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Pembrolizumab in combination with epacadostat for unresectable or metastatic melanoma

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LAY SUMMARY

Melanoma is a cancer of the skin and can occur anywhere on the skin. Unusual moles, exposure to sunlight and sunburn can affect the risk of having melanoma. When the cancer has spread into the bones, the lymph nodes or glands nearby it is said to be at the advanced (metastatic) stage. Often at this stage the cancer cannot be removed surgically (unresectable). Symptoms of metastatic melanoma may include weight loss, loss of appetite and feeling extremely tired (fatigued).

Pembrolizumab is a type of immunotherapy. It stimulates the body's immune system to fight cancer cells. Pembrolizumab targets and blocks a protein called PD-L1 on the surface of certain immune cells called T-cells. Blocking the PD-L1 protein triggers the T-cells to find and kill cancer cells. Epacadostat is an agent that blocks an enzyme called IDO1, which is implicated in the growth and spread of cancer cells. Pembrolizumab is administered by injection while epacadostat is administered orally. If approved, pembrolizumab and epacadostat have the potential to prolong survival without cancer progression in patients with metastatic or unresectable malignant melanoma who have not been treated previously.

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TARGET GROUP

Malignant melanoma (unresectable or metastatic) – first-line; in combination with epacadostat

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda®; MK-3475; SCH-900475) is a humanized monoclonal immunoglobulin (Ig) G4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1) with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, pembrolizumab binds to PD-1, an inhibitory signalling receptor expressed on the surface of activated T-cells, and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumour cells. The ligands for PD-1 include programmed cell death ligand 1 (PD-L1), overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on antigen-presenting cells (APCs). Activated PD-1 negatively regulates T-cell activation and plays a key role in tumour evasion from host immunity.[1]

Epacadostat (INCB-024360) is an inhibitor of indoleamine 2,3-dioxygenase (IDO1), with potential immunomodulating and antineoplastic activities. Epacadostat targets and binds to IDO1, an enzyme responsible for the oxidation of tryptophan into kynurenine. By inhibiting IDO1 and decreasing kynurenine in tumour cells, epacadostat increases and restores the proliferation and activation of various immune cells, including dendritic cells (DCs), NK cells and T-lymphocytes, as well as interferon (IFN) production, and a reduction in tumour-associated regulatory T-cells (Tregs). Activation of the immune system, which is suppressed in many cancers, inhibits the growth of IDO1-expressing tumour cells.[5]

In the ongoing phase III trial (NCT02752074), pembrolizumab is administered intravenously every 3 weeks starting at Day 1 in combination with epacadostat that is administered orally daily starting at Day 1 (doses and treatment duration not reported).[2]

Pembrolizumab is currently licensed in the EU under its commercial name Keytruda for the following indications:

- As monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- As monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
- As monotherapy is indicated for the treatment of 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.
- As monotherapy is indicated for the treatment of 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.

- As monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- As monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.[3]

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 relate to the activity of the immune system causing inflammation of body organs. Most will resolve following appropriate treatment or on stopping pembrolizumab.[4]

Additional Phase III trials of pembrolizumab are registered for the following indications:

- Head/Neck 1L: NCT02358031;
- Head/Neck 2L: NCT02252042;
- Gastric/Gastroesophageal 2L: NCT02370498;
- Colorectal 1L: NCT02563002;
- Esophageal/Esophagogastric 2L: NCT02564263;
- Multiple Myeloma 1L: NCT02579863 (on clinical hold);
- Multiple Myeloma 3L or beyond: NCT02576977 (on clinical hold);
- Bladder/Renal 1L: NCT02853305;
- Bladder/Renal 2L: NCT02256436;
- Mesothelioma 2L: NCT02991482;
- Hepatocellular Carcinoma 2L: NCT02702401;
- Small Cell Lung Cancer 1L: NCT03066778.

Pembrolizumab in combination with epacadostat is currently under development for the treatment of metastatic renal cell carcinoma, non-small cell lung cancer, bladder cancer and recurrent or metastatic head and neck squamous cell carcinoma.[5]

Epacadostat is not currently licenced in the EU for any indication.[6]

INNOVATION and/or ADVANTAGES

Drugs like pembrolizumab that target the PD-1 pathway may provide antitumor immunity, especially in PD-L1 positive tumours. Various cancers, such as melanoma, hepatocellular carcinoma, glioblastoma, lung, kidney, breast, ovarian, pancreatic, and oesophageal cancers, as well as haematological malignancies, have positive PD-L1 expression, and this expression has been correlated with poor prognosis.[7]

Epacadostat has a different mechanism of action that blocks an enzyme called IDO1, which is implicated in the growth and spread of cancer cells.

The pembrolizumab and epacadostat combination therapy has the potential to prolong the time without cancer progression through the combined mechanisms of action.[8] If licensed, pembrolizumab in combination with epacadostat will offer an additional treatment option for first-line treatment of patients with unresectable or metastatic malignant melanoma.

DEVELOPER

Merck Sharp & Dohme Corp. and Incyte Corp.

