Karen Reckamp, MD, MS

Immunotherapy for Advanced NSCLC

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

grant/research support: ACEA,Takeda/Ariad, Bristol Myers Squibb, Boehringer Ingelheim, Pfizer, Xcovery, Adaptimmune, AbbVie, Genentech, Guardant, Novartis, Seattle Genetics, Loxo Oncology
consultant: Amgen, Takeda/Ariad, Astellas, Tesaro, Euclises

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Immunotherapy for advanced NSCLC—current landscape

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Professor
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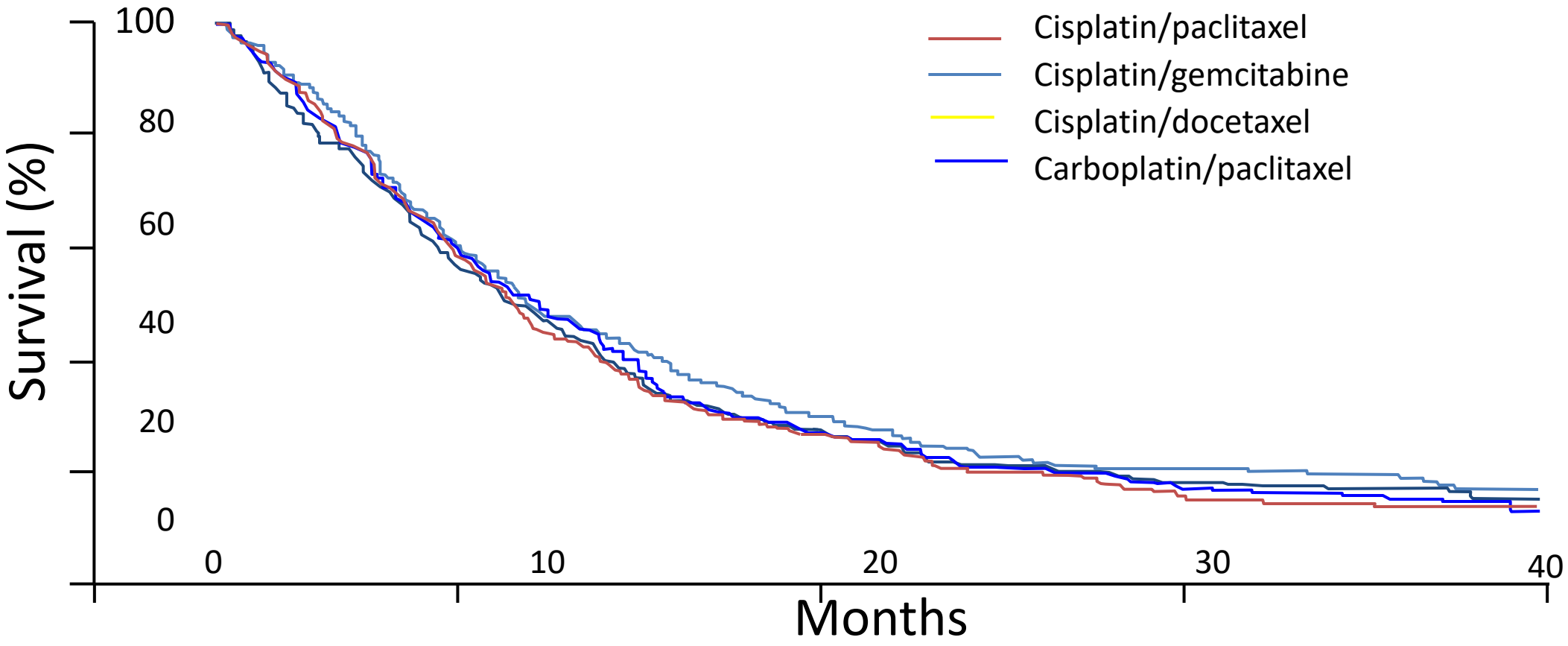
Medical Director, Clinical Research Operations
City of Hope Comprehensive Cancer Center

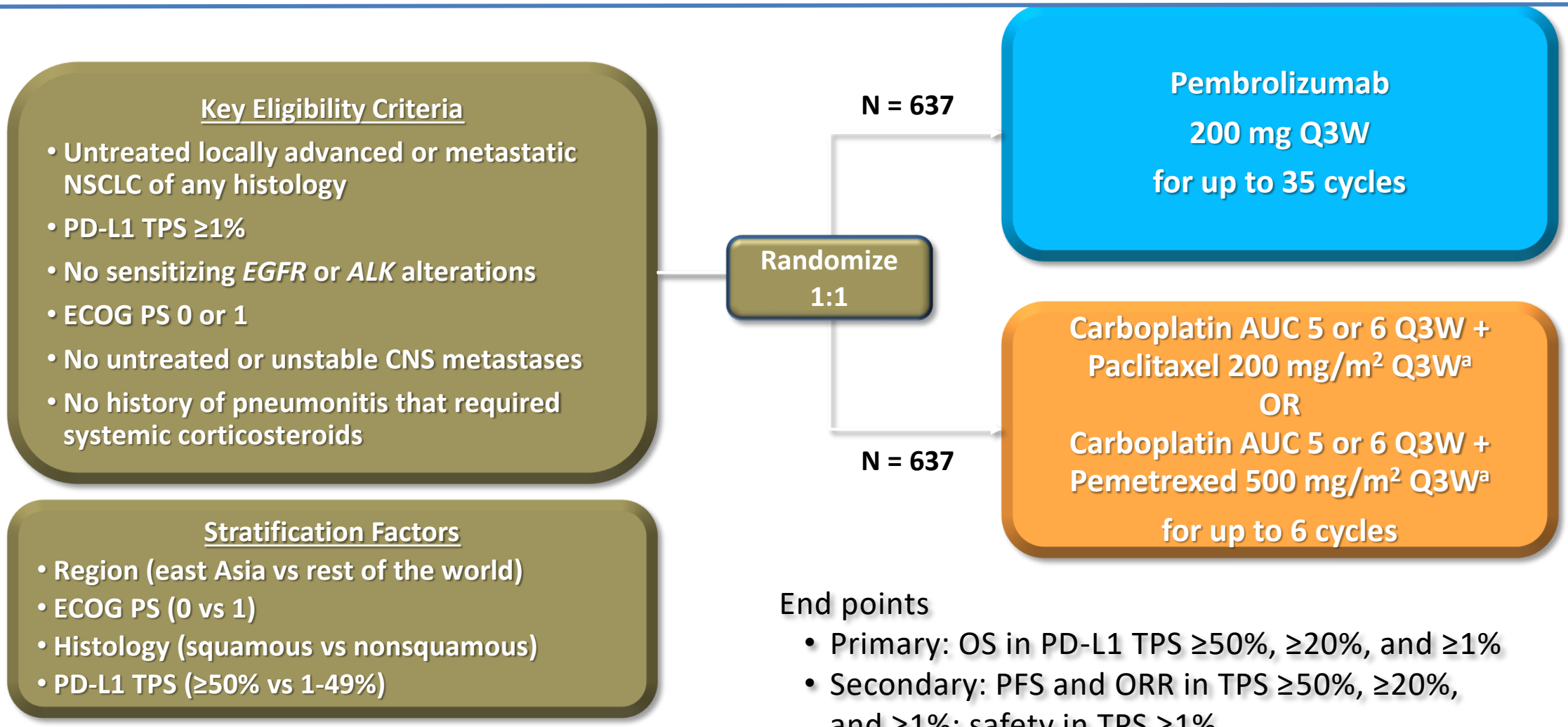
First-Line Chemotherapy for Advanced or Metastatic NSCLC: E1594



Schiller et al. N Engl J Med. 2002;346:92.

Immune therapy updates (AACR and ASCO)

KEYNOTE-042 Study Design



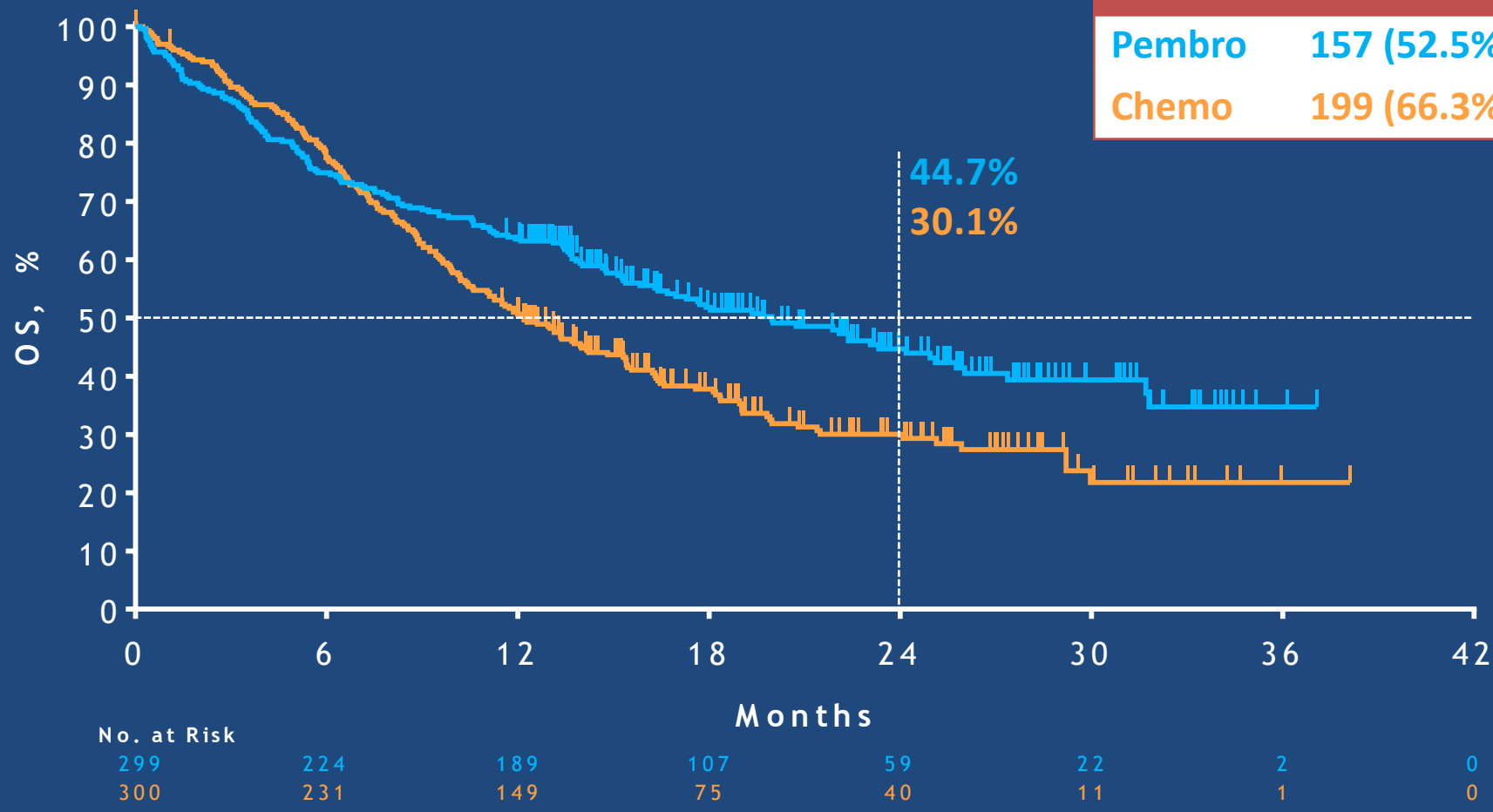
End points

- Primary: OS in PD-L1 TPS ≥50%, ≥20%, and ≥1%
- Secondary: PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety in TPS ≥1%

Lopes G et al ASCO 2018

Keynote 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%)		



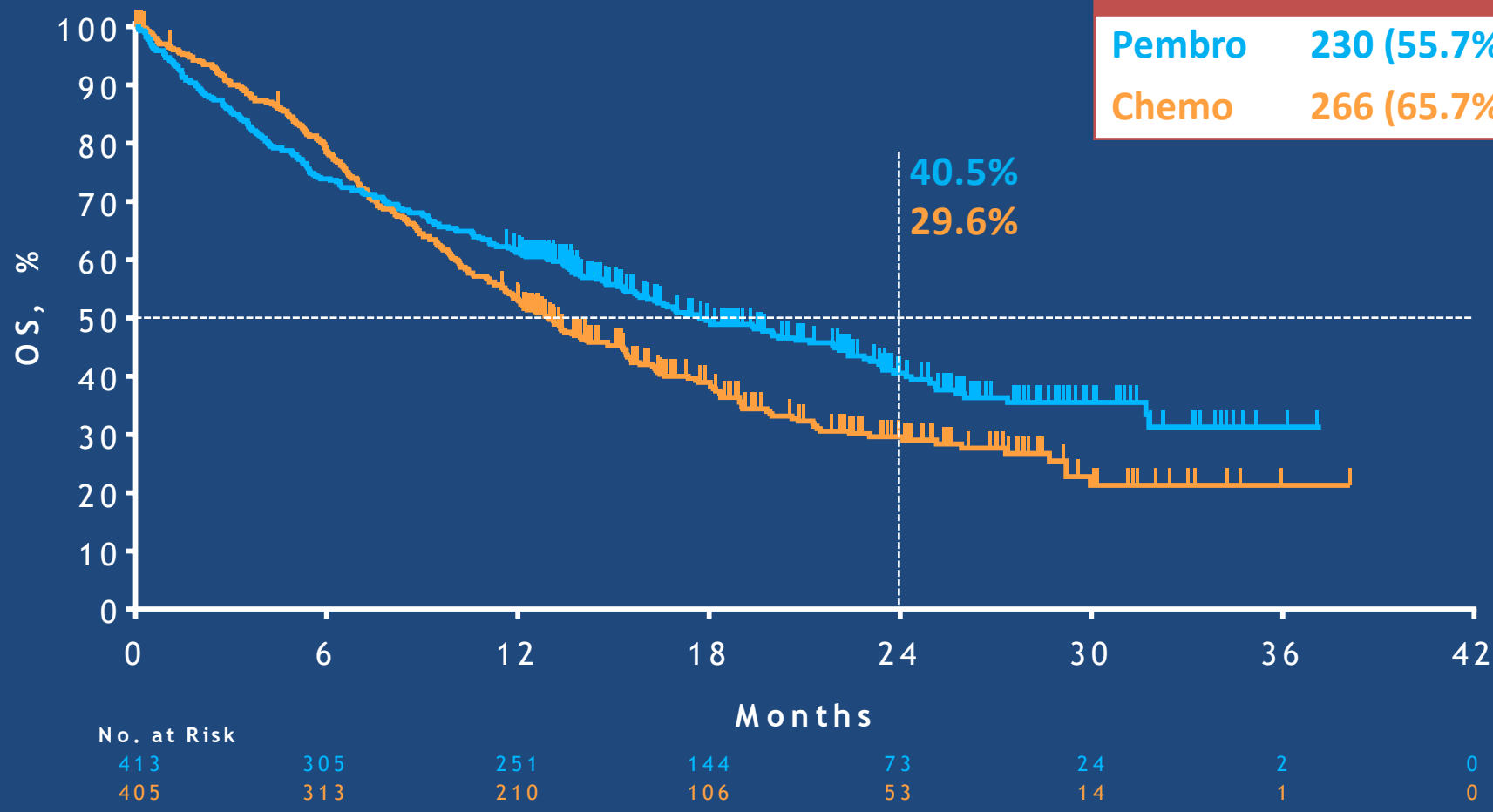
Median (95% CI)
20.0 mo (15.4-24.9)
12.2 mo (10.4-14.2)

Data cutoff date: Feb 26, 2018.

