

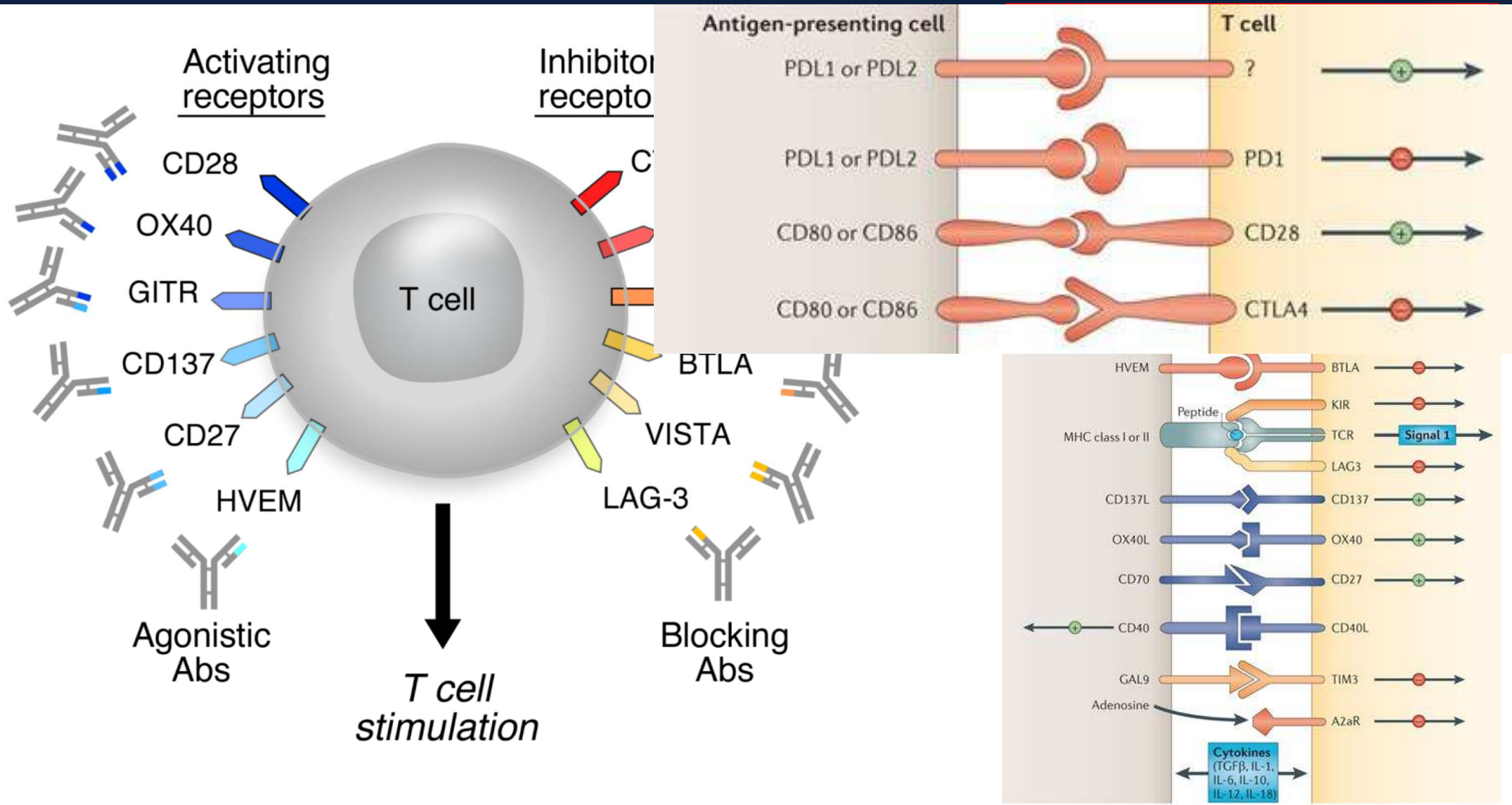


Optimal 1L NSCLC treatment with Immunotherapy

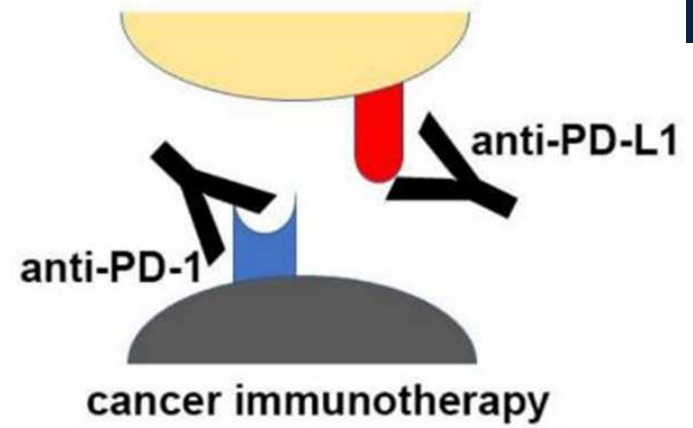
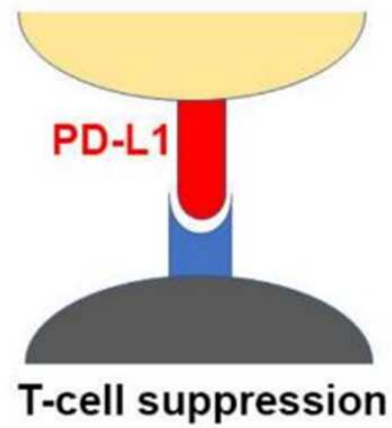
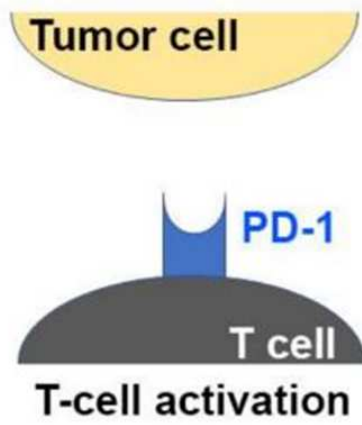
義大癌治療醫院
胸腔內科
陳俊榮醫師

Disclaimer

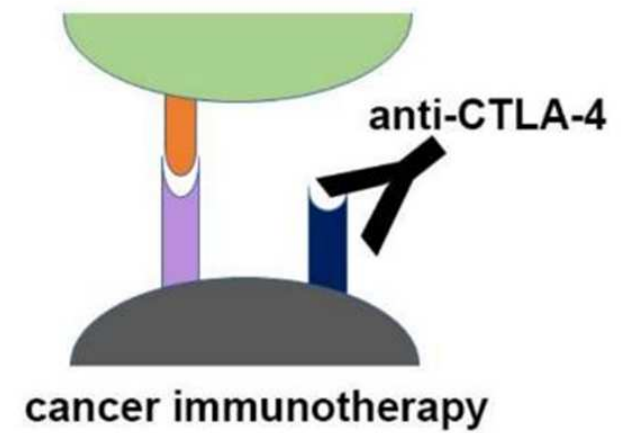
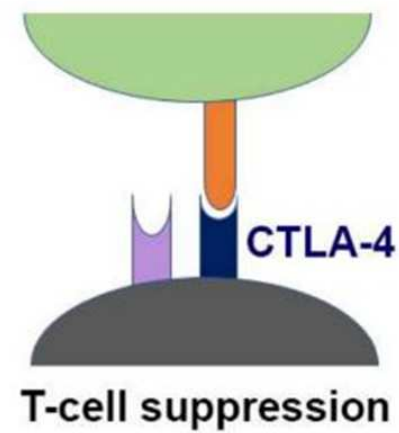
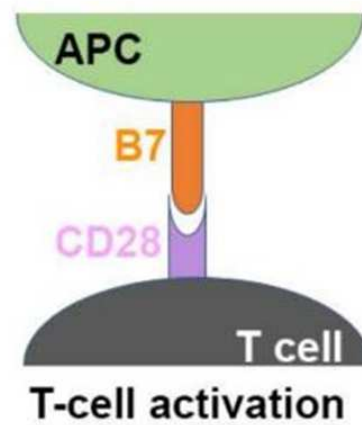
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A



B





National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 6.2020 — June 15, 2020

[NCCN.org](https://www.nccn.org)

[NCCN Guidelines for Patients®](#)

PD-L1 ≥1%

- **First-line therapy***
 - ▶ Pembrolizumab³⁴⁻³⁶
 - ▶ (Carboplatin or cisplatin)/pemetrexed/pembrolizumab (nonsquamous)³⁷
 - ▶ Carboplatin/paclitaxel/bevacizumab**/atezolizumab (nonsquamous)³⁸
 - ▶ Carboplatin/(paclitaxel or albumin-bound paclitaxel)/pembrolizumab (squamous)³⁹
 - ▶ Carboplatin/albumin-bound paclitaxel/atezolizumab (nonsquamous)⁴⁰
 - ▶ Nivolumab/ipilimumab⁴¹
 - ▶ Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (nonsquamous)⁴²
 - ▶ Nivolumab + ipilimumab + paclitaxel + carboplatin (squamous)⁴²

PD-L1 ≥50%

- **First-line therapy**
 - ▶ Atezolizumab⁴³

PD-L1 EXPRESSION POSITIVE (≥50%)^{jj}

FIRST-LINE THERAPY^{oo}

PD-L1 expression positive (≥50%) and *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET* exon 14 skipping mutation, and *RET* negative and no contraindications to PD-1 or PD-L1 inhibitors^{hhh}

Adenocarcinoma, large cell, NSCLC NOS

Squamous cell carcinoma

PS 0-2

- **Preferred**
Pembrolizumab (category 1)
or
(Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)
or
Atezolizumab

- **Other Recommended**
Carboplatin + paclitaxel + bevacizumab^{ss} + atezolizumab (category 1)
or
Carboplatin + albumin-bound paclitaxel + atezolizumab
or
Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)
- **Useful in Certain Circumstances**
Nivolumab + ipilimumab

- **Preferred**
Pembrolizumab (category 1)
or
Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)
or
Atezolizumab

- **Other Recommended**
Nivolumab + ipilimumab + paclitaxel + carboplatin
- **Useful in Certain Circumstances**
Nivolumab + ipilimumab

Response or stable disease

Progression

- Continuation maintenance^{oo}
- Pembrolizumab (category 1)ⁱⁱⁱ
 - Pembrolizumab + pemetrexed (category 1)^{jjj}
 - Atezolizumab and bevacizumab (category 1)^{kkk}
 - Atezolizumab^{lll}

See Systemic Therapy or Subsequent Therapy,^{mmm}
[Adenocarcinoma \(NSCL-32\)](#)

Response or stable disease

Progression

- Continuation maintenance^{oo}
- Pembrolizumab (category 1)^{iii,nnn}
 - Atezolizumab^{lll}

See Systemic Therapy or Subsequent Therapy,^{mmm}
[Squamous Cell Carcinoma \(NSCL-33\)](#)

[See PD-L1 expression positive \(≥1%–49%\) NSCL-31](#)

PD-L1 EXPRESSION POSITIVE (≥1%–49%)^{jj}

FIRST-LINE THERAPY^{oo}

PD-L1 expression positive (≥1%–49%) and *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET* exon 14 skipping mutation, and *RET* negative and no contraindications to PD-1 or PD-L1 inhibitors^{hhh}

PS 0–2

Adenocarcinoma, large cell, NSCLC NOS

Squamous cell carcinoma

Preferred
(Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)

Other Recommended
Carboplatin + paclitaxel + bevacizumab^{ss} + atezolizumab (category 1)

or
Carboplatin + albumin-bound paclitaxel + atezolizumab

or
Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)

Useful in Certain Circumstances
Nivolumab + ipilimumab or Pembrolizumab (category 2B)^{ooo}

Preferred
Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)

Other Recommended
Nivolumab + ipilimumab + paclitaxel + carboplatin

Useful in Certain Circumstances
Nivolumab + ipilimumab or Pembrolizumab (category 2B)^{ooo}

Response or stable disease

Progression

Continuation maintenance^{oo}
• Pembrolizumab (category 1)ⁱⁱⁱ
• Pembrolizumab + pemetrexed (category 1)^{jjj}
• Atezolizumab and bevacizumab (category 1)^{kkk}
• Atezolizumab^{lll}

See Systemic Therapy or Subsequent Therapy,^{mmm}
[Adenocarcinoma \(NSCL-32\)](#)

Response or stable disease

Progression

Continuation maintenance^{oo}
• Pembrolizumab^{iii,nnn}

See Systemic Therapy or Subsequent Therapy,^{mmm}
[Squamous Cell Carcinoma \(NSCL-33\)](#)

[See PD-L1 expression positive \(≥50%\) NSCL-30](#)

Four FDA Approvals for First-line Advanced or Metastatic NSCLC

October 2016

FIRST-LINE MONOTHERAPY

For nonsquamous or squamous mNSCLC with high PD-L1 expression (TPS $\geq 50\%$) and no EGFR or ALK genomic tumor aberrations.

August 2018

FIRST-LINE COMBINATION

For nonsquamous mNSCLC with no EGFR or ALK genomic tumor aberrations, in combination with pemetrexed and platinum chemotherapy.

