Martedì 18 giugno

Nuovi farmaci immunoterapici in oncologia

Immunoterapia nel NSCLC

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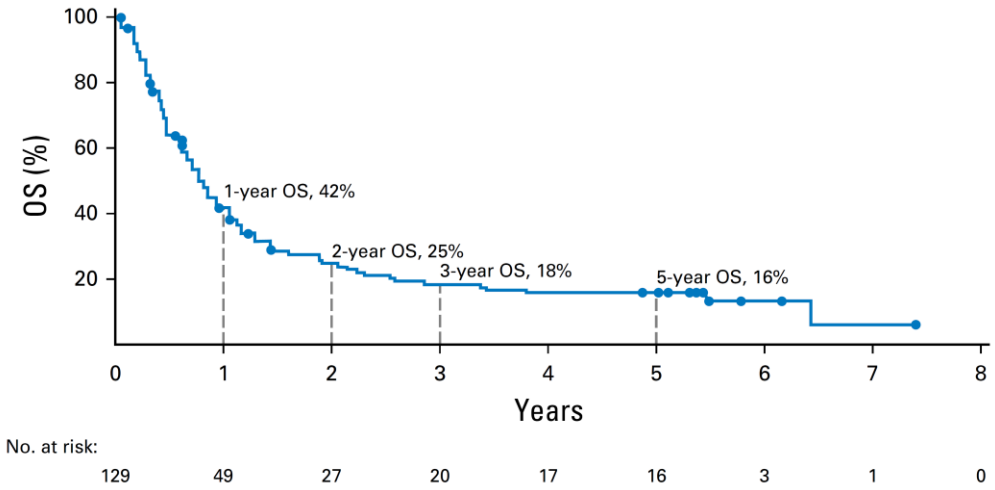
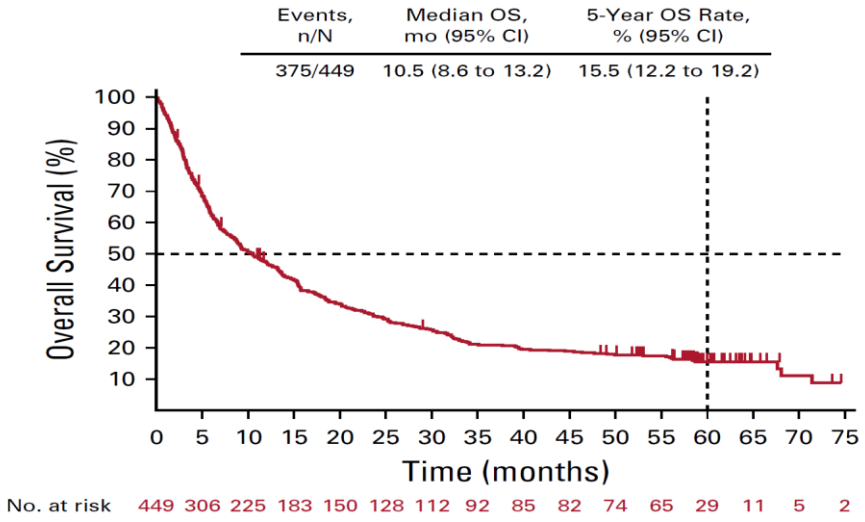
Negrar di Valpolicella - Verona

5-yr OS with anti-PD1 in advanced NSCLC

CA209-003 – Nivolumab in pretreated pts (n=129)



KEYNOTE-001 – Pembrolizumab in pretreated pts (n=449)

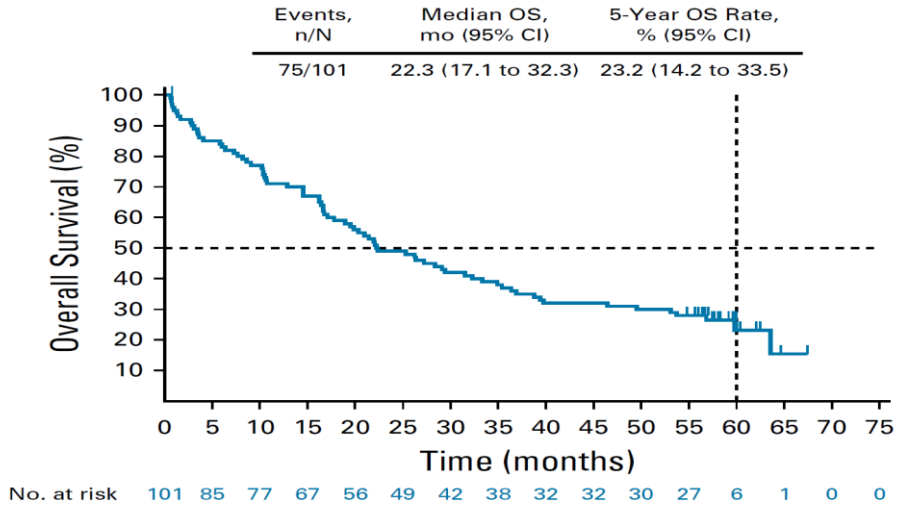


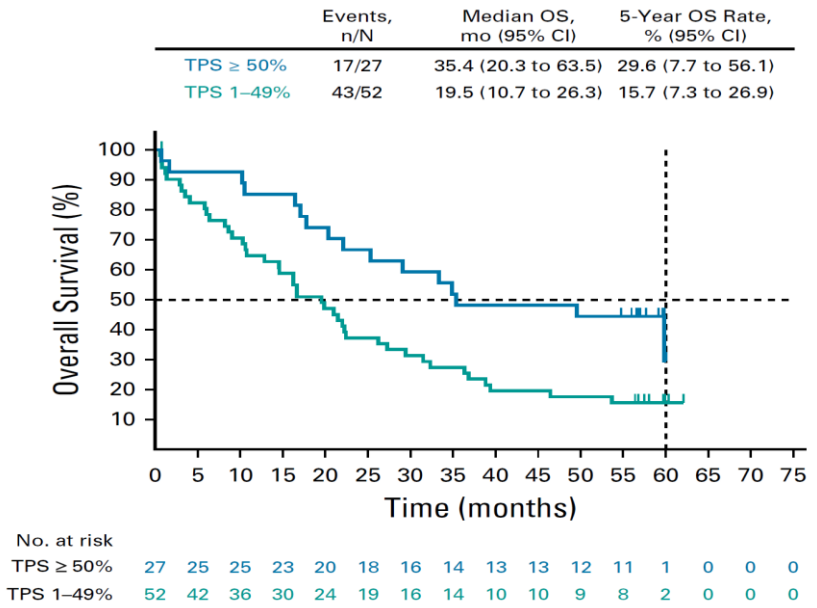
≈15% pretreated pts

Gettinger S et al. J Clin Oncol 2018;36(17):1675-1684. Garon EB, et al. J Clin Oncol 2019 *in press*

5-yr OS with anti-PD1 in advanced NSCLC

KEYNOTE-001 – Pembrolizumab in naïve pts (n=101)





≈25%
naïve pts

≈30%
naïve pts
with high PDL1 expression

Garon EB, et al. J Clin Oncol 2019 *in press*

2nd-line studies in advanced NSCLC

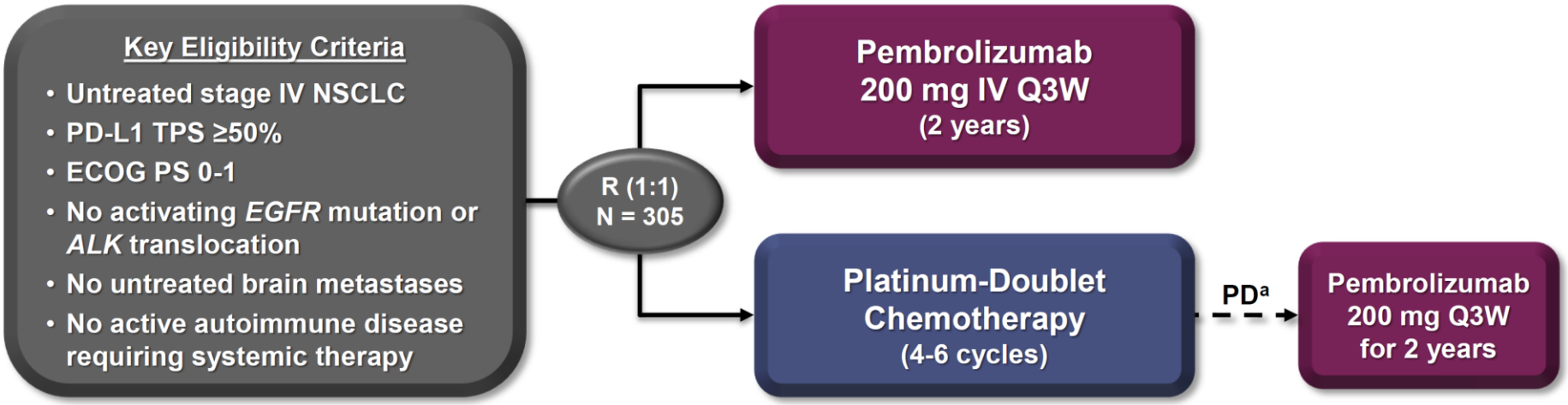
	Nivolumab		Pembrolizumab	Atezolizumab
Study Phase	CheckMate-017 [1] III	CheckMate-057 [2] III	KEYNOTE-010 [3] II/III	OAK [4] III
n	135 vs 137	292 vs 290	345 vs 346 vs 343	425 vs 425^{+}
Histology	SQ (100%)	Non-SQ (100%)	SQ (21%) Non-SQ (79%)	SQ (26%) Non-SQ (74%)
PD-L1	All comers	All comers	TPS≥1%	All comers
IHC test target	28-8 Dako TC	28-8 Dako TC	22C3 Dako TC	SP 142 Ventana TC and IC
Schedule	3 mg/kg Q 14d	3 mg/kg Q 14d	2 mg/kg, 10 mg/kg Q 21d	1200 mg Q 21d
Control Arm	Docetaxel 75 mg/m^2 Q 21d	Docetaxel 75 mg/m^2 Q 21d	Docetaxel 75 mg/m^2 Q 21d	Docetaxel 75 mg/m^2 Q 21d
Line	100% 2nd	88% 2nd 11% 3rd	69% 2nd 20% 3rd	75% 2nd 25% 3rd
mOS	9.2 vs 6.0 HR 0.59, p<0.001	12.2 vs 9.4 HR 0.73, p=0.002	10.4 vs 12.7 vs 8.5 HR 0.71, p=0.0008*	13.8 vs 9.6 HR 0.73, p=0.0003
1-yr survival	42% vs 24%	51% vs 39%	43.2% vs 52.3% vs 34.6%	55% vs 41%
TRAEs ≥ G3	7% vs 55%	10% vs 54%	13% vs 16% vs 35%	15% vs 43%

*pembrolizumab 2 mg/kg vs docetaxel; $^{+}$primary analysis population

1) Brahmer J, et al. N Engl J Med 2015;373(2):123-35. 2) Borghaei H, et al. N Engl J Med 2015;373(17):1627-39.
3) Herbst RS, et al. Lancet 2016;387(10027):1540-50. 4) Rittmeyer A, et al. Lancet 2017;389(10066):255-265.

