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PV-10 for locally advanced cutaneous melanoma

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LAY SUMMARY

Cutaneous melanoma is a type of skin cancer. It is the most aggressive and life-threatening form of skin cancer, and can appear anywhere on the body. Locally advanced cutaneous melanoma means the cancer has spread from the skin to the nearby tissue and lymph nodes. The symptoms of advanced melanoma may not appear until years after the diagnosis and removal of the original melanoma. For some people, a change to an existing mole or freckle, or a change in normal-looking skin is the first sign. General symptoms of advanced melanoma may include weight loss, loss of appetite and fatigue. Melanoma is the fifth most common cancer in the UK with a third of people diagnosed under the age of 55 years.

PV-10 is an investigational new medicinal product that contains 10% rose bengal disodium. PV-10 is given as an injection directly into the affected skin lesion. PV-10 acts by destroying tumour cells and inducing the body's immune response against tumour cells. PV-10 is being developed for the treatment of locally advanced cutaneous melanoma in patients who are not candidates for targeted therapy and/or an immune checkpoint inhibitor (treatments that help the body recognise and attack cancer cells). If licensed, PV-10 may offer a new treatment option for this patient group with a potential of durable local control and restricted toxicity to the injection site.

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TARGET GROUP

Melanoma (cutaneous, locally advanced); in patients not candidates for targeted therapy and not candidates for an immune checkpoint inhibitor).

TECHNOLOGY

DESCRIPTION

PV-10 (10% rose bengal disodium) is an investigational new drug that contains a sterile, nonpyrogenic 10% solution of rose bengal in 0.9% saline. Rose bengal disodium is currently in use as a pink stain for diagnosing suspected damage to conjunctival and corneal cells. PV-10 is a small molecule agent for intralesional (IL) injection into tumours. After IL injection, PV-10 accumulates in tumour lysosomes resulting in rapid lysis of tumour cells. This primary ablative effect may induce a secondary tumour-specific T cell–mediated antitumor immune response.[1,2,3]

In the phase III clinical trial (NCT02288897), subjects will receive IL PV-10 to all study lesions on study day 1. PV-10 would be re-administered at 28-day intervals until complete response, disease progression or study termination occurs. Details about PV-10 dose are not reported.[4] In the phase II clinical trial (NCT00521053), patients received a single IL injection of PV-10 to uniformly infiltrate each of up to 20 study lesions on day 0 (i.e., ≤10 target and ≤10 non-target dermal lesions) using 0.5 mL PV-10 per cm^3 of lesion volume. Treatment could be repeated at weeks 8, 12, and 16 for new non-target lesions or existing target or non-target lesions not exhibiting complete response. PV-10 was not injected into nodal or visceral lesions.[1,5]

PV-10 is not currently licensed for any indication in the EU/UK.[6,7]

INNOVATION and/or ADVANTAGES

There are currently few drug therapies that can provide rapid, sustained reduction of tumour burden with low toxicity. Results from the phase II trial showed that IL PV-10 yielded durable local control with high rates of complete response. Moreover, toxicity was confined predominantly to the injection site.[1] Additionally, acute exposure of antigenic tumour fragments to antigen presenting cells is thought to produce a bystander response in un-injected tumours. This mechanism is unique in that it leads to immediate reduction in tumour burden concomitant with immunological activation. A significant amount of PV-10 is required to ablate the cancer cells, which helps to explain why no hair loss or stomach lining problems have been observed to date in clinical trials.[8]

If licensed, PV-10 will offer a new treatment option, with potential for reduced systemic toxicity in patients with locally advanced cutaneous melanoma who are not candidates for targeted therapy and/or an immune checkpoint inhibitor.

DEVELOPER

Provectus Biopharmaceuticals, Inc.

REGULATORY INFORMATION/ MARKETING PLANS

PV-10 was designated an orphan drug in the USA for the treatment of metastatic melanoma in December 2006.[9]

PATIENT GROUP

BACKGROUND

Malignant melanoma is the most aggressive and life-threatening form of skin cancer. It develops in the cells that give the skin its colour (melanocytes) 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.[10]

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.[11] Mutations in a gene called BRAF (B-Raf proto-oncogene, serine/threonine kinase), occurs in almost 50% of melanoma cases. BRAF V600E mutations are the most frequently identified cancer-causing mutations in melanoma.[12,13]

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]

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.[15]

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.[16] 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.[17]

In England in 2016 there were 13,748 registrations of newly diagnosed cases of malignant melanoma of skin (ICD-10 code C43).[18] Across the UK, the European age-standardised incidence rate for malignant melanoma is expected to increase from 30.44 per 100,000 persons (15,413 cases) to 32.42 per 100,000 persons (22,175 cases) in 2035.[19]

In England in 2016/2017 there were 18,514 hospital admissions with a primary diagnosis of malignant melanoma of skin (ICD-10 code C43), resulting in 11,378 bed days and 15,255 day cases.[20]

