National Cancer Control Programme

NCCP Technology Review Committee (TRC)

Meeting Notes

Date of Meeting:	**22nd April 2024 at 4.30pm**
Venue:	**Teleconference via MS Teams**
Assessment:	Pembrolizumab (Keytruda®)
	Trastuzumab deruxtecan (Enhertu®)

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 MS Teams
Dr Neil Barrett	Consultant Haematologist, Children's Health Ireland - Crumlin	By MS Teams
Dr Dearbhaile Collins	Consultant Medical Oncologist, Cork University Hospital: ISMO nominee **(Chair)**	By MS Teams
Prof Michaela Higgins	Consultant Medical Oncologist, Cork University Hospital: ISMO nominee	By MS Teams
Ms Fiona Mulligan	PCRS representative	By MS Team
Dr Susan Spillane	HTA Directorate: HIQA nominee	By MS Team
Non-member invited specialists present		
Dr Oscar Breathnach	Medical Oncologist, Beaumont: ISMO nominee	
Dr Patrick Hayden	Consultant Haematologist, St James's :IHS representative	
Dr Dearbhaile O'Donnell	Medical Oncologist, St. James's Hospital: ISMO nominee	
Prof Michael O'Dwyer	Consultant Haematologist, Galway :IHS representative	
Observers present		
Ms Patricia Heckmann	AND NCCP	By MS Teams
Ms Helena Desmond	Senior Pharmacist, NCCP	By MS Teams
Ms Ciara Ryan	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 March 25th were reviewed and an amendment was made.	
3	**Drugs/Technologies for consideration**	
	Pembrolizumab (Keytruda®) **(Ref. TRC 152)** *In combination with lenvatinib (Lenvima®) for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.* The clinical aspects of this indication were discussed, endometrial cancer (EC) falls into two molecular subtypes, mismatch repair proficient (pMMR) and mismatch repair deficient (dMMR). Patients with dMMR are more likely to respond to immune checkpoint inhibitors (ICIs) and immunotherapy (I-O) base treatments, whereas the pMMR population (accounting for two thirds of the EC population) are less likely to respond to ICI's and I-O alone. Currently most patients with pMMR receive chemotherapy which is associated with a low response rate, with progression free survival (PFS) of approximately 3 months. The supporting evidence for this indication is the KEYNOTE-775 trial, a phase III, open label trial which compared the efficacy and safety of pembrolizumab-plus-lenvatinib with the physician's choice of doxorubicin or paclitaxel chemotherapy in patients with advanced EC who had disease progression after at least one platinum-based therapy. The study enrolled 827 patients and the study population included patients with both dMMR and pMMR EC. At the data cut off of March 2022, the study showed, that in the overall population (both the dMMR and the pMMR) PFS was 7.2 months in the pembrolizumab-plus-lenvatinib arm versus 3.8 months in the chemotherapy arm. Overall survival (OS) was 18.3months in the pembrolizumab-plus-lenvatinib arm versus 11.4 months in the chemotherapy arm. Updated result shows an improvement in OS of 18.7 months with pembrolizumab-plus-lenvatinib vs 11.9 months in the chemotherapy arm, showing a significant improvement. In the pMMR population the study showed a median PFS of 6.6 months in the pembrolizumab-plus-lenvatinib arm versus 3.8 months in the chemotherapy arm, updated to 6.7 months versus 3.8 months at the most recent data cut. OS in the pMMR population was 17.4 months in the pembrolizumab-plus-lenvatinib vs 12 months in the chemotherapy arm with a hazard ratio (HR) of 0.68. The safety profile of pembrolizumab-plus-lenvatinib was discussed, noting that pembrolizumab is well tolerated, while lenvatinib tends to be poorly tolerated, however this can be managed with dose reductions. The use of pembrolizumab-plus-lenvatinib in the treatment of EC has shown statistically significant improvement in outcomes, however, currently there is no ICIs approved for reimbursement for EC in the Irish public health sector, and there is a strong desire among the clinicians to have this treatment option available for this patient cohort, who have a real clinical need. The pharmacoeconomic aspects as outlined in the HTA assessment carried out by the NCPE were discussed, noting that the licensed indication is for all comers and that the applicant did not apply any restriction to the application for reimbursement. The positioning of pembrolizumab-plus-lenvatinib in the treatment pathway and relevant comparators were discussed. The supporting evidence was outlined, noting that the data from the data cut of March 2022 were used in the NCPE assessment, which showed a PFS benefit, with a HR of 0.56 in the overall population and the HR for OS was 0.65. The NCPE Review Group highlighted a number of limitations regarding the supporting evidence, such as open label nature of the trial, the trial population and duration of treatment for pembrolizumab, noting that a stopping rule of 2 years (35 cycles) was implemented in the trial, while the licenced indication permits the use of pembrolizumab until disease	

