ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Nivolumab in sorafenib-naive and sorafenib-experienced patients with advanced hepatocellular carcinoma: 5-year follow-up from CheckMate 040☆

A. B. El-Khoueiry[1]*, J. Trojan[2], T. Meyer[3], T. Yau[4], I. Melero[5], M. Kudo[6], C. Hsu[7,8], T.-Y. Kim[9], S.-P. Choo[10], Y.-K. Kang[11], W. Yeo[12], A. Chopra[13], S. Soleymani[14], J. Yao[15], J. Neely[16], M. Tschaika[17], T. H. Welling[18] & B. Sangro[19]

[1]Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Los Angeles, USA; [2]Department of Medicine, Goethe University Hospital and Cancer Center, Frankfurt, Germany; [3]Department of Oncology, Royal Free Hospital, London, UK; [4]Department of Medicine, University of Hong Kong, Hong Kong, China; [5]Department of Immunology, Clinica Universidad de Navarra and CIBERONC, Pamplona, Spain; [6]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan; [7]Department of Medical Oncology, National Taiwan University Cancer Center, Taipei, Taiwan; [8]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; [9]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea; [10]Division of Medical Oncology, National Cancer Center and Curie Oncology, Singapore, Republic of Singapore; [11]Department of Oncology, Asan Medical Center, University of Ulsan, Seoul, Korea; [12]Department of Clinical Oncology, Chinese University of Hong Kong, Hong Kong, China; [13]Department of Medical Oncology, Johns Hopkins Singapore International Medical Centre, Singapore, Republic of Singapore; [14]Global Biometrics & Data Sciences, Bristol Myers Squibb, Princeton, USA; [15]Informatics and Predictive Sciences, Bristol Myers Squibb, Princeton, USA; [16]Translational Medicine, Bristol Myers Squibb, Princeton, USA; [17]Oncology Clinical Development, Bristol Myers Squibb, Princeton, USA; [18]Perlmutter Cancer Center and Department of Surgery, NYU Langone Health, New York, USA; [19]Liver Unit and HPB Oncology Area, Clinica Universidad de Navarra and CIBEREHD, Pamplona, Spain

Available online XXX

Background: Patients with advanced hepatocellular carcinoma (aHCC) have a poor prognosis and high mortality. Nivolumab monotherapy demonstrated clinical benefit with an acceptable safety profile in patients with aHCC in the CheckMate 040 study. Five-year follow-up of the sorafenib-naive and sorafenib-experienced groups of CheckMate 040 is presented here.

Patients and methods: Patients received nivolumab monotherapy at dose levels of 0.1-10.0 mg/kg (dose-escalation phase) or 3 mg/kg (dose-expansion phase) every 2 weeks until disease progression or unacceptable toxicity. Primary endpoints were safety and tolerability (dose escalation), and objective response rate (ORR) by blinded independent central review (BICR) and by investigator as per RECIST version 1.1 (dose expansion).

Results: Eighty sorafenib-naive and 154 sorafenib-experienced patients were treated. Minimum follow-up in both groups was 60 months. ORR as per BICR was 20% [95% confidence interval (CI) 12% to 30%] and 14% (95% CI 9% to 21%) in the sorafenib-naive and sorafenib-experienced groups, respectively. Responses occurred regardless of HCC etiology or baseline tumor cell programmed death-ligand 1 (PD-L1) expression levels. Median overall survival (OS) was 26.6 months (95% CI 16.6-30.6 months) and 15.1 months (95% CI 13.0-18.2 months) in sorafenib-naive and sorafenib-experienced patients, respectively. The 3-year OS rates were 28% in the sorafenib-naive and 20% in the sorafenib-experienced groups; 5-year OS rates were 14% and 12%, respectively. No new safety signals were identified; grade 3/4 treatment-related adverse events were observed in 33% and 21% of patients in the sorafenib-naive and sorafenib-experienced groups, respectively. Biomarker analyses showed that baseline PD-L1 expression $\geq$1% was associated with higher ORR and longer OS compared with PD-L1 $<$1%. In the sorafenib-naive group, patients with OS $\geq$3 years exhibited higher baseline CD8 T-cell density compared with those with OS $<$1 year.

Conclusion: With 5 years of follow-up, nivolumab monotherapy continued to provide durable clinical benefit with manageable safety in sorafenib-naive and sorafenib-experienced patients with aHCC.

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

INTRODUCTION

Liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer deaths globally.[1] Hepatocellular carcinoma (HCC) is the predominant type of liver cancer and is often diagnosed at advanced stages; the 5-year survival rate for advanced HCC (aHCC) is ~3%.[1,2] First-line systemic therapy options for patients with unresectable HCC include immuno-oncology-based combinations such as

*Correspondence to: Dr Anthony B. El-Khoueiry, USC Norris Comprehensive Cancer Center, 1975 Zonal Avenue, Los Angeles, CA 90033, USA. Tel: +1-323-865-3900

E-mail: elkhouei@usc.edu (A. B. El-Khoueiry).

☆Note: This study was previously presented in part at the International Liver Cancer Association conference (ILCA), Virtual, 2-5 September 2021.

atezolizumab plus bevacizumab and tremelimumab plus durvalumab[3-7]; other recommended therapies include sorafenib, lenvatinib, pembrolizumab, durvalumab, and nivolumab (useful in certain circumstances if ineligible for tyrosine kinase inhibitors or other anti-angiogenic agents).[5,6,8-11] Subsequent-line systemic therapy options following disease progression (second or later lines) for Child—Pugh class A disease include regorafenib, cabozantinib, and ramucirumab [in patients with α-fetoprotein (AFP) ≥400 ng/ml only]; however, these treatments provide only a modest survival benefit [median overall survival (OS) 8.5-10.6 months].[5,12-14] In the United States, pembrolizumab and nivolumab plus ipilimumab are also subsequent-line therapy options for Child—Pugh A disease.[5]

CheckMate 040 is an open-label, multicohort, phase I/II study of nivolumab alone or in combination with other agents in patients with aHCC.[15] In this study, nivolumab provided durable objective responses [objective response rate (ORR) 14%; median duration of response (DOR) not reached] and clinically meaningful survival (median OS 15.1 months)[16] to patients previously treated with sorafenib and had a manageable safety profile.[17,18] Long-term follow-up data can provide valuable information to clinicians regarding the efficacy and safety of anticancer therapies over extended treatment periods.[19] Three-year follow-up data from CheckMate 040 showed maintenance of ORR benefit with nivolumab, regardless of tumor cell programmed death-ligand 1 (PD-L1) expression levels or HCC etiology, and no new safety signals were identified.[20,21] Here we report efficacy, safety, and biomarker analyses from the 5-year follow-up of the sorafenib-naive and sorafenib-experienced groups of CheckMate 040.

