How to Choose Front-Line Therapy for Metastatic NSCLC without Driver Mutations.

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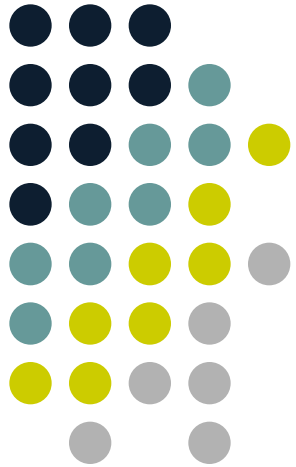
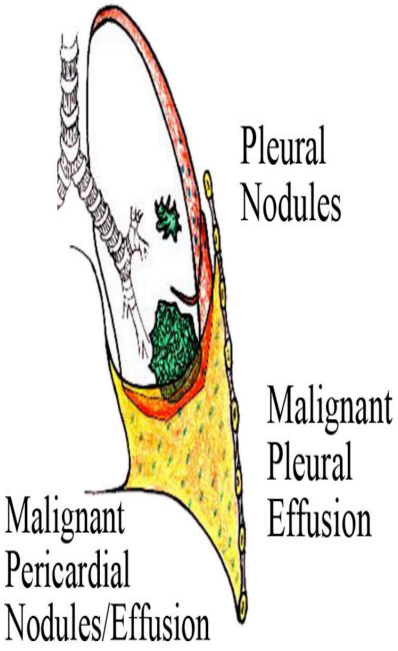


AJCC 8: Stage IVA and IVB

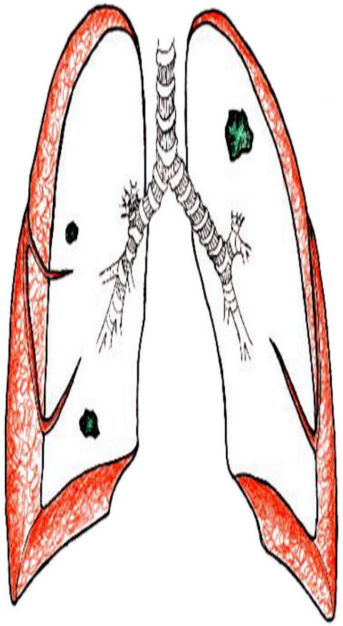
Stage IVA

Stage IVB

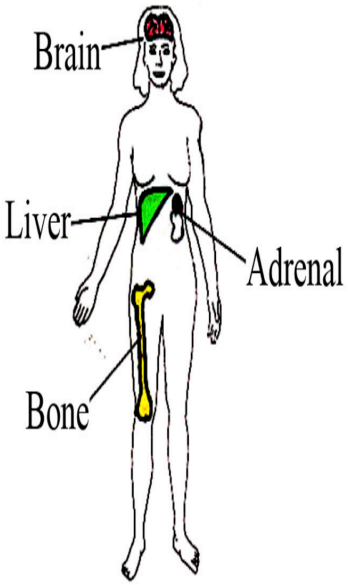
M1a Pl Dissem



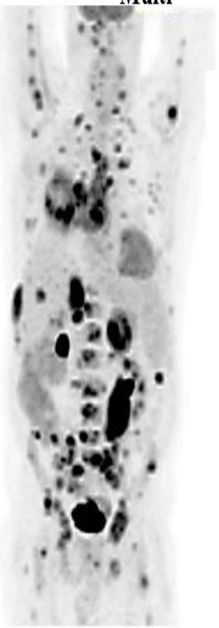
M1a Contra Nod



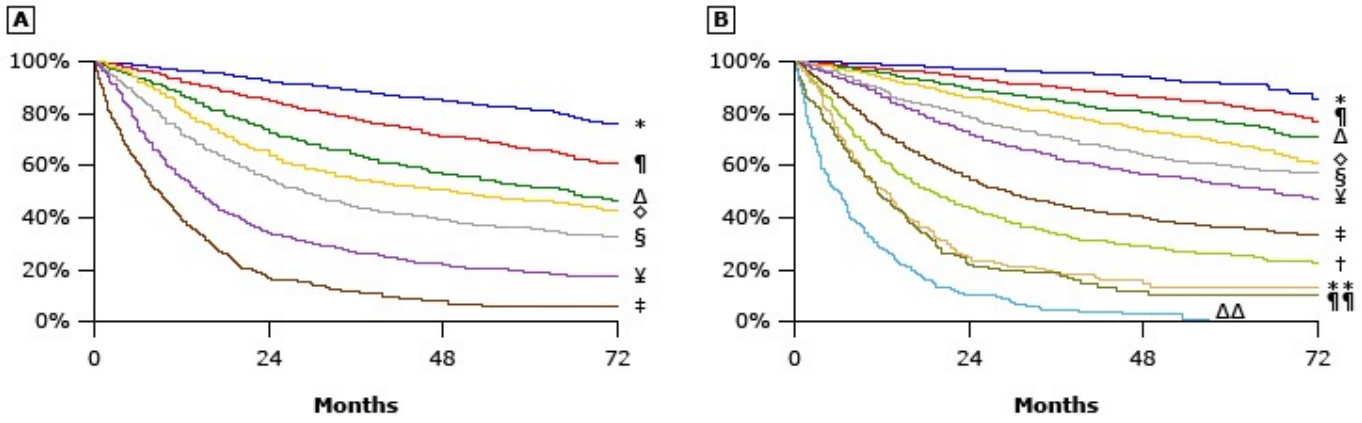
M1b Single



M1c Multi



Overall survival by clinical stage according to the seventh edition (A) and the eighth edition (B) groupings using the entire database available for the eighth edition



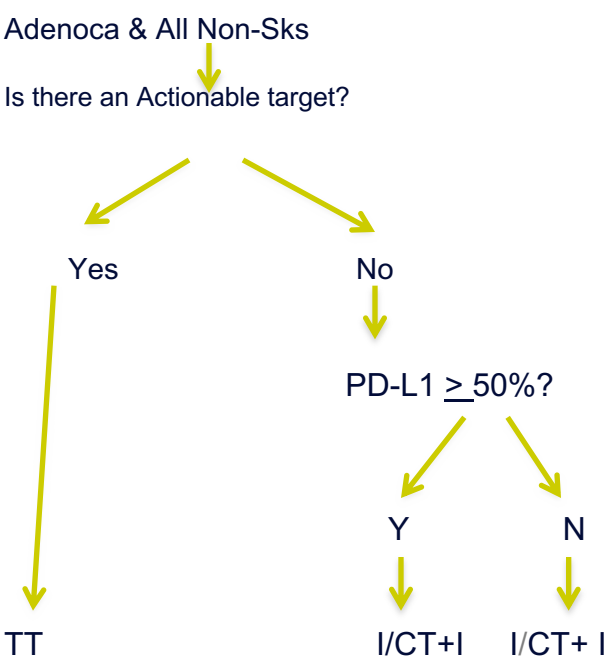
7th edition	Events / N	MST	24 month	60 month
* IA	1119 / 6303	NR	93%	82%
¶ IB	768 / 2492	NR	85%	66%
Δ IIA	424 / 1008	66.0	74%	52%
◇ IIB	382 / 824	49.0	64%	47%
§ IIIA	2139 / 3344	29.0	55%	36%
¥ IIIB	2101 / 2624	14.1	34%	19%
‡ IV	664 / 882	8.8	17%	6%

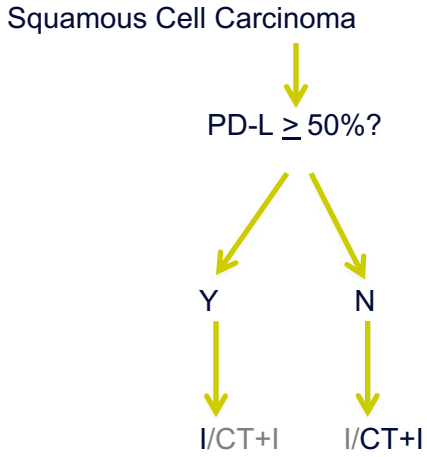
8th edition	Events / N	MST	24 month	60 month
* IA1	68 / 781	NR	97%	92%
¶ IA2	505 / 3105	NR	94%	83%
Δ IA3	546 / 2417	NR	90%	77%
◇ IB	560 / 1928	NR	87%	68%
§ IIA	215 / 585	NR	79%	60%
¥ IIB	605 / 1453	66.0	72%	53%
‡ IIIA	2052 / 3200	29.3	55%	36%
† IIIB	1551 / 2140	19.0	44%	26%
** IIIC	831 / 986	12.6	24%	13%
¶¶ IVA	336 / 484	11.5	23%	10%
ΔΔ IVB	328 / 398	6.0	10%	0%

Overall survival by clinical stage according to the seventh edition (A) and the eighth edition (B) groupings using the entire database available for the eighth edition. Survival is weighted by type of database submission: registry versus other.

N: number of patients; MST: median survival time; NR: not reached.

Treatment Algorithm (as of 04/2022)





PDL1- ≥ 50% – (Non-Sq): KN189/IMPower130/KN42/KN24/IMPower110/Empower1. (Sq): KN42/24/IMPower110/Empower1/KN407/CK9LA

PDL1>1-49% – (Non-Sq): KN189/IMPower130/KN42 (Sq): KN407/KN42/CK9LA

PDL1<1% – (Non-Sq): KN189/IMPower130/CK9LA. (Sq): KN407/CK9LA. TMB (High) - CK 227

(Non-Sks = non-smokers; TT = Targeted Therapy; I = Immunotherapy; CT = Chemotherapy)

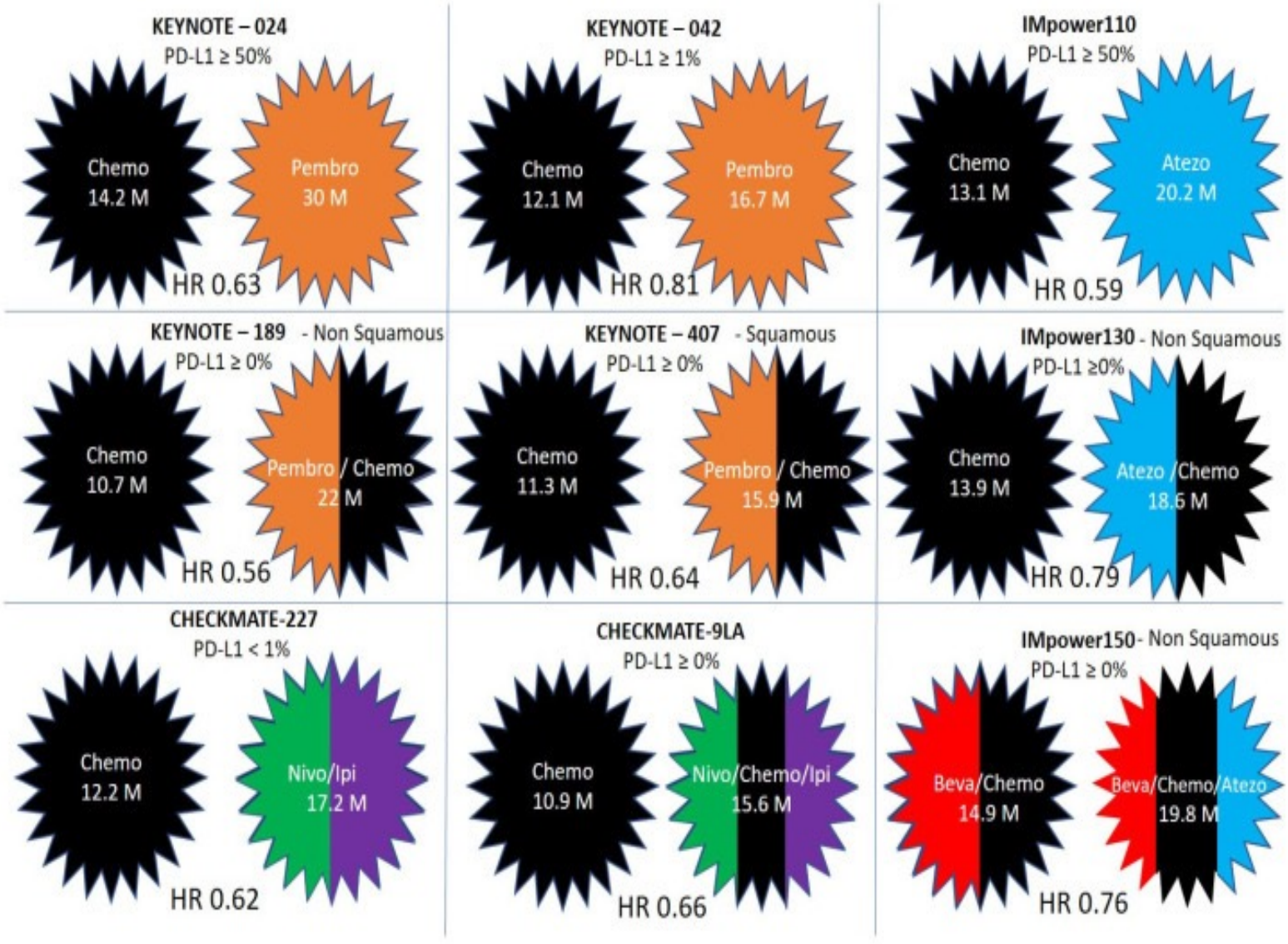
Key Phase III Studies in NSCLC

Nasser et al. doi: 10.3390/ph13110373

Phase III IO trials in Advanced-NSCLC

Nasser et al. doi: 10.3390/ph13110373

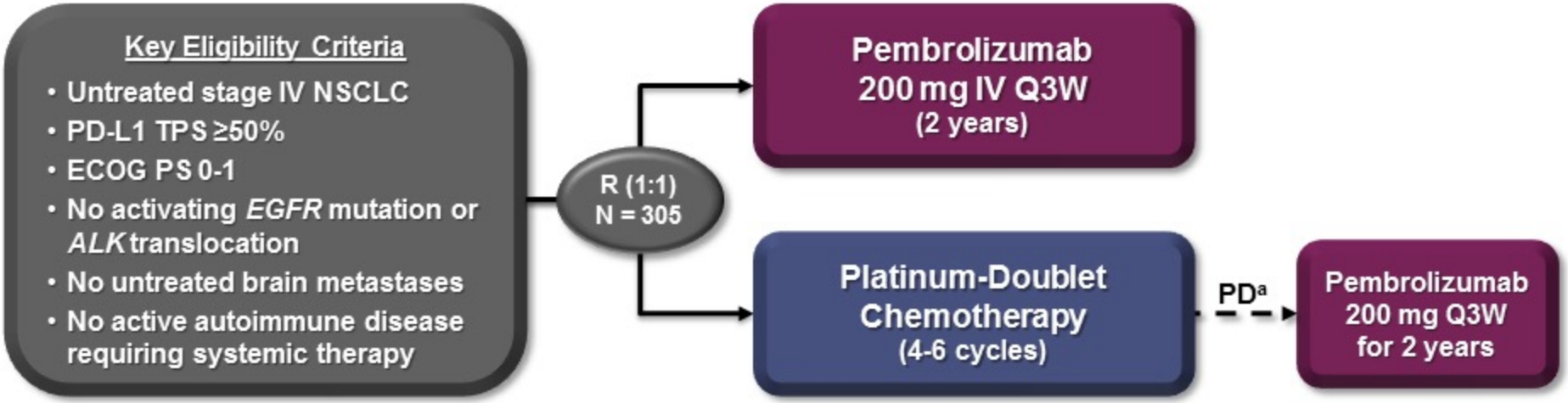
	Pathology	PDL-1	Arm I (OS)	Arm II (OS)	HR
KEYNOTE-024	squamous (18%) and nonsquamous (82%)	≥50%	Pembro	Chemotherapy	
			30 months	14.2 months	0.63
KEYNOTE-042	squamous (38%) and nonsquamous (62%)	≥1%	Pembro	Chemo	
			16.7 months	12.1 months	0.81
KEYNOTE-189	nonsquamous	Any level	Pembro/Pem/Plat	Plat/Pem	
			22 months	10.7 month	0.56
KEYNOTE-407	squamous	Any level	Pembro/Carbo/Tax	Carbo/Taxane	
			15.9 months	11.3 months	0.64
CHECKMATE-227	squamous (28%) and nonsquamous (72%)	Any level ≥1% <1%	Ipi/Nivo	Chemotherapy	
			17.1 months	14.9 months	0.79
			17.2 months	12.2 months	0.62
CHECKMATE 9LA	squamous and nonsquamous	Any level	Ipi/Nivo/Chemo	Plat/Pem or Taxane	
			15.6 months	10.9 months	0.66
IMpower110	squamous (25%) and nonsquamous (75%)	≥50%	Atezo	Plat/Pem or Gem	
			20.2 months	13.1 months	0.59
IMpower130	non-squamous	Any level	Atezo/Carbo/NbT	Carbo/NbT	
			18.6 months	13.9 months	0.79
IMpower150	non-squamous	Any level	Atezo/Bev/Carbo/Pac	Bev/Carbo/Pac	
			19.8 months	14.9 months	0.76



Nasser et al. doi: 10.3390/ph13110373

M Reck. ESMO 2016.

