

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA268; Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma

This guidance was issued in December 2012.

The review date for this guidance is November 2014.

1. Recommendation

The guidance should be incorporated into an on-going clinical guideline. The current Patient Access Scheme for ipilimumab will remain in place. That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost effectiveness of ipilimumab within its licensed indication for previously treated unresectable stage III or IV malignant melanoma.

3. Current guidance

- 1.1. Ipilimumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.

4. Rationale¹

No new relevant clinical evidence has been found that would be expected to affect the recommendations of TA268.

5. Implications for other guidance producing programmes

NICE is currently developing a clinical guideline for the assessment and management of melanoma, which is due to be published in July 2015. The draft scope for the guideline indicates that TA268 should be incorporated in the guideline.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January, 2011 onwards were reviewed. Additional searches of clinical trials registries and other

¹ A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

At the time of publication for TA268 (December 2012), ipilumab was indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy. In November 2013, the European Commission extended the indication for ipilimumab for the first-line treatment of adult patients with advanced (unresectable or metastatic) melanoma. The extension of the marketing authorisation was supported by data derived from phase 2 and phase 3 studies conducted in people with advanced melanoma, as well as from 2 retrospective observational studies in people with previously untreated advanced melanoma. In July 2014 NICE technology appraisal guidance 319 recommended ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. Section 6 of TA319 recommended further research into the relative effectiveness of ipilimumab when given as a first-line or second-line treatment.

The company has confirmed they intend to continue the patient access scheme agreed in TA268 without any changes. The cost of ipilimumab is unchanged from that in TA268 (i.e. £3750 for 50 mg and £15,000 for 200 mg, excluding VAT). Section 6 of TA268 recommended further research with regard to trials investigating biomarkers and the impact of ipilimumab on subgroups based on mutation type, but the literature review did not identify any such studies, and neither did it identify any studies (published or in development) that would be likely to lead to a change in the current recommendations.

NICE TA269 (issued in December 2012) recommended vemurafenib as a possible treatment for unresectable or metastatic melanoma with the BRAF V600 mutation. In TA269, ipilimumab was listed as a comparator in the NICE scope for people with previously treated malignant melanoma. However, people with previously treated malignant melanoma were not considered in the manufacturer's submission, so comparisons with ipilimumab were not presented. The ERG report stated that the rationale for this was: "Due to a lack of RCT or historical control data on the outcomes experienced by previously treated BRAF V600 mutation positive patients and the magnitude of the ICERs estimated in the previously untreated model (£89,613/QALY and above) and the significant uncertainty associated with the setting in which RCT data was available, a complete decision analytic model investigating the cost-effectiveness of vemurafenib as a second-line treatment based upon the single arm BRIM2 study (inherently subject to more uncertainty) has not been constructed and it does not appear possible to robustly demonstrate that vemurafenib should be considered cost-effective in this setting."

There is a clinical guideline for melanoma in development (anticipated publication date, July 2015). The NICE scope says that both TA268 and TA269 will be incorporated into the guideline.

In summary, there have been no changes to the acquisition cost of ipilimumab or the patient access scheme and the extended indication for ipilimumab does not affect the current recommendation for TA268. In addition, although vemurafenib could now

be considered a comparator for ipilimumab, there does not appear to be sufficient evidence that would change the current recommendation of TA268 in the second line setting. Overall, the new evidence is unlikely to lead to a change in the recommendations of the original guidance.

8. Implementation

A submission from Implementation is included in Appendix 3.

9. Equality issues

No equality issues were identified during the scoping exercise or appraisal process of TA268.

GE paper sign off: Janet Robertson, 2 December 2014

Contributors to this paper:

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE’s work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	<p>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	Yes

Options	Consequence	Selected – ‘Yes/No’
The guidance should be updated in an on-going clinical guideline.	<p>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.</p> <p>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</p>	No
The guidance should be transferred to the ‘static guidance list’.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

- i. The technology falls within the scope of a clinical guideline (or public health guidance)
- ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement
- iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment
- iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;
 - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
 - There is evidence of unjustified variation across the country in access to a treatment
 - There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff
- v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Technology appraisal TA319 Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. Published: July 2014. Review date: June 2017

Technology appraisal TA269 Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma Published: December 2012. Review date: November 2014

Public health guidelines PH32 Skin cancer prevention: information, resources and environmental changes Published: January 2011. Review date: April 2017

NICE guidelines CSGSTIM Improving outcomes for people with skin tumours including melanoma Published: May 2006. In May 2010 NICE published a partial update of this guidance.

