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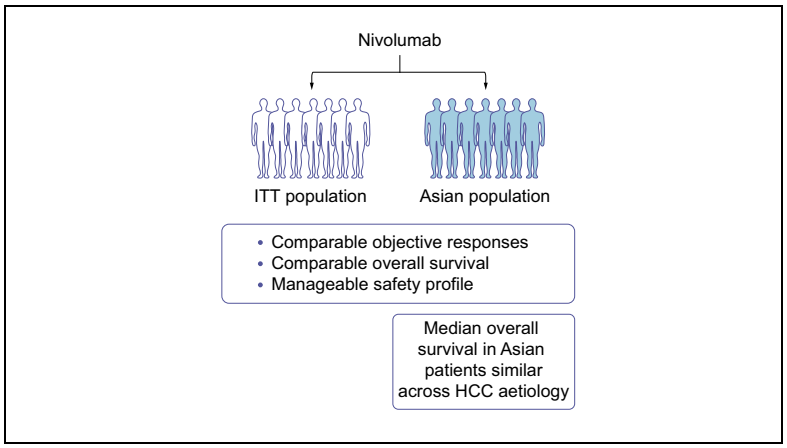
Nivolumab in advanced hepatocellular carcinoma: Sorafenib-experienced Asian cohort analysis

Graphical abstract



Highlights

- Objective responses and survival were comparable between intent-to-treat (ITT) overall population and Asian cohort.
- Median overall survival in Asian patients was similar across HCC aetiologies.
- Nivolumab had a manageable safety profile in both the ITT overall population and Asian cohort.

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Lay summary

The CheckMate 040 study evaluated the safety and efficacy of nivolumab in patients with advanced hepatocellular carcinoma who were refractory to previous sorafenib treatment or chemotherapy. This subanalysis of the data showed that treatment responses and safety in patients in Asia were similar to those of the overall treatment population, providing support for nivolumab as a treatment option for these patients.

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Nivolumab in advanced hepatocellular carcinoma: Sorafenib-experienced Asian cohort analysis

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Background & Aims: Nivolumab, an immune checkpoint inhibitor, is approved in several countries to treat sorafenib-experienced patients with HCC, based on results from the CheckMate 040 study (NCT01658878). Marked differences exist in HCC clinical presentation, aetiology, treatment patterns and outcomes across regions. This analysis assessed the safety and efficacy of nivolumab in the Asian cohort of CheckMate 040.

Methods: CheckMate 040 is an international, multicentre, open-label, phase I/II study of nivolumab in adults with advanced HCC, regardless of aetiology, not amenable to curative resection or local treatment and with/without previous sorafenib treatment. This analysis included all sorafenib-experienced patients in the intent-to-treat (ITT) overall population and Asian cohort. The analysis cut-off date was March 2018.

Results: There were 182 and 85 patients in the ITT population and Asian cohort, respectively. In both populations, most patients were older than 60 years, had BCLC (Barcelona Clinic Liver Cancer) Stage C disease, and had received previous systemic therapy. A higher percentage of Asian patients had HBV infections, extrahepatic metastases and prior therapies. Median follow-up was 31.6 and 31.3 months for the ITT and Asian patients, respectively. Objective response rates were 14% and 15% in the ITT population and Asian cohort, respectively. In the Asian cohort, patients with HBV, HCV or those who were uninfected had objective response rates of 13%, 14% and 21%, respectively. The median duration of response was longer in the ITT (19.4 months) *vs.* Asian patients (9.7 months). Median overall survival was similar between the ITT (15.1 months) and Asian patients (14.9 months), and unaffected by aetiology in Asian patients. The nivolumab safety profile was similar and manageable across both populations.

Conclusion: Nivolumab safety and efficacy are comparable between sorafenib-experienced ITT and Asian patients.

Lay summary: The CheckMate 040 study evaluated the safety and efficacy of nivolumab in patients with advanced hepatocellular carcinoma who were refractory to previous sorafenib treatment or chemotherapy. This subanalysis of the data showed that treatment responses and safety in patients in Asia were similar to those of the overall treatment population, providing support for nivolumab as a treatment option for these patients.

Clinical trial number: NCT01658878.

Introduction

Worldwide, liver cancer is predicted to be the fourth most common cause of cancer-related mortality, accounting for an estimated 782,000 deaths in 2018, with most liver cancers HCC.[1] However, there are global differences in HCC incidence and trends, with Eastern and Southeast Asia having among the highest incidence of liver cancer.[1] This difference in HCC incidence between Asian and non-Asian regions is related to the high incidence of chronic viral hepatitis in Asia.[2,3] Most Asian countries have high rates of HBV infection,[2] with the exception of Japan, which has the highest rate of HCV infection of all industrialised countries.[4] The incidence of HCC is trending downward in Asian regions, associated with improved control of HBV and HCV, whereas it is increasing in non-Asian regions, mainly related to non-viral etiologies. Genomic studies indicate differences in genetic mutations and signatures in HCC tumours with different aetiologies, suggesting that the genomic profile of HCC in Asian regions differs from that in non-Asian regions.[3]

Keywords: HCC; Hepatocellular carcinoma; Liver cancer; Nivolumab; PD-1 inhibitor; Immuno-oncology; Asian; CheckMate.
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Not only is HCC a heterogeneous disease in terms of incidence, aetiology and genomic profiles, but there is also a range of therapeutic options that involve different treatment disciplines, including oncology, hepatology, surgery and interventional radiology. Consequently, substantial heterogeneity in management trends has been observed and a range of HCC management guidelines exist.[5] These differences can result in diverse HCC trial outcomes.[3] The pivotal first-line trials of sorafenib showed similar hazard ratios (HRs) for survival in the Western and Asian trials; however, the median overall survival (OS) differed, with values of 10.7 months in the West and 6.5 months in Asia Pacific.[6,7] Recently, the regorafenib phase III second-line trial also showed a trend toward better OS, progression-free survival (PFS), and time to progression outcomes in Asia *vs.* the rest of the world.[8] Thus, understanding the differences in drug treatment outcomes between patient populations with advanced HCC in different regions is important to optimise the treatment approach.

