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ORIGINAL ARTICLE

First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743

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Background: In the phase III CheckMate 743 study (NCT02899299), first-line nivolumab plus ipilimumab significantly improved overall survival (OS) versus chemotherapy in patients with unresectable malignant pleural mesothelioma (MPM). We report updated data with 3-year minimum follow-up.

Patients and methods: Adults with previously untreated, histologically confirmed, unresectable MPM and Eastern Cooperative Oncology Group performance status of $\leq$1 were randomized 1 : 1 to nivolumab (3 mg/kg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks) for up to 2 years, or six cycles of platinum plus pemetrexed chemotherapy. This report includes updated efficacy and safety outcomes, exploratory biomarker analyses including four-gene inflammatory expression signature score, and a post hoc efficacy analysis in patients who discontinued treatment due to treatment-related adverse events (TRAEs).

Results: With a median follow-up of 43.1 months, nivolumab plus ipilimumab continued to prolong OS versus chemotherapy. Median OS was 18.1 versus 14.1 months [hazard ratio (95% confidence interval), 0.73 (0.61—0.87)], and 3-year OS rates were 23% versus 15%, respectively. Three-year progression-free survival rates were 14% versus 1%, and objective response rates were 40% versus 44%. At 3 years, 28% versus 0% of responders had an ongoing response. Improved survival benefit with nivolumab plus ipilimumab versus chemotherapy was observed across subgroups, including histology. A high score of the four-gene inflammatory signature appeared to correlate with improved survival benefit with nivolumab plus ipilimumab. No new safety signals were observed with nivolumab plus ipilimumab, despite patients being off therapy for 1 year. In patients who discontinued nivolumab plus ipilimumab due to TRAEs, median OS was 25.4 months, and 34% of responders maintained their responses for $\geq$3 years after discontinuation.

Conclusions: With 3 years' minimum follow-up, nivolumab plus ipilimumab continued to provide long-term survival benefit over chemotherapy and a manageable safety profile, supporting the regimen as standard-of-care treatment for unresectable MPM, regardless of histology.

Key words: CTLA-4, dual immunotherapy, first-line, immune checkpoint inhibitors, overall survival, PD-L1

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INTRODUCTION

Immune checkpoint inhibition has transformed the first-line treatment landscape for various tumors. Nivolumab plus ipilimumab has demonstrated durable and long-term survival

in multiple cancers, including melanoma, renal cell carcinoma, and non-small-cell lung cancer (NSCLC).[1-5] Nivolumab, a fully human anti-programmed death-1 antibody, and ipilimumab, a fully human anti-cytotoxic T-lymphocyte antigen-4 antibody, are immune checkpoint inhibitors that have distinct but complementary mechanisms of action.[6-8] Nivolumab restores the antitumor function of T cells while ipilimumab induces *de novo* antitumor T-cell responses, including an increase in the number of memory T cells.[6,9]

CheckMate 743 (NCT02899299) is the first phase III study to demonstrate an overall survival (OS) benefit with nivolumab plus ipilimumab versus chemotherapy as a first-line treatment of patients with unresectable malignant pleural mesothelioma (MPM). The study met its primary endpoint at a prespecified interim analysis (minimum follow-up 22.1 months) with statistically improved OS [median 18.1 months with nivolumab plus ipilimumab versus 14.1 months with chemotherapy; hazard ratio (HR) (96.6% confidence interval, CI), 0.74 (0.60-0.91)]; 2-year OS rates were 41% versus 27%.[10] Clinical benefit with nivolumab plus ipilimumab was also observed across subgroups, regardless of histology or programmed death-ligand 1 (PD-L1) expression. Based on these findings, nivolumab plus ipilimumab was approved for first-line treatment of unresectable MPM in the United States, European Union, and other countries.[11-15] Additionally, nivolumab plus ipilimumab is now a preferred therapy option for first-line or subsequent (if not administered in first line) systemic treatment of unresectable MPM in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®).[16,†]

To date, long-term clinical efficacy and safety outcomes with immunotherapy in MPM have not been reported. Here, we report updated efficacy and safety data from CheckMate 743, with a 3-year minimum follow-up to demonstrate the benefit of dual immunotherapy, and a *post hoc* analysis of efficacy outcomes in patients who discontinued treatment due to treatment-related adverse events (TRAEs). We also report the results of prespecified exploratory analyses of the effects of biomarkers, including a four-gene inflammatory expression signature score and tumor mutational burden (TMB), on efficacy outcomes.

PATIENTS AND METHODS

Patients

Eligibility criteria, baseline demographics, and disease characteristics for patients enrolled in CheckMate 743 have been described previously.[10] Eligible adult patients had histologically confirmed unresectable MPM that was not amenable to curative therapy, had not received prior systemic therapy, and had Eastern Cooperative Oncology Group performance status ≤ 1.

Trial design and treatment

CheckMate 743 is an open-label, randomized, phase III trial evaluating first-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable MPM (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.01.074). Histology (epithelioid versus non-epithelioid) and sex were stratification factors. Patients were randomized 1 : 1 to receive nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, or cisplatin (75 mg/m^2) or carboplatin (area under the concentration—time curve 5 mg/ml/min) plus pemetrexed (500 mg/m^2) every 3 weeks for up to six cycles. Treatment continued until disease progression, unacceptable toxicity, or for up to 2 years in the nivolumab plus ipilimumab arm. Immunotherapy was permitted to continue beyond disease progression if prespecified criteria were met.[10]

This trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. The study protocol and amendments were approved by an institutional review board or independent ethics committee at each site. All patients provided written informed consent. The Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

Endpoints and assessments

The primary endpoint of OS, secondary endpoints of progression-free survival (PFS), objective response rate (ORR), a duration of response (DOR), and disease control rate (DCR), and exploratory endpoints of safety and tolerability from the prespecified interim analysis have been reported previously.[10] Here, we report OS, PFS, ORR, and DOR with a 3-year minimum follow-up, in addition to exploratory safety and biomarker analyses.

Immune-mediated adverse events (IMAEs) were analyzed to further characterize adverse events (AEs) of special clinical interest. IMAEs include AEs occurring within 100 days of the last dose of nivolumab or ipilimumab, regardless of causality, treated with immune-modulating medication, and with no clear alternate etiology based on investigator assessment or with an immune-mediated etiological component. Endocrine AEs were included in the analysis regardless of treatment since these events are often managed without immunosuppression. Time to onset and time to resolution of IMAEs and use of corticosteroids and immune-modulating medication to manage these events in the nivolumab plus ipilimumab arm were assessed.

