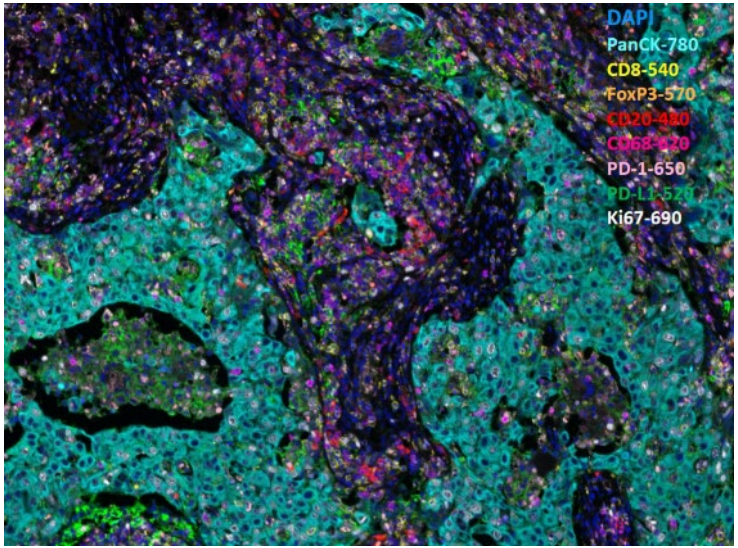


Focus on controversial subgroups for immunotherapy in non-AGA NSCLC

Pr Solange Peters, MD-PhD
Lausanne University Hospital & Ludwig Institute
Switzerland

DISCLOSURE INFORMATION

I have received education grants, provided consultation, attended advisory boards and/or provided lectures for the following organizations, from whom I have received honoraria (all fees to institution):

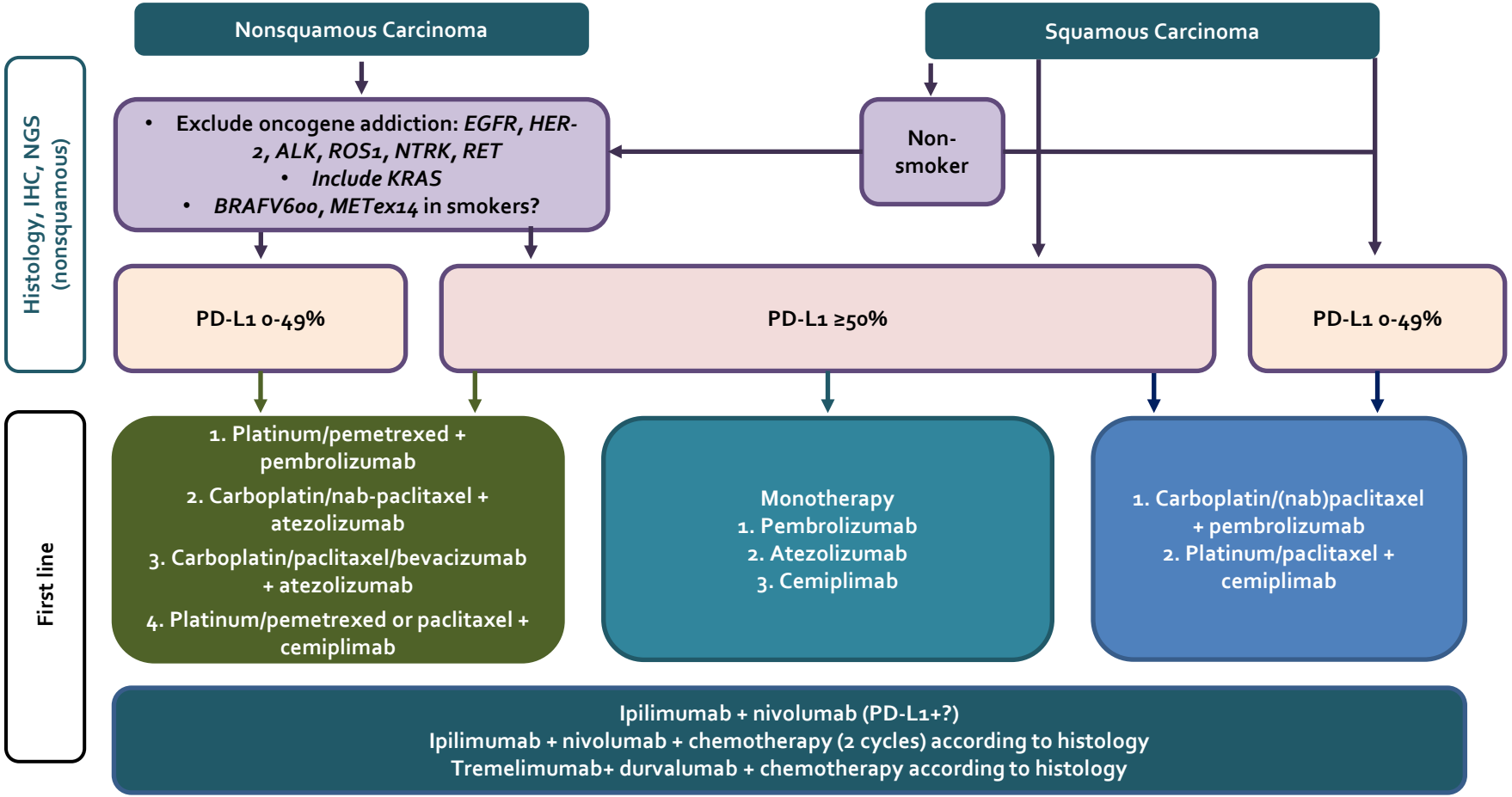
Consultation / Advisory role: AbbVie, AiCME, Amgen, Arcus, AstraZeneca, Bayer, Beigene, BerGenBio, Biocartis, BioInvent, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, ecancer, Eli Lilly, Elsevier, F-Star, Fishawack, Foundation Medicine, Genzyme, Gilead, GSK, Illumina, Imedex, IQVIA, Incyte, Ipsen, iTeos, Janssen, Medscape, Medtoday, Merck Sharp and Dohme, Merck Serono, Merrimack, Mirati, Novartis, Novocure, OncologyEducation, Pharma Mar, Phosplatin Therapeutics, PER, Peerview, Pfizer, Regeneron, RMEI, Roche/Genentech, RTP, Sanofi, Seattle Genetics, Takeda, Vaccibody.

Board of Director role: Galenica SA

Talk in a company's organized public event: AiCME, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, ecancer, Eli Lilly, Foundation Medicine, GSK, Illumina, Imedex, Ipsen, Medscape, Merck Sharp and Dohme, Mirati, Novartis, PER, Peerview, Pfizer, Roche/Genentech, RTP, Sanofi, Takeda.

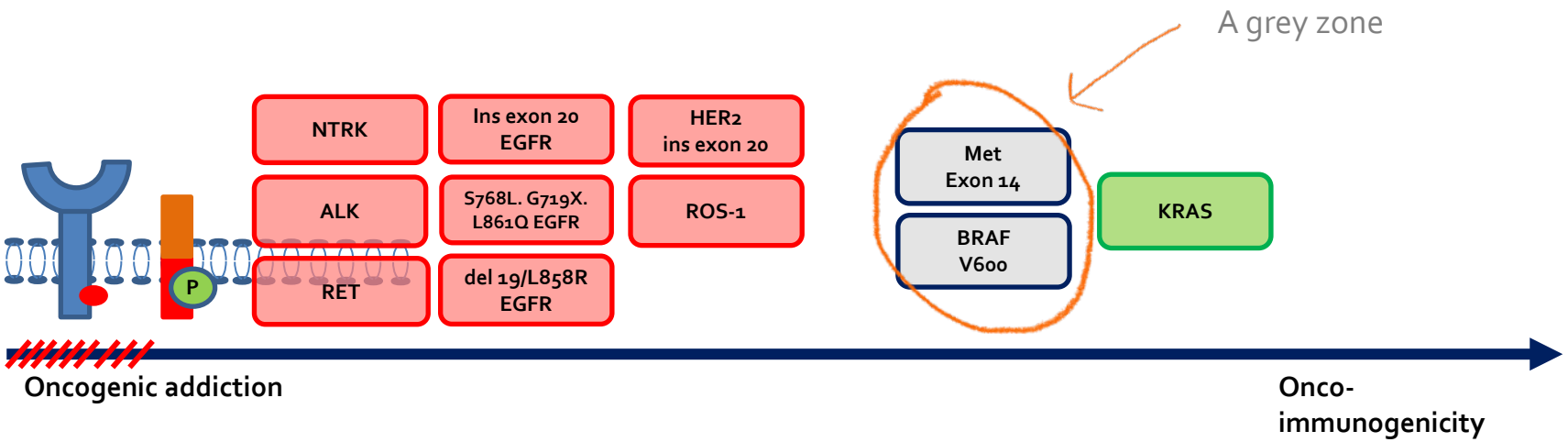
Receipt of grants/research supports: Principal investigator in trials (institutional financial support for clinical trials) sponsored by Amgen, AstraZeneca, Beigene, Bristol-Myers Squibb, GSK, Merck Sharp and Dohme, Roche/Genentech.

Immunotherapy is a standard for advanced NSCLC



WHICH BIOMARKERS ARE REQUIRED FOR TREATMENT DECISION-MAKING PRIOR TO INITIATING IO-BASED TREATMENT ?

Targetable biomarkers in NSCLC & IO

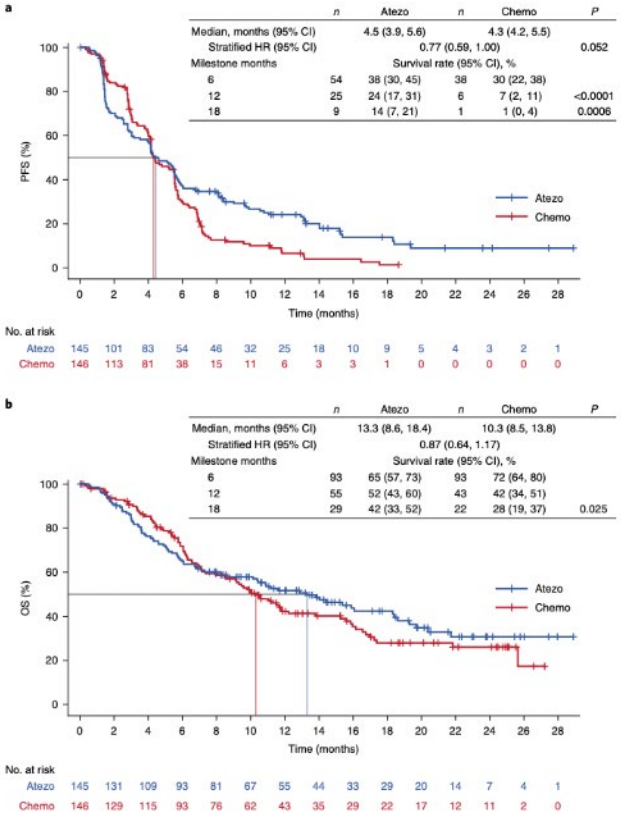


Tumor heterogeneity, a gradient from oncogenic addiction to immunogenicity

TMB

WHICH BIOMARKERS ARE REQUIRED FOR TREATMENT DECISION-MAKING PRIOR TO INITIATING IO-BASED TREATMENT ?

Where are we with TMB?



nature medicine ARTICLES
https://doi.org/10.1038/s41591-022-01933-w
Check for updates
OPEN

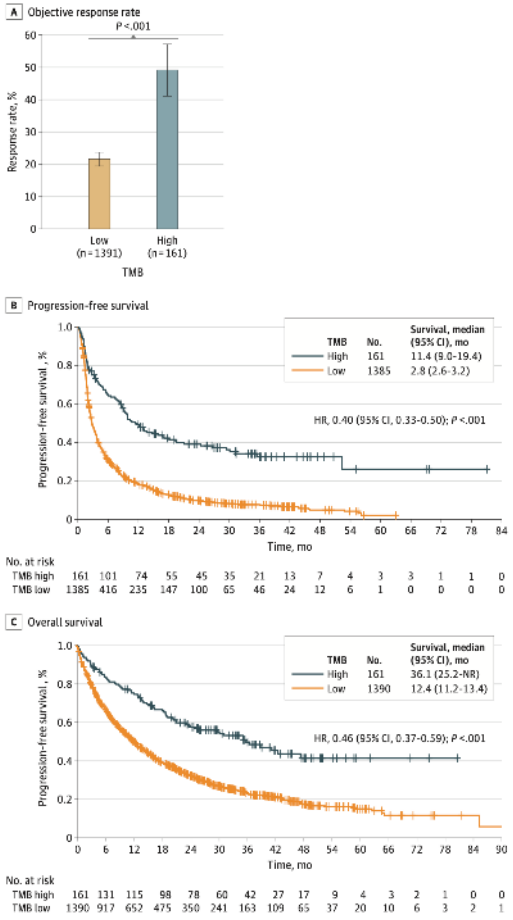
Atezolizumab versus chemotherapy in advanced or metastatic NSCLC with high blood-based tumor mutational burden: primary analysis of BFAST cohort C randomized phase 3 trial

- The bTMB CTA ≥16 cutoff was determined to be equivalent to a F1L CDx value of 13.6 mut/Mb.
- PFS using F1L CDx (including indels) longer with atezolizumab, HR of 0.71 (95% CI: 0.52, 0.96; descriptive P=0.028).
- The optimal HR of 0.56 was achieved at bTMB ≥20 mut/Mb by F1L CDx .

Peters, Nat Med 2022

The future is accurate neoantigen identification (HLA-matched) and specific T-cell response assessment

A very high threshold needed?



JAMA Oncology | Original Investigation

Association of High Tumor Mutation Burden in Non-Small Cell Lung Cancers With Increased Immune Infiltration and Improved Clinical Outcomes of PD-L1 Blockade Across PD-L1 Expression Levels

- Pooled analysis of the MSKCC, DFCI, and SU2C/Mark Foundation cohorts.
- Normalizing IMPACT, DFCI Oncopanel, and WES, with «high TMB» being TMB *z* score of greater than 1.16
- **Patients with NSCLC and a high harmonized TMB *z* score of 1.16 or higher (corresponding to ≥19.0 for MSKCC, ≥19.3 for DFCI cohort, and ≥16.0 mutations per Mb for the SU2C) had significantly better outcomes (RR, PFS & OS)**

Wolchok NEJM 2017; Garon NEJM 2015

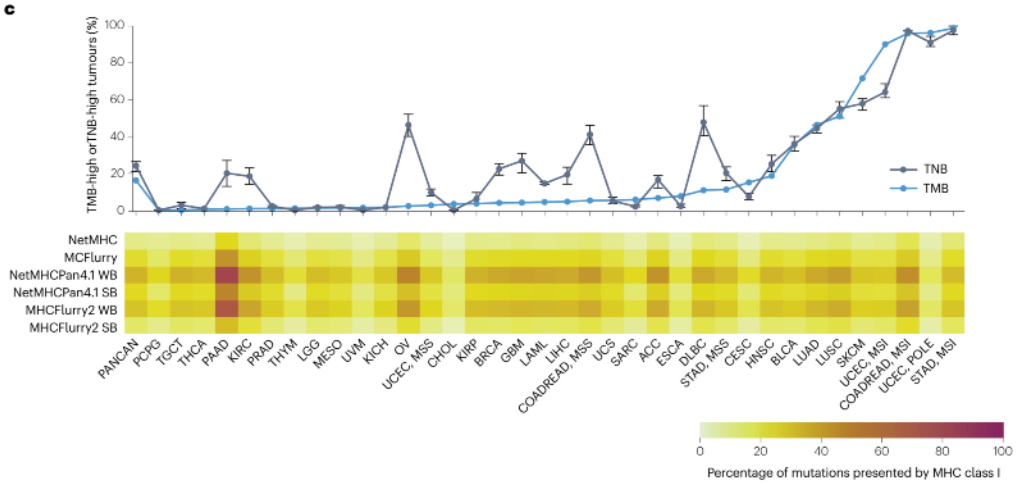
nature reviews clinical oncology
https://doi.org/10.1038/s41571-024-00932-9

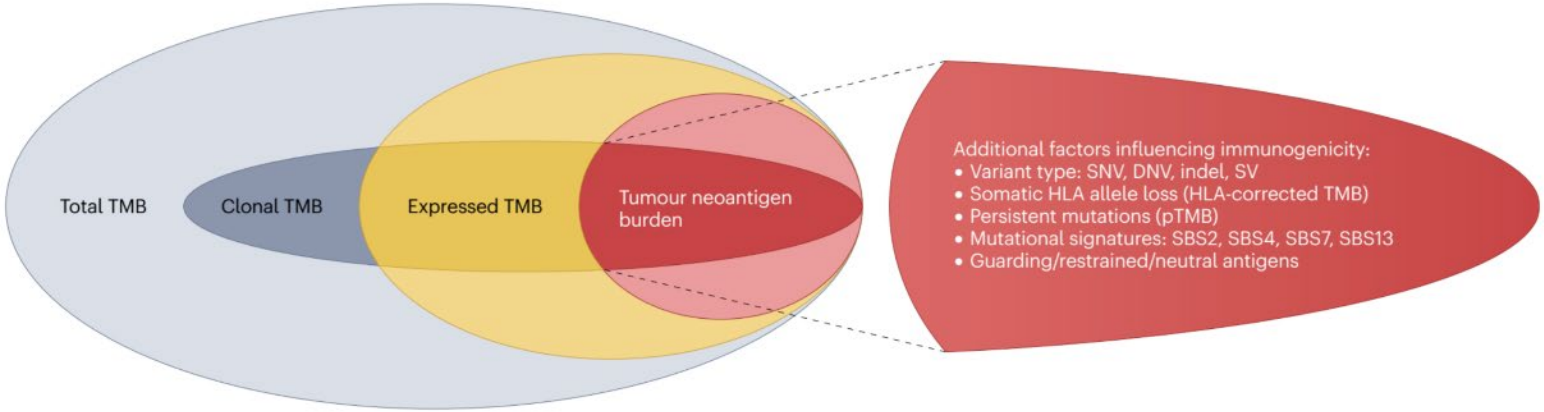
Review article

Check for updates

Tumour mutational burden: clinical utility, challenges and emerging improvements

Jan Budczies[1,2,210], Daniel Kazdal[1,2,3,10], Michael Menzel[1,3], Susanne Beck[1,3], Klaus Kluck[1,3], Christian Altbürger[1,3], Constantin Schwab[1,3], Michael Allgäuer[1,3], Aysel Ahadova[4,5], Matthias Kloor[4,5], Peter Schirmacher[1,3], Solange Peters[6], Alwin Krämer[7,8], Petros Christopoulos[7,9] & Albrecht Stenzinger[1,2,3]

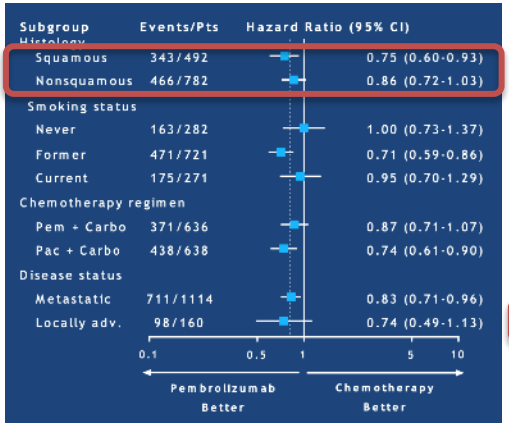




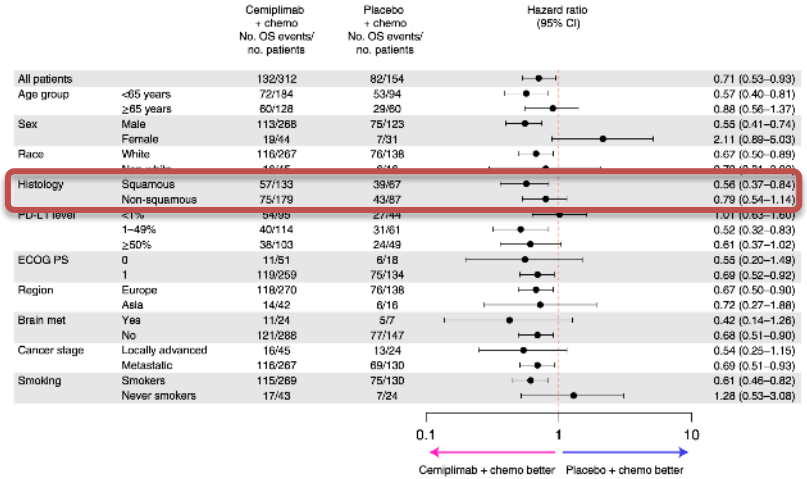
Histological subtype

WHICH BIOMARKERS ARE REQUIRED FOR TREATMENT DECISION-MAKING PRIOR TO INITIATING IO-BASED TREATMENT ?

