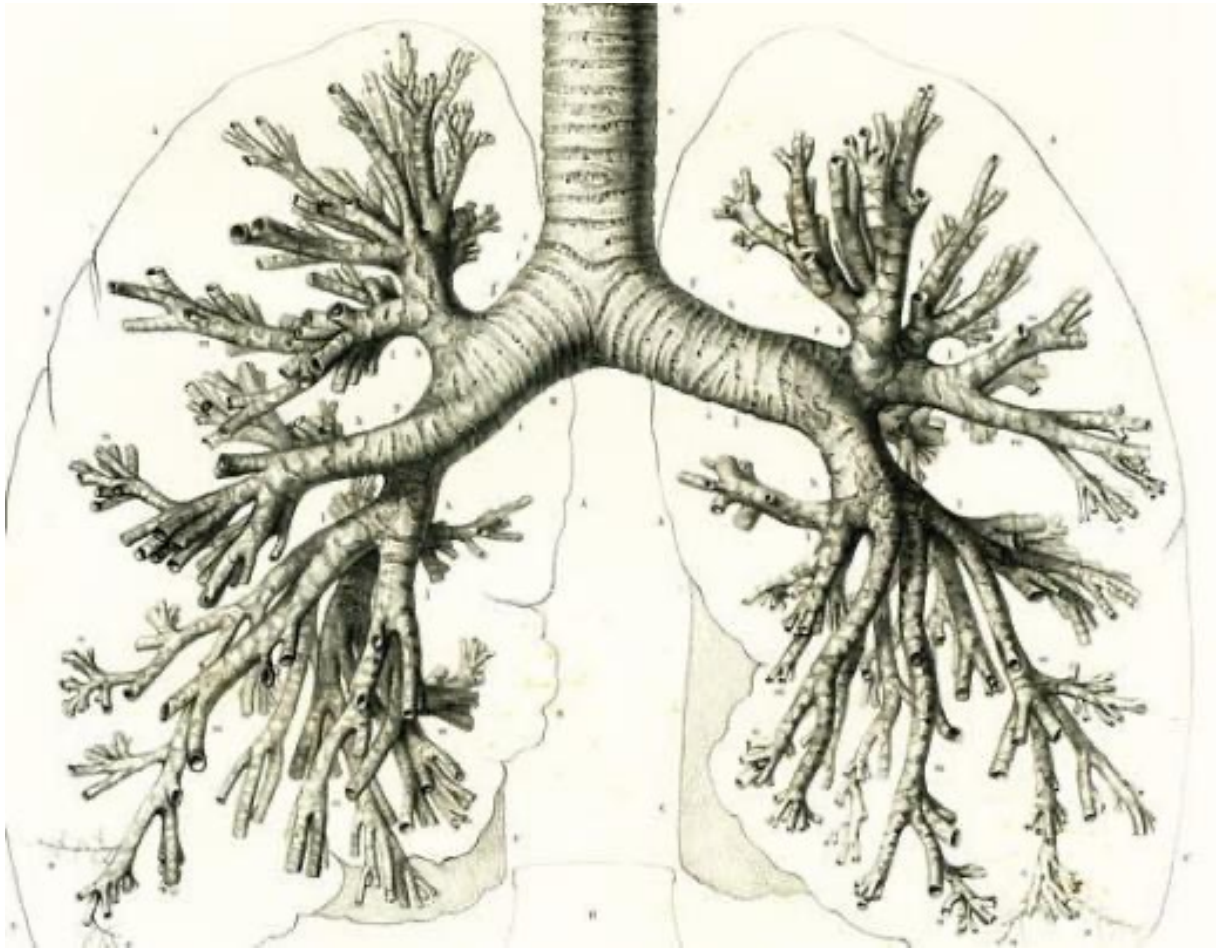
Immune checkpoint inhibitors in management of non-small cell lung cancer: practical questions and perspectives



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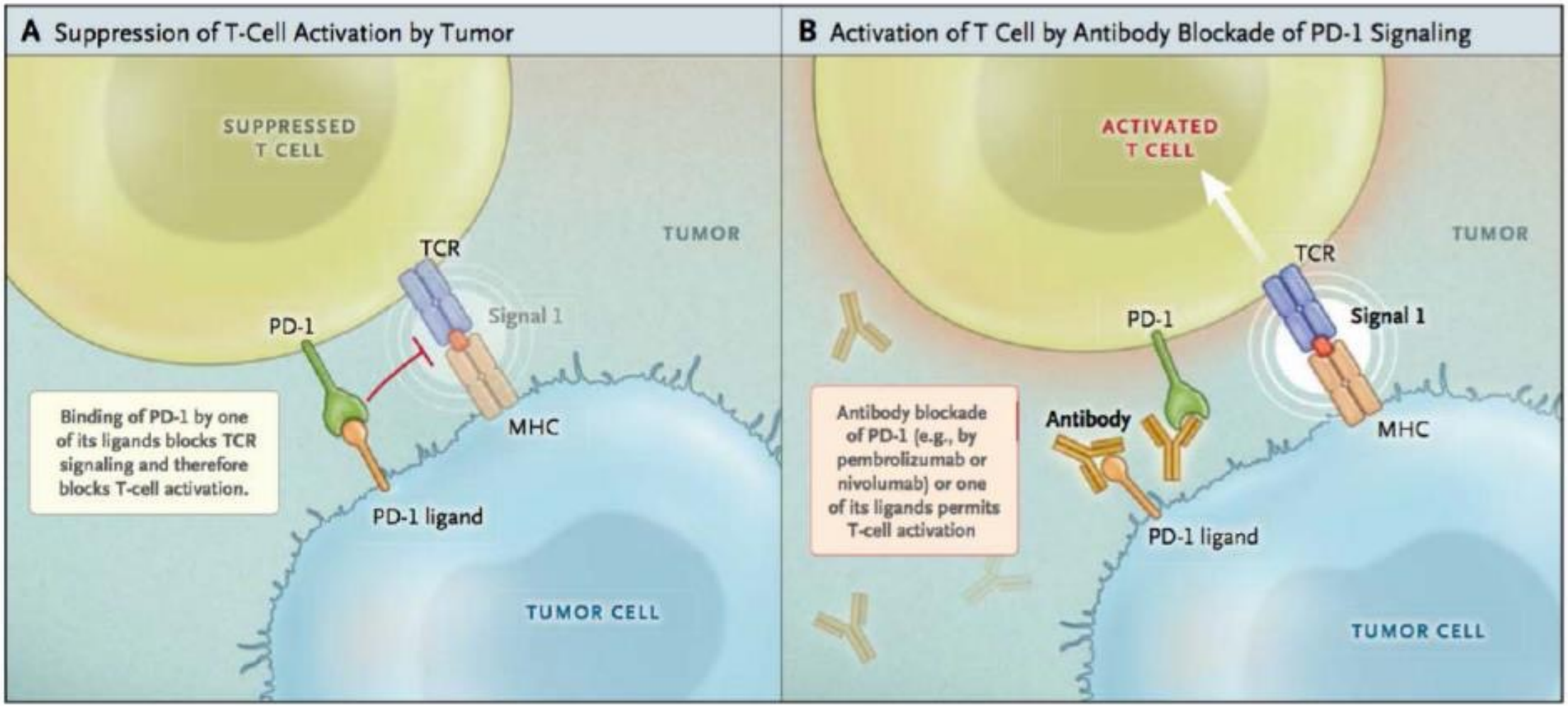
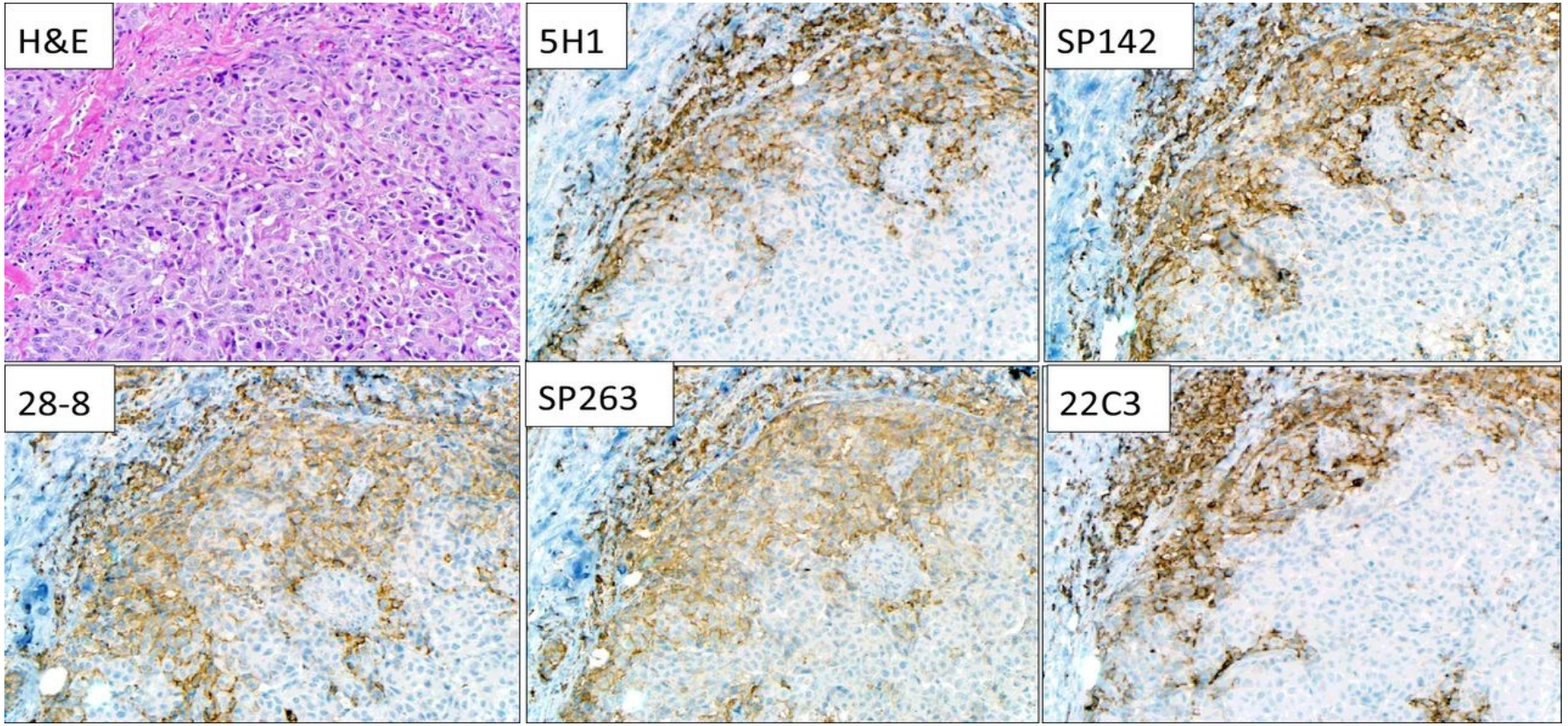
Immune checkpoints



