

KEYNOTE-859: First-line treatment (KEYTRUDA® [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).



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

Intended for UK Healthcare Professionals only.

For the KEYTRUDA Prescribing Information, please click the following [link](#) or the PI button located on each slide.

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Slide deck navigation



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**Gastric cancer
overview**

**KEYNOTE-859:
Overview**

**KEYNOTE-859:
Results**

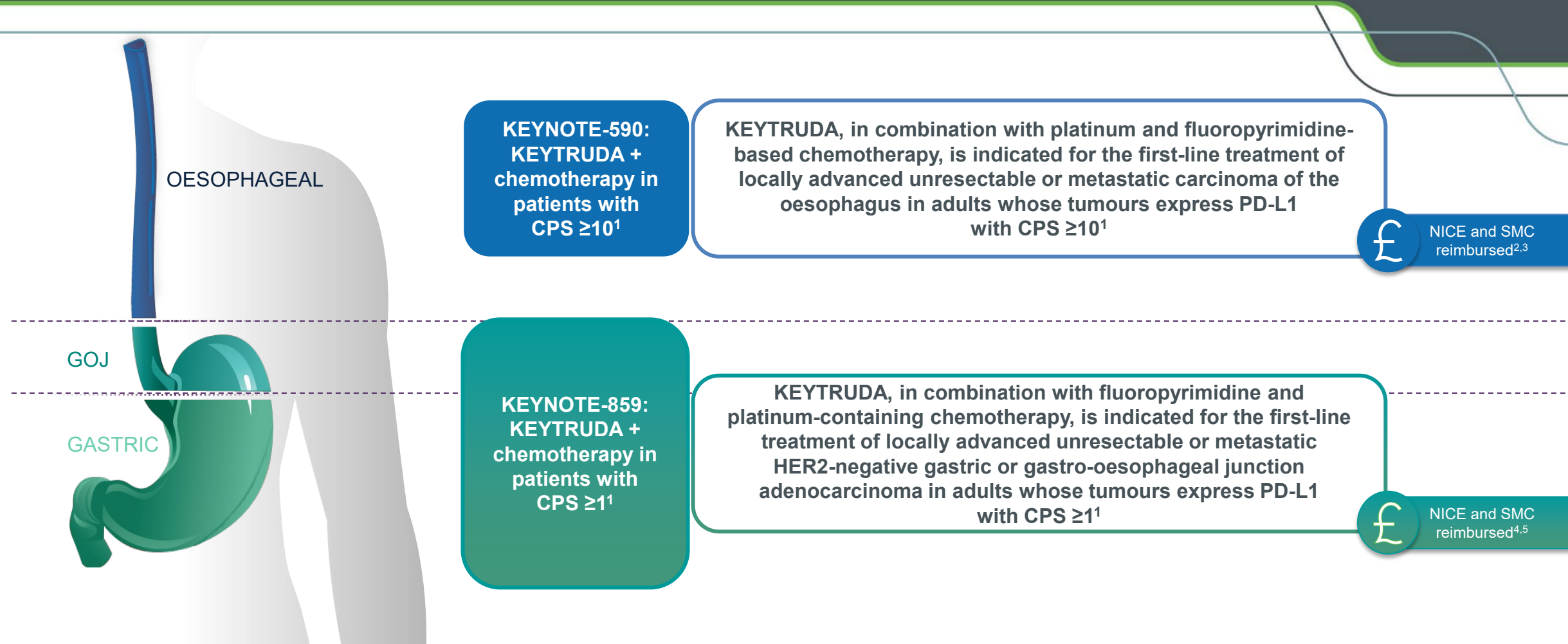
**KEYNOTE-859:
Summary**

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

KEYTRUDA licensed and reimbursed oesophago-gastric indications in the UK



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; PI, prescribing information; SMC, Scottish Medicines Consortium.

1. KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available at: <https://www.medicines.org.uk/emc/product/2498/smpc#about-medicine> Accessed September 2024;

2. SMC Medicines Advice (SMC2420) April 2022. Available at: [pembrolizumab-keytruda-final-april-2022-amended-4522-for-website.pdf](https://www.scottishmedicines.org.uk/about-us/latest-update/july-2024-decisions-news-release/) ([scottishmedicines.org.uk](https://www.scottishmedicines.org.uk)). Accessed September 2024; 3. NICE. Technology appraisal guidance [TA737] October 2021. Available at: <https://www.nice.org.uk/guidance/ta737>. Accessed September 2024; 4 SMC Medicines Advice. July 2024 news release. Available at: <https://www.scottishmedicines.org.uk/about-us/latest-update/july-2024-decisions-news-release/>. Accessed September 2024; 5. NICE. Technology appraisal guidance [GID-TA11039]. In development. Available at: <https://www.nice.org.uk/guidance/indevelopment/gid-ta11039>. Accessed September 2024.



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

^aData collected from 2017–2019; ^bData collected from 2016–2018; ^cData 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 September 2024.



Chemotherapy treatment for advanced HER2-negative gastric or GOJ cancer is associated with poor survival outcomes¹



Patients with HER2-negative tumours

~80% of patients with advanced GOEJ cancer have **HER2-negative** tumours²



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



KEYNOTE-859

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 **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 cancer⁴



KEYNOTE-859: Study design^{1,2}

Multicentre, randomised, double-blind, placebo-controlled Phase 3 trial

Patients enrolled until 3 October 2022 (N=1579)

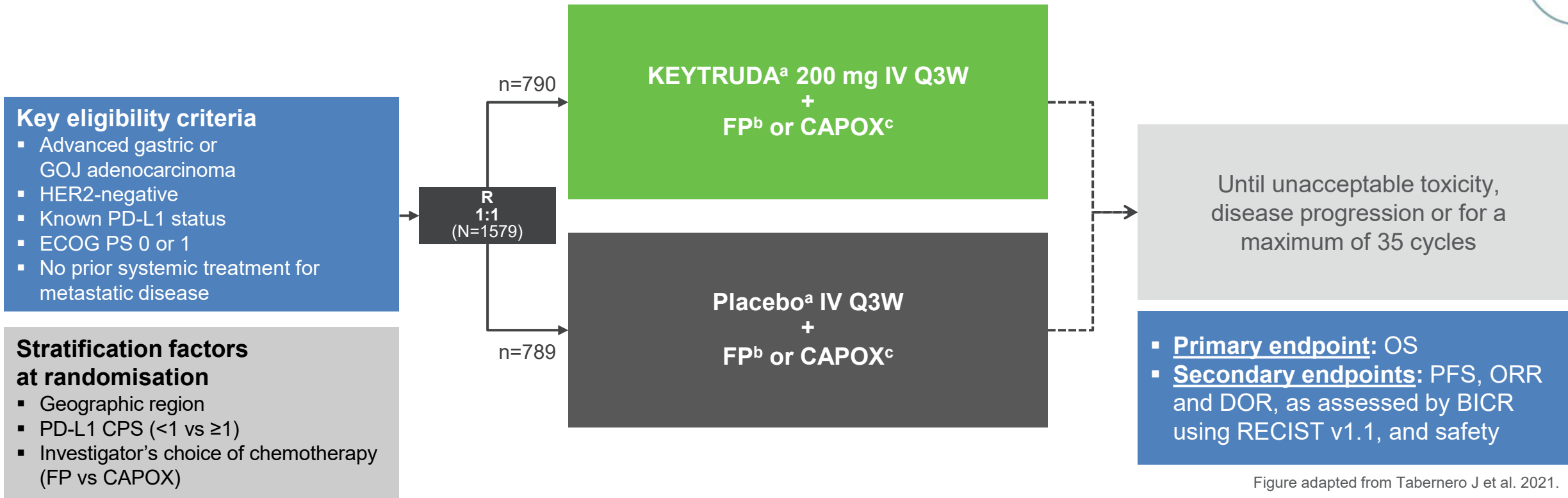


Figure adapted from Tabernero J et al. 2021.

^aAdministered on Day 1 of each cycle; ^bCisplatin 80 mg/m² IV Q3W + 5-FU 800 mg/m²/day IV on Days 1–5; ^cOxaliplatin 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.



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.

