MSD Oncology

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

Including 5-year pooled analysis for squamous and non-squamous PD-L1 TPS <1% mNSCLC

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KEYTRUDA® (pembrolizumab)

MSD

External websites and abbreviations

Links to external websites

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Abbreviations

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

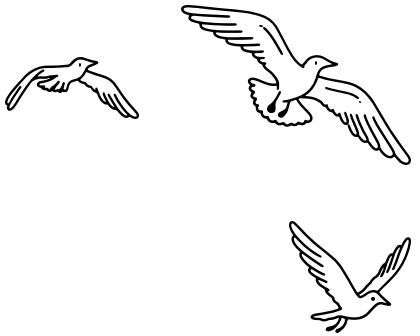
There is an urgent unmet need for treatment options for patients with mNSCLC and low PD-L1 expression

- Patient outcomes remain suboptimal with standard chemotherapeutics and durable disease control is rarely achieved[1]
- 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 patients are treated first-line with chemotherapy alone, they have lower chances of survival compared to those treated with chemotherapy plus immunotherapy, chemotherapy plus bevacizumab, or immunotherapy alone[3]

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

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.

2023 ESMO guidelines recommended KEYTRUDA in combination with chemotherapy for the first-line treatment of non-oncogene-addicted mNSCLC irrespective of PD-L1 expression[1]

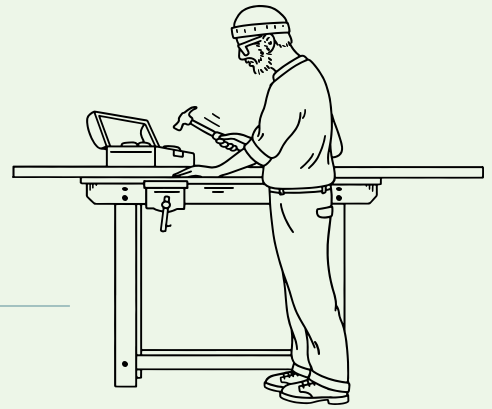


- Highest level of evidence (**I**) and recommendation grade (**A**)
- Established as a **standard treatment option** for patients with any PD-L1 score and PS 0–1, and without contraindications to IO
- Magnitude of clinical benefit recognised with an **ESMO-MCBS score of 4**

1. Hendriks LE, *et al. Ann Oncol*. 2023;24(4):339–357.

KEYTRUDA® (pembrolizumab) mNSCLC indications[1]

- 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



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

KEYTRUDA is the first and only immunotherapy to present 5-year data in three first-line mNSCLC indications licensed in the UK[1-7]

Evaluate

Histological + PD-L1 testing at diagnosis

Result

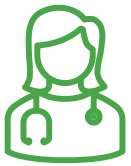
Squamous			Non-squamous		
PD-L1 non-expressers / unknown	PD-L1 1-49%	PD-L1 ≥50%	PD-L1 non-expressers / unknown	PD-L1 1-49%	PD-L1 ≥50%

1st Line

KEYTRUDA (Q3W/Q6W) + carboplatin-paclitaxel/nab-paclitaxel **KEYNOTE-407**			KEYTRUDA (Q3W/Q6W) + platinum chemotherapy and pemetrexed **KEYNOTE-189**		
	KEYTRUDA (Q3W/Q6W) **KEYNOTE-024**			KEYTRUDA (Q3W/Q6W) **KEYNOTE-024**	

Previously treated

	KEYTRUDA monotherapy (Q3W/Q6W)			KEYTRUDA monotherapy (Q3W/Q6W)	



The recommended dose of KEYTRUDA is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an infusion over 30 minutes[7]

1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Garassino MC *et al. J Clin Oncol* 2023:41:1992–1998; 3. Paz-Ares L *et al. N Engl J Med* 2018;379:2040–2051; 4. Novello S *et al. J Clin Oncol* 2023:41:1999–2006; 5. Reck M *et al. N Engl J Med* 2016;375:1823–1833; 6. Reck M *et al. J Clin Oncol* 2021;39:2339–2349; 7. KEYTRUDA Summary of Product Characteristics.

KEYNOTE-189

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

Post-hoc exploratory pooled analysis

Including KEYNOTE-189 and KEYNOTE-407, 5-year survival with KEYTRUDA (pembrolizumab) plus chemotherapy for mNSCLC with PD-L1 TPS <1%

KEYNOTE-189: KEYTRUDA

(pembrolizumab) plus chemotherapy for the first-line treatment of metastatic, non-squamous, *EGFR/ALK*-wild-type NSCLC[1]

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

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	23.1 (18.6–30.9)[3]
5-year follow-up	8 March 2022	3	64.6 (60.1–72.4)[4]

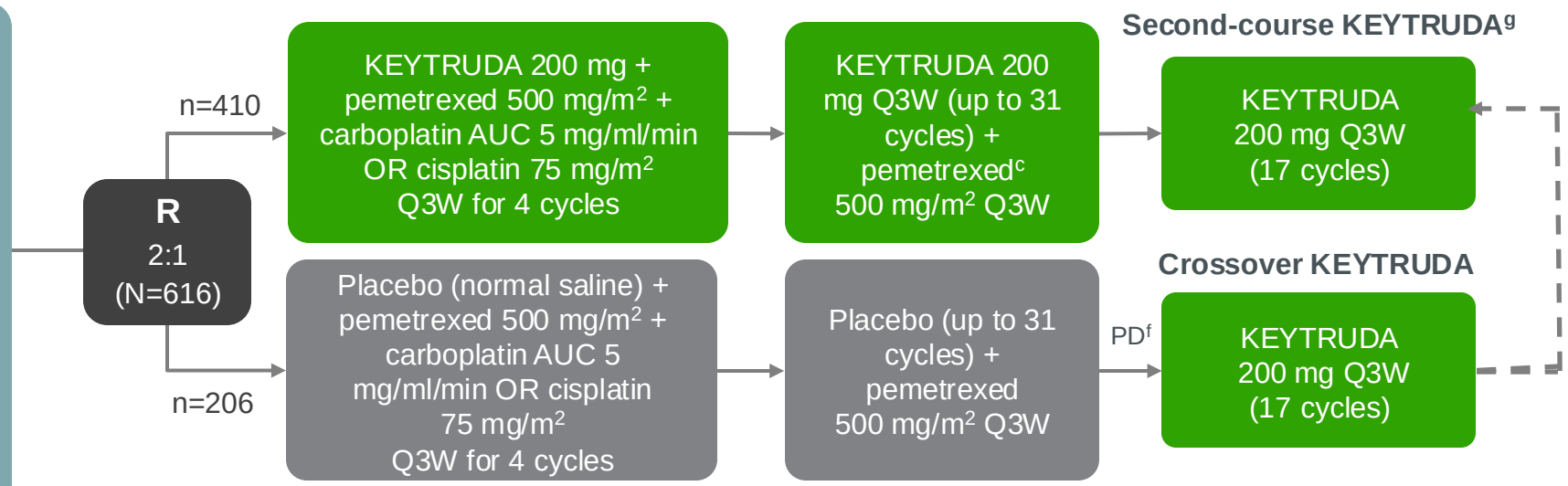
1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Garassino *MC et al. Lancet Oncol*. 2020;21:387–397; 3. Gadgeel S *et al. J Clin Oncol.* 2020;38(14):1505–1517; 4. Garassino MC, *et al. J Clin Oncol*. 2023;41(11):1992-1998.

KEYNOTE-189: Study design[1–3]

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; 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 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 KEYTRUDA monotherapy, PD had to have been verified by blinded, independent, central radiological review and all safety criteria had to have been met. [g]Patients who had SD or better after completing 35 cycles of KEYTRUDA or had stopped trial treatment after achieving CR and received ≥8 cycles of treatment, but then experienced PD, could receive second-course KEYTRUDA for 17 cycles if they had received no new anticancer treatment since the last dose of KEYTRUDA.

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

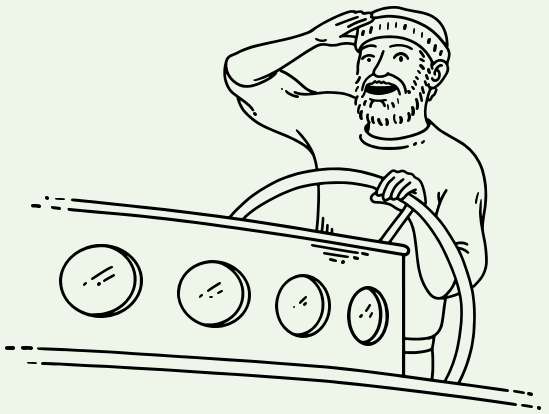
- Actual enrolment: 616 patients

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 KEYTRUDA 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]

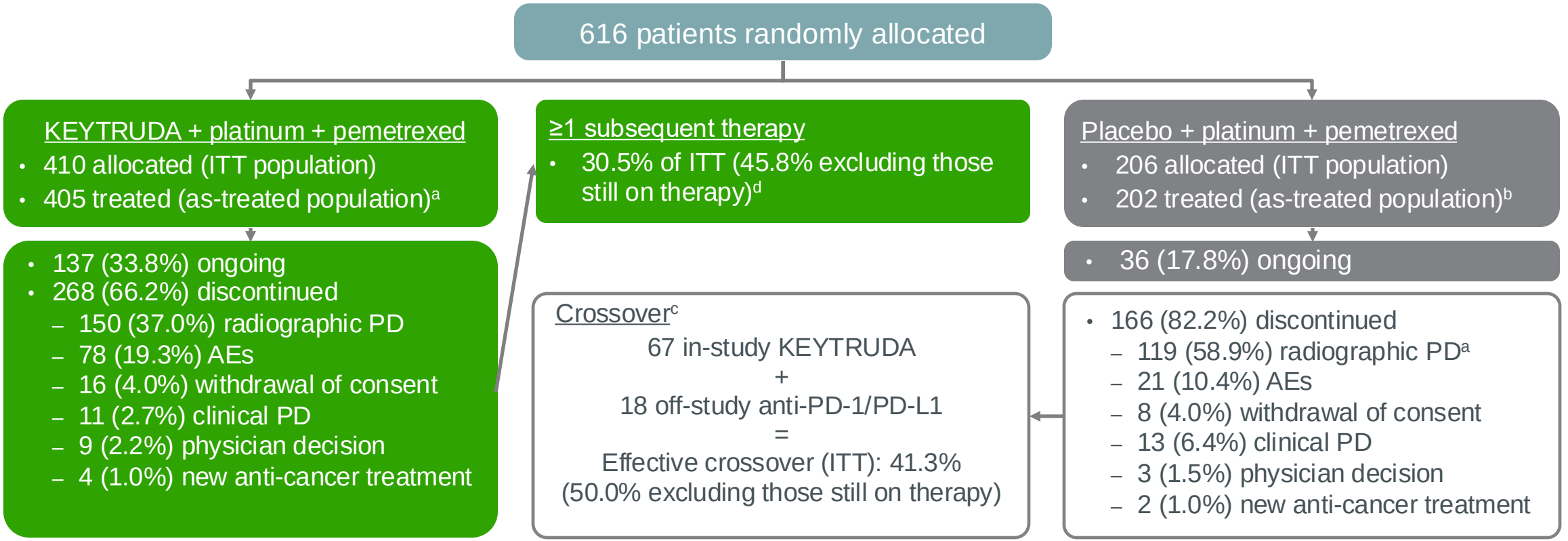
- Analysis cut-off date: 8 March 2022
- Results presented: ESMO 2022
- Median follow-up: 64.6 months (range: 60.1–72.4 months)
- This analysis was not subject to further significance testing

[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;41(11):1992-1998.

KEYNOTE-189: Disposition of study treatment[1]

Median follow-up: 10.5 months



Adapted from Gandhi L et al. N Engl J Med 2018 (and supplementary appendix).

Data 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])[2]. [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).[2]

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: Key baseline characteristics[1]

Median follow-up: 10.5 months

Characteristic, n (%)[a]	Pembro–plat–pem (n=410)	Placebo–plat–pem (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]	Pembro–plat–pem (n=410)	Placebo–plat–pem (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.

Data 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 KEYTRUDA + 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.

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

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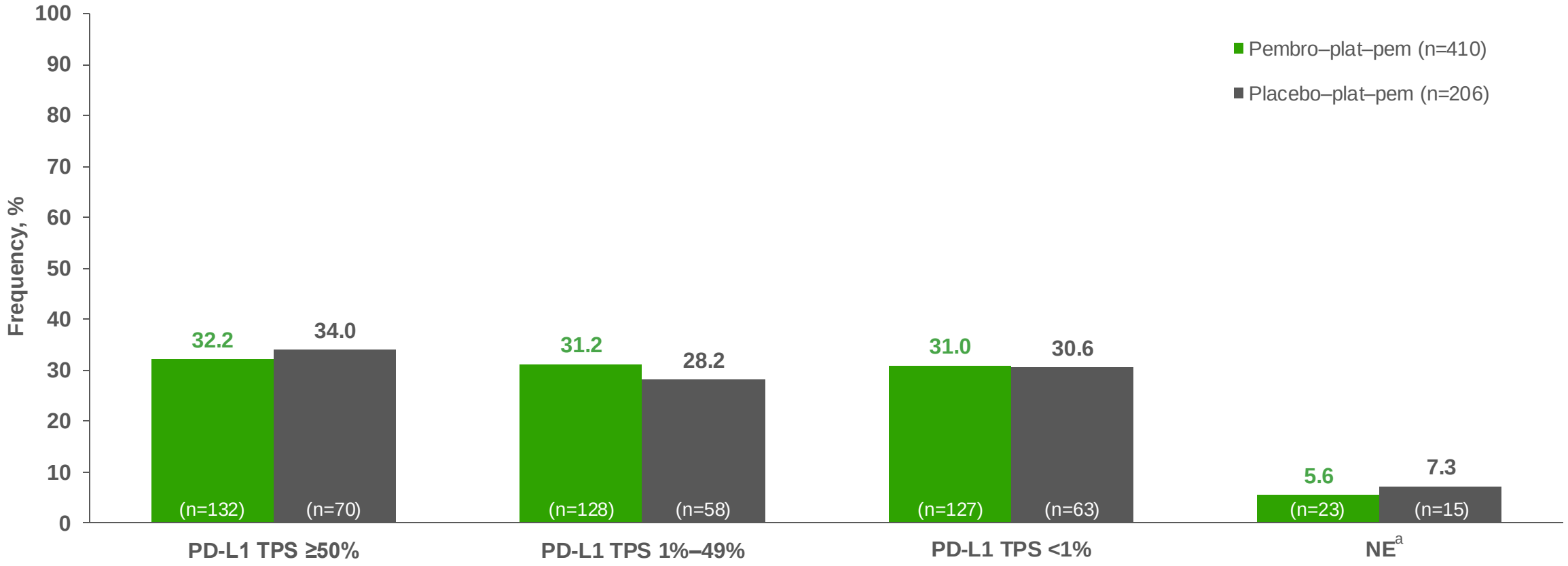
KEYNOTE-189: Baseline characteristics – Frequency of PD-L1 TPS subgroups[1]

Median follow-up: 10.5 months



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

Data 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.

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

1

KEYNOTE-189: Primary endpoint outcomes[a]

Primary outcomes with KEYTRUDA + 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: 23.1 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

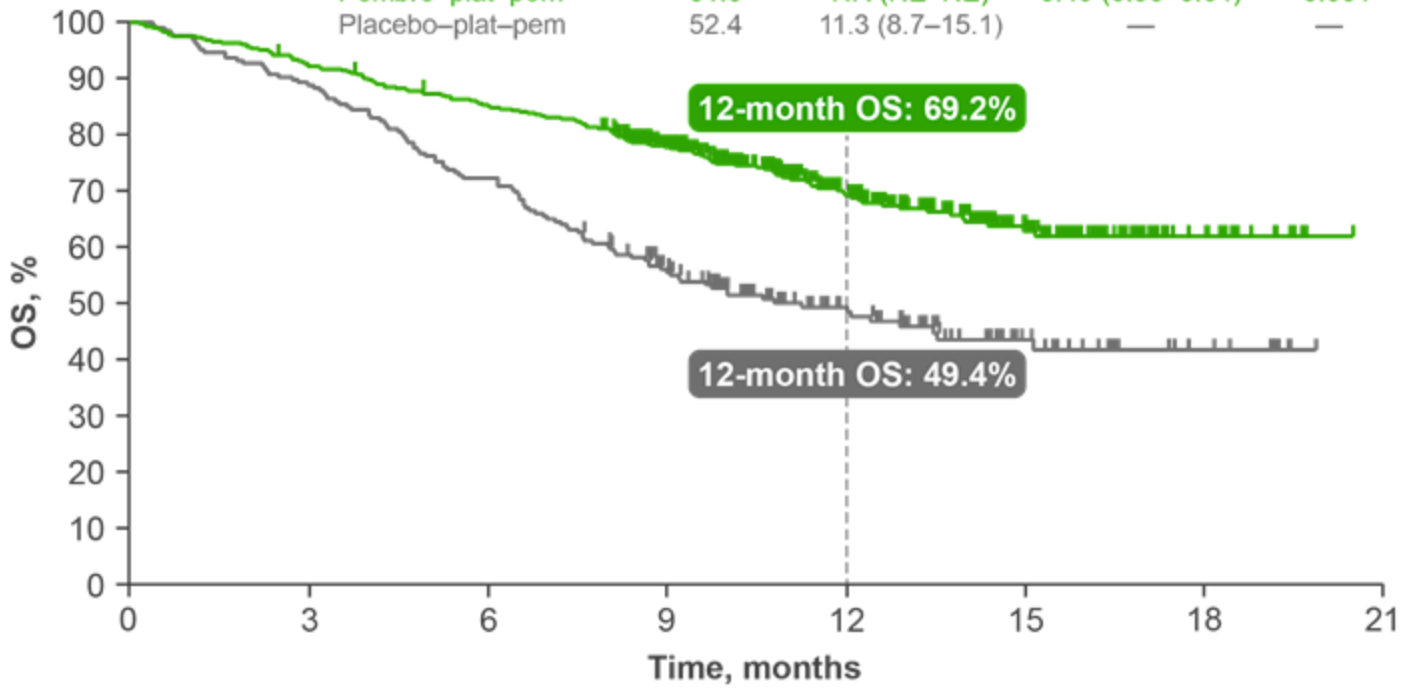
[a]**OS and PFS were both primary endpoints.**

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;41(11):1992-1998.

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

Median follow-up: 10.5 months

Treatment arm	Events, %	Median, months (95% CI)	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.

Data cut-off date: 8 November 2017.
[a]OS and PFS were both primary endpoints. [b]Kaplan-Meier estimate.
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.

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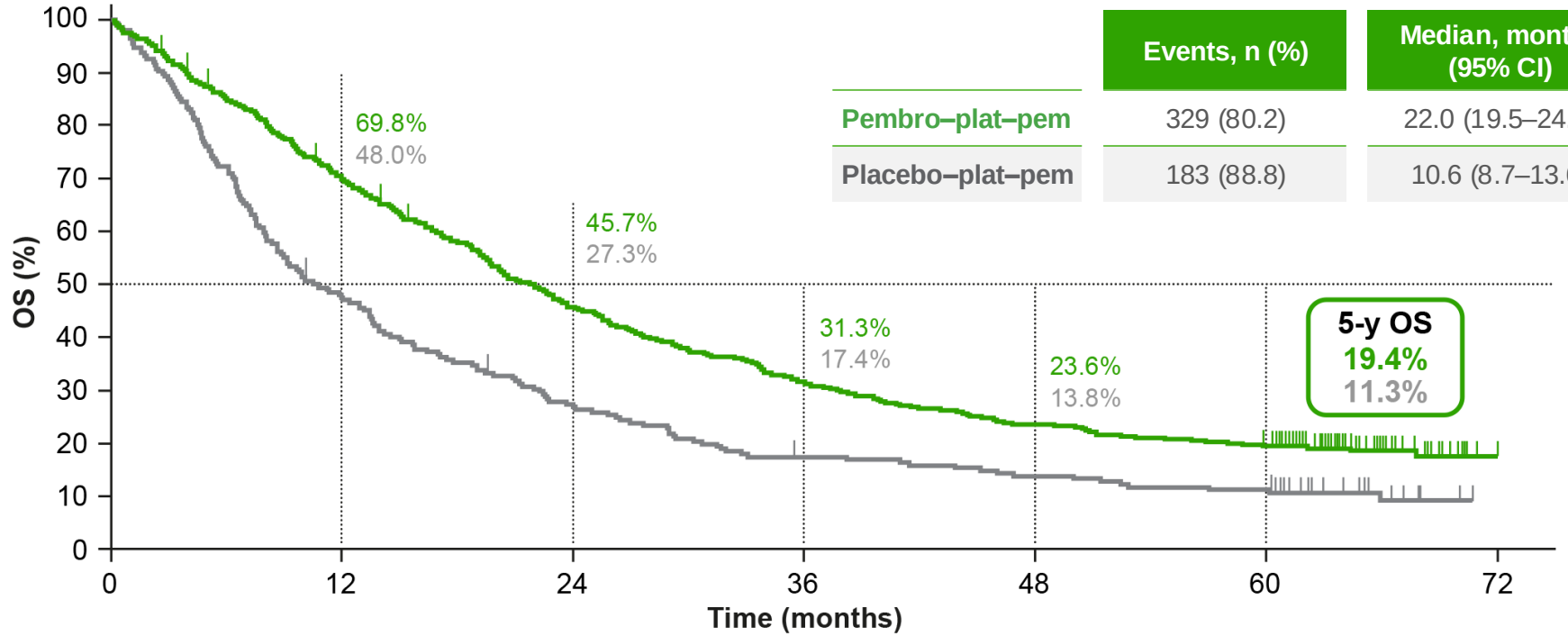
KEYNOTE-189: Exploratory analysis – OS in the ITT population (5-year update)[1,a–c]

Median follow-up: 64.6 months. No statistical conclusions can be drawn from this analysis



	Events, n (%)	Median, months (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.

Data cut-off date: 8 March 2022.

[a]OS and PFS were both primary endpoints. [b]Kaplan-Meier estimate. [c]Statistical significance was met for the primary endpoints in IA1 (2018).

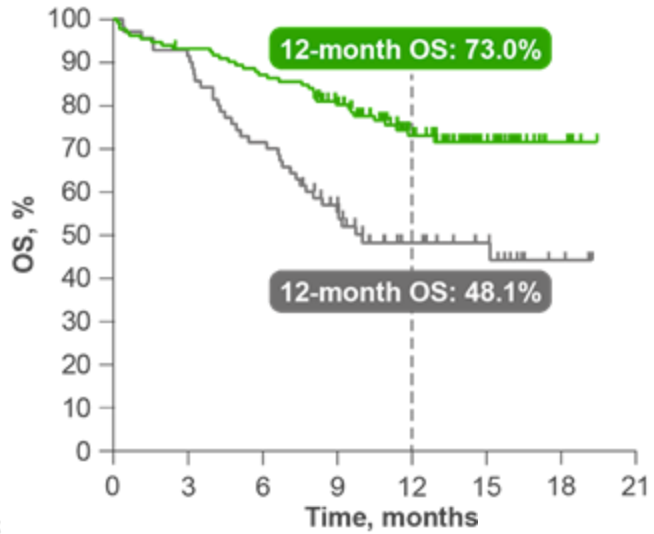
1. Garassino MC, *et al. J Clin Oncol*. 2023;41(11):1992-1998.

