Pembrolizumab (Keytruda®) with fluoropyrimidine and platinum-containing chemotherapy for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma

General information

Drug description [1]

Pembrolizumab (Keytruda®) is a programmed death receptor-1 (PD-1)-blocking antibody.

Indication [2]

Pembrolizumab (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 gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Incidence

- In Austria, in 2020, the age-standardised[1] incidence rate of gastric cancer was 17.8 per 100,000 men and 8.8 per 100,000 women [3].
- The median age of disease onset is 71 years for men and 76 years for women and is higher than that of cancer overall (70 years for men, 69 years for women) [4].

Current treatment

- **For the first-line therapy of stage IV gastric cancer and adenocarcinoma of the oesophagus and the oesophagogastric junction, Onkopedia recommends [4, 5]:**
  - The aim of therapy is usually non-curative. The first priority is systemic drug therapy, supplemented in individual cases by local therapeutic measures.
  - Active symptom control and supportive measures such as nutritional counselling, psychosocial support, and palliative care are an integral part of treatment.
  - The prognosis of patients with locally advanced and irresectable or metastatic gastric cancer is unfavourable.
  - Studies evaluating the benefit of chemotherapy have shown a median survival of less than one year. However, there is evidence that chemotherapy can prolong the survival of patients with advanced gastric cancer compared to the best supportive therapy alone and maintain QoL longer.
  - Chemotherapy:
    - The standard of care for first-line chemotherapy of advanced gastric cancer is a platinum-fluoropyrimidine doublet. Oxaliplatin and cisplatin are comparably effective, with a more favourable side effect profile for oxaliplatin. This may contribute to a trend toward better efficacy, especially in patients > 65 years.
    - Fluoropyrimidines can be administered by infusion (5-FU) or orally (capecitabine or S-1). Oral fluoropyrimidines are comparably effective to infused 5-FU.
    - Capecitabine is approved in combination with a platinum derivative and has been studied with both cis- and oxaliplatin in European patients.
    - S-1 is established as a standard of care in Japan and approved in Europe for palliative first-line therapy in combination with cisplatin.
    - Infused 5-FU should be preferred over oral medications in patients with dysphagia or other feeding problems.
    - In elderly or frail patients, results of the phase III GO-2 trial support a dose-reduced application of oxaliplatin-fluoropyrimidine chemotherapy (to 80% or 60% of the standard dose from the beginning), resulting in fewer side effects with comparable efficacy.
    - The addition of docetaxel to a platinum-fluoropyrimidine combination (3-weekly DCF regimen) improved radiographic response rates and prolonged OS in a historical phase III trial but also resulted in significantly increased side effects.
    - Other phase II trials examined modified docetaxel-platinum-fluoropyrimidine triplets showed reduced toxicity compared with DCF in some cases.
    - However, the higher response rate of a triplet (37% versus 25% does not translate into prolonged survival in recent trials, which included effective second-line regimens. In the phase III JCOG1013 trial, patients with advanced gastric cancer received either cisplatin plus S-1 or cisplatin plus S-1 and docetaxel. There were no differences in radiographic response, PFS, or OS. Therefore, with increased toxicity and uncertain impact on OS, no recommendation can be made for first-line docetaxel-platinum-fluoropyrimidine therapy, so a platinum-fluoropyrimidine doublet remains the standard approach. In individual cases, e.g., when fast tumour regression is urgently required, first-line therapy with a platinum-fluoropyrimidine-docetaxel triplet may be indicated.

[1] European Standard Population 2013.

- Irinotecan-5-FU has been compared with cisplatin-5-FU and with epirubicin-cisplatin-capecitabine in randomized phase III trials and showed comparable survival with controllable side effects. Irinotecan-5-FU can therefore be considered a treatment alternative to platinum-fluoropyrimidine doublets according to scientific evidence, however, irinotecan has no approval in Europe for gastric cancer.

