SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna

Immunotherapy in lung cancer

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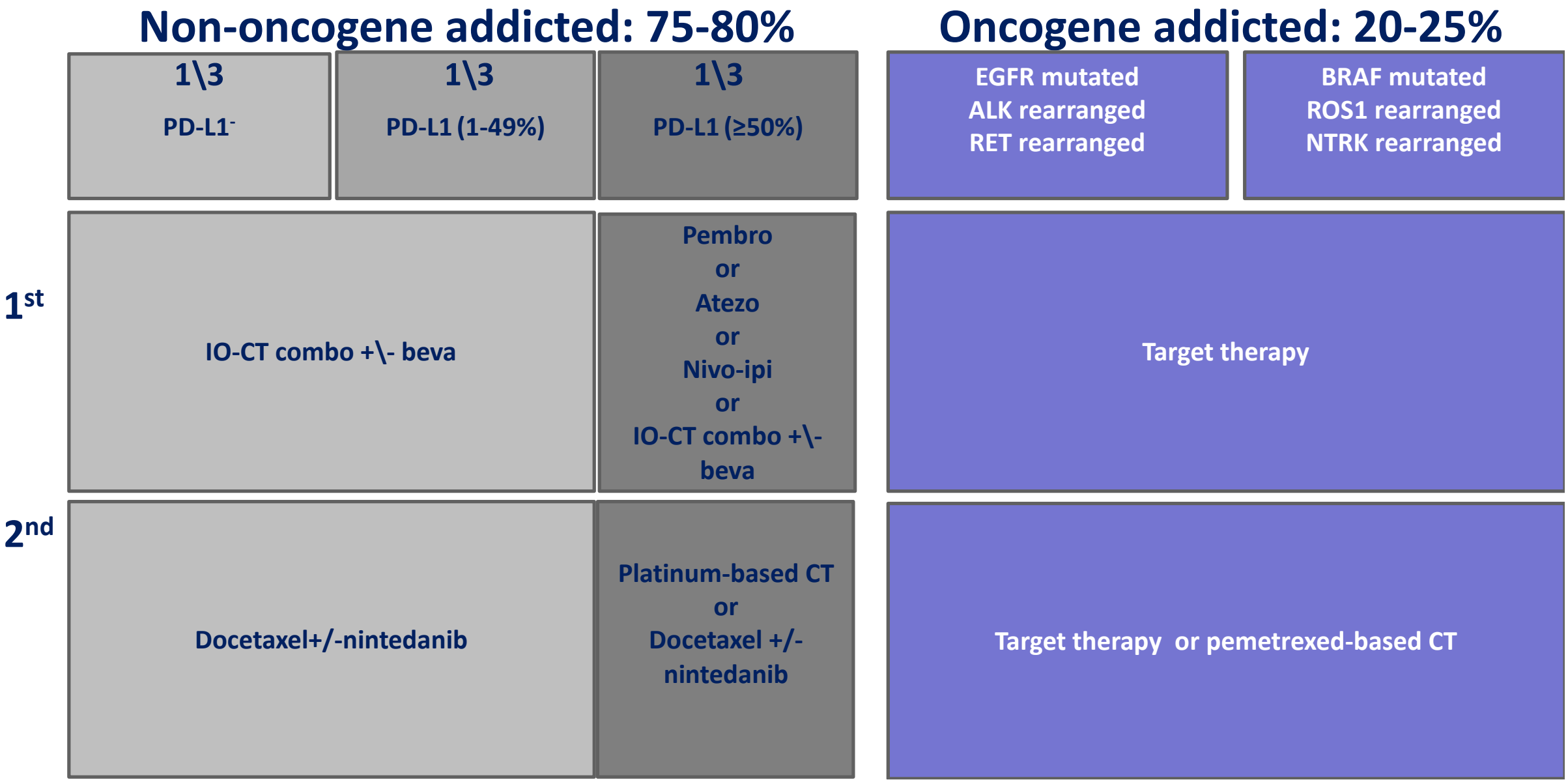
Disclosures

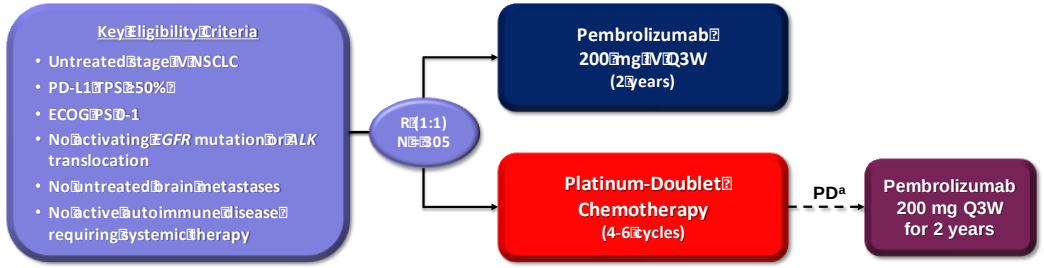
- **Dr Cappuzzo discloses the following conflicts of interest:**
  - Fees for membership of an advisory board from Roche, AstraZeneca, BMS, Pfizer, Takeda, Lilly and MSD

Options in metastatic non-small-cell lung cancer in 2020



Options in NSCLC PD-L1 ≥50%: monotherapy

KEYNOTE-024 Study design



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

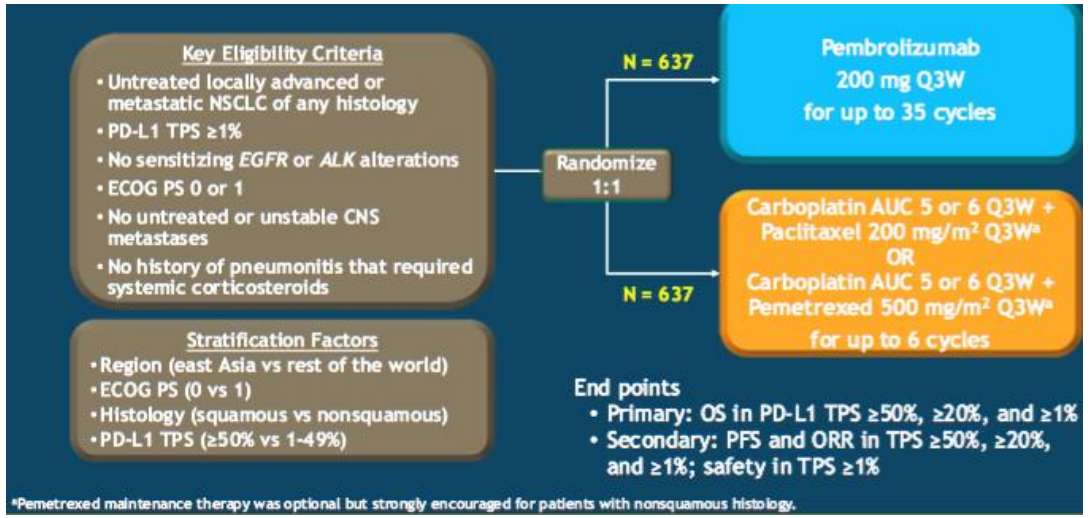
Secondary: OS, ORR, safety

Exploratory: DOR

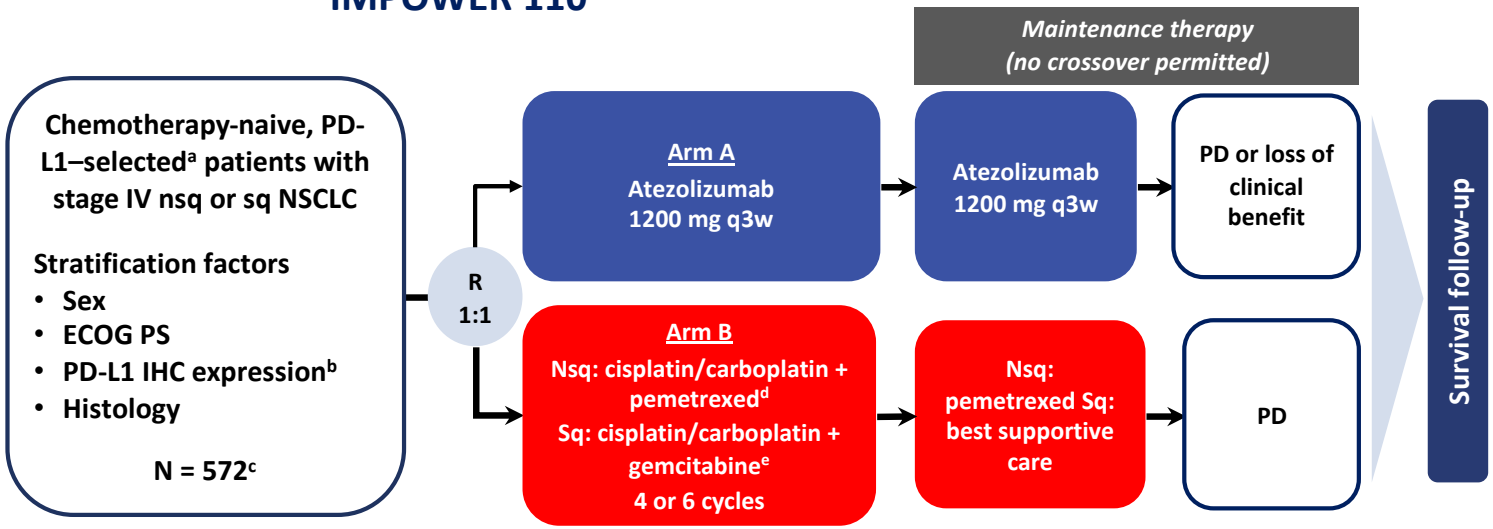
[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

Reck M, et al. NEJM 2016

KEYNOTE 042



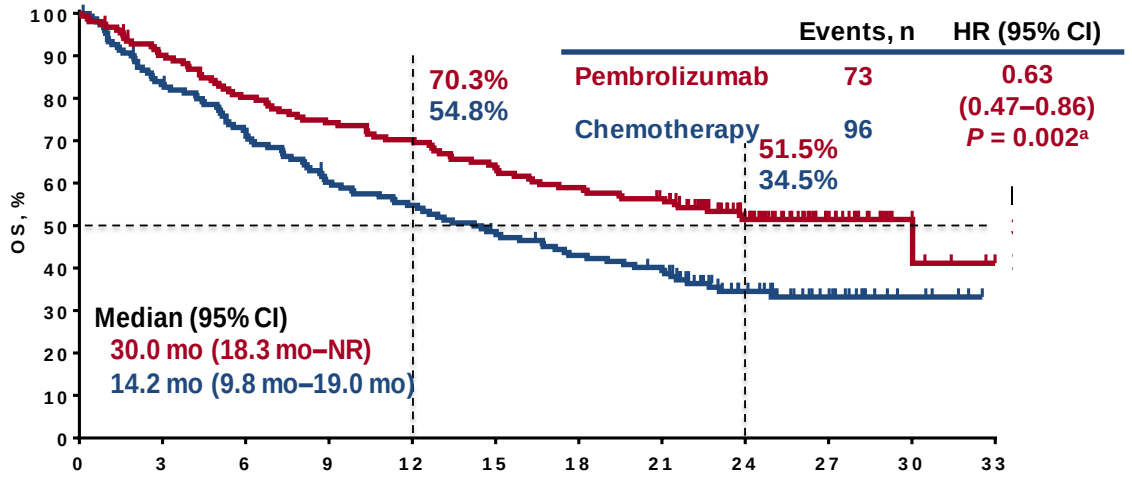
IMPOWER 110



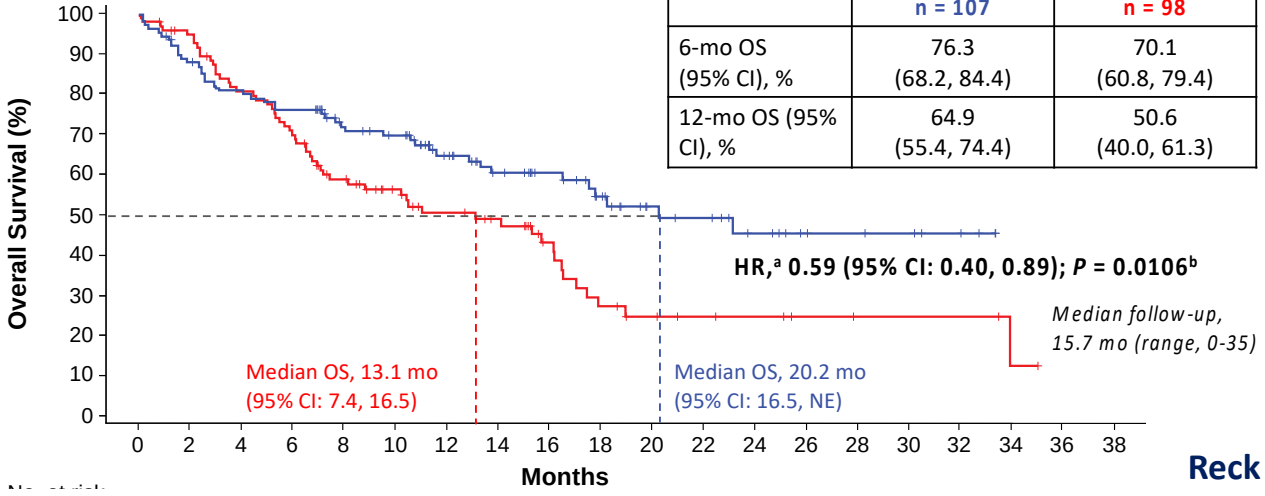
Reck M et al. J Clin Oncol. 2019; Mok T et al. Lancet 2019; Spigel D, et al. ESMO 2019

Mono-immunotherapy superior to platinum-based CT in PD-L1 ≥50%

OS in KEYNOTE-024

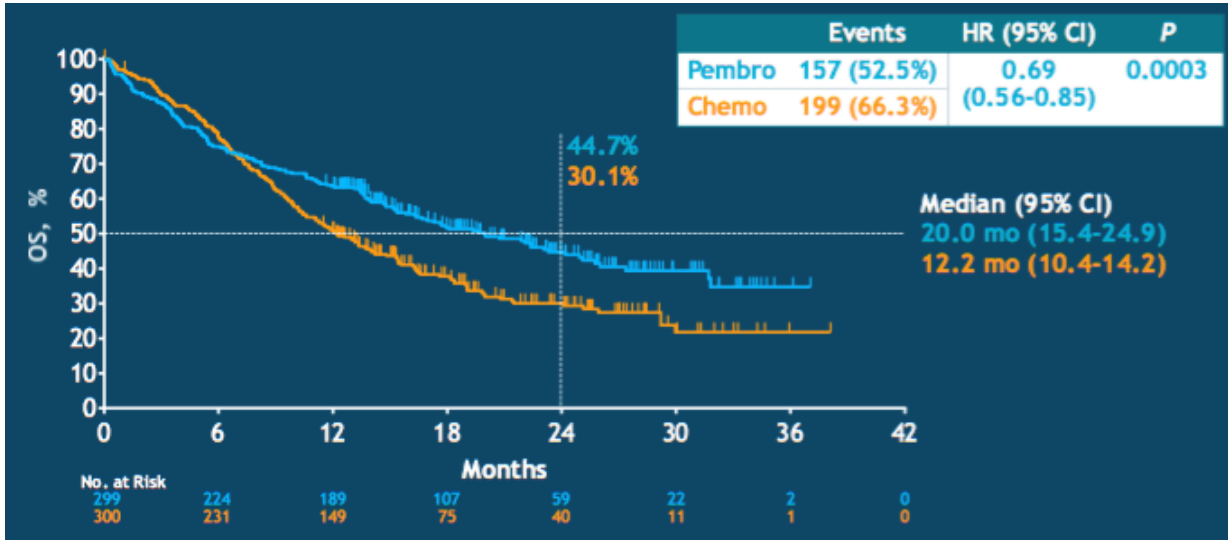


OS in IMPOWER 110



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)

OS in KEYNOTE-042



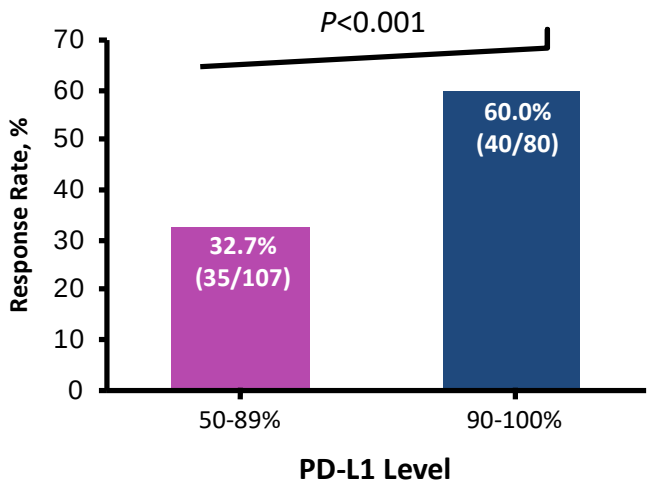
HR~ 0.6

Reck M et al. J Clin Oncol. 2019; Mok T et al. Lancet 2019; Spigel D, et al. ESMO 2019

PD-L1 ≥50% patients are not equal

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

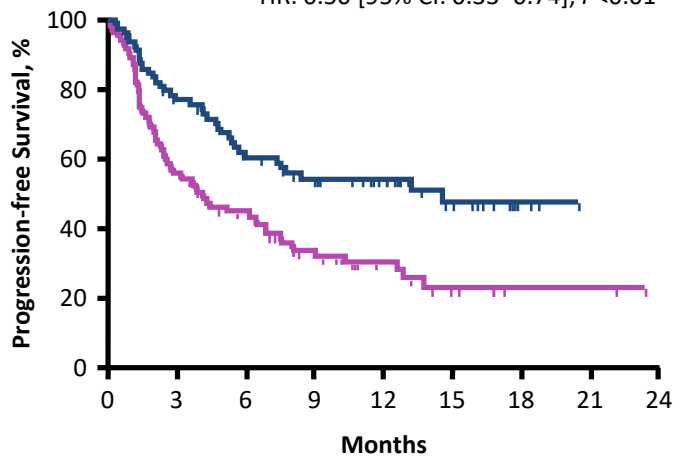
ORR



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

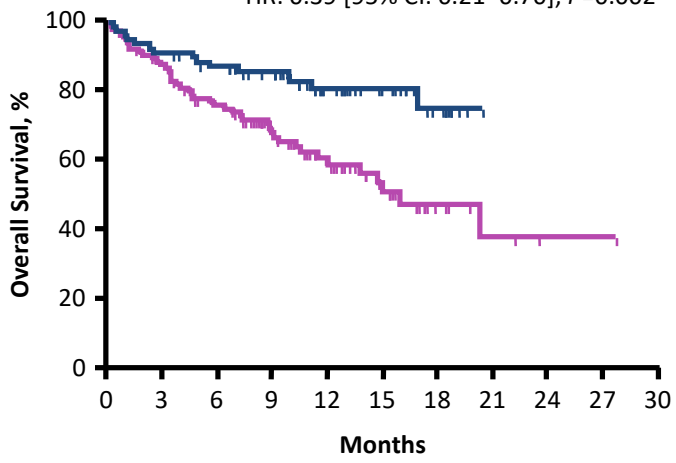


No. at risk									
PD-L1 90-100%	80	58	44	34	27	12	3	0	0
PD-L1 50-89%	107	59	42	25	13	6	2	2	0

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



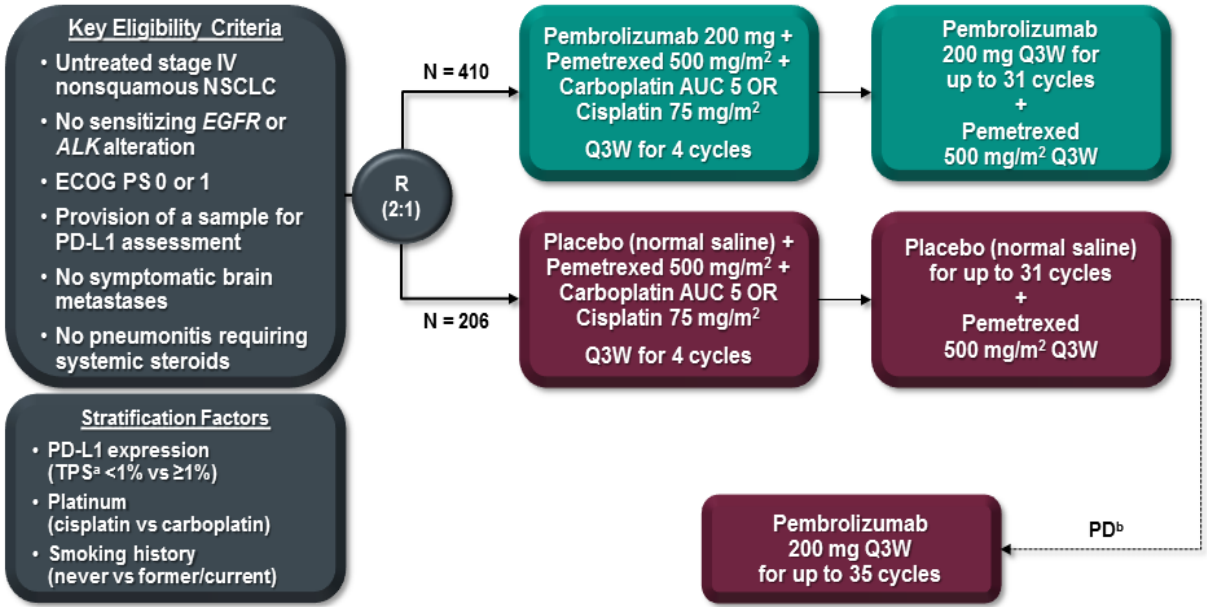
No. at risk											
PD-L1 90-100%	80	73	66	57	38	22	10	0	0	0	0
PD-L1 50-89%	107	92	75	51	33	18	8	4	1	1	0

