Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

“Coke or Pepsi”: How to Decide on First-Line Treatment for Metastatic NSCLC Without Driver Mutations?

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ACI, Lung Cancer, 2022

#LearnACI

Disclosures

- **Research Support (Clinical Trials):**
  - Millennium, Merck/Celgene, BMS/Lilly
- **Advisory Board/Consultant:**
  - BMS, Lilly, Genentech, Celgene, Pfizer, Merck, EMD-Serono, Boehringer Ingelheim, Astra Zeneca, Novartis, Genmab, Regeneron, BioNTech, Cantargia AB, Amgen, Abbvie, Axiom, PharmaMar, Takeda, Huya Bio, GLG, Daiichi, Guardant, Natera, Oncocyte, Beigene, iTeo
- **Scientific Advisory Board:**
  - Sonnetbio (Shares), Inspira (Rgenix, Shares), Nucleai (Shares)
- **Data and Safety Monitoring Board:**
  - University of Pennsylvania, CAR T Program, Takeda, Incyte, Novartis
- **Employment:**
  - Fox Chase Cancer Center

I will be discussing non-FDA approved indications during my presentation.

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It is good to have options!

- Treatment landscape for metastatic NSCLC is a lot different now
- For tumors without a molecular driver:

PD-L1 ≥50%
• Checkpoint inhibitor alone • Chemotherapy plus checkpoint inhibitor • I-O/I-O combination (?)

PD-L1 <50%
• Checkpoint inhibitor alone (?) • Chemotherapy plus checkpoint inhibitor • I-O/I-O combination

The Benefit of I-O Monotherapy Is Established in NSCLC With High PD-L1 Expression, But Needs Remain for PD-L1 Low Expressors

Outcomes in NSCLC With High PD-L1 Expression

Trial	Treatment	PD-L1	ORR	Median PFS	Median OS
KEYNOTE-024[1,2]	Pembrolizumab (n=154)	≥50%	44.8%	10.3 mo	30 mo
IMpower110[3]	Atezolizumab (n=107)	TC3; IC3	38.3%	8.1 mo	20.2 mo
EMPOWER-Lung 1[4,5]	Cemiplimab (n=283)	≥50%	39.2%	8.2 mo	NR

Outcomes in NSCLC With Lower or Unselected PD-L1 Expression

Trial	Treatment	PD-L1	ORR	Median PFS	Median OS
CheckMate 026[6]	Nivolumab (n=211)	≥5%	26%	4.2 mo	14.4 mo
CheckMate 017[7]	Nivolumab (n=135)	Any	20%	3.5 mo	9.2 mo
CheckMate 057[8]	Nivolumab (n=292)	Any	19%	2.3 mo	12.2 mo
KEYNOTE-042[9]	Pembrolizumab (n=637)	≥1%	27%	6.5 mo	16.7 mo
IMpower110[3]	Atezolizumab (n=277)	TC1/2/3 IC1/2/3	29%	5.7 mo	17.5 mo
OAK[10]	Atezolizumab (n=425)	Any	15%	2.8 mo	13.8 mo
POPLAR[11]	Atezolizumab (n=144)	Any	15%	2.7 mo	12.6 mo

IC = tumor-infiltrating immune cell; I-O = immuno-oncology; NR = not reported; NSCLC = non–small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival; TC = tumor cell.

1. Reck M et al. *N Engl J Med*. 2016;375:1823-1833; 2. Reck M et al. *J Clin Oncol*. 2019;37:537-546; 3. Spigel D et al. ESMO 2019. Abstract 6256. 5; 4. Sezer A et al. ESMO 2020. Abstract LBA52; 5. Sezer A et al. *Lancet*. 2021;397:592-604; 6. Carbone DP et al. *N Engl J Med*. 2017;376:2415-2426; 7. Brahmer J et al. *N Engl J Med*. 2015;373:123-135; 8. Borghaei H et al. *N Engl J Med*. 2015;373:1627-1639; 9. Mok TSK et al. *Lancet*. 2019;393:1819-1830; 10. Fehrenbacher L et al. *J Thorac Oncol*. 2018;13:1156-1170; 11. Fehrenbacher L et al. *Lancet*. 2016;387:1837-1846.

Single Agent PD-(L)-1 Inhibitors

PD-L1 High Group

KEYNOTE-024 5-Year Survival Update: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced NSCLC

J. Brahmer, ESMO 2020

Key eligibility criteria

- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* tranlocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

R (1:1)
N = 305

Pembrolizumab
200 mg IV Q3W
(2 years)

Platinum-Doublet Chemotherapy
(4-6 cycles)

PD[a]

Pembrolizumab
200 mg Q3W
for 2 years

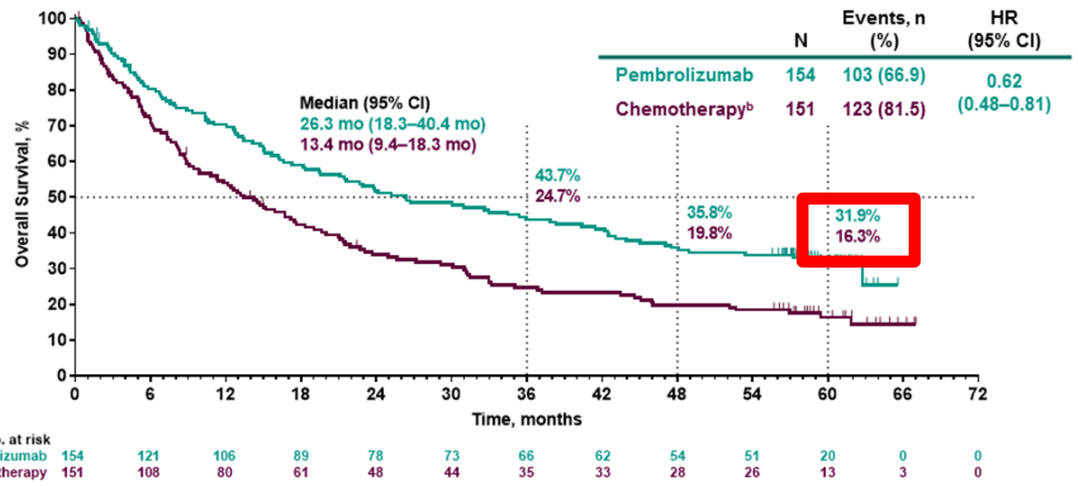
Key endpoints

- Primary: Progression-free survival (PFS) (RECIST v1.1 per blinded, independent central review)
- Secondary: OS, ORR, safety
- Exploratory: Duration of response (DoR)

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

J Brahmer. ESMO 2020

Overall Survival[a]



[a]ITT population.
[b]Effective crossover rate from chemotherapy to anti–PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-[L]1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-[L]1 therapy). Data cutoff: June 1, 2020.

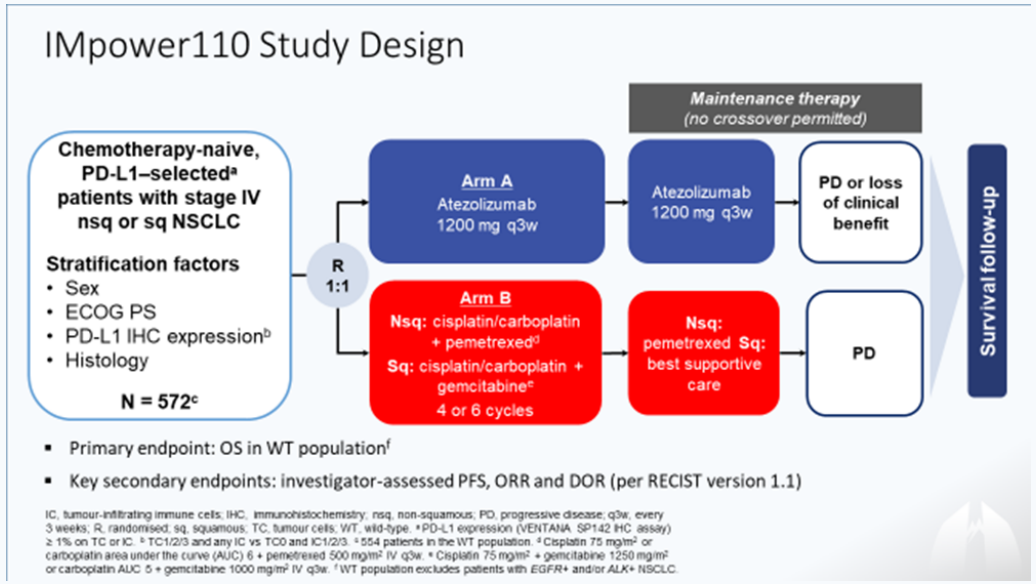
J Brahmer. ESMO 2020

Baseline Characteristics

Characteristic	Pembrolizumab N = 154	Chemotherapy N = 151	35 Cycles (2 Years) of Pembrolizumab N = 39[a]	Second Course of Pembrolizumab N = 12[b]
Age, y, median (range)	64.5 (33–90)	66.0 (38–85)	61.0 (43–80)	60.0 (43–77)
Male	92 (59.7)	95 (62.9)	25 (64.1)	8 (66.7)
ECOG PS 1	99 (64.3)	98 (64.9)	23 (59.0)	9 (75.0)
East Asian enrollment site	21 (13.6)	19 (12.6)	8 (20.5)	3 (25.0)
Squamous histology	29 (18.8)	27 (17.9)[c]	2 (5.1)	1 (8.3)
Current/former smoker	149 (96.8)	132 (87.4)	37 (94.9)	12 (100.0)
Treated brain metastases	18 (11.7)	10 (6.6)	9 (23.1)	1 (8.3)
Prior neoadjuvant therapy	3 (1.9)	1 (0.7)	0	0
Prior adjuvant therapy	6 (3.9)	3 (2.0)	0	0

