Pre-Operative and Metastatic Setting Biomarkers for Immunotherapy in Lung Cancer

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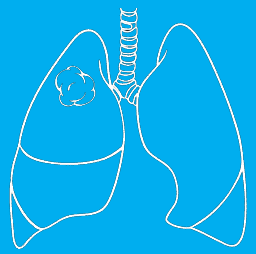
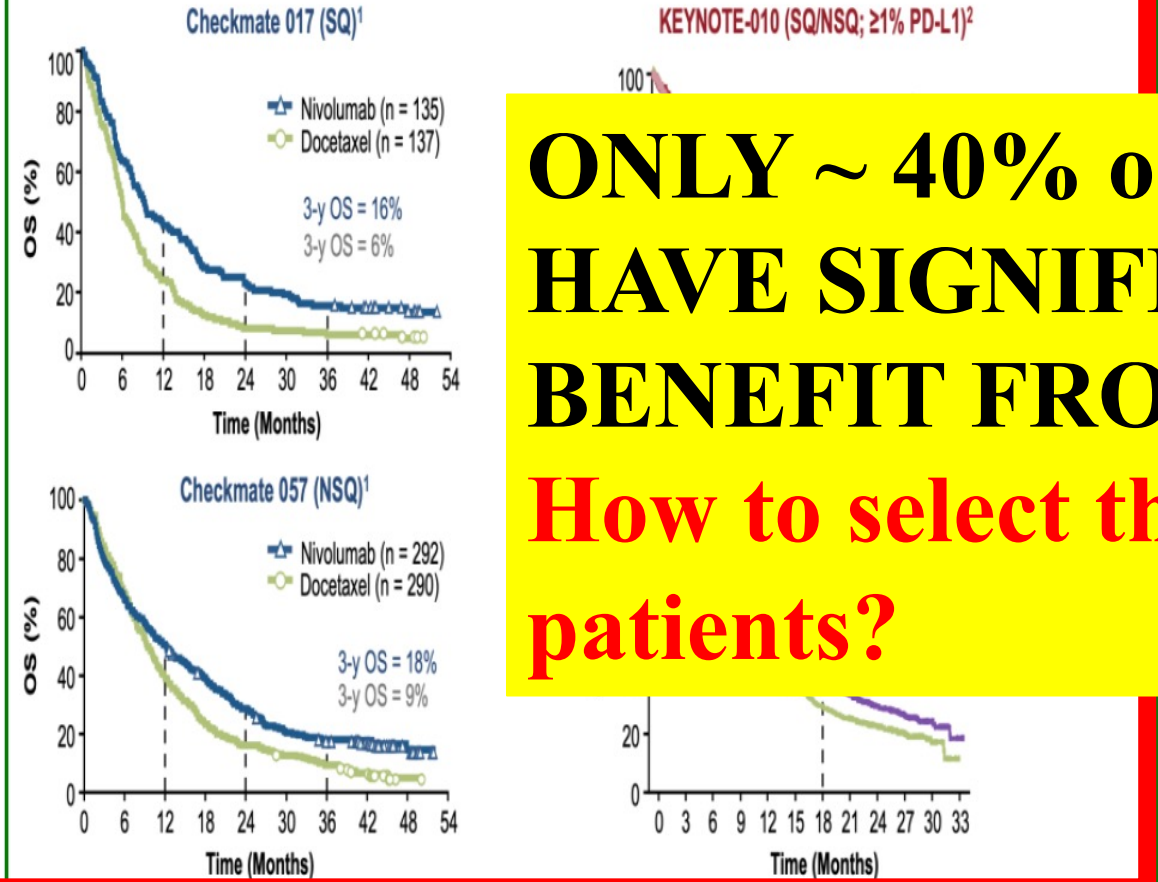


Mount Sinai

The Tisch Cancer Institute

Immunotherapy – The Game Changer

Pretreated Patients



ONLY ~ 40% of NSCLC WILL HAVE SIGNIFICANT BENEFIT FROM IO!

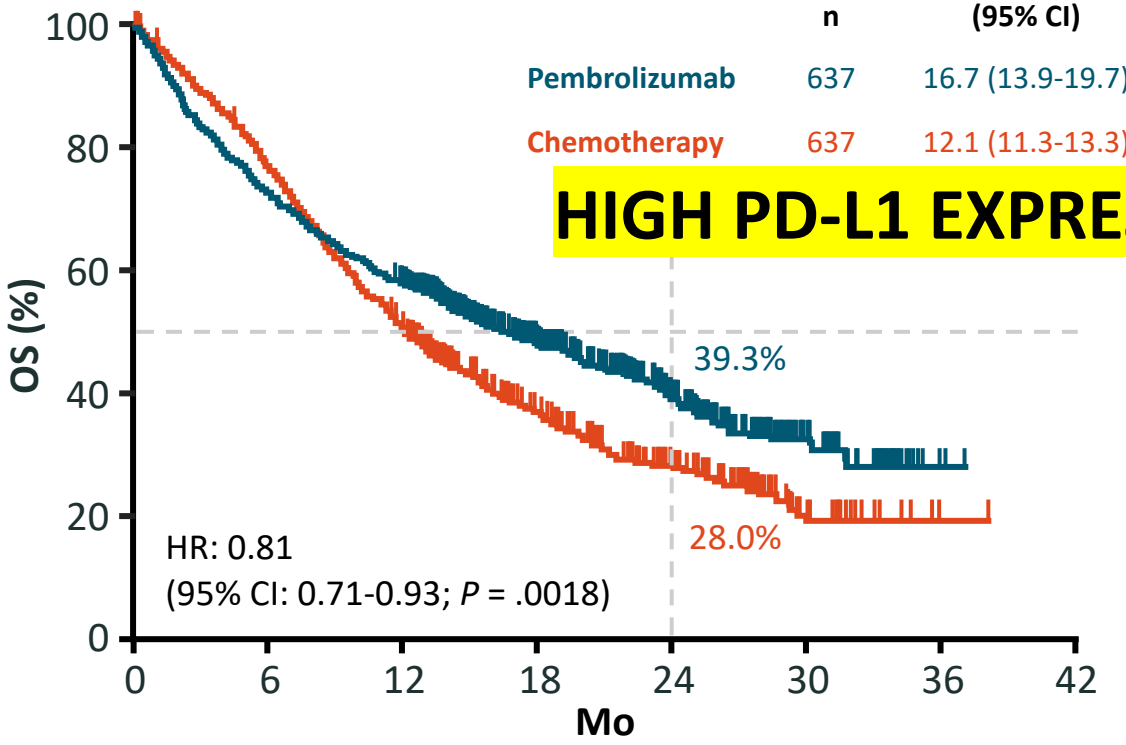
How to select the right patients?

Untreated Patients

KEYNOTE-042: First-line Pembrolizumab in PD-L1+ Advanced NSCLC

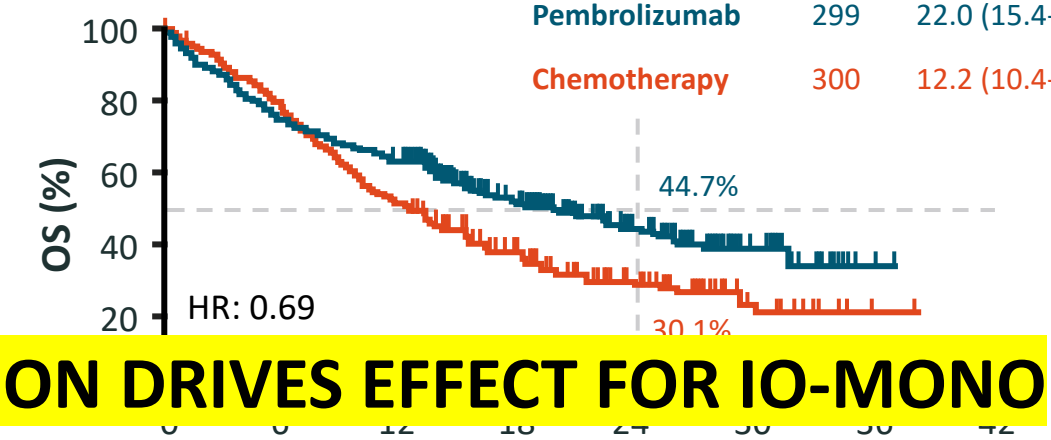
OS: PD-L1 TPS ≥1%

	Pts, n	Median OS, Mo (95% CI)
Pembrolizumab	637	16.7 (13.9-19.7)
Chemotherapy	637	12.1 (11.3-13.3)



OS: PD-L1 TPS ≥50%

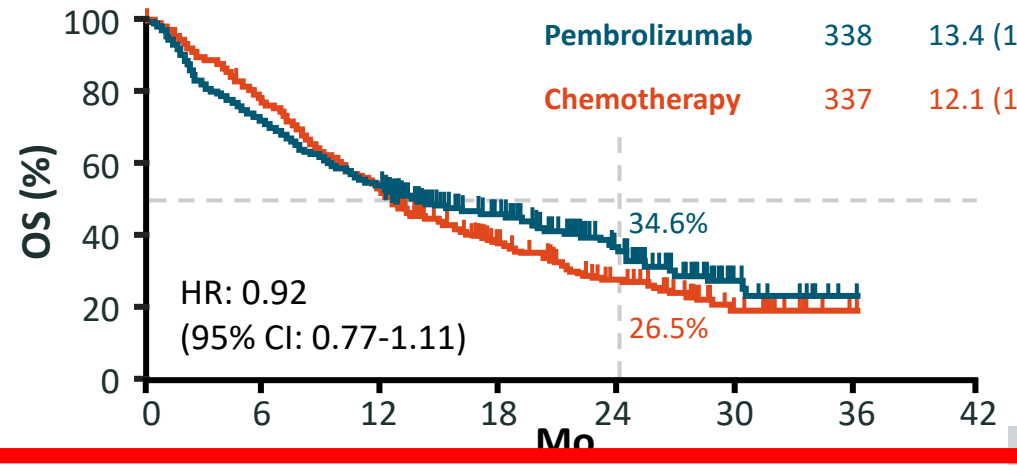
	Pts, n	Median OS, Mo (95% CI)
Pembrolizumab	299	22.0 (15.4-24.9)
Chemotherapy	300	12.2 (10.4-14.2)



HIGH PD-L1 EXPRESSION DRIVES EFFECT FOR IO-MONO

OS: PD-L1 TPS ≥1%-49%*

	Pts, n	Median OS, Mo (95% CI)
Pembrolizumab	338	13.4 (1.7-18.2)
Chemotherapy	337	12.1 (11.0-14.0)



Mok. Lancet. 2019;393:1819.

*Exploratory analysis; no alpha allocated to this comparison.

