National Cancer Control Programme

NCCP Technology Review Committee (TRC)

Meeting Notes

Date of Meeting:	**21st October 2024 at 4.30pm**
Venue:	**Teleconference via MS Teams**
Assessment:	Carfilzomib (Kyprolis®)
	Erdafitinib (Balversa®)
	Ropeginterferon alfa-2b (Besremi®)

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		
Dr Neil Barrett	Consultant Haematologist, Children's Health Ireland - Crumlin	By MS Teams
Dr Oscar Breathnach	Medical Oncologist, Beaumont: ISMO nominee	By MS Teams
Dr Dearbhaile Collins	Consultant Medical Oncologist, Cork University Hospital: ISMO nominee **(Chair)**	By MS Teams
Dr Patrick Hayden	Consultant Haematologist, St James's :IHS representative	By MS Teams
Prof Michael O'Dwyer	Consultant Haematologist, Galway :IHS representative	By MS Teams
Ms Fiona Mulligan	PCRS representative	By MS Teams
Dr Adrian Murphy	Medical Oncologist, Beaumont: ISMO nominee	By MS Teams
Non-member invited specialists present		
Dr Claire Andrews	Consultant Haematologist, St Vincent's University Hospital Dublin	By MS Teams
Apologies (members)		
NCPE representative	National Centre for Pharmacoeconomics (NCPE)	
Dr Dearbhaile O'Donnell	Medical Oncologist, St. James's Hospital: ISMO nominee	
Dr Susan Spillane	HTA Directorate: HIQA nominee	
Observers present		
Ms Aishling McLoughlin	Chief I Pharmacist, NCCP	By MS Teams
Ms Elizabeth Breen	Chief II Pharmacist, NCCP	By MS Teams
Ms Helena Desmond	Senior Pharmacist, NCCP	By MS Teams

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 August 26th and September 23rd were reviewed and agreed.	
3	**Drugs/Technologies for consideration**	
	Carfilzomib (Kyprolis®) (**Ref. TRC 160)** *In combination with dexamethasone and daratumumab (KdD) as a triplet regimen for the treatment of adult patients with relapsed and/or refractory multiple myeloma (R/RMM) who have received at least one prior therapy.* The clinical aspects of this indication were discussed. It was noted that carfilzomib is currently approved for reimbursement in combination with lenalidomide and dexamethasone, and in combination with dexamethasone for this patient cohort. The supporting evidence for this indication comes from the CANDOR trial, a phase III, randomised, open-label clinical trial which to compared the use of carfilzomib in combination with daratumumab and dexamethasone (KdD) versus carfilzomib plus dexamethasone (Kd) in patients with MM who had received one prior therapy. The trial demonstrated a progression free survival (PFS) benefit with KdD compared to Kd, PFS for KdD was 27.9 months versus 15 months with Kd showing over 1 year improvement in PFS with the addition of daratumumab to Kd. Overall response rate (ORR) was slightly better with KdD versus Kd (84% vs 74%) and the minimal residual disease (MRD) rate (10^{-5}) was 28% with KdD as opposed to 9% with Kd. It noted that in the CANDOR trial treatment continued for up to a maximum of 5 years, however in the licensed indication treatment maybe be continued until disease progression, however with a PFS of 27.9 months, a very small cohort of patients the would receive treatment beyond 5 years. The safety profile was discussed, serious adverse events were reported in 56% of patients in the KdD arm and 46% in the kd arm. The most common adverse events were anaemia (2% versus 1%), diarrhoea (2% versus 0%), pyrexia (4% versus 2%) and pneumonia (12% versus 9%). In relation to carfilzomib with the known cardiac risks, death due to adverse events within 30 days of the last dose occurred in 10% of patients in the KdD arm versus 5% in the Kd arm, however the most common cause of death was infections 5% versus 3%. It was noted the clinicians are very familiar with all agents in this regimen. There is a strong desire among the clinicians to have KdD available for this patient cohort, especially those who have had prior to exposure to lenalidomide or for those refractory to lenalidomide. PFS with the current treatment options for this subgroup is less than 1 year. In the CANDOR study, in the lenalidomide refractory subgroup there was no difference in PFS, demonstrating that this combination is far superior and highly active in comparison to the currently available options. It was noted that since 2021, the ESMO clinical guidelines have recommended KdD as a preferred treatment option for this patient cohort. The pharmacoeconomic aspects as outlined in the HTA assessment carried out by the NCPE were discussed. The relevant comparators and the positioning of KdD in the treatment pathway was outlined. The supporting evidence was outlined, issues with design & conduct and limitation of the CANDOR trial were highlighted, such as the stopping rule of maximum 5 years, lack of a statistically significant improvement in overall survival (OS), open-label nature of the trial for example. The cost effectiveness model (CEM) was outlined and limitations of treatment effectiveness in the CEM were noted such as, long-term extrapolation of relatively short term data from the trials, the Applicant base case uses different survival distributions to extrapolate PFS, extrapolation of the OS data in the comparison with pomalidomide plus bortezomib and dexamethasone is based on the PFS:OS	

