Pembrolizumab (Keytruda®) with gemcitabine and cisplatin for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma (BTC)

General information

Drug description [1]

Pembrolizumab (Keytruda®) is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody.

Indication [2]

Pembrolizumab (Keytruda®), in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic BTC in adults.

Incidence [3]

BTC is a rare disease, accounting for less than 1% of malignant tumours.
The incidence rate in Europe, Australia and the U.S. is 0.3-3.5 per 100,000 persons. There is a higher incidence of BTC in countries with a high rate of trematode infections.

Current treatment [3]

For the first-line therapy of stage IV BTC, Onkopedia recommends the following:

- When systemic therapy is indicated, the general health condition, the comorbidities, the preferences of the patients, as well as the toxicity of the planned regimes have to be considered.
- Resection of the primary tumour is not recommended in case of metastasis.
- Response to chemotherapy should be verified regularly by medical imaging.
- For first-line palliative chemotherapy, the standard of care is defined by the British ABC-02 study. Results of this phase 3 trial showed a significant improvement of OS (median 3.6 months; HR 0.64; p<0.001) in patients who received gemcitabine/cisplatin combination therapy as compared to patients with gemcitabine monotherapy. The regimen of gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on days 1, 8 and 22 was well tolerated. There was no difference between the two treatment groups regarding the occurrence of severe renal dysfunction (CTCAE grade 3 and 4; 1.5% vs. 1%), nausea (4.0% vs. 3.5%; p=0.78) and vomiting (5.1% vs. 5.5%; p=0.65). This data is confirmed by the results of a randomised, Japanese phase 2 trial (3.5 months; HR 0.69, p=0.139).
- In patients with deteriorated general health conditions (ECOG≥2), gemcitabine monotherapy can be administered alternatively.
- In case of impaired renal function, oxaliplatin can be used instead of cisplatin.

Regulatory status

EMA [2]

Approval status for this indication: On 9 November 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 gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic BTC in adults.

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.

FDA [4, 5]

Approval status for this indication: On 31 October 2023, the FDA approved pembrolizumab (Keytruda®) to be used with gemcitabine and cisplatin for locally advanced unresectable or metastatic BTC.

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.
- 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 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 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 combined positive score (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 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. ❖ 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. ❖ in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test. This indication is approved under accelerated approval based on tumour response rate and durability of response.

- 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 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;
  - 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.
- 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.
- in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma.
- for the treatment of patients with locally advanced or metastatic oesophageal or gastroesophageal junction (tumours with epicentre 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.

❖ in combination 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 in adults whose tumours express PD-L1 with a CPS ≥ 1.	❖ Adult cHL and adult 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 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

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

Costs [6]

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

Warnings and precautions [4]

- **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-966 NCT04003636	1,069 (1:1)	pembrolizumab 200 mg IV every 3 weeks + gemcitabine (1000 mg/m^2 IV on days 1 and 8 every 3 weeks) and cisplatin (25 mg/m^2 IV on days 1 and 8 every 3 weeks	placebo IV every 3 weeks + gemcitabine (1000 mg/m^2 IV on days 1 and 8 every 3 weeks) and cisplatin (25 mg/m^2 IV on days 1 and 8 every 3 weeks	OS in the ITT population	25.6 months	**ongoing**[1], randomised, double-blind, placebo-controlled, multicentre, phase 3 study	PD-1	Merck Sharp & Dohme	KEYNOTE-966 trial [8]

Inclusion criteria[2]	Exclusion criteria	Patient characteristics at baseline (I vs. C)

[1] The KEYNOTE-966 trial is currently ongoing; the estimated study completion date is 11/2024.
[2] For detailed in- and exclusion criteria, please see trial protocol.

