National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

NCCP Technology Review Committee (TRC)

Meeting Notes

Date of Meeting:	**September 25th 2018 at 4.30pm**
Venue :	**Teleconference / NCCP Offices**
Assessment:	Pertuzumab (Perjeta®) Ribociclib (Kisqali®) Venetoclax (Venclexta®) Ixazomib (Ninlaro®)

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Attendance:

Members present		
Ms. Patricia Heckmann	NCCP Chief Pharmacist **- Chair**	
Dr. Ronan Desmond	Consultant Haematologist: IHS representative	By 'phone
Dr. Patricia Harrington	Head of Assessment, HTA Directorate: HIQA nominee	By 'phone
NCPE Representative	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. Deirdre O'Mahony	Medical Oncologist Cork University Hospital: ISMO nominee	By 'phone
Non-member invited specialists present		
None		
Apologies (members)		
Dr. Oscar Breathnach	Medical Oncologist Beaumont: ISMO nominee	
Dr. Michael Fay	Consultant Haematologist: IHS representative	
Mr. Shaun Flanagan	Pharmacist: HSE Corporate Pharmaceutical Unit	
Dr. Ray McDermott	Medical Oncologist AMNCH/Vincent's: ISMO nominee	
Dr. Eve O'Toole	Research Group Lead, NCCP	
Dr. John Quinn	Consultant Haematologist: IHS representative	
Dr. Cecily Quinn	Consultant Histopathologist St. Vincent's: Nominee Faculty of Pathology	
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**	
	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 3rd 2018 were agreed. It was noted that all actions from the previous meeting had been completed.	
2	**Drugs/Technologies for consideration**	
	Pertuzumab (Perjeta®) *Pertuzumab In combination with trastuzumAB and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence* It was noted that the HSE Drugs Group had asked the NCCP to convene a clinical advisory group to consider the evidence for the adjuvant and neoadjuvant indications for this drug. The views of this group, as set out in the clinical guideline for the indication were noted as follows: *"With inclusion of pertuzumab, there is improved pathological complete response rate, however we do not as yet have evidence relating to overall survival. There is increased toxicity with the addition of pertuzumab. The current data do not allow for the selections of a subset of patients that may benefit from the addition of pertuzumab to neo-adjuvant treatment.* *These data need to be revisited with findings in the adjuvant setting together with overall survival data when available. The recommendation of the NCCP SACT Breast Cancer Clinical Advisory group is: for unselected patients with HER2-positive breast cancer requiring neo-adjuvant treatment, there is a modest benefit for the use of pertuzumab. There are no data to support identification of a subgroup who would benefit from the addition of pertuzumab to trastuzumab and the standard SACT."* It was stated that the HSE Drugs Group may choose to consider the indications for adjuvant and neoadjuvant treatment together but as the HTAs are being done separately, the TRC is providing its recommendations separately. It was suggested that it may be beneficial for the HSE Drugs Group to request clinical input from the Breast Clinical Advisory Group to provide insight into the consideration of the two indications, particularly regarding the continuum of care and the context of neoadjuvant treatment. It was noted that the drug regimen is developed on the basis of the clinical guideline and regimens are subject to updating as evidence becomes available. Patient cohorts may be amended downwards on the basis of new evidence and it is possible to remove indications from the ODMS reimbursed list. Similarly, patient cohorts may be expanded but this would be subject to a revised budget impact assessment. It was noted that the HTA was completed in 2016 and no new evidence has been presented. It is expected that any new evidence emerging is likely to be in the adjuvant setting. Dr. Deirdre O'Mahony outlined the clinical guidelines for the indication under consideration. The clinical efficacy data are based on the NeoSphere trial which was a multicentre, open-label, phase II study in treatment-naïve	

women (n=417) with HER2-positive breast cancer. The majority of patients were less than 65 years old.

