MSD Oncology

KEYNOTE-859: First-line treatment (pembrolizumab plus chemotherapy) of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma

Please refer to the full KEYTRUDA® (pembrolizumab) Summary of Product Characteristics (SmPC) 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/ (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) 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 click the following links for the KEYTRUDA Prescribing Information: Great Britain; Northern Ireland.

MSD

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

Job code: GB-ESO-00025. Date of preparation: February 2024.

Slide deck navigation

Click the links below to navigate to the section of interest

Gastric cancer overview

KEYNOTE-859: Overview

KEYNOTE-859: Results

KEYNOTE-859: Summary

Appendix

- To access the navigation page, click the ‘Home’ icon
- The links in this slide deck will redirect you to third-party websites where indicated. Please note that MSD does not:
  - Review or control the content of any third-party website
  - Endorse and have responsibility for the accuracy, content, practices or standards of any third-party sources

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PI, prescribing information.

KEYTRUDA® (pembrolizumab) licensed indication

- KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or GOJ adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥1

CPS, combined positive score; GOJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability-high; PD-L1, programmed death ligand-1; PI, prescribing information.

KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498/smpc#about-medicine (GB); https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc (NI). Accessed January 2024.

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In the UK, there are ~4200 deaths due to gastric cancer per year[a]

Gastric cancer is the **17th most commonly diagnosed cancer** in the UK[b]

In the UK, **approximately 6500** new cases of gastric cancer are diagnosed each year[b]

Approximately 17% of patients with gastric cancer **in England will survive their cancer for ≥10 years**[c]

Gastric cancer has the highest incidence rate in those aged **85–89 years**[b]

2 in 3 cases of gastric cancer are in men[b]

[a]Data collected from 2017–2019; [b]Data collected from 2016–2018; [c]Data collected from 2013–2017.

PI, prescribing information.

Cancer Research UK. Stomach cancer statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer. Accessed January 2024.

Chemotherapy treatment for advanced HER2-negative gastric or GOJ cancer is associated with poor survival outcomes[1]

Patients with HER2-negative tumours

~80% of patients with advanced GOJ or gastric adenocarcinoma have **HER2-negative** tumours[2]

IO therapy

Recent studies have showed that the addition of **IO therapy** to chemotherapy **improves clinical outcomes,** including OS, in patients with advanced HER2-negative **gastric or GOJ cancer**[3]

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KEYTRUDA in combination with chemotherapy has been shown to **improve clinical outcomes** in patients with advanced cancer, and was recently investigated in patients with advanced HER2-negative PD-L1 positive **gastric or GOJ cancer**[4]

IO + chemotherapy has become an important treatment option in patients with gastric or GOJ cancer. **KEYNOTE-859** provides additional data on treatment options available for patients with advanced HER2-negative gastric or GOJ cancer with a CPS ≥1[4]

GOJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; IO, immuno-oncology; OS, overall survival; PD-L1, programmed death ligand-1; PI, prescribing information.

1. Sexton RE et al. *Cancer Metastasis Rev* 2020;39:1179–1203; 2. Ross JS et al. *Gastrointest Cancer Res* 2011;4:62–66; 3. Janjigian YY et al. *Lancet Oncol* 2021;398:27–40; 4. Rha SY et al. *Lancet Oncol* 2023;24:1181–1195.

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KEYNOTE-859: Study design[1,2]

Multicentre, randomised, double-blind, placebo-controlled Phase 3 trial
Patients enrolled until 3 October 2022 (N=1579)

Key eligibility criteria
- Advanced gastric or GOJ adenocarcinoma
- HER2-negative
- Known PD-L1 status
- ECOG PS 0 or 1
- No prior systemic treatment for metastatic disease

Stratification factors at randomisation
- Geographic region
- PD-L1 CPS (<1 vs ≥1)
- Investigator's choice of chemotherapy (FP vs CAPOX)

R
1:1
(N=1579)

n=790 → **KEYTRUDA[a] 200 mg IV Q3W + FP[b] or CAPOX[c]**

n=789 → **Placebo[a] IV Q3W + FP[b] or CAPOX[c]**

Patients were treated until disease progression, unacceptable toxicity or for a maximum of 35 cycles

- **Primary endpoint**: OS
- **Secondary endpoints**: PFS, ORR and DOR, as assessed by BICR using RECIST v1.1, and safety

Figure adapted from Tabernero J et al. 2021

[a]Administered on Day 1 of each cycle; [b]Cisplatin 80 mg/m² IV Q3W + 5-FU 800 mg/m²/day IV on Days 1–5; [c]Oxaliplatin 130 mg/m² IV Q3W + capecitabine 1000 mg/m² BID on Days 1–14.

