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Our reference
2024025309

Date 30 August 2024
Subject Advisory report on ipilimumab (Yervoy®)

Dear Ms Agema,

On 15 July 2024, you asked us to carry out a review for using ipilimumab in combination with nivolumab for treating patients with resectable stage III melanoma according to the NADINA regimen. Note that the National Health Care Institute received a related request from prescribers (WIN-O melanoma) for an accelerated assessment of the 'NADINA indication' (on 14 June 2024).

The following is an elaboration of that advisory report.

Background
The indication (treatment strategy) investigated in the NADINA study is for an off-label indication that was not studied by the manufacturer but by an academic research group. This is a multicentre, randomised, phase 3 study in patients with operable, macroscopic stage III melanoma.

In this study, two courses of neoadjuvant ipilimumab plus nivolumab (i.e. before surgery) followed by adjuvant treatment (i.e. after surgery) for high-risk patients only were compared against the standard treatment of 12 courses of adjuvant nivolumab for all patients. Ipilimumab is in the lock procedure for expensive medicines for this indication (and others); nivolumab has been temporarily admitted to the basic package for all indications that meet established medical science and medical practice, with a broad financial arrangement.

The results of the NADINA study have recently been published.[1] Based on this, and after consultation with the fourteen melanoma centres in the Netherlands, the professional group has indicated that they no longer wish to deny patients with macroscopic stage III melanoma the NADINA regimen, given its high effectiveness.

The National Health Care Institute notes that the assessment of the NADINA study fits within the broader issue of package management around adjuvant and neoadjuvant treatments in oncology, which is currently being developed by the

[1] Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma | New England Journal of Medicine (nejm.org)

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National Health Care Institute at the request of the Association of Dutch Healthcare Insurers. This is because issues have arisen in practice that relate to uncertainties about the efficacy of the medicinal products and the impact on society of using them in the adjuvant and neoadjuvant settings. This is also in line with the recently published report *Passende zorg voor mensen met kanker; waardegedreven zorg in de oncologie* (Appropriate care for people with cancer; value-driven care in oncology).[2] The initiatives to improve the efficiency of oncological care, such as the NADINA study set up by the professional group, are an important building block for the National Health Care Institute for this. At the request of the Ministry of Health, Welfare and Sport (hereinafter also "VWS") and within the framework of the report to be issued by the Healthcare Institute on package management of adjuvant and neoadjuvant treatments in oncology and as part of it, we are assessing the above-mentioned off-label use through an abbreviated procedure.

The standard treatment and considerations about it
Patients with operable, macroscopic stage III melanoma are now routinely treated with immunotherapy (nivolumab, pembrolizumab) or the combination of a BRAF/MEK inhibitor in the case of a BRAF/600 mutation, as per the current guidelines after lymph node removal.[3] This adjuvant treatment can reduce the risk of recurrence or distant metastases, and the time taken for them to appear. The aim is to achieve longer average survival, at the population level. However, a large proportion of these patients would never develop metastases and will therefore have been overtreated. These patients generally have a long overall survival figure. A proportion of these patients will also still develop recurrences despite adjuvant treatment and therefore will not have benefited sufficiently from it. Moreover, treatment can be accompanied by side effects that can be severe, long-lasting and sometimes permanent (e.g. endocrine side effects).

There is evidence that neoadjuvant immunotherapy treatment is more effective than adjuvant treatment because it can achieve an early, broad immune response.[4] [5] There is backing for this in the assumption that the tumour is still present before the surgery, rather than just malignant residual cells when immunotherapy is used after surgery. Moreover, the immune response appears to be activated for long periods. This is confirmed by the SWOG S1801 study in patients with stage III/IV melanoma. In this study, treatment in which 3 out of 18 cycles of pembrolizumab were given before surgery, instead of all 18 cycles after surgery, resulted in longer event-free survival (EFS).[6] In practice, this has led to a preference for pembrolizumab being administered according to what is known as the SWOG schedule. Additionally, adding ipilimumab – a CTLA-4 inhibitor – to a PD-1 inhibitor such as nivolumab has previously been shown to increase

[2] *Signalement Passende zorg voor mensen met kanker – Waardegedreven oncologische zorg* | Part 2 |

[3] In practice, the combination BRAF/MEK inhibitor is scarcely used anymore; data was presented at ASCO 2024 showing no benefit versus anti-PD-1 treatment in high-risk patients with stage II melanoma https://doi.org/10.1200/JCO.2024.42.16_suppl.9573

[4] Liu *et al.* Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. Cancer Discov 2016;6:1382-99.

[5] Blank CU *et al.* Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med 2018;241:655-61.

[6] Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma | New England Journal of Medicine (nejm.org)

treatment efficacy, e.g. in studies in patients with stage IV melanoma[7].

