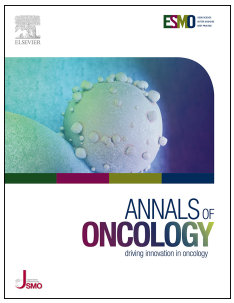

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Nivolumab in sorafenib-naive and sorafenib-experienced patients with advanced hepatocellular carcinoma: 5-year follow-up from CheckMate 040

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Highlights

- At 5 years of follow-up, nivolumab monotherapy continued to provide durable clinical benefit in patients with advanced HCC
- Objective response rate was 20% in the sorafenib (SOR)-naive group and 14% in the SOR-experienced group
- 3-year OS rates were 28% in the SOR-naive and 20% in the SOR-experienced group; 5-year rates were 14% and 12%, respectively
- The safety profile of nivolumab monotherapy was manageable and no new safety signals were identified
- Higher ORR and longer OS were noted with baseline PD-L1 ≥1% versus <1% and were more prominent in the SOR-experienced group

Abstract (293/300 words)

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 cohorts of CheckMate 040 are 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 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 per BICR was 20% (95% CI 12-30) and 14% (95% CI 9-21) 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) and 15.1 months (95% CI 13.0-18.2) 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 group; 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% in the sorafenib-naive and sorafenib-experienced patients, respectively. Biomarker analyses showed that baseline PD-L1 expression ≥1% was associated with higher ORR and longer OS compared with PD-L1 <1%. In the sorafenib-naive group, patients with OS ≥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.

ClinicalTrials.gov number: NCT01658878

Key words (maximum of 6): 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 approximately 3%.[1,2] First-line systemic therapy options for patients with unresectable HCC include immuno-oncology-based combinations such as 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 alpha-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 (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 cohorts 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, Singapore, Spain, Taiwan, United Kingdom, 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 (ECOG) 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 per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1).[23]

Patients in both the dose escalation (cohort 1) and the 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 prior to treatment initiation. Patients were required to have Child-Pugh scores of 7 or less (Child-Pugh A or B7) in the dose escalation phase, and 6 or less (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 x 10^3/μL) was required. Additional eligibility criteria are included in the **Supplementary Appendix**.

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 prior to enrollment.

Procedures

Details of the CheckMate 040 study design have been published previously.[15] Briefly, patients in the dose-escalation phase were administered intravenous (IV) 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 (i.e. C1D1 to C1D42). In the dose-expansion phase, patients received nivolumab 3 mg/kg IV 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 Appendix**.

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 of CR or partial response [PR], divided by the number of treated patients) by blinded independent central review (BICR) and investigator assessments per RECIST v1.1. Key secondary endpoints included progression-free survival (PFS) and time to progression (TTP), by BICR and/or investigator assessment 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 Appendix**.

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 best overall response (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) 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 appendix**.

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 performed using SAS software (version 9.2 or higher; SAS Institute, Cary, NC, USA).

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, approximately 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 Appendix**.

RESULTS

Baseline characteristics and patient disposition

The clinical data cutoff for this analysis was November 02, 2020. Between November 26, 2012 and August 8, 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 cutoff) in both sorafenib-naive and sorafenib-experienced groups was 60 months. The median follow-up (time from first dose to

data cutoff) was 62.9 months (range 60-94) in the sorafenib-naive group and 62.8 months (range 60-86) in the sorafenib-experienced group. Median age of patients was 65 years (range 20-83) and 63 years (range 19-81) in the sorafenib-naïve 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; 122 patients (52%) were uninfected (**Table 1**). Most patients with prior sorafenib treatment (91%) progressed on or after sorafenib (**Supplemental Table S1**).

At data cutoff, 79 patients (99%) in the sorafenib-naive group and 151 patients (98%) in the sorafenib-experienced group had discontinued therapy (**Supplemental Table S2**). The most common reason for treatment discontinuation in both groups was disease progression (sorafenib-naive: 62 patients [78%]; sorafenib-experienced: 126 patients [82%]; **Supplemental Table S2**). 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 (**Supplemental Table S3**).

