MSD Oncology

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

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

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

Prescribing information can be found by clicking this link. If using a downloaded version of this material, please ensure that you are accessing the most recent version of the prescribing information.

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

GB-PDO-02376. Date of preparation: October 2022.

MSD

Merck Sharp & Dohme (UK) Limited
Registered Office: 120 Moorgate, London
EC2M 6UR, United Kingdom
Registered in England No. 233687

External websites and abbreviations

Links to external sites

- The links in this slide deck will redirect you to third-party websites. Please note that:
  - MSD does not review or control the content of any third-party website
  - MSD does not endorse and are not responsible for the accuracy, content, practices or standards of any third-party sources

Abbreviations

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

KEYTRUDA® (pembrolizumab) metastatic NSCLC indications

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

KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/2498/smpc. NI: https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4fdfab6767ccbe&type=smpc

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

KEYNOTE-189: Definition of analyses

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

1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Garassino MC *et al. Lancet Oncol*. 2020;21:387–397; 3. Gadgeel S *et al*. Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May–4 June, 2019, Chicago, USA; 4. Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

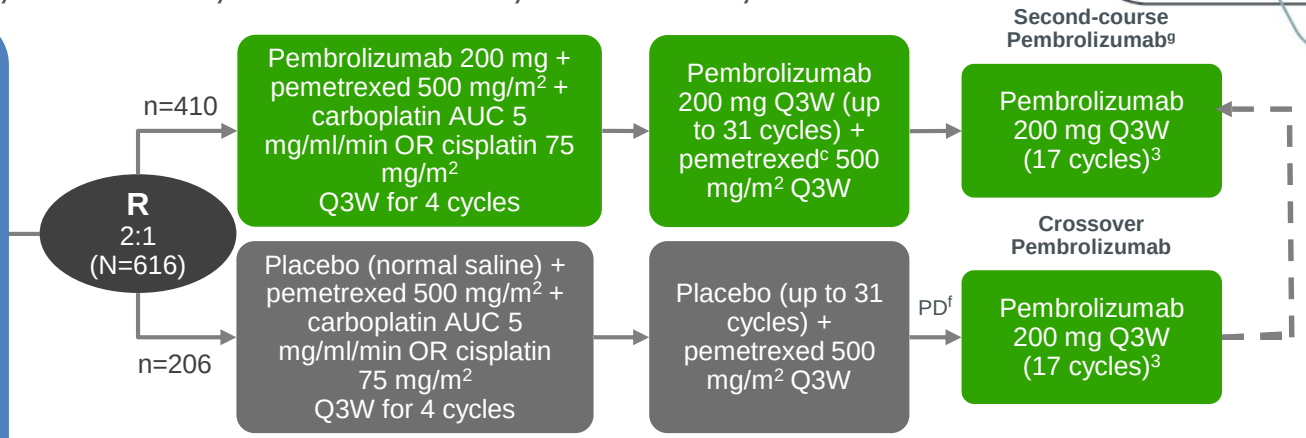
Gandhi L *et al*. *N Engl J Med* 2018;378:2078–2092 (and supplementary appendix).

KEYNOTE-189: Study design[1]

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

Key eligibility criteria

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



Stratification factors

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

Endpoints[c]

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

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

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

1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092 (and supplementary appendix); 2. Gandhi L *et al.* Presented at the 2018 American Association for Cancer Research (AACR) Annual Meeting, 14–18 April, 2018, Chicago, USA; 3. Gray JE *et al.* Presented virtually at the 2020 World Conference on Lung Cancer (WCLC). 28–31 January 2021.

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

- Planned enrolment: 570 patients
  - Actual enrolment: 616 patients
- Overall alpha for the study: strictly controlled at one-sided α=0.025
  - The study had 90% power to show an HR of 0.70 for PFS at one-sided α=0.0095 (based on 468 events) and an HR of 0.70 for OS at one-sided α=0.0155 (based on 416 deaths) for the comparison between the pembrolizumab combination and placebo combination groups
  - The protocol specified two interim analyses before the final analysis
- First interim analysis (reviewed by an external, independent data monitoring committee)
  - Planned to occur after enrolment was complete and ~370 PFS events had been observed[a]
  - Analysis cut-off date: 8 November 2017
  - Results published: 16 April 2018
  - Median follow up: 10.5 months (range: 0.2–20.4 months)
  - Observed number of events: 410 for PFS; 235 for OS
  - One-sided α levels:[b] 0.00559 for PFS; 0.00128 for OS

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

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

KEYNOTE-189: Statistical considerations (updated analyses)

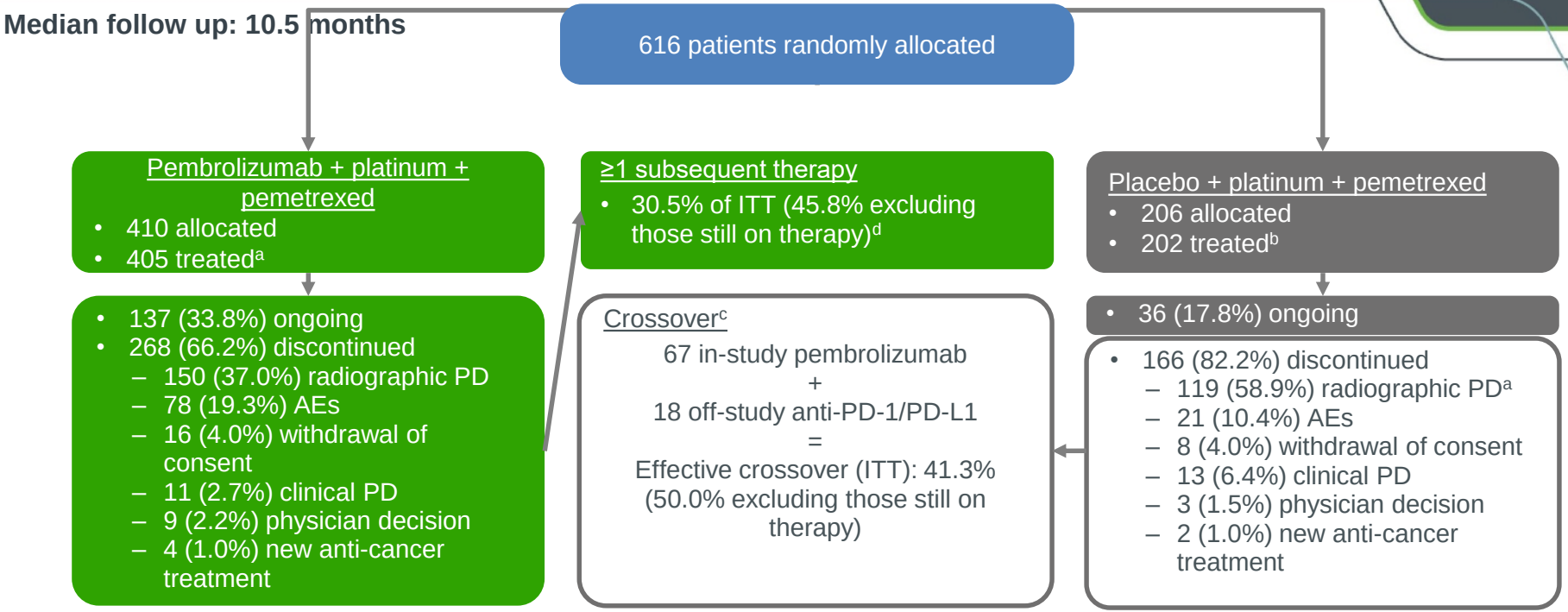
- Updated analysis[1]
  - Analysis cut-off date: 21 September 2018
  - Results presented: ASCO 2019
  - Median follow up (study):[a] 23.1 months (range: 18.6–30.9 months)
  - Median follow up (survival):[b] 18.7 months (range: 0.2–30.9 months)
  - This analysis was not subjected to further significance testing

- 5-year efficacy and safety outcomes update2
  - Analysis cut-off date: 8 March 2022
  - Results presented: EMSO 2022
  - Median follow up: 64.6 months (range: 60.1–72.4 months)
  - This analysis was not subject to further significance testing

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

1. Gadgeel S *et al.* Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May–4 June, 2019, Chicago, USA; 2. Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

KEYNOTE-189: Disposition of study treatment



Analysis cut-off date: 8 November 2017.

Adapted from: Gandhi L et al. AACR 2018.

[a]Two AEs, one clinical PD, one death and one protocol violation. [b]Two withdrawals of consent, one protocol violation and one physician decision. [c]An additional 13 patients received other subsequent therapy (6.3% of ITT [7.6% excluding those still on therapy]). [d]45.8%=125/273, where 273 is derived from the ITT population (410) minus the number of patients with ongoing treatment (137), and 125 is derived from subsequent treatment in 30.5% of the ITT population (410).

