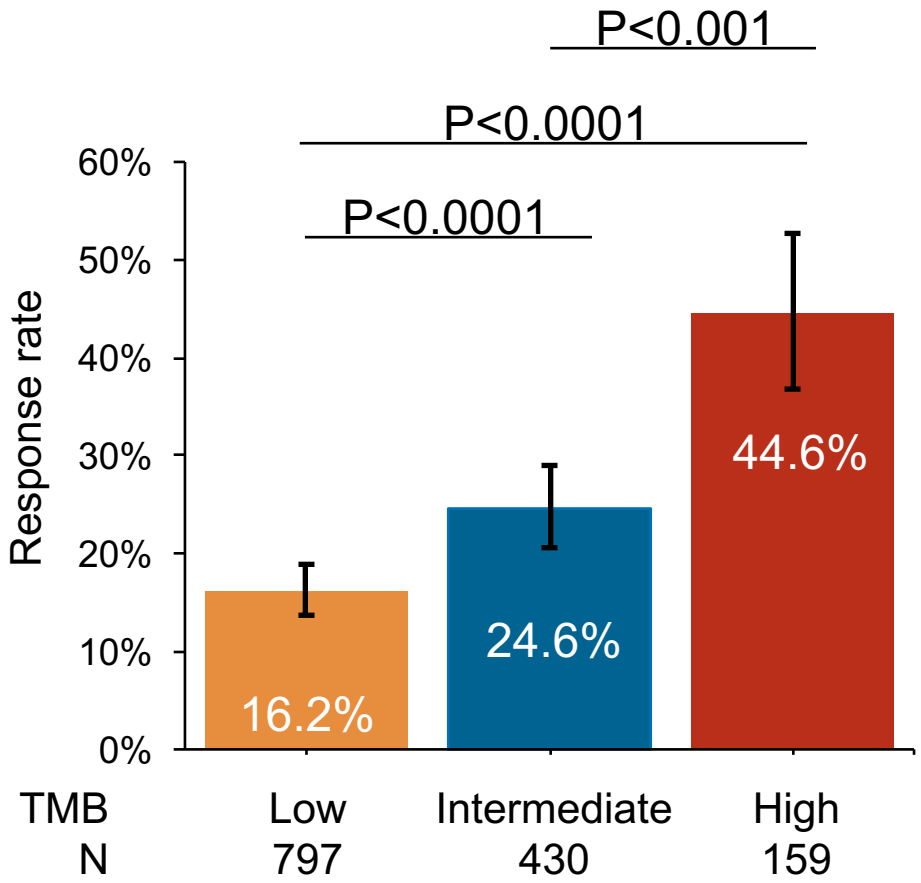


Percentile	TMB z-score	DFCI TMB	MSKCC TMB	Foundation TMB	TCGA TMB (mutation count)
10th	-1.04	4.81	2.27	2.83	1.84 (55)
20th	-0.47	7.22	3.89	4.45	3.35 (101)
30th	-0.24	8.42	4.78	5.30	4.18 (125)
40th	0.00	9.87	5.90	6.36	5.25 (158)
50th	0.17	11.07	6.89	7.27	6.10 (183)
60th	0.45	13.24	8.76	8.97	7.58 (228)
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 NI, et al. *JCO Precis Oncol*, 2019;3:PO.19.00171

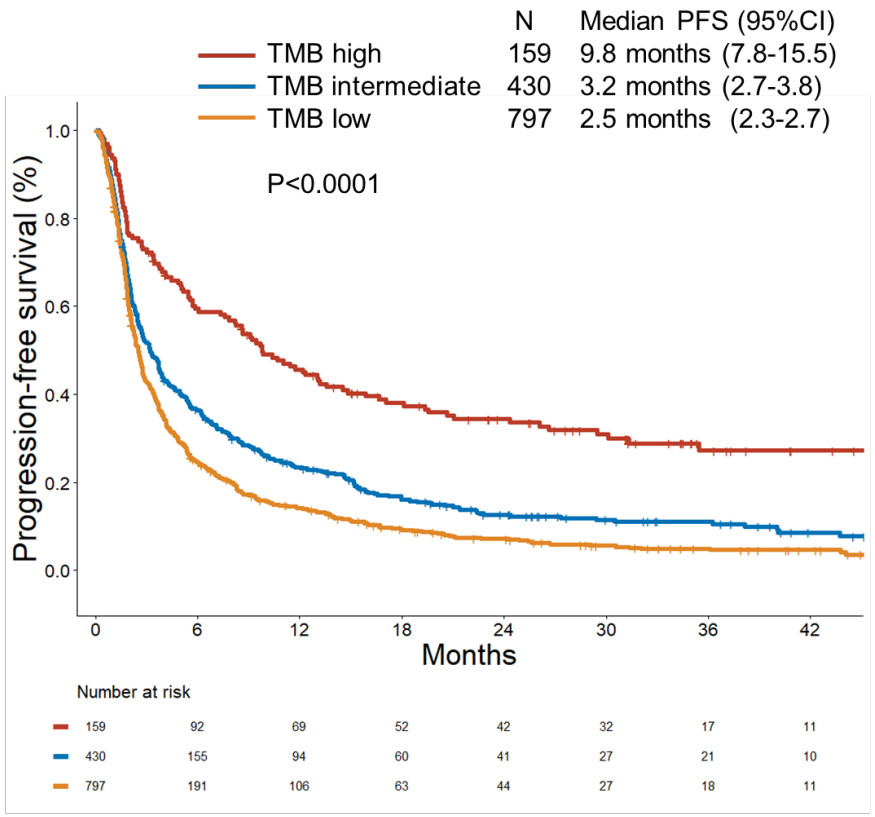
TMB Groupings & PD-1 Response in NSCLC



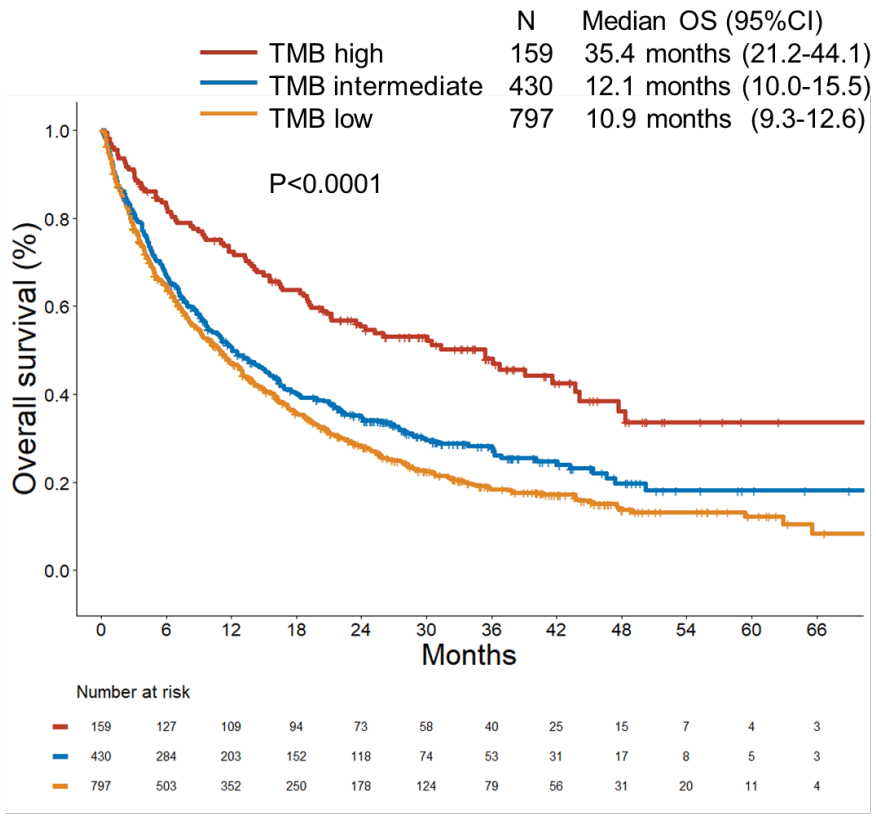


Ricciuti B, et al, Under Revision

TMB Groupings & PD-1 Response in NSCLC



	PFS HR [95%CI], P
TMB high vs TMB low	0.39 [0.32-0.48], P<0.0001
TMB high vs TMB intermediate	0.57 [0.42-0.65], P<0.0001
TMB intermediate vs TMB low	0.76 [0.67-0.86], P<0.0001

