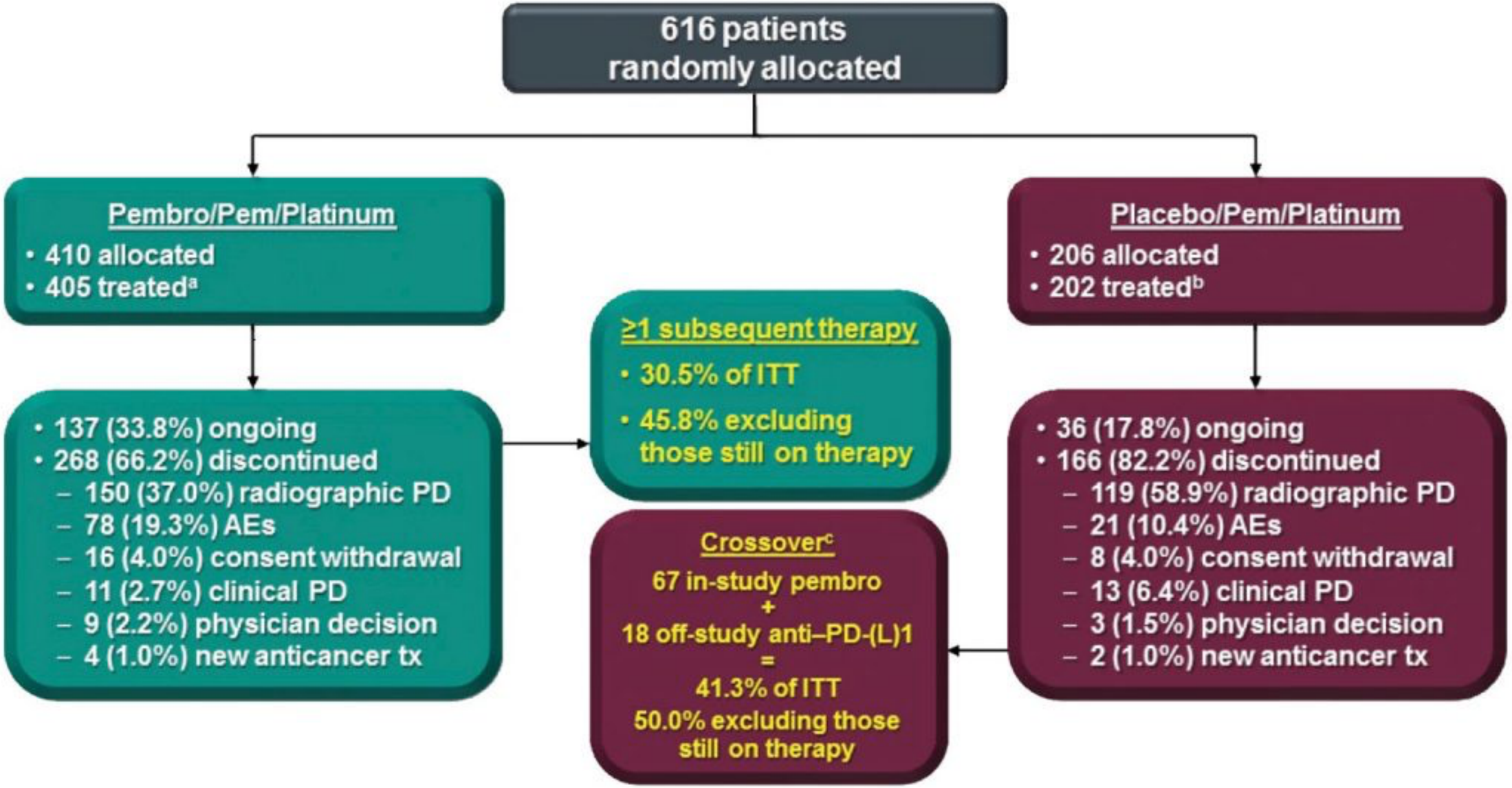
KEYNOTE-189

KEYNOTE-189 (PD1/PDL1-126)



KEYNOTE-189 (PD1/PDL1-126)

Primary Endpoint: OS, PFS
Secondary Endpoint: ORR, DOR, Safety

Non-Sq

化学療法未治療の非小細胞肺癌患者（１次治療）
- EGFR遺伝子変異　陰性
- ALK融合遺伝子　陰性
- PD-L１発現
  (TPS≧1%, 1%<TPS)

R

Pembrolizumab
CBDCA(AUC=5)+Pem(500mg/m2)
or
CDDP(75mg/m2)+Pem(500mg/m2)
（Non-Sq Pem維持療法許容）
Up to 4 cycles

CBDCA(AUC=5)+Pem(500mg/m2)
or
CDDP(75mg/m2)+Pem(500mg/m2)
（Non-Sq Pem維持療法許容）
Up to 4 cycles

	全体		TPS<1%		TPS1-49%		TPS≧50%	
	PFS	OS	PFS	OS	PFS	OS	PFS	OS
Pembrolizumab	8.8ヵ月	未達	6.1ヵ月	15.2ヵ月	9.0ヵ月	未達	9.4ヵ月	未達
	HR=0.52 p<0.00001	HR=0.49 p<0.00001	HR=0.75	HR=0.59	HR=0.55	HR=0.55	HR=0.36	HR=0.42
CBDCA+Pem or CDDP+Pem	4.9ヵ月	11.3ヵ月	5.1ヵ月	12ヵ月	4.9ヵ月	12.9ヵ月	4.7ヵ月	10ヵ月

※後治療としてPD-1/PD-L1抗体のクロスオーバー許容：Pembro群30/410(7.3%)，化療群87/206(42.2%)

A New Era for NSCLC Treatment!