Lopes et al ASCO 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)

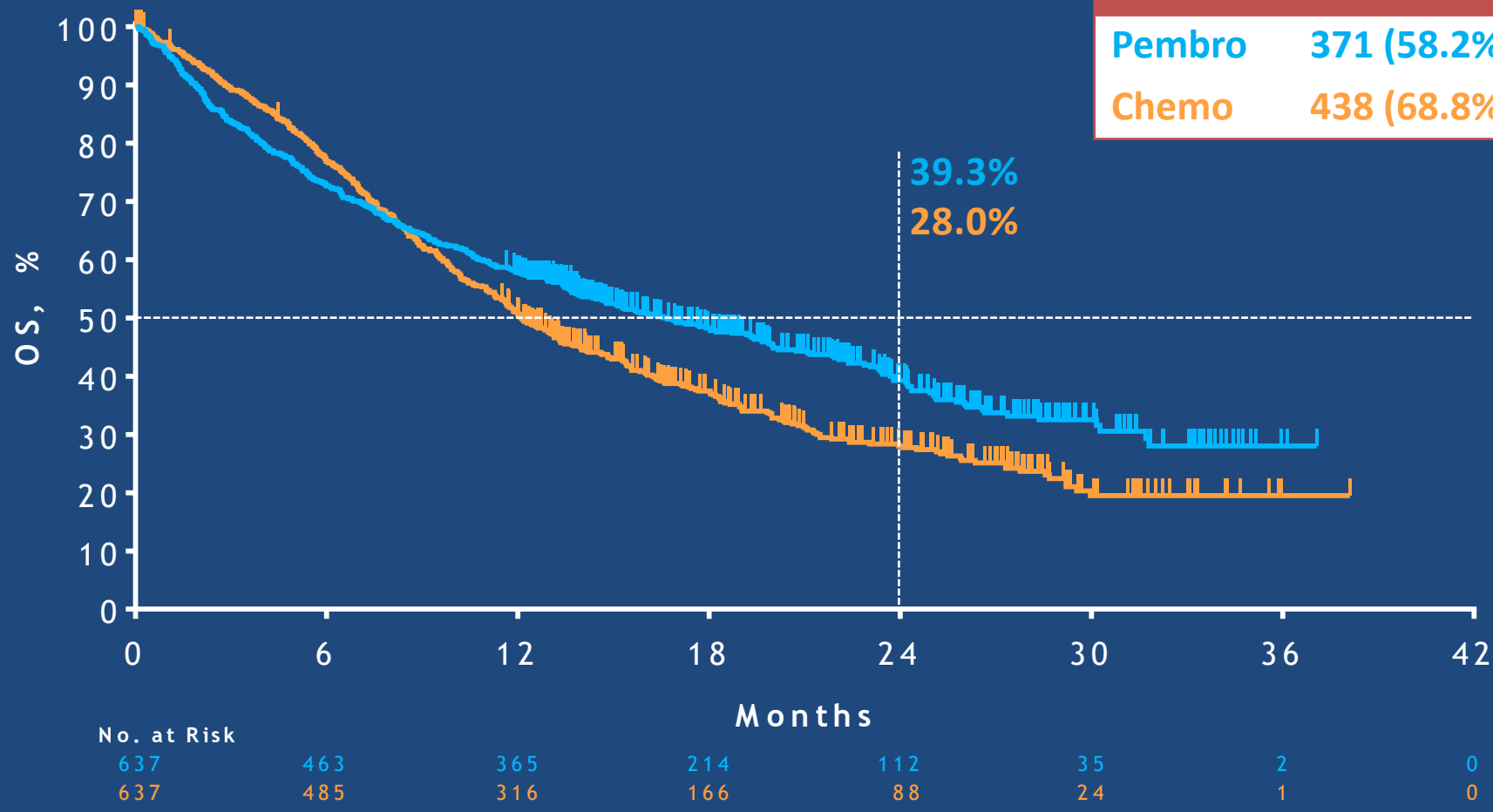
17.7 mo (15.3-22.1)

13.0 mo (11.6-15.3)

Lopes et al ASCO 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)

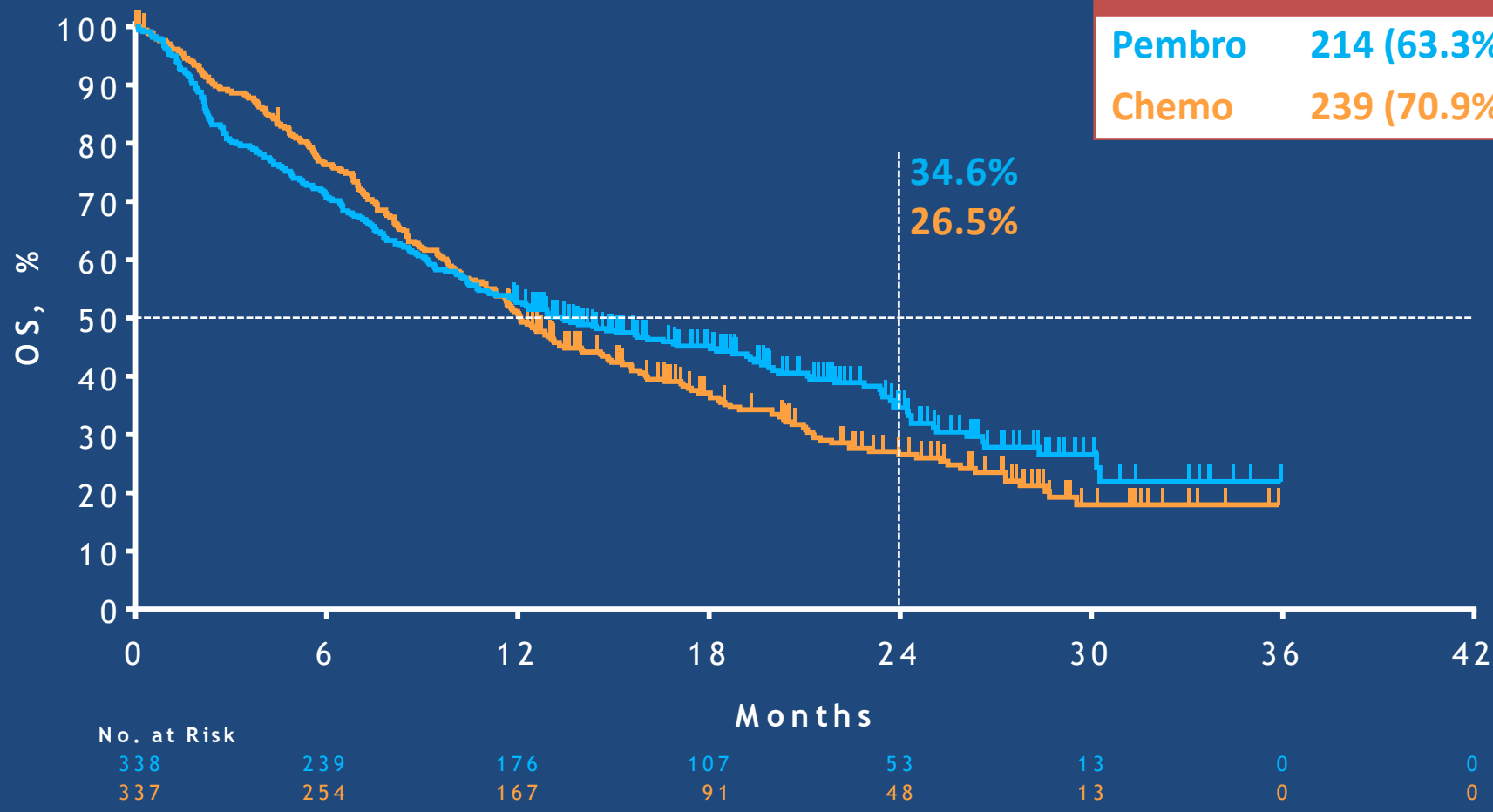
16.7 mo (13.9-19.7)

12.1 mo (11.3-13.3)

Lopes et al ASCO 2018

Overall Survival: TPS ≥1-49%

	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)

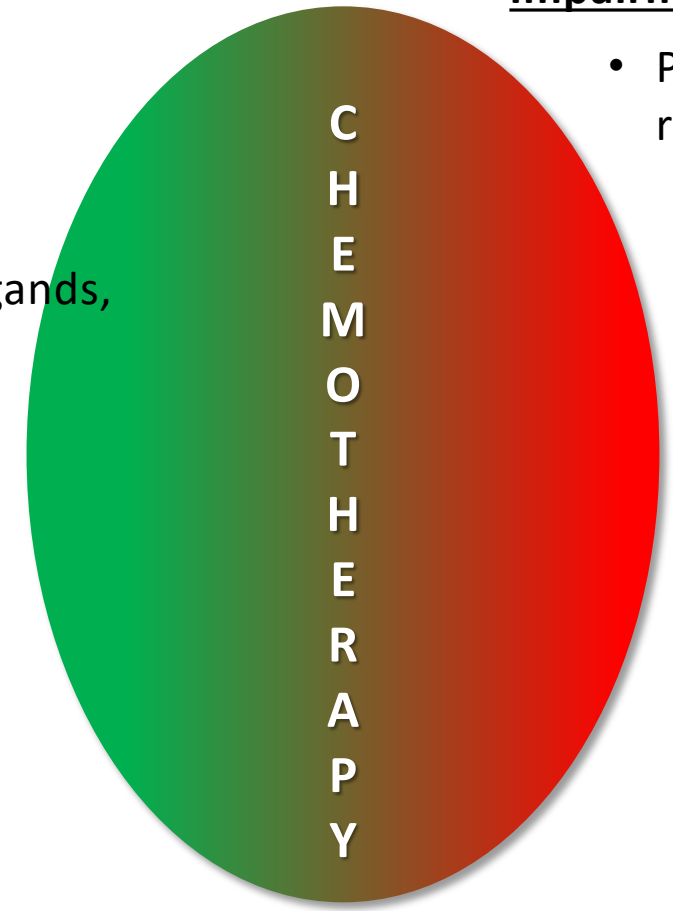
[a]**No alpha allocated to this comparison.**

Lopes et al ASCO 2018

Chemotherapy Has Complex and Pleiotropic Effects on Antitumor Immune Responses

Promotion of Antitumor Immune Response

- Antigen shedding and presentation
  - Release of cancer antigens
  - Upregulation of MHC I
  - Enhanced DC activation
- Altered immune regulatory receptors, ligands, and cytokines
  - Increased T_{eff} function, proliferations, and recruitment
- Activation of innate immunity
  - e.g., STING, RIG-1, TLR9
- Favorable effect on immune regulatory cells
  - Suppression of T_{regs}, MDSCs, etc



Impairment of Antitumor Immune Response

- Post chemotherapy Induction of immune regulatory receptors, ligands, and cytokines
  - e.g., negative feedback from IFNγ
  - Decreased T_{eff} function
- Unfavorable effect on immune regulatory cells
  - Reduced number of circulating lymphocytes
  - Increased number of circulating monocytes, MDSCs, etc

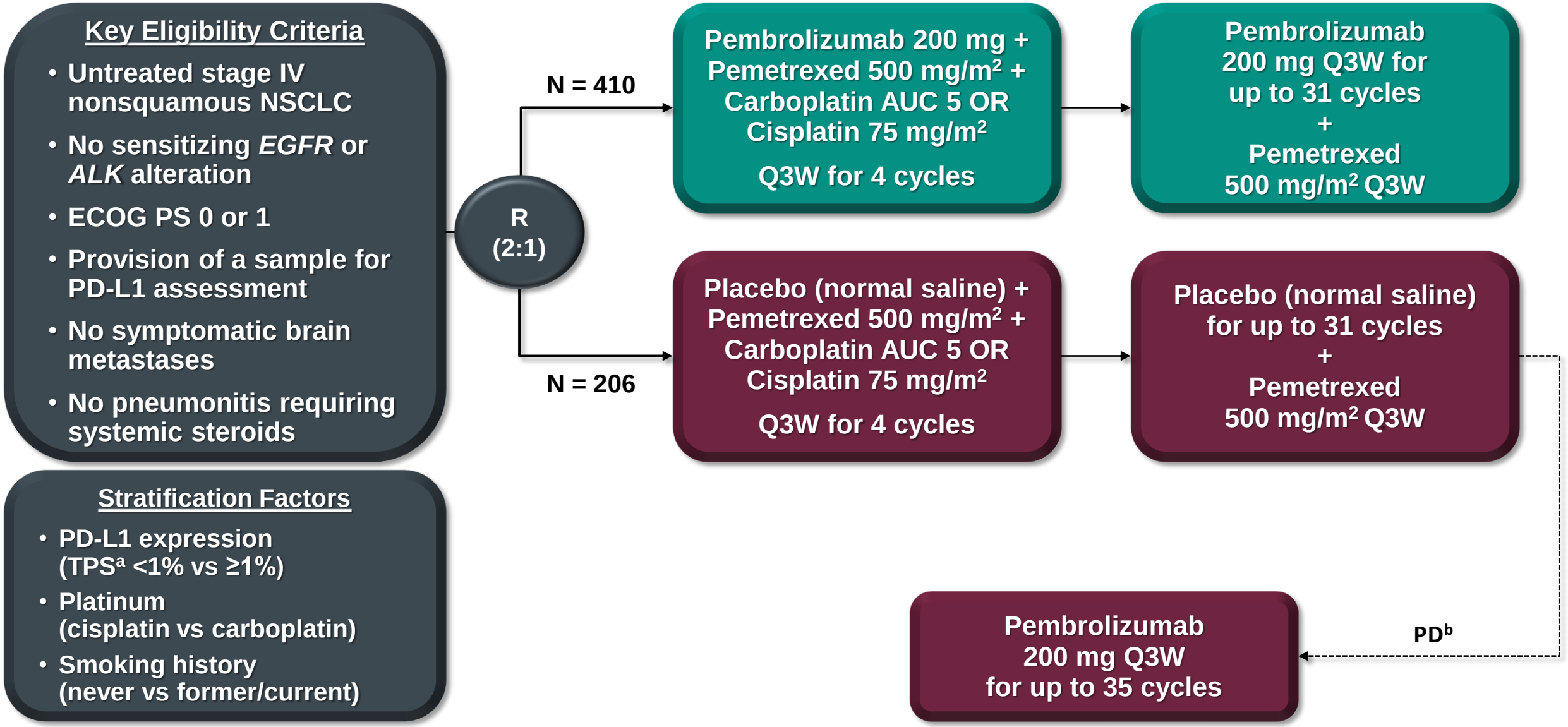
Enhances positive immune effects of chemotherapy

Anti–PD-1

Reduces negative immune effects of chemotherapy

Bracci L et al. *Cell Death Differ* 2014;21:15-25. Roselli M et al. *Oncoimmunology* 2013;2:e27025. Galluzzi L et al. *Cancer Cell* 2015;28:690-714. Medler TR et al. *Trends Cancer* 2015;1:66-75. van Meir H et al. *Oncoimmunology* 2017;6:e1267095. Peng J et al. *Cancer Res* 2015;75:5034-5045. Zhang P et al. *Cancer Sci* 2016;107:1563-1571. Novosiadly RD et al. 18th IASLC World Conference on Lung Cancer; Oct 15-18, 2017; abstract P3.07-006.

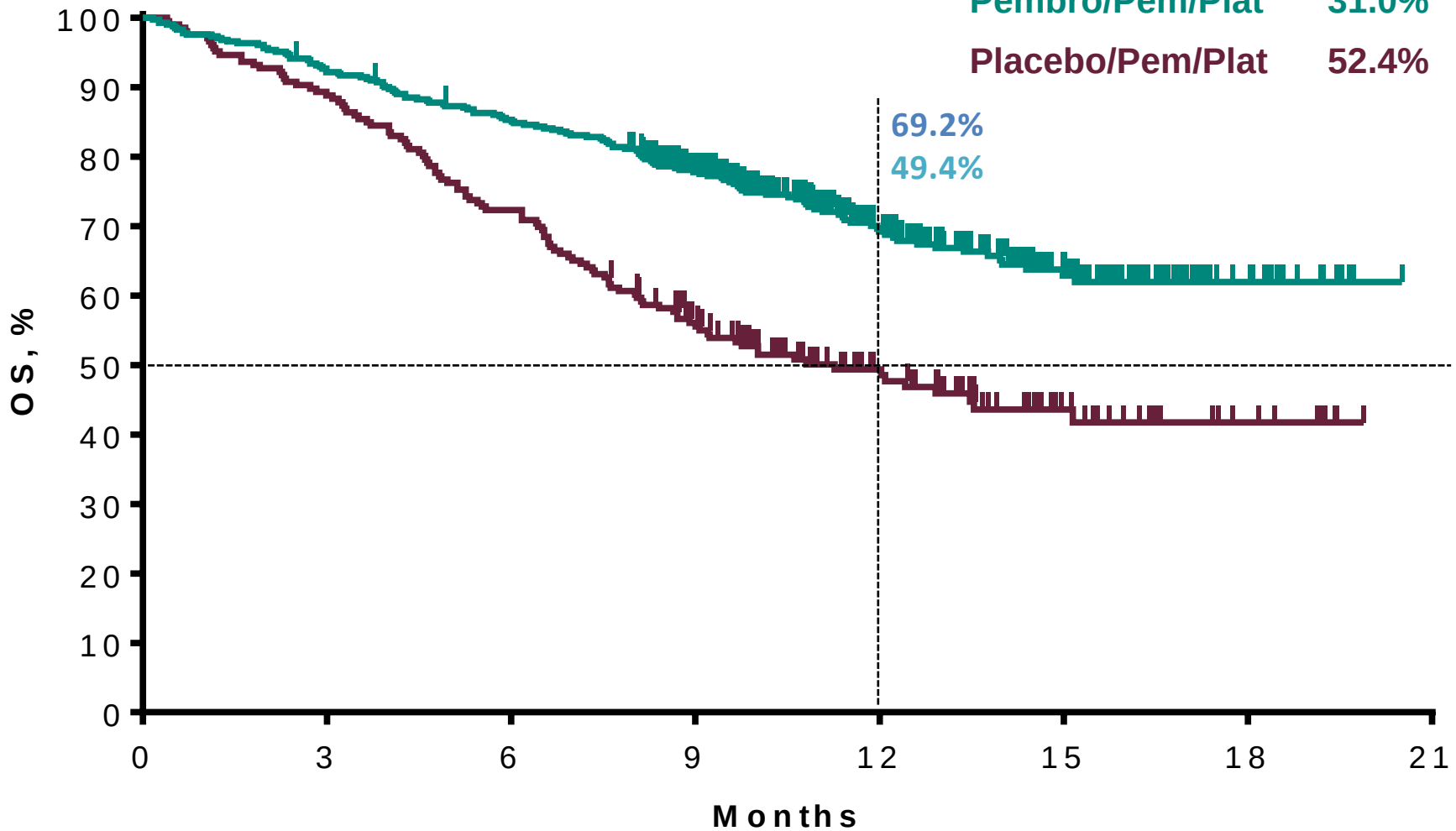
KEYNOTE-189 Study Design (NCT02578680)



[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.