- Immunotherapy:
  - The phase III CheckMate 649 trial evaluated the addition of nivolumab to chemotherapy (capecitabine-oxaliplatin or 5-FU/folinic acid-oxaliplatin) in patients with previously untreated gastric, oesophagogastric junction, or esophageal adenocarcinoma. The study included patients regardless of tumour PD-L1 status; the dual primary endpoints were OS and PFS. Approximately 60% of the study population had tumours with a PD-L1 CPS ≥ 5. Nivolumab plus chemotherapy yielded a significant improvement over chemotherapy alone in OS (14.4 vs. 11.1 months, HR 0.71, 98.4% CI 0.59-0.86; p < 0.0001) and PFS (7.7 vs. 6.0 months, HR 0.68, 98% CI 0.56-0.81; p < 0.0001) in patients with a PD-L1 CPS ≥ 5.
  - The Asian phase II/III ATTRACTION-04 trial also showed a significant improvement in PFS with nivolumab and first-line chemotherapy, but with no significant improvement in OS compared to first-line chemotherapy alone. The most likely reason for the lack of survival benefit (> 17 months in both arms) is that many patients received post-progression therapies including immunotherapy after first-line therapy.
  - The multinational randomized phase III Keynote 859 trial included 1589 patients with advanced incurable gastric cancer. Patients received either platinum-fluoropyrimidine plus pembrolizumab or the same chemotherapy plus placebo every 3 weeks. OS was prolonged in the pembrolizumab group (HR 0.78, 95% CI 0.70-0.87, p < 0.0001). The effect was most pronounced in the subgroup with a PD-L1 CPS ≥ 10 (HR 0.64), whereas efficacy was lower for CPS < 10 (HR 0.86). The results thus complement the positive trial data from the phase III Keynote 590 study, which led to EU approval of pembrolizumab in combination with platinum-fluoropyrimidine chemotherapy for adenocarcinoma of the oesophagus and esophagogastric junction.
  - Positive phase III trial data were also presented on two immune checkpoint (PD-1) inhibitors not currently approved in Europe. Sintilimab in combination with oxaliplatin and capecitabine improved OS in the phase III ORIENT-16 trial. In the phase III Rationale-305 study, tislelizumab prolonged OS in combination with platinum-fluoropyrimidine or platinum-investigator-choice chemotherapy in patients with a positive PD-L1 score. PD-L1 was evaluated according to a scoring system not yet established internationally (the so-called Tumor Area Proportion score). ORIENT-16 and Rationale-305 have not been fully published to date but support the overall assessment that PD-1 immune checkpoint inhibitors can improve the efficacy of chemotherapy (depending on PD-L1 expression).

- Claudin 18.2
  - Data from the multinational phase III Spotlight trial were recently presented. These show that in patients with advanced irresectable gastric cancer and tumour claudin18.2 expression in ≥ 75% of tumour cells, zolbetuximab, a chimeric monoclonal IgG1 antibody directed against claudin18.2, in combination with FOLFOX chemotherapy prolongs OS (median 18.23 vs. 15.54 months, HR 0.750, p = 0.0053). The main side effects of zolbetuximab are nausea and vomiting, especially during the first applications.
  - The results of the phase III Spotlight trial are largely confirmed by the multinational phase III GLOW trial, in which the chemotherapy doublet was used as a control therapy or combination partner for zolbetuximab. It remains to be seen whether the EMA will grant approval to zolbetuximab in patients with claudin 18.2-positive metastatic and previously untreated gastric cancer.

Regulatory status

EMA [2]	FDA [1]
Approval status for this indication: On 12 October 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Keytruda®. The CHMP adopted a new indication as follows: ❖ 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 gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.	**Approval status for this indication**: not approved **Other indications**: Keytruda® is indicated: ❖ for the treatment of patients with unresectable or metastatic melanoma. ❖ for the adjuvant treatment of adult and paediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection. ❖ in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumour aberrations. ❖ in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.