Patients were randomised to receive one of the following neoadjuvant regimens for 4 cycles prior to surgery:

- Trastuzumab plus docetaxel (TD; n=107)
- Pertuzumab plus trastuzumab and docetaxel (PTD, n=107)
- Pertuzumab plus trastuzumab (PT; n=107)
- Pertuzumab plus docetaxel (PD; n=107)

Randomisation was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER or PgR positivity. The primary endpoint was post-surgery pathologic complete response. Secondary efficacy endpoints were clinical response rate, breast conserving surgery rate (T2-3 tumours only), disease-free survival (DFS), and PFS.

A statistically significant improvement in pathological complete response rate (ypT0/is) was observed in patients receiving Pertuzumab plus trastuzumab and docetaxel compared to patients receiving trastuzumab and docetaxel (45.8% vs 29.0%, p value = 0.0141). The PFS and DFS at 5 year follow up show large and overlapping confidence intervals and do not demonstrate significant improvement with the addition of neoadjuvant pertuzumab. The primary end point of pathological complete response rate was significantly improved with neoadjuvant pertuzumab. Neoadjuvant pertuzumab added to docetaxel and trastuzumab does not improve DFS or PFS but does improve pathological complete response rate.

The NCPE assessment found that the evidence was poor and the cost effectiveness of pertuzumab in combination with trastuzumab and chemotherapy for this indication had not been demonstrated. It was not recommended by the NCPE for reimbursement.

The TRC took into consideration the NCPE assessment and the views of the Breast Clinical Advisory Group that the evidence was not sufficiently strong for this indication in the neoadjuvant setting at this time but that this position should be reconsidered when the results of the study on the use of the drug in adjuvant setting are available. Clinicians reported that patients have been enquiring about this treatment for some time. It was unanimously agreed not to recommend this indication to the HSE Drugs Group. However, it was agreed to revisit this if and when a patient sub-group can be identified in the adjuvant setting.

(Decision: TRC040)

Ribociclib (Kisqali®)

Ribociclib is indicated in combination with an aromatase inhibitor for the treatment of postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy

It was noted at the outset that XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. XXXXXXXXXXXXXXX. The indication under consideration has a narrow patient population as it is specifically for first line treatment in post-menopausal women. It provides an alternative treatment in the population of post menopausal women in combination with an aromatase inhibitor. The drug appears to be a less costly option than the standard of care but is not as effective. The side effect profile is different to the standard of care so it therefore provides an alternative in patients who cannot tolerate other treatment.

Evidence for ribociclib in combination with the primary comparator, letrozole, compared to letrozole monotherapy was derived from the

randomised, double-blind, placebo-controlled, phase III MONALESSA-2 trial. Eligible patients (n=668) were randomised (1:1) to ribociclib (in combination with letrozole) or placebo (in combination with letrozole). Treatment continued until disease progression, unacceptable toxicity, death or discontinuation. Dose reductions were permitted to manage adverse events. The primary end point was locally assessed progression-free survival, according to RECIST, version 1.1. The key secondary end point was overall survival. Other secondary end points included the overall response rate (complete or partial response), the clinical benefit rate (overall response plus stable disease lasting 24 weeks or more), safety, and quality-of-life assessments. Palbociclib in combination with letrozole was included as a second primary comparator.

The efficacy results demonstrated a statistically significant improvement in PFS in patients receiving ribociclib plus letrozole compared to patients receiving placebo plus letrozole in the full analysis set (hazard ratio of 0.556, 95% CI: 0.429, 0.720, one sided stratified log-rank test p-value 0.00000329) with clinically meaningful treatment effect. A more mature update of efficacy data found that the median PFS was 25.3 months [95% confidence interval (CI) 23.0–30.3] for ribociclib plus letrozole and 16.0 months (95% CI 13.4–18.2) for placebo plus letrozole (hazard ratio 0.568; 95% CI 0.457–0.704; log-rank P = 9.63 × 10−8). The ORR was 42.5% versus 28.7% for all patients treated with ribociclib plus letrozole versus placebo plus letrozole, respectively, and 54.5% versus 38.8%, respectively, for patients with measurable disease.

There is variance in the dosing schedule and toxicities, with ribociclib having higher incidence of diarrhoea and a greater requirement for cardiac monitoring compared with alternative treatments. It was noted that ribociclib has been available on an access programme and that clinicians are comfortable with this and similar treatments.

