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

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GB-PDO-03145 | Date of preparation: October 2024.

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.

MSD Oncology

KEYNOTE-407: KEYTRUDA® (pembrolizumab) plus carboplatin-paclitaxel/nab-paclitaxel for the first-line treatment of metastatic squamous NSCLC

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

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

KEYTRUDA® (pembrolizumab)

MSD

External websites and abbreviations

Links to external websites

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 is not responsible for the accuracy, content, practices or standards of any third-party sources

Abbreviations

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

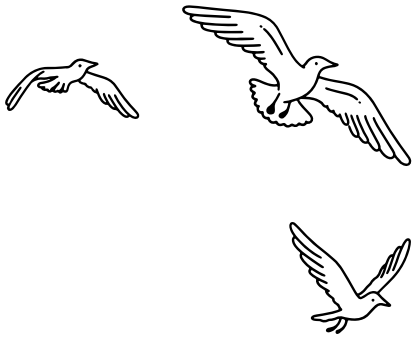
There is an urgent unmet need for treatment options for patients with mNSCLC and low PD-L1 expression

- Patient outcomes remain suboptimal with standard chemotherapeutics and durable disease control is rarely achieved[1]
- 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]

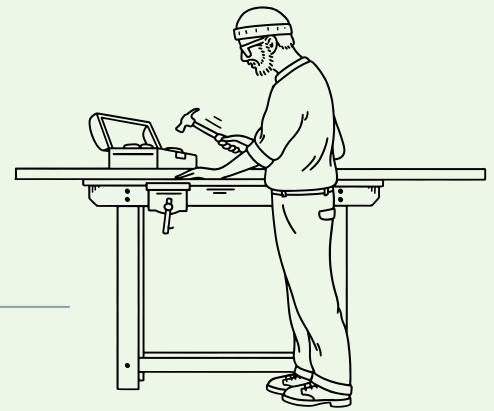


- Highest level of evidence (**I**) and recommendation grade (**A**)
- Established as a **standard treatment option** for patients with any PD-L1 score and PS 0–1, and without contraindications to IO
- Magnitude of clinical benefit recognised with an **ESMO-MCBS score of 4**

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

KEYTRUDA® (pembrolizumab) metastatic NSCLC 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 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.
Please note that clicking this link will redirect you to external websites, for which MSD does not review or control the content.

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	1st Line	Previously treated
Squamous		
PD-L1 non-expressers / unknown	KEYTRUDA (Q3W/Q6W) + carboplatin-paclitaxel/nab-paclitaxel **KEYNOTE-407**	
PD-L1 1-49%	KEYTRUDA (Q3W/Q6W) **KEYNOTE-024**	KEYTRUDA monotherapy (Q3W/Q6W)
PD-L1 ≥50%	KEYTRUDA (Q3W/Q6W) **KEYNOTE-024**	KEYTRUDA monotherapy (Q3W/Q6W)
Non-squamous		
PD-L1 non-expressers / unknown	KEYTRUDA (Q3W/Q6W) + platinum chemotherapy and pemetrexed **KEYNOTE-189**	
PD-L1 1-49%	KEYTRUDA (Q3W/Q6W) **KEYNOTE-024**	KEYTRUDA monotherapy (Q3W/Q6W)
PD-L1 ≥50%	KEYTRUDA (Q3W/Q6W) **KEYNOTE-024**	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-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: Definition of analyses

Analysis	Cut-off date	Slide symbol	Median follow-up (range), months
Original/second interim	3 April 2018	1	7.8 (0.1–19.1)[1]
Updated analysis	9 May 2019	2	14.3 (0.1–31.3)[2]
5-year follow-up	23 February 2022	3	56.9 (49.9–66.2)[3]

1. Paz-Ares L *et al. N Engl J Med* 2018;379:2040–2051; 2. Paz-Ares L *et al. J Thorac Oncol* 2020:15:1657–1669; 3. Novello S *et al. J Clin Oncol* 2023:41:1999–2006.

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: Statistical considerations (original analysis)[1]

Planned enrolment: 560 patients

- Actual enrolment: 559 patients

Study protocol specified three interim analyses prior to the final analysis

Overall alpha for study: strictly controlled at one-sided α=0.025[a]

- Trial was determined to have 90% power for PFS and 85% power for OS, with a target HR of 0.70 and critical α of 0.01 for both

Second interim analysis (IA2)[b]

- Second analysis of OS and PFS
  - Planned to occur after ~332 PFS events observed
- Statistical methods
  - Difference in OS and PFS: stratified log-rank test
- Analysis cut-off date: 3 April 2018
  - External data monitoring committee meeting: 21 May 2018
  - Patients with a PFS event: 349
  - Number of deaths: 205
  - Superiority thresholds (one-sided): 0.008 for PFS; 0.0029 for OS
  - Median follow-up:[c] 7.8 months (range: 0.1–19.1 months)
- Results published: 25 September 2018

[a]Using the graphical method of Maurer and Bretz. [b]All interim analyses were reviewed by an external, independent data monitoring committee.
[c]Defined as the time from randomisation to the date of death or data cut-off, whichever occurred first.

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

KEYNOTE-407: Statistical considerations (updated analyses)

Updated analysis[1]

- Analysis cut off-date: 9 May 2019
- Results presented: ESMO 2019
- Median follow-up (study)[a]: 14.3 (0.1–31.3) months
- This analysis was not subjected to further significancy testing

5-year update:[2]

- Analysis cut off-date: 23 February 2022
- Results presented: ESMO 2022
- Median follow-up (study)[a]: 56.9 months (range: 49.9–66.2 months)
- This analysis was not subjected to further significancy testing

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

1. Paz-Ares L *et al. J Thorac Oncol* 2020:15:1657–1669; 2. Novello S *et al. J Clin Oncol* 2023:41:1999–2006.

KEYNOTE-407: Disposition of study treatment – original/second interim analysis[1,2]

Median follow-up: 7.8 months

559 patients randomly allocated

Pembrolizumab + carb-pac/nabpac
- 278 allocated (ITT population)
- 278 treated (as-treated population)
- 121 (43.5%) ongoing
- 157 (56.5%) discontinued
  - 86 (30.9%) radiographic PD
  - 48 (17.3%) AEs
  - 13 (4.7%) clinical PD
  - 5 (1.8%) withdrawal of consent
  - 5 (1.8%) physician decision
  - 0 lost to follow-up

≥1 subsequent therapy
15.8% of ITT (28.0% excluding those still on therapy)[a]

Crossover[b]
75 in-study pembrolizumab
+
14 off-study anti-PD-1/PD-L1
=
Effective crossover (ITT): 31.7% (42.8% excluding those still on therapy)

Placebo + carb-pac/nabpac
- 281 allocated (ITT population)
- 280 treated (as-treated population)
- 72 (25.7%) ongoing
- 208 (74.3%) discontinued
  - 140 (50.0%) radiographic PD
  - 25 (8.9%) AEs
  - 26 (9.3%) clinical PD
  - 9 (3.2%) withdrawal of consent
  - 6 (2.1%) physician decision
  - 2 (0.7%) lost to follow-up

Adapted from Paz-Ares L et al. N Engl J Med 2018 (and supplementary appendix); Paz-Ares L et al. ASCO 2018.

Data cut-off date: 3 April 2018.
[a]28.0%=44/157, where 157 is derived from the ITT population (278) minus the number of patients with ongoing treatment (121), and 44 is derived from subsequent treatment in 15.8% of the ITT population (278). [b]An additional 21 patients received other subsequent therapy (7.5% of the ITT population; 10.1% excluding those still on therapy).

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

Median follow-up: 7.8 months

Characteristic, n (%)[a]	Pembrolizumab + carb-pac/nabpac (n=278)	Placebo + carb-pac/nabpac (n=281)
Age, median (range), years	65 (29–87)	65 (36–88)
<65 years	127 (45.7)	127 (45.2)
Male sex	220 (79.1)	235 (83.6)
ECOG PS		
0	73 (26.3)	90 (32.0)
1	205 (73.7)	191 (68.0)
Brain metastases	20 (7.2)	24 (8.5)
Smoking status		
Former/current	256 (92.1)	262 (93.2)
Never	22 (7.9)	19 (6.8)
Region of enrolment		
East Asia	54 (19.4)	52 (18.5)
Rest of the World	224 (80.6)	229 (81.5)

Characteristic, n (%)[a]	Pembrolizumab + carb-pac/nabpac (n=278)	Placebo + carb-pac/nabpac (n=281)
PD-L1 TPS[b]		
<1%	95 (34.2)	99 (35.2)
≥1%	176 (63.3)	177 (63.0)
1–49%	103 (37.1)	104 (37.0)
≥50%	73 (26.3)	73 (26.0)
NE[c]	7 (2.5)	5 (1.8)
Prior thoracic radiotherapy	17 (6.1)	22 (7.8)
Prior neoadjuvant or adjuvant therapy	5 (1.8)	8 (2.8)

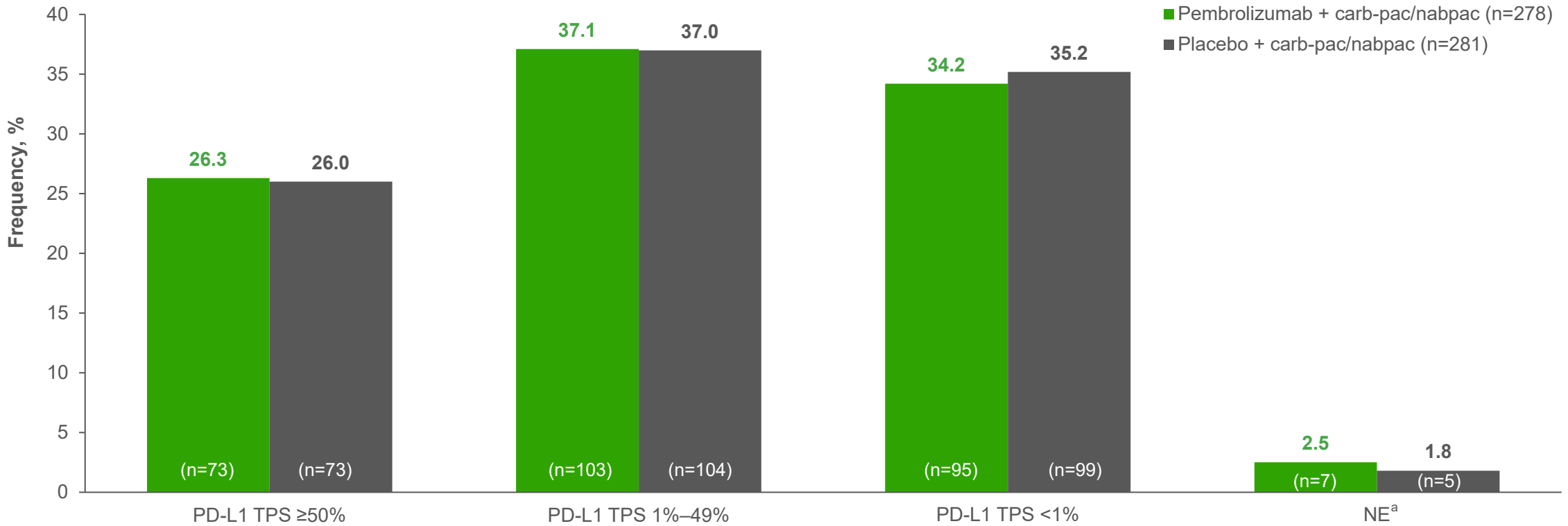
Adapted from Paz-Ares L et al. N Engl J Med 2018.

Data cut-off date: 3 April 2018.
[a]Unless otherwise stated. [b]PD-L1 TPS was defined as the percentage of tumour cells with membranous PD-L1 expression.[c]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. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051.

KEYNOTE-407: Baseline characteristics – frequency of PD-L1 TPS subgroups[1]

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]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 analyses of efficacy by TPS.

