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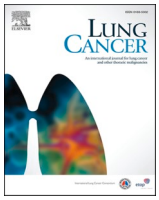

Nivolumab and ipilimumab in the real-world setting in patients with mesothelioma

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ABSTRACT

Objectives: Nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4) is a new first-line treatment combination for patients with pleural mesothelioma. Nivolumab-ipilimumab improved the survival, however, 30.3% of the patients suffered from grade 3–4 treatment related adverse events (TRAE's) and TRAE's led to discontinuation in 23.0% of all patients. Here, we present the first real-world data of nivolumab plus ipilimumab in patients with malignant mesothelioma treated in two mesothelioma expert centers.

Methods: Clinical data of patients with mesothelioma treated with nivolumab and ipilimumab were prospectively collected. Clinical parameters were obtained every visit, CT scans were evaluated every 12 weeks and adverse events were assessed continuously during the treatment. Data on grade 2–5 TRAE's and activity (overall response rate (ORR), duration of response (DOR), disease control rate (DCR), median progression-free survival (mPFS) and median overall survival (mOS) were reported.

Results: Between January 2021 and August 2022, 184 patients were treated with nivolumab plus ipilimumab. The median follow-up was 12.1 months (95 %CI 11.1 – 13.1). Grade 3–4 TRAEs were seen in 27.7 % of the patients and 25.0 % discontinued immunotherapy treatment early because of TRAE's. ORR was 21.7 % (95 % CI 15.7–27.7), median DOR was 5.7 months (IQR 3.2–8.7) and DCR at 12 weeks 56.0 % (95 % CI 48.8–63.2). The mPFS was 5.5 months (95 %CI 4.1–6.9), mOS was 14.1 months (95 % CI 11.1–18.2).

Conclusions: Nivolumab plus ipilimumab had an equal efficacy in a real-world comparable population but also a high risk of TRAE's, leading to discontinuation of treatment in 25% of the patients.

1. Introduction

Mesothelioma is a rare and aggressive malignancy with a poor prognosis. Without treatment, the median survival time ranges between six and nine months [1]. As the diagnosis usually is made at an advanced stage most patients are not eligible for surgery and designated for palliative systemic treatment [2]. Treatment in first-line with a combination of platinum and pemetrexed resulted in a median survival benefit of three months [3]. The addition of bevacizumab resulted in an additional survival benefit of nearly three months [4]. Recently, a randomized phase 3 trial showed clinically meaningful activity with a significant improvement of overall survival (OS) using the combination of nivolumab (anti-programmed cell death protein-1 (PD-1)) and ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)) compared to chemotherapy (18.1 months (95 % CI 16.8–21.4) and 14.1 months (95 % CI 12.4–16.2), respectively, HR = 0.74, p = 0.0020) [5,6]. In this study, 30 % of the patients treated with nivolumab plus ipilimumab suffered from grade 3 and 4 adverse events (26 % and 4 %, respectively), and 23.0 % discontinued at least one of the treatment components due to treatment-related adverse events (TRAE's). This has led to a Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved first-line treatment option for patients with unresectable mesothelioma [7,8].

The patients enrolled in clinical trials are often subjected to stringent

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selection criteria that may not necessarily reflect the real-world population. Because side effects might be more prominent in a more fragile patient population and survival benefit less pronounced, a description of real-world data on nivolumab plus ipilimumab combination in patients with mesothelioma is urgently needed. This article describes safety and activity of this treatment combination in patients who were treated in an expanded access program (EAP) in the Netherlands from January 2021 to August 2022.

2. Methods

2.1. Study design and procedures

Data were collected from patients with mesothelioma, who were treated with nivolumab intravenously at a dose of 360 mg or 4.5 mg/kg every 3 weeks and ipilimumab at a dose of 1 mg/kg every 6 weeks as part of a named patient program (NPP). Data was collected prospectively in the Erasmus Medical Center (Rotterdam, the Netherlands) and the Antoni van Leeuwenhoek Hospital (Amsterdam, the Netherlands), who serve as referral centers for patients with mesothelioma in the Netherlands. These two hospitals accounted for 97 % of all patients treated with nivolumab plus ipilimumab in the Netherlands in the given time period.

