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ORIGINAL ARTICLE

Nivolumab plus ipilimumab combination therapy in patients with advanced hepatocellular carcinoma previously treated with sorafenib: 5-year results from CheckMate 040☆

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Background: Nivolumab plus ipilimumab demonstrated promising clinical activity and durable responses in sorafenib-treated patients with advanced hepatocellular carcinoma (HCC) in the CheckMate 040 study at 30.7-month median follow-up. Here, we present 5-year results from this cohort.

Patients and methods: Patients were randomized 1 : 1 : 1 to arm A [nivolumab 1 mg/kg plus ipilimumab 3 mg/kg Q3W (four doses)] or arm B [nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W (four doses)], each followed by nivolumab 240 mg Q2W, or arm C (nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W). The primary objectives were safety, tolerability, investigator-assessed objective response rate (ORR), and duration of response (DOR) per RECIST version 1.1.

Results: A total of 148 patients were randomized across treatment arms. At 60-month minimum follow-up (62.6-month median follow-up), the ORR was 34% ($n = 17$), 27% ($n = 13$), and 29% ($n = 14$) in arms A, B, and C, respectively. The median DOR was 51.2 months [95% confidence interval (CI) 12.6 months-not estimable (NE)], 15.2 months (95% CI 7.1 months-NE), and 21.7 months (95% CI 4.2 months-NE), respectively. The median overall survival (OS) was 22.2 months (34/50; 95% CI 9.4-54.8 months) in arm A, 12.5 months (38/49; 95% CI 7.6-16.4 months) in arm B, and 12.7 months (40/49; 95% CI 7.4-30.5 months) in arm C; 60-month OS rates were 29%, 19%, and 21%, respectively. In an exploratory analysis of OS by response (6-month landmark), the median OS was meaningfully longer for responders versus nonresponders for all arms. No new safety signals were identified with longer follow-up. There were no new discontinuations due to immune-mediated adverse events since the primary analysis.

Conclusions: Consistent with the primary analysis, the arm A regimen of nivolumab plus ipilimumab continued to demonstrate clinically meaningful responses and long-term survival benefit, with no new safety signals in patients with advanced HCC following sorafenib treatment, further supporting its use as a second-line treatment in these patients.

Key words: advanced hepatocellular carcinoma, nivolumab, ipilimumab, checkpoint inhibitor, immunotherapy, sorafenib

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INTRODUCTION

Liver cancer is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide.[1] Hepatocellular carcinoma (HCC), which accounts for 75%-85% of primary liver cancers,[1] is frequently diagnosed at advanced stages where survival outcomes are poor; the

reported 5-year survival rate for advanced HCC is ∼3%.[2,3] The first-line standard of care in advanced HCC includes immunotherapy-based regimens and tyrosine kinase inhibitors such as sorafenib.[3,4] In patients whose cancer progresses following first-line treatment with sorafenib, subsequent-line systemic therapy options for Child—Pugh class A disease are regorafenib, cabozantinib, and ramucirumab [in patients with alpha-fetoprotein (AFP) ≥400 ng/ml only)[3]; however, overall survival (OS) following these therapies is poor (median OS 8.5-10.6 months).[5-7] In the United States, the combination of the programmed cell death protein 1 (PD-1) inhibitor nivolumab with the cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitor ipilimumab and pembrolizumab monotherapy are also approved as subsequent-line therapy options for Child—Pugh A disease.[3]

Nivolumab monotherapy has demonstrated a durable objective response rate [ORR 14%; median duration of response (DOR) not reached], clinically meaningful survival (median OS 15.6 months),[8] and manageable safety in patients with advanced HCC previously treated with sorafenib in the CheckMate 040 study.[9,10] The combination of nivolumab plus ipilimumab has been shown to promote antitumor immune responses by distinct but complementary mechanisms; efficacy has been observed in several tumor types, including metastatic colorectal cancer, advanced renal cell carcinoma, and advanced melanoma.[11-13] Different doses and schedules of nivolumab plus ipilimumab were evaluated in patients with advanced HCC who were previously treated with sorafenib (intolerant to or progressed on sorafenib) in CheckMate 040.[14] With a median follow-up of 30.7 months, the arm A regimen [nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks (Q3W) for four doses followed by nivolumab 240 mg every 2 weeks (Q2W) until intolerance or disease progression] demonstrated durable clinical benefit with an ORR of 32% [95% confidence interval (CI) 20% to 47%] and median OS of 22.8 months (95% CI 9.4 months-not reached).[14] Based on these results, the arm A regimen of nivolumab plus ipilimumab is approved in the United States for patients with advanced HCC previously treated with sorafenib.[15,16]

Long-term follow-up data provide updated information regarding the efficacy and safety of anticancer therapies over extended treatment periods.[17] At a minimum follow-up of 44 months, nivolumab plus ipilimumab continued to demonstrate clinically meaningful responses and long-term survival benefits in advanced HCC.[18] Here, we present the 5-year results of efficacy, safety, and exploratory biomarker analyses from this cohort of the CheckMate 040 study.

PATIENTS AND METHODS

Study design and participants

CheckMate 040 is a multicenter, open-label, multicohort, phase I/II randomized study in patients with advanced HCC (ClinicalTrials.gov identifier: NCT01658878). Details of the CheckMate 040 study design have been published previously.[14] In brief, participants for this cohort were enrolled at 31 centers in 10 countries/territories in Asia, Europe, and North America. Eligible patients were at least 18 years of age with histologically confirmed advanced HCC with or without hepatitis B virus (HBV) or hepatitis C virus (HCV) infections; ineligible for surgical or locoregional therapies; intolerant to or progressed on sorafenib, with at least one measurable previously untreated lesion per RECIST version 1.1[19]; Child—Pugh class A; and an Eastern Cooperative Oncology Group performance status of 0 or 1.[20] Randomization procedures were described previously.[14]

CheckMate 040 was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Study protocol and amendments were approved by the institutional review boards or independent ethics committees at each study site, and all patients provided written informed consent before enrollment.