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

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

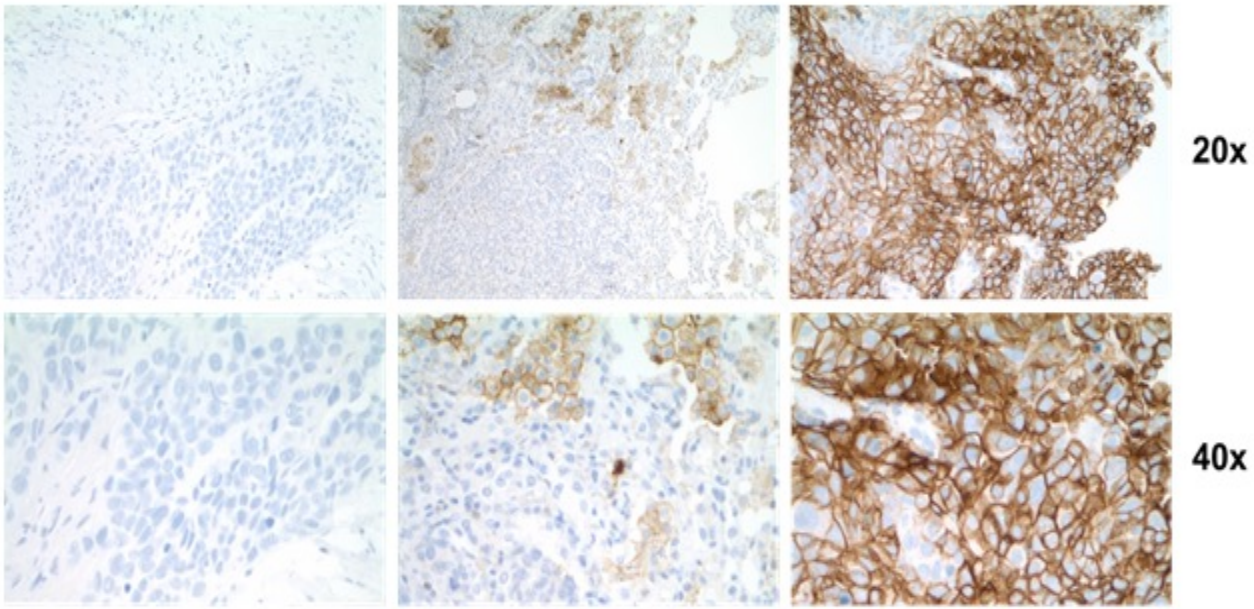
Secondary: OS, ORR, safety

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.

PD-L1 Expression and Pembrolizumab

- PD-L1 TPS cutpoint of 50% was identified in KEYNOTE-001 using independent training and validation sets[1]
- FDA-approved and CE-marked companion diagnostic: PD-L1 IHC 22C3 pharmDx (Dako)

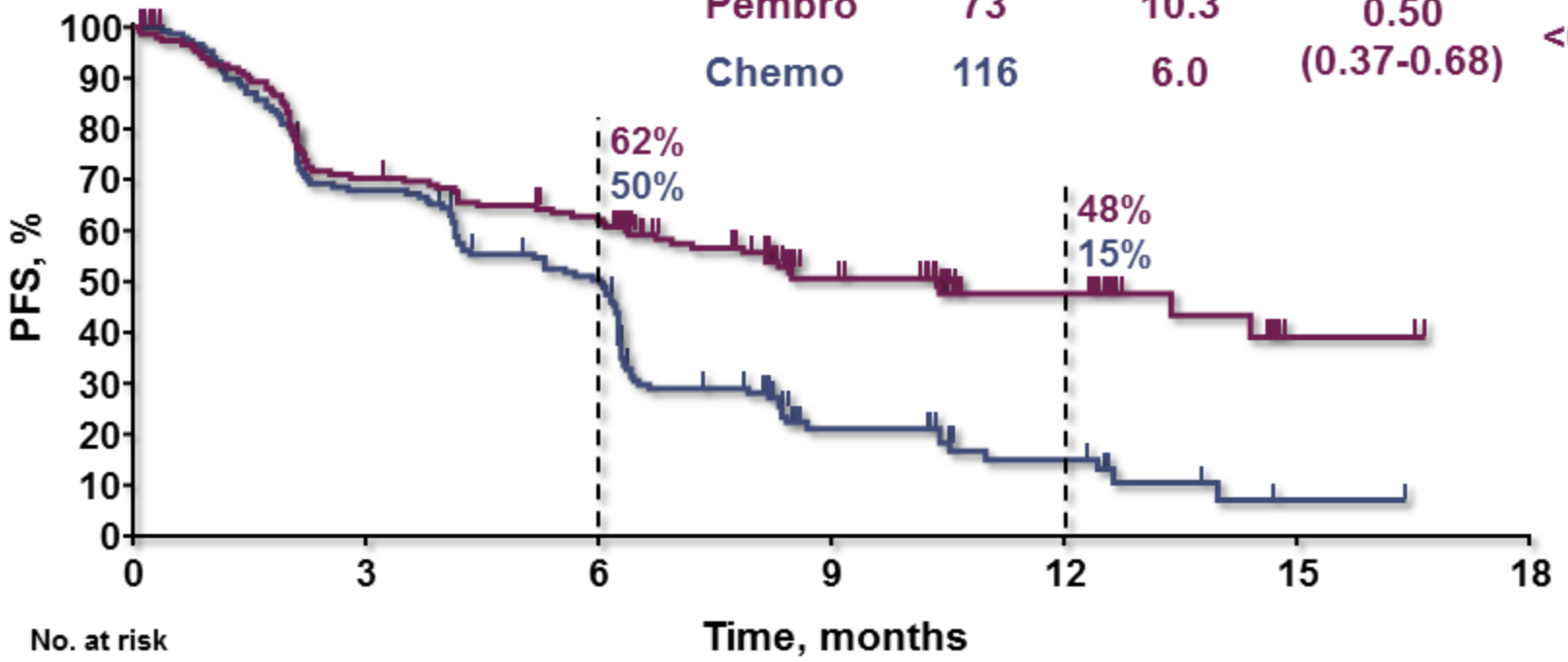


1. Garon EB et al. *N Engl J Med*. 2015;372:2018-2028.
PD-L1 staining images from Herbst RS et al. *J Clin Oncol*, 2016;34(15_suppl): abstr 3030.

M Reck. ESMO 2016.

Progression-Free Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



No. at risk

154	104	89	44	22	3	1
151	99	70	18	9	1	0

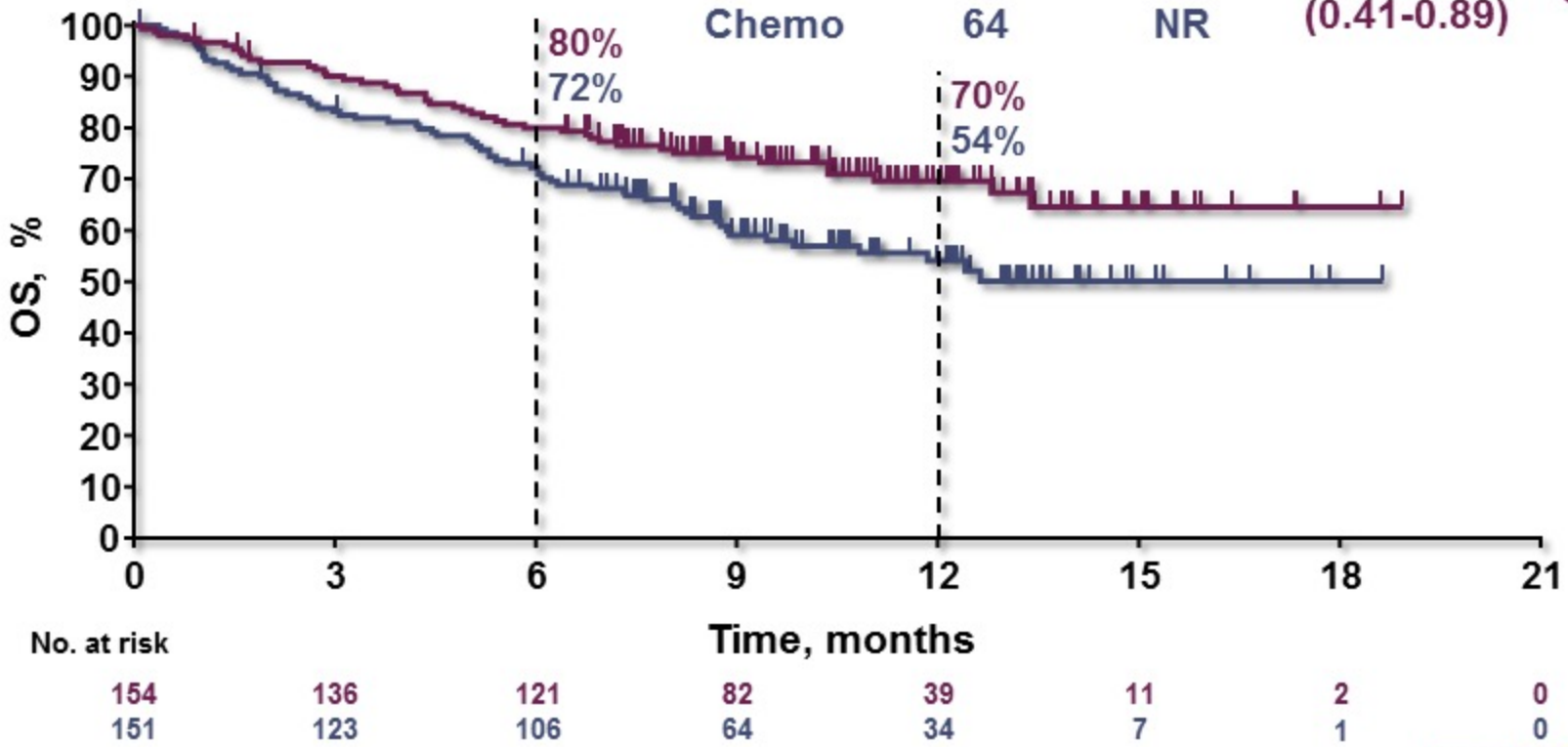
Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

COPENHAGEN 2016 ESMO congress

M Reck. ESMO 2016.

Overall Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		



Data cut-off: May 9, 2016.

KEYNOTE-042 Study Design

Key Eligibility Criteria

- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥1%
- No sensitizing *EGFR* or *ALK* alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Stratification Factors

- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (squamous vs nonsquamous)
- PD-L1 TPS (≥50% vs 1-49%)

Randomize 1:1

N = 637 → Pembrolizumab 200 mg Q3W for up to 35 cycles

N = 637 → Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m^2 Q3W[a] OR Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m^2 Q3W[a] for up to 6 cycles

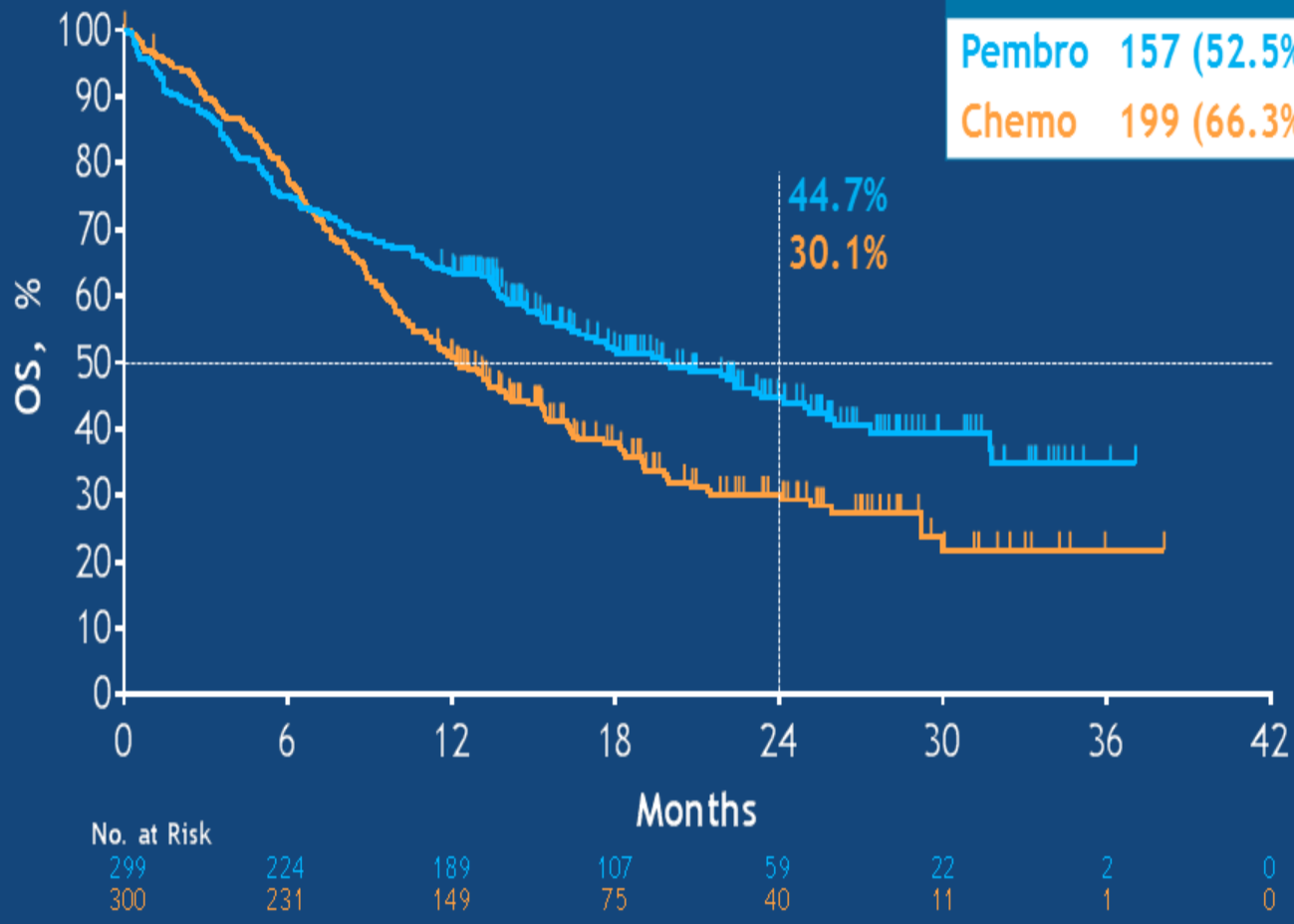
End points

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

[a]Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

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%)		

