National Cancer Control Programme

NCCP Technology Review Committee (TRC)

Meeting Notes

Date of Meeting:	**26th August 2024 at 4.30pm**
Venue:	**Teleconference via MS Teams**
Assessment:	Ciltacabtagene autoleucel (CARVYKTI®)
	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 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
Ms Fiona Mulligan	PCRS representative	By MS Teams
Prof Michael O'Dwyer	Consultant Haematologist, Galway :IHS representative	By MS Teams
Non-member invited specialists present		
Prof Fergal Kelleher	Medical Oncologist, St James's Hospital	By MS Teams
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	
Dr Susan Spillane	HTA Directorate: HIQA nominee	
Observers present		
Ms Elizabeth Breen	Chief II Pharmacist, NCCP	By MS Teams
Ms Helena Desmond	Senior Pharmacist, NCCP	By MS Teams
Dr Derville O'Shea	Consultant Haematologist, Cork University Hospital	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 May 27th were reviewed and agreed	
3	**Drugs/Technologies for consideration**	
	Ciltacabtagene autoleucel (CARVYKTI®) (**Ref. TRC 156**) *For the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.* The clinical aspects of this indication were discussed, and it was noted that due to the availability of new agents with different and improved mechanisms of action, survival rates of myeloma have improved dramatically over the past 30 years, with a median survival of approximately 8 years versus between 2 to 3 years, however patients continue to relapse. The supporting evidence for this indication comes from the CARTITUDE-1 study a phase 1b/2, open label, single-arm, multicentre study which evaluated the use of ciltacabtagene autoleucel for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who had received at least three prior lines of anti-myeloma therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on or within 12 months after the last regimen. In this study, 97 patient were treated with ciltacabtagene autoleucel, and the study showed an overall response rate (ORR), the primary endpoint, of 98%, and of these, 82.5% achieved a stringent complete response (sCR), with 55% of patients achieving minimal residual disease (MRD) or stable MRD negativity at a level of $1x10^{-5}$, for over 12 months. At the latest follow up median progression free survival (PFS) was 34.9 months. A median PFS for almost 35 months is remarkable in a patient population who historically have really poor survival rates, where the overall survival (OS) for rates for patients who are triple class refractory is less than 1 year. The safety profile of ciltacabtagene autoleucel was discussed, associated toxicities, are cytokine release syndrome (CRS), however the rate of grade 3 or 4 CRS was about 5% and there was a relative low incidence of severe ICANS, haematological toxicity was the greatest toxicity due to lymphodepletion. It was noted that the associated toxicities are manageable. There is a strong desire among the clinicians to have ciltacabtagene autoleucel available to this patient cohort, who have an unmet need. The pharmacoeconomic aspects as outlined in the HTA assessment carried out by the NCPE were discussed. It was noted that CAR-T therapy is currently available at one accredited treatment centre in Ireland. The international guidelines for the treatment of RRMM were outlined, along with the current standard of care (SOC), relevant comparators and the positioning of ciltacabtagene autoleucel within the treatment pathway. The supporting clinical evidence was outlined, the NCPE Review Group highlighted a number of limitations regarding the supporting evidence, such as the single arm, open label nature of the study, immaturity of the data and the uncertainty of the PFS and OS benefit due to the relapsing nature of the disease. The cost effectiveness analysis was discussed and the modelling used was outlined. In terms of the cost, the total cost for a single ciltacabtagene autoleucel infusion, a once off treatment, is €385,350 excluding VAT and €481,950 including VAT. The treatment course costs for the relevant comparators were outlined, and the cost of hospitalisation is assumed to capture the cost of ciltacabtagene autoleucel administration. The ICERS were outlined, the Applicant's base case ICER is €96,892 per QALY. The NCPE review group made a number of changes to address some of the limitations identified, the cost of additional treatment and amendments to the duration of hospital stay to account for the cost ciltacabtagene autoleucel administration. The NCPE adjusted base case is €122,926 per QALY. There is	