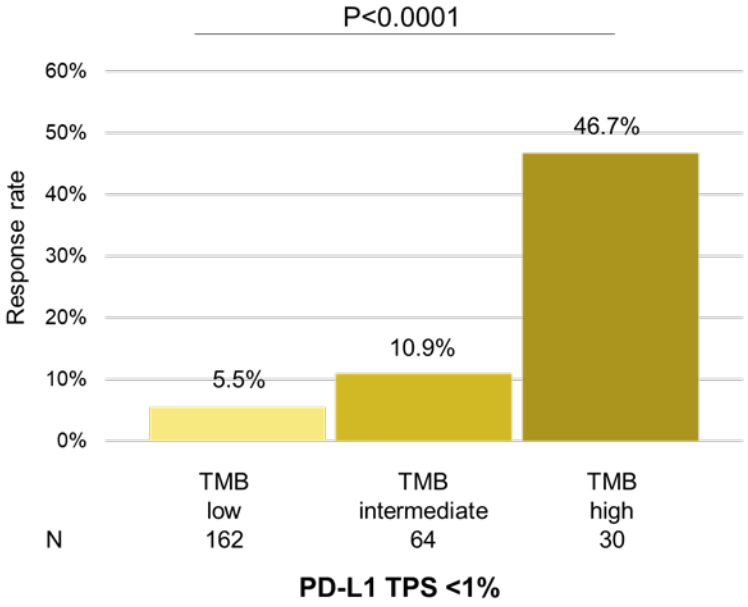


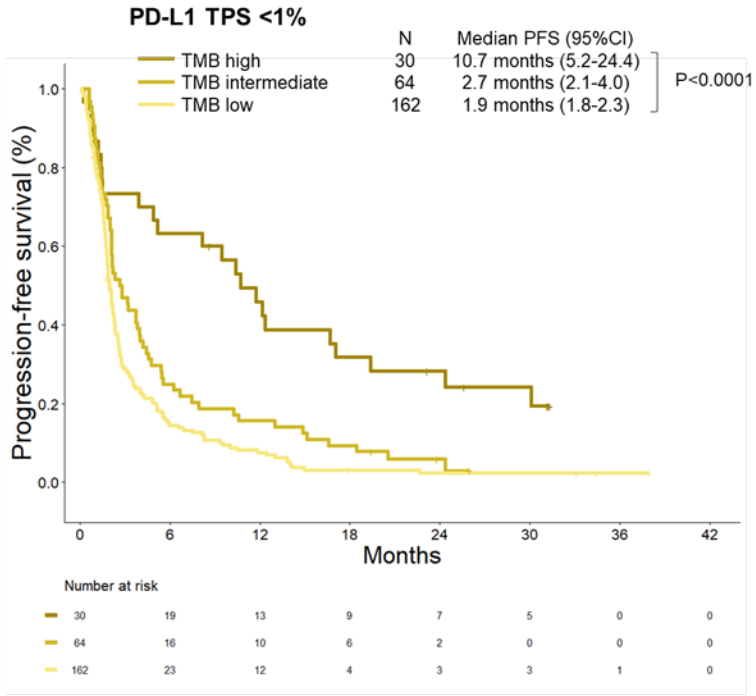
	OS HR [95%CI], P
TMB high vs TMB low	0.46 [0.37-0.58], P<0.0001
TMB high vs TMB intermediate	0.56 [0.43-0.71], P<0.0001
TMB intermediate vs TMB low	0.84 [0.73-0.96], P=0.01

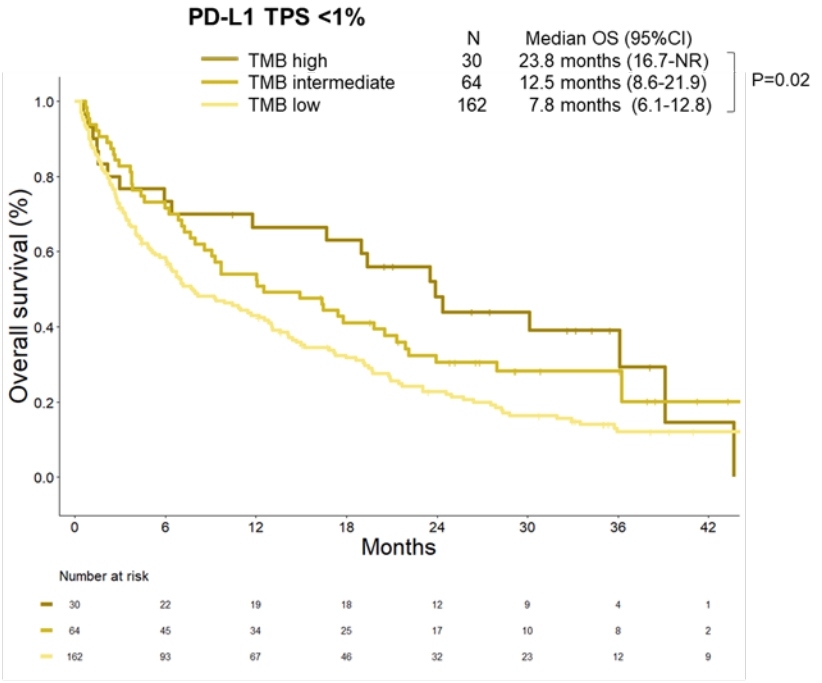
Ricciuti B, et al, Under Revision

TMB Groupings & PD-1 Response in NSCLC

PD-L1 Negative (TPS <1%) NSCLC







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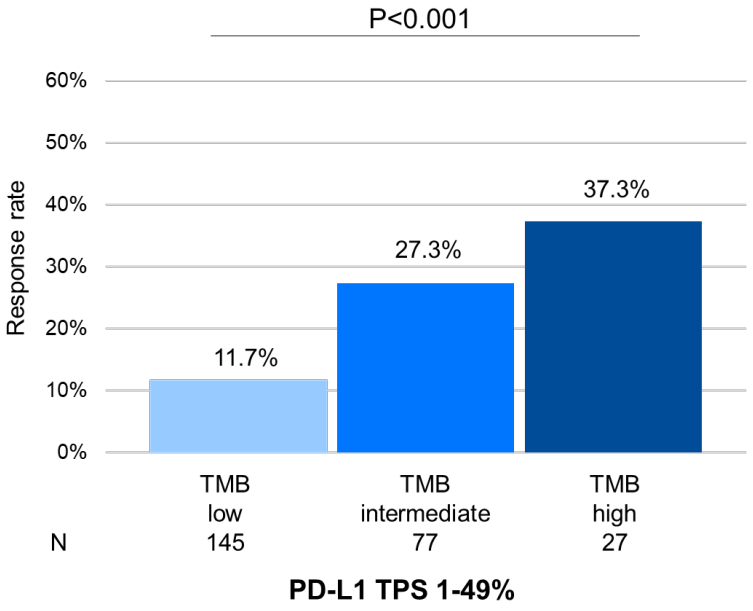
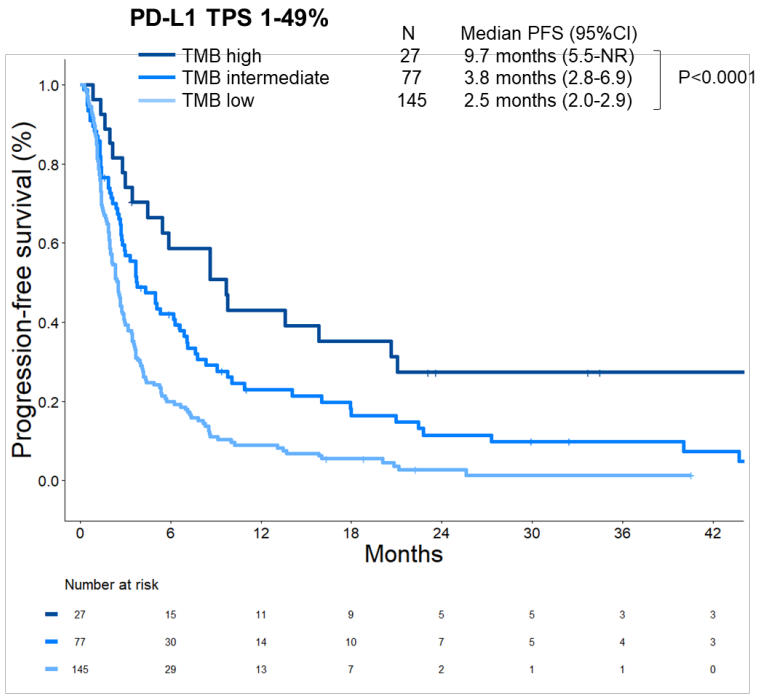
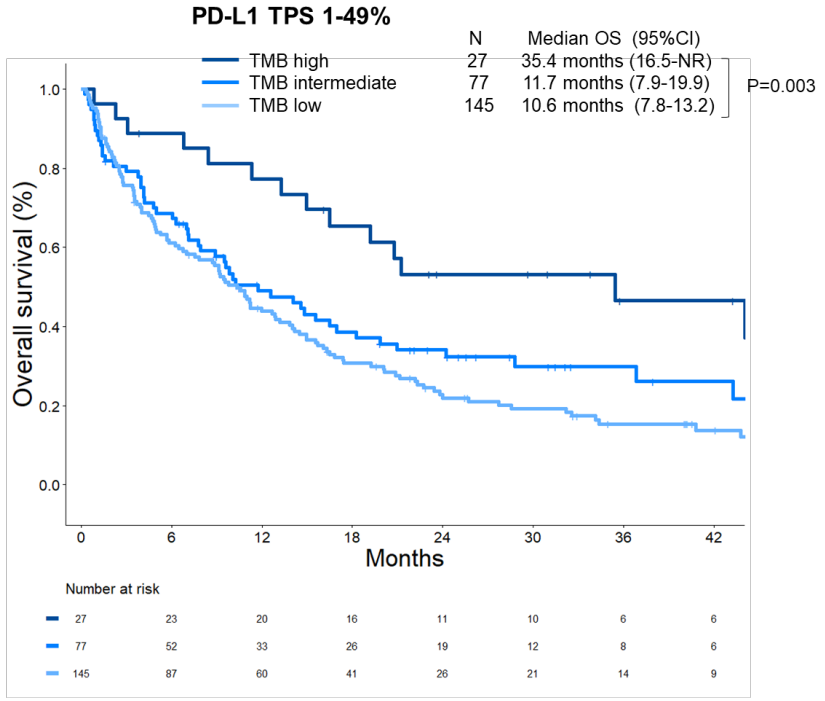
TMB Groupings & PD-1 Response in NSCLC