In recent years, there has been interest in using immunotherapy to treat many tumour types, including HCC. Nivolumab, a fully human IgG4 antiprogrammed death-1 monoclonal antibody, inhibits immune checkpoint signalling. Nivolumab treatment improves survival compared with chemotherapy across several tumour types, including melanoma,[9] non-small cell lung cancer[10,11] and renal cell carcinoma.[12] The phase I/II CheckMate 040 study (NCT01658878; CA209-040) investigated nivolumab treatment in patients with advanced HCC. In the dose-expansion phase of this study, patients received nivolumab 3 mg/kg, and the objective response rate (ORR) was 20%, with a median duration of response (DOR) of 9.9 months and a 9-month OS rate of 74%.[13] The nivolumab safety profile was consistent with that observed in other tumour types and no new safety signals were observed. Nivolumab is approved in various countries, including the USA, Canada, Taiwan, Hong Kong and Australia, for patients with advanced HCC who were previously treated with sorafenib. Similarly, the phase II pembrolizumab trial also confirmed promising efficacy with good tolerability for checkpoint inhibitor therapy in patients with advanced HCC. Interestingly, the pembrolizumab trial demonstrated a trend in ORR in patients in the USA *vs.* those elsewhere (26% *vs.* 15%, respectively), again suggesting regional variation in treatment outcomes.[14] The pembrolizumab plus best supportive care phase III trial in patients previously treated with systemic therapy failed to meet its coprimary endpoints for PFS and OS *vs.* placebo plus best supportive care, but did show a clinically meaningful improvement in OS survival (HR 0.78) and an ORR of 17%.[15]

Given the observed differences in treatment outcome with various systemic therapies, particularly with targeted agents, and the trend towards varying regional ORRs in patients with advanced HCC treated with pembrolizumab, it is important to understand possible differences in nivolumab treatment outcomes in non-Asian *vs.* Asian populations. Thus, this analysis assesses the safety and efficacy profile of nivolumab in patients recruited from Asia *vs.* those of the broader intent-to-treat (ITT) patient population in the CheckMate 040 study.

Patients and methods

Study design

The multicentre, open-label, phase I/II CheckMate 040 study included dose-escalation and -expansion cohorts to evaluate nivolumab efficacy and safety in patients with advanced HCC with or without chronic viral hepatitis (patients with HBV had detectable HBsAg, HBeAg, or HBV DNA; patients with HCV had detectable HCV RNA). Patients aged 18 years or older with histologically confirmed HCC, previously treated with sorafenib or naïve and/or intolerant to sorafenib, and not amenable to curative resection or local treatment, were eligible for the study. Study design details have been previously published.[13]

This analysis includes patients from both the dose-escalation and -expansion phases of the study. The ITT population included sorafenib-experienced patients from the global ITT population, and the Asian cohort included all such patients from the ITT population who were recruited in Asian countries (Fig. S1). Most patients received nivolumab 3 mg/kg (ITT, n = 154; Asian, n = 76). Fewer patients received either lower doses of 0.1 mg/kg (ITT, n = 5; Asian, n = 3), 0.3 mg/kg (ITT, n = 7; Asian, n = 3), or 1.0 mg/kg (ITT, n = 6; Asian, n = 2), or a higher dose of 10 mg/kg (ITT, n = 10; Asian, n = 1).

Endpoints and assessments

The primary endpoints in CheckMate 040 were safety and tolerability for the dose-escalation phase and ORR by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 for the dose-expansion phase.[13] Key secondary endpoints included ORR for the dose-escalation phase, complete response (CR) rate, disease control rate (DCR; the proportion of patients whose best overall response was CR, partial response [PR], or stable disease [SD; where predefined SD criteria must have been met at least once within ~6 weeks of the first nivolumab dose]), DOR, OS and response stratified by tumour programmed death-ligand 1 (PD-L1) expression. Disease assessments were performed by BICR per RECIST v.1.1[16] using computed tomography (CT) or magnetic resonance imaging (MRI). Tumour assessment by modified RECIST (mRECIST; by BICR) was an exploratory endpoint.

Tumour biopsies collected at baseline, either fresh or archival, were used retrospectively for the analysis of tumour PD-L1 expression by immunohistochemistry using the PD-L1 IHC 28-8 pharmDx assay (Dako, an Agilent Technologies Inc. company, Santa Clara, CA, USA; for further details regarding the materials used, please refer to the CTAT table and Supplementary information). Additional details on measurement of tumour PD-L1 expression are described in the appendix of the primary paper for this study.[13]

Safety was assessed continuously during treatment and for up to 30 days after the last dose or until all treatment-related adverse events (TRAEs) were resolved to baseline levels or deemed irreversible by the investigator.[13] Select adverse events (AEs) were defined as events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention, such as immunosuppressants and/or endocrine replacement therapy. These included gastrointestinal AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, hypersensitivity AEs and endocrinopathies. Patients received a survival follow-up assessment every 3 months.

Study oversight

The CheckMate 040 study was approved by the institutional review board or independent ethics committee at each site and was conducted in accordance with Good Clinical Practice guidelines defined by the International Council on Harmonisation. All patients provided written informed consent to participate based on the principles of the Declaration of Helsinki.

Statistical analyses

Two-sided 95% confidence intervals (CIs) were estimated using the Clopper–Pearson method for ORR, CR rate and DCR. Kaplan–Meier methodology was used to determine medians and 95% CIs for DOR, OS and OS rate.

Results

Patients

The cut-off date for this analysis was March 2018. There were 182 patients in the ITT population and 85 patients in the Asian cohort. Asian patients were recruited from Japan (n = 26), Hong Kong (n = 24), Taiwan (n = 17), South Korea (n = 13), and Singapore (n = 5).

Table 1 shows the baseline patient characteristics. Patients in the ITT population and Asian cohort were comparable in terms of median age, sex distribution and liver function status by Child–Pugh scoring. The dominant aetiology was HBV in the Asian cohort (55%) and uninfected (non-hepatitis virus related) in the ITT population (49%). Of interest, 28% of the patients in the Asian cohort had non-viral HCC and 32% of the ITT population had HBV-related HCC.

Overall, most patients were staged as Barcelona Clinic Liver Cancer (BCLC) C in both the Asian cohort and ITT population. Most patients with HBV-related HCC and non-viral HCC were also staged as BCLC C in both populations. For HCV-related HCC, a larger proportion of patients were staged as BCLC B in the Asian cohort (29%) compared with the ITT population (17%).

The Asian cohort had a slightly higher percentage of patients with extrahepatic metastases compared with the ITT population (82% *vs.* 71%, respectively). The presence of vascular invasion and an alpha-fetoprotein (AFP) score ≧400 μg/L at baseline was comparable between the two populations. The Asian cohort had a slightly higher frequency of surgical resection (78% *vs.* 67%, respectively) and a higher frequency of locoregional therapy (75% *vs.* 57%, respectively) compared with the ITT population. Most patients had progressed on sorafenib: 74% in the ITT population and 78% in the Asian cohort. A higher percentage of patients in the Asian cohort (35%) had received two or more prior therapies compared with the ITT population (23%). When baseline characteristics of the Asian cohort were compared directly to the non-Asian cohort (*i.e.* all patients recruited outside of Asia), there was a similar trend toward more extrahepatic metastases and a greater number of prior systemic therapies in the Asian cohort (Table S1).

