National Cancer Control Programme

NCCP Technology Review Committee (TRC)

Meeting Notes

Date of Meeting:	**1st May 2025 at 1.15pm**
Venue:	**Teleconference via MS Teams**
Assessment:	Axicabtagene ciloleucel (Yescarta®)
	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		
NCPE representative	National Centre for Pharmacoeconomics (NCPE)	By MS Teams
Dr Neil Barrett	Consultant Haematologist, Children's Health Ireland – Crumlin **(Chair)**	By MS Teams
Dr Dearbhaile Collins	Medical Oncologist, Cork University Hospital: ISMO nominee	By MS Teams
Patrick Hayden	Consultant Haematologist, St James's Hospital: IHS representative	By MS Teams
Fiona Mulligan	PCRS representative	By MS Teams
Ms Aishling McLoughlin	Chief I Pharmacist, NCCP (Deputy Chair)	By MS Teams
Dr Dearbhaile O'Donnell	Medical Oncologist, St James's Hospital: ISMO nominee	By MS Teams
Hazel O'Sullivan	Medical Oncologist, Cork University Hospital: ISMO nominee	By MS Teams
Non-member invited specialists present		
Dr Emily Harold	Medical Oncologist, St James's Hospital	By MS Teams
Apologies (members)		
Dr Oscar Breathnach	Medical Oncologist, Beaumont: ISMO nominee	
Dr Susan Spillane	HTA Directorate: HIQA nominee	
Observers present		
Ms Patricia Heckmann	AND, 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 March 31st 2025 were reviewed and agreed.	
3	**Drugs/Technologies for consideration**	
	Axicabtagene ciloleucel (Yescarta®) (Ref. TRC 172) *For the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.* The clinical aspects of this indication were discussed, noting that axicabtagene ciloleucel is currently approved for the treatment of DLBCL and primary mediastinal large B cell lymphoma (PMBCL), after two or more lines of systemic therapy, accounting for over 95% of CAR-T activity nationally. The supporting evidence for this indication comes from the ZUMA-7 trial, a phase III, multicentre, randomised, open-label trial which evaluated the use of axicabtagene ciloleucel versus standard of care (SOC) in the treatment of adult patients with DLBCL and HGBL that had relapsed within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy. It was noted that the population evaluated in the ZUMA-7 trial is narrower than that of the licenced indication. The current SOC treatment for this patient cohort is chemoimmunotherapy followed by high dose therapy and autologous stem cell transplant (HDT-auto-SCT), however administration of high dose chemotherapy is challenging in patients greater than 65 years of age, making approximately 50% of this patient cohort ineligible for current SOC, but eligible for CAR-T up to their early 80's. Over 300 patients were randomly assigned to the ZUMA-7 trial, the primary efficacy endpoint was event free survival (EFS). Key secondary endpoints were objective response rate (ORR) and overall survival (OS).The study showed superior EFS and OS with axicabtagene ciloleucel, at the primary analysis, EFS was 8.3 months in the axicabtagene ciloleucel arm compared to 2 months in the SOC arm, at a further follow up, the 24 months EFS was 41% with axicabtagene ciloleucel versus 16% with SOC. OS at 2 years was 61% with axicabtagene ciloleucel versus 52% with SOC and the 4 year OS was 54.6% versus 46%. The study also showed that in the axicabtagene ciloleucel arm patients with DLBCL and HGBL demonstrated superior efficacy compared to SOC with OS and a HR of 0.73. There is a desire among the clinicians to have axicabtagene ciloleucel available for this group, DLBCL is an aggressive disease, and transplant suitability depends on the persons tolerance of intensive treatment and is not generally suitable in patients over 70 years of age, therefore as a result approximately 50% of patients whose disease has relapsed following first line chemo-immunotherapy are not eligible for this approach. It was also noted that axicabtagene ciloleucel is currently recommended by international clinical guidelines (NCCN) for this indication and has been approved by NICE in the UK for this patient cohort. The pharmacoeconomic aspects as outlined in the HTA assessment carried out by the NCPE were discussed. The supporting evidence was discussed, and a number of concerns were highlighted, such the response rates in the SOC arm in the trial, the definition of EFS and the open label nature of the trial. In terms of OS, the ZUMA-7 trial demonstrated a significant OS benefit, however the data is still immature. At the data cut of January 2023, the median OS had not been reached for the axicabtagene ciloleucel arm, and there is uncertainty with the extrapolations in the cost effectiveness analysis. The safety profile was discussed noting that toxicities were in line with what is generally known with axicabtagene ciloleucel, and no new safety concerns were identified. The cost effectiveness analysis and the modelling used was outlined. In terms of cost, the total cost of axicabtagene ciloleucel to the HSE is €294,860 excluding VAT, and €368,977 including VAT,	

