Velimogene aliplasmid (Allovectin)
for advanced or metastatic malignant melanoma

SUMMARY

Velimogene aliplasmid is intended to be used for the treatment of stage III or IV recurrent malignant melanoma in chemotherapy-naive patients. It can be delivered in an outpatient setting and if licensed, it will provide an additional treatment option for this patient group. Velimogene aliplasmid is a plasmid DNA-based immunotherapeutic designed to stimulate the immune response in local tumours and distal metastases.

Malignant melanoma is the fifth most common cancer in the UK with an age-standardised incidence rate of 17.2 and 17.3 per 100,000 population in males and females respectively. In 2010, there were 1,945 deaths registered in England and Wales. The prognosis for advanced disease is poor, with 5-year survival rates of approximately 40-50% for stage III disease and 7-20% for stage IV.

Current treatments include dacarbazine, temozolomide, ipilimumab or interferon alpha. Velimogene aliplasmid is currently in phase III clinical trials studying its effect on response rates and overall survival in combination with dacarbazine and against dacarbazine alone. Results are expected in Q2-3 2013.
TARGET GROUP

- Malignant melanoma: stage III or IV, recurrent, chemotherapy-naive.

TECHNOLOGY

DESCRIPTION

Velimogene aliplasmid (Allovectin; VCL-1005) is a plasmid DNA-based immunotherapeutic designed to stimulate both innate and adaptive immune responses in local tumours and distal metastases. It expresses two genes (HLA-B7 and β2 microglobulin) that together form an MHC class 1 complex. Velimogene aliplasmid primes the immune system to recognise and destroy tumour cells through an allogeneic anti-tumour response, restores tumour-associated antigen presentation via MHC class 1, and boosts the immune response through a lipid/DNA induced danger signal. In clinical trials, velimogene aliplasmid was administered via single site intralesional injection at 2mg, once weekly for 6 weeks, repeated after two weeks’ rest.

INNOVATION and/or ADVANTAGES

Velimogene aliplasmid can be delivered in an outpatient setting and does not require pre- or post-medication. If licensed, it will provide an additional treatment option for this patient group.

DEVELOPER

Vical Inc.

AVAILABILITY, LAUNCH OR MARKETING

Velimogene aliplasmid is a designated orphan drug in the USA and is in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Malignant melanoma is a type of skin cancer that arises from melanocyte cells and may develop from moles (nevi). The main risk factor for developing melanoma is exposure to ultraviolet radiation from natural or artificial sources, e.g. the sun or sunbeds. People with very fair skin, sun-sensitive skin, large numbers of nevi, dysplastic nevi, or a family history of malignant melanoma, have an increased risk of disease. Stage III melanoma describes tumours of any thickness, with or without ulceration that have spread to one or more lymph nodes. In stage IV (metastatic), the cancer has spread to distant sites, such as the lung, liver, brain, bone, soft tissue or gastrointestinal tract.
NHS or GOVERNMENT PRIORITY AREA


CLINICAL NEED and BURDEN OF DISEASE

The incidence of malignant melanoma has more than quadrupled over the last 30 years\(^4\) and it is the fifth most common cancer in the UK, accounting for 4% of all new cases\(^5\). In 2010, the overall age-standardised incidence rate for malignant melanoma in the UK was 17.2 and 17.3 per 100,000 population in males and females respectively\(^5\). The number of new cases registered in 2010 was 11,396 in England and Wales\(^5\). Incidence rates increase steadily with age, but are disproportionately high in young adults (15-34 years), with more than two people of this age group diagnosed every day in the UK\(^4\). Between 2008 and 2010, 957 young adults were affected, with an incidence rate range of 1.0-7.6 and 1.7-14.2 per 100,000 population in males and females respectively\(^5\).

Survival rates have been continually improving for the last 30 years, with an overall 5-year survival rate of 83.6% and 91.6% for males and females respectively\(^8\). The prognosis for advanced disease is poor, with 5-year survival rates of approximately 40-50% for stage III disease\(^7\) and 7-20% for stage IV disease\(^8\). Late stage diagnoses are more common in people aged over 65, with approximately 20% of those aged over 65 being diagnosed at a late stage, in comparison to around 7% of 15-64 year-olds\(^5\). 1,945 deaths from malignant melanoma were registered in England and Wales during 2010\(^9\), and in 2010-11, there were 13,035 hospital admissions in England, accounting for 13,362 finished consultant episodes and 13,849 bed days (ICD C43)\(^10\). The population likely to be eligible to receive velimogene aliplasmd could not be estimated from available sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Ipilimumab for previously treated unresectable stage III or IV malignant melanoma. (ID73). Expected date of issue to be confirmed\(^11\).
- NICE technology appraisal in development. Ipilimumab in combination with dacarbazine for previously untreated unresectable stage III or IV malignant melanoma. (ID74). Expected date of issue to be confirmed\(^12\).
- NICE technology appraisal in development. Vemurafenib for the treatment of unresectable locally advanced or metastatic BRAFV600 mutation positive malignant melanoma. (ID498). Expected December 2012\(^13\).
- NICE interventional procedure guidance in development. Electrochemotherapy for the treatment of malignant melanoma. Expected Spring 2013\(^16\).
- NICE public health guidance. Skin cancer prevention: information, resources and environmental changes. (PH32). January 2011\(^17\).
Other Guidance

- European Society for Medical Oncology. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2012^{18}.
- Royal College of Physicians. The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines. 2007^{20}.