Ribas *NEJM* 2015

PD-L1 in lung cancer



Remember that PD-L1 is a *qualitative* score (both TPS and CPS)

Remember that PD-L1 is a *continuous* variable (not binary) variable

Assay heterogeneity

Table 1. Approved and Investigational PD-L1 Diagnostic Assays in NSCLC

	Nivolumab		Pembrolizumab		Atezolizumab	Durvalumab	Avelumab
Antibody clone	28-8	SP263	22C3	SP263	SP142	SP263	73-10
Assay developer	Dako[5,25]	Ventana[24]	Dako[22,23]	Ventana[24]	Ventana[6]	Ventana[16]	Dako[55]
PD-L1 immunohistochemistry scoring*	TC	TC	TC	TC	TC and/or tumor-infiltrating IC	TC	TC
PD-L1 levels evaluated in clinical trials	TC: ≥ 1%, ≥ 5%, ≥ 10%[5]	TC: ≥ 1%, ≥ 5%, ≥ 10%[5]	TC: ≥ 1%, ≥ 50%[22]	TC: ≥ 1%, ≥ 50%[22]	TC: ≥ 50% (TC3)† IC: ≥ 10% (IC3)† [6,15]	TC: ≥ 25%[16]	TC: ≥ 1%[56]
PD-L1 level in first-line therapy	NA	NA	TC ≥ 50%	TC ≥ 50%	NA	NA	NA
PD-L1 level in second-line therapy	None	None	TC ≥ 1%	TC ≥ 1%	None	NA	NA
Diagnostic status	Complementary: testing not required US/EU: NSQ NSCLC Japan: SQ and NSQ NSCLC	Complementary: testing not required EU: NSQ NSCLC	Companion: testing required US/EU/Japan: SQ and NSQ NSCLC	Companion: testing required EU: SQ and NSQ NSCLC	Complementary: testing not required US/EU: SQ and NSQ NSCLC	Not yet approved for durvalumab	Not yet approved for avelumab
Approved IVD PD-L1 expression levels	US/EU/Japan: all patients eligible	EU: all patients eligible	US/EU/Japan: ≥ 50% (previously untreated); ≥ 1% (previously treated)		US: all patients eligible	Not available for NSCLC	Not available for NSCLC

Abbreviations: IC, immune cells; IVD, in vitro diagnostic; NA, not applicable; NSCLC, non–small-cell lung cancer; NSQ, non-squamous; PD-L1, programmed death-ligand 1; SQ, squamous; TC, tumor cells.
*All assays score cells at any intensity.
†TC0 < 1%, TC1 1% to < 5%, TC2 5% to < 50%, TC3 ≥ 50%, IC0 < 1%, IC1 1% to < 5%, IC2 5% to < 10%, IC3 ≥ 10%.

There are multiple assays to test for PD-L1 with different scoring guidelines and thresholds

28-8 (ipilimumab + nivolumab): 1%, 5% and 10%

22C3 (pembrolizumab): <1%, 1-49%, and ≥50%

*Buttner et al JCO 2017

Caveats with PD-L1 testing

- **Cytologic materials excluded from PD-L1 assessment in trials**
  - Nearly 1/3 of lung samples are FNAs or from pleural sample
  - How well do FNA reliably represent immune compartment?
- **Potential spatial heterogeneity**
  - To what extent is their concordance between primary and metastatic sites. Some controversy here[1-2]
- **Potential dynamic heterogeneity**
  - PDL1 is not a static variable! Cancers and immune microenvironment evolve in response to anti-cancer therapies[3]

[1]Sakakibara Clin Lung Cancer 2017
[2]Midha JCO 2017
[3]Choe Clin Lung Cancer 2017

Caveats with PD-L1 reporting

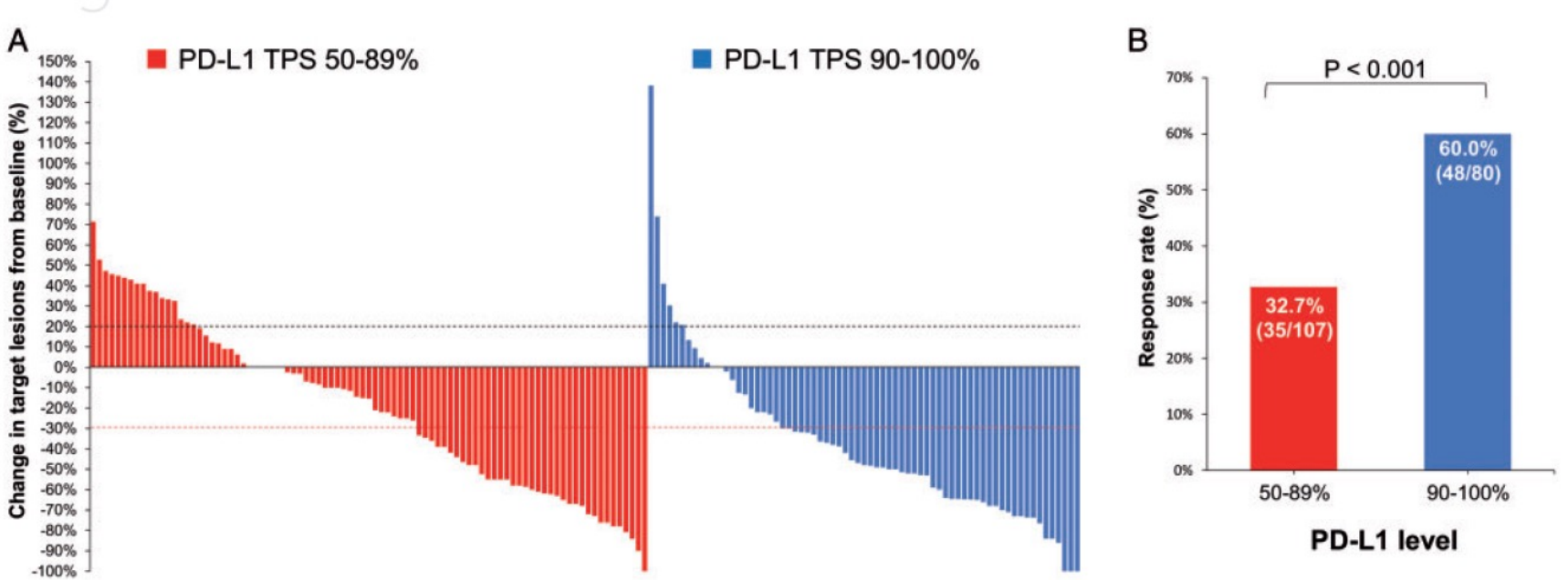


Figure 2. (A) The best objective response to pembrolizumab is shown as a percent change of target lesions from baseline in evaluable patients in patients with a non-small-cell lung cancer programmed death-ligand 1 (PD-L1) expression level of 50%–89% versus 90%–100%. (B) Histograms showing the response rate to first-line pembrolizumab in the PD-L1 expression 50%–89% versus 90%–100% groups.

