MSD Oncology

KEYTRUDA® (pembrolizumab), in combination with platinum- and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER2-negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with CPS ≥10

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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/ 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: 020 8154 8000).
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GB-PDO-01965. Date of preparation: March 2022.

MSD
Merck Sharp & Dohme (UK) Limited
Registered Office: 120 Moorgate, London
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Registered in England No. 233687

Slide deck navigation

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Pembrolizumab and chemotherapy overview

The pembrolizumab plus chemotherapy licence

Current treatment landscape/ patient pathway

The pembrolizumab plus chemotherapy licence[1,2]

KEYTRUDA™

\+ Platinum-based chemotherapy

\+ Fluoropyrimidine-based chemotherapy

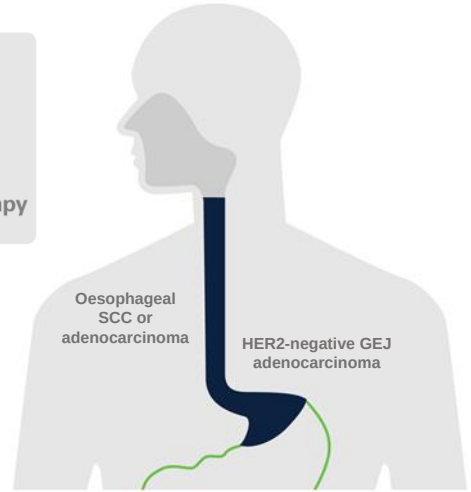
Timing and dosing of KEYTRUDA

200 mg Q3W or 400 mg Q6W administered as an IV infusion over 30 minutes

Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy

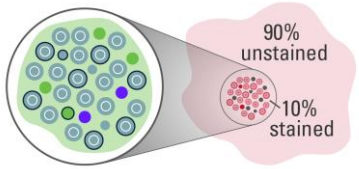
1L

No prior chemotherapy



Is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER2-negative GEJ adenocarcinoma

CPS scoring captures PD-L1 expression on both tumour and tumour-infiltrating cells



Tumour cell

Tumour-associated immune cells

PD-L1-expressing cells

$$\text{CPS} = \frac{\text{Number of PD-L1 positive cells (tumour cells, lymphocytes and macrophages)}}{\text{Total number of viable tumour cells}} \times 100$$

Among the 749 patients in KEYNOTE-590, 383 (51%) had tumours that expressed PD-L1 with a CPS ≥10 based on the PD-L1 IHC 22C3 pharmDxTM kit[2]

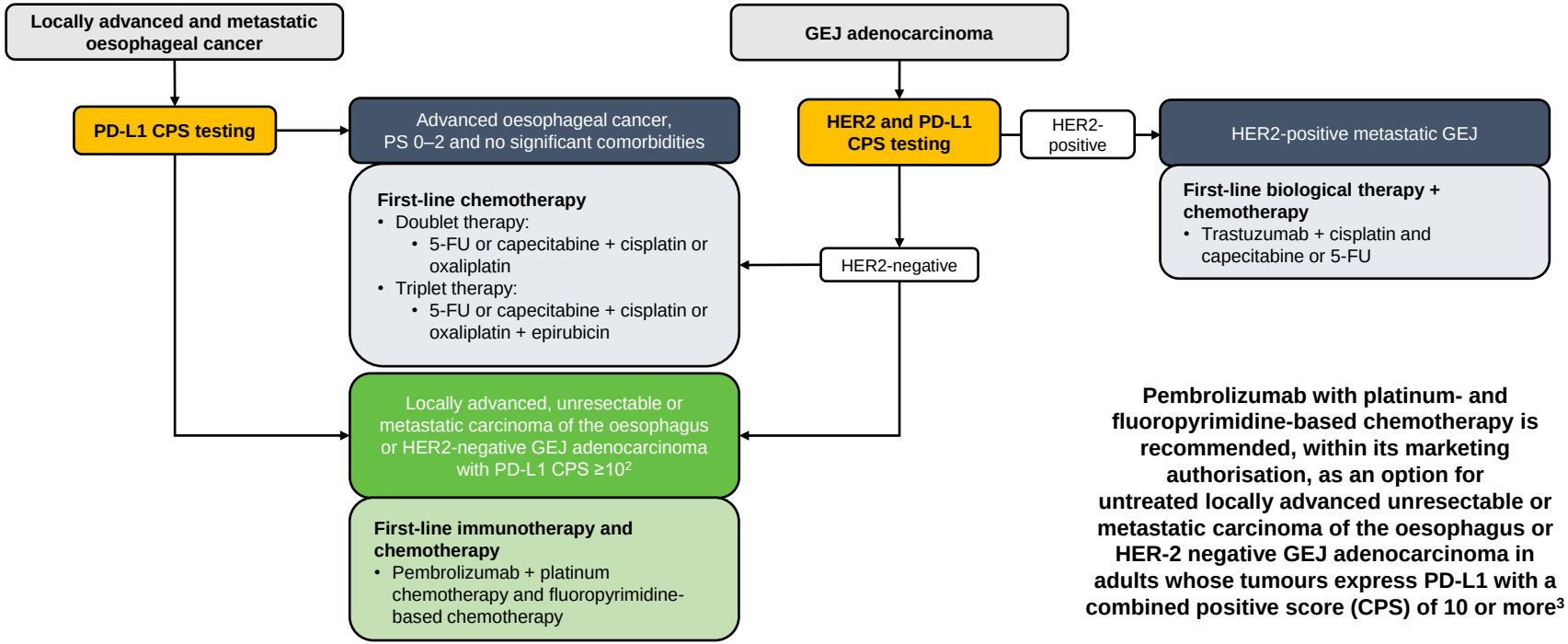
For adults whose tumours express PD-L1 with a CPS ≥10

For more information on the mode of action of pembrolizumab, click here. By clicking on this link you will be taken to an MSD promotional website

1L, first-line; CPS, combined positive score; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death ligand-1; SCC, squamous cell carcinoma.

1. PD-L1 IHC 22C3 pharmDx interpretation manual – Gastric or Gastroesophageal Junction Adenocarcinoma. Agilent Dako. Available at: https://www.agilent.com/cs/library/usermanuals/public/29219_pd-l1-ihc-22C3-pharmdx-gastric-interpretation-manual_us.pdf. Accessed March 2022; 2. KEYTRUDA (pembrolizumab) SmPC. Available at: https://www.emcpi.com/pi/33162 (GB) and https://www.emcpi.com/pi/ni/378 (NI). Accessed March 2022.

Current treatment landscape in first-line locally advanced or metastatic oesophageal cancer and GEJ adenocarcinoma[1–3]



Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy is recommended, within its marketing authorisation, as an option for untreated locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative GEJ adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score (CPS) of 10 or more[3]

Figure adapted from NICE Palliative management for people with oesophageal and gastric cancer.
5-FU, 5-fluorouracil; CPS, combined positive score; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; NICE, National Institute for Health and Care Excellence; PD-L1, programmed death ligand-1; PS, performance status.
1. Palliative management for people with oesophageal and gastric cancer. NICE. Updated 15 June 2021. Available at: https://pathways.nice.org.uk/pathways/oesophageal-and-gastric-cancer. Accessed March 2022.
2. Oesophago-gastric cancer: assessment and management in adults. NICE. Available at: https://www.nice.org.uk/guidance/ng83/chapter/Recommendations. Accessed March 2022. 3. KEYTRUDA (pembrolizumab) SmPC. Available at: https://www.emcpi.com/pi/33162 (GB) and https://www.emcpi.com/pi/ni/378 (NI). Accessed October 2021. 3. NICE guidance on pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastroesophageal junction cancer. Available at: https://www.nice.org.uk/guidance/gid-ta10613/documents/final-appraisal-determination-document. Accessed March 2022.

KEYNOTE-590 overview

Study design

Baseline characteristics

Definition of analyses

KEYNOTE-590: Study design[1,2]

Randomised, double-blind, placebo-controlled Phase 3 study

Key eligibility criteria
- Locally advanced unresectable or metastatic EAC or ESCC or advanced/metastatic GEJ Siewert type 1 adenocarcinoma
- Treatment naive
- ECOG PS 0 or 1
- Measurable disease (RECIST v1.1)

R
1:1
(N=749)

(n=373)

KEYTRUDA (pembrolizumab) 200 mg IV Q3W for ≤35 cycles
+
chemotherapy
(5-FU 800 mg/m² IV for Days 1–5 Q3W for ≤35 cycles + cisplatin 80 mg/m² IV Q3W for ≤6 cycles)

(n=376)

Placebo[a]
+
chemotherapy
(5-FU 800 mg/m² IV for Days 1–5 Q3W for ≤35 cycles + cisplatin 80 mg/m² IV Q3W for ≤6 cycles)

Disease progression or unacceptable toxicity

Stratification factors
- Asia vs non-Asia regions
- ESCC vs EAC
- ECOG PS 0 vs 1

- Dual primary endpoints: OS and PFS (RECIST v1.1, investigator)
- Secondary endpoint: ORR (RECIST v1.1, investigator)
- Tumour response assessed at Week 9 then Q9W (RECIST v1.1, investigator)

Analysis cut-off date: 2 July 2020. Median follow up 22.6 months.
Figure adapted from Kato K ESMO 2020.
[a]Normal saline administered by IV infusion Q3W for ≤35 cycles.
5-FU, 5-fluorouracil; EAC, oesophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, oesophageal squamous-cell carcinoma; GEJ, gastroesophageal junction; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q9W, every 9 weeks; R, randomisation; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1.
1. Kato K et al. Presented at the European Society of Medical Oncology (ESMO) Virtual Congress 2020, 19–21 September 2020; 2. Sun JM et al. *Lancet* 2021;398:759–71.

