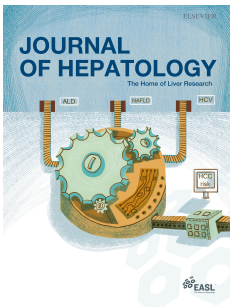

CheckMate 040 Cohort 5: A phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis

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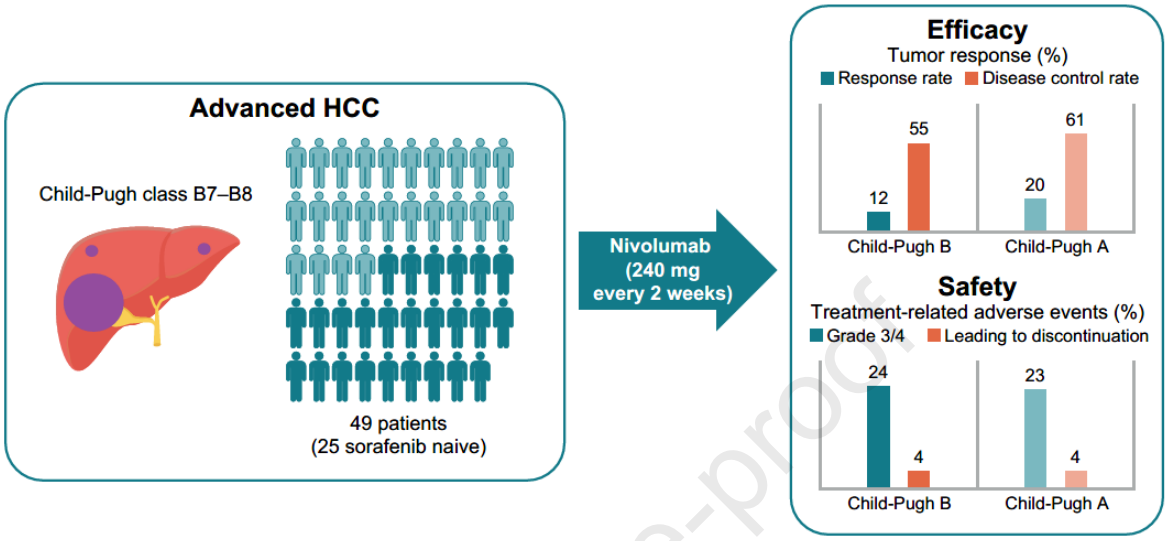
Graphical Abstract



JHEPAT-D-20-01803R2

CheckMate 040 Cohort 5: A phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis

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Data sharing

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

Conflict of interest statement: MK reports receiving personal fees from Bristol Myers Squibb Company, Bayer, Eisai, MSD, and Ono Pharmaceutical and receiving grants from Eisai, Otsuka, Taiho Pharmaceutical, EA Pharma, Takeda, AbbVie, and Gilead

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Author Contributions: MK, IM, ABE and BS conceived and designed the study. MK, AM, AS, IM, ACG, MA, SP, ABE, RK, BE, KN, YI, FD, OC, MR and BS recruited patients and collected the data. YS, JC, TW and MT analysed the data. All authors

interpreted the data and were involved in development, review, and approval of the manuscript.

Clinical trial number: NCT01658878.

Lay summary: In patients with advanced HCC, almost all systemic therapies require very good liver function, *i.e.* Child-Pugh A liver function. The evidence from this study suggests that nivolumab shows clinical activity and an acceptable safety profile in patients with HCC with Child-Pugh B status who have mild to moderate impairment of liver function or liver decompensation that might rule out other therapies, so should be further studied.

Abstract (275/275 words)

Background & Aims: Patients with advanced hepatocellular carcinoma (aHCC) and Child-Pugh B liver function are often excluded from clinical trials. In previous studies, overall survival for these patients treated with sorafenib was ~3-5 months; thus, new treatments are needed. Nivolumab, alone or in combination with ipilimumab, is conditionally approved in the United States to treat patients with aHCC who previously received sorafenib. We describe nivolumab monotherapy outcomes in patients with Child-Pugh B status.

