Health Technology Appraisal

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab with ipilimumab within its marketing authorisation for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency.

Background

Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum). Metastatic colorectal cancer refers to disease that has spread beyond the large intestine and nearby lymph nodes. This type of cancer often first spreads to the liver, but metastases may also occur in other parts of the body including the lungs, brain and bones. Most colorectal cancers are adenocarcinomas, these start in glands that line the insides of the colon and rectum.

There are around 42,900 new cases of colorectal cancer each year in the UK, accounting for 11% of all cancers[1]. Around 4 in 10 (43%) new cases of colorectal cancer in the UK were in people aged over 75 years, but it can affect young people too[1].

Mismatch repair (MMR) is a process where cells of the body recognise and repair nucleotide mismatches or insertion of excess DNA during replication of the DNA as cells divide. Deficiencies in MMR (dMMR) are associated with genomic instability and the accumulation of simple repetitive DNA sequences, which are known as microsatellites (MSI)[2].The accumulation of numerous MSI is classified as an MSI high (MSI-H) phenotype and, if these MSI affect regions of the genome associated with apoptosis (programmed cell death) and cell growth, it can result in the development of tumours. The proportion of tumours associated with MSI-H metastatic colorectal cancer is estimated to be around 3.5%[3].

Metastatic colorectal cancer treatment aims to prolong survival and improve quality of life. Treatment can involve a combination of surgery (to resect the primary tumour or the metastases), chemotherapy (to make the tumour or metastases resectable, or to manage the cancer), biological therapy, and radiotherapy[4]. Combinations of chemotherapy drugs for treating metastatic colorectal cancer include flurouracil, folinic acid and oxaliplatin (FOLFOX), flurouracil, folinic acid and irinotecan (FOLFIRI), capecitabine plus oxaliplatin

(CAPOX) and folinic acid plus fluorouracil plus oxaliplatin plus irinotecan (FOLFOXIRI).

The following treatment options are recommended by NICE for untreated metastatic colorectal cancer:

- Capecitabine (NICE technology appraisal 61)
- Cetuximab with FOLFOX or FOLFIRI for tumours that express epidermal growth factor receptor and are RAS wild-type (NICE technology appraisal 439)
- Panitumumab with FOLFOX or FOLFIRI for tumours that are RAS wild-type (NICE technology appraisal 439)
- Pembrolizumab for tumours with MSI-H or dMMR for a maximum of 2 years (NICE technology appraisal 709)

The technology

Nivolumab with ipilimumab (Opdivo and Yervoy, Bristol Myers Squibb) does not currently have a marketing authorisation in the UK for untreated unresectable or metastatic colorectal cancer with MSI-H or dMMR. It does have a marketing authorisation for the treatment of MSI-H or dMMR metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy. Nivolumab with ipilimumab has been studied in clinical trials compared with chemotherapy which include adults with previously untreated, recurrent or metastatic colorectal cancer.

Intervention	Nivolumab with ipilimumab
Population	People aged 12 years and older with previously untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatched repair deficiency

Comparators	For all people: • Pembrolizumab • Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) • Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) • Capecitabine plus oxaliplatin (CAPOX) • Capecitabine For people with RAS-mutant metastatic colorectal cancer: • Folinic acid plus fluorouracil plus oxaliplatin plus irinotecan (FOLFOXIRI) For people with RAS wild-type metastatic colorectal cancer: • Panitumumab in combination with FOLFOX or FOLFIRI For people with EGFR expressing, RAS wild-type metastatic colorectal cancer: • Cetuximab in combination with FOLFOX or FOLFIRI
Subgroups	If evidence allows, subgroups based on RAS mutation status will be considered.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • 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 and cost of biosimilar and generic products should be taken into account. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will 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 technology appraisals**: Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (2021) NICE technology appraisal guidance 709 Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (2017) NICE technology appraisal guidance 439 Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer (2003) NICE technology appraisal guidance 61 **Related technology appraisals in development:** Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments NICE technology appraisal guidance [ID6298] Publication expected July 2024 Fruquintinib for previously treated metastatic colorectal cancer NICE technology appraisal guidance [ID6274] Publication expected September 2024

	Tucatinib with trastuzumab for previously treated HER2-positive colorectal cancer NICE technology appraisal guidance [ID6227] Publication date to be confirmed **Related NICE guidelines**: Colorectal cancer (2020) NICE Guideline NG151. **Related diagnostics guidance:** Molecular testing for Lynch syndrome in people with colorectal cancer. NICE diagnostics guidance DG27. Publication: February 2017. **Related quality standards**: Colorectal cancer (2012) NICE Quality Standard QS20
Related National Policy	The NHS Long Term Plan (2019) NHS Long Term Plan

References

1. Cancer Research UK, Bowel cancer statistics. Accessed February 2024
2. Lorenzi, M et al. Epidemiology of Microsatellite Instability High (MSI-H) and Deficient Mismatch Repair (dMMR) in Solid Tumours: A Structured Literature Review. Journal of Oncology (2020)
3. Koopman, M et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. British journal of cancer vol. 100,2 (2009): 266-73
4. Cancer Research UK, Treatment for advanced bowel cancer. Accessed February 2024