Pembrolizumab (Keytruda®) 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 (GEJ) adenocarcinoma

General information

Drug description [1]

Pembrolizumab (Keytruda®) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD -L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Keytruda® potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Indication [2]

Pembrolizumab (Keytruda®), in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score (CPS) ≥ 1.

Incidence

In Austria, in 2020, the age-standardised incidence rate[1] of gastric cancer was 17.8 per 100,000 men and 8.8 per 100,000 women [3].
The age-standardised incidence rate of oesophageal cancer (in Austria, in 2020[2]) was 9.1/100,000 men and 2.0/100,00 women [3]. Squamous cell carcinomas account for 50% of all cancers of the oesophagus. The proportion of adenocarcinomas, which occur almost exclusively at the oesophago-gastric junction, has risen to over 40% in recent years [4].

Current treatment

For the treatment of HER2-positive gastric cancer, Onkopedia recommends [5]:

- HER2 positivity is defined in gastric cancer as the presence of protein expression with immunohistochemistry score (IHC) of 3+ or IHC 2+ and concomitant gene amplification on in situ hybridisation (ISH), HER2/CEP17 ratio ≥ 2.0. HER2 diagnosis should be quality-controlled.
- Trastuzumab should be added to chemotherapy in patients with HER2-positive advanced gastric cancer. The recommendation is based on data from the phase III ToGA trial, showing a higher response rate and prolonged survival for trastuzumab-cisplatin-fluoropyrimidine chemotherapy vs. chemotherapy alone using the above selection criteria; the additional trastuzumab side effects are minor and controllable.
- Combinations of trastuzumab and oxaliplatin plus fluoropyrimidine show comparable results to the historical cisplatin-containing ToGA regimen.

For the treatment of adenocarcinomas of the GEJ, Onkopedia recommends [4]:

- In patients with adenocarcinomas of the oesophago-gastric junction (AEG) of category ≥T3 or N+, perioperative chemotherapy is another evidence-based and well-established therapeutic option.
- Perioperative chemotherapy consisting of an anthracycline, a platinum derivative, and a fluoropyrimidine (epirubicin, cisplatin, and 5-FU; ECF) has long been considered the standard perioperative therapy based on data from the MAGIC trial. However, more recent data demonstrate that chemotherapy according to the FLOT regimen (5-fluorouracil/folinic acid/oxaliplatin/docetaxel) is superior to ECF or a combination of epirubicin, cisplatin, and capecitabine in patients with locally advanced AEG (≥cT2 and/or cN+). Perioperative FLOT resulted in a significant prolongation of progression-free (HR 0.75) and overall survival (HR 0.77; 0.63-0.94, p=0.012). This effect was consistent across all relevant subgroups such as age, histologic subtype, and localisation. The rate of perioperative complications was comparable in both arms.
- Comparative data between preoperative radio chemotherapy and perioperative chemotherapy for locally advanced AEG failed to demonstrate a statistically significant survival benefit with the addition of radiotherapy. However, a single phase 3 trial indicates that suboptimal preoperative chemotherapy (PLF regimen) can be improved by adding chemoradiotherapy (HR 0.65; 0.42-1.01, p=0.055). In addition, the studies demonstrate improved local tumour control and an increase in the rate of histologically complete remissions and R0 resections with chemoradiotherapy. The systemic therapeutic effect appears to be lower with preoperative radio chemotherapy due to a lower cumulative dose of chemotherapy.
- In summary, both therapeutic concepts are currently considered equivalent in AEG. In patients with extensive local tumours, preoperative radio chemotherapy may be favoured due to the high risk of incomplete resection and local recurrence, otherwise perioperative chemotherapy may be favoured. Direct comparison between the two therapeutic modalities is currently being

[1] European Standard Population 2013.
[2] European Standard Population 2013.

investigated in several phase III trials. However, only one of these trials has the currently accepted standard of perioperative therapy with FLOT in the comparator arm, so that relevant questions will remain unanswered by these trials as well. The suggestion that perioperative chemotherapy may not be effective in patients with signet ring carcinomas or microsatellite unstable adenocarcinomas is not justified according to recent study results.