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

KEYNOTE-189: Key baseline characteristics

Median follow up: 10.5 months

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

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

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

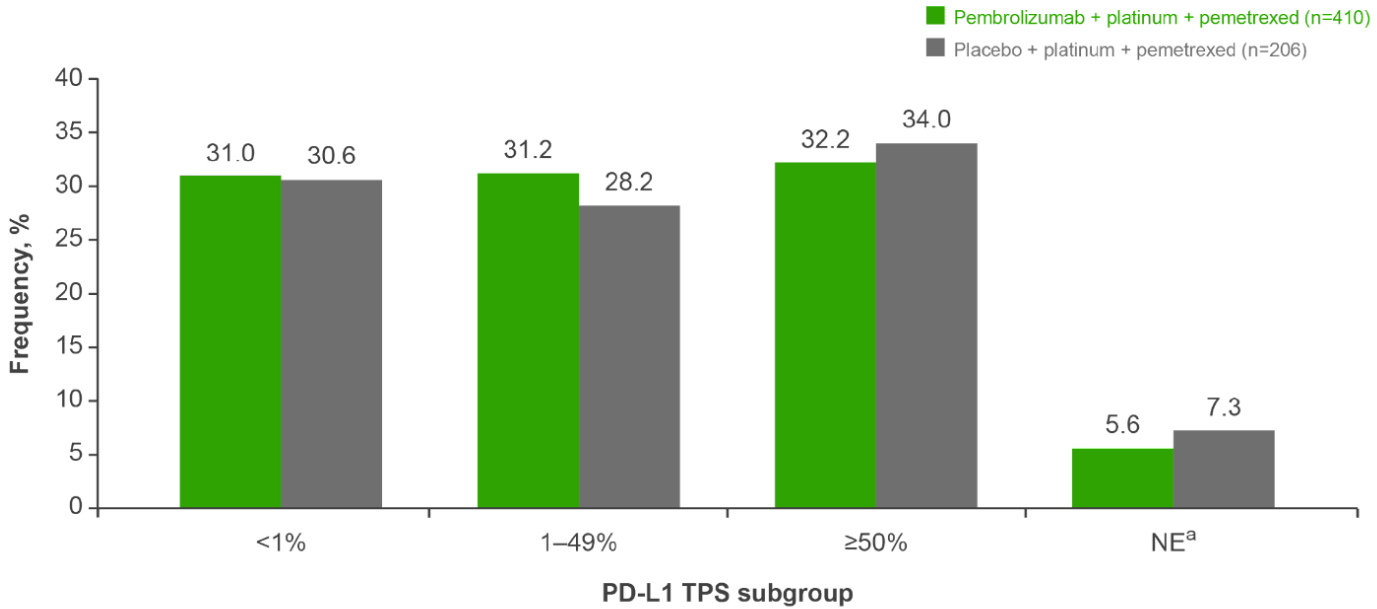
Analysis cut-off date: 8 November 2017.

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

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

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

Median follow up: 10.5 months



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

Analysis cut-off date: 8 November 2017.

[a]NE refers to specimens with an inadequate number of tumour cells or no tumour cells seen; these patients were included in the PD-L1 TPS <1% group for randomisation stratification but excluded from the analysis of efficacy by TPS.

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

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

- Primary outcomes with pembrolizumab + platinum + pemetrexed in the ITT population were as follows:
  - **Original analysis (median follow up: 10.5 months)[1]**
    - OS: 51% reduced risk of death vs. placebo + platinum + pemetrexed
      - HR: 0.49; 95% CI: 0.38–0.64; p<0.001
    - PFS: 48% reduced risk of progression or death vs. placebo + platinum + pemetrexed
      - HR: 0.52; 95% CI: 0.43–0.64; p<0.001
  - **Updated analysis (median follow up: 18.7 months)[2]**
    - OS: 44% reduced risk of death vs. placebo + platinum + pemetrexed
      - HR: 0.56; 95% CI: 0.45–0.70; p = not tested
    - PFS: 52% reduced risk of progression or death vs. placebo + platinum + pemetrexed
      - HR: 0.48; 95% CI: 0.40–0.58; p = not tested
  - **5-year update (median follow up: 64.6 months)[3]**
    - OS: 40% reduced risk of death vs. placebo + platinum + pemetrexed
      - HR: 0.60; 95% CI: 0.50–0.72; p = not tested
    - PFS: 50% reduced risk of progression vs. placebo + platinum + pemetrexed
      - HR: 0.50; 95% CI: 0.42–0.60; p = not tested

1

2

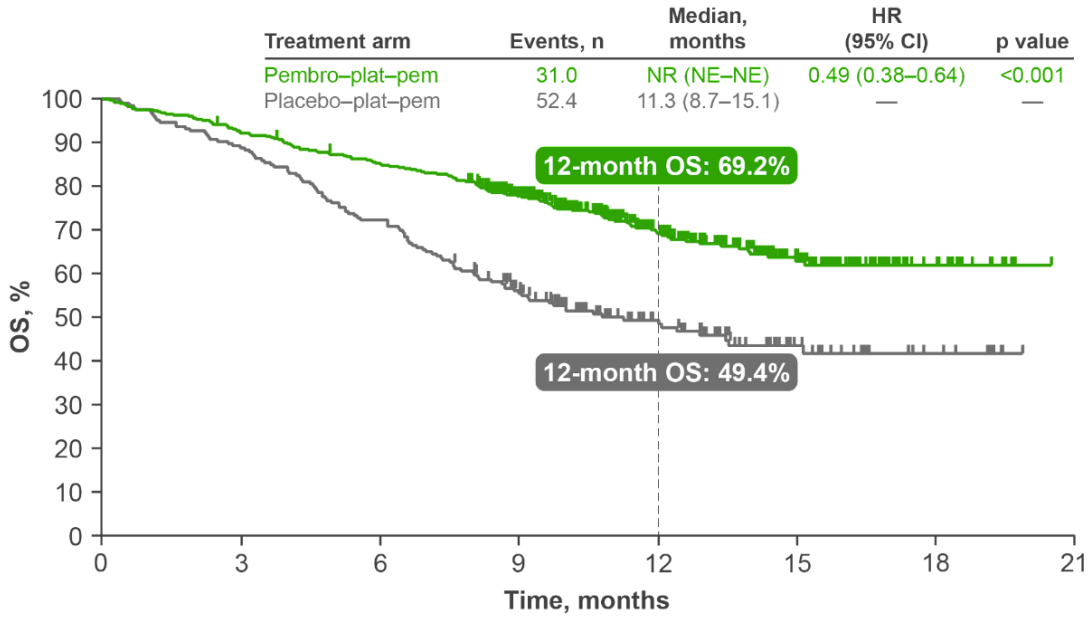
3

[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.* Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May – 4 June, 2019, Chicago, USA. 3. Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

Median follow up: 10.5 months



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

Analysis cut-off date: 8 November 2017.

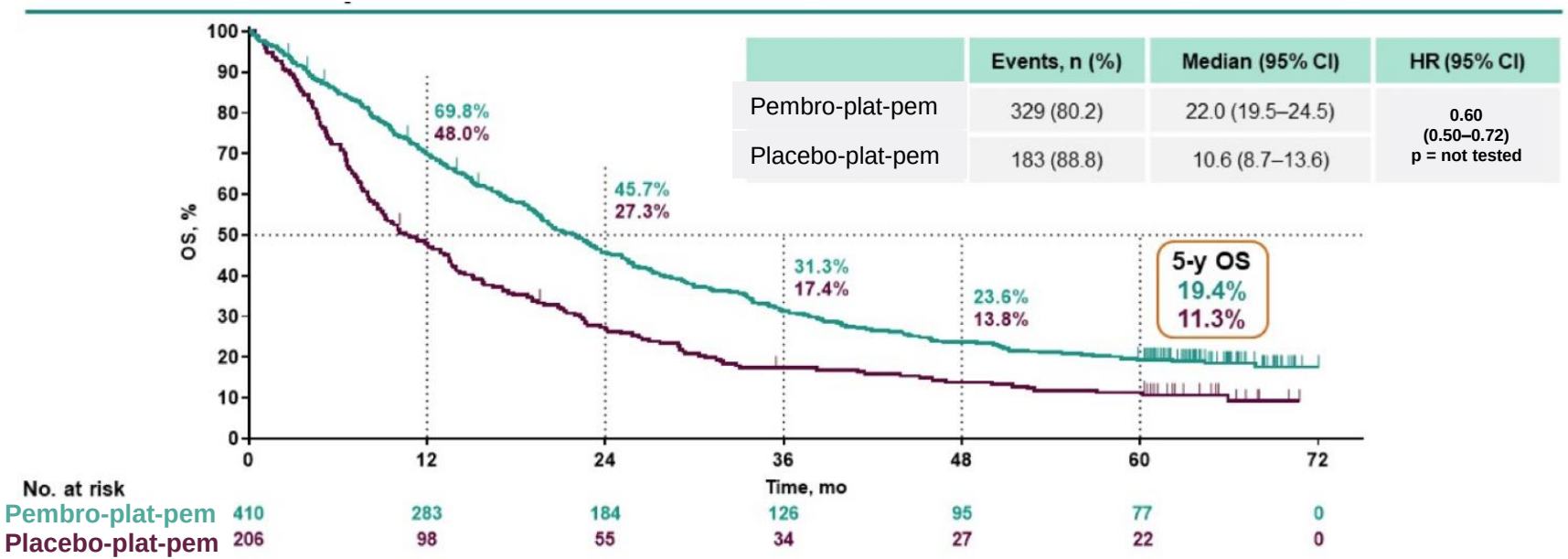
[a]OS and PFS were both primary endpoints.