Table 1. Baseline patient characteristics.

Patient characteristic	ITT population (n = 182)	Asian cohort (n = 85)
Median age (range), years	63 (19–81)	62 (22–81)
Male, n (%)	139 (76)	65 (76)
Race, n (%)		
Asian	91 (50)	85 (100)
Chinese	49 (27)	45 (53)
Japanese	25 (14)	25 (29)
Korean	13 (7)	13 (15)
Other Asian	3 (2)	1 (1)
Asian Indian	1 (1)	1 (1)
White	87 (48)	0
Black	4 (2)	0
HCC aetiology, n (%)		
HCV infected	35 (19)	14 (16)
HBV infected	58 (32)	47 (55)
Uninfected	89 (49)	24 (28)
BCLC stage all patients, n (%)		
B	17 (9)	5 (6)
C	162 (89)	80 (94)
BCLC stage HBV, n (%)		
B	2 (3)	1 (2)
C	56 (97)	46 (98)
BCLC stage HCV, n (%)		
B	6 (17)	4 (29)
C	26 (74)	10 (71)
BCLC stage uninfected, n (%)		
B	9 (10)	0 (0)
C	80 (90)	24 (100)
Extrahepatic metastases, n (%)	129 (71)	70 (82)
Vascular invasion, n (%)	55 (30)	24 (28)
Child–Pugh score of 5–6, n (%)	180 (99)	84 (99)
AFP ≥400 μg/L, n (%)*	67 (37)	37 (44)
Prior therapy, n (%)		
Surgical resection	122 (67)	66 (78)
Radiotherapy	45 (25)	23 (27)
Local treatment for HCC	104 (57)	64 (75)
Sorafenib	182 (100)	85 (100)
Reason for sorafenib discontinuation†		
Disease progression	135 (74)	66 (78)
Toxicity	39 (21)	16 (19)
Other	10 (5)	4 (5)
Number of prior therapies, n (%)		
1	141 (77)	55 (65)
2	20 (11)	14 (16)
≥3	21 (12)	16 (19)

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ITT, intent-to-treat.
*AFP data were not available in five ITT patients and in one Asian patient.
†Some patients had more than one reason for sorafenib discontinuation.

Efficacy

Treatment responses to nivolumab are shown in Table 2. The ORRs were comparable between the Asian cohort (15%) and ITT population (14%). There was a slightly higher percentage of patients with progressive disease (PD) in the Asian cohort (47%) compared with the ITT population (39%). Comparable DCRs were observed between the Asian cohort (49%) and ITT population (55%). Notably, the median DOR (95% CI) was shorter for the Asian cohort (9.7 months [5.6–not evaluable]) than for the ITT population (19.4 months [9.7–not evaluable]). The median time to response in the Asian cohort (2.8 months) was comparable with that of the ITT population (2.7 months) (Fig. 1). Ongoing responses were seen in one of 13 responders in the Asian cohort and in seven of 26 responders in the ITT population. When tumour responses in the Asian cohort were compared directly with the non-Asian cohort, ORRs of 15% and 13% were reported in the Asian and non-Asian patients, respectively; the median DOR was not evaluable in the non-Asian cohort because less than half of the responders had progressed (Table S2). The ORR was also analysed using mRECIST by BICR; under these criteria, the ORR was 24% in the Asian cohort, 13% in the non-Asian cohort and 18% in the ITT population (Table S2).

Reductions from baseline in tumour burden were seen in both the Asian cohort and ITT population irrespective of HCC aetiology (Fig. 2). In both populations, no marked differences in outcomes were observed relative to tumour PD-L1 expression (Table 2). Objective responses occurred regardless of PD-L1 tumour expression across all aetiologies. Responses in both populations were also not affected by age categorisation (<65 years *vs.* ≥65 years; Table S3).

Table 2. Antitumour activity.

Activity	ITT population (n = 182)*				Asian cohort (n = 85)*			
	Uninfected (n = 89)	HBV (n = 58)	HCV (n = 35)	All (n = 182)	Uninfected (n = 24)	HBV (n = 47)	HCV (n = 14)	All (n = 85)
ORR, n (%)[†,‡]	12 (13)	7 (12)	7 (20)	26 (14)	5 (21)	6 (13)	2 (14)	13 (15)
CR	1 (1)	3 (5)	1 (3)	5 (3)	0	2 (4)	1 (7)	3 (4)
PR	11 (12)	4 (7)	6 (17)	21 (12)	5 (21)	4 (9)	1 (7)	10 (12)
SD, n (%)[†,§]	43 (48)	18 (31)	11 (31)	72 (40)	9 (38)	15 (32)	5 (36)	29 (34)
PD, n (%)[†]	28 (32)	29 (50)	13 (37)	70 (39)	9 (38)	25 (53)	6 (43)	40 (47)
DCR, n (%)[†,¶]	56 (63)	26 (45)	18 (51)	100 (55)	14 (58)	21 (45)	7 (50)	42 (49)
KM Median DOR (95% CI), months[#]	11.3 (8.3–NE)	NE (2.8–NE)	NE (3.2–NE)	19.4 (9.7–NE)	9.4 (5.6–11.2)	NE (2.8–NE)	6.4 (3.2–9.7)	9.7 (5.6–NE)
PD-L1 expression ≥1%, n (%)[**]	12 (14)	13 (22)	9 (26)	34 (19)	3 (13)	10 (21)	3 (21)	16 (19)
ORR, n/N (%; 95% CI)[††]	5/12 (42; 15.2–72.3)	2/13 (15; 1.9–45.4)	3/9 (33; 7.5–70.1)	10/34 (29; 15.1–47.5)	1/3 (33; 0.8–90.6)	0/10 (0; 0.0–30.8)	1/3 (33; 0.8–90.6)	2/16 (13; 1.6–38.3)
PD-L1 expression <1%, n (%)[**]	60 (67)	43 (74)	25 (71)	128 (70)	20 (83)	36 (77)	11 (79)	67 (79)
ORR, n/N (%; 95% CI)[††]	13/60 (22; 12.1–34.2)	5/43 (12; 3.9–25.1)	7/25 (28; 12.1–49.4)	25/128 (20; 13.1–27.5)	7/20 (35; 15.4–59.2)	5/36 (14; 4.7–29.5)	3/11 (27; 6.0–61.0)	15/67 (22; 13.1–34.2)

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; ITT, intent-to-treat; KM, Kaplan-Meier; NE, not estimable; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

*Tumour responses were not evaluable in 12 ITT patients and in three Asian patients.