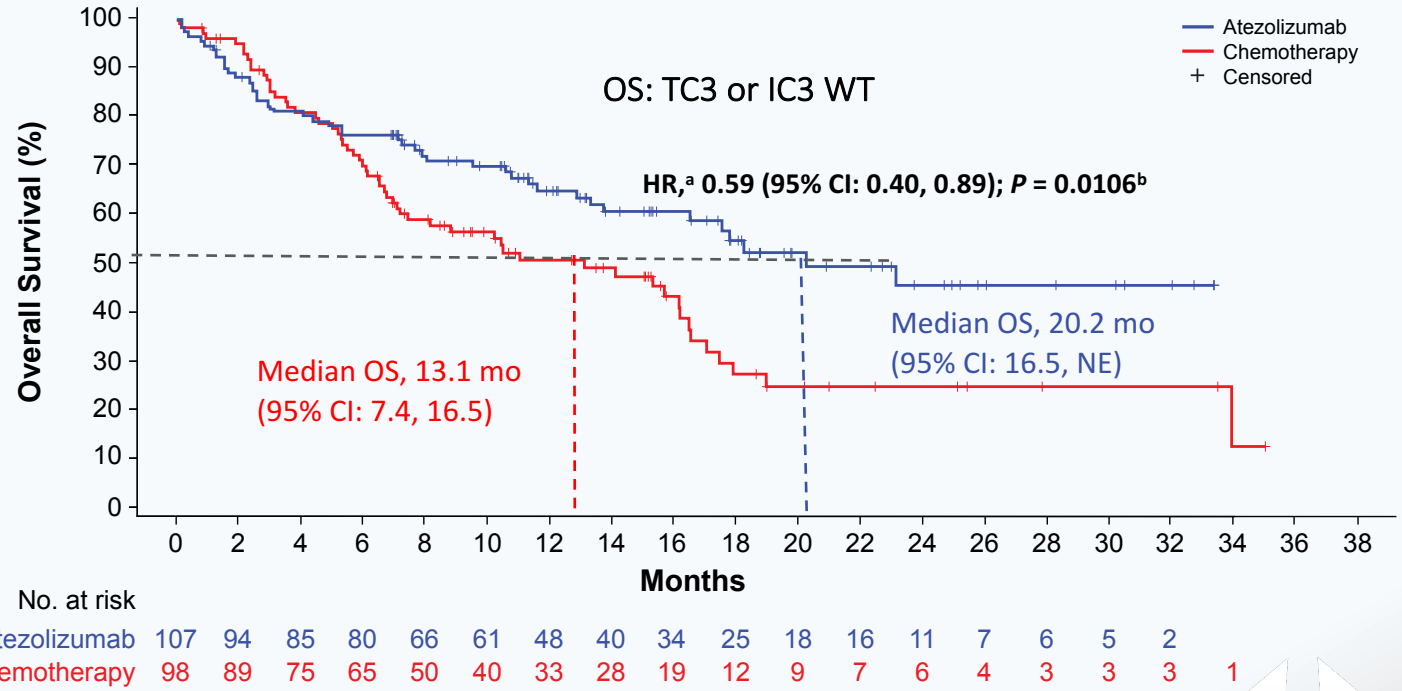
[a]Includes only those patients initially allocated to pembrolizumab who received 35 cycles (2 years) of pembrolizumab according to actual exposure assessment. [b]Includes only those patients initially allocated to pembrolizumab who received a second course of pembrolizumab therapy according to actual exposure assessment. [c]Includes patients with squamous cell carcinoma and poorly differentiated squamous cell carcinoma. Data in table are n (%), unless otherwise noted. Data cutoff: June 1, 2020.

PD-L1 High Groups



IC, tumour-infiltrating immune cells; IHC, immunohistochemistry; nsq, non-squamous; PD, progressive disease; q3w, every 3 weeks; R, randomised; sq, squamous; TC, tumour cells; WT, wild-type. [a] PD-L1 expression (VENTANA SP142 IHC assay) ≥ 1% on TC or IC. [b] TC1/2/3 and any IC vs TC0 and IC1/2/3. [c] 554 patients in the WT population. [d] Cisplatin 75 mg/m² or carboplatin area under the curve (AUC) 6 + pemetrexed 500 mg/m² IV q3w. [e] Cisplatin 75 mg/m² + gemcitabine 1250 mg/m² or carboplatin AUC 5 + gemcitabine 1000 mg/m² IV q3w. [f] WT population excludes patients with *EGFR*+ and/or *ALK*+ NSCLC.

Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo OS (95% CI), %	76.3 (68.2, 84.4)	70.1 (60.8, 79.4)
12-mo OS (95% CI), %	64.9 (55.4, 74.4)	50.6 (40.0, 61.3)

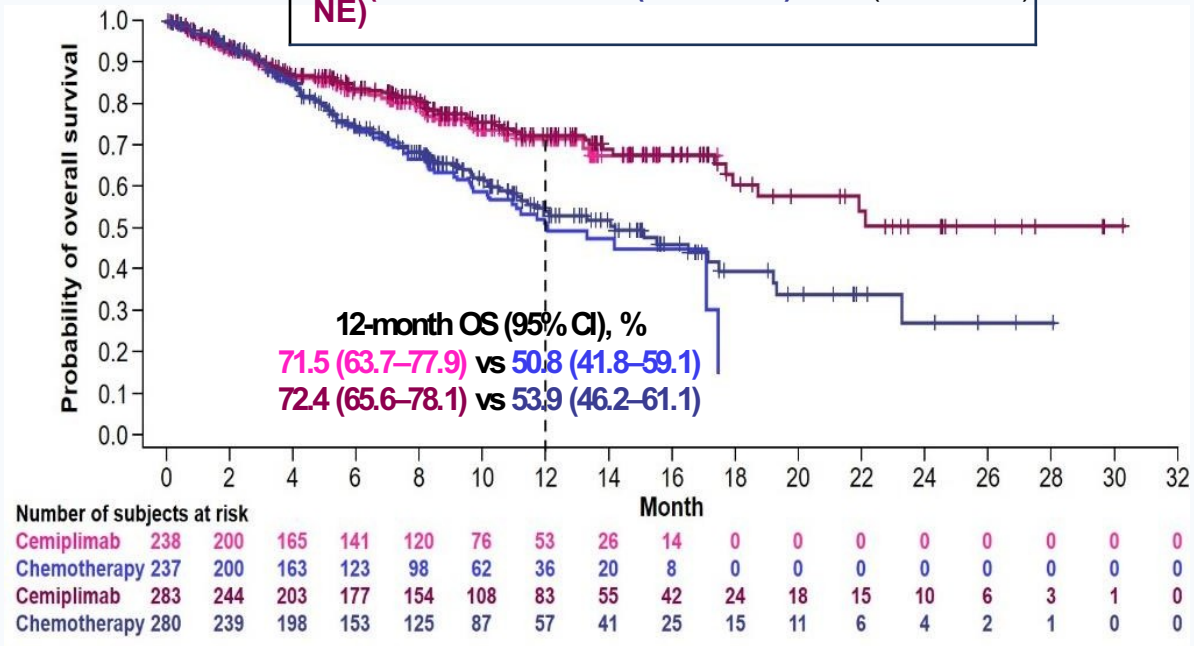


Spigel, Impower 110, Interim OS, ESMO, 2019

EMPOWER-Lung 1: Cemiplimab Monotherpay PD-L1 ≥ 50%
Primary Outcomes were Similar Between the N=475 and N=563 Populations

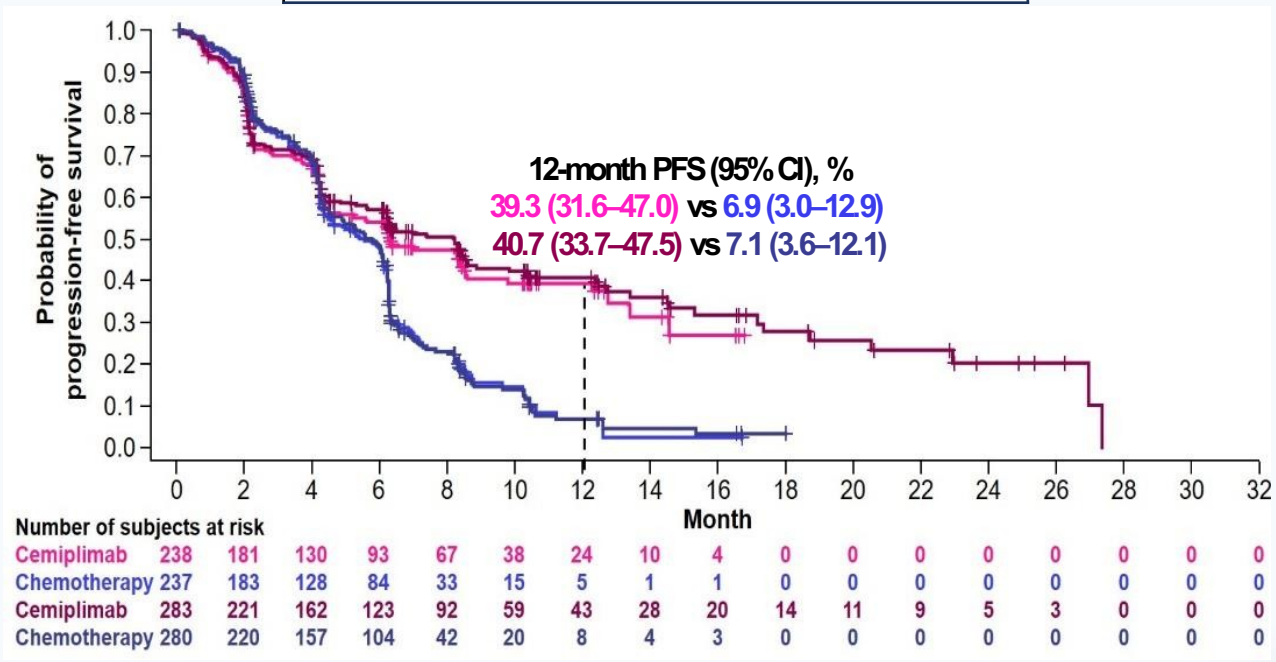
OS

Median, months (95% CI)			HR (95% CI)
NR (NE–NE)	vs	12.1 (10.2–17.5)	0.57 (0.40–0.80)
NR (17.9–NE)	vs	14.2 (11.2–17.5)	0.57 (0.42–0.77)



PFS

Median, months (95% CI)			HR (95% CI)
6.3 (4.5–8.5)	vs	5.6 (4.3–6.2)	0.60 (0.47–0.77)
8.2 (6.1–8.8)	vs	5.7 (4.5–6.2)	0.54 (0.43–0.68)



Cemiplimab (N=475)
Cemiplimab (N=563)
Chemotherapy (N=475)
Chemotherapy (N=563)

CI, confidence interval; HR, hazard ratio; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