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

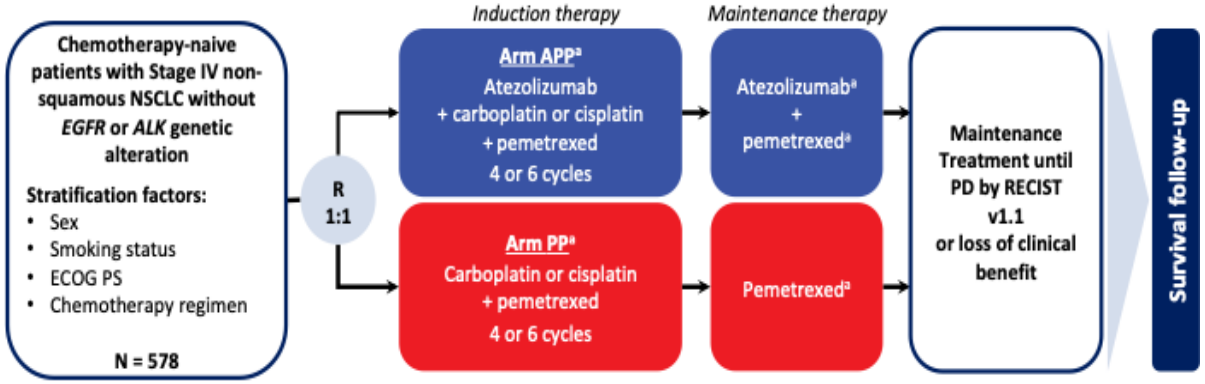
Aguilar EJ et al. *Ann Oncol*. 2019

Chemo-immunotherapy in non-squamous NSCLC

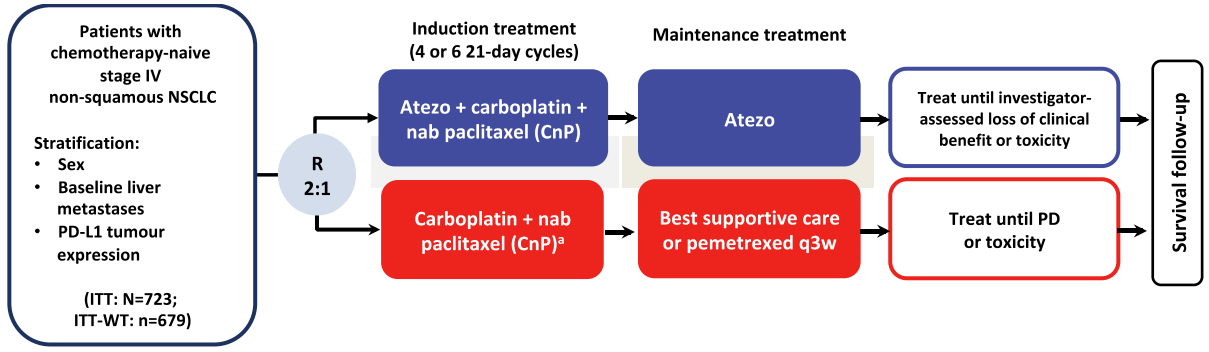
Keynote 189: *EGFR*^{wt}/*ALK*^{wt} NSCLC



IMPOWER 132: All non-squamous NSCLC



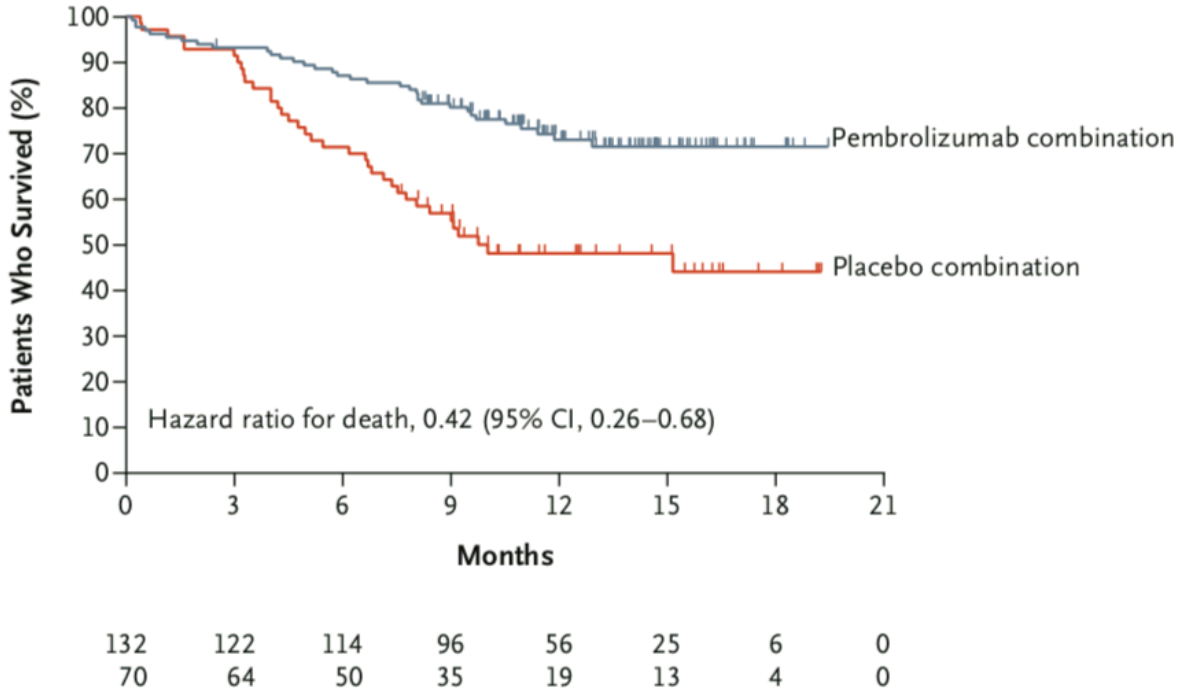
IMPOWER 130: All non-squamous NSCLC



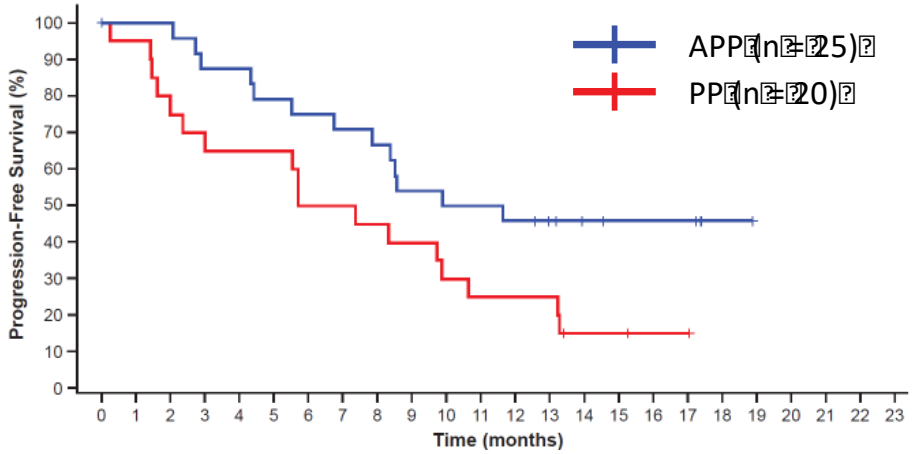
Gandhi L et al. NEJM 2018; Barlesi F et al. ESMO 2018; West J et al Lancet Oncol 2019

Options in NSCLC PD-L1 ≥50%: chemo-immunotherapy in non-squamous

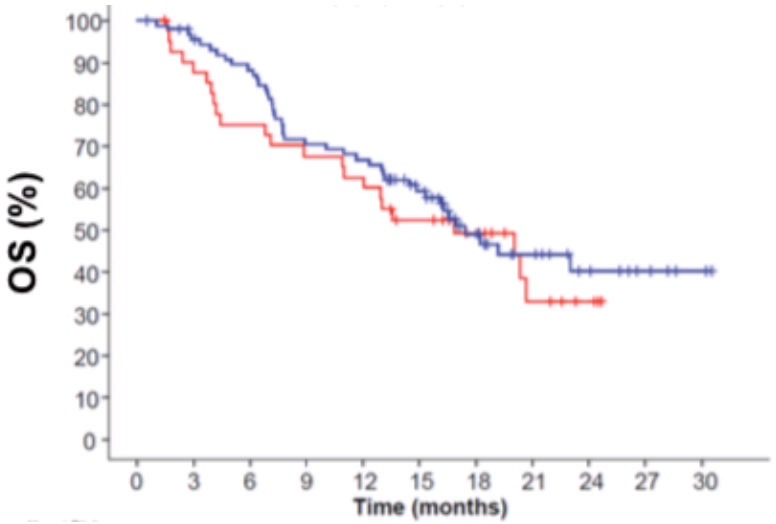
OS Keynote 189 PD-L1 ≥50%



OS IMPOWER 132 PD-L1 ≥50%



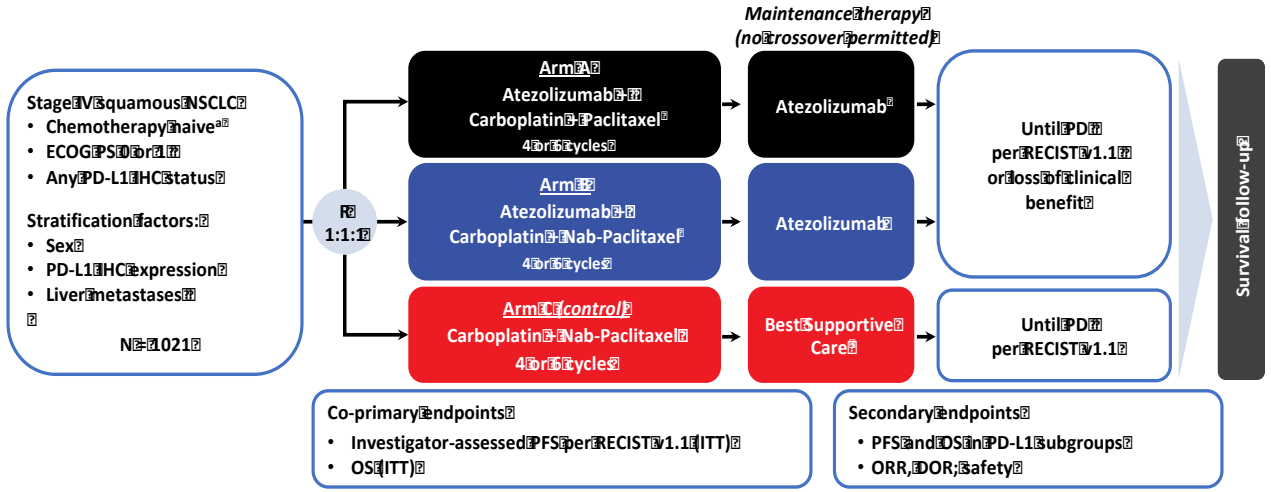
OS IMPOWER 130 PD-L1 ≥50%



Gandhi L et al. NEJM 2018; Barlesi F et al. ESMO 2018; West J et al Lancet Oncol 2019

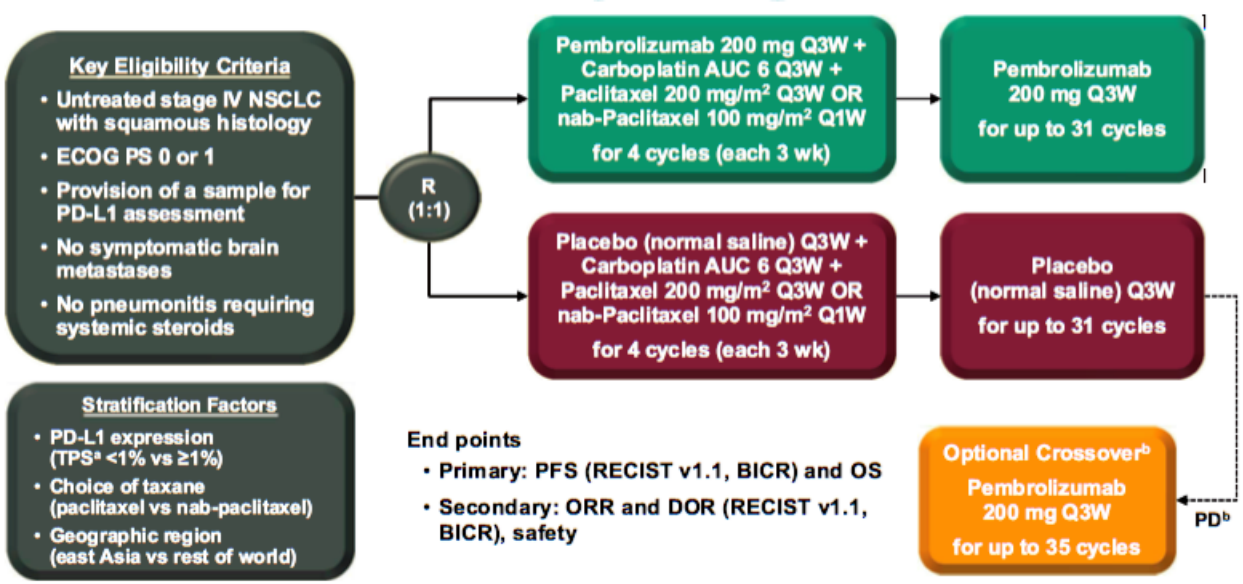
Immunotherapy plus chemotherapy in squamous NSCLC: phase III trial design

IMPOWER 131



Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m² IV qw; paclitaxel 200 mg/m² IV q3w.
[a]Patients with sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory.

KEYNOTE 407

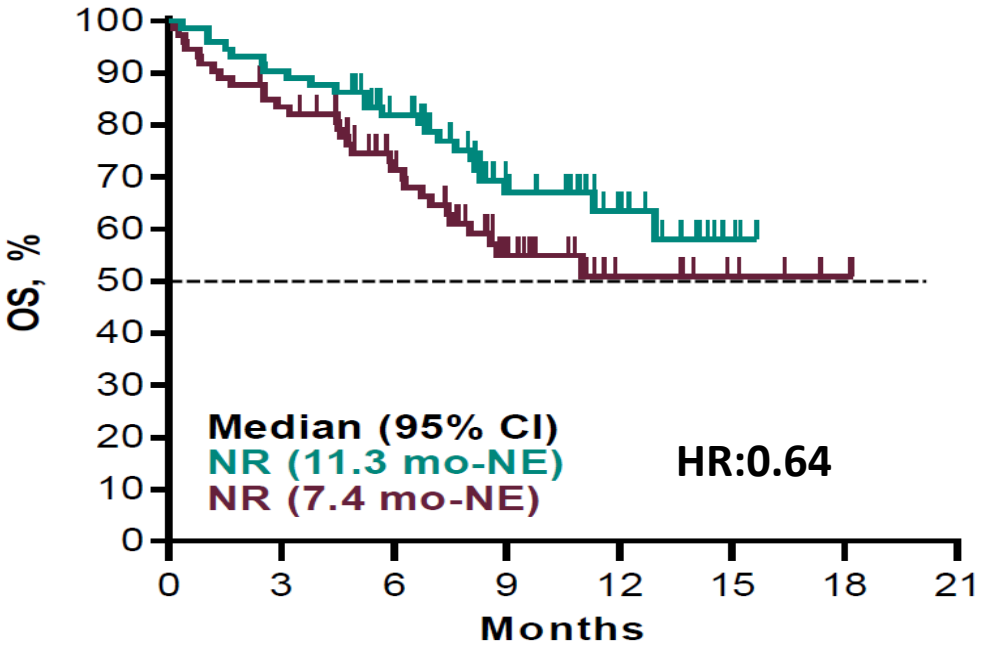


BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.
[b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and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

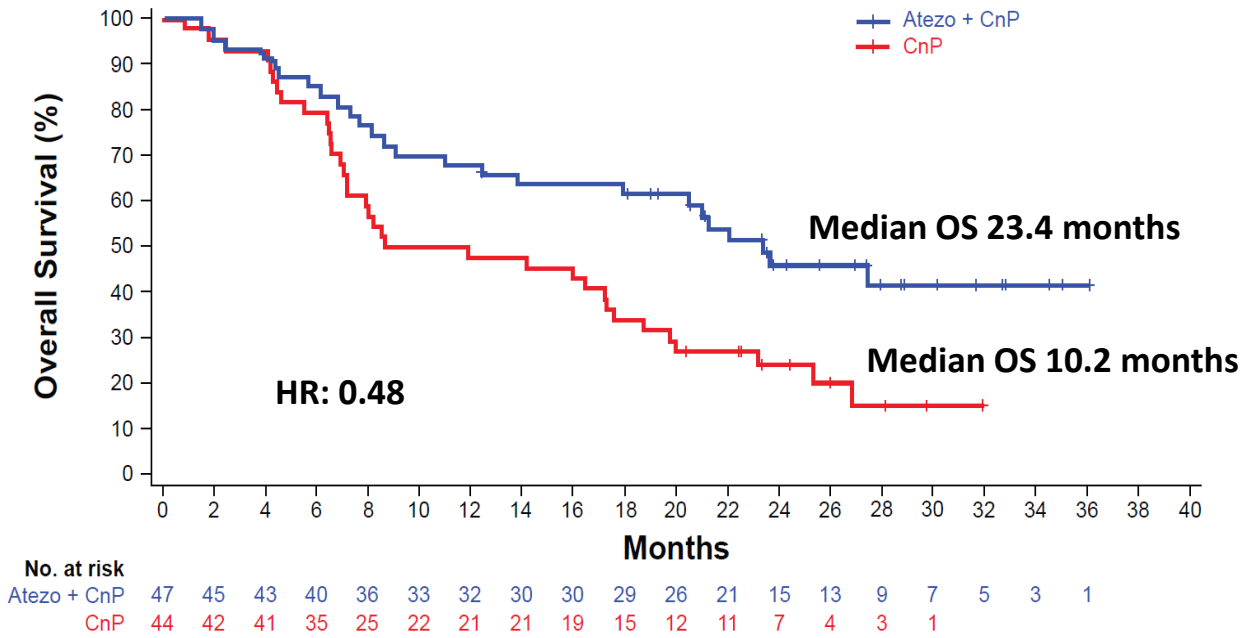
Jotte R et al. ASCO 2018; Paz Ares L, et al. NEJM 2018

Chemoimmunotherapy in PD-L1 ≥50% in squamous histology

Keynote 407



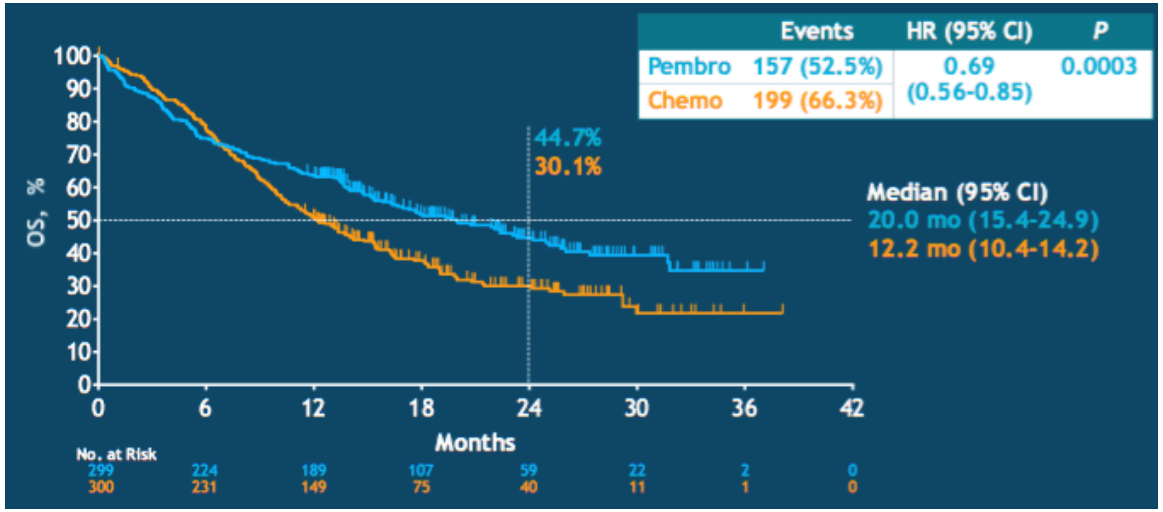
IMPOWER 131



Paz Ares L, et al. NEJM 2018; Cappuzzo F et al WCLC 2019

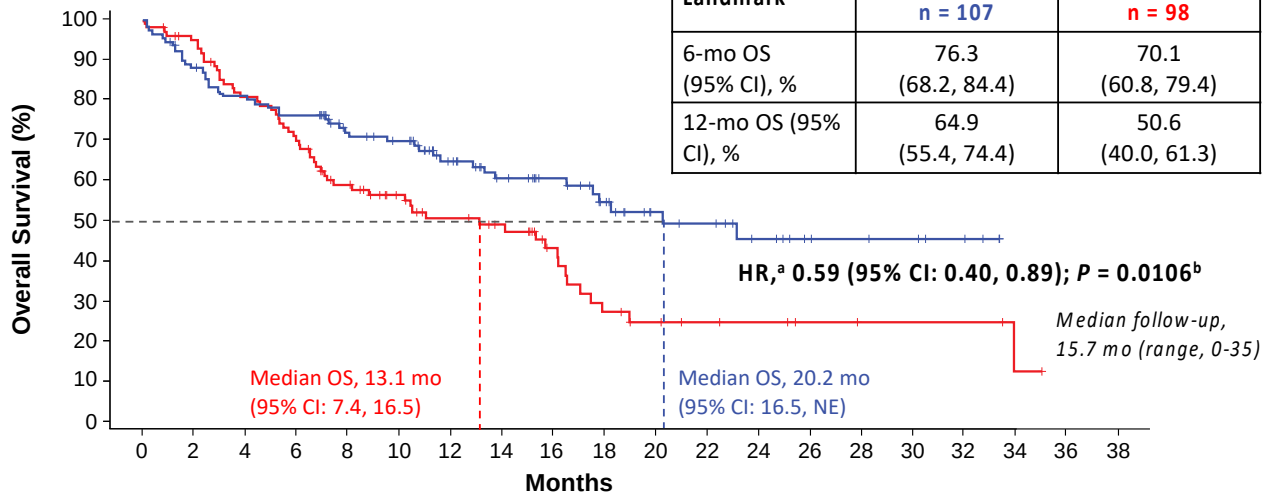
Mono-immunotherapy versus chemo-immunotherapy
Indirect comparison of OS in PD-L1 ≥50%

