NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Pembrolizumab with gemcitabine and cisplatin for untreated advanced biliary tract cancer

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of pembrolizumab with gemcitabine and cisplatin within its marketing authorisation for treating untreated advanced biliary tract cancer.

Background

The biliary tract includes the organs and ducts that make and store bile. The liver and gallbladder are connected to the small bowel by a network of small tubes called ducts which carry bile.[1,2] Biliary tract cancers (BTC) affect the various locations of the bile ducts and the gallbladder. The cancers include intrahepatic and extrahepatic cholangiocarcinomas (cancers of the bile duct), gallbladder carcinomas, and ampullary carcinoma.[3]

The incidence rate of BTC in England is 3.58 per 100,000.[4] BTCs have a mortality rate of 3.64 per 100,000 population in England.[4] Currently, there are no UK wide statistics available for bile duct cancer and gallbladder cancer survival by stage.

Surgery remains the curative intent treatment option leading to long-term survival for people diagnosed with resectable biliary tract carcinomas. Unfortunately, most people with BTCs are diagnosed with either unresectable locally-advanced or metastatic disease. People with unresectable tumours are offered palliative treatment. The treatments vary depending on Eastern Cooperative Oncology Group (ECOG) performance status (PS), molecular profiling and disease distribution.[5-7]

Chemotherapy is typically used in the first-line treatment of BTC that cannot be surgically removed.[7] People with unresectable BTC and who are in good general health, are typically offered chemotherapy with a combination of cisplatin and gemcitabine. For some BTC, oxaliplatin might be offered instead of cisplatin, especially if there are any concerns over kidney function. People with poorer overall health might be offered single-agent chemotherapy with gemcitabine, fluorouracil (5-FU) or capecitabine alone. People who experience cancer progression following first-line treatment can be offered further chemotherapy. BTCs express Programmed death-ligand 1 (PD-L1) and high levels of soluble PD-L1 correlate with poor prognosis in BTC are offered chemotherapy.[5-7]

Radiotherapy in addition to chemotherapy may also be offered to some people to relieve symptoms.[8] Aside from chemotherapy, targeted therapies are being assessed. However, there is limited established evidence for the use of targeted therapy.[5-7]

The technology

Pembrolizumab (Keytruda, MSD) with gemcitabine and cisplatin does not currently have a marketing authorisation in the UK for untreated advanced biliary tract cancer. It has been studied in clinical trials in people with advanced and/or unresectable biliary tract carcinoma.

Pembrolizumab as a monotherapy or in combination with various medicinal products is currently licensed in the UK for the following related indications:

- Renal cell carcinoma
- Colorectal cancer
- Oesophageal carcinoma

Intervention(s)	Pembrolizumab with gemcitabine and cisplatin
Population(s)	People with untreated advanced/unresectable biliary tract carcinoma.
Subgroups	If evidence allows, results by level of PD-L1 expression will be considered

Comparators	Established clinical management without pembrolizumab which include:
	• Gemcitabine with cisplatin
	• For people with poor kidney function:
	  ○ Gemcitabine with oxaliplatin
	• For people with poor overall health:
	  ○ Gemcitabine alone
	  ○ Fluorouracil (5-FU) alone
	  ○ Capecitabine alone
	• Durvalumab with gemcitabine and cisplatin [ID4031], subject to NICE evaluation

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates (including overall response rates) • time to treatment discontinuation • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related appraisals in development:** Durvalumab with gemcitabine and cisplatin for untreated advanced biliary tract cancer NICE technology appraisal guidance. Publication date to be confirmed Infigratinib for cholangiocarcinoma [ID3992] NICE technology appraisal guidance. Publication date to be confirmed **Related Guidelines:** Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement (2021) NICE technology appraisal guidance 722 **Guidelines in development:** Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cholangiocarcinoma or pancreatic adenocarcinoma NICE interventional procedures guidance. Publication date to be confirmed **Related Interventional Procedures:** Irreversible electroporation for primary liver cancer (2019) NICE interventional procedures guidance 664 Irreversible electroporation for treating pancreatic cancer (2017) NICE interventional procedures guidance 579 Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic

	cancer in the liver (2021) NICE interventional procedures guidance 691 Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma (2018) NICE interventional procedures guidance 630 Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer (2014) NICE interventional procedures guidance 488 Photodynamic therapy for bile duct cancer (2005) NICE interventional procedures guidance 134 Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cancer (2018) NICE interventional procedures guidance 614 Cryotherapy for the treatment of liver metastases (2010) NICE interventional procedures guidance 369 SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver (2012) NICE diagnostics guidance 5 The SpyGlass direct visualisation system for diagnostic and therapeutic procedures during endoscopy of the biliary system (2015) NICE MedTech innovation briefing 21 **Related Public Health Guidance/Guidelines:** ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2016 **Related Quality Standards:** http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp Suspected cancer Quality standard [QS124] Published: 30 June 2016. Last updated: 05 December 2017 Liver disease Quality standard [QS152] Published: 29 June 2017
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018) NHS England Funding and Resource 2018/19: Supporting 'Next Steps for the NHS Five Year Forward View' NHS England (2017) Next steps on the five year forward view NHS England (2014) NHS Five year forward view NHS England (2013) Hepatobiliary and Pancreas (Adult) NHS Standard Contract. Reference A02/S/a.

	NHS England (2018) Manual for prescribed specialised services 2018/19 Chapter 105. Specialist cancer services (adults) NHS England (2016) Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) as a treatment option for patients with Hepatocellular carcinoma or Cholangiocarcinoma (16022/P). NHS England (2019) Selective internal radiation therapy (SIRT) for the treatment of chemotherapy refractory or intolerant, unresectable primary Intrahepatic cholangiocarcinoma (all ages) Clinical Commissioning Policy. Reference 170112P. NHS England (2020) The use of Stereotactic Ablative Radiotherapy (SABR) as a treatment option for patients with Hepatocellular carcinoma or Cholangiocarcinoma Clinical Commissioning Policy. NHS England (2013/14) NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) (Chapter 131) Department of Health and Social Care (2016) NHS outcomes framework 2016 to 2017

Questions for consultation

Have all relevant comparators for pembrolizumab with gemcitabine and cisplatin been included in the scope?

- Are the following combination treatments used in clinical practice in the NHS?
  - capecitabine with oxaliplatin (XELOX) / gemcitabine with capecitabine (Link to source from National Library of Medicine)
- Is radiotherapy also offered alongside chemotherapy? If yes, under what circumstances would this be used in clinical practice in the NHS?

Which treatments are considered to be established clinical practice in the NHS for people with untreated advanced biliary tract cancer?

How does established clinical practice in the NHS differ based on a person's overall health condition and kidney function?

- Is gemcitabine with oxaliplatin offered to people with poor kidney function?
  - What parameters are used to determine poor kidney function (for example, estimated glomerular filtration rate (eGFR))?
- Are gemcitabine alone or fluorouracil (5-FU) alone or capecitabine alone offered to people with poor overall health?
  - What parameters are used to determine poor overall health (for example, ECOG PS)?

- Would there be people with untreated advanced biliary tract cancer who would receive either cisplatin alone or oxaliplatin alone?

Are there any subgroups (for example disease stage or histology) of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider pembrolizumab will fit into the existing care pathway for untreated advanced biliary tract cancer?

How will people eligible for pembrolizumab be identified?

- Will implementation of additional testing be required to facilitate the use of this technology in clinical practice in the NHS?

Would pembrolizumab be a candidate for managed access in BTC?

Do you consider pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of pembrolizumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pembrolizumab with gemcitabine and cisplatin will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

References

1. National Health Services (NHS). What is bile duct cancer? -Bile duct cancer (cholangiocarcinoma). Available from: https://www.nhs.uk/conditions/bile-duct-cancer/ [Accessed 08 July 2022].

2.Macmillan Cancer Support. Bile duct cancer (cholangiocarcinoma). Available from: https://www.macmillan.org.uk/cancer-information-and-support/bile-duct-cancer [Accessed 08 July 2022].

3. Valle, Juan W., et al. "Biliary tract cancer." The Lancet 397.10272 (2021): 428-444.

4. Public Health England. National Cancer Intelligence Network Rare and less common cancers - Incidence and Mortality in England, 2010 to 2013. 2015. Available from: https://ammf.org.uk/wp-content/uploads/2015/06/Rare_and_less_common_cancers_For-AMMF-web_0-1.pdf [Accessed 08 July 2022].

5. Lamarca, A., J. Edeline, and L. Goyal. "How I treat biliary tract cancer." ESMO open 7.1 (2022): 100378.

6. Valle, Juan W., et al. "Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." Annals of Oncology 27 (2016): v28-v37.

7. Macmillan Cancer Support. Bile duct cancer (cholangiocarcinoma). Available from: https://www.macmillan.org.uk/cancer-information-and-support/bile-duct-cancer [Accessed 08 July 2022].

8. BMJ Best Practice (Cholangiocarcinoma) https://bestpractice.bmj.com/topics/en-gb/721/treatment-algorithm [Accessed 08 July 2022].