A *post hoc* analysis was conducted to determine efficacy in patients in the nivolumab plus ipilimumab arm who discontinued all components of study treatment due to TRAEs (reported between the first dose and 30 days after the last dose of study treatment). OS from randomization, ORR, and DOR were evaluated.

Biomarkers. Exploratory analyses were conducted on baseline tumor samples to evaluate candidate biomarkers, including a

† To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

four-gene inflammatory expression signature, TMB, and lung immune prognostic index (LIPI), that may be associated with efficacy. As previously reported, the four-gene inflammatory signature score measured expression of *CD8A*, *STAT1*, *LAG3*, and *CD274* (*PD-L1*).[17-19] Analysis of the four-gene inflammatory signature was carried out via RNA sequencing of baseline formalin-fixed, paraffin-embedded tumor samples, and z-scores were calculated using log-transformed counts per million. High or low scores were ranked relative to the median z-score value across the dataset. For the TMB analysis, tumor tissue TMB [defined as the total number of somatic missense mutations excluding variants in the Genome Aggregation Database (gnomAD)] was evaluated using whole-exome sequencing of matched tumor and normal blood samples. TMB tertiles were designated as low [<32 total mutations (<1.60 mut/Mb)], intermediate [32-41 total mutations (1.60-2.05 mut/Mb)], or high [≥41 total mutations (≥2.05 mut/Mb)]. LIPI scores were assessed by lactate dehydrogenase (LDH) levels and derived neutrophil-to-lymphocyte ratio [dNLR; neutrophils/(white blood cells − neutrophils)] from peripheral blood samples and were characterized as poor [dNLR ≥3 and LDH ≥ upper limit of normal (ULN)], intermediate (dNLR <3 or LDH < ULN), or good (dNLR <3 and LDH < ULN).

Statistical analyses

All patients randomly assigned to treatment were included in demographic and efficacy analyses. Analyses for OS and PFS were stratified by sex and histology. HRs and 95% CIs were estimated using a stratified Cox proportional hazards model with treatment group as a single covariate. Survival curves and rates were estimated using the Kaplan—Meier method. Corresponding 95% CIs were derived based on the Greenwood formula for variance derivation and on log—log transformation applied on the survivor function. Exact two-sided 95% CIs were calculated for ORR and disease control rate using the Clopper—Pearson method. Prespecified descriptive subgroup analyses for OS, summarized using HRs (with 95% CIs), were calculated using an unstratified Cox proportional hazards model. Safety analyses included all patients who received at least one dose of the study drug. All statistical analyses were conducted using SAS software (version 9.2; SAS Institute Inc., Cary, NC).

RESULTS

Patients and treatment

As previously reported, 605 patients were randomized to nivolumab plus ipilimumab ($n = 303$) or chemotherapy ($n = 302$).[10] Among all randomized patients, 300 in the nivolumab plus ipilimumab arm and 284 in the chemotherapy arm received at least one dose of study treatment (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2022.01.074). Baseline characteristics were generally well balanced across arms (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.01.074). As of the 7 May 2021 database lock, the minimum and median follow-ups for OS were 35.5 and 43.1 months, respectively. All patients had completed or discontinued therapy in both treatment arms and had been off therapy for ≥1 year; median duration of treatment was 5.6 months with nivolumab plus ipilimumab and 3.5 months with chemotherapy (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.01.074). Subsequent systemic therapy was received by 136 patients (44.9%) in the nivolumab plus ipilimumab arm and 128 patients (42.4%) in the chemotherapy arm; subsequent immunotherapy was received by 12 patients (4.0%) and 65 patients (21.5%), respectively; and subsequent chemotherapy was received by 131 patients (43%) and 99 patients (33%), respectively (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.01.074).

Efficacy

OS. With a 3-year minimum follow-up, nivolumab plus ipilimumab continued to show OS benefit versus chemotherapy in all randomized patients (Figure 1A). Median (95% CI) OS was 18.1 months (16.8-21.0 months) with nivolumab plus ipilimumab versus 14.1 months (12.4-16.3 months) with chemotherapy [HR (95% CI), 0.73 (0.61-0.87)]; 3-year OS rates (95% CI) were 23.2% (18.4% to 28.2%) versus 15.4% (11.5% to 19.9%). OS benefits were also seen across most patient subgroups (Figure 2). Consistent with results from the primary database lock, OS was improved with nivolumab plus ipilimumab versus chemotherapy in both epithelioid [HR (95% CI), 0.85 (0.69-1.04)] and non-epithelioid [HR (95% CI), 0.48 (0.34-0.69)] histology subgroups (Figure 1B and C). Although the benefit appeared to be greater in the non-epithelioid histology subgroup, median OS was similar with nivolumab plus ipilimumab in the epithelioid [18.2 months (95% CI, 16.9-21.9 months)] and non-epithelioid [18.1 months (95% CI, 12.2-22.8 months)] histology subgroups; 3-year OS rates were 24% and 22%, respectively. In contrast, median (95% CI) OS and 3-year OS rates differed with chemotherapy across histology subgroups; these were 16.7 months (14.9-20.3 months) and 19% in the epithelioid histology subgroup, and 8.8 months (7.4-10.2 months) and 4% in the non-epithelioid histology subgroup (Figure 1B and C). As reported previously,[10] the magnitude of OS benefit with nivolumab plus ipilimumab versus chemotherapy was greater in patients with tumor PD-L1 expression ≥1% [HR (95% CI), 0.71 (0.57-0.88); Supplementary Figure S3A, available at https://doi.org/10.1016/j.annonc.2022.01.074] compared with those with tumor PD-L1 expression <1% [HR (95% CI), 0.99 (0.69-1.43)] (Supplementary Figure S3B, available at https://doi.org/10.1016/j.annonc.2022.01.074). Importantly, median OS with nivolumab plus ipilimumab was similar in patients with tumor PD-L1 expression ≥1% [18.0 months (95% CI, 16.8-21.4 months)] and PD-L1 <1% [17.3 months (95% CI, 10.1-23.9 months)], while in the chemo arm, OS was lower in patients with tumor PD-L1 expression ≥1% [13.3 months (95% CI, 11.6-15.4 months)] than in patients with tumor PD-L1 <1% [16.6 months (95% CI, 13.4-20.8 months)]. Notably, PD-L1 was not a stratification factor in this study.

