# Nivolumab, Pomalidomide, and Elotuzumab Combination Regimens for Treatment of Relapsed and Refractory Multiple Myeloma: Results from the Phase 3 CheckMate 602 Study

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## Abstract

**Prior preclinical studies suggest combining nivolumab with pomalidomide/dexamethasone (NPd) +/- elotuzumab (NE-Pd) may increase multiple myeloma (MM) treatment efficacy. In this study, patients with RRMM were randomized 3:3:1 to receive NPd (n = 75), Pd (n = 71), or NE-Pd (n = 24). The 3 treatment arms had similar PFS, ORR, and OS outcomes. Nivolumab-containing arms were associated with a less favorable safety profile versus Pd.**

**Background:** Preclinical studies suggest that combining nivolumab, a programmed death-1 (PD-1) immune checkpoint inhibitor, with pomalidomide/dexamethasone (Pd) with or without elotuzumab, an antisignaling lymphocytic activation molecule F7 monoclonal antibody, may improve multiple myeloma (MM) treatment efficacy. **Patients and Methods:** The phase 3 CheckMate 602 study (NCT02726581) assessed the efficacy and safety of nivolumab plus pomalidomide/dexamethasone (NPd) and NPd plus elotuzumab (NE-Pd). Eligible patients (aged ≥ 18 years) had measurable MM after ≥ 2 prior lines of therapy, that included an immunomodulatory drug (IMiD) and proteasome inhibitor (PI), each for ≥ 2 consecutive cycles, alone or combined, and were refractory to their last line of therapy. Patients were randomized 3:3:1 to receive NPd, Pd, or NE-Pd. The primary endpoint was progression-free survival (PFS); overall response rate (ORR) was a key secondary endpoint. **Results:** At a median follow-up of 16.8 months, PFS was similar between treatment arms (Pd, 7.3 months [95% CI, 6.5-8.4]; NPd, 8.4 months [95% CI, 5.8-12.1]; NE-Pd, 6.3 months [95% CI,

*Abbreviations:* AE, adverse event; BOR, best overall response; CMH, Cochran–Mantel–Haenszel; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FcγR, Fc gamma receptor; FDA, United States Food and Drug Administration; ImiD, immunomodulatory; IMWG, International Myeloma Working Group; KM, Kaplan–Meier; Ld, lenalidomide plus dexamethasone; NE-Pd, nivolumab plus pomalidomide/dexamethasone and elotuzumab; NK, natural killer; NPd, nivolumab plus pomalidomide and dexamethasone; OR, odds ratio; Pd, pomalidomide and dexamethasone; PD-1, programmed death-1; PD-L1, programmed-death ligand; PI, proteasome inhibitor; PS, performance status; RRMM, relapsed/refractory multiple myeloma; SAE, serious adverse event; SLAMF7, signaling lymphocytic activation molecule family member 7; sSLAMF7, soluble signaling lymphocytic activation molecule family member 7; TTR, time to response.

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2.4-11.1]). ORR was similar in the Pd (55%), NPd (48%), and NE-Pd (42%) arms. Nivolumab-containing arms were associated with a less favorable safety profile versus Pd, including a higher rate of thrombocytopenia (NPd, 25.0%; NE-Pd, 16.7%; Pd, 15.7%), any-grade immune-mediated adverse events (NPd, 13.9%; NE-Pd, 16.7%; Pd, 2.9%), and adverse events leading to discontinuation (NPd, 25.0%; NE-Pd, 33.3%; Pd, 18.6%). No new safety signals were identified. **Conclusion:** CheckMate 602 did not demonstrate clinical benefit of nivolumab (+/- elotuzumab) plus Pd versus Pd for patients with relapsed/refractory MM (RRMM).

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## Introduction

Over the past decade, the management of multiple myeloma (MM) has greatly improved due to the introduction of immunomodulatory drugs (IMiD), proteasome inhibitors (PIs), and monoclonal antibodies[1,2]; and more recently chimeric antigen receptor-T cell therapy and bispecific T cell engagers.[2-6] However, the prognosis for patients with relapsed/refractory multiple myeloma (RRMM) remains poor with a median overall survival (OS) of 12.4 months.[7] Therefore, there is a need for novel combinations to improve outcomes for patients with RRMM.

MM cells may evade immune surveillance by suppressing immune responses through the programmed death 1 (PD-1) pathway, via upregulation of programmed death-ligand (PD-L1).[8] Evidence suggests that PD-1 is over-expressed on both $CD8^+$ T cells and natural killer (NK) cell subsets in patients with MM.[9,10] Therefore, PD-L1 mediated suppression of PD-1 is a potential mechanism in place to confer immune escape of MM.[8] Nivolumab, a PD-1 immune checkpoint inhibitor that blocks PD-L1 interaction and disrupts MM-mediated PD-1 signaling, demonstrated modest activity as monotherapy in patients with RRMM in a phase 1b study.[6] The lack of clinically meaningful efficacy with nivolumab monotherapy could potentially be attributed to several mechanisms, including poor antigen presentation, lack of agonistic signaling, immune suppressive cells, low mutational burden of MM cells, and senescence of tumor-specific T cells in the tumor microenviroment.[11] Pomalidomide, an IMiD agent, may sensitize MM cells to PD-1 blockade, and has demonstrated efficacy when combined with low-dose (40 mg/day) dexamethasone for RRMM.[12] Elotuzumab, an antisignaling lymphocytic activation molecule F7 (SLAMF7) monoclonal antibody, directly activates NK cells and facilitates antibody-dependent cell-mediated cytotoxicity.[13,14] Preclinical studies suggest that PD-1 blockade may enhance the efficacy of elotuzumab.[1,15] In mouse tumor models expressing SLAMF7, the combination of elotuzumab and anti–PD-1 treatment promoted tumor-infiltrating NK and $CD8^+$ T cell activation, potentially due to targeting different cell populations within the tumor.[15] Therefore, nivolumab plus pomalidomide and dexamethasone (NPd) may increase clinical benefit in patients with RRMM compared to nivolumab monotherapy or pomalidomide and dexamethasone (Pd) and combining NPd with elotuzumab may further increase clinical benefit. The CheckMate 602 study was designed to assess the efficacy and safety of the combination of nivolumab plus Pd (NPd) compared with Pd in patients with RRMM. NPd in combination with elotuzumab (NE-Pd) was also investigated. In August and September 2017, the United States Food and Drug Administration (FDA) investigated safety concerns in combination therapies involving pembrolizumab and IMiDs in patients with RRMM.[16,17] This prompted the FDA to put a partial hold on clinical studies involving anti–PD-1 therapies in patients with MM, including the CheckMate 602 study. This partial clinical hold was subsequently lifted, but following a futility analysis, performed at the request of the FDA, CheckMate 602 demonstrated insufficient improvement in progression-free survival (PFS) with NPd versus Pd; as such, the study was closed for enrolment in August 2018, although study participants were allowed to continue treatment. Here we report the efficacy and safety results plus exploratory biomarker analyses of NPd and NE-Pd combination regimens for the treatment of patients with RRMM following early discontinuation of CheckMate 602 post-FDA intervention.

## Methods

### *Patients and Study Design*

CheckMate 602 (NCT02726581) is a phase 3, open-label, randomized study in patients with RRMM. Eligible patients were aged $\geq$ 18 years, had Eastern Cooperative Oncology Group performance status (ECOG PS) scores of $\leq$ 2, and received $\geq$ 2 prior lines of therapy, including $\geq$ 2 consecutive cycles of an IMiD agent and PI, alone or in combination. Patients were excluded if they had received prior treatment with pomalidomide or nivolumab (or any PD-1 or PD-L1 inhibitor). Patients with solitary bone or extramedullary plasmacytoma disease or active plasma cell leukemia were also excluded. This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and all patients provided written informed consent.