In progress

Diagnosis of skin cancer: The VivaScope imaging system (and other alternative technologies identified in scoping) Anticipated publication date: November 2015

Clinical guideline Melanoma: assessment and management of melanoma Anticipated publication date: July 2015

Technology appraisal Dabrafenib for the treatment of BRAF V600 mutation positive, unresectable, advanced or metastatic melanoma. Anticipated publication date: December 2014

Technology appraisal Melanoma (resected stage IV, high risk stage III) - ipilimumab (adjuvant) [ID721] Referral date: July 2014. Anticipated publication date: TBC

Referred - QSs and CGs

Skin cancer (including melanoma) Referred

Suspended/terminated

Technology appraisal Temozolomide for the treatment of advanced and metastatic melanoma Status: suspended. The manufacturer of temozolomide advised that regulatory approval for this technology is not being sought at the present time. The Institute has therefore decided to remove this appraisal from its current work programme.

Technology appraisal Paclitaxel (as albumin-bound nanoparticles) for the first-line treatment of metastatic melanoma Status: Suspended Referral date: October 2013. The manufacturer will no longer be pursuing a licensing application for nab paclitaxel in this indication, therefore, NICE has decided to suspend this appraisal on its current work programme.

Details of changes to the indications of the technology

Indication considered in original appraisal	Current indication (for this appraisal)
Ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.	YERVOY is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults

Registered and unpublished trials

Trial name and registration number	Details
Ipilimumab or High-Dose Interferon Alfa-2b in Treating Patients With High-Risk Stage III-IV Melanoma That Has Been Removed by Surgery (NCT01274338)	Estimated Enrolment: 1545 This study is currently recruiting participants Estimated Primary Completion Date: May 2018
Dabrafenib and Trametinib Followed by Ipilimumab and Nivolumab or Ipilimumab and Nivolumab Followed by Dabrafenib and Trametinib in Treating Patients With Stage III-IV BRAFV600 Melanoma (NCT02224781)	Estimated Enrolment: 300 This study is not yet open for participant recruitment Estimated Primary Completion Date: April 2016
HD IL-2 + Ipilimumab in Patients With Metastatic Melanoma (PROCLIVITY 02) (NCT01856023)	Estimated Enrolment: 100 This study is currently recruiting participants Estimated Study Completion Date: January 2018
A National Phase IV Study With Ipilimumab for Patients With Advanced Malignant Melanoma. (Ipi4) (NCT02068196)	This study is currently recruiting participants Estimated Enrolment: 100 Estimated Study Completion Date: December 2019
Phase 3 Trial in Subjects With Metastatic Melanoma Comparing 3 mg/kg Ipilimumab Versus 10 mg/kg Ipilimumab (NCT01515189)	This study is ongoing, but not recruiting participants Estimated Enrolment: 700 Estimated Study Completion Date: December 2016

Trial name and registration number	Details
Efficacy Study of Ipilimumab Versus Placebo to Prevent Recurrence After Complete Resection of High Risk Stage III Melanoma (NCT00636168)	<p>This study is ongoing, but not recruiting participants</p> <p>Enrolment: 1211</p> <p>Estimated Study Completion Date: September 2019</p>
Study to Evaluate the Safety and Efficacy of Two Different Dosing Schedules of Pembrolizumab (MK-3475) Compared to Ipilimumab in Participants With Advanced Melanoma (MK-3475-006/KEYNOTE-006) (NCT01866319)	<p>This study is ongoing, but not recruiting participants.</p> <p>Estimated Enrolment: 645</p> <p>Estimated Study Completion Date: March 2016</p>

Additional information

Bristol-Myers Squibb provides ipilimumab with a discount agreed in the patient access scheme. It is Bristol-Myers Squibbs' intention to continue this scheme without any changes.