Methods: This phase 1/2, open-label, non-comparative, multicentre trial (27 centres) included patients with Child-Pugh B (B7-B8) aHCC. Patients received intravenous nivolumab 240 mg every 2 weeks until unacceptable toxicity or disease progression. Primary endpoints were objective response rate (ORR) by investigator assessment (using Response Evaluation Criteria in Solid Tumors v1.1) and duration of response

(DOR). Safety was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

Results: Twenty-five sorafenib-naive and 24 sorafenib-treated patients began treatment between November 2016 and October 2017 (median follow-up, 16.3 months). Investigator-assessed ORR was 12% (95% CI 5–25%) with six patients responding; disease control rate was 55% (95% CI 40–69%). Median time to response was 2.7 months (interquartile range, 1.4–4.2), and median DOR was 9.9 months (95% CI 9.7–9.9). Treatment-related adverse events (TRAEs) were reported in 25 patients (51%) and led to discontinuation in two patients (4%). The most frequent grade 3/4 TRAEs were hypertransaminasemia (n=2), and amylase increase and aspartate aminotransferase increase (n=2 each). The safety of nivolumab was comparable to that of patients with Child-Pugh A aHCC.

Conclusions: Nivolumab showed clinical activity and favourable safety with manageable toxicities, suggesting it could be suitable for patients with Child-Pugh B aHCC.

Introduction

Liver cancer is the sixth most common cancer and the third most common cause of cancer death globally.[1] Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer,[2] and is often diagnosed at advanced stages,[3] when survival rates are generally low.[2] Liver cirrhosis is a risk factor for developing HCC, the severity of which is assessed using the Child-Pugh score, based on laboratory values and clinical assessments, and categorized as Child-Pugh A, B, or C.[4].

Patients with Child-Pugh B HCC have compromised liver function and there are few treatment options and limited efficacy and safety data for this patient population.[5, 6] In the United States, sorafenib is a recommended first-line systemic treatment for select patients with Child-Pugh A or B HCC whereas, in Europe, sorafenib is recommended as an option in the first-line setting for patients with Child-Pugh A HCC only.[4, 7] Nivolumab is conditionally approved in the United States for patients with Child-Pugh A or B HCC as first-line therapy in certain circumstances and as second-line therapy.[4, 7] Historical overall survival (OS) for patients with Child-Pugh B HCC is much lower than OS in patients with Child-Pugh A HCC, with a median OS of 2.5–5.4 months versus 6.1–13.6 months, respectively, for sorafenib-treated patients.[5, 8-11] This trend was also observed in the GIDEON study, a large, prospective, observational study that assessed sorafenib (800-mg initial dose) safety and use in real-life clinical practice in patients with advanced HCC (aHCC) that included Child-Pugh A (n = 1968) and Child-Pugh B (n = 666) class patients.[11] In this real-world setting, median OS was 13.6 months in Child-Pugh A patients and 5.2 months in Child-Pugh B patients. While several new drugs have shown efficacy in and been approved as first- and second-line therapies for patients with Child-Pugh A HCC,[3, 12-17] patients with Child-Pugh B

aHCC are generally excluded from clinical trials of novel therapies because of their poor prognosis.[18] Given the poor prognosis for patients with Child-Pugh B aHCC and their exclusion from most clinical trials, new treatment options for this patient population are needed.

Nivolumab, a fully human immunoglobulin G4 monoclonal antibody that inhibits programmed death-1 immune checkpoint signalling, is conditionally approved (either alone or in combination with ipilimumab) in the United States, Canada, Taiwan, Hong Kong, and Australia for sorafenib-treated patients with aHCC.[19] Nivolumab's approval for HCC was based on results from the dose-escalation and -expansion cohorts of CheckMate 040 (NCT01658878), primarily in Child-Pugh A patients.[3] The objective response rate (ORR) based on blinded independent central review (BICR) was 15% in patients treated with nivolumab 3 mg/kg in the dose-escalation phase and 20% in the dose-expansion phase, with 9-month OS rates of 66% and 74%, respectively. CheckMate 040, comprising 6 cohorts, is a phase 1/2 study of nivolumab alone or combined with other agents in patients with aHCC.[3] We report data from the Child-Pugh B cohort of CheckMate 040 who were treated with nivolumab alone. To the best of our knowledge, this is the first prospective study of immunotherapy in patients with Child-Pugh B aHCC.