Other indications: Keytruda® is indicated:

- as monotherapy for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.
- as monotherapy for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection.
- as monotherapy for the adjuvant treatment of adults with non-small cell lung carcinoma (NSCLC) who are at high risk of recurrence following complete resection and platinum-based chemotherapy.
- as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
- in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.
- in combination with carboplatin and either paclitaxel or nab paclitaxel for the first-line treatment of metastatic squamous NSCLC in adults.
- as monotherapy for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving Keytruda®.
- as monotherapy for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.
- as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10.
- as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1.
- as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 (TPS≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumour aberrations, and is:
  - Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
  - metastatic.
- as a single agent for the treatment of patients with metastatic NSCLC whose tumours express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda®.
- as a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC.
- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
- for the treatment of adult patients with relapsed or refractory cHL.
- for the treatment of paediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.
- for the treatment of adult and paediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy. Limitations of Use: Keytruda® is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
- in combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. This indication is approved under accelerated approval based on tumour response rate and durability of response.
- as a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for any platinum-containing chemotherapy, or
  - who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- as a single agent for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy.
- for the treatment of adult and paediatric patients with unresectable or metastatic MSI-H or dMMR solid tumours, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- for the treatment of patients with unresectable or metastatic MSI-H or dMMR CRC as determined by an FDA-approved test.
- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma. This indication is approved under accelerated approval based on tumour response rate and durability of response.

❖ as monotherapy for the treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy. ❖ in combination with axitinib, for the first-line treatment of advanced renal cell carcinoma (RCC) in adults. ❖ in combination with lenvatinib, for the first-line treatment of advanced RCC in adults. ❖ as monotherapy for the adjuvant treatment of adults with RCC at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. ❖ as monotherapy for adults with MSI-H or dMMR colorectal cancer (CRC) in the following settings: • first-line treatment of metastatic CRC. • treatment of unresectable or metastatic CRC after previous fluoropyrimidine based combination therapy. ❖ as monotherapy for the treatment of the following MSI-H or dMMR tumours in adults: • advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation. • unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy. ❖ in combination with platinum and fluoropyrimidine-based 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. ❖ in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer (TNBC) at high risk of recurrence. ❖ in combination with chemotherapy, for the treatment of locally recurrent unresectable or metastatic TNBC in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease. ❖ in combination with lenvatinib, for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.	❖ for the treatment of patients with locally advanced or metastatic oesophageal or gastroesophageal junction (tumours with epicenter 1 to 5 centimetres above the gastroesophageal junction) carcinoma that is not amenable to surgical resection or definitive chemoradiation either: • in combination with platinum- and fluoropyrimidine-based chemotherapy, or • as a single agent after one or more prior lines of systemic therapy for patients with tumours of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test. ❖ in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test. ❖ as a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test. ❖ for the treatment of patients with HCC who have been previously treated with sorafenib. This indication is approved under accelerated approval based on tumour response rate and durability of response. ❖ for the treatment of adult and paediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma. ❖ in combination with axitinib, for the first-line treatment of adult patients with advanced RCC. ❖ in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC. ❖ for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. ❖ in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. ❖ as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. ❖ for the treatment of adult and paediatric patients with unresectable or metastatic tumour mutational burden-high (TMB-H) (≥10 mutations) solid tumours, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on tumour response rate and durability of response. Limitations of Use: The safety and effectiveness of Keytruda® in paediatric patients with TMB-H central nervous system cancers have not been established. ❖ for the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation. ❖ for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery. ❖ in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥10) as determined by an FDA approved test. ❖ Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400 mg Every 6 Weeks

❖ in combination with chemotherapy with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1. ❖ in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.	• for use at an additional recommended dosage of 400 mg every 6 weeks for cHL and PMBCL Lymphoma in adults. This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Manufacturer

The manufacturer of Keytruda® is Merck Sharp & Dohme B.V. [6]

Costs

4 ml Keytruda® concentrate for solution for infusion 25 mg/ml = € 3,428.00 (ex-factory price) [6]

Warnings and precautions [1]

- **Immune-mediated adverse reactions**
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue based on severity and type of reaction.
- **Infusion-related reactions**
  - Interrupt, slow the rate of infusion, or permanently discontinue Keytruda® based on the severity of the reaction.
- **Complications of allogeneic HSCT**: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.
- Treatment of patients with **multiple myeloma** with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and to use effective methods of contraception.