5-FU, 5-fluorouracil; BICR, blinded independent central review; BID, twice a day; CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; DOR, duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; FP, 5-fluorouracil and cisplatin; GOJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PI, prescribing information; Q3W, every 3 weeks; R, randomisation; RECIST v1.1, Response Evaluation Criteria In Solid Tumors Version 1.1.

1. Tabernero J et al. *Future Oncol* 2021;17:2847–2855; 2. Rha SY et al. *Lancet Oncol* 2023;24:1181–1195.

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KEYNOTE-859: Baseline characteristics

Characteristic	KEYTRUDA + FP or CAPOX (n=790)	Placebo + FP or CAPOX (n=789)
Age, median (IQR), years	61 (52–67)	62 (52–69)
Age ≥65 years, n (%)	304 (38)	310 (39)
Male sex, n (%)	527 (67)	544 (69)
Geographic region, n (%)		
Asia	263 (33)	262 (33)
Western Europe, Israel, North America and Australia	201 (25)	202 (26)
Rest of world	326 (41)	325 (41)
ECOG PS, n (%)		
0	281 (36)	301 (38)
1	509 (64)	488 (62)
Disease status,[a] n (%)		
Locally advanced	28 (4)	30 (4)
Metastatic	761 (96)	759 (96)
Primary tumour location,[b] n (%)		
Adenocarcinoma of the GOJ	149 (19)	185 (23)
Adenocarcinoma of the stomach	640 (81)	603 (76)

Characteristic	KEYTRUDA + FP or CAPOX (n=790)	Placebo + FP or CAPOX (n=789)
MSI-H status[c] high, n (%)	39 (5)	35 (4)
PD-L1 status,[d] n (%)		
CPS ≥1 at baseline	618 (78)	617 (78)
CPS ≥10 at baseline	279 (35)	272 (34)
Combination chemotherapy at randomisation		
CAPOX	682 (86)	681 (86)
FP	108 (14)	108 (14)
Histological subtype,[e] n (%)		
Diffuse	318 (40)	301 (38)
Indeterminate	186 (24)	215 (27)
Intestinal	284 (36)	273 (35)
Liver metastases present[f]	314 (40)	311 (39)
Prior gastrectomy/oesophagectomy[g]	172 (22)	162 (21)

Table adapted from Rha SY et al. 2023

Analysis cut-off date: 3 October 2022.

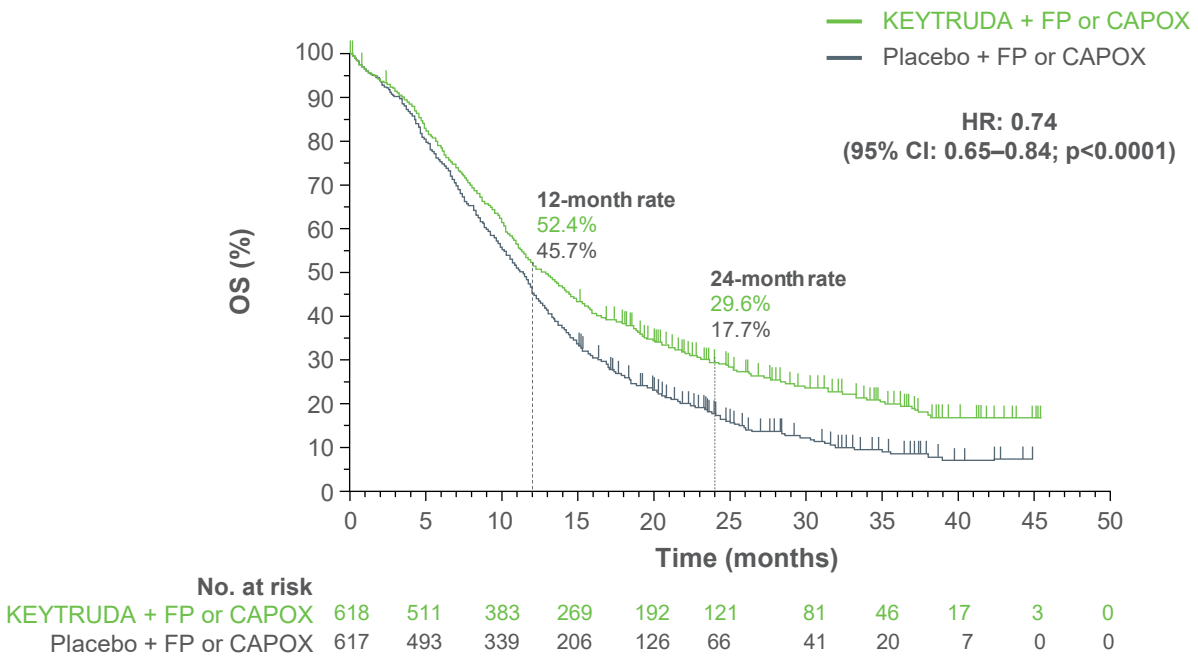
[a]Missing in 1 patient (<1%) in the KEYTRUDA + FP or CAPOX group; [b]Other in 1 patient (<1%) in the placebo + FP or CAPOX group and missing in 1 patient (<1%) in the KEYTRUDA + FP or CAPOX group; [c]Missing in 110 patients (14%) in the KEYTRUDA + FP or CAPOX group and in 114 patients (14%) in the placebo + FP or CAPOX; [d]Missing in 2 patients (<1%) in the KEYTRUDA + FP or CAPOX group; [e]Unknown in 1 patient (<1%) and missing in 1 patient (<1%) in the KEYTRUDA + FP or CAPOX group; [f]Missing in 1 patient (<1%) in the KEYTRUDA + FP or CAPOX group; [g]Missing in 5 patients (1%) in each group.