Methods

Study design and participants

CheckMate 040 was a phase 1/2, open-label, clinical trial. The Child-Pugh B cohort was conducted at 27 sites in 5 countries. Eligibility criteria included Child-Pugh B (B7–B8)

histologically confirmed aHCC not eligible for surgical and/or locoregional therapy. Additional inclusion criteria included no prior sorafenib treatment or documented radiographic progression on or intolerance of sorafenib; Eastern Cooperative Oncology Group performance status of 0 or 1; no to mild ascites; ≥1 untreated lesion measurable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; total bilirubin <3 mg/dL; aspartate aminotransferase and alanine aminotransferase ≤5x the upper limit of normal, and adequate hematologic function. Patients were eligible to enrol if they had nonviral HCC or hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, defined as a) chronic HBV infection (detectable HBV surface antigen or HBV DNA with a requirement for antiviral therapy and HBV DNA <500 IU/mL); or b) active or resolved HCV infection (detectable HCV RNA or antibody).

Key exclusion criteria included known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC; history of hepatic encephalopathy within 2 weeks of screening; history of hepatorenal syndrome; paracentesis for treatment of ascites within 2 weeks of screening; active brain or leptomeningeal metastases; active co-infection with both HBV and HCV; and prior liver transplant.

This 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 for Harmonisation. All patients provided written informed consent to participate based on the principles of the Declaration of Helsinki. All authors had access to the study data and reviewed and approved the final manuscript.

Procedures

Patients received nivolumab 240-mg flat dose intravenously for 30 minutes every 2 weeks until unacceptable toxicity or disease progression per RECIST v1.1. On-treatment safety procedures included physical examinations, Child-Pugh-B score assessment, and evaluation of adverse events (AEs), concurrent medications, and vital signs. Efficacy procedures included tumour imaging (computed tomography or magnetic resonance imaging) every 6 weeks up to 48 weeks, and every 12 weeks thereafter. The first follow-up visit occurred approximately 35 days after the last dose of study drug. A second follow-up occurred 80 days later. Survival follow-up visits occurred approximately every 3 months after the second follow-up.

Outcomes

The primary endpoints of the study were ORR based on investigator assessment using RECIST v1.1 and duration of response (DOR). ORR was defined as the proportion of all treated patients whose best overall response (BOR) was complete response (CR) or partial response (PR). For a BOR of CR or PR, the initial response assessment must have been confirmed by a consecutive assessment no less than 4 weeks later.

Secondary endpoints included disease control rate (DCR), time to response (TTR), time to progression (TTP), TTP rate, progression-free survival (PFS), OS, OS rate, and association between biomarkers and efficacy. Exploratory endpoints included BOR and ORR by BICR-assessed tumour response (using modified RECIST and RECIST v1.1); safety analysis including AEs, treatment-related AEs (TRAEs), serious AEs (SAEs), and serious TRAEs using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0; and health-related quality of life (HRQoL) as measured by Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) and European Quality of Life 5 Dimensions questionnaire (EQ-5D). Standard laboratory

procedures were used to measure alpha-fetoprotein (AFP); complete and differential blood counts were used to quantify neutrophils and lymphocytes.

Select AEs and immune-mediated AEs (IMAEs) were also assessed. Select AEs were defined as events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine replacement therapy. IMAEs were events considered as potential immune-mediated events by the investigator occurring within 100 days of the last dose, regardless of causality, treated with immune-modulating medication, with the exception of endocrine events.

Patient-reported outcomes

To assess patient-reported outcomes (PROs), the 3-level version of the EQ-5D (EQ-5D-3L) and FACT-Hep questionnaires were administered before clinical activities at baseline on cycle 1 day 1 and every other cycle thereafter. Item responses FACT-Hep were 0 (“not at all”), 1 (“a little bit”), 2 (“somewhat”), 3 (“quite a bit”), and 4 (“very much”). For HRQoL analyses, patients with a baseline assessment and at least 1 subsequent assessment were included, comprising the PRO population. Mixed-model with repeated measures (MMRM) analyses were conducted for EQ-5D-3L and FACT-Hep using baseline PRO scores and visits (as a repeated measure) as covariates. Clinically meaningful median time to deterioration was calculated with corresponding 95% CIs. Timepoints with at least 10 patients were considered evaluable. Clinically meaningful changes were prespecified and are defined in the Supplementary Methods.[20, 21]

Statistical analysis

ORR, DCR, and the corresponding 2-sided 95% exact CIs were calculated using the Clopper-Pearson method; DOR, TTP, PFS, and OS were analysed by the Kaplan-Meier method. AEs, TRAEs, SAEs, and serious TRAEs were tabulated using worst grade per NCI CTCAE v4.0. On-study laboratory parameters, including haematology, chemistry, liver function, and renal function, were summarized using worst grade per NCI CTCAE v4.0.

