

## NCCP Technology Review Committee (TRC)

### Meeting Notes

<b>Date of Meeting:</b>	March 7 <sup>th</sup> 2018 at 5.00pm
<b>Venue :</b>	Teleconference / NCCP Offices
<b>Assessment:</b>	Trametinib (Mekinist®) Nivolumab (Opdivo®)

TEXT FOR REDACTION DUE TO DELIBERATIVE PROCESS HIGHLIGHTED IN YELLOW

TEXT FOR REDACTION DUE TO COMMERCIAL SENSITIVITY IS HIGHLIGHTED IN PINK

TEXT FOR REDACTION DUE TO CONFIDENTIALITY IS HIGHLIGHTED IN BLUE

#### Attendance:

##### Members present

Ms. Patricia Heckmann	NCCP Chief Pharmacist - Chair	
Dr. Ronan Desmond	Consultant Haematologist: IHS representative	By 'phone
Mr. Shaun Flanagan	Pharmacist: HSE Corporate Pharmaceutical Unit	By 'phone
Dr. Patricia Harrington	Head of Assessment, HTA Directorate: HIQA nominee	By 'phone
Dr. Laura McCullagh	National Centre for Pharmacoeconomics (NCPE)	By 'phone
Dr. Deirdre O'Mahony	Medical Oncologist Cork University Hospital: ISMO nominee	By 'phone

##### Non-member invited specialists present

None

##### Apologies (members)

Dr. Oscar Breathnach	Medical Oncologist Beaumont: ISMO nominee
Dr. Michael Fay	Consultant Haematologist: IHS representative
Dr. John Quinn	Consultant Haematologist: IHS representative
Dr. Ray McDermott	Medical Oncologist AMNCH/Vincent's: ISMO nominee
Dr. Deirdre Murray	NCCP Health Intelligence
Dr. Dearbhaile O'Donnell	Medical Oncologist St. James's: ISMO nominee
Dr. Eve O'Toole	Research Group Lead, NCCP
Dr. Cecily Quinn	Consultant Histopathologist St. Vincent's: Nominee Faculty of Pathology

##### Observers present

Dr. Jerome Coffey	National Director, NCCP
Ms. Ciara Mellett	Programme Manager NCCP

Item	Discussion	Actions
1	<p><b>Notes of previous meeting and matters arising</b></p> <p>The notes of the meeting on November 13<sup>th</sup> 2017 were agreed.</p> <p>Members were reminded of the confidentiality of the documents circulated for the TRC and reminded to bear this in mind in relation to the storage and disposal of documentation.</p> <p>In addition to the conflict of interest forms signed by all members previously, members were asked to raise any conflicts of interest that they had in relation to any drug for discussion prior to the commencement of the discussion of that item. No conflicts were raised during the meeting.</p>	
2	<p><b>Drugs/Technologies for consideration</b></p> <p><b>Trametinib (Mekinist®)</b>  <i>In combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation</i></p> <p>The clinical guideline for the drug was outlined by Dr. Deirdre O'Mahony. It was noted that an NCCP rapid evidence review had previously been completed in relation to this drug by the relevant clinical advisory group.</p> <p>The relative efficacy of trametinib and dabrafenib was investigated in two Phase III randomised controlled trials (RCTs), COMBI-D versus dabrafenib and placebo, and COMBI-V versus vemurafenib. The two trials were almost identical in terms of patient population and trial design; the main difference was the double blind design of COMBI-D which had progression free survival (PFS) as the primary endpoint, and the open-label design of COMBI-V which had overall survival (OS) as the primary endpoint. Treatment beyond disease progression was permitted in both trials.</p> <p>The combination of trametinib and dabrafenib was associated with a statistically significant increase in PFS in both trials. Combination treatment was associated with a median PFS of 11 months (95% CI 8, 13.9) in COMBI-D and 12.6 months (95% CI 10.7, 15.5) in COMBI-V, and a HR for PFS or death of 0.67 (0.53, 0.84, p=0.0004) and 0.61 (0.51, 0.73. p&lt;0.01) respectively.</p> <p>The combination of trametinib and dabrafenib was associated with a statistically significant increase in OS in both trials. Combination treatment was associated with a median OS of 25.1 months (95% CI 19.2, not reached) in COMBI-D and 25.6 months (95% CI 22.6, not reached) in COMBI-V, and a HR for OS of 0.71 (0.55, 0.92, p=0.01) and 0.66 (0.53, 0.81. p&lt;0.001) respectively. The overall response rate (defined as complete or partial response) was 69% and 66% in COMBI-D and COMBI-V respectively. In both trials, there was significant use of post-progression systemic anti-cancer treatment, including ipilimumab, pembrolizumab and nivolumab, and so the totality of the OS benefit cannot be attributed to trametinib and dabrafenib alone.</p> <p>Inclusion criteria for the indication include ECOG performance-status score of 0 -1. Combination treatment was associated with a lower number of Grade ≥3 AEs than either dabrafenib or vemurafenib monotherapy, and with a slightly higher number of serious AEs. However, clinicians now have significant experience of combined treatment in these drug classes and management of the toxicities in this setting does not pose any concern for medical oncologists.</p> <p>L. McCullagh outlined the NCPE assessment of the submitted indication. Trial data was as per D. O'Mahony's summary.</p>	

