MSD Oncology

# **KEYNOTE-590**: KEYTRUDA® (pembrolizumab) plus chemotherapy for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a 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).
(**please note that the MHRA Yellow Card link will redirect you to an external website, for which MSD does not review or control the content**)

CPS, combined positive score; MHRA, Medicines and Healthcare products Regulatory Agency; PD-L1, programmed death ligand-1.

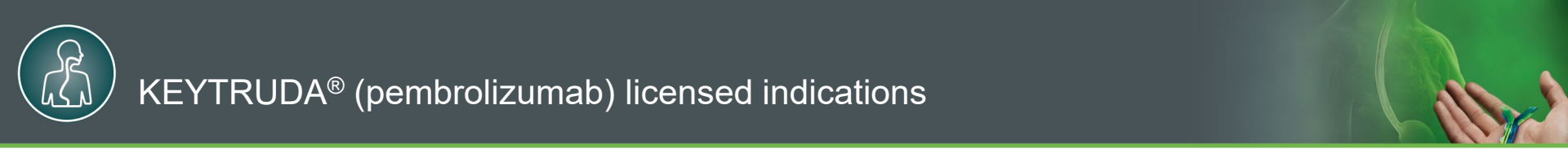
**Intended for UK Healthcare Professionals only.**
**For the KEYTRUDA Prescribing Information, please click the following link or the PI button located on each slide.**



MSD

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

# KEYTRUDA® (pembrolizumab) licensed indications



- KEYTRUDA, in combination with platinum- and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥10

CPS, combined positive score; PD-L1, programmed death ligand-1.
KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498. Accessed February 2024.

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# NICE technology appraisal guidance [TA737] remains in place

- 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 HER2-negative GOJ adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥10

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CPS, combined positive score; GOJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; NICE, National Institute for Health and Care Excellence; PD-L1, programmed death ligand-1.

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/ta737/resources/pembrolizumab-with-platinum-and-fluoropyrimidinebased-chemotherapy-for-untreated-advanced-oesophageal-and-gastrooesophageal-junction-cancer-pdf-82611259544005. Accessed February 2024.

# Slide deck navigation

Click the links below to navigate to the section of interest

**Pembrolizumab and chemotherapy overview**

**KEYNOTE-590 overview**

**KEYNOTE-590 results**

**Appendix**

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- The links in this slide will redirect you to third-party websites where indicated. Please note that:
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# Pembrolizumab and chemotherapy overview

**The pembrolizumab plus chemotherapy licence**

**Current treatment landscape/ patient pathway**

PI

# The pembrolizumab plus chemotherapy licence[1,2]

**KEYTRUDA™**

\+ Platinum-based chemotherapy

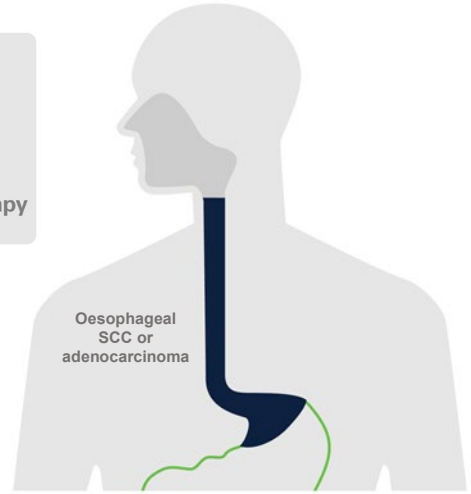
\+ Fluoropyrimidine-based chemotherapy

**Timing and dosing of KEYTRUDA**

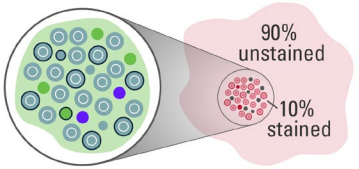
200 mg Q3W or 400 mg Q6W administered as an IV infusion over 30 minutes

**1L**

No prior chemotherapy




**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]

**Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in 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; 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 – Esophageal Agilent Dako. Available at: https://www.agilent.com/cs/library/usermanuals/public/29439-d67239-pd-l1-ihc22c3-ec-kn590-int-man-en.pdf Accessed February 2024; 2. KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498. Accessed February 2024.

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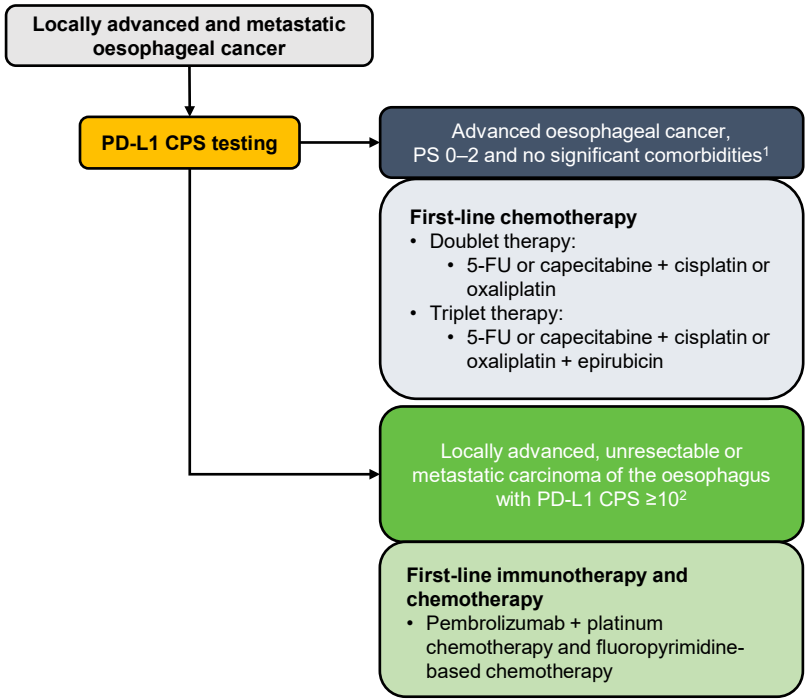
# Current treatment landscape in first-line locally advanced or metastatic oesophageal cancer[1,2]




