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Nivolumab and daratumumab combination regimens for the treatment of relapsed and refractory multiple myeloma: results of a randomized phase I/II clinical trial

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Purpose: The phase I/II trial CheckMate 039 (NCT01592370) evaluated the safety, tolerability, and efficacy of nivolumab-daratumumab (ND) in patients with relapsed/refractory multiple myeloma (RRMM).

Methods: Patients with RRMM were randomized to receive ND with or without pomalidomide-dexamethasone (Pd) in cohort A and ND or D monotherapy in cohort B. The primary endpoint was safety. Secondary endpoints included minimal residual disease (MRD) negativity status, overall response rate (ORR), duration of response, and progression-free survival (PFS).

Results: Cohort A (n = 11) was terminated early due to safety concerns observed with immunomodulatory agents and checkpoint inhibitor combinations in other clinical trials. In the small number of patients treated in cohort A, no new safety concerns were observed but patients who received NDPd had numerically more

grade 3/4 adverse events (AEs) and serious AEs compared with ND. Grade 3/4 AEs occurring in ≥ 1 patient in the ND group was anemia (3/6 patients); in the NDPd group, these were neutropenia (3/5 patients), upper respiratory tract infection (2/6 patients), and pneumonia (2/6 patients). In cohort B (n = 63), AE rates were similar between ND and D (any-grade: 87.8% vs 95.5%; grade 3/4: 53.7% vs 45.5%). Grade 3/4 AEs occurring in ≥ 1 patient in the ND group were neutropenia (19.5%), anemia (9.8%), thrombocytopenia (9.8%), and bronchitis (7.3%); in the D group these were anemia and pneumonia (both 9.1%). Immune-mediated AEs for ND were consistent with the known safety profile of nivolumab. In cohort A, all patients (5/5) receiving NDPd and 4/6 receiving ND achieved a response. In cohort B, the ORR with ND was numerically higher than D (22/41 [53.7%] vs 9/22 [40.9%]) and both groups had a median PFS of 6.6 months. ND also showed promising MRD negativity results (next-generation sequencing 10^{-5}, 24.0%; next-generation flow 10^{-5}, 22.2%).

Conclusion: NDPd demonstrated no new safety signals and encouraging efficacy despite its early termination. ND was well tolerated with a manageable toxicity and few AEs leading to discontinuation, and demonstrated a numerically higher ORR but equivalent PFS compared with D. Any clinical benefits to OS require a longer follow-up.

Clinical trial registration: https://clinicaltrials.gov/, identifier NCT01592370.

KEYWORDS

relapsed/refractory, multiple myeloma, phase I/II, nivolumab, daratumumab, pomalidomide, checkpoint inhibition, immunotherapy

1 Introduction

Improved outcomes have been observed in patients with multiple myeloma (MM) who have received combination therapy treatment. The management of newly diagnosed and early-line relapse MM has significantly improved in the past decade due to the introduction of immunomodulatory agents, proteasome inhibitors (PIs), and monoclonal antibodies (mAbs) (1, 2). Despite this, MM remains incurable and inevitably progresses to a relapsing-remitting course with remission periods becoming shorter and outcomes worsening following each relapse (3, 4). Therefore, there is a need for novel combinations to improve outcomes for patients with relapsed/refractory MM (RRMM).

Immune checkpoint inhibitors targeting programmed death-1 (PD-1) have been explored in MM, driven by unprecedented clinical outcomes in solid tumors and Hodgkin lymphoma (5). PD-1 mediates inhibitory signals on T cells upon ligand binding leading to impaired host antitumor immune response (6). Nivolumab is a fully human IgG4 mAb, optimized with an S228P mutation to prevent FAB-arm exchange, that acts as a PD-1 checkpoint inhibitor, disrupting engagement between the PD-1 receptor and its ligands PD-L1 and PD-L2 (5, 7). Disruption of the PD-1/PD-L1/-L2 axis reduces the inhibition of the immune system, including antitumor responses, mediated by the PD-1 pathway (5). Nivolumab may have therapeutic potential in MM due to frequent expression of PD-L1 by MM cells and subpopulations of immune cells, and has been shown to play a role in mediating inhibition of immunity in the bone marrow milieu of patients with MM (8–10). However, PD-1 pathway blockade in MM has not demonstrated efficacy as a monotherapy (11). The lack of clinically meaningful efficacy has multiple proposed 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 microenvironment (12). When used as combination therapy, previous early-stage trials using an alternative PD-1 inhibitor, pembrolizumab, in combination with either lenalidomide or pomalidomide and dexamethasone, demonstrated promising efficacy and safety results (13, 14). However, safety signals identified in the subsequent phase III KEYNOTE-183 and -185 trials, which used a combination checkpoint inhibitor agent plus immunomodulatory drug regimen, resulted in early termination due to an unfavorable benefit–risk profile (15, 16).

The introduction of mAbs, especially daratumumab, changed the treatment landscape for patients with MM (1). Daratumumab is a human IgG1 mAb that mediates its killing effect of CD38-expressing MM cells through antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and direct apoptosis via cross-linking (17, 18). An additional part of the efficacy of daratumumab may be attributed to the reduction of immune suppression from CD38 cells while

enhancing T-cell immunity (19). Daratumumab is approved as part of combination regimens for patients with newly diagnosed MM, and as a monotherapy or part of combination regimens for patients with RRMM (2, 20, 21). The rationale for combining daratumumab with nivolumab is partially based on observations from other studies where the upregulation of CD38 on T cells resulted in PD-1/PD-L1 blockade resistance (19, 22), and it was hypothesized that combining nivolumab and daratumumab may overcome daratumumab and/or nivolumab resistance. As the addition of pomalidomide and dexamethasone to daratumumab has demonstrated a good efficacy response (23, 24), it was hypothesized that adding pomalidomide and dexamethasone to nivolumab and daratumumab may enhance these effects, with potential synergistic and potentiating effects that may result in improved clinical benefit.

CheckMate 039 (cohorts A and B) was designed to determine the safety and efficacy of nivolumab-daratumumab combinations in patients with RRMM. Here we report data on the safety and preliminary efficacy of nivolumab-daratumumab (ND) and nivolumab-daratumumab-pomalidomide-dexamethasone (NDPd) combination regimens for the treatment of patients with RRMM. Biomarker data from ND and daratumumab monotherapy (D) treatments are also presented.

2 Methods

2.1 Study design and patients

CheckMate 039 was a multicenter, randomized, open-label phase I/II trial (NCT01592370). In cohort A, patients were aged ≥ 18 years, had received ≥ 2 prior lines of therapy, and had disease that was refractory to lenalidomide and a PI and refractory to the last line of treatment. In cohort B, patients were aged ≥ 18 years, had received ≥ 3 prior lines of therapy including an immunomodulatory agent and a PI, or were refractory to an immunomodulatory agent and a PI. Patients also had ECOG PS scores of 0 or 1, consented to bone marrow aspirate or biopsy, and had measurable disease. Patients were excluded if they had received prior therapy with a PD-1 inhibitor, other checkpoint inhibitor or anti-CD38 mAb, had active plasma cell leukemia, or had a history of central nervous system involvement.

This trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Approval was received from the Institutional Review Board and Independent Ethics Committee, and all patients provided written informed consent.

2.2 Study treatments

Patients in cohort A were randomized 1:1 to receive NDPd or ND until recruitment was terminated in light of the safety concerns arising from other trials using an immunomodulatory agent with a PD-1 inhibitor (15, 16). Cohort B was subsequently opened, with patients randomly assigned 2:1 to receive ND or D (Figure 1). Randomization in both cohorts was performed using an interactive voice response system after informed consent was obtained and screening was complete. Treatment was administered in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, or the patient met other discontinuation criteria.

In cohort A, patients in the ND group received nivolumab 240 mg IV on day 15 in cycle 1, days 1 and 15 in cycles 2–6, and 480 mg IV on day 1 of each subsequent cycle. Daratumumab 16 mg/kg IV was administered on days 1, 8, 15, and 22 in cycles 1 and 2, days 1 and 15 in cycles 3–6, and on day 1 of each subsequent cycle. Patients in the NDPd group received the same ND dosing, plus pomalidomide 4 mg orally (PO) daily on days 1–21 of each cycle and dexamethasone 40 mg PO (20 mg for patients aged > 75 years) on days 1, 8, 15, and 22, in weeks daratumumab was not administered, or 20 mg IV prior to daratumumab and 20 mg PO following daratumumab (16 mg IV and 4 mg PO for patients aged > 75 years).

In cohort B, patients in the ND group received nivolumab 240 mg IV on day 15 of cycle 1, and 480 mg IV on day 1 of cycle 2 and each subsequent cycle. Daratumumab was given as 16 mg/kg IV on days 1, 8, 15, and 22 of cycles 1 and 2, days 1 and 15 of cycles 3–6, and on day 1 of each subsequent cycle. Patients could opt to receive the first daratumumab dose split over 2 days (8 mg/kg for days 1 and 2 of cycle 1). Patients in the D group received the same daratumumab dosing as those in the ND group.

2.3 Endpoints

The primary endpoint was the number of adverse events (AEs), serious adverse events (SAEs), and immune-mediated AEs (IMAEs) from the time of informed consent up to 100 days after the last dose of the study drug. The secondary endpoints were minimal residual disease (MRD) negativity status, overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS). Overall survival (OS) was considered exploratory. Biomarkers were considered exploratory and retrospective.

2.4 Assessments

Safety assessments included assessments of AEs, clinical laboratory tests (hematology, chemistry), vital sign measurements, and physical examination with assessment of ECOG PS. Vital signs, AEs, and laboratory tests were assessed on days 1, 8, 15, and 22 of cycles 1 and 2, days 1 and 15 of cycles 3–6, and day 1 of each subsequent cycle. Physical examination was performed on day 1 of each cycle.

Efficacy was assessed per International Myeloma Working Group criteria and was based on analysis of molecular and cytometry MRD, serum and urine protein electrophoresis (SPEP and UPEP) with immunofixation, serum free light chain (sFLC) (for patients with sFLC-only disease), corrected calcium (serum calcium and serum albumin), imaging, and bone marrow assessments. MRD, SPEP, UPEP, and sFLC assessments were done centrally, while bone lesion, extramedullary plasmacytoma, bone marrow disease, and corrected calcium assessments were done at local

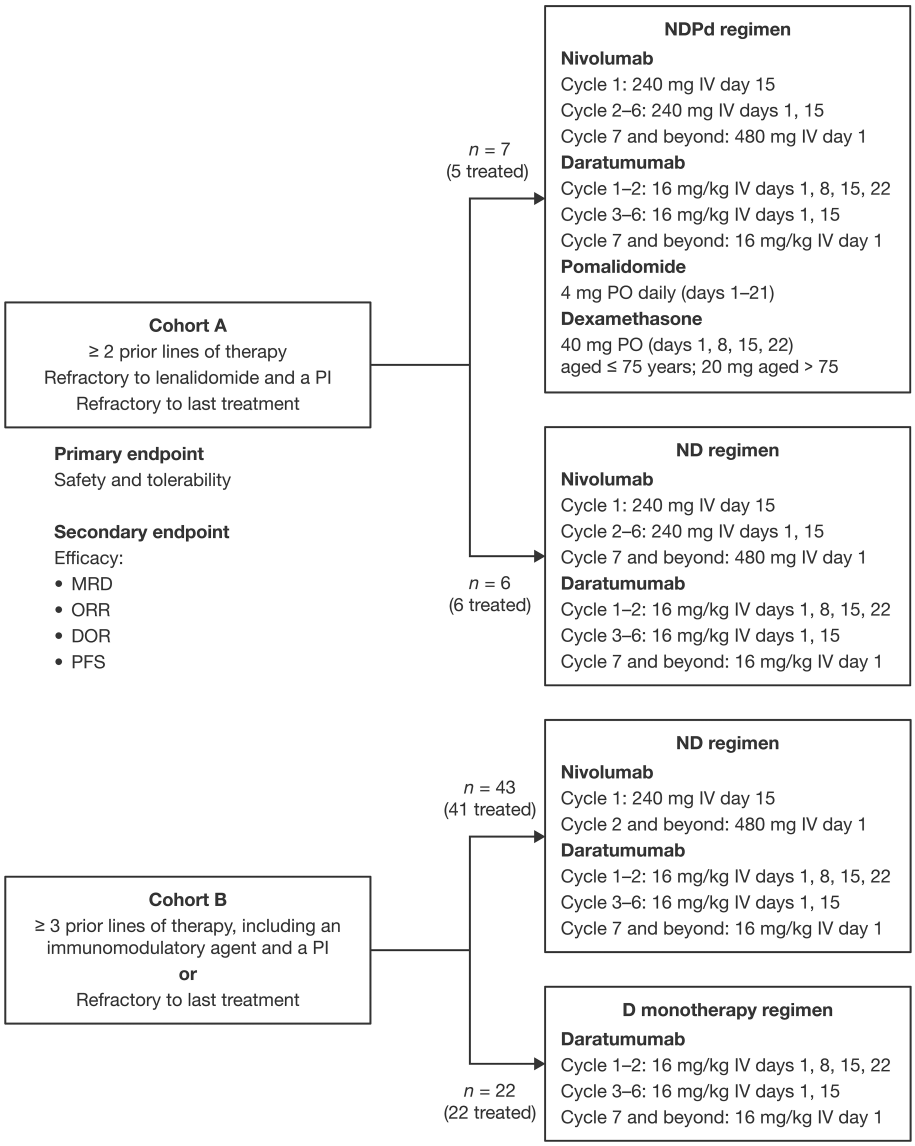

FIGURE 1
Study design. D, daratumumab monotherapy; DOR, duration of response; IV, intravenous; MRD, minimal residual disease; ND, nivolumab-daratumumab; NDPd, nivolumab-daratumumab-pomalidomide-dexamethasone; ORR, overall response rate; PI, proteasome inhibitor; PFS, progression-free survival; PO, orally.

laboratories. MRD was assessed (sensitivity level of 10^{-5}) from bone marrow aspirates collected at screening (next-generation sequencing [NGS]), day 1 of cycle 4 or at achievement of very good partial response (VGPR) or better (whichever occurred first) (NGS and next-generation flow [NGF]), and every 6 cycles until disease progression (NGS and NGF). All other assessments were done on day 1 of every cycle until progression, even if the patient was on subsequent therapy.

