National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

NCCP Technology Review Committee (TRC)

Meeting Notes

Date of Meeting:	**November 20th 2018 at 4.30pm**
Venue :	**Teleconference / NCCP Offices**
Assessment:	Atezolizumab (Tecentriq®) Dinutuximab beta (Qarziba®)

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. Oscar Breathnach	Medical Oncologist, Beaumont: ISMO nominee	By 'phone
Dr. Gerard Crotty	Consultant Haematologist, MRH Tullamore: IHS representative	By 'phone
Dr. Ronan Desmond	Consultant Haematologist, Tallaght Hospital: IHS representative	By 'phone
Dr. Michael Fay	Consultant Haematologist, Mater Hospital: IHS representative	By 'phone
Mr. Shaun Flanagan	Pharmacist: HSE Corporate Pharmaceutical Unit	By 'phone
Dr. Patricia Harrington	Head of Assessment, HTA Directorate: HIQA nominee	By 'phone
Ms. Patricia Heckmann	NCCP Chief Pharmacist **- Chair**	
Dr. Laura McCullagh	National Centre for Pharmacoeconomics (NCPE)	By 'phone
Dr. Deirdre Murray	NCCP Health Intelligence	By 'phone
Dr. Deirdre O'Mahony	Medical Oncologist, Cork University Hospital: ISMO nominee	By 'phone
Non-member invited specialists present		
Dr. Cormac Owens	Consultant Paediatric Oncologist, OLCH Crumlin	By 'phone
Apologies (members)		
Dr. Ray McDermott	Medical Oncologist, TUH/St. Vincent's: ISMO nominee	
Dr. Cecily Quinn	Consultant Histopathologist, St. Vincent's: Nominee Faculty of Pathology	
Dr. Dearbhaile O'Donnell	Medical Oncologist, St. James's: ISMO nominee	
Dr. Eve O'Toole	Research Group Lead, NCCP	
Observers present		
Ms. Ciara Mellett	National Programmer Manager, NCCP	

Item	Discussion	Actions
1	**Introduction & reminder re. conflict of interest & confidentiality**	
	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. It was noted that Dr. John Quinn had stepped down from the TRC. He was thanked for his service and commitment to the work of the Committee. The Irish Haematology Society has nominated Dr. Gerard Crotty, Consultant Haematologist at the Midland Regional Hospital, Tullamore, to the Committee in place of Dr. Quinn. Dr. Crotty was welcomed to the Committee. It was also noted that Dr. Cormac Owens, Consultant Paediatric Oncologist at Our Lady's Children's Hospital Crumlin had been invited to join the meeting specifically to outline the clinical efficacy of Dinutuximab.	
2	**Notes of previous meeting and matters arising**	
	The notes of the meeting on October 16th 2018 were agreed. It was noted that all actions from the previous meeting had been completed.	
3	**Drugs/Technologies for consideration**	
	Dinutuximab beta (Qarziba®) *For the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures. In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, Qarziba® should be combined with interleukin-2 (IL-2)* Dr. Cormac Owens was invited to join the meeting to outline the clinical efficacy of the drug. He outlined the clinical guideline, which was particularly focussed on the high-risk neuroblastoma patients but also covers patients with refractory disease. Currently approximately 10 children are diagnosed each year in Ireland with neuroblastoma, approximately half of whom have high-risk disease and the remainder being non-metastatic. The survival rate in this patient cohort was 25-40% prior to the advent of immunotherapy. Availability of dinutuximab would further enhance the survival rates in this patient group. Dinutuximab has also been shown to increase the time to progression and relapse in those patients where it does not result in cure. Prescriptive authority for the drug will lie with consultant paediatric oncologists. The clinical guideline provides for dose modification, where necessary, with dose reduction of up to 50% or temporary interruption of infusion depending on the physician's evaluation of the severity of adverse reaction to the drug. There is currently no other anti-GD2 monoclonal antibody immunotherapy available on the market, since the previous form of anti-GD2 immunotherapy (dinutuximab, ch14.18/SP2/0) which held marketing authorisation in Europe prior to March 22, 2017, was withdrawn from the market after this date.	