Patients were randomized 3:3:1 to receive NPd, Pd, or NE-Pd and stratified by prior lines of therapy (2 vs. 3+) and International Staging System (ISS) disease stage (I–II vs. III; Figure S1). Patients in the Pd arm could cross over to the NE-Pd arm at disease progression. Treatment was administered in 28-day cycles until disease progression, development of unacceptable toxic effects, or withdrawal of consent. Patients in the NPd and NE-Pd arms received intravenous nivolumab at a dose of 240 mg of every 2 weeks in cycles 1-4 and 480 mg every 4 weeks at cycle 5+. Patients in the NE-Pd arm received intravenous elotuzumab at a dose of 10 mg/kg of body weight on days 1, 8, 15, and 22 during cycles 1-2, days 1 and 15 during cycles 3-4 and 20 mg/kg on day 1 of each cycle 5+. In the NPd, Pd, and NE-Pd arm, patients received oral pomalido-

mide at a dose of 4 mg per day on days 1 through 21 of each cycle. Patients received oral dexamethasone at a dose of 40 mg (patients ≤ 75 years) or 20 mg (patients > 75 years) per week, except on the days of elotuzumab administration, when patients in the elotuzumab arm received dexamethasone orally (28 mg in patients ≤ 75 years or 8 mg in patients > 75 years) or intravenously (8 mg).

### *Endpoints and Assessments*

The primary endpoint compared investigator-assessed PFS between the NPd and Pd arms; PFS was defined as the time from randomization to the date of the first documented tumor progression or death due to any cause. Secondary endpoints included investigator-assessed objective response rate (ORR), time to objective response (TTR), duration of response (DOR), and OS in the NPd and Pd arms. ORR was defined as the proportion of randomized patients who achieve a best overall response (BOR) of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) using International Myeloma Working Group (IMWG) criteria. TTR was defined as the time from the date of randomization to the date of the first sCR, CR, VGPR, or PR and was only evaluated in patients with a response. DOR was defined as the time between the date of the first response to the date of the first objectively documented tumor progression as assessed by independent review committee according to modified IMWG criteria or death from any cause prior to subsequent anticancer therapy. OS was defined as the time between the date of randomization and the date of death due to any cause and was censored on the last date a patient was known to be alive. Exploratory analyses included evaluating the safety and efficacy of patients treated with NE-Pd and assessment of ORR, PFS, TTR, and DOR in patients who crossed over from the Pd arm to NE-Pd. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

### *Biomarkers*

Pretreatment baseline bone marrow aspirates and blood samples were collected from informed consenting patients. PD-L1 expression was assessed from bone marrow aspirate and whole blood using a multi-analyte flow cytometric assay developed at LabCorp and analyzed in FlowJo (BD Biosciences, Franklin Lakes, NJ). Briefly, the molecules of equivalent soluble fluorochrome and percentage of PD-L1 positive cells on MM cells (CD38++/CD138+) were reported using sequential gating of the total nucleated cell count (SSC-A x FSC-A), dual positivity of CD38 and CD138 (CD38++/CD138+), and finally a histogram of PD-L1 expression. The PD-L1 expression score was calculated as the percentage of PD-L1 positive tumor (MM) plasma cells divided by the percentage of PD-L1 positive immune normal cells. The PD-L1 status was determined by flow cytometry where the threshold score for positive PD-L1 expression was ≥ 10%. Fluorescence in situ hybridization was used to analyze bone marrow aspirate for the identification of cytogenic markers including t (4;14), t (14;16), t (11;14), t (6;14), t (14,20), 1q gains/amplification, del(17p), and del(1p). Soluble SLAMF7 (sSLAMF7) was assessed using serum protein analysis from peripheral blood. Fc gamma receptor (Fc$\gamma$R) genes were analyzed by single nucleotide polymorphism polymerase chain reaction of peripheral blood. Bone marrow aspirate and peripheral blood samples were evaluated at a central laboratory.

### *Statistical Analysis*

In total, 348 patients (262 PFS events) were planned to be randomized at 1:1 ratio to Pd versus NPd arms to ensure 90% power to detect a target hazard ratio (HR) of 0.667. This sample size accounts for the primary efficacy endpoint of PFS at a 2-sided alpha of 0.05 with 2 interim analyses; the first being early futility and the second was efficacy. On August 23, 2018, enrolment was permanently discontinued based on insufficient clinical benefit observed at an interim futility analysis for PFS. By that time, 170 patients were randomized in the study.

Demographic and baseline characteristics were summarized for all randomized patients by treatment arm using descriptive statistics. PFS was analyzed using a 2-sided, log-rank test stratified by prior lines of therapy and ISS stage at study entry. The HR and the corresponding confidence intervals (CIs) were estimated using a stratified Cox proportional hazards model using treatment as a single covariate. PFS curves, PFS medians with 2-sided 95% CIs, and PFS rates at select milestone with 95% CIs were estimated using Kaplan–Meier (KM) methodology. OS medians were evaluated by the KM product-limit method within each treatment arm. Median values along with 2-sided 95% CIs based on the log–log transformation were calculated. ORR analyses were conducted using a 2-sided Cochran–Mantel–Haenszel (CMH) test stratified by prior lines of therapy and ISS stage at study entry to compare the N-Pd and Pd arms. Associated odds ratios (ORs) and 95% CIs were calculated. Additionally, ORRs and corresponding 95% CIs were calculated using the Clopper–Pearson method for the N-Pd and Pd arms. DOR and TTR were calculated for participants who achieved sCR, CR, VGPR, or PR. Median values of DOR, along with 2-sided 95% CIs were calculated using KM product-limit method. Summary statistics of TTR are presented. AEs, treatment-related AEs, and serious AEs (SAEs) were assessed using descriptive statistics. PD-L1, cytogenetic markers, and sSLAMF7 biomarkers were investigated using descriptive statistics, comparing the prevalence and association with response (ORR and BOR) and survival (OS and PFS). The association between sSLAMF7 and BOR was also estimated using descriptive statistics. The association between sSLAMF7 and the ISS was analyzed using a nonparametric Wilcoxon test. The association between sSLAMF7 and the OS/PFS were estimated using KM methodology, with the HRs and 95% CIs calculated. Statistical analyses were carried out in SAS version 9.4 (SAS Institute, Cary, NC).

## Results

### *Patient Disposition*

Patients were enrolled between August 2016 and August 2018 at 70 sites in 14 countries. Following the FDA's decision to place a partial clinical hold to investigate safety concerns in combination therapies involving IMiD agents and anti–PD-1 therapies in patients with RRMM, a futility analysis was conducted. Based on this futility analysis, this study was closed to enrollment in 2018 with just 170 of the planned 348 patients randomized.