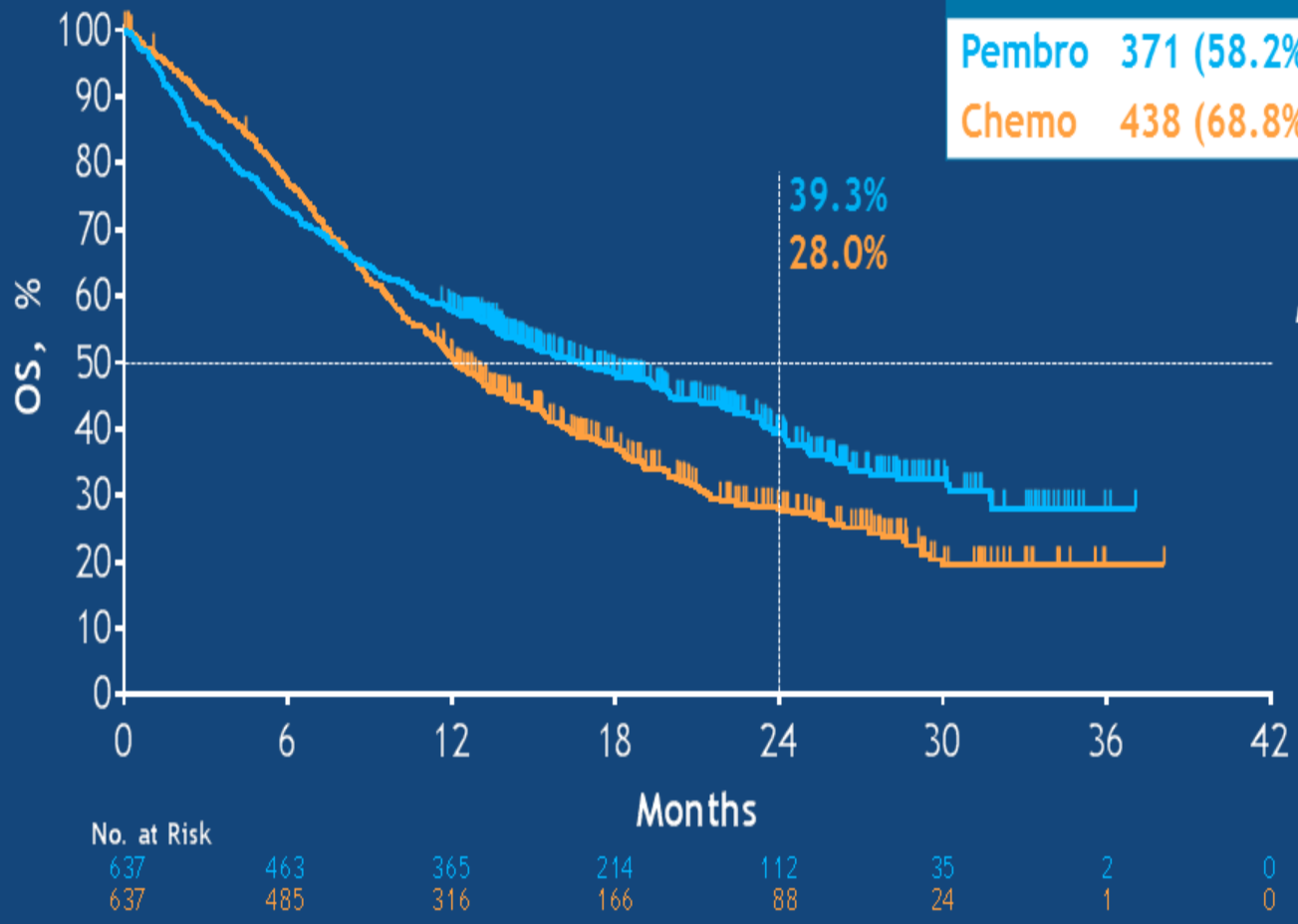


Median (95% CI)
20.0 mo (15.4-24.9)
12.2 mo (10.4-14.2)

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)

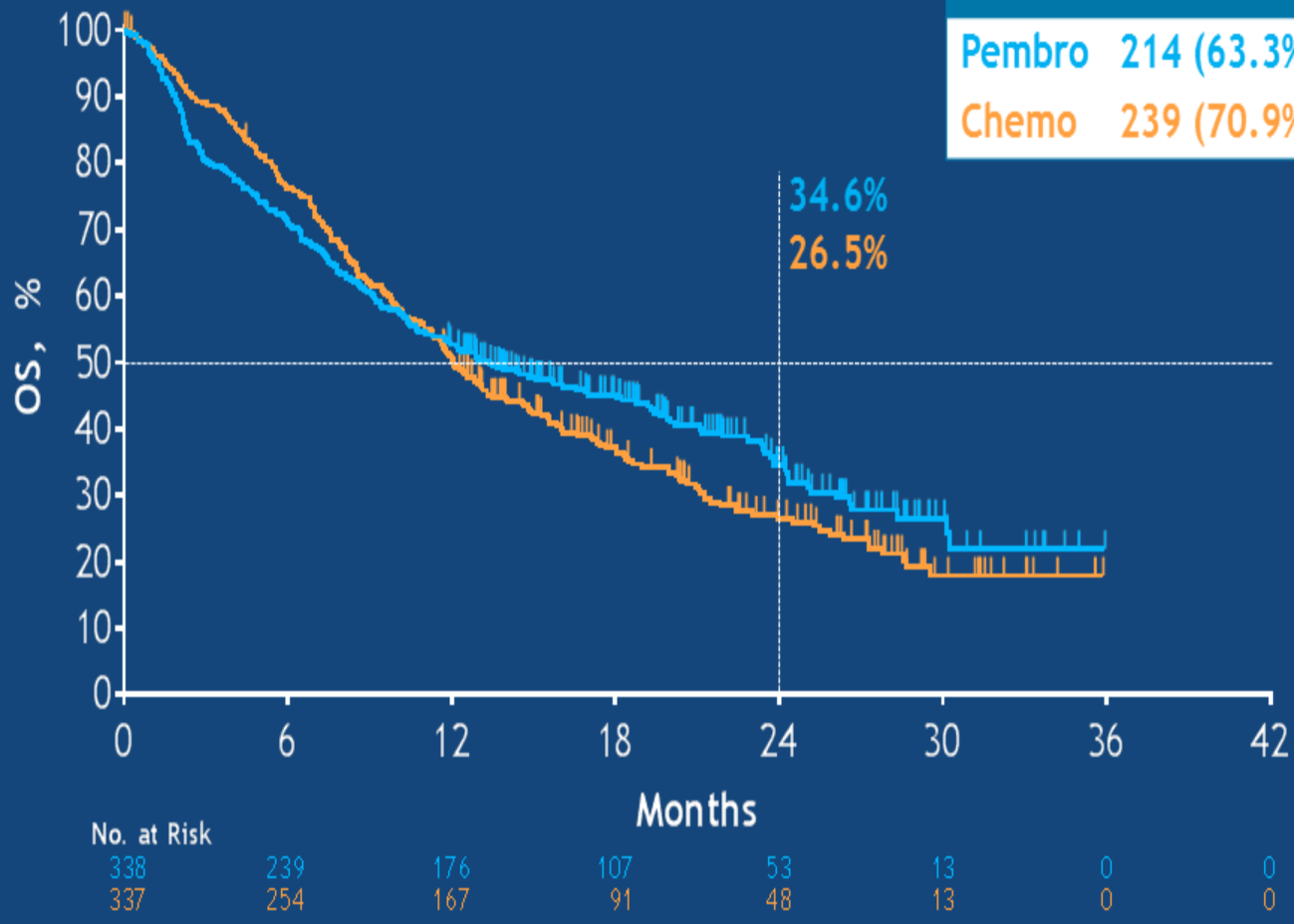
16.7 mo (13.9-19.7)

12.1 mo (11.3-13.3)

Data cutoff date: Feb 26, 2018.

Overall Survival: TPS ≥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)

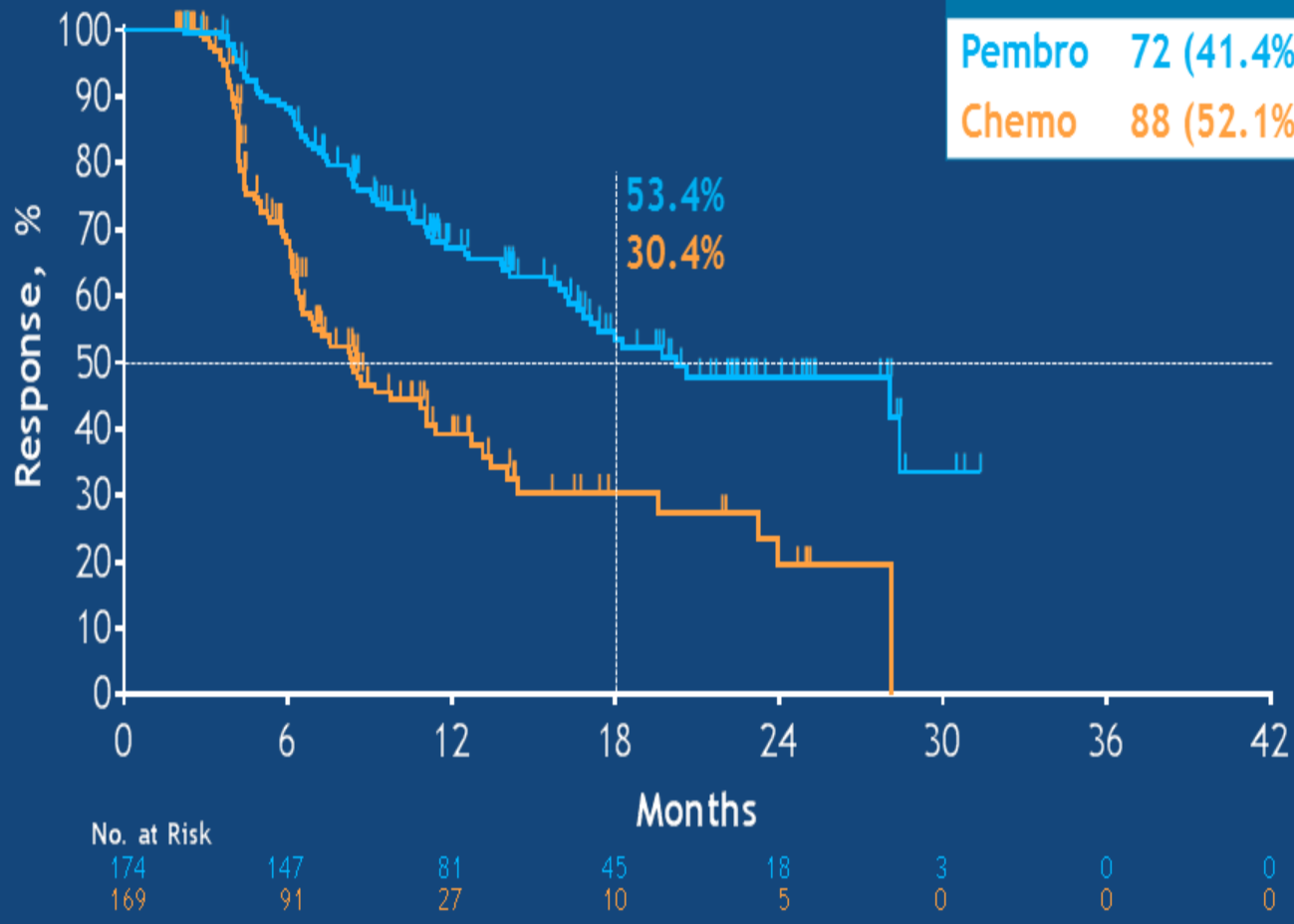
[a]No alpha allocated to this comparison.

Data cutoff date: Feb 26, 2018.