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

Median follow-up: 10.5 months. No statistical conclusions can be drawn from exploratory endpoints

PD-L1 TPS ≥50%

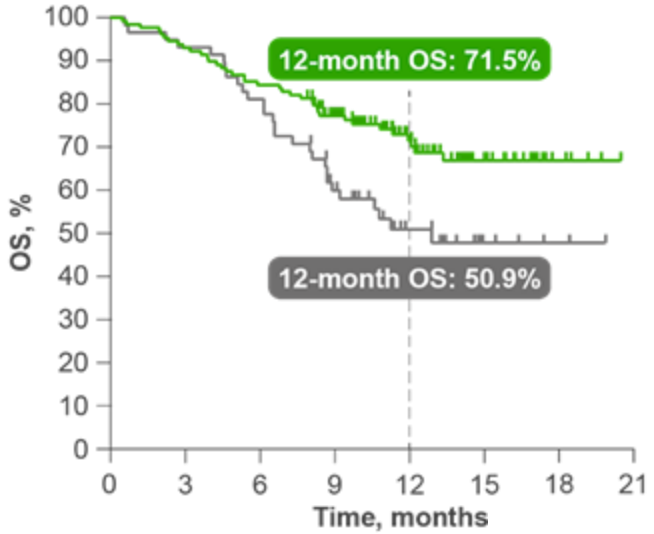
Treatment arm	Events, %	Median, months (95% CI)	HR (95% CI)	p value[b]
Pembro–plat–pem	25.8	NR (NE–NE)	0.42 (0.26–0.68)	0.0001
Placebo–plat–pem	51.4	10.0 (7.5–NE)	—	—



No. at risk								
Pembro–plat–pem	132	122	114	96	56	25	6	0
Placebo–plat–pem	70	64	50	35	19	13	4	0

PD-L1 TPS 1–49%

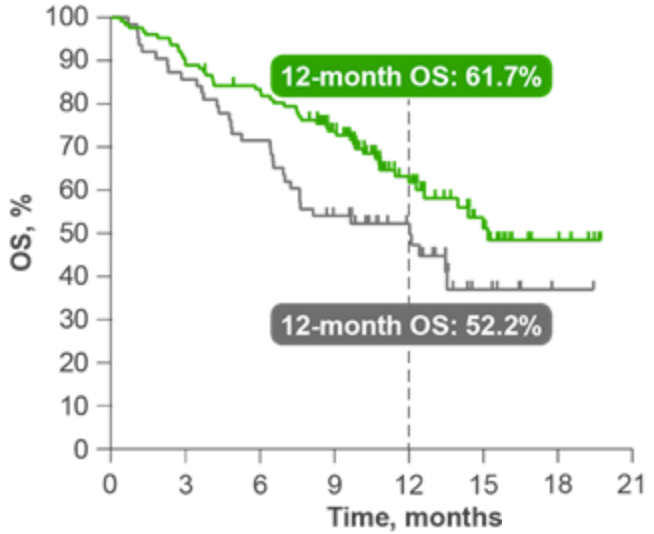
Events, %	Median, months (95% CI)	HR (95% CI)	p value[b]
28.9	NR (NE–NE)	0.55 (0.34–0.90)	0.0081
48.3	12.9 (8.7–NE)	—	—



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

PD-L1 TPS <1%

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



	127	113	104	79	42	20	6	0
	63	54	45	32	21	6	1	0

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

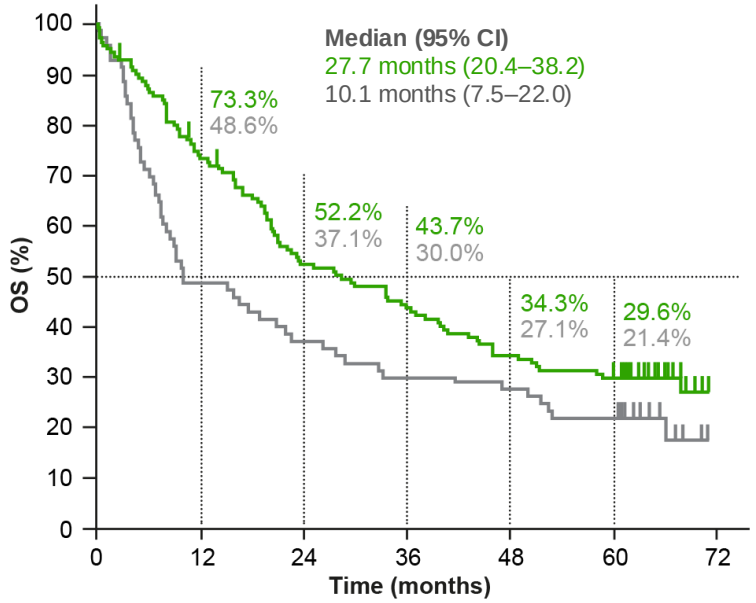
Data cut-off date: 8 November 2017.
[a]Kaplan-Meier estimate. [b]Nominal and one-sided.
1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Gandhi L *et al*. Presented at the 2018 American Association for Cancer Research (AACR) Annual Meeting, 14–18 April, 2018, Chicago, USA.

KEYNOTE-189: Exploratory analysis – OS by PD-L1 TPS (5-year update)[1,a]

Median follow-up: 64.6 months. No statistical conclusions can be drawn from this analysis

PD-L1 TPS ≥50%

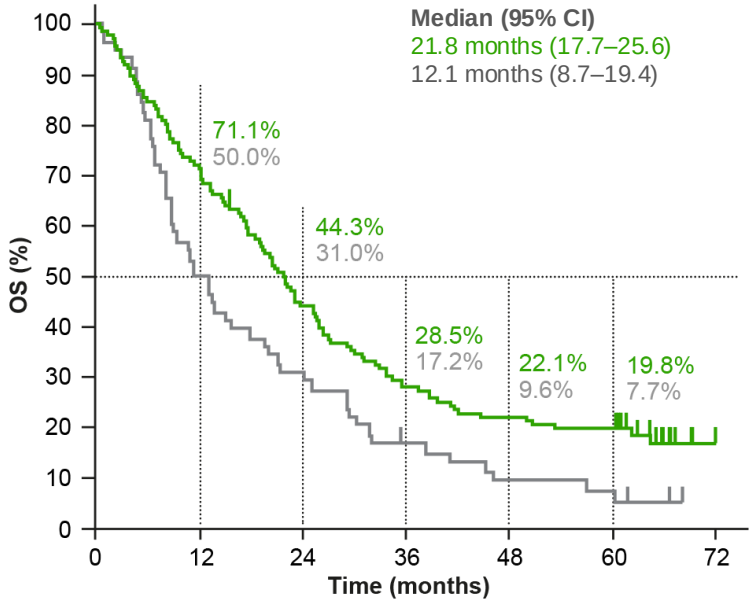
Treatment group	Events, n (%)	HR (95% CI)	5-year OS rate, % (95% CI)
Pembro–plat–pem	92 (69.7)	0.68 (0.49–0.96)	29.6 (22.0–37.6)
Placebo–plat–pem	56 (80.0)		21.4 (12.7–31.6)



Pembro–plat–pem	132	95	67	56	44	37	0
Placebo–plat–pem	70	34	26	21	19	15	0

PD-L1 TPS 1–49%

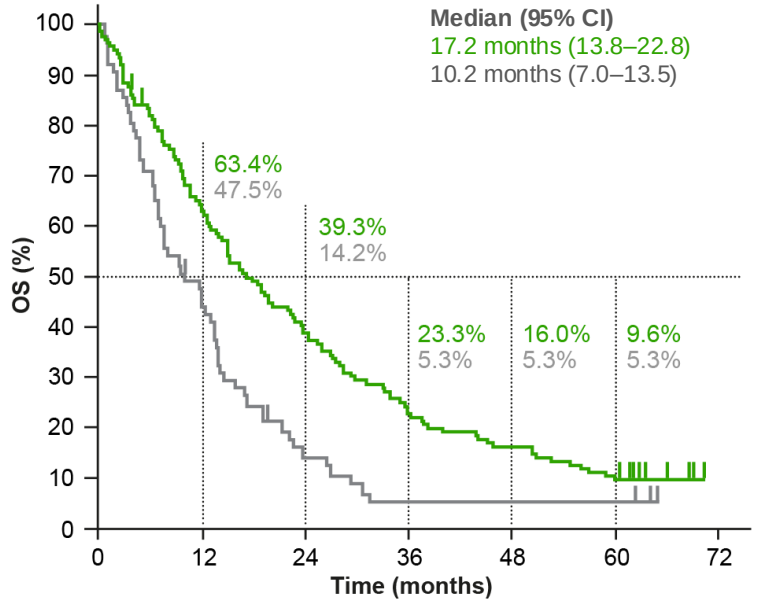
Events, n (%)	HR (95% CI)	5-year OS rate, % (95% CI)
104 (81.3)	0.65 (0.46–0.90)	19.8 (13.4–27.1)
54 (93.1)		7.7 (2.5–16.6)



Pembro–plat–pem	128	91	56	36	28	25	0
Placebo–plat–pem	58	29	18	9	5	4	0

PD-L1 TPS <1%

Events, n (%)	HR (95% CI)	5-year OS rate, % (95% CI)
113 (89.0)	0.55 (0.39–0.76)	9.6 (5.3–15.6)
58 (92.1)		5.3 (1.4–13.2)



Pembro–plat–pem	127	79	49	29	20	12	0
Placebo–plat–pem	63	29	8	3	3	3	0

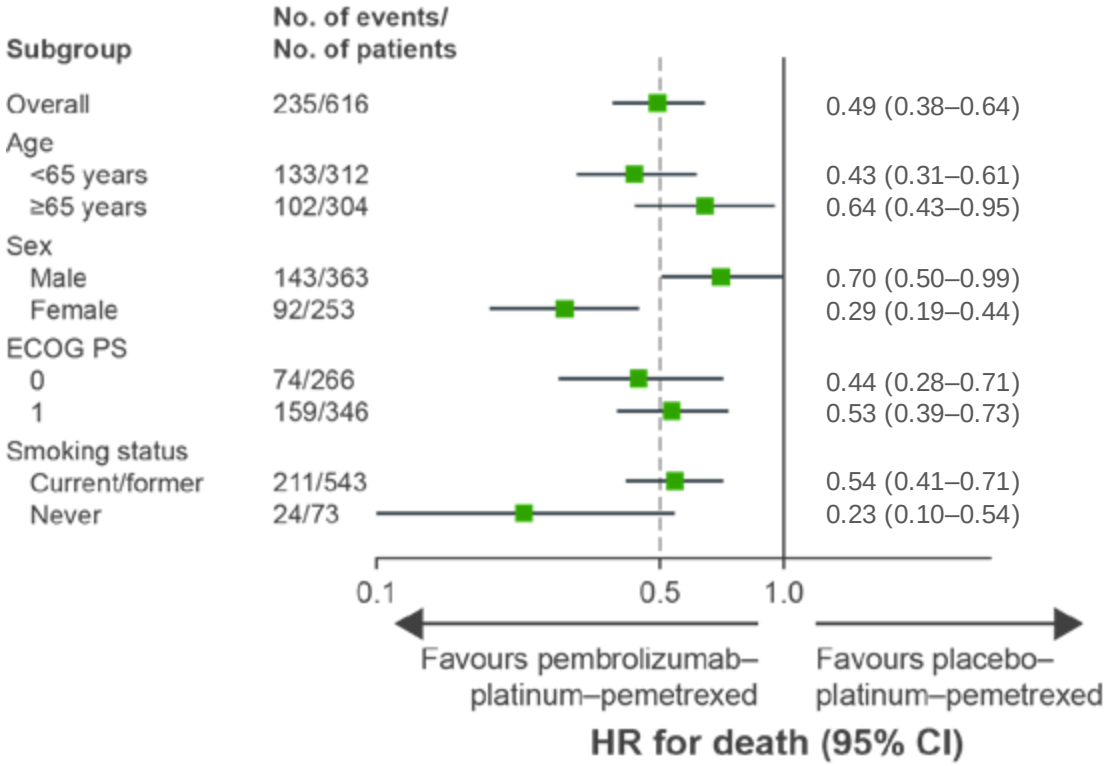
Adapted from Garassino MC et al. J Clin Oncol 2023.

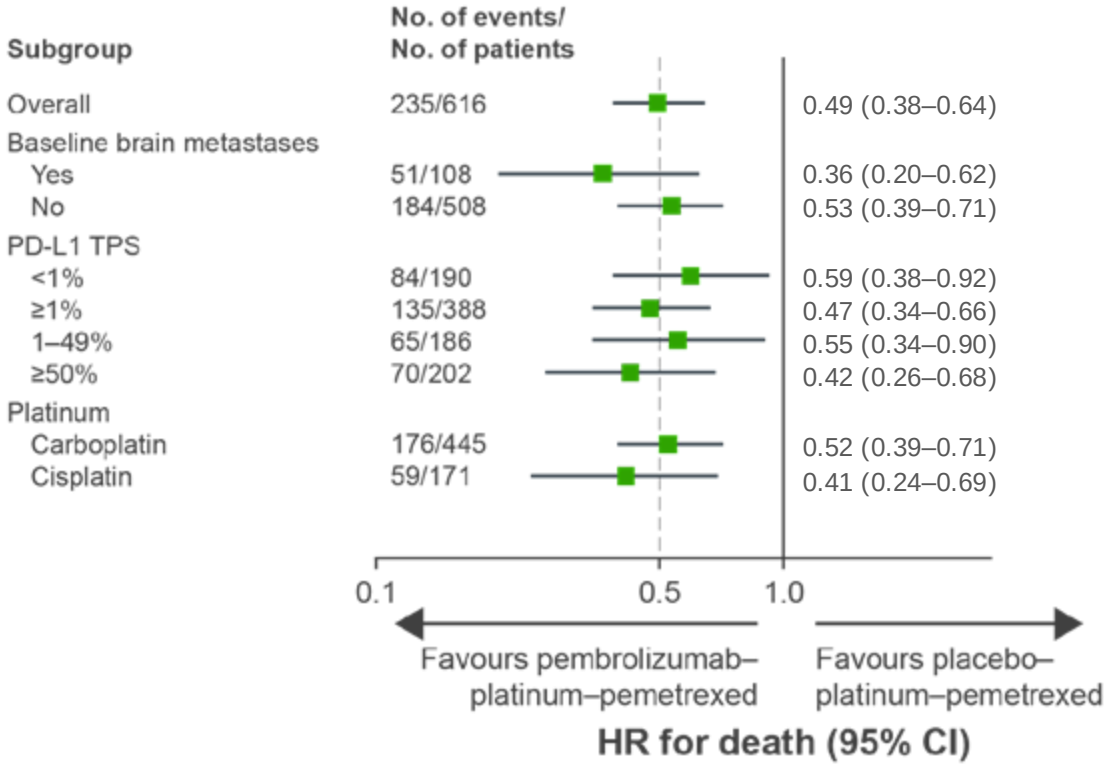
Data cut-off date: 8 March 2022.
[a]Kaplan-Meier estimate.

1. Garassino MC, et al. *J Clin Oncol*. 2023;41(11):1992-1998.

KEYNOTE-189: Exploratory endpoint – OS in key subgroups (original analysis)[1]

Median follow-up: 10.5 months. No statistical conclusions can be drawn from exploratory endpoints





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

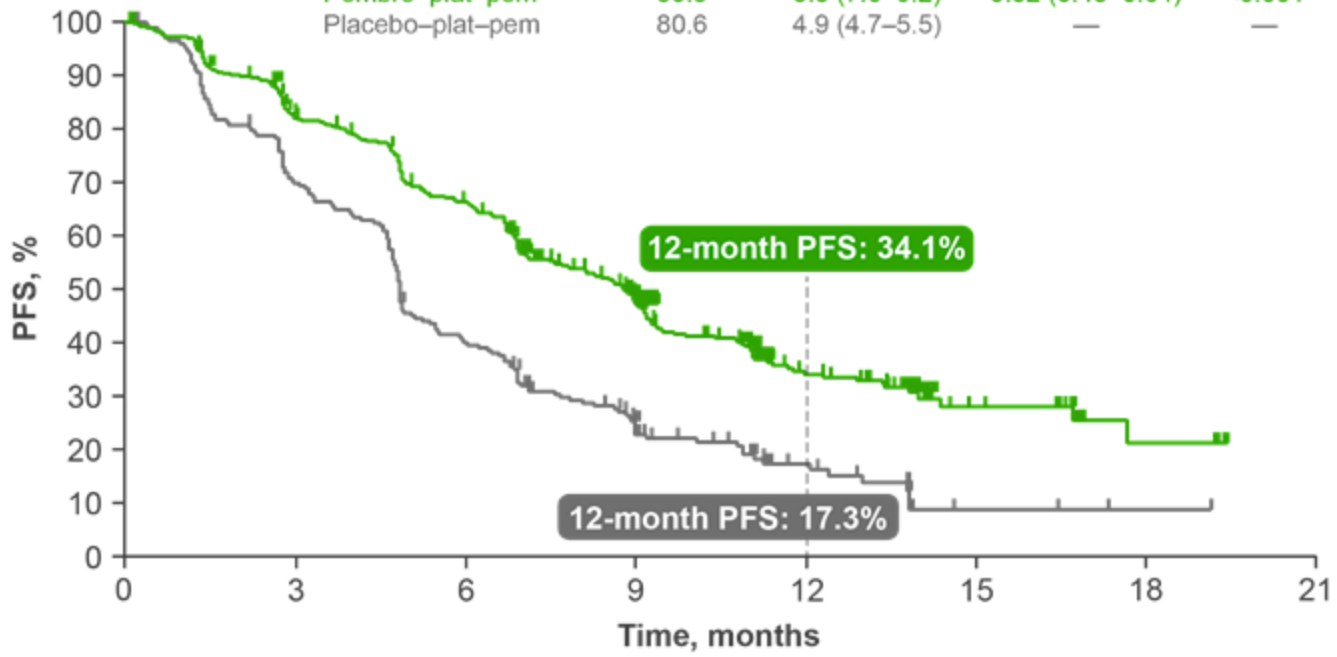
Data cut-off date: 8 November 2017.

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

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

Median follow-up: 10.5 months

Treatment arm	Events, %	Median, months (95% CI)	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)	—	—



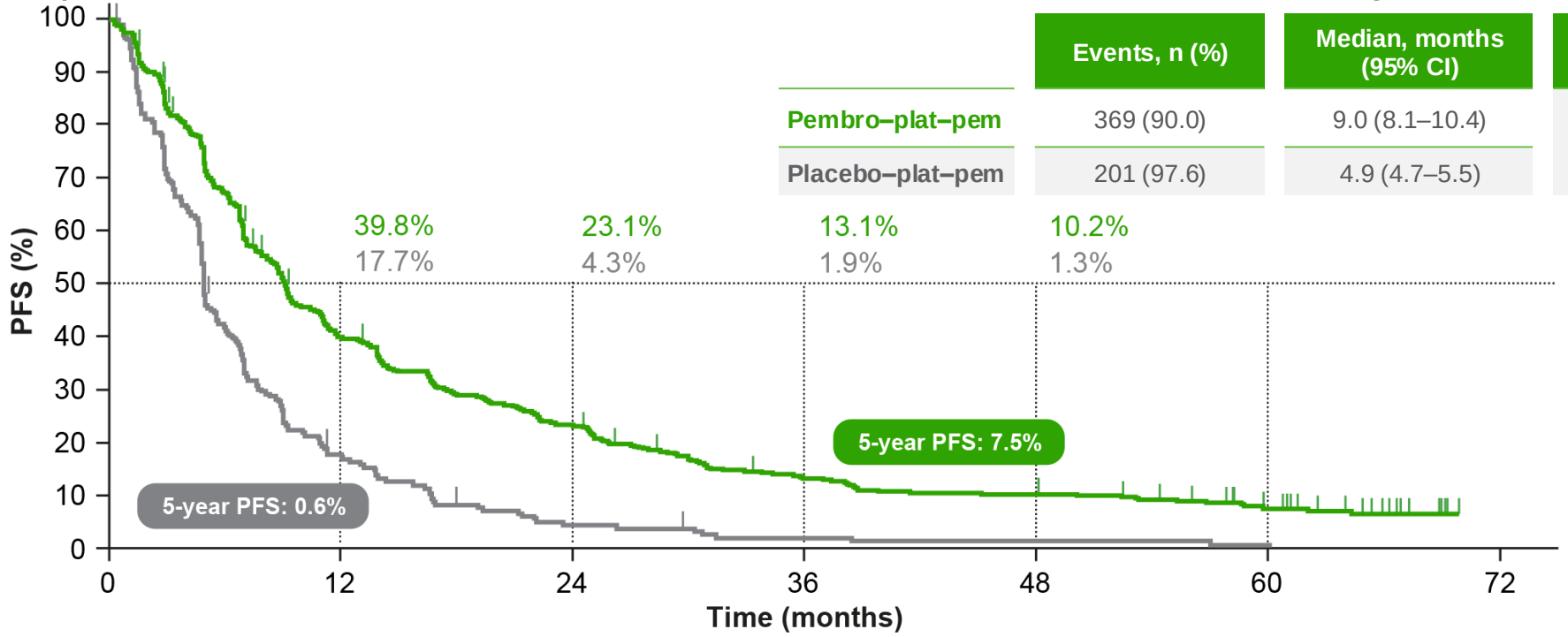
No. at risk								
Pembro–plat–pem	410	322	256	149	60	17	5	0
Placebo–plat–pem	206	141	80	40	16	3	1	0

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

Data cut-off date: 8 November 2017.
[a]OS and PFS were both primary endpoints. [b]Kaplan-Meier estimate. [c]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: Exploratory analysis – PFS in the ITT population (5-year update)[1,a–d]

Median follow-up: 64.6 months. No statistical conclusions can be drawn from this analysis



	Events, n (%)	Median, months (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.

Data cut-off date: 8 March 2022.
[a]OS and PFS were both primary endpoints. [b]Kaplan-Meier estimate. [c]Statistical significance was met for the primary endpoints in IA1 (2018). [d]Assessed using RECIST v1.1 by blinded, independent, central radiological review.

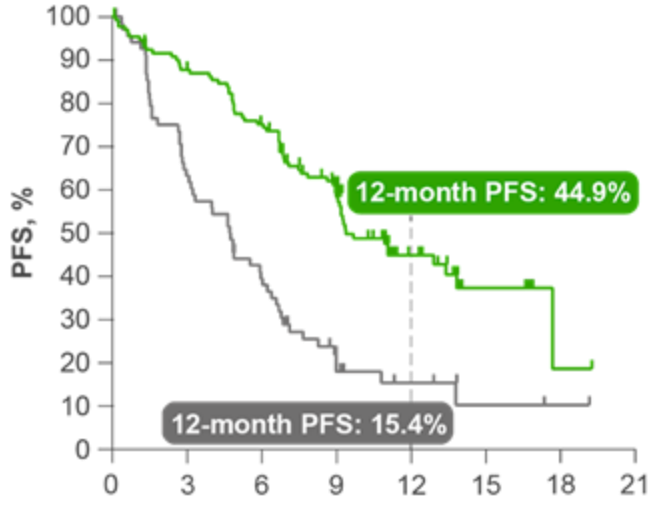
1. Garassino MC, et al. *J Clin Oncol*. 2023;41(11):1992-1998.

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

Median follow-up: 10.5 months. No statistical conclusions can be drawn from exploratory endpoints

PD-L1 TPS ≥ 50%

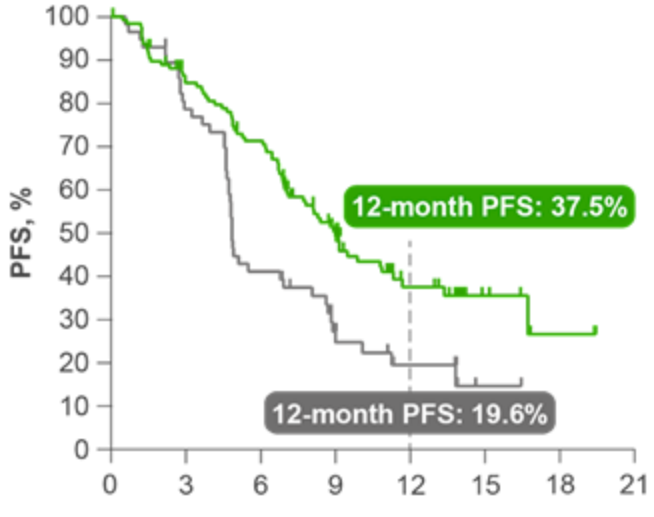
Treatment arm	Events, %	Median, months (95% CI)	HR (95% CI)	p value[b]
Pembro–plat–pem	51.5	9.4 (9.0–13.8)	0.36 (0.25–0.52)	<0.00001
Placebo–plat–pem	80.0	4.7 (3.1–6.0)	—	—



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

PD-L1 TPS 1–49%

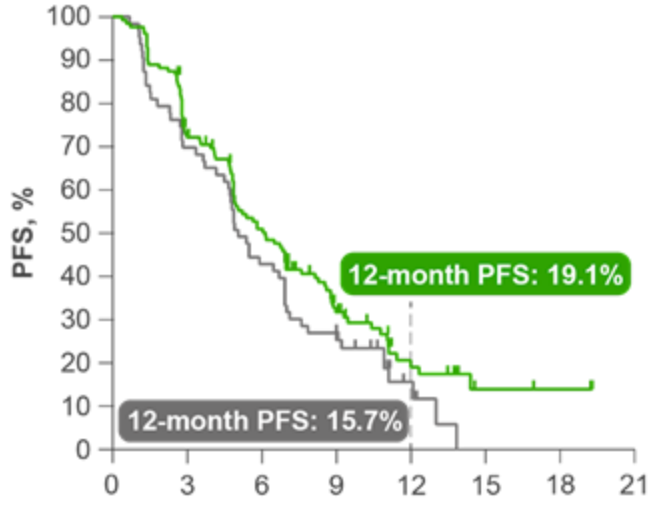
Events, %	Median, months (95% CI)	HR (95% CI)	p value[b]
54.7	9.0 (7.1–11.3)	0.55 (0.37–0.81)	0.0010
75.9	4.9 (4.7–6.9)	—	—



	128	101	84	47	21	6	2	0
	58	44	23	11	6	1	0	0

PD-L1 TPS <1%

Events, %	Median, months (95% CI)	HR (95% CI)	p value[b]
72.4	6.1 (4.9–7.6)	0.75 (0.53–1.05)	0.0476
85.7	5.1 (4.5–6.9)	—	—



	127	88	60	31	12	3	2	0
	63	44	27	16	4	0	0	0

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

Data cut-off date: 8 November 2017.