PD-L1 Low (TPS 1-49%) NSCLC







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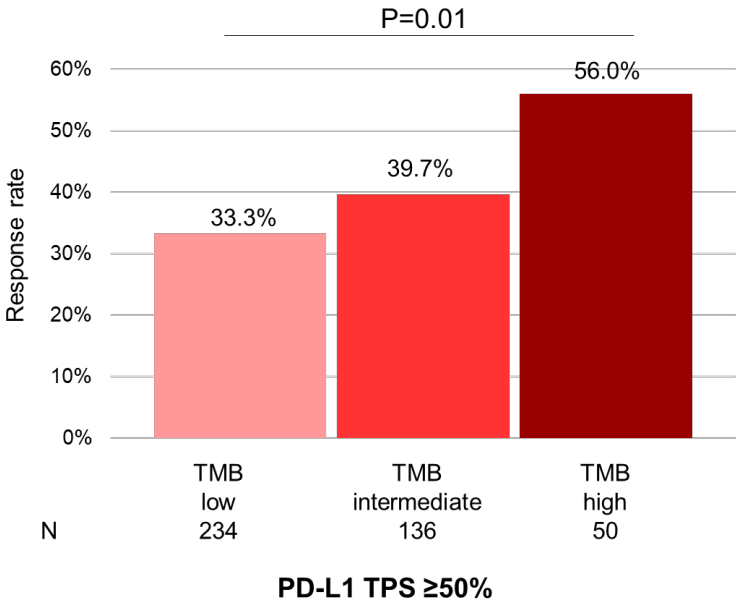
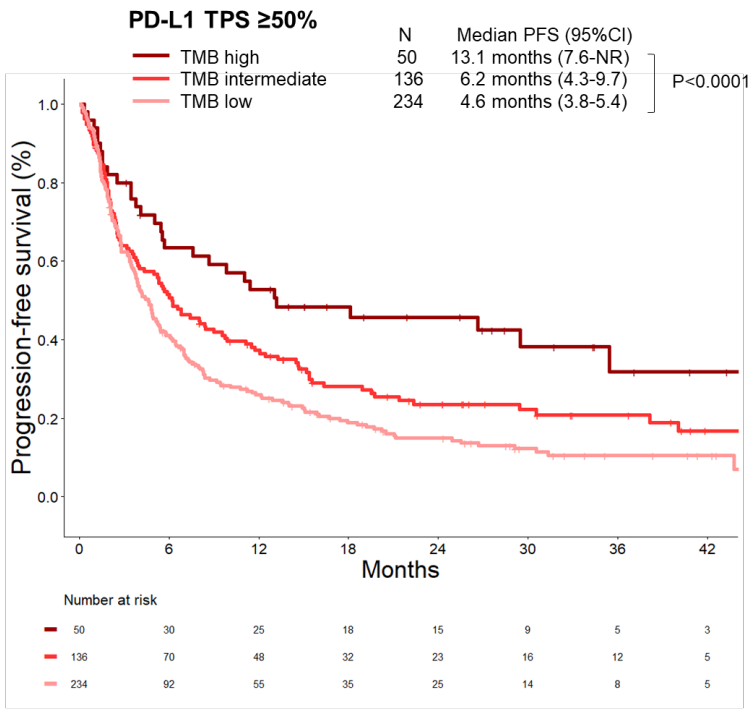
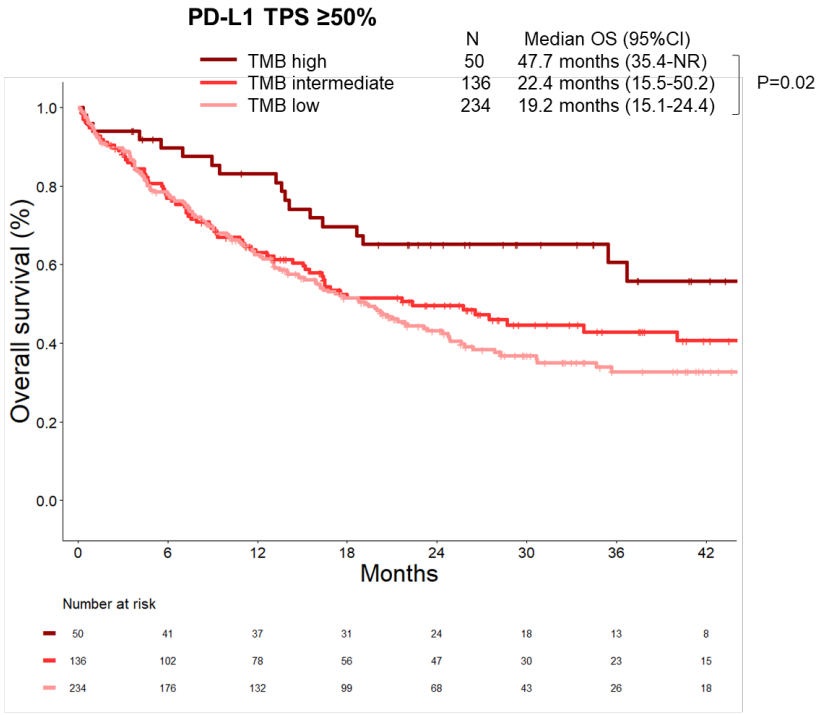
TMB Groupings & PD-1 Response in NSCLC

PD-L1 High (TPS ≥50%) NSCLC







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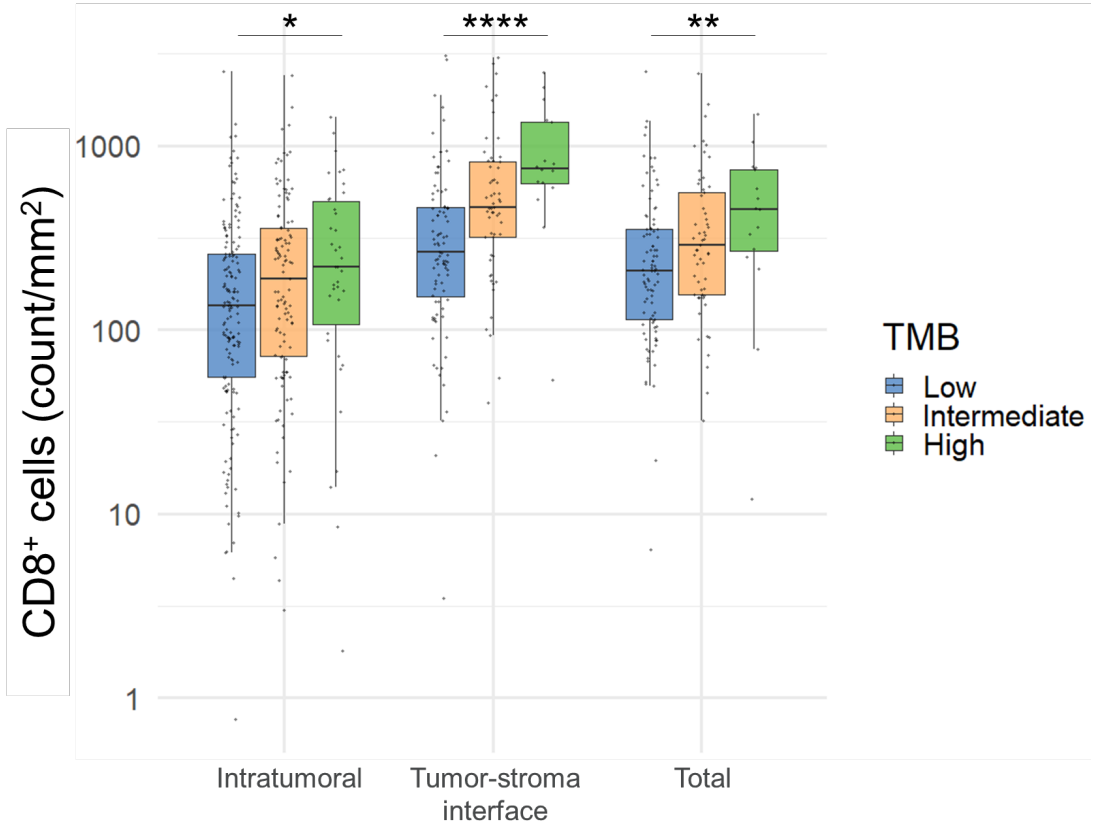
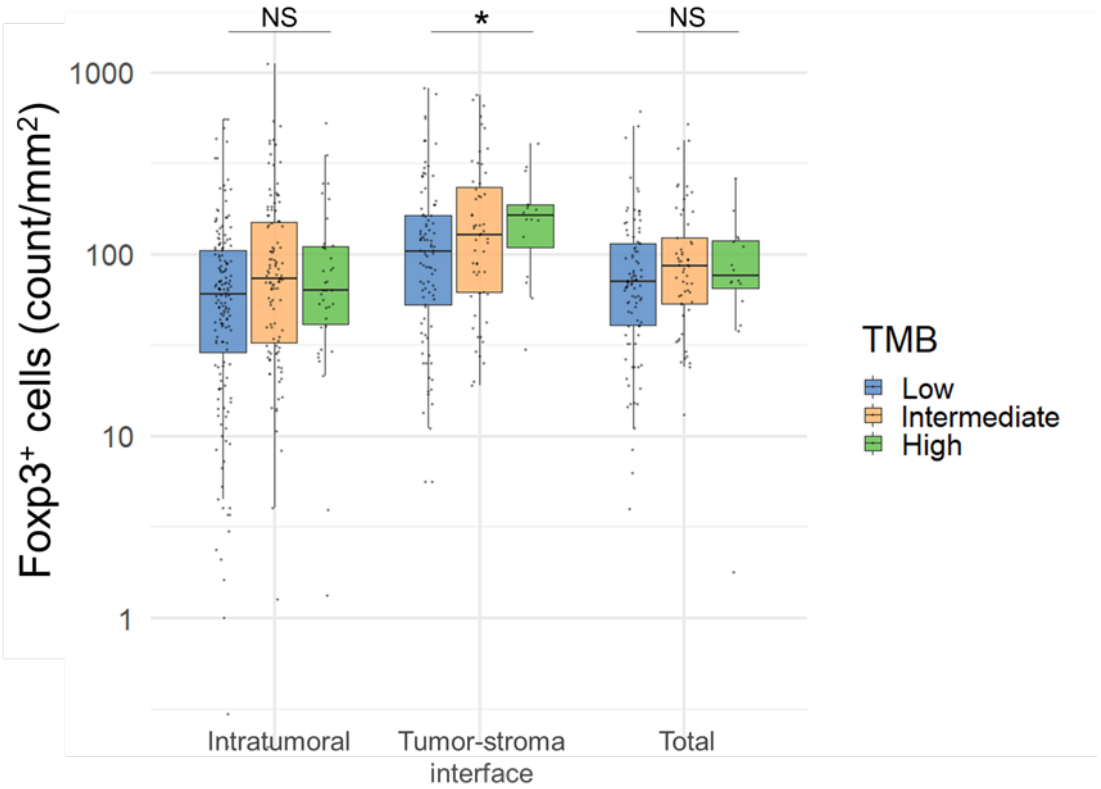
TMB Groupings & Have Distinct Cell Populations