Study characteristics [7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
KEYNOTE-859 NCT03675737	1,579 (1:1)	pembrolizumab 200 mg IV every 3 weeks for up to 35 cycles +	placebo + investigator's choice of chemotherapy[3]	OS in the ITT-population, and the populations with a PD-L1 CPS of ≥1	31.0 months	**ongoing**[4], multicentre, double-blind, placebo-controlled,	PD-L1	Merck Sharp and Dohme	KEYNOTE-859 [8]

[3] Fluorouracil (IV 800 mg/m^2 per day) administered continuously on days 1–5 of each 3-week cycle + cisplatin (IV 80 mg/m^2) administered on day 1 of each 3-week cycle or capecitabine (oral, 1000 mg/m^2) administered twice daily on days 1–14 of each 3-week cycle plus oxaliplatin (IV, 130 mg/m^2) administered on day 1 of each 3-week cycle.

[4] The KEYNOTE-859 trial is currently ongoing; estimated study completion date is September 2024.

		investigator's choice of chemotherapy[2]		and PD-L1 CPS of ≥10		randomised, phase 3 trial			

Inclusion criteria[5]	Exclusion criteria	Patient characteristics at baseline (I vs. C in the PD-L1 CPS ≥ 1 population, n=618 vs. n=617)
❖ ≥18 years with histologically- or cytologically- confirmed diagnosis of locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma, with known PD-L1 expression status. ❖ HER2 negative cancer. ❖ Measurable disease per RECIST 1.1 as assessed by investigator assessment. ❖ Provided archival tumour tissue sample or newly obtained core, incisional or excisional biopsy of a tumour lesion not previously irradiated. ❖ Provided tumour tissue sample deemed adequate for PD-L1 biomarker analysis. ❖ Provided tumour tissue sample for MSI biomarker analysis. ❖ ECOG performance status of 0 or 1 (within 3 days prior to the start of study intervention). ❖ Adequate organ function, as defined in the Supplementary appendix. ❖ Male participants are eligible to participate if they agree to the following during the intervention period and for at least 95 days after the last dose of chemotherapy: Refrain from donating sperm plus	❖ Squamous cell or undifferentiated gastric cancer. ❖ Major surgery, open biopsy, or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study intervention. ❖ Pre-existing peripheral neuropathy >Grade 1. ❖ Positive urine pregnancy test within 24 hours for urine or within 72 hours for serum prior to randomization or treatment allocation. ❖ Previous therapy for locally advanced, unresectable, or metastatic gastric/gastroesophageal junction cancer. ❖ Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor. ❖ Received prior systemic anticancer therapy including investigational agents within 4 weeks prior to randomization. ❖ Received prior radiotherapy within 2 weeks prior to start of study intervention. ❖ Received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention. ❖ Currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention. ❖ Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study intervention. ❖ Known additional malignancy that is progressing or has required active treatment within the past 5 years. ❖ Known active CNS metastases and/or carcinomatous meningitis. ❖ Severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients. ❖ Active autoimmune disease that has required systemic treatment in past 2 years. ❖ History of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease. ❖ Active infection requiring systemic therapy. ❖ Known history of HIV infection, Hepatitis B or known active Hepatitis C virus.	❖ Age, years: 62 vs. 63 ❖ <65 years: 61% vs. 59% ❖ ≥65 years: 39% vs. 41% ❖ Male sex: 68% vs. 73% ❖ Race: • American Indian or Alaskan Native: 4% vs. 5% • Asian: 33% vs. 33% • Black or African American: 1% vs. 1% • Multiple: 5% vs. 4% • Native Hawaiian or other Pacific Islander: <1% vs. <1% • White: 55% vs. 56% • Missing: 1% vs. 1% ❖ ECOG performance status • 0: 36% vs. 37% • 1: 64% vs. 63% ❖ Primary tumour location • Gastro-oesophageal junction: 20% vs. 27% • Stomach: 80% vs. 73% • Other: 0 vs. 0 • Missing: <1% vs. 0 ❖ Disease status: • Locally advanced: 4% vs. 4% • Metastatic: 96% vs. 96% • Missing: <1% vs. 0 ❖ Histological subtype: • Diffuse: 38% vs. 36% • Intestinal: 39% vs. 35% • Indeterminate: 23% vs. 29% • Unknown: <1% vs. 0 • Missing: <1% vs. 0 ❖ Liver metastases:

[2] Fluorouracil (IV 800 mg/m^2 per day) administered continuously on days 1–5 of each 3-week cycle + cisplatin (IV 80 mg/m^2) administered on day 1 of each 3-week cycle or capecitabine (oral, 1000 mg/m^2) administered twice daily on days 1–14 of each 3-week cycle plus oxaliplatin (IV, 130 mg/m^2) administered on day 1 of each 3-week cycle.

[5] For detailed in- and exclusion criteria, please see Supplementary Appendix.

either be abstinent from heterosexual intercourse or must agree to use contraception. ❖ A female participant is eligible to participate if she is not pregnant, not breastfeeding, not a woman of childbearing potential, or using a contraceptive method that is highly effective if she is a woman of childbearing potential.	❖ Known history of active tuberculosis. ❖ Participants with hypokalemia, hypomagnesemia or hypocalcemia. ❖ Known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study. ❖ Pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study. ❖ Had an allogenic tissue/solid organ transplant. ❖ Known severe hypersensitivity (≥ Grade 3) to any of the study chemotherapy agents. ❖ Grade ≥2 audiometric hearing loss.	• No: 58% vs. 59% • Yes: 42% vs. 41% • Missing: <1% vs. 0 ❖ Prior gastrectomy or oesophagectomy: • No: 82% vs. 82% • Yes: 18% vs. 17% • Missing: <1% vs. 0 ❖ Microsatellite instability status: • High: 6% vs. 5% • Low or microsatellite stable: 81% vs. 81% • Unknown: 0 vs. <1% • Missing: 13% vs. 14% ❖ PD-L1 CPS: • ≥1: 100% vs. 100% • <1: 0 vs. 0 • ≥10: 45% vs. 44% • <10: 55% vs. 56% • Missing: <1% vs. 0 ❖ Choice of chemotherapy: • Capecitabine and oxaliplatin: 85% vs. 86% • Flurouracil and cisplatin: 15% vs. 14%