^aMissing in 1 patient (<1%) in the KEYTRUDA + FP or CAPOX group; ^bOther in 1 patient (<1%) in the placebo + FP or CAPOX group and missing in 1 patient (<1%) in the KEYTRUDA + FP or CAPOX group; ^cMissing in 110 patients (14%) in the KEYTRUDA + FP or CAPOX group and in 114 patients (14%) in the placebo + FP or CAPOX;

^dMissing in 2 patients (<1%) in the KEYTRUDA + FP or CAPOX group; ^eUnknown in 1 patient (<1%) and missing in 1 patient (<1%) in the KEYTRUDA + FP or CAPOX group;

^fMissing in 1 patient (<1%) in the KEYTRUDA + FP or CAPOX group; ^gMissing in 5 patients (1%) in each group.

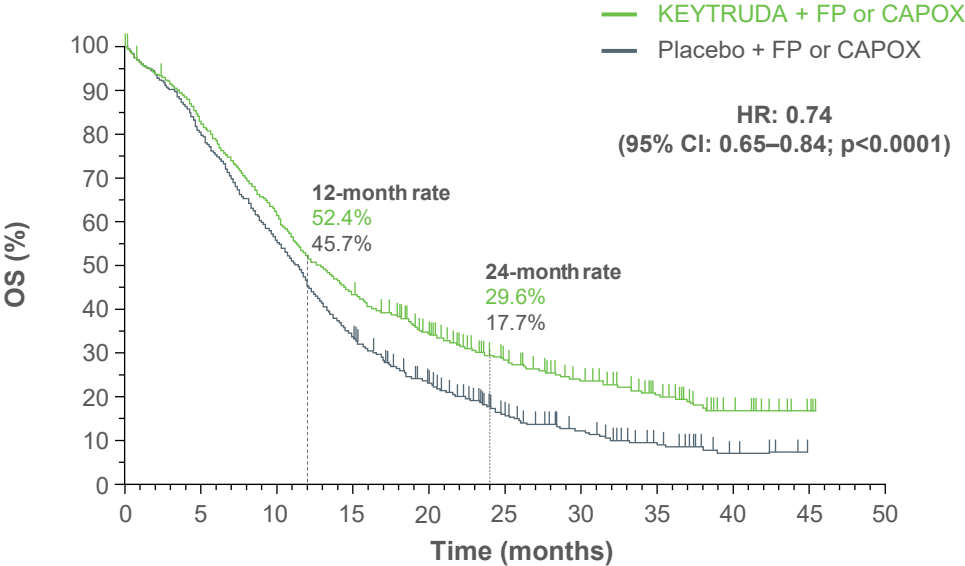
CAPOX, capecitabine + oxaliplatin; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; FP, 5-fluorouracil + cisplatin; GOJ, gastro-oesophageal junction; IQR, interquartile range; ITT, intention-to-treat; MSI-H, microsatellite instability-high; PD-L1, programmed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



No. at risk	618	511	383	269	192	121	81	46	17	3	0
KEYTRUDA + FP or CAPOX	618	511	383	269	192	121	81	46	17	3	0
Placebo + FP or CAPOX	617	493	339	206	126	66	41	20	7	0	0