A detailed description of eligibility criteria and procedures of the clinical study is provided in the **Data Supplements**. We cross-checked the number of patients in our study with the data from the Expanded Access Program by BMS. The data cut-off was January 15th, 2023 for all analyses, except for overall survival, for which the data cut-off was July 1st, 2023. All patients who received at least 1 cycle of nivolumab-ipilimumab were included in the toxicity and response analysis. Clinical parameters were obtained every visit. CT scans were evaluated using modified RECIST version 1.1 every 12 weeks [9]. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [10] and assessed continuously during the treatment and for patients who discontinued until 30 days after the last treatment. All procedures were conducted in accordance with the Declaration of Helsinki. According to national guidelines, no ethical committee approval was needed for the collection of the clinical data.

The primary objective was to investigate safety in terms of TRAE's. We report data on grade 2–5 TRAE's which were requiring steroid treatment, and/or were reason for discontinuing immunotherapy. Secondary objective was to describe the real-world activity of nivolumab

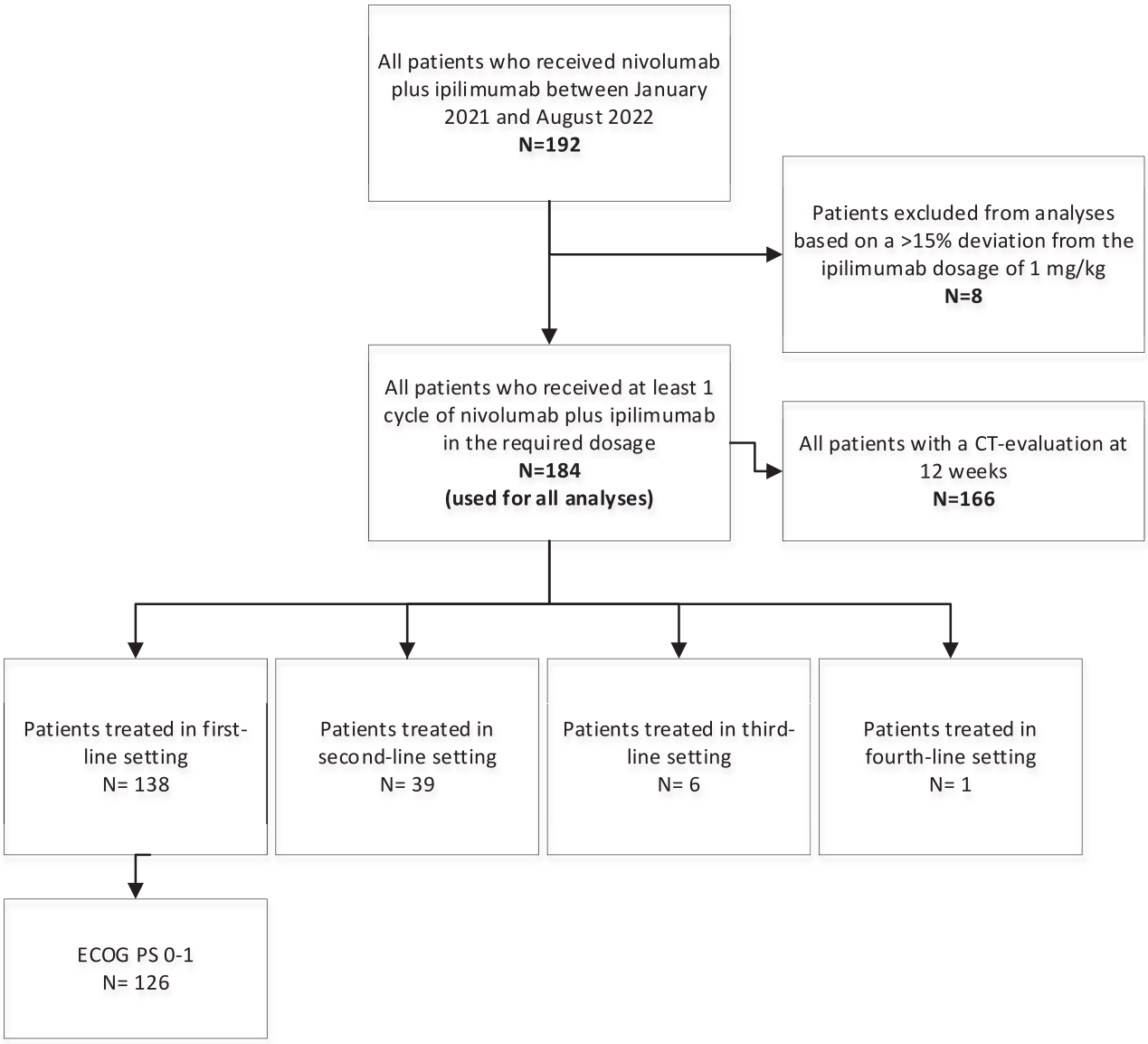

Fig. 1. Consort diagram.

plus ipilimumab. A detailed description of the outcome measurements is provided in the **Data Supplements**.

The statistical analysis is described in the **Data Supplements**.

3. Results

3.1. Patient characteristics

Between January 1st, 2021, and August 1st, 2022, 192 patients started treatment with nivolumab plus ipilimumab. Eight patients were excluded from analyses due to > 15 % deviation in the administered dosage of 1 mg/kg ipilimumab (Fig. 1).

184 Patients were included in our analyses of which 86.4 % were men. The median age at start of treatment was 71 years (IQR 66–76), with the highest percentage in the subcategory 65–75 years (49 %). 53 patients (29 %) had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 and 113 patients (61 %) had an ECOG PS of 1 at the start of treatment. 138 patients (74 %) of the patients had not received any previous line of treatment. (Table 1).

3.2. Clinical outcomes in the real-world setting