OS in KEYNOTE-042

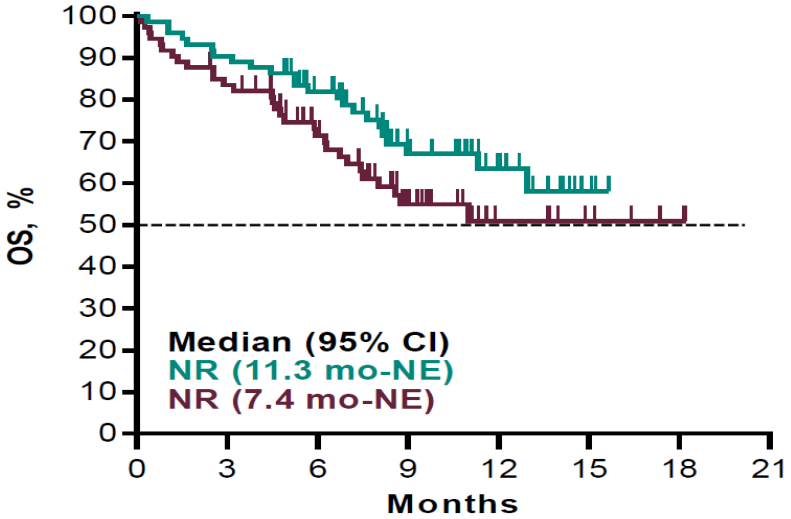


OS in IMPOWER 110

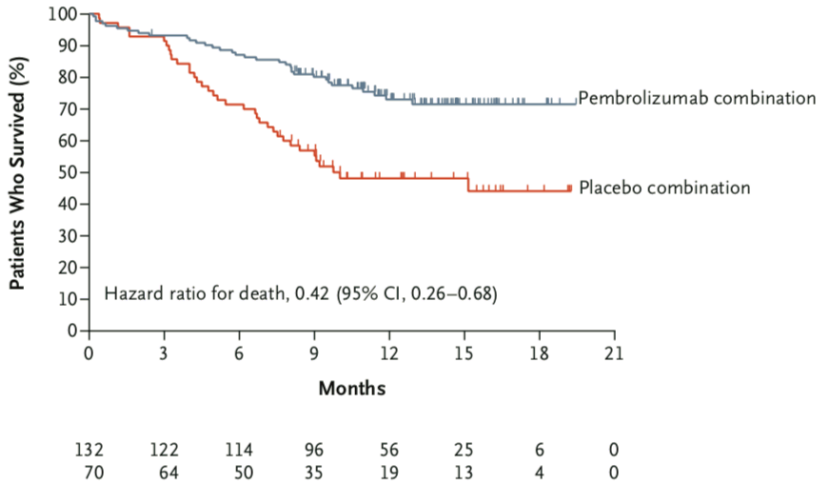
Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo OS (95% CI), %	76.3 (68.2, 84.4)	70.1 (60.8, 79.4)
12-mo OS (95% CI), %	64.9 (55.4, 74.4)	50.6 (40.0, 61.3)



OS in KEYNOTE 407



OS in KEYNOTE 189



Reck M et al. J Clin Oncol. 2019
Spigel D, et al. ESMO 2019
Paz Ares L, et al. NEJM 2018
Gandhi L et al. NEJM 2018

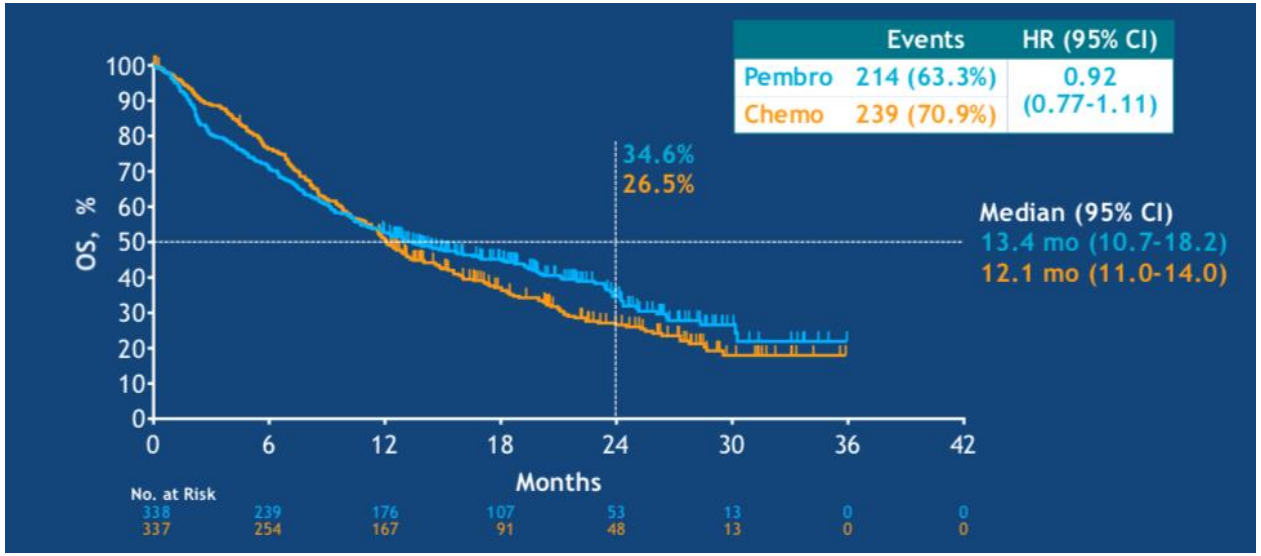
Adverse events with IO single agent versus IO+CT combo

Trial	Grade 3-5 AE with IO (%)	Grade 3-5 AE with IO+CT (%)
Keynote 024	26.0*	-
Keynote 042	17.8*	-
Checkmate 026	17.6*	-
Keynote 189	-	67.2**
Keynote 407	-	69.8**
IMPOWER 150	-	57.0-62.0**
IMPOWER 131	-	73.0**

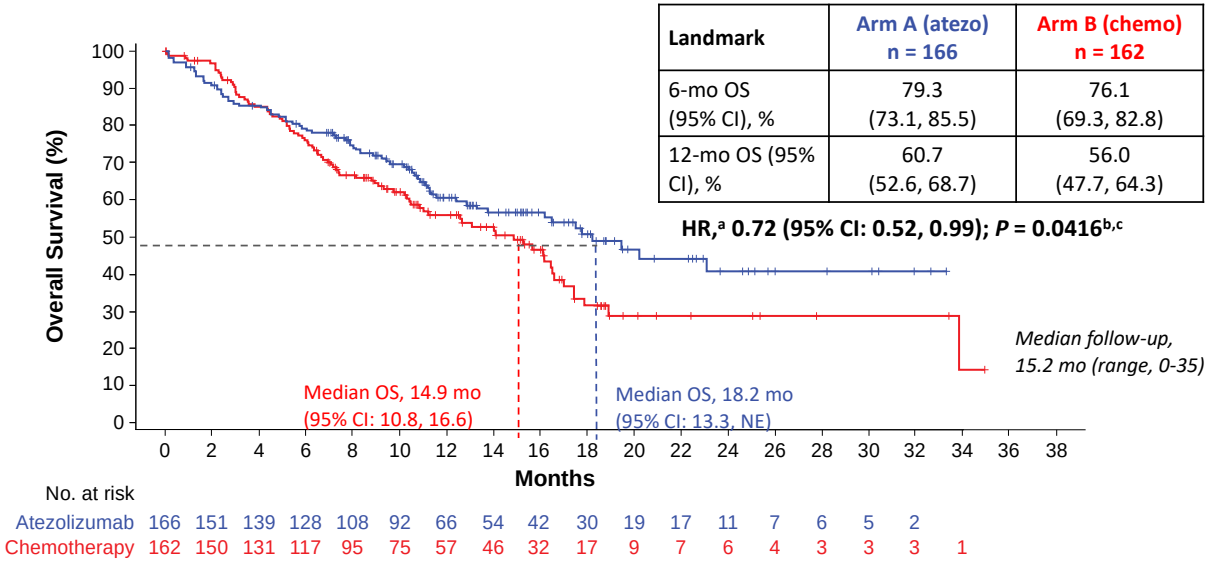
*Lower to platinum-based chemotherapy
** Similar to platinum-based chemotherapy

Mono-immunotherapy not superior to platinum-based CT in PD-L1 1-49%

OS in KEYNOTE-042



OS in IMpower110

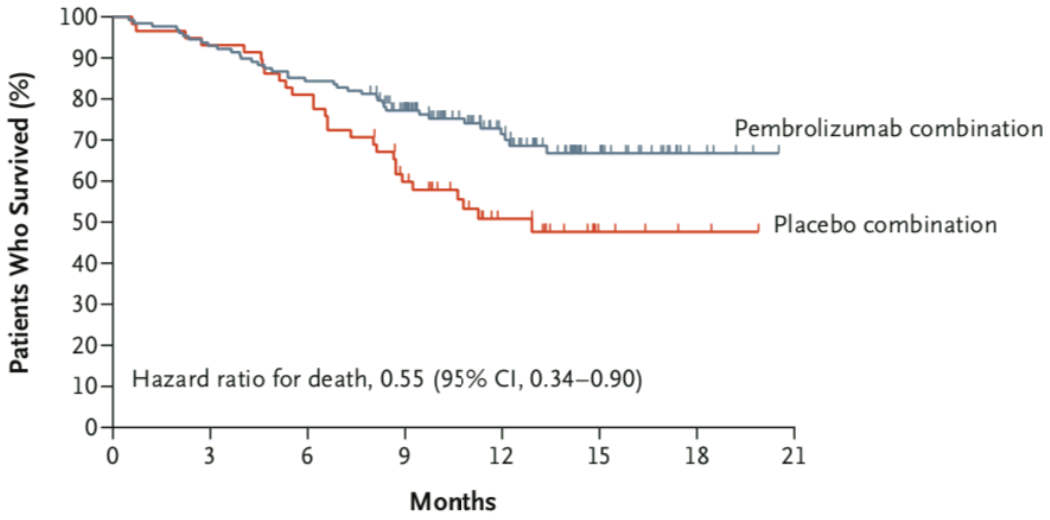


Landmark	Arm A (atezo) n = 166	Arm B (chemo) n = 162
6-mo OS (95% CI), %	79.3 (73.1, 85.5)	76.1 (69.3, 82.8)
12-mo OS (95% CI), %	60.7 (52.6, 68.7)	56.0 (47.7, 64.3)

Lopes G. et al ASCO 2018; Spigel D, et al. ESMO 2019

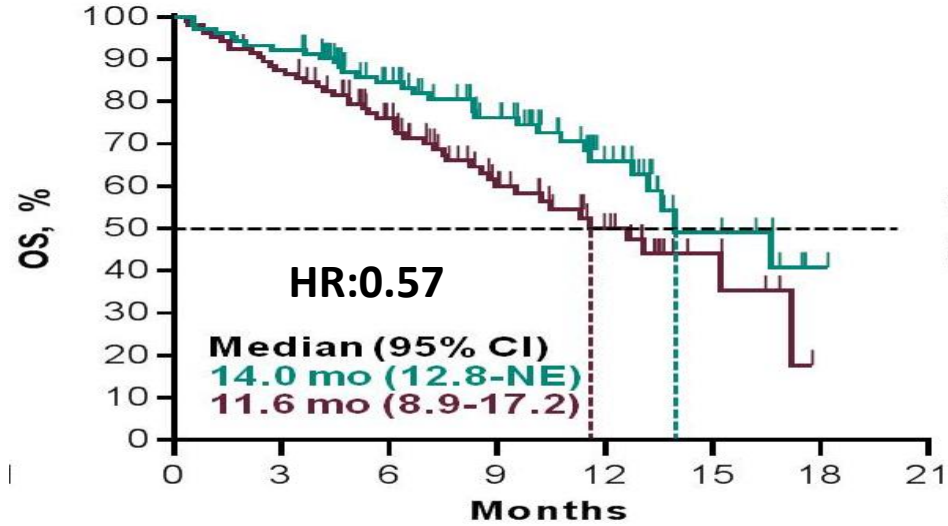
Chemoimmunotherapy in PD-L1 1-49%: KEYNOTE 189 and 407

KEYNOTE 189: Non-Squamous



No. at Risk								
Pembrolizumab combination	128	119	108	84	52	21	5	0
Placebo combination	58	54	47	32	17	5	2	0

KEYNOTE 407: Squamous

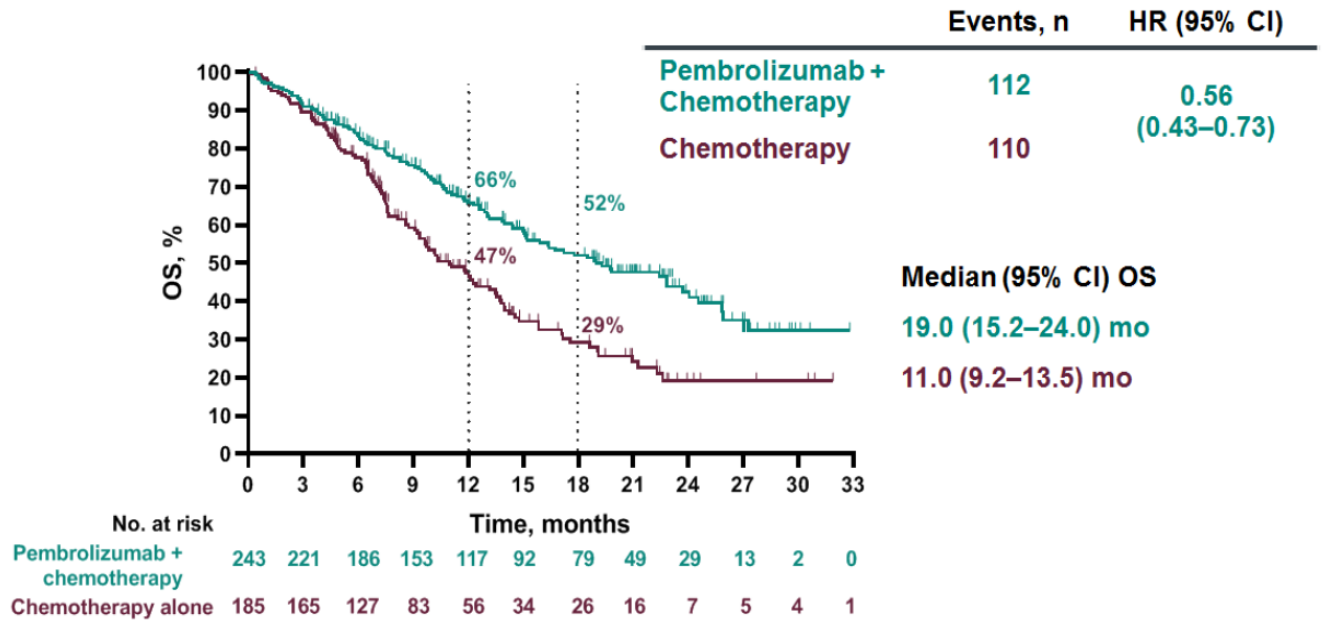


No. at Risk								
	103	95	68	50	25	9	1	0
	104	90	66	37	21	6	0	0

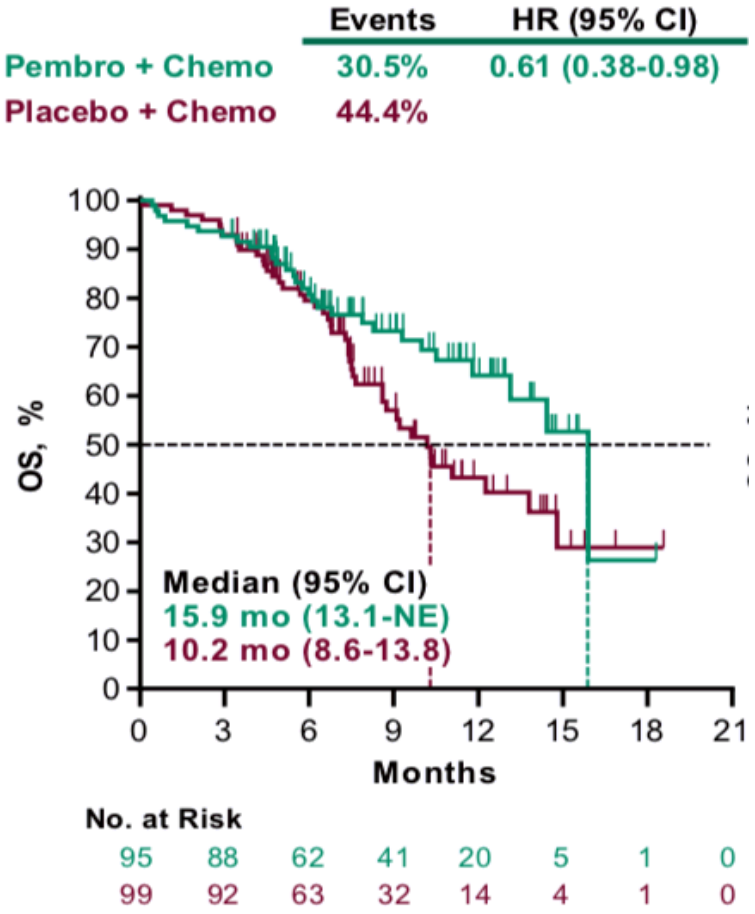
Ghandi L et al NEJM 2018; Paz Ares L, et al. NEJM 2018

Chemoimmunotherapy in PD-L1 <1% in non-squamous and in squamous histology

Pooled analysis in non-squamous

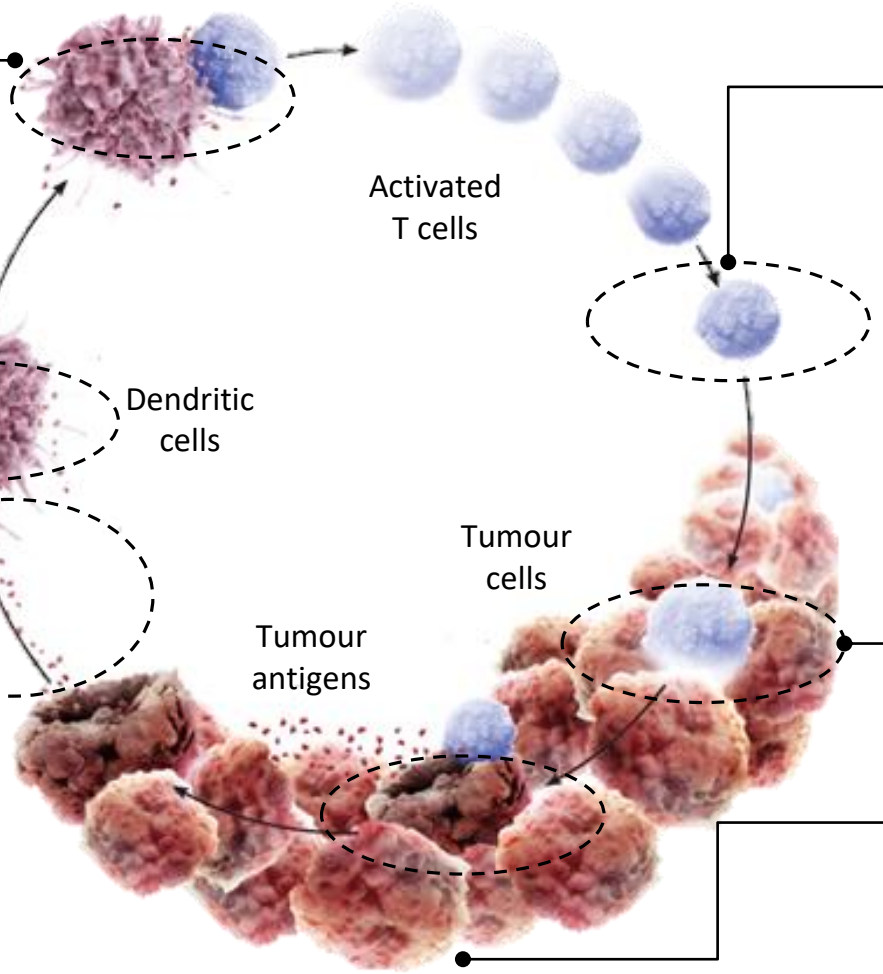


KEYNOTE 407



Borghaei H et al. WCLC 2019; Paz Ares L, et al. NEJM 2018

Rationale for combining atezolizumab with bevacizumab and chemotherapy



Atezolizumab

Promotes T-cell activation by allowing B7.1 co-stimulation[1]

Bevacizumab

Promotes DC maturation[2,11,12]

Chemotherapy

Promotes tumour cell death triggering the release of antigens[1,2]

Bevacizumab

Normalises the tumour vasculature, increasing T-cell infiltration[2–6]