2.5 Biomarkers

Sanger method sequencing for Fc gamma receptor (FcγR) single-nucleotide polymorphisms (SNP), whole exome sequencing (WES), RNA-sequencing, gene signature score (GES), and flow cytometry were used to determine potential biomarkers (Supplemental Methods).

2.6 Statistical analysis

The 'treated' population included all patients who received ≥ 1 dose of nivolumab and/or daratumumab; the 'biomarker' population included all 'treated' patients with available biomarker data. An additional 'pooled ND' population was analyzed *post hoc* and encompassed all patients who received ND from cohorts A and B. Patient demographics and baseline characteristics were collected at screening and summarized.

AEs were coded using MedDRA 23.1 and graded according to NCI CTCAE version 4. The exact ORR, DOR, and PFS with a

corresponding 95% confidence interval (CI) were determined per treatment group, with the best overall response tabulated. Kaplan–Meier methodology was used to estimate median DOR and PFS and their 95% CIs. MRD analysis included the frequency of MRD negativity, time to negativity, and persistent negativity for ≥ 6 or 12 months.

For the biomarker analysis, the association between baseline gene expression was evaluated by Spearman's correlation coefficient in patients who received ND or D. The GES used median score as the cutoff to define GES.high and GES.low. The association between OS/PFS and GES was evaluated by Cox regression model for patients who received ND.

The sample size of both cohorts was not powered for statistical hypothesis testing as this was a phase I/II trial to evaluate the safety profile and potential clinical benefit of ND combination therapy.

3 Results

3.1 Patient disposition

Thirteen patients from 5 US sites were randomized in cohort A and 11 were treated (ND, *n* = 6; NDPd, *n* = 5); 2 patients failed to meet eligibility criteria (history of primary biliary cirrhosis, *n* = 1; administrative reason by sponsor, *n* = 1) and were not treated. At data cutoff (September 25, 2020) there was 1 patient in each group continuing with treatment; reasons for discontinuing treatment included disease progression (ND, *n* = 3; NDPd, *n* = 3), patient withdrawal from study (ND, *n* = 1; NDPd, *n* = 1), and maximum clinical benefit (ND, *n* = 1).

A total of 65 patients from 10 sites in the USA, Poland, France, Belgium, and Greece were randomized in cohort B; 63 were treated (ND, *n* = 41; D, *n* = 22). Two randomized patients were not treated due to failing to meet eligibility criteria (ECOG PS > 1, *n* = 1) and investigator decision (patient not eligible for further treatment after bronchopneumonia, *n* = 1). At data cutoff, 7 patients receiving ND and 6 receiving D were on active study treatment. Most patients in cohort B discontinued treatment due to disease progression (ND, *n* = 31, 75.6%; D, *n* = 14, 63.6%).

3.2 Baseline patient demographics and disease characteristics

Baseline demographics and disease characteristics were generally balanced between treatment groups in both cohorts (Table 1; Table S1). In cohort A, patients had a median time from diagnosis of 3.2 years, received a median of 2 (range, 2–7) prior lines of therapy, and 63.6% were double refractory to lenalidomide and a PI. In cohort B, patients had a median time from diagnosis of 5.4 years, received a median of 3 (range, 1–7) prior lines of therapy, and 71.4% were double refractory to lenalidomide and a PI.

Among pooled patients who received ND (*n* = 47), median time since diagnosis was 4.8 (range, 0.6–15.6) years, and 70.2% were double refractory to lenalidomide and a PI (Table S2).

TABLE 1 Baseline demographics and disease characteristics.

Characteristic, *n* (%)	Cohort A			Cohort B		
	ND (*n* = 6)	NDPd (*n* = 5)	Total (*N* = 11)	ND (*n* = 41)	D (*n* = 22)	Total (*N* = 63)
Age, median (range), years	65.5 (57–68)	69.0 (56–82)	67.0 (54–82)	68.0 (45–82)	65.5 (48–81)	68.0 (45–82)
< 75	6 (100.0)	4 (80.0)	10 (91.0)	35 (85.4)	18 (81.8)	53 (84.1)
Sex, male	3 (50.0)	4 (80.0)	7 (63.6)	17 (41.5)	14 (63.6)	31 (49.2)
Race						
White	5 (83.3)	5 (100.0)	10 (90.9)	36 (87.8)	19 (86.4)	55 (87.3)
Black or African American	0	0	0	1 (2.4)	2 (9.1)	3 (4.8)
Other	1 (16.7)	0	1 (9.1)	4 (9.8)	1 (4.5)	5 (7.9)
Time from diagnosis, median (range), years	2.7 (0.9–13.5)	3.8 (2.5–7.7)	3.2 (0.9–13.5)	5.3 (0.6–15.6)	5.7 (0.6–13.6)	5.4 (0.6–15.6)
Prior lines of therapy, median (range)	2 (2–4)	3 (2–7)	2.0 (2–7)	3.0 (1–7)	3.0 (1–7)	3.0 (1–7)
Refractory to prior lines of therapy						
PI	5 (83.3)	3 (60.0)	8 (72.7)	29 (70.7)	17 (77.3)	46 (73.0)
Lenalidomide	5 (83.3)	5 (100.0)	10 (90.9)	38 (92.7)	20 (90.6)	58 (92.1)
Lenalidomide and PI	4 (66.7)	3 (60.0)	7 (63.6)	29 (70.7)	16 (72.7)	45 (71.4)
Last prior therapy	6 (100.0)	5 (100.0)	11 (100.0)	33 (80.5)	15 (68.2)	48 (76.2)
ISS stage III	2 (33.3)	1 (20.0)	3 (27.3)	17 (41.5)	8 (36.4)	25 (39.7)
High-risk cytogenetics[a]	1 (16.7)	1 (20.0)	2 (18.2)	6 (14.6)	4 (18.2)	10 (15.9)
ECOG PS						
0	3 (50.0)	0	3 (27.3)	12 (29.3)	9 (40.9)	21 (33.3)
1	3 (50.0)	5 (100.0)	8 (72.7)	29 (70.7)	13 (59.1)	42 (66.7)

[a]High risk is defined as having any of del(17p) (with 10% cutoff) or (4;14) or t(14;16) chromosomal abnormality.

D, daratumumab monotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; Len, lenalidomide; ND, nivolumab-daratumumab; NDPd, nivolumab-daratumumab-pomalidomide-dexamethasone; PI, proteasome inhibitor.