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

1

KEYNOTE-407: Primary endpoint outcomes[a]

Primary outcomes with pembrolizumab + carb-pac/nabpac (n=278) vs. placebo + carb-pac/nabpac (n=281) in the ITT population were as follows:

Original analysis[1] (median follow-up: 7.8 months)

- OS: 36% reduced risk of death vs. placebo + carb-pac/nabpac
  - HR: 0.64; 95% CI: 0.49–0.85; p<0.001
- PFS: 44% reduced risk of progression or death vs. placebo + carb-pac/nabpac
  - HR: 0.56; 95% CI: 0.45–0.70; p<0.001

5-year follow-up[2] (median follow-up: 56.9 months)

- OS: 29% reduced risk of death vs. placebo + carb-pac/nabpac
  - HR: 0.71; 95% CI: 0.59–0.85; p = not tested
- PFS: 38% reduced risk of progression vs. placebo + carb-pac/nabpac
  - HR: 0.62; 95% CI: 0.52–0.74; p = not tested

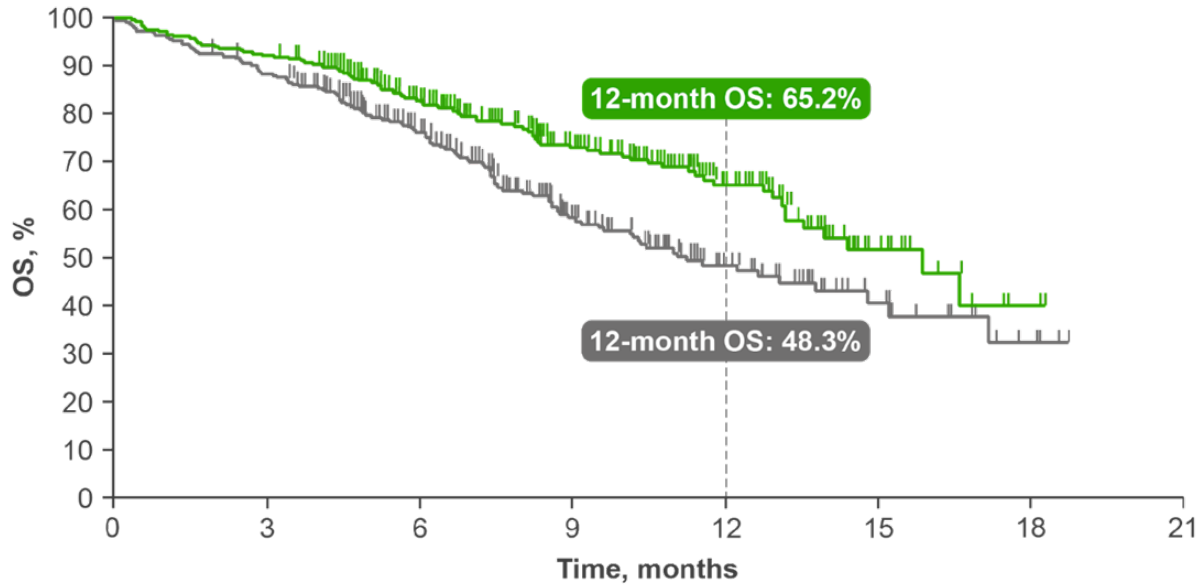
[a]**OS and PFS were both primary endpoints.**

1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051; 2. Novello S *et al. J Clin Oncol* 2023; 41(11):1999–2006.

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)	—	—



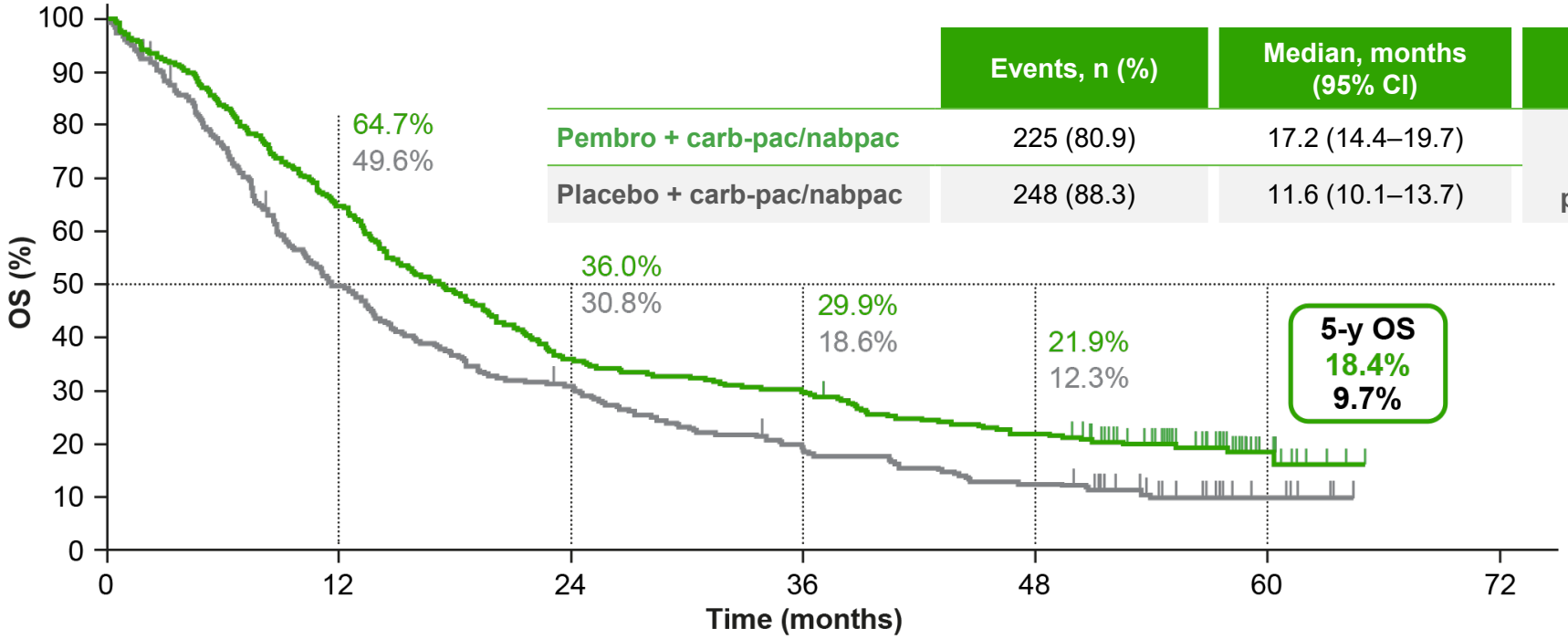
No. at risk								
Pembrolizumab + carb-pac/nabpac	278	256	188	124	62	17	2	0
Placebo + carb-pac/nabpac	281	246	175	93	45	16	4	0

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

Median follow-up: 56.9 months. No statistical conclusions can be drawn from this analysis



	Events, n (%)	Median, months (95% CI)	HR (95% CI)
Pembro + carb-pac/nabpac	225 (80.9)	17.2 (14.4–19.7)	0.71 (0.59–0.85) p = not tested
Placebo + carb-pac/nabpac	248 (88.3)	11.6 (10.1–13.7)	

No. at risk

Pembro + carb–pac/nabpac	278	180	100	83	60	10	0
Placebo + carb–pac/nabpac	281	137	84	50	33	7	0

Adapted from Novello S et al. J Clin Oncol 2023.

17

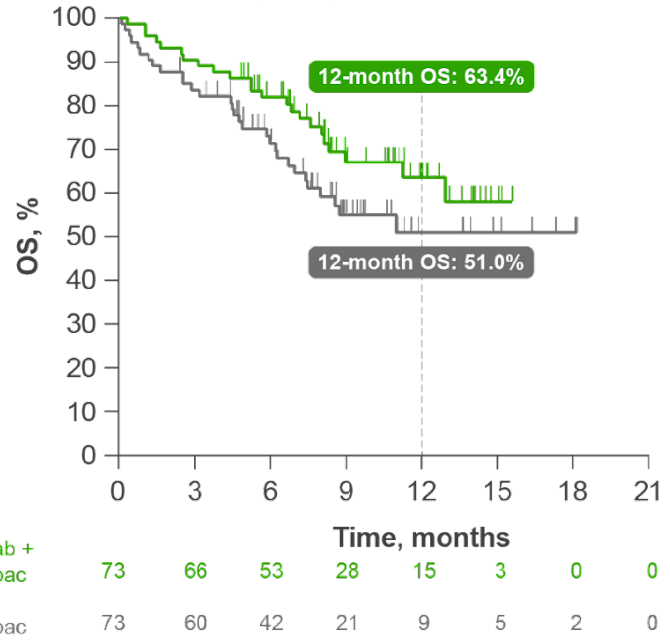
Data cut-off date: 23 February 2022.
[a]OS and PFS were both primary endpoints. [b]Kaplan-Meier estimate. [c]Statistical significance was met for the primary endpoints in IA1 (2018).
1. Novello S *et al. J Clin Oncol* 2023; 41(11):1999–2006.

KEYNOTE-407: Exploratory endpoint – OS by PD-L1 TPS (original analysis)[1,2,a]

Median follow-up: 7.8 months. No statistical conclusions can be drawn from exploratory endpoints

PD-L1 TPS ≥50%

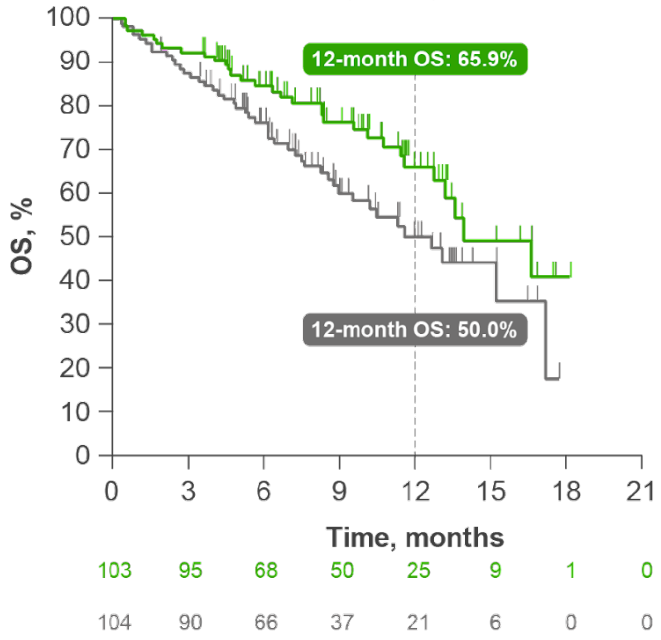
Treatment arm	Events, %	Median, months (95% CI)	HR (95% CI)
Pembrolizumab + carb-pac/nabpac	31.5	NR (11.3–NE)	0.64 (0.37–1.10)
Placebo + carb-pac/nabpac	41.1	NR (7.4–NE)	—



No. at risk								
Pembrolizumab + carb-pac/nabpac	73	66	53	28	15	3	0	0
Placebo + carb-pac/nabpac	73	60	42	21	9	5	2	0

PD-L1 TPS 1%–49%

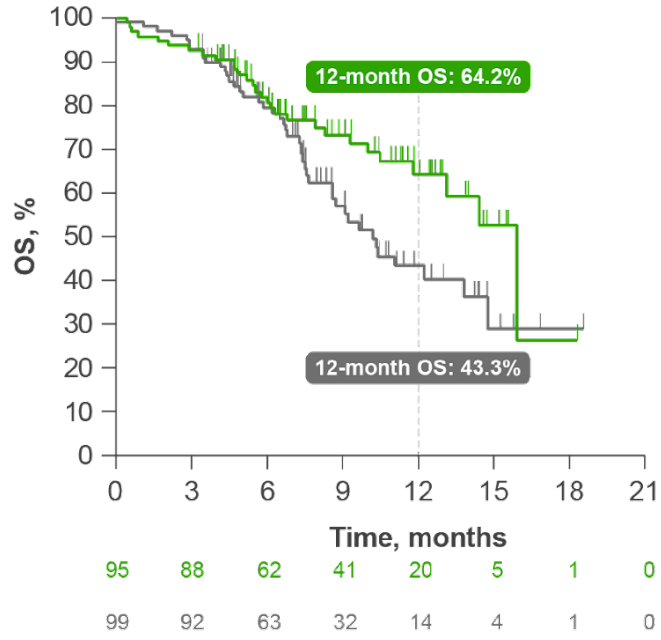
Events, %	Median, months (95% CI)	HR (95% CI)
30.1	14.0 (12.8–NE)	0.57 (0.36–0.90)
43.3	11.6 (8.9–17.2)	—



Pembrolizumab + carb-pac/nabpac	103	95	68	50	25	9	1	0
Placebo + carb-pac/nabpac	104	90	66	37	21	6	0	0

PD-L1 TPS <1%

Events, %	Median, months (95% CI)	HR (95% CI)
30.5	15.9 (13.1–NE)	0.61 (0.38–0.98)
44.4	10.2 (8.6–13.8)	—



Pembrolizumab + carb-pac/nabpac	95	88	62	41	20	5	1	0
Placebo + carb-pac/nabpac	99	92	63	32	14	4	1	0

Adapted from Paz-Ares L et al. N Engl J Med 2018 (and supplementary appendix); Paz-Ares L et al. ASCO 2018.