Bevacizumab

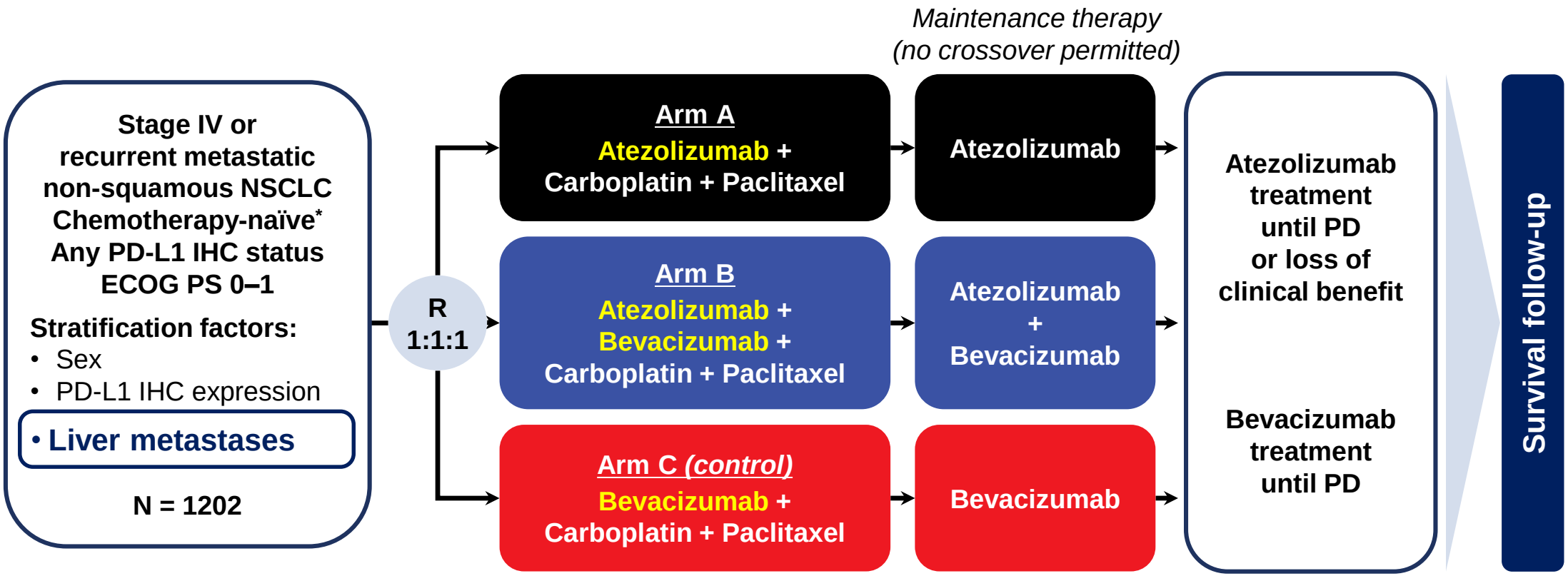
Decreases the activity of immunosuppressive cells (MDSCs and Tregs)[2,3,7–10]

Atezolizumab

Restores anticancer immunity[1] with activity further enhanced through VEGF-mediated immunomodulatory effects

1. Chen & Mellman. Immunity 2013; 2. Hegde, et al. Semin Cancer Biol 2017; 3. Wallin, et al. Nat Commun 2016; 4. Goel, et al. Physiol Rev 2011; 5. Motz, et al. Nat Med 2014; 6. Hodi, et al. Cancer Immunol Res 2014; 7. Gabrilovich & Nagaraj. Nat Rev Immunol 2009; 8. Roland, et al. PLoS One 2009; 9. Facciabene, et al. Nature 2011; 10. Voron, et al. J Exp Med 2015; 11. Gabrilovich, et al. Nat Med 1996; 12. Oyama, et al. J Immunol 1998

IO and bevacizumab in NSCLC: IMpower150 trial design

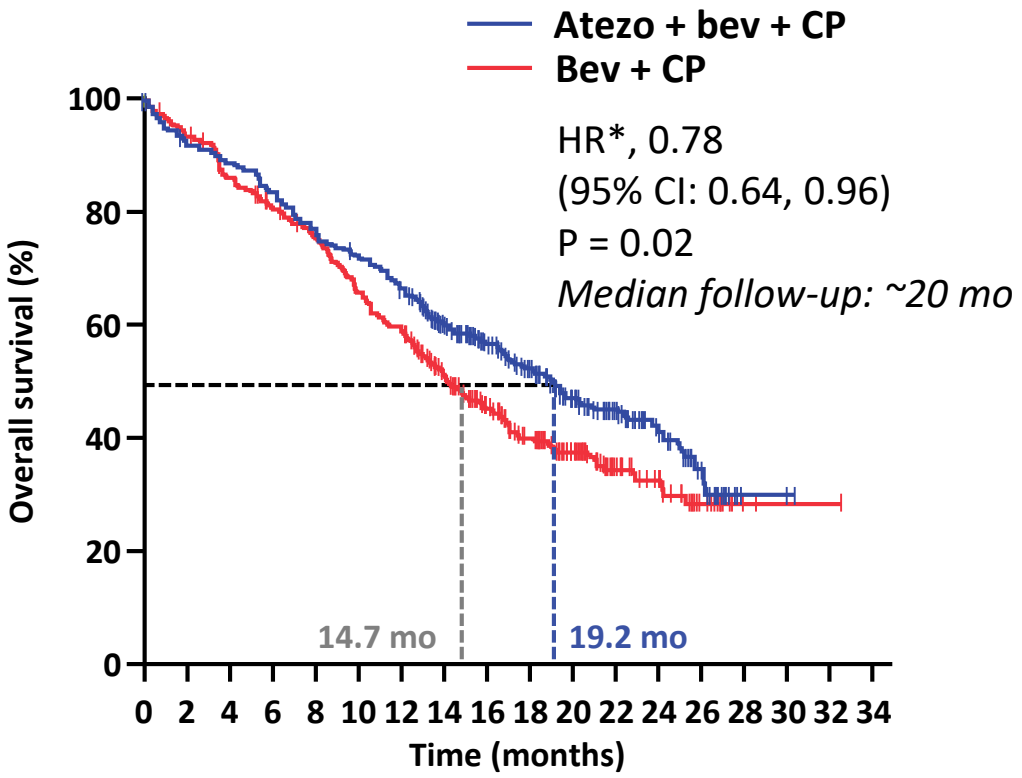


Allowed inclusion of patients with a sensitising EGFR mutation or ALK translocation must have disease progression or intolerance to treatment with one or more approved targeted therapies.

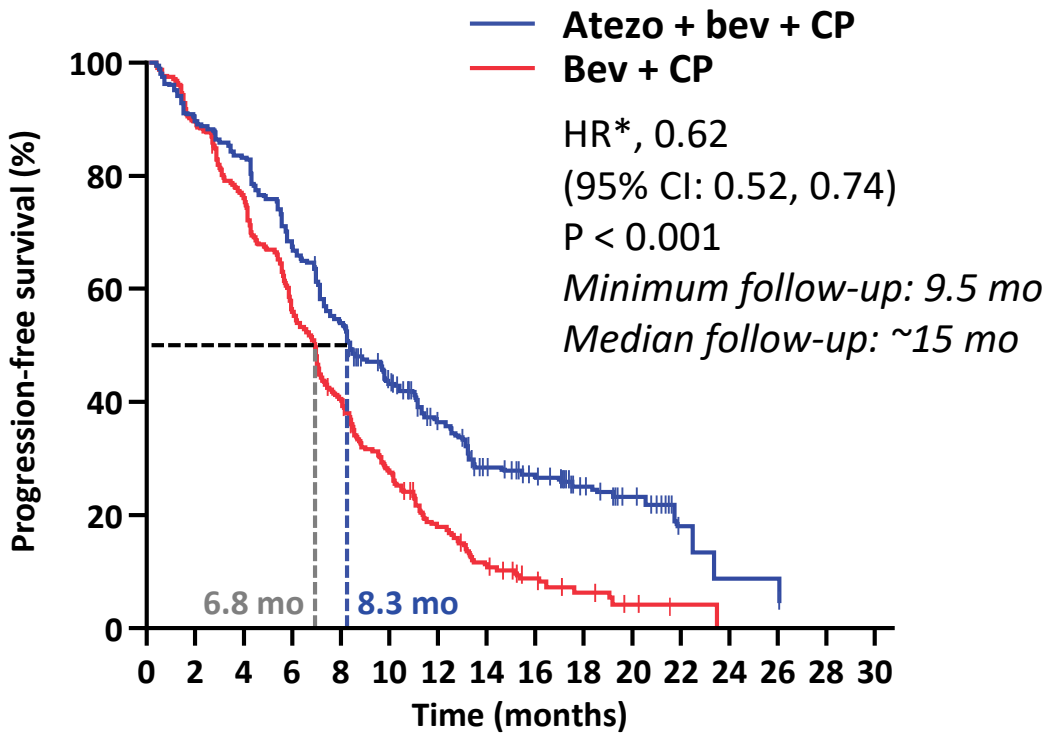
Socinski MA et al. N Engl J Med 2018

IMpower150 met its co-primary endpoints of OS and PFS in the ITT-WT population

OS



PFS



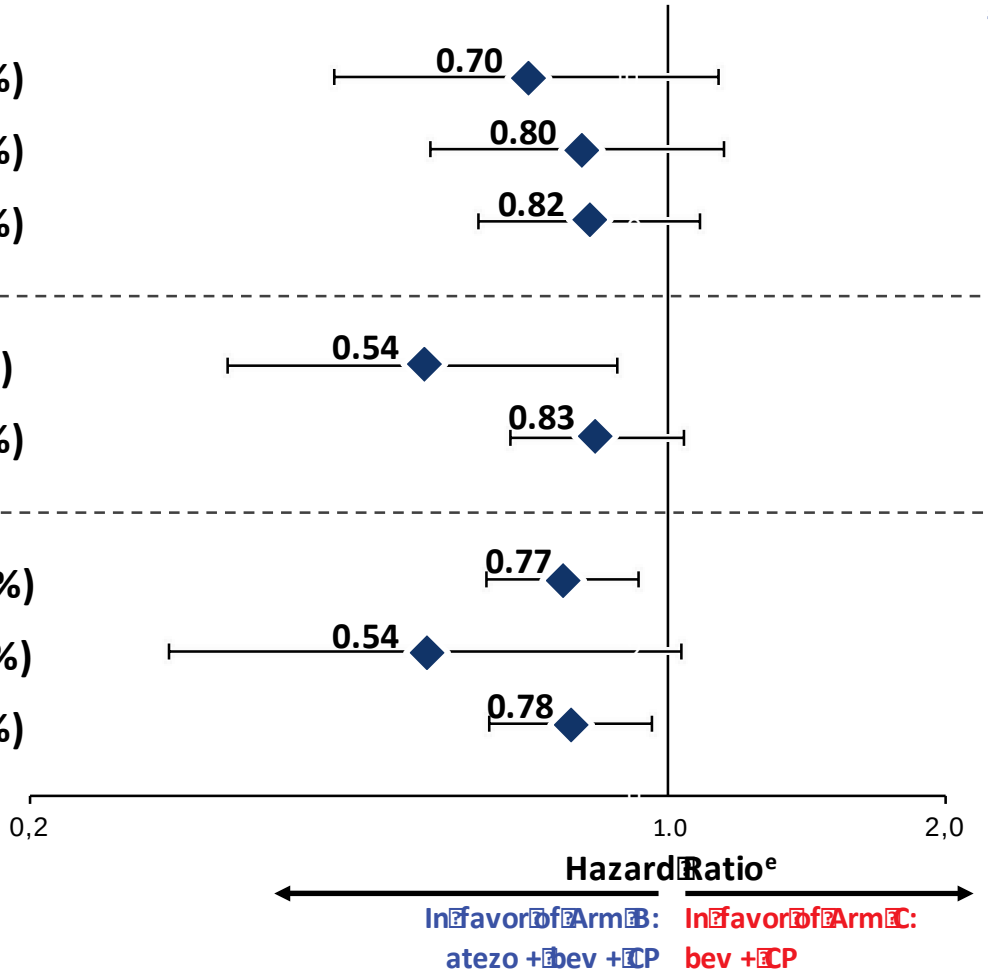
*Stratified HR

Data cut-off: 22 January 2018 (OS); 15 September 2017 (PFS)

Socinski MA et al. N Engl J Med 2018

OS in Key Subgroups (Arm B vs Arm C)

Subgroup	n (%)[a]	Median OS, mo	
		Arm B	Arm C
PD-L1–High (TC3 or IC3) WT	136 (20%)	25.2	15.0
PD-L1–Low (TC1/2 or IC1/2)[b] WT	226 (32%)	20.3	16.4
PD-L1–Negative (TC0 and IC0) WT	339 (49%)	17.1	14.1
Liver Metastases WT	94 (14%)	13.2	9.1
No Liver Metastases WT	602 (86%)	19.8	16.7
ITT (including *EGFR/ALK*+)	800 (100%)	19.8	14.9
EGFR/ALK+ only[c]	104[d] (13%)	NE	17.5
ITT-WT	696 (87%)	19.2	14.7



Socinski MA et al. N Engl J Med 2018

BEAT:
Phase II randomized trial comparing atezolizumab versus atezolizumab plus bevacizumab as first-line treatment in PD-L1+ advanced metastatic NSCLC

Inclusion criteria
- Histologically confirmed diagnosis of stage IV non-squamous NSCLC
- No evidence of *EGFR* sensitizing mutations or *ALK* or *ROS1* rearrangements
- Availability of tumor tissue
- PD-L1 expression ≥1%
- No previous chemotherapy
- ECOG Performance status 0-1
- Age ≥ 18 years
- Measurable disease RECIST v1.1

R
1:1

Atezolizumab 1200 mg i.v., every 3 weeks until disease progression, toxicity or patient refusal to continue
N= 103

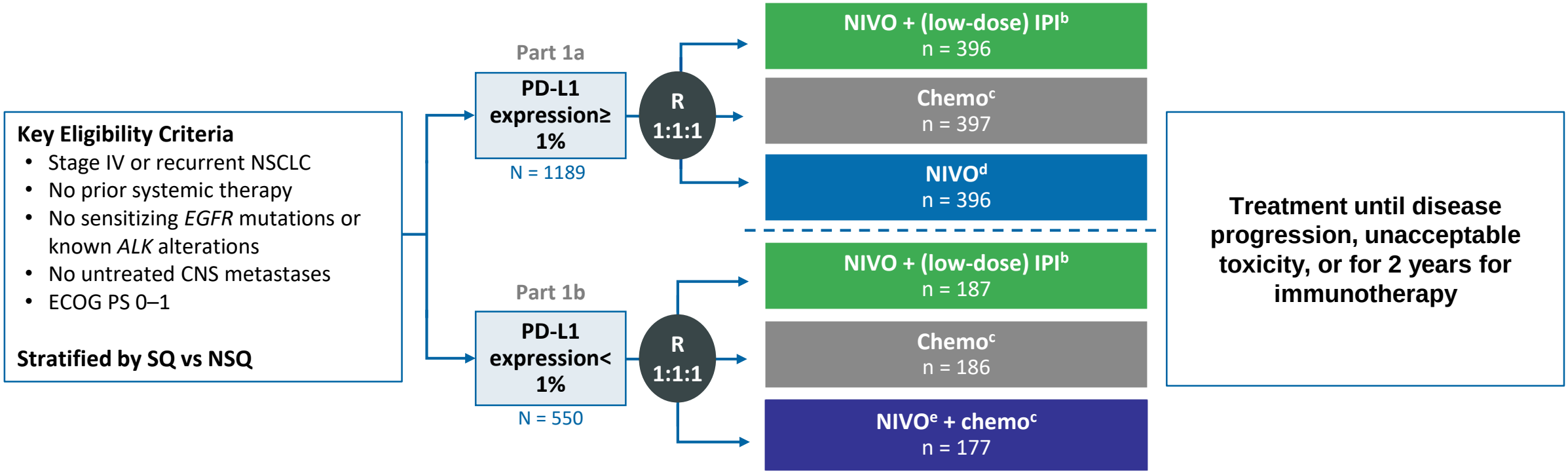
Atezolizumab 1200 mg i.v., every 3 weeks + bevacizumab 15 mg/kg every 3 weeks until disease progression, toxicity or patient refusal to continue
N= 103

Primary:
- Overall Survival (OS) at 18 months in patients treated with atezolizumab alone versus atezolizumab-bevacizumab combination

Secondary:
- Response rate (RR)
- Progression-free survival (PFS)
- Toxicity
- Correlation with tumor biomarkers in tumor tissue

- Participating Centers: 20 Italian institutions
- Study Duration 24 months

Chemo-free options: CheckMate 227 Part 1 Study Design



Independent co-primary endpoints: NIVO + IPI vs chemo

- PFS in high TMB (≥10 mut/Mb) population[f]
- OS in PD-L1 ≥ 1% population[g]

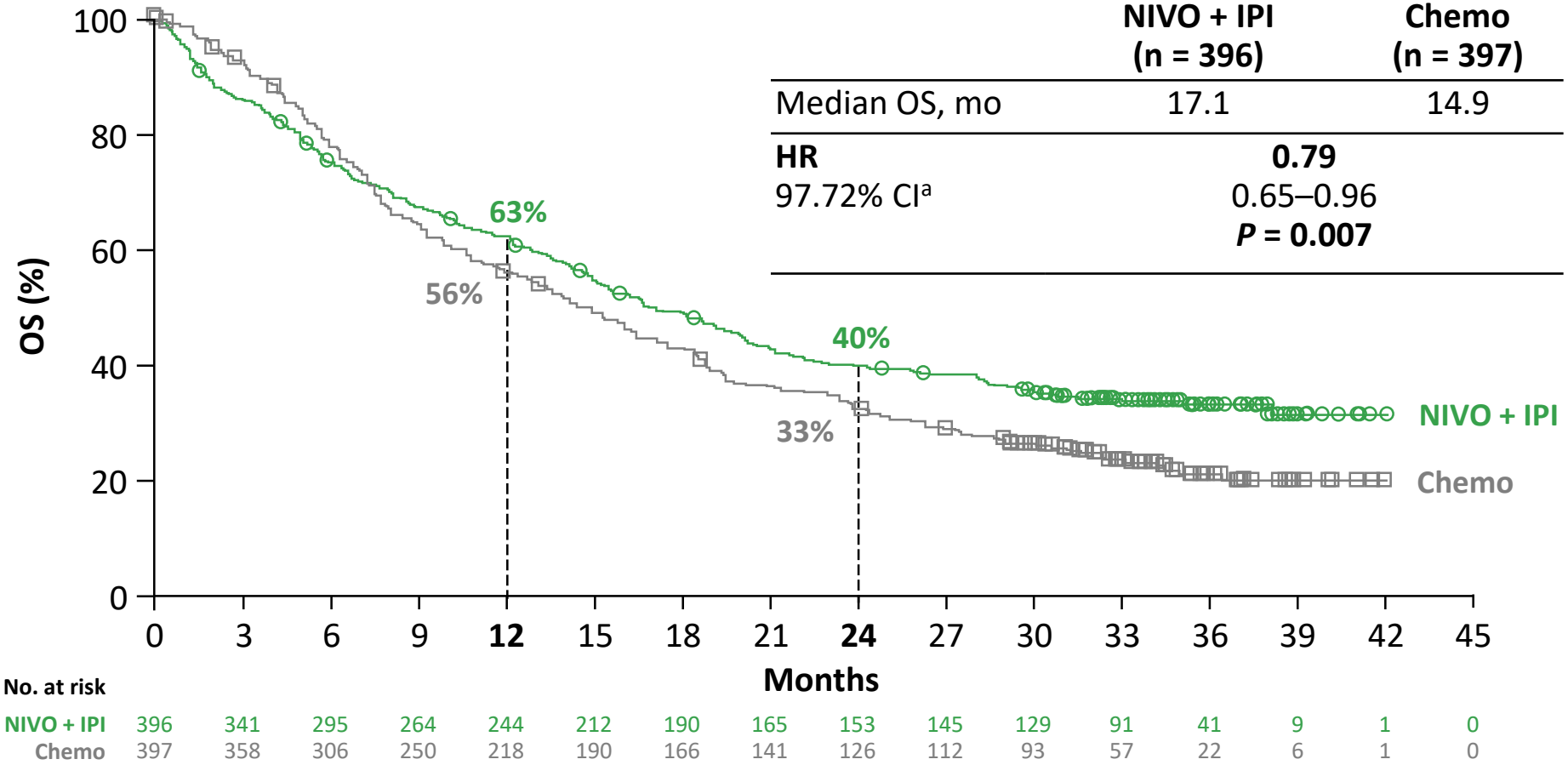
Secondary endpoints (PD-L1 hierarchy):

- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

Hellmann MD et al NEJM 2019

Primary Endpoint: OS With NIVO + IPI vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a
NIVO + IPI
Chemo
NIVO



	NIVO + IPI (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	14.9
HR	**0.79**	
97.72% CI[a]	0.65–0.96	
	***P* = 0.007**	