October 2018

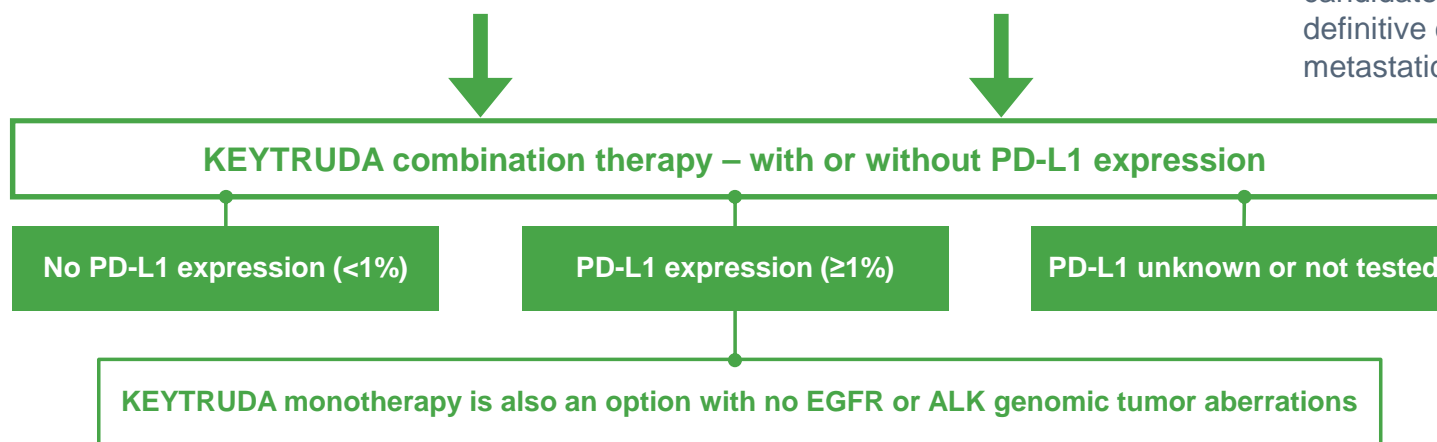
FIRST-LINE COMBINATION

For squamous mNSCLC, in combination with carboplatin + paclitaxel or paclitaxel protein-bound.

April 2019





FIRST-LINE MONOTHERAPY

For nonsquamous or squamous NSCLC with PD-L1 expression (TPS $\geq 1\%$), with no EGFR or ALK genomic tumor aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic.



ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; FDA = Food and Drug Administration; mNSCLC = metastatic non-small cell lung cancer; PD-L1 = programmed death ligand 1.

Summary of National Comprehensive Cancer Network[®] (NCCN[®]) Recommendations for Pembrolizumab (KEYTRUDA) as First-line Treatment in mNSCLC^{1,a}

	Pembrolizumab (KEYTRUDA) In Combination With Chemotherapy	Pembrolizumab (KEYTRUDA) Monotherapy
TPS ≥50% ^b	CATEGORY 1 ^c and PREFERRED ^d 	CATEGORY 1 ^c and PREFERRED ^d 
TPS 1%–49% ^b	CATEGORY 1 ^c and PREFERRED ^d 	CATEGORY 2B ^e Useful in Certain Circumstances ^f
TPS <1% ^b	CATEGORY 1 ^c and PREFERRED ^d 	Not recommended

^{ooo} Pembrolizumab monotherapy can be considered in PD-L1 1%–49%, in patients with poor PS or other contraindications to combination chemotherapy.

^aSee the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for detailed recommendations, including other options. ^bPatients with negative test results for EGFR, ALK, ROS1, or BRAF. ^cNCCN Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. ^dNCCN Preferred interventions are interventions based on superior efficacy, safety, and evidence; and, when appropriate, affordability. ^eNCCN Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. ^fPembrolizumab monotherapy can be considered in PD-L1 1%–49%, in patients with poor performance status, or other contraindications to combination chemotherapy.

ALK = anaplastic lymphoma kinase; BRAF = B-Raf proto-oncogene, serine/threonine kinase; EGFR = epidermal growth factor receptor; mNSCLC = metastatic non-small cell lung cancer; PD-L1 = programmed death ligand 1; ROS1 = ROS proto-oncogene 1, receptor tyrosine kinase; TPS = tumor proportion score.

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1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Non-Small Cell Lung Cancer V.3.2020.

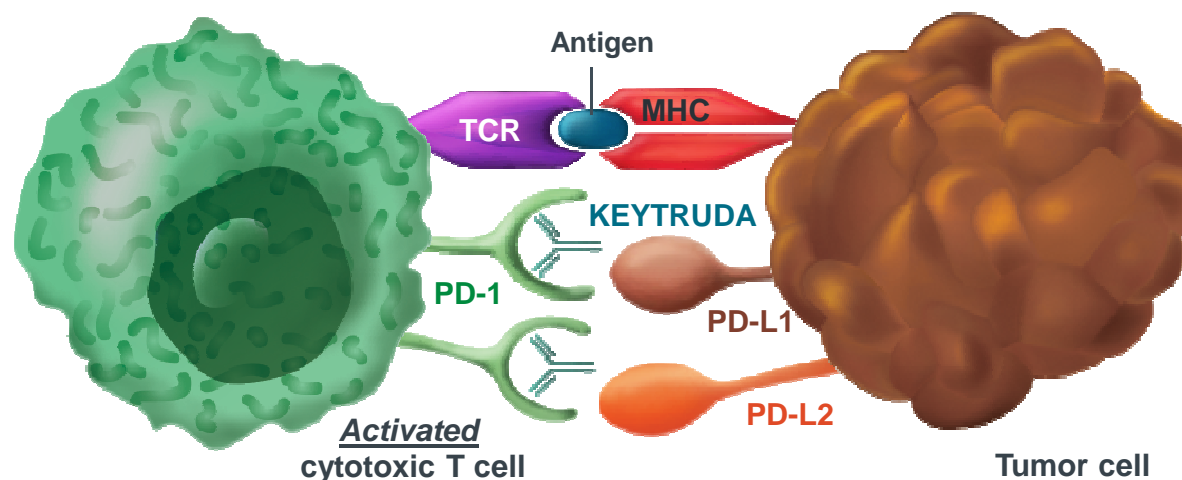
© National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed February 12, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org.





KEYTRUDA and Chemotherapy: Combining 2 Different Mechanisms of Action

KEYTRUDA Activates the Antitumor Immune Response



- KEYTRUDA is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2.
- KEYTRUDA releases PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.
- While having an effect on the tumor cell, this could also affect normal, healthy cells.¹

MHC = major histocompatibility complex; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; TCR = T-cell receptor.
1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252–264.

Program Highlights

Discussion of:



A patient with nonsquamous mNSCLC

Case sharing



KEYNOTE-189 Final analysis (ASCO 2020)

A double-blind, phase 3 trial¹



A patient with squamous mNSCLC

Case sharing



KEYNOTE-407 Final analysis (ESMO 2019)

A double-blind, phase 3 trial²

mNSCLC = metastatic non-small cell lung cancer.

1. Rodríguez-Abreu D et al. *ASCO 2020*. 2. Paz-Ares L et al. *ESMO 2019*

Protocol-Specified Final Analysis of KEYNOTE-189: Pemetrexed-Platinum Chemotherapy With or Without Pembrolizumab in Patients With Previously Untreated Metastatic Nonsquamous NSCLC

D. Rodríguez-Abreu¹; S.F. Powell²; M.J. Hochmair³; S. Gadgeel⁴;
E. Esteban⁵; E. Felip⁶; G. Speranza⁷; M. Dómine⁸; S.Y.-S. Cheng⁹;
H.G. Bischoff¹⁰; N. Peled¹¹; M. Reck¹²; R. Hui¹³; E.B. Garon¹⁴;
M. Boyer¹⁵; T. Kurata¹⁶; J. Yang¹⁷; T. Bas¹⁷; F. Souza¹⁷; M.C. Garassino¹⁸

¹Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; ²Sanford Health, Sioux Falls, SD, USA; ³Department of Respiratory and Critical Care Medicine and Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, Vienna, Austria; ⁴Karmanos Cancer Institute, Detroit, MI, USA (currently at University of Michigan, Ann Arbor, MI, USA); ⁵Hospital Universitario Central de Asturias, Oviedo, Spain; ⁶Vall d'Hebron University, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; ⁷Centre Intégré de Cancérologie de la Montérégie, Hôpital Charles-Le Moyne, Greenfield Park, QC, Canada; ⁸Hospital Universitario Fundación Jiménez Díaz, IIS-FJD, Madrid, Spain; ⁹Sunnybrook Health Sciences Centre, Toronto, ON, Canada; ¹⁰Thoraxklinik, Heidelberg, Germany; ¹¹Davidoff Cancer Center, Tel Aviv University, Petah Tikva, Israel (currently at Soroka Medical Center, Ben-Gurion University, Beer-Sheeva, Israel); ¹²LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; ¹³Westmead Hospital and University of Sydney, Sydney, NSW, Australia; ¹⁴David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; ¹⁵Chris O'Brien Lifehouse, Camperdown, NSW, Australia; ¹⁶Kansai Medical University Hospital, Osaka, Japan; ¹⁷Merck & Co., Inc., Kenilworth, NJ, USA; ¹⁸Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

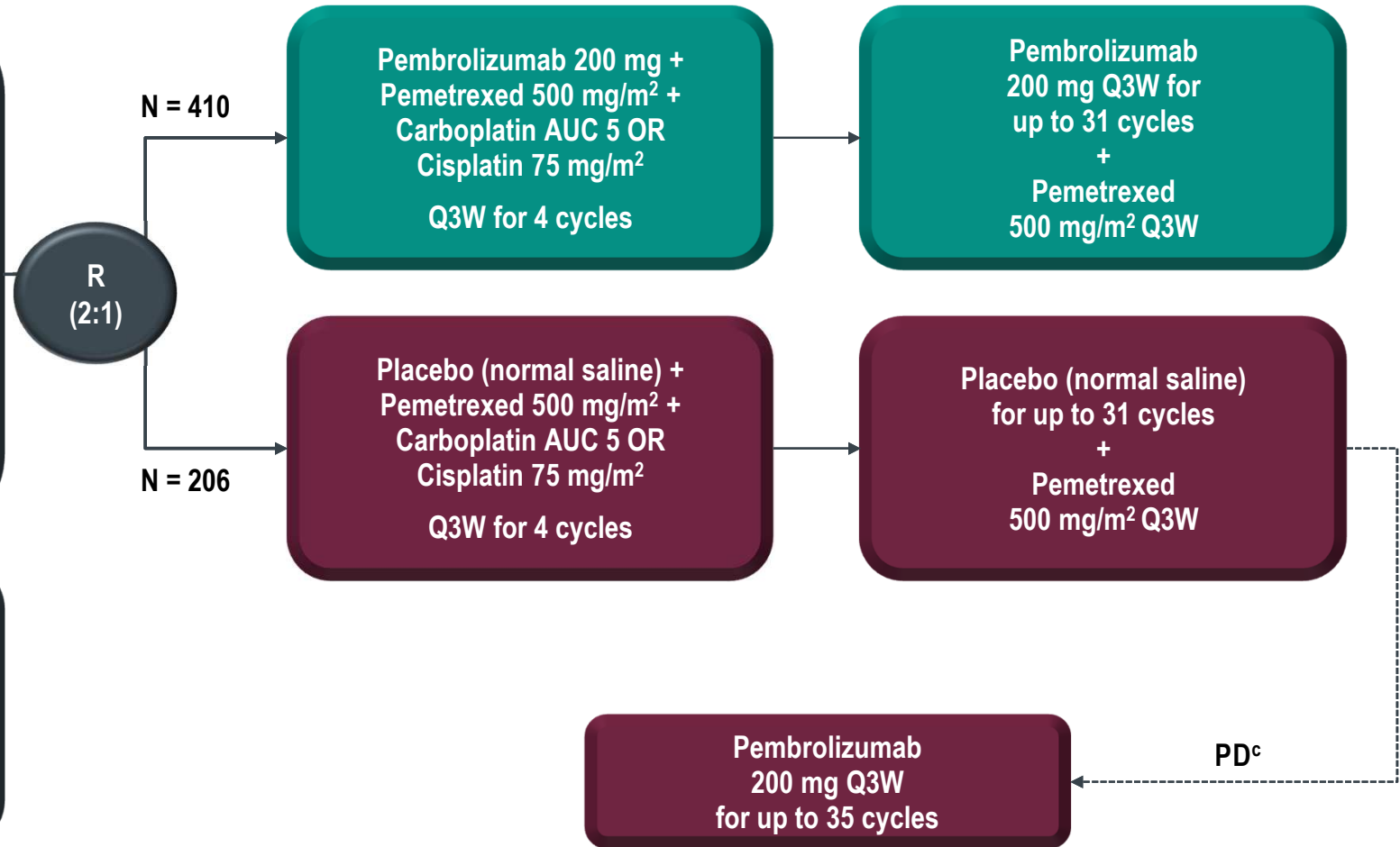
KEYNOTE-189 Study Design

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^a
- No pneumonitis requiring systemic steroids

Stratification Factors

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



^aPatients with asymptomatic untreated brain metastases (without neurological symptoms, no requirement for corticosteroids, no or minimal surrounding edema, and no lesion >1.5 cm) were eligible, but required regular brain imaging. Those with previously treated brain metastases were eligible if clinically stable for at least 2 weeks and, had no evidence of new or enlarging brain metastases and had been off steroids 3 days prior to dosing with study medication. ^bPercentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. ^cPatients could cross over 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.

1. Gandhi L et al. N Engl J Med 2018;378:2078–2092 (and supplementary appendix); 2. Gandhi L et al. Presented at the 2018 American Association for Cancer Research (AACR) Annual Meeting, 14–18 April, 2018, Chicago, USA.