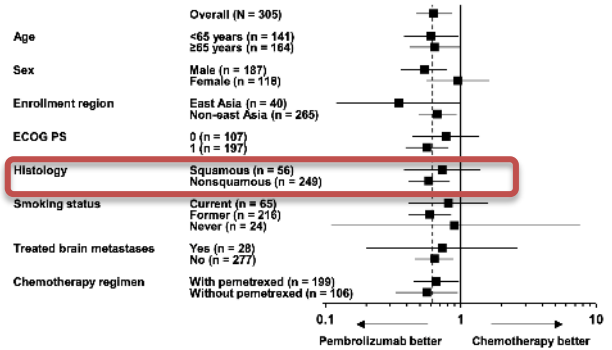
Histology and anti-PD1 activity



KEYNOTE-042 : PD-L1 pos

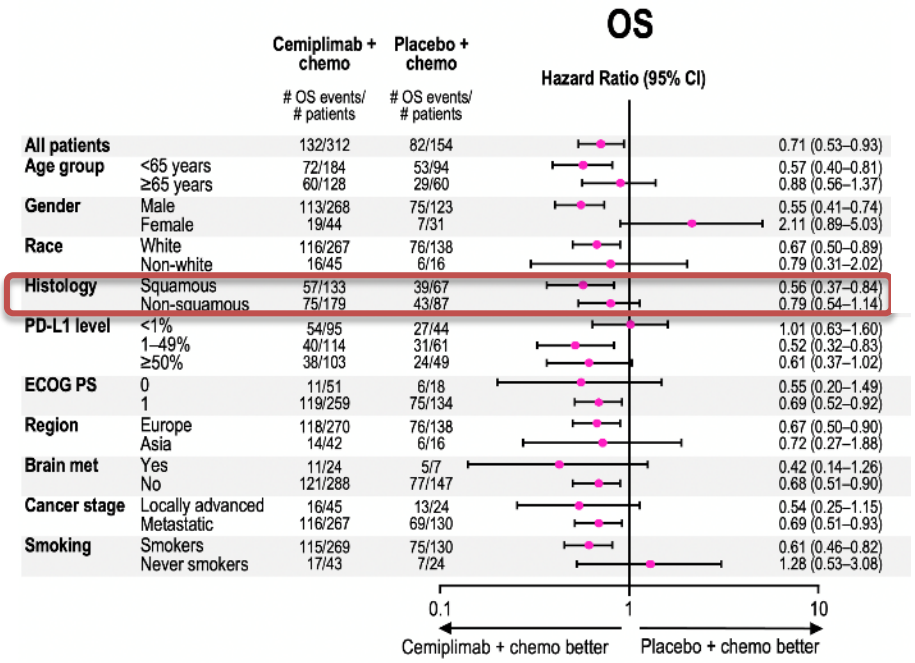


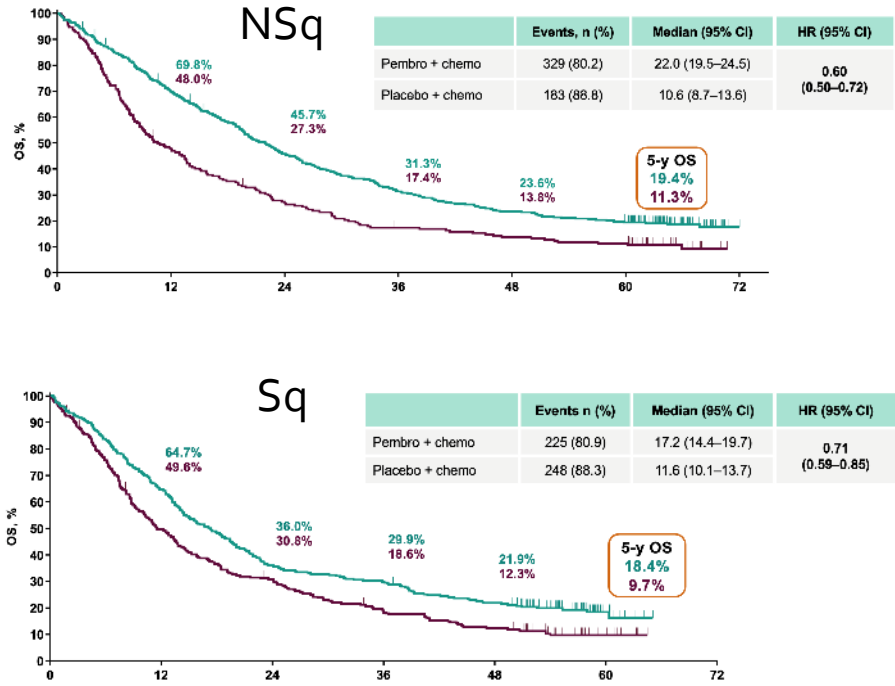
EMPOWER-Lung 1 : PD-L1 high



KEYNOTE024 : PD-L1 high

EMPOWER-Lung 3 and KEYNOTE 189/407

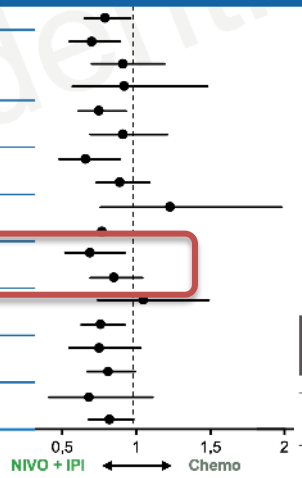




CheckMate 227 (PD-L1+) and 9LA

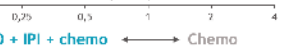
Subgroup	Median OS, months: NIVO + IPI n = 396	Chemo n = 397	Unstratified HR
Overall (n = 793)	17.1	14.9	0.79[a]
< 65 years (n = 406)	19.7	16.0	0.70
65 to <75 years (n = 306)	16.6	14.5	0.91
≥ 75 years (n = 81)	13.5	11.4	0.92
Male (n = 515)	18.7	14.0	0.75
Female (n = 278)	16.6	16.2	0.91
ECOG PS 0 (n = 269)	24.4	17.5	0.66
ECOG PS 1 (n = 519)	14.6	12.7	0.89
Never smoker (n = 107)	15.2	19.6	1.23
Smoker (n = 674)	18.1	14.1	0.77
Squamous (n = 236)	14.8	9.2	0.69
Non-squamous (n = 557)	19.4	17.2	0.85
Liver metastases (n = 156)	9.5	11.9	1.05
No liver metastases (n = 637)	19.9	16.3	0.76
Bone metastases (n = 208)	13.4	10.0	0.75
No bone metastases (n = 585)	18.8	16.7	0.81
CNS metastases (n = 81)	16.8	13.4	0.68
No CNS metastases (n = 712)	17.1	14.9	0.82

Unstratified HR (95% CI)



Subgroup	Median OS, mo: NIVO + IPI + chemo n = 361	Chemo n = 358	Unstratified HR
All randomized (N = 719)	15.8	11.0	0.73
< 65 years (n = 354)	15.9	10.7	0.64
≥ 65 to < 75 years (n = 295)	19.0	11.9	0.78
≥ 75 years (n = 70)	8.5	11.5	1.04
Male (n = 504)	14.2	9.8	0.72
Female (n = 215)	22.2	15.9	0.75
ECOG PS 0 (n = 225)	27.1	14.1	0.54
ECOG PS 1 (n = 492)	13.6	9.7	0.83
Never smoker (n = 98)	14.1	14.4	1.08
Smoker (n = 631)	16.7	10.4	0.68
SQ (n = 227)	14.5	9.1	0.63
NSQ (n = 492)	17.8	12.0	0.78
Liver metastases (n = 154)	10.2	8.1	0.89
No liver metastases (n = 565)	19.3	12.4	0.72
Bone metastases (n = 207)	11.9	8.3	0.73
No bone metastases (n = 512)	19.7	12.4	0.74
CNS metastases (n = 123)	19.9	7.9	0.47
No CNS metastases (n = 596)	15.6	11.8	0.79
PD-L1 < 1% (n = 264)	17.7	9.8	0.67
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.70
PD-L1 1-49% (n = 233)	15.2	10.4	0.70
PD-L1 ≥ 50% (n = 174)	18.9	12.9	0.67

Unstratified HR (95% CI)



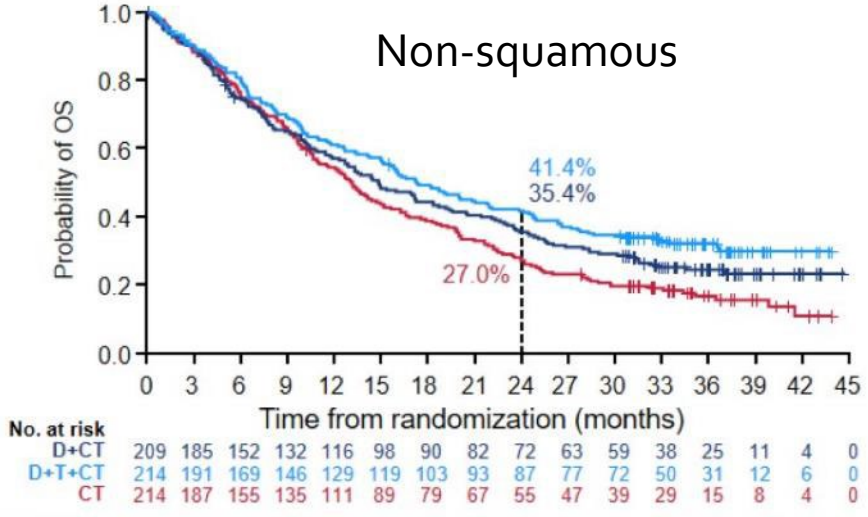
POSEIDON: the outlier?

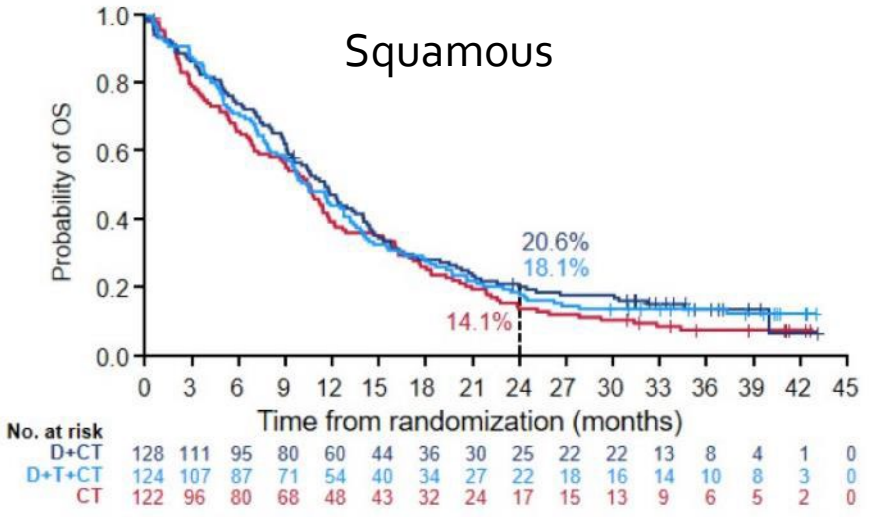
OS

	D+CT	D+T+CT	CT
Events, n/N (%)	154/209 (73.7)	145/214 (67.8)	173/214 (80.8)
mOS, months (95% CI)	**14.8** (11.8–18.3)	**17.2** (14.9–21.8)	**13.1** (10.6–15.1)
HR* (95% CI)	**0.82** (0.66–1.03)	**0.70** (0.56–0.87)	–

OS

	D+CT	D+T+CT	CT
Events, n/N (%)	109/128 (85.2)	106/124 (85.5)	111/122 (91.0)
mOS, months (95% CI)	**11.5** (9.4–14.0)	**10.4** (8.4–12.7)	**10.5** (8.0–11.7)
HR* (95% CI)	**0.84** (0.64–1.10)	**0.88** (0.68–1.16)	–



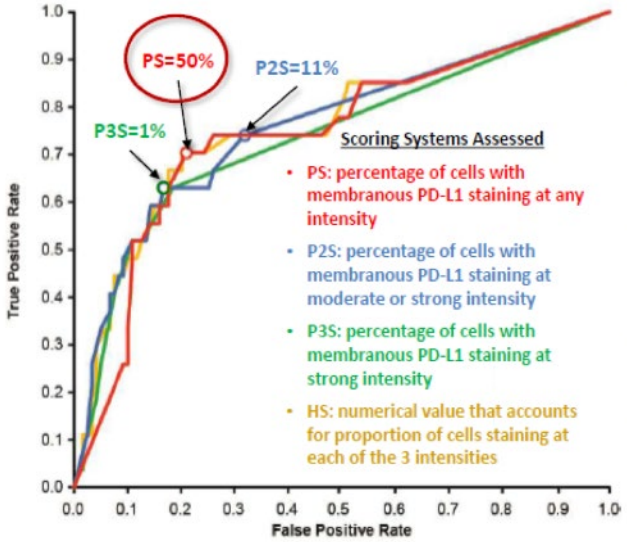


PD-L1

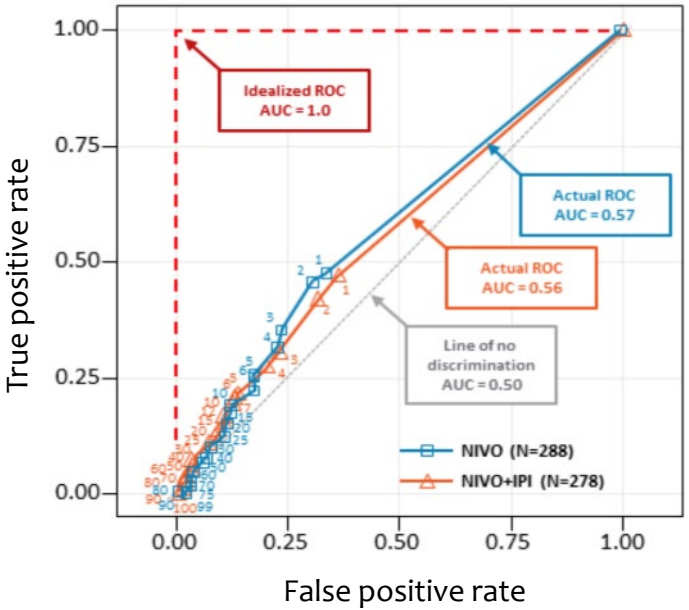
WHICH BIOMARKERS ARE REQUIRED FOR TREATMENT DECISION-MAKING PRIOR TO INITIATING IO-BASED TREATMENT ?

Performance of PD-L1 is variable across cancer types

NSCLC



Melanoma



- **A cut off value of 50% has been defined in NSCLC**
- The shoulder of the ROC curve is taken to be the point that achieves the best true positive and the best false positive rate

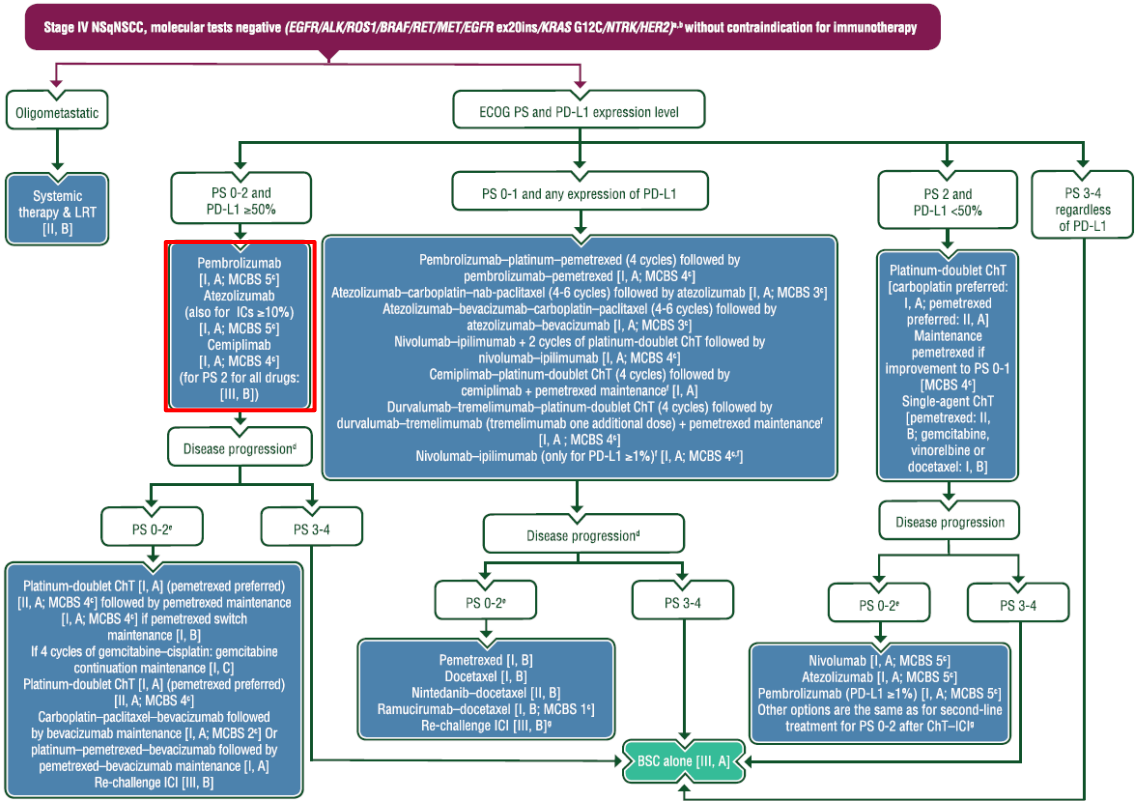
Wolchok NEJM 2017; Garon NEJM 2015

	Trial	N (IO/chemo) PD-L1≥50%	Inclusion	Primary endpoint	PD-L1 Ab	Cross-over*
Pembrolizumab[1]	KN-024	154/151	PD-L1 ≥ 50%, no EGFR, ALK	PFS (OS key 2◦)	22C3	66%
Pembrolizumab[1]	KN-042	299/300	PD-L1 ≥ 1%, no EGFR, ALK	OS PD-L1≥50%, PD-L1≥20%, PD-L1≥1%	22C3	NA
Cemiplimab[2]	EMPOWER-Lung 1	283/280[&]	PD-L1 ≥ 50% No never-smokers, EGFR, ALK, ROS1	OS, PFS	22C3	74%
Atezolizumab[3]	Impower 110	107/98	PD-L1 ≥ 50%, IC ≥ 10%, No EGFR, ALK	OS, PD-L1 ≥ 50%, PD-L1 ≥ 5%, PD-L1 ≥ 1%,	SP142	34.7% (NPT)
Nivolumab[4]	CheckMate 026	88/126	PD-L1 ≥ 1% No EGFR, ALK	PFS PD-L1 ≥ 5% (OS 2◦)	28-8	60.8%
Durvalumab[5]	MYSTIC	118/107	any PDL1 No EGFR, ALK	OS, PFS PD-L1 TC ≥25% (modified endpoint)	SP263	NA
Avelumab[6]	Javelin 100	281/345 (qw+q2w)	PD-L1 ≥ 1% No EGFR, ALK	OS, PFS PD-L1 ≥ 80% (comparable to ≥50% for 22C3) q2w, qw	73-10	31-35%

[1]Brahmer et al, ESMO 2020, Reck et al, JCO 2021;39:2339-2349. Cho et al, JTO 2021;16(3S):S225. [2]Sezer et al, Lancet 2021;397:592-604. Özgüroğlu et al, Annal of Onc 2022; 33:s7:S1421.[3]Jassem et al, JTO 2021;16:1872-82 (updated exploratory). Spigel et al, Annal Onc 2019;30(5):v915. Herbst et al, NEJM 2020; 383:1328-1339. [4]Carbone et al, NEJM 2017;376:2415-26. [5]Rivzi et al, JAMA Oncol. 2020;6(5):661-674. [6]Reck et al, WCLC 2022;OA15.03. *Chemo>IO in high PD-L1. & Partial retesting of PD-L1. NPT:non-protocol treatment.

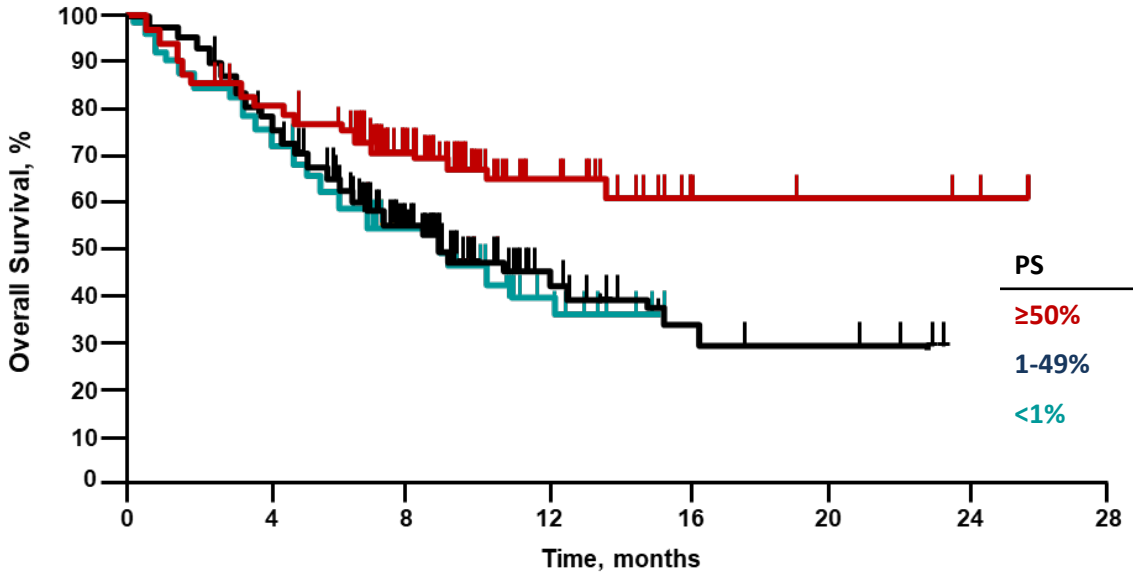
PD-L1 High

WHICH BIOMARKERS ARE REQUIRED FOR TREATMENT DECISION-MAKING PRIOR TO INITIATING IO-BASED TREATMENT ?