relationship. In terms of the results, the Applicant base case ICERs versus pomalidomide plus bortezomib and dexamethasone (pom+bor+dex) and daratumumab in combination with bortezomib and dexamethasone (dar+bor+dex), are between 443k to 548k per QALY. The Applicant also presented results for the lenalidomide exposed population, the ICER for Kd increases relative to licensed population, ICER for dar+bor+dex remains similar whereas the ICER for pom+bor+dex decreases. The NCPE adjusted base case results in only one change that affects the comparison with Kd only. ICERs for dar+bor+dex and pom+bor+dex remain the same. In both the Applicant analysis and the NCPE adjusted base case analysis, KdD has 0% probability of being cost-effective at 20k/45k QALY threshold. Pom+bor+dex has the highest probability of being cost-effective. Price-ICER relationship shows that even at zero cost (100% rebate on carfilzomib), the ICERs are not cost-effective for any comparison. In terms of the budget impact (BI), the Applicant restricted patient numbers to those who had received prior lenalidomide, the NCPE review groups had concerns with this as it is not a pre-requisite and likely underestimates the patient population and budget impact. Estimated update of 5% in year 1 rising to 25% in year 5, will proportionately displace Kd, dar+bor+dex and pom+bor+dex. The 5-year net drug BI is estimated to be €33.87 million (including VAT) and €30.66 million (excluding VAT). The NCPE recommends that KdD not be considered for reimbursement.

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 160)

Erdafitinib Balversa® (**Ref. TRC 161)**

As monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (mUC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting.

The clinical aspects of this indication were discussed, erdafitinib targets *FGFR3* genetic alterations, which affects approximately 20% of patients with urothelial carcinoma (UC). The supporting evidence for this indication is the THOR study, a phase III, randomised, open-label study, investigating the use of erdafitinib for the treatment of adult patients with unresectable or mUC who are harbouring susceptible *FGFR3* genetic alterations, and who had previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting. The trial compared erdafitinib to chemotherapy, the chemotherapy of choice was docetaxel or vinflunine, it was noted that vinflunine is not used in clinical practice in Ireland. THOR was a positive study in favour of erdafitinib with approximately 4 months absolute improvement in overall survival (OS) with 12 months in the erdafitinib arm versus 8 months with chemotherapy arm, with a hazard ratio (HR) of 0.64 and progression free survival (PFS) of 5.6 months versus 2.7 months, similar duration of response were seen. The safety profile of erdafitinib was discussed, the toxicities expected for this class of drugs, such as hyperphosphataemia, which is well known for this class of drugs. One in five patients tested across the board will have *FGFR3* genetic alterations, and therefore is desire among the clinicians to have a targeted therapy available for this patient cohort.

The pharmacoeconomic aspects as outlined in the rapid review assessment carried out by the NCPE were discussed. The positioning of erdafitinib in the current treatment pathway was noted and the relevant comparator was outlined, noting that mUC landscape is rapidly evolving. The cost effectiveness analysis and the modelling used was notedn terms of the budget impact (BI), based on list prices, erdafitinib is cost saving when VAT