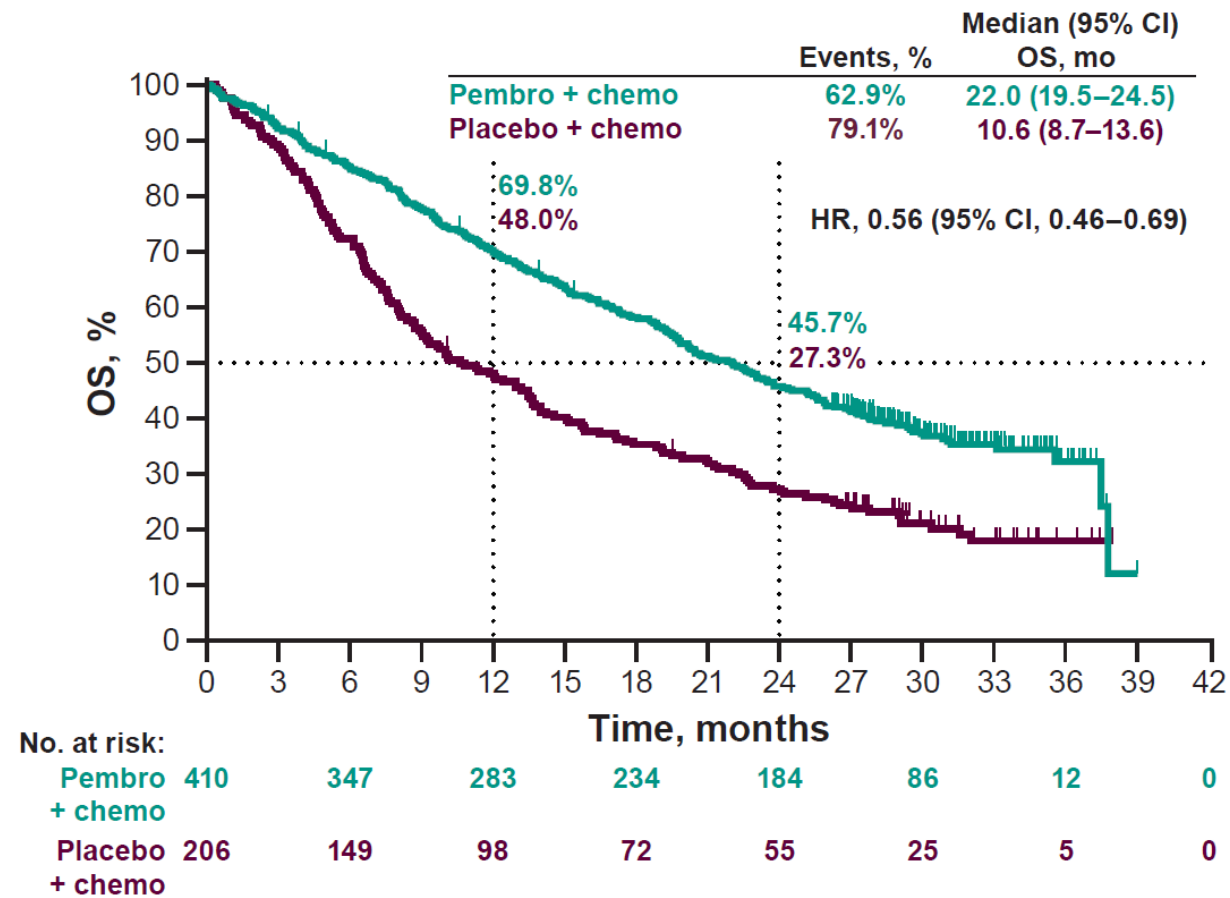
Statistical Analysis Considerations

- HRs and 95% CI were based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS $\geq 1\%$ vs $< 1\%$), platinum chemotherapy (cisplatin vs carboplatin), and smoking status (never vs former/current)
- No alpha was assigned to these analyses
- Events for PFS2 analysis were characterized as:
 - Time from randomization to investigator-assessed disease progression that led to cessation of second-line therapy
 - Start of third-line therapy for patients who stopped second-line therapy without disease progression
 - Time from randomization to death for patients who either stopped second-line therapy without disease progression and did not initiate third-line therapy or did not receive second-line therapy
 - Patients were censored for PFS2 at the time of last known survival if they were alive and either had not received second-line therapy or had stopped second-line therapy without disease progression and had not initiated third-line therapy.
- Data cutoff date for this protocol-specified final analysis was May 20, 2019
 - Median time from randomization to data cutoff was 31.0 (range, 26.5–38.8) months
 - Median follow-up (time from randomization to death or data cutoff) was 18.8 (range, 0.2–38.8) months

Patients

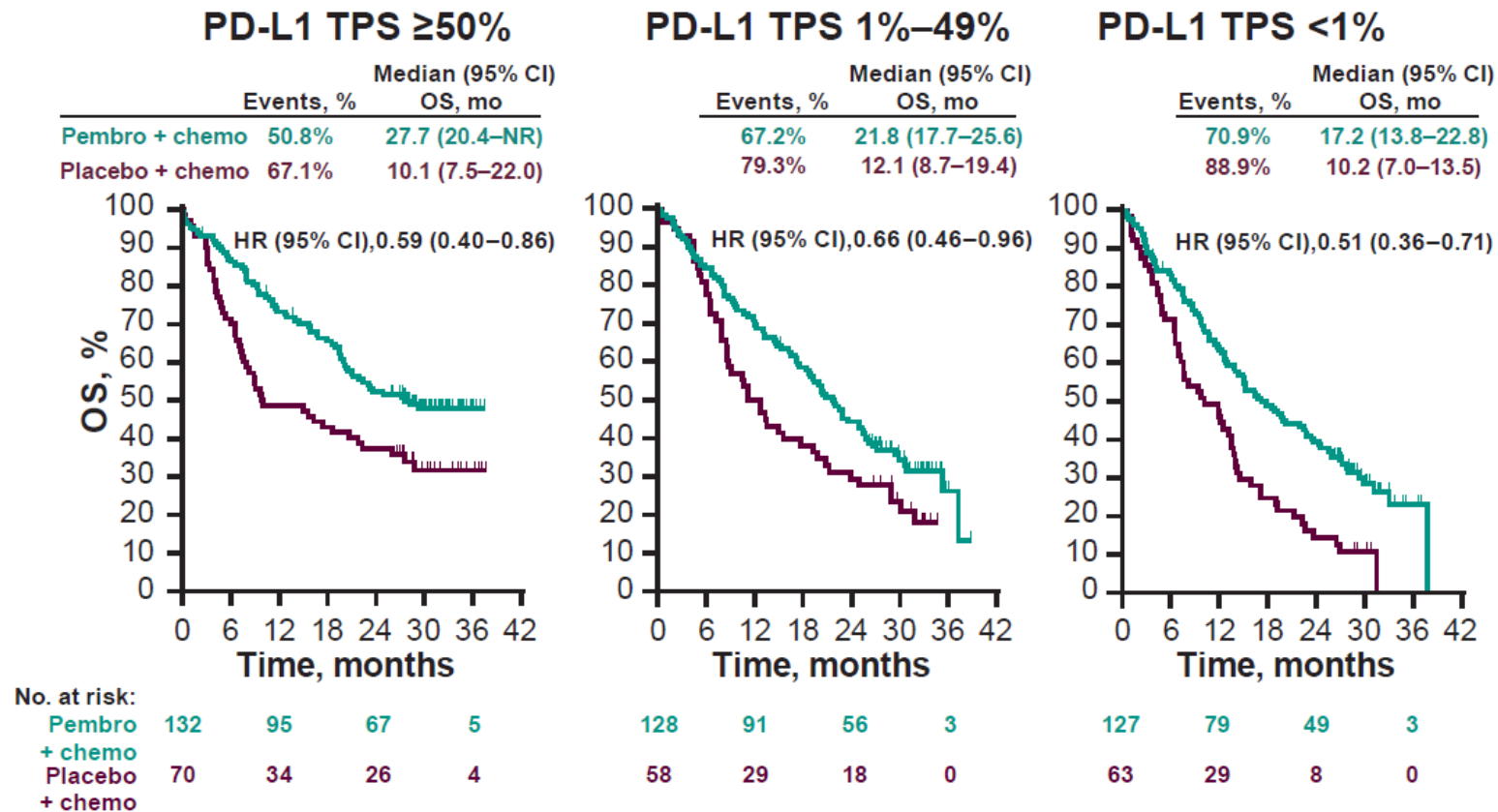
- 17 patients in the pembrolizumab plus pemetrexed-platinum arm and 1 patient in the placebo plus pemetrexed-platinum arm were still receiving initially assigned treatment at the time of data cutoff
 - In the placebo plus pemetrexed-platinum arm, 84 patients received on-study pembrolizumab crossover treatment; 29 additional patients received subsequent anti-PD-1 or anti-PD-L1 immunotherapy (pembrolizumab, nivolumab, atezolizumab, or avelumab)

Kaplan-Meier Estimate of OS in the ITT Population



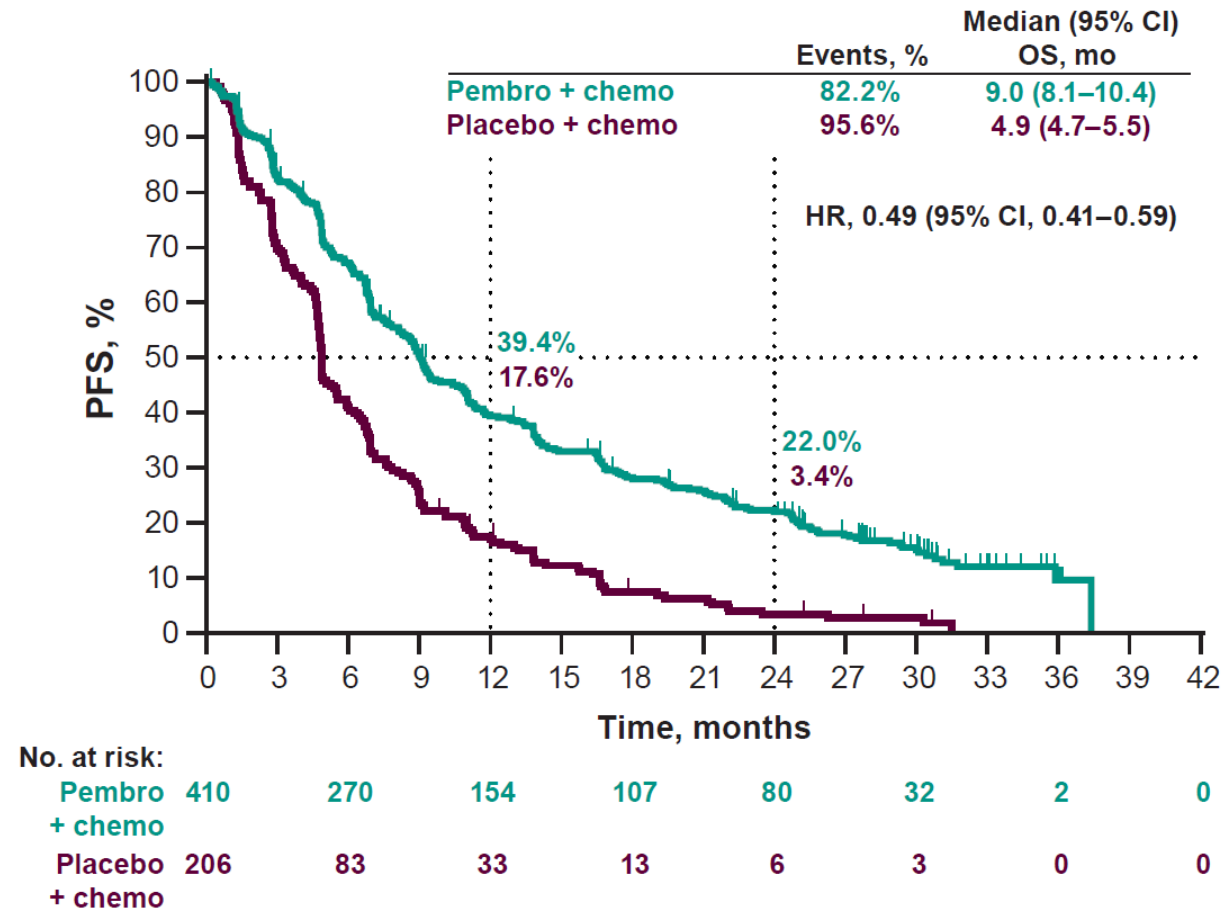
Chemo, chemotherapy with pemetrexed + platinum; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; Pembro, pembrolizumab.

Kaplan-Meier Estimates of OS in Subgroups Defined by Baseline PD-L1 TPS



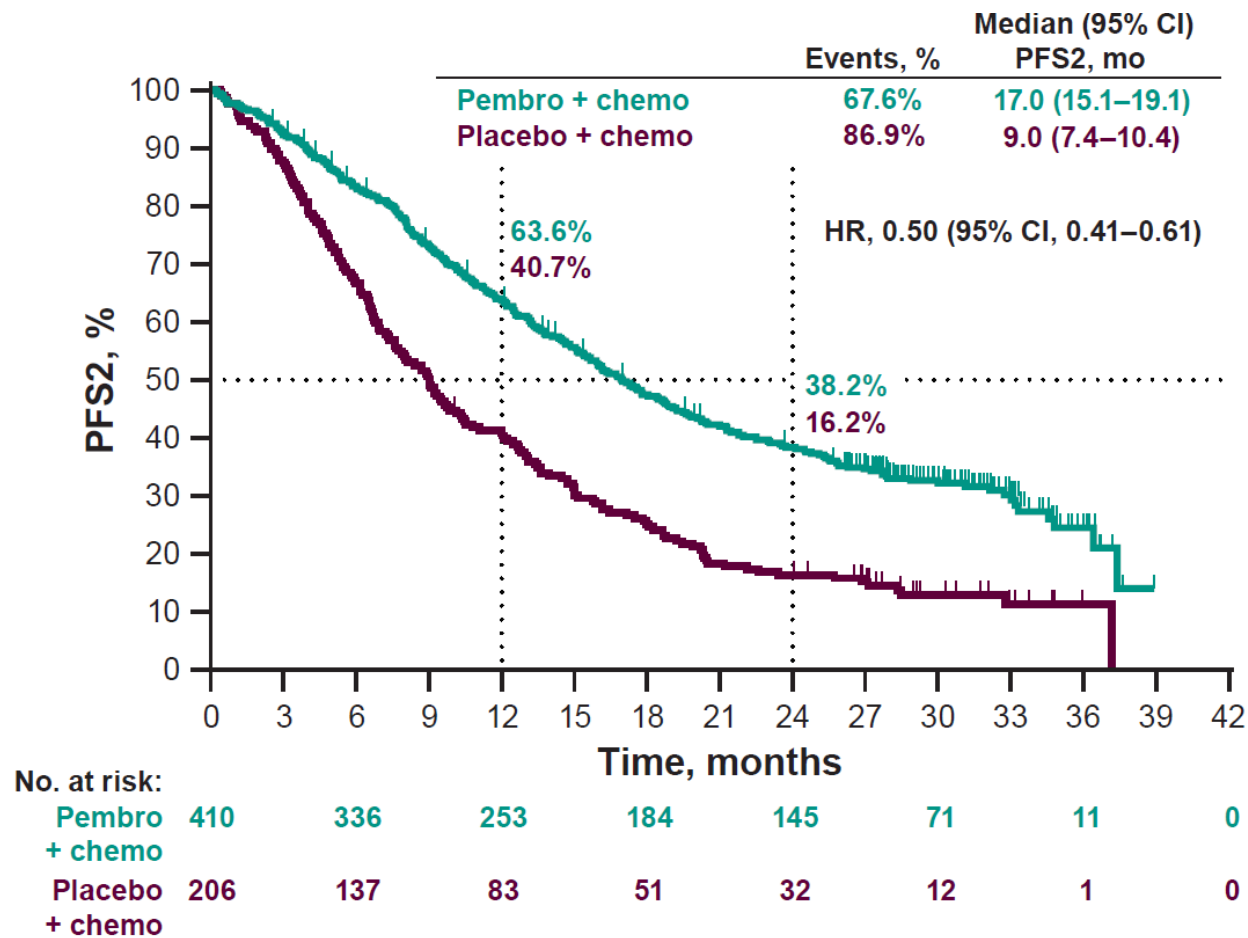
Chemo, chemotherapy with pemetrexed + platinum; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; Pembro, pembrolizumab.