Slide credit: clinicaloptions.com

FDA-approved regimens for advanced/metastatic NSCLC not harboring tumor genomic alterations

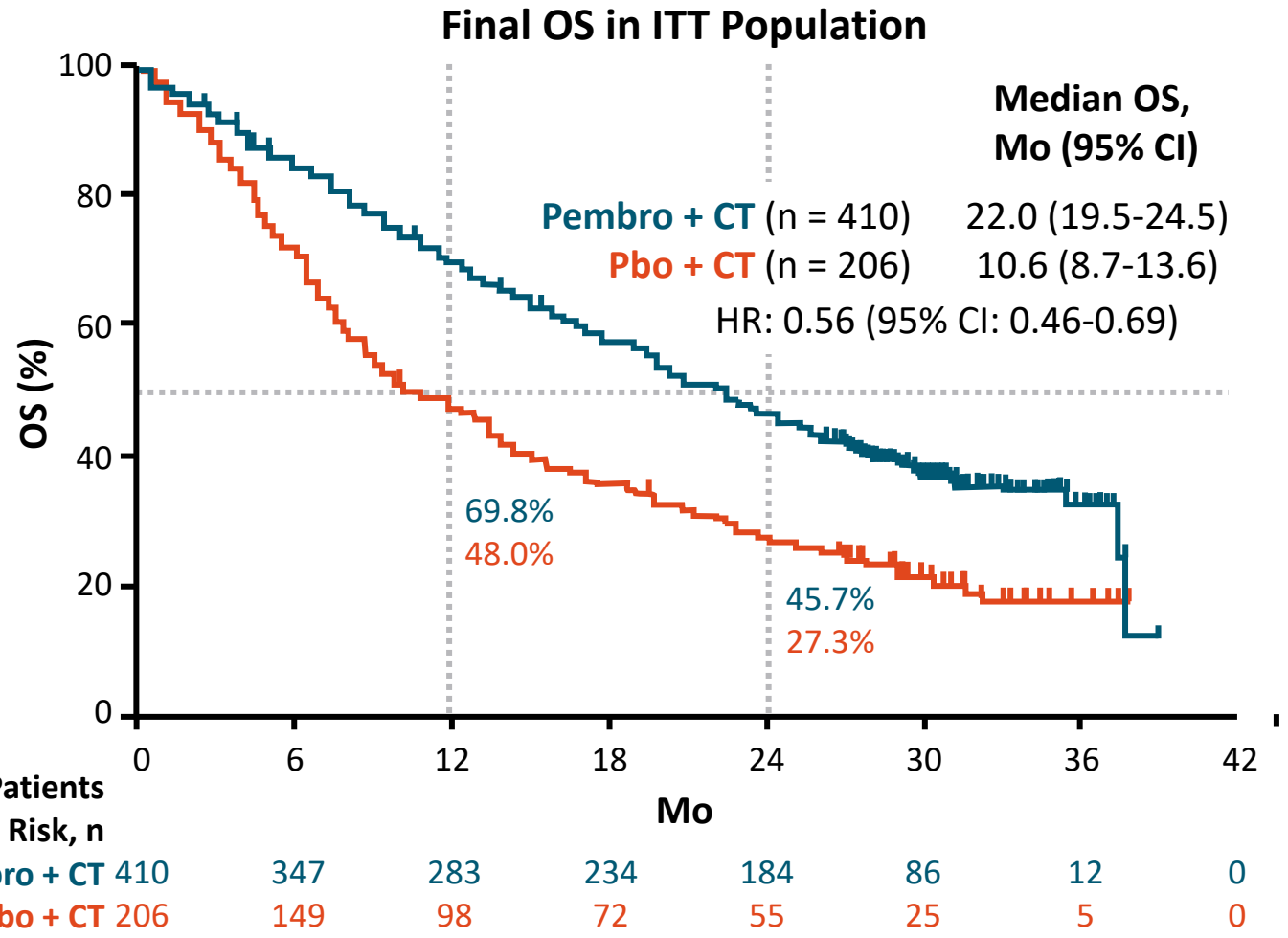
PD-L1 level	Regimen	Histology	Approval endpoint
≥ 50%	**Pembrolizumab**	NSCLC	**OS** & PFS
	Atezolizumab [a]	NSCLC	**OS**
	Cemiplimab	NSCLC	**OS** & PFS
≥ 1%	**Pembrolizumab**	NSCLC	**OS**
	Nivolumab + Ipilimumab	NSCLC	**OS**
None	**Pembrolizumab** + Platinum + Pemetrexed [b]	NSq-NSCLC	**OS** & PFS
	Pembrolizumab + Carboplatin + Paclitaxel	Sq-NSCLC	**OS** & PFS
	Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel	NSq-NSCLC	**OS** & PFS
	Atezolizumab + Carboplatin + Nab-paclitaxel	NSq-NSCLC	**OS** & PFS
	Nivolumab + Ipilimumab + Platinum doublet	NSCLC	**OS**

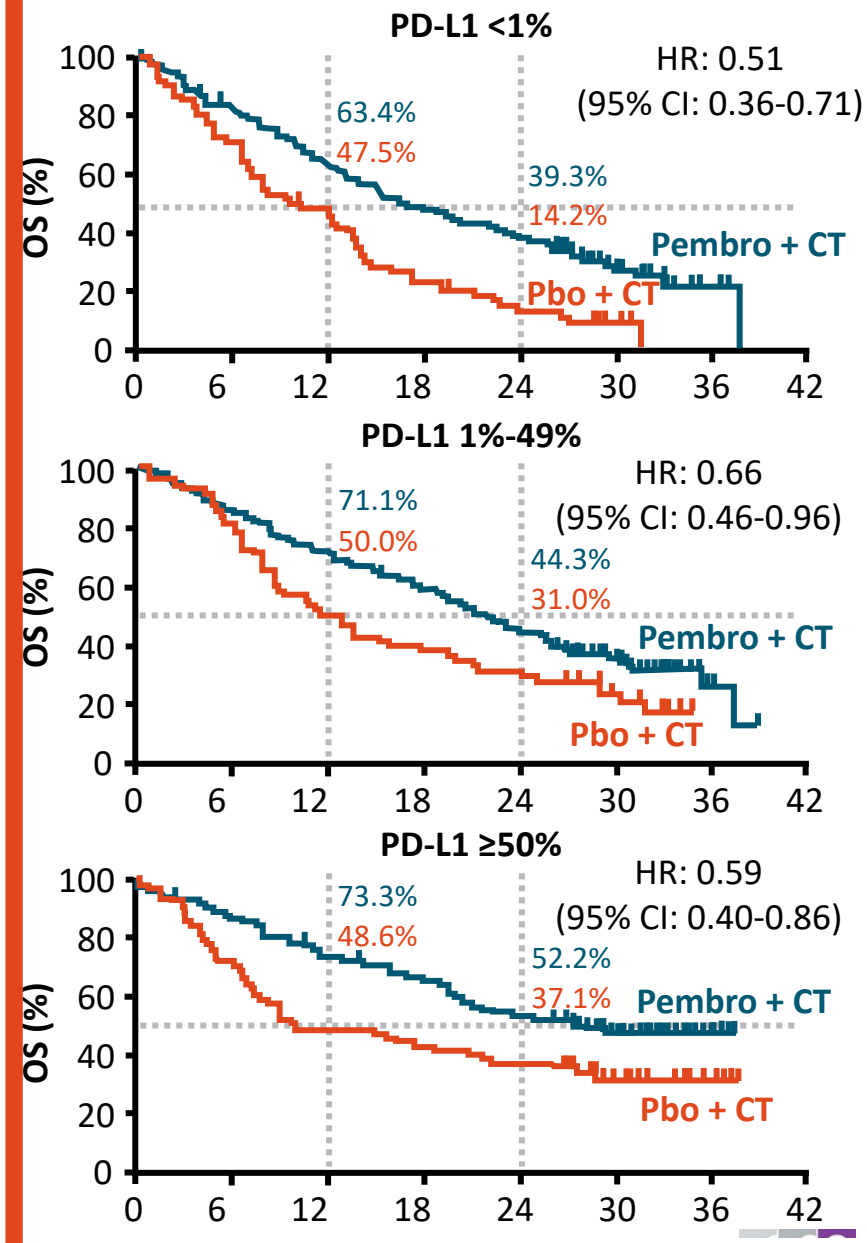
Abbreviations: NSCLC=non-small cell lung cancer; Nsq=non-squamous; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival; Sq=squamous.

[a] PD-L1 high population for atezolizumab defined as PD-L1 staining ≥ 50% of tumor cells or tumor-infiltrating immune cells covering ≥ 10% of the tumor area.

[b] Initial Accelerated approval in 2017 based on PFS.

KEYNOTE-189: 1L Pembrolizumab + Chemotherapy for Adv Nonsq NSCLC

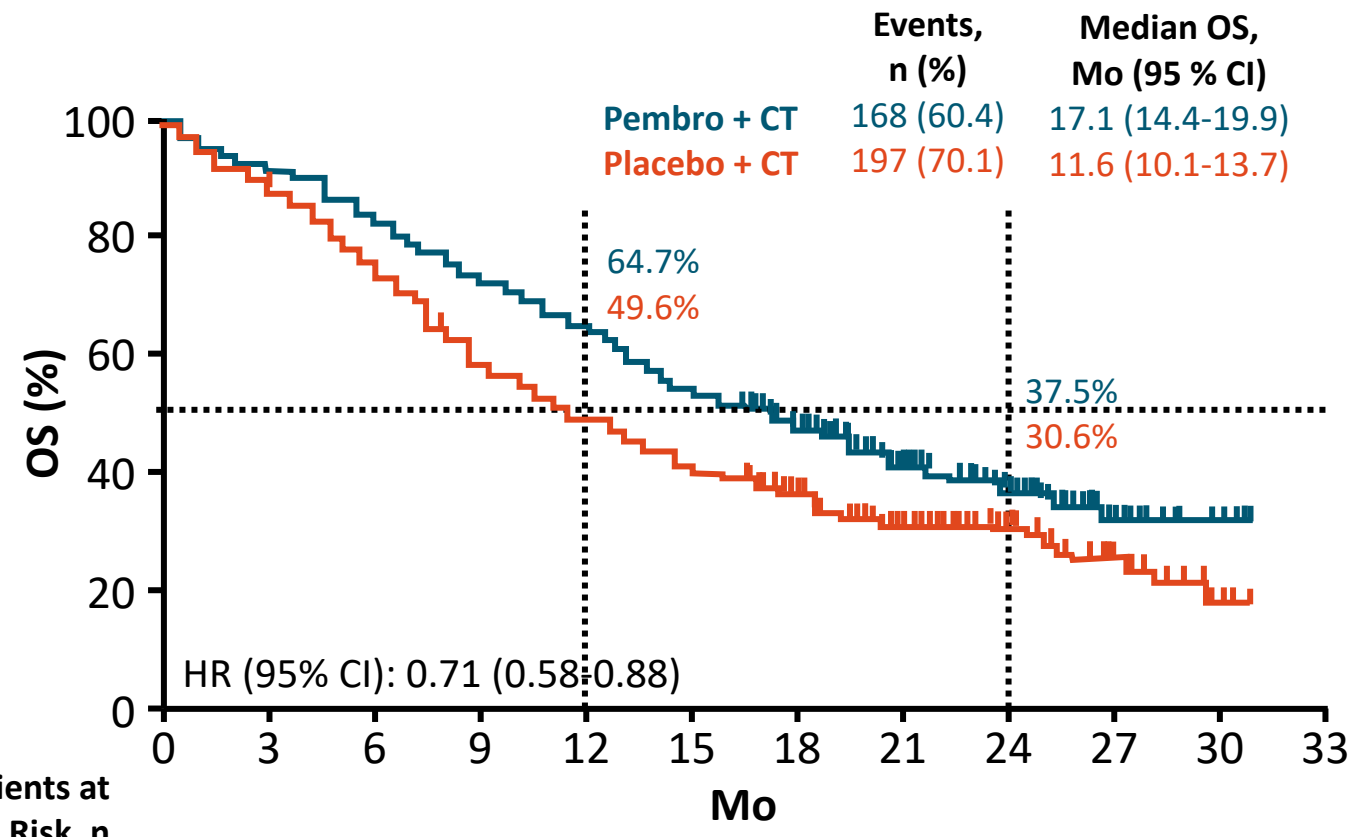




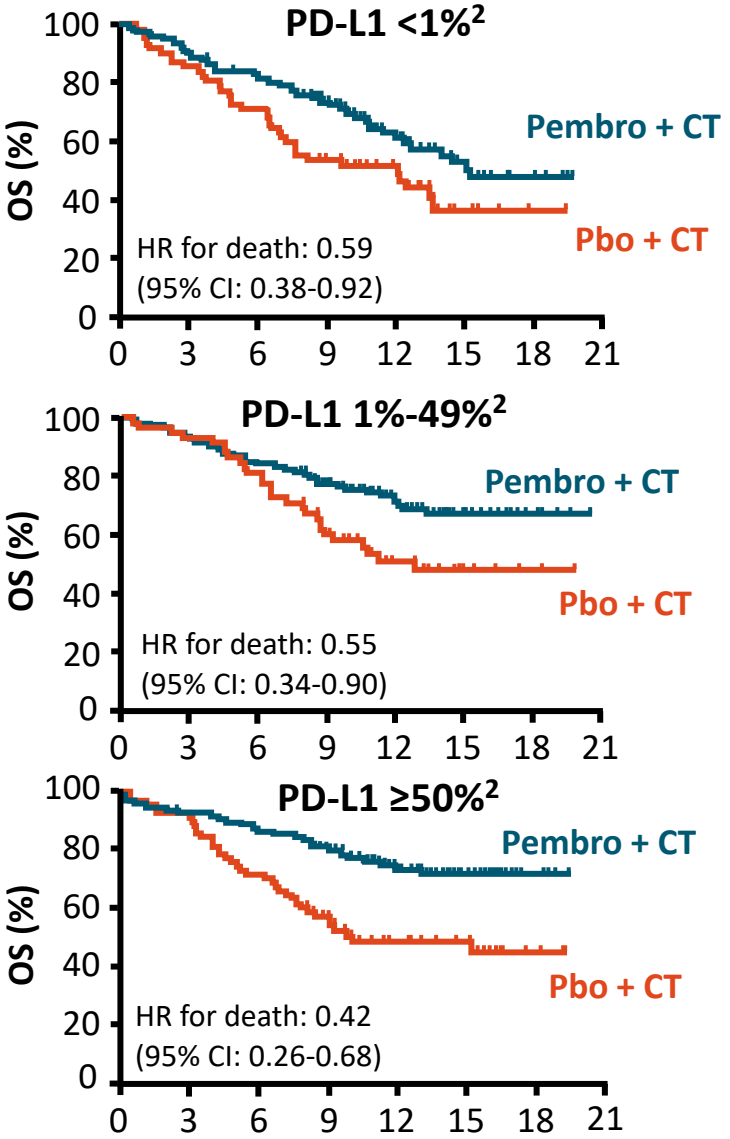
Rodríguez-Abreu. Ann Oncol. 2021;32:881.

