rapid communication

Nivolumab Alone and With Ipilimumab in Previously Treated Metastatic Urothelial Carcinoma: CheckMate 032 Nivolumab 1 mg/kg Plus Ipilimumab 3 mg/kg Expansion Cohort Results

Padmanee Sharma, MD, PhD[1]; Arlene Siefker-Radtke, MD[1]; Filippo de Braud, MD[2]; Umberto Basso, MD[3]; Emiliano Calvo, MD, PhD[4]; Petri Bono, MD, PhD[5,6]; Michael A. Morse, MD[7]; Paolo A. Ascierto, MD[8]; Jose Lopez-Martin, MD, PhD[9]; Peter Brossart, MD[10]; Kristoffer Rohrberg, MD, PhD[11]; Begoña Mellado, MD, PhD[12]; Bruce S. Fischer, MD[13]; Stephanie Meadows-Shropshire, PhD[13]; Abdel Saci, PhD[13]; Margaret K. Callahan, MD, PhD[14,15]; and Jonathan Rosenberg, MD[14,15]

abstract

PURPOSE CheckMate 032 is an open-label, multicohort study that includes patients with unresectable locally advanced or metastatic urothelial carcinoma (mUC) treated with nivolumab 3 mg/kg monotherapy every 2 weeks (NIVO3), nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks (NIVO3+IPI1), or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks (NIVO1+IPI3). We report on the expanded NIVO1+IPI3 cohort and extended follow-up for the NIVO3 and NIVO3+IPI1 cohorts.

METHODS Patients with platinum-pretreated mUC were enrolled in this phase I/II multicenter study to receive NIVO3, NIVO3+IPI1, or NIVO1+IPI3 until disease progression or unacceptable toxicity. Primary end point was investigator-assessed objective response rate per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, including duration of response.

RESULTS Seventy-eight patients were treated with NIVO3 (minimum follow-up, 37.7 months), 104 with NIVO3+IPI1 (minimum follow-up, 38.8 months), and 92 with NIVO1+IPI3 (minimum follow-up, 7.9 months). Objective response rate was 25.6%, 26.9%, and 38.0% in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively. Median duration of response was more than 22 months in all arms. Grade 3 or 4 treatment-related adverse events occurred in 21 (26.9%), 32 (30.8%), and 36 (39.1%) patients treated with NIVO3, NIVO3+IPI1, and NIVO1+IPI3, respectively. Grade 5 treatment-related pneumonitis occurred in one patient each in the NIVO3 and NIVO3+IPI1 arms.

CONCLUSION With longer follow-up, NIVO3 demonstrated sustained antitumor activity alone and in combination with ipilimumab. NIVO1+IPI3 provided the greatest antitumor activity of all regimens, with a manageable safety profile. This result not only supports additional study of NIVO1+IPI3 in mUC, but demonstrates the potential benefit of immunotherapy combinations in this disease.

J Clin Oncol 37:1608-1616. © 2019 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on March 29, 2019 and published at jco.org on May 17, 2019: DOI https://doi.org/10.1200/JCO.19.00538

Processed as a Rapid Communication manuscript.

Clinical trial information: NCT01928394.

INTRODUCTION

Immunotherapies have become a standard of care for previously treated metastatic urothelial carcinoma (mUC).[1] Programmed death 1 (PD-1) immune checkpoint inhibitor nivolumab is approved as monotherapy for patients with locally advanced or mUC who experienced progression after platinum-containing chemotherapy.[2] In the single-arm, phase II CheckMate 275 trial, nivolumab demonstrated a clinically meaningful objective response rate (ORR) of 20.4%, median overall survival (OS) of 8.6 months, 1-year OS rate of 40%, and a tolerable safety profile with median follow-up of 24.5 months.[3]

Other immunotherapy monotherapies for platinum-resistant mUC include pembrolizumab, atezolizumab, durvalumab, and avelumab,[1] with reported median OS ranging from 6.5 months to 18.2 months and ORR ranging from 13.4% to 21.1% in programmed death ligand 1 (PD-L1) unselected patients.[4-8] Of phase III trials reported in this setting, OS benefit was observed in one study of pembrolizumab versus investigator's choice of chemotherapy.[4,9] The clear benefits observed with immune checkpoint monotherapies demand investigation of how outcomes might be improved with combination therapies.

Combination treatments are under investigation in mUC to optimize the antitumor effects of immune checkpoint inhibition.[10] Combined inhibition of PD-1 and cytotoxic T-lymphocyte antigen-4 with nivolumab and ipilimumab has demonstrated benefit in several tumor types.[11-14] This treatment is approved for the treatment of patients with microsatellite instability–high or mismatch repair–deficient metastatic colorectal cancers that have progressed after combination therapy with fluoropyrimidine, oxaliplatin, and irinotecan, as well as intermediate- and poor-risk patients with previously untreated advanced renal cell carcinoma (RCC) and in patients with previously untreated metastatic melanoma.[2,15]

CheckMate 032 evaluates several advanced tumor types.[16] Patients in the locally advanced or metastatic platinum-pretreated urothelial carcinoma (UC) cohort received nivolumab monotherapy (nivolumab 3 mg/kg every 2 weeks [NIVO3]) or one of two nivolumab plus ipilimumab combination regimens (nivolumab 3 mg/kg + ipilimumab 1 mg/kg [NIVO3+IPI1] every 3 weeks for four doses followed by nivolumab monotherapy maintenance or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg [NIVO1+IPI3] every 3 weeks for four doses followed by nivolumab monotherapy maintenance). Interim results for patients with mUC who received NIVO3 (minimum follow-up, 9 months),[16] outcomes with NIVO3 after longer follow-up (minimum follow-up, 24 months),[17] and initial results for the combination treatment arms (minimum follow-up, 3.9 months [NIVO1+IPI3] and 14.5 months [NIVO3+IPI1])[18] have been reported. Here, we report the results from CheckMate 032 with extended follow-up data from all three treatment arms (minimum follow-up, 37.7 months, 38.8 months, and 7.9 months in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively).

METHODS

Study Design and Participants

CheckMate 032 is a multicenter, open-label, multiarm, phase I/II trial.[16] Patients in the UC cohort were enrolled at 38 sites in eight countries. Eligible patients were age 18 years or older with histologically or cytologically confirmed UC of the renal pelvis, ureter, bladder, or urethra; had experienced disease progression after receiving one or more previous platinum-based chemotherapy for metastatic or locally advanced unresectable disease; had experienced recurrence within 1 year of completing platinum-based neoadjuvant or adjuvant treatment; or had refused standard treatment with chemotherapy for metastatic or locally advanced unresectable disease. Patients had Eastern Cooperative Oncology Group performance status of 0 or 1 and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Key exclusion criteria were active brain metastases, history of or active autoimmune disease, conditions that required systemic corticosteroids (> 10 mg per day prednisone equivalent), and any prior treatment with experimental antitumor vaccines or a modulator of T-cell function or immune checkpoint pathway.

Patients in the UC cohort were assigned to treatment with either NIVO3, NIVO3+IPI1, or NIVO1+IPI3. Patients were randomly assigned among treatment arms that were open at the time of enrollment. The NIVO1+IPI3 arm was later expanded via protocol amendment. Additional patients were enrolled in this arm after enrollment was closed for the NIVO3 and NIVO3+IPI1 arms.

The protocol was approved by the institutional review board or independent ethics committee at each site and conducted in accordance with Good Clinical Practice guidelines according to International Conference on Harmonisation guidelines. All patients provided written informed consent to participate, per the Declaration of Helsinki.

Procedures

Patients received treatment with NIVO3, NIVO3+IPI1, or NIVO1+IPI3 until disease progression or unacceptable toxicity. Dose reductions were not permitted. Treatment beyond disease progression was permitted if a patient tolerated study treatment and experienced investigator-assessed clinical benefit. Patients in the NIVO3 arm could switch to NIVO3+IPI1 or NIVO1+IPI3 combination treatment after disease progression if they met protocol-specified criteria. Patients who achieved an initial objective response that lasted 3 or more months could hold treatment. In the case of subsequent progression, patients could undergo re-exposure with the combination treatment if they achieved an initial objective response or stable disease that lasted 3 or more months, had subsequent documented disease progression, and met other predefined criteria.

Tumor assessments were performed using computed tomography or magnetic resonance imaging at baseline, every 6 weeks (±1 week) from the first dose for the first 24 weeks, then every 12 weeks (±1 week) thereafter. Assessments were completed by the investigator, per RECIST v1.1. Safety assessments were completed continuously. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Tumor PD-L1 expression was assessed retrospectively from mandatory tumor biopsies using the Dako PD-L1 immunohistochemical 28-8 pharmDx kit (Dako, Santa Clara, CA).

Outcomes

Primary end point was ORR, per the investigator, which required confirmation per RECIST v1.1. ORR was further characterized by the duration of response (DOR). ORR was also evaluated by blinded independent central review (BICR) in the NIVO3 and NIVO1+IPI3 arms to evaluate efficacy in the NIVO1+IPI3 expansion cohort.

Secondary end points included progression-free survival (PFS), OS, and safety and tolerability. Treatment-related select AE categories were those with a potential inflammatory mechanism that required more frequent monitoring or unique intervention, such as immunosuppressants or endocrine replacement therapy. Efficacy by tumor PD-L1 expression was an exploratory end point.

Statistical Analysis

The study was conducted with a one-stage design with a sample size of 60 to 100 patients in the NIVO3 and NIVO3+IPI1 arms for 90% to 97% power to reject the null hypothesis of 10% response rate if the true response rate was 25% with a two-sided type I error rate of 5%. For the NIVO1+IPI3 arm, initial enrollment of 26 patients was planned, of which six patients were enrolled for safety evaluation while the NIVO3 arm was open, and 20 patients after the other two arms completed enrollment; there were 26 patients in the NIVO1+IPI3 arm at the initial disclosure of results with minimum follow-up of 3.9 months.[18] The protocol was amended in October 2016 to expand the NIVO1+IPI3 arm to enroll 92 patients—an additional 66 patients. On the basis of a 19.6% ORR for nivolumab monotherapy,[7] this would provide 93% power to reject the null hypothesis of a 19.6% ORR if the true ORR was 35% with a two-sided type I error rate of 5%. We analyzed ORR using the Clopper-Pearson method.[19] DOR was analyzed using the Kaplan-Meier methodology, and median values along with two-sided 95% CI were calculated using the Brookmeyer and Crowley method.[20] PFS and OS were summarized descriptively using the Kaplan-Meier method. Safety outcomes were tabulated using the worst grade according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, by system organ class and preferred term. All analyses were performed in all treated patients from each arm. Analyses reported here were completed when the primary end point of ORR could be evaluated in all treated patients.

