National Horizon Scanning Centre

Ipilimumab (MDX-010) for unresectable stage III or IV metastatic melanoma - first or second line treatment

April 2008

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Ipilimumab (MDX-010) for unresectable stage III or IV metastatic melanoma - first or second line treatment

Target group
- Metastatic melanoma – unresectable stage III or IV:
  - First line in combination with dacarbazine
  - Second line monotherapy

Technology description
Ipilimumab (MDX-010) is an intravenous (IV) fully-human anti-cytotoxic T-lymphocyte antigen-4 (anti-CTLA-4) monoclonal antibody. CTLA-4 is an inducible receptor expressed by T-lymphocytes which, when activated, inhibits T-lymphocyte proliferation and function. Ipilimumab blocks CTLA-4, preventing binding of B7 molecules which enables continued CD28-mediated enhancement of T-lymphocyte receptor signalling.

Ipilimumab is currently in phase II and III clinical trials for metastatic melanoma, and phase II clinical trials for lung cancer, prostate cancer, bladder cancer, breast cancer, and pancreatic cancer.

Innovation and/or advantages
Ipilimumab is a biologic agent with a novel mechanism of action and available survival data from phase II studies are promising.

Developer
Bristol-Myers Squibb; Medarex

Availability, launch or marketing dates, and licensing plans:
In phase III clinical trials.

NHS or Government priority area:
This topic is relevant to the NHS Cancer Plan (2000).

Relevant guidance
- NICE Cancer Service Guidance. Improving outcomes for people with skin tumours including melanoma. 2006¹.
- NICE Cancer Service Guidance. Improving supportive and palliative care for adults with cancer. 2004².
- SIGN. National clinical guideline on cutaneous melanoma. 2003³ (updated 2004).
- British Association of Dermatologists and the Melanoma Study Group. UK guidelines for the management of cutaneous melanoma. 2002⁴.
- Canadian clinical practice guideline (for the Program in Evidence-Based Care and Cancer Care Ontario): temozolomide for the treatment of metastatic melanoma. 2006⁵.
- Cutaneous malignant melanoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. 2007⁶.

Clinical need and burden of disease
The incidence of malignant melanoma is increasing in England and Wales, with rates doubling approximately every 10-20 years⁷. There were 7,363 new cases of malignant melanoma registered in England in 2004, and 1,622 deaths in England and Wales in 2005⁸. Although malignant melanoma prognosis and survival has improved over the
years, advanced disease still has limited treatment options and generally low survival rates. Younger patients tend to have higher survival rates than older patients; women have a higher survival and lower age-specific mortality rate than men, whilst higher survival rates have been noted in the most affluent, compared to the least affluent societal groups.

Five-year survival for stage III disease is around 40-50%, and for stage IV disease around 20-30% (median survival is between 6-9 months).

**Existing comparators and treatments**

Single-agent chemotherapy with dacarbazine (DTIC), an alkylating agent administered intravenously.

A 2007 Cochrane review found that cytotoxic alternatives to DTIC, including temozolomide, cisplatin, carboplatin, vinca alkaloids, taxanes and nitrosoureas had not been shown to improve on standard chemotherapy with DTIC. Combination chemotherapies had also failed to demonstrate any significant benefit, except for a small increase in response rates. Chemoimmunotherapy (e.g. DTIC combined with interleukin-2 or interferon) was not found to prolong survival compared to chemotherapy alone, and a short-term increase in clinical response was associated with a higher rate of serious adverse events.

**Efficacy and safety**

<table>
<thead>
<tr>
<th>Trial code, name, phase</th>
<th>CA184-024&lt;sup&gt;14&lt;/sup&gt;</th>
<th>Dacarbazine with ipilimumab vs. dacarbazine with placebo; phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA184-007&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Ipilimumab with or without budesonide; phase II.</td>
<td></td>
</tr>
<tr>
<td>Sponsor</td>
<td>BMS; Medarex.</td>
<td>BMS; Medarex.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Completed.</td>
</tr>
<tr>
<td>Location</td>
<td>Europe, USA, Canada, South America, Africa.</td>
<td></td>
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<tr>
<td></td>
<td>Europe, USA, Canada.</td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, double-blind, placebo control.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Randomised; double blind.</td>
<td></td>
</tr>
<tr>
<td>Participants in trial</td>
<td>n=500 (expected); adults; treatment naïve stage III or IV melanoma.</td>
<td></td>
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<tr>
<td></td>
<td>Randomised to:</td>
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<tr>
<td></td>
<td>Arm A: Ipilimumab 10mg/kg every 3 wks for 10 wks, then 10mg/kg every 12 wks starting at wk 24; and dacarbazine 850mg/m² every 3 wks for 22 wks; or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm B: Placebo given at the same schedule as ipilimumab in arm A and dacarbazine the same as in arm A.</td>
<td></td>
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<tr>
<td></td>
<td>n=110 (expected); adults; unresectable stage III or IV malignant melanoma.</td>
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<tr>
<td></td>
<td>Randomised to:</td>
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</tr>
<tr>
<td></td>
<td>Arm A: Ipilimumab with budesonide; or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm B: Ipilimumab without budesonide.</td>
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<tr>
<td>Follow-up</td>
<td>Until death or termination of study.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumour re-staging at week 24; then until death.</td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Progression free survival (PFS).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adverse events (diarrhoea grade 2,3,4).</td>
<td></td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Efficacy; safety; quality of life (QoL).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Safety; objective response rate; disease control rate; PFS; overall survival (OS).</td>
<td></td>
</tr>
<tr>
<td>Key results</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Expected reporting date</td>
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<tr>
<td>Adverse effects</td>
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<td></td>
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<tr>
<td>Trial code, name, phase</td>
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<td>Status</td>
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<td>CA184-02216, Ipilimumab</td>
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<td>CA184-00817, Ipilimumab</td>
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<td>CA184-02518, Extension study</td>
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<td>Ongoing</td>
</tr>
</tbody>
</table>

**Estimated cost and cost impact**

The cost of ipilimumab has not yet been determined.

Dacarbazine 850mg/m² IV once every 3 weeks for 22 weeks for an average 1.7m² person costs around £338 (assuming wastage). This does not include service costs associated with IV administration.

**Potential or intended impact – speculative**

**Patients**

- ☑ Reduced morbidity
- ☑ Reduced mortality or increased survival
- ☑ Quicker, earlier or more accurate diagnosis or identification of disease
- ☐ Other:
- ☐ Improved quality of life for patients and/or carers
- ☐ None identified

**Services**

- ☑ Increased use: an additional IV treatment option
- ☑ Service reorganisation required
- ☐ Staff or training required
- ☐ Decreased use
- ☐ Other:
- ☐ None identified

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References


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