Procedures

Patients were randomized 1 : 1 : 1 to receive three different dosing regimens of intravenous nivolumab plus ipilimumab. Patients in arm A received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg Q3W (for four doses), and those in arm B received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W (for four doses); these regimens were followed by nivolumab 240 mg Q2W in both arms. Patients in arm C received nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg every 6 weeks. Treatment continued until unacceptable toxicity, disease progression per RECIST version 1.1, or withdrawal of consent, with no limit for the duration of treatment. Treatment delays up to 6 weeks (arms A and B) or 12 weeks (arm C) from the last dose of nivolumab and ipilimumab were allowed; dose reductions were not permitted. Treatment beyond the initial investigator-assessed progression was permitted.

Outcomes

The primary objectives were assessment of safety and tolerability and investigator-assessed ORR [proportion of patients with best overall response of complete response (CR) plus partial response (PR)] and DOR (time from the first confirmed CR or PR to the date of progression; derived for responders only) per RECIST version 1.1. Additional objectives were the evaluation of antitumor activities (time to progression and progression-free survival) by blinded independent central review (BICR) and investigator assessment, disease control rate (DCR), OS, time to response, ORR and DOR per BICR, and determination of the potential association between selected biomarkers [e.g. programmed death-ligand 1 (PD-L1)] and clinical efficacy. These key outcomes are defined in Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2024.03.005.

Assessments

Tumors were assessed using computed tomography or magnetic resonance imaging at baseline, every 6 weeks for 48 weeks, and every 12 weeks thereafter until disease progression. CR or PR was confirmed by a second scan at least 4 weeks after the initial response. Safety was assessed

using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 continuously throughout treatment and for 100 days after the last treatment, and adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities version 23.1.[21] Causal relationship of AEs to study drug was determined by the investigator. Immune-mediated adverse events (IMAEs) were recorded and defined as events, regardless of causality, occurring within 100 days of the last dose for which patients received immune-modulating medication for the treatment of the event; endocrine events were included as IMAEs, although they are often managed without immunosuppression. Detailed biomarker methods are described in Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2024.03.005.

Statistical analyses

Efficacy analyses were carried out in all randomized patients. ORR, DCR, and their corresponding two-sided 95% exact CIs were calculated by the Clopper—Pearson method. The Kaplan—Meier method was used to estimate medians and the corresponding 95% CIs for DOR, OS, progression-free survival, and time to progression. Conditional landmark analysis of OS was conducted in patients who had the best overall response available after the start of therapy and who had survived at least 6 months on treatment; this analysis excluded patients who died or were censored for other reasons before this timepoint. Six months was selected as the landmark timepoint to limit lead-time bias. Safety was analyzed in all patients who received at least one dose of study treatment and summarized using descriptive statistics. Statistical analyses were carried out using SAS software (version 9.02 or higher; SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics and patient disposition

Between 4 January 2016 and 26 September 2016, 148 patients were randomized to the three treatment arms: 50 patients to arm A, 49 patients to arm B, and 49 patients to arm C, as previously described.[14] At the clinical cutoff (28 September 2021), the minimum follow-up (time from randomization of the last patient to data cutoff) was 60 months. The median follow-up (time from randomization to data cutoff) was 62.6 months (range 60-69 months) for all randomized patients in this study. Baseline patient demographics and disease characteristics were comparable across the three randomized treatment arms (Table 1). The majority of patients had Barcelona Clinic Liver Cancer (BCLC) stage C (≥86%); HBV infections represented the most common baseline HCC-associated etiology across the three treatment arms. Extrahepatic spread (EHS) or vascular invasion was reported in 86%-92% of patients (Table 1). Patients with AFP ≥400 μg/l ranged from 37% to 50% across the treatment arms and patients with tumor cell PD-L1 ≥1% ranged from 16% to 20%. Most patients (≥98% across arms) had received prior sorafenib therapy; the most common reason for sorafenib discontinuation was disease progression (Table 1). Across the three arms, 28% of patients had received two or more prior lines of therapy, which included tyrosine kinase inhibitors, chemotherapy, and other targeted agents (Table 1).

At data cutoff, 45 patients (92%), 47 patients (96%), and 45 patients (94%) had discontinued therapy in arms A, B, and C, respectively (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.03.005). Disease progression was the most common reason for treatment discontinuation (arm A, 53%; arm B, 73%; and arm C, 77% of patients). The percentage of patients discontinuing the treatment regimen because of study drug toxicity was highest in arm A (24%), followed by arm B (10%) and arm C (4%). In arms A, B, and C, 20 patients (40%), 22 patients (45%), and 25 patients (51%) received at least one subsequent line of therapy (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.03.005); the most common was systemic therapy.

Efficacy

ORR by investigator assessment was 34% (95% CI 21% to 49%), 27% (95% CI 15% to 41%), and 29% (95% CI 17% to 43%) in arms A, B, and C, respectively; ORR by BICR assessment was 32% (95% CI 20% to 47%), 31% (95% CI 18% to 45%), and 31% (95% CI 18% to 45%), respectively (Table 2). The median DOR by investigator assessment was 51.2 months [95% CI 12.6 months-not estimable (NE)] in arm A, 15.2 months (95% CI 7.1 months-NE) in arm B, and 21.7 months (95% CI 4.2 months-NE) in arm C (Table 2). Deep responses and sustained reduction in tumor burden were observed across all treatment arms regardless of baseline HCC etiology (Supplementary Figures S2 and S3, available at https://doi.org/10.1016/j.annonc.2024.03.005).