	a 0% probability of cost effectiveness at either the €20,000/QALY or €45,000/QALY threshold and a 59.1% reduction in the price to wholesaler would be required to meet the €45,000/QALY threshold. In terms of the budget impact (BI), the BI model assumed that 10 patients will be treated in year 1, increasing to 15 patients by year 5, however there is the potential for the number of treated patients to increase if the capacity within Ireland increases. The cumulative 5-year net BI was estimated to be €30.3 million including VAT, or €23.89 million excluding VAT, noting at this does not consider the extra costs of ciltacabtagene autoleucel infusion such as apheresis, bridging and conditioning therapy,. The NCPE recommends that ciltacabtagene autoleucel be not considered for reimbursement unless 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 156)* Pembrolizumab (Keytruda®) (**Ref. TRC 157)** *For the adjuvant treatment of adults and adolescent (≥12 years of age) with stage IIB or IIC melanoma following complete resection.* The clinical aspects of this indication were discussed. Since 1994 the incidence of melanoma has been increasing, with the most recent data from 2021, showing 1,263 cases per year in Ireland, which represents almost 5% of all invasive tumours. The supporting evidence for this indication is the KEYNOTE-716, a randomised, double-blind, placebo-controlled, phase III study which evaluated the use of adjuvant pembrolizumab in the treatment of stage IIB and IIC melanoma in adults and adolescents aged 12 years and older who have undergone complete resection. There were a number of read outs for this study, in the first publication, April 2022, after a median follow up of 14.4 months, 11% of patients in the pembrolizumab group and 17% of patients in the placebo group had a first recurrence or died, with a hazard ratio (HR) of 0.65 and a confidence interval (CI) of 0.46 to 0.92 and a p value of 0.0066. At a further publication, December 2022 pembrolizumab significantly improved distant metastasis-free survival (DMFS) with a HR of 0.64 with a CI of 0.47 to 0.88 and a p value of 0.0029 compared with placebo. In the final publication, the final analysis for recurrence-free survival (RFS) (the primary endpoint), with a median follow up of 39.4 months, the estimated 36 month DMFS was 84.4% for pembrolizumab compared to 74.7% for placebo with a HR of 0.059, CI 0.844 to 0.76.The estimated 36 month RFS was 76.2% for pembrolizumab and 63% for placebo, HR of 0.62, with a CI 0.49 to 0.76. Overall the toxicity rate at the 36 month follow up, rate of grade 3 or 4 toxicity was found to be 17%. With regard to an unmet need, the prevalence of stage IIB and IIC melanoma is similar to stage III melanoma, accounting for 7% of new melanoma diagnosis. With regard to survival rates, stage IIB has a 5-year survival rate of 87% and 10-year survival rate of 82% and stage IIC has a has a 5-year survival rate of 82% and 10-year survival rate of 75%. There is desire among the clinicians to have this treatment available for this patient cohort. The pharmacoeconomic aspects as outlined in the HTA assessment carried out by the NCPE were discussed. The international guidelines for the treatment of melanoma, along with the current standard of care (SOC) and comparators were outlined, noting that the SOC for this patient cohort is routine surveillance. The supporting evidence was outlined, the NCPE Review Group highlighted a number of limitations regarding the supporting evidence, such as the immaturity of the data, at the fourth interim analysis, the RFS was still immature, with only 24% of patients in the pembrolizumab arm and 35.6% of patients in placebo arm had experienced a RFS event. The median DMFS had not been reached in either group at the fourth interim analysis,	

	however there was a statistically significant reduction noted at the third interim analysis 3 and the HR further decreased at the interim analysis 4, however the OS data remains immature. Other limitations highlighted were the limited number of adolescents enrolled, and uncertainty regarding the impact of adjuvant pembrolizumab on the sequencing and the efficacy of subsequent treatment in the advanced setting. The cost effectiveness analysis was discussed and the modelling used was outlined. In terms of cost, the cost per treatment course (12 months) for the adult population, assuming 400mg very 6 weeks of pembrolizumab is administered is €94,573 including VAT and €76,888 excluding VAT. The Applicant's base case ICER was €50,665 per QALY. A number of changes were made to the NCPE-adjusted base case and the NCPE adjusted base case is €57496 per QALY. The probabilities of cost effectiveness at €45,000/QALY threshold is 40.8% and a reduction in the price to wholesaler in order to achieve and ICER of €45,000/QALY would be 22.97%. In terms of the budget impact (BI), this indication is associated with a large BI, the applicant estimated that 48 patients will be treated in year 1 rising to 50 in year 5. The 5-year gross BI by the applicant is estimated to be €24.4 million including VAT and €19.5 million excluding VAT. The NCPE changed one assumption in terms of estimating the number of patients, and assumed a higher proportion of patients would be eligible for treatment based on clinical opinion received, and the NCPE-adjusted base case BI estimates are €27.6 million (€22 million excluding VAT). The NCPE recommends that pembrolizumab 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 unanimous to recommend approval of this indication to the HSE Drugs Group. *(Decision: TRC 157)*	
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 September 23rd 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	26/08/2024	NCCP to communicate recommendations to HSE Drugs Group.	NCCP	Completed
24/01	26/08/2024	Apply for CPD	NCCP	Completed