**Table 1** Baseline Demographic and Clinical Characteristics (Randomized Population)

| | Pd (n = 71) | NPd (n = 75) | NE-Pd (n = 24) | NE-Pd Crossover[a] (n = 8) | Total (N = 170) |
|---|---|---|---|---|---|
| Median age (range), y | 67.0 (35-83) | 68.0 (34-81) | 66.5 (30-83) | 65.0 (60-77) | 67.0 (30-83) |
| Age category, n (%) | | | | | |
| < 65 | 29 (40.8) | 32 (42.7) | 10 (41.7) | 4 (50.0) | 71 (41.8) |
| ≥ 65 | 42 (59.2) | 43 (57.3) | 14 (58.3) | 4 (50.0) | 99 (58.2) |
| Male sex, n (%) | 46 (64.8) | 51 (68.0) | 16 (66.7) | 4 (50.0) | 113 (66.5) |
| Race, n (%) | | | | | |
| White | 64 (90.1) | 72 (96.0) | 19 (79.2) | 8 (100.0) | 155 (91.2) |
| Black or African American | 5 (7.0) | 3 (4.0) | 5 (20.8) | 0 | 13 (7.6) |
| Median (range) time from diagnosis to randomization, mo | 56.8 (5.7-185.3) | 47.4 (5.0-204.5) | 40.3 (11.3-125.4) | 51.7 (13.5-98.8) | 49.7 (5.0-204.5) |
| Median (range) prior lines of therapy, n | 3.0 (2-7) | 3.0 (2-7) | 3.0 (2-8) | 3.0 (2-3) | 3.0 (2-8) |
| Refractory to prior lines of therapy, n (%) | | | | | |
| Refractory to lenalidomide | 60 (84.5) | 63 (84.0) | 21 (87.5) | 8 (100.0) | 144 (84.7) |
| Refractory to lenalidomide and PI | 54 (76.1) | 57 (76.0) | 17 (70.8) | 7 (87.5) | 128 (75.3) |
| Refractory to last prior therapy | 62 (87.3) | 63 (84.0) | 21 (87.5) | 8 (100.0) | 146 (85.9) |
| ISS stage III at study entry, n (%) | 19 (26.8) | 22 (29.3) | 7 (29.2) | 0 | 48 (28) |
| ECOG PS score, n (%) | | | | | |
| 0 | 24 (33.8) | 33 (44.0) | 9 (37.5) | 0 | 66 (38.8) |
| 1 | 36 (50.7) | 35 (46.7) | 15 (62.5) | 7 (87.5) | 86 (50.6) |
| 2 | 10 (14.1) | 6 (8.0) | 0 | 1 (12.5) | 16 (9.4) |
| Cytogenetics[b] | | | | | |
| High risk cytogenetics, n (%)[c] | 15 (21.1) | 17 (22.7) | 5 (20.8) | 3 (37.5) | 37 (21.8) |
| del(17p) | 6 (8.5) | 7 (9.3) | 2 (8.3) | 1 (12.5) | 15 (8.8) |
| t (4;14) | 6 (8.5) | 7 (9.3) | 4 (16.7) | 0 | 17 (10.0) |
| t (14;16) | 4 (5.6) | 4 (5.3) | 1 (4.2) | 2 (25.0) | 9 (5.3) |
| Standard-risk cytogenetics[d] | 26 (36.6) | 39 (52.0) | 8 (33.3) | 2 (25.0) | 73 (42.9) |
| Not evaluable[e] | 30 (42.3) | 19 (25.3) | 11 (45.8) | 3 (37.5) | 60 (35.3) |

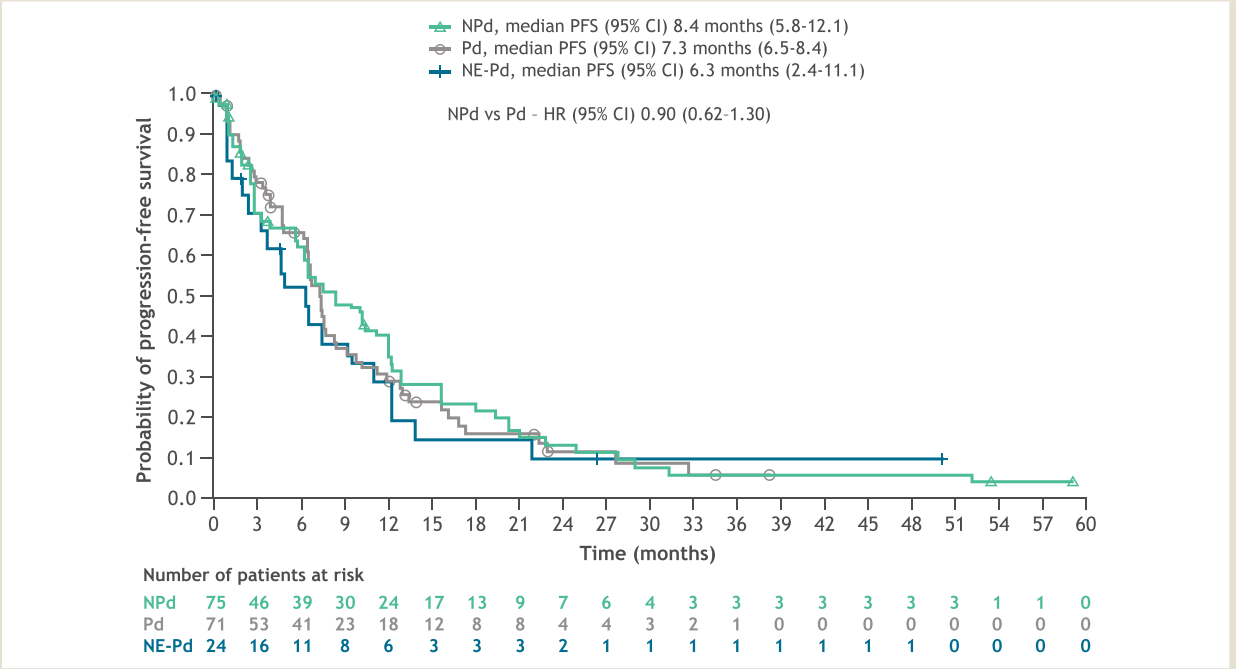
Abbreviations: ISS = international staging system; NE-Pd = nivolumab plus elotuzumab and pomalidomide plus dexamethasone; NPd = nivolumab and pomalidomide plus dexamethasone; Pd = pomalidomide plus dexamethasone; PI = proteasome inhibitor.
[a] Patients who crossed over into the NE-Pd arm from Pd arm;
[b] Patients in the NE-Pd crossover column are based on baseline evaluations before or at the first dose of initially assigned study treatment (Pd), whichever is closest to this first dose;
[c] High-risk cytogenetics abnormalities included del(17p), t(4;14), and t(14;16);
[d] Standard-risk cytogenetics was defined as absence of del(17p), t(4;14), and t(14;16)
[e] Not evaluable consisted of patients with missing information, and thus could not be categorized into high or standard risk.

Of these 170 patients, 71, 75, and 24 were randomized to the Pd, NPd, and NE-Pd arms, respectively; 70 were treated with Pd, 72 with NPd, and 24 with NE-Pd (Table S1). Upon disease progression, 8 patients in the Pd arm crossed over to the NE-Pd arm. At database lock (April 11, 2022), all patients (100%; n = 166) had discontinued study treatment; most commonly due to disease progression (Pd, 71.4% [n = 50]; NPd, 65.3% [n = 47]; NE-Pd, 66.7% [n = 16]). A higher proportion of patients in the NPd (8.3%; n = 6) and NE-Pd (8.3%; n = 2) arms discontinued treatment due to study drug toxicity than in the Pd arm (4.3%; n = 3). One patient discontinued their participation in the study due to study closure; however, the patient continued study treatment (NPd) on a poststudy drug program.

