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2024015204

National Health Care Institute
Care
Medicinal Products

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Date 23 May 2024
Re: Package advice for the lock procedure medicinal product nivolumab-relatlimab (Opdualag®)

Our reference
2024015204

Dear Ms Dijkstra,

The National Health Care Institute recommends that you evaluate the 'combination therapy nivolumab-relatlimab (Opdualag®) for the treatment of advanced melanoma with tumour cell PD-L1 expression < 1%'. The reason for this advice was nivolumab-relatlimab being placed in the lock procedure for expensive medicinal products.

Registered indication
Nivolumab-relatlimab is indicated for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%.

Claim by the marketing authorisation holder
Nivolumab-relatlimab, for the first-line treatment of advanced melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%, has a therapeutic added value over nivolumab as a monotherapy.

Package advice
The National Health Care Institute recommends that nivolumab-relatlimab, for the treatment of advanced melanoma with tumour cell PD-L1 expression < 1%, not be included in the basic health care package. The National Health Care Institute has determined that nivolumab-relatlimab does not meet the legal criterion of 'established medical science and medical practice' (SWP) for the indication mentioned.

We explain the preparation of this package advice below.

General
At your request, the National Health Care Institute assesses whether care should be part of the standard health insurance package from the perspective of the basic healthcare package paid from joint premiums.

The National Health Care Institute normally first assesses whether the effectiveness (SWP compliance) of the new intervention has been sufficiently

demonstrated. If this is the case, the National Health Care Institute performs an integral assessment on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity[4] and feasibility[5]. The Scientific Advisory Board (WAR) advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. Stakeholders are consulted during the process.

Since nivolumab-relatlimab does not meet the legal criterion of 'the established medical science and medical practice' for the relevant indication, the full weighting of the four package criteria and advice from the Insured Package Advisory Committee (ACP) is not relevant in this case.

Background
The guideline recommends a programmed cell death ligand 1 (PD-L1) inhibitor (nivolumab or pembrolizumab) as first-line treatment for unresectable stage III and IV melanoma. In patients with so-called negative risk factors, such as the presence of brain metastases or elevated lactate dehydrogenase, nivolumab-ipilimumab combination therapy is recommended.

The Working Group Immunotherapy Netherlands for Oncology (WIN-O) sees a place for nivolumab-relatlimab as a first-line treatment in patients with PD-L1 expression <1% without negative risk factors or with negative risk factors who are not eligible for nivolumab-ipilimumab due to toxicity. In the current practice, these patients are treated with nivolumab or pembrolizumab monotherapy.

This assessment compares nivolumab-relatlimab with nivolumab monotherapy, which is considered equivalent to pembrolizumab by Dutch melanoma therapists[6].

In March 2023, the CieBOM committee of the Dutch Association of Medical Oncology (NVMO) gave a positive advice for nivolumab-relatlimab. The CieBOM conducted the assessment on an earlier data cut-off (a median follow-up duration of 13.2 months) than used in this dossier and on the basis of the old PASKWIL criteria. The PASKWIL criteria have since been tightened (as of May 2023).

Effectiveness
The efficacy and safety of nivolumab-relatlimab was evaluated in the RELATIVITY-047 study in patients with unresectable or metastatic melanoma who had not received prior treatment in this setting. The study is a multicentre, phase II/III, double-blind study in which patients were randomised 1:1 to receive either nivolumab-relatlimab or nivolumab monotherapy. Based on the results of this

[1] Real-world package management 4 (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[2] Assessment of the established medical science and medical practice (2023). National Health Care Institute. Via www.zorginstituutnederland.nl.

[3] Cost-effectiveness report (2015).. National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[4] Necessity is related to both the medical need due to the severity of a disease for the patient (burden of disease) and the need to insure something. See the report on real-world package management 4 (2023).

[5] The package criterion of feasibility deals with whether it is feasible or sustainable to include a specific form of care in the basic health care package. It is therefore mainly a test of a number of implementation aspects such as health care organisation, support, ethical and legal aspects, budget impact and so on. See the report on real-world package management 4 (2023).

[6] Medical Oncology | WIN-O status determination: treatment of metastatic melanoma in 2016. https://medischeoncologie.nl/artikelen/2016/februari/editie-1/plaatsbepaling-win-o-behandeling-van-het-gemetastaseerd-melanoom-anno-2016

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study, EMA limited the indication of nivolumab-relatlimab to a subgroup, i.e. patients with PD-L1 expression <1%.

The National Health Care Institute concluded that patients treated with the combination treatment nivolumab-relatlimab did not live a clinically relevant longer life than those treated with nivolumab alone. This was observed for the subgroup and the overall study population. However, patients with PD-L1 expression <1% who were treated with nivolumab-relatlimab had a longer progression-free survival (PFS) compared to nivolumab treatment. This effect on the surrogate outcome PFS was statistically significant and clinically relevant according to the PASKWIL criteria.

Based on GRADE, the National Health Care Institute has sufficient confidence that there is no clinically relevant effect on overall survival (OS), and therefore sees no need to assess a surrogate endpoint such as PFS. In this case, a clinically relevant effect on the PFS does not appear to translate into a clinically relevant effect on the OS.

Quality of life and adverse effects
The quality of life of patients with tumour cell PD-L1 expression < 1% treated with nivolumab-relatlimab does not show a clinically relevant difference compared to patients treated with nivolumab. However, treatment with nivolumab-relatlimab resulted in a clinically relevant increase in serious adverse effects related to the treatment and a clinically relevant increase in the number of discontinuations due to adverse effects compared to nivolumab.

Thus, the prolongation of the progression-free period in this case does not translate into a clinically relevant improvement in the quality of life. It should be noted that the quality of life of the study population was already very good, such that it was likely not possible to improve the quality of life to a clinically relevant degree. The fact that the quality of life did not show a clinically relevant difference between both treatment arms despite the clinically relevant increase in toxicity is favourable, but not sufficient to determine an added value.

Combination treatment
When a new treatment is added to the standard treatment in the form of a combination treatment (new + standard treatment), there must be demonstrable added value to the standard treatment for health care to comply with the established medical science and medical practice. In that case, the conclusion of equal value is not sufficient.

Conclusion
Taken together, nivolumab-relatlimab does not result in clinically relevant longer survival or clinically relevant improvement in quality of life. However, the toxicity and the number of patients who discontinued treatment due to these adverse reactions showed a clinically relevant increase. In the absence of a clinically relevant improvement of the beneficial effects, a clinically relevant increase of adverse effects is unacceptable.

The National Health Care Institute concludes that nivolumab-relatlimab has no demonstrated added value over nivolumab monotherapy and therefore does not meet the established medical science and medical practice.

The National Health Care Institute recommends that nivolumab-relatlimab, for the treatment of advanced melanoma with tumour cell PD-L1 expression < 1%, not be included in the basic health care package.

Should you need any further information, please do not hesitate to contact us. The pharmacotherapeutic report is attached.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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