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}

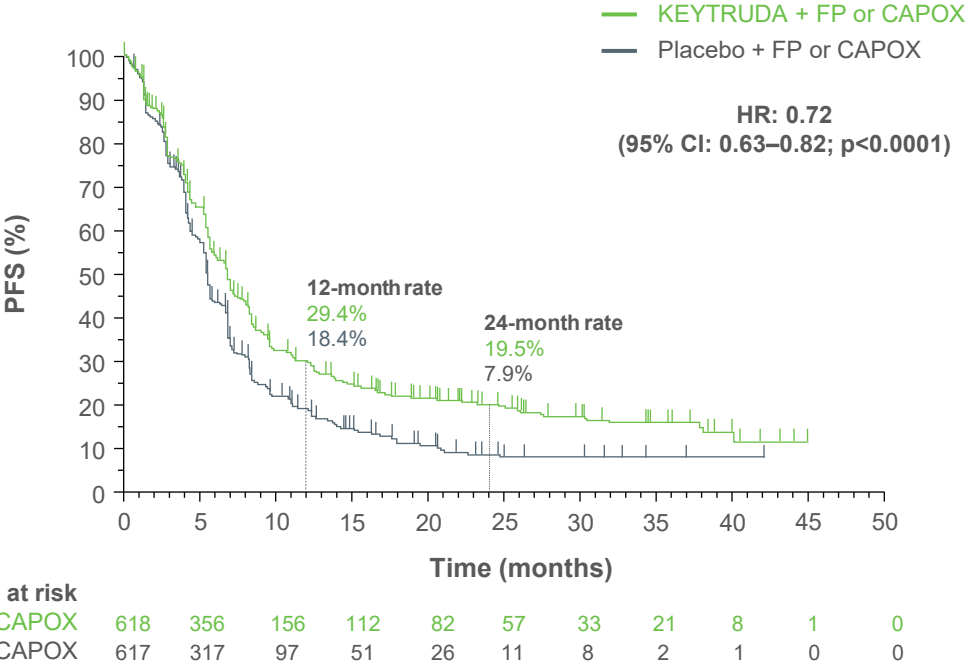
Analysis cut-off date: 3 October 2022.
^aOS in the PD-L1 CPS ≥1 population was an alpha-controlled analysis; ^bOS was compared between treatment arms using the log-rank test stratified by the randomisation stratification factors; the magnitude of the treatment effect was assessed using a Cox regression model stratified by the randomisation stratification factors; ^cBased 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.
^aPFS in the PD-L1 CPS ≥ 1 population was an alpha-controlled analysis; ^bPFS 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;
^cAssessed by BICR using RECIST v1.1; ^dBased 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: ORR and DOR in the PD-L1 CPS ≥ 1 population^{1,2}

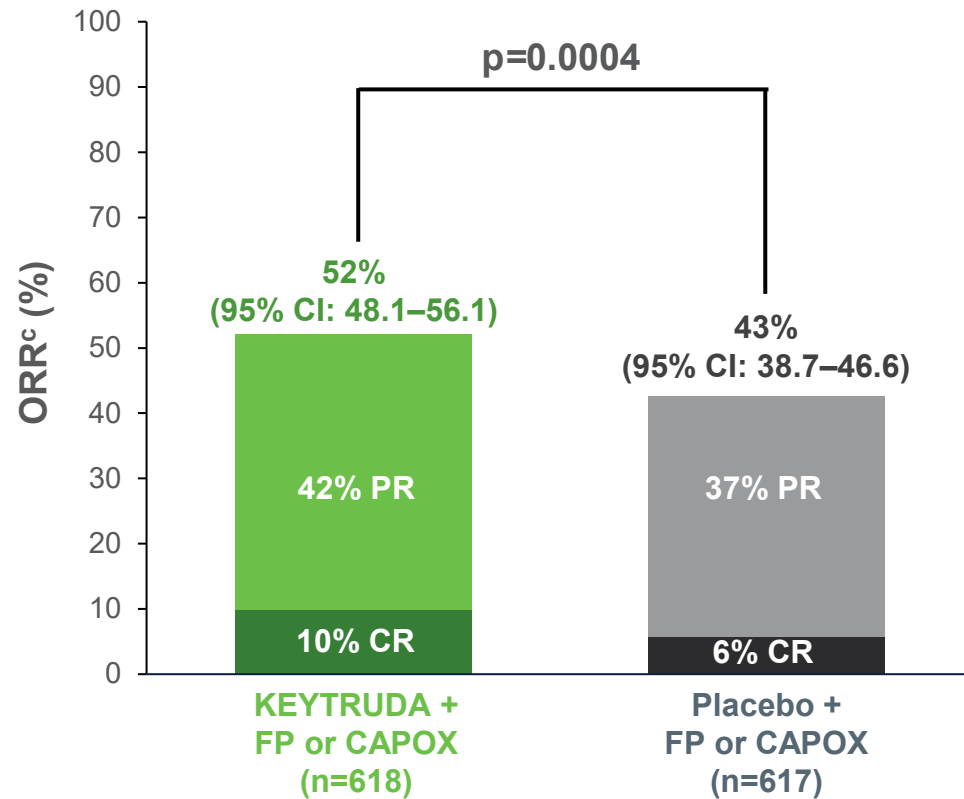


Figure adapted from Rha SY et al. 2023.^{1,2}

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

^aAlong 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;

^bORR was compared between treatment arms using the Miettinen and Nurminen method stratified by the randomisation stratification factors;

^cAssessed 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.