Duration of Response: TPS ≥1%

(RECIST v1.1, BICR)

	Events
Pembro	72 (41.4%)
Chemo	88 (52.1%)



Median (range)

20.2 mo (2.1+ to 31.2+)

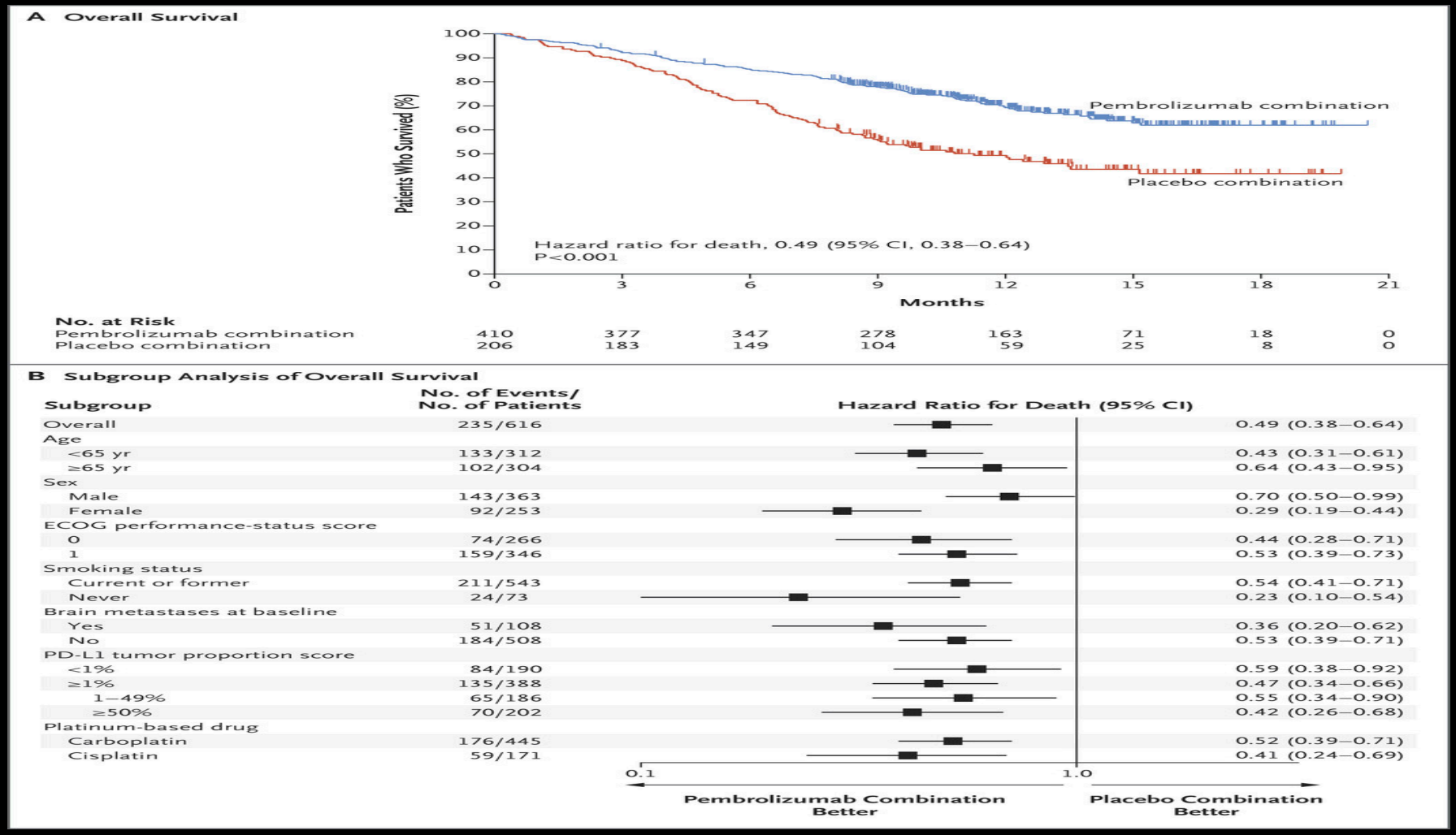
8.3 mo (1.8+ to 28.1)

Median DOR for pembro vs chemo: 20.2 mo vs 10.8 mo for TPS ≥50%, 20.2 mo vs 8.3 mo for TPS ≥20%, and 17.4 mo vs 8.2 mo for TPS 1-49%.

Data cutoff date: Feb 26, 2018.

Study of Platinum+Pemetrexed Chemotherapy With or Without Pembrolizumab (MK-3475) in Participants With First Line Metastatic Non-squamous Non-small Cell Lung Cancer (MK-3475-189/KEYNOTE-189)
NCT02578680

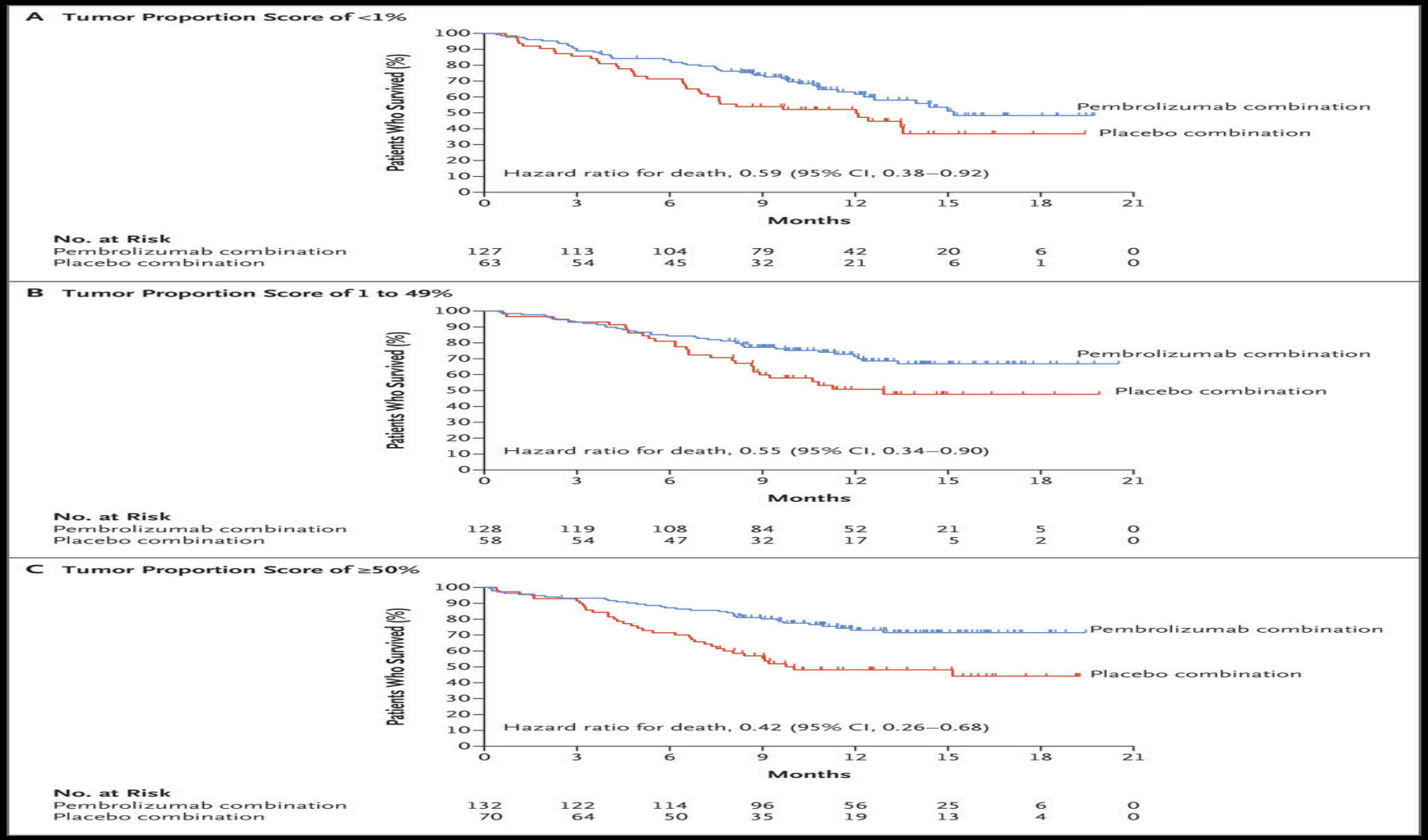
Overall Survival in the Intention-to-Treat Population.



L Gandhi et al. N Engl J Med 2018;378:2078-2092.

The NEW ENGLAND JOURNAL of MEDICINE

Overall Survival, According to PD-L1 Tumor Proportion Score.



L Gandhi et al. N Engl J Med 2018;378:2078-2092.

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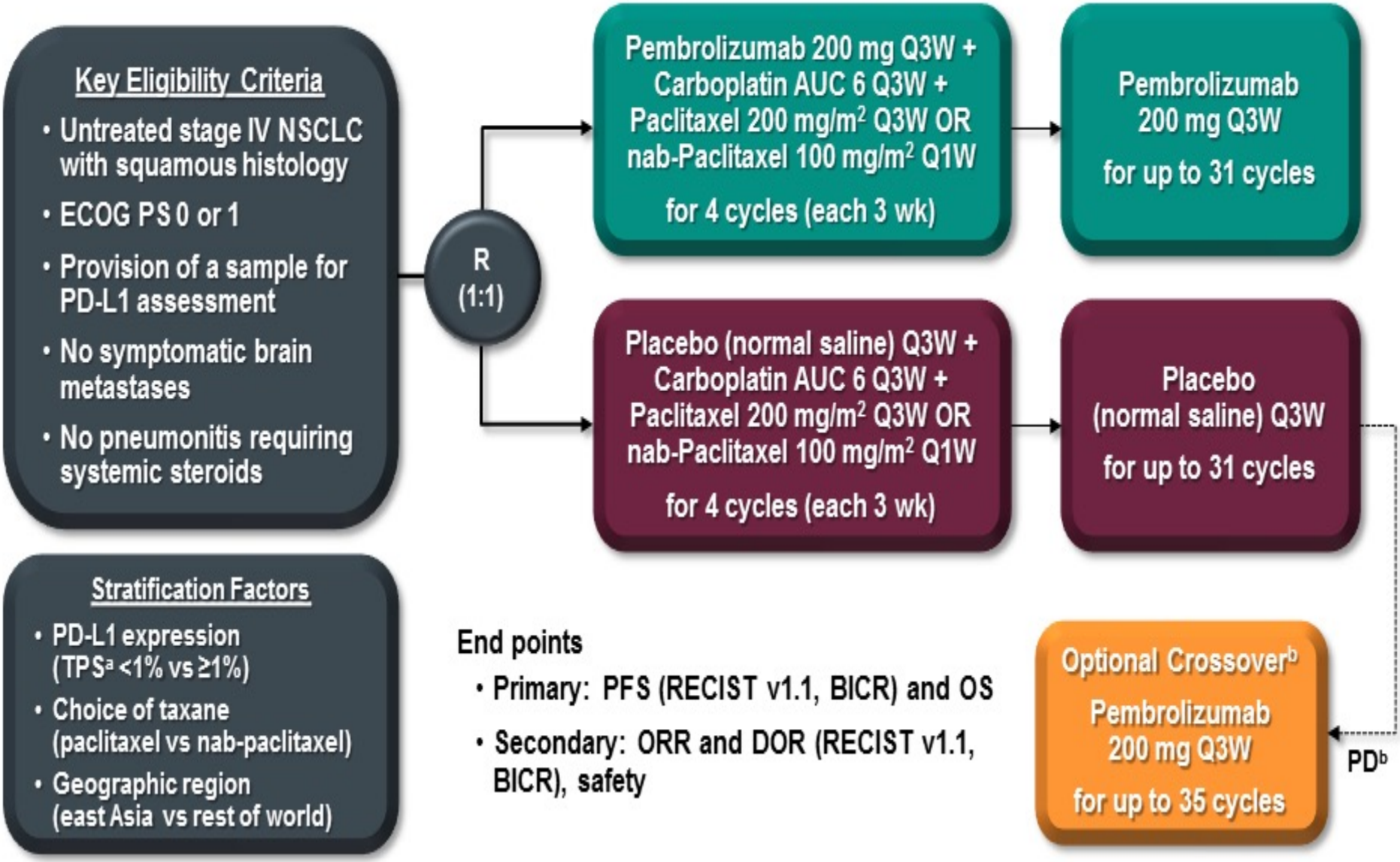
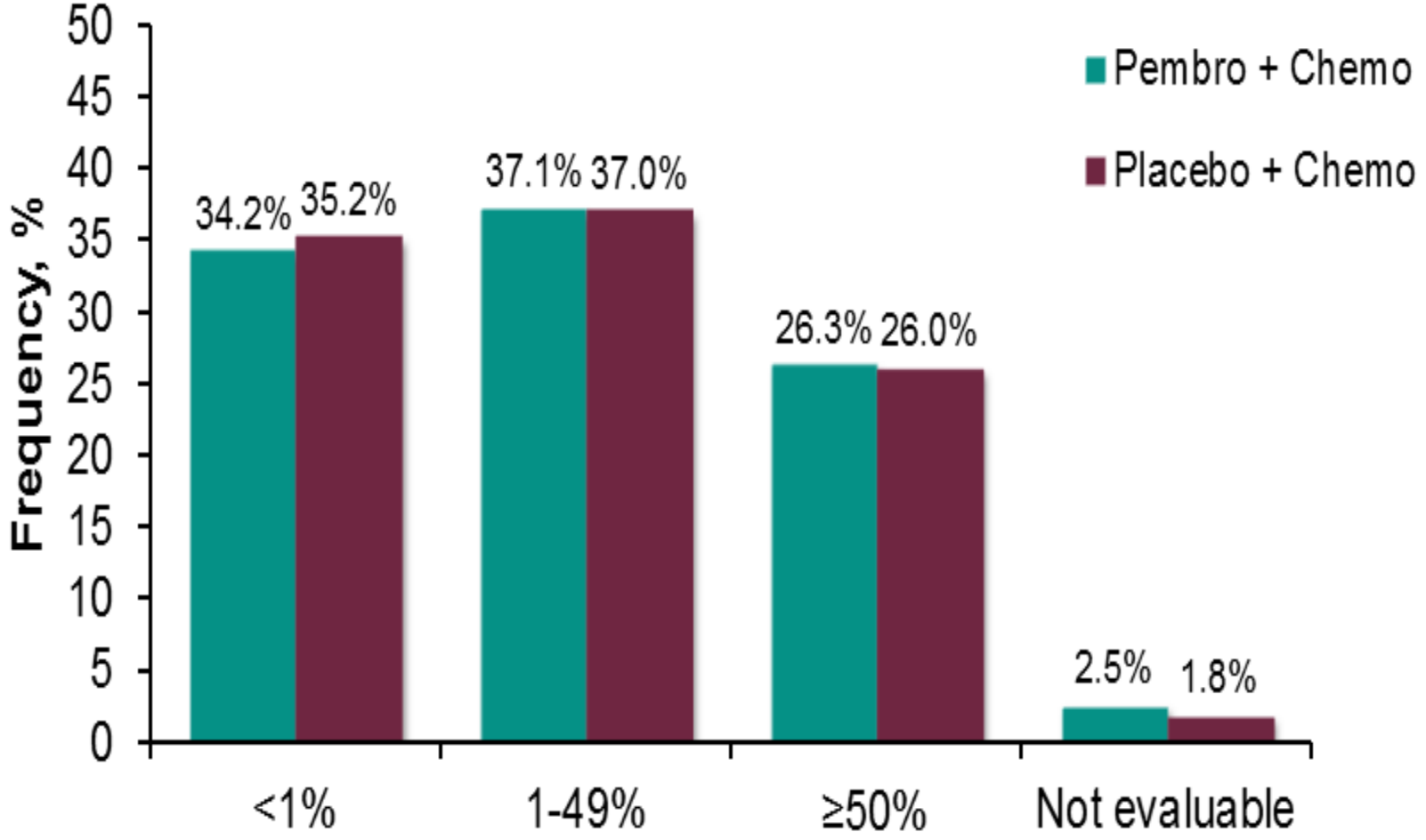
KEYNOTE-407 Study Design (NCT02775435)