Pembrolizumab in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥10[2]

Figure adapted from NICE Palliative management for people with oesophageal and gastric cancer.
5-FU, 5-fluorouracil; CPS, combined positive score; NICE, National Institute for Health and Care Excellence; PD-L1, programmed death ligand-1; PS, performance status.
1. Oesophago-gastric cancer: assessment and management in adults. NICE. Available at: https://www.nice.org.uk/guidance/ng83/chapter/Recommendations. Accessed February 2024; 2. KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498. Accessed February 2024.

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# KEYNOTE-590 overview

**Study design**

**Baseline characteristics**

**Definition of analyses**

# KEYNOTE-590: Study design

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

### Key eligibility criteria
- Locally advanced unresectable or metastatic EAC or ESCC or advanced/metastatic GOJ 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/m$^2$ IV for Days 1–5 Q3W for ≤35 cycles + cisplatin 80 mg/m$^2$ IV Q3W for ≤6 cycles)**

(n=376)

**Placebo[a]**
**+**
**chemotherapy**
**(5-FU 800 mg/m$^2$ IV for Days 1–5 Q3W for ≤35 cycles + cisplatin 80 mg/m$^2$ IV Q3W for ≤6 cycles)**

Until disease progression, unacceptable toxicity or for a maximum of 35 cycles

### 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; GOJ, gastro-oesophageal 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.
Sun JM et al. *Lancet* 2021;398:759–771.

# KEYNOTE-590: Baseline characteristics in the ITT population

| 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) |
| GOJ | 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 in adults whose tumours express **PD-L1 with a 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; GOJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; ITT, intention to treat; PD-L1, programmed death ligand-1.
Sun JM et al. *Lancet* 2021;398:759–771.

# 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;398:759–771; 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

- OS in PD-L1 CPS ≥10 population (first interim analysis)
- OS in PD-L1 CPS ≥10 population (12-month follow-up analysis)
- PFS in PD-L1 CPS ≥10 population (first interim analysis)
- PFS in PD-L1 CPS ≥10 population (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.

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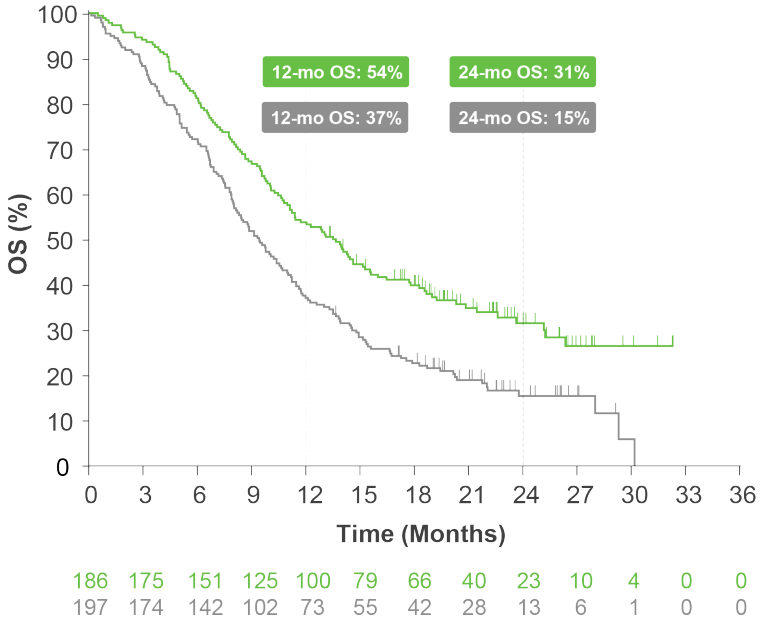
# KEYNOTE-590: OS in the PD-L1 CPS ≥10 population (first interim analysis)[1,2]

| 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 plus 5-FU versus placebo plus cisplatin plus 5-FU was superior for OS in patients with PD-L1 CPS ≥10**