Efficacy

At the 5-year follow-up, BICR-assessed ORR was 20% (95% CI 12-30) and 14% (95% CI 9-21) in the sorafenib-naive and sorafenib-experienced groups, respectively; investigator-assessed ORR was 23% (95% CI 14-33) and 20% (95% CI 14-27), respectively (**Table 2**). 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 per BICR. Responses occurred independent of HCC etiology or tumor cell PD-L1 expression levels (**Figure 1** and

Supplemental Table S4). Median DOR per BICR was 22.6 months (95% CI 11.1-not evaluable [NE]) in the sorafenib-naive group and 39.7 months (95% CI 9.7-NE) in the sorafenib-experienced group (**Table 2**). Among the patients with an initial BOR of CR per BICR (n = 8; 3 patients in the sorafenib-naive and 5 patients in the sorafenib-experienced group), disease progression was reported in 1 patient in each treatment group; among those with CR per investigator assessment (n = 6; 1 patient in the sorafenib-naive and 5 patients in the sorafenib-experienced group), 2 patients in the sorafenib-experienced group had disease progression (**Table 2**). In the sorafenib-experienced group, 3 out of 5 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) and 15.1 months (95% CI 13.0-18.2) in the sorafenib-naive and sorafenib-experienced groups, respectively; 3-year OS rates were 28% (95% CI 18-38) and 20% (95% CI 14-27) and 5-year OS rates were 14% (95% CI 7-23) and 12% (95% CI 7-18), respectively (**Figure 2**). HCC etiology did not affect median OS in either group (**Supplemental Figure S1** and **Supplemental Table S4**). In landmark analyses of OS from month 6, median OS was longer in responders (CR + PR) vs non-responders (progressive disease [PD] + stable disease [SD] + non-CR/non-PD) in both sorafenib-naive and sorafenib-experienced groups (**Supplemental Figure S2**). Among responders, median OS was 48.1 months (95% CI 30.6-NE) in the sorafenib-naive group and not reached (26.7-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) and 20.2 months (95% CI 15.6-26.0), respectively (**Supplemental Figure S2**).

Among 25 patients with an OS of at least 5 years, 21 patients discontinued study treatment: seven (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]; adverse event 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) in the sorafenib-naive group and 106.2 weeks (range 14.1-263.1) in the sorafenib-experienced group. In an exploratory analysis, ORR assessed using mRECIST 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 (range 0-66.3+) months in the sorafenib-naive group and 5.1 (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 sorafenib-experienced group. The median cumulative nivolumab dose was 27.5 (range 0.3-413.2) mg/kg and 32.3 (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 1.0-14.3 months and 0.0-3.3 months in the sorafenib-naive and sorafenib-experienced groups, respectively (**Supplemental Table S5**).

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 (**Supplemental Table S6**). 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; **Supplemental Table S6**). 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 (**Supplemental Table S6**). 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 (**Supplemental Table S7**); 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; **Supplemental Table S7**). One treatment-related death (pneumonitis; <1%) was reported in the sorafenib-experienced group (**Table 3**).

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 (**Supplemental Table S8**). 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 (**Supplemental Figure S1** and **Supplemental Table S4**). In the sorafenib-naive group only, presence of vascular invasion at baseline also appeared to be associated with shorter OS (**Supplemental Table S8**).

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 of 8.1% [range 1.6-19.5] in the 8 patients who had a best overall response of CR per BICR; 6 of these 8 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 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 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 approximately 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 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 (≤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 5% or less 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 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%-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 ≥ 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 towards 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 ≥3 years. Additionally, the current analysis showed that baseline tumor cell PD-L1 expression ≥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 cohorts.[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-evaluable 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 3 study of nivolumab in combination with ipilimumab versus sorafenib/lenvatinib as a first-line therapy in aHCC is in progress (CheckMate 9DW).

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FIGURES

Figure legends

Figure 1. Efficacy by etiology in (A) sorafenib-naive and (B) sorafenib-experienced patients and efficacy 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 per Response Evaluation Criteria in Solid Tumors 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 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.

Figure 2. Kaplan-Meier analysis of OS with nivolumab in (A) sorafenib-naive and (B) sorafenib-experienced patients.

Filled circles denote censored patients. Sorafenib-experienced patients treated with nivolumab 3 mg/kg.

CI, confidence interval; OS, overall survival.

Figure 3. Overall survival (OS) by baseline (A) CD8 T cell density, (B) liver function (ALBI) score, and (C) Child-Pugh score.

Sorafenib-experienced patients treated with nivolumab 3 mg/kg. The horizontal line in middle of 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.

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

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

ALBI, albumin-bilirubin; CD8, cluster of differentiation 8; mo, months; OS; overall survival.

TABLES

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 *n* (%) unless otherwise noted.

AFP, alpha-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 (eight 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).

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 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.