CAPOX, capecitabine + oxaliplatin; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; FP, 5-fluorouracil + cisplatin; GOJ, gastro-oesophageal junction; IQR, interquartile range; ITT, intention-to-treat; MSI-H, microsatellite instability-high; PD-L1, programmed death ligand-1.

Rha SY et al. *Lancet Oncol* 2023;24:1181–1195.

KEYNOTE-859: Primary endpoint – OS in patients with PD-L1 CPS ≥1[a,1,2]

Median (IQR) follow-up time: 31.0 (23.0–38.3) months



OS[b]	KEYTRUDA + FP or CAPOX (n=618)	Placebo + FP or CAPOX (n=617)
Patients with event, %	75.1	85.3
Median OS[c] (95% CI), months	13.0 (11.6–14.2)	11.4 (10.5–12.0)

Figure and table adapted from Rha SY et al. 2023[1,2]

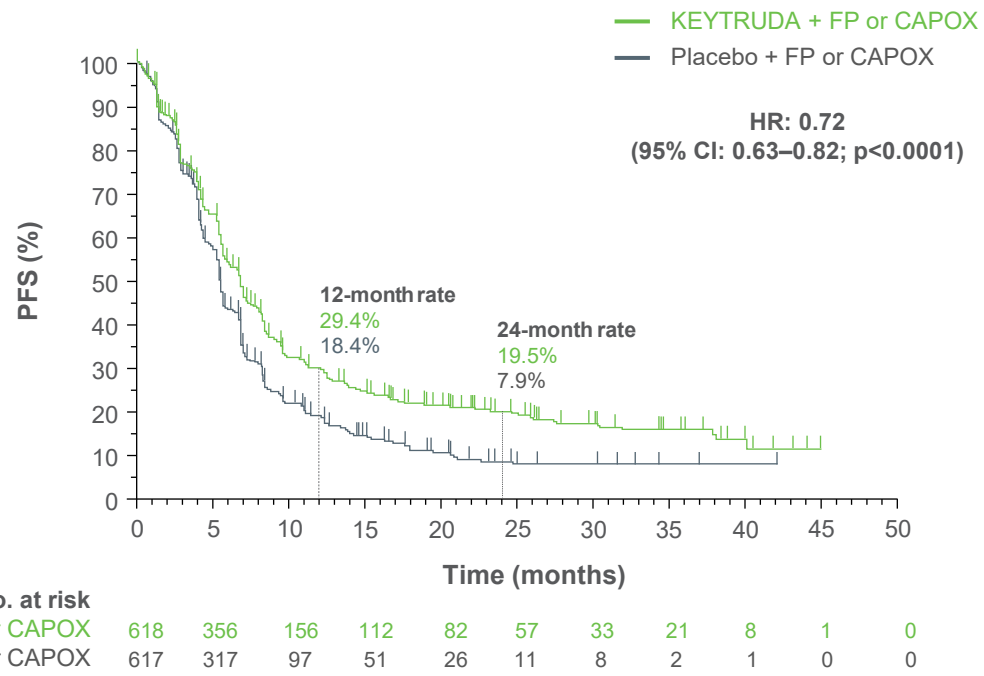
Analysis cut-off date: 3 October 2022.
[a]OS in the PD-L1 CPS ≥1 population was an alpha-controlled analysis; [b]OS was compared between treatment arms using the log-rank test stratified by the randomisation stratification factors; the magnitude of the treatment effect was assessed using a Cox regression model stratified by the randomisation stratification factors; [c]Based on Kaplan–Meier estimates.

CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CPS, combined positive score; FP, 5-fluorouracil and cisplatin; HR, hazard ratio; IQR, interquartile range; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PI, prescribing information.

1. Rha SY et al. *Lancet Oncol* 2023;24:1181–1195; 2. Rha SY et al. Poster presented at American Society of Clinical Oncology (ASCO) Congress 2023, 2–6 June 2023, Chicago, USA.

KEYNOTE-859: Secondary endpoint – PFS in patients with PD-L1 CPS ≥1[a,1,2]

Median (IQR) follow-up time: 31.0 (23.0–38.3) months



PFS[b,c]	KEYTRUDA + FP or CAPOX (n=618)	Placebo + FP or CAPOX (n=617)
Patients with event, %	71.7	78.3
Median PFS[d] (95% CI), months	6.9 (6.0–7.2)	5.6 (5.4–5.7)

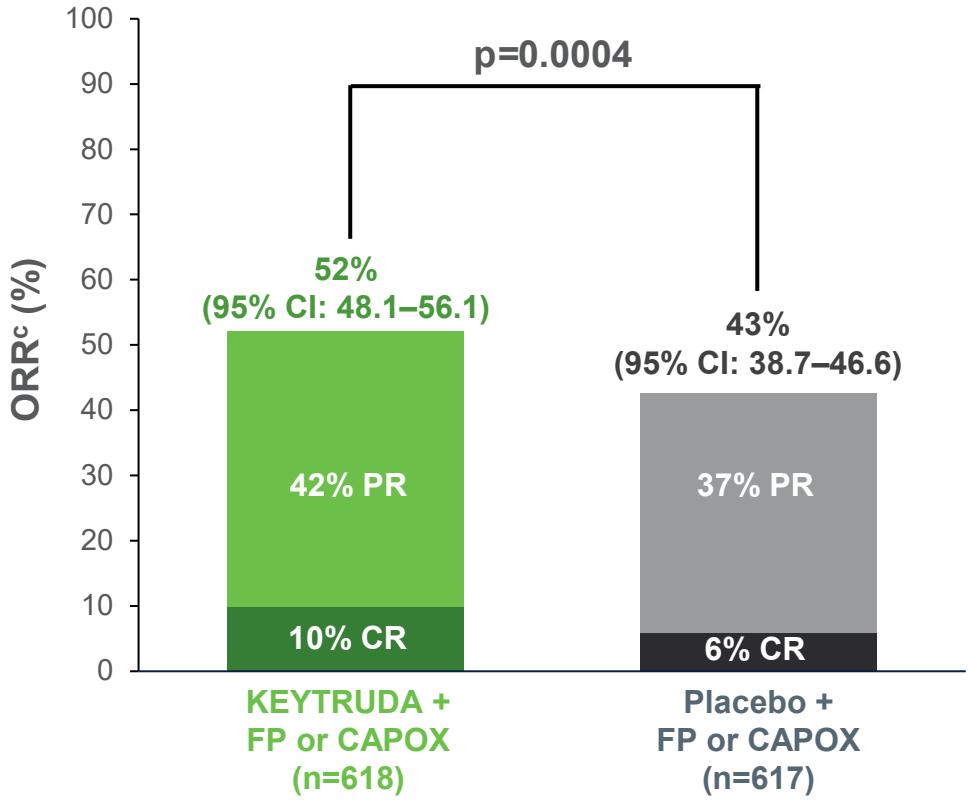
Figure and table adapted from Rha SY et al. 2023[1,2]

Analysis cut-off date: 3 October 2022.
[a]PFS in the PD-L1 CPS ≥1 population was an alpha-controlled analysis; [b]PFS was compared between treatment arms using the log-rank test stratified by the randomisation stratification factors; the magnitude of the treatment effect was assessed using a Cox regression model stratified by the randomisation stratification factors; [c]Assessed by BICR using RECIST v1.1; [d]Based on Kaplan–Meier estimates.

