Cost-effectiveness of nivolumab with ipilimumab (Opdivo® with Yervoy®) for the treatment of advanced (unresectable or metastatic) melanoma.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of nivolumab (Opdivo®) with ipilimumab (Yervoy®). Following NCPE assessment of the applicant’s submission, nivolumab (Opdivo®) with ipilimumab (Yervoy®) is not considered cost-effective for the treatment of advanced (unresectable or metastatic) melanoma and therefore is not recommended for reimbursement at the submitted price.

The HSE asked the NCPE to carry out an assessment of the applicant’s (Bristol-Myers Squibb) economic dossier on the cost effectiveness of nivolumab (Opdivo®) with ipilimumab (Yervoy®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics
The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.
Summary

In April 2016, Bristol-Myers Squibb submitted a dossier examining the cost-effectiveness of nivolumab with ipilimumab for the treatment of advanced melanoma. Review of the dossier commenced following approval of the combination by the European Medicines Agency (EMA) on 27th June 2016. Final information was received on the 11th October 2016.

Nivolumab and ipilimumab are both licensed as monotherapy for the treatment of advanced melanoma. When given in combination (referred to as the Regimen), nivolumab is administered at a dose of 1mg/kg every three weeks (Q3W) concomitantly with ipilimumab 3mg/kg Q3W, for a total of 4 doses of combination treatment. Following completion of this induction treatment, nivolumab is administered at a dose of 3mg/kg every 2 weeks (Q2W), as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. No specific dose reductions are recommended.

In the submission, the comparators included were ipilimumab monotherapy, pembrolizumab, and dabrafenib and trametinib combination therapy. The company updated the analysis to include nivolumab monotherapy at the request of the NCPE.

1. Comparative effectiveness of nivolumab with ipilimumab

Relative efficacy outcomes for the comparison with nivolumab monotherapy and ipilimumab were derived from the CheckMate 067 study. This study was a randomised, double blind, placebo controlled three arm trial, comparing the Regimen or nivolumab monotherapy to ipilimumab. In total over 900 patients with advanced melanoma were randomised to the study, in a 1:1:1 manner. Treatment with nivolumab beyond progressive disease in the event of continuing clinical benefit was permitted.

The co-primary endpoints of the study are progression free survival (PFS) and overall survival (OS). Published PFS results and PFS and OS results from an unplanned interim analysis were included in the submission. In the published PFS results, both the combination of nivolumab and ipilimumab, and nivolumab monotherapy were associated with statistically significant increases in PFS compared to ipilimumab monotherapy. The median PFS was
11.5 months, 6.87 months and 2.9 months for the Regimen, nivolumab monotherapy and ipilimumab monotherapy respectively.

The EMA reviewed the effectiveness of the Regimen considering PD-L1 expression as a biomarker for efficacy, and found that a statistically significant improvement in PFS with the Regimen compared to nivolumab was only found in patients with PD-L1 expression <1.5 and 10%. The statistically significant difference compared to ipilimumab was found across all groups regardless of PD-L1 expression. Two members of the Committee for Medicinal Products for Human Use (CHMP) voted against granting the marketing authorisation for the Regimen, on the grounds of the substantial additive toxicity in the absence of proven OS benefit. OS data is to be submitted to the EMA for review by the 31st March 2017.

The applicant presented a network meta-analysis to derive comparative treatment effects versus pembrolizumab. The network included three trials, CheckMate 067, Keynote 006 and Keynote 002. A fixed effects model was implemented using ‘netmeta’ in R. Published PFS and OS results were implemented in the model, and the unpublished interim OS results from CheckMate 067 were used as an estimate of projected OS with the Regimen. The RG believe that the NMA underestimates the treatment effect of pembrolizumab compared to ipilimumab and the Regimen. It should be noted that the results from the NMA for the comparison of pembrolizumab and the Regimen are not implemented directly in the model. Rather, a parametric survival curve for the reference treatment (ipilimumab) is created, and then relative treatment effects for pembrolizumab versus the reference treatment are taken from the NMA and applied in the model.

The comparison of the Regimen to dabrafenib/trametinib was conducted using a naïve indirect treatment comparison (ITC) rather than a NMA, using the COMBI-D and CheckMate 067 trials. There are significant differences between the patient populations in terms of age, gender, BRAF status and previous treatments. The ITC does not provide point estimates of the relative difference between the treatments. The parametric survival curves for dabrafenib/trametinib were estimated by digitising the published K-M curves, and creating pseudo-patient level datasets using the Guyot method, to which the parametric survival curves were fitted. Parametric survival curves were fitted to the patient level data from CheckMate 067. These curves were implemented in a portioned survival approach, to calculate the relative costs and QALYs of dabrafenib/trametinib compared to the Regimen.
No adjustment for covariates was conducted. The naïve ITC against dabrafenib/trametinib is unreliable in the view of the NCPE.

