

**NIHR Innovation Observatory
Evidence Briefing: April 2018**

**Atezolizumab in combination with cobimetinib for
BRAF wild-type metastatic melanoma – first line**

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LAY SUMMARY

Melanoma is a type of skin cancer. Around half of melanomas will have changes to a gene called BRAF which has been known to increase the activity of the MEK/ERK pathway in the cells which causes growth and spread of cancer cells. The main sign of melanoma are changes to moles which can include changes in size, shape and colour of the mole and pain, bleeding or crusting of the mole. People who are most at risk of developing melanoma are those with genetic mutations (such as the BRAF mutation), those with fair skin who burn easily and those who are exposed to the sun or use sunbeds. In metastatic melanoma, the cancer has spread from the skin to other parts of the body.

The combination of atezolizumab (given by injection) and cobimetinib (given orally) is being developed specifically for metastatic melanoma. Atezolizumab works by activating immune cells to recognise and attack cancer cells and cobimetinib works by blocking the MEK/ERK pathway and so stops the cancer cells from growing. This combination has not been used together before in melanoma, but have shown potential to slow down the growth and spread of melanoma. If licenced atezolizumab and cobimetinib may provide a treatment option for people with metastatic melanoma who do not have BRAF mutations - known as BRAF wild-type metastatic melanoma.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. 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

Melanoma (BRAF wild-type, metastatic) – first line

TECHNOLOGY

DESCRIPTION

Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to programmed death-ligand 1 (PD-L1) (may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumor immune response in the tumour microenvironment). Atezolizumab provides a dual blockade of the PD-1 and B7.1 receptors found on T cells and antigen presenting cells, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumor immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist.¹

Cobimetinib (Cotellic) 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.²

It has been suggested that MEK inhibitors such as cobimetinib and anti-PDL antibodies such as atezolizumab may have a synergistic effect in the treatment of tumours. It is hypothesised that MEK inhibitors increases intratumoral T-cell accumulation and upregulate PDL1 expression by tumour cells, thereby sensitising the tumour to the inhibitory effect of anti-PD1 antibody.³

In the phase III clinical trial (NCT03273153), 840mg atezolizumab is administered by intravenous infusion on days 1 and 15 of a 28 day cycle and 60mg cobimetinib is administered orally once daily from days 1 to 21 of a 28 day cycle until investigator determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, pregnancy or whatever occurs first.⁴

Atezolizumab monotherapy is licenced for use in the EU for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible and for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.¹ The most common side effects (affecting more than 1 in 10 people) associated with treatment with atezolizumab monotherapy include: decreased appetite, dyspnoea, nausea, vomiting, diarrhoea, rash, pruritus, arthralgia, pyrexia, fatigue and asthenia.¹

Cobimetinib is licenced for use in combination with vemurafenib in the EU for the treatment of BRAF V600 mutation-positive melanoma tumour status confirmed by a validated test.² The most common side effects (affecting more than 1 in 10 people) associated with treatment with cobimetinib in combination with vemurafenib include: anaemia, serous retinopathy, blurred vision, hypertension, haemorrhage, diarrhoea, nausea, vomiting, photosensitivity, rash, rash maculo-papular, dermatitis acneiform, hyperkeratosis, pyrexia and chills.²

The combination of atezolizumab and cobimetinib has not been licenced for the treatment of any indication in the EU.^{1,2}

Atezolizumab in combination with Cobimetinib are currently in development for a range of other cancer indications, e.g. metastatic pancreatic ductal adenocarcinoma⁵, pre-operation, ER+, HER2-breast cancer⁶ and unresectable metastatic bile duct cancer⁷.

INNOVATION and/or ADVANTAGES

If licensed, atezolizumab and cobimetinib will offer an additional treatment option for patients with BRAF wild type, advanced (Stage IIIc and IV) melanoma. Treatments for this patient group have been identified as an unmet need by key opinion leaders:⁸

“[A main clinical unmet need is that we don’t have] something with a decent response rate in the BRAF wild-type patients.”

EU Key Opinion Leader

DEVELOPER

Roche Products Ltd

REGULATORY INFORMATION/ MARKETING PLANS

Atezolizumab in combination with cobimetinib is a designated orphan drug in the USA for treatment of patients with stage IIIb, IIIc and IV melanoma.⁹

PATIENT GROUP

BACKGROUND

Melanoma is a type of skin cancer which originates in a type of cell called melanocytes between the dermis and epidermis layers of the skin.¹⁰ About 50% of melanomas are associated with mutations in the BRAF (serine/threonine-protein kinase B-Raf) gene, with BRAFV600E being the most common mutation, accounting for 90% BRAF mutations.¹¹