1st-line Pembrolizumab in PDL1 ≥ 50% pts

KEYNOTE-024



Key End Points

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

Secondary: OS, ORR, safety

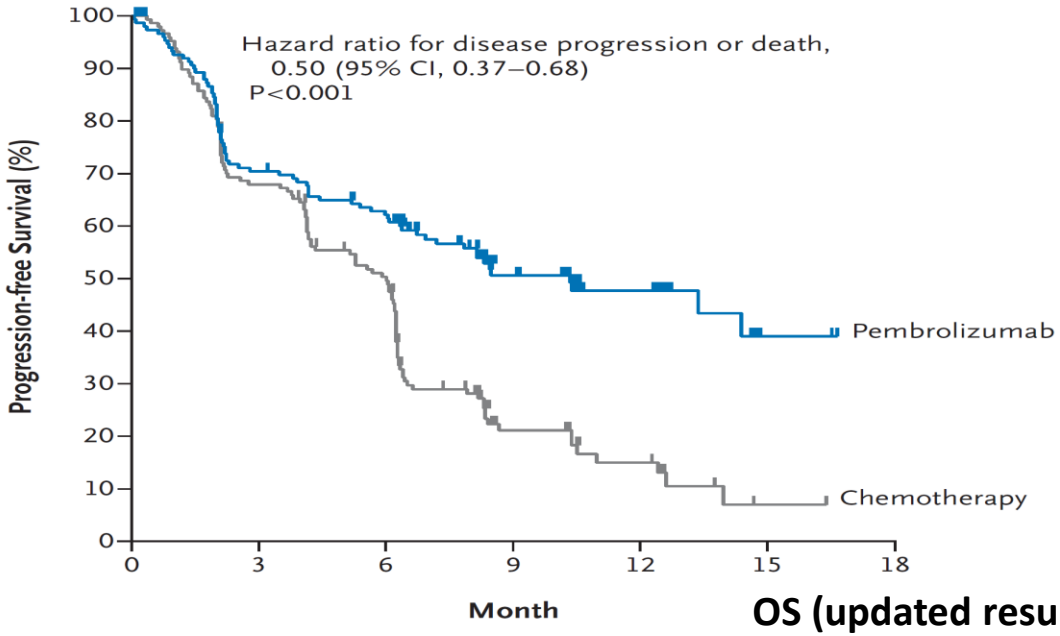
Exploratory: DOR

[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.

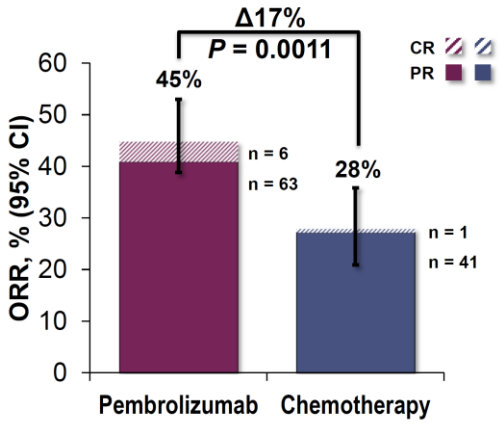
Reck M, et al. N Engl J Med 2016;375(19):1823-1833.
Reck M, et al. J Clin Oncol 2019;37(7):537-546.

1st-line Pembrolizumab in PDL1 ≥ 50% pts

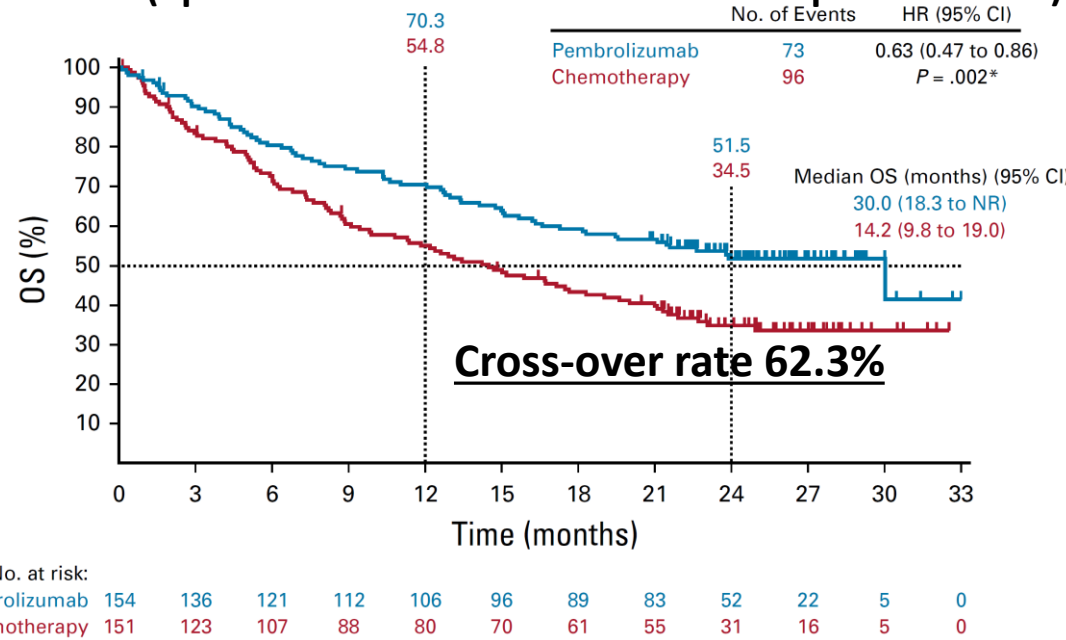
PFS



RR



OS (updated results at a median follow-up of 25.2 mos)



Reck M, et al. N Engl J Med 2016;375(19):1823-1833.
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1st-line Pembrolizumab in PDL1 ≥ 50% pts

Adverse Event	No. of Patients (%)			
	Pembrolizumab (n = 154)		Chemotherapy (n = 150)	
Treatment-related AEs†				
Any grade	118 (76.6)		135 (90.0)	
Grade 3-5	48 (31.2)		80 (53.3)	
Serious	35 (22.7)		31 (20.7)	
Led to discontinuation	21 (13.6)		16 (10.7)	
Led to death	2 (1.3)		3 (2.0)	
AEs with possible immune etiology occurring in ≥ 0% of patients	Any Grade	Grade 3 or 4§	Any Grade	Grade 3 or 4§
Any	52 (33.8)	20 (13.2)	8 (5.3)	1 (0.7)
Hypothyroidism	16 (10.4)	0	3 (2.0)	0
Pneumonitis	12 (7.8)	4 (2.6)	1 (0.7)	1 (0.7)
Hyperthyroidism	11 (7.1)	0	2 (1.3)	0
Infusion reactions	8 (5.2)	1 (0.6)	2 (1.3)	0
Severe skin reactions	8 (5.2)	8 (5.2)	0	0
Colitis	6 (3.9)	3 (1.9)	0	0
Thyroiditis	4 (2.6)	0	0	0
Myositis	3 (1.9)	0	0	0
Hepatitis	1 (0.6)	1 (0.6)	0	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0
Nephritis	1 (0.6)	1 (0.6)	0	0
Pancreatitis	1 (0.6)	1 (0.6)	0	0
Type 1 diabetes	1 (0.6)	1 (0.6)	0	0
Uveitis	1 (0.6)	1 (0.6)	0	0

Grade 3-5 AEs
31.2% vs 53.3%

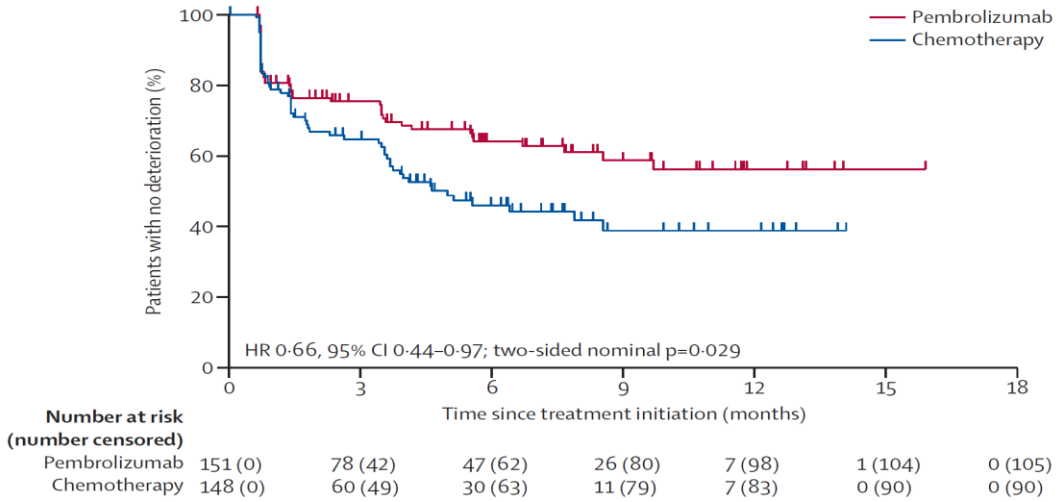
irAEs
33.8% (any grade)
13.2% (G3-4)

G3-4 pneumonitis
2.6%

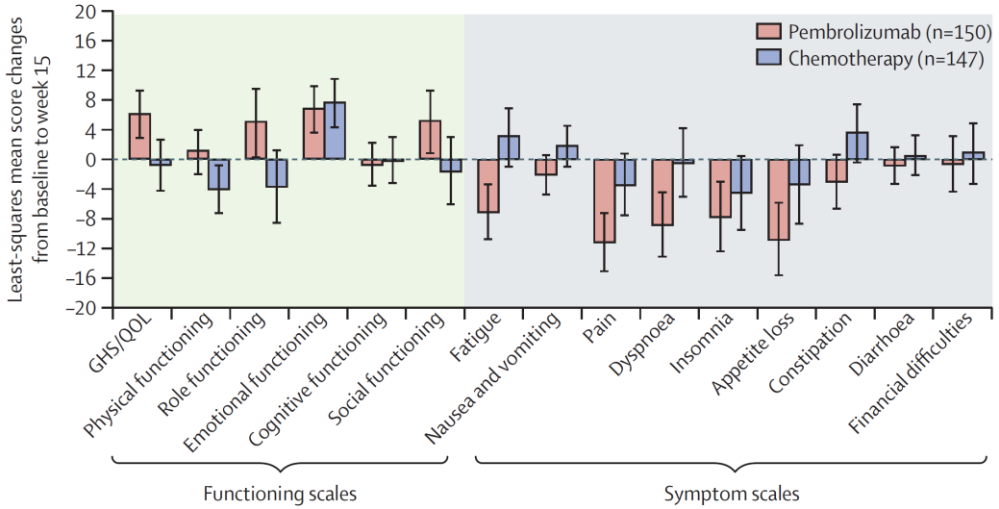
Reck M, et al. N Engl J Med 2016;375(19):1823-1833.
Reck M, et al. J Clin Oncol 2019;37(7):537-546.