**Tumour cell PD-L1 expression was not evaluable in 20 ITT patients and in two Asian patients.

†Reported by BICR using RECIST v1.1.

‡Defined as CR + PR.

§Stable disease was reported as non-CR/non-PD in two patients in the ITT population.

¶DCR defined as CR + PR + SD.

††ORR by investigator assessment using RECIST v1.1.

Fig. 1. Characterisation of response. (A) ITT population (n = 26 responses). (B) Asian cohort (n = 13 responses). Tumour response assessed by BICR using RECIST v1.1; bars represent time to progression (in months). Abbreviations: BICR, blinded independent central review; ITT, intent-to-treat; NE, not estimable; RECIST, Response Evaluation Criteria in Solid Tumours.

Median OS (95% CI) was comparable between the Asian cohort (14.9 [11.6–18.9] months) and ITT population (15.1 [13.2–18.2] months) (Fig. 3A). OS rates at 12, 18, and 24 months were similarly comparable. Median OS (95% CI) for the non-

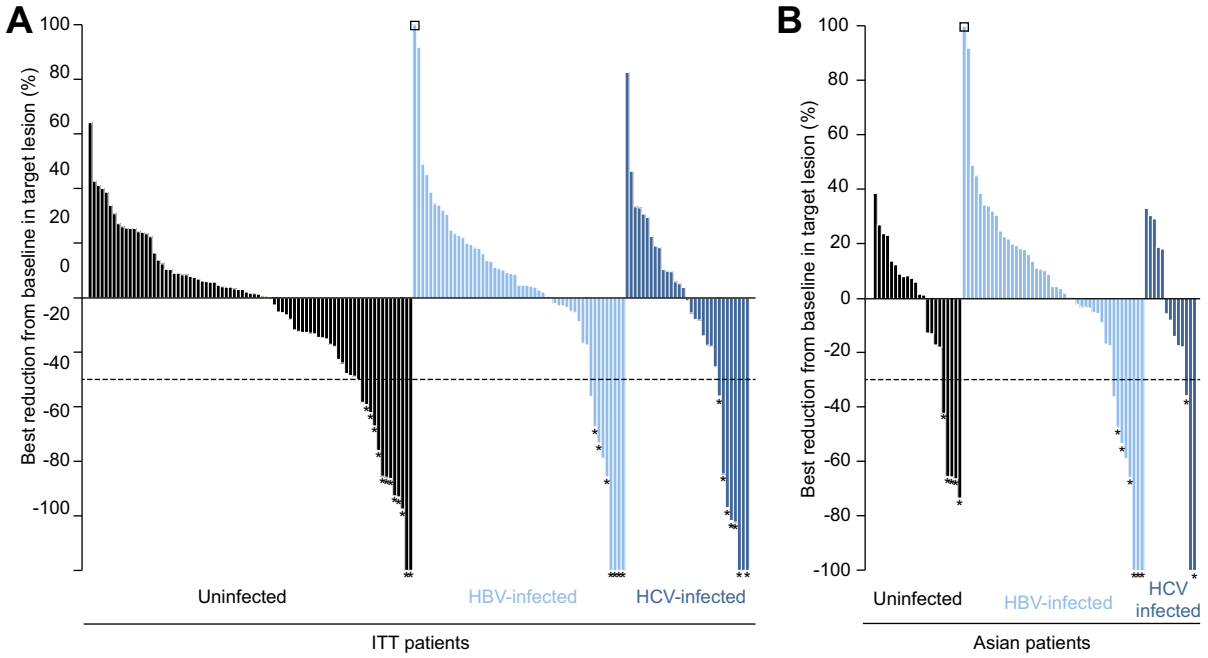


Fig. 2. Waterfall plots depicting the best reduction in target lesions by aetiology. (A) ITT population. (B) Asian cohort. Dashed line indicates a 30% reduction, consistent with a response per RECIST v1.1. The asterisk represents responders; the square symbol represents percentage change truncated to 100%. Abbreviations: ITT, intent-to-treat; RECIST, Response Evaluation Criteria in Solid Tumours.

Asian cohort was similar to that noted earlier, at 15.6 (11.3–20.2) months (Fig. 3B). Survival in both populations was also similar across HCC aetiology (Fig. 4) and when categorised by age (<65 years *vs.* ≥65 years; Fig. S2). In both the Asian cohort and ITT population, 100% of patients achieving a CR survived up to 24 months from the date of randomisation (Fig. S3).

Safety

The frequency of any grade TRAEs was comparable between the Asian cohort and ITT population (74% and 79%, respectively; Table 3). The frequency of Grade 3/4 TRAEs was similarly comparable between the Asian cohort (16%) and ITT population (19%). The most common TRAEs of any grade in both populations were pruritus, rash and fatigue. TRAEs of laboratory measures were infrequent in both populations, with <10% of patients experiencing TRAEs of any grade and ≤5% of patients experiencing Grade 3/4 TRAEs for each laboratory parameter assessed. Of note, increases in aminotransferases were infrequent in both populations. In the Asian cohort, no TRAEs of ascites or encephalopathy were reported; in the ITT population, any grade treatment-related ascites was only reported in one patient (0.5%) and no patients had encephalopathy. In the Asian cohort, 11% (5/47) of patients with HBV had >1 log increase in HBV DNA and 21% (3/14) of patients with HCV had >1 log decrease in HCV RNA from baseline. In the ITT population, 9% (5/58) of patients with HBV and 26% (9/35) of patients with HCV had >1 log increase in HBV DNA and >1 log decrease in HCV RNA from baseline, respectively. Changes in viral kinetics were not associated with nivolumab-related significant hepatic AEs.

In both populations, the most common select TRAEs (sTRAEs) of any grade were skin and gastrointestinal events (Table 3 and Table S4). Grade 3/4 sTRAEs were infrequent in both populations, each occurring in <5% of patients. In the Asian cohort, Grade 3/4 gastrointestinal, hepatic, skin and adrenal insufficiency sTRAEs each occurred in ~1% (1/85) of patients.

Most sTRAEs were Grade 1/2 in severity, and few required immune-modulating therapy (Table 3). In both populations, the most common sTRAE category for which patients received immune-modulating therapy was skin, with 33% and 23% in the Asian cohort and ITT population, respectively, receiving topical corticosteroids. Systemic corticosteroid use was reported for any grade AEs in 15% and 17% of Asian and ITT patients, respectively.