KEYNOTE-407: 1L Pembrolizumab + Chemotherapy for Adv Sq NSCLC

OS in ITT Population[1]



Patients at Risk, n											
Pembro + CT	278	256	232	203	180	150	119	80	46	14	4	0
Pbo + CT	281	245	210	163	137	113	91	61	36	16	3	0



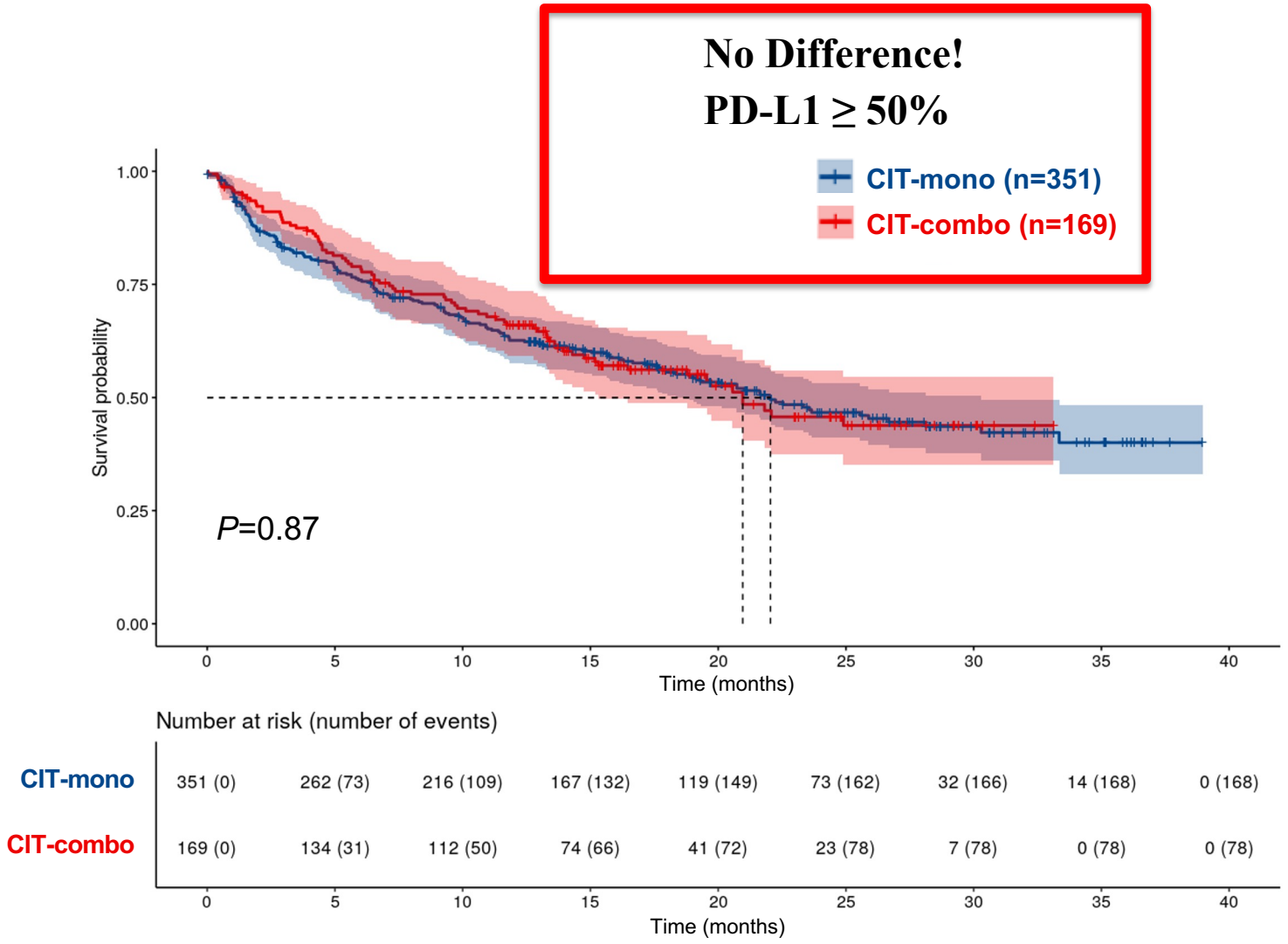
1. Paz-Ares. J Thorac Oncol. 2020;15:1657. 2. Gandhi. NEJM. 2018;378:2078.

Primary outcome: overall survival

Unadjusted analysis

	CIT-mono (n=351)	CIT-combo (n=169)
Events, n (%)	168 (49)	78 (46)
OS, mo Median (95% CI)	22.05 (18.33, 30.29)	20.96 (15.31, NA)
Follow-up, mo Median (IQR)	23.46 (15.74, 28.71)	19.92 (14.92, 26.25)

CIT-combo vs CIT-mono (reference)	Hazard ratio (95% CI)	*P* value
Unadjusted analysis	0.98 (0.75, 1.28)	0.868
Adjusted analysis	1.03 (0.77, 1.39)	0.833

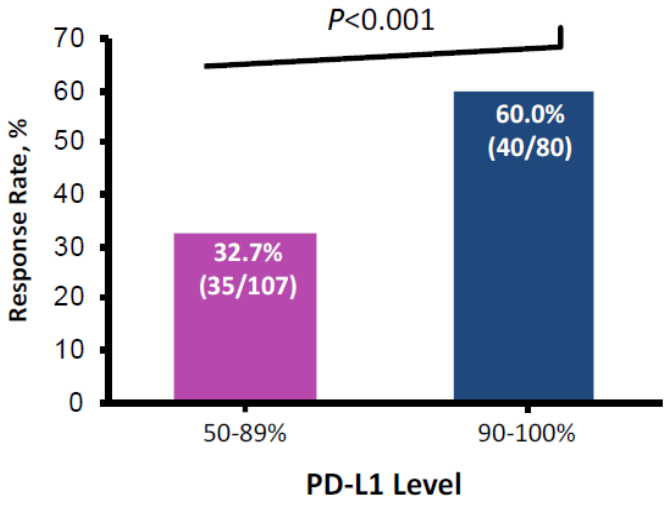


Peters S; ESMO 2020

PD-L1 ≥50% patients are not equal

Mono-immunotherapy more effective in patients with PD-L1 ≥90%

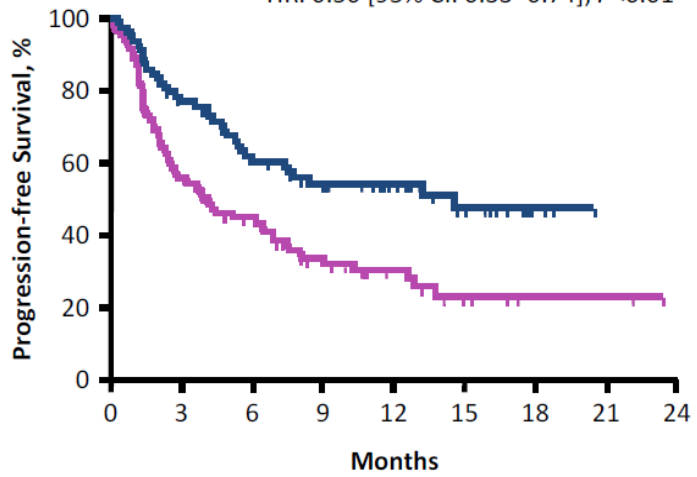
ORR



PFS

	N	mPFS (95% CI)
PD-L1 90–100%	80	14.5 mo (6.0–NR)
PD-L1 50–89%	107	4.1 mo (1.7–6.6)

HR: 0.50 [95% CI: 0.33–0.74], *P*<0.01

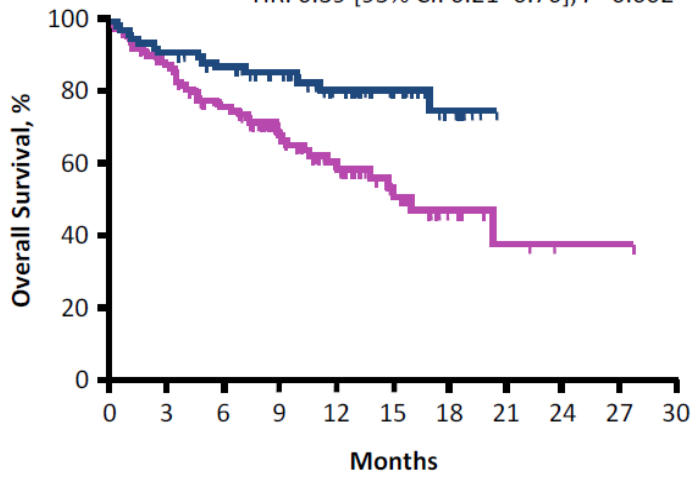


No. at risk									
PD-L1 90-100%	80	58	44	34	27	12	3	0	0
PD-L1 50-89%	107	59	42	25	13	6	2	2	0

OS

	N	mOS (95% CI)
PD-L1 90–100%	80	NR (NR–NR)
PD-L1 50–89%	107	15.9 mo (11.2–20.7)