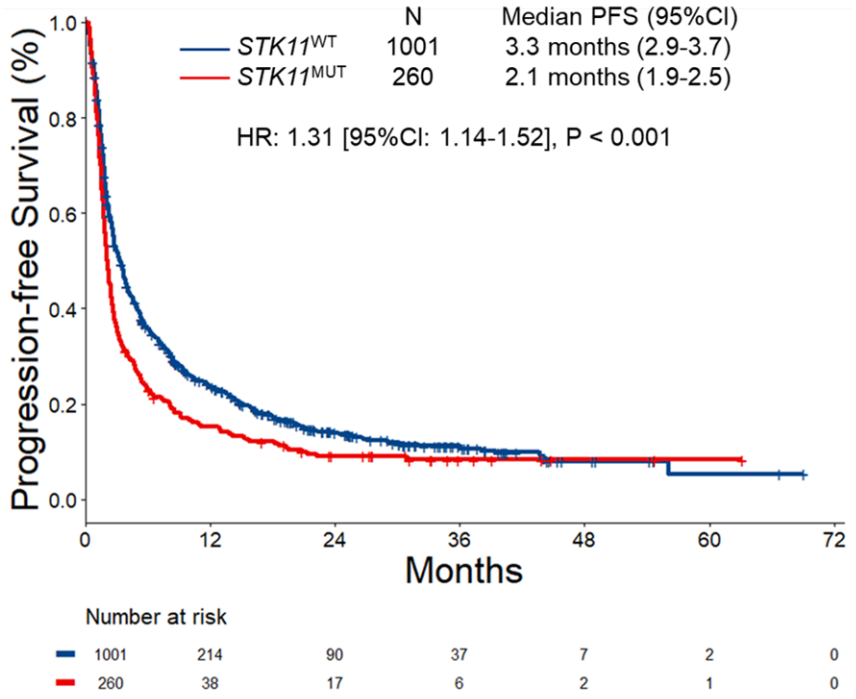


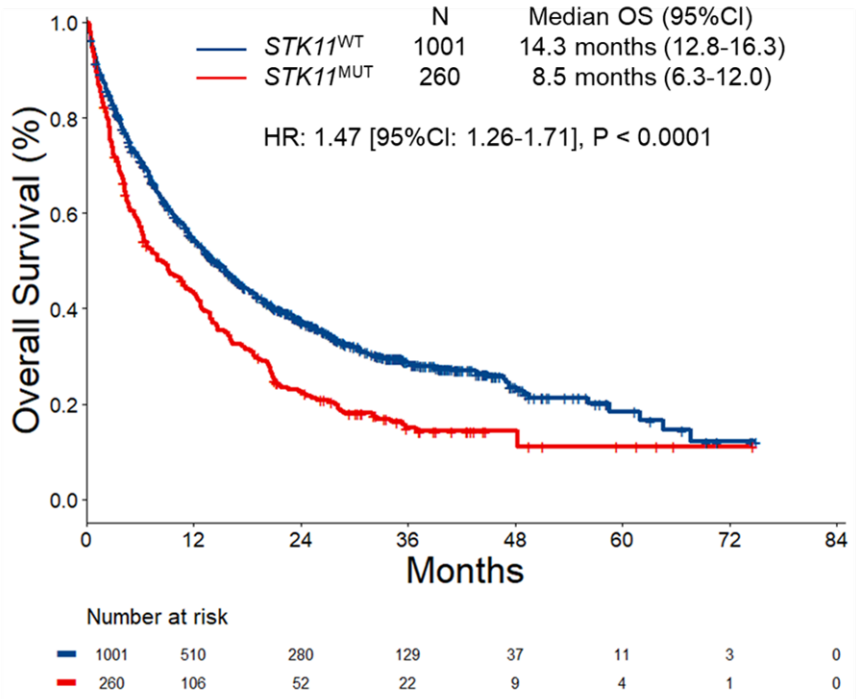
Ricciuti B, et al, Under Revision

Other Genomic Factors Impacting Immunothearpy Efficacy

Impact of STK11/LKB1 mutations

Impact of STK11 mutation on immunotherapy efficacy in <u>all comers</u> with NSCLC

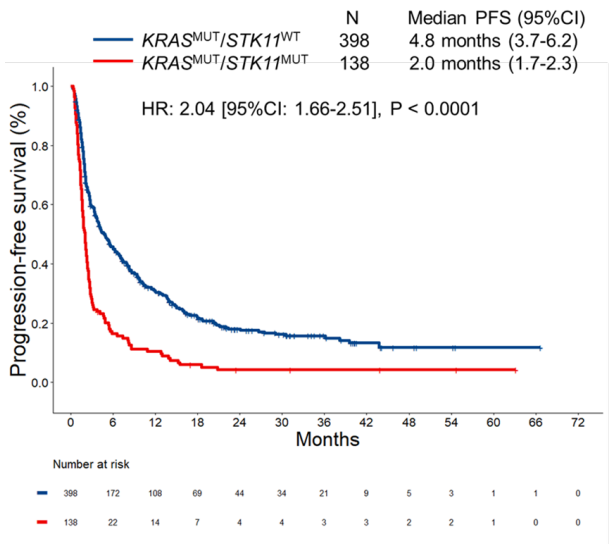


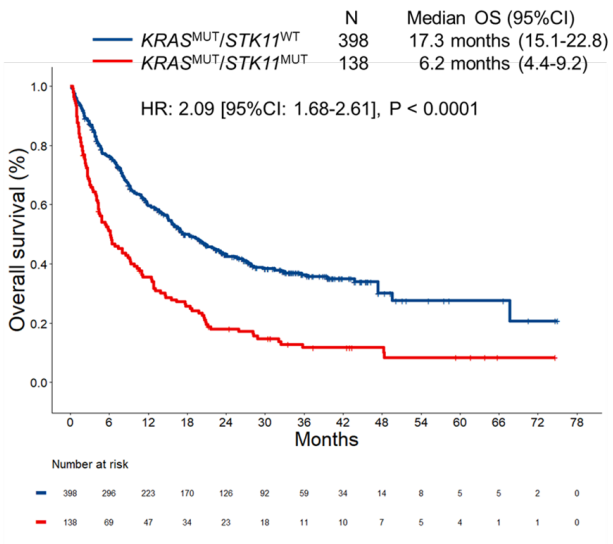


Ricciuti, B, et al *J Thorac Oncol*. 2021 Nov 2;S1556-0864(21)03284-6.