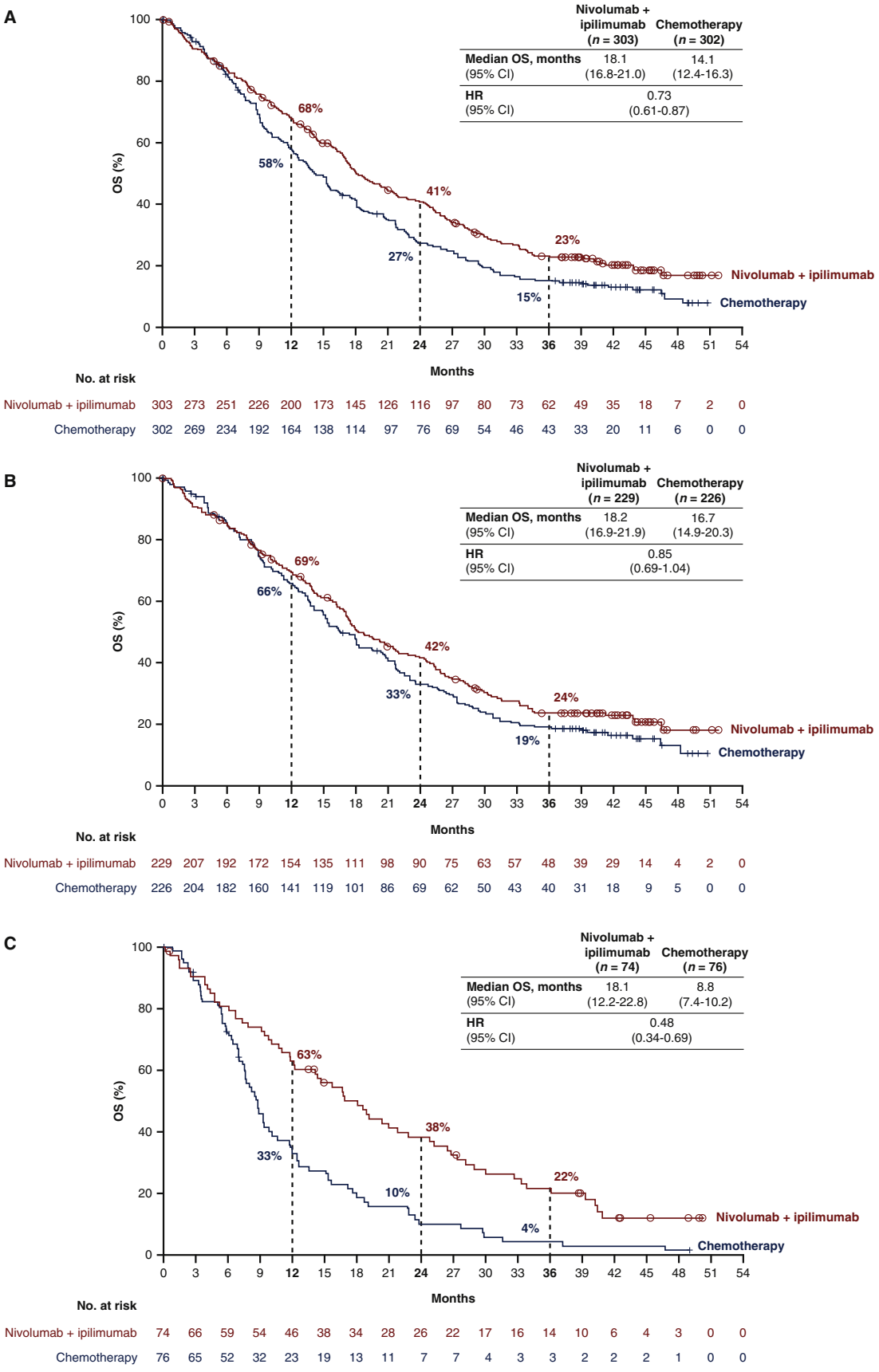

Figure 1. OS in (A) all randomized patients, (B) patients with epithelioid histology, and (C) patients with non-epithelioid histology.
CI, confidence interval; HR, hazard ratio; OS, overall survival.

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Subgroup	Median OS, months (95% CI) Nivolumab + ipilimumab (*n* = 303)	Chemotherapy (*n* = 302)	Unstratified HR (95% CI)
All randomized (*N* = 605)	18.1 (16.8-21.0)	14.1 (12.4-16.3)	0.75[a] (0.63-0.90)
Age, years			
<65 (*n* = 167)	17.2 (13.1-28.0)	13.3 (10.6-18.3)	0.78 (0.55-1.11)
≥65 to <75 (*n* = 281)	20.3 (17.3-24.9)	14.5 (11.6-17.4)	0.67 (0.52-0.87)
≥75 (*n* = 157)	16.9 (11.0-21.8)	15.5 (11.7-19.1)	0.91 (0.64-1.29)
Male (*n* = 467)	**17.5 (16.2-20.7)**	**13.7 (11.7-15.5)**	**0.73 (0.60-0.90)**
Female (*n* = 138)	**21.1 (15.7-25.9)**	**18.0 (12.6-23.8)**	**0.82 (0.56-1.20)**
ECOG PS 0 (*n* = 242)	20.7 (17.5-25.9)	19.5 (15.2-22.8)	0.90 (0.67-1.19)
ECOG PS ≥1[b] (*n* = 363)	17.0 (14.1-20.3)	11.6 (9.0-13.9)	0.66 (0.52-0.83)
Never smoker (*n* = 249)	17.9 (14.1-25.2)	14.1 (11.8-17.6)	0.74 (0.56-0.97)
Former smoker[c] (*n* = 318)	17.6 (15.5-20.3)	14.9 (11.6-17.9)	0.79 (0.62-1.01)
Epithelioid (*n* = 455)	**18.2 (16.9-21.9)**	**16.7 (14.9-20.3)**	**0.85 (0.69-1.04)**
Non-epithelioid[d,e] (*n* = 150)	**18.1 (12.2-22.8)**	**8.8 (7.4-10.2)**	**0.48 (0.34-0.69)**
PD-L1 <1% (*n* = 135)	17.3 (10.1-23.9)	16.6 (13.4-20.8)	0.99 (0.69-1.43)
PD-L1 ≥1%[f] (*n* = 451)	18.0 (16.8-21.4)	13.3 (11.6-15.4)	0.71 (0.57-0.88)