RESULTS

Patients in the CheckMate 032 UC cohort were enrolled from June 5, 2014, to September 28, 2017. There were 78, 104, and 92 treated patients in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively. Patients were randomly assigned between the NIVO3 and NIVO3+IPI1 arms, which were enrolling at the same time. In contrast, 86 of 92 treated patients in the NIVO1+IPI3 arm were enrolled after the other two arms completed enrollment, thus leading to the differing lengths of follow-up. Baseline demographic and clinical characteristics were generally similar across treatment arms; however, more patients in the NIVO3+IPI1 and NIVO1+IPI3 arms had two or more Bellmunt risk factors and liver metastasis compared with the NIVO3 arm (Table 1). Two patients (1.9%) in the NIVO3+IPI1 arm and three patients (3.3%) in the NIVO1+IPI3 arm did not receive prior chemotherapy. More than 60% of patients in each arm received two or more prior treatment regimens.

Patients received a median of 8.5 nivolumab doses (range, one to 93 doses) in the NIVO3 arm, 4.0 nivolumab doses (range, one to 87 doses), and 4.0 ipilimumab doses (range one to eight doses) in the NIVO3+IPI1 arm, and 4.0 nivolumab doses (range, one to 102 doses) and 3.0 ipilimumab doses (range, one to eight doses) in the NIVO1+IPI3 arm. In the NIVO3+IPI1 and NIVO1+IPI3 arms, 53 (50.9%) and 44 (47.8%) patients, respectively, received all four doses of the combination. Median duration of therapy was 3.5 months (95% CI, 2.3 to 5.1 months), 2.1 months (95% CI, 1.4 to 2.3 months), and 3.2 months (95% CI, 2.1 to 6.9 months) in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively. At the data cutoff, seven (9.0%), eight (7.7%), and 22 patients (23.9%) were continuing treatment in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively. Disease progression was the most common reason for discontinuation (Fig 1). In the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, 26 (33.3%), 28 (26.9%), and 16 patients (17.4%), respectively, received subsequent systemic therapy.

Confirmed ORR, per investigator, was 25.6% (95% CI, 16.4% to 36.8%) in the NIVO3 arm, 26.9% (95% CI, 18.7% to 36.5%) in the NIVO3+IPI1 arm, and 38.0% (95% CI, 28.1% to 48.8%) in the NIVO1+IPI3 arm (Table 2 and Appendix Fig A1A, online only). In the NIVO1+IPI3 arm, ORR was 23.8% (95% CI, 12.1% to 39.5%) in patients with tumor PD-L1 less than 1% at baseline and 58.1% (95% CI, 39.1% to 75.5%) in patients with tumor PD-L1 expression of 1% or greater at baseline (Appendix Fig A1A and Appendix Table A1, online only). ORR, per BICR, was concordant with the per-investigator assessment in the NIVO3 and NIVO1+IPI3 arms (Table 2 and Appendix Fig A1B). ORR by tumor PD-L1 expression level, per BICR, was also concordant with investigator review in the NIVO3 and NIVO1+IPI3 arms (Appendix Fig A1B).

Median time to response, per investigator, was 2.0 months (range, 1.0 to 8.3 months), 1.4 months (range, 1.1 to 11.1 months), and 1.4 months (range, 1.1 to 5.1 months) in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively. Median DOR was 30.5 months (95% CI, 8.3 months to not estimable [NE]) in the NIVO3 arm, 22.3 months (95% CI, 12.8 months to NE) in the NIVO3+IPI1 arm, and 22.9 months (95% CI, 9.8 months to NE) in the NIVO1+IPI3 arm. Median DOR in each arm was similar regardless of baseline tumor PD-L1 expression (Appendix Table A1). Median tumor change from baseline was +1.9%, 0%, and −30.0% in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively (Fig 2). Several patients in each arm demonstrated prolonged reduction in target lesions from baseline (Appendix Fig A2,

TABLE 1. Baseline Demographic and Clinical Characteristics

Characteristic	NIVO3 (n = 78)	NIVO3+IPI1 (n = 104)	NIVO1+IPI3 (n = 92)
Median age (range), years	65.5 (31-85)	63.0 (39-83)	64.0 (38-83)
Age, years, No (%)			
≥ 65	41 (52.6)	47 (45.2)	45 (48.9)
≥ 75	10 (12.8)	18 (17.3)	11 (12.0)
Male, No. (%)	54 (69.2)	81 (77.9)	74 (80.4)
Region, No. (%)			
United States	59 (75.6)	74 (71.2)	31 (33.7)
Rest of the world	19 (24.4)	30 (28.8)	61 (66.3)
Race, No. (%)			
White	72 (92.3)	90 (86.5)	87 (94.6)
Black or African American	4 (5.1)	4 (3.8)	3 (3.3)
Asian	1 (1.3)	4 (3.8)	1 (1.1)
Other	1 (1.3)	6 (5.8)	1 (1.1)
ECOG PS, No (%)			
0	42 (53.8)	40 (38.5)	41 (44.6)
1	36 (46.2)	64 (61.5)	51 (55.4)
Baseline liver metastasis, No. (%)	20 (25.6)	37 (35.6)	33 (35.9)
Baseline visceral metastasis, No. (%)	64 (82.1)	92 (88.5)	76 (82.6)
Baseline lymph node only metastasis, No. (%)	13 (16.7)	11 (10.6)	15 (16.3)
Baseline creatinine clearance,mL/min, No. (%)			
< 60	25 (32.1)	36 (34.6)	26 (28.3)
≥ 60	53 (67.9)	68 (65.4)	66 (71.7)
Percent tumor PD-L1 expression, No. (%)			
< 1	43 (55.1)	56 (53.8)	42 (45.7)
≥ 1	26 (33.3)	31 (29.8)	31 (33.7)
Not quantifiable	9 (11.5)	17 (16.3)	19 (20.7)
No. of Bellmunt risk factors, No. (%)			
0	27 (34.6)	26 (25.0)	29 (31.5)
1	39 (50.0)	42 (40.4)	35 (38.0)
≥ 2	12 (15.4)	36 (34.6)	28 (30.4)
No. of prior regimens, No. (%)			
0	0	2 (1.9)	3 (3.3)
1	27 (34.6)	36 (34.6)	29 (31.5)
≥ 2	51 (65.4)	66 (63.5)	60 (65.2)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; PD-L1, programmed death ligand 1.

online only) and durable responses (Appendix Fig A3, online only).

Median PFS was 2.8 months (95% CI, 1.5 to 5.3 months), 2.6 months (95% CI, 1.4 to 3.9 months), and 4.9 months (95% CI, 2.7 to 6.6 months) in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms (Fig 3). Six-month PFS rates in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms were 36.3%, 32.3%, and 41.7%, respectively. Twelve-month PFS rates in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms were 17.9%, 22.6%, and 25.9%, respectively. In patients with baseline PD-L1 expression less than 1%, median PFS was 2.8 months (95% CI, 1.4 to 5.9 months), 2.7 months (95% CI, 1.4 to 3.9 months), and 4.3 months (95% CI, 1.5 to 6.4 months) in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively. In patients with PD-L1 expression of 1% or greater, median PFS was 2.7 months (95% CI, 1.2 to 10.8 months), 3.4 months (95% CI, 1.4 to 11.0 months), and 6.6 months (95% CI, 3.8 to 27.6 months) in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms (Appendix Fig A4, online only). Median OS was 9.9 months (95% CI, 7.3 to 21.1 months) in the NIVO3 arm, 7.4 months (95% CI, 5.6 to 11.0 months) in the NIVO3+IPI1 arm, and 15.3 months (95% CI, 10.1 to 27.6 months) in the NIVO1+IPI3 arm (Fig 4). Twelve-month OS rates were 47.3%, 38.3%, and 56.9% in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively. In patients with PD-L1 expression less than 1%, median OS was 10.4 months (95% CI, 6.5 to 26.0 months), 7.4 months (95% CI, 5.0 to 10.6 months), and 14.9 months (95% CI, 5.6 to 27.6 months) in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively, and 12.9 months (95% CI, 2.8 months to NE), 10.8 months (95% CI, 4.6 months to NE), and 24.1 months (95% CI, 10.2 months to NE) in patients with PD-L1 expression of 1% or greater (Appendix Fig A5, online only).

Any-grade treatment-related AEs (TRAEs) occurred in 66 (84.6%), 88 (84.6%), and 74 patients (80.4%) in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively (Table 3). Grade 3 to 4 TRAEs occurred in 21 (26.9%), 32 (30.8%), and 36 patients (39.1%) in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms. Grade 5 treatment-related pneumonitis occurred in one patient each in the NIVO3 and NIVO3+IPI1 arms. No grade 5 TRAEs occurred in the NIVO1+IPI3 arm. Any-grade treatment-related serious AEs occurred in nine (11.5%), 26 (25.0%), and 25 patients (27.2%) in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively, whereas grade 3 to 4 treatment-related serious AEs occurred in six (7.7%), 21 (20.2%), and 20 patients (21.7%). In the NIVO3 arm, three patients (3.8%) discontinued treatment as a result of grade 3 or greater TRAEs. In the NIVO3+IPI1 and NIVO1+IPI3 arms, 12 (11.5%) and 10 patients (10.9%), respectively, discontinued treatment because of grade 3 or greater TRAEs.

Treatment-related select AEs included endocrine, GI, hepatic, pulmonary, renal, and skin events (Table 3).

