National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

NCCP Technology Review Committee (TRC)

Meeting Notes

Date of Meeting:	**May 29th 2018 at 4.30pm**
Venue :	**Teleconference / NCCP Offices**
Assessment:	Osimertinib (Tagrisso®) 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		
Ms. Patricia Heckmann	NCCP Chief Pharmacist **- Chair**	
Dr. Oscar Breathnach	Medical Oncologist Beaumont: ISMO nominee	By 'phone
Dr. Michael Fay	Consultant Haematologist: IHS representative	By 'phone
Mr. Shaun Flanagan	Pharmacist: HSE Corporate Pharmaceutical Unit	By 'phone
Dr. Laura McCullagh	National Centre for Pharmacoeconomics (NCPE)	By 'phone
Dr. Deirdre Murray	NCCP Health Intelligence	By 'phone
Dr. Dearbhaile O'Donnell	Medical Oncologist St. James's: ISMO nominee	By 'phone
Dr. Eve O'Toole	Research Group Lead, NCCP	
Dr. John Quinn	Consultant Haematologist: IHS representative	By 'phone
Non-member invited specialists present		
None		
Apologies (members)		
Dr. Ronan Desmond	Consultant Haematologist: IHS representative	
Dr. Patricia Harrington	Head of Assessment, HTA Directorate: HIQA nominee	
Dr. Deirdre O'Mahony	Medical Oncologist Cork University Hospital: ISMO nominee	
Dr. Cecily Quinn	Consultant Histopathologist St. Vincent's: Nominee Faculty of Pathology	
Dr. Ray McDermott	Medical Oncologist AMNCH/Vincent's: ISMO nominee	

Observers present	
Ms. AnneMarie DeFrein	Deputy Chief Pharmacist, NCCP

Item	Discussion	Actions
1	**Notes of previous meeting and matters arising**	
	The notes of the meeting on March 7th 2018 were agreed. 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.	
2	**Drugs/Technologies for consideration**	
	Osimertinib (Tagrisso®) *For the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor [EGFR] T790M mutation positive non-small cell lung cancer [NSCLC]* L. McCullagh outlined the NCPE assessment of the submitted indication, as above. This was submitted in March 2017 and a resubmission with additional information was made in Jan 2018. The usual dose is 80mg OD, continued until progression or toxicity. The primary use of this drug is expected to be in the 2L setting if a patient has progressed on 1L TKI. The comparator for osimertinib is current standard of care which consists of platinum-doublet chemotherapy (PDC). The AURA3 study was a pivotal phase III, open-label, comparative, randomised study conducted in 419 patients with advanced EGFR T790M mutation-positive NSCLC in second-line therapy versus PDC. There was a statistically significant improvement in progression-free survival (PFS) for patients on osimertinib compared to patients on chemotherapy (10.1 months vs 4.4 months, +5.7 months, HR 0.30, 95% CI: 0.23, 0.41 p<0.001). The immaturity of the data (26.0%) at the time of the first overall survival (OS) analysis prevents firm conclusions on the benefits of osimertinib in improving survival (immature HR 0.72, 99.96% CI 0.34, 1.52). A high level of treatment-switching (67.1% crossover) from PDC to osimertinib after progression also confounds interpretation of results. An initial submission of evidence supporting comparative efficacy in OS applied adjusted indirect comparison methodology to pooled single arms of osimertinib phase II studies, and the control arm of a phase III study containing PDC. The NCPE review group considered the AURA3 study, adjusted for crossover, to be the most appropriate source of OS data for use in the cost-effectiveness model, as it directly addresses the clinical aspect of the decision problem in the target population, without the need for subset-selection, matching, trimming and indirect comparison. The applicant submitted results of OS analysis based on AURA3 (data cut-off 2, DCO2) adjusted for crossover in the January 2018 resubmission, and updated this with data from AURA3 (DCO3) in March 2018. The updated analysis used the rank-preserving structural failure time (RPSFT) model to adjust the OS of patients who crossed over from PDC to osimertinib, and presented results based on various methodologies. The adjusted OS HR estimates ranged from XXXXXXXXXXXXXXXXXXXXXXXXXXX. This analysis was updated on request from the NCPE on the basis of more mature data from AURA3 DCO3. The adjusted HR estimates on the basis of this update ranged from XXXXXXXXXXXXXXXXXXXXXXXXXXX. Notwithstanding the provision of the AURA3-DCO3 OS results adjusted for crossover, as requested by the NCPE review group, there remains no robust evidence of an overall survival advantage with osimertinib to support the applicant's model. The safety was better than PDC, mostly grade 1 or 2. G3 and higher was more frequent with the PDC arms. The analysis utilised a partitioned-survival model including three health states; progression free, progressed disease, and death to model costs and	