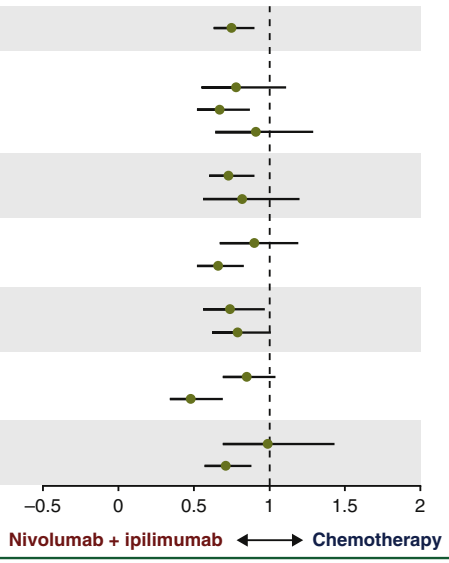

Figure 2. OS in patient subgroups.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.
Current smoker: An adult who has smoked 100 cigarettes in their lifetime and who currently smokes cigarettes regularly.
Former smoker: An adult who has smoked at least 100 cigarettes in their lifetime but who had quit smoking.
Never smoker: An adult who has never smoked, or who has smoked less than 100 cigarettes in their lifetime.
[a]Stratified HR 0.73.
[b]One patient in the chemotherapy group had a baseline ECOG PS score of 2 (protocol deviation).
[c]Twenty-six patients were current smokers; smoking status of 12 patients was unknown.
[d]Includes sarcomatoid, mixed, and other.
[e]One patient was changed from epithelioid to non-epithelioid after the primary analysis.
[f]PD-L1 expression level was not reported for 19 patients.

PFS, ORR, and DOR. Median (95% CI) PFS was 6.8 months (5.6-7.4 months) with nivolumab plus ipilimumab versus 7.2 months (6.9-8.0 months) with chemotherapy [HR (95% CI), 0.92 (0.76-1.11)]; estimated PFS rates at 3 years were 14% versus 1% (Figure 3A). ORRs were 40% in the nivolumab plus ipilimumab arm versus 44% in the chemotherapy arm (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.01.074). Notably, an additional three patients treated with nivolumab plus ipilimumab had a complete response since the last database lock for a total of eight patients with a complete response. Median (95% CI) DOR was 11.6 months (8.2-16.8 months) in the nivolumab plus ipilimumab arm versus 6.7 months (5.6-7.1 months) in the chemotherapy arm. Among responders, the 3-year DOR rate was 28% versus 0%, respectively (Figure 3B).

OS by exploratory biomarkers. Of the 605 patients in the all-randomized population, 327 (54%) samples were RNA-evaluable; 165 were in the nivolumab plus ipilimumab arm and 162 were in the chemotherapy arm. Baseline characteristics (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.01.074) and survival in the RNA-evaluable population for nivolumab plus ipilimumab versus chemotherapy [median (95% CI) OS, 17.9 (15.8-21.0) versus 13.0 (10.9-15.4) months; Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2022.01.074] were comparable to the all-randomized population. In the exploratory biomarker analyses, a high four-gene inflammatory signature score appeared to correlate with an improved survival benefit with nivolumab plus ipilimumab. Median (95% CI) OS was 21.8 months (16.9-33.2 months) in patients with a high four-gene inflammatory signature score versus 16.8 months (12.0-18.6 months) in patients with a low score [HR (95% CI), 0.57 (0.40-0.82)] in the nivolumab plus ipilimumab arm; 3-year OS rates were 35% versus 15%, respectively (Figure 4A). No such predictive impact was seen in the chemotherapy arm; median (95% CI) OS was 11.6 months (9.5-15.2 months) versus 15.2 months (11.1-20.8 months) in patients with a high and a low four-gene inflammatory signature score, respectively [HR (95% CI), 1.14 (0.82-1.59)] (Figure 4B).

In all randomized patients, TMB was evaluable in 160 (53%) patients in the nivolumab plus ipilimumab arm and 135 (45%) patients in the chemotherapy arm; median TMB was low [35 total mutations (1.75 mut/Mb)]. Baseline characteristics of the patients were similar in the DNA-assessable and all-randomized populations (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.01.074), as was OS [median (95% CI) OS, 17.8 months (15.8-20.7 months) for nivolumab plus ipilimumab versus 12.9 months (10.2-15.6 months) with chemotherapy; Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2022.01.074]. TMB did not correlate with OS benefit regardless of TMB tertile.

LIPI was evaluable in 296 (98%) patients in the nivolumab plus ipilimumab arm and 277 (92%) patients in the