The median OS was 22.2 months (95% CI 9.4-54.8 months) in arm A, 12.5 months (95% CI 7.6-16.4 months) in arm B, and 12.7 months (95% CI 7.4-30.5 months) in arm C; 36-month OS rates were 42%, 26%, and 30%, respectively, and 60-month OS rates were 29%, 19%, and 21%, respectively (Figure 1). An exploratory analysis of OS was conducted by the best overall response of patients at the 6-month landmark. The median OS was meaningfully longer for responders [best overall response of CR or PR at landmark; not reached in arms A and B, 63.2 months (95% CI 31.2 months-NE) in arm C] versus nonresponders [best overall responses other than CR or PR at landmark; arm A, 15.6 months (95% CI 9.0-29.6 months); arm B, 12.5 months (95% CI 8.0-14.2 months); arm C, 19.5 months (95% CI 8.6-30.5 months); Figure 2].

Biomarker analyses

Responses were observed in arms A and B regardless of viral etiology; responses were also observed in all treatment arms regardless of tumor cell PD-L1 expression or baseline AFP status, although comparisons are limited due to the

Table 1. Baseline patient demographics and clinical characteristics

Patients	Arm A NIVO1 + IPI3 Q3W (*n* = 50)	Arm B NIVO3 + IPI1 Q3W (*n* = 49)	Arm C NIVO3 Q2W + IPI1 Q6W (*n* = 49)	Total (*N* = 148)
Age (years), median (range)	61 (18-80)	65 (34-83)	58 (32-79)	60 (18-83)
Male, *n* (%)	43 (86)	37 (76)	40 (82)	120 (81)
Race, *n* (%)				
Asian	37 (74)	27 (55)	30 (61)	94 (64)
White	12 (24)	20 (41)	15 (31)	47 (32)
Black or African American	1 (2)	1 (2)	3 (6)	5 (3)
Other/not reported	0	1 (2)	1 (2)	2 (1)
BCLC stage, *n* (%)				
A	2 (4)	0	0	2 (1)
B	5 (10)	4 (8)	3 (6)	12 (8)
C	43 (86)	45 (92)	46 (94)	134 (91)
Child–Pugh score[a], *n* (%)				
5	41 (82)	38 (78)	32 (65)	111 (75)
6	9 (18)	9 (18)	15 (31)	33 (22)
Vascular invasion[b], *n* (%)	18 (36)	14 (29)	20 (41)	52 (35)
Extrahepatic spread[b], *n* (%)	40 (80)	40 (82)	42 (86)	122 (82)
Vascular invasion or extrahepatic spread[b], *n* (%)	43 (86)	44 (90)	45 (92)	132 (89)
AFP ≥ 400 μg/l, *n* (%)	25 (50)	18 (37)	22 (45)	65 (44)
Tumor cell PD-L1 ≥1%, *n* (%)	10 (20)	10 (20)	8 (16)	28 (19)
HCC etiology[c], *n* (%)				
HCV positive	7 (14)	14 (29)	12 (24)	33 (22)
HBV positive	28 (56)	21 (43)	26 (53)	75 (51)
Uninfected	13 (26)	11 (22)	9 (18)	33 (22)
Number of prior systemic regimens, *n* (%)				
0	0	1 (2)	1 (2)	2 (1)
1	36 (72)	34 (69)	35 (71)	105 (71)
2	11 (22)	6 (12)	10 (20)	27 (18)
≥3	3 (6)	8 (16)	3 (6)	14 (9)
Prior therapy, *n* (%)				
Surgical resection	33 (66)	33 (67)	26 (53)	92 (62)
Radiotherapy	14 (28)	18 (37)	16 (33)	48 (32)
Local HCC treatment	29 (58)	33 (67)	29 (59)	91 (61)
Sorafenib[d]	50 (100)	48 (98)	48 (98)	146 (99)
Prior second-line therapies, *n* (%)				
Monotherapy[e]	9 (18)	10 (20)	11 (22)	30 (20)
Combination therapy[f]	4 (8)	4 (8)	4 (8)	12 (8)
Prior third- and subsequent-line therapies[g], *n* (%)				
Monotherapy[h]	3 (6)	9 (18)	1 (2)	13 (9)
Combination therapy[i]	1 (2)	7 (14)	3 (6)	11 (7)
Duration of prior sorafenib treatment, median (IQR), months	4.8 (3.0-11.0)	3.8 (2.6-9.5)	4.2 (2.4-7.4)	4.3 (2.6-9.8)
Reasons for sorafenib discontinuation, *n* (%)				
Disease progression	44 (88)	41 (84)	38 (78)	123 (84)
Toxicity	5 (10)	7 (14)	10 (20)	22 (15)
Completed treatment/other	1 (2)	2 (4)	1 (2)	4 (3)

Data reported in this table are for all randomized patients.

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CRF, case report form; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; IQR, interquartile range; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PD-L1, programmed death-ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

[a]Three patients (arm B: *n* = 1; arm C: *n* = 2) had a Child–Pugh score of 7; one patient in arm B had a Child–Pugh score of ≥9.

[b]Derived from CRF data.

[c]Seven patients overall (arm A: *n* = 2; arm B: *n* = 3; and arm C: *n* = 2) were reported to have both HBV and HCV as risk factors for HCC; four of these patients no longer had active viral replication for either virus, one had chronic hepatitis B (arm A), and two had chronic hepatitis C (arm C).

[d]Data not available for two patients.

[e]Monotherapies in the second-line setting were sorafenib, TKM PLK1, axitinib, cabozantinib, ramucirumab, capecitabine, OPB 111077, thalidomide, lenalidomide, tivantinib, regorafenib, fluorouracil, tepotinib, and MRX64.

[f]Combination therapies in the second-line setting were capecitabine + oxaliplatin + PEG BCT 100, cisplatin + fluorouracil, cisplatin + doxorubicin, tegafur + uracil, fluorouracil + leucovorin + oxaliplatin, cisplatin + doxorubicin + fluorouracil, and fluorouracil + oxaliplatin.