Hendriks LE, et al. 2023 Ann Oncol;34:358-76.

OS by PD-L1 Expression
Pembrolizumab KEYNOTE-001



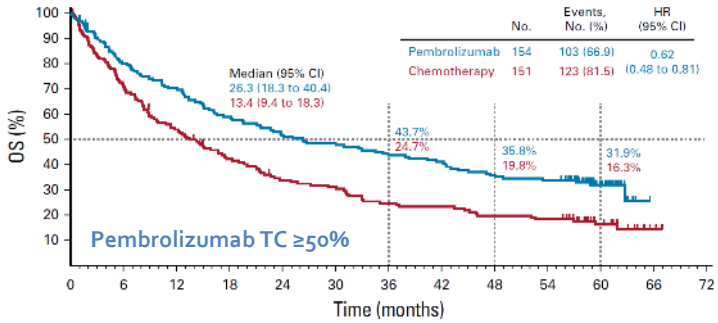
PS	Median (95% CI), mo
≥50%	NR (13.7-NR)
1-49%	8.8 (6.8-12.4)
<1%	8.8 (5.5-12.0)

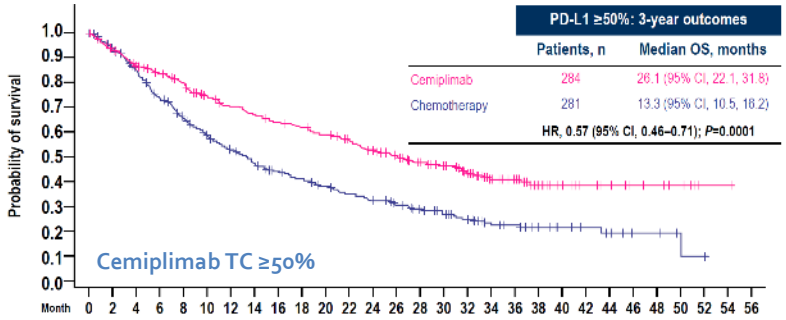
n at risk

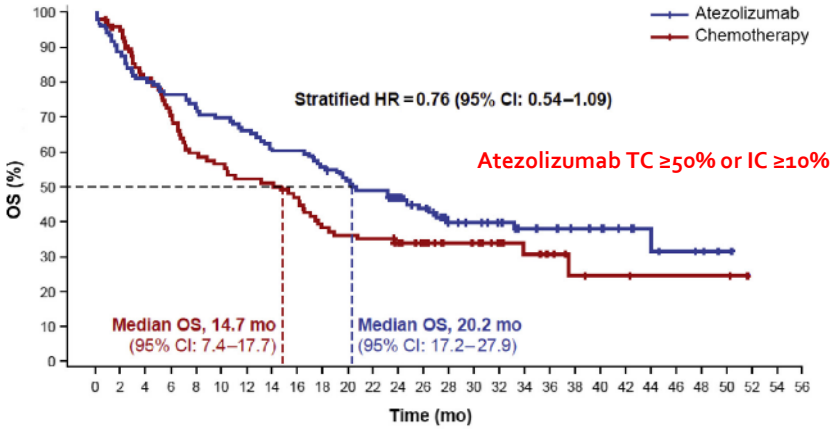
PS ≥50%	119	92	56	22	5	4	3	0
PS 1-49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

Garon EB et al. *N Engl J Med.* 2015;372(18):1700-1709.

The 50% TC cut-off is validated first line in NSCLC

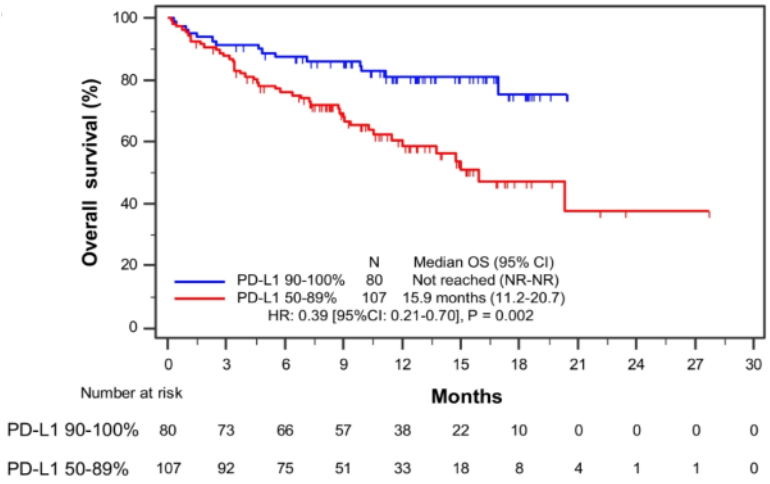


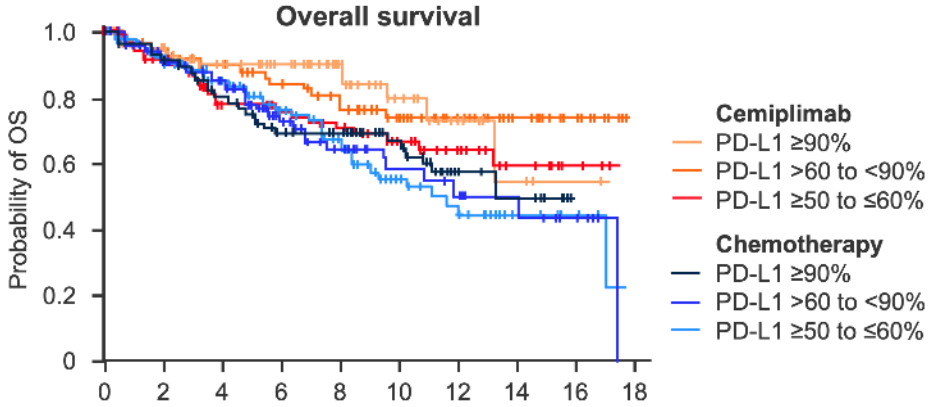


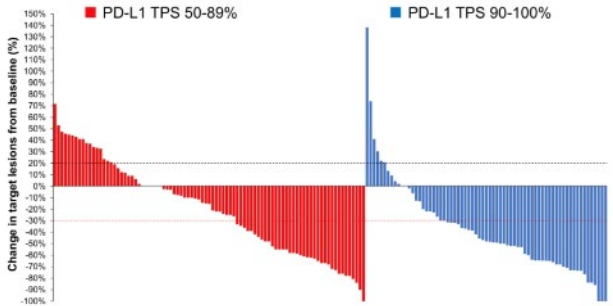


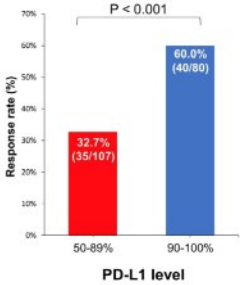
Reck, WCLC 2019; Brahmer, ESMO 2020; Aguilar, Ann Oncol 2019, Herbst, NEJM 2019

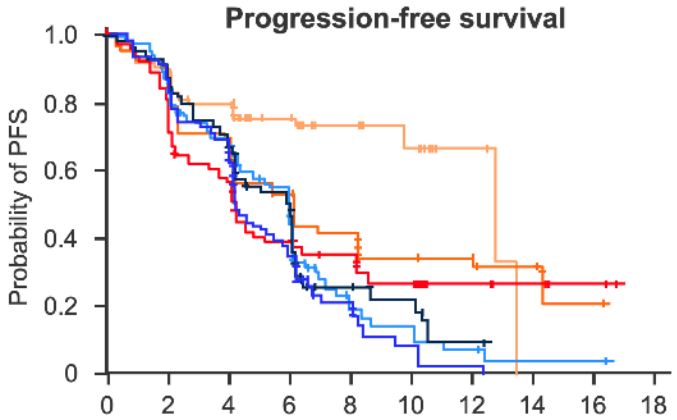
Clinical continuum: anti PD(L)-1 in very high PD-L1





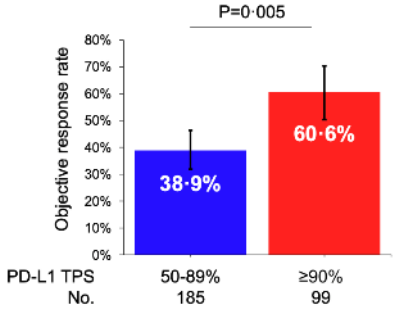


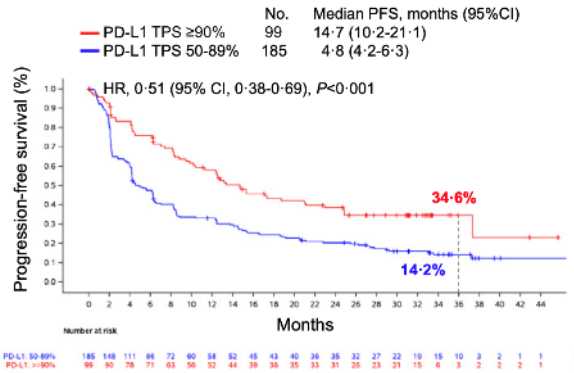


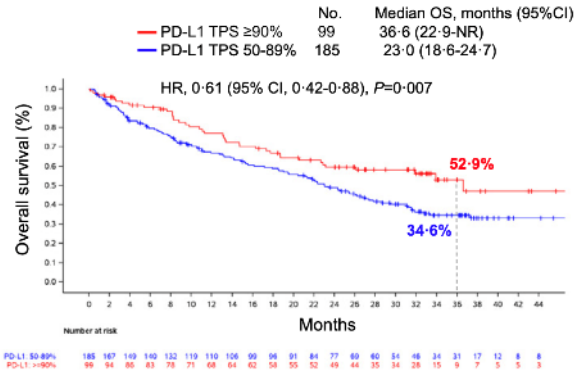


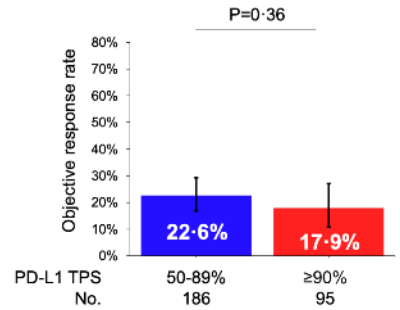
Aguilar, Ann Oncol 2019; Kilickap, WCLC 2020

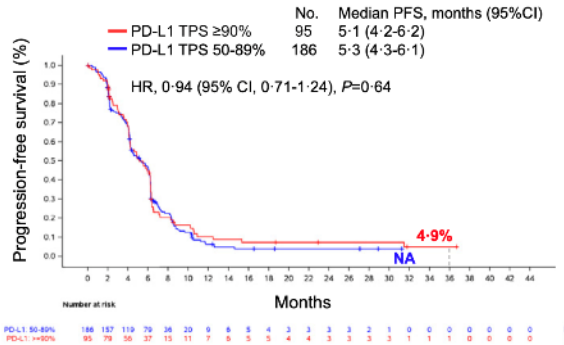
3 years FU for cemiplimab in EMPOWER-Lung 1

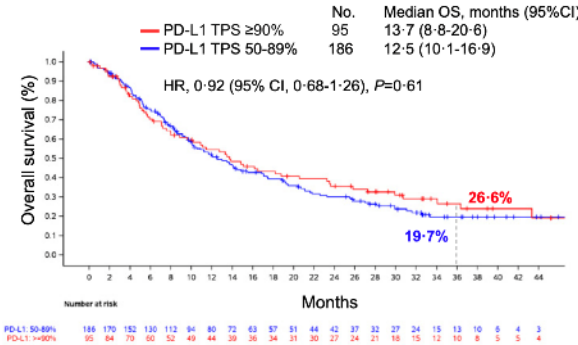












Ricciuti et al, JTO CRR 2024 in press

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

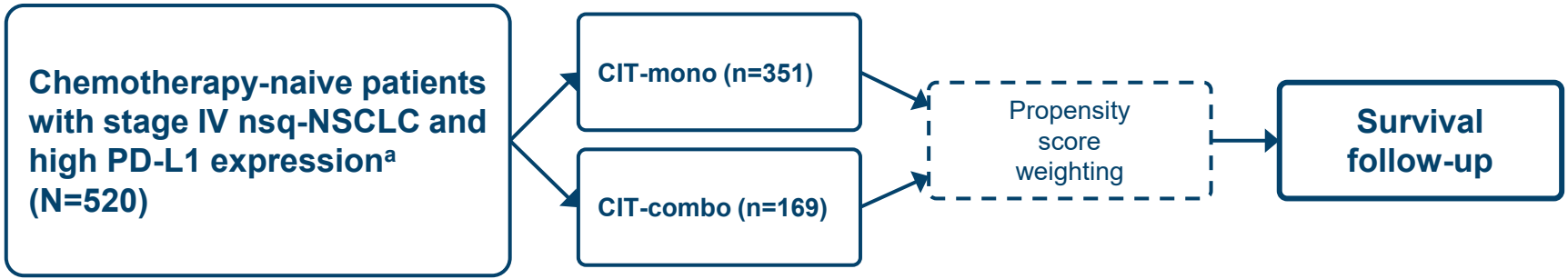
ANNALS OF ONCOLOGY

ORIGINAL ARTICLE

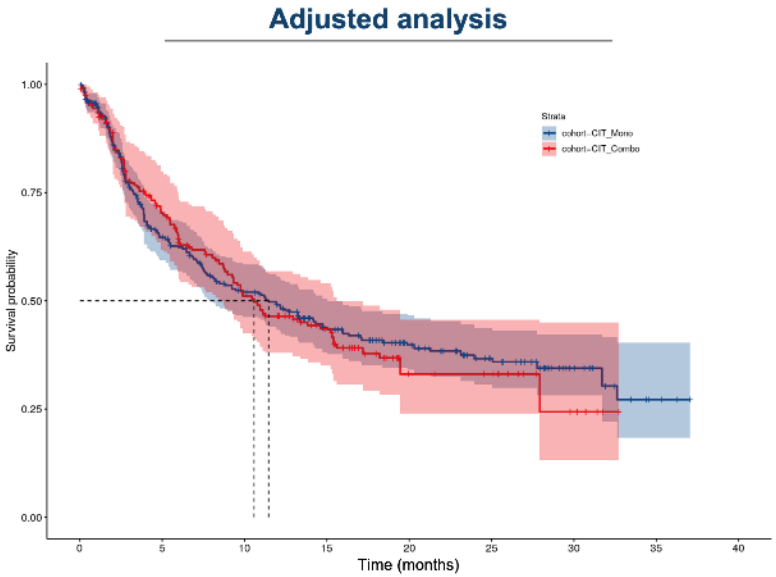
Effectiveness of PD-(L)1 inhibitors alone or in combination with platinum-doublet chemotherapy in first-line (1L) non-squamous non-small-cell lung cancer (Nsq-NSCLC) with PD-L1-high expression using real-world data

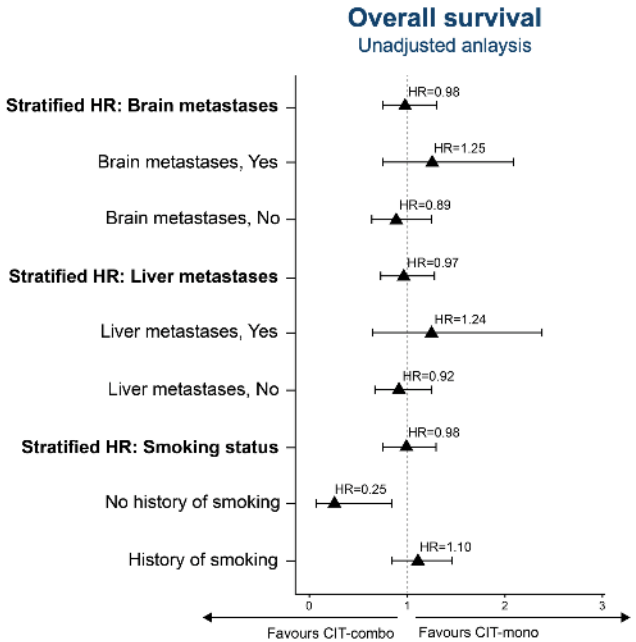
M. Pérol[1*], E. Felip[2†], U. Dafni[3,4], L. Polito[5], N. Pal[6], Z. Tsourti[4], T. G. N. Ton[6], D. Merritt[7], S. Morris[7], R. Stahel[8*‡] & S. Peters[9‡]

- Primary outcome was overall survival (OS) among treatment initiators
- Subgroup analyses were conducted to evaluate the influence of brain metastases, liver metastases and smoking history



Chemotherapy might not be needed in PD-L1 ≥50%





CIT-combo vs CIT-mono (reference)	Hazard ratio (95% CI)	*P* value
Unadjusted analysis	1.01 (0.78, 1.05)	0.957
Adjusted analysis	1.04 (0.78, 1.37)	0.811

Group	Patients	Events, n (%)	Median rwPFS (95% CI), mo
CIT-mono	351	170 (48)	11.5 (8.12, 15.01)
CIT-combo	169	87 (52)	10.8 (8.97, 15.31)

[a] Proportional hazards assumption is violated in the unadjusted model (Schoenfeld residual test).

The propensity score model included metastatic type, age, race, ECOG performance status score, brain metastases, smoking status, sex, liver metastases, time to 1L treatment start.

What does RWD tell us about real & adequate expectations? FDA analysis

2022 ASCO ANNUAL MEETING

FDA

Outcomes of anti-PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score ≥50%: FDA Pooled Analysis

Oladimeji Akinboro[1], Jonathon Vallejo[1], Erica Nakajima[1], Yi Ren[1], Pallavi Mishra-Kalyani[1], Erin Larkins[1], Paz Velasco[1], Nicole Diezner[1], Matthieu Lucksen[1], ShengHui Tang[1], Marthe Donoghue[1,2], Richard Pazdur[1,2], Julia A. Beaver[1,2], Harpreet Singh[1,2]

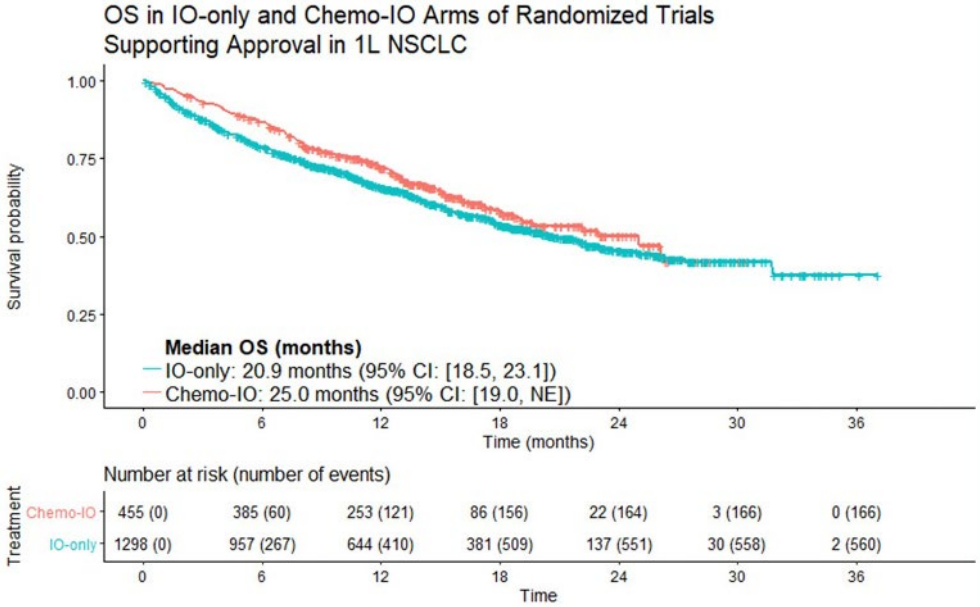
[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration

[2]Oncology Center of Excellence, U.S. Food and Drug Administration

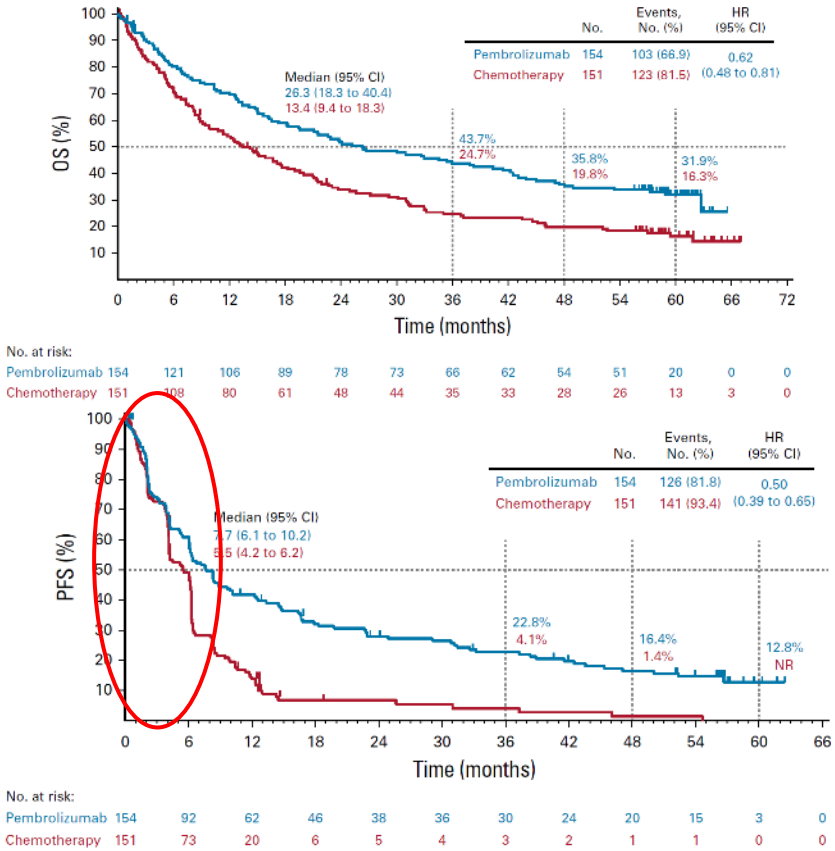
Oladimeji Akinboro, MD, MPH

	Chemo-IO (*N*=455)	IO-alone (*N*=1,298)
OS		
Median, months (95% CI)	25.0 (19.0, NE)	20.9 (18.5, 23.1)
HR (95% CI)	0.82 (0.62, 1.08)	
PFS		
Median, months (95% CI)	9.6 (8.4, 11.1)	7.1 (6.3, 8.3)
HR (95% CI)	0.69 (0.55, 0.87)	
ORR		
% (95% CI)	61 (56, 66)	43 (41, 46)
Odds ratio	1.2 (1.1, 1.3)	

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR=hazards ratio; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.