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

KEYNOTE-189: OS in the ITT population in the 5-year update

(exploratory analysis, p not tested)[a]

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



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

Adapted from Garassino MC et al. ESMO 2022.

Analysis cut-off date: 8 March 2022. No statistical conclusions can be drawn from this analysis.

[a]OS and PFS were both primary endpoints.

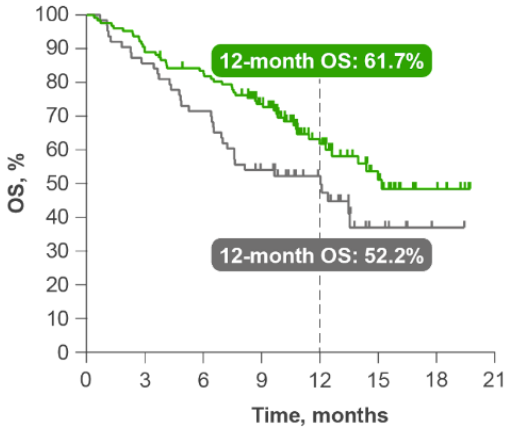
1. Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

Median follow up: 10.5 months

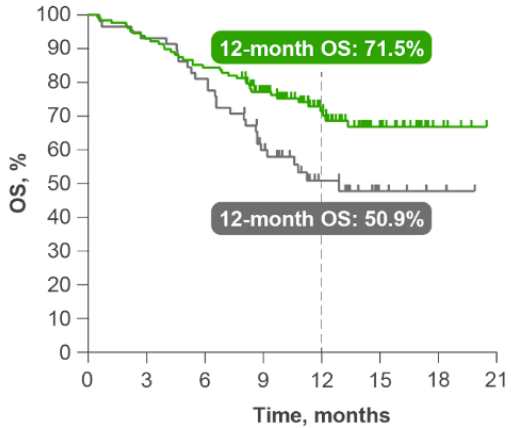
PD-L1 TPS <1%

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



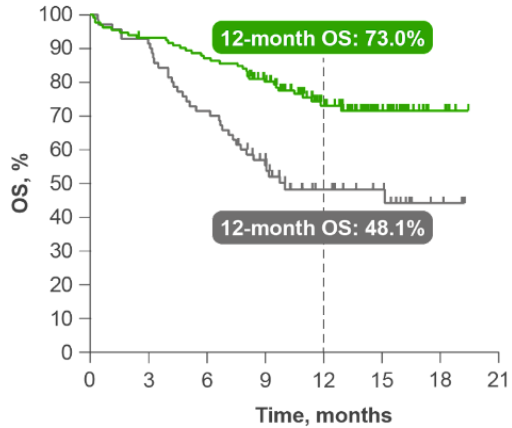
PD-L1 TPS 1–49%

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



PD-L1 TPS ≥50%

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



No. at risk

Pembro–plat–pem	127	113	104	79	42	20	6	0
Placebo–plat–pem	63	54	45	32	21	6	1	0

Pembro–plat–pem	128	119	108	84	52	21	5	0
Placebo–plat–pem	58	54	47	32	17	5	2	0

Pembro–plat–pem	132	122	114	96	56	25	6	0
Placebo–plat–pem	70	64	50	35	19	13	4	0

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

Analysis cut-off date: 8 November 2017.

[a]No statistical conclusions can be drawn from exploratory endpoints. [b]Nominal and one-sided.

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

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

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

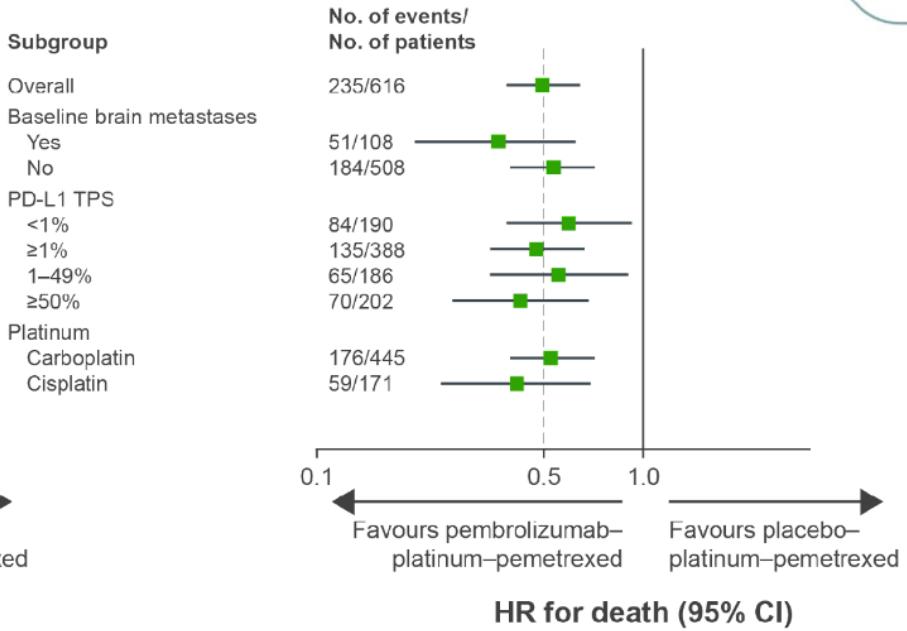
	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro-plat-pem (n = 132)	Placebo-plat-pem (n = 70)	Pembro-plat-pem (n = 128)	Placebo-plat-pem (n = 58)	Pembro-plat-pem (n = 127)	Placebo-plat-pem (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4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

Adapted from Garassino MC et al. ESMO 2022.

Analysis cut-off date: 8 March 2022.
[a]No statistical conclusions can be drawn from exploratory endpoints. [b]Kaplan-Meier estimate.
Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

Median follow up: 10.5 months



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

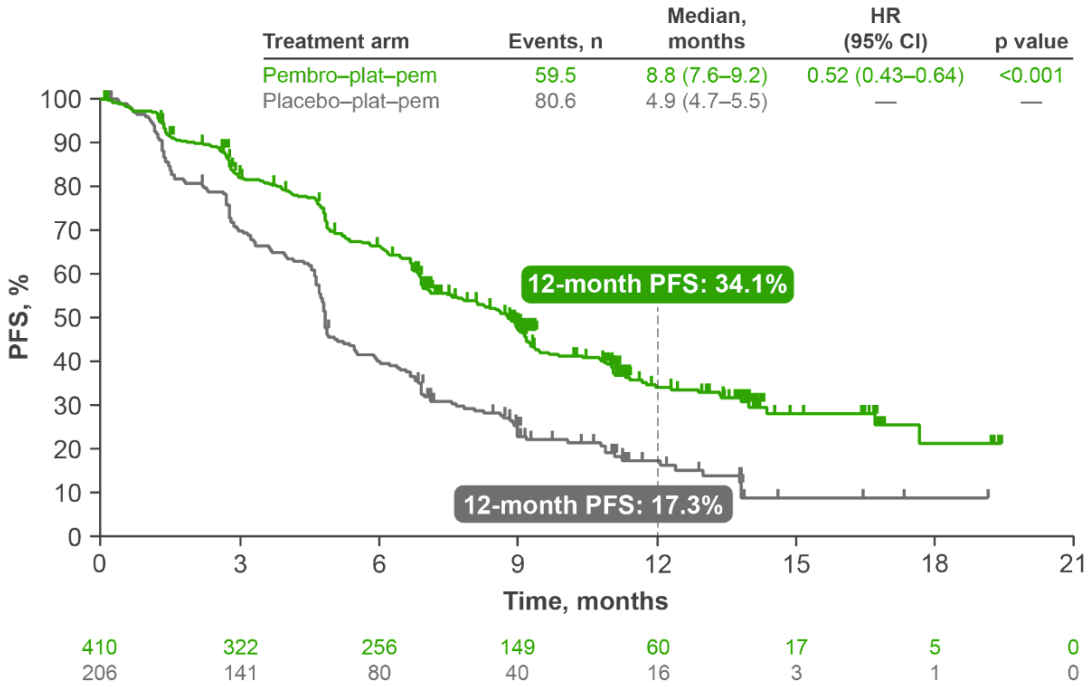
Analysis cut-off date: 8 November 2017.