3.3 Duration of treatment

In cohort A, patients in the ND group had a median duration of treatment of 26.1 and 28.1 weeks for nivolumab and daratumumab, respectively. The duration of treatment was longer for patients in the NDPd group, with a median of 68.3, 73.0, and 71.3 weeks of treatment for nivolumab, daratumumab, and pomalidomide, respectively. In cohort B, the ND group had a median duration of treatment of 30.1 and 32.1 weeks for nivolumab and daratumumab, respectively, and the D group had a median duration of treatment of 22.6 weeks.

3.4 Safety

In cohort A, all patients who received ND (n = 6) or NDPd (n = 5) experienced an AE of any grade (Table 2). Grade 3/4 AEs were reported in 3/6 patients who received ND and all 5 patients who received NDPd. The most common grade 3/4 AEs reported were anemia (3/6 patients) in the ND group and neutropenia (3/5 patients) in the NDPd group. Drug-related grade 3/4 AEs were reported for 2/6 patients in the ND group, who experienced 3 AEs (anemia, n = 1; neutropenia, n = 1; thrombocytopenia, n = 1) and all 5 patients in the NDPd group (including neutropenia, n = 3; upper respiratory tract infection, n = 2; and reduced neutrophil count, n = 2). SAEs were reported for 2/6 patients in the ND group, all of which were grade 3/4, and included pneumonia (n = 1), MM progression (n = 1), and dyspnea (n = 1); these were not considered drug related. All 5 patients who received NDPd experienced SAEs, of which 4 patients experienced grade 3/4 SAEs with only pneumonia (n = 2) occurring in more than 1 patient. None of these SAEs led to treatment discontinuation. Two patients experienced drug-related SAEs, which included peripheral edema (n = 1), pneumonia (n = 1), and upper respiratory tract infection (n = 1). IMAEs were experienced by patients in both treatment groups, the most common being 2 patients in each group experiencing infusion-related reactions. No AEs leading to discontinuation and no grade 5 AEs were reported in cohort A. One patient in the ND group died due to disease progression.

In cohort B, 36 (87.8%) patients who received ND and 21 (95.5%) who received D experienced AEs of any grade. Grade 3/4 AEs were reported in 22 (53.7%) patients in the ND group and 10 (45.5%) patients in the D group. The most common grade 3/4 AEs reported for the ND group were neutropenia (19.5%), thrombocytopenia (9.8%), and anemia (9.8%); in the D group these were anemia and pneumonia (each 9.1%). There were 11 (26.8%) patients in the ND group and 2 (9.1%) in the D group with drug-related grade 3/4 AEs. With ND, these included blood disorders (17.1% [9.8% neutropenia, 7.3% thrombocytopenia, 2.4% anemia, 2.4% granulocytopenia, and 2.4% lymphopenia]), reduced neutrophil count (2.4%), and vertigo (2.4%); with D, these included pneumonia (4.5%) and reduced lymphocyte count (4.5%). Grade 3/4 SAEs were reported in 24.4% of patients in the ND group and 27.3% of patients in the D group. The most common grade 3/4 SAEs reported in the ND and D group were infections (ND group, 14.6% [7.3% bronchitis]; D group, 13.6% [9.1% pneumonia]). There was one grade 3/4 drug-related SAE in each group (ND, vertigo; D, pneumonia). One patient in the D group had a grade 5 sudden cardiac death. IMAEs were recorded in both groups, with 1 grade 3/4 IMAE of enterocolitis reported for the ND group initially treated with antibiotics and an antifungal, followed by steroids. Treatment was not reattempted as enterocolitis developed about 6 weeks after coming off treatment due to disease progression. IMAEs of infusion-related reactions (grade 1/2) were reported for 10 patients in the ND group and 2 patients in the D group, and included chills, cough, shortness of breath, and flushing. AEs for 4 patients in the ND group (due to disease progression) and 2 patients in the D group (pneumonia, n = 1; pulmonary embolism, n = 1) led to study drug discontinuation. There were 8 deaths in the ND group, 7 from disease progression and 1 from influenza A, and 6 deaths in the D group due to disease progression (n = 3), sudden cardiac death (n = 1), multi-organ failure (n = 1), and pulmonary embolism (n = 1). None of the deaths were considered related to the study treatment, as assessed by the investigator.

The safety data for the pooled ND-treated population reflected the AE rates reported for the individual cohorts (Table S4).

3.5 Efficacy

In cohort A, the median follow-up duration was 30.6 months for ND and 41.5 months for NDPd. Four out of 6 treated patients in the ND group achieved a response, while all 5 patients in the NDPd group responded, with 1 patient in each group having achieved a complete response (CR) (Table 3). A median PFS (mPFS) of 7.6 months was achieved with ND and 17.0 months with NDPd; median DOR and OS were not reached, and the 1-year OS was 100% in both treatment groups. However, due to the small patient numbers, interpretation of the PFS and OS data should be undertaken with caution. With ND, 1 patient died at 22.5 months, and the other 5 patients were censored at 2.0, 15.4, 38.7, 42.5, and 43.7 months. With NDPd, no deaths were reported, and all were censored after 3 years (range, 37.3–44.5 months).

In the ND group, MRD negativity was observed in 1 of 3 NGS MRD-evaluable patients but was not observed in the single NGF MRD-evaluable patient. In the NDPd group, MRD negativity was not observed in either of the 2 NGS MRD-evaluable patients but was observed in 1 of 3 NGF MRD-evaluable patients. MRD negativity persisted for 7 months in the ND patient and 35 months in the NDPd patient.

In cohort B, the median duration of follow-up was 14.3 months for ND and 12.6 months for D. Patients who received ND achieved an ORR of 53.7%, with 10/41 (24.4%) having achieved deep responses of ≥ VGPR (Table 3). The median DOR among the 22 responders was 7.2 (95% CI, 4.0–16.6) months. Patients in the D group achieved an ORR of 40.9%, with 6/22 (27.3%) having achieved deep responses of ≥ VGPR. The median DOR among the 9 responders was not reached. mPFS was 6.6 months in both groups (Table 3; Figure 2). Median OS was not reached, and the 1-year OS was 81.3% (95% CI, 64.6–90.6) and 71.2% (95% CI, 46.6–86.0) in the ND and D groups, respectively. Survival data beyond 1 year are not reported as the minimum follow-up for cohort B was only 1 year. There were 8/41 (19.5%) patients who received ND and 6/22 (27.3%) who received D who had died at the time of the data cutoff.

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TABLE 2 Select adverse events reported for patients in cohorts A and B.

