MSD Oncology

PI

KEYNOTE-048: KEYTRUDA® (pembrolizumab) ± chemotherapy vs EXTREME in 1L HNSCC

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Please refer to the full KEYTRUDA Summary of Product Characteristics and Risk Minimisation Materials for Patients before prescribing KEYTRUDA

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ (**this links to an external site**) or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to Merck Sharp & Dohme (UK) Limited (Tel: 0208 154 8000).

Please click the following links for the KEYTRUDA SmPC and prescribing information: Great Britain; Northern Ireland.
If using a downloaded version of this material, please ensure that you are accessing the most recent version of the prescribing information

EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy.

GB-OHN-00380. Date of preparation: November 2021

MSD

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KEYTRUDA® (pembrolizumab) HNSCC indications

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- KEYTRUDA as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥1
- The dose of KEYTRUDA studied in the original KEYNOTE-048 study was 200 mg every 3 weeks (Q3W). The SmPC-recommended dose of KEYTRUDA has since been updated to 200 mg Q3W or 400 mg every 6 weeks (Q6W) administered as an intravenous infusion over 30 minutes
- The original KEYNOTE-048 study included all HNSCC patients irrespective of CPS expression
  - Where possible, only data for the CPS ≥1 population is shown throughout the deck; however, some data originate from the total population and could not be separated. These examples will be highlighted where relevant throughout the deck
- Patients with HNSCC should be selected for treatment with KEYTRUDA as monotherapy or in combination with platinum and 5-FU chemotherapy based on the tumour expression of PD-L1 confirmed by a validated test
- Refer to the Summary of Product Characteristics before prescribing, in order to help reduce the risks associated with KEYTRUDA

5-FU, 5 fluorouracil; CPS, combined positive score; HNSCC, head and neck squamous cell carcinoma; PD-L1, programmed death ligand-1; Q3W, every 3 weeks; Q6W, every 6 weeks; SmPC, Summary of Product Characteristics.

KEYTRUDA (pembrolizumab) SmPC.

Presentation layout

PI

Main body

Original study: Pembrolizumab monotherapy (median follow up 11.5 months) and pembrolizumab + chemotherapy (median follow up 13 months) groups with **PD-L1 expression CPS ≥1**

Appendix

Original study: Pembrolizumab monotherapy (median follow up 11.5 months) and pembrolizumab + chemotherapy (median follow up 13 months) groups with **PD-L1 expression CPS ≥20**

Original study: Pembrolizumab monotherapy (median follow up 11.5 months) and pembrolizumab + chemotherapy (median follow up 13 months) groups with **PD-L1 expression CPS ≥1 and <20**

Long-term follow up: Pembrolizumab monotherapy (median follow up 45 months) and pembrolizumab + chemotherapy (median follow up 44.5 months)

Exploratory assessment: **Therapy following** pembrolizumab monotherapy and pembrolizumab ± chemotherapy

CPS, combined positive score; PD-L1, programmed death ligand-1.

KEYNOTE-048: Definition of analyses

Study	Analysis	Cut-off date	Slide symbol	Median follow up
Original	Second interim[1]	13 June 2018	I	Pembrolizumab monotherapy: 11.7 months[1] Pembrolizumab + chemotherapy: 13.0 months[1]
Original	Final[2,3]	25 February 2019	II	Pembrolizumab monotherapy: 11.5 months[1] Pembrolizumab + chemotherapy: 13.0 months[1]
Long-term follow up	Post-hoc[4]	18 February 2020	III	Pembrolizumab monotherapy: 45.0 months[4] Pembrolizumab + chemotherapy: 44.5 months[4]
Exploratory outcome assessment	Subsequent therapy (PFS2)[5]	25 February 2019	IV	–

PFS2, progression-free survival after next-line therapy.

1. Burtness B et al. Lancet 2019:394;1915–28; 2. Burtness B et al. *Lancet* 2019:394;1915–28 (suppl. appx.); 3. KEYTRUDA (pembrolizumab) SmPC.; 4. Greil R et al. Presented at ESMO Virtual Congress 2020; 19–21 September 2020; 5. Harrington K et al. Presented at ASCO 2020; 29 May–2 June 2020.

Slide deck navigation

- Each section of this presentation can be accessed via the Contents slide

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KEYNOTE-048: Original study – final analysis Pembrolizumab + monotherapy vs EXTREME (PD-L1 expression CPS ≥1)	OS, PFS, ORR/DoR, AEs, AEOSIs, Summary
KEYNOTE-048: Original study – final analysis Pembrolizumab + chemotherapy vs EXTREME (PD-L1 expression CPS ≥1)	OS, PFS, ORR/DoR, AEs, AEOSIs, Summary
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KEYNOTE-048: Original study – final analysis Pembrolizumab + monotherapy vs EXTREME (PD-L1 expression CPS ≥20	OS, PFS, ORR/DoR, Summary
KEYNOTE-048: Original study – final analysis Pembrolizumab + chemotherapy vs EXTREME (PD-L1 expression CPS ≥20	OS, PFS, ORR/DoR, Summary
KEYNOTE-048: Original study – exploratory subgroup analysis PD-L1 CPS ≥1 and <20	Pembrolizumab monotherapy: OS/PFS, Pembrolizumab monotherapy: ORR/DoR, Pembrolizumab + chemotherapy: OS/PFS , Pembrolizumab + chemotherapy: ORR/DoR
KEYNOTE-048: Long-term follow up Pembrolizumab ± chemotherapy vs EXTREME	Study overview, Pembrolizumab monotherapy OS: CPS ≥1, Pembrolizumab monotherapy OS: CPS ≥20, Pembrolizumab + chemotherapy OS: CPS ≥1, Pembrolizumab + chemotherapy OS: CPS ≥20, Pembrolizumab monotherapy DoR: CPS ≥1, Pembrolizumab monotherapy DoR: CPS ≥20, Pembrolizumab + chemotherapy DoR: CPS ≥1, Pembrolizumab + chemotherapy DoR: CPS ≥20, Adverse Events, Summary
KEYNOTE-048: PFS2 exploratory outcome assessment First subsequent therapy following progressive disease	Study overview, Study design, Assessment, First subsequent therapy, Pembrolizumab monotherapy: CPS ≥1, Pembrolizumab monotherapy: CPS ≥20, Pembrolizumab + chemotherapy: CPS ≥1, Pembrolizumab + chemotherapy: CPS ≥20, Summary

- To access the Contents slide from anywhere in the presentation, click the ‘Home’ icon

- To access the Prescribing Information (PI) slide from anywhere in the presentation, click the ‘PI’ icon

PI

- Numbers denote the study analysis. Click the symbol to navigate back to the Definition of analyses slide

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Key data from KEYNOTE-048: Contents

PI

Click the links below to navigate to the section of interest

Section	Sub-section
Main body	
KEYNOTE-048: Original study	Study overview, Study design, Endpoints, Patient disposition, Baseline characteristics
KEYNOTE-048: Original study – final analysis Pembrolizumab + monotherapy vs EXTREME (PD-L1 expression CPS ≥1)	OS, PFS, ORR/DoR, AEs, AEOSIs, Summary
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KEYNOTE-048: Original study – exploratory subgroup analysis PD-L1 CPS ≥1 and <20	Pembrolizumab monotherapy: OS/PFS, Pembrolizumab monotherapy: ORR/DoR, Pembrolizumab + chemotherapy: OS/PFS , Pembrolizumab + chemotherapy: ORR/DoR
KEYNOTE-048: Long-term follow up Pembrolizumab ± chemotherapy vs EXTREME	Study overview, Pembrolizumab monotherapy OS: CPS ≥1, Pembrolizumab monotherapy OS: CPS ≥20, Pembrolizumab + chemotherapy OS: CPS ≥1, Pembrolizumab + chemotherapy OS: CPS ≥20, Pembrolizumab monotherapy DoR: CPS ≥1, Pembrolizumab monotherapy DoR: CPS ≥20, Pembrolizumab + chemotherapy DoR: CPS ≥1, Pembrolizumab + chemotherapy DoR: CPS ≥20, Adverse Events, Summary
KEYNOTE-048: PFS2 exploratory outcome assessment First subsequent therapy following progressive disease	Study overview, Study design, Assessment, First subsequent therapy, Pembrolizumab monotherapy: CPS ≥1, Pembrolizumab monotherapy: CPS ≥20, Pembrolizumab + chemotherapy: CPS ≥1, Pembrolizumab + chemotherapy: CPS ≥20, Summary

AE, adverse event; AEOSI, adverse event of special interest; CPS, combined positive score; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; ORR, objective response rate; PFS, progression-free survival; PFS2, progression-free survival after next-line therapy; PD-L1, programmed death ligand-1.

PI

KEYNOTE-048: Original study

Click the links below to navigate to the section of interest

KEYNOTE-048: Original study overview

PI

- A multicentre, randomised, open-label, active-controlled study in patients with histologically or cytologically confirmed metastatic or recurrent HNSCC of the oropharynx, oral cavity, hypopharynx or larynx, who had not received prior systemic therapy for recurrent or metastatic disease and who were considered incurable with local therapies
- Patients with progressive disease within 6 months of curatively intended systemic treatment given for locoregionally advanced disease, symptomatic central nervous system metastases, a history of non-infectious pneumonitis that required glucocorticoids or active autoimmune disease were ineligible for the study
- Findings from the protocol:
  - Second interim analysis
  - Final analysis

HNSCC, head and neck squamous cell carcinoma.
Burtness B et al. *Lancet* 2019:394;1915–28.

KEYNOTE-048 original study design: Pembrolizumab ± chemotherapy vs EXTREME[1,2]

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Multi-centre, randomised, open-label, active-controlled Phase III study

Key eligibility criteria

- SCC of the oropharynx, oral cavity, hypopharynx or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment[a]
- Known p16 status in the oropharynx[b]
- ≥1 tumour lesion measurable per RECIST v1.1

Stratification factors

- PD-L1 expression (TPS ≥50% vs <50%)
- p16 status in the oropharynx (positive vs negative)
- ECOG PS (0 vs 1)

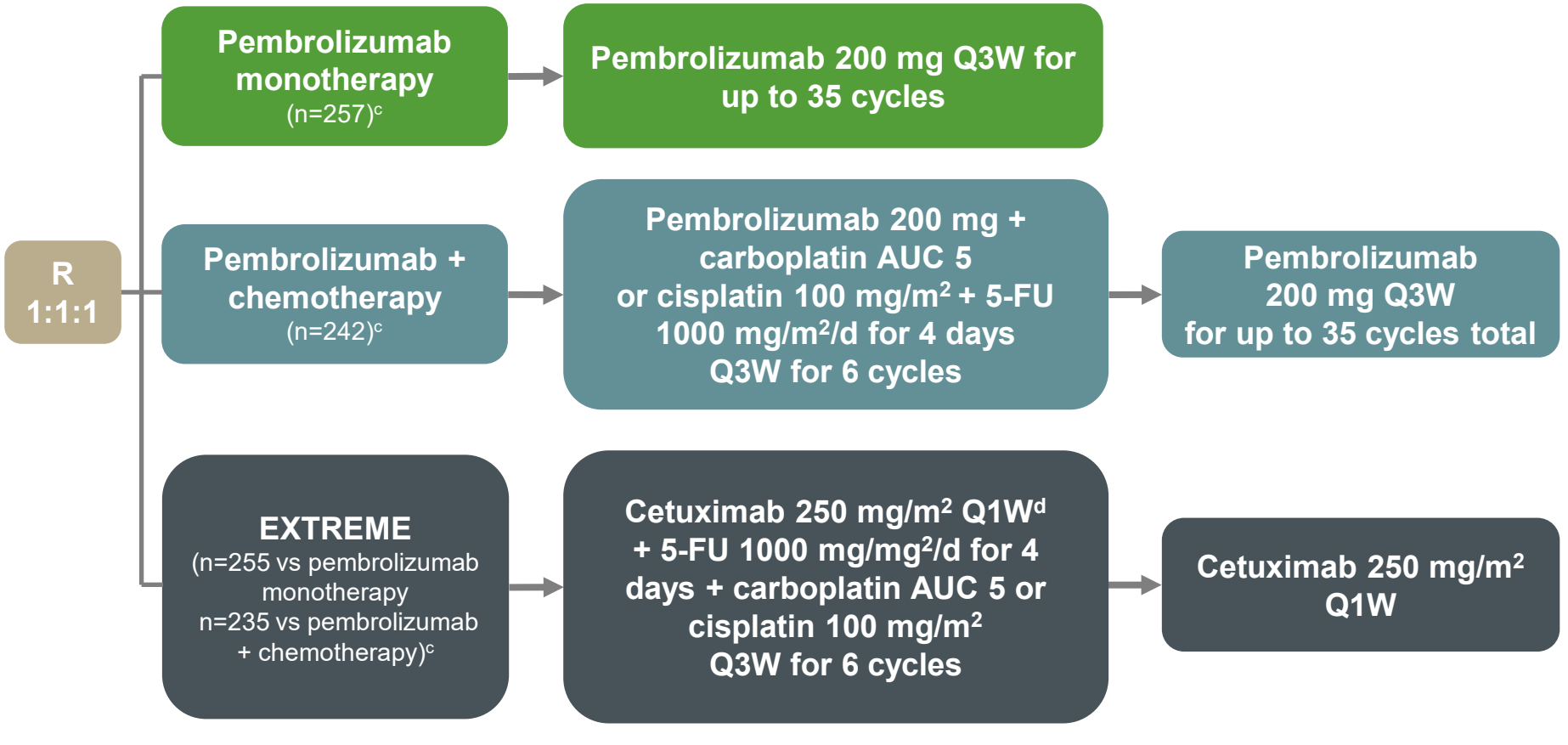

Figure adapted from Burtness B et al. *Lancet* 2019 and KEYTRUDA (pembrolizumab) SmPC.

[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = % of tumour cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 histology assay (Ventana), cutpoint for positivity = 70%. [c]Full trial data included all participants regardless of PD-L1 status. Data has been adapted to reflect CPS ≥1 population, as per KEYTRUDA license. [d]Following a loading dose of 400 mg/m^2.

5-FU, 5 fluorouracil; AUC 5, desired carboplatin exposure of 5 mg/ml; ECOG, Eastern Cooperative Oncology Group; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; IHC, immunohistochemistry; p16, cyclin-dependent kinase inhibitor 2A; PD-L1, programmed death ligand-1; PS, performance status; Q1W, every week; Q3W, every 3 weeks; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumors; R/M, recurrent/metastatic; SCC, squamous cell carcinoma; SmPC, Summary of Product Characteristics; TPS, tumour proportion score.

1. Burtness B et al. Lancet 2019:394;1915–28; 2. KEYTRUDA (pembrolizumab) SmPC.

KEYNOTE-048 studied the efficacy and safety of pembrolizumab ± chemotherapy vs EXTREME[1,2]

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Endpoints were assessed in the CPS ≥1[a], CPS ≥20[a], and ITT population:

Primary

- Overall survival
  - *Endpoint achieved superiority*
- Progression-free survival
  - *Endpoint not met*

Secondary

- Progression-free survival[b] rates at 6 and 12 months
- Objective response rate[b]
- Change from baseline and time to deterioration in QoL[c]
- Safety and tolerability[d]

Exploratory

- Duration of response[b]
- Progression-free survival after next-line therapy (PFS2)[e]

Figure adapted from KEYTRUDA (pembrolizumab) SmPC and Harrington K et al. Presented at American Society of Clinical Oncology (ASCO) Annual Meeting 2020. 29 May–2 June 2020

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3pharmDx assay. CPS, combined positive score = number of PD-L1 positive cells (tumour cells, lymphocytes, macrophages) divided by the total number of tumour cells x 100. [b]Assessed per RECIST v1.1 by blinded independent central review. [c]To be presented at a later date. [d]Safety was evaluated in the total population only. [e]Defined as the time from randomisation to objective tumour progression on next-line therapy or death from any cause.

EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; ITT, intention to treat; HNSCC, head and neck squamous cell carcinoma; PD-L1, programmed death ligand-1; PFS2, progression-free survival after next-line therapy; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC.; 2. Harrington K et al. Presented at American Society of Clinical Oncology (ASCO) Annual Meeting 2020. 29 May–2 June 2020.

Disposition of all randomised patients[a]

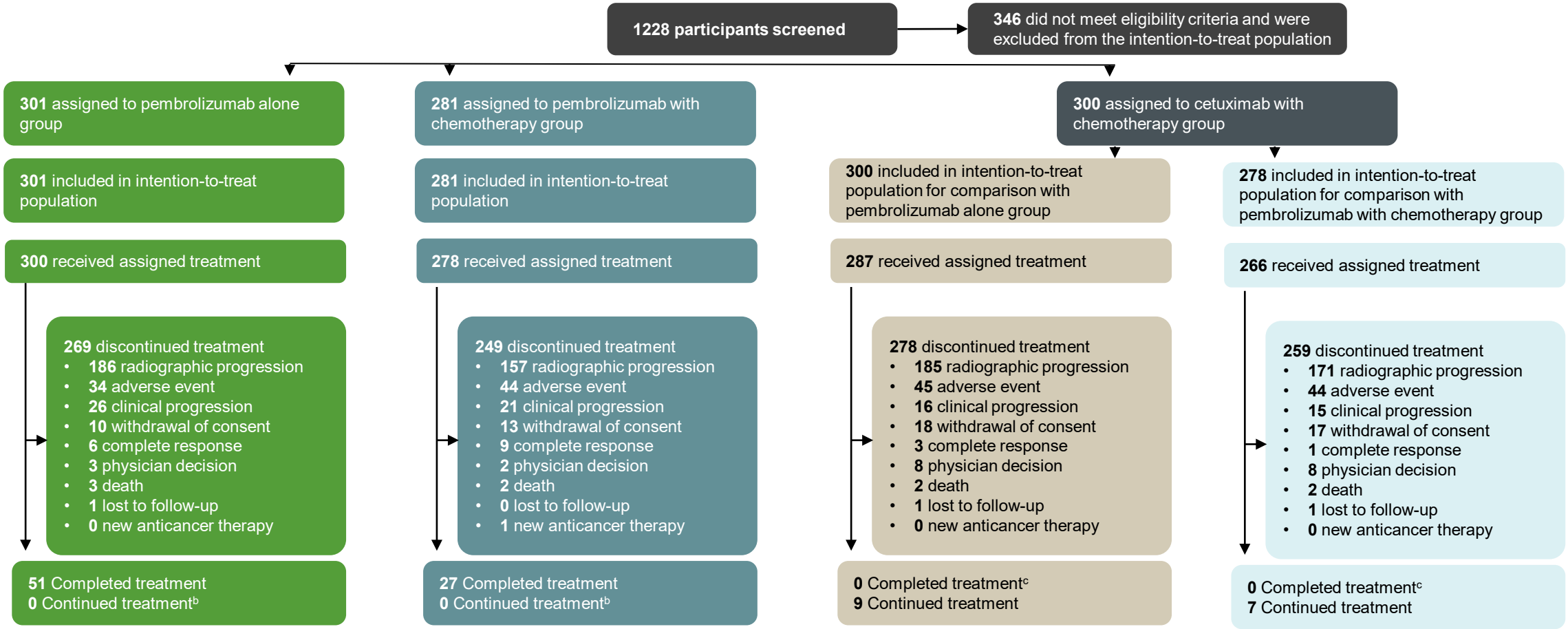

Figure adapted from Burtness B et al. *Lancet* 2019.

[a]Includes all participants regardless of PD-L1 status, which is not reflective of KEYTRUA's licensed indication. [b]No participants were eligible to continue treatment in the pembrolizumab alone or pembrolizumab + chemotherapy groups because all participants were enrolled long enough to receive the maximum 35 cycles of pembrolizumab. [c]No participants were eligible to complete treatment in the cetuximab with chemotherapy group because there is no maximum duration of cetuximab.

There was an enrolment hold for the pembrolizumab + chemotherapy arm from August 13, 2015 to October 2, 2015.

Burtness B et al. *Lancet* 2019:394;1915–28.

Baseline characteristics in the intention-to-treat (ITT) population[a]

Characteristic, n (%)	Pembrolizumab monotherapy vs EXTREME		Pembrolizumab + chemotherapy vs EXTREME[b]	
	Pembrolizumab (N=301)	EXTREME (N=300)	Pembrolizumab + chemotherapy (N=281)	EXTREME (N=278)
Age, median (range), years	62.0 (56.0–68.0)	61.0 (54.5–68.0)	61.0 (55.0–68.0)	61.0 (55.0–68.0)
Male	250 (83)	261 (87)	224 (80)	242 (87)
ECOG PS 1	183 (61)	183 (61)	171 (61)	170 (61)
Current/former smoker	239 (79)	234 (78)	224 (80)	215 (77)
p16 positive (oropharynx)	63 (21)	67 (22)	60 (21)	61 (22)
PD-L1 status				
TPS ≥50%	67 (22)	66 (22)	66 (23)	62 (22)
CPS ≥20	133 (44)	122 (41)	126 (45)	110 (40)
CPS ≥1	257 (85)	255 (85)	242 (86)	235 (85)
Disease status[c]				
Metastatic	216 (72)	203 (68)	201 (72)	187 (67)
Recurrent only[d]	82 (27)	94 (31)	76 (27)	88 (32)

Table adapted from Burtness B et al. *Lancet* 2019.

[a]ITT population includes all participants regardless of PD-L1 status, which is not reflective of KEYTRUA's licensed indication. [b]Only includes participants randomly allocated to the EXTREME group while the pembrolizumab + chemotherapy group was open for enrolment. c3 patients in the pembrolizumab arm, 3 patients in the EXTREME arm, and 4 patients in the pembrolizumab + chemotherapy arm had newly diagnosed, non-metastatic disease. [d]Recurrent only includes participants with locally recurrent disease and disease that has spread to cervical lymph nodes.

CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; ITT, intention-to-treat; PS, performance status; p16, cyclin-dependent kinase inhibitor 2A; PD-L1, programmed death ligand-1; TPS, tumour proportion score.

Burtness B et al. *Lancet* 2019:394;1915–28.

KEYNOTE-048: Original study – final analysis

Pembrolizumab monotherapy vs EXTREME

PD-L1 expression CPS ≥1

Click the links below to navigate to the section of interest

EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy.

OS for pembrolizumab monotherapy vs EXTREME in patients with PD-L1 expression CPS ≥1 (final analysis)[1,2]

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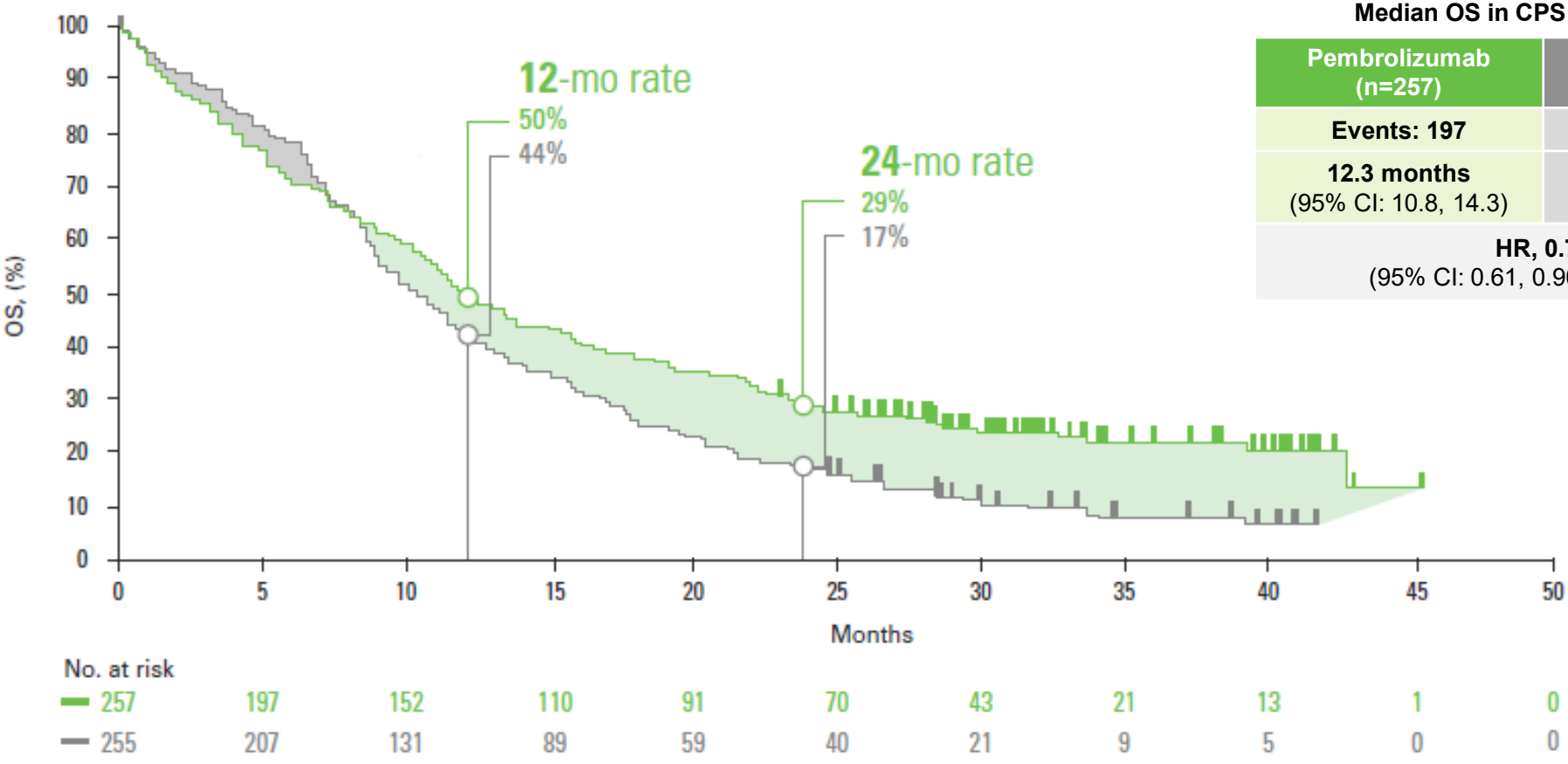
Pembro vs EXTREME

OS

CPS ≥1

KEYNOTE-048: OS in CPS ≥1 population



Median OS in CPS ≥1 population

Pembrolizumab (n=257)	EXTREME (n=255)
Events: 197	**Events: 229**
12.3 months (95% CI: 10.8, 14.3)	**10.3 months** (95% CI: 9.0, 11.5)
HR, 0.74 (95% CI: 0.61, 0.90); p=0.00133	

Figure adapted from KEYTRUDA (pembrolizumab) SmPC and Burtness B et al. *Lancet* 2019 (suppl. appx.). Median follow-up 11.5 months for pembrolizumab monotherapy.

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC.; 2. Burtness B et al. *Lancet* 2019:394;1915–28 (suppl. appx.).

PFS for pembrolizumab monotherapy vs EXTREME in patients with PD-L1 expression of CPS ≥1 (final analysis)[1,2]

PI

Pembro vs EXTREME

PFS

CPS ≥1

KEYNOTE-048: PFS in CPS ≥1 population[1]

PFS	Pembrolizumab (n=257)	EXTREME (n=255)
Number (%) of patients with event	228 (89%)	237 (93%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 6.0)
Hazard ratio[a] (95% CI)	1.13 (0.94, 1.36)	
p-Value[b]	0.89580	

PFS (multiple primary endpoint) statistical significance was not met[2]

Table adapted from KEYTRUDA (pembrolizumab) SmPC. PFS assessed per RECIST v1.1 by blinded independent central radiologic review.

[a]Based on the stratified Cox proportional hazard model. [b]Based on stratified log-rank test.

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; PFS, progression free survival; PD-L1, programmed death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC.; 2. Burtness B et al. *Lancet* 2019:394;1915–28.

Response for pembrolizumab monotherapy vs EXTREME in patients with PD-L1 expression CPS ≥1 (final analysis)[1]

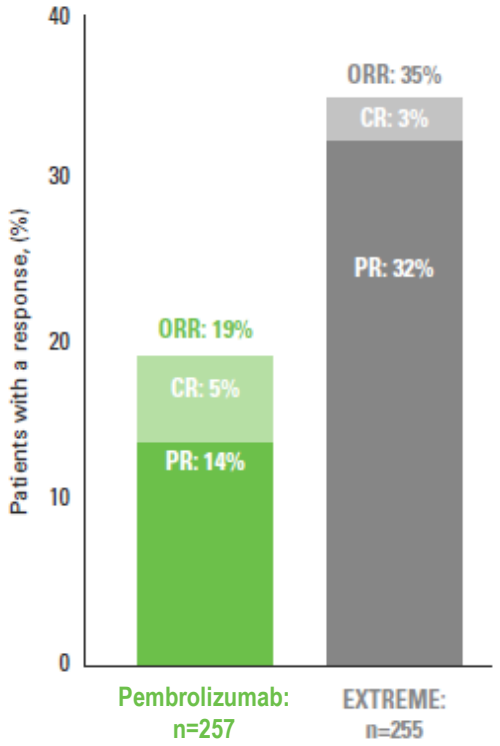
PI

Pembro vs EXTREME

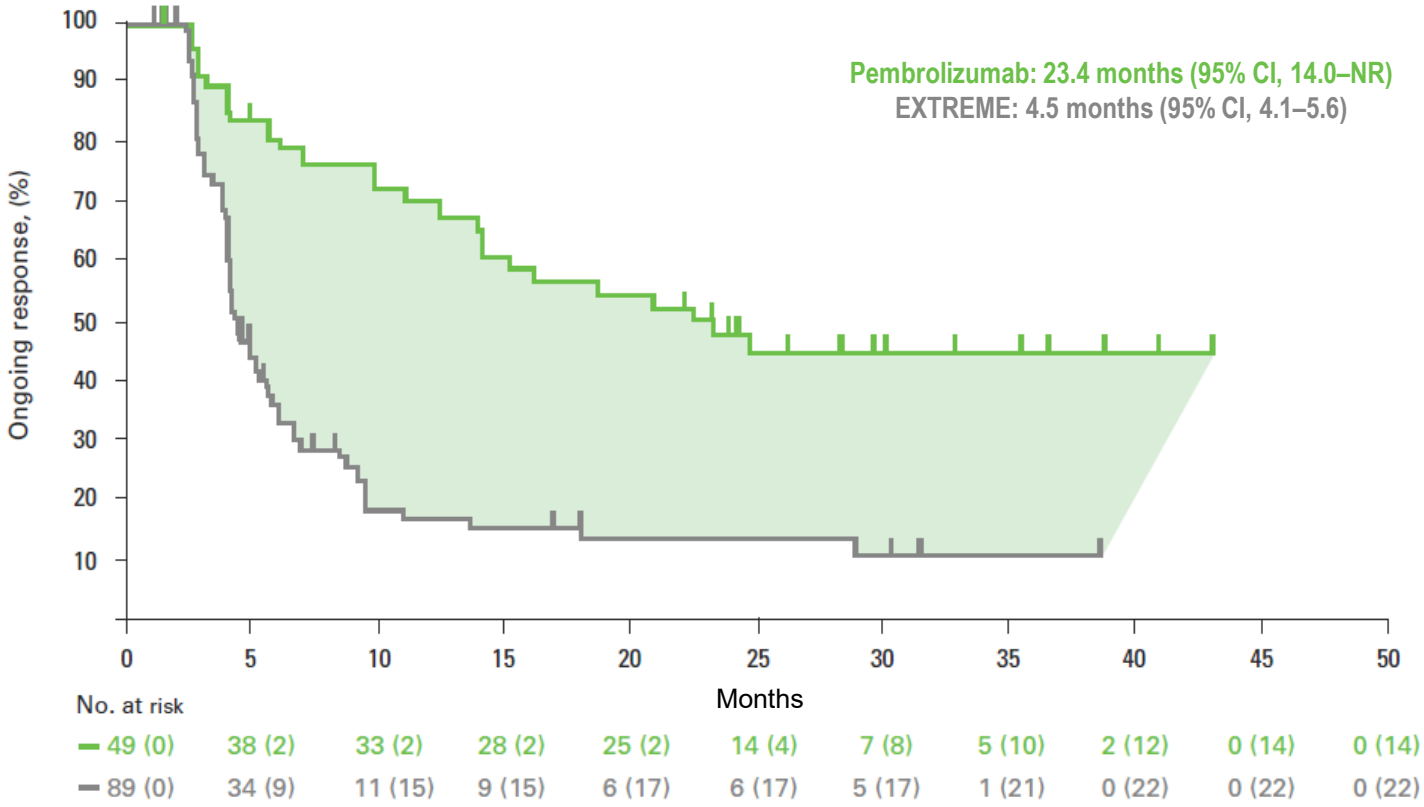
Response

CPS ≥1

KEYNOTE-048: ORR in CPS ≥1 population[a,1]



KEYNOTE-048: Median DoR in CPS ≥1 population[1]



Endpoints were not powered for statistical comparison

Figures adapted from KEYTRUDA (pembrolizumab) SmPC and Burtness B et al. *Lancet* 2019 (suppl. appx.).

Response assessed per RECIST v1.1 by blinded central radiologic review. Median follow-up 11.5 months for pembrolizumab monotherapy.

[a]In patients with measurable disease per central review baseline. A further 28% of patients in the pembrolizumab monotherapy arm and 33% of patients in the EXTREME arm had stable disease[2].

CI, confidence interval; CPS, combined positive score; CR, complete response; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; NR, not reached; ORR, objective response rate; PD-L1, programmed death ligand-1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SmPC, Summary of Product Characteristics.

1. Burtness B et al. *Lancet* 2019:394;1915–28 (suppl. appx.).

All-cause AEs for pembrolizumab monotherapy vs EXTREME in the as-treated population (final analysis)[1]

PI

- **A favourable safety profile** of pembrolizumab monotherapy compared with EXTREME regimen was demonstrated, with the exception of hypothyroidism and pneumonitis, which is reflected in the SmPC

Please refer to the SmPC and Risk Management Materials for patients for further details before prescribing

Where possible, only data for the CPS ≥1 population is shown throughout the deck; however, some safety data originate from the total population and could not be separated. These include the AEs shown on slides 19–21.

AE, adverse event; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; SmPC, Summary of Product Characteristics.

1. Burtness B et al. *Lancet* 2019:394;1915–1928;

Any-cause AEs for pembrolizumab monotherapy vs EXTREME in the as-treated population (final analysis)

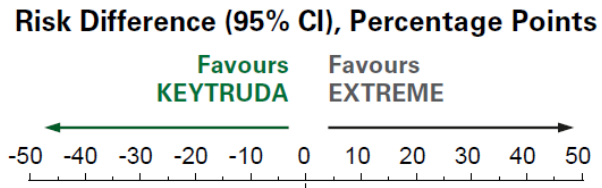
PI

Pembro vs EXTREME

Safety

Total population

Risk difference for AEs of any cause with incidence ≥15%[1]



	Incidence, n (%)	
	KEYTRUDA (N=300)	EXTREME (N=287)
Hypothyroidism	54 (18)	18 (6)
Weight decreased	44 (15)	60 (21)
Fatigue	83 (28)	102 (36)
Asthenia	17 (6)	45 (16)
Hypokalaemia	23 (8)	53 (18)
Constipation	59 (20)	95 (33)
Decreased appetite	45 (15)	85 (30)
White blood cell count decreased	4 (1)	47 (16)
Platelet count decreased	3 (1)	49 (17)
Vomiting	33 (11)	80 (28)
Diarrhoea	46 (15)	99 (34)
Neutrophil count decreased	1 (<1)	57 (20)
Thrombocytopenia	6 (2)	71 (25)
Mucosal inflammation	13 (4)	81 (28)
Stomatitis	9 (3)	81 (28)
Anaemia	62 (21)	134 (47)
Acneiform dermatitis	8 (3)	83 (29)
Rash	30 (10)	111 (39)
Neutropenia	6 (2)	94 (33)
Nausea	49 (16)	147 (51)
Hypomagnesaemia	12 (4)	116 (40)

ALL AEs	Pembrolizumab (n=300)	EXTREME (n=287)
Grade 3–5 AEs[a1]	55%	83%
AEs leading to death[a]	8%	10%
TRAEs leading to death	1%	3%
Discontinuation rate due to AEs[a2]	12%	28%

Immune-related adverse events (IRAEs) have occurred in patients receiving KEYTRUDA. Most IRAEs were reversible and manageable. Refer to the Summary of Product Characteristics before prescribing KEYTRUDA to help minimise the risks associated with treatment.[3]

Figure and table adapted from Burtness B et al. *Lancet* 2019.

[a]Any cause that occurred in ≥5% patients.. Data are n (%). Adverse events are presented according to the Medical Dictionary for Regulatory Affairs system organ class.

AE, adverse event; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; TRAE, treatment-related adverse event.

1. Burtness B et al. *Lancet* 2019:394;1915–1928; 2. Burtness B et al. *Lancet* 2019:394;1915–1928 (suppl. Appx.) 3. KEYTRUDA (pembrolizumab) SmPC.

Adverse events of special interest[a] for pembrolizumab monotherapy vs EXTREME in the as-treated population (final analysis)[1]

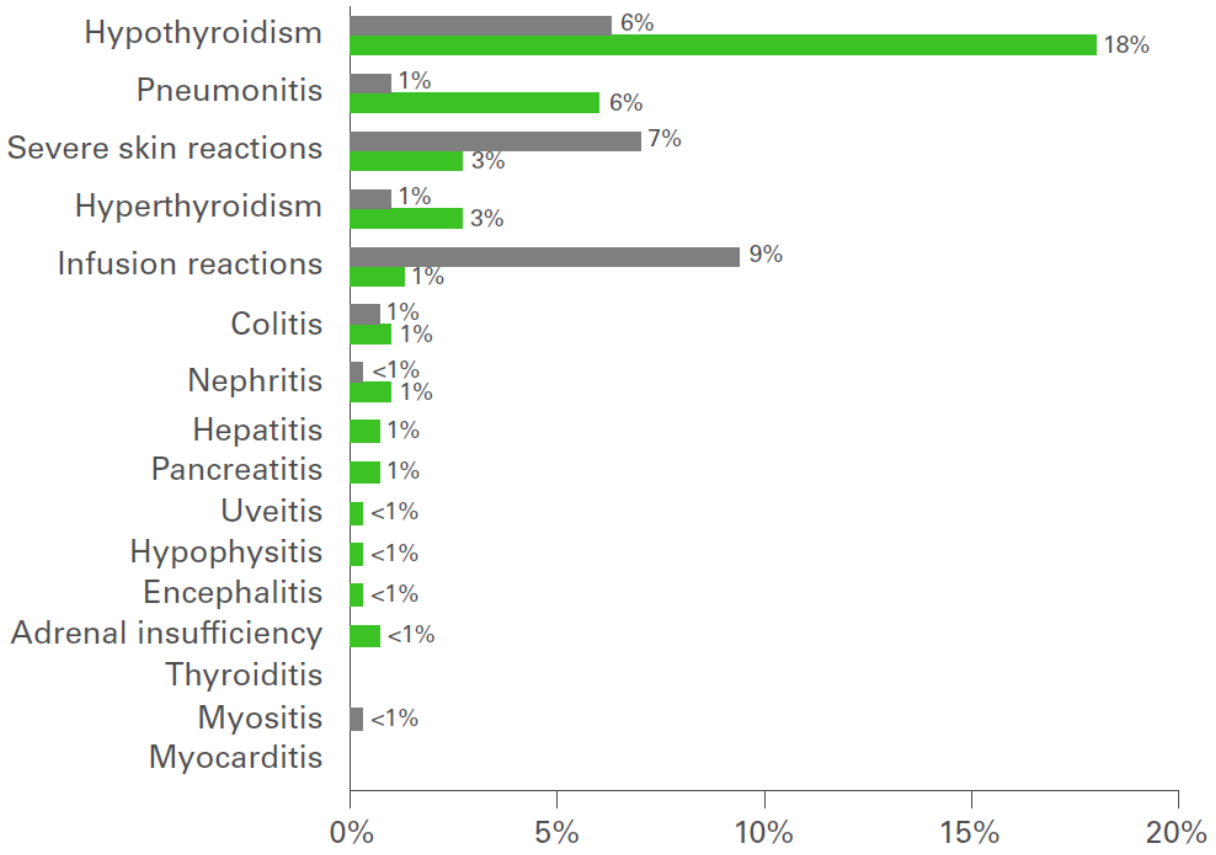
PI

Pembro vs EXTREME

Safety

Total population

Incidence of AEOSI to KEYTRUDA[1]



ALL AEOSIs	Pembrolizumab (n=300)	EXTREME (n=287)
Any Grade AEOSI[a]	31%	24%
Grade 3–5 AEOSI[a]	7%	10%
AEOSI[a] leading to death	0.3%[b]	0%

Figure and table adapted from Burtness B et al. *Lancet* 2019.

[a]AEOSI, which were based on a pre-specified list of preferred terms by the sponsor and are considered to be medically equivalent to immune-mediated events and infusion-related reactions. [b]Pneumonitis (n=1).

AEOSI, Adverse event of special interest; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy.

1. Burtness B et al. *Lancet* 2019:394;1915–1928 (suppl. appx.).

Summary: Pembrolizumab monotherapy vs EXTREME for PD-L1 expression of CPS ≥1 (final analysis)[1,2]

PI

85% of pembrolizumab monotherapy patients (n=257/301) in KEYNOTE-048 had PD-L1 expression of CPS ≥1.[1]

Pembrolizumab monotherapy vs EXTREME in this population:[1,2]

- Achieved clinical and statistical significance and superiority for primary endpoint of OS (final analysis)
  - 26% reduction in risk of death (HR, 0.74; 95% CI: 0.61, 0.90; p=0.00133)
- PFS (multiple primary endpoints) statistical significance was not met
- Demonstrated a **favourable overall safety profile** in the as-treated patient population vs EXTREME with the exception of hypothyroidism and pneumonitis
  - Refer to the previous slides and the SmPC for more details

Pembrolizumab monotherapy SmPC dosing: Fixed dose regimen Q3W (200 mg) or Q6W[a] (400 mg) intravenously over 30 minutes[2]

[a]400 mg Q6W dosing based on SmPC, not investigated in KEYNOTE-048. Median follow-up 11.5 months for pembrolizumab monotherapy.
CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; SmPC, Summary of Product Characteristics.

1. Burtness B et al. *Lancet* 2019:394;1915–28; 2. KEYTRUDA (pembrolizumab) SmPC.

KEYNOTE-048: Original study – final analysis

Pembrolizumab + chemotherapy vs EXTREME

PD-L1 expression CPS ≥1

Click the links below to navigate to the section of interest

EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy.

OS for pembrolizumab + chemotherapy vs EXTREME in patients with PD-L1 expression CPS ≥1 (final analysis)[1,2]

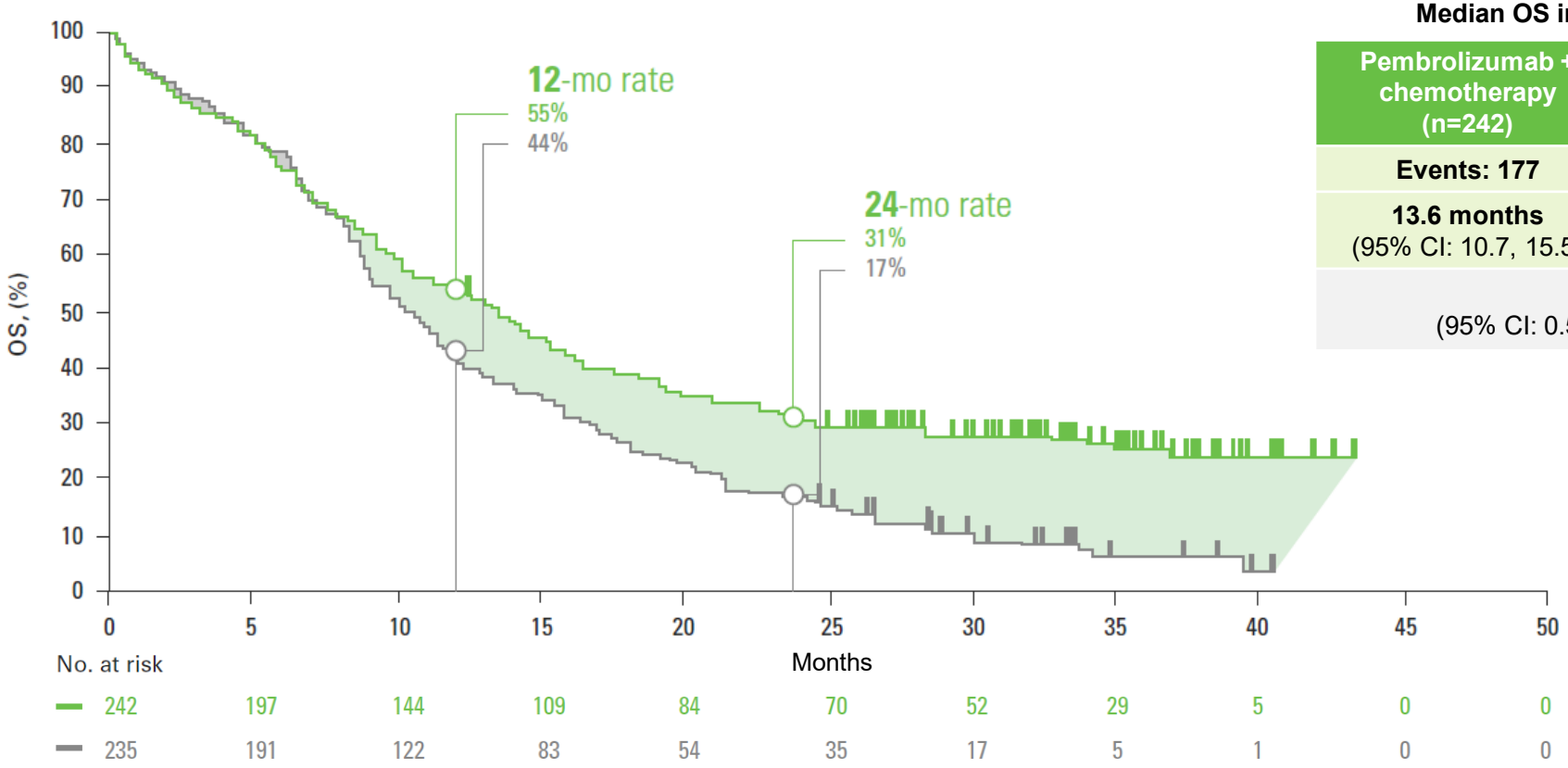
PI

Pembro + chemo vs EXTREME

OS

CPS ≥1

KEYNOTE-048: OS in CPS ≥1 population



Median OS in CPS ≥1 population[2]

Pembrolizumab + chemotherapy (n=242)	EXTREME (n=235)
Events: 177	**Events: 213**
13.6 months (95% CI: 10.7, 15.5)	**10.4 months** (95% CI: 9.1, 11.7)
HR, 0.65 (95% CI: 0.53, 0.80); p=0.00002	

Figure adapted from KEYTRUDA (pembrolizumab) SmPC and Burtness B et al. *Lancet* 2019. Median follow-up 13.0 months for pembrolizumab in combination with chemotherapy.

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC; 2. Burtness B et al. *Lancet* 2019:394;1915–28.

PFS for pembrolizumab + chemotherapy vs EXTREME in patients with PD-L1 expression CPS ≥1 (final analysis)[1,2]

PI

Pembro + chemo vs EXTREME

PFS

CPS ≥1

KEYNOTE-048: PFS in CPS ≥1 population[1]

PFS	Pembrolizumab + chemo (n=242)	EXTREME (n=235)
Number (%) of patients with event	212 (88%)	221 (94%)
Median in months (95% CI)	5.1 (4.7, 6.2)	5.0 (4.8, 6.0)
Hazard ratio[a] (95% CI)	0.84 (0.69, 1.02)	
p-Value[b]	0.03697	

PFS (multiple primary endpoints) statistical significance was not met[2]

Table adapted from KEYTRUDA (pembrolizumab) SmPC.

PFS assessed per RECIST v1.1 by blinded independent central review. [a]Based on the stratified Cox proportional hazard model. [b]Based on stratified log-rank test.

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; PFS, progression free survival; PD-L1, programmed death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC.; 2. Burtness B et al. *Lancet* 2019:394;1915–28.

Response to pembrolizumab + chemotherapy vs EXTREME in patients with PD-L1 expression CPS ≥1 (final analysis)[1,2]

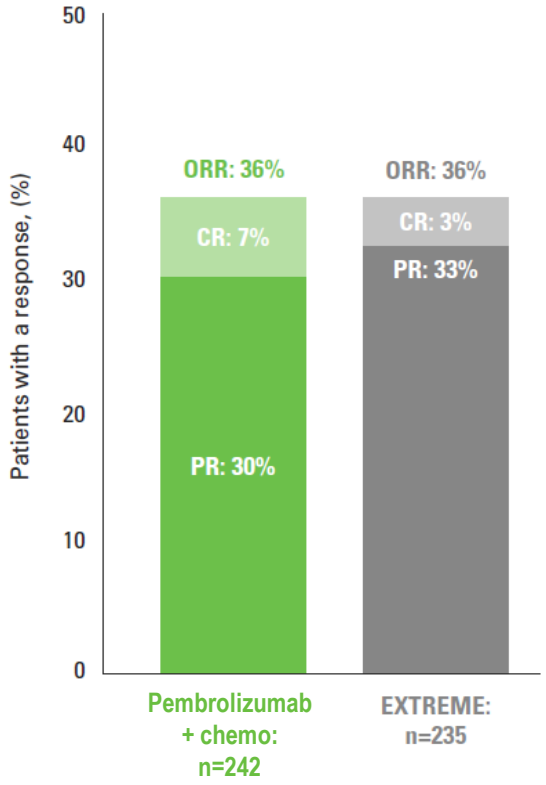
PI

Pembro + chemo vs EXTREME

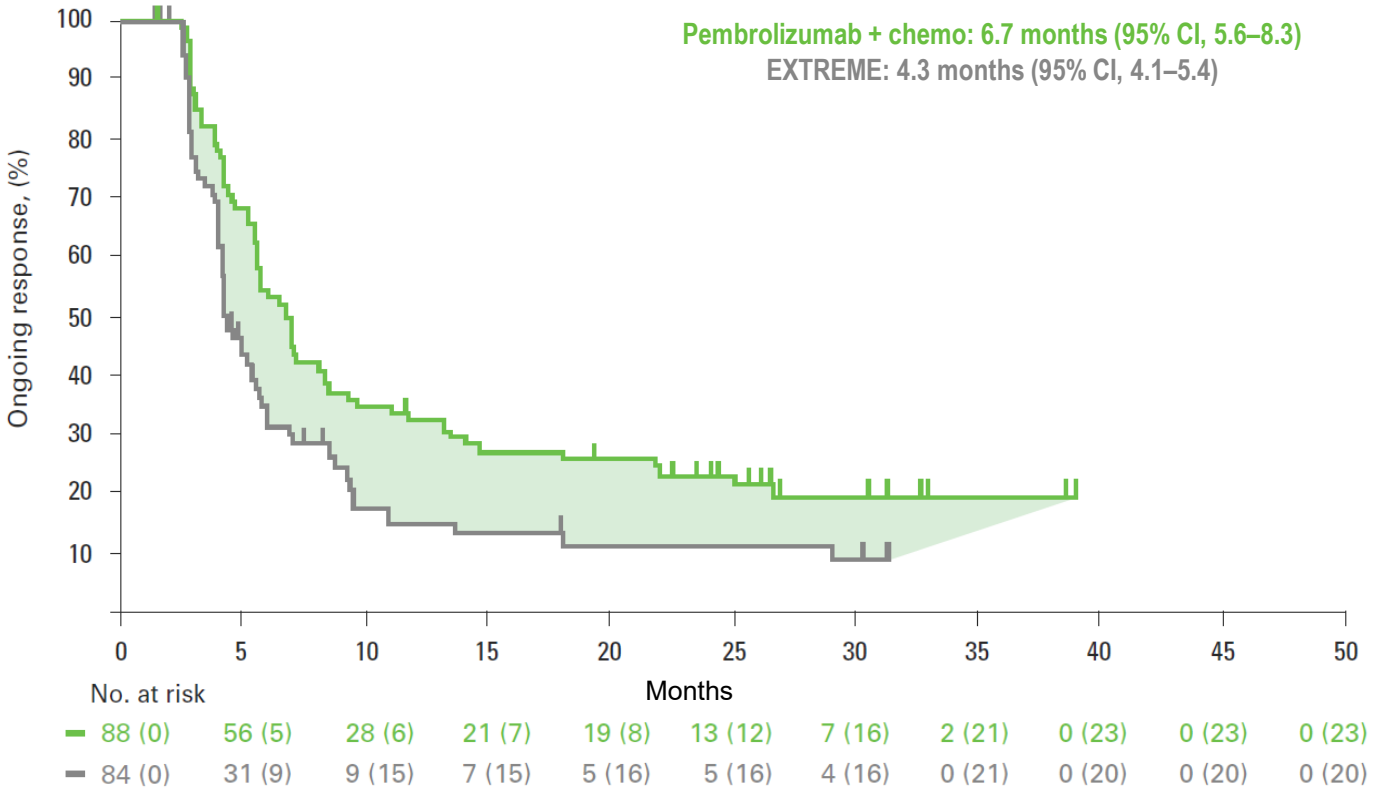
Response

CPS ≥1

KEYNOTE-048: ORR in CPS ≥1 population[a,1]



KEYNOTE-048: Median DoR in CPS ≥1 population[2]



Endpoints were not powered for statistical comparison

Figures adapted from KEYTRUDA (pembrolizumab) SmPC and Burtness B et al. *Lancet* 2019 (suppl. appx.).

Response assessed per RECIST v1.1 by blinded, independent central radiologic review. Median follow-up 13.0 months for pembrolizumab in combination with chemotherapy.

[a]In patients with measurable disease per central review baseline. A further 26% of patients in the pembrolizumab + chemotherapy arm and 33% of patients in the EXTREME arm had stable disease[2].

CI, confidence interval; CPS, combined positive score; CR, complete response; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; ORR, objective response rate; PD-L1, programmed death ligand-1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC.; Accessed April 2021; 2. Burtness B et al. *Lancet* 2019:394;1915–1928 (suppl. appx.).

All-cause AEs for pembrolizumab + chemotherapy vs EXTREME in the as-treated population (final analysis)[1,2]

PI

- **Pembrolizumab + chemotherapy showed an overall comparable safety profile** with EXTREME, with higher incidence of SAEs (both all causality and drug-related) and AEs (both all causality and drug-related) leading to deaths and leading to drug discontinuation in the pembrolizumab + chemotherapy arm compared to chemotherapy alone[2]
- The most common AEs were anaemia, nausea, constipation, fatigue, neutropenia, vomiting, and mucosal inflammation with a higher incidence of hypothyroidism, pyrexia, and blood creatinine increase in pembrolizumab + chemotherapy compared to chemotherapy alone[2]
- Increased frequency of skin-related AEs, electrolyte alterations, and infusion-related reactions were observed with standard treatment vs pembrolizumab + chemotherapy, consistent with the known toxicities of cetuximab included in the control regimen[2]

In general, the frequency of adverse reactions for pembrolizumab + chemotherapy is observed to be higher than for pembrolizumab monotherapy or chemotherapy alone, reflecting the contributions of each of these components. Physicians should exercise their own clinical judgment on the benefit to risk balance.[1]

Please refer to the SmPC and Risk Management Materials for patients for further details before prescribing

Where possible, only data for the CPS ≥1 population is shown throughout the deck; however, some safety data originate from the total population and could not be separated. These include the AEs shown on slides 28–30.

AE, adverse event; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; SAE, serious adverse event; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC. 2. Burtness B et al. *Lancet* 2019:394;1915–28.

All-cause AEs for pembrolizumab + chemotherapy vs EXTREME in the as-treated population (final analysis)

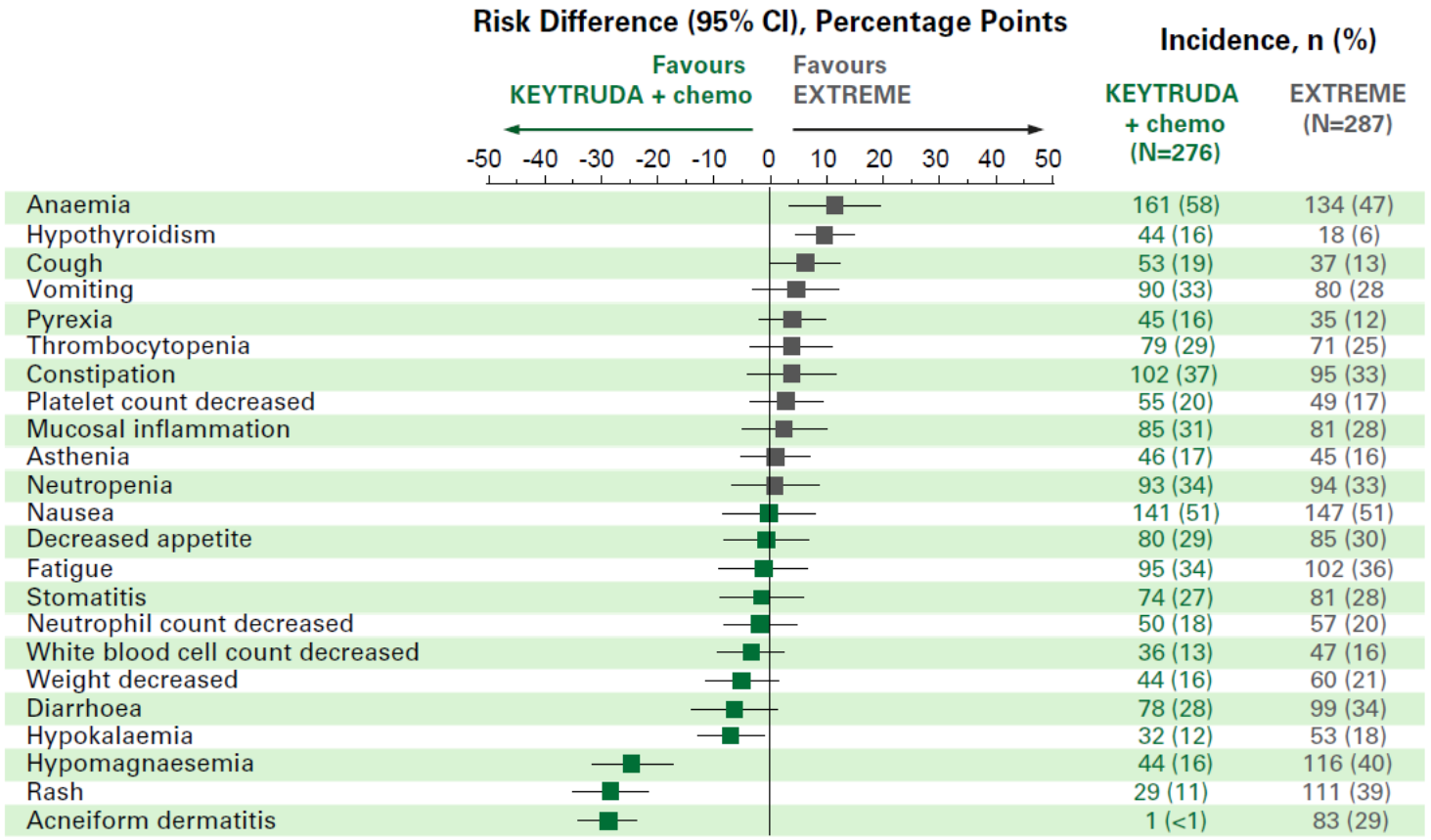
PI

Pembro + chemo vs EXTREME

Safety

Total population

Risk difference for AEs of any cause with incidence ≥15%[1]



ALL AEs	Pembrolizumab + chemo (n=276)	EXTREME (n=287)
Grade 3–5 AEs[a1]	85%	83%
AEs leading to death[a]	12%	10%
TRAEs leading to death	4%	3%
Discontinuation rate due to AEs[a2]	33%	28%

Immune-related adverse events (IRAEs) have occurred in patients receiving KEYTRUDA. Most IRAEs were reversible and manageable. Refer to the Summary of Product Characteristics before prescribing KEYTRUDA to help minimise the risks associated with treatment.[3]

Figure and table adapted from Burtness B et al. *Lancet* 2019.

[a]Any cause that occurred in ≥5% patients.. Data are n (%). Adverse events are presented according to the Medical Dictionary for Regulatory Affairs system organ class.

AE, adverse event; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; TRAE, treatment-related adverse event.

1. Burtness B et al. *Lancet* 2019:394;1915–1928; 2. Burtness B et al. *Lancet* 2019:394;1915–1928 (suppl. Appx.) 3. KEYTRUDA (pembrolizumab) SmPC.

Adverse events of special interest[a] to pembrolizumab + chemotherapy vs EXTREME in the as-treated population (final analysis)

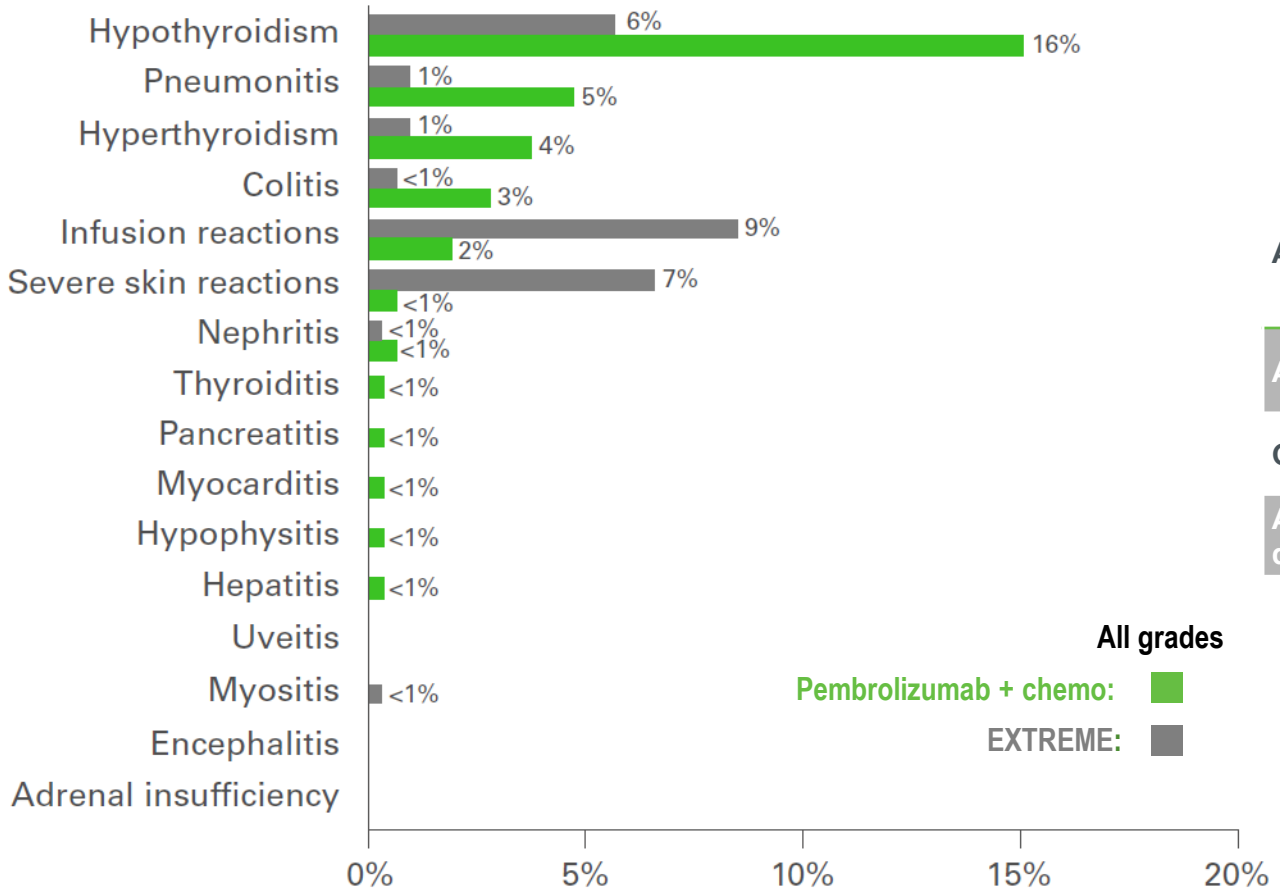
PI

Pembro + chemo vs EXTREME

Safety

Total population

AEOSI[a] in the as-treated population



ALL AEOSIs	Pembrolizumab + chemotherapy (n=276)	EXTREME (n=287)
Any Grade AEOSI[a]	26%	24%
Grade 3–5 AEOSI[a]	5%	10%
AEOSI[a] leading to death	0.4%[b]	0%

Figure and table adapted from Burtness B *et al., Lancet* 2019.

[a]Adverse events of special interest, which were based on a pre-specified list of preferred terms by the sponsor and are considered to be medically equivalent to immune-mediated events and infusion-related reactions. [b]Pneumonitis (n=1).

AEOSI, adverse event of special interest; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy.

1. Burtness B et al. *Lancet* 2019:394;1915–1928 (suppl. appx.).

II

Summary: Pembrolizumab + chemotherapy vs EXTREME for PD-L1 expression of CPS ≥1 (final analysis) [1,2]

PI

86% of pembrolizumab + chemotherapy patients (n=242/281) in KEYNOTE-048 had PD-L1 expression of CPS ≥1.[1]

Pembrolizumab + chemotherapy vs EXTREME in this population: [1,2]

- Achieved clinical and statistical significance and superiority for primary endpoint of OS (final analysis)
  - 35% reduction in risk of death (HR 0.65; 95% CI: 0.53, 0.80; p=0.00002)
- PFS (multiple primary endpoints) statistical significance was not met[1]
- Demonstrated a **comparable safety profile** in the as-treated patient population with some exceptions from both treatment arms
  - Refer to the previous slides and the SmPC for more details

Pembrolizumab + chemotherapy SmPC dosing: Fixed dose regimen Q3W (200 mg) or Q6W[a] (400 mg) intravenously over 30 minutes[2]

[a]400 mg Q6W dosing based on SmPC, not investigated in KEYNOTE-048. Median follow-up of 13.0 months for pembrolizumab in combination with chemotherapy.

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; Q3W, every 3 weeks; SmPC, Summary of Product Characteristics.

1. Burtness B et al. *Lancet* 2019:394;1915–28; 2. KEYTRUDA (pembrolizumab) SmPC.

Appendix

Click the links below to navigate to the section of interest

EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy.

PI

KEYNOTE-048: Original study – final analysis

Pembrolizumab monotherapy vs EXTREME

PD-L1 expression CPS ≥20

Click the links below to navigate to the section of interest

EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy.

OS for pembrolizumab monotherapy vs EXTREME in patients with PD-L1 expression CPS ≥20 (final analysis)[1,2]

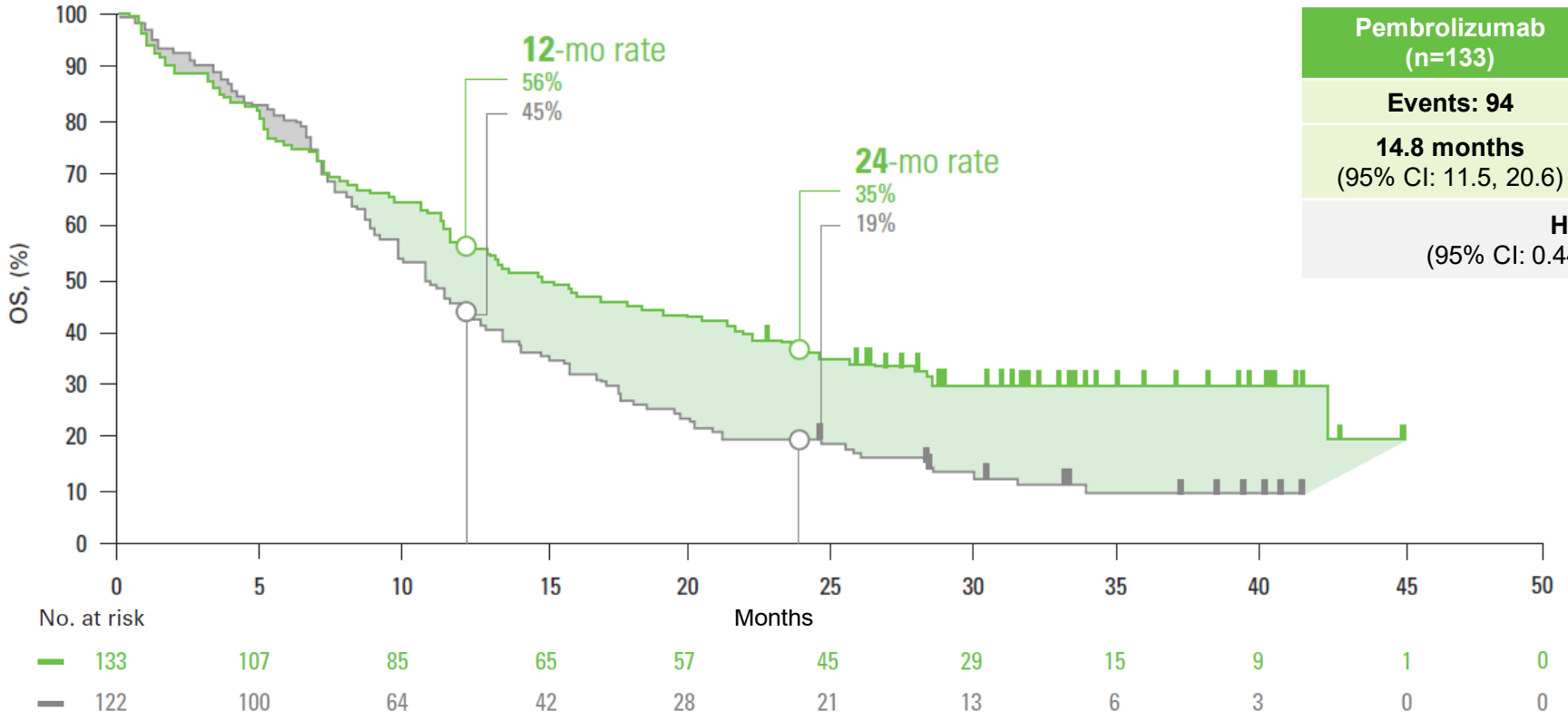
PI

Pembro vs EXTREME

OS

CPS ≥20

KEYNOTE-048: OS in CPS ≥20 population[2]



Median OS in CPS ≥20 population[2]

Pembrolizumab (n=133)	EXTREME (n=122)
Events: 94	**Events: 108**
14.8 months (95% CI: 11.5, 20.6)	**10.7 months** (95% CI: 8.8, 12.8)
HR, 0.58 (95% CI: 0.44, 0.78); p=0.0001	

Figure adapted from Burtness B et al. *Lancet* 2019 (suppl. appx.).

Median follow-up 11.5 months for pembrolizumab monotherapy. n= 133 (52%) vs standard treatment n= 122 (48%).

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC; 2. Burtness B et al. *Lancet* 2019:394;1915–28 (suppl. appx.).

PFS for pembrolizumab monotherapy vs EXTREME in patients with PD-L1 expression of CPS ≥20 (final analysis)[1,2]

PI

Pembro vs EXTREME

PFS

CPS ≥20

KEYNOTE-048: PFS in CPS ≥20 population[1]

PFS	Pembrolizumab (n=133)	EXTREME (n=122)
Number (%) of patients with event	115 (86.5%)	114 (93.4%)
Median in months (95% CI)	3.4 (3.2, 3.8)	5.3 (4.8, 6.3)
Hazard ratio[a] (95% CI)	0.99 (0.76, 1.29)	
p-Value[b]	0.46791	

PFS (multiple primary endpoints) statistical significance was not met[2]

Table adapted from KEYTRUDA (pembrolizumab) SmPC.

PFS assessed per RECIST v1.1 by blinded independent central radiologic review. [a]Based on the stratified Cox proportional hazard model. [b]Based on stratified log-rank test.

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; PD-L1, programmed death ligand-1; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC; 2. Burtness B et al. *Lancet* 2019:394;1915–28.

Response to pembrolizumab monotherapy vs EXTREME in patients with PD-L1 expression CPS ≥20 (final analysis)[1]

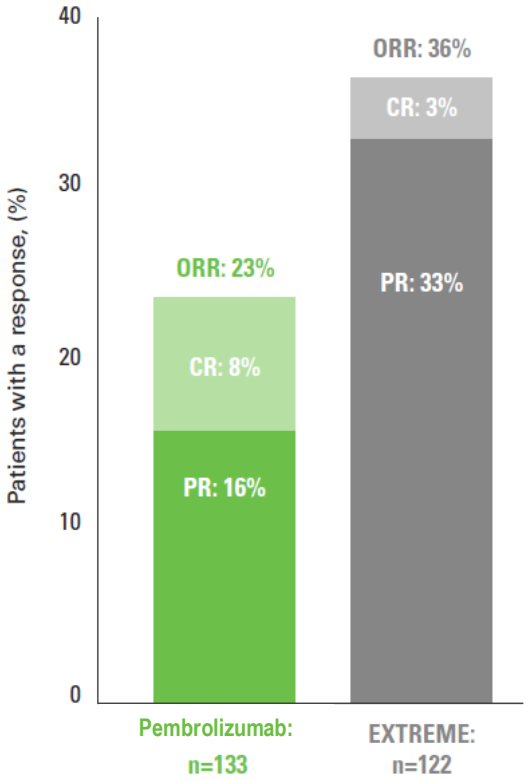
PI

Pembro vs EXTREME

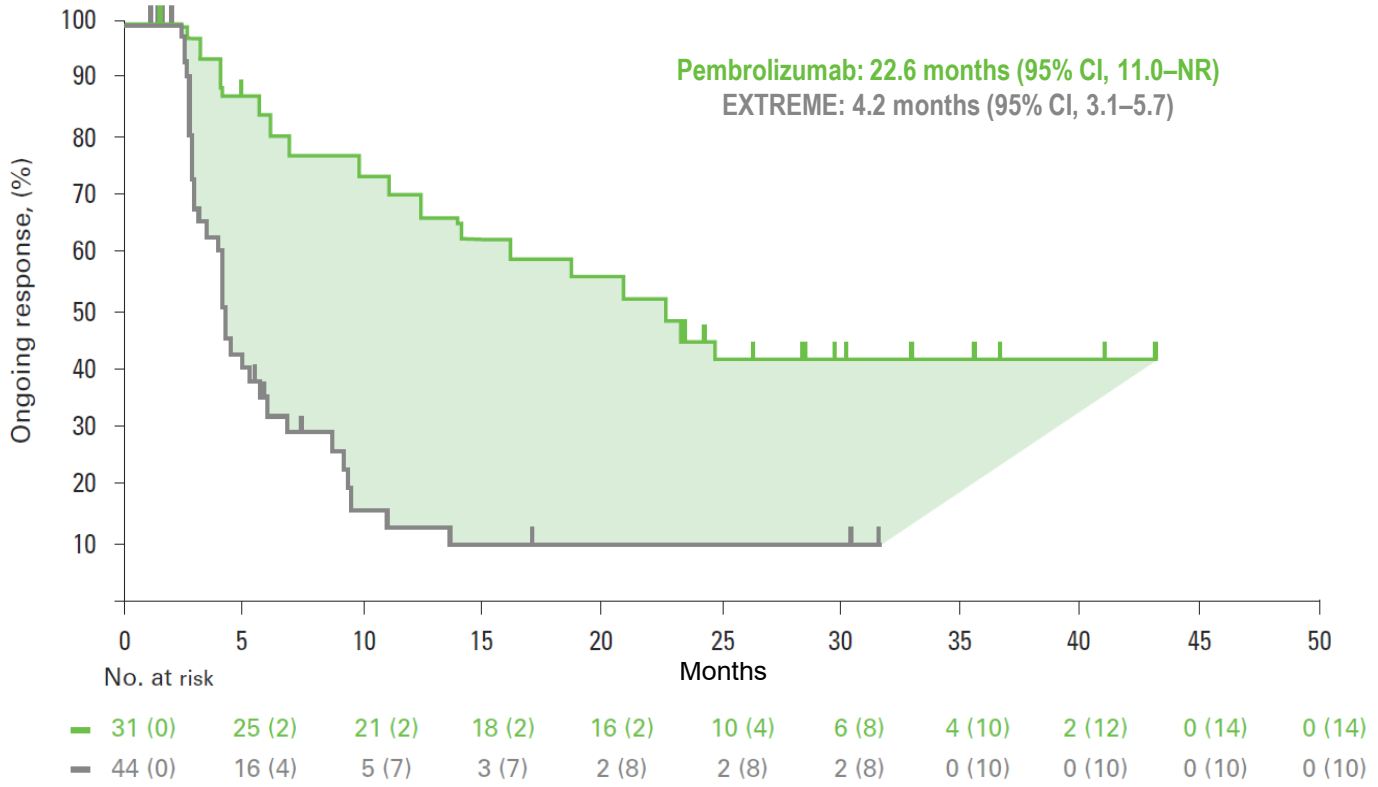
Response

CPS ≥20

KEYNOTE-048: ORR in CPS ≥20 population[a,1]



KEYNOTE-048: Median DoR in CPS ≥20 population[1]



Endpoints were not powered for statistical comparison

Figures adapted from Burtness B et al. Lancet 2019 (suppl. appx.).

Response assessed per RECIST v1.1 by blinded independent central radiologic review. Median follow-up 11.5 months for pembrolizumab monotherapy.

[a]In patients with measurable disease per central review baseline. A further 30% of patients in the pembrolizumab monotherapy arm and 35% of patients in the EXTREME arm had stable disease.

CI, confidence interval; CPS, combined positive score; CR, complete response; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; NR, not reached; ORR, objective response rate; PD-L1, programmed death ligand-1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Burtness B et al. Lancet 2019:394;1915–28 (suppl. appx.)

Summary: Pembrolizumab monotherapy vs EXTREME for PD-L1 expression of CPS ≥20 (final analysis)[1–3]

PI

Pembrolizumab monotherapy vs EXTREME in patients with PD-L1 expression levels of CPS ≥20:

- Achieved clinical and statistical significance and superiority for primary endpoint of OS (final analysis)[1]
  - 42% reduction in risk of death (HR, 0.58; 95% CI: 0.44, 0.78; p=0.0001)
- PFS statistical significance was not met[2]
- Demonstrated durable DoR in patients who responded to treatment[3]
- Refer to the previous sections and SmPC for pembrolizumab monotherapy safety data

Pembrolizumab monotherapy SmPC dosing: Fixed dose regimen Q3W (200 mg) or Q6W[a] (400 mg) intravenously over 30 minutes[2]

[a]400 mg Q6W dosing based on SmPC, not investigated in KEYNOTE-048. Median follow-up 11.5 months for pembrolizumab monotherapy.

CI, confidence interval; CPS, combined positive score; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 week; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC.; 2. Burtness B et al. *Lancet* 2019:394;1915–28.; 3. Burtness B et al. *Lancet* 2019:394;1915–28 (suppl. appx.);

PI

KEYNOTE-048: Original study – final analysis

Pembrolizumab + chemotherapy vs EXTREME

PD-L1 expression CPS ≥20

Click the links below to navigate to the section of interest

EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy.

OS for pembrolizumab + chemotherapy vs EXTREME in patients with PD-L1 expression CPS ≥20 (final analysis)[1,2]

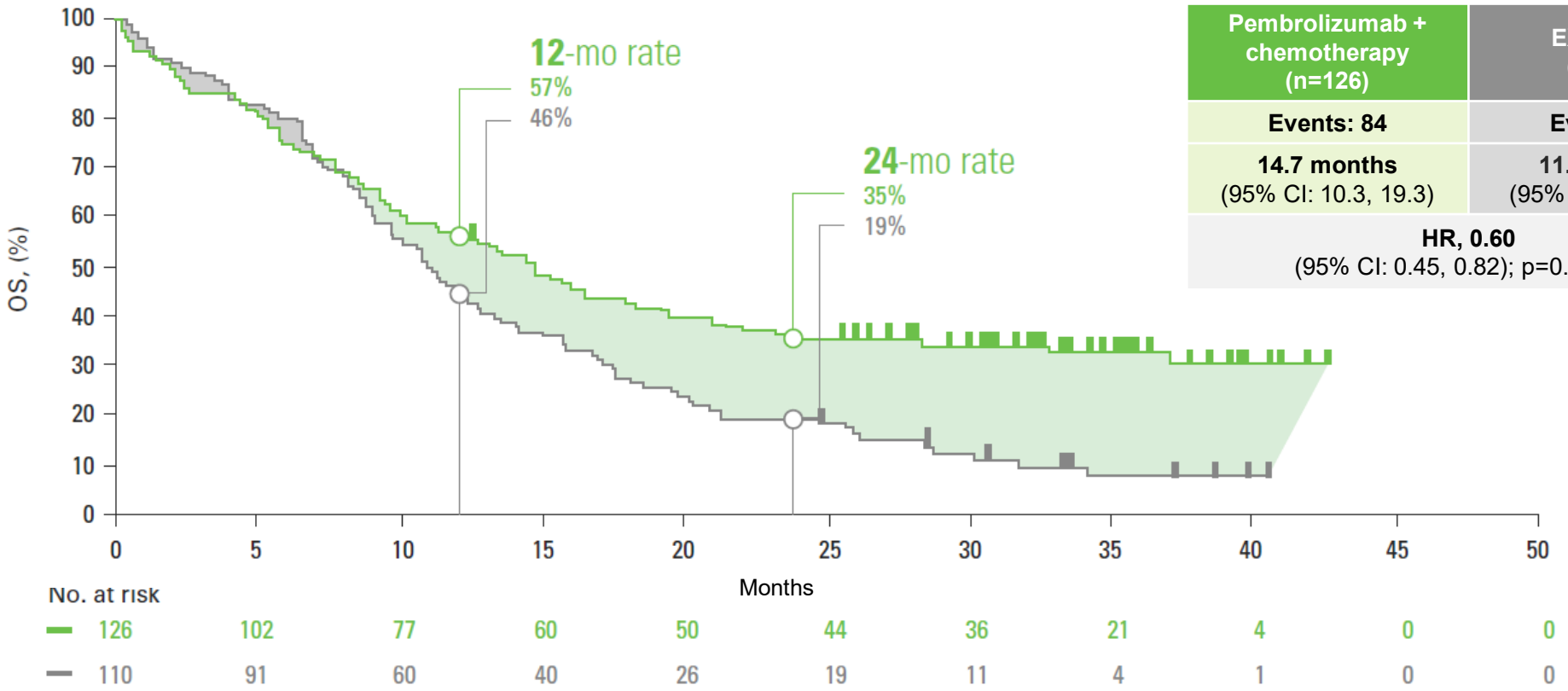
PI

Pembro + chemo vs EXTREME

OS

CPS ≥20

KEYNOTE-048: OS in CPS ≥20 population[2]



Median OS in CPS ≥20 population[2]

Pembrolizumab + chemotherapy (n=126)	EXTREME (n=110)
Events: 84	**Events: 98**
14.7 months (95% CI: 10.3, 19.3)	**11.0 months** (95% CI: 9.2, 13.0)
HR, 0.60 (95% CI: 0.45, 0.82); p=0.00044)	

Figure adapted from Burtness B et al. *Lancet* 2019. Median follow-up 13.0 months for pembrolizumab in combination with chemotherapy.

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC.; 3. Burtness B et al. *Lancet* 2019:394;1915–28.

PFS for pembrolizumab + chemotherapy vs EXTREME in patients with PD-L1 expression CPS ≥20 (final analysis)[1,2]

PI

Pembro + chemo vs EXTREME

PFS

CPS ≥20

KEYNOTE-048: PFS in CPS ≥20 population[1]

PFS	Pembrolizumab + chemo (n=126)	EXTREME (n=110)
Number (%) of patients with event	106 (84.1%)	104 (94.5%)
Median in months (95% CI)	5.8 (4.7, 7.6)	5.3 (4.9, 6.3)
Hazard ratio[a] (95% CI)	0.76 (0.58, 1.01)	
p-Value[b]	0.02951	

PFS (multiple primary endpoints) statistical significance was not met[2]

Table adapted from KEYTRUDA (pembrolizumab) SmPC.

PFS assessed per RECIST v1.1 by blinded independent central review. [a]Based on the stratified Cox proportional hazard model. [b]Based on stratified log-rank test.

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; PD-L1, programmed death ligand-1; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC; 2. Burtness B et al. *Lancet* 2019:394;1915–28.

Response to pembrolizumab + chemotherapy vs EXTREME in patients with PD-L1 expression CPS (final analysis) ≥20[1]

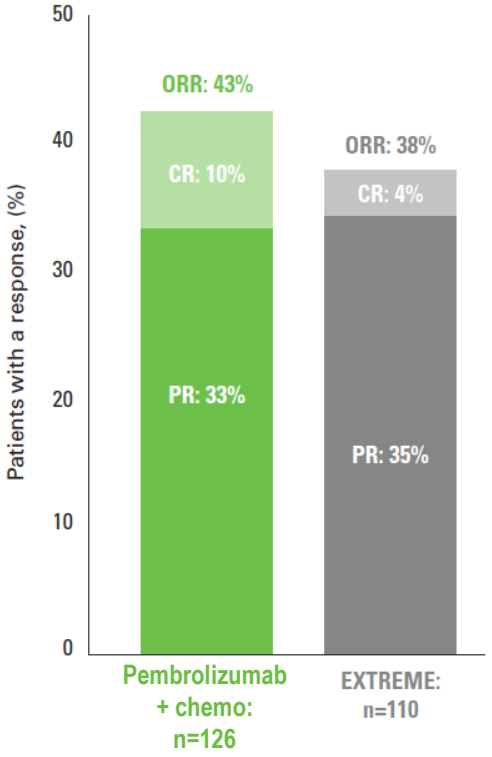
PI

Pembro + chemo vs EXTREME

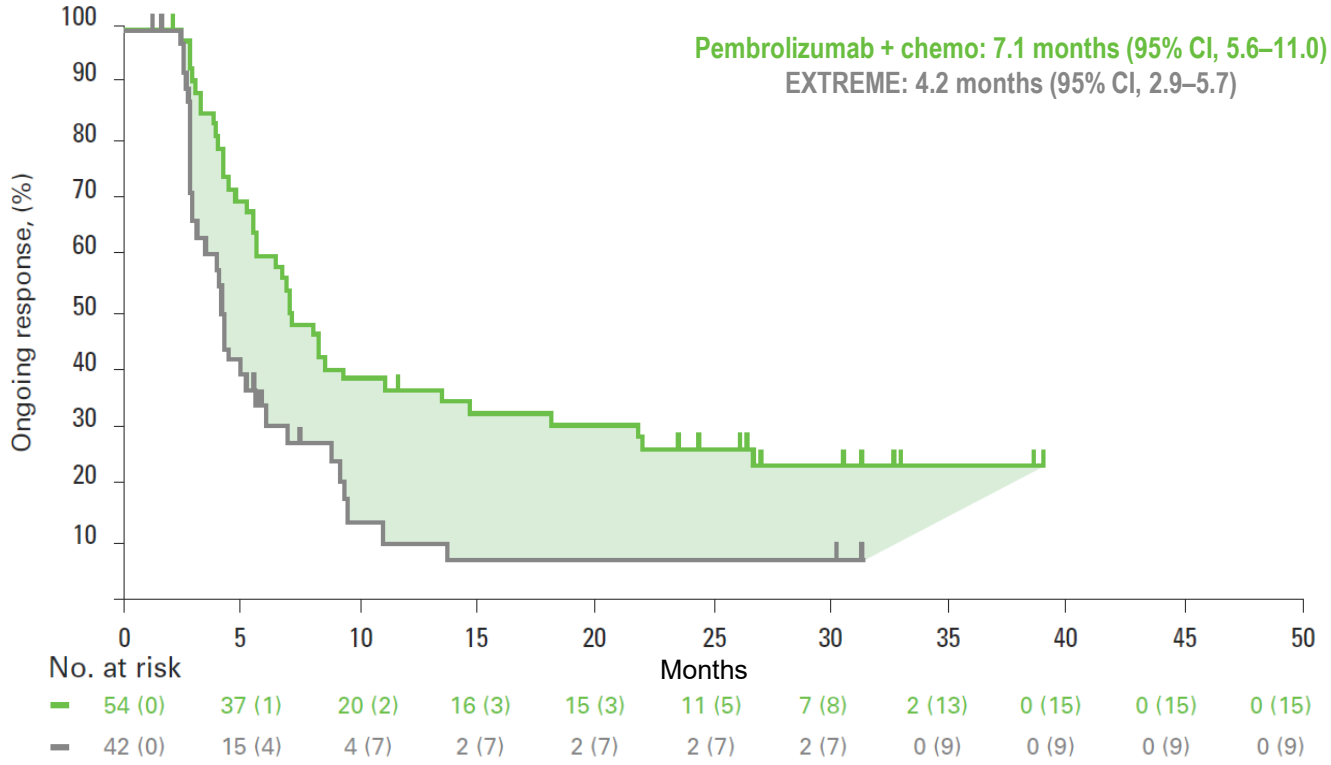
Response

CPS ≥20

KEYNOTE-048: ORR in CPS ≥20 population[a,1]



KEYNOTE-048: Median DoR in CPS ≥20 population[1]



Endpoints were not powered for statistical comparison

Figures adapted from Burtness B et al. *Lancet* 2019 (suppl. appx.).

Response assessed per RECIST v1.1 by blinded, independent central radiologic review. Median follow-up 13.0 months for pembrolizumab in combination with chemotherapy.

[a]In patients with measurable disease per central review baseline. A further 23% in the pembrolizumab + chemotherapy arm and 35% in the EXTREME arm had stable disease[2].

CI, confidence interval; CPS, combined positive score; CR, complete response; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; ORR, objective response rate; PD-L1, programmed death ligand-1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Burtness B et al. *Lancet* 2019:394;1915–28 (suppl. appx.).

Summary: Pembrolizumab + chemotherapy vs EXTREME for PD-L1 expression of CPS ≥20 (final analysis)[1–3]

PI

Pembrolizumab + chemotherapy vs EXTREME in patients with PD-L1 expression levels of CPS ≥20:

- Achieved clinical and statistical significance and superiority for primary endpoint of OS (final analysis)[1]
  - 40% reduction in risk of death (HR, 0.60; 95% CI; 0.45, 0.82; p=0.00044)
- PFS statistical significance was not met[2]
- Demonstrated durable DoR in patients who responded to treatment[3]
- Refer to the previous sections and SmPC for pembrolizumab + chemotherapy safety data

Pembrolizumab + chemotherapy SmPC dosing: Fixed dose regimen Q3W (200 mg) or Q6W[a] (400 mg) intravenously over 30 minutes[2]

[a]400 mg Q6W dosing based on SmPC, not investigated in KEYNOTE-048. Median follow-up 13.0 months for pembrolizumab in combination with chemotherapy.

CI, confidence interval; CPS, combined positive score; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; SmPC, Summary of Product Characteristics.

1. KEYTRUDA (pembrolizumab) SmPC.; 2. Burtness B et al. *Lancet* 2019:394;1915–28. 3. Burtness B et al. Lancet 2019:394;1915–28 (suppl. appx.).

KEYNOTE-048: Original study – exploratory subgroup analysis

PD-L1 expression CPS ≥1 and <20

Click the links below to navigate to the section of interest

Pembrolizumab monotherapy: OS/PFS
Pembrolizumab monotherapy: ORR/DoR
Pembrolizumab + chemotherapy: OS/PFS
Pembrolizumab + chemotherapy: ORR/DoR

An exploratory subgroup analysis was performed in KEYNOTE-048 in patients whose tumours expressed PD-L1 CPS ≥1 to <20

Pembrolizumab monotherapy: n=124 (48%) vs. standard treatment[a]: n=133 (52%)

Efficacy results for pembrolizumab as monotherapy vs EXTREME by PD-L1 expression (CPS ≥1 to <20)

Endpoint	Pembrolizumab monotherapy n=124	EXTREME n=133
OS		
Number (%) of patients with event	103 (83.1)	121 (91.0)
Median in months (95% CI)	10.8 (9.0, 12.6)	10.1 (8.7, 12.1)
Hazard ratio[b] (95% CI)	0.86 (0.66, 1.12)	
OS rate at 6 months (95% CI)	67.6 (58.6, 75.1)	78.0 (70.0, 84.2)
OS rate at 12 months (95% CI)	44.0 (35.1, 52.5)	42.4 (33.9, 50.7)
OS rate at 24 months (95% CI)	22.0 (15.1, 29.6)	15.9 (10.3, 22.6)
PFS		
Number (%) of patients with event	113 (91.1)	123 (92.5)
Median in months (95% CI)	2.2 (2.1, 2.9)	4.9 (3.8, 6.0)
Hazard ratio[b] (95% CI)	1.25 (0.96, 1.61)	
PFS rate at 6 months (95% CI)	24.2 (17.1, 32.0)	41.4 (32.8, 49.7)
PFS rate at 12 months (95% CI)	17.5 (11.4, 24.7)	12.1 (7.2, 18.5)
PFS rate at 24 months (95% CI)	8.3 (4.3, 14.1)	6.3 (2.9, 11.5)

Exploratory subgroup analysis is not powered for statistical comparison

Table adapted from KEYTRUDA (pembrolizumab) SmPC.

[a]EXTREME: Cetuximab, platinum, and 5-FU; [b]Based on the stratified Cox proportional hazard model.

5-FU, 5 fluorouracil; CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; NR; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; SmPC, Summary of Product Characteristics.

KEYTRUDA (pembrolizumab) SmPC.

An exploratory subgroup analysis was performed in KEYNOTE-048 in patients whose tumours expressed PD-L1 CPS ≥1 to <20

PI

Pembrolizumab monotherapy: n=124 (48%) vs. standard treatment[a]: n=133 (52%)

Efficacy results for pembrolizumab as monotherapy vs EXTREME by PD-L1 expression (CPS ≥1 to <20)

Endpoint	Pembrolizumab monotherapy n=124	EXTREME n=133
Objective response rate		
ORR[b] (95% CI)	14.5 (8.8, 22.0)	33.8 (25.9, 42.5)
Response duration		
Number of responders	18	45
Median in months (range)	NR (1.5+, 38.9+)	5.0 (1.4+, 38.7+)

Exploratory subgroup analysis is not powered for statistical comparison

Table adapted from KEYTRUDA (pembrolizumab) SmPC.

[a]EXTREME: Cetuximab, platinum, and 5-FU; [b]Response: Best objective response as confirmed complete response or partial response.

5-FU, 5 fluorouracil; CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; NR, not reached; ORR, objective response rate; PD-L1, programmed death ligand-1; SmPC, Summary of Product Characteristics.

KEYTRUDA (pembrolizumab) SmPC.

An exploratory subgroup analysis was performed in KEYNOTE-048 in patients whose tumours expressed PD-L1 CPS ≥1 to <20

PI

Pembrolizumab plus chemotherapy: n=116 (45%) vs. standard treatment[a]: n=125 (49%)

Efficacy results for pembrolizumab plus chemotherapy vs EXTREME by PD-L1 expression (CPS ≥1 to <20)

Endpoint	Pembrolizumab + chemotherapy n=116	EXTREME n=125
OS		
Number (%) of patients with event	93 (80.2)	115 (92.0)
Median in months (95% CI)	12.7 (9.4, 15.3)	9.9 (8.6, 11.5)
Hazard ratio[b] (95% CI)	0.71 (0.54, 0.94)	
OS rate at 6 months (95% CI)	76.7 (67.9, 83.4)	77.4 (69.0, 83.8)
OS rate at 12 months (95% CI)	52.6 (43.1, 61.2)	41.1 (32.4, 49.6)
OS rate at 24 months (95% CI)	25.9 (18.3, 34.1)	14.5 (9.0, 21.3)
PFS		
Number (%) of patients with event	106 (91.4)	117 (93.6)
Median in months (95% CI)	4.9 (4.2, 5.3)	4.9 (3.7, 6.0)
Hazard ratio[b] (95% CI)	0.93 (0.71, 1.21)	
PFS rate at 6 months (95% CI)	40.1 (31.0, 49.0)	40.0 (31.2, 48.5)
PFS rate at 12 months (95% CI)	15.1 (9.1, 22.4)	11.3 (6.4, 17.7)
PFS rate at 24 months (95% CI)	8.5 (4.2, 14.7)	5.0 (1.9, 10.1)

Exploratory subgroup analysis is not powered for statistical comparison

Table adapted from KEYTRUDA (pembrolizumab) SmPC.

[a]EXTREME: Cetuximab, platinum, and 5-FU; [b]Based on the stratified Cox proportional hazard model.

5-FU, 5 fluorouracil; CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; NR; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; SmPC, Summary of Product Characteristics.

KEYTRUDA (pembrolizumab) SmPC.

An exploratory subgroup analysis was performed in KEYNOTE-048 in patients whose tumours expressed PD-L1 CPS ≥1 to <20

PI

Pembrolizumab plus chemotherapy: n=116 (45%) vs. standard treatment[a]: n=125 (49%)

Efficacy results for pembrolizumab plus chemotherapy vs EXTREME by PD-L1 expression (CPS ≥1 to <20)

Endpoint	Pembrolizumab + chemotherapy n=116	EXTREME n=125
Objective response rate		
ORR[b] (95% CI)	29.3 (21.2, 38.5)	33.6 (25.4, 42.6)
Response duration		
Number of responders	34	42
Median in months (range)	5.6 (1.6+, 25.6+)	4.6 (1.4+, 31.4+)

Exploratory subgroup analysis is not powered for statistical comparison

Table adapted from KEYTRUDA (pembrolizumab) SmPC.

[a]EXTREME: Cetuximab, platinum, and 5-FU; [b]Response: Best objective response as confirmed complete response or partial response.

5-FU, 5 fluorouracil; CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; NR, not reached; ORR, objective response rate; PD-L1, programmed death ligand-1; SmPC, Summary of Product Characteristics.

KEYTRUDA (pembrolizumab) SmPC.

KEYNOTE-048: Long-term follow up

Pembrolizumab ± chemotherapy vs EXTREME

Click the links below to navigate to the section of interest

EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy.

KEYNOTE-048: Long-term follow up

PI

Study overview

- The findings of the original KEYNOTE-048 study, as previously presented, led to the approval of pembrolizumab as first-line treatment for recurrent or metastatic HNSCC[1,2]
- Objective of this analysis: to present 4-year follow-up data (data cut-off: 18 February 2020)[3,4]

1. Burtness B et al. *Lancet* 2019:394;1915–28; 2. KEYTRUDA (pembrolizumab) SmPC.; 3. Greil R et al. Presented at ESMO Virtual Congress 2020; 19–21 September 2020; 4. NCT02358031. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02358031. Accessed February 2021.

Long-term OS for pembrolizumab monotherapy vs EXTREME in patients with PD-L1 expression CPS ≥1: 4-year follow-up data

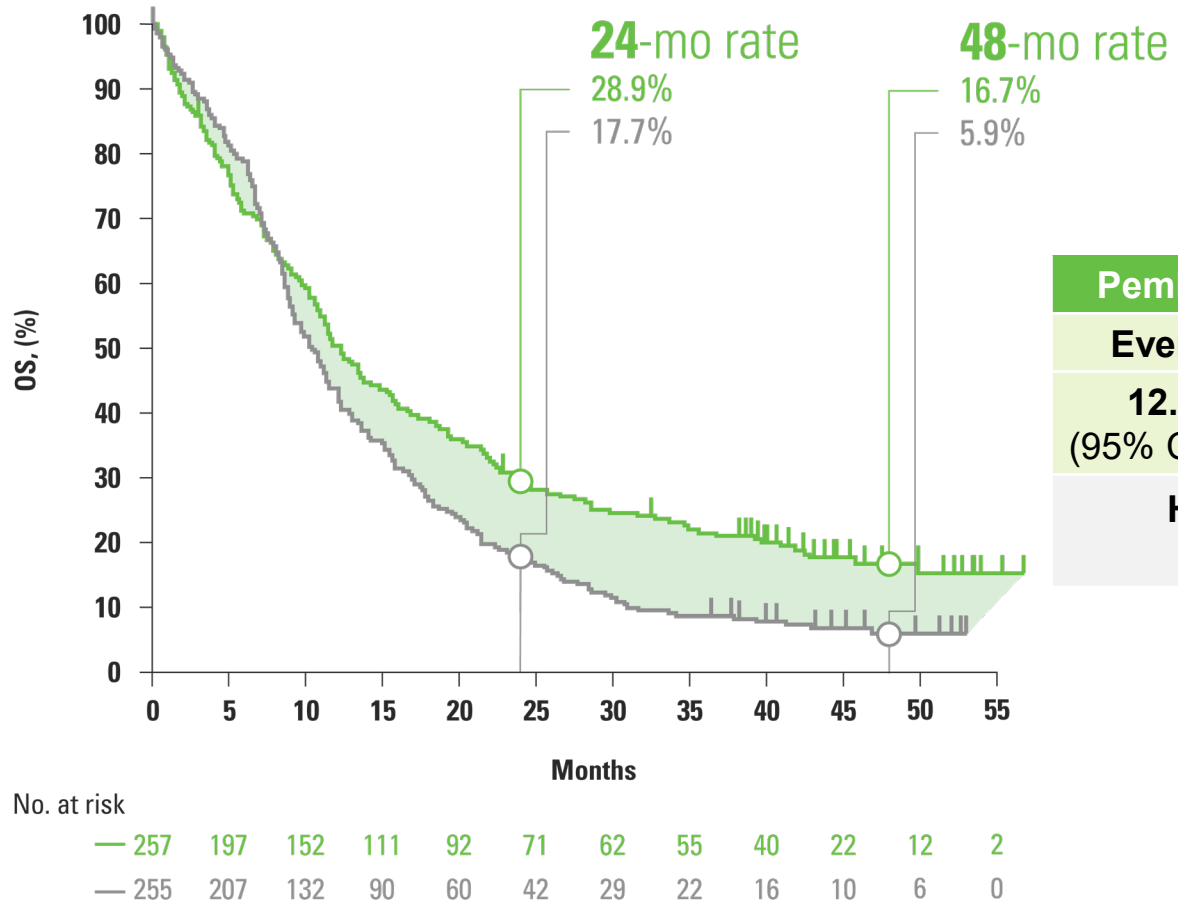
PI

Pembro vs EXTREME

OS

CPS ≥1

KEYNOTE-048: OS in CPS ≥1 population



Median OS in CPS ≥1

Pembrolizumab	EXTREME
Events: 81.7%	**Events: 92.9%**
12.3 months (95% CI: 10.8, 14.8)	**10.4 months** (95% CI: 9.0, 11.7)
HR: 0.71 (95% CI: 0.61, 0.89); p=0.00080[a]	

Analysis was not powered for statistical comparison

Figure adapted from Greil et al. ESMO 2020. Median follow up 45.0 months for pembrolizumab monotherapy. Data cut-off: 18 February 2020. [a]Nominal, unadjusted one-sided p-value based on log-rank test.
CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; mo, month; OS, overall survival; PD-L1, programmed death ligand-1.
Greil R et al. Presented at ESMO Virtual Congress 2020; 19–21 September 2020.

Long-term OS for pembrolizumab monotherapy vs EXTREME in patients with PD-L1 expression CPS ≥20: 4-year follow-up data

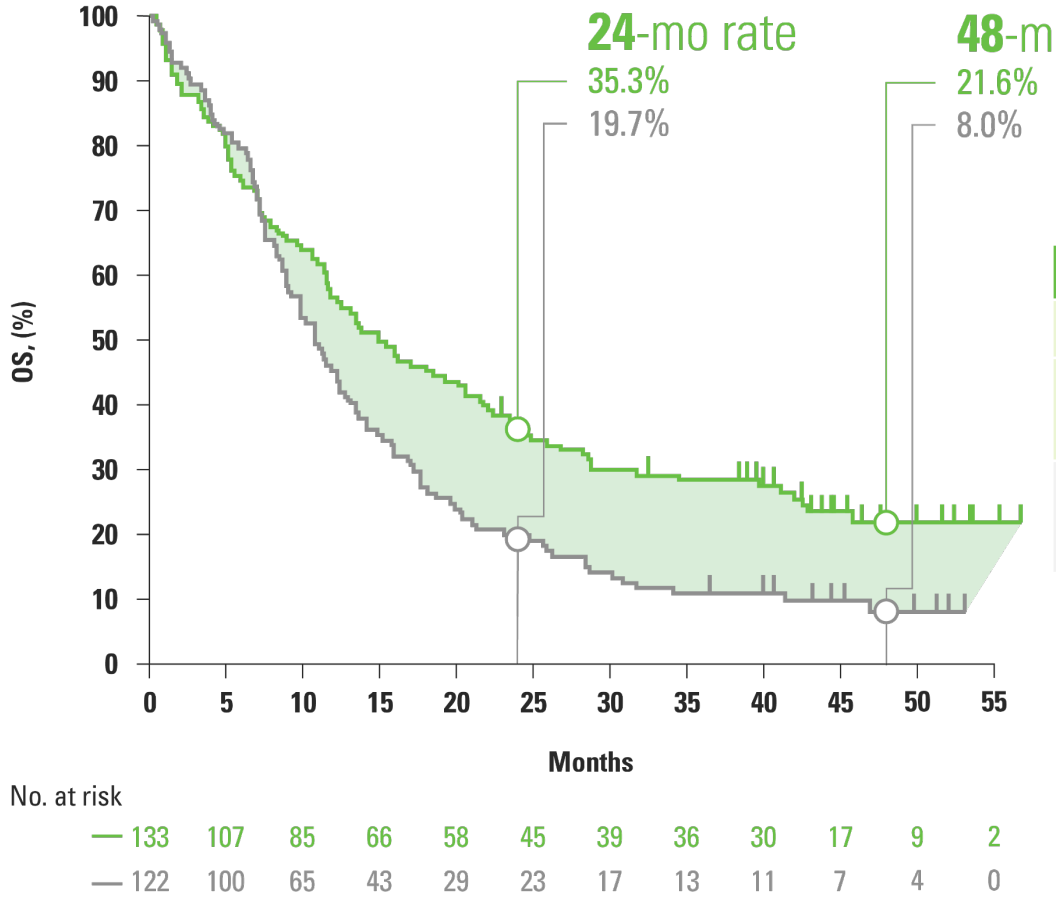
PI

Pembro vs EXTREME

OS

CPS ≥20

KEYNOTE-048: OS in CPS ≥20 population



Median OS in CPS ≥20

Pembrolizumab	EXTREME
Events: 75.9%	**Events: 91.0%**
14.9 months (95% CI: 11.5, 20.6)	**10.8 months** (95% CI: 8.8, 12.8)
HR: 0.61 (95% CI: 0.46, 0.81); p=0.00034[a]	

Analysis was not powered for statistical comparison

Figure adapted from Greil et al. ESMO 2020. Median follow up 45.0 months for pembrolizumab monotherapy. Data cut-off: 18 February 2020. [a]Nominal, unadjusted one-sided p-value based on log-rank test.
CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; mo, month; OS, overall survival; PD-L1, programmed death ligand-1.
Greil R et al. Presented at ESMO Virtual Congress 2020; 19–21 September 2020.

Long-term OS for pembrolizumab + chemotherapy vs EXTREME in patients with PD-L1 expression CPS ≥1: 4-year follow-up data

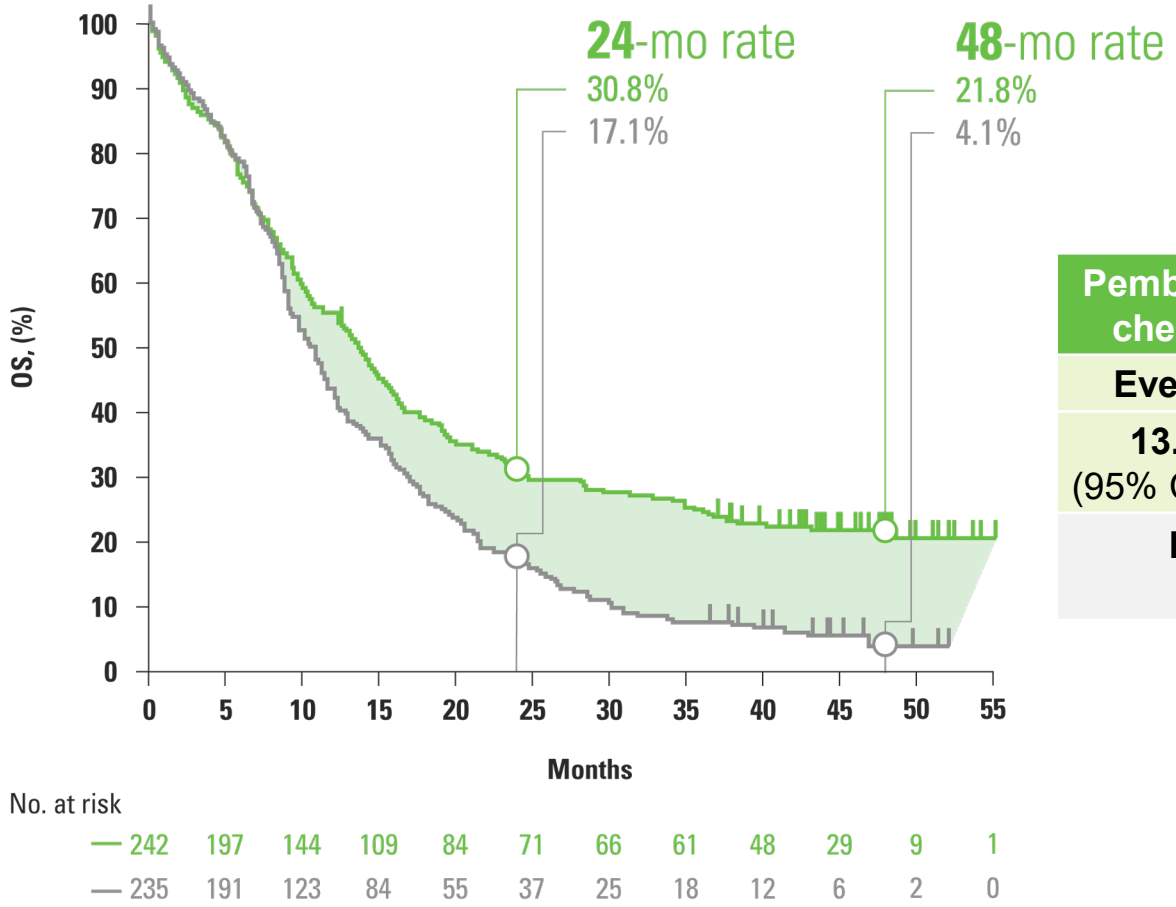
PI

Pembro + chemo vs EXTREME

OS

CPS ≥1

KEYNOTE-048: OS in CPS ≥1 population



Median OS in CPS ≥1

Pembrolizumab + chemotherapy	EXTREME
Events: 78.1%	**Events: 94.0%**
13.6 months (95% CI: 10.7, 15.5)	**10.6 months** (95% CI: 9.1, 11.7)
HR, 0.64 (95% CI: 0.53, 0.78); p=0.00001[a]	

Analysis was not powered for statistical comparison

Figure adapted from Greil et al. ESMO 2020. Median follow up 44.5 months for pembrolizumab + chemotherapy. Data cut-off: 18 February 2020. [a]Nominal, unadjusted one-sided p-value based on log-rank test.
CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; mo, month; OS, overall survival; PD-L1, programmed death ligand-1.
Greil R et al. Presented at ESMO 2020; 19–21 September 2020.

Long-term OS for pembrolizumab + chemotherapy vs EXTREME in patients with PD-L1 expression CPS ≥20: 4-year follow-up data

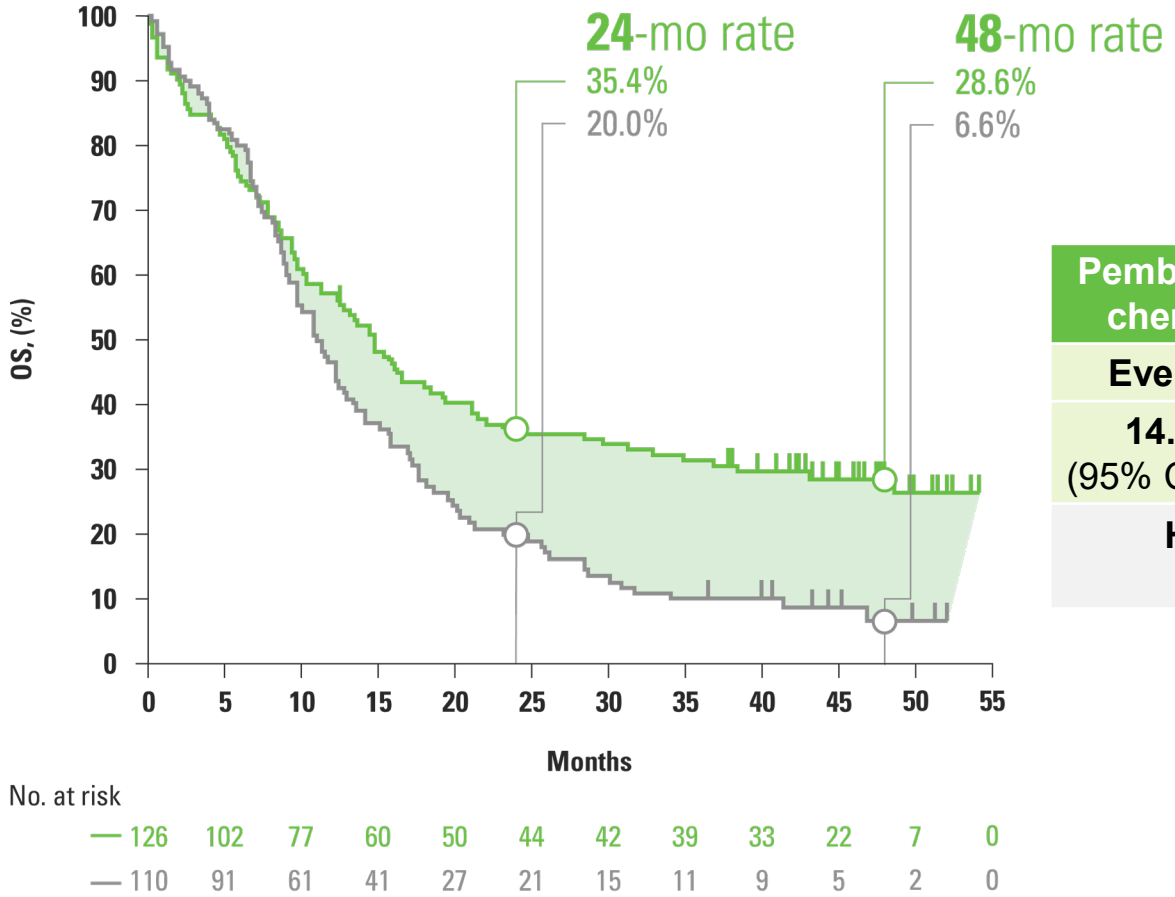
PI

Pembro + chemo vs EXTREME

OS

CPS ≥20

KEYNOTE-048: OS in CPS ≥20 population



Median OS in CPS ≥20

Pembrolizumab + chemotherapy	EXTREME
Events: 71.4%	**Events: 91.8%**
14.7 months (95% CI: 10.3, 19.3)	**11.1 months** (95% CI: 9.2, 13.0)
HR, 0.62 (95% CI: 0.46, 0.84); p=0.00082[a]	

Analysis was not powered for statistical comparison

Figure adapted from Greil et al. ESMO 2020. Median follow up 44.5 months for pembrolizumab + chemotherapy. Data cut-off: 18 February 2020. [a]Nominal, unadjusted one-sided p-value based on log-rank test.
CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; mo, month; OS, overall survival; PD-L1, programmed death ligand-1.
Greil R et al. Presented at ESMO 2020; 19–21 September 2020.

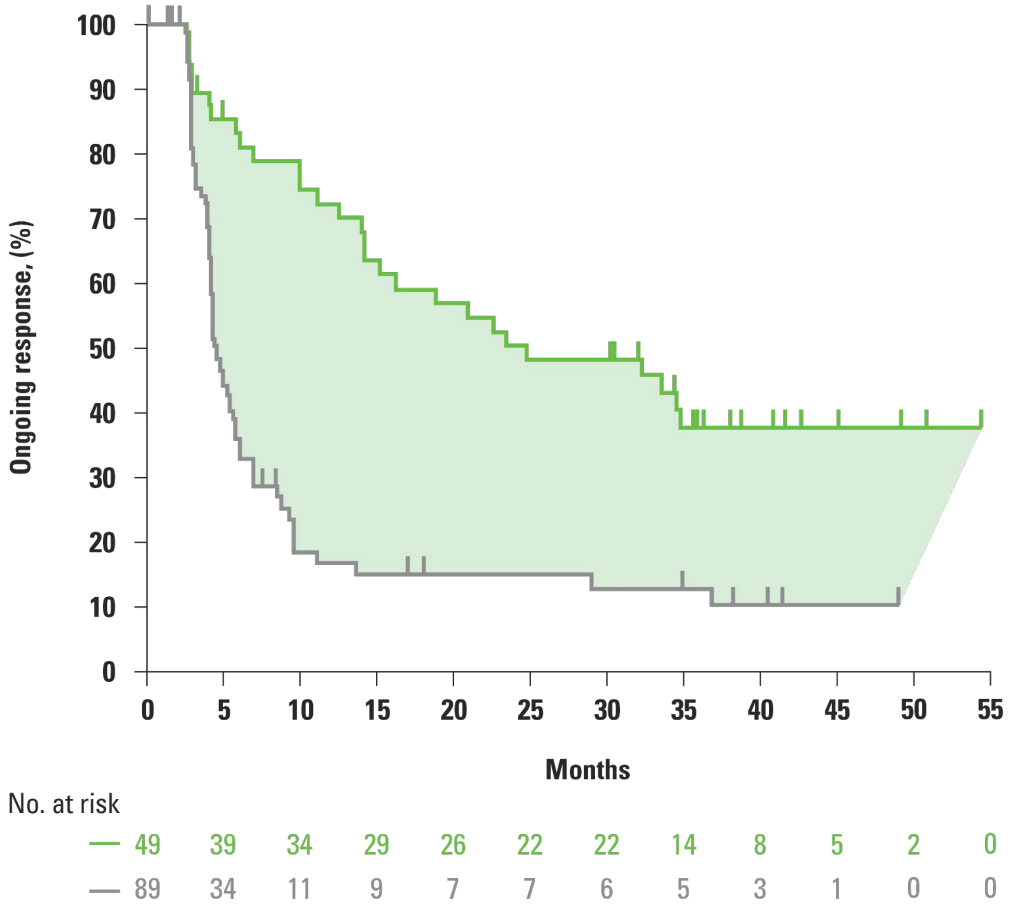
Long-term DoR for pembrolizumab monotherapy vs EXTREME in patients with PD-L1 expression CPS ≥1: 4-year follow-up data

Pembro vs EXTREME

DoR

CPS ≥1

KEYNOTE-048: DoR in CPS ≥1 population



Median DoR in CPS ≥1

Pembrolizumab	EXTREME
ORR: 19.1%	**ORR: 34.9%**
24.8 months (range: 1.5+ to 54.4+)	**4.5 months** (range: 1.2+ to 49.1+)

Analysis was not powered for statistical comparison

Figure adapted from Greil et al. ESMO 2020. Median follow up 45.0 months for pembrolizumab monotherapy. Data cut-off: 18 February 2020.

CPS, combined positive score; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; ORR, overall response rate; PD-L1, programmed death ligand-1.

Greil R et al. Presented at ESMO 2020; 19–21 September 2020.

Long-term DoR for pembrolizumab monotherapy vs EXTREME in patients with PD-L1 expression CPS ≥20: 4-year follow-up data

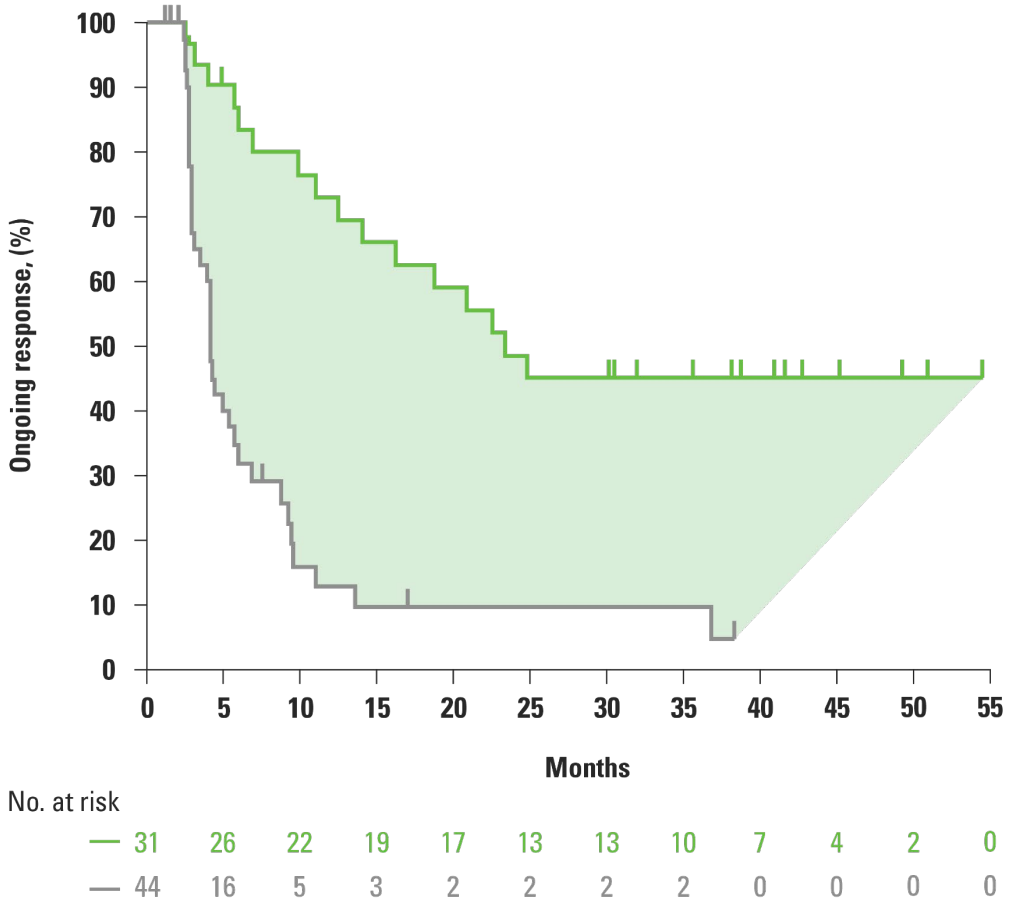
PI

Pembro vs EXTREME

DoR

CPS ≥20

KEYNOTE-048: DoR in CPS ≥20 population



Median DoR in CPS ≥20

Pembrolizumab	EXTREME
ORR: 23.3%	**ORR: 36.1%**
23.4 months (range: 2.7 to 54.4+)	**4.2 months** (range: 1.2+ to 38.2+)

Analysis was not powered for statistical comparison

Figure adapted from Greil et al. ESMO 2020. Median follow up 45.0 months for pembrolizumab monotherapy. Data cut-off: 18 February 2020.

CPS, combined positive score; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; ORR, overall response rate; PD-L1, programmed death ligand-1.

Greil R et al. Presented at ESMO 2020; 19–21 September 2020.

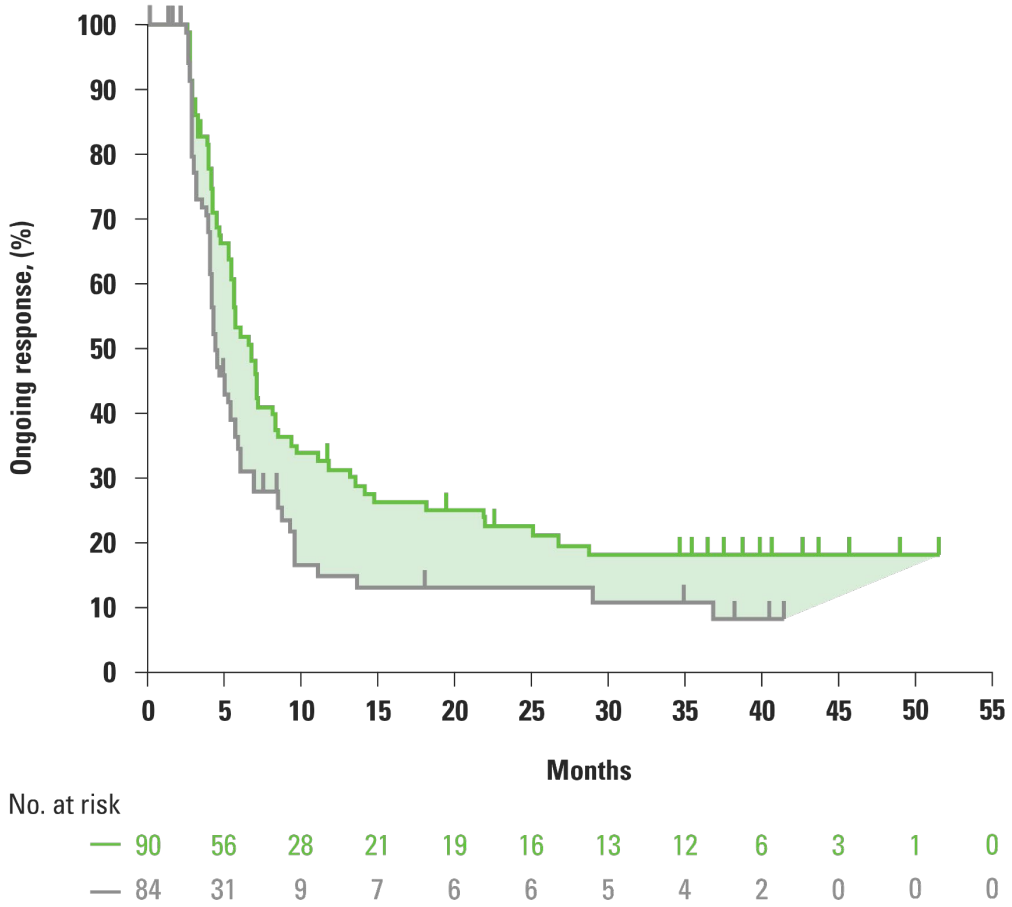
Long-term DoR for pembrolizumab + chemotherapy vs EXTREME in patients with PD-L1 expression CPS ≥1: 4-year follow-up data

Pembro + chemo vs EXTREME

DoR

CPS ≥1

KEYNOTE-048: DoR in CPS ≥1 population



Median DoR in CPS ≥1

Pembrolizumab + chemotherapy	EXTREME
ORR: 37.2%	**ORR: 35.7%**
6.7 months (range: 1.6+ to 51.5+)	**4.3 months** (range: 1.2+ to 41.4+)

Analysis was not powered for statistical comparison

Figure adapted from Greil et al. ESMO 2020. Median follow up 44.5 months for pembrolizumab + chemotherapy. Data cut-off: 18 February 2020.

CPS, combined positive score; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; ORR, overall response rate; PD-L1, programmed death ligand-1.

Greil R et al. Presented at ESMO 2020; 19–21 September 2020.

Long-term DoR for pembrolizumab + chemotherapy vs EXTREME in patients with PD-L1 expression CPS ≥20: 4-year follow-up data

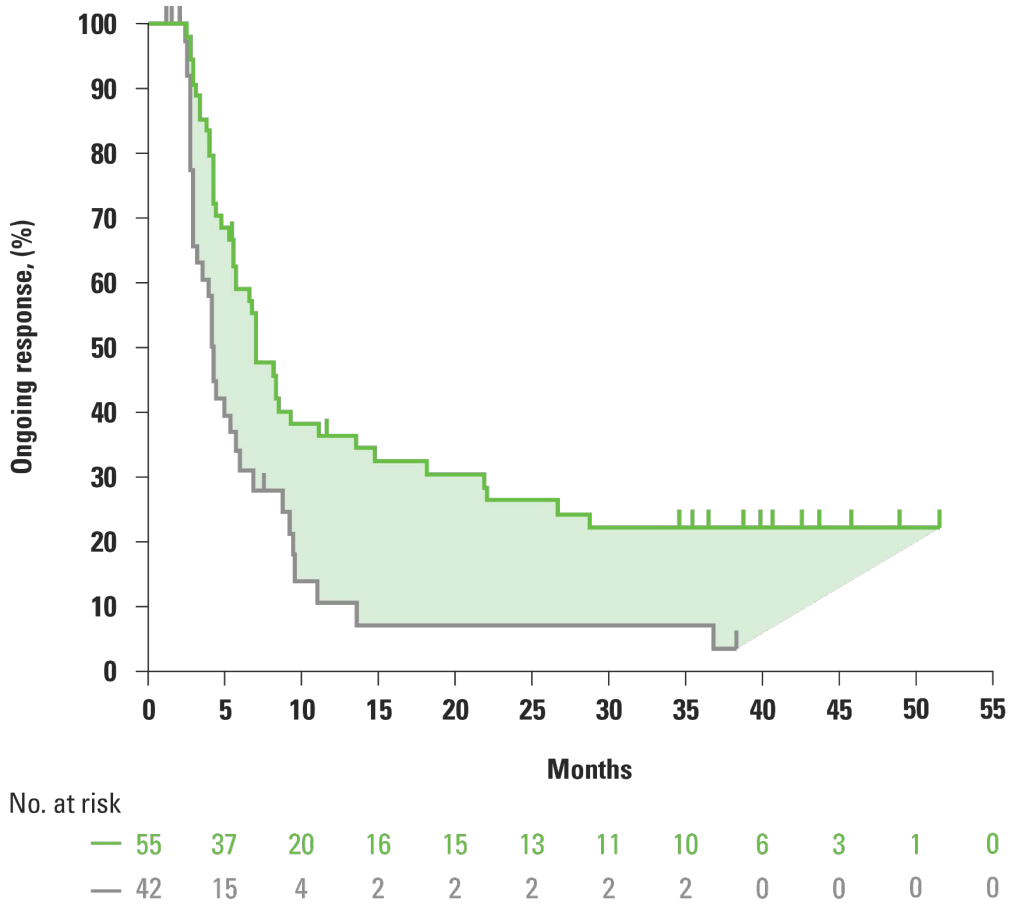
PI

Pembro + chemo vs EXTREME

DoR

CPS ≥20

KEYNOTE-048: DoR in CPS ≥20 population



Median DoR in CPS ≥20

Pembrolizumab + chemotherapy	EXTREME
ORR: 43.7%	**ORR: 38.2%**
7.0 months (range: 2.1+ to 51.5+)	**4.2 months** (range: 1.2+ to 38.2+)

Analysis was not powered for statistical comparison

Figure adapted from Greil et al. ESMO 2020. Median follow up 44.5 months for pembrolizumab + chemotherapy. Data cut-off: 18 February 2020.

CPS, combined positive score; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; ORR, overall response rate; PD-L1, programmed death ligand-1.

Greil R et al. Presented at ESMO 2020; 19–21 September 2020.

Long-term safety with pembrolizumab ± chemotherapy vs EXTREME: 4-year follow-up data

PI

Pembro vs EXTREME

Safety

Total population

TRAEs, %	Pembrolizumab monotherapy n=300	EXTREME n=287
Any grade	58.3	96.9
Grade 3–5	17.0	69.3

Pembro + chemo vs EXTREME

Safety

Total population

TRAEs, %	Pembrolizumab + chemotherapy n=276	EXTREME n=287
Any grade	95.7	96.9
Grade 3–5	71.7	69.3

Where possible, only data for the CPS ≥1 population is shown throughout the deck; however, some safety data originate from the total population and could not be separated. These include the AEs shown here.

Figure adapted from Greil et al. ESMO 2020. Median follow up 45.0 months for pembrolizumab monotherapy and 44.5 months for pembrolizumab + chemotherapy. Data cut-off: 18 February 2020.
5-FU, 5 fluorouracil; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; TRAE, treatment-related adverse event.
Greil R et al. Presented at ESMO 2020; 19–21 September 2020.

Long-term follow up with pembrolizumab ± chemotherapy vs EXTREME: Summary[1–3]

PI

- Long-term follow up OS outcome is in line with the original analysis for[1]:
  - Pembrolizumab monotherapy vs EXTREME in PD-L1 CPS ≥1 and CPS ≥20 populations
  - Pembrolizumab + chemotherapy vs EXTREME in PD-L1 CPS ≥1 and CPS ≥20 populations
- DoR with pembrolizumab monotherapy or pembrolizumab + chemotherapy vs EXTREME is in line with the original analysis[1]
- Safety signals remain comparable for pembrolizumab ± chemotherapy vs EXTREME with longer follow up[2]
  - Refer to the previous slides and SmPC for more details

Figure adapted from Greil et al. ESMO 2020. Median follow up 45.0 months for pembrolizumab monotherapy and 44.5 months for pembrolizumab + chemotherapy. Data cut-off: 18 February 2020.
CPS, combined positive score; DoR, duration of response; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; OS, overall survival; PD-L1, programmed death ligand-1.

1. Greil R et al. Presented at ESMO 2020; 19–21 September 2020; 2. Greil R et al. ESMO Virtual Congress 2020;915M0; 3. KEYTRUDA (pembrolizumab) SmPC.

KEYNOTE-048: PFS2 exploratory outcome assessment

First subsequent therapy following progressive disease

Click the links below to navigate to the section of interest

PI

Study overview

- The findings of the original KEYNOTE-048 study, as previously presented, led to the approval of pembrolizumab as first-line treatment for recurrent or metastatic HNSCC[1,2]
- Subsequent systemic therapy for patients progressing on first-line pembrolizumab-based therapy was not analysed in the original study
- Objective of this analysis: to present PFS after subsequent line of therapy (PFS2) to assess the effect of first-line pembrolizumab monotherapy or pembrolizumab + chemotherapy vs EXTREME and subsequent anticancer therapy on patient outcomes (data cut-off: 25 February 2019)[3]

1. Burtness B et al. *Lancet* 2019:394;1915–28; 2. KEYTRUDA (pembrolizumab) SmPC.; 3. Harrington K et al. Presented at ASCO 2020; 29 May–2 June 2020.

IV

KEYNOTE-048 exploratory outcome assessment study design: First subsequent therapy following progressive disease

PI

Key eligibility criteria

- SCC of the oropharynx, oral cavity, hypopharynx or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment[a]
- Known p16 status in the oropharynx[b]

Stratification factors

- PD-L1 expression[a] (TPS ≥50% vs <50%)
- p16 status in the oropharynx (positive vs negative)
- ECOG PS (0 vs 1)

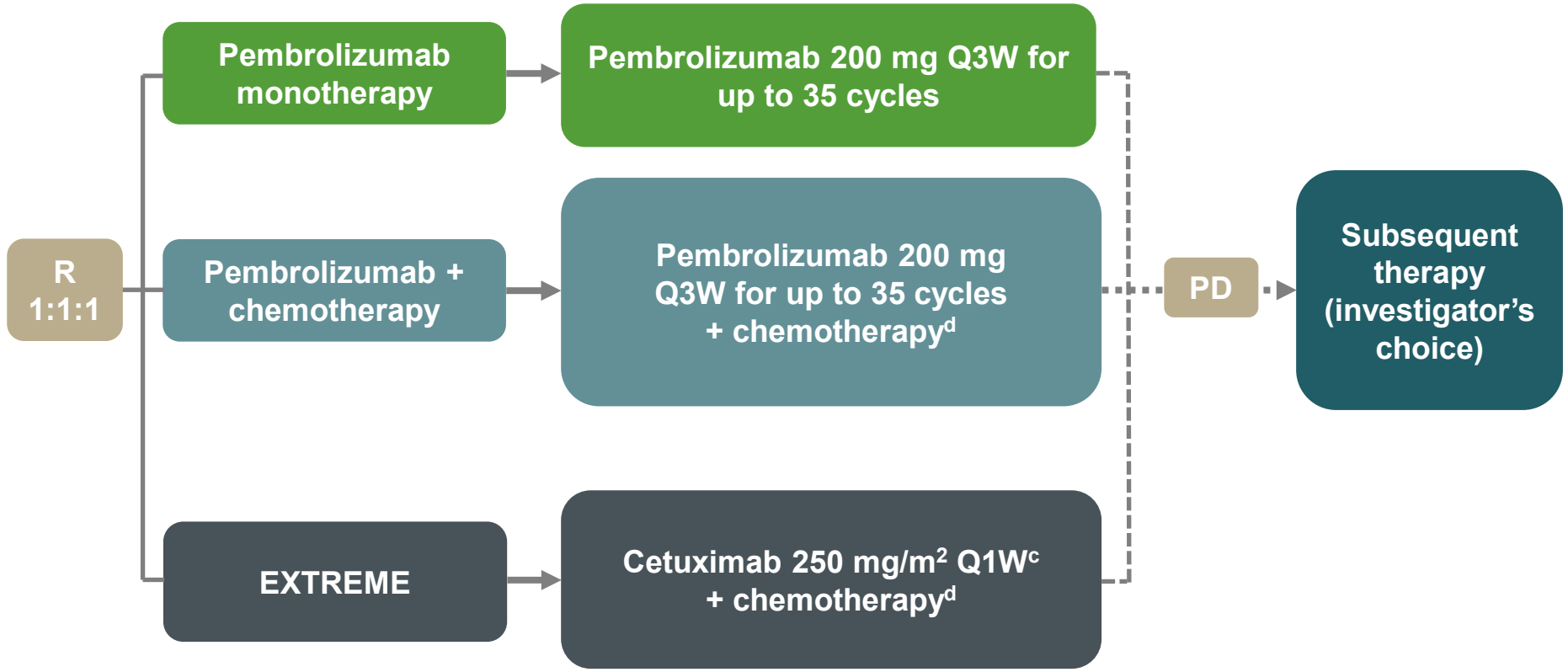


Figure adapted from Harrington et al. ASCO 2020.

[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = % of tumour cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 histology assay (Ventana), cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m^2; after completion of platinum agent and 5-FU, cetuximab could be continued until PD for patients with stable disease. [d]Carboplatin AUC 5 OR cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/day for 4 days for 6 cycles of 3 weeks. 5-FU, 5 fluorouracil; AUC 5, desired carboplatin exposure of 5 mg/mL; ECOG, Eastern Cooperative Oncology Group; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; IHC, immunohistochemistry; p16, cyclin-dependent kinase inhibitor 2A; PD, progressive disease; PD-L1, programmed death ligand-1; PS, performance status; Q1W, every week; Q3W, every 3 weeks; R, randomised; R/M, recurrent/metastatic; SCC, squamous cell carcinoma; TPS, tumour proportion score.

Harrington K et al. Presented at ASCO 2020; 29 May–2 June 2020.

IV

KEYNOTE-048 exploratory outcome assessment: Assessment of first subsequent therapy following progressive disease

PI

- PFS2: time from randomisation to objective tumour progression on next-line therapy or death from any cause
  - Exploratory outcome assessed in patients receiving subsequent therapy after first-line therapy

Patients who did not receive second-line therapy or who stopped second-line therapy without PD and did not start third-line therapy	Patients who stopped second-line therapy with PD	Patients who stopped second-line therapy without PD and started third-line therapy
Counted as an event at the time of death if the patient died Censored at the time of last known survival if the patient was alive	Counted as an event at the time of PD	Counted as an event at the start of third-line therapy

CI, confidence interval; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; HR, hazard ratio; PD, progressive disease; PD-L1, programmed death ligand-1; PS, performance status.
Harrington K et al. Presented at ASCO 2020; 29 May–2 June 2020.

IV

KEYNOTE-048 exploratory outcome assessment: First subsequent therapy following progressive disease

First subsequent therapy (n, %)	Pembrolizumab monotherapy (n=301)	Pembrolizumab + chemotherapy (n=281)	EXTREME (n=300)
Any new anticancer treatment[a]	148 (49.2)	115 (40.9)	159 (53.0)
Chemotherapy	135 (44.9)	88 (31.3)	102 (34.0)
EGFR inhibitor	59 (19.6)	37 (13.2)	19 (6.3)
Immune checkpoint inhibitor	6 (2.0)	12 (4.3)	50 (16.7)
Other immunotherapy	1 (0.3)	0 (0.0)	6 (2.0)
Kinase inhibitor	1 (0.3)	7 (2.5)	1 (0.3)
Other	2 (0.7)	1 (0.4)	2 (0.7)

Where possible, only data for the CPS ≥1 population is shown throughout the deck; however, some data originate from the total population and could not be separated. These include the populations shown here.

Table adapted from Harrington K et al. ASCO 2020. Data cut-off: 25 February 2019 (final analysis). [a]A patient is counted only once for each therapy group, but a patient could be counted in more than one therapy group.
EGFR, epidermal growth factor receptor; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy.
Harrington K et al. Presented at ASCO 2020; 29 May–2 June 2020.

KEYNOTE-048 exploratory outcome assessment: PFS2 for patients initially randomised to pembrolizumab monotherapy vs EXTREME with PD-L1 expression CPS ≥1

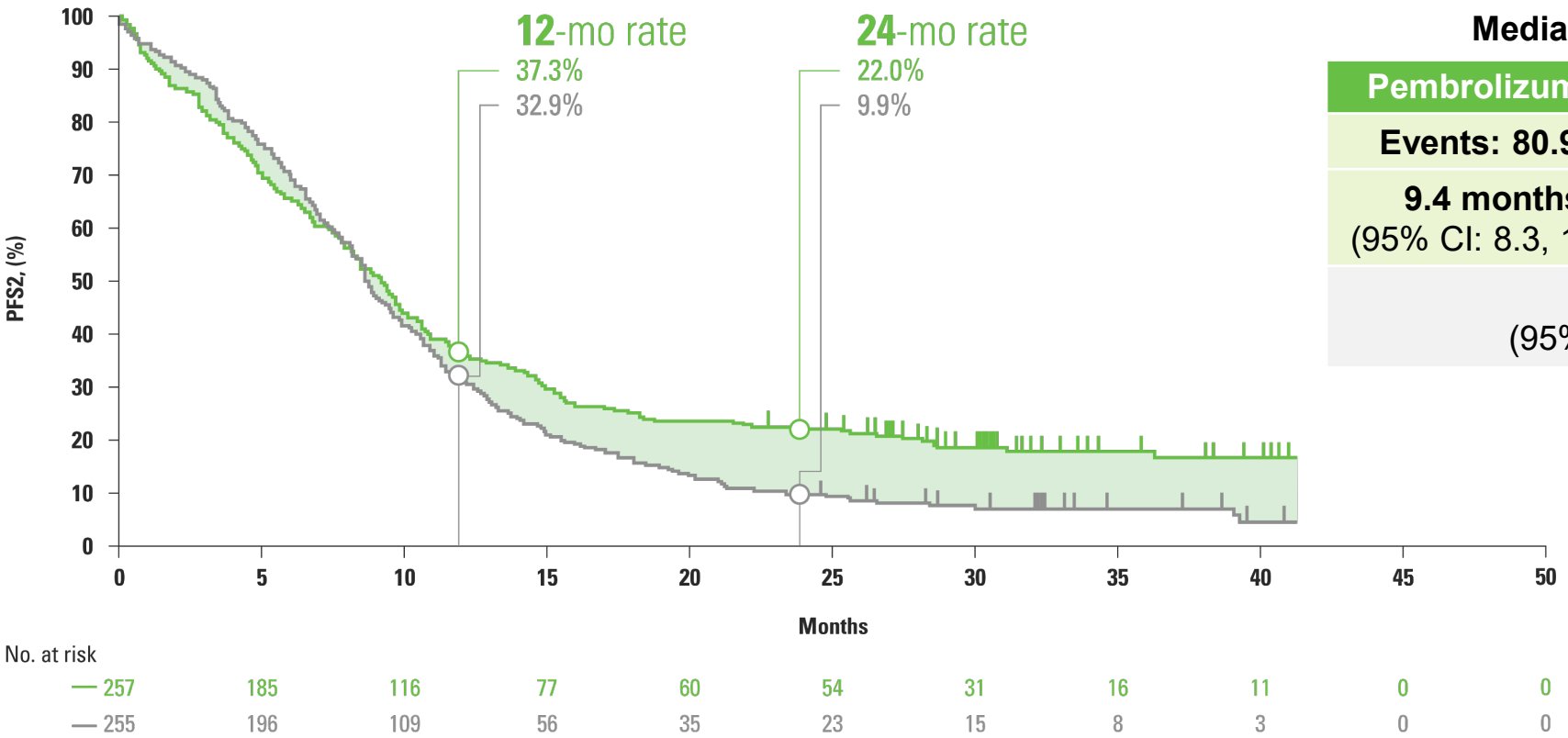
PI

Pembro vs EXTREME

PFS2

CPS ≥1

KEYNOTE-048: PFS2 in CPS ≥1 population



Median PFS2 in CPS ≥1

Pembrolizumab	EXTREME
Events: 80.9%	**Events: 92.5%**
9.4 months (95% CI: 8.3, 10.2)	**8.8 months** (95% CI: 8.3, 9.8)
HR, 0.80 (95% CI: 0.66, 0.96)	

Endpoint was not powered for statistical comparison

Figure adapted from Harrington K et al. ASCO 2020. PFS2 analysis involved patients in the ITT population with PD-L1 CPS ≥1. Data cut-off: 25 February 2019 (final analysis).

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; ITT, intention-to-treat; mo, month; PD-L1, programmed death ligand-1; PFS2, progression-free survival after next-line therapy.

Harrington K et al. Presented at ASCO 2020; 29 May–2 June 2020.

IV

KEYNOTE-048 exploratory outcome assessment: PFS2 for patients initially randomised to pembrolizumab monotherapy vs EXTREME with PD-L1 expression CPS ≥20

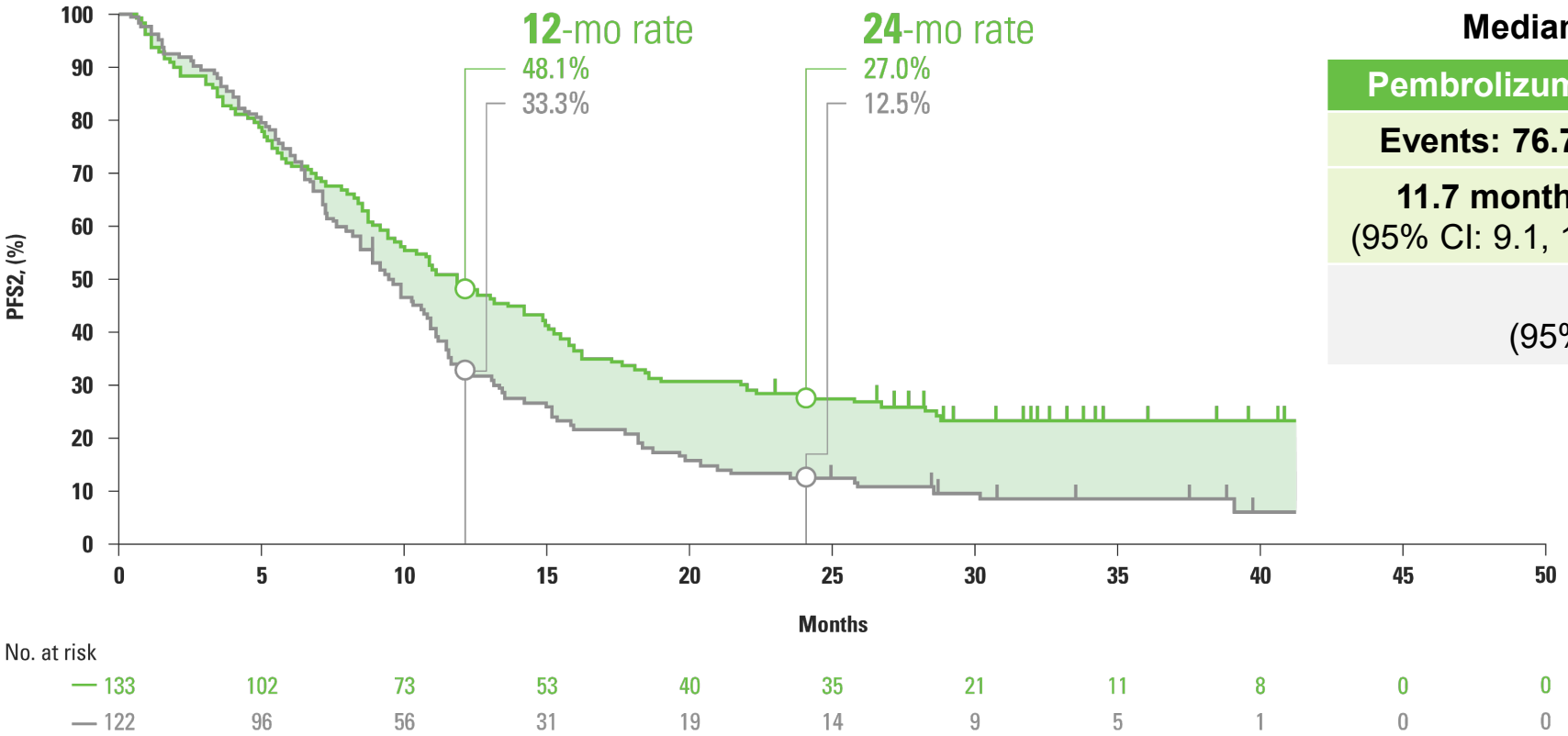
PI

Pembro vs EXTREME

PFS2

CPS ≥20

KEYNOTE-048: PFS2 in CPS ≥20 population



Median PFS2 in CPS ≥20

Pembrolizumab	EXTREME
Events: 76.7%	**Events: 91.0%**
11.7 months (95% CI: 9.1, 14.8)	**9.4 months** (95% CI: 7.9, 10.8)
HR, 0.64 (95% CI: 0.48, 0.84)	

Endpoint was not powered for statistical comparison

Figure adapted from Harrington K et al. ASCO 2020. PFS2 analysis involved patients in the ITT population with PD-L1 CPS ≥20. Data cut-off: 25 February 2019 (final analysis).

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; ITT, intention-to-treat; mo, month; PD-L1, programmed death ligand-1; PFS2, progression-free survival after next-line therapy.

Harrington K et al. Presented at ASCO 2020; 29 May–2 June 2020.

IV

KEYNOTE-048 exploratory outcome assessment: PFS2 for patients initially randomised to pembrolizumab + chemotherapy vs EXTREME with PD-L1 expression CPS ≥1

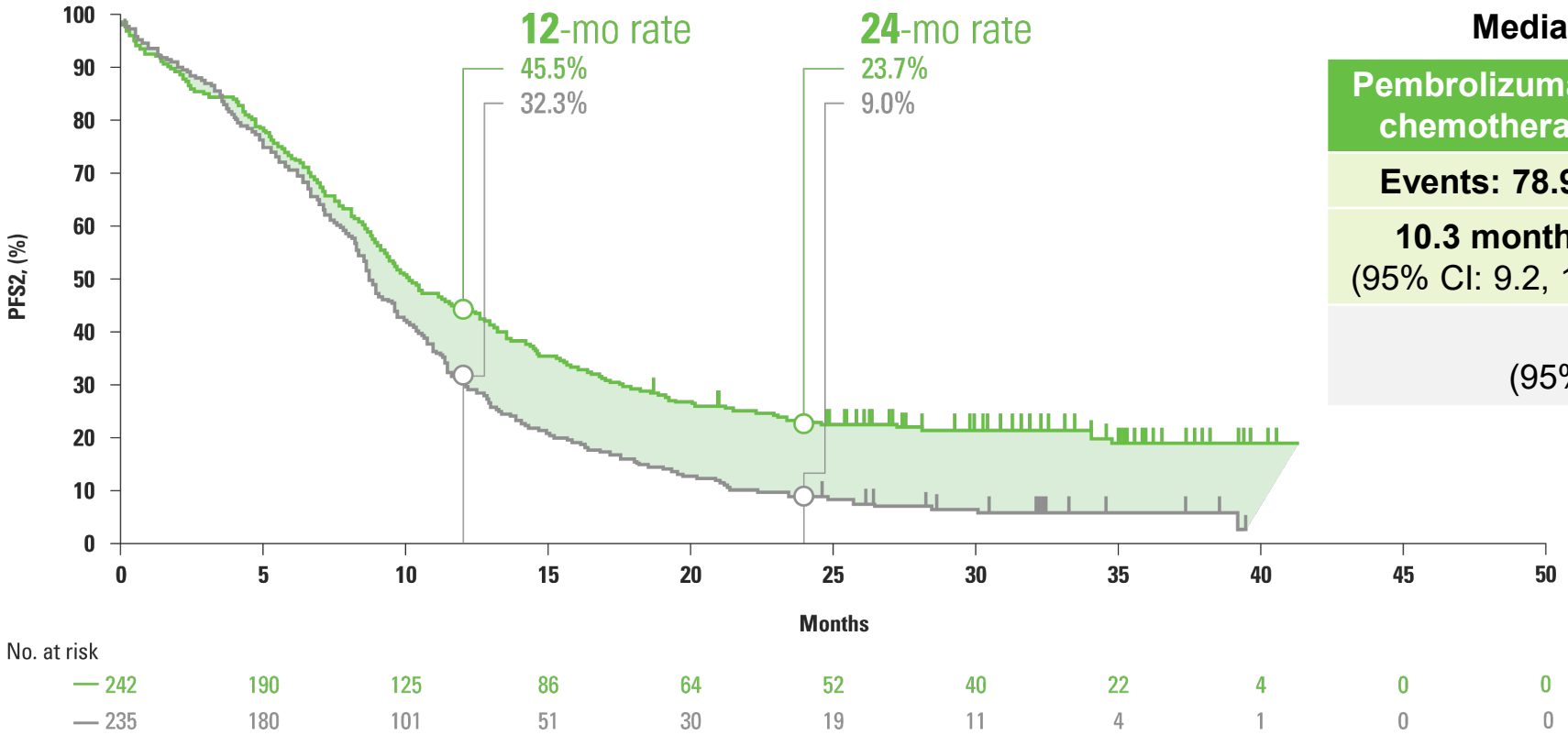
PI

Pembro + chemo vs EXTREME

PFS2

CPS ≥1

KEYNOTE-048: PFS2 in CPS ≥1 population



Median PFS2 in CPS ≥1

Pembrolizumab + chemotherapy	EXTREME
Events: 78.9%	**Events: 93.2%**
10.3 months (95% CI: 9.2, 12.5)	**8.9 months** (95% CI: 8.4, 9.8)
HR, 0.66 (95% CI: 0.54, 0.80)	

Endpoint was not powered for statistical comparison

Figure adapted from Harrington K et al. ASCO 2020. PFS2 analysis involved patients in the ITT population with PD-L1 CPS≥1. Data cut-off: 25 February 2019 (final analysis).

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; ITT, intention-to-treat; mo, month; PD-L1, programmed death ligand-1; PFS2, progression-free survival after next-line therapy.

Harrington K et al. Presented at ASCO 2020; 29 May–2 June 2020.

IV

KEYNOTE-048 exploratory outcome assessment: PFS2 for patients initially randomised to pembrolizumab + chemotherapy vs EXTREME with PD-L1 expression CPS ≥20

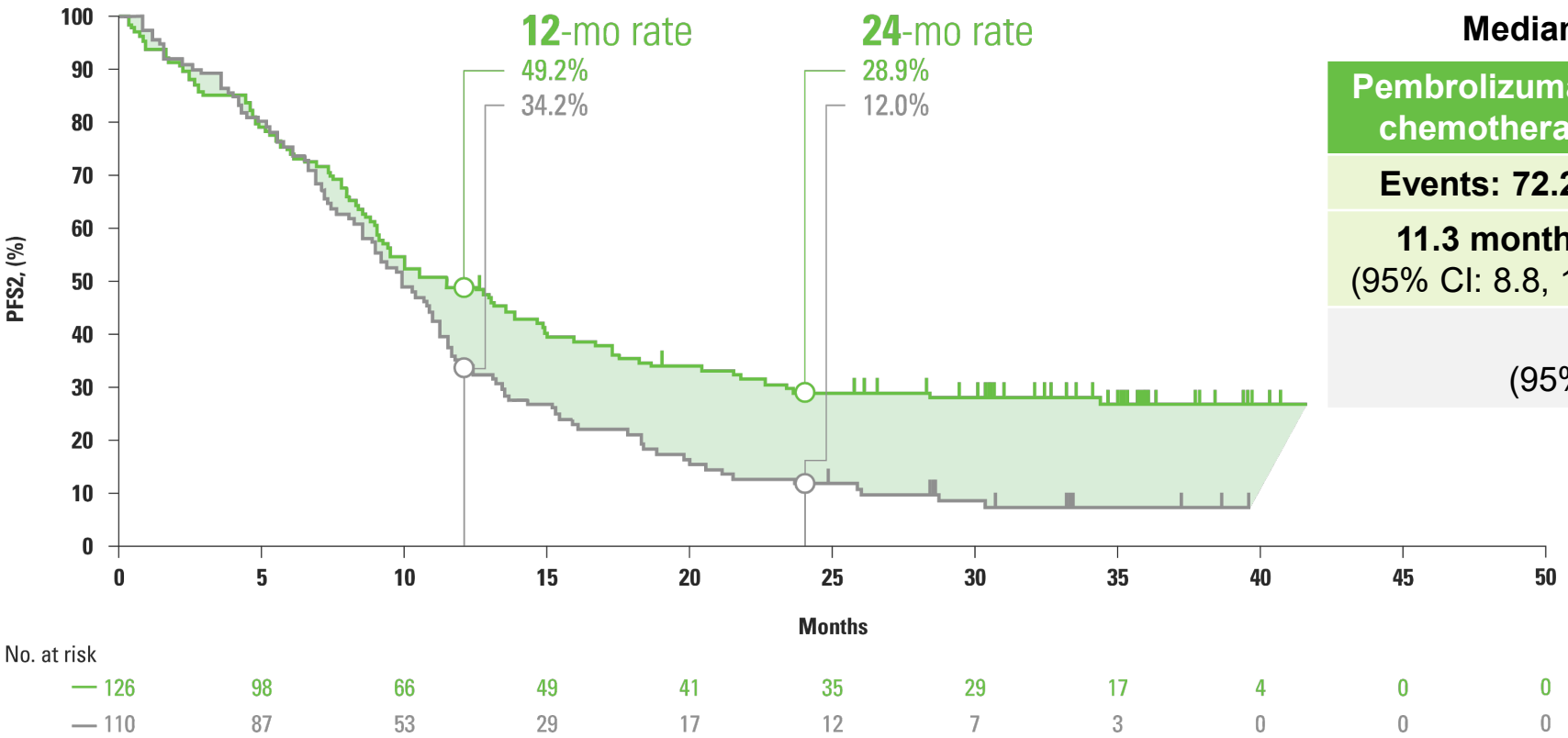
PI

Pembro + chemo vs EXTREME

PFS2

CPS ≥20

KEYNOTE-048: PFS2 in CPS ≥20 population



Median PFS2 in CPS ≥20

Pembrolizumab + chemotherapy	EXTREME
Events: 72.2%	**Events: 90.9%**
11.3 months (95% CI: 8.8, 14.7)	**9.7 months** (95% CI: 8.4, 11.0)
HR, 0.63 (95% CI: 0.47, 0.84)	

Endpoint was not powered for statistical comparison

Figure adapted from Harrington K et al. ASCO 2020. PFS2 analysis involved patients in the ITT population with PD-L1 CPS ≥20. Data cut-off: 25 February 2019 (final analysis).

CI, confidence interval; CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HR, hazard ratio; ITT, intention-to-treat; mo, month; PD-L1, programmed death ligand-1; PFS2, progression-free survival after next-line therapy.

Harrington K et al. Presented at ASCO 2020; 29 May–2 June 2020.

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KEYNOTE-048 exploratory outcome assessment: Pembrolizumab ± chemotherapy vs EXTREME PFS2 data summary

PI

Pembrolizumab monotherapy vs EXTREME:

- Median PFS2 for pembrolizumab monotherapy was 9.4 months vs 8.8 months for EXTREME in patients with PD-L1 CPS ≥1
- Median PFS2 for pembrolizumab monotherapy was 11.7 months vs 9.4 months for EXTREME in patients with PD-L1 CPS ≥20

Pembrolizumab + chemotherapy vs EXTREME:

- Median PFS2 for the pembrolizumab + chemotherapy was 10.3 months vs 8.9 months for EXTREME in patients with PD-L1 CPS ≥1
- Median PFS2 for the pembrolizumab + chemotherapy was 11.3 months vs 9.7 months for EXTREME in patients with PD-L1 CPS ≥20

Endpoint was not powered for statistical comparison

CPS, combined positive score; EXTREME, cetuximab + 5-fluorouracil + platinum-based chemotherapy; HNSCC, squamous cell carcinoma of the head and neck; PD, progressive disease; PD-L1, programmed death ligand-1; PFS2, progression-free survival after next-line therapy; R/M, recurrent/metastatic.

Harrington K et al. Presented at American Society of Clinical Oncology (ASCO) Annual Meeting 2020. 29 May–2 June 2020.

IV

KEYTRUDA® (pembrolizumab)

Please click the following links for the KEYTRUDA SmPC and prescribing information:
Great Britain; Northern Ireland.

If using a downloaded version of this material, please ensure that you are accessing the most recent version of the prescribing information

Pooled safety data of KEYTRUDA across all indications and AE management can be found in the Summary of Product Characteristics (SmPC).

Refer to the Summary of Product Characteristics before prescribing KEYTRUDA to help minimise the risks associated with treatment.

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ (**this links to an external site**) or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to MSD, UK (Tel: 0208 154 8000).

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MSD medical information (0208 154 8000, medicalinformationuk@msd.com).

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