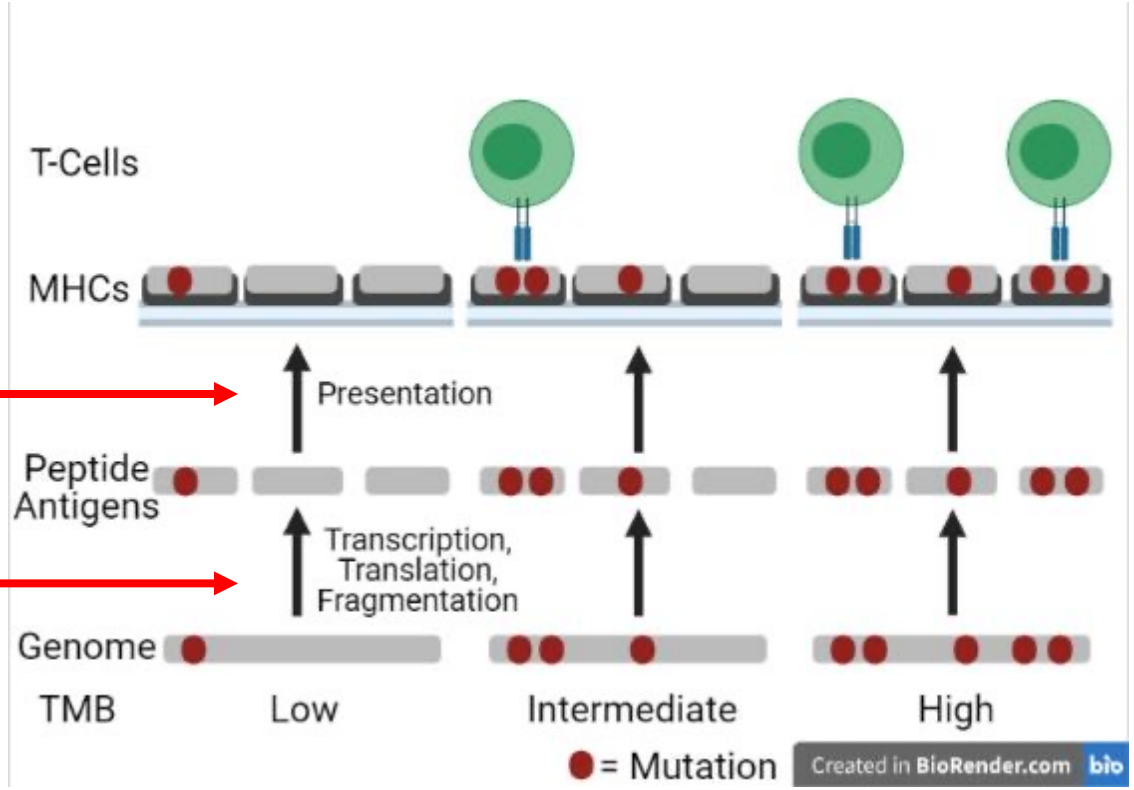
PD-L1 is a continuous variable, but trials will analyze data as categorical variable.

- KEYNOTE-189: PD-L1 (22C3) <1%, 1-49%, and ≥ 50%
- Checkmate 227: PD-L1 (28-8) <1% vs >1%

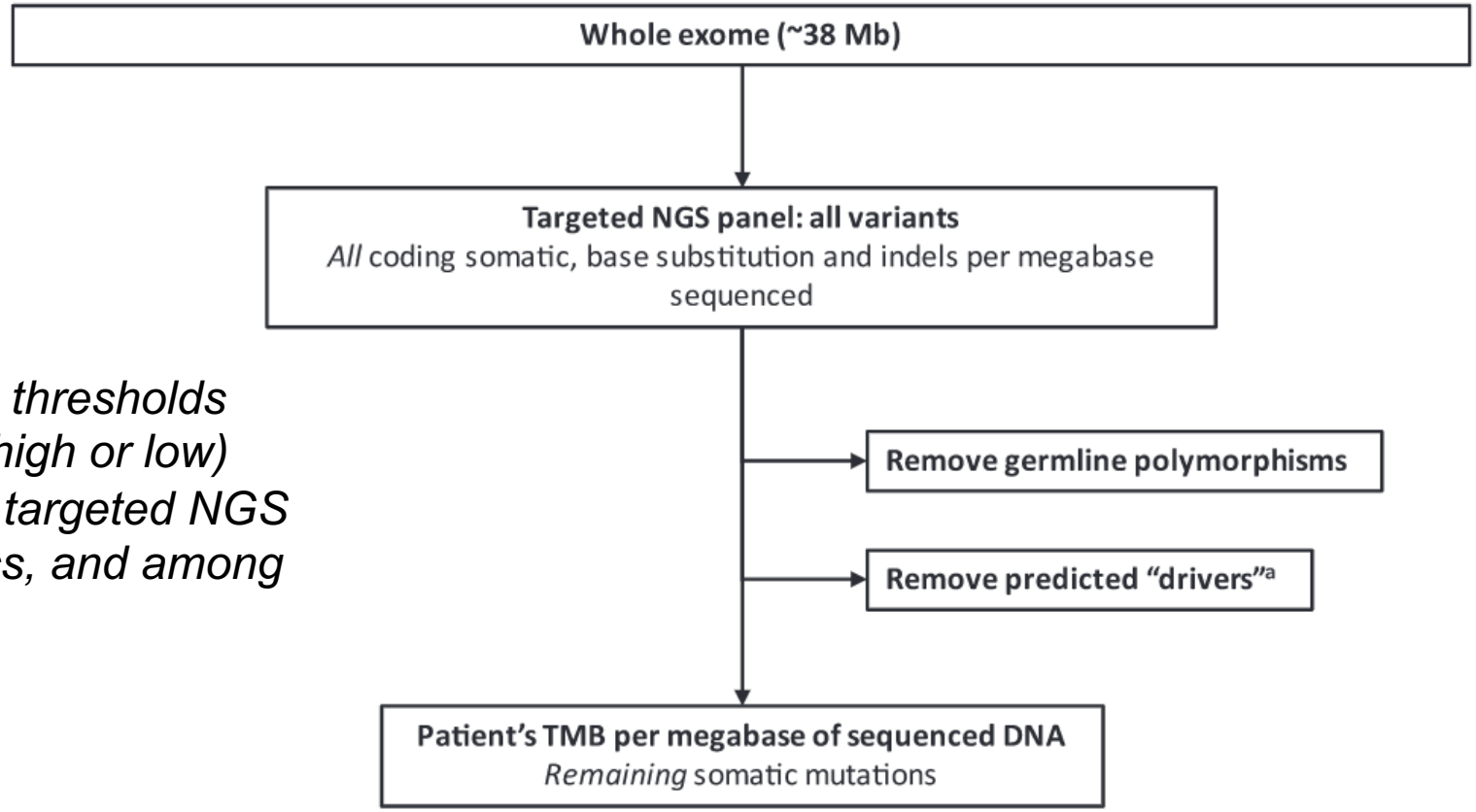
Tumor mutation burden

Tumor mutational burden (TMB) is a numeric index that expresses the number of mutations per megabase (muts/Mb) harbored by tumor cells in a neoplasm.

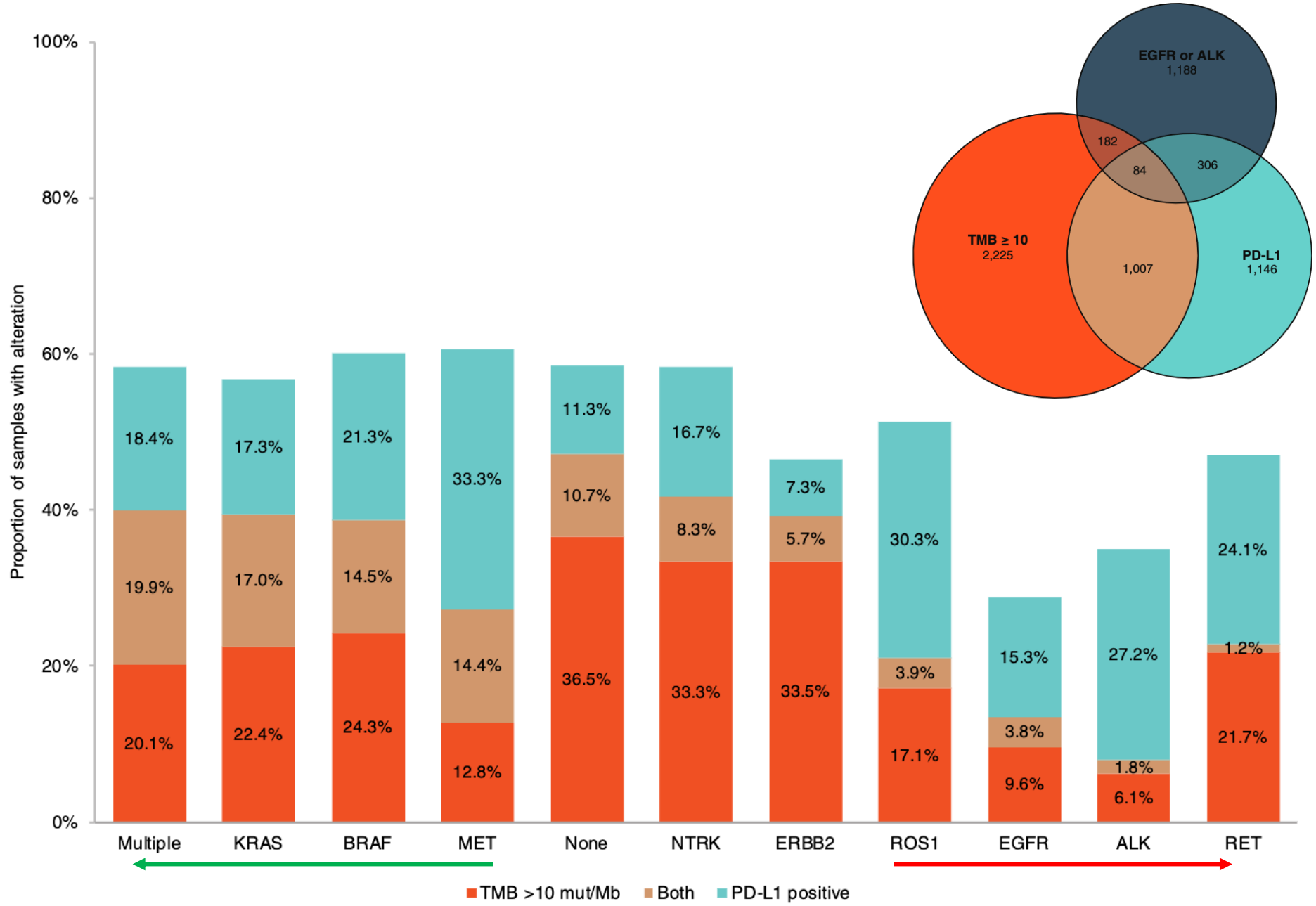
Key assumption - *direct link between protein coding changes and number of potential neoantigens within tumor genome*