1997 — Discovery of *EGFR* mutations in LUAD sensitive to gefitinib and erlotinib

2000 — Docetaxel shown to benefit patients with 2L NSCLC

2004 — EGFR inhibitors enter clinical development

2006 — Bevacizumab shown activity with cytotoxic therapy in 1L NSCLC

2007 — *ALK* rearrangements identified in NSCLC

2007 — Gefitinib shown better activity than cytotoxic therapy in LUAD

2008 — Pemetrexed shown activity in 1L LUAD

2009 — Crizotinib (first ALK Inhibitor) shown to be effective in ALK positive NSCLC

2010 — TCGA Genomic Characterization of LUSC completed

2010 — Nivolumab shown to be effective in NSCLC

2011 — *RET* and *ROS* fusions described in LUAD

2011 — TCGA Genomic Characterization of LUAC completed

2011 — Crizotinib shown to be superior to cytotoxic therapy in 1L ALK positive NSCLC

2011 — Immune checkpoint blockers shown to be superior to docetaxel in 2L NSCLC

2011 — Osimertinib shown to be effective in NSCLC

2011 — Mutational burden associated with responses to immune checkpoint inhibitors

2011 — Osimertinib shown to be superior to cytotoxic therapy in previously treated *EGFR T790M*

2011 — Alectinib shown to be superior to crizotinib in 1L ALK positive NSCLC

2011 — Pembrolizumab shown activity in PD-L1 high NSCLC

2011 — **Keynote 189**

For untreated non-squamous NSCLC

2018

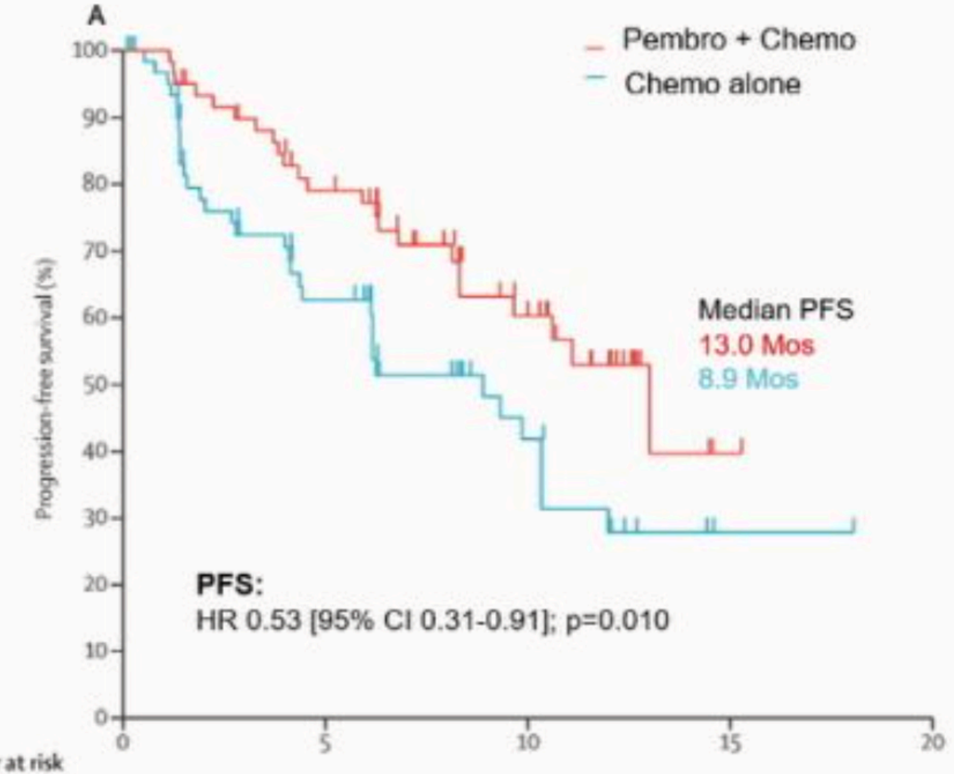
Legend

- Chemotherapy
- Angiogensis
- Genomic
- Targeted Therapy
- Immunotherapy

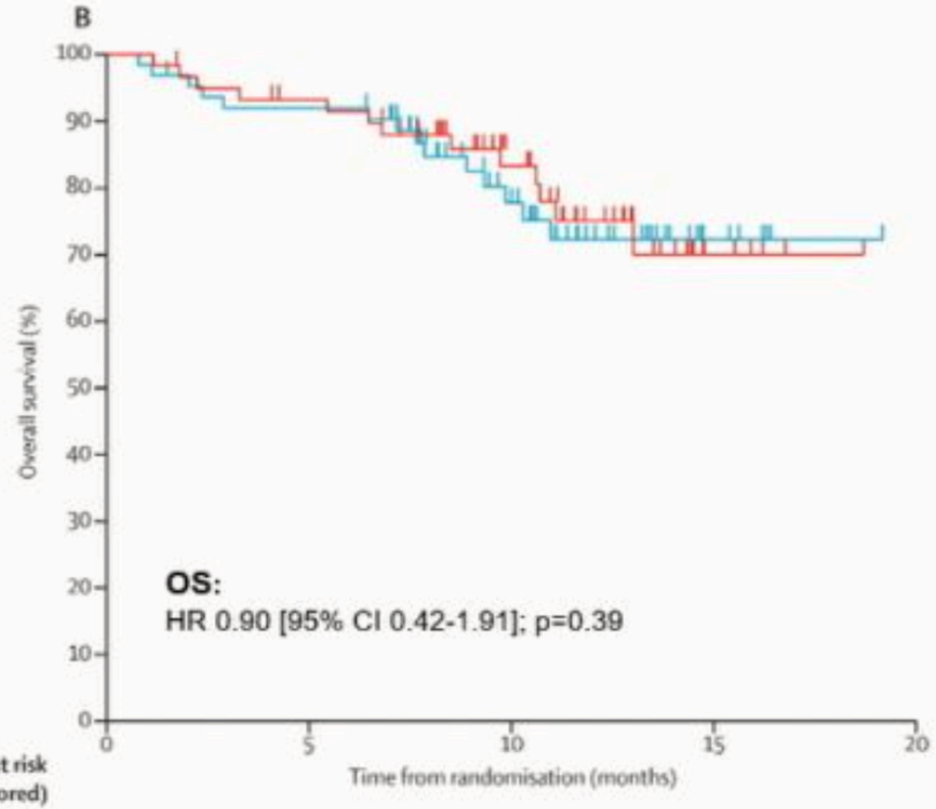
1L = First-line; 2L = Second Line

R S Herbst *et al. Nature* **553**, 446–454 (2018)

Keynote 21: Phase 2 study of carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous NSCLC



Number at risk (number censored)					
Pembrolizumab plus chemotherapy	60 (0)	43 (5)	20 (20)	1 (36)	0 (37)
Chemotherapy	63 (0)	32 (10)	13 (21)	1 (29)	0 (30)