- ❖ The treatment of locally advanced adenocarcinomas is currently independent of HER2 status. For perioperative chemotherapy, phase II data suggest a higher histopathological complete response (pCR) rate in patients treated with the combination of chemotherapy (FLOT) and the anti-HER2 antibody trastuzumab. However, results from phase III trials are not to be expected in the short term. In the context of combined preoperative chemoradiotherapy (CROSS regimen), the addition of trastuzumab does not improve outcomes.
- ❖ In patients with AEG ≥ stage IB who have received resection without pretreatment (e.g., due to misclassified tumour stage prior to surgery), adjuvant therapy can be administered if there is an increased risk of local recurrence, such as extensive lymph node involvement (pN2-3). However, according to data from an Asian phase III trial, combined radio chemotherapy does not result in a (further) improvement of disease-free survival compared with combination chemotherapy alone (ARTIST2 trial).
- ❖ After R1 resection, adjuvant radio chemotherapy is recommended because of the high risk of local recurrence.

Regulatory status

EMA [1, 2]

Approval status for this indication: On 20 July 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Keytruda®.

<u>The CHMP adopted a new indication as follows:</u>

- ❖ Keytruda®, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥1.

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 first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD -L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
- ❖ as monotherapy for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy.
- ❖ 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

FDA [6, 7]

Approval status for this indication: On 5 May 2021, the FDA granted accelerated approval to pembrolizumab (Keytruda®), 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 GEJ adenocarcinoma.

- ✓ This application was granted priority review.
- ✓ This indication is approved under accelerated approval based on tumour response rate and durability of response.

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 non squamous 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.
- ❖ 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®.
- ❖ for the treatment of patients with resectable (tumours ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- ❖ 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.

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 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 with:
    - 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.
- ❖ 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-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.
- ❖ for the treatment of patients with locally advanced or metastatic oesophageal or gastroesophageal junction (GEJ) (tumours with epicenter 1 to 5 cm above the GEJ) 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).

- 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 or HER-2 negative gastroesophageal junction adenocarcinoma, 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 at high risk of recurrence.

❖ in combination with chemotherapy, for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer 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.

❖ 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.

❖ for the treatment of adult and paediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (this indication is approved under accelerated approval based on tumour response rate and durability of response).

❖ 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/megabase) 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 cHL and adult primary mediastinal large B-cell lymphoma (PMBCL): Additional dosing regimen of 400 mg every 6 weeks for use at an additional recommended dosage of 400 mg every 6 weeks for cHL and PMBCL 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.

Manufacturer

Keytruda® is manufactured by Merck Sharp & Dohme B.V.

Costs

4 ml Keytruda® concentrate for solution for infusion 25 mg/ml = € 3,428.00 [8]

Warnings and precautions [6]

❖ **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 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 method of contraception.

Study characteristics [9-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
KEYNOTE-811, ML-3475-811 NCT03615326	264[3]/411[4] (1:1)	pembrolizumab 200 mg IV once every 3 weeks + trastuzumab 6 mg/ kg IV once every 3 weeks following an initial loading dose of 8 mg/kg + chemotherapy[5]	placebo (normal saline or dextrose IV once every 3 weeks + trastuzumab 6 mg/kg IV once every 3 weeks following an initial loading dose of 8 mg/kg + chemotherapy[6]	PFS (assessed per RECIST, version 1.1, by BICR) + OS	ITT-population: 8.4 vs. 7.7 months Efficacy population: 11.1 vs. 10.4 months	**ongoing**[7], global, randomised, double-blind, placebo-controlled, phase III study	PD-1, HER2	Merck Sharp & Dohme Corp	KEYNOTE-811 [10]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (efficacy population, n=133 vs. n=131)
❖ Patients ≥18 years with previously untreated histologically or cytologically confirmed locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma ❖ HER2-positive disease, defined as either IHC 3+ or IHC 2+ in combination with ISH+ (or FISH), as assessed by BICR on primary or metastatic tumour ❖ Measurable disease per RECIST v1.1 by site investigator.	❖ Previously received neoadjuvant or adjuvant therapy for locally advanced or metastatic disease (if it was completed ≥6 months before randomisation without disease progression) ❖ Major surgery, open biopsy or significant traumatic injury ≤28 days before randomisation, or anticipated need for major surgery during the study treatment period ❖ Radiotherapy ≤14 days of randomisation ❖ Known additional malignancy that is progressing or has necessitated active treatment within the past 5 years (except BCC or SCC of the skin that has undergone potentially curative treatment or in situ cervical cancer)	❖ Median age: 62 vs. 61 years ❖ Patients ≥65 years: 41.4% vs. 40.5% ❖ Male sex: 84.2% vs. 79.4% ❖ ECOG PS 0: 48.9% vs. 45.0% ❖ ECOG PS 1: 51.1% vs. 55.0% ❖ Primary location at diagnosis: • Gastroesophageal junction: 27.8% vs. 32.1% • Stomach: 72.2% vs. 67.9% ❖ No. of metastatic sites:

[3] Efficacy population.
[4] Safety population (all enrolled patients)
[5] Either 5-flurouracil (800 mg/m^2 of BSA administered IV on days 1–5 of each 3-week cycle) and cisplatin (80 mg/ m^2 administered IV once every 3 weeks) or capecitabine (1000 mg/m^2 administered orally twice daily on days 1–14 of each 3-week cycle) and oxaliplatin (130 mg/m^2 administered IV once every 3 weeks). All treatment is continued for up to 35 cycles (~2 years) or until disease progression, unacceptable toxic effects, investigator decision, or participant withdrawal of consent.
[6] Either 5-flurouracil (800 mg/m2 of BSA administered IV on days 1–5 of each 3-week cycle) and cisplatin (80 mg/ m2 administered IV once every 3 weeks) or capecitabine (1000 mg/m2 administered orally twice daily on days 1–14 of each 3-week cycle) and oxaliplatin (130 mg/m2 administered IV once every 3 weeks). All treatment is continued for up to 35 cycles (~2 years) or until disease progression, unacceptable toxic effects, investigator decision, or participant withdrawal of consent.
[7] Estimated study completion date is 12/2024.

❖ Willing to use adequate contraception methods throughout the study and for 7 months after the last dose of study treatment ❖ ECOG PS 0 or 1 ❖ Life expectancy ≥6 months ❖ Willing to provide a tumour tissue sample adequate for PD-L1 and MSI biomarker analysis ❖ Adequate cardiac function, defined as left ventricular ejection fraction ≥55% as determined by MUGA scan or ECHO and QT interval calculated according to the Fridericia method (≤470 ms for men and ≤480 ms for women) ❖ Adequate hematologic function, defined as ANC ≥1500/µl, platelet count ≥100,000/µl and haemoglobin ≥9.0 g/dl or ≥5.6 mmol/l ❖ Adequate renal function, defined as creatinine ≤1.5 × ULN or measured or calculated creatinine clearance ≥60 ml/min for those with creatinine levels 1.5 × ULN ❖ Adequate hepatic function, defined as total bilirubin ≤1.5 × ULN or direct bilirubin ≤ULN for those with total bilirubin levels 1.5 × ULN, ALT/AST levels ≤2.5 × ULN or ≤5 × ULN for those with liver metastases, and albumin ≥2.5 g/dl ❖ Adequate coagulation function, defined as INR ≤1.5 × ULN, unless the patient is receiving anticoagulant therapy with PT or aPTT/PTT is within the therapeutic range ❖ Written informed consent.	❖ Known active CNS metastases and/or carcinomatous meningitis (patients with previously treated brain metastases may be eligible if disease is radiologically and clinically stable) ❖ Active autoimmune disease that has necessitated systemic treatment (other than replacement therapy) in the past 2 years ❖ Diagnosis of immunodeficiency or receiving long-term systemic steroid therapy (≥10 mg/day prednisone equivalent) or any other form of immunosuppression therapy within 7 days before the first dose of study treatment ❖ History of (non-infectious) pneumonitis treated with steroids or current pneumonitis ❖ History of active tuberculosis ❖ Active infection necessitating systemic therapy ❖ Poorly controlled diarrhoea ❖ Accumulation of pleural, ascitic or pericardial fluid necessitating drainage or diuretic drugs ≤2 weeks before enrolment ❖ History or current evidence of any condition, therapy, or laboratory abnormality that might confound the study results or interfere with study participation ❖ Peripheral neuropathy grade >1 ❖ Psychiatric or substance abuse disorder that could impede cooperation with study requirements ❖ Positive urine pregnancy test ≤72h before randomisation (females of childbearing potential) ❖ Pregnant or breastfeeding or expecting to conceive or father children within the projected study duration ❖ Active or clinically significant cardiac disease ❖ Known history of HIV, HBV or HCV infection ❖ Known hypersensitivity (grade ≥3) to any of the study drugs or their excipients ❖ Active infection necessitating systemic therapy ❖ Allogeneic tissue or solid organ transplant ❖ Previous treatment with anti-PD-1, anti-PD-L1 or anti-PD-L2, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA4, OX40 and CD137) ❖ Immunised with live vaccine ≤30 days before first dose of study treatment ❖ Participation in study of investigational agent or device ≤4 weeks before the first dose of study treatment	• 0–2: 53.4% vs. 58.8% • ≥3: 46.6% vs. 41.2% ❖ Previous gastrectomy or oesophagostomy: • Yes: 16.5% vs. 19.1% • No: 83.5% vs. 80.9% ❖ PD-L1 combined positive score: • ≥1: 88.0% vs. 85.5% • <1: 12.0% vs. 14.5% ❖ HER2 status: • IHC 1 +: 0 vs. 0 • IHC 2+ ISH equivocal: 0 vs. 0 • IHC 2+ ISH positive: 18.0% vs. 20.6% • IHC 3+: 82.0% vs. 79.4% ❖ MSI status: • MSI-high: 0.8% vs. 0.8% • Non-MSI-high: 90.2 vs. 91.6 • Unknown: 9.0% vs. 7.6% ❖ Sum of target lesions at baseline: • < median: 46.6% vs. 49.6% • ≥ median: 46.6% vs.46.6% • Missing: 6.8% vs. 3.8% ❖ Chosen chemotherapy regimen: • Capecitabine and oxaliplatin: 86.5% vs. 87.8% • 5-fluorouracil and cisplatin: 13.5% vs. 12.2%

