ORIGINAL ARTICLE

Programmed Death 1 Blockade With Nivolumab in Patients With Recurrent Malignant Pleural Mesothelioma

Josine Quispel-Janssen, MD,[a,*] Vincent van der Noort, PhD,[b] Jeltje F. de Vries, PhD,[b] Marion Zimmerman,[a] Ferry Lalezari, MD,[c] Erik Thunnissen, MD, PhD,[d] Kim Monkhorst, MD, PhD,[e] Robert Schouten, MD,[a] Laurel Schunselaar, MS,[f] Maria Disselhorst, MD,[a] Houke Klomp, MD, PhD,[g] Koen Hartemink, MD, PhD,[g] Sjaak Burgers, MD, PhD,[a] Wieneke Buikhuisen, MD,[a] Paul Baas, MD, PhD[a]

[a]*Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands*
[b]*Biometrics Department, Netherlands Cancer Institute, Amsterdam, The Netherlands*
[c]*Department of Radiology, Netherlands Cancer Institute, Amsterdam, The Netherlands*
[d]*Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands*
[e]*Department of Pathology, Netherlands Cancer Institute, Amsterdam, The Netherlands*
[f]*Division of Oncogenomics, Oncode Institute within Netherlands Cancer Institute, Amsterdam, The Netherlands*
[g]*Department of Surgery, Netherlands Cancer Institute, Amsterdam, The Netherlands*

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ABSTRACT

Introduction: Malignant pleural mesothelioma (MPM) has limited treatment options and a poor outcome. Programmed death 1/programmed death ligand 1 (PD-L1) checkpoint inhibitors have proven efficacious in several cancer types. Nivolumab is a fully humanized monoclonal antibody against programmed death 1 with a favorable toxicity profile. In MPM, the immune system is considered to play an important role. We therefore tested nivolumab in recurrent MPM.

Methods: In this single-center trial, patients with MPM received nivolumab 3 mg/kg intravenously every 2 weeks. Primary endpoint was the disease control rate at 12 weeks. Pre- and on-treatment biopsy specimens were obtained to analyze biomarkers for response.

Results: Of the 34 patients included, 8 patients (24%) had a partial response at 12 weeks and another 8 had stable disease resulting in a disease control rate at 12 weeks of 47%. One reached a partial response at 18 weeks. In 4 patients with stable disease, the tumor remained stable for more than 6 months. Treatment-related adverse events of any grade occurred in 26 patients (76%), most commonly fatigue (29%) and pruritus (15%). Grades 3 and 4 treatment-related adverse events were reported in 9 patients (26%), with pneumonitis, gastrointestinal disorders, and laboratory disorders mostly seen. One treatment-related death was due to pneumonitis and probably initiated by concurrent amiodarone therapy. PD-L1 was expressed on tumor cells in nine samples (27%), but did not correlate with outcome.

Conclusions: Single-agent nivolumab has meaningful clinical efficacy and a manageable safety profile in pre-treated patients with mesothelioma. PD-L1 expression does not predict for response in this population.

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*Corresponding author.

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Address for correspondence: Josine Quispel-Janssen, MD, Department of Thoracic Oncology, Netherlands Cancer Institute, Postbus 90203, 1006 BE Amsterdam, The Netherlands. E-mail: thoraxoncologie@nki.nl

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Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor arising from mesothelial cells of the pleural cavity and is strongly related to (occupational) asbestos exposure. Although the use of asbestos is banned in most western countries, this disease will continue to score victims over the next decade because of the long latency time.[1]

MPM is refractory to the vast majority of drugs and has a dismal prognosis: most patients die within 2 years after diagnosis. The standard treatment for patients with advanced disease is chemotherapy consisting of a platinum-antifolate combination.[2] There is no registered second-line therapy because no study has shown a survival benefit in this setting.[3] Improving the outcome is urgently needed, but remains a huge challenge due to the difficulty of response evaluation and the heterogeneity of the disease. The success of new treatment approaches such as immunotherapy in other cancer types gives hope to these patients.

Immunotherapy enhances the ability of the patients own immune system to recognize and destroy tumor cells. Tumors can evade this immunosurveillance by upregulating inhibitory signals such as the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway.[4] Blockade of this pathway by PD-1 inhibitors resulted in long-lasting responses, as was first shown in melanoma.[5] It has shown efficacy in many other cancer types, including lung cancer and renal cell carcinoma.[6-8]

Nivolumab (BMS-936558) is a fully human monoclonal antibody that binds PD-1 on activated immune cells and disrupts binding of PD-1 to its ligand PD-L1. This process will prevent downregulation of cytotoxic T cells and augment the host-antitumor response. Nivolumab is registered in several countries for the treatment of advanced melanoma and is approved for the second-line treatment of NSCLC after previous platinum-containing chemotherapy. To date, nivolumab shows a mild toxicity profile as hematologic toxicities are rare and the majority of nonhematological toxicities are low grade and manageable. The safety profile of nivolumab monotherapy is similar across tumor types.

Despite all positive reports about checkpoint inhibitors, not all tumors respond well to this treatment. Therefore, it is crucial to find predictive biomarkers that enable us to withhold treatment from patients that are unlikely to respond and thus prevent time loss and unwanted side effects. The most frequently studied biomarker is PD-L1 expression. In MPM, expression of PD-L1 was shown by several groups, especially on sarcomatoid MPM.[9-12] PD-L1 expression is also present on immune cells as is assessed in several tumor types.[13] Emerging data reveal that other factors such as mutational load, general immune status, and the tumor microenvironment may play an important role in evoking a response. Therefore, we designed this single-arm phase II trial with an emphasis on biomarker research.

Methods

Study Design and Participants

In this prospective, single-arm, single-center, phase II trial, a Simons' minimax design was used.

Patients aged 18 years or older with MPM were eligible for study participation if they had disease recurrence after at least one chemotherapy regimen, WHO performance status 0 or 1, measurable disease and adequate liver, renal, and bone marrow functions including lactate dehydrogenase (LDH). In addition, C-reactive protein (CRP), amylase, lipase, thyroid stimulating hormone, and free thyroxine 4 were measured. Tumors had to be accessible for repeated biopsies by thoracoscopy or a computed tomographic (CT) – or ultrasound-guided transthoracic approach. Key exclusion criteria were symptomatic central nervous system metastasis, autoimmune disease or systemic immunosuppressive therapy.

The study protocol was approved by the institutional ethics committee and conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from all participants. The trial was registered at ClinicalTrials.gov, number NCT02497508.

Procedures

Treatment consisted of biweekly intravenous administration of nivolumab 3 mg/kg, a fully humanized immunoglobulin G4 antibody targeting PD-1 (Opdivo, Bristol-Meyers Squibb, New York, New York). Dose and treatment schedule were based on data from a phase I trial.[14] No dose escalations or reductions were allowed. Dose delays were permitted for protocol-defined reasons. Treatment continued for a maximum of 1 year or until disease progression or unacceptable toxicity.

Tumor response was assessed with CT scans every 6 weeks (every 8 weeks after 24 weeks of treatment) using a combination of Response Evaluation Criteria In Solid Tumors (RECIST) modified for mesothelioma and RECIST modified for immunotherapeutic agents.[15,16] A partial response (PR) was defined as a decrease of $\geq$30% of the sum of target lesions, measured according to RECIST modified for mesothelioma (unidimensional measurements of tumor thickness perpendicular to the chest wall or the mediastinum). Progressive disease (PD) was defined as an increase of $\geq$20% of target lesions, confirmed by another CT scan at least 4 weeks apart.

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