PATIENTS AND METHODS

Study design and patients

CheckMate 040 is an international, multicenter, multicohort, open-label, non-comparative, phase I/II study in patients with aHCC with or without chronic viral hepatitis (ClinicalTrials.gov identifier: NCT01658878). The study was conducted at 38 sites in 11 countries (Canada, Germany, Hong Kong, Italy, Japan, Republic of Korea, Republic of Singapore, Spain, Taiwan, UK, and United States). Eligible patients were at least 18 years of age with histologically confirmed aHCC (not amenable to curative surgery or local treatment), with an Eastern Cooperative Oncology Group performance status of 0 or 1,[22] and were sorafenib naive or sorafenib treated (intolerant to or progressed on sorafenib), with at least one measurable lesion as per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1).[23]

Patients in both the dose-escalation (cohort 1) and dose-expansion (cohort 2) phases could be infected with hepatitis B virus (HBV), hepatitis C virus (HCV), or be uninfected; patients with chronic HBV infection were required to have an HBV DNA viral load <100 IU/ml at screening and be on antiviral therapy before treatment initiation. Patients were required to have Child—Pugh scores of ≤7 (Child—Pugh A or B7) in the dose-escalation phase, and ≤6 (Child—Pugh A) in the dose-expansion phase; adequate organ and marrow function (e.g. bilirubin levels ≤3 mg/dl; albumin ≥2.8 g/dl; platelets ≥60 × 10^3/μl) was required. Additional eligibility criteria are included in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.12.008.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines developed by the International Council for Harmonisation and in compliance with the study protocol. Study protocol and amendments were approved by the institutional review board or independent ethics committee at each study site, and all patients provided written informed consent before enrollment.

Procedures

Details of the CheckMate 040 study design have been published previously.[15] Briefly, patients in the dose-escalation phase were administered intravenous (i.v.) nivolumab (0.1, 0.3, 1, 3, and 10 mg/kg) every 2 weeks (q2w) until a confirmed complete response (CR), disease progression, unacceptable toxicity, or completion of 2 years of therapy. Dose-limiting toxicities were determined up to 2 weeks after the third nivolumab dose. In the dose-expansion phase, patients received nivolumab 3 mg/kg i.v. q2w, until disease progression, unacceptable toxicity, or study discontinuation. In both the dose-escalation and dose-expansion phases, nivolumab dose delay was permitted for up to 6 weeks from the last dose; treatment beyond initial investigator-assessed progression was permitted. Criteria for treatment beyond progression are reported in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.12.008.

Outcomes

The primary endpoint of the dose-escalation phase was safety and tolerability of nivolumab in patients with aHCC. For the dose-expansion phase, the primary endpoint was ORR [best overall response (BOR) of CR or partial response (PR), divided by the number of treated patients] by blinded independent central review (BICR) and investigator assessments as per RECIST v1.1. Key secondary endpoints included progression-free survival (PFS) and time to progression (TTP), by BICR and/or investigator assessment as per RECIST v1.1; OS; and investigation of potential associations between selected biomarkers and clinical efficacy measures. Exploratory endpoints included assessment of antitumor activity by BICR assessment using modified RECIST (mRECIST).[24] Definitions of key endpoints can be found in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.12.008.

Assessments

Tumors were assessed using computed tomography or magnetic resonance imaging of chest, abdomen, and pelvis at baseline, every 6 weeks for 48 weeks, and every 12

weeks thereafter until disease progression or treatment discontinuation. A BOR of CR or PR was confirmed by a second scan at least 4 weeks after initial response. Safety was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 continuously throughout treatment and for 100 days after last treatment, and adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities version 23.1. Any causal relationship of AEs to study drug was determined by the investigator. Immune-mediated adverse events (IMAEs) were also recorded. IMAEs were defined as events, regardless of causality, occurring within 100 days of the last dose for which patients received immune-modulating medication for treatment of the event; endocrine events were included as IMAEs, although they are often managed without immunosuppression.

Pretreatment tumor samples (archival or recent) were required for biomarker evaluation. Baseline tumor cell PD-L1 expression and CD8 T-cell density were assessed by immunohistochemistry. Biomarkers [CD8 T-cell density, albumin—bilirubin (ALBI) grades, and Child—Pugh scores] were assessed for their association with OS and summarized as boxplots using medians and interquartile ranges (boxes include the 25th, 50th, and 75th percentiles). Additional biomarker methods can be found in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.12.008.

Statistical analyses

Efficacy and safety were analyzed in all patients who received at least one dose of study treatment. The two-sided 95% exact confidence interval (CI) for ORR was calculated by the Clopper—Pearson method. Response-evaluable patients had baseline and at least one on-study tumor assessment. The Kaplan—Meier product-limit method was used to determine medians for DOR and corresponding 95% CIs; PFS, TTP, and OS were estimated using Kaplan—Meier techniques. Patient characteristics and safety data were summarized using descriptive statistics. Statistical analyses were carried out using SAS software (version 9.2 or higher; SAS Institute, Cary, NC).

In the dose-escalation phase, sample size at each dose level was based on the observed toxicity and not on statistical considerations; 3-6 patients were evaluated at each dose level using a 3 + 3 design. In the dose-expansion phase, ∼100 additional uninfected patients (50 who progressed on sorafenib and 50 who were sorafenib naive or intolerant), 50 HCV-infected patients, and 50 HBV-infected patients received nivolumab 3 mg/kg using a parallel design. If 50 patients were treated with nivolumab 3 mg/kg in any of the four additional expansion arms, and 20% were responders (BOR of PR or CR), the lower bound of the 95% CI of the response rate was estimated to be 10% using the Clopper—Pearson method. Additional statistical methods used for the biomarker analyses can be found in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.12.008.

RESULTS

Baseline characteristics and patient disposition

The clinical data cut-off for this analysis was 2 November 2020. Between 26 November 2012 and 8 August 2016, 262 patients were treated: 48 patients in the dose-escalation phase and 214 patients in the dose-expansion phase, as described previously.[15] A total of 80 sorafenib-naive patients [dose escalation (nivolumab 0.1-10 mg/kg q2w): $n = 11$; dose expansion (nivolumab 3 mg/kg q2w): $n = 69$] and 154 sorafenib-experienced patients (dose escalation: $n = 9$; dose expansion: $n = 145$; nivolumab 3 mg/kg q2w in both phases) were treated. The minimum follow-up (time from first dose of the last patient to data cut-off) in both sorafenib-naive and sorafenib-experienced groups was 60 months. The median follow-up (time from first dose to data cut-off) was 62.9 months (range 60-94 months) in the sorafenib-naive group and 62.8 months (range 60-86 months) in the sorafenib-experienced group. Median age of patients was 65 years (range 20-83 years) and 63 years (range 19-81 years) in the sorafenib-naive and sorafenib-experienced groups, respectively (Table 1). Most patients had Barcelona Clinic Liver Cancer stage C (90%), extrahepatic spread (≥60%), Child—Pugh score 5 (∼70%), and tumor cell PD-L1 expression <1% (∼70%; Table 1). In terms of HCC etiology, 55 patients (24%) were infected with HBV, of which 54 patients had active HBV infections; 57 patients (24%) were infected with HCV, of which 51 patients had active HCV infections; and 122 patients (52%) were uninfected (Table 1). Most patients with prior sorafenib treatment (91%) progressed on or after sorafenib (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.12.008).

At data cut-off, 79 patients (99%) in the sorafenib-naive group and 151 patients (98%) in the sorafenib-experienced group had discontinued therapy (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.12.008). The most common reason for treatment discontinuation in both groups was disease progression [sorafenib naive: 62 patients (78%); sorafenib experienced: 126 patients (82%); Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.12.008]. In the sorafenib-naive and sorafenib-experienced groups, 47 patients (59%) and 82 patients (53%), respectively, received subsequent therapy, the most common being systemic therapy [in 34 patients (43%) and 58 patients (38%), respectively]. Four patients (5%) and 11 patients (7%), respectively, received subsequent immunotherapy (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.12.008).