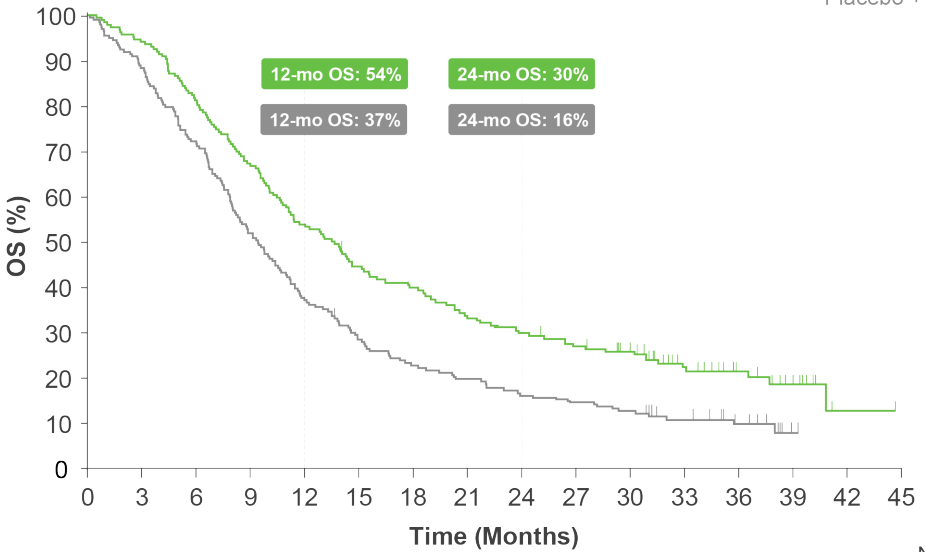
- **38% reduction in the risk of death with KEYTRUDA (pembrolizumab) plus cisplatin plus 5-FU (n=186) versus placebo plus cisplatin plus 5-FU (n=197) (HR=0.62; 95% CI: 0.49–0.78, p<0.0001)**
- **Median OS with KEYTRUDA (pembrolizumab) plus cisplatin plus 5-FU was 13.5 months (95% CI: 11.1–15.6) versus 9.4 months (95% CI: 8.0–10.7) with placebo plus cisplatin plus 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;398:759–771.

# 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) | — |




No. at risk

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 186 | 175 | 151 | 125 | 100 | 81 | 73 | 62 | 55 | 48 | 42 | 25 | 15 | 8 | 1 | 0 KEYTRUDA (pembrolizumab) + cisplatin + 5-FU |
| 197 | 174 | 142 | 102 | 73 | 55 | 44 | 38 | 31 | 28 | 23 | 15 | 8 | 1 | 0 | 0 Placebo + cisplatin + 5-FU |

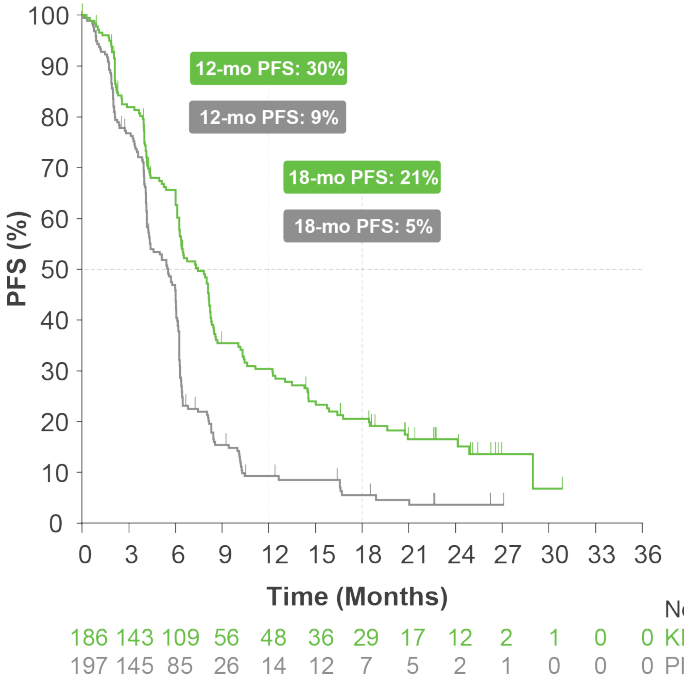
**KEYTRUDA (pembrolizumab) plus cisplatin plus 5-FU versus placebo plus cisplatin plus 5-FU was superior for OS in patients with PD-L1 CPS ≥10**

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

**No statistical conclusions can be drawn from this analysis. 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.**
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 plus 5-FU versus placebo plus cisplatin plus 5-FU was superior for PFS in patients with PD-L1 CPS ≥10**

