**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

# Dabrafenib for treating unresectable, advanced or metastatic BRAF$^{V600}$ mutation-positive melanoma mutation-positive melanoma (STA)

**Response to consultee and commentator comments on the draft scope**

| Section | Consultees | Comments | Action |
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| Background information | British Association of Dermatologists | We agree with the correct use of the term "melanoma", instead of what has been used previously, i.e. "malignant melanoma", which is incorrect. | Comment noted. The term 'malignant melanoma' has been changed throughout the scope to 'melanoma'. |
| | GlaxoSmithKline | 1. GSK propose that NICE reflect the position in the treatment pathway of the BRAF-inhibitors, specifically vemurafenib. DTIC has, until recently, been the only routinely used first-line treatment for patients with metastatic melanoma. However, for patients with BRAFV600 positive disease, vemurafenib is being increasingly used in this setting. According to market research data, 92% of eligible patients in the UK are currently receiving vemurafenib).<br>"People with V600 BRAF positive unresectable stage IIIc or IV (metastatic) disease are usually managed by a specialist oncologist and current first-line standard care normally involves the administration of vemurafenib."<br>2. GSK propose acknowledging that the five year survival rates are based on population statistics prior to the availability of targeted therapies for patients with V600 BRAF mutation-positive metastatic melanoma and therefore may not reflect the current | Comments noted. The background has been updated to reflect the change from dacarbazine to vemurafenib in first-line treatment for people with BRAF V600 positive melanoma.<br>The five year survival rates have been updated and are based on the most up to date statistics available. |

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| | | prognosis for people with this diagnosis. | |
| | NCRI/RCP/ RCR/ACP/JCCO | The statement that first line standard care for unresectable stage III or IV melanoma normally involves administration of dacarbazine is no longer true. The norm is currently to stratify patients by BRAF mutation status and those with BRAF mutant melanoma (almost 50% of all melanomas) will most often be offered vemurafenib. In those patients who are not eligible for vemurafenib, many will be offered a clinical trial in preference to dacarbazine. Therefore, while dacarbazine remains an option, it can no longer be considered the standard of care for all patients. | Comment noted. The background has been updated to reflect the change from dacarbazine to vemurafenib in first-line treatment for people with BRAF V600 positive melanoma. |
| | Roche Products | The description of standard of care in malignant melanoma is incomplete. Following NICE approval in TA269, vemurafenib is considered standard of care in the treatment of unresectable stage III or IV (metastatic) disease. | Comment noted. The background has been updated to reflect the change from dacarbazine to vemurafenib in first-line treatment for people with BRAF V600 positive melanoma. |
| The technology/ intervention | GlaxoSmithKline | Dabrafenib monotherapy is now licensed in Europe.<br>"The European Commission has granted marketing authorisation for dabrafenib (Tafinlar™) as an oral targeted treatment indicated in monotherapy for unresectable melanoma (melanoma that cannot be removed by surgery) or metastatic melanoma (melanoma which has spread to other parts of the body) in adult patients with a BRAF V600 mutation." | Comment noted. The scope has been updated to reflect dabrafenib's change in regulatory status and its indication. |
| | NCRI/RCP/ RCR/ACP/JCCO | Yes | Comment noted. |

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| | Roche Products | Dabrafenib has held a UK marketing authorisation since 28/08/2013. | Comment noted. The scope has been updated to reflect dabrafenib's change in regulatory status and its indication. |
| Population | British Association of Dermatologists | Yes. | Comment noted. |
| | GlaxoSmithKline | GSK propose that the population be amended to Adults with advanced or metastatic BRAFV600 mutation-positive melanoma. | Comment noted. Guidance will be issued in line with marketing authorisation. |
| | NCRI/RCP/ RCR/ACP/JCCO | Yes. | Comment noted. |
| | Roche Products | Given that trametinib monotherapy has only been studied in BRAF mutation positive cutaneous melanoma, it may be appropriate to consider this sub-group separately. | Comment noted. Cutaneous melanoma represents the vast majority of melanomas and trametinib will only be appraised within its licensed indication. |
| Comparators | Bristol-Myers Squibb | For people whose malignant melanoma has metastasised to the brain:<br>Just comparing to radiotherapy (in scope) might be restrictive. Melanoma patients with brain metastases may also receive temozolomide in some cases. | Comment noted. Temozolomide has been added to the scope as a comparator treatment for people whose melanoma has metastasised to the brain. |

