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# Pembrolizumab for stage IV colorectal carcinoma – first line

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## LAY SUMMARY

Colorectal or bowel cancer is a cancer that begins in the large bowel and is the fourth most common cancer in the UK. Metastatic/advanced colorectal cancer, or Stage IV, occurs when the cancer has spread to another part of the body; this is most commonly to the liver. A small proportion of colorectal cancer cases develop due to deficiencies in a repair mechanism for DNA; this may contribute to an increase in potential faulty (mutated) DNA. A high rate of this mutation is known as high microsatellite instability or mismatch repair deficient. These subsets of patients may have outcomes which are worse than those observed in the overall metastatic colorectal cancer population.

The most common treatment options for advanced colorectal cancer in the UK is surgery, radiotherapy and chemotherapy. Pembrolizumab is a type of immunotherapy that is delivered intravenously by a drip and that works by targeting specific proteins that stimulate an immune response attacking the cancer cells. It increases the body's natural ability to identify and kill cancer cells. If licenced, pembrolizumab will offer an additional first line treatment option for patients with advanced colorectal cancer and prolong the time without cancer progression and overall survival.



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## TARGET GROUP

Colorectal carcinoma (Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR), stage IV) – first line

## TECHNOLOGY

### DESCRIPTION

Pembrolizumab (Keytruda®) is a monoclonal antibody, a type of protein that binds to and blocks a receptor called programmed death-1 (PD-1) receptor. 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. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to ligands 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.[1] Some cancers can make a protein that combines with PD-1 to switch off the activity of certain cells of the immune system preventing them from attacking the cancer. By blocking PD-1, pembrolizumab stops the cancer from switching off these immune cells, thereby increasing the ability of the immune system to kill the cancer cells.[2]

In the phase III trial (NCT02563002/KEYNOTE-177) participants receive pembrolizumab 200 mg intravenously on day 1 of each 21-day cycle (Q3W) for up to 35 treatments (approximately 2 years). Participants that have stopped the initial course of pembrolizumab and have stable disease but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 year additional).[3]

Pembrolizumab monotherapy is licensed in the UK for the following indications in adult patients:[4]

- advanced (unresectable or metastatic) melanoma in adults
- metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no Epidermal Growth Factor Receptor (EGFR)or Anaplastic lymphoma kinase (ALK) positive tumour mutations – first line
- 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 pembrolizumab
- adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (see section 5.1)
- 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.[a]

[a] A conditional restriction has been placed by the EMA on the use of Keytruda after early data from this clinical trial showed reduced survival when used as first-line treatments for urothelial cancer (cancer of the bladder and urinary tract) in patients with low levels of a protein called PD-L1. EMA, 1 June 2018, EMA/364553/2018

The most common side effects with pembrolizumab (which may affect more than 1 in 10 people) are diarrhoea, nausea (feeling sick), itching, rash and tiredness, most of which are mild to moderate in severity. Other common side effects of pembrolizumab related to the activity of the immune system causing inflammation of body organs. Most will resolve following appropriate treatment or on stopping pembrolizumab.[2]

Pembrolizumab is in phase III trials in Europe/USA for the following indications:[5]

- Breast Cancer
- Melanoma
- Non-small cell lung cancers
- Small cell lung cancer
- Head and Neck cancers
- Hodgkin lymphoma
- Renal cell carcinoma (post nephrectomy)
- Hepatocellular carcinoma

## INNOVATION and/or ADVANTAGES

If licensed, pembrolizumab will offer an additional treatment option for the first line treatment of Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) stage IV colorectal cancer. Pembrolizumab has the potential to prolong progression-free survival and overall survival compared to current standard of care chemotherapy options for this patient group.[3]

## DEVELOPER

Merck Sharp & Dohme Ltd

## PATIENT GROUP

## BACKGROUND

Colorectal cancer (CRC) is a malignant tumour arising from the lining of the large intestine (colon and rectum); almost two-thirds (62%) of all bowel cancers arise from the colon and nearly one-third (29%) arise from the rectum (including the anus). There are a number of different histological types of colorectal cancer including: adenocarcinoma, squamous cell carcinoma, carcinoid tumour, sarcoma, and lymphoma.[6, 7]

Symptoms of colorectal cancer may include: bleeding from the rectum or blood in the stools, a change in normal bowel habits, a lump in the rectum or abdomen, weight loss, pain in the abdomen or rectum, and anaemia. Sometimes a tumour may obstruct the bowel, which can result in symptoms including abdominal pains, feeling bloated, constipation, and vomiting. Individuals with colorectal cancer may exhibit a number of disease related symptoms such as weight loss, fatigue, and appetite loss; with research suggesting that such symptoms may predict shortened survival.[8, 9]

The cause of colorectal cancer in most people remains unknown, although lifestyle-related risk factors such as physical inactivity, obesity, smoking and high alcohol intake are believed to increase risk. A diet high in fibre and low in saturated fat may reduce risk, whilst a diet high in red or processed meats may increase risk. Family history, age (over 65 years) and inherited conditions or related bowel conditions may greatly increase an individual's risk of colorectal cancer. A small percentage (<5%) of colorectal cancers occur in people with a genetic predisposition, including familial adenomatous polyposis and hereditary nonpolyposis coli (Lynch syndrome).[10]

Up to one in five colorectal cancers show high-level microsatellite instability. Microsatellites are short repetitive segments of DNA sequences, which are prone to mismatch during replication. DNA mismatch errors are normally repaired by mismatch repair (MMR) protein complexes. Functional loss of the MMR system results in accumulation of DNA errors, a condition of genetic hypermutability i.e. microsatellite instability (MSI). MSI status is a marker for better prognosis and also a predictive factor for the response to treatment with fluorouracil chemotherapy. Patients with MSI-H colorectal cancers have better prognosis than those with microsatellite stable (MSS) or low-level microsatellite instability (MSI-L) colorectal cancer.[11] Screening all incident CRC diagnoses (universal screening) for MSI via Polymerase Chain Reaction (PCR) or reflex immunohistochemistry (rIHC) for mismatch repair-deficient (dMMR) phenotype is increasingly undertaken to determine adjuvant treatment, and to predict response to chemotherapeutic agents and immune-checkpoint inhibitors.[12]

## CLINICAL NEED and BURDEN OF DISEASE

Bowel cancer is the fourth most common cancer in the UK (2015), accounting for 12% of all new cases. It is the third most common cancer in both males (13% of the male total) and females (11%) separately. In 2015, there were 41,804 new cases of bowel cancer in the UK: 23,082 in males and 18,722 in females. The crude incidence rate shows that there are 72 new bowel cancer cases for every 100,000 males in the UK and 56.7 for every 100,000 females. The European Age-Standardised incidence rate for male in the UK is 85.3 per 100,000 persons and for female is 57.2 per 100,000 persons.[13]

An estimated 230,200 people who had been diagnosed with bowel cancer between 1991 and 2010 were alive in the UK at the end of 2010.[13] In England in 2016 there were a total of 23,485 registrations of newly diagnosed cases of malignant neoplasm of colon (ICD-10 code C18).[14]

Admitted patient care statistics for England for 2016-17 recorded a total of 91,802 admissions of which 68,093 were days cases (ICD-10 code C18).[15]

Bowel cancer survival is improving and has more than doubled in the last 40 years in the UK.[16] For adults diagnosed between 2011 and 2015 in England, the Age-Standardised five year survival for men was 60.8 % and for women 60.1% (ICD-10 code for cancer, colorectum, C18 to C20 including C21.8).[17]

In England and Wales in 2016 there were a total of 8,277 deaths registered for malignant neoplasm of the colon (ICD-10 code C18).[18]

# PATIENT PATHWAY

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal guidance. Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy. (TA242). January 2012
- NICE technology appraisal guidance. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (TA118). January 2007. Updated January 2012
- NICE technology appraisal guidance. Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (TA212). December 2010
- NICE clinical guideline in development. Colorectal cancer: diagnosis and management (update) (GID-NG10060). Expected publication date: October 2019
- NICE clinical guideline. Colorectal cancer: diagnosis and management (CG131). December 2014.
- NICE cancer service guideline. Improving outcomes in colorectal cancer (CSG5). June 2004
- NICE quality standard. Colorectal cancer. (QS20). August 2012

### NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Colorectal: Transanal endoscopic microsurgery (TEMS) (Adult). A08/S/e

### OTHER GUIDANCE

- Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. 2018.[19]
- ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. 2016.[20]

## CURRENT TREATMENT OPTIONS

Treatment of metastatic colorectal cancer may involve a combination of surgery, chemotherapy, radiotherapy and supportive care. When possible, surgical removal (resection) or destruction of the primary tumour and metastases may be considered. Treatment for metastatic colorectal cancer aims to prolong survival, improve quality of life and/or make the primary tumour or metastases suitable for resection. Chemotherapy options include: folinic acid plus fluorouracil plus oxaliplatin (FOLFOX), folinic acid plus fluorouracil plus irinotecan (FOLFIRI), capecitabine plus oxaliplatin (XELOX), single-agent irinotecan, capecitabine or tegafur with uracil (in combination with folinic acid). Chemotherapy may be combined with biological agents such as EGFR inhibitors (cetuximab or panitumumab) or VEGF inhibitors (bevacizumab). If standard therapies are unsuccessful, not tolerated or contraindicated,

people are treated with supportive care to manage the symptoms and complications of the condition.[21]

## EFFICACY and SAFETY

| | |
|---|---|
| **Trial** | **KEYNOTE-177, NCT02563002, MK-3475-177, EudraCT Number 2015-002024-89, JAPIC-CTI 163238; adults 18 years old and over; pembrolizumab vs standard of care; phase III** |
| **Sponsor** | Merck Sharp & Dohme Ltd |
| **Status** | Ongoing |
| **Source of Information** | Trial registry[3] |
| **Location** | Not reported |
| **Design** | Randomised, active-controlled, open label, parallel assignment |
| **Participants** | n= (308); 18 years or older, confirmed dMMR or MSI-H stage IV colorectal carcinoma. |
| **Schedule** | Randomised to:<br>• Pembrolizumab 200 mg intravenously on day 1 of each 21-day cycle (Q3W) for up to 35 treatments (approximately 2 years); or,<br>• 1 of 6 possible standard chemotherapy regimens: mFOLFOX6, or mFOLFOX6+bevacizumab 5 mg/kg intravenously on day 1 of each 2-week cycle, or mFOLFOX6+cetuximab 400 mg/m$^2$ intravenously over 2 hours then 250 mg/m$^2$ over 1 hour weekly in each 2-week cycle, or FOLFIRI, or FOLFIRI+bevacizumab 5 mg/kg intravenously on day 1 of each 2-week cycle, or FOLFIRI+cetuximab 400 mg/m$^2$ intravenously over 2 hours then 250 mg/m$^2$ over 1 hour weekly in each 2-week cycle. |
| **Follow-up** | Active treatment for 2 years, if disease progresses after discontinuation of the initial course of pembrolizumab, a second course of pembrolizumab can be initiated for up to 17 cycles (approximately 1 year additional). Follow up N/S. |
| **Primary Outcomes** | • Progression-free Survival [ Time Frame: Up to 57 months ]<br>• Overall Survival [ Time Frame: Up to 57 months ] |
| **Secondary Outcomes** | • Overall Response Rate [ Time Frame: Up to 57 months ] |
| **Key Results** | - |
| **Adverse effects (AEs)** | - |
| **Expected reporting date** | Study completion date reported as September 2019. |

## ESTIMATED COST and IMPACT

### COST

The NHS indicative price for pembrolizumab 4ml vial is £2,630 (hospital only); this equates to 100mg (4 x 25mg per ml).[22]

## IMPACT – SPECULATIVE

### IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

### IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

### IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

### OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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