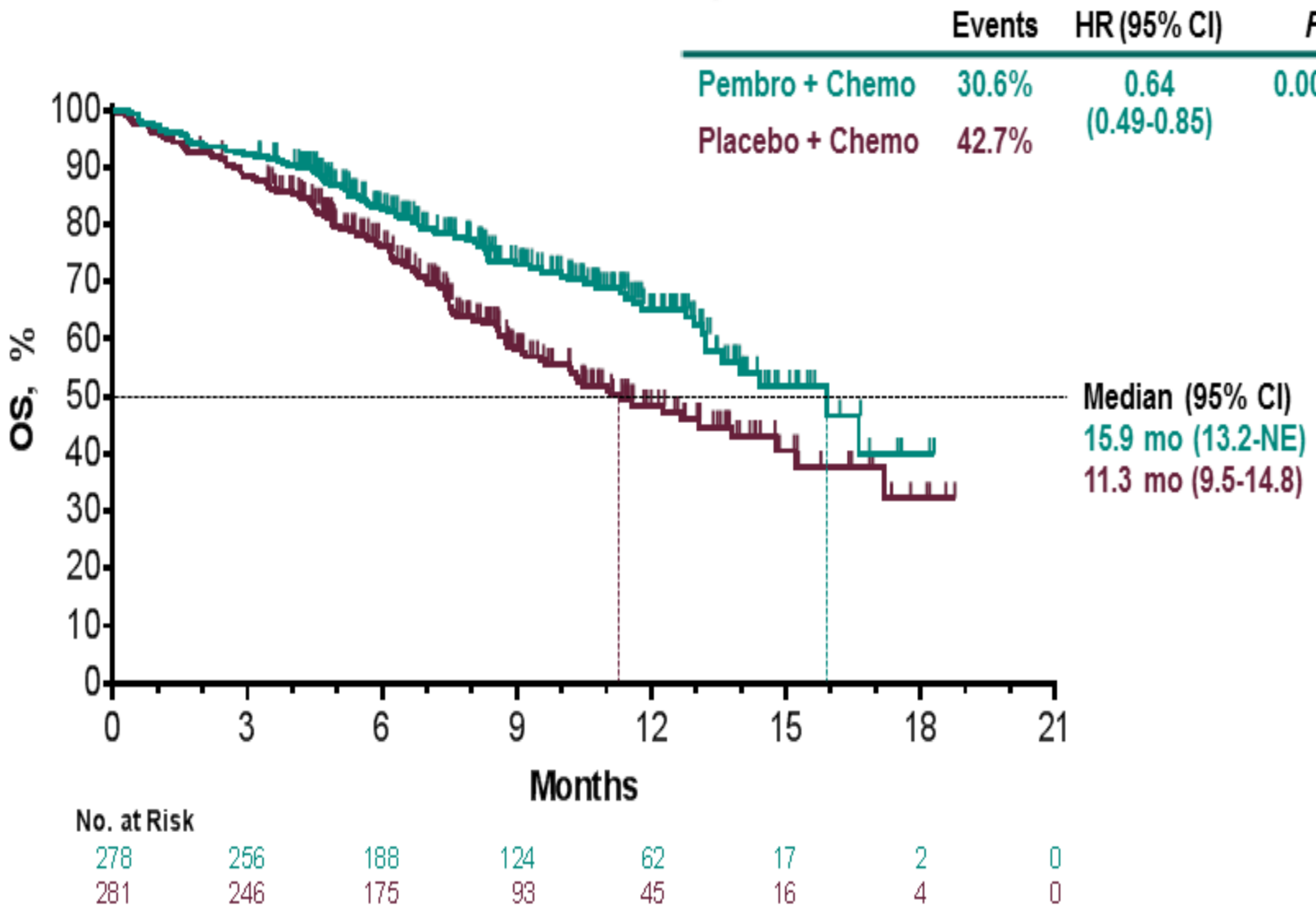
BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and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

Frequency of PD-L1 TPS Categories



Not evaluable refers to specimens with an inadequate number of tumor cells or no tumor cells seen; these patients were included in the PD-L1 TPS <1% group for randomization stratification but excluded from analyses of efficacy by TPS. Data cutoff date: Apr 3, 2018.

Overall Survival at IA2, ITT

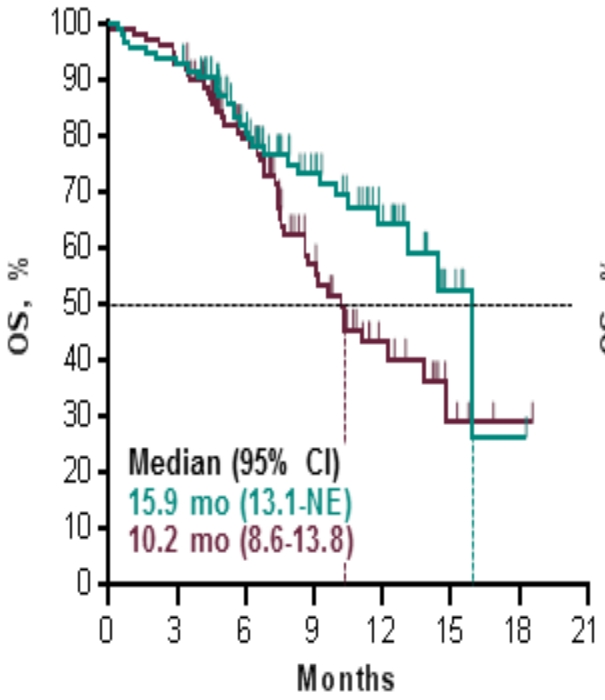


Data cutoff date: Apr 3, 2018.

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%	

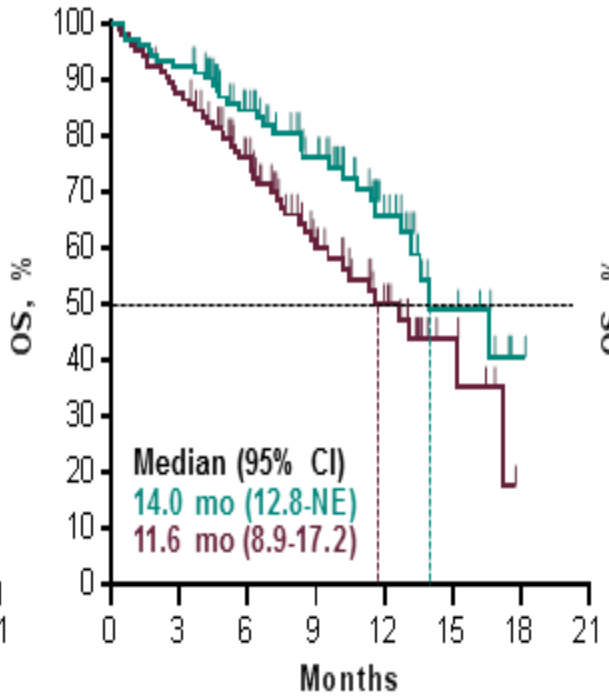


No. at Risk

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%	

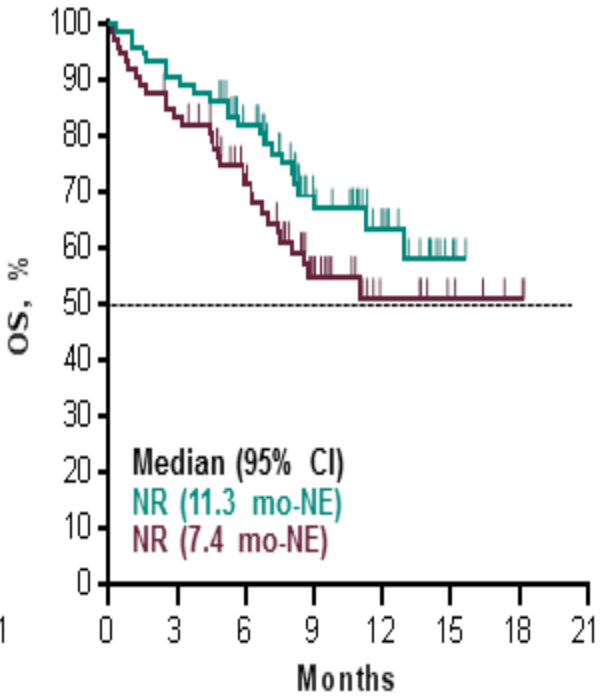


No. at Risk

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%	



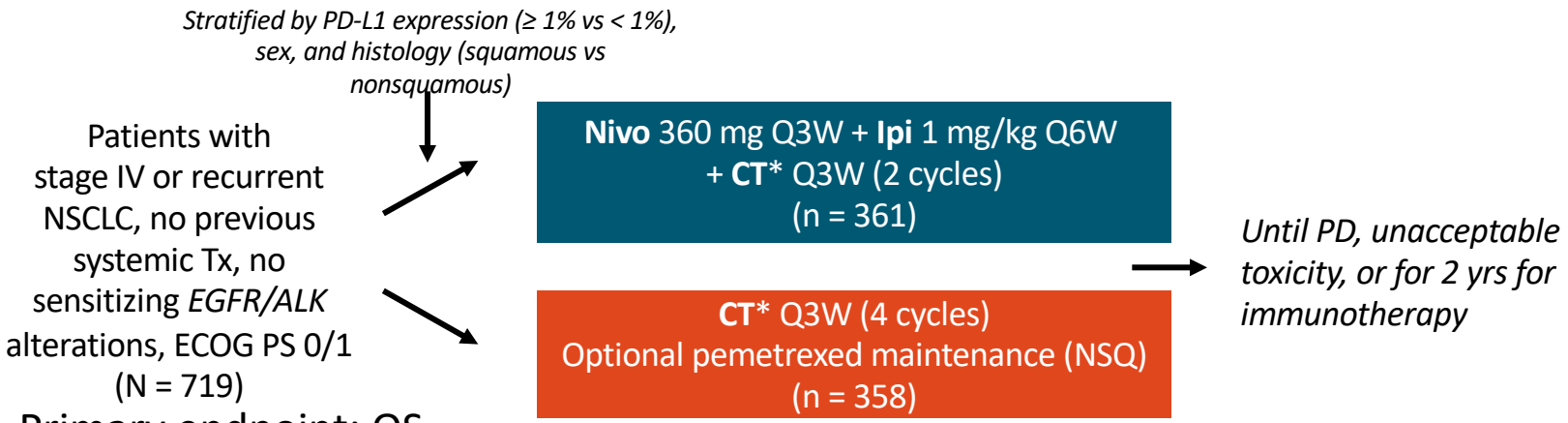
No. at Risk

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

Data cutoff date: Apr 3, 2018.

CheckMate 9LA: Study Design

- Randomized, open-label, phase III study



*Pts with NSQ: pemetrexed + cisplatin or carboplatin; pts with SQ: paclitaxel + carboplatin.

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, efficacy by tumor PD-L1 expression

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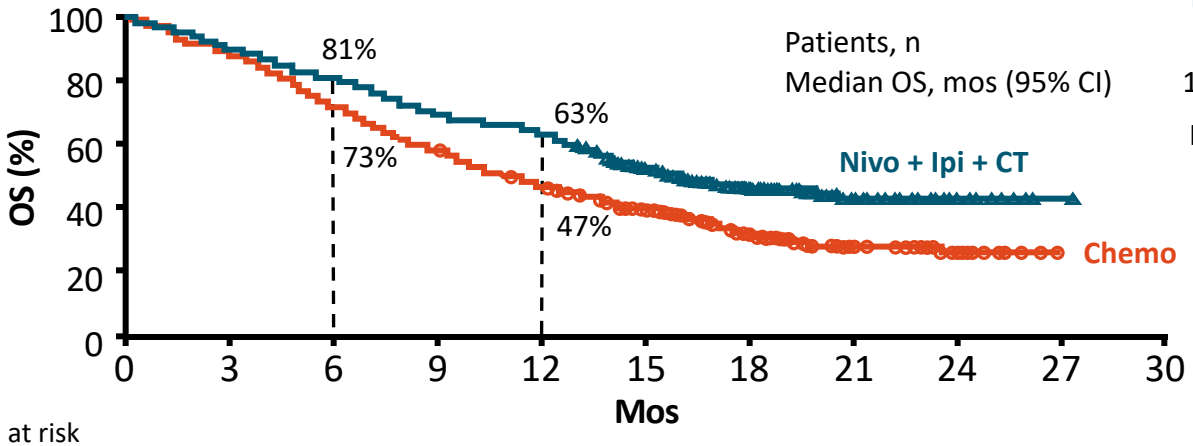
CheckMate 9LA: Interim and Updated OS Results

- Interim analysis (minimum FU 8.1 mos) median OS, Nivo + Ipi + CT vs CT: 14.1 vs 10.7 mos; HR: 0.69 (95% CI: 0.55-0.87); *P* = .0006; met primary endpoint
- Updated results (minimum FU 12.7 mos)



	Nivo + Ipi + CT	CT
Patients, n	361	358
Median OS, mos (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)

HR: 0.66 (95% CI: 0.55-0.80)

No. at risk											
Nivo + Ipi + CT	361	326	292	250	227	153	86	33	10	1	0
Chemo	358	319	260	208	166	116	67	26	11	0	0

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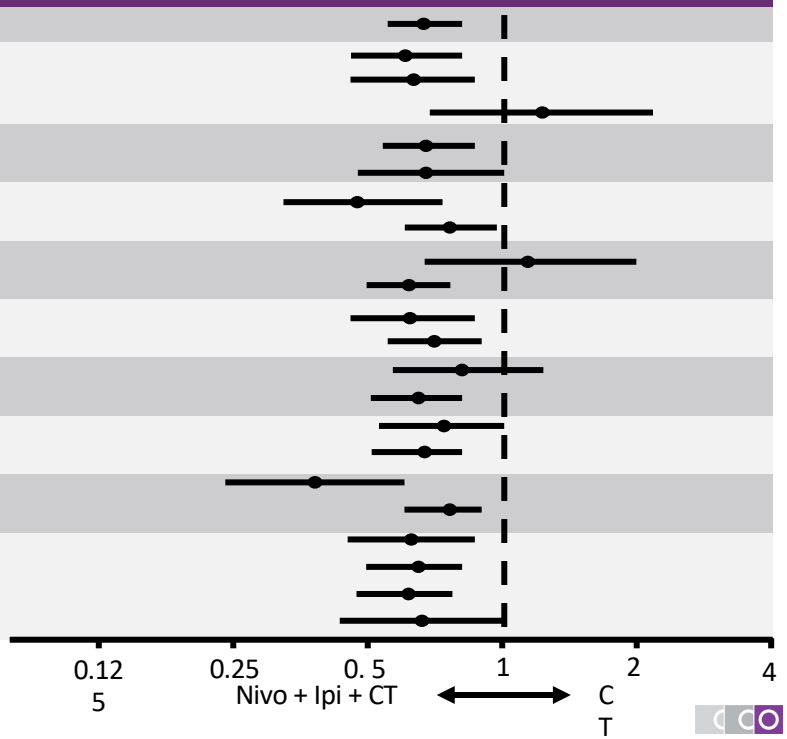
CheckMate 9LA: OS Subgroup Analysis