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| | GlaxoSmithKline | The monotherapies, dabrafenib and trametinib, are named as interventions in this appraisal and they will be compared against existing standard of care (vemurafenib and dacarbazine). However, they are also named as comparators and GSK propose removing them from this position in the scope as clinically, they will not be competing standards of care in the future. As treatments for metastatic melanoma continue to evolve, GSK expect limited uptake of the monotherapies once the combination is licensed.<br>There is insufficient evidence from the clinical trials with which to build an economic argument for:<br>• the use of these treatments in people with BRAFV600 mutation-positive metastatic melanoma who have received prior therapy:<br>• the majority of patients in the phase II combination study (81% overall) had not received prior systemic anti-cancer regimens for advanced or metastatic disease. The forthcoming phase III study (COMBI-D) comparing combination therapy versus dabrafenib excluded patients who had received prior systemic anti-cancer treatment for Stage IIIC (unresectable) or Stage IV (metastatic) melanoma. | Comment noted. For the Appraisal Committee to be able to make recommendations for the interventions included in the remit and scope, a fully incremental analysis including all interventions and comparators is required. No action required. |
| | | BREAK-3, the pivotal study for dabrafenib monotherapy, was limited to patients who had not received previous antitumour therapy for unresectable or metastatic melanoma (other than interleukin 2)<br>METRIC, the pivotal study for trametinib monotherapy, included patients with ≤1 prior chemotherapy for advanced or metastatic disease (excluding BRAF/ MEK inhibitors or ipilimumab); approximately half of the patients in this study had received prior | Comment noted. The marketing authorisation for dabrafenib monotherapy is not limited to people with previously untreated melanoma. No change required. |

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| | | chemotherapy patients whose malignant melanoma has metastasised to the brain dabrafenib monotherapy was investigated in patients in a single arm phase 2 study of BRAFV600 mutation-positive melanoma patients with brain metastases, with and without prior local therapy. There is no specific clinical evidence supporting the efficacy of combination therapy with dabrafenib/trametinib in patients with BRAFV600 mutation-positive metastatic melanoma confined only to the brain, although a Phase II study is in development.<br>In line with the above we recommend that NICE remove the requirement for comparisons with the following:<br>For people with previously treated malignant melanoma:<br>• dacarbazine<br>• ipilimumab<br>• vemurafenib<br>For people whose malignant melanoma has metastasised to the brain:<br>• radiotherapy | |
| | NCRI/RCP/ RCR/ACP/JCCO | Agreed, but with the following caveats:<br>During the course of this appraisal, ipilimumab is likely to obtain a European license for use in previously untreated metastatic melanoma (already licensed in USA). | Comment noted. For a NICE technology appraisal, the relevant comparators are those in current clinical practice at the time the appraisal is commenced.<br><br>Comment noted. Ipilimumab and |

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| | | Patients with brain metastases are eligible for vemurafenib and ipilimumab systemic therapy, both of which have reported activity in these patients, with the potential to prolong life. Radiotherapy as an appropriate comparator is questionable: the type of radiotherapy needs to be clarified. In general, 2 types of radiotherapy are used in the treatment of melanoma brain metastases: high dose targeted 'radiosurgery', which may be offered to patients with low number and volume of brain mets, with potential curative intent. These patients may in some cases undergo surgical intervention. Alternatively, whole brain radiotherapy tends to be reserved for patients beyond systemic therapy - its role is very limited and there is no evidence of survival benefit. | vemurafenib have been added as comparators for people with brain metastases. The term 'radiotherapy' as used in the scope encompasses both types of radiotherapy used in the treatment of melanoma brain metastases. |
| | Roche Products | Vemurafenib can also be used within its licenced indication for the treatment of malignant melanoma that has metastasised to the brain. | Comment noted. Vemurafenib has been added to the scope as a comparator in brain metastases. |
| Outcomes | British Association of Dermatologists | Yes. | Comment noted. |
| | GlaxoSmithKline | The scope specifies the most relevant outcomes for people with | Comment noted. |