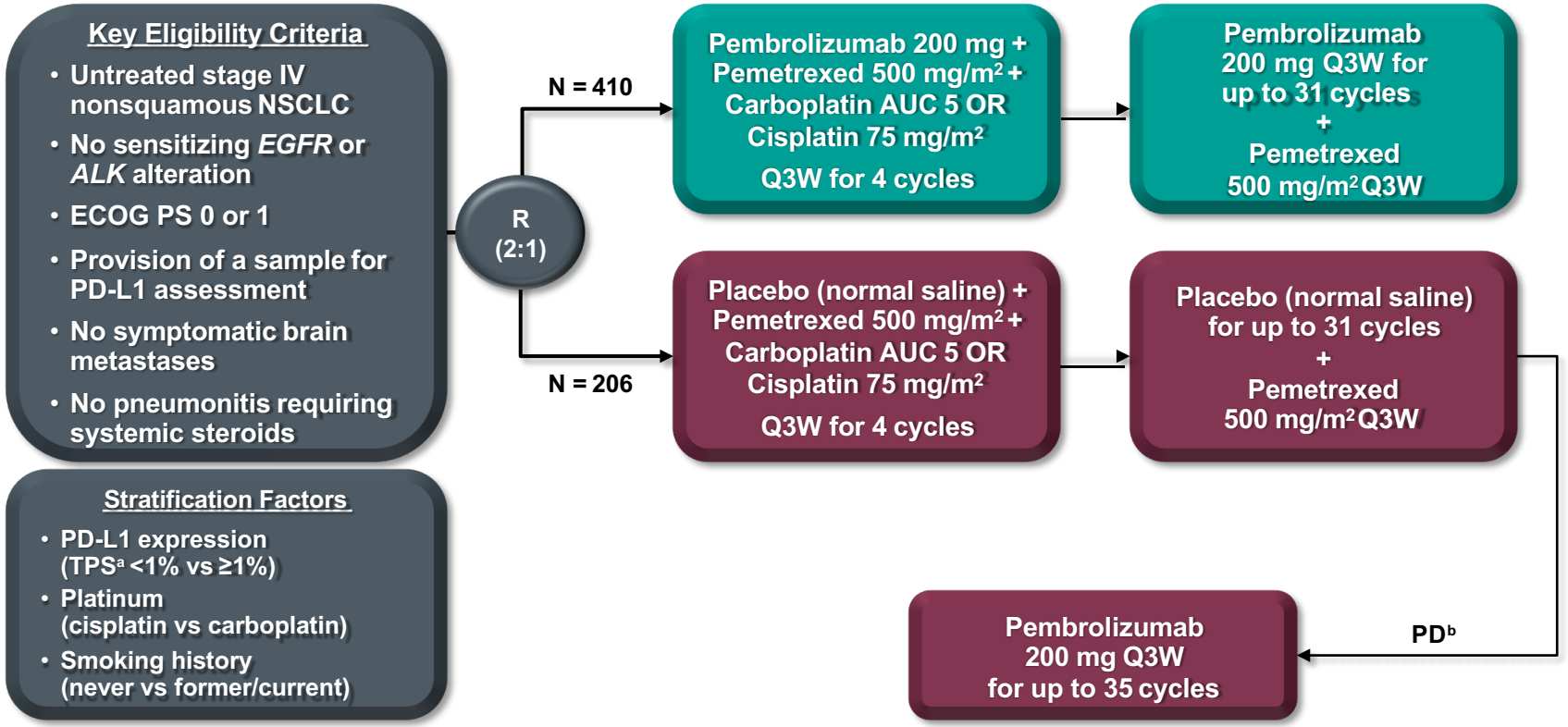
Data cut-off date: March 1, 2020

Saadetting Kilickap, 2020, WCLC

Chemotherapy plus PD-(L)-1 Inhibitors

PD-L1 High Group

KEYNOTE-189 Study Design (NCT02578680)

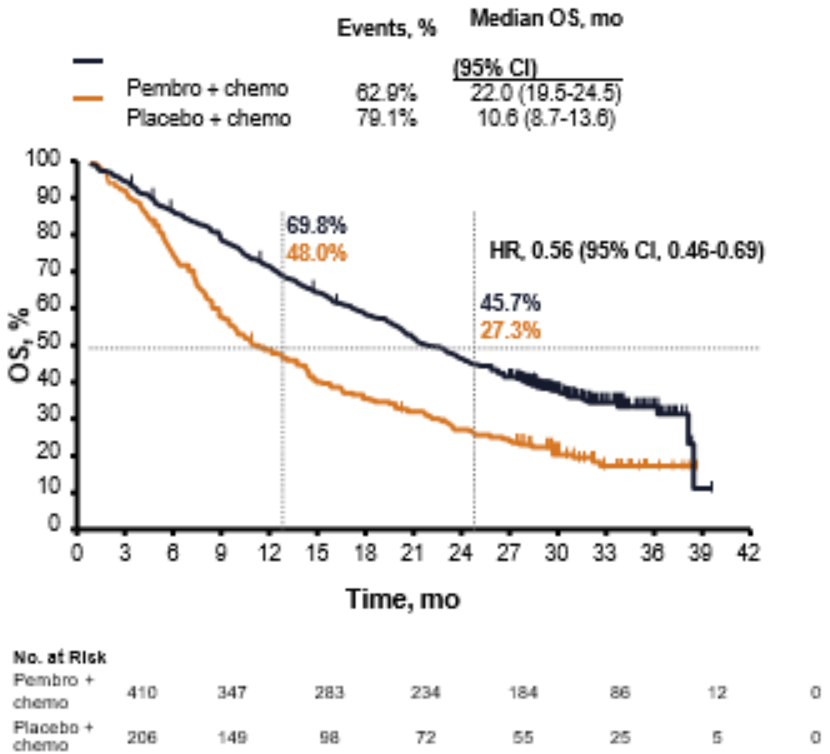


[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

Gandhi L, et al. AACR Annual Meeting; Chicago, Illinois, April 14-18, 2018; Abstract CT075

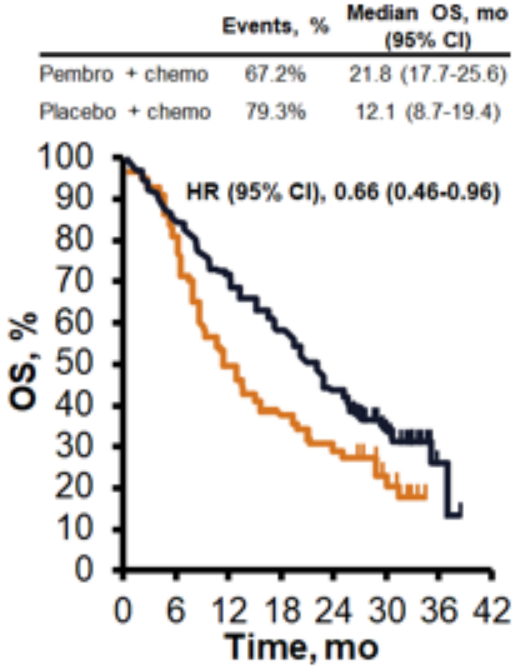
KEYNOTE-189 Final Analysis: OS by PD-L1 status[1]

OS PD-L1 ≥50%



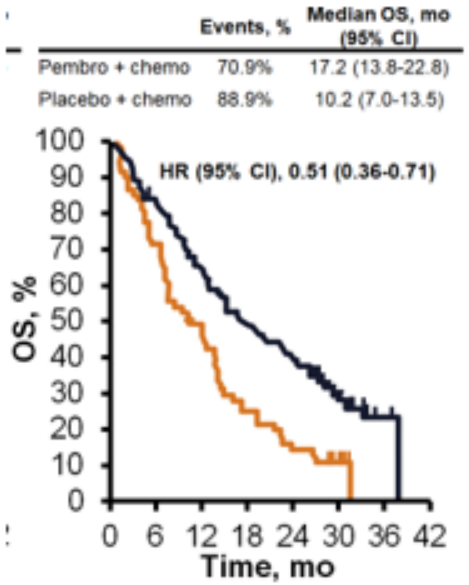
OS: HR = 0.58
(95% CI, 0.46-0.89
Median OS: 22 vs. 10.6 mo

OS PD-L1 1-49%



OS: HR = 0.66
(95% CI, 0.46-0.96)
Median OS: 21.8 vs 12.1 mo

OS PD-L1 <1%



OS: HR = 0.51
(95% CI, 0.36-0.71)
Median OS: 17.2 vs 10.2 mo

Forde, WCLC 2021

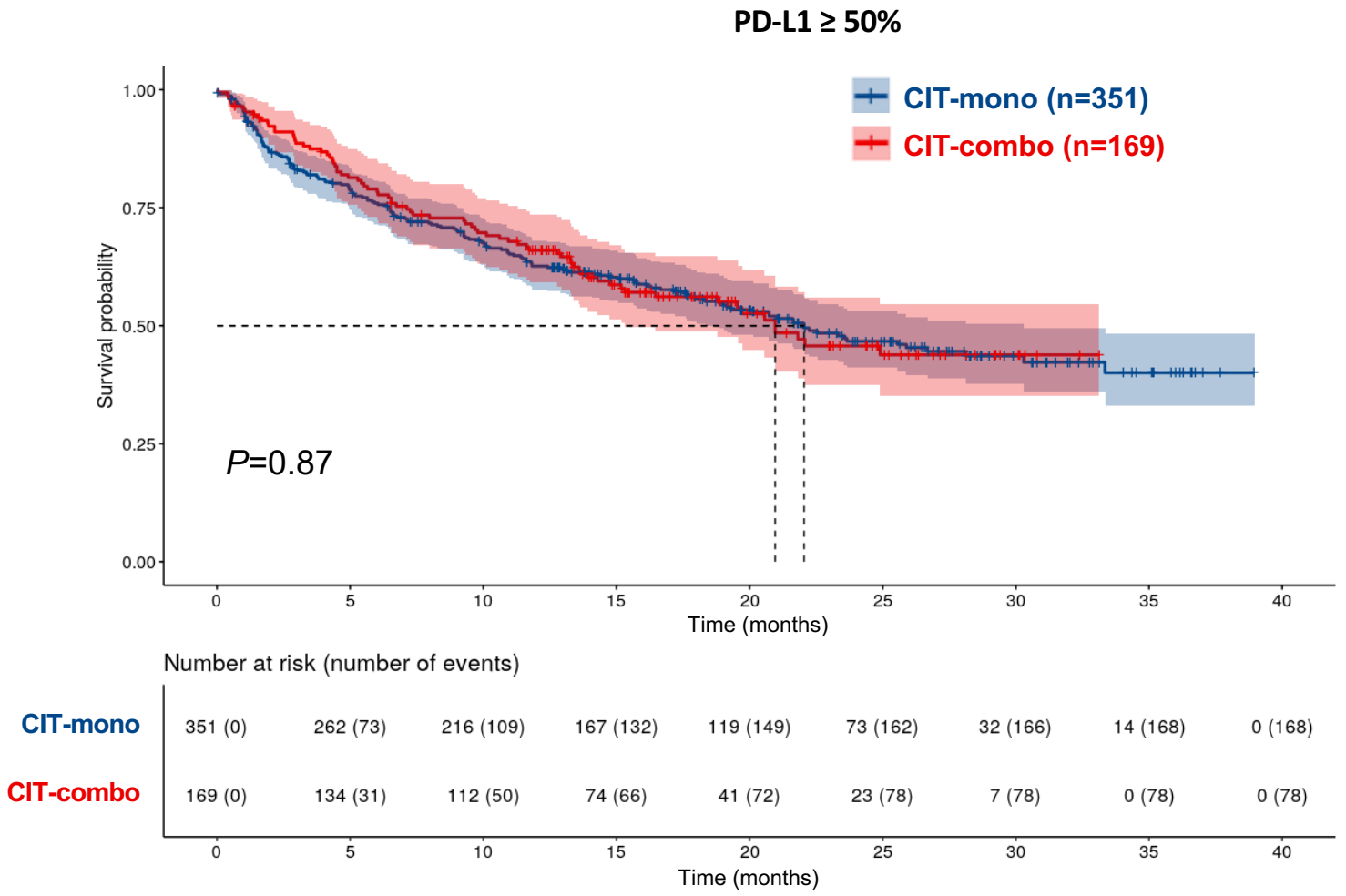
1. Rodriguez-Abreu D et al. ASCO 2020. Abstract 9582.

