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HEALTH TECHNOLOGY BRIEFING
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Spartalizumab in addition to dabrafenib and trametinib for unresectable or metastatic BRAF V600 mutant melanoma – first-line

NIHRIO ID	23924	**NICE ID**	9959
Developer/Company	Novartis	**UKPS ID**	648356

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

SUMMARY

Spartalizumab in addition to dabrafenib and trametinib, is in clinical development for patients with previously untreated unresectable or metastatic BRAF V600 mutant melanoma. Malignant melanoma is the most aggressive and life-threatening form of skin cancer. General symptoms of advanced melanoma may include weight loss, loss of appetite and fatigue. Factors associated with a higher risk of developing melanoma include a fair skin, exposure to sunlight and other sources of ultraviolet (UV) energy, and a history of sunburn or moles.

Spartalizumab with dabrafenib and trametinib presents a new combination for this indication. Spartalizumab works by improving the activity of a type of white blood cells called T-cells thereby increasing the ability of the immune system to kill cancer cells. Dabrafenib inhibits a protein called BRAF which prevents tumour cells from growing. Trametinib inhibits the growth of cell lines with a mutation in BRAF protein. If licensed, spartalizumab in addition to dabrafenib and trametinib will offer an additional option for previously untreated patients with unresectable or metastatic BRAF V600 mutant melanoma.

PROPOSED INDICATION

Previously untreated patients with unresectable or metastatic BRAF V600 mutant melanoma – first-line.[1, a]

TECHNOLOGY

DESCRIPTION

Spartalizumab (PDR001) is a humanised monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed death-1 (PD-1, PCD-1), with immune checkpoint inhibitory and antineoplastic activities. Upon administration, spartalizumab binds to PD-1 expressed on activated T-cells and blocks the interaction with its ligands, programmed cell death 1 ligand 1 (PD-L1, PD-1L1) and PD-1 ligand 2 (PD-L2, PD-1L2). The inhibition of ligand binding prevents PD-1-mediated signalling and results in both T-cell activation and the induction of T-cell-mediated immune responses against tumour cells. PD-1, an immunoglobulin (Ig) superfamily transmembrane protein and inhibitory receptor, negatively regulates T-cell activation.[2]

In the phase III clinical trial (COMBI-i, NCT02967692) spartalizumab will be administered via intravenous infusion over 30 minutes (up to 2 hours) once every 4 or 8 weeks along with dabrafenib orally twice daily (150 mg) for days 1-28 of a 28-day cycle and trametinib orally once daily (2 mg) for days 1-28 of a 28-day cycle.[1]

INNOVATION AND/OR ADVANTAGES

Management of unresectable or metastatic BRAF V600 mutation-positive melanoma is changing rapidly with the availability of new immunotherapy and other targeted treatments, both of which improve the overall survival (OS) of patients with metastatic disease.[3,4]

Despite the recent progress with these agents, both therapeutic approaches have limitations. While BRAF inhibitors (BRAFis) and MEK inhibitors (MEKis) have a high overall response rate (ORR) in patients with BRAF mutated melanoma, their effect can be short-lived with the majority of patients developing resistance to these drugs and subsequent progressive disease. Immunotherapy agents can lead to durable responses for some patients, but the ORR is lower, and there is not a clear biomarker indicating which patients are more likely to benefit. There has been interest in combining targeted therapy and immunotherapy in patients with advanced disease due to the complementary strengths and weaknesses of these two therapeutic approaches. Additionally, preclinical and clinical data have shown that BRAFis and MEKis affect the tumour microenvironment and tumour immunogenicity in many ways, providing further support for the investigation of combinations with immunotherapy.[4]

The combination of the BRAF V600 inhibitor dabrafenib and the MEK inhibitor trametinib have induced deep and rapid responses that have extended survival to 3 years or longer for this patient population.[5] Preliminary results from COMBI-i indicate that spartalizumab can be combined with dabrafenib and trametinib with a manageable safety profile and demonstrate promising activity in patients with *BRAF* V600–mutant melanoma.[6]

[a] Information provided by Novartis on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Spartalizumab does not currently have Marketing Authorisation in the EU/UK for any indication as monotherapy or combination therapy.

Dabrafenib and trametinib are licensed in the UK as monotherapy or in combination with each other for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.[7,8]

Dabrafenib in combination with trametinib are indicated for the adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection and for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.[7,8]

Common or very common side effects of dabrafenib include alopecia; decreased appetite; arthralgia; asthenia; chills; constipation; cough; diarrhoea; fever; headache; hyperglycaemia; hypophosphataemia; influenza-like illness; myalgia; nausea; neoplasms; pain in extremity; photosensitivity reaction; skin reactions and vomiting.[9]

Common or very common side effects of trametinib include abdominal pain; alopecia; anaemia; asthenia; bradycardia; constipation; cough; dehydration; diarrhoea; dry mouth; dyspnoea; eye inflammation; fever; haemorrhage; hypersensitivity; hypertension; increased risk of infection; intracranial haemorrhage; left ventricular dysfunction; lymphoedema; mucositis; nausea; oedema; respiratory disorders; skin reactions; stomatitis; vision disorders and vomiting.[10]

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.[11]

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.[12] Symptoms of advanced melanoma can develop years after the original melanoma was diagnosed and removed. For some people, a change to an existing mole or freckle, or a change in normal-looking skin is the first sign. 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.[13]

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.[14]

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.[15] 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.[16]