[g]Four patients in arm B and one patient in arm C received prior therapies in the fourth-line setting; two patients in arm B received therapies in the fifth-line setting.

[h]Monotherapies in the third-line and higher settings were pazopanib, sorafenib, enzalutamide, ramucirumab, bevacizumab, doxorubicin, capecitabine, MSC2156119J, TKM 080301, FGF401, and DCR MYC 102.

[i]Combination therapies in the third-line and higher settings were doxorubicin + fluorouracil + mitomycin, cisplatin + fluorouracil, gemcitabine + oxaliplatin, fluorouracil + leucovorin + oxaliplatin, cisplatin + epirubicin + fluorouracil, and fluorouracil + oxaliplatin.

Table 2. Efficacy outcomes

All randomized patients	Arm A NIVO1 + IPI3 Q3W (*n* = 50)		Arm B NIVO3 + IPI1 Q3W (*n* = 49)		Arm C NIVO3 Q2W + IPI1 Q6W (*n* = 49)	
	INV	BICR	INV	BICR	INV	BICR
ORR, *n* (%)[a,b]; 95% CI	17 (34); 21-49	16 (32); 20-47	13 (27); 15-41	15 (31); 18-45	14 (29); 17-43	15 (31); 18-45
CR, *n* (%)	1 (2)	4 (8)	1 (2)	3 (6)	0	1 (2)
PR, *n* (%)	16 (32)	12 (24)	12 (24)	12 (24)	14 (29)	14 (29)
SD, *n* (%)	15 (30)	9 (18)	9 (18)	5 (10)	8 (16)	9 (18)
Non-CR/non-PD, *n* (%)	0	2 (4)	0	1 (2)	0	0
PD, *n* (%)	16 (32)	20 (40)	24 (49)	24 (49)	22 (45)	21 (43)
TTR, median (range), months	2.6 (1.2-12.8)	2.0 (1.1-12.8)	2.6 (1.2-4.1)	2.6 (1.2-5.5)	1.6 (1.2-5.5)	2.7 (1.2-8.7)
DOR, median (95% CI), months	51.2 (12.6-NE)	17.5 (8.3-NE)	15.2 (7.1-NE)	22.2 (4.4-NE)	21.7 (4.2-NE)	16.6 (4.3-NE)
DCR, *n* (%)[c]; 95% CI	32 (64); 49-77	27 (54); 39-68	22 (45); 31-60	21 (43); 29-58	22 (45); 31-60	24 (49); 34-64
DDC, median (95% CI)[d], months	NA	16.6 (8.3-28.4)	NA	16.5 (7.0-55.3)	NA	11.5 (5.5-23.2)
PFS, median (95% CI), months	6.8 (2.7-16.4)	3.9 (2.6-8.3)	2.7 (1.4-4.2)	1.6 (1.3-6.9)	2.7 (1.4-4.4)	2.6 (1.3-4.5)

Data are for all randomized patients unless otherwise noted.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; DDC, duration of disease control; DOR, duration of response; INV, investigator assessment; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NA, not assessed; NE, not estimable; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; SD, stable disease; TTR, time to response.

[a]Objective response was defined as the proportion of patients with the best overall response of CR + PR.

[b]Response was unable to be determined for 10 patients by INV (2, 3, and 5 patients in arms A, B, and C, respectively), and 11 patients by BICR (3, 4, and 4 patients in arms A, B, and C, respectively).

[c]Disease control was defined as the proportion of patients with the best overall response of CR, PR, SD, or non-CR/non-PD.

[d]Assessed in patients with disease control.

small sample size (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.03.005).

To identify patient characteristics that may impact OS in response to nivolumab plus ipilimumab, an exploratory analysis of disease characteristics and select biomarkers at baseline was conducted in those with median OS <1 year versus ≥3 years. Given the small sample size, no statistical testing was conducted; therefore any associations are descriptive only. In arm A, a higher proportion of patients with baseline AFP <400 μg/l had an OS ≥3 years compared with those with AFP ≥400 μg/l. In arms B and C, there was a trend for longer OS in patients with HCV infection compared with those with uninfected HCC etiology (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.03.005). In all treatment arms, a higher proportion of patients with OS <1 year had EHS compared with those with OS ≥3 years. No differences in OS were observed between patients with high density of cluster of differentiation 8 (CD8)-positive cells in their baseline tumor tissue specimens (≥5.7%) versus those with low CD8 positivity (<5.7%) across all treatment arms (Figure 3). Among the patients who had OS ≥3 years, nine patients (18%), six patients (12%), and eight patients (16%) received subsequent therapy in arms A, B, and C, respectively (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.03.005). Of these, two patients in arm A and one patient in arm B received subsequent immunotherapy, suggesting no clinically meaningful impact of subsequent therapies on the long-term survival of patients.

Safety

Among all treated patients, the median duration of treatment was 5.1 months (95% CI 2.7-9.3 months), 2.3 months (95% CI 1.4-6.3 months), and 4.0 months (95% CI 2.1-6.7 months) in arms A, B, and C, respectively (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2024.03.005). Across the three arms, the majority of the patients received nivolumab or ipilimumab at a relative dose intensity of ≥90% (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2024.03.005).

Any-grade treatment-related adverse events (TRAEs) were reported in 46 patients (94%), 35 patients (71%), and 39 patients (81%), in arms A, B, and C, respectively; grade 3/4 TRAEs were reported in 27 patients (55%), 15 patients (31%), and 17 patients (35%), respectively (Table 3). The most common grade 3/4 TRAEs (in ≥10% of patients in any treatment arm) were increased aspartate aminotransferase, increased alanine aminotransferase, increased lipase, and hyponatremia (Table 3). Importantly no cases of hepatic failure due to treatment were reported. One treatment-related death was reported in arm A in the primary analysis due to a serious TRAE of grade 5 pneumonitis within 100 days after the last dose of study drugs[14]; no additional grade 5 events were observed at the 5-year follow-up. A summary of all deaths during the study is provided in Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2024.03.005.