Efficacy

At the 5-year follow-up, BICR-assessed ORR was 20% (95% CI 12% to 30%) and 14% (95% CI 9% to 21%) in the sorafenib-naive and sorafenib-experienced groups, respectively; investigator-assessed ORR was 23% (95% CI 14% to 33%) and 20% (95% CI 14% to 27%), respectively (Table 2).

Table 1. Baseline patient demographics and clinical characteristics

Patients	Sorafenib naive (n = 80)	Sorafenib experienced[a] (n = 154)
Age, years		
Median (range)	65 (20-83)	63 (19-81)
≥65 years	42 (53)	68 (44)
Male	68 (85)	118 (77)
Race		
White	46 (58)	71 (46)
Asian	28 (35)	80 (52)
Black/African American/ other	6 (8)	3 (2)
ECOG PS		
0	47 (59)	100 (65)
1	33 (41)	54 (35)
BCLC stage[b,c]		
B	7 (9)	14 (9)
C	72 (90)	138 (90)
Extrahepatic spread[c]	48 (60)	110 (71)
Vascular invasion[c]	27 (34)	44 (29)
Etiology[d]		
Uninfected	47 (59)	75 (49)
HBV[e]	8 (10)	47 (31)
HCV[e]	25 (31)	32 (21)
Child–Pugh score[c]		
5	58 (73)	104 (68)
6	19 (24)	48 (31)
>6	3 (4)	2 (1)
AFP ≥400 µg/l[c,f]	27 (34)	57 (37)
ALBI		
Grade 1	33 (41)	78 (51)
Grade 2	47 (59)	76 (49)
Tumor cell PD-L1 expression[c,g]		
<1%	56 (70)	110 (71)
≥1%	11 (14)	26 (17)
Prior treatment		
Surgical resection	41 (51)	101 (66)
Radiotherapy	6 (8)	37 (24)
Local treatment for HCC	37 (46)	90 (58)

Data are presented as n (%) unless otherwise noted.
AFP, α-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; CRF, case report form; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IVRS, interactive voice response system; PD-L1, programmed death-ligand 1.
[a]Sorafenib-experienced patients treated with nivolumab 3 mg/kg.
[b]Two patients in the sorafenib-experienced group were BCLC stage A.
[c]Derived from CRF data.
[d]Derived from IVRS data.
[e]Fifty-four patients had active HBV infections (8 in the sorafenib-naive group and 46 in the sorafenib-experienced group); 51 patients had active HCV infections (23 in the sorafenib-naive group and 28 in the sorafenib-experienced group). No active infections with both HBV and HCV were reported.
[f]Nine patients did not have baseline AFP values (four in the sorafenib-naive group and five in the sorafenib-experienced group).
[g]Thirty-one patients had PD-L1 expression levels that were not quantifiable at baseline (13 in the sorafenib-naive group and 18 in the sorafenib-experienced group).

Deepening of response was seen in the sorafenib-experienced group after the 14.8-month follow-up,[16] with one additional patient having a PR that converted to a CR as per BICR. Responses occurred independent of HCC etiology or tumor cell PD-L1 expression levels (Figure 1 and Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2023.12.008). Median DOR as per BICR was 22.6 months [95% CI 11.1 months-not evaluable (NE)] in the sorafenib-naive group and 39.7 months (95% CI 9.7 months-NE) in the sorafenib-experienced group (Table 2). Among the patients with an initial BOR of CR as per BICR (n = 8; 3 patients in the sorafenib-naive group and five patients in the sorafenib-experienced group), disease progression was reported in one patient in each treatment group; among those with CR as per investigator assessment (n = 6; 1 patient in the sorafenib-naive group and 5 patients in the sorafenib-experienced group), two patients in the sorafenib-experienced group had disease progression (Table 2). In the sorafenib-experienced group, three out of five patients with a BOR of CR had a DOR of at least 24 months.

The median OS was 26.6 months (95% CI 16.6-30.6 months) and 15.1 months (95% CI 13.0-18.2 months) in the sorafenib-naive and sorafenib-experienced groups, respectively; 3-year OS rates were 28% (95% CI 18% to 38%) and 20% (95% CI 14% to 27%) and 5-year OS rates were 14% (95% CI 7% to 23%) and 12% (95% CI 7% to 18%), respectively (Figure 2). HCC etiology did not affect median OS in either group (Supplementary Figure S1 and Table S4, available at https://doi.org/10.1016/j.annonc.2023.12.008). In landmark analyses of OS from month 6, median OS was longer in responders (CR + PR) versus non-responders [progressive disease (PD) + stable disease (SD) + non-CR/non-PD] in both sorafenib-naive and sorafenib-experienced groups (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.12.008). Among responders, median OS was 48.1 months (95% CI 30.6 months-NE) in the sorafenib-naive group and not reached (26.7 months-NE) in the sorafenib-experienced group; median OS in patients with a BOR of SD + non-CR/non-PD was 27.6 months (95% CI 17.4-35.8 months) and 20.2 months (95% CI 15.6-26.0 months), respectively (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.12.008).

Among 25 patients with an OS of at least 5 years, 21 patients discontinued study treatment: 7 (88%) in the sorafenib-naive group [due to disease progression (n = 6); study drug toxicity (n = 1)] and 14 (82%) in the sorafenib-experienced group [due to disease progression (n = 8); study drug toxicity (n = 2); patient request to discontinue study treatment (n = 2); AE unrelated to study drug (n = 1); maximum clinical benefit (n = 1; CR)]. Median duration of treatment among these patients was 46.7 weeks (range 4.1-222.1 weeks) in the sorafenib-naive group and 106.2 weeks (range 14.1-263.1 weeks) in the sorafenib-experienced group. In an exploratory analysis, ORR assessed using mRECIST as per BICR was 24% in the sorafenib-naive group and 18% in the sorafenib-experienced group (Table 2).

Safety

Among all treated patients (patients who received at least one dose of study medication), median duration of therapy was 4.5 months (range 0-66.3+ months) in the sorafenib-naive group and 5.1 months (range 0-64.0+ months) in the sorafenib-experienced group. The median number of nivolumab doses administered was 10 (range 1-142) in the sorafenib-naive group and 11 (range 1-133) in the

Table 2. Best overall response and antitumor activity with nivolumab

All randomized	Sorafenib naive (n = 80)		Sorafenib experienced[a] (n = 154)	
	BICR[b]	INV	BICR	INV
ORR, n (%; 95% CI)	16 (20; 12-30)	18 (23; 14-33)	22 (14; 9-21)	31 (20; 14-27)
Best overall response, n (%)				
Complete response	3[c] (4)	1 (1)	5[c] (3)	5[d] (3)
Partial response	13 (16)	17 (21)	17 (11)	26 (17)
Stable disease	26 (33)	32 (40)	65 (42)	65 (42)
Progressive disease	32 (40)	26 (33)	59 (38)	53 (34)
Unable to determine	4 (5)	4 (5)	8 (5)	5 (3)
ORR by mRECIST, n (%; 95% CI)	19 (24; 15-35)	NA	28 (18; 12-25)	NA
Median TTR (range),[e] months	2.7 (1.3-5.5)[f]		2.8 (1.2-7.0)[g]	
Median DOR (95% CI),[e,h] months	22.6 (11.1-NE)[f]		39.7 (9.7-NE)[g]	