Real World Data
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

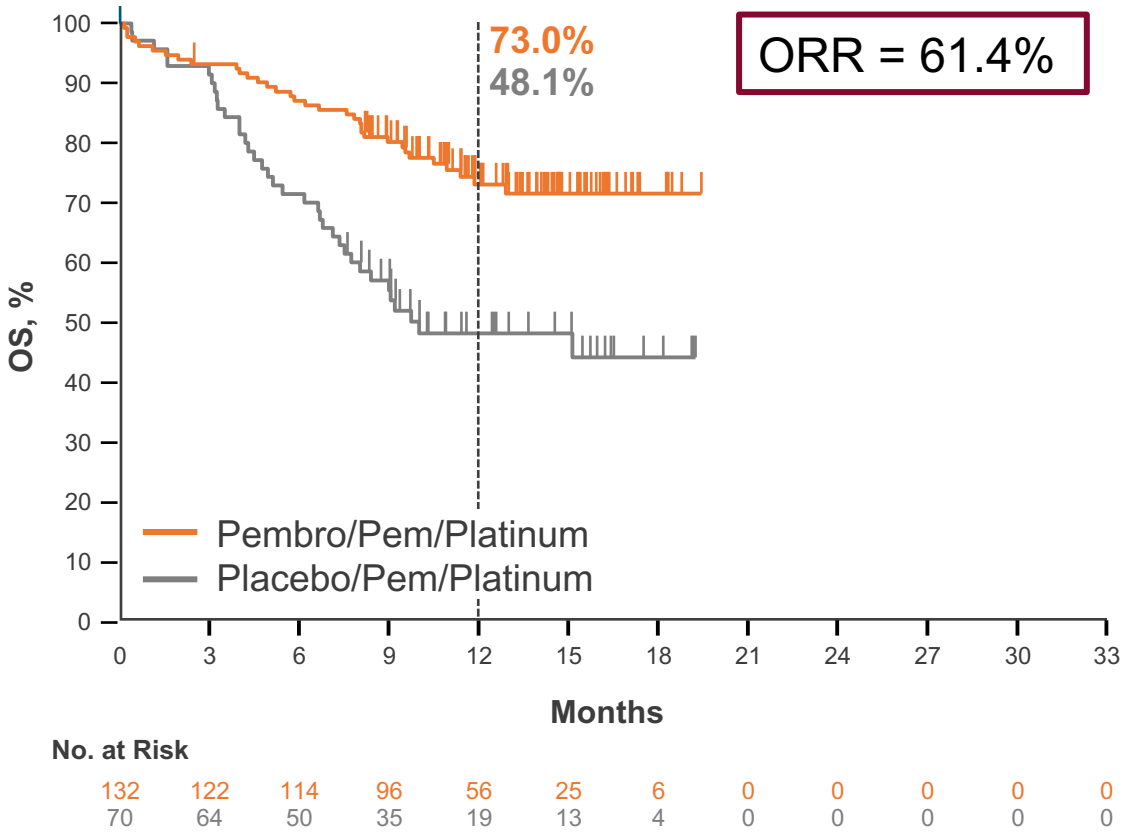


Peters S; ESMO 2020

KEYNOTE-189 (TPS ≥ 50%) vs KEYNOTE-024

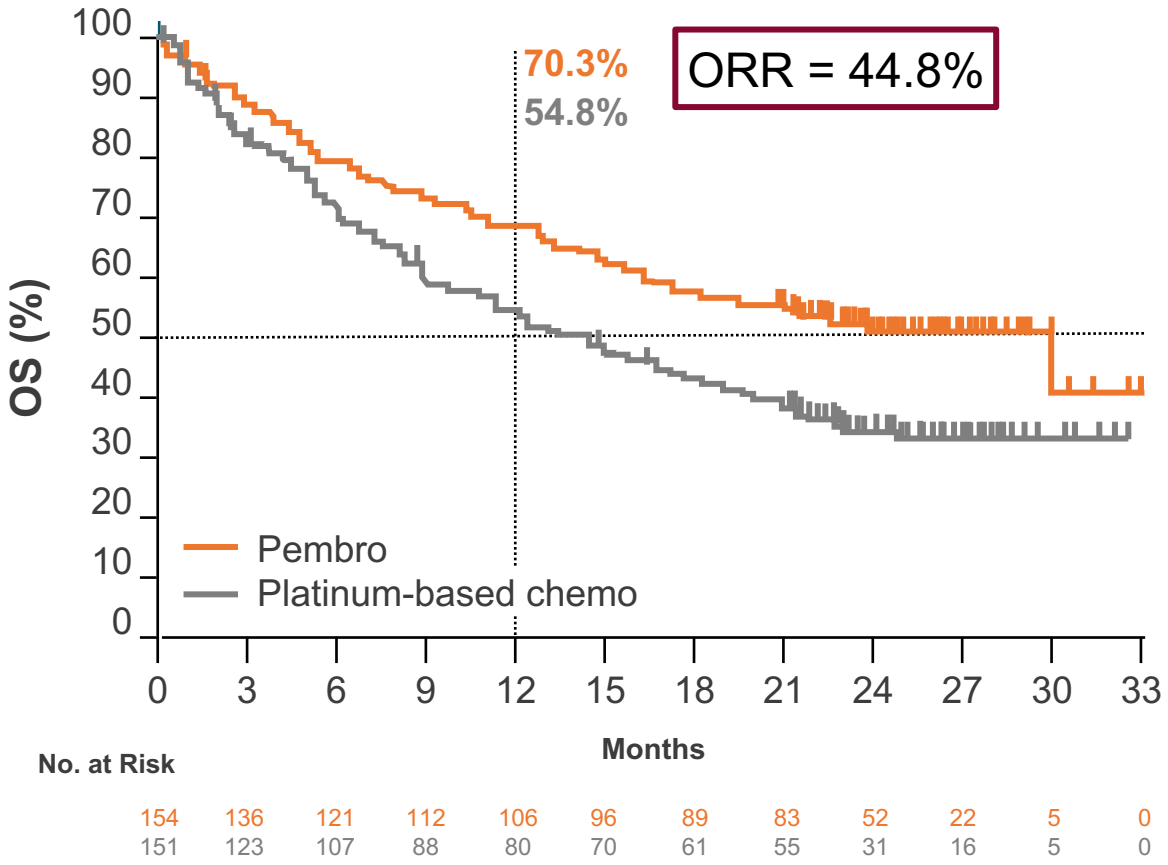
KEYNOTE-189

HR (95% CI): 0.42 (0.26-0.68); *P* = .0001[a]



KEYNOTE-024[1]

HR (95% CI): 0.63 (0.47-0.86); *P* = .002[a]



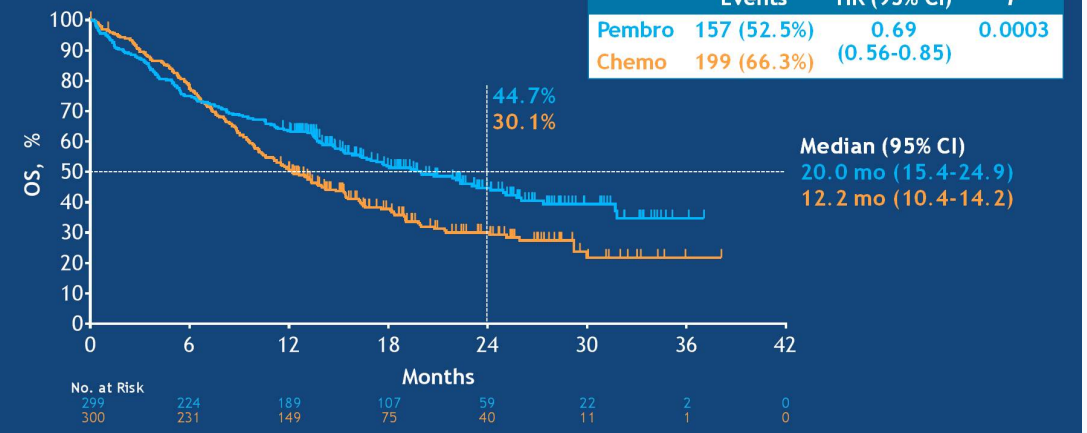
[A]Normal P value. 1. Brahmer J et al. 18th IASLC World Conference on Lung Cancer: Oct 15-18, 2017; abstract OA17.06. Herbst RS, AACR Annual Meeting; Chicago, Illinois, April 14-18, 2018; Abstract CT075 Discussant

Single Agent PD-(L)-1 Inhibitors

PD-L1 Low Group

Keynote 042; OS in All Sub Groups, KN-042

Overall Survival: TPS ≥50%

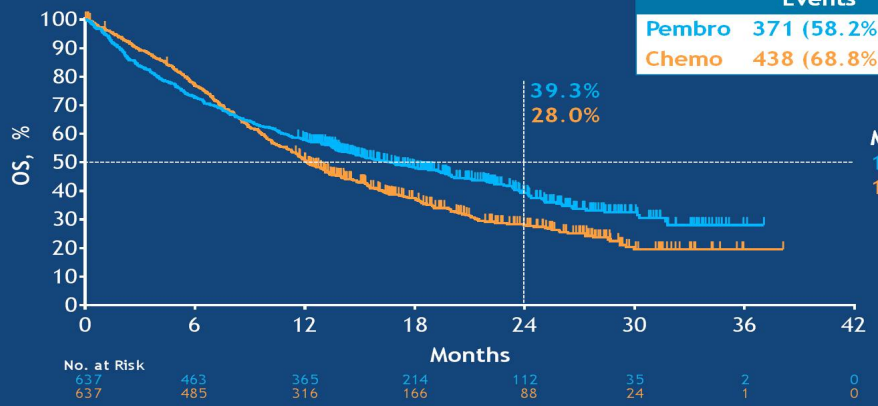


	Events	HR (95% CI)	P
Pembro	157 (52.5%)	0.69 (0.56-0.85)	0.0003
Chemo	199 (66.3%)		

Median (95% CI)
20.0 mo (15.4-24.9)
12.2 mo (10.4-14.2)

Data cutoff date: Feb 26, 2018.

Overall Survival: TPS ≥1%

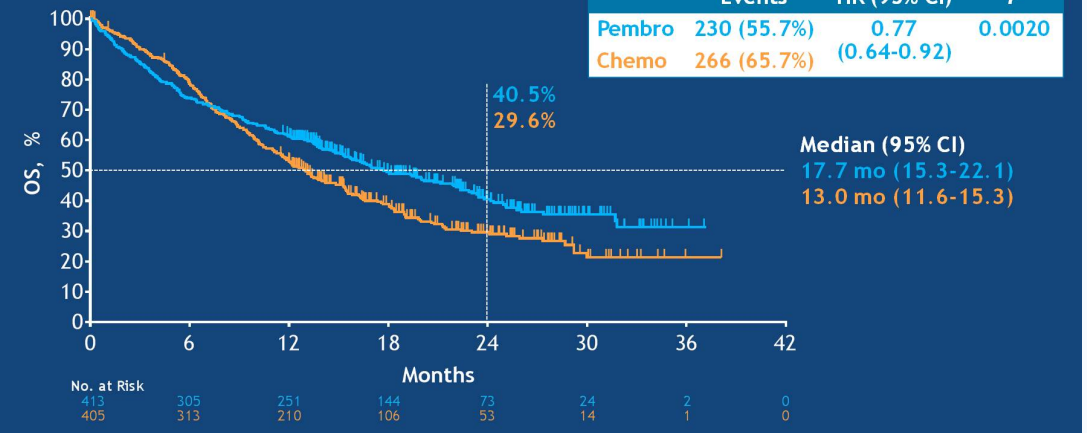


	Events	HR (95% CI)	P
Pembro	371 (58.2%)	0.81 (0.71-0.93)	0.0018
Chemo	438 (68.8%)		

Median (95% CI)
16.7 mo (13.9-19.7)
12.1 mo (11.3-13.3)

Data cutoff date: Feb 26, 2018.