Efficacy (I vs. C), interim analysis data	**Safety** (I vs. C), interim analysis data
<u>Interim analysis, data cutoff 17 June 2020; median follow-up 12.0 months</u> **ORR[8]:** 74.4% (95% CI, 66.2–81.6) vs. 51.9% (95% CI, 43.0–60.7); statistically significant 22.7% improvement in ORR in the pembrolizumab group (95% CI, 11.2–33.7; p=0.00006)	**AEs of grade 3–5:** 57.1% vs. 57.4% **AEs of grade 3-5 leading to discontinuation of any study treatment**: 24.4% vs. 25.9%

[8] ORR for the first 264 participants enrolled (efficacy population).

Responses, median change from baseline: –65% vs. –49%; ≥80% decrease from baseline, 32.3% vs. 14.8% **Complete responses**: 11.3% vs. 3.1% **Ongoing response at data cutoff among responders**: 50.5% vs. 44.1% **Response duration of at least 6 months** (by Kaplan-Meier estimation): 70.3% vs. 61.4% **Response duration of at least 9 months** (by Kaplan-Meier estimation): 58.4% vs. 51.1% **Median response duration**: 10.6 months (range, 1.1+ - 16.5+) vs. 9.5 months (range, 1.4+ - 15.4+) Efficacy results at the second interim analysis for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥ 1 [1]: Median PFS: 10.8 vs. 7.2 months; HR 0.7 (95% CI, 0.58-0.85), p=0.0001 Median OS: 20.5 vs. 15.6 months; HR 0.79 (95% CI, 0.64-0.98); p-Value=0.0143 ORR: 73% (95% CI, 67.7-78.1) vs. 58% (95%CI, 52.6-64.1); p-Value=0.00008 Complete response: 14% vs. 10% Partial response: 59% vs. 49% Median response duration: 11.3 vs. 9.5 months % with duration ≥ 6 months: 75% vs. 67% % with duration ≥ 12 month: 49% vs. 41%	**AEs with a possibly immune-mediated cause and/or infusion reactions:** 33.6% vs. 20.8% **Deaths from AEs:** 3.2% vs. 4.6%; these were attributed to study treatment by investigators in 0.9% vs. 0.9% and were considered immune-mediated in 1.4% vs. 0.5% of participants

Patient-reported outcomes

- ❖ According to the KEYNOTE-811 trial protocol**, HRQoL** (assessed using the EORTC QLQ-C30 and EORTC QLQ-STO22) and **characterisation of utilities** (assessed using the EQ-5D-5L questionnaire) were determined as exploratory endpoints.
- ❖ Currently, there are no results available

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2C	-	ORR: +22.5%	-	RR is increased ≥20% but no improvement in toxicity/QoL/ PFS/OS	2	-	NA	-	2
Adapted	Since the results of the primary endpoints were not reported yet, the adapted ESMO-MCBS is not applicable.										

Risk of bias (RCT) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	unclear unclear risk	yes low risk	unclear[9] unclear risk	yes[10] high risk	**unclear**

Ongoing trials [14]

NCT number/trial name	Description	Estimated study completion date
NCT03615326/ KEYNOTE-811	Please see above.	12/2024

Available assessments

- ❖ In 2019, NIHR published a **Health Technology Briefing** "Pembrolizumab in addition to trastuzumab and chemotherapy for HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma – First-line" [15].