Adverse events, *n* (%)	Cohort A				Cohort B			
	ND (*n* = 6)		NDPd (*n* = 5)		ND (*n* = 41)		D (*n* = 22)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Total patients with an AE[a]	6 (100.0)	3 (50.0)	5 (100.0)	5 (100.0)	36 (87.8)	22 (53.7)	21 (95.5)	10 (45.5)
Anemia	4 (66.7)	3 (50.0)	4 (80.0)	0	9 (22.0)	4 (9.8)	4 (18.2)	2 (9.1)
Neutropenia	1 (16.7)	1 (16.7)	4 (80.0)	3 (60.0)	9 (22.0)	8 (19.5)	1 (4.5)	0
Thrombocytopenia	1 (16.7)	1 (16.7)	1 (20.0)	0	5 (12.2)	4 (9.8)	1 (4.5)	1 (4.5)
Pneumonitis	1 (16.7)	0	0	0	1 (2.4)	0	0	0
Angina pectoris	0	0	1 (20.0)	0	0	0	0	0
Diarrhea	1 (16.7)	0	4 (80.0)	1 (20.0)	6 (14.6)	1 (2.4)	3 (13.6)	0
Upper respiratory tract infection	2 (33.3)	0	4 (80.0)	2 (40.0)	8 (19.5)	0	3 (13.6)	0
Bronchitis	1 (16.7)	0	0	0	8 (19.5)	3 (7.3)	0	0
Pneumonia	1 (16.7)	1 (16.7)	3 (60.0)	2 (40.0)	3 (7.3)	1 (2.4)	3 (13.6)	2 (9.1)
Infusion-related reaction	2 (33.3)	0	2 (40.0)	0	10 (24.4)	0	4 (18.2)	0
Pruritus	1 (16.7)	0	4 (80.0)	0	3 (7.3)	0	0	0
Hypothyroidism	1 (16.7)	0	0	0	1 (2.4)	0	0	0
Total patients with an SAE[a]	2 (33.3)	2 (33.3)	5 (100.0)	4 (80.0)	12 (29.3)	10 (24.4)	8 (36.4)	6 (27.3)
Anemia	1 (16.7)	1 (16.7)	0	0	0	0	0	0
Dyspnea	1 (16.7)	1 (16.7)	0	0	1 (2.4)	1 (2.4)	0	0
Hypoxia	1 (16.7)	1 (16.7)	0	0	0	0	0	0
Pneumonitis	1 (16.7)	0	0	0	1 (2.4)	0	0	0
Pneumonia	1 (16.7)	1 (16.7)	2 (40.0)	2 (40.0)	1 (2.4)	1 (2.4)	3 (13.6)	2 (9.1)
MM progression	1 (16.7)	1 (16.7)	0	0	4 (9.8)	3 (7.3)	0	0
Specific IMAEs[b]								
Infusion-related reaction	2 (33.3)	0	2 (40.0)	0	10 (24.4)	0	4 (18.2)	0
Hypothyroidism	1 (16.7)	0	0	0	1 (2.4)	0	0	0
Diarrhea	1 (16.7)	0	4 (80.0)	1 (20.0)	6 (14.6)	1 (2.4)	4 (18.2)	0
Enterocolitis	0	0	0	0	1 (2.4)	1 (2.4)	0	0
Adrenal insufficiency	0	0	0	0	3 (7.3)	0	0	0
Rash	0	0	1 (20.0)	0	2 (4.9)	0	1 (4.5)	0

[a]There was a single instance of a grade 5 AE/SAE for one patient who had a sudden cardiac death in the D group of cohort B.
[b]There was no total value for patients with an IMAE available, so only the number of patients with specific IMAE were listed.
AE, adverse event; D, daratumumab monotherapy; IMAE, immune-mediated adverse event; ND, nivolumab-daratumumab; NDPd, nivolumab-daratumumab-pomalidomide-dexamethasone; SAE, serious adverse event.

In the ND group, MRD negativity was observed in 6/25 (24.0%) NGS MRD-evaluable patients and in 6/27 (22.2%) NGF MRD-evaluable patients (MRD negativity by both NGS and NGF was documented in 3 patients). In the D group, MRD negativity was observed in 0/11 NGS MRD-evaluable patients and in 1/16 (6.3%) NGF MRD-evaluable patients (Table 3). Persistent MRD negativity for ≥ 6 months was observed in 4 patients (1 via NGS, 3 via NGF) in the ND group and 1 patient in the D group (via NGF).

For the pooled ND-treated population, ORR was 55.3%, with 4 patients (8.5%) having achieved a CR/stringent CR (sCR) (Table

S3). The median DOR and PFS among the pooled ND population were 7.2 months and 6.6 months, respectively. MRD negativity for evaluable patients was 25.0% when determined by NGS and 21.4% by NGF.

3.6 Biomarkers

Biomarker data were available for a subset of patients treated with ND (n = 47; cohort A, n = 6; cohort B, n = 41) or D (n = 22, cohort B only). Somatic mutation data, obtained from 19 of 47 ND-treated patients, showed that *KRAS* was the most frequently mutated gene, with more *KRAS* mutations detected in responders (5/11, 45.5%) than in non-responders (2/8, 25%) (Figure 3A). No *KRAS* mutations were detected in the D group (data available for 9 of 22 patients). Analysis of RNA gene expression by evaluating gene set enrichment of HALLMARK gene sets from the Molecular Signatures Database (MSigDB; Broad Institute, Inc., Cambridge, MA) in the ND group indicated that HALLMARK.KRAS.UP-high patients showed a trend of better OS compared with HALLMARK.KRAS.UP-low patients, but no trends were associated with PFS (Figure S1). There were no trends identified in the D group. In a similar analysis on pre-treatment tumor samples (ND, n = 14; D, n = 6), statistically significant gene sets that were differentially enriched based on response were analyzed (Figure 3B). Two of the most enriched gene sets in samples from patients who achieved VGPR or better response were the HALLMARK_KRAS_SIGNALLING_UP and HALLMARK_MYC_TARGETS_V2 gene sets. The HALLMARK_KRAS_SIGNALLING_UP gene set was enriched among patients who achieved VGPR or better compared with patients who achieved partial response (PR) or less, which is consistent with the association observed between *KRAS* mutation and response (Figures 3B, C). The gene set most enriched in VGPR or better pre-treatment samples was HALLMARK_MYC_TARGETS_V2 (Figures 3B, D), while the gene set with the largest negative enrichment score in PR or less pre-treatment samples was ISG_RS (Figures 3B, E).

FcγR polymorphisms showed that patients in the ND group with *FCGR2A*-131 H/R or *FCGR3A*-158 F/F genotypes had a slight trend towards better ORR than other *FCGR2A*-131 or *FCGR3A*-158 genotypes (Figure S2). However, the analysis was not powered to evaluate associations between FcγR polymorphisms and PFS. No similar ORR trend was observed in the D group. Immunophenotyping analysis by flow cytometry indicated a trend towards natural killer (NK) cell depletion in response to daratumumab in the D and ND groups (data not shown). Single cell RNAseq (scRNAseq) data from peripheral blood mononuclear cells (PBMCs) taken at baseline indicated a higher number of NK cells in responders compared with non-responders in both the ND and D groups (data not shown). There were no significant associations observed between fluorescence *in situ* hybridization and prognosis, tumor mutational burden and prognosis or other factors, or serum cytokine and clinical response (data not shown).