Keynote 189—Overall Survival, ITT

	Events	HR (95% CI)	*P*
Pembro/Pem/Plat	31.0%	0.49 (0.38-0.64)	<0.00001
Placebo/Pem/Plat	52.4%		



Median (95% CI)

NR (NE-NE)

11.3 mo (8.7-15.1)

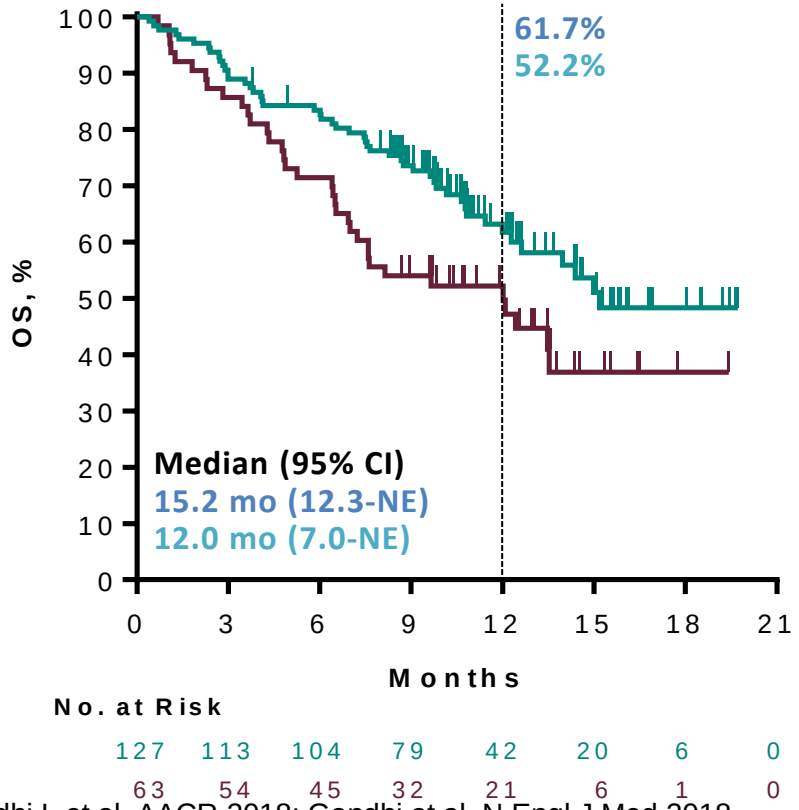
Gandhi L et al. AACR 2018; Gandhi et al. N Engl J Med 2018

Data cutoff date: Nov 8, 2017.

Overall Survival by PD-L1 TPS

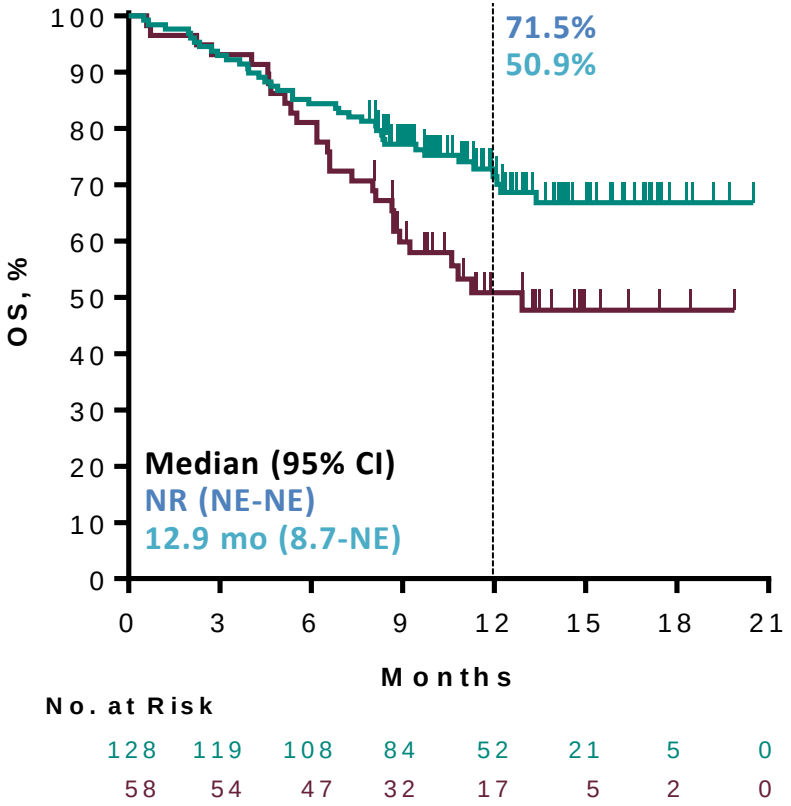
TPS <1%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	38.6%	0.59 (0.38-0.92)	0.0095
Placebo/Pem/Plat	55.6%		



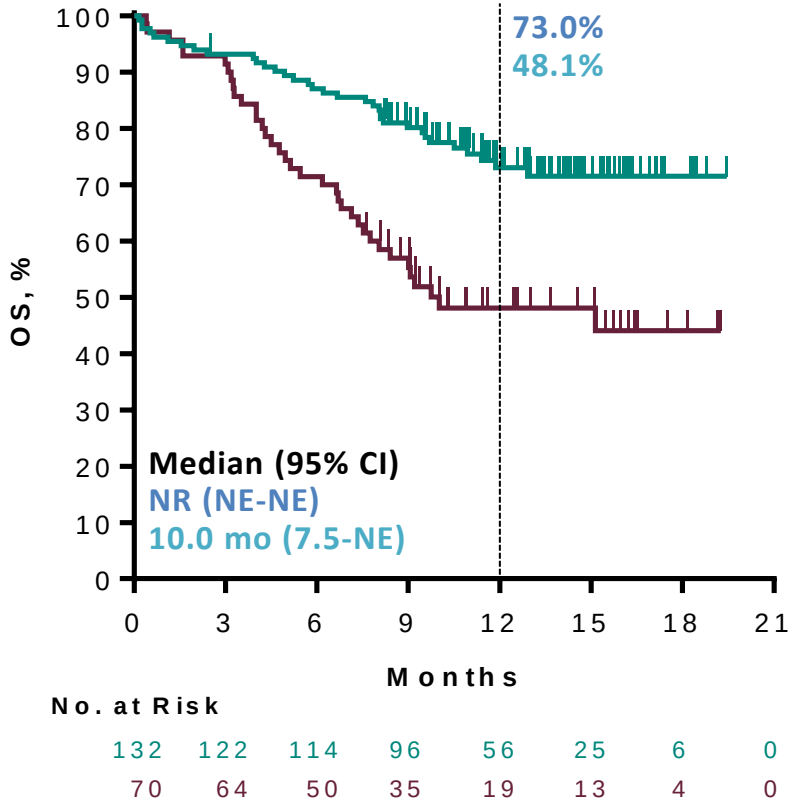
TPS 1-49%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	28.9%	0.55 (0.34-0.90)	0.0081
Placebo/Pem/Plat	48.3%		



TPS ≥50%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	25.8%	0.42 (0.26-0.68)	0.0001
Placebo/Pem/Plat	51.4%		



Gandhi L et al. AACR 2018; Gandhi et al. N Engl J Med 2018

[a]Nominal and one-sided. Data cutoff date: Nov 8, 2017.

Summary of Adverse Events

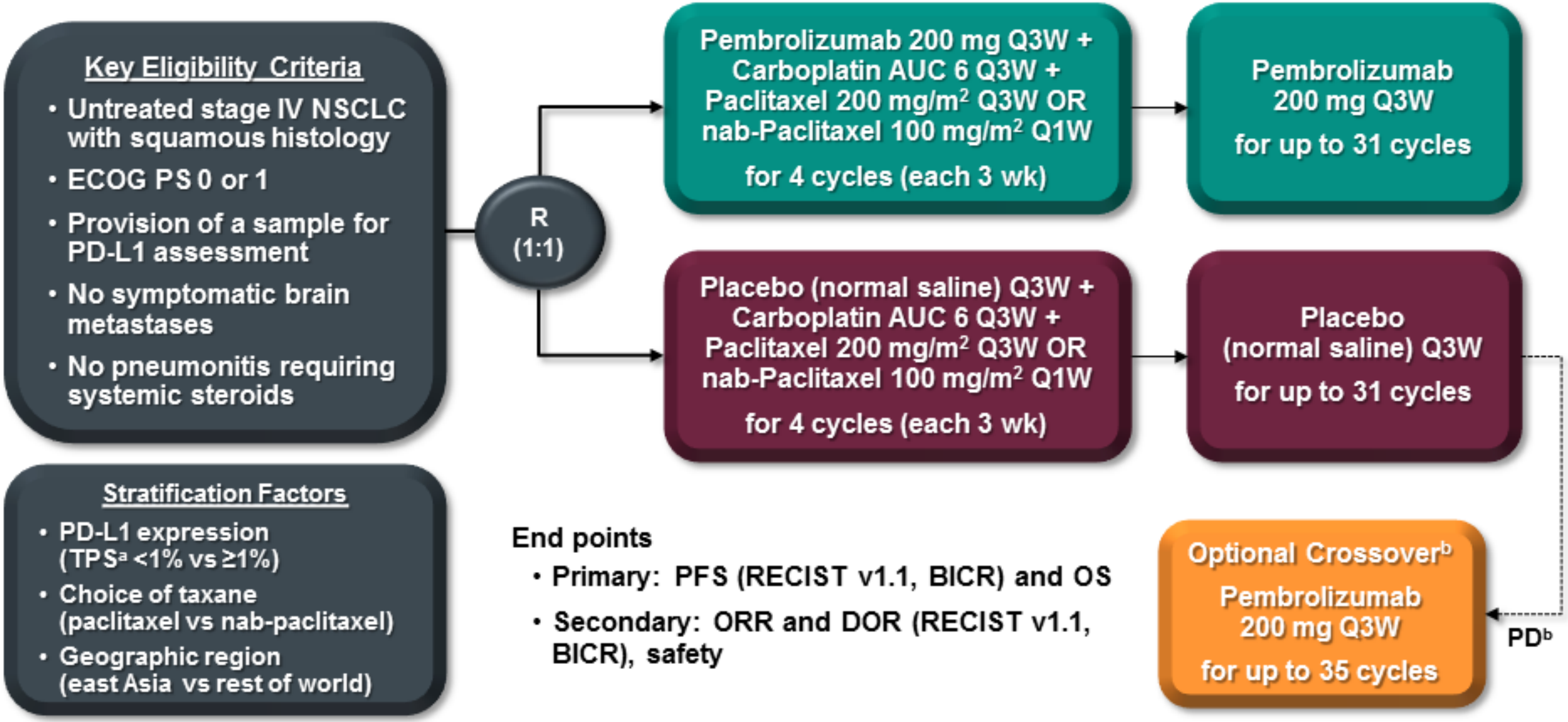
	Pembro/Pem/Platinum N = 405	Placebo/Pem/Platinum N = 202
All cause	404 (99.8%)	200 (99.0%)
Grade 3-5	272 (67.2%)	133 (65.8%)
Led to death	27 (6.7%)	12 (5.9%)
Led to discontinuation		
All treatment[a]	56 (13.8%)	16 (7.9%)
Any treatment	112 (27.7%)	30 (14.9%)
Immune mediated	92 (22.7%)	24 (11.9%)
Grade 3-5	36 (8.9%)	9 (4.5%)
Led to death	3 (0.7%)	0

Gandhi L et al. AACR 2018; Gandhi et al. N Engl J Med 2018

[a]Includes patients who discontinued pembrolizumab or placebo, pemetrexed, and carboplatin for an adverse event at any time and patients who discontinued pembrolizumab or placebo and pemetrexed for an adverse event after completing 4 cycles of platinum.

Data cutoff date: Nov 8, 2017.

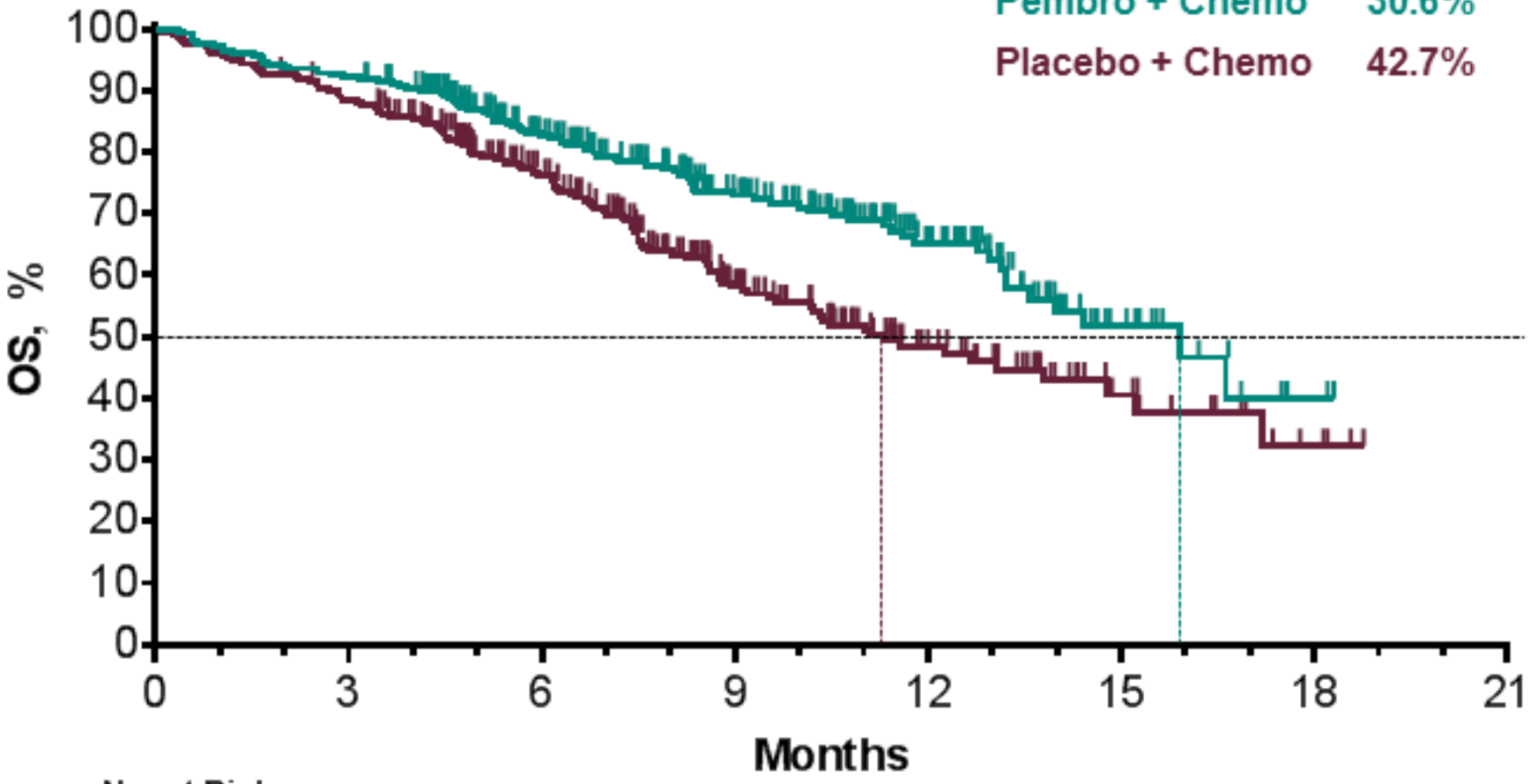
KEYNOTE-407 Study Design (NCT02775435)



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.