Table 3. Summary of TRAEs

n (%)	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]				
Pruritis	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)

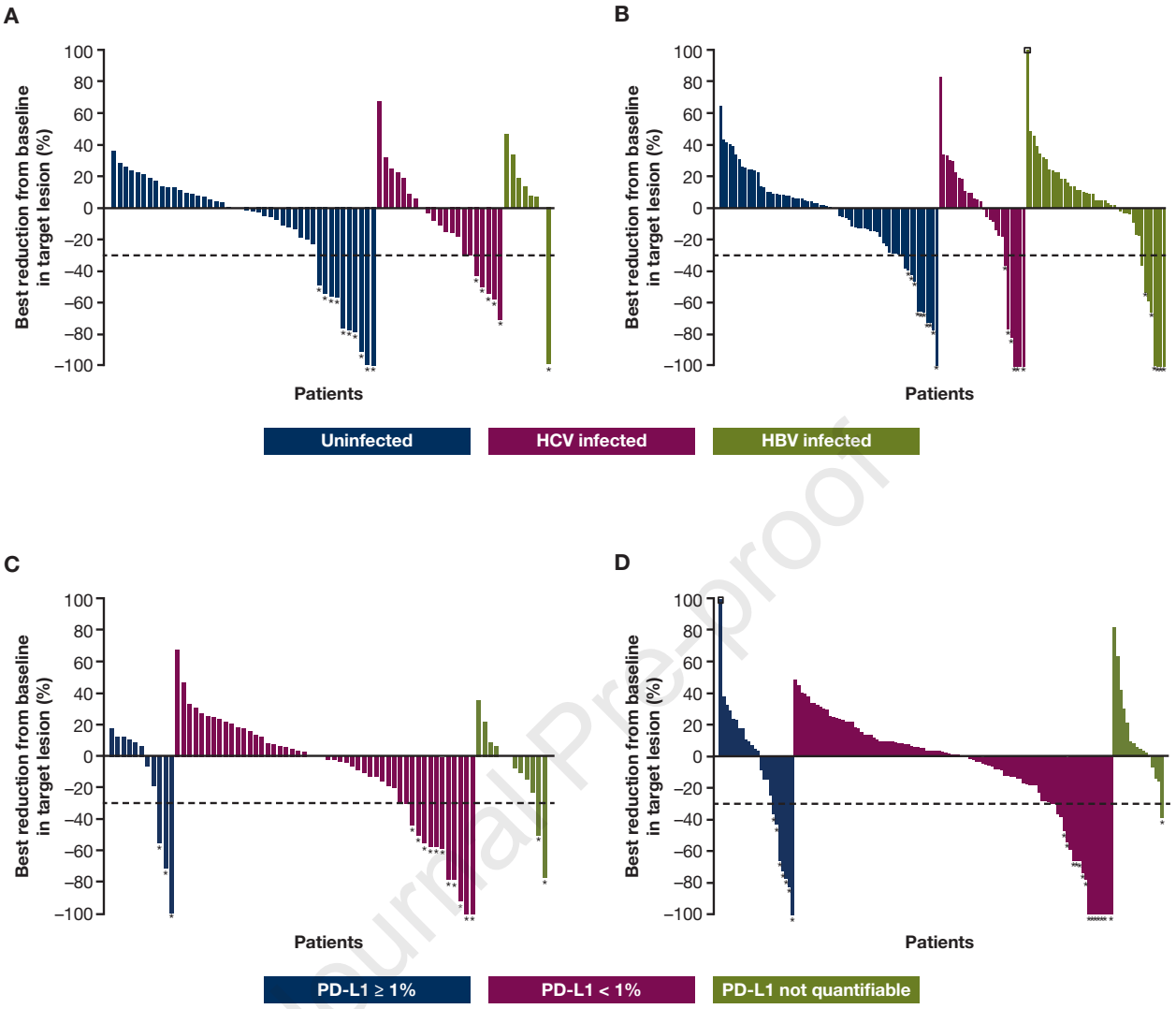
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