4 Discussion

In this phase I/II trial of patients with RRMM, ND therapy showed numerically higher ORR and comparable PFS versus D, with an encouraging level of MRD negativity achieved in the ND group of cohort B. Combination therapies were well tolerated, with few AEs leading to discontinuation of treatment and toxicities being manageable and within the expected profile of the individual agents. Despite the small sample size, the addition of pomalidomide and dexamethasone to ND demonstrated an efficacy signal comparable to ND. Although a small number of patients were treated with an immune checkpoint inhibitor and immunomodulatory agent combination (i.e., NDPd) in this study, no new safety concerns were observed in the limited number of patients who were enrolled prior to cohort closure, even with the long follow-up of 41.5 months, despite patients having a numerically higher number of grade 3/4 AEs and SAEs compared with ND.

The ND combination regimens were well tolerated in both cohorts. In cohort A there were no patient discontinuations due to AEs; a single death due to disease progression occurred in the ND group. There were numerically more AEs and SAEs in the NDPd group, most notably cytopenias, infections, diarrhea, and pruritus, compared with the ND group. These differences were likely a reflection of pomalidomide being part of this combination regimen, as these AEs are consistent with its known safety profile (25, 26). While excess cardiac AEs and mortality were identified in the KEYNOTE-183 and -185 trials, there did not appear to be any unifying causes of death or unique AE patterns that could be attributed to the experimental arms of these studies (15, 16, 27). Furthermore, there was no evidence in the KEYNOTE-183 or -185 studies demonstrating that adding pembrolizumab to an immunomodulatory agent accelerated MM progression. Although a limited number of patients were treated with NDPd in cohort A of this study, with a minimum of 37 months, there were no excess grade ≥ 3 cardiac events or deaths reported compared with the immunomodulatory agent-free combination of ND. In this cohort, the safety profile of NDPd was manageable. Overall, these findings do not support a mechanism of action effect due to the checkpoint inhibitor and immunomodulatory agent combination, but due to the small numbers within the NDPd group, interpretation is limited.

In cohort B, the rates of AEs and SAEs were similar between treatment groups, and reflective of the known safety profile of nivolumab and daratumumab. Further, the rate of discontinuations due to the study drugs was low and none of the deaths were related to the study drugs.

All patients in the NDPd group of cohort A (n = 5) responded to treatment, compared with 4/6 (66.7%) patients in the ND group. While these efficacy data are encouraging, no definitive conclusions can be drawn due to the small cohort size (n = 11) and no DPd group as a comparison.

In cohort B, response rates were numerically higher in the ND group compared with the D group, and the ND group had

TABLE 3 Efficacy results for cohort A and cohort B.

Outcome	Cohort A		Cohort B	
	ND (*n* = 6)	NDPd (*n* = 5)	ND (*n* = 41)	D (*n* = 22)
Overall response rate, *n* (%) (95% CI)	4 (66.7) (22.3–95.7)	5 (100.0) (47.8–100.0)	22 (53.7) (37.4–69.3)	9 (40.9) (20.7–63.6)
Best overall response, *n* (%)				
Stringent complete response	0	0	2 (4.9)	0
Complete response	1 (16.7)	1 (20.0)	1 (2.4)	1 (4.5)
Very good partial response	2 (33.3)	1 (20.0)	7 (17.1)	5 (22.7)
Partial response	1 (16.7)	3 (60.0)	12 (29.3)	3 (13.6)
Minimal response	0	0	2 (4.9)	1 (4.5)
Stable disease	2 (33.3)	0	11 (26.8)	10 (45.5)
Progressive disease	0	0	6 (14.6)	1 (4.5)
Duration of response, median (95% CI), months	NA (6.5–NA)	NA (9.30–NA)	7.2 (4–16.6)	NA (2.2–NA)
Progression-free survival, median (95% CI), months	7.6 (3.2–NA)	17.0 (NA–NA)	6.6 (4.7–10.3)	6.6 (3.0–12.8)
Overall survival, median (95% CI), months	NA (22.5–NA)	NA	NA	NA (11.9–NA)
MRD negativity by NGS				
Evaluable patients	3	2	25	11
Patients with MRD negativity,[a] *n* (%)	1 (33.3)	0	6 (24.0)	0
Time to first negativity, median (range), months	3.0 (3.0–3.0)	–	2.8 (1.8–13.9)	–
Duration of negativity, median (range), months	7.0 (7.0–7.0)	–	5.6 (0.0–11.5)	–
Persistent negativity for ≥ 6 months,[b] *n* (%)	1 (100)	–	1 (16.7)	–
Persistent negativity for ≥ 12 months,[b] *n* (%)	0	–	0	–
MRD negativity by NGF				
Evaluable patients	1	3	27	16
Patients with MRD negativity,[a] *n* (%)	0	1 (33.3)	6 (22.2)	1 (6.3)
Time to first negativity, median (range), months	–	7.4 (7.4–7.4)	2.9 (0.8–14.8)	2.9 (2.9–2.9)
Duration of negativity, median (range), months	–	NA (34.9–34.9)	NA (0.00–11.1)	9.9 (9.9–9.9)
Persistent negativity for ≥ 6 months,[b] *n* (%)	–	1 (100.0)	3 (50.0)	1 (100.0)
Persistent negativity for ≥ 12 months,[b] *n* (%)	–	1 (100.0)	0	0

[a]Percentages were based on the number of evaluable patients.
[b]Percentages were calculated based on the number of patients with a response.
CI, confidence interval; D, daratumumab monotherapy; MRD, minimal residual disease; NA, not available; ND, nivolumab-daratumumab; NDPd, nivolumab-daratumumab-pomalidomide-dexamethasone; NGF, next generation flow; NGS, next generation sequencing.

encouraging MRD negativity levels. However, mPFS was comparable between the two groups. The lack of difference in the mPFS, despite the higher ORR with the ND group, was potentially due to only 10/22 (45.5%) patients in the ND group compared with 6/9 (66.7%) in the D group achieving a ≥ VRPR, resulting in a shorter PFS in those who had a PR. The longer mPFS observed in the D group compared with that in the daratumumab monotherapy registrational SIRIUS trial may be attributable to the more favorable baseline disease characteristics of the patients in this study (CheckMate 039 vs SIRIUS: median lines of prior therapy, 3 vs 5; double-refractory patients, 73% vs 95%) (28). In general, this study did not demonstrate that combining nivolumab and daratumumab improves clinical outcome compared with daratumumab monotherapy, despite prior data indicating PD-1/PD-L1 combined with daratumumab could increase responses (29, 30).

In the pooled ND population, ORR and safety data were in line with the individual cohorts, with only minor differences in the number of previous lines of therapy and the dosing of nivolumab. The ORR in the combined ND group in this trial was 55.3%, while the ORR in the D group was 40.9%. A previous trial that evaluated nivolumab monotherapy in 27 patients with MM reported stable disease as the best response achieved (in 63% of patients) (11). These data suggest potential better response rates for the ND combination compared with each agent alone. However, no conclusions can be drawn from this small trial, which was not designed to compare the two regimens.