Kaplan-Meier Estimate of **PFS** in the ITT Population Based on Blinded Independent Central Review per RECIST Version 1.1



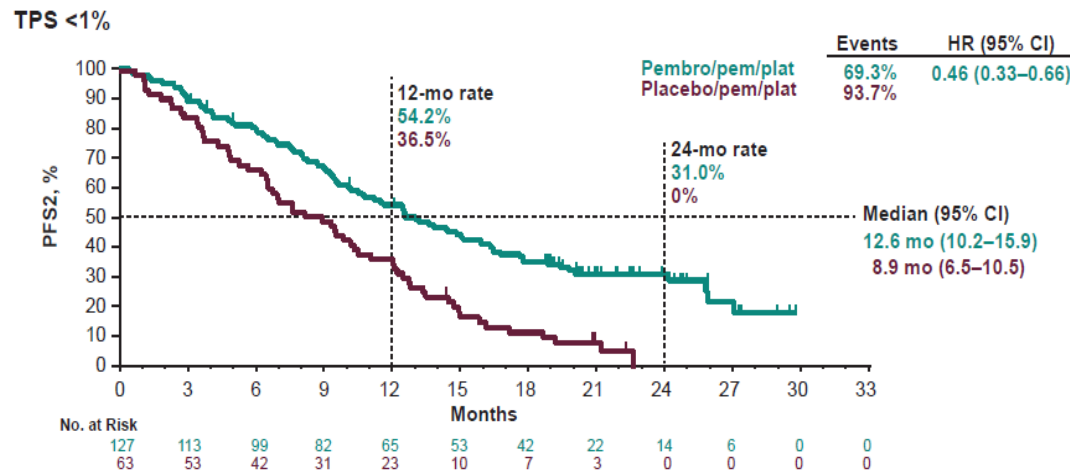
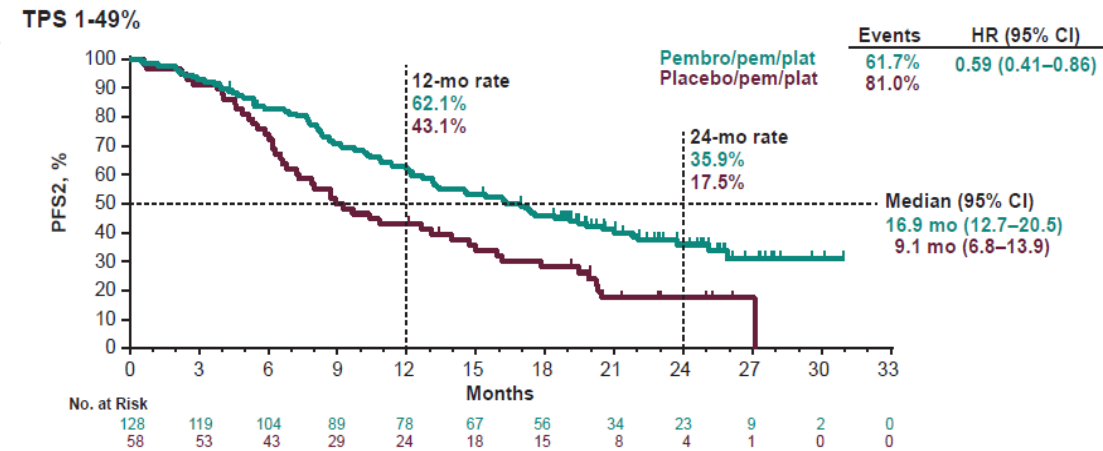
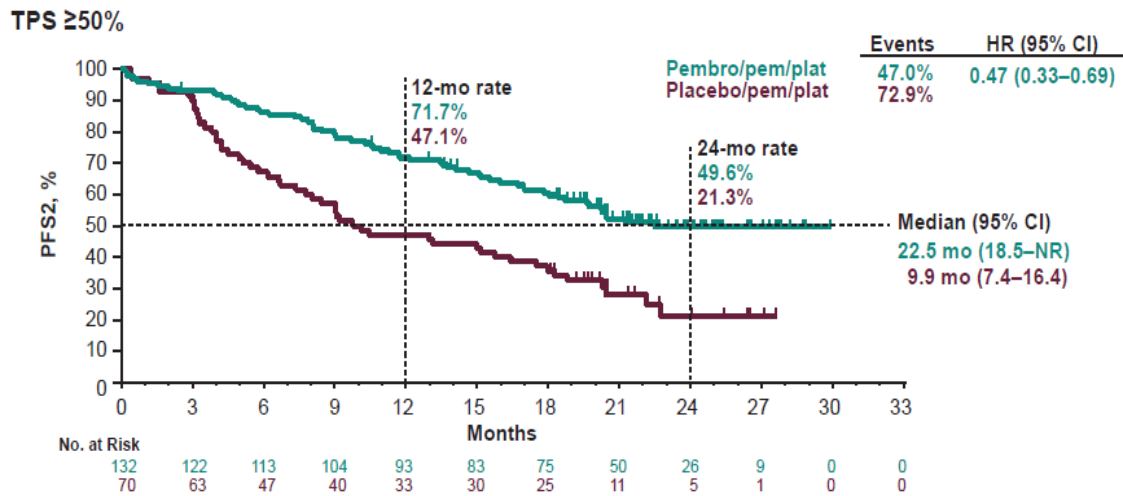
Chemo, chemotherapy with pemetrexed + platinum; HR, hazard ratio; ITT, intent-to-treat; Pembro, pembrolizumab; PFS, progression-free survival.

Kaplan-Meier Estimate of **PFS2** in the ITT Population Based on Investigator Review per RECIST Version 1.1



Chemo, chemotherapy with pemetrexed + platinum; HR, hazard ratio; ITT, intent-to-treat; Pembro, pembrolizumab; PFS2, progression-free survival after the next line of therapy.

Kaplan-Meier Estimates of PFS2 in PD-L1 TPS Subgroups (ITT)



PFS^a and PFS2^b by PD-L1 TPS

	TPS ≥50%		TPS 1%–49%		TPS <1%	
	Pembro + Chemo (n = 132)	Placebo + Chemo (n = 70)	Pembro + Chemo (n = 128)	Placebo + Chemo (n = 58)	Pembro + Chemo (n = 127)	Placebo + Chemo (n = 63)
PFS						
Events, %	72.7	94.3	83.6	94.8	89.8	96.8
Median, mo	11.1	4.8	9.4	4.9	6.2	5.1
HR (95% CI)	0.35 (0.25–0.49)		0.53 (0.38–0.74)		0.67 (0.49–0.93)	
PFS2						
Events, %	53.8	74.3	69.5	89.7	78.0	95.2
Median, mo	22.5	9.9	16.9	9.1	12.6	8.1
HR (95% CI)	0.52 (0.36–0.75)		0.57 (0.40–0.81)		0.47 (0.33–0.66)	

Chemo, chemotherapy with pemetrexed

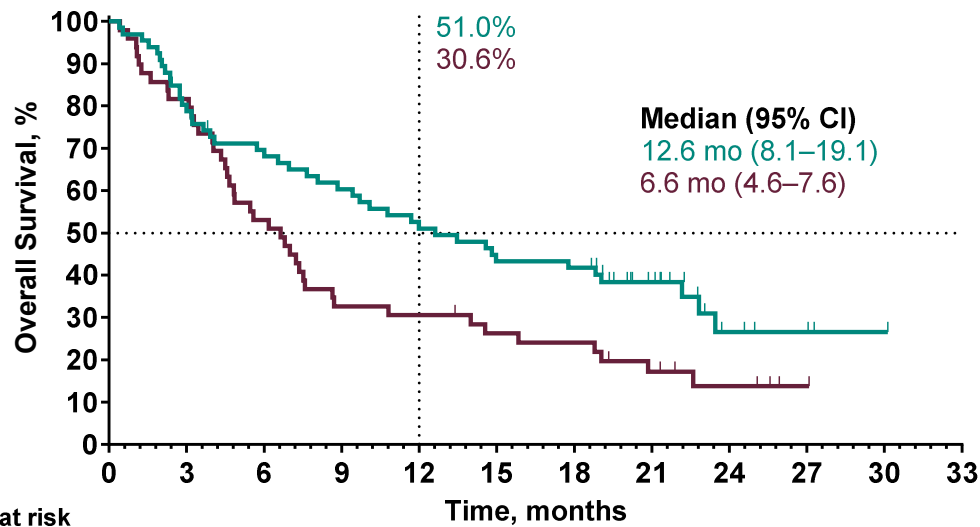
+ platinum; HR, hazard ratio; Pembro, pembrolizumab; PFS, progression-free survival; PFS2, progression-free survival after the next line of therapy; TPS, tumor proportion score.

^aBased on Blinded Independent Central Review per RECIST Version 1.1; ^bBased on Investigator Review per RECIST Version 1.1.

Overall Survival: Liver Metastases

With Liver Metastases

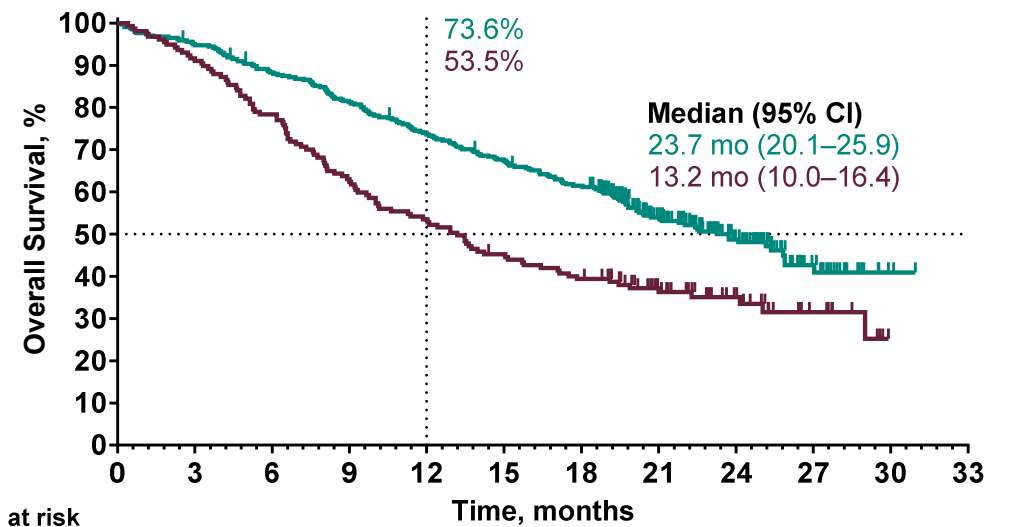
	Events, n (%)	HR (95% CI)
Pembro/Pem/Plat	43 (65.2)	0.62
Placebo/Pem/Plat	41 (83.7)	(0.39–0.98)



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33
Pembro/Pem/Plat	66	52	45	39	33	28	27	16	5	2	1	0
Placebo/Pem/Plat	49	40	26	16	15	12	11	7	4	0	0	0

