Nivolumab with ipilimumab for advanced melanoma – first line

SUMMARY

Nivolumab is intended to be used in combination with ipilimumab as first line therapy for the treatment of advanced unresectable melanoma. If licensed, it will provide an additional treatment option for this patient group. Nivolumab is a fully human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1). PD-1 is expressed on the surface of activated lymphocytes and acts as part of an immune checkpoint pathway. Nivolumab does not currently have Marketing Authorisation in the EU for any indication, however, it is preregistration in the EU for advanced melanoma (first and subsequent line) and non-small cell lung cancer.

Melanoma is the fifth most common cancer in the UK, accounting for 4% of all new cases. In 2011, there were 11,121 new diagnoses in England, equating to an age-standardised incidence rate of 17.3 per 100,000 population. Melanoma is the second most common cancer in the 15-34 age group, and is almost twice as common in young women as in young men. Metastatic disease, which presents in around 10% of new diagnoses, is associated with an extremely poor prognosis, with a median survival of 6-10 months, and a five-year survival of 5-22%.

Current treatment options include biological therapy (vemurafenib, dabrafenib, ipilimumab), chemotherapy (dacarbazine, temozolomide, cisplatin or carboplatin), immunotherapy and radiotherapy. Nivolumab with and without ipilimumab is currently in phase III clinical trials comparing its effect on overall survival and progression free survival against treatment with ipilimumab. This trial is expected to complete in 2015.
TARGET GROUP

- Melanoma: advanced (stage III or IV); unresectable – first line; in combination with ipilimumab

TECHNOLOGY

DESCRIPTION

Nivolumab (MDX-1106, ONO-4538) is a fully human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1). PD-1 is expressed on the surface of activated lymphocytes and acts as part of an immune checkpoint pathway. PD-1 blockade by nivolumab may activate T-cell responses and promote an anti-tumour immune response. Ipilimumab is a recombinant, human anti-CTLA-4 monoclonal antibody. In clinical trials\(^1\), nivolumab was administered via intravenous (IV) infusion at 1mg/kg, with ipilimumab, IV, at 3mg/kg, both every 3 weeks for 4 doses, followed by nivolumab, IV, at 3mg/kg, every 2 weeks.

Nivolumab is preregistration in the EU for melanoma (advanced, first and subsequent line) and non-small cell lung cancer (metastatic, second and subsequent line). It is also in phase III clinical trials for head and neck cancer (metastatic, recurrent), melanoma (advanced, second and subsequent line), non-small cell lung cancer (advanced, first line, and metastatic, second and subsequent line), renal cancer (advanced or metastatic, second and subsequent line), and in phase II trials for diffuse large B cell lymphoma, follicular lymphoma, glioblastoma, Hodgkin’s disease, oesophageal cancer and ovarian cancer.

Ipilimumab is licensed in the EU for the treatment of advanced melanoma in adults. It is also in phase III clinical trials for advanced melanoma (adjuvant therapy and first line in metastatic disease), non-small cell lung cancer (combination therapy), prostate cancer, and small cell lung cancer, and in phase II trials for specific melanoma patient subgroups (brain metastases, and first line in children and adolescents), non-small cell lung cancer (metastatic disease), ovarian cancer and urogenital cancer.

INNOVATION and/or ADVANTAGES

If licensed, nivolumab with ipilimumab will offer an additional treatment option for this patient group.

DEVELOPER

Bristol-Myers Squibb.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.
**PARTIENT GROUP**

**BACKGROUND**

Melanoma is a type of cancer arising from melanocytes that most commonly occurs in the skin, although it may also manifest in the eye, or in tissues that line areas inside the body, such as the anus or rectum, nose, mouth, lungs or other areas. Whilst many melanomas arise in an existing mole (nevus), around half start with a change in normal-looking skin. Signs of melanoma in existing moles may include asymmetry, change of shape, change in colour and/or diameter, or an evolving appearance (including the area becoming raised or dome-shaped), itchiness, pain, bleeding or crustiness. The main risk factor for developing melanoma is exposure to ultraviolet radiation from natural sunlight or through the artificial light used in sunbeds. People with fair skin, sun-sensitive skin, large numbers of nevi, dysplastic nevi, reduced immunity, or a family history of malignant melanoma, have an increased risk of disease. Metastatic melanoma describes disease which has spread to other parts of the body, most commonly the lungs, liver or brain, bones, or to distant lymph nodes or areas of the skin.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:


**CLINICAL NEED and BURDEN OF DISEASE**

Melanoma is the fifth most common cancer in the UK, accounting for 4% of all new cases. Incidence has increased more than fivefold since the mid-1970s, and in 2011, there were 11,121 new diagnoses of melanoma in England, equating to an age-standardised incidence rate of 17.3 per 100,000 population. Incidence increases with age, however melanoma rates are disproportionately high in younger people, with more than one third of all cases occurring in people under the age of 55. Melanoma is the second most common cancer in the 15-34 age group, and is almost twice as common in young women as in young men. Metastatic disease, which presents in around 10% of new diagnoses, is associated with an extremely poor prognosis, with a median survival of 6-10 months and a five-year survival rate of 5-22%. In 2012-13, there were 14,194 hospital admissions in England due to melanoma (ICD10:C43), accounting for 14,510 finished consultant episodes and 12,022 bed days. In England and Wales, 1,920 deaths were registered during 2012-13.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Dabrafenib and trametinib for treating advanced unresectable or metastatic BRAF V600 mutation positive melanoma [ID605]. Expected date of issue to be confirmed.
• NICE technology appraisal in development. Melanoma (resected stage IV, high risk stage III) – ipilimumab (adjuvant) [ID721]. Expected date of issue to be confirmed.
• NICE technology appraisal in development. Paclitaxel (as albumin-bound nanoparticles) for the first line treatment of metastatic melanoma [ID570]. Suspended July 2014.
• NICE technology appraisal. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation positive melanoma (TA321). October 2014.
• NICE technology appraisal. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (TA319). July 2014.
• NICE technology appraisal. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269). December 2012.
• NICE technology appraisal. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). December 2012.

• NICE public health guidance. Skin cancer prevention: information, resources and environmental changes (PH32). January 2011.
• NICE cancer service guidance. Improving outcomes for people with skin tumours including melanoma. 2010.

Other Guidance

• American Society of Clinical Oncology. Sentinel lymph node biopsy for melanoma: ASCO and SSO joint clinical practice guideline. 201214.
• European Society for Medical Oncology. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 201215.
• American Academy of Dermatology (AAD). Guidelines of care for the management of primary cutaneous melanoma. 201116.
• British Association of Dermatologists. Revised UK guidelines for the management of cutaneous melanoma. 201017.
• Royal College of Physicians. The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines. 200718.

CURRENT TREATMENT OPTIONS

Non-surgical treatment modalities including immunotherapy, chemotherapy, radiation therapy, or a combination of these treatments may be offered for inoperable stage III and IV disease (locally advanced or metastatic disease)20. Treatment options include21,22,23,24,25:

• Biological therapy:
  o Ipilimumab for previously untreated unresectable stage III or IV malignant melanoma.
  o Ipilimumab is also recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy.
  o Vemurafenib for inoperable stage III and IV BRAF mutant melanoma.
  o Dabrafenib for inoperable stage III and IV BRAF mutant melanoma (subject of an ongoing appraisal by NICE).
  o Immunotherapy – interferon-alpha and interleukin-2.