HR: 0.39 [95% CI: 0.21–0.70], *P*=0.002



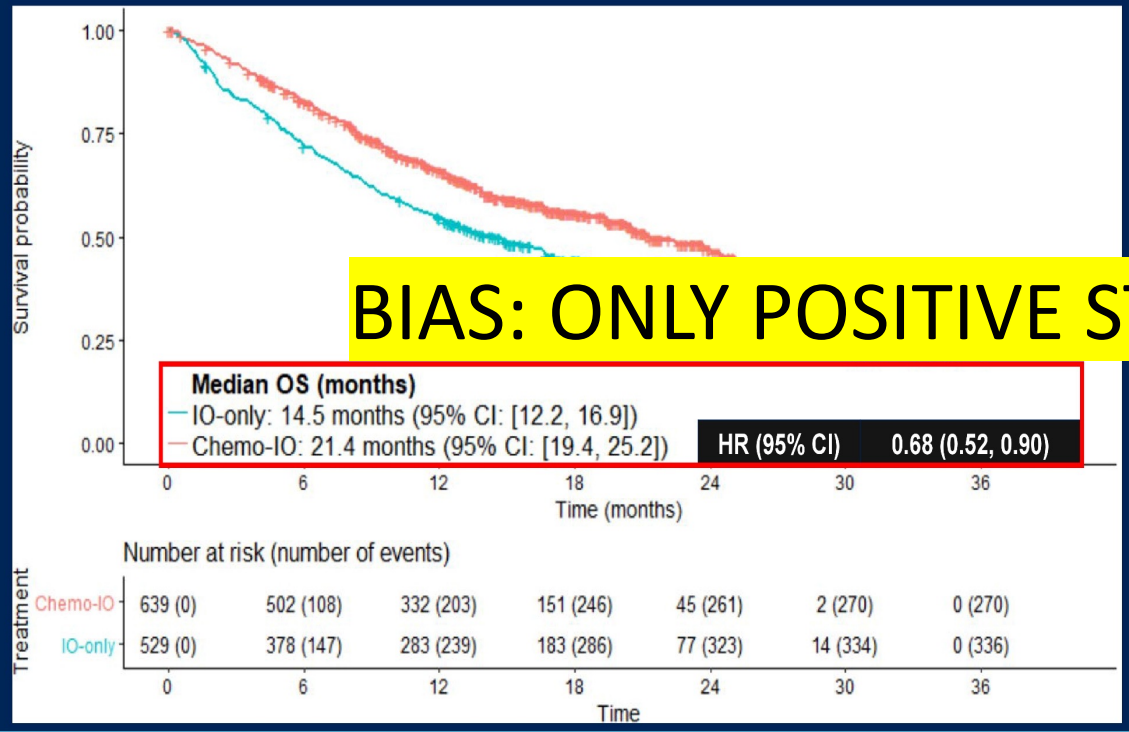
No. at risk											
PD-L1 90-100%	80	73	66	57	38	22	10	0	0	0	0
PD-L1 50-89%	107	92	75	51	33	18	8	4	1	1	0

Clinical outcomes significantly improved for 1L NSCLC patients with PD-L1 ≥90%, when treated with I-O monotherapy

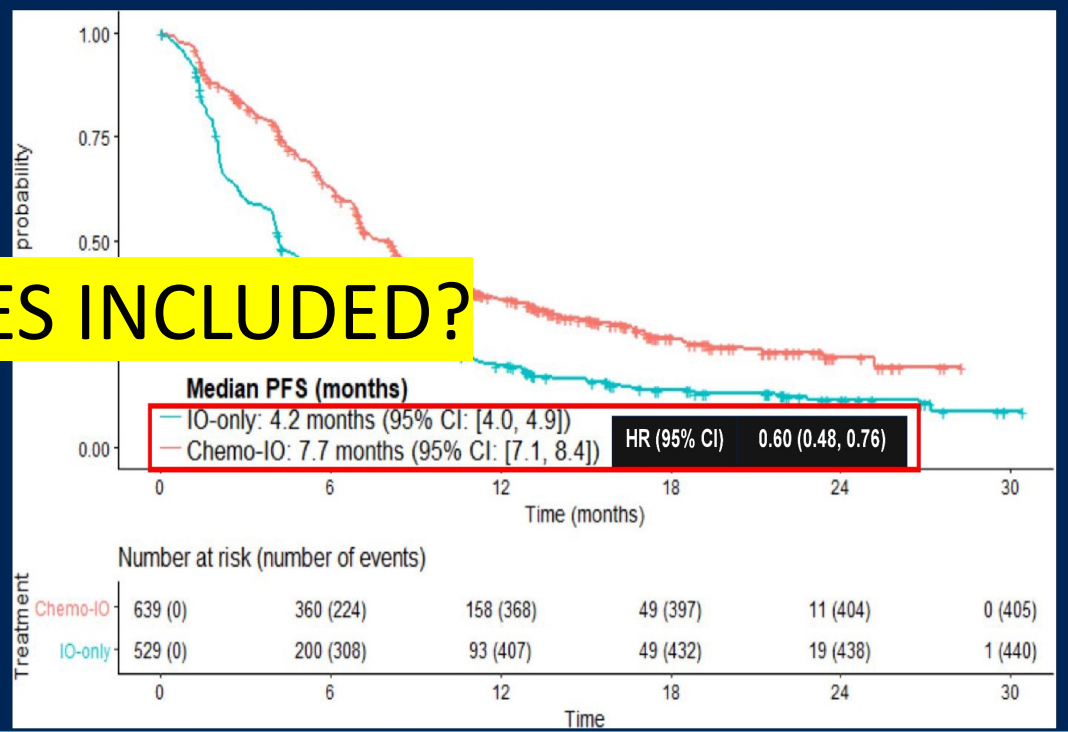
Aguilar EJ et al. *Ann Oncol*. 20

FDA Pooled Analysis

Exploratory OS: NSCLC PDL1 1-49%



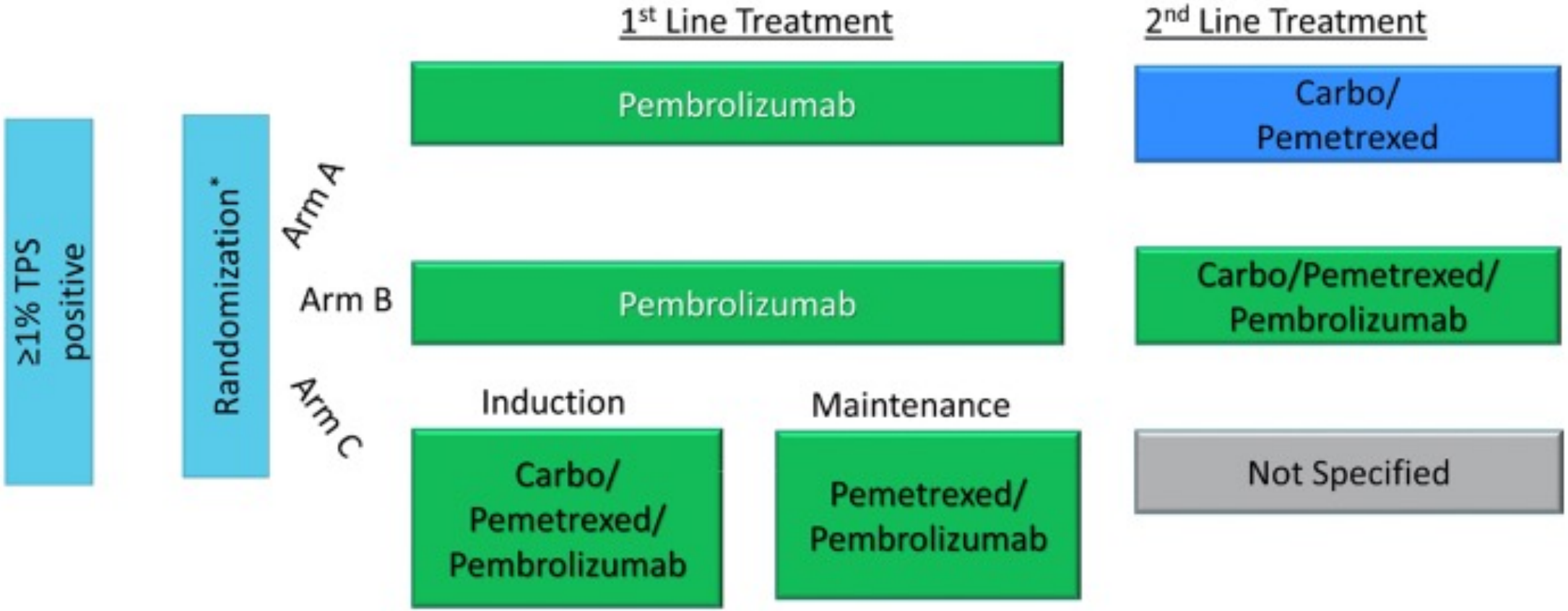
Exploratory PFS: NSCLC PDL1 1-49%



BIAS: ONLY POSITIVE STUDIES INCLUDED?

INSIGNA

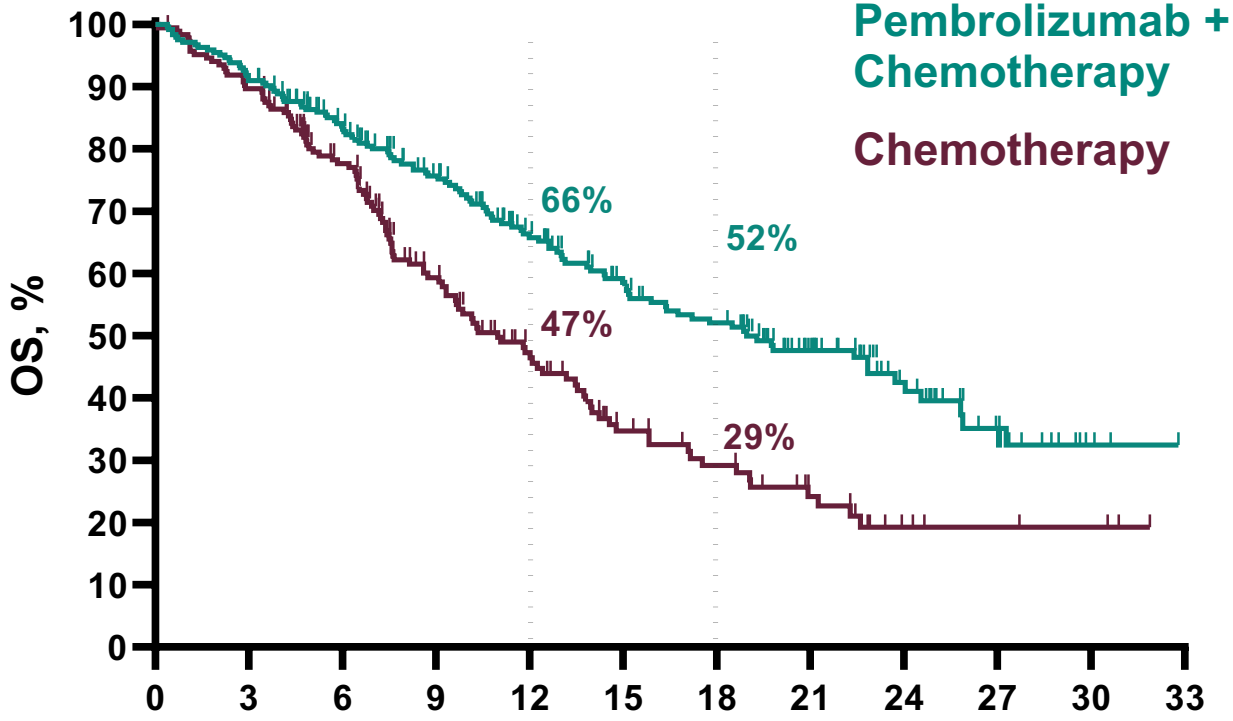
Sequential vs Combination Administration of Pembrolizumab in Advanced NSCLC



SWOG-ECOG collaboration NCTN NCI network (A. Chiang, H. Borghaei)

Overall Survival

Patients Without Tumor PD-L1 Expression (TPS <1%)



	Events, n	HR (95% CI)
Pembrolizumab + Chemotherapy	112	0.56 (0.43–0.73)
Chemotherapy	110	