[a]No statistical conclusions can be drawn from exploratory endpoints.

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

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

Median follow up: 10.5 months



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

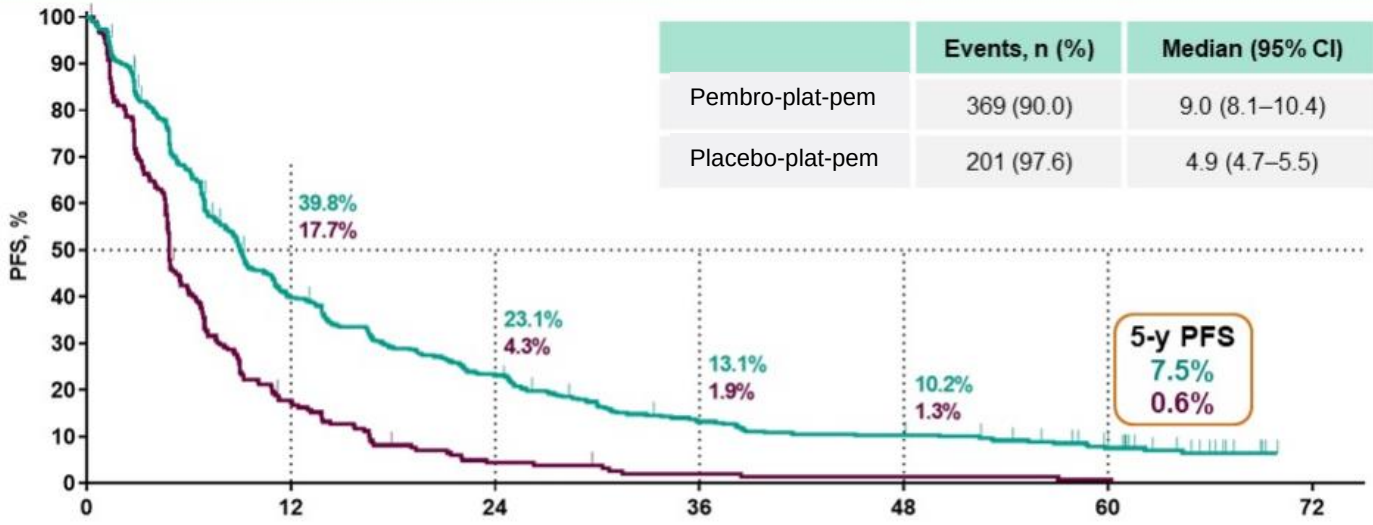
Analysis cut-off date: 8 November 2017.

[a]OS and PFS were both primary endpoints. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review.

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

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

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



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

Adapted from Garassino MC et al. ESMO 2022.

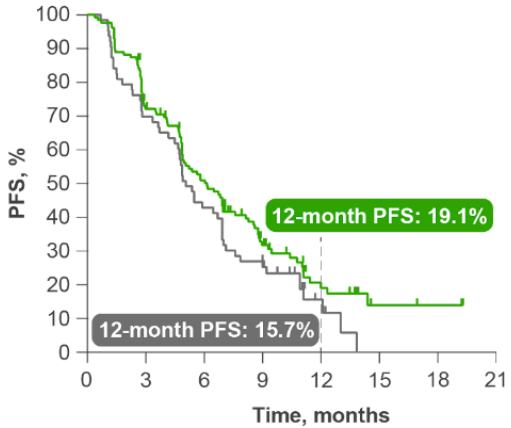
Analysis cut-off date: 8 March 2022. No statistical conclusions can be drawn from this analysis.
[a]OS and PFS were both primary endpoints. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review.
Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

Median follow up: 10.5 months

PD-L1 TPS <1%

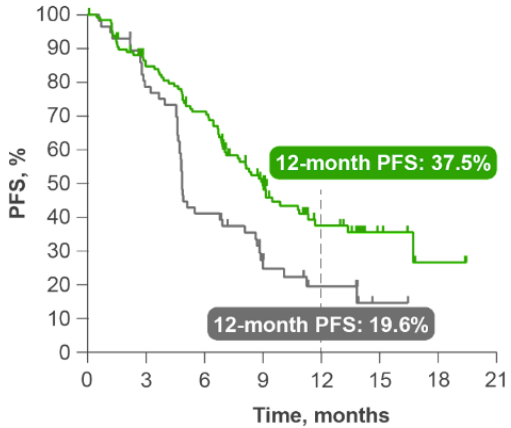
Treatment arm	Events, %	Median, months	HR (95% CI)	p value[c]
Pembro–plat–pem	72.4	6.1 (4.9–7.6)	0.75 (0.53–1.05)	0.0476
Placebo–plat–pem	85.7	5.1 (4.5–6.9)	—	—



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

PD-L1 TPS 1–49%

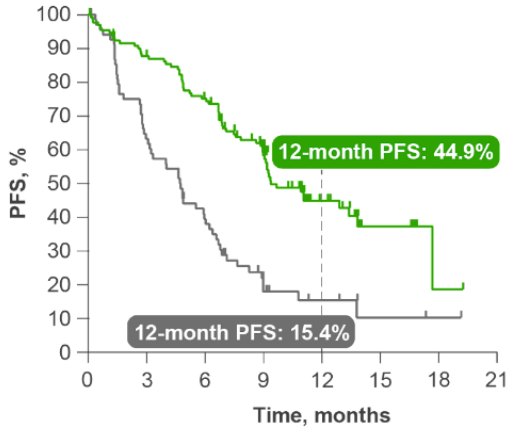
Events, %	Median, months	HR (95% CI)	p value[c]
54.7	9.0 (7.1–11.3)	0.55 (0.37–0.81)	0.0010
75.9	4.9 (4.7–6.9)	—	—



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

PD-L1 TPS ≥50%

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



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

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

Analysis cut-off date: 8 November 2017.

[a]No statistical conclusions can be drawn from exploratory endpoints. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [c]Nominal and one-sided.

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

KEYNOTE-189: PFS by PD-L1 TPS in the 5-year update

(exploratory analysis, p not tested)[a,b]

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

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

Adapted from Garassino MC et al. ESMO 2022.

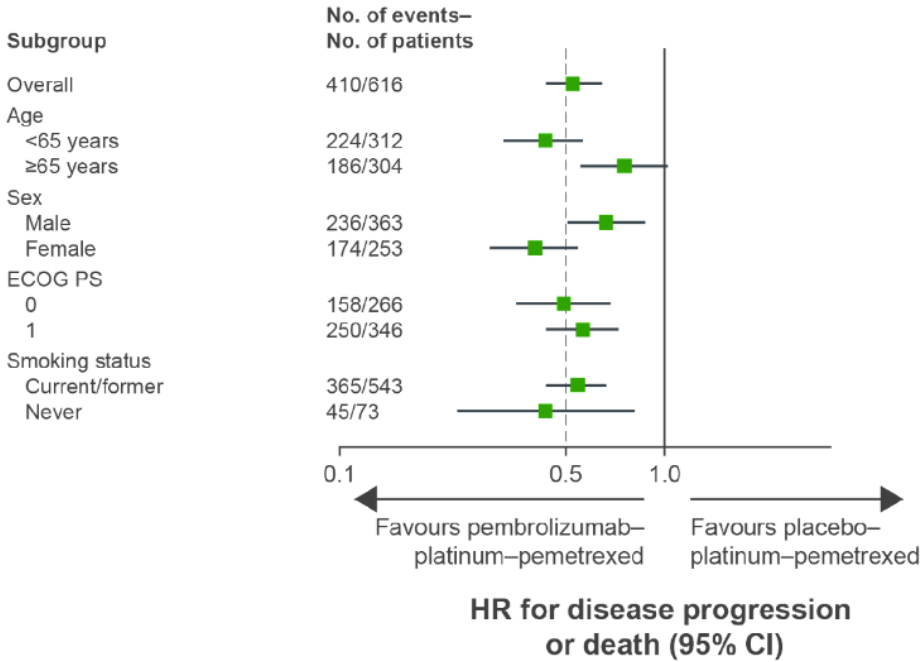
Analysis cut-off date: 8 March 2022.