According to the SIOPEN HR-NBL-1 trial protocol (SIOPEN 2014), combination differentiation therapy (isotretinoin) and immunotherapy (with ch14.18/CHO) is now regarded as standard of care in patients with high-risk neuroblastoma following myeloablative therapy. Dinutuximab beta EUSA is currently the only anti-GD2 monoclonal antibody immunotherapy available for the treatment of high-risk neuroblastoma patients.

The major clinical challenge with this treatment is the management of side effects, which include significant neuropathic pain and capillary leakage. In the clinical trial, up to 30% of the patients in the IL2 arm dropped out due to toxicities. However, the treatment has very promising efficacy and has been found to be well tolerated with the continuous 10 day infusion with few side effects.

There are essentially three patient cohorts for consideration:

1. Front-line patients who have responded well to treatment. There is strong evidence to support the benefit of the antibody in this cohort.
2. Refractory patients – small number of patients which makes it difficult to assess efficacy. These patients can be continued on front-line treatment with a view to reaching a minimal level of residual disease when they would then benefit from the antibody treatment.
3. Relapsed patients – small number of these patients so also difficult to assess efficacy. The clinical utility of giving the antibody to patients who have already received it in front line treatment is questionable.

It was noted that the HTA had included the relapsed and refractory patients in one cohort. It was stated that funding had been secured from the HSE for a small number of patients, off trial, pending completion of the reimbursement process.

Dr. Laura McCullagh outlined the NCPE assessment of the indication. Dinutuximab beta has an orphan designation. Retinoic acid (RA) was chosen by the applicant as the most appropriate comparator, even though in real world practice use of RA is complementary to, not an alternative for, anti-GD2 immunotherapy. This was considered broadly appropriate by the NCPE.

The clinical evidence for the population with high-risk neuroblastoma came from APN311-302, an open-label phase 3 trial comparing dinutuximab beta plus RA (n=189) with dinutuximab beta plus RA plus interleukin-2 (n=190). The primary outcome in the trial was event-free survival at 3 years, with overall survival, overall response, incidence of relapsed or refractory disease and safety as secondary outcomes. Results from APN311-302 showed that 55.4% of people randomised to dinutuximab beta and isotretinoin without interleukin-2 had not had an event at 3 years compared with 61.2% in the group having interleukin-2 (p=0.3202). For overall survival, 64.1% of people randomised to dinutuximab beta and RA without interleukin-2 were still alive at 3 years compared with 69.1% in the group having interleukin-2 (p=0.6114).

The clinical evidence for the relapsed/refractory (R/R) population (in the economic model) came from APN311-202, a prospectively designed observational study, in which 36.8% of people with relapsed disease had not had an event at 3 years compared with 44.6% of people with refractory disease. Given the small numbers of patients in each subgroup, the observational nature of the study, and the high degree of censoring in each study, the NCPE consider that the event-free and overall survival results should be interpreted with caution. As there was no direct evidence comparing dinutuximab beta with RA, the applicant presented a comparison of dinutuximab beta-containing regimens versus historical controls who did

not receive dinutuximab beta for both the high risk and R/R populations. For the high risk population, the applicant conducted a matched adjusted indirect comparison (MAIC) analysis of APN311-302 versus a group receiving RA alone in the RCT published by Yu et al (2010).

The most common adverse reactions that were reported in clinical trials were pyrexia (88%) and pain (77%) that occurred despite analgesic treatment. Other frequent adverse reactions were hypersensitivity (63%), thrombocytopenia (62%), vomiting (57%), diarrhoea (51%), increased transaminases (53%), pruritus (49%), capillary leak syndrome (40%) and hypotension (39%).