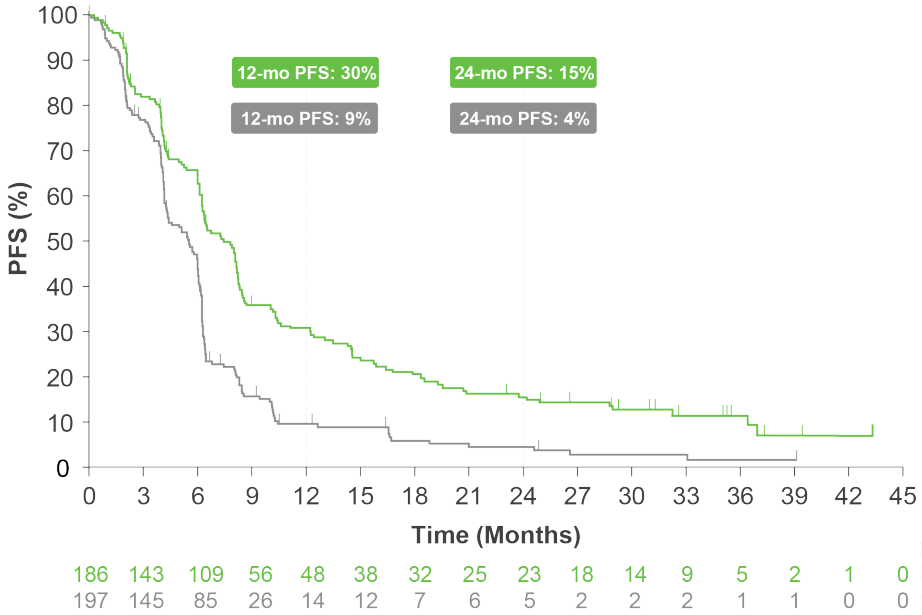
- **49% reduction in the risk of disease progression or death with KEYTRUDA (pembrolizumab) plus cisplatin plus 5-FU (n=186) versus placebo plus cisplatin plus 5-FU (n=197) (HR=0.51; 95% CI: 0.41–0.65; p<0.0001)**
- **Median PFS with KEYTRUDA (pembrolizumab) plus cisplatin plus 5-FU was 7.5 months (95% CI: 6.2–8.2) versus 5.5 months (95% CI: 4.3–6.0) with placebo plus cisplatin plus 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;398:759–771.

# 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 plus 5-FU versus placebo plus cisplatin plus 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 plus 5-FU (n=186) versus placebo plus cisplatin plus 5-FU (n=197) (HR=0.51; 95% CI: 0.41–0.65)**
- **Median PFS with KEYTRUDA (pembrolizumab) plus cisplatin plus 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 plus 5-FU**

**No statistical conclusions can be drawn from this analysis. The PFS forest plot for the key subgroups within the KEYNOTE-590 study is in the appendix. Click here to view.**

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

Click here to access the immune-mediated AE 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 SmPC here.

**Analysis cut-off date: 2 July 2020. Median follow-up 22.6 months.**
Table adapted from Kato K ESMO 2020.
[a]Unless stated otherwise.
AE, adverse event; CPS, combined positive score; HER2, human epidermal growth factor receptor 2; 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;398:759–771.

# 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 in adults whose tumours express **PD-L1 with a CPS ≥10.**

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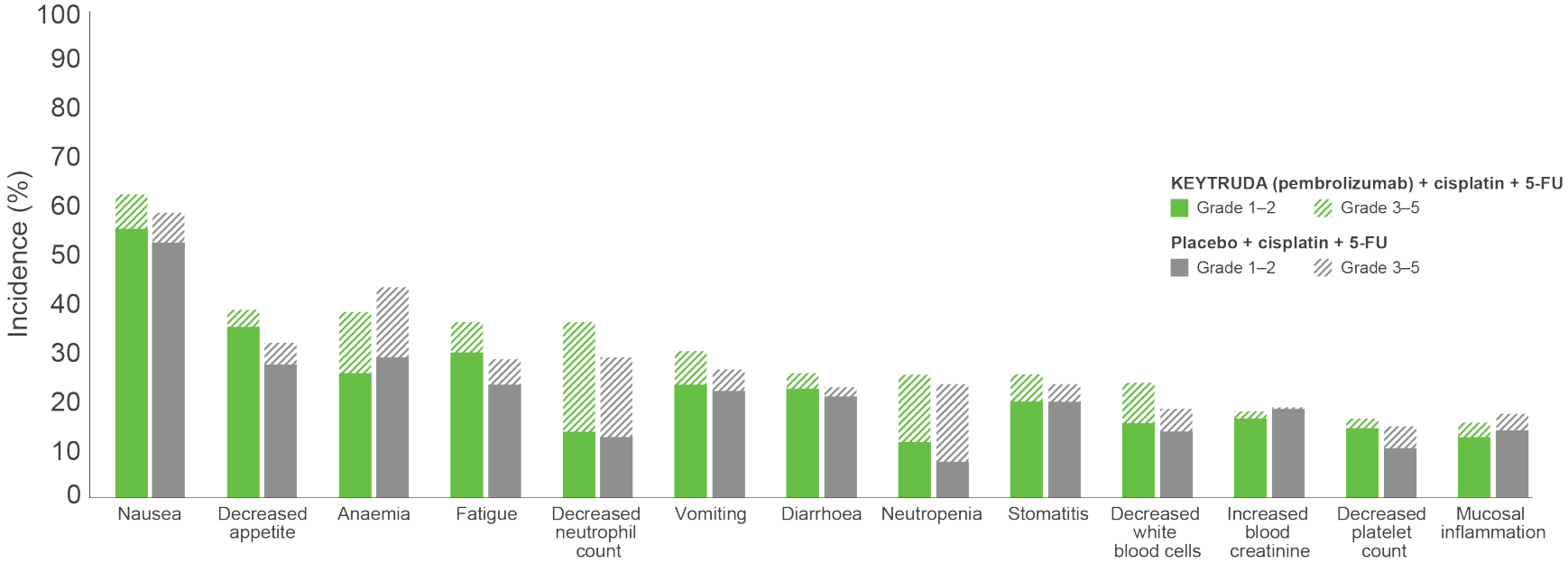
AE, adverse event; CPS, combined positive score; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death ligand-1.
Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

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




Click here to access the immune-mediated AE slide deck for adverse event management of pembrolizumab + chemotherapy combinations.
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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.
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;398:759–771.