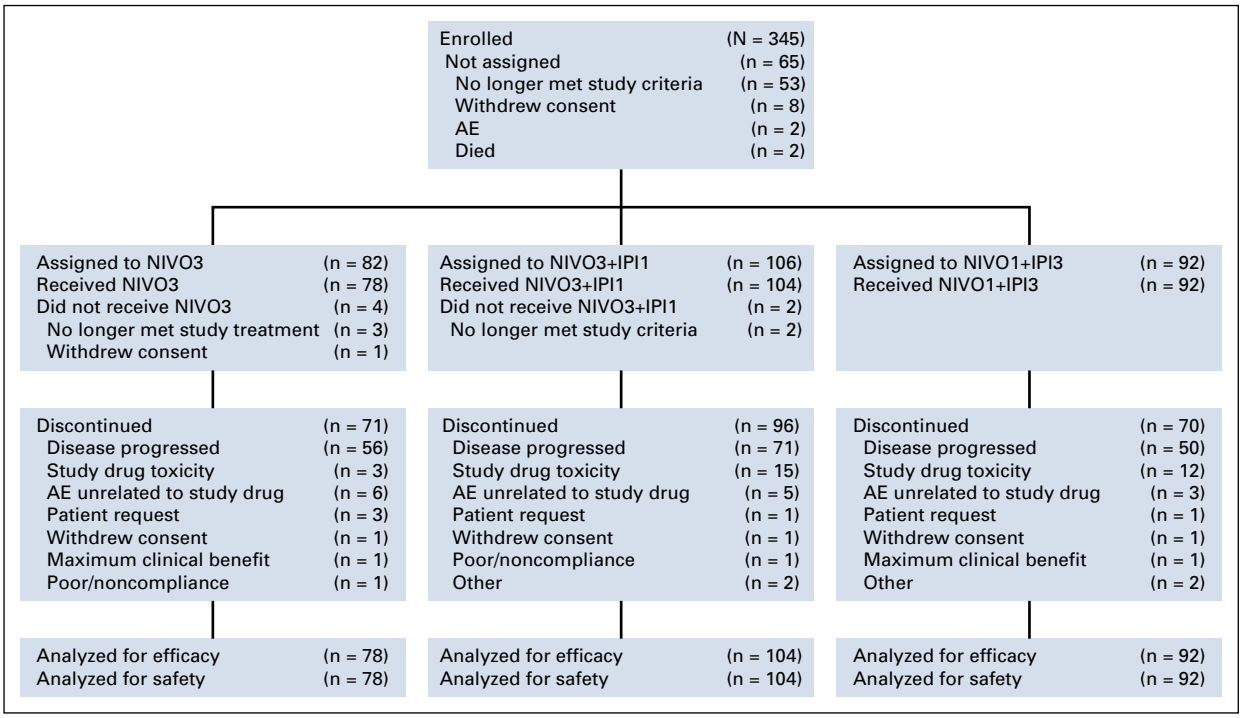


FIG 1. CONSORT diagram. AE, adverse event; NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks.

Anygrade treatment-related select AEs that occurred in 10% or more of patients were endocrine (n = 9; 11.5%), GI (n = 11; 14.1%), and skin (n = 34; 43.6%) in the NIVO3 arm; endocrine (n = 24; 23.1%), GI (n = 26; 25.0%), hepatic (n = 29; 27.9%), and skin (n = 44; 42.3%) in the NIVO3+IPI1 arm; and endocrine (n = 22; 23.9%), GI (n = 32; 34.8%), hepatic (n = 15; 16.3%), and skin (n = 42; 45.7%) in the NIVO1+IPI3 arm (Table 3). Most patients received immune-modulating medication for grade 3 to 4 treatment-related select AEs (Appendix Table A2, online only). In all arms, the majority of grade 3 to 4 treatment-related select AEs resolved when immune-modulating medication was initiated (Appendix Table A2).

DISCUSSION

In CheckMate 032, NIVO3 continues to provide antitumor benefit with durable responses and prolonged OS with longer follow-up. Our results show evidence of clinical activity with combined PD-1 and cytotoxic T-lymphocyte

TABLE 2. Best Overall Response Per Investigator and Per BICR

	Per Investigator			Per BICR	
Response	**NIVO3 (n = 78)**	**NIVO3+IPI1 (n = 104)**	**NIVO1+IPI3 (n = 92)**	**NIVO3 (n = 78)**	**NIVO1+IPI3 (n = 92)**
ORR, No. (%)	20 (25.6)	28 (26.9)	35 (38.0)	16 (20.5)	34 (37.0)
95% CI	16.4 to 36.8	18.7 to 36.5	28.1 to 48.8	12.2 to 31.2	27.1 to 47.7
Best overall response, No. (%)					
Complete response	8 (10.3)	8 (7.7)	6 (6.5)	9 (11.5)	14 (15.2)
Partial response	12 (15.4)	20 (19.2)	29 (31.5)	7 (9.0)	20 (21.7)
Stable disease	21 (26.9)	24 (23.1)	23 (25.0)	27 (34.6)	24 (26.1)
Progressive disease	30 (38.5)	44 (42.3)	20 (21.7)	31 (39.7)	21 (22.8)
Unable to determine/not reported	7 (9.0)	8 (7.7)	14 (15.2)	4 (5.1)	13 (14.1)

Abbreviations: BICR, blinded independent central review; NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; ORR, objective response rate.

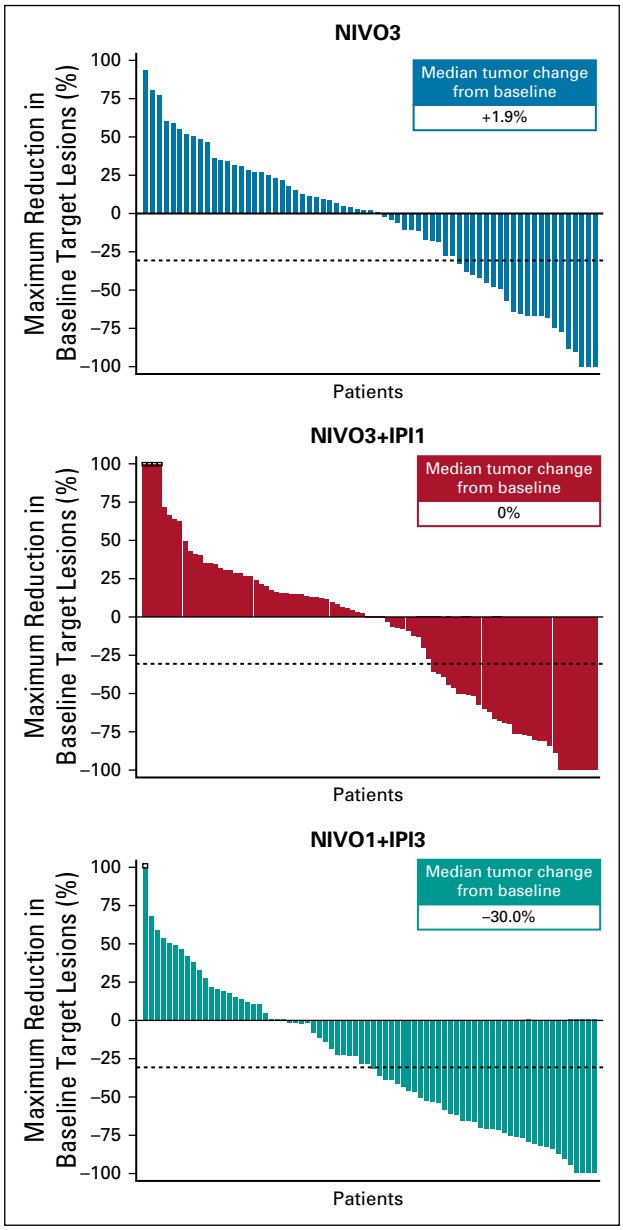


FIG 2. Best tumor change from baseline in target lesion per investigator. NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks.

antigen-4 inhibition in mUC, as previously observed with nivolumab plus ipilimumab across several tumor types.[11-14] Especially promising efficacy was observed with the NIVO1+IPI3 combination, which resulted in the highest ORRs relative to the NIVO3 and NIVO3+IPI1 arms, although the study design precludes direct comparison. Furthermore, ORR with the NIVO1+IPI3 combination is higher than has been previously reported with other currently approved anti–PD-1 and anti–PD-L1 monotherapy agents, although this should be interpreted with caution.[4-8] The promising efficacy observed with the NIVO1+IPI3 combination was also reflected in the prolonged OS and the greater proportion of patients with increased reduction in target lesions from baseline relative to the NIVO3 and NIVO3+IPI1 arms. However, additional follow-up will help fully characterize the clinical activity of the NIVO1+IPI3 combination regimen.

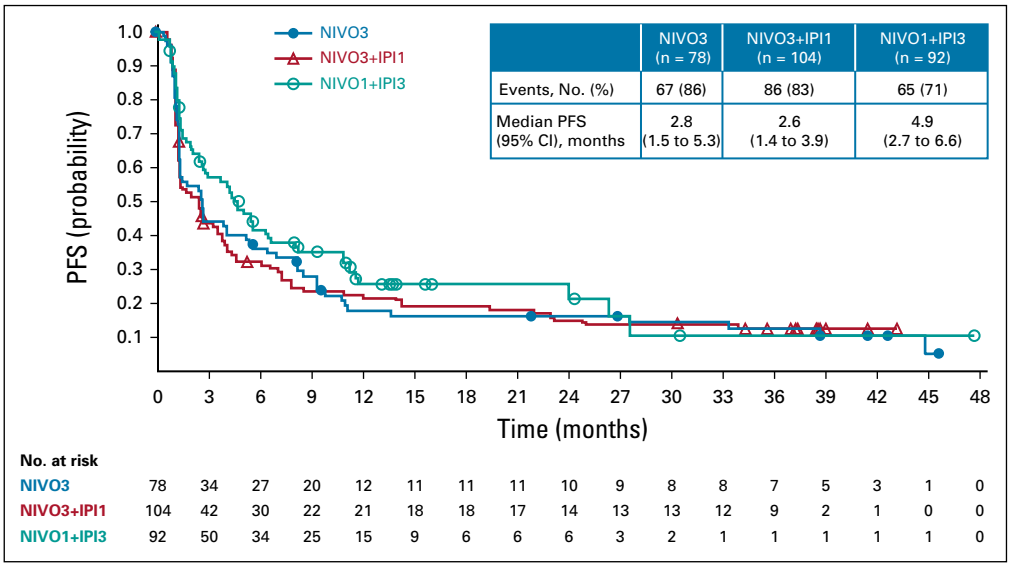
Responses were observed regardless of PD-L1 expression levels in all treatment arms. In this initial analysis of the NIVO1+IPI3 expansion cohort, ORR was highest in patients with baseline tumor PD-L1 expression of 1% or greater. This finding was consistent with ORR as assessed by BICR. Responses per investigator or per BICR in patients with baseline tumor PD-L1 expression less than 1% were similar across regimens; however, analysis of ORR by PD-L1 expression levels was exploratory and limited by the small numbers of patients in these subgroups.

