National Cancer Control Programme

# NCCP Technology Review Committee (TRC)

## Meeting Notes

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| **Date of Meeting:** | **27th May 2024 at 4.30pm** |
| **Venue:** | **Teleconference via MS Teams** |
| **Assessment:** | Ibrutinib (Imbruvica®) |
| | 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:**

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| **Members present** | | |
| NCPE representative | National Centre for Pharmacoeconomics (NCPE) | By MS Teams |
| Dr Dearbhaile Collins | Consultant Medical Oncologist, Cork University Hospital: ISMO nominee **(Chair)** | By MS Teams |
| Dr Patrick Hayden | Consultant Haematologist, St James's :IHS representative | |
| Dr Dearbhaile O'Donnell | Medical Oncologist, St. James's Hospital: ISMO nominee | By MS Teams |
| Prof Michael O'Dwyer | Consultant Haematologist, Galway :IHS representative | By MS Teams |
| Dr Susan Spillane | HTA Directorate: HIQA nominee | By MS Team |
| **Non-member invited specialists present** | | |
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| Dr Neil Barrett | Consultant Haematologist, Children's Health Ireland - Crumlin | |
| Dr Oscar Breathnach | Medical Oncologist, Beaumont: ISMO nominee | |
| Ms Fiona Mulligan | PCRS representative | |
| **Observers present** | | |
| Ms Helena Desmond | Senior Pharmacist, NCCP | By MS Teams |
| Ms Elizabeth Breen | Chief II Pharmacist, NCCP | By MS Teams |
| Dr Derville O'Shea | Consultant Haematologist, Cork University Hospital | By MS Teams |

| Item | Discussion | Actions |
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| 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. | |
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| 2 | **Notes of previous meeting and matters arising** | |
| | The notes of the previous meeting on April 22nd were reviewed and agreed | |
| 3 | **Drugs/Technologies for consideration** | |
| | Ibrutinib (Imbruvica®) **(Ref. TRC 154)**<br>*In combination with venetoclax is indicated for the treatment of adult patients with previously untreated CLL.*<br><br>The clinical aspects of this indication were discussed, and a summary of the current treatment landscape for CLL was provided. The supporting evidence for this indication comes from two clinical trials, the GLOW trial, which evaluated the use of ibrutinib plus venetoclax in the unfit, older population (≥65 years), and the CAPTIVATE trial which evaluated this combination in a fit younger population. The GLOW trial, a small (n=211), phase III, open label trial which compared the efficacy and safety of fixed duration of ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab in previously untreated CLL patients without del 17p or known TP53 mutations. At the primary analysis data cut with 27 months follow up, there was a significantly longer progression free survival (PFS) with ibrutinib plus venetoclax compared to chlorambucil plus obinutuzumab, with an overall follow up at 58 months there was a 77% reduction in death or progression. At a median follow up of 34 months, the estimated 30-month PFS rate was 80% in the ibrutinib plus venetoclax arm versus 35% in the chlorambucil plus obinutuzumab arm. At a median follow up of 46 months the estimated 42-month PFS rate was 74% with ibrutinib plus venetoclax versus 24% with chlorambucil plus obinutuzumab, a threefold greater PFS. In terms of the secondary outcomes there was a higher complete response (CR) rate in those treated with ibrutinib plus venetoclax, however the overall response rate (OOR) was similar between the two treatment arms. In terms of MRD, there was a threefold greater MRD negativity in the bone marrow with ibrutinib plus venetoclax compared to chlorambucil plus obinutuzumab. The CAPTIVATE trial, a non-comparative, phase 2, open-label trial which evaluated the efficacy and safety of ibrutinib plus venetoclax in a younger fitter population. The trial included two patient groups, patients with standard risk disease and those with high risk disease (patients with del(17p)/TP53 mutations). The study showed a response rate of 96% in both groups, CR was about 60% in both groups and the median duration of response had not been reached, ranging between 4.3 and 22 months. At 4 years, the PFS was 80%. There is a desire among the clinicians to have ibrutinib plus venetoclax available, it would provide an additional treatment option to the current pathway. It will represent the first all oral, once daily, chemotherapy free, fixed duration regimen and its ease of administration has potential to improve day ward chair capacity. The reported incidence of tumour lysis syndrome (TLS) associated with this treatment is low due to the phased introduction of single agent ibrutinib for the first three cycles, then the addition of venetoclax thereafter, therefore reducing the requirement on inpatient beds. Ibrutinib plus venetoclax has been shown to be well tolerated in all age groups, leading to very long remissions with 80% PFS at 4 years and specifically in patients subgroups of patients such as IGHV mutated, and that this might represent a cure.<br><br>The pharmacoeconomic aspects as outlined in the HTA assessment carried out by the NCPE were discussed. The current standard of care (SOC) and relevant comparators were outlined. The NCPE Review Group highlighted a number of key limitations with the supporting evidence such as the lack of direct comparator evidence against the venetoclax in combination with obinutuzumab, the most relevant comparator across all subgroups of this population, the immaturity of the PFS and OS data in both trials, open label nature of the CAPTIVATE trial, the use of non-blinded investigator | |