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; INV, investigator assessed; mRECIST, modified RECIST; NA, not available; NE, not evaluable; ORR, objective response rate; PD, progressive disease; TTR, time to response.
[a]Sorafenib-experienced patients treated with nivolumab 3 mg/kg.
[b]Two patients had best overall response reported as non-CR/non-PD by BICR.
[c]One patient had disease progression after an initial complete response.
[d]Two patients had disease progression after an initial complete response.
[e]Evaluated in patients who had an objective response as per BICR.
[f]Sixteen responders in the sorafenib-naive arm.
[g]Twenty-two responders in the sorafenib-experienced arm.
[h]Median computed using the Kaplan–Meier method.

sorafenib-experienced group. The median cumulative nivolumab dose was 27.5 mg/kg (range 0.3-413.2 mg/kg) and 32.3 mg/kg (range 3.0-405.6 mg/kg) in the sorafenib-naive and sorafenib-experienced groups, respectively; 68 patients (85%) and 122 patients (79%) received a relative nivolumab dose intensity ≥90%, respectively. Any-grade treatment-related adverse events (TRAEs) were reported in 64 patients (80%) in the sorafenib-naive group and 121 patients (79%) in the sorafenib-experienced group; grade 3/4 TRAEs were reported in 26 patients (33%) and 33 patients (21%), respectively, and no grade 5 events were reported (Table 3). The most frequent grade 3/4 TRAEs (in ≥5% of patients) were increases in aspartate aminotransferase [AST; n = 8 (10%)], lipase [n = 8 (10%)], amylase [n = 7 (9%)], and alanine aminotransferase [ALT; n = 5 (6%)] in the sorafenib-naive group and increase in lipase [n = 7 (5%)] in the sorafenib-experienced group (Table 3). Grade 3/4 TRAEs leading to discontinuation occurred in two patients (3%) in the sorafenib-naive group [ALT increase: n = 2 (3%); AST increase: n = 1 (1%); liver function test increase: n = 1 (1%)] and in three patients (2%) in the sorafenib-experienced group [ALT increase, AST increase, hepatitis, polyarthritis, and pneumonitis in one patient each (<1%)]. Grade 3/4 TRAEs leading to discontinuation occurred between 1.0 and 14.3 months and 0.0 and 3.3 months in the sorafenib-naive and sorafenib-experienced groups, respectively (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2023.12.008).

The most commonly reported IMAEs of any grade (in ≥5% of patients) were rash [n = 13 (16%)], hepatitis [n = 5 (6%)], and hypothyroidism/thyroiditis [n = 5 (6%)] in the sorafenib-naive group and rash [n = 16 (10%)], hepatitis [n = 8 (5%)], hypothyroidism/thyroiditis [n = 8 (5%)], and diarrhea/colitis [n = 7 (5%)] in the sorafenib-experienced group (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2023.12.008). Grade 3/4 IMAEs were reported in ≤5% of patients in each group; the most commonly reported grade 3/4 IMAE was hepatitis [n = 4 (5%) in the sorafenib-naive group and n = 7 (5%) in the sorafenib-experienced group; Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2023.12.008]. IMAEs began within a median of 0.14-69.5 weeks in the sorafenib-naive group and 4.0-41.0 weeks in the sorafenib-experienced group; IMAEs resolved within a median of 0.14-26.3 weeks and 0.14-22.0 weeks, respectively (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2023.12.008). Eight patients (10%) in the sorafenib-naive group and 20 patients (13%) in the sorafenib-experienced group required corticosteroids for the management of IMAEs.

Any-grade TRAEs with potential immunologic etiology occurred in 40% (skin), 20% (hepatic), 15% (gastrointestinal), 13% (endocrine), and 1% (pulmonary) of patients in the sorafenib-naive group and in 31% (skin), 9% (hepatic), 17% (gastrointestinal), 8% (endocrine), 1% (pulmonary), and 0.6% (renal) of patients in the sorafenib-experienced group (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.12.008); most were grade 1-2; no grade 5 events were reported. TRAEs of potential immunologic etiology began within a median of 2.2-21.0 weeks in the sorafenib-naive group and 2.2-48.0 weeks in the sorafenib-experienced group, depending on organ category. Median time to resolution was 2.6-18.1 weeks in the sorafenib-naive group and 3.1-17.9 weeks in the sorafenib-experienced group (median was not reached for endocrine and pulmonary events in the sorafenib-experienced group; Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.12.008). One treatment-related death (pneumonitis; <1%) was reported in the sorafenib-experienced group (Table 3).