The ORR, per investigator, was 38.0% (37.0% by BICR) with NIVO1+IPI3. In previous reports of PD-1– and PD-L1–targeted monotherapies, including pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab, in a PD-L1–unselected population of patients with mUC, ORR ranged from 13.4% to 21.1%.[4-8] Previously, the highest ORR reported with immunotherapy in the platinum-pretreated population was 21.1% at median follow-up of 27.7 months in the KEYNOTE-045 trial of pembrolizumab versus investigator's choice of chemotherapy.[4]

Median OS of 15.3 months and the 1-year OS rate in this study of 56.9% were also promising. In studies of other immune checkpoint inhibitor monotherapies in this setting, median OS ranged from 6.5 to 10.5 months and 1-year OS rate ranged from 39% to 55%.[4-9] Durable responses with nivolumab plus ipilimumab treatments have been observed in patients with melanoma and RCC.[11,14] Longer follow-up with NIVO1+IPI3 in patients with mUC will indicate whether durability of response holds true in this malignancy.

In CheckMate 032, patients in the mUC cohort were heavily pretreated. The proportion of patients who received two or more prior regimens (65.2%) was greater than that reported in several other trials of immunotherapy agents in the previously treated mUC setting.[5,6,21] The results in this heavily pretreated population are encouraging as it is known that these patients have limited subsequent treatment options. Patients also had a high rate of visceral metastases at baseline, which is associated with poor prognosis.[22] In addition, more than one third of patients had baseline liver metastases and approximately one third of patients had two or more Bellmunt risk factors in both combination arms, which further highlights the notable efficacy of NIVO1+IPI3, even in patients with poor prognoses and high unmet need.

The safety profiles of the three nivolumab-containing regimens were similar and consistent with the previously

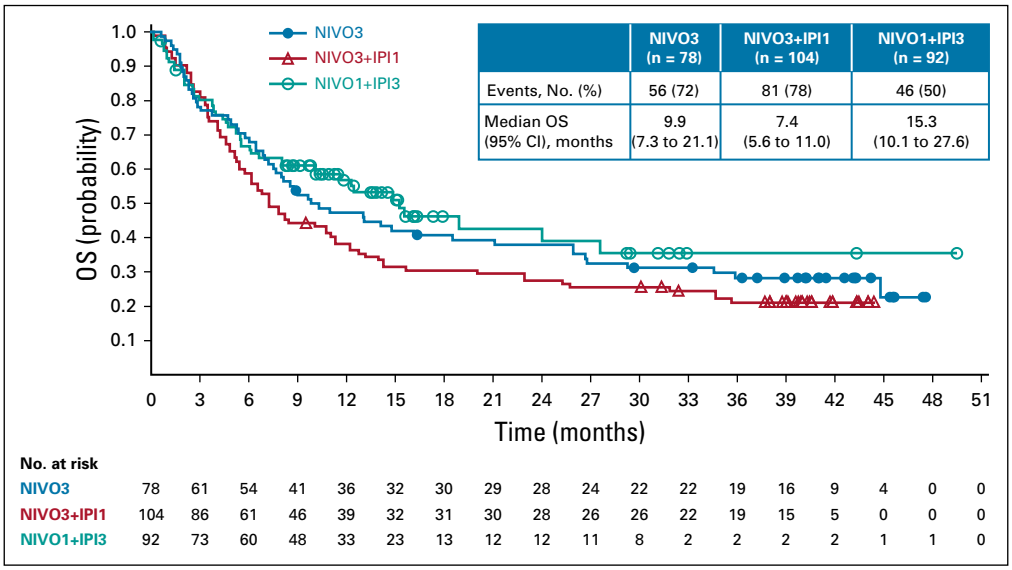


	NIVO3 (n = 78)	NIVO3+IPI1 (n = 104)	NIVO1+IPI3 (n = 92)
Events, No. (%)	67 (86)	86 (83)	65 (71)
Median PFS (95% CI), months	2.8 (1.5 to 5.3)	2.6 (1.4 to 3.9)	4.9 (2.7 to 6.6)

FIG 3. Progression-free survival per investigator. NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; PFS, progression-free survival.

reported safety profile of nivolumab monotherapy in CheckMate 032,[16] and the incidence of certain AEs was consistent with the safety profiles of nivolumab plus ipilimumab in other cancer types.[11,14] However, the incidence of high-grade TRAEs or high-grade treatment-related select AEs and the use of immune-modulating medication for high-grade treatment-related select AE resolution was highest in the NIVO1+IPI3 arm and may have arisen because of ipilimumab dose-related toxicity. Grade 3 to 4 treatment-related select AEs largely resolved with the use of immune-modulating medication. No new safety signals were observed with NIVO1+IPI3 in patients with mUC, and the incidence of both any-grade TRAEs and grade 3 or greater TRAEs was lower than has been reported in patients with unresectable stage III or IV melanoma.[11] Similarly, the safety profile of NIVO3+IPI1 in the current study was consistent with that in patients with previously untreated advanced RCC who received the same dosing schedule of the NIVO plus IPI combination.[14]

This study is limited by the fact that it was not designed to directly compare outcomes among treatment arms, which each have a different length of follow-up, or with a standard current practice comparator. However, the ongoing phase III CheckMate 901 trial will further evaluate the NIVO1+IPI3 combination versus chemotherapy in patients with previously untreated mUC (ClinicalTrials.gov identifier: NCT03036098). The relatively small sample size in each arm of the current study could also be a limitation, especially in evaluating the effects of tumor PD-L1 expression on efficacy. Longer-term follow-up is needed to further characterize the efficacy and safety of the NIVO1+IPI3 combination.



	NIVO3 (n = 78)	NIVO3+IPI1 (n = 104)	NIVO1+IPI3 (n = 92)
Events, No. (%)	56 (72)	81 (78)	46 (50)
Median OS (95% CI), months	9.9 (7.3 to 21.1)	7.4 (5.6 to 11.0)	15.3 (10.1 to 27.6)

FIG 4. Overall Survival. NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; OS, overall survival.

TABLE 3. Treatment-Related Adverse Events in 10% or More of Patients and Treatment-Related Select Adverse Events

	NIVO3 (n = 78)		NIVO3+IPI1 (n = 104)		NIVO1+IPI3 (n = 92)	
Adverse Event	**Any Grade**	**Grade 3 to 4**	**Any Grade**	**Grade 3 to 4**	**Any Grade**	**Grade 3 to 4**
Treatment-related adverse event	66 (84.6)	21 (26.9)*	88 (84.6)	32 (30.8)*	74 (80.4)	36 (39.1)
Diarrhea	10 (12.8)	0	24 (23.1)	5 (4.8)	30 (32.6)	9 (9.8)
Pruritus	26 (33.3)	0	30 (28.8)	2 (1.9)	29 (31.5)	0
Fatigue	28 (35.9)	2 (2.6)	33 (31.7)	3 (2.9)	24 (26.1)	0
Decreased appetite	6 (7.7)	0	17 (16.3)	0	15 (16.3)	0
Maculopapular rash	17 (21.8)	3 (3.8)	19 (18.3)	2 (1.9)	15 (16.3)	3 (3.3)
Nausea	10 (12.8)	1 (1.3)	8 (7.7)	1 (1.0)	13 (14.1)	1 (1.1)
Hypothyroidism	6 (7.7)	0	14 (13.5)	0	12 (13.0)	0
Rash	6 (7.7)	0	13 (12.5)	2 (1.9)	12 (13.0)	1 (1.1)
Elevated ALT	3 (3.8)	0	20 (19.2)	6 (5.8)	12 (13.0)	6 (6.5)
Elevated AST	1 (1.3)	1 (1.3)	16 (15.4)	4 (3.8)	10 (10.9)	2 (2.2)
Lipase increased	13 (16.7)	5 (6.4)	10 (9.6)	6 (5.8)	5 (5.4)	4 (4.3)
Arthralgia	12 (15.4)	0	9 (8.7)	0	6 (6.5)	0
Anemia	9 (11.5)	1 (1.3)	12 (11.5)	1 (1.0)	6 (6.5)	0
Dyspnea	8 (10.3)	2 (2.6)	8 (7.7)	1 (1.0)	2 (2.2)	0
Dry skin	8 (10.3)	0	10 (9.6)	0	5 (5.4)	0
Hyperthyroidism	4 (5.1)	0	13 (12.5)	0	6 (6.5)	0
Amylase increased	7 (9.0)	4 (5.1)	11 (10.6)	1 (1.0)	6 (6.5)	2 (2.2)
Select adverse event						
Endocrine	9 (11.5)	0	24 (23.1)	3 (2.9)	22 (23.9)	2 (2.2)
GI	11 (14.1)	1 (1.3)	26 (25.0)	8 (7.7)	32 (34.8)	15 (16.3)
Hepatic	6 (7.7)	2 (2.6)	29 (27.9)	7 (6.7)	15 (16.3)	9 (9.8)
Pulmonary*	2 (2.6)	0	7 (6.7)	1 (1.0)	5 (5.4)	2 (2.2)
Renal	7 (9.0)	2 (2.6)	7 (6.7)	0	3 (3.3)	1 (1.1)
Skin	34 (43.6)	3 (3.8)	44 (42.3)	2 (1.9)	42 (45.7)	4 (4.3)

NOTE. Data are presented as No. (%).

Abbreviations: NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks.

*Two grade 5 pneumonitis events were reported, one in the NIVO3 group and one in the NIVO3+IPI1 group.

In summary, these results show the continued clinical benefit with NIVO3 monotherapy and highlight the especially promising efficacy of NIVO1+IPI3 combination therapy in patients with platinum-pretreated locally advanced or mUC from CheckMate 032. The safety profile of this combination was manageable and similar to that of the NIVO3 and NIVO3+IPI1 regimens. These results provide a strong rationale by which to evaluate NIVO1+IPI3 in the first-line setting for mUC.