• Chemotherapy – although dacarbazine has been the standard chemotherapy for melanoma, its use has been rapidly reducing as new molecular targeted and immunotherapies have been introduced that offer survival benefit. It remains an option
for a minority of patients in the first, second or third line setting. Other options may include:
- Temozolamide.
- Cisplatin or carboplatin.
- Vinca alkaloids – vindesine.
- Paclitaxel.
- Nitrosoureas – carmustine.
- Carboplatin and paclitaxel in combination.
- Dacarbazine and a vinca alkaloid in combination.
- Radiotherapy may be used to palliate locally advanced or metastatic disease where the main goal is symptom control or adjuvantly for high risk lymph node basins.
- Surgery – excision of the primary tumour, affected lymph nodes and in-transit recurrent disease.
- Other:
  - Imiquimod for lentigo maligna.
  - Isolated limb perfusion – with melphalan, for recurrent disease within a limb.
  - Isolated limb infusion.
  - Electrochemotherapy (with bleomycin) – palliative for recurring in-transit metastases and also for fungating lesions.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>CheckMate 067, NCT01844505, CA209-067, 2012-005371-13; nivolumab alone vs nivolumab with ipilimumab vs ipilimumab alone; phase III</th>
<th>CheckMate 069, NCT01927419, CA209-069, 2013-002018-11; nivolumab with ipilimumab vs ipilimumab; phase II</th>
<th>CheckMate 218, NCT02186249, CA209-218; nivolumab with ipilimumab</th>
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<tbody>
<tr>
<td>Source of information</td>
<td>Trial registry¹.</td>
<td>Trial registry²⁵.</td>
<td>Trial registry²⁶, manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>EU (not UK) and USA.</td>
<td>USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
<td>Expanded access.</td>
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<td>Participants</td>
<td>n=915 (planned); aged ≥18 years; melanoma; unresectable stage III or IV, treatment naïve.</td>
<td>n=150 (planned); aged ≥18 years; melanoma; unresectable stage III or IV; no prior systemic treatment for unresectable or metastatic melanoma; BRAF V600-positive or V600 wild-type.</td>
<td>Aged ≥18 years; melanoma; unresectable stage III or IV; anti-CTLA-4 treatment naïve.</td>
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<td>Schedule</td>
<td>Randomised to nivolumab, 3mg/kg IV, every 2 weeks with placebo matching ipilimumab on weeks 1 and 4, and placebo matching nivolumab; or nivolumab 1mg/kg IV, with ipilimumab</td>
<td>Randomised to nivolumab, 1mg/kg IV with ipilimumab, 3mg/kg IV, every 21 days for 4 cycles, then nivolumab, 3mg/kg IV, every 2 weeks; or placebo, IV, with ipilimumab, 3mg/kg</td>
<td>All participants receive nivolumab, 1mg/kg IV, with ipilimumab, 3mg/kg IV, every 3 weeks for 4 cycles; followed by nivolumab, 3mg/kg IV, every 2 weeks.</td>
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¹ Expert opinion - it is likely that most of the alternative cytotoxic chemotherapies will no longer be used outside of a research setting given the limited evidence base supporting activity.
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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost(^{0,})</th>
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<tr>
<td>Dacarbazine</td>
<td>250mg/m(^2) IV for 5 days, every 3 weeks</td>
<td>£80.10 per 21 day cycle</td>
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<tr>
<td>Vemurafenib (Zelboraf)</td>
<td>960mg oral, twice daily, until disease progression</td>
<td>£91,000 per year</td>
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<tr>
<td>Ipilimumab (Yervoy)</td>
<td>3mg/kg IV, every 21 days, for up to 4 cycles</td>
<td>£75,000 per course of 4 cycles</td>
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**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: *Fortnightly administration for up to 2 years; toxicity management issues, particularly immune related toxicities and endocrinopathies*\(^{d}\).  ☐ Decreased use of existing services

☐ Re-organisation of existing services  ☐ Need for new services

☐ Other:  ☐ None identified

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\(^{b}\) EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer, a quality of life measure for cancer patients.

\(^{c}\) Based on an average weight of 77.9kg and average surface area of 1.88m\(^2\). Assumes wastage.

\(^{d}\) Expert person opinion.
Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other decrease in costs:
- Other:
  - uncertain unit cost compared to existing treatments.

Other Issues

- Clinical uncertainty or other research question identified:
- None identified

REFERENCES