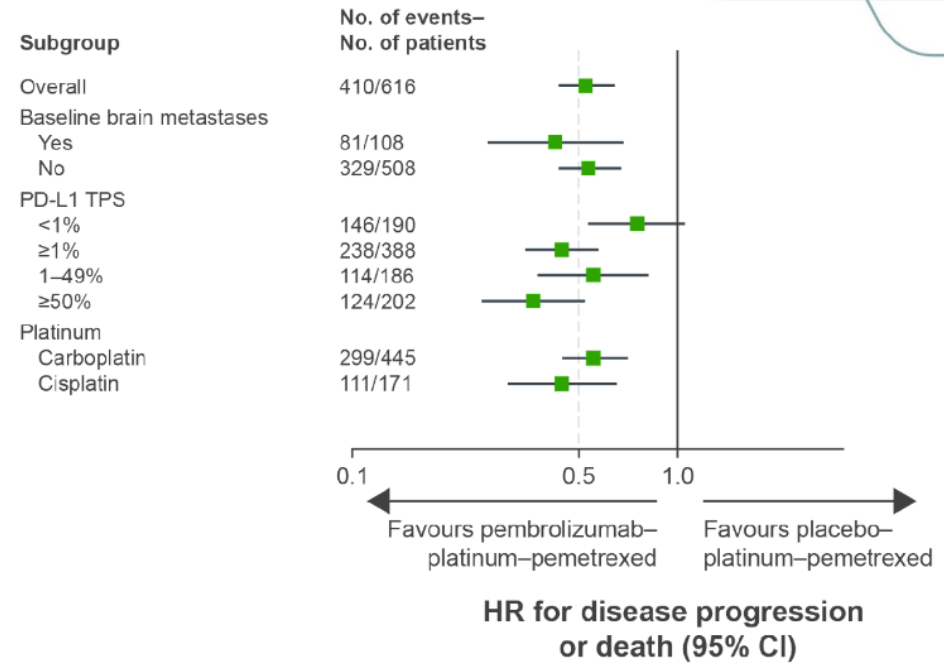
[a]No statistical conclusions can be drawn from this analysis. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [c]Kaplan-Meier estimate.

Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

Median follow up: 10.5 months





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

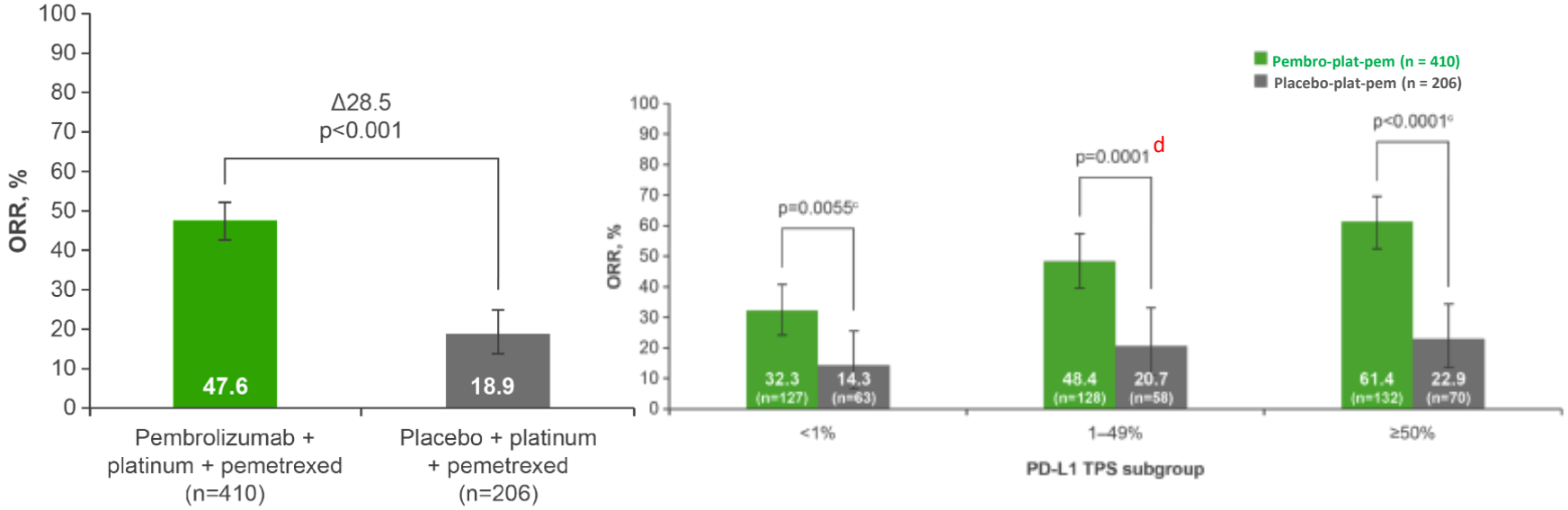
Analysis cut-off date: 8 November 2017.

[a]Exploratory endpoint. No statistical conclusions can be drawn from exploratory endpoints. [b]Assessed using RECIST v1.1 by blinded, independent, central radiological review.

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

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

Median follow up: 10.5 months



Analysis cut-off date: 8 November 2017.

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

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

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

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

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

Adapted from Garassino MC et al. ESMO 2022.

Analysis cut-off date: 8 March 2022.

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

Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

Median follow up: 10.5 months

Best response and DOR

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

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

Analysis cut-off date: 8 November 2017.

[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [b]An additional 27 (6.6%) patients in the pembrolizumab + platinum + pemetrexed arm and 25 (12.1%) in the placebo + platinum + pemetrexed arm did not have ≥2 evaluable sets of radiographic images.2 [c]+ denotes a response that was ongoing at the analysis cut-off date. dThe proportion of patients with a confirmed complete or partial response or stable disease.

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

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

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

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

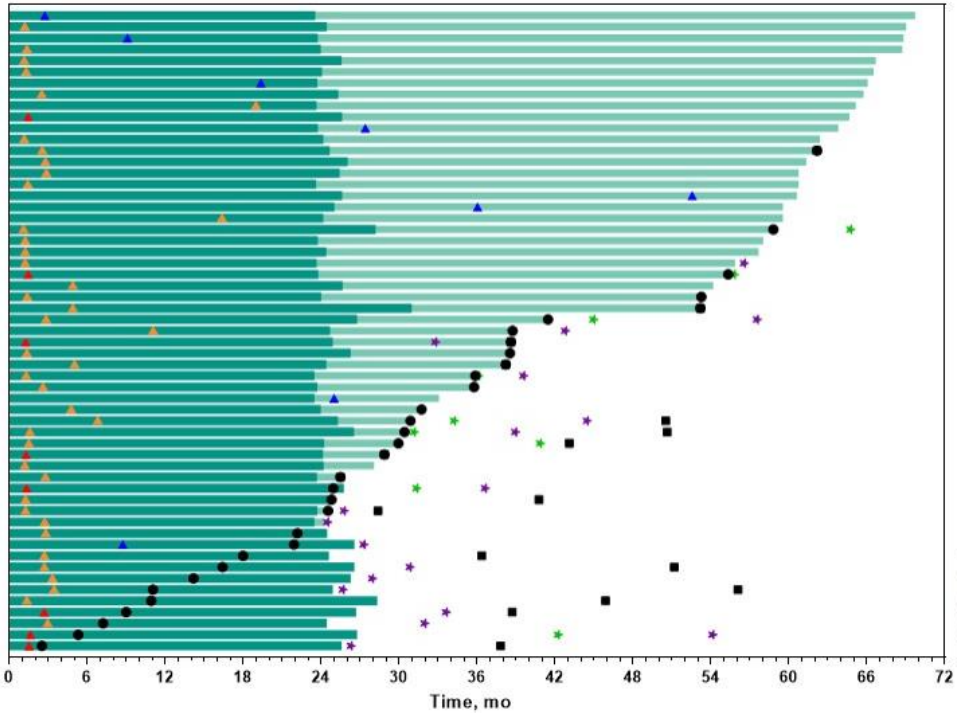
Adapted from Garassino MC et al. ESMO 2022.

Analysis cut-off date: 8 March 2022.

[a]Kaplan-Meier estimate.

Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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



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

Adapted from Garassino MC et al. ESMO 2022.

Analysis cut-off date: 8 March 2022.

[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [b]Kaplan-Meier estimate. [c]Approximately 5 years after randomisation.

Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

Median follow up: 10.5 months

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

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

Analysis cut-off date: 8 November 2017.

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

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

Median follow up: 10.5 months

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

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

Analysis cut-off date: 8 November 2017.

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

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

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

Median follow up: 18.7 months

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

Adapted from: Gadgeel S et al. ASCO 2019.

Analysis cut-off date: 21 September 2018.

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

Gadgeel S *et al.* Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May–4 June, 2019, Chicago, USA.

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

Median follow up: 64.6 months

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

Adapted from Garassino MC et al. ESMO 2022.