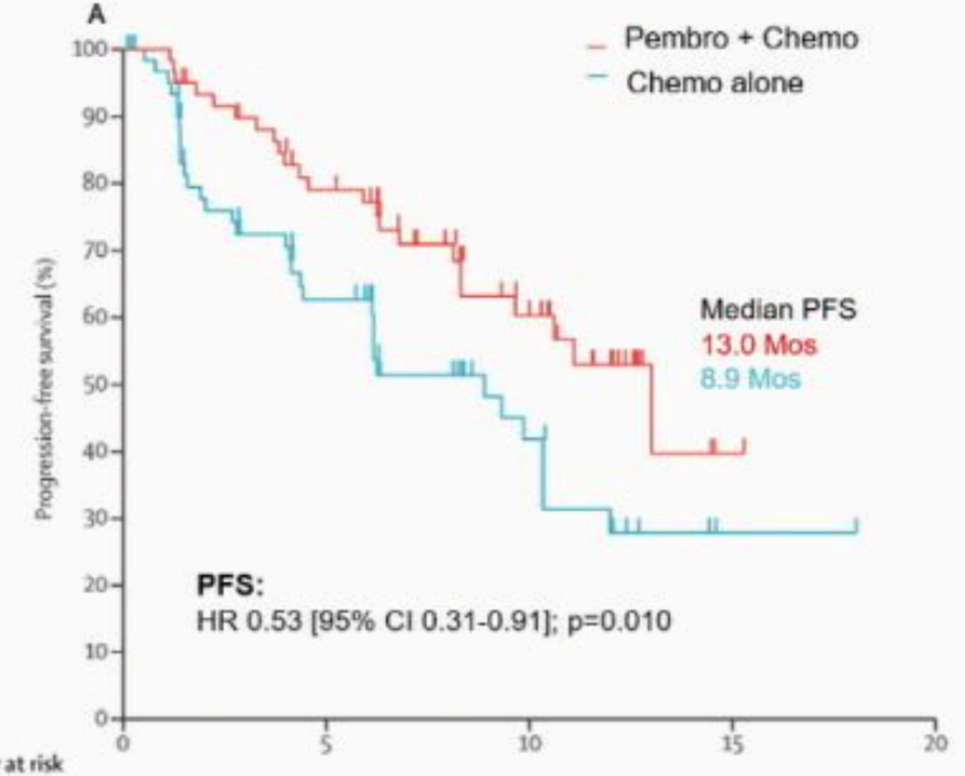
Number at risk (number censored)					
Pembrolizumab plus chemotherapy	60 (0)	53 (3)	33 (18)	5 (42)	0 (47)
Chemotherapy	63 (0)	57 (1)	31 (20)	6 (43)	0 (49)

YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER

Langer CJ et al. *Lancet Onc* 2016 Nov; 17(11):1497-1508

Keynote 21: Phase 2 study of carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous NSCLC



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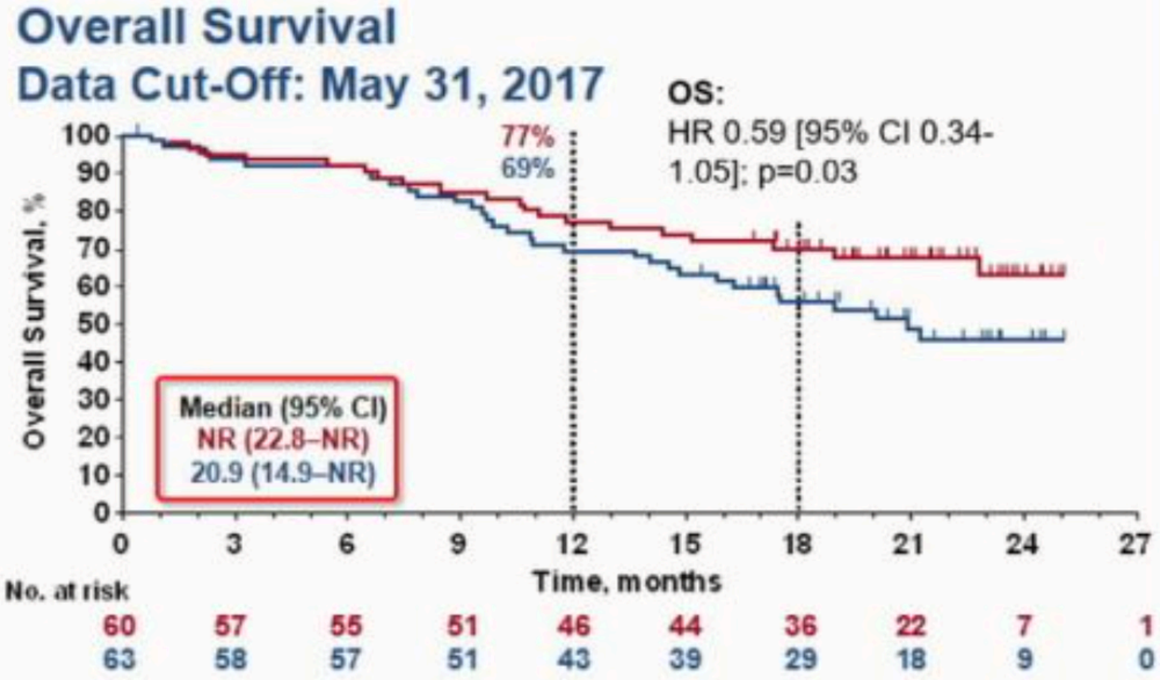

Updated data from WCLC 2017
Langer & Borghaei

YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER

Langer CJ et al. *Lancet Onc* 2016 Nov; 17(11):1497-1508

Keynote 189: Schema (616 patients)

Key Eligibility Criteria

- Untreated stage IV nonsquamous NSCLC
- No sensitizing *EGFR* or *ALK* alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification Factors

- PD-L1 expression (TPS[a] <1% vs ≥1%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

R (2:1)

N = 410

Pembrolizumab 200 mg + Pemetrexed 500 mg/m^2 + Carboplatin AUC 5 OR Cisplatin 75 mg/m^2 Q3W for 4 cycles

→ Pembrolizumab 200 mg Q3W for up to 31 cycles + Pemetrexed 500 mg/m^2 Q3W

N = 206

Placebo (normal saline) + Pemetrexed 500 mg/m^2 + Carboplatin AUC 5 OR Cisplatin 75 mg/m^2 Q3W for 4 cycles