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

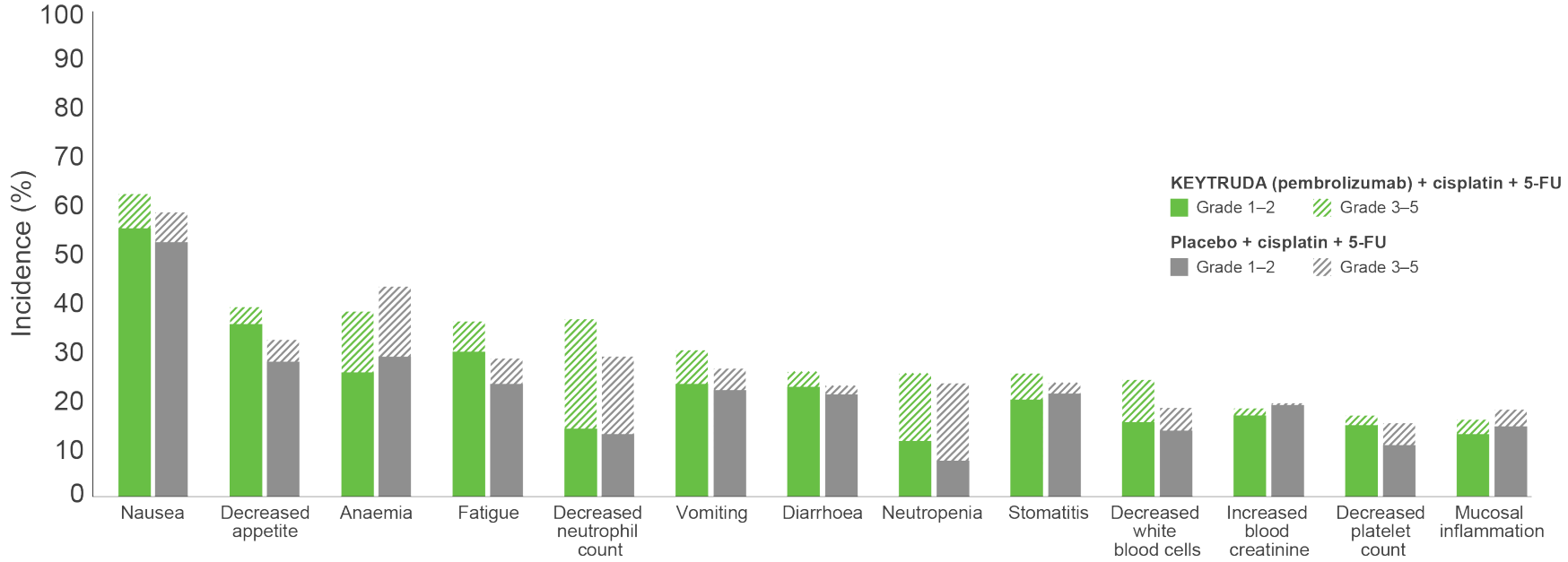


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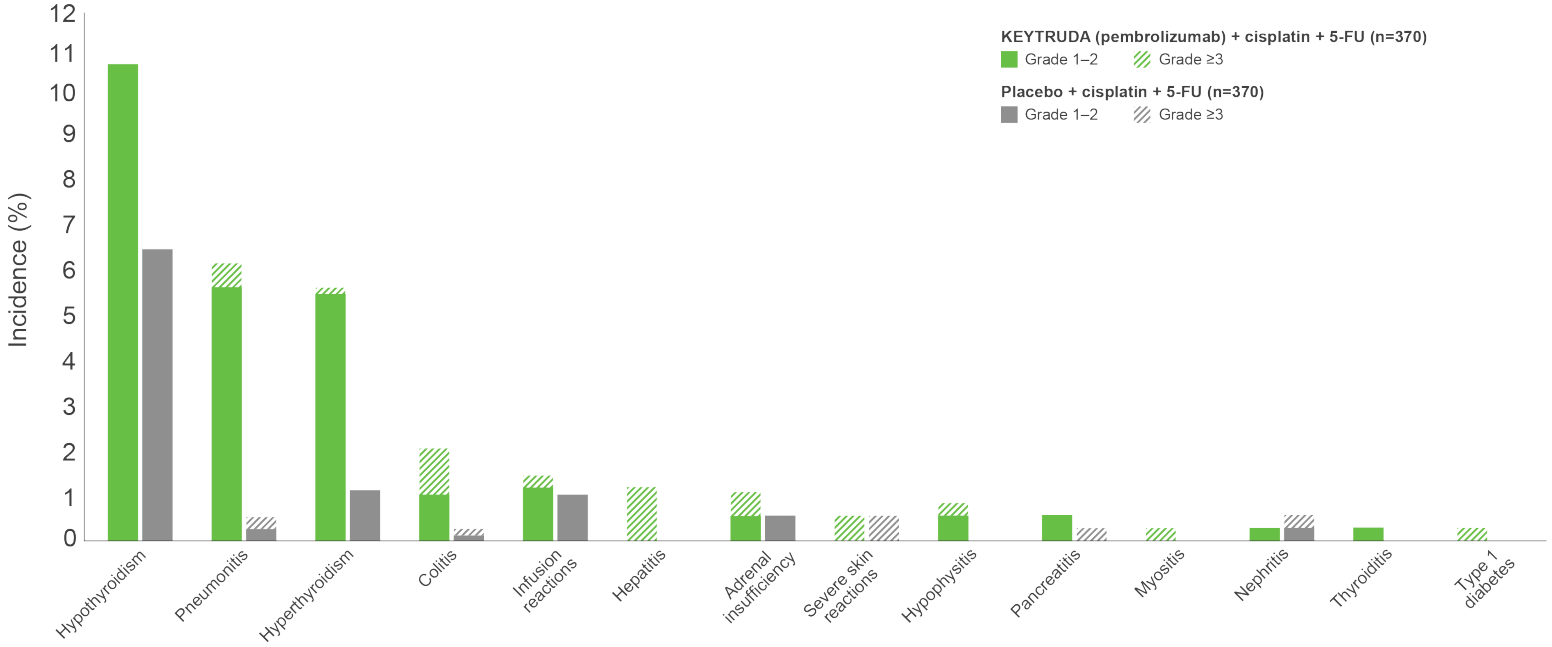
Figure adapted from Metges JP ASCO-GI 2022
AE, adverse event.
Metges JP et al. Presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium 2022, 20–22 January 2022.