Overall Survival at IA2, ITT

	Events	HR (95% CI)	*P*
Pembro + Chemo	30.6%	0.64 (0.49-0.85)	0.0008
Placebo + Chemo	42.7%		



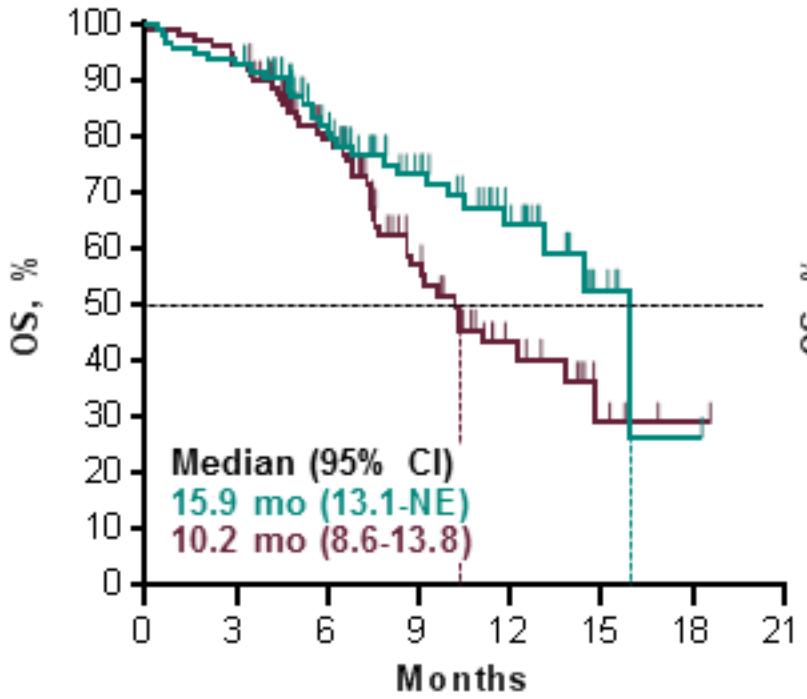
No. at Risk							
278	256	188	124	62	17	2	0
281	246	175	93	45	16	4	0

Data cutoff date: Apr 3, 2018.

Overall Survival at IA2 by PD-L1 TPS

TPS <1%

	Events	HR (95% CI)
Pembro + Chemo	30.5%	0.61 (0.38-0.98)
Placebo + Chemo	44.4%	

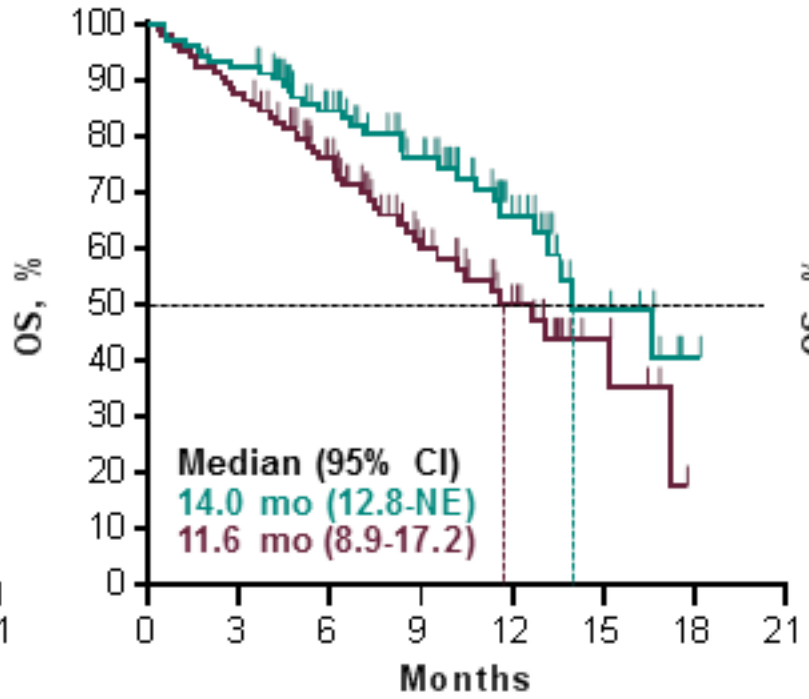


No. at Risk

95	88	62	41	20	5	1	0
99	92	63	32	14	4	1	0

TPS 1-49%

	Events	HR (95% CI)
Pembro + Chemo	30.1%	0.57 (0.36-0.90)
Placebo + Chemo	43.3%	

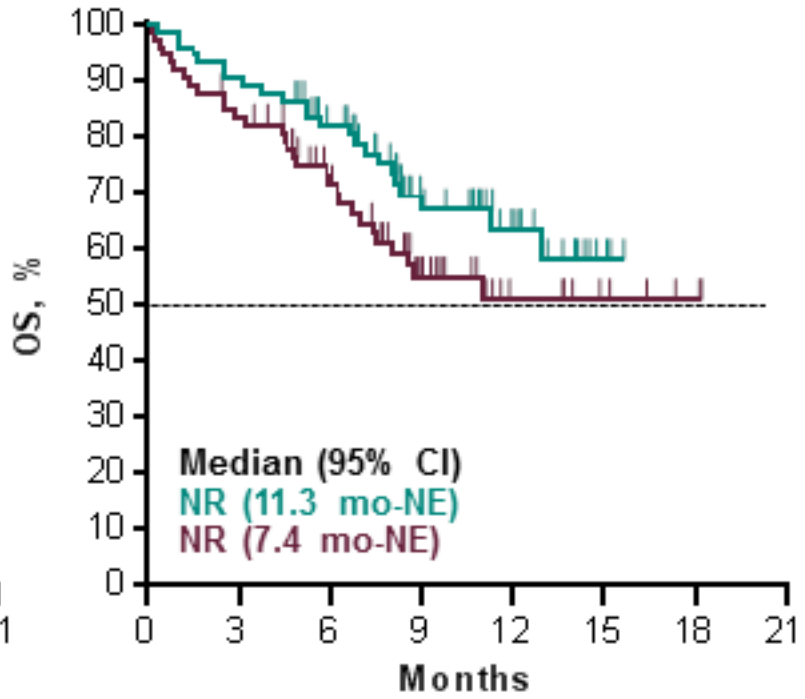


No. at Risk

103	95	68	50	25	9	1	0
104	90	66	37	21	6	0	0

TPS ≥50%

	Events	HR (95% CI)
Pembro + Chemo	31.5%	0.64 (0.37-1.10)
Placebo + Chemo	41.1%	

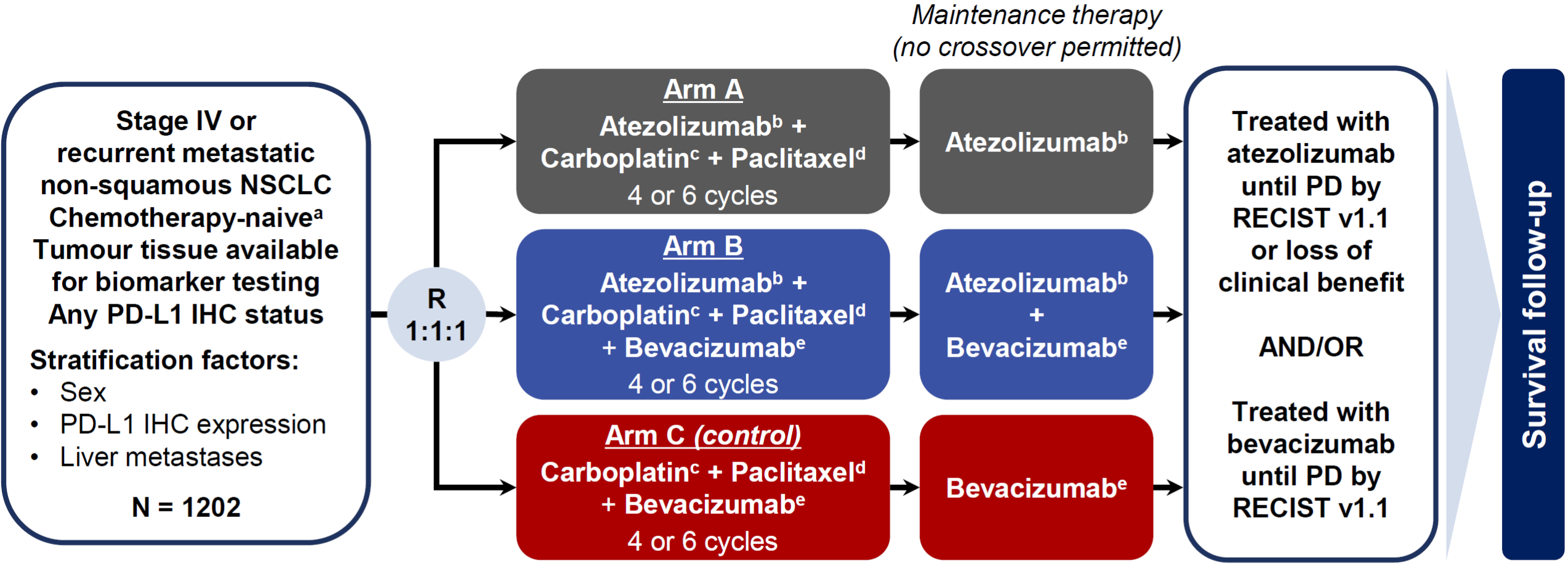


No. at Risk

73	66	53	28	15	3	0	0
73	60	42	21	9	5	2	0

Data cutoff date: Apr 3, 2018.

IMPower150—Study Design



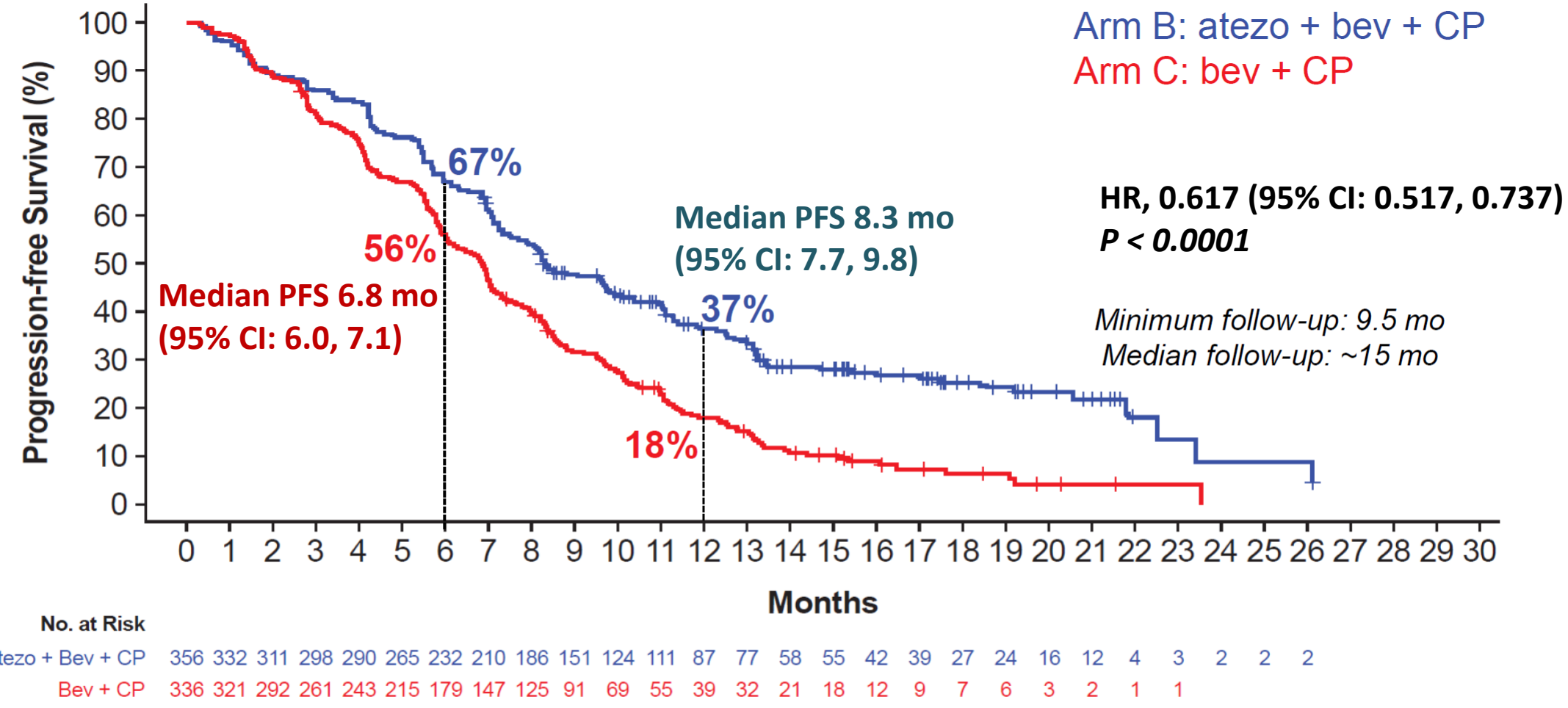
The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

Kowanetz M, Socinski M, et al. ASCO 2018
IMpower150: Efficacy Across Subgroups

[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. [b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

Reck M, et al. IMpower150 PFS analysis.

PFS in ITT (Arm B vs. Arm C)

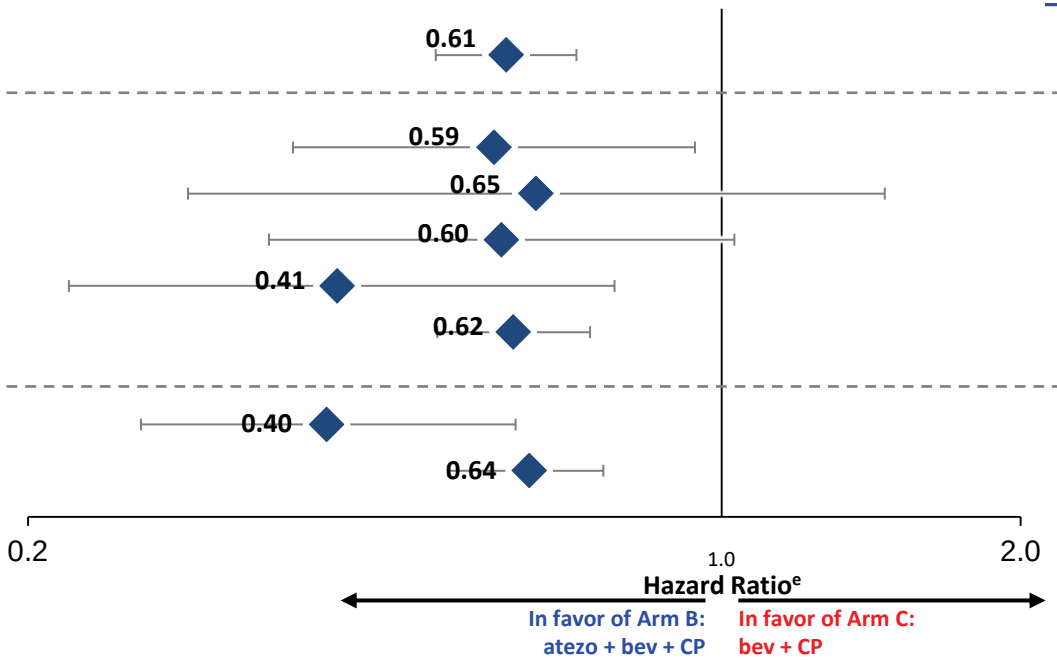


INV, investigator.
Data cutoff: September 15, 2017

Reck M, et al. IMpower150 PFS analysis.