❖ ≥18 years with a histologically confirmed diagnosis of advanced (metastatic) and/or unresectable (locally advanced) BTC (intra-or extrahepatic) cholangiocarcinoma or gallbladder cancer. ❖ Measurable disease based on RECIST 1.1, as determined by the site investigator. ❖ Lesions situated in a previously treated area by either radiotherapy, photodynamic therapy or arterial embolization are considered measurable if progression has been shown in such lesions and they meet the criteria for measurable disease per RECIST 1.1. ❖ Participants with past or ongoing HCV infection are eligible for the study. ❖ Male participants are eligible to participate if they agree to the following during the intervention period and for at least 180 days after the last dose of chemotherapy: • Refrain from donating sperm PLUS either: • Be abstinent from heterosexual intercourse as their preferred and usual lifestyle and agree to remain abstinent OR • Must agree to use contraception unless confirmed to be azoospermia • Male participants must also agree to use a male condom when engaging in any activity that allows for the passage of ejaculation to another person of any sex. • Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Female Participants ❖ A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: • Is not a woman of childbearing potential OR • Is a woman of childbearing potential and using a contraceptive method that is highly effective, with low user dependency, or be abstinent from heterosexual intercourse as	❖ Previous systemic therapy for advanced (metastatic) or unresectable (locally advanced) biliary tract cancer (intra-or extrahepatic cholangiocarcinoma or gallbladder cancer), apart from neoadjuvant/adjuvant therapy which is allowed. ❖ Neoadjuvant/adjuvant therapy should have been completed at least 6 months prior to diagnosis of advanced and/or unresectable disease, and participants should not have received gemcitabine and/or cisplatin in the neoadjuvant/adjuvant setting. ❖ Participants who received prior neoadjuvant/adjuvant therapy with R2 postoperative pathology of the oncologic resection are excluded. ❖ Has ampullary cancer. ❖ Has small cell cancer, neuroendocrine tumours, lymphoma, sarcoma, mixed tumour histology and/or mucinous cystic neoplasms. ❖ Has an active autoimmune disease that has required systemic treatment in the past 2 years. ❖ Replacement therapy is not considered a form of systemic treatment and is allowed. ❖ Has undergone major surgery and has not recovered adequately from the procedure and/or complications from the surgery prior to starting study intervention. ❖ A woman of childbearing potential who has a positive urine pregnancy test within 24 hours prior to administration of study intervention. ❖ Has 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. ❖ Has received prior anticancer therapy for advanced unresectable BTC (intra-or extra hepatic cholangiocarcinoma or gallbladder cancer), including investigational agents within 4 weeks prior to randomization. ❖ Has not recovered (ie, AE ≤Grade 1 or baseline) from AEs due to previously administered anticancer therapy. ❖ Has received prior radiotherapy within 2 weeks of start of study intervention. ❖ Has received a live vaccine within 30 days prior to the first dose of study intervention. ❖ Has a 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. ❖ Has a known additional invasive malignancy that is progressing or has required active treatment within the past 3 years. ❖ Has severe hypersensitivity (≥Grade 3) to pembrolizumab, gemcitabine, or cisplatin and/or any of their excipients.	❖ Median age: 64.0 vs. 63.0 ❖ <65 years: 50% vs. 56% ❖ ≥65: 50% vs. 44% ❖ Male sex: 53% vs. 51% ❖ Geographical region • Asia: 45% vs. 46% • Not Asia: 55% vs. 54% ❖ ECOG performance status • 0: 48% vs. 43% • 1: 51% vs. 57% • ≥2: <1% vs. 0 ❖ Site of origin: • Extrahepatic: 18% vs. 20% • Gallbladder: 22% vs. 22% • Intrahepatic: 60% vs. 58% ❖ Disease status • Locally advanced: 11% vs. 12% • Metastatic: 89% vs. 88% ❖ Biliary stent or drain • No: 94% vs. 92% • Yes: 6% vs. 8% ❖ Previous chemotherapy administered as neoadjuvant or adjuvant therapy • No: 91% vs. 91% • Yes: 9% vs. 9% ❖ No previous photodynamic therapy: 100% vs. 100% ❖ Previous radiotherapy • No: 96% vs. 95% • Yes: 4% vs. 5% ❖ Antibiotic use within month of study start • No: 45% vs. 49% • Yes: 55% vs. 51% ❖ Microsatellite instability status • Microsatellite instability high: 1% vs. 1% • Microsatellite stable: 81% vs. 79% • Unknown: 18% vs. 21% ❖ Hepatitis B status