BICR, blinded independent central review; CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CPS, combined positive score; FP, 5-fluorouracil and cisplatin; HR, hazard ratio; IQR, interquartile range; PD-L1, programmed death ligand-1; PFS, progression-free survival; PI, prescribing information; RECIST v1.1, Response Evaluation Criteria In Solid Tumors Version 1.1.

1. Rha SY et al. *Lancet Oncol* 2023;24:1181–1195; 2. Rha SY et al. Poster presented at American Society of Clinical Oncology (ASCO) Congress 2023, 2–6 June 2023, Chicago, USA.

KEYNOTE-859: Secondary Endpoints - ORR and DOR in the PD-L1 CPS ≥1 population[1,2]



DOR	KEYTRUDA + FP or CAPOX (n=322)	Placebo + FP or CAPOX (n=263)
Median DOR[c] (95% CI), months	8.3 (7.0–10.9)	5.6 (5.4–6.9)
% with duration ≥12 months	41.2	25.6
% with duration ≥24 months	30.0	11.1

Figure adapted from Rha SY et al. 2023[1,2]

[a]Along with OS, PFS and ORR in the overall population, OS, PFS and ORR in the PD-L1 CPS ≥1 and CPS ≥10 populations were alpha-controlled analyses;
[b]ORR was compared between treatment arms using the Miettinen and Nurminen method stratified by the randomisation stratification factors;
[c]Assessed by BICR using RECIST v1.1.

BICR, blinded independent central review; CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CPS, combined positive score; CR, complete response; DOR, duration of response; FP, 5-fluorouracil and cisplatin; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PI, prescribing information; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors Version 1.1.

1. Rha SY et al. *Lancet Oncol* 2023;24:1181–1195; 2. Rha SY et al. Poster presented at American Society of Clinical Oncology (ASCO) Congress 2023, 2–6 June 2023, Chicago, USA.

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KEYNOTE-859: Safety results – AEs in the as-treated population

Median (IQR) follow-up time: 31.0 (23.0–38.3) months

AEs	KEYTRUDA + FP or CAPOX (n=785)	Placebo + FP or CAPOX (n=787)
AEs of any cause (any grade), n (%)	776 (99)	771 (98)
TRAEs, n (%)	751 (96)	736 (94)
Grade 3–5	466 (59)	402 (51)
Serious	184 (23)	146 (19)
Led to death	8 (1)[a]	16 (2)[b]
Led to discontinuation of any drug	207 (26)	158 (20)

Table adapted from Rha SY et al. 2023.

Analysis cut-off date: 3 October 2022. The as-treated population included all patients who were randomised and received ≥1 dose of study treatment.

[a]n=1 each due to diarrhoea, peripheral embolism, pneumonitis, pulmonary haemorrhage, sepsis, septic shock, thrombotic thrombocytopenia purpura and death (cause unknown); [b]n=3 due to septic shock, n=2 due to acute myocardial infarction and n=1 each due to cerebral haemorrhage, cerebrovascular accident, diarrhoea, gastric perforation, hepatic function abnormal, neurotoxicity, pneumonitis, pulmonary embolism, sepsis, sudden death and urosepsis.

AE, adverse event; CAPOX, capecitabine + oxaliplatin; FP, 5-fluorouracil + cisplatin; IQR, interquartile range; PI, prescribing information; TRAE, treatment-related adverse event.

Rha SY et al. *Lancet Oncol* 2023;24:1181–1195.

KEYNOTE-859: Safety results – TRAEs in ≥15% of patients in the as-treated population[1,2]