KEYNOTE-590: Baseline characteristics in the ITT population[1,2]

Characteristic, n (%)[a]	KEYTRUDA (pembrolizumab) + cisplatin/5-FU (n=373)	Placebo + cisplatin/5-FU (n=376)
Median age (range), years	64.0 (28–94)	62.0 (27–89)
≥65 years of age	172 (46)	150 (40)
Male sex	306 (82)	319 (85)
Asia region	196 (53)	197 (52)
ECOG PS 1	223 (60)	225 (60)
Metastatic disease	344 (92)	339 (90)
Unresectable/locally advanced	29 (8)	37 (10)
Squamous cell carcinoma	274 (73)	274 (73)
Adenocarcinoma	99 (27)	102 (27)
Oesophageal	58 (16)	52 (14)
GEJ	41 (11)	50 (13)
PD-L1 CPS ≥10	186 (50)	197 (52)
Oesophageal squamous cell carcinoma	143 (38)	143 (38)
Adenocarcinoma	43 (12)	54 (14)

These data comprise the full ITT population. Please note that the licensed indication for pembrolizumab is in locally advanced, unresectable or metastatic carcinoma of the oesophagus or HER2-negative gastroesophageal junction adenocarcinoma with **PD-L1 CPS ≥10**

Analysis cut-off date: 2 July 2020. Median follow up 22.6 months.
Table adapted from Kato K ESMO 2020.
[a]Unless stated otherwise.
ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ITT, intention to treat; PD-L1, programmed death ligand-1.
1. Kato K et al. Presented at the European Society of Medical Oncology (ESMO) Virtual Congress 2020, 19–21 September 2020; 2. Sun JM et al. *Lancet* 2021;398:759–71.

KEYNOTE-590 definition of analyses[1,2]

Analysis	Cut-off date	Slide symbol	Median follow up
First interim[1]	2 July 2020	I	22.6 months
12-month follow up[2]	9 July 2021	II	34.8 months

1. Sun JM et al. *Lancet* 2021;398:759–71; 2. Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

KEYNOTE-590 results

Primary endpoint outcomes	OS in PD-L1 CPS ≥10 population (first interim analysis)	OS in PD-L1 CPS ≥10 population (12-month follow up analysis)	PFS in key subgroups (first interim analysis)
PFS in key subgroups (12-month follow up analysis)	Summary of AEs in all treated patients (first interim analysis)	Summary of AEs in all treated patients (12-month follow up analysis)	Selected AEs with >15 % incidence in each arm (first interim analysis)
Selected AEs with >15 % incidence in each arm (12-month follow-up interim analysis)	Selected AEs of special interest (first interim analysis)	Pembrolizumab Dosing	KEYNOTE-590: Summary

AE, adverse event; CPS, combined-positive score; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.

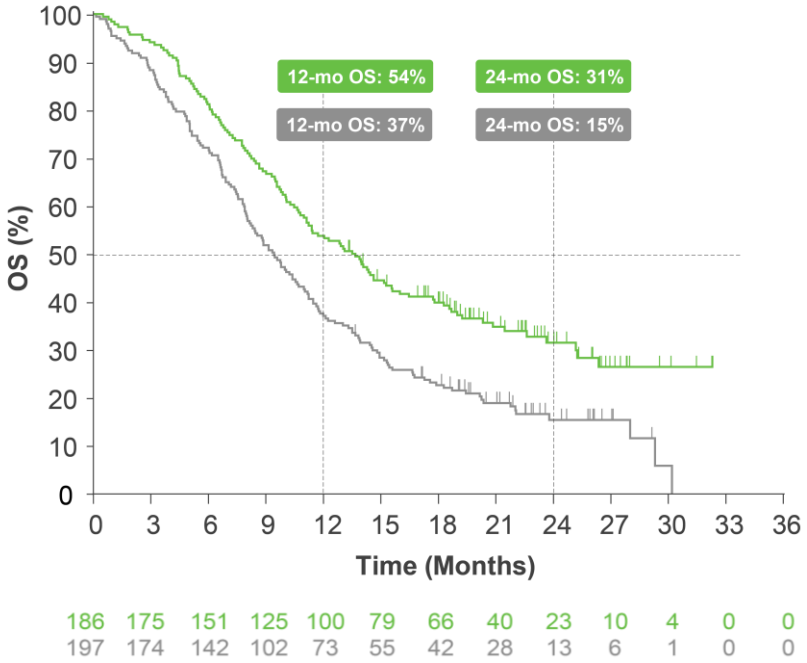
KEYNOTE-590: Primary endpoint outcomes[1,2]

- Primary outcomes with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU in the PD-L1 CPS ≥10 population were as follows:
  - First-interim analysis (median follow up: 22.6 months)[1]
    - OS: 38% reduced risk of death vs. placebo plus cisplatin/5-FU
      - HR: 0.62; 95% CI: 0.49–0.78, p<0.0001
    - PFS: 49% reduced risk of progression or death vs. placebo plus cisplatin/5-FU
      - HR: 0.51; 95% CI: 0.41–0.65; p<0.0001
  - 12-month follow-up analysis (median follow up: 34.8 months)[2]
    - OS: 36% reduced risk of death vs. placebo plus cisplatin/5-FU
      - HR: 0.64; 95% CI: 0.51–0.80
    - PFS: 49% reduced risk of progression or death vs. placebo plus cisplatin/5-FU
      - HR: 0.51; 95% CI: 0.41–0.65

5-FU, 5-flourouracil; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.

1. Sun JM et al. *Lancet* 2021;398:759–71; 2. Metges JJP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

KEYNOTE-590: OS in the PD-L1 CPS ≥10 population (first interim analysis)[1,2]



Treatment arm	Events (%)	Median (95% CI), months	HR (95% CI)	p value
KEYTRUDA (pembrolizumab) + cisplatin/5-FU	67	13.5 (11.1–15.6)	0.62 (0.49–0.78)	<0.0001
Placebo + cisplatin/5-FU	84	9.4 (8.0–10.7)	—	—

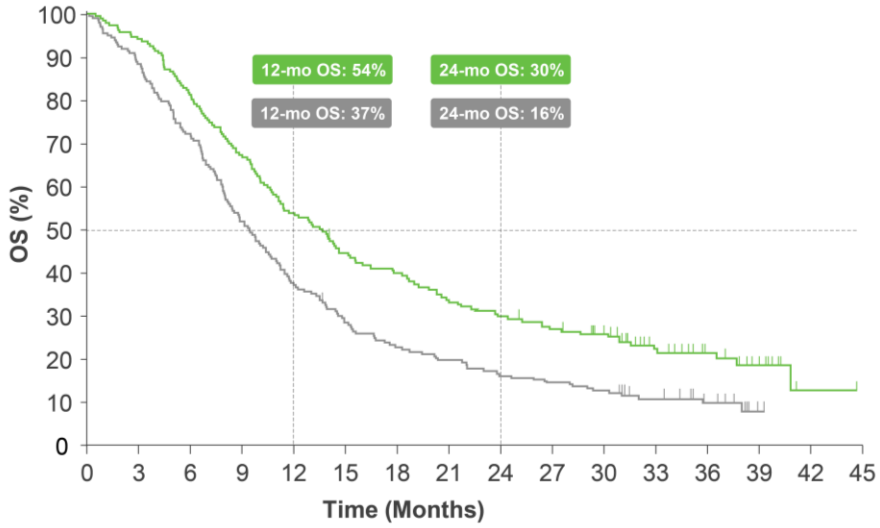
KEYTRUDA (pembrolizumab) plus cisplatin/5-FU versus placebo plus cisplatin/5-FU was superior for OS in patients with PD-L1 CPS ≥10

- **38% reduction in the risk of death with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU (n=186) versus placebo plus cisplatin/5-FU (n=197) (HR=0.62; 95% CI: 0.49–0.78, p<0.0001)**
- **Median OS with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU was 13.5 months (95% CI: 11.1–15.6) versus 9.4 months (95% CI: 8.0–10.7) with placebo plus cisplatin/5-FU**

The OS forest plot for the key subgroups within the KEYNOTE-590 study is in the appendix. Click here to view.

