National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Vemurafenib for the treatment of unresectable locally advanced or metastatic BRAF^{V600} mutation-positive malignant melanoma

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	British Association of Dermatologists	Yes, we think so.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	This is appropriate	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	It is appropriate to refer this topic to NICE for appraisal	Comment noted. No action required.
	Roche Products	We agree this is an appropriate topic.	Comment noted. No action required.
Wording	British Association of Dermatologists	Yes, the wording appears appropriate.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	Yes	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	Yes	Comment noted. No action required.
	Roche Products	The remit refers to BRAF^{V600e}, however this should be changed to BRAF^{v600} to reflect the expected license indication.	Comment noted. The scope has been amended accordingly.

Section	Consultees	Comments	Action
Timing Issues	British Association of Dermatologists	As this technology does not yet have a UK marketing authorisation, we judge the urgency of the appraisal as appropriate for its completion to be synchronised with the granting of the marketing authorisation.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	No comments	No action required.
	NCRI/RCP/RCR/ACP/JCCO	Very urgent; this drug is likely to be licensed later in 2011 and is the first ever targeted therapy to show a benefit in melanoma.	Comment noted. No action required.
	Roche Products	[redacted]	Comment noted. No action required.
Additional comments on the draft remit	British Association of Dermatologists	No comments	No action required.
	Commissioning Support Appraisals Service (CSAS)	No comments	No action required.
	NCRI/RCP/RCR/ACP/JCCO	No comments	No action required.
	Roche Products	No comments	No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	British Association of Dermatologists	The background information is accurate and complete.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	Accurate	Comment noted. No action required.

Section	Consultees	Comments	Action
	NCRI/RCP/RCR/ACP/JCCO	Generally accurate but 5 year survival for Stage IV disease is not as high as 20-30% and figures for incidence of melanoma differ from CRUK CancerStats. Advanced melanoma is generally refractory to all treatment modalities and little progress has ever been made in this regard.	Comment noted. Scope background section has been updated to in line with data from CRUK.
	Roche Products	20-30% survival at year 5 for Stage IV seems to be an over-estimate we consider the survival rate to be <15% given the results of the DTIC arm from RCT data (Bedikan et al, 2006)	Comment noted. Scope background section has been updated in line with data from CRUK.
The technology/ intervention	British Association of Dermatologists	It appears so.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	Accurate	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	Yes	Comment noted. No action required.
	Roche Products	Correct except BRAFV600e should be changed to BRAFv600	Comment noted. The scope has been amended accordingly.
Population	British Association of Dermatologists	The population is defined appropriately.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	Accurate	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	Yes	Comment noted. No action required.

Section	Consultees	Comments	Action
	Roche Products	Licence is expected to be for use in patients with unresectable Stage IIIc or Stage IV melanoma who test positive for the BRAF V600 mutation. Hence BRAFV600e should be changed to BRAFv600 and the eligible patient population specified as having unresectable stage IIIc and IV diseases	Comment noted. Consultees agreed that 'unresectable locally advanced or metastatic melanoma' captured stage IIIc and IV disease and reflected terminology used in clinical practice. The scope has been amended accordingly.
Comparators	British Association of Dermatologists	Yes. None of the alternatives to dacarbazine can justifiably be described as 'best supportive care'.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	Dacarbazine could also be used as a comparator for patients with previously treated malignant melanoma (it is currently being used as a comparator in the technology appraisal for ipilimumab-which is being tested in a population with previously treated stage III or IV malignant melanoma). Carboplatin-based chemotherapy could also be used as a comparator for these patients (again, it is being used as a comparator of ipilimumab). A technology appraisal is currently underway for ipilimumab which could potentially also be used as a comparator, if approved. In addition, surgery could be used in some cases (to remove melanoma and affected lymph nodes).	Comment noted. Consultees agreed that neither dacarbazine nor carboplatin-based chemotherapy could be considered standard 2nd line treatment for this patient group. Ipilimumab is undergoing NICE appraisal and has been added as a comparator for previously treated patients (subject to the outcome of the ongoing appraisal).
	NCRI/RCP/RCR/ACP/JCCO	Yes	Comment noted. No action required.
	Roche Products	No comment	No action required.

Section	Consultees	Comments	Action
Outcomes	British Association of Dermatologists	We think so.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	Appropriate	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	Yes	Comment noted. No action required.
	Roche Products	No comment	No action required.
Economic analysis	British Association of Dermatologists	An appropriate time horizon would reasonably relate to 5 year survival.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	Appropriate	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	No comments	No action required.
	Roche Products	No comment	No action required.
Equality and Diversity	British Association of Dermatologists	There do not appear to be any equality or discrimination issues.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	No comments	No action required.
	NCRI/RCP/RCR/ACP/JCCO	No suggestions	Comment noted. No action required.
	Roche Products	No comments	No action required.

Section	Consultees	Comments	Action
Innovation	British Association of Dermatologists	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* Yes, this technology is innovative and does appear to have a significant therapeutic potential, but may not prove to be a 'step change'.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* Innovative	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* This is without question a step change in the management of advanced melanoma.	Comment noted. No action required.
	Roche Products	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* Vemurafenib represents a step-change in the management of this condition. It provides unprecedented response rates and rapid time to response resulting in substantial improvement to both PFS and OS in a disease area currently bereft of effective	Comment noted. No action required.