Overall Survival: TPS ≥20%

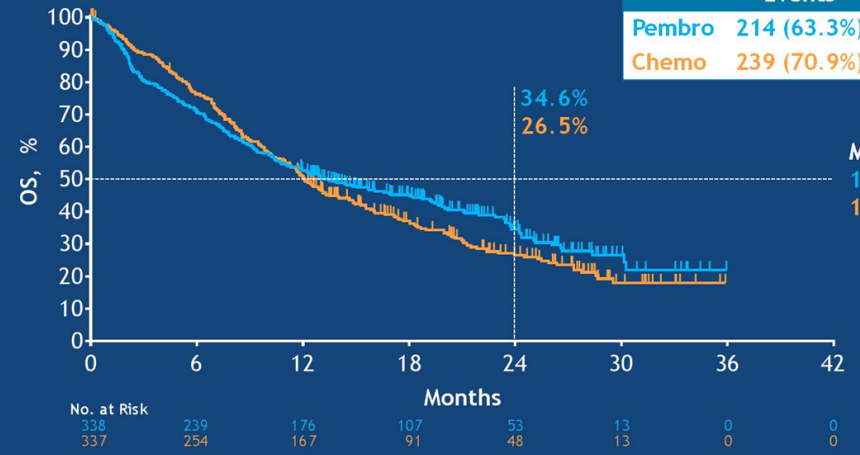


	Events	HR (95% CI)	P
Pembro	230 (55.7%)	0.77 (0.64-0.92)	0.0020
Chemo	266 (65.7%)		

Median (95% CI)
17.7 mo (15.3-22.1)
13.0 mo (11.6-15.3)

Data cutoff date: Feb 26, 2018.

Overall Survival: TPS ≥1-49% (Exploratory Analysis[a])



	Events	HR (95% CI)
Pembro	214 (63.3%)	0.92 (0.77-1.11)
Chemo	239 (70.9%)	

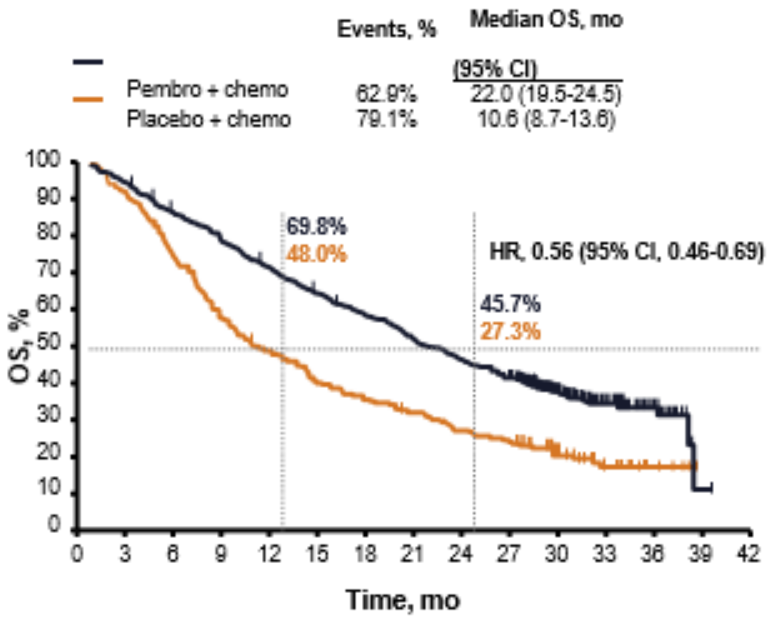
Median (95% CI)
13.4 mo (10.7-18.2)
12.1 mo (11.0-14.0)

[a]No alpha allocated to this comparison.

Data cutoff date: Feb 26, 2018.

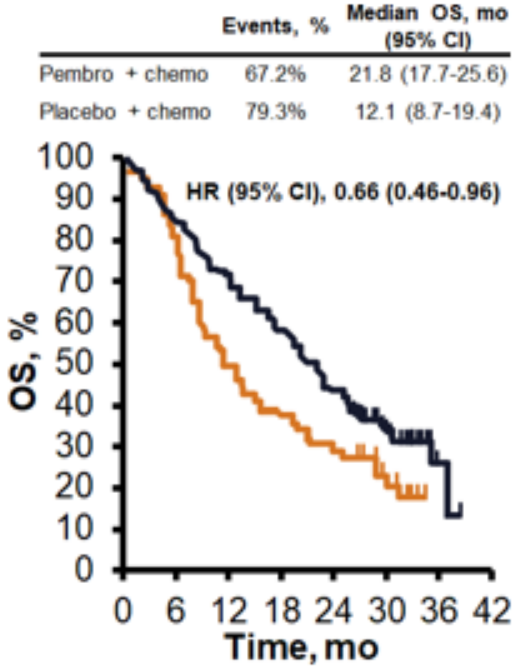
KEYNOTE-189 Final Analysis: OS by PD-L1 status[1]

OS PD-L1 ≥50%



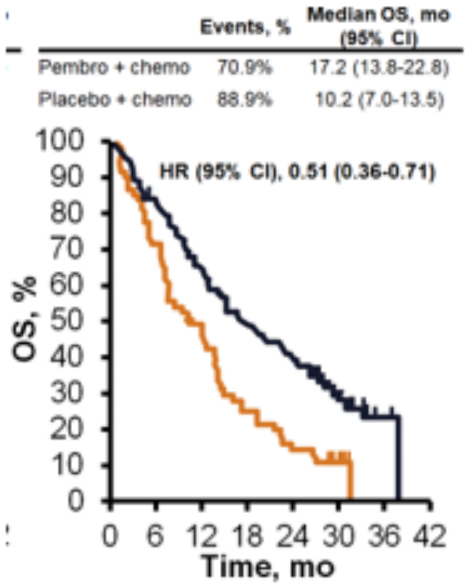
OS: HR = 0.58
(95% CI, 0.46-0.89
Median OS: 22 vs. 10.6 mo

OS PD-L1 1-49%



OS: HR = 0.66
(95% CI, 0.46-0.96)
Median OS: 21.8 vs 12.1 mo

OS PD-L1 <1%



OS: HR = 0.51
(95% CI, 0.36-0.71)
Median OS: 17.2 vs 10.2 mo

Forde, WCLC 2021

1. Rodriguez-Abreu D et al. ASCO 2020. Abstract 9582.

Real World Data: Flatiron Analysis

Table 4
OS with I-O monotherapy stratified by subgroup.

	Squamous NSCLC					Non-squamous NSCLC				
	n	Median OS (95 % CI), Months	12-Month OS Rate, %	24-Month OS Rate, %	36-Month OS Rate, %	n	Median OS (95 % CI), Months	12-Month OS Rate, %	24-Month OS Rate, %	36-Month OS Rate, %
All patients	875	11.3 (9.8–12.8)	48.7	27.8	18.2	2166	14.1 (12.4–15.8)	52.9	38.5	29.9
Age, years										
<65	167	11.9 (7.3–15.9)	49.3	31.3	20.0	534	20.1 (14.3–23.7)	57.1	44.5	37.8
≥65 to <75	302	12.5 (9.6–14.8)	51.5	29.7	20.4	673	13.5 (11.0–17.3)	52.1	40.7	31.4
≥75	406	11.1 (8.3–13.2)	46.2	24.3	15.8	959	12.7 (11.0–14.7)	51.0	33.4	24.1
Tumor PD-L1 expression										
<1%	52	11.0 (6.2–19.1)	47.2	29.5	24.6	102	13.4 (8.9–18.8)	52.9	26.6	19.9
1%–49 %	157	12.1 (6.6–15.3)	50.6	25.5	17.0	239	9.1 (6.8–12.1)	43.7	32.1	22.8
≥50 %	536	11.9 (10.0–14.1)	49.8	29.7	17.9	1582	15.3 (13.4–17.5)	54.5	39.6	31.6
Unknown	130	8.5 (4.9–12.5)	42.8	22.0	19.2	243	11.7 (8.1–16.9)	49.4	39.6	27.1
Brain metastases										
With	42	2.9 (2.0–4.2)	19.8	16.5	16.5	317	14.5 (9.0–21.0)	51.7	40.8	33.6
Without	833	12.1 (10.5–13.7)	50.1	28.4	18.5	1849	14.1 (12.4–15.9)	53.1	38.1	29.3

CI, confidence interval; I-O, immuno-oncology; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1.

Table 2
OS with I-O plus chemotherapy stratified by subgroup.

	Squamous NSCLC*			Non-squamous NSCLC			
	n	Median OS (95 % CI), Months	12-Month OS Rate, %	n	Median OS (95 % CI), Months	12-Month OS Rate, %	24-month OS Rate, %
All patients	814	10.6 (9.3–11.8)	45.1	3457	12.0 (11.3–12.8)	49.9	32.5
Age, years							
<65	230	8.9 (7.1–11.2)	38.7	1230	13.2 (12.0–15.1)	52.8	34.9
≥65 to <75	318	14.5 (11.4–19.9)	55.3	1296	12.3 (11.1–13.7)	50.6	33.7
≥75	266	9.3 (7.7–11.1)	37.5	931	10.1 (9.2–11.5)	45.2	27.8
Tumor PD-L1 expression							
<1%	209	8.7 (7.7–12.4)	42.3	1064	10.2 (9.3–11.7)	45.4	28.3
1%–49 %	252	10.2 (8.9–13.1)	43.3	967	11.8 (10.5–13.5)	49.1	29.5
≥50 %	120	12.3 (9.3–NR)	50.9	679	19.1 (15.5–22.1)	61.0	42.7
Unknown	233	10.6 (8.0–14.5)	46.5	747	10.3 (8.8–12.7)	46.4	32.1
Brain metastases							
With	42	6.7 (1.7–11.1)	32.1	468	10.8 (8.8–12.7)	45.7	29.2
Without	772	11.1 (9.4–12.1)	45.9	2989	12.3 (11.4–13.3)	50.6	33.0

CI, confidence interval; I-O, immuno-oncology; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1.
* In the squamous cohort, there were 5 patients available for follow-up at 24 months.