The above considerations led the profession to design the multicentre, phase 3 RCT 'NADINA' study to answer the question of whether short neoadjuvant immunotherapy with ipilimumab plus nivolumab followed by adjuvant treatment of high-risk patients only is indeed more effective than adjuvant treatment alone. This was after earlier phase 2 studies had examined the rationale for the presumed improved efficacy of neoadjuvant use of this combination and an optimum dosing regimen. [8] [9]

Assessment of the NADINA study

Study design

Patients (n=423) with operable, macroscopic stage III melanoma were randomised into two groups in the NADINA study. One group received the standard treatment with surgery first, followed by twelve courses of adjuvant immunotherapy with nivolumab; the other received two neoadjuvant immunotherapy treatments with ipilimumab and nivolumab before surgery. Only the patients in the neoadjuvant group who showed only a partial response (or none at all) subsequently received adjuvant nivolumab treatment or targeted therapy (in the case of a BRAF/600 mutation) after surgery. This treatment strategy is referred to hereinafter as the NADINA regimen. The primary endpoint of this study was event-free survival (EFS), defined as the time from randomisation to the occurrence of progression to non-operable melanoma before surgery, disease recurrence or death due to melanoma or treatment.

Results

In the group with the NADINA regimen, the estimated EFS after 12 months was higher than in the adjuvant group (83.7% versus 57.2%; hazard ratio=0.32; p<0.001%), based on 28 and 72 events occurring, respectively. In the group of patients treated according to the NADINA regimen, 59% of patients no longer needed adjuvant treatment because of a complete or virtually complete response.[10] The hazard ratio determined for the difference in EFS easily meets the limits for clinical relevance as accepted by the profession for adjuvant treatments (HR<0.6).[11]

Adverse effects (grade 3 or higher) related to systemic therapy occurred more frequently in the neoadjuvant group than in the adjuvant group (29.7% versus 14.7%). Endocrinopathies related to systemic treatment occurred more frequently in the neoadjuvant group than in the adjuvant group (30.7% versus 9.9%) and they also lasted for longer. In the neoadjuvant group, fewer patients discontinued treatment because of an adverse event (9% versus 14.4%).

Other considerations

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[7] Zimmer *et al.* Adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): a randomized, double-blind, placebo-controlled, phase 2 trial. Lancet 202;395:1558-68.

[8] Rozeman AE *et al.* Survival and biomarker analysis from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. Nat Med 2021;27:256-63.

[9] The Optimal Neo-adjuvant Combination Scheme of Ipilimumab and nivolumab [OpACIN-neo] study and the Personalized Response-Driven Adjuvant Therapy after OpACIN [PRADO] study

[10] 47.2% complete pathological response and 11.8% virtually complete pathological response (0-10% tumour tissue)

[11] PASKWIL criteria 2023 About the advice – NVMO

Based on the SWOG S1801 study, the practice recently switched to the off-label SWOG regimen (in which three courses of neoadjuvant pembrolizumab are given) in patients with stage III/IV melanoma, because of the longer disease-free survival that can be achieved with it (estimated 2-year EFS 72% versus 49%; HR 0.58; p=0.004).

The NADINA regimen seems more effective than the SWOG regimen mentioned above for pembrolizumab in improving event-free survival. It should be noted, however, that the study designs were not entirely comparable. The SWOG S1801 study included patients at stages IIIb to IVc and with in-transit metastases only, whereas the NADINA study included stage IIIb to IIId patients with macroscopic glandular metastases, with or without in-transit metastases. Moreover, the regimens were not directly compared in a clinical trial.

Because the course of the disease is long-term, no results are currently available for the crucial outcome measure of overall survival (OS). Based on appropriate research, the National Health Care Institute considered it acceptable in this case to reach a positive opinion based on EFS as a surrogate measure of outcome for OS. The effect on EFS was deemed to have more than met the PASKWIL criteria used by the profession for adjuvant and neoadjuvant treatments. The NADINA regimen also leads to less of a burden for a significant proportion of patients, as adjuvant treatment is no longer required. Taking account of potential toxicity due to the addition of ipilimumab neoadjuvant, the National Health Care Institute's opinion is that the NADINA regimen has added value over standard treatment, even if it transpires that no clinically relevant effect on OS can ultimately be demonstrated. Moreover, waiting until data on OS is available could also mean that patients are unfairly being denied effective treatment.

At the moment when longer-term data becomes available, that may be grounds for the National Health Care Institute to carry out a reassessment.

Conclusion
Based on the above, the National Health Care Institute concludes that neoadjuvant (off-label) treatment with ipilimumab plus nivolumab followed by adjuvant treatment in high-risk patients only meets the criterion of established medical science and medical practice. The NADINA regimen gives a clinically relevant gain in event-free survival compared with current standard treatment, but is associated with more side effects. Because only high-risk patients receive adjuvant treatment, overtreatment is avoided. As a result, fewer patients are exposed to the unfavourable effects that may be associated with adjuvant treatment.

Budget impact analysis (BIA)
The National Health Care Institute has chosen to give a brief description of the expected costs if the NADINA regimen is introduced and reimbursed. A standard BIA is less suitable in this case because it does not compare the costs in different treatment lines, which is highly relevant in this efficiency issue. The professional group estimates that about 500 patients with macroscopic stage III melanoma will be eligible for treatment using the NADINA regimen each year in the Netherlands. About 20% of these patients are expected to receive the adjuvant and/or neoadjuvant SWOG regimen with pembrolizumab. A total of some 400 patients therefore are expected to start the NADINA regimen.