The median follow-up time of all patients was 12.1 months (n = 184; 95 % CI 11.1 – 13.1 months) with a minimum of 5.5 months follow-up. For OS an extra survival sweep was done with a median follow-up time of 17.1 months (95 % CI 16.4–18.5). The patients received a median number of 6 cycles of nivolumab (range: 1–29) and 3 cycles of ipilimumab (range: 1–14). Ninety patients (49 %) received ≥ 4 cycles.

TRAE's of grade 2–5 that required additional treatment were observed in 86 patients (46.7 %), including 48 patients (26.1 %) with grade 3 or 4 TRAE's (Table 2). The most common grade 3 or 4 TRAE's were hepatitis (7.0 %) and colitis (6.5 %). Three grade 5 TRAE's were found, one hepatitis, one myositis and one cardiomyositis. Infusion related reactions occurred in 45 of 184 patients (24.5 %). Multiple grade 2–5 toxicities occurred in the 86 patients. Of those, 79 patients received corticosteroids. Within this group, some patients received additional immunosuppressant agents; infliximab was administered in five patients, cellcept, tocilizumab, methotrexate and azathioprine were administrated in one patient. Other TRAE-treatment included thyroid suppletion or antidiabetica. Twenty-five percent of the patients discontinued nivolumab plus ipilimumab treatment earlier due to TRAE's (Table S1). This was 30 % of the patients who had discontinued treatment at time of data cut-off. Only one patient (0.5 %) discontinued ipilimumab earlier. The median time to develop toxicity in all patients with TRAE's was 9 weeks. The timing of any TRAE after initiation of treatment is shown in Fig. S1.

The objective response rate (ORR) was 21.7 % (40 out of 184 patients; 95 % CI 16.0–28.4), and 40 % had stable disease (SD) as the best result (Table 3), resulting in a disease control rate (DCR) at 12 weeks of 56.0 % (95 % CI 48.8–63.2). mPFS was 5.4 months (95 % CI 4.5–6.4) and mOS was 14.1 months (95 % CI 11.6–16.6) (Fig. 2). The 6-months PFS rate was 46 % (95 % CI: 38.8–53.6) and the 6-months OS rate was 76 % (95 % CI: 69.9–82.1). The duration of response was 5.7 months (IQR 3.2–8.7).

We also performed subgroup analyses on PFS (Fig. S2-S4) and OS (Fig. S5-7). PFS and OS seem to be correlated with ECOG PS; a worse ECOG PS results in impaired PFS and OS. We did not find a correlation between PFS and OS with age or histologic subtype.