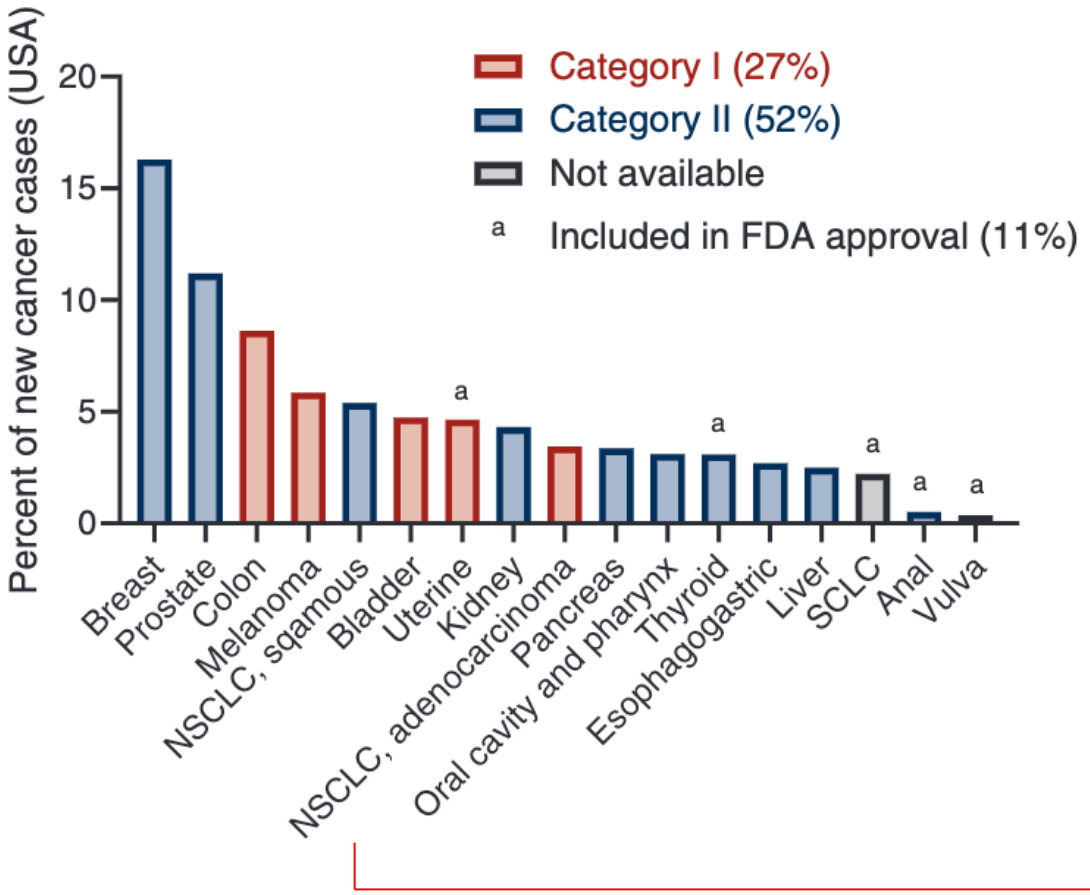
How TMB is calculated

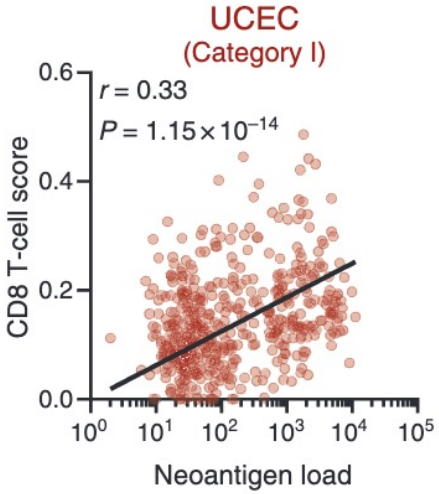


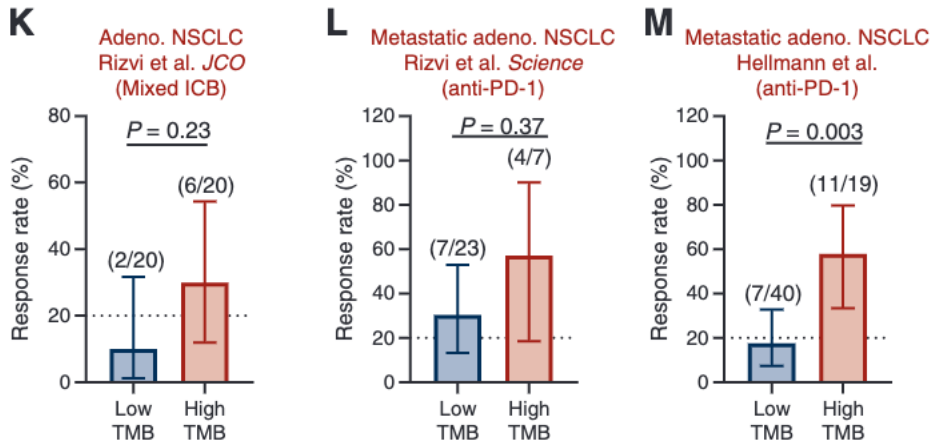
Controversy – *TMB thresholds (i.e. what counts as high or low) varies widely across targeted NGS panels, bioinformatics, and among different neoplasms*

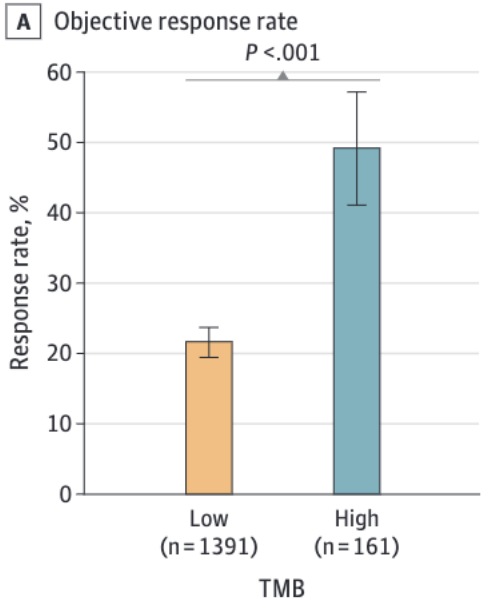

EGFR or ALK
1,188
182
84
306
TMB ≥ 10
2,225
1,007
PD-L1
1,146
100%
80%
60%
40%
20%
0%
Proportion of samples with alteration
18.4%
19.9%
20.1%
17.3%
17.0%
22.4%
21.3%
14.5%
24.3%
33.3%
14.4%
12.8%
11.3%
10.7%
36.5%
16.7%
8.3%
33.3%
7.3%
5.7%
33.5%
30.3%
3.9%
17.1%
15.3%
3.8%
9.6%
27.2%
1.8%
6.1%
24.1%
1.2%
21.7%
Multiple
KRAS
BRAF
MET
None
NTRK
ERBB2
ROS1
EGFR
ALK
RET
TMB >10 mut/Mb
Both
PD-L1 positive

