NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Roche
   - British Association of Dermatologists
   - NHS England – provided a no comment response.

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Company	**<u>Inappropriate approach to overcoming the uncertainty of the indirect treatment comparison to dabrafenib</u>** We do not agree with the view that an assumption of complete interchangeability between vemurafenib and dabrafenib is a more robust approach to compare cobimetinib + vemurafenib to dabrafenib than the indirect treatment comparison (ITC) presented in our submission. Two key criticisms of the NMA have been highlighted within the appraisal documentation (ERG report, pre-meeting briefing, Appraisal Committee Meeting [ACM] slide deck and ACD): heterogeneity between studies included in the NMA, and; the sparse evidence network. Regarding heterogeneity between studies included in the NMA, the ERG considered the trials as broadly comparable, based on selected characteristics. For balance we believe the ACD should also make reference to this assessment by the ERG. The ERG report and ACD also highlighted differences in the trial design of studies included in the NMA – in particular, patient crossover – and a concern that lack of adjustment mean the studies are not comparable to coBRIM. Taking into account earlier appraisals in melanoma, we remain of the view that our approach to conducting the ITC to dabrafenib (including handling of crossover) was justified. During the assessment of dabrafenib monotherapy (TA321), it was necessary for the manufacturer to conduct an ITC. The ITC conducted in the appraisal of cobimetinib incorporated both studies included in the ITC of TA321 (as well as additional studies). During appraisal TA321, the ERG stated: 'because of the problem of adjusting for crossover in the individual trials it is more appropriate to use the unadjusted hazard ratios in the indirect treatment comparison.' Whilst we agree there is potential bias due to crossover, the consistency of results from the NMA vs. observed trial results, along with supporting scenario analyses using the ITC results from the random effects model, are supportive of the base-case results of the ITC.	Comments noted. Section 4.6 of the FAD has been updated. See section 4.7 of the FAD.

Consultee	Comment [sic]	Response
	We consider it more robust to utilise results from the ITC, rather than the strong assumption of clinical interchangeability between two drugs for which no head to head data are available. Whilst we acknowledge the NMA is only informed by one trial for each pairwise comparison, all available evidence was included (as acknowledged by the ERG), and so can be considered a robust representation of the evidence.	
Company	**Unbalanced description of the adverse event profile of comparators** Section 4.3 of the ACD refers to discussion at the ACM regarding the adverse event profiles of the two comparators, vemurafenib and dabrafenib monotherapy. As we understood, the discussion was in reference to monotherapy BRAF inhibitor treatments being associated with different adverse event profiles. Within the ACD, only the adverse events more common with vemurafenib than dabrafenib are listed. To give a more balanced account, the adverse events more common with dabrafenib than vemurafenib should also be listed.	Comments noted. Section 4.3 has been updated.
Company	**Misleading discussion regarding scenario analyses in which cobimetinib price is set to £0** We wish to clarify points made during the committee meeting, within the slide deck presented during the committee meeting, and within the ACD. Within the company submission, and based on guidance from NICE, the base-case analysis and scenarios analyses were explored using the list price for vemurafenib. We were advised that results incorporating the PAS for vemurafenib should not be presented (or discussed / referred to) within the main submission document: such presentation and discussion should only be presented as part of a confidential appendix. When considering the list price for vemurafenib, at zero cost cobimetinib, the additional cost of vemurafenib (through extension of PFS provided by the addition of cobimetinib) leads to an ICER which exceeds the standard cost-effectiveness thresholds. It is, therefore, factually accurate to state there is no cobimetinib price which could be cost-effective, when in combination with vemurafenib at list price. This is another example which highlights the limitations of standard HTA methodology when assessing combination treatments in metastatic disease. These limitations have been previously recognised (Session IP19 ISPOR European congress 2015; Pertuzumab NICE Appraisal ID523), with a NICE Decision Support Unit (DSU) Technical Support Document (TSD) unable to offer a	Comments noted. See section 4.14 of the FAD.