AVAILABILITY, LAUNCH or MARKETING

Pembrolizumab has been designated by the U.S. Food and Drug Administration as a breakthrough therapy and orphan drug for a number of different indications.[9] In the EU, pembrolizumab has been approved to treat advanced cases of melanoma, non-small cell lung cancer, and Classical Hodgkin Lymphoma.[10]

Epacadostat was designated an orphan drug in the USA for metastatic melanoma in 2016.[11]

BACKGROUND

Cutaneous melanoma is a cancer of the skin. In its early stages, melanoma is normally asymptomatic and can often be cured by surgery (resection). However, it can spread or metastasise to nearby lymph nodes (stage III) or to other parts of the body (stage IV). Most melanomas occur in people with pale skin. Risk factors include: skin that tends to burn in the sun, having several moles, intermittent sun exposure and sunburn.[12] The risk of melanoma also increases with age; it is more common in older people. Around half of people diagnosed in the UK with melanoma are aged 65 and over. However, younger people can also develop it and it is now the second most common cancer in adults under the age of 50.[13]

The stage of melanoma describes how deeply it has grown into the skin and whether it has spread. At stages 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. Stage III melanoma indicates 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 are more likely to spread to other distant parts of the body (stage IV melanoma) than earlier melanoma stages.[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.[14] General symptoms of advanced melanoma may include weight loss, loss of appetite and fatigue.[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.[11]

In 2014, there were 15,419 new cases of melanoma skin cancer in the UK of which 7,717 (~50%) were in males and 7,702 (~50%) in females. The crude incidence rate shows that there are 24 new melanoma skin cancer cases for every 100,000 males in the UK and 24 for every 100,000 females.[13] There were around 2,500 malignant melanoma deaths in the UK in 2014.[13]

Survival for melanoma skin cancer is strongly related to stage of the disease at diagnosis. Five-year survival rates for melanoma skin cancer show a gradual decrease in survival between Stages I and IV. In men, five-year relative survival ranges from more than 100% at Stage I to 8% at Stage IV for patients diagnosed during 2002-2006 in the former Anglia Cancer Network.[13] In women, five-year survival ranges from 100% at Stage I to 25% at Stage IV.[13] At stage III, five-year survival rates in men and women are estimated to be around 50 and 55%.[12]

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 code C43).[16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (TA357). October 2015.
- NICE technology appraisal. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (TA319). July 2014.
- NICE clinical guideline. Melanoma: assessment and management (NG14). July 2015.
- NICE quality standard. Skin cancer (QS130). September 2016.
- NICE public health guidance. Skin cancer prevention (PH32). January 2011.

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: Chemotherapy (Children, Teenagers and Young Adults). B15/S/b.
- NHS England. 2013/14 NHS standard contract for cancer: skin (adult). A12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England Manual for Prescribed Specialised Services 2016/17. Chapter 105. Specialist cancer services (adults).
- Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1–5.

OTHER GUIDANCE

- Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G and Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. 2015. *Annals of Oncology* 26 (Sup 5):v126-132.

CURRENT TREATMENT OPTIONS

Surgery (tumour removal and wide local excision) is the main treatment for early (stage I) and medium stage (stage II and III) melanoma. Surgical removal of lymph nodes is also considered if there is evidence of microscopic spread. Early recognition of melanoma and accurate diagnosis present the

best opportunities for cure. Adjuvant chemotherapy and immunotherapy following tumour removal are not widely used in UK practice.[12]

The recommendations for first-line treatment of metastatic disease are under debate. Reasonable approaches include antiPD1 therapies and, for BRAF-mutated melanomas, combinations of BRAF inhibitors with MEK inhibitors. BRAFi/MEKi inhibitor combos offer high response rates (70%) and rapid response induction associated with symptom control, with a progression-free survival (PFS) of ~12 months. Anti-PD1 therapy, and to a lesser extent ipilimumab, offer lower response rates in the range, but many responses are durable.[17]

EFFICACY and SAFETY

Trial	Keynote-252 / ECHO-301, NCT02752074; pembrolizumab + epacadostat vs. pembrolizumab + placebo; phase III
Sponsor	Incyte Corporation and Merck Sharp & Dohme Corp.
Status	Ongoing
Source of Information	Trial registry[18]
Location	11 EU (incl. UK), Australia, Canada, Chile, Israel, Japan, Republic of Korea, Mexico, New Zealand, Russian Federation, South Africa, Switzerland, United States.
Design	Randomised, placebo-controlled
Participants	N=706; aged 18 onwards; male and female; melanoma, unresectable stage III or IV.
Schedule	Randomised to pembrolizumab administered intravenously every 3 weeks starting at Day 1 (Week 1) + epacadostat administered orally daily starting at Day 1 (Week 1) or pembrolizumab administered intravenously every 3 weeks starting at Day 1 (Week 1) + placebo administered orally daily starting at Day 1 (Week 1). Doses not reported.
Follow-up	Follow-up 2 years
Primary Outcomes	Progression-free survival Overall survival
Secondary Outcomes	Objective response rate Safety and tolerability
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study estimated primary completion date May 2018.

ESTIMATED COST and IMPACT

COST

Pembrolizumab is already marketed in the UK for the treatment of different types of cancers. The cost of pembrolizumab 25mg/1ml concentrate for solution for infusion vials is £2,630 (hospital only) and 50mg powder for solution for infusion is £1,315 (hospital only).[19]

The cost of epacadostat is not yet known.

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: *trial efficacy results not yet available*
- ☐ None identified

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