### *Baseline Demographics*

Baseline demographics were generally balanced between treatment arms (Table 1). Median (range) age was 67.0 (35.0–83.0), 68.0 (34.0-81.0), and 66.5 (30.0-83.0) years for Pd, NPd, and NE-Pd arms, respectively. In total, 64.8% (n = 46), 68.0% (n = 51), and 66.7% (n = 16) of patients were male in the Pd, NPd, and NE-Pd arms, respectively. Baseline ECOG PS of 0 was reported in 33.8% (n = 24), 44.0% (n = 33), and 37.5% (n = 9) of patients in the Pd, NPd, and NE-Pd arms, respectively; baseline ECOG PS of 2 was reported in 14.1% (n = 10), 8.0% (n = 6), and 0% of patients. Patients who crossed over to the NE-Pd arm were more likely to be white (100%), refractory to lenalidomide (100%), and have a baseline ECOG performance score of 1 (87.5%; n = 7). In total, 26.8% (n = 19), 29.3% (n = 22) and 29.2% (n = 7) of patients in the Pd, NPd, and NE-Pd arms, respectively, had ISS stage III at study entry. Patients in the Pd, NPd, and NE-Pd cohorts received a median of 3.0 (2-7), 3.0 (2-7), and 3.0 (2-8), prior lines of therapy, respectively. The median duration of the line of treatment prior to study entry was 7.9 months, 7.2 months, 6.2 months in the Pd, NPd, and NE-Pd arm, respectively, and 2.1 months in those who crossed over to NE-Pd.

**Figure 1** PFS per investigator assessment. Median PFS was estimated using Kaplan–Meier method in treated patients (N = 170). NE-Pd, nivolumab plus elotuzumab and pomalidomide plus dexamethasone; NPd, nivolumab and pomalidomide plus dexamethasone; Pd, pomalidomide plus dexamethasone; PFS, progression-free survival.




### *Efficacy*

At a median follow up of 16.8 months, the investigator-assessed median PFS was similar between Pd (7.3 [95% CI, 6.5-8.4] months), NPd (8.4 [95% CI, 5.8-12.1] months), and NE-Pd arms (6.3 [95% CI, 2.4-11.1] months; Figure 1). The HR for risk of progression or death with NPd versus Pd was 0.90 (95% CI, 0.62-1.30). Thus, there was no PFS benefit of NPd versus Pd. The lack of PFS benefit was consistently observed across key patient subgroups, defined according to baseline characteristics. All patients who crossed over to NE-Pd experienced disease progression, with a median PFS of 1.3 (95% CI, 0.7-2.3) months (Figure S2).

The ORR was numerically similar between treatment arms; 55% (95% CI, 43-67) in the Pd arm, 48% (95% CI, 36-60) in the NPd arm, and 42% (95% CI, 22-63) of patients in the NE-Pd arm had a PR or better (odds ratio of Pd versus NPd, 0.76; 95% CI, 0.39-1.46; Table 2). There were no responders in the NE-Pd crossover arm. A CR was achieved by 2.8% (n = 2), 4.0% (n = 3), and 0% (n = 0) of patients in the Pd, NPd, and NE-Pd arms, respectively. The median (range) TTR was numerically shorter in the Pd (2.9 [1.0–31.6]) and NPd arms (2.9 [1.0-52.7]) than in the NE-Pd arm (4.2 [1.0-41.2]; Table 2). The median DOR was 6.5 (95% CI, 5.6-11.1), 8.5 (95% CI, 6.5-13.8), and 9.2 months (95% CI, 1.3-18.2) in the Pd, NPd, and NE-Pd arms, respectively (Table 2). Median OS was similar between Pd and NPd arms (21.4 [95% CI, 17.9-27.6] months versus 24.9 [95% CI, 15.6-34.4] months; HR 0.79, (95% CI, 0.53-1.19; Figure 2); however, OS was numerically shorter in the NE-Pd arm (13.0 [95% CI, 4.4-44.4] months). In total, 52.9% (n = 90) of patients received subsequent systemic cancer therapy; most commonly daratumumab (28.8%, n = 49; Table S2).

### *Safety*

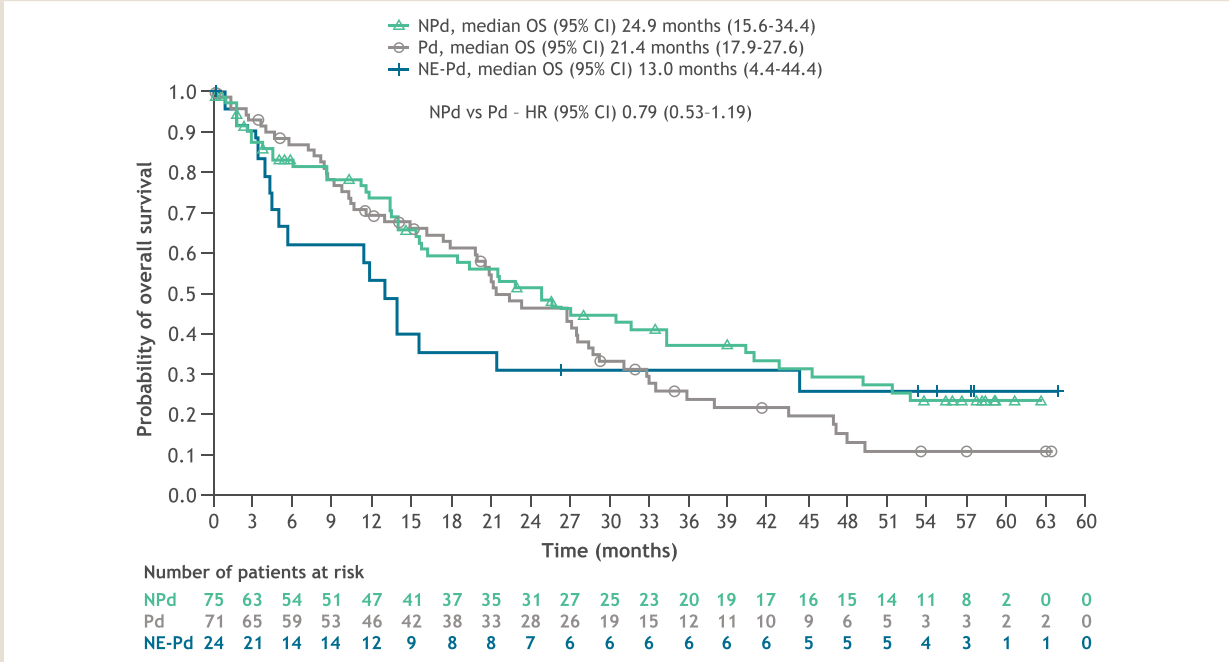
AEs were reported in 97.1% (n = 68), 98.6%, (n = 71), and 100% (n = 24) of patients in the Pd, NPd, and NE-Pd treatment arms, respectively, with grade 3/4 AEs occurring in 65.7% (n = 46), 72.2% (n = 52), and 54.2% (n = 13) of patients, and grade 5 AEs in 15.7% (n = 11), 15.3% (n = 11), and 37.5% (n = 9) of patients (Table 3). The most common hematological AEs were neutropenia (Pd, 31.4%; NPd, 33.3%; and NE-Pd, 41.7%), anemia (Pd, 28.6%; NPd, 37.5%; and NE-Pd, 45.8%), and thrombocytopenia (Pd, 15.7%; NPd, 25.0%; and NE-Pd, 16.7%). Any-grade infections and infestations occurred in 81.4% (n = 57), 80.6% (n = 58), and 79.2% (n = 19) of patients in the Pd, NPd, and NE-Pd treatment arms, respectively; grade 5 infections were reported in 2.9% (n = 2), 5.6% (n = 4), and 12.5% (n = 3) of patients in the Pd, NPd, and NE-Pd treatment arms. Patients in the NPd arm (52.8% [n = 38]) had a higher incidence of grade 3/4 SAEs compared with the Pd (n = 40.0% [n = 28]) and NE-Pd (50.0% [n = 12]) arms (Table 3). Any grade treatment-related adverse events (TRAEs) were proportionally slightly higher in the nivolumab-containing arms (Pd, 81.4%; NPd, 91.7%; NE-Pd, 87.6%); but grade 3/4 TRAEs were reported in approximately 60% of all treatment arms (Table S3). Any grade immune-mediated AEs were reported in 2.9% (n = 2), 13.9% (n = 10), and 16.7% (n = 4) of patients in the Pd, NPd, and NE-Pd treatment arms, respectively. Any-grade AEs