1st-line Pembrolizumab in PDL1 ≥ 50% pts

Time to deterioration of the composite of cough, chest pain, and dyspnoea in the QLQ-LC13



Change from baseline to week 15 in QLQ-C30 functioning and symptom scales



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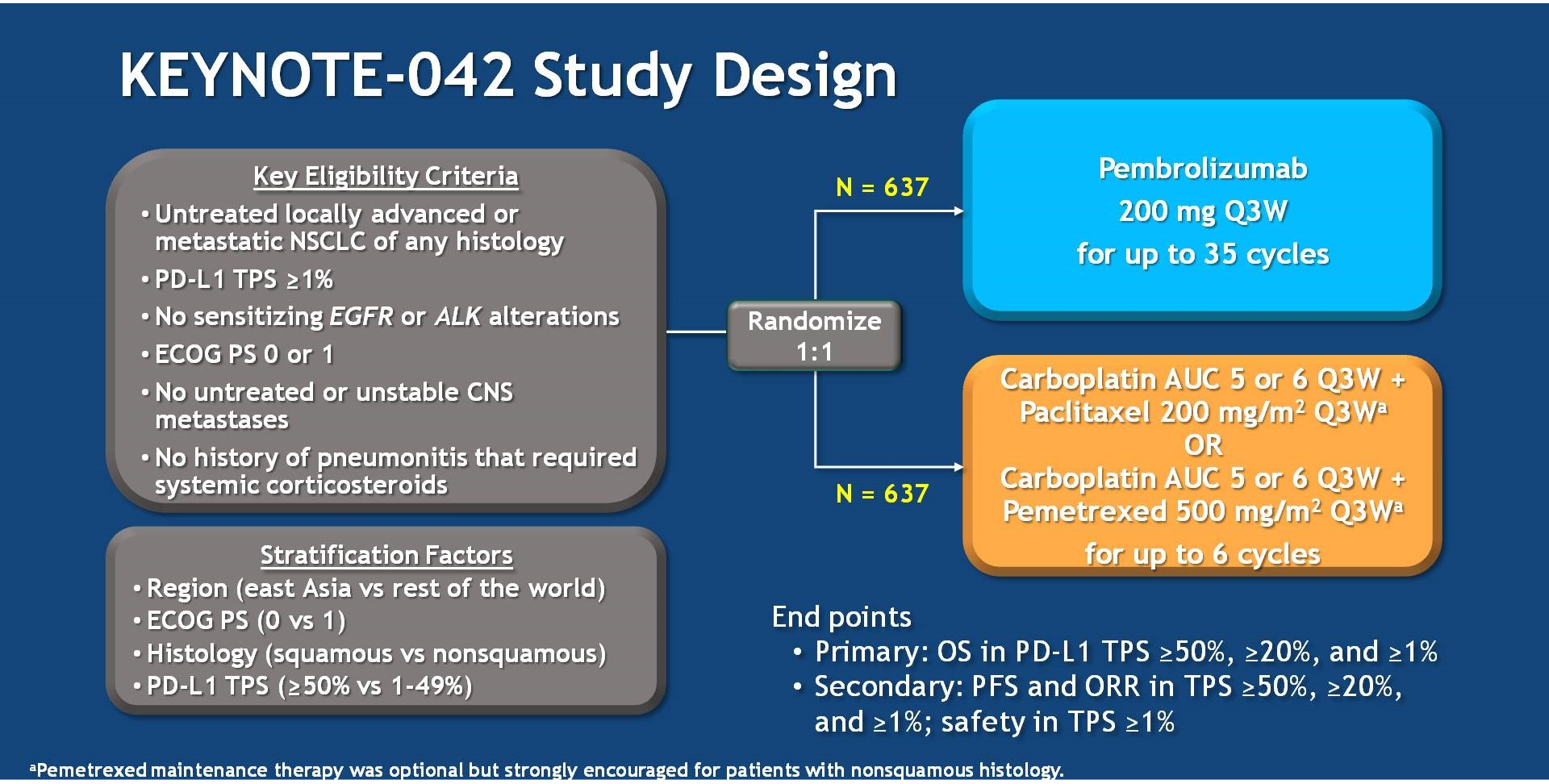
Reck M, et al. J Clin Oncol 2019;37(7):537-546.

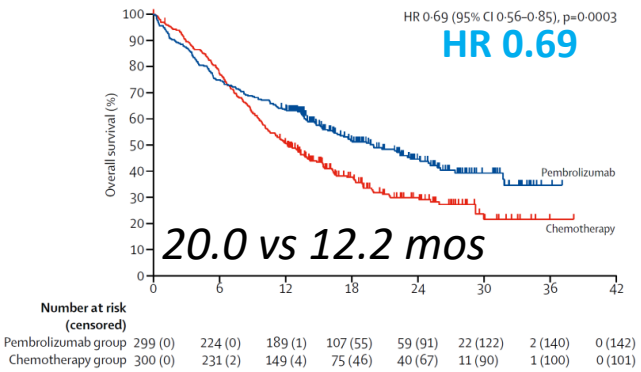
1st-line Pembrolizumab in PDL1 < 50% pts?



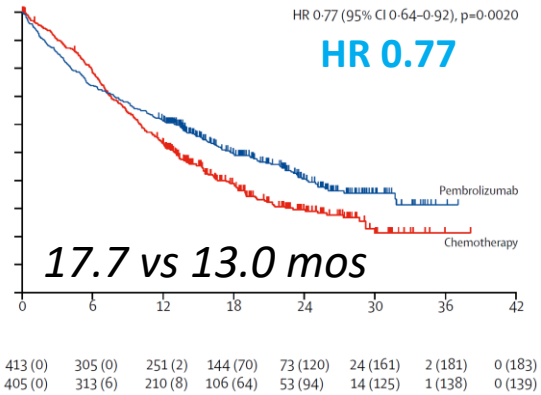
Mok TSK, et al. Lancet. 2019;393(10183):1819-1830.

1st-line Pembrolizumab in PDL1 < 50% pts?

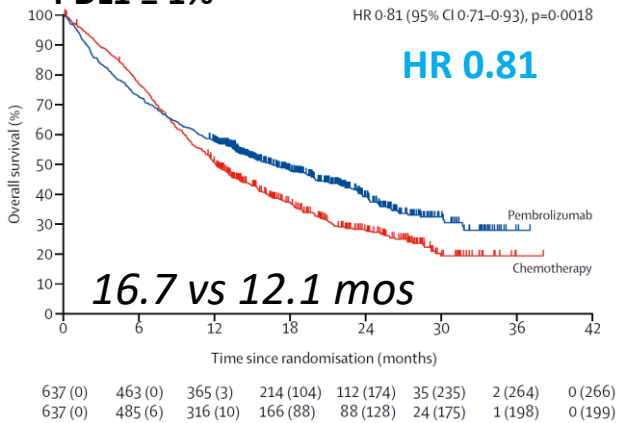
PDL1 ≥ 50%

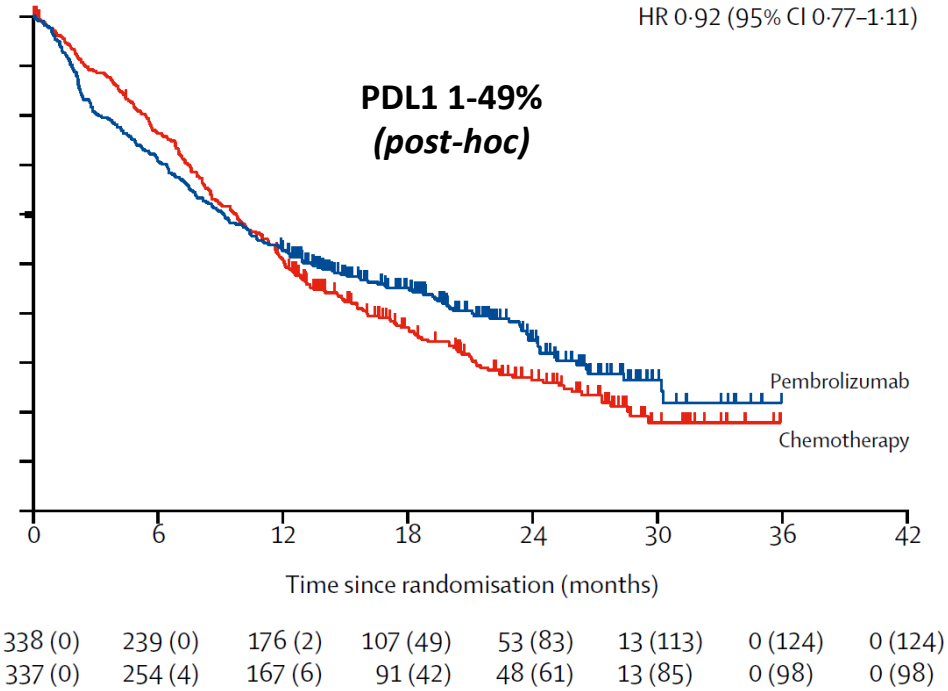


PDL1 ≥ 20%



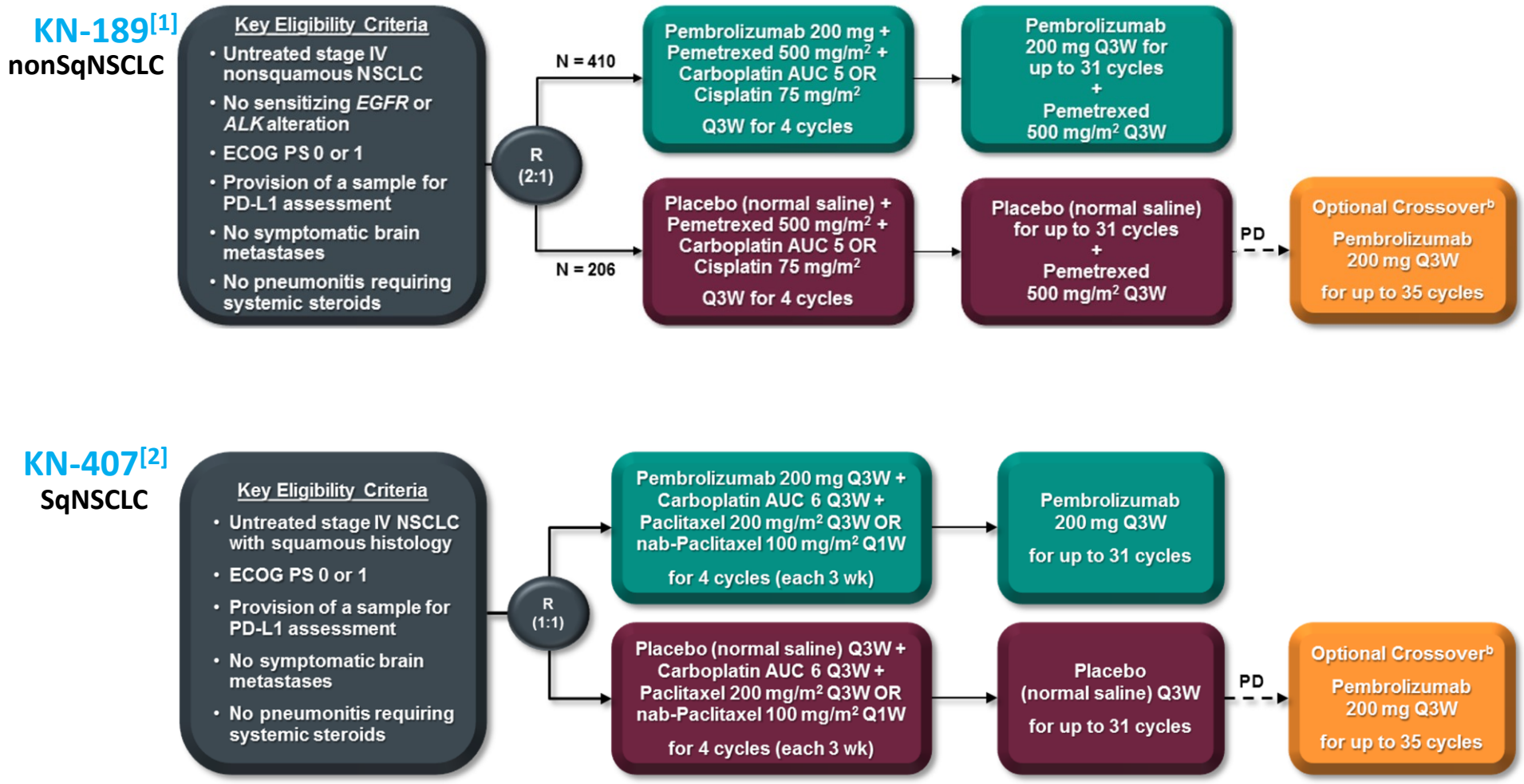
PDL1 ≥ 1%





Mok TSK, et al. Lancet. 2019;393(10183):1819-1830.