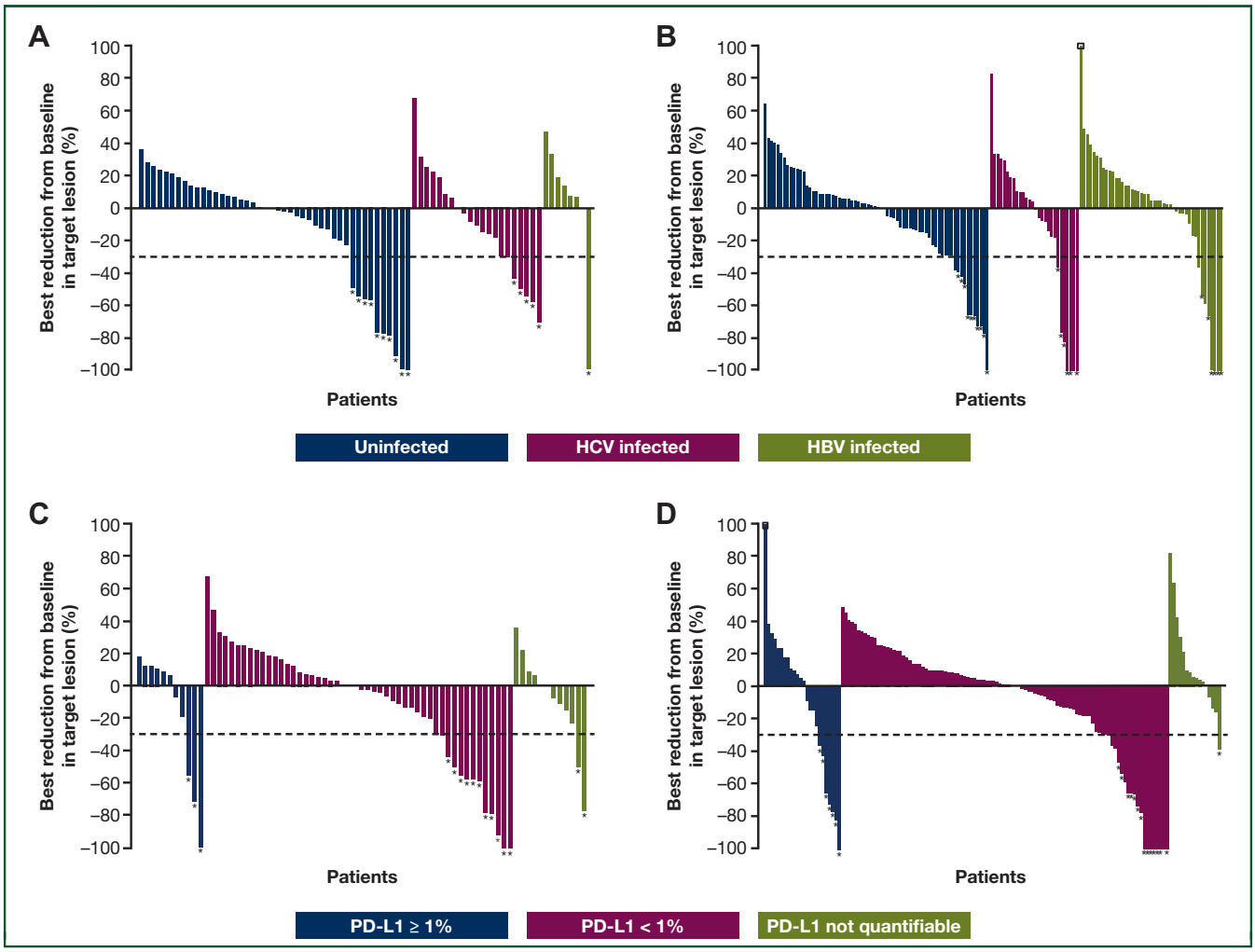


Figure 1. Efficacy by etiology and tumor cell PD-L1 expression. Waterfall plots depicting change from baseline in target lesion by etiology in (A) sorafenib-naive and (B) sorafenib-experienced patients and by tumor cell PD-L1 expression in (C) sorafenib-naive and (D) sorafenib-experienced patients. Negative/positive value means maximum tumor reduction/minimum tumor increase. Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy. Horizontal reference line indicates the 30% reduction consistent with a response as per RECIST v1.1. Asterisk symbol represents responders; square symbol represents percentage change truncated to 100%. Tumor cell PD-L1 expression levels were determined from archival or fresh biopsies; sorafenib-experienced patients were treated with nivolumab 3 mg/kg. Response evaluable: patients with (i) a best overall response of CR, PR, SD, non-CR/non-PD, or PD; (ii) target lesion(s) assessed at baseline; and (iii) at least one on-study time point with all baseline target lesion(s) assessed.

CR, complete response; HBV, hepatitis B virus; HCV, hepatitis C virus; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.

Biomarker analyses

An exploratory analysis of disease characteristics and select biomarkers at baseline was conducted in patients with OS <1 year versus OS ≥3 years to identify characteristics that might have affected OS. Given the small sample size, no statistical testing was conducted so these associations are descriptive only.

The proportion of patients with baseline extrahepatic spread or AFP ≥400 µg/l was higher in patients with OS <1 year versus OS ≥3 years, whereas the proportion of patients with baseline tumor cell PD-L1 expression ≥1% was higher in patients with OS ≥3 years versus OS <1 year (Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2023.12.008). ORR and median OS were higher among patients with baseline tumor cell PD-L1 expression ≥1% than those with PD-L1 <1%, with these differences being more prominent in the sorafenib-experienced group (Supplementary Figure S1 and Table S4, available at https://doi.org/10.1016/j.annonc.2023.12.008). In the sorafenib-naive group only, presence of vascular invasion at baseline also appeared to be associated with shorter OS (Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2023.12.008).

In the sorafenib-naive group, patients with OS ≥3 years exhibited a higher median baseline CD8 T-cell density than those with OS <1 year; in the sorafenib-experienced group, baseline CD8 T-cell density was similar in patients with OS <1 year versus ≥3 years (Figure 3A). Of note, median CD8 T-cell density was 8.1% (range 1.6% to 19.5%) in the eight patients who had a BOR of CR as per BICR; six of these eight patients (75%) had median OS ≥3 years. In both the sorafenib-naive and -experienced groups, patients with baseline ALBI grade 2 had a shorter OS than those with ALBI grade 1 (Figure 3B). Baseline Child–Pugh score did not

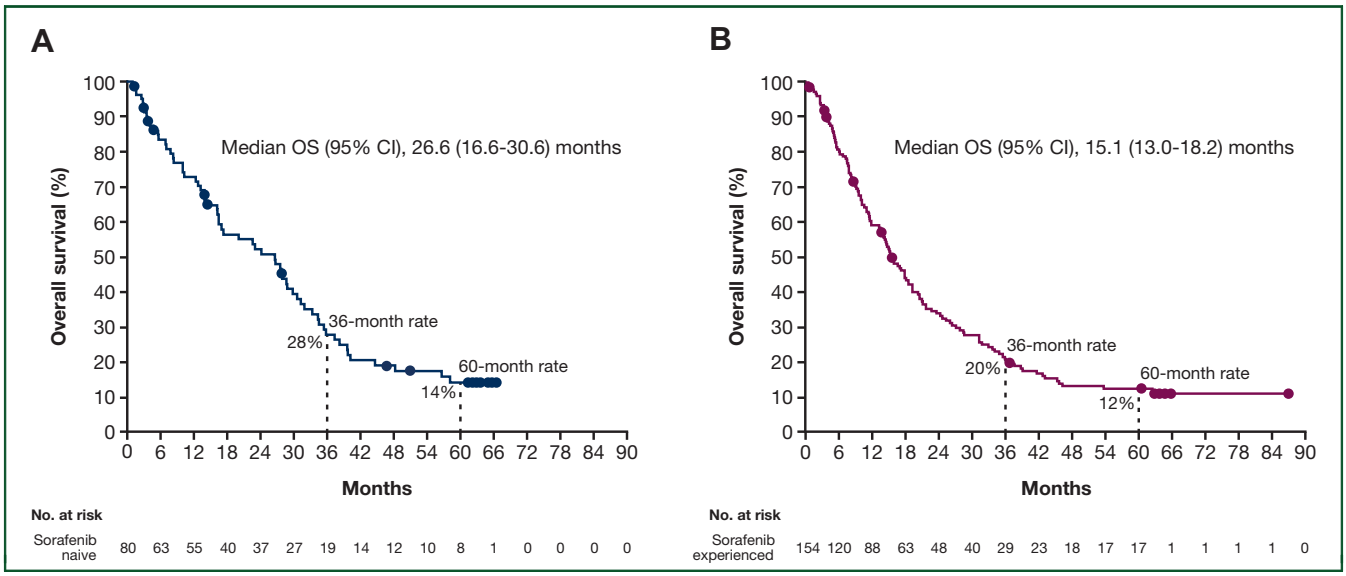


Figure 2. Kaplan—Meier plots of survival. OS with nivolumab in (A) sorafenib-naive and (B) sorafenib-experienced patients. Filled circles denote censored patients. Sorafenib-experienced patients were treated with nivolumab 3 mg/kg.
CI, confidence interval; OS, overall survival.

appear to be associated with OS in the sorafenib-naive group, but in the sorafenib-experienced group, patients with a baseline Child—Pugh score of 6 had a shorter OS than patients with a Child—Pugh score of 5 (Figure 3C).

DISCUSSION

To our knowledge, this is the longest duration of follow-up reported for an immunotherapy in patients with aHCC. In the dose-escalation and dose-expansion phases of the CheckMate 040 study, after a minimum follow-up of 5 years, nivolumab monotherapy continued to provide clinical benefit in patients with aHCC, with an ORR of 20% in the sorafenib-naive group and 14% in the sorafenib-experienced group as per BICR. Among all treated patients, responses were observed regardless of HCC etiology or baseline tumor cell PD-L1 expression levels. CheckMate 040 was conducted at a time when the standard of care for unresectable HCC was limited to multikinase inhibitors, with a median OS benefit of ∼11 months.[9,13] In contrast, at the CheckMate 040 5-year follow-up, median OS was 26.6 months in the sorafenib-naive group and 15.1 months in the sorafenib-experienced group; 5-year OS rates were 14% and 12%, respectively. There was no clear effect of etiology on survival as OS benefit was observed regardless of HCC