→ Placebo (normal saline) for up to 31 cycles + Pemetrexed 500 mg/m^2 Q3W

PD[b] → Pembrolizumab 200 mg Q3W for up to 35 cycles

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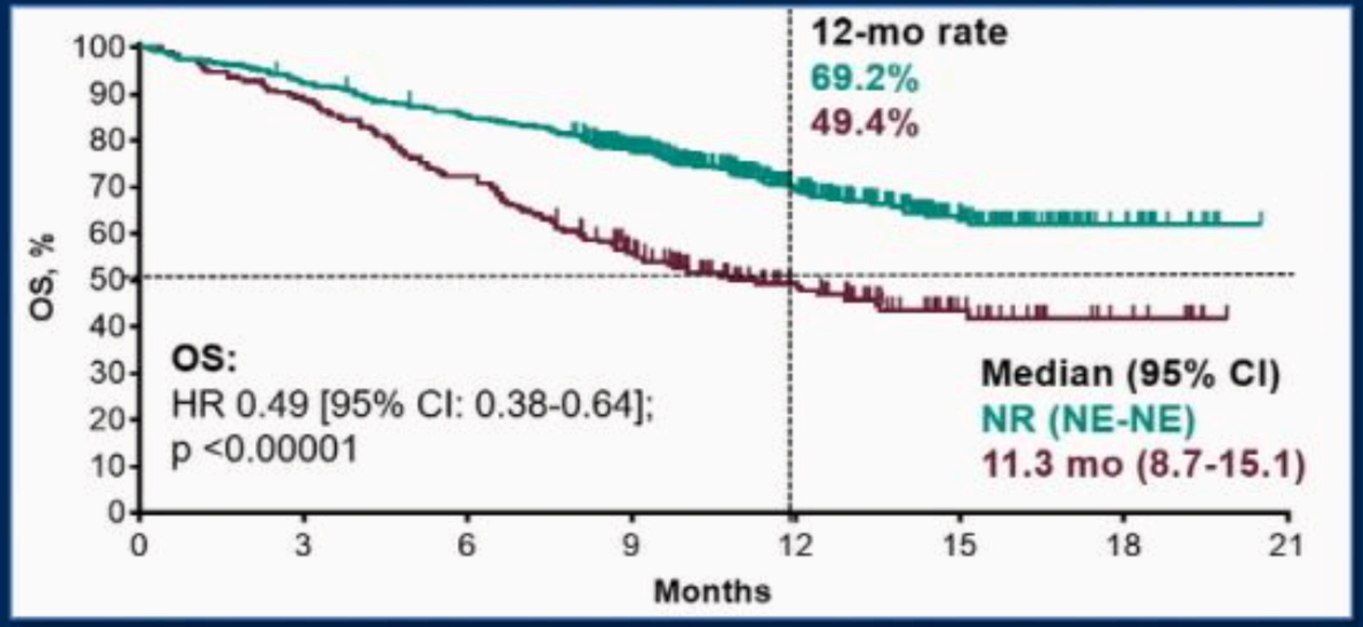
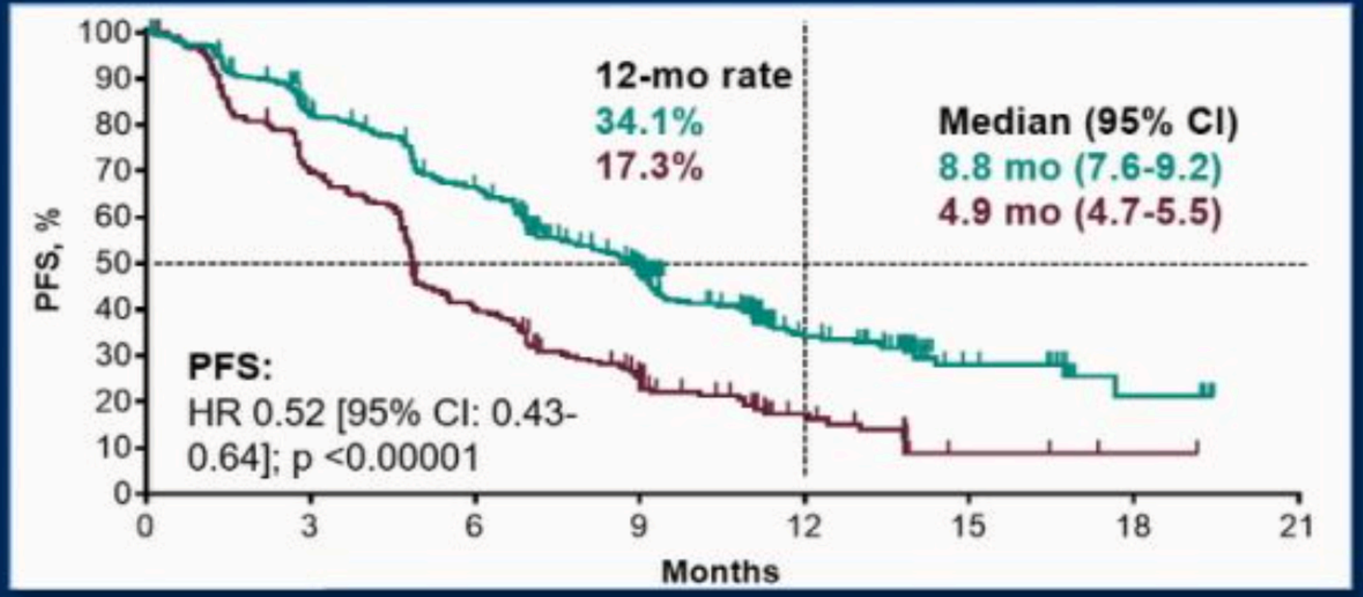
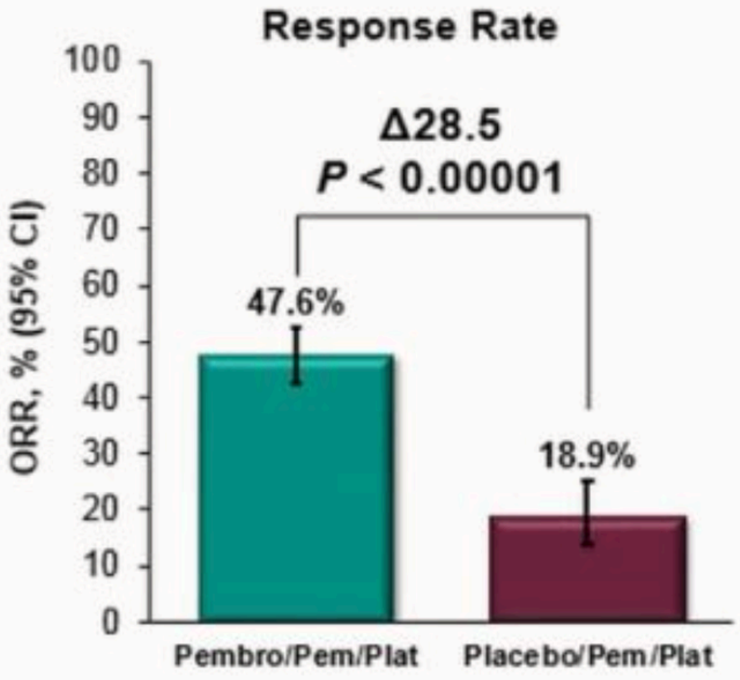
[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety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