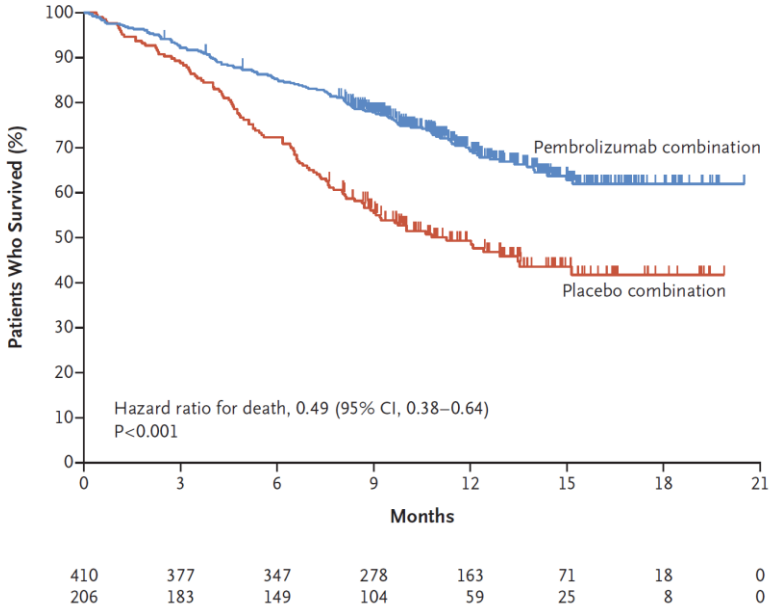
1st-line Pembro + Chemo combinations



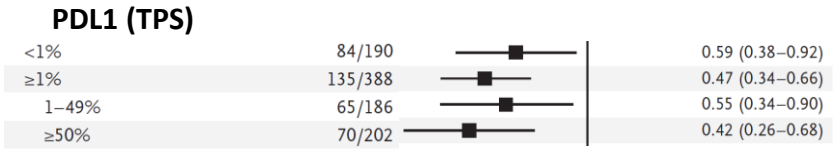
1) Gandhi L, et al. N Engl J Med 2018;378(22):2078-2092. 2) Paz-Ares L et al. N Engl J Med 2018;379(21):2040-2051.

1st-line Pembro + Chemo combinations

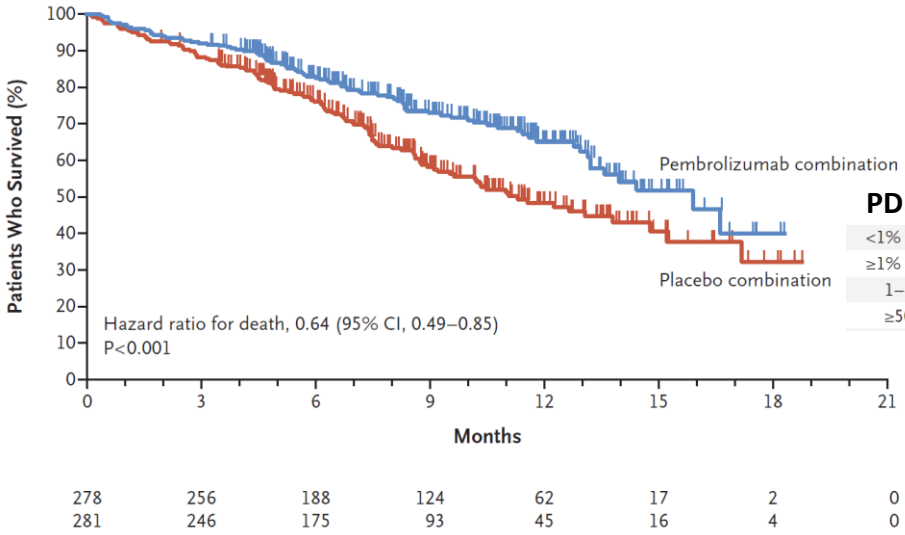
KN-189[1]
nonSqNSCLC



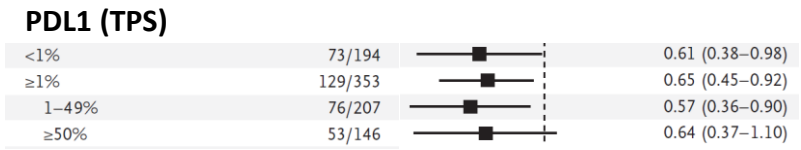
NR vs 11.3 mos
1-yr survival: 69.2% vs 49.4%



KN-407[2]
SqNSCLC



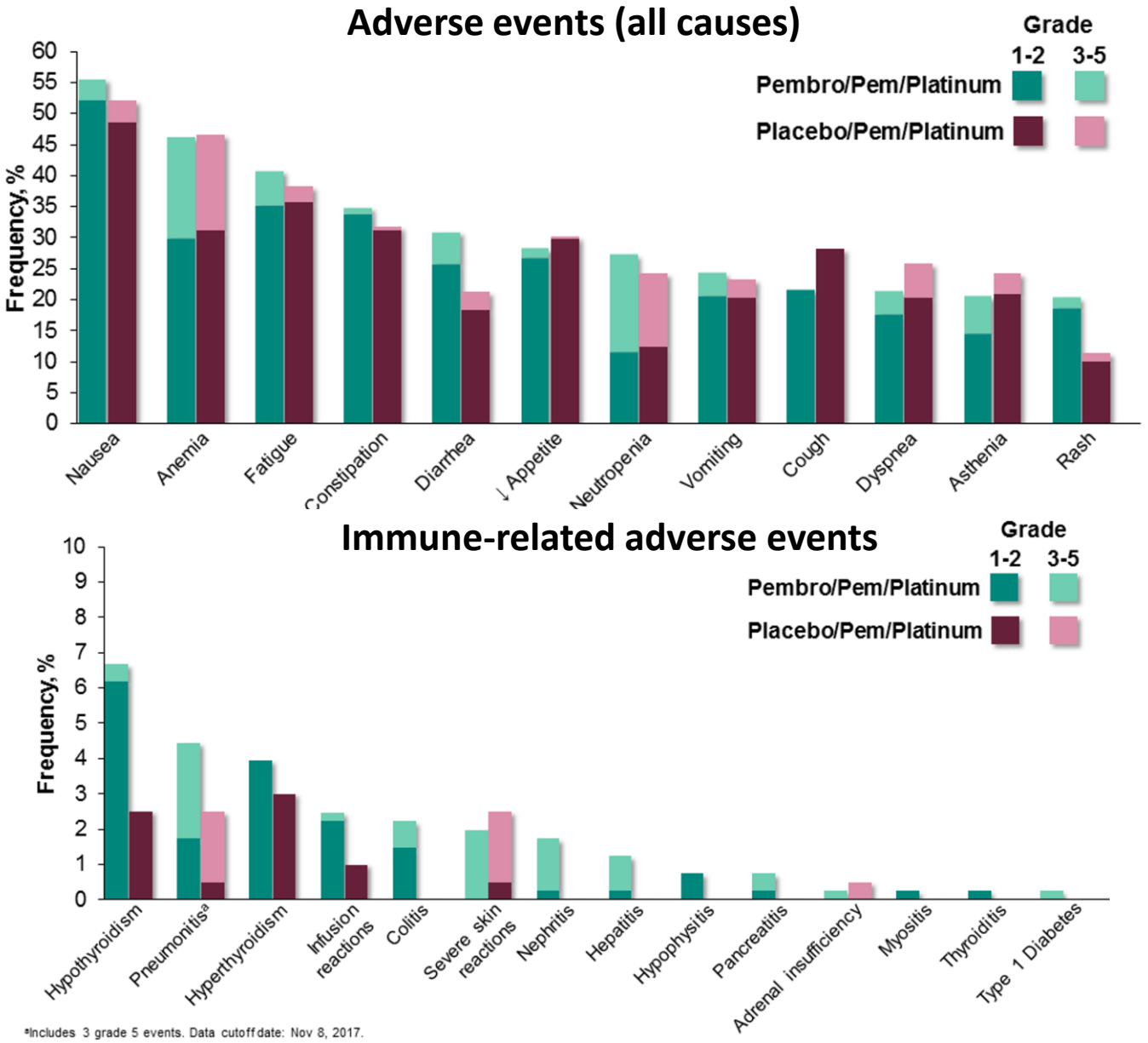
15.9 vs 11.3 mos
1-yr survival: 65.2% vs 48.3%



1) Gandhi L, et al. N Engl J Med 2018;378(22):2078-2092. 2) Paz-Ares L et al. N Engl J Med 2018;379(21):2040-2051.