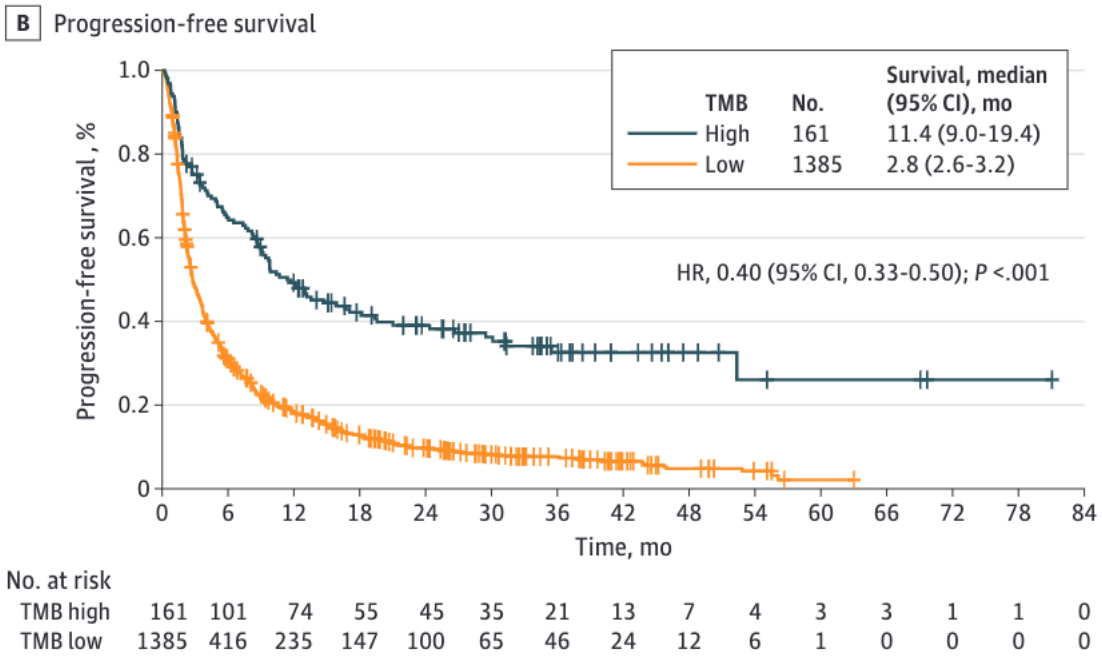
TMB-High relevant when CD8 T cells correlate with neoantigen load

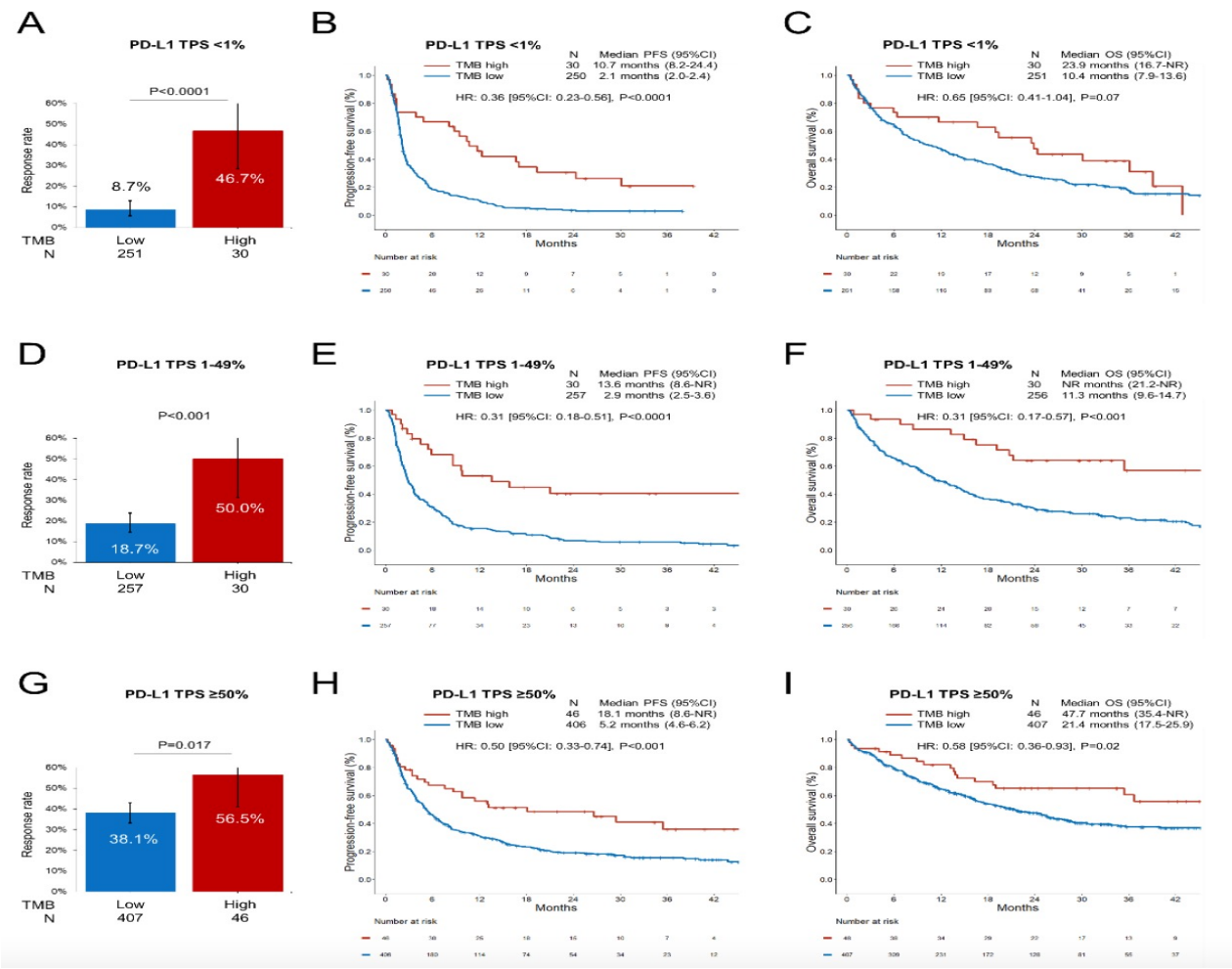












High TMB (>19 Muts/Mb) associated with improved ORR and PFS in mNSCLC.

Subset analysis shows benefit irrespective of PDL1

A patient has an EGFR Exon 19 deletion and a PD-L1 of 80%.

What therapy should I use first?

Advanced NSCLC*

Oncogene driver

- **EGFR:** Osimertinib**, erlotinib, afatinib, gefitinib, erlotinib + ramucirumab
- **ALK:** Alectinib**, brigatinib, lorlatinib, crizotinib, ceritinib
- **ROS1:** Entrectinib**, crizotinib, ceritinib
- **RET:** Selpercatinib**, pralsetinib**, cabozantinib
- **BRAF V600E:** Dabrafenib / trametinib**
- **MET Exon 14:** Capmatinib, tepotinib, crizotinib
- **NTRK:** Larotrectinib, entrectinib
- **EGFR Exon 20†:** Amivantamab, mobocertinib
  KRAS G12C†: Sotorasib
  HER2†: Trastuzumab deruxtecan (T-Dxd)

No driver mutation

Non-squamous	Squamous
PDL1 ≥ 1% - Pembrolizumab - Platinum + pemetrexed + pembrolizumab - Carboplatin + paclitaxel + bevacizumab + atezolizumab - Carboplatin + abraxane + atezolizumab - Nivolumab + ipilimumab - Nivolumab + ipilimumab + platinum + pemetrexed **PDL1 ≥ 50% (including above)** - Atezolizumab - Cemiplimab	**PDL1 ≥ 1%** - Pembrolizumab - Platinum + paclitaxel + pembrolizumab - Carboplatin + paclitaxel + bevacizumab + atezolizumab - Carboplatin + abraxane + pembrolizumab - Nivolumab + ipilimumab - Nivolumab + ipilimumab + platinum + paclitaxel **PDL1 ≥ 50% (including above)** - Atezolizumab - Cemiplimab

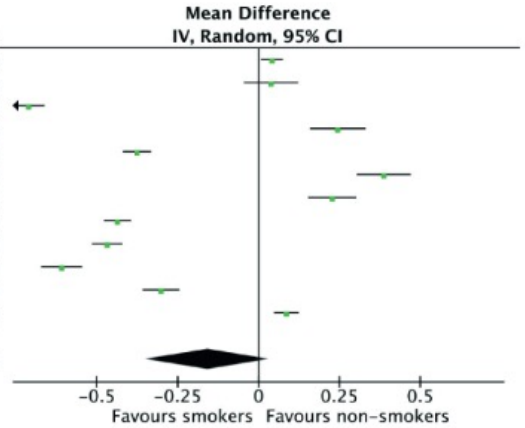
*Locally advanced (not amenable to chemoXRT) or metastatic
**Indicates preferred options
†Second line setting only