In the Asian cohort, there was a total of 29 events in which patients were rechallenged with nivolumab after experiencing an immune-mediated AE, three of which were Grade 3/4 events. Of the 11 events in which the rechallenge outcome was recorded by the investigator, 10 patients did not experience a recurrence of the AE after rechallenge and one patient experienced a recurrence of rash.

A total of 60 Asian and 130 ITT patients died during the study. The most common cause of death in both populations was disease progression (Asian, n = 56, 66%; ITT, n = 119, 65%). One Asian patient died of a serious TRAE (Grade 5 pneumonitis) that occurred >100 days after nivolumab discontinuation because of disease progression and after subsequent sorafenib treatment. This event was considered by investigators to be related to both nivolumab and sorafenib treatment. In the other cases in the Asian cohort, causes of death were unrelated to study drug, and listed as intracranial haemorrhage (n = 1), suspected infection (n = 1), and indeterminable (n = 1).

Patient disposition

The median follow-up was comparable for both populations at the time of this database lock: 31.3 (28.4–51.0) and 31.6 (28.3–63.8) months for the Asian cohort and ITT population, respectively. In both populations, 4% continued to receive nivo-

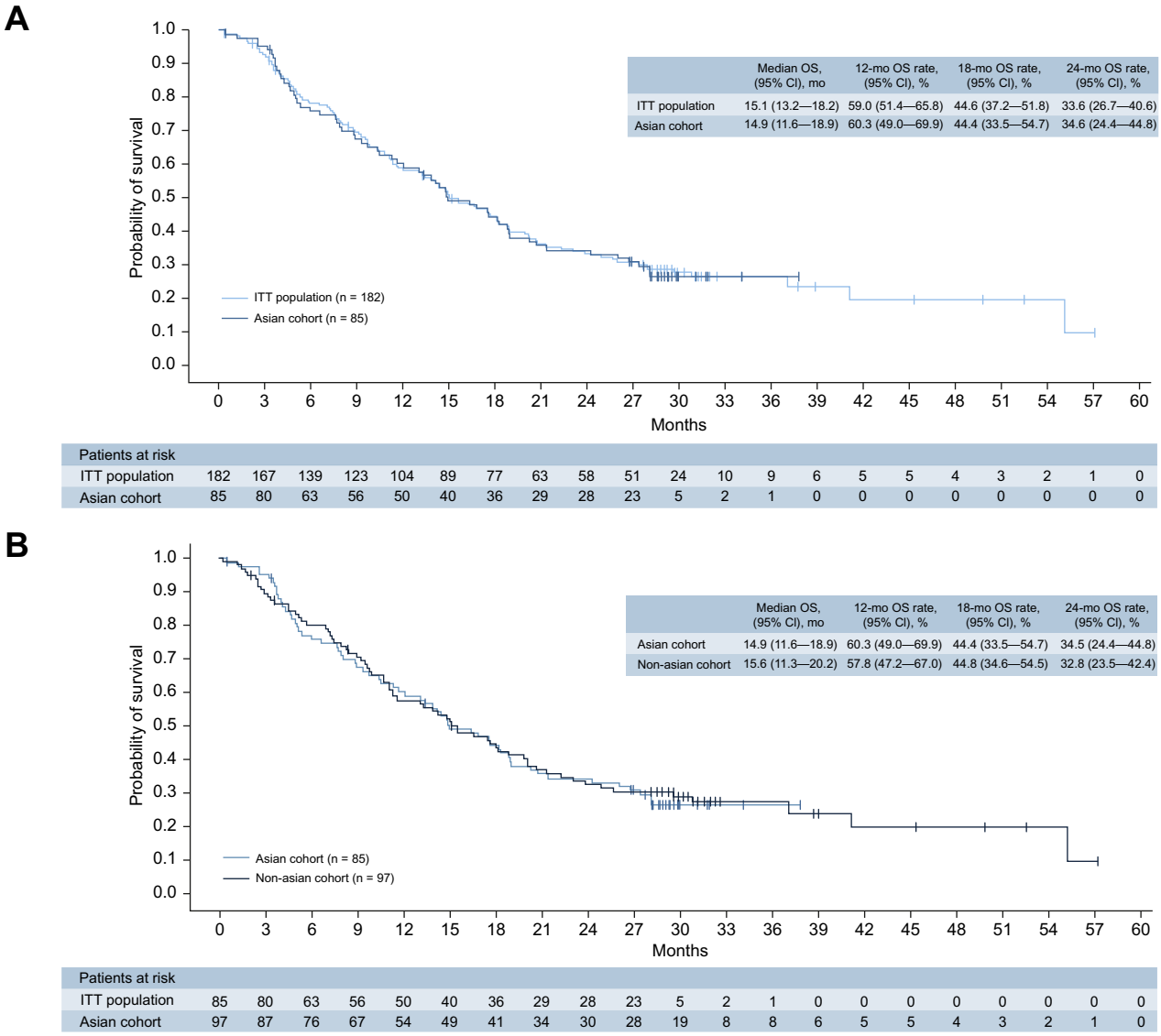
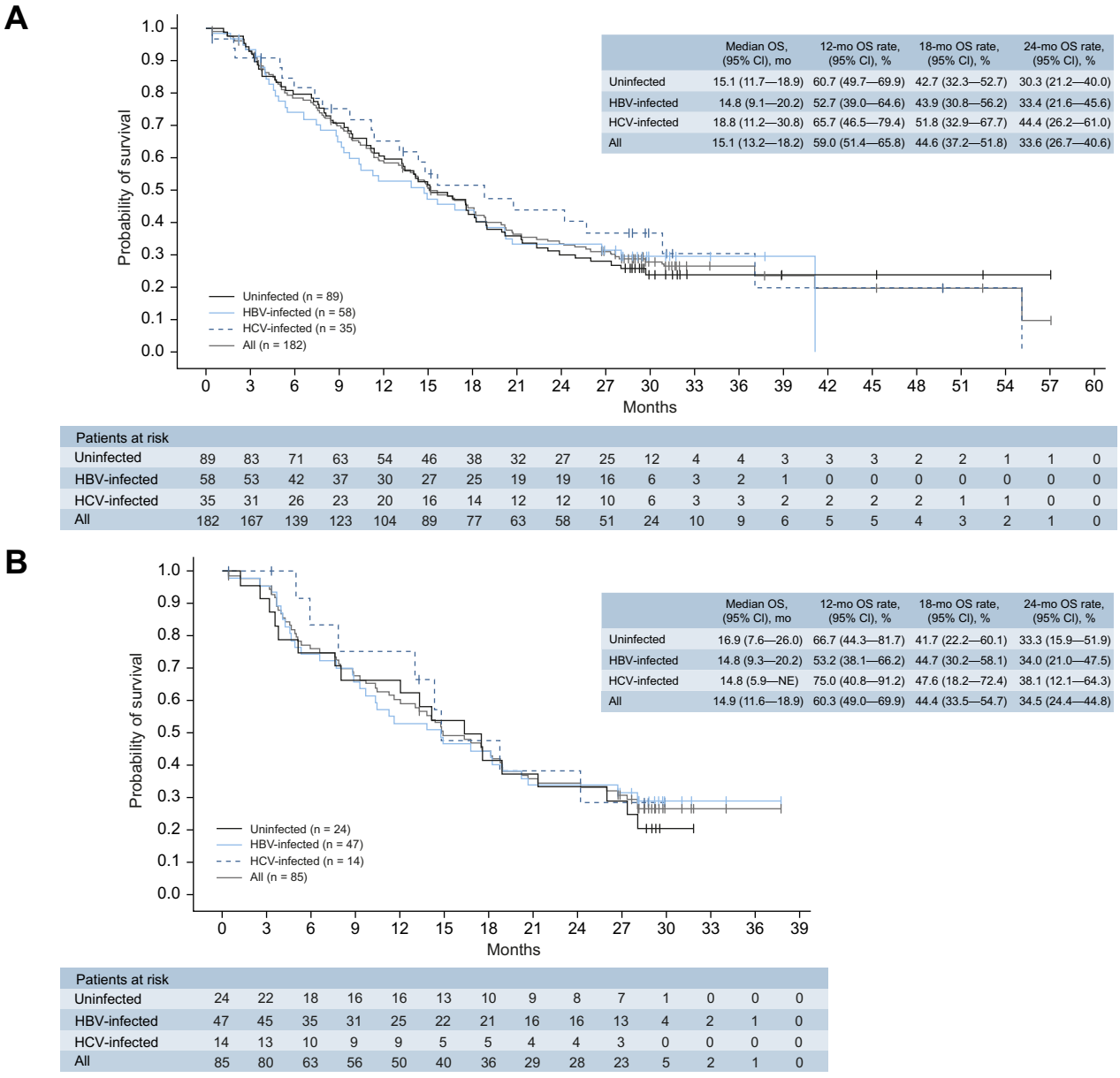