1st-line Pembro + Chemo combinations

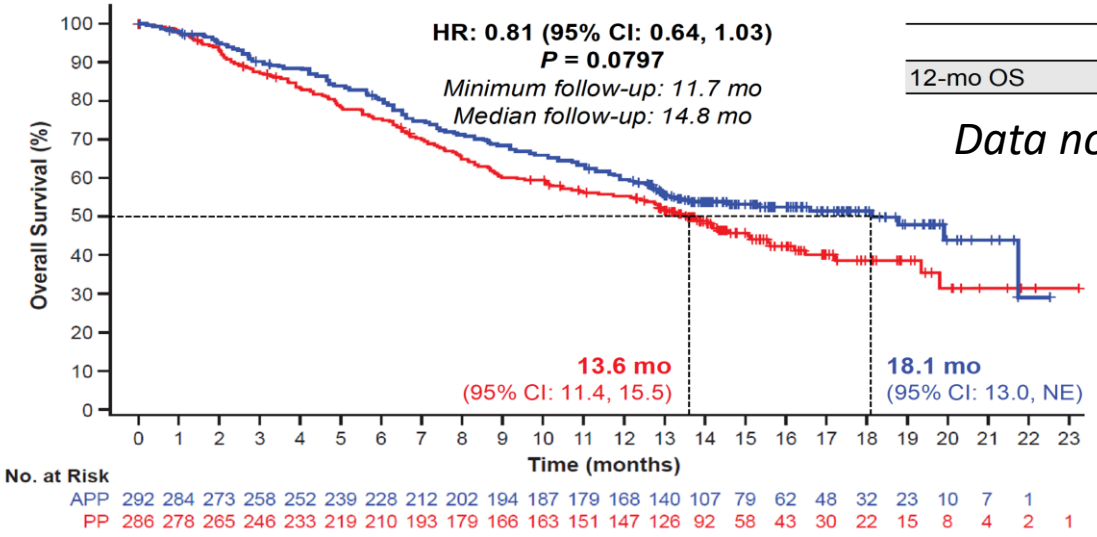
KN-189[1]
nonSqNSCLC



Gandhi L, et al. N Engl J Med 2018;378(22):2078-2092

1st-line Atezo + Chemo combinations

IMpower 132[1]
nonSqNSCLC

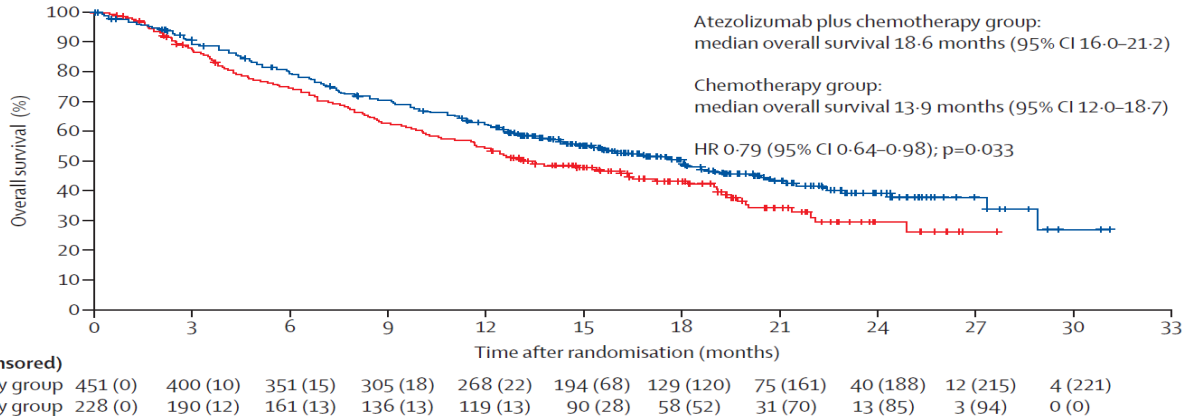


	APP	PP
12-mo OS	59.6%	55.4%

Data not mature

IMpower 130[2]
SqNSCLC

	Overall survival at 12 months	Overall survival at 24 months
Atezolizumab plus chemotherapy group	63·1% (95% CI 58·6–67·7)	39·6% (95% CI 33·6–45·7)
Chemotherapy group	55·5% (95% CI 48·9–62·2)	30·0% (95% CI 21·7–38·2)



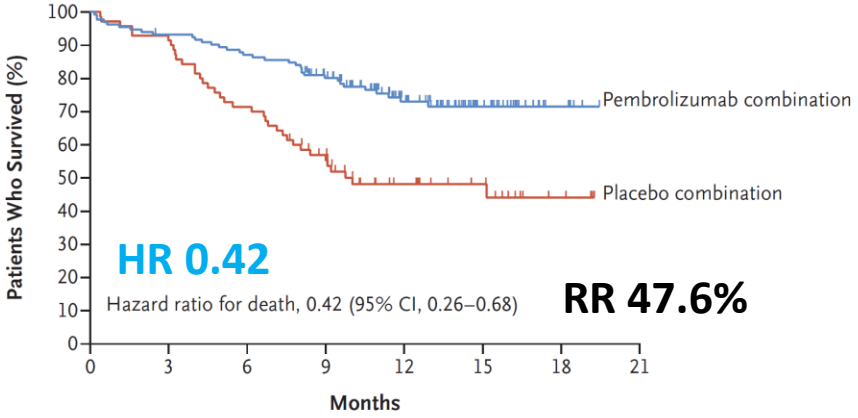
1. Vassiliki A, et al. WCLC 2018. 2. West H, et al. Lancet Oncol 2019 *in press*

ICI/chemo combination or single agent for PDL1 ≥ 50% pts?

Pembro/CTx vs Placebo/CTx

KN-189

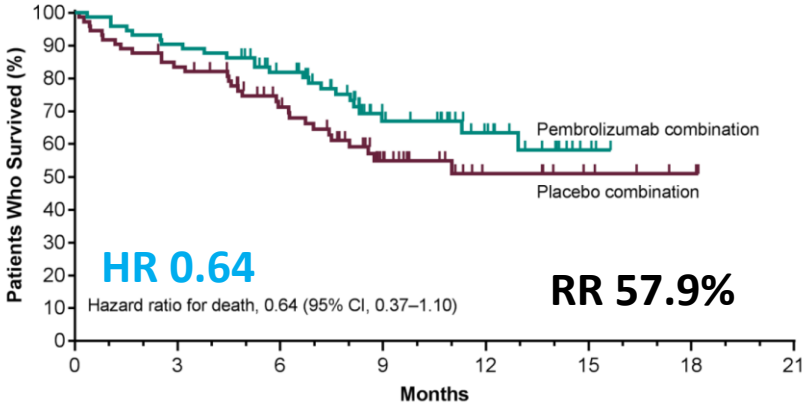
nonSqNSCLC, PDL1 ≥ 50%



RR 47.6%

KN-407

SqNSCLC, PDL1 ≥ 50%



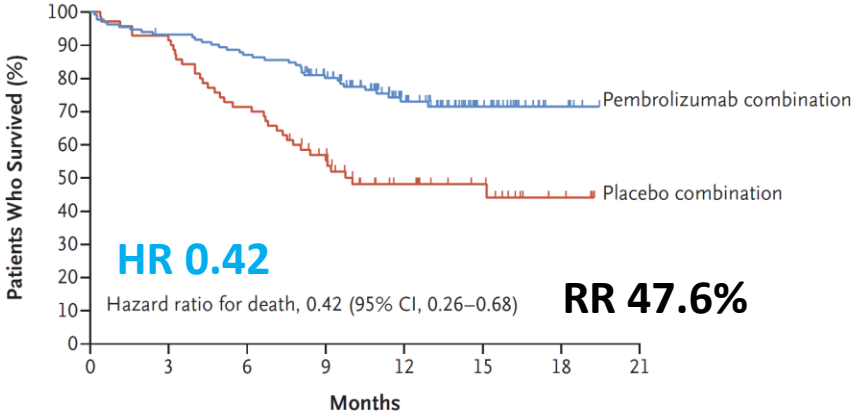
RR 57.9%

1) Gandhi L, et al. N Engl J Med 2018;378(22):2078-2092. 2) Paz-Ares L et al. N Engl J Med 2018;379(21):2040-2051.

ICI/chemo combination or single agent for PDL1 ≥ 50% pts?