Caution with ICI monotherapy in never smokers

A Comparison of HR (OS) between smokers and non-smokers

Study or Subgroup	smokers log[HR]	SD	Total	non-smokers log[HR]	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Achim Rittmeyer 2016	-0.30110509	0.09348545	694	-0.34249031	0.21224072	156	8.4%	0.04 [0.01, 0.08]
D.P. Carbone 2017	0.05826891	0.11913852	475	0.01980263	0.32492504	59	8.3%	0.04 [-0.05, 0.12]
Fabrice Barlesi 2018	-0.18632958	0.11600412	657	0.52472853	0.28374091	133	8.4%	-0.71 [-0.76, -0.66]
Fabrice Barlesi 2018-2	-0.18632958	0.12475812	511	-0.43078292	0.35760167	67	8.3%	0.24 [0.16, 0.33]
H. Borghaei 2015	-0.35667494	0.10943765	458	0.01980263	0.23533706	118	8.4%	-0.38 [-0.42, -0.33]
Howard West 2019	-0.21072103	0.11494529	548	-0.597837	0.38801708	84	8.3%	0.39 [0.30, 0.47]
L. Gandhi 2018	-0.61618614	0.10929965	543	-0.84397007	0.32116197	73	8.3%	0.23 [0.15, 0.30]
Luis Paz-Ares 2019	-0.31471075	0.08397495	614	0.12221763	0.24093408	132	8.4%	-0.44 [-0.48, -0.40]
M.D. Hellmann 2019	-0.26136476	0.09257793	674	0.20701417	0.2442688	107	8.4%	-0.47 [-0.52, -0.42]
Martin Reck 2020	-0.4780358	0.09098851	622	0.13102826	0.31578427	97	8.3%	-0.61 [-0.67, -0.55]
Ramaswamy Govindan 2017	-0.12783337	0.09272982	656	0.17395331	0.26291453	83	8.3%	-0.30 [-0.36, -0.24]
Yi-Long Wu 2019	-0.31471075	0.1414058	354	-0.40047757	0.22188029	150	8.4%	0.09 [0.05, 0.12]
Total (95% CI)			**6806**			**1259**	**100.0%**	**-0.16 [-0.35, 0.03]**

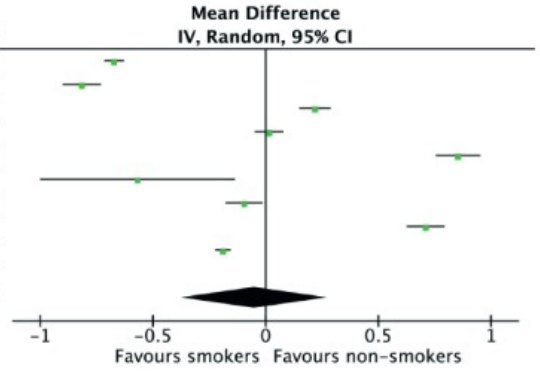
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 1758.52$, df = 11 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: Z = 1.64 (P = 0.10)



B Comparison of HR (PFS) between smokers and non-smokers

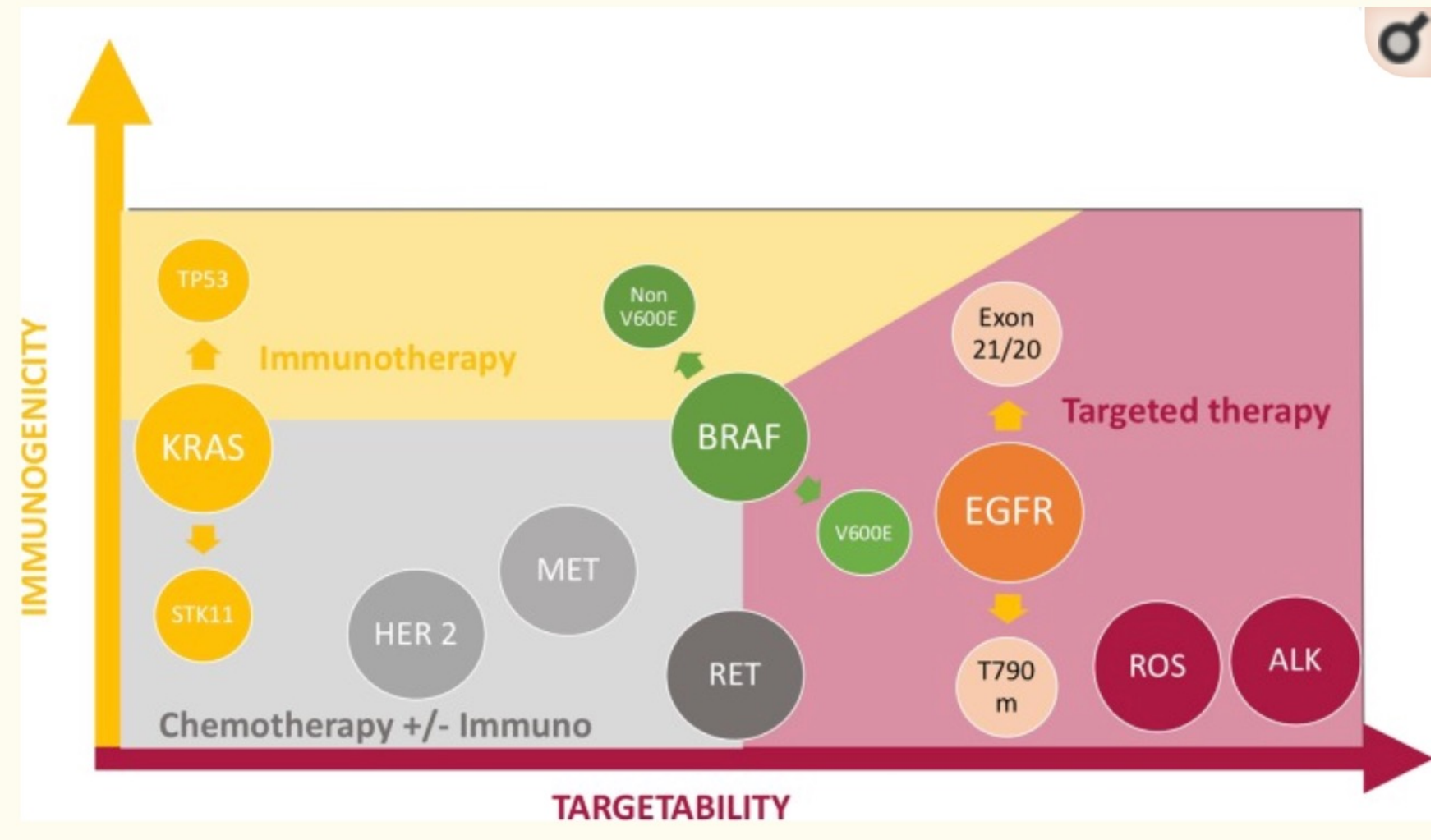
Study or Subgroup	smokers log[HR]	SD	Total	non-smokers log[HR]	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Caicun Zhou 2019	-0.73396918	0.18065945	257	-0.0618754	0.24141405	155	11.4%	-0.67 [-0.72, -0.63]
D.P. Carbone 2017	0.10436002	0.11373407	475	0.92028275	0.33286207	59	11.3%	-0.82 [-0.90, -0.73]
Fabrice Barlesi 2018-2	-0.49429632	0.10001074	511	-0.71334989	0.2892101	67	11.3%	0.22 [0.15, 0.29]
Howard West 2019	-0.4462871	0.09528406	548	-0.46203546	0.29672214	84	11.3%	0.02 [-0.05, 0.08]
L. Gandhi 2018	-0.61618614	0.14007852	543	-1.46967597	0.43020381	73	11.3%	0.85 [0.75, 0.95]
Martin Reck 2016	-0.67334455	0.15584415	281	-0.10536052	1.08012921	24	9.5%	-0.57 [-1.00, -0.14]
Robert Jotte 2020	-0.35667494	0.08706713	627	-0.26136476	0.31254465	55	11.3%	-0.10 [-0.18, -0.01]
S.J. Antonia 2017	-0.52763274	0.11232445	649	-1.23787436	0.3405615	64	11.3%	0.71 [0.63, 0.79]
Yi-Long Wu 2019	-0.32850407	0.12385404	354	-0.13926207	0.19588539	150	11.4%	-0.19 [-0.22, -0.16]
Total (95% CI)			**4245**			**731**	**100.0%**	**-0.05 [-0.37, 0.27]**

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 1709.96$, df = 8 ($P < 0.00001$); $I^2 = 100\%$
Test for overall effect: Z = 0.31 (P = 0.75)