[9] KEYNOTE-811 is currently ongoing; currently only interim analysis data is available. Results for predefined endpoints (i.e., QoL) are currently not available.
[10] The study was designed by academic advisors and employees of the study sponsor.

- According to NICE, an **appraisal** for "Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer [ID3742]" is **in development**; expected publication date is January 2024 [16].
- No further assessments were identified.

Other aspects and conclusions

- In July 2023, the **CHMP adopted a positive opinion** recommending a change to the terms of the marketing authorisation for Keytruda® in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. In May 2021, the **FDA granted accelerated approval** to Keytruda®, 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 GEJ adenocarcinoma.
- **KEYNOTE-811** (NCT03615326) is an **ongoing**, randomised, double-blind, placebo-controlled phase 3 study of pembrolizumab plus trastuzumab and chemotherapy for unresectable or metastatic, HER2-positive gastric or gastroesophageal junction adenocarcinoma. Eligible participants are aged ≥18 years, have previously untreated, unresectable or metastatic, histologically or cytologically confirmed adenocarcinoma of the stomach or GEJ that is HER2-positive as assessed by central review; have measurable disease per RECIST, version 1.1, as assessed by the investigator; have ECOG PS of 0 or 1; have life expectancy of more than 6 months; have adequate organ function; and have provided a tumour sample adequate for assessment of PD-L1 and MSI status. For the wide range of exclusion criteria, please see trial protocol.
- The **dual primary endpoints** are **PFS** assessed per RECIST, version 1.1, by BICR and **OS**; results are currently **not available**.
- **HRQoL** was determined as an exploratory endpoint; results are currently **not available**.
- **The original ESMO-MCBS** was applied, resulting in a **final adjusted magnitude of clinical benefit grade of 2.** Since the results of the primary endpoints were not reported yet, the adapted ESMO-MCBS is not applicable.
- Since the KEYNOTE-811 trial is currently ongoing and final analysis data is not available, the **risk of bias is unclear**. However, the risk is increased by its industry-funded background.
- Beside the KEYNOTE-811, no ongoing trials were identified for this pembrolizumab and trastuzumab plus chemotherapy for this indication.
- In conclusion, the **availability of data** for the assessed indication is **poor**. From the KEYNOTE-811 trial, only **interim analysis data of secondary endpoints** is currently available. Final analysis data of the dual primary endpoints is required urgently.

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Abbreviations: AE=adverse event, AEG=adenocarcinomas of the esophago-gastric junction, AJ=adjustment, ALK=anaplastic lymphoma kinase, ANC= absolute neutrophil count, aPTT= partial thromboplastin time , ASCT=autologous stem cell transplant, BCC=basal cell carcinoma, BICR=blinded independent central review, C=comparator, cHL=classical Hodkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CPS=combined positive score, cSCC=cutaneous squamous cell cancer, dMMR=mismatch repair deficient, ECF=epirubicin, cisplatin and 5-FU, 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, EQ-5D-5L= EuroQol Group 5-Dimension 5-Level questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FISH=fluorescence in situ hybridization, FLOT=5-fluorouracil/folinic acid/oxaliplatin/docetaxel, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GEJ=gastroesophageal junction, HBV= hepatitis B virus, HCV=hepatitis C virus, HER2=Human epidermal growth factor receptor 2, HIV=human immunodeficiency virus, HNSCC=head and neck squamous cell carcinoma, HSCT=haematopoietic stem cell transplantation, HR=hazard ratio, I=intervention, IHC=immunohistochemistry score, Int.=intention, ISH=in situ hybridization, ITT=intention-to-treat, IV=intravenous, MG=median gain, MSI=microsatellite instability, MSI-H=microsatellite instability-high, n=number of patients, NA=not available, NICE=National Institute for Health Care Excellence, MUGA=multigated acquisition, ORR=overall response rate, OS=overall survival, pCR=pathological complete response, PD-1=anti–programmed death 1, PD-L1= programmed death ligand 1, PE=primary endpoint, PFS=progression-free survival, PLF=paclitaxel, leucovorin and 5-Fu , 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, RR=response rate, SCC=squamous cell carcinoma, SAE=serious adverse event, ST=standard treatment, TNBC=triple-negative breast cancer, TPS=tumour proportion score, ULN=upper limit normal

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