The earlier melanomas are identified, the easier they are to treat. The most recognisable sign of melanoma are the development of new moles or changes to existing moles, including: increase in size, change of shape (particularly development of an irregular edge), change of colour (e.g. getting darker, more patchy or multishaded – especially those with 3 or more different shaded of brown or black), loss of symmetry, itching or pain, bleeding and crusting and looking inflamed. Melanomas in men are most common on the back (accounting for 38% cases in men) and in women are most common on the legs (accounting for 42% cases in women).¹²

The main risk factor of melanoma is ultra-violet (UV) radiation exposure, through exposure to the sun or sunbeds. Exposure to UV radiation leads to can cause damage to the DNA within skin cells which over time can accumulate, leading to uncontrolled cell growth and cancer.¹⁰ Other risk factors for development of melanoma include: having fair skin and freckling, sun exposure during childhood, intermittent sun exposure, sunburn, sunbed use, having more moles in the body, genetics (e.g. familial atypical multiple mole melanoma syndrome and mutations of the CDKN2A gene) and a personal history of melanoma or other cancers.¹³

The stage of melanoma describes how deeply it has grown into the skin and whether it has spread. At stage I and II, there is no evidence that the tumour has spread anywhere else in the body, although there is a possibility of microscopic spread. At these early stages melanoma is normally asymptomatic and can often be cured by surgery (resection). Stage III melanoma means that the melanoma cells have spread into skin, lymph vessels, or lymph glands close to the melanoma. Stage III melanomas are considered intermediate to high risk as they more likely to spread to other distant parts of the body (stage IV melanoma) than in earlier melanoma stages.¹⁴

CLINICAL NEED and BURDEN OF DISEASE

Melanoma is the 5th most common cancer in the UK, accounting for 4% of all new cancer cases. Approximately 50% melanoma cases will not contain a BRAF mutation.¹¹

The age standardised incidence rate of melanoma in the UK in 2015 was 26 per 100,000 people, equivalent to 15,906 new cases. Of the approximately 70% cases of melanoma where a stage of disease at diagnosis is recorded, 9% were diagnosed at stage III-IV. Incidence rates of melanoma are projected to rise by 7% in the UK between 2014 and 2035.¹⁵

In 2011 to 2015, there were 58,129 people in the UK with malignant melanoma. Of these, the 1 year survival rate was 97.8% and the 5 year survival rate was 91.7%.¹⁶ Survival rates for melanoma are strongly correlated with stage at diagnosis with 1 year survival rate 100% in men and women with stage I melanoma compared with 92% and 47% survival in men and 96% and 54% survival in women with stage III and IV melanoma respectively.¹⁷

In the UK in 2014 there were 2,459 deaths from malignant melanoma, accounting for 2% of total cancer deaths and, the age standardised mortality rate was 4 per 100,000 which is projected to fall by 15% by 2035.¹⁸

The 2016/2017 Hospital Episode Statistics recorded a total of 18,935 finished consultant episodes (FCE), 18,514 admissions, 15,255 day cases and 11,378 FCE bed days for malignant melanoma of skin (ICD-10: C43).¹⁹

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance proposed. Encorafenib in combination with binimetinib for treating advanced (unresectable or metastatic) BRAF V600 mutation – positive melanoma (GID-TA10217). Expected publication date TBC.
- NICE technology appraisal guidance in development. Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma (ID1226). Expected publication date 26 December 2018.
- NICE technology appraisal guidance. Cobimetinib in combination with Vemurafenib for treating unresectable or metastatic BRAF V600 mutation- positive melanoma (TA414). October 2016.
- NICE technology appraisal guidance. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation – positive malignant melanoma (TA 269). December 2012. Last updated January 2015.

- NICE technology appraisal guidance. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation – positive melanoma (TA321). October 2014.
- NICE guideline. Melanoma: assessment and management (NG14). July 2015.
- NICE quality standard. Skin cancer (QS130). September 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: skin (adult). A12/S/b.
- 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.

OTHER GUIDANCE

National Comprehensive Cancer Network (NCCN). NCCN Guidelines for patients: Melanoma. 2018.²⁰

European Dermatology Forum (EDF), European Association of Dermato-Oncology (EADO) and European Organisation for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – Update 2016. 2016²¹

European Society for Medical Oncology (ESMO). Cutaneous Melanoma: ESMO Clinical Practice Guidelines. 2015²²

British Association of Dermatologists. Revised U.K. guidelines for the management of cutaneous melanoma 2010. 2010.²³

CURRENT TREATMENT OPTIONS

Treatment of melanoma depends on the stage at diagnosis. Surgery (excision of the abnormal mole and surrounding skin) the main treatment for stage 0-II melanoma. Topical Imiquimod can be used for stage 0 melanoma if surgery to remove the entire lesion with a 0.5 cm clinical margin would lead to unacceptable disfigurement or morbidity²⁴ At the time of producing this briefing, adjuvant chemotherapy and immunotherapy following tumour removal are not widely used in UK practice.¹⁴

The first treatment option in those with stage III melanoma will be surgery to remove the abnormal mole and the surrounding area (wide local excision). In those with metastasis to the lymph nodes, surgery to remove the local lymph nodes (lymph node dissection) will be performed. In those with stage IIIb and IIIc melanoma radiotherapy may be offered if the risk reduction in cancer reoccurrence is thought to outweigh the potential adverse events. If the melanoma has spread between the main melanoma site and the lymph nodes (in-transit metastasis) surgery to remove the cancer is the first line treatment.