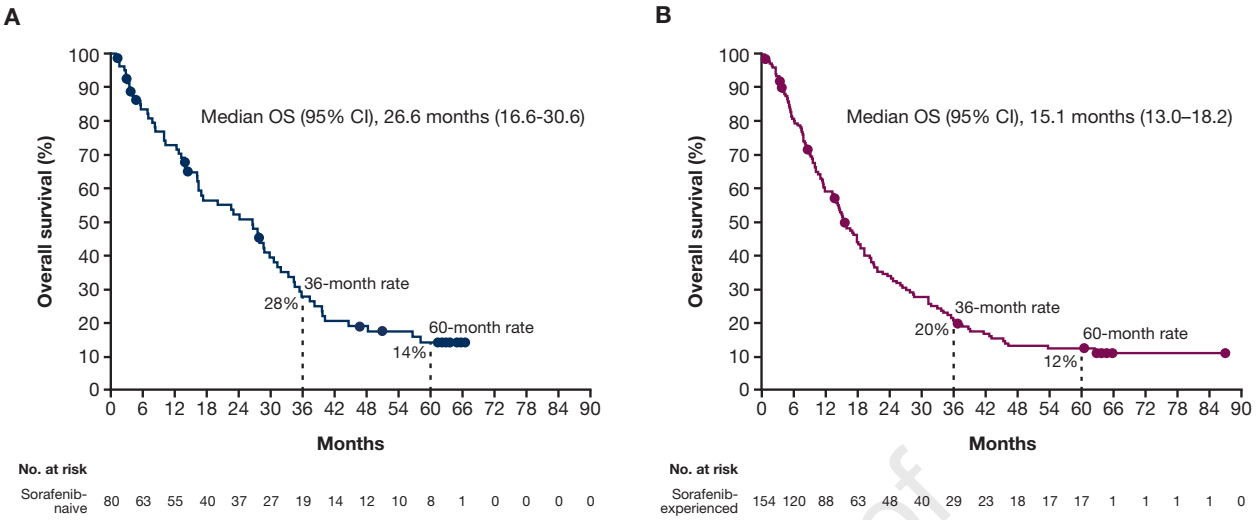
[a]Sorafenib-experienced patients treated with nivolumab 3 mg/kg.

[b]Includes events reported between first dose and 100 days after last dose of study therapy according to 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.





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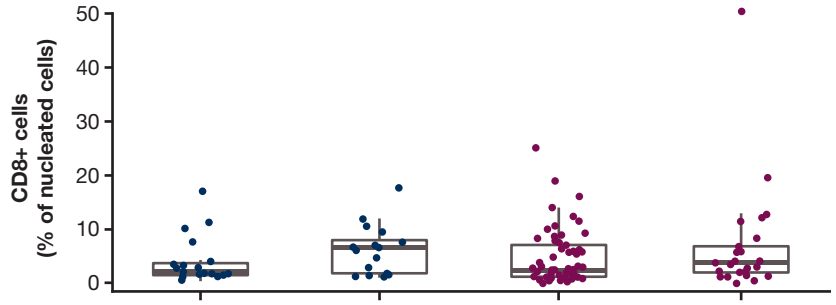
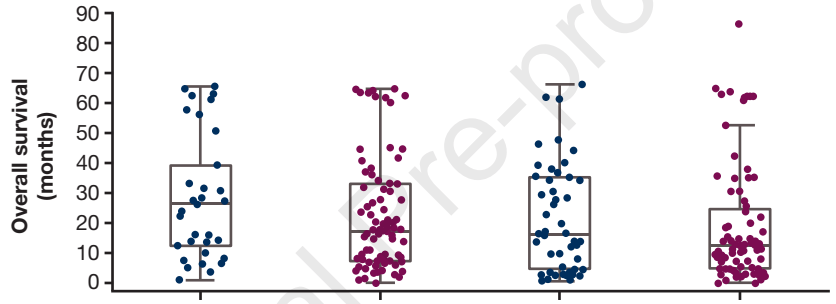


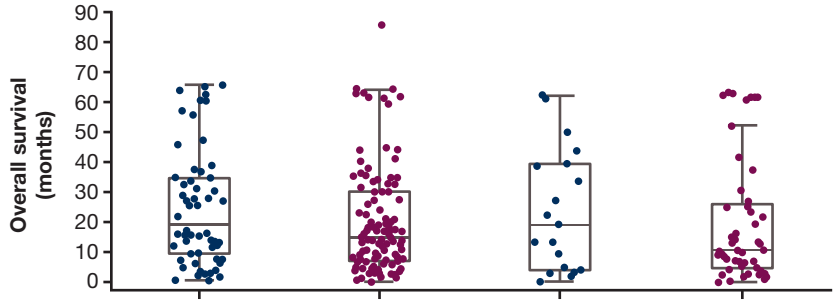
	Sorafenib-naive		Sorafenib-experienced	
	OS < 1 year (*n* = 20)	OS ≥ 3 years (*n* = 16)	OS < 1 year (*n* = 57)	OS ≥ 3 years (*n* = 25)
CD8+ cells (% of nucleated cells), median (range)[a]	2.2 (0.6–17.1)	6.5 (1.2–17.8)	2.5 (0.1–25.1)	3.8 (0.1–50.4)

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)