Fig. 3. Kaplan–Meier analysis of overall survival. (A) ITT population and Asian cohort. (B) Asian and non-Asian cohorts. Abbreviations: ITT, intent-to-treat; OS, overall survival.

lumab at the time of database lock. The primary reason for discontinuing nivolumab treatment was disease progression in both the Asian (91%) and ITT (84%) populations. After progression on nivolumab, a slightly larger percentage of patients in the Asian cohort received any subsequent therapy compared with the ITT population (62% *vs.* 52%, respectively). In particular, more patients in the Asian cohort received systemic therapy and local therapy compared with patients in the ITT population. Additional details on subsequent treatments are provided in Table 4.

Discussion

In this analysis of the CheckMate 040 data, the efficacy and safety of nivolumab treatment in sorafenib-experienced patients with advanced HCC was compared between the Asian cohort and ITT population. After a median follow-up of ~31 months in each population, ORR and DCR were similar, despite the slightly higher proportion of HBV-related HCC, extrahepatic metastases and heavy pretreatment in the Asian cohort. The differences in patient baseline characteristics between these populations are consistent with previous reports that Asian patients tend to have more advanced disease and receive more prior therapies than patients treated in the West.[3] Clinically meaningful objective responses occurred in both populations regardless of HCC aetiology, age or tumour PD-L1 expression. Of note, there was a trend toward shorter median DOR for the Asian cohort at 9.7 months compared with 19.4 months for the ITT population, with overlapping confidence intervals, although the Asian cohort had small patient numbers and the subanalysis was not powered to detect a difference in DOR. The median DOR reported here for the ITT population was substantially longer than that reported in other advanced HCC trials. For example, the RESORCE trial reported a DOR of 3.5 months with regorafenib treatment[8] and the KEYNOTE-224 study reported a DOR of at least 9 months in 77% of patients following pembrolizumab treatment.[14] Therefore, even though the median DOR was numerically shorter in the Asian cohort compared with the ITT population, it was substantially longer than that reported for regorafenib and compa-



	Median OS, (95% CI), mo	12-mo OS rate, (95% CI), %	18-mo OS rate, (95% CI), %	24-mo OS rate, (95% CI), %
Uninfected	15.1 (11.7—18.9)	60.7 (49.7—69.9)	42.7 (32.3—52.7)	30.3 (21.2—40.0)
HBV-infected	14.8 (9.1—20.2)	52.7 (39.0—64.6)	43.9 (30.8—56.2)	33.4 (21.6—45.6)
HCV-infected	18.8 (11.2—30.8)	65.7 (46.5—79.4)	51.8 (32.9—67.7)	44.4 (26.2—61.0)
All	15.1 (13.2—18.2)	59.0 (51.4—65.8)	44.6 (37.2—51.8)	33.6 (26.7—40.6)

Patients at risk																				
Uninfected	89	83	71	63	54	46	38	32	27	25	12	4	4	3	3	3	2	2	1	1	0
HBV-infected	58	53	42	37	30	27	25	19	19	16	6	3	2	1	0	0	0	0	0	0	0
HCV-infected	35	31	26	23	20	16	14	12	12	10	6	3	3	2	2	2	2	1	1	0	0
All	182	167	139	123	104	89	77	63	58	51	24	10	9	6	5	5	4	3	2	1	0

	Median OS, (95% CI), mo	12-mo OS rate, (95% CI), %	18-mo OS rate, (95% CI), %	24-mo OS rate, (95% CI), %
Uninfected	16.9 (7.6—26.0)	66.7 (44.3—81.7)	41.7 (22.2—60.1)	33.3 (15.9—51.9)
HBV-infected	14.8 (9.3—20.2)	53.2 (38.1—66.2)	44.7 (30.2—58.1)	34.0 (21.0—47.5)
HCV-infected	14.8 (5.9—NE)	75.0 (40.8—91.2)	47.6 (18.2—72.4)	38.1 (12.1—64.3)
All	14.9 (11.6—18.9)	60.3 (49.0—69.9)	44.4 (33.5—54.7)	34.5 (24.4—44.8)