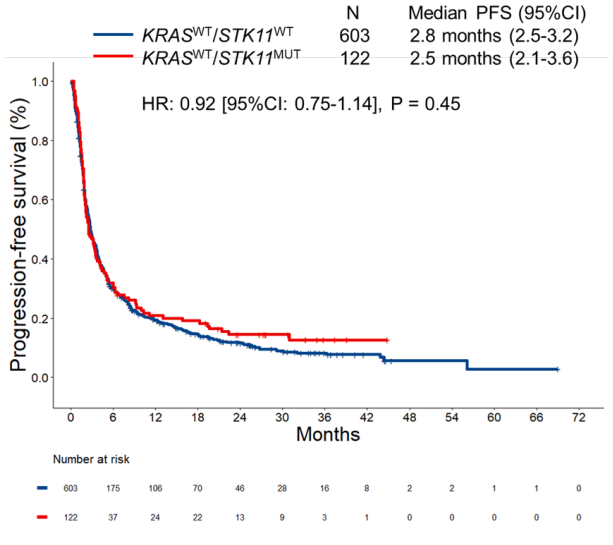
Impact of STK11/LKB1 mutations

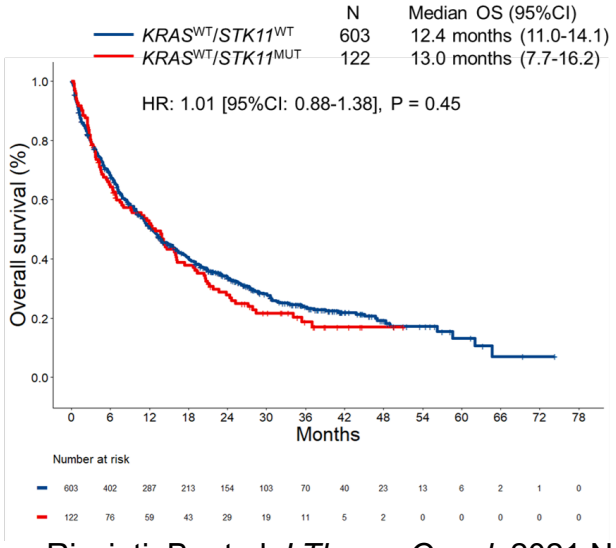
KRAS mutant NSCLC





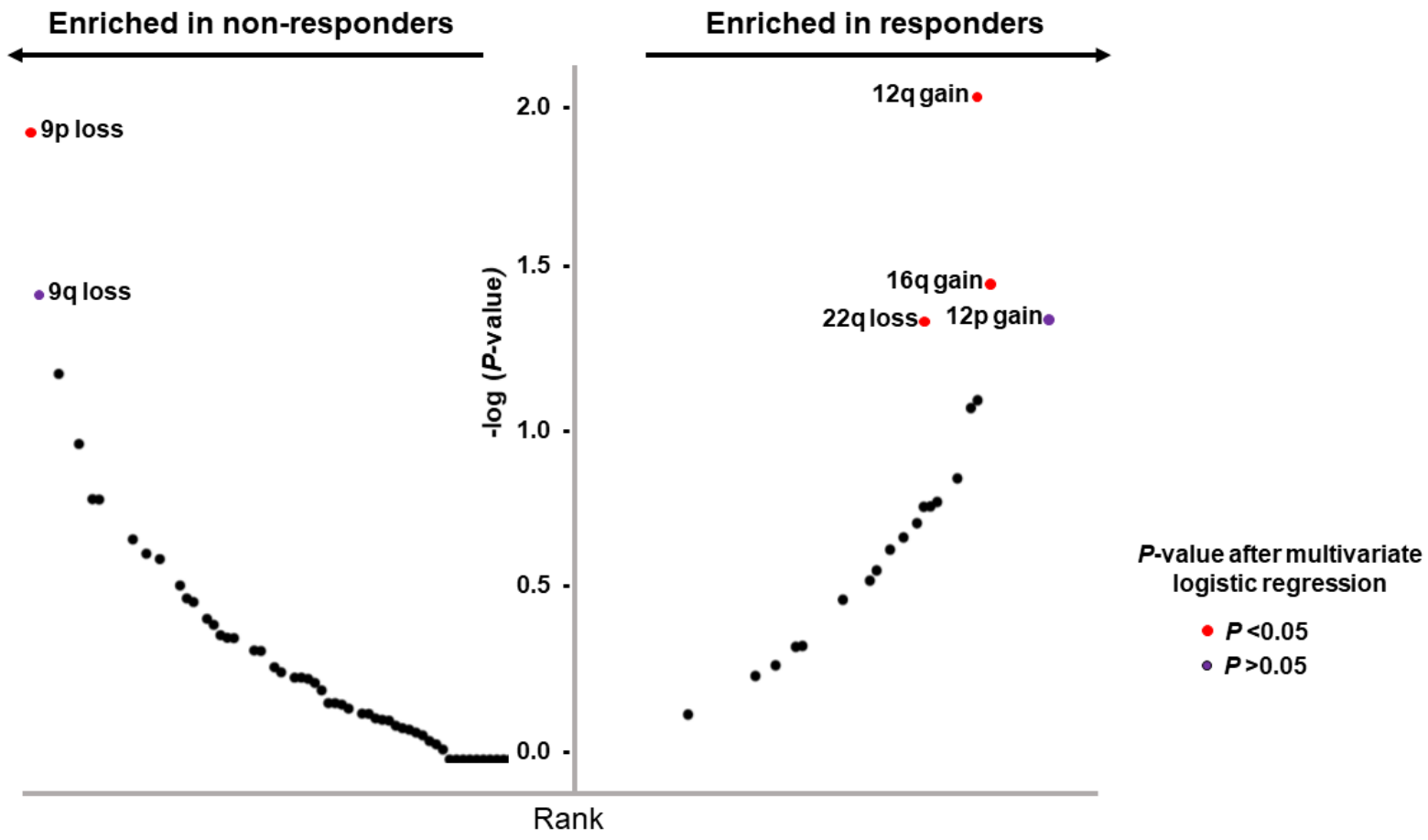
KRAS wild-type NSCLC





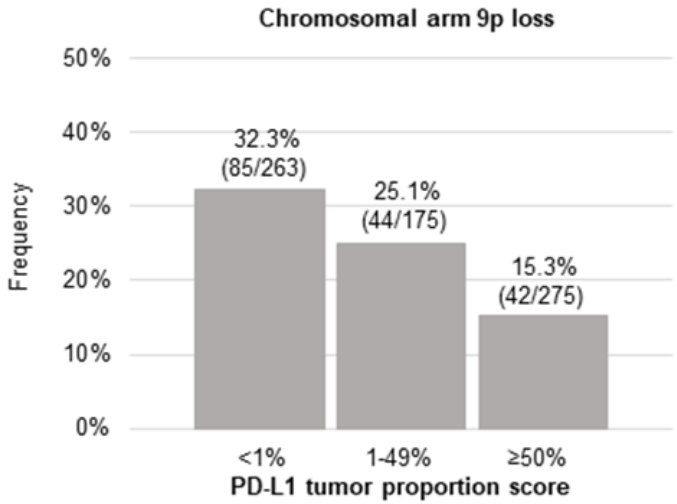
Ricciuti, B, et al *J Thorac Oncol*. 2021 Nov 2;S1556-0864(21)03284-6.