Ipilimumab - 1st line, treatment naïve advanced (unresectable or metastatic) melanoma (NHS England, 2014 Cancer drug fund decision summaries)

Appendix 3 – Implementation submission

Contents

1. Routine healthcare activity data
2. Implementation studies from published literature
3. Qualitative input from the field team
4. Implementation studies from shared learning
5. Appendix A: Healthcare activity data definitions

Please contact Liesl Millar regarding any queries Liesl.Millar@nice.org.uk

1. Routine healthcare activity data

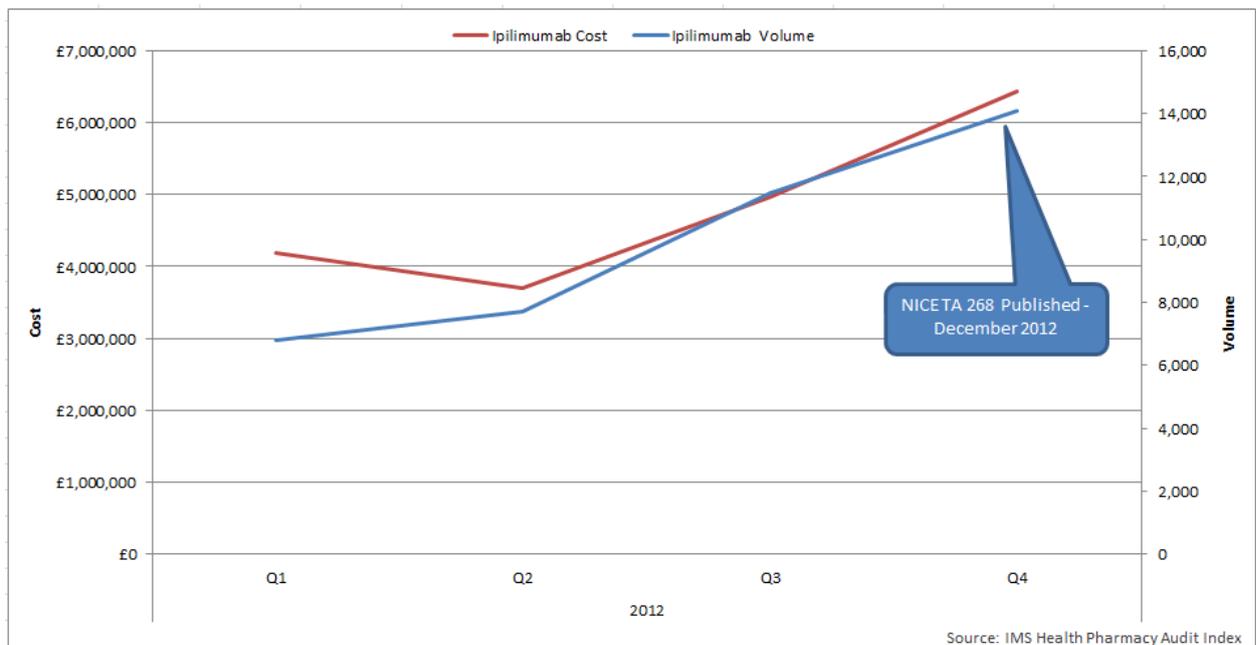
ePACT data

This section presents electronic prescribing analysis and cost tool (ePACT) data on the net ingredient cost (NIC) and volume of drugs prescribed in hospitals and or the community and dispensed in the community in England. Unfortunately no data relating to ipilimumab was available.

Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of ipilimumab prescribed and dispensed in hospitals in England between January 2000 and January 2012.

Figure 3 Cost and volume of ipilimumab prescribed in hospitals in England between January 2012 and December 2012.



2. Implementation studies from published literature

No uptake information was found on the [uptake database](#) website for TA 268.

3. Qualitative input from the field team

The implementation field team have not recorded any feedback in relation to this guidance.

4. Implementation studies from shared learning

A search of the [shared learning](#) website highlighted no examples of TA268 being implemented.

Healthcare activity data definitions

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.