Median (IQR) follow-up time: 31.0 (23.0–38.3) months

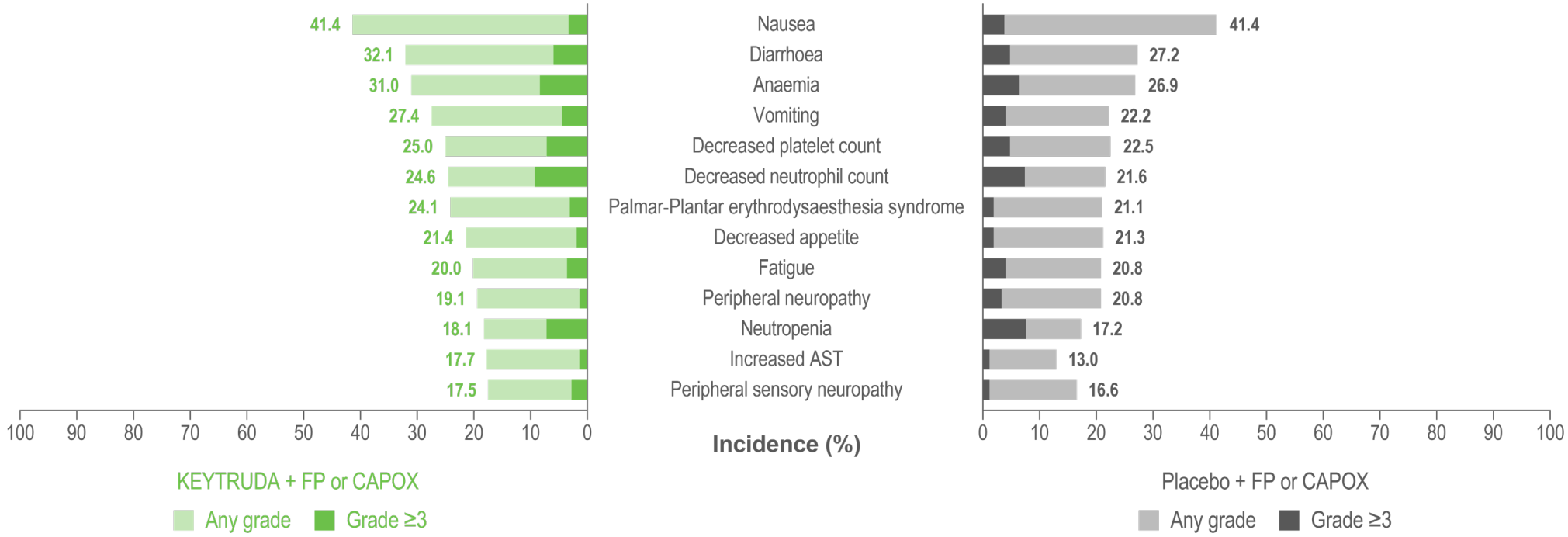

Figure adapted from Rha SY et al. 2023

The safety profile was as expected for the KEYTRUDA + chemotherapy regimen

Analysis cut-off date: 3 October 2022. The as-treated population included all patients who were randomised and received ≥1 dose of study treatment.

AST, aspartate aminotransferase; CAPOX, capecitabine + oxaliplatin; FP, 5-fluorouracil + cisplatin; IQR, interquartile range; PI, prescribing information; TRAE, treatment-related adverse event.

1. Rha SY et al. *Lancet Oncol* 2023;24:1181–1195; 2. Rha SY et al. Presented at the European Society for Medical Oncology (ESMO) Virtual Plenary 2023, 16 February 2023. Abstract VP1-2023.

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Conclusions

- KEYTRUDA as first-line treatment provided statistically significant and clinically meaningful improvement in OS compared with placebo when both were used in combination with FP or CAPOX in patients with PD-L1 CPS ≥1 status (HR: 0.74 [95% CI: 0.65–0.84]; p<0.0001)
- Patients treated with KEYTRUDA + FP or CAPOX also showed a statistically significant improvement in PFS compared with those treated with placebo + FP or CAPOX in patients with PD-L1 CPS ≥1 status (0.72 [95% CI: 0.63–0.82]; p<0.0001)
- No new safety signals for KEYTRUDA were observed in the study, and the tolerability profile was as expected for a KEYTRUDA + chemotherapy regimen

CAPOX, capecitabine + oxaliplatin; CI, confidence interval; CPS, combined positive score; FP, 5-fluorouracil + cisplatin; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PI, prescribing information.

Rha SY et al. *Lancet Oncol* 2023;24:1181–1195.

