Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to MSD (Tel: 0208 1548000). By clicking this link, you will be redirected to the MHRA website.

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1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092 (and supplementary appendix). 2. Garassino MC *et al. J Clin Oncol* 2023:41:1992–1998. 3. Keytruda Summary of Product Characteristics. 4. Novello S *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022. 5. Paz-Ares L *et al. N Engl J Med* 2018;379:2040–2051 (and supplementary appendix). 6. Reck M *et al. N Engl J Med* 2016;375:1823–1833. 7. Reck M *et al. J Clin Oncol* 2021;39:2339–2349.

GB-PDO-02655. Date of preparation August 2023

MSD Oncology

KEYNOTE-189: KEYTRUDA® (pembrolizumab) plus chemotherapy for the first-line treatment metastatic, non-squamous, *EGFR/ALK*-wild-type NSCLC

KEYTRUDA® is the first immunotherapy to present 5-year data in three 1st line metastatic NSCLC indications licensed in the UK[1–7]

These slides are provided to UK healthcare professionals as a data resource for personal education.
To ensure compliance with all relevant codes and regulations, these slides must not be amended.

KEYTRUDA® (pembrolizumab)

MSD

External websites and abbreviations

Links to external sites

The links in this slide deck will redirect you to third-party websites. Please note that:

- MSD does not review or control the content of any third-party website
- MSD does not endorse and are not responsible for the accuracy, content, practices or standards of any third-party sources

Abbreviations

Definitions of all abbreviations used in this deck can be found at the end of the presentation

There is an urgent unmet need for treatment options for patients with mNSCLC and low PD-L1 expression

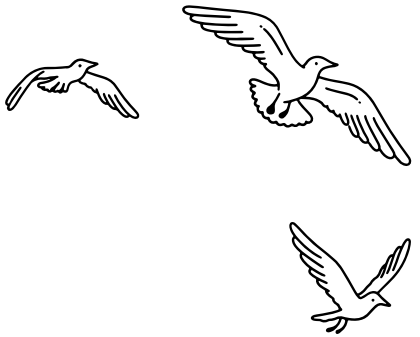
- Patient outcomes remain suboptimal with standard chemotherapeutics and durable disease control is rarely achieved[1,2]
- The median OS is 8–12 months for patients receiving supportive care in addition to induction platinum-based chemotherapy[2]
- Many patients may not survive long enough to receive second-line therapy[3]
- When they are treated first-line with chemotherapy alone, they have lower chances of survival and progression to option second-line treatment[3]

- High expressors (TPS ≥50%) with no contraindications to use of immunotherapy:
  KEYTRUDA monotherapy is a standard first-line option[4]

Low PD-L1 expression is often associated with immunologically cold tumour microenvironment, having low immunogenicity and insufficient T cell infiltration[5,6]

1. Leonetti A *et al. Drug Resist Updat* 2019;46:100644; 2. Chen *R et al. J Hematol Oncol* 2020;13:58. 3. Bazhenova L *et al Cancer Treat Res Commun* 2022;33:100637; 4. ESMO Guidelines. Available at: https://www.esmo.org/content/download/227453/3874538; 5. Aujla S et al. J Thorac Oncol 2022;17:675–687; 6. Holmen Olofsson G *et al. Int J Mol Sci* 2020;21:3816.

2023 EMSO guidelines recommended pembrolizumab in combination with chemotherapy for the 1L treatment of non-oncogene-addicted metastatic non-squamous NSCLC[1]

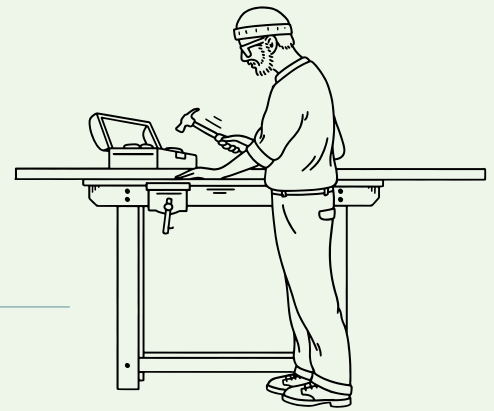


- Highest level of evidence (**I**) and recommendation grade (**A**)
- Established as a **standard treatment option** for patients with any PD-L1 score and PS 0–1
- Magnitude of clinical benefit recognised with an **ESMO-MCBS score of 4**

1. Hendriks LE, *et al. Ann Oncol*. 2023; S0923-7534(22)04785-8; https://doi.org/10.1016/j.annonc.2022.12.009.

KEYTRUDA® (pembrolizumab) metastatic NSCLC indications

- KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic, squamous NSCLC in adults
- KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic, non-squamous NSCLC in adults whose tumours have no *EGFR*- or *ALK*-positive mutations
- KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% TPS with no *EGFR*- or *ALK*-positive tumour mutations
- KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR- or ALK-positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA
- The recommended dose of KEYTRUDA in adults is either 200 mg Q3W or 400 mg Q6W administered intravenously over 30 minutes. For the use of KEYTRUDA as part of combination therapy, see the Summary of Product Characteristics (SmPC) for the concomitant therapies
- Refer to the Summary of Product Characteristics and Risk Minimisation materials available on the EMC website before prescribing, in order to help reduce the risks associated with KEYTRUDA



KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/2498/smpc

KEYNOTE-189: Definition of analyses

Analysis	Cut-off date	Slide symbol	Median follow up (range)
Original/interim	8 November 2017	1	10.5 (0.2–20.4)[1,2]
Updated	21 September 2018	2	18.7 (0.2–30.9)[3]
5-year follow up	8 March 2022	3	64.6 (60.1–72.4)[4]

1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Garassino *MC et al. Lancet Oncol*. 2020;21:387–397; 3. Gadgeel S *et al. J Clin Oncol.* 2020;38(14):1505–1517; 4. Garassino MC *et al. J Clin Oncol*. 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: KEYTRUDA

(pembrolizumab) plus chemotherapy for the first-line treatment of metastatic, non-squamous, EGFR/ALK-wild-type NSCLC

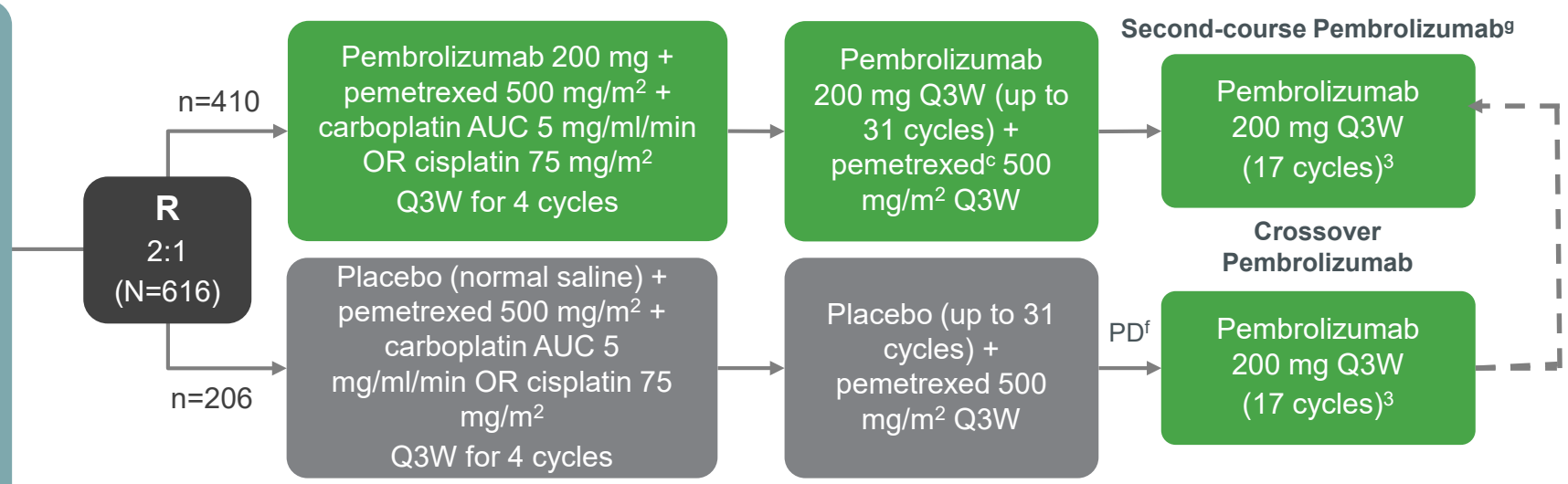
Gandhi L *et al*. *N Engl J Med* 2018;378:2078–2092 (and supplementary appendix).

KEYNOTE-189: Study design[1]

Multicentre, randomised, active-controlled, double-blind, Phase 3 trial

Key eligibility criteria

- Untreated metastatic, non-squamous NSCLC
- No sensitising *EGFR* or *ALK* mutations
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic CNS metastases[a]
- No history of non-infectious pneumonitis requiring use of glucocorticoids, no active autoimmune disease and no systemic immunosuppressive treatment
- <30 Gy of RT to the lung in the previous 6 months



Stratification factors

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

Endpoints[c]

- Primary: OS, PFS[d]
- Secondary: ORR,[d] DOR,[d] safety[e]
- Exploratory: Effect of PD-L1 expression on efficacy, PFS2, PROs

Adapted from: Gandhi L et al. N Engl J Med 2018 (and supplementary appendix); Gray JE et al. WCLC 2020.

[a]Patients were permitted to enrol if their brain lesions were previously treated, clinically stable for ≥2 weeks without evidence of new or enlarging lesions, and steroid-free for ≥3 days prior to receiving study treatment. [b]Percentage of tumour cells with membrane PD-L1 staining, as assessed using the PD-L1 IHC 22C3 pharmDx assay. [c]Efficacy was assessed in the ITT population. [d]Assessed by blinded, independent central review per RECIST 1.1. [e]Assessed in all patients who received ≥1 dose of study medication. [f]To be eligible for crossover to pembrolizumab monotherapy, PD had to have been verified by blinded, independent, central radiological review and all safety criteria had to have been met.[2] [g]Patients who had SD or better after completing 35 cycles of pembrolizumab or had stopped trial treatment after achieving CR and received ≥8 cycles of treatment, but then experienced PD, could receive second-course pembrolizumab for 17 cycles if they had received no new anticancer treatment since the last dose of pembrolizumab.

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;
3. Gray JE *et al.* Presented virtually at the 2020 World Conference on Lung Cancer (WCLC). 28–31 January 2021.

KEYNOTE-189: Statistical considerations (original analysis)[1]

Planned enrolment: 570 patients

- Actual enrolment: 616 patients

Overall alpha for the study: strictly controlled at one-sided α=0.025

- The study had 90% power to show an HR of 0.70 for PFS at one-sided α=0.0095 (based on 468 events) and an HR of 0.70 for OS at one-sided α=0.0155 (based on 416 deaths) for the comparison between the pembrolizumab combination and placebo combination groups
- The protocol specified two interim analyses before the final analysis

First interim analysis (reviewed by an external, independent data monitoring committee)

- Planned to occur after enrolment was complete and ~370 PFS events had been observed[a]
- Analysis cut-off date: 8 November 2017
- Results published: 16 April 2018
- Median follow up: 10.5 months (range: 0.2–20.4 months)
- Observed number of events: 410 for PFS; 235 for OS
- One-sided α levels:[b] 0.00559 for PFS; 0.00128 for OS

[a]It was anticipated that there would be ~242 OS events at that time. [b]Multiplicity adjusted based on the observed number of events using the O'Brien-Fleming spending function.[2]

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

KEYNOTE-189: Statistical considerations (updated analyses)

Updated analysis[1]

- Analysis cut-off date: 21 September 2018
- Results presented: ASCO 2019
- Median follow up (study):[a] 23.1 months (range: 18.6–30.9 months)
- Median follow up (survival):[b] 18.7 months (range: 0.2–30.9 months)
- This analysis was not subjected to further significance testing

5-year efficacy and safety outcomes update[2]

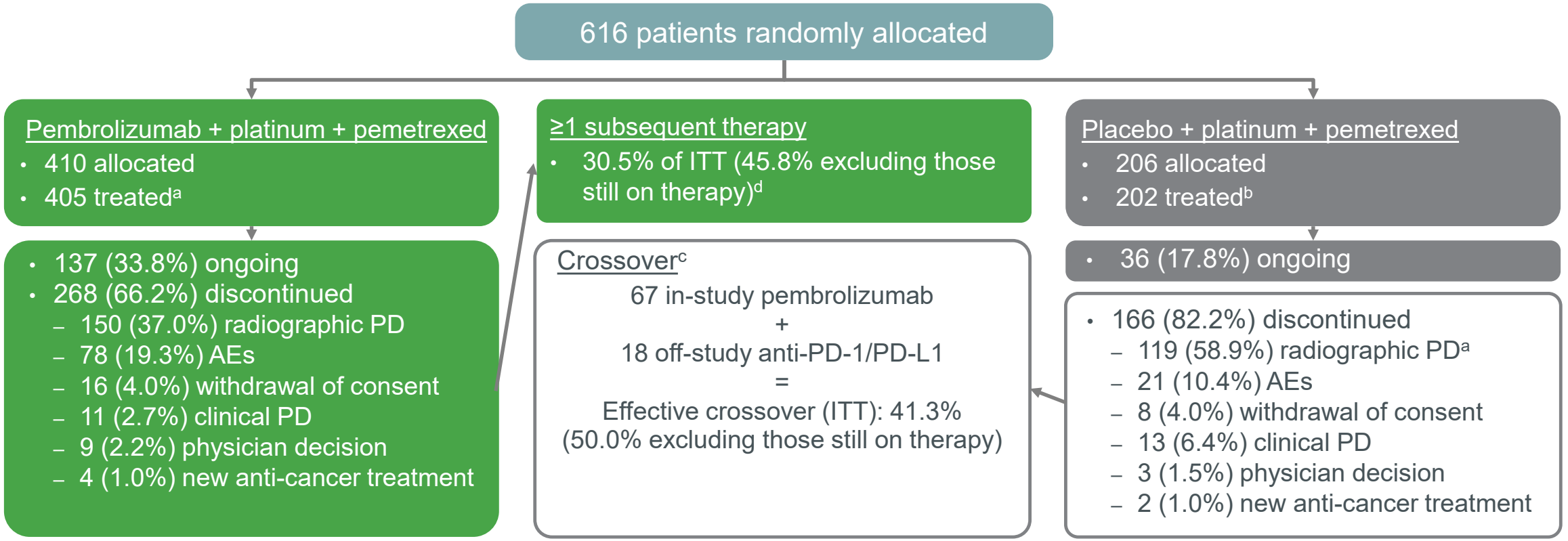
- Analysis cut-off date: 8 March 2022
- Results presented: EMSO 2022
- Median follow up: 64.6 months (range: 60.1–72.4 months)
- This analysis was not subject to further significance testing

[a]Time from randomisation to death or database cut off, whichever occurred first. [b]Time from randomisation to database cut off.

1. Gadgeel S *et al. J Clin Oncol.* 2020;38(14):1505–1517; 2. Garassino MC *et al. J Clin Oncol*. 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: Disposition of study treatment

Median follow up: 10.5 months



Adapted from: Gandhi L et al. AACR 2018.

11

Analysis cut-off date: 8 November 2017.
[a]Two AEs, one clinical PD, one death and one protocol violation. [b]Two withdrawals of consent, one protocol violation and one physician decision. [c]An additional 13 patients received other subsequent therapy (6.3% of ITT [7.6% excluding those still on therapy]). [d]45.8%=125/273, where 273 is derived from the ITT population (410) minus the number of patients with ongoing treatment (137), and 125 is derived from subsequent treatment in 30.5% of the ITT population (410).
Gandhi L *et al. N Engl J Med* 2018;378:2078–2092 (and supplementary appendix).

KEYNOTE-189: Key baseline characteristics

Median follow up: 10.5 months

Characteristic, n (%)[a]	Pembrolizumab + platinum + pemetrexed (n=410)	Placebo + platinum + pemetrexed (n=206)
Age, median (range), years	65.0 (34.0–84.0)	63.5 (34.0–84.0)
<65 years	197 (48.0)	115 (55.8)
Male sex[b]	254 (62.0)	109 (52.9)
ECOG PS[c]		
0	186 (45.4)	80 (38.8)
1	221 (53.9)	125 (60.7)
2	1 (0.2)	0
Brain metastases	73 (17.8)	35 (17.0)
Smoking status		
Former/current	362 (88.3)	181 (87.9)
Never	48 (11.7)	25 (12.1)

Characteristic, n (%)[a]	Pembrolizumab + platinum + pemetrexed (n=410)	Placebo + platinum + pemetrexed (n=206)
PD-L1 TPS[d]		
<1%	127 (31.0)	63 (30.6)
≥1%	260 (63.4)	128 (62.1)
1–49%	128 (31.2)	58 (28.2)
≥50%	132 (32.2)	70 (34.0)
NE[e]	23 (5.6)	15 (7.3)
Prior thoracic radiotherapy	28 (6.8)	20 (9.7)
Prior neoadjuvant therapy	5 (1.2)	6 (2.9)
Prior adjuvant therapy	25 (6.1)	14 (6.8)

Adapted from: Gandhi L et al. N Engl J Med 2018.