Keynote 189: Met All Primary Endpoints







Subgroup Analyses

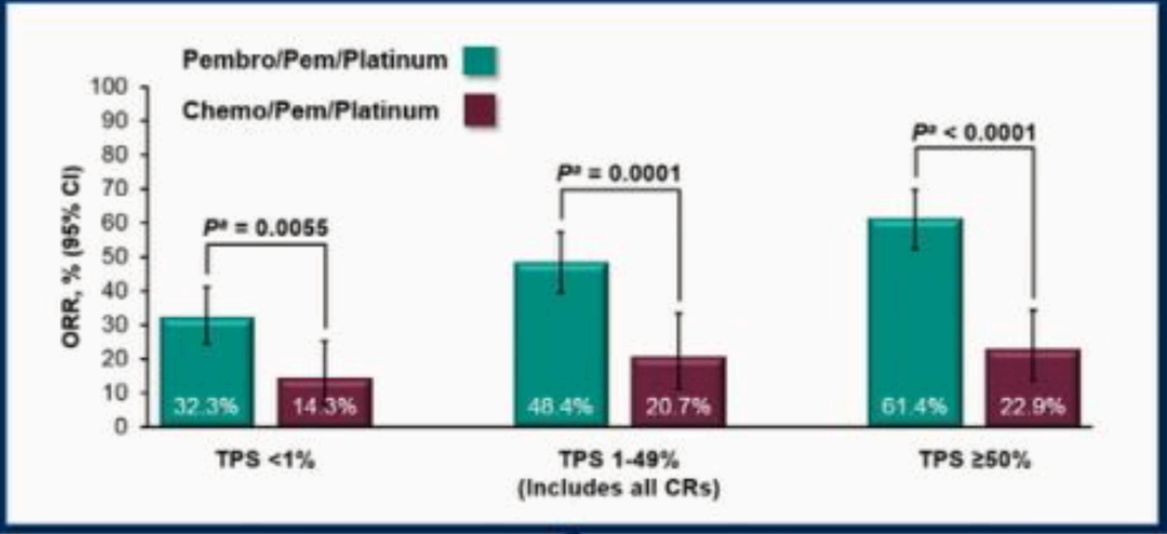
OS: Positive across all subgroups

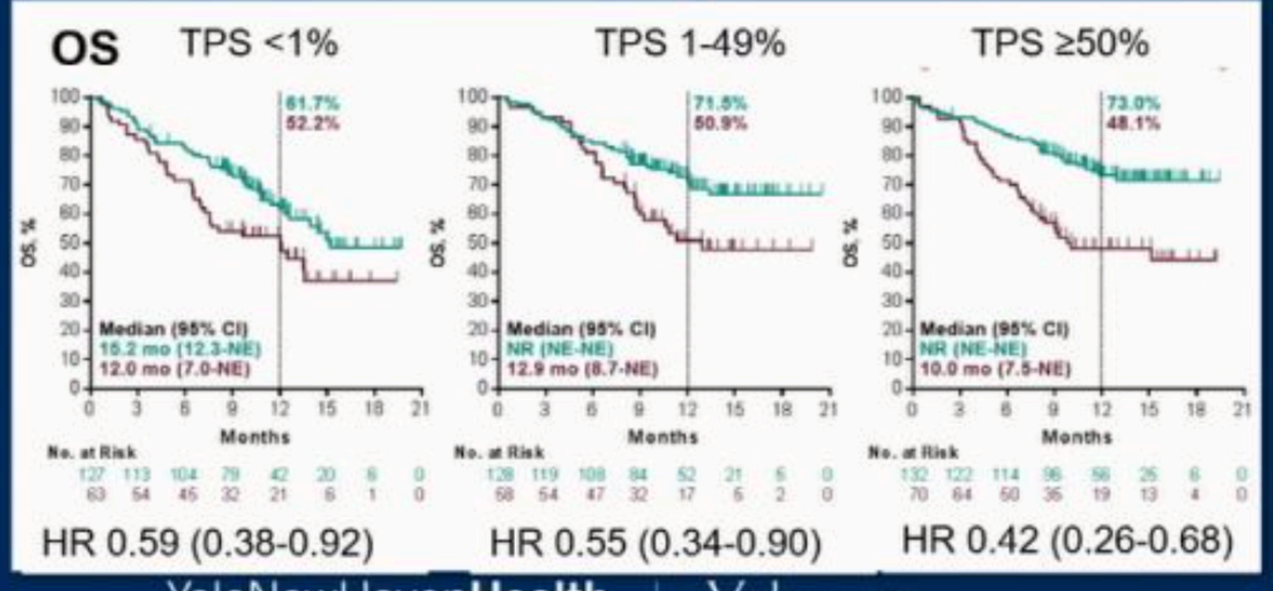
PFS: Positive across all subgroups except for PD-L1 TPS <1%

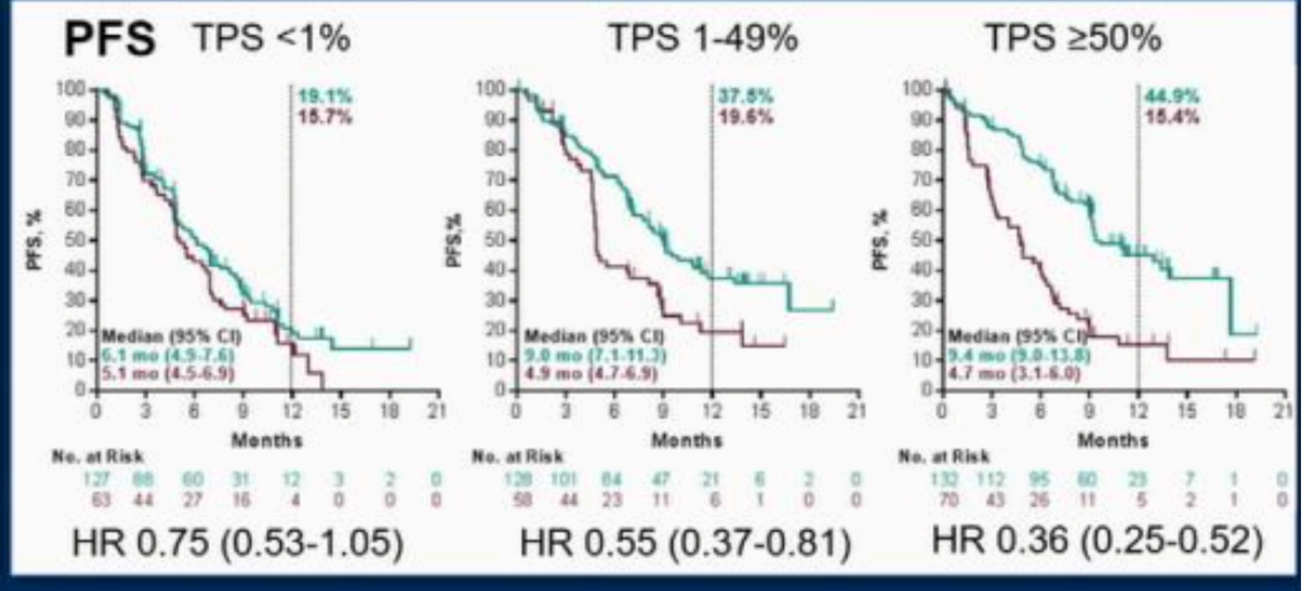
Summary of Adverse Events

	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

Keynote 189: Results by PD-L1 status (Exploratory)