	and the weighted average cost of SOC chemotherapy is [redacted] In terms of subsequent treatment costs for the axicabtagene ciloleucel arm, as it is assumed that patients will not be retreated with axicabtagene ciloleucel in later lines of treatment, and subsequent treatment cost are [redacted]. For the SOC arm, for those eligible for third line axicabtagene ciloleucel the cost is [redacted] In terms of the results of the cost effectiveness analysis for the Applicant's base case, the ICER is €68,803/QALY. The NCPE adjusted base case the ICER is €101,256/QALY, and a 45.1% reduction to the price to the wholesaler is required to reach the threshold of €45,000 per QALY. In terms of the budget impact (BI), the Applicant provided two BI models, one based on the eligible population as per the licence indication, and the second based on transplant eligible population as per the supporting Zuma-7 trial. For the whole eligible population it is estimated that 28 patients will be treated in year 1, increasing to 37 in year 5. The net BI over 5 years is estimated to be €55.64 million including VAT and €44.44 million excluding VAT. In the transplant eligible sub-population it is estimated that 15 patients will be treated in year 1 increasing to 22 in year 5, and the net BI over 5 years is estimated to be €31.09 million including VAT and €24.84 million excluding VAT. The NCPE recommends that axicabtagene ciloleucel not be considered for reimbursement unless 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 subject to an improvement in cost. *(Decision: TRC 172)* **Nivolumab (Opdivo®) (Ref. TRC 173)** *In combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer in the following setting: First line treatment of unresectable or metastatic colorectal cancer (mCRC).* The clinical aspects of this indication were discussed, a brief overview of the use of immunotherapy (IO) for this patient cohort was provided, with the first single agent IO (pembrolizumab), approved for use in 2017, moving to combination IO (nivolumab plus ipilimumab) in 2022 in the second line setting based on the CheckMate 142 trial. During this time there has been a paradigm shift in the way dMMR or MSI-H CRC is treated, suggesting a lack of efficacy with chemotherapy options for this cohort. Considering the efficacy data for combination IOs in this setting, in terms of complete responses, and also seen in clinical practice in later lines, approximately a third of patients with unresectable disease may convert to rescetable disease. Also, a significant proportion of patients are still alive at 4 and 5 years, considering that overall survival (OS) for all comers with metastatic CRC is only 16% at 5 years. The data for this indication is compelling, the supporting evidence for this indication is the CheckMate 8HW trial, an ongoing, three arm, phase III, open label, randomised trial evaluating nivolumab plus ipilimumab compared to nivolumab alone or standard of care (SOC) chemotherapy in patients MSI-H or dMMR mCRC. The arms of interest to this indication are the nivolumab plus ipilimumab versus chemotherapy. The study showed that at 12 months the progression free survival (PFS) with nivolumab plus ipilimumab was 79% compared to 21% with SOC chemotherapy. At 24 months that benefit seems to be preserved with a 24 month PFS of 72% with nivolumab plus ipilimumab versus 14% in the chemotherapy arm with a HR of 0.21 in favour of nivolumab plus ipilimumab. The relevant comparator was discussed, and it was noted that following an update of this trial at GI ASCO regarding the single agent nivolumab arm versus nivolumab plus ipilimumab arm, the median PFS with single agent nivolumab was 39.3months, however PFS in the nivolumab plus ipilimumab has not yet been reached at 47 months of follow up. When considering that the 5 year OS data for all comers is 16%, and acknowledging, that there is only 4 years of data, this PFS is impressive. The safety profile	

	was discussed, toxicity rates with any grade toxicity was slightly higher in the nivolumab plus ipilimumab arm, 71% with single agent nivolumab compared to 81% with nivolumab plus ipilimumab. However, grade 3 to 4 treatment related toxicities leading to discontinuation was 9% with nivolumab plus ipilimumab compared to 4% with single agent nivolumab. It was noted that patient related outcomes from the CheckMate 142 trial informs that this regimen in practice is well tolerated. There is a strong desire among the clinicians to have nivolumab plus ipilimumab available for this patient cohort, and considers that this will be an evolving SOC. It was also noted that nivolumab plus ipilimumab for this patient cohort was recently approved by NICE in the UK. The pharmacoeconomic aspects as outlined in the rapid review (RR) assessment carried out by the NCPE were discussed, noting that a full HTA was not recommended. The relevant comparators were outlined and the supporting evidence was discussed. The NCPE Review Group highlighted a number of limitations in the trial such as the open label nature of the trial, the lack of comparator evidence against pembrolizumab and the immaturity of the OS data. It was acknowledged that the PFS benefit was considered compelling and clinically meaningful, however the review group highlighted concerns regarding the uncertainty of the OS data and if this will translate into an OS benefit. The safety profile was discussed, noting that while nivolumab plus ipilimumab was more toxic than single agent nivolumab, no new safety concerns were identified. In terms of the cost, based on the mean duration of treatment in the supporting trial, the cost of nivolumab plus ipilimumab in year 1 is estimated to be [redacted] and in year 2 is estimated to be [redacted]. This compares to pembrolizumab which is estimated to cost [redacted] including VAT in year 1 and [redacted] VAT and [redacted] in year 2. In terms of the budget impact (BI), the 5-year gross BI, considering only nivolumab plus ipilimumab, is estimated to be €11.91 million including VAT and €9.5 million excluding VAT. The 5-year net BI results in a cost saving based on the list price of €1.42million including VAT and €1.13million excluding VAT, as nivolumab plus ipilimumab are cheaper based on list price, however a PAS is in place for nivolumab plus ipilimumab, and pembrolizumab and when the PAS are considered, the cost savings are not realised. The recommendation by the NCPE was not to recommend a full HTA and that nivolumab plus ipilimumab not be considered for reimbursement at the submitted price. Having considered the clinical efficacy of the indication, the committee members agreed unanimously to recommend approval of this indication to the HSE Drugs Group subject to an improvement in cost. *(Decision: TRC 173)*	
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 Monday May 26th 2025	
6	**Any other business / Next meeting**	

The meeting concluded at 14.20pm.

Actions arising from meeting:

Ref.	Date of	Details of action	Responsible	Update

	meeting			
25/04	01/05/2025	NCCP to communicate recommendations to HSE Drugs Group.	NCCP	Complete
25/04	01/05/2025	Apply for CPD	NCCP	Complete