Ipilimumab (Yervoy) for malignant melanoma – adjuvant therapy

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Ipilimumab (Yervoy) for malignant melanoma – adjuvant therapy

Target group
- Malignant melanoma: high risk stage III, completely resected – first line adjuvant therapy.

Technology description
Ipilimumab (Yervoy) is a T-cell potentiator which specifically blocks the inhibitory signal of STLA-4, resulting in T-cell activation, proliferation and lymphocyte infiltration into tumours, leading to tumour cell death. Ipilimumab is administered intravenously (IV) at 10mg/kg over 90 minutes, every 3 weeks for 4 doses, then every 12 weeks.

Ipilimumab is licensed in the EU for previously treated advanced (unresectable or metastatic) melanoma. Recognised adverse effects (AEs) include: decreased appetite, diarrhoea, vomiting, nausea, rash, pruritus, fatigue, injection site reaction and pyrexia. Ipilimumab is associated with immune-related adverse reactions which can be severe or life-threatening, involving the gastrointestinal, liver, skin, nervous, endocrine or other organ systems.

Ipilimumab is in phase III clinical trials for non-small cell lung (in combination with paclitaxel and carboplatin), prostate and small cell lung cancers, and in phase II trials for non-small cell lung (advanced) and urogenital cancers.

Innovation and/or advantages
If licensed, ipilimumab would offer an additional treatment option for this patient group.

Developer
Bristol-Myers Squibb Pharmaceuticals Limited.

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

NHS or Government priority area
This topic is relevant to Improving Outcomes: A Strategy for Cancer (2011).

Relevant guidance
- NICE public health guidance. Skin cancer prevention: information, resources and environmental changes. 2011.
- NICE cancer service guidance. Improving outcomes for people with skin tumours including melanoma. 2010.
Clinical need and burden of disease

Malignant melanoma is the least common but most serious type of skin cancer and the sixth most common cancer in the UK\(^9\). The incidence of malignant melanoma in the UK has more than quadrupled over the last 30 years\(^10\). In 2008, 10,295 new cases of malignant melanoma were registered in England and Wales\(^10\). Incidence rates increase steadily with age, but are disproportionately high in young adults (15-34 years); it is the second most common cancer in this age group with more than two young adults diagnosed every day in the UK\(^9\). In 2008, the overall age-standardised incidence rate for malignant melanoma in the UK was 15.9 and 16.5 per 100,000 population in males and females respectively\(^9\).

Survival rates have been continually improving for the last 30 years, with a 5-year survival rate of 81% for men and 90% for women\(^11\). Based on the updated AJCC\(^a\) melanoma staging criteria, multivariate analysis shows a 97% 5-year survival rate for stage IA disease, but the prognosis for stage IV with visceral metastases is poor, with only a 33% 1-year survival\(^12\). Prognosis is even worse if serum lactate dehydrogenase is elevated\(^13\). Approximately 93% of 15-64 year-olds and 80% of those aged over 64 years present with resectable, stage I/II disease\(^9\). In 2008, there were 1,839 registered deaths due to malignant melanoma in England and Wales\(^14\) and in 2010-11 there were 13,035 hospital admissions, accounting for 13,849 bed days\(^15\) (ICD10 C43).

Existing comparators and treatments

There is currently no standard adjuvant therapy\(^b\). A range of treatments may be used to treat malignant melanoma depending on the tumour stage and site among other factors. These include\(^6,16\):
- Surgery to remove melanoma, affected lymph nodes and secondary tumours.
- Chemotherapy with dacarbazine (DTIC), temozolomide, carboplatin, paclitaxel, vinblastine, carmustine – standard therapy for non-resectable/metastatic melanoma.
- Isolated limb perfusion with melphalan – for recurrent disease within a limb.
- Radiotherapy.
- Biological therapy with interferon alpha and interleukin-2 – use varies in UK.
- Ipilimumab and vemurafenib – for advanced disease (not recommended by NICE).

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00636168, CA184-029; EORTC 18071; adults; ipilimumab vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Bristol-Myers Squibb.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^17).</td>
</tr>
<tr>
<td>Location</td>
<td>EU (inc UK), USA, Canada, Australia and Russia.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=950 (planned); adults; complete resection of stage III melanoma with confirmed metastases to lymph node. Randomised to ipilimumab, IV, 10mg/kg, or placebo, 4 times every 21 days until week 24, then every 12 weeks until week 156, or until disease progression.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period 3 years; follow-up until distant progression and death.</td>
</tr>
</tbody>
</table>

\(^a\) AJCC – American Joint Committee on Cancer.

\(^b\) Expert correspondence
### Primary outcome
Recurrence-free survival.

### Secondary outcomes
Overall survival; distant metastases-free survival; quality of life adjusted survival.

### Expected reporting date
Not reported.

#### Estimated cost and cost impact
At current published prices, a single dose of ipilimumab at 10mg/kg costs £60,000 per dose\(^{18,c}\).

#### Claimed or potential impact – speculative

**Patients**
- **☑** Reduced mortality or increased length of survival
- **☑** Reduction in associated morbidity or improved quality of life for patients and/or carers
- **☐** Quicker, earlier or more accurate diagnosis or identification of disease
- **☐** None identified

**Services**
- **☐** Increased use
- **☐** Service organisation
- **☐** Staff requirements
- **☐** Decreased use
- **☐** Other:
- **☑** None identified

**Costs**
- **☑** Increased unit cost compared to alternative
- **☐** Increased costs: more patients coming for treatment
- **☐** Increased costs: capital investment needed
- **☐** New costs:
- **☐** Savings:
- **☐** Other:

**Other issues**
- **☐** Clinical uncertainty or other research question identified:
- **☑** None identified

### References


\(^{c}\) Based on an average weight of 76.9kg, assumes wastage.
13 Zhuang L, Scolyer RA, Murali R et al. Lactate dehydrogenase 5 expression in melanoma increases with disease progression and is associated with expression of Bcl-XL and Mcl-1, but not Bcl-2 proteins. Modern Pathology 2010;23:45-53.