Consultee	Comment [sic]	Response
	solution (Davis S 2014). We acknowledge at zero cost cobimetinib, the combination may be cost-effective when considering the existing PAS for vemurafenib, however this scenario is reliant on making a new product freely available. Paragraph 4.14 also describes the existence of a positive price for cobimetinib, which leads to a cost-effective result (when also incorporating the existing PAS for vemurafenib). It was our understanding – based on guidance from NICE – that we were not allowed to refer to these scenarios within the main body of our submission. Nevertheless, whilst a positive price is possible, this scenario requires a very large discount on the price of cobimetinib. We do not believe that such scenarios are sustainable for manufacturers, and do not consider them to be supportive of expanding patient access to innovative technologies. The committee considers it is possible for cobimetinib to be cost-effective at £0 (or very large discount), when considering the discount already provided to the NHS with vemurafenib. As acknowledged in the DSU-TSD, it is the methodology underlying the current approach to HTA, in combination with the application of the recognised cost-effectiveness thresholds across all appraisals (i.e. whether a combination treatment or otherwise), which leads to such levels of discount being required. Paragraph 4.14 of the ACD suggests the committee's preferred solution for the methodological short-falls when assessing combination therapies is for manufacturers to provide new, innovative therapies with significant discounts. This is not a solution we regard as being sustainable, and we urge NICE – in collaboration with industry and the Department of Health – to find a solution to this perverse phenomenon, in order to ensure the availability of innovative technologies in the future.	
British Association of Dermatologists	On behalf of the British Association of Dermatologists, thank you for the opportunity to comment on the Appraisal Consultation Document. We understand that the combination therapy has not been approved because the QALY gained is not cost-effective for the NHS at the current price of the medication compared to single BRAF treatment. We wish to point out that, with combination treatment, there are significantly less number of SCCs and keratoacanthomas which have a cost implication as they require excision, usually under a dermatologist. The rate of SCC/KA development in single agent BRAF is about 20% reduced to around 9% with combination treatment.	Comments noted. See section 4.12 of the FAD.

Comments received from clinical experts and patient experts

None received

Comments received from commentators

Commentator	Comment [sic]	Response
NHS England	We have no comments regarding the current recommendation	No action required.

Comments received from members of the public

None received.

1st Floor,
10 Spring Gardens,
London
SW1A 2BU

BY EMAIL

7th July 2016

RE: Cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

Dear Meindert,

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the appraisal of cobimetinib in combination with vemurafenib for the treatment of unresectable or metastatic BRAF V600 mutation-positive melanoma. We are disappointed by the negative Appraisal Consultation Document (ACD) issued by NICE, despite the committee's conclusion that cobimetinib plus vemurafenib is clinically effective compared with vemurafenib alone.

In relation to the assumptions applied in the cost-effectiveness model, we broadly agree with the committee's preferred assumptions, as outlined in section 4.11. However, we have concerns regarding the committee's assessment of the network meta-analysis (NMA), and their preferred assumption of interchangeable clinical efficacy between the two comparators, vemurafenib and dabrafenib (as monotherapy treatments). Additionally, we do not believe the ACD presents information on the adverse event profiles of the comparator treatments in a balanced manner.

We also request NICE clarify the statements about the scenario of free of charge cobimetinib, in which the combination would remain above the acceptable ICER range.

The following document provides further detail on these concerns.

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
Hertfordshire
AL7 1TW
Health Economics and
Strategic Pricing
Tel. +44(0)1707 361032
Fax +44(0)1707 384123

Yours sincerely,

[redacted]

Roche Products Limited

Inappropriate approach to overcoming the uncertainty of the indirect treatment comparison to dabrafenib

We do not agree with the view that an assumption of complete interchangeability between vemurafenib and dabrafenib is a more robust approach to compare cobimetinib + vemurafenib to dabrafenib than the indirect treatment comparison (ITC) presented in our submission.

Two key criticisms of the NMA have been highlighted within the appraisal documentation (ERG report, pre-meeting briefing, Appraisal Committee Meeting [ACM] slide deck and ACD): heterogeneity between studies included in the NMA, and; the sparse evidence network.

Regarding heterogeneity between studies included in the NMA, the ERG considered the trials as broadly comparable, based on selected characteristics. For balance we believe the ACD should also make reference to this assessment by the ERG.

The ERG report and ACD also highlighted differences in the trial design of studies included in the NMA – in particular, patient crossover – and a concern that lack of adjustment mean the studies are not comparable to coBRIM. Taking into account earlier appraisals in melanoma, we remain of the view that our approach to conducting the ITC to dabrafenib (including handling of crossover) was justified. During the assessment of dabrafenib monotherapy (TA321), it was necessary for the manufacturer to conduct an ITC. The ITC conducted in the appraisal of cobimetinib incorporated both studies included in the ITC of TA321 (as well as additional studies). During appraisal TA321, the ERG stated: '*because of the problem of adjusting for crossover in the individual trials it is more appropriate to use the unadjusted hazard ratios in the indirect treatment comparison*.' Whilst we agree there is potential bias due to crossover, the consistency of results from the NMA vs. observed trial results, along with supporting scenario analyses using the ITC results from the

random effects model, are supportive of the base-case results of the ITC.