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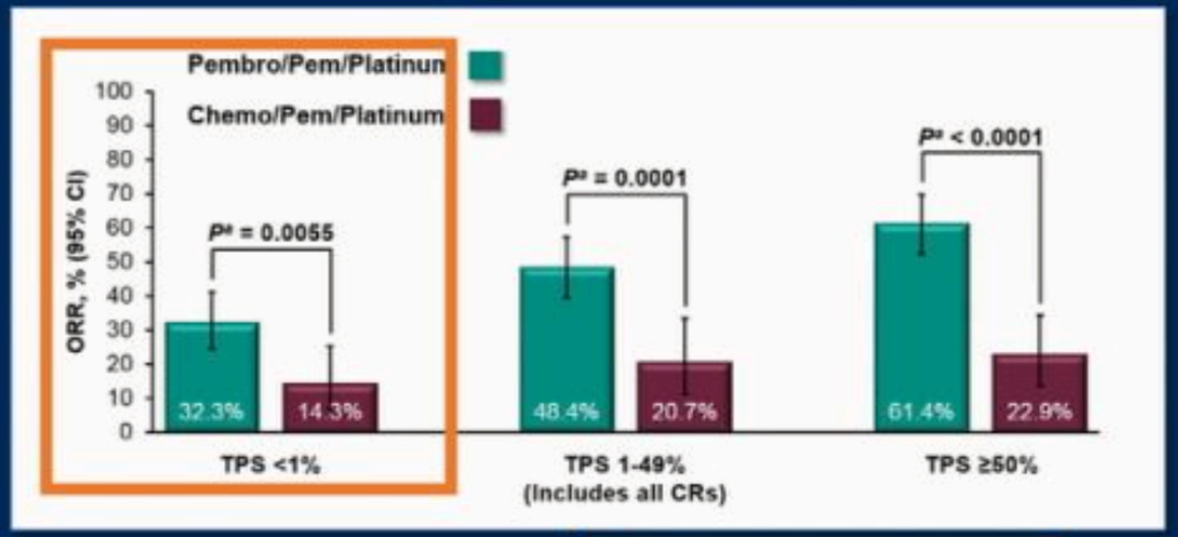
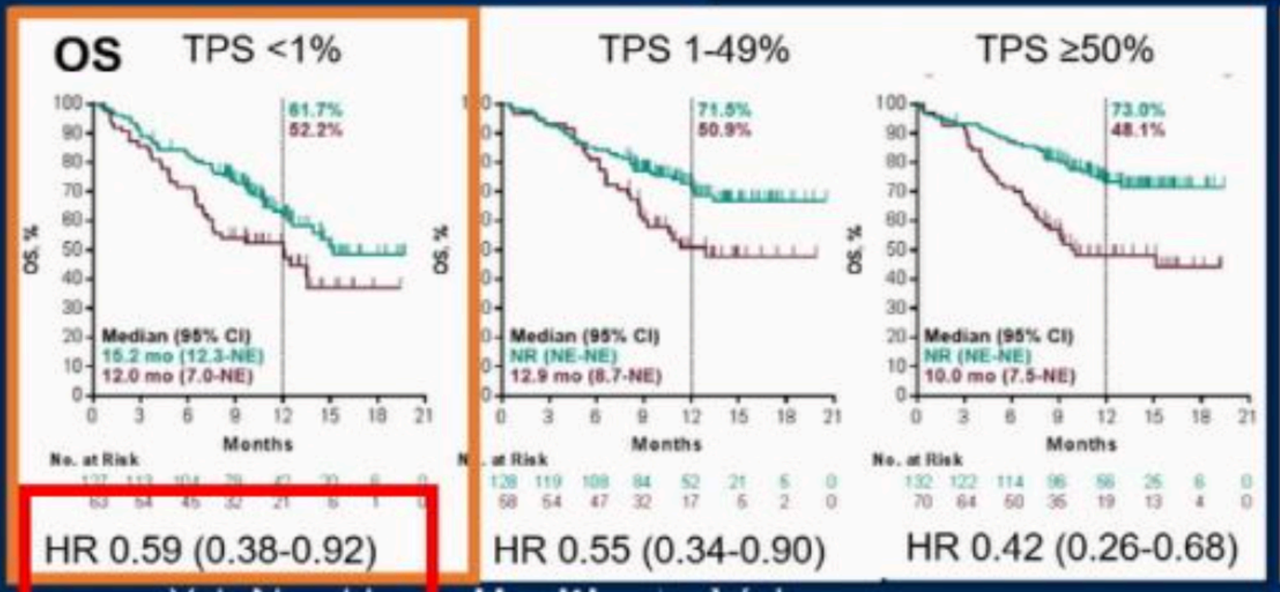
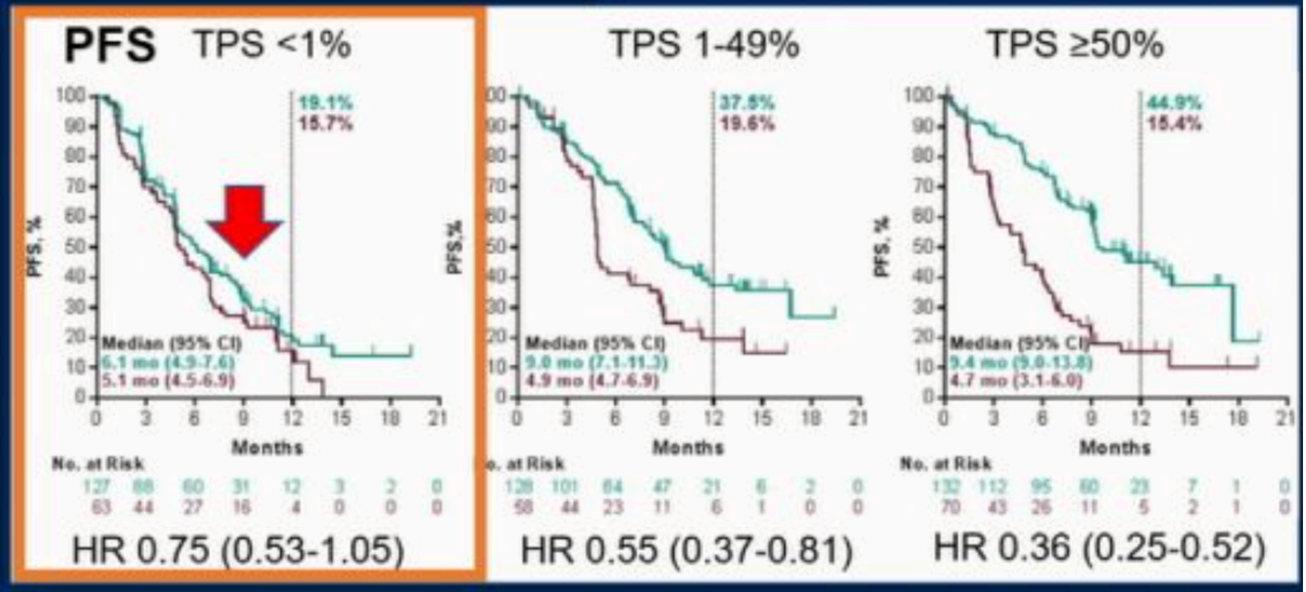
Keynote 189: Results by PD-L1 status (Exploratory)