In addition, we analyzed the group of patients who discontinued treatment due to TRAE's (n = 46). The mPFS of this group was 8.02 months (95 %CI 5.39 – NA), compared to 5.4 months (95 % CI 4.5–6.4) for the whole cohort of patients. For mOS, this was 16.1 months (95 % CI 9.7 – NA) compared to 14.1 months (95 % CI 11.1–18.2).

Table 1
Baseline characteristics.

	All patients (n = 184)
Age, median in years (IQR)	71 (66–76)
< 65	39 (21.2 %)
≥ 65 to < 75	91 (49.5 %)
≥ 75	54 (29.3 %)
Sex, n	
Male	159 (86.4 %)
Female	25 (13.6 %)
ECOG performance status, n	
0	53 (28.8 %)
1	113 (61.4 %)
2	8 (4.3 %)
3	2 (1.1 %)
Missing	8 (4.3 %)
Histology, n	
Epithelioid	103 (56.0 %)
Non-epithelioid	76 (41.3 %)
Sarcomatoid	48 (26.1 %)
Mixed	28 (15.2 %)
Epithelioid peritoneal	3 (1.6 %)
Mixed peritoneal	1 (0.5 %)
Missing	1 (0.5 %)
Line of treatment, n	
No pre-treatment	138 (75.0 %)
2nd line	39 (21.2 %)
3rd line	6 (3.3 %)
4rd line	1 (0.5 %)

Table 2
Number of patients experiencing most common TRAE's requiring immunosuppressant treatment.

	All patients (n = 184)			
	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Colitis	7 (3.8)	12 (6.5)	0	0
Pneumonitis	5 (2.7)	7 (3.8)	2 (1.1)	0
Hepatitis	4 (2.2)	11(6.0)	1 (0.5)	1(0.5)
Endocrinopathy	16 (8.7)	2 (1.1)	2 (1.1)	0
Dermatitis	4 (2.2)	4 (2.2)	0	0
Nephritis	2 (1.1)	0	1 (0.5)	0
Myocarditis	1 (0.5)	0	1 (0.5)	1 (0.5)
Musculoskeletal toxicity	21 (11.4)	4 (2.2)	0	1 (0.5)
Myasthenia	0	1 (0.5)	0	0
Other toxicities	3 (1.6)	7 (3.8)	1 (0.5)	0

Table 3
Objective response rate by mrecist per histological subtype of all patients who were evaluable for response.

Histology		Frequency (n)	Percentage (%)
All histologies	Complete response	1	0.5
	Partial response	39	21.2
	Stable disease	63	34.2
	Progressive disease*	81	44.0
	Total	184	100
Epithelioid	Complete response	0	0
	Partial response	20	20.6
	Stable disease	30	30.9
	Progressive disease	47	48.5
	Total	97	100
Non-epithelioid	Complete response	1	1.6
	Partial response	18	28.1
	Stable disease	30	46.9
	Progressive disease	15	23.4
	Total	64	100
Epithelioid peritoneal	Stable disease	3	100
Mixed peritoneal	Partial response	1	100
Subtype unknown	Stable disease	1	100

* 18 patients had clinical deterioration.