**Table 2** Investigator-Assessed Treatment Response in the Randomized Population

| | Pd (n = 71) | NPd (n = 75) | NE-Pd (n = 24) | NE-Pd Crossover[a] (n = 8) |
|---|---|---|---|---|
| ORR, n (%)[b] | 39 (54.9) | 36 (48.0) | 10 (41.7) | 0 |
| 95% CI | 42.7-66.8 | 36.3-59.8 | 22.1-63.4 | 0.0-0.0 |
| OR (95% CI)[c] | 0.76 (0.39-1.46) | | | |
| Best overall response, n (%) | | | | |
| ≥ VGPR | 11 (15.5) | 16 (21.3) | 4 (16.7) | 0 |
| Stringent CR | 1 (1.4) | 3 (4.0) | 2 (8.3) | 0 |
| CR | 2 (2.8) | 3 (4.0) | 0 | 0 |
| VGPR | 8 (11.3) | 10 (13.3) | 2 (8.3) | 0 |
| PR | 28 (39.4) | 20 (26.7) | 6 (25.0) | 0 |
| Median time (range) to objective response, mo | 2.86 (1.0-31.6) | 2.91 (1.0-52.7) | 4.22 (1.0-41.2) | N/A |
| Median DOR (95% CI), mo | 6.47 (5.55-11.07) | 8.51 (6.47-13.83) | 9.23 (1.28-18.20) | N/A |

Abbreviations: CR = complete response; DOR = duration of response; ISS, International Staging System; NE-Pd, nivolumab plus elotuzumab and pomalidomide plus dexamethasone; NPd = nivolumab and pomalidomide plus dexamethasone; OR = odds ratio; ORR = overall response rate; Pd = pomalidomide plus dexamethasone; PR = partial response; VGPR = very good partial response.
[a] Patients who crossed over into the NE-Pd arm from Pd arm.
[b] Stringent CR+CR+VGPR+PR, confidence interval is based on the Clopper–Pearson method.
[c] Stratified by prior lines of therapy and ISS stage at randomization.

**Figure 2** OS by treatment arm. Median OS was estimated using Kaplan–Meier method in treated patients (N = 170). Abbreviations: NE-Pd = nivolumab plus elotuzumab and pomalidomide plus dexamethasone; NPd = nivolumab and pomalidomide plus dexamethasone; OS = overall survival; Pd = pomalidomide plus dexamethasone.




leading to discontinuation were numerically higher in nivolumab-containing arms, with 25.0% (n = 18) and 33.3% (n = 8) in the NPd and NE-Pd arms, respectively, and 18.6% (n = 13) in the Pd arm (Table S4). Overall, 118 patients died (Pd, 77.1%; NPd, 65.3%; NE-Pd, 70.8%); Table S4); most commonly due to disease progression (Pd, 58.6%; NPd, 38.9%; NE-Pd, 45.8%). In CheckMate 602, 1 patient (in the NPd arm) died from study drug toxicity, specifically from complications of pneumonitis. Deaths within 30 days of the last treatment dose occurred in 5.7%, 16.7%, and 20.8% of patients in the Pd, NPd, and NE-Pd arms, respectively; deaths within 100 days of the last treatment dose occurred in 18.6%, 27.8%, 45.8%, respectively.

### *Biomarker Analyses*

An analysis was performed to determine whether the lack of clinical benefit after combining nivolumab with pomalidomide

**Table 3** Adverse Events by System Organ Class in ≥ 15% of Patients in the Treated Population

| Variable, n (%) | Pd (n = 70) | | | NPd (n = 72) | | | NE-Pd (n = 24) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade 3-4 | Grade 5 | Any Grade | Grade 3-4 | Grade 5 | Any Grade | Grade 3-4 | Grade 5 |
| Any | 68 (97.1) | 46 (65.7) | 11 (15.7) | 71 (98.6) | 52 (72.2) | 11 (15.3) | 24 (100.0) | 13 (54.2) | 9 (37.5) |
| Infections and infestations | 57 (81.4) | 26 (37.1) | 2 (2.9) | 58 (80.6) | 25 (34.7) | 4 (5.6) | 19 (79.2) | 10 (41.7) | 3 (12.5) |
| Other respiratory tract infections[a] | 36 (51.4) | 2 (2.9) | 0 | 33 (45.8) | 4 (5.6) | 0 | 5 (20.8) | 1 (4.2) | 0 |
| Pneumonia | 26 (37.1) | 14 (20.0) | 0 | 16 (22.2) | 9 (12.5) | 0 | 8 (33.3) | 7 (29.2) | 0 |
| General disorders and administration site conditions | 43 (61.4) | 10 (14.3) | 0 | 55 (76.4) | 14 (19.4) | 2 (2.8) | 19 (79.2) | 4 (16.7) | 0 |
| Hematologic | 40 (57.1) | 31 (44.3) | 0 | 43 (59.7) | 34 (47.2) | 0 | 16 (66.7) | 13 (54.2) | 0 |
| Neutropenia | 22 (31.4) | 19 (27.1) | 0 | 24 (33.3) | 20 (27.8) | 0 | 10 (41.7) | 8 (33.3) | 0 |
| Anemia | 20 (28.6) | 10 (14.3) | 0 | 27 (37.5) | 18 (25.0) | 0 | 11 (45.8) | 6 (25.0) | 0 |
| Thrombocytopenia | 11 (15.7) | 5 (7.1) | 0 | 18 (25.0) | 13 (18.1) | 0 | 4 (16.7) | 3 (12.5) | 0 |
| Gastrointestinal | 38 (54.3) | 6 (8.6) | 0 | 44 (61.1) | 6 (8.3) | 0 | 15 (62.5) | 4 (16.7) | 0 |
| Diarrhea | 17 (24.3) | 1 (1.4) | 0 | 22 (30.6) | 1 (1.4) | 0 | 5 (20.8) | 1 (4.2) | 0 |
| Constipation | 15 (21.4) | 0 | 0 | 17 (23.6) | 0 | 0 | 4 (16.7) | 0 | 0 |
| Nausea | 11 (15.7) | 1 (1.4) | 0 | 14 (19.4) | 0 | 0 | 4 (16.7) | 0 | 0 |
| Respiratory, thoracic, and mediastinal disorders | 31 (44.3) | 8 (11.4) | 0 | 37 (51.4) | 10 (13.9) | 0 | 13 (54.2) | 4 (16.7) | 0 |
| Skin and subcutaneous tissue disorders | 20 (28.6) | 2 (2.9) | 0 | 27 (37.5) | 2 (2.8) | 0 | 8 (33.3) | 1 (4.2) | 0 |
| Rash | 8 (11.4) | 0 | 0 | 11 (15.3) | 2 (2.8) | 0 | 3 (12.5) | 0 | 0 |
| Renal and urinary disorders | 11 (15.7) | 5 (7.1) | 0 | 17 (23.6) | 9 (12.5) | 0 | 8 (33.3) | 4 (16.7) | 0 |
| Neoplasms benign, malignant, and unspecified | 10 (14.3) | 2 (2.9) | 7 (10.0) | 17 (23.6) | 10 (13.9) | 5 (6.9) | 9 (37.5) | 3 (12.5) | 6 (25.0) |
| Endocrine | 2 (2.9) | (0) | 0 | 7 (9.7) | 0 | 0 | 4 (16.7) | 0 | 0 |
| SAEs | 36 (51.4) | 28 (40.0) | 4 (5.7) | 48 (66.7) | 38 (52.8) | 5 (6.9) | 16 (66.7) | 12 (50.0) | 4 (16.7) |
| Treatment-related SAEs | 16 (22.9) | 13 (18.6) | 0 | 22 (30.6) | 18 (25.0) | 0 | 7 (29.2) | 5 (20.8) | 0 |
| Immune-mediated AEs[b] | 2 (2.9) | 0 | 0 | 10 (13.9) | 5 (6.9) | 0 | 4 (16.7) | 1 (4.2) | 0 |