	is considered and has a BI when VAT is excluded. Cost savings in terms of net BI of €43,245 over 5 years when VAT is considered. Erdafitinib is associated with a net drug BI of €271,025 when VAT is not considered. Edrafitinib is oral while enfortumab vedotin is administered intravenously, therefore there is a potential for future cost savings for the wider healthcare budget. The NCPE recommends that erdafitinib not be considered for reimbursement at the submitted price. There is uncertainty regarding comparative effectiveness versus enfortumab vedotin and the mUC landscape is rapidly evolving. Having considered the clinical efficacy of the indication in this patient cohort the committee members agreed unanimously to recommend approval of this indication to the HSE Drugs Group. *(Decision: TRC 161)* Ropeginterferon alfa-2b Besremi® (**Ref. TRC 162)** *Ropeginterferon alfa-2b is indicated as monotherapy in adults for the treatment of polycythaemia vera (PV) without symptomatic splenomegaly.* The clinical aspects of this indication were discussed. The use of pegylated interferon (peginterferon alfa-2a) for the treatment of myeloproliferative neoplasms (MPN) has increased over the past 10 years in place of non-pegylated interferon due to reduced toxicity. Peginterferon alfa-2a, the current available treatment option, with a once weekly dosing schedule is experiencing a world-wide shortage. Ropeginterferon alfa-2b, a treatment licensed specifically for PV, provides an alternative treatment option in the first line treatment for patients with MPN, in particular, younger patients, who are either unsuitable for hydroxyurea or ruxolitinib, child bearing potential or pregnant. Ropeginterferon alfa-2b is administered once every two weeks and is associated with less toxicities, such as flu-like symptoms for example. The supporting evidence for this indication comes from the PROUD-PV study, a phase III, open label, randomised, controlled, parallel-group, non-inferiority study which evaluated the use of ropeginterferon alfa-2b compared to hydroxyurea in the treatment of PV without splenomegaly. The PROUD-PV study demonstrated that after 1 year, there was very little difference in the complete haematological response (CHR) with ropeginterferon alfa-2b compared to hydroxyurea. However it was noted that that the longer patients remain on interferon, the better the response, the difference between interferon, and all other treatments for MPN is that interferon results in disease modification by achieving a molecular remission in patients, and recent studies have shown that patients with PV treatment with interferon prevents the development of myelofibrosis. There is a strong desire among the clinicians to have ropeginterferon alfa-2b available for this patient cohort, especially for young patients, and the availability of treatment with a dosing schedule of once every two weeks would provide more tolerable treatment option for patient cohort. The pharmacoeconomic aspects as outlined in the HTA assessment carried out by the NCPE were discussed. The relevant comparators and the positioning of popeginterferon alfa-2b in the treatment pathway was outlined, noting that this represents a narrow subgroup of the licence. The supporting evidence was outlined and the limitations of clinical trials were noted, a robust assessment of benefit of ropeginterferon alfa 2b versus hydroxyurea was not possible based on exploratory nature of non-inferiority assessment, only a minority of PROUD-PV population represent the Applicant target population and no direct evidence versus ruxolitinib or pegylated interferon. The cost effectiveness model (CEM) was outlined. The annual cost of roppeginterferon alfa-2b is estimated to be €46,704 (including VAT) and €37,522 (excluding VAT), assuming 20 pens delivered per year, however this is likely to be underestimated by the lack of accounting for pen wastage. The cost is similar to ruxolitinib at a dose of 26.7mg/day but approximately double the cost of ruxolitinib at a dose of 20mg/day. The annual cost of	

	pegylated interferon is around a quarter the cost of ropeginterferon. Ropeginterferon alfa 2-b is dominated by ruxolitinib, meaning it is a less effective and more costly option. The CEM results are highly uncertain given limitations of the model structure and the supporting assumptions. In terms of the budget impact (BI), the applicant included prevalent patients but not incident patients in patient population calculations. The NCPE adjusted base case analysis estimates that the five-year net drug BI impact of ropgeinterferon is €9.6 million (including VAT) and €7.3 million (excluding VAT). The NCPE recommends that ropeginterferon alfa 2-b not be considered for reimbursement unless cost-effectiveness can be improved. 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 162)*	
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 November 25th 2024	
6	**Any other business / Next meeting**	

The meeting concluded at 17.45pm.

Actions arising from meeting:

Ref.	Date of meeting	Details of action	Responsible	Update
24/01	21/10/2024	NCCP to communicate recommendations to HSE Drugs Group.	NCCP	Completed
24/01	21/10/2024	Apply for CPD	NCCP	Completed