In England and Wales in 2016 there were 2,080 deaths with malignant melanoma of skin (ICD-10 code C43) recorded as the underlying cause.[21] The latest published survival statistics for melanoma of skin (2016, patients diagnosed in 2011-2015) report 1-year survival rate of 97.8% and 5-year survival rate of 91.7% (age-standardised).[22] In 2012, the proportion of people in the UK diagnosed with melanoma at stage III disease was 3%. Five-year survival rates are approximately 50-55% for stage III disease.[23]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Nivolumab for adjuvant treatment of resected stage III and IV melanoma (GID-TA10286). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Pembrolizumab with epacadostat for untreated malignant melanoma (GID-TA10330). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence (GID-TA10247). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma (GID-TA10188). Expected December 2018.
- NICE technology appraisal. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (TA357). September 2017.
- NICE technology appraisal guidance. Nivolumab in combination with ipilimumab for treating advanced melanoma (TA400). July 2016.
- NICE technology appraisal guidance. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269). January 2015.
- NICE clinical 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: 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

- Scottish Intercollegiate Guidelines Network (SIGN). Cutaneous melanoma (SIGN 146). 2017.[24]
- European Society for Medical Oncology (ESMO). Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[25]

CURRENT TREATMENT OPTIONS

For stage III melanoma, NICE guidelines states:[16]

- Consider completion lymphadenectomy for people whose sentinel lymph node biopsy shows micro-metastases
- Offer therapeutic lymph node dissection to people with palpable stage IIIB–IIIC melanoma or nodal disease detected by imaging
- Do not offer adjuvant radiotherapy to people with stage IIIA melanoma
- Do not offer adjuvant radiotherapy to people with stage IIIB or IIIC melanoma unless a reduction in the risk of local recurrence is estimated to outweigh the risk of significant adverse effects
- Adjuvant chemotherapy and immunotherapy following tumour removal are not widely used in UK practice.[23]

EFFICACY and SAFETY

Trial	NCT02288897, **PV-10-MM-31; 18 years and older; PV-10 vs dacarbazine, temozolomide or talimogene laherparepvec; phase III**
Sponsor	Provectus Biopharmaceuticals, Inc
Status	Ongoing
Source of Information	Trial registry[4]
Location	EU (not UK), USA, Mexico, and Australia
Design	Randomised, active-controlled, parallel assignment
Participants	n=225 (planned); aged 18 years and older; melanoma; recurrent, satellite or in-transit locally advanced cutaneous or subcutaneous melanoma metastases; not a candidate for treatment with an immune checkpoint inhibitor; not a candidate for targeted therapy with BRAF or combined BRAF/MEK inhibitors.
Schedule	Randomised to: Intralesional PV-10 to all study lesions on study day 1. PV-10 should be re-administered at 28-day intervals until complete response, disease progression or study termination occurs. Or (a)Dacarbazine (intravenously at 850 m/m^2) or temozolomide (orally at 200 mg/m^2 daily for 5 consecutive days), administered at consecutive 28-day intervals, or (b) intralesional talimogene laherparepvec administered on an initial 21 interval followed by consecutive 14 day intervals, until complete response, disease progression or study termination occurs.
Follow-up	Active treatment period: until complete response, disease progression or study termination occurs. Follow up period: 18 months
Primary Outcomes	Progression-free survival (PFS) [Time frame: assessed every 12 weeks up to 18 months]

Secondary Outcomes	Time Frame: Assessed every 12 weeks up to 18 months - Complete response rate (CRR) - Duration of complete response - Overall survival (OS) Time Frame: Assessed every 4 weeks until 28 days after last treatment - Number of participants with adverse events
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as October 2018.

Trial	NCT00521053**, PV-10-MM-02; 18 years and older; PV-10; phase II**
Sponsor	Provectus Pharmaceuticals
Status	Published
Source of Information	Publication,[1] Trial registry[5]
Location	USA and Australia
Design	Single group assignment, open label
Participants	n=80; 18 years and older; melanoma; metastatic (stage III or stage IV)
Schedule	Patients received intralesional PV-10 into up to 20 cutaneous and subcutaneous lesions up to four times over a 16-week period
Follow-up	Active treatment period: 16 weeks Follow up period: 52 weeks
Primary Outcomes	Objective Response Rate (ORR) of PV-10 treated lesions [Time frame: 52 weeks]
Secondary Outcomes	Time frame: 52 weeks - Objective response rate of untreated bystander lesions - PFS - OS
Key Results	For target lesions, the best overall response rate was 51%, and the complete response rate was 26%. Median time to response was 1.9 months, and median duration of response was 4.0 months, with 8% of patients having no evidence of disease after 52 weeks. Response was dependent on untreated disease burden, with complete response achieved in 50% of patients receiving PV-10 to all of their disease. Response of target lesions correlated with bystander lesion regression and the occurrence of loco regional blistering. Intralesional PV-10 yielded durable local control with high rates of complete response. Toxicity was confined predominantly to the injection site. Cutaneous bystander tumour regression is consistent with an immunologic response secondary to ablation.[1]

Adverse effects (AEs)	Adverse events were predominantly mild to moderate and loco regional to the treatment site, with no treatment-associated grade 4 or 5 adverse events.[1]

ESTIMATED COST and IMPACT

COST

The cost of PV-10 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

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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