[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [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 analysis – PFS by PD-L1 TPS (5-year update)[1,a,b]

Median follow-up: 64.6 months. No statistical conclusions can be drawn from this analysis

PD-L1 TPS ≥50%

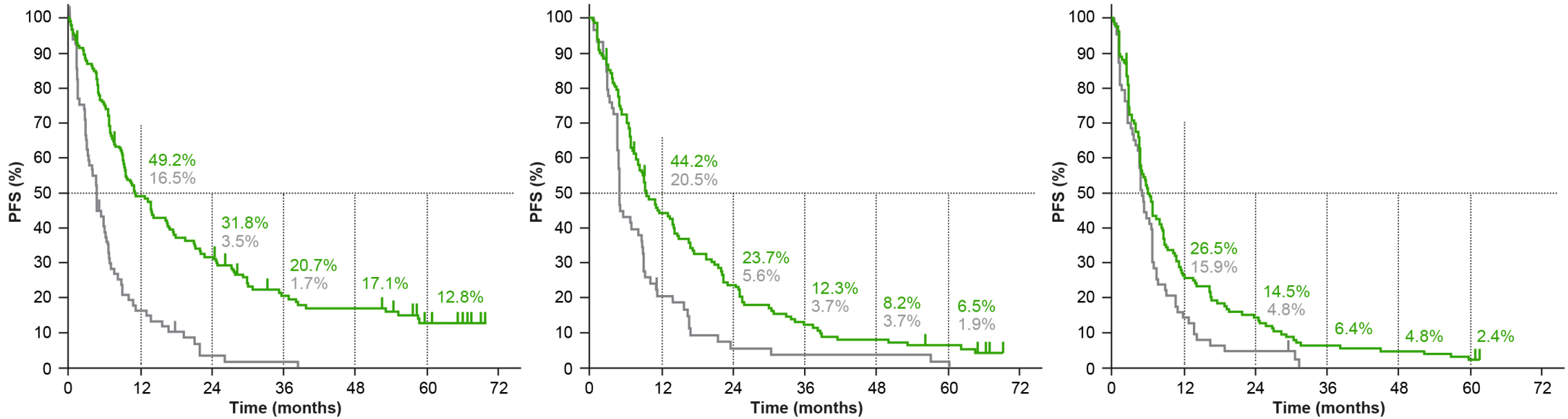
Treatment group	Events, n (%)	Median, months (95% CI)	HR (95% CI)	5-year PFS rate,% (95% CI)
Pembro–plat–pem	109 (82.6)	11.3 (9.1–16.5)	0.35	12.8 (7.4–19.8)
Placebo–plat–pem	67 (95.7)	4.8 (3.1–6.2)	(0.25–0.49)	–

PD-L1 TPS 1–49%

Treatment group	Events, n (%)	Median, months (95% CI)	HR (95% CI)	5-year PFS rate,% (95% CI)
Pembro–plat–pem	118 (92.2)	9.4 (8.1–13.8)	0.57	6.5 (3.1–11.8)
Placebo–plat–pem	57 (98.3)	4.9 (4.7–8.6)	(0.41–0.80)	1.9 (0.2–8.7)

PD-L1 TPS <1%

Treatment group	Events, n (%)	Median, months (95% CI)	HR (95% CI)	5-year PFS rate,% (95% CI)
Pembro–plat–pem	122 (96.1)	6.2 (4.9–8.3)	0.67	2.4 (0.7–6.3)
Placebo–plat–pem	62 (98.4)	5.1 (4.5–6.8)	(0.49–0.92)	–



No. at risk

Pembro–plat–pem	132	63	40	23	19	10	0
Placebo–plat–pem	70	11	2	1	0	0	0

Pembro–plat–pem	128	54	29	15	10	6	0
Placebo–plat–pem	58	11	3	2	2	1	0

Pembro–plat–pem	127	33	18	8	6	3	0
Placebo–plat–pem	63	10	3	0	0	0	0

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

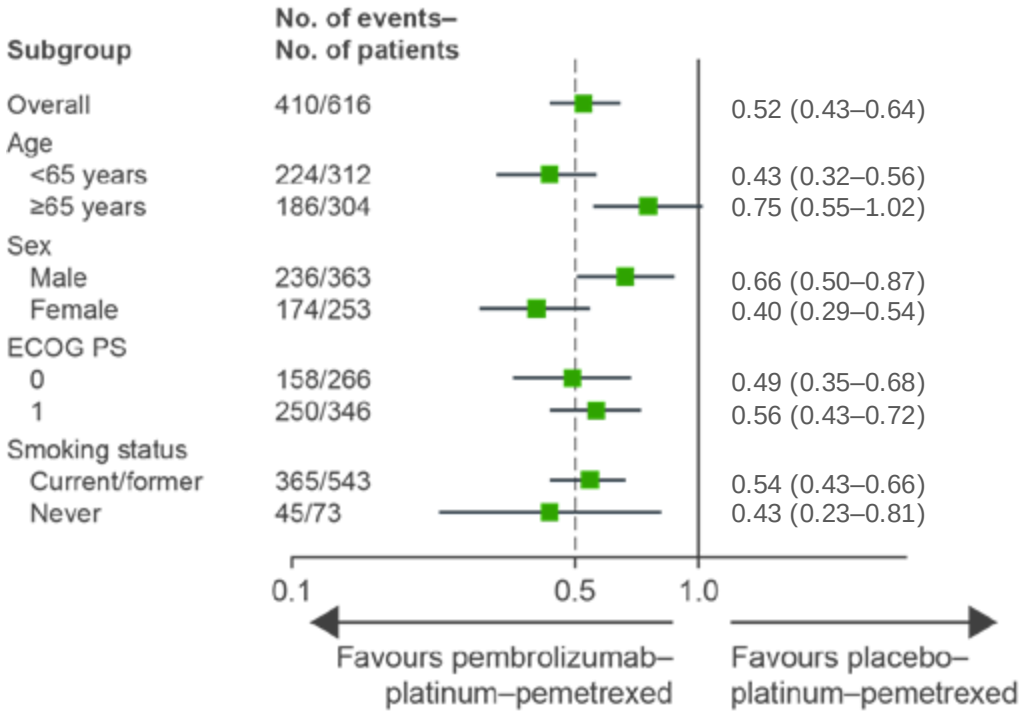
Data cut-off date: 8 March 2022.

[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [b]Kaplan-Meier estimate.

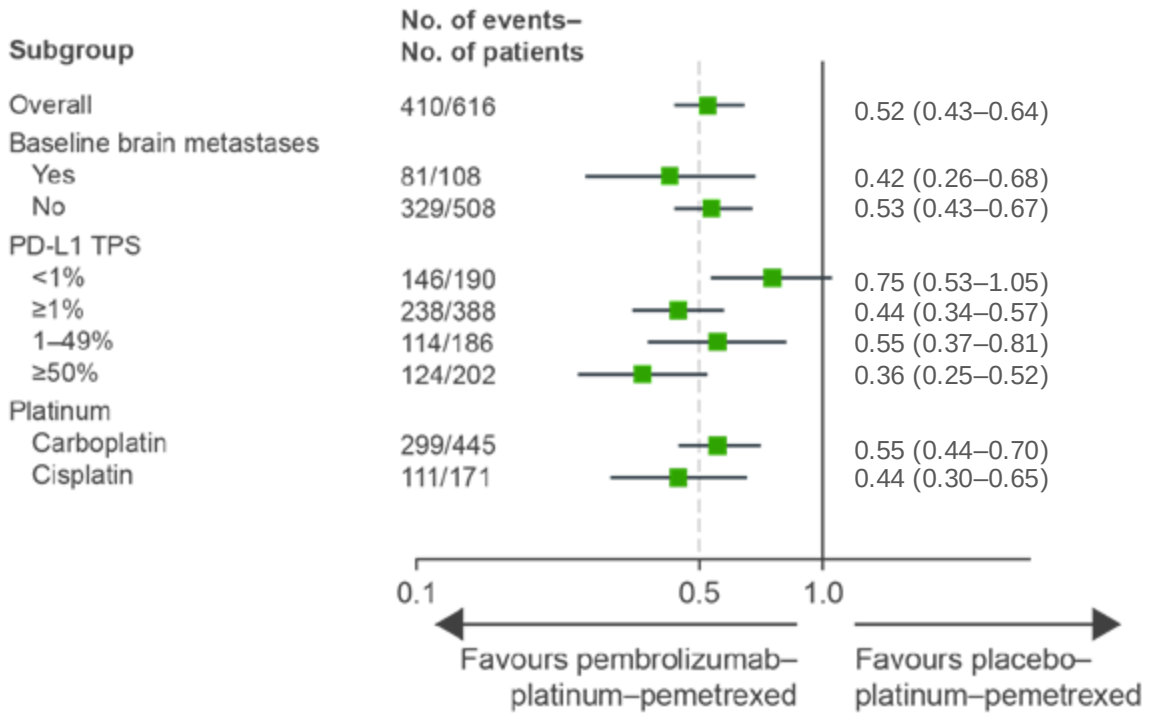
1. Garassino MC, *et al. J Clin Oncol*. 2023;41(11):1992-1998.

KEYNOTE-189: Exploratory endpoint – PFS in key subgroups (original analysis)[1,a]

Median follow-up: 10.5 months. No statistical conclusions can be drawn from exploratory endpoints



HR for disease progression or death (95% CI)



HR for disease progression or death (95% CI)

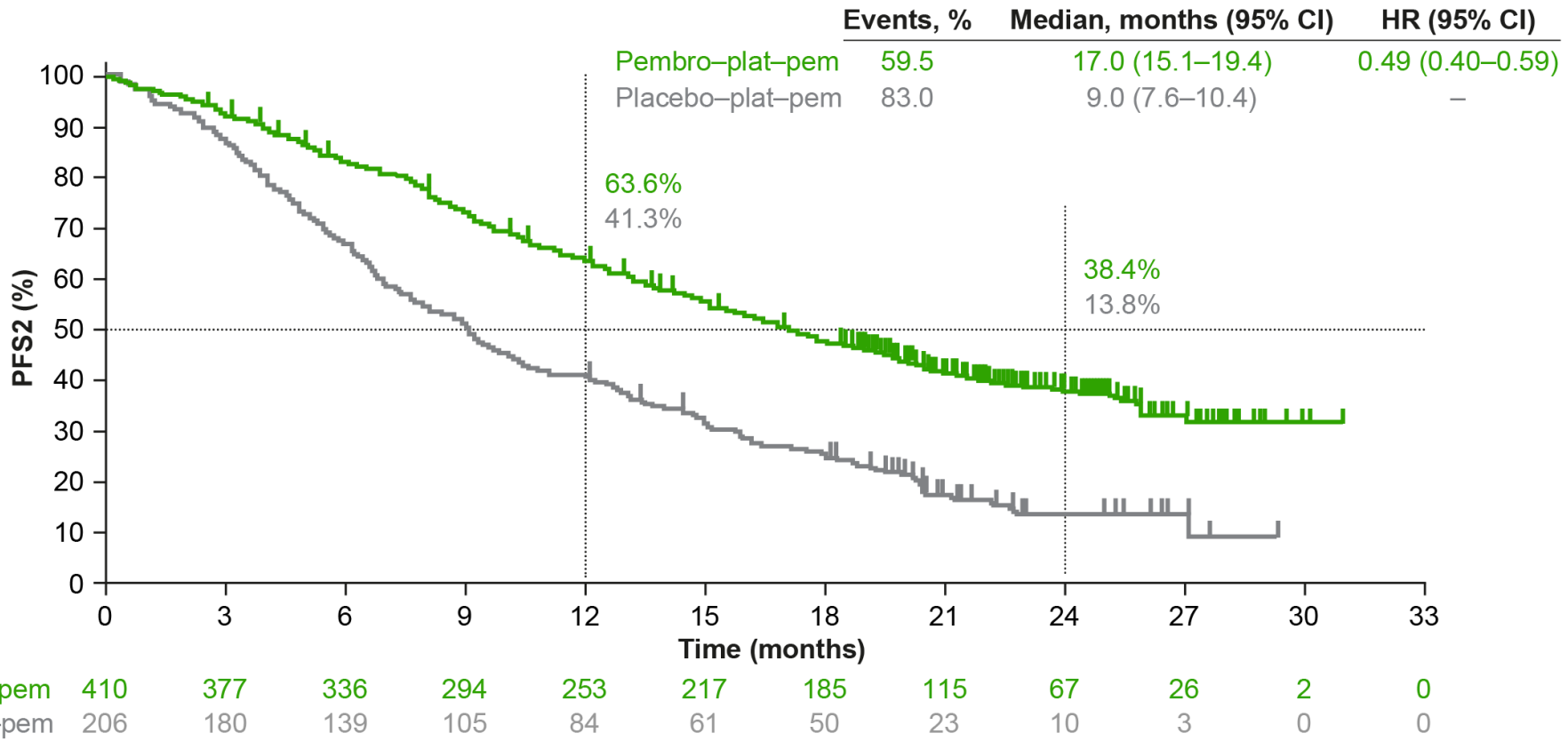
Adapted from Gandhi L et al. N Engl J Med 2018.

Data cut-off date: 8 November 2017.
[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review
1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092..

1

KEYNOTE-189: Exploratory endpoint – PFS2 (updated analysis)[1,a–c]

Median follow-up: 23.1 months. No statistical conclusions can be drawn from exploratory endpoints



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

Data cut-off date: 21 September 2018.

[a]Defined as the time from randomisation to second or subsequent tumour progression on next line of treatment or death. [b]Assessed using RECIST v1.1 by investigator review. [c]Kaplan-Meier estimate.

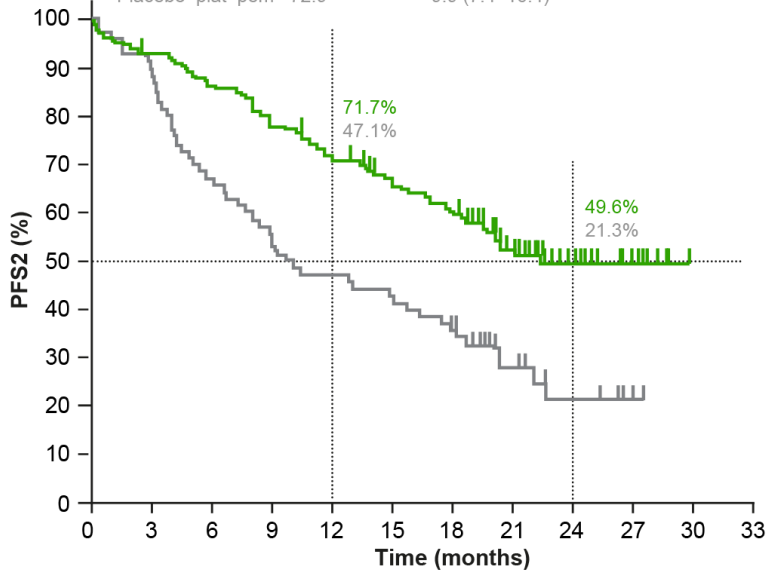
1. Gadgeel S. et al. *J Clin Oncol*. 2020;1903136.

KEYNOTE-189: Exploratory endpoint – PFS2 by PD-L1 TPS (updated analysis)[1,a,b]

Median follow-up: 23.1 months. No statistical conclusions can be drawn from exploratory endpoints

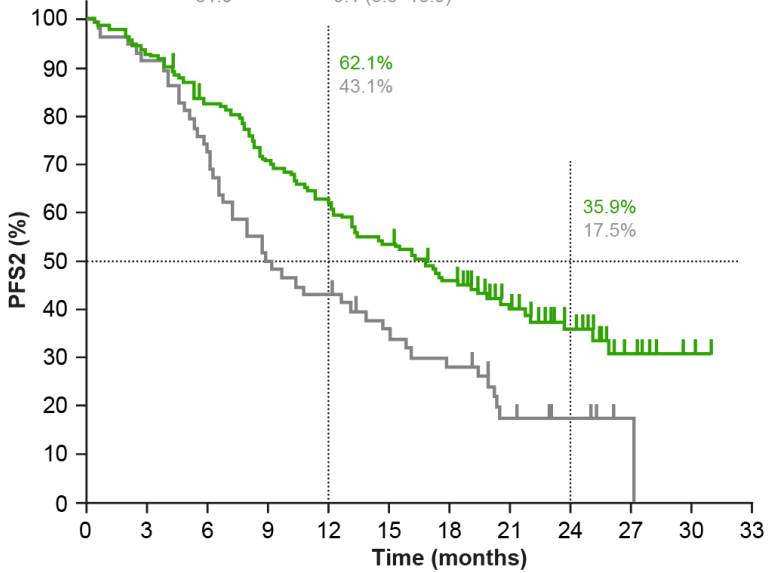
PD-L1 TPS ≥50%

	Events, %	Median, months (95% CI)	HR (95% CI)
Pembro–plat–pem	47.0	22.5 (18.5–NR)	0.47 (0.33–0.69)
Placebo–plat–pem	72.9	9.9 (7.4–16.4)	–



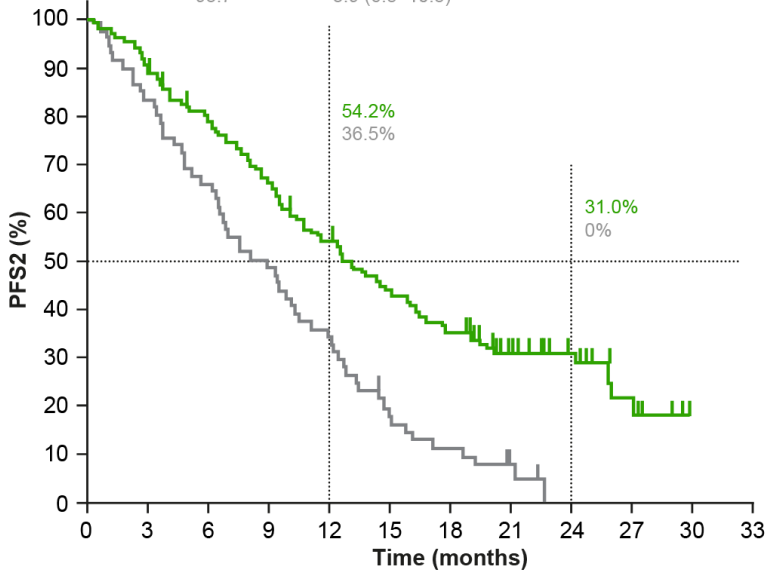
PD-L1 TPS 1–49%

	Events, %	Median, months (95% CI)	HR (95% CI)
Pembro–plat–pem	61.7	16.9 (12.7–20.5)	0.59 (0.41–0.86)
Placebo–plat–pem	81.0	9.1 (6.8–13.9)	–



PD-L1 TPS <1%

	Events, %	Median, months (95% CI)	HR (95% CI)
Pembro–plat–pem	69.3	12.6 (10.2–15.9)	0.46 (0.33–0.66)
Placebo–plat–pem	93.7	8.9 (6.5–10.5)	–



No. at risk												
Pembro–plat–pem	132	122	113	104	93	83	75	50	26	9	0	0
Placebo–plat–pem	70	63	47	40	33	30	25	11	5	1	0	0
Pembro–plat–pem	128	119	104	89	78	67	56	34	23	9	2	0
Placebo–plat–pem	58	53	43	29	24	18	15	8	4	1	0	0
Pembro–plat–pem	127	113	99	82	65	53	42	22	14	6	0	0
Placebo–plat–pem	63	53	42	31	23	10	7	3	0	0	0	0

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

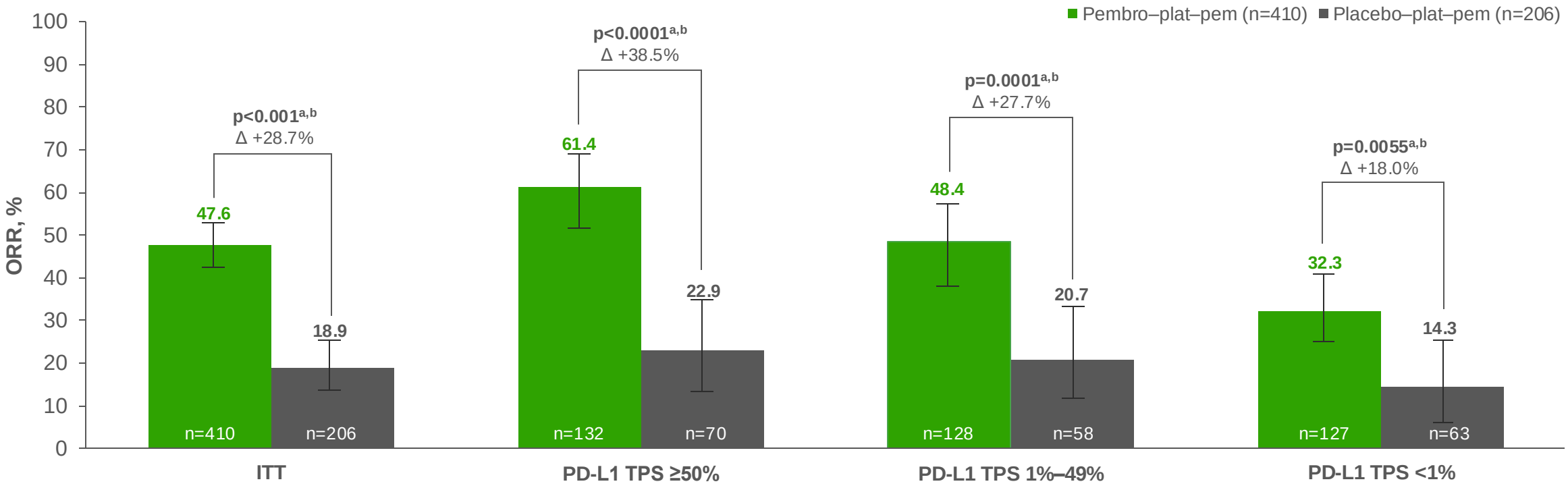
Data cut-off date: 21 September 2018.

[a]Defined as the time from randomisation to second or subsequent tumour progression on next line of treatment or death. [b]Assessed using RECIST v1.1 by investigator review. [c]Kaplan-Meier estimate.

1. Gadgeel S. et al. *J Clin Oncol*. 2020;1903136.

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

Median follow-up: 10.5 months. No statistical conclusions can be drawn from exploratory endpoints

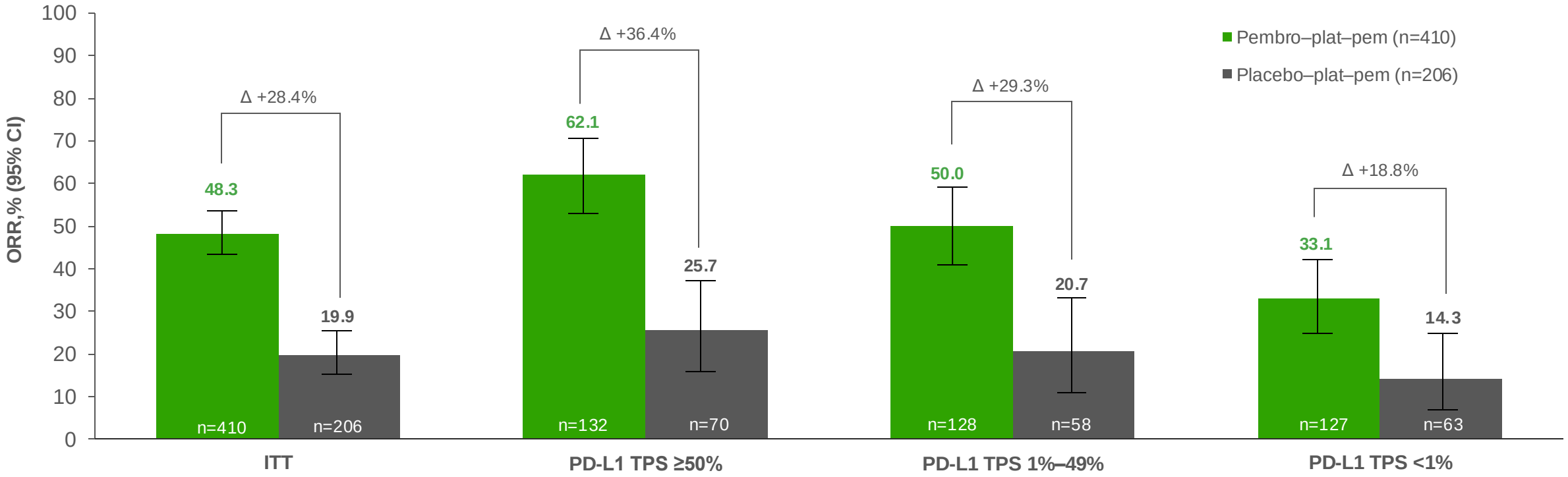


Adapted from Gandhi L et al. N Engl J Med 2018; Gandhi L et al. AACR 2018.