KEYNOTE-024 : A word of caution?

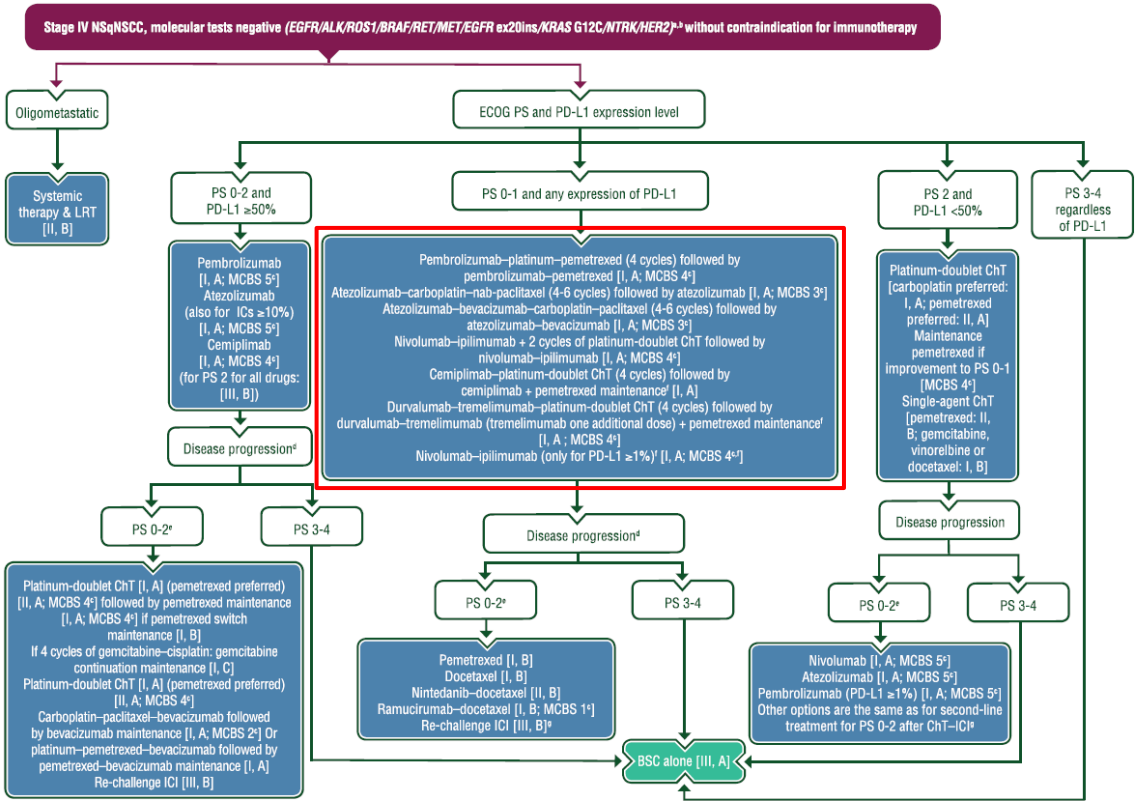


- 1/3 of patients experience **progressive disease at first assessment**
- A surprisingly **small proportion of patients receive second-line therapy**
  - RWD **25%**
  - KEYNOTE-024: **53%**
  - KEYNOTE-042: **46%**
  - EMPOWER-Lung 1: **32%**

Reck M, et al. J Clin Oncol 2021;39:2339-49

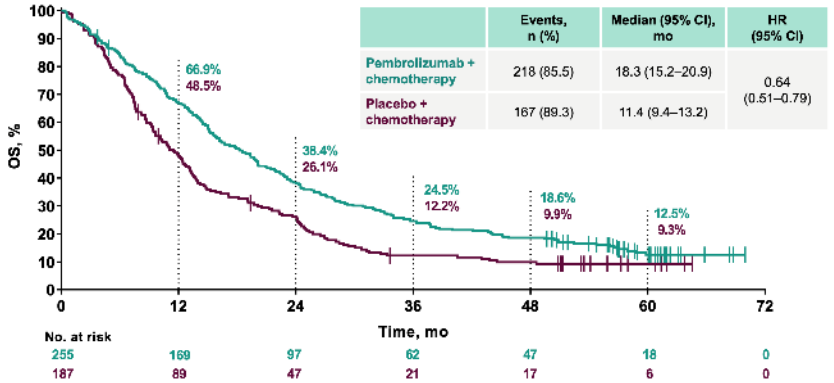
PD-L1 negative

WHICH BIOMARKERS ARE REQUIRED FOR TREATMENT DECISION-MAKING PRIOR TO INITIATING IO-BASED TREATMENT ?

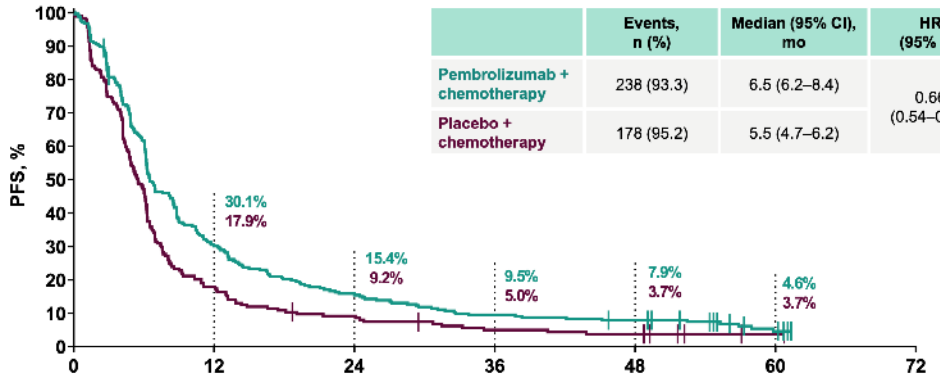


Hendriks LE, et al. 2023 Ann Oncol;34:358-76.

Pooled pembro/chemo data in PD-L1 negative NSCLC



	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembrolizumab + chemotherapy	218 (85.5)	18.3 (15.2–20.9)	0.64 (0.51–0.79)
Placebo + chemotherapy	167 (89.3)	11.4 (9.4–13.2)	



	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembrolizumab + chemotherapy	238 (93.3)	6.5 (6.2–8.4)	0.66 (0.54–0.81)
Placebo + chemotherapy	178 (95.2)	5.5 (4.7–6.2)	

KN189 Global, March 8, 2022; KN189 Japan Extension, February 7, 2023; KN407 Global, February 23, 2022; KN407 China Extension, February 10, 2023.
Gadgeel, WCLC 2023

Cancer Therapy: Clinical

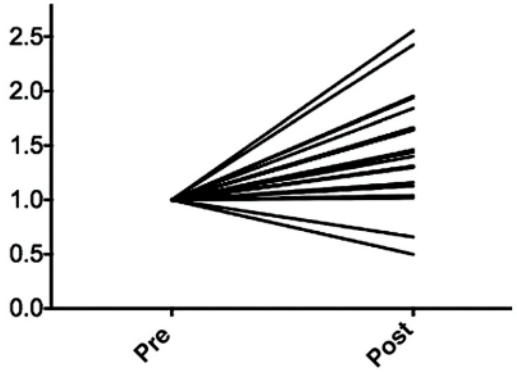
Clinical Cancer Research

CTLA4 Blockade Broadens the Peripheral T-Cell Receptor Repertoire

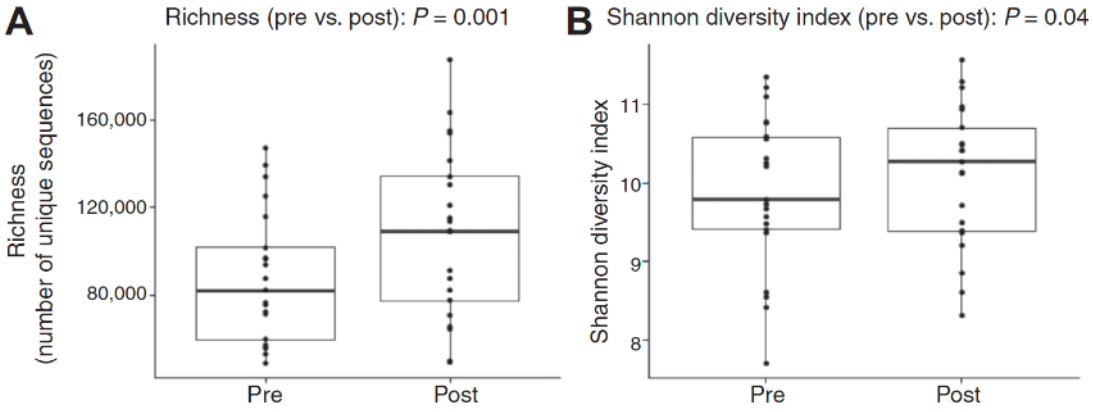
Lidia Robert[1], Jennifer Tsoi[2], Xiaoyan Wang[1,3], Ryan Emerson[7,8], Blanca Homet[1,9], Thinle Chodon[1], Stephen Mok[1,2], Rong Rong Huang[4], Alistair J. Cochran[4], Begoña Comin-Anduix[5,6], Richard C. Koya[5,6], Thomas G. Graeber[2,6], Harlan Robins[7,8], and Antoni Ribas[1,2,5,6]

Science Translational Medicine AAAS

Anti–CTLA-4 therapy broadens the melanoma-reactive CD8+ T cell response
Pia Kvistborg *et al.*
Sci Transl Med **6**, 254ra128 (2014);
DOI: 10.1126/scitranslmed.3008918

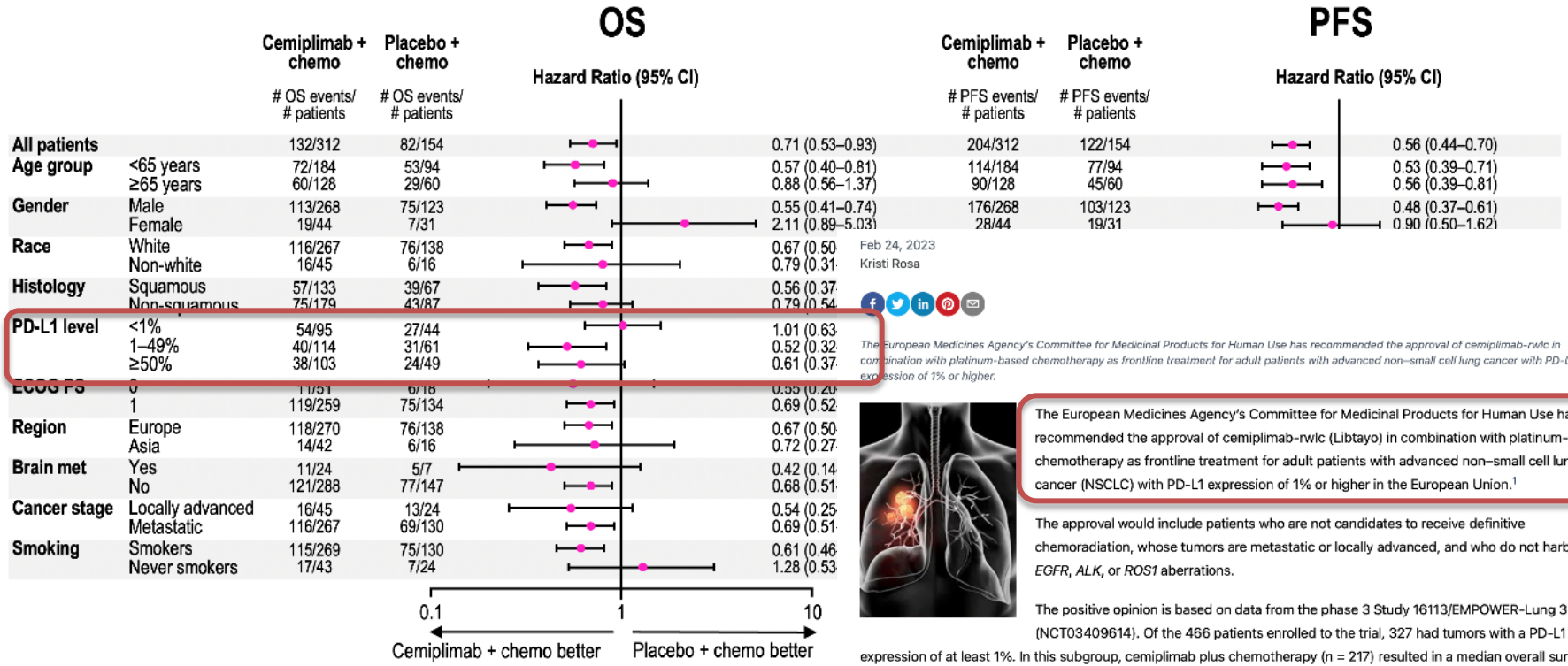


Normalized TCR V-beta CDR3 repertoire diversity.
Analysis comparing baseline and post-tremelimumab PBMC samples,



Richness and Shannon index for diversity. Differences in richness for total number of unique productive sequences (P . 0.001;A) and Shannon index for diversity of the repertoire (P . 0.04; B).

EMPOWER-Lung 3 : what bout negative PD-L1



Feb 24, 2023
Kristi Rosa

The European Medicines Agency's Committee for Medicinal Products for Human Use has recommended the approval of cemiplimab-rwlc in combination with platinum-based chemotherapy as frontline treatment for adult patients with advanced non–small cell lung cancer with PD-L1 expression of 1% or higher.

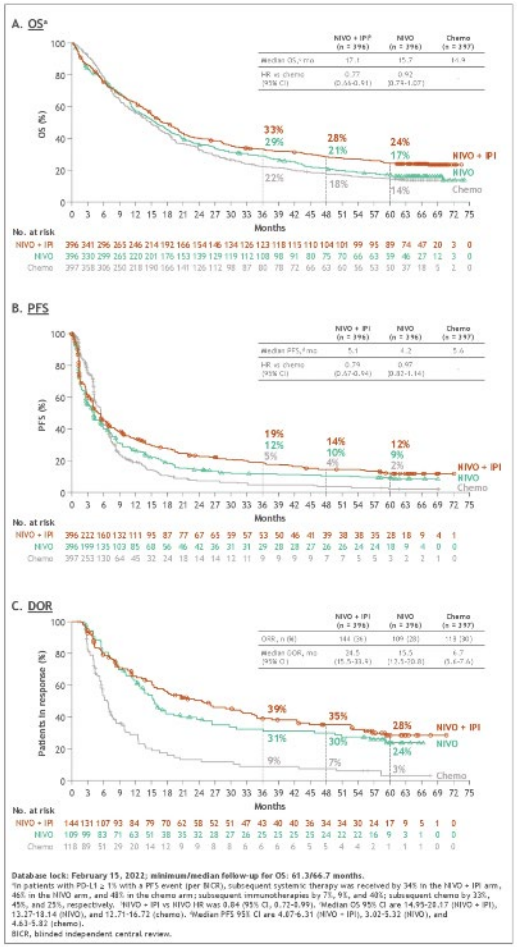
The European Medicines Agency's Committee for Medicinal Products for Human Use has recommended the approval of cemiplimab-rwlc (Libtayo) in combination with platinum-based chemotherapy as frontline treatment for adult patients with advanced non–small cell lung cancer (NSCLC) with PD-L1 expression of 1% or higher in the European Union.[1]

The approval would include patients who are not candidates to receive definitive chemoradiation, whose tumors are metastatic or locally advanced, and who do not harbor *EGFR*, *ALK*, or *ROS1* aberrations.

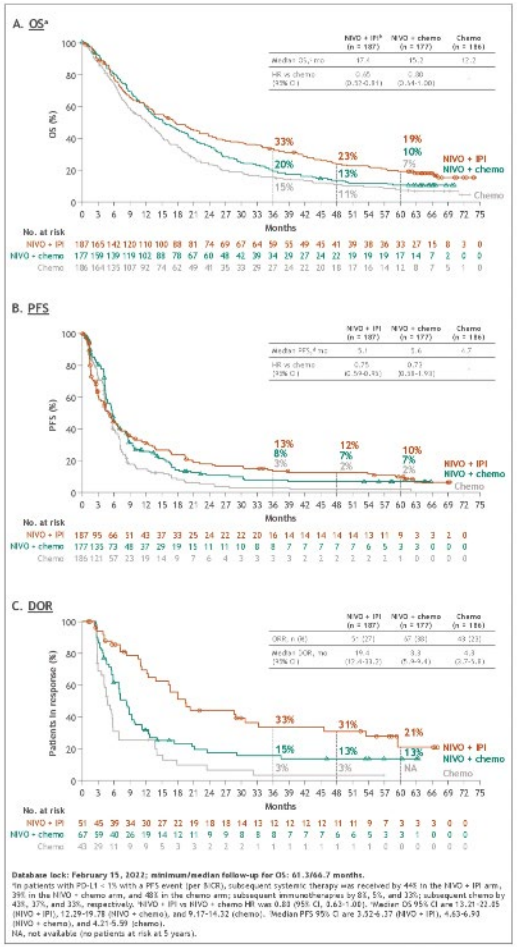
The positive opinion is based on data from the phase 3 Study 16113/EMPOWER-Lung 3 trial (NCT03409614). Of the 466 patients enrolled to the trial, 327 had tumors with a PD-L1 expression of at least 1%. In this subgroup, cemiplimab plus chemotherapy (n = 217) resulted in a median overall survival (OS) of 22 months vs 13 months with chemotherapy alone (n = 110) at a median follow-up of 16 months; this translated to a 45% relative reduction in the risk of death (HR, 0.55; 95% CI, 0.39-0.78). With a longer median follow-up of 28 months, cemiplimab/chemotherapy continued to showcase a meaningful survival benefit in this group (HR, 0.51; 95% CI, 0.38-0.69).

