ORIGINAL ARTICLE

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

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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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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.

Patients were allowed to continue treatment beyond initial radiologic progression in the absence of clinical deterioration. If the subsequent CT scan did not confirm progression, the initial progression was considered to be pseudoprogression, and the patient was allowed to continue treatment with nivolumab. New lesions did not define progression, but were added to the total sum of tumor burden, according to RECIST modified for immunotherapeutic agents. Nontarget lesions could contribute to the designation of overall progression, but PD was never concluded solely on the basis of increased lymph nodes. Stable disease (SD) was defined as not having complete response (CR), PR, or PD.

Laboratory testing was performed before each nivolumab administration. Pulmonary function was assessed at baseline and after 6 weeks. Tumor tissue specimens were obtained before and after 3 courses of nivolumab by means of thoracoscopy or ultrasound- or CT-guided transthoracic biopsies.

PD-L1 expression on formalin-fixed, paraffin-embedded tissue samples was assessed with immunohistochemistry using monoclonal antibody 28-8 according to the manufacturer (PD-L1 IHC 28-8 PharmDx, EnVision FLEX Visualisation System, Autostainer Link 48, Agilent Dako, Santa Clara, California). At least 100 neoplastic cells were scored for membranous staining and a tissue sample was considered positive if more than 1% of tumor cells stained positive. Expression was quantified in five categories: 1% to 5% positive cells, 5% to 10%, 10% to 25%, 25% to 50% and $\geq$50% positive cells.

Outcomes

The disease control rate (DCR) at 12 weeks was the primary endpoint of this study. DCR was defined by the number of patients with CR, PR, and SD as a percentage of the total number of patients in the study. Secondary endpoints included DCR at 6 months, clinical benefit rate, objective response rate, progression-free survival (PFS), overall survival (OS), and safety. Patients with CR and PR, and patients with long-term SD ($\geq$6 months) were considered to have clinical benefit. PFS was defined as the time interval from the date of start of treatment to the date of the first documented tumor progression or death due to any cause, whichever occurred first. OS was defined as the time interval from the date of start of treatment to the date of death due to any cause. Safety was assessed by incidence of adverse events, reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analysis

Based on our hypothesis that treatment with nivolumab will increase the DCR at 12 weeks from 20% to 40%, a Simon mini-max design with a sample size of 33 patients was chosen with an interim analysis for futility after 18 patients, allowing the study to continue only if at least 5 of the first 18 patients had disease control. This design with an early stop for futility was chosen because of the limited number of patients with this rare tumor type. Treatment with nivolumab was deemed successful if the study was not stopped at the interim analysis and at least 11 patients of the 33 showed disease control. When the true DCR in the population is 40%, the chosen numbers guarantee that the power of declaring success will be 80% whereas the probability of making a type I error (defined as declaring success when the true DCR was 20% or less) is controlled at 0.05. PFS and OS were calculated using the Kaplan-Meier method. All patients who received at least one dose of nivolumab and had at least one radiologic evaluation were considered evaluable. All patients who received at least one dose of nivolumab and had at least one follow-up visit were included in the safety analysis. Cut-off for survival analysis was January 2018. Fisher's exact test was used to analyze the correlation between PD-L1 expression and response.

Role of the Funding Source

The study was designed by the authors and financially supported by Bristol-Meyers Squibb which included medication supply.

Results

Between July 2015 and June 2016, 38 patients gave informed consent. Of these, 34 patients fulfilled the entry criteria and received study treatment. Thirty-three patients were evaluated; 1 patient died due to cardiac disease before the response evaluation (Fig. 1). At the interim analysis, 5 of 18 patients had a PR and 4 had SD. Disease control was thus reached in more than 5 patients allowing the trial to continue. Baseline