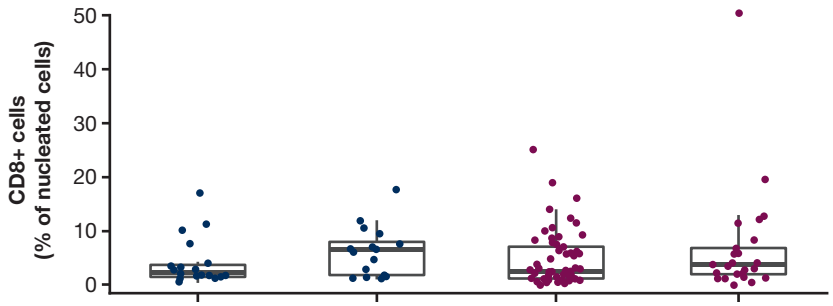
Table 3. Summary of TRAEs

	Sorafenib naive (n = 80)		Sorafenib experienced[a] (n = 154)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All TRAEs[b]	64 (80)	26 (33)	121 (79)	33 (21)
Serious TRAEs	4 (5)	4 (5)	15 (10)	7 (5)
TRAEs leading to discontinuation	5 (6)	2 (3)	5 (3)	3 (2)
Treatment-related deaths[c]	0		1[d] (<1)	
TRAEs reported in ≥10% of patients in any group[b]				
Pruritus	19 (24)	0	29 (19)	1 (<1)
Fatigue	17 (21)	0	38 (25)	3 (2)
Rash	13 (16)	1 (1)	25 (16)	1 (<1)
Diarrhea	12 (15)	1 (1)	24 (16)	2 (1)
Nausea	8 (10)	0	14 (9)	0
AST increased	12 (15)	8 (10)	9 (6)	6 (4)
Amylase increased	11 (14)	7 (9)	6 (4)	2 (1)
ALT increased	10 (13)	5 (6)	12 (8)	4 (3)
Lipase increased	8 (10)	8 (10)	8 (5)	7 (5)

Data are presented as n (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.
[a]Sorafenib-experienced patients treated with nivolumab 3 mg/kg.
[b]Includes events reported between first dose and 100 days after last dose of study therapy according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[c]Treatment-related deaths are reported regardless of timeframe.
[d]One death due to pneumonitis.

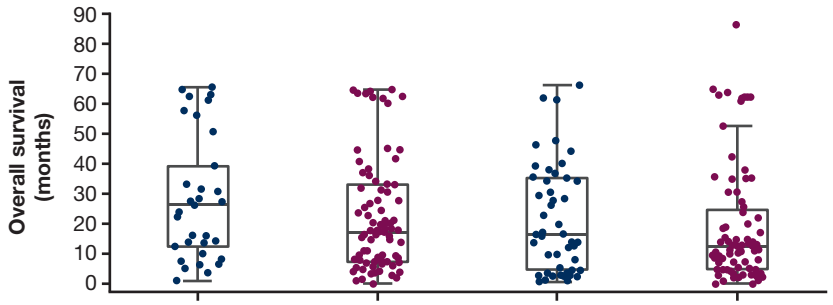
https://doi.org/10.1016/j.annonc.2023.12.008

A



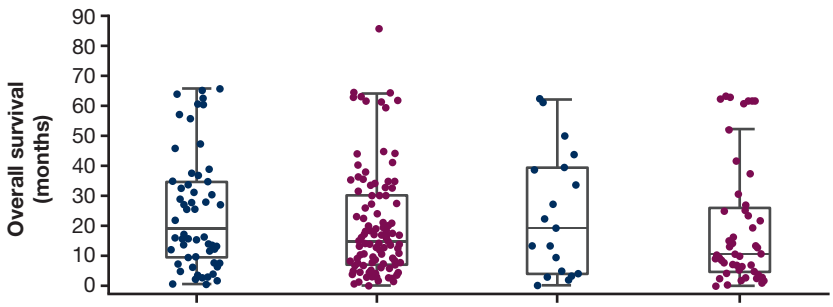
	Sorafenib naive		Sorafenib experienced	
	OS < 1 year (*n* = 20)	OS ≥ 3 years (*n* = 16)	OS < 1 year (*n* = 57)	OS ≥ 3 years (*n* = 25)
CD8+ cells (% of nucleated cells), median (range)[a]	2.2 (0.6-17.1)	6.5 (1.2-17.8)	2.5 (0.1-25.1)	3.8 (0.1-50.4)

B



	ALBI grade 1		ALBI grade 2	
	Sorafenib naive (*n* = 33)	Sorafenib experienced (*n* = 78)	Sorafenib naive (*n* = 47)	Sorafenib experienced (*n* = 76)
OS, median (range), months	26.7 (1.5-65.6)	17.9 (0.4-64.9)	16.6 (1.0-66.3)	13.1 (0.4-86.5)

C



	Child–Pugh score 5		Child–Pugh score 6[b]	
	Sorafenib naive (*n* = 58)	Sorafenib experienced (*n* = 104)	Sorafenib naive (*n* = 19)	Sorafenib experienced (*n* = 48)
OS, median (range), months	20.1 (1.5-66.3)	15.4 (0.4-86.5)	20.1 (1.0-62.7)	11.5 (0.4-64.0)

Figure 3. Overall survival (OS) by baseline biomarkers and disease characteristics. OS by baseline (A) CD8 T-cell density, (B) liver function (ALBI) score, and (C) Child–Pugh score. Sorafenib-experienced patients were treated with nivolumab 3 mg/kg. The horizontal line in the middle of the box indicates the median, the lower and upper ends of the boxes represent the 25th and 75th percentiles, and the whiskers represent the most extreme points within 1.5 of the interquartile range, with spots indicating outliers.

ALBI, albumin—bilirubin; CD8, cluster of differentiation 8; OS; overall survival.

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

[b]OS trends among patients with a Child—Pugh score ≥7 are not shown due to low patient numbers.

etiology in both groups. Of note, the study was not powered to compare outcomes across etiologies and therefore, the data should be interpreted in the context of this limitation. The long-term benefit of nivolumab in sorafenib-naive and sorafenib-experienced patients with aHCC at this 5-year follow-up was consistent with data from earlier follow-up analyses.[15,20,25]

The safety profile of nivolumab monotherapy was manageable with low rates of discontinuation due to TRAEs ($\leq$6%) in both sorafenib-naive and sorafenib-experienced groups, and no new safety signals were identified since the earlier follow-up analyses.[15] The majority of IMAEs were grade 1 or 2, with rash, hepatitis, and hypothyroidism/thyroiditis being the most commonly reported events in both groups. Grade 3/4 TRAEs with potential immunologic etiology occurred in $\leq$5% of patients across most organ categories in both groups [with the exception of hepatic events in the sorafenib-naive group (13%)] and were manageable using protocol-specified management guidelines. One treatment-related death (pneumonitis) was reported in the sorafenib-experienced group. The safety profile reported in this long-term follow-up study was generally consistent with that previously reported for nivolumab in HCC[15,21] and in other tumor types.[26-29]

Based on promising efficacy and safety data from the dose-escalation and dose-expansion cohorts of CheckMate 040,[15] the phase III CheckMate 459 study investigated nivolumab versus sorafenib in previously untreated patients with aHCC.[10] Nivolumab showed numerically improved ORR compared with sorafenib (15% versus 7%, respectively) and a favorable safety profile, but no statistically significant improvement in OS.[10] Confounding factors, such as the higher proportion of patients in the sorafenib group that received subsequent immuno-oncology therapies compared with the nivolumab group and time-varying hazard ratios (HRs) due to the delayed separation of OS curves, may have affected the OS findings with nivolumab.[10] Furthermore, nivolumab monotherapy has demonstrated clinical activity (ORR 12%) with manageable safety in patients with aHCC and Child–Pugh B liver function.[30] Together, these results demonstrate that patients with aHCC, even with compromised liver function, may derive some benefit from nivolumab monotherapy.