their preferred and usual lifestyle during the intervention period and for at least through 210 days after the last dose of chemotherapy or through 120 days after the last dose of pembrolizumab or placebo, whichever is greater, and agrees not to donate eggs to others or freeze/store for her own use for the purpose of reproduction during this period. • must have a negative highly sensitive pregnancy test before the first dose of study intervention. ❖ Provided documented informed consent for the study. ❖ ECOG PS of 0 or 1. ❖ Archival tumour tissue sample or newly obtained core or excisional biopsy of a tumour lesion not previously irradiated for biomarker analysis. ❖ Life expectancy of greater than 3 months. ❖ Adequate organ function, as defined in the study protocol.	❖ Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis. ❖ Has an active infection requiring systemic therapy, apart from HBV and HCV. ❖ Has dual active HBV infection and HCV infection at study entry. ❖ Has a known history of human immunodeficiency virus infection. ❖ Has a known history of, or any evidence of, CNS metastases and/or carcinomatous meningitis, as assessed by local site investigator. ❖ Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator. ❖ Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study. ❖ Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study. ❖ Has had an allogenic tissue/solid organ transplant.	• Any viral hepatitis B: 31% vs. 31% • Chronic infection: 3% vs. 3% • Clinically resolved infection: 28% vs. 28% • No viral hepatitis B: 69% vs. 68% • Missing: 1% vs. 1% ❖ Hepatitis C status • Any viral hepatitis C: 4% vs. 3% • Active infection: <1% vs. <1% • Previous infection: 3% vs. 2% • No viral hepatitis C: 96% vs. 97% • Missing: 0 vs. <1% ❖ PD-L1 combined positive score • <1: 21% vs. 21% • ≥1: 68% vs. 68% • Unknown: 11% vs. 11%

Efficacy (I vs. C)	**Safety** (I vs. C, n=524 vs. n=529)
<u>First interim analysis: Data cutoff: 15 December 2021; median follow-up 13.6 months</u> **Median PFS:** 6.5 months (95% CI 5.7–6.9) vs. 5.6 months (95% CI, 5.1–6.6); HR 0.86 (95% CI, 0.75–1.00); p=0.023 **Estimated 6-month PFS**: 52% (95% CI 48–57) vs. 46% (95% CI, 42–50) **Estimated 12-month PFS**: 25% (95% CI, 21–30) vs. 20% (95% CI, 16–24) **CR or PR**: 29% (95% CI, 25-33) vs. 29% (95% CI, 25-33); efficacy boundary for a statistically significant ORR benefit for the pembrolizumab group was not met, treatment difference 0.2 percentage points (95% CI, –5.2-5.6); p=0.47 **Median duration of response**: 9.7 months (95% CI, 6.9-12.2) vs. 6.9 months (95% CI, 5.7-8.2) **<u>Final analysis (Data cutoff 15 December 2022):</u>** **Median OS:** 12.7 months (95% CI, 11.5–13.6) vs. 10.9 months (95% CI, 9.9–11.6); HR 0.83 (95% CI, 0.72–0.95); p=0.0034 **Estimated 12-month OS rates:** 52% (95% CI. 47–56) vs. 44% (95% CI, 40–48) **Estimated 24-month OS rates**: 25% (95% CI 21–29) vs. 18% (95% CI, 15–22) **PFS:** HR 0.87 (95% CI, 0.76–0.99) **Estimates of ongoing response at 24 months**: 18% (95% CI, 11–26) vs. 6% (95% CI, 2–13)	**AEs of any cause**: 99% vs. <100% **Maximum toxicity grade 3 or 4:** 79% vs. 75% **AEs leading to death**: 6% vs. 9% **AEs leading to discontinuation of one or more study drugs:** 26% vs. 23% **Discontinuation of all study drugs:** 7% vs. 7% **TRAES (at final analysis)**: 93%[3] vs. 94%[4] **Treatment-related AEs leading to death**: 2% vs. 1% **Potentially immune-mediated AEs and infusion reactions** (at final analysis): 22% vs. 13%[5] **Potentially immune-mediated AE that led to death** (=pneumonitis): <1% vs. 0