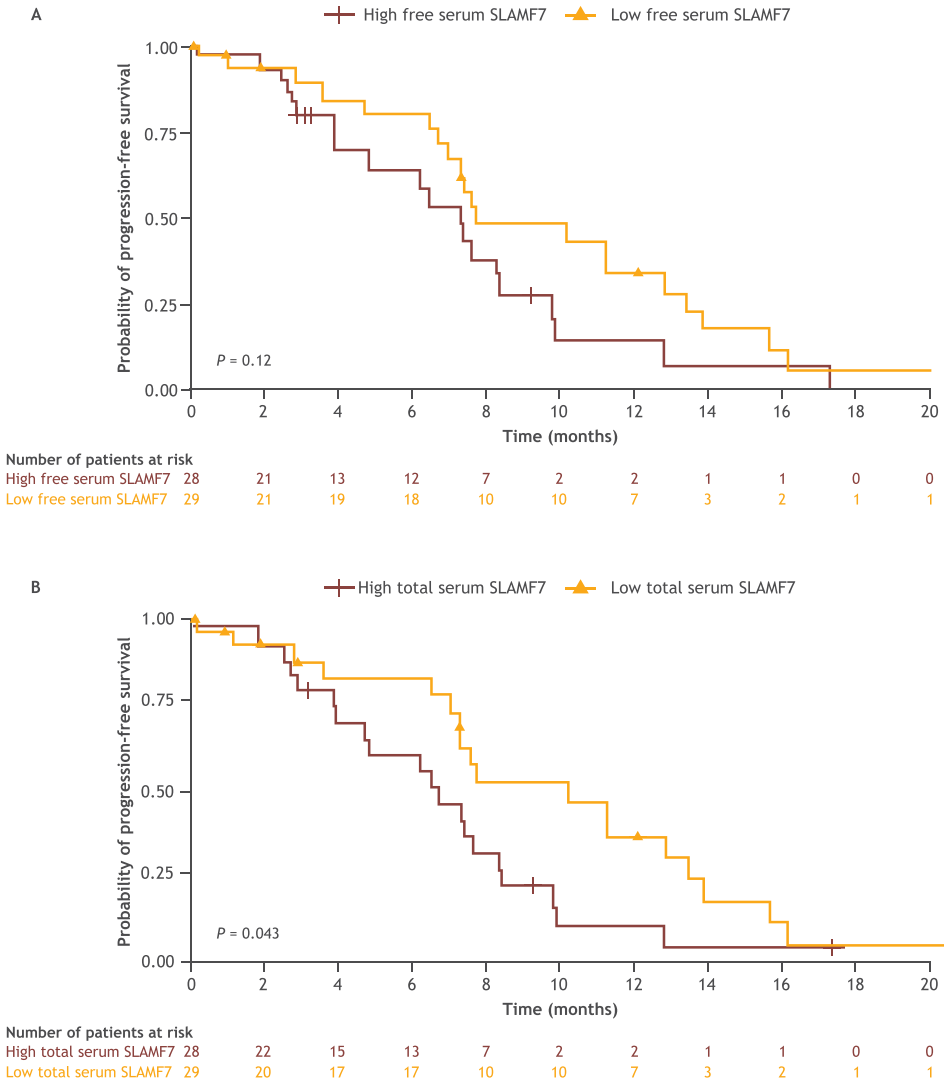
Abbreviations: AE = adverse event; NE-Pd = nivolumab plus elotuzumab and pomalidomide plus dexamethasone; NPd = nivolumab and pomalidomide plus dexamethasone; Pd = pomalidomide plus dexamethasone; SAE = serious adverse event.
[a] Includes upper respiratory tract infections, respiratory tract infections, and bronchitis.
[b] Includes events reported between first dose and 100 days after last dose of study drugs.

observed in CheckMate 602 could be attributed to the presence or absence of key biomarkers. To determine whether higher PD-L1 expression score impacted OS, a subpopulation analysis was performed using a PD-L1 cutoff score of ≥ 10%. The NE-Pd arm tended to have a poorer OS and PFS compared to NPd and Pd irrespective of PD-L1 score (Figure S3). Using a median sSLAMF7 cutoff, both baseline low free-sSLAMF7 and low total-sSLAMF7 subgroups were associated with improved PFS (HR = 0.602, 95% CI [0.315-1.152]; and HR = 0.514, 95% CI [0.267-0.99], respectively) versus the high-sSLAMF7 subgroup in the Pd arm (Figure 3). At the baseline level, low free-sSLAMF7 and low total-sSLAMF7 were also associated with improved OS (HR = 0.333, 95% CI, 0.133-0.836; and HR = 0.332, 95% CI, 0.132-0.833, respectively) versus the high-sSLAMF7 subgroup in the Pd arm (Figure 4). Finally, patients with chromosome 1q gain or amplification had lower ORR in the Pd and NPd arms, but not in the NE-Pd arm, compared with patients without a 1q mutation (Figure S4). No notable difference was observed among Fc$\gamma$R polymorphisms (Figure S5).

## Discussion

CheckMate 602 was designed to evaluate whether the addition of nivolumab to Pd would improve the clinical benefit (PFS) compared to Pd in patients with RRMM. Recruitment to CheckMate 602 was halted early (September 2017) by the FDA due to safety concerns involving anti–PD-1 therapies in patients with MM observed in KEYNOTE-183 and KEYNOTE-185.[16-18] Consequently, a lower number of patients were enrolled than originally planned, meaning the analysis of CheckMate 602 was not adequately powered, and the results are descriptive. In the KEYNOTE-183, which investigated pembrolizumab plus Pd in patients with RRMM, and KEYNOTE-185 phase 3 studies, which investigated pembrolizumab plus lenalidomide and dexamethasone (Ld) in transplant-ineligible patients with newly diagnosed MM, there was an imbalance in the proportion of deaths between treatment arms.[16,17] In KEYNOTE-183, 4 treatment-related deaths occurred in the pembrolizumab plus Pd arm versus none in the Pd arm, and in KEYNOTE-185, 6 treatment-related deaths occurred in the pembrolizumab plus Ld arm versus 2 in the Ld arm.[16,17]

