National Cancer Control Programme

NCCP Technology Review Committee (TRC)

Meeting Notes

Date of Meeting:	**27th March 2023 at 4.30pm**
Venue :	**Teleconference**
Assessment:	Daratumumab (Darzalex/FASPRO®)
	Nivolumab (Opdivo®) x 2 indications
	Pembrolizumab (Keytruda®)

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		
NCPE representative	National Centre for Pharmacoeconomics (NCPE)	By 'phone
Ms AnneMarie De Frein	NCCP Chief I Pharmacist – Chair	By 'phone
Dr Oscar Breathnach	Medical Oncologist, Beaumont: ISMO nominee	By 'phone
Dr Michael Fay	Consultant Haematologist, Mater Hospital: IHS representative	By 'phone
Prof Michaela Higgins	Medical Oncologist, St. Vincent's University Hospital: ISMO nominee	By 'phone
Prof Michael O'Dwyer	Consultant Haematologist, Galway : IHS representative	By 'phone
Ms Susan Spillane	HTA Directorate: HIQA nominee	By 'phone
Non-member invited specialists present		

Apologies (members)		
Dr Ronan Desmond	Consultant Haematologist, Tallaght University Hospital: IHS representative	
Patricia Heckmann	AND, NCCP	
Dr Dearbhaile O'Donnell	Medical Oncologist, St. James's Hospital: ISMO nominee	
Ms Ellen McGrath	PCRS representative	
Observers present		
Ms Helena Desmond	Senior Pharmacist, NCCP	By 'phone
Ms Margaret Triggs	Chief II Pharmacist, NCCP	By' phone
Dr Derville O'Shea	Consultant Haematologist, Cork University Hospital: NCCP Clinical Lead for Haemato-Oncology	By 'phone

Item	Discussion	Actions
1	**Introduction & reminder re. conflict of interest & confidentiality**	
	Members were reminded 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.	
2	**Notes of previous meeting and matters arising**	
	The notes of the previous meeting on January 23rd were agreed.	
3	**Drugs/Technologies for consideration**	
	Daratumumab (Darzalex/FASPRO®) **(Ref. TRC 128)** *In combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd) for the treatment of adult patients with newly diagnosed light chain amyloidosis* The clinical aspects of this indication were discussed, noting that daratumumab is currently reimbursed for a number of indications and clinicians are very familiar with this drug and its typical side effects. The supporting evidence for this indication is the phase III ANDROMEDA trial which evaluated the safety and efficacy of daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd) vs bortezomib, cyclophosphamide and dexamethasone (VCd) alone in patients with newly diagnosed systemic AL amyloidosis. The primary endpoint was complete haematological response (CHR) rate. It is expected that the introduction of daratumumab will be an addition to the current standard of care (SOC) VCd in first line treatment for newly diagnosed patients. . It will provide the first licensed treatment option in the current treatment pathway for this patient cohort. The safety profile was discussed, noting that the side effects are consistent with the known safety profile of the drugs individually and the underling disease itself, it was also highlighted that the magnitude of benefit received from the addition of daratumumab to the current SOC makes up for any slight increase in toxicity. There is a strong desire among clinicians to have this treatment option available for this cohort of patients, as the addition of daratumumab to the current SOC has demonstrated a clinically meaningful benefit in terms of achieving rapid response and control of disease. This is especially welcomed in patients with cardiac amyloidosis where a rapid response is key to slowing the progression of disease. It was discussed that this is seem as a major advance by the myeloma community and that although it may take time to see gains on overall survival, patients will benefit from increased disease control. There was some discussion on duration of treatment, noting this was limited to 24 cycles in the trial but is not limited within the licensed indication and associated summary of product characteristics. The pharmacoeconomic aspects as outlined in the HTA assessment carried out by the NCPE were discussed. A number of uncertainties were highlighted by the review group, such as the duration of treatment, and the benefit of continuing until disease progression rather than treating for a maximum of 24 treatment cycle as per the trial. Other concerns leading to uncertainties were the open label nature of the trial, the surrogate primary end point of complete haematological response (CHR) as opposed to overall survival (OS), a key secondary endpoint. At the interim analysis 1, in terms of CHR, 53.3% of patients in the D-VCd arm achieved CHR versus 18.1% in the VCd arm, while the OS data was immature with only 13.8% of patients experiencing an OS. The cost effectiveness model used was discussed, treatment with daratuzumumab is associated with a high cost and high ICERS. The NCPE did not adjust the base case as there are number of uncertainties associated with the structural aspects of the model, so a range of ICERS were determined ranging from €66,254 to 95,420 per QALY.	