Subgroup	Median OS, mos		Unstratified HR
	Nivo + Ipi + CT n = 361	CT n = 358	
All randomized (N = 719)	15.6	10.9	0.66*
< 65 yrs (n = 354)	15.6	10.7	0.61
65 to < 75 yrs (n = 295)	19.4	11.9	0.62
≥ 75 yrs (n = 70)	8.5	11.5	1.21
Male (n = 504)	14.1	9.8	0.66
Female (n = 215)	19.4	15.8	0.68
ECOG PS 0 (n = 225)	NR	15.4	0.48
ECOG PS 1 (n = 492)	13.6	9.7	0.75
Never smoker (n = 98)	14.1	17.8	1.14
Smoker (n = 621)	15.6	10.4	0.62
Squamous (n = 227)	14.5	9.1	0.62
Non-squamous (n = 492)	17.0	11.9	0.69
Liver metastases (n = 154)	10.2	8.1	0.83
No liver metastases (n = 565)	19.4	12.4	0.64
Bone metastases (n = 207)	11.9	8.3	0.74
No bone metastases (n = 512)	20.5	12.4	0.65
CNS metastases (n = 122)	NR	7.9	0.38
No CNS metastases (n = 597)	15.4	11.8	0.75
PD-L1 < 1% (n = 264)	16.8	9.8	0.62
PDL-L1 ≥ 1% (n = 407)	15.8	10.9	0.64
PD-L1 1-49% (n = 233)	15.4	10.4	0.61
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66



Minimum follow-up: 12.7 mos

*Stratified HR; unstratified HR: 0.67 (95% CI: 0.55-0.81)

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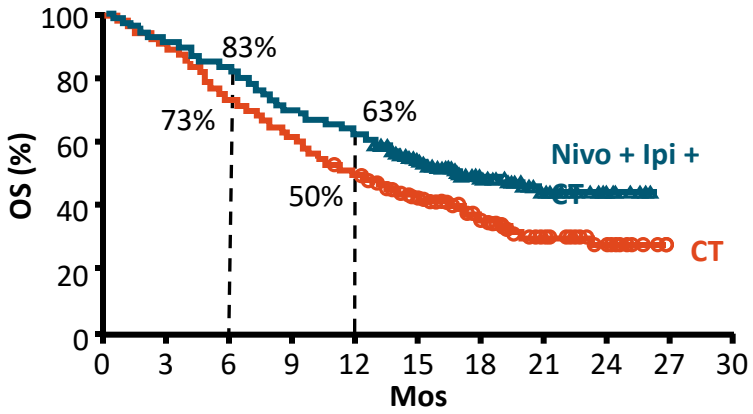
CheckMate 9LA: OS By Histology

NSQ NSCLC

	Nivo + Ipi + CT	CT
Patients, n	246	246
Median OS, mos (95% CI)	17.0 (14.0-NR)	11.9 (9.9-14.1)

HR: 0.69 (95% CI: 0.55-0.87)



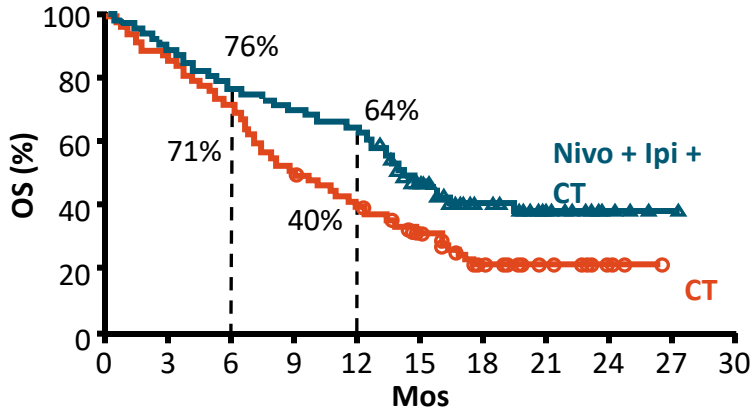
No. at risk

Nivo + Ipi + CT	246	224	204	170	154	107	62	20	6	0	0
CT	246	223	180	152	122	87	53	18	9	0	0

SQ NSCLC

	Nivo + Ipi + CT	CT
Patients, n	115	112
Median OS, mos (95% CI)	14.5 (13.1-19.4)	9.1 (7.2-11.6)

HR: 0.62 (95% CI: 0.55-0.88)



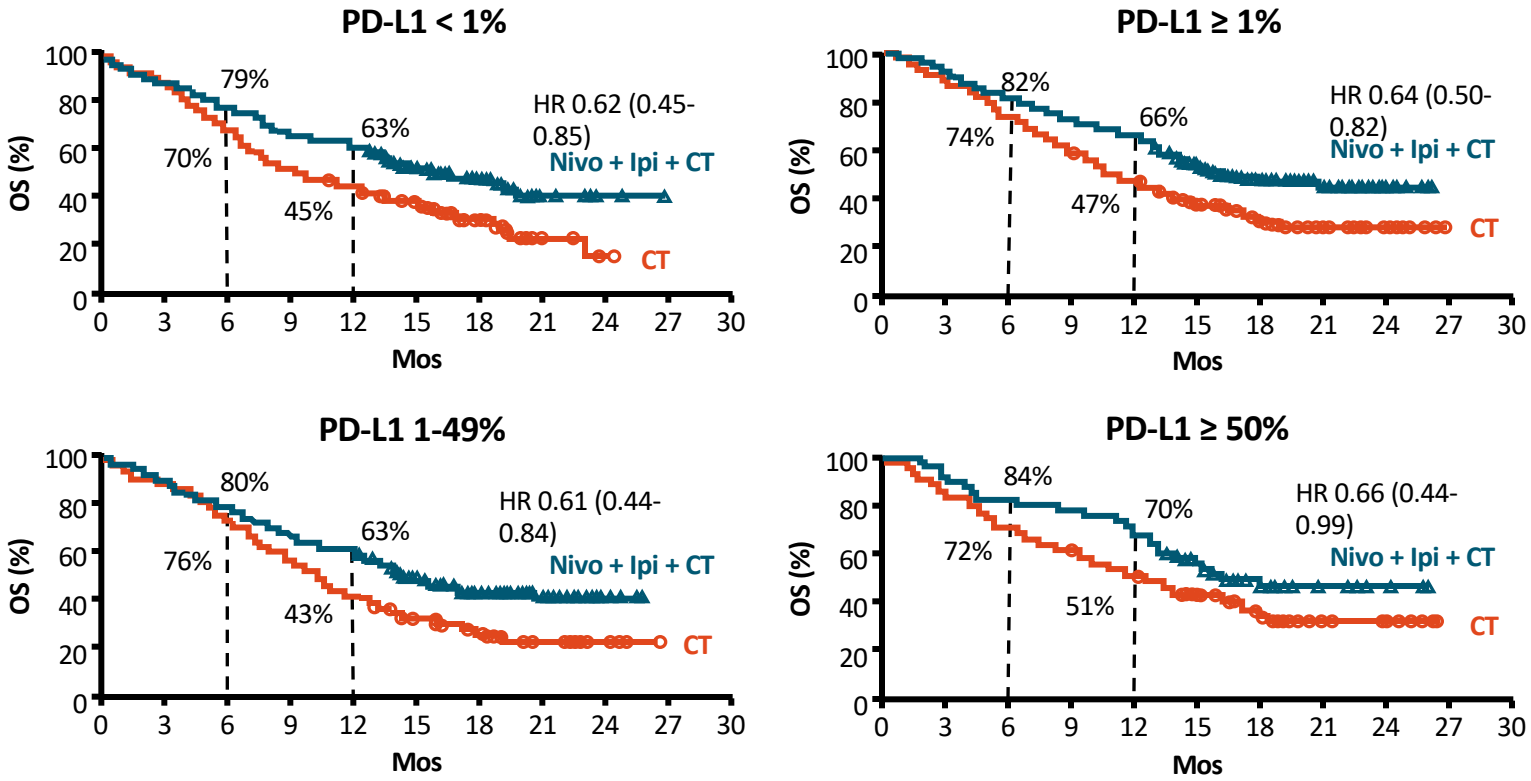
No. at risk

Nivo + Ipi + CT	115	102	88	80	73	46	24	13	4	1	0
CT	112	96	80	56	44	29	14	8	2	0	0

Reck. ASCO 2020. Abstr 9501. Reproduced with permission.

Slide credit: clinicaloptions.com

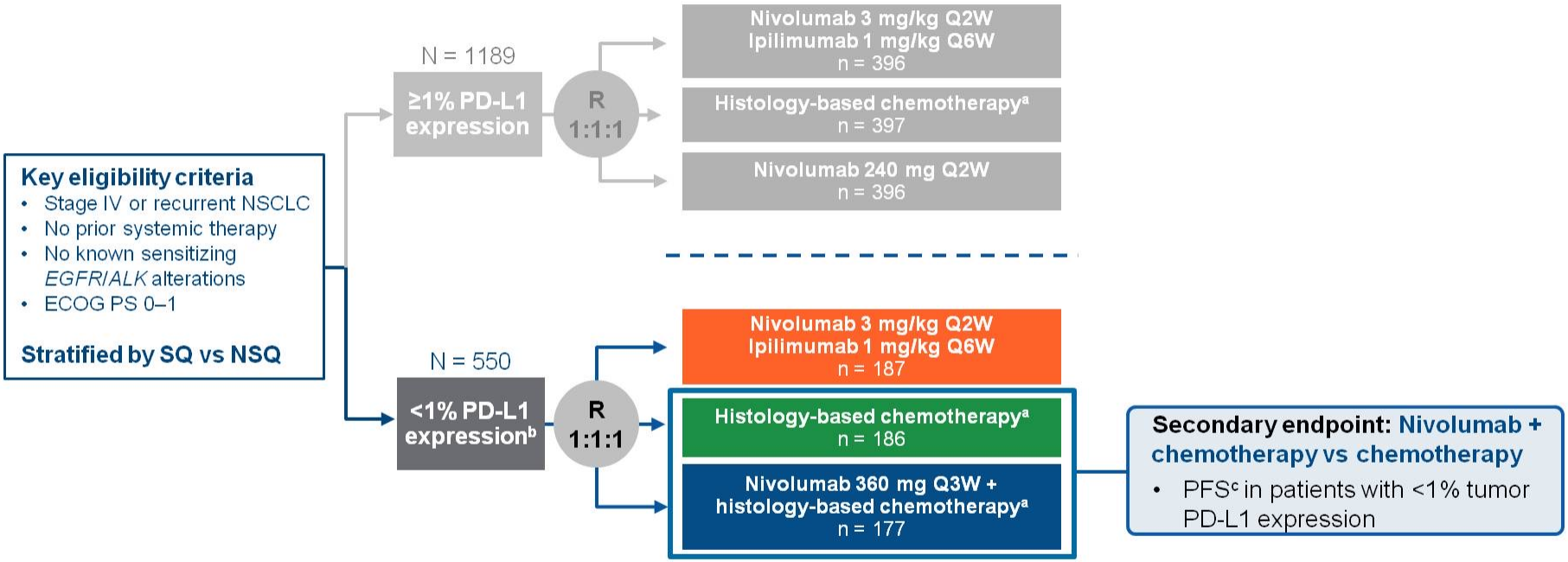
CheckMate 9LA: OS By PD-L1 Expression



Reck. ASCO 2020. Abstr 9501. Reproduced with permission.

Slide credit: clinicaloptions.com

CheckMate 227 Part 1 Study Design

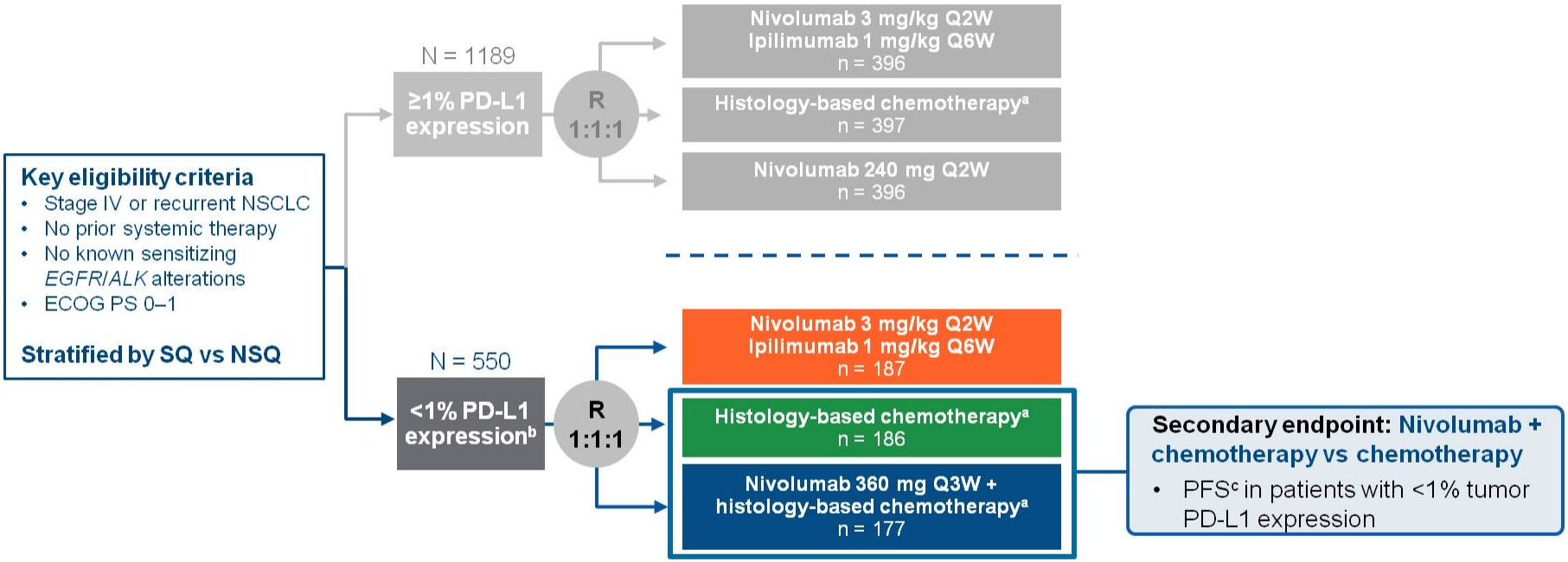


- Co-primary endpoints: OS in PD-L1–selected populations and PFS[c] in TMB-selected populations treated with nivolumab + ipilimumab vs chemotherapy

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

[a]**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; [b]One patient was randomized with <1% tumor PD-L1 expression in IVRS, but was subsequently found to have ≥1% tumor PD-L1 expression; [c]Per BICR