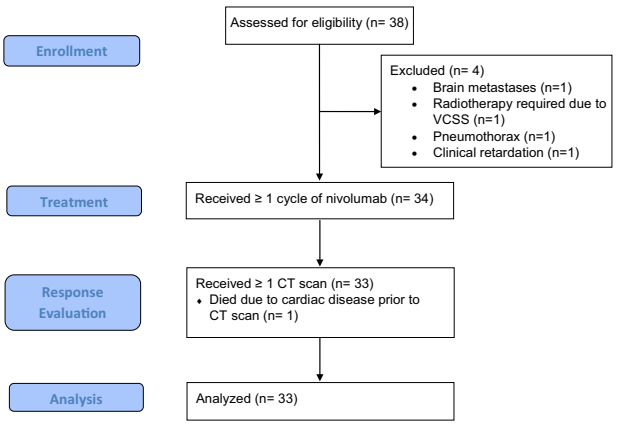

Figure 1. CONSORT flow diagram. VCSS, Vena Cava Superior syndrome; CT, computed tomography.

Table 1. Patient Characteristics

Demographic Variable	Patients (n = 34)
Age, median in years (range)	67 (50-81)
Sex	
Male	28 (82%)
Female	6 (18%)
WHO performance score	
0	18 (53%)
1	16 (47%)
Histologic subtype	
Epithelioid	28 (82%)
Sarcomatoid	2 (6%)
Mixed	4 (12%)
Previous local therapy	
Surgery	3 (9%)
Radiotherapy	5 (15%)
Disease stage	
I-III	24 (71%)
IV	10 (29%)

characteristics are shown in Table 1. With a median age of 67 years, a male predominance (82%) and a majority of epithelial subtype, our study population was representative for the general mesothelioma population.

Most patients received one prior line of systemic treatment; one patient received two lines. Pleurectomy/decortication was performed in four patients. Five patients received radiotherapy before start of study treatment. Median time from the initial diagnosis of mesothelioma to the start of study enrolment was 12.3 months. One-quarter of patients started nivolumab treatment within 3 months after completing their previous chemotherapy.

The median number of doses nivolumab administered was 7 (interquartile range: 3 – 17.25) and the median duration of treatment was 2.8 months (95% confidence interval [CI]: 1.8 – 6). Dose delays occurred 11 times in nine patients. In seven cases in six patients this was due to toxicity. Administrative or personal requests caused the other dose delays. Post-study treatment was given in nine patients (27%), mostly gemcitabine or vinorelbine.

At 12 weeks, a PR was observed in 8 patients of the 34 in the intention-to-treat group (24%, 95% CI: 11% – 42%). Eight patients had SD, resulting in a DCR of 47% (95% CI: 30%–65%). Seventeen patients had PD after 12 weeks. One patient with SD at 12 weeks eventually reached a PR after 18 weeks resulting in a total of nine patients (26%) with a PR. In four patients with SD at 12 weeks, the tumor remained stable for more than 6 months. In total, 13 patients (nine with PR and four with long-term SD; 39%) were considered to have clinical benefit from their treatment with nivolumab.

Three patients had an initial increase in tumor burden of more than 20% followed by a PR which was considered to be pseudoprogression.

The median follow-up was 27.5 months (95% CI: 19.3–upper boundary of CI not attained); the minimum follow-up was 1.9 months. Median time to response in the nine responders was 2.6 months (95% CI: 2.3–upper boundary of CI not attained). The median duration of response was 7.0 months (95% CI: >3.0). Two patients with a PR had to discontinue treatment due to adverse events (pneumonitis and pneumonitis in combination with nausea). Their responses lasted 3 and 8 months, respectively. One of the responding patients received only one dose of nivolumab. Five patients with clinical benefit discontinued study treatment after 1 year according to protocol rules, with two of them having ongoing clinical benefit. Responses and duration of treatment of all patients are visualized in the swimmer plot in Figure 2.

Median PFS was 2.6 months (95% CI: 2.23 – 5.49) and at 6 months, 29% of patients (95% CI: 18% – 50%) were free of progression (Fig. 3*A*). Median OS was 11.8 months (95% CI: 9.7–15.7) (Fig. 3*B*). At 6 months the OS was 74% (95% CI: 60%– 90%) and after 1 year 50% (95% CI: 36% – 70%).