Patients at risk														
Uninfected	24	22	18	16	16	13	10	9	8	7	1	0	0	0
HBV-infected	47	45	35	31	25	22	21	16	16	13	4	2	1	0
HCV-infected	14	13	10	9	9	5	5	4	4	3	0	0	0	0
All	85	80	63	56	50	40	36	29	28	23	5	2	1	0

Fig. 4. Kaplan–Meier analysis of overall survival stratified by aetiology. (A) ITT population. (B) Asian cohort. Abbreviations: ITT, intent-to-treat; NE, not estimable; OS, overall survival.

rable to pembrolizumab, and is clinically meaningful. Additionally, a separate *ad hoc* analysis of other cohorts in CheckMate 040 demonstrated a DOR comparable with nivolumab in sorafenib-naïve Asian *vs.* ITT patients; median DOR in the Asian cohort was not evaluable, with a range from 13.8 to >29.0 months, compared with a median (range) DOR of 22.6 months (from 4.2 to >29.0 months) in the ITT population (data not shown). Despite the difference in DOR, the median OS was comparable between the two populations, with similar OS rates at various time points. Based on this similar OS, and the fact that the DOR was not evaluable for many subgroups, it is not clear that DOR was significantly different between the Asian cohort and the ITT population. However, one cannot discount that the differences in patient baseline characteristics between these populations, including a higher proportion of HBV-related HCC, extrahepatic metastases and heavy pretreatment in the Asian cohort, might affect DOR. Data from larger studies could provide greater clarity on this outcome.

The heterogeneity of HCC is reflected in the observed regional differences in the disease, as well as its aetiology, clinical presentation and management approaches. The confluence of these differences can result in variations in drug treatment outcomes. Differences in survival outcomes have been reported in systemic HCC trials, possibly related to different etiological responses or as a result of disease-stage migration related to practice differences.[3] Aside from the sorafenib and regorafenib phase III trials, the ramucirumab phase III second-line trial similarly showed regional differences in outcomes for OS with HRs of 0.75, 0.83 and 0.65 in the Americas, Europe, Israel and Australia (combined); Asia (excluding Japan); and Japan, respectively. Regional differences were also observed for PFS.[17] The lenvatinib phase III first-line trial showed an OS HR of 0.86 in

Table 3. Treatment-related adverse events.*

Adverse events	ITT population (n = 182)		Asian cohort (n = 85)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs				
Any TRAE, n (%)	143 (79)	34 (19)	63 (74)	14 (16)
TRAEs (≥10%)†, n (%)				
Pruritus	37 (20)	1 (1)	22 (26)	0
Rash	33 (18)	1 (1)	15 (18)	0
Fatigue	42 (23)	4 (2)	12 (14)	0
Decreased appetite	15 (8)	1 (1)	9 (11)	0
Diarrhoea	27 (15)	2 (1)	8 (9)	1 (1)
Laboratory TRAEs (≥5%)†, n (%)				
Platelet count decreased	9 (5)	4 (2)	8 (9)	3 (4)
Lipase increased	12 (7)	8 (4)	4 (5)	4 (5)
ALT increase	16 (9)	5 (3)	4 (5)	0
AST increased	16 (9)	7 (4)	3 (4)	1 (1)
Amylase increased	11 (6)	2 (1)	2 (2)	1 (1)
Blood bilirubin increased‡	4 (2)	0	1 (1)	0
sTRAEs				
sTRAEs, n (%)				
Skin§	61 (34)	3 (2)	32 (38)	1 (1)
GI¶	29 (16)	2 (1)	9 (11)	1 (1)
Hypothyroidism	7 (4)	0	6 (7)	0
Hepatic**	22 (12)	8 (4)	5 (6)	1 (1)
Adrenal insufficiency	2 (1)	1 (1)	2 (2)	1 (1)
Hyperthyroidism	1 (1)	0	1 (1)	0
Thyroiditis	1 (1)	0	1 (1)	0
Pneumonitis	2 (1)	1 (1)	1 (1)	0
Renal	2 (1)	0	1 (1)	0
Hypersensitivity/infusion-related reaction	7 (4)	0	1 (1)	0
Requiring immune-modulating therapy, n (%)				
Skin††	26 (14)	3 (2)	18 (21)	1 (1)
GI‡‡	6 (3)	2 (1)	2 (2)	1 (1)
Adrenal insufficiency	2 (1)	0	2 (2)	0
Hypersensitivity/infusion-related reaction	3 (2)	0	1 (1)	0
Pneumonitis	2 (1)	1 (1)	1 (1)	0
Thyroiditis	1 (1)	0	1 (1)	0
ALT increase	2 (1)	2 (1)	0	0
AST increase	1 (1)	1 (1)	0	0
Hepatitis	1 (1)	1 (1)	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ITT, intent-to-treat; sTRAE, select TRAE; TRAE, treatment-related adverse event.
*Includes events reported between first dose and 30 days after last dose of study therapy. Event terms were reported by investigators and were not predefined.
**Includes increases in ALT, AST, blood alkaline phosphatase, blood bilirubin and aminotransferases; hyperbilirubinemia; hepatitis; liver disorder.
†Reported in ≥10% or ≥5% of all patients in any population, any grade.
‡Blood bilirubin increases were reported in <5% of all patients.
§Includes pruritus; rash; rash maculopapular; pruritus generalised; pemphigoid; rash pruritic; skin exfoliation; eczema; erythema; palmar-plantar erythrodysaesthesia syndrome; rash papular.
¶Includes diarrhoea; colitis; enteritis; frequent bowel movements.
††Includes pruritus; rash; rash maculopapular; pemphigoid; rash pruritic.
‡‡Includes diarrhoea; colitis.

the Asia-Pacific region *vs.* 1.08 in the Western region and a greater trend favouring lenvatinib for PFS in Asia Pacific than in the West.[18] Conversely, the cabozantinib phase III second-line trial showed an opposite trend with an OS HR of 1.01 in Asia *vs.* 0.71 in other geographical regions and, when assessed by race, an OS HR of 0.86 in Asians *vs.* 0.75 in non-Asians. No difference in PFS were observed.[19] Thus, understanding the potential differences in drug treatment outcomes is important to optimise individual patient outcomes and appreciate the potential implications for clinical trial design.