CheckMate 227: adding a CTLA-4 is active in negative PD-L1

Positive PD-L1 cohort

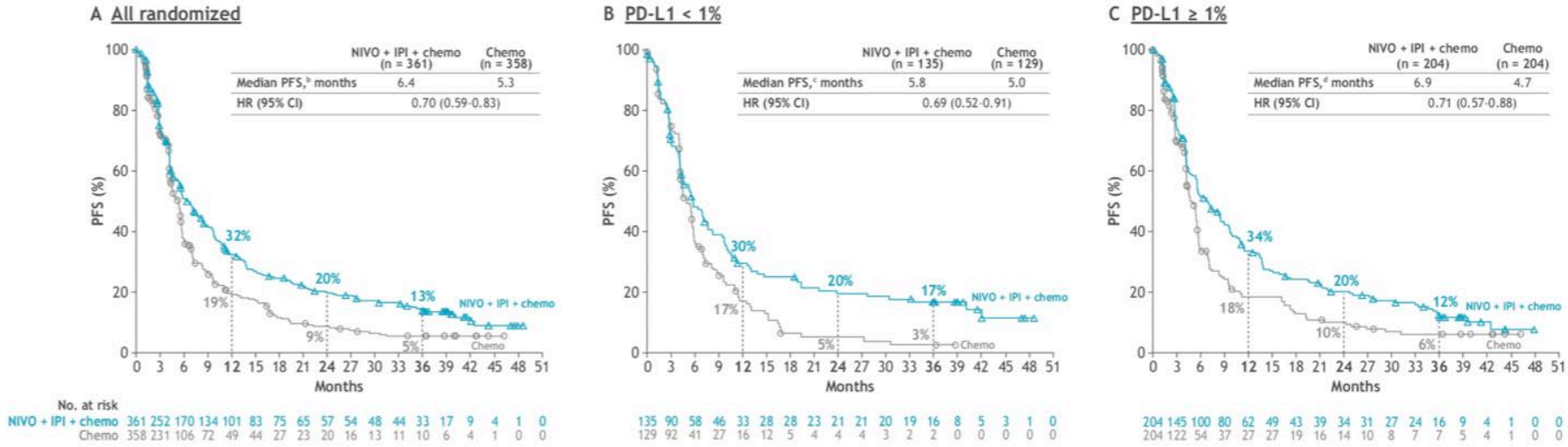


Negative PD-L1 cohort

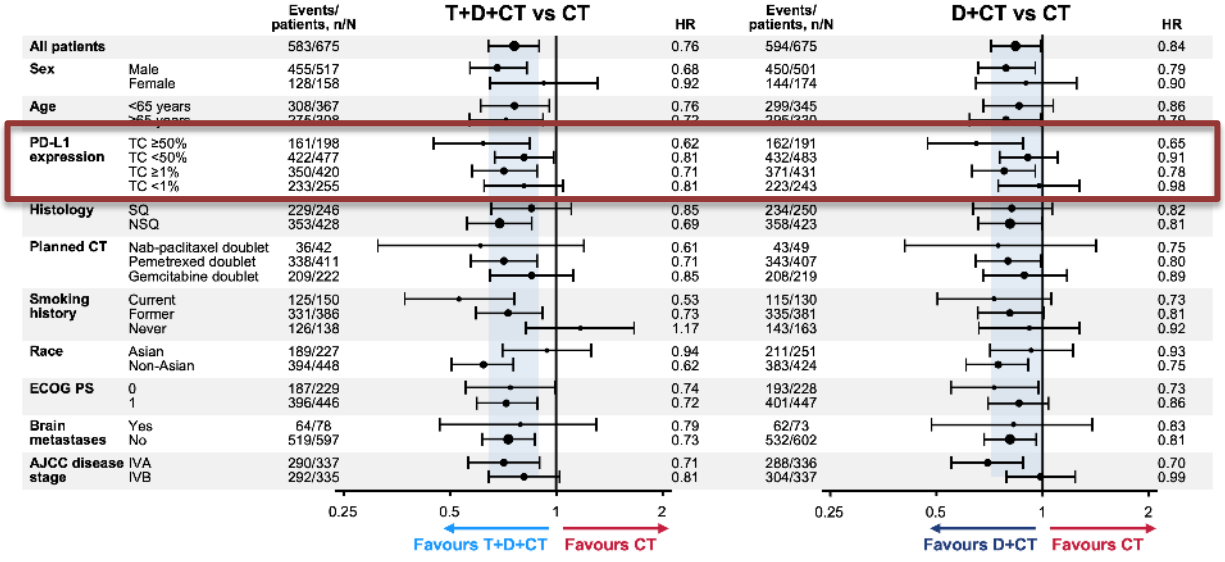


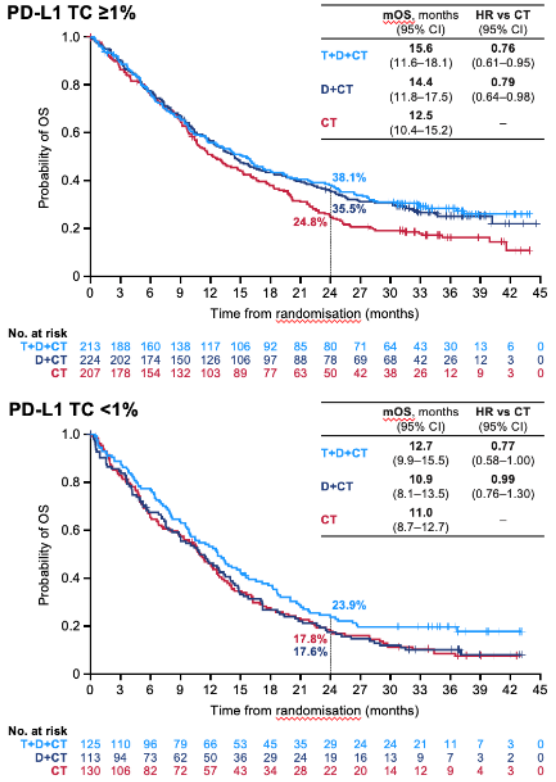
Brahmer ASCO 22

Adding a CTLA-4 to chemo/nivo: CheckMate 9LA



Adding a CTLA-4 improves OS in negative PD-L1 in POSEIDON



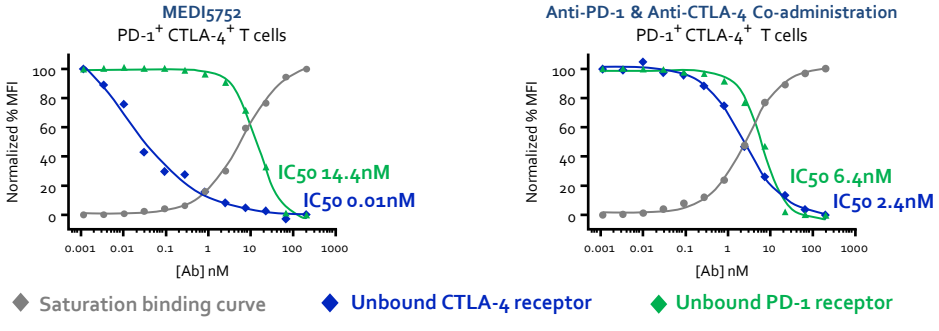


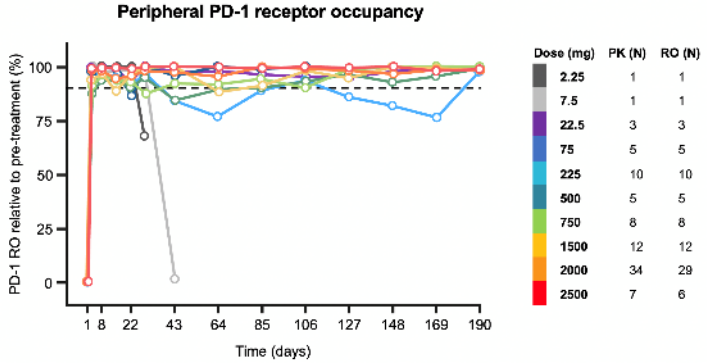
HRs calculated using an unstratified Cox proportional hazards model; DCO 12 Mar 2021.

Johnson, WCLC 2021; Garon WCLC 2022; Peters ESMO IO 2023

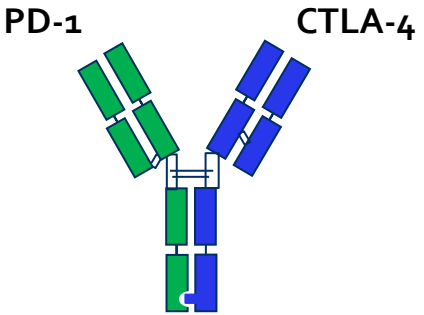
MEDI5752 enhances CTLA-4 blockade on PD-1+ T cells

On activated T cells, MEDI5752 achieves comparable PD-1 binding and significantly greater CTLA-4 binding *vs.* co-administration





A monovalent bispecific antibody



Affinity to human CTLA-4: 0.42 nM

Affinity to human PD-1: 0.81 nM

Fc isotype: human IgG1-TM (reduced ADCC)

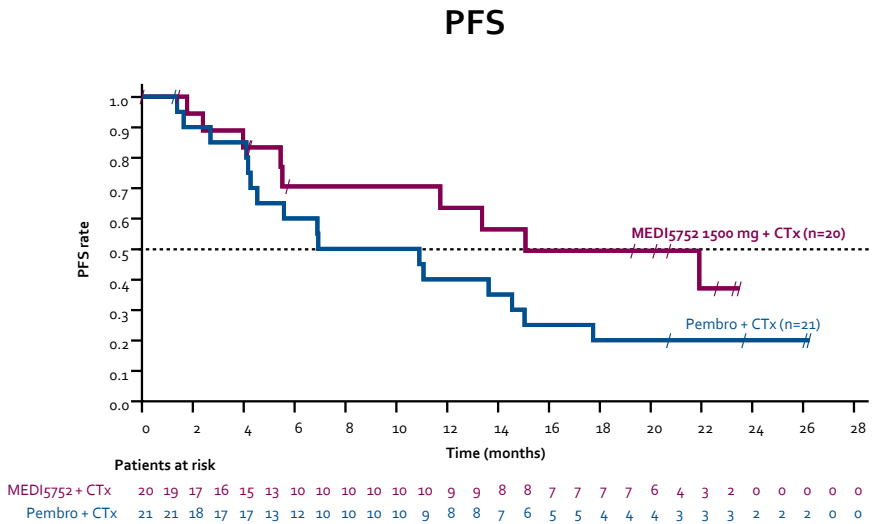
CTLA-4 arm = Tremelimumab arm

CHO cell receptor occupancy assay assessed by flow cytometry; Reprinted with permission from Dovedi S, et al Cancer Discov. 2021

ADCC, antibody-dependent cellular cytotoxicity, CTLA-4, cytotoxic T-lymphocyte associated protein-4; PD-1, programmed death-1

Bispecific MEDI5752 1500 mg + CTx better han pembrolizumab + CTx in first-line non-squamous NSCLC

1L Non-squamous NSCLC	Randomised cohort (N=41)	
	MEDI5752 1500 mg + CTx (n=20)	Pembrolizumab + CTx (n=21)
Median follow-up, months (range)	22.8 (0.8–26.9)	14.5 (1.6–27.9)
ORR, n (%)	10 (50.0)	10 (47.6)
Disease control rate, n (%)	17 (85.0)	20 (95.2)
Median DOR, months (95% CI)	20.5 (4.1–NE)	9.9 (2.8–NE)
Median PFS, months	15.1	8.9
Median OS, months	NR	16.5
ORR, PD-L1 <1%, n/N (%) (95% CI)	5/9 (55.6) (21.2–86.3)	3/10 (30.0) (6.7–65.2)
Median PFS, PD-L1 <1%, months	13.4	9



CTx, chemotherapy; CR, complete response; DOR, duration of response; ITT, intent-to-treat; PFS, median progression-free survival; NR, not reached; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PR, partial response; uPR, unconfirmed partial response

Data cut-off 12 July 2022.

Where Does Anti-CTLA-4 Fit?

PD-L1 <1%

		PFS			OS		
		Median PFS (months)	3-y PFS	5-y PFS	Median OS (months)	3-y OS	5-y OS
Non-squamous	CheckMate 227[1,2]	-	-	-	17.5	**35%**	**17.5%**
	CheckMate 9LA[3,4]	6.4	**16%**	-	18.6	25%	-
	KEYNOTE-189[5]	6.2	**4.8%**	2.4%	17.2	23.3%	**9.6%**
Squamous	CheckMate 227[1,2]	-	-	-	16.3	**34%**	**16.3%**
	CheckMate 9LA[3,4]	5.3	**19%**	-	15.3	25%	-
	KEYNOTE-407[6]	6.3	**11.6%**	7.1%	15.0	22.1%	**10.7%**

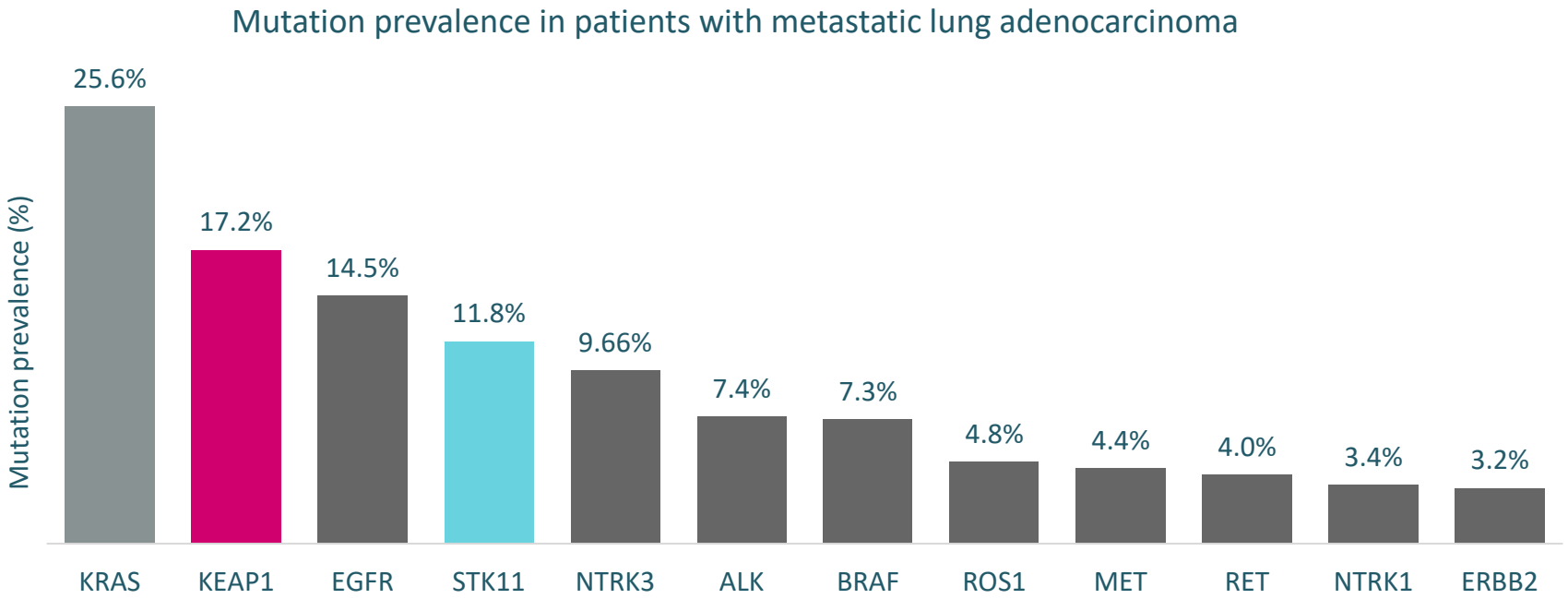
Not intended to be a cross-trial comparison.

1. Brahmer JR, et al. *J Clin Oncol.* 2022;41(6):1200-1212. 2. Paz-Ares LG, et al. *J Thorac Oncol.* 2022;17(2):289-308. 3. Paz-Ares LG, et al. Presented at: ASCO 2022. Abstract LBA 9026. 4. Carbone DP, et al. *J Immunother Cancer.* 2024;12(2):e008189. 5. Garassino MC, et al. Presented at: ESMO 2022. Abstract 973MO. 6. Novello S, et al. *J Clin Oncol.* 2023;41(11):1999-2006.

STK11/KEAP-1

WHICH BIOMARKERS ARE REQUIRED FOR TREATMENT DECISION-MAKING PRIOR TO INITIATING IO-BASED TREATMENT ?

STK11 and *KEAP1* mutations occur frequently in NSCLC



National Cancer Institute. TCGA-LUAD for adenocarcinomas and TCGA-LUSC for squamous cell. Available at: https://portal.gdc.cancer.gov/. Accessed April 2024.

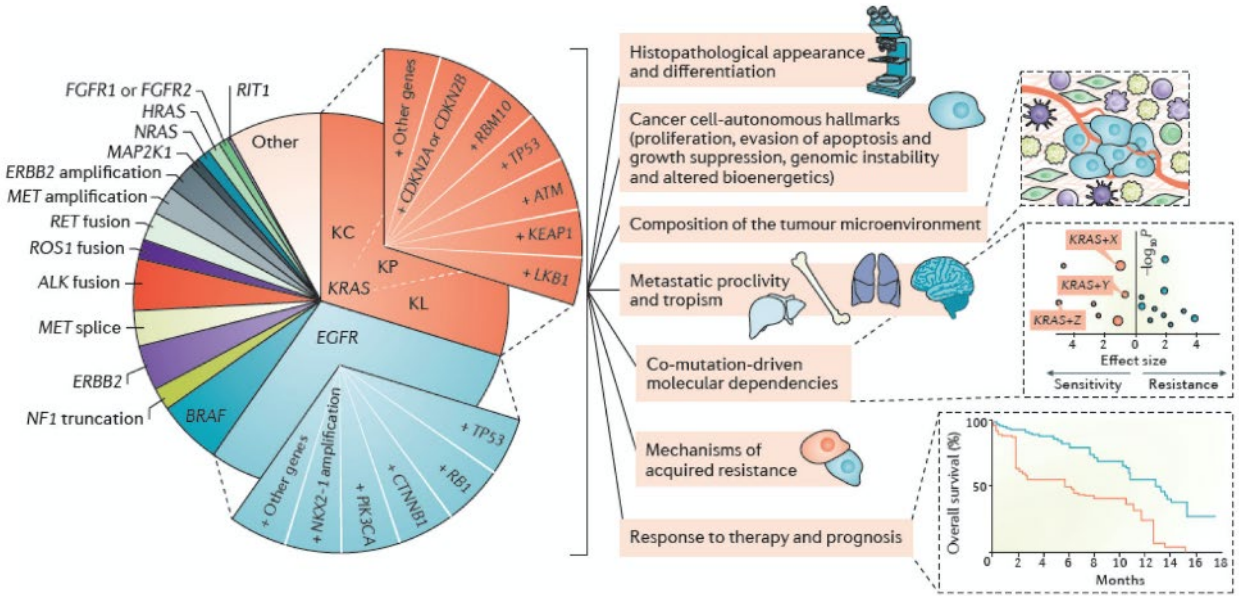
STK11 and *KEAP1* mutations can be detected by NGS, but only if it is a broad panel that includes those genes

	Assay name	Company	*STK11*	*KRAS*	*KEAP1*	Sample type
Decentralised (in-house) assays	TruSight Oncology 500[1]	Illumina	+	+	+	FFPE
	TruSight Oncology 500 High-Throughput[1]	Illumina	+	+	+	FFPE
	TruSight Oncology 500 ctDNA assay v2[2]	Illumina	+	+	+	ctDNA
	TruSight Tumor 170[3]	Illumina	+	+	-	FFPE
	Illumina AmpliSeq Focus[4]	Illumina	-	+	-	FFPE
	Illumina Comprehensive Panel[5]	Illumina	+	+	-	FFPE
	Oncomine™ Focus Assay[6]	Thermo Fisher	-	+	-	FFPE
	Oncomine™ Comprehensive Assay[7]	Thermo Fisher	+	+	-	FFPE
	Oncomine™ Precision Assay[8]	Thermo Fisher	-	+	-	FFPE
	Oncomine™ Dx Target Test[9]	Thermo Fisher	-	+	-	FFPE
	Archer® VariantPlex® Comprehensive Thyroid and Lung (CTL)[10]	Diagnostic Longwood	+	+	-	FFPE
	AmoyDx® HANDLE Classic NGS Panel[11]	Amoy Diagnostics	+	+	+	FFPE
Centralised (outsourced)	Guardant360® CDx[12]	Guardant Health	+	+	-	ctDNA
	FoundationOne® CDx[13]	Foundation Medicine	+	+	+	FFPE
	FoundationOne® Liquid CDx[14]	Foundation Medicine	+	+	+	ctDNA

There are few commercially available NGS platforms that cover biomarkers for immunosuppressive status

Limitations in focusing on a single mutation

- Co-mutations constitute major determinants of tumor molecular diversity and can impact cancer hallmarks; determine prognosis; predict response to systemic therapies and influence mechanisms of innate and acquired resistance
- Co-occurring alterations can function as robust, and in many settings more precise, biomarkers of therapeutic response than single-gene predictors.

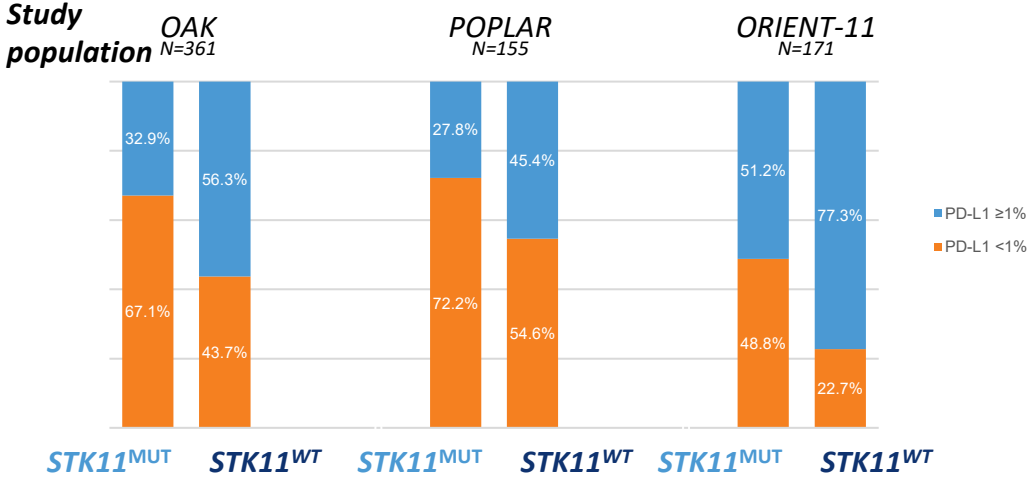


Skoulidis, Nat Rev Can 2019

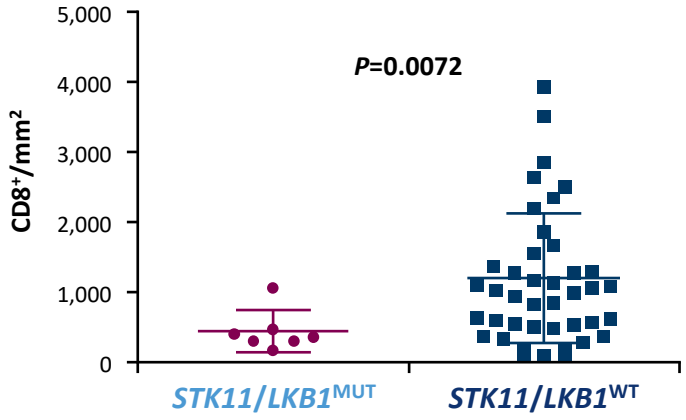
STK11 mutations are characterised as having 'cold' tumour microenvironments

- When compared with wild-type tumours, *STK11* mutations are associated with a lack of PD-L1 expression and decreased infiltration of CD8 T cells[1,2]

PD-L1 expression[1]



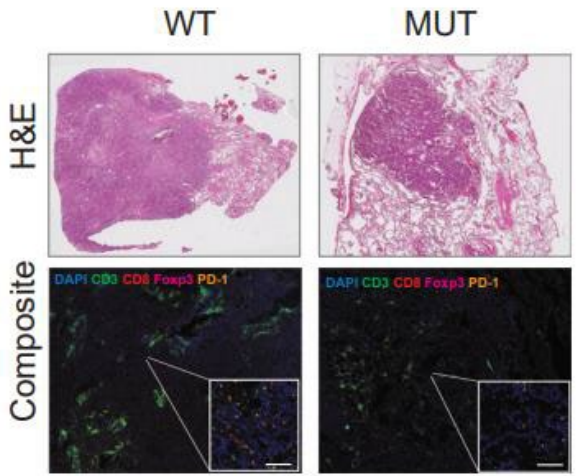
T-cell infiltration[2]

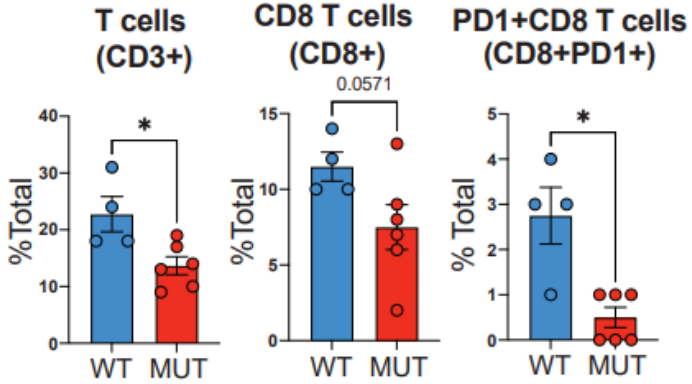


1. Adapted from: Li A, et al. *J Thorac Oncol.* 2023;18(12):1714-1730 [supplementary data]; 2. Skoulidis F, et al. *J Clin Oncol.* 2019;37(Suppl 15):Abstract 102 (Presented at ASCO 2019).