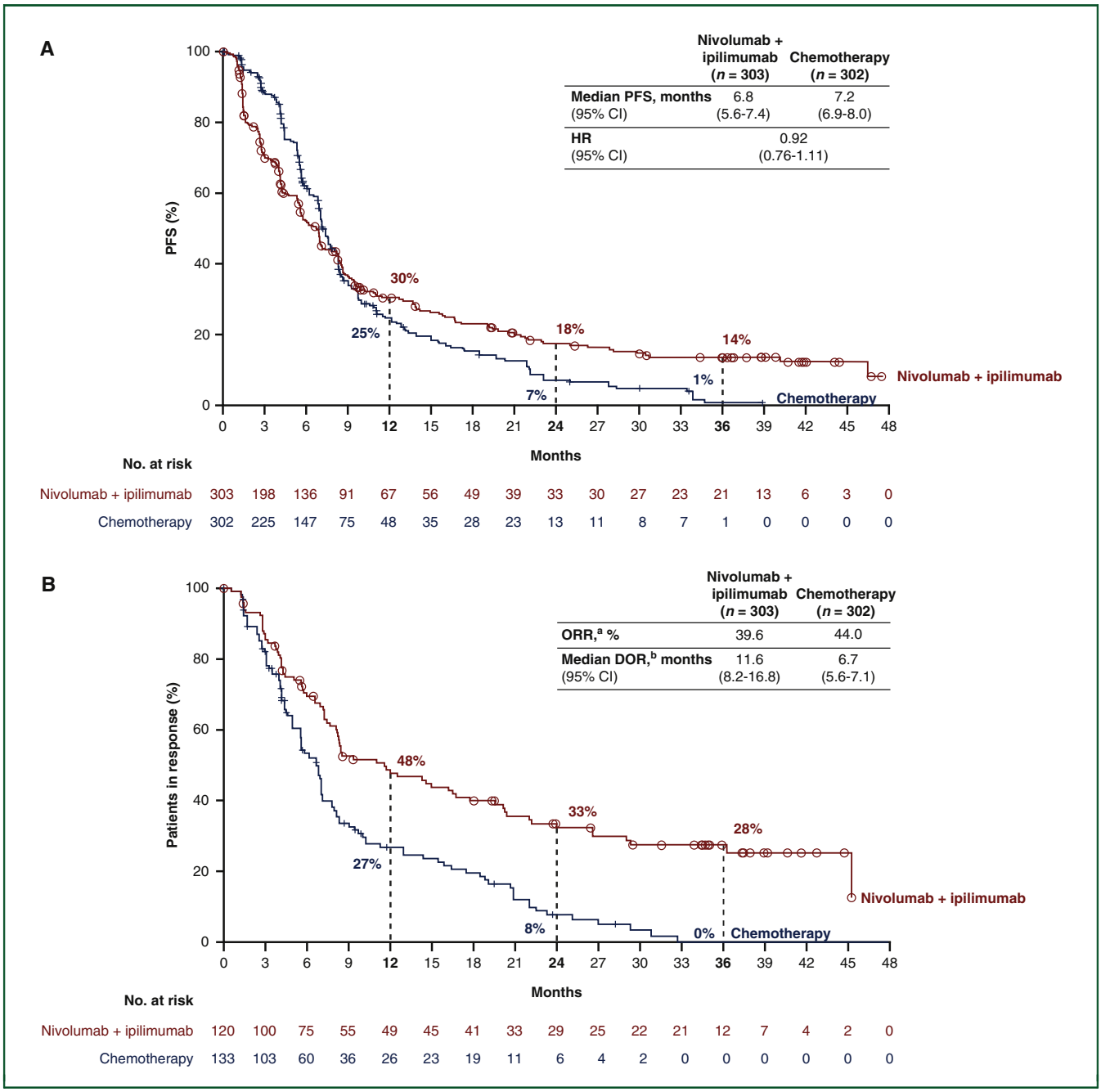

Figure 3. (A) PFS and (B) ORR and DOR in all randomized patients. Response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1, by blinded independent central review.

CI, confidence interval; DOR, duration of response; HR, hazard ratio; ORR, overall response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

[a]Eight patients (seven with epithelioid histology and one with non-epithelioid histology) treated with nivolumab plus ipilimumab and zero patients treated with chemotherapy had a complete response.

[b]DOR was calculated in patients with a response (nivolumab plus ipilimumab: $n = 120$, chemotherapy: $n = 133$).

chemotherapy arm. LIPI score was prognostic for OS; however, this score did not have a predictive signal with OS favoring nivolumab plus ipilimumab versus chemotherapy across all LIPI scores (Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2022.01.074).

Safety. Incidences of any-grade and grade 3 or 4 TRAEs, TRAEs leading to discontinuation, and serious TRAEs were largely unchanged since the primary database lock (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.01.074). Any-grade TRAEs occurred in 80% of patients treated with nivolumab plus ipilimumab and 82% of patients treated with chemotherapy; grade 3 or 4 TRAEs occurred in 31% and 32% of patients, respectively. The most common any-grade TRAEs were diarrhea (21%), pruritus (16%), and rash (14%) in the nivolumab plus ipilimumab arm, and nausea (37%), anemia (36%), and neutropenia (25%) in the chemotherapy arm. TRAEs leading to discontinuation of any component of the regimen occurred in 23% of patients treated with nivolumab plus ipilimumab

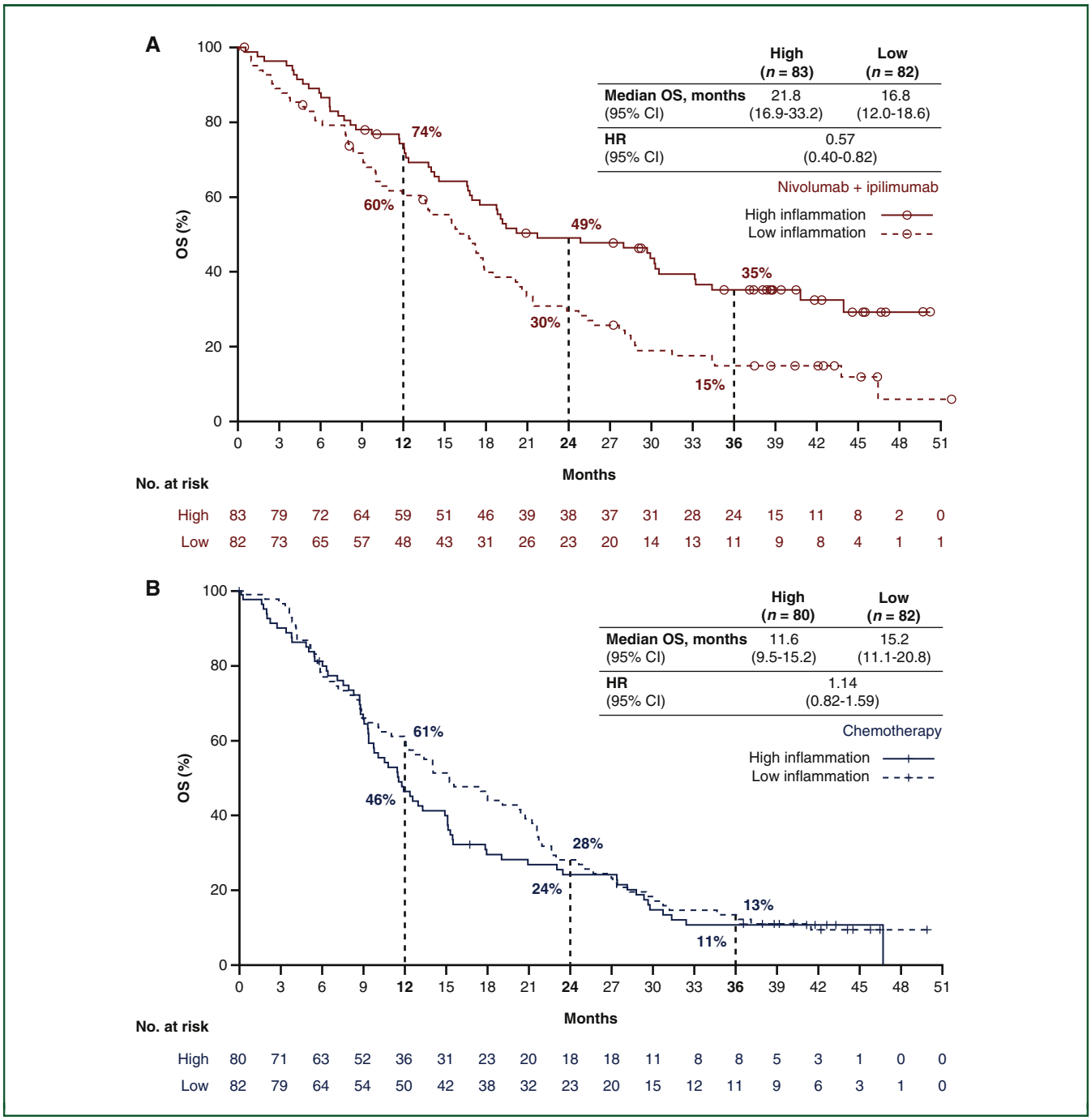

Figure 4. OS by four-gene inflammatory signature score in patients treated with (A) nivolumab plus ipilimumab and (B) chemotherapy.
CI, confidence interval; HR, hazard ratio; OS, overall survival.

and 16% of patients treated with chemotherapy; TRAEs leading to discontinuation of all components of the regimen occurred in 17% and 8% of patients, respectively. The most common any-grade TRAEs leading to discontinuation were colitis and diarrhea (both 2%) in the nivolumab plus ipilimumab arm and anemia (4%) in the chemotherapy arm. Any-grade serious TRAEs occurred in 21% of patients in the nivolumab plus ipilimumab arm and 8% in the chemotherapy arm. No additional treatment-related deaths occurred in either treatment arm since the primary database lock.