	benefits of treatment over a lifetime horizon. PFS outcomes were based on DCO1 of the AURA3 study and OS outcomes were based on crossover-adjusted analysis of DCO3 of the AURA3 study, extrapolated over a lifetime horizon using parametric extrapolation. The OS data was extrapolated over the time horizon of the model using parametric modelling. The median estimated OS durations were similar across models, consistent with a similar fit to the short-term observed data. However the mean osimertinib OS durations predicted by each of these models varies significantly, from 31.76 months to 43.09 months. The applicant's chosen models for long-term extrapolation of OS and PFS benefits predict a survival advantage of 18.92 months for osimertinib compared with PDC. Survival benefits were predicted to continue for over 2 years after disease progression and also for almost 22 months after patients are assumed to have discontinued treatment. The NCPE has concerns regarding the mean OS predicted by the model and consequently the extent of OS benefit predicted. Health-related quality of life (HRQoL) utilities were applied to the three model health states and utility decrements due to grade 3/4 adverse events were also included. Utility values were derived from the AURA3 study. The HRQoL of the very select clinical trial population may not be representative of the cohort of patients eligible for treatment. This is reflected in the very high values for the progression free state (0.823) and the progressed disease state (0.727). The progression free utility value lacks face validity as it is higher than the EQ-5D-3L index population norm for people of the same age. The incremental cost per QALY (incremental cost-effectiveness ratio (ICER)) for the applicant's base case was €116,785/QALY. The probability of cost-effectiveness at a willingness to pay threshold of €45,000/QALY was 0%. The NCPE did not consider that the applicant's submitted model and resulting ICER are a complete reflection of the cost effectiveness of osimertinib, and explored the impact of alternative utility values, treatment durations and treatment efficacy estimates on cost effectiveness results. The NCPE implemented a number of changes to the model based on plausible alternative assumptions, resulting in increases in the ICER up to €241,953/QALY. This ICER still reflects the potential for an OS benefit with osimertinib. If the assumed OS advantage with osimertinib is removed, the ICER increases to over €1.5 million/QALY. Osimertinib is submitted for reimbursement under the High-tech drug scheme. The proposed ex-manufacturer price is €6200 for 30 tablets. The reimbursement cost for a treatment course is dependent on treatment duration, which is patient-specific depending on response and tolerance, but on the basis of current evidence could range from an average of XXXXXXX per patient. Based on the applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is approximately €24.9 million, plausibly increasing to over €30 million if treatment durations are longer. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. In conclusion, the NCPE assessment of osimertinib has demonstrated additional benefit in PFS and some evidence of benefit in OS, though the size of the OS gain is very uncertain. There is a very low probability of cost effectiveness and a high probability that the ICER far exceeds the cost effectiveness threshold for existing treatments. The NCPE recommends that osimertinib (Tagrisso®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. Oscar Breathnach outlined the clinical guideline for this indication of 2L patients with NSCLC post 1L TKI in EGFR+ patients. The incidence is approx 15% in Caucasian patients (higher in Asian patients). The target group display the t790m mutation. The dose is 80mg/day and this is a well tolerated drug which has been shown to have a prolonged PFS over the PDC. A more recent stufy in 1L versus TKI has shown superiority but is not considered here for this indication. The inclusion criteria are as per the study, patients with locally advanced or metastatic EGFR mutated NSCLC, Positive determination of T790M mutation status, disease progression after first-line EGFR-TKI therapy, ECOG 0-1,	

acceptable organ function. Exclusions include patients with a past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD. Treatment is continued to progression. Baseline tests include QT interval. Most side effects are modest and easily controlled. No renal adjustment is required. Currently available on expanded access programmes and in many other countries.
It was stated that clinical experience to data has shown that the drug matches the study predictions and appears to offer better CNS protection in terms of metastatic disease to brain compared with standard of care treatment.