PFS Benefit in Arm B was Observed in Key Populations

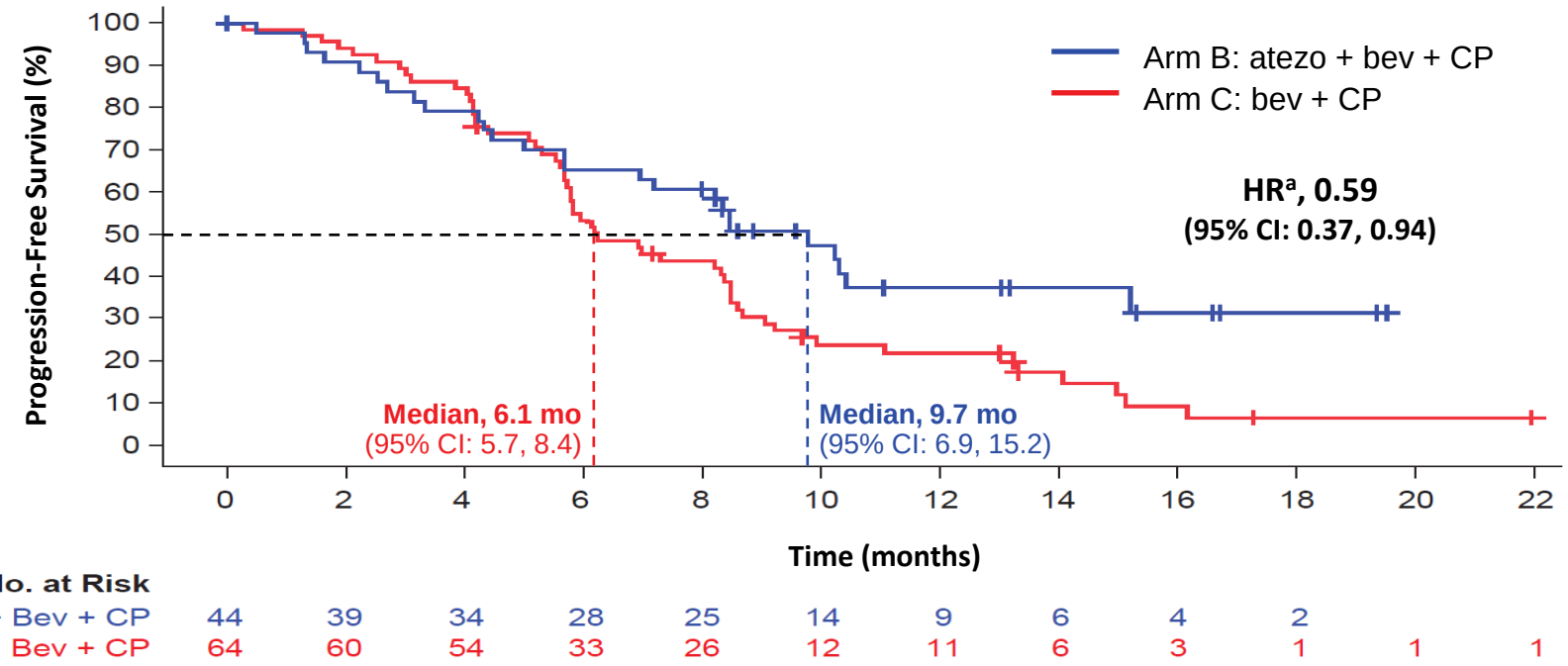
Populations	n (%)[a]	Median PFS, mo Arm B	Median PFS, mo Arm C
ITT (including *EGFR*/*ALK*+)	800 (100%)	8.3	6.8
EGFR/*ALK*+ only[b]	108 (14%)	9.7	6.1
ALK rearrangement[c]	34 (31%)	8.3	5.9
EGFR mutation[c]	80 (74%)	10.2	6.9
Exon 19 deletion or L858R[d]	59 (74%)	10.2	6.1
ITT-WT	692 (87%)	8.3	6.8
Liver metastases	110 (14%)	8.2	5.4
No liver metastases	690 (86%)	8.3	7.0



Atezo, atezolizumab; bev, bevacizumab; CP, carboplatin + paclitaxel.
[a] Prevalence % for ITT, *EGFR/ALK*+ only, ITT-WT, liver metastases, and no liver metastases out of ITT (n=800); prevalence % for *ALK* rearrangement and *EGFR* mutation out of *EGFR/ALK*+ only (n=108); prevalence % for exon 19 deletion of L858R out of *EGFR* mutation (n=80).
[b] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[c] 6 patients had both *EGFR* mutation and *ALK* rearrangement.
[d] Other *EGFR* mutations include L861Q, G719X, S7681, exon 20 insertion, T790M, and other.
[e] Stratified HRs for ITT and ITT-WT populations; unstratified HRs for all other subgroups.
Data cutoff: September 15, 2017

Kowanetz M, Socinski M, et al. AACR 2018
IMpower150: Efficacy Across Subgroups

PFS for Arm B vs C in *EGFR/ALK*+ Patients



- Anti–PD-L1/PD-1 *monotherapy* has not shown significant benefit in patients with *EGFR/ALK* genetic alterations
- Most other clinical trials of PD-L1/PD-1 inhibitors in 1L NSCLC exclude patients with *EGFR* mutations

Kowanetz M, Socinski M, et al. AACR 2018
IMpower150: Efficacy Across Subgroups

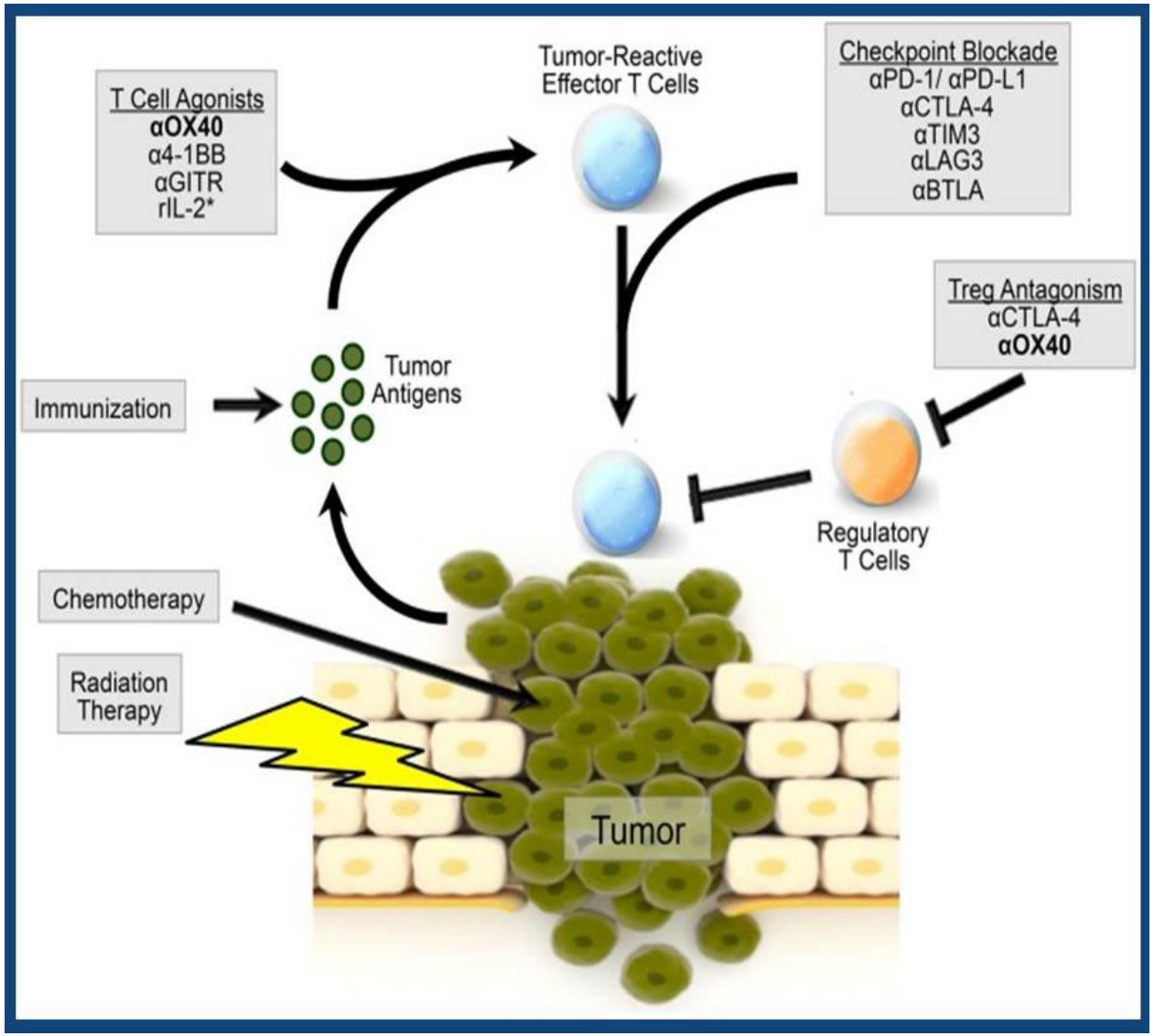
Atezo, atezolizumab; bev, bevacizumab; CP, carboplatin + paclitaxel.
[a] Unstratified HRs. Data cutoff: September 15, 2017

Impower 150: Conclusions

- Atezo/ bevacizumab/chemo given first-line for nonsquamous metastatic NSCLC prolonged PFS compared with bevacizumab/chemo, regardless of PD-L1 expression
- Median OS was 19.2 mo for Atezo arm vs 14.4 mo for control (HR 0.775, 95% CI [0.619, 0.970]; p = 0.0262).
- First randomized study to demonstrate significant benefit with checkpoint blockade among *EGFR*-positive/*ALK*-positive patients

Combination immune therapy

Combination Immunotherapy Strategies



Linch SN Front Oncol 2015: 5:34

PD1/PDL1 inhibitors with other IO

Clinical Trial	Indication	Anti-PD-1/PD-L1	Other Therapy	Phase
Combination With Immunotherapy				
Inhibitory molecules				
CTLA-4				
NCT01454102 (Checkmate-012)	NSCLC	Nivolumab	Ipilimumab	I
NCT02477826 (Checkmate-227)	NSCLC	Nivolumab	Ipilimumab	III
NCT02039674 (KEYNOTE-021)	NSCLC	Pembrolizumab	Ipilimumab	I/II
NCT02000947	NSCLC	Durvalumab	Tremelimumab	Ib
NCT02352948 (ARCTIC)	Stage IIIB/IV NSCLC	Durvalumab	Tremelimumab	III
NCT02453282 (MYSTIC)	Advanced or metastatic NSCLC	Durvalumab	Tremelimumab	III
NCT02542293 (NEPTUNE)	Advanced or metastatic NSCLC	Durvalumab	Tremelimumab	III
IDO				
NCT02327078 (ECHO-204)	Selected advanced tumors	Nivolumab	Epacadostat (IDO inhibitor)	I/II
NCT02318277 (ECHO-203)	Selected advanced tumors	Durvalumab	Epacadostat (IDO inhibitor)	I/II
NCT02178722 (ECHO-202)	Selected advanced tumors	Pembrolizumab	Epacadostat (IDO inhibitor)	I/II
NCT02298153 (ECHO-110)	Advanced NSCLC and urothelial carcinoma	Atezolizumab	Epacadostat (IDO inhibitor)	I
NCT02471846	Solid tumor	Atezolizumab	GDC-0919 (IDO inhibitor)	I

Qiao M et al. Clin Lung Cancer 2017

PD1/PDL1 inhibitors and immune modulators

Clinical Trial	Indication	Anti-PD-1/PD-L1	Other Therapy	Phase
Other Inhibitory Molecules				
NCT01968109	Solid tumor	Nivolumab	BMS-986016 (anti-LAG3)	I/2a
NCT02966548	Advanced solid tumor	Nivolumab	BMS-986016 (anti-LAG3)	I
NCT02460224	Advanced malignancies	PDR001	LAG525 (anti-LAG3)	I/II
NCT03005782	Advanced malignancies	REGN2810 (anti—PD-1)	REGN3767 (anti-LAG3)	I
NCT02817633	Advanced solid tumor	Anti—PD-1 (not known)	TSR-022 (anti-TIM3)	I
NCT02608268	Advanced malignancies	PDR001	MBG453 (anti-TIM3)	I-Ib/2
Stimulatory Molecules				
NCT02179918	Solid tumors	Pembrolizumab	PF-05082566 (anti-CD137)	Ib

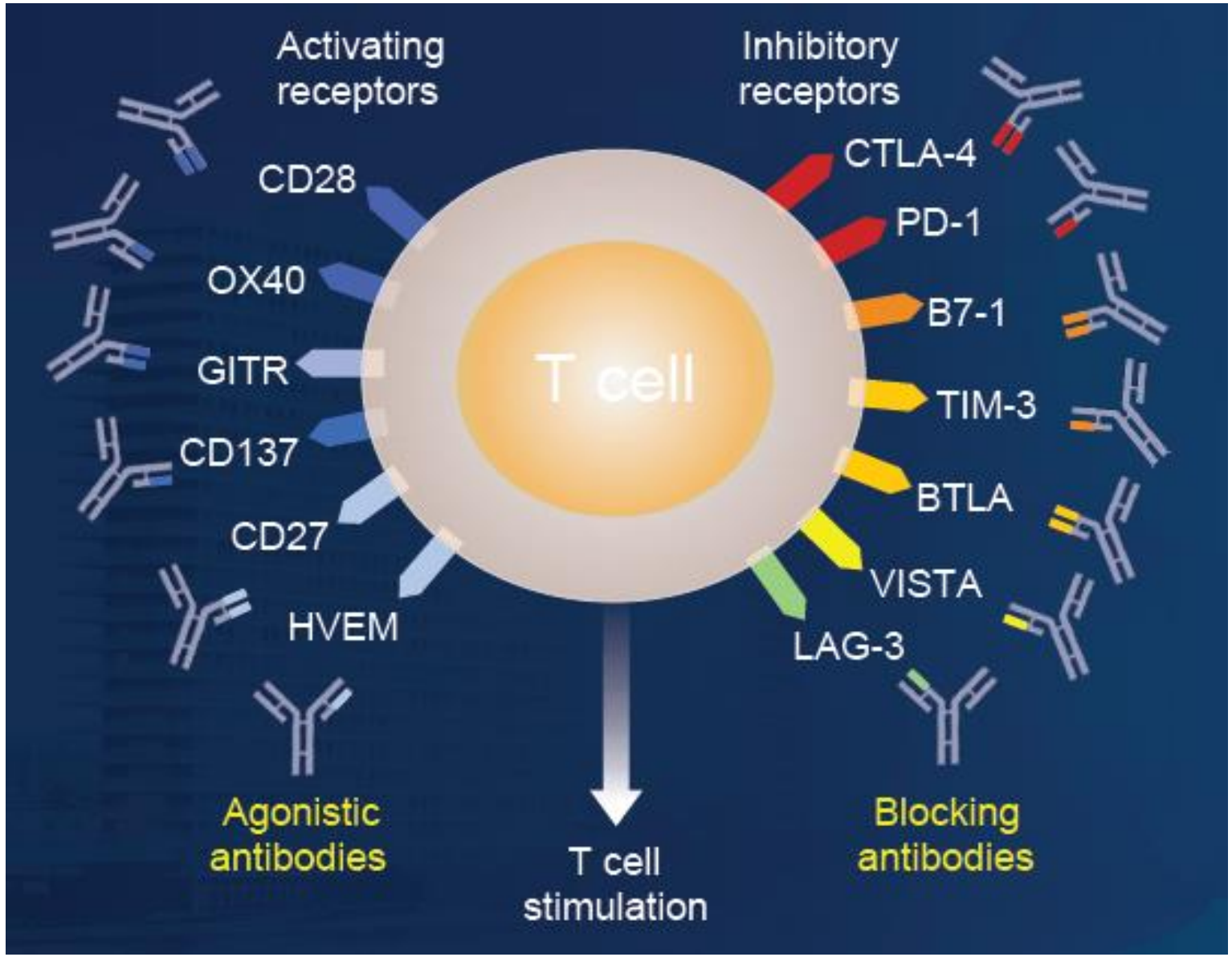
Qiao M et al. Clin Lung Cancer 2017

PD1/PDL1 inhibitors and targeted therapy

Combination With Targeted Therapy				
NCT01633970	Advanced solid tumor	Atezolizumab	Bevacizumab	Ib
NCT02443324	G/GEJ adenocarcinoma, NSCLC, UC, biliary tract cancer	Pembrolizumab	Ramucirumab	I
NCT01454102 (Checkmate-012)	Stage IIIB/IV NSCLC	Nivolumab	Bevacizumab	I
NCT02366143 (IMpower-150)	Stage IV nonsquamous NSCLC	Atezolizumab	Bevacizumab	III
NCT02039674	Advanced NSCLC	Pembrolizumab	Bevacizumab	I/II
NCT01633970	Advanced or metastatic solid tumors	Atezolizumab	Bevacizumab	Ib
NCT02856425	Advanced solid tumors	Pembrolizumab	Nintedanib	Ib
NCT03083041	Advanced NSCLC	SHR-1210	Apatinib	II
NCT02039674 (KEYNOTE-021)	NSCLC	Pembrolizumab	Erlotinib/gefitinib Bevacizumab	I/II
NCT01454102 (Checkmate-012)	Stage III/IV NSCLC	Nivolumab	Erlotinib Bevacizumab (maintenance)	I
NCT02088112	NSCLC ($EGFR^+$)	Durvalumab	Gefitinib	I
NCT02630186	Advanced/metastatic NSCLC ($EGFR^+$)	Atezolizumab	Rociletinib (CO-1686)	Ib/2
NCT02143466 (TATTON)	Advanced NSCLC ($EGFR^+$)	Durvalumab	Osimertinib	I
NCT02364609	Stage III/IV NSCLC ($EGFR^+$)	Pembrolizumab	Afatinib	I/Ib
NCT01998126	Stage IV NSCLC ($EGFR^+$ or ALK^+)	Nivolumab	Erlotinib/crizotinib	I
NCT02013219	NSCLC ($EGFR^+$ or ALK^+)	Atezolizumab	Erlotinib/alectinib	Ib
NCT02393625	NSCLC (ALK^+)	Nivolumab	Ceritinib	I
NCT02511184	NSCLC (ALK^+)	Pembrolizumab	Crizotinib	Ib
NCT02574078 (Checkmate-370)	Advanced NSCLC	Nivolumab	Erlotinib/crizotinib	I/II
NCT02451930	Stage IV NSCLC	Pembrolizumab	Necitumumab	Ib