Zhao *Frontier Oncol* 2021

A word on waiting for molecular testing



Mhanna *Curr Treat Options Oncol* 2019

Higher iRAE with sequential immunotherapy and targeted therapy

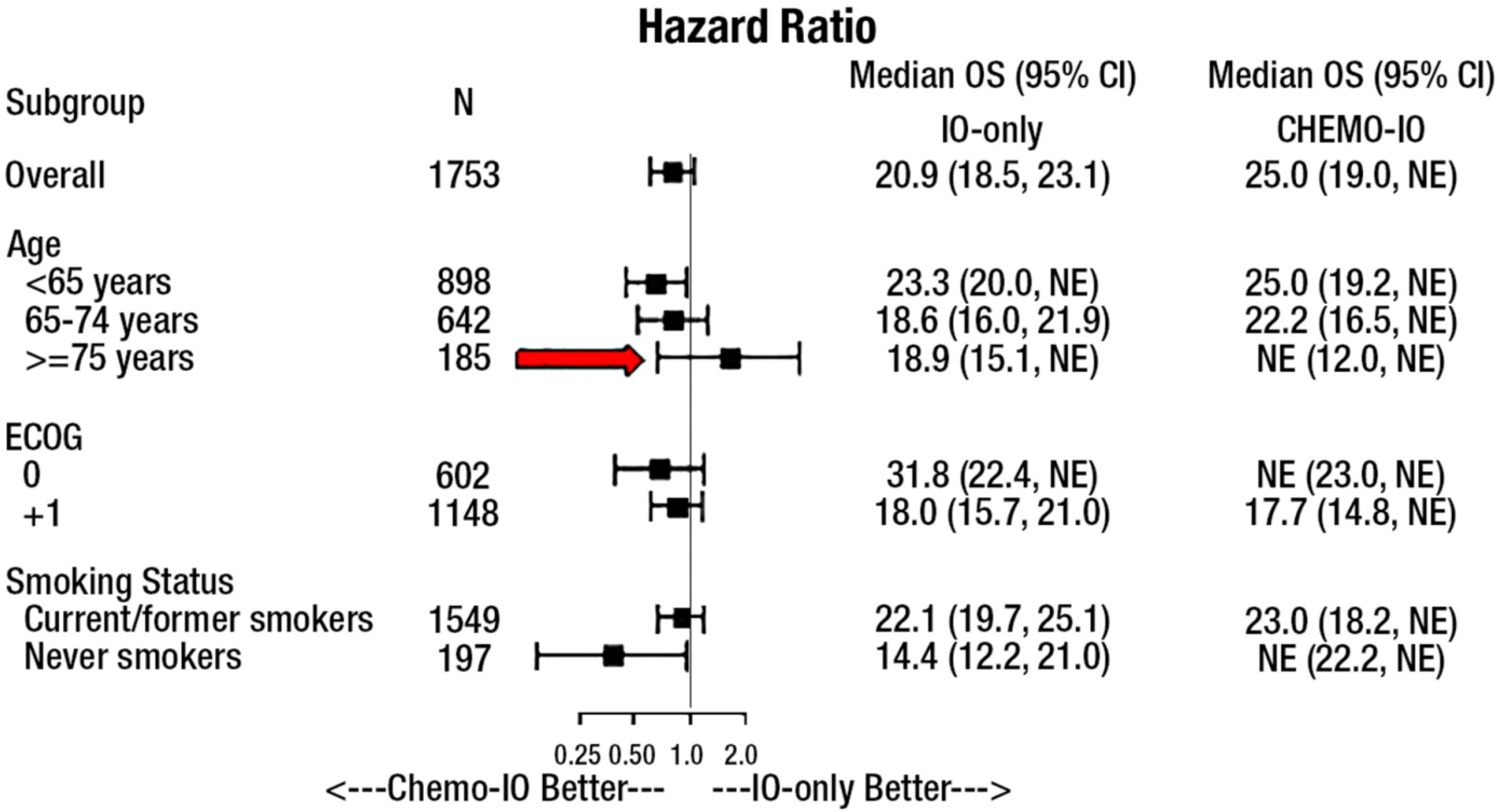
- Remember that checkpoint inhibitors have long half lives!
- Multiple studies have shown marked increase in immune toxicity when TKI is given after checkpoint inhibitor therapy[1-3]
- Especially in **never/light smoker** with lung cancer, my practice
  - If clinically stable → wait for molecular testing (NGS) to rule out ”drive oncogenes” such as *EGFR, ALK, ROS1, RET*
  - If symptomatic (needs urgent therapy) → start chemotherapy for 1-2 cycles and *hold immunotherapy* until molecular results.

[1]Schoenfeld *Annal Oncol* 2019; [2]Oshima *JAMA Onc* 2019; [3] Lin *JTO* 2019

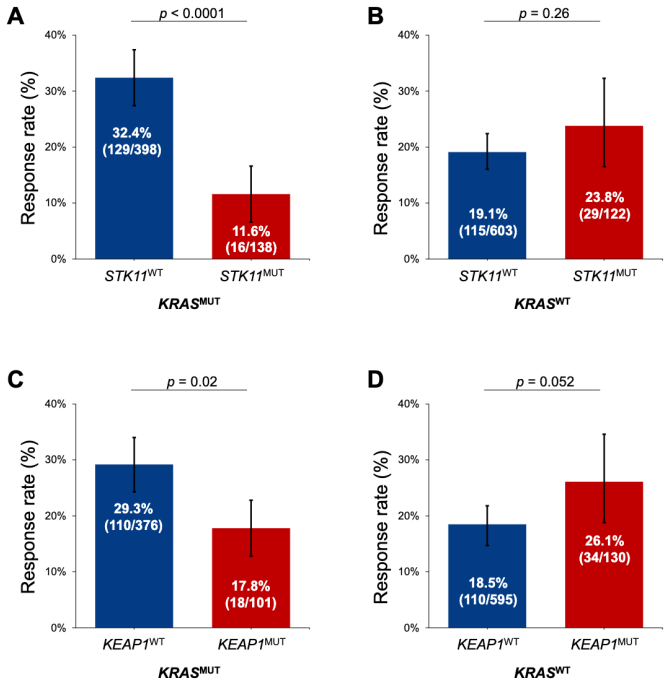
45 pack-year smoker has stage IV NSCLC. She is minimally symptomatic. NGS with KRAS G12C, STK11, TP53. PD-L1 85%

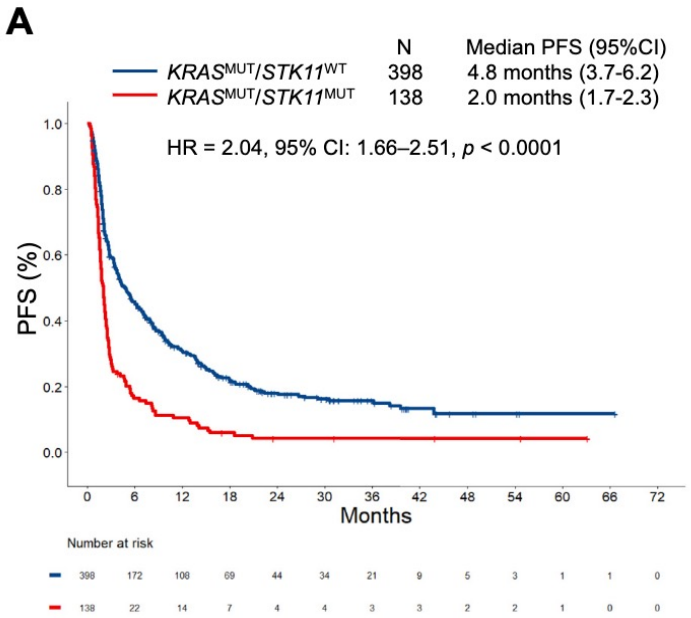
Should I use chemo-ICI or ICI alone?

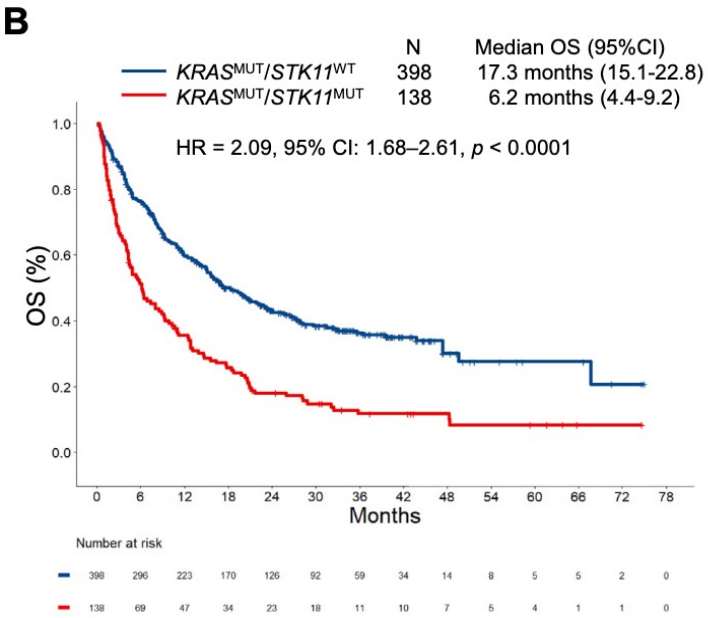
Chemotherapy + ICI versus ICI for PDL1 ≥ 50%



STK11 and *KEAP1* negative prognostic markers to ICI among KRAS NSCLC







Ricciuti J Thorac Oncol 2022

Personal practice perspective for PD-L1 ≥ 50%

ICI monotherapy	Chemotherapy + ICI
Heavy smoker	Never smoker or light smoking history
Minimally symptomatic	Symptomatic and would be benefit from cytoreduction from chemotherapy
KRAS mutation without STK11, KEAP1, TP53	+/- KRAS mutation with STK11, KEAP1, TP53
CKD Stage III or borderline renal dysfunction	Excellent renal function

65 pack-year smoker has stage IV NSCLC. He is on maintenance ipilumumab + nivolumab for 3 years. NGS with actionable drivers. PD-L1 90%

How long should I continue ICI?