The NCPE assessment was considered. Based on the company's submission, the NCPE found the proposed indication to be cost effective and recommended it for reimbursement.

Based on the cost effectiveness of the drug in this setting and the clinical benefit of an alternative treatment being available for this patient population, it was unanimously agreed to recommend approval for this indication. (Decision: TRC041)

Venetoclax (Venclexta®)

As monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor.

As monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor

It was stated that a rapid review of this indication had been completed and there was insufficient evidence for a full HTA to be definitive. Updated trial information and XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. It is anticipated that this therapy would displace idelalisib in appropriate cases and is therefore not an additive therapy. The data appear to show increased clinical efficacy of this drug but it is more costly overall due to patients being on treatment for a longer period (over two years versus 11.4 months for the comparator).

R. Desmond outlined the clinical guidelines for this indication, which is

aimed at a high risk group of patients. Treatment for patients with CLL with 17p deletion or TP53 mutation was limited and had a poor prognosis prior to the availability idelalisib and ibrutinib. The indication under consideration will provide an alternative treatment for those patients who have failed on, or cannot tolerate treatment with, idelalisib or ibrutinib. The main toxicity associated with this drug is tumour lysis. Evidence of clinical efficacy is provided in a number of studies:

(i) Trial 1: Patients with CLL harbouring 17p deletion or TP53 mutation

In a phase 2, open label study evaluating venetoclax monotherapy for patients with relapsed/refractory, Del (17p) CLL, 107 patients were included from the main cohort and 51 enrolled in the safety expansion. The primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). At a median follow-up of 23.1 months (0-44.2), an overall response by independent review was achieved in 77% of patients (122/158) with 20% CR/Cri (32/158). Among patients who received prior B-cell receptor inhibitor (BCRi) therapy (n=18), ORR was 61% and CR rate was 11%, with 12-month PFS and OS estimates of 50% and 54%, respectively.

By intention to treat, 30% (48/158) patients demonstrated peripheral blood (PB) MRD negativity by flow cytometry and confirmed by Next Generation Sequencing (NGS) in 21/29 patients who had an evaluable matched time point specimen. Combining available flow cytometry and NGS data- 25% (40/158) of total patients or 40% (40/101) of evaluable patients were MRD negative in the PB. 11% (18/158) and 24% (18/74)) were MRD negative in the Bone Marrow (BM), respectively.

(ii) Trial 2: Patients with relapsed- refractory CLL who have failed a or developed an intolerance to a B-cell receptor pathway inhibitor

The efficacy and safety of Venetoclax in patients with CLL who had been previously treated with and failed ibrutinib or idelalisib therapy were evaluated in an open-label, multi-centre, non-randomised, two armed phase 2 study (M14-032). The primary efficacy endpoint was ORR according to IWCLL updated NCI-WG guidelines. Median PFS, DOR and OS were not reached with median follow up of approximately 24.7 months for all patients (n=127).

(iii) Pooled analysis across three monotherapy studies to evaluate impact of disease bulk, number of prior therapies and prognostic factors on responses and outcome

A pooled analysis study across three venetoclax monotherapy studies (M12-175, M13-982 and M14-032) evaluated impact of disease bulk, number of prior therapies and prognostic factors on responses and outcomes utilising a target maintenance dose of 400mg Venetoclax. ORR across all three studies was similar regardless of disease bulk, but patient with nodes <5cm had a higher CR rate (odd ratio: 3.711 (95% CI: 1.904-7.23) (p=.0001). CR, PFS and OS were most favourable in patients where venetoclax was used early in the patient treatment sequence.

(iv) Real world evidence

A retrospective analysis (n=683) across 9 US centres treated with a Kinase Inhibitor (KI) (Ibrutinib/Idelalisib) or Venetoclax was studied. Treatment in patients that discontinued ibrutinib and then treated with Venetoclax had a trend towards better PFS than those treated with Idelalisib (p=0.06).