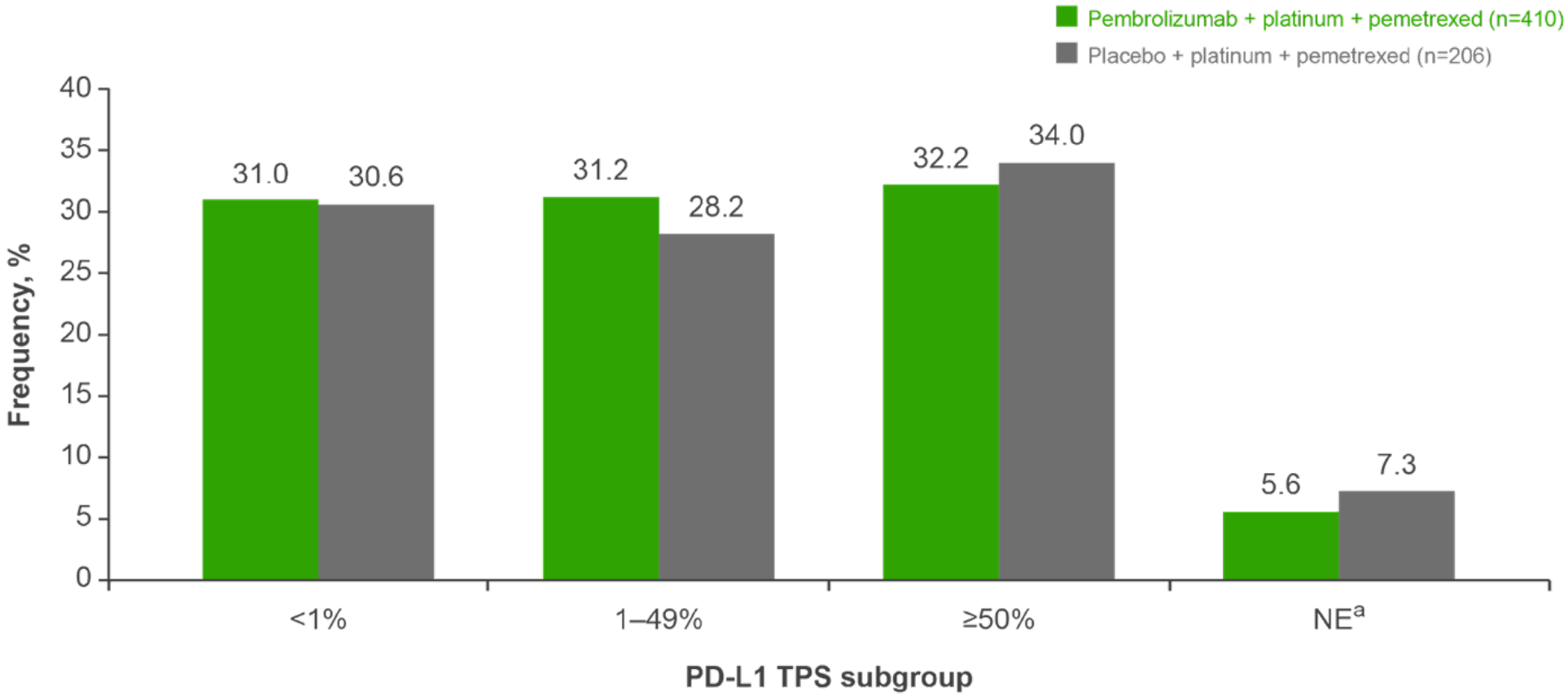
Analysis cut-off date: 8 November 2017.
[a]Unless otherwise stated. [b]There was a significant between-group difference in the proportion of men (p=0.04). [c]Data regarding ECOG PS status were missing for two patients (0.5%) in the pembrolizumab + platinum + pemetrexed group, and in one patient (0.5%) in the placebo + platinum + pemetrexed arm. [d]PD-L1 TPS was defined as the percentage of tumour cells with membranous PD-L1 expression. [e]PD-L1 expression could not be evaluated because specimens had an inadequate number of tumour cells or no tumour cells. For stratification purposes, patients with PD-L1 expression that could not be evaluated were included in the subgroup with PD-L1 TPS <1%; these patients were excluded from analyses of efficacy according to PD-L1 TPS.

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

1

KEYNOTE-189: Baseline characteristics – frequency of PD-L1 TPS subgroups

Median follow up: 10.5 months



Adapted from: Gandhi L et al. N Engl J Med 2018.

13

Analysis cut-off date: 8 November 2017.
[a]NE refers to specimens with an inadequate number of tumour cells or no tumour cells seen; these patients were included in the PD-L1 TPS <1% group for randomisation stratification but excluded from the analysis of efficacy by TPS.
Gandhi L *et al. N Engl J Med* 2018;378:2078–2092.

1

KEYNOTE-189: Primary endpoint outcomes[a] (1)

Primary outcomes with pembrolizumab + platinum + pemetrexed in the ITT population were as follows:

Original analysis (median follow up: 10.5 months)[1]

- OS: 51% reduced risk of death vs. placebo + platinum + pemetrexed
  - HR: 0.49; 95% CI: 0.38–0.64; p<0.001
- PFS: 48% reduced risk of progression or death vs. placebo + platinum + pemetrexed
  - HR: 0.52; 95% CI: 0.43–0.64; p<0.001

Updated analysis (median follow up: 18.7 months)[2]

- OS: 44% reduced risk of death vs. placebo + platinum + pemetrexed
  - HR: 0.56; 95% CI: 0.45–0.70; p = not tested
- PFS: 52% reduced risk of progression or death vs. placebo + platinum + pemetrexed
  - HR: 0.48; 95% CI: 0.40–0.58; p = not tested

5-year update (median follow up: 64.6 months)[3]

- OS: 40% reduced risk of death vs. placebo + platinum + pemetrexed
  - HR: 0.60; 95% CI: 0.50–0.72; p = not tested
- PFS: 50% reduced risk of progression vs. placebo + platinum + pemetrexed
  - HR: 0.50; 95% CI: 0.42–0.60; p = not tested

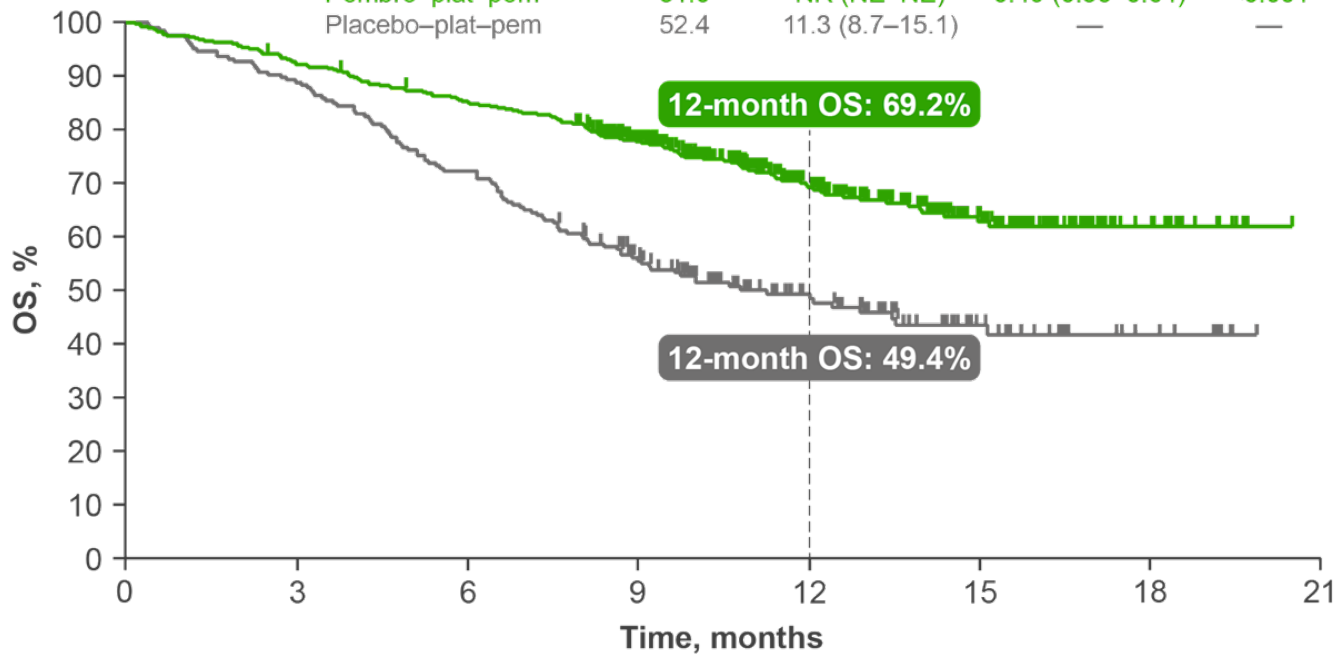
[a]OS and PFS were both primary endpoints.

1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Gadgeel S *et al. J Clin Oncol.* 2020;38(14):1505–1517; 3. Garassino MC *et al. J Clin Oncol.* 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: 1-year landmark OS in the ITT population (original analysis)[a,1,2]

Median follow up: 10.5 months

Treatment arm	Events, n	Median, months	HR (95% CI)	p value
Pembro–plat–pem	31.0	NR (NE–NE)	0.49 (0.38–0.64)	<0.001
Placebo–plat–pem	52.4	11.3 (8.7–15.1)	—	—



No. at risk								
Pembro–plat–pem	410	377	347	278	163	71	18	0
Placebo–plat–pem	206	183	149	104	59	25	8	0

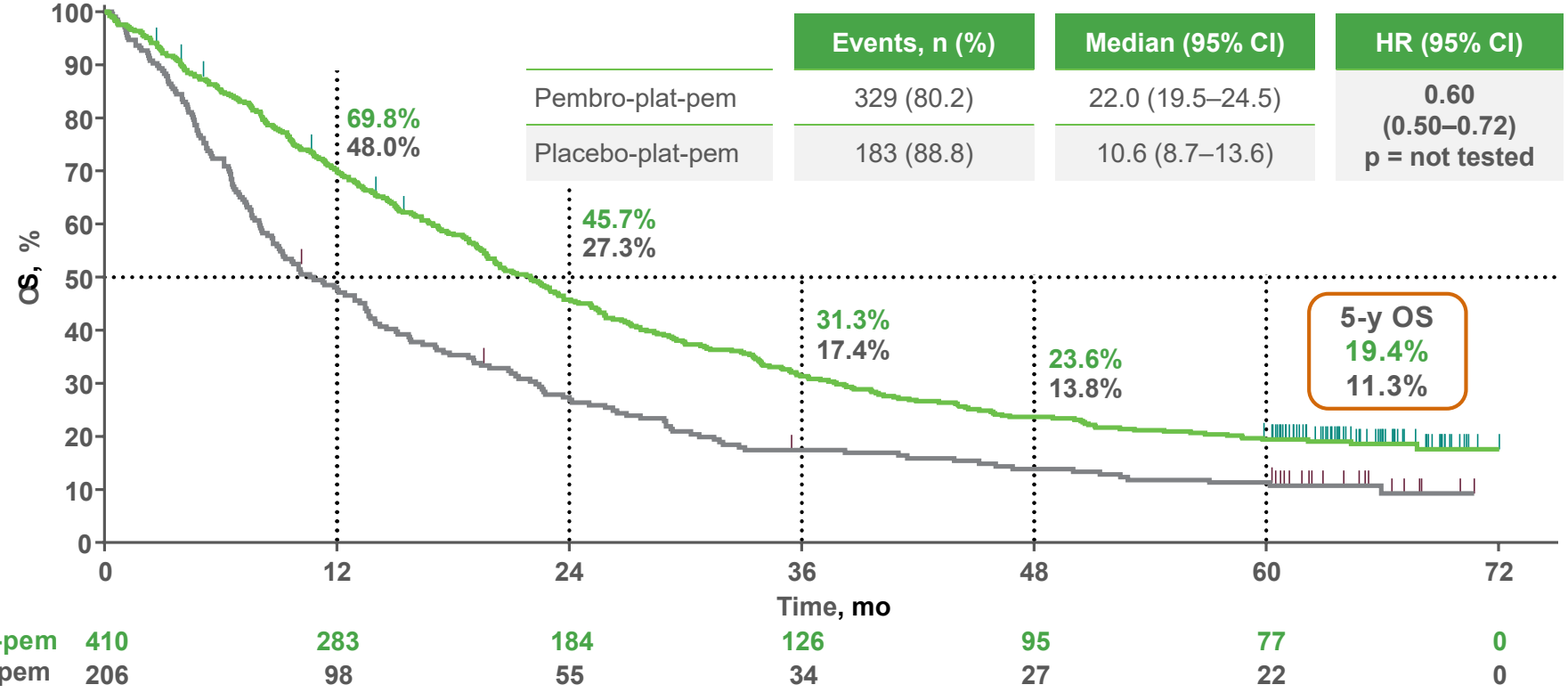
Adapted from: Gandhi L et al. N Engl J Med 2018; Gandhi L et al. AACR 2018.

Analysis cut-off date: 8 November 2017.
[a]OS and PFS were both primary endpoints.

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

KEYNOTE-189: OS in the ITT population in the 5-year update
(exploratory analysis, p not tested)[a]

Median follow up: 64.6 months. Statistical significance was met for the primary endpoints in Interim Analysis 1 (2018)



	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro-plat-pem	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72) p = not tested
Placebo-plat-pem	183 (88.8)	10.6 (8.7–13.6)	

No. at risk							
Pembro-plat-pem	410	283	184	126	95	77	0
Placebo-plat-pem	206	98	55	34	27	22	0

Adapted from Garassino MC et al. J Clin Oncol 2023.

Analysis cut-off date: 8 March 2022. No statistical conclusions can be drawn from this analysis.
[a]OS and PFS were both primary endpoints.

