National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

NCCP Technology Review Committee (TRC)

Meeting Notes

Date of Meeting:	**October 16th 2018 at 5.00pm**
Venue :	**Teleconference / NCCP Offices**
Assessment:	Avelumab (Bavencio®) Cabozantinib (Cabometyx®) Inotuzumab (Besponsa®)

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CONTAINS COMMERCIALLY CONFIDENTIAL INFORMATION

Attendance:

Members present		
Mr. Shaun Flanagan (Acting Chair)	Pharmacist: HSE Corporate Pharmaceutical Unit	By 'phone
Dr. Michael Fay	Consultant Haematologist, Mater Hospital: IHS representative	
Dr. Patricia Harrington	Head of Assessment, HTA Directorate: HIQA nominee	By 'phone
NCPE Representative	National Centre for Pharmacoeconomics (NCPE)	By 'phone
Dr. Ray McDermott	Medical Oncologist, AMNCH/Vincent's: ISMO nominee	By 'phone
Dr. Deirdre Murray	NCCP Health Intelligence	By 'phone
Dr. Deirdre O'Mahony	Medical Oncologist, Cork University Hospital: ISMO nominee	By 'phone
Dr. Eve O'Toole	Research Group Lead, NCCP	
Non-member invited specialists present		
None		
Apologies (members)		
Dr. Oscar Breathnach	Medical Oncologist, Beaumont: ISMO nominee	
Dr. Ronan Desmond	Consultant Haematologist, Tallaght Hospital:IHS representative	
Ms. Patricia Heckmann	NCCP Chief Pharmacist **- Chair**	
Dr. John Quinn	Consultant Haematologist, Beaumont: IHS representative	
Dr. Cecily Quinn	Consultant Histopathologist, St. Vincent's: Nominee Faculty of Pathology	
Dr. Dearbhaile O'Donnell	Medical Oncologist, St. James's: ISMO nominee	
Observers present		
Dr. Jerome Coffey	National Director, NCCP	
Ms. Ciara Mellett	National Programmer Manager, NCCP	

Item	Discussion	Actions
1	**Notes of previous meeting and matters arising**	
	Shaun Flanagan chaired the meeting. Members were reminded of the confidentiality of documentation and discussions. In addition to the conflict of interest forms signed by all members previously, members were asked 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. No conflicts were raised during the meeting. The notes of the meeting on September 25th 2018 were agreed. It was noted that all actions from the previous meeting had been completed.	
2	**Drugs/Technologies for consideration**	
	Avelumab (Bavencio®) *As monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC)* The NCPE representative outlined the NCPE pharmacoeconomic assessment of this indication. In the company's submission, chemotherapy, in the form of carboplatin plus etoposide or single-agent carboplatin in first-line (1L) patients and topotecan in second-line (2L+) patients, was the comparator investigated. This was considered broadly appropriate by the NCPE. Currently there are no comparative trials of avelumab in patients with metastatic MCC (mMCC). The evidence to support efficacy was based on the JAVELIN Merkel 200 study. This study is an ongoing Phase II, open-label, multi-centre, single arm study aiming to evaluate the efficacy and safety of avelumab in adult patients with mMCC. The study is in two parts: Part A including patients who have failed at least one line of prior chemotherapy (2L+ cohort; n=88) with follow-up ongoing, and Part B in patients with no prior systemic therapy for metastatic disease (1L cohort; target enrolment: n=112). The primary endpoint for Part A (2L+ cohort) was confirmed best overall response (BOR) and for Part B (1L cohort) was durable response rate (DRR). Overall survival (OS) and progression-free survival (PFS) were included as secondary endpoints in both cohorts. For the 2L+ cohort (Part A) results are based on the most recent completed data-cut at (minimum for all patients) 18-months follow-up. For the 1L cohort (Part B) results are based on the latest data available. This included 39 patients, 29 of which had at least 3-months follow-up. The NCPE review team has concerns that the small number of patients and limited follow-up in the 1L cohort will lead to uncertainty in the clinical-effectiveness results for these patients. The median PFS was 2.7 months (95%CI 1.4,6.9) for the 88 patients with 18-month follow-up in the 2L+ cohort and 9.1 months (95%CI 1.9, NE) for the 39 patients with 3-month follow-up in the 1L cohort. Median OS was 12.6 months (95%CI 7.5,19.0) for the 2L+ cohort and not reached in the 1L cohort. To establish estimates of relative effectiveness for use in the economic model, the applicant conducted a retrospective observational study with the aim of investigating clinical outcomes of chemotherapy treatment. A naïve comparison with avelumab was performed based on analyses conducted by the applicant concluding that patient characteristics (other than previously received chemotherapy) do not appear predictive of outcomes in mMCC. The NCPE review team had concerns regarding the methods used to derive this conclusion and felt that a simulated treatment comparison may have been	