Data cut-off date: 3 April 2018.

[a]**Kaplan-Meier estimates.**

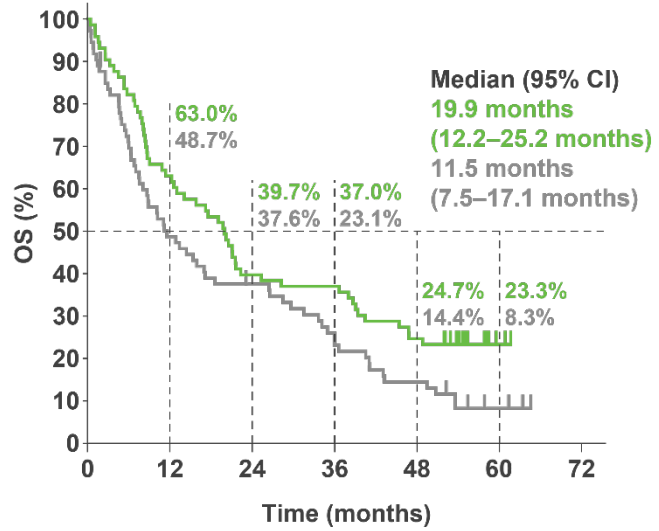
1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051 (and supplementary appendix); 2. Paz-Ares L *et al.* Presented at American Society of Clinical Oncology (ASCO) Annual Meeting 2018, 1–5 June, 2018, Chicago, USA.

KEYNOTE-407: Exploratory analysis – OS by PD-L1 TPS (5-year update)[1,a]

Median follow-up: 56.9 months. No statistical conclusions can be drawn from this analysis

PD-L1 TPS ≥50%

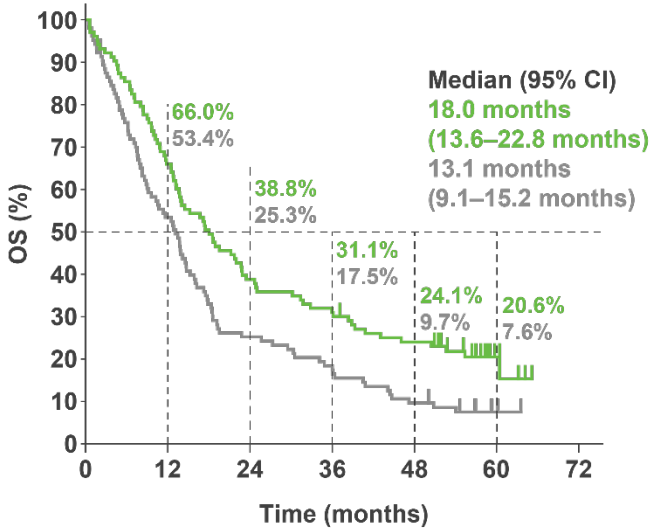
Treatment group	Events, n (%)	HR (95% CI)	5-year OS rate, % (95% CI)
Pembro + carb-pac/nabpac	56 (76.7)	0.68	23.3 (14.4–33.5)
Placebo + carb-pac/nabpac	65 (89.0)	(0.47–0.97)	8.3 (3.2–16.4)



No. at risk:							
Pembro + carb-pac/nabpac	73	46	29	27	18	2	0
Placebo + carb-pac/nabpac	73	35	26	16	10	3	0

PD-L1 TPS 1%–49%

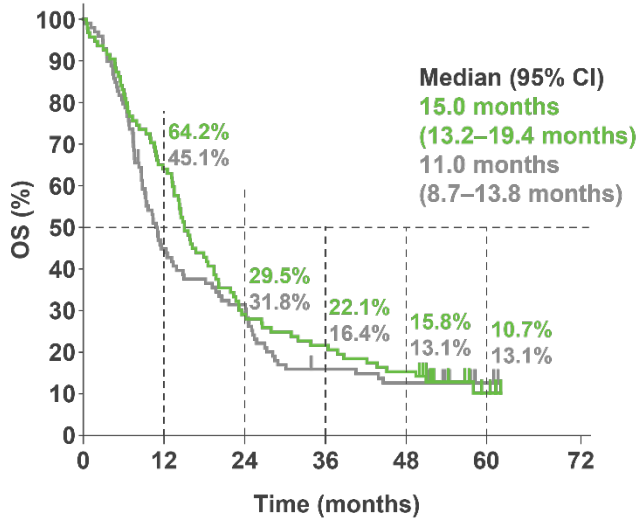
Treatment group	Events, n (%)	HR (95% CI)	5-year OS rate, % (95% CI)
Pembro + carb-pac/nabpac	82 (79.6)	0.61	20.6 (13.2–29.0)
Placebo + carb-pac/nabpac	95 (91.3)	(0.45–0.83)	7.6 (3.5–13.8)



No. at risk:							
Pembro + carb-pac/nabpac	103	68	40	32	24	5	0
Placebo + carb-pac/nabpac	104	55	26	18	10	1	0

PD-L1 TPS <1%

Treatment group	Events, n (%)	HR (95% CI)	5-year OS rate, % (95% CI)
Pembro + carb-pac/nabpac	83 (87.4)	0.83	10.7 (4.8–19.2)
Placebo + carb-pac/nabpac	85 (85.9)	(0.61–1.13)	13.1 (7.3–20.7)



No. at risk:							
Pembro + carb-pac/nabpac	95	61	28	21	15	3	0
Placebo + carb-pac/nabpac	99	44	31	15	12	3	0

Adapted from Novello S et al. J Clin Oncol 2023.

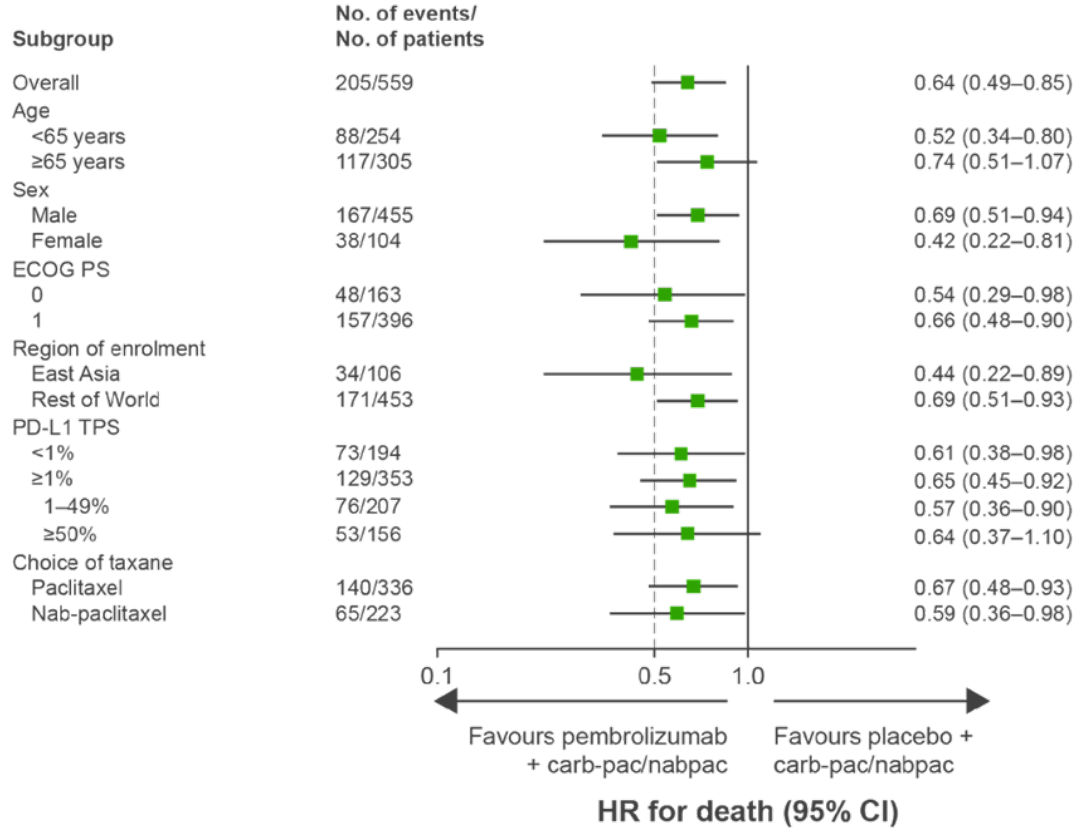
Data cut-off date: 23 February 2022.

[a]Kaplan-Meier estimates.

1. Novello S *et al. J Clin Oncol* 2023; 41(11):1999–2006.

KEYNOTE-407: Exploratory endpoint – OS in key subgroups (original analysis)[1]

Median follow-up: 7.8 months. No statistical conclusions can be drawn from exploratory endpoints



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

Data cut-off date: 3 April 2018.

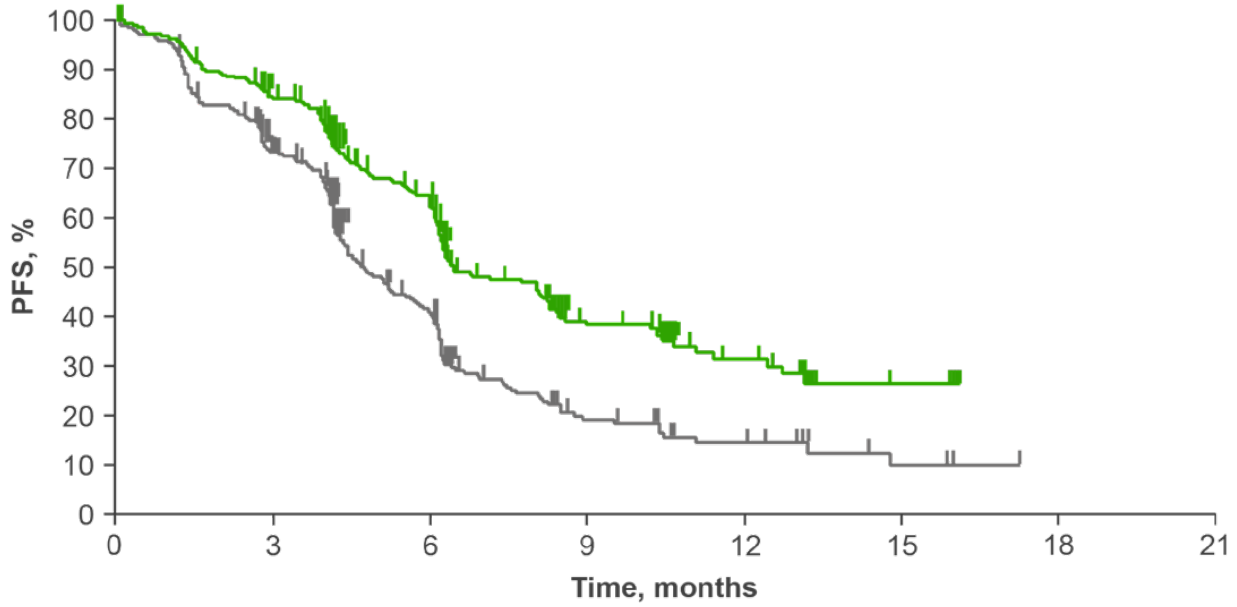
1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051.

1

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.