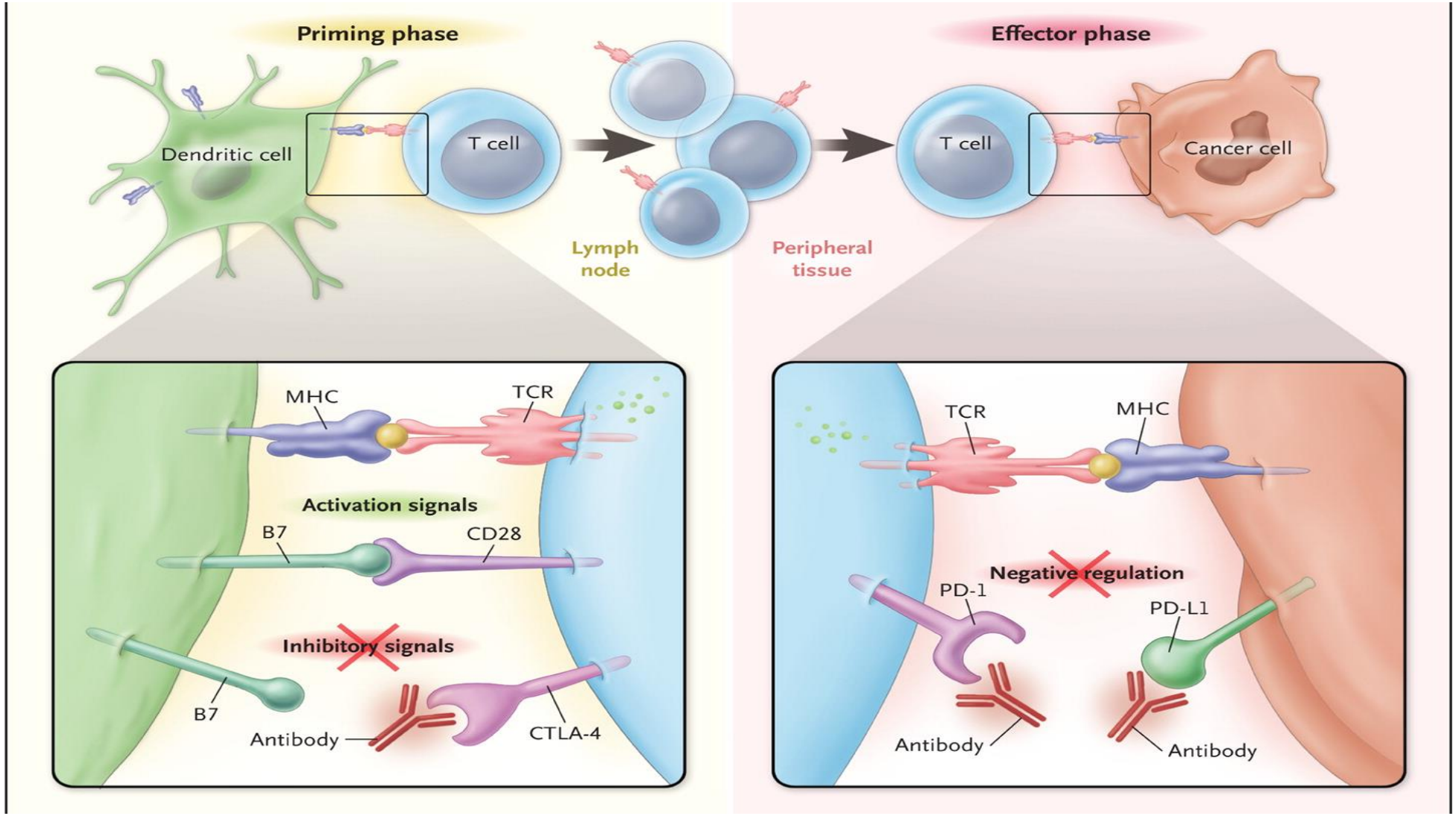
Qiao M et al. Clin Lung Cancer 2017

T cell immune checkpoints as targets for cancer therapy



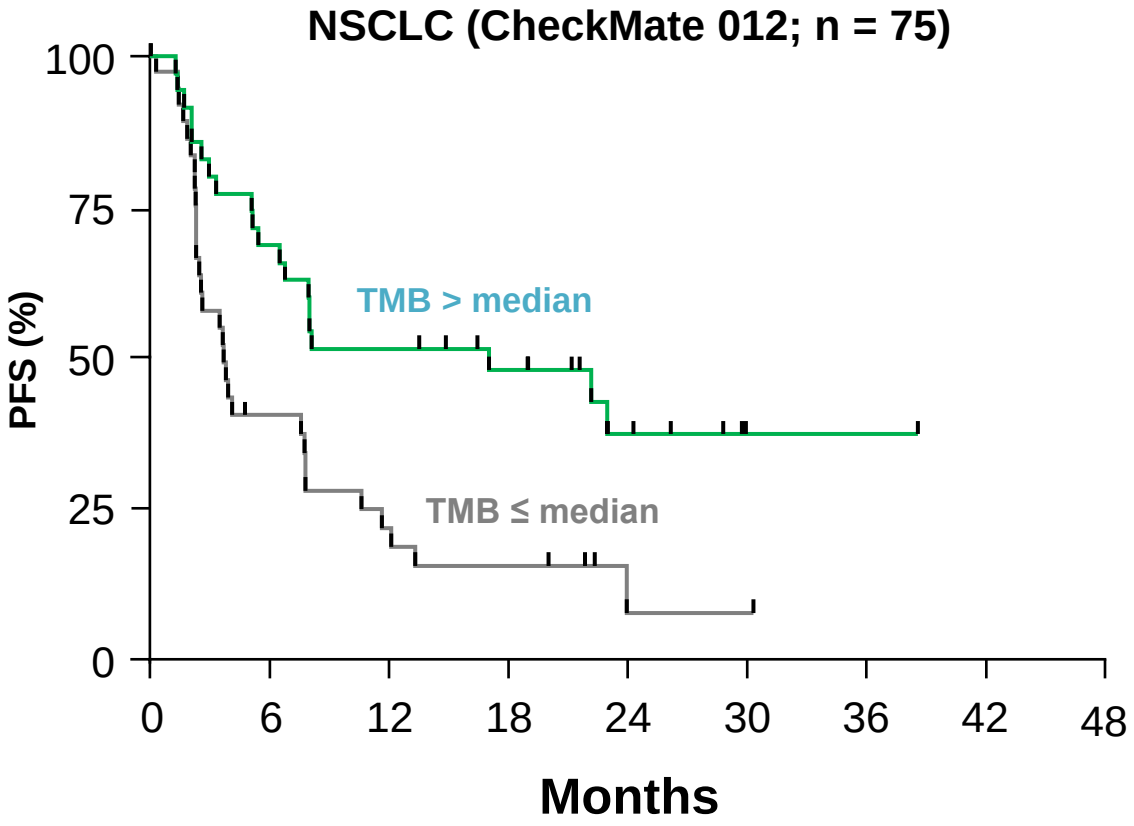
Mellman I et al. Nature 2011; 480:481-489

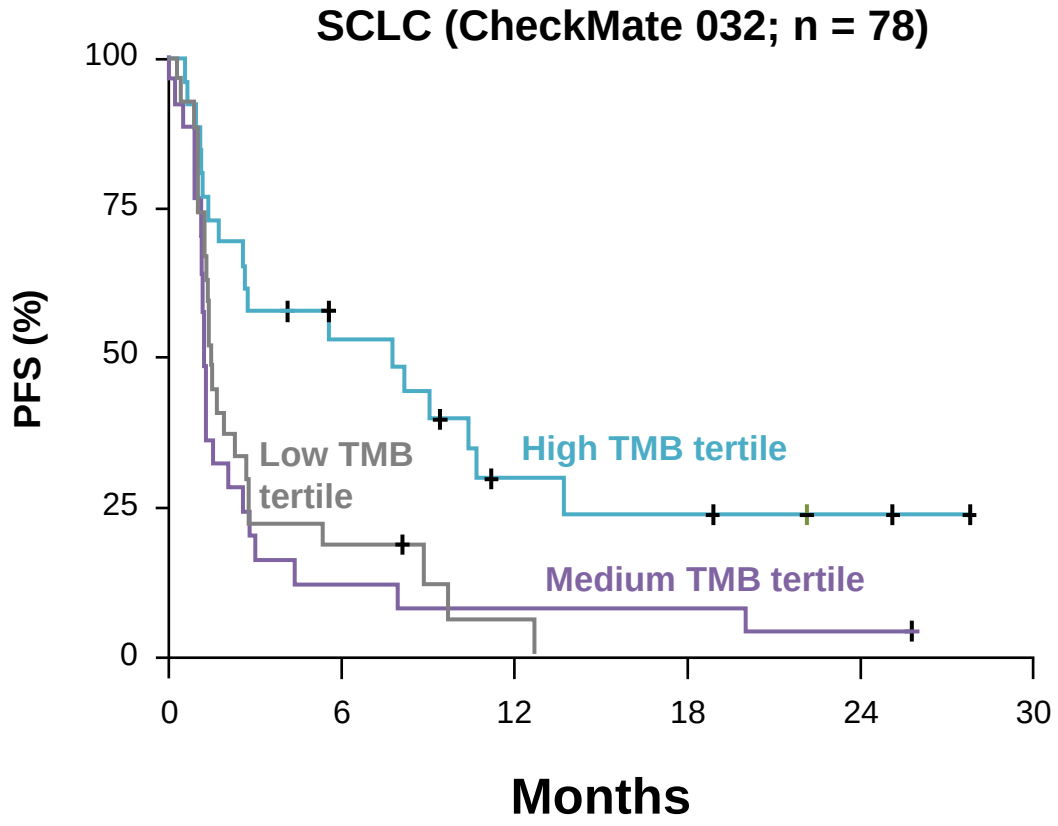
CTLA-4 and PD-1/PD-L1 Checkpoint Blockade



Ribs A. N Engl J Med. 2012;366:2517-2519.

Preliminary Analyses of TMB in Lung Cancers Treated With Nivolumab + Ipilimumab

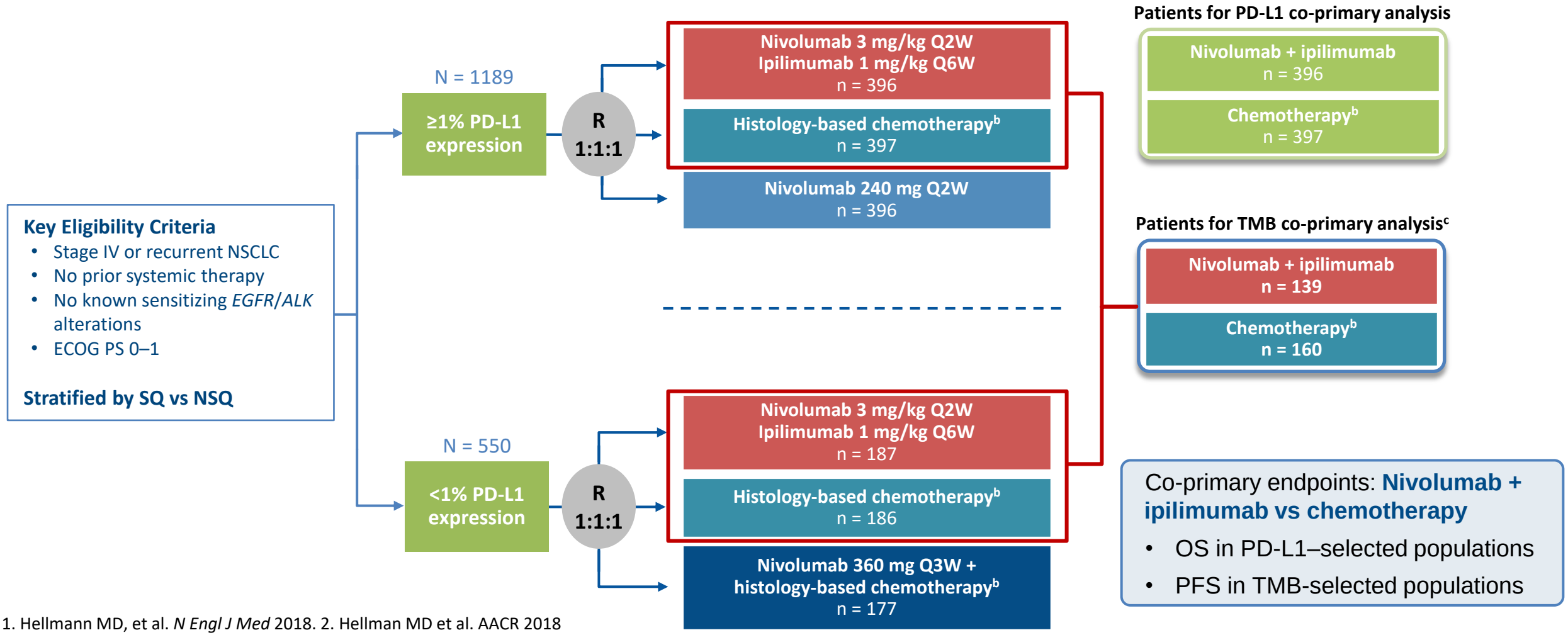




- Whole exome sequencing in tumor tissue samples from patients with NSCLC and SCLC treated with nivolumab + ipilimumab demonstrates the potential of TMB as an independent biomarker of efficacy, distinct from PD-L1[1,2]

1. Hellmann MD, et al. *Cancer Cell* 2018. doi: https://doi.org/10.1016/j.ccell.2018.03.018. Epub; 2. Hellmann MD, et al. *Cancer Cell* (in press) 2018.

CheckMate 227 Part 1 Study Design[a]



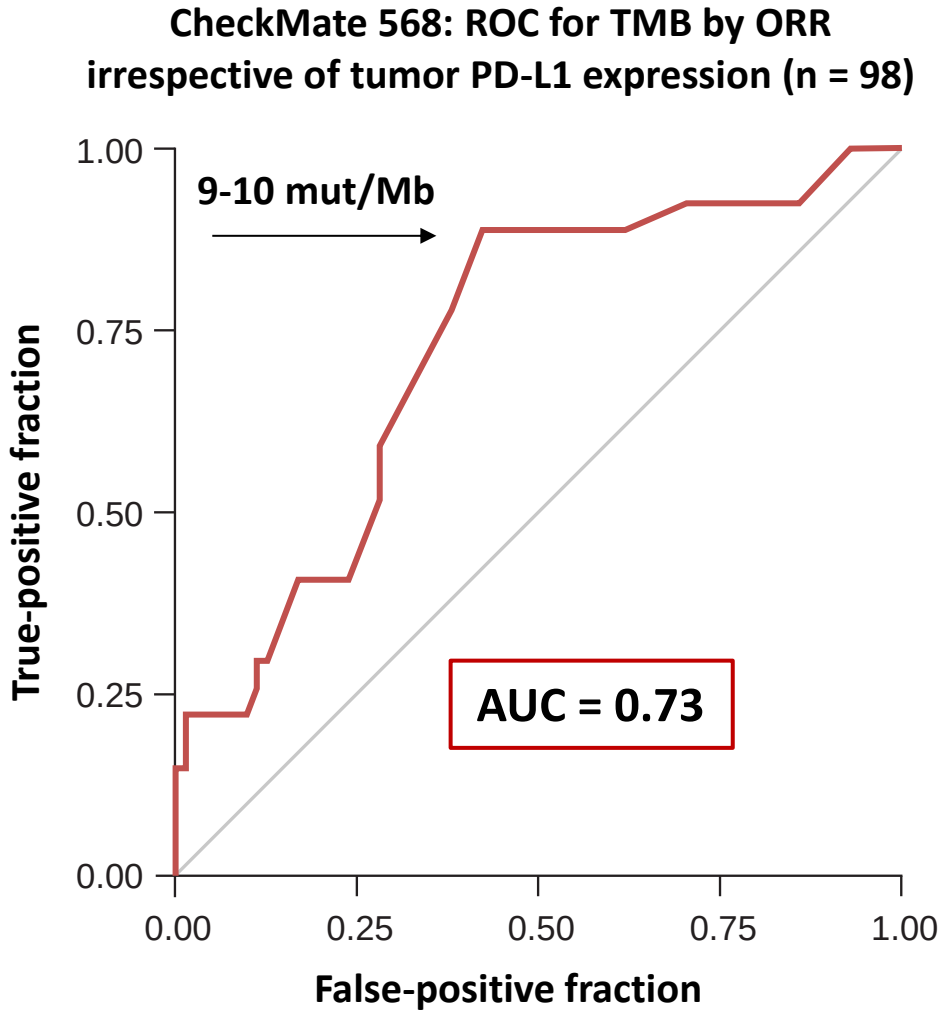
1. Hellmann MD, et al. *N Engl J Med* 2018. 2. Hellman MD et al. AACR 2018

Database lock: January 24, 2018; minimum follow-up: 11.2 months

[a]NCT02477826 [b]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; [c]The TMB co-primary analysis was conducted in the subset of patients randomized to nivolumab + ipilimumab or chemotherapy who had evaluable TMB ≥10 mut/Mb