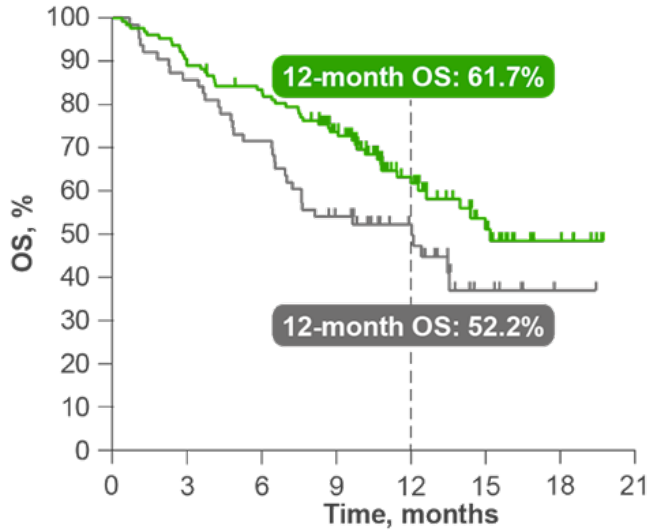
1. Garassino MC *et al. J Clin Oncol.* 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: Exploratory endpoint – 1-year landmark OS by PD-L1 TPS (original analysis)[a,1,2]

Median follow up: 10.5 months

PD-L1 TPS <1%

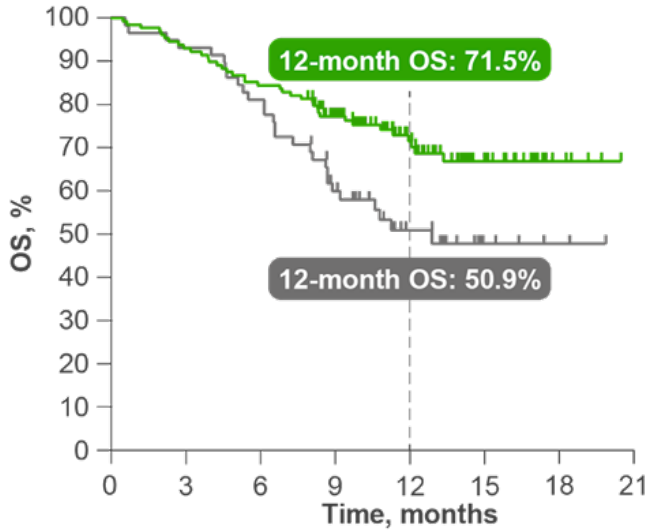
Treatment arm	Events, %	Median, months	HR (95% CI)	p value[b]
Pembro–plat–pem	38.6	15.2 (12.3–NE)	0.59 (0.38–0.92)	0.0095
Placebo–plat–pem	55.6	12.0 (7.0–NE)	—	—



No. at risk								
Pembro–plat–pem	127	113	104	79	42	20	6	0
Placebo–plat–pem	63	54	45	32	21	6	1	0

PD-L1 TPS 1–49%

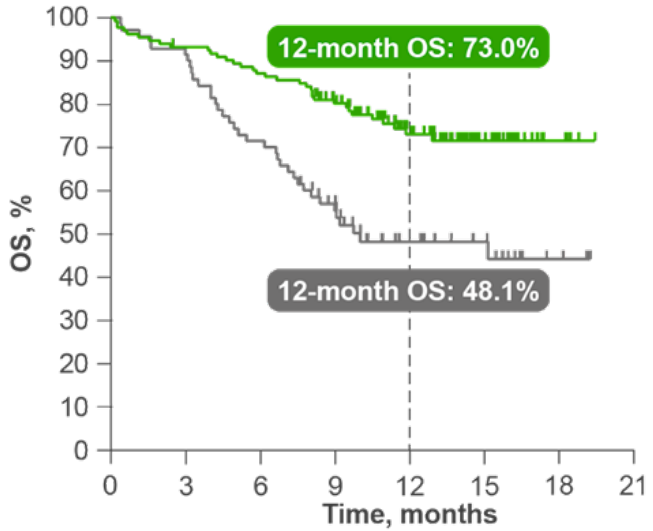
Events, %	Median, months	HR (95% CI)	p value[b]
28.9	NR (NE–NE)	0.55 (0.34–0.90)	0.0081
48.3	12.9 (8.7–NE)	—	—



	128	119	108	84	52	21	5	0
	58	54	47	32	17	5	2	0

PD-L1 TPS ≥50%

Events, %	Median, months	HR (95% CI)	p value[b]
25.8	NR (NE–NE)	0.42 (0.26–0.68)	0.0001
51.4	10.0 (7.5–NE)	—	—



	132	122	114	96	56	25	6	0
	70	64	50	35	19	13	4	0

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

Analysis cut-off date: 8 November 2017.
[a]No statistical conclusions can be drawn from exploratory endpoints. [b]Nominal and one-sided.

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

KEYNOTE-189: Exploratory endpoint – OS by PD-L1 TPS (5-year update)[a]

Median follow up: 64.6 months. Statistical significance was met for the primary endpoints in Interim Analysis 1 (2018)

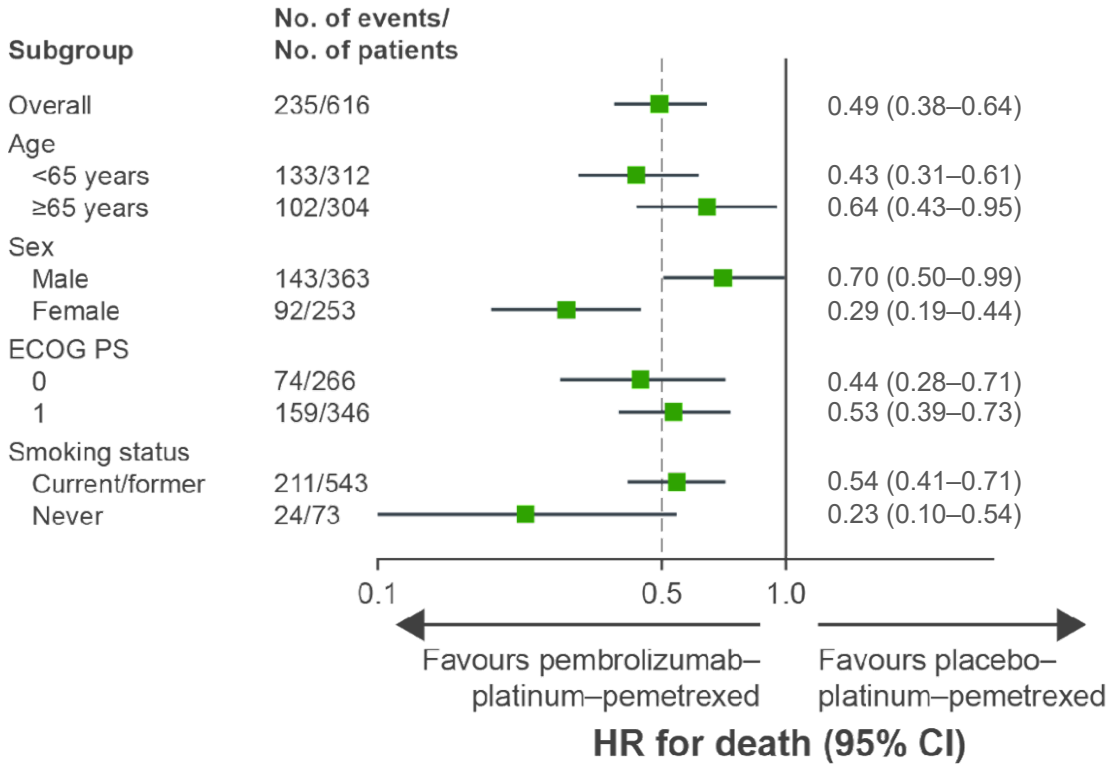
	PD-L1 TPS ≥50%		PD-L1 TPS 1%-49%		PD-L1 TPS <1%	
	Pembro-plat-pem (n = 132)	Placebo-plat-pem (n = 70)	Pembro-plat-pem (n = 128)	Placebo-plat-pem (n = 58)	Pembro-plat-pem (n = 127)	Placebo-plat-pem (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

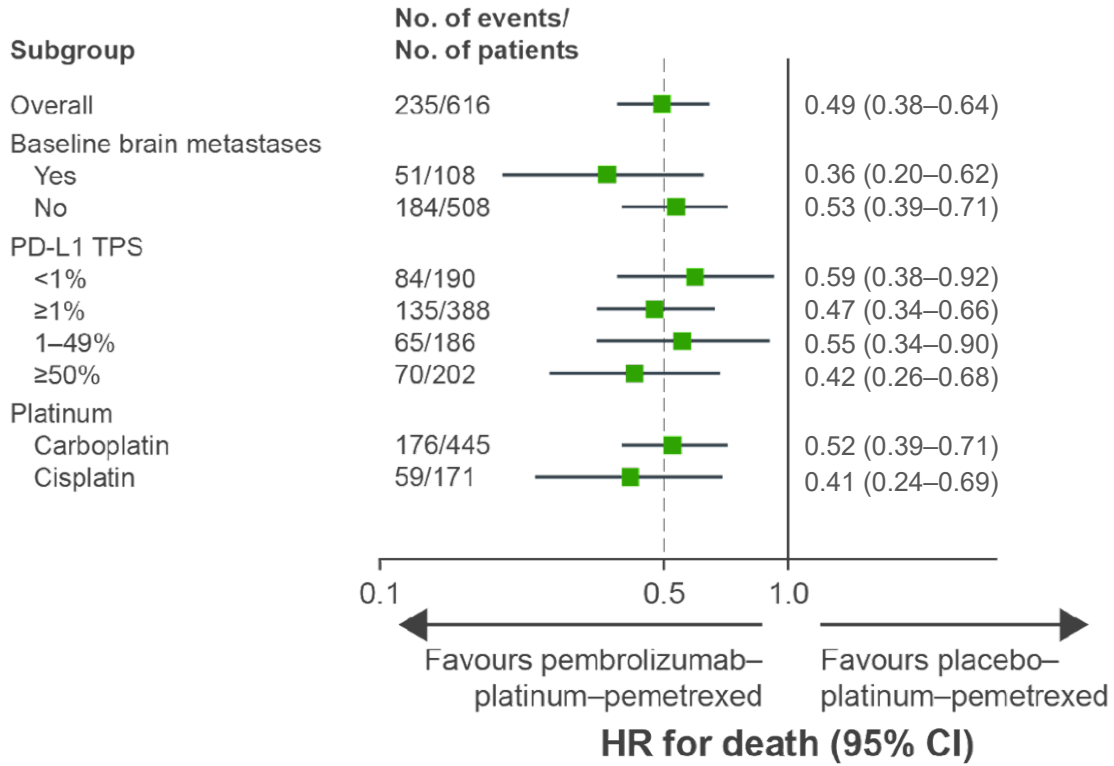
Adapted from Garassino MC et al. J Clin Oncol 2023.

Analysis cut-off date: 8 March 2022.
[a]No statistical conclusions can be drawn from exploratory endpoints. [b]Kaplan-Meier estimate.
Garassino MC *et al. J Clin Oncol.* 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: Exploratory endpoint – OS in key subgroups (original analysis)[a]

Median follow up: 10.5 months





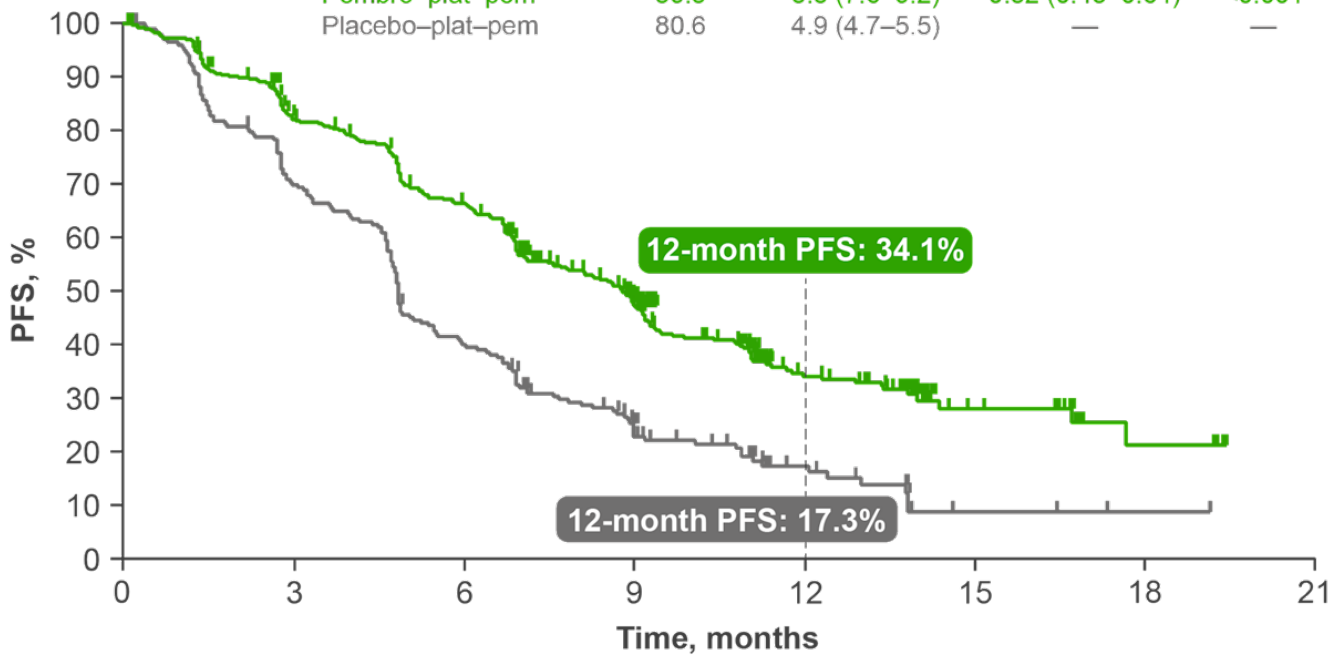
Adapted from: Gandhi L et al. N Engl J Med 2018.

Analysis cut-off date: 8 November 2017.
[a]No statistical conclusions can be drawn from exploratory endpoints.
Gandhi L *et al. N Engl J Med* 2018;378:2078–2092.

KEYNOTE-189: 1-year landmark PFS in the ITT population (original analysis)[a,b,1,2]

Median follow up: 10.5 months

Treatment arm	Events, n	Median, months	HR (95% CI)	p value
Pembro–plat–pem	59.5	8.8 (7.6–9.2)	0.52 (0.43–0.64)	<0.001
Placebo–plat–pem	80.6	4.9 (4.7–5.5)	—	—



No. at risk								
Pembro–plat–pem	410	322	256	149	60	17	5	0
Placebo–plat–pem	206	141	80	40	16	3	1	0

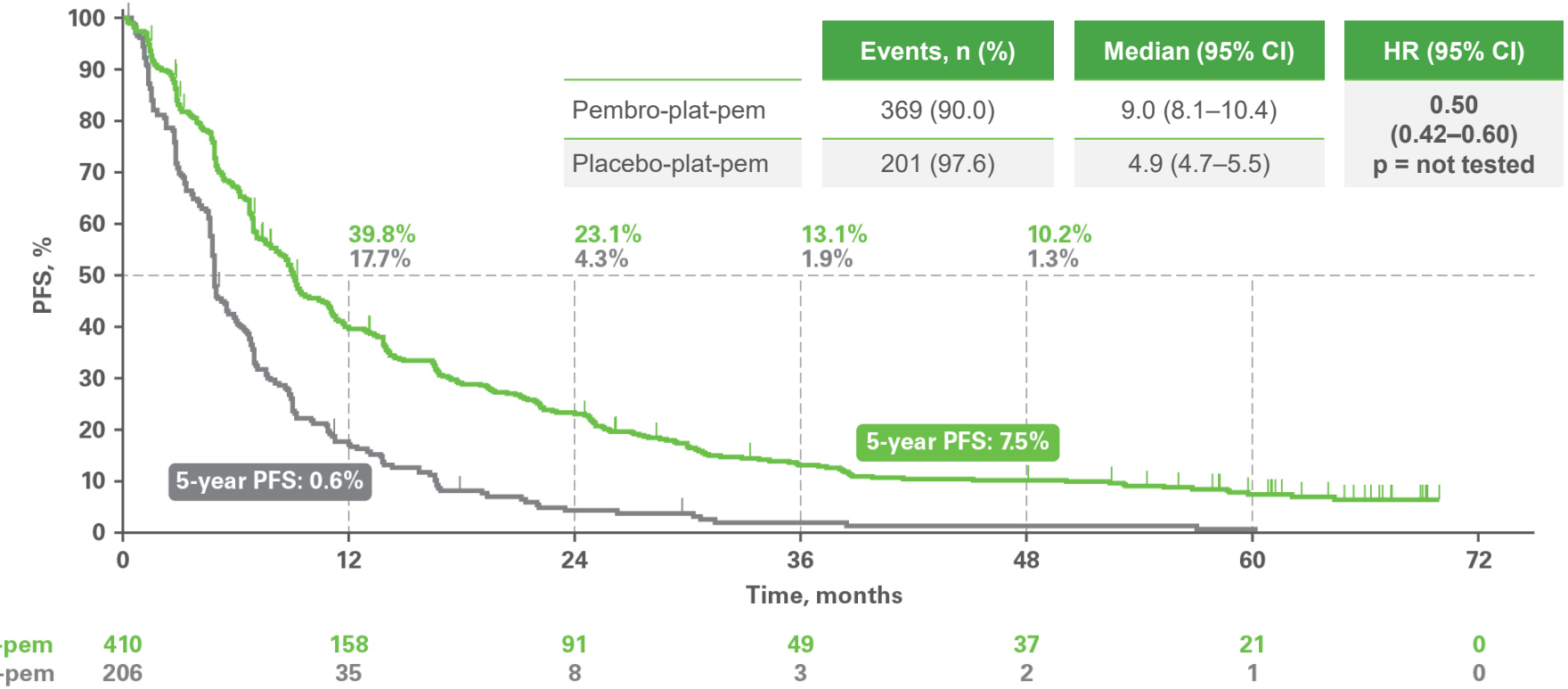
Adapted from: Gandhi L et al. N Engl J Med 2018; Gandhi L et al. AACR 2018.

Analysis cut-off date: 8 November 2017.
[a]OS and PFS were both primary endpoints. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review.