Median (95% CI) OS

Pembrolizumab + Chemotherapy: 19.0 (15.2–24.0) mo

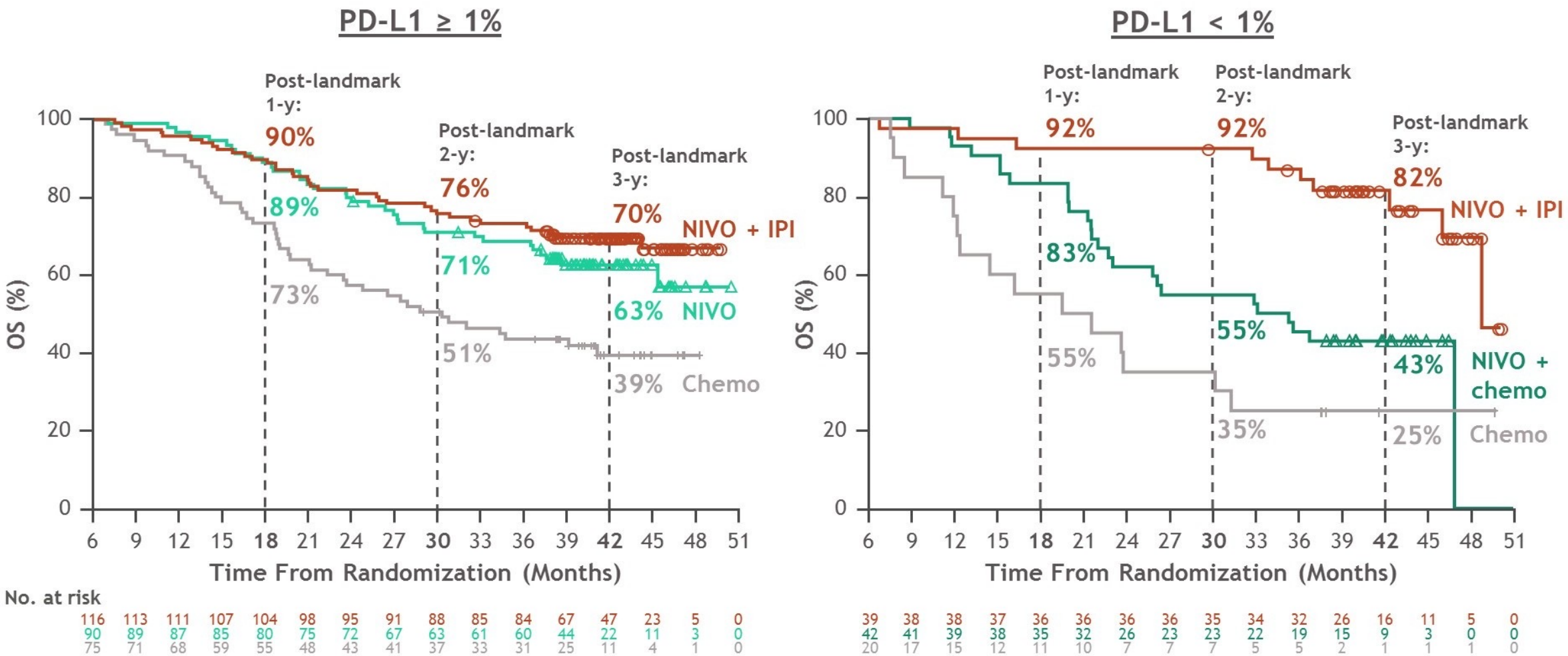
Chemotherapy: 11.0 (9.2–13.5) mo

No. at risk												
Pembrolizumab + chemotherapy	243	221	186	153	117	92	79	49	29	13	2	0
Chemotherapy alone	185	165	127	83	56	34	26	16	7	5	4	1

Borghaei, WCLC 2019

Data cutoff dates: KN021G, December 1, 2017; KN189, September 21, 2018; KN407, April 3, 2018. Pooled analysis

Post-landmark OS in responders (CR or PR) at 6 months[a]



Database lock: February 28, 2020; minimum follow-up for post-landmark OS: 31.7 months. Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), NIVO (240 mg Q2W), and NIVO (360 mg Q3W) plus chemo.
[a]Post-landmark analysis was performed among only patients who were alive at 6 months; CR or PR was based on assessment at 6 months.

CURRENT TREATMENT PARADIGM: Advanced NSCLC (Non-Oncogenic)

PD-L1 < 1%

2 cycles of chemo plus Ipi/Nivo

OR

Chemo plus IO

PD-L1 1-49%

Chemo plus IO

PD-L1 ≥ 50%

Single agent IO

OR

Chemo plus IO

OR

Ipi/Nivo

DOES HISTOLOGY MATTER?

BRIEF REPORT

IASLC

Check for updates

Programmed Death-Ligand 1 Tumor Proportion Score and Overall Survival From First-Line Pembrolizumab in Patients With Nonsquamous Versus Squamous NSCLC

Deborah B. Doroshow, MD, PhD,[a,*] Wei Wei, MD, PhD,[b] Swati Gupta, PhD,[c] Jon Zugazagoitia, MD,[d] Charles Robbins, BS,[e] Blythe Adamson, PhD,[f] David L. Rimm, MD, PhD[e,g,h]

WE NEED TO LEARN MORE ABOUT HISTOLOGY IMPACT

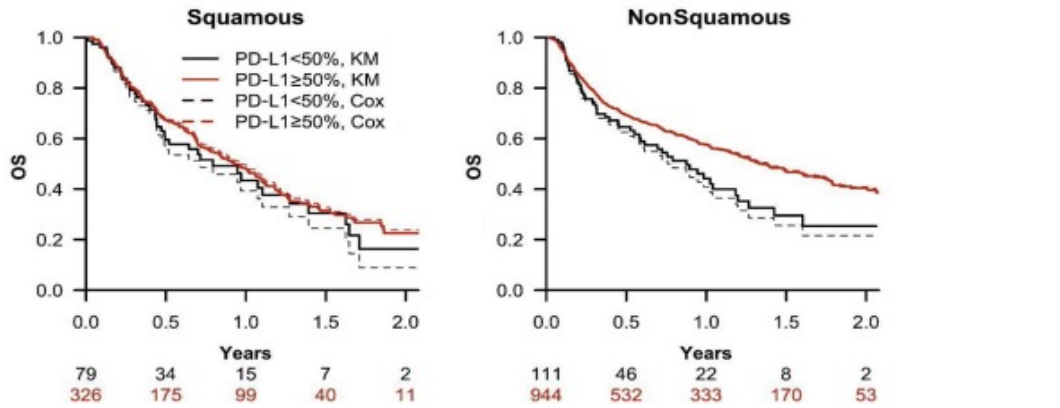
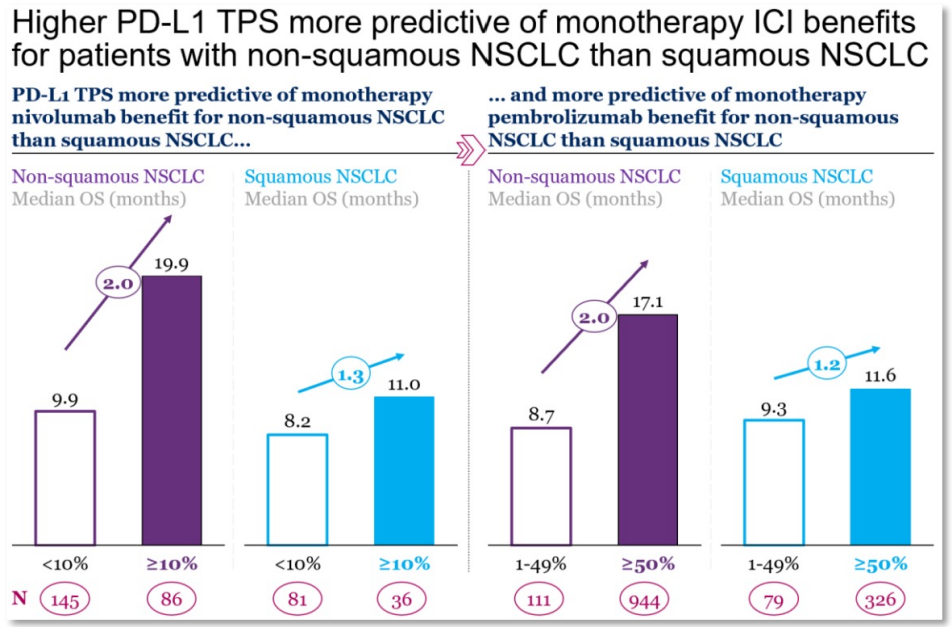


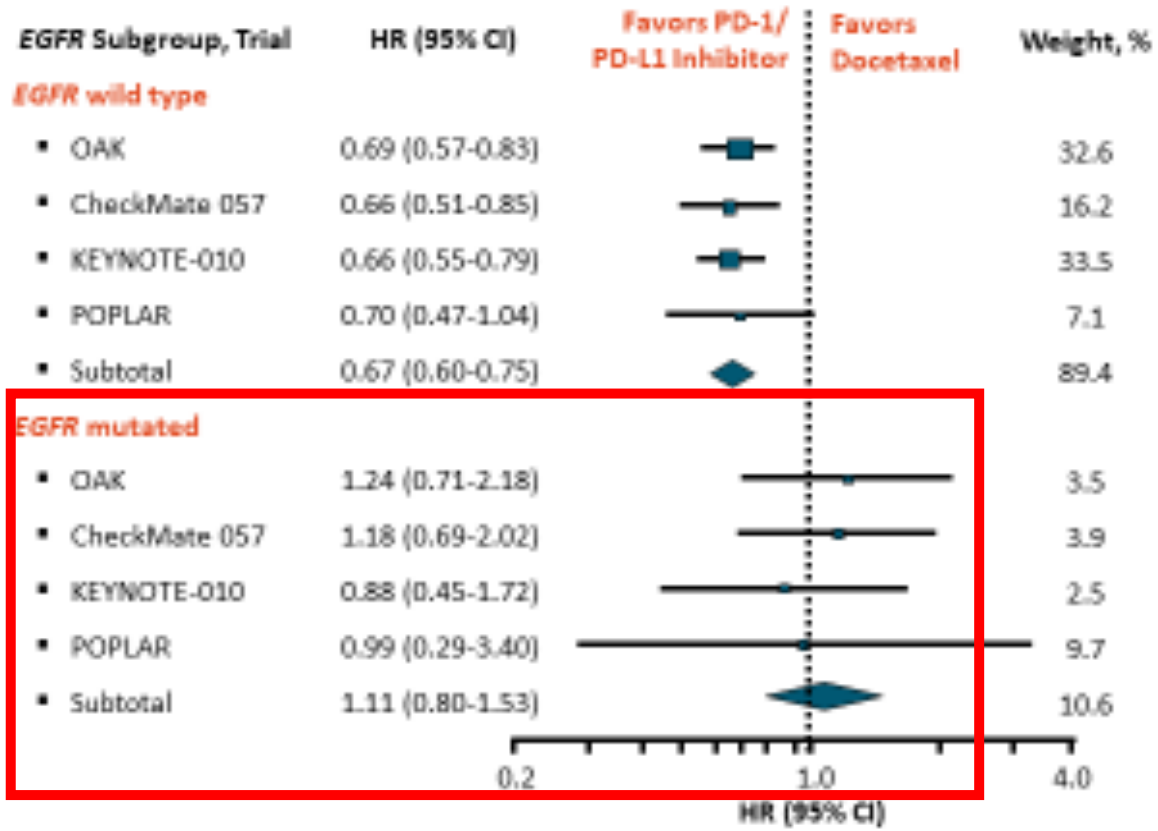
Figure 1. Overall survival for monotherapy ICI by PD-L1 TPS and NSCLC histology



Meshulami et al, Clin Lung Cancer 2023

Specific Genomic Predictors of Lack of Benefit With ICI-Based Therapy in Advanced NSCLC: *EGFR* Mutations

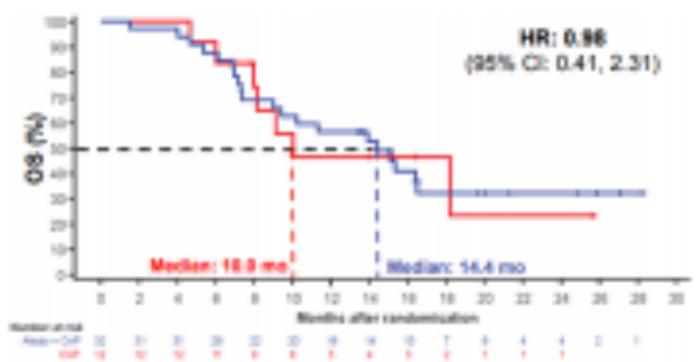
Single-Agent ICI Therapy[1]