. The budget impact (BI) was outlined (consider the list price), with a 5 year gross BI estimated to be €24 million including VAT and €19.3 million excluding VAT based on the assumption of maximum treatment duration of 24 cycles. The net 5 year BI was estimated to be €22million including VAT and 18.1 million excluding VAT. Considering the NCPE review group recommended that daratumumab in combination with VCd) not be considered for reimbursement unless cost can be improved relevant to existing treatments.

Having considered the clinical efficacy of the indication in this patient cohort the committee members agreed by majority to recommend approval of this indication to the HSE Drugs Group.

(Decision: TRC 128)

Nivolumab (Opdivo®) (**Ref. TRC 129)**

For the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

The clinical aspects of this indication were discussed. The supporting evidence for this indication is the phase III, randomised, double blind, placebo controlled CheckMate 577 study, which evaluated the safety and efficacy of nivolumab as monotherapy for the treatment of adult patients with stage II or III carcinoma of the oesophagus or GEJ who had completed pre-operative chemoradiotherapy followed by surgery. The study showed an improvement in disease free survival (DFS) of approximately 22 months with nivolumab versus 10 months with placebo and a distant metastases free survival of 30% vs 17%. The study demonstrated that in early stage of disease that immunotherapy has an advantage in survival in a disease historically associated with poor outcomes. The safety profile was discussed nothing that nivolumab is associated with manageable side effects which most oncologist are now quite used to dealing with. There is a strong desire among clinicians to have this treatment option available to this patient cohort, noting the opportunity to bring clinically meaningful benefit to a population in an earlier treatment setting.

The pharmacoeconomic aspects as outlined in the HTA carried out by the NCPE were discussed. The NCPE review group highlighted concerns regarding the key efficacy endpoints and models in terms of age of the study population, noting that adjustments to the model were made. In terms of the cost effectiveness, the ICER was outlined based on the applicants base case at €29,521 per QALY and the NCPE review group QALY which is below the €45k/QALY threshold. The budget impact (BI) was discussed, noting that it is a sizable amount but when proposed PAS offer is considered the adjusted NCPE 5 year NET BI is estimated to be million including VAT and million excluding VAT. The recommendation of the NCPE review group was to recommend reimbursement subject to the PAS offer being agreed.

Having considered the clinical efficacy of the indication in this patient cohort the committee members agreed by a majority to recommend approval of this indication to the HSE Drugs Group.

(Decision: TRC 129)

Nivolumab (Opdivo®) (**Ref. TRC 130)**

In combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%

The clinical aspects of this indication were discussed. The supporting evidence for this indication is the phase III, randomised, open label CheckMate 648 study, which evaluated the safety and efficacy of nivolumabin combination with chemotherapy for the treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) with tumour cell programmed death ligand 1 (PD-L1) expression ≥1%. The study showed at 24 months an overall survival (OS) of 30% with nivolumab in combination with chemotherapy vs 12% with chemotherapy alone, demonstrating a significant improvement in survival for this patient cohort. The safety profile was discussed nothing that nivolumab is associated with manageable side effects which most oncologist are now quite used to dealing with. There is a strong desire among clinicians to have this treatment option available to this patient cohort as this marks the first notable advance in treatment showing benefit to patients in this space over the past 20 to 30 years.