CheckMate 227 Part 1 Study Design



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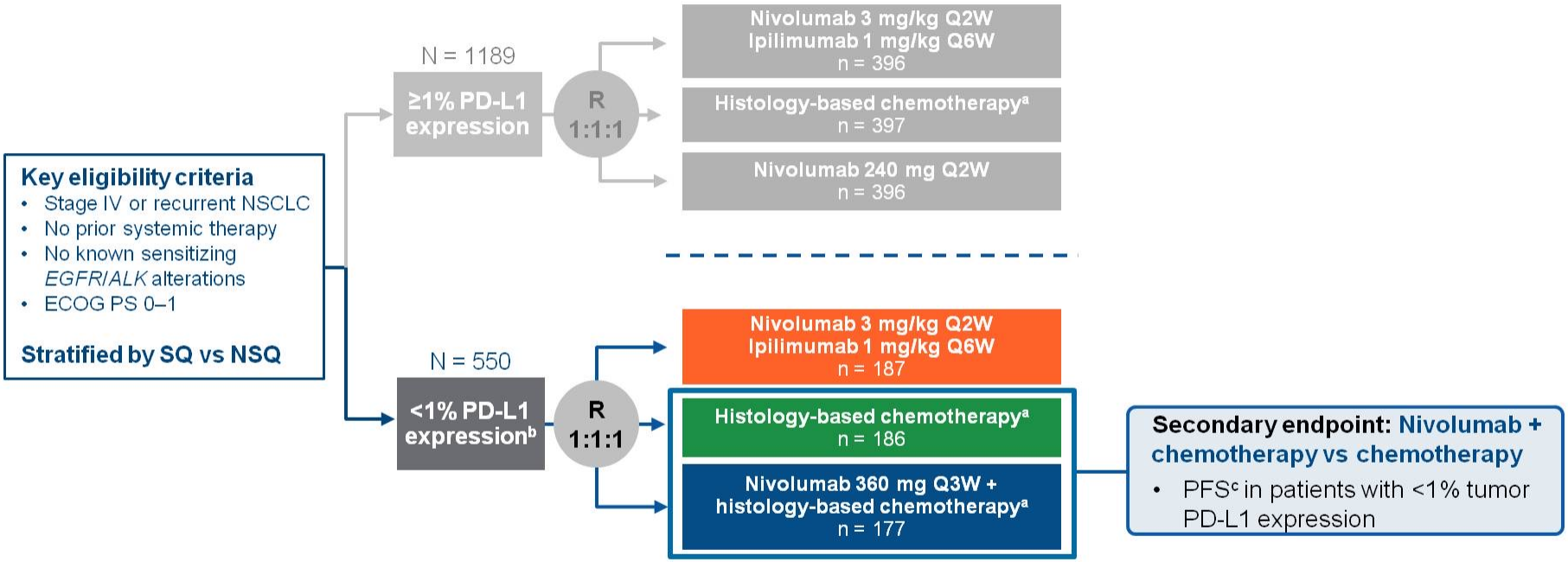
CheckMate 227 Part 1 Study Design



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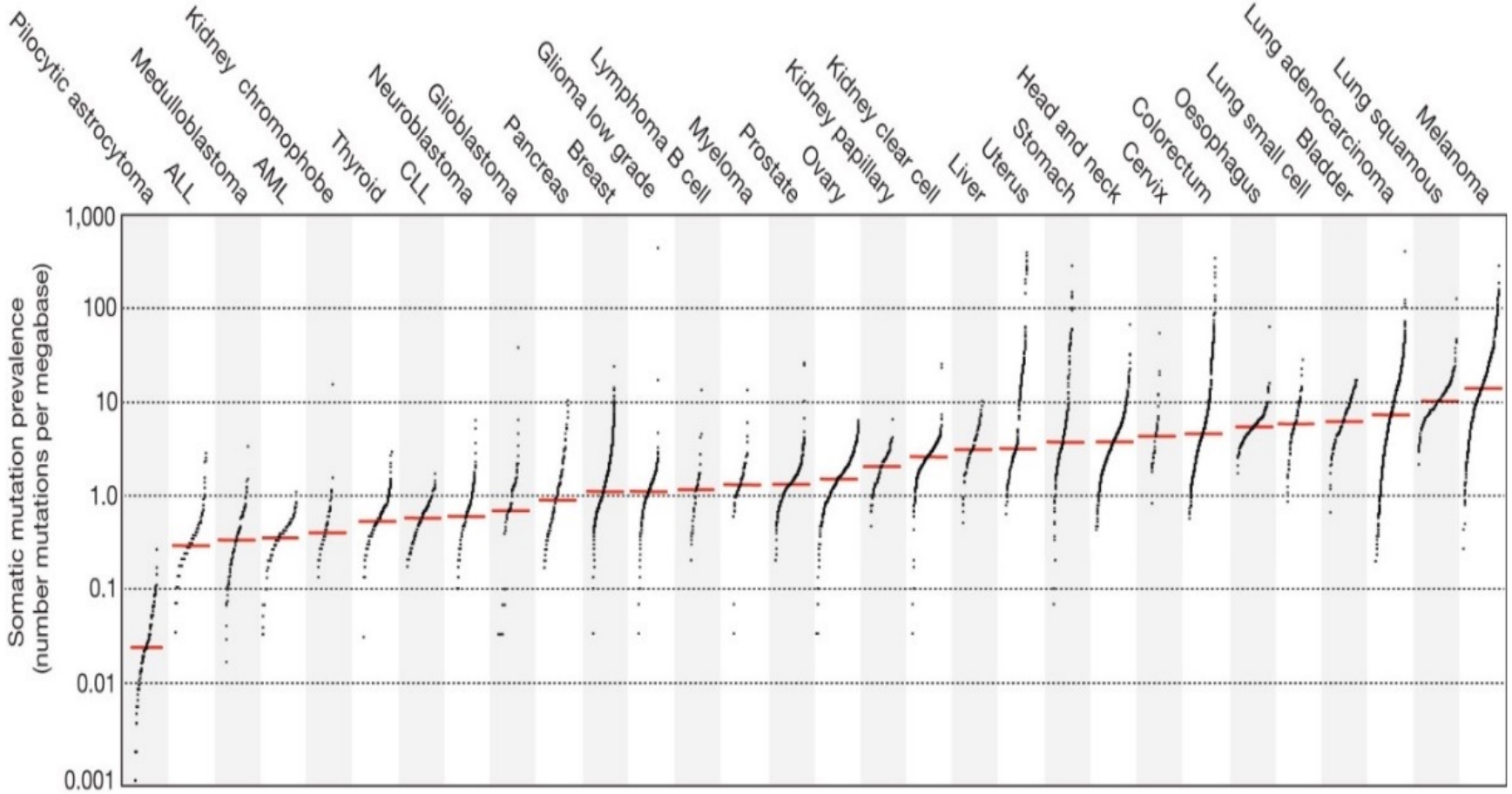
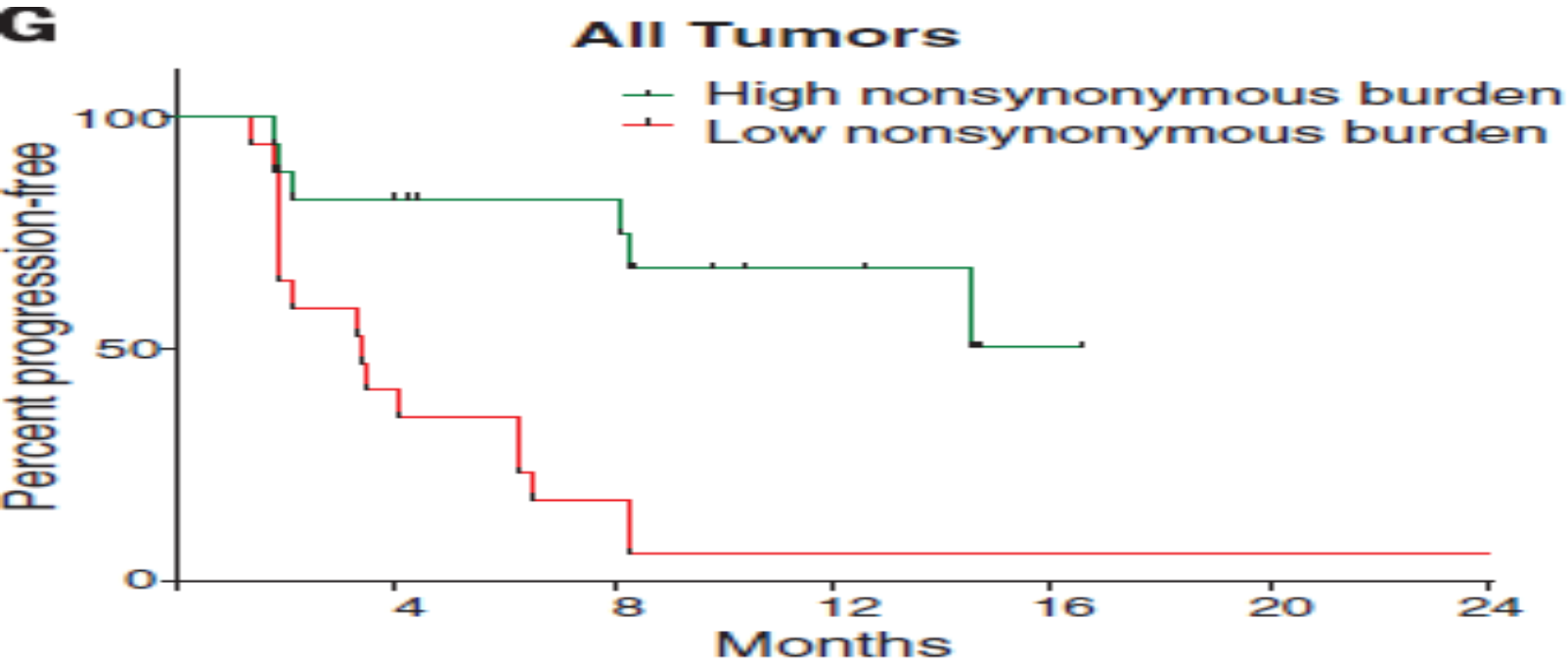
Mutational Load and Correlation with NSCLC Histology



Alexandrov, Nature 2013

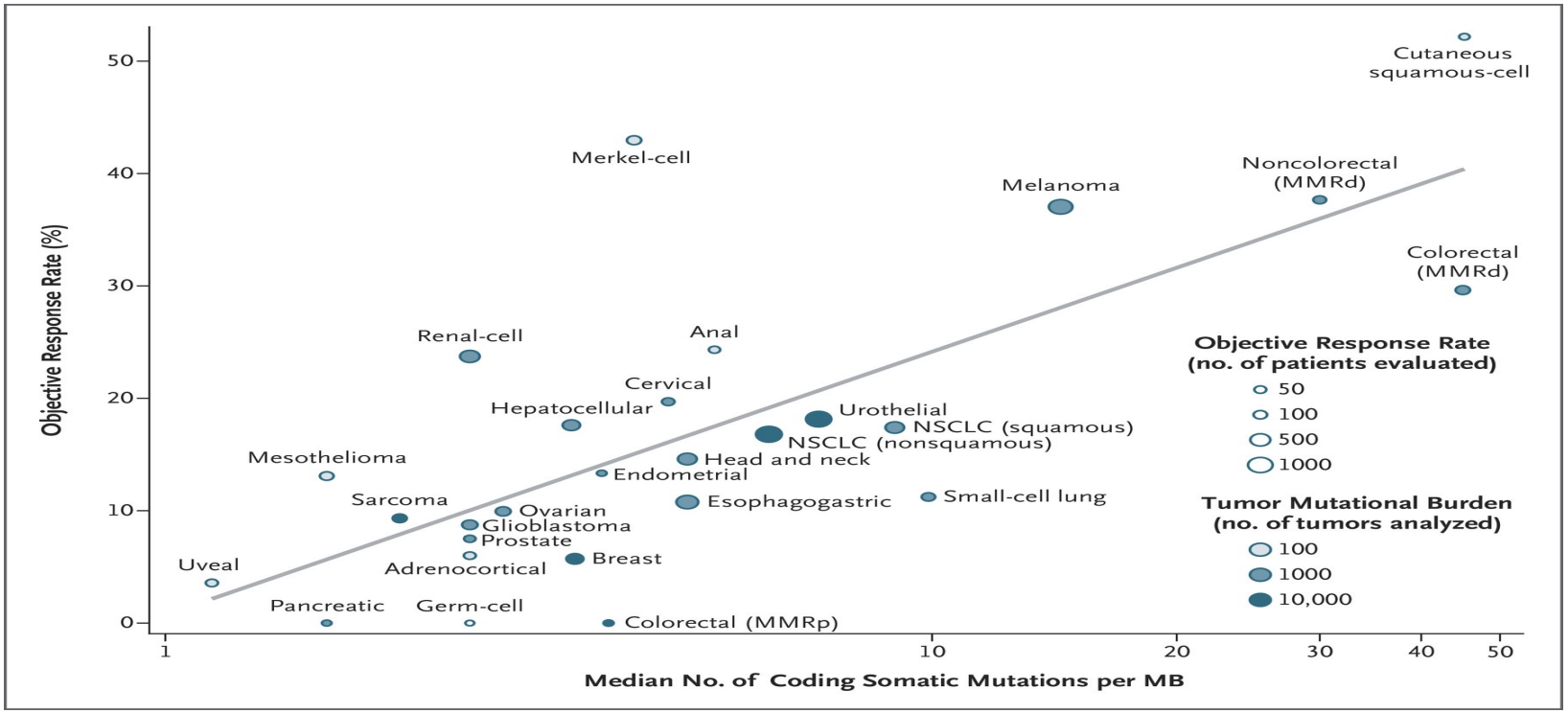
Heavy Mutational Load Associated with Better Outcomes to Immuno-Oncology Agents

Outcomes with pembrolizumab

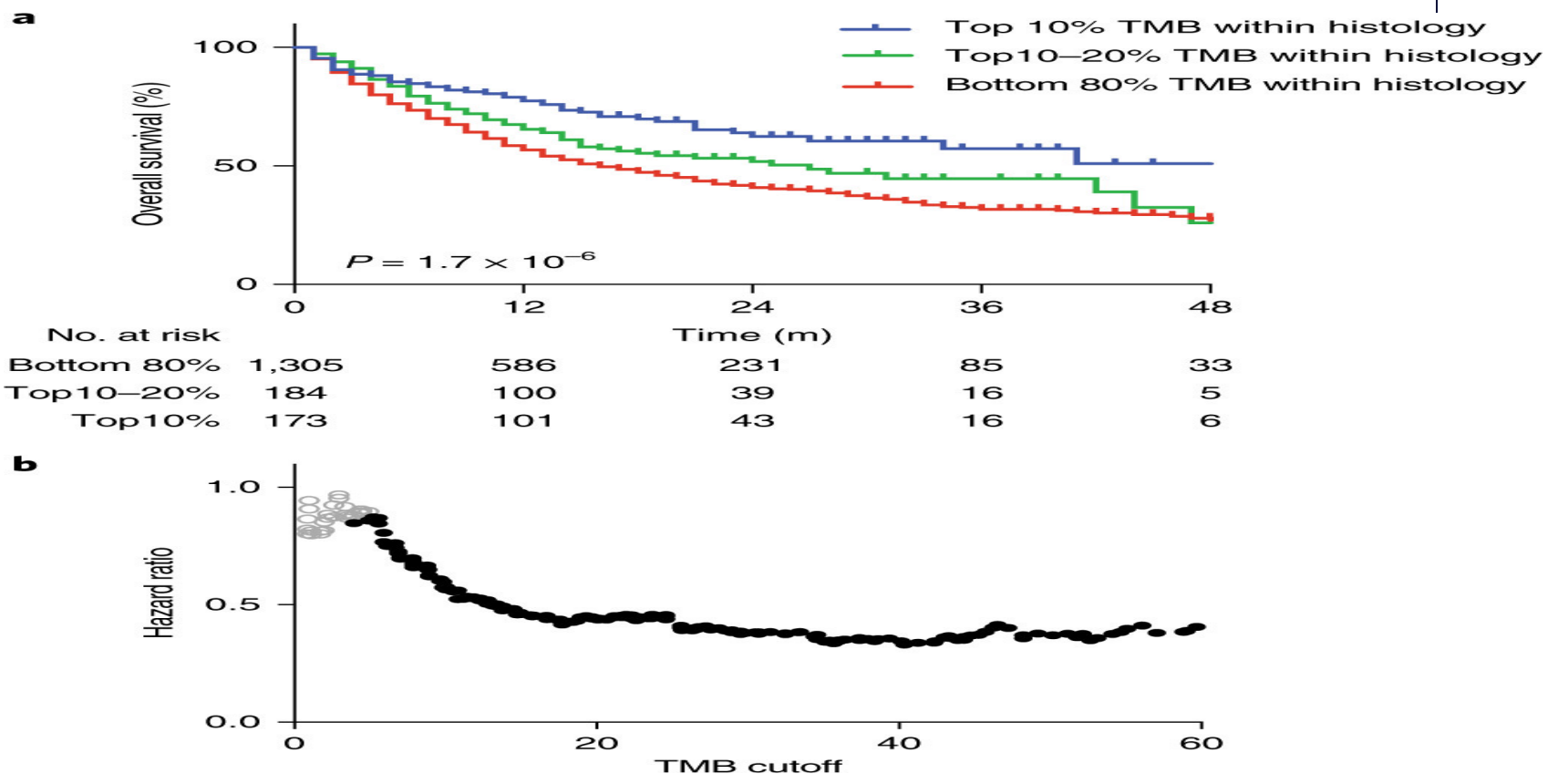


Rizvi, Science 2015

Response Rate by Tumor Type & TMB



Effect of mutational load on overall survival after ICI treatment.