AFFILIATIONS

[1]The University of Texas MD Anderson Cancer Center, Houston, TX
[2]Istituto Nazionale dei Tumori, Milan, Italy
[3]Istituto Oncologico Veneto–Istituto di Ricovero e Cura a Carattere Scientifico, Padua, Italy
[4]START Madrid–Centro Integral Oncológico Clara Campal, Madrid, Spain
[5]Helsinki University Hospital, Helsinki, Finland
[6]University of Helsinki, Helsinki, Finland
[7]Duke University Medical Center, Durham, NC
[8]Istituto Nazionale Tumori–Istituto di Ricovero e Cura a Carattere Scientifico, Fondazione G. Pascale, Naples, Italy
[9]Hospital Universitario 12 de Octubre, Madrid, Spain
[10]University Hospital of Bonn, Bonn, Germany
[11]Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark
[12]Hospital Clinic of Barcelona, Institut D'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain
[13]Bristol-Myers Squibb, Princeton, NJ
[14]Memorial Sloan Kettering Cancer Center, New York, NY
[15]Weill Cornell Medical College, New York, NY

CORRESPONDING AUTHOR

Padmanee Sharma, MD, PhD, The University of Texas MD Anderson Cancer Center, 1155 Pressler St, Unit 1374, Houston, TX 77030; e-mail: padsharma@mdanderson.org.

EQUAL CONTRIBUTION

M.K.C. and J.R. contributed equally to this work.

PRIOR PRESENTATION

Presented at the European Society for Medical Oncology 2018 Congress, Munich, Germany, October 19-23, 2018.

SUPPORT

Sponsored by Bristol-Myers Squibb and funded in part through National Cancer Institute Cancer Center Support Grant No. P30-CA008748.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.00538.

AUTHOR CONTRIBUTIONS

Conception and design: All authors

Provision of study material or patients: Padmanee Sharma, Arlene Siefker-Radtke, Fillippo de Braud, Umberto Basso, Emiliano Calvo, Petri Bono, Michael A. Morse, Paulo A. Ascierto, Jose Lopez-Martin, Peter Brossart, Kristoffer Rohrberg, Begoña Mellado, Margaret K. Callahan, Jonathan Rosenberg

Collection and assembly of data: All authors

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors thank the patients and their families who are making this study possible; Wen Hong Lin, who served as medical monitor; Ana Moreno and Candice Mayne, who served as protocol managers; and Dako, an Agilent Technologies, Inc. company, for collaborative development of the programmed death ligand 1 immunohistochemistry 28-8 pharmDx assay. Professional medical writing and editorial assistance were provided by Nicolette Belletier, PhD, and Lawrence Hargett of PAREXEL, funded by Bristol-Myers Squibb.

REFERENCES

1. National Comprehensive Cancer Network: Bladder cancer (version 5.2018). https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf
2. Bristol-Myers Squibb: Opdivo (nivolumab) [package insert]. Princeton, NJ, Bristol-Myers Squibb, 2018
3. Sharma P, Baron A, Necchi A, et al: Nivolumab monotherapy in patients with advanced platinum-resistant urothelial carcinoma: Efficacy and safety update and association between biomarkers and overall survival in CheckMate 275. Cancer Res 78, 2018 (abstr CT178)
4. Bellmunt J, de Wit R, Vaughn DJ, et al: Two-year follow-up from the phase 3 KEYNOTE-045 trial of pembrolizumab (pembro) vs investigator's choice (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer (UC). J Clin Oncol 36, 2018 (abstr 410)
5. Powles T, Durán I, van der Heijden MS, et al: Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): A multicentre, open-label, phase 3 randomised controlled trial. Lancet 391:748-757, 2018
6. Patel MR, Ellerton J, Infante JR, et al: Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): Pooled results from two expansion cohorts of an open-label, phase 1 trial. Lancet Oncol 19:51-64, 2018
7. Sharma P, Retz M, Siefker-Radtke A, et al: Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. Lancet Oncol 18:312-322, 2017
8. O'Donnell P MC, Keam B, Kim S-W, et al: Updated efficacy and safety profile of durvalumab monotherapy in urothelial carcinoma. Cancer Res 78, 2018 (abstr CT301)
9. Bellmunt J, de Wit R, Vaughn DJ, et al: Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 376:1015-1026, 2017
10. Khalil DN, Smith EL, Brentjens RJ, et al: The future of cancer treatment: Immunomodulation, CARs and combination immunotherapy. Nat Rev Clin Oncol 13: 273-290, 2016 [Erratum: Nat Rev Clin Oncol 13:394, 2016]
11. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al: Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 377: 1345-1356, 2017
12. Overman MJ, McDermott R, Leach JL, et al: Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): An open-label, multicentre, phase 2 study. Lancet Oncol 18:1182-1191, 2017
13. Hellmann MD, Ciuleanu TE, Pluzanski A, et al: Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 378:2093-2104, 2018
14. Motzer RJ, Tannir NM, McDermott DF, et al: Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 378:1277-1290, 2018
15. Bristol-Myers Squibb: Yervoy (ipilimumab) [package insert]. Princeton, NJ, Bristol-Myers Squibb, 2018
16. Sharma P, Callahan MK, Bono P, et al: Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): A multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol 17:1590-1598, 2016
17. Sharma P, Callahan MK, Bono P, et al: Nivolumab monotherapy in metastatic urothelial carcinoma: Longer-term efficacy and safety results from the CheckMate 032 study. J Clin Oncol 36, 2018 (abstr 414)
18. Sharma P, Callahan MK, Calvo E, et al: Efficacy and safety of nivolumab plus ipilimumab in metastatic urothelial carcinoma: First results from the phase I/II CheckMate 032 study. J Immunother Cancer 4, 2016 (abstr O3)
19. Clopper PJ, Pearson ES: The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26:404-413, 1934
20. Brookmeyer R, Crowley J: A confidence interval for the median survival time. Biometrics 38:29-41, 1982
21. Powles T, O'Donnell PH, Massard C, et al: Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: Updated results from a phase 1/2 open-label study. JAMA Oncol 3:e172411, 2017
22. Saito K, Urakami S, Komai Y, et al: Impact of C-reactive protein kinetics on survival of patients with advanced urothelial carcinoma treated by second-line chemotherapy with gemcitabine, etoposide and cisplatin. BJU Int 110:1478-1484, 2012

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Nivolumab Alone and With Ipilimumab in Previously Treated Metastatic Urothelial Carcinoma: CheckMate 032 Nivolumab 1 mg/kg Plus Ipilimumab 3 mg/kg Expansion Cohort Results

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Padmanee Sharma
Stock and Other Ownership Interests: Jounce Therapeutics, Neon Therapeutics, Jounce Therapeutics (I), Neon Therapeutics (I), Constellation Pharmaceuticals, Oncolytics, BioAtla, Forty-Seven, Apricity, Polaris, Marker Therapeutics, Codiak Biosciences, ImaginAb, BioAtla (I), Forty-Seven (I), Apricity (I), Polaris (I), Marker Therapeutics (I), Codiak Biosciences (I), ImaginAb (I), Tvardi Therapeutics (I), Hummingbird, Hummingbird (I), Optera, Optera (I), Dragonfly Therapeutics, Dragonfly Therapeutics (I)
Consulting or Advisory Role: Constellation Pharmaceuticals, Jounce Therapeutics, Neon Therapeutics, Amgen (I), Jounce Therapeutics (I), Neon Therapeutics (I), BioAtla, Pieris Pharmaceuticals, Oncolytics, Merck, Forty-Seven, Polaris, Apricity, Marker Therapeutics, Codiak Biosciences, ImaginAb, Forty-Seven (I), Apricity (I), Polaris (I), Marker Therapeutics (I), Codiak Biosciences (I), ImaginAb (I), Tvardi Therapeutics (I), Hummingbird, BioAtla (I), Hummingbird (I), Bristol-Myers Squibb (I), Merck (I), Optera, Optera (I), Dragonfly Therapeutics, Dragonfly Therapeutics (I)
Patents, Royalties, Other Intellectual Property: Patent licensed to Jounce, patents licensed to Bristol-Myers Squibb, Jounce, and Merck (I)

Arlene Siefker-Radtke
Consulting or Advisory Role: Janssen Pharmaceuticals, Merck, National Comprehensive Cancer Network, Eli Lilly, Bristol-Myers Squibb, AstraZeneca, BioClin Therapeutics, Bavarian Nordic, Seattle Genetics, Nektar, Genentech, Inovio Pharmaceuticals, EMD Serono
Research Funding: National Institutes of Health, Michael and Sherry Sutton Fund for Urothelial Cancer, Janssen Pharmaceuticals, Takeda, Bristol-Myers Squibb, BioClin Therapeutics, Nektar
Patents, Royalties, Other Intellectual Property: Methods of characterizing and treating molecular subsets of muscle-invasive bladder cancer

Filippo de Braud
Consulting or Advisory Role: Ignyta, Pfizer, Amgen, Novartis, Daiichi Sankyo, Bristol-Myers Squibb, Servier, Dompè, Pierre Fabre, Roche, Octimet, Incyte
Speakers' Bureau: MSD Oncology, Novartis, Bristol-Myers Squibb, Roche, Menarini, Pfizer
Research Funding: Novartis (Inst), Roche (Inst), MSD Oncology (Inst), Ignyta (Inst), MedImmune (Inst), Nektar (Inst), Bristol-Myers Squibb (Inst), Merck Serono (Inst), Bayer (Inst), Celgene (Inst), GlaxoSmithKline (Inst), Boehringer Ingelheim (Inst), Eli Lilly (Inst), Pfizer (Inst), Servier (Inst)
Travel, Accommodations, Expenses: Roche, Amgen, Bristol-Myers Squibb, Celgene, Daiichi Sankyo

Umberto Basso
Consulting or Advisory Role: Roche, Janssen-Cilag, Pierre Fabre, Pfizer, Novartis, Incyte
Travel, Accommodations, Expenses: Novartis, Bristol-Myers Squibb, Pfizer, Sanofi, Astellas Pharma, Janssen-Cilag
Other Relationship: Ipsen

Emiliano Calvo
Employment: START, HM Hospitales Group
Leadership: START
Stock and Other Ownership Interests: START, Oncoart Associated, International Cancer Consultants
Honoraria: HM Hospitales Group
Consulting or Advisory Role: Novartis, Nanobiotix, Janssen-Cilag, PsiOxus Therapeutics, Seattle Genetics, EUSA Pharma, AbbVie, Celgene, AstraZeneca, Guidepoint Global, Genentech, GLG Pharma, Pfizer, Servier, Amcure
Speakers' Bureau: Novartis
Research Funding: AstraZeneca, Novartis, BeiGene, START
Travel, Accommodations, Expenses: Genentech
Other Relationship: President and founder of Foundation INTHEOS (Investigational Therapeutics in Oncological Sciences)