Without Liver Metastases

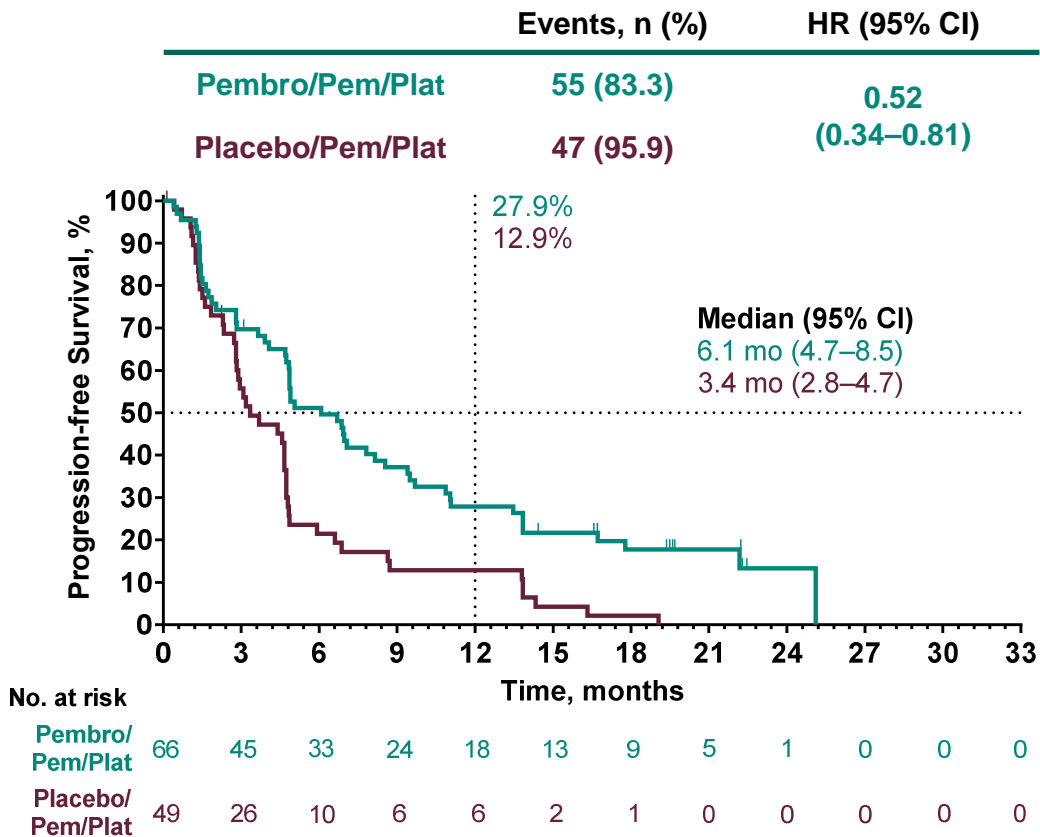
	Events, n (%)	HR (95% CI)
Pembro/Pem/Plat	170 (49.4)	0.58
Placebo/Pem/Plat	103 (65.6)	(0.45–0.74)



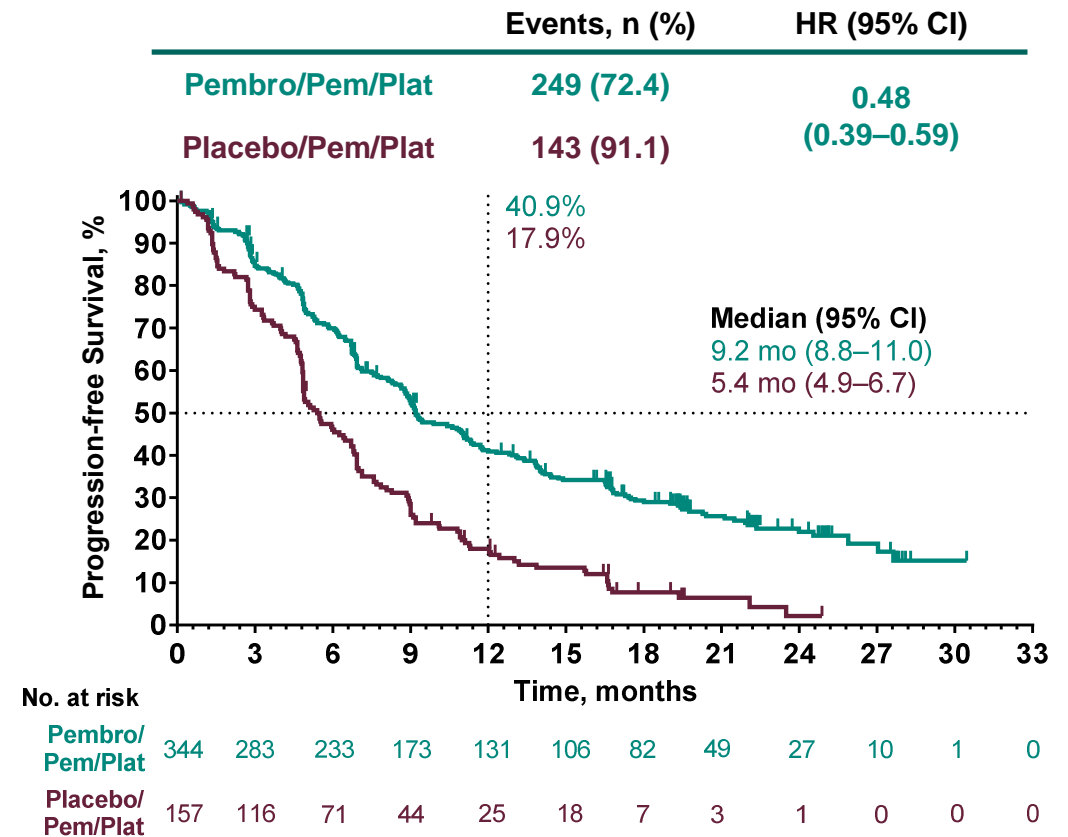
No. at risk	0	3	6	9	12	15	18	21	24	27	30	33
Pembro/Pem/Plat	344	325	301	277	250	228	207	128	74	26	1	0
Placebo/Pem/Plat	157	143	123	99	84	70	61	38	22	10	0	0

Progression-Free Survival: **Liver Metastases** (RECIST v1.1, BICR)

With Liver Metastases



Without Liver Metastases

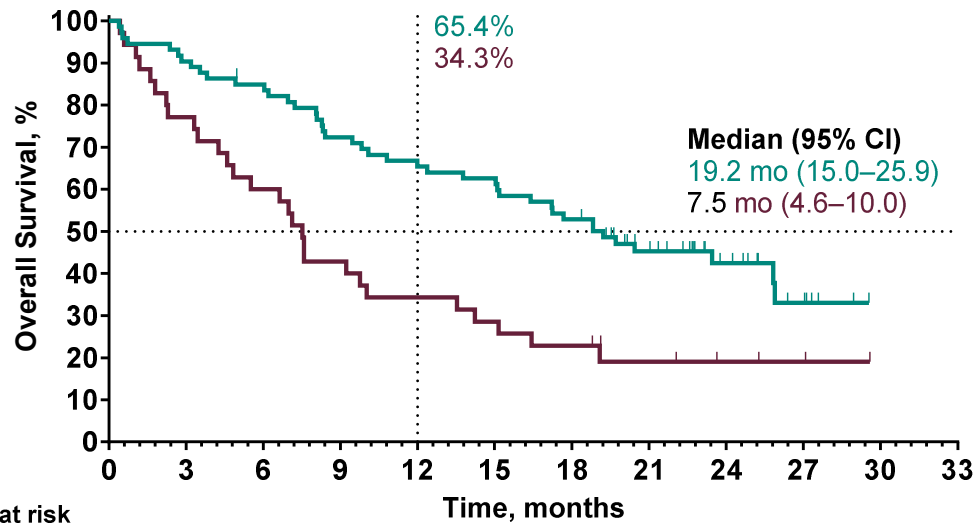


BICR, blinded independent central review.
Data cutoff date: September 21, 2018.

Overall Survival: Brain Metastases

With Brain Metastases

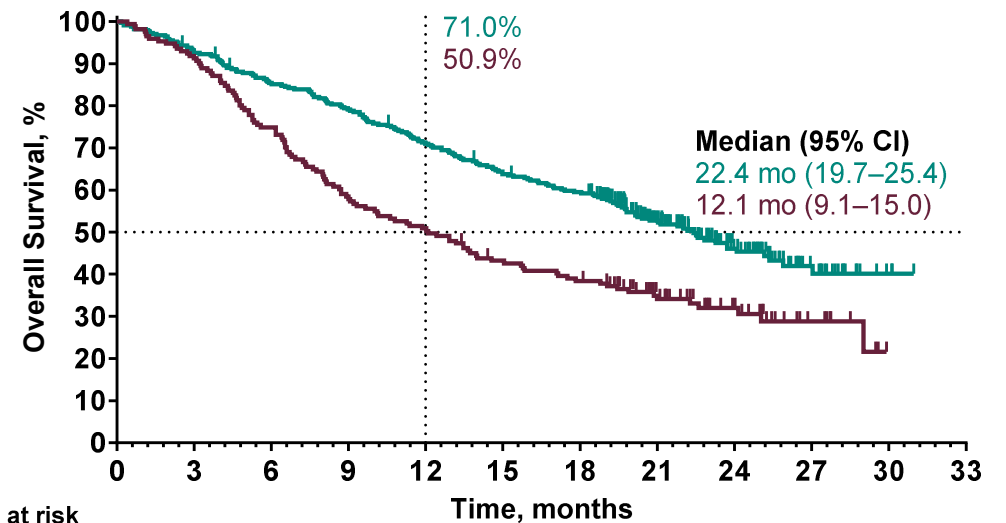
	Events, n (%)	HR (95% CI)
Pembro/Pem/Plat	42 (57.5)	0.41
Placebo/Pem/Plat	28 (80.0)	(0.24–0.67)



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33
Pembro/Pem/Plat	73	66	61	52	47	45	38	25	14	5	0	0
Placebo/Pem/Plat	35	27	21	15	12	10	8	5	3	1	0	0

Without Brain Metastases

	Events, n (%)	HR (95% CI)
Pembro/Pem/Plat	171 (50.7)	0.59
Placebo/Pem/Plat	116 (67.8)	(0.46–0.75)



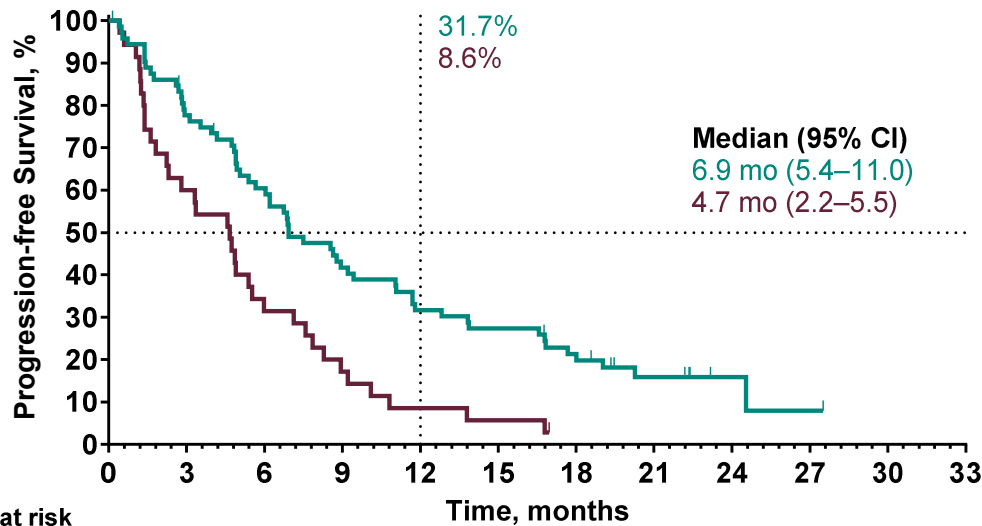
No. at risk	0	3	6	9	12	15	18	21	24	27	30	33
Pembro/Pem/Plat	337	311	285	264	236	211	196	119	65	23	2	0
Placebo/Pem/Plat	171	156	128	100	87	72	64	40	23	9	0	0

Progression-Free Survival: Brain Metastases (RECIST v1.1, BICR)

With Brain Metastases

Events, n (%) HR (95% CI)

Pembro/Pem/Plat	59 (80.8)	0.42
Placebo/Pem/Plat	34 (97.1)	(0.27–0.67)

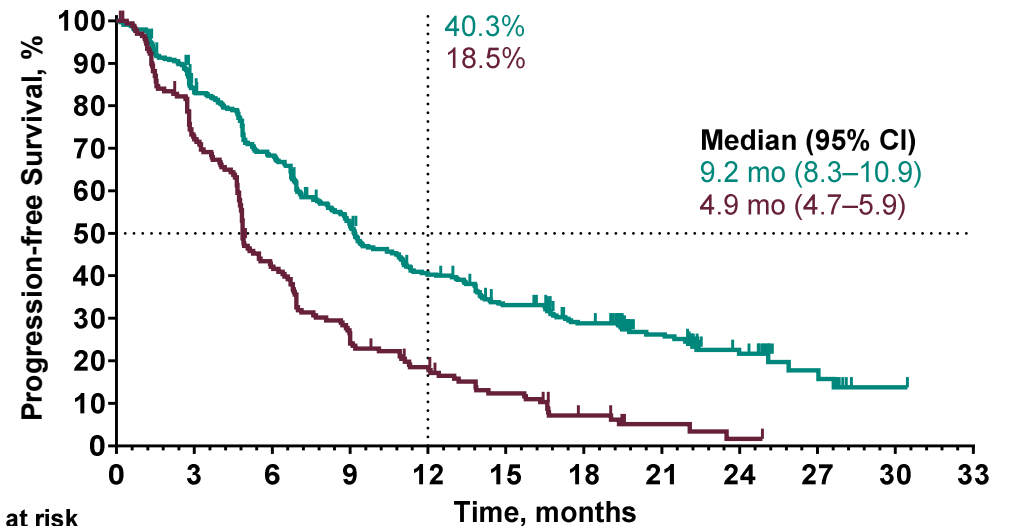


No. at risk	0	3	6	9	12	15	18	21	24	27	30	33
Pembro/Pem/Plat	73	55	42	29	22	19	14	7	2	1	0	0
Placebo/Pem/Plat	35	21	11	6	3	2	0	0	0	0	0	0