To estimate the budgetary impact of reimbursing the NADINA regimen, it will have to be compared against the current treatment situation and the costs thereof. For each situation (current versus expected), an overview will be given for the 400 patients expected to receive a different therapy. This only considered the costs of the medicines; some other cost items will be discussed below (only textually).

Current situation:
Patients receive 8 courses of pembrolizumab in the adjuvant and/or neoadjuvant setting. The patients receive 400 mg pembrolizumab by intravenous infusion every 6 weeks. The pharmacy purchase price of pembrolizumab is €2,624.37 per vial containing 100 mg pembrolizumab. Four vials are required per administration, so the cost per administration is €10,497.48. The treatment cost per patient is in total 8 x €10,497.48 = €83,979.84.

Total cost for the current situation: all 400 patients are treated with pembrolizumab at €83,979.84 per patient, making the overall cost €33,591,936.00 per year.

Expected situation based on the NADINA regimen:
Patients receive two courses of ipilimumab/nivolumab in the neoadjuvant setting. This requires 80 mg ipilimumab and 240 mg nivolumab per course. Subsequently, 59% of patients no longer require additional (adjuvant) treatment and 41% do. This adjuvant treatment consists of 11 courses of nivolumab monotherapy (at 4-week intervals), with 480 mg given per administration.
The pharmacy purchase price for a 50 mg vial of ipilimumab is €3,268.49. The pharmacy purchase price for a 240 mg vial of nivolumab is €2,430.15. For the neoadjuvant phase, 2 vials of ipilimumab and 1 vial of nivolumab are assumed per administration. This makes the total cost for the neoadjuvant phase €17,934.26 per patient.
The adjuvant phase (11 courses) needs 2 vials of nivolumab per administration. This takes the total cost for this phase to €53,463.30 per patient.

Total cost for the expected situation: all 400 patients receive neoadjuvant treatment with ipilimumab/nivolumab at €17,934 per patient. Subsequently, 41% of patients are still treated with nivolumab monotherapy at €53,463 per patient. This makes the overall cost €15,941,685 per year for this patient population. This includes €7,173,704 for the neoadjuvant setting (€5,229,584 for ipilimumab and €1,944,120 for nivolumab) and €8,767,981 in the adjuvant setting (nivolumab only).

Budget impact analysis conclusion
Off-label neoadjuvant treatment with ipilimumab plus nivolumab in patients with macroscopic stage III melanoma is expected to yield savings of €17,650,250.80 (i.e. €17.7 million) per year.
Please note, though, that there are several caveats to the calculation:

- The calculations used pharmacy purchase prices, but an undisclosed price has been negotiated for nivolumab and pembrolizumab. This means the savings in the costs of medicinal products are likely to be lower.
- Only costs in the adjuvant and neoadjuvant settings were considered, and therefore the costs of any follow-up treatments were not included. It is possible that patients treated using the NADINA regimen will actually lead to higher treatment costs at a later stage (e.g. due to longer survival).

This is however currently uncertain and it therefore cannot be included in the calculation by the National Health Care Institute.

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Besides these medication costs, various other aspects are worth mentioning. Adjuvant melanoma treatment has implications for the organisation of care e.g. because of more monitoring procedures and more pathological and radiological examinations, as well as because outpatient treatment will be needed. The reduction in adjuvant treatments under the NADINA regimen will save on costs and staffing requirements. It has moreover also been pointed out by the professional group that better planning of surgery is attainable through neoadjuvant treatment, as there is currently often a 4 to 6-week wait for lymph node removal. Two neoadjuvant cycles of ipilimumab plus nivolumab can now be given in the waiting period.

Cost-effectiveness
The treatment strategy according to the NADINA regimen includes the medicinal product ipilimumab (Yervoy®). This medicinal product is in the lock procedure for expensive drugs. The National Health Care Institute has not carried out a pharmacoeconomic analysis for this indication. There are various reasons for this. The NADINA regimen is an off-label application in which the manufacturer has not been involved. Introducing this scheme is also expected to be associated with substantial cost savings compared to the standard treatment. The cost impact for ipilimumab in neoadjuvant treatment according to the NADINA regimen is €5,229,584 per year. Given that cost impact, the National Health Care Institute also sees no grounds for commissioning a cost-effectiveness analysis: the NADINA regimen improves treatment effectiveness and goes hand in hand with reduced costs.

Advice
The NADINA study into patients with operable, macroscopic stage III melanoma has shown that off-label neoadjuvant treatment with ipilimumab plus nivolumab followed by adjuvant treatment after surgery for high-risk patients only (known as the NADINA regimen) meets established medical science and medical practice. The NADINA regimen leads to a clinically relevant gain in event-free survival. Because only high-risk patients are given the adjuvant treatment, fewer patients are exposed to the unfavourable effects that may be associated with the adjuvant treatment. In addition, the NADINA regimen also yields savings in costs and resources. Using this regimen therefore contributes to the principles of appropriate care. Implementation is assured because the professional group broadly supports the NADINA regimen for patients with operable, macroscopic stage III melanoma.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board
National Health Care Institute

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