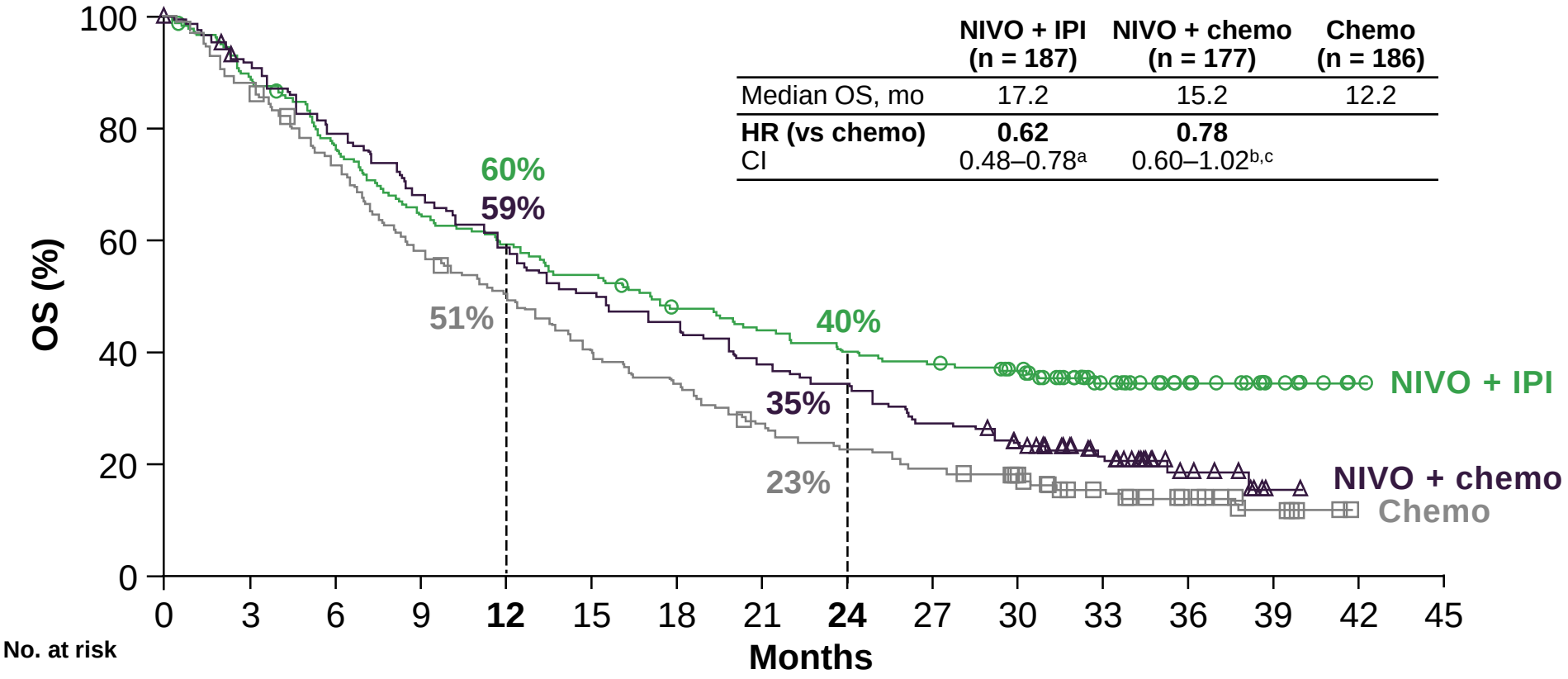
Hellmann MD et al NEJM 2019

OS With NIVO + IPI and NIVO + Chemo vs Chemo in Patients With Tumor PD-L1 Expression < 1% (Exploratory Analysis)

Part 1b

NIVO + IPI
Chemo
NIVO + chemo

	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS, mo	17.2	15.2	12.2
HR (vs chemo)	**0.62**	**0.78**	
CI	0.48–0.78[a]	0.60–1.02[b,c]	



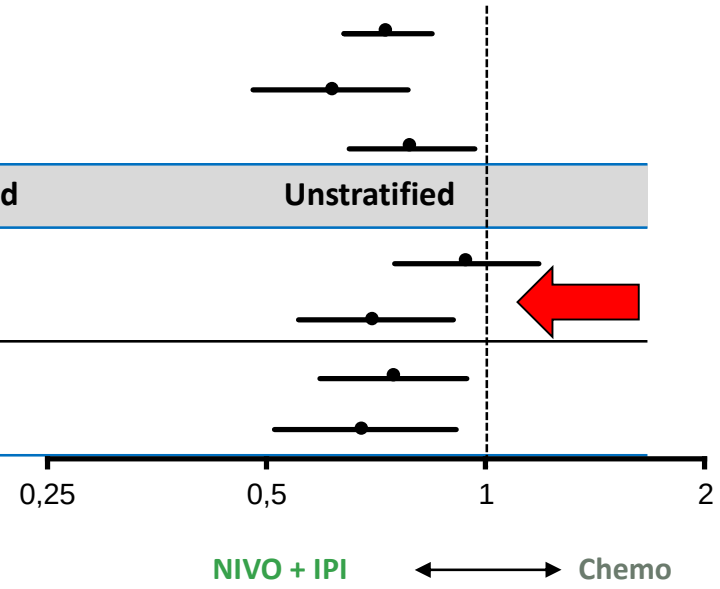
No. at risk

NIVO + IPI	187	165	142	120	110	100	87	80	73	69	59	34	19	8	2	0
NIVO + chemo	177	159	139	119	102	88	78	67	60	48	40	23	9	1	0	0
Chemo	186	164	135	107	92	74	62	49	41	35	29	19	12	5	0	0

Hellmann MD et al NEJM 2019

OS for NIVO + IPI vs Chemo by Tumor PD-L1 Expression, TMB Status, and Combined Subgroups in All Randomized Patients

		Median OS, months		HR	HR (95% CI)
		NIVO + IPI n = 583	Chemo n = 583		
Randomized groups				**Stratified**	**Stratified**
PD-L1	All randomized (N = 1166)	17.1	13.9	0.73	
	PD-L1 < 1% (n = 373)	17.2	12.2	0.62	
	PD-L1 ≥ 1% (n = 793)	17.1	14.9	0.79[a]	
Additional exploratory subgroups analyses[b,c]				**Unstratified**	**Unstratified**
PD-L1	1–49% (n = 396)	15.1	15.1	0.94	
	≥ 50% (n = 397)	21.2	14.0	0.70	
TMB[d] (mut/Mb)	low, < 10 (n = 380)	16.2	12.6	0.75	
	high, ≥ 10 (n = 299)	23.0	16.4	0.68	



Hellmann MD et al NEJM 2019

Nivolumab+ipilimumab and platinum-based CT: October 22, 2019 BMS press release

Bristol-Myers Squibb

Press Release

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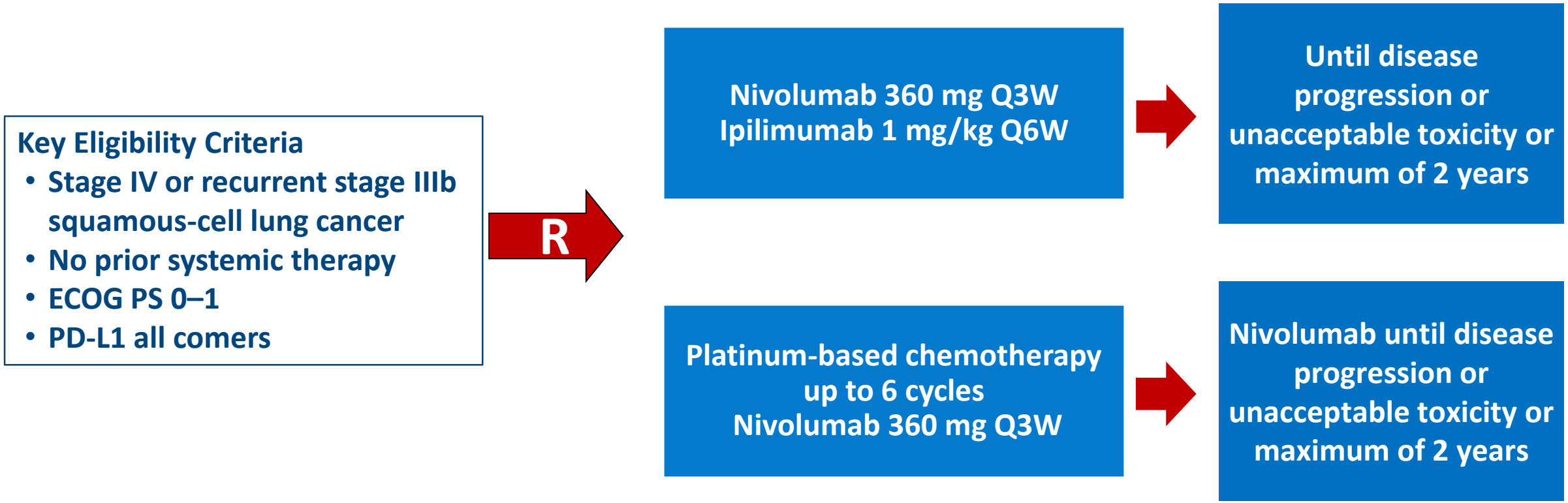
CheckMate -9LA, a Phase 3 Trial Evaluating Opdivo (nivolumab) Plus Low-Dose Yervoy (ipilimumab) Combined with Chemotherapy, Meets Primary Endpoint Demonstrating Superior Overall Survival Compared to Chemotherapy Alone in First-Line Lung Cancer

Study evaluated Opdivo plus low-dose Yervoy given concomitantly with two cycles of chemotherapy vs. chemotherapy alone for the first-line treatment of advanced non-small cell lung cancer

SQUINT: study design: Phase II, randomized, non comparative study



Primary endpoints:

- OS at 12 months in Arm A and Arm B

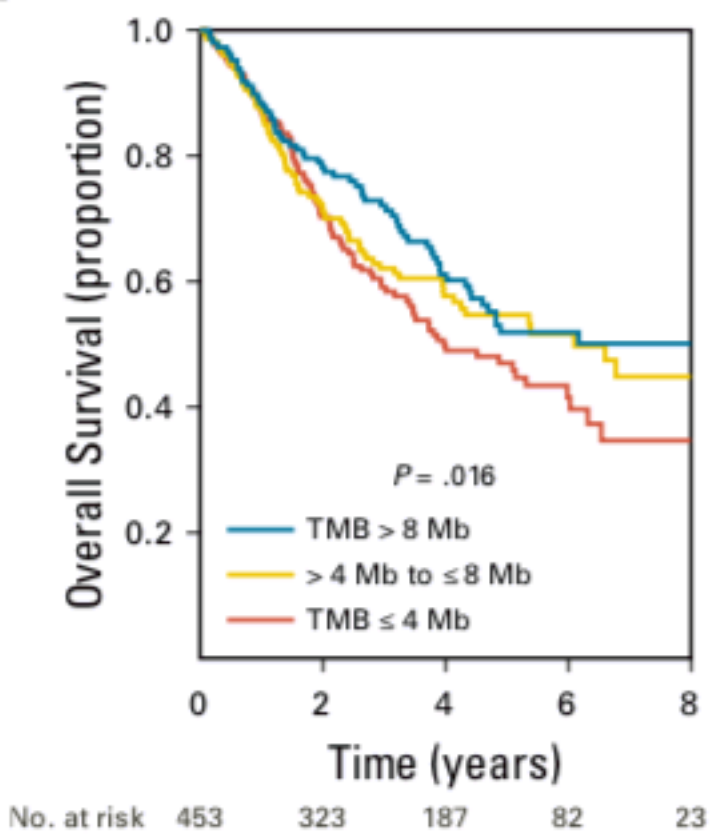
Select secondary endpoints:

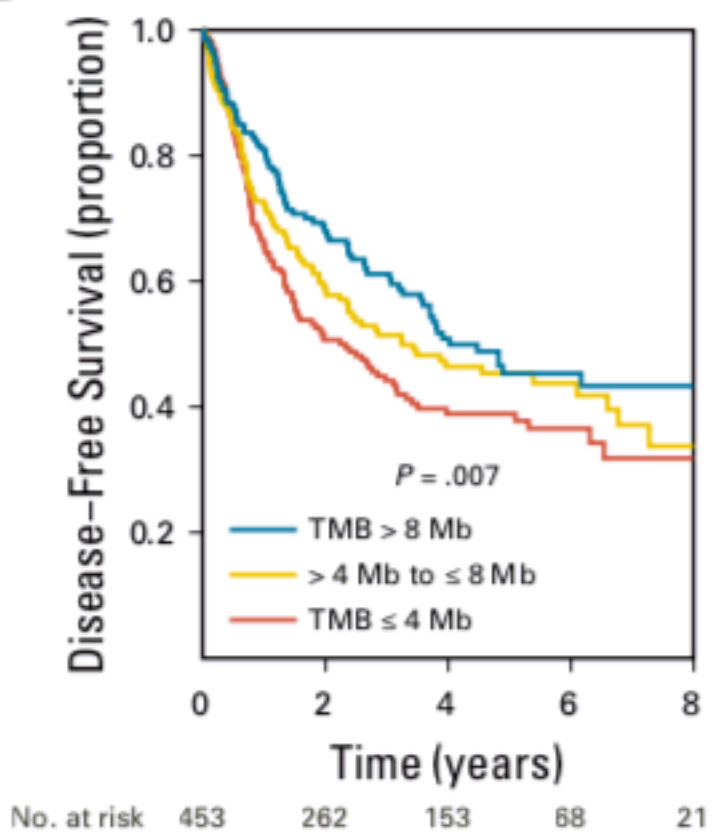
- RR, median PFS and median OS in Arm A and B
- RR, median PFS and median OS in patients with or without bone metastases

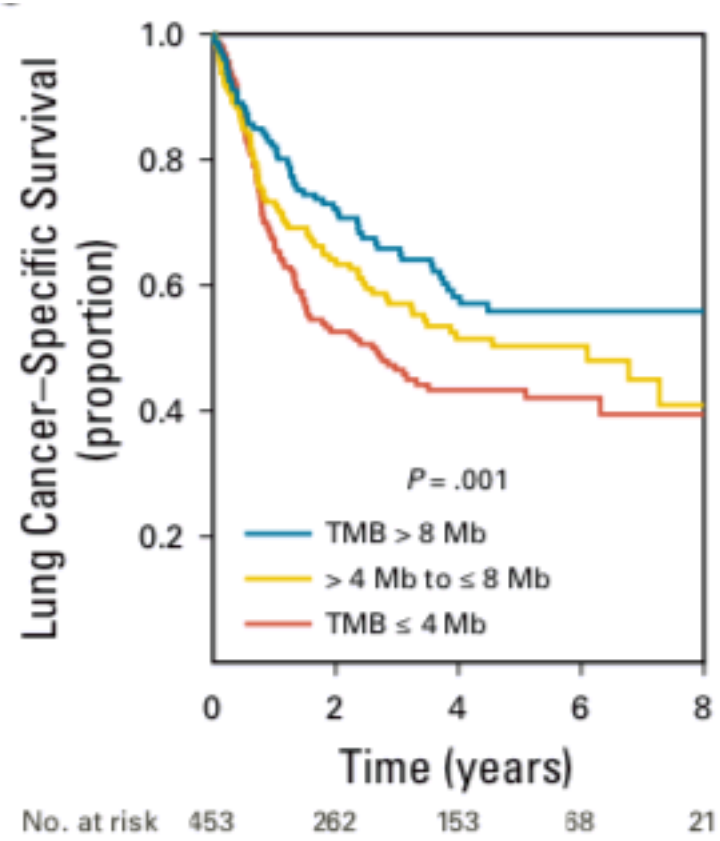
Landi L et al ESMO 2019

TMB is a positive prognostic factor

Retrospective analysis on 908 resected NSCLC



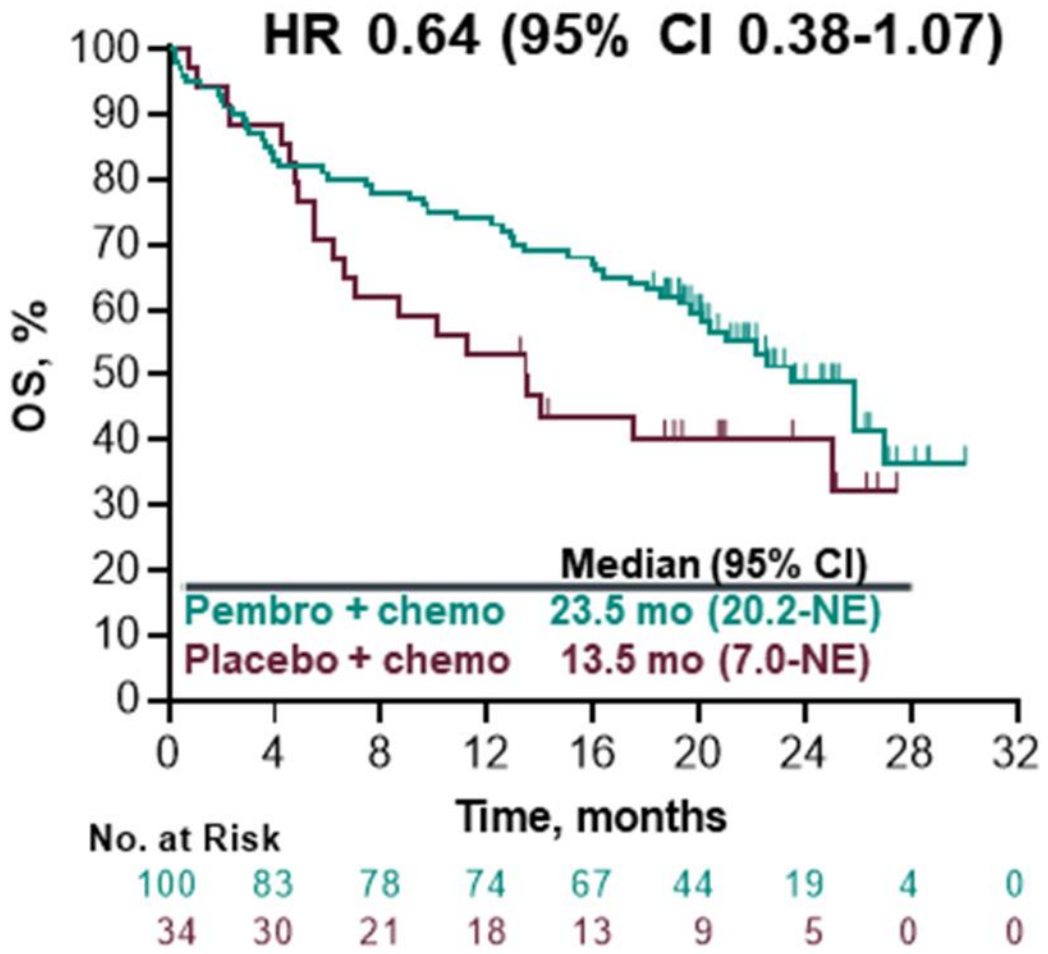




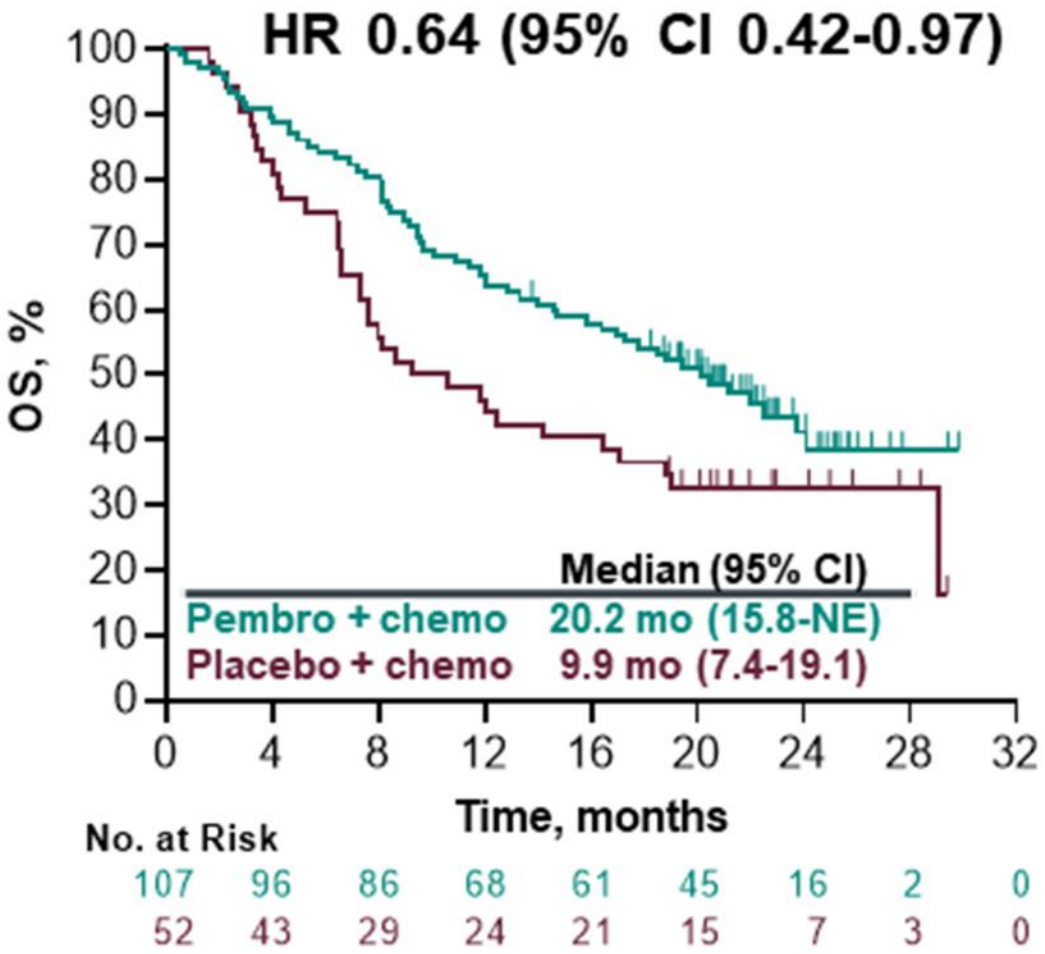
Devarakonda S et al. JCO 2018

TMB in KEYNOTE-189: Impact on OS-PD-L1 all comers

tTMB ≥175 mut/exome



tTMB <175 mut/exome

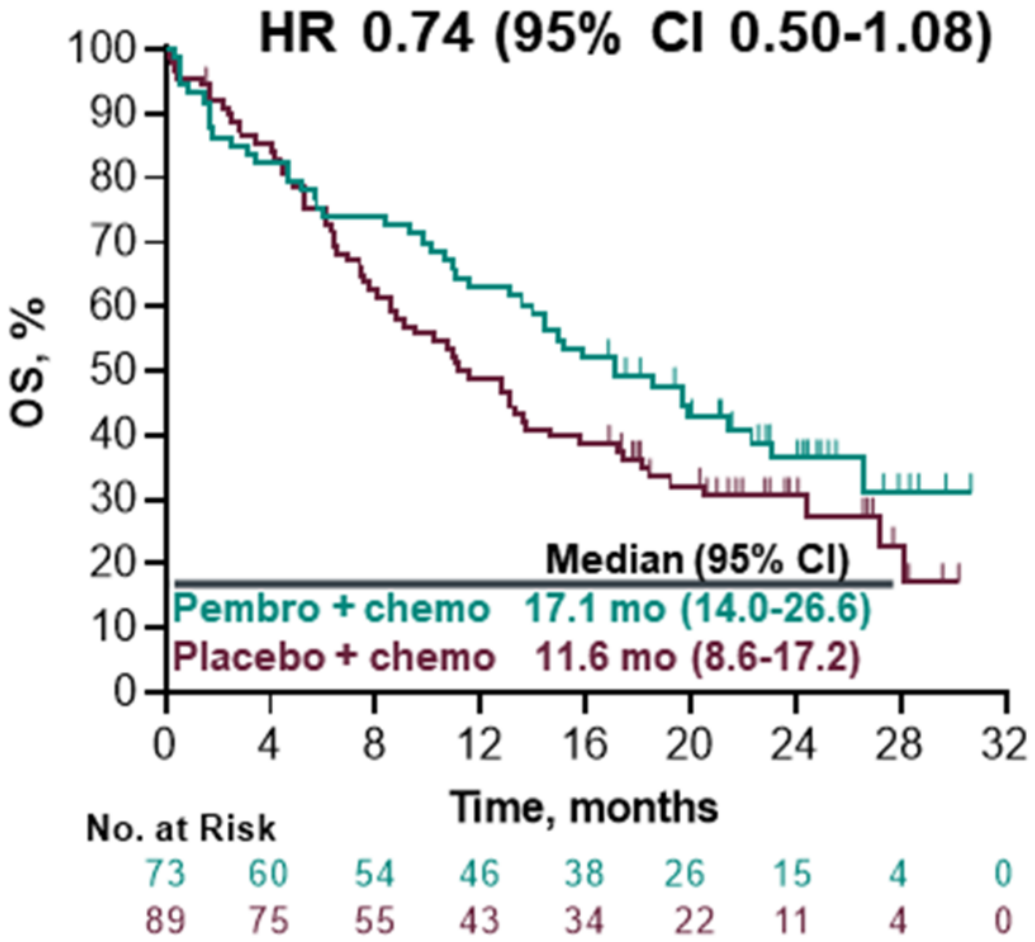


Data cutoff date: Sep 21, 2018.