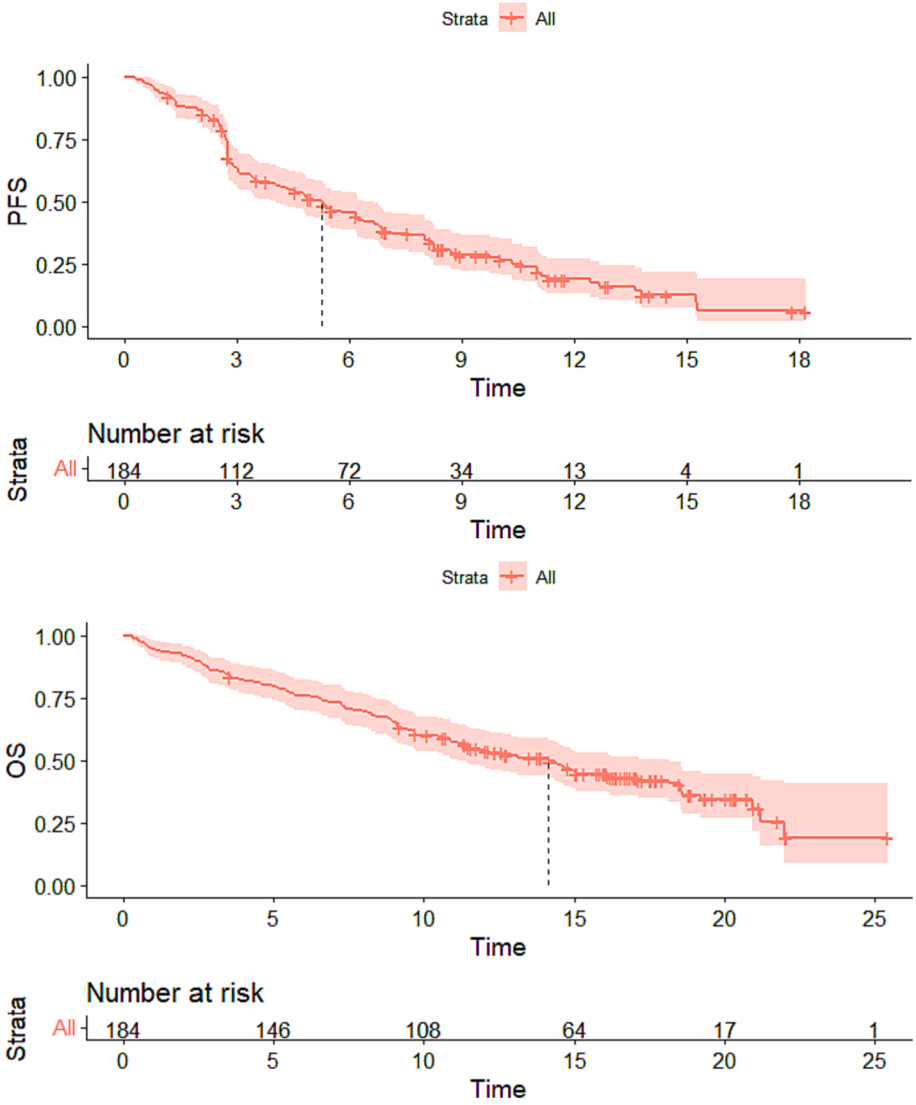

Fig. 2. Progression-free survival (pfs) and overall survival (OS) in months. A. PFS in months, dotted line shows median PFS (5.4 months (95 % CI 4.5–6.4)). B. OS in months, dotted line shows median OS (14.1 months (95 % CI 11.1–18.2)).

3.3. Additional analyses

As a consequence of the nature of real-world setting, the included patient population exhibited a meaningful heterogeneity. Subsequently, we performed several subgroup analyses.

3.4. Adverse events in patients treated with a different dosage

Eight patients had received a deviating dosage of treatment and therefore excluded from the analyses (Fig. 1). Two of them experienced a TRAE. One patient had hyperthyroidism, which occurred 9 weeks after initial treatment that required medication, while the other patient had grade 3 musculoskeletal toxicity, which occurred 19 weeks after the initial treatment and required corticosteroids. Both patients had received 100 mg ipilimumab with an average weight of 70 kg.

3.5. Corticosteroids

Seventy-nine patients needed corticosteroids due to adverse events, of whom 27 patients had stable disease and 27 patients had partial response. Twenty-five patients had progressive disease.

3.6. Performance status < 2 and first-line treatment (inclusion criteria of the CheckMate-743)

In our cohort, 5.4 % of the patients had an ECOG PS of ≥ 2 and 25 % of the patients were treated in second or further lines of treatment. In a subgroup analysis excluding these patients (Fig. 1; total included patients n = 126), we found a median PFS of 6.2 months (95 % CI 4.8 – 7.6), ORR of 26.3 % and DCR 62.7 % (53.6–71.1). Median OS was 14.9 months (11.6 – 18.3) (Fig. S8).

3.7. TRAE's and discontinuation of treatment related to age and ECOG PS

Since we were interested in safety, we performed several analyses to evaluate the frequency of TRAE's and the numbers of patients who discontinued treatment due to toxicity between age categories and ECOG PS (Table S2-S5). Relatively most toxicities occurred in the elder patient population. In addition, among the patients aged > 75 years, 29.6 % discontinued treatment due to TRAEs, compared to 24.2 % in patients aged 65–74 years and 20.5 % in patients aged < 65 years. Toxicity did not seem to be correlated to ECOG PS.