Petri Bono
Employment: Terveystalo
Stock and Other Ownership Interests: TILT Biotherapeutics, Faron Pharmaceuticals (I)
Consulting or Advisory Role: Pfizer, Novartis, MSD Oncology, Bristol-Myers Squibb, Orion Pharma, Ipsen, Faron Pharmaceuticals, Oncorena
Travel, Accommodations, Expenses: Faron Pharmaceuticals, MSD Oncology

Michael A. Morse
Stock and Other Ownership Interests: PhytoChem
Honoraria: Genentech, Novartis, Sanofi, Regeneron, Lexicon, Ipsen, Onyx Pharmaceuticals, Bayer, Taiho Pharmaceutical, Etubics, EMD Serono, Boehringer Ingelheim, Merrimack Pharmaceuticals, Eisai, Eli Lilly, Merck, Exelixis
Speakers' Bureau: Genentech, Novartis, Celgene, Taiho Pharmaceutical, Lexicon, Ipsen, Merck, Exelixis, Advanced Accelerator Applications, Eisai
Research Funding: Precision Biologics (Inst), Bristol-Myers Squibb (Inst), Onyx Pharmaceuticals (Inst), Eisai (Inst), Lexicon (Inst), MedImmune (Inst), Advanced Accelerator Applications (Inst), AlphaVax (Inst), Merck (Inst)
Patents, Royalties, Other Intellectual Property: Vaccines against antigens involved in therapy resistance and methods of using same patent number: 9956276, pharmaceutical product, medical food or dietary supplement for preventing cancer and inflammatory disease: publication number: 20170246136, compositions and methods for modulating and redirecting immune responses: publication number: 20170015758

Paolo A. Ascierto
Consulting or Advisory Role: Bristol-Myers Squibb, Genentech, Merck Sharp & Dohme, Novartis, Amgen, Array BioPharma, Merck Serono, Pierre Fabre, Newlink Genetics, Genmab, Incyte, MedImmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore
Research Funding: Bristol-Myers Squibb (Inst), Genentech (Inst), Array BioPharma (Inst)
Travel, Accommodations, Expenses: Merck Sharp & Dohme

Jose Lopez-Martin
Stock and Other Ownership Interests: PharmaMar
Consulting or Advisory Role: Novartis, Eli Lilly, Roche, GlaxoSmithKline, MSD Oncology, Celgene, Caris Life Sciences, Bayer, Pfizer, Pierre Fabre, Bristol-Myers Squibb, Bristol-Myers Squibb (Inst), Roche (Inst), Amgen, PharmaMar
Patents, Royalties, Other Intellectual Property: PharmaMar
Travel, Accommodations, Expenses: Roche, MSD Oncology, Roche, Bristol-Myers Squibb

Peter Brossart
Honoraria: Bristol-Myers Squibb, MSD
Consulting or Advisory Role: Bristol-Myers Squibb, MSD, Amgen, Roche, AstraZeneca
Research Funding: Bristol-Myers Squibb
Travel, Accommodations, Expenses: Bristol-Myers Squibb, MSD, AstraZeneca

Kristoffer Rohrberg
Research Funding: Eli Lilly (Inst), Genentech (Inst), Bristol-Myers Squibb (Inst), Symphogen (Inst), Pfizer (Inst), Novartis (Inst), Merck (Inst)
Travel, Accommodations, Expenses: Roche, Roche, Sanofi

Begoña Mellado
Consulting or Advisory Role: Pfizer, Roche, AstraZeneca, Bayer, Astellas Pharma, Janssen Pharmaceuticals, Roche (I), Pfizer (I), Amgen (I)
Research Funding: Roche, Janssen Pharmaceuticals, Bayer
Travel, Accommodations, Expenses: Janssen-Cilag, Roche (I)

Bruce S. Fischer
Employment: Bristol-Myers Squibb
Stock and Other Ownership Interests: Bristol-Myers Squibb

Stephanie Meadows-Shropshire
Employment: Bristol-Myers Squibb
Stock and Other Ownership Interests: Bristol-Myers Squibb
Research Funding: Bristol-Myers Squibb (Inst)
Travel, Accommodations, Expenses: Bristol-Myers Squibb

Abdel Saci
Employment: Bristol-Myers Squibb
Stock and Other Ownership Interests: Bristol-Myers Squibb

Margaret K. Callahan
Employment: Bristol-Myers Squibb (I), Celgene (I), Kleo Pharmaceuticals (I), Bristol-Myers Squibb (I)
Consulting or Advisory Role: AstraZeneca, Moderna Therapeutics, Merck
Research Funding: Bristol-Myers Squibb (Inst)
Other Relationship: Clinical Care Options, Potomac Center for Medical Education

Jonathan Rosenberg
Stock and Other Ownership Interests: Merck, Illumina
Honoraria: UpToDate, Bristol-Myers Squibb, AstraZeneca, Medscape, Vindico, Peerview, Chugai Pharma
Consulting or Advisory Role: Eli Lilly, Merck, Agensys, Genentech, Sanofi, AstraZeneca, MedImmune, Bristol-Myers Squibb, EMD Serono, Seattle Genetics, Bayer, Inovio Pharmaceuticals, BioClin Therapeutics, QED Therapeutics, Adicet Bio, Sensei Biotherapeutics, Fortress Biotech, Pharmacyclics, Western Oncolytics
Research Funding: Genentech (Inst), Oncogenex (Inst), Agensys (Inst), Mirati Therapeutics (Inst), Novartis (Inst), Viralytics (Inst), Genentech (Inst), Incyte (Inst), Seattle Genetics (Inst), Bayer (Inst), AstraZeneca (Inst)
Patents, Royalties, Other Intellectual Property: Predictor of platinum sensitivity (Inst)
Travel, Accommodations, Expenses: Genentech, Bristol-Myers Squibb

No other potential conflicts of interest were reported.

APPENDIX

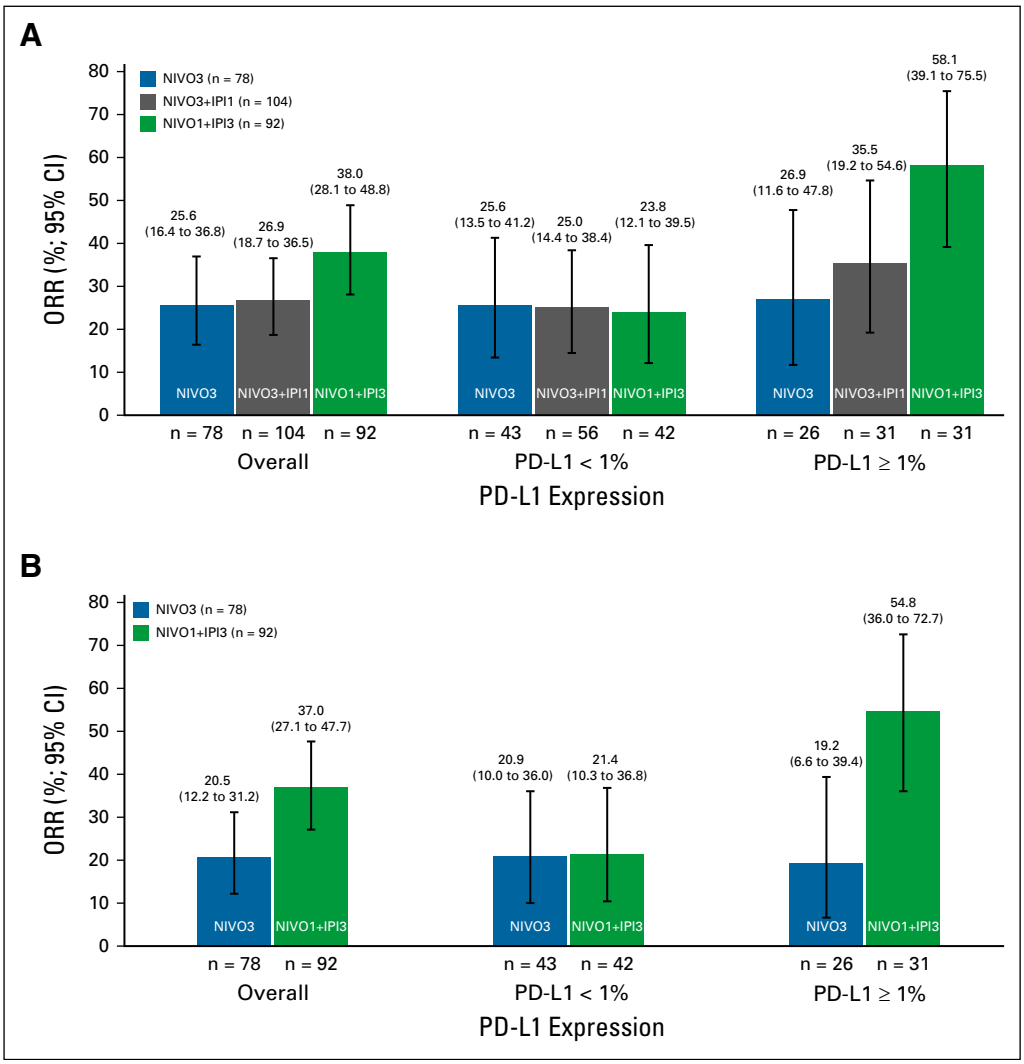


FIG A1. Objective response rate by tumor programmed death ligand 1 (PD-L1) expression (A) per investigator and (B) per blinded independent central review. NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; ORR, objective response rate.