Section	Consultees	Comments	Action
		treatment options. In recognition of this the presentation of the PHIII trial data was recently presented during the plenary session of ASCO 2011.	
Other considerations	British Association of Dermatologists	We have no suggestions for additional issues in the proposed appraisal.	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	None	Comment noted. No action required.
Questions for consultation	British Association of Dermatologists	*Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* We are not aware of health-related benefits resulting from the use of this technology that are not included in the QALY calculation. -This technology is likely to be used to treat individuals with melanoma which carries the BRAF V600 mutation (about 50% of cases). -Dacarbazine is currently commonly used as a single agent treatment of metastatic melanoma. -The appropriate comparators appear to have been chosen.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	A clinical stage II trial (BRIM2) has reported tumour shrinkage in 52% of trial participants with previously treated BRAF V600E mutation positive metastatic melanoma. A stage III trial (BRIM3) reported higher overall survival and progression-free survival after treatment with vemurafenib compared to dacarbazine chemotherapy. Therefore, vemurafenib is likely to be used on both treatment naive and previously treated patients. Additional comparators are listed above. As defined by the scope, vemurafenib can only be used on patients with the BRAF V600E mutation.	Comment noted. No action required.

Section	Consultees	Comments	Action
	NCRI/RCP/RCR/ACP/JCCO	*Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* Patients with advanced melanoma are often very symptomatic and vemurafenib can often result in a rapid improvement in symptoms and quality of life, which may not be captured in the QALY calculation but is of significant benefit. *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Data from the Phase I, II and III clinical trials should be available to the Appraisal Committee. *Is vemurafenib likely to be used in routine clinical practice for both treatment-naïve and previously treated patients with metastatic melanoma?* Yes *Is it likely to be an appropriate treatment for patients with either stage III or IV disease?* Unresectable stage III and stage IV only *Have the most appropriate comparators for the treatment of locally advanced or metastatic BRAFV600E mutation-positive malignant melanoma been included in the scope?* *Yes* *Are there any other comparators which should be included?* No	Comments noted. The Committee will consider the innovative nature of vemurafenib, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure. No action required.

Section	Consultees	Comments	Action
	NCRI/RCP/RCR/ACP/JCCO (continued)	*Is dacarbazine routinely used for second or subsequent line treatment of advanced or metastatic malignant melanoma* No *How should best supportive care be defined in the context of malignant melanoma?* Symptom management *Are there subgroups of people in whom the technology is expected to be more clinically effective and cost effective?* Only those with BRAF mutations benefit but it is unknown beyond this what may predict greater vs lesser benefit	Comment noted. No action required.
	Roche Products	*Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* The majority of the health benefits are expected to be captured within the QALY measure. However benefits associated with the patient convenience of having oral rather than IV therapy is unlikely to be captured within this metric. *Is vemurafenib likely to be used in routine clinical practice for both treatment-naïve and previously treated patients with metastatic melanoma? Is it likely to be an appropriate treatment for patients with either stage III or IV disease?* Vemurafenib is expected to be used in routine clinical practice primarily in the 1st line setting with some 2nd line use. *Are there subgroups of people in whom the technology is expected to be more clinically effective and cost effective?*	Comment noted. The Committee will consider the innovative nature of vemurafenib, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure. No action required.

Section	Consultees	Comments	Action
		There are no subgroups that have been identified to be more clinically or cost-effective. *NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process .* We agree the STA process is the appropriate process for this appraisal.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Healthcare Improvement Scotland
Macmillan Cancer Support
Medicines and Healthcare products Regulatory Agency (MHRA)
Royal College of Nursing

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Vemurafenib for the treatment of unresectable locally advanced or metastatic, BRAF^{V600} mutation positive malignant melanoma

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

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.	CANCERactive	NICE		Removed	Organisation have requested to be removed from the list.
2.	Chinese National Healthy Living Centre	NICE		Removed	Organisation have requested to be removed from the list.
3.	Factor 50	NICE		Added	This organisation has an area of interest directly related to this appraisal and meets the selection criteria to participate in this appraisal.

4.	Sue Ryder Care	NICE		Removed	Organisation have requested to be removed from the list.
5.	Action for Sick Children	NICE		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal.
6.	Association for Children with Life Threatening or Terminal Conditions	NICE		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal.
7.	CLIC Sargent	NICE		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal.

8.	Help Adolescents with Cancer	NICE		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal.
9.	National Alliance of Childhood Cancer Parent Organisations	NICE		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal.
10.	National Children's Bureau	NICE		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal.
11.	Action for Children (formerly known as) NCH – The Children's Charity	NICE		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal.

12.	Well Child	NICE		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal.
13.	Teenage Cancer Trust	NICE		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal.
14.	British Association of Skin Cancer Specialist Nurses	NICE		Added	This organisation has an area of interest directly related to this appraisal and meets the selection criteria to participate in this appraisal.
15.	British Oncological Association (BOA)	NICE		Removed	The organisation cease to exist