	more appropriate. The NCPE review team recommended that any conclusions around comparative effectiveness made from a naïve comparison of single-arm studies should be treated with caution. The NCPE review team had concerns regarding the lack of long-term safety data. Separate cost effectiveness models were conducted for the 2L+ and 1L cohorts. Clinical efficacy inputs for avelumab were derived from JAVELIN for the 2L+ cohort, with the hazard ratios applied to 2L+ data used to derive estimates for the 1L cohort. Clinical efficacy inputs for chemotherapy were derived from a retrospective observational study. Patient characteristics were derived from the JAVELIN study. Utility values were derived from the 2L+ cohort of the JAVELIN study and base case utilities were applied based on time to death. The same utilities were used for both the 2L+ and 1L cohorts and for avelumab and chemotherapy patients. Survival outcomes from JAVELIN were extrapolated to the full time horizon of the model using spline models for the 2L+ cohort. Data for the 1L cohort in the JAVELIN study was considered too immature to use in modelling, therefore clinical expert opinion was sought, by the applicant, to estimate hazard ratios (HRs) suitable for application to the 2L+ data to estimate OS and PFS. A HR of 0.8 was estimated for OS and, as the clinicians did not feel able to provide an estimate for PFS, a value of 1.0 was applied. Parametric survival models were fitted to the data from the observational study to extrapolate OS and PFS outcomes for chemotherapy patients for both the 1L and 2L+ cohorts. Based on the company's submission, the ICER for the 2L+ cohort was €41,894 per QALY. The ICER for the 1L cohort was €58,679. Due to considerable uncertainty in the clinical evidence used to inform the economic model the NCPE suggested a number of changes to the model based on plausible alternative assumptions. These related to rebates, consistent discounting formula, assumptions regarding the level of use of topotecan and paclitaxel, patient weight for dosage calculation, pre-medication costs and changes to the extrapolation approach. This resulted in an increase in the ICER for the 2L+ cohort to €54,540 per QALY and €130,984 per QALY for the 1L cohort. The applicant presented a probabilistic sensitivity analysis for each patient cohort but the NCPE had concerns regarding the particular sensitivity of this model to the choice of OS curve for avelumab and assumptions regarding time on treatment. The NCPE review team requested further sensitivity analyses using various alternative HRs for the 1L cohort. The average total cost of treatment per patient was €101,164. The applicant estimates that there would be 6 eligible patients with mMCC in year 1, rising to 14 in year 5. The applicant estimates the 5-year gross budget impact to be approximately €2.1million. Due to the relatively low cost of chemotherapy there is negligible difference between the gross and net budget impact analyses. The NCPE assessment is that this indication should not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. R. McDermott outlined the clinical guidelines for the drug, stating that there were few treatment options in this patient cohort, for whom outcomes tend to be poor due to the difficulty in treating this disease. Due to the small number of patients involved, this can be considered an orphan disease. It was noted that the data is relatively immature. The side effects were noted and clinicians are accustomed to dealing with these through the use of other PDL1 inhibitors. Testing of patients for hepatitis is an important step in the clinical pathway for this treatment. Clinicians have experience of using this treatment due to an extended access programme which has been in place. The clinical view is that this indication offers a potentially major step forward in treatment for this patient cohort. However, the committee members were concerned with the immaturity of the data, particularly in the first line setting. The ICER in the second line setting is more favourable	

and there is some potential that this may improve further.