Data cutoff date: March 8, 2022

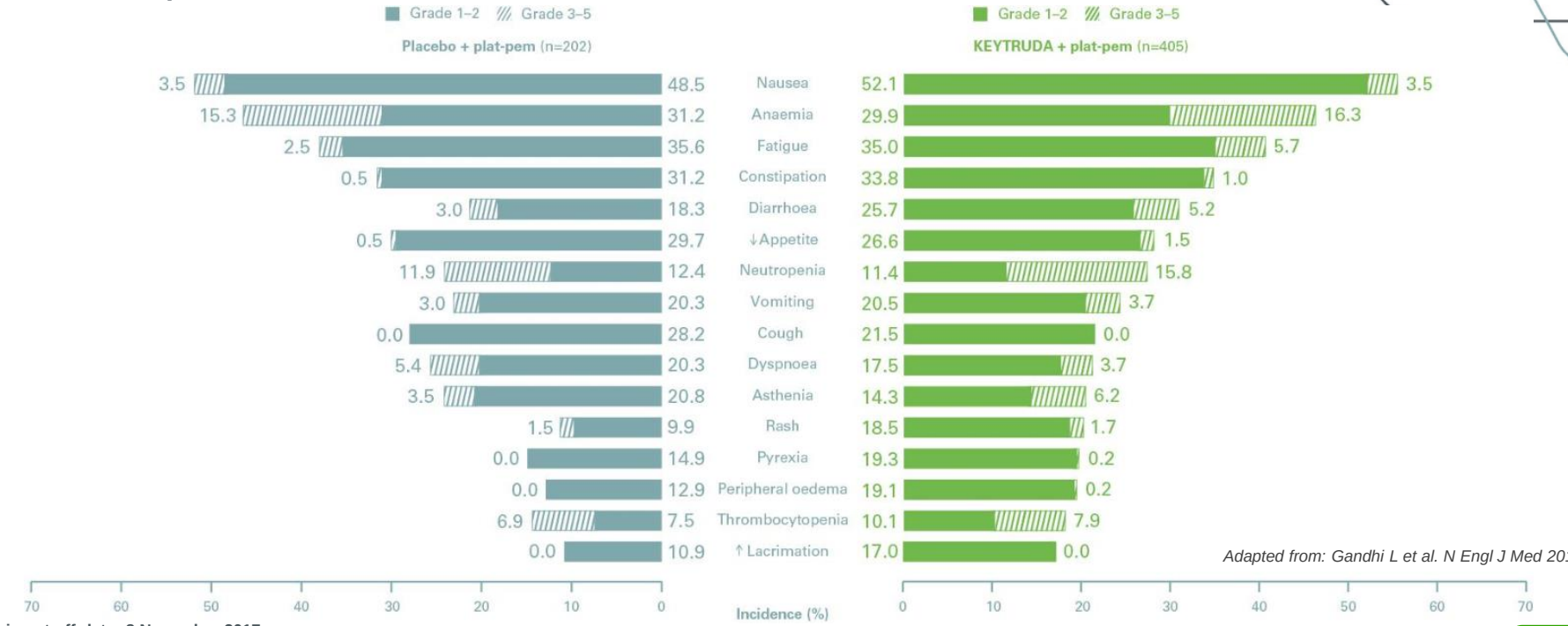
[a]All deaths were previously reported in Rodriguez-Abreu D *et al. Ann Oncol* 2021,32:881-895.

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

Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

Median follow up: 10.5 months



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

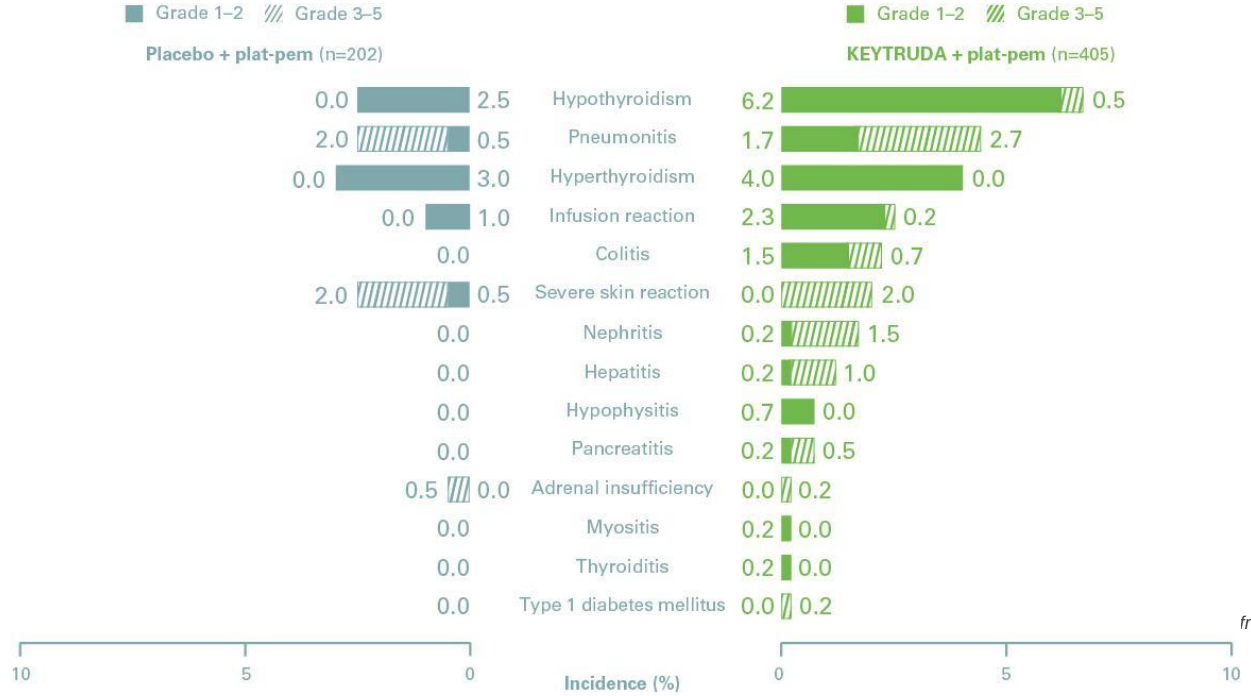
Analysis cut-off date: 8 November 2017.

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

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

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

Median follow up: 10.5 months



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

Analysis cut-off date: 8 November 2017.

[a]Regardless of attribution to a trial drug by the investigator. [b]AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0. [c]Includes three Grade 5 AEs in the pembrolizumab group.

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

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

Median follow up: 10.5 months

- Acute kidney injury
  - Frequency: 5.2% (n=21) vs. 0.5% (n=1) in the pembrolizumab + platinum + pemetrexed vs. placebo + platinum + pemetrexed arms, respectively
    - Grade 3–5 frequency:[a] 2.0% (n=8) vs. 0%, respectively
    - Grade 5 frequency: 0.5% (n=2) with pembrolizumab + platinum + pemetrexed
  - Grade ≤3 acute kidney injury had resolved or was resolving in 47% (9/19) of patients at the analysis cut-off date
- Nephritis[b,c]
  - Any-grade frequency: 1.7% (n=7) vs. 0% in the pembrolizumab + platinum + pemetrexed vs. placebo + platinum + pemetrexed arms, respectively
    - Grade 3–5 frequency: 1.5% (n=6) vs. 0%
    - Grade 5 frequency: 0%

Analysis cut-off date: 8 November 2017.

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

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

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

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

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

Analysis cut-off date: 21 September 2018.

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

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

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

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

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

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

Adapted from: Garassino MC et al. AACR 2019.

Analysis cut-off date: 21 September 2018.

[a]**No other data was reported with this analysis. This analysis was post-hoc and exploratory, and no statistical conclusions can be drawn.** [b]Unless otherwise stated. [c]25 patients had both liver and brain metastases.

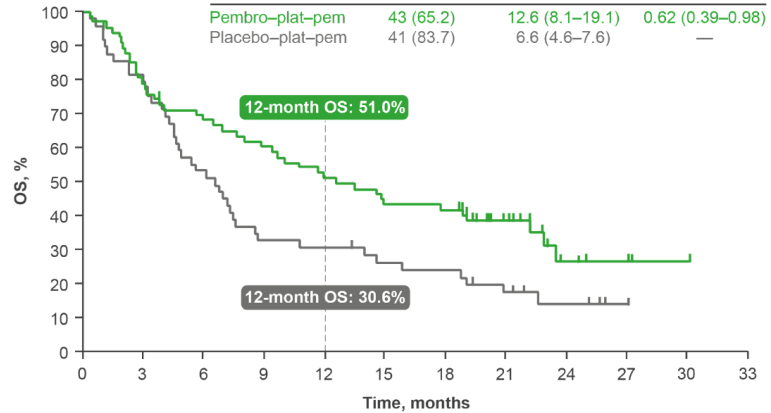
Garassino MC *et al.* Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April, 2019, Atlanta, USA.