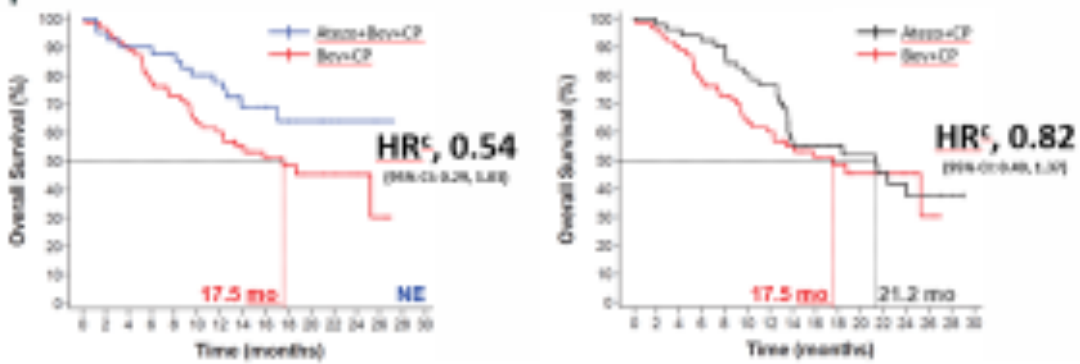
- *EGFR* mutations associated with lack of benefit to single-agent ICI therapy regardless of PD-L1 status

ICI + Chemotherapy[2,3]

IMpower130*



IMpower150*



- *EGFR* mutations associated with lack of benefit to chemo-IO combination therapy

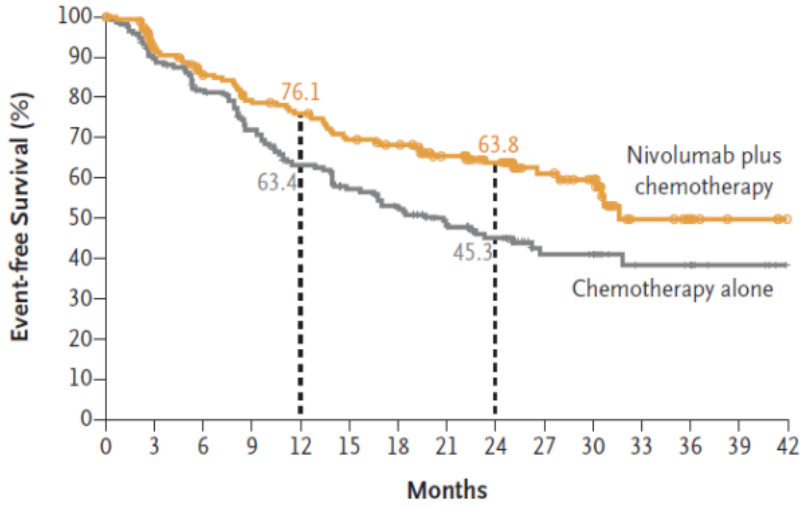
1. Lee. JAMA Oncol. 2018;4:210. 2. Cappuzzo. ESMO 2018. Abstr 2887. 3. Socinski. ASCO 2018. Abstr 9002. **EGFR/ALK+* subgroup.

Slide credit: clinicaloptions.com

Neoadjuvant chemoimmunotherapy-CM 816

Eligibility:
Stage IB (>4 cm)-
IIIA NSCLC (7th Ed)

A

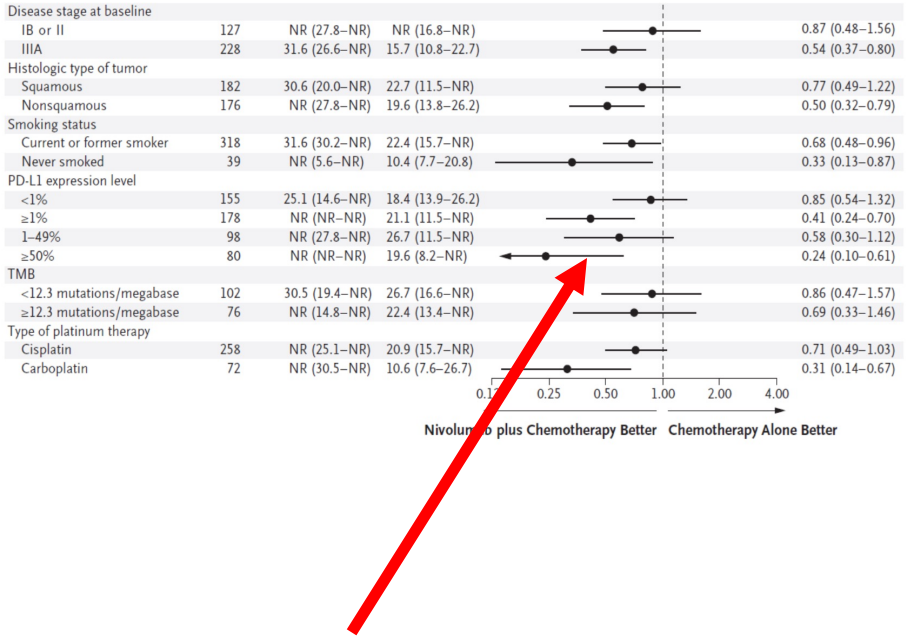


No. at Risk

Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

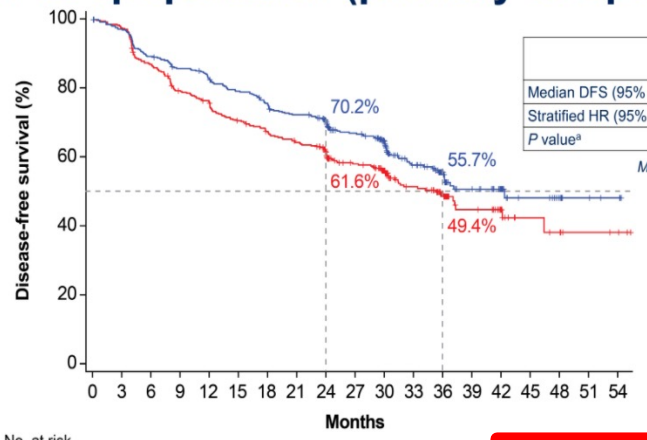


Primary end point EFS and pCR: 24% vs 2.2%

Forde et al, N Engl J Med 2022; 386:1973

IMpower010 : ADJUVANT ATEZOLIZUMB

IMpower010: DFS in the all-randomized stage II-IIIA population (primary endpoint)



	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

Median follow-up: 32.2 mo (range, 0-57.5)

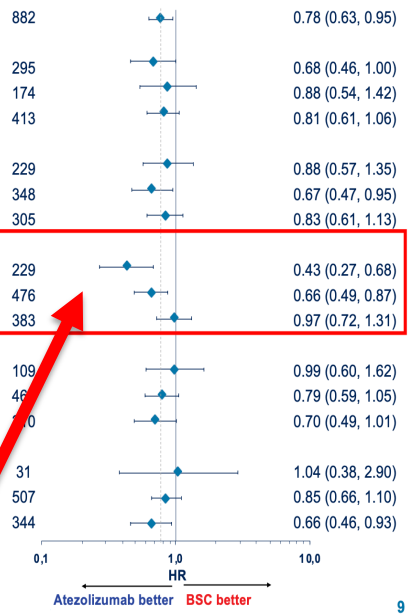
No. at risk

Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48
BSC	440	412	366	331	314	292	277	263	230	182	146	102	71	35

Clinical cutoff: January 21, 2021. [a] Stratified log-rank. [b] Crossed the significance boundary for DFS.

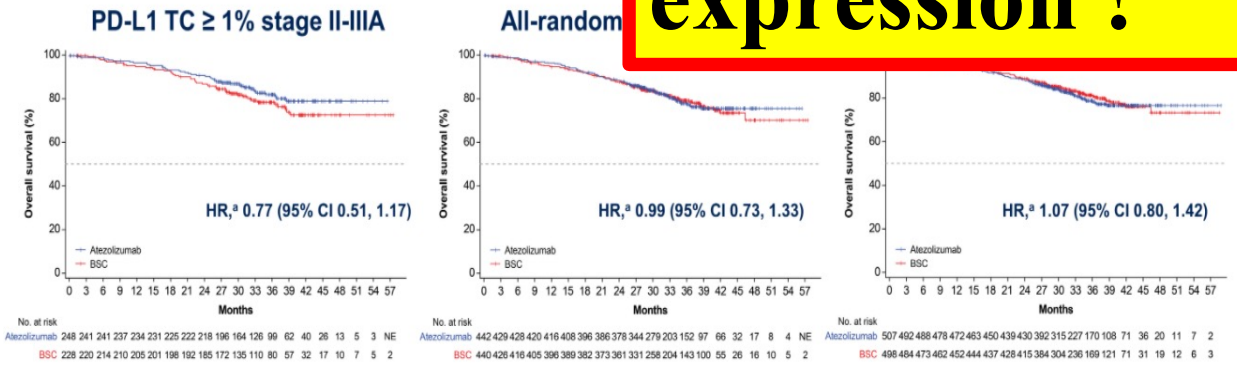
IMpower010: DFS in key subgroups of the all-randomized stage II-IIIA population

Subgroup	N	HR (95% CI)[a]
All patients	882	0.78 (0.63, 0.95)
Age		
<65 y	544	0.79 (0.61, 1.03)
≥65 y	338	0.76 (0.54, 1.05)
Sex		
Male	589	0.76 (0.59, 0.99)
Female	293	0.80 (0.57, 1.13)
Race		
White	631	0.78 (0.61, 1.00)
Asian	227	0.82 (0.55, 1.22)
ECOG PS		
0	491	0.72 (0.55, 0.95)
1	388	0.87 (0.64, 1.18)
Stage		
IIA	295	0.68 (0.46, 1.00)
IIB	174	0.88 (0.54, 1.42)
IIIA	413	0.81 (0.61, 1.06)
Regional lymph node stage (pN)		
N0	229	0.88 (0.57, 1.35)
N1	348	0.67 (0.47, 0.95)
N2	305	0.83 (0.61, 1.13)
SP263 PD-L1 status		
TC≥50%	229	0.43 (0.27, 0.68)
TC≥1%	476	0.66 (0.49, 0.87)
TC<1%	383	0.97 (0.72, 1.31)
***EGFR* mutation status**		
Yes	109	0.99 (0.60, 1.62)
No	46	0.79 (0.59, 1.05)
Unknown	[illegible]	0.70 (0.49, 1.01)
***ALK* rearrangement status**		
Yes	31	1.04 (0.38, 2.90)
No	507	0.85 (0.66, 1.10)
Unknown	344	0.66 (0.46, 0.93)



Adjuvant Immunotherapy: Effect driven by high PD-L1 expression !

IMpower010: early OS data DFS analysis



Wakeele ASCO 21

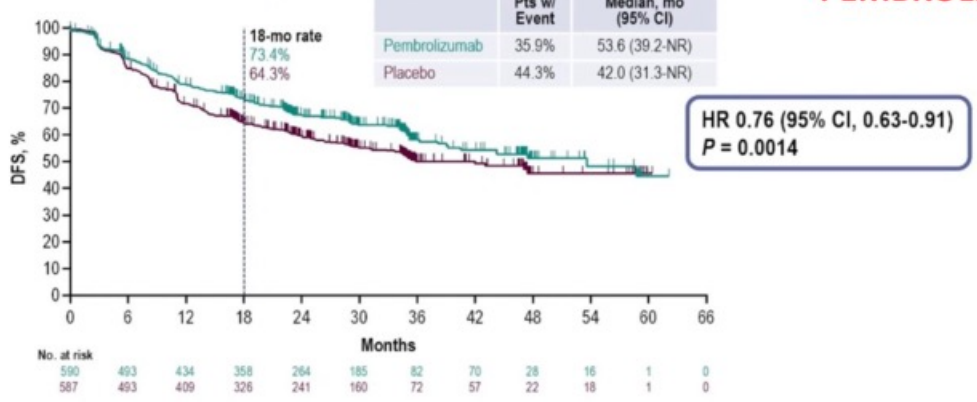
ADJUVANT PEMBROLIZUMAB;NO CORRELATION TO PD-L1

PLENARY

16, 17 & 18 MARCH 2022

DFS, Overall Population

ADJUVANT PEMBROLIZUMAB



	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)

HR 0.76 (95% CI, 0.63-0.91)
P = 0.0014

ESMO VIRTUAL PLENARY

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

AL PLENARY

16, 17 & 18 MARCH 2022

WHAT ABOUT THE PD-L1 NEGATIVES?