Without Brain Metastases

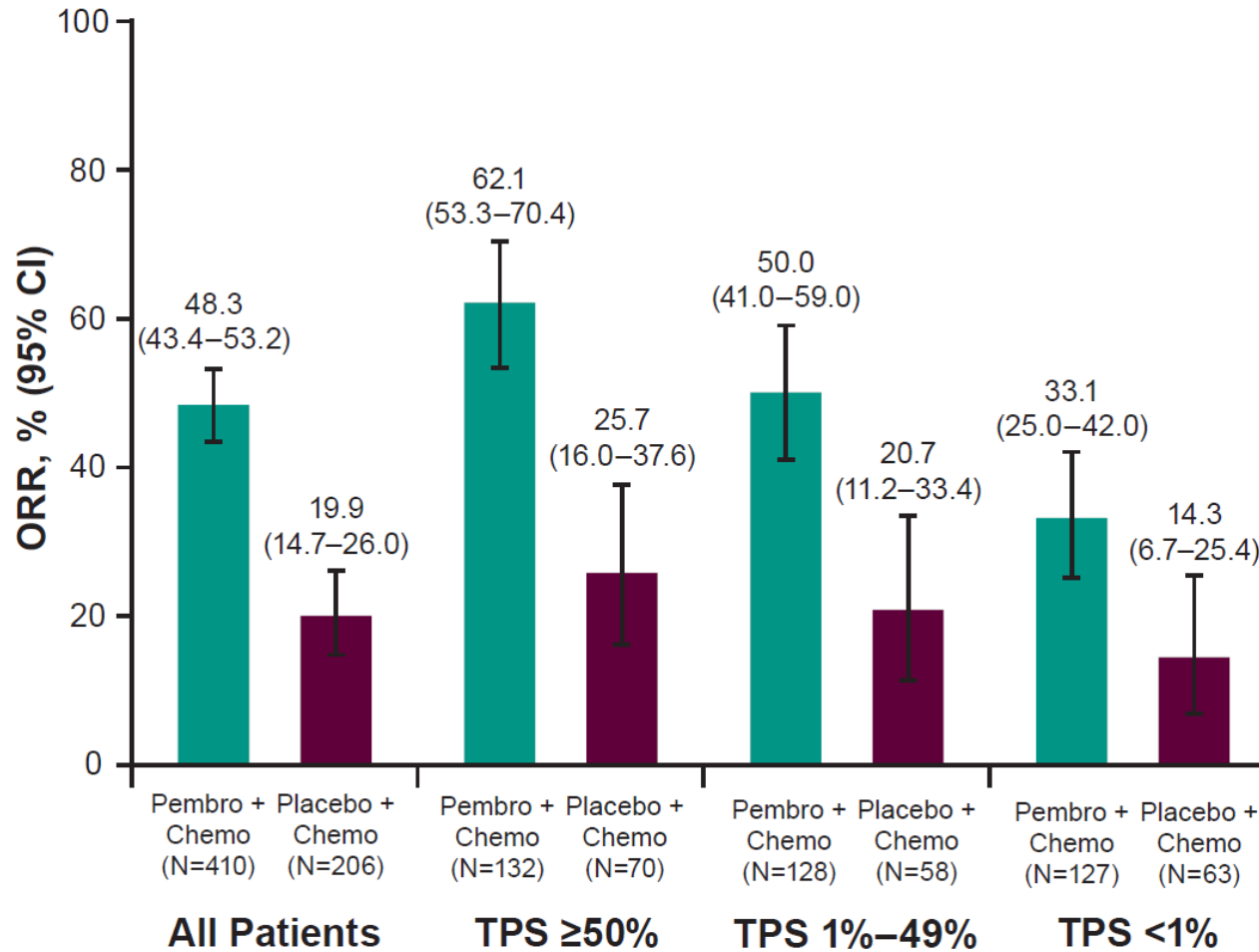
Events, n (%) HR (95% CI)

Pembro/Pem/Plat	245 (72.7)	0.48
Placebo/Pem/Plat	156 (91.2)	(0.39–0.59)



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33
Pembro/Pem/Plat	337	273	224	168	127	100	77	47	26	9	1	0
Placebo/Pem/Plat	171	121	70	44	28	18	8	3	1	0	0	0

Objective Response Based on Blinded Independent Central Review per RECIST Version 1.1



Chemo, chemotherapy with pemetrexed + platinum; ORR, overall response rate; Pembro, pembrolizumab; TPS, tumor proportion score.

Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab

- 56 patients in the pembrolizumab plus pemetrexed-platinum arm completed 35 cycles (~2 years) of pembrolizumab treatment
 - ORR was **85.7%** (4 complete response, 44 partial response, 8 stable disease)
 - Median OS was not reached (95% CI, not reached)

Summary of AEs

	Pembro + Chemo (N = 405)	Placebo + Chemo (N = 202)
AEs, n (%)		
Any grade	404 (99.8)	200 (99.0)
Grades 3–5	292 (72.1)	135 (66.8)
Led to death ^a	29 (7.2)	14 (6.9)
Led to discontinuation of any treatment component	146 (36.0)	35 (17.3)
Immune-mediated AEs and infusion reactions, n (%)		
Any grade	110 (27.2)	26 (12.9)
Grades 3–5	49 (12.1)	9 (4.5)

AE, adverse event; Chemo, chemotherapy with pemetrexed + platinum; Pembro, pembrolizumab.

^aEight (2.0%) patients in the pembro + pemetrexed-platinum arm and 2 (1.0%) patients in the placebo + pemetrexed-platinum arm died of AEs attributed to study treatment by the investigator.

Conclusions

- In this protocol-specified final analysis of the KEYNOTE-189 study pembrolizumab plus pemetrexed-platinum improved OS, PFS, PFS2, and ORR over placebo plus pemetrexed-platinum regardless of PD-L1 expression
 - ORR was high among patients who received 35 cycles of pembrolizumab; most were alive at the time of analysis
- Pembrolizumab plus pemetrexed-platinum had manageable toxicity
- Pembrolizumab plus pemetrexed-platinum is a standard-of-care therapy for patients with newly diagnosed metastatic nonsquamous NSCLC

Key Takeaway

- **With long-term follow-up, pembrolizumab plus pemetrexed-platinum continued to improve efficacy outcomes over placebo plus pemetrexed-platinum, with median OS and PFS approximately twice as long compared with placebo plus pemetrexed-platinum.**

KEYNOTE-189: Results Timeline

**1L combo
Always double**

**1L
一線及早合併**

**2X
療效可獲得兩倍**

OS
PFS
PFS2
ORR



Primary Analysis¹
Data cutoff date:
Nov,8 2017

Updated Analysis²
Data cutoff date:
Sep,21 2018

ASCO20 Virtual
Final Analysis³
Data cutoff date:
May,20 2019

Median follow-up, months		10.5	23.1	31
Efficacy, (KEYTRUDA combo vs chemotherapy)	mOS, mos	NR vs 11.3 (HR=0.49 [95%CI,0.38-0.64] ; P<0.001)	22.0 vs 10.7 (HR=0.56 [95%CI,0.45-0.70])	22.0 vs 10.6 (HR=0.56 [95%CI,0.46-0.69])
	Survival rate	12-mo OS: 69.2% vs 49.4%	12-mo OS: 70.0% vs 48.1% 24-mo OS:45.5% vs 29.9%	12-mo OS: 69.8% vs 48.0% 24-mo OS: 45.7% vs 27.3%
	mPFS	8.8 vs 4.9 (HR=0.52 [95%CI,0.43-0.64] ; P<0.001)	9.0 vs 4.9 (HR=0.48 [95%CI,0.40-0.58])	9.0 vs 4.9 (HR=0.49 [95%CI,0.41-0.59])
	mPFS2	-	17.0 vs 9.0 (HR=0.49 [95%CI,0.40-0.59])	17.0 vs 9.0 (HR=0.50 [95%CI,0.41-0.61])
	Response rate	47.6% vs 18.9% (P<0.001)	48.0% vs 19.4%	48.3% vs 19.9%
	mDoR, mos	11.2 vs 7.8	12.4 vs 7.1	-

1.Gandhi L et al. N Engl J Med. 2018;378(22): 2078-2092 ; 2.Gadgeel S et al. J Clin Oncol 2020;38(14):1505-1517 ; 3.Rodriguez-Abreu D et al. presented at ASCO annual meeting 2020; May 29-31,2020 ; virtual meeting. Abstract 9582.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) Category 1 PREFERRED Recommendation¹

CATEGORY 1 PREFERRED recommendation for patients with mNSCLC whose PD-L1 levels are <50% or are unknown^{1,a}

Pembrolizumab (KEYTRUDA), in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.

^aPembrolizumab/carboplatin (or cisplatin)/pemetrexed is recommended (category 1 preferred) as first-line therapy for certain patients with metastatic nonsquamous NSCLC.

Preferred intervention = Intervention that is based on superior efficacy, safety, and evidence, and, when appropriate affordability.

Category 1 = Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; mNSCLC = metastatic non-small cell lung cancer; NCCN[®] = National Comprehensive Cancer Network[®]; PD-L1 = programmed death ligand 1.

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NCCN Guidelines[®] Subsequent Therapy Recommendations

- After progression on pembrolizumab + pemetrexed + carboplatin or cisplatin, NCCN Guidelines[®] recommend the following systemic therapies as options^{1,a}:
 - Docetaxel +/- ramucirumab (category 2A)^b
 - Gemcitabine (category 2A)^b

^aSee NCCN Guidelines[®] for detailed recommendations.

^bCategory 2A = Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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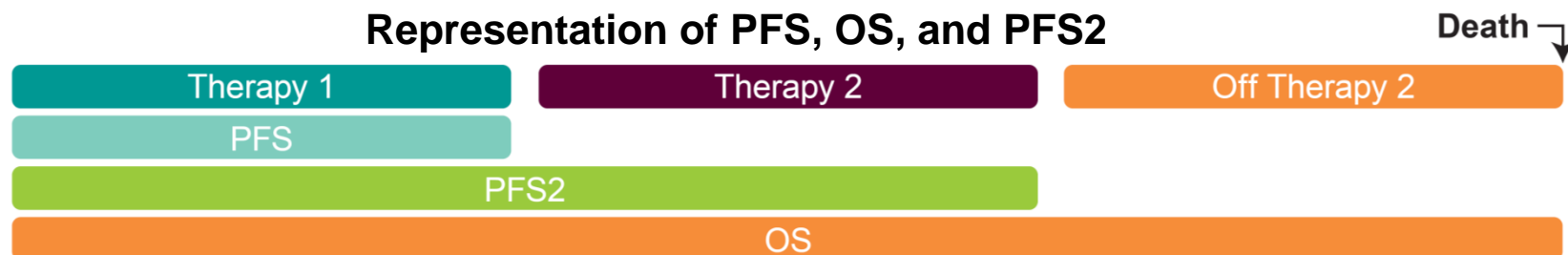
Pembrolizumab Plus Chemotherapy in Metastatic Squamous NSCLC: Final Analysis and Progression After the Next Line of Therapy (PFS2) in KEYNOTE-407

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J. Rodríguez Cid¹¹; I. Okamoto¹²; S. Lee¹³; R. Ramlau¹⁴;
V. Vladimirov¹⁵; Y. Cheng¹⁶; X. Deng¹⁷; T. Bas¹⁷; B. Piperdi¹⁷;
B. Halmos¹⁸

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Background

- Pembrolizumab plus platinum-based chemotherapy is a standard of care for the first-line treatment of advanced non–small-cell lung cancer (NSCLC)¹
- In the phase 3 KEYNOTE-407 study,¹ pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel significantly improved clinical outcomes over placebo plus chemotherapy in patients with previously untreated metastatic squamous NSCLC at a median follow-up of 7.8 months
 - Hazard ratio (HR) for overall survival (OS), 0.64 (P<0.001)
 - HR for progression-free survival (PFS), 0.56 (P<0.001)
 - Pembrolizumab plus chemotherapy had manageable toxicity, with no new safety signals observed
- PFS after the next line of therapy (PFS2) is defined by the European Medicines Agency as the time from randomization to objective tumor progression on next-line treatment or death from any cause, whichever occurs first, and can be used to assess the impact of crossover on OS and whether therapy in one line positively or negatively affects efficacy of the next line of therapy²



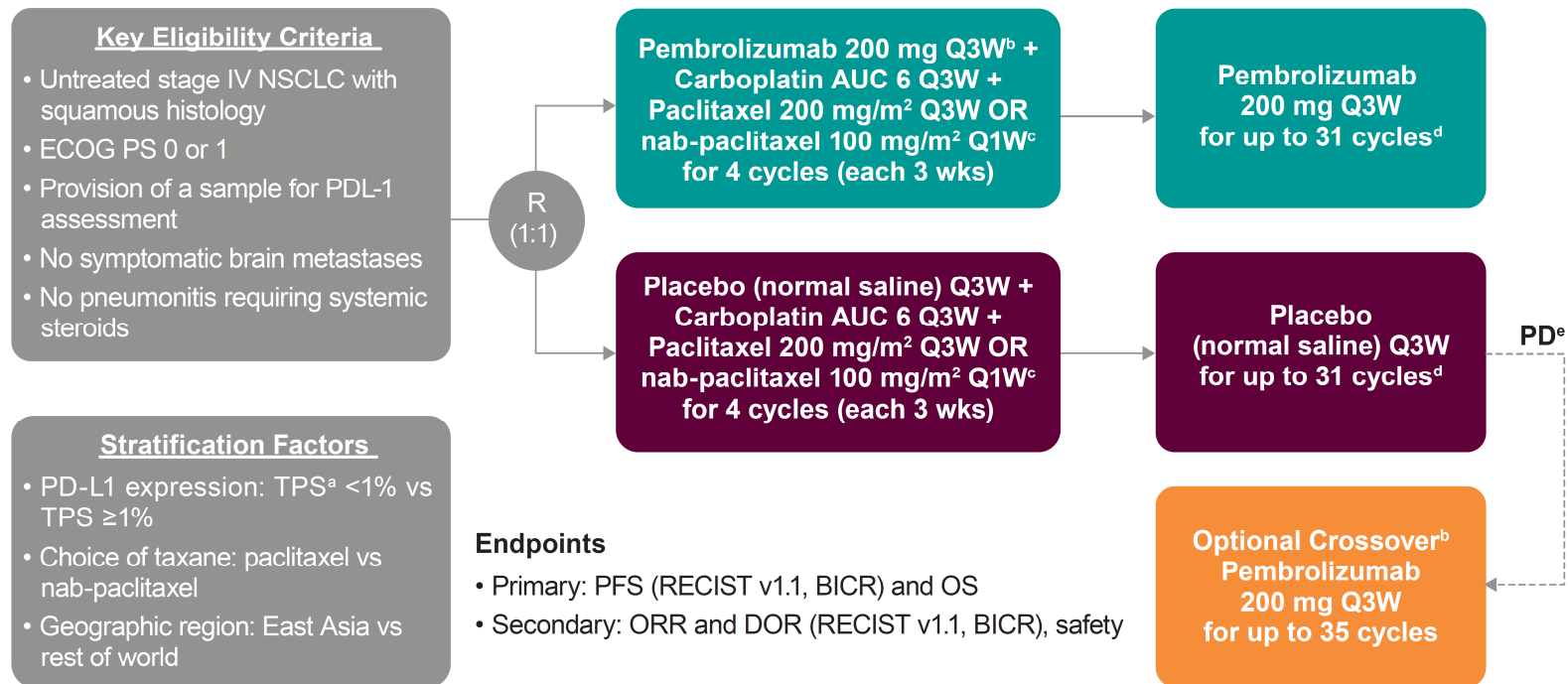
1. Paz-Ares L, et al. *N Engl J Med*. 2018;379(21):2040-2051.