IMAEs requiring immune-modulating medications were more frequently reported in arm A than in arm B or C (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2024.03.005). The proportion of patients who had IMAEs requiring treatment with topical or systemic steroids remained consistent with the primary analysis (36% versus 35%, respectively). IMAEs began within a median of 2.1-254.3 weeks across treatment arms; most IMAEs resolved when treated using established, per-protocol-defined algorithms, with a median time to resolution of

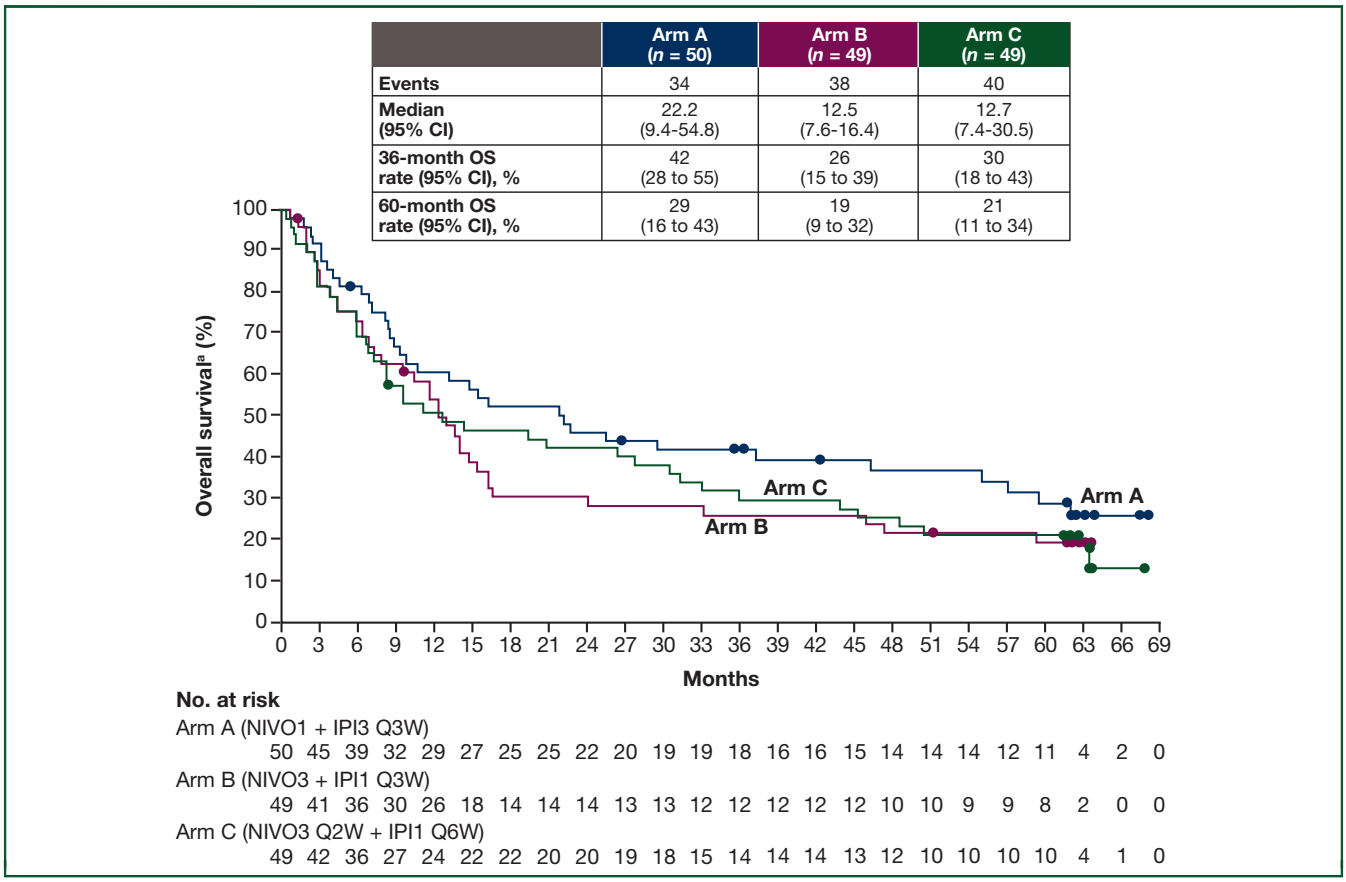

Figure 1. Overall survival.
[a]Median follow-up, 62.6 months; minimum follow-up, 60 months.
CI, confidence interval; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; OS, overall survival; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

0.1-39.1 weeks across organ categories (Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2024.03.005). The most common any-grade IMAEs leading to discontinuation were hepatitis [three patients (6%)], pneumonitis [three patients (6%)], and diarrhea/colitis [two patients (4%)] in arm A; hepatitis [two patients (4%)] and rash [one patient (2%)] in arm B; and nephritis and renal dysfunction [one patient (2%)] and adrenal insufficiency [one patient (2%)] in arm C (Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2024.03.005); no additional discontinuations occurred due to IMAEs since the primary analysis.[14]

DISCUSSION

To our knowledge, these data constitute the longest duration of follow-up reported for an immunotherapy combination in previously treated patients with advanced HCC. At a minimum follow-up of 60 months, the arm A regimen of nivolumab plus ipilimumab continued to demonstrate clinically meaningful responses and long-term survival benefit in patients with advanced HCC who were sorafenib intolerant or refractory. ORRs per investigator assessment were 34%, 27%, and 29% in arms A, B, and C, respectively. Responses were deep and durable across treatment arms, with a median DOR of 51.2 months in arm A. Among the three dosing regimens, arm A continued to demonstrate the highest survival benefit with a median OS of 22.2 months and a landmark 5-year OS rate of 29%. The separation of the OS curve of arm A from those of arms B and C that was observed in the primary analysis[14] continued with long-term follow-up. The safety profile of nivolumab plus ipilimumab was manageable, and no new safety signals were identified. The observed long-term clinical benefit of nivolumab plus ipilimumab reported in this analysis is consistent with reports in other solid tumors.[22-24]