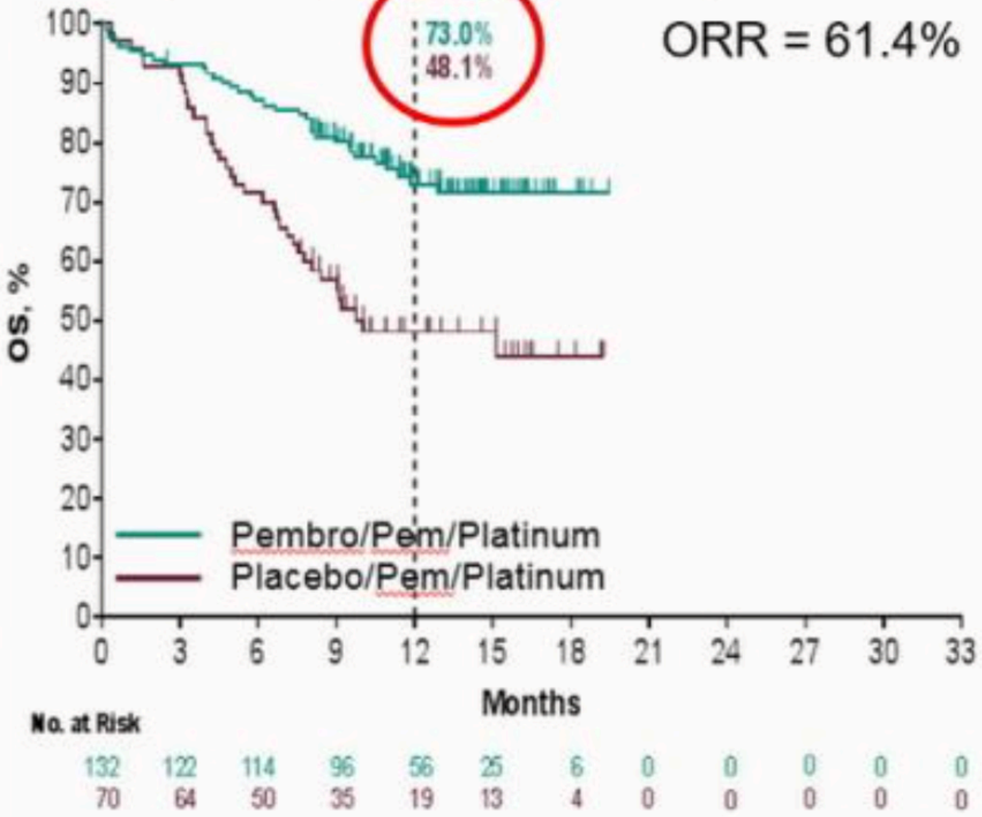




KEYNOTE-189 (TPS ≥50%) vs KEYNOTE-024

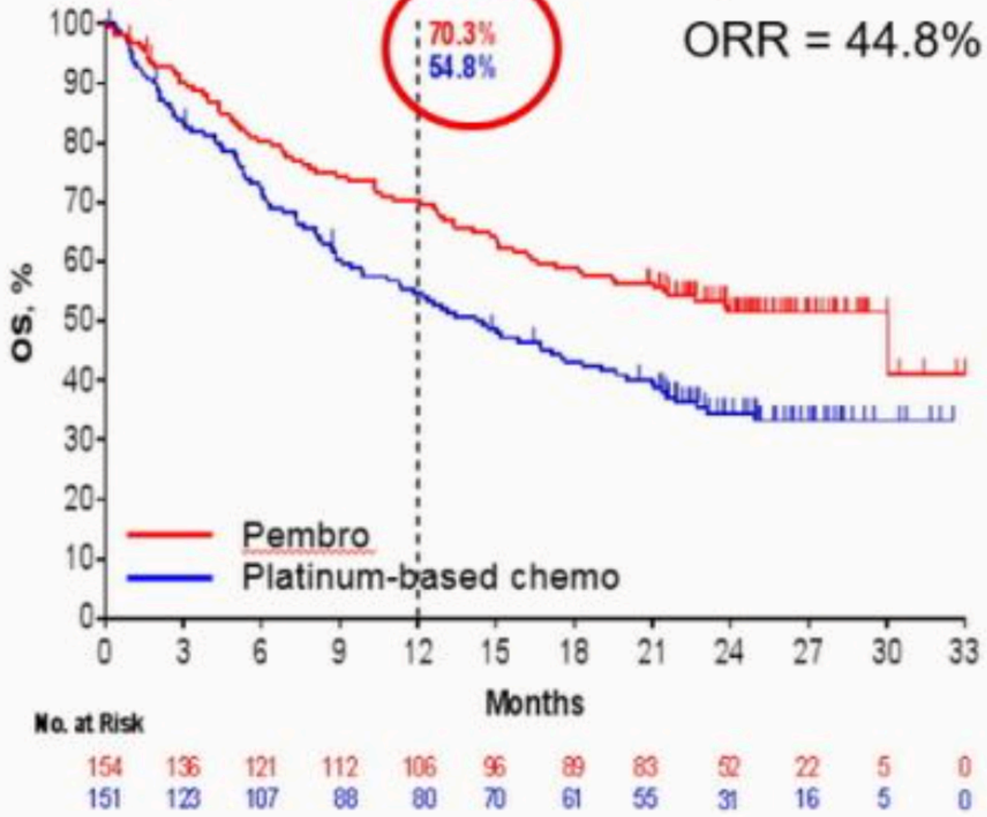
KEYNOTE-189

HR (95% CI): 0.42 (0.26-0.68); *P* = 0.0001[a]