Non- Squamous IO Monotherapy

PD-L1	MOS	12 m OS Rate %	36 m OS Rate %
<1%	13.4	52.9	19.9
1%-49%	9.1	43.7	22.8
≥ 50%	15.3	54.5	31.6

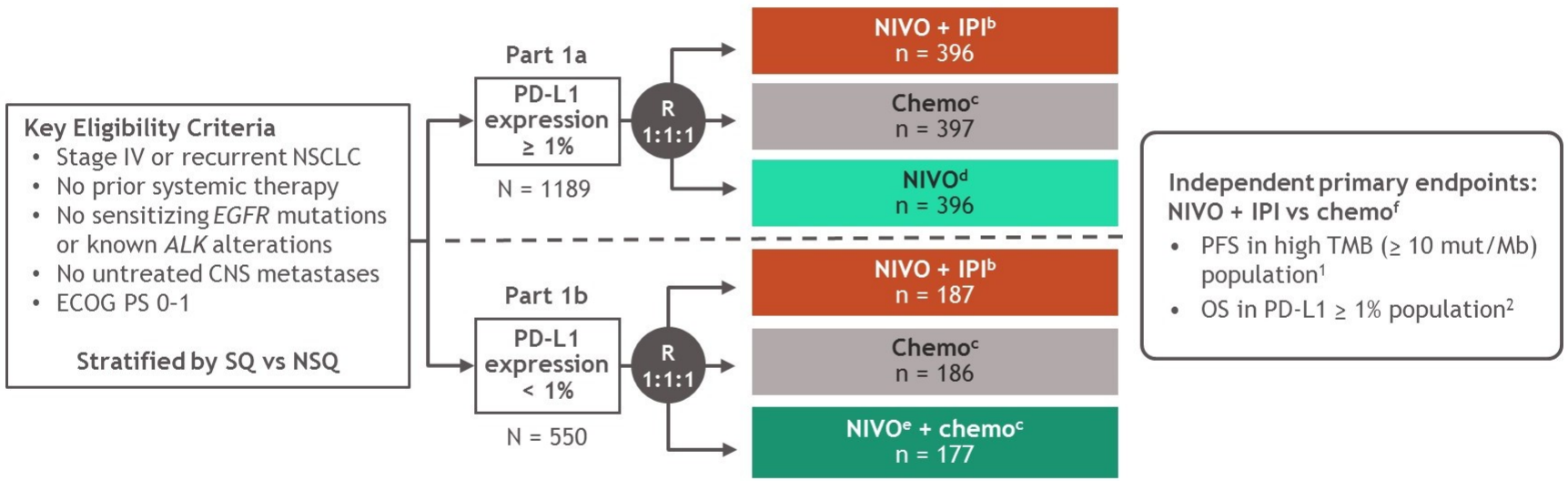
Non- Squamous IO + Chemotherapy

PD-L1	MOS	12 m OS Rate %	24 m OS Rate %
<1%	10.2	45.4	28.3
1%-49%	11.8	49.1	29.5
≥ 50%	19.1	61.0	42.7

Waterhouse David; Lung Cancer, Vol. 156, Jun 2021

IO/IO Combinations

CheckMate 227[a] Part 1 study design

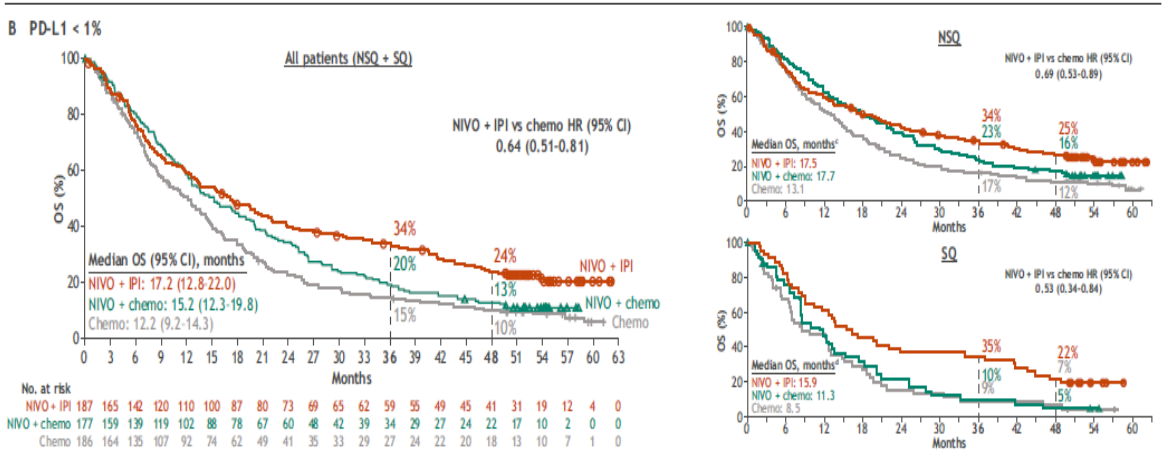


Database lock: February 28, 2020; minimum / median follow-up for OS: 37.7 months / 43.1 months.

Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy; [a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]NSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; SQ: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]Both endpoints were met; results were previously reported.

1. Hellmann MD, et al. *N Engl J Med* 2018;378(22):2093-2104; 2. Hellmann MD, et al. *N Engl J Med* 2019;381(21):2020-2031.

CM-227, Four Year Data



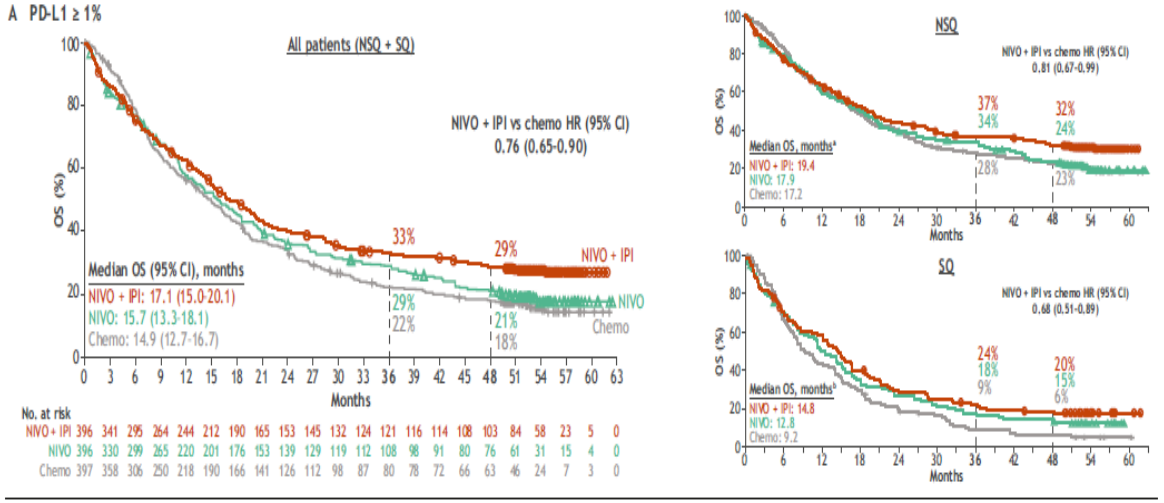
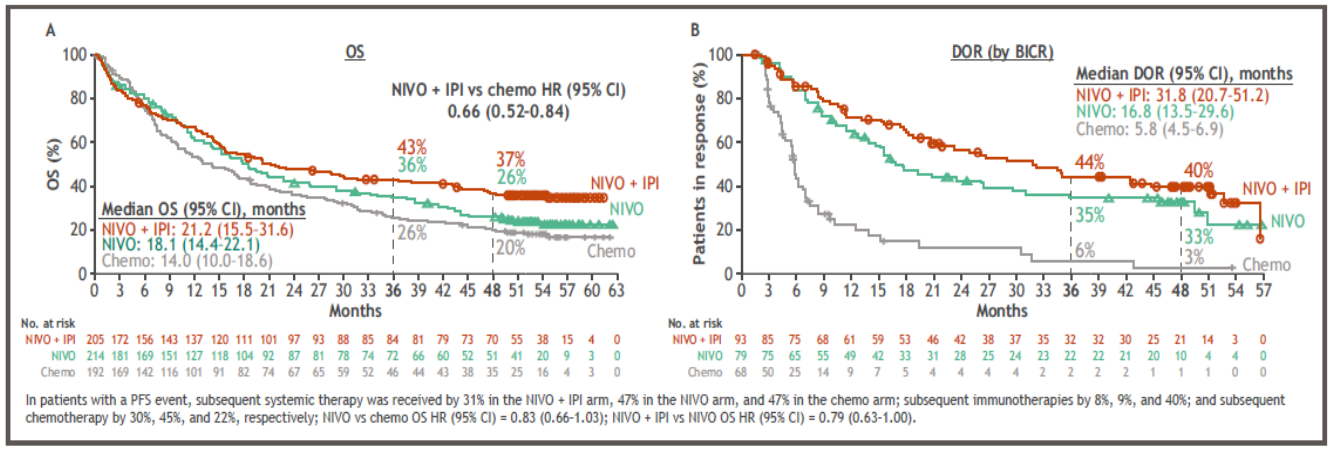


Figure 4. Efficacy in patients with PD-L1 ≥ 50%



In patients with a PFS event, subsequent systemic therapy was received by 31% in the NIVO + IPI arm, 47% in the NIVO arm, and 47% in the chemo arm; subsequent immunotherapies by 8%, 9%, and 40%; and subsequent chemotherapy by 30%, 45%, and 22%, respectively; NIVO vs chemo OS HR (95% CI) = 0.83 (0.66-1.03); NIVO + IPI vs NIVO OS HR (95% CI) = 0.79 (0.63-1.00).

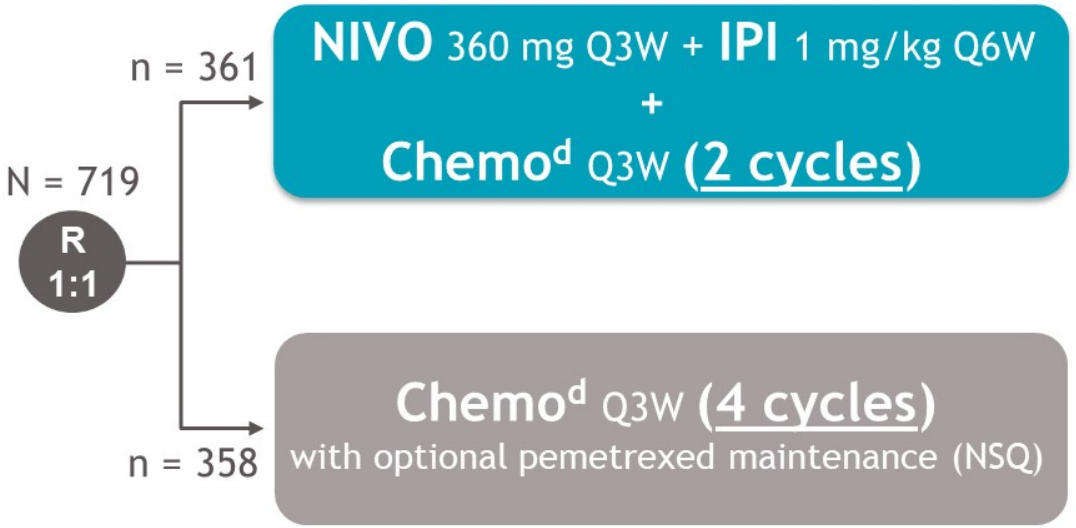
Paz-Ares; 4 Year OS, ASCO 2021

CheckMate 9LA study design[a]

Key eligibility criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint
- OS

Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Exploratory endpoints
- Safety

DBL: February 18, 2021; minimum / median follow-up for OS: 24.4 months / 30.7 months.