The biomarker analyses were exploratory and performed retrospectively to assess multiple objectives including disease monitoring, surrogate clinical endpoints, risk stratification, identification of potential subgroups, and response predictions. The main biomarker findings of interest focused on *KRAS* mutations and RNA expression. With respect to RNA gene expression, HALLMARK_KRAS_SIGNALLING was enriched among responders, with a trend of better OS in HALLMARK.KRAS.UP-high patients compared with HALLMARK.KRAS.UP-low patients in the ND group. Similarly, *KRAS* was shown to be the most frequently mutated gene, and *KRAS* mutations were more prevalent in ND responders compared with non-responders. This suggested that either a more heavily mutated *KRAS* population was controlled just as effectively with ND compared with D alone, the 2:1 randomization for ND:D presented opportunities for more patients with *KRAS* mutations to enroll to the ND group at trial start, or the data were skewed due to having limited sample numbers. While the slight differences in response rates between ND and D could be related to

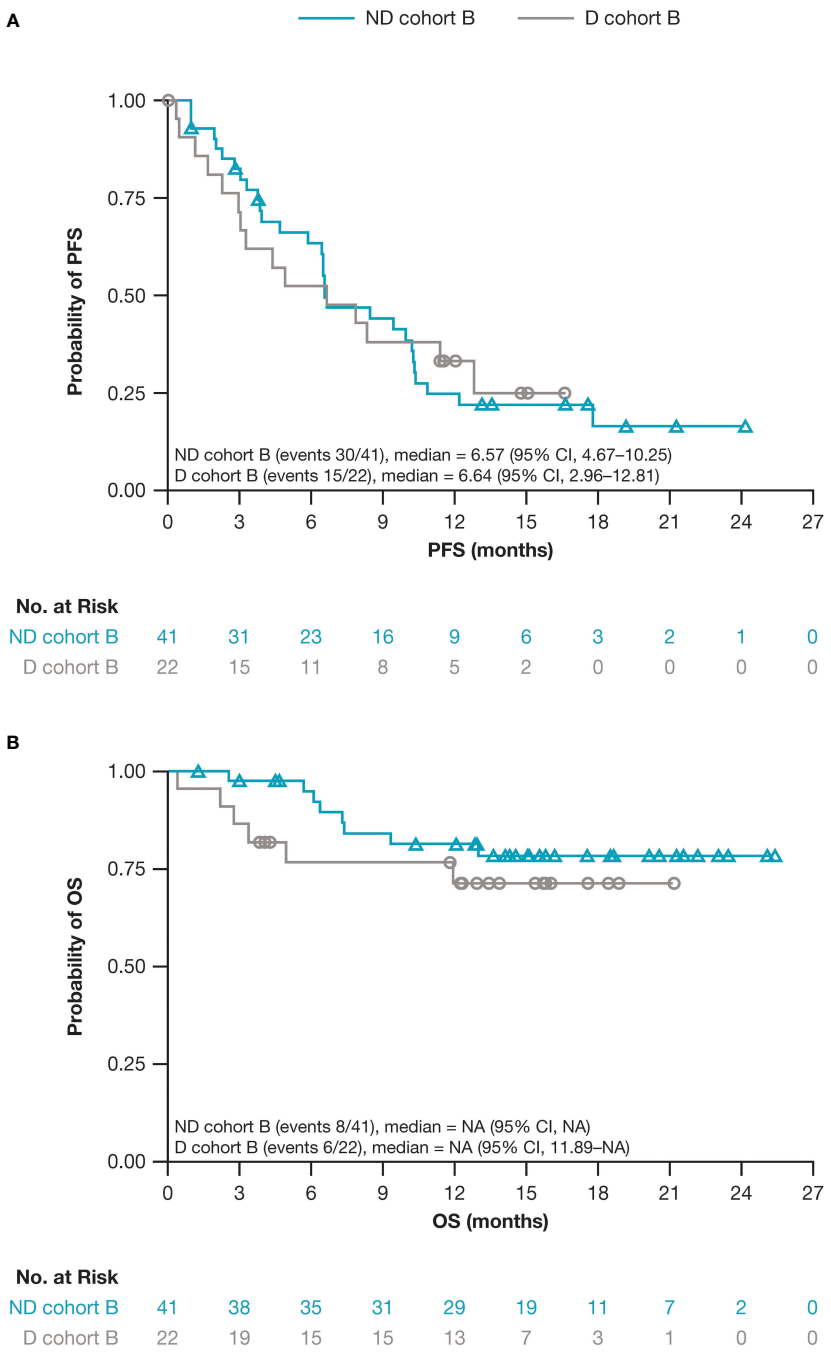

FIGURE 2
Kaplan–Meier estimates for **(A)** PFS and **(B)** OS for patients who received ND versus D in cohort B. CI, confidence interval; D, daratumumab monotherapy; NA, not available; ND, nivolumab-daratumumab; OS, overall survival; PFS, progression-free survival.

KRAS mutations detected in the ND group, this is speculative. However, this interpretation is interesting given the role that neoantigens play in generating antitumor activity. Specifically, it has been demonstrated that shared neoantigens are detectable in *KRAS* in patients with RRMM, with neoantigen-specific T-cell expansion having been associated with antitumor activity *in vitro* and clinical response *in vivo* (31). Additionally, a recent study in lung cancer demonstrated that *KRAS* mutations correlated with superior efficacy of PD-1 inhibitors (32). In addition to HALLMARK_KRAS_SIGNALLING, the enrichment of HALLMARK_MYC_TARGETS_V2 in pre-treatment samples for patients who achieved a VGPR or better is consistent with published data describing *MYC* regulation of the antitumor immune response through anti-CD47 and PD-L1 (33). In contrast, enrichment of ISG_RS in pre-treatment samples in patients who achieved a PR or less is consistent with data in melanoma and lung cancer demonstrating an association between interferon-stimulated genes and resistance to checkpoint blockade (34).

FCGR2A-131 H/R or *FCGR3A*-158 F/F FcγR polymorphisms were associated with better ORR in the ND group compared with D. However, the analysis was not powered to evaluate associations

