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HEALTH TECHNOLOGY BRIEFING
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Atezolizumab in addition to cobimetinib and vemurafenib for BRAF mutated metastatic melanoma

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Developer/Company	Roche Products Ltd	**UKPS ID**	645036

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Atezolizumab in addition to cobimetinib and vemurafenib is in development for the treatment of BRAF mutated metastatic melanoma. Melanoma is a type of skin cancer which arises from the pigment cells (melanocytes) in the skin and is the most aggressive and life-threatening form of skin cancer. BRAF is a type of gene that drives rapid tumour growth and approximately half of all melanomas have mutations in the BRAF gene. Factors associated with a higher risk of developing melanoma include fair skin, exposure to sunlight and other sources of ultraviolet energy, and a history of sunburn or moles.

Atezolizumab is a type of immunotherapy that helps the body's immune system attack the cancer and interferes with the ability of tumour cells to grow and spread. Cobimetinib and vemurafenib are targeted therapies that block specific pathways to stop the growth of tumour cells in BRAF mutated melanoma. The addition of atezolizumab to cobimetinib and vemurafenib has the potential to optimize the sequencing of targeted therapy and immunotherapy for patients with BRAF mutant metastatic melanoma.

PROPOSED INDICATION

Treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.[1]

TECHNOLOGY

DESCRIPTION

Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to programmed death ligand 1 (PD-L1) and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour 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.[2]

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.[3] Vemurafenib (Zelboraf) is an inhibitor of BRAF serine-threonine kinase. Mutations in the BRAF gene result in constitutive activation of BRAF proteins, which can cause cell proliferation without associated growth factors.[4]

Atezolizumab in addition to cobimetinib and vemurafenib is in development for the treatment of unresectable, locally advanced or metastatic BRAF metastatic melanoma. In the run-in period of the clinical trial NCT02908672, participants randomised to the experimental arm receive vemurafenib 960 mg orally twice a day (PO BID) along with cobimetinib 60 mg orally once daily (PO QD) on days 1 to 21 followed by vemurafenib 720mg PO BID on days 22 to 28. From cycle 1 onwards participants receive atezolizumab 840 mg intravenous (IV) infusion on day 1 and 15, cobimetinib 60 mg PO QD on days 1 to 21, vemurafenib 720 mg PO BID on days 1 to 28 of each 28-day cycle. Study treatment continues until investigator-determined disease progression, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurs first.[1]

INNOVATION AND/OR ADVANTAGES

Combination therapy with BRAF and MEK inhibitors improves response, survival and cutaneous toxicity compared with BRAF inhibitor monotherapy, and are now standard of care. Immunotherapy with anti-PD-1 antibodies in metastatic melanoma is effective regardless of BRAF mutation status. BRAF fusion genes result from translocations involving intact BRAF kinase domains. These cause MAPK pathway activation in vitro and respond to MEK inhibition in vivo, showing promise as a novel molecular target in the 30% of patients without other identifiable driver mutations. Future gains in therapeutic benefit will result from combining targeted therapy with immunotherapy as well as optimizing the sequencing of targeted therapy and immunotherapy.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Atezolizumab in addition to cobimetinib and vemurafenib does not currently have a marketing authorisation for any indication in the EU/UK.

Cobimetinib is indicated for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.[3]

Atezolizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC):[2]

- after prior platinum-containing chemotherapy, or
- who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%

Atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.[2]

Atezolizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving atezolizumab.[2]

The most common adverse reactions (>10%) to atezolizumab as monotherapy were fatigue, decreased appetite, nausea, cough, dyspnoea, pyrexia, diarrhoea, rash, back pain, vomiting, asthenia, arthralgia, musculoskeletal pain, pruritus and urinary tract infection. The most common adverse reactions (≥20%) to atezolizumab given in combination with other agents were fatigue, rash, nausea, peripheral neuropathy, diarrhoea, arthralgia, constipation, decreased appetite, anaemia and musculoskeletal pain.[2]

PATIENT GROUP

DISEASE BACKGROUND

Malignant melanoma is the most aggressive and life-threatening form of skin cancer. It develops in the melanocytes, the cells that produce melanin, and has a very high tendency to spread to other parts of the body. Malignant melanoma occurs among all adequately studied racial and ethnic groups. The frequency of its occurrence is closely associated with the constitutive colour of the skin and depends on the geographical zone. Incidence among dark-skinned ethnic groups is 1 per 100,000 per year or less, but among light-skinned Caucasians up to 50 per 100,000 and higher in some areas of the world.[6]