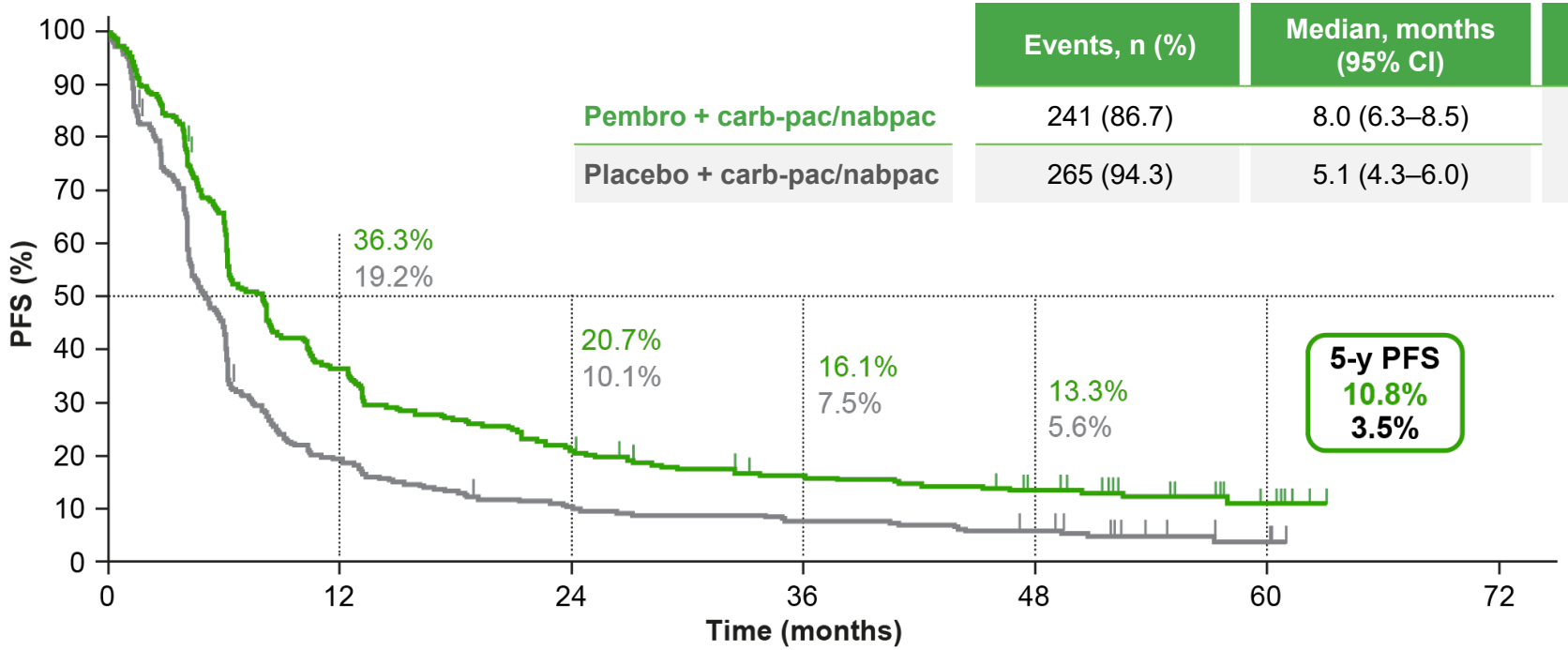
Data cut-off date: 3 April 2018.
[a]OS and PFS were both primary endpoints. [b]Kaplan-Meier estimate. [c]Assessed using RECIST v1.1 by blinded, independent, central radiological review.

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

Median follow-up: 56.9 months. No statistical conclusions can be drawn from this analysis

	Events, n (%)	Median, months (95% CI)	HR (95% CI)
Pembro + carb-pac/nabpac	241 (86.7)	8.0 (6.3–8.5)	0.62 (0.52–0.74) p = not tested
Placebo + carb-pac/nabpac	265 (94.3)	5.1 (4.3–6.0)	



No. at risk

Pembro + carb-pac/nabpac	278	100	56	40	30	7	0
Placebo + carb-pac/nabpac	281	53	27	20	14	1	0

Adapted from Novello S et al. J Clin Oncol 2023.

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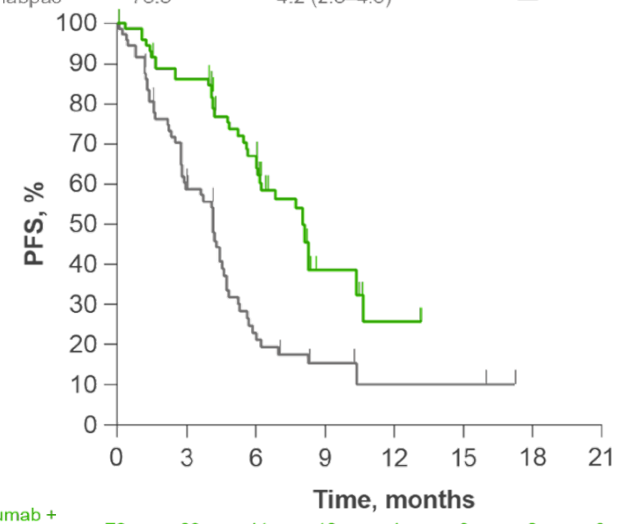
Data cut-off date: 23 February 2022.
[a]Kaplan-Meier estimate. [b]Assessed using RECIST v1.1 by blinded, independent, central review.
1. Novello S *et al. J Clin Oncol* 2023; 41(11):1999–2006.

KEYNOTE-407: Exploratory endpoint – PFS by PD-L1 TPS (original analysis)[1,2,a,b]

Median follow-up: 7.8 months. No statistical conclusions can be drawn from exploratory endpoints

PD-L1 TPS ≥50%

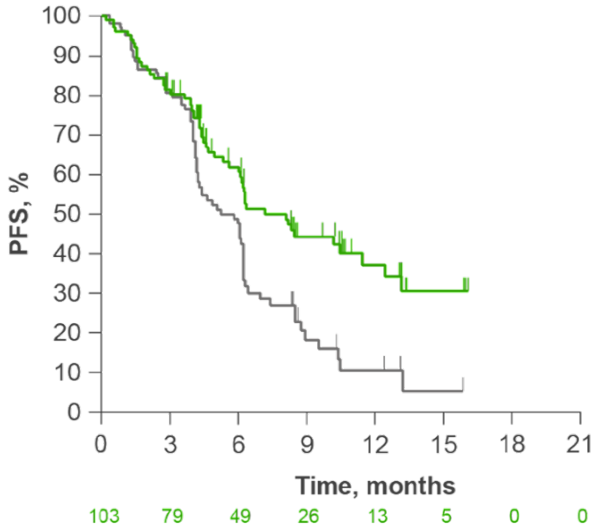
Treatment arm	Events, %	Median, months (95% CI)	HR (95% CI)
Pembrolizumab + carb-pac/nabpac	53.4	8.0 (6.1–10.3)	0.37 (0.24–0.58)
Placebo + carb-pac/nabpac	75.3	4.2 (2.8–4.6)	—



No. at risk								
Pembrolizumab + carb-pac/nabpac	73	60	41	12	4	0	0	0
Placebo + carb-pac/nabpacl	73	38	13	5	2	2	0	0

PD-L1 TPS 1%–49%

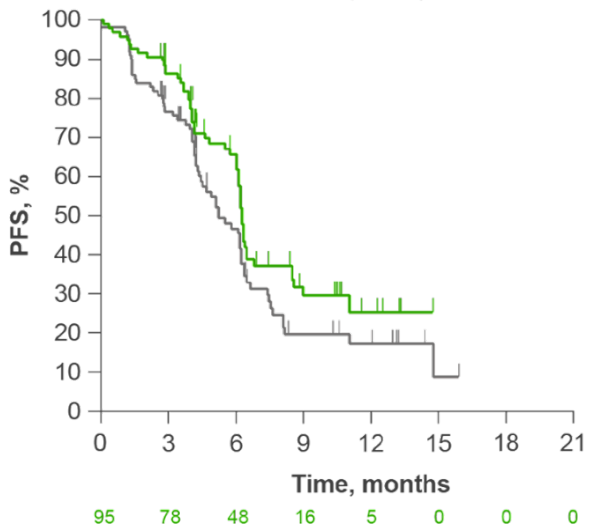
Events, %	Median, months (95% CI)	HR (95% CI)
52.4	7.2 (6.0–11.4)	0.56 (0.39–0.80)
70.2	5.2 (4.2–6.2)	—



	103	79	49	26	13	5	0	0
	104	79	40	8	4	1	0	0

PD-L1 TPS <1%

Events, %	Median, months (95% CI)	HR (95% CI)
57.9	6.3 (6.1–6.5)	0.68 (0.47–0.98)
67.7	5.3 (4.4–6.2)	—



	95	78	48	16	5	0	0	0
	99	71	35	11	6	1	0	0

Adapted from Paz-Ares L et al. N Engl J Med 2018 (and supplementary appendix); Paz-Ares L et al. ASCO 2018.

Data cut-off date: 3 April 2018.

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

1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051 (and supplementary appendix); 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: Exploratory analysis – PFS by PD-L1 TPS (5-year update)[1,a,b]

Median follow-up: 56.9 months. No statistical conclusions can be drawn from this analysis

TPS ≥50%

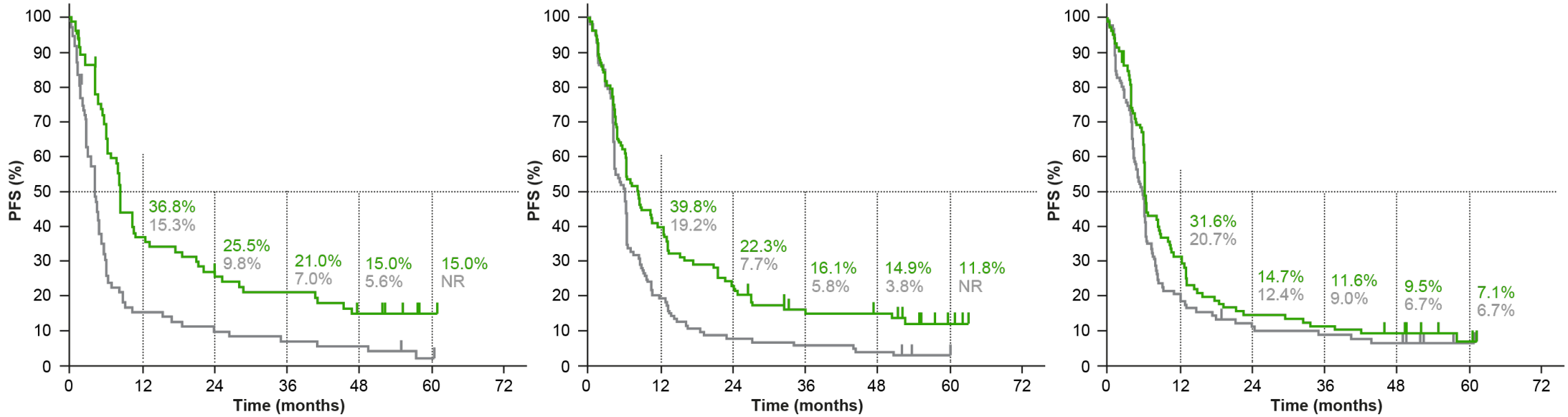
Treatment group	Events, n (%)	Median, months (95% CI)	HR (95% CI)	5-year PFS rate,% (95% CI)[b]
Pembro + carb–pac/nabpac	60 (82.2)	8.3 (6.2–10.7)	0.48	15.0 (7.8–24.4)
Placebo + carb–pac/nabpac	70 (95.9)	4.2 (2.9–4.8)	(0.33–0.69)	NR

TPS 1–49%

Treatment group	Events, n (%)	Median, months (95% CI)	HR (95% CI)	5-year PFS rate,% (95% CI)[b]
Pembro + carb–pac/nabpac	89 (86.4)	8.2 (6.2–11.4)	0.60	11.8 (6.1–19.6)
Placebo + carb–pac/nabpac	101 (97.1)	6.0 (4.2–6.2)	(0.45–0.81)	NR

TPS <1%

Treatment group	Events, n (%)	Median, months (95% CI)	HR (95% CI)	5-year PFS rate,% (95% CI)[b]
Pembro + carb–pac/nabpac	87 (91.6)	6.3 (6.1–8.5)	0.70	7.1 (2.6–14.6)
Placebo + carb–pac/nabpac	91 (91.9)	5.9 (4.4–6.2)	(0.52–0.95)	6.7 (2.8–13.1)



No. at risk																			
Pembrolizumab + carb–pac/nabpac	73	26	17	14	9	1	0	103	41	23	13	11	3	0	95	30	14	11	8	3	0
Placebo + carb–pac/nabpac	73	11	7	5	4	0	0	104	20	8	6	4	0	0	99	20	11	8	6	1	0

Adapted from Novello S et al. J Clin Oncol 2023.