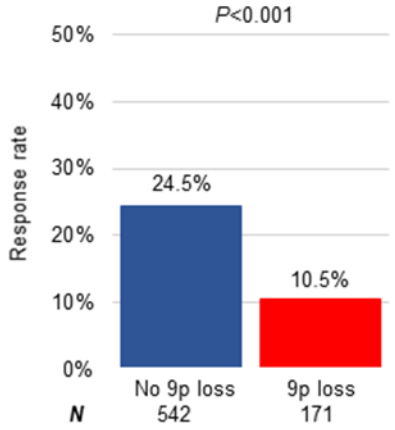
Aneuploidy and Immunotherapy Efficacy

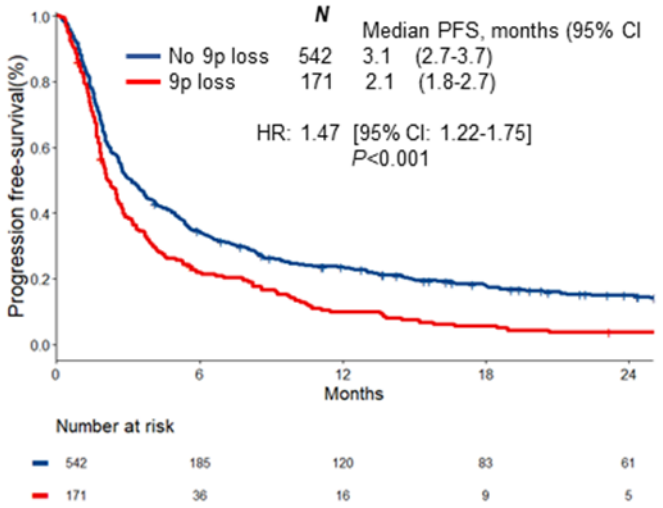


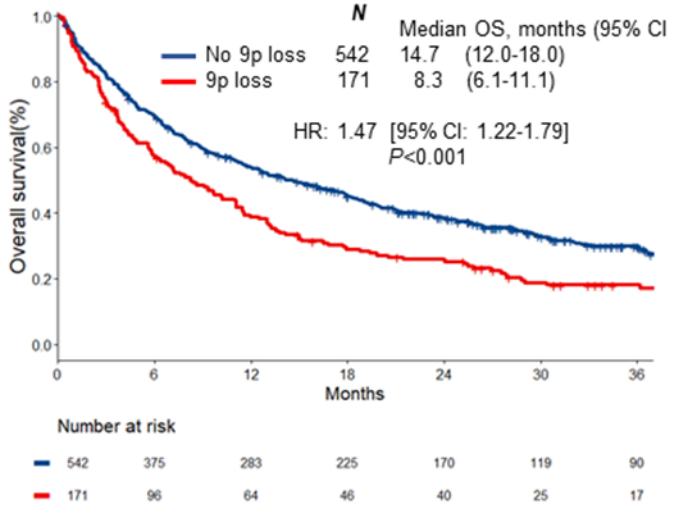
Alessi JV, unpublished

Impact of 9p Loss on Immunotherapy Efficacy





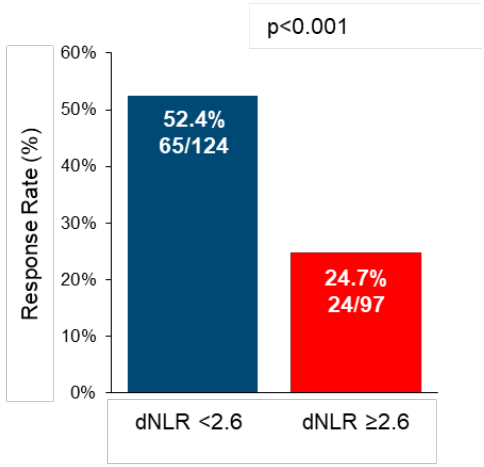


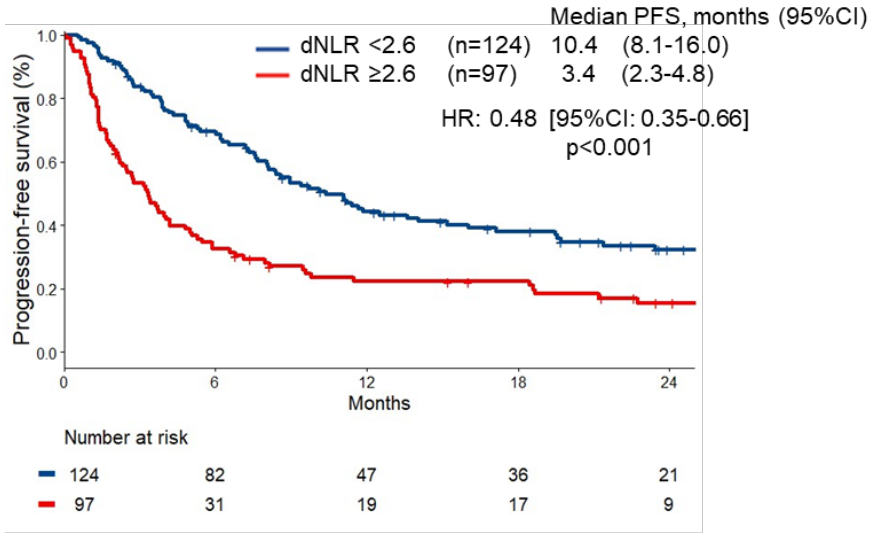


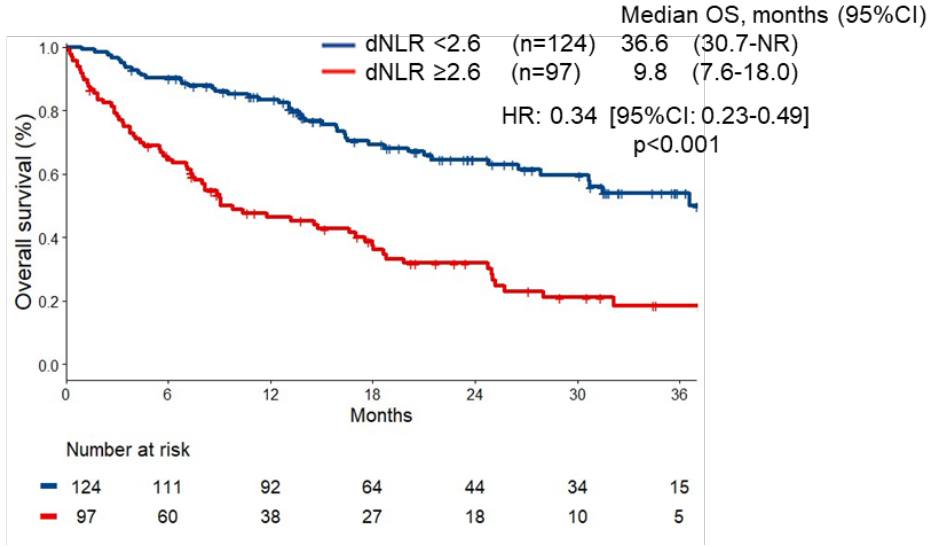
Alessi JV, unpublished

Circulating Factors

Neutrophil-Lymphocyte Ratio (dNLR) & PD-1 Efficacy

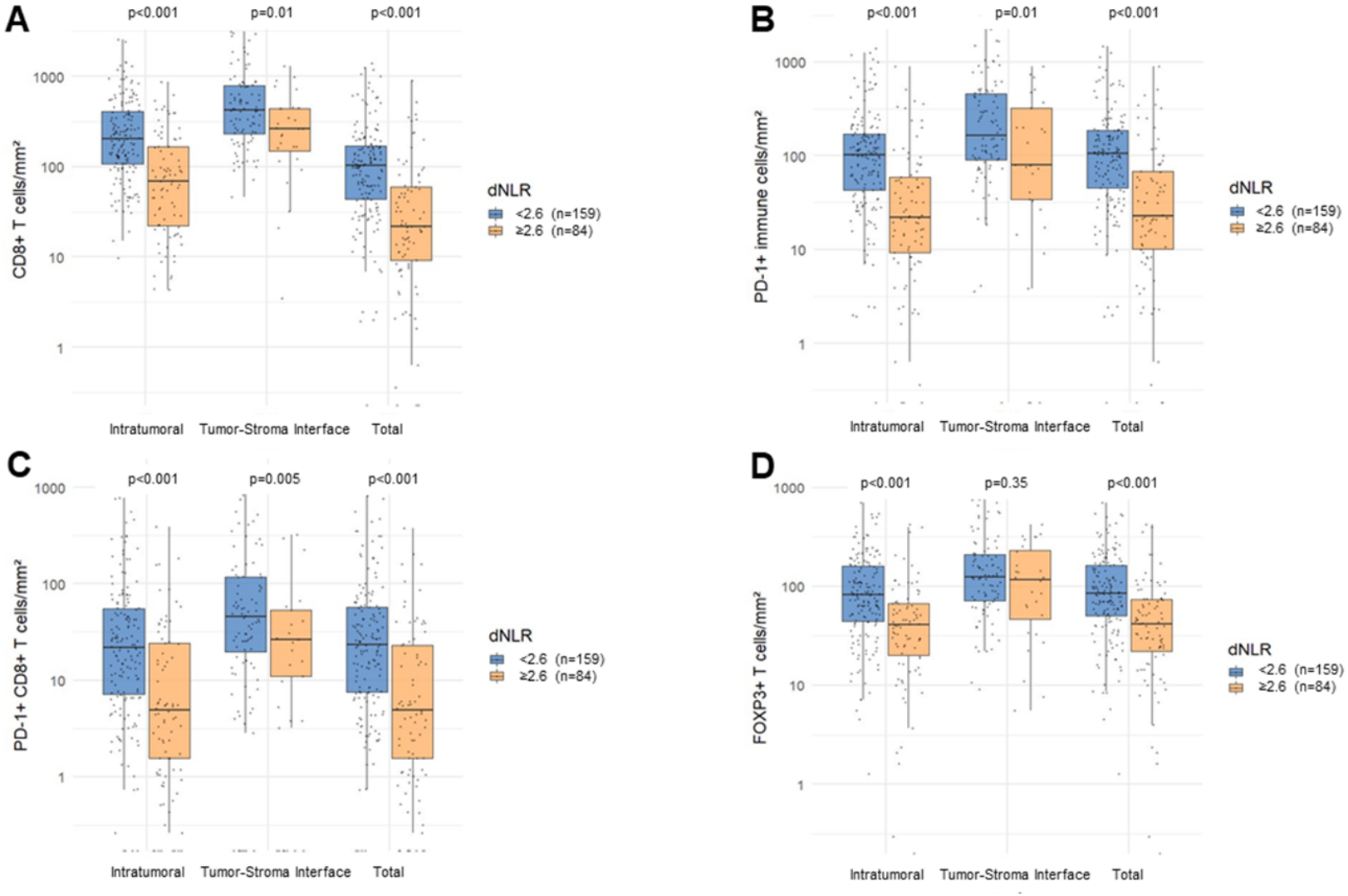






Alessi JV, et al, *J Immunother Cancer*. 2021 Nov;9(11):e003536.

High peripheral blood dNLR correlates with low tumor immune cell infiltration

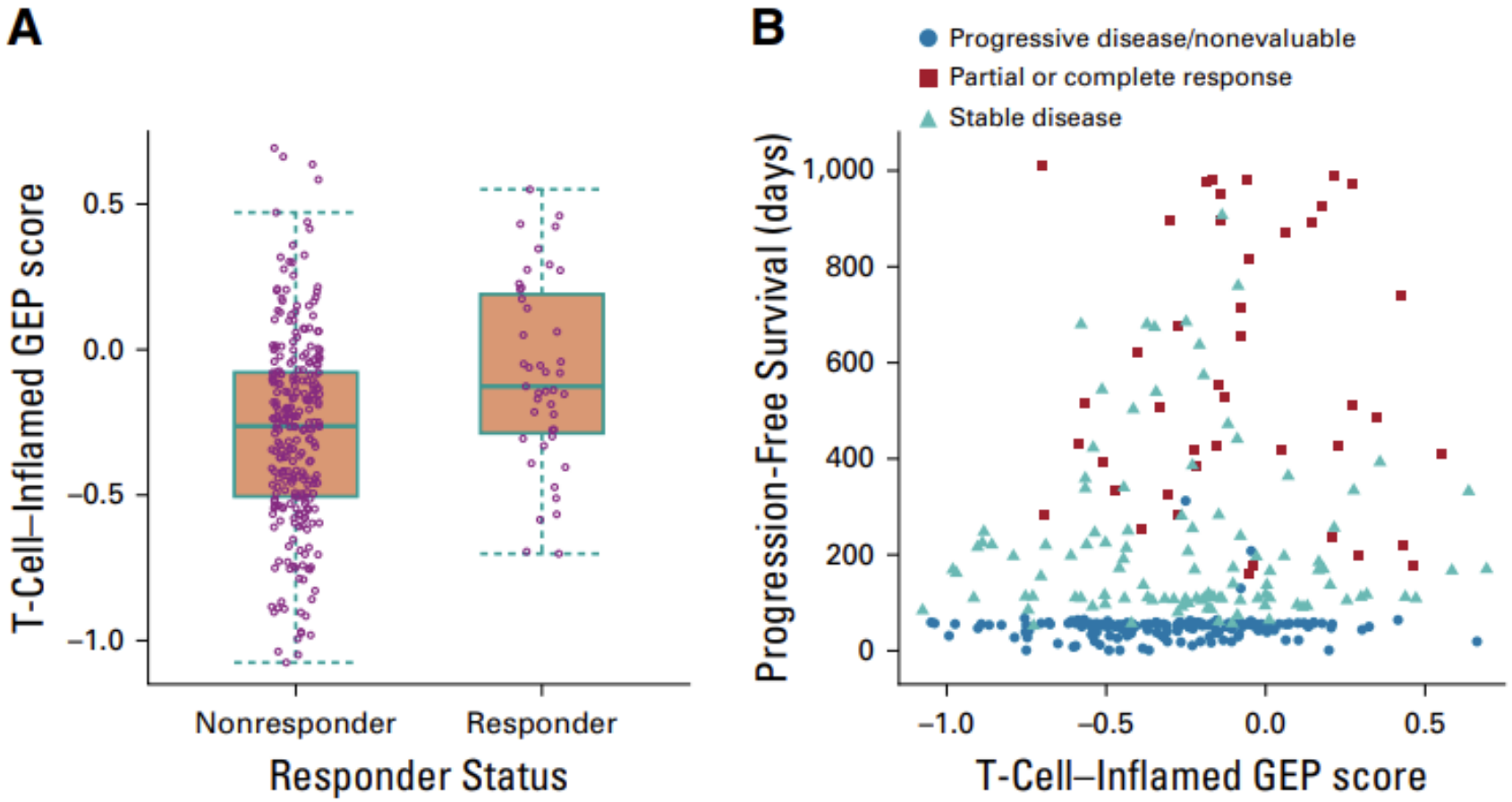


Alessi JV, et al, *J Immunother Cancer*. 2021 Nov;9(11):e003536.