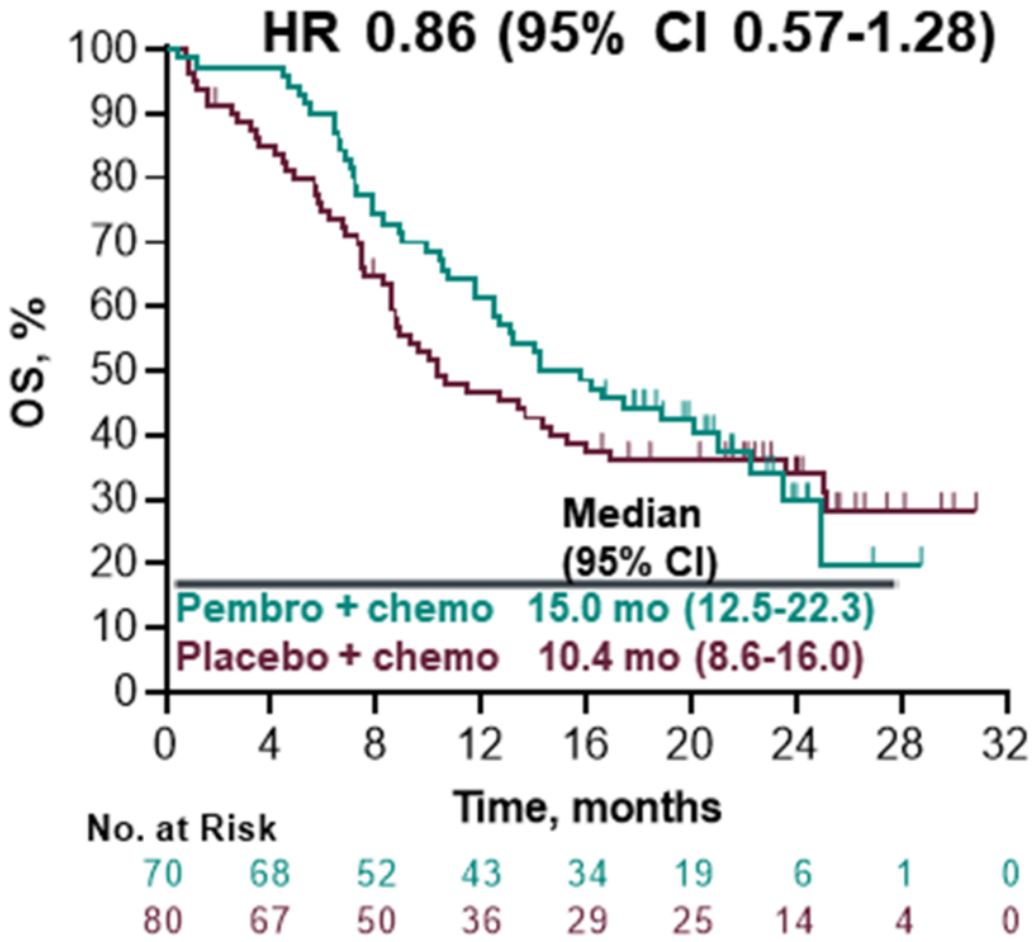
Paz-Ares L et al. ESMO 2019

TMB in KEYNOTE-407: Impact on OS-PD-L1 all comers

tTMB ≥175 mut/exome



tTMB <175 mut/exome

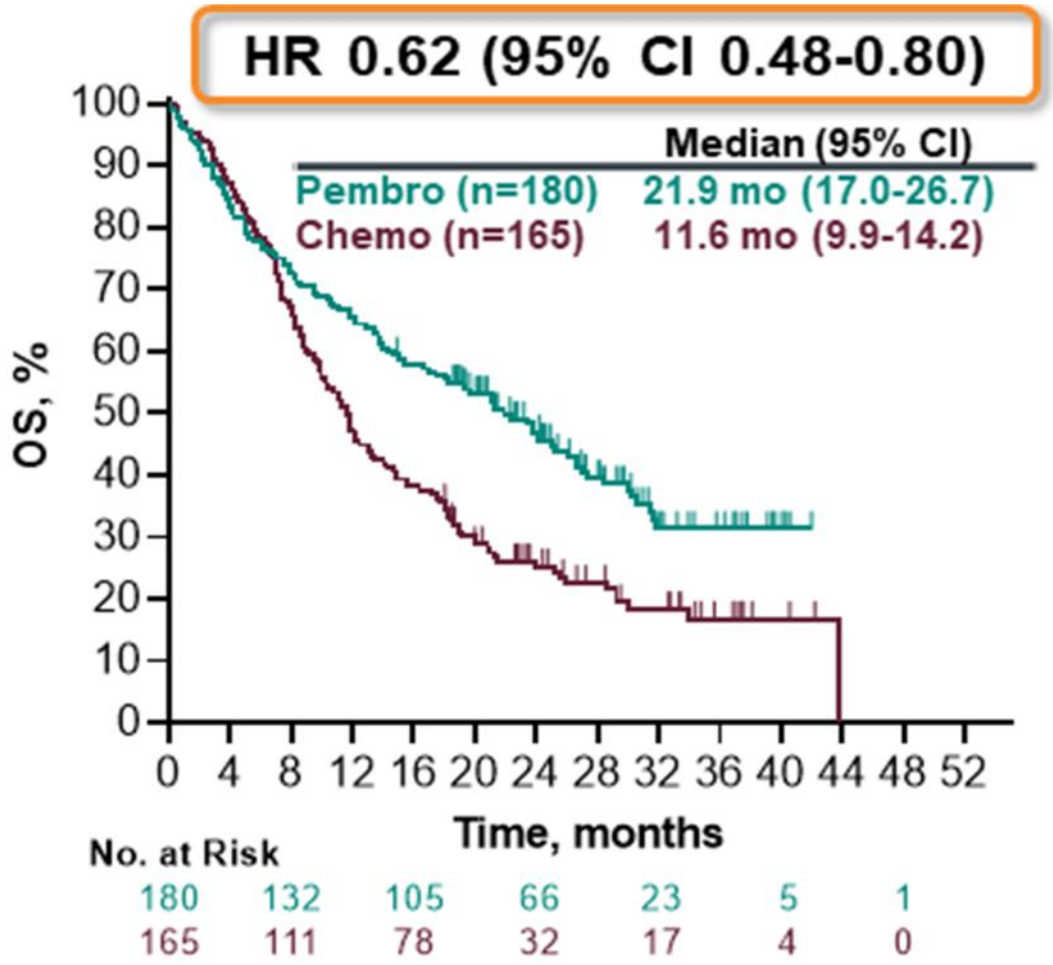


Data cutoff date: May 9, 2019.

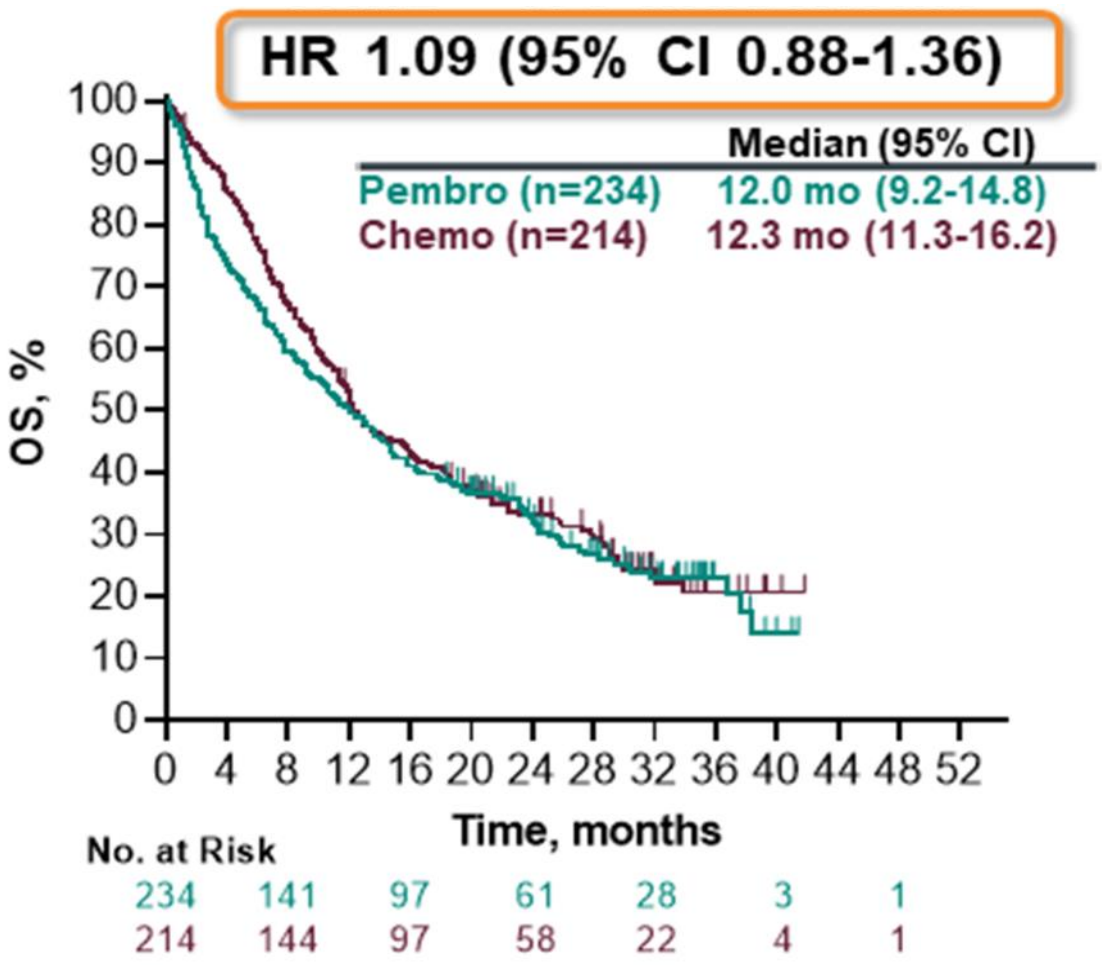
Paz-Ares L et al. ESMO 2019

TMB in KEYNOTE-042: Impact on OS-PD-L1+

tTMB ≥175 mut/exome



tTMB <175 mut/exome



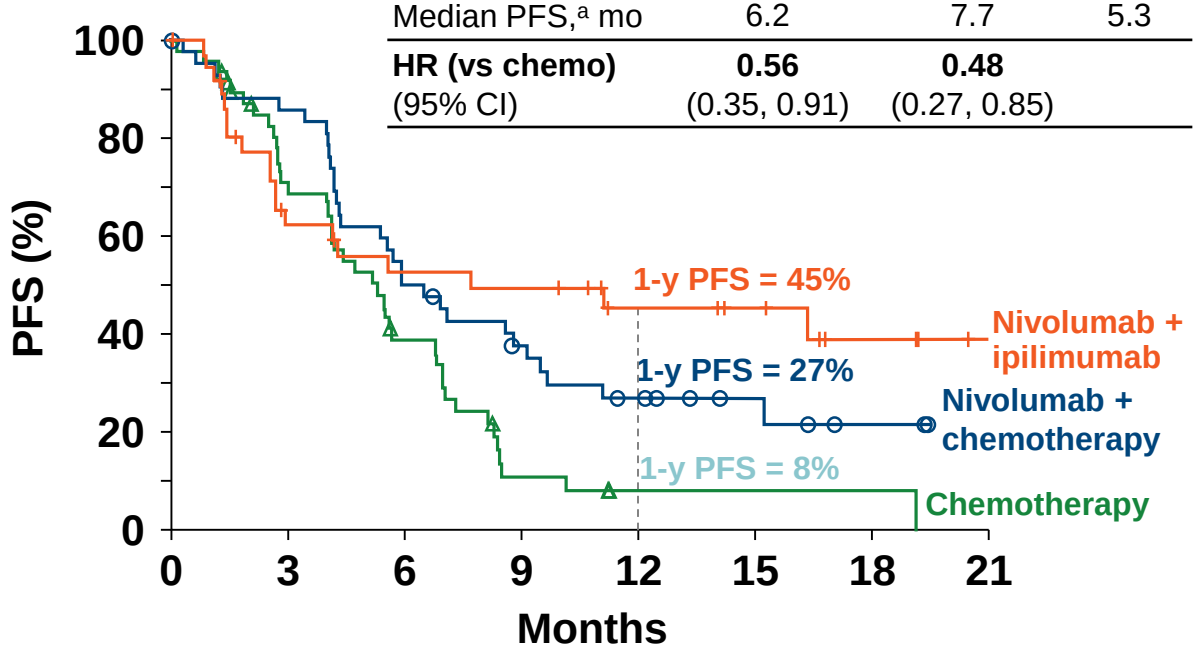
[a]All patients were PD-L1-positive (TPS ≥1%). Data cutoff date: Sep 4, 2018.

Herbst R et al. ESMO 2019

PFS: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab By TMB

TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

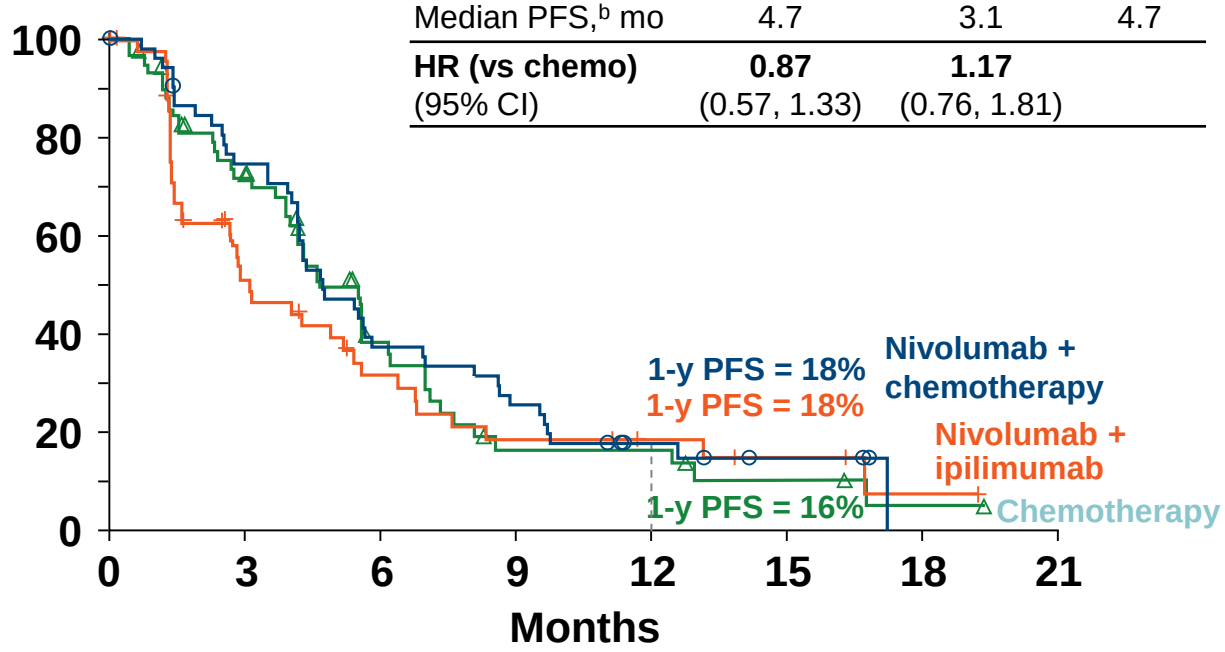
	Nivo + chemo (n = 43)	Nivo + ipi (n = 38)	Chemo (n = 48)
Median PFS,[a] mo	6.2	7.7	5.3
HR (vs chemo)	**0.56**	**0.48**	
(95% CI)	(0.35, 0.91)	(0.27, 0.85)	



No. at risk								
Nivo + chemo	43	36	21	14	9	5	2	0
Nivo + ipi	38	20	16	15	10	8	4	1
Chemo	48	30	16	4	1	1	1	0

TMB <10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 54)	Nivo + ipi (n = 52)	Chemo (n = 59)
Median PFS,[b] mo	4.7	3.1	4.7
HR (vs chemo)	**0.87**	**1.17**	
(95% CI)	(0.57, 1.33)	(0.76, 1.81)	

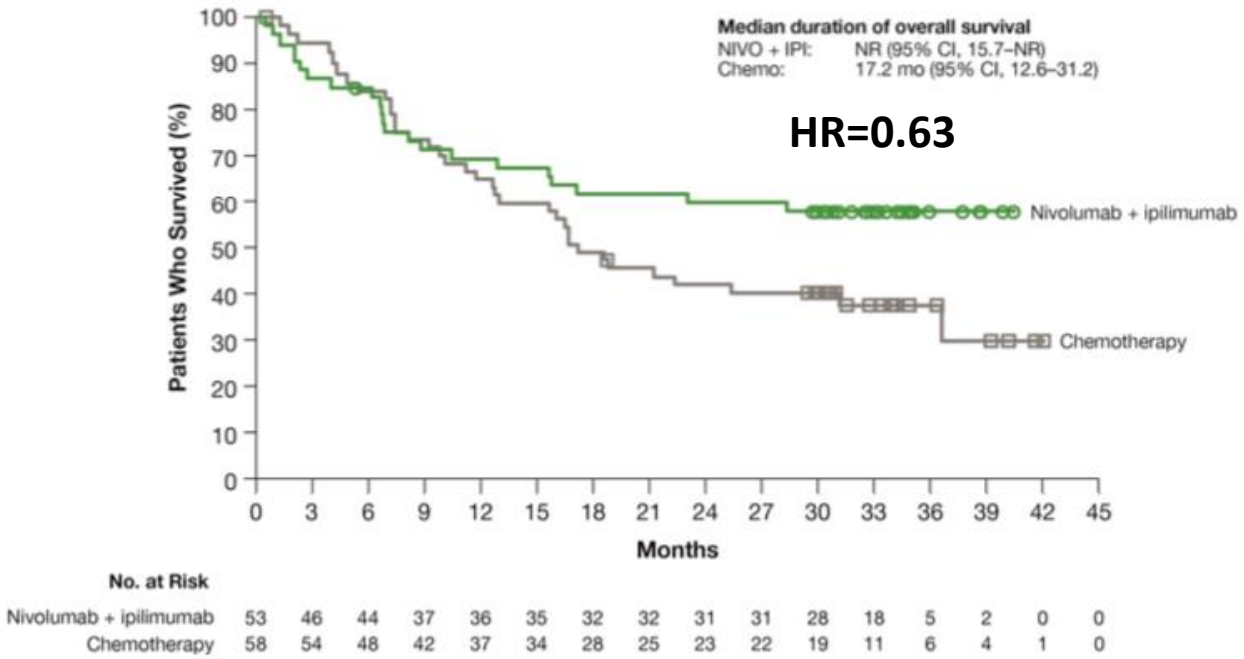


No. at risk								
Nivo + chemo	54	38	19	13	6	3	0	0
Nivo + ipi	52	22	12	7	5	3	1	0
Chemo	59	39	16	6	6	3	1	0