The pharmacoeconomic aspects as outlined in the rapid review assessment carried out by the NCPE were discussed, noting that a full HTA was recommended, subject to the price being reduced, which has not been submitted to date. It was also noted that there is also another alternate combination treatment with immunotherapy and chemotherapy in the assessment process for this patient cohort, though in a broader indication. In terms of the cost effectiveness, the budget impact (BI) was outlined and based on the proposed price and the PAS currently in place the 5 year gross BI is estimated to be and the 5 year net BI is estimated to be , which the NCPE would recommend is reasonable not to proceed to a full HTA.

Having considered the clinical efficacy of the indication in this patient cohort the committee members agreed by a majority to recommend approval of this indication to the HSE Drugs Group.

(Decision:TRC130)

Pembrolizumab Keytruda® ((**Ref. TRC 131)**

In combination with, platinum and fluoropyrimidine-based chemotherapy for the first-line treatment for patients with locally advanced unresectable or metastatic carcinoma of the oesophageal or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS≥10.

The clinical aspects of this indication were discussed, noting that pembrolizumab is approved for reimbursement across multiple indications and used widely in medical oncology. The supporting evidence for this indication is the phase III, randomised, double blind, placebo controlled KEYNOTE-590 study in patients with previously untreated, locally advanced, unresectable or metastatic oesophageal carcinoma or gastroesophageal junction carcinoma (Siewert type I) regardless of PD-L1 status. The study showed overall median survival of 13.5 months with pembrolizumab plus chemotherapy versus 9 months with chemotherapy alone, an advantage of approximately 4 months. In the pembrolizumab arm 26% vs 6% of patients achieved a survival advantage in a disease with relatively few options. There is a strong desire among clinicians to have this treatment option available to this patient cohort, noting that this is seen as the first clinical meaningful

	advance in treatment for this patient cohort over the past 20 to 30 years. The pharmacoeconomic aspects as outlined in the HTA assessment carried out by the NCPE were discussed, nothing at that there is also another alternate combination treatment with immunotherapy and chemotherapy in the assessment process for a sub-cohort of this patient population. The NCCP review group raised a number of uncertainties with the supporting data with regards to the overall survival (OS) modelling and the generalisability of the OS data to the Irish clinical practice. In terms of the cost effectiveness, the ICER was outlined based on the applicant's base case at €73,791 per QALY. The NCPE carried out a number of adjustments to the base case to give a NCPE adjusted ICER of at €100,158 per QALY. Considering the current PAS in place for pembrolizumab the NCEP adjusted based case reduces to However this does not address the uncertainties with regard to the modelling for OS. The budget impact (BI) was outlined and considering the PAS the 5 year gross BI is estimated to be NCPE review group recommended that pembrolizumab not be considered for reimbursement unless cost can be improved relevant to existing treatments. Having considered the clinical efficacy of the indication in this patient cohort the committee members agreed by a majority to recommend approval of this indication to the HSE Drugs Group. *(Decision:TRC131)*	
4	**Update on other drugs in the reimbursement process**	
	An update had been shared with the group in the documentation for the meeting	
5	**Next meeting**	
	The proposed date for the next meeting is April 24th 2023	
6	**Any other business / Next meeting**	
	TRC Membership Changes: Prof Michael O'Dwyer has been nominated by the IHS as a new member to the TRC. Prof O'Dwyer, will replace Dr O'Shea, who as the National Clinical Lead for Haemato-Oncology, is an observer at the NCCP-TRC. The Chair welcomed Prof O' Dwyer to the committee. It was also announced that Dr Dearbhaile Collins will be joining the committee as ISMO representative and Prof Michaela Higgins will step back from full membership but will remain available as an alternate member as required. CPD: It was discussed that the NCCP will apply to the RCPI for CPD credits for each NCCP-TRC meeting for the clinicians in attendance and will issue certificates once a year in April. It was noted that there will be a post-meeting evaluation to facilitate this process of obtaining CPD points.	NCCP

The meeting concluded at 5.44pm.

Actions arising from meeting:

Ref.	Date of meeting	Details of action	Responsible	Update
23/01	27/03/2023	NCCP to communicate recommendations to HSE Drugs Group.	NCCP	Complete
23/01	27/03/2023	Apply for CPD	NCCP	Complete