In patients treated with nivolumab plus ipilimumab, the most common any-grade IMAEs were rash (13%), hypothyroidism/thyroiditis (12%), and diarrhea/colitis (9%), and the most common grade 3 or 4 IMAEs were hepatitis (5%), diarrhea/colitis (4%), and rash (3%) (Table 1). Median time to onset and time to resolution for any-grade and grade 3 or 4 IMAEs are presented in Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2022.01.074. Hypersensitivity had the shortest time to onset (2.1 weeks); no other IMAEs occurred within the first month of treatment. Most non-endocrine IMAEs resolved during the study period;

Table 1. Summary of immune-mediated adverse events by category in patients treated with nivolumab plus ipilimumab

	Nivolumab plus ipilimumab (n = 300)	
Category Preferred term (occurring in ≥1% patients)	Any grade *n* (%)	Grade 3 or 4 *n* (%)
Endocrine		
Hypothyroidism/thyroiditis	36 (12.0)	0
Hypothyroidism	34 (11.3)	0
Hypophysitis	12 (4.0)	3 (1.0)
Hypophysitis	6 (2.0)	0
Hypopituitarism	6 (2.0)	3 (1.0)
Hyperthyroidism	11 (3.7)	0
Hyperthyroidism	11 (3.7)	0
Adrenal insufficiency	7 (2.3)	2 (0.7)
Adrenal insufficiency	7 (2.3)	2 (0.7)
Non-endocrine		
Rash	40 (13.3)	8 (2.7)
Rash	21 (7.0)	4 (1.3)
Rash maculopapular	10 (3.3)	1 (0.3)
Rash pruritic	3 (1.0)	0
Diarrhea/colitis	26 (8.7)	12 (4.0)
Diarrhea	18 (6.0)	6 (2.0)
Colitis	10 (3.3)	7 (2.3)
Pneumonitis	20 (6.7)	6 (2.0)
Pneumonitis	13 (4.3)	4 (1.3)
Interstitial lung disease	6 (2.0)	2 (0.7)
Hepatitis	18 (6.0)	14 (4.7)
Alanine aminotransferase increased	6 (2.0)	5 (1.7)
Aspartate aminotransferase increased	6 (2.0)	3 (1.0)
Immune-mediated hepatitis	6 (2.0)	3 (1.0)
Hepatitis	3 (1.0)	3 (1.0)
Nephritis/renal dysfunction	9 (3.0)	5 (1.7)
Acute kidney injury	6 (2.0)	5 (1.7)
Blood creatine increased	4 (1.3)	0
Hypersensitivity	5 (1.7)	1 (0.3)

median times to resolution ranged from 0.1 to 17.1 weeks, with hypersensitivity having the shortest time to resolution. Systemic corticosteroids (≥40 mg) were used for management of IMAEs in most patients with non-endocrine events; median duration of treatment ranged from 0.1 to 4.4 weeks; few endocrine IMAEs (14.8%) required treatment with systemic corticosteroids (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2022.01.074). Dose delays and treatment discontinuations due to individual IMAEs occurred in <5% of patients (Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2022.01.074).

Outcomes in patients who discontinued nivolumab plus ipilimumab due to TRAEs. A *post hoc* analysis of patients who discontinued all components of nivolumab plus ipilimumab due to TRAEs was conducted (n = 52). Baseline characteristics were similar between patients who discontinued due to TRAEs and the all-randomized population (Supplementary Table S9, available at https://doi.org/10.1016/j.annonc.2022.01.074). These patients received a median (range) of 9 doses (1-47) of nivolumab and 3 doses (1-16) of ipilimumab; median (range) treatment duration was 4.3 months (0.0-22.5 months). Median (95% CI) OS was 25.4 (17.9-40.2) months from randomization, and the 3-year OS rate was 37% (Figure 5). Among these patients, 35 (67%) had an objective response (Supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2022.01.074), and responders had a median DOR after treatment discontinuation of 20 months with 34% (95% CI, 14% to 56%) of responders having an ongoing response at ≥3 years.

DISCUSSION

To our knowledge, these results from CheckMate 743 with a follow-up of at least 3 years represent the first long-term survival data in a phase III study evaluating first-line immunotherapy in patients with unresectable MPM. Nivolumab plus ipilimumab continued to provide durable and long-term survival benefit versus chemotherapy despite patients being off therapy for ≥1 year. Overall, 23% of patients treated with nivolumab plus ipilimumab were alive at 3 years, and 14% remained progression-free. The response benefit was durable in the nivolumab plus ipilimumab arm; 28% of responders remained in response at 3 years compared with none in the chemotherapy arm. Furthermore, nivolumab plus ipilimumab continued to provide clinical benefit versus chemotherapy across the patient subgroups assessed.[10] Consistent with previous reports, benefit with nivolumab plus ipilimumab was seen in both epithelioid and non-epithelioid subgroups. No new safety signals were identified.