Analysis cut-off date: 2 July 2020. Median follow up 22.6 months.
Figure adapted from Kato K ESMO 2020.
5-FU, 5-fluorouracil; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1.
1. Kato K et al. Presented at the European Society of Medical Oncology (ESMO) Virtual Congress 2020, 19–21 September 2020; 2. Sun JM et al. *Lancet* 2021;398:759–71.

KEYNOTE-590: OS in the PD-L1 CPS ≥10 population (12-month follow-up analysis)



Treatment arm	Events (%)	Median (95% CI), months	HR (95% CI)
KEYTRUDA (pembrolizumab) + cisplatin/5-FU	80	13.6 (11.1–15.2)	0.64 (0.51–0.80)
Placebo + cisplatin/5-FU	90	9.4 (8.0–10.7)	—

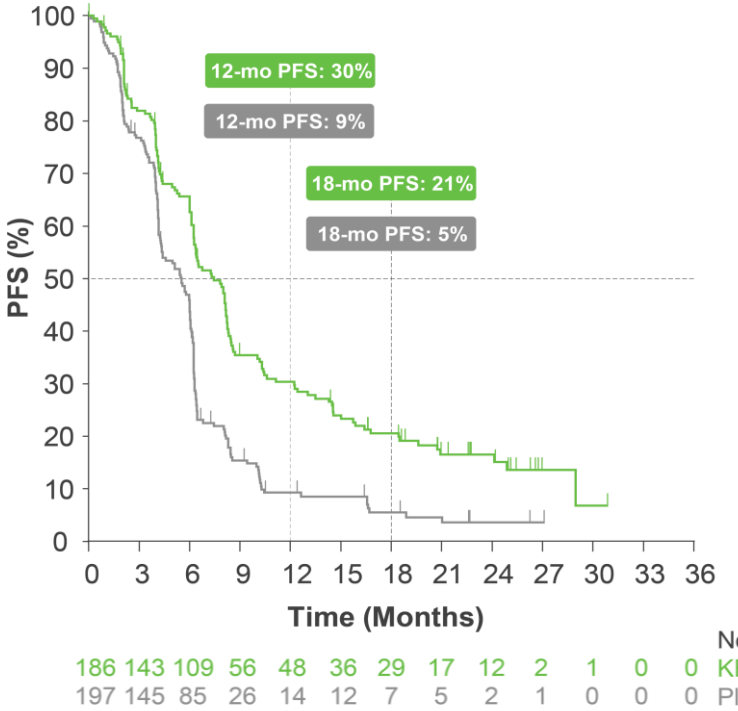
KEYTRUDA (pembrolizumab) plus cisplatin/5-FU versus placebo plus cisplatin/5-FU was superior for OS in patients with PD-L1 CPS ≥10

- **36% reduction in the risk of death with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU (n=186) versus placebo plus cisplatin/5-FU (n=197) (HR=0.64; 95% CI: 0.51–0.80)**
- **Median OS with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU was 13.6 months (95% CI: 11.1–15.2) versus 9.4 months (95% CI: 8.0–10.7) with placebo plus cisplatin/5-FU**

The OS forest plot for the key subgroups within the KEYNOTE-590 study is in the appendix. Click here to view.

Analysis cut-off date: 9 July 2021. Median follow up 34.8 months. No statistical conclusions can be drawn from this analysis.
Figure adapted from Metges JP ASCO-GI 2022.
5-FU, 5-fluorouracil; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1.
Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

KEYNOTE-590: PFS in the PD-L1 CPS ≥10 population (first interim analysis)[1,2]



Treatment arm	Events (%)	Median (95% CI), months	HR (95% CI)	p value
KEYTRUDA (pembrolizumab) + cisplatin/5-FU	75	7.5 (6.2–8.2)	0.51 (0.41–0.65)	<0.0001
Placebo + cisplatin/5-FU	88	5.5 (4.3–6.0)	—	—

KEYTRUDA (pembrolizumab) plus cisplatin/5-FU versus placebo plus cisplatin/5-FU was superior for PFS in patients with PD-L1 CPS ≥10

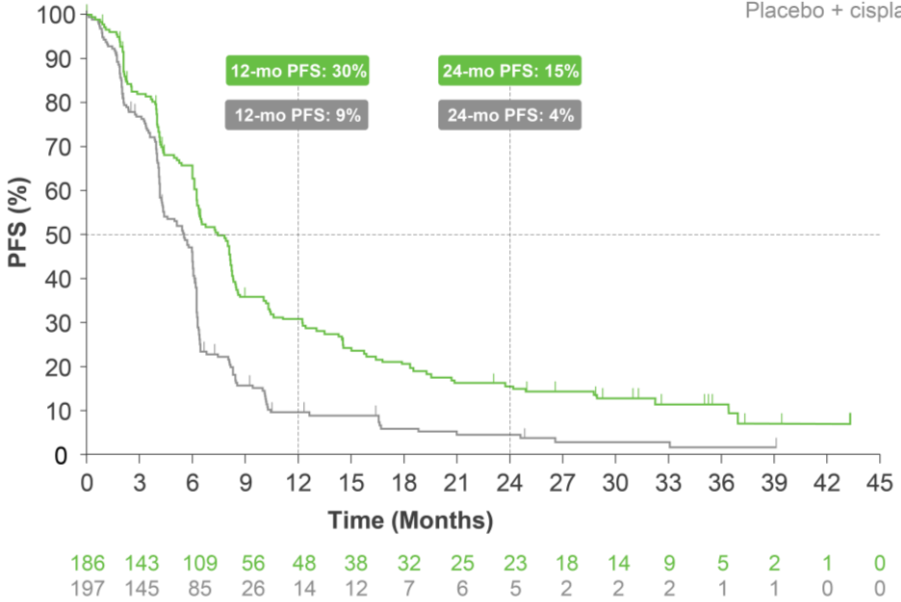
- **49% reduction in the risk of disease progression or death with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU (n=186) versus placebo plus cisplatin/5-FU (n=197) (HR=0.51; 95% CI: 0.41–0.65; p<0.0001)**
- **Median PFS with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU was 7.5 months (95% CI: 6.2–8.2) versus 5.5 months (95% CI: 4.3–6.0) with placebo plus cisplatin/5-FU**

The PFS forest plot for the key subgroups within the KEYNOTE-590 study is in the appendix. Click here to view.

Analysis cut-off date: 2 July 2020. Median follow up 22.6 months.
Figure adapted from Kato K ESMO 2020.
5-FU, 5-fluorouracil; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.
1. Kato K et al. Presented at the European Society of Medical Oncology (ESMO) Virtual Congress 2020, 19–21 September 2020; 2. Sun JM et al. *Lancet* 2021;398:759–71.

KEYNOTE-590: PFS in the PD-L1 CPS ≥10 population (12-month follow-up analysis)

Treatment arm	Events (%)	Median (95% CI), months	HR (95% CI)
KEYTRUDA (pembrolizumab) + cisplatin/5-FU	80	7.5 (6.2–8.2)	0.51 (0.41–0.65)
Placebo + cisplatin/5-FU	90	5.5 (4.3–6.0)	—



KEYTRUDA (pembrolizumab) plus cisplatin/5-FU versus placebo plus cisplatin/5-FU was superior for PFS in patients with PD-L1 CPS ≥10

- **49% reduction in the risk of disease progression or death with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU (n=186) versus placebo plus cisplatin/5-FU (n=197) (HR=0.51; 95% CI: 0.41–0.65)**
- **Median PFS with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU was 7.5 months (95% CI: 6.2–8.2) versus 5.5 months (95% CI: 4.3–6.0) with placebo plus cisplatin/5-FU**

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Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

KEYNOTE-590: Summary of AEs in all treated patients (first interim analysis)[1,2]

AEs, n (%)[a]	KEYTRUDA (pembrolizumab) + cisplatin/5-FU (n=370)	Placebo + cisplatin/5-FU (n=370)
Any	370 (100)	368 (99.5)
Treatment-related	364 (98.4)	360 (97.3)
Grade ≥3	266 (71.9)	250 (67.6)
Led to discontinuation	72 (19.5)	43 (11.6)
Led to death	9 (2.4)	5 (1.4)
Immune-mediated AEs and infusion reactions	95 (25.7)	43 (11.6)
Grade ≥3	26 (7.0)	8 (2.2)

These data comprise the full ITT population. Please note that the licensed indication for pembrolizumab is in locally advanced, unresectable or metastatic carcinoma of the oesophagus or HER2-negative gastroesophageal junction adenocarcinoma with PD-L1 CPS ≥10.

Click here to access the irAE slide deck for adverse event management of pembrolizumab + chemotherapy combinations.
Further information on the safety of pembrolizumab plus chemotherapy combinations can be found in the GB SmPC here or NI SmPC here.