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.

^an=1 each due to diarrhoea, peripheral embolism, pneumonitis, pulmonary haemorrhage, sepsis, septic shock, thrombotic thrombocytopenia purpura and death (cause unknown); ^bn=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

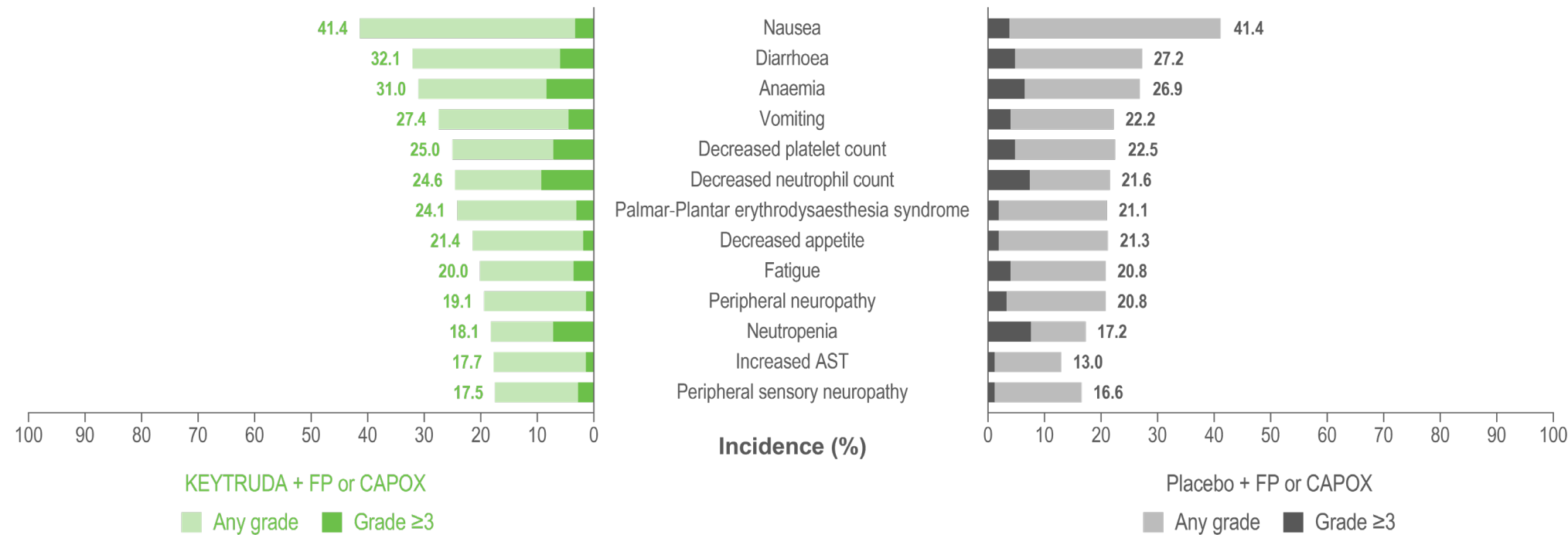


Figure adapted from Rha SY et al. 2023.

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.