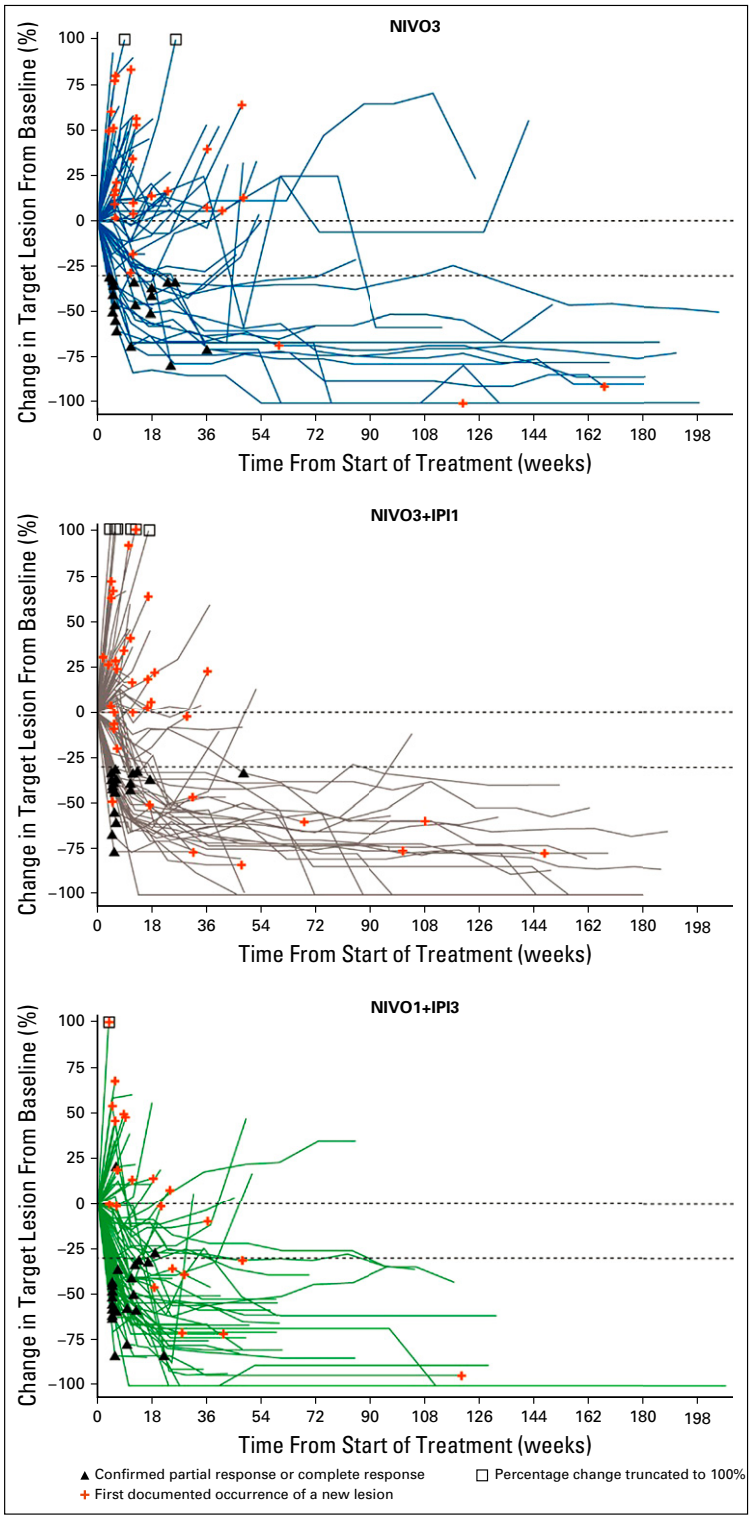


FIG A2. Percent reduction from baseline in target lesions per investigator. Horizontal reference line indicates the 30% reduction consistent with a protocol-defined criteria response. Assessments are per investigator assessment using protocol-defined criteria. Crossover patients are truncated at the crossover date. NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks.

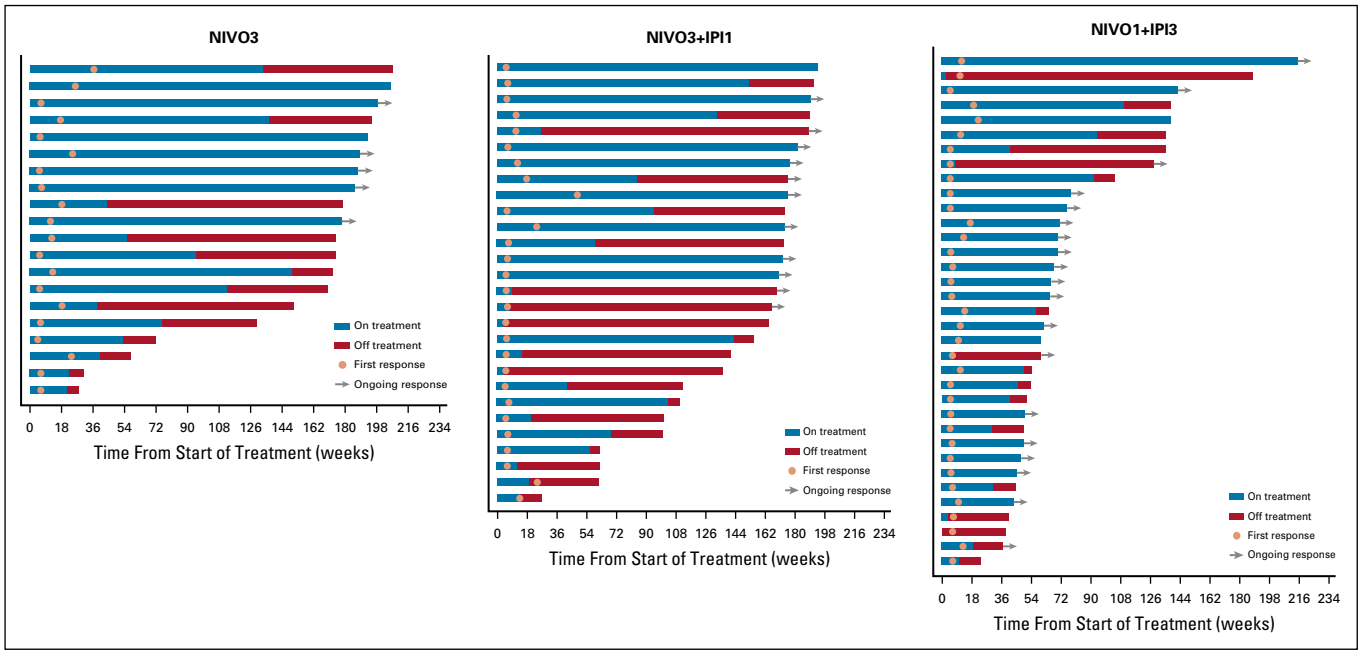


FIG A3. Time to and duration of response per investigator. NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks.

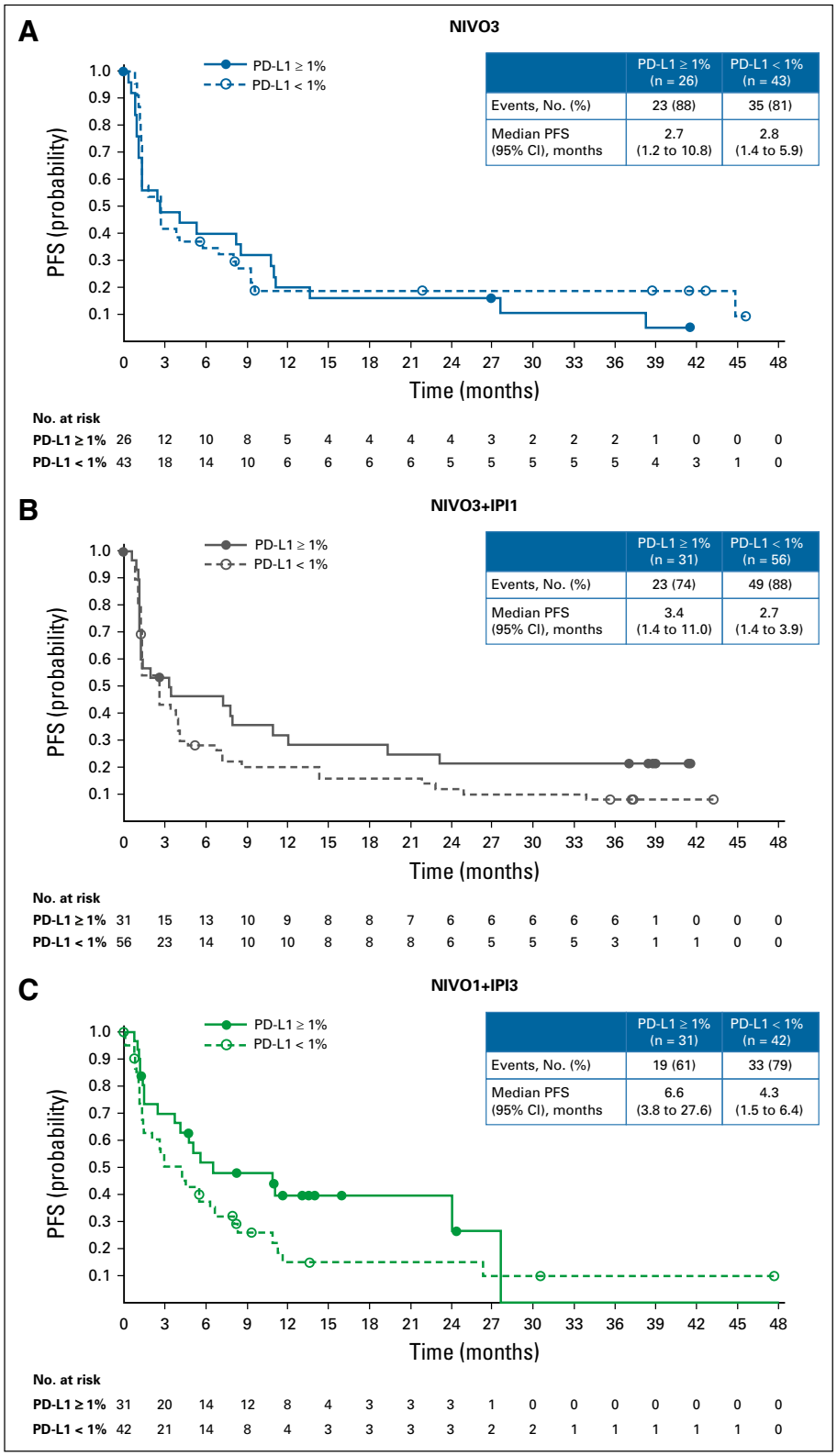


FIG A4. Progression-free survival (PFS) by tumor programmed death ligand 1 (PD-L1) expression per investigator. (A) NIVO3 (nivolumab 3 mg/kg monotherapy every 2 weeks). (B) NIVO3+IPI1 (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks). (C) NIVO1+IPI3 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks).