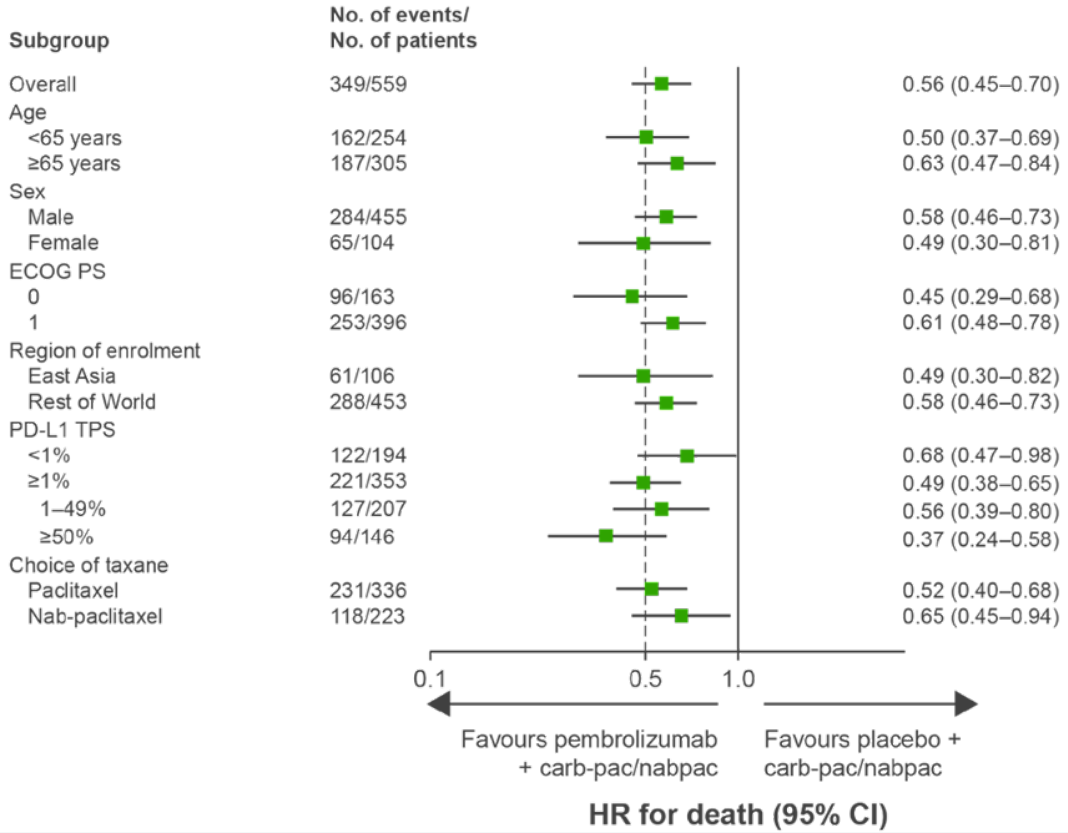
Data cut-off date: 23 February 2022.

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

1. Novello S *et al. J Clin Oncol* 2023; 41(11):1999–2006..

KEYNOTE-407: Exploratory endpoint – PFS in key subgroups (original analysis)[1,a]

Median follow-up: 7.8 months. No statistical conclusions can be drawn from exploratory endpoints



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

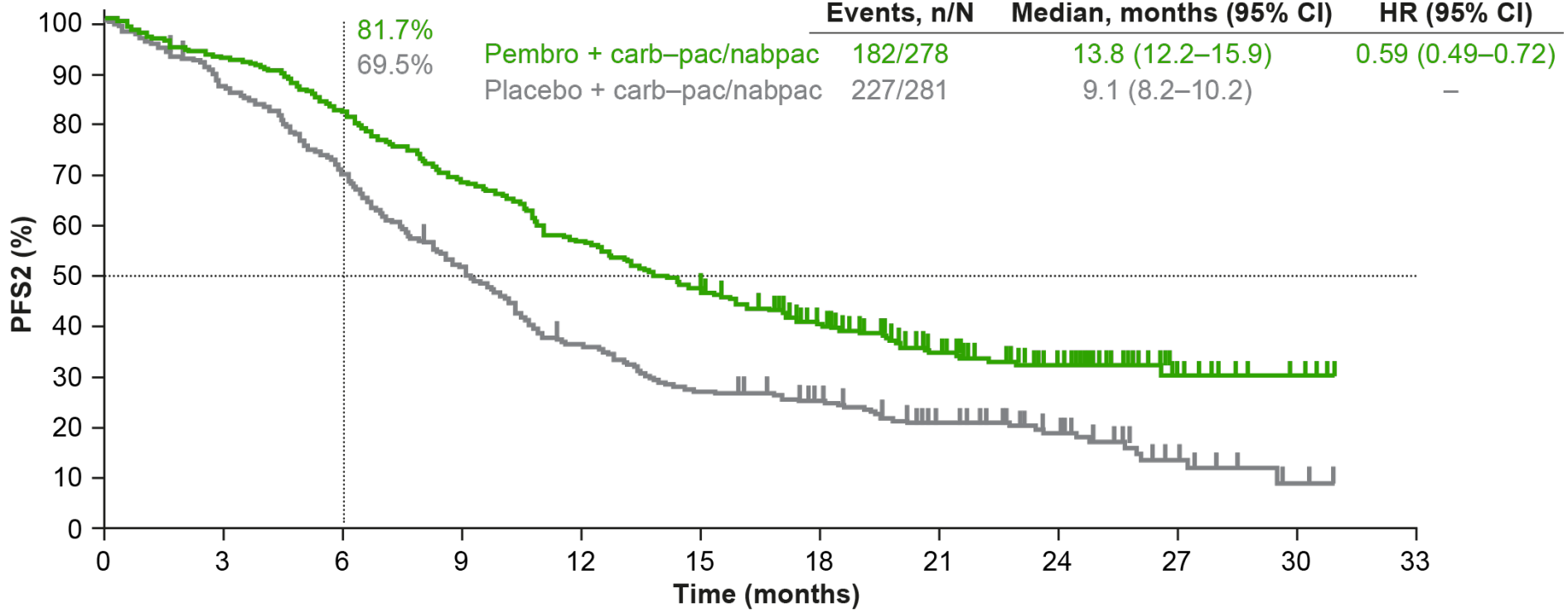
Data cut-off date: 3 April 2018.

[a]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.

KEYNOTE-407: Exploratory analysis – PFS2 (updated analysis)[1,2,a–c]

Median follow-up: 14.3 months. No statistical conclusions can be drawn from this analysis



	Events, n/N	Median, months (95% CI)	HR (95% CI)
Pembro + carb–pac/nabpac	182/278	13.8 (12.2–15.9)	0.59 (0.49–0.72)
Placebo + carb–pac/nabpac	227/281	9.1 (8.2–10.2)	–

No. at risk												
Pembro + carb–pac/nabpac	278	256	227	189	157	127	98	67	39	10	4	0
Placebo + carb–pac/nabpac	281	241	193	142	99	74	62	42	24	9	2	0

Adapted from Adapted from Paz-Ares L et al. J Thorac Oncol 2018; Paz-Ares L.et al ESMO 2019.

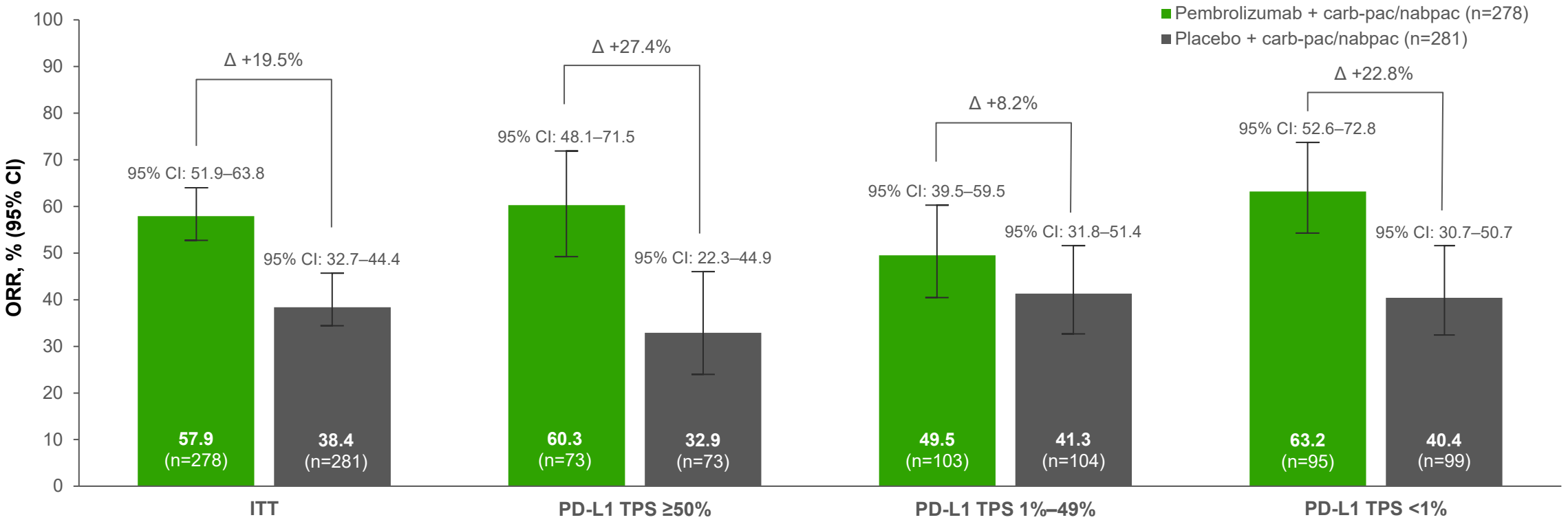
Data cut-off date: 9 May 2019.

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

1. Paz-Ares L *et al. J Thorac Onco* 2020 Oct;15(10):1657-1669; 2. Paz-Ares L *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 27 September – 1 October, 2019.

KEYNOTE-407: ORR in the ITT population and exploratory endpoint of ORR by PD-L1 TPS (original analysis)[1,a,b]

Median follow-up: 7.8 months. ORR was not subject to statistical testing at IA2 – no statistical conclusions can be drawn



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

Data cut-off date: 3 April 2018.

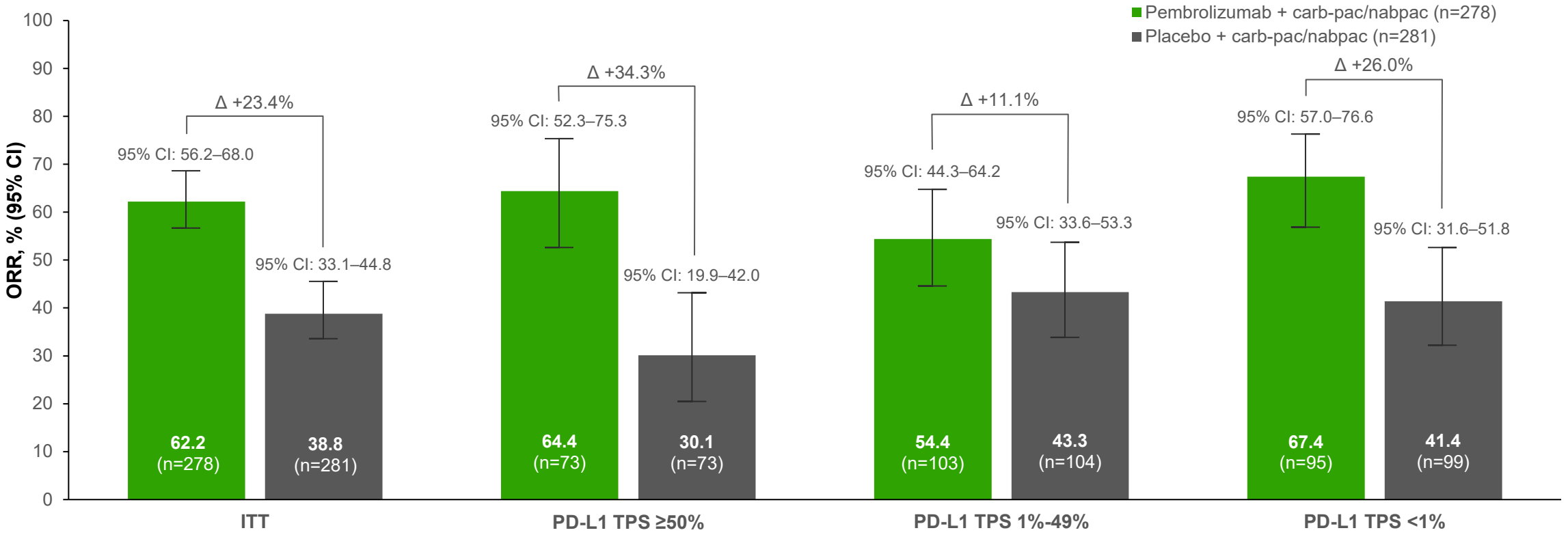
[a]At the first interim analysis (cut-off date: 27 October 2017), the response rate was formally tested and shown to be significantly higher in the pembrolizumab + carb-pac/nabpac group of 101 patients (58.4% [95% CI: 48.2–68.1%) than in the placebo + carb-pac/nabpac group of 103 patients (35.0% [95% CI: 25.8–45.0%]), p<0.001. [b]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 (and supplementary appendix).

1

KEYNOTE-407: Exploratory analysis – ORR in the ITT population and exploratory endpoint ORR by PD-L1 TPS (5-year update)[1,a]

Median follow-up: 56.9 months. No statistical conclusions can be drawn from this analysis



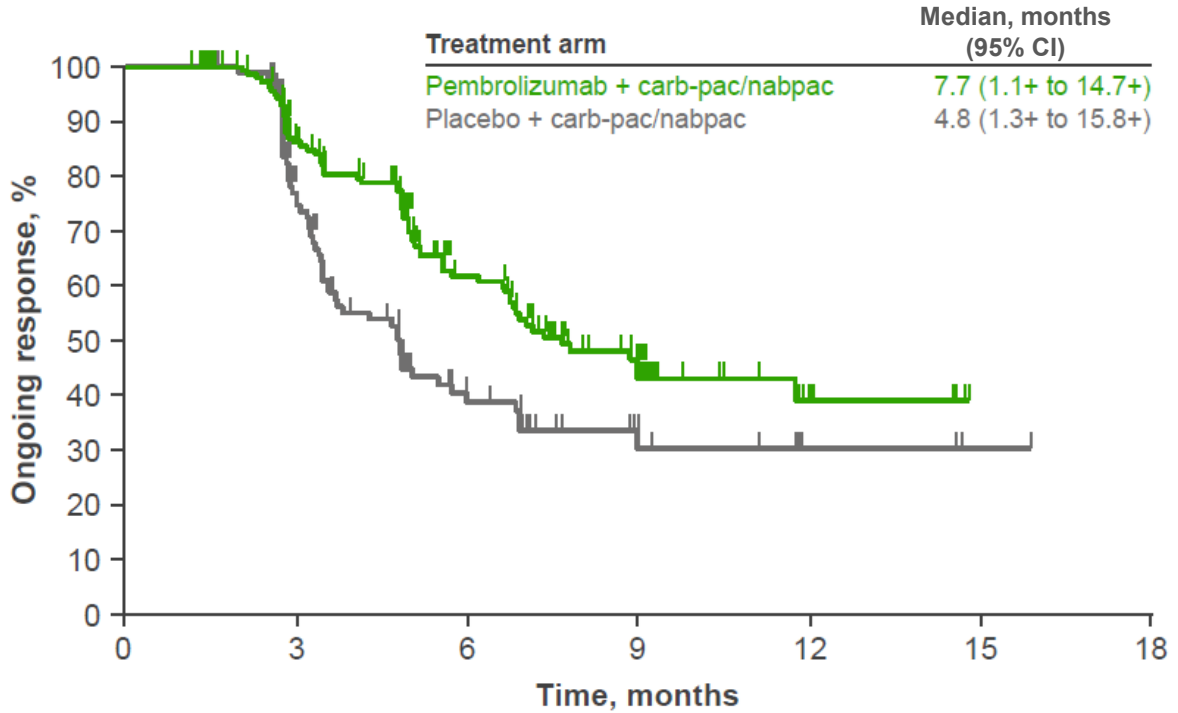
Adapted from Novello S et al. J Clin Oncol 2023.

Data cut-off date: 23 February 2022.
[a]Assessed using RECIST v1.1 by blinded, independent, central review.

1. Novello S *et al. J Clin Oncol* 2023; 41(11):1999–2006.

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

Median follow-up: 7.8 months. No statistical conclusions can be drawn from this analysis



No. at risk							
Pembrolizumab + carb-pac/nabpac	161	120	65	27	5	0	0
Placebo + carb-pac/nabpac	108	69	25	10	3	1	0

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

Data cut-off date: 3 April 2018.
[a]Kaplan-Meier estimate. [b]+ denotes a response that was ongoing at the analysis cut-off date. [c]Assessed using RECIST v1.1 by blinded, independent, central review.

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

1

KEYNOTE-407: Exploratory analysis – DOR in the ITT population and exploratory endpoint of DOR by PD-L1 TPS (5-year update)[1,a,b]

Median follow-up: 56.9 months. No statistical conclusions can be drawn from this analysis

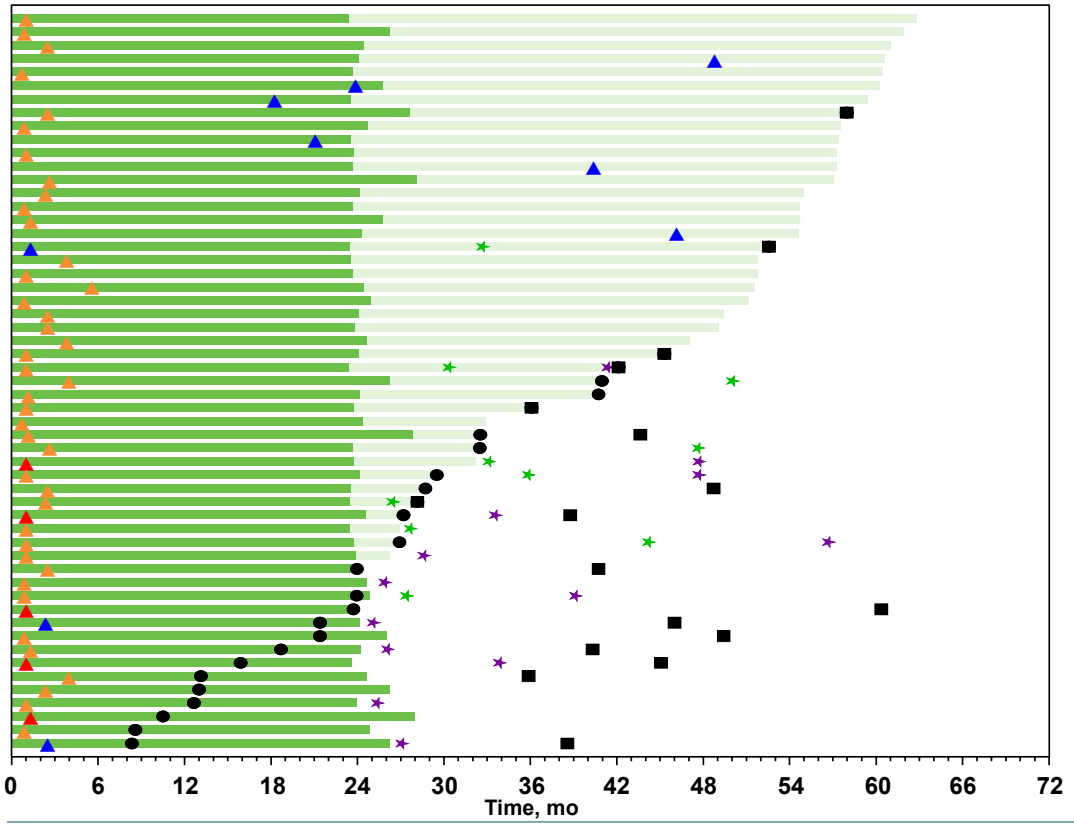
	ITT		PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembrolizumab + carb-pac/nabpac	Placebo + carb-pac/nabpac	Pembrolizumab + carb-pac/nabpac	Placebo + carb-pac/nabpac	Pembrolizumab + carb-pac/nabpac	Placebo + carb-pac/nabpac	Pembrolizumab + carb-pac/nabpac	Placebo + carb-pac/nabpac
DOR Median, months (95% CI)	9.0 (1.3+ to 61.5+)	4.9 (1.3+ to 58.6+)	10.4 (2.7 to 59.4+)	4.6 (1.3+ to 58.6+)	11.1 (1.3+ to 61.5+)	4.8 (2.0 to 58.6+)	6.9 (1.4+ to 58.9+)	5.7 (1.4+ to 55.8+)

Adapted from Novello S et al. 2023.

Data cut-off date: 23 February 2022.
[a]Assessed using RECIST v1.1 by blinded, independent, central review. [b]Kaplan-Meier estimates.
1. Novello S et al. *J Clin Oncol* 2023; 41(11):1999–2006.

KEYNOTE-407: Exploratory analysis – Outcomes in patients who completed 35 cycles of pembrolizumab (5-year update)[1,2]

Median follow-up: 56.9 months. No statistical conclusions can be drawn from this analysis



	(n=55)
ORR (95% CI),[a] %	90.9 (80.0–97.0)
Best overall response, n (%)	
CR	9 (16.4)
PR	41 (74.5)
Median DOR (range),[b] mo	NR (7.1 to 61.5+)
3-y OS rate after completing 35 cycles[c]	69.5%
Alive without PD or subsequent therapy, n (%)	24 (43.6)

CR
PR
SD
PD
Death
First course follow-up
First course treatment
Second-course pembrolizumab
Began subsequent therapy

Adapted from Novello S et al. J Clin Oncol 2023; Novello S et al ESMO 2022.

Data cut-off date: 23 February 2022.
[a]Assessed using RECIST v1.1 by blinded, independent, central review. [b]Kaplan-meier estimates. [c]Approximately 5 years after randomisation.

1. Novello S et al. *J Clin Oncol* 2023; 41(11):1999–2006; 2. Novello S et al. Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

KEYNOTE-407: Exposure to study treatment (original analysis)[1]

Median follow-up: 7.8 months

n (%)[a]	Pembrolizumab + carb-pac/nabpac (n=278)	Placebo + carb-pac/nabpac (n=280)
Treatment duration, months, mean (SDev)	6.3 (4.1)	4.7 (3.5)
Treatment cycles		
Mean (SDev)	9.3 (5.8)	7.3 (5.0)
Median (range)	8 (1–27)	6 (1–27)
4 doses of carboplatin	219 (78.8)	205 (73.2)
4 doses of paclitaxel	133/169 (78.7)	119/167 (71.3)
5–11 doses of nab-paclitaxel	72/109 (66.1)	73/113 (64.6)
12 doses of nab-paclitaxel	25/109 (22.9)	24/113 (21.2)
≥5 doses of pembrolizumab or placebo	214 (77.0)	189 (67.5)

Adapted from Paz-Ares L et al. ASCO 2018.

Data cut-off date: 3 April 2018.
[a]Unless otherwise stated.

1. 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.

1

KEYNOTE-407: Summary of AEs in all treated patients (5-year update)[1,2]

Median follow-up: 56.9 months

Adverse event, n (%)	All treated patients		35 cycles of pembrolilzumab (n=55)
	Pembrolizumab + carb-pac/nabpac (n=278)	Placebo + carb-pac/nabpac (n=280)	
Any	274 (98.6)	275 (98.2)	55 (100)
Grade 3–5	208 (74.8)	196 (70.0)	35 (63.6)
Led to treatment discontinuation[a]			
Any treatment	80 (28.8)	37 (13.2)	3 (5.5)
All treatments	48 (17.3)	21 (7.5)	0
Led to death	32 (11.5)	20 (7.1)	0
Immune-mediated AEs and infusion reactions[b]	99 (35.6)	26 (9.3)	21 (38.2)
Grade 3–5	37 (13.3)	9 (3.2)	1 (1.8)[c]

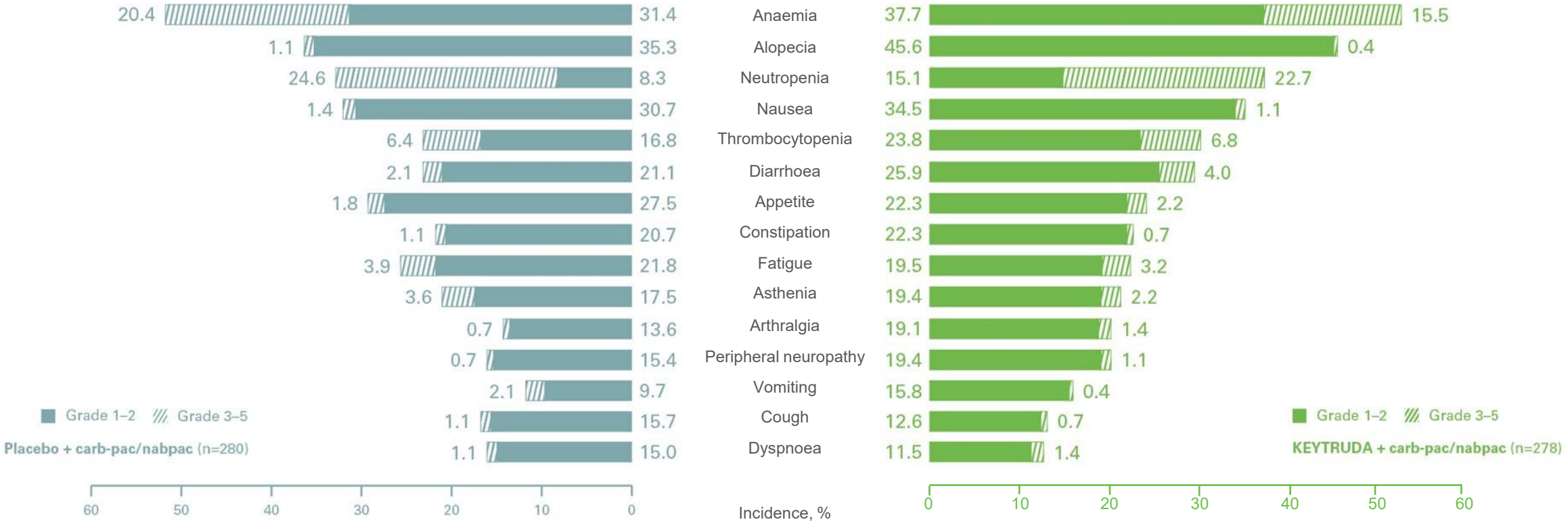
Adapted from Novello S et al. J Clin Oncol 2023; Novello S et al. ESMO 2022.

Data cut-off date: 23 February 2022.
[a]Includes patients who discontinued pembrolizumab or placebo, carboplatin, and taxane owing to an AE at any time and patients who discontinued pembrolizumab or placebo owing to an AE after completing four 3-week cycles of carboplatin and taxane. [b]Events considered regardless of attribution to treatment or immune relatedness by the investigator. [c]There was 1 Grade 3 event of colitis; there were no Grade 4 or Grade 5 immune-mediated AEs or infusion reactions among patients who completed 35 cycles of pembrolizumab.

1. Novello S et al. *J Clin Oncol* 2023; 41(11):1999–2006; Novello S et al. Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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.

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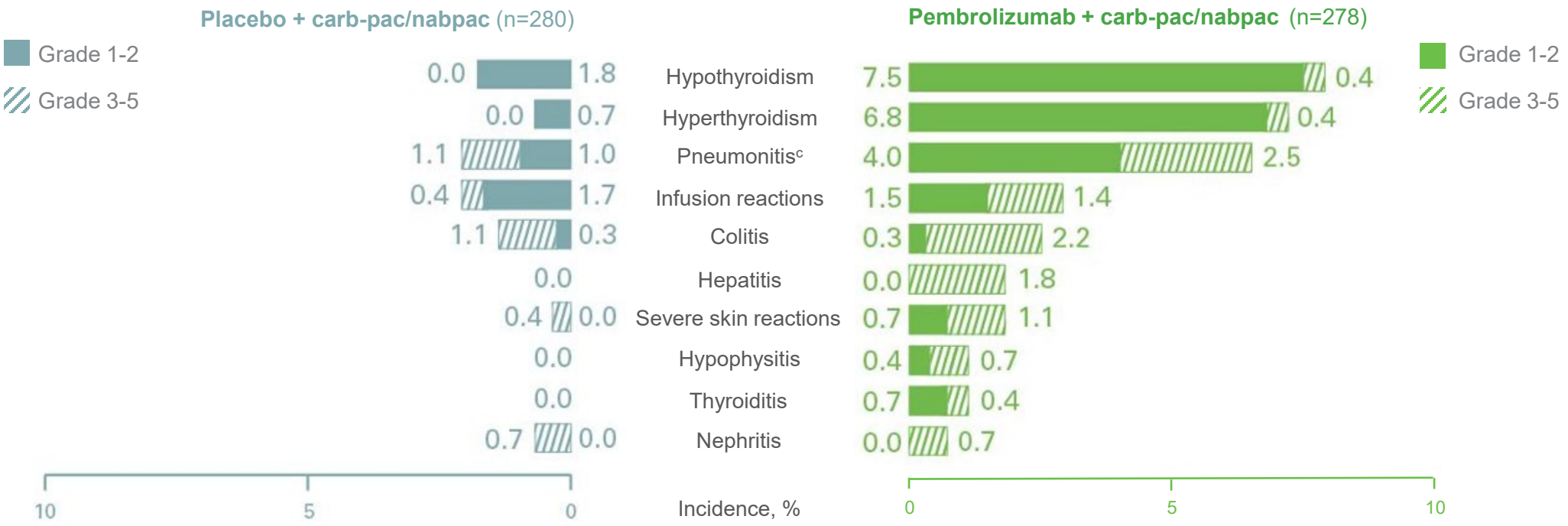
Data cut-off date: 3 April 2018.
[a]AEs that occurred during crossover from the placebo + carb-pac/nabpac group to pembrolizumab monotherapy were excluded. [b]AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

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.

KEYNOTE-407: Exploratory endpoint – QLQ-C30 completion and compliance rates[1,a,b]

Median follow-up: 7.8 months. No statistical conclusions can be drawn from exploratory endpoints

		Pembrolizumab + carb-pac/nabpac (n=276), n (%)	Placebo + carb-pac/nabpac (n=278), n (%)
Baseline		254 (92.0)	264 (95.0)
Week 3	Completion	228 (82.6)	237 (85.3)
	Compliance	228/265 (86.0)	237/266 (89.1)
Week 6	Completion	226 (81.9)	204 (73.4)
	Compliance	226/253 (89.3)	204/251 (81.3)
Week 9	Completion	187 (67.8)	199 (71.6)
	Compliance	187/233 (80.3)	199/225 (88.4)
Week 12	Completion	194 (70.3)	177 (63.7)
	Compliance	194/227 (85.5)	177/224 (79.0)
Week 15	Completion	191 (69.2)	165 (59.4)
	Compliance	191/224 (85.3)	165/201 (82.1)
Week 18	Completion	191 (69.2)	162 (58.3)
	Compliance	191/217 (88.0)	162/187 (86.6)

Adapted from Mazieres J et al. J Clin Oncol 2020.

Data cut-off date: 3 April 2018.

[a]Completion rate was defined as the proportion of patients in the analysis population at each time point who completed ≥ 1 assessment. [b]Compliance rate was defined as the percentage of patients who completed the PRO questionnaire among those who were expected to complete the instrument at each time point (e.g. those who had not discontinued study treatment).

1. Mazieres J *et al. J Clin Oncol* 2020;38:271–280.

KEYNOTE-407: Exploratory endpoint – QLQ-LC13 completion and compliance rates[1,a,b]

Median follow-up: 7.8 months. No statistical conclusions can be drawn from exploratory endpoints

		Pembrolizumab + carb-pac/nabpac (n=275), n (%)	Placebo + carb-pac/nabpac (n=278), n (%)
Baseline		252 (91.6)	263 (94.6)
Week 3	Completion	227 (82.5)	237 (85.3)
	Compliance	227/265 (85.7)	237/266 (89.1)
Week 6	Completion	226 (82.2)	204 (73.4)
	Compliance	226/253 (89.3)	204/251 (81.3)
Week 9	Completion	187 (68.0)	197 (70.9)
	Compliance	187/233 (80.3)	197/225 (87.6)
Week 12	Completion	192 (69.8)	175 (62.9)
	Compliance	192/227 (84.6)	175/224 (78.1)
Week 15	Completion	191 (69.5)	164 (59.0)
	Compliance	191/224 (85.3)	164/201 (81.6)
Week 18	Completion	191 (69.5)	162 (58.3)
	Compliance	191/217 (88.0)	162/187 (86.6)

Adapted from Mazieres J et al. J Clin Oncol 2020.

Data cut-off date: 3 April 2018.

[a]Completion rate was defined as the proportion of patients in the analysis population at each time point who completed ≥ 1 assessment. [b]Compliance rate was defined as the percentage of patients who completed the PRO questionnaire among those who were expected to complete the instrument at each time point (e.g. those who had not discontinued study treatment).

1. Mazieres J *et al. J Clin Oncol* 2020;38:271–280.

KEYNOTE-407: Exploratory endpoint – Change from baseline to weeks 9 and 18 in EORTC QLQ-C30 GHS/QoL scores[1]

Median follow-up: 7.8 months. No statistical conclusions can be drawn from exploratory endpoints

	Pembrolizumab + carb-pac/nabpac (n=276)	Placebo+ carb-pac/nabpac (n=278)
Baseline, mean (SDev)	n=254 63.9 (20.4)	n=264 62.7 (21.3)
Week 9, mean (SDev)	n=187 66.0 (18.5)	n=199 62.1 (19.6)
Change from baseline to week 9,[a,b] LS mean (95% CI)	n=276 1.8 (-0.9 to 4.4)	n=278 -1.8 (-4.4 to 0.7)
Difference in LS mean between treatment groups (95% CI)	3.6 (0.3 to 6.9) *p*=0.0337[c]	
Week 18, mean (SDev)	n=191 68.9 (19.3)	n=162 65.2 (17.1)
Change from baseline to week 18,[a,b] LS mean (95% CI)	n=276 4.3 (1.7 to 6.9)	n=278 -0.6 (-3.3 to 2.2)
Difference in LS mean between treatment groups (95% CI)	4.9 (1.4 to 8.3) *p*=0.0060[c]	

Adapted from Mazieres J et al. J Clin Oncol 2020.

Data cut-off date: 3 April 2018.
[a]Key PRO endpoint. [b]Based on cLDA model with EORTC QLQ-C30 global health status/ quality of life scores as the response variable and treatment-by-study-visit interaction, and randomisation stratification factors as covariates. [c]p values are 2-sided and nominal.

1. Mazieres J *et al. J Clin Oncol* 2020;38:271–280.

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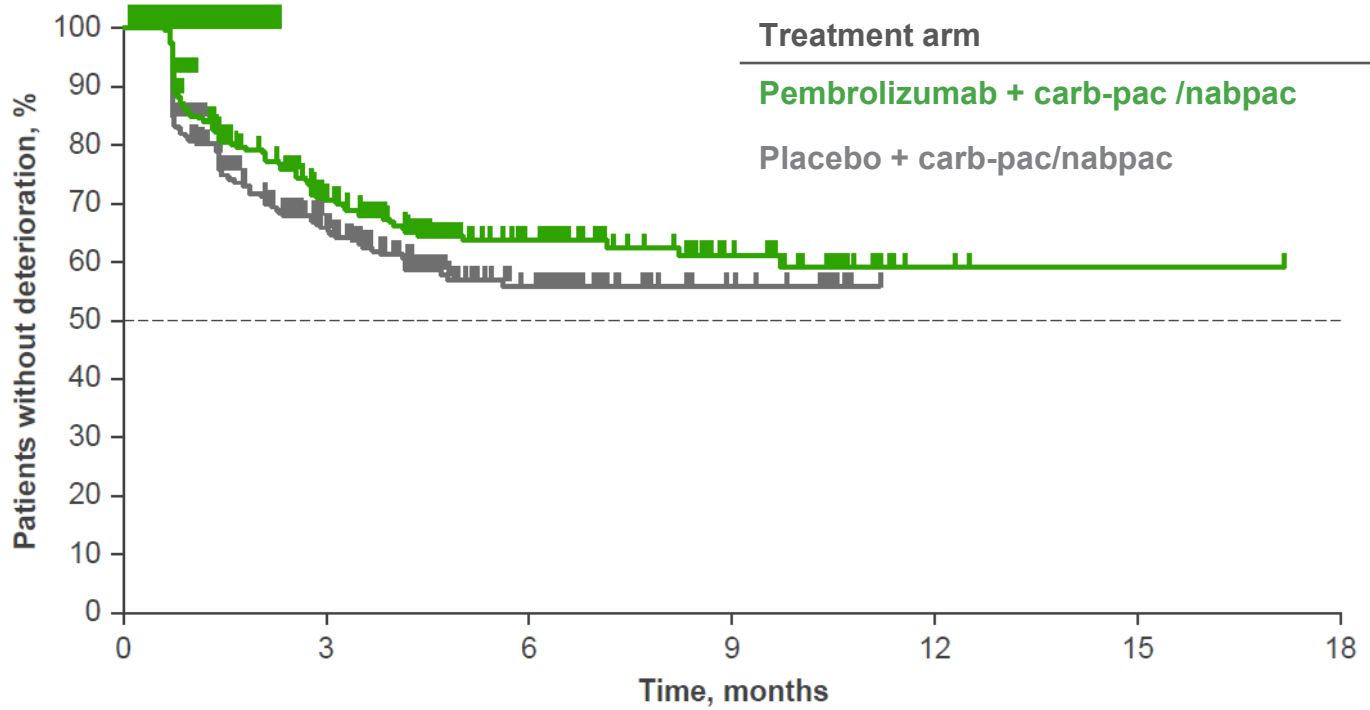
KEYNOTE-407: Exploratory endpoint – Time to deterioration in composite endpoint of cough, chest pain or dyspnoea[1,a]

Median follow-up: 7.8 months. No statistical conclusions can be drawn from exploratory endpoints



Treatment arm	Events, n (%)	HR (95% CI)	p value
Pembrolizumab + carb-pac /nabpac	81 (29.3)	0.79	0.125[b]
Placebo + carb-pac/nabpac	94 (33.8)	(0.58–1.06)	

Adapted from Mazieres J et al. J Clin Oncol 2020.

