Ipilimumab/nivolumab (Yervoy/Opdivo®) for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 29 May 2019

Zorginstituut Nederland carried out an assessment of the medicinal product ipilimumab/nivolumab (Yervoy®/Opdivo®) and concluded as follows.

Zorginstituut Nederland has completed its assessment of ipilimumab in combination with nivolumab (Yervoy®/Opdivo®) for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma. The Minister of Health, Welfare and Sport placed ipilimumab in combination with nivolumab in the "waiting room" (*sluis*) for expensive medicinal products.

The *Zorginstituut* assessed the above-mentioned combination treatment based on the four package criteria[1] effectiveness,[2] cost-effectiveness,[3] necessity and feasibility. Assessing from the perspective of the basic package which is paid from collective premiums, the *Zorginstituut* looks at whether new care is better than what is currently available. In doing this we look not only at the degree of certainty that has been achieved, from a scientific perspective and from the perspective of societal support, but also at efficiency aspects. The *Zorginstituut* was advised by two independent committees: the Scientific Advisory Board (WAR) which examines data on established medical science and medical practice and determines the cost-effectiveness, and the Insured Package Advisory Committee (ACP) which considers the societal assessment. Stakeholders are also consulted during the process.

Integral consideration of the package criteria and package advice
Ipilimumab in combination with nivolumab complies with the statutory criterion 'established medical science and medical practice' for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma and a Karnofsky score ≥70 (or a comparable test).

Based on an interim analysis a reduction in mortality risk was found in response to treatment with ipilimumab in combination with nivolumab compared to the standard treatment with sunitinib. The 18-month survival was 75% (95% BI: 70-78) in the ipilimumab+nivolumab arm compared to 60% (95% BI: 55-65) in the sunitinib arm. This reduction in mortality risk is considerable and meets the PASKWIL criteria that specialists use to determine a clinically relevant effect.

Furthermore, a significant and clinically relevant difference was observed on cancer-specific questionnaires about quality of life, in favour of ipilimumab plus nivolumab compared to the standard treatment.

The use of ipilimumab plus nivolumab for the above-mentioned indication will be accompanied by additional costs estimated at €25.9 million in the 3rd year after inclusion in the package (€27.5 million including drug administration costs). The costs of ipilimumab alone amount to €15.8 million (€16.1 million including drug

[1] Package Management in Practice 3 (2013). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[2] Assessment of Established Medical Science and Medical Practice: updated version (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[3] Cost-effectiveness report (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

administration costs). The actual costs of nivolumab are unknown, because of a confidential financial arrangement with the manufacturer.

The manufacturer estimates a cost-effectiveness ratio (ICER) of €60,397/QALY. In view of the disorder's high burden of disease, a reference value of €80,000/QALY is relevant. The chance that nivolumab plus ipilimumab is cost-effective in comparison with sunitinib is approximately 80% at this reference value. The *Zorginstituut* feels the cost-effectiveness analysis is of sufficient quality, although there are a number of important uncertainties regarding the assessment of the cost-effectiveness, because the overall survival data are still immature and thus form an uncertain factor in the cost-effectiveness analysis. However, the effect of the chosen extrapolation on the ICER seems to be limited. Moreover, Dutch patients seem older than the patient population on which the model was based, which may result in a more unfavourable cost-effectiveness in Dutch practice.

The *Zorginstituut* advises the Minister, based on the following considerations, to start price negotiations for the combination ipilimumab/nivolumab.

- The conclusions on overall survival are based on an interim analysis, which means uncertainty still exists about the added value in the long term compared to the standard treatment.
- Furthermore, the added value of the combination therapy compared to nivolumab monotherapy is unclear, and as a consequence the possible synergistic effect of the combination therapy is unknown.
- Various therapies are available for this disease, and new therapies will be developed that will compete with this combination therapy.
- The cost-effectiveness of the comparative treatment, sunitinib, has never been established. The costs of this comparative treatment are considerable, i.e., €250,000 per patient.

We recommend that, as part of the price negotiations, the Minister makes agreements on collecting additional data in order to identify the group of patients who will benefit most from this combination treatment, and thus promote appropriate use. In addition, the *Zorginstituut* suggests the Minister might want to re-consider earlier agreements made on the price of nivolumab.

Appropriate use

The combination therapy is currently used for the treatment of melanomas only. The medical professional association has indicated that treatment will be limited to centres that are already experienced with administering this therapy. The patients' association states that research has shown that most complications occur within six months after starting treatment. They suggest that a logical and desirable step would be to extend this initiation and stabilisation period in experienced centres to 6 months. In addition, the patients' association feels it is important that hospitals have sufficient multidisciplinary expertise relating to renal cancer and its treatment.

Evaluation

If ipilimumab (in combination with nivolumab) is accepted into the insured package based on the outcome of price negotiations, the *Zorginstituut* will actively monitor its use. The *Zorginstituut* plans to inform the Ministry in 2022 about the results of these measurements, based on current insights.

The *Zorginstituut* will review, among other things:

- The extent to which the number of patients originally estimated corresponds to the number of patients actually treated;
- Cost developments relative to the original estimation, part of which is monitoring the actual price of ipilimumab (in combination with nivolumab);
- Care consumption with a view to assessing starting points for appropriate use.

If this monitoring indicates strong discrepancies from the current estimates, this may be a reason for the *Zorginstituut* to reassess the position of ipilimumab (in combination with nivolumab).

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The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.