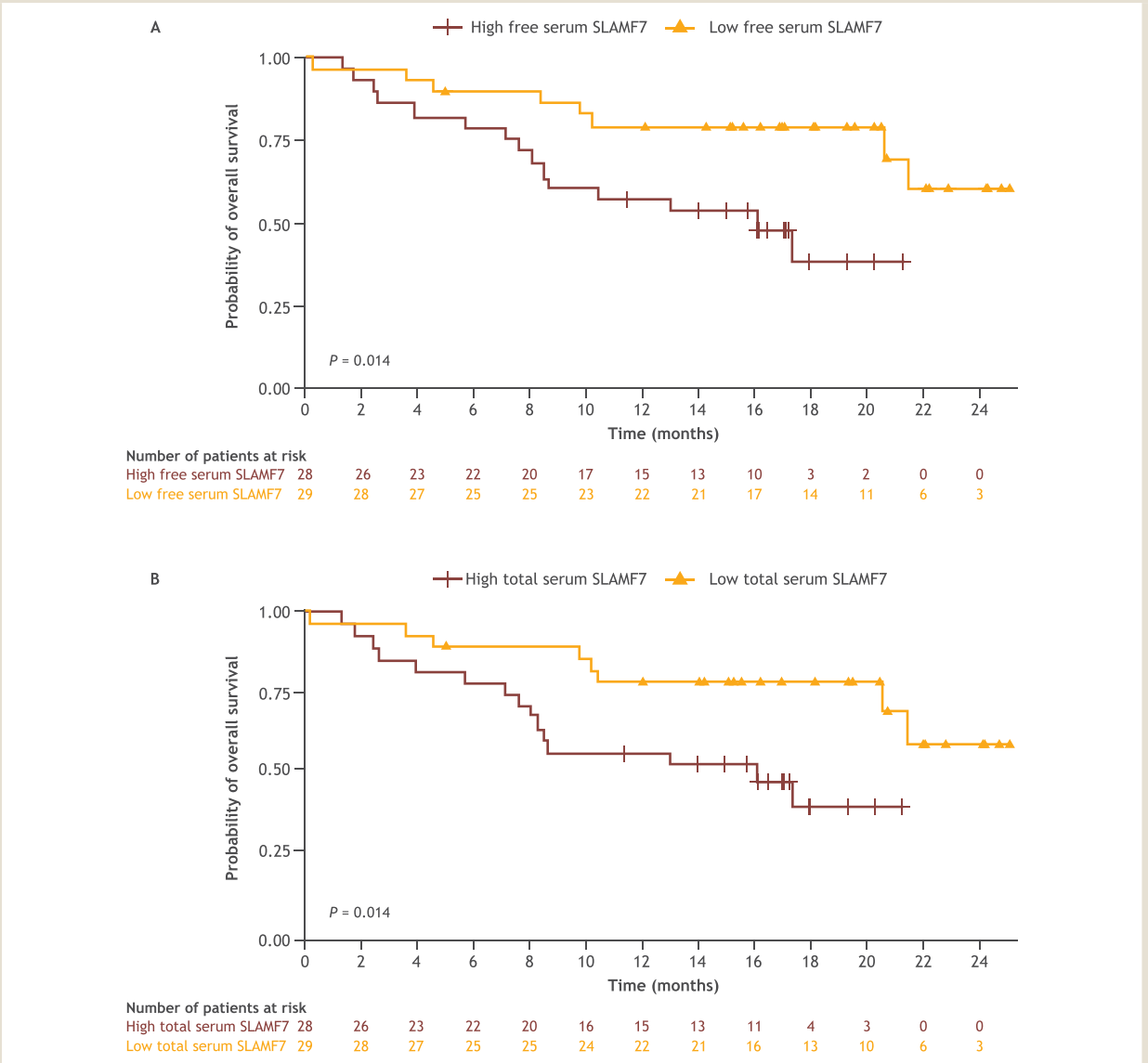
**Figure 3** PFS in patients receiving Pd by (A) high and low free SLAMF7 and (B) high and low total SLAMF7. Median PFS was estimated using Kaplan–Meier method in patients who were evaluable for serum SLAMF7 and receiving Pd (n = 57). High and low SLAMF7 were based on the median cutoff. Abbreviations: Pd = pomalidomide plus dexamethasone; PFS = progression-free survival; SLAMF7 = signaling lymphocytic activation molecule F7.




In CheckMate 602, only 1 patient (in the NPd arm) died due to study drug toxicity. The unfavorable benefit–risk profile observed in KEYNOTE-183 and KEYNOTE-185 led the FDA to put both studies on hold[16,17] and place other clinical studies evaluating the combination of anti–PD-1 therapies (including CheckMate 602) on partial clinical hold.[16] Based on an ad hoc futility analysis requested by the FDA, enrolment to CheckMate 602 closed in 2018 with 170 of the expected 348 patients randomized.

The ad hoc futility analysis for the CheckMate 602 study projected a very low conditional power to detect statistical significance, leading to final termination of enrollment and consequently inadequate statistical power. There was no difference in median PFS across treatment arms with the 170 randomized patients (Pd, 7.3 months; NPd, 8.4 months; and NE-Pd, 6.3 months). Additionally, OS was similar between the Pd and NPd treatment arms (21.4 and 24.9 months, respectively), but numerically shorter in the NE-Pd arm (13.0 months). In the KEYNOTE-183 phase 3 study, which enrolled patients with RRMM previously treated with ≥ 2 lines of therapy (excluding pomalidomide) who were refractory to the last line, the median PFS of pembrolizumab plus Pd (5.6 months, 95% CI, 3.7-7.5) was numerically lower compared with the Pd only arm (8.4 months, 95% CI, 5.9-not reached).[16] The median PFS in the treatments arms of KEYNOTE-183 study[14] was comparable to those in the CheckMate 602 study.[16] In the KEYNOTE-185 study, which investigated efficacy and safety of pembrolizumab plus lenalidomide-dexamethasone (Ld) compared to Ld only in patients

**Figure 4** OS in patients receiving Pd by (A) high and low free SLAMF7 and (B) high and low total SLAMF7. Median OS was estimated using Kaplan–Meier method in patients who were evaluable for serum SLAMF7 and receiving Pd (n = 57). High and low SLAMF7 were based on the median cutoff. Abbreviations: OS = overall survival; Pd = pomalidomide plus dexamethasone; SLAMF7 = signaling lymphocytic activation molecule F7.




with newly diagnosed MM, median PFS was not reached; however, PFS estimates were similar in the 2 arms at 6 months with values of 82% and 85% ($P = 0.75$), respectively.[17] Collectively, KEYNOTE-183, KEYNOTE-185, and CheckMate 602 studies suggest that the addition of nivolumab or pembrolizumab to Pd (or Ld) does not increase median PFS compared to control arms. The addition of elotuzumab to NPd in CheckMate 602 also provided no further clinical benefit to patients with RRMM. Data from ELOQUENT-3 demonstrated that elotuzumab combined with Pd led to significantly longer OS (29.8 vs. 17.4 months) versus Pd in patients with RRMM.[19] The mechanism leading to worse outcomes when elotuzumab was added to NPd in CheckMate 602 is unclear and requires further investigation. It should be noted that in comparison to CheckMate 602, ELOQUENT-3 was an adequately powered, 2-arm study.

Most patients in CheckMate 602 experienced at least 1 AE. The incidence of grade 3/4 AEs was higher in the NPd arm, although grade 5 AEs were more common in the NE-Pd arm. The nivolumab-containing arms (NPd and NE-Pd) had higher proportions of patients who experienced neutropenia, thrombocytopenia, and anemia versus Pd. However, the incidence of any-grade neutropenia (31%) and thrombocytopenia (16%) was lower than

reported in a phase 2 study (58% and 50%, respectively) in patients with RRMM who had received ≥ 2 prior lines of therapy and were treated with pembrolizumab plus Pd.[20] In CheckMate 602, numerically higher incidences of any-grade SAEs, immune-mediated AEs, and AEs leading to discontinuation were observed in the nivolumab-containing arms (NPd and NE-Pd) compared with the Pd arm. Most patients discontinued study treatment due to disease progression; however, more patients discontinued due to study drug toxicity in the nivolumab-containing arms (NPd and NE-Pd) versus Pd. Notably, discontinuations due to infections were more frequent in the NPd and NE-Pd arms than the Pd arm. More deaths were reported in the Pd arm than NPd and NE-Pd arms, most commonly due to disease progression; however, grade 5 infections were more common in the nivolumab-containing arms (NPd and NE-Pd) versus Pd. The imbalance in the proportion of deaths between treatment arms in patients in KEYNOTE-183[16] and KEYNOTE-185[17] was not observed in CheckMate 602. Additionally, cardiac-related deaths reported in KEYNOTE-183 and KEYNOTE-185 were not observed in the nivolumab-pomalidomide containing arms in CheckMate 602.[16-18]