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

KEYNOTE-189: PFS in the ITT population in the 5-year update (exploratory analysis, p not tested)[a,b]

Median follow up: 64.6 months. Statistical significance was met for the primary endpoints in Interim Analysis 1 (2018)



	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro-plat-pem	369 (90.0)	9.0 (8.1–10.4)	**0.50 (0.42–0.60) p = not tested**
Placebo-plat-pem	201 (97.6)	4.9 (4.7–5.5)	

Adapted from Garassino MC et al. J Clin Oncol 2023.

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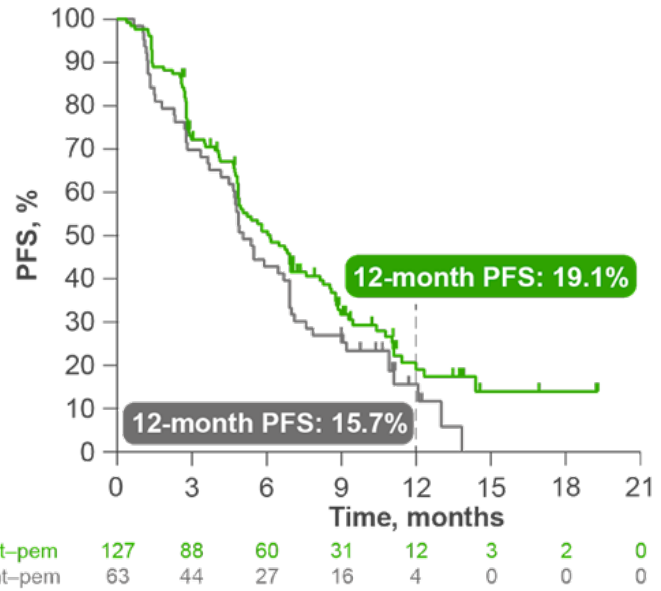
Analysis cut-off date: 8 March 2022. No statistical conclusions can be drawn from this analysis.
[a]OS and PFS were both primary endpoints. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review.
Garassino MC *et al. J Clin Oncol.* 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: Exploratory endpoint – 1-year landmark PFS by PD-L1 TPS (original analysis)[a,b,1,2]

Median follow up: 10.5 months

PD-L1 TPS <1%

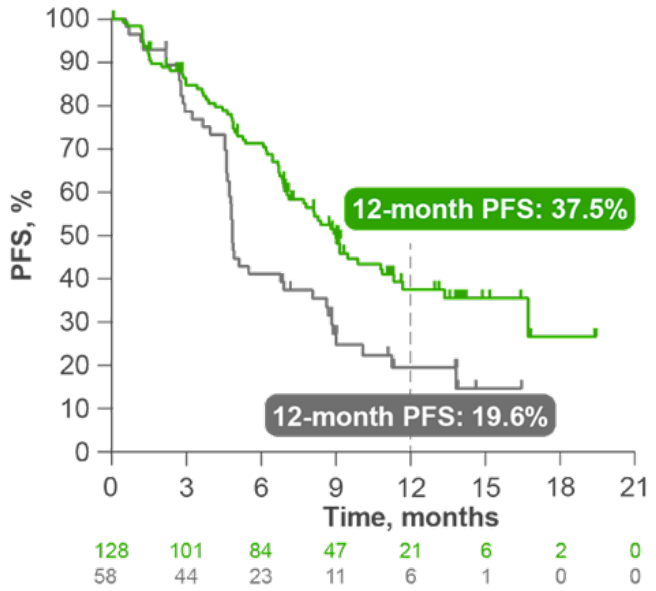
Treatment arm	Events, %	Median, months	HR (95% CI)	p value[c]
Pembro–plat–pem	72.4	6.1 (4.9–7.6)	0.75 (0.53–1.05)	0.0476
Placebo–plat–pem	85.7	5.1 (4.5–6.9)	—	—



No. at risk								
Pembro–plat–pem	127	88	60	31	12	3	2	0
Placebo–plat–pem	63	44	27	16	4	0	0	0

PD-L1 TPS 1–49%

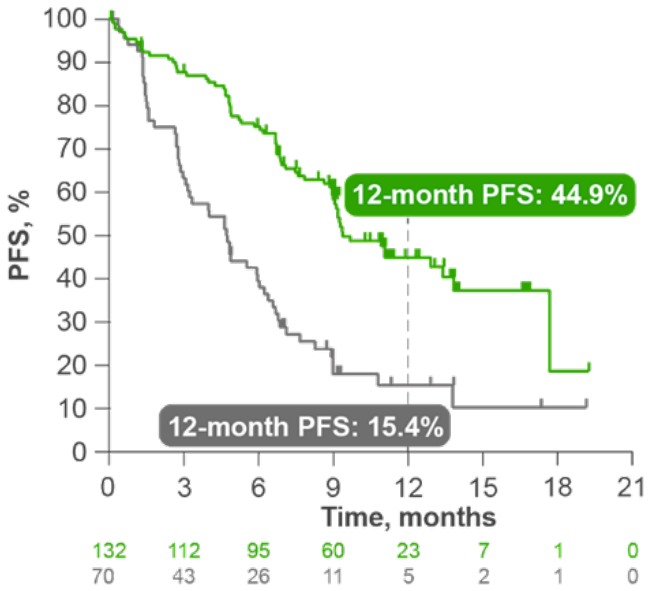
Events, %	Median, months	HR (95% CI)	p value[c]
54.7	9.0 (7.1–11.3)	0.55 (0.37–0.81)	0.0010
75.9	4.9 (4.7–6.9)	—	—



No. at risk								
Pembro–plat–pem	128	101	84	47	21	6	2	0
Placebo–plat–pem	58	44	23	11	6	1	0	0

PD-L1 TPS ≥50%

Events, `%	Median, months	HR (95% CI)	p value[c]
51.5	9.4 (9.0–13.8)	0.36 (0.25–0.52)	<0.00001
80.0	4.7 (3.1–6.0)	—	—



No. at risk								
Pembro–plat–pem	132	112	95	60	23	7	1	0
Placebo–plat–pem	70	43	26	11	5	2	1	0

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

Analysis cut-off date: 8 November 2017.
[a]No statistical conclusions can be drawn from exploratory endpoints. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [c]Nominal and one-sided.
1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Gandhi L *et al*. Presented at the 2018 American Association for Cancer Research (AACR) Annual Meeting, 14–18 April, 2018, Chicago, USA.

KEYNOTE-189: PFS by PD-L1 TPS in the 5-year update (exploratory analysis, p not tested)[a,b]

Median follow up: 64.6 months. Statistical significance was met for the primary endpoints in Interim Analysis 1 (2018)

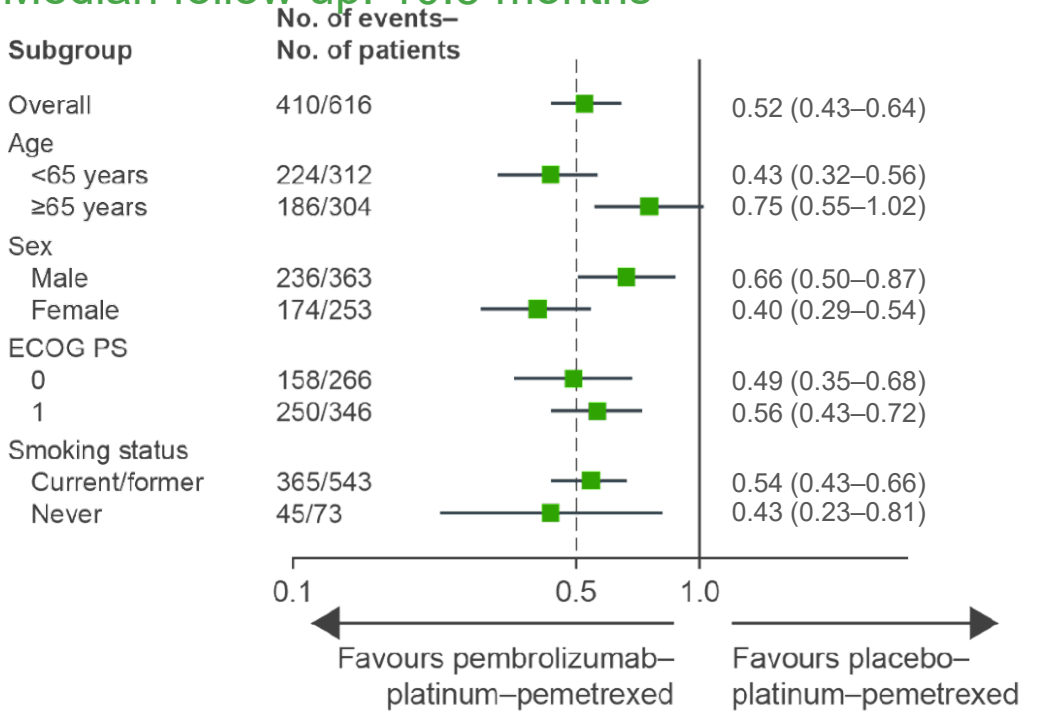
	PD-L1 TPS ≥50%		PD-L1 TPS 1%-49%		PD-L1 TPS <1%	
	Pembro-plat-pem (n = 132)	Placebo-plat-pem (n = 70)	Pembro-plat-pem (n = 128)	Placebo-plat-pem (n = 58)	Pembro-plat-pem (n = 127)	Placebo-plat-pem (n = 63)
PFS HR (95% CI)	0.35 (0.25–0.49)		0.57 (0.41–0.80)		0.67 (0.49–0.92)	
5-y PFS rate,[c] %	12.8	0	6.5	1.9	2.4	0

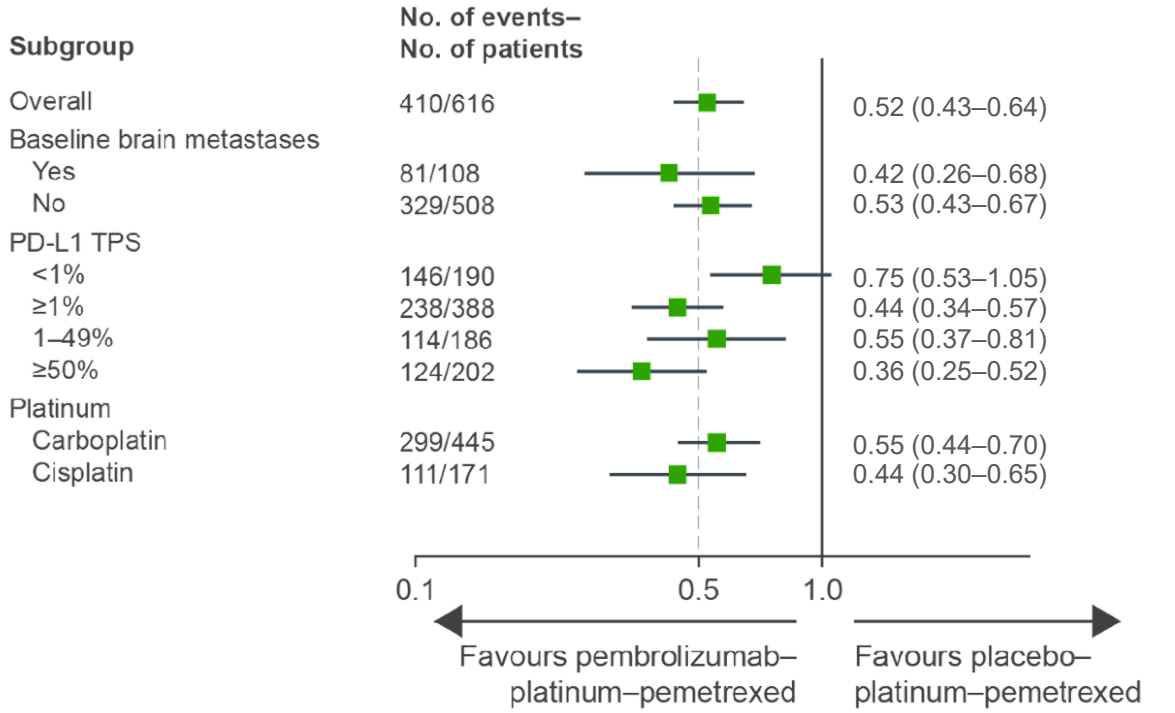
Adapted from Garassino MC et al. J Clin Oncol 2023.

Analysis cut-off date: 8 March 2022.
[a]No statistical conclusions can be drawn from this analysis. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [c]Kaplan-Meier estimate.
Garassino MC *et al. J Clin Oncol*. 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: Exploratory endpoint – PFS in key subgroups (original analysis)[a,b]

Median follow up: 10.5 months





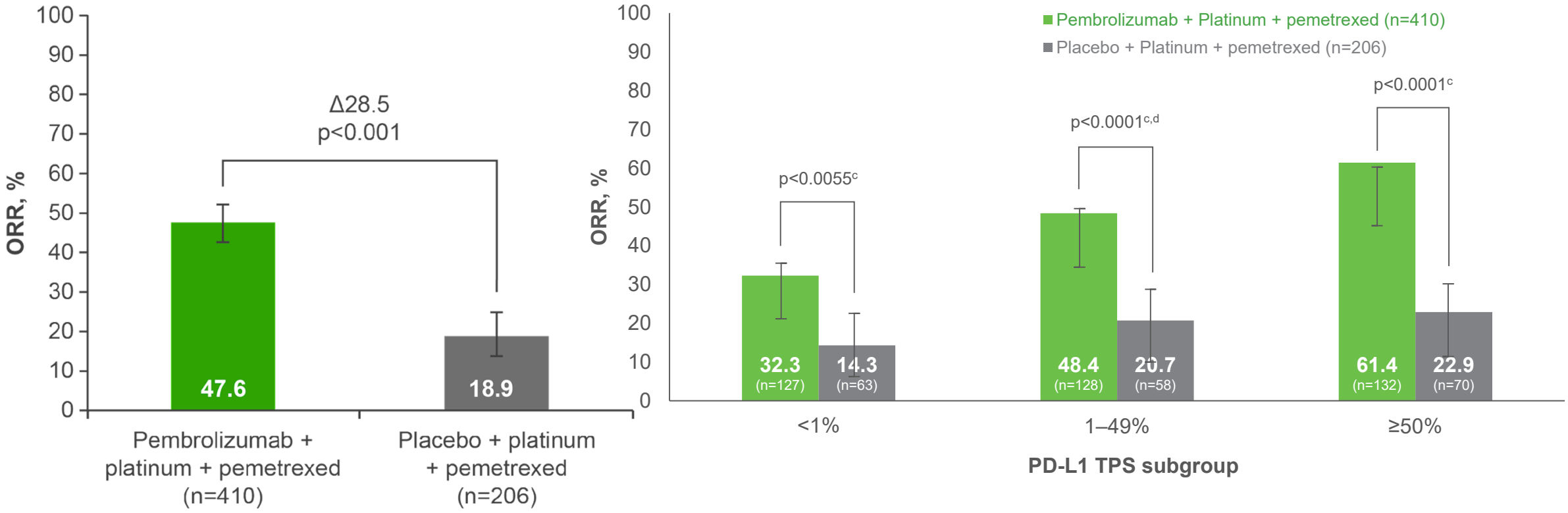
Adapted from: Gandhi L et al. N Engl J Med 2018.

Analysis cut-off date: 8 November 2017.
[a]Exploratory endpoint. No statistical conclusions can be drawn from exploratory endpoints. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review.