Data cut-off date: 8 November 2017.
[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [b]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: Exploratory analysis – ORR in the ITT population and exploratory endpoint ORR by PD-L1 TPS (5-year update)[1,a]

Median follow-up: 64.6 months. No statistical conclusions can be drawn from this analysis



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

Data cut-off date: 8 March 2022.

[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review.

1. Garassino MC, *et al. J Clin Oncol*. 2023;41(11):1992-1998.

KEYNOTE-189: DOR and DCR in the ITT population (original analysis)[1,2,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.

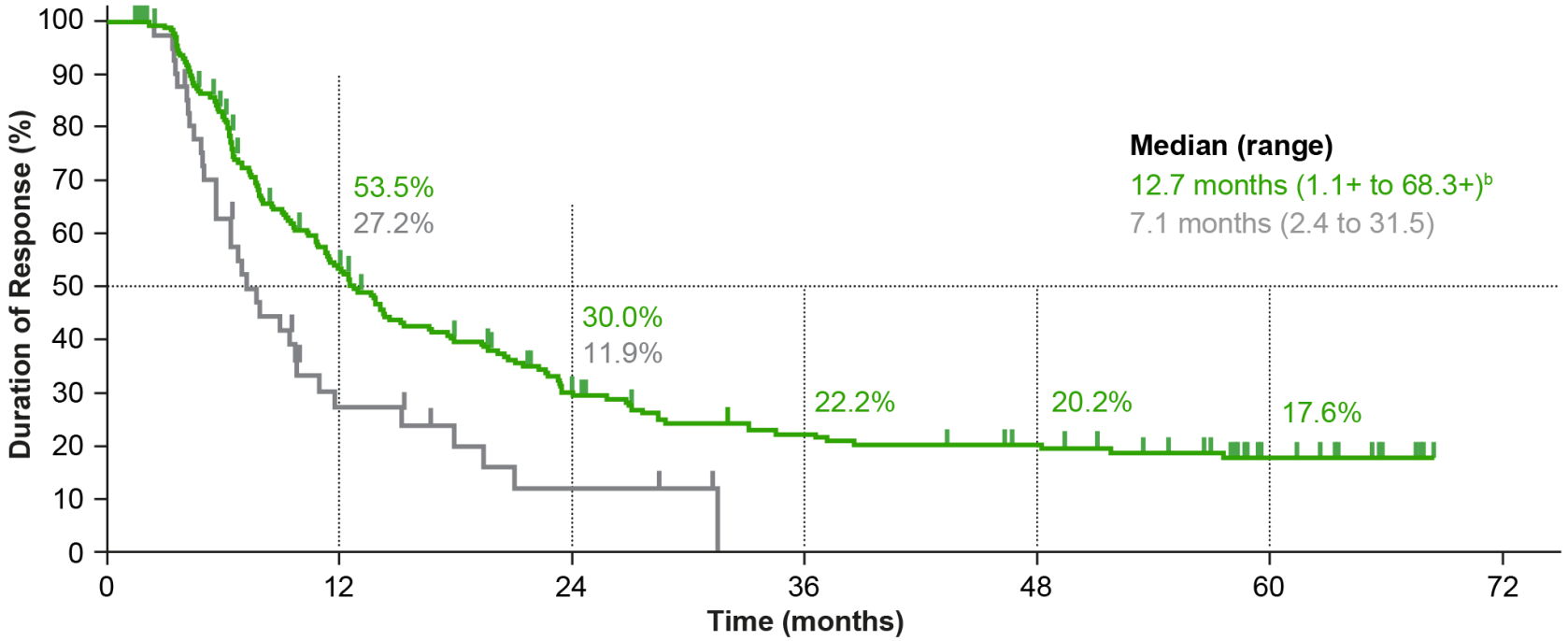
Data cut-off date: 8 November 2017.

[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.

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: Exploratory analysis – DOR in the ITT population (5-year update)[1,a]

Median follow-up: 64.6 months. No statistical conclusions can be drawn from this analysis



No. at risk							
Pembro–plat–pem	198	95	48	33	27	11	0
Placebo–plat–pem	41	9	3	0	0	0	0

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

Data cut-off date: 8 March 2022.
[a]Kaplan-Meier estimate. [b]+ denotes a response that was ongoing at the analysis cut-off date.
1. Garassino MC *et al. J Clin Oncol*. 2023;41(11):1992-1998.

KEYNOTE-189: Exploratory analysis – DOR by PD-L1 TPS (5-year update)[1,a]

Median follow-up: 64.6 months. No statistical conclusions can be drawn from this analysis

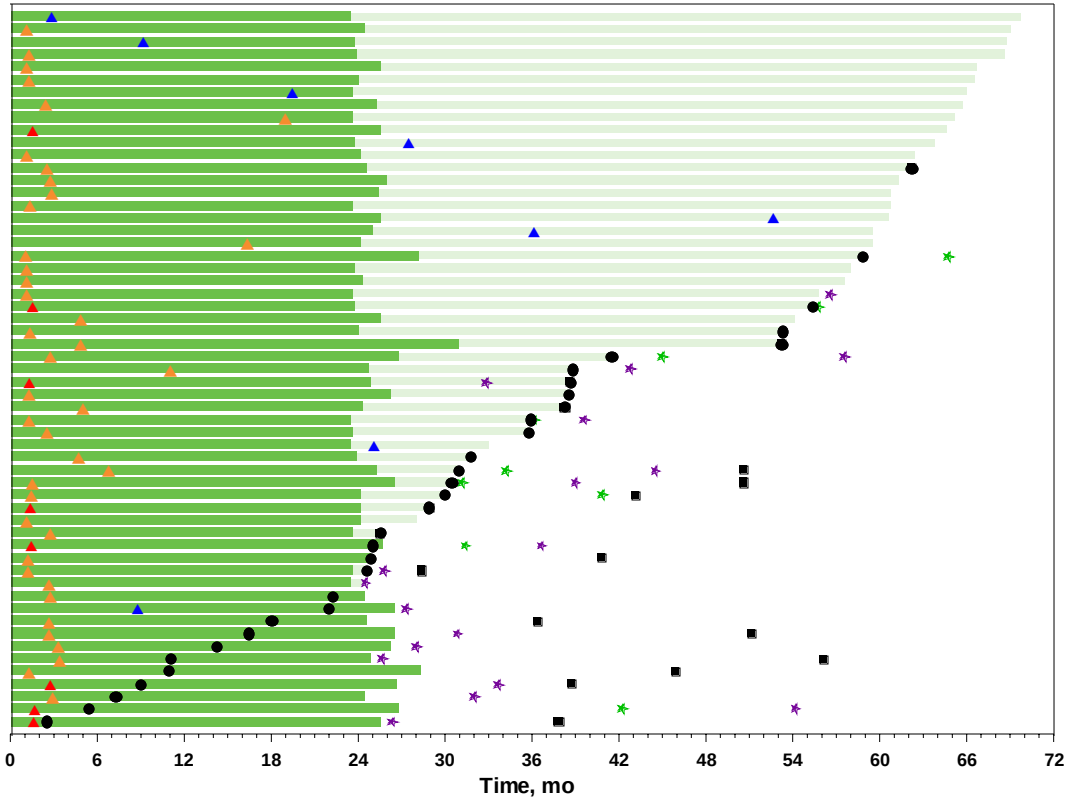
	PD-L1 TPS ≥50%		PD-L1 TPS 1%-49%		PD-L1 TPS <1%	
	Pembro–plat–pem	Placebo–plat–pem	Pembro–plat–pem	Placebo–plat–pem	Pembro–plat–pem	Placebo–plat–pem
DOR Median (range), mo[b]	15.3 (1.2+ to 68.3+)	7.1 (3.4 to 31.5)	13.6 (2.1+ to 67.6+)	7.6 (2.4 to 31.0+)	10.8 (1.1+ to 59.4+)	7.8 (4.1 to 28.3+)

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

Data cut-off date: 8 March 2022.
[a]Kaplan-Meier estimate. [b]+ denotes a response that was ongoing at the analysis cut-off date.
1. Garassino MC, *et al. J Clin Oncol*. 2023;41(11):1992-1998.

KEYNOTE-189: Exploratory analysis – Outcomes in patients who completed 35 cycles of pembrolizumab (5-year update)[1,2]

Median follow-up: 64.6 months. No statistical conclusions can be drawn from this analysis



	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.

Data 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.
1. Garassino MC, *et al. J Clin Oncol*. 2023;41(11):1992-1998; 2. Garassino MC, *et al.* Presented at the 2022 European Society for Medical Oncology (ESMO) Annual Meeting, 9–13 September, 2022, Paris, France.

KEYNOTE-189: Exposure to study treatment in the as-treated population (original analysis)[1,2]

Median follow-up: 10.5 months

	Pembro–plat–pem (n=405)	Placebo–plat–pem (n=202)
Treatment duration, mean (± SDev), months	7.4 (4.7)	5.4 (4.3)
Treatment cycles, n		
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.

Data 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)[1,a]

Median follow-up: 10.5 months

AE, n (%)	Pembro–plat–pem (n=405)	Placebo–plat–pem (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.

Data 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.

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

1

KEYNOTE-189: Summary of AEs in the as-treated population (updated analysis)[1,a]

Median follow-up: 23.1 months

AE, n (%)	Pembro–plat–pem (n=405)	Placebo–plat–pem (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)

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

Data 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 armdied 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)[1,2]

Median follow-up: 64.6 months

Adverse event, n (%)	All treated patients		35 cycles of pembro (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; Garassino MC et al. ESMO 2022.

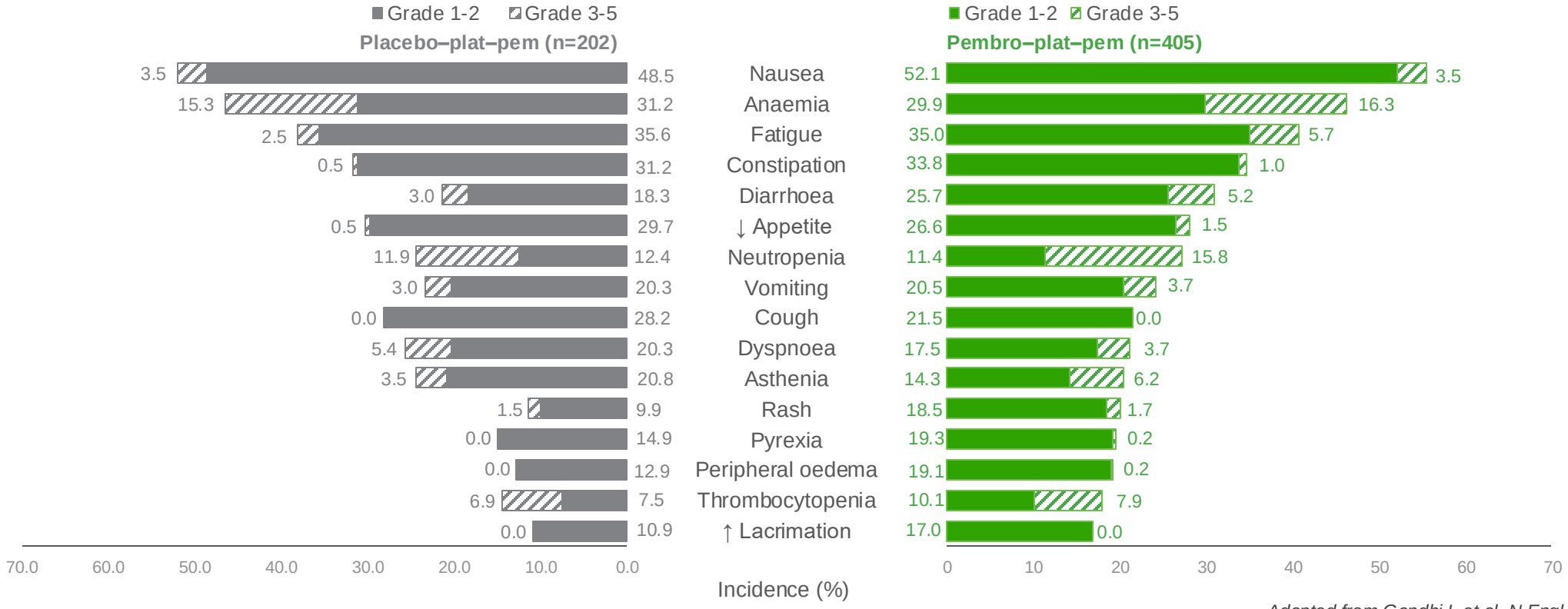
Data cut-off date: March 8, 2022.

[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.

1. Garassino MC, *et al. J Clin Oncol*. 2023;41(11):1992-1998; 2. Garassino MC, *et al.* Presented at the 2022 European Society for Medical Oncology (ESMO) Annual Meeting, 9–13 September, 2022, Paris, France.

KEYNOTE-189: All-cause AEs occurring in ≥15% of patients in the as-treated population (original analysis)[1,a,b]

Median follow-up: 10.5 months



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

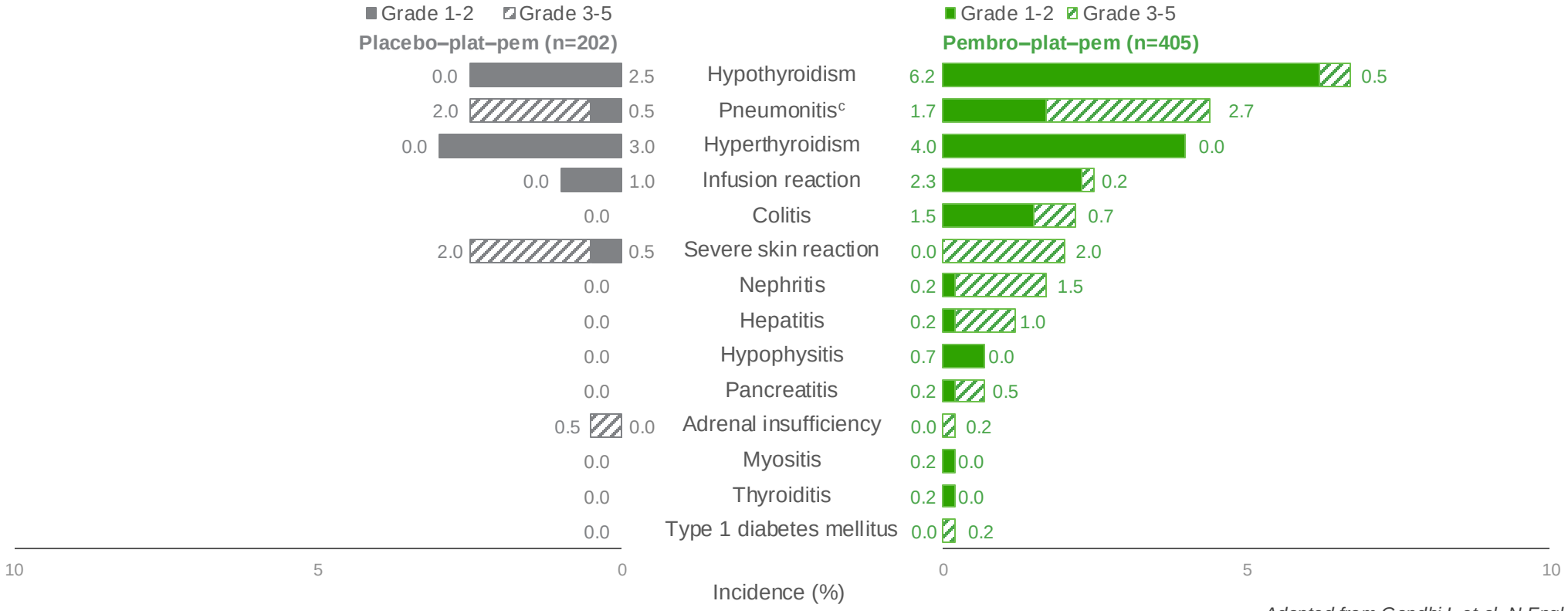
Data cut-off date: 8 November 2017.
[a]AEs that occurred during crossover from the placebo-combination group to pembrolizumab monotherapy are excluded. [b]AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

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

1

KEYNOTE-189: Immune-mediated AEs in the as-treated population (original analysis)[1,a,b]

Median follow-up: 10.5 months



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

40

Data 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.

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

1

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 pembro–plat–pem vs. placebo–plat–pem arms, respectively
  - Grade 3–5 frequency:[a] 2.0% (n=8) vs. 0%, respectively
  - Grade 5 frequency: 0.5% (n=2) with pembro–plat–pem
- 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 pembro–plat–pem vs. placebo–plat–pem arms, respectively
  - Grade 3–5 frequency: 1.5% (n=6) vs. 0%, respectively
  - Grade 5 frequency: 0%

Data 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]

Median follow-up: 18.7 months. No statistical conclusions can be drawn from this exploratory analysis

- Extrapulmonary metastases to sites such as the liver and brain frequently occur in metastatic NSCLC and can be associated with a poor prognosis[1]
- **Objective of current analysis**: retrospectively evaluate outcomes among patients with baseline liver or brain metastases[2]
- 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)[2]

Data cut-off date: 21 September 2018.

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

1. Gibson AJW *et al. Med Oncol* 2018;35:117; 2. 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 – Key baseline characteristics[1,a]

Median follow-up: 18.7 months. No statistical conclusions can be drawn from this exploratory analysis

Characteristic, n (%)[b]	Pembro–plat–pem (n=410)	Placebo–plat–pem (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]	Pembro–plat–pem (n=410)	Placebo–plat–pem (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)

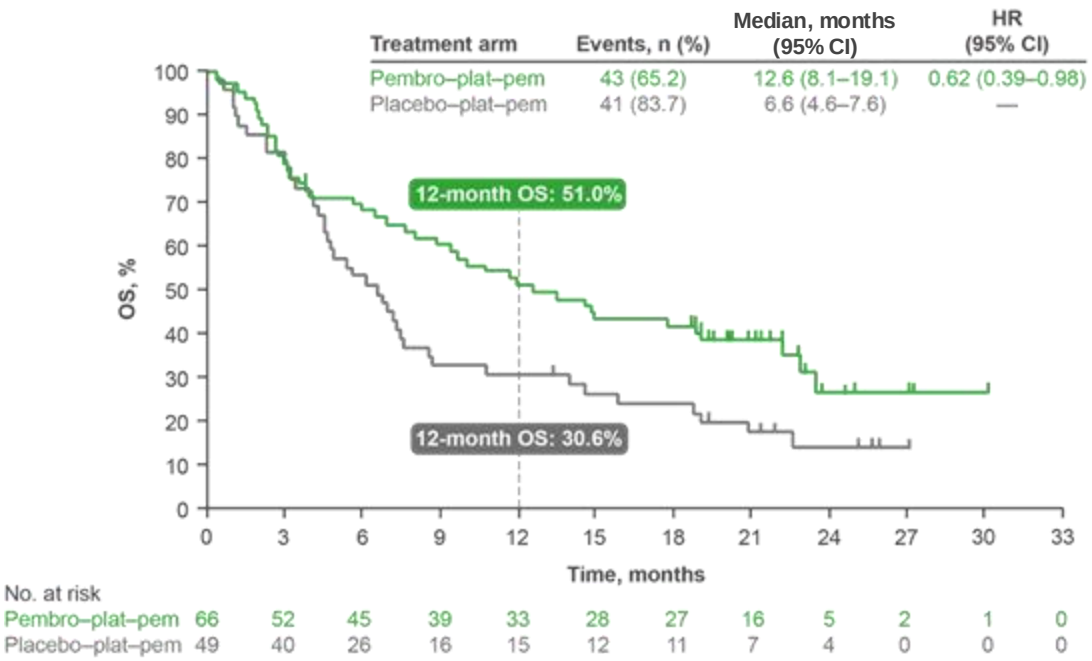
Adapted from Garassino MC et al. AACR 2019.

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

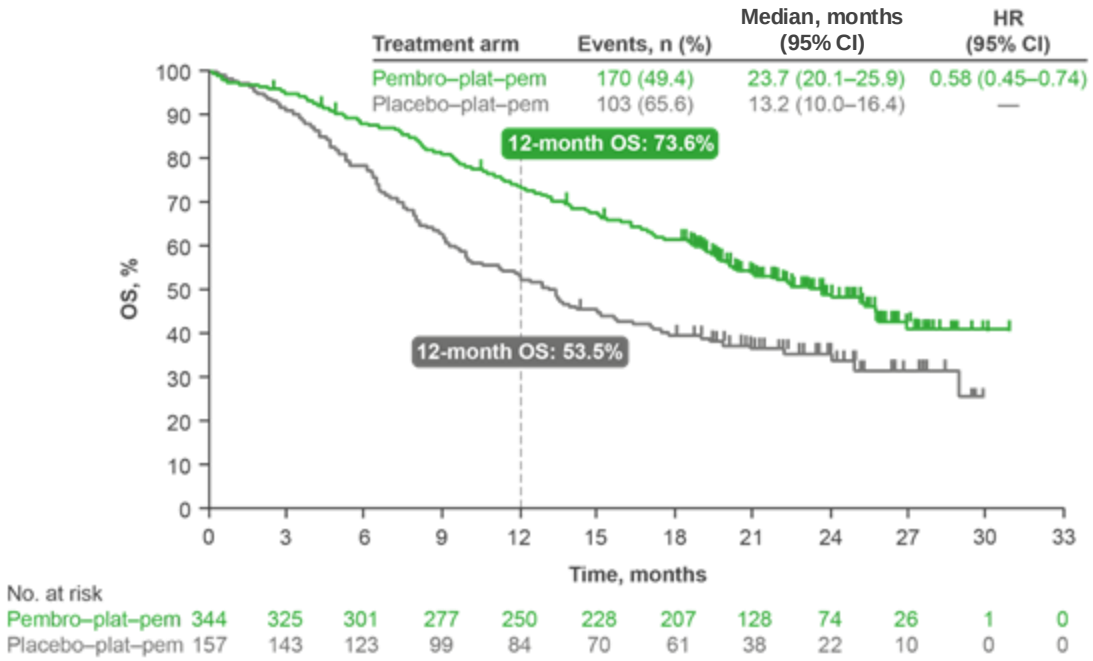
KEYNOTE-189: Post-hoc analysis – OS in patients with liver metastases[1,a]

Median follow-up: 18.7 months. No statistical conclusions can be drawn from this exploratory analysis

Patients with liver metastases



Patients without liver metastases



Adapted from Garassino MC et al. AACR 2019.

Data cut-off date: 21 September 2018.

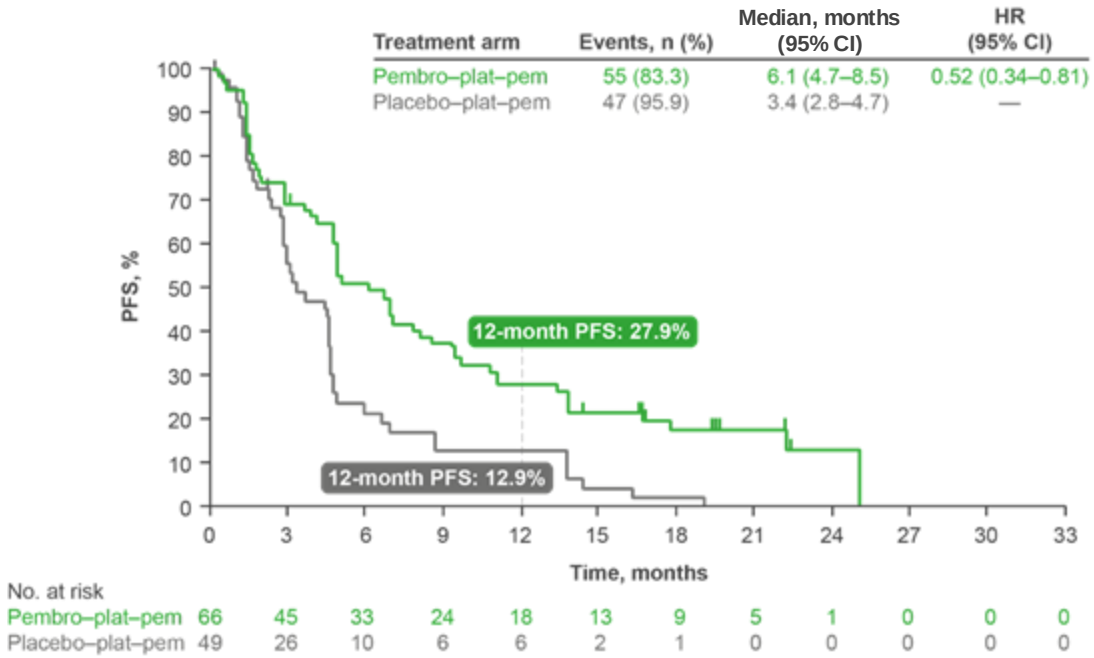
[a]No other data was reported with this analysis.