4. Discussion

To the best of our knowledge this is the first full paper reported real-world cohort study conducted to date to evaluate the safety and activity of nivolumab plus ipilimumab in patients with mesothelioma. In the Netherlands, two hospitals have been designated as center of expertise for patients with mesothelioma: Erasmus Medical Center (Rotterdam) and Antoni van Leeuwenhoek Hospital (Amsterdam). All patients who were treated in one of these hospitals in the given time period are reported, which accounted for 97 % of all patients treated with nivolumab plus ipilimumab in the Netherlands. This 97 % is based on the data from the number of applications to BMS for access to the drugs and is based on the fact that other hospitals in the Netherlands were in a preliminary stage of implementing the combination treatment nivolumab plus ipilimumab. As both centers already had experience with this combination treatment and were both amongst the highest including centers in the CheckMate-743 study both centers are well experienced in recognizing and treating TRAE's.

Regarding toxicity, the frequency of TRAE's in our real world population was comparable to the CheckMate-743 study [5] (26 % versus 30 %), and no new safety signals were reported (Table 2). We found a similar percentage of discontinuation of treatment due to TRAE's among the patients in our real-world cohort compared to the CheckMate-743 study (25 % versus 23 %).

In our real-world population, we found a numerically lower PFS of 5.4 months compared to 6.8 months in the CheckMate-743 trial (Table 4) and OS (14.1 months versus 18.1 months). This can be explained by the fact that the characteristics of the patients treated in our real-world cohort did not match well with those of the patients in the CheckMate-743 trial. The most relevant difference is the proportion of patients in our cohort with a higher ECOG PS (Table 4) as this factor is known to be negatively associated with outcome and shown in Fig. S5. We also observed a lower duration of response and objective response rate.

It is noteworthy to mention that the small differences we found in the median age of our population (71 years compared to 69 years observed in the clinical trial, the bigger proportion of men (86 % compared to 77 %) and the lower proportion of epithelioid histology (56 % compared to 76 %), seem to have only a small influence on the outcomes as in subgroup analyses no differences were observed between the groups (Fig. S3, S7).

A large difference with the CheckMate-743 was seen in baseline histologic subtype, where we included more patients with sarcomatoid subtype (Table 4). This is likely caused by a referral bias, as the benefit from nivolumab plus ipilimumab in the CheckMate-743 trial was more prominent in the non-epithelial subgroup. As a consequence that part of the epithelial subgroup will not be referred to one of the referral centers and be treated with chemotherapy. Chemotherapy could be administered at the local hospital, whilst nivolumab plus ipilimumab was only available at EMC and NKI. Hence, we believe the difference in histological subtype reflects the real-world situation at the time. At present doublet immunotherapy is available in more centers as registered treatment for all histological subtypes.

We included all different lines of treatment in all analyses. In an extensive prognostic model, developed by de Gooijer et al, the value of line of treatment seemed limited [16]. Thus, possibly this is not the most important baseline characteristic to take into account in the analyses. The fact that we even found patients treated in a different line or histology signifies the thoroughness of our search to include all mesothelioma patients treated with nivolumab plus ipilimumab.

Our study is subject to several limitations. Due to its clinical character, some information, such as low-grade adverse events, was not reported, because this might have been without therapeutic consequences. Moreover, our study included three patients with peritoneal mesothelioma, which was not an exclusion criterion in the named patient program. Whether the outcomes of ICI in peritoneal mesothelioma are comparable to that of pleural mesothelioma is unclear. The patient population in a real-world cohort differs from a trial cohort is commonly seen [11,12].

Due to a limited number of patients, adequate statistical testing to confirm correlations was not possible. To address this limitation, a larger database is required to increase the statistical power and ensure that any observed trends or associations are robust. Nevertheless, possible trends in descriptive statistics are informative as well. For example, the observation that a higher incidence of TRAE's may be present, despite being treated in highly experienced centers, warrants clinicians to be cautious when prescribing nivolumab and ipilimumab and to closely monitor patients for potential adverse events. Also, we advise centralization of this treatment to ensure that patients are treated by a dedicated and experienced team.