In England in 2017 there were 13,740 registrations of newly diagnosed cases of malignant melanoma of skin (ICD-10 code C43).[17] 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.[18]

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.[19]

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.[20] 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).[21]

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.[22]

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.[23]

NICE has estimated that the patient population for unresectable or metastatic BRAF V600 mutant melanoma is small (approximately 1,000 patients annually).[24]

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.[15]

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 targeted therapies in the care pathway for mutation-positive

melanoma. There is also no consensus on whether first-line treatment should be targeted therapies or immunotherapies.[3]

CURRENT TREATMENT OPTIONS

NICE has recommended the following treatment options for treating unresectable or metastatic BRAF V600 mutant melanoma:[25]

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

PLACE OF TECHNOLOGY

If licensed, spartalizumab in addition to dabrafenib and trametinib will offer an additional option for previously untreated patients with unresectable or metastatic BRAF V600 mutant melanoma.

CLINICAL TRIAL INFORMATION

Trial	**COMBI-i, NCT02967692, EudraCT 2016-002794-35; adults aged 18 yrs and older; spartalizumab vs placebo, both in combination with dabrafenib and trametinib; phase III**
Sponsor	Novartis Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry;[1,26] Abstract[6]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, placebo-controlled
Participants	n=538 (planned); adults aged 18 yrs and older; melanoma; BRAF V600 mutant; unresectable and/or metastatic; previously untreated
Schedule	Spartalizumab will be administered via intravenous infusion over 30 min (up to 2 hrs) once every 4 or 8 wks. Dabrafenib will be administered orally twice daily (150 mg) for days 1-28 of a 28-day cycle. Trametinib will be administered orally once daily (2 mg) for days 1-28 of a 28-day cycle.
Follow-up	Active treatment for 2 yrs, follow-up 5 yrs
Primary Outcomes	• Safety Run-In (Part 1): Incidence of dose limiting toxicities (DLTs) [Time frame: 8 wks] • Biomarker cohort (Part 2): Immune microenvironment and biomarker modulation [Time frame: 2 yrs] • Randomised (Part 3): Progression-Free Survival (PFS), investigator assessed by RECIST 1.1 [Time frame: Up to disease progression or death due to any cause, whichever occurs first (5 yrs)]
Secondary Outcomes	• Overall survival [Time frame: Up to death due to any cause (5 yrs)] • Overall response rate [Time frame: Up to disease progression or death due to any cause, whichever occurs first (5 yrs)]

	• Duration of response [Time frame: Up to disease progression or death due to any cause, whichever occurs first (5 yrs)] • Disease control rate [Time frame: Up to disease progression or death due to any cause, whichever occurs first (5 yrs)] • Global health status/quality of life score of the EORTC QLQ-C30 [Time frame: Up to 60 days post progression (5 yrs)] • Global health status/quality of life score of the FACT-M subscale [Time frame: Up to 60 days post progression (5 yrs)] • Global health status/quality of life score of the EQ-5D-5L [Time frame: Up to 60 days post progression (5 yrs)] • Time to 10 point definitive deterioration in overall quality of life score from EORTC QLQ-C30 [Time frame: Up to 60 days post progression (5 yrs)] • PFS by PD-L1 expression [Time frame: Up to disease progression or death due to any cause, whichever occurs first (5 yrs)] • OS by PD-L1 expression [Time frame: Up to disease progression or death due to any cause, whichever occurs first (5 yrs)]
Key Results	Preliminary results indicate that spartalizumab can be combined with dabrafenib and trametinib with a manageable safety profile and demonstrate promising activity in pts with BRAF V600 mutant melanoma. At data cut-off (16 Jul 2017; median follow-up, 2.7 mths), all 9 pts completed the 8-wk dose-limiting toxicity (DLT) period, during which 1 DLT (transaminitis [AST and ALT > 8 × ULN]; n = 1) occurred. All 9 pts responded: 3 (33%) achieved a complete response (confirmed, n = 1), and 6 (67%) had partial responses (confirmed, n = 1).
Adverse effects (AEs)	AEs of any grade occurring in > 3 pts included pyrexia (n = 9), headache (n = 6), chills (n = 4), and vomiting (n = 4). Grade 3/4 AEs reported in > 1 pt included hepatitis (n = 3), increased lipase (n = 2), and increased transaminases (n = 2). AEs leading to discontinuation occurred in 2 pts (22%; transaminitis, n = 1; grade 3 hepatitis, n = 1) who permanently discontinued spartalizumab but were still receiving dabrafenib and trametinib at the data cut-off.
Expected reporting date	Primary completion date reported as Sep 2019

ESTIMATED COST

The cost of spartalizumab is not yet known.

Dabrafenib is already marketed in the UK; a pack of 28 x 50mg capsules costs £933.33 and a pack of 28 x 75mg costs £1,400.[9]

Trametinib is also marketed in the UK, a pack of 30 x 0.5mg tablets costs £1,200 and a pack of 30 x 2mg tablets costs £4,800.[10]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma (TA562). February 2019.
- 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. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269). December 2012. Updated January 2015.
- NICE technology appraisal guidance. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA321). October 2014.
- NICE clinical guideline. Melanoma: assessment and management (NG14). July 2015.
- NICE quality standard. Skin cancer (QS130). September 2016.

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.[27]
- 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. 2016.[28]
- European Society for Medical Oncology (ESMO). Cutaneous Melanoma: ESMO Clinical Practice Guidelines. 2015.[29]

ADDITIONAL INFORMATION

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