Immune Microenvironment

Gene Expression Profile (GEP) & PD-1 Efficacy

KEYNOTE-028 (Across 20 Cancers)



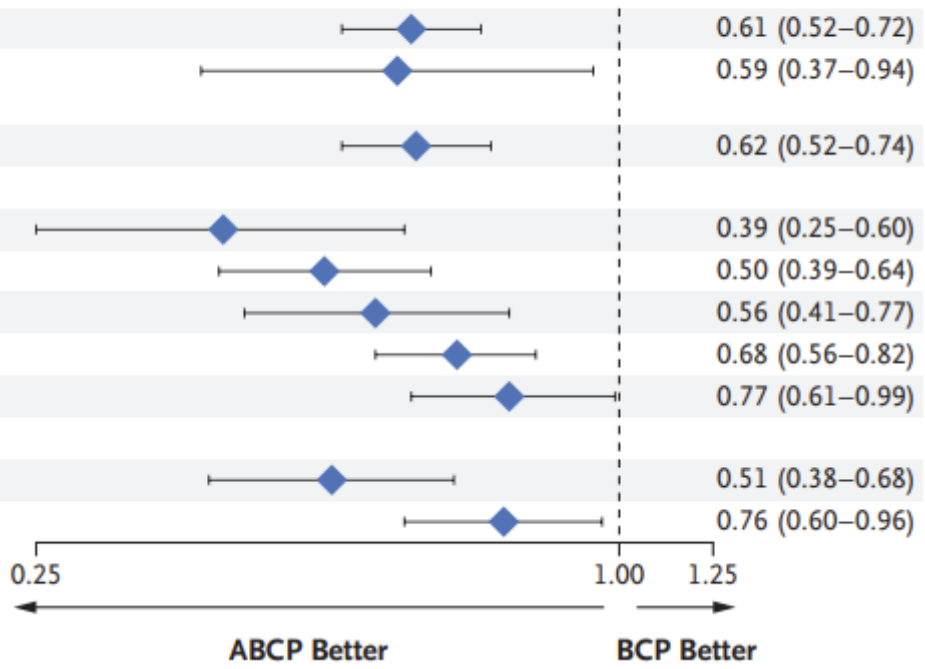
Ott PA, et al, *J Clin Oncol*, 2019 Feb 1;37(4):318-327.

Effector T-cell (Teff) Gene Signature

IMpower150

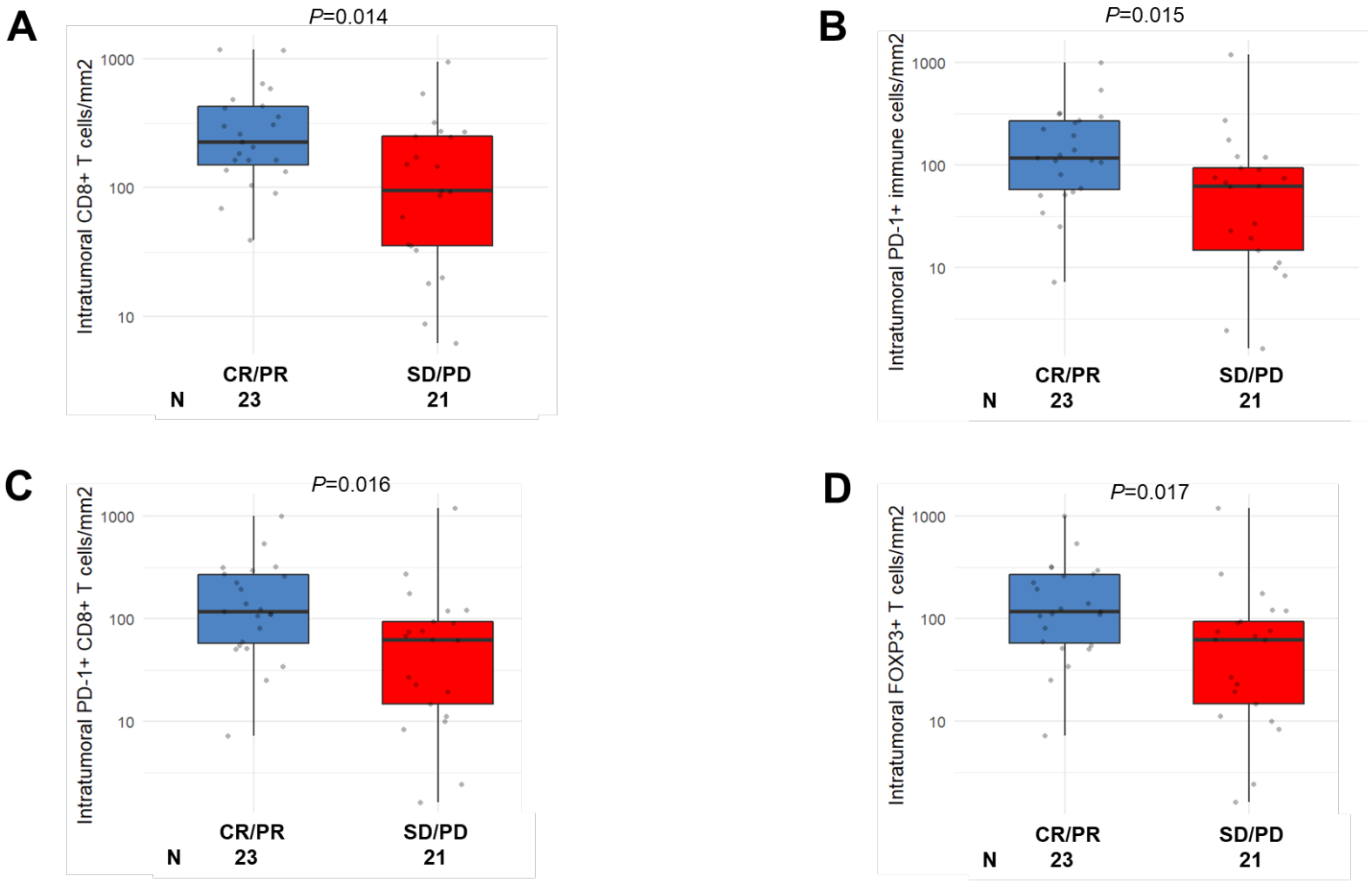
B Hazard Ratios for Disease Progression or Death in Biomarker Subgroups

Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio (95% CI)
		ABCP	BCP	
ITT population	800 (100)	8.3	6.8	0.61 (0.52–0.72)
Patients with *EGFR* or *ALK* genetic alternations	108 (14)	9.7	6.1	0.59 (0.37–0.94)
WT population	692 (87)	8.3	6.8	0.62 (0.52–0.74)
PD-L1 subgroups (in the WT population)				
TC3 or IC3	135 (20)	12.6	6.8	0.39 (0.25–0.60)
TC1/2/3 or IC1/2/3	354 (51)	11.0	6.8	0.50 (0.39–0.64)
TC1/2 or IC1/2	224 (32)	8.3	6.6	0.56 (0.41–0.77)
TC0/1/2 and IC0/1/2	557 (80)	8.0	6.8	0.68 (0.56–0.82)
TC0 and IC0	338 (49)	7.1	6.9	0.77 (0.61–0.99)
Teff subgroups (in the WT population)				
High gene-signature expression	284 (43)	11.3	6.8	0.51 (0.38–0.68)
Low gene-signature expression	374 (57)	7.3	7.0	0.76 (0.60–0.96)



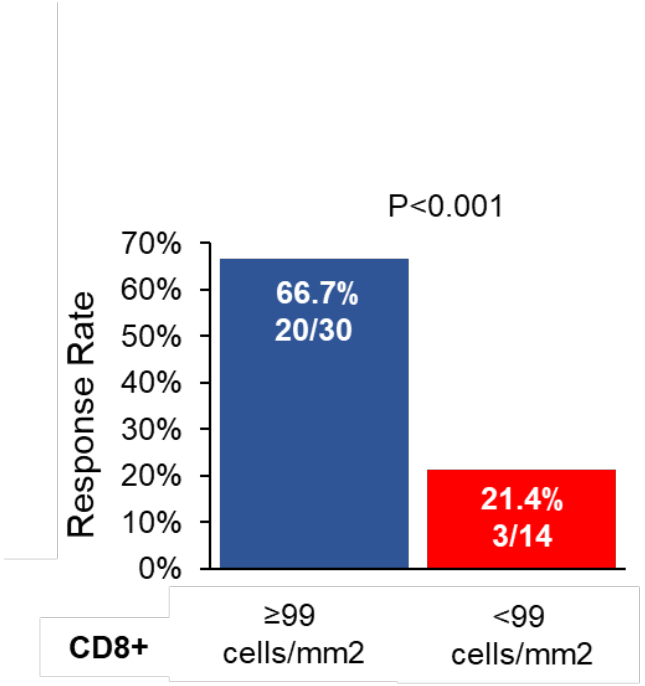
Ott PA, et al, *J Clin Oncol*, 2019 Feb 1;37(4):318-327.

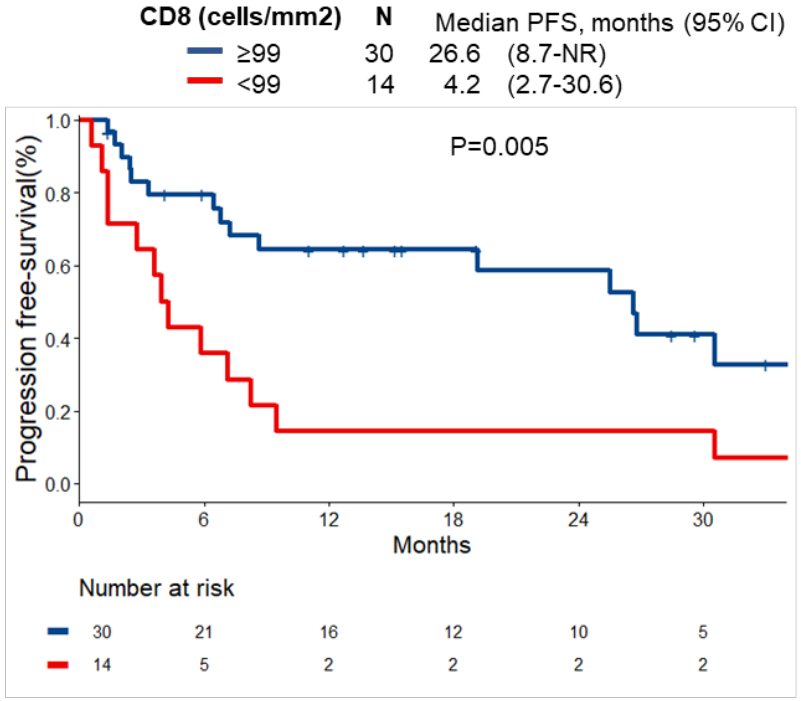
Immunoprofile & 1st Line Pembrolizumab Response