PEARLS Trial

PD-L1 TPS		
<1%	195/465	0.78 (0.58-1.03)
1-49%	160/379	0.67 (0.48-0.92)
≥50%	117/333	0.82 (0.57-1.18)

Impower 010

PD-L1 status by SP263				
TC <1%	181/383	36·1 (30·2-N	202/383	37·0 (28·6-NE)
TC ≥1%	248/476	NE (36·1-	228/476	35·3 (29·0-NE)
TC 1-49%	133/247	32·8 (-NE)	114/247	31·4 (24·0-NE)
TC ≥50%	115/229	NE ·3-NE)	114/229	35·7 (29·7-NE)

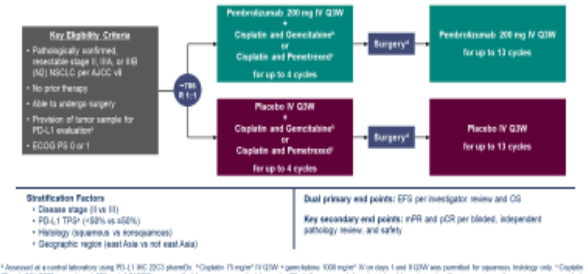
0·97 (0·72-1·31)
0·66 (0·49-0·87)
0·87 (0·60-1·26)
0·43 (0·27-0·68)

Felip E et al, Lancet 2021, Paz-Ares L et al ESMO Plenary 2022

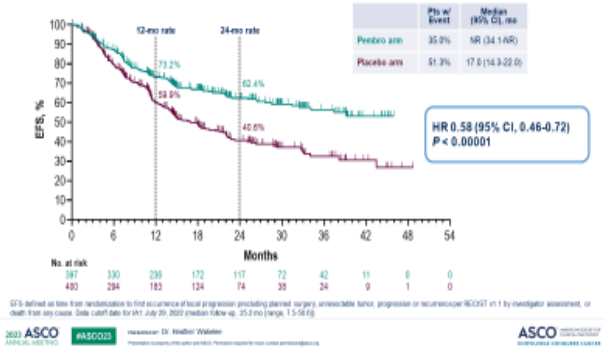
ESMO VIRTUAL PLENARY

ADJUVANT PEMBROLIZUMAB+ CHEMOTHERAPY: RESECTABLE NSCLC

KEYNOTE-671 Study Design
Randomized, Double-Blind, Phase 3 Trial

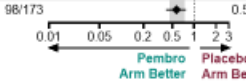


Event-Free Survival

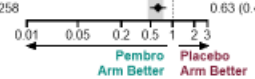


Event-Free Survival in Subgroups

Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	139/397	205/400	0.58 (0.46-0.72)
Age			
<65 y	74/221	113/214	0.53 (0.39-0.71)
≥65 y	65/176	92/186	0.64 (0.46-0.88)
Sex			
Female	31/118	55/116	0.44 (0.28-0.68)
Male	108/279	150/284	0.63 (0.49-0.80)
Race			
White	85/250	123/239	0.54 (0.41-0.72)
All others	46/134	70/145	0.62 (0.42-0.89)
Geographic region			
East Asia	43/123	57/121	0.66 (0.45-0.99)
Not east Asia	96/274	148/279	0.54 (0.41-0.69)
Smoking status			
Current	37/96	57/103	0.52 (0.34-0.78)
Former	84/247	128/250	0.57 (0.43-0.75)
Never	18/54	20/47	0.68 (0.36-1.30)
Histology			
Nonsquamous	73/226	107/227	0.58 (0.43-0.78)
Squamous	66/171	98/173	0.57 (0.41-0.77)



Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	139/397	205/400	0.58 (0.46-0.72)
Pathologic stage			
II	34/118	48/121	0.65 (0.42-1.01)
IIIA	80/217	124/225	0.54 (0.41-0.72)
IIIB	25/62	33/54	0.52 (0.31-0.88)
pN status			
pN0	51/148	70/142	0.57 (0.40-0.82)
pN1	25/81	33/71	0.60 (0.36-1.01)
pN2	63/168	102/187	0.57 (0.42-0.78)
PD-L1 TPS			
<1%	63/138	80/151	0.77 (0.55-1.07)
1-49%	44/127	62/115	0.51 (0.34-0.75)
≥50%	32/132	63/134	0.42 (0.28-0.65)
EGFR mutation			
No	31/111	64/127	0.48 (0.31-0.74)
Yes	1/14	10/19	0.09 (0.01-0.74)
Unknown	107/272	131/254	0.64 (0.49-0.83)
***ALK* translocation**			
No	29/104	76/133	0.41 (0.26-0.62)
Unknown	106/281	128/258	0.63 (0.49-0.82)



ie prespecified analysis plan, subgroups with <30 participants are excluded from the forest plot. Subgroups for stage IIIA and IIIB and pN status were post hoc; all other subgroups were prespecified.
cutoff date for IA1: July 29, 2022.

AEGEN-STUDY: Perioperative Durvalumab

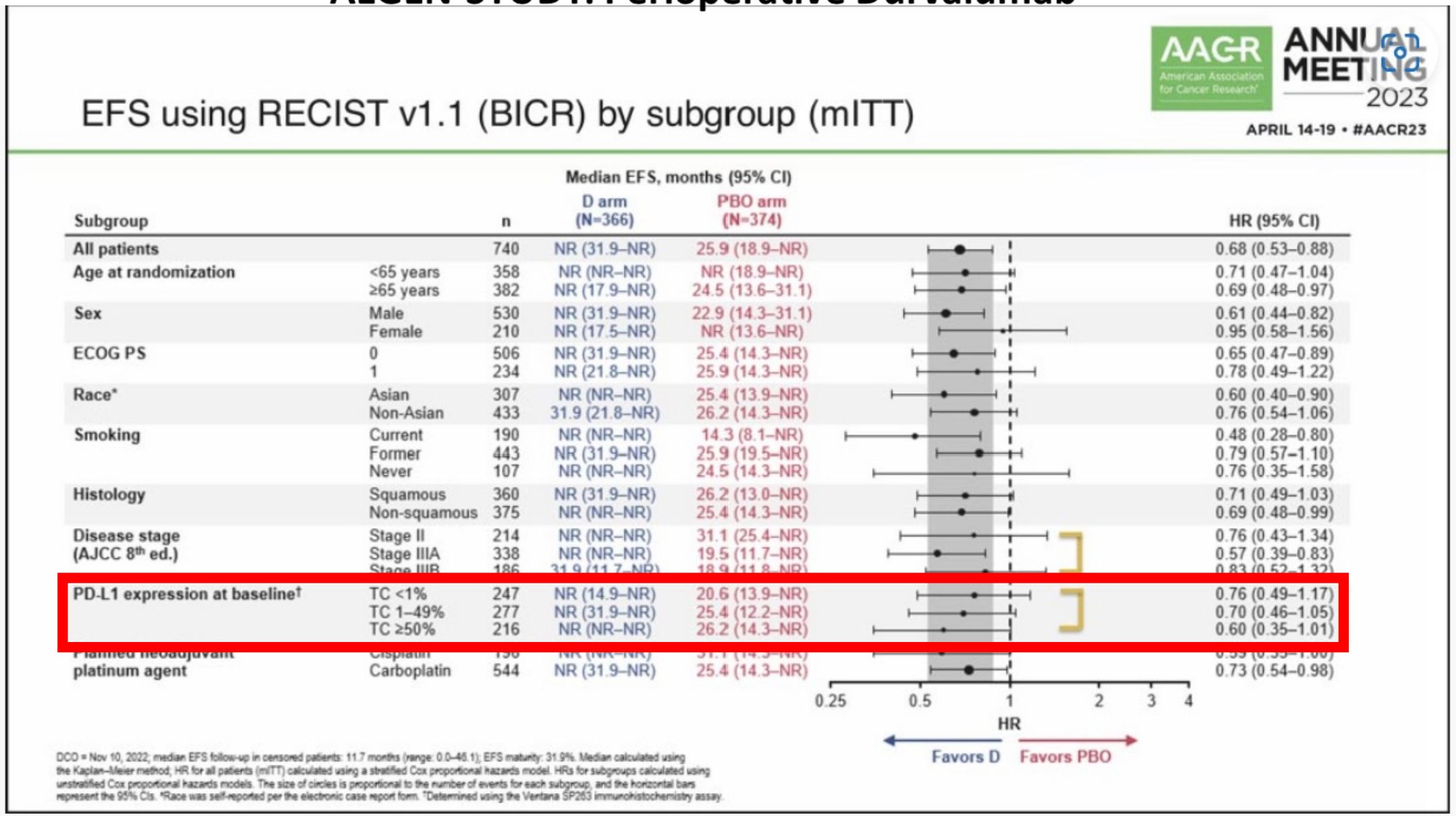
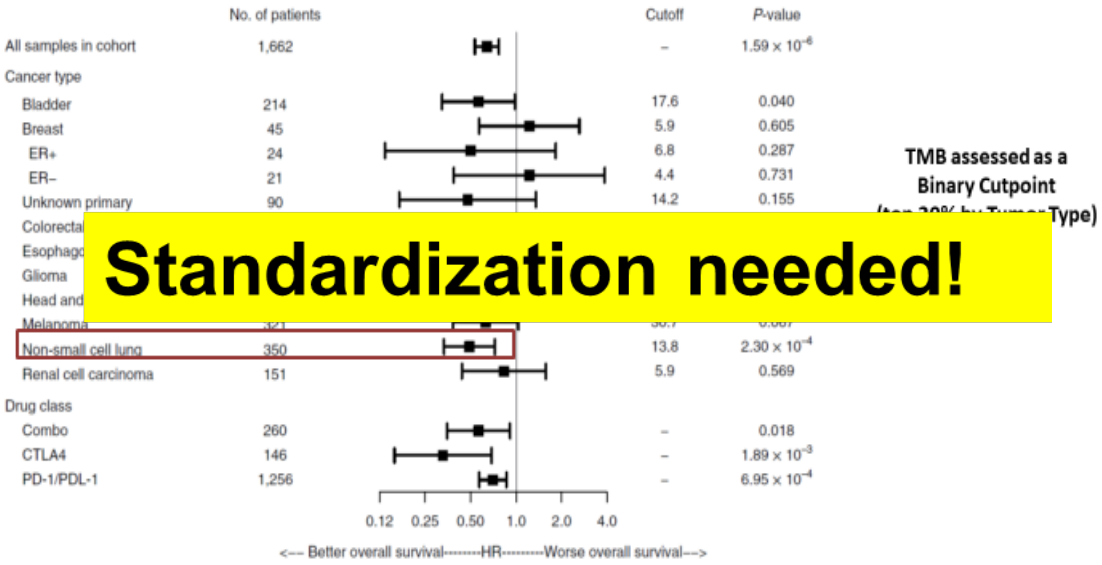


Fig. 3

Heymach J et al; AACR 2023

Association of TMB with OS in patients with various types of cancer treated with CPIs (MSK-IMPACT)



Standardization needed!

Samstein, et. al., Nature Genetics 2019

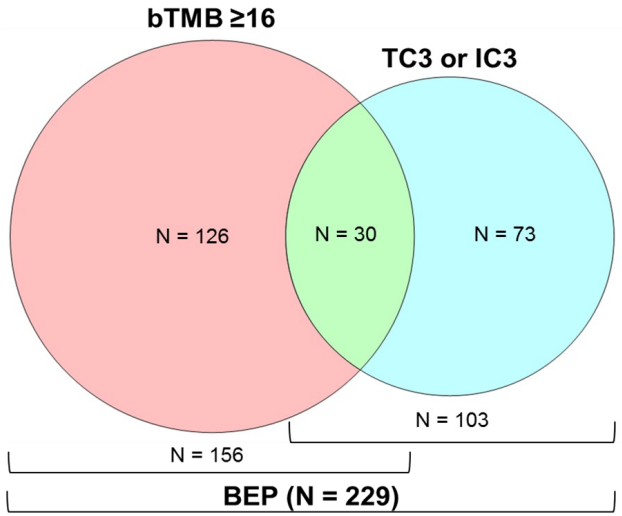
TMB Challenges

- **Only a minority of mutations produce neoantigens**
- TMB cut-off values require validation?