2. EMA guideline on the evaluation of anticancer medicinal products in man. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf

Study Design, Participants, and Treatment

- KEYNOTE-407 (NCT02775435)¹ is an international, randomized, double-blind, placebo-controlled phase 3 study comparing pembrolizumab or placebo plus carboplatin and paclitaxel/nab-paclitaxel as first-line therapy for the treatment of stage IV squamous NSCLC
- After positive results from the second interim analysis, patients in the placebo arm were unblinded to stop placebo

KEYNOTE-407 Study Design



AUC, area under the curve; BICR, blinded independent central review; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; Q1W, every week; Q3W, every 3 weeks; R, randomization; TPS, tumor proportion score.

^aPercentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA).

^bPatients with documented disease progression who were benefiting clinically could continue open-label pembrolizumab monotherapy to complete a total of 35 cycles.

^cPatients received investigator's choice of paclitaxel (200 mg/m²; day 1) or nab-paclitaxel (100 mg/m²; days 1, 8, 15).

^dTreatment continued until radiographic disease progression (investigator review, immune-related RECIST), unacceptable toxicity, investigator's decision, or withdrawal of patient consent.

^ePatients could cross over to pembrolizumab 200 mg Q3W during combination therapy or monotherapy if PD was confirmed by blinded, independent central radiologic review and safety criteria were met.

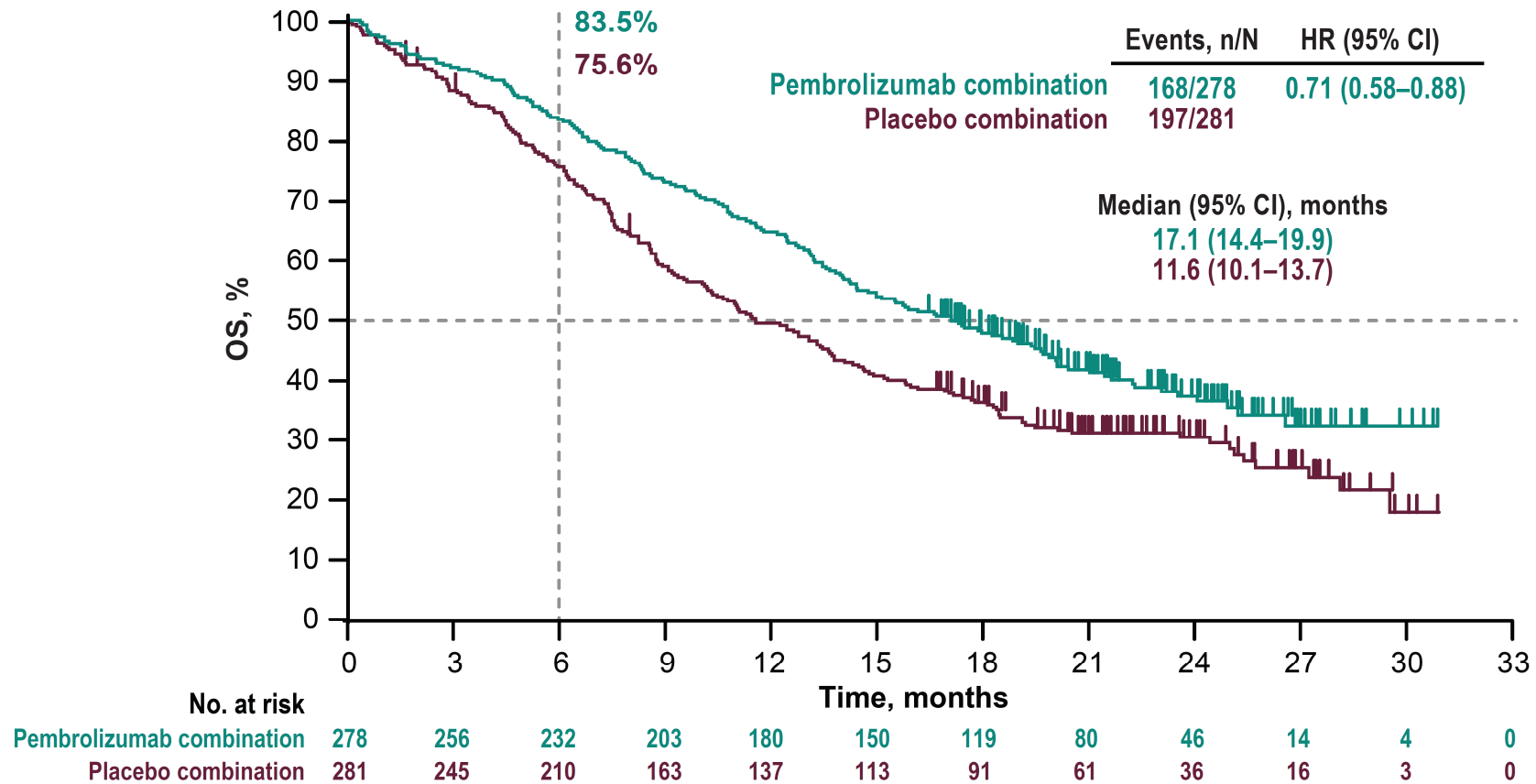
Patient Demographic and Baseline Disease Characteristics (ITT)

- At the time of this analysis (data cutoff, May 9, 2019), median follow-up was 14.3 months (range, 0.1–31.3 months)
 - 40 patients (14.4%) in the pembrolizumab combination arm and 5 (1.8%) in the placebo combination arm were continuing to receive initially assigned study treatment as of the data cutoff date
 - Subsequent therapy was received by 32.0% of 278 patients in the pembrolizumab combination arm and 59.4% of 281 patients in the placebo combination arm (40.1% crossed over on study; 49.1% in total received subsequent anti-PD-[L]1 therapy on study/outside of crossover)

Characteristic	Pembrolizumab Combination ^a n = 278	Placebo Combination ^a n = 281
Age, median (range), y	65.0 (29–87)	65.0 (36–88)
Men	220 (79)	235 (84)
ECOG PS 1	205 (74)	191 (68)
Current or former smoker	256 (92)	262 (93)
Enrolled in east Asia	54 (19)	52 (19)
PD-L1 TPS		
<1%	95 (34)	99 (35)
≥1%	176 (63)	177 (63)
1%–49%	103 (37)	104 (37)
≥50%	73 (26)	73 (26)
Unknown	7 (3)	5 (2)
Paclitaxel chosen as taxane	169 (61)	167 (59)
Prior thoracic radiation	17 (6)	22 (8)
Prior (neo)adjuvant therapy	5 (2)	8 (3)

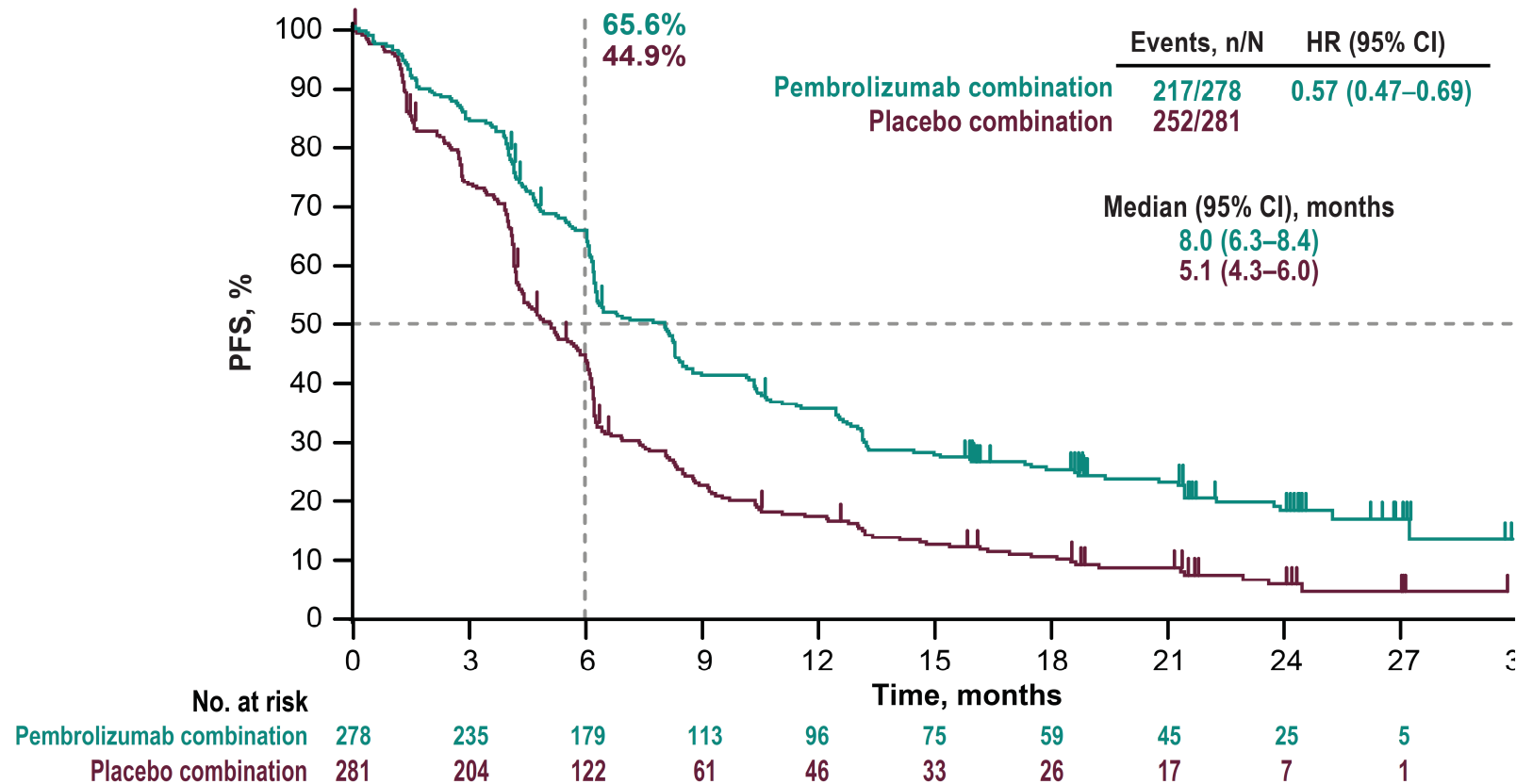
^aData are presented as n (%) unless otherwise noted.
ITT, intention-to-treat.

Kaplan-Meier Estimates of OS in the Total Population (ITT)



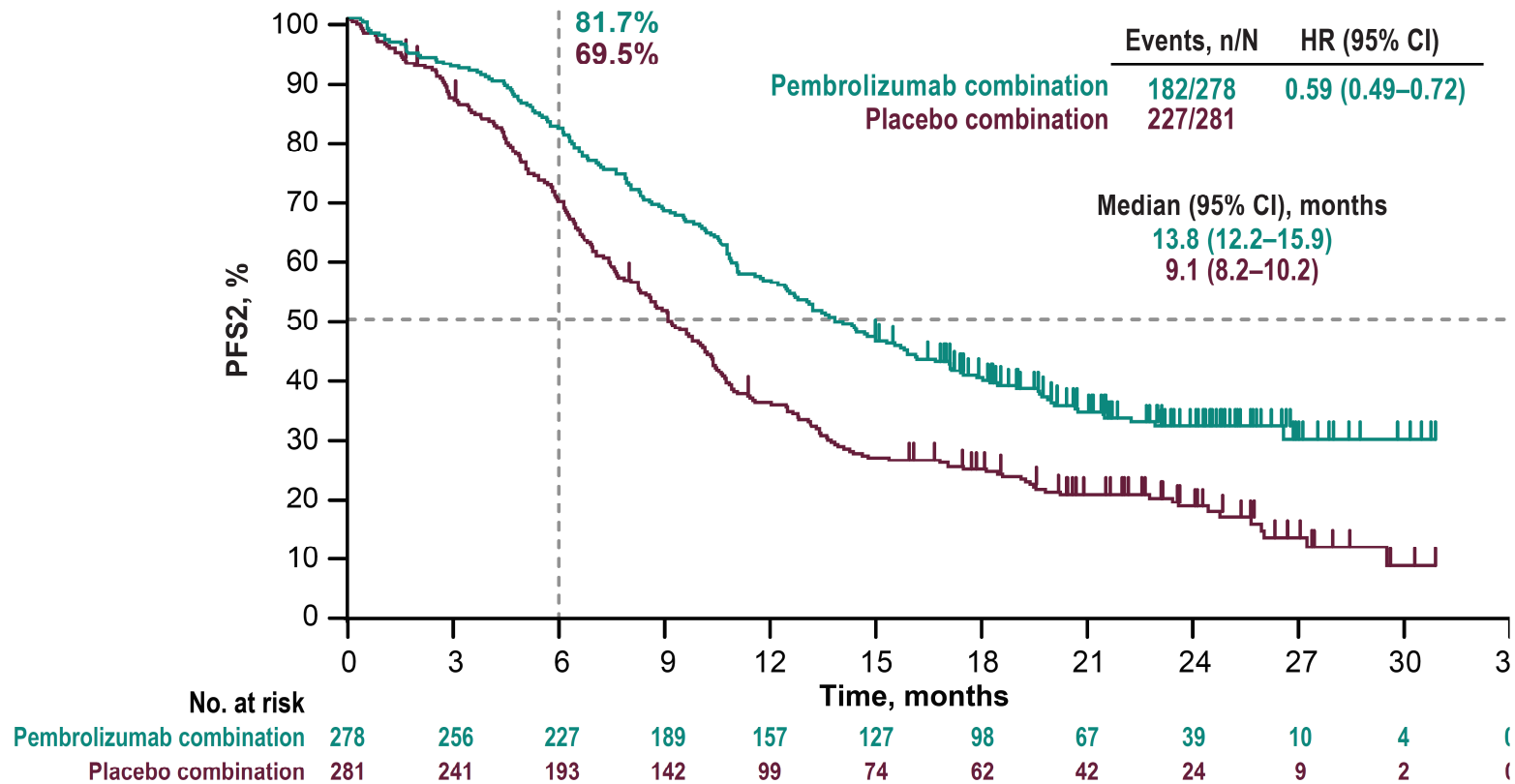
n, number of patients who died; N, number of patients in the group; NR, not reached.