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

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

Patients with liver metastases

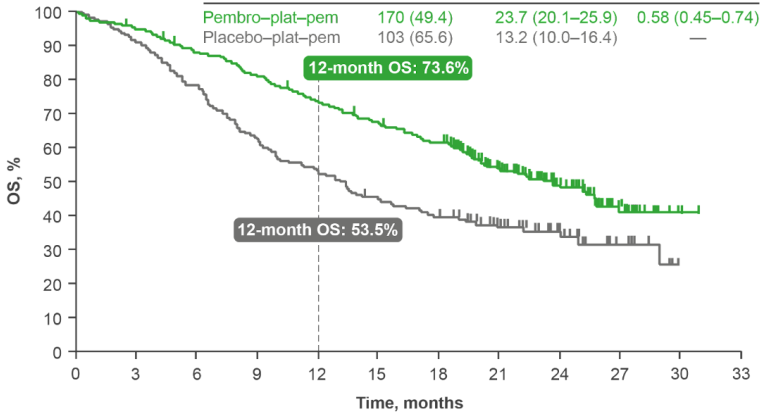
Treatment arm	Events, n (%)	Median (95% CI), months	HR (95% CI)
Pembro–plat–pem	43 (65.2)	12.6 (8.1–19.1)	0.62 (0.39–0.98)
Placebo–plat–pem	41 (83.7)	6.6 (4.6–7.6)	—



No. at risk												
Pembro–plat–pem	66	52	45	39	33	28	27	16	5	2	1	0
Placebo–plat–pem	49	40	26	16	15	12	11	7	4	0	0	0

Patients without liver metastases

Treatment arm	Events, n (%)	Median (95% CI), months	HR (95% CI)
Pembro–plat–pem	170 (49.4)	23.7 (20.1–25.9)	0.58 (0.45–0.74)
Placebo–plat–pem	103 (65.6)	13.2 (10.0–16.4)	—



No. at risk												
Pembro–plat–pem	344	325	301	277	250	228	207	128	74	26	1	0
Placebo–plat–pem	157	143	123	99	84	70	61	38	22	10	0	0

Adapted from: Garassino MC et al. AACR 2019.

Analysis cut-off date: 21 September 2018.

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

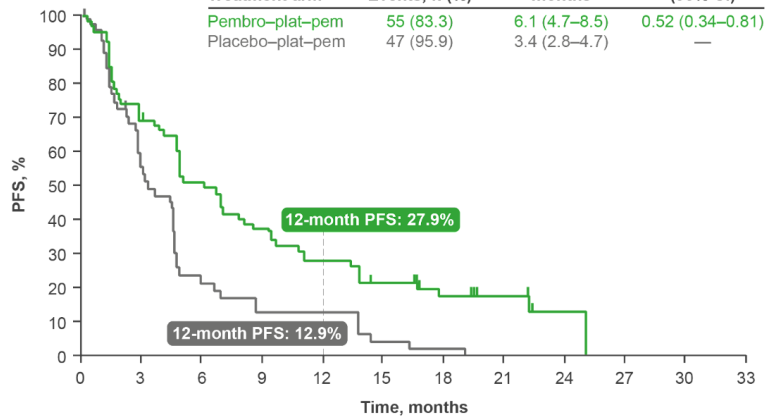
Garassino MC *et al.* Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April, 2019, Atlanta, USA.

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

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

Patients with liver metastases

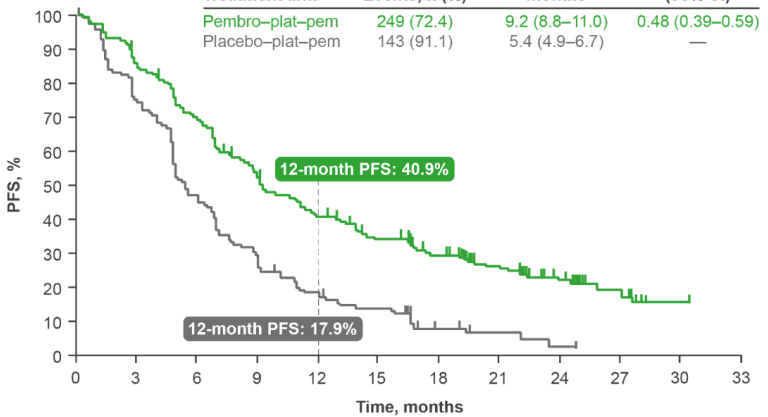
Treatment arm	Events, n (%)	Median (95% CI), months	HR (95% CI)
Pembro–plat–pem	55 (83.3)	6.1 (4.7–8.5)	0.52 (0.34–0.81)
Placebo–plat–pem	47 (95.9)	3.4 (2.8–4.7)	—



No. at risk												
Pembro–plat–pem	66	45	33	24	18	13	9	5	1	0	0	0
Placebo–plat–pem	49	26	10	6	6	2	1	0	0	0	0	0

Patients without liver metastases

Treatment arm	Events, n (%)	Median (95% CI), months	HR (95% CI)
Pembro–plat–pem	249 (72.4)	9.2 (8.8–11.0)	0.48 (0.39–0.59)
Placebo–plat–pem	143 (91.1)	5.4 (4.9–6.7)	—



No. at risk												
Pembro–plat–pem	344	283	233	173	131	106	82	49	27	10	1	0
Placebo–plat–pem	157	116	71	44	25	18	7	3	1	0	0	0

Adapted from: Garassino MC et al. AACR 2019.

Analysis cut-off date: 21 September 2018.

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

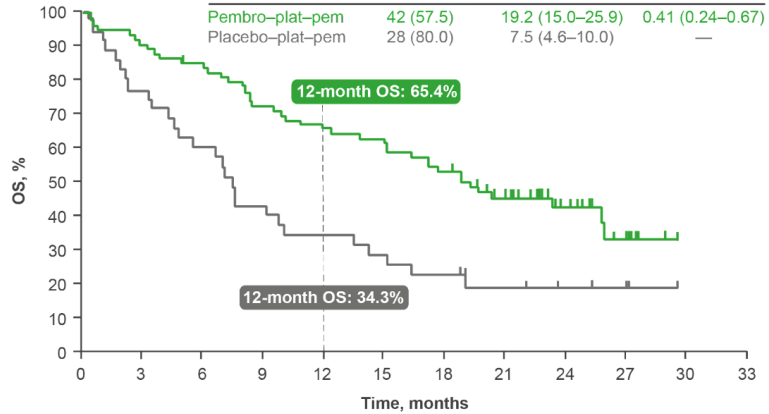
Garassino MC *et al.* Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April, 2019, Atlanta, USA.

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

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

Patients with brain metastases

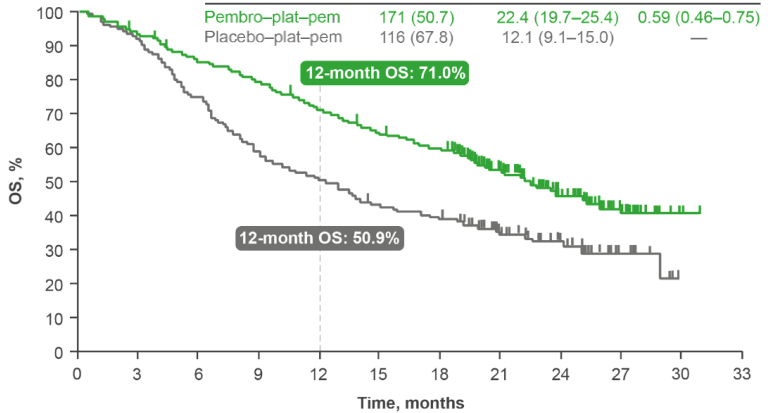
Treatment arm	Events, n (%)	Median (95% CI), months	HR (95% CI)
Pembro–plat–pem	42 (57.5)	19.2 (15.0–25.9)	0.41 (0.24–0.67)
Placebo–plat–pem	28 (80.0)	7.5 (4.6–10.0)	—



No. at risk												
Pembro–plat–pem	73	66	61	52	47	45	38	25	14	5	0	0
Placebo–plat–pem	35	27	21	15	12	10	8	5	3	1	0	0

Patients without brain metastases

Treatment arm	Events, n (%)	Median (95% CI), months	HR (95% CI)
Pembro–plat–pem	171 (50.7)	22.4 (19.7–25.4)	0.59 (0.46–0.75)
Placebo–plat–pem	116 (67.8)	12.1 (9.1–15.0)	—



No. at risk												
Pembro–plat–pem	337	311	285	264	236	211	196	119	65	23	2	0
Placebo–plat–pem	171	156	128	100	87	72	64	40	23	9	0	0

Adapted from: Garassino MC et al. AACR 2019.

Analysis cut-off date: 21 September 2018.