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| | | BRAFV600 mutation-positive metastatic melanoma. | |
| | NCRI/RCP/ RCR/ACP/JCCO | Yes. | Comment noted. |
| Economic analysis | NCRI/RCP/ RCR/ACP/JCCO | Yes. | Comment noted. |
| Equality | GlaxoSmithKline | GSK does not consider that the scope requires amendment in light of equality considerations. | Comment noted. |
| | NCRI/RCP/ RCR/ACP/JCCO | No issues. | Comment noted. |
| Other considerations | GlaxoSmithKline | No additional considerations | Comment noted. |
| Innovation | British Association of Dermatologists | Yes. | Comment noted. |
| | GlaxoSmithKline | The innovative combination of a MEK inhibitor with a BRAF inhibitor promises to deliver a step-change advancement in the treatment of patients with BRAFV600 mutation positive metastatic melanoma, over and above that offered by the current standard of care (targeted BRAF inhibitor monotherapy) for the following reasons:<br>The typical development of resistance to monotherapy BRAF inhibition due to signal transduction along alternative pathways to stimulate MEK and then ERK with eventual cell proliferation, has limited median progression-free survival to around 5 months.<br>There is a paucity of available licenced treatment options for second line treatment for these patients. Ipilimumab is slow to have an effect and this only occurs unpredictably in a minority of | Comments noted. Please include statements on innovation within the manufacturer's submission. |

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| | | patients, although the effect is durable.<br>Our improved understanding of the MAPK pathway and mechanisms of resistance has both led to the rapid development (within 4 years) of the novel MEK inhibitor, trametinib as well as its study in combination with dabrafenib.<br>Combination of dabrafenib and trametinib has almost doubled PFS and OS, and increased RR by around 50%, with patients achieving at least complete stabilisation of disease, relative to BRAF inhibitor monotherapy efficacy.<br>Combination of dabrafenib and trametinib has mitigated against debilitating skin toxicity found with vemurafenib, although there are some unique toxicities associated with combination therapy that have been shown to be manageable.<br>It is anticipated that the combination of dabrafenib and trametinib will meet the end of life criteria by offering an extension to life of at least three additional months versus vemurafenib – the current standard of care, in a small patient population with a life expectancy of less than 24 months where there is no alternative treatment of comparable benefit. The assessment of this medicine under these criteria makes allowances for some of the benefit that may not be captured in the QALY for patients with a severe disease and a short life expectancy. | |
| | NCRI/RCP/ RCR/ACP/JCCO | The combination, dabrafenib+trametinib, is likely to represent a step change in treatment of BRAF mutant melanoma, offering longer PFS and OS gains, with potentially fewer toxicities compared with vermurafenib alone.<br><br>As a single agent, dabrafenib is equivalent to vemurafenib in terms of efficacy, but associated toxicities are different compared with vemurafenib: photosensitivity and skin rash are likely to be | Comments noted. |