The company presented a Bayesian network meta-analysis (NMA). The NPCE had a number of concerns surrounding some of the assumptions employed for the NMA, particularly for the comparison with pembrolizumab. Among these concerns are the considerable heterogeneity between the included trials and the assumption of proportional hazards between treatments. The NPCE also had concerns about the choice to implement data from the open-label COMBI-V trial to model baseline survival in the model, without using any of the COMBI-D data.

For the cost-effectiveness analysis, the key effectiveness inputs into the model were PFS and OS. Inputs for the comparison of trametinib and dabrafenib with vemurafenib are modelled directly using data from COMBI-V. Inputs for the comparison with dabrafenib monotherapy and pembrolizumab are derived from the NMA. Cost effectiveness was investigated using a partitioned survival model with a 30 year time horizon. The model assumes patients receive treatment until disease progression for all treatments, and assumes dose intensity of 100% for the model base case.

The NPCE implemented a number of changes to the model, including removing the assumption of no wastage of dispensed treatment, amending the distribution of patients across subsequent therapies to reflect the current treatment guidelines and Irish drug reimbursement patterns, assuming the same utility decrement for vemurafenib and dabrafenib in the pre-progression state, and allowing treatment costs to accrue up to 60 months rather than ceasing at the end of trial follow up.

The applicant estimates that between 57 and 64 patients are eligible for treatment annually, and assumes a 40% market share of first line treatment, with 23 patients receiving treatment annually. The applicant estimates the gross budget impact at €18.3 million and the estimated net budget impact at €12.2 million, over 5 years. The NPCE consider that the applicant's assessment underestimates potential market share, and estimated a gross budget impact of between €22.6 and €27 million, and a net budget impact of between €16.5 and €19 million.

The ICERs were as follows:

Trametinib and dabrafenib versus Vemurafenib - €177,275

Trametinib and dabrafenib versus Dabrafenib - €244,822

Trametinib and dabrafenib versus Pembrolizumab - €126,128

The NPCE conclusion is that Trametinib (Mekinist®) is not considered cost-effective in combination with dabrafenib for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation and therefore is not recommended for reimbursement at the submitted price.

S. Flanagan confirmed that there had been engagement with the company since the NPCE review was undertaken and a significantly improved offering has been provided by the company, which significantly improves the cost effectiveness. It was noted that other combination therapies involving MEK inhibitors have been approved previously. The indication currently under discussion was previously considered by the HSE Drugs Group and it is understood that both the Drugs Group and the HSE Leadership Team were in favour of approval for reimbursement, subject to receiving the views of the Technology Review Committee on the clinical effectiveness of the drug.

Having considered the NPCE assessment and the clinical guideline for the drug, the committee agreed that, while another form of combination therapy is available for this patient cohort, this indication offers an alternative combination which is deemed to be clinically beneficial. Some members maintained concerns regarding cost effectiveness, notwithstanding the improvement on this as a result of the company's improved offering.

It was agreed, by majority, to recommend this drug for approval to the HSE Drugs Group. (Decision No. TRC032)





<b>4</b>	<b>Any other business / Next meeting</b>	
	There was no other business.	

The meeting concluded at 17:45.

**Actions arising from meeting:**

Ref.	Date of meeting	Details of action	Responsible	Update
18/01	08/03/18	Recommendations of the Group to be communicated to the HSE Drugs Group.	S. Flanagan (& NCCP letter to HSE Drugs Group chair)	
18/02	08/03/18	Update on drugs currently in reimbursement process to be circulated by e-mail.	P. Heckmann	