Data from CheckMate 040 cohorts 1 and 2, in which 98% of patients had Child-Pugh A class,[3] are presented for indirect comparison.

Results

Between August 19, 2016, and October 27, 2017, 49 patients with aHCC in the Child-Pugh B cohort of CheckMate 040 were enrolled and included in the analysis. As of the data cutoff of September 25, 2018, all 49 patients were treated with nivolumab. Most patients had a Child-Pugh score of B7 (76%; **Table 1**), and the model for end-stage liver disease – sodium (MELD-Na) median score was 12 (interquartile range: 10–14). Vascular invasion and extrahepatic metastases were observed in 29% and 41% of patients, respectively. One patient had Child-Pugh A6 class; this patient had Child-Pugh B7 class prior to allocation that improved to Child-Pugh A6 on the day of the first treatment dose.

Eight patients (16%) were infected with HBV and 21 (43%) with HCV; 20 patients (41%) were uninfected. Of the 8 patients with HBV, 5 were sorafenib naive, and 3 were sorafenib treated. Three patients (38%) had resolved HBV (detectable hepatitis B surface antibody and undetectable hepatitis B surface antigen) and did not require antiviral medication, while 5 patients (63%) received concomitant systemic antiviral medication of entecavir (n = 3), telbivudine (n = 1), or adefovir (n = 1). Of the 21 patients

with HCV, 8 were sorafenib naive, and 13 were sorafenib treated. No patients with HCV received systemic antiviral medications. Twenty-six patients (53%) had a platelet count below the lower limit of normal, and the median platelet count at baseline was 138 $x10^9$/L.

At baseline, 47 patients (96%) were receiving medication, most commonly diuretics (65% of patients), antacids (55%), beta blockers (39%), diabetes therapy (31%), and antihypertensives (29%).

Disease progression was the most common reason for treatment discontinuation (78%; **Table 2**). Three patients (6%) discontinued because of an unrelated AE, 2 patients (4%) discontinued because of study-drug toxicity, and 2 patients (4%) died. No treatment-related deaths were reported.

Ten patients (20%) received subsequent therapy after nivolumab treatment, including systemic therapy (n = 6; cisplatin, gemcitabine, lenvatinib, regorafenib, or sorafenib), intra-arterial therapy (n = 3; 2 received transarterial chemoembolization; 1 received transarterial embolization), radiotherapy (n = 2), and surgery (n = 2; 1 responder had partial hepatectomy; 1 non-responder had laminectomy; both occurring after disease progression). Some patients received more than 1 type of subsequent therapy.

With a median follow-up of 16.3 months, ORR and DCR by investigator assessment were 12% (95% CI 5–25) (all PR) and 55% (95% CI 40–69), respectively (**Table 3**; see **Supplementary Table 1** for RECIST 1.1 data by BICR). Median TTR was 2.7 months (interquartile range, 1.4–4.2), and median DOR was 9.9 months (95% CI 9.7–9.9; **Table 3**). One patient had ongoing response at the data cutoff (**Fig. 1**); 5 other responders were off treatment because of disease progression. Of 6 patients with response, 3 were

sorafenib naive, and 3 were sorafenib treated; deep responses were observed in some responders (**Fig. 2**).

Median OS for all Child-Pugh B patients was 7.6 months (95% CI 4.4–10.5; **Fig. 3**). Median OS (95% CI) for sorafenib-naive and -treated patients was 9.8 months (3.7–14.3) and 7.4 months (2.3–12.1), respectively. Median OS [95% CI] was similar in patients with Child-Pugh scores of B7 and B8 (7.6 months [4.1–14.3] and 7.4 months [1.6–10.5], respectively). Median PFS (95% CI) for all Child-Pugh B patients was 2.7 months (1.6–4.0); median PFS for sorafenib-naive and -treated patients was 3.4 months (1.6–4.1) and 2.2 months (1.4–4.2), respectively. For the 6 patients with CR/PR, median OS was not reached (95% CI 10.4–not reached). Overall survival was 9.8 months (5.1–14.3) for patients with stable disease (SD) and 6.8 months (2.3–10.5) for patients with progressive disease (PD).