The committee unanimously agreed that based on the immaturity of the data available in the first line setting, they had insufficient information to arrive at a conclusion. (Decision: TRC044)

In relation to the second line setting, based on the unmet clinical need in this patient cohort and on the potential cost effectiveness of the drug, it was unanimously agreed to recommend approval for reimbursement to the HSE Drugs Group for this indication in the second line setting.
(Decision: TRC045)

Cabozantinib (Cabometyx®)

The treatment of advanced renal cell carcinoma (RCC) in adults following prior VEGF targeted therapy

R. McDermott outlined the clinical guidelines for this indication. The safety and efficacy of cabozantinib for the treatment of renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy were evaluated in a randomized, open-label, multicenter Phase 3 study (METEOR). Patients (N=658) with advanced RCC with a clear cell component who had previously received at least 1 prior VEGF receptor tyrosine kinase inhibitor (VEGFR TKI) were randomized (1:1) to receive cabozantinib (N=330) or everolimus (N=328). Patients could have received other prior therapies, including cytokines, and antibodies targeting VEGF, the programmed death 1 (PD-1) receptor, or its ligands. Patients with treated brain metastases were allowed. Progression-free survival (PFS) was assessed by a blinded independent radiology review committee, and the primary analysis was conducted among the first 375 subjects randomized. Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS).
Tumour assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter. Median progression-free survival was 7.4 months with cabozantinib and 3.8 months with everolimus. The rate of progression or death was 42% lower with cabozantinib than with everolimus (hazard ratio, 0.58; 95% confidence interval [CI] 0.45 to 0.75; P<0.001). The objective response rate was 21% with cabozantinib and 5% with everolimus (P<0.001). A planned interim analysis showed that overall survival was longer with cabozantinib than with everolimus (hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; P=0.005) but did not cross the significance boundary for the interim analysis. In a subsequent unplanned interim analysis of OS, a statistically significant improvement was demonstrated for patients randomized to cabozantinib as compared with everolimus (320 events, median of 21.4 months vs. 16.5 months; HR=0.66 [0.53, 0.83], p=0.0003; Figure 2). Comparable results for OS were observed with a follow-up analysis (descriptive) at 430 events. Adverse events were managed with dose reductions; doses were reduced in 60% of the patients who received cabozantinib and in 25% of those who received everolimus. Discontinuation of study treatment owing to adverse events occurred in 9% of the patients who received cabozantinib and in 10% of those who received everolimus.

The particular clinical efficacy of this indication is in patients who have failed prior therapy, those with a heavy burden of disease and those with bone metastases. The side effects seen with this drug are similar to those of other TKIs, which clinicians are familiar with. In the study, which included patients in Ireland, there were more thromboembolic events recorded than with other TKIs. It was noted that the NCCN guideline recommends the use of cabozantinib in the first line setting. It is expected that it will be used in the Irish setting in second line, and likely third line, settings. The clinical view is that this is a valuable drug which is important for the treatment of this subset of patients with poor prognosis.

The NCPE representative stated that the NCPE's assessment had been based on the clear-cell RCC patient population, which is believed to relate to 80-90% of the population. The HSE will need to consider that the market authorisation is based on the entire patient cohort. It was stated that since the time of the NCPE's assessment, a discount provided by the company has resulted in a considerable change to the ICERs. In comparison with Nivolumab, which is considered the most appropriate comparator, Cabozantinib offers a better clinical XXXXXXXXXXXXXXXXXX in this patient cohort. It is expected that there will be XXXXXXXXXX overall budget impact due to offsets to the use of Nivolumab.

Based on the clinical need identified in this patient cohort and the cost effectiveness of the drug, it was unanimously agreed to recommend approval for reimbursement of this indication to the HSE Drugs Group.
(Decision: TRC046)

Inotuzumab (Besponsa®)

As monotherapy for the treatment of adults with relapsed or refractory CD22+ Bcell precursor ALL. Adult patients with Ph+ relapsed or refractory B cell prescursor ALL should have failed treatment with at least one TKI

M. Fay outlined the clinical guidelines for this drug. The safety and efficacy of inotuzumab in patients with relapsed or refractory CD22-positive ALL were evaluated in an open-label, international, multicentre, Phase 3 study (INO-VATE 1022) in which patients were randomised to receive inotuzumab (N=164 [164 received treatment) or Investigator's choice of chemotherapy (N=162 [143 received treatment]), specifically fludarabine plus cytarabine plus granulocyte colony-stimulating factor (FLAG) (N=102 [93 received treatment]), mitoxantrone/cytarabine (MXN/Ara-C) (N=38 [33 received treatment]), or high dose cytarabine (HIDAC) (N=22 [17 received treatment]). Of the 326 patients who underwent randomization, the first 218 (109 in each group) were included in the primary intention-to-treat analysis of complete remission. The rate of complete remission was significantly higher in the inotuzumab ozogamicin group than in the standard-therapy group (80.7% [95% confidence interval {CI}, 72.1 to 87.7] vs. 29.4% [95% CI, 21.0 to 38.8], P<0.001. Among the patients who had complete remission, a higher percentage in the inotuzumab ozogamicin group had results below the threshold for minimal residual disease (0.01% marrow blasts) (78.4% vs. 28.1%, P<0.001).