Furthermore, this study involved a heterogeneous population including patients with a fixed dosing scheme based on a pharmacological rationale [13]. In addition, nationwide new immunotherapy dose schemas are under development or are being tested [14,15]. To be sure that the results of the patients in our study were not dose dependent and to allow proper comparison with the CheckMate-743 trial, we calculated the dose deviation for each patient and excluded those who deviated more than 15 % from the standard dosage of ipilimumab.

Our real-world data of patients with mesothelioma treated with nivolumab plus ipilimumab confirmed activity at the expense of a substantial number of TRAE's. The median PFS of patients treated in our real-life program is comparable with the study population, but only when the same selection criteria are applied, omitting patients with poor

Table 4
Comparison between the patients treated with nivolumab and ipilimumab in the CheckMate-743 trial and our real-world setting.

	CheckMate-743	This study	This study exclusively 1st line + ECOG 0–1
Patient number	303	184	126
Median age, years (IQR)	69 (65–75)	71 (66–76)	72 (66–77)
Proportion men, n (%)	234 (77 %)	159 (86 %)	87 %
1st Treatment line, n (%)	303 (100 %)	138 (75 %)	100 %
Epithelial histology, n (%)	229 (76 %)	103 (56 %)	55 %
ECOG PS 0, n (%)	114 (38 %)	53 (29 %)	34 %
Median duration of treatment, months (IQR)	5.6 (2.0–11.4)	3.0 (1.0 – 6.0)	4.1 (2.1 – 6.2)
Median number nivolumab cycles, n (IQR)	12.0 (5.0–23.5)	6 (range 1–29)	7 (4–12)
Median number ipilimumab cycles, n (IQR)	4.0 (2.0–7.0)	3 (1–14)	4 (2–6)
DCR, % (95 %CI)	77 % (71.4–81.2)	56.0 % (48.8–63.2)	62.7 % (53.6–71.1)
ORR, % (95 % CI)	40 % (34.1–45.4)	21.7 % (16.0–28.4)	26.3 % (18.7–34.8)
Median duration of response, months	11 (95 %CI 8.1–11.5)	5.7 (IQR 3.2–8.7)	5.7 (IQR 3.3—8.5)
Median PFS, months (95 % CI)	6.8 (5.6–7.4)	5.4 (4.5–6.4)	6.2 (4.8–7.6)
Median OS, months (95 %CI)	18.1 (16.8–21.4)	14.1 (11.1–18.2)	15.01 (12.1–18.0)
Median follow-up time, months (IQR)	29.7 (26.7–32.9)	9.8 (5.9–13.2)	–
Patients with TRAE's grade 3–4, n (%)	91 (30 %)	48 (26 %)	32(25 %)
Patients with TRAE's grade 5, n (%)	3 (1.0 %)	3 (1.5 %)	3 (2.4 %)
TRAE's as reason of discontinuation nivo/ipi, n (%)	69 (23 %)	46 (25 %)	31 (25 %)
Early discontinuation ipilimumab, continuing monotherapy nivolumab	9 %	0.5 %	–

Abbreviations: DCR, disease control rate; ORR, overall response rate, PFS, progression-free survival; OS, overall survival; IQR, interquartile range.

prognostic characteristics. We recommend to prescribe nivolumab-ipilimumab with caution.

5. Role of the funding source

Nivolumab and ipilimumab were provided free of charge by BMS. The pulmonology department of the Erasmus MC received an unrestricted grant from BMS. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication. BMS was not involved in the study design, data collection, data analysis and interpretation of the data. BMS has read the manuscript and approved the final version for submission.

CRediT authorship contribution statement

D.W. Dumoulin: . **L.H. Douma:** Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing, Formal analysis, Methodology. **M.M. Hofman:** Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing, Methodology. **V. van der Noort:** . **R. Cornelissen:** Investigation, Writing – review & editing. **C.J. de Gooijer:** Investigation, Writing – review & editing. **J.A. Burgers:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **J.G.J.V. Aerts:** Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2023.107440.

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