The stage of melanoma refers to the thickness, depth of penetration, and the degree to which the melanoma has spread. More advanced melanomas (stages III and IV) have metastasised to other parts of the body.[7] Symptoms of advanced melanoma can develop years after the original melanoma was diagnosed and removed. The most common sign of melanoma is the appearance of a new mole or a change in an existing mole.[8] The symptoms also depend on which parts of the body the melanoma has spread to. General symptoms of advanced melanoma may include weight loss, loss of appetite and fatigue.[9]

Factors that are associated with a higher risk of developing melanoma include a fair complexion, exposure to sunlight and other sources of ultraviolet (UV) energy, and a history of sunburns or moles.[10]

BRAF mutations are found in just under half of patients with metastatic melanoma. The incidence of BRAF mutations decreases with age. Almost all patients <30 years with cutaneous melanoma have BRAF-mutant (BRAFm) melanoma. The V600E mutation occurs in between 70–90% of patients with BRAFm melanoma. The V600K is the second most common

(10–30%), occurring more frequently in older patients and those with chronic sun-damaged skin.[5]

CLINICAL NEED AND BURDEN OF DISEASE

Melanoma is the third most common skin cancer in the UK. It accounts for more cancer deaths than all other skin cancers combined.[11] Furthermore, melanoma is the fifth most common cancer overall in the UK. Skin cancer rates in Great Britain are more than 4 times higher than they were in the late 1970s.[12]

In England in 2017 there were 13,740 registrations of newly diagnosed cases of malignant melanoma of skin (ICD-10 code C43).[13] Across the UK, the European age-standardised incidence rate for malignant melanoma is expected to increase by 7% between 2014 and 2035 to 32 cases per 100,000 people. It is projected that 22,175 cases of melanoma skin cancer (11,897 males, 10,278 females) will be diagnosed in the UK in 2035.[14]

In England in 2017/2018 there were 19,911 hospital admissions with a primary diagnosis of malignant melanoma of skin (ICD-10 code C43), 20,416 finished consultant episodes, resulting in 11,088 bed days and 16,650 day cases.[15]

In England and Wales in 2017 there were 2,106 deaths with malignant melanoma of skin (ICD-10 code C43) recorded as the underlying cause.[16] The latest published survival statistics for melanoma of skin (2016, patients diagnosed between 2012 and 2016) report 1-year survival rate of 98% and 5-year survival rate of 91.6% (age-standardised).[17]

More melanoma skin cancer patients with a known stage are diagnosed at an early stage (91% are diagnosed at stage I or II), than a late stage (9% are diagnosed at stage III or IV). Late stage at diagnosis is associated with higher deprivation. Among adults aged 15-99 years in England, 10% of those in the most deprived areas are diagnosed at stage III or IV, versus 8% in the least deprived areas. Late stage melanoma is more common in adults aged 60-79 years (10% diagnosed at stage III or IV) versus those aged 15-59 years (8% diagnosed at stage III or IV). Late stage diagnosis is more common in males in England. Among adults aged 15-99 years, 10% of males are diagnosed at stage III or IV versus 7% of females.[18]

Survival statistics fall with more advanced stages of melanoma. Around 50% of people diagnosed with stage III melanoma will be alive 5 years later. At stage IV, five-year relative survival is around 8% in men and around 25% in women.[19] The disease-free interval between primary and metastatic disease is shorter in patients with V600K compared with V600E BRAF melanoma; however, the evidence on overall survival in established metastatic disease is conflicting.[5]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Advanced or metastatic melanoma is currently treated using systemic anticancer treatments such as targeted therapies, immunotherapy or cytotoxic chemotherapy. Completion lymphadenectomy for people whose sentinel lymph node biopsy shows micro-metastases should be considered in addition to therapeutic lymph node dissection for people with palpable stage IIIB-IIIC melanoma or nodal disease detected by imaging.[11]

Management of unresectable or metastatic BRAF V600 mutant melanoma is changing rapidly with the availability of new immunotherapy and other treatments, however, it is difficult to

determine the position of immunotherapy and targeted therapies in the care pathway for mutation-positive melanoma. There is no consensus on whether first-line treatment should be targeted therapies or immunotherapies.[20]

CURRENT TREATMENT OPTIONS

For unresectable or metastatic BRAF V600 mutant melanoma, NICE guidelines recommend the following targeted therapy options in adults:[21]

- Encorafenib with binimetinib
- Trametinib with dabrafenib
- Dabrafenib
- Vemurafenib

The following immunotherapies are recommended by NICE for treating previously untreated advanced melanoma;[21]

- Nivolumab with ipilimumab
- Nivolumab monotherapy
- Pembrolizumab monotherapy
- Ipilimumab monotherapy

The following immunotherapies are recommended by NICE for treating previously treated advanced melanoma;[21]

- Pembrolizumab after ipilimumab
- Ipilimumab monotherapy

PLACE OF TECHNOLOGY

If licensed, atezolizumab in addition to cobimetinib and vemurafenib may offer an additional treatment option for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