In the safety population, the most frequent grade 3 or higher non-haematologic adverse events with inotuzumab ozogamicin were liver-related. Venoocclusive liver disease of any grade occurred in 15 patients (11%) who received inotuzumab ozogamicin and in 1 patient (1%) who received standard therapy.

The principal clinical utility of the drug is to bridge patients to remission to facilitate stem cell transplant. It provides an alternative to standard salvage chemotherapy.

The NCPE representative outlined the NCPE assessment of this indication. In the submission, the chemotherapy regimen FLAG-IDA (fludarabine, idarubicin, cytarabine and filgrastim) was the comparator investigated. At the request of the NCPE, a comparison with blinatumomab was also presented. Comparative efficacy with blinatumomab was derived from matched adjusted indirect comparison (MAIC) between INO-VATE and the TOWER study. The NCPE expressed concern that this method was associated with significant uncertainty and conclusions on cost effectiveness from this comparison should be treated with caution.

For the cost-effectiveness analysis, the key effectiveness inputs in the model were OS, PFS CR/CRi, and rate of HSCT, derived from the INO-VATE study, and for the comparison with blinatumomab, from the MAIC. The NCPE had concerns regarding the use of the FLAG-subgroup of the INO-VATE SOC arm as a surrogate for FLAG-IDA, as it is likely to underestimate the efficacy of SOC treatment. Survival outcomes from INO-VATE were extrapolated to the full-time horizon of the model.

The ICER in the applicant's base case was €68,920/QALY. The NCPE implemented a number of changes to the model based on plausible alternative assumptions. The NCPE consider that it is likely the ICER falls within a range of €52,183/QALY (incremental costs €63,962, incremental QALYs 1.226) to €84,983/QALY (incremental costs €104,166, incremental QALYs 1.226). The reimbursement cost for a treatment course of three cycles (10 vials) for a patient is €94,217 ex VAT and €117,148 including VAT. Based on the applicant estimate of the eligible population and assuming 100% market share, the projected gross budget impact of the drug acquisition over the first five years is €5.815 million including VAT. The net budget impact is €5.554 million including VAT. These estimates are highly sensitive to treatment duration and are based on the assumption of only three cycles per eligible patient. The use of inotuzumab will likely be associated with cost offsets through reduced hospitalisation which are not included in the NCPE's estimates.

The NCPE assessment of inotuzumab demonstrated additional benefit in terms of increased remission rates, increased rates of HSCT and a statistically significant improvement in OS, but the magnitude of this benefit in the long-term is uncertain. There is a low probability of cost-effectiveness and a high probability that the ICER exceeds the cost-effectiveness threshold for existing treatments. The NCPE recommends that inotuzumab should be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments.

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There was some discussion regarding the comparison with FLAG-IDA. The company felt that FLAG-IDA was the most appropriate comparator and used data on FLAG as a surrogate of FLAG-IDA. There is an important consideration regarding the potential for patients to reach the lifetime maximum dose.

The indication will be clinically beneficial in a relatively small group of patients. There is the potential for this drug to be administered on an outpatient basis, versus continuous infusion for Blinatumumab. However, the significant risk of liver toxicity with Inotuzumab is an important consideration that will need to be addressed on a patient by patient basis.

On the basis of the clinical benefits for a relatively small population of patients, the committee unanimously agreed to recommend this indication for approval to the HSE Drugs Group on the basis of an improvement in cost effectiveness. (Decision: TRC047)

3	**Update on other drugs in the reimbursement process**	
	An update on the drugs that are in the reimbursement process was circulated to members in advance of the meeting.	
4	**Any other business / Next meeting**	
	There was no other business.	

The meeting concluded at 18.15.

Actions arising from meeting:

Ref.	Date of meeting	Details of action	Responsible	Update
18/08	16/10/18	Recommendations of the Group to be communicated to the HSE Drugs Group.	S. Flanagan (& NCCP letter to HSE Drugs Group chair)	