https://doi.org/10.1038/s41588-018-0312-8

FDA Approval Summary: Pembrolizumab for the Treatment of Tumor Mutational Burden–High Solid Tumors

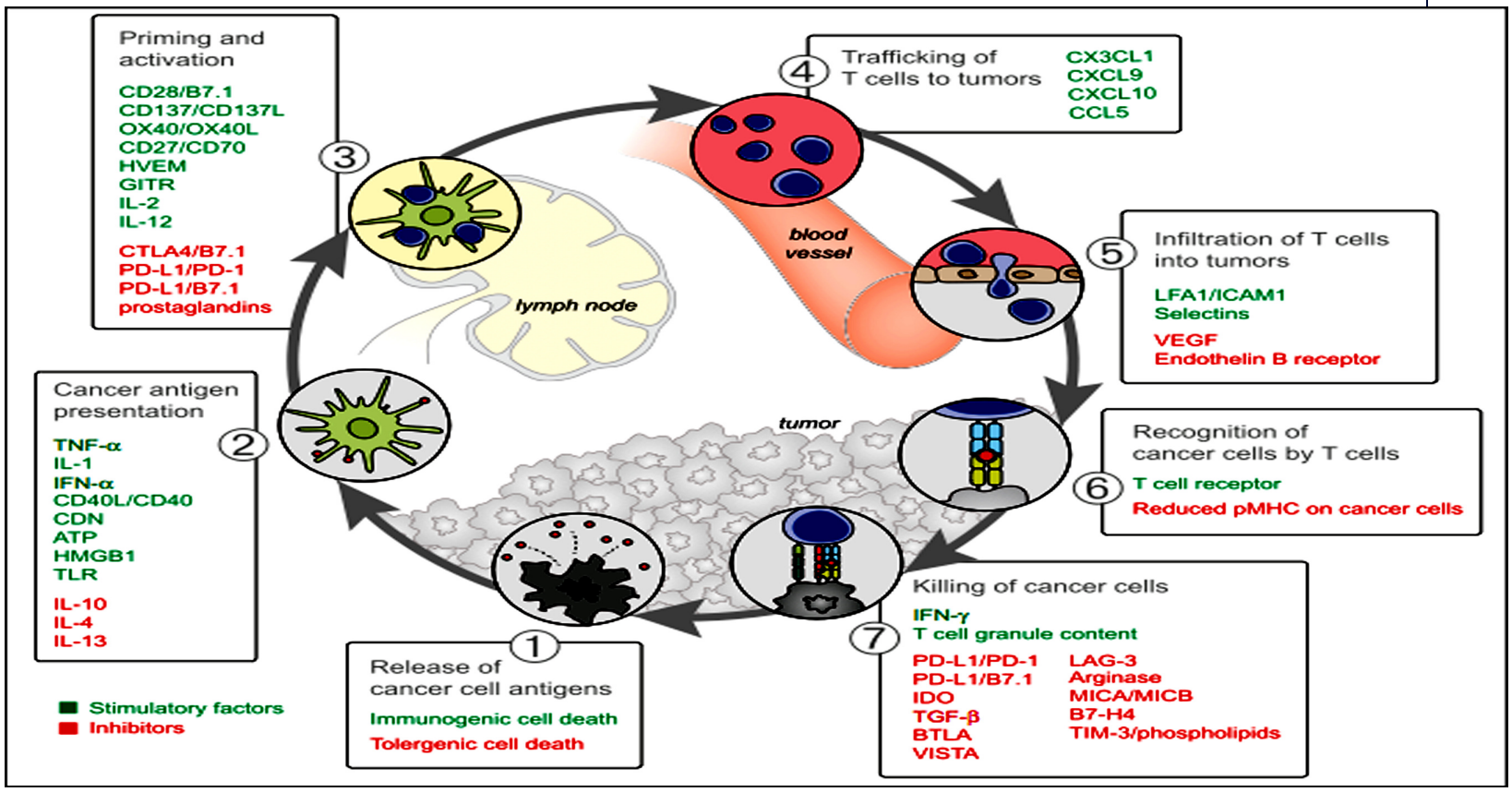
The FDA approved pembrolizumab on June 16, 2020, for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high [TMB-H; ≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. FDA granted the approval based on a clinically important overall response rate (29%; 95% confidence interval, 21-39) and duration of response (57% of responses lasting ≥ 12 months) in the subset of patients with TMB-H solid tumors (*n* = 102) spanning nine different tumor types enrolled in a multicenter single-arm trial (KEYNOTE-158). The efficacy of pembrolizumab was supported by the results of whole-exome sequencing (WES) analyses of TMB in additional patients enrolled across multiple pembrolizumab clinical trials, and a scientific understanding of the effects of PD-1 inhibition. Overall, the adverse event profile of pembrolizumab was similar to the adverse event profile observed in prior trials that supported the approval of pembrolizumab in other indications. This approval of pembrolizumab is the first time that the FDA has approved a cancer treatment for an indication based on TMB, and the fourth based on the presence of a biomarker rather than the primary site of origin

DOI: 10.1158/1078-0432.CCR-21-0327

Incidence of MSI High in various tumors.

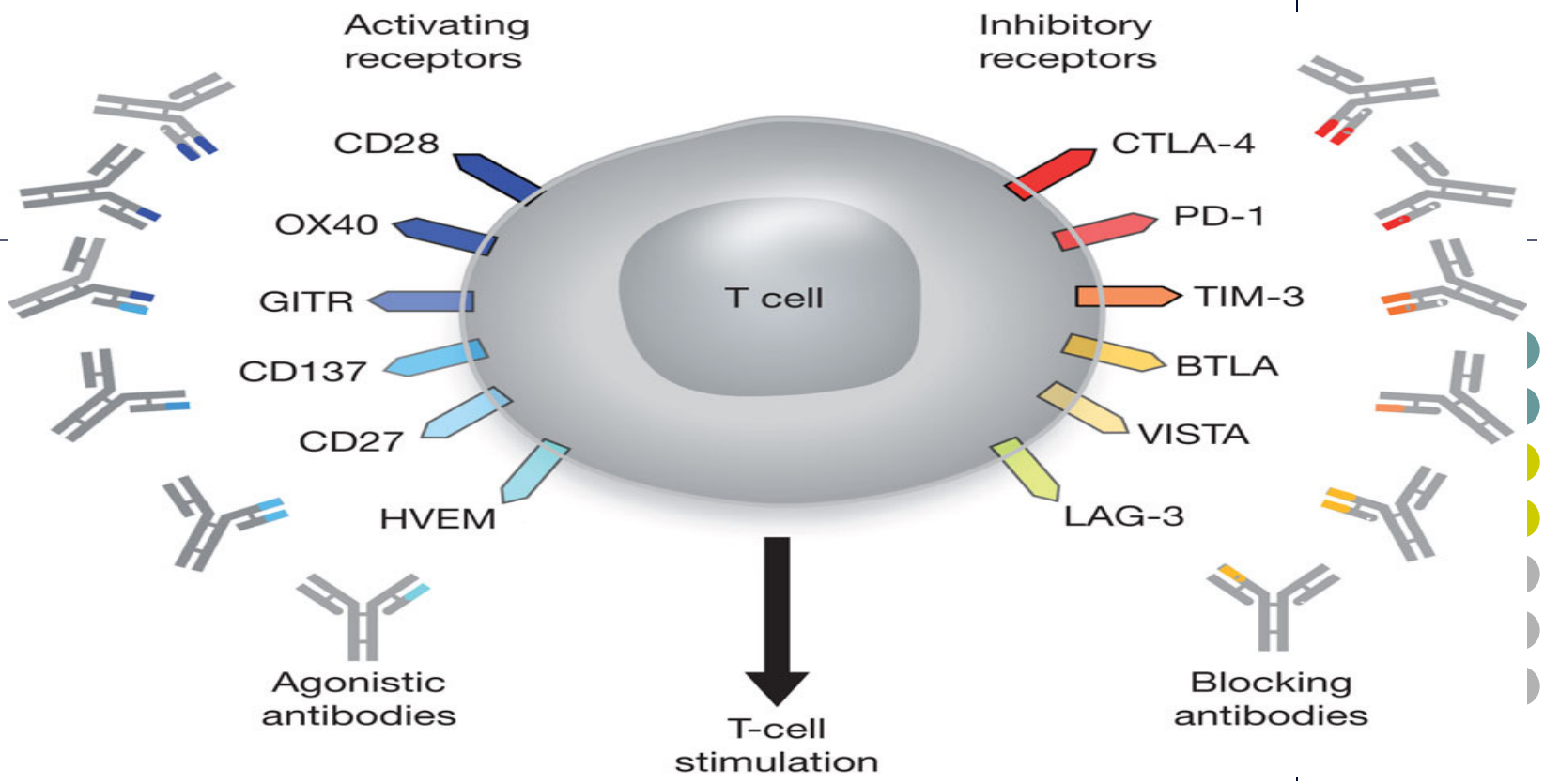
Cancer	Match	Foundation	Caris
Gastroesophageal	7/142 (4.9%)	6/400 (1.5%)	
Esophageal SCC	1/19 (5.3%)		
Gastric/GEJ Adenoca	4/79 (5.1%)		6/91 (6.2%)*
Esophageal Adenoca	2/44 (4.5%)		9/91 (0%)**
CRC	20/723 (2.8%)	42/1185 (3.5%)	38/888 (4.1%)
Rectal Adenoca	1/205 (0.5%)		
Colon Adenoca	19/518 (3.7%)		
Small bowel Adenoca	1/27 (3.7%)	6/70 (8.6%)	1/35 (2.8%)***
Panceatic Adenoca	1/267 (0.4%)	1/459 (0.2%)	7/316 (2.2%)
Uterine	34/237 (14.3%)	39/277 (14.1%)	62/365 (14.5%)
Prostate	7/122 (5.7%)	11/178 (6.2%)	3/128 (2.3%)
Breast	8/566 (1.4%)	2/1459 (0.1%)	2/705 (0.3%)
NSCLC	2/244 (0.8%)	5/2112 (0.2%)	9/1042 (0.9%)
SCLC	2/65 (3.1%)		1/52 (0.9%)
Hepatobiliary	4/166 (2.4%)	9/389 (2.3%)	
Gallbladder	1/37 (2.7%)		
Cholangiocarcinoma	3/129 (2.3%)		3/89 (3.3%)
HCC			0/30 (0%)
GBM	1/47 (2.1%)		2/431 (0.5%)
Neuroendocrine NOS	1/99 (1%)	1/431 (0.2%)	3/124 (2.4%)
Panc Neuroendocrine	2/28 (7.1%)		
CUP		22/815 (2.7%)	6/421 (1.4%)

The the anti-tumor immune response



Chen and Mellman, 2013. Immunity. 25;39(1):1-10

T cell targets for immunoregulatory antibody therapy



Mellman Nature: 480-489, 2011

Artificial Intelligence–Powered Spatial Analysis of Tumor-Infiltrating Lymphocytes as Complementary Biomarker for Immune Checkpoint Inhibition in Non–Small-Cell Lung Cancer

Sehhoon Park, MD, PhD et al

ascopubs.org/journal/JCO on March 10, 2022
DOI https://doi.org/10.1200/JCO.21.02010

Novel imaging biomarkers predict outcomes in stage III unresectable non-small cell lung cancer treated with chemoradiation and durvalumab

Jazieh K, et al.

J Immunother Cancer 2022;10:e003778.
doi:10.1136/jitc-2021-003778

Treatment Algorithm (as of 04/2022)

NSCLC	PDL1 ≥ 50%	PDL1 - 1-49%	PDL1 <1%	Studies
Non-Squamous	*Pembrolizumab *Atezolizumab *Cemiplimab *Plat/Pem/Pembro Plat/NbT/Atezo or Carbo/Pac/Ipi/Nivo	*Plat/Pem/Pembro Plat/NbT/Atezo Plat/Pac/Bev/Atezo Carbo/Pac/Ipi/Nivo	*Plat/Pem/Pembro Plat/NbT/Atezo Plat/Pac/Bev/Atezo Carbo/Pac/Ipi/Nivo *Ipi/Nivo (if TMB >10 Muts/Mb)	KN-24 KN-42 IMPower-110 EMPower-1 KN-189 IMPower-130 CK9LA CK227
Squamous	*Pembrolizumab *Atezolizumab *Cemiplimab	*Plat/Pac/Pembro *Plat/NbT/Atezo *Carbo/Pac/Ipi/Nivo Pembro	*Plat/Pac/Pembro *Plat/NbT/Atezo Carbo/Pac/Ipi/Nivo *Ipi/Nivo (if TMB >10 Muts/Mb	KN-24 KN-42 IMPower-110 EMPower-1 KN-407 IMPower130 CK9LA CK227

Conclusions

1. Lung cancer mortality has dropped by approximately 30% since the 1990s
2. Improvement in therapeutic modalities are one of the reasons for this decrease in mortality
3.
4. The advent of Immunotherapy had had a dramatic impact in the lung cancer therapeutic landscape
5. The search for an optimal biomarker to better predict benefit and/or toxicity from immunotherapy continues
6. Development of novel checkpoint inhibitors and novel combinations are an area of active investigation

Thank YOU!

Gracias!