Other immune checkpoint inhibitors have shown clinical benefit in patients with aHCC.[3,4,6,7,31-33] In sorafenib-experienced patients, ORRs of 13% to 18% have been reported with pembrolizumab monotherapy.[31-33] Combinations of immuno-oncologic agents have demonstrated significant improvements over sorafenib in the first-line setting in patients with unresectable HCC and are now considered the standard of care.[3,4,7] Atezolizumab plus bevacizumab significantly improved OS [HR 0.58 (95% CI 0.42-0.79); $P < 0.001$] and ORR (27.3% versus 11.9%, respectively; $P < 0.001$) versus sorafenib,[3] and tremelimumab plus durvalumab significantly improved OS versus sorafenib [HR 0.78 (96.02% CI 0.65-0.93); $P = 0.0035$]; ORR was 20.1% with tremelimumab plus durvalumab and 5.1% with sorafenib.[4] The ORRs reported with nivolumab monotherapy in the current 5-year follow-up of CheckMate 040 were similar to those reported with other single-agent or combination immunotherapies in aHCC. However, cross-trial comparisons should be interpreted with caution due to differences in study design and patient characteristics between studies.

Several studies have explored prognostic and predictive biomarkers in HCC.[14,20,25,34-40] However, reliable predictive markers that would guide patient selection for single-agent anti-PD-1 therapy are lacking. In the current study, baseline AFP $\geq$400 μg/l and extrahepatic spread were associated with shorter OS, consistent with previous reports from CheckMate 040 and other studies.[25,35] Baseline vascular invasion was associated with poor OS among previously untreated patients with unresectable HCC,[35] and a similar finding was observed in the current analysis for the sorafenib-naive group. Poor baseline liver function has been associated with poor prognosis in HCC,[35,38] and the current analysis supports this observation as patients with higher baseline Child–Pugh and ALBI scores had shorter OS compared with those who had lower scores. Tumor inflammation, as measured by higher baseline tumor CD8 T-cell density, showed a trend toward improved OS in the 33.2-month follow-up from CheckMate 040[20,25]; in the current analysis, higher baseline CD8 T-cell density occurred among sorafenib-naive patients with OS $\geq$3 years. Additionally, the current analysis showed that baseline tumor cell PD-L1 expression $\geq$1% was associated with longer OS, consistent with the 33.2-month follow-up.[25] Together, these exploratory biomarker analyses may identify important factors associated with OS in patients with aHCC treated with nivolumab.

Limitations of this study include the open-label design and lack of a control arm, which may have influenced interpretation of the results. Patients in the sorafenib-naive group were treated with a range of nivolumab doses (0.1-10 mg/kg) in the dose-escalation phase, whereas patients in the sorafenib-experienced group were all treated with 3 mg/kg. However, these dose differences are not expected to affect efficacy and safety outcomes in these groups.[41,42] Further, prior therapies might have influenced the tumor microenvironment in both sorafenib-naive and sorafenib-experienced patients, which might have affected outcomes. The biomarker analyses were exploratory and only included biomarker-assessable patients; given the small sample size of the analysis, further validation of these biomarkers is required.

For patients who have contraindications to first-line immunotherapy combinations, sorafenib remains an important treatment option. Nivolumab monotherapy may benefit patients who discontinue sorafenib due to toxicity or disease progression. In this 5-year follow-up from CheckMate 040, nivolumab monotherapy continued to provide durable clinical benefit in sorafenib-naive and sorafenib-experienced patients with aHCC. The safety profile was manageable, with low proportions of patients discontinuing therapy due to TRAEs, demonstrating the long-term benefit of nivolumab monotherapy in patients with aHCC. A phase III study of nivolumab in combination with

ipilimumab versus sorafenib/lenvatinib as a first-line therapy in aHCC is in progress (CheckMate 9DW).

ACKNOWLEDGEMENTS

We thank the patients and their families for making the study possible; the clinical study teams who participated in the study; the global trial manager for this study, Rachel Parr; Dako (an Agilent Technologies company, Santa Clara, CA) for collaborative development of the PD-L1 IHC 28-8 pharmDx assay; Bristol Myers Squibb (Princeton, NJ); and Ono Pharmaceutical Company Ltd. (Osaka, Japan). The study was supported by Bristol Myers Squibb. All authors contributed to, and approved, the manuscript. Medical writing and editorial assistance were provided by Dhivya Ramalingam, PhD, of Parexel, funded by Bristol Myers Squibb.

FUNDING

This work was supported by Bristol Myers Squibb (no grant number).

DISCLOSURE

ABE reports consultancy fees from ABL Bio, Agenus, AstraZeneca/MedImmune, Bayer, Bristol Myers Squibb, Eisai, Exelixis, Gilead Sciences, Merck, Pieris Pharmaceuticals, QED Therapeutics, Qurient, Roche, Senti Biosciences, Servier, and Tallac Therapeutics; honoraria from ABL Bio, Agenus, AstraZeneca/MedImmune, Bayer, Bristol Myers Squibb, Eisai, Exelixis, EMD Serono, Gilead Sciences, Merck, Roche/Genetech, QED Therapeutics, Qurient, Roche, Senti Biosciences, Servier, and Tallac Therapeutics; and research grants from AstraZeneca, Astex Pharmaceuticals, and Fulgent Genetics. JT reports advisory honoraria from Amgen, AstraZeneca, Bayer Healthcare, Bristol Myers Squibb, Eisai, Ipsen, Merck Serono, Merck, Sharp & Dohme, Lilly Imclone, Onkowissen TV, PCI Biotech, Roche, and Servier; speaker fees from Amgen, AstraZeneca, Bioprojet, Bristol Myers Squibb, Eisai, Ipsen, Medac, Merck Serono, Merck, Sharp & Dohme, Lilly Imclone, Roche, Servier, and Streamed Up; and research funding from Roche and Ipsen. TM reports consultancy fees from Adaptimmune, AstraZeneca, Beigene, Bristol Myers Squibb, Eisai, Ipsen, Merck, Sharp & Dohme, and Roche; and research funding (to institution) from Merck, Sharp & Dohme. TY reports consultancy fees from AstraZeneca, Bristol Myers Squibb, and Merck, Sharp & Dohme Oncology. IM reports consultancy fees from AstraZeneca/MedImmune, Bayer, Bristol Myers Squibb, EMD Serono, F-Star, Genmab, Gossamer Bio, Lilly, Merck, Sharp & Dohme, Numab, PharmaMar, Roche, Tusk Therapeutics, Highlight Therapeutics, Alligator Bioscience, Genentech, CatalYm GmbH, BioLineRx, Boston Pharma, Janssen, HotSpot Therapeutics, Inc., ImmuneSensor Therapeutics, Inc., and Monopteros Therapeutics; honoraria from Alligator Biosciences, AstraZeneca/MedImmune, Bayer, Bristol Myers Squibb, Lilly, Roche/Genentech, Tusk Therapeutics, Moderna, and CatalYm GmbH; travel support from Bristol Myers Squibb, Incyte, Merck, Sharp & Dohme, and Roche/Genentech; and research grants from Alligator Biosciences, Bristol Myers Squibb, AstraZeneca, Genmab, Pfizer, and Roche/Genentech. MK reports consultancy fees from AstraZeneca, Chugai/Roche, and Eisai; honoraria from AstraZeneca, Bayer, Chugai/Roche, Eisai, Lilly Japan, and Takeda; and research funding (to institution) from Abbvie, Chugai/Roche, EA Pharma, Eisai, GE Healthcare, Gilead Sciences, Otsuka, and Taiho Pharmaceuticals. CH reports honoraria from AstraZeneca, Bayer, Bristol Myers Squibb/Ono Pharmaceutical, Eisai, Ipsen, Merck, Sharp & Dohme, Novartis, PharmaEngine, Roche, and TTY Biopharm. **T-YK** is the founder of IMBdx, Inc., and has received research funds from Bayer Korea. **S-PC** reports honoraria from AstraZeneca, Bristol Myers Squibb, Eisai, Ipsen, and Roche; consulting or advisory roles in AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, MSD Oncology, and Roche; stock and other ownership interests in Bristol Myers Squibb/Celgene; and travel, accommodations, and expenses from Bristol Myers Squibb and Taiho Pharmaceutical. **Y-KK** reports consulting fees from ALX Oncology, Amgen, Blueprint, Bristol Myers Squibb, Daehwa, Macrogenics, Merck, Novartis, Roche, Surface Oncology, and Zymeworks. AC reports honoraria from AstraZeneca, DKSH, Guardant, Ipsen, Janssen, Merck, MSD, and Roche; and travel support from Merck. SS, JY, JN, and MT report being employees of and owing stock in Bristol Myers Squibb. BS reports consultancy fees from Adaptimmune, AstraZeneca, Bayer, Bristol Myers Squibb, Boston Scientific, Eisai, Eli Lilly, Incyte, Ipsen, Merck, Sharp & Dohme, Roche, Sanofi, Sirtex Medical, Terumo; speaker fees from AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Eli Lilly, Incyte, Ipsen, Roche, Sirtex Medical, Terumo; research grants (to Institution) from Bristol Myers Squibb and Sirtex Medical. All other authors have declared no conflicts of interest.