Members discussed the NCPE assessment and clinical guideline. It was noted that this drug is approved in 19 countries worldwide. XXXXXXXXXXXXXXXXX. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. There are a lot of uncertainties as is clear from the HTA but there is a PFS of 10.1 versus 4.4 months and an immature OS. The company's estimate of OS is 19months versus PDC. A better safety profile is seen and this is a well tolerated drug which is orally administered so more convenient for the patient.

Having considered the NCPE assessment and the clinical guideline for the drug, the committee agreed that, this drug is deemed to be clinically beneficial but concerns remain regarding the high cost. All members maintained concerns regarding cost effectiveness.

It was unanimously agreed, to recommend this drug for approval to the HSE Drugs Group pending financial discussion with the company and an improvement in price. (Decision No. TRC034)

Pembrolizumab (Keytruda®)
As monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV

John Quinn outlined the clinical guideline for pembrolizumab as per the above indication noting that the group had already discussed this previously for the use of nivolumab in part of the indications and that it had been approved for reimbursement.
The efficacy of pembrolizumab was investigated in KEYNOTE-087 and KEYNOTE-013, two multicentre, open-label studies for the treatment of 241 patients with cHL. These were not randomised, had small patient numbers with R/R HL which is about 10-15% of all HL. These are difficult patients to treat. The adverse events are well known, none new to note here. The use of pembrolizumab looks effective as a treatment and in line with nivolumab data.
P. Heckmann added that the NCCP had carried out a review with the NCCP Clinical Advisory Group (CAG) for lymphoma as there are overlapping indications here for nivolumab and pembrolizumab. The CAG members were happy that there is no clinical reason to prevent Drugs group from choosing one agent to be used in preference to another based on a cost differential in those overlapping indications.

L. McCullagh outlined the NCPE's assessment of the rapid review submitted. KEYNOTE-087 was a single-arm phase II study of pembrolizumab in three cohorts of patients with rrHL, defined on the basis of lymphoma progression after
(1) autologous stem cell transplantation (ASCT) and subsequent brentuximab vedotin (BV);
(2) salvage chemotherapy and BV, and thus, ineligible for ASCT because of chemoresistant disease; and
(3) ASCT, but without BV after transplantation.
EMA did not approve the use of pembrolizumab in cohort 3, so only Cohort 1 and 2 were granted approval. The dose is 200mg every 3 weeks. The

	recommended dose is 200 mg every three weeks (Q3W) by intravenous infusion over a 30-minute period. In the pivotal trial for product authorisation, treatment duration was limited to 2 years; no treatment duration is specified in the product license. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX No HTA has been carried out so there is no economic evaluation. This is in part due to the high level of uncertainty associated with the data currently. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXX In relation to the potential for separate assessment of the individual indications included in the application, L. McCullagh clarified that there are no budget impact data to evaluate the indications separately. . S. Flanagan stated two indications are included in the application, of which the clinical need for one is currently met by an existing agent which is also XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. However, the second indication relates to the transplant ineligible patients who have failed BV, for which is an unmet clinical need. Taking into account the current unmet need in the transplant ineligible patients who have failed BV, it was unanimously agreed, to recommend this drug for approval to the HSE Drugs Group. However it was recommended that the decision by Drugs Group on availability should consider other drugs in the class for overlapping indications. (Decision No. TRC035)	
3	**Update on other drugs in the reimbursement process**	
	P. Heckmann undertook to circulate, by e-mail, an update on the drugs that are in the reimbursement process.	
4	**Any other business / Next meeting**	
	There was no other business.	

The meeting concluded at 17.50.

Actions arising from meeting:

Ref.	**Date of meeting**	**Details of action**	**Responsible**	**Update**
18/03	28/05/18	Recommendations of the Group to be communicated to the HSE Drugs Group.	S. Flanagan (& NCCP letter to HSE Drugs Group chair)	
18/04	28/05/18	Update on drugs currently in reimbursement process to be circulated by e-mail.	P. Heckmann	