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

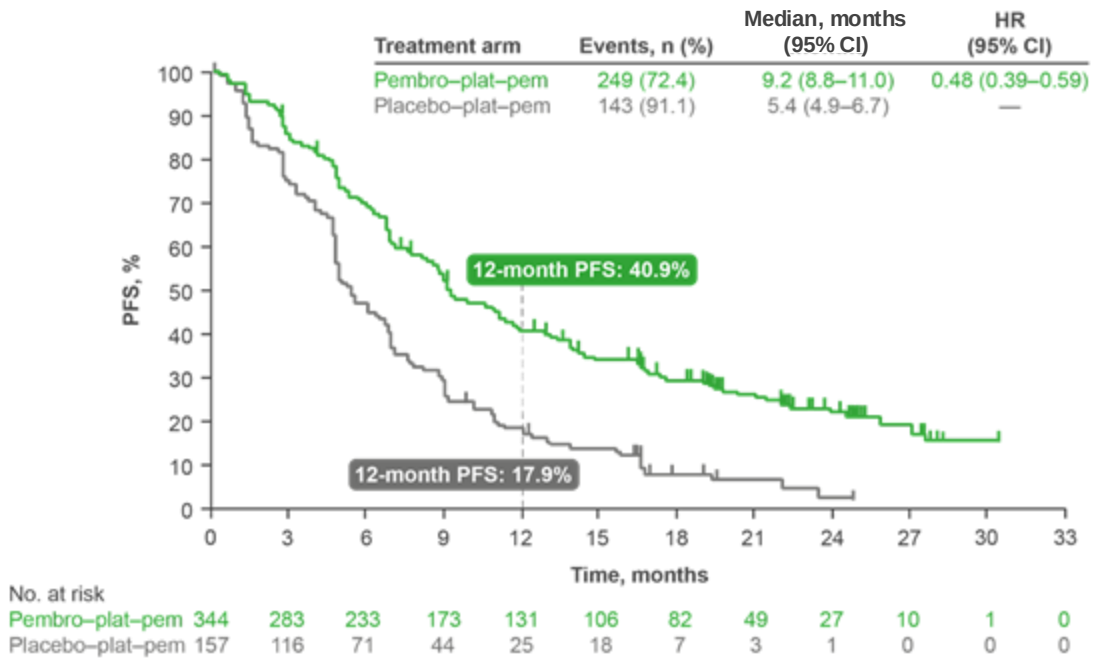
KEYNOTE-189: Post-hoc analysis – PFS in patients with liver metastases[1,a,b]

Median follow-up: 18.7 months. No statistical conclusions can be drawn from this exploratory analysis

Patients with liver metastases



Patients without liver metastases



Adapted from Garassino MC et al. AACR 2019.

Data cut-off date: 21 September 2018.

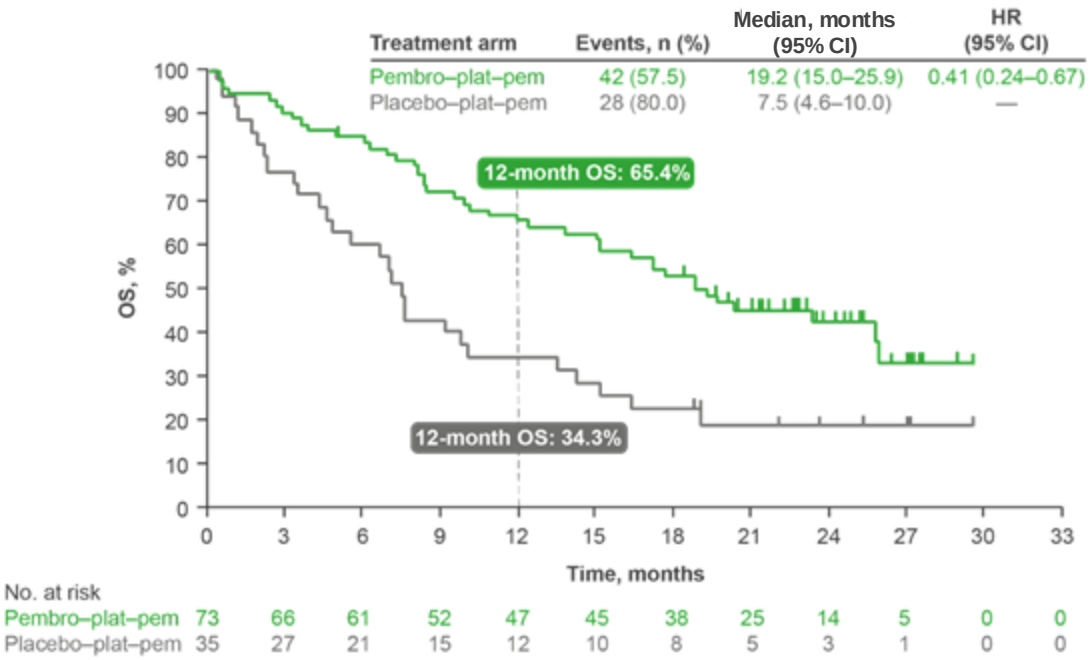
[a]No other data was reported with this analysis. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review.

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

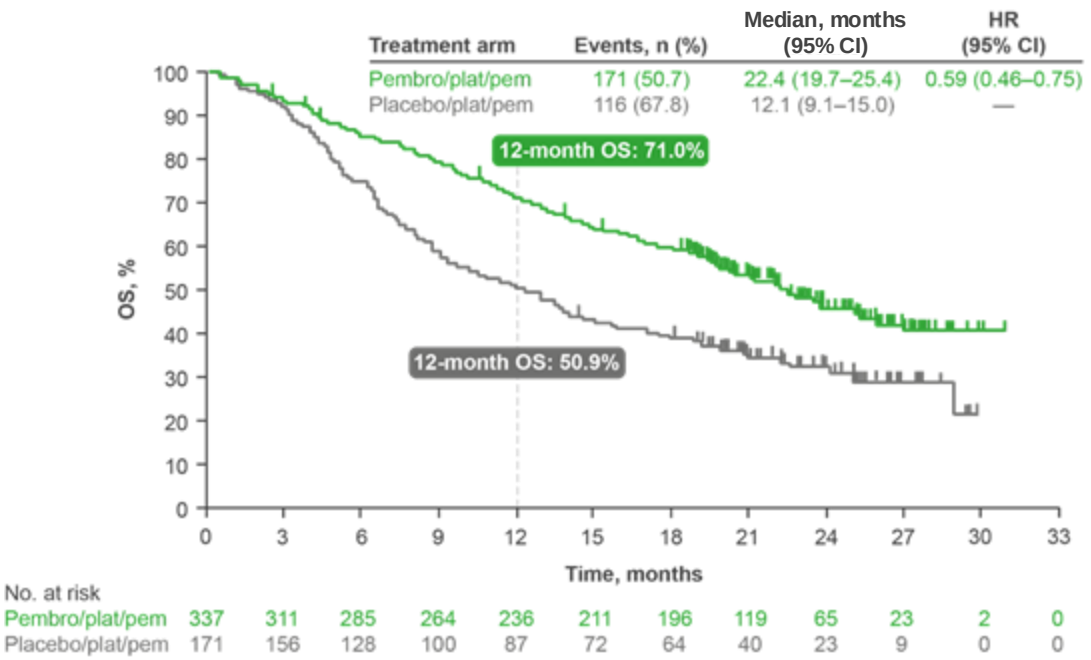
KEYNOTE-189: Post-hoc analysis – OS in patients with brain metastases[1,a]

Median follow-up: 18.7 months. No statistical conclusions can be drawn from this exploratory analysis

Patients with brain metastases



Patients without brain metastases



Adapted from Garassino MC et al. AACR 2019.

Data cut-off date: 21 September 2018.

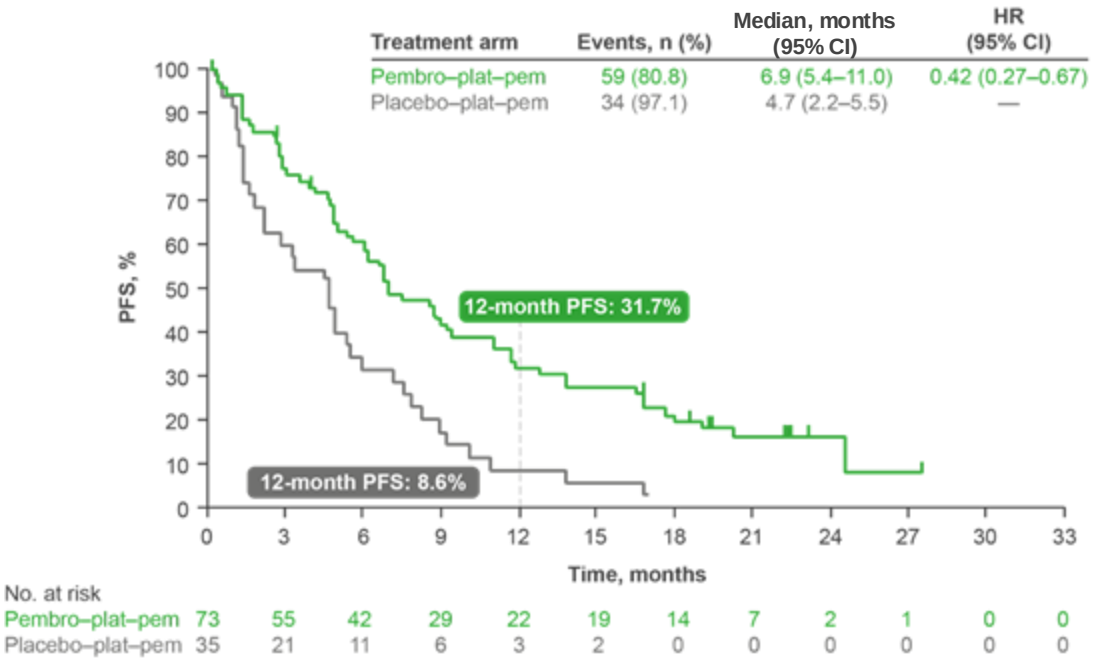
[a]No other data was reported with this analysis.

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

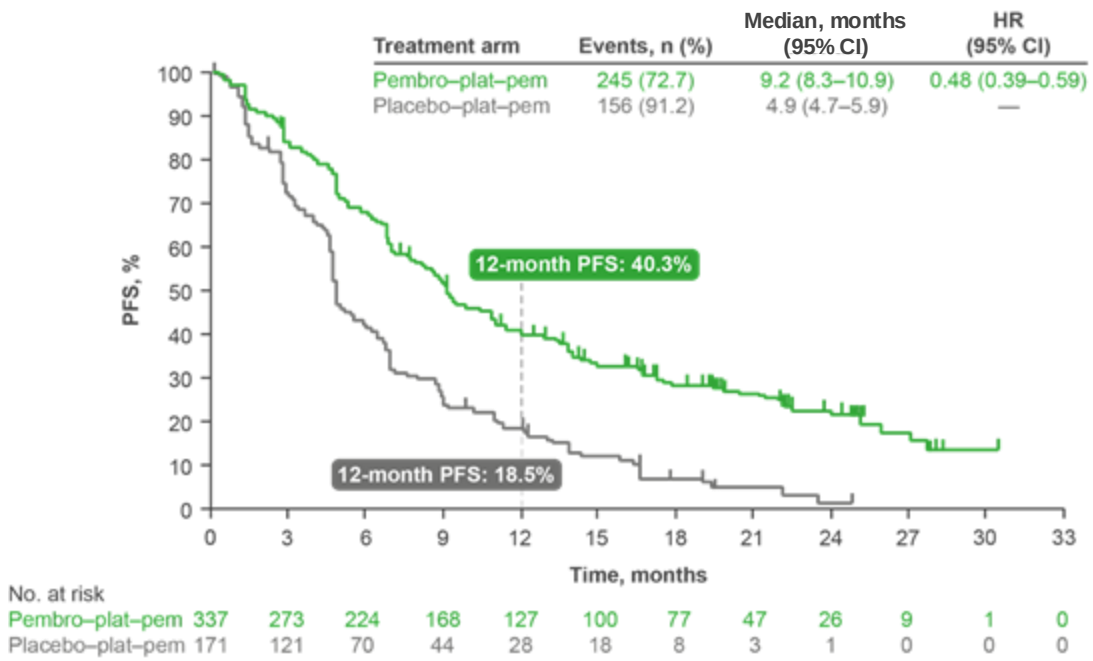
KEYNOTE-189: Post-hoc analysis – PFS in patients with brain metastases[1,a,b]

Median follow-up: 18.7 months. No statistical conclusions can be drawn from this exploratory analysis

Patients with brain metastases



Patients without brain metastases



Adapted from Garassino MC et al. AACR 2019.

Data 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.

1. 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: Exploratory endpoint – QLQ-C30 completion and compliance rates[1,a,b]

Median follow-up: 10.5 months. No statistical conclusions can be drawn from exploratory endpoints

		Pembro–plat–pem (n=402) n (%) or n/N (%)	Placebo–plat–pem (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%)

Adapted from Garassino MC et al. Lancet Oncol 2020.

Data cut-off date: 8 November 2017.
[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.

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

KEYNOTE-189: Exploratory endpoint – QLQ-LC13 completion and compliance rates[1,a,b]

Median follow-up: 10.5 months. No statistical conclusions can be drawn from exploratory endpoints

		Pembro–plat–pem (n=402) n (%) or n/N (%)	Placebo–plat–pem (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%)

Adapted from Garassino MC et al. Lancet Oncol 2020.

Data cut-off date: 8 November 2017.
[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.

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

KEYNOTE-189: Exploratory endpoint – EORTC QLQ-C30 GHS[1]

Median follow-up: 10.5 months. No statistical conclusions can be drawn from exploratory endpoints

	Pembro–plat–pem (n=402)	Placebo–plat–pem (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)[c]	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)[c]	3.6 (−0.1 to 7.2) p=0.053	
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]	

Adapted from Garassino MC et al. Lancet Oncol 2020.

Data cut-off date: 8 November 2017.
[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.

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

1

KEYNOTE-189: Exploratory endpoint – QLQ-C30 GHS/QoL and functional and symptom subscales[1]

Median follow-up: 10.5 months. No statistical conclusions can be drawn from exploratory endpoints

Mean QLQ-C30 GHS/QoL scores:

- Improved from baseline to week 9 in both the pembro–plat–pem and placebo–plat–pem group
- Deteriorated in both groups from week 9 onwards; however, scores in the pembro–plat–pem group remained above baseline whereas those in the placebo–plat–pem 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 pembro–plat–pem group than in the placebo–plat–pem group for most functional and symptom scales at week 21
  - Symptom scale scores for dyspnoea and pain improved in the pembro–plat–pem group and worsened/remained stable in the placebo–plat–pem group

Data cut-off date: 8 November 2017.

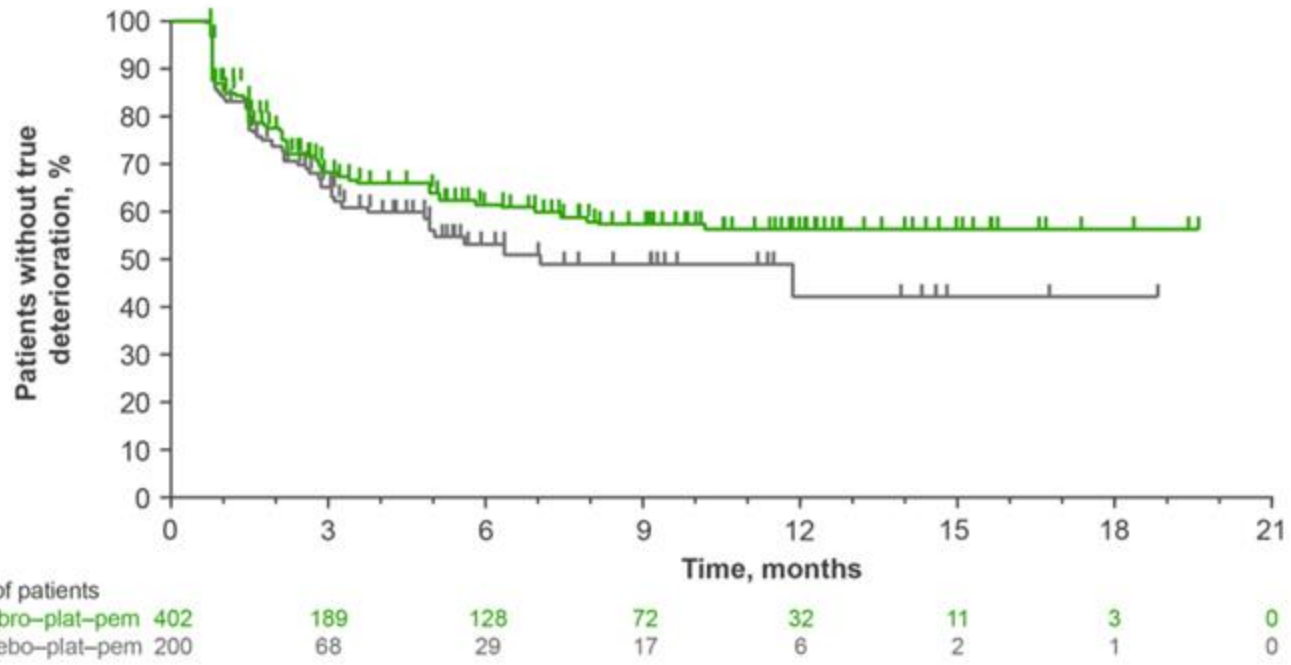
1. Garassino MC *et al. Lancet Oncol*. 2020;21:387–397.

1

KEYNOTE-189: Exploratory endpoint – Time to deterioration analysis Composite endpoint of cough, chest pain and dyspnoea[1]

Median follow-up: 10.5 months. No statistical conclusions can be drawn from exploratory endpoints

Treatment arm[a]	Events, %	Median, months (95% CI)	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)	–	



Adapted from Garassino MC et al. Lancet 2020.

Data cut-off date: 8 November 2017.
[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.
1. Garassino MC *et al. Lancet Oncol*. 2020;21:387–397.

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KEYNOTE-189: Efficacy summary

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)[1]
- Superior PFS, with a 48% reduction in the risk of progression or death (HR: 0.52, p<0.001)[1]
- Superior ORR (47.6% vs. 18.9%, p<0.001) and improved DOR[1]
- The treatment effect on OS was consistent across all PD-L1 subgroups, including PD-L1 TPS <1% and 1–49%[a,1]
- 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 non-squamous 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.**

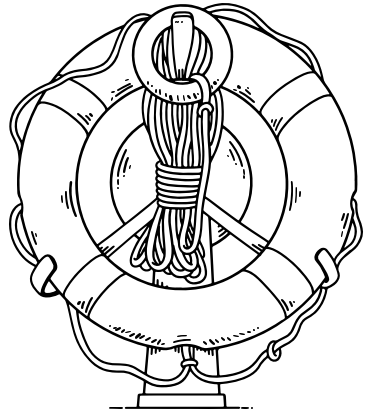
1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Garassino MC *et al.* Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April 2019, Atlanta, USA;
3. Garassino MC, *et al. J Clin Oncol*. 2023;41(11):1992-1998.

KEYNOTE-189: Safety summary

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]



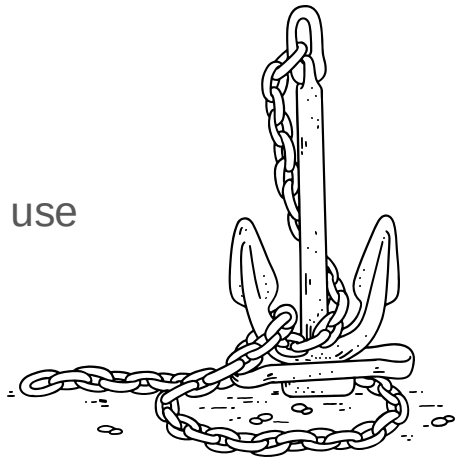
[a]**This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn.**

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;41(11):1992-1998.

KEYNOTE-189: HRQoL summary[1]

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
- At a median 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
- These data complement the superior efficacy observed with pembrolizumab + platinum + pemetrexed over placebo + platinum + pemetrexed in the KEYNOTE-189 study and support the use of pembrolizumab + platinum + pemetrexed as first-line therapy for metastatic, non-squamous NSCLC



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

Post-hoc exploratory pooled analysis (KEYNOTE-189, KEYNOTE-407)

5-year survival with KEYTRUDA® (pembrolizumab) plus chemotherapy for mNSCLC with PD-L1 TPS <1%[1]

1. Gadgeel S et al. 5-year survival of pembrolizumab plus chemotherapy for metastatic NSCLC with PD-L1 tumor proportion score <1%. Presented at the WCLC, 9-12 September 2023, Singapore. 2023

KEYNOTE-189: KEYTRUDA

(pembrolizumab) plus chemotherapy for the first-line treatment of metastatic, non-squamous, *EGFR/ALK*-wild-type NSCLC[1]

Skip ahead to KEYNOTE-407

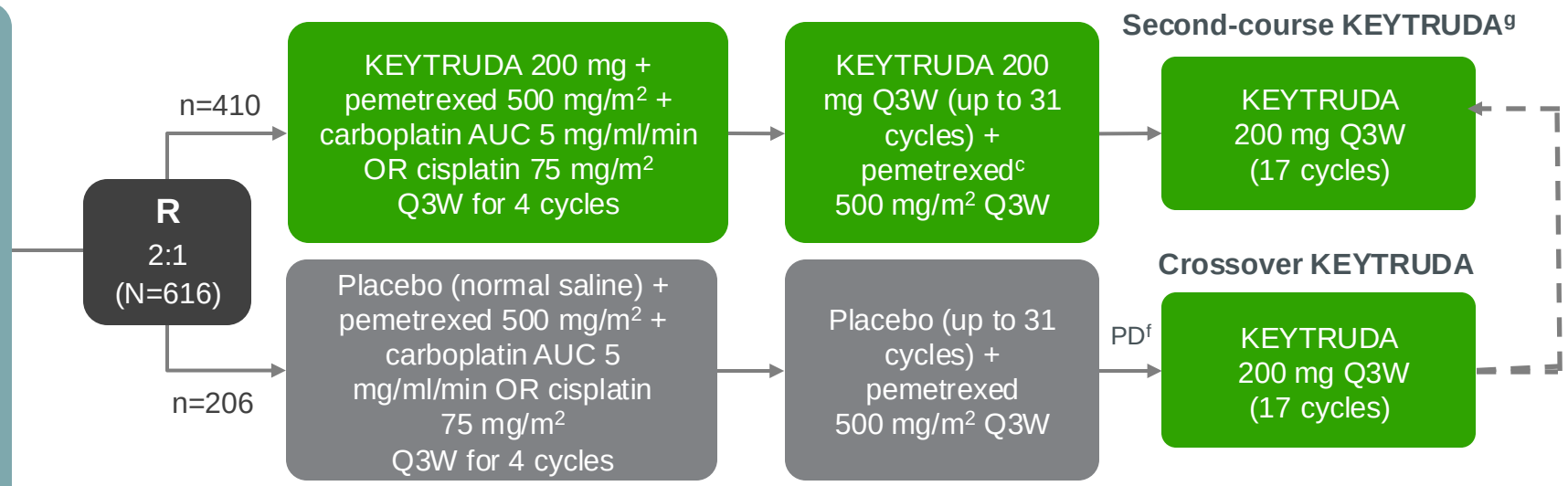
1. Gandhi L *et al*. *N Engl J Med* 2018;378:2078–2092 (and supplementary appendix).

KEYNOTE-189: Study design[1–3]

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; Gray JE et al. WCLC 2020.