KEAP1 mutations are also associated with diminished PD-L1 expression and reduced T-cell infiltration

- *KEAP1*-mutated tumours have decreased infiltration of total CD3 T cells, CD8 T cells and PD1-expressing CD8 T cells compared with wild-type tumours





*P<0.05. Based on a preclinical murine model

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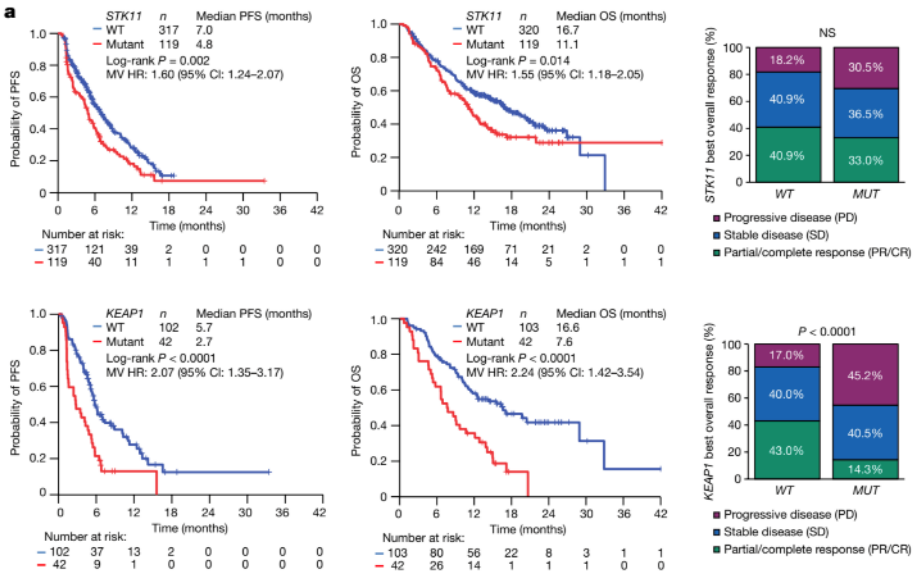
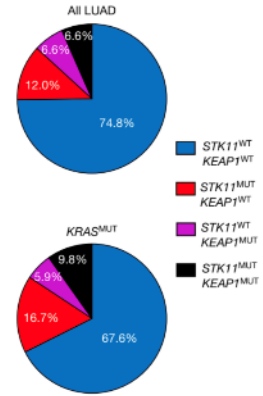
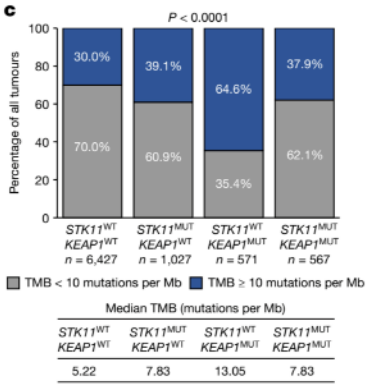
Zavitsanou AM, et al. *Cell Rep*. 2023;42:113295.

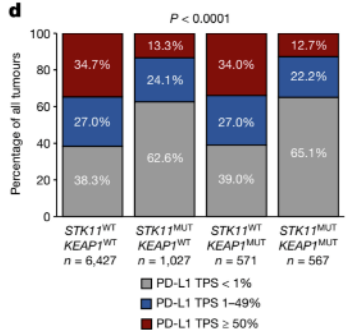
Article

CTLA4 blockade abrogates *KEAP1*/*STK11*-related resistance to PD-(L)1 inhibitors



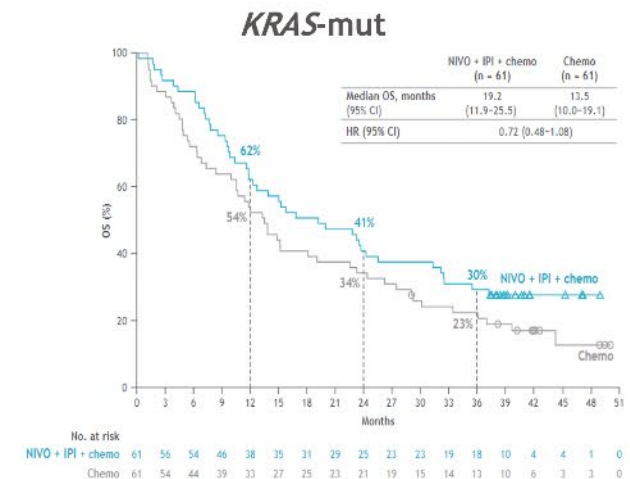


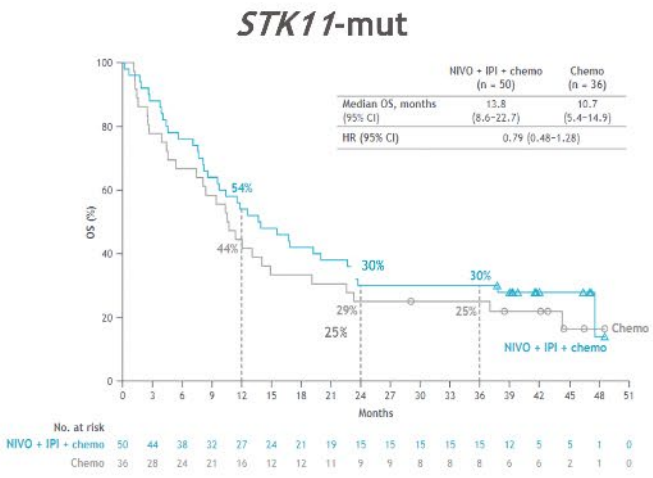


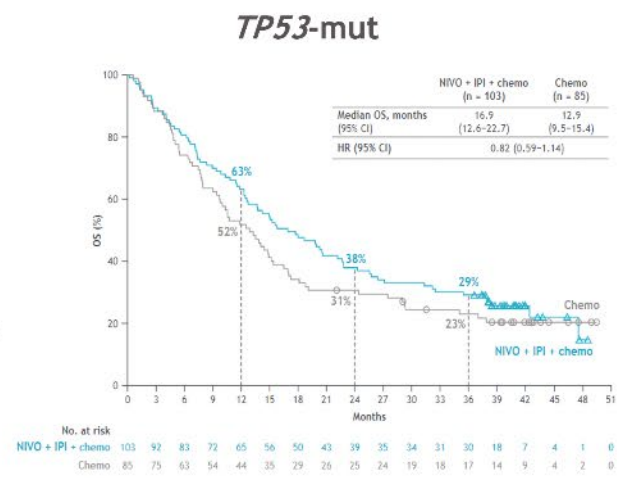


Addition of a CTLA-4 might improve outcomes in immunotherapy resistant biomarker-defined subgroups

CheckMate 9LA: Exploratory analysis of OS by mutational status: *KRAS*m, *TP53*m and *STK11*m



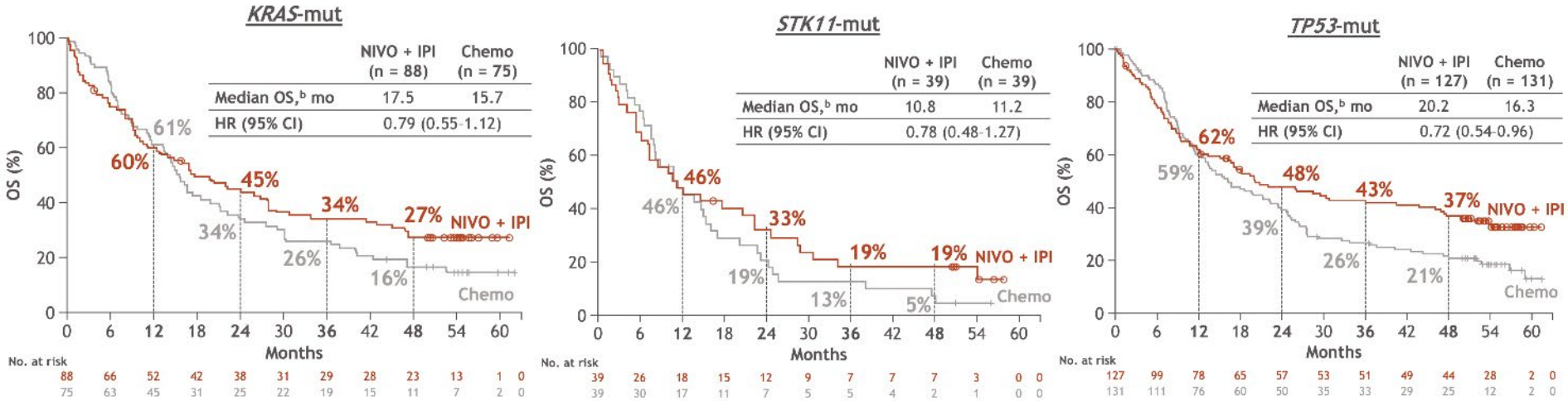




1. Paz-Ares LG, et al. Oral presentation at ASCO 2022 (Abstract LBA 9026); 2. Peters S, et al. Poster presented at WCLC 2022 (Poster OA 15.04)

Exploratory analyses suggest addition of a CTLA-4 might improve outcomes in biomarker-defined subgroups

CheckMate 227: Exploratory analysis of OS by mutational status: *KRAS*m, *TP53*m and *STK11*m[1]



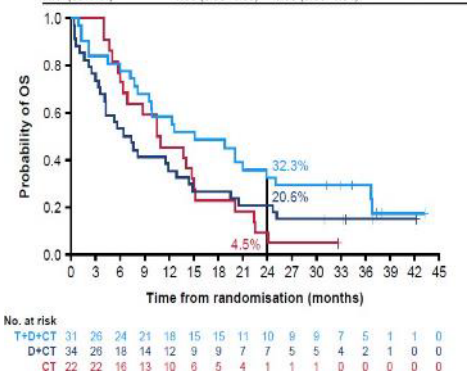
Ramalingam, ESMO IO 2022

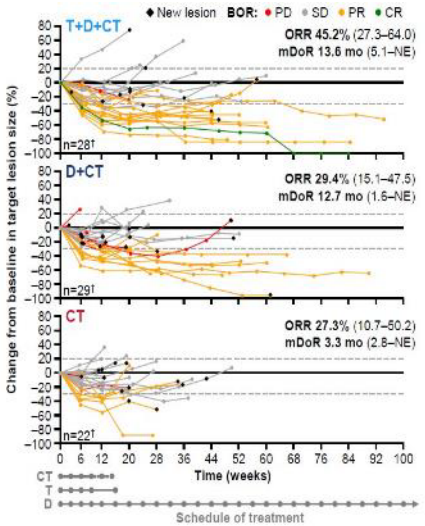
Exploratory analyses suggest addition of a CTLA-4 might improve outcomes in biomarker-defined subgroups

POSEIDON: *STK11*m and *KRAS*m sub-analyses

***STK11*m**

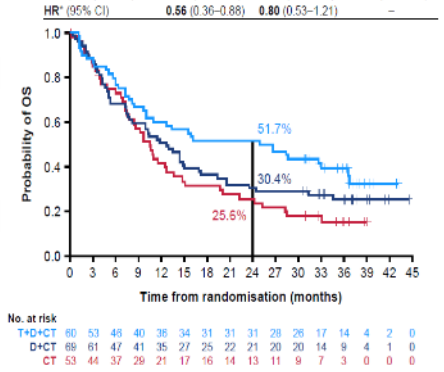
	T+D+CT	D+CT	CT
Events, n/N	24/31	29/34	21/22
mOS, mo (95% CI)	**15.0** (8.2–23.8)	**6.9** (3.6–12.9)	**10.7** (6.0–14.9)
HR* (95% CI)	**0.56** (0.30–1.03)	**1.03** (0.59–1.84)	–

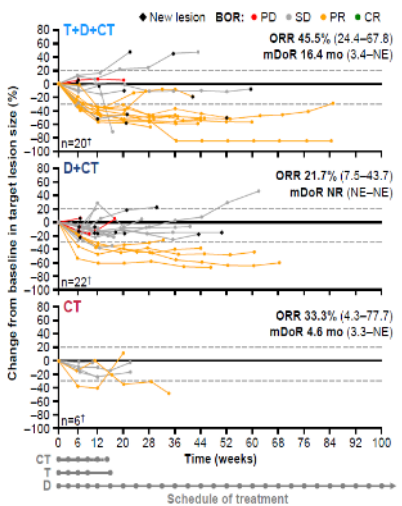




***KRAS*m**

	T+D+CT	D+CT	CT
Events, n/N	38/60	51/69	43/53
mOS, mo (95% CI)	**25.7** (9.9–36.5)	**12.6** (7.5–16.9)	**10.4** (7.5–13.6)
HR* (95% CI)	**0.56** (0.36–0.88)	**0.80** (0.53–1.21)	–



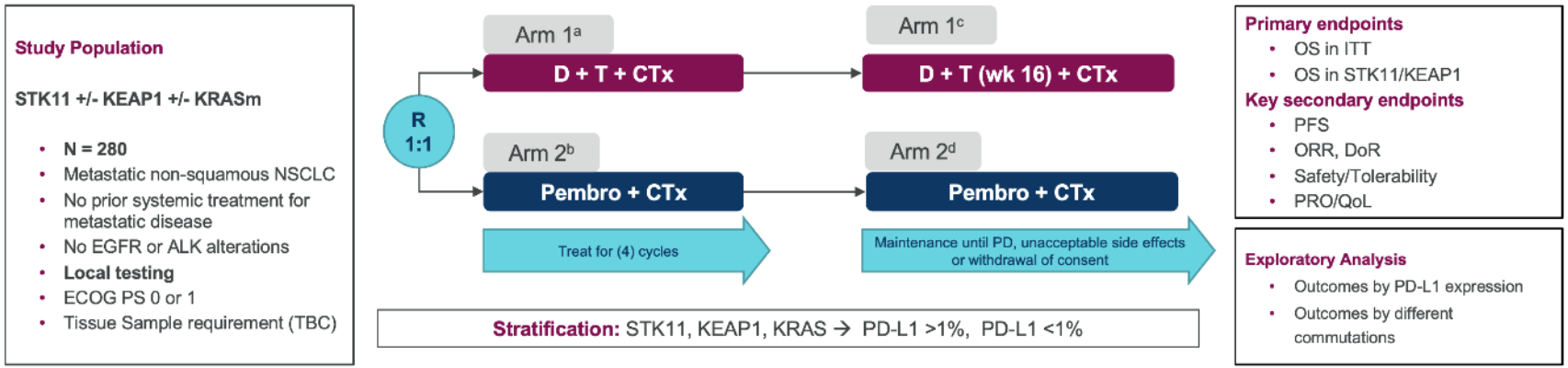


1. Paz-Ares LG, et al. Oral presentation at ASCO 2022 (Abstract LBA 9026); 2. Peters S, et al. Poster presented at WCLC 2022 (Poster OA 15.04)

TRITON: An ongoing phase III trial

TRITON

Phase IIIb randomized, open-label, multicenter study



[a]Durvalumab 1500 mg Q3W + tremelimumab 75 mg Q3W + (platinum + pemetrexed 500 mg/m^2 Q3W); tremelimumab (permitted up to 5 cycles). [b]Pembrolizumab 200 mg Q3W + (platinum + pemetrexed 500 mg/m^2 Q3W).
[c]Durvalumab 1500 mg Q4W + tremelimumab 75 mg (one dose at week 16 only) + pemetrexed 500 mg/m^2 Q3W. [d]Pembrolizumab 200 mg Q3W + pemetrexed 500 mg/m^2 Q3W.

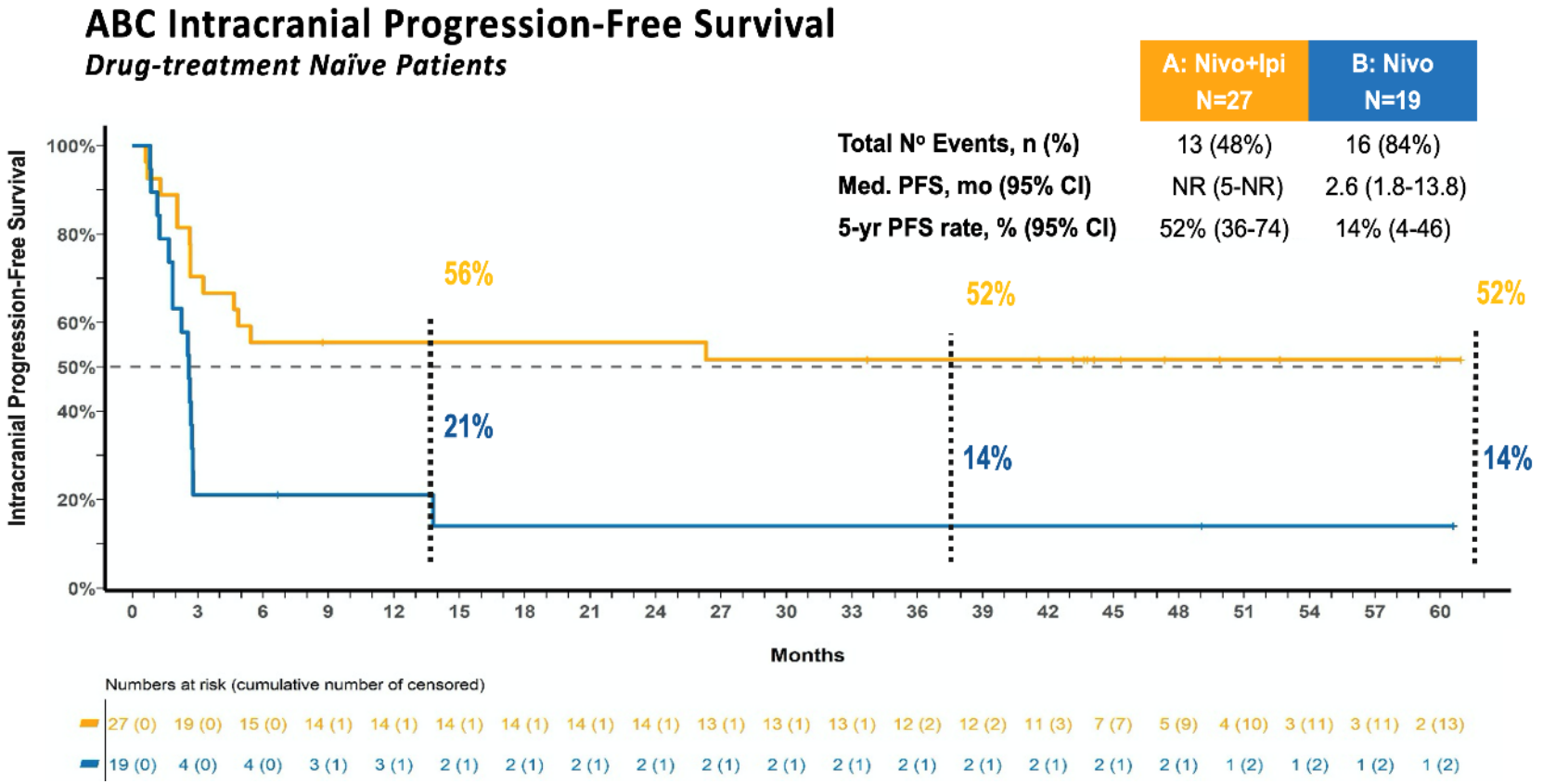
Participants must have tumors with STK11 or KEAP1 or KRAS mutations. Co-mutations are also allowed

WHAT CLINICAL CHARACTERISTICS MIGHT DICTATE DIFFERENTIAL DECISION-MAKING PROCESS

Brain Metastases

WHAT CLINICAL CHARACTERISTICS MIGHT DICTATE DIFFERENTIAL DECISION-MAKING PROCESS

Ipi/nivo more active option for melanoma CNS lesions



Long, ASCO 2021

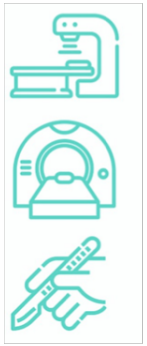
What can immunotherapy offer for patients with brain mets?