Patient-reported outcomes [8, 10]
❖ PROs were assessed using the EORTC QLQ-C30, EORTC QLQ-BIL21, and EQ-5D-5L questionnaires.

[3] Including 70% with a maximum toxicity of grade 3 or 4, 19% who discontinued one or more study drugs, and 3% who discontinued all study drugs.
[4] Including 69% with a grade 3 or 4 event, 15% who discontinued one or more study drugs, and 3% who discontinued all study drugs.
[5] Including 7% in the pembrolizumab group and 4% in the placebo group who had a grade 3 or 4 AE.

- The analysis population included all treated patients who completed ≥1 HRQoL assessment for the specific endpoint.
- A constrained longitudinal analysis model (covariates: treatment, time, treatment by time interaction, and stratification factors) was used to compare least squares mean (LSM) score changes from baseline to week 18 (ie, latest timepoint that completion was ≥ 60% and compliance was ≥80%) in QLQ-C30 global health status (GHS)/QoL, physical functioning (PF), and role functioning (RF), QLQ-BIL21 jaundice and pain, and EQ-5D-5L visual analogue scale (VAS).
- A stratified Cox proportional hazards model was used to assess the magnitude of the between-arm difference in time to deterioration (TTD) in GHS/QoL, PF, RF, jaundice, and pain (ie, time to first onset of ≥10-point deterioration from baseline in each scale/subscale confirmed by ≥10-point deterioration from baseline at the next visit; established as clinically relevant).
- Questionnaire compliance was >87% from baseline to week 18 in both arms.
- LSM changes from baseline to week 18 in QLQ-C30 GHS/QoL, PF, and RF, QLQ-BIL21 jaundice and pain, and EQ-5D-5L VAS were similar between arms.
- TTD was also similar between arms: median NR vs. 21.2 months for GHS/QoL (HR 0.86, 95% CI, 0.70-1.07), NR vs. 12.0 months for PF (HR 0.95, 95% CI, 0.78-1.17), 6.5 months vs. 5.8 months for RF (HR 0.98, 95% CI, 0.81-1.18), NR vs. NR for jaundice (HR 1.20, 95% CI, 0.94-1.54), and NR vs. NR for pain (HR 0.79, 95% CI, 0.59-1.05).
- Among evaluable participants in the pembrolizumab group (n=518) and placebo group (n=517), the least-squares mean change from baseline to week 18 in the GHS QoL of the EORTC QLQ-C30 at the final analysis was –2.5 (95% CI, –4.5 to –0.5) in both groups (difference in LSM 0.0, 95% CI, –2.5 to 2.6).
- HRQoL was maintained when pembrolizumab was added to gemcitabine/cisplatin.

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	≤12 months	OS: +1.8 months	0.83 (0.72-0.95)	HR >0.70 OR gain <1.5 months	1	-	maintained	-	1
Adapted	NC	2A	≤12 months	OS: +1.8 months	0.83 (0.72-0.95)	HR >0.70 OR gain <1.5 months	1	-	maintained	-	1

Risk of bias (RCT) [12]

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	yes low risk	yes low risk	unclear[6] unclear risk	yes[7] high risk	unclear

Ongoing trials [13]