Reference	Sequencing Type	Threshold
Rizvi, Science 2015	WES	5 mut/Mb Nonsynonymous missense
Kowanetz, ESMO 2017		10 mut/Mb
Carbone, NEJM 2017	WES	7 mut/Mb Nonsynonymous missense
Rizvi, JCO 2018	IMPACT-MSKCC	7 mut/Mb Nonsynonymous
Hellmann, NEJM 2018		10 mut/Mb
Velcheti, ASCO 2018		16 mut/Mb

Factors to standardize:
- sequencing depth, mutations included, filtering process

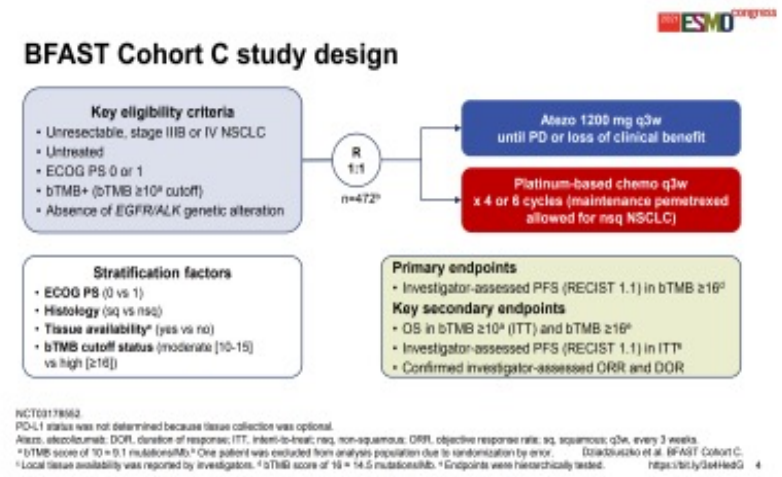
Tumor mutational burden in blood (bTMB) is associated with Atezolizumab efficacy in 2nd-Line+ NSCLC (POPLAR & OAK Trials)

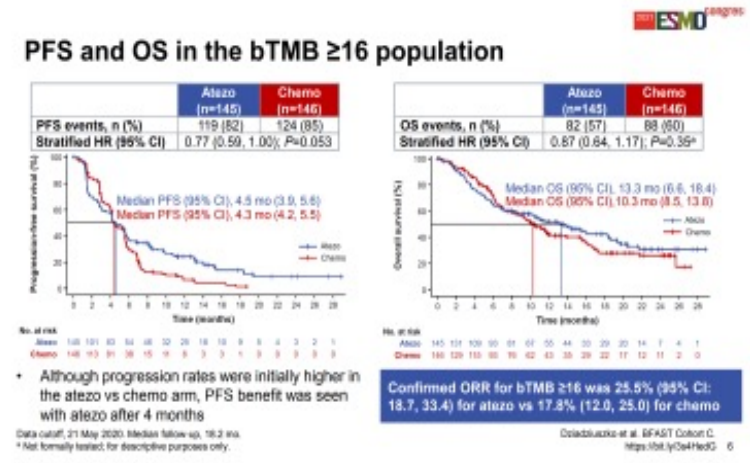


	PFS HR (95% CI)
bTMB ≥16	0.64 (0.46, 0.91)
TC3 or IC3	0.62 (0.41, 0.93)
bTMB ≥16 + TC3 or IC3	0.38 (0.17, 0.85)

Gandara DR, et al.: ESMO17 & NatureMed 2018

PROSPECTIVE STUDY OF BLOOD-TMB: "NEGATIVE"





R. Dziadziuszko et al.
J Thorac Oncol 16,(12); 2040-2050, 2023

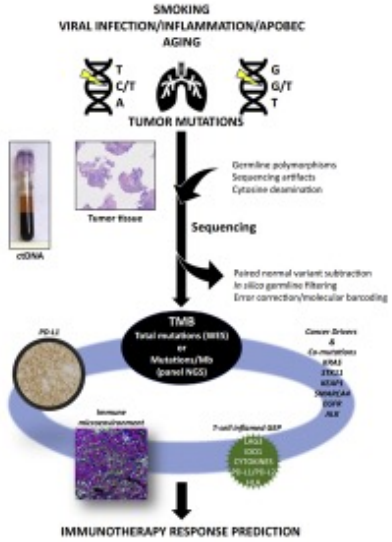
REVIEW ARTICLE

IASLC

1418 Sholl et al Journal of Thoracic Oncology Vol. 15 No. 9

The Promises and Challenges of Tumor Mutation Burden as an Immunotherapy Biomarker: A Perspective from the International Association for the Study of Lung Cancer Pathology Committee

Lynette M. Sholl, MD,[a,b,*] Fred R. Hirsch, MD, PhD,[c,d] David Hwang, MD, PhD,[e] Johan Botling, MD, PhD,[f] Fernando Lopez-Rios, MD, PhD, FIAC,[g] Lukas Bubendorf, MD,[h] Mari Mino-Kenudson, MD,[i] Anja C. Roden, MD,[j] Mary Beth Beasley, MD,[d] Alain Borczuk, MD,[k] Elisabeth Brambilla, MD, PhD,[l] Gang Chen, MD,[m] Teh-Ying Chou, MD, PhD,[n] Jin-Haeng Chung, MD, PhD,[o] Wendy A. Cooper, MD,[p] Sanja Dacic, MD, PhD,[q] Sylvie Lantuejoul, MD, PhD,[l,r] Deepali Jain, MD,[s] Dongmei Lin, MD,[t] Yuko Minami, MD, PhD,[u] Andre Moreira, MD, PhD,[k] Andrew G. Nicholson, MD,[v,w] Masayuki Noguchi, MD,[x] Mauro Papotti, MD,[y] Giuseppe Pelosi, MD,[z,aa] Claudia Poleri, MD,[bb] Natasha Rekhtman, MD, PhD,[cc] Ming-Sound Tsao, MD,[dd] Erik Thunnissen, MD, PhD,[ee] William Travis, MD,[cc] Yasushi Yatabe, MD, PhD,[ff] Akihiko Yoshida, MD, PhD,[ff] Jillian B. Daigneault, PhD,[gg] Ahmet Zehir, PhD,[bb] Solange Peters, MD, PhD,[hh] Ignacio I. Wistuba, MD,[ii] Keith M. Kerr, MD,[jj] John W. Longshore, PhD[kk]



TMB: COMPLEX!

REFINEMENTS NEEDED!

J Thorac Oncol 15 (9); 1409-24. 2020

Lung-MAP Composite Signature for Immune Checkpoint Inhibitor (ICI) Efficacy in Advanced Squamous Cell Lung Cancer (SCC)

SWOG

David R. Gandara, Xing Hua, Khaled Tolba, David Fabrizio, Lee Albacker, Sarah Gaffey, Meagan Montesion, Geoff Oxnard, Stacey Adam, Fred R. Hirsch, Karen Kelly, Roy Herbst, Michael LeBlanc, Michael Wu, Mary Redman, David Kazero

ABSTRACT

Methods

RESULTS

COMPOSITE BIOMARKER SCORE: (PD-L1/TMB/HLA) CORRELATES WITH BETTER IO-OUTCOME (Gandara et al. SITC 2022)

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

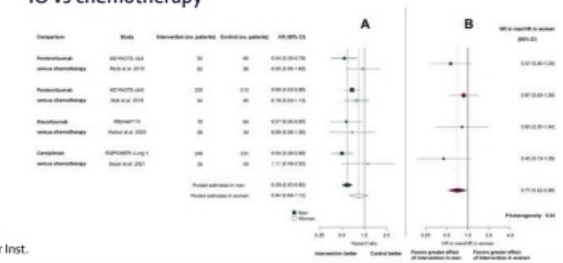
Adaptive immunity: Enhanced in females[1]

- 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)

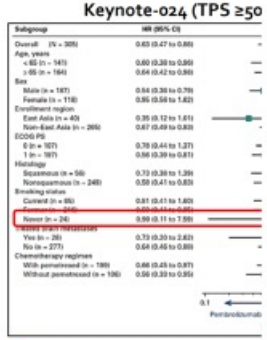
Meta-analyses: OS results for lung cancer patients receiving IO vs chemotherapy[2]



1. Vavalà T, et al. Int J Mol Sci. 2021;22:11942. 2. Condorti F, et al. J Natl Cancer Inst.

The Problem of Never Smoker

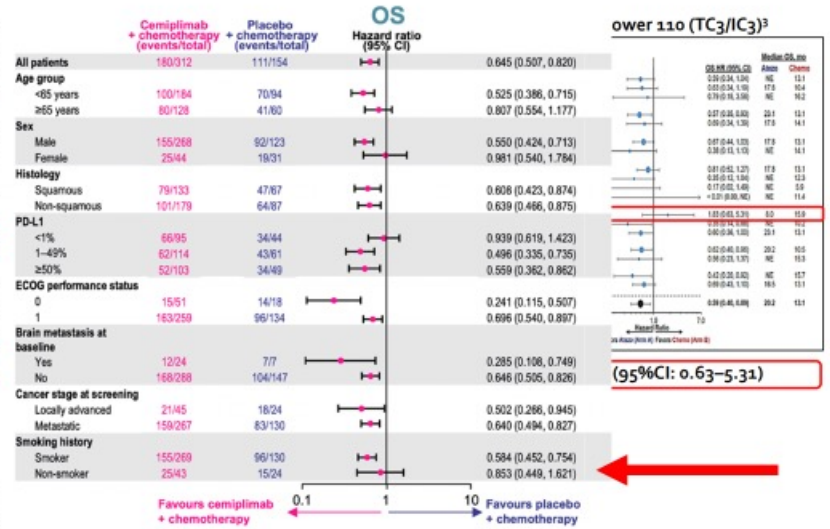
Keynote-024 (TPS ≥50



HR, 0.9 (95%CI: 0.11–7

CI, confidence interval; HR, hazard ratio; IC, imr

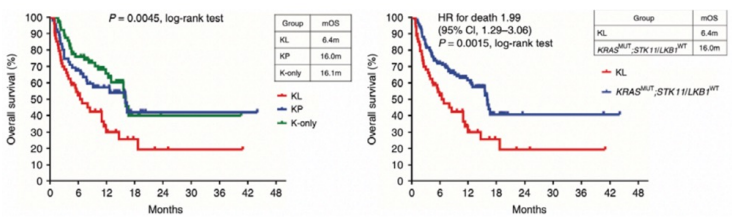
1. Reck M et al, *J Clin Oncol.* 2019;37:537–46. 2. I

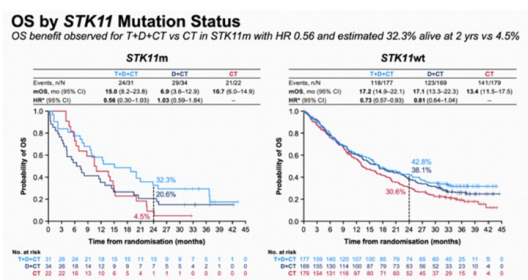


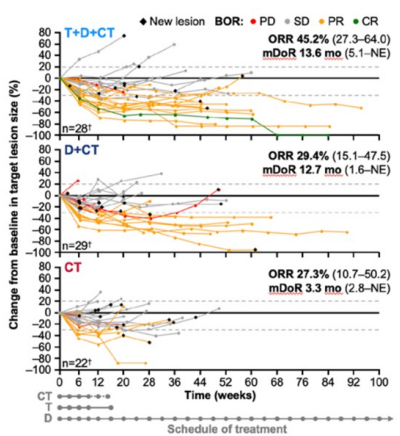
ower 110 (TC_3/IC_3)[3]

(95%CI: 0.63–5.31)

Impact of immune-modulating mutations







Skoulidis F et al, *Cancer Discovery*, 2018, Peters WCLC 2023

CONCLUSIONS

PD-L1 Assay validated an[illegible] utcome, particularly in <u>advanced NSCLC</u>.

The use of PD-L1 express[illegible] tting more <u>unclear</u>!

<u>Poor IO response/outcom</u>[illegible] on 20 molecular "drivers", Females, Never[illegible] 91

TMB

THANKS; See you in NYC!