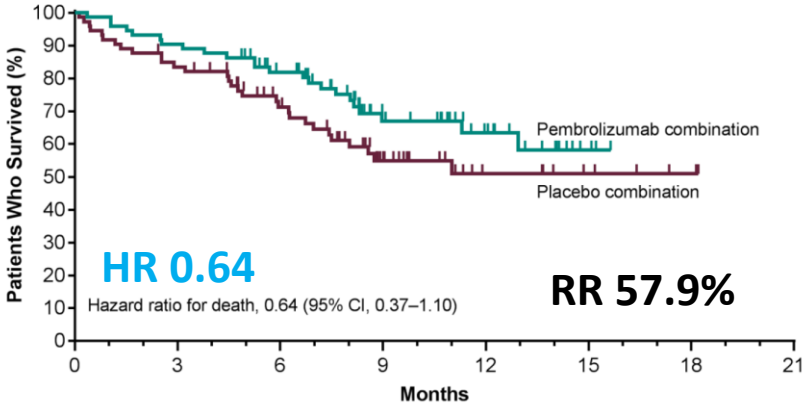
Pembro/CTx vs Placebo/CTx

KN-189
nonSqNSCLC, PDL1 ≥ 50%



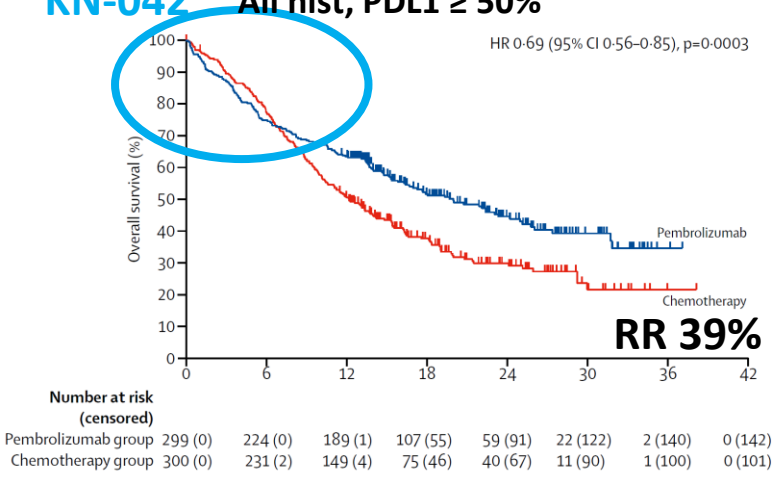
RR 47.6%

KN-407
SqNSCLC, PDL1 ≥ 50%



RR 57.9%

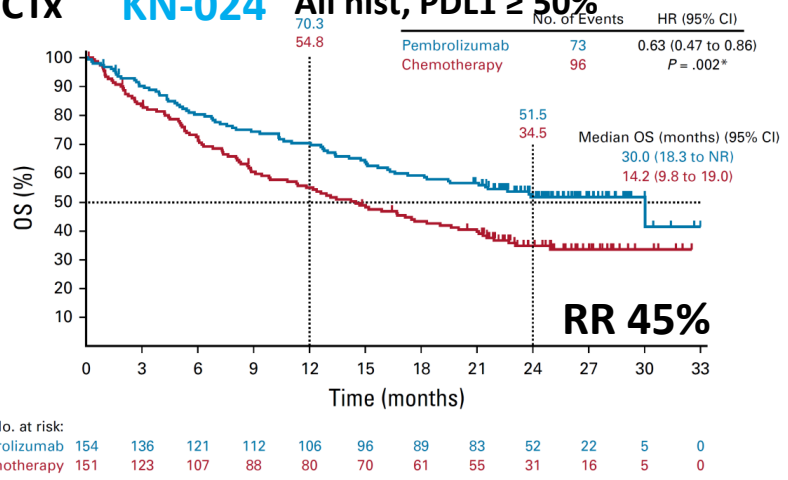
KN-042
All hist, PDL1 ≥ 50%



RR 39%

Pembro vs CTx

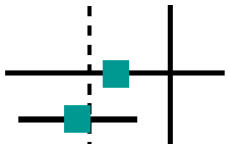
KN-024
All hist, PDL1 ≥ 50%



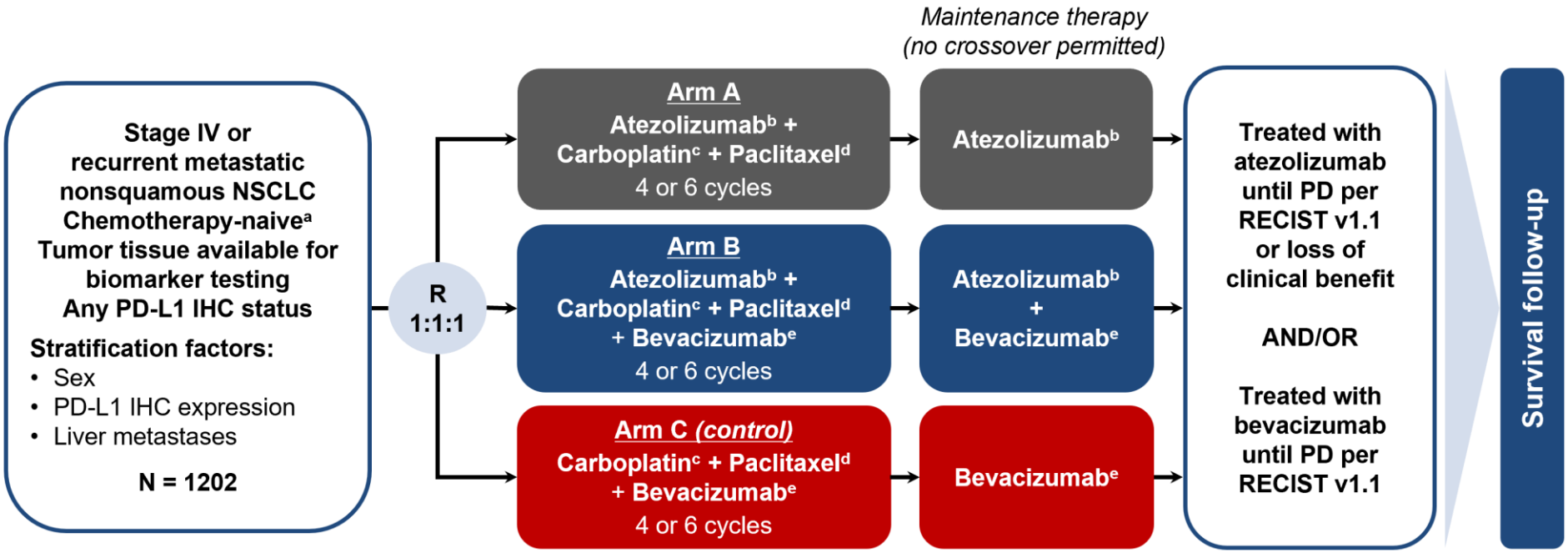
RR 45%

KN-024 Histology

Squamous (n = 56)	0.73 (0.38 to 1.39)
Nonsquamous (n = 249)	0.58 (0.41 to 0.83)



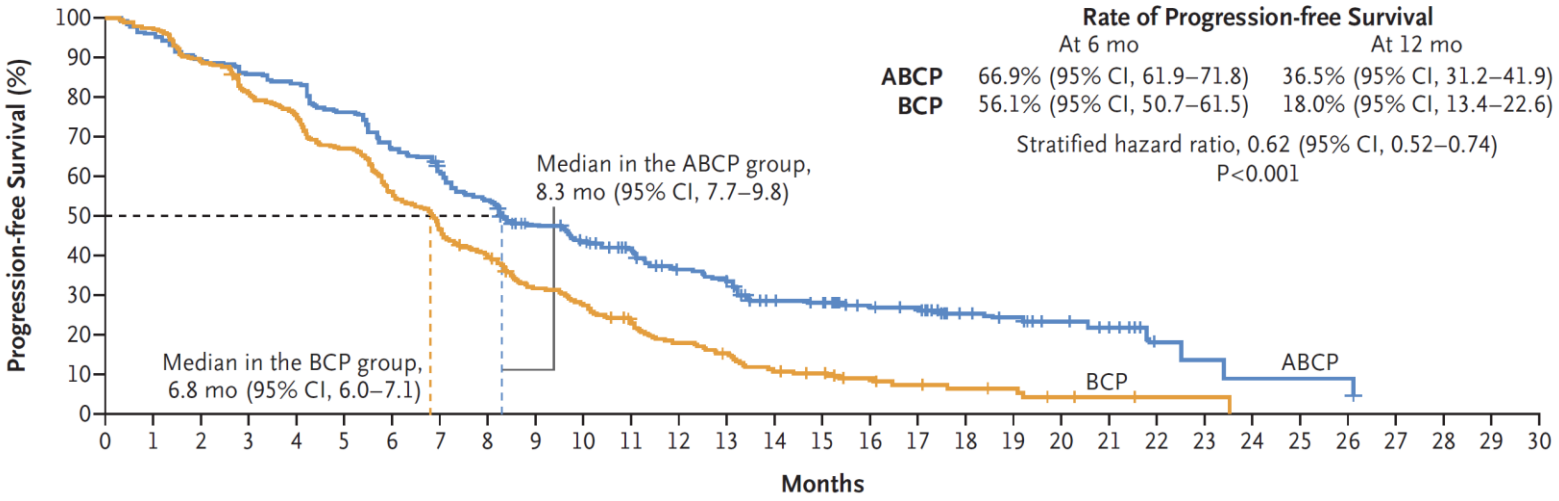
IMpower-150

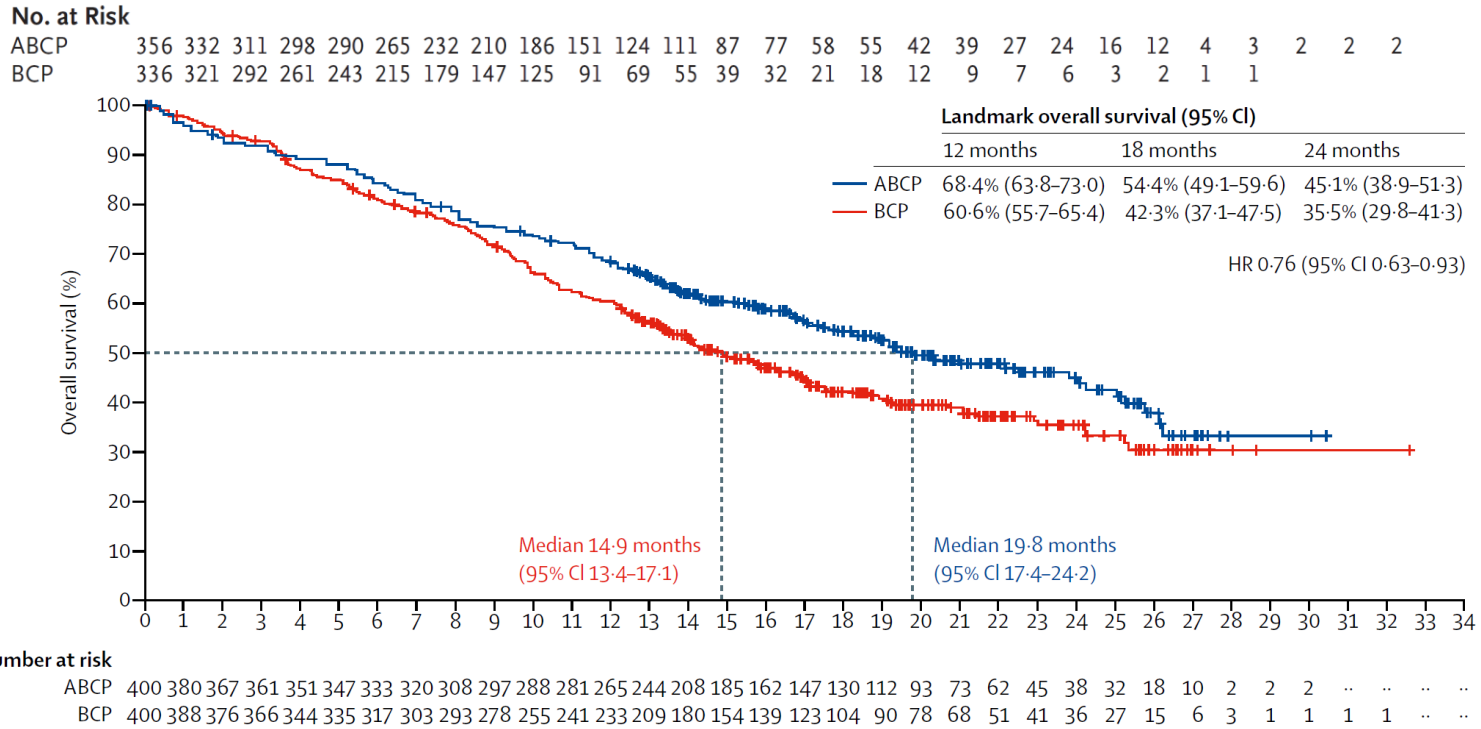


[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg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

Socinski MA et al. NSCLC. N Engl J Med 2018;378(24):2288-2301.