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

KEYNOTE-189: ORR in the ITT population[a,1] and exploratory endpoint ORR by PD-L1 TPS[b,c,1,2] (original analysis)

Median follow up: 10.5 months



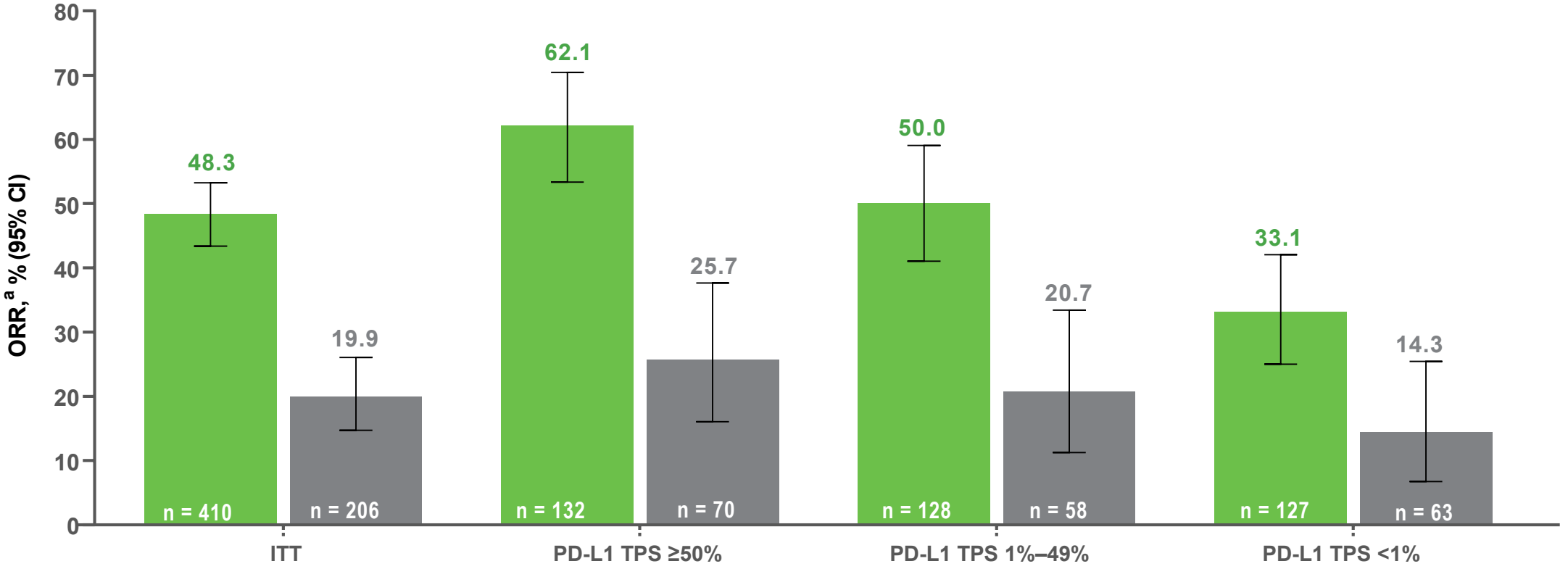
Adapted from: Gandhi L et al. N Engl J Med 2018; Gandhi L et al. AACR 2018.

Analysis cut-off date: 8 November 2017.
[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [b]No confirmatory clinical conclusion can be drawn from exploratory endpoints. [c]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [d]Nominal and one-sided.

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.

KEYNOTE-189: ORR in the ITT population and exploratory endpoint ORR by PD-L1 TPS in the 5-year update (exploratory analysis, p not tested)

Median follow up: 64.6 months. Statistical significance was met for the primary endpoints in Interim Analysis 1 (2018).



Adapted from Garassino MC et al. J Clin Oncol 2023.

Analysis cut-off date: 8 November 2017.
[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review.

Garassino MC *et al. J Clin Oncol.* 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: DOR and DCR in the ITT population (original analysis)[a]

Median follow up: 10.5 months

Best response and DOR

Best response,[b] n (%)	Pembro-plat-pem (n=410)	Placebo-plat-pem (n=206)
CR	2 (0.5)	1 (0.5)
PR	193(47.1)	38 (18.4)
SD	152 (37.1)	106 (51.5)
PD	36 (8.8)	36 (17.5)
DOR, months	**Pembro-plat-pem (n=195)**	**Placebo-plat-pem (n=39)**
Median	11.2	7.8
Range[c]	1.1+ to 18.0+	2.1+ to 16.4+
	Pembro-plat-pem	**Placebo-plat-pem**
DCR, %[d]	84.6	70.4

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

Analysis cut-off date: 8 November 2017.
[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [b]An additional 27 (6.6%) patients in the pembrolizumab + platinum + pemetrexed arm and 25 (12.1%) in the placebo + platinum + pemetrexed arm did not have ≥2 evaluable sets of radiographic images.[2] [c]+ denotes a response that was ongoing at the analysis cut-off date. [d]The proportion of patients with a confirmed complete or partial response or stable disease.
Gandhi L *et al. N Engl J Med* 2018;378:2078–2092 (and supplementary appendix)

KEYNOTE-189: DOR in the ITT population and by PD-L1 TPS in the 5-year update (exploratory analysis, p not tested)

Median follow up: 64.6 months. Statistical significance was met for the primary endpoints in Interim Analysis 1 (2018).

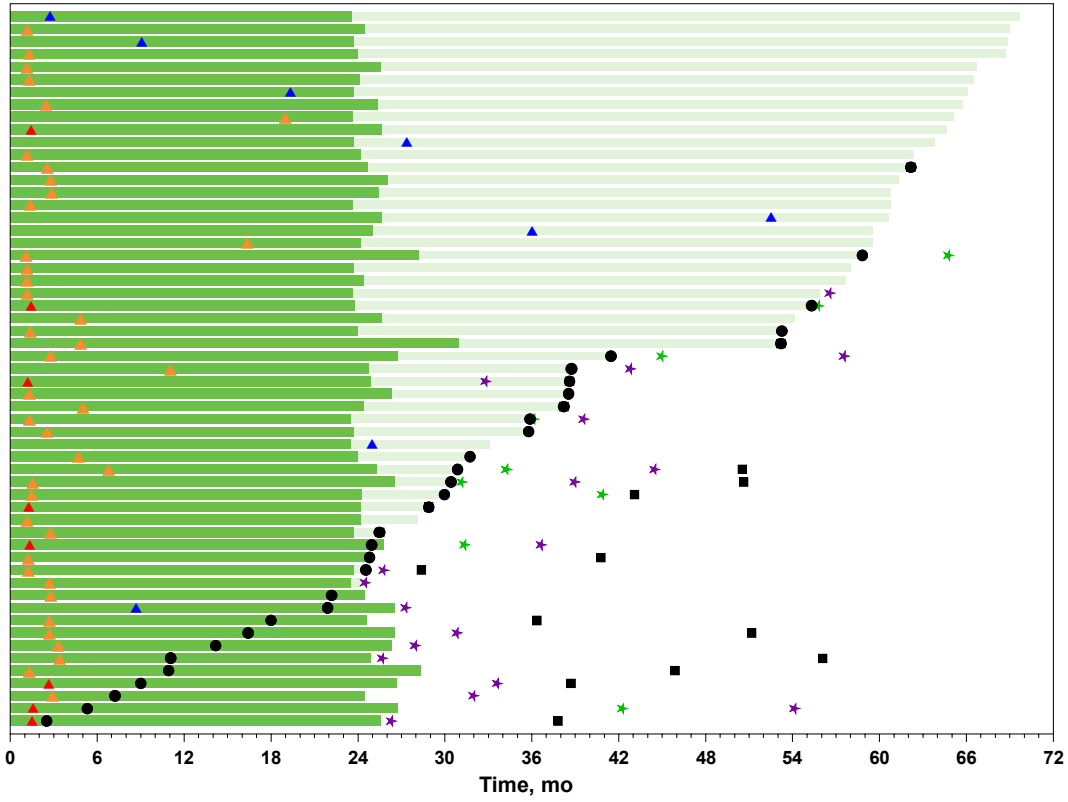
	ITT		PD-L1 TPS ≥50%		PD-L1 TPS 1%-49%		PD-L1 TPS <1%	
	Pembro-plat-pem	Placebo-plat-pem	Pembro-plat-pem	Placebo-plat-pem	Pembro-plat-pem	Placebo-plat-pem	Pembro-plat-pem	Placebo-plat-pem
DOR[a] Median (range), mo	12.7 (1.1+ to 68.3+)	7.1 (2.4 to 31.5)	15.3 (1.2+ to 68.3+)	7.1 (3.4 to 31.5)	13.6 (2.1+ to 67.6+)	7.6 (2.4 to 31.0+)	10.8 (1.1+ to 59.4+)	7.8 (4.1 to 28.3+)

Adapted from Garassino MC et al. J Clin Oncol 2023.

Analysis cut-off date: 8 March 2022.
[a]Kaplan-Meier estimate.

Garassino MC *et al. J Clin Oncol*. 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: Outcomes in patients who completed 35 cycles of Pembrolizumab in the 5-year update (exploratory analysis, p not tested)



	n = 57
ORR (95% CI),[a] %	86.0 (74.2–93.7)
Best overall response, n (%)	
CR	8 (14.0)
PR	41 (71.9)
Median DOR (range),[b] mo	57.7 (4.2 to 68.3+)
3-y OS rate after completing 35 cycles[c]	71.9%
Alive without PD or subsequent therapy, n (%)	23 (40.4)

Adapted from Garassino MC et al. J Clin Oncol 2023.

Analysis cut-off date: 8 March 2022.
[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [b]Kaplan-Meier estimate. [c]Approximately 5 years after randomisation.
Garassino MC *et al. J Clin Oncol.* 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: Exposure to study treatment (original analysis)[1,2]

Median follow up: 10.5 months

	Pembrolizumab + platinum + pemetrexed (n=405)	Placebo + platinum + pemetrexed (n=202)
Treatment duration, mean (± SDev), months	7.4 (4.7)	5.4 (4.3)
Treatment cycles, months		
Mean (± SDev)	10.9 (6.4)	8.1 (5.7)
Median (range)	10.0 (1–30)	7 (1–26)
4 cycles of platinum, n (%)	334 (82.5)	150 (74.3)
≥5 cycles of pemetrexed, n (%)	310 (76.5)	135 (66.8)
≥5 cycles of pembrolizumab or placebo, n (%)	320 (79.0)	138 (68.3)

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

Analysis cut-off date: 8 November 2017.

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

KEYNOTE-189: Summary of AEs in the as-treated population (original analysis)[a]

Median follow up: 10.5 months

AE, n (%)	Pembrolizumab + platinum + pemetrexed (n=405)	Placebo + platinum + pemetrexed (n=202)
All causes	404 (99.8)	200 (99.0)
Grade 3–5[b]	272 (67.2)	133 (65.8)
Led to death	27 (6.7)	12 (5.9)
Led to discontinuation		
All treatment[c]	56 (13.8)	16 (7.9)
Any treatment component	112 (27.7)	30 (14.9)
Immune-mediated[d]	92 (22.7)	24 (11.9)
Grade 3–5[b]	36 (8.9)	9 (4.5)
Led to death	3 (0.7)[e]	0

Adapted from: Gandhi L et al. N Engl J Med 2018.

Analysis cut-off date: 8 November 2017.
[a]All patients who had undergone randomisation and received ≥1 dose of the assigned combination therapy. AEs that occurred during crossover from the placebo-combination group to pembrolizumab monotherapy are excluded. [b]AEs graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0. [c]Includes patients who discontinued pemetrexed, a platinum-based drug and pembrolizumab or placebo because of an AE at any time, and patients who discontinued pemetrexed and pembrolizumab or placebo for an AE after completing 4 cycles of a platinum-based drug. [d]Regardless of attribution to trial drug by the investigator. [e]All deaths were due to pneumonitis.

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

KEYNOTE-189: Summary of AEs in the as-treated population (updated analysis at 18.7 months of median follow up)[a]

Median follow up: 18.7 months[1]

AE, n (%)	Pembrolizumab + platinum + pemetrexed (n=405)	Placebo + platinum + pemetrexed (n=202)
All causes	404 (99.8)	200 (99.0)
Grade 3–5	291 (71.9)	135 (66.8)
Led to death[b]	29 (7.2)	14 (6.9)
Led to discontinuation of any treatment component	136 (33.6)	33 (16.3)
Immune-mediated	107 (26.4)	26 (12.9)
Grade 3–5	44 (10.9)	9 (4.5)
Led to death	2 (0.5)	0

Adapted from: Gadgeel S et al. J Clin Oncol. 2020.

Analysis cut-off date: 21 September 2018.
[a]Median (range) duration of exposure to originally allocated study treatment was 7.2 months (0.03–30.4) in the pembrolizumab + platinum + pemetrexed arm and 4.2 months (0.03–25.0) in the placebo + platinum + pemetrexed arm.[2] [b]8 (2.0%) of patients in the pembrolizumab + platinum + pemetrexed arm and 2 (1.0%) in the placebo + platinum + pemetrexed arm died from AEs attributed to study treatment by the investigator.[1]

1. Gadgeel S *et al. J Clin Oncol.* 2020;38(14):1505–1517; 2. Gadgeel S *et al.* Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May – 4 June, 2019, Chicago, USA.

KEYNOTE-189: Summary of AEs in the as-treated population (5-year update)

Median follow up: 64.6 months

Adverse event, n (%)	All treated patients		35 cycles of pembrolizumab (n = 57)
	Pembro-plat-pem n = 405	Placebo-plat-pem n = 202	
Any AE	404 (99.8)	200 (99.0)	57 (100)
Grade 3–5	295 (72.8)	136 (67.3)	38 (66.7)
Led to discontinuation of any treatment component	145 (35.8)	35 (17.3)	19 (33.3)
Led to death[a]	29 (7.2)	14 (6.9)	0
Treatment-related AE	377 (93.1)	183 (90.6)	56 (98.2)
Grade 3–5	212 (52.3)	85 (42.1)	27 (47.4)
Immune-mediated AEs and infusion reactions[b]	113 (27.9)	27 (13.4)	23 (40.4)
Grade 3–5	52 (12.8)	9 (4.5)	7 (12.3)

Adapted from Garassino MC et al. J Clin Oncol 2023.

Data cutoff date: March 8, 2022

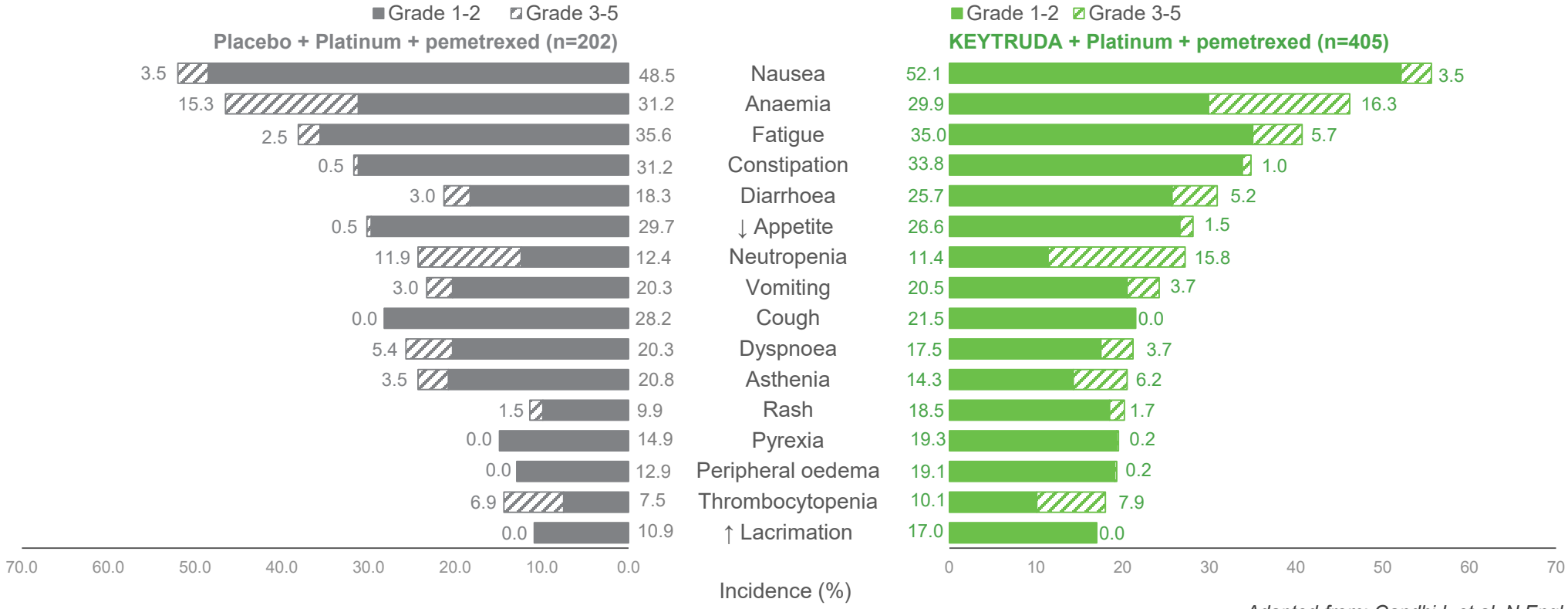
[a]All deaths were previously reported in Rodriguez-Abreu D et al. Ann Oncol 2021,32:881-895.

[b]Events considered regardless of attribution to treatment or immune relatedness by the investigator.