Benefit—risk profile is a key consideration for clinicians when selecting treatment options for patients with MPM. Of particular importance are AEs and discontinuation of treatment due to TRAEs. With 3 years' follow-up in CheckMate 743, the safety profile of nivolumab plus ipilimumab was consistent with the previous report, with no change in the overall rate of TRAEs[10] and no long-term toxicities. IMAEs were mostly grade 1 or 2 and tended to resolve with systemic corticosteroid treatment. Overall, 17% of patients discontinued all components of the nivolumab plus ipilimumab regimen due to any-grade TRAEs. A *post hoc* analysis in this patient population showed that the long-term survival benefit was not negatively impacted compared with all randomized patients (3-year OS rates, 37% and 23%, respectively). Furthermore, responses were durable with over one-third of responders remaining in response for ≥3 years after treatment discontinuation. These findings are consistent with reports from similar analyses conducted with nivolumab plus ipilimumab, with or without chemotherapy, in several advanced-stage cancers including NSCLC.[1-3,20,21] The durable clinical benefit thus observed with nivolumab plus ipilimumab for MPM is likely to be reflective of the biological effect of ipilimumab on the immune system via induction of memory T cells.[6,9]

Biomarkers that can reliably predict efficacy benefits are of high clinical relevance. PD-L1 expression is a well-established biomarker for predicting response to immunotherapy in NSCLC, melanoma, and other advanced solid tumors.[22-28] However, the role of PD-L1 as a biomarker in predicting treatment outcomes with immunotherapy in MPM is not established, and findings from various studies have been inconsistent.[29-33] As reported previously in CheckMate 743, OS outcomes with nivolumab plus

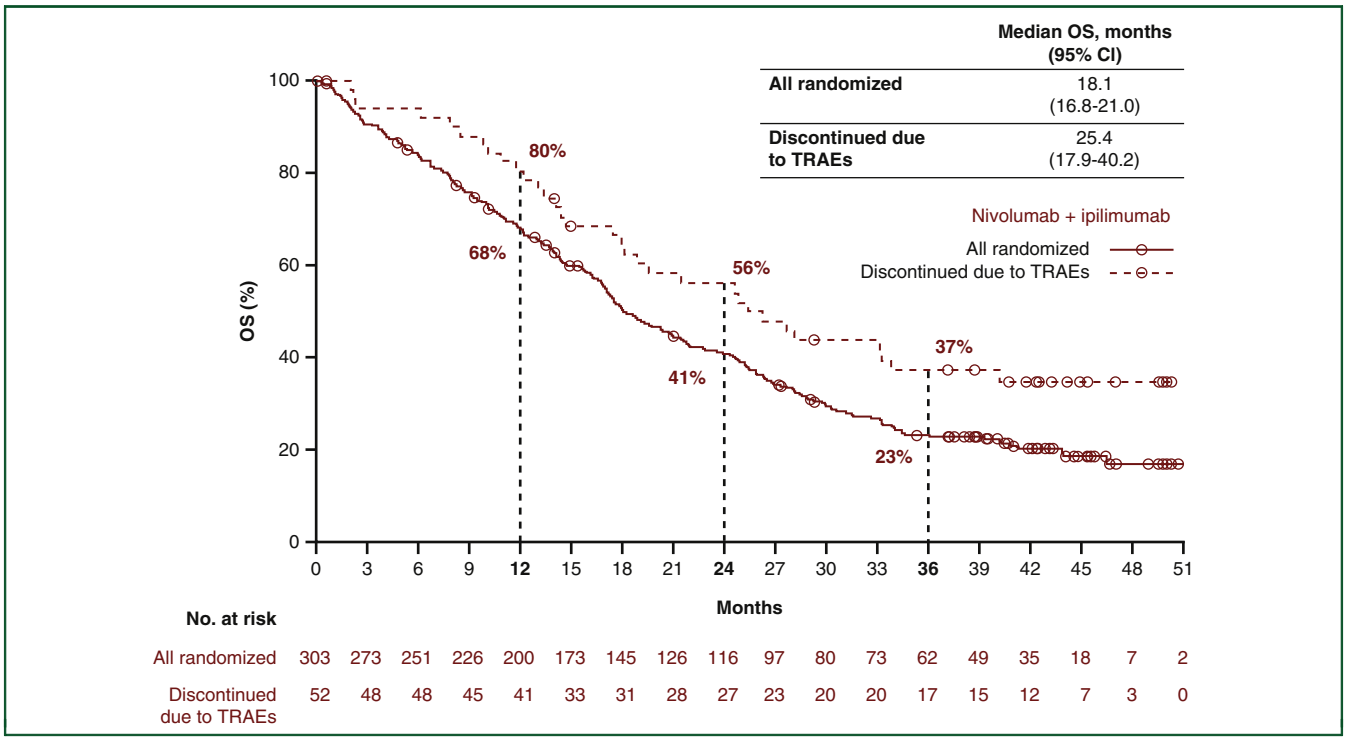

Figure 5. OS in patients who discontinued all components of the study regimen due to TRAEs.
CI, confidence interval; OS, overall survival; TRAE, treatment-related adverse event.

ipilimumab were similar in patients with tumor PD-L1 expression ≥1% and <1%, confirming the absence of a signal for predictive ability of PD-L1 for immunotherapy in MPM. However, with chemotherapy, survival was longer in patients with tumor PD-L1 expression <1% compared with those with PD-L1 ≥1%. These findings are similar to published reports of the negative prognostic value of PD-L1 expression in MPM and suggest that absence of PD-L1 expression might impact the clinical benefit of chemotherapy.[34] It should be noted that PD-L1 expression was not a stratification factor in CheckMate 743, and these results should be interpreted with caution due to potential imbalances in patient groups.

More recently, the four-gene inflammatory signature, which assesses the impact of inflammation in the tumor microenvironment on clinical outcomes, has emerged as a biomarker of interest. An exploratory efficacy analysis of various inflammatory signatures (4-gene inflammatory signature score, CD8 T-cell signature, and Gajewski 13-gene inflammatory signature) conducted in patients with gastric/gastroesophageal junction cancer (GC/GEJC) treated with immunotherapy validated the association of the four-gene inflammatory signature score with response.[35] Furthermore, clinical studies in GC/GEJC and other advanced cancers have shown improved survival with nivolumab plus ipilimumab in patients with a high versus low four-gene inflammatory signature score.[17-19] In CheckMate 743, the data suggest that a high four-gene inflammatory signature score may correlate with improved survival benefit with nivolumab plus ipilimumab in MPM; median OS with nivolumab plus ipilimumab was 5 months longer in patients with a high four-gene inflammatory signature score compared with those with a low score. In contrast, no such correlation was observed with chemotherapy. While TMB is of high clinical interest in predicting treatment outcomes with immunotherapy in solid tumors, its precise definition and relevance are not yet fully determined.[4,36] Overall, patients with MPM tend to have low TMB with only ∼1.2% reaching the most standard cut-off used in other tumor indications to predict response (10 mut/Mb).[4,37,38] Consistent with previously published reports, no definitive correlation between TMB and survival benefit with immunotherapy was seen in CheckMate 743.[23,32,36,39-42] Clinical characteristics such as LIPI score have been shown as prognostic for survival in patients with various cancers, including NSCLC.[43,44] In CheckMate 743, LIPI score also appeared to be prognostic, with prolonged survival observed in patients with a good LIPI score compared with those with an intermediate or poor LIPI score across both treatment arms. Additionally, while not predictive, there was a trend for improved OS with nivolumab plus ipilimumab versus chemotherapy across all LIPI scores, although the poor LIPI score subgroup had a smaller number of patients.