Improvement to Child-Pugh A class, an exploratory endpoint, represents the first timepoint at which a patient improved from Child-Pugh B to Child-Pugh A class and maintained for ≥6 months. Five patients (4/6 with PR and 1/21 with SD) improved from Child-Pugh B to Child-Pugh A class during the study, with improvement sustained for ≥6 months (**Fig. 1**). Conversely, 30 patients had a deterioration from baseline in Child-Pugh status: 1 from A6 to B7; 21 from B7 to B8 (n=10), B9 (n=9), or C10 (n=2); and 8 from B8 to B9 (n=3), C10 (n=3), and C11 (n=2).

Median OS was 11.3 months (95% CI 7.3–16.0) for patients with baseline AFP <400 µg/L and 4.4 months (95% CI 7.1–10.35) for patients with baseline AFP ≥400 µg/L. In these subgroups, ORR was 14.0% (95% CI 4.0–32.7%) and 11% (95% CI 1.3–33.1%), respectively. Changes in AFP level over time by response status (responder or non-responder) are shown in **Supplementary Fig. 1**. In responders, a subset of patients

had a downward trend, while others had stable or fluctuating levels. Analyses of BOR and DCR for patients by AFP status are shown in **Supplementary Table 2**. Among patients with a neutrophil-to-lymphocyte ratio (NLR) ≤3 (n = 24), ORR and DCR by investigator assessment were 13% (95% CI 2.7–32.4%) and 58% (95% CI 36.6–77.9%), respectively. Analyses of BOR and DCR for patients by NLR status are shown in **Supplementary Table 3**.

In most patients (55%), albumin-bilirubin (ALBI) grades remained stable from baseline, with worsening from baseline in 39% of patients based on maximum postbaseline value compared with baseline (see Supplementary Fig. 1). All 6 responders maintained stable ALBI grades for ≥6 months (see **Supplementary Fig. 2**). Five patients with SD and 2 patients with PD had stable or improved ALBI grades for ≥6 months. Among patients with SD and PD, 11 (52%) and 6 (40%) patients, respectively, had worsening of ALBI grade.

Any-grade TRAEs were reported in 25 patients (51%; **Table 4**). Grade 3/4 TRAEs were reported in 12 patients (24%). The most frequent any-grade TRAEs were pruritus (n = 6; 12%) and asthenia (n = 3; 6%). The most frequent grade 3/4 TRAEs were hypertransaminasemia (n = 2; 4%), amylase increase (n = 2; 4%), and aspartate aminotransferase increase (n = 2, 4%; **Table 4**). In addition to hepatic investigations reported in **Table 4**, treatment-related amylase increase and lipase increase (both asymptomatic) were also reported. Two patients (4%) had a TRAE leading to discontinuation in the Child-Pugh B cohort (grade 3 hepatic function abnormal [n = 1]; grade 2 hyperbilirubinemia plus grade 3 hypertransaminasemia [n = 1]), a rate comparable to that observed in the Child-Pugh A cohort (4%). Two patients had serious

TRAEs approximately 1 month after their last dose of nivolumab (Stevens-Johnson syndrome [n = 1]; abnormal hepatic function [n = 1]).

Select TRAEs, including endocrine, gastrointestinal, skin, and hepatic events, are shown in **Supplementary Table 4**. The most common select TRAEs were skin events. Hepatic select TRAEs were reported in 4 patients (8%); grade 3/4 hepatic select TRAEs were reported in 2 patients (4%). The median time to onset for select TRAEs ranged from 3.9 weeks for hepatic events to 21.5 weeks for gastrointestinal events.

The most common IMAEs reported in the Child-Pugh B cohort included hepatitis (n = 1) and rash (n = 5; **Table 5**). Immune-mediated rash resolved in 4 of 5 patients; the case of immune-mediated hepatitis did not resolve by the data cutoff date. One serious IMAE of Stevens-Johnson syndrome occurred in a patient who had already discontinued nivolumab and was receiving subsequent therapy; no IMAEs led to treatment discontinuation.