Post-hoc exploratory analysis

ICI monotherapy (PD-L1 ≥ 50%)	KEYNOTE-001, 010, 024 & 042 (pooled analysis); EMPOWER-Lung 1
Dual ICI ± chemo (any PD-L1)	CheckMate-227 & CheckMate-9LA
Chemo + ICI (any PD-L1)	KEYNOTE-021, 407 & 189 (pooled analysis)

Specific BrM trials

ICI monotherapy (PD-L1 ≥ 1%)	NCT02085070
Dual ICI ± chemo (any PD-L1)	CheckMate-817; NIVIPI-Brain (ongoing)
Chemo + ICI (any PD-L1)	ATEZO-Brain (*); CAP-BRAIN



Previoulsy treated and controlled BrM (attrition)

Corticosteroids ≤10mg PDN

Untreated BrM

Measurable disease in the CNS

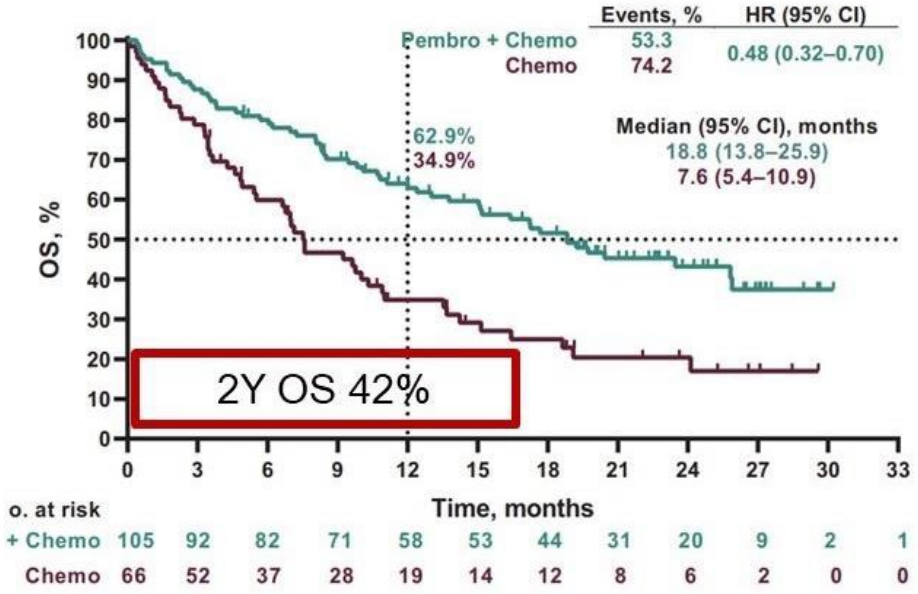
(*) Corticosteroids ≤ 4mg DXM

BrM = Brain metastases

Nadal, ETOP 2024

Pooled analysis KEYNOTE 021-189-407: 1L pembro + chemo

171 / 1298 (13%) had BrM
20 /171 received prior brain RT (12%)
Asymptomatic, no steroids



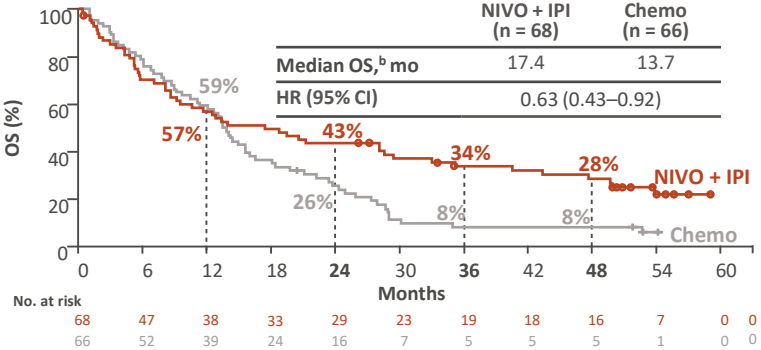
- Higher benefit in terms of OS in patients with brain mets (HR=0.48) compared to those without brain mets (HR=0.63)
- Patients without brain mets still have a 5 months better mOS in both arms
- Chemo is an obvious confounder

Powell et al. J Thorac Oncol 2021

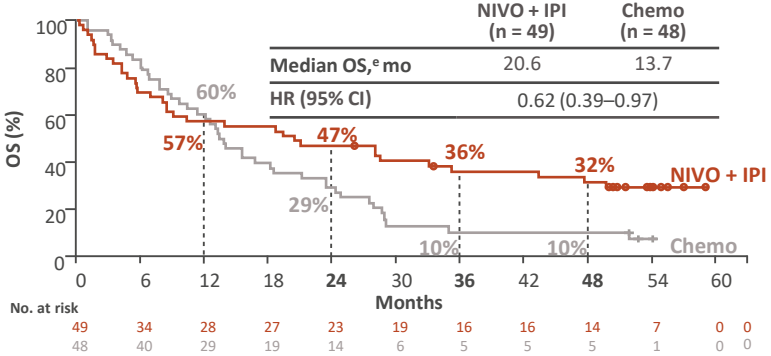
CheckMate 227: a higher magnitude of benefit if brain mets

With baseline brain metastases[a]

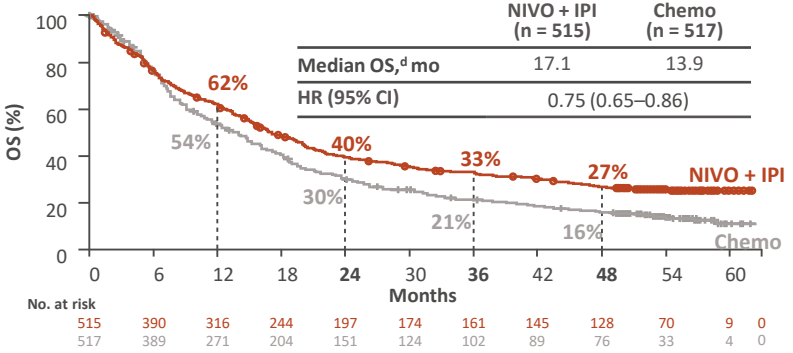
All randomized

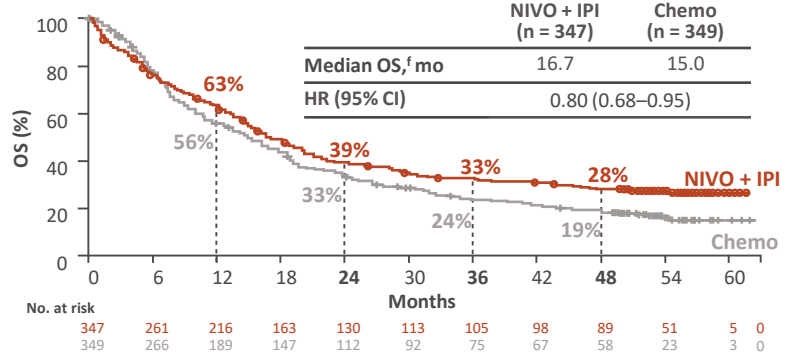


PD-L1 ≥ 1%



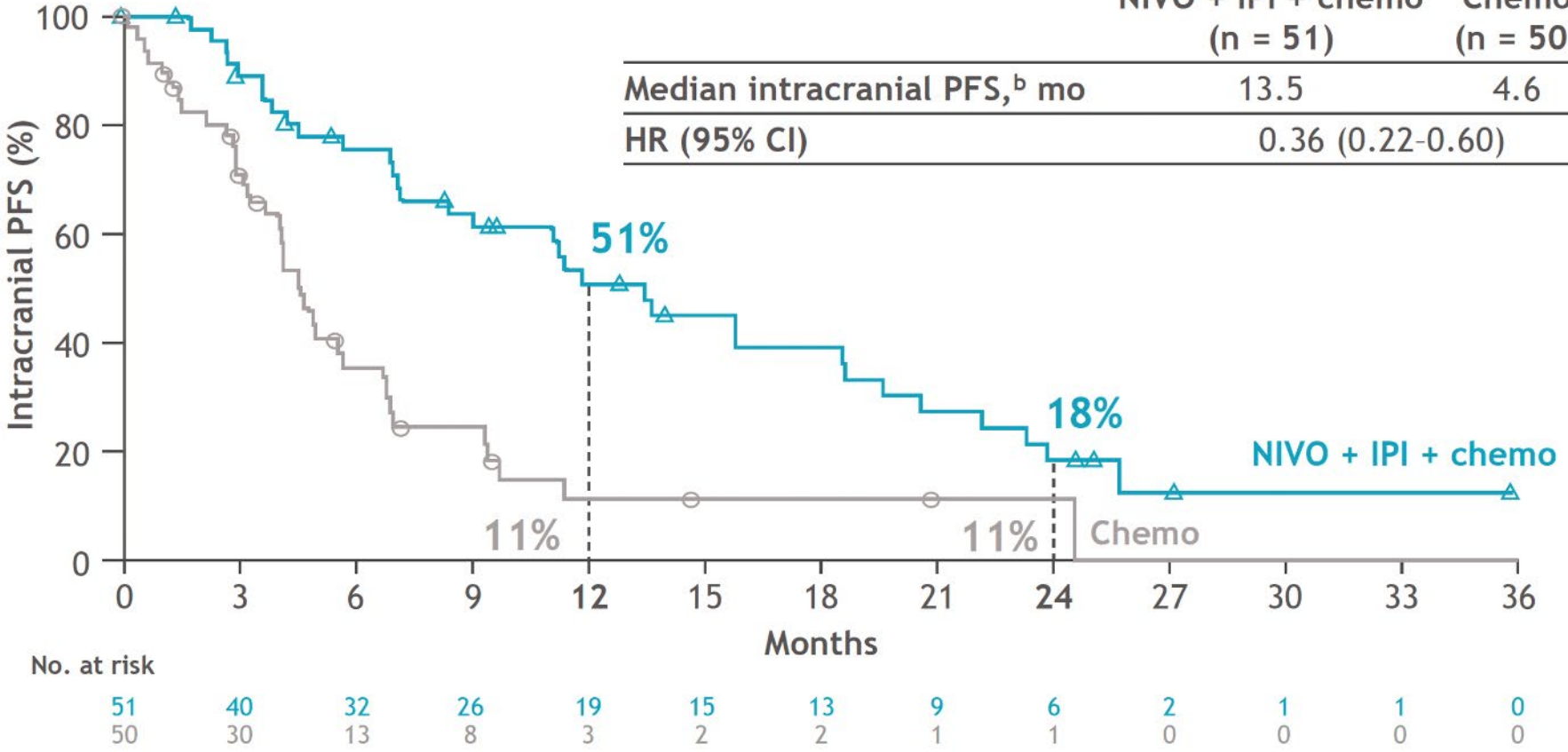
Without baseline brain metastases[c]





Reck, ESMO IO 2021

CheckMate 9LA: a higher magnitude of benefit if brain mets

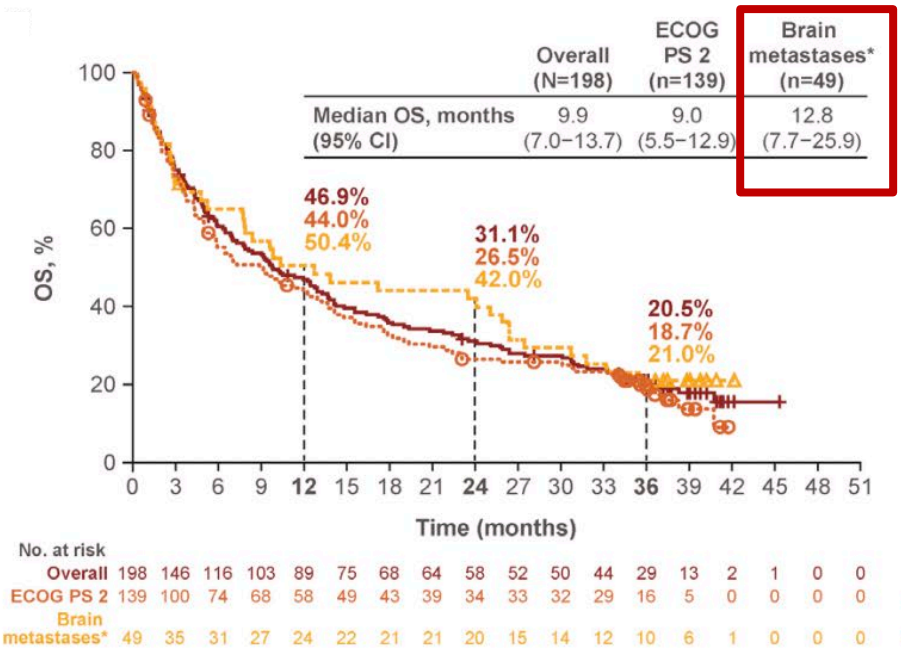


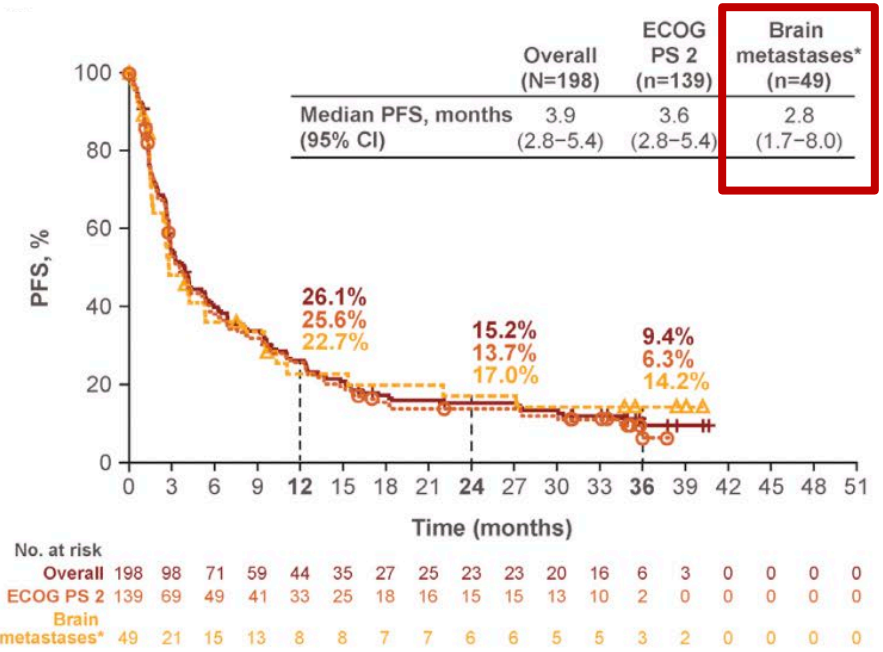
	NIVO + IPI + chemo (n = 51)	Chemo (n = 50)
Median intracranial PFS,[b] mo	13.5	4.6
HR (95% CI)	0.36 (0.22-0.60)	

Dual ICI in patients with untreated BrM yielded a 2y OS rate of 31%

CheckMate-817 (n=49)
IPI + NIVO

Asymptomatic and untreated brain metastases
Measurable CNS disease not required
Corticosteroids ≤10mg PDN





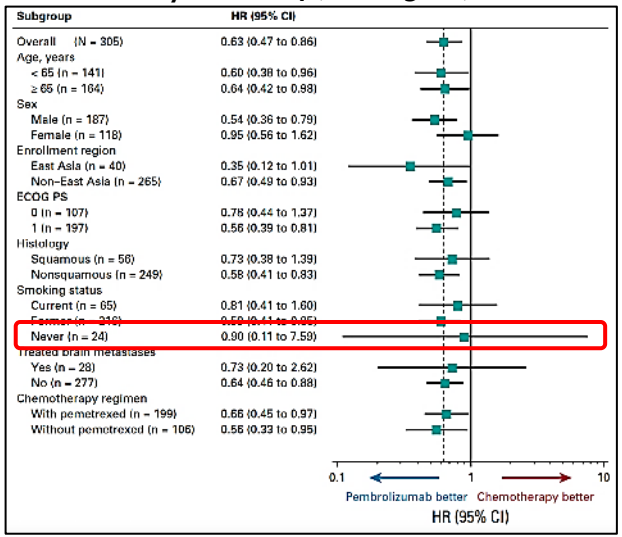
Ready et al. JITC 2023

Smoking habit

WHAT CLINICAL CHARACTERISTICS MIGHT DICTATE DIFFERENTIAL DECISION-MAKING PROCESS

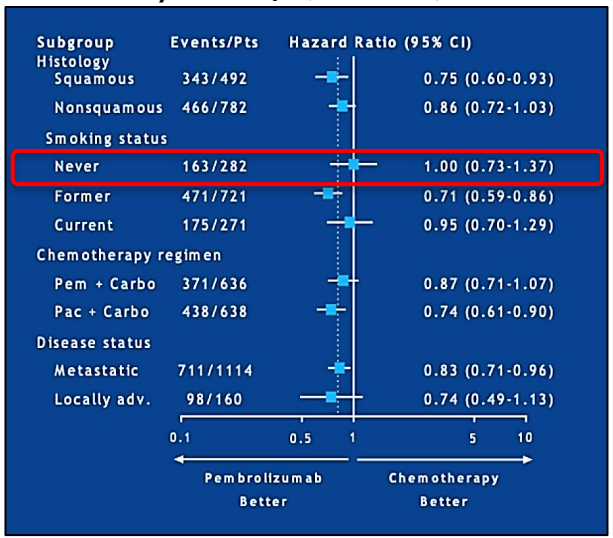
The Problem of Never Smoker

Keynote-024 (TPS ≥50%)[1]



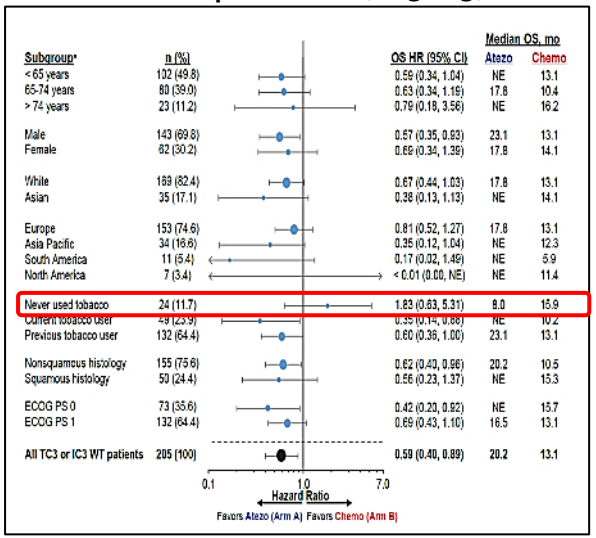
HR, 0.9 (95%CI: 0.11–7.59)

Keynote-042 (TPS ≥1%)[2]



HR, 1.00 (95%CI: 0.73–1.37)

IMpower 110 (TC3/IC3)[3]



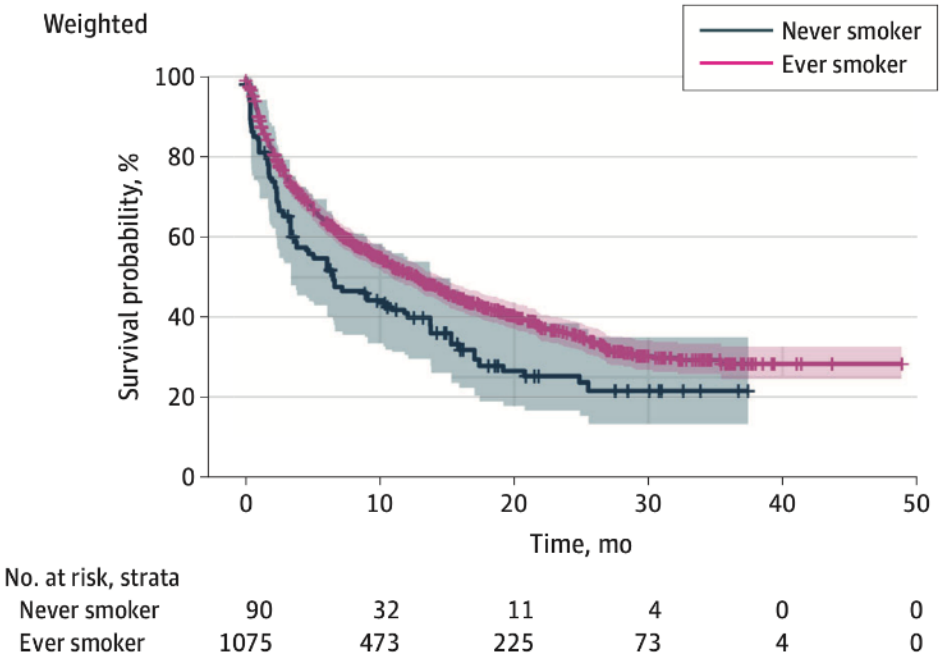
HR, 1.83 (95%CI: 0.63–5.31)