It is noteworthy that although only ∼50% of patients from CheckMate 743 had tumors that were mutation evaluable, results of these exploratory analyses of genomic biomarkers represent the largest comprehensive biomarker dataset from a randomized phase III study in first-line unresectable MPM. However, being exploratory in nature, these analyses are limited by potential imbalances in the patient populations and are not statistically powered to detect the treatment effect. Additionally, the

four-gene inflammatory signature score is still evolving and its applicability in clinical practice is not fully established.[19,45] Further prospective studies are needed to elucidate the inflammatory gene signature that can predict efficacy benefits with immunotherapy in first-line MPM. Additional clinical research is warranted to confirm the potential of these and other novel biomarkers, such as neoantigen identification matched to human leukocyte antigen,[46] to inform treatment decisions and patient selection.

MPM is a difficult disease to treat and patients have a poor prognosis. Many targeted therapies have failed to improve outcomes in MPM. Despite being included in some treatment guidelines, bevacizumab added to platinum plus pemetrexed chemotherapy is not currently approved by regulators.[47] The prolonged survival and increased durability of response observed with first-line nivolumab plus ipilimumab in unresectable MPM in CheckMate 743, together with subsequent approval of this regimen, demonstrate that significant progress has been made.[14,47] Several studies with immunotherapy-based regimens are ongoing in MPM and will provide further insights into treatment of this disease.[31,48-51]

In conclusion, with an additional year of follow-up, these 3-year data from CheckMate 743 confirm nivolumab plus ipilimumab as a standard-of-care treatment for unresectable MPM regardless of histology. Extended follow-up as well as further evaluation of candidate biomarkers of efficacy of immunotherapy in MPM are of continued interest and warrant further investigation.

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DISCLOSURES

SP reports advisory/consultancy roles for AbbVie, Amgen, AstraZeneca, Bayer, Beigene, Biocartis, Boehringer Ingelheim, BMS, Clovis, Daiichi Sankyo, Debiopharm, ecancer, Eli Lilly, Foundation Medicine, Illumina, Imedex, IQVIA, Incyte, Janssen, Medscape, MSD, Merck Serono, Merrimack, Novartis, Pharma Mar, Phosplatin Therapeutics, PER, Pfizer, PRIME, Regeneron, Roche/Genentech, RTP, Sanofi, Seattle Genetics, and Takeda; has received research funding from Amgen, AstraZeneca, Biodesiex, Boehringer Ingelheim, BMS, Clovis, GSK, Illumina, Lilly, MSD, Merck Serono, Mirati, Novartis, Phosplatin Therapeutics, Pfizer, Roche/Genentech, as well as trial investigator roles for Amgen, AstraZeneca, Biodesiex, Boehringer Ingelheim, BMS, Clovis, GSK, Illumina, Lilly, MSD, Merck Serono, Mirati, Novartis, Phosplatin Therapeutics, Pfizer, Roche/Genentech; and has had speaker engagements for AstraZeneca, Boehringer Ingelheim, BMS, ecancer, Eli Lilly, Illumina, Medscape, MSD, Novartis, PER, Pfizer, PRIME, Roche/Genentech, RTP, Sanofi, and Takeda. **AS** has received advisory/consultancy roles for AstraZeneca, BMS, MSD, and Roche; speaker engagements and expert testimony for AstraZeneca, BMS, and MSD; has received travel support from AstraZeneca, BMS, MSD, and Roche; and research funding from BMS. **RC** has received speaker fees from Roche, Pfizer, and BMS; and has participated in advisory boards for Roche, MSD, and Spectrum. **YO** reports advisory board roles for BMS, MSD, and AstraZeneca. **LG** reports advisory roles for AstraZeneca, BMS, Boehringer Ingelheim, MSD, Roche, Takeda, AbbVie, Pfizer, and Novartis. **TT** has received honoraria for advisory board participation, financial support, travel support for conferences, and speaker fees, all from BMS. **IM** has received non-financial congress support from Pfizer and Roche. **SH** has participated in advisory boards for Takeda and AstraZeneca. **PB** reports advisory/consultancy roles for BMS, Takeda, Beigene, AstraZeneca, MSD, Roche, Epizyme, Trizell, and Daiichi Sankyo; and has received research funding from BMS. **AKN** has received honoraria for consultant/advisory roles for Bayer, PharmAbcine, Trizell, Roche, Boehringer Ingelheim, MSD, Douglas Pharmaceuticals, and Atara Biotherapeutics; received research funding from Douglas Pharmaceuticals and AstraZeneca; and travel support from Boehringer Ingelheim and AstraZeneca. **NF** has received honoraria from BMS and ONO Pharmaceuticals and reports advisory/consultancy roles and receiving research funding from ONO Pharmaceuticals. **AST** has received advisory board roles for Ariad, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, EMD Serono, Genentech, Merck, Novartis, Roche, Seattle Genetics, Sellas Life Science, and Takeda; and has received research grants from EMD Serono, Epizyme, Millennium, Polaris, and Seattle Genetics. **ASM** has received honoraria for advisory roles from AbbVie, AstraZeneca, BMS, Genentech, and Janssen; travel support from AbbVie and Roche; received research funding from Novartis, Verily, Mark Foundation, and NIH; and is a non-remunerated member of the Mesothelioma Applied Research Foundation board. **SP** has participated in advisory boards for Amgen, AstraZeneca, Bayer, Beigene, Blueprint, BMS, Daiichi Sankyo, Guardant Health, Janssen, Lilly, Merck KGaA, Novartis, Roche, and Takeda; and has been a clinical trial investigator for Amgen, AstraZeneca, Boehringer

Ingelheim, Daiichi Sankyo, Roche, Takeda, Ariad, Celgene, GSK, MSD, Trizell, and Turing Point Therapeutics. **XZ**, **NH**, **DB**, and **TS** are employees of BMS. **TS** also has BMS stocks. **GZ** receives honoraria from AstraZeneca, BMS, and Roche; reports advisory/consultancy roles for AstraZeneca, BMS, Roche, MSD, Da Volterra, and Inventiva; has received travel support from AstraZeneca, BMS, Roche, Boehringer, AbbVie, and Pfizer; and research funding from Roche and Inventiva. **MAK** has declared no conflicts of interest.

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