KEYNOTE-024[1]

HR (95% CI): 0.63 (0.47-0.86); *P* = 0.002[a]

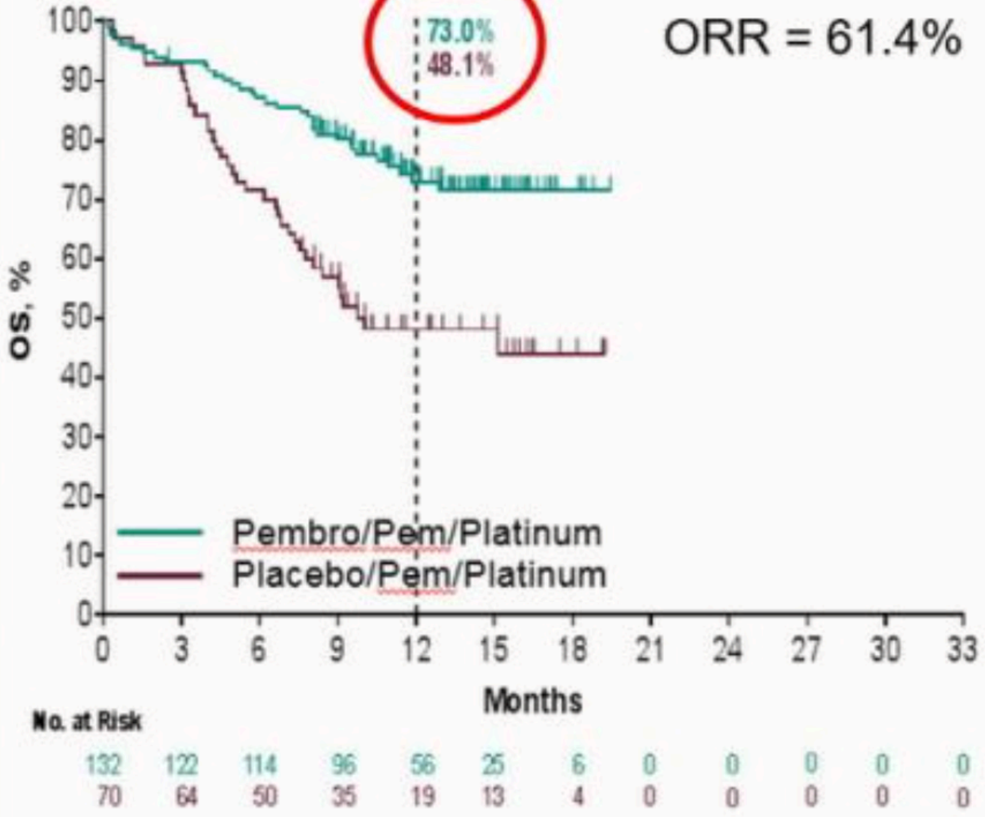


[a]Nominal *P* value. 1. Brahmer J et al. 18th IASLC World Conference on Lung Cancer; Oct 15-18, 2017; abstract OA17.06.

KEYNOTE-189 (TPS ≥50%) vs KEYNOTE-024

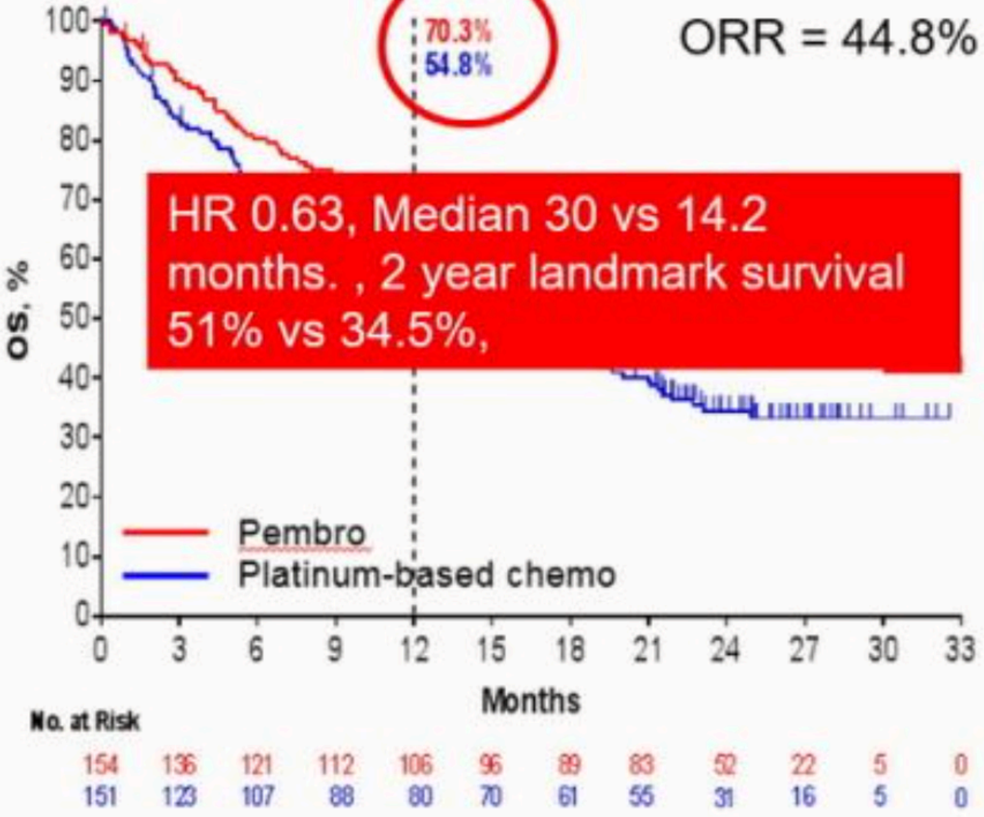
KEYNOTE-189

HR (95% CI): 0.42 (0.26-0.68); *P* = 0.0001[a]



KEYNOTE-024[1]

HR (95% CI): 0.63 (0.47-0.86); *P* = 0.002[a]



[a]Nominal *P* value. 1. Brahmer J et al. 18th IASLC World Conference on Lung Cancer; Oct 15-18, 2017; abstract OA17.06.