To understand the lack of clinical benefit observed when nivolumab (+/− elotuzumab) was combined with Pd, a biomarker analysis was conducted to investigate the association of SLAMF7 and PD-L1 expression with survival (OS and PFS) and evaluate baseline tumor mutational burden (TMB) by treatment arm (Pd, NPd, or NE-Pd). sSLAMF7 is expressed on MM cells and is a predictive biomarker of elotuzumab therapy.[21] As such, the low expression of sSLAMF7 observed in CheckMate 602 could potentially explain the poor responses to NE-Pd. In CheckMate 602, lower total SLAMF7 levels were associated with improved survival in patients who received Pd, but not in patients treated with NPd or NE-Pd. Fc$\gamma$R polymorphisms are predictors of response to monoclonal antibody therapies[22,23]; however, in CheckMate 602, no association between Fc$\gamma$R polymorphisms and response were observed. Additionally, baseline PD-L1-expression ≥ 10% correlated with improved survival in all treatment arms and there was no statistical difference in baseline TMB-score between Pd, NPd, and NE-Pd arms (data not shown). As such, the available biomarker assessment provided no further insights into why the combination of nivolumab (+/− elotuzumab) with Pd did not improve clinical efficacy versus Pd.

The small number of patients (n = 8) who crossed over from the Pd arm to NE-Pd arm limited the ability to evaluate the efficacy of treatment with nivolumab plus elotuzumab after progression on Pd. Consequently, biomarker sample size from the NE-Pd arm was less than half of that compared to the Pd and NPd arms, further limiting the ability to compare between arms. Additionally, the dynamic effect of treatment on the immune environment was not measured in this study, with biomarker samples only taken prior to treatment initiation.

CheckMate 602 did not demonstrate an improvement in PFS, response rates, or OS in patients with RRMM with the addition of nivolumab (+/− elotuzumab) to Pd. No new safety signals were identified; however, nivolumab-containing arms were associated with a less favorable safety profile, with higher rates of thrombocytopenia, immune-mediated AEs, and AEs leading to discontinuation. Further studies are needed to evaluate the use of PD-1/PD-L1 blockade (including nivolumab) as a novel combination treatment with other antimyeloma therapies, especially with CAR T cell therapy and T cell engagers.[24-27]

### *Clinical Practice Points*

What is already known about this subject?

- Despite the introduction of immunomodulatory agents, proteasome inhibitors, monoclonal antibodies, and more recently chimeric antigen receptor T cell therapy and bispecific T cell engagers, multiple myeloma (MM) is still not curable.
- Preclinical studies suggest that combining nivolumab (+/− elotuzumab) with pomalidomide/dexamethasone (Pd) may increase MM treatment efficacy.

What are the new findings?

- In CheckMate 602, progression-free survival (PFS), overall response rate, and overall survival (OS) were similar across treatment arms (Pd, NPD, NE-Pd); therefore, the addition of nivolumab or nivolumab and elotuzumab to Pd provided no further clinical benefit for patients with RRMM.
- Although no new safety signals were identified, nivolumab-containing arms were associated with a less favorable safety profile versus Pd, with higher rates of thrombocytopenia, immune-mediated adverse events (AEs), and AEs leading to discontinuation.
- There was no correlation between signaling lymphocytic activation molecule family member 7 (SLAMF7) and programmed-death ligand (PD-L1) expression and survival (OS/PFS); therefore, the assessment provided no further insights into the lack of clinical efficacy observed in CheckMate 602.

How might it impact on clinical practice in the foreseeable future?

- The outcomes of this study do not support nivolumab (+/− elotuzumab) plus Pd as treatments for patients with MM.
- Future studies are needed to evaluate whether different combination therapies with programmed death-1/PD-L1 checkpoint inhibitors may improve clinical outcomes in patients with MM, for example, combination with T cell redirected therapies.

## Data Sharing Statement

Bristol Myers Squibb company policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

## Disclosure

AO: honoraria from and data safety monitoring or advisory boards for Bristol Myers Squibb, GlaxoSmithKline, Janssen, and Sanofi. RH: grants (to institution) from Amgen, Bristol Myers Squibb, Celgene, Janssen, Novartis, and Takeda; consulting for AbbVie, Amgen, Bristol Myers Squibb, Celgene, Janssen, Novartis, PharmaMar, and Takeda; honoraria from Amgen, Bristol Myers Squibb, Celgene, Janssen, PharmaMar, and Takeda; travel expenses from Amgen, Celgene, Janssen, and Takeda; and data safety monitoring or advisory boards for Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Oncopeptides, Sanofi, and

Takeda. I Spicka: consulting fees and honoraria from, and data safety monitoring or advisory boards for Amgen, Bristol Myers Squibb, Celgene, Janssen-Cilag, Novartis, Sanofi, and Takeda; travel expenses from Amgen, Bristol Myers Squibb, Celgene, and Janssen-Cilag. I Sandhu: consulting fees from Amgen, Bristol Myers Squibb/Celgene, Janssen, Kite/Gilead, Pfizer, Sanofi, and Takeda. YCC: grants from Amgen and Takeda; consulting fees from Janssen; honoraria from Amgen, GlaxoSmithKline, and Takeda; travel expenses from Janssen; and data safety monitoring or advisory boards for Janssen. MC: honoraria from AbbVie, Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Roche, Sanofi, and Takeda. JB: grants (to institution) from 2seventy-bio, AbbVie, Acetylon, Amgen, Bluebird bio, C4 Therapeutics, CARsgen, Cartesian Therapeutics, Celgene, Celularity, CRISPR Therapeutics, EMD Serono, Fate Therapeutics, Genentech, GlaxoSmithKline, Ichnos Sciences, Incyte, Janssen, Karyopharm, Lilly, Novartis, Poseida, Sanofi, Takeda, Teva, and Zentalis; and consulting fees (to institution) from Bluebird bio, Bristol Myers Squibb, Celgene, CRISPR Therapeutics, Janssen, Kite Pharma, Legend Biotech, Secura Bio, and Takeda. KJ, PD, and YW: employees of Bristol Myers Squibb. MB: employee of, has stock in, and received travel support from Bristol Myers Squibb. RLM-M: employee of and has stock in Bristol Myers Squibb and stock in MacroGenics. DP: employee of and has stock in Bristol Myers Squibb. LJC: grants (to institution) from Amgen, Genentech, Ionis, and Janssen; consulting fees from Adaptive Biotechnologies, Amgen, Bristol Myers Squibb, Janssen, and Sanofi; and honoraria from Adaptive Biotechnologies, Janssen, and Sanofi.

## CRediT authorship contribution statement

**Albert Oriol:** Writing – review & editing, Validation, Supervision, Investigation. **Roman Hájek:** Project administration, Investigation, Data curation. **Ivan Spicka:** Investigation. **Irwindeep Sandhu:** Investigation. **Yael C. Cohen:** Investigation. **Moshe E. Gatt:** Investigation. **José Mariz:** Investigation. **Michele Cavo:** Investigation. **Jesús Berdeja:** Investigation. **Kexin Jin:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis. **Merav Bar:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis. **Prianka Das:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis. **Ross La Motte-Mohs:** Writing – review & editing, Writing – original draft, Validation, Formal analysis. **Yu Wang:** Writing – review & editing, Writing – original draft, Validation, Formal analysis. **Deepak Perumal:** Writing – review & editing, Writing – original draft, Validation, Formal analysis. **Luciano J. Costa:** Investigation, Data curation.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2024.05.014.

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