2. Safety of nivolumab with ipilimumab

The most frequent adverse events (AEs) in the Regimen arm (pooled data from CheckMate 069, 067 and 004) were rash (51%), fatigue (43%), diarrhoea (42%), pruritus (35%), nausea (25%), pyrexia (19%), decreased appetite and hypothyroidism (15%), and vomiting and colitis (14%). The majority of these were Grade 1-2. In CheckMate 067, the incidence of Grade 3-4 AEs was 68.7% and the incidence of discontinuations due to Treatment-related AEs (TRAEs) was 36.4% in the Regimen arm. The incidence of Grade 3-4 AEs with the Regimen was higher in almost every AE category compared to nivolumab monotherapy.

Four deaths due to study drug toxicity were reported with the Regimen, due to drug-related neutropenia, pneumonitis, ventricular arrhythmia and sudden death. In total, 20 patients treated with the Regimen in CheckMate 067/069 died for reasons other than disease progression; 11 of these deaths were due to pulmonary events. The incidence of pulmonary AEs was higher in the Regimen arm than with nivolumab monotherapy (7.6% versus 2%)

The identified risks associated with the Regimen are stated in the European Public Assessment Report (EPAR) as follows: immune-related pneumonitis, colitis, hepatitis, nephritis or renal dysfunction, endocrinopathies, rash, other immune-related AEs, and severe infusion reactions. The EPAR identifies potential safety concerns including use in patients with autoimmune disease and patients already receiving systemic immunosuppressants before starting nivolumab. As recommended by the Pharmacovigilance Risk Assessment Committee (PRAC), routine pharmacovigilance measures are to be supplemented by a pharmacoepidemology study (CA209234)

The RG have serious concerns surrounding the comparative safety of the Regimen to nivolumab monotherapy, in light of the EPAR finding that clinical benefit compared to nivolumab is seen only in patients with low levels of PD-L1 expression. The RG feel that the broad population label indicated in the licence (no restriction according to PD-L1 expression) means there is a risk of exposure to a more toxic treatment for patients who will not receive any additional benefit compared to treatment with nivolumab monotherapy.
3. Cost effectiveness of nivolumab with ipilimumab

For the cost-effectiveness analysis, the key effectiveness inputs were PFS and OS. Cost effectiveness was investigated using a health state model with a 30 year time horizon. The model simulates patients through three health states: ‘Progression-free’, ‘Progressive disease’, and ‘Death’. All health states are mutually exclusive, and death is the absorbing state. All patients start in the progression-free state; transitions to the death state could occur from either the progression-free or progressive disease states. Patient characteristics, dose intensity, utility measurements and adverse event frequency used in the model are derived from CheckMate 067. Patients in the ‘Progressive disease’ state are assumed to receive one line of subsequent treatment, based on the proportion of patients who received subsequent systemic therapy in Checkmate 067. Subsequent treatments included in the model are ipilimumab, pembrolizumab and dabrafenib/trametinib.

PFS and OS from the CheckMate 067 trial are extrapolated to the full time horizon of the model using parametric extrapolations. The NCPE had concerns over a number of assumptions employed in these extrapolations and the sensitivity analyses showed that they were a major source of uncertainty in the model. The model appeared to overestimate PFS and OS for all treatments compared to the pivotal trial results. In addition, survival extrapolation had to be modified by setting the background mortality as the minimum mortality rate for each cycle, so that the projected OS didn’t fall below the general population mortality.

Resource use in the model was based on the MELODY study, and captured costs for drug acquisition and administration, hospital and home care resource use, monitoring and follow up, management of AEs and terminal care costs. Resource use was modelled using 4 health states. In addition, two once-off costs were applied, for treatment initiation and death. The incidence of AEs was based on the clinical trial data, but only AEs recorded by the Investigator as ‘drug related’ were included in the model (treatment-related AEs or TRAEs); a ‘per patient’ cost of AEs per treatment arm was estimated and applied in the model. Health state utility values were derived from the CheckMate 067 trial. The company applied a utility value of 0.7954 in the progression free state and 0.7625 in the progressed state. A variety of longitudinal mixed linear models were applied to the data from the CheckMate 067 trial to derive an AE utility decrement to apply in the model to the Regimen and ipilimumab.
acquisition costs were based on list prices, and a cost of €0 was implemented for trametinib as it has been available at zero cost to the HSE for one year. The model assumed that treatment with nivolumab would be discontinued at 18 months for the majority of patients, regardless of their response to treatment.