Efficacy (I vs. C)	**Safety** (I vs. C, n=785 vs. n=787)
Data cutoff 3 October 2022; median follow-up: 31.0 months (IQR 23.0-38.3) **ITT population (n=790 vs. n=789)** **Median OS**: 12.9 months (95% CI, 11.9–14.0) vs. 11.5 months (10.6–12.1); HR 0.78 (95% CI, 0.70–0.87); p<0.0001 **Median PFS**: 6.9 months (95% CI, 6.3–7.2) vs. 5.6 months (95% CI, 5.5–5.7); HR 0.76 (95% CI, 0.67–0.85); p<0.0001 **ORR:** 51% (9% CR, 42% PR) vs. 42% (6% CR, 36% PR); between-group difference 9.3% (95% CI, 4.4–14.1); p<0.0001 **Median DOR**: 8.0 months (95% CI, 7.0–9.7) vs. 5.7 months (95% CI, 5.5–6.9) **PD-L1 CPS of ≥1 population (n=618 vs. n=617)** **Median OS:** 13.0 months (95% CI,11.6–14.2) vs. 11.4 months (10.5–12.0); HR 0.74 (95% CI, 0.65–0.84); p<0.0001 **Median PFS**: 6.9 months (95% CI, 6.0–7.2) vs. 5.6 months (95% CI, 5.4–5.7); HR 0.72 (95% CI, 0.63–0.82); p<0.0001 **ORR:** 52% (10% CR, 42% PR) vs. 43% (6% CR, 37% PR); between-group difference 9.5% (95% CI, 3.9–15.0); p=0.0004 **Median DOR**: 8.3 months (95% CI, 7.0–10.9) vs. 5.6 months (95% CI, 5.4–6.9) **PD-L1 CPS of ≥10 (n=279 vs. n=272)** **Median OS**: 15.7 months (95% CI, 13.8–19.3) vs. 11.8 months (95% CI, 10.3–12.7); HR 0.65 (95% CI, 0.53–0.79); p<0.0001 **Median PFS**: 8.1 months (95% CI, 6.8–8.5) vs. 5.6 months (95% CI, 5.4–6.7); HR 0.62 (95% CI, 0.51–0.76); p<0.0001 **ORR**: 61% (13% CR, 48% PR) vs. 43% (5% CR, 38% PR); between-group difference 17.5% (95% CI, 9.3–25.5); p<0.0001 **Median DOR**: 10.9 months (95% CI 8.0–13.8) vs. 5.8 months (95% CI, 5.3–7.0)	**AEs of any cause:** 99% vs. 98% **TRAEs:** 96% vs. 94% **TRAEs grade ≥3:** 59% vs. 51% **TRAEs leading to treatment discontinuation:** 26% vs. 20% **Serious TRAEs:** 23% vs. 19% **AEs leading to death:** 8% vs. 7% **Death due to TRAEs:** 1% vs. 2% **Potentially immune-mediated AEs:** 27% vs. 9% **Potentially immune-mediated AEs grade 3–5 events:** 8% vs. 2% **Deaths due to potentially immune-mediated AE:** <1% vs. <1% (pneumonitis)

Patient-reported outcomes

❖ Compliance rates for the EORTC QLQ-C30 and EORTC QLQ-STO22 were comparable and higher than 95% in both pembrolizumab and placebo groups at baseline.

- From baseline to week 18, least-squares mean changes were similar between arms in QLQ-C30 global health status/QoL and favoured pembrolizumab vs. placebo in the QLQ-STO22 pain scale.
- Similarly, time to true deterioration was similar between groups in QLQ-C30 global health status/QoL and favoured pembrolizumab versus placebo in the QLQ-STO22 pain scale.

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	≤12months	OS: +1.6 months	0.74 (0.65–0.84)	HR ≤0.65 AND gain ≥1.5-<2.0 months	2	-	-	-	2
Adapted	NC	2A	≤12months	OS: +1.6 months	0.74 (0.65–0.84)	HR >0.70 OR gain <1.5 months	1	-	-	-	1

Risk of bias (RCT) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting is unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	yes low risk	yes low risk	unclear[6] unclear risk	yes[7] high risk	unclear

Ongoing RCTs [12]

NCT number/trial name	Description	Estimated study completion date
NCT03675737/ KEYNOTE-859	Please see above.	09/2024

Available assessments

- The assessment "Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]" is currently in development by NICE; the expected publication date is May 2024 [13].
- No further assessments were identified via CADTH, ICER and G-BA.