Garassino MC *et al. J Clin Oncol*. 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: All-cause AEs occurring in ≥15% of patients in the as-treated population (original analysis)[a,b]

Median follow up: 10.5 months

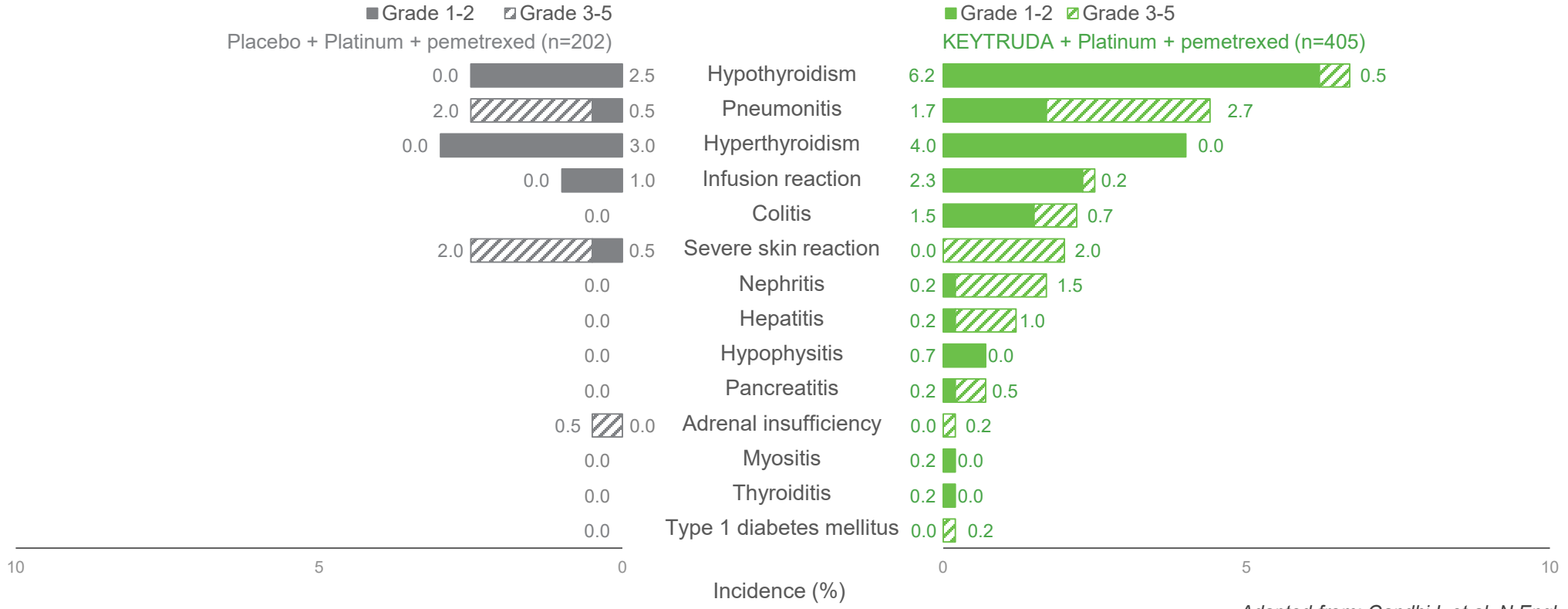


Adapted from: Gandhi L et al. N Engl J Med 2018.

Analysis cut-off date: 8 November 2017.
[a]AEs that occurred during crossover from the placebo-combination group to pembrolizumab monotherapy are excluded. [b]AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.
Gandhi L *et al. N Engl J Med* 2018;378:2078–2092.

KEYNOTE-189: Immune-mediated AEs in the as-treated population (original analysis)[a,b]

Median follow up: 10.5 months



Adapted from: Gandhi L et al. N Engl J Med 2018.

Analysis cut-off date: 8 November 2017.
[a]Regardless of attribution to a trial drug by the investigator. [b]AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0. [c]Includes three Grade 5 AEs in the pembrolizumab group.
Gandhi L *et al. N Engl J Med* 2018;378:2078–2092.

KEYNOTE-189: Renal events (original analysis)[1,2]

Median follow up: 10.5 months

Acute kidney injury

- Frequency: 5.2% (n=21) vs. 0.5% (n=1) in the pembrolizumab + platinum + pemetrexed vs. placebo + platinum + pemetrexed arms, respectively
  - Grade 3–5 frequency:[a] 2.0% (n=8) vs. 0%, respectively
  - Grade 5 frequency: 0.5% (n=2) with pembrolizumab + platinum + pemetrexed
- Grade ≤3 acute kidney injury had resolved or was resolving in 47% (9/19) of patients at the analysis cut-off date

Nephritis[b,c]

- Any-grade frequency: 1.7% (n=7) vs. 0% in the pembrolizumab + platinum + pemetrexed vs. placebo + platinum + pemetrexed arms, respectively
  - Grade 3–5 frequency: 1.5% (n=6) vs. 0%
  - Grade 5 frequency: 0%

Analysis cut-off date: 8 November 2017.
[a]Led to discontinuation of all trial therapy in all eight patients in the pembrolizumab combination group. [b]Includes preferred terms of autoimmune nephritis, nephritis and tubulointerstitial nephritis.[2] [c]Nephritis occurred in carboplatin-treated patients only.[1]

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.

KEYNOTE-189: Post-hoc analysis – Evaluation of outcomes in patients with baseline brain and liver metastases[a,1,2]

Median follow up: 18.7 months. This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn

- Extrapulmonary metastases to sites such as the liver and brain frequently occur in metastatic NSCLC and can be associated with a poor prognosis[2]
- **Objective of current analysis**: retrospectively evaluate outcomes among patients with baseline liver or brain metastases[1]
- The analysis was post-hoc and exploratory. Results were not controlled for multiplicity. The cut-off date for this analysis was 21 September 2018; median follow up was 18.7 months (range: 0.2–30.9 months)[1]

Analysis cut-off date: 21 September 2018.
[a]No other data was reported with this analysis.

1. Garassino MC *et al.* Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April, 2019, Atlanta, USA.; 2. Gibson AJW *et al. Med Oncol* 2018;35:117;

KEYNOTE-189: Post-hoc analysis – key baseline characteristics[a]

Median follow up: 18.7 months. This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn

Characteristic, n (%)[b]	Pembrolizumab + platinum + pemetrexed (n=410)	Placebo +platinum + pemetrexed (n=206)
Age, median (range), years	65.0 (34–84)	63.5 (34–84)
Male sex	254 (62)	109 (53)
ECOG PS 1	220 (54)	125 (61)
Liver metastases[c]	66 (16)	49 (24)
Stable brain metastases[c]	73 (18)	35 (17)
Previously treated	43 (10)	23 (11)

Characteristic, n (%)[b]	Pembrolizumab platinum + pemetrexed (n=410)	Placebo + platinum + pemetrexed (n=206)
Former/current smoker	362 (88)	181 (88)
PD-L1 TPS ≥1%	260 (63)	128 (62)
Carboplatin chosen	297 (72)	148 (72)
Prior thoracic radiation	29 (7)	19 (9)
Prior neoadjuvant therapy	5 (1)	6 (3)
Prior adjuvant therapy	25 (6)	14 (7)

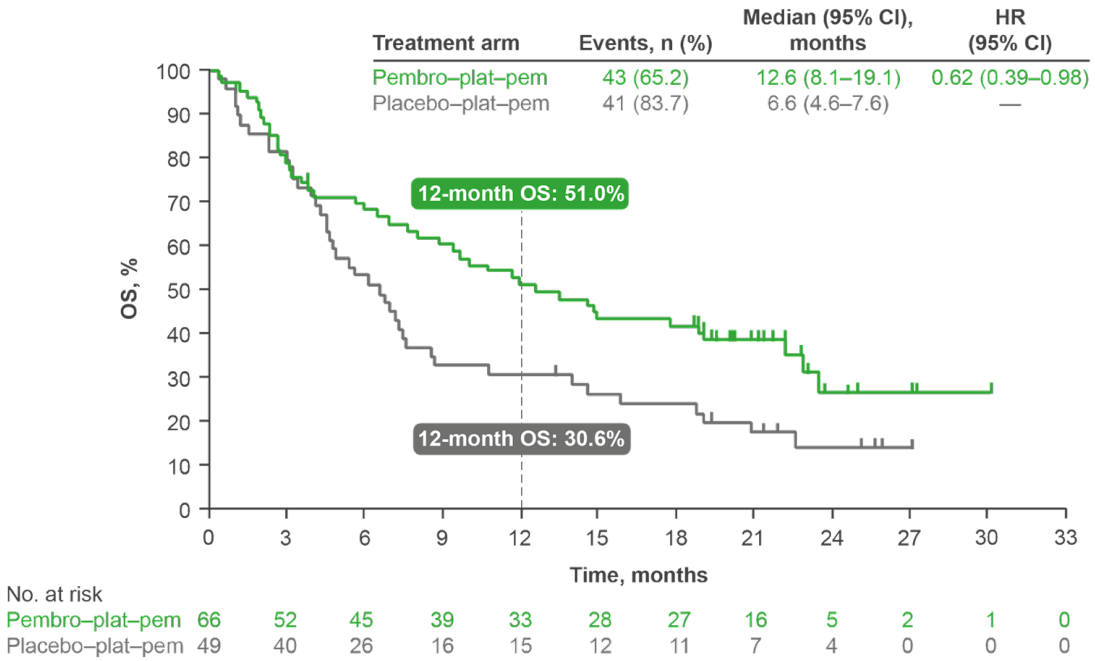
Adapted from: Garassino MC et al. AACR 2019.

Analysis cut-off date: 21 September 2018.
[a]No other data was reported with this analysis. This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn. [b]Unless otherwise stated.
[c]25 patients had both liver and brain metastases.
Garassino MC *et al.* Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April, 2019, Atlanta, USA.

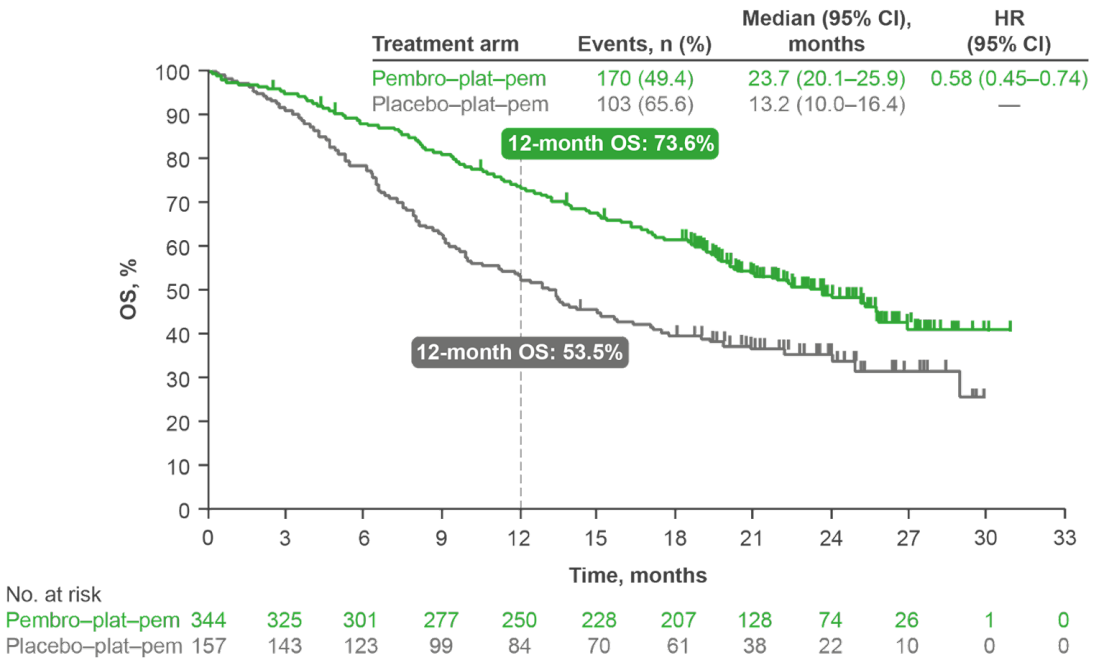
KEYNOTE-189: Post-hoc analysis – OS in patients with liver metastases[a]

Median follow up: 18.7 months. This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn

Patients with liver metastases



Patients without liver metastases



Adapted from: Garassino MC et al. AACR 2019.

Analysis cut-off date: 21 September 2018.

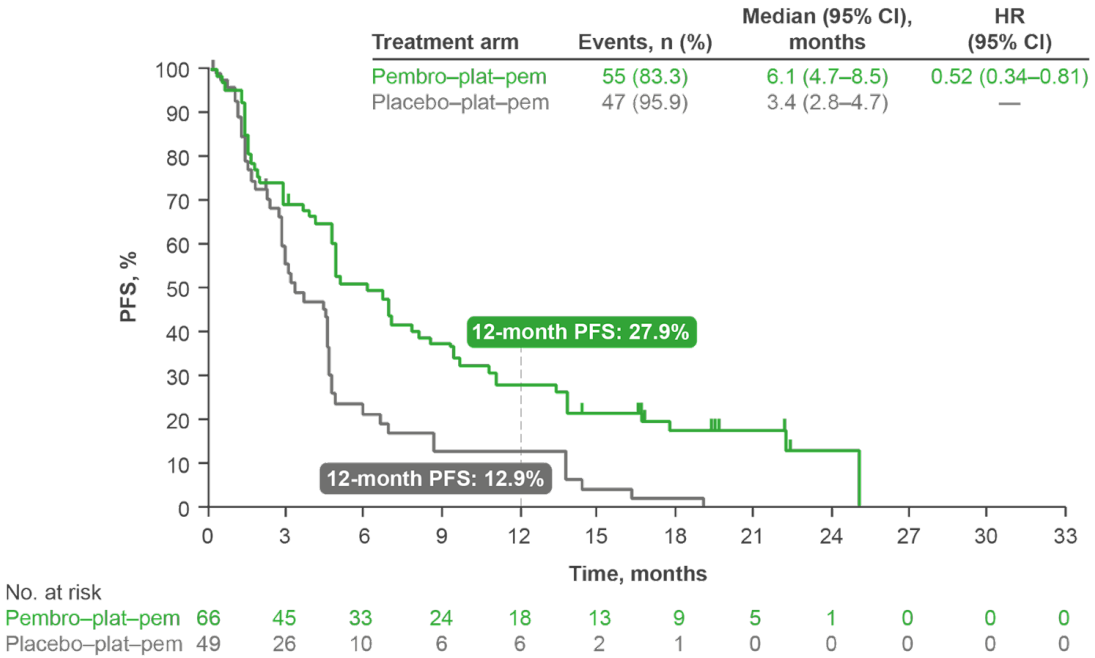
[a]**No other data was reported with this analysis.**

Garassino MC *et al*. Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April, 2019, Atlanta, USA.

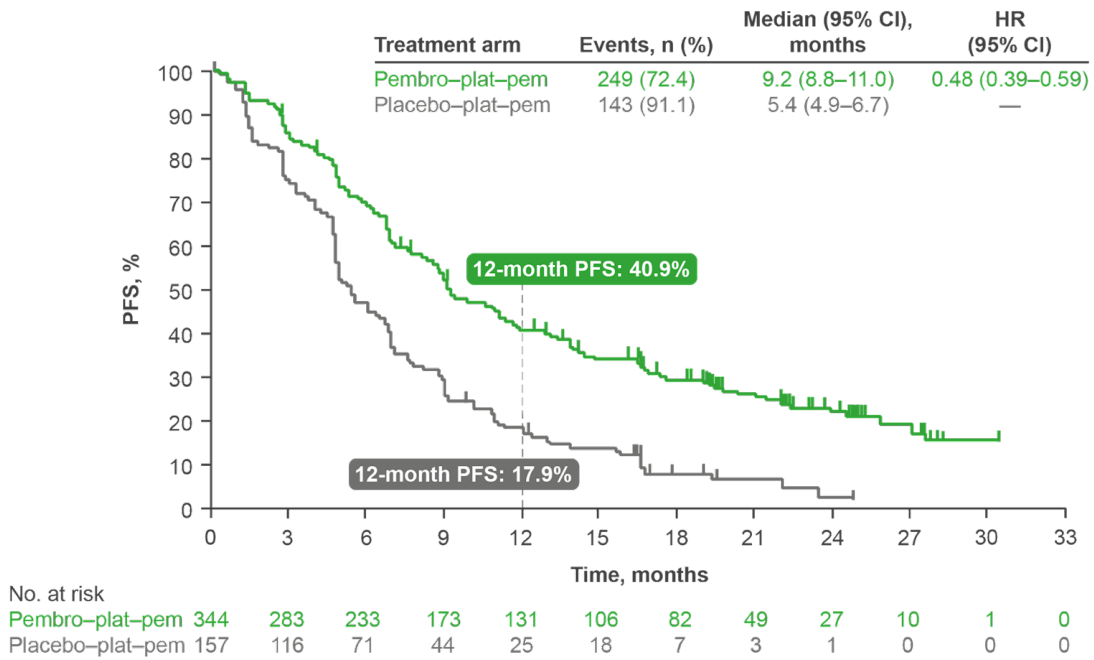
KEYNOTE-189: Post-hoc analysis – PFS in patients with liver metastases[a,b]

Median follow up: 18.7 months. This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn

Patients with liver metastases



Patients without liver metastases



Adapted from: Garassino MC et al. AACR 2019.