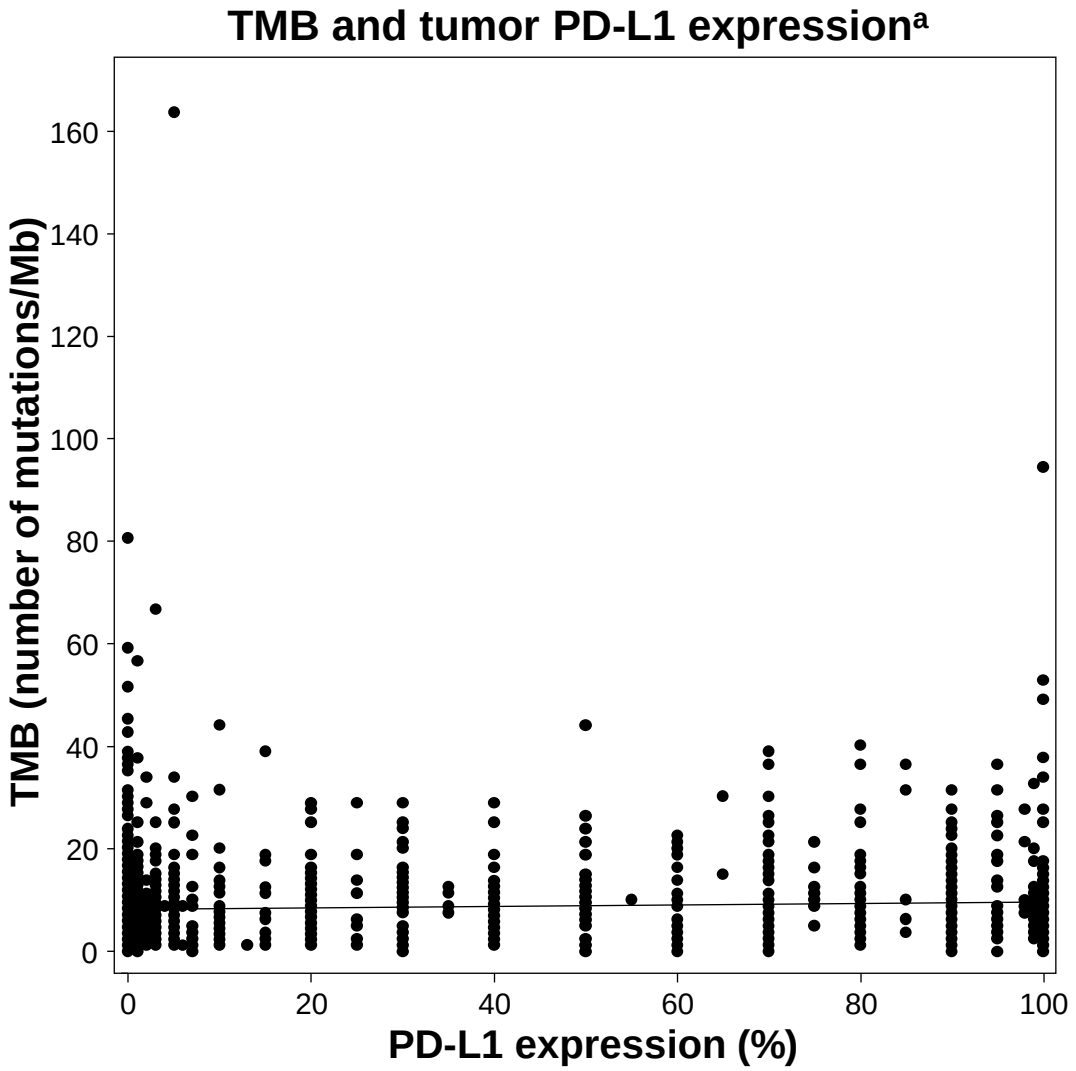
Selection of TMB ≥10 mut/Mb Cutoff Using FoundationOne CDx™

- Retrospective testing from CheckMate 026, 012, and 568 informed selection of the TMB cutoff (≥10 mut/Mb)[1–3]
- ORR increased in patients with higher TMB, and plateaued at TMB ≥10 mut/Mb

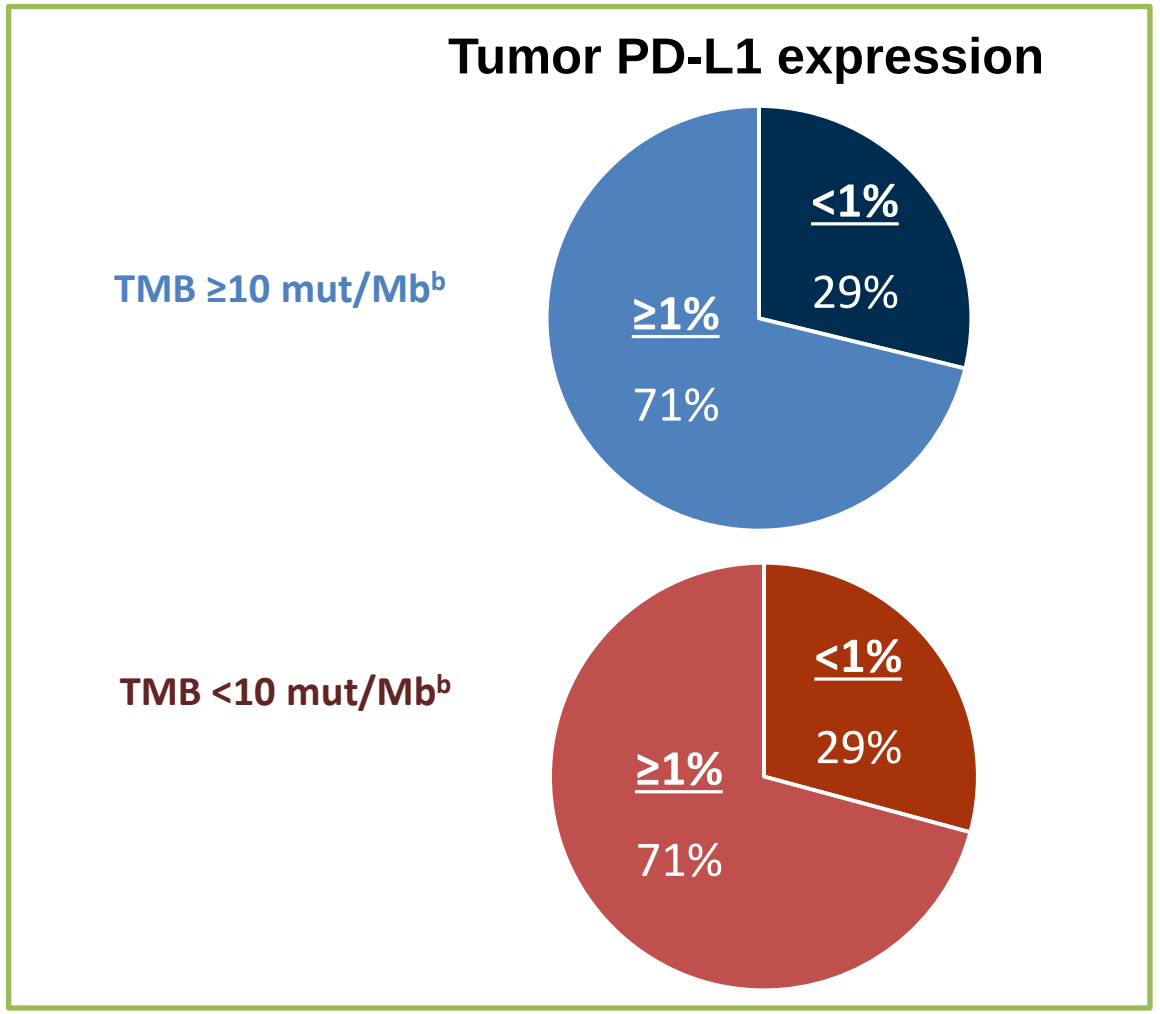


1. Carbone DP, et al. *N Engl J Med* 2017:376;2415–2426; 2. Hellmann MD, et al. *Cancer Cell* 2018. doi: https://doi.org/10.1016/j.ccell.2018.03.018. Epub; 3. Ramalingam S, et al. Presented at AACR Annual Meeting; April 14–18, 2018; Chicago, IL, USA. CT078.

TMB and Tumor PD-L1 Expression



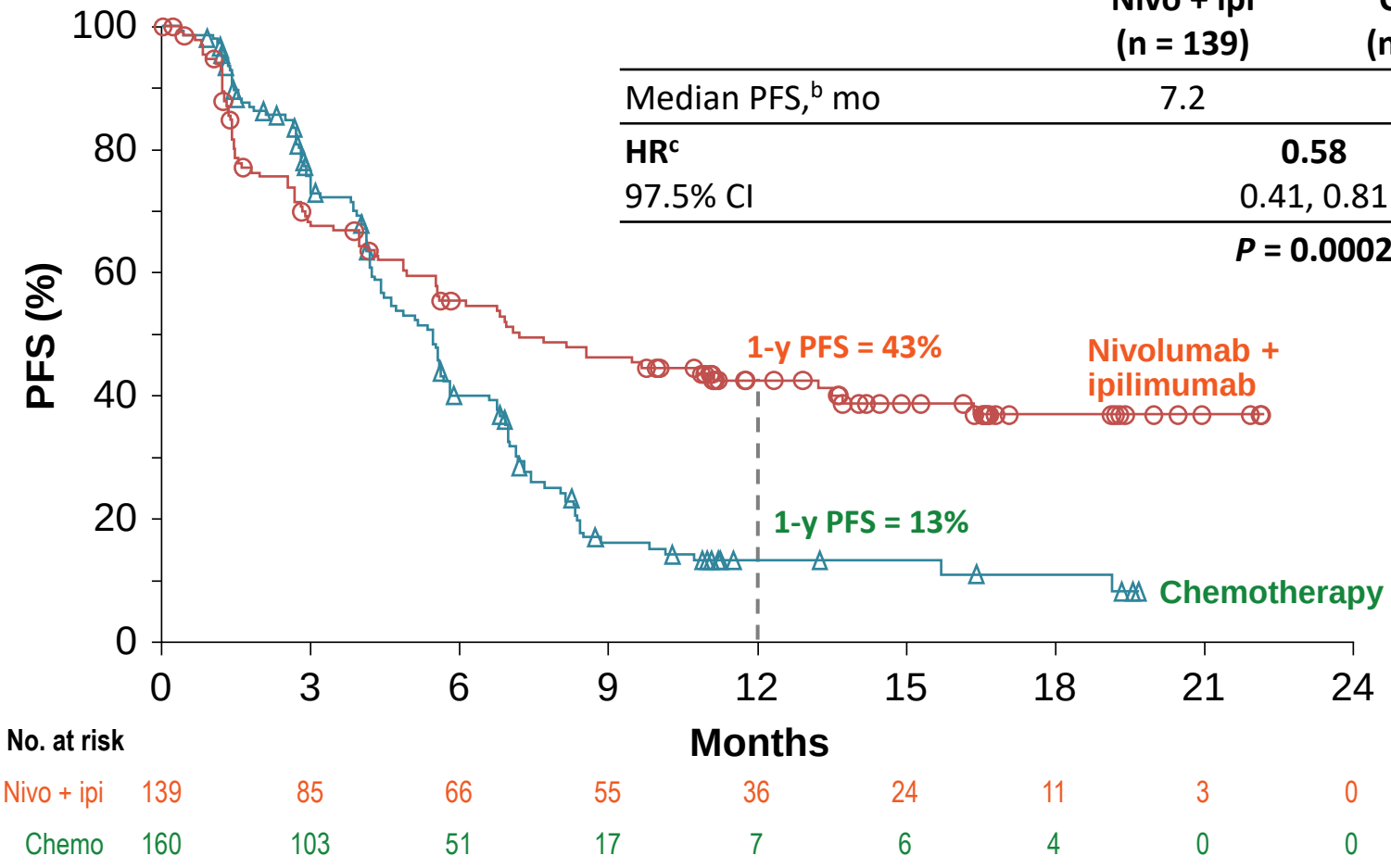
- **58% had TMB-evaluable samples;**
- **44% ≥10 mut/Mb**



1. Hellmann MD, et al. *N Engl J Med* 2018. 2. Hellman MD et al. AACR 2018

[a]Symbols (dots) in the scatterplot may represent multiple data points, especially for patients with <1% tumor PD-L1 expression. The black line shows the relationship between TMB and PD-L1 expression as described by a linear regression model; [b]Among patients in the nivolumab +ipilimumab and chemotherapy arms; TMB ≥10 mut/Mb, n = 299; TMB <10 mut/Mb, n = 380

PFS in Patients With High TMB (≥10 mut/Mb)[a]



	Nivo + ipi (n = 139)	Chemo (n = 160)
Median PFS,[b] mo	7.2	5.4
HR[c]	**0.58**	
97.5% CI	0.41, 0.81	
	***P* = 0.0002**	

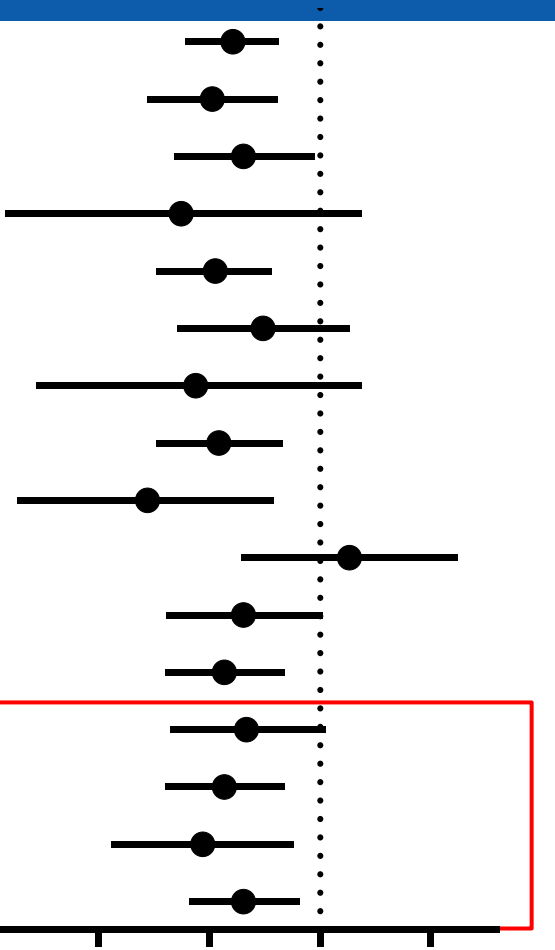
- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)[d]

1. Hellmann MD, et al. *N Engl J Med* 2018. 2. Hellman MD et al. AACR 2018

[a]Per blinded independent central review (BICR); median (range) of follow-up in the co-primary analysis population was 13.6 mo (0.4, 25.1) for nivo + ipi and 13.2 mo (0.2, 26.0) for chemo; [b]95% CI: nivo + ipi (5.5, 13.2 mo), chemo (4.4, 5.8 mo); [c]95% CI: 0.43, 0.77 mo; [d]The *P*-value for the treatment interaction was 0.0018

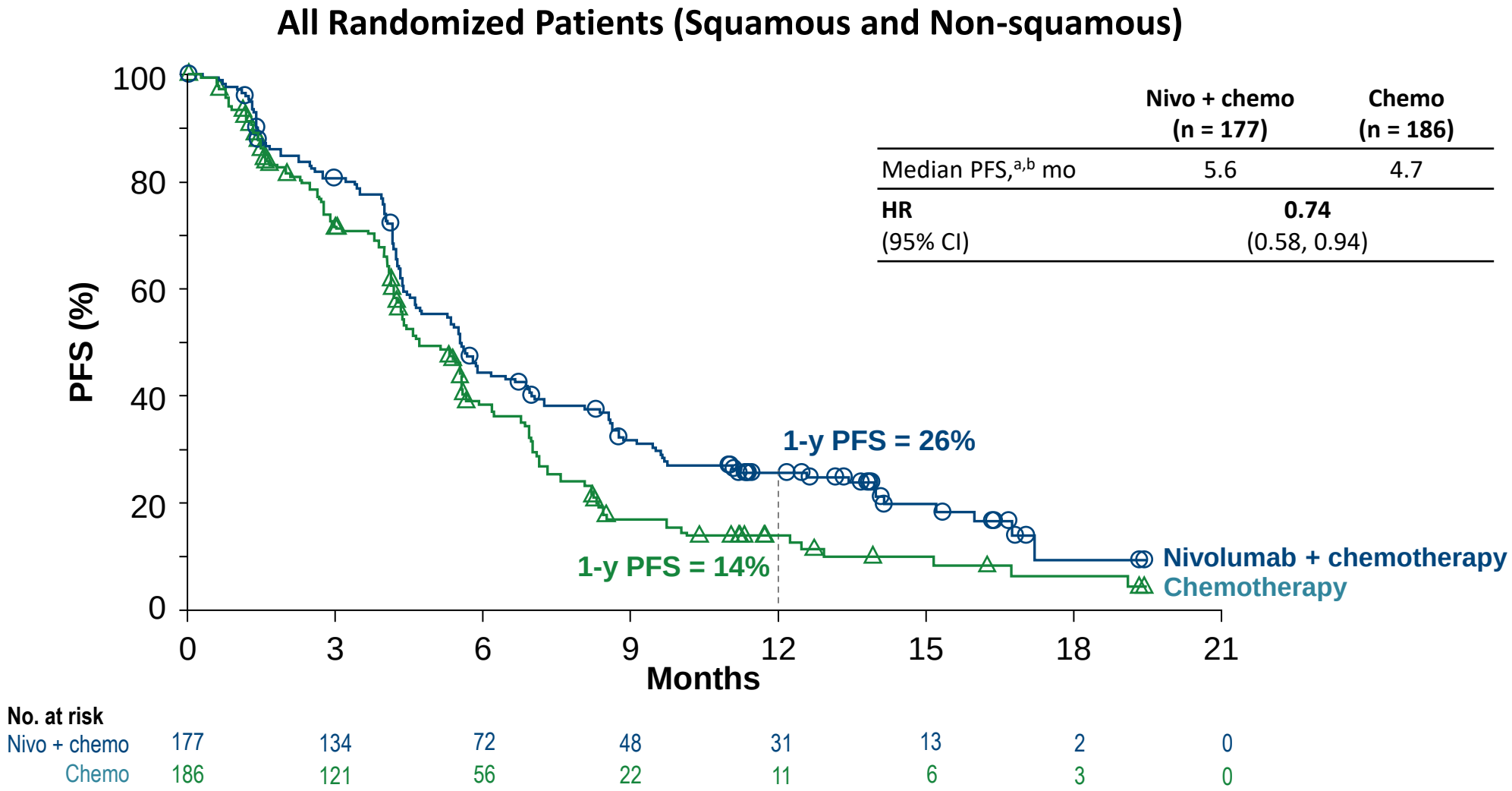
PFS Subgroup Analyses With High TMB (≥10 mut/Mb)