Kaplan-Meier Estimates of **PFS** per RECIST version 1.1 by BICR in the Total Population (ITT)



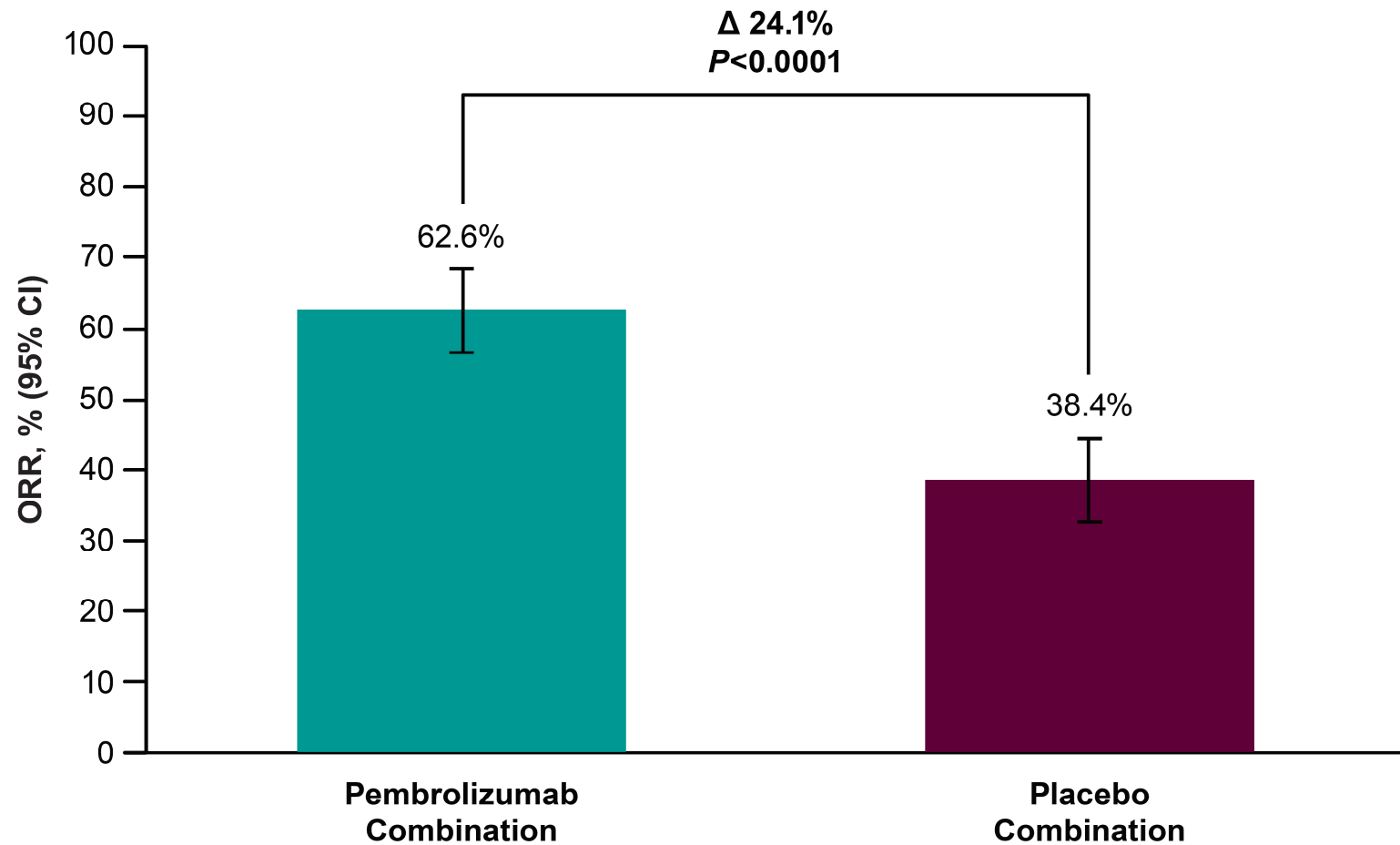
n, number of patients who had disease progression or died; N, number of patients in the group.

Kaplan-Meier Estimates of PFS2 in the Total Population (ITT)

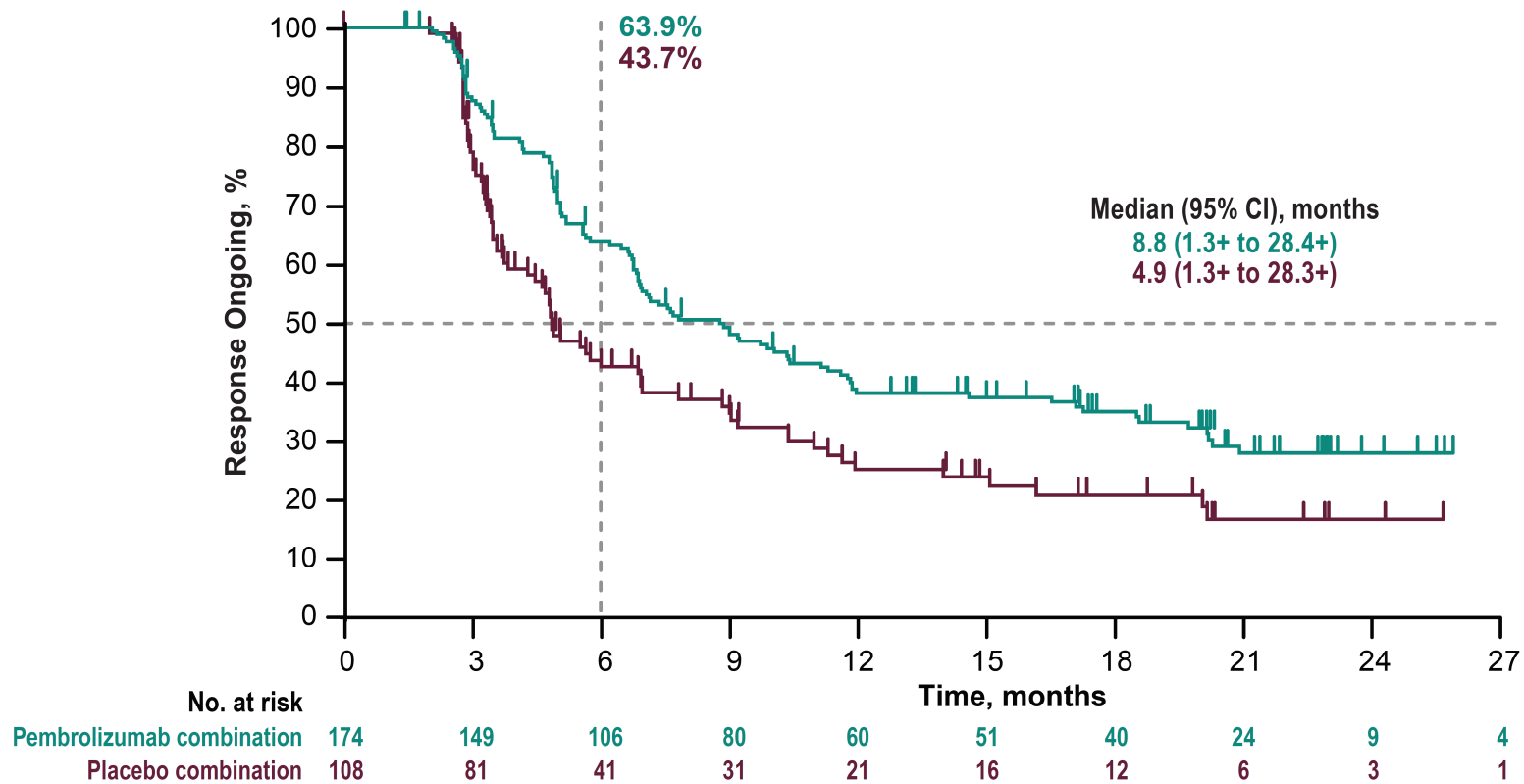


n, number of patients who had disease progression or died; N, number of patients in the group.

Response per RECIST Version 1.1 by BICR in the Total Population (ITT): Confirmed **ORR**



Response per RECIST Version 1.1 by BICR in the Total Population (ITT): Kaplan-Meier Estimate of **DOR**



+, no progressive disease as of last disease assessment before data cutoff date.

Summary of OS, PFS, ORR, DOR, and PFS2 in the Total Population (ITT) and Across PD-L1 TPS Groups

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)

+, no progressive disease as of last disease assessment before data cutoff date.

Safety

- Median (range) treatment duration was 7.1 months (0.1–26.3 months) for the pembrolizumab combination and 4.6 months (0.1–24.1 months) for the placebo combination

Incidence of All-Cause AEs and Immune-Mediated AEs and Infusion Reactions

Event	Pembrolizumab Combination ^a n = 278	Placebo Combination ^a n = 280
Any AE	274 (99)	275 (98)
Grade 3–5	206 (74)	195 (70)
Leading to discontinuation		
Any treatment	76 (27)	37 (13)
All treatments ^b	45 (16)	20 (7)
Leading to death	31 (11)	19 (7)
Treatment-related	12 (4)	5 (2)
Immune-related AEs and infusion reactions	98 (35)	25 (9)
Grade 3–5	37 (13)	9 (3)

^aData are presented as n (%).

^bIncludes patients who discontinued pembrolizumab or placebo, carboplatin, and taxane for an AE at any time and patients who discontinued pembrolizumab or placebo for an AE after completing 4 cycles of carboplatin and taxane.

Conclusions

- In this protocol-specified final analysis of KEYNOTE-407, pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel continued to demonstrate improved OS, PFS, ORR, and DOR versus placebo plus chemotherapy in patients with previously untreated metastatic squamous NSCLC
 - Results were consistent across PD-L1 TPS groups, including in patients with PD-L1 TPS <1%
- PFS2 was substantially improved for patients treated with pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel
- Pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel had a manageable safety profile
- These results continue to support pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel as a standard-of-care first-line treatment for patients with metastatic squamous NSCLC, regardless of PD-L1 expression status

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) Category 1 PREFERRED Recommendation¹

CATEGORY 1 PREFERRED recommendation for patients with mNSCLC whose PD-L1 levels are <50% or are unknown^{1,a}

KEYTRUDA[®], in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

^aPembrolizumab/carboplatin/paclitaxel (or paclitaxel protein-bound) is recommended (category 1 preferred) as first-line therapy for certain patients with metastatic squamous NSCLC.

Preferred intervention = Intervention that is based on superior efficacy, safety, and evidence, and, when appropriate affordability.

Category 1 = Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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mNSCLC = metastatic non–small cell lung cancer; NCCN[®] = National Comprehensive Cancer Network[®]; PD-L1 = programmed death ligand 1.

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NCCN Guidelines[®] Subsequent Therapy Recommendations

- After progression on pembrolizumab + carboplatin + paclitaxel or paclitaxel protein-bound, NCCN Guidelines[®] recommend the following systemic therapies as options^{1,a}:
 - Docetaxel +/- ramucirumab (category 2A)^b
 - Gemcitabine (category 2A)^b

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KEYTRUDA Combination in 1L Metastatic NSCLC

- Use **KEYTRUDA + platinum/pemetrexed** for patients with metastatic nonsquamous NSCLC, with or without PD-L1 expression and with no EGFR or ALK genomic tumor aberrations.



KEYTRUDA: Combination Therapy

51% reduction in risk of death
with **KEYTRUDA + platinum/pemetrexed**
vs platinum/pemetrexed alone
(HR=0.49^a; 95% CI, 0.38–0.64; *P*<0.0001)^b

- **KEYTRUDA is also indicated in combination with carboplatin and either paclitaxel or paclitaxel protein-bound** for the first-line treatment of patients with metastatic squamous NSCLC, with or without PD-L1 expression.
- **Immune-mediated adverse reactions, which may be severe or fatal**, can occur in any organ system or tissue in patients receiving KEYTRUDA. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes.

^aBased on the stratified Cox proportional hazard model. ^bBased on stratified log-rank test.

1L = first line; ALK = anaplastic lymphoma kinase; CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; programmed death ligand 1.

NSCLC = non-small cell lung cancer; PD-L1 =

Personalize Your Approach With KEYTRUDA as a First-line Treatment Option in mNSCLC

Overall survival consistently demonstrated across four phase 3 clinical trials with first-line KEYTRUDA

Nonsquamous Combination

In patients with or without PD-L1 expression (KEYNOTE-189)

- KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non–small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

Squamous Combination

In patients with or without PD-L1 expression (KEYNOTE-407)

- KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

Nonsquamous and Squamous Monotherapy

In patients with PD-L1 TPS $\geq 1\%$ (KEYNOTE-024&042)

- KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 (TPS $\geq 1\%$) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
 - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
 - metastatic.

KEYTRUDA TFDA indication overview