Impower-150: PFS and OS data

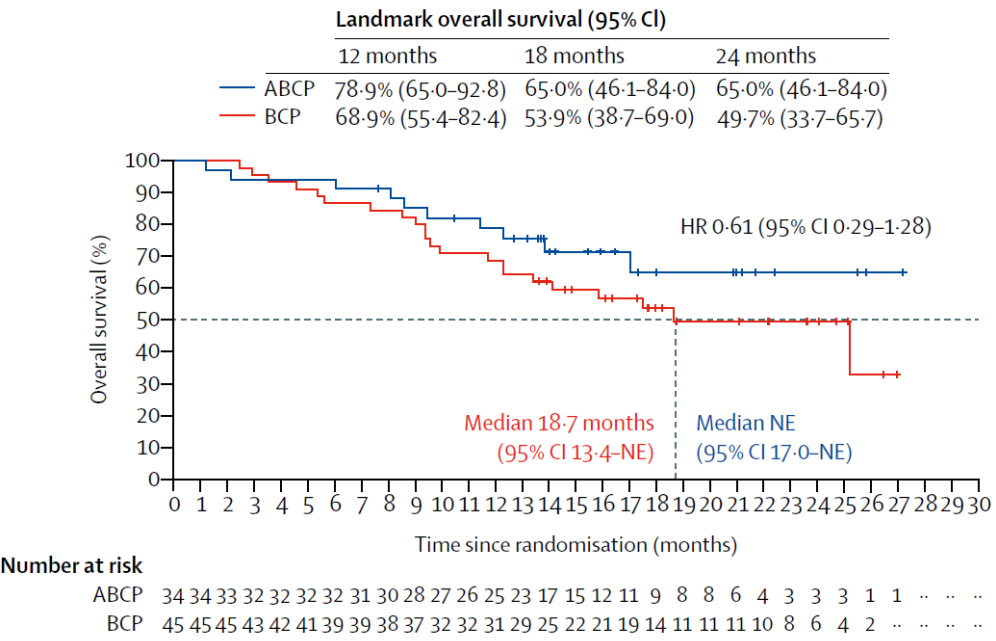




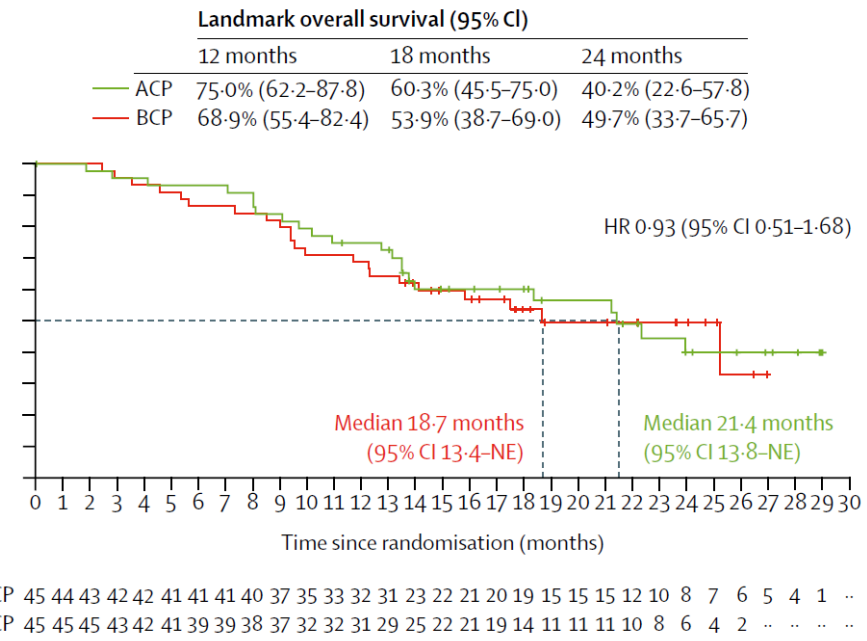
Socinski MA et al. NSCLC. N Engl J Med 2018;378(24):2288-2301. Reck M, et al. Lancet Respir Med 2019;7(5):387-401.

Impower-150: *EGFR*mut population

A



B



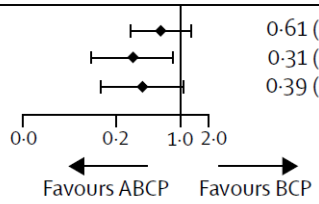
Number at risk

ABCP	34	34	33	32	32	32	32	31	30	28	27	26	25	23	17	15	12	11	9	8	8	6	4	3	3	3	1	1	..	..	..
BCP	45	45	45	43	42	41	39	39	38	37	32	32	31	29	25	22	21	19	14	11	11	11	10	8	6	4	2	..	..	..	..

ACP	45	44	43	42	42	41	41	41	40	37	35	33	32	31	23	22	21	20	19	15	15	15	12	10	8	7	6	5	4	1	..
BCP	45	45	45	43	42	41	39	39	38	37	32	32	31	29	25	22	21	19	14	11	11	11	10	8	6	4	2	..	..	..	..

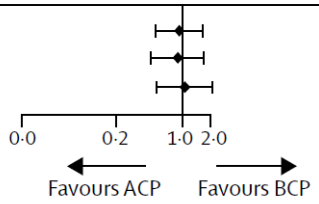
C

	n (%)	HR (95% CI)	Median overall survival, months	
			ABCP	BCP
EGFR mutation	79 (100)	0·61 (0·29–1·28)	NE	18·7
Sensitising *EGFR* mutation*	58 (73)	0·31 (0·11–0·83)	NE	17·5
Previously received TKI therapy	50 (63)	0·39 (0·14–1·07)	NE	17·5



D

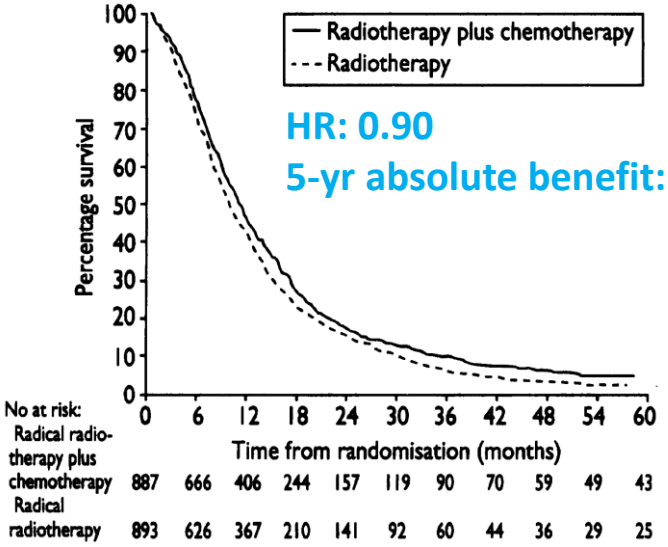
n (%)	HR (95% CI)	Median overall survival, months	
		ACP	BCP
90 (100)	0·93 (0·51–1·68)	21·4	18·7
65 (72)	0·90 (0·47–1·74)	21·2	17·5
56 (62)	1·05 (0·53–2·09)	14·0	17·5



Reck M, et al. Lancet Respir Med 2019;7(5):387-401.

Locally advanced, unresectable stage III NSCLC

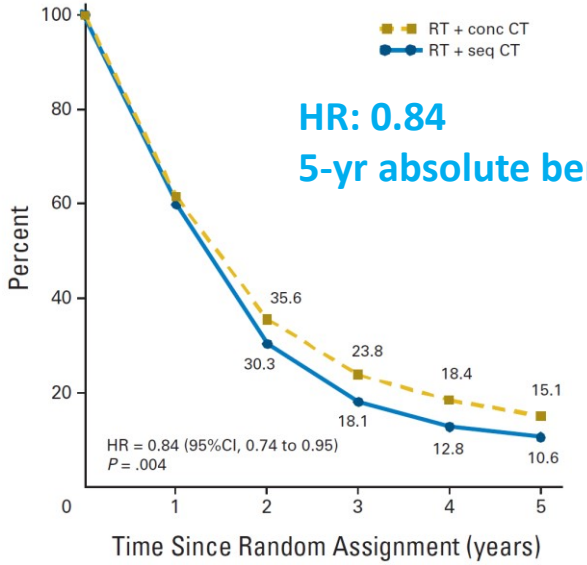
RTx vs RTx+CTx



HR: 0.90

5-yr absolute benefit: +2%

Concomitant vs sequential RTx/CTx



HR: 0.84

5-yr absolute benefit: +4.5%

Deaths/Person-Years by Period

	0y–1y	1y–2y	2y–3y	3y–4y	> 4y
RT+ conc CT (n = 603)	240/498	147/276	67/171	30/116	37/186
RT+ seq CT (n = 602)	253/491	171/242	70/129	30/ 83	23/126

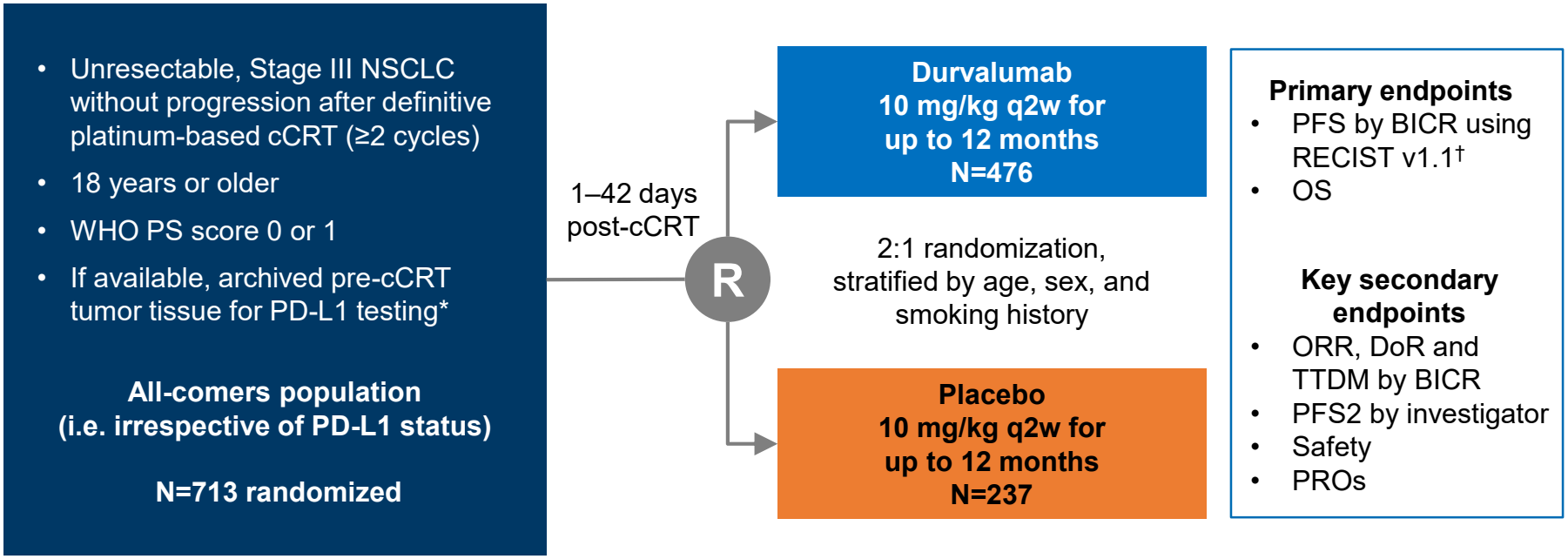
Median PFS: 6-11 mos

Median OS: 25-30 mos

2-yr OS: 50-55%

5-yr OS: 15-30%

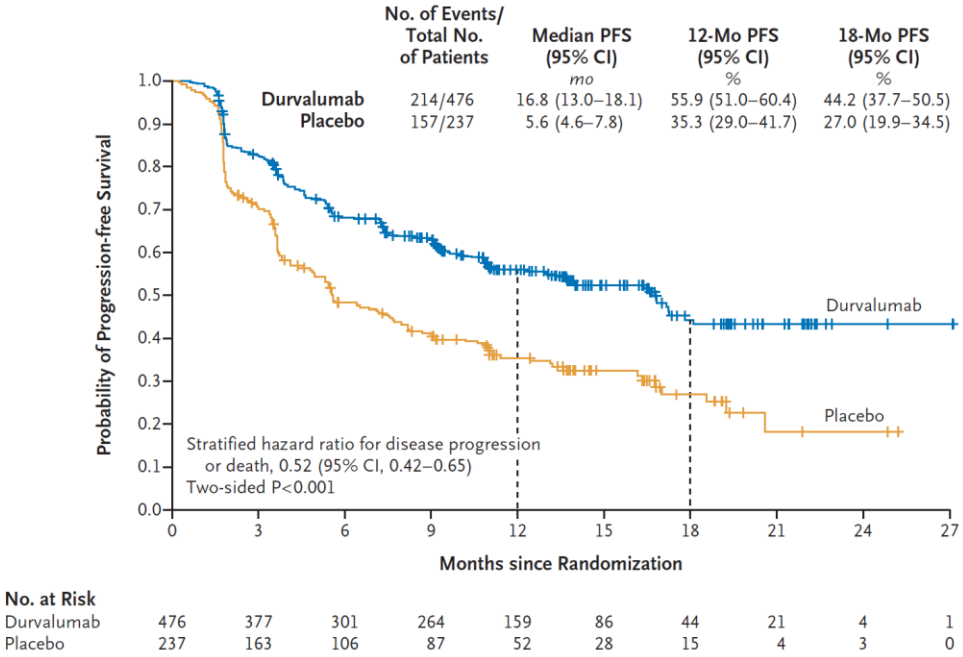
PACIFIC: maintenance durvalumab after RTx/CTx