Efficacy outcomes with nivolumab plus ipilimumab from this long-term follow-up were consistent with those from earlier analyses at 30.7 and 44 months of follow-up.[14,18] In arm A, investigator-assessed ORR increased from 32% at 30.7 months to 34% at 60 months. BICR-assessed outcomes remained consistent at all three follow-ups, with ORR and DCR of 32% and 54%, respectively. Objective response to nivolumab plus ipilimumab at the 6-month landmark was associated with long-term OS benefit across all three arms, with substantially improved median OS and 3-year OS rates in responders when compared with nonresponders.

Checkpoint inhibitors and their combination with other anticancer agents have shown promising clinical activity in advanced HCC.[25-31] In patients previously treated with sorafenib, pembrolizumab monotherapy provided an ORR of

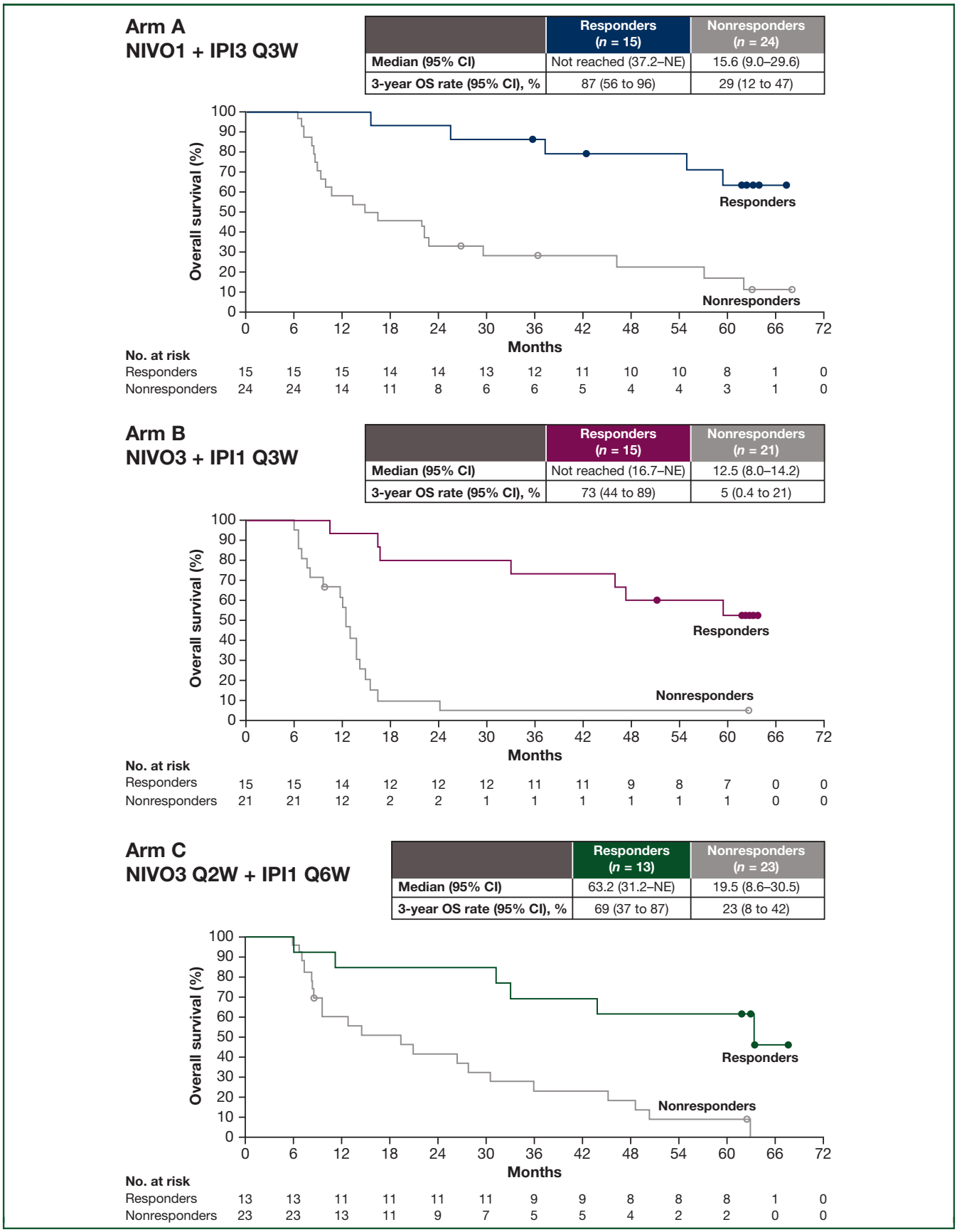

Figure 2. Landmark analysis of OS by best overall response[a].

