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.

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

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

GB-PDO-02656. Date of preparation August 2023

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 NSLC indications licensed in the UK[1–7]

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

KEYTRUDA® (pembrolizumab)

MSD

External websites and abbreviations

Links to external sites

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

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

Abbreviations

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

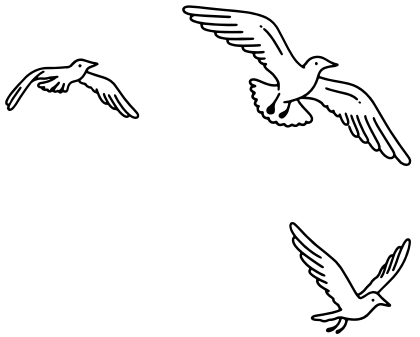
There is an urgent unmet need for treatment options for patients with mNSCLC and low PD-L1 expression

- Patient outcomes remain suboptimal with standard chemotherapeutics and durable disease control is rarely achieved[1,2]
- The median OS is 8–12 months for patients receiving supportive care in addition to induction platinum-based chemotherapy[2]
- Many patients may not survive long enough to receive second-line therapy[3]
- When they are treated first-line with chemotherapy alone, they have lower chances of survival and progression to option second-line treatment[3]
- High expressors (TPS ≥50%) with no contraindications to use of immunotherapy:
  KEYTRUDA monotherapy is a standard first-line option[4]

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

1. Leonetti A *et al. Drug Resist Updat* 2019;46:100644; 2. Chen Q *et al. Nanomicro Lett* 2021;13:92; 3. Bazhenova L *et al Cancer Treat Res Commun* 2022;33:100637; 4. ESMO Guidelines. Available at: https://www.esmo.org/content/download/227453/3874538; 5. Aujla S et al. J Thorac Oncol 2022;17:675–687; 6. Holmen Olofsson G *et al. Int J Mol Sci* 2020;21:3816.

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

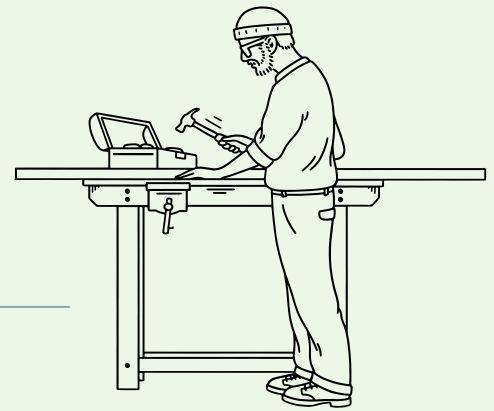


- Highest level of evidence (**I**) and recommendation grade (**A**)
- Established as a **standard treatment option** for patients with any PD-L1 score and PS 0–1
- Magnitude of clinical benefit recognised with an **ESMO-MCBS score of 4**

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

KEYTRUDA® (pembrolizumab) metastatic NSCLC indications

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



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

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

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]
5-year follow-up	23 February 2022	2	56.9 (49.9–66.2)[2]

1. Paz-Ares L *et al. N Engl J Med* 2018;379:2040–2051; 2. Novello S et al. Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

KEYNOTE-407: KEYTRUDA

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

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

KEYNOTE-407: Study design[1–3]

Randomised, double-blind, Phase 3 trial

Key eligibility criteria

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

R
1:1
(N=559)

n=278

Pembrolizumab 200 mg Q3W + carboplatin AUC 6 mg/ml/min Q3W + paclitaxel 200 mg/m^2 Q3W OR nab-paclitaxel 100 mg/m^2 Q1W for 4 cycles Q3W

Pembrolizumab 200 mg Q3W (up to 31 cycles)

n=281

Placebo (normal saline) Q3W + carboplatin AUC 6 mg/ml/min Q3W + paclitaxel 200 mg/m^2 Q3W OR nab-paclitaxel 100 mg/m^2 Q1W for 4 cycles Q3W

Placebo (normal saline) Q3W (up to 31 cycles)

PD[c]

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

Stratification factors

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

Endpoints

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

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)

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.

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

KEYNOTE-407: Statistical considerations (updated analyses)

5-year update

Analysis cut-off date: 23 February 2022

Results presented: ESMO 2022

Median follow-up: 56.9 months (range: 49.9–66.2 months)

- This analysis was not subject to further significance testing

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

KEYNOTE-407: Disposition of study treatment[1,2]

Median follow up: 7.8 months

559 patients randomly allocated

Pembrolizumab + carb-pac/nabpac
- 278 allocated
- 278 treated

- 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
- 280 treated

- 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.

Analysis 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

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)

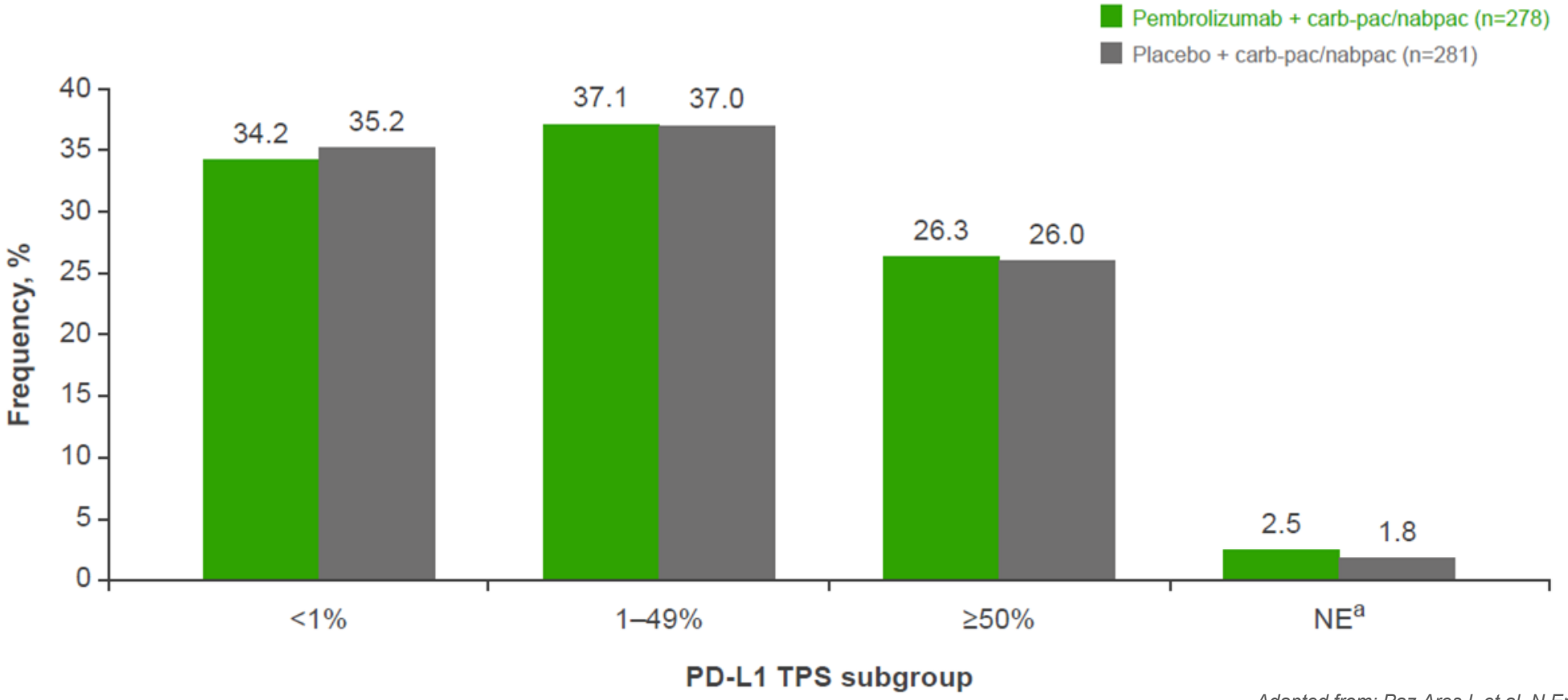
Adapted from: Paz-Ares L et al. N Engl J Med 2018.

Analysis 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.

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

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

Median follow up: 7.8 months



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

13

Analysis 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.

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

1

KEYNOTE-407: Primary endpoint outcomes[a,1–3]

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 (median follow up: 7.8 months)[1,2]

- 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 (median follow up: 56.9 months)[3]

- 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

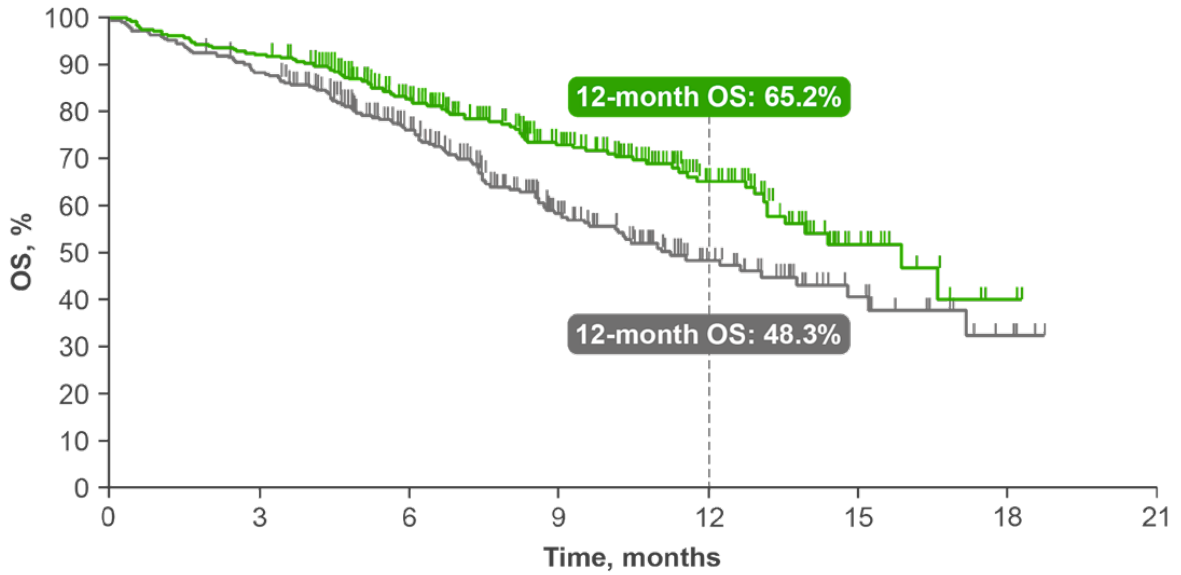
[a]**OS and PFS were both primary endpoints.**

1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051; 2. Paz-Ares L et al. Presented at the 2019 European Society for Medical Oncology (ESMO) Congress, 27 September–1 October 2019, Barcelona, Spain; 3. Novello S *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

Median follow up: 7.8 months

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

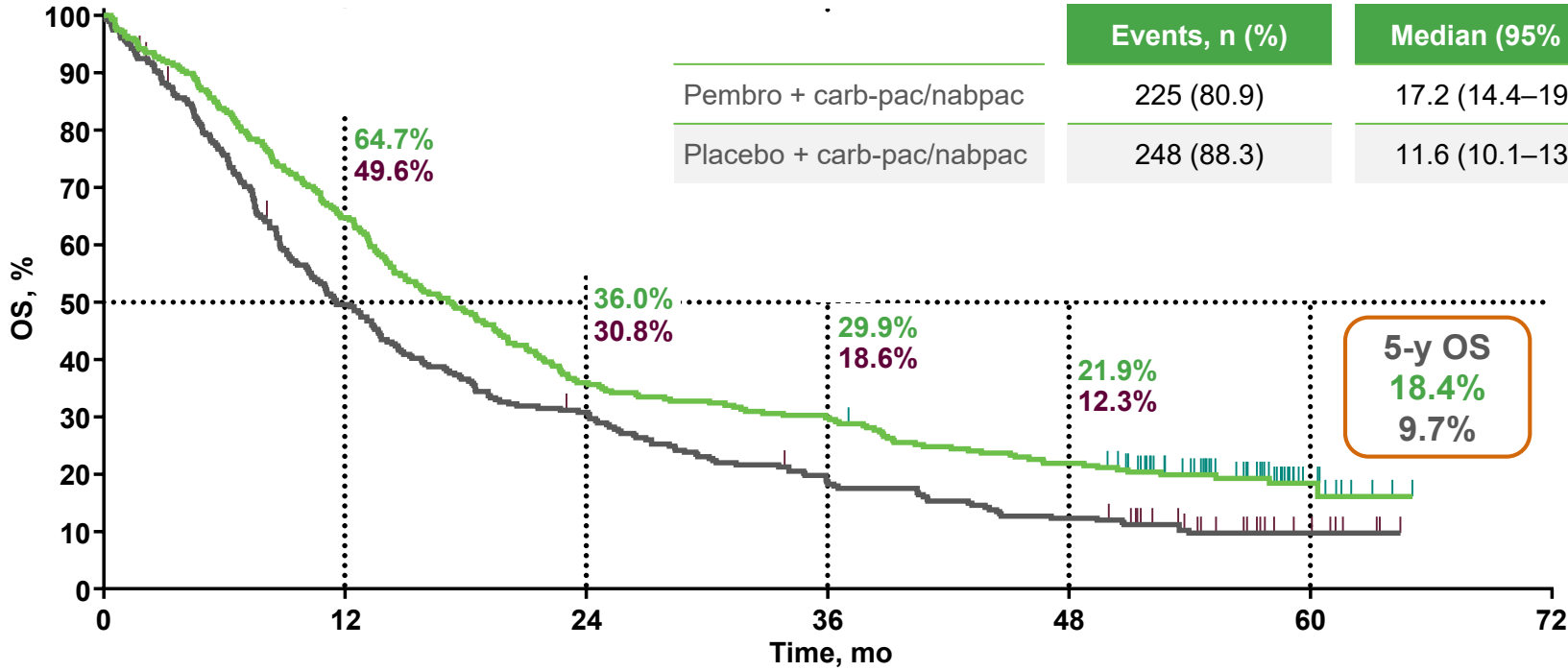
Adapted from: Paz-Ares L et al. N Engl J Med 2018 (and supplementary appendix).

Analysis cut-off date: 3 April 2018.
[a]OS and PFS were both primary endpoints. [b]Curves are Kaplan–Meier estimates.
Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051 (and supplementary appendix).

KEYNOTE-407: OS in the ITT population in the 5-year update

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

Median follow up: 56.9 months. No statistical conclusions can be drawn from exploratory endpoints.



	Events, n (%)	Median (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)	

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. ESMO 2022.

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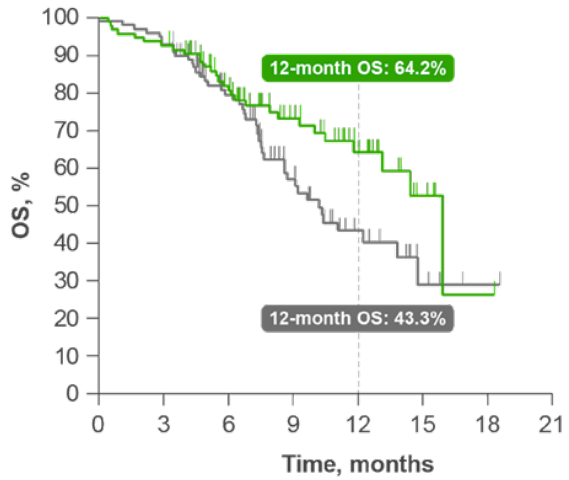
Analysis cut-off date: 23 February 2022. No statistical conclusions can be drawn from this analysis.
[a]OS and PFS were both primary endpoints. [b]Curves are Kaplan–Meier estimates.
Novello S *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

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

TPS <1%

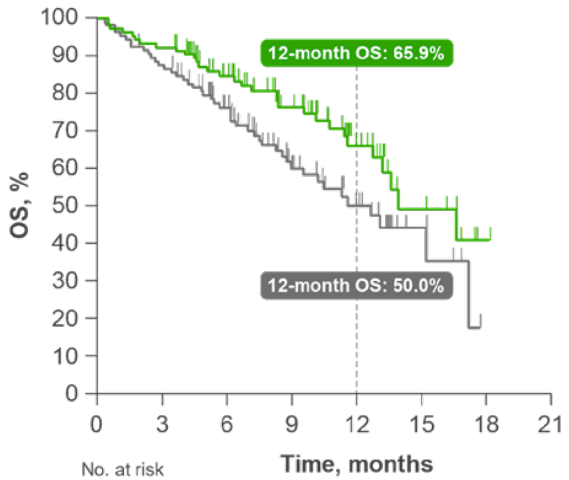
Treatment arm	Events, %	Median (95% CI), months	HR (95% CI)
Pembrolizumab + carb-pac/nabpac	30.5	15.9 (13.1–NE)	0.61 (0.38–0.98)
Placebo + carb-pac/nabpac	44.4	10.2 (8.6–13.8)	—



No. at risk								
Pembrolizumab + carb-pac/nabpac	95	88	62	41	20	5	1	0
Placebo + carb-pac/nabpac	99	92	63	32	14	4	1	0

TPS 1–49%

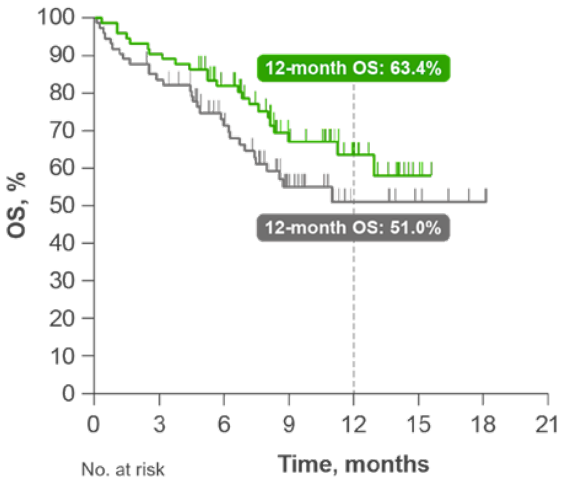
Treatment arm	Events, %	Median (95% CI), months	HR (95% CI)
Pembrolizumab + carb-pac/nabpac	30.1	14.0 (12.8–NE)	0.57 (0.36–0.90)
Placebo + carb-pac/nabpac	43.3	11.6 (8.9–17.2)	—



No. at risk								
Pembrolizumab + carb-pac/nabpac	103	95	68	50	25	9	1	0
Placebo + carb-pac/nabpac	104	90	66	37	21	6	0	0

TPS ≥50%

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

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

Analysis cut-off date: 3 April 2018.
[a]No statistical conclusions can be drawn from exploratory endpoints. [b]Curves are Kaplan–Meier estimates.
Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051 (and supplementary appendix).

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

Median follow up: 56.9 months. No statistical conclusions can be drawn from exploratory endpoints.

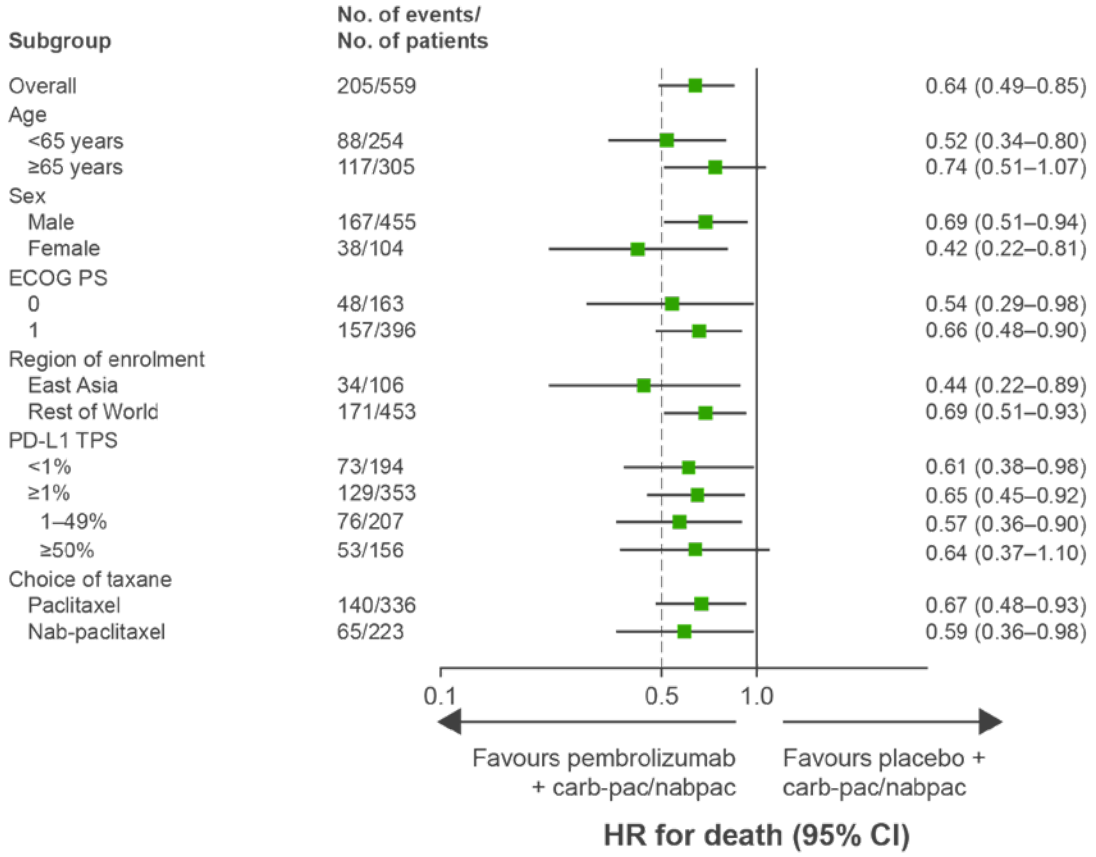
	PD-L1 TPS ≥50%		PD-L1 TPS 1%-49%		PD-L1 TPS <1%	
	Pembro + carb-pac/nabpac (n = 73)	Placebo + carb-pac/nabpac (n = 73)	Pembro + carb-pac/nabpac (n = 103)	Placebo + carb-pac/nabpac (n = 104)	Pembro + carb-pac/nabpac (n = 95)	Placebo + carb-pac/nabpac (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.65 (0.46–0.90)		0.83 (0.61–1.13)	
5-y PFS rate,[b] %	23.3	8.3	20.6	7.6	10.7	13.1

Adapted from Novello S et al. ESMO 2022.

Analysis cut-off date: 23 February 2022.
[a]No statistical conclusions can be drawn from exploratory endpoints. [b]Kaplan-Meier estimate.
Novello S *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

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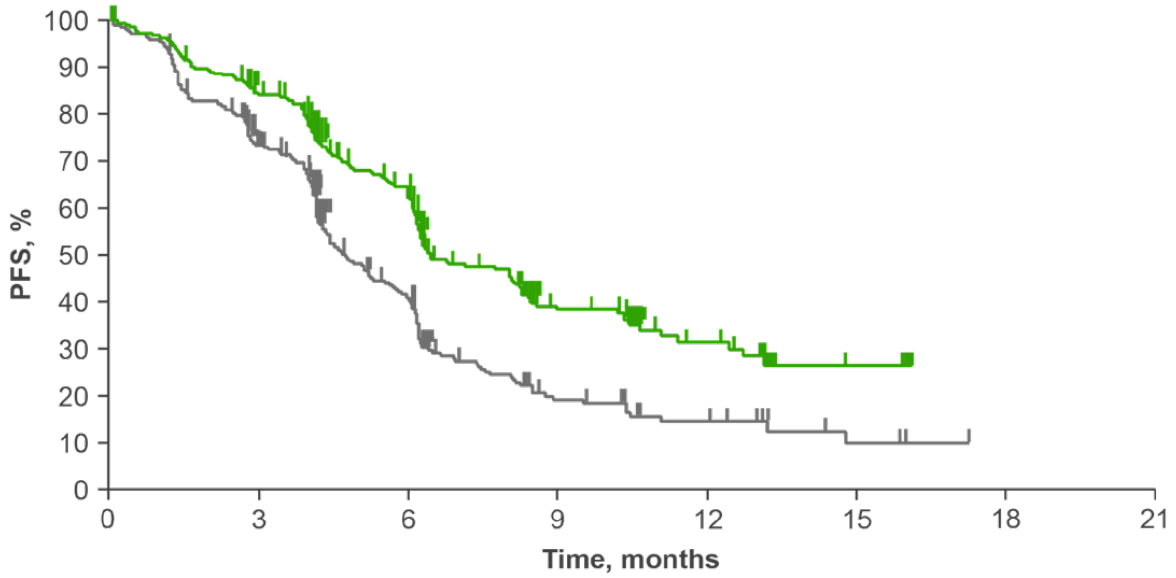
Analysis cut-off date: 3 April 2018.
[a]No statistical conclusions can be drawn from exploratory endpoints.
Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051.

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

Median follow up: 7.8 months

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

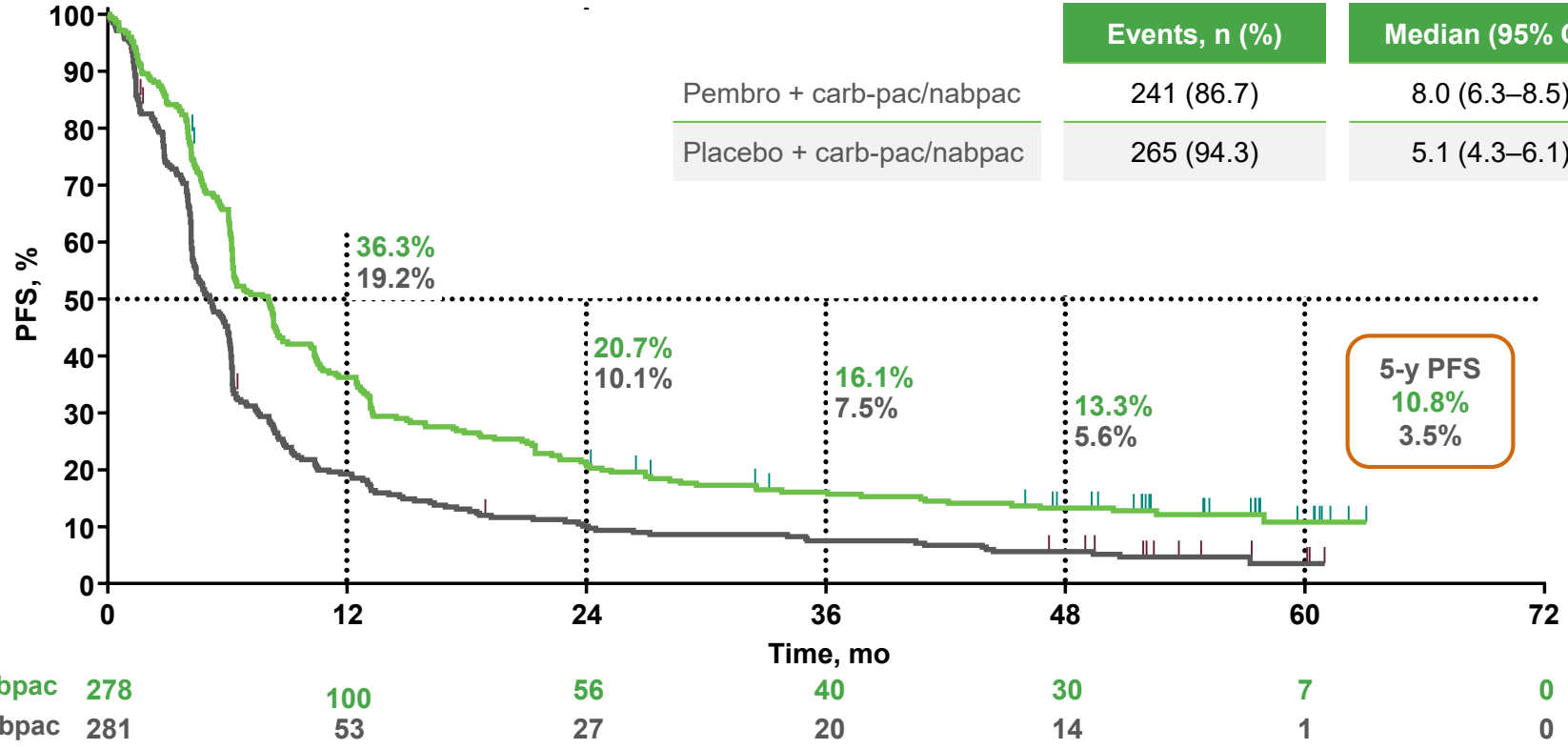
Analysis cut-off date: 3 April 2018.
[a]OS and PFS were both primary endpoints. [b]PFS was assessed using RECIST v1.1 by blinded, independent, central radiological review. [c]Curves are Kaplan–Meier estimates.
Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051 (and supplementary appendix).

KEYNOTE-407: PFS in the ITT population in the 5-year update

(exploratory analysis, p not tested)[a–c]

Median follow up: 56.9 months. No statistical conclusions can be drawn from exploratory endpoints.

	Events, n (%)	Median (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 (4.3–6.1)	



Adapted from: Novello S et al. ESMO 2022.

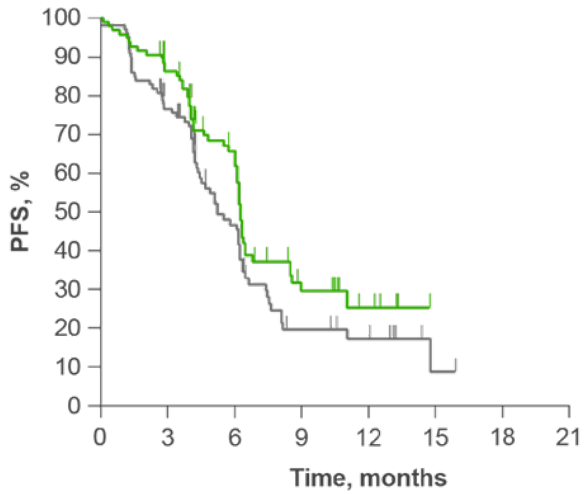
Analysis cut-off date: 23 February 2022. No statistical conclusions can be drawn from this analysis.
[a]OS and PFS were both primary endpoints. [b]PFS was assessed using RECIST v1.1 by blinded, independent, central review. [c]Curves are Kaplan–Meier estimates.
Novello S *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

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

TPS <1%

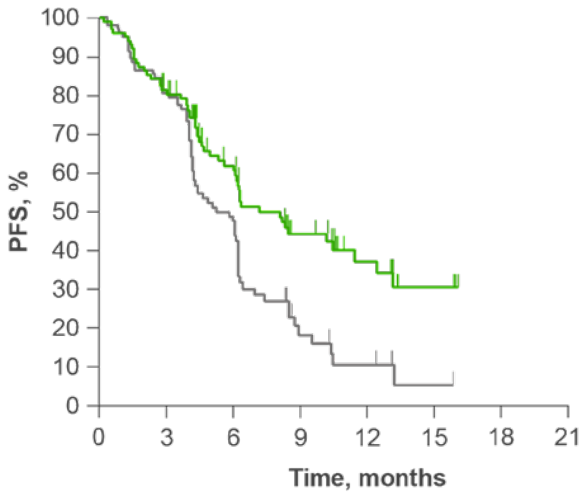
Treatment arm	Events, %	Median (95% CI), months	HR (95% CI)
Pembrolizumab + carb-pac/nabpac	57.9	6.3 (6.1–6.5)	0.68 (0.47–0.98)
Placebo + carb-pac/nabpac	67.7	5.3 (4.4–6.2)	—



No. at risk								
Pembrolizumab + carb-pac/nabpac	95	78	48	16	5	0	0	0
Placebo + carb-pac/nabpacl	99	71	35	11	6	1	0	0

TPS 1–49%

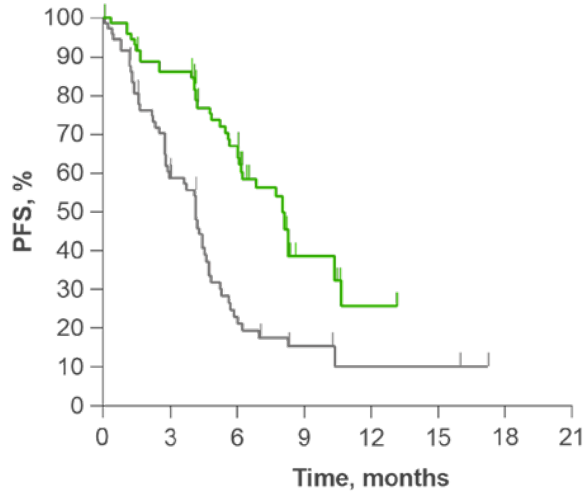
Events, %	Median (95% CI), months	HR (95% CI)
52.4	7.2 (6.0–11.4)	0.56 (0.39–0.80)
70.2	5.2 (4.2–6.2)	—



No. at risk								
Pembrolizumab + carb-pac/nabpac	103	79	49	26	13	5	0	0
Placebo + carb-pac/nabpacl	104	79	40	8	4	1	0	0

TPS ≥50%

Events, %	Median (95% CI), months	HR (95% CI)
53.4	8.0 (6.1–10.3)	0.37 (0.24–0.58)
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

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

Analysis cut-off date: 3 April 2018.
[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [b]Curves are Kaplan–Meier estimates.
Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051 (and supplementary appendix).

KEYNOTE-407: Exploratory endpoint – PFS by PD-L1 TPS (5-year update)[a]

Median follow up: 56.9 months. No statistical conclusions can be drawn from exploratory endpoints

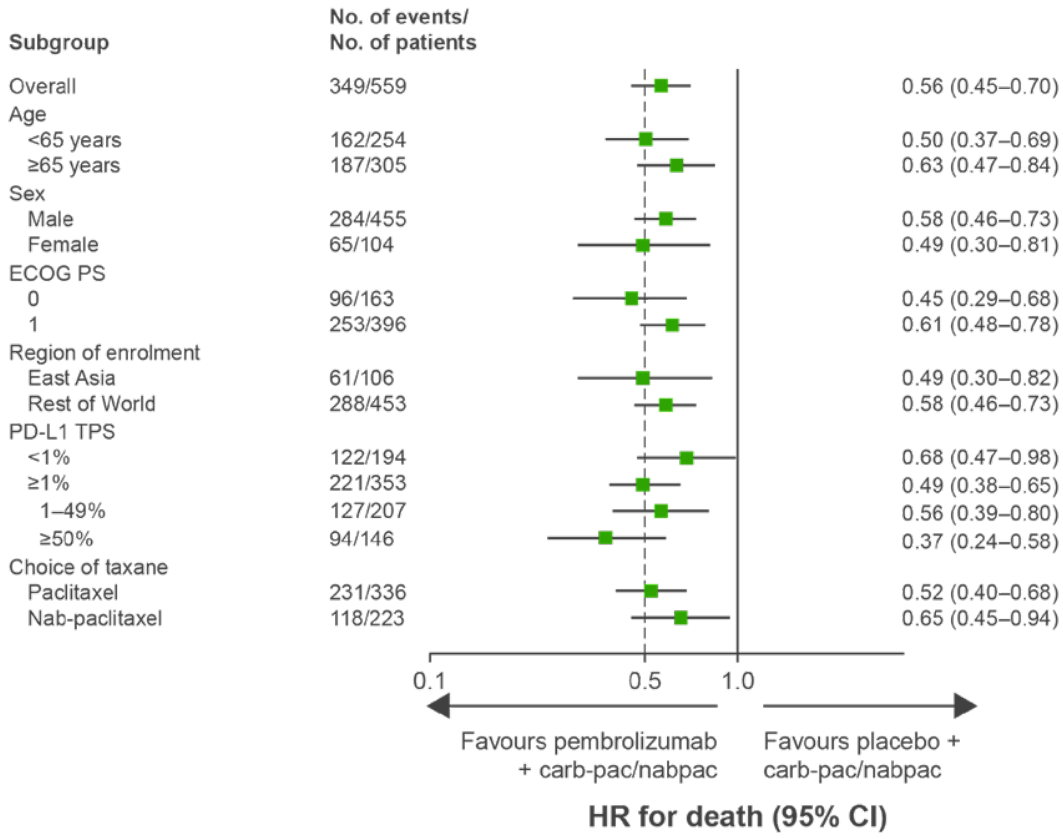
	PD-L1 TPS ≥50%		PD-L1 TPS 1%-49%		PD-L1 TPS <1%	
	Pembro + carb-pac/nabpac (n = 73)	Placebo + carb-pac/nabpac (n = 73)	Pembro + carb-pac/nabpac (n = 103)	Placebo + carb-pac/nabpac (n = 104)	Pembro + carb-pac/nabpac (n = 95)	Placebo + carb-pac/nabpac (n = 99)
OS HR (95% CI)	0.48 (0.33–0.69)		0.60 (0.45–0.81)		0.70 (0.52–0.95)	
5-y OS rate,[b] %	15.0	NR	11.8	NR	7.1	6.7

Adapted from: Novello S et al. ESMO 2022.

Analysis cut-off date: 23 February 2022.
[a]PFS was assessed using RECIST v1.1 by blinded, independent, central review. [b]Kaplan–Meier estimates.
Novello S *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

KEYNOTE-407: Exploratory endpoint – PFS in key subgroups (original analysis)

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.

24 **Analysis cut-off date: 3 April 2018.**

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

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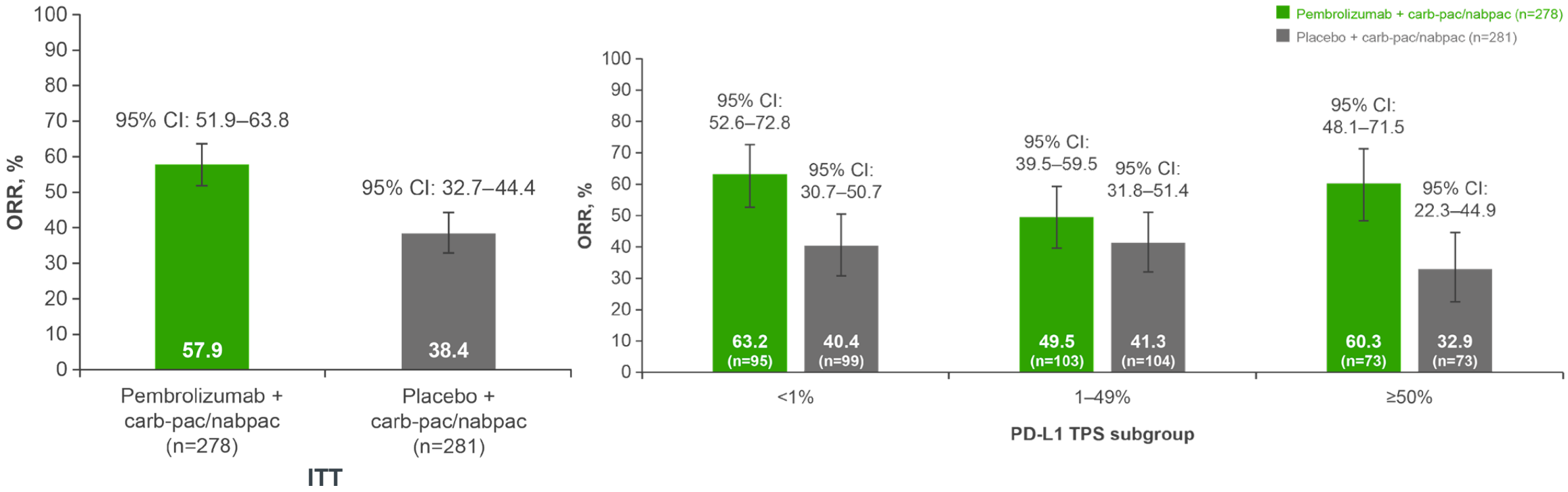
KEYNOTE-407: ORR in the ITT population and exploratory endpoint of ORR by PD-L1 TPS (original analysis)[a–c]

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



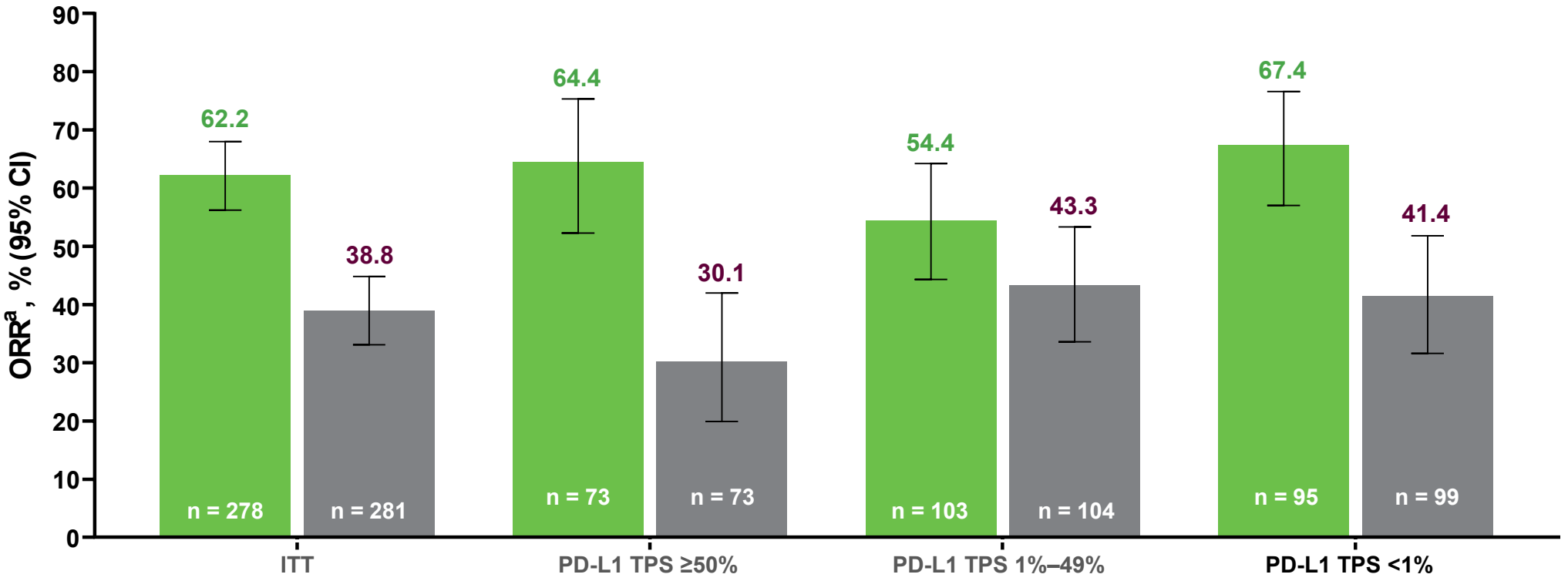
Adapted from: Paz-Ares L et al. N Engl J Med 2018 (and supplementary appendix).

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

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: ORR in the ITT population and exploratory endpoint of ORR by PD-L1 TPS in the 5-year update (exploratory analysis, p not tested)[a,b]

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

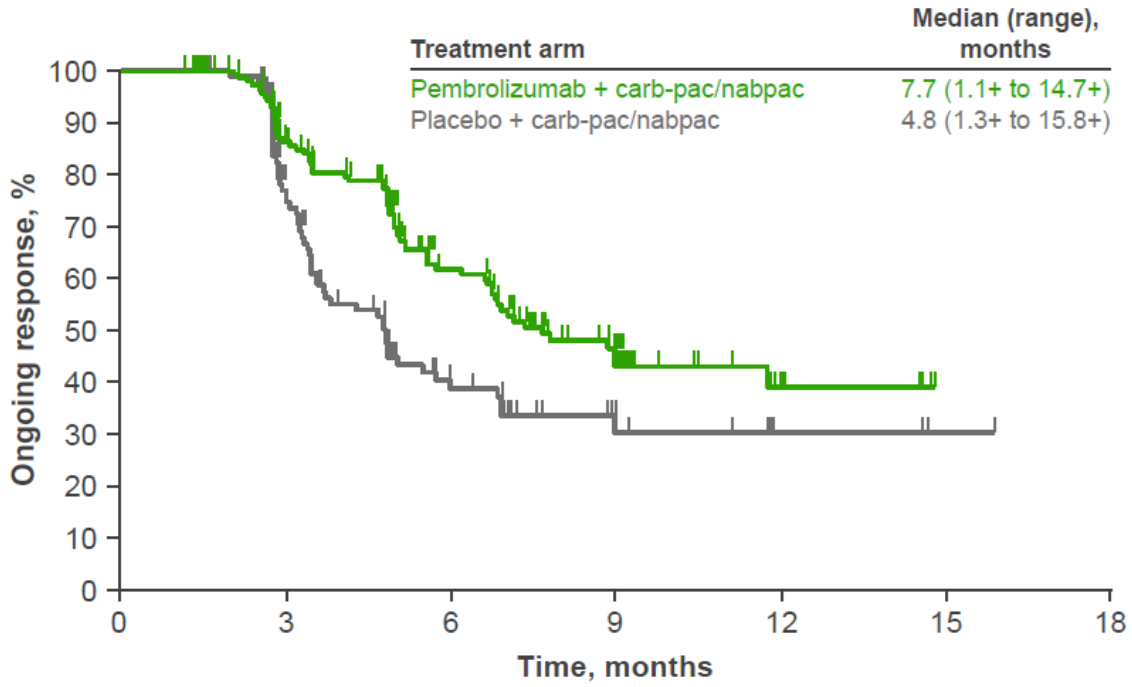


Adapted from: Novello S et al. ESMO 2022.

Analysis cut-off date: 23 February 2022.
[a]Assessed using RECIST v1.1 by blinded, independent, central review. [b]No statistical conclusions can be drawn from this analysis or from exploratory endpoints.
Novello S *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

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

Median follow up: 7.8 months. DOR was not subject to statistical testing – no statistical conclusions can be drawn.[a]



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).

Analysis cut-off date: 3 April 2018.
[a]Assessed using RECIST v1.1 by blinded, independent, central radiological review. [b]Curves are Kaplan–Meier estimates.
Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051 (and supplementary appendix).

KEYNOTE-407: DOR in the ITT population and exploratory endpoint of DOR by PD-L1 TPS in the 5-year update (exploratory analysis, p not tested)[a–c]

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

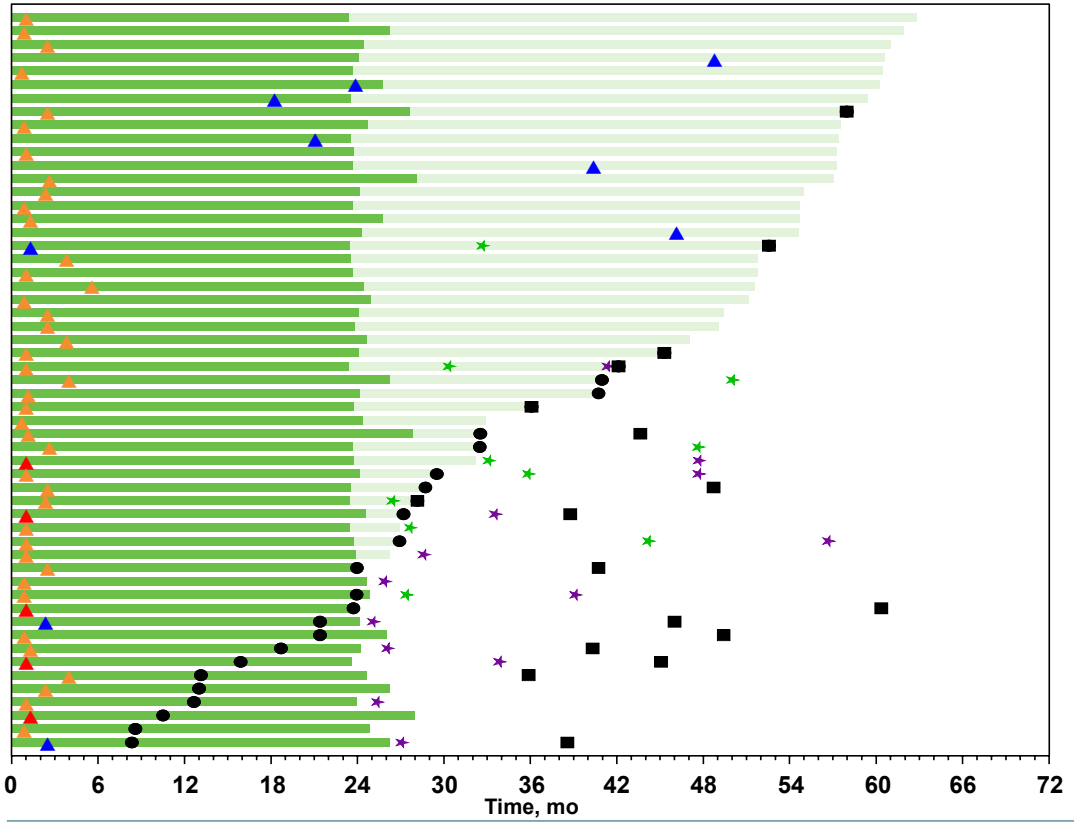
	ITT		PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + carb-pac/nabpac	Placebo + carb-pac/nabpac	Pembro + carb-pac/nabpac	Placebo + carb-pac/nabpac	Pembro + carb-pac/nabpac	Placebo + carb-pac/nabpac	Pembro + carb-pac/nabpac	Placebo + carb-pac/nabpac
DOR Median (range), mo	9.0 (1.3+ to 61.5+)	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. ESMO 2022.

Analysis cut-off date: 23 February 2022.
[a]Assessed using RECIST v1.1 by blinded, independent, central review. [b]No statistical conclusions can be drawn from this analysis or from exploratory endpoints. [c]Kaplan–Meier estimates.
Novello S *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

KEYNOTE-407: Outcomes in patients who completed 35 cycles of pembrolizumab in the 5-year update (exploratory analysis, p not tested)

Median follow up: 56.9 months



	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. ESMO 2022.

Analysis 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.
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)

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.

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

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[a]	37 (13.3)	18 (6.4)
Any treatment	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[b]	1 (0.4)	1 (0.4)

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

Analysis cut-off date: 3 April 2018.
[a]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. [b]Both deaths were due to pneumonitis.

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

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KEYNOTE-407: Summary of AEs in all treated patients (5-year update)

Median follow up: 56.9 months

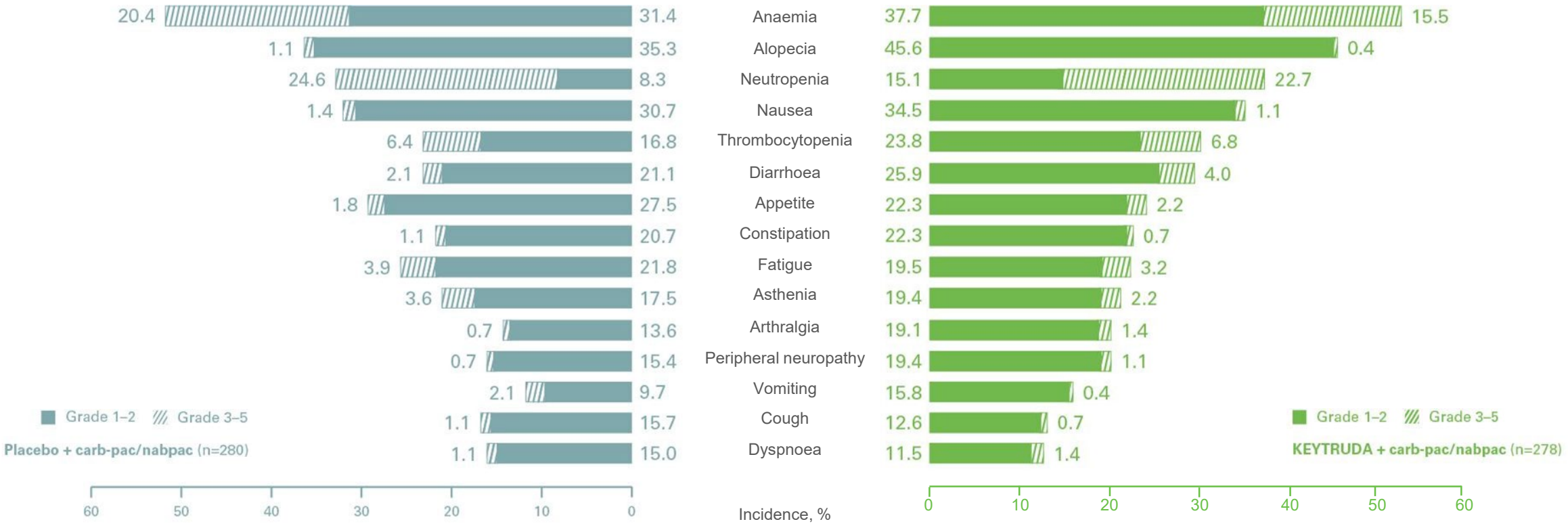
Adverse event, n (%)	All treated patients		35 cycles of pembro n = 55
	Pembro-plat-pem n = 278	Placebo-plat-pem n = 280	
Any	274 (98.6)	275 (98.2)	55 (100)
Grade 3–5	208 (74.8)	196 (70.0)	35 (63.6)
Led to treatment discontinuation[a]			
Any treatment	80 (28.8)	37 (13.2)	3 (5.5)
All treatments	48 (17.3)	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. ESMO 2022.

Analysis 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.
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)[a]

Median follow up: 7.8 months



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

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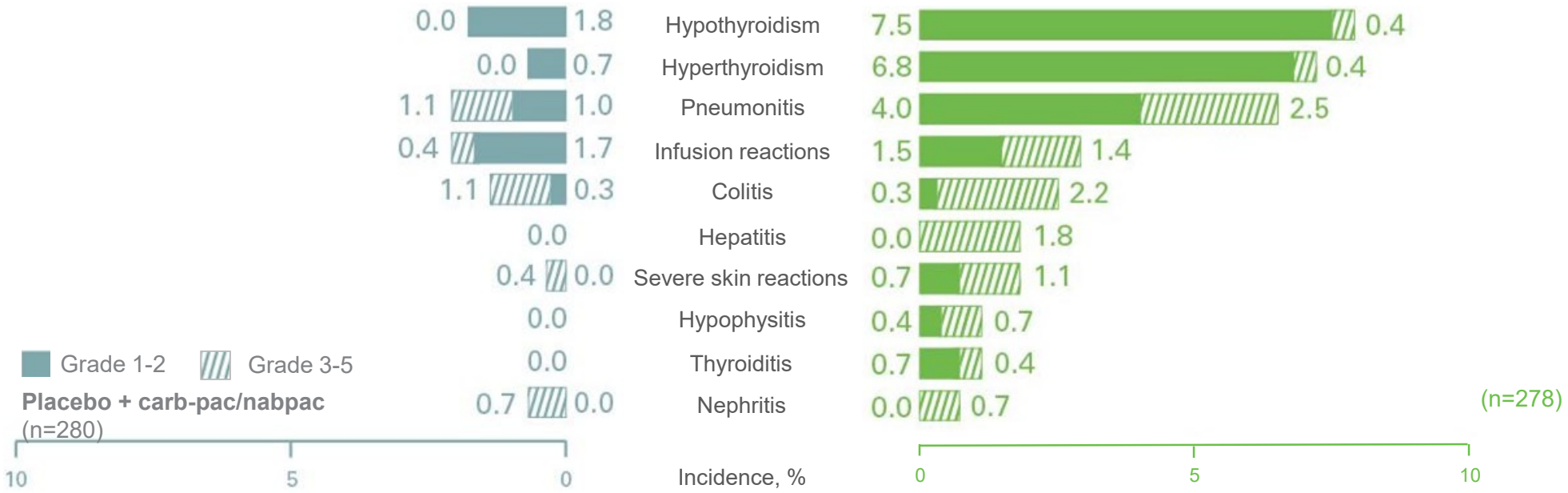
Analysis cut-off date: 3 April 2018.
[a]AEs that occurred during crossover from the placebo + carb-pac/nabpac group to pembrolizumab monotherapy were excluded.
Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051.

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

Median follow up: 7.8 months



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

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

KEYNOTE-407: QLQ-C30 Completion[a] and compliance[b] rates

Median follow up: 7.8 months. This analysis was exploratory and no statistical conclusions can be drawn

		Pembrolizumab + carb-pac/nabpac (n=246), 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)

Analysis cut-off date: 3 April 2018. HRQoL was an exploratory endpoint.
[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).

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

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KEYNOTE-407: QLQ-LC13 Completion[a] and compliance[b] rates

Median follow up: 7.8 months. This analysis was exploratory and no statistical conclusions can be drawn

		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)

Analysis cut-off date: 3 April 2018. HRQoL was an exploratory endpoint.
[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).

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

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KEYNOTE-407: Change from baseline to Weeks 9 and 18 in EORTC QLQ-C30 GHS/QoL scores

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]	

Analysis cut-off date: 3 April 2018. HRQoL was an exploratory endpoint.
[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.

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

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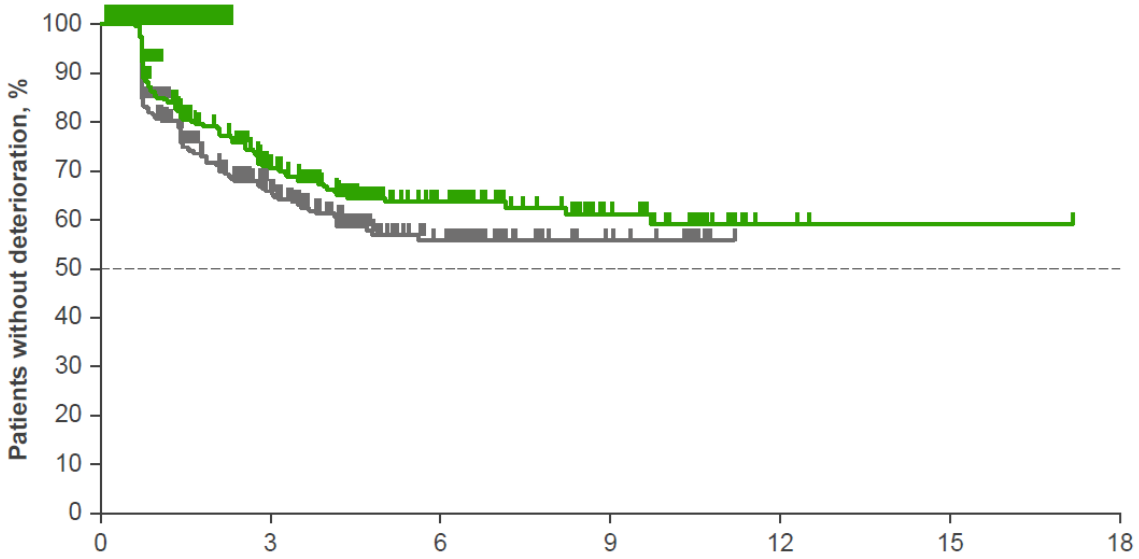
KEYNOTE-407: Time to deterioration in composite endpoint of cough, chest pain or dyspnoea[a]

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)	



No. at risk							
Pembrolizumab + carb-pac/nabpac	276	139	78	32	3	1	0
Placebo + carb-pac/nabpac	278	121	49	16	0	0	0

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

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

KEYNOTE-407: EORTC QLQ-C30 GHS/QoL

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

Analysis cut-off date: 3 April 2018. HRQoL was an exploratory endpoint.
[a]Key PRO endpoint.
Mazieres J *et al. J Clin Oncol* 2020;38:271–280.

KEYNOTE-407: EORTC QLQ-C30 functional and symptom subscale scores

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 Week 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

Analysis cut-off date: 3 April 2018. HRQoL was an exploratory endpoint.

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

1

KEYNOTE-407: Efficacy summary[1,2]

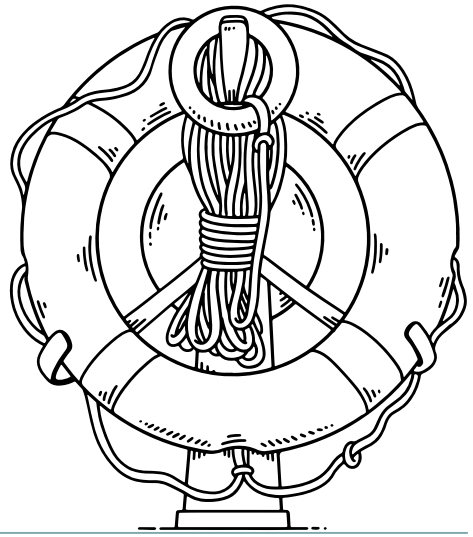
- Treatment with pembrolizumab + carb-pac/nabpac in patients with untreated, metastatic, squamous NSCLC demonstrated (compared with placebo + carb-pac/nabpac):[1,2]
  - Superior OS, with a 36% reduction in the risk of death (HR: 0.64, p<0.001)
  - Superior PFS, with a 44% reduction in the risk of progression 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]
- 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)[3]
  - Benefits were observed despite an effective crossover rate of 50.9%[3]
  - OS and PFS benefits were seen irrespective of baseline PD-L1 expression[3]
- Patients who received 35 cycles of pembrolizumab had durable responses, and experienced long-term OS[3]

[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 (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.

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; 3. Novello S *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022.

KEYNOTE-407: Safety summary[1,2]

- 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]

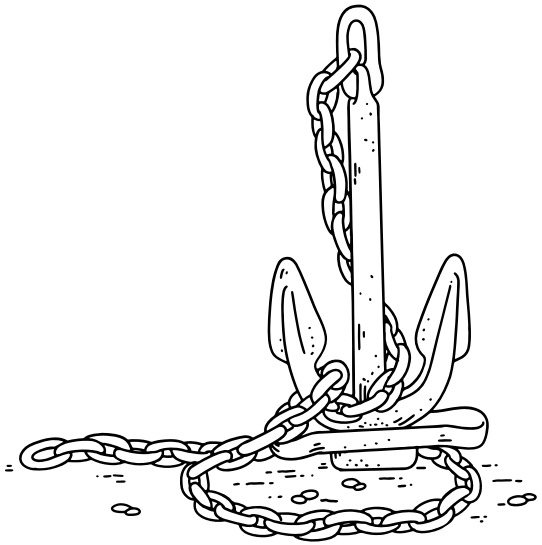


1. Paz-Ares L *et al. N Engl J Med* 2018; 379:2040–2051; 2. Novello S *et al.* Presented at the European Society for Medical Oncology (ESMO) meeting, 9–13 September 2022; 3. Paz-Ares L *et al. J Thorac Oncol* 2020;15:1657–1669.

KEYNOTE-407: HRQoL summary

HRQoL was an exploratory endpoint.

- 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.

PD-L1 expression in mNSCLC patients

Immunohistochemical evaluation of PD-L1

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

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

- Single-agent immunotherapy
- Combination immunotherapy

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

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

***TPS <1%.**

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

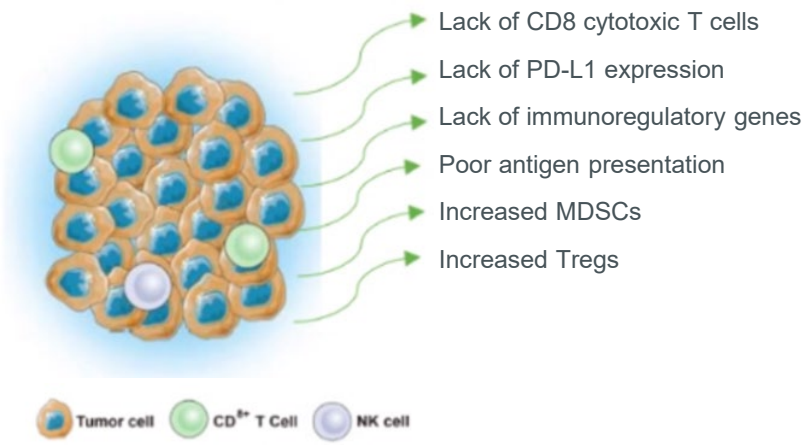
Immune checkpoint inhibitors, in combination with chemotherapy, can help improve outcomes, harnessing the patient's immune system against cancer[1,2]

This is a hypothesis based on experimental models

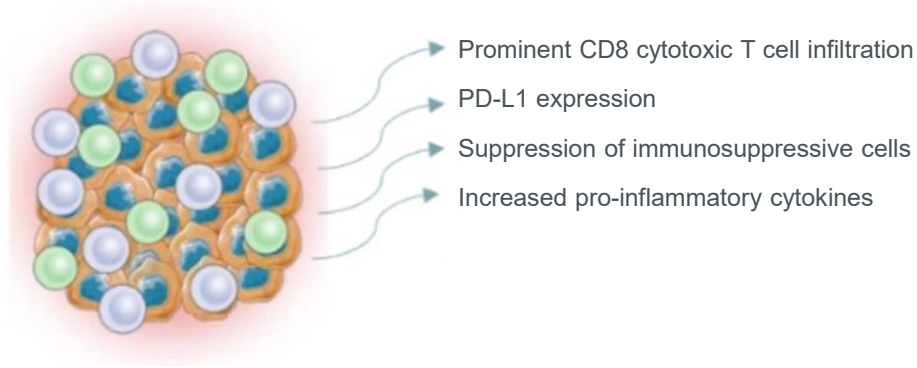
Some NSCLCs are cold tumours that lack activated tumour-specific T cells[7] → Absence of tumour-specific T cells is a mechanism of primary resistance to ICIs[7] → Effective combination therapy can turn cold tumours into hot tumours that are sensitive to ICIs[7]

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

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



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



***TPS <1%.**

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

Abbreviations

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

Abbreviations

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

OS	PFS	ORR / DOR	Safety
ITT	ITT	ORR (ITT + PDL-1 TPS)	AEs
PDL-1 TPS	PDL-1 TPS	DOR (ITT [original analysis])	All cause AEs
Key subgroups	Key subgroups	DOR (ITT + PD-L1 TPS [5 year])	Immune mediated AEs

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

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

KEYTRUDA offers flexibility of dosing

Administered as an IV infusion

Over 30 minutes

200 mg Q3W or 400 mg Q6W

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

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

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