A lifetime horizon of 90 years was adopted in the economic model. In its original model the applicant used Kaplan–Meier data from APN311-302 and from ANBL0032 (as reported by Yu et al. 2010) up to 70 months and then extrapolated event-free and overall survival. However, the NCPE noted that the longer-term data from ANBL0032 (Saramango et al 2015) included up to 12 years of RA data. The NCPE considered it more appropriate to use the longer term data (Saramango et al 2015) because this would reduce the uncertainty that arises from extrapolating data. The applicant submitted a revised analysis which used the longer-term data for the comparator arm and extrapolated event-free and overall survival.

A number of base case deterministic ICER results were presented as part of the applicant's analysis. In the high risk population, the ICER was €110,864/QALY. The ICER in the R/R population was €44,308/QALY. The NCPE had concerns with the clinical evidence used in the economic model and suggested a number of changes to the model including:

- Extrapolation from the full Kaplan-Meier model
- Application of the corrected discount rate of 5% rather than the 2.5% included in the model.
- The use of longer term Kaplan Meier data for the RA population.
- Implementation of a Bayesian model average.

Based on these changes, the ICER for the high risk population was €150,994/QALY and €63,486/QALY in the R/R population.

The cost per patient per treatment course is approximately €217,598 and €237,868 for the high risk and R/R populations, respectively. The applicant estimated that 7 patients (5 high risk and 2 R/R) would start dinutuximab beta therapy each year. The five year cumulative gross drug budget impact is estimated to be in the range of €7.4m to €7.8million. Since dinutuximab beta does not result in cost offsets due to displacement of other drugs, the net budget impact is the same as the gross budget impact. Following assessment of the applicant's submission, the NCPE recommends that dinutuximab beta (Qarziba®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.

It was acknowledged by the TRC members that given the small number of patients and the fact that neuroblastoma is a rare disease in children, it is difficult to assess the pharmacoeconomic impact of the drug.

Having considered the clinical efficacy of the indication, the particular unmet clinical need in this relatively small patient cohort, as well as the pharmacoeconomic assessment by the NCPE, it was agreed unanimously to recommend approval of this indication to the HSE Drugs Group, subject to an

	improvement in the cost effectiveness of the drug, which is [redacted]. (Decision: TRC048) **Atezolizumab (Tecentriq®)** *As monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving atezolizumab.* P. Heckmann outlined the indication under consideration and noted that the clinical guideline and NCPE assessment agree that there is an alternative immunotherapy treatment available for this patient cohort; nivolumab. As noted in the NCPE review there is little between the drugs in terms of efficacy and side effects. The clinical guideline notes that the treatment cycle of atezolizumab every three weeks, versus nivolumab every two weeks is advantageous. Sequencing of treatment with nivolumab and atezolizumab is not currently supported by evidence and would be unlikely to be effective. Atezolizumab offers an alternative immunotherapy option. The NCPE assessment conclusion states that the atezolizumab demonstrated additional benefit in terms of a statistically significant improvement in overall survival and an improved safety profile compared with docetaxel, but the magnitude of this benefit in the long-term is uncertain. The NCPE recommend that atezolizumab should not be considered for reimbursement unless the cost-effectiveness can be improved relative to existing treatments. Having considered the clinical efficacy of the indication, as well as the pharmacoeconomic assessment by the NCPE, it was agreed unanimously to recommend approval of this indication to the HSE Drugs Group with the caveat as set out the in the NCPE conclusion (as above) for improved cost effectiveness relative to other treatments, which is subject to engagement by the company. (Decision: TRC049)	
4	**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.	
5	**Any other business / Next meeting**	
	There was no other business.	

The meeting concluded at 5.30pm.

Actions arising from meeting:

Ref.	Date of meeting	Details of action	Responsible	Update
18/09	20/11/18	Recommendations of the Group to be communicated to the HSE Drugs Group.	S. Flanagan (& NCCP letter to HSE Drugs Group chair)	