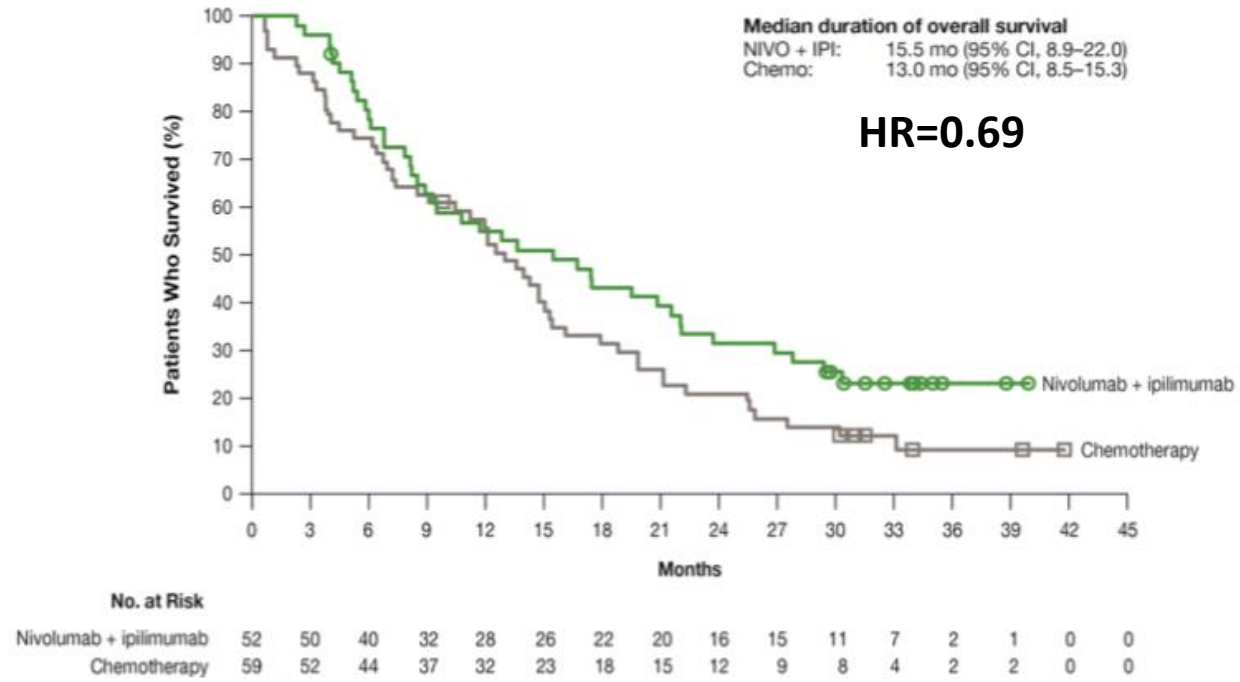
Borghaei H et al. ASCO 2018

OS with Nivolumab + Ipilimumab versus chemotherapy by TMB in CheckMate 227 trial

PD-L1≥50%/TMB high



PD-L1<1%/TMB low

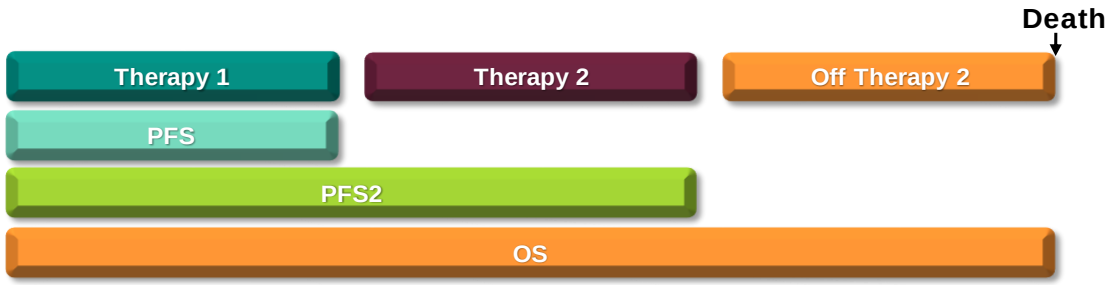


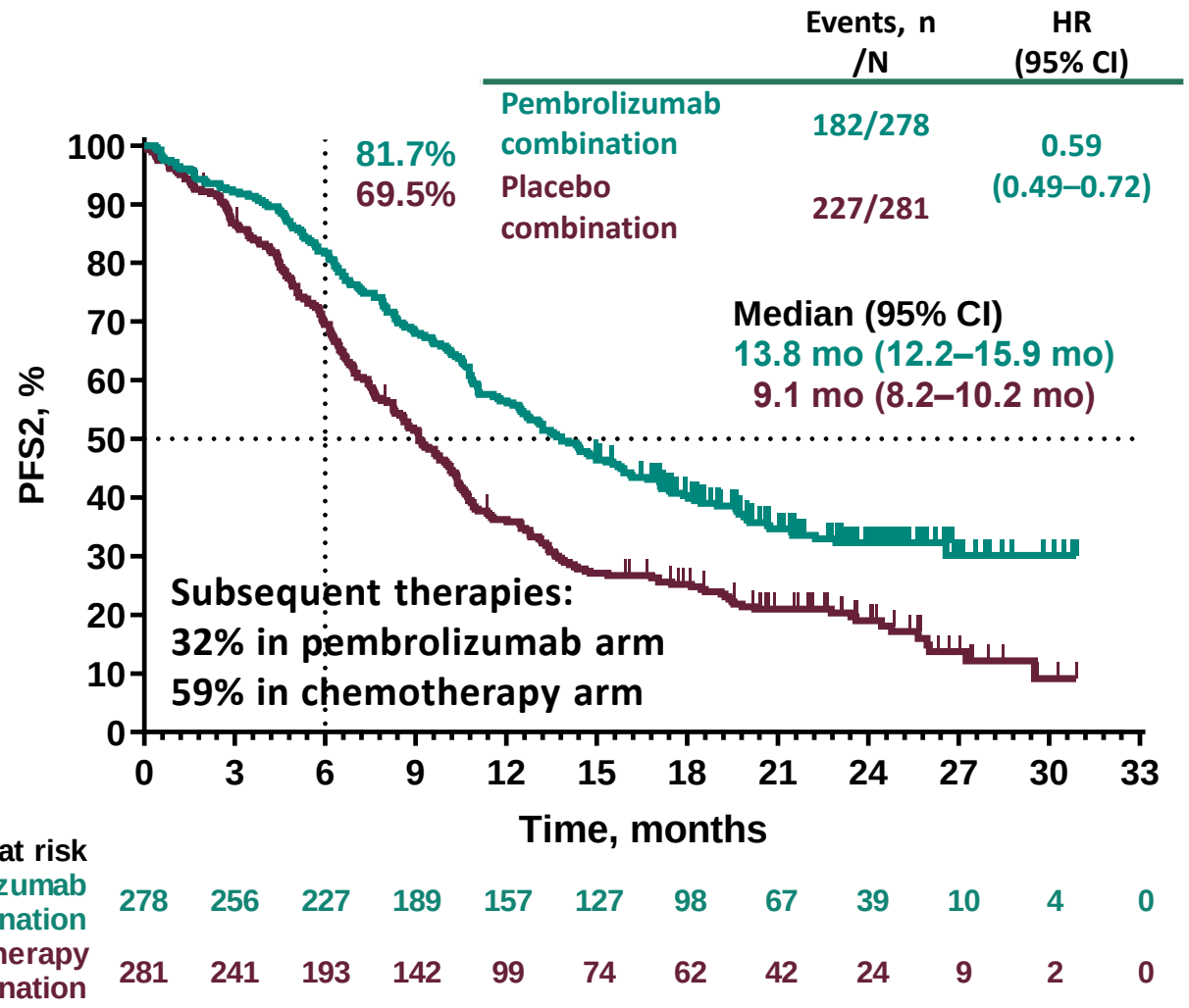
Hellmann MD et al. NEJM 2019

What is the best place for immunotherapy?
PFS 2 analysis in KEYNOTE 407

- PFS2 defined by EMA as time from randomization to objective tumor progression on next-line treatment or death from any cause
- Can be used to assess impact of crossover on OS and whether therapy in one line positively or negatively affects efficacy of the next line of therapy

Representation of PFS, OS, and PFS2





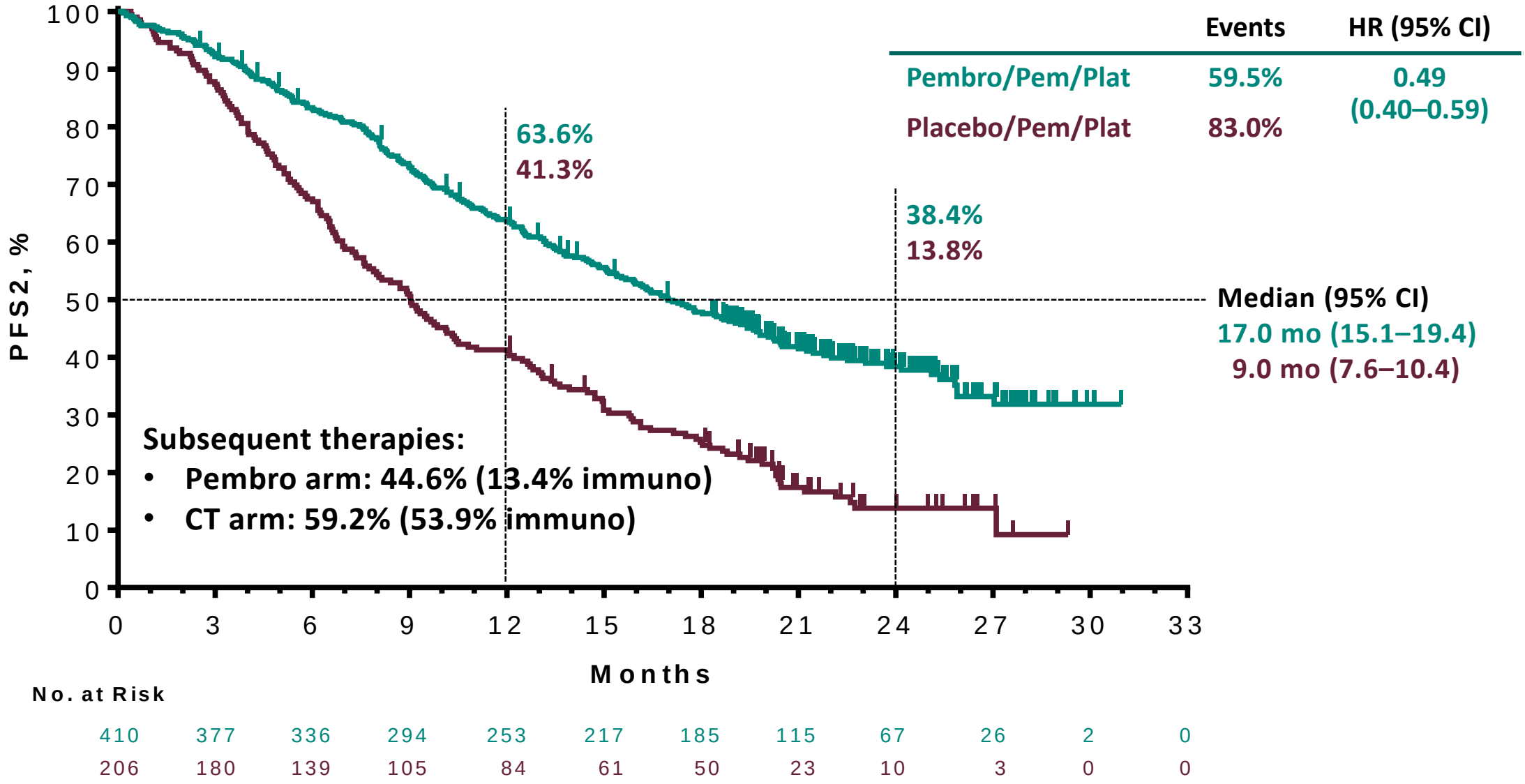
Paz Ares L, et al. ESMO 2019

PFS2 improvement irrespective of PD-L1 expression

End Point	Total N = 559	TPS ≥50% N = 146	TPS 1–49% N = 207	TPS <1% N = 194
OS, HR (95% CI)	0.71 (0.58–0.88)	0.79 (0.52–1.21)	0.59 (0.42–0.84)	0.79 (0.56–1.11)
PFS, HR (95% CI)	0.57 (0.47–0.69)	0.43 (0.29-0.63)	0.52 (0.38–0.71)	0.67 (0.49–0.91)
ORR, pembrolizumab combination vs placebo combination	62.6% vs 38.4%	64.4% vs 30.1%	55.3% vs 42.3%	67.4% vs 41.4%
DOR, median (range), mo, pembrolizumab combination vs placebo combination	8.8 (1.3+ to 28.4+) vs 4.9 (1.3+ to 28.3+)	9.2 (2.7 to 25.8+) vs 4.6 (1.3+ to 28.3+)	10.4 (1.3+ to 28.4+) vs 4.8 (2.0 to 22.8+)	6.9 (1.4+ to 25.4+) vs 5.7 (1.4+ to 25.6+)
PFS2, HR (95% CI)	0.59 (0.49–0.72)	0.61 (0.40–0.91)	0.51 (0.37–0.72)	0.61 (0.44–0.85)

Paz Ares L, et al. ESMO 2019

PFS2 in KEYNOTE 189 trial

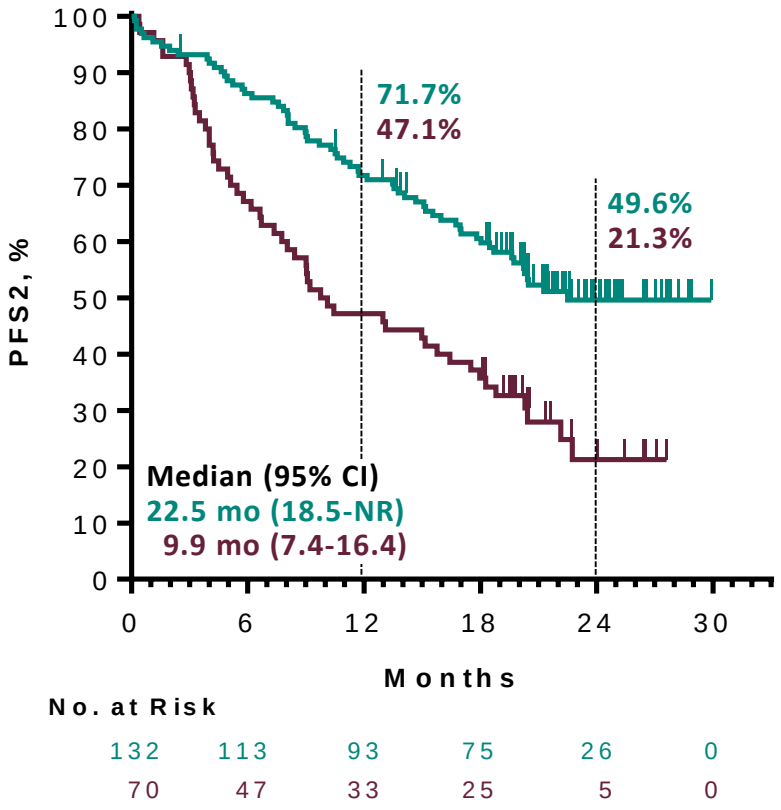


Gadgeel S et al ASCO 2019

PFS2 by PD-L1 TPS in KEYNOTE 189 trial

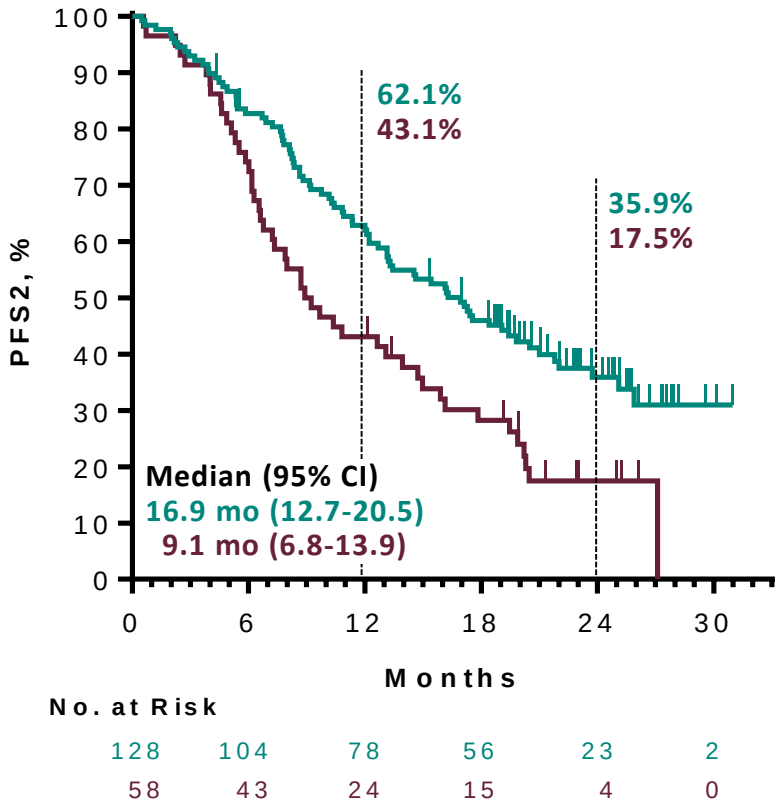
TPS ≥50 %

	Events	HR (95% CI)
Pembro/Pem/Plat	47.0%	0.47 (0.33–0.69)
Placebo/Pem/Plat	72.9%	



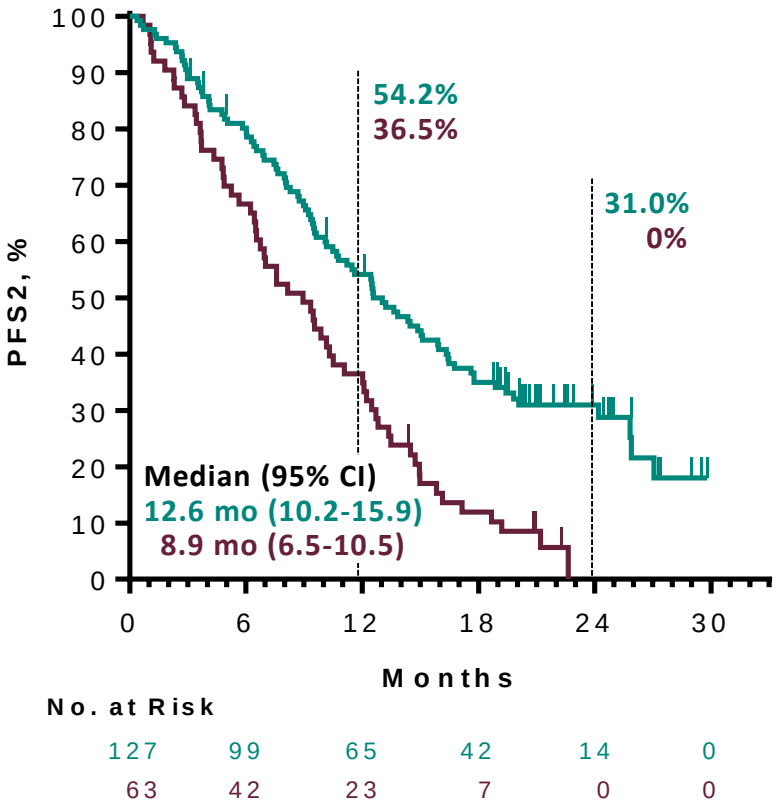
TPS 1-49%

	Events	HR (95% CI)
Pembro/Pem/Plat	61.7%	0.59 (0.41–0.86)
Placebo/Pem/Plat	81.0%	



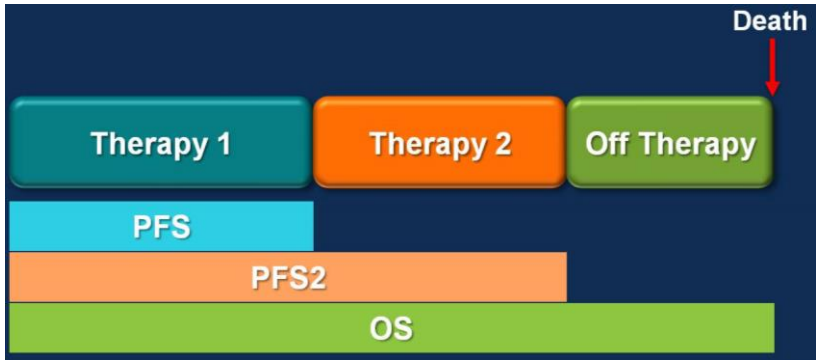
TPS <1%

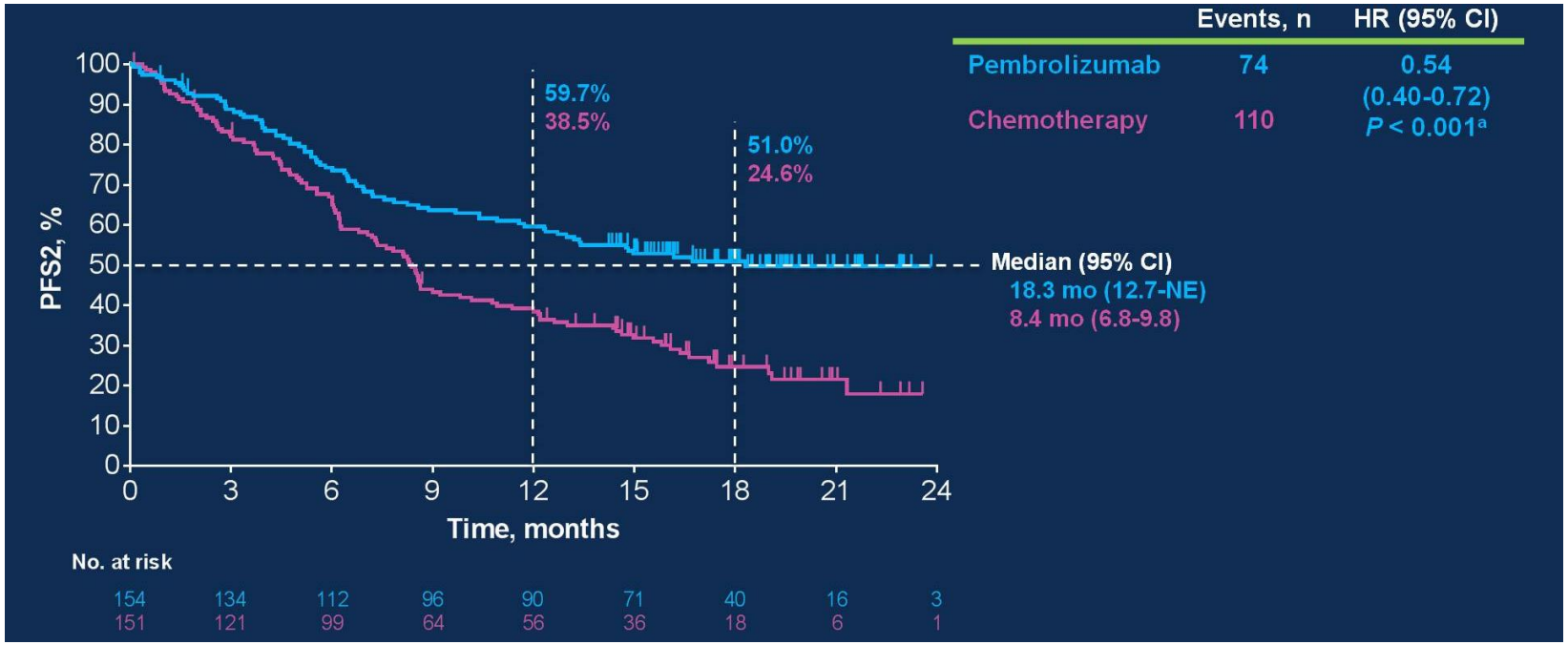
	Events	HR (95% CI)
Pembro/Pem/Plat	69.3%	0.46 (0.33–0.66)
Placebo/Pem/Plat	93.7%	