Other aspects and conclusions

- In October 2023, the **CHMP adopted a new indication** for Keytruda®, in combination with fluoropyrimidine and platinum-containing chemotherapy, indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. This indication is currently **not approved by the FDA.**
- **KEYNOTE-859** (NCT03675737) is an **ongoing**, double-blind, randomised, **phase 3 trial**, comparing the efficacy and safety of pembrolizumab plus chemotherapy with placebo plus chemotherapy in participants with locally advanced or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma. Eligible patients were ≥18 years, had histologically or cytologically confirmed adenocarcinoma of the stomach or gastroesophageal junction that was locally advanced but unresectable or metastatic, had received no previous treatment for their cancer, had tumours that were HER2-negative, had measurable disease per RECIST version 1.1 by investigator assessment, had provided tumour tissue adequate for PD-L1 assessment, had an ECOG PS of 0 or 1, and adequate organ function. Patients were excluded if they had squamous cell or undifferentiated gastric cancer, a known history of hepatitis B infection, a known history of active hepatitis C infection, a diagnosis of immunodeficiency or history of receiving chronic systemic immunosuppressant therapy, known history of HIV disease, active autoimmune disease requiring treatment, or active CNS metastases.
- The **primary endpoint** was **OS** in the ITT population, and the populations with a PD-L1 CPS ≥1 and PD-L1 CPS ≥10. Median OS in the ITT population was 12.9 months vs. 11.5 months (HR 0.78; 95% CI 0.70–0.87; p<0.0001), in participants with a PD-L1 CPS ≥1 13.0 months vs. 11.4 months (HR 0.74; 95% CI 0.65–0.84; p<0.0001), and in participants with a PD-L1 CPS ≥10 15.7 months vs. 11.8 months (HR 0.65; 95% CI 0.53–0.79; p<0.0001).
- Analysis of **PROs** showed that, from baseline to week 18, least-squares mean changes were similar between arms in QLQ-C30 global health status/QoL.
- The original and adapted **ESMO-MCBS** were applied, resulting in a **final adjusted magnitude of clinical benefit grade of 2 and 1**, respectively.

[6] KEYNOTE-859 is ongoing; currently, only interim analysis data is available.
[7] The study funder had a role in the study design, data collection, data analysis, data interpretation, and writing of the report.

- ❖ Since the KEYNOTE-859 trial is currently ongoing and only interim analysis results are available, the **risk of bias is considered unclear**. However, the risk is increased by the role of the sponsor in study design data collection, data analysis and data interpretation.
- ❖ Currently, RUBY is the only ongoing phase 3 trial evaluating the assessed indication. There is a large number of phase 2 trials, evaluating pembrolizumab in various combinations in patients with gastric or gastro-oesophageal junction adenocarcinoma.
- ❖ Since there is **limited data** for pembrolizumab treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1, final analysis data from the KEYNOTE-859 trial, and further phase 3 data is required.

First published: 11/2023

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplantation, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CPS=combined positive score, CRC=colorectal cancer, cSCC=Cutaneous Squamous Cell Cancer, dMMR=Deficient mismatch repair gene expression, DCF=docetaxel, cisplatin, and fluorouracil, DOR=duration of response, ECOG=Eastern Cooperative Oncology Group, EGFR=Epidermal growth factor receptor, EMA=European Medicines Agency, EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, FOLFOX=5-fluorouracil, leucovorin, and oxaliplatin, G-BA=Gemeinsamer Bundesausschuss, HCC=hepatocellular carcinoma, HER2=human epidermal growth factor receptor 2, HIV=human immunodeficiency virus, HNSCC=Head and neck squamous cell carcinoma, HR=hazard ratio, HSCT=Haematopoietic stem cell transplantation, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, ITT=intention-to-treat, MG=median gain, MSI-H=microsatellite instability-high, n=number of patients, NICE=National Institute for Health Care Excellence, NSCLC=non-small cell lung cancer, OS=overall survival, PD-1=Programmed Cell Death Protein 1, PD-L1=programmed death-1 ligand, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PMBCL=Primary Mediastinal Large B-Cell Lymphoma, QoL=quality of life, RCC=renal cell carcinoma, RECIST=Response evaluation criteria in solid tumors, SAE=serious adverse event, ST=standard treatment, TMB-H=tumour mutational burden-high, TNBC=triple-negative breast cancer, TPS=tumour proportion score, TRAE=treatment-related adverse event

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