EXISTING COMPARATORS and TREATMENTS

Treatment for advanced malignant melanoma aims to shrink or control the growth of primary and secondary tumours, and relieve associated symptoms^{22}. Current treatments for advanced disease include^{23,24}:

- Chemotherapy – dacarbazine, temozolomide, cisplatin, carboplatin, vinblastine, taxanes, carmustine, vemurafenib.
- Biological therapy – ipilimumb, interferon alpha, interleukin 2.
- Surgery – to remove the primary tumour, affected lymph nodes or secondary tumours.
- Radiotherapy – to shrink advanced tumours and reduce symptoms.
- Isolated limb perfusion – with melphalan, for recurrent disease within a limb.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00003647, CDR0000066736, VCL-1005-301; velimogene aliplasmid with or without dacarbazine; phase III.</th>
<th>NCT00395070, LX01-315; velimogene aliplasmid vs dacarbazine or temozolomide; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Vical.</td>
<td>Vical.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Abstract^{25}, trial registry^{26}.</td>
<td>Trial registry^{27}.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
<td>EU, USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=202; aged 18 years and older; malignant melanoma; stage III or IV; 1 or more unresectable metastatic tumours; dacarbazine indicated as first line chemotherapy; chemotherapy naive.</td>
<td>n=375; aged 18 years and older; malignant melanoma; stage III or IV; may have had previous surgery, radiation or biologic treatment; chemotherapy naive.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to dacarbazine, 800mg/m², IV, on day 0 of a 28 day cycle, with or without velimogene aliplasmid, 10µg, single site intratumoural injection on days 3 and 10 of a 28 day cycle.</td>
<td>Randomised to velimogene aliplasmid, 2mg intralesional injection into single lesion, once weekly for 6 weeks, repeated following 2 weeks rest, or dacarbazine, 1,000mg/m², IV, repeated every 28 days, or temozolomide, 150-200mg/m², oral, once daily for 5 days, repeated every 28 days.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment until disease progression; follow-up not reported.</td>
<td>Active treatment up to 24 months; follow-up until death.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Response rate; overall survival.</td>
<td>Response rate^{3}.</td>
</tr>
</tbody>
</table>

^{3} Overall response rate at ≥24 weeks after randomisation.
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<tr>
<th>Secondary outcome/s</th>
<th>Benefits; safety. No quality of life measurement included in trial outcomes.</th>
<th>Safety and tolerability; overall survival. No quality of life measurement included in trial outcomes.</th>
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<tbody>
<tr>
<td>Expected reporting date</td>
<td>Q2/3 2013.</td>
<td>Not reported.</td>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of velimogene aliplasmid is not yet known. The costs of selected treatments for advanced malignant melanoma are summarised below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit cost[^28]^b,28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dacarbazine</td>
<td>200-250mg/m² for 5 days every 21 days[^29]</td>
<td>£14.32 - £16.50 per cycle</td>
</tr>
<tr>
<td>Vemurafenib (Zelboraf)</td>
<td>960mg twice daily[^30]</td>
<td>£1,750 per week</td>
</tr>
<tr>
<td>Ipilimumab (Yervoy)</td>
<td>3mg/kg every 21 days[^31]</td>
<td>£18,750 per cycle</td>
</tr>
</tbody>
</table>

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- ☑ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☑ Other: *administration in an outpatient setting*
- ☑ No impact identified

**Impact on Services**

- ☐ Increased use of existing services
- ☐ Decreased use of existing services
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☑ Other: *administration in an outpatient setting*
- ☑ None identified

**Impact on Costs**

- ☐ 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:
- ☑ None identified

**REFERENCES**


[^28]: Based on average adult bodyweight of 77.9kg and body surface area of 1.88m². Assumes wastage.
11 National Institute for Health and Clinical Excellence. Ipilimumab for previously treated unresectable stage III or IV malignant melanoma (ID73). Technology appraisal in development. Expected date of issue to be confirmed.
12 National Institute for Health and Clinical Excellence. Ipilimumab in combination with dacarbazine for previously untreated unresectable stage III or IV malignant melanoma (ID74). Technology appraisal in development. Expected date of issue to be confirmed.


Electronic Medicines Compendium. Dacarbazine 100mg, 200mg, 500mg, 1000mg. http://www.medicines.org.uk/EMC/medicine/1088/SPC/Dacarbazine+100mg%2c+200mg%2c+500mg%2c+1000mg/ Accessed 29 October 2012.