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

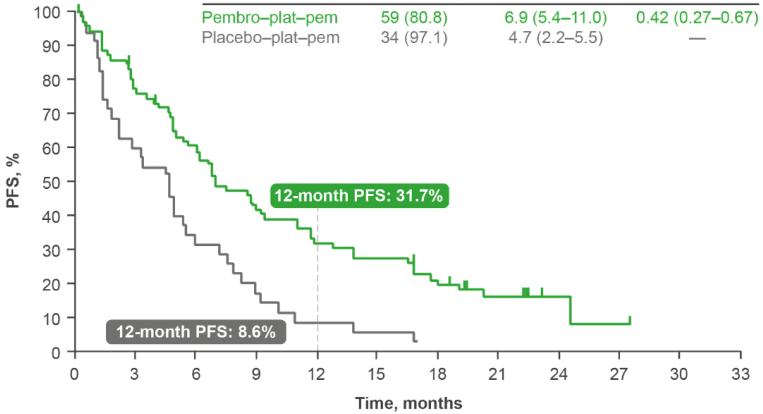
Garassino MC *et al.* Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April, 2019, Atlanta, USA.

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

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

Patients with brain metastases

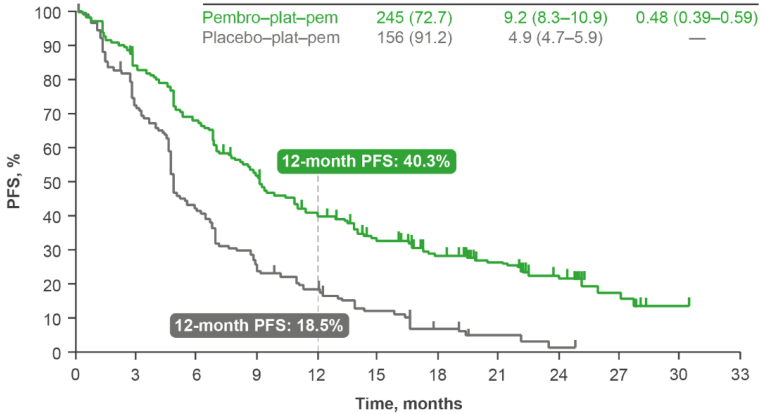
Treatment arm	Events, n (%)	Median (95% CI), months	HR (95% CI)
Pembro–plat–pem	59 (80.8)	6.9 (5.4–11.0)	0.42 (0.27–0.67)
Placebo–plat–pem	34 (97.1)	4.7 (2.2–5.5)	—



No. at risk												
Pembro–plat–pem	73	55	42	29	22	19	14	7	2	1	0	0
Placebo–plat–pem	35	21	11	6	3	2	0	0	0	0	0	0

Patients without brain metastases

Treatment arm	Events, n (%)	Median (95% CI), months	HR (95% CI)
Pembro–plat–pem	245 (72.7)	9.2 (8.3–10.9)	0.48 (0.39–0.59)
Placebo–plat–pem	156 (91.2)	4.9 (4.7–5.9)	—



No. at risk												
Pembro–plat–pem	337	273	224	168	127	100	77	47	26	9	1	0
Placebo–plat–pem	171	121	70	44	28	18	8	3	1	0	0	0

Adapted from: Garassino MC et al. AACR 2019.

Analysis cut-off date: 21 September 2018.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

KEYNOTE-189: HRQoL EORTC QLQ-C30 GHS

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

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

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

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

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

QLQ-C30 GHS/QoL and functional and symptom subscales

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

- Mean QLQ-C30 GHS/QoL scores:
  - Improved from baseline to Week 9 in both the pembrolizumab + platinum + pemetrexed group and placebo + platinum + pemetrexed group
  - Deteriorated in both groups from Week 9 onwards; however, scores in the pembrolizumab + platinum + pemetrexed group remained above baseline whereas those in the placebo + platinum + pemetrexed group did not

- QLQ-C30 functional and symptom subscales:
  - Were similar for both treatment groups across all domains at Week 12
  - Mean score changes from baseline were generally better in the pembrolizumab + platinum + pemetrexed group than in the placebo + platinum + pemetrexed group for most functional and symptom scales at Week 21
    - Symptom scale scores for dyspnoea and pain improved in the pembrolizumab + platinum + pemetrexed group and worsened/remained stable in the placebo + platinum + pemetrexed group

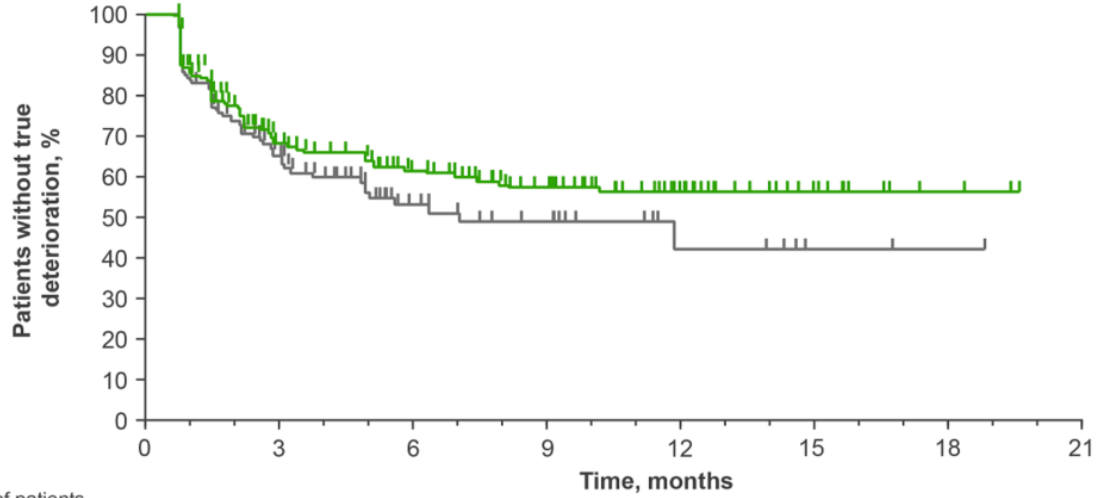
Analysis cut-off date: 8 November 2017. HRQoL was an exploratory endpoint.

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

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

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

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



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

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

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

[a]p value is 2-sided and nominal [b]Post-baseline assessments were not available for 56 patients in the pembro–plat–pem group and for 33 patients in placebo–plat–pem group.

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

KEYNOTE-189: Efficacy summary[1–3]

- Treatment with pembrolizumab + platinum + pemetrexed in patients with untreated metastatic, non-squamous NSCLC with no *EGFR*/*ALK* mutations compared with placebo + platinum + pemetrexed (median follow up: 10.5 months) yielded[1]:
  - Superior OS, with a 51% reduction in the risk of death (HR: 0.49, p<0.001)
  - Superior PFS, with a 48% reduction in the risk of progression or death (HR: 0.52, p<0.001)
  - Superior ORR (47.6% vs. 18.9%, p<0.001) and improved DOR
  - The treatment effect on OS was consistent across all PD-L1 subgroups, including PD-L1 TPS <1% and 1–49%[a]
  - The treatment effect was consistent for OS and PFS in a post-hoc analysis of patients with liver or brain metastases (median follow up: 18.7 months)[b,2]
- In the 5-year follow up, treatment with pembrolizumab + platinum + pemetrexed continued to demonstrate OS and PFS benefit in patients with previously untreated metastatic nonsquamous NSCLC compared with placebo + platinum + pemetrexed (median follow up: 64.6 months)[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.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

KEYNOTE-189: Safety summary[1–7]

- Pembrolizumab + platinum + pemetrexed in patients with untreated metastatic, non-squamous NSCLC with no *EGFR*/*ALK* mutations compared with placebo + platinum + pemetrexed displayed a generally manageable safety profile (median follow up: 10.5 months):[1]
  - The addition of pembrolizumab did not appear to increase the frequency of AEs that are commonly associated with chemotherapy regimens involving pemetrexed and a platinum-based drug[1]
  - The frequency of deaths due to pneumonitis in the pembrolizumab + platinum + pemetrexed arm was consistent with the frequency previously observed with pembrolizumab monotherapy in advanced NSCLC[1–4]
  - No new safety signals were identified in the post-hoc analysis for liver and brain metastases (median follow up: 18.7 months)[a,5]
- In the 5-year update, toxicity was manageable, which is consistent with previous reports.[6–8]

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

1. Gandhi L *et al. N Engl J Med* 2018;378:2078–2092; 2. Reck M *et al. N Engl J Med* 2016;375:1823–1833; 3. Herbst RS *et al. Lancet* 2016;387:1540–1550; 4. Garon EB *et al. N Engl J Med* 2015;372:2018–2028;
5. Garassino MC *et al.* Presented at the 2019 American Association for Cancer Research (AACR) Annual Meeting, 29 March–18 April 2019, Atlanta, USA; 6. Rodríguez-Abreu D *et al.* Ann Oncol. 2021;32:881–895; 7. Gadgeel S *et al.* J Clin Oncol. 2020;38:1505–1517; 8. Garassino MC *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

KEYNOTE-189: HRQoL summary

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

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

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

Abbreviations

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

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

Abbreviations

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