Biomarkers

Pre-treatment biopsy specimens were obtained from all patients according to study protocol, and 33 of 34 patients who received at least one course of nivolumab were evaluable for PD-L1 expression. PD-L1 expression on more than 1% of tumor cells was seen in nine samples (27%) of which seven (78%) were epithelioid, one (11%) sarcomatoid, and one (11%) mixed type. PD-L1 expression was positive in four of nine patients (44%) with a PR. Of all 13 patients who experienced clinical benefit, five (38%) had PD-L1 expression whereas PD-L1 expression was shown in four (20%) of 20 patients without clinical benefit (Table 2, section on pre-treatment biopsy). On-treatment biopsy specimens were obtained from 31 patients with 27 samples being evaluable. In four cases there was no accessible tumor left to biopsy, or no viable tumor was found in the specimen. Of the 13 patients with clinical benefit, 11 samples were evaluable and 3 (27%) were PD-L1–positive. Of the patients without clinical benefit, 3 of 16 evaluable samples (19%) were PD-L1 –positive (Table 2, section on on-treatment biopsy). There was no correlation between PD-L1 expression in pre-treatment biopsy specimens compared to on-treatment biopsy specimens. PD-L1 expression in neither pre-treatment nor on-treatment biopsy specimens correlated with outcome ($p = 0.43$ and 0.66, respectively).

Blood biomarkers such as LDH, CRP, lymphocytes, and neutrophil-to-lymphocyte ratio (NLR) were analyzed