progression. In terms of the cost, the Applicant implemented a 2-year stopping rule in their base case, however the NCCP review group removed this to align with the license. In the Applicant's base case, the cost of treatment per course of pembrolizumab-plus-lenvatinib is [redacted] based on a mean duration of 43.29 weeks for pembrolizumab and 55.23 weeks for lenvatinib. The NCPE adjusted base case was estimated to be [redacted] based on a median PFS of 78.67 weeks (26.22 cycles), the median duration of lenvatinib was the same as the Applicant's estimation of 55.23 weeks. The Applicants ICERS is €121,749 per QALY. Changes were made in the NCPE-adjusted base case, such as the removal of the stopping rule which resulted in a NCPE-adjusted base case ICER of €197,770 per QALY, noting if a stopping a stopping rule were to be implemented the NCPE-adjusted base case ICER is estimated [redacted]. There is 0% probability of cost effectiveness at both the Applicant's and the NCEP base case and a reduction of 98.55% is required for pembrolizumab to be cost effective at the €45,000 per QALY. In terms of the budget impact (BI), 20 patients are estimated to be treated in year 1, increasing to 29 in year 5. The Applicant's estimation did not include patents who received platinum based treatment in the neoadjuvant/adjuvant setting and estimated that 36% of patients will be eligible for treatment in the second line setting. Based on the Applicants assumption the estimated 5-year net BI is €12.72M including VAT. Using the NCPE-adjusted base case assumptions based on the mean treatment duration and that 42.5% of patients will be eligible for treatment in the second line setting, the 5-year net BI was estimated to be €33.784M including VAT. The NCPE recommends that pembrolizumab-plus-lenvatinib not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. The clinicians put forward the proposal of aligning the treatment duration with supporting clinical trial KEYNOTE-775 trial, and implement a 2-year stopping rule with a maximum treatment duration of 35 cycles. This will be discussed with the NCCP Gynaecology Clinical Advisory Group (CAG).

Having considered the clinical efficacy of the indication in this patient cohort there was a split vote where 3 committee members recommended the approval of this indication to the HSE Drugs Group subject to an improvement in cost and the proposal of implementing at 2-year stopping rule, while 3 members recommended that this indication not be approved for reimbursement.

(Decision: TRC 152)

Trastuzumab deruxtecan (Enhertu®) **(Ref. TRC 153)**

As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

The clinical aspects of this indication were discussed. The supporting evidence for this indication is the DESTINY 03 study, a phase III, open label trial which evaluated the use of trastuzumab deruxtecan compared with trastuzumab emtansine in adult patients with unresectable or metastatic HER2-positive breast cancer who had received previous treatment with trastuzumab and a taxane for metastatic disease or developed disease recurrence during or within 6 months of completing neo-adjuvant or adjuvant treatment involving trastuzumab or a taxane. At a median study follow up period of approximately 28 months, the primary endpoint of progression free survival (PFS) was significantly improved at 28.8 months with trastuzumab deruxtecan versus 6.8 months with trastuzumab emtansine (the current standard of care (SOC) for this patient cohort), showing that trastuzumab deruxtecan is a highly active drug. While the overall survival (OS) data is immature, the hazard ratio (HR) looks extremely promising as do the survival rates at 12 and 24 months. The safety profile of trastuzumab

	deruxtecan was discussed, noting that it is a quite toxic drug. However, by participating in clinical trials and expanding access programmes, clinicians have experience with its use and managing the associated side effects, it was also noted that it would not be used in patients with poor performance status, pneumonitis or cardiac disease. There is strong desire among the clinicians to have this treatment available for this cohort of patients, a treatment which has shown a significant improvement compared to the current SOC, noting that it is recommended by other jurisdictions e.g. NICE and international guidelines such as NCCN. The pharmacoeconomic aspects as outlined in the HTA assessment carried out by the NCPE were discussed. The positioning of trastuzumab deruxtecan in the current treatment pathway was discussed. The supporting evidence and safety profile was outlined. The cost effectives modelling was discussed, and a number of concerns were highlighted by the NCCP review group, such as the patient characteristics (approx.60% of patients enrolled were Asian), and immaturity of the OS data. In terms of cost, the total cost per treatment course for trastuzumab deruxtecan [redacted] treatment course for trastuzumab emtansine. It was noted, that the Applicant assumed that 50% of cases would be subjected to vial sharing, however the NCPE review group did not consider this reasonable and in the NCPE adjusted base case 100% vial wastage is assumed. Applicant's base case ICER was €71,279 per QALY. A number of changes were made to the NCCP base case for patient characteristics, removal of vial sharing, and subsequent treatments, resulting in a NCPE-adjusted base case ICER of €111,193 per QALY. There is 0% probability of cost effectiveness in the NCPE base case and a 41.2% reduction in the price to the wholesaler is required in order for the willingness to pay threshold of €45,000 per QALY to be reached. In terms of the budget impact (BI) the Applicant assumes that [redacted] will be eligible for treatment in year 1 increasing to [redacted] in year 5. The NCCP review group made a number of changes for the NCPE BI estimates. Under the Applicants assumptions the 5-year gross BI is estimated to be €59.4 million including VAT and the 5-year net BI is estimated to be €42.9 million including VAT. In the NCPE adjusted base case the 5-year gross BI is estimated to be €66.5 million including VAT and 5-year net BI is estimated to be €40.5 million including VAT. The NCPE recommends that trastuzumab deruxtecan be considered for reimbursement if the cost-effectiveness can be improved relative 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 153)*	
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 May 27th 2024	
6	**Any other business / Next meeting**	

The meeting concluded at 17.44pm.

Actions arising from meeting:

Ref.	Date of meeting	Details of action	Responsible	Update
24/01	22/04/2024	NCCP to communicate recommendations to HSE Drugs Group.	NCCP	Complete
24/01	22/04/2024	Apply for CPD	NCCP	Complete