Subgroup	Nivo + ipi n	Chemo n	Unstratified HR (95% CI)
Overall	139	160	0.58 (0.43, 0.77)
<65 years	73	83	0.51 (0.34, 0.77)
≥65 years	66	77	0.62 (0.40, 0.97)
≥75 years	13	14	0.42 (0.14, 1.30)
Male	98	106	0.52 (0.36, 0.74)
Female	41	54	0.70 (0.41, 1.20)
North America	14	16	0.46 (0.17, 1.30)
Europe	77	87	0.53 (0.36, 0.79)
Asia	21	32	0.34 (0.15, 0.75)
Rest of world	27	25	1.20 (0.61, 2.36)
ECOG PS 0	56	49	0.62 (0.38, 1.02)
ECOG PS 1	82	110	0.55 (0.38, 0.80)
Squamous	44	56	0.63 (0.39, 1.04)
Non-squamous	95	104	0.55 (0.38, 0.80)
PD-L1 <1%	38	48	0.48 (0.27, 0.85)
PD-L1 ≥1%	101	112	0.62 (0.44, 0.88)



1. Hellmann MD, et al. *N Engl J Med* 2018. 2. Hellman MD et al. AACR 2018

PFS: Nivolumab + Chemotherapy vs Chemotherapy in Patients With <1% Tumor PD-L1 Expression



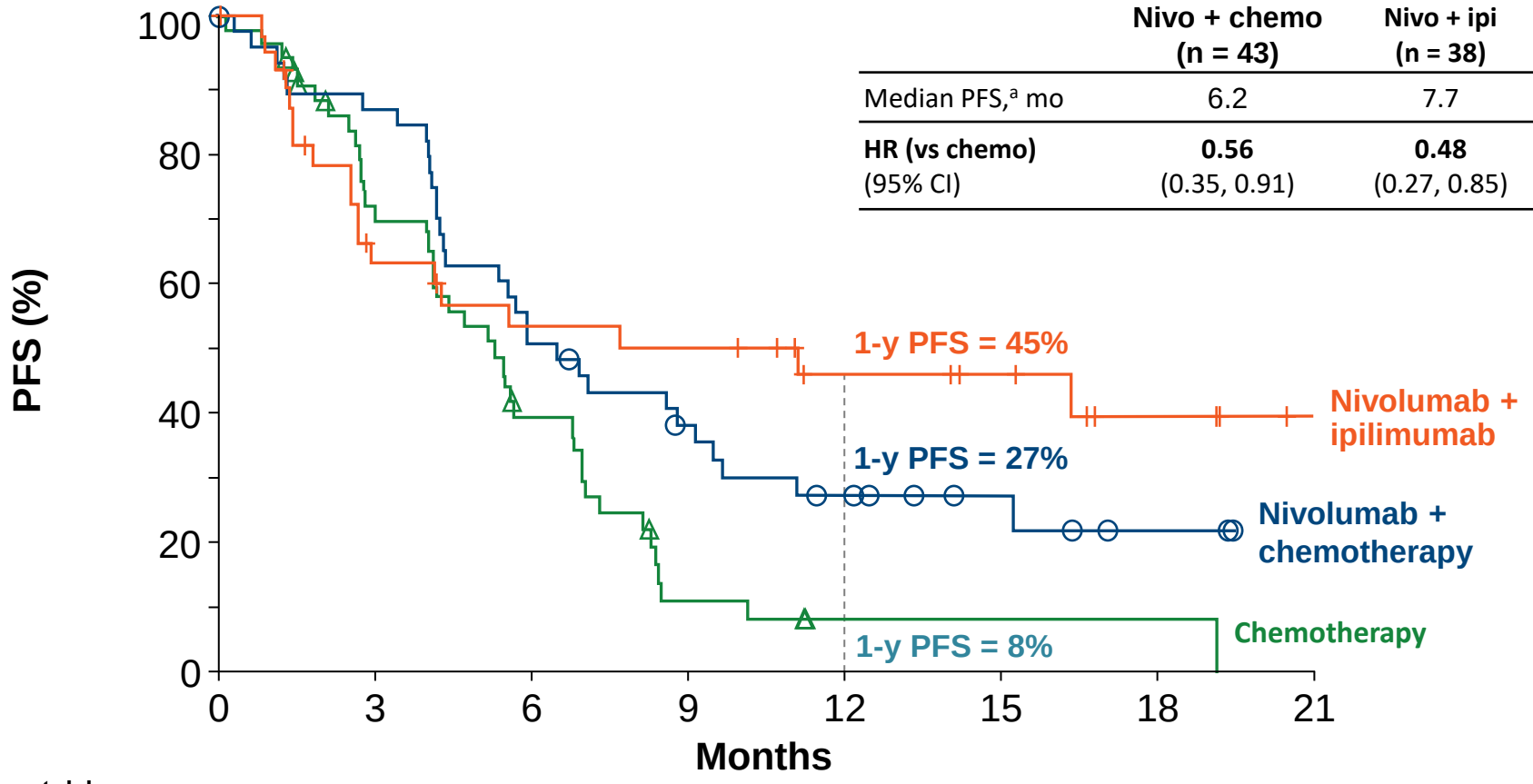
	Nivo + chemo (n = 177)	Chemo (n = 186)
Median PFS,[a,b] mo	5.6	4.7
HR	**0.74**	
(95% CI)	(0.58, 0.94)	

Borghael et al ASCO 2018

[a]95% CI: nivo + chemo (4.6, 6.7 mo), chemo (4.3, 5.6 mo); [b]In the nivo + ipi arm (n = 187), median (95% CI) PFS was 4.4 (3.1, 6.0), 1-y PFS was 29%, and HR vs chemo was 0.79 (0.62, 1.01)

PFS: Nivolumab/Chemotherapy and Nivolumab/Ipilimumab in 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) (95% CI)	**0.56** (0.35, 0.91)	**0.48** (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

Borghael et al ASCO 2018
Exploratory analysis
[a]95% CI: nivo + chemo (4.3, 9.1 mo), nivo + ipi (2.7, NR mo), chemo (4.0, 6.8 mo)

Safety Summary of Treatment-Related AEs

	Nivolumab + chemotherapy (n = 172)		Nivolumab + ipilimumab (n = 185)		Chemotherapy (n = 183)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE,[a] %	92	52	74	25	77	35
TRAE leading to discontinuation,[b] %	13	8	16	10	14	9
Median number of doses received, n	8.5 for nivolumab (Q3W) 4–7 for chemo (Q3W)		8.0 for nivolumab (Q2W) 3.0 for ipilimumab (Q6W)		4–7 for chemo (Q3W)	

- There were 4 treatment-related deaths in the nivolumab + chemo arm, 7 in both nivolumab + ipilimumab arms in Part 1,[c] and 6 in both chemo arms in Part 1[d]

Borghael et al ASCO 2018

[a]Includes events reported between first dose and 30 days after last dose of study drug; [b]For nivolumab + ipilimumab, these events include TRAEs leading to discontinuation of ipilimumab or both study drugs (patients could not discontinue nivolumab without discontinuing ipilimumab); for nivolumab + chemo, patients who discontinued nivolumab or chemo or both were counted as having a TRAE leading to discontinuation; [c]Nivolumab + ipilimumab arms, n = 576; [d]Chemo arms, n = 570

Summary

By the numbers…

Reck et al NEJM 2016; Brahmer et al WCLC 2017; Lopes et al ASCO 2018; Gandhi et al NEJM 2018; Paz Ares et al ASCO 2018; Hellman et al NEJM 2018; Socinski et al ASCO 2018

	Pembro (PD-L1≥ 50%)	Pembro (PD-L1≥ 1%)	Carbo/ pem/ pembro (non-squam)	Carbo/ taxane/ pembro (SCC)	Ipi/nivo (TMB >10)	Carbo/pacli /atezo /bev
ORR (%)	44.8	27.3	47.6	58.4	45.3	56
DOR (months)	NR	20.2	11.2	7.7	68% @12 mo	11.5
Median PFS (months)	10.3	5.4	8.8	6.4	7.2	8.3
12 mo PFS (%)	~50	28	34.1	~33	43	38
Median OS (months)	30	16.7	NR	15.9	23 (prelim)	19.2
12 mo OS (%)	70.3	60	69.2	~75	67	67
24 mo OS (%)	na	39	na	na	na	43

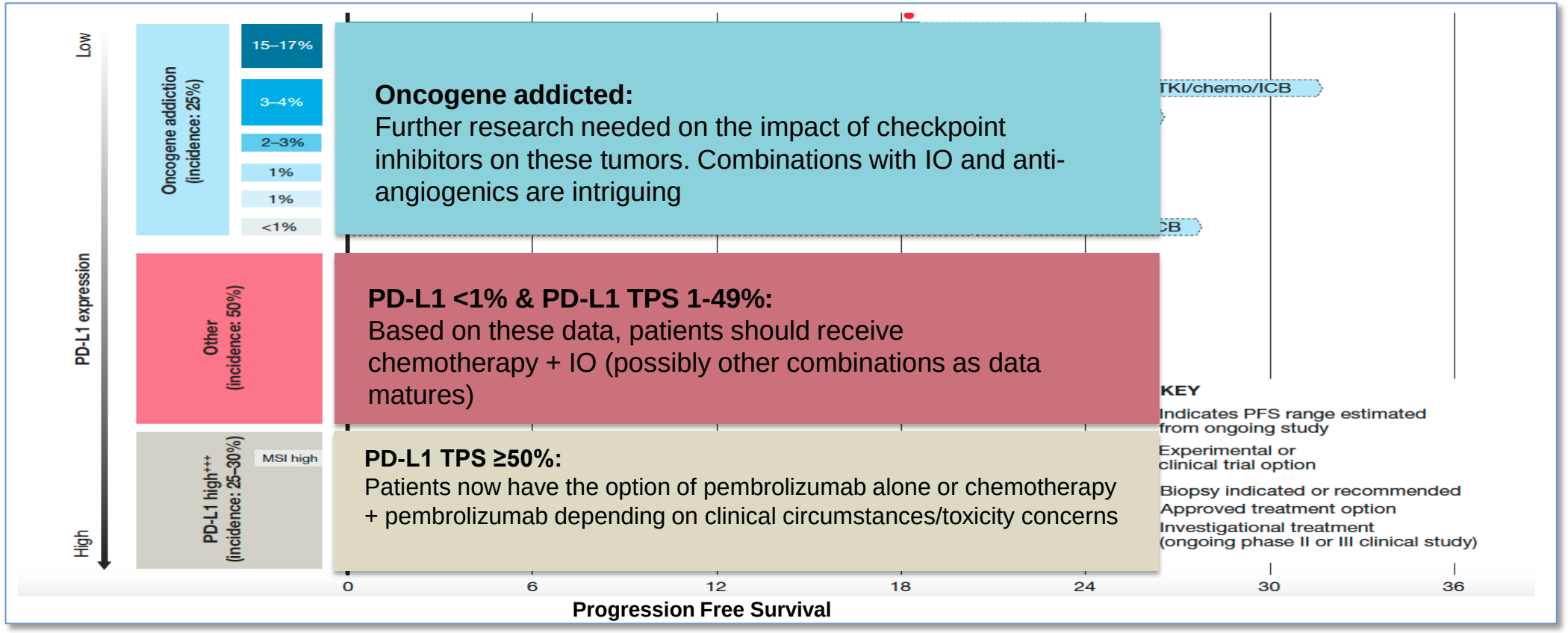
Change in treatment paradigms

- First-line, no actionable mutation, nonsquamous NSCLC, PD-L1 <50%—platinum, pemetrexed, pembrolizumab
- First-line, no actionable mutation, squamous NSCLC, PD-L1 <50%—carboplatin, paclitaxel or nab-paclitaxel, pembrolizumab
- First-line, no actionable mutation, NSCLC, PD-L1 ≥50%—pembrolizumab

Interesting data, not time to change yet

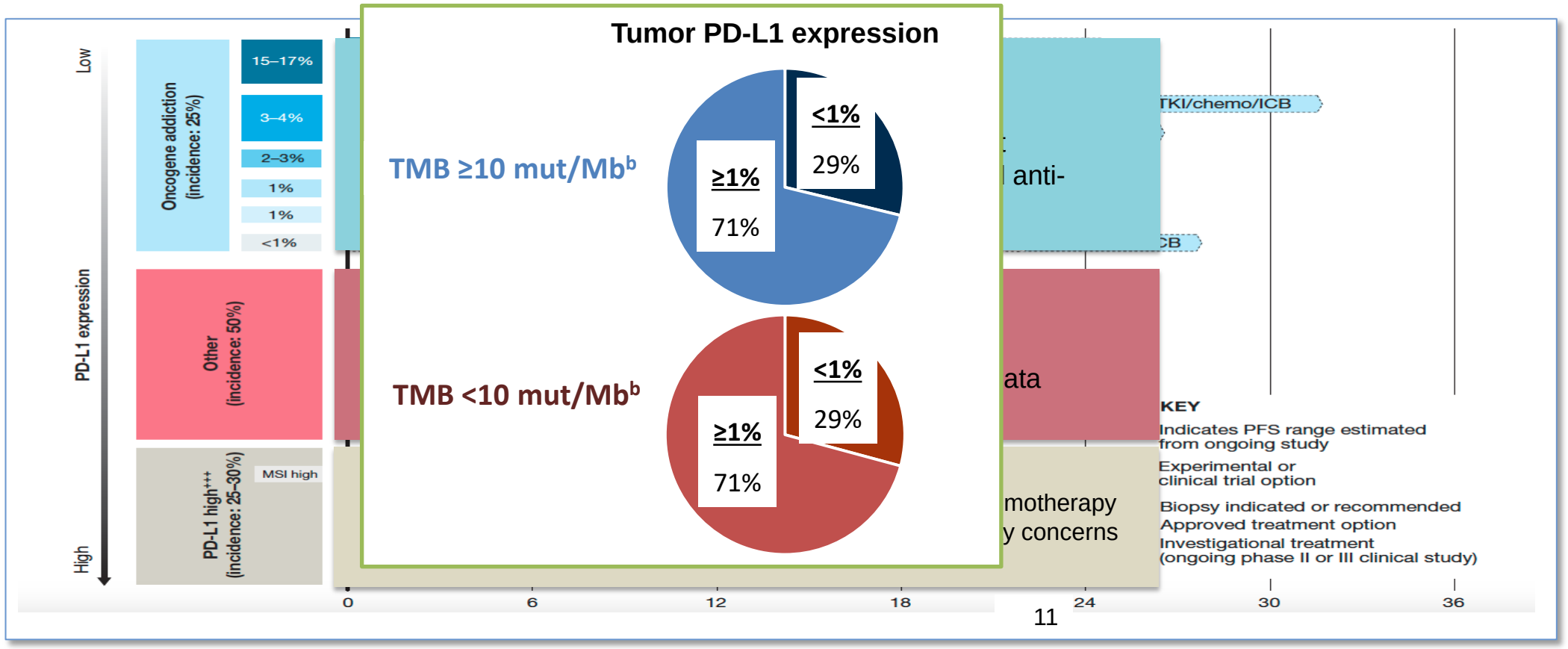
- First-line, no actionable mutation, NSCLC, any PD-L1, high TMB—ipilimumab and nivolumab
- First-line cytotoxic therapy with *EGFR/ALK* alteration after TKI therapy—carboplatin, paclitaxel, atezolizumab and bevacizumab
- First-line, no actionable mutation, NSCLC, PD-L1 1-49%—pembrolizumab? Most of the result driven by PD-L1 ≥ 50%

Advanced NSCLC and IO therapy—August 2018



Nature. 2018 Jan 24;553(7689):446-454.

Advanced NSCLC and IO therapy—layering in TMB



Nature. 2018 Jan 24;553(7689):446-454.

Thank you!