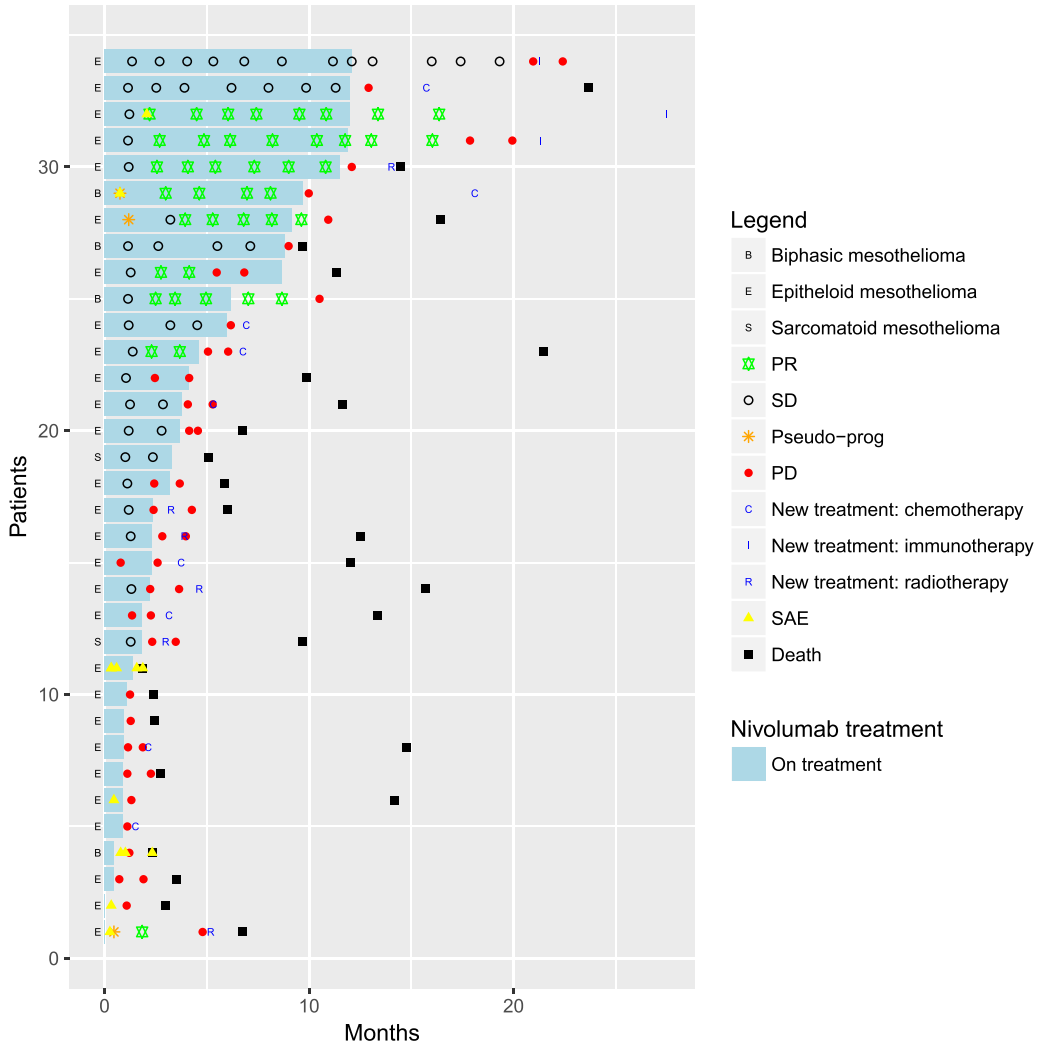

Figure 2. Efficacy of nivolumab in swimmer plot organized by treatment duration. PR, partial response; SD, stable disease; SAE, serious adverse event.

with respect to outcome. LDH, CRP, and absolute leucocyte count at baseline and at 6 weeks did not predict response or progressive disease. Neither was a change from baseline to week 6 in these parameters related to outcome. However, an increase in NLR of more than 25% from baseline to week 6 correlated with nonresponse.

Toxicity

All 34 patients who started study treatment were included in the safety analysis. Treatment-related adverse events of any grade occurred in 26 patients (76%), most commonly fatigue (29%) and pruritus (15%) (Table 3). Grades 3 and 4 treatment-related adverse events were reported in 9 (26%) patients. There was one treatment-related death. This patient received amiodarone for atrial fibrillation and developed respiratory symptoms and radiologic changes consistent with pneumonitis within 4 weeks after start of treatment. In retrospection, subtle signs of interstitial lung disease were already discernable before nivolumab treatment, which suggests that amiodarone initiated the pneumonitis. Both amiodarone and nivolumab were stopped immediately and the patient was treated with corticosteroids. Over the course of several weeks, he deteriorated and died, while at that time, disease progression was also suspected.

Pneumonitis was reported in three other cases. One of these patients who had a PR developed grade 2 pneumonitis that resolved with corticosteroid treatment, but recurred after restart of nivolumab. Study treatment was therefore discontinued permanently. Two patients were admitted to the hospital with respiratory symptoms and radiologic changes suggestive of pneumonitis in combination with disease progression. After start of treatment with corticosteroids, both turned out to have pseudoprogression. One of the patients successfully restarted nivolumab after resolution of symptoms and had a PR that lasted 9.5 months. The other experienced