assessment for the endpoints. The cost effectiveness analysis was discussed and the modelling used was outlined. Review Group highlighted the lack of direct head to head data for ibrutinib plus venetoclax versus venetoclax plus obinutuzumab as a key limitation, limiting the review group the ability to determine the relative benefit of ibrutinib plus venetoclax resulting in an uncertainty in both the relative effectiveness and cost effectiveness of ibrutinib plus venetoclax. In terms of the cost, the cost for treatment with ibrutinib plus venetoclax differs based on the different subpopulations. The cost for ibrutinib plus venetoclax is about [redacted] in year 1, in the fit subpopulation the cost is about [redacted] for both the unfit and high risk subpopulations. Compared to the available comparators venetoclax plus obinutuzumab still has a substantial cost of [redacted] chlorambucil plus obinutuzumab has a cost of [redacted] and ibrutinib monotherapy had a cost [redacted] year 1 and 2. It was noted that these costs do not include the PAS discount that is already in place for these comparators and that a PAS was not included in this application, and ibrutinib plus venetoclax still have a substantial price premium over the current comparators. In the applicants base case ibrutinib plus venetoclax is dominant for the fit and unfit subpopulations (more effective and less costly) compared to all comparators. In the high risk subpopulation ibrutinib plus venetoclax versus venetoclax plus obinutuzumab is also dominant, compared to ibrutinib monotherapy and acalabrutinib monotherapy ibrutinib plus venetoclax is less costly and less effective. The review group noted a degree of uncertainty associated with the assumptions used to inform the results and raised concerns regarding the reliability of the ICERS. The Review Group were unable to undertake a NCPE-adjusted base case analysis, however the review group performed a scenario analysis. In the fit subpopulation if equal efficacy with ibrutinib plus venetoclax versus venetoclax plus obinutuzumab is assumed in terms of PFS, this ICER is €262,777 per QALY. In the fit subpopulation ibrutinib plus venetoclax versus FCR using baseline risk the ICER is [redacted] In the unfit and high risk subpopulation ibrutinib plus venetoclax versus venetoclax plus obinutuzumab if equal efficacy is assumed, ibrutinib plus venetoclax becomes dominated (more costly, less effective) In the high risk subpopulation ibrutinib plus venetoclax versus ibrutinib, and adjusting for time on treatment, ibrutinib plus venetoclax becomes less costly and less effective. In terms of the budget impact (BI), the applicant estimated that 30 patients will be treated in year 1, increasing to 99 patients by year 5, resulting in a 5-year gross BI of €41.7million excluding VAT. The 5-year net BI was estimated to be €18.7million including VAT, and €20.6 million excluding VAT. The NCPE recommends that venetoclax versus ibrutinib not be considered for reimbursement unless 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.