40

Analysis cut-off date: 21 September 2018.

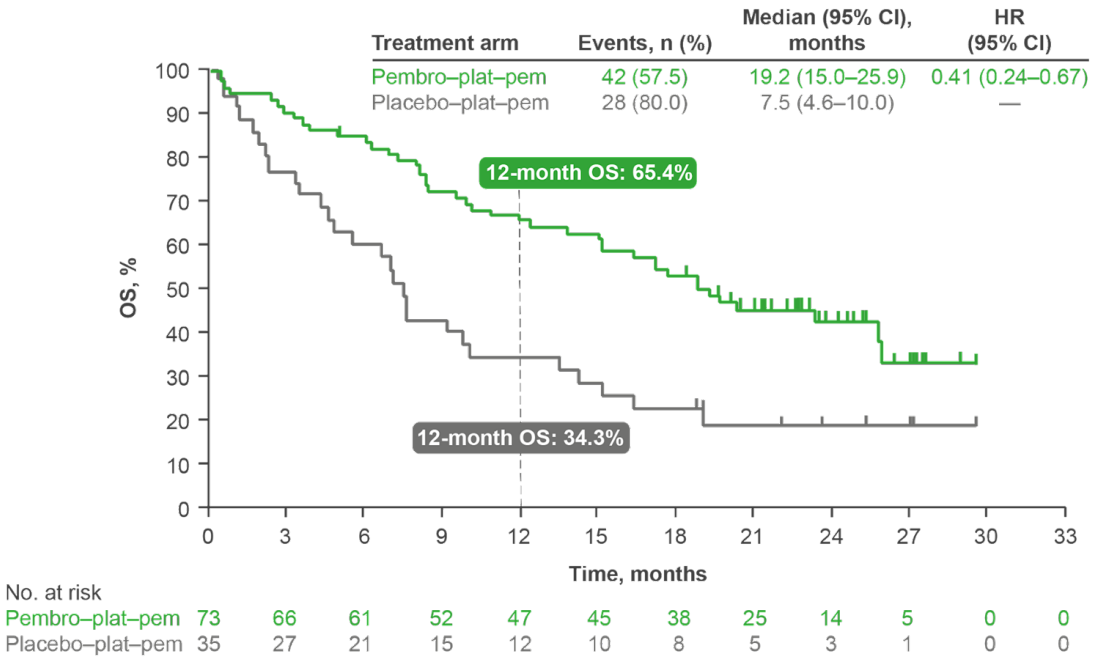
[a]No other data was reported with this analysis. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review.

Garassino MC *et al*. Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April, 2019, Atlanta, USA.

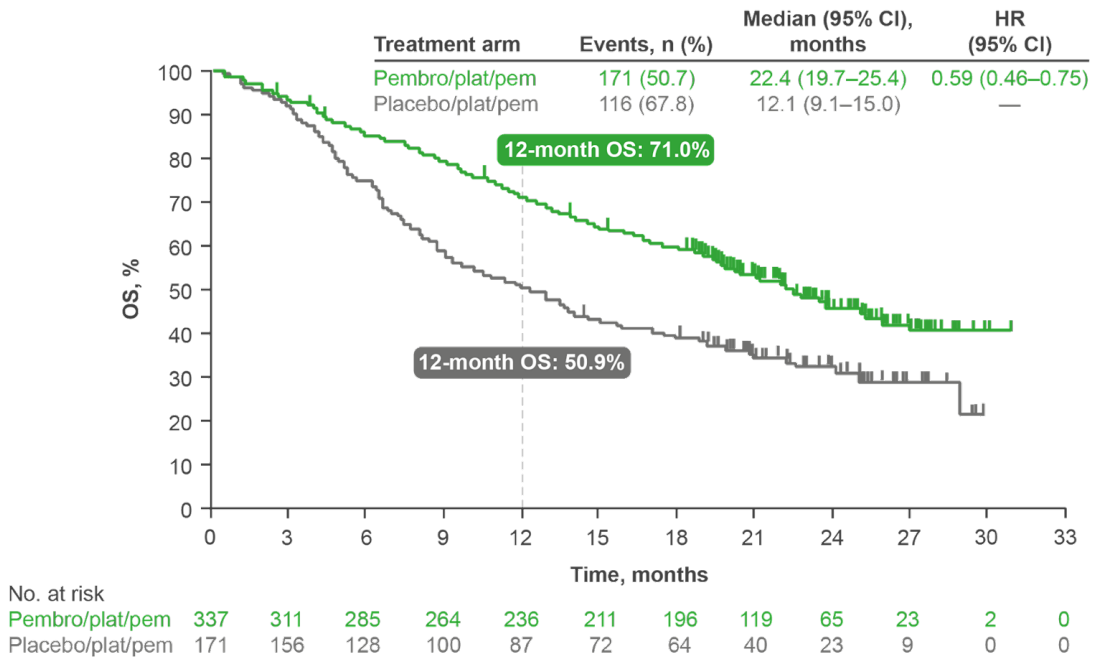
KEYNOTE-189: Post-hoc analysis – OS in patients with brain metastases[a]

Median follow up: 18.7 months. This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn

Patients with brain metastases



Patients without brain metastases



Adapted from: Garassino MC et al. AACR 2019.

41

Analysis cut-off date: 21 September 2018.

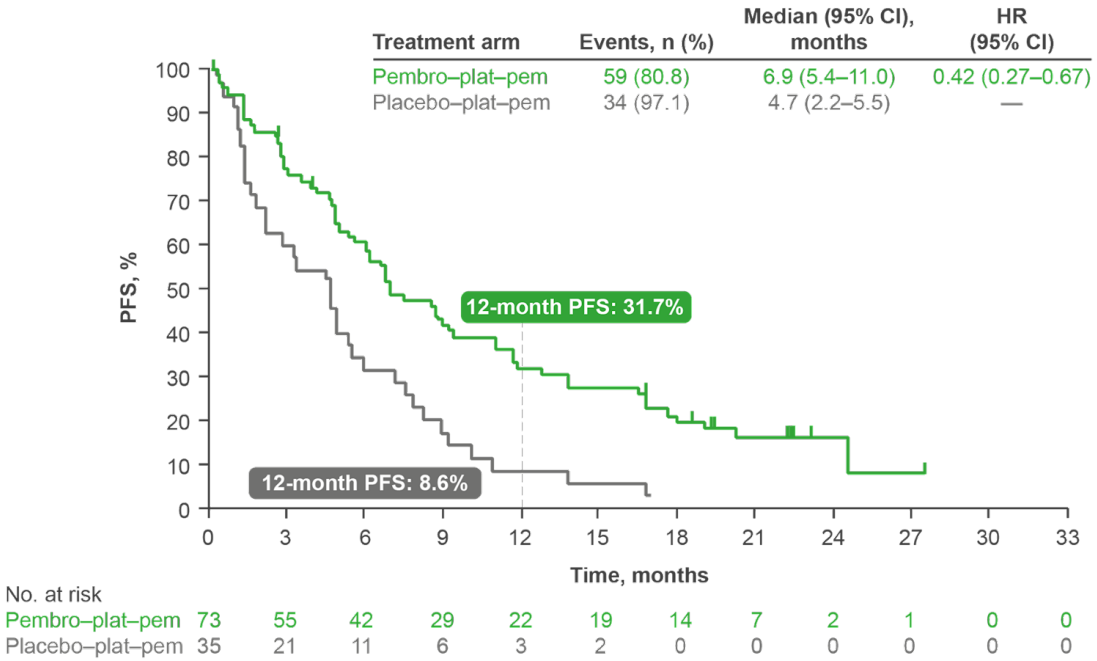
[a]**No other data was reported with this analysis.**

Garassino MC *et al*. Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April, 2019, Atlanta, USA.

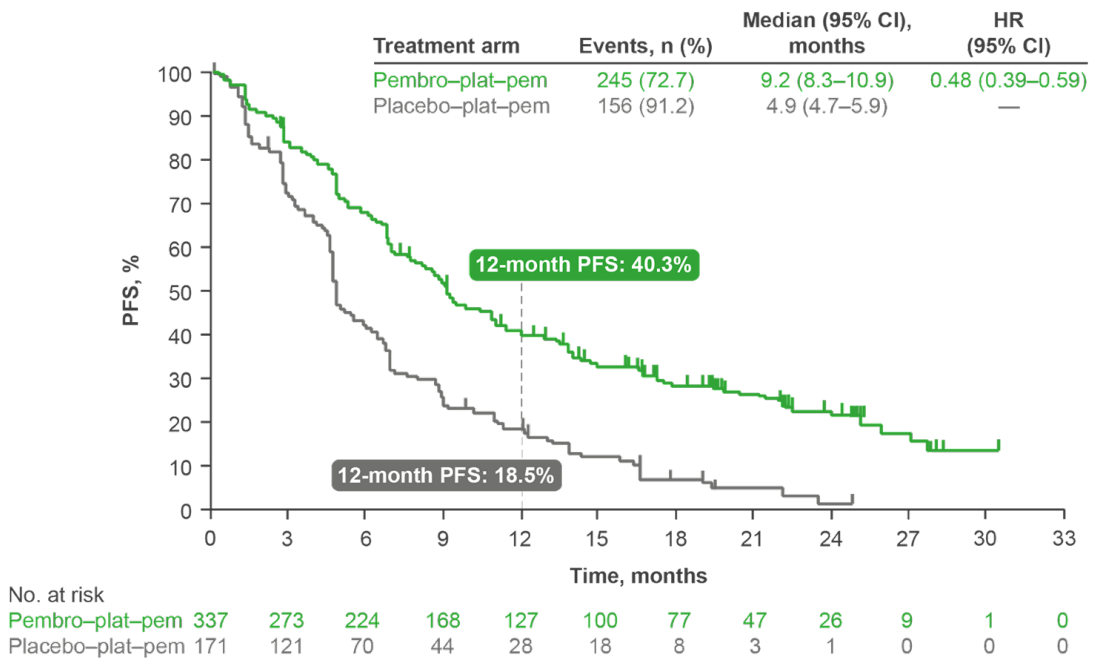
KEYNOTE-189: Post-hoc analysis – PFS in patients with brain metastases[a,b]

Median follow up: 18.7 months. This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn

Patients with brain metastases



Patients without brain metastases



Adapted from: Garassino MC et al. AACR 2019.

Analysis cut-off date: 21 September 2018.

[a]No other data was reported with this analysis. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review.

Garassino MC *et al*. Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April, 2019, Atlanta, USA.

KEYNOTE-189: QLQ-C30 Completion[a] and compliance[b] rates

Median follow up: 10.5 months. This analysis was exploratory, and no statistical conclusions can be drawn

		Pembrolizumab + platinum + pemetrexed (n=402) n (%) or n/N (%)	Placebo + platinum + pemetrexed (n=200) n (%) or n/N (%)
Baseline		359 (89%)	180 (90%)
Week 3	Completion Compliance	362 (90%) 362/389 (93%)	171 (86%) 171/186 (92%)
Week 6	Completion Compliance	342 (85%) 342/360 (95%)	154 (77%) 154/175 (88%)
Week 9	Completion Compliance	308 (77%) 308/342 (90%)	140 (70%) 140/156 (89%)
Week 12	Completion Compliance	319 (79%) 319/354 (90%)	149 (75%) 149/167 (89%)
Week 21	Completion Compliance	249 (62%) 249/326 (76%)	91 (46% 91/143 (64%)
Week 30	Completion Compliance	210 (52%) 210/278 (76%)	63 (32%) 63/88 (72%)

Analysis cut-off date: 8 November 2017. HRQoL was an exploratory endpoint.
[a]Completion was defined as completing at least one item among the total patient-reported outcome analysis population. [b]Compliance was defined as completing at least one item at each timepoint, as listed in the numerator for each group, among patients who were expected to complete at each timepoint (e.g. among those who had not discontinued study treatment), as listed in the denominator for each group

Garassino MC *et al. Lancet Oncol*. 2020;21:387–397.

KEYNOTE-189: QLQ-LC13 Completion[a] and compliance[b] rates

Median follow up: 10.5 months. This analysis was exploratory, and no statistical conclusions can be drawn

		Pembrolizumab + platinum + pemetrexed (n=402) n (%) or n/N (%)	Placebo + platinum + pemetrexed (n=200) n (%) or n/N (%)
Baseline		357 (89%)	179 (90%)
Week 3	Completion Compliance	361 (90%) 361/389 (93%)	170 (85%) 170/186 (91%)
Week 6	Completion Compliance	341 (85%) 341/360 (95%)	153 (77%) 153/175 (87%)
Week 9	Completion Compliance	306 (76%) 306/341 (90%)	140 (70%) 140/158 (89%)
Week 12	Completion Compliance	317 (79%) 317/354 (90%)	148 (74%) 148/167 (89%)
Week 21	Completion Compliance	245 (61%) 245/326 (75%)	90 (45%) 90/143 (63%)
Week 30	Completion Compliance	211 (53%) 211/278 (76%)	63 (32%) 63/88 (72%)

Analysis cut-off date: 8 November 2017. HRQoL was an exploratory endpoint.
[a]Completion was defined as completing at least one item among the total patient-reported outcome analysis population. [b]Compliance was defined as completing at least one item at each timepoint, as listed in the numerator for each group, among patients who were expected to complete at each timepoint (e.g. among those who had not discontinued study treatment), as listed in the denominator for each group

Garassino MC *et al. Lancet Oncol*. 2020;21:387–397.

KEYNOTE-189: HRQoL EORTC QLQ-C30 GHS

Median follow up: 10.5 months. This analysis was exploratory, and no statistical conclusions can be drawn

	Pembrolizumab + platinum + pemetrexed (n=402)	Placebo + platinum + pemetrexed (n=200)
Baseline, mean (SD)	n=359[a] 62.0 (21.3)	n=180[a] 60.6 (21.4)
Week 12, mean (SD)	N=319[a] 63.8 (21.5)	n=150[a] 61.1 (20.8)
Change from baseline to Week 12, LS mean (95% CI)	n=402[b] 1.0 (−1.3 to 3.2)	n=200[b] −2.6 (−5.8 to 0.5)
Difference in LS mean between treatment groups (95% CI)	36 (−0.1 to 7.2) p=0.053[d]	
Week 21, mean (SD)	n=248[a] 67.0 (19.4)	n=91[a] 62.6 (24.1)
Change from baseline to Week 21, LS mean (95% CI)[c]	n=402[b] 1.3 (−1.2 to 3.6)	n=200[b] −4.0 (−7.7 to −0.3)
Difference in LS mean between treatment groups (95% CI)	5.3 (1.1 to 9.5) p=0.014[d]	

Analysis cut-off date: 8 November 2017. HRQoL was an exploratory endpoint.
[a]Number of patients who completed EORTC QLQ-C30 global health status/quality of life at the noted time point. [b]Number of patients in analysis population. [c]Based on cLDA model with EORTC QLQ-C30 global health status/quality of life scores as response variable, treatment by study visit interaction and stratification factors for randomisation as covariates. [d] p values are 2-sided and nominal.

Garassino MC *et al. Lancet Oncol*. 2020;21:387–397.

KEYNOTE-189: HRQoL QLQ-C30 GHS/QoL and functional and symptom subscales

Median follow up: 10.5 months. This analysis was exploratory, and no statistical conclusions can be drawn

Mean QLQ-C30 GHS/QoL scores:

- Improved from baseline to Week 9 in both the pembrolizumab + platinum + pemetrexed group and placebo + platinum + pemetrexed group
- Deteriorated in both groups from Week 9 onwards; however, scores in the pembrolizumab + platinum + pemetrexed group remained above baseline whereas those in the placebo + platinum + pemetrexed group did not

QLQ-C30 functional and symptom subscales:

- Were similar for both treatment groups across all domains at Week 12
- Mean score changes from baseline were generally better in the pembrolizumab + platinum + pemetrexed group than in the placebo + platinum + pemetrexed group for most functional and symptom scales at Week 21
  - Symptom scale scores for dyspnoea and pain improved in the pembrolizumab + platinum + pemetrexed group and worsened/remained stable in the placebo + platinum + pemetrexed group

Analysis cut-off date: 8 November 2017. HRQoL was an exploratory endpoint.

