National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

NCCP Technology Review Committee (TRC)

Meeting Notes

Date of Meeting:	**March 7th 2018 at 5.00pm**
Venue :	**Teleconference / NCCP Offices**
Assessment:	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	**Notes of previous meeting and matters arising**	
	The notes of the meeting on November 13th 2017 were agreed. 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. 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.	
2	**Drugs/Technologies for consideration**	
	Trametinib (Mekinist®) *In combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation* 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. 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. 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<0.01) respectively. 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<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. 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. L. McCullagh outlined the NCPE assessment of the submitted indication. Trial data was as per D. O'Mahony's summary.	

	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 NCPE 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 NCPE 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 NCPE 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 NCPE 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 NCPE 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 NCPE 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)	

Nivolumab (Opdivo®)
Treatment of squamous cell carcinoma of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy

Dr. Deirdre O' Mahony outlined the clinical guideline for the indication under consideration, which is for patients with refractory or relapsed SCCHN. It was noted that Nivolumab has previously been approved for reimbursement for other indications.

The safety and efficacy of single agent nivolumab for the treatment of recurrent squamous-cell carcinoma of the head and neck in patients whose disease had progressed within 6 months after platinum-based chemotherapy was evaluated in a randomized, openlabel, phase 3 trial (CA209141 Checkmate 141). Patients received nivolumab (at a dose of 3 mg per kilogram of body weight) every two weeks or standard. single-agent systemic therapy (methotrexate, docetaxel, or cetuximab). The primary end point was overall survival. Additional end points included progression-free survival, rate of objective response, safety, and patient-reported quality of life.

The median overall survival was 7.5 months (95% confidence interval [CI], 5.5 to 9.1) in the nivolumab group versus 5.1 months (95% CI, 4.0 to 6.0) in the group that received standard therapy. Overall survival was significantly longer with nivolumab than with standard therapy (hazard ratio for death, 0.70; 97.73% CI, 0.51 to 0.96; P=0.01), and the estimates of the 1-year survival rate were approximately 19 percentage points higher with nivolumab than with standard therapy (36.0% vs. 16.6%).

The median progression-free survival was 2.0 months (95% CI, 1.9 to 2.1) with nivolumab versus 2.3 months (95% CI, 1.9 to 3.1) with standard therapy (hazard ratio for disease progression or death, 0.89; 95% CI, 0.70 to 1.13; P=0.32). The rate of progression-free survival at 6 months was 19.7% with nivolumab versus 9.9% with standard therapy. The response rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group, and tumour reductions were more durable with nivolumab than with standard therapy. On exploratory analyses, neither PD-L1 expression nor p16 status were statistically significant predictive biomarkers for survival benefit from nivolumab therapy.

The inclusion criteria in the clinical guideline will dictate which patients will receive treatment with this indication. The inclusion criteria include an ECOG of 0-1. The majority of patients in Ireland with SCCHN would not have such a good ECOG score so the population that will be availing of this treatment will be relatively small. While there are toxicities associated with the treatment, these are well tolerated once patients are carefully chosen. Consultant medical oncologists are well accustomed to managing these toxicities and there are guidelines available to support this. It is anticipated that immunotherapy in this setting will displace the current second line therapy (docetaxel, cetuximab. methotrexate).

L. McCullagh outlined the NCPE's rapid review of the submitted indication. Trial data was as per D. O'Mahony's summary. XXXXXXXXXXXXXXXXXXXXX
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The clinical efficacy and findings of the trial were discussed. It was agreed that this treatment would only be used in patients that maintain good performance status and it would provide an alternative to existing treatment in these patients where this is a strong unmet need. In this context, it is difficult to be definitive on the likely number of patients but is expected to be a relatively small number of patients. It is possible that there may be a subset of patients who will gain a benefit and will continue on longer-term treatment. It is not possible to quantify the number of such patients and the associated cost.

It was stated that a significant commercial offering has been received from the company. The budget impact is therefore expected to be relatively small due to the small number of patients. XXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXX.

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.

In relation to the clinical guideline, it was agreed to amend the section relating to the prevalent population re:

(i) The 6 month progression cut-off was not highlighted in the trial. It is expected that patients with progression of more than 6 months will be unlikely to have an ECOG of 0-1.
(ii) There is no evidence to support excluding patients who are ineligible for platinum treatment.

These amendments to the clinical guideline were agreed.

Some concerns remained regarding the hazard ratios and the cost per patient. Notwithstanding these, the Committee took into account the NCPE assessment, the clinical guideline for the drug, and particular findings including the high ECOG performance requirements, the trial drop-out rates and number of deaths among poor performance status patients within the first four months. The committee also considered the low budget impact, the potential clinical benefits for a small number of patients and the unmet need in this cohort. On balance, it was agreed, by majority, to recommend this drug for approval to the HSE Drugs Group. (Decision No. TRC033)

3	Update on other drugs in the reimbursement process	
	P. Heckmann undertook to circulate, by e-mail, an update on the drugs that are in the reimbursement process.	

4	**Any other business / Next meeting**	
	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	