Hazard ratios (95%CIs) in never-smokers

CI, confidence interval; HR, hazard ratio; IC, immune cell; TC, tumor cell; TPS, tumor proportion score

1. Reck M et al, *J Clin Oncol.* 2019;37:537–46. 2. Lopes G et al, ASCO 2018, abstract LBA4; Herbst R et al, N *Engl* J Med. 2020;383:1328–39

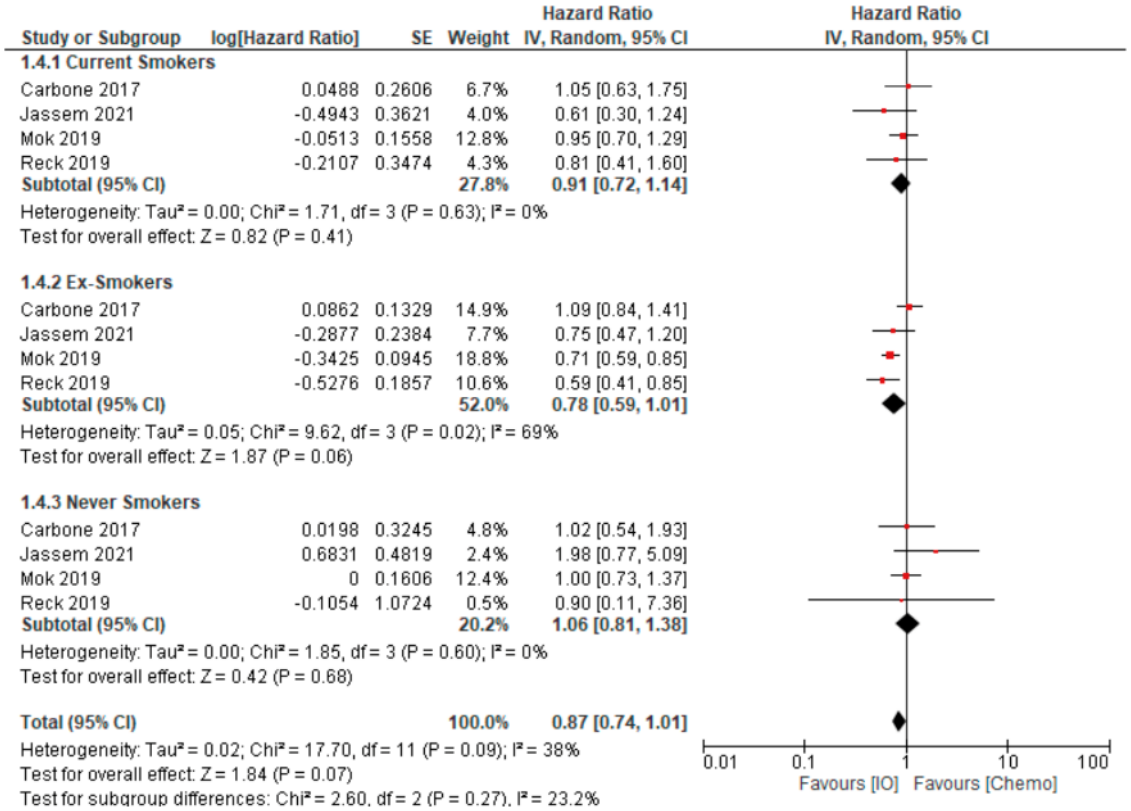
Never Smoker represent an unmet need



Retrospective cohort study of 1166 patients selected from a nationwide real-world database originating from more than 280 US cancer clinics – pembro monotherapy

Popat, JAMA network 2022.

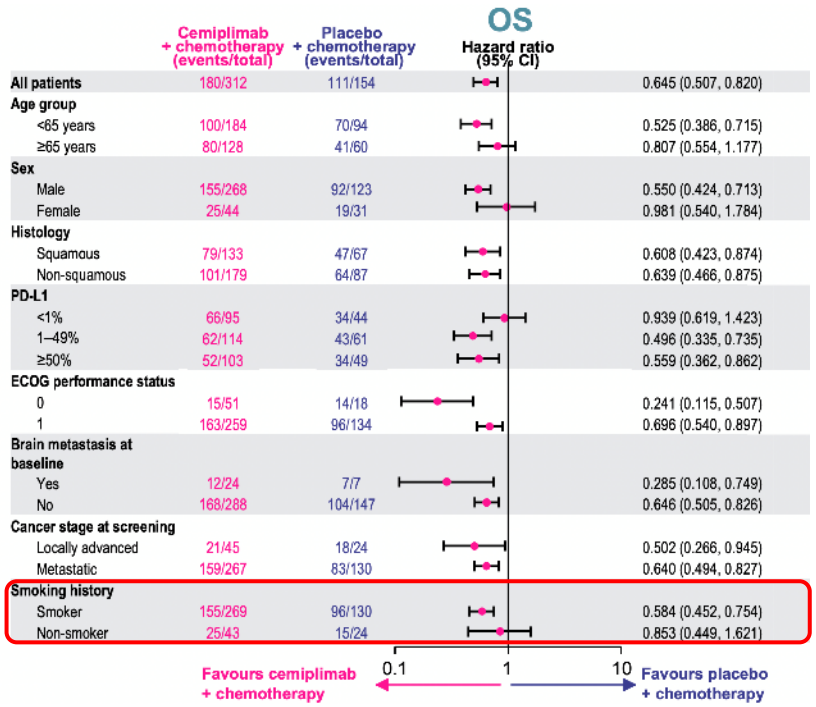
Pooled analysis first line IO vs chemo by smoking habit



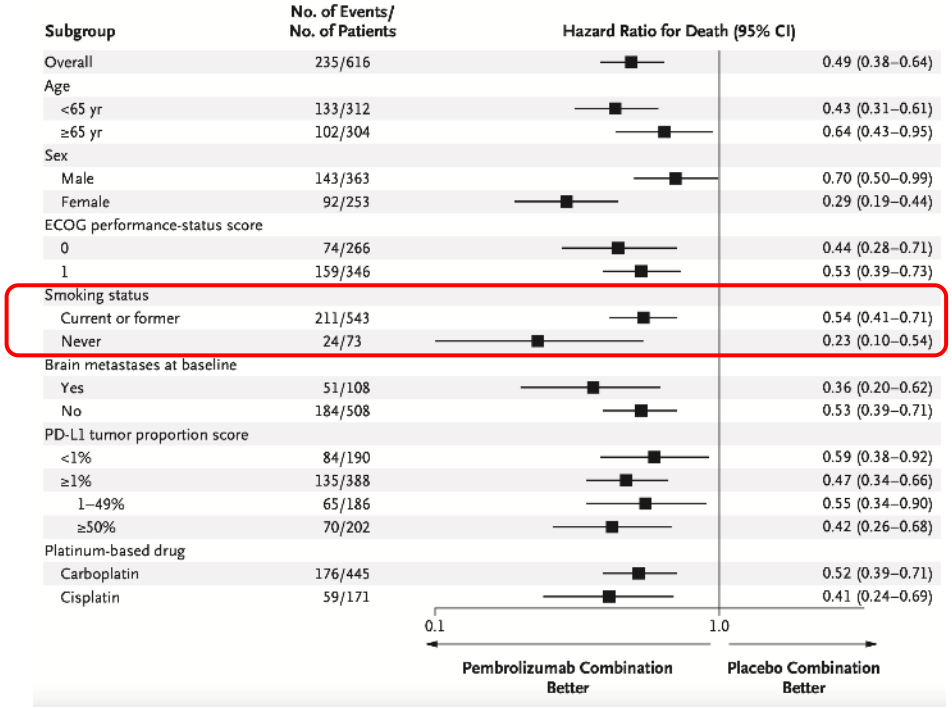
Corke, Curr Oncology 2022

An hetergenous small subgroup that should receive chemo-IO

Empower-Lung 3



KEYNOTE-189



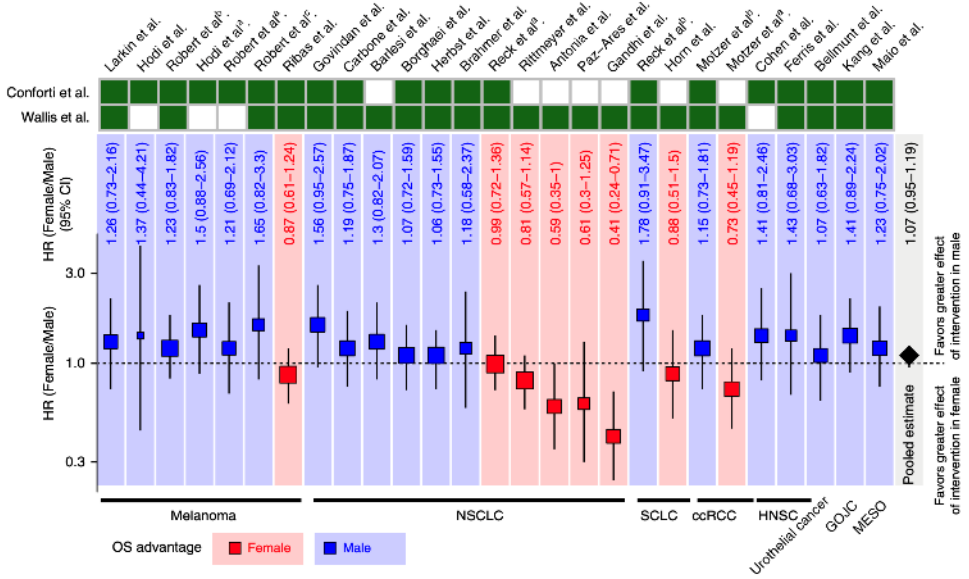
Gender

WHAT CLINICAL CHARACTERISTICS MIGHT DICTATE DIFFERENTIAL DECISION-MAKING PROCESS

Sex-associated molecular differences for cancer immunotherapy

Youqiong Ye[1,2], Ying Jing[2], Liang Li[3], Gordon B. Mills[4], Lixia Diao[5✉], Hong Liu[6✉] & Leng Han[2,7✉]

nature COMMUNICATIONS



- No clear conclusion for whether gender is associated with immunotherapy response
- Gender effects differ between melanoma and NSCLC and render inappropriate meta-analysis pooling cancer types

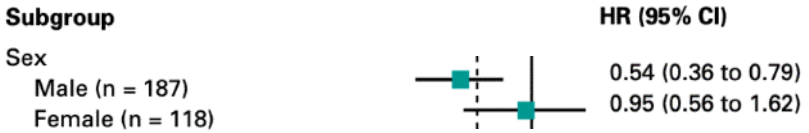
Proportion of females accros trials

	Trial	Subgroup	% Females	
			Chemo	IO
Pembrolizumab[1]	KN-024		37%	40%
Pembrolizumab[1]	KN-042	PD-L1≥50%	30%	31%
Cemiplimab[2]	EMPOWER-Lung 1	PD-L1≥50%	18%	12%
Atezolizumab[3]	IMpower110	PD-L1 ≥ 50%	35%	26%
Nivolumab[4]	CheckMate 026	PD-L1 ≥ 50%	44%	25%
Durvalumab[5]	MYSTIC	PDL1 ≥ 50%	35%	31%
Avelumab[6]	Javelin 100	PDL1 ≥ 80%	27-28%	23-26%

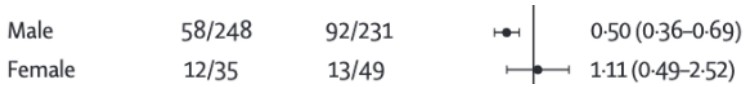
[1]Brahmer et al, ESMO 2020, Reck et al, JCO 2021;39:2339-2349. Mok et al, Lancet 2019; 393(10183):P1819-1830. Cho et al, JTO 2021;16(3S):S225. [2]Sezer et al, Lancet 2021;397:592-604. Özgüroğlu et al, Annal of Onc 2022; 33:s7:S1421.[3]Jassem et al, JTO 2021;16:1872-82 (updated exploratory). Spigel et al, Annal Onc 2019;30(5):v915. [4]Carbone et al, NEJM 2017;376:2415-26. [5]Rivzi et al, JAMA Oncol. 2020;6(5):661-674. [6]Reck et al, WCLC 2022;OA15.03.

OS by sex

KN-024



Empower-1



IMpower110

High PDL1
(SP142 TC_3/IC_3 WT)

KN-042

PD-L1≥1%

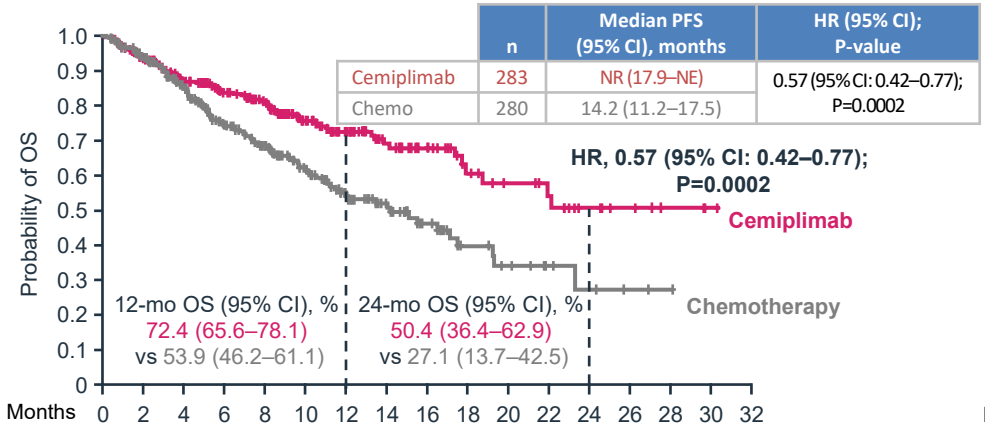
Javelin100

PD-L1≥80%

Reck et al, JCO 2019; 37(7):537-546. [2]Sezer et al, Lancet 2021;397:592-604. Spigel et al, EMSO 2019. Mok et al, ELCC 2019. Reck et al, WCLC 2023;OA15.03

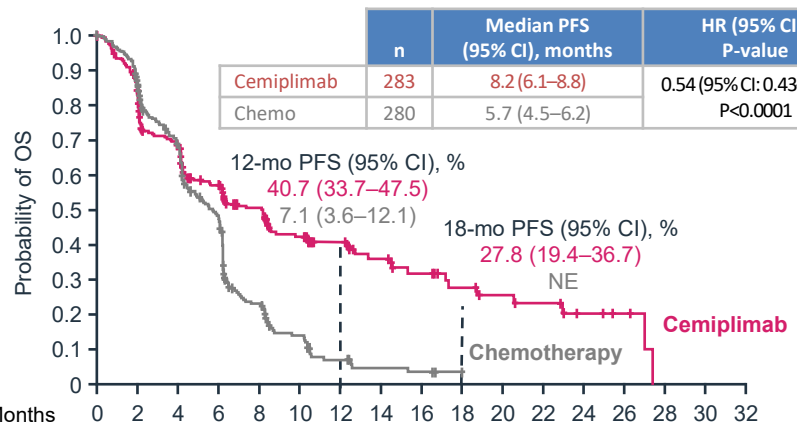
Empower-lung 1 trial - cemiplimab: Sex effect

OS in the PD-L1 ≥50% population



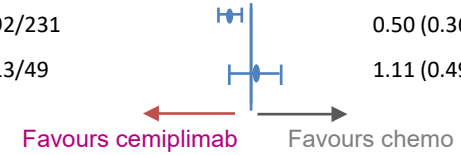
	n	Median PFS (95% CI), months	HR (95% CI); P-value
Cemiplimab	283	NR (17.9–NE)	0.57 (95% CI: 0.42–0.77); P=0.0002
Chemo	280	14.2 (11.2–17.5)	

PFS in the PD-L1 ≥50% population



	n	Median PFS (95% CI), months	HR (95% CI); P-value
Cemiplimab	283	8.2 (6.1–8.8)	0.54 (95% CI: 0.43–0.68); P<0.0001
Chemo	280	5.7 (4.5–6.2)	

Sex	Events cemiplimab	Events chemo	HR for OS (95% CI)
Male	58/248	92/231	0.50 (0.36–0.69)
Female	12/35	13/49	1.11 (0.49–2.52)



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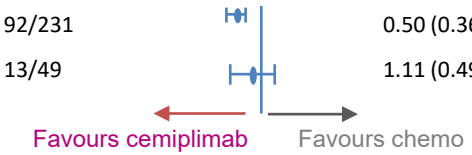


Sezer A, et al. Lancet. 2021;369:592–604.

Impact of sex on IO-based therapy outcomes

Innate immunity: Enhanced in females[1]

- Neutrophils phagocytic capacity
- Macrophagic activation
- Macrophagic phagocytic capacity
- APC efficiency
- Dendritic cell activities
- Toll-like receptors gene expression pathway

Adaptive immunity: Enhanced in females[1]

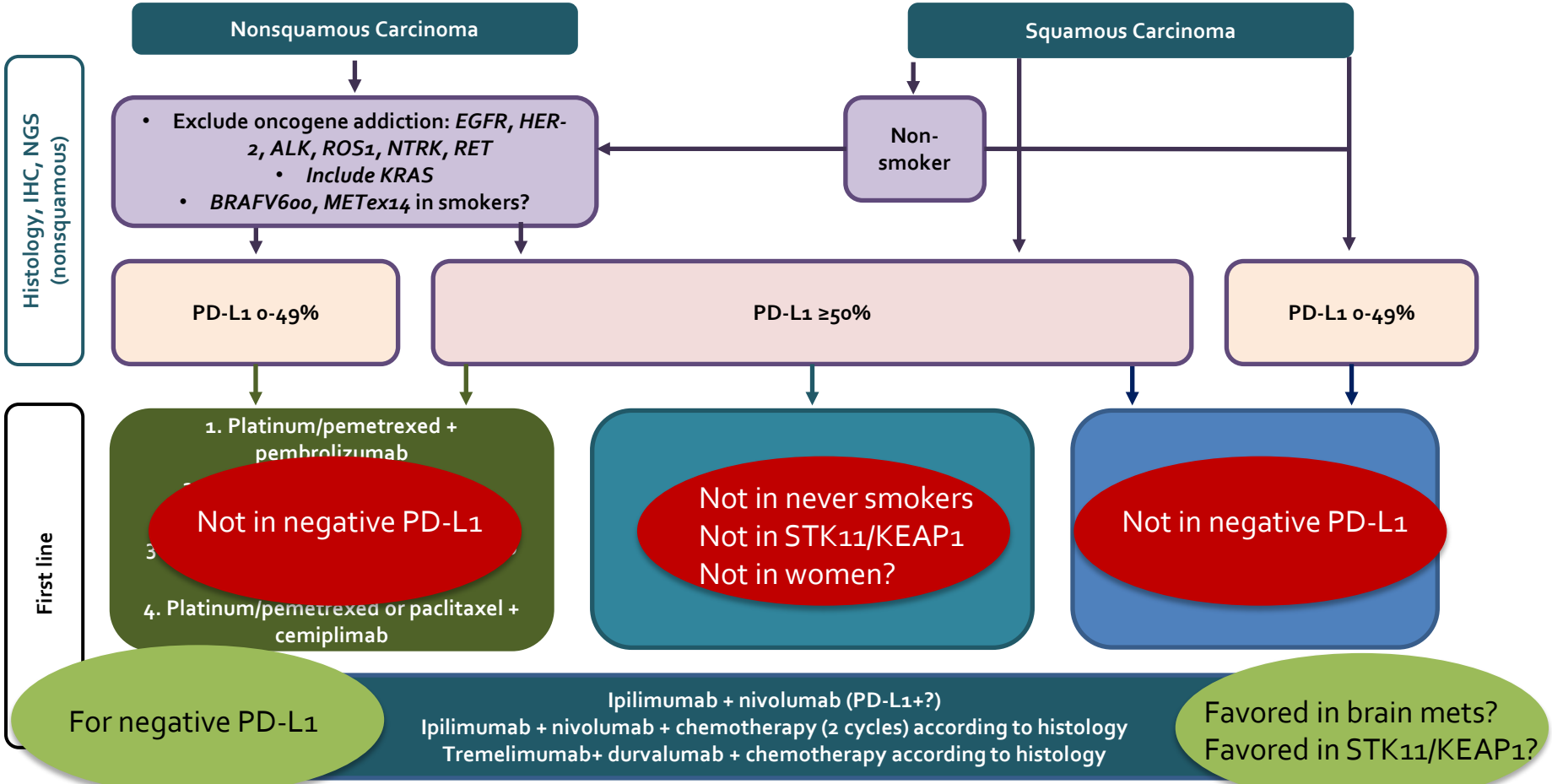
- CD_4+ T-cell count; CD_4/CD8 T-cell ratio
- T-cell proliferation
- Activated T-cell count
- T-cell cytotoxicity
- B-cell count
- Antibody production

Meta-analyses: OS results for lung cancer patients receiving IO, IO + chemotherapy vs chemotherapy[2]

		Pooled OS HRs (95% CI)	
		IO (PD-[L]1)	IO (PD-[L]1) + chemo
Male	vs chemo	0.78 (0.60–1.00)	0.76 (0.64–0.91)
Female	vs chemo	0.97 (0.79–1.19)	0.44 (0.25–0.76)
Female vs male		0.83 (0.65–1.06)	1.70 (1.16–2.49)

1. Vavalà T, et al. Int J Mol Sci. 2021;22:11942. 2. Condorti F, et al. J Natl Cancer Inst. 2019;111:djz094 and ESMO open 2021

Adapting the algorithm?



THANK YOU

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