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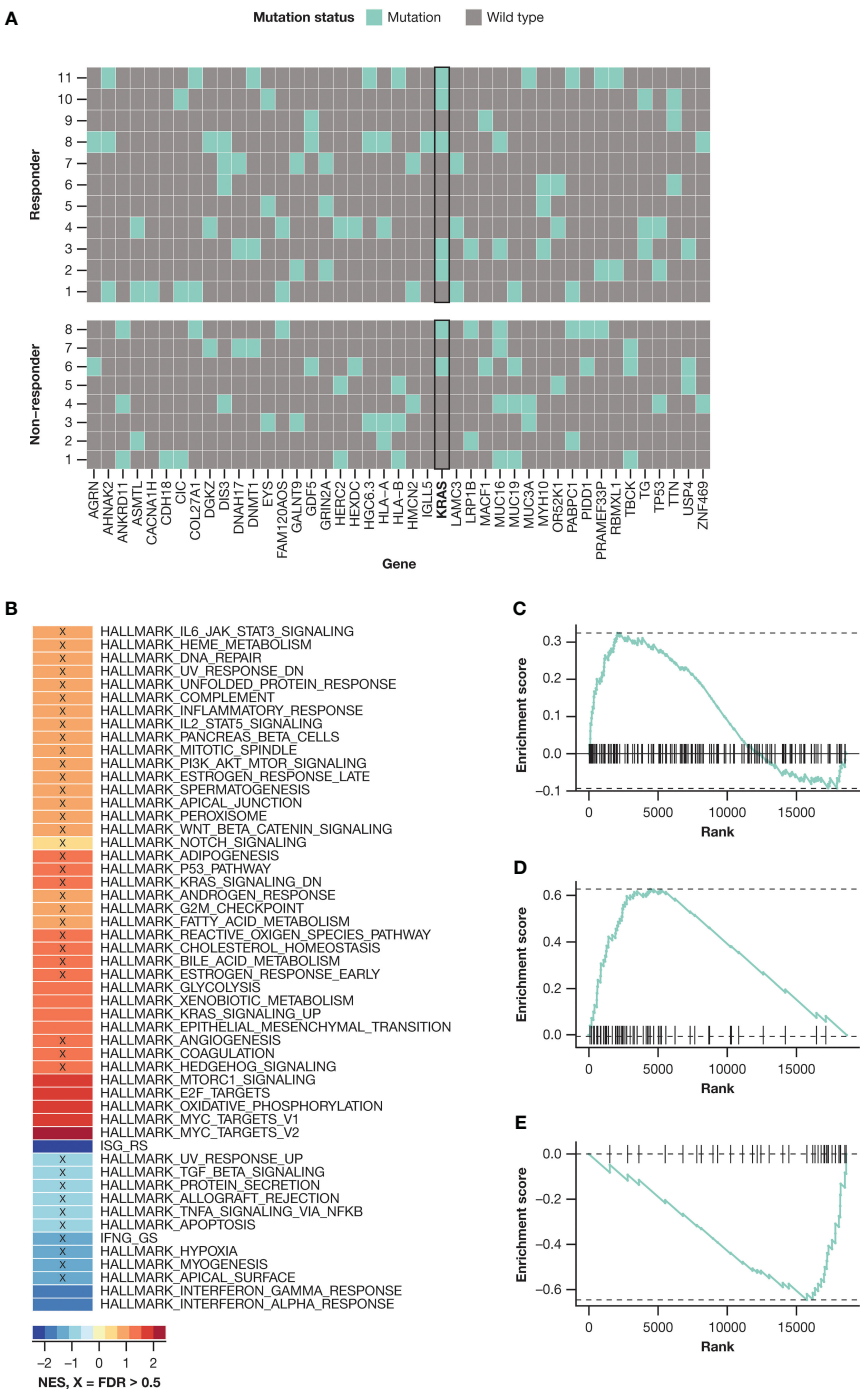

FIGURE 3
KRAS activation: **(A)** *KRAS* mutation prevalence in the ND group; **(B)** gene set enrichment analysis evaluating Hallmark gene set collections from MSigDB on CD138-selected cells collected at baseline, comparing patients achieving ≥ VGPR with those achieving < VGPR; gene set enrichment graphs for **(C)** KRAS_SIGNALLING_UP gene set, **(D)** MYC_TARGETS_V2 gene set, and **(E)** ISG_RS gene set. FDR, false discovery rate; ND, nivolumab-daratumumab; NES, normalized enrichment score; VGPR, very good partial response.

between FcγR polymorphisms and PFS. Although *FCGR2A*/*FCGR3A* polymorphisms have been demonstrated to influence clinical outcome in patients with MM treated with daratumumab monotherapy (35), and other cancers and interactions with some cancer treatments (36–38), the significance of the association between *FCGR2A*-131 H/R or *FCGR3A*-158 F/F FcγR polymorphisms and improved ORR in our study and its effect on PFS are unclear.

Immunophenotyping by flow cytometry did not demonstrate appreciable differences between ND and D (data not shown), consistent with the clinical narrative. However, the differences

observed were consistent with the activity of daratumumab on NK cells with no additive effect of nivolumab to daratumumab. Higher baseline NK cell numbers in PBMCs from scRNAseq data also seemed to trend with responders in both ND and D cohorts compared to non-responders, consistent with the activity of daratumumab.

The trial was limited by its small sample size and that it was not powered for statistical comparisons between treatment groups in either cohort. While the results in cohort A suggest promising efficacy with no new safety signals for the NDPd combination, the small sample size and lack of a DPd control group did not allow robust assessment. Additionally, while the median follow-up duration for cohort A was over 30 months, cohort B had a relatively short median follow-up period of just over 12 months. A longer duration of follow-up and further analyses would allow more accurate assessment of PFS, calculation of median DOR and OS, and determine any long-term cumulative side effects. The median OS was not reached for all treatment groups, which limits the ability to compare the regimens to similar combination therapy trials. Finally, the biomarker data were not sufficient to evaluate the potential mechanism of action via which nivolumab may overcome daratumumab resistance.

In conclusion, although recruitment of cohort A was halted due to safety concerns observed in other trials investigating the combination of a PD-1–targeted immune checkpoint inhibitor agent plus an immunomodulatory agent, there were no new safety signals reported with the NDPd combination despite a higher number of grade 3/4 and serious AEs compared with ND. The efficacy observed in the NDPd treatment group was encouraging but limited by the small sample size and lack of a control arm. The ND combinations in both cohorts were well tolerated with manageable toxicity and few AEs leading to discontinuation. The ND combination showed numerically higher ORR but equivalent PFS compared with D, while the OS was not reached. A longer follow-up period will be required to determine any clinical benefits to OS.

Data availability statement

The datasets presented in this article are not readily available in order to protect patient confidentiality and maintain privacy. Bristol Myers Squibb policy on data sharing and how to request access to the datasets may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html. Requests to access the datasets should be directed to https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

Ethics statement

Approval was received from the Institutional Review Board and Independent Ethics Committee at each study site. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

A-OA: Investigation, Writing – review/editing. AL: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review/editing. TW: Investigation, Writing – review/editing. KJ: Investigation, Writing – review/editing. DD: Investigation, Methodology, Writing – review/editing. CT: Investigation, Writing – review/editing. AS: Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review/editing. XL: Conceptualization, Investigation, Writing – review/editing. RS: Investigation, Writing – review/editing. AK: Investigation, Supervision, Writing – review/editing. SK: Investigation, Methodology, Supervision, Writing – review/editing. MG: Investigation, Writing – review/editing. JL: Investigation, Writing – original draft, Writing – review/editing. Y-MJ: Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – review/editing. MB: Data curation, Writing – original draft, Writing – review/editing. PD: Data curation, Writing – original draft, Writing – review/editing. YW: Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review/editing. KD: Data curation, Formal analysis, Methodology, Visualization, Writing – review/editing. NS: Data curation, Formal analysis, Investigation, Methodology. DP: Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review/editing. RM-M: Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review/editing. KM: Formal analysis, Visualization, Writing – review/editing. MD: Investigation, Writing – review/editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author AS declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frhem.2023.1244494/full#supplementary-material

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