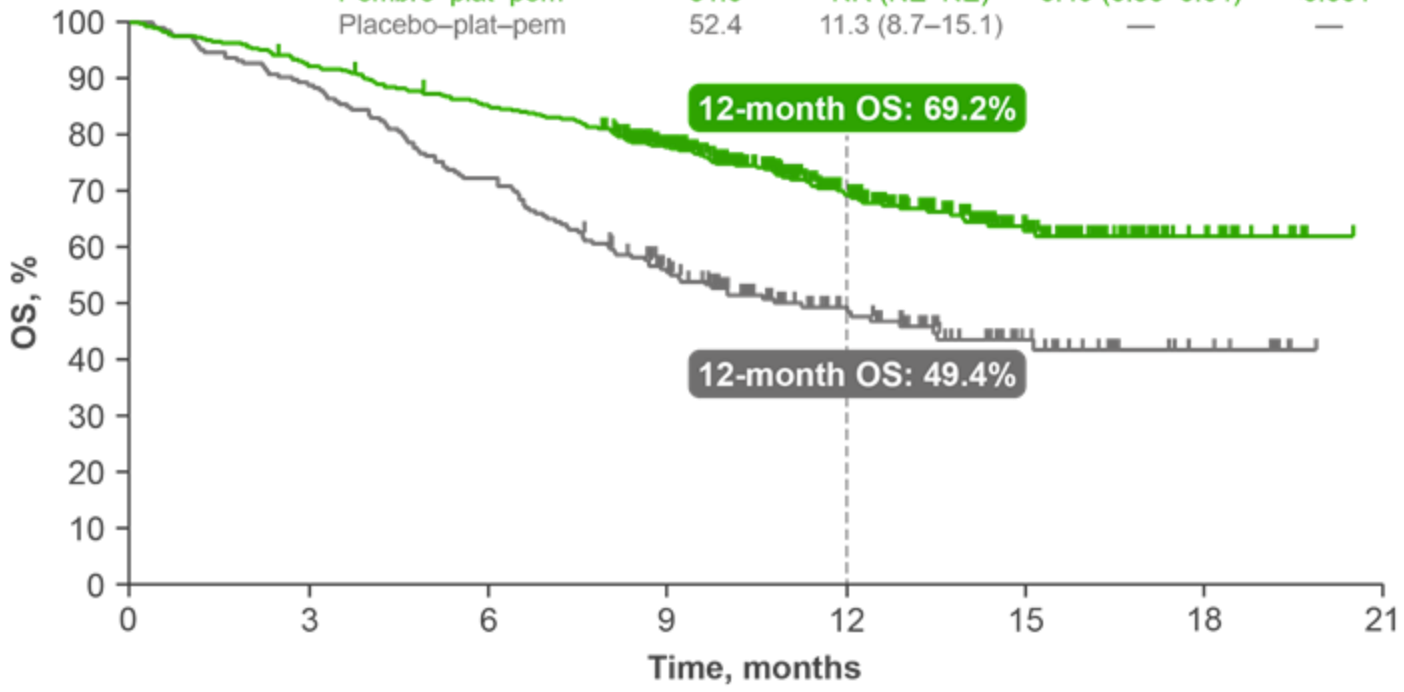
[a]Patients were permitted to enrol if their brain lesions were previously treated, clinically stable for ≥2 weeks without evidence of new or enlarging lesions, and steroid-free for ≥3 days prior to receiving study treatment. [b]Percentage of tumour cells with membrane PD-L1 staining, as assessed using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

1. Gandhi L *et al*. *N Engl J Med* 2018;378:2078–2092 (and protocol); 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: 1-year landmark OS in the ITT population (original analysis)[1,2,a,b]

Median follow-up: 10.5 months

Treatment arm	Events,%	Median, months (95% CI)	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.

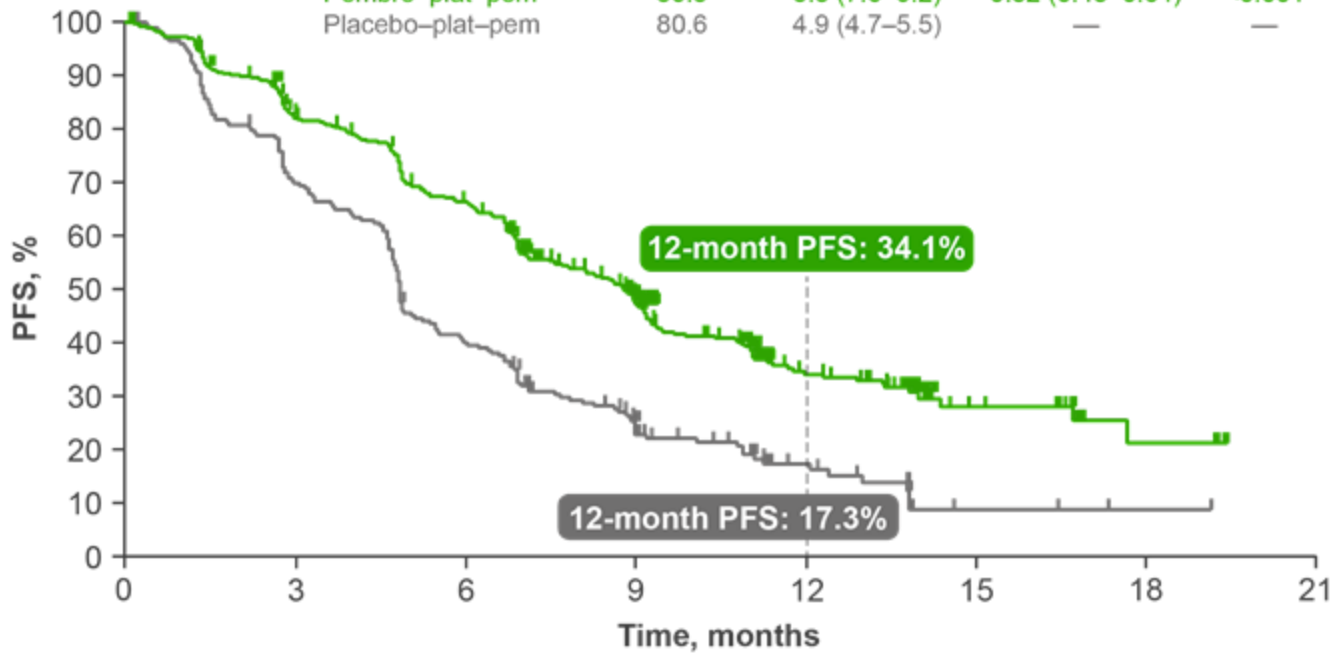
Data cut-off date: 8 November 2017.
[a]OS and PFS were both primary endpoints. [b]Kaplan-Meier estimate.
1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Gandhi L *et al.* Presented at the 2018 American Association for Cancer Research (AACR) Annual Meeting, 14–18 April, 2018, Chicago, USA.

1

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

Median follow-up: 10.5 months

Treatment arm	Events, %	Median, months (95% CI)	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.

Data cut-off date: 8 November 2017.
[a]OS and PFS were both primary endpoints. [b]Kaplan-Meier estimate. [c]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: Summary of AEs in the as-treated population (original analysis)[1,a]

Median follow-up: 10.5 months

AE, n (%)	Pembro–plat–pem (n=405)	Placebo–plat–pem (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.

Data 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.

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

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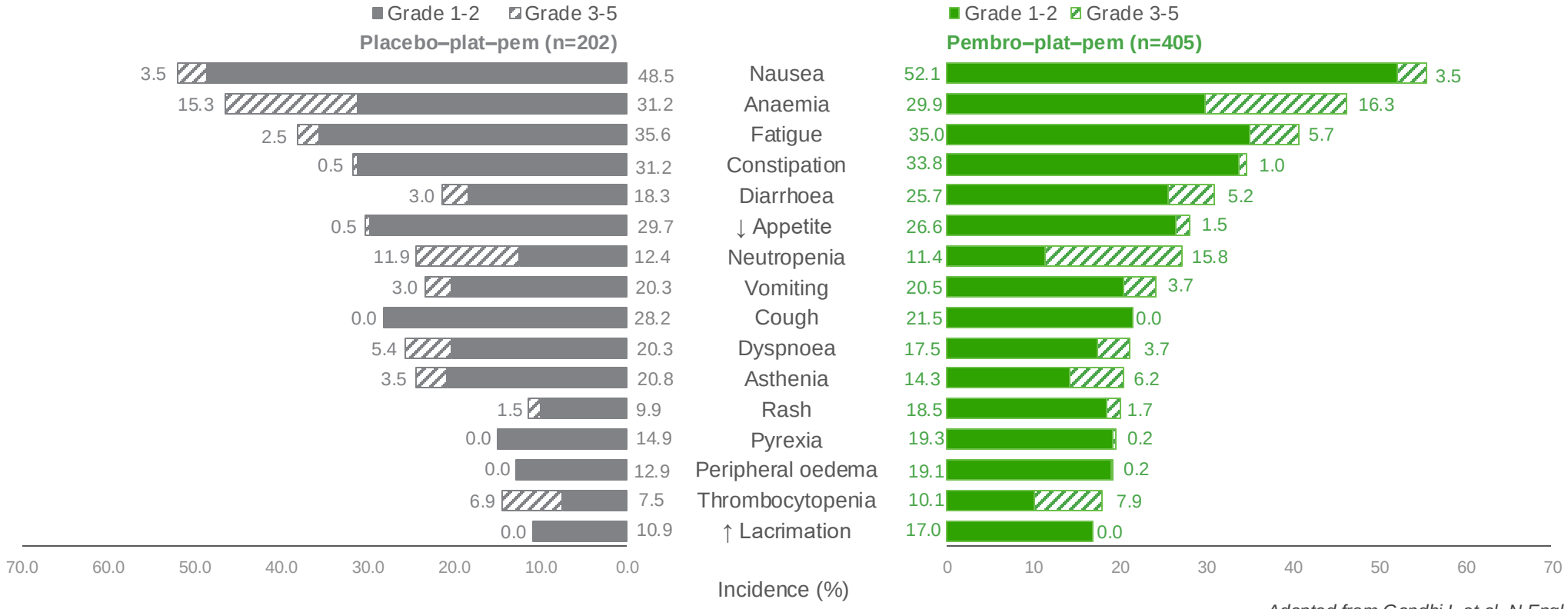
KEYNOTE-189: All-cause AEs occurring in ≥15% of patients in the as-treated population (original analysis)[1,a,b]

Median follow-up: 10.5 months



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

62

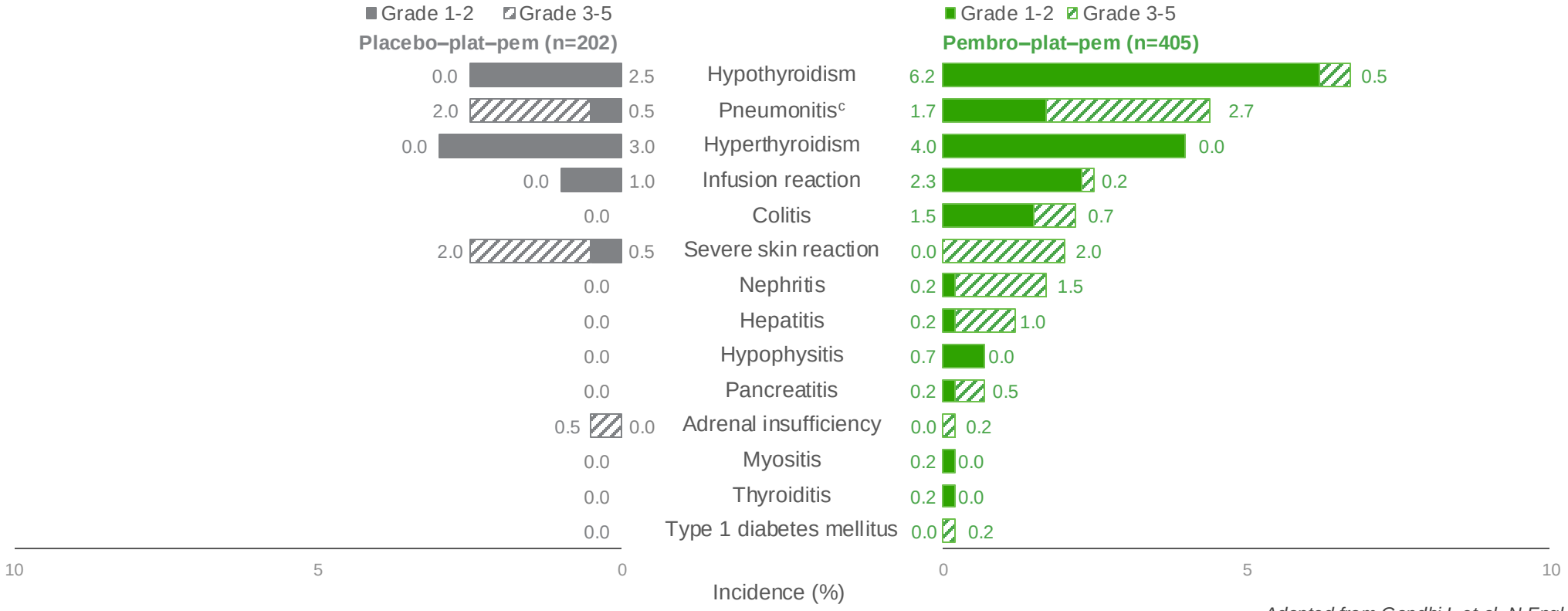
Data cut-off date: 8 November 2017.
[a]AEs that occurred during crossover from the placebo-combination group to pembrolizumab monotherapy are excluded. [b]AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

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

1

KEYNOTE-189: Immune-mediated AEs in the as-treated population (original analysis)[1,a,b]

Median follow-up: 10.5 months



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

63

Data 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.

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

1

KEYNOTE-407: KEYTRUDA

(pembrolizumab) plus carboplatin-paclitaxel/nab-paclitaxel for the first-line treatment of metastatic, squamous NSCLC[1]

1. Paz-Ares L *et al. N Engl J Med* 2018;379:2040–2051 (and supplementary appendix).

KEYNOTE-407: Study design[1–3]

Randomised, double-blind, Phase 3 trial

Key eligibility criteria

- Untreated stage IV NSCLC with squamous histology
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic CNS metastases
- No history of non-infectious pneumonitis requiring use of glucocorticoids, no active autoimmune disease and no systemic immunosuppressive treatment

R
1:1
(N=559)

n=278 → Pembrolizumab 200 mg Q3W + carboplatin AUC 6 mg/ml/min Q3W + paclitaxel 200 mg/m^2 Q3W OR nab-paclitaxel 100 mg/m^2 Q1W for 4 cycles Q3W → Pembrolizumab 200 mg Q3W (up to 31 cycles)

n=281 → Placebo (normal saline) Q3W + carboplatin AUC 6 mg/ml/min Q3W + paclitaxel 200 mg/m^2 Q3W OR nab-paclitaxel 100 mg/m^2 Q1W for 4 cycles Q3W → Placebo (normal saline) Q3W (up to 31 cycles)

PD[c]

Optional crossover:[c] Pembrolizumab 200 mg Q3W (up to 35 cycles)

Stratification factors

- PD-L1 expression (TPS[a] <1% vs. ≥1%)
- Choice of taxane (paclitaxel vs. nab-paclitaxel)
- Geographic region (East Asia vs. rest of World)

Endpoints

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

Adapted from Paz-Ares L et al. N Engl J Med 2018; Paz-Ares L et al. ASCO 2018; Robinson AG et al. ELCC 2021.

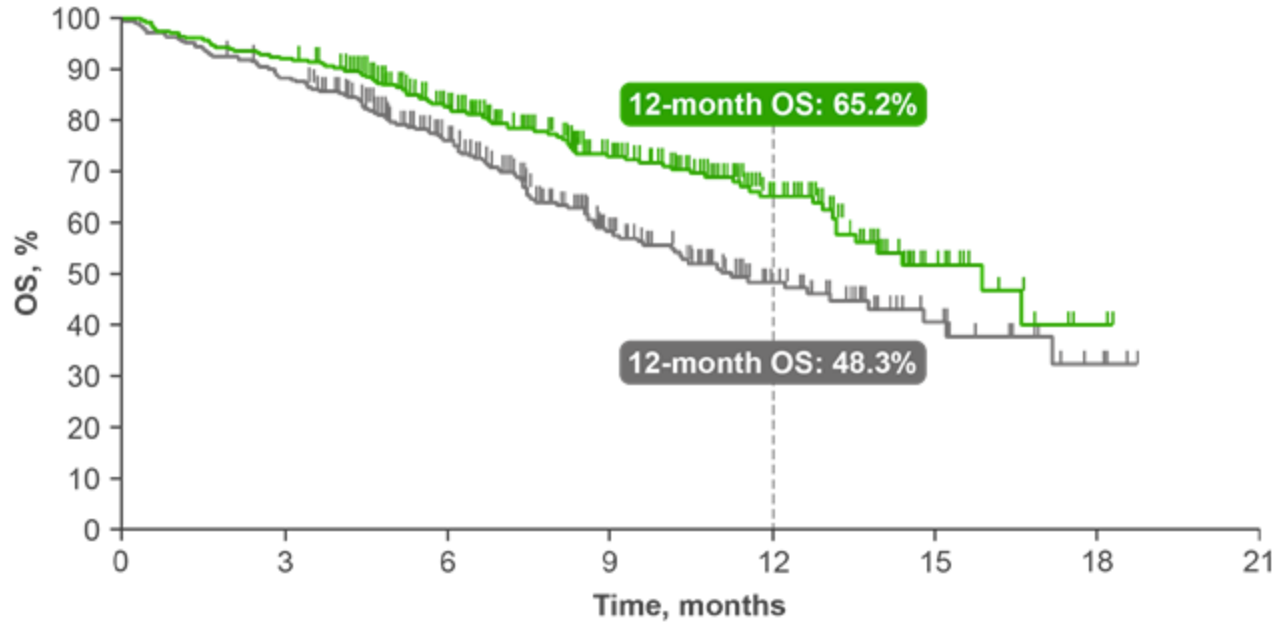
[a]Percentage of tumour cells with membrane PD-L1 staining, as assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Assessed by blinded, independent central review per RECIST v1.1. [c]Patients in the placebo arm could cross over to pembrolizumab 200mg Q3W during the induction or maintenance phase. To be eligible for crossover, PD must have been verified by blinded, independent, central radiological review and all safety criteria had to have been met.

1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051 (and protocol); 2. Paz-Ares L *et al.* Presented at American Society of Clinical Oncology (ASCO) Annual Meeting 2018, 1–5 June, 2018, Chicago, USA;
3. Robinson AG *et al.* Presented at the European Lung Cancer Virtual Congress (ELCC) 2021, 25–27 March 2021.

KEYNOTE-407: OS in the ITT population (original analysis)[1,2,a,b]

Median follow-up: 7.8 months

Treatment arm	Events, %	Median, months (95% CI)	HR (95% CI)	p value
Pembrolizumab + carb-pac/nabpac	30.6	15.9 (13.2–NE)	0.64 (0.49–0.85)	<0.001
Placebo + carb-pac/nabpac	42.7	11.3 (9.5–14.8)	—	—



No. at risk								
Pembrolizumab + carb-pac/nabpac	278	256	188	124	62	17	2	0
Placebo + carb-pac/nabpac	281	246	175	93	45	16	4	0

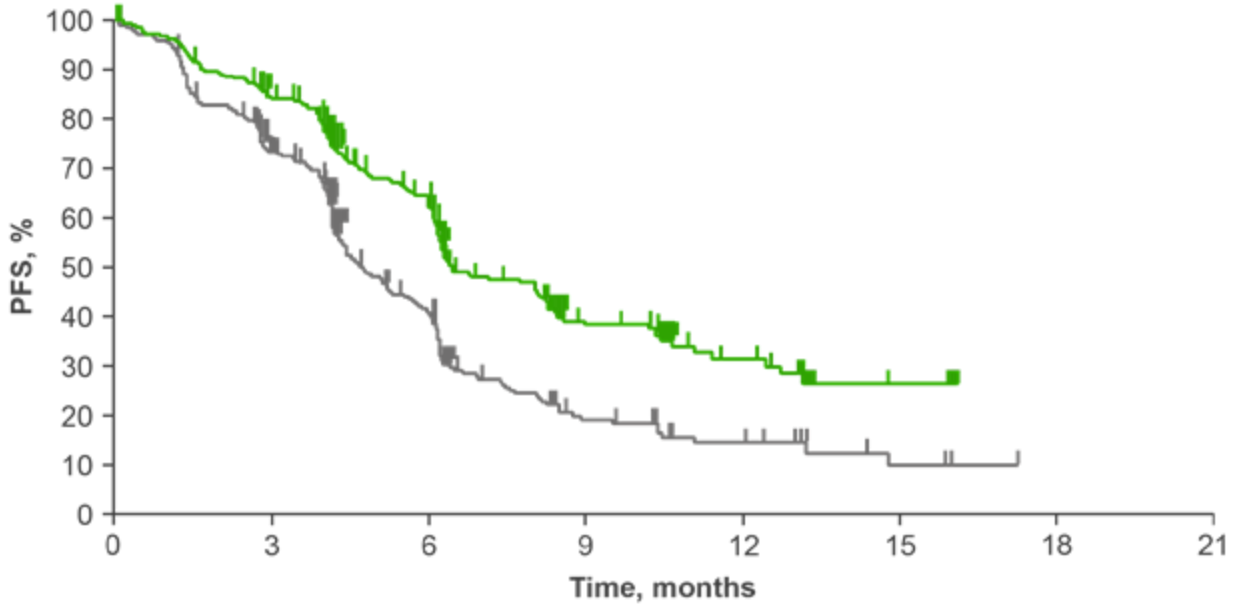
Adapted from Paz-Ares L et al. N Engl J Med 2018; Paz-Ares L et al. ASCO 2018.

Data cut-off date: 3 April 2018.
[a]OS and PFS were both primary endpoints. [b]Kaplan–Meier estimate.
1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051; 2. Paz-Ares L *et al.* Presented at American Society of Clinical Oncology (ASCO) Annual Meeting 2018, 1–5 June, 2018, Chicago, USA.

KEYNOTE-407: PFS in the ITT population (original analysis)[1,2,a–c]

Median follow-up: 7.8 months

Treatment arm	Events, %	Median, months (95% CI)	HR (95% CI)	p value
Pembrolizumab + carb-pac/nabpac	54.7	6.4 (6.2–8.3)	0.56 (0.45–0.70)	<0.001
Placebo + carb-pac/nabpac	70.1	4.8 (4.3–5.7)	—	—



No. at risk								
Pembrolizumab + carb-pac/nabpac	278	223	142	57	23	5	0	0
Placebo + carb-pac/nabpac	281	190	90	26	12	4	0	0

Adapted from Paz-Ares L et al. N Engl J Med 2018; Paz-Ares L et al. ASCO 2018.

Data cut-off date: 3 April 2018.
[a]OS and PFS were both primary endpoints. [b]Kaplan–Meier estimate. [c]Assessed using RECIST v1.1 by blinded, independent, central radiological review.
1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051; 2. Paz-Ares L *et al.* Presented at American Society of Clinical Oncology (ASCO) Annual Meeting 2018, 1–5 June, 2018, Chicago, USA.

KEYNOTE-407: Summary of AEs in the as-treated population (original analysis)[1,a]

Median follow-up: 7.8 months

n (%)	Pembrolizumab + carb-pac/nabpac (n=278)	Placebo + carb-pac/nabpac (n=280)
All-cause AEs	273 (98.2)	274 (97.9)
Grade 3–5	194 (69.8)	191 (68.2)
Led to death	23 (8.3)	18 (6.4)
Treatment related	10 (3.6)	6 (2.1)
Led to discontinuation		
All treatment[b]	37 (13.3)	18 (6.4)
Any treatment[c]	65 (23.4)	33 (11.8)
Immune-mediated AEs and infusion reactions	80 (28.8)	24 (8.6)
Grade 3–5	30 (10.8)	9 (3.2)
Led to death[d]	1 (0.4)	1 (0.4)

Adapted from Paz-Ares L et al. N Engl J Med 2018.

Data cut-off date: 3 April 2018.
[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]Includes 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. [c]Patients could have discontinued one, two, or all agents for a given adverse event. [d]Both deaths were due to pneumonitis.

1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051.

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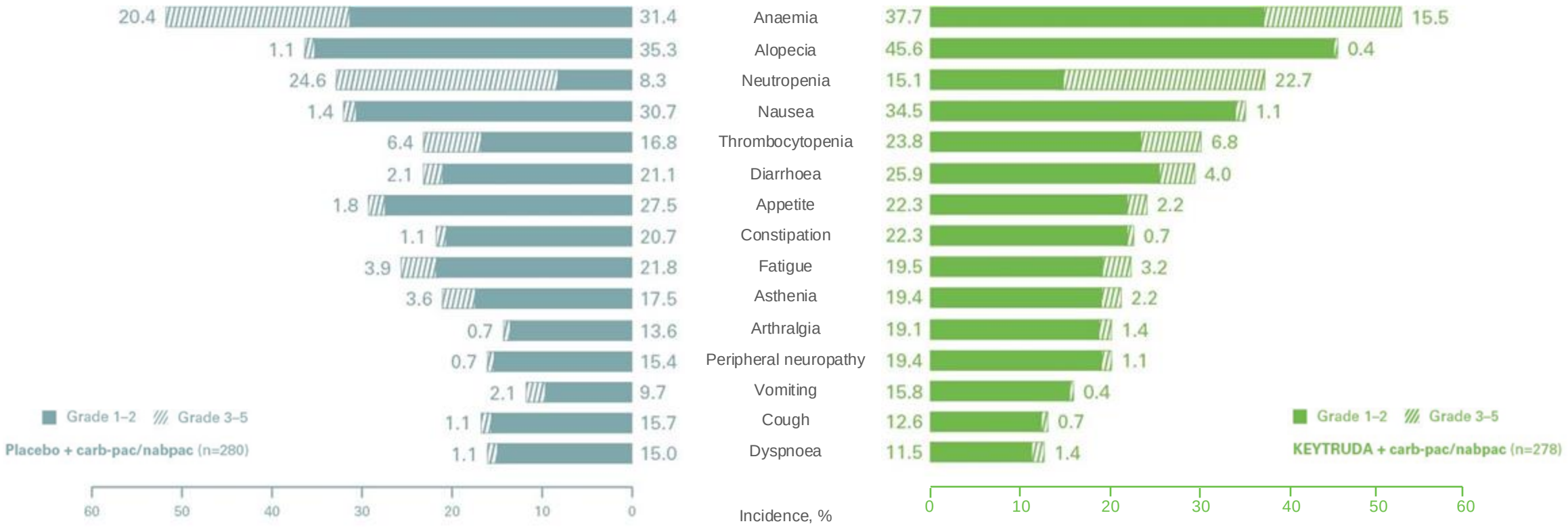
KEYNOTE-407: All-cause AEs occurring in ≥15% of patients in the as-treated population (original analysis)[1,a,b]

Median follow-up: 7.8 months



Adapted from Paz-Ares L et al. N Engl J Med 2018.