Notably, in this analysis, the median OS in uninfected patients and in patients with HBV or HCV was similar, which suggests that HCC aetiology does not have a significant impact on nivolumab survival outcomes. This differs from a meta-analysis and pooled exploratory analysis, which suggested that the impact of sorafenib treatment in patients with advanced HCC is dependent on their hepatitis status.[20,21]

In general, this analysis demonstrated that nivolumab safety in the Asian cohort was consistent with that in the ITT population, and no new safety signals were observed. Regarding hepatic parameters, there was little, if any, difference between the Asian cohort and the ITT population, despite 71% of the Asian cohort having underlying hepatitis. In both populations, the most commonly reported TRAEs were pruritus, rash and fatigue, which are typical AEs associated with immune checkpoint inhibitors.[22] This safety profile is consistent with nivolumab use in other tumour types, including melanoma,[9] non-small cell lung cancer,[10,11] renal cell carcinoma,[12] Hodgkin lymphoma[23] and squamous cell carcinoma of the head and neck.[24]

Limitations of this study include that it was a *post hoc* analysis of a single arm, open-label, phase II trial. The sample sizes were relatively small, thus not allowing in-depth comparison of the Asian cohort with a non-Asian cohort. Therefore, comparisons between the Asian cohort and the ITT population must

Table 4. Subsequent therapy after nivolumab progression.

Therapy	ITT population (n = 182)	Asian cohort (n = 85)
Any subsequent therapy, n (%)	94 (52)	53 (62)
Radiotherapy	40 (22)	22 (26)
Surgery	17 (9)	9 (11)
Systemic therapy	62 (34)	36 (42)
Chemotherapy	45 (25)	37 (43)
Targeted therapy	37 (20)	20 (24)
Immune checkpoint inhibitor	9 (5)	5 (6)
Other immunotherapy	5 (3)	5 (6)
Experimental therapy	18 (10)	9 (11)
Other	10 (5)	9 (11)
Local therapy	34 (19)	24 (28)
TACE	24 (13)	19 (22)
HAI chemotherapy	5 (3)	5 (6)
Other	10 (5)	4 (5)
Radiofrequency ablation	3 (2)	3 (4)

HAI, hepatic artery infusion; ITT, intent-to-treat; TACE, transcatheter arterial chemoembolisation.

be interpreted with caution. Validation of the observations seen in this subanalysis will be forthcoming from the ongoing phase III CheckMate 459 trial, which will provide a larger data set for the evaluation of regional differences (ClinicalTrials.gov identifier NCT02576509).

Conclusion

In this analysis of sorafenib-experienced patients with advanced HCC in the CheckMate 040 study, nivolumab treatment elicited durable responses and promising long-term survival, with similar responses and survival outcomes in both Asian and ITT populations. Responses were observed across HCC aetiologies and occurred irrespective of tumour PD-L1 expression. Nivolumab was well tolerated, with similar safety profiles in both Asian and ITT populations; no new safety signals were observed. The ongoing, global, open-label, phase III CheckMate 459 study is evaluating nivolumab as a first-line therapy in patients with advanced HCC, including in Asian patients in China, Hong Kong, Japan, South Korea, Singapore, and Taiwan (ClinicalTrials.gov identifier NCT02576509).

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Conflict of interest

T.Y. reports receiving honoraria from Bristol-Myers Squibb (BMS) and has a consulting or advisory role at BMS. C.H. reports receiving honoraria from Bayer Schering Pharma, BMS, MSD Oncology and TTY Biopharm. S-P.C. reports receiving honoraria from BMS; has received honoraria and speaker fees from Bayer Schering Pharma and Lilly; has an advisory role and has received honoraria from Sirtex Medical, Eisai and Ipsen; has a consulting or advisory role at BMS; and received research funding from BMS. Y-K.K. reports having a consulting or advisory role at Lilly/Im Clone, Taiho Pharmaceutical, Ono Pharmaceutical Co., Roche/Genentech and Novartis and received research funding from LSK Biopharma. W.Y. reports receiving honoraria from Pfizer; and has a consulting advisory role at Lilly and Novartis. A.C. reports receiving honoraria from Bayer Schering Pharma and Janssen Oncology; has a consulting or advisory role at Astellas Pharma, AstraZeneca, Bayer Schering Pharma, Boehringer Ingelheim, Lilly, MSD Oncology and Mundipharma; has served in speakers' bureau for BMS and Roche Molecular Diagnostics; received travel accommodations and expenses from Boehringer Ingelheim, BMS and Merck Serono; and has other relationships with BMS. M.I. reports receiving honoraria from Abbott Japan, Bayer Yakuhin, BMS Japan, Chugai Pharma, Daiichi Sankyo, Eisai, Lilly Japan, Nobelpharma, Novartis, Otsuka, Taiho Pharmaceutical and Yakult Honsha; has served as a consulting or advisory role for Bayer Yakuhin, Eisai, Kyowa Hakko Kirin, NanoCarrier, Novartis and Shire; and has received research funding from ASLAN Pharmaceuticals, AstraZeneca, Baxter, Bayer Yakuhin, BMS, Chugai Pharma, Eisai, Kowa, Kyowa Hakko Kirin, Lilly Japan, Merck Serono, NanoCarrier, Ono Pharmaceutical, Taiho Pharmaceutical, Yakult and Zeria Pharmaceutical. R.K. reports receiving research funding from BMS, Eisai, Ono Pharmaceutical, MSD, AstraZeneca, EA Pharma, Takeda and Chugai; and has received honoraria from MSD, Mitsubishi Tanabe Pharma, Shionogi & Co., GE Healthcare Japan and Daiichi Sankyo. M.M. reports receiving research funding from Bayer, Bayer (Inst), Kowa (Inst), Kyowa Hakko Kirin, Kyowa Hakko Kirin (Inst), Pfizer, Taiho Pharmaceutical and Yakult Honsha. H.Z., J. A. and C.D.C. report employment by BSM and holding stock options and other ownership interests at BSM. M.K. reports lecturing for MSD, Bayer, Eisai and Ajinomoto; has received grants from Otsuka, Taiho, AbbVie, Daiichi Sankyo, Medico's Hirata, Astellas Pharma, Chugai, BSM, Bayer, Eisai, MSD, Ajinomoto, Takeda and Sumitomo Dainippon; and has held an advisory or consulting role at Eisai, Bayer, Kowa, MSD, BMS, Chugai, Taiho, Eli Lilly and Ono Pharmaceutical Co. T-Y.K., M-M.H., K.N. and Y. C. have nothing to disclose.

Authors' contributions

J.A. and C.D.C. conceived and designed the study. T.Y., C.H., T-Y. K., S-P.C., Y-K.K., M-M.H., K.N., W.Y., A.C., M.I., R.K., M.M., Y.C. and M.K. recruited patients and collected the data. H.Z., J.A. and C.D.C. analysed the data. All authors interpreted the data and were involved in the development, review and approval of the manuscript.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.05.014.

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Author names in bold designate shared co-first authorship

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