Data cut-off date: 3 April 2018.
[a]Key PRO endpoint. [b]p values are 2-sided and nominal, based on the stratified log-rank test.

1. Mazieres J *et al. J Clin Oncol* 2020;38:271–280.

KEYNOTE-407: Exploratory endpoint – EORTC QLQ-C30 GHS/QoL[1]

Median follow-up: 7.8 months. No statistical conclusions can be drawn from exploratory endpoints

Mean QLQ-C30 GHS/QoL scores:[a]

- Were above baseline at all time points for the pembrolizumab + carb-pac/nabpac group (Weeks 3–36)
  - The largest improvements were observed from Weeks 18–36
- Were below baseline at all time points for the placebo + carb-pac/nabpac group (Weeks 3–36)

Changes in QLQ-C30 GHS/QoL status:

- In comparison to placebo + carb-pac/nabpac group:
  - Fewer patients reported a deterioration in GHS/QoL status (Week 9: 26.1% vs 29.5%; Week 18: 22.8% vs 31.3%) in the pembrolizumab + carb-pac/nabpac group
  - More patients reported an improvement in GHS/QoL status (Week 9: 30.4% vs 24.5%; Week 18: 36.2% vs 27.7%) in the pembrolizumab + carb-pac/nabpac group

Data cut-off date: 3 April 2018.
[a]Key PRO endpoint.

1. Mazieres J *et al. J Clin Oncol* 2020;38:271–280.

1

KEYNOTE-407: Exploratory endpoint – EORTC QLQ-C30 functional and symptom subscale scores[1]

Median follow-up: 7.8 months. No statistical conclusions can be drawn from exploratory endpoints

QLQ-C30 functional scales:

- Change from baseline scores were numerically superior for the pembrolizumab + carb-pac/nabpac group vs. the placebo + carb-pac/nabpac group for all functional scales at week 9 and week 18
  - In the pembrolizumab + carb-pac/nabpac group, there were minimal changes from baseline in physical, cognitive, role and social function scales at weeks 9 and 18. Improvements in emotional functioning scores occurred at both time points in this group
  - Scores declined from baseline for physical and role functioning in the placebo + carb-pac/nabpac group at week 9 and week 18. Minimal changes were also reported for cognitive and social functioning but improvements in emotional functioning occurred at both time points

QLQ-C30 symptom scales:

- Change from baseline scores improved in most scales at week 9, with further improvements at week 18 in both treatment groups
- At week 9 and 18, the pembrolizumab + carb-pac/nabpac group was numerically superior with regard to fatigue, pain, dyspnoea and insomnia, whereas the placebo + carb-pac/nabpac group group was numerically superior in the nausea/vomiting, appetite loss, constipation and diarrhoea scales
- Financial difficulties were worse in pembrolizumab + carb-pac/nabpac group at week 9 compared to the placebo + carb-pac/nabpac; however, at week 18 these were worse in the placebo + carb-pac/nabpac vs the pembrolizumab + carb-pac/nabpac group

Data cut-off date: 3 April 2018.

1. Mazieres J *et al. J Clin Oncol* 2020;38:271–280.

1

KEYNOTE-407: Efficacy summary

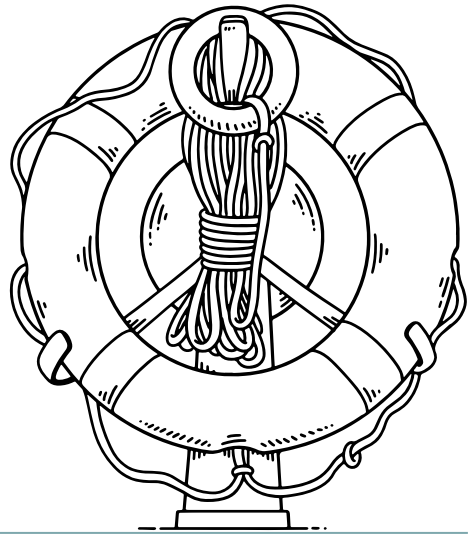
- Treatment with pembrolizumab + carb-pac/nabpac in patients with untreated, metastatic, squamous NSCLC demonstrated (compared with placebo + carb-pac/nabpac):[1]
  - Superior OS, with a 36% reduction in the risk of death (HR: 0.64, p<0.001)
  - Superior PFS, with a 44% reduction in the risk of progression or death (HR: 0.56, p<0.001)
  - Treatment effect on OS was consistent across all PD-L1 subgroups, including the <1% and 1–49% subgroups[a]
  - Improved ORR (57.9% vs. 38.4%) and median DOR (7.7 vs. 4.8 months) was observed[b,c]
- In the 5-year follow-up, treatment with pembrolizumab + carb-pac/nabpac continued to demonstrate an OS and PFS benefit in patients with previously untreated, metastatic, squamous NSCLC compared with placebo + carb-pac/nabpac (median follow-up: 56.9 months; p not tested)[2]
  - Benefits were observed despite an effective crossover rate of 50.9%[2]
  - OS and PFS benefits were seen irrespective of baseline PD-L1 expression[2]
- Patients who received 35 cycles of pembrolizumab had durable responses, and experienced long-term OS[2]

[a]PD-L1 subgroup analyses were exploratory endpoints – no statistical conclusions can be drawn. [b]Not tested for significance – no statistical conclusions can be drawn. [c]At the first interim analysis (Data cut-off date: 27 October 2017), the response rate was formally tested and shown to be significantly higher in the pembrolizumab + carb-pac/nabpac group of 101 patients (58.4% [95% CI: 48.2–68.1%) than in the placebo + carb-pac/nabpac group of 103 patients (35.0% [95% CI: 25.8–45.0%]), p<0.001.

1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051 (and supplementary appendix); 2. Novello S et al. *J Clin Oncol* 2023; 41(11):1999–2006.

KEYNOTE-407: Safety summary

- Pembrolizumab + carb-pac/nabpac displayed a generally manageable tolerability profile[1]
- The frequency of AEs for the combination was observed to be higher than that for each agent alone, reflecting the contributions of each agent[1]
- Rates of discontinuation were shown to be higher with pembrolizumab + carb-pac/nabpac[1]
- In the 5-year follow-up, toxicity was manageable, which was consistent with previous reports[2]

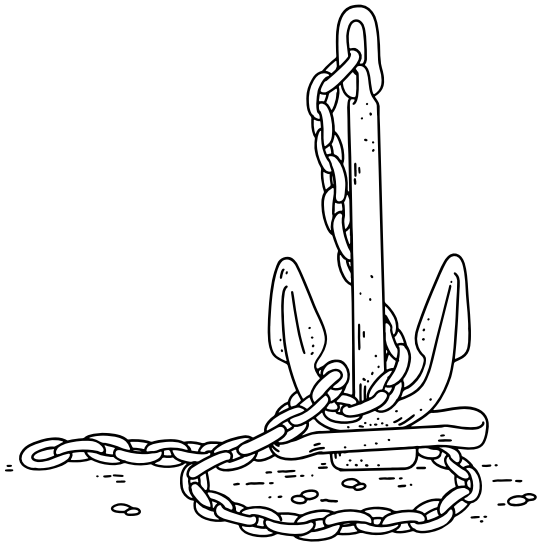


1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051; 2. Novello S et al. *J Clin Oncol* 2023; 41(11):1999–2006.

KEYNOTE-407: HRQoL summary

HRQoL was an exploratory endpoint. No statistical conclusions can be drawn from exploratory endpoints

- Pembrolizumab + carb-pac/nabpac maintained or improved QoL compared with baseline, and improved QoL compared with placebo + carb-pac/nabpac[1]
- At Weeks 9 and 18, patients who received pembrolizumab + carb-pac/nabpac had improved GHS/QoL scores compared with baseline and those who received placebo + carb-pac/nabpac[1]
- Pembrolizumab + carb-pac/nabpac showed a numerical improvement in time to deterioration in cough, chest pain or dyspnoea compared with the control group (HR: 0.79, 95% CI: 0.58–1.06; p=0.125); the median time to deterioration in this endpoint was not reached in either group[1]
- In KEYNOTE-407, the HRQoL findings, along with the improved efficacy seen in the pembrolizumab + carb-pac/nabpac, support its use as first-line therapy for patients with metastatic squamous NSCLC[1]



1. Mazieres J *et al. J Clin Oncol* 2020;38:271–280.

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]

47

***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]

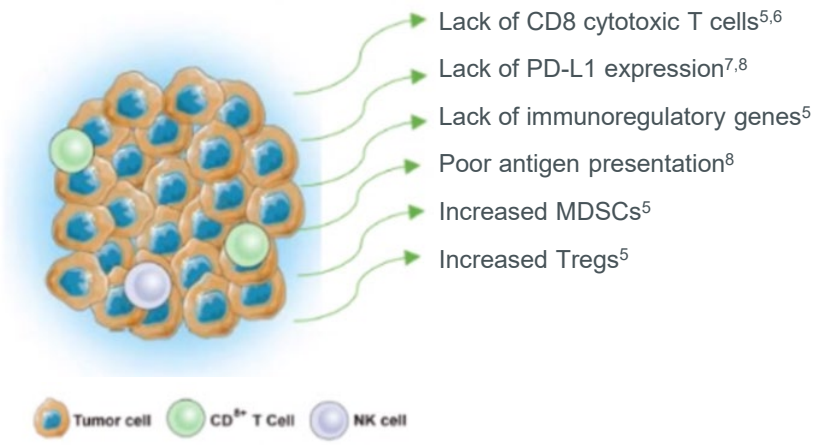
Absence of tumour-specific T cells is a mechanism of primary resistance to ICBs [2]

This is a hypothesis based on experimental models

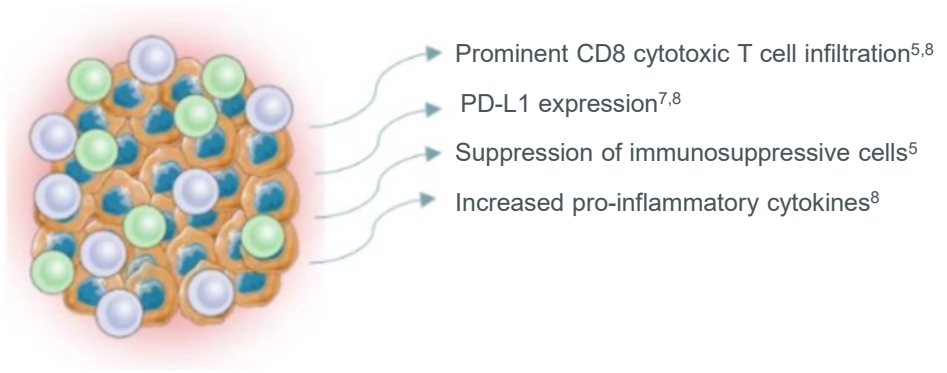
Effective combination therapy can turn cold tumours into hot tumours that are sensitive to ICBs[2]

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
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
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 after second-line therapy
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
TME	Tumour microenvironment
TPS	Tumour proportion score

OS	PFS	ORR / DOR	Safety	HRQoL
ITT	ITT	ORR (ITT + PD-L1 TPS)	AEs	QLQ-C30
PD-L1 TPS	PD-L1 TPS	DOR (ITT [original analysis])	All cause AEs	QLQ-LC13
Key subgroups	Key subgroups	DOR (ITT + PD-L1 TPS [5 year])	Immune mediated AEs	Time to deterioration
	PFS2			

KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/2498/smpc.
Please note that clicking this link 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
Please note that clicking this link will redirect you to external websites, for which MSD does not review or control the content.