The NCPE representative outlined the findings from the NCPE rapid review for venetoclax. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX and the increased

timeframe for treatment on venetoclax were noted. A full HTA was not undertaken so the cost effectiveness analysis using the €45,000/QALY was not undertaken in this case. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX.

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The TRC members considered the significant unmet clinical need for patients who have failed idelalisib and/or ibrutinib. It is considered to be relatively rare for patients to be refractory to both idelalisib and ibrutinib so it is expected that the number of patients availing of venetoclax would be relatively small. The treatment is more clinically effective and more costly overall due to longer patient tolerance of the treatment which is positive in this group of high-risk patients where alternatives are limited. It was unanimously agreed to recommend approval of this indication to the HSE Drugs Group. (Decision: TRC042)

Ixazomib (Ninlaro®)

In combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy

The clinical guideline for this indication was outlined by R. Desmond. This therapy provides the first oral proteasome inhibitor for this patient cohort, where all prior treatments were parenteral. There are several treatment options in this patient population but Ixazomib has a number of advantages over alternatives.

The efficacy and safety of ixazomib in combination with lenalidomide and dexamethasone was evaluated in an international randomised, double-blind, placebo-controlled, multi-centre Phase III superiority study (C16010) in patients with relapsed and/or refractory multiple myeloma who had received at least one prior therapy. 722 patients (intent-to-treat [ITT] population) were randomised in a 1:1 ratio to receive either the combination of ixazomib, lenalidomide, and dexamethasone ("IXA+LEN+DEX") (N=360; NINLARO regimen) or placebo, lenalidomide and dexamethasone ("LEN+DEX") (N=362; placebo regimen) until disease progression or unacceptable toxicity.

Progression-free survival was significantly longer in the ixazomib group than in the placebo group at a median follow-up of 14.7 months (median progression-free survival, 20.6 months vs. 14.7 months; hazard ratio for disease progression or death in the ixazomib group, 0.74; P = 0.01); a benefit with respect to progression-free survival was observed with the ixazomib regimen, as compared with the placebo regimen, in all prespecified patient subgroups, including in patients with high-risk cytogenetic abnormalities. The rates of overall response were similar in both arms of the study, as were those in the "very good partial response" category. Exclusion criteria included patients who were refractory to lenalidomide or proteasome inhibitor-based therapy at any line. Side effects were generally well tolerated.

From a clinical perspective, it was noted that the results of the study for this indication were not as impressive as other recent treatments for myeloma.

