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2022023318

Our reference
2022023318

Date 23 June 2022
Subject Position of nivolumab for dMMR MSI

Dear Mr Kuipers,

I would like to inform you about our position regarding the application of nivolumab in adult patients with locally advanced or metastatic solid tumours that are deficient in mismatch repair (dMMR) or show microsatellite instability (MSI) and that have failed to respond to the standard treatment(s) or where no standard treatment exists or is indicated.

We conclude that the above-mentioned application of nivolumab meets the established medical science and medical practice (SW&P). This treatment is therefore one of the benefits to be insured under the Dutch Health Insurance Act (Zvw).

Background
In 2016, the Drug Rediscovery Protocol (DRUP) study was set up by Dutch oncologists.[1] In this study registered medicinal products are off-label applied in different cancers but with the same sites of action. In the meantime, the data collection for one of the cohorts has been finalised and the question arises whether the medicinal product in the relevant patient population complies with the SW&P.[2]

This is the completed DRUP cohort of patients treated with nivolumab with dMMR or MSI tumours. A request has been made to the National Health Care Institute by the health insurers and oncologists for the assessment of this application of nivolumab. In view of the special situation, the National Health Care Institute carries out this assessment in the context of risk-oriented package management

[1] van der Velden DL, Hoes LR, van der Wijngaart H, et al. The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs. Nature 2019; 574: 127-31

[2] Pisters-van Roy A vWvD-KS, van Saase L, Voest E. Kostendeling met farmaceuten brengt dure kankermedicatie binnen bereik. 2019: pages. Accessed via https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/kostendeling-met-farmaceuten-brengt-dure-kankermedicatie-binnen-bereik.htm

in the form of a pilot.

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Assessment approach in the context of a pilot
The starting point for this assessment does not differ from the existing assessment methodology for determining whether the product meets the SW&P. However, the process differs in a number of areas:

1 There is no claim for reimbursement, supported by a reimbursement file, from a marketing authorisation holder.
2 At the time of our assessment, the report of the DRUP study is only available as (so far) unpublished material. Because this is unpublished material, an independent statistician has, at the request of the National Health Care Institute, verified the analyses based on the study's raw data.
3 This is a single-arm, non-randomised study. The Dutch Society of Medical Oncology (NVMO) recently established clinical relevance limits for single-arm, non-randomised studies (PASKWIL-NRS criteria).[3] The application of these criteria has not yet been evaluated by the National Health Care Institute.
4 It concerns a tumour-agnostic indication, in which the medicinal product is used in various tumour types but with the same molecular sites of action. The National Health Care Institute's experience with tumour-agnostic indications is still limited.

That is why we carry out this assessment in the form of a pilot.

Assessment outcome
In the single-arm, non-randomised DRUP study, nivolumab was applied off-label to 137 patients with locally advanced or metastatic solid dMMR/MSI tumours. Median (progression-free) survival had not yet been reached after a median follow-up period of 11.5 months (95% confidence interval [CI] 10.2 – 13.6). An indirect comparison with a historical control group is not possible, because patients have previously not been structurally examined for the presence of dMMR/MSI, which hampers an estimation about the absolute or relative difference in (progression-free) survival compared to best supportive care.
Of the 137 patients, 50 had a confirmed response (ORR 36.5% [95% CI 28.4 – 45.1]). The median duration of the response (DoR) had not yet been reached at the time of the data cut-off; the estimates based on extrapolation vary between 62-69 months. Both patients with colon carcinoma (about 50% of patients) and other patients have shown a response to nivolumab. This supports the tumour-agnostic performance of nivolumab.

The National Health Care Institute has sufficient confidence that the effect found in terms of the ORR in combination with the DoR translates into a clinically relevant effect on the OS and/or quality of life. The Institute has taken into account that the result for ORR can be directly attributed to the medicinal product, since it is assumed that without a medicinal product, a tumour in the palliative setting will not shrink as a result of natural course (ORR=0%). In addition, a long duration of response provides clinical benefit by slowing disease progression. In addition, given the rare genetic mutation, especially in the metastasized setting, there may be too few patients to set up a randomised study. Moreover, because of the tumour-agnostic indication it is not certain that randomisation leads to prognostically comparable patient groups.

[3] cieBOM. 'We hebben de lat hoog gelegd'. 2021: pages. Accessed via https://www.nvmo.org/bom/we-hebben-de-lat-hoog-gelegd/?meta

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Other important arguments for this confidence are:

- There is a sufficiently large group that is responding to nivolumab. The responses in this group also continued for a long time. The follow-up duration is still too limited, so the median DoR has not yet been reached, but the most conservative estimate (i.e., the lower limit of the 95%CI based on extrapolation) is 22 months. This is twice as long as the clinical relevance limit stated by the NVMO (ORR > 20%; DoR > 12 months).
- The benefit/risk balance of nivolumab is positive for previous indications. In the DRUP study, treatment with nivolumab resulted in few patients who stopped prematurely. There does not seem to be a negative impact on the quality of life.
- The effect of nivolumab in the DRUP study seems consistent with the effect of other immune therapies, such as pembrolizumab, for dMMR/MSI indications. It is expected that we can extend this (relative) effect of immune therapies to nivolumab in dMMR/MSI solid tumours, especially given that there is no longer an active standard treatment in the current (last line) setting.

Conclusion
The application of nivolumab in adult patients with locally advanced or metastasized solid tumours that are deficient in mismatch repair (dMMR) or show microsatellite instability (MSI) and have failed to respond to the standard treatment(s) or where no standard treatment exists or is indicated, meets the established medical science and medical practice and is thus an insurable benefit.

Finally
By now, a registered and good immune therapy (pembrolizumab) has become available in the first line for patients with colorectal carcinoma (about 50% of the DRUP screening population). In practice, this patient group will not be eligible for the last line treatment with nivolumab. Therefore, the number of patients with MSI status who have not yet had immune therapy in the last line of the metastatic setting is not expected to be large.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board