NCT number/trial name	Description	Estimated study completion date
NCT04003636/KEYNOTE-966	Please see above.	11/2024
NCT04924062/KEYNOTE-966/China Extension Study	The China extension study will include participants previously enrolled in China in the global study for MK-3475-966 (NCT04003636) plus those enrolled during the China extension enrolment period.	11/2024
NCT05429697	Phase 2/3 study designed to assess the antitumor activity of combination therapy of SMT-NK (allogeneic natural killer cells) and pembrolizumab vs. pembrolizumab monotherapy in patients with advanced BTC.	06/2026

Available assessments

- The NICE appraisal "Pembrolizumab with gemcitabine and cisplatin for untreated advanced biliary tract cancer [ID4034]" was delayed in August 2023 and will be rescheduled when further information is available [14].
- NIHR published a Health Technology Briefing "Pembrolizumab in combination with gemcitabine and cisplatin for previously untreated advanced/unresectable biliary tract cancer" in November 2021 [15].
- No assessments were identified via ICER, CADTH and G-BA.

Other aspects and conclusions

[6] KEYNOTE-966 is ongoing.

[7] In collaboration with the academic authors, authors employed by the study funder contributed to study design, data analysis, data interpretation, and writing of the report. The funder maintained the study database and ensured data were collected according to the protocol.

- In November 2023, the **CHMP adopted a new indication** for Keytruda®, in combination with gemcitabine and cisplatin, indicated for the first-line treatment of locally advanced unresectable or metastatic BTC in adults. In October 2023, the **FDA approved** Keytruda® to be used with gemcitabine and cisplatin for locally advanced unresectable or metastatic BTC.
- **KEYNOTE-966** (NCT04003636) is an **ongoing**, randomised, double-blind, placebo-controlled, phase 3 trial, comparing pembrolizumab in combination with gemcitabine and cisplatin with gemcitabine and cisplatin alone for patients with advanced BTC. **Eligible participants** were ≥18 years old, had previously untreated, unresectable, locally advanced or metastatic BTC, had disease measurable per RECIST version 1.1 and had an ECOG PS of 0 or 1. Patients were **excluded** if they had ampullary cancer or had an active autoimmune disease that required systemic treatment in the previous 2 years.
- The **primary endpoint of OS** was evaluated in the ITT population. Median OS was **significantly improved**: 12.7 months (95% CI, 11.5–13.6) vs. 10.9 months (95% CI, 9.9–11.6); HR 0.83 (95% CI, 0.72–0.95); one-sided p=0.0034.
- The **original and adapted ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit **grade of 1** each.
- Since the KEYNOTE-966 trial is currently ongoing, the **risk of bias** was considered **unclear**. However, it is increased by the industry-funded background of the trial.
- Besides the KEYNOTE-966 trial, 2 further ongoing phase 2/3 trials evaluating pembrolizumab in patients with BTC, were identified.
- The KEYNOTE-966 trial is currently ongoing; hence, **final analysis data** and data from the China extension study are required to further assess the role of pembrolizumab in addition to chemotherapy in patients with BTC.

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplantation, BTC=biliary tract cancer, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CPS=combined positive score, CR=complete response, cSCC=cutaneous squamous cell carcinoma, CTCAE=Common Terminology Criteria for Adverse Events, dMMR=mismatch repair-deficiency, ECOG PS=Eastern Cooperative Oncology Group performance status, 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, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GHS=global health status, HBV= hepatitis B virus, HCC=hepatocellular carcinoma, HCV=hepatitis c virus, HSCT=Haematopoietic stem cell transplantation, HR=hazard ratio, 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, NR=not reached, NSCLC=non-Small Cell Lung Cancer, ORR=objective response rate, OS=overall survival, PD-1= programmed death-1, PD-L1= programmed death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, RCC=renal cell carcinoma, RECIST=Response Evaluation Criteria in Solid Tumours, SAE=serious adverse event, ST=standard treatment, TMB-H=tumour mutational burden-high, TPS=tumour proportion score, TRAE=treatment-related adverse event, TTD=time to deterioration, VAS=visual analogue scale

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