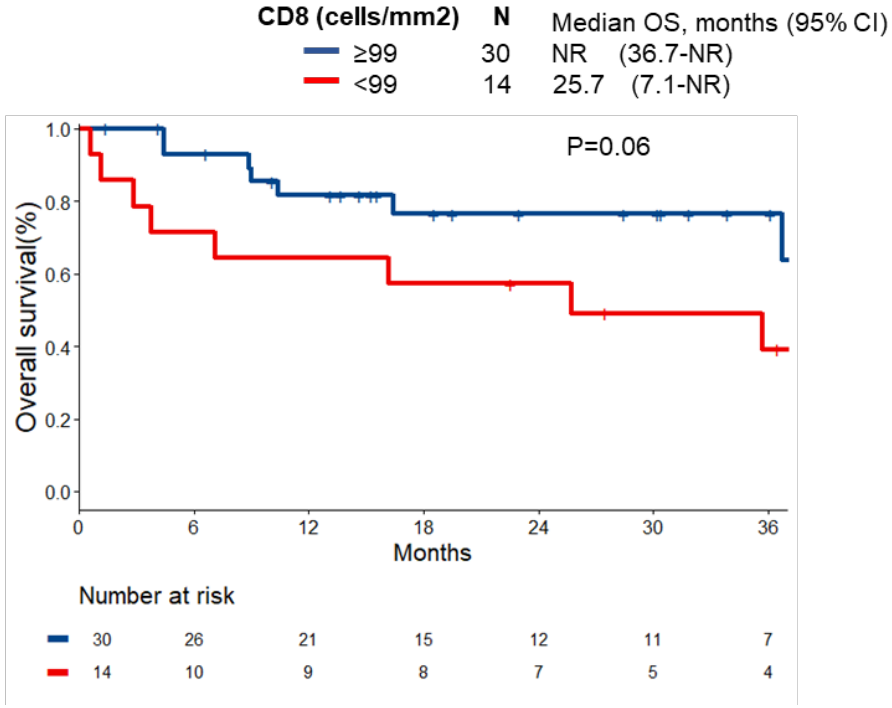


Alessi JV, Unpublished

Immunoprofile & 1st Line Pembrolizumab Response





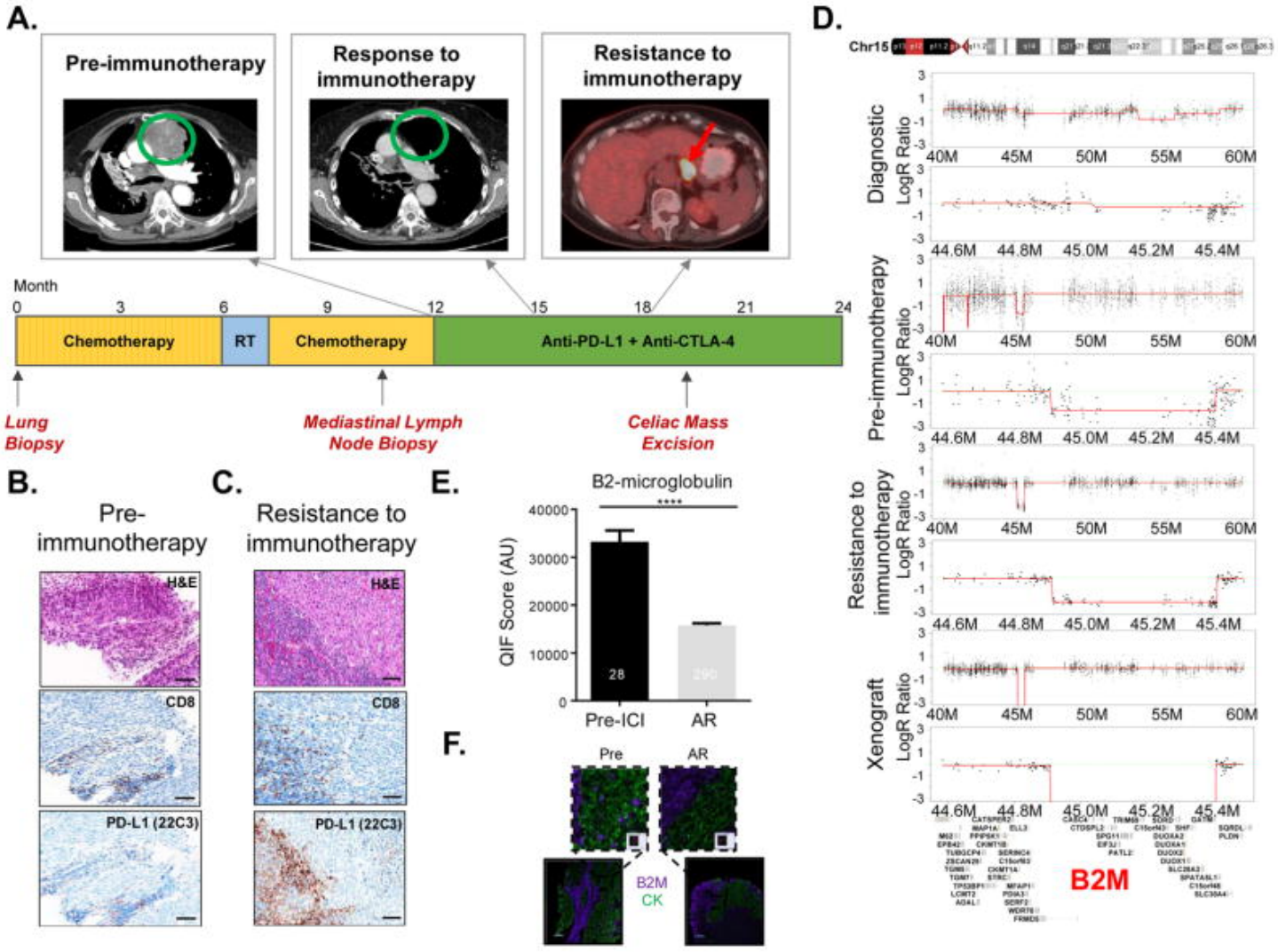


Alessi JV, Unpublished

What mediates acquired resistance to immunotherapy in lung cancer?

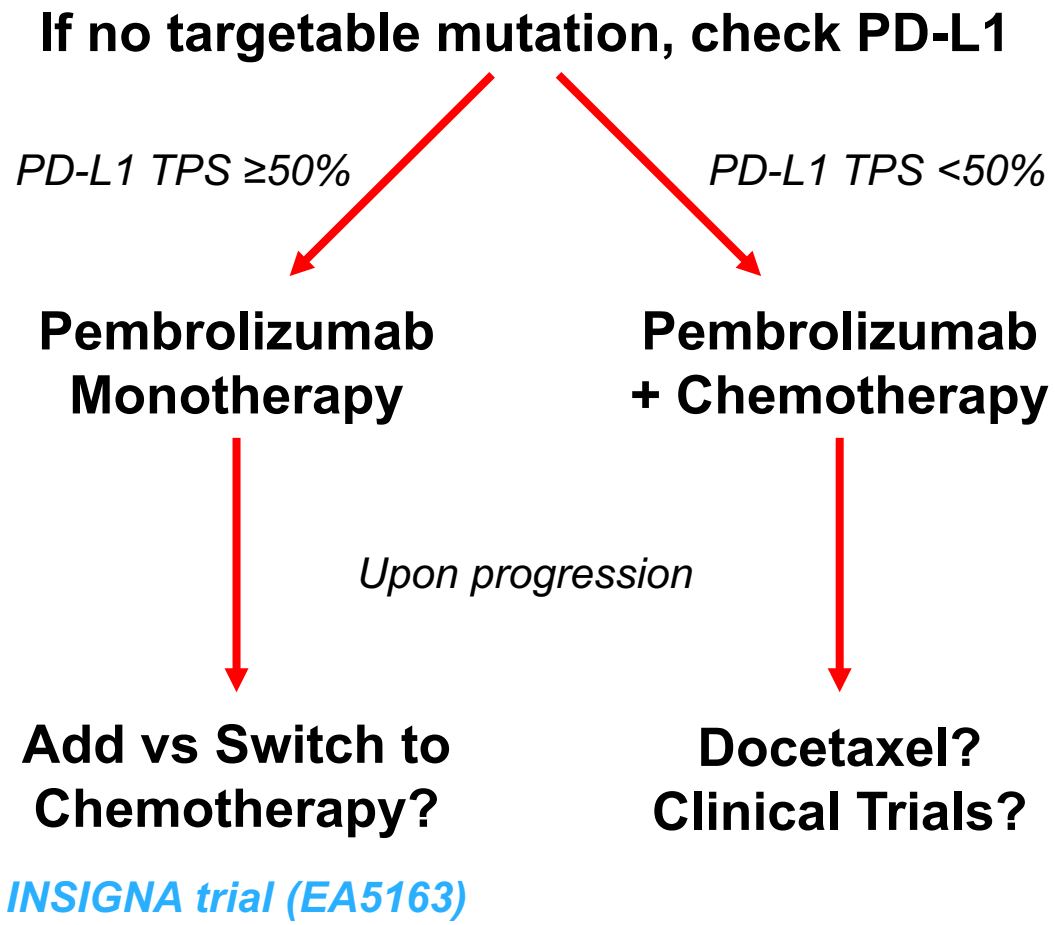
Impaired HLA Class I Antigen Presentation

14 ICI-resistant lung cancer samples



Gettinger S, et al, *Cancer Discov*. 2017 Dec;7(12):1420-1435.

Management of Resistance to Immunotherapy



Conclusions

- Several clinical, pathologic, genomic, and immunologic factors impact primary response and resistance to immune checkpoint inhibitors in lung cancer
- New strategies need to be considered for integrating multiple, continuous biomarkers (e.g. PD-L1 expression, TMB, TILs) to predict response and resistance to immunotherapy
- Mechanisms of primary and acquired resistance to PD-1 inhibitors are still not well understood
- Additional diagnostics and therapeutics are necessary to make precision immunotherapy a reality in clinic to prevent and overcome treatment resistance

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