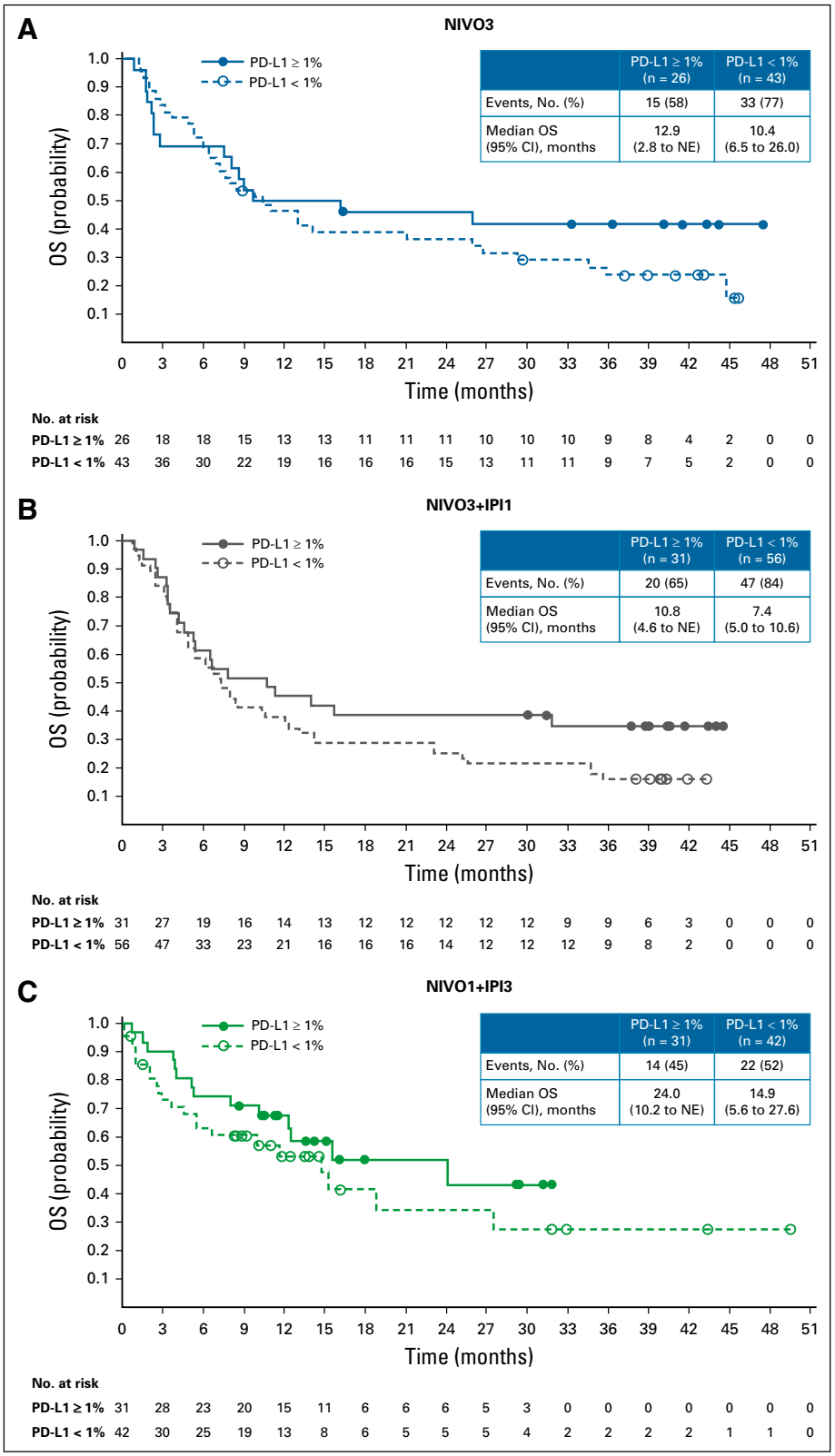


FIG A5. Overall survival (OS) by tumor programmed death ligand 1 (PD-L1) expression. (A) NIVO3 (nivolumab 3 mg/kg monotherapy every 2 weeks). (B) NIVO3+IPI1 (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks). (C) NIVO1+IPI3 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks). NE, not estimable.

List of Study Sites and Investigators

Study Site	Principal Investigator
Righospitalet, Copenhagen, Denmark	Ulrik Lassen
Helsinki University Hospital, Helsinki, Finland	Petri Bono
University of Bonn, Bonn, Germany	Peter Brossart
Nationales Centrum Fuer Tumorerkrakungen Heidelberg, Heidelberg, Germany	Dirk Jaeger
Azienda Ospedaliera S Orsola-Malpighi, Bologna, Italy	Andrea Ardizzoni
Instituto Nazionale Tumori Fondazione G Pascale, Naples, Italy	Paolo A. Ascierto
Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale Tumori Milano, Milan, Italy	Filippo de Braud
Istituto Oncologico Veneto, Padova, Italy	Valentina Guarneri
Hospital Madrid Norte Sanchinarro, Madrid, Spain	Emiliano Calvo
University Hospital 12 de Octubre, Madrid, Spain	José Lopez-Martin
Fundacion Jimenez Diaz, Madrid, Spain	Victor Moreno Garcia
Hospital Clinic of Barcelona, Barcelona, Spain	Noemi Reguart
Royal Marsden Hospital, Sutton, United Kingdom	Ian Chau
The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom	Thomas Ronald Jeffry Evans
H Lee Moffitt Cancer Center and Research Institute, Tampa, FL	Scott Antonia
Levine Cancer Institute, Charlotte, NC	Asim Amin
Tennessee Oncology, Nashville, TN	Johanna Bendell
Vanderbilt-Ingram Cancer Center, Nashville, TN	David Chism
Yale University, New Haven, CT	Joseph Eder
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD	Dung T. Le
Duke Cancer Institute, Durham, NC	Michael Morse
Dana-Farber Cancer Institute, Boston, MA	Patrick A. Ott
Winship Cancer Institute, Atlanta, GA	Rathi N. Pillai
Memorial Sloan Kettering Cancer Center, New York, NY	Margaret Callahan
The University of Texas MD Anderson Cancer Center, Houston, TX	Padmanee Sharma
Oregon Health and Science University, Portland, OR	Matthew Taylor

TABLE A1. Best Overall Response and Duration of Response by Tumor PD-L1 Expression per Investigator

	NIVO3		NIVO3+IPI1		NIVO1+IPI3	
Response	**PD-L1 < 1% (n = 43)**	**PD-L1 ≥ 1% (n = 26)**	**PD-L1 < 1% (n = 56)**	**PD-L1 ≥ 1% (n = 31)**	**PD-L1 < 1% (n = 42)**	**PD-L1 ≥ 1% (n = 31)**
ORR, No. (%)	11 (25.6)	7 (26.9)	14 (25.0)	11 (35.5)	10 (23.8)	18 (58.1)
95% CI	13.5 to 41.2	11.6 to 47.8	14.4 to 38.4	19.2 to 54.6	12.1 to 39.5	39.1 to 75.5
Best overall response, No. (%)						
Complete response	5 (11.6)	3 (11.5)	3 (5.4)	3 (9.7)	3 (7.1)	2 (6.5)
Partial response	6 (14.0)	4 (15.4)	11 (19.6)	8 (25.8)	7 (16.7)	16 (51.6)
Stable disease	12 (27.9)	7 (26.9)	11 (25.0)	6 (19.4)	14 (33.3)	5 (16.1)
Progressive disease	18 (41.9)	9 (34.6)	24 (42.9)	13 (41.9)	9 (21.4)	6 (19.4)
Unable to determine/not reported	2 (4.7)	3 (11.5)	4 (7.1)	1 (3.2)	9 (21.4)	2 (6.5)
	n = 11	n = 7	n = 14	n = 11	n = 10	n = 18
Median duration of response, months	40.8	19.4	21.5	NR	21.4	22.9
95% CI	5.6 to NE	8.3 to 37.1	7.1 to NE	6.7 to NE	1.8 to NE	8.6 to 26.5

Abbreviations: NE, not estimable; NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1 nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NR, not reached; ORR, objective response rate; PD-L1, programmed death ligand 1.

TABLE A2. Time to Onset and Resolution of Grade 3 to 5 Treatment-Related Select Adverse Events for Which Immune-Modulating Medication Was Initiated, by Category

Variable	NIVO3	NIVO3+IPI1	NIVO1+IPI3
Median time to onset of grade 3-5 treatment-related select adverse events, weeks (range)			
Endocrine	n = 0	n = 3	n = 2
	—	15.7 (11.7-24.7)	9.8 (8.9-10.7)
GI	n = 1	n = 8	n = 15
	4.9 (4.9-4.9)	7.4 (0.3-20.7)	7.9 (1.6-53.1)
Hepatic	n = 2	n = 7	n = 9
	35.1 (6.1-64.1)	11.3 (3.0-96.0)	9.1 (4.6-42.7)
Pulmonary	n = 1	n = 2	n = 2
	4.4 (4.4-4.4)	6.0 (3.9-8.1)	3.9 (2.6-5.3)
Renal	n = 2	n = 0	n = 1
	84.6 (31.1-138.1)	—	9.0 (9.0-9.0)
Skin	n = 3	n = 2	n = 4
	7.9 (1.1-54.3)	43.6 (19.7-67.6)	3.8 (2.1-6.0)
No. of patients receiving immune-modulating medication for grade 3 to 4 treatment-related select adverse events, No. (%)			
Endocrine	0	1 (33.3)	2 (100.0)
GI	1 (100.0)	7 (87.5)	14 (93.3)
Hepatic	2 (100.0)	5 (71.4)	6 (66.7)
Pulmonary	1 (100.0)	1 (50.0)	2 (100.0)
Renal	1 (50.0)	0	1 (100.0)
Skin	2 (66.7)	2 (100.0)	4 (100.0)
No. of patients whose grade 3 to 4 treatment-related select adverse events resolved when immune-modulating medication was initiated, No. (%)			
Endocrine	n = 0	n = 3	n = 2
	—	1 (33.3)	0 (0)
GI	n = 1	n = 7	n = 15
	1 (100.0)	6 (85.7)	14 (93.3)
Hepatic	n = 2	n = 6	n = 7
	1 (50.0)	6 (100.0)	5 (71.4)
Pulmonary	n = 1	n = 1	n = 2
	0 (0)	0 (0)	2 (100.0)
Renal	n = 1	n = 0	n = 1
	1 (100.0)	—	1 (100.0)
Skin	n = 2	n = 2	n = 4
	2 (100.0)	1 (50.0)	4 (100.0)

Abbreviations: NIVO3, nivolumab 3 mg/kg monotherapy every 2 weeks; NIVO3+IPI1 nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks; NIVO1+IPI nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks.