

**NIHR Innovation Observatory
Evidence Briefing: June 2017**

**Atezolizumab (Tecentriq) and Cobimetinib
(Cotellic) for advanced/metastatic colorectal
cancer - third line**

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LAY SUMMARY

Colorectal cancer (CRC) is a cancer that starts in the colon or the rectum. CRC is a common type of cancer in men and women and is responsible for a fourth of all cancer deaths. Like many other types of cancers, CRC is associated with many risk factors such as family history, increasing age, and lifestyle (smoking, alcohol and diet). The most common symptoms of CRC are blood in the stool, stomach discomfort and pain when passing stool, unexplained weight loss, constipation and diarrhoea. In advanced or metastatic CRC (mCRC), the disease has spread to distant organs, most commonly to the liver and the lungs. About one in four people with CRC in the UK have mCRC.

The combination of atezolizumab (Tecentriq), given by injection, and cobimetinib (Cotellic), given orally, is being developed to increase the options available for the treatment of mCRC. This treatment combination will target people that have received at least two previous treatments and did not show any improvements or who initially benefitted but whose disease has since progressed. It is thought that this treatment combination will increase the survival rates for people with mCRC.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Colorectal cancer (advanced/metastatic) – third line

TECHNOLOGY

DESCRIPTION

The technology consists of atezolizumab (Tecentriq; anti-PDL1; MPDL3280A; RG7446;) in combination with cobimetinib (Cotellic; GDC-0973; RG7421).

Atezolizumab is a monoclonal antibody that binds to and inactivates a protein called programmed death-ligand 1 (PD-L1), which leads to downstream activation of T cells that can detect and attack tumour cells.¹ PD-L1 binds to two known inhibitory receptors expressed on activated T cells (PD-1 and B7.1) to inhibit T-cell proliferation, cytokine production and cytolytic activity and thus restrict tumour cell killing.²⁻⁴ Cobimetinib is a reversible, selective, allosteric, oral inhibitor that blocks the mitogen-activated protein kinase (MAPK) pathway by targeting the mitogen-activated extracellular signal-regulated kinase (MEK) 1 and MEK 2 which results in inhibition of phosphorylation of the extracellular signal-regulated kinase (ERK) 1 and ERK 2. Therefore, cobimetinib blocks the cell proliferation induced by the MAPK pathway through inhibition of the MEK1/2 signalling node.⁵

The combination of atezolizumab and cobimetinib is currently under development as a third line (3L) treatment of advanced or metastatic colorectal cancer (mCRC).^{6,7} The ongoing phase III study is a multicentre, open-label, three-arm, randomised study in participants with unresectable locally advanced or metastatic colorectal cancer (CRC) who have received at least two prior regimens of cytotoxic chemotherapy for metastatic disease. The study compares regorafenib, a standard therapy in this setting, to cobimetinib plus atezolizumab, and atezolizumab monotherapy.⁸ In the experimental arm, participants will receive cobimetinib 60 milligram (mg) orally on days 1 to 21 plus atezolizumab 840 mg intravenous (IV) on day 1 and day 15 in a 28-day cycle until disease progression according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1, unacceptable toxicity, death, participant's or physician decision's to withdraw, or pregnancy, whichever occurs first.⁸

Atezolizumab does not currently have Marketing Authorisation in the EU for any indication but is currently marketed for the treatment of metastatic transitional (Urothelial) tract cancer, transitional Cell Carcinoma (Urothelial Cell Carcinoma) in the United States and Canada, and for non-small cell lung cancer in the United States alone.⁹

Cobimetinib is currently licenced in the EU for the treatment of metastatic melanoma (in combination with vemurafenib).¹⁰ The most common adverse effects (>10%) observed in a phase III study¹¹ that explored the safety and efficacy of cobimetinib in combination with vemurafenib were anaemia, serous retinopathy, blurred vision, hypertension, haemorrhage, diarrhoea, nausea, vomiting, photosensitivity, rash, maculopapular rash, dermatitis acneiform, hyperkeratosis pyrexia, and chills.¹²

Atezolizumab was fast-tracked under the UK's Early Access to Medicines Scheme (EAMS) for the treatment of urothelial carcinoma.⁹ Atezolizumab is also currently in phase III trials for a range of other cancers, alone and in combination, including:

- breast cancer,

- renal cell carcinoma (kidney cancer),
- non-small cell lung cancer,
- small cell lung cancer,
- advanced ovarian cancer,
- metastatic melanoma
- other solid tumours,
- multiple myeloma,
- diffuse large B-cell lymphoma (DLBCL) and
- paediatric cancers.

Cobimetinib is currently in phase III trials for metastatic melanoma and in phase II trials for haematological disorders, metastatic brain tumours and metastatic breast cancer.¹⁰

INNOVATION and/or ADVANTAGES

If licensed, atezolizumab in combination with cobimetinib will offer an additional treatment option for people with unresectable locally advanced or metastatic colorectal cancer who have received at least two prior regimens of cytotoxic chemotherapy for metastatic disease. This combination will potentially extend overall survival, progression-free survival and improve time to deterioration of key CRC symptoms.

DEVELOPER

F. Hoffmann-La Roche Ltd. (Roche Products Ltd.)

AVAILABILITY, LAUNCH or MARKETING

The combination of Atezolizumab and cobimetinib is not currently marketed in the EU for any indication.

PATIENT GROUP

BACKGROUND

Colorectal cancer (CRC) is a cancer that starts in the colon or the rectum.¹³ CRC is one of the most common types of cancers diagnosed; it is the third most common cancer among men and the second most common in women, worldwide.¹⁴ CRC is a high-mortality cancer, with mortality rates just behind lung, liver, and stomach cancers in men, and breast and lung cancers in women.¹⁵ Most cases of CRC present as adenocarcinomas, but other types of CRC include gastrointestinal carcinoid tumours, gastrointestinal stromal tumours, primary colorectal lymphoma, leiomyosarcoma, melanoma, and squamous cell carcinoma.¹⁶

CRC is associated with several well-established risk factors. While some of these risk factors, such as family history, personal history, having a chronic inflammatory bowel disease (IBD), increasing age, and being male, are non-modifiable, other lifestyle-related risk factors, such as smoking, diet, physical

inactivity, and alcohol intake, can be changed to reduce the risk of developing CRC.^{17, 18} The most common symptoms of CRC are rectal bleeding, blood in the stool, anaemia, abdominal discomfort, unexplained weight loss, pain in bowel movement, feeling the bowel does not empty fully, constipation and diarrhoea lasting more than several days.¹⁹

In advanced or metastatic CRC (mCRC), the disease has spread to a distant organ or a distant set of lymph nodes. The liver and the lungs are the most common sites of distant metastases for colon or rectal cancer; up to 50% of colorectal metastases occur in the liver only, and in about half of these the appearance is synchronous with the primary tumour.²⁰

CLINICAL NEED and BURDEN OF DISEASE

Most colorectal cancers develop slowly over a period of 10 to 20 years. CRC has a strong relationship with age, and it is most commonly diagnosed in patients older than 65 years.^{21, 22} In 2012, CRC accounted for almost 10% of the global cancer incidence burden.²³ The worldwide prevalence of CRC is estimated to be about 3.26 million in men and women that survive up to five years after their diagnosis.¹⁵

In the UK, the number of people living with and beyond a diagnosis of CRC is increasing, predicted to rise from 240,000 in 2010 to 630,000 by 2040.²⁴ Cancer Research UK estimated that around 41,265 new cases (approximately 110 cases diagnosed every day) of CRC were diagnosed in 2014.²⁵ The incidence of CRC in the UK is forecasted to grow by 1.72% annually to almost 50,000 new cases by 2025.²⁶

The Cancer Research UK data showed that there were 15,903 deaths (44 deaths every day) due to CRC in the UK and 57% of people diagnosed with CRC survive for 10 or more years in 2010-11, in England and Wales.²⁵ The number of people with advanced or metastatic CRC (mCRC) at diagnosis is estimated to be about 10,957, accounting for about 26% of all cases of CRC in the UK in 2015.^{27, 28}

The overall five-year relative survival of CRC patients in England is 50.7%.²⁹ The five-year survival decreases if the cancer is found at a more advanced stage. When diagnosed at its earliest stage, more than 9 in 10 people with bowel cancer will survive their disease for five years or more, compared with less than 1 in 10 people when diagnosed at the latest stage.²⁵

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal in development. Colorectal cancer (metastatic) - MABp1 (after previous treatment) [ID917] (GID-TA10065). Expected date of issue to be confirmed.
- NICE Technology appraisal in development. Nintedanib for previously treated metastatic colorectal cancer [ID1030] (GID-TA10138). Expected date of issue to be confirmed.
- NICE Technology appraisal in development. Pembrolizumab for previously treated metastatic colorectal cancer that has high microsatellite instability or mismatch repair deficiency [ID1071] (GID-TA10110) Expected date of issue to be confirmed.

- NICE Technology appraisal in development. Nivolumab for metastatic colorectal cancer with or without high microsatellite instability [ID1136] (GID-TA10165) Expected publication date: April 2018
- NICE Technology appraisal guidance. Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (TA439). March 2017
- NICE Technology appraisal guidance. Trifluridine–tipiracil for previously treated metastatic colorectal cancer (TA405). August 2016
- NICE Technology appraisal guidance. Regorafenib for metastatic colorectal cancer after treatment for metastatic disease (terminated appraisal) (TA334) February 2015
- NICE Technology appraisal guidance. Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy (Ta307) March 2014
- 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 in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (TA212). December 2010
- NICE Technology appraisal guidance. Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer (TA61). May 2003 NICE Clinical Guidelines - Colorectal cancer: diagnosis and management (update). (GID-NG10060) Expected publication date: 09 October 2019
- NICE Clinical Guidelines - 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. NICE Diagnostic guidance. Molecular testing strategies for Lynch syndrome in people with colorectal cancer. (DG27). February 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for colorectal: Cytoreductive surgery (Adult). A08/S/f
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- 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.

CURRENT TREATMENT OPTIONS

Multimodal treatment, namely the combination of chemotherapy and hepatic surgery, is the best therapeutic strategy for resectable and potentially resectable Stage IV patients. In mCRC patients,

chemotherapy rather than surgery is the standard of care. Treatment is prioritised to control symptoms if at any point the patient has symptoms from the primary tumour.³⁰

NICE recommends the following sequence of chemotherapy for mCRC:³⁰

- A) Oxaliplatin and irinotecan in combination with fluoropyrimidines
- FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment or
 - FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment or
 - XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment.
- B) Raltitrexed
- Consider raltitrexed only for patients with advanced colorectal cancer who are intolerant to 5-fluorouracil and folinic acid, or for whom these drugs are not suitable (for example, patients who develop cardiotoxicity). Fully discuss the risks and benefits of raltitrexed with the patient.
- C) Capecitabine and tegafur with uracil³¹
- Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer.
 - The choice of regimen (intravenous 5-fluorouracil and folinic acid or one of the oral therapies) should be made jointly by the individual and the clinician(s) responsible for treatment. The decision should be made after an informed discussion between the clinician(s) and the patient; this discussion should take into account contraindications and the side-effect profile of the agents as well as the clinical condition and preferences of the individual.
 - The use of capecitabine or tegafur with uracil to treat metastatic colorectal cancer should be supervised by oncologists who specialise in colorectal cancer.
- D) Biological agents in metastatic colorectal cancer.³²
- Cetuximab is recommended, within its marketing authorisation, as an option for previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in adults in combination with:
 - 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or
 - 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).³²
 - Panitumumab is recommended, within its marketing authorisation, as an option for previously untreated RAS wild-type metastatic colorectal cancer in adults in combination with:
 - FOLFOX or
 - FOLFIRI.
 - NICE does not recommend bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for people with metastatic colorectal cancer.³³

- E) Trifluridine–tipiracil is recommended, within its marketing authorisation, as an option for treating metastatic colorectal cancer, that is:
- in adults who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor (VEGF) agents and anti-epidermal growth factor receptor (EGFR) agents, or when these therapies are not suitable.³⁴

EFFICACY and SAFETY

Trial	COTEZO; IMblaze370, NCT02788279, GDCT0263583, EudraCT-2016-000202-11, GO30182; atezolizumab in combination with cobimetinib versus atezolizumab monotherapy versus regorafenib; phase III
Sponsor	F. Hoffmann-La Roche Ltd; Genentech Inc
Status	Ongoing, not recruiting
Source of Information	Trial registry, ⁸ company, ³⁵ GlobalData ⁹
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active-controlled, parallel assignment, no masking (open label)
Participants	n=360; age 18 years and older; colorectal cancer; unresectable locally advanced or metastatic; participants who have received at least two prior regimens of cytotoxic chemotherapy for metastatic disease.
Schedule	<p>Participants were randomised to one of 3 intervention arms:</p> <ol style="list-style-type: none"> 1. Experimental: atezolizumab Participants will receive atezolizumab monotherapy 1200 mg IV on day 1 in a 21-day cycle. 2. Experimental: cobimetinib + atezolizumab Participants will receive cobimetinib 60 milligram (mg) orally on days 1 to 21 plus atezolizumab 840 mg intravenous (IV) on day 1 and day 15 in a 28-day cycle. 3. Active Comparator: regorafenib Participants will receive regorafenib 160 mg orally on days 1 to 21 in a 28-day cycle. <p>Treatment in all of the 3 arms continued until disease progression according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1, unacceptable toxicity, death, participant's or physician decision's to withdraw, or pregnancy, whichever occurs first.</p>
Follow-up	Treatment cycle (as in schedule) continued until disease progression according to RECIST Version 1.1, unacceptable toxicity, death, participant's or physician decision's to withdraw, or pregnancy, whichever occurred first.
Primary Outcomes	Overall Survival (OS) [Time Frame: Baseline up to death (up to 3 years)]

Secondary Outcomes	Progression-free Survival (PFS) according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 [Time Frame: Baseline up to 3 years], Percentage of Participants with Investigator-assessed Objective Response of Complete Response (CR) or Partial Response (PR) per RECIST Version 1.1 [Time Frame: Baseline up to 3 years], Duration of Response (DOR) based on RECIST Version 1.1 [Time Frame: Baseline up to 3 years], Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life-C30 questionnaire (EORTC QLQ-C30) score [Time Frame: Baseline, 6-month survival follow-up (assessed up to 3 years)].
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Recruitment completed. Expected primary complete date is in February 2019.

ESTIMATED COST and IMPACT

COST

The cost of the drug is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|---|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other: | <input checked="" type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|--|---|
| <input checked="" type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
|--|---|

Other increase in costs

Other reduction in costs

Other

None identified

OTHER ISSUES

Clinical uncertainty or other research question identified

None identified

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