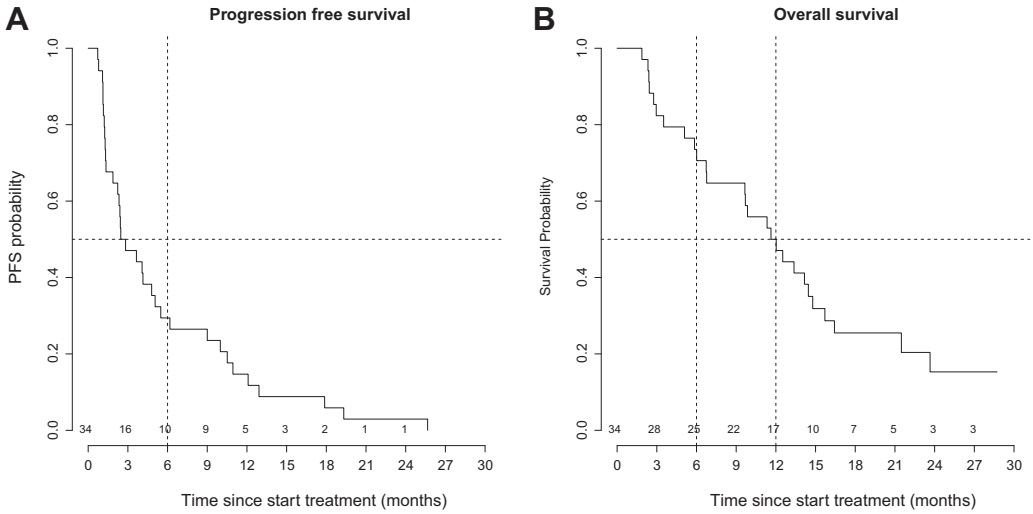

Figure 3. (*A*) Progression-free survival. (*B*) Overall survival. PFS, progression-free survival.

worsening of his pre-existing nausea simultaneously with his respiratory symptoms; therefore, study treatment was discontinued. Despite discontinuation after only one course, he developed a PR. One patient died before response evaluation due to cardiac disease unrelated to study treatment.

Discussion

Until now, results in second-line MPM therapy have been disappointing with response rates varying between 7% and 20%.[3,17] Our study shows that single-agent nivolumab has promising anticancer activity in this PD-L1–unselected population of patients with progressive MPM after previous systemic treatment. With a DCR of 47% at 12 weeks, our trial met its primary endpoint. In addition to the nine patients with a PR, there were four patients who had SD for a period longer than 6 months, suggesting a clear clinical benefit. This makes the 26% objective response rate in this trial encouraging for a disease that is notoriously difficult to treat. At first glance, a median PFS of 2.6 months does not seem spectacular, but the median OS of 11.8 months is very promising in this cohort of pre-treated patients. These results are in line with outcomes of other immuno-oncology trials for which OS is mainly driven by a small group of patients with long lasting responses. Furthermore, our results are consistent with those of the recently published phase I study with pembrolizumab that reported a response rate of 20%.[18] Patients in that trial were selected to have more than 1% PD-L1 expression. The subsequent phase II study was performed in an unselected group of mesothelioma patients and showed a comparable response rate of 21%.[19] The reported DCR of 76% at 12 weeks in this pembrolizumab trial may look superior to our results, but the limited number of patients in these trials is likely to render the difference insignificant. We consider

Table 2. PD-L1 Expression

	PD-L1 + 1-5%	PD-L1 + 5-10%	PD-L1 + 10-25%	PD-L1 + 25-50%	PD-L1 + >50%	PD-L1 −	Biopsy not Evaluable	Total
Pre-treatment biopsy[a]								
Clinical benefit +	1	0	0	2	2	8	0	13
Clinical benefit −	1	0	1	1	1	15	1	20
Patient not evaluable	0	0	0	0	0	1	0	1
Total	2	0	1	3	3	24	1	34
On-treatment biopsy[b]								
Clinical benefit +	2	0	0	0	1	8	2	13
Clinical benefit −	1	0	1	1	0	13	2	18
Patient not evaluable	0	0	0	0	0	0	3	3
Total	3	0	1	1	1	21	7	34

[a]PD-L1 expression in pre-treatment biopsy specimens of 34 patients that were included. Patients with a PR and patients with long-term SD (≥6 months) were considered to have clinical benefit. PD-L1 expression did not correlate with outcome ($p = 0.43$).
[b]PD-L1 expression in on-treatment biopsies. PD-L1 expression did not correlate with outcome ($p = 0.66$).
PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease.