KEYNOTE-859: Safety results – immune-mediated AEs^{1,2}

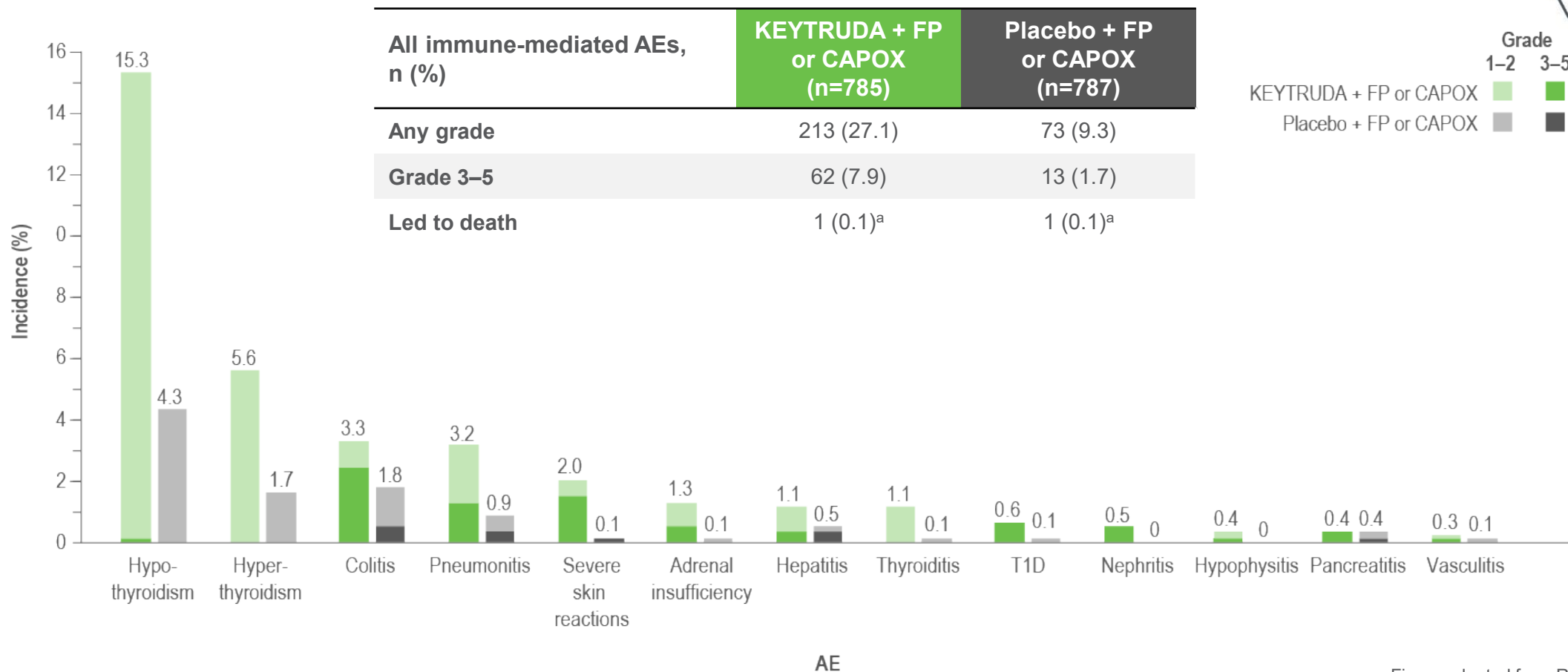


Figure adapted from Rha SY et al. 2023.

Analysis cut-off date: 3 October 2022. The as-treated population included all patients who were randomised and received ≥1 dose of the study treatment. Figure presenting immune-mediated AEs with incidence in ≥2 participants, based on a list of terms prepared by the funder and considered regardless of attribution to trial treatment by the investigator. Related terms were included.

^aOne participant in each arm due to pneumonitis.

AE, adverse event; CAPOX, capecitabine + oxaliplatin; FP, 5-fluorouracil + cisplatin; PI, Prescribing Information; T1D, type 1 diabetes.

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) 2023, 16 February 2023. Abstract VP1-2023.



KEYTRUDA 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 KEYTRUDA until disease progression or unacceptable toxicity¹
- 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 observed¹
- It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed¹
- No dose reductions of KEYTRUDA are recommended. KEYTRUDA should be withheld or discontinued to manage AEs as described within the SmPC¹
- When administering KEYTRUDA in combination with intravenous chemotherapy, KEYTRUDA should be administered first¹

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 regimen²



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 + CAPOX also showed a statistically significant improvement in PFS compared with those treated with placebo + FP + 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