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| | | more common with vemurafenib, while pyrexia will be more common with dabrafenib. The availability of 2 agents in this class will benefit patients who are unable to tolerate one or other agent. | |
| | Roche Products | Dabrafenib monotherapy is a specific inhibitor of the mutated BRAF protein, with a mode of action similar to vemurafenib, and therefore should not be considered an innovative agent. | Comment noted. |
| Questions for consultation | GlaxoSmithKline | Are BRAF inhibitors likely to be used in sequence? If so, where in the sequence would dabrafenib and trametinib (alone and in combination) most likely be used?<br>The question of sequencing of BRAF or MEK inhibitors, or their combination, with ipilimumab is currently being debated and is the subject of ongoing interventional research.<br>The unique patterns of response with ipilimumab can influence treatment choice. It may take weeks or months to build a complete immune response to a tumour because of the immunotherapy's mode of action; responses to ipilimumab may not be detectable until week 12 of treatment. Patients with rapidly progressing disease may not have the time available to respond to subsequent immunotherapy.<br>In the absence of prospective clinical data to guide the treatment sequence, experts suggest that certain patients – those with symptomatic, bulky, rapidly growing disease or those with high serum lactate dehydrogenase concentrations – are less likely to benefit from immunotherapy and so may be candidates for first line BRAF inhibitor therapy.<br>Ipilimumab currently has a marketing authorisation for the treatment of adult patients with previously-treated advanced | Comments noted. |

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| | | melanoma. It is also recommended by NICE in this indication (NICE TA268). Therefore, eligible patients who progress on a first line BRAF inhibitor or on combination therapy can currently go on to receive ipilimumab. For that reason, the BRAF inhibitors are likely to be used initially in the front-line setting, in whom these treatments have been predominantly studied.<br><br>Dabrafenib/trametinib combination therapy is expected to replace BRAF monotherapies as a first line standard of care due to the improved efficacy and manageable safety profile.<br><br>With regards to sequencing of the BRAF and MEK monotherapies, studies have suggested that BRAF resistance mechanisms likely confer resistance to MEK inhibitor monotherapy, therefore MEK monotherapy has shown minimal clinical activity in patients who have progressed on a BRAF inhibitor.<br><br>Are the comparators listed routinely used in clinical practice? Are there any subgroups of people in whom the technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?<br><br>Vemurafenib and to a more limited extent dacarbazine are routinely used first-line treatments in clinical practice.<br><br>Dabrafenib monotherapy and trametinib monotherapy are not commercially available for use in the UK and are therefore not routinely used in clinical practice.<br><br>The listed comparators for previously-treated patients, and patients with melanoma that has metastasised to the brain are those routinely used in clinical practice.<br><br>There are no particular subgroups (of BRAFV600 mutation positive patients) in whom the technologies are expected to be | |

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| | | more effective or cost-effective than other groups. | |
| | NCRI/RCP/ RCR/ACP/JCCO | Unlike in renal cancer, there is currently no convincing evidence that BRAF or MEK inhibitors can be used in sequence. In particular, patients progressing after a BRAFi experience very little benefit from a MEKi or BRAFi+MEKi combination | Comment noted. |
| Any additional comments on the draft scope | British Association of Dermatologists | Any additional comments on the draft scope<br>We feel that the reference to the guidance "Cancer Service Guidance, May 2010, 'Improving outcomes for people with skin tumours including melanoma (update): the management of low-risk basal cell carcinomas in the community' " is inappropriate – it is not relevant to the subject matter. | Comment noted. Reference to this guidance has been removed, as suggested. |

The National Cancer Research Institute, Royal College of Physicians, Royal College of Radiologists, Association of Clinical Pathologists, and Joint Collegiate Council for Oncology submitted a joint response to the draft scope consultation.

**The following consultees/commentators indicated that they had no comments on the draft scope**

Department of Health
Royal College of Nursing

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**Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)**

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| **Version of matrix of consultees and commentators reviewed:** Provisional matrix of consultees and commentators sent for consultation | | | | | |
| **Summary of comments, action taken, and justification of action:** | | | | | |
| | Proposal: | Proposal made by: | | Action taken: Removed/Added/Not included/Noted | Justification: |
| 1. | Children's Society | NICE Secretariat | | Included | This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria they have been included in the list of consultee and commenators under 'patient groups' |

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| 2. | British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS) | British Association Dermatologists | | Not included. | This organisation is not closely related to the appraisal topic as per our inclusion criteria and therefore has not been included in the list of consultee and commentators. |