# KEYNOTE-590: Selected AEs of special interest[a] (first interim analysis)




Click here to access the immune-mediated AEs deck for adverse event management of pembrolizumab + chemotherapy combinations.
Further information on the safety of pembrolizumab plus chemotherapy combinations can be found in the SmPC here.

**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.**
[a]Immune-mediated AEs and infusion reactions were based on a list of terms specified by the sponsor, regardless of attribution to any study treatment by investigators.
AE, adverse event.
Sun JM et al. *Lancet* 2021;398:759–771.

# 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) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498. Accessed February 2024; 2. Lala M *et al. Eur J Cancer* 2020;131:68–75.

PI

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

- KEYTRUDA (pembrolizumab) plus cisplatin plus 5-FU is a licensed immunotherapy for locally advanced, unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥10

- KEYTRUDA (pembrolizumab) plus cisplatin plus 5-FU versus placebo + cisplatin plus 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 plus 5-FU versus placebo plus cisplatin plus 5-FU was superior for PFS in patients with PD-L1 CPS ≥10
  - First interim analysis: HR: 0.51, 95% CI: 0.41–0.65; p<0.0001[1,2]
  - 12-month follow-up analysis: HR: 0.51, 95% CI: 0.41–0.65[3]

- Grade ≥3 AEs occurred in 71.9% of patients in the KEYTRUDA (pembrolizumab) plus cisplatin plus 5-FU and 67.6% of patients in the placebo plus cisplatin plus 5-FU arm. Click here for the full list of AEs
  - Of those treated, patients in the KEYTRUDA plus cisplatin plus 5-FU group had a higher proportion of discontinuations of trial drugs compared with the placebo plus cisplatin plus 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 plus 5-FU compared with those receiving placebo plus cisplatin plus 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]

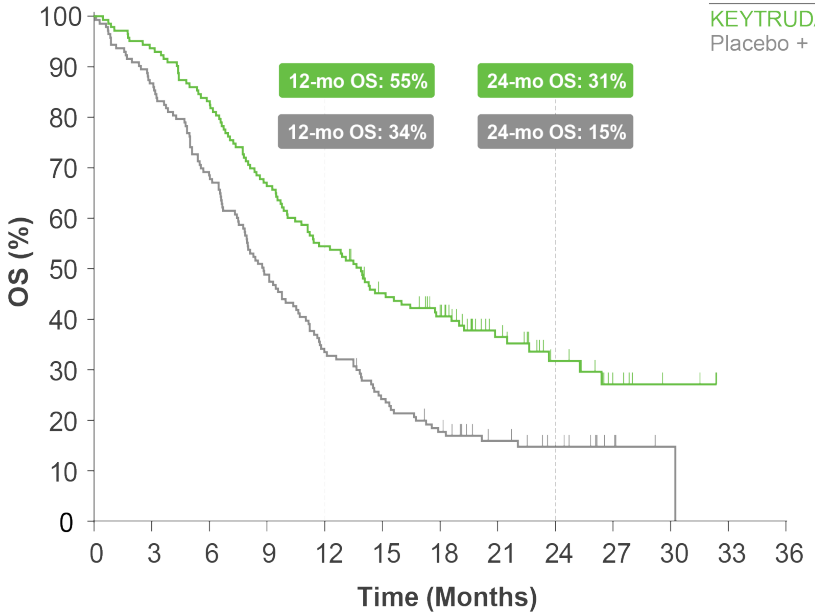
**Interim analysis cut-off date: 2 July 2020 (median follow-up 22.6 months); 12-month follow-up analysis cut-off date: 9 July 2021 (median follow-up 34.8 months).**
CI, confidence interval; CPS, combined positive test score; AE, adverse event; HR, hazard ratio; OS, overall survival; PD-L1, programmed 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;398:759–771; 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 the key subgroup of ESCC (12-month follow-up analysis)
- PFS in key subgroups All patients (first interim 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 plus 5-FU versus placebo plus cisplatin plus 5-FU was superior for OS in patients with ESCC and PD-L1 CPS ≥10**

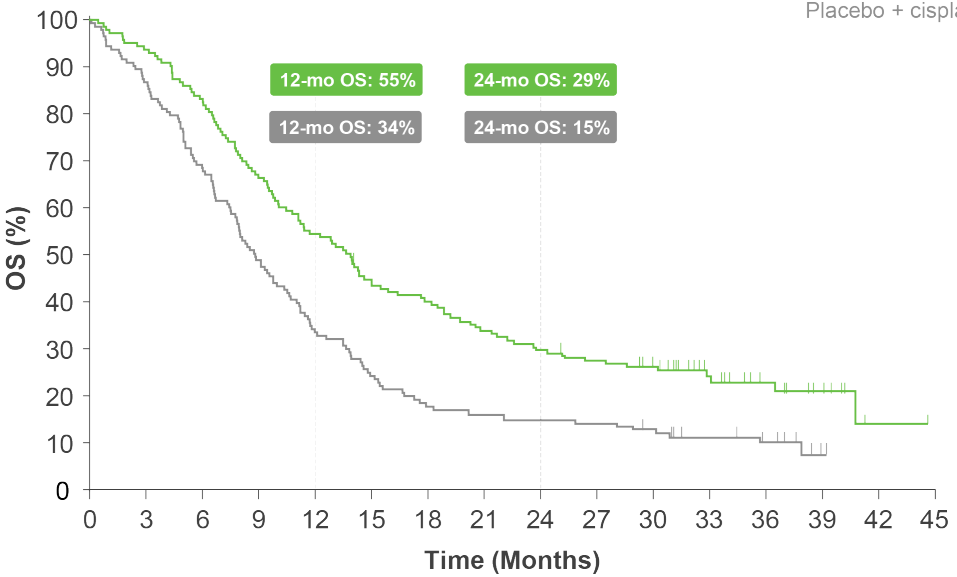
- **43% reduction in the risk of death with KEYTRUDA (pembrolizumab) plus cisplatin plus 5-FU (n=143) versus placebo plus cisplatin plus 5-FU (n=143) (HR=0.57; 95% CI: 0.43–0.75, p<0.0001)**
- **Median OS with KEYTRUDA (pembrolizumab) plus cisplatin plus 5-FU was 13.9 months (95% CI: 11.1–17.7) versus 8.8 months (95% CI: 7.8–10.5) with placebo plus cisplatin plus 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.
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;398:759–771.

# 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) | — |




No. at risk

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 143 | 134 | 119 | 96 | 78 | 63 | 57 | 48 | 42 | 38 | 33 | 19 | 12 | 7 | 1 | 0 |
| 143 | 124 | 99 | 70 | 48 | 34 | 25 | 23 | 21 | 20 | 17 | 10 | 7 | 1 | 0 | 0 |

KEYTRUDA (pembrolizumab) + cisplatin + 5-FU

Placebo + cisplatin + 5-FU

**KEYTRUDA (pembrolizumab) plus cisplatin plus 5-FU versus placebo plus cisplatin plus 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 plus 5-FU (n=143) versus placebo plus cisplatin plus 5-FU (n=143) (HR=0.59; 95% CI: 0.45–0.7)**
- **Median OS with KEYTRUDA (pembrolizumab) plus cisplatin plus 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 plus 5-FU**

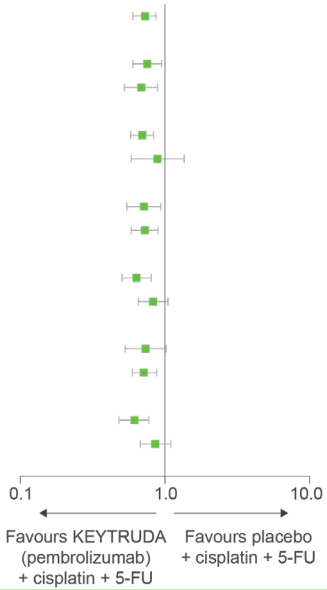
**No statistical conclusions can be drawn from this analysis. The OS forest plot for the key subgroups within the KEYNOTE-590 study is in the appendix. Click here to view.**

**Analysis cut-off date: 9 July 2021. Median follow-up 34.8 months.**
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**

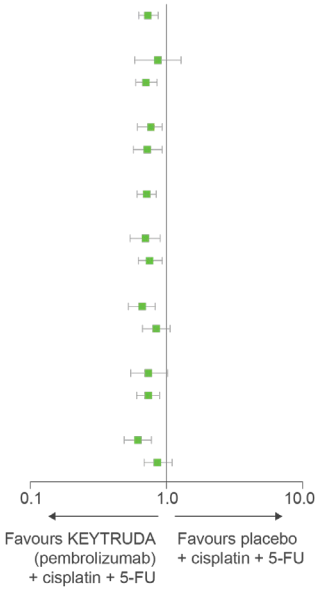
Please note that the licensed indication for pembrolizumab is in locally advanced, unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express **PD-L1 with a CPS ≥10**

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

# 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% C |
|---|---|---|
| **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) |



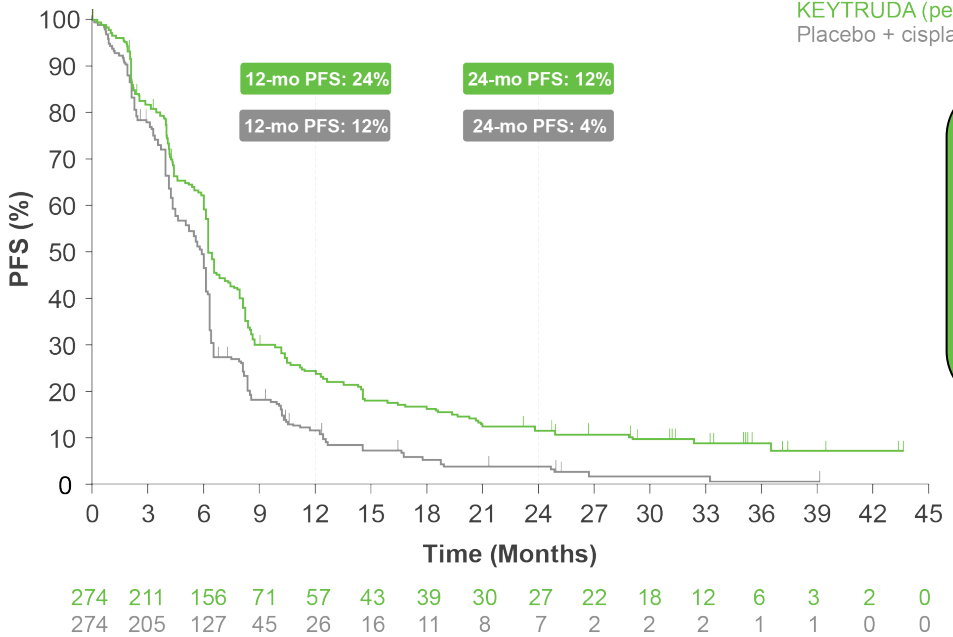

**Only the ESCC and CPS ≥10 subgroups were powered to show statistically significant results. All other results are exploratory**

Please note that the licensed indication for pembrolizumab is in locally advanced, unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express **PD-L1 with a 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 updated analysis: PFS in the prespecified subgroup of 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 plus 5-FU versus placebo plus cisplatin plus 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 plus 5-FU (n=274) versus placebo plus cisplatin plus 5-FU (n=274) (HR=0.65; 95% CI: 0.54–0.78)**
- **Median PFS with KEYTRUDA (pembrolizumab) plus cisplatin plus 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 plus 5-FU**

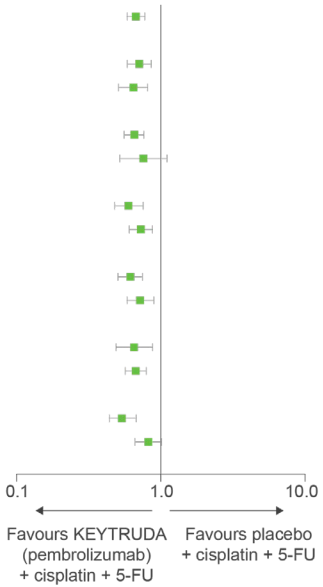
**No statistical conclusions can be drawn from this analysis. The PFS forest plot for the key subgroups within the KEYNOTE-590 study is in the appendix. Click here to view.**

**Analysis cut-off date: 9 July 2021. Median follow-up 34.8 months.**
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.

# 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 in adults whose tumours express **PD-L1 with a CPS ≥10**

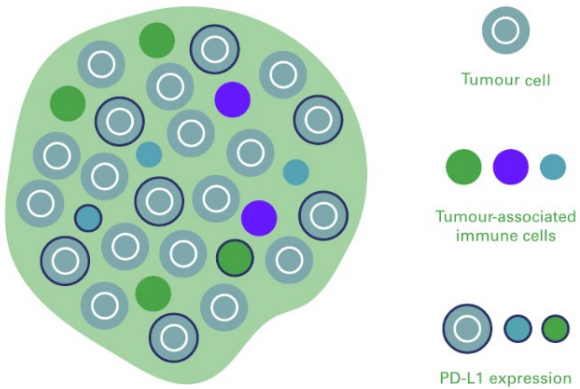
**Analysis cut-off date: 2 July 2020. Median follow-up 22.6 months.**
Figure adapted from Kato K ESMO 2020.
CI, confidence interval; CPS, combined positive test score; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, oesophageal squamous cell carcinoma; HER2, human epidermal growth factor receptor 2; ITT, intention to treat; PD-L1, programmed death ligand-1; PFS, progression-free survival.
Sun JM et al. *Lancet* 2021;398:759–771.

# 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. By clicking on this link you will be taken to an MSD promotional website.

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 – Esophageal Agilent Dako. Available at: https://www.agilent.com/cs/library/usermanuals/public/29439-d67239-pd-l1-ihc22c3-ec-kn590-int-man-en.pdf Accessed February 2024.

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

| AEs, n (%)[a] | KEYTRUDA (pembrolizumab) + cisplatin + 5-FU (n=370) | | Placebo + cisplatin + 5-FU (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.**

Table adapted from Sun JM et al. 2021.

[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] | KEYTRUDA (pembrolizumab) + cisplatin + 5-FU (n=370) | | Placebo + cisplatin + 5-FU (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] | KEYTRUDA (pembrolizumab) + cisplatin + 5-FU (n=370) | | Placebo + cisplatin + 5-FU (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.**

Table adapted from Sun JM et al. 2021.

[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.