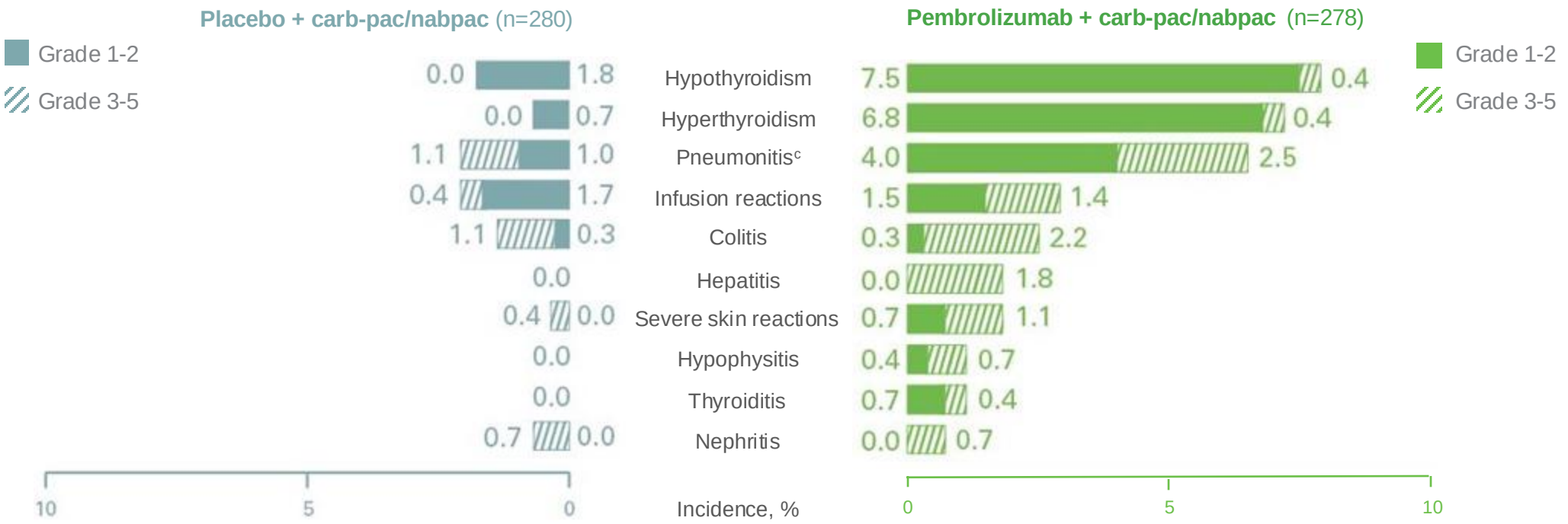
Data cut-off date: 3 April 2018.
[a]AEs that occurred during crossover from the placebo + carb-pac/nabpac group to pembrolizumab monotherapy were excluded. [b]AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051.

1

KEYNOTE-407: Immune-mediated AEs and infusion reactions in the as-treated population (original analysis)[1,a,b]

Median follow-up: 7.8 months



Adapted from Paz-Ares L et al. N Engl J Med 2018.

Data cut-off date: 3 April 2018.
[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 one patient in each trial arm who had Grade 5 pneumonitis.

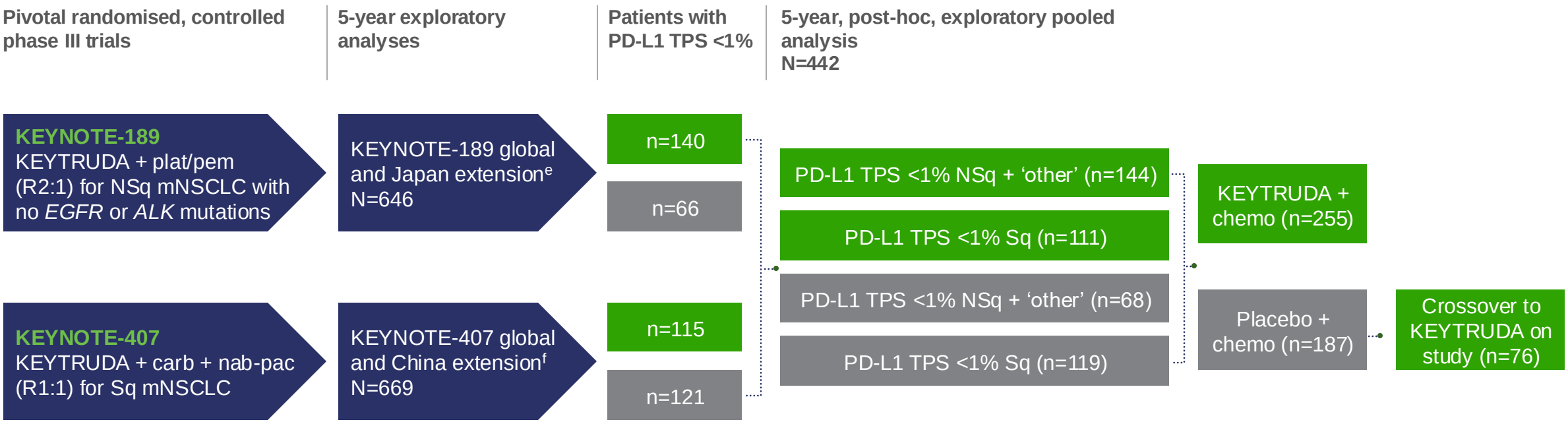
1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051.

Post-hoc exploratory pooled analysis (KEYNOTE-189, KEYNOTE-407)

5-year survival with KEYTRUDA® (pembrolizumab) plus chemotherapy for mNSCLC with PD-L1 TPS <1%[1]

1. Gadgeel S et al. 5-year survival of pembrolizumab plus chemotherapy for metastatic NSCLC with PD-L1 tumor proportion score <1%. Presented at the WCLC, 9-12 September 2023, Singapore. 2023

KEYNOTE-189 & KEYNOTE-407: Post-hoc exploratory pooled analysis – PD-L1 non-expresser subgroups (5-year update)[1–4,a–d]



Adapted from Gadgeel S, et al. J Thor Oncol 2024.

The exploratory pooled analysis included patient data from KEYNOTE-189 global (data cut-off March 8, 2022) and Japan extension (data cut-off February 7, 2023) and the KEYNOTE-407 global (data cut-off February 23, 2022) and China extension (data cut-off February 10, 2023).

[a]All 442 patients had PD-L1 TPS <1% [negative]. [b]PD-L1 expression was centrally assessed using PD-L1 IHC 22C3 pharmDX (Agilent Technologies, Carpinteria, CA). [c]Tumour response was assessed per RECIST-v1.1 by blinded independent central review (BICR). [d]Efficacy was evaluated in the intention-to-treat population and safety in the as-treated population. [e]Included 40 patients from the Japan extension.[5] [f]Included 125 patients from the China extension.[6]

1. Gadgeel S *et al. J Thor Oncol.* 2024. DOI:https://doi.org/10.1016/j.jtho.2024.04.011; 2. Garassino MC *et al. J Clin Oncol.* 2023;41(11):1992-8; 3. Novello S *et al. J Clin Oncol.* 2023;41(11):1999-2006; 4. Gadgeel S et al. 5-year survival of pembrolizumab plus chemotherapy for metastatic NSCLC with PD-L1 tumor proportion score <1%. In: WCLC, 9-12 September 2023, Singapore. 9-12 September 2023; 5. Horinouchi H *et al. Cancer Sci*. 2021; 112(8):3255–3265; 6. Cheng Y *et al. J Thor Oncol*. 2021;2(10):100225.

KEYNOTE-189 & KEYNOTE-407: Post-hoc exploratory pooled analysis – baseline disease characteristics (5-year update)[1,a]

Median follow-up: 60.7 months

	Pembro + chemo (n=255)	Placebo + chemo (n=187)	Completed 35 cycles of pembro (n=27)
Age, median (range), y	65 (31–87)	64 (43–82)	63 (31–74)
Men	181 (71.0)	148 (79.1)	24 (88.9)
ECOG PS 1	165 (64.7)	123 (65.8)	17 (63.0)
Squamous histology	111 (43.5)	119 (63.6)	18 (66.7)
Current or former smoker	225 (88.2)	175 (93.6)	26 (96.3)
Brain metastases	40 (15.7)	26 (13.9)	2 (7.4)
Liver metastases	35 (13.7)	40 (21.4)	3 (11.1)
Prior neoadjuvant therapy	4 (1.6)	4 (2.1)	0
Prior adjuvant therapy	14 (5.5)	8 (4.3)	1 (3.7)
Prior radiotherapy	47 (18.4)	34 (18.2)	1 (3.7)

Adapted from Gadgeel S, et al. J Thor Oncol 2024.

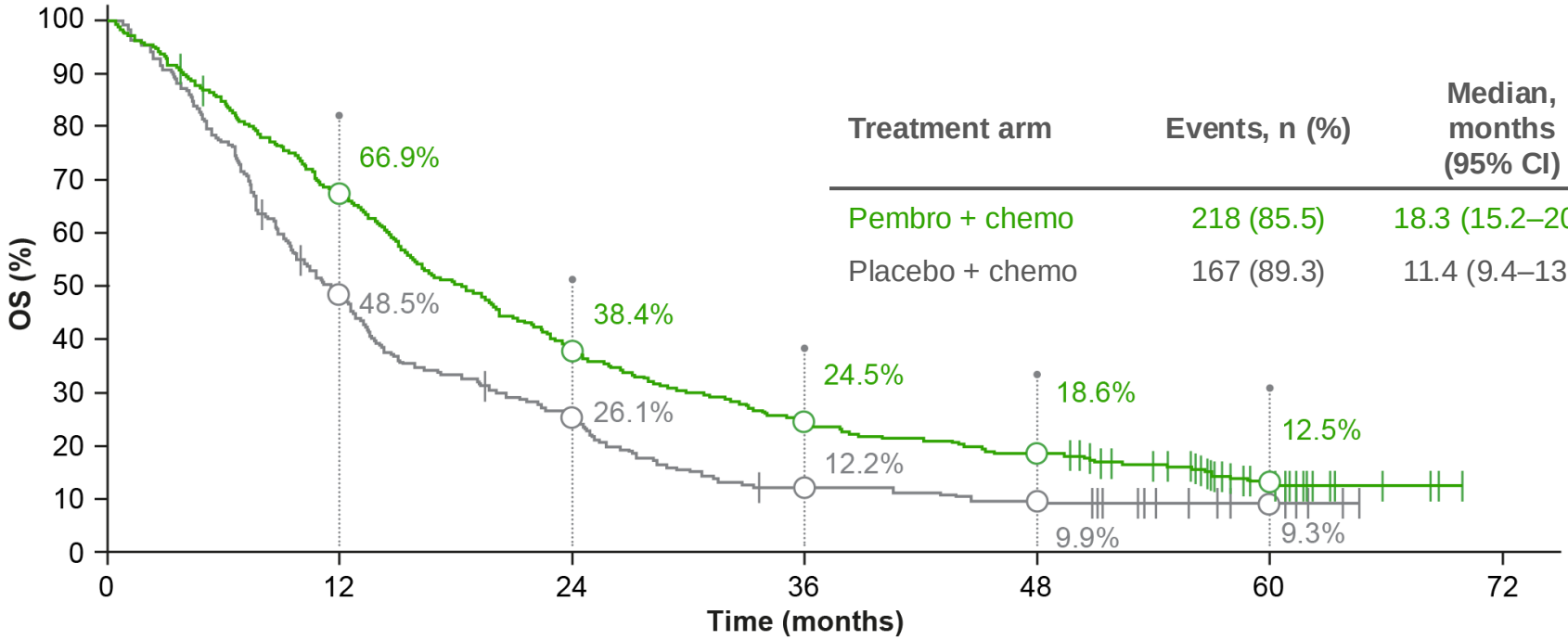
The exploratory pooled analysis included patient data from KEYNOTE-189 global (data cut-off March 8, 2022) and Japan extension (data cut-off February 7, 2023) and the KEYNOTE-407 global (data cut-off February 23, 2022) and China extension (data cut-off February 10, 2023).

[a]Vaules are n(%) unless noted otherwise.

1. Gadgeel S *et al. J Thor Oncol.* 2024. DOI:https://doi.org/10.1016/j.jtho.2024.04.011.

KEYNOTE-189 & KEYNOTE-407: Post-hoc exploratory pooled analysis – OS for PD-L1 non-expresser patients (5-year update)[1,a]

Median follow-up: 60.7 months. No statistical conclusions can be drawn from this exploratory analysis



Treatment arm	Events, n (%)	Median, months (95% CI)	HR (95% CI)
Pembro + chemo	218 (85.5)	18.3 (15.2–20.9)	0.64 (0.51–0.79)
Placebo + chemo	167 (89.3)	11.4 (9.4–13.2)	–

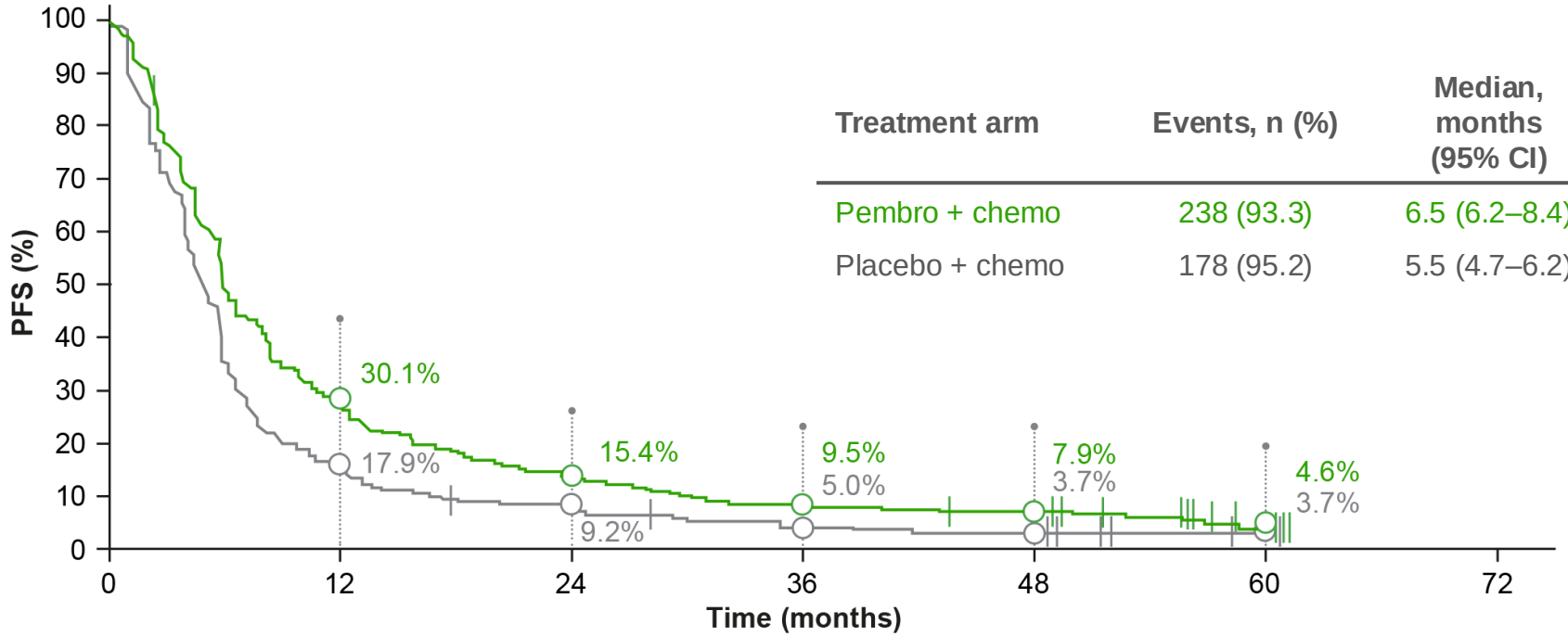
Adapted from Gadgeel S, et al. J Thor Oncol 2024.

The exploratory pooled analysis included patient data from KEYNOTE-189 global (data cut-off March 8, 2022) and Japan extension (data cut-off February 7, 2023) and the KEYNOTE-407 global (data cut-off February 23, 2022) and China extension (data cut-off February 10, 2023).
[a]Kaplan-Meier estimate.

1. Gadgeel S *et al. J Thor Oncol.* 2024. DOI:https://doi.org/10.1016/j.jtho.2024.04.011.

KEYNOTE-189 & KEYNOTE-407: Post-hoc exploratory pooled analysis – PFS for PD-L1 non-expresser patients (5-year update)[1,a,b]

Median follow-up: 60.7 months. No statistical conclusions can be drawn from this exploratory analysis



Treatment arm	Events, n (%)	Median, months (95% CI)	HR (95% CI)
Pembro + chemo	238 (93.3)	6.5 (6.2–8.4)	0.66 (0.54–0.81)
Placebo + chemo	178 (95.2)	5.5 (4.7–6.2)	–

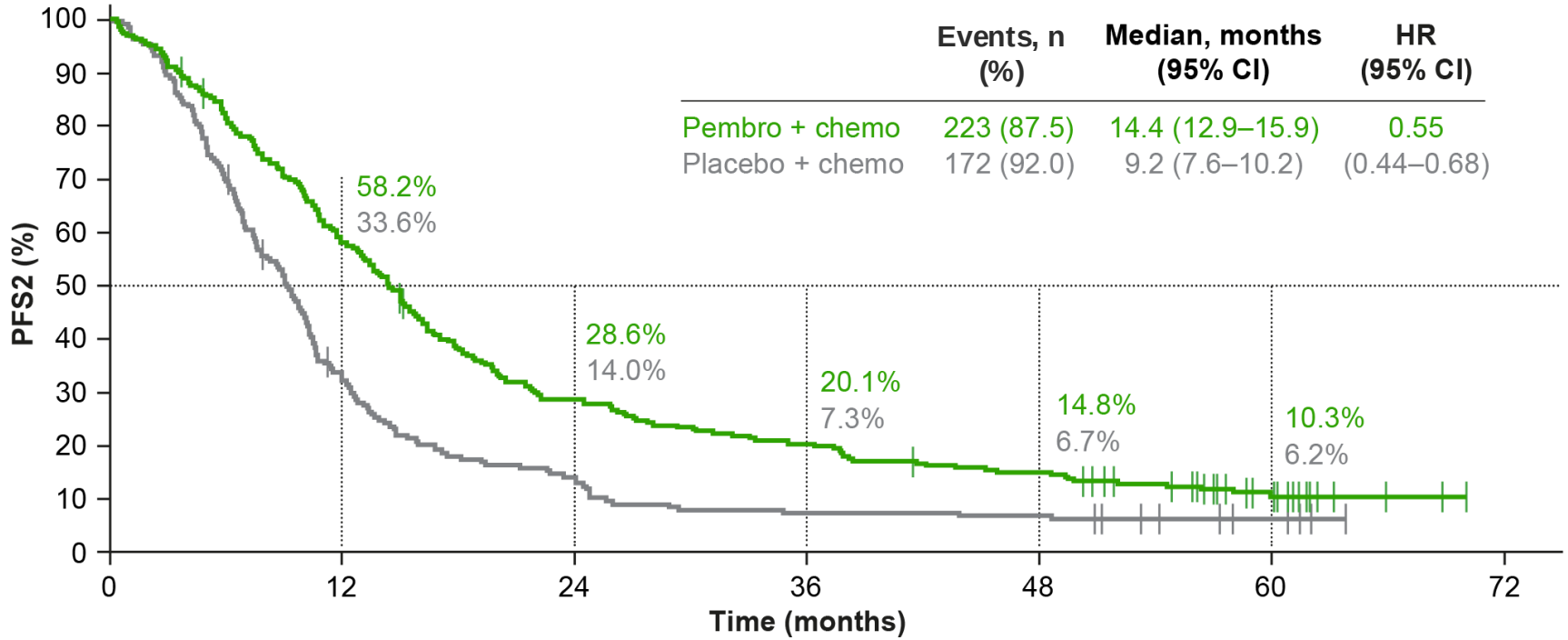
Adapted from Gadgeel S, et al. J Thor Oncol 2024.

The exploratory pooled analysis included patient data from KEYNOTE-189 global (data cut-off March 8, 2022) and Japan extension (data cut-off February 7, 2023) and the KEYNOTE-407 global (data cut-off February 23, 2022) and China extension (data cut-off February 10, 2023).
[a]Assessed using RECIST-v1.1 by blinded independent central review. [b]Kaplan-Meier estimate.

1. Gadgeel S *et al. J Thor Oncol.* 2024. DOI:https://doi.org/10.1016/j.jtho.2024.04.011.

KEYNOTE-189 & KEYNOTE-407: Post-hoc exploratory pooled analysis – PFS2 for PD-L1 non-expresser patients (5-year update)[1,a-c]

Median follow-up: 60.7 months. No statistical conclusions can be drawn from this exploratory analysis



	Events, n (%)	Median, months (95% CI)	HR (95% CI)
Pembro + chemo	223 (87.5)	14.4 (12.9–15.9)	0.55
Placebo + chemo	172 (92.0)	9.2 (7.6–10.2)	(0.44–0.68)

No. at risk							
Pembro + chemo	255	147	71	50	36	14	0
Placebo + chemo	187	60	25	13	12	5	0

Adapted from Gadgeel S, et al. J Thor Oncol 2024.

The exploratory pooled analysis included patient data from KEYNOTE-189 global (data cut-off March 8, 2022) and Japan extension (data cut-off February 7, 2023) and the KEYNOTE-407 global (data cut-off February 23, 2022) and China extension (data cut-off February 10, 2023).

[a]Defined as the time from randomisation to second or subsequent tumour progression on next line of treatment or death. [b]Assessed using RECIST-v1.1 by investigator review. [c]Kaplan-Meier estimate.

1. Gadgeel S *et al. J Thor Oncol.* 2024. DOI:https://doi.org/10.1016/j.jtho.2024.04.011.

KEYNOTE-189 & KEYNOTE-407: Post-hoc exploratory pooled analysis – Antitumour activity and DOR for PD-L1 non-expresser patients (5-year update)[1,a]

Median follow-up: 60.7 months. No statistical conclusions can be drawn from this exploratory analysis

	Pembro + chemo (n=255)	Placebo + chemo (n=187)
ORR (95% CI), %	50.6 (44.3–56.9)	33.2 (26.5–40.4)
Best overall response, n (%)		
Complete response	4 (1.6)	5 (2.7)
Partial response	125 (49.0)	57 (30.5)
Stable disease[b]	88 (34.5)	79 (42.2)
Progressive disease	20 (7.8)	31 (16.6)
Not evaluable[c]	11 (4.3)	6 (3.2)
No assessment[d]	7 (2.7)	9 (4.8)
Median DOR (range), mo	7.6 (1.1+ to 59.4+)	5.5 (1.4+ to 55.8+)

Adapted from Gadgeel S, et al. WCLC 2024.