If surgery is not possible, the following can be offered: chemotherapy directly into the leg or arm where the melanoma is (known as isolated limb infusion or isolated limb perfusion), radiotherapy, chemotherapy combined with an electric current (electrochemotherapy), carbon dioxide laser or imiquimod cream.²⁵

There are several options for the treatment of stage IV melanoma, including:^{26, 24, 27, 28}

- Surgery
- Radiotherapy
- Anticancer therapies such as vemurafenib, Dabrafenib, ipilimumab, pembrolizumab, nivolumab, imiquimod cream, trametinib, cobimetinib
- Regional or Systemic Chemotherapy: decarbazine

EFFICACY and SAFETY

Trial	IMspire170, NCT03273153, EudraCT-2016-004387; Atezolizumab and Cobimetinib vs. pembrolizumab; phase III
Sponsor	Hoffmann-La Roche
Status	Ongoing - recruiting
Source of Information	Trial registry ⁴
Location	10 EU countries (incl UK), USA, Australia, Republic of Korea, New Zealand and Russian Federation.
Design	Randomised, active-controlled, parallel assignment
Participants	n=450 (planned); aged 18 years and older; melanoma; BRAFV600 wild-type status; stage IV (metastatic) or stage IIIc (unresectable); naive to prior systemic anti-cancer therapy
Schedule	<p>Participants were randomised to one of two treatment arms:</p> <ol style="list-style-type: none"> 1. 60mg of cobimetinib tablets taken orally once daily on a 21 days on, 7 days off schedule and 840mg atezolizumab given intravenously on day 1 and day 15 of a 28 day cycle until investigator-determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first. 2. 200mg of pembrolizumab administered intravenously every 3 weeks until investigator-determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first.
Follow-up	Active treatment until investigator-determined disease progression, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first.
Primary Outcomes	Progression Free Survival (PFS) as Determined by the Independent Review Committee (IRC) [Time Frame: Up to 7 years]
Secondary Outcomes	<ul style="list-style-type: none"> • PFS as Determined by the Investigator [Time Frame: Up to 7 years] • Objective Response Rate: defined as the % of participants with a complete response (CR) or a partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator through the use of RECIST v1.1 [Time Frame: Up to 7 years] • Disease Control Rate (DCR): defined as the proportion of participants with a CR, a PR, or stable disease at 16 weeks [Time Frame: Up to 7 years] • Overall Survival (OS): defined as the time from randomization to death from any cause [Time Frame: Up to 7 years] • Duration of Objective Response: defined as the time from the first occurrence of a documented objective response to disease progression, as

	<p>determined by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first [Time Frame: Up to 7 years]</p> <ul style="list-style-type: none"> • Two-year Landmark Survival [Time Frame: At 2 years] • Change From Baseline in Health-related Quality of Life (HRQoL) Scores [Time Frame: Up to 7 years] • Number of Participants with Adverse Events (AEs) [Time Frame: Up to 7 years] • Number of Participants with Abnormal Vital Signs: include temperature pulse rate, respiratory rate, and systolic and diastolic blood pressure. [Time Frame: Up to 7 years] • Number of Participants With Laboratory Abnormalities [Time Frame: Up to 7 years] • Plasma Concentration of Cobimetinib [Time Frame: Days 1 and 15 of Cycle 1] • Serum Concentration of Atezolizumab [Time Frame: Day 1 of Cycle 1, 2, 3 and 30 days after treatment discontinuation] • Percentage of Participants with Anti-drug Antibodies (ADAs) [Time Frame: Day 1 of Cycle 1, 2, 3 and 30 days after treatment discontinuation]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date is 30 October 2024

ESTIMATED COST and IMPACT

COST

Atezolizumab is marketed in the UK for the treatment of urothelial carcinoma and non-small cell lung cancer; a 1200mg vial (60mg/mL) costs £3808.²⁹

Cobimetinib is marketed in the UK for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma in combination with Vemurafenib; a pack of 63 20mg tablets costs £4276.³⁰

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 |
|---|---|

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: *additional costs for IV administration in clinic* Other reduction in costs

Other None identified

OTHER ISSUES

Clinical uncertainty or other research question identified None identified

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