	The potential use of this drug is unclear given the other options available for 2nd and subsequent lines of treatment. However, this indication provides an oral option of treatment which may be particularly beneficial for younger patients and those who failed autologous transplant. The NCPE representative outlined the key points from the NCPE's assessment. There is a high level of uncertainty in the clinical benefit of IXA+LEN+DEX vs LEN+DEX. The main issue relates to the immaturity of the OS data, with median OS not being reached. In addition, PFS appears to have worsened suggesting that the data may not yet have reached maturity and the potential remains that it could worsen further on extended follow-up. Direct comparison and matching adjusted indirect comparisons were presented but included reliance on a non-randomised study and results that were highly variable. Cost-utility analyses comparing IXA+LEN+DEX with LEN+DEX, BOR+DEX, CAR+LEN+DEX, CAR+DEX and BOR+LEN+DEX, in patients who had received 1+ prior lines of therapy, were submitted by the applicant. In addition, cost-utility analyses comparing IXA+LEN+DEX with LEN+DEX and POM+DEX in patients who had received 2+ prior lines of therapy were also presented. Survival curves modelling OS and PFS were used to inform treatment effectiveness in the model. The main efficacy outcomes used in the model were PFS, OS and time on treatment (ToT). For the IXA+LEN+DEX versus LEN+DEX comparison, treatment efficacy was based on multivariate parametric survival curves fitted to data from the TMM-1 trial. For the IXA+LEN+DEX versus BOR+DEX, CAR+LEN+DEX, CAR+DEX and POM+DEX comparisons, comparative efficacy was based on estimates from a network meta-analysis (NMA). For the IXA+LEN+DEX versus BOR+LEN+DEX comparison, comparative efficacy was based on a STC. HRs for PFS and OS were applied to parametric curves fit to the LEN+DEX data from the TMM-1 trial for all of these comparisons. The NCPE review team identified a number of key issues and uncertainties with the economic model including the assumption that relative treatment effects last for the duration of the model, when this assumption is not supported by the immature TMM-1 data. In addition, the review team had concerns that time on treatment may be overestimated in the model. Median ToT for LEN+DEX in the TMM-1 trial was 14.7 months. In contrast, median ToT observed in clinical practice for LEN-based regimens using real-world data from Ireland was 21weeks. The parametric curve fit to the ToT data was shown to have a considerable impact on the final ICER. There was also uncertainty regarding the approach to modelling treatment costs in the model and using ToT may lead to an underestimation of treatment costs due to it being shorter than PFS. Furthermore, the model appears to be especially sensitive to parameters related to OS. The results of the cost effectiveness analysis were as follows: *1+ prior lines of treatment (Applicant base case)* • The incremental cost due to treatment with IXA+LEN+DEX versus LEN+DEX was €195,494 for a QALY gain of 0.29 resulting in an ICER of €668,357 per QALY. • The incremental cost due to treatment with IXA+LEN+DEX versus BOR+DEX was €331,218 for a QALY gain of 0.85 resulting in an ICER of €387,742 per QALY. 2+ prior lines of treatment (Applicant base case) • The incremental cost due to treatment with IXA+LEN+DEX versus LEN+DEX was €251,100 for a QALY gain of 0.97 resulting in an ICER of €260,328 per QALY. • The incremental cost due to treatment with IXA+LEN+DEX versus POM+DEX was €242,743 for a QALY gain of 1.68 resulting in an ICER of €144,535 per QALY.	

	A number of changes were implemented in the model for the preferred base case including applying a cap on treatment effect rather than assuming a treatment effect for the entire modelling period and using PFS to model treatment costs rather than ToT. These changes resulted in higher final ICERs. Assuming the treatment benefit associated with both IXA+LEN+DEX and LEN+DEX declines from 32-months over a 5-year time horizon, resulted in an ICER €703,426 per QALY. Assuming that treatment benefit associated with both IXA+LEN+DEX and LEN+DEX declines from 32-months over a 5-year time horizon and using PFS to model treatment costs in preference to ToT resulted in an ICER of €986,235 per QALY. The Review Group note that there is a high level of uncertainty with the cost-effectiveness estimates which can only be addressed when further clinical evidence becomes available. The annual cost per patient, including all relevant fees, mark-ups and rebates, is estimated as €145,280 for IXA+LEN+DEX and €82,375 for IXA alone. Predicted patient numbers applied in the budget impact analysis were: 19 (year 1), 42 (year 2), 61 (year 3), and 75 (years 4 & 5). The estimated gross budget impact over five years is €39.3m and the net budget impact is €15.7m. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. TRC members discussed the clinical and cost effectiveness assessments. It was noted that myeloma is now largely managed as a chronic disease and patients will generally go through multiple lines of treatment. The availability of another line of treatment is helpful in this context. XXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. It is expected that few patients would be on this treatment for more than 18 cycles. It is expected that relatively few patients would be treated with IXA+LEN+DEX; most would be expected to receive velcade or bortezomib with IXA+LEN. It is anticipated that the main patient cohort for this treatment would be young patients who have relapsed on other treatments. Members expressed concern regarding the higher budget impact given the relatively poor trial data. On the basis XXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXX that the indication provides an alternative clinical option for what is expected to be a relatively small number of patients, it was unanimously agreed to recommend approval of this indication to the HSE Drugs Group. (Decision: TRC043)	
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 18.00.

Actions arising from meeting:

Ref.	Date of meeting	Details of action	Responsible	Update
18/07	25/09/18	Recommendations of the Group to be communicated to the HSE Drugs Group.	S. Flanagan (& NCCP letter to HSE Drugs Group chair)	