[a]Patients who died or were censored by 6 months were excluded from this analysis. Responder is defined as PR or CR within 6 months after study therapy; nonresponder is defined as the best overall response (per BICR by RECIST version 1.1) other than PR and CR, or PR or CR not within 6 months after study therapy.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NE, not evaluable; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; OS, overall survival; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

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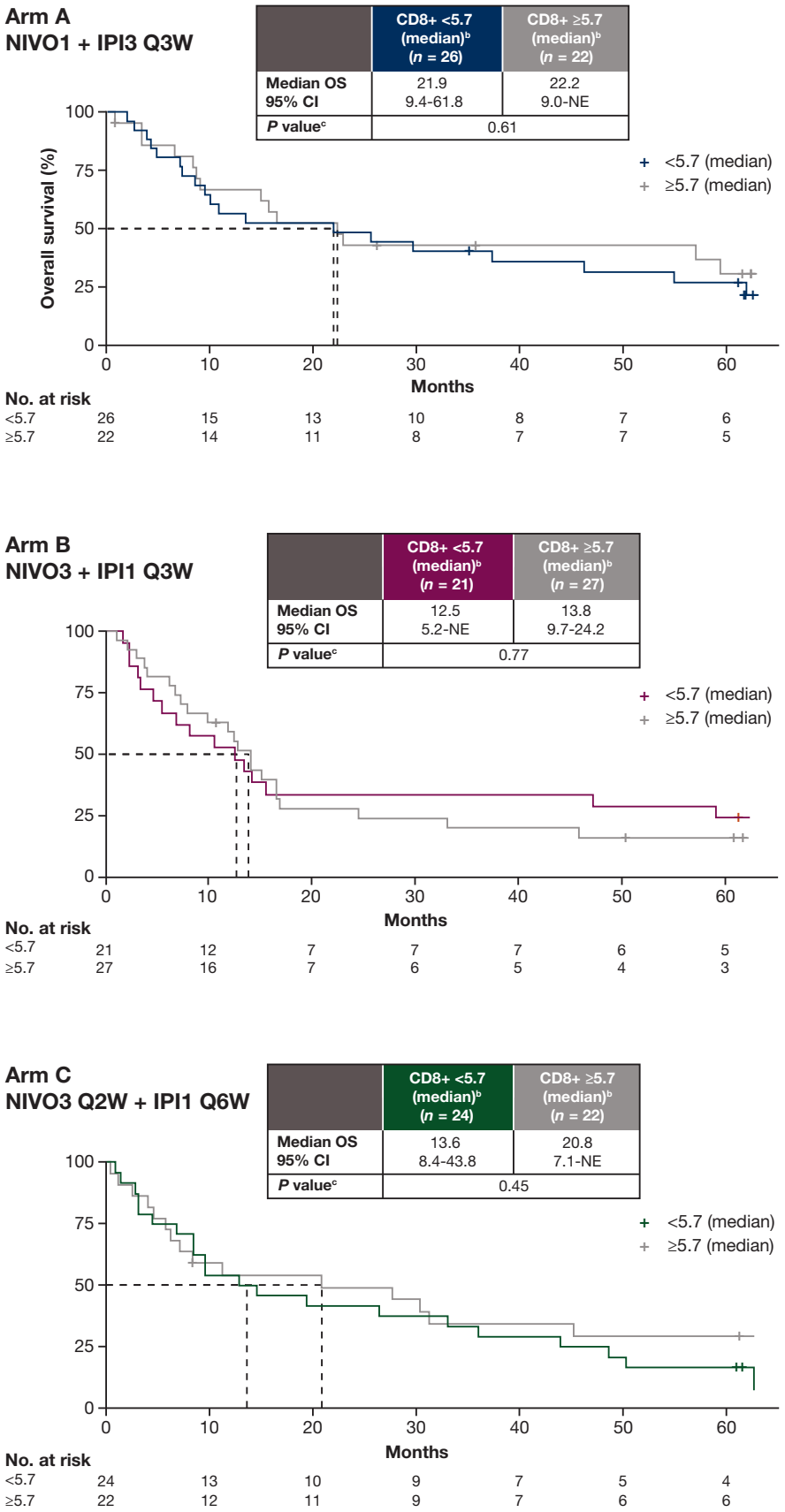

Figure 3. OS by baseline CD8[a] levels.

[a]CD8 immunohistochemistry was carried out on archival or fresh tumor samples.

[b]The median cutoff of 5.7% is based on CD8 data across the three treatment arms.

[c]*P* values were calculated by log-rank test.

CD8, cluster of differentiation 8; CI, confidence interval; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NE, not evaluable; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; OS, overall survival; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

Table 3. Treatment-related adverse events in all treated patients

Adverse event[a]	Arm A NIVO1 + IPI3 Q3W (n = 49)		Arm B NIVO3 + IPI1 Q3W (n = 49)		Arm C NIVO3 Q2W + IPI1 Q6W (n = 48)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAE	46 (94)	27 (55)	35 (71)	15 (31)	39 (81)	17 (35)
Any serious TRAE	11 (22)	10 (20)	11 (22)	8 (16)	9 (19)	8 (17)
Any TRAE leading to discontinuation	10 (20)	5 (10)	5 (10)	4 (8)	2 (4)	1 (2)
Treatment-related deaths[b]	1 (2)[c]		0		0	
TRAEs reported in ≥10% of patients in any arm						
Pruritus	22 (45)	2 (4)	16 (33)	0	16 (33)	1 (2)
Rash	15 (31)	2 (4)	13 (27)	2 (4)	9 (19)	0
Diarrhea	12 (24)	2 (4)	6 (12)	1 (2)	8 (17)	1 (2)
AST increase	10 (20)	8 (16)	10 (20)	4 (8)	6 (13)	2 (4)
Hypothyroidism	10 (20)	0	4 (8)	0	5 (10)	0
Fatigue	9 (18)	1 (2)	6 (12)	0	5 (10)	0
ALT increase	8 (16)	4 (8)	7 (14)	3 (6)	4 (8)	0
Maculopapular rash	8 (16)	2 (4)	4 (8)	0	3 (6)	0
Lipase increase	7 (14)	6 (12)	7 (14)	4 (8)	9 (19)	5 (10)
Decreased appetite	6 (12)	0	4 (8)	0	4 (8)	0
Malaise	6 (12)	1 (2)	3 (6)	0	3 (6)	0
Cortisol decrease	5 (10)	0	2 (4)	0	1 (2)	0
Hyponatremia	5 (10)	5 (10)	2 (4)	2 (4)	0	0
Nausea	5 (10)	0	4 (8)	0	1 (2)	0
Pyrexia	2 (4)	0	4 (8)	0	5 (10)	0
Abdominal pain	0	0	5 (10)	0	2 (4)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; TRAE, treatment-related adverse event.
[a]Includes events reported between the first dose and 30 days after the last dose of study therapy.
[b]Treatment-related deaths were reported regardless of the time frame.
[c]One event of pneumonitis.