[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

CheckMate-9LA

PD-L1 < 1%: efficacy outcomes

OS

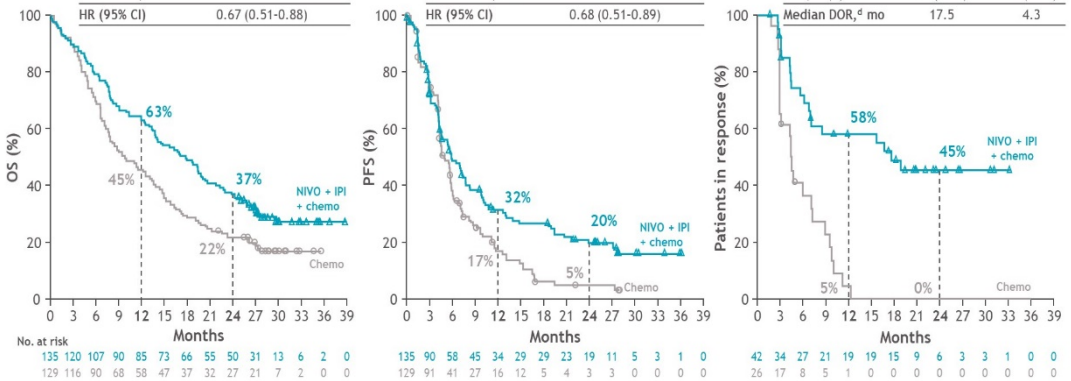
	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
Median OS,[b] mo	17.7	9.8
HR (95% CI)	0.67 (0.51-0.88)	

PFS[a]

	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
Median PFS,[c] mo	5.8	4.9
HR (95% CI)	0.68 (0.51-0.89)	

DOR[a]

	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
ORR, n (%)	42 (31.1)	26 (20.2)
Median DOR,[d] mo	17.5	4.3



- Exploratory analysis of OS by histology in PD-L1 < 1% (HR; NIVO + IPI + chemo vs chemo): 0.75[e] (NSQ) and 0.48[f] (SQ)
  - 2-year OS rates were 38% vs 26% (NSQ) and 33% vs 11% (SQ)

[a]Per BICR; [b]95% CI = 13.7-20.3 (NIVO + IPI + chemo) and 7.7-13.5 (chemo); [c]95% CI = 4.4-7.6 (NIVO + IPI + chemo) and 4.2-5.6 (chemo); [d]95% CI = 8.5-20.7 (NIVO + IPI + chemo) and 4.3-9.6 (chemo); [e]95% CI = 0.53-0.95 (NSQ); [f]95% CI = 0.28-0.81 (SQ).

CheckMate 9LA (NIVO + IPI + chemo vs chemo in 1L NSCLC): 2-year update

PD-L1 ≥ 1%: efficacy outcomes

OS

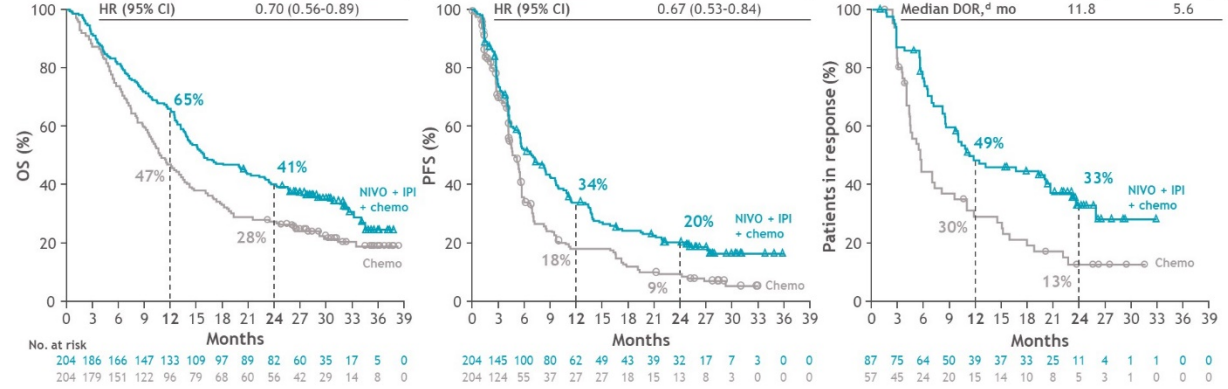
	NIVO + IPI + chemo (n = 204)	Chemo (n = 204)
Median OS,[b] mo	15.8	10.9
HR (95% CI)	0.70 (0.56-0.89)	

PFS[a]

	NIVO + IPI + chemo (n = 204)	Chemo (n = 204)
Median PFS,[c] mo	7.0	5.0
HR (95% CI)	0.67 (0.53-0.84)	

DOR[a]

	NIVO + IPI + chemo (n = 204)	Chemo (n = 204)
ORR, n (%)	87 (42.6)	57 (27.9)
Median DOR,[d] mo	11.8	5.6



- Exploratory analysis of OS by histology in PD-L1 ≥ 1% (HR; NIVO + IPI + chemo vs chemo): 0.71[e] (NSQ) and 0.70[f] (SQ)
  - 2-year OS rates were 42% vs 29% (NSQ) and 38% vs 26% (SQ)

CheckMate 9LA (NIVO + IPI + chemo vs chemo in 1L NSCLC): 2-year update

PD-L1 ≥ 50%: efficacy outcomes

OS

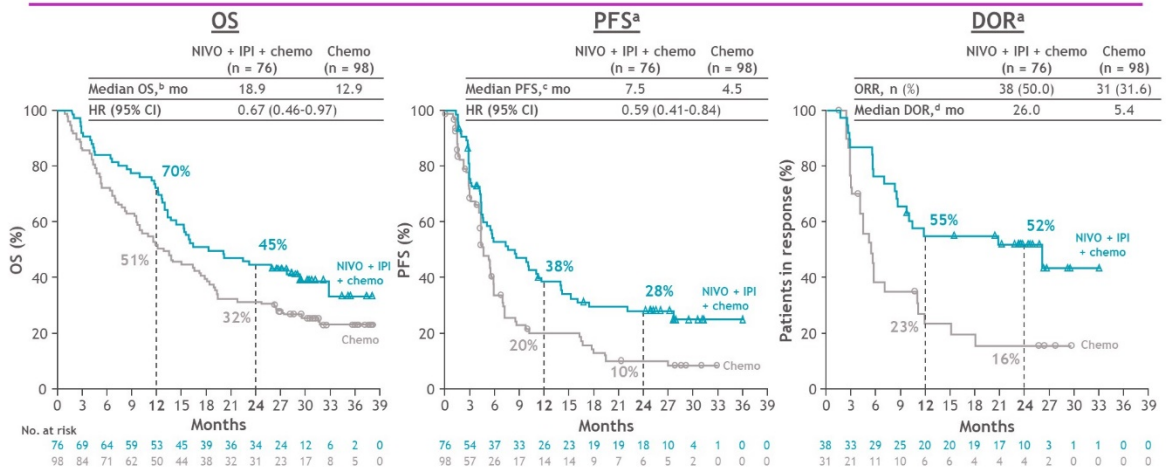
	NIVO + IPI + chemo (n = 76)	Chemo (n = 98)
Median OS,[b] mo	18.9	12.9
HR (95% CI)	0.67 (0.46-0.97)	

PFS[a]

	NIVO + IPI + chemo (n = 76)	Chemo (n = 98)
Median PFS,[c] mo	7.5	4.5
HR (95% CI)	0.59 (0.41-0.84)	

DOR[a]

	NIVO + IPI + chemo (n = 76)	Chemo (n = 98)
ORR, n (%)	38 (50.0)	31 (31.6)
Median DOR,[d] mo	26.0	5.4



[a]Per BICR; [b]95% CI = 13.1-32.5 (NIVO + IPI + chemo) and 9.4-17.6 for (chemo); [c]95% CI = 4.4-11.5 (NIVO + IPI + chemo) and 4.1-5.6 (chemo); [d]95% CI = 8.6-NR (NIVO + IPI + chemo) and 3.9-10.9 (chemo).

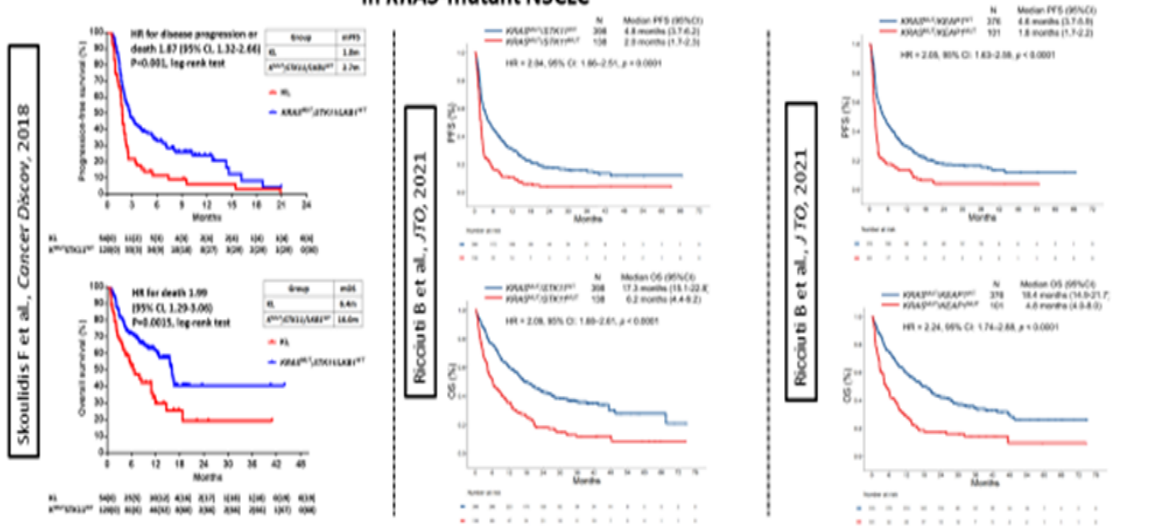
Reck, M; ASCO 2021

Choice of Treatment and Other Factors

Molecular Determinants of Efficacy

IASLC 2022 Targeted Therapies of Lung Cancer Meeting
FEBRUARY 22-26, 2022 | WORLDWIDE VIRTUAL EVENT

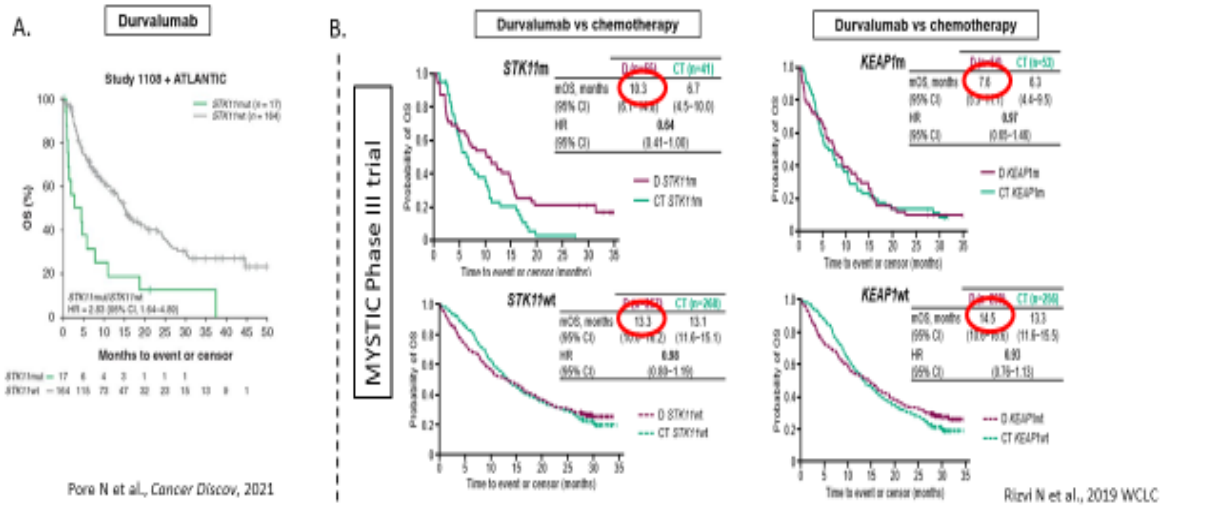
STK11 and *KEAP1* alterations drive inferior clinical outcomes with PD-1 axis inhibitor monotherapy in *KRAS*-mutant NSCLC