Gadgeel S et al ASCO 2019

PFS2 in KEYNOTE 024 trial





Crossover to

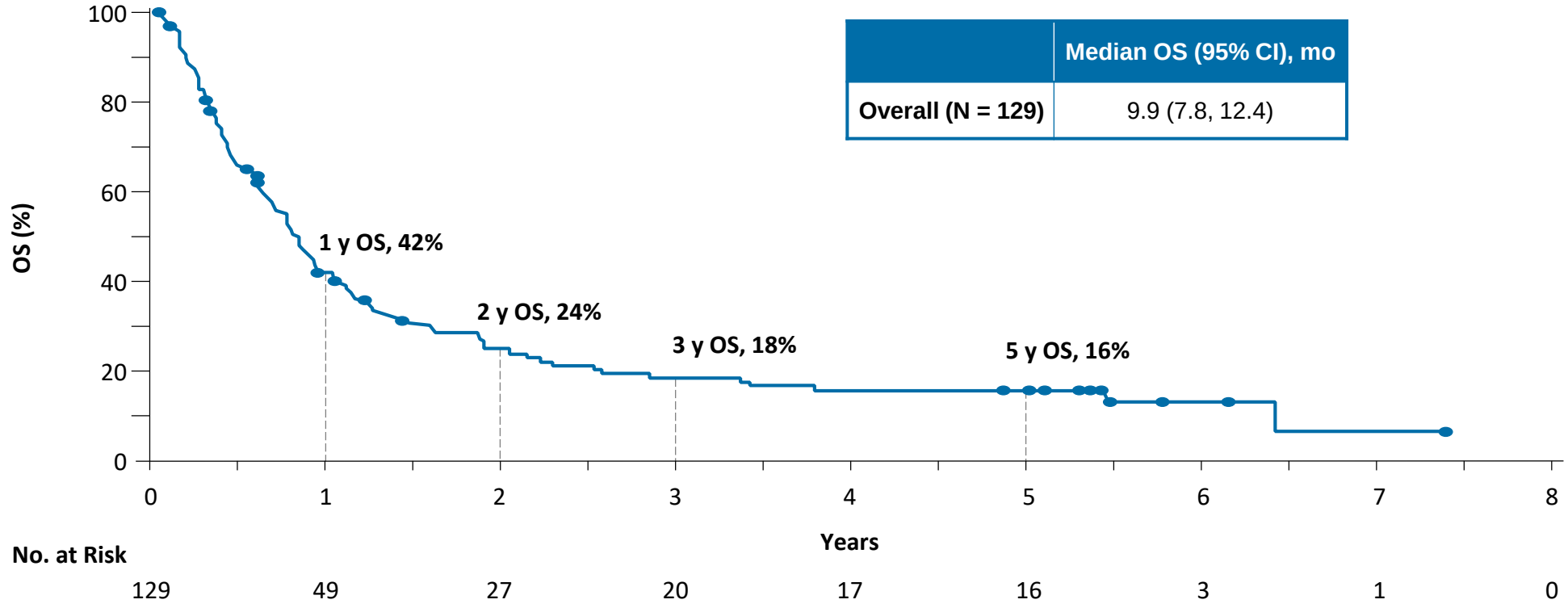
- **Platinum-doublets= 87.5%**
- **Pembrolizumab= 81.4%**

Key messages:

- **Immunotherapy first is better**

Brahmer JR, et al. ASCO 2017

Who are long-term survivors? 5-Year Estimates of OS in CA209-003: Phase 1 Nivolumab in Advanced NSCLC

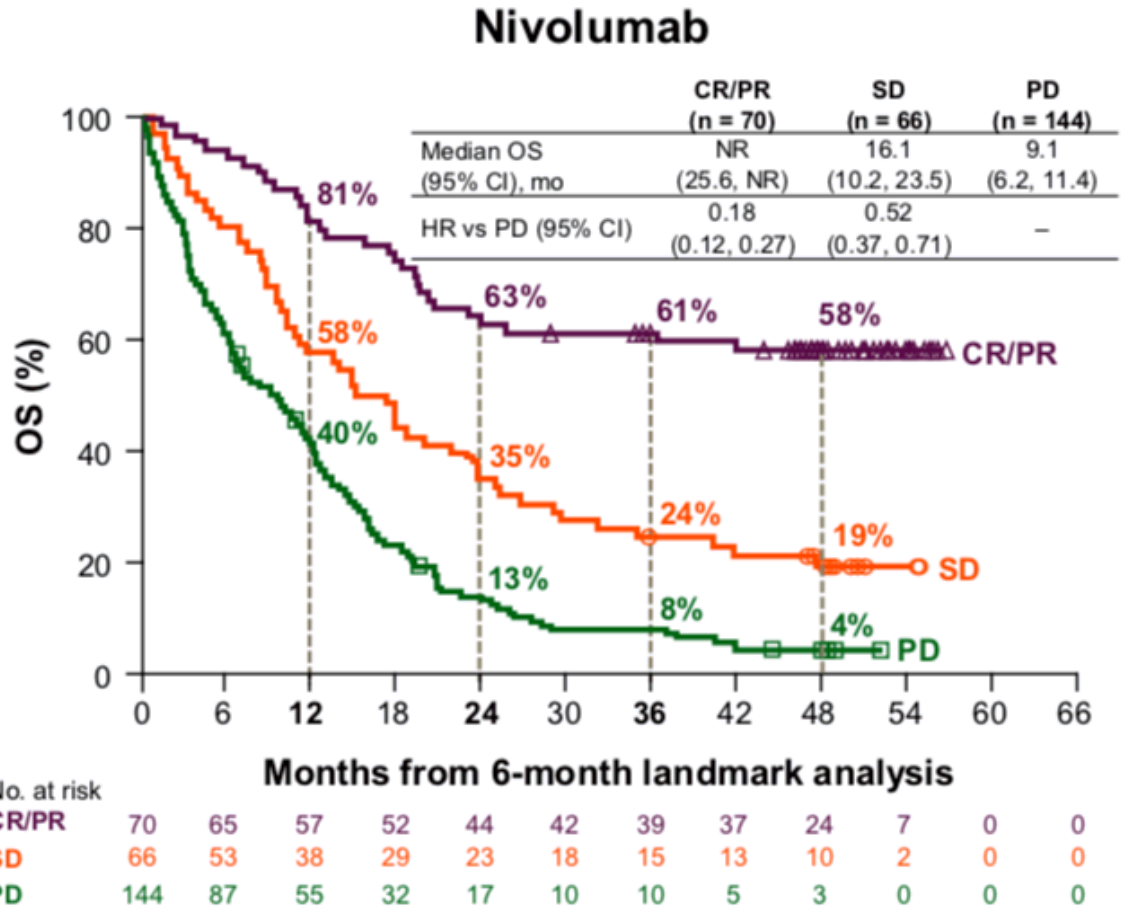


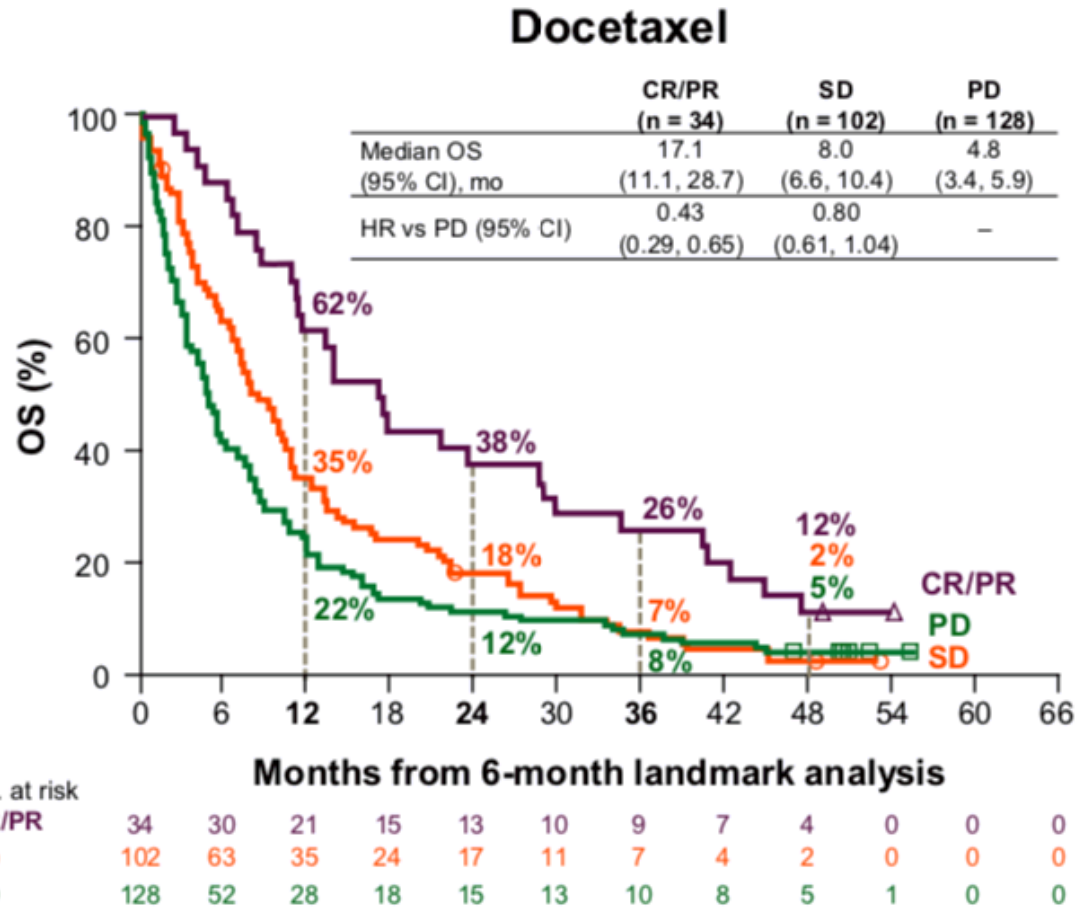
	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

No difference in squamous and non-squamous histology (5 years survival 16% and 15%)

Brahamer J et al. AACR 2017

Who are long-term survivors?
Landmark analysis of OS according to response in Checkmate 017/057

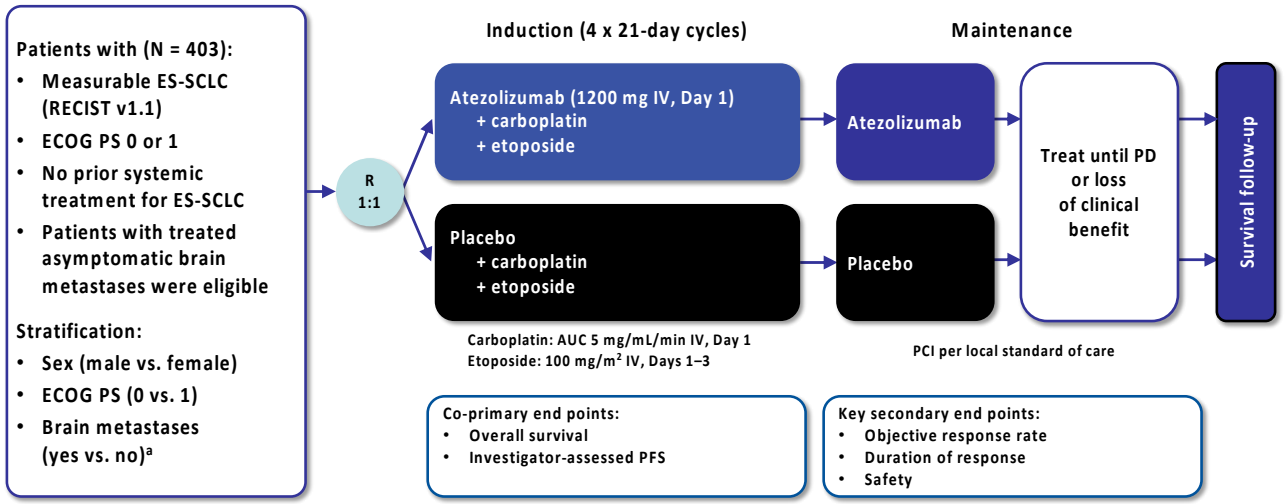




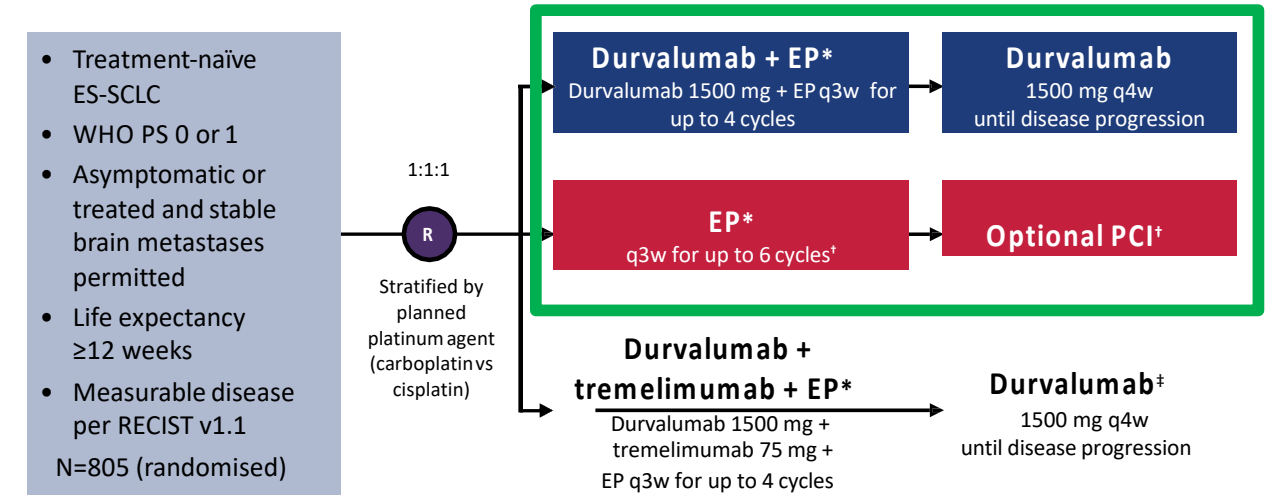
Brahamer J et al. AACR 2017

Immunotherapy in first-line small-cell-lung cancer

IMPOWER 133



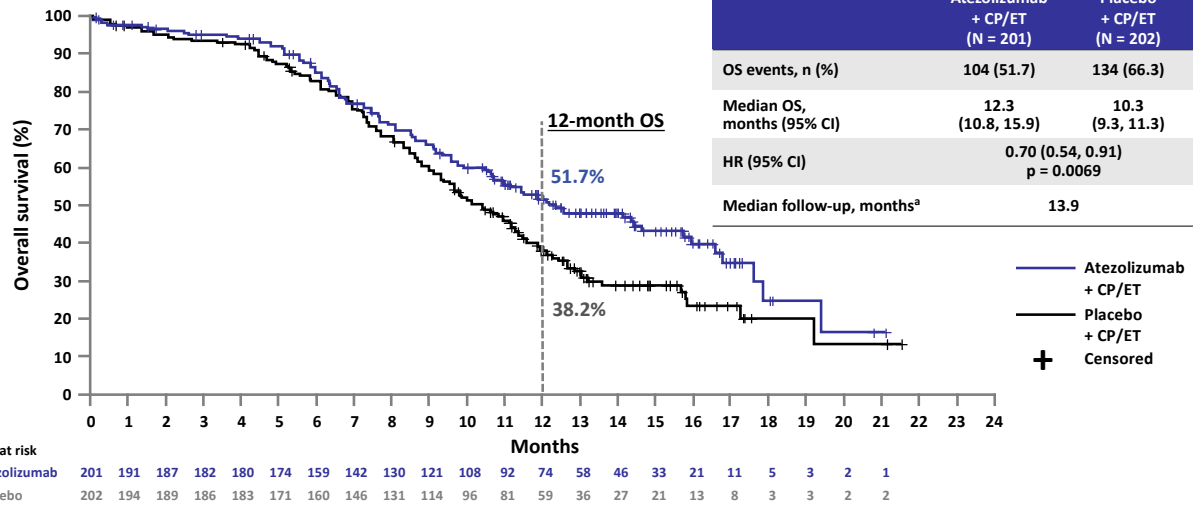
CASPIAN



Horn L et al NEJM 2018; Paz-Ares L et al WCLC 2019

Overall survival

IMPOWER 133



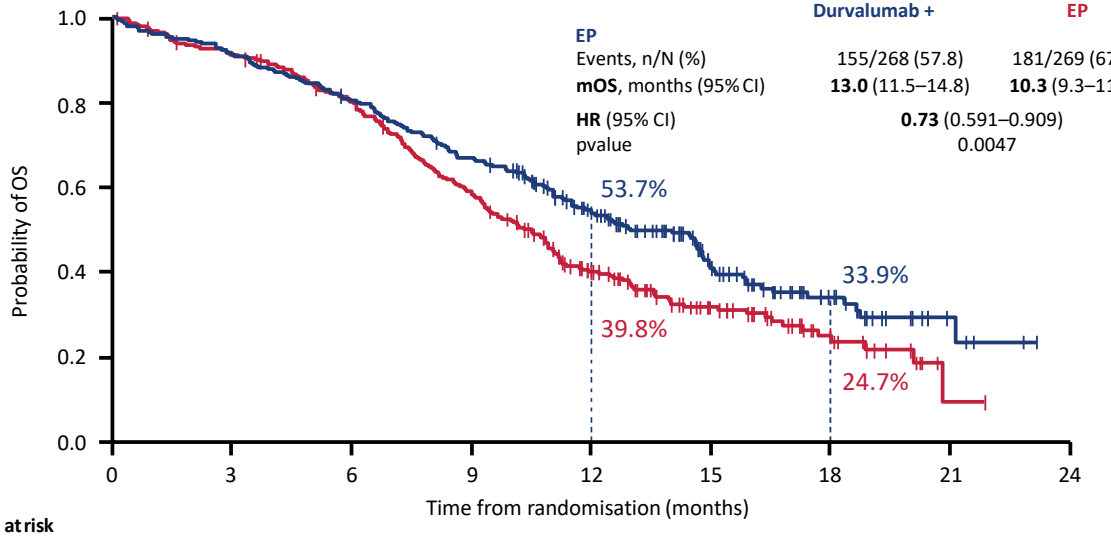
	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)
HR (95% CI)	0.70 (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

No. at risk

Atezolizumab	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1
Placebo	202	194	189	186	183	171	160	146	131	114	96	81	59	36	27	21	13	8	3	3	2	2

- [a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

CASPIAN



	Durvalumab + EP	EP
Events, n/N (%)	155/268 (57.8)	181/269 (67.3)
mOS, months (95% CI)	13.0 (11.5–14.8)	10.3 (9.3–11.2)
HR (95% CI)	0.73 (0.591–0.909)	
pvalue	0.0047	

No. at risk

Durvalumab + EP	268	244	214	177	116	57	25	5	0
EP	269	242	209	153	82	44	17	1	0

Horn L et al NEJM 2018; Paz-Ares L et al WCLC 2019

Conclusions

- Immunotherapy alone or in combination is the standard of care in first-line NSCLC
  - Combo seems superior to single agent in PD-L1 ≥50%, with more toxicity
  - In combination with chemotherapy irrespective of PD-L1
  - The addition of bevacizumab to chemotherapy and immunotherapy is effective particularly in some subgroups
  - Chemo-free combinations is a new option
- At the present time TMB seems prognostic and is not useful for defining candidates for immunotherapy
- Chemoimmunotherapy marginally but significantly prolongs survival in SCLC