The NCPE implemented a number of changes to the model, including the removal of arbitrary rules regarding treatment duration for nivolumab, costs were updated to reflect the IPHA agreement (August 2016), all causality AEs were implemented in the model rather than treatment related AEs, alternative mechanisms for extrapolating OS and PFS were implemented and alternative scenarios from the NMA were implemented also. The results of the final incremental analysis are presented in the table below. The ICER for the Regimen versus ipilimumab was €47,748/QALY (incremental costs €101,354, incremental QALYs 2.12). Pembrolizumab and nivolumab monotherapy were dominated treatment options in the model, predicted to be associated with higher treatment costs and lower QALY gains than other treatments.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Costs</th>
<th>LYs</th>
<th>QALYs</th>
<th>Costs v’s baseline</th>
<th>QALYs v’s baseline</th>
<th>Incremental ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>€142,259</td>
<td>2.95</td>
<td>2.29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabrafenib/Trametinib</td>
<td>€222,159</td>
<td>3.80</td>
<td>2.97</td>
<td>€79,900</td>
<td>0.68</td>
<td>€118,002</td>
</tr>
<tr>
<td>Regimen</td>
<td>€243,613</td>
<td>5.64</td>
<td>4.42</td>
<td>€101,354</td>
<td>2.12</td>
<td>€14,850</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>€251,405</td>
<td>4.43</td>
<td>3.49</td>
<td>€109,146</td>
<td>1.20</td>
<td>Dominated</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>€387,364</td>
<td>4.43</td>
<td>3.48</td>
<td>€245,105</td>
<td>1.19</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

The NCPE examined a number of alternative scenarios in the economic model. In most scenarios, the model outputs changed, but the conclusions were robust. Implementing the confidential discounts available to the HSE had a considerable effect on the model outputs, and the conclusions were not robust to these changes.
4. **Budget impact of drug**

The list price of nivolumab is €589 and €1,474 per 40mg and 100mg vial respectively, exclusive of VAT. The list price of ipilimumab is €4,015.08 and €16,005.75 per 50mg and 200mg vial respectively, exclusive of VAT.

The budget impact model (BIM) assumes increasing incidence of melanoma at a rate of 3.7% annually, assumes 24% patients diagnosed will test positive for the BRAF mutation, and 60% patients will require subsequent treatments. The company predict that the Regimen will achieve 66% market share of first line BRAF negative patients from year 1 onwards.

The RG estimate the gross BI for the drug acquisition cost alone to be in approximately €55.6 million over 5 years, based on the company’s estimates of market share. The gross BI including drug acquisition costs, treatment administration costs and AEs is approximately €61 million.

The RG estimate the net BI for the drug acquisition cost alone to be in approximately -€8 million over 5 years, based on the company’s estimates of market share. The net BI including drug acquisition costs, treatment administration costs and AEs is approximately €6.5 million.

5. **State if any patient submissions were received, and name submitting organisations.**

A patient group submission was received from Melanoma Support Ireland, and was included in full in the final submission to the HSE.

6. **Conclusion**

The manufacturer is applying for reimbursement of nivolumab in combination with ipilimumab (the Regimen), as a hospital only drug for the treatment of advanced melanoma. In the model, evidence of effect is derived from one double blind, placebo controlled Phase III trial CheckMate 067. Only PFS data has been published to date for CheckMate 067.
The NCPE have a number of concerns regarding the cost-effectiveness model presented for nivolumab with ipilimumab:

- the risk-benefit profile of the Regimen in comparison to PD-L1 monotherapy is insufficiently characterised in the absence of OS data;
- the assumptions employed in the NMA were inappropriate and produced measures of treatment effect which were not in line with published measures from randomised controlled trials;
- the methods of extrapolation of PFS and OS data in the model were associated with significant uncertainty and in a validation exercise were shown to predict outcomes in excess of those seen in clinical trials;
- the implementation of inappropriate and arbitrary stopping rules for some interventions and not others introduces unnecessary bias into the model;
- The modelling of pembrolizumab was inappropriate and produced estimates of treatment cost that were far in excess of those predicted by published models.

Following NCPE assessment of the applicant’s submission, cost-effectiveness of the Regimen for the treatment of advanced melanoma has not been demonstrated and therefore it is not recommended for reimbursement at the submitted price. Review of the cost-effectiveness of the Regimen is recommended when the OS results from CheckMate 067 become available.