F. Skoulidis; The University of Texas MD Anderson Cancer Center; USA; @FSkoulidis

IASLC 2022 Targeted Therapies of Lung Cancer Meeting
FEBRUARY 22-26, 2022 | WORLDWIDE VIRTUAL EVENT

STK11 and *KEAP1* alterations are associated with shorter OS with durvalumab and platinum doublet chemotherapy in the 1st line therapeutic setting



F. Skoulidis; The University of Texas MD Anderson Cancer Center; USA; @FSkoulidis

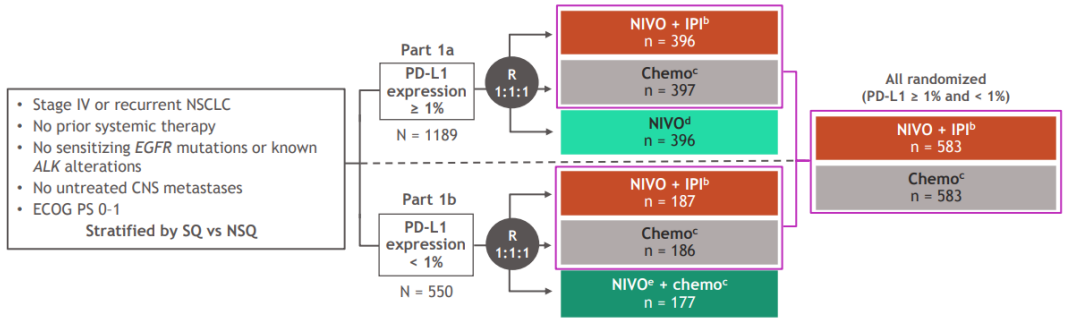
STK11 and *KEAP1* alterations and clinical outcomes in the KEYNOTE-189 Phase III trial

	STK11				*KEAP1*			
	With Mutation		Without Mutation		With Mutation		Without Mutation	
	Pembro + Chemo (n = 36)	Placebo + Chemo (n = 18)	Pembro + Chemo (n = 168)	Placebo + Chemo (n = 67)	Pembro + Chemo (n = 45)	Placebo + Chemo (n = 23)	Pembro + Chemo (n = 159)	Placebo + Chemo (n = 62)
ORR, % (95% CI)	31 (16-48)	17 (4-41)	49 (41-57)	16 (8-27)	36 (22-51)	17 (5-39)	48 (40-56)	16 (8-28)
PFS, median, mo (95% CI)	6 (4-9)	5 (5-9)	10 (8-14)	5 (5-5)	5 (4-11)	5 (5-9)	10 (8-14)	5 (5-5)
PFS, HR (95% CI)	0.81 (0.44-1.47)		0.38 (0.27-0.52)		0.65 (0.38-1.12)		0.38 (0.28-0.53)	
OS, median, mo (95% CI)	17 (5-NR)	8 (7-NR)	23 (20-NR)	12 (8-25)	13 (7-NR)	9 (7-NR)	24 (20-NR)	12 (8-NR)
OS, HR (95% CI)	0.75 (0.37-1.50)		0.59 (0.41-0.85)		0.81 (0.44-1.49)		0.57 (0.39-0.84)	

Gadgeel SM et al, AACR Annual Meeting 2020

STK11 and *KEAP1* alterations and clinical outcomes with ipi/nivo in Part 1 of CheckMate 227

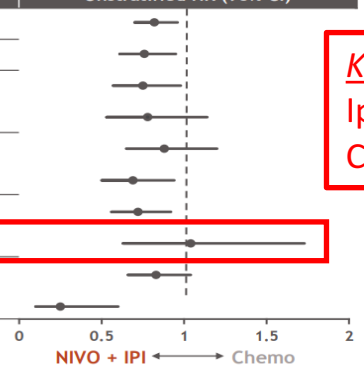
A.



PD-L1 <1% : 29%
PD-L1 ≥1% : 71%
PD-L1 ≥50%: 37%
TMB≥10Mut/Mb : 40%
TMB<10Mut/Mb : 60%

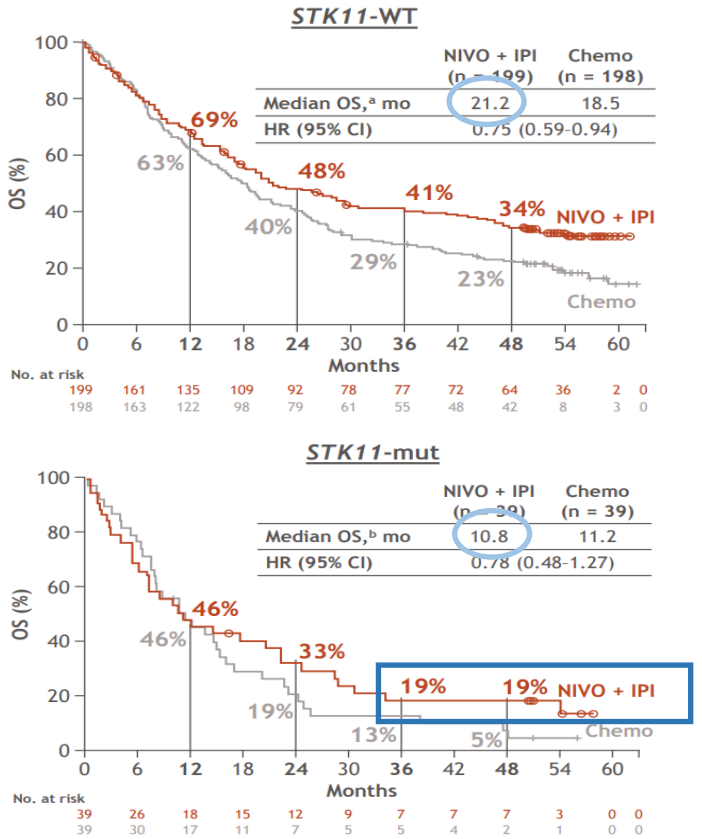
B.

Subgroup, n[b]	4-y PFS rate, % NIVO + IPI	4-y PFS rate, % Chemo	Median PFS, mo NIVO + IPI	Median PFS, mo Chemo	Unstratified HR
NSQ (n = 419, 419)	14	3	5.2	5.6	0.82
Mut-eval (n = 238, 237)	14	3	5.6	5.6	0.76
KRAS-WT (n = 150, 162)	19	6	5.6	5.6	0.75
KRAS-mut (n = 88, 75)	17	2	5.4	5.8	0.78
TP53-WT (n = 111, 106)	10	5	5.4	5.6	0.88
TP53-mut (n = 127, 131)	24	7	5.8	6.6	0.69
STK11-WT (n = 199, 198)	19	6	8.1	6.1	0.72
STK11-mut (n = 39, 39)	13	0	2.8	4.3	1.04
KEAP1-WT (n = 218, 219)	16	6	5.5	5.8	0.83
KEAP1-mut (n = 20, 18)	41	0	11.1	2.9	0.25



KEAP1^{MUT}(N=38)
Ipi/Nivo: mOS 24.4m
Chemo: mOS 8.9m

C.

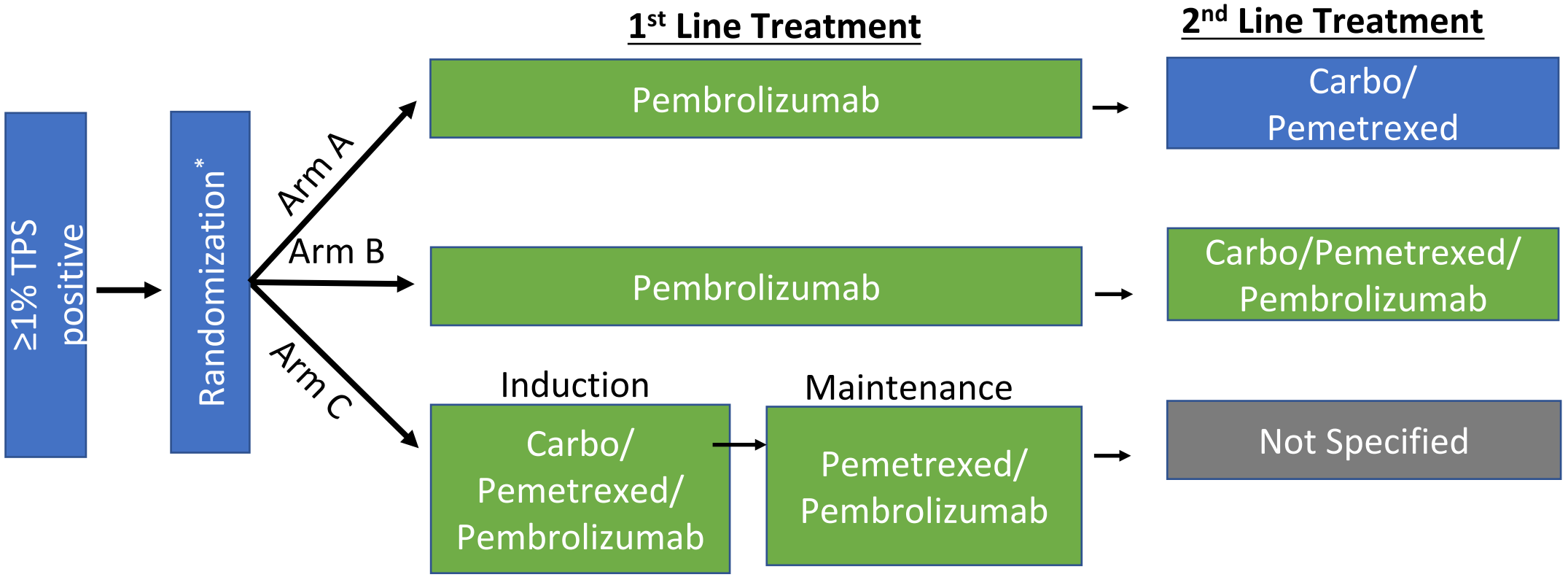


Ramalingam S et al., ESMO Immuno-Oncology Congress,2021

How Can you Decide…?

- In the absence of randomized trials to guide treatment the best option is based on:
  - Patient preference
  - Disease burden
  - Consideration of toxicities
  - Performance status
  - Co-mutations and other potential biomarkers

INSIGNA: A Randomized, Phase III Study of Firstline **I**mmunotherapy alone or in Combination with Chemotherapy in Induction/Maintenance or Post-progression in Advanced **N**onsquamous Non-Small Cell Lung Cancer (NSCLC) with Immunobiomarker **SIGN**ature-driven **A**nalysis



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