Appendix



KEYNOTE-859: HRQoL analysis

LSM score change from baseline to Week 18 in EORTC QLQ-STO22 symptom scales

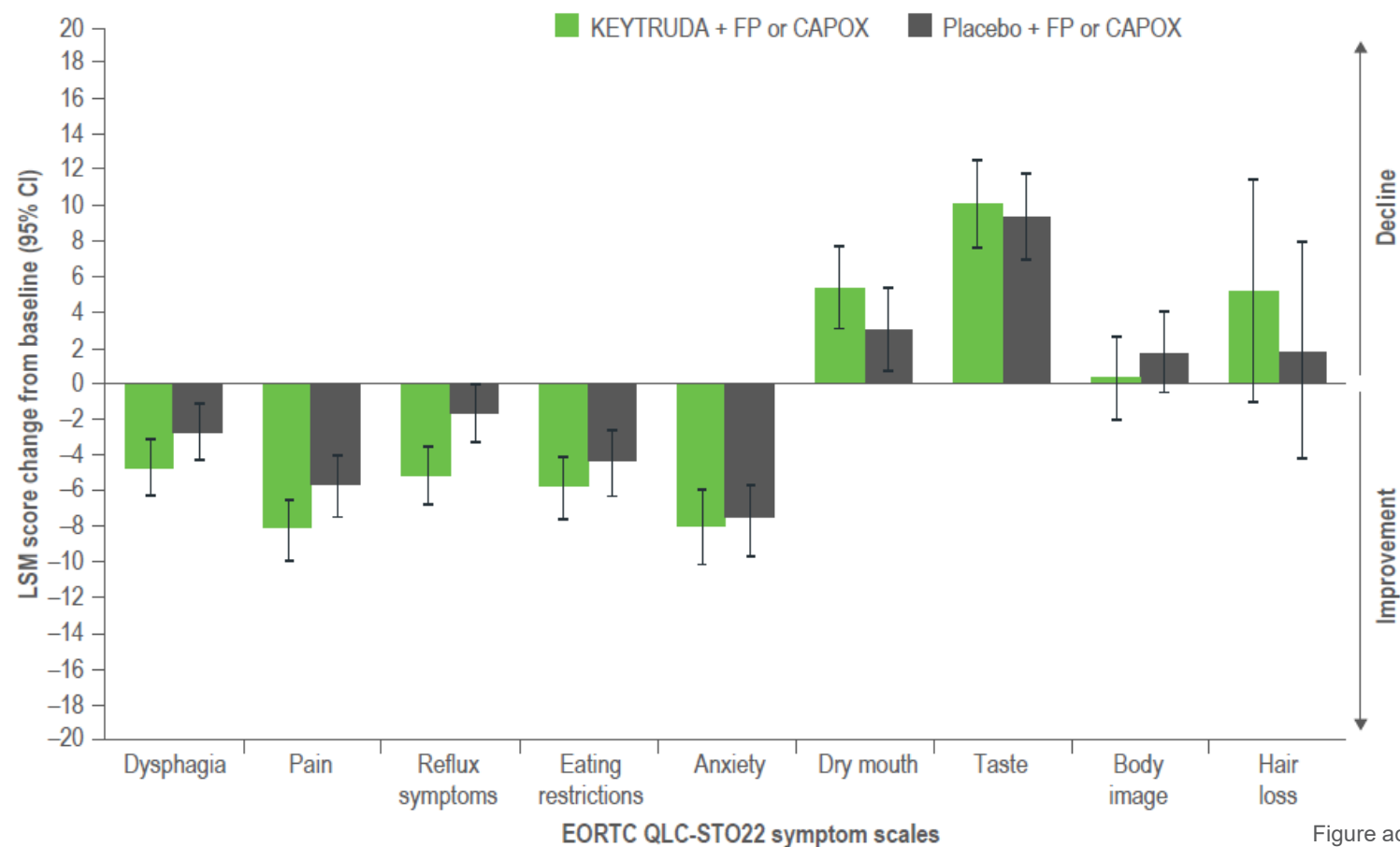


Figure adapted from Lowery M et al. 2023.

Analysis cut-off date: 3 October 2022.

CAPOX, capecitabine + oxaliplatin; CI, confidence interval; EORTC QLQ-STO22, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach 22; FP, 5-fluorouracil + cisplatin; HRQoL, health-related quality of life; LSM, least squares mean; PI, Prescribing Information.

Lowery M et al. Presented at the European Society for Medical Oncology (ESMO) 2023, 20–24 October 2023. Abstract 1516P.