Garassino MC *et al. Lancet Oncol.* 2020;21:387–397.

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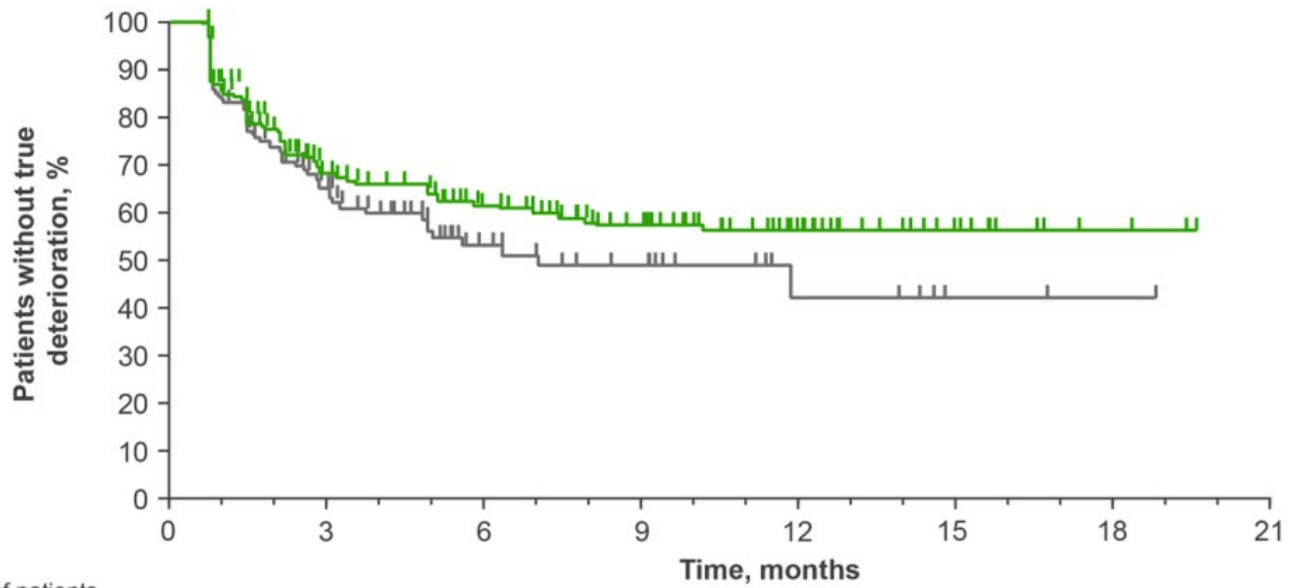
KEYNOTE-189: Time to deterioration analysis
Composite endpoint of cough, chest pain and *dyspnoea

Median follow up: 10.5 months. This analysis was exploratory, and no statistical conclusions can be drawn

Treatment arm[a]	Events, %	Median (95% CI), months	HR (95% CI)	p value
Pembro–plat–pem	32.1	NR (10.2–NR)	0.81 (0.60–1.09)	0.161[b]
Placebo–plat–pem	33.0	7.0 (4.8–NR)	–	



No. of patients							
Pembro–plat–pem	402	189	128	72	32	11	3	0
Placebo–plat–pem	200	68	29	17	6	2	1	0

Adapted from: Garassino MC et al. Lancet. 2020.

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Analysis cut-off date: 8 November 2017. HRQoL was an exploratory endpoint.
[a]p value is 2-sided and nominal. [b]Post-baseline assessments were not available for 56 patients in the pembro–plat–pem group and for 33 patients in placebo–plat–pem group.
Garassino MC *et al. Lancet Oncol*. 2020;21:387–397

KEYNOTE-189: Efficacy summary[1–3]

Treatment with pembrolizumab + platinum + pemetrexed in patients with untreated metastatic, non-squamous NSCLC with no *EGFR/ALK* mutations compared with placebo + platinum + pemetrexed (median follow up: 10.5 months) yielded[1]:

- Superior OS, with a 51% reduction in the risk of death (HR: 0.49, p<0.001)
- Superior PFS, with a 48% reduction in the risk of progression or death (HR: 0.52, p<0.001)
- Superior ORR (47.6% vs. 18.9%, p<0.001) and improved DOR
- The treatment effect on OS was consistent across all PD-L1 subgroups, including PD-L1 TPS <1% and 1–49%[a]
- The treatment effect was consistent for OS and PFS in a post-hoc analysis of patients with liver or brain metastases (median follow up: 18.7 months)[b,2]

In the 5-year follow up, treatment with pembrolizumab + platinum + pemetrexed continued to demonstrate OS and PFS benefit in patients with previously untreated metastatic nonsquamous NSCLC compared with placebo + platinum + pemetrexed (median follow up: 64.6 months; p not tested)[3]

- Benefits were observed despite an effective crossover rate of 57% from placebo + platinum + pemetrexed to subsequent anti-PD-L1 therapy during/outside study[3]
- Benefits were observed in OS and PFS irrespective of baseline PD-L1 expression[3]

Patients who received 35 cycles of pembrolizumab (~2 years) had durable responses, with 72% patients alive at 3 years (~5 years from randomisation)[3]

[a]Exploratory endpoint – no statistical conclusions can be drawn. [b]This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn.

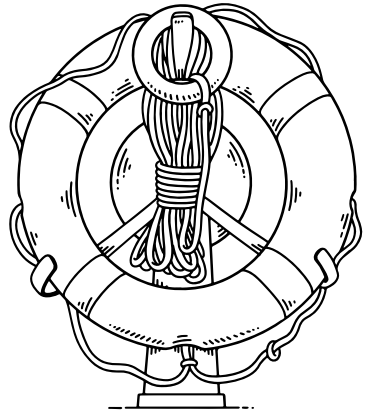
1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Garassino MC *et al.* Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April 2019, Atlanta, USA;
3. Garassino MC *et al. J Clin Oncol.* 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: Safety summary[1–7]

Pembrolizumab + platinum + pemetrexed in patients with untreated metastatic, non-squamous NSCLC with no *EGFR/ALK* mutations compared with placebo + platinum + pemetrexed displayed a generally manageable safety profile (median follow up: 10.5 months):[1]

- The addition of pembrolizumab did not appear to increase the frequency of AEs that are commonly associated with chemotherapy regimens involving pemetrexed and a platinum-based drug[1]
- The frequency of deaths due to pneumonitis in the pembrolizumab + platinum + pemetrexed arm was consistent with the frequency previously observed with pembrolizumab monotherapy in advanced NSCLC[1–4]
- No new safety signals were identified in the post-hoc analysis for liver and brain metastases (median follow up: 18.7 months)[a,5]

In the 5-year update, toxicity was manageable, which is consistent with previous reports[6–8]



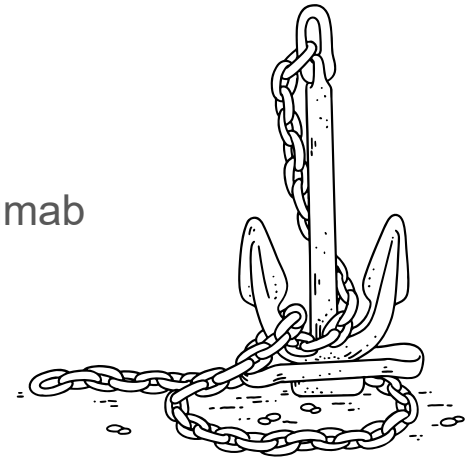
[a]**This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn.**

1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Reck M *et al. N Engl J Med* 2016;375:1823–1833; 3. Herbst RS *et al. Lancet* 2016;387:1540–1550; 4. Garon EB *et al. N Engl J Med* 2015;372:2018–2028; 5. Garassino MC *et al.* Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April 2019, Atlanta, USA; 6. Rodríguez-Abreu D *et al. Ann Oncol*. 2021;32:881–895; 7. Gadgeel S *et al. J Clin Oncol*. 2020;38:1505–1517; 8. Garassino MC *et al. J Clin Oncol.* 2023:JCO2201989. doi: 10.1200/JCO.22.01989.

KEYNOTE-189: HRQoL summary

This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn

- Pembrolizumab + platinum + pemetrexed maintained or improved QoL (evaluated using the EORTC QLQ-C30) compared with placebo + platinum + pemetrexed in patients with previously untreated metastatic, non-squamous NSCLC without sensitising *EGFR* mutations or *ALK* translocations[1]
- At median a follow up of 10.5 months, median time to true deterioration in the composite endpoint of increased cough, chest pain or dyspnoea was not reached among patients treated with pembrolizumab + platinum + pemetrexed vs. 7.0 months among those who received placebo + platinum + pemetrexed[1]
- These data complement the superior efficacy observed with pembrolizumab + platinum + pemetrexed over placebo–plat–pem in the KEYNOTE-189 study and support use of pembrolizumab + platinum + pemetrexed as first-line therapy for metastatic, non-squamous NSCLC[1]



1. Garassino MC *et al. Lancet Oncol*. 2020;21:387–397.

PD-L1 expression in mNSCLC patients

Immunohistochemical evaluation of PD-L1

Is based on TPS, which is the % of viable tumour cells showing partial or complete membrane staining at any intensity.[1,2]

PD-L1 expression levels can affect approaches to treating patients:[2,3]

- Single-agent immunotherapy
- Combination immunotherapy

The prevalence of PD-L1 expression in patients with NSCLC ranges from **24%–60%**[4]

Of patients with mNSCLC, **~30%** have tumours with PD-L1 expression **<1%***[5,6]

***TPS <1%.**

1. Sajjadi E *et al. Ecancermedicalscience* 2020;14:1150; 2. Ettinger DS *et al. J Natl Compr Canc Netw* 2021;19:254-266; 3. Vrankar M *et al. Radiat Oncol* 2020;15:247; 4. Yu H *et al. J Thorac Oncol* 2016;11:964-975; 5. Aggarwal C *et al. Ann Oncol* 2016;27:1060P; 6. Holmes M *et al. J Thorac Oncol* 2019;14:S506.

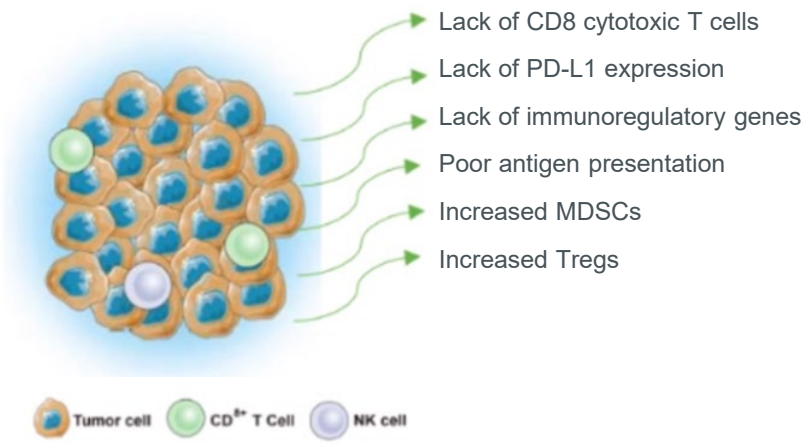
Immune checkpoint inhibitors, in combination with chemotherapy, can help improve outcomes, harnessing the patient's immune system against cancer[1,2]

This is a hypothesis based on experimental models

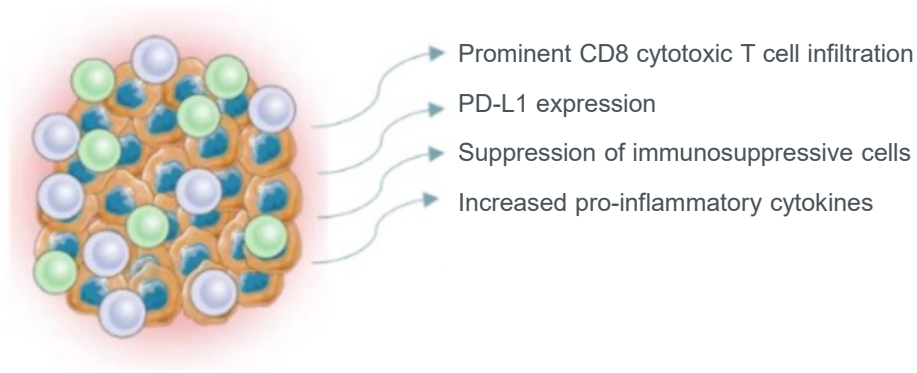
Some NSCLCs are cold tumours that lack activated tumour-specific T cells[7] → Absence of tumour-specific T cells is a mechanism of primary resistance to ICIs[7] → Effective combination therapy can turn cold tumours into hot tumours that are sensitive to ICIs[7]

Chemotherapy, through its induction of immunogenic cell death (ICD), can turn a ‘cold tumour’ into a ‘hot tumour’:
Converting a cold tumour microenvironment into a hot tumours can enable increased expression of PD-L1 and sensitize the tumour to PD-1 blockade[7–9]

Cold tumours are characterised by decreased immunogenicity and an immunosuppressive TME[3,6,7,10,11]



Hot tumours are characterised by an inflammatory profile and an immunosuppressive TME[3,6,7,10,11]



1. Kersten K *et al. Front Immunol*. 2015;6:516. 2. Roselli M *et al. Oncoimmunology*. 2013;2(10):e27025. 3. Aujla S *et al. J Thorac Oncol*. 2022;17(5):675–687. 4. Yu W *et al. Cell Death Dis*. 2020;11:506. 5. Holmen Olofsson G *et al. Int J Mol Sci*. 2020;21(11):3816. 6. Chen Q *et al. Nanomicro Lett*. 2021;13(1):92. 7. Wu M *et al. J Hematol Oncol*. 2022;15(1):24. 8. Liu YT *et al. Theranostics*. 2021;11(11):5365–5386. 9. Ledys F *et al. Cancers (Basel)*. 2021;13(23):5999. 10. Leonetti A *et al. Drug Resist Updat*. 2019;46:100644. 11. Ren X *et al. Front Immunol*. 2022;13:790113.

Abbreviations

Abbreviation	Definition
AE	Adverse event
ALK	Anaplastic lymphoma kinase
AUC	Area under the curve
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CNS	Central nervous system
CR	Complete response
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMC	Electronic Medicines Compendium
EORTC	European Organisation for Research and Treatment of Cancer
GHS	Global health status
Gy	Gray
HR	Hazard ratio
HRQoL	Health-related quality of life

Abbreviation	Definition
IHC	Immunohistochemistry
ITT	Intention-to-treat
LS	Least squares
mg	Milligram(s)
MHRA	Medicines and Healthcare Products Regulatory Agency
n	Number of patients
NE	Not evaluable
NR	Not reached
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand-1
PFS	Progression-free survival
PFS2	Progression after second-line therapy
Pembro–plat–pem	Pembrolizumab + platinum + pemetrexed
Placebo–plat–pem	Placebo + platinum + pemetrexed

Abbreviations

Abbreviation	Definition
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QoL	Quality of life
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-LC3	Quality of Life Questionnaire Lung Cancer 13
R	Randomised
RECIST v1.1	Response Evaluation Criteria In Solid Tumors Version 1.1
RT	Radiotherapy
SD	Stable disease
SDev	Standard deviation
SE	Standard error
TPS	Tumour proportion score

OS

- ITT
- PDL-1 TPS
- Key subgroups

PFS

- ITT
- PDL-1 TPS
- Key subgroups

ORR/DOR/DCR

- ORR (ITT + PDL-1 TPS)
- DOR/DCR (ITT [original analysis])
- DOR (ITT +PD-L1 TPS [5 year])

Brain/liver Mets

- OS
- PFS

Safety

- AEs
- All cause AEs
- Immune mediated AEs
- Renal AEs

KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/2498/smpc

Please note that clicking these links will redirect you to external websites, for which MSD does not review or control the content.

KEYTRUDA offers flexibility of dosing

Administered as an IV infusion

Over 30 minutes

200 mg Q3W or 400 mg Q6W

- The 200 mg Q3W (once every 3 weeks) regimen has been assessed in phase 2 and 3 registration studies across a multitude of indications of KEYTRUDA. An exposure-response evaluation, using modelling and simulation, led to the approval of the 400 mg Q6W (once every 6 weeks) dosing for monotherapy and combination therapy.

KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/2498/smpc

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