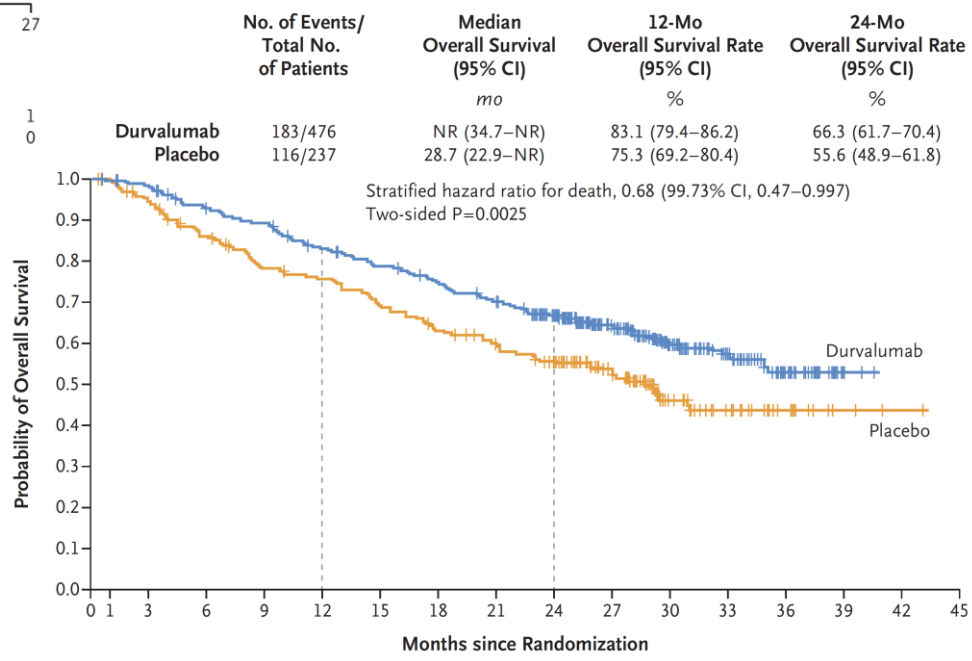


*Using the Ventana SP263 immunohistochemistry assay
†Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression. BICR, blinded independent central review; cCRT, concurrent CRT; PFS2, time to second progression; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis. ClinicalTrials.gov number: NCT02125461

Antonia SJ, et al. N Engl J Med 2017;377(20):1919-1929.
Antonia SJ, et al. N Engl J Med 2018;379(24):2342-2350.

PACIFIC: PFS and OS results



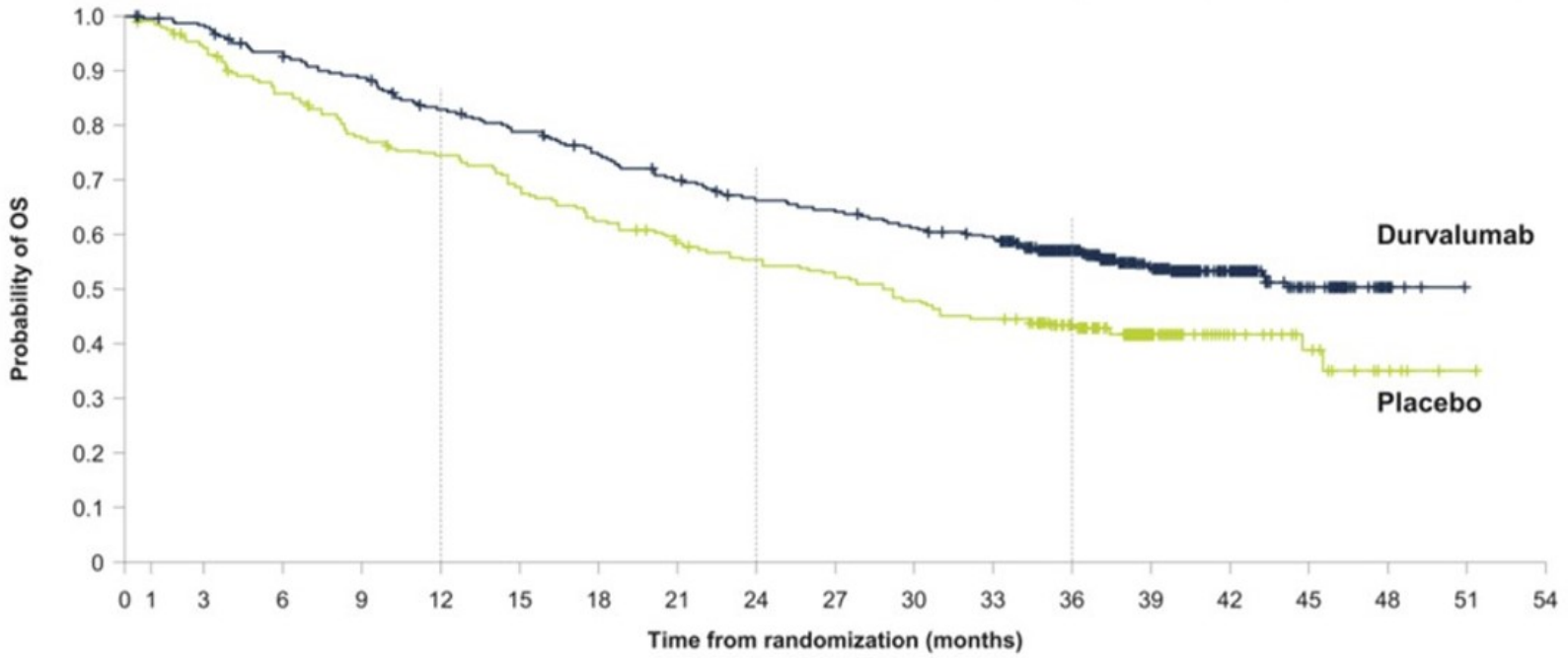


Antonia SJ, et al. N Engl J Med 2017;377(20):1919-1929.
Antonia SJ, et al. N Engl J Med 2018;379(24):2342-2350.

PACIFIC: updated OS results

	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
Durvalumab	210/476 (44.1)	NR (38.4–NR)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	57.0 (52.3–61.4)
Placebo	134/237 (56.5)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.5 (37.0–49.9)

Stratified hazard ratio for death, 0.69 (95% CI, 0.55–0.86)
Stratified hazard ratio for death from the primary analysis,[9] 0.68 (95% CI, 0.53–0.87)



No. at risk																		
Durvalumab	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1	0

NR, not reached

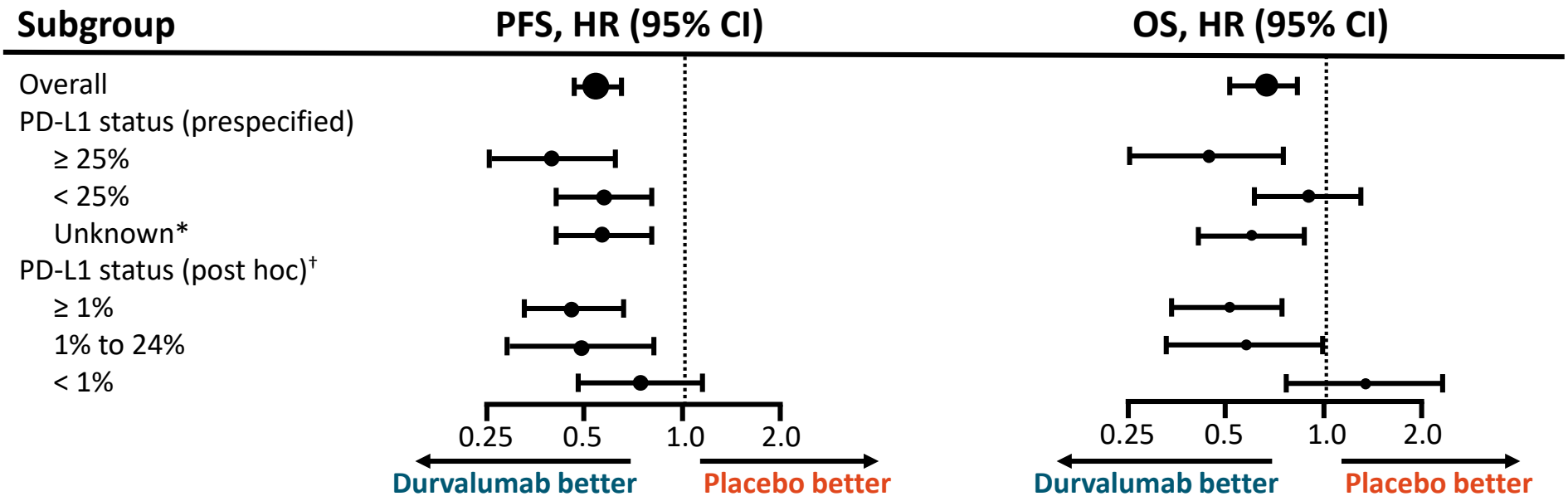
Gray JE, et al. ASCO 2019

PACIFIC: safety data

AE, n (%)	Durvalumab (n = 475)	Placebo (n = 234)
Any AE	460 (96.8)	222 (94.9)
▪ Grade 3/4	145 (30.5)	61 (26.1)
▪ Outcome of death	21 (4.4)	15 (6.4)
▪ Leading to discontinuation	73 (15.4)	23 (9.8)
Serious AEs	138 (29.1)	54 (23.1)
Pneumonitis/radiation pneumonitis	161 (33.9)	58 (24.8)
▪ Grade 3/4	17 (3.6)	7 (3.0)
▪ Outcome of death	5 (1.1)	5 (2.1)
▪ Leading to discontinuation	30 (6.3)	10 (4.3)

Antonia SJ, et al. N Engl J Med 2017;377(20):1919-1929.
Antonia SJ, et al. N Engl J Med 2018;379(24):2342-2350.

PACIFIC: subgroup analysis according to PDL1 status



*Unknown PD-L1 status in 37% of patients; testing not required, obtained pre-CRT.
†1% cutoff used in unplanned post hoc analysis requested by a health authority.

Antonia SJ, et al. N Engl J Med 2017;377(20):1919-1929.
Antonia SJ, et al. N Engl J Med 2018;379(24):2342-2350.

Conclusion

Stage IV NSCLC

- **5yr OS 15-30% with single agent anti-PD1**

- **For pts with PDL1 ≥ 50%:**
  1st-line single agent pembrolizumab OR chemo/ICI combination

- **For pts with PDL1 <50%:**
  1st-line chemo/ICI combination

- **For pts with driver mutations:**
  Atezo+Bev+Chemotherapy after failure of target T

Unresectable stage III NSCLC

- **Maintenance durvalumab SoC**
  (for pts with PDL1 ≥ 1% not progressing after RTx/CTx)

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