Trial design and endpoints

D.I.C.I.P.L.E (IFCT-1701)

Double Immune Checkpoint Inhibitors in any PD-L1 stage IV non-small Lung CancEr

Multicenter, non-inferiority, randomized phase III trial

Histogically-proven stage IV NSCLC:
- Measurable disease
- PS 0-1
- 18 – 75 years
- Any PDL1
- w/o EGFR/ALK alterations
- chemo & i.o naive

n = 1360

Nivolumab 3mg /kg q2w + **Ipilimumab** 1 mg/kg q6w

At 6 months patients with disease control Randomized 1:1

n = 868

Stratification factors:
- SCC/non-SCC
- PD-L1 (<1%, 1-49%, ≥50%)
- Ever smokers/never-smokers
- response: PR/SD
- PS = 0 *vs.* PS=1

Arm A

Nivolumab 3mg /kg q2w + **Ipilimumab** 1 mg/kg q6w

Prog

Platinum-based doublet recommended

Arm B

Observation

Prog

Nivolumab 3mg /kg q2w + **Ipilimumab** 1 mg/kg q6w

- Primary endpoint : **PFS from randomization**
- Secondary endpoints : safety and tolerance, overall survival, quality of life, PD-L1 tumour expression prognostic and predictive value
- CT-scan f.u q8 weeks for 1 year, then q12 weeks in both arms

Exploratory biomarkers studies

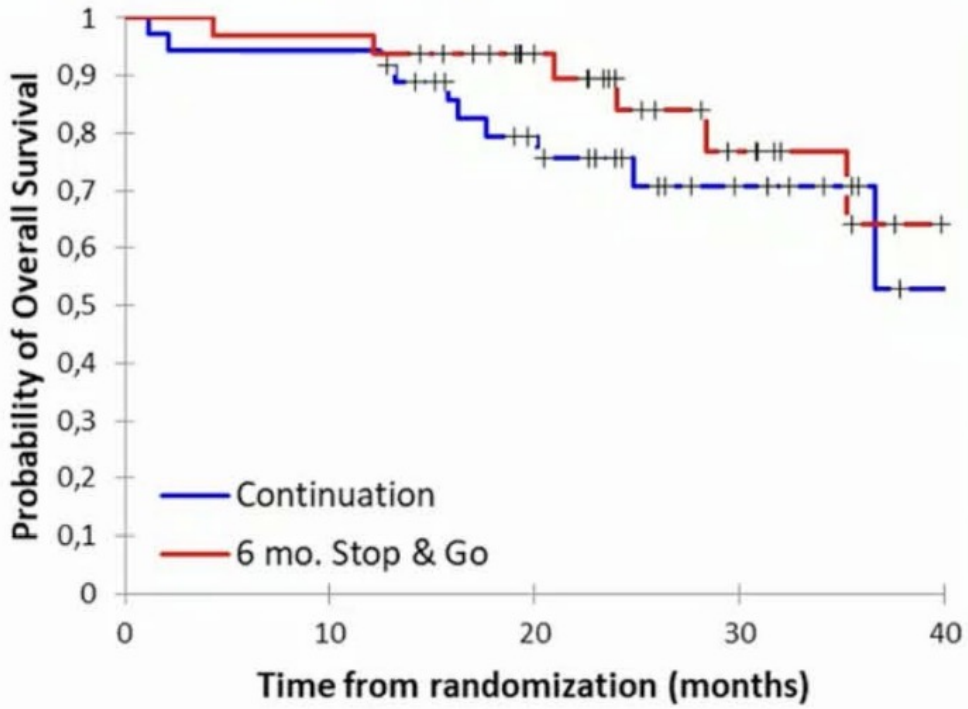
ClinicalTrials.gov: NCT03469960

PARIS 2022 ESMO congress

Presented by Gerard Zalcman, M.D. Bichat Hospital (APHP), Paris, France

Efficacy: Overall Survival

Per protocol population



Number at risk					
Continuation	36	34	22	9	2
6 mo. Stop & Go	32	31	22	10	2

Terminated early due Ipi+Nivo combination no longer being reimbursed in Europe

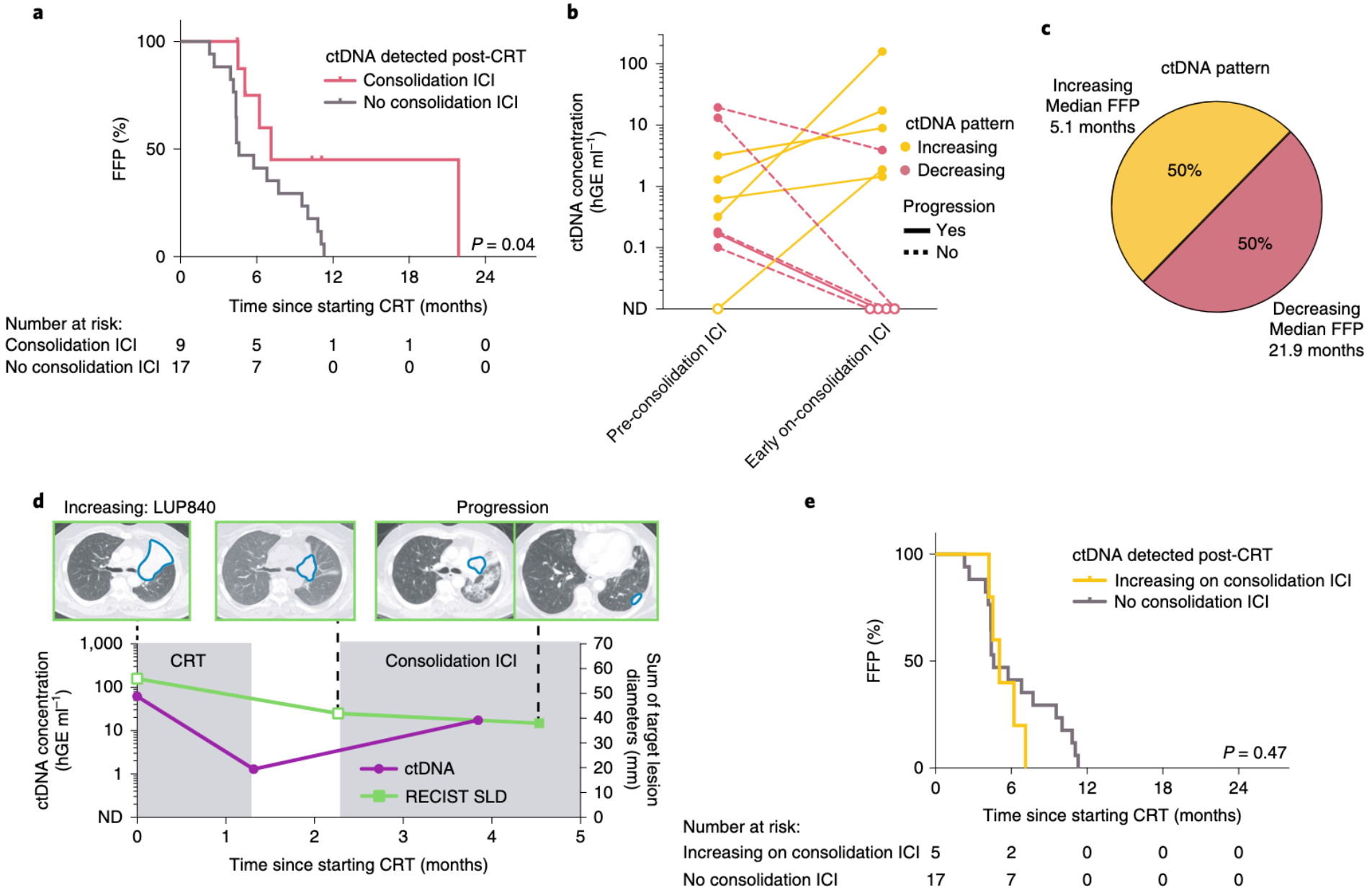
	Arm A Continuation (N= 36)	Arm B Stop & Go (N = 32)
Event : N (%)	10 (27.8)	6 (18.7)
Median OS: months [95% CI]	NR [36.7-NR]	NR [35.2-NR]
12-m OS: % [95% CI]	94.4 [79.6-98.6]	96.9 [79.8-99.5]
18-m OS: % [95% CI]	79.3 [61.3-89.6]	93.7 [77.2-98.4]
p=0.33		

Median follow-up [95% CI] : 26 months [24-31] from randomization

Personal practice pattern for duration of maintenance ICI (+/- pemetrexed)

- I typically continue pemetrexed *and* pembrolizumab for non-squamous NSCLC for up to two years
  - Potentially higher rates of renal toxicity with this approach
  - Six months may be reasonable given IFCT findings

- Potential use case for tissue-informed MRD monitoring?


a
100
50
0
FFP (%)
ctDNA detected post-CRT
Consolidation ICI
No consolidation ICI
P = 0.04
0
6
12
18
24
Time since starting CRT (months)
Number at risk:
Consolidation ICI 9 5 1 1 0
No consolidation ICI 17 7 0 0 0
b
100
10
1
0.1
ND
ctDNA concentration (hGE ml−1)
ctDNA pattern
Increasing
Decreasing
Progression
Yes
No
Pre-consolidation ICI
Early on-consolidation ICI
c
ctDNA pattern
Increasing
Median FFP
5.1 months
50%
50%
Decreasing
Median FFP
21.9 months
d
Increasing: LUP840
Progression
1,000
100
10
1
ND
ctDNA concentration (hGE ml−1)
CRT
Consolidation ICI
ctDNA
RECIST SLD
70
60
50
40
30
20
10
0
Sum of target lesion diameters (mm)
0
1
2
3
4
5
Time since starting CRT (months)
e
100
50
0
FFP (%)
ctDNA detected post-CRT
Increasing on consolidation ICI
No consolidation ICI
P = 0.47
0
6
12
18
24
Time since starting CRT (months)
Number at risk:
Increasing on consolidation ICI 5 2 0 0 0
No consolidation ICI 17 7 0 0 0

THANK YOU

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