We consider it more robust to utilise results from the ITC, rather than the strong assumption of clinical interchangeability between two drugs for which no head to head data are available. Whilst we acknowledge the NMA is only informed by one trial for each pairwise comparison, all available evidence was included (as acknowledged by the ERG), and so can be considered a robust representation of the evidence.

Unbalanced description of the adverse event profile of comparators

Section 4.3 of the ACD refers to discussion at the ACM regarding the adverse event profiles of the two comparators, vemurafenib and dabrafenib monotherapy. As we understood, the discussion was in reference to monotherapy BRAF inhibitor treatments being associated with *different* adverse event profiles. Within the ACD, only the adverse events more common with vemurafenib than dabrafenib are listed. To give a more balanced account, the adverse events more common with dabrafenib than vemurafenib should also be listed.

Misleading discussion regarding scenario analyses in which cobimetinib price is set to £0

We wish to clarify points made during the committee meeting, within the slide deck presented during the committee meeting, and within the ACD.

Within the company submission, and based on guidance from NICE, the base-case analysis and scenarios analyses were explored using the list price for vemurafenib. We were advised that results incorporating the PAS for vemurafenib should not be presented (or discussed / referred to) within the main submission document: such presentation and discussion should only be presented as part of a confidential appendix.

When considering the list price for vemurafenib, at zero cost cobimetinib, the additional cost of vemurafenib (through extension of PFS provided by the addition of cobimetinib) leads to an ICER which exceeds the standard cost-effectiveness thresholds. It is, therefore, factually accurate to state there is no cobimetinib price which could be cost-effective, when in combination with vemurafenib at list price. This is another example which highlights the limitations of standard HTA methodology when assessing combination treatments in metastatic disease. These limitations have been previously recognised (Session IP19 ISPOR European congress 2015; Pertuzumab NICE Appraisal ID523), with a NICE Decision Support Unit (DSU) Technical Support Document (TSD) unable to offer a solution (Davis S 2014).

We acknowledge at zero cost cobimetinib, the combination may be cost-effective when considering the existing PAS for vemurafenib, however this scenario is reliant on making a new product freely available. Paragraph 4.14 also describes the existence of a positive price for cobimetinib, which leads to a cost-effective result (when also incorporating the existing PAS for vemurafenib). It was our understanding – based on guidance from NICE – that we were not allowed to refer to these scenarios within the main body of our submission. Nevertheless, whilst a positive price is possible, this scenario requires a very large discount on the price of cobimetinib. We do not believe that such scenarios are sustainable for manufacturers, and do not consider them to be supportive of expanding patient access to innovative technologies.

The committee considers it is possible for cobimetinib to be cost-effective at £0 (or very large discount), when considering the discount already provided to the NHS with vemurafenib. As acknowledged in the DSU-TSD, it is the methodology underlying the current approach to HTA, in combination with the application of the recognised cost-effectiveness thresholds across all

appraisals (i.e. whether a combination treatment or otherwise), which leads to such levels of discount being required. Paragraph 4.14 of the ACD suggests the committee's preferred solution for the methodological short-falls when assessing combination therapies is for manufacturers to provide new, innovative therapies with significant discounts. This is not a solution we regard as being sustainable, and we urge NICE – in collaboration with industry and the Department of Health – to find a solution to this perverse phenomenon, in order to ensure the availability of innovative technologies in the future.

References

Davis S. Assessing technologies that are not cost-effective at a zero price. Decision Support Unit, 2014

NICE Technology Appraisal 321, and related documentation. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation‑positive melanoma. October 2014

Session IP19 ISPOR European congress 2015; Pertuzumab NICE Appraisal ID523

Comments on NICE Appraisal Consultation Document for the Single Technology Appraisal on cobimetinib in combination with vemurafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID815]

British Association of Dermatologists
Therapy & Guidelines sub-committee

On behalf of the British Association of Dermatologists, thank you for the opportunity to comment on the Appraisal Consultation Document.

We understand that the combination therapy has not been approved because the QALY gained is not cost-effective for the NHS at the current price of the medication compared to single BRAF treatment. We wish to point out that, with combination treatment, there are significantly less number of SCCs and keratoacanthomas which have a cost implication as they require excision, usually under a dermatologist. The rate of SCC/KA development in single agent BRAF is about 20% reduced to around 9% with combination treatment.