CLINICAL TRIAL INFORMATION

Trial	**TRILOGY, NCT02908672, EudraCT2016-002482-54; atezolizumab in addition to cobimetinib and vemurafenib and vemurafenib placebo vs atezolizumab placebo in addition to cobimetinib and vemurafenib; phase III**
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[1]
Location	EU (incl UK), USA, Canada, and other countries
Design	Randomised, double-blind, placebo-controlled
Participants	n=513; ≥ 18 years of age; previously untreated BRAFV600 mutation-positive; unresectable, locally advanced or metastatic melanoma
Schedule	Randomised to one of two experimental arms: 1) Atezolizumab + cobimetinib + vemurafenib + vemurafenib placebo • **Run-In Period (Cycle 1=28 days)**: Subjects receive 960 mg of atezolizumab (four, 240 mg tablets) twice a day orally, 60 mg of cobimetinib (three, 20 mg tablets) four time a day orally on Days 1 to 21, 720 mg of vemurafenib (three, 240 mg tablets) twice a day on

	Days 22 to 28 and vemurafenib placebo (1 tablet) twice a day orally on Days 22 to 28 • **Triple Combination Period (Cycle 2 onwards):** Subjects receive 840 mg of atezolizumab intravenous infusion on Day 1 and 15, 60 mg of cobimetinib (three, 20 mg tablets) four time a day orally on Days 1 to 21, 720 mg of vemurafenib (three, 240 mg tablets) twice a day orally on Days 1 to 28, and vemurafenib placebo (1 tablet) twice a day orally on Days 1 to 28 of each 28-day cycle 2) Atezolizumab placebo + cobimetinib + vemurafenib • **Run-In Period (Cycle 1=28 days):** Subjects receive 960 mg of vemurafenib (four, 240 mg tablets) twice a day orally, 60 mg of cobimetinib (three, 20 mg tablets) once a day orally on Days 1 to 21, 960 mg of vemurafenib (four, 240 mg tablets) twice a day orally on Days 22 to 28 • **Triple Combination Period (Cycle 2 onwards):** Subjects receive atezolizumab placebo intravenous infusion on Day 1 and 15, 60 mg of cobimetinib (three, 20 mg tablets) once a day orally on Days 1 to 21 and 960 mg of vemurafenib (four, 240 mg tablets) twice a day orally on Days 1 to 28 of each 28-day cycle
Follow-up	Up to approximately 90 months
Primary Outcomes	Time frame: Baseline up to disease progression or death due to any cause, whichever occurs first (up to approximately 90 months) • Progression-Free Survival (PFS), as determined by Investigator using Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1
Secondary Outcomes	Time frame: Baseline up to disease progression or death due to any cause, whichever occurs first (up to approximately 90 months) • Progression-Free Survival (PFS), as determined by Independent Review Committee using RECIST v1.1 • Percentage of participants with objective response, as determined by Investigator using RECIST v1.1 • Duration of response, as determined by Investigator using RECIST v1.1 • Overall survival Time frame: 2 years • Percentage of participants who have survived at 2 years Time frame: Baseline up to end of treatment (approximately 90 months) • Time to deterioration in global health status using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status Scale Score • Time to deterioration in physical functioning using EORTC QLQ-C30 Physical Functioning Scale Score Time frame: Baseline up to 6 months after the last dose of study treatment (approximately 90 months) • Percentage of participants with adverse events and serious adverse events Time frame: Pre-infusion Day 1 of Cycles 1-4; 30 minutes post-infusion Day 1 of Cycles 1 and 4; at atezolizumab discontinuation (up to approximately 90 months)(1 Cycle = 28 days):

	• Serum Concentration of Atezolizumab Time frame: Pre-dose (0 hour) and 3 to 6 hours post dose on Day 15 of Cy 1 and 4 (1 Cy = 28 days) • Plasma concentration of cobimetinib • Plasma concentration of vemurafenib Time frame: Pre-infusion Day 1 of Cycles 1-4; at atezolizumab discontinuation (up to approximately 90 months)(1 Cycle=28 days) (approximately up to 90 months) • Percentage of participants with Anti-Drug Antibodies (ADA) to atezolizumab
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as October 2019. Estimated study completion date reported as July 2023.

ESTIMATED COST

The cost of atezolizumab 60mg/1ml concentrate for solution for infusion vial is £3807.69. The cost of cobimetinib (as cobimetinib hemifumarate) 20mg x 63 tablets is £4275.67, and vemurafenib 240mg x 56 tablets is £1750.00 (hospital only).[22,23,24]

RELEVANT GUIDANCE

NICE GUIDANCE

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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). NCCN Guidelines for patients: Melanoma. 2018.[25]
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ADDITIONAL INFORMATION

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