DATA SHARING

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

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. Available at https://seer.cancer.gov/statfacts/html/livibd.html. Accessed May 20, 2022.
3. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894-1905.
4. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid*. 2022;1:EVIDoa2100070.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatocellular carcinoma V.1. 2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed March 10, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org.

6. Abou-Alfa GK, Chan SL, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. *J Clin Oncol*. 2022;40. 379-379.
7. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76:862-873.
8. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391:1163-1173.
9. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378-390.
10. Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2022;23:77-90.
11. Laethem J-LV, Borbath I, Karwal M, et al. Pembrolizumab (pembro) monotherapy for previously untreated advanced hepatocellular carcinoma (HCC): phase 2 KEYNOTE-224 study. *J Clinl Oncol*. 2021;39:4074.
12. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379:54-63.
13. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389:56-66.
14. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20:282-296.
15. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389:2492-2502.
16. El-Khoueiry AB, Melero I, Yau TC, et al. Impact of antitumor activity on survival outcomes, and nonconventional benefit, with nivolumab (NIVO) in patients with advanced hepatocellular carcinoma (aHCC): subanalyses of CheckMate-040. *J Clin Oncol*. 2018;36:475.
17. Julien K, Leung HT, Fuertes C, et al. Nivolumab in advanced hepatocellular carcinoma: safety profile and select treatment-related adverse events from the CheckMate 040 study. *Oncologist*. 2020;25:e1532-e1540.
18. Meyer T, Melero I, Yau T, et al. Hepatic safety and biomarker assessments in sorafenib-experienced patients with advanced hepatocellular carcinoma treated with nivolumab in the CheckMate-040 study. Paper presented at the European Association for the Study of the Liver; April 11-15, 2018; Paris, France.
19. Elimova E, Moignard S, Li X, et al. Updating reports of phase 3 clinical trials for cancer. *JAMA Oncol*. 2021;7:593-596.
20. Melero I, Neely J, Sangro B, et al. Assessment of inflammation biomarkers in relation to clinical outcomes in nivolumab-treated patients with advanced hepatocellular carcinoma in CheckMate 040. *Cancer Res*. 2019;79:2675.
21. Yau T, Hsu C, Kim TY, et al. Nivolumab in advanced hepatocellular carcinoma: sorafenib-experienced Asian cohort analysis. *J Hepatol*. 2019;71:543-552.
22. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.
23. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.
24. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010;30:52-60.
25. Sangro B, Melero I, Wadhawan S, et al. Association of inflammatory biomarkers with clinical outcomes in nivolumab-treated patients with advanced hepatocellular carcinoma. *J Hepatol*. 2020;73:1460-1469.
26. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17:883-895.
27. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372:320-330.
28. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803-1813.
29. 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*. 2016;17:1590-1598.
30. Kudo M, Matilla A, Santoro A, et al. CheckMate 040 cohort 5: a phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis. *J Hepatol*. 2021;75:600-609.
31. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol*. 2018;19:940-952.
32. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol*. 2020;38:193-202.
33. Qin S, Chen Z, Fang W, et al. Pembrolizumab plus best supportive care versus placebo plus best supportive care as second-line therapy in patients in Asia with advanced hepatocellular carcinoma (HCC): phase 3 KEYNOTE-394 study. *J Clin Oncol*. 2022;40:383.
34. Wei Z, Zhang Y, Lu H, et al. Serum alpha-fetoprotein as a predictive biomarker for tissue alpha-fetoprotein status and prognosis in patients with hepatocellular carcinoma. *Transl Cancer Res*. 2022;11:669-677.
35. Bruix J, Cheng AL, Meinhardt G, et al. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. *J Hepatol*. 2017;67:999-1008.
36. Kalathil SG, Lugade AA, Miller A, et al. PD-1(+) and Foxp3(+) T cell reduction correlates with survival of HCC patients after sorafenib therapy. *JCI Insight*. 2016;1:e86182.
37. Ma WJ, Wang HY, Teng LS. Correlation analysis of preoperative serum alpha-fetoprotein (AFP) level and prognosis of hepatocellular carcinoma (HCC) after hepatectomy. *World J Surg Oncol*. 2013;11:212.
38. Bronowicki J-P, Kudo M, Lencioni R, et al. Gideon: a retrospective analysis of prognostic factors for survival. *J Hepatol*. 2015;62:S451-S452.
39. Zhu AX, Abbas AR, de Galarreta MR, et al. Molecular correlates of clinical response and resistance to atezolizumab in combination with bevacizumab in advanced hepatocellular carcinoma. *Nat Med*. 2022;28:1599-1611.
40. Neely J, Yao J, Kudo M, et al. Abstract 2145: Genomic and transcriptomic analyses related to the clinical efficacy of first-line nivolumab in advanced hepatocellular carcinoma from the phase 3 CheckMate 459 trial. *Cancer Res*. 2022;82:2145.
41. Feng Y, Wang X, Bajaj G, et al. Nivolumab exposure-response analyses of efficacy and safety in previously treated squamous or nonsquamous non-small cell lung cancer. *Clin Cancer Res*. 2017;23:5394-5405.
42. Wang X, Feng Y, Bajaj G, et al. Quantitative characterization of the exposure-response relationship for cancer immunotherapy: a case study of nivolumab in patients with advanced melanoma. *CPT Pharmacometrics Syst Pharmacol*. 2017;6:40-48.