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Pembrolizumab dosing[1,2]

Administered as an IV infusion

Over 30 minutes

Every 3 weeks

Adults: 200 mg

Every 6 weeks

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

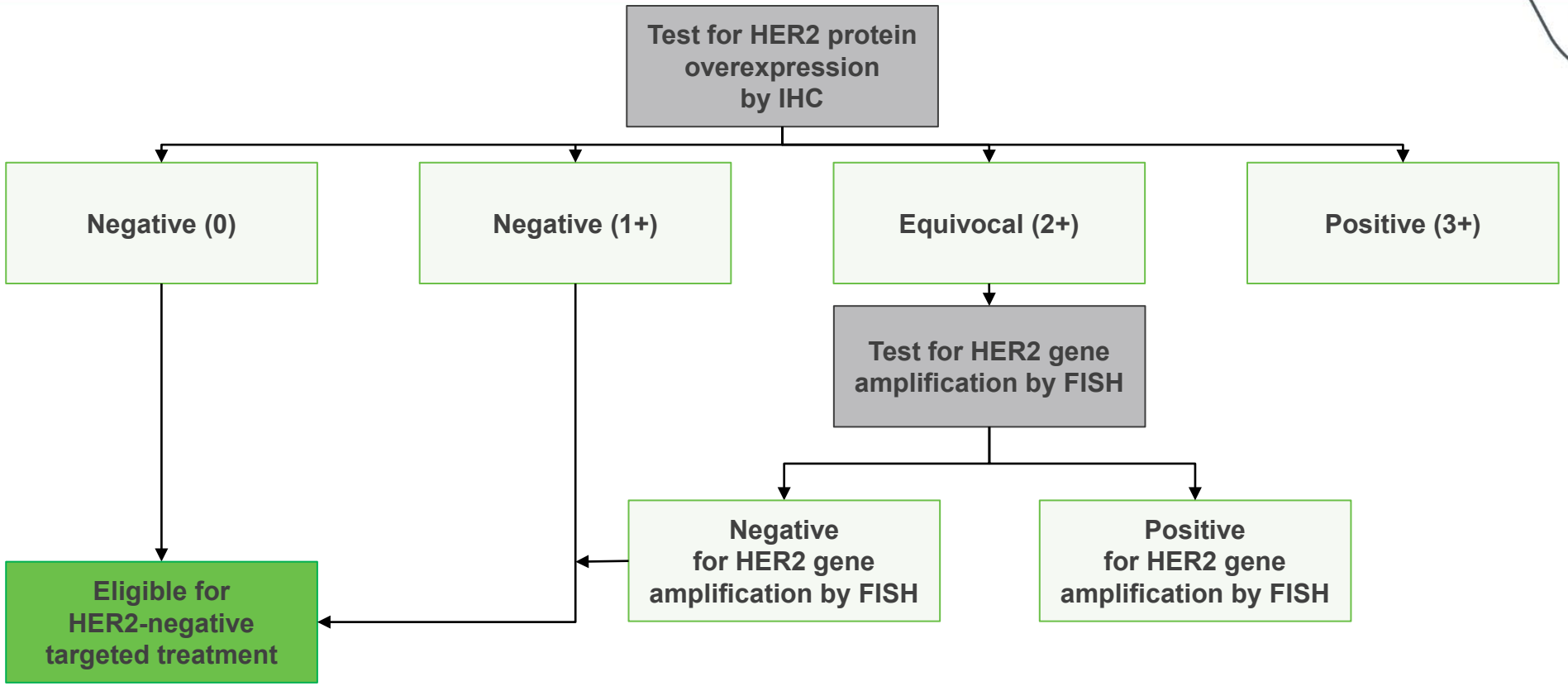
The only regimen assessed in all clinical Phase 2 and 3 registration studies for KEYTRUDA was the 200 mg Q3W dosing. The study that led to the approval of the Q6W for monotherapy and combination patients assessed the 400 mg Q6W dosing schedule based on an exposure–response evaluation using modelling 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.

Appendix

HER2 testing can help to identify patients with gastric or GOJ adenocarcinoma who are eligible for HER2-targeted treatment[1,2]



- IHC or FISH tests are used to identify cancer cells with a high level of HER2 protein[1]
- For patients with HER2-negative disease, treatment is guided by PD-L1 status[2]

Figure adapted from Abrahao-Machado LF al. 2016.

CPS, combined positive score; FISH, fluorescence *in situ* hybridisation; GOJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed death ligand-1; PI, prescribing information.

1. Abrahao-Machado LF et al. *World J Gastroenterol* 2016;22:4619–4625; 2. KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498/smpc#about-medicine (GB); https://www.emcmedicines.com/en-gb/northernireland/medicine?id=ce680467-8438-4e60-ab4f-dfab6767ccbe&type=smpc (NI). Accessed January 2024.

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