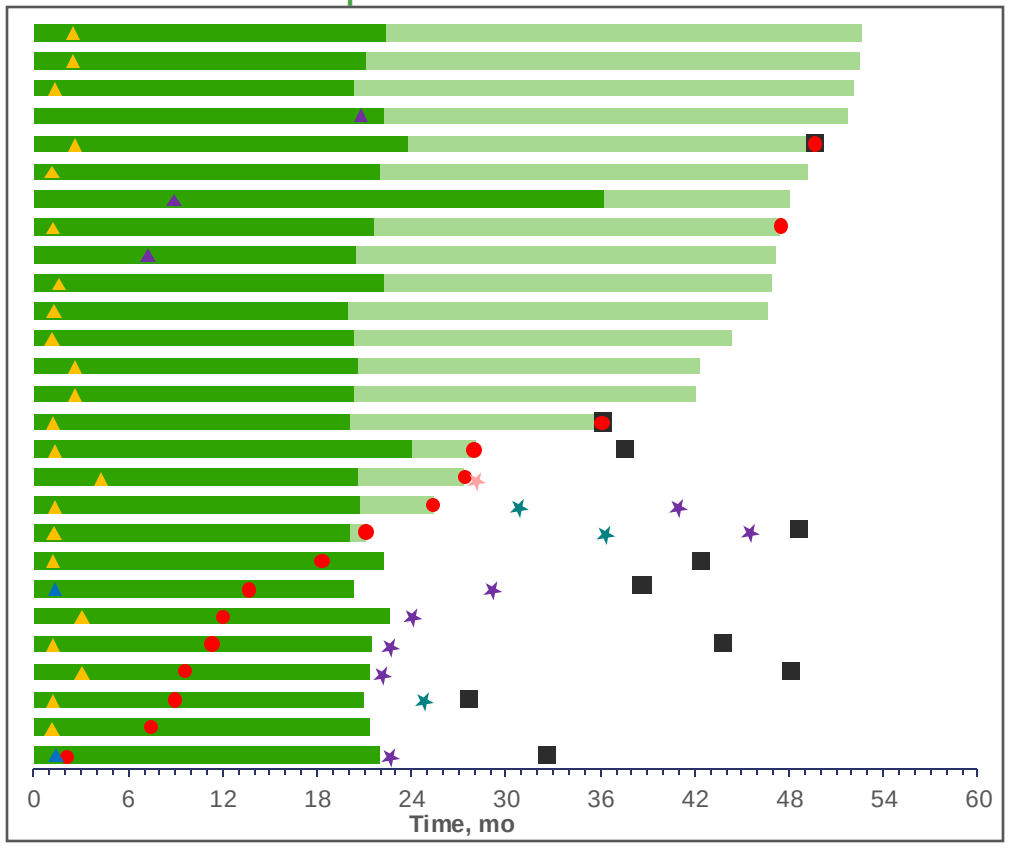
The exploratory pooled analysis included patient data from KEYNOTE-189 global (data cut-off March 8, 2022) and Japan extension (data cut-off February 7, 2023) and the KEYNOTE-407 global (data cut-off February 3, 2022) and China extension (data cut-off February 10, 2023).

[a]Assessed using RECIST-v1.1 by blinded independent central review. [b]Includes SD and non-CR/non-PD. [c]Postbaseline assessment(s) available but not evaluable or CR/PR/SD <6 weeks from randomisation. [d]No postbaseline assessment available for response evaluation.

1. Gadgeel S et al. 5-year survival of pembrolizumab plus chemotherapy for metastatic NSCLC with PD-L1 tumor proportion score <1%. In: WCLC, 9-12 September 2023, Singapore. 9-12 September 2023.

KEYNOTE-189 & KEYNOTE-407: Post-hoc exploratory pooled analysis – Outcomes in patients who completed 35 cycles (5-year update)[1,2]

Median follow-up: 60.7 months. No statistical conclusions can be drawn from this exploratory analysis



Outcome	Patients who completed 35 cycles[a] n=27
ORR[b] (95% CI), %	92.6 (75.7–99.1)
Best overall response, n (%)	
Complete response	3 (11.1)
Partial response	22 (81.5)
Stable disease[c]	2 (7.4)
Median DOR (range), mo	55.1 (7.4–59.3+)
3-year OS rate after completing 35 cycles, %	56.7
Alive without PD or subsequent therapy, n (%)	12 (44.4)

Adapted from Gadgeel S, et al. WCLC 2023.

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The exploratory pooled analysis included patient data from KEYNOTE-189 global (data cut-off March 8, 2022) and Japan extension (data cut-off February 7, 2023) and the KEYNOTE-407 global (data cut-off February 23, 2022) and China extension (data cut-off February 10, 2023).

[a]Patients with PD-L1 TPS <1%. [b]Response assessed per RECIST v1.1 per blinded independent central review. [c]Includes SD and non-CR/non-PD.

1. Gadgeel S *et al. J Thor Oncol.* 2024. DOI:https://doi.org/10.1016/j.jtho.2024.04.011; 2. Gadgeel S et al. 5-year survival of pembrolizumab plus chemotherapy for metastatic NSCLC with PD-L1 tumor proportion score <1%. In: WCLC, 9-12 September 2023, Singapore. 9-12 September 2023.

KEYNOTE-189 & KEYNOTE-407: Post-hoc exploratory pooled analysis – summary of safety data (5-year update)[1]

Median follow-up: 60.7 months

AEs, n (%)	Pembro + chemo (n=254)	Placebo + chemo n=186
Treatment-related AEs	245 (96.5)	175 (94.1)
Grade 3-5	150 (59.1)	114 (61.3)
Led to discontinuation	72 (28.3)	17 (9.1)
Led to death[a]	14 (5.5)	1 (0.5)
Immune-mediated AEs and infusion reactions	78 (30.7)	20 (10.8)
Grade 3-5	32 (12.6)	6 (3.2)
Led to death	2 (0.8)	0

Adapted from Gadgeel S, et al. J Thor Oncol 2024.

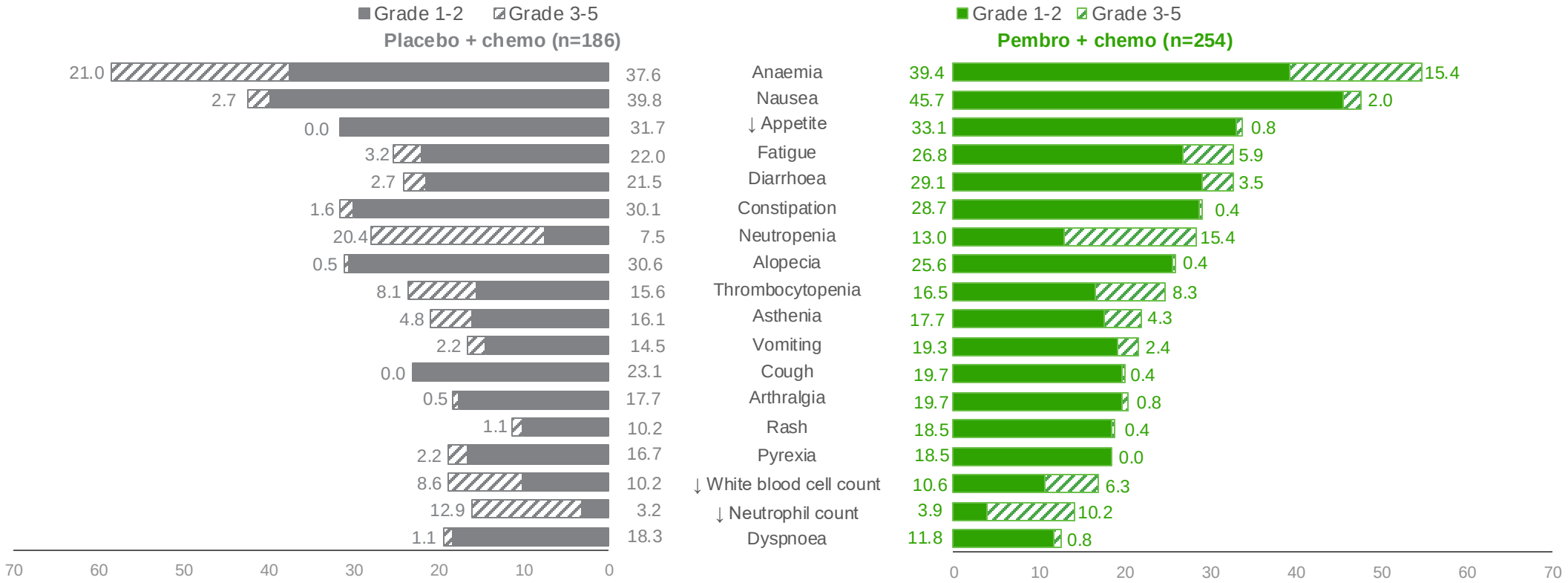
The exploratory pooled analysis included patient data from KEYNOTE-189 global (data cut-off March 8, 2022) and Japan extension (data cut-off February 7, 2023) and the KEYNOTE-407 global (data cut-off February 23, 2022) and China extension (data cut-off February 10, 2023).

[a]Treatment-related AEs that led to death were: death, pneumonia, and pneumonitis (each n=2); acute kidney injury, cardiac arrest, cardiac failure, encephalopathy, hepatic failure, neutropenic sepsis, pulmonary hemorrhage, respiratory failure, and septic shock (each n ¼ 1) in the pembrolizumab plus chemotherapy group; and septic shock (n=1) in the placebo plus chemotherapy group

1. Gadgeel S *et al. J Thor Oncol.* 2024. DOI:https://doi.org/10.1016/j.jtho.2024.04.011.

KEYNOTE-189 & KEYNOTE-407: Post-hoc exploratory pooled analysis – AEs occurring in ≥15% of patients in either treatment group (5-year update)[1,a]

Median follow-up: 60.7 months



Adapted from Gadgeel S, et al. J Thor Oncol 2024.

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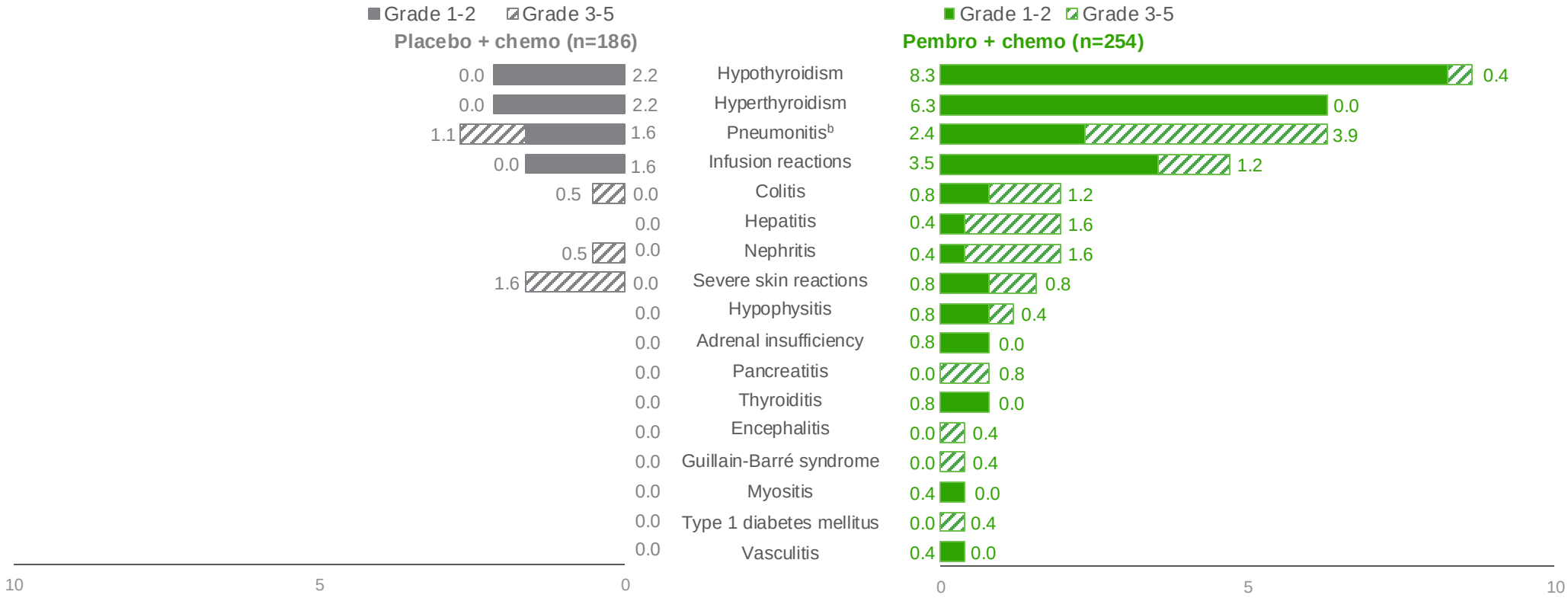
The exploratory pooled analysis included patient data from KEYNOTE-189 global (data cut-off March 8, 2022) and Japan extension (data cut-off February 7, 2023) and the KEYNOTE-407 global (data cut-off February 23, 2022) and China extension (data cut-off February 10, 2023).

[a]**Treatment-related AEs that led to death were: death, pneumonia, and pneumonitis (each n ¼ 2); acute kidney injury, cardiac arrest, cardiac failure, encephalopathy, hepatic failure, neutropenic sepsis, pulmonary haemorrhage, respiratory failure, and septic shock (each n ¼ 1) in the pembrolizumab plus chemotherapy group; and septic shock (n ¼ 1) in the placebo plus chemotherapy group**

1. Gadgeel S *et al. J Thor Oncol.* 2024. DOI:https://doi.org/10.1016/j.jtho.2024.04.011.

KEYNOTE-189 & KEYNOTE-407: Post-hoc exploratory pooled analysis – ImAEs and infusion reactions (5-year update)[1,a]

Median follow-up: 60.7 months



Adapted from Gadgeel S, et al. J Thor Oncol 2024.

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The exploratory pooled analysis included patient data from KEYNOTE-189 global (data cut-off March 8, 2022) and Japan extension (data cut-off February 7, 2023) and the KEYNOTE-407 global (data cut-off February 23, 2022) and China extension (data cut-off February 10, 2023).
[a]Immune-mediated adverse events and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator. [b]2 patients experienced grade 5 pneumonitis.

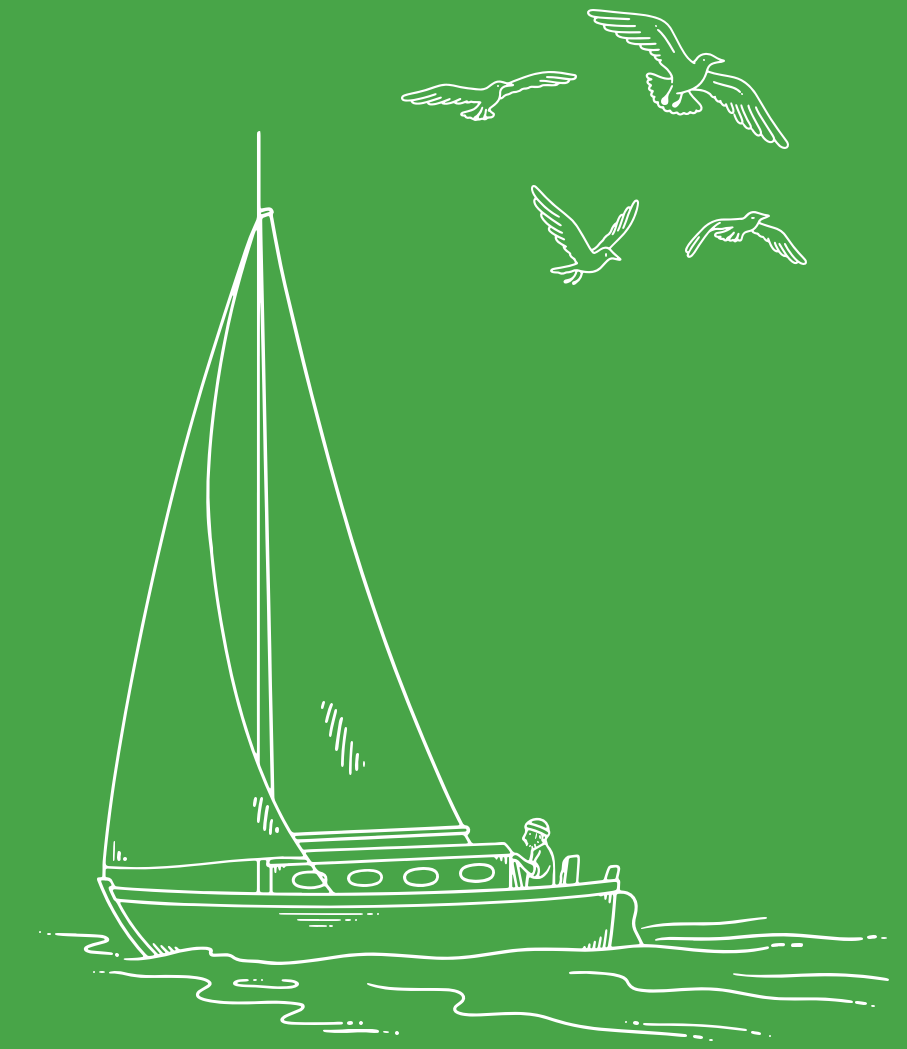
1. Gadgeel S *et al. J Thor Oncol.* 2024. DOI:https://doi.org/10.1016/j.jtho.2024.04.011.

KEYNOTE-189 & KEYNOTE-407: Post-hoc exploratory pooled analysis – summary of efficacy and safety data at 5-year follow-up[1]

- The 5-year pooled analysis data shows pembrolizumab plus chemotherapy demonstrated numerical improvements in OS, PFS and ORR compared with chemotherapy alone in this exploratory analysis of with patients with previously untreated mNSCLC PD-L1 TPS <1% without *EGFR/ALK* alterations enrolled in KEYNOTE-189 and KEYNOTE-407
- Pembrolizumab plus chemotherapy had a manageable toxicity profile
- Patients in this subgroup who completed 35 cycles (~2 years) of pembrolizumab experienced durable responses and 57% were alive 3 years after completion of 35 cycles (~5 years after randomisation)
- These results continue to support pembrolizumab plus chemotherapy as a standard-of-care first-line therapy for mNSCLC patients with PD-L1 TPS <1%

1. Gadgeel S *et al. J Thor Oncol.* 2024. DOI:https://doi.org/10.1016/j.jtho.2024.04.011.

Appendices



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]

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]

Some NSCLCs are cold tumours that lack activated tumour-specific T cells[2]

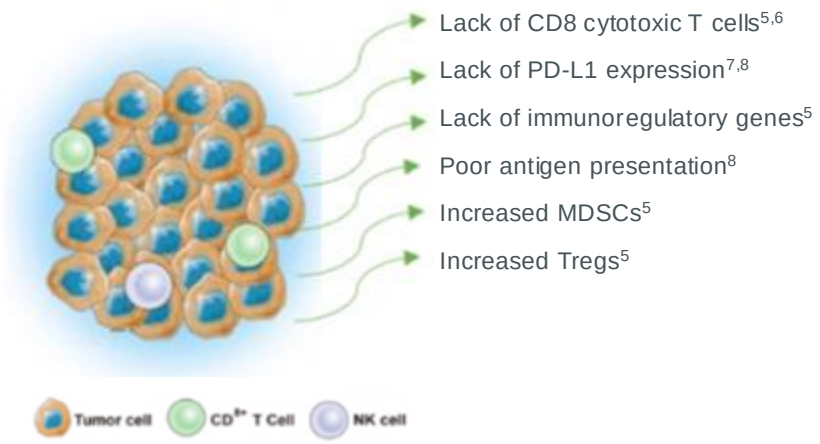
Absence of tumour-specific T cells is a mechanism of primary resistance to ICBs [2]

This is a hypothesis based on experimental models

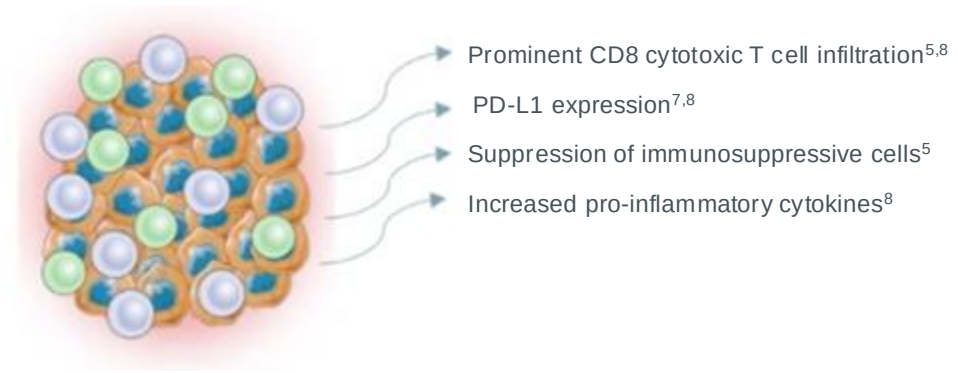
Effective combination therapy can turn cold tumours into hot tumours that are sensitive to ICBs[2]

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 tumour can enable increased expression of PD-L1 and sensitize the tumour to PD-1 blockade[3,4]

Cold tumours are characterised by decreased immunogenicity and an immunosuppressive TME[5]



Hot tumours are characterised by an inflammatory profile and an immunosuppressive TME[5,8]



Adapted from Ren X et al. Front Immunol 2022.

1. Kersten K *et al. Front Immunol*. 2015;6:516. 2. Wu M *et al. J Hematol Oncol*. 2022;15(1):24. 3. Liu YT *et al. Theranostics*. 2021;11(11):5365–5386. 4. Ledys F *et al. Cancers (Basel)*. 2021;13(23):5999. 5. Chen Q *et al. Nanomicro Lett*. 2021;13(1):92. 6. Holmen Olofsson G *et al. Int J Mol Sci*. 2020;21(11):3816. 7. Leonetti A *et al. Drug Resist Updat*. 2019;46:100644. 8. Ren X *et al. Front Immunol.* 2022;13:790113.

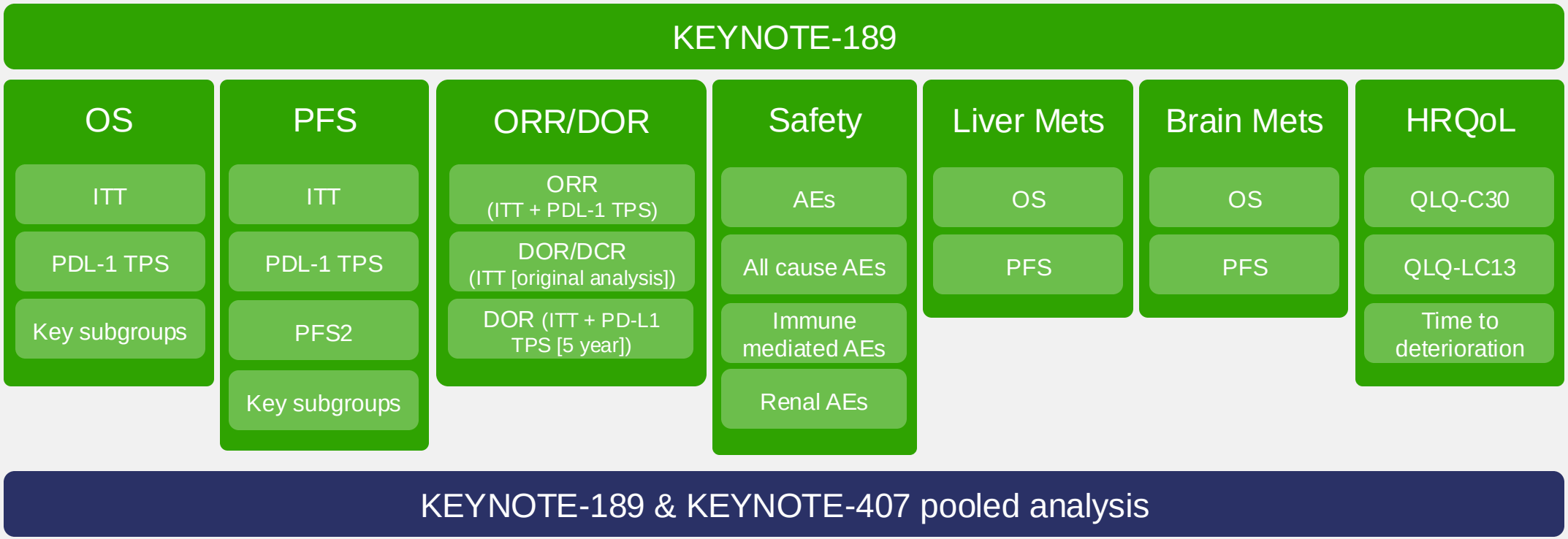
Abbreviations

Abbreviation	Definition
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
Carb–pac/nabpac	Carboplatin-paclitaxel/nab-paclitaxel
CD8	Cluster of differentiation 8
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CNS	Central nervous system
CR	Complete response
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
ESMO	European Society for Medical Oncology
ESMO-MCBS	ESMO's magnitude of clinical benefit scale
GHS	Global health status
Gy	Grey
HR	Hazard ratio
HRQoL	Health-related quality of life
IHC	Immunohistochemistry

Abbreviation	Definition
ITT	Intention-to-treat
LS	Least squares
MDSCs	Myeloid-derived suppressor cells
mg	Milligram(s)
mNSCLC	Metastatic non-small cell lung cancer
MHRA	Medicines and Healthcare Products Regulatory Agency
n	Number of patients
NE	Not evaluable
NR	Not reached
NSCLC	Non-small cell lung cancer
NSq	Non-squamous
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand-1
PFS	Progression-free survival
PFS2	Progression-free survival 2
Pembro–plat–pem	Pembrolizumab + platinum + pemetrexed
Placebo–plat–pem	Placebo + platinum + pemetrexed
PR	Partial response

Abbreviations

Abbreviation	Definition
PRO	Patient-reported outcome
PS	Performance status
Q1W	Every 1 week
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 Tumours version 1.1
RT	Radiotherapy
SD	Stable disease
SDev	Standard deviation
Sq	Squamous
TME	Tumour microenvironment
TPS	Tumour proportion score



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