Table 3. Treatment-Related Adverse Events

Adverse Events	Any Grade	Grade 3-4	Grade 5
Any	26 (76%)	9 (26%)	1 (3%)
General disorders			
Fatigue	10 (29%)	0	
Fever	3 (9%)	0	
Infusion-related reaction	2 (6%)	0	
Pruritus	5 (15%)	0	
Allergic reaction	2 (6%)	1	
Respiratory disorders			
Pneumonitis	4 (12%)	2	1
Gastrointestinal disorders			
Nausea	3 (9%)	1	
Vomiting	1 (3%)	1	
Colitis	0 (0%)		
Laboratory abnormalities			
Liver biochemistry	2 (6%)	2	
Other			
Acute kidney injury	1 (3%)	1	
Pericardial effusion	1 (3%)	1	

the efficacy of pembrolizumab and nivolumab to be comparable as is the case in second-line studies in NSCLC.[7,20] The JAVELIN trial reported 9.4% responders with avelumab, a PD-L1 inhibitor. Thus far, there is no good explanation for this difference other than a variation in patient selection.[21]

Despite a higher rate of pneumonitis, the safety profile in our study was similar to those noted in previous nivolumab trials and to the phase II study with pembrolizumab. The fatal case with pneumonitis was most likely initiated by use of amiodarone and enhanced by nivolumab. A detailed retrospective analysis of the CT scans identified a barely noticeable interstitial lung disease already present before start of nivolumab. Amiodarone is well known for its risk of drug interactions and pneumonitis. To our knowledge, this is the first observation of a fatal outcome of this combination. Of the three other patients with pneumonitis, only one had a typical presentation; two others had pneumonitis simultaneously with pseudoprogression, which is likely to have aggravated respiratory symptoms. All three cases recovered completely.

Pseudoprogression was seen in three patients (9%), which is within the expected range.[22] We did not see any cases of hyperprogression as was recently defined as time-to-treatment failure less than 2 months, more than 50% increase in tumor burden compared to pre-immunotherapy imaging, and a greater than 2-fold increase in progression pace.[23,24] Most adverse events were manageable with established guidelines.

PD-L1 expression as a biomarker of response has been analyzed in various studies using different antibodies and staining procedures. Studies comparing different PD-L1 assays suggest that three assays do not differ much from each other (SP263, 28-8, 22C3), but none give 100% interchangeable results.[25,26] In our trial, the 28-8 assay was used showing PD-L1 expression in 27% of tumors, which is consistent with previous reports of MPM.[9-12] Responses were seen irrespective of PD-L1 expression and pre-treatment PD-L1 expression did not correlate with on-treatment expression levels. Several clinical trials have shown that PD-L1 expressing tumors enrich for response.[7,20] However, PD-L1 is frequently expressed nonhomogenously throughout a tumor, which may lead to sampling errors. In addition, PD-L1 expression on tumor cells can be a result of innate or adaptive immune resistance.[27-29] In case of innate resistance, tumors express PD-L1 without the presence of active immune cells in the tumor micro-environment and as a consequence, PD-1 blockade will not be able to elicit a response. Both factors compromise the predictive value of PD-L1 expression as a biomarker.

Because of these concerns about PD-L1, several other biomarkers are currently evaluated for their predictive value in cancer immunotherapy. Blank et al.[30] designed the cancer immunogram that takes into account parameters such as mutational load, lymphocyte count, CRP, and LDH to describe a comprehensive immune status. We investigated the possibility to predict response by using blood biomarkers, including a selection of biomarkers from the cancer immunogram. LDH, CRP, and absolute lymphocyte count did not correlate with response in our patient set. However, a rise in NLR from baseline to week 6 did predict for nonresponse. None of the patients with an increase had a response except for one. In this patient, the rise in NLR was caused by use of corticosteroids which is known to induce an increase in neutrophil levels.[31] After discontinuation of corticosteroids, the NLR decreased sharply in this patient. NLR has prognostic value in several tumor types including MPM, but its merit as a predictive parameter must be validated in a larger patient cohort. Since time to response is fairly long in immunotherapy, it may be convenient to have a marker that predicts nonresponse at an early time point to withhold a potentially toxic treatment.[32] However, in our cohort, no meaningful difference in NLR increase was observed between patients with progression and those with SD.

In conclusion, nivolumab has meaningful clinical activity and an acceptable safety profile in second-line treatment in an unselected population of patients with mesothelioma. Further studies with a combination of checkpoint inhibitors (ipilimumab and nivolumab) are ongoing.

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