18.3% and a median OS of 13.2 months.[28] In sorafenib-experienced patients with advanced HCC, nivolumab monotherapy provided an ORR of 14%, median OS of 15.2 months, and a 5-year OS rate of 12%.[27] While indirect cross-trial and cross-cohort comparisons have limited interpretability, the ORR and OS improvements observed with nivolumab plus ipilimumab in the current 5-year follow-up were apparently higher than those observed with anti-PD-1 monotherapies. It should be noted that 28% of patients in this cohort received two or more prior lines of therapy, and this proportion was similar in all arms. Recently, the first-line combination of a single dose of the anti-CTLA-4 monoclonal antibody tremelimumab with continued treatment with the anti-PD-L1 agent durvalumab was shown to improve OS versus sorafenib in advanced HCC in a phase III clinical trial.[26] Clinical benefit has also been reported with other combinations of PD-1/PD-L1 inhibitors with targeted agents in HCC in the first- and second-line settings.[31] While the first-line treatment landscape for advanced HCC is shifting from tyrosine kinase inhibitors to immunotherapy-based regimens, retrospective studies suggest that the combination of nivolumab plus ipilimumab may still have antitumor activity in patients who received prior immunotherapy-based regimens, likely due to the distinct and complementary mechanisms of action.[32-34] Prospective evaluation of the combination of nivolumab plus ipilimumab in second-line postimmunotherapy-based treatment is ongoing.[34]

The subgroup analyses by patient disease characteristics were exploratory. As the treatment arms were heterogeneous with small numbers of patients across subgroups, definitive conclusions should not be drawn. Survival benefits and responses to nivolumab plus ipilimumab were observed in all treatment arms regardless of tumor cell PD-L1 expression or baseline AFP status. Numerically higher ORR and longer median OS were observed in the PD-L1 ≥1% subgroup compared with the PD-L1 <1% subgroup in arm C. While responses were also observed regardless of viral etiology in arms A and B, there were no responses detected in arm C for uninfected patients, albeit it was a small subgroup with only nine patients. In arms B and C, patients who were HCV positive showed a trend for numerically higher ORR and longer OS compared with those who were HBV positive or uninfected; however, the small sample size of the HCV-positive subgroup precludes any conclusive association, and these patients could have had other prognostically positive disease-specific baseline characteristics. The exploratory analysis of OS by patient disease characteristics identified baseline AFP <400 μg/l, HCV infection, and absence of EHS as prognostic factors associated with longer OS, although the sample size was too small to draw any definitive conclusions. Pretreatment tumor T-cell infiltration as measured by CD8 density, a hallmark predictor of responses to immuno-oncology therapy, has previously shown a trend toward improved survival in the nivolumab monotherapy cohort of CheckMate 040 of sorafenib-naive and sorafenib-experienced patients with advanced HCC.[35-37] The baseline CD8 density was not associated with OS in the present study for patients treated with nivolumab plus ipilimumab, potentially due to an ipilimumab-induced increase in CD8 density in

tumor tissue as previously reported.[38] This result suggests that preexisting inflammation in the tumor microenvironment may not be necessary for survival benefit with the nivolumab plus ipilimumab combination in advanced HCC. This is also reminiscent of findings reported in patients with metastatic melanoma.[39]

Safety outcomes with nivolumab plus ipilimumab at the 5-year follow-up were consistent with those previously reported at 30.7 and 44 months.[14,18] Patients in arm A had a higher incidence of TRAEs, TRAEs leading to discontinuation, and IMAEs than those in arm B or C. However, the safety profile was consistent with that reported in previous studies for nivolumab and ipilimumab monotherapies and for the nivolumab plus ipilimumab combination in other solid tumors.[12,13,40-44] Most IMAEs resolved following treatment according to standard algorithms within 4-39 weeks across categories; no additional discontinuations due to IMAEs or treatment-related deaths were observed since the primary analysis.[14]

Limitations of this phase II study have been previously described and include its open-label study design, the relatively small patient population, and the lack of a control arm.[14] We also note that the treatment arms were not fully balanced with respect to their prognostic factors due to the absence of stratification, and the study design was not intended to compare the cohorts with sufficient statistical power. In addition, because all patients had preserved liver function with Child—Pugh A status at baseline, the clinical benefit of nivolumab plus ipilimumab in patients with worse liver function remains unevaluated. Such studies have previously been conducted for nivolumab monotherapy in advanced HCC and have shown clinical benefit in patients with Child—Pugh B status.[45]

Nivolumab plus ipilimumab continued to provide durable and clinically meaningful responses along with long-term survival benefits and manageable safety over 5 years of follow-up in sorafenib-treated patients with advanced HCC. These results further support the use of the arm A regimen (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg Q3W for four doses, followed by nivolumab 240 mg Q2W) as second-line treatment for advanced HCC and are a step toward achieving long-term survival benefit of >4 years, even for those patients treated at an advanced stage of their disease. Nivolumab plus ipilimumab remains an effective second-line treatment and an alternative option for patients with advanced HCC who received prior immunotherapy- or tyrosine kinase inhibitor-based regimens, with Food and Drug Administration approval for treatment in patients previously treated with sorafenib. A randomized phase III study comparing first-line nivolumab plus ipilimumab versus lenvatinib or sorafenib in advanced HCC is in progress (CheckMate 9DW: NCT04039607).

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DATA SHARING

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

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