Analysis cut-off date: 2 July 2020. Median follow up 22.6 months.
Figure adapted from Kato K ESMO 2020.
[a]Unless stated otherwise.
AE, adverse event; CPS, combined positive score; HER2, human epidermal growth factor receptor 2; irAE, immune-related adverse event; PD-L1, programmed death ligand-1.
1. Kato K et al. Presented at the European Society of Medical Oncology (ESMO) Virtual Congress 2020, 19–21 September 2020; 2. Sun JM et al. *Lancet* 2021;398:759–71.

KEYNOTE-590: Summary of AEs in all treated patients (12-month follow-up analysis)

AEs, n (%)	KEYTRUDA (pembrolizumab) + cisplatin/5-FU (n=373)	Placebo + cisplatin/5-FU (n=376)
Any	373 (100)	374 (99.5)
Treatment-related	367 (98.4)	366 (97.3)
Grade ≥3	268 (71.9)	255 (67.6)
Led to discontinuation	79 (21.1)	47 (12.4)
Led to death	9 (2.4)	5 (1.4)
Immune-mediated AEs and infusion reactions	100 (26.8)	52 (13.8)
Grade ≥3	26 (7.0)	8 (2.2)

These data comprise the full ITT population. Please note that the licensed indication for pembrolizumab is in locally advanced, unresectable or metastatic carcinoma of the oesophagus or HER2-negative gastroesophageal junction adenocarcinoma with PD-L1 CPS ≥10.

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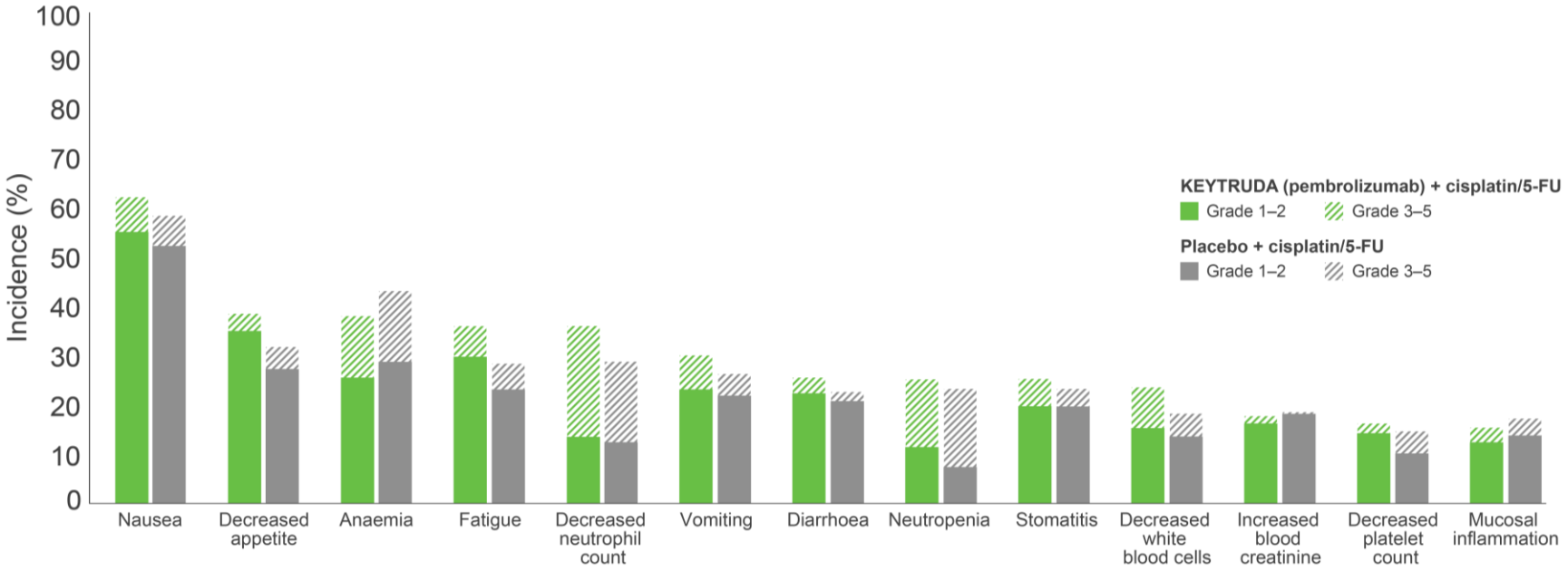
Analysis cut-off date: 9 July 2021. Median follow up 34.8 months.
Figure adapted from Metges JP ASCO-GI 2022
AE, adverse event; CPS, combined positive score; HER2, human epidermal growth factor receptor 2; irAE, immune-related adverse event; PD-L1, programmed death ligand-1.
Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

KEYNOTE-590: Selected AEs with >15% incidence in either arm (first interim analysis)[1,2]



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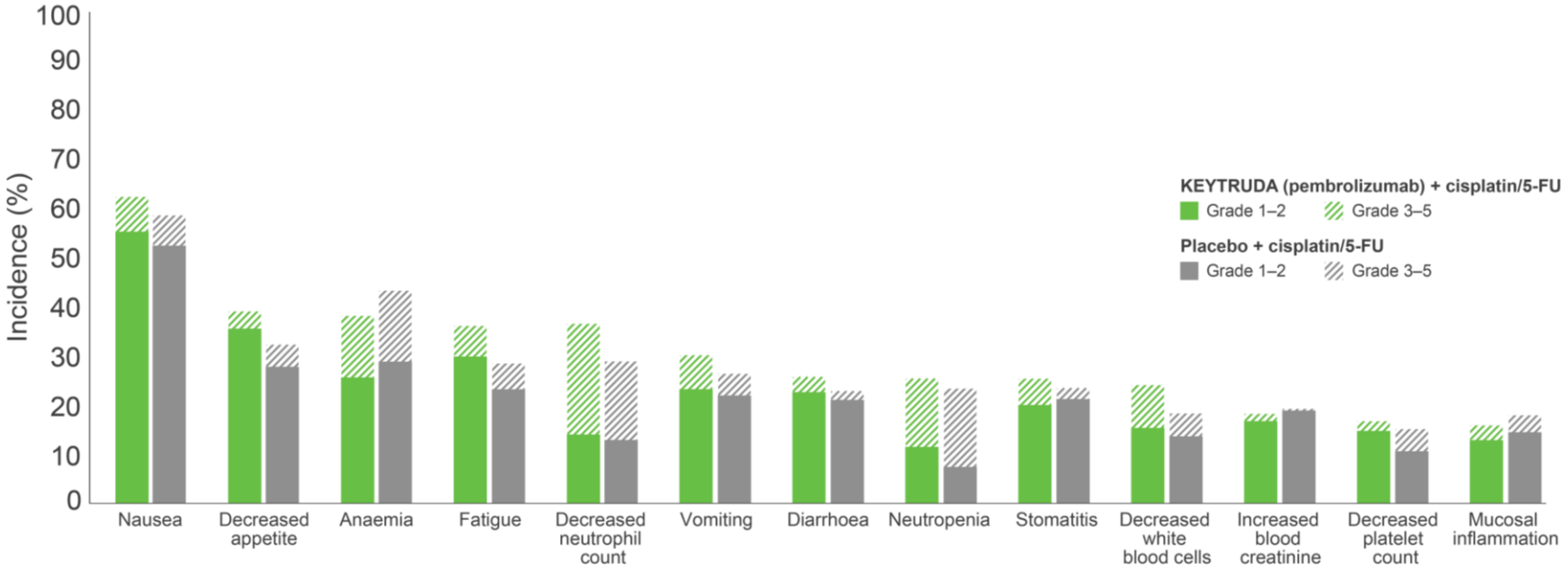
Analysis cut-off date: 2 July 2020. Median follow up 22.6 months. The values indicated are the percentage of patients who were randomly assigned to a treatment group and received at least one dose of study treatment.
Figure adapted from Kato K ESMO 2020.
AE, adverse event; irAE, immune-related adverse events.
1. Kato K et al. Presented at the European Society of Medical Oncology (ESMO) Virtual Congress 2020, 19–21 September 2020; 2. Sun JM et al. *Lancet* 2021;398:759–71.

KEYNOTE-590: Selected AEs with >15% incidence in either arm (12-month follow-up analysis)



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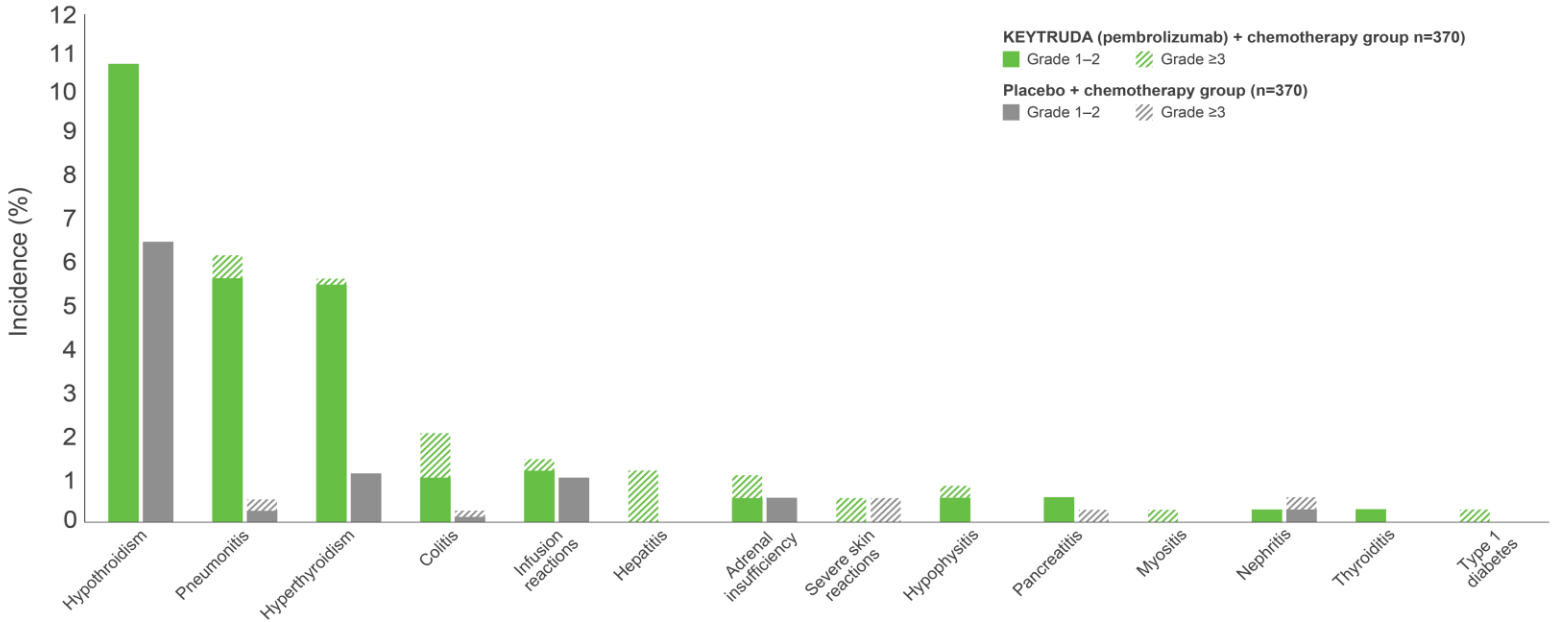
AE, adverse event.
Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

KEYNOTE-590: Selected AEs of special interest (first interim analysis)



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AE, adverse event; irAE, immune-related adverse event.
Sun JM et al. *Lancet* 2021;398:759–71.

Pembrolizumab dosing[1,2]

Administered as an IV infusion

Over 30 minutes

Adults: 200 mg

Adults: 400 mg

- Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity
- Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed
- It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed
- No dose reductions of pembrolizumab are recommended. Pembrolizumab should be withheld or discontinued to manage AEs as described within the SmPC
- When administering pembrolizumab in combination with intravenous chemotherapy, pembrolizumab should be administered first

The only regimen assessed in all clinical Phase 2 and 3 registration studies for KEYTRUDA was the 200 mg Q3W dosing. The study that led to the approval of the Q6W for monotherapy and combination patients assessed the 400 mg Q6W dosing schedule based on an exposure–response evaluation using modelling and simulation. It concluded that the 400 mg Q6W dosing regimen for KEYTRUDA monotherapy and combination is predicted to have a similar efficacy and safety profile as the approved 200 mg Q3W dosing regimen[2]

5-FU, 5-fluorouracil; AE, adverse event; IV, intravenous; Q3W, every 3 weeks; Q6W, every 6 weeks; SmPC, Summary of Product Characteristics.

1.KEYTRUDA (pembrolizumab) SmPC. KEYTRUDA (pembrolizumab) SmPC. Available at: https://www.emcpi.com/pi/33162 (GB) and https://www.emcpi.com/pi/ni/378 (NI). Accessed March 2022.
2. Lala M *et al. Eur J Cancer* 2020;131:68–75.

KEYNOTE-590: Summary for patients with PD-L1 CPS ≥10[1–3]

- KEYTRUDA (pembrolizumab) plus cisplatin/5-FU is the first licensed immunotherapy for adults with locally advanced, unresectable or metastatic carcinoma of the oesophagus or HER2-negative gastroesophageal junction adenocarcinoma with PD-L1 CPS ≥10

- KEYTRUDA (pembrolizumab) plus cisplatin/5-FU versus placebo + cisplatin/5-FU was superior for OS in patients with PD-L1 CPS ≥10
  - First interim analysis: HR: 0.62, 95% CI: 0.49–0.78; p<0.0001[1,2]
  - 12-month follow-up analysis: HR: 0.64, 95% CI: 0.51–0.80[3]

- KEYTRUDA (pembrolizumab) plus cisplatin/5-FU versus placebo plus cisplatin/5-FU was superior for PFS in patients with PD-L1 CPS ≥10
  - First interim and 12-month follow-up analyses: HR: 0.51, 95% CI: 0.41–0.65; p<0.0001[1–3]

- Grade ≥3 AEs occurred in 71.9% of patients in the KEYTRUDA (pembrolizumab) plus cisplatin/5-FU and 67.6% of patients in the placebo plus cisplatin/5-FU arm. Click here for the full list of AEs
  - Of those treated, patients in the KEYTRUDA plus cisplatin/5-FU group had a higher proportion of discontinuations of trial drugs compared with the placebo plus cisplatin/5-FU group:
    - First interim analysis: 19.5% vs 11.6%[1]
    - 12-month follow-up analysis: 21.1% vs 12.4%[3]
  - Immune-mediated and infusion-related reactions were experienced more frequently by patients who received KEYTRUDA plus cisplatin/5-FU compared with those receiving placebo plus cisplatin/5-FU, although no new safety signals were observed:
    - First interim analysis: 25.7% vs 11.6%[1,2]
    - 12-month follow-up analysis: 26.8% vs 13.8%[3]

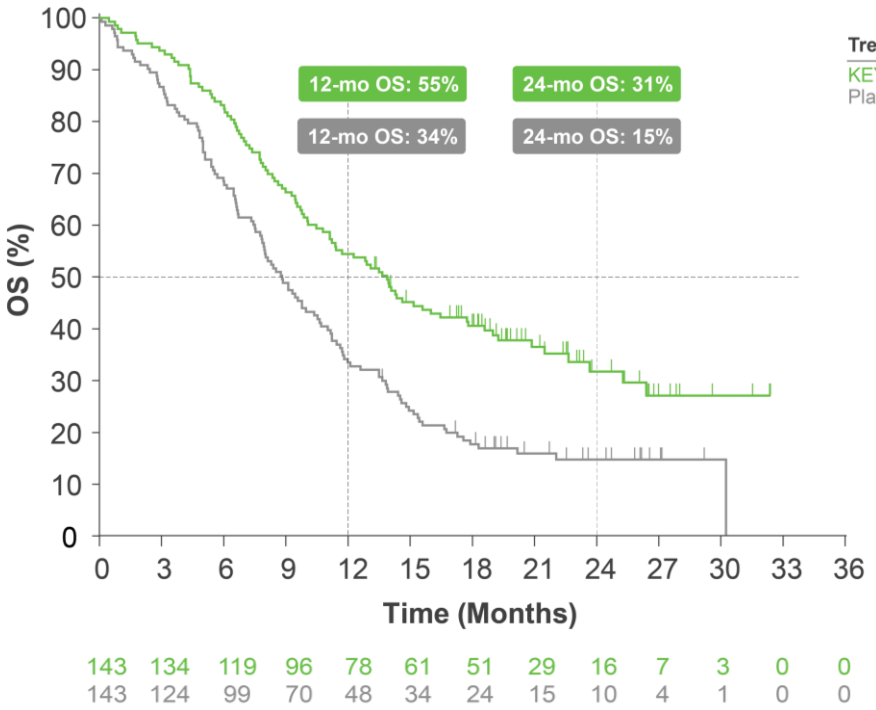
Interim analysis cut-off date: 2 July 2020 (median follow up 22.6 months); 12-month follow-up analysis cut-off date: 9 July 2021 (median follow up 34.8 months).
CI, confidence interval; CPS, combined positive test score; AE, adverse event; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1.
1. Kato K et al. Presented at the European Society of Medical Oncology (ESMO) Virtual Congress 2020, 19–21 September 2020; 2. Sun JM et al. *Lancet* 2021;398:759–71; 3. Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

Appendix

- OS in ESCC CPS ≥10 population (first interim analysis)
- OS in ESCC CPS ≥10 population (12-month follow-up analysis)
- OS in key subgroups All patients (first interim analysis)
- OS in key subgroups All patients (12-month follow-up analysis)
- PFS in key subgroups All patients (first interim analysis)
- PFS in key subgroups PD-L1 CPS ≥10 (12-month follow-up analysis)
- PFS in key subgroups ESCC (12-month follow-up analysis)
- CPS testing
- KEYNOTE-590: Full list of AEs (1)
- KEYNOTE-590: Full list of AEs (2)

AE, adverse event; CPS, combined positive score; ESCC, oesophageal squamous-cell carcinoma; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.

KEYNOTE-590: OS in the ESCC PD-L1 CPS ≥10 population (first interim analysis)



Treatment arm	Events (%)	Median (95% CI), months	HR (95% CI)	p value
KEYTRUDA (pembrolizumab) + cisplatin/5-FU	66	13.9 (11.1–17.7)	0.57 (0.43–0.75)	<0.0001
Placebo + cisplatin/5-FU	85	8.8 (7.8–10.5)	—	—

KEYTRUDA (pembrolizumab) plus cisplatin/5-FU versus placebo plus cisplatin/5-FU was superior for OS in patients with ESCC and PD-L1 CPS ≥10

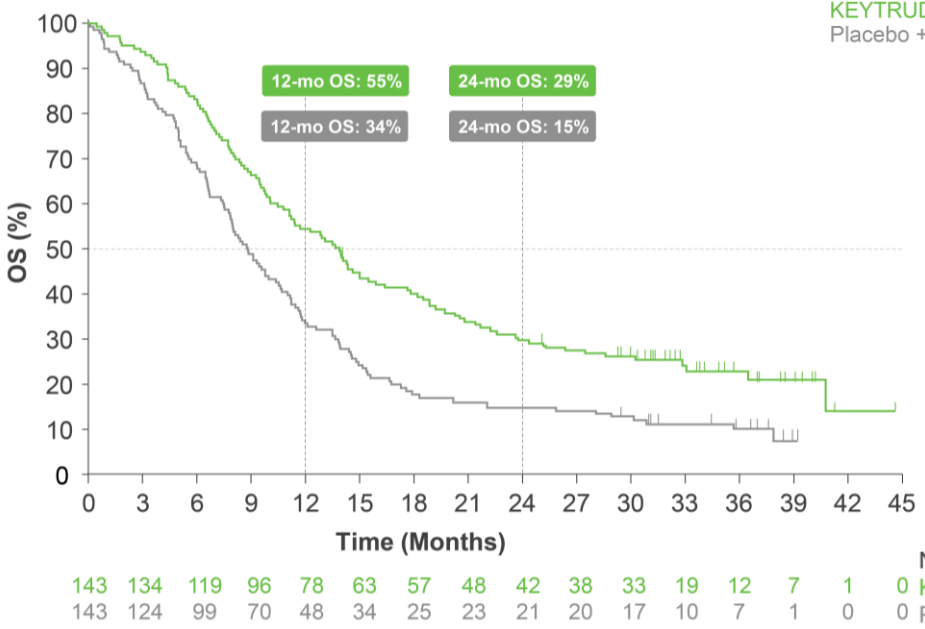
- **43% reduction in the risk of death with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU (n=143) versus placebo plus cisplatin/5-FU (n=143) (HR=0.57; 95% CI: 0.43–0.75, p<0.0001)**
- **Median OS with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU was 13.9 months (95% CI: 11.1–17.7) versus 8.8 months (95% CI: 7.8–10.5) with placebo plus cisplatin/5-FU**

The OS forest plot for the key subgroups within the KEYNOTE-590 study is in the appendix. Click here to view.

Analysis cut-off date: 2 July 2020. Median follow up 22.6 months.
Figure adapted from Kato K ESMO 2020.
5-FU, 5-fluorouracil; CI, confidence interval; CPS, combined positive score; ESCC, oesophageal squamous cell carcinoma; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1.
Sun JM et al. *Lancet* 2021 398:759–771

KEYNOTE-590: OS in the ESCC PD-L1 CPS ≥10 population (12-month follow-up analysis)

Treatment arm	Events (%)	Median (95% CI), months	HR (95% CI)
KEYTRUDA (pembrolizumab) + cisplatin/5-FU	78	13.9 (11.11–16.0)	0.59 (0.45–0.76)
Placebo + cisplatin/5-FU	90	8.8 (7.8–10.5)	—



KEYTRUDA (pembrolizumab) plus cisplatin/5-FU versus placebo plus cisplatin/5-FU was superior for OS in patients with ESCC and PD-L1 CPS ≥10

- **41% reduction in the risk of death with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU (n=143) versus placebo plus cisplatin/5-FU (n=143) (HR=0.59; 95% CI: 0.45–0.7)**
- **Median OS with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU was 13.9 months (95% CI: 11.1–16.0) versus 8.8 months (95% CI: 7.8–10.5) with placebo plus cisplatin/5-FU**

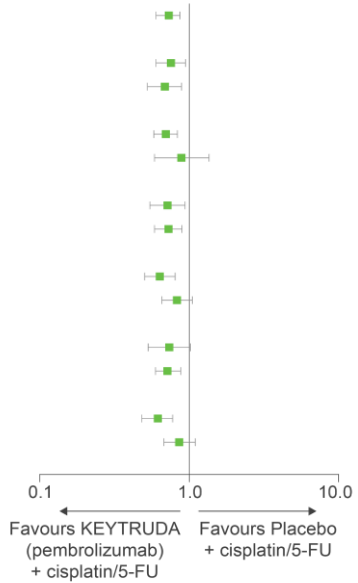
The OS forest plot for the key subgroups within the KEYNOTE-590 study is in the appendix. Click here to view.

Analysis cut-off date: 9 July 2021. Median follow up 34.8 months. No statistical conclusions can be drawn from this analysis.
Figure adapted from Metges JP ASCO-GI 2022.
5-FU, 5-fluorouracil; CI, confidence interval; CPS, combined positive score; ESCC, oesophageal squamous cell carcinoma; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1.
Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

KEYNOTE-590: OS in key subgroups – All patients (first interim analysis)

These data compromise the full ITT population. Please note that based on the evidence from this trial pembrolizumab is NOT licenced for patients with CPS<10. For information on the licence please click here

Subgroup	No. of events/No. of patients	Hazard ratio (95% CI)
Overall	571/749	0.73 (0.62–0.86)
Age, yr		
<65	332/427	0.76 (0.61–0.95)
≥65	239/322	0.69 (0.53–0.89)
Sex		
Male	482/625	0.70 (0.58–0.84)
Female	89/124	0.89 (0.59–1.35)
ECOG PS		
0	207/299	0.72 (0.55–0.94)
1	362/448	0.73 (0.59–0.90)
Geographic region		
Asia	288/393	0.64 (0.51–0.81)
Non-Asia	283/365	0.83 (0.66–1.05)
Histology		
Adenocarcinoma	159/201	0.74 (0.54–1.02)
ESCC	412/548	0.72 (0.60–0.88)
PD-L1 status		
CPS≥10	289/383	0.62 (0.49–0.78)
CPS<10	271/347	0.86 (0.68–1.10)



Only the ESCC and CPS ≥10 subgroups were powered to show statistically significant results. All other results are exploratory

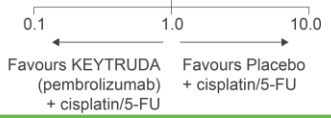
Please note that the licensed indication for pembrolizumab is in locally advanced, unresectable or metastatic carcinoma of the oesophagus or HER2-negative gastroesophageal junction adenocarcinoma with PD-L1 CPS ≥10

Analysis cut-off date: 2 July 2020. Median follow up 22.6 months.
Figure adapted from Kato K ESMO 2020.
CI, confidence interval; CPS, combined positive test score; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, oesophageal squamous cell carcinoma; HER2, human epidermal growth factor receptor 2; ITT, intention to treat; OS, overall survival; PD-L1, programmed death ligand-1.
1. Kato K et al. Presented at the European Society of Medical Oncology (ESMO) Virtual Congress 2020, 19–21 September 2020; 2. Sun JM et al. *Lancet* 2021;398:759–71.

KEYNOTE-590: OS in key subgroups – All patients (12-month follow-up analysis)

These data compromise the full ITT population. Please note that based on the evidence from this trial pembrolizumab is NOT licenced for patients with CPS<10. For information on the licence please click here

Subgroup	No. of events/No. of patients	Hazard ratio (95% CI)
Overall	644/749	0.73 (0.63–0.86)
Age, yr		
<65	379/427	0.76 (0.62–0.93)
≥65	265/322	0.72 (0.56–0.91)
Sex		
Male	543/625	0.71 (0.60–0.84)
Female	101/124	0.86 (0.58–1.27)
Disease status		
Metastatic	588/683	0.72 (0.61–0.84)
ECOG PS		
0	238/299	0.70 (0.54–0.90)
1	404/448	0.75 (0.62–0.92)
Geographic region		
Asia	330/393	0.66 (0.53–0.82)
Non-Asia	314/356	0.83 (0.67–1.04)
Histology		
Adenocarcinoma	179/201	0.73 (0.55–0.99)
ESCC	465/548	0.73 (0.61–0.88)
PD-L1 status		
CPS≥10	326/383	0.64 (0.51–0.80)
CPS<10	302/347	0.84 (0.67–1.06)



Only the ESCC and CPS ≥10 subgroups were powered to show statistically significant results. All other results are exploratory

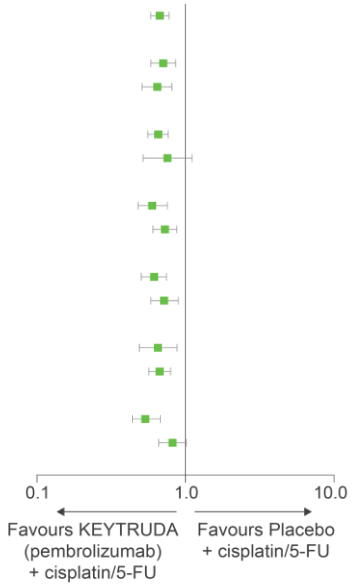
Please note that the licensed indication for pembrolizumab is in locally advanced, unresectable or metastatic carcinoma of the oesophagus or HER2-negative gastroesophageal junction adenocarcinoma with PD-L1 CPS ≥10

Analysis cut-off date: 9 July 2021. Median follow up 34.8 months.
Figure adapted from Metges JP ASCO-GI 2022.
CI, confidence interval; CPS, combined positive test score; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, oesophageal squamous cell carcinoma; HER2, human epidermal growth factor receptor 2; ITT, intention to treat; OS, overall survival; PD-L1, programmed death ligand-1.
Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

KEYNOTE-590: PFS in key subgroups – All patients (first interim analysis)

These data compromise the full ITT population. Please note that based on the evidence from this trial pembrolizumab is NOT licenced for patients with CPS<10. For information on the licence please click here

Subgroup	No. of events/No. of patients	Hazard ratio (95% CI)
Overall	630/749	0.65 (0.55–0.76)
Age, yr		
<65	372/427	0.69 (0.56–0.85)
≥65	258/322	0.62 (0.48–0.80)
Sex		
Male	537/625	0.63 (0.53–0.75)
Female	93/124	0.74 (0.49–1.12)
ECOG PS		
0	248/299	0.57 (0.45–0.74)
1	380/448	0.71 (0.58–0.87)
Geographic region		
Asia	333/393	0.59 (0.47–0.73)
Non-Asia	297/356	0.70 (0.56–0.89
Histology		
Adenocarcinoma	167/201	0.63 (0.46–0.87)
ESCC	463/548	0.65 (0.54–0.78)
PD-L1 status		
CPS≥10	314/383	0.51 (0.41–0.65)
CPS<10	302/347	0.80 (0.64–1.01)



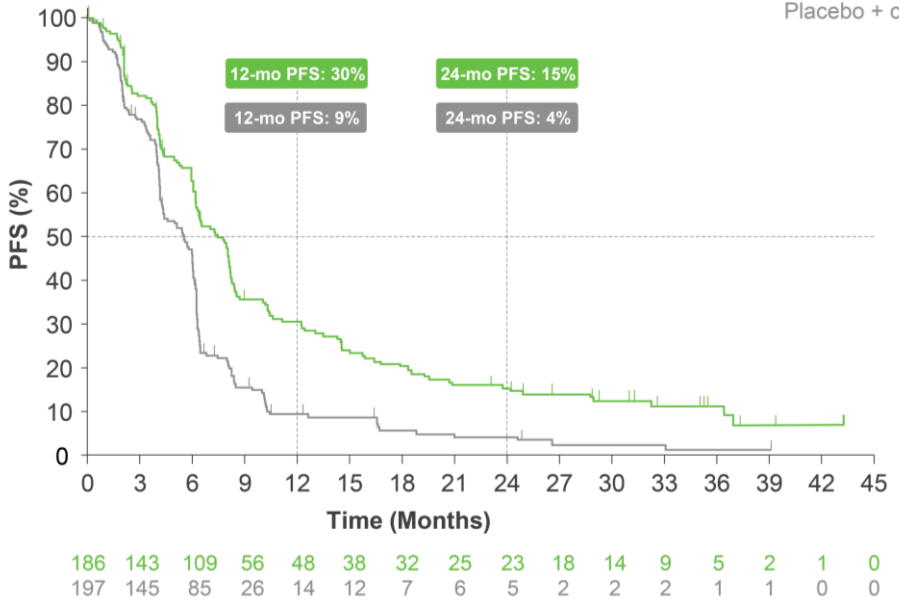
Only the ESCC and CPS ≥10 subgroups were powered to show statistically significant results. All other results are exploratory

Please note that the licensed indication for pembrolizumab is in locally advanced, unresectable or metastatic carcinoma of the oesophagus or HER2-negative gastroesophageal junction adenocarcinoma with PD-L1 CPS ≥10

Analysis cut-off date: 2 July 2020. Median follow up 22.6 months.
Figure adapted from Kato K ESMO 2020.
CI, confidence interval; CPS, combined positive test score; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, oesophageal squamous cell carcinoma; HER2, human epidermal growth factor receptor 2; ITT, intention to treat; PD-L1, programmed death ligand-1; PFS, progression-free survival.
1. Kato K et al. Presented at the European Society of Medical Oncology (ESMO) Virtual Congress 2020, 19–21 September 2020; 2. Sun JM et al. *Lancet* 2021;398:759–71.

KEYNOTE-590: PFS in prespecified subgroups (PD-L1 CPS ≥10) (12-month follow-up analysis)

Treatment arm	Events (%)	Median (95% CI), months	HR (95% CI)
KEYTRUDA (pembrolizumab) + cisplatin/5-FU	80	7.5 (6.2–8.2)	0.51 (0.41–0.65)
Placebo + cisplatin/5-FU	90	5.5 (4.3–6.0)	—



KEYTRUDA (pembrolizumab) plus cisplatin/5-FU versus placebo plus cisplatin/5-FU was superior for PFS in patients with PD-L1 CPS ≥10

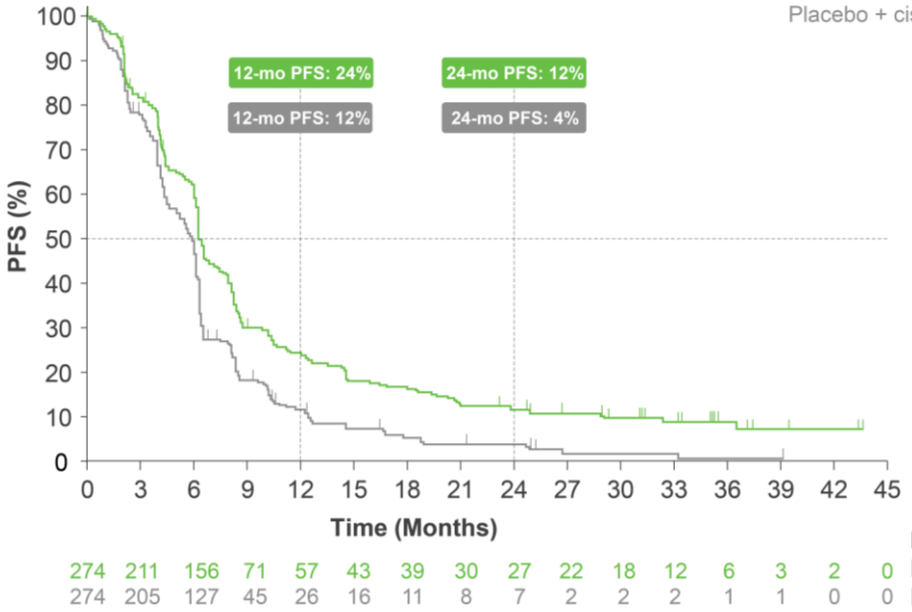
- **49% reduction in the risk of disease progression or death with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU (n=186) versus placebo plus cisplatin/5-FU (n=197) (HR=0.51; 95% CI: 0.41–0.64)**
- **Median PFS with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU was 7.5 months (95% CI: 6.2–8.2) versus 5.5 months (95% CI: 4.3–6.0) with placebo plus cisplatin/5-FU**

The PFS forest plot for the key subgroups within the KEYNOTE-590 study is in the appendix. Click here to view.

Analysis cut-off date: 9 July 2021. Median follow up 34.8 months. No statistical conclusions can be drawn from this analysis.
Figures adapted from Metges JP ASCO-GI 2022.
5-FU, 5-fluorouracil; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; PD-L1, programmed death ligand-1; PFS, progression-free survival.
Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

KEYNOTE-590 updated analysis: PFS in prespecified subgroups (ESCC) (12-month follow-up analysis)

Treatment arm	Events (%)	Median (95% CI), months	HR (95% CI)
KEYTRUDA (pembrolizumab) + cisplatin/5-FU	82	6.3 (6.2–7.1)	0.65 (0.54–0.78)
Placebo + cisplatin/5-FU	90	5.8 (5.0–6.1)	—



KEYTRUDA (pembrolizumab) plus cisplatin/5-FU versus placebo plus cisplatin/5-FU was superior for PFS in patients with ESCC

- **35% reduction in the risk of disease progression or death with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU (n=274) versus placebo plus cisplatin/5-FU (n=274) (HR=0.65; 95% CI: 0.54–0.78)**
- **Median PFS with KEYTRUDA (pembrolizumab) plus cisplatin/5-FU was 6.3 months (95% CI: 6.2–7.1) versus 5.8 months (95% CI: 5.0–6.1) with placebo plus cisplatin/5-FU**

The PFS forest plot for the key subgroups within the KEYNOTE-590 study is in the appendix. Click here to view.

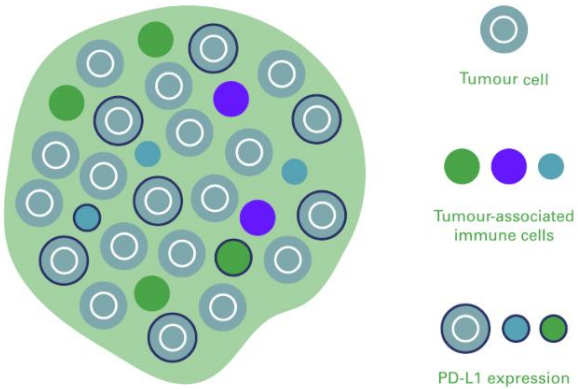
Analysis cut-off date: 9 July 2021. Median follow up 34.8 months. No statistical conclusions can be drawn from this analysis.
Figures adapted from Metges JP ASCO-GI 2022.
5-FU, 5-fluorouracil; CI, confidence interval; CPS, combined positive score; ESCC, oesophageal squamous-cell carcinoma; HR, hazard ratio; PFS, progression-free survival.
Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

CPS testing

CPS – a snapshot of the tumour microenvironment

- The CPS scoring algorithm offers a snapshot of PD-L1 expression by incorporating both tumour and immune cells
- This helps identify patients for the most appropriate treatment
- The PD-L1 22C3 IHC pharmDx assay, scored using the CPS algorithm, is used to define eligibility for treatment with pembrolizumab + chemotherapy

$$\text{CPS} = \frac{\text{\#PD-L1 staining cells (tumour cells, lymphocytes, macrophages)}}{\text{Total \#viable tumour cells}} \times 100$$



For further information on CPS testing, click here

Figure adapted from pharmDx PD-L1 IHC 22C3 manual.
CPS, combined positive score; IHC, immunohistochemistry; PD-L1, programmed death ligand-1.
PD-L1 IHC 22C3 pharmDx interpretation manual – Gastric or Gastroesophageal Junction Adenocarcinoma. Agilent Dako. Available at: https://www.agilent.com/cs/library/usermanuals/public/29219_pd-l1-ihc-22C3-pharmdx-gastric-interpretation-manual_us.pdf. Accessed March 2022. Accessed March 2022.

KEYNOTE-590: Full AE list (first interim analysis) [1]

AEs, n (%)[a]	Pembrolizumab plus chemotherapy group (n=370)		Placebo plus chemotherapy group (n=370)	
	Any	Grade ≥3	Any	Grade ≥3
Any	370 (100)	318 (86)	368 (99)	308 (83)
Treatment-related adverse events[b]				
Nausea	233 (63)	26 (7)	220 (59)	24 (6)
Decreased appetite	145 (39)	13 (4)	119 (32)	16 (4)
Anaemia	143 (39)	46 (12)	162 (44)	54 (15)
Fatigue	135 (36)	23 (6)	107 (29)	20 (5)
Decreased neutrophil count	135 (36)	84 (23)	109 (29)	62 (17)
Vomiting	110 (30)	23 (6)	99 (27)	18 (5)
Diarrhoea	97 (26)	12 (3)	85 (23)	7 (2)
Neutropenia	96 (26)	53 (14)	88 (24)	60 (16)
Stomatitis	96 (26)	21 (6)	93 (25)	14 (4)
Decreased white blood cells	89 (24)	32 (9)	69 (19)	18 (5)
Increased blood creatine	67 (18)	5 (1)	70 (19)	1 (<1)
Decreased platelet count	61 (16)	7 (2)	56 (15)	17 (5)
Mucosal inflammation	59 (16)	12 (3)	65 (18)	13 (4)
Leukopenia	24 (6)	6 (2)	28 (8)	11 (3)
Thrombocytopenia	25 (7)	5 (1)	33 (9)	10 (3)
Tinnitus	33 (9)	2 (1)	25 (7)	0
Hyperthyroidism	19 (5)	0	2 (1)	0
Hypothyroidism	38 (10)	0	22 (6)	0
Constipation	50 (14)	0	63 (17)	0
Asthenia	45 (12)	12 (3)	35 (9)	4 (1)
Malaise	43 (12)	2 (1)	39 (11)	4 (1)
Increased aspartate aminotransferase	18 (5)	3 (1)	19 (5)	2 (1)
Decreased lymphocyte count	21 (6)	7 (2)	20 (5)	5 (1)
Decreased weight	43 (12)	4 (1)	47 (13)	8 (2)
Dehydration	20 (5)	8 (2)	16 (4)	8 (2)

The analysis cut-off date was 2 July 2020; median follow-up was 22.6 months.

[a]Unless otherwise stated; [b]Treatment-related adverse events with incidence of 5% or higher in any group are shown; treatment-related grade 5 events included febrile neutropenia, diarrhoea, multiple organ dysfunction, hepatic failure, pneumonia, acute kidney injury, interstitial lung disease, pneumonitis, and pulmonary embolism, which each occurred in one patient in the pembrolizumab plus chemotherapy group, and febrile neutropenia, death, multiple organ dysfunction syndrome, sepsis, and interstitial lung disease, which each occurred in one patient in the placebo plus chemotherapy group. AE, adverse event.

Sun JM et al. *Lancet* 2021;398:759–771.

KEYNOTE-590: Full AE list (first interim analysis) [2]

AEs, n (%)[a]	Pembrolizumab plus chemotherapy group (n=370)		Placebo plus chemotherapy group (n=370)	
	Any	Grade ≥3	Any	Grade ≥3
Treatment-related adverse events continued[b]				
Hypokalaemia	34 (9)	17 (5)	41 (11)	19 (5)
Hypomagnesaemia	21 (6)	2 (1)	14 (4)	3 (1)
Hyponatraemia	32 (9)	20 (5)	40 (11)	20 (5)
Dysgeusia	34 (9)	0	32 (9)	0
Peripheral neuropathy	32 (9)	1 (<1)	32 (9)	0
Peripheral sensory neuropathy	34 (9)	1 (<1)	29 (8)	1 (<1)
Hiccups	40 (11)	0	33 (9)	0
Pneumonitis	20 (5)	7 (2)	0	0
Alopecia	51 (14)	0	39 (11)	0
Pruritus	23 (6)	1 (<1)	8 (2)	0
Rash	29 (8)	0	18 (5)	1 (<1)

AEs, n (%)[a]	Pembrolizumab plus chemotherapy group (n=370)		Placebo plus chemotherapy group (n=370)	
	Any	Grade ≥3	Any	Grade ≥3
Adverse events of special interest[c]				
Hypothyroidism	40 (11)	0	24 (6)	0
Pneumonitis	23 (6)	2 (1)	2 (1)	1 (<1)
Hyperthyroidism	21 (6)	1 (<1)	3 (1)	0
Colitis	8 (2)	4 (1)	6 (2)	3 (1)
Infusion reactions	6 (2)	1 (<1)	4 (1)	0
Hepatitis	5 (1)	5 (1)	0	0
Adrenal insufficiency	4 (1)	2 (1)	2 (1)	0
Severe skin reactions	4 (1)	4 (1)	2 (1)	2 (1)
Hypophysitis	3 (1)	1 (<1)	0	0
Pancreatitis	2 (1)	0	1 (<1)	1 (<1)
Myositis	1 (<1)	1 (<1)	0	0
Nephritis	1 (<1)	0	2 (1)	1 (<1)
Thyroiditis	1 (<1)	0	0	0
Type 1 diabetes	1 (<1)	1 (<1)	0	0

The analysis cut-off date was 2 July 2020; median follow-up was 22.6 months.

[a]Unless otherwise stated; [b]Treatment-related adverse events with incidence of 5% or higher in any group are shown; treatment-related grade 5 events included febrile neutropenia, diarrhoea, multiple organ dysfunction, hepatic failure, pneumonia, acute kidney injury, interstitial lung disease, pneumonitis, and pulmonary embolism, which each occurred in one patient in the pembrolizumab plus chemotherapy group, and febrile neutropenia, death, multiple organ dysfunction syndrome, sepsis, and interstitial lung disease, which each occurred in one patient in the placebo plus chemotherapy group; [c]Immune-mediated adverse events and infusion reactions were based on a list of terms specified by the sponsor, regardless of attribution to any study treatment by investigator. AE, adverse event.

Sun JM et al. *Lancet* 2021;398:759–771.