*(Decision: TRC 154)*

Nivolumab (Opdivo®) (**Ref. TRC 155)**

*As monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC.*

The clinical aspects of this indication were discussed. The supporting evidence for this indication is the Checkmate 274 trial, a phase III, randomised, placebo-controlled, double-blinded trial which compared nivolumab to placebo in patients with MIUC after radical surgery with or without previous neoadjuvant cisplatin-based combination chemotherapy. The trial evaluated the use of nivolumab in all comers, those with and without PD-L1 expression. The trial showed a disease free survival (DFS) advantage with the use of nivolumab for all comers, but predominantly in

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| | patients with PD-L1 expression ≥ 1%. To note, only 282 patients in the trial had a PD-L1 expression ≥ 1%, and based on that data, the marketing authorisation for nivolumab in this indication is restricted to the PD-L1 population. At the data cut of August 2020 (primary analysis), for patients in the PD-L1 group 74% of patients in the nivolumab arm were free from relapse compared to 55.7% on the placebo group, a 20% difference. At a later read out in early 2023, with 36 months follow up, 56% of patients in the nivolumab arm were free of relapse compared to 37% of patients in the placebo arm. While there is a relapse rate in both arms, the difference is maintained in the updated data, showing a very significant advantage, however the overall survival (OS) data is immature. There is desire among the clinicians to have this treatment available for this cohort of patients who have a high risk of relapse and typically an overall poor prognosis.<br><br>The pharmacoeconomic aspects as outlined in the HTA assessment carried out by the NCPE were discussed The current standard of care (SOC) and relevant comparators were discussed, noting that the SOC for this patient cohort is routine surveillance. The supporting evidence was outlined, noting that the data from the October 2022 data cut was used to inform the NCPE assessment. The median DFS was 52.6 months in the nivolumab arm compared to 8.4 months in the placebo arm, resulting in a HR of 0.52. At the data cut, 43.6% of patients had a DFS event in the nivolumab arm compared to 62.7% in the placebo arm. The median non-urothelial tract recurrence free survival (NUTRFS) was 52.6 months in the nivolumab arm vs 8.4 months in the placebo arm. The NCPE Review Group highlighted the key limitations regarding the supporting evidence, such as the lack of OS data, which has been a challenge for this HTA, while there is an indication of DFS, the ICERS are based on the assumption of OS benefit. The absence of a standardised definition of high risk of recurrence, was also considered a limitation. The cost effectiveness analysis was discussed and the modelling used. The review group highlighted concerns regarding the lack of evidence of the impact of adjuvant treatment with nivolumab on OS resulting in uncertainty in the reliability of the cost effectiveness estimates, it is unclear if the improvement in DFS will translate into improvement in OS.<br>In terms of cost, the total cost of nivolumab including VAT is € The Applicant's base case ICER was €20,412 per QALY, based on an OS benefit. A number of changes were made to the NCPE adjusted base case, and the NCPE adjusted base case is €34,103 per QALY. There is 0% probability of cost effectiveness at the €20,000 per QALY threshold, but there is a 100% probability of cost effectiveness at the €45,000 per QALY threshold. In terms of the budget impact (BI), the estimated number of patients eligible for treatment is 41 in year 1, increasing to 43 in year 5. In terms of those treated, the estimated number of patients is 18 in year 1, increasing to 37 patients by year 5. The 5-year gross BI is estimated to be €9.2 million including VAT and €7.36 million excluding VAT, this does not account for the PAS that is currently in place for nivolumab. The NCPE recommends that nivolumab not be considered for reimbursement unless the cost-effectiveness can be improved relative to existing treatments.<br><br>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.<br><br>*(Decision: TRC 155)* | |
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| **4** | **Update on other drugs in the reimbursement process** | |
| | An update had been shared with the group in the documentation for the meeting | |
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| **5** | **Next meeting** | |
| | The proposed date for the next meeting is June 24th 2024 | |

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| 6 | Any other business / Next meeting | |
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The meeting concluded at 18.10pm.

**Actions arising from meeting:**

| Ref. | Date of meeting | Details of action | Responsible | Update |
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| 24/01 | 27/05/2024 | NCCP to communicate recommendations to HSE Drugs Group. | NCCP | Complete |
| 24/01 | 27/05/2024 | Apply for CPD | NCCP | Complete |
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