The HRQoL analysis population included 37 patients. Completion rates were >70% at all evaluable timepoints. The MMRM results showed that the overall EQ-5D visual analogue scale score (least squares [LS] means, –3.2 [95% CI –8.5 to 2) remained stable over time relative to baseline, with no clinically meaningful decline observed through week 36. Similarly, overall utility index (LS means, –0.06 [95% CI –0.118 to –0.007]) scores by MMRM remained stable over time relative to baseline with no clinically meaningful decline observed through week 28 (**Supplementary Fig. 3**).

FACT-Hep showed similar results through week 20, with no clinically meaningful decline observed in 11 (91.7%) of 12 evaluable timepoints across FACT-Hep total and hepatobiliary cancer subscale (HCS; see **Supplementary Fig. 3**). The LS means for FACT-Hep total and HCS subscales were –7.9 and –3.6 months, respectively. Most

symptoms showed minimal changes during the treatment period. Across all evaluable timepoints, reported mean scores on disease-specific symptoms of discomfort/pain in stomach and presence of diarrhoea were not above 1 (“a little bit”). Scores on swelling/cramps in stomach did not change through week 12 and decreased between weeks 16 and 28.

Discussion

To our knowledge, this is the first prospective clinical report of immunotherapy in patients with Child-Pugh B aHCC, who are typically excluded from pivotal trials of systemic agents for the treatment of HCC. In the few retrospective and prospective studies of sorafenib that have included patients with Child-Pugh B class HCC, a median OS of approximately 3–5 months has been reported.[5, 8-11] Although indirect comparisons should be undertaken with caution, the median OS observed with nivolumab in this prospective study was 7.6 months, suggesting a potential clinical benefit for nivolumab in both sorafenib-naïve and sorafenib-treated patients with Child-Pugh B aHCC. Patients with Child-Pugh B scores of B7 and B8 had a similar median OS (7.6 and 7.4 months, respectively). Median OS was longer in sorafenib-naive patients than in sorafenib-treated patients (9.8 [95% CI 3.7–14.3] *vs.* 7.4 months [95% CI 2.3–12.1], respectively), although the 95% CIs overlapped. The longer OS observed in sorafenib-naïve patients compared with sorafenib-treated patients was expected, given the fact that the sorafenib-naïve patients were receiving first-line therapy.

The 12% ORR in patients with Child-Pugh B class was slightly lower than the 15% to 20% observed in patients with Child-Pugh A class in the dose-escalation and dose-expansion phases of CheckMate 040,[3] even though there was a higher proportion of sorafenib-naïve patients in the Child-Pugh B cohort. However, the Child-Pugh B cohort

had a smaller number of patients than the Child-Pugh A cohort and the 95% CIs for ORR in the Child-Pugh A and B cohorts overlapped, so this finding should be interpreted with caution. Furthermore, median follow-up was longer in the Child-Pugh A cohort than in the Child-Pugh B cohort (30.0 *vs.* 16.3 months, respectively), as was median treatment duration (5.0 *vs.* 2.3 months, respectively), and the Child-Pugh B and A cohorts had different baseline characteristics, all of which could potentially contribute to the difference in ORR between the Child-Pugh B and A cohorts. Despite the ORR being lower in the Child-Pugh B cohort than in the Child-Pugh A cohort, the DCR rate was similar in these two cohorts (55% *vs.* 61%, respectively).

In this analysis, responses were observed regardless of viral infection status, baseline AFP levels, or baseline inflammatory status, although the number of patients with HBV or HCV infection was too small to draw conclusions on the effect of aetiology. Only 8 patients in this study were HBV infected. The clinical benefit of nivolumab in patients with high AFP and NLR was marginal, reflecting the poor prognosis associated with the presence of these biomarkers in HCC. Of the responders, 3 were HCV infected, and 3 were uninfected.

Stable liver function was observed in patients with clinical benefit, evidenced by stable or improved Child-Pugh scores and ALBI grades while on study. Five of the 6 responders improved from Child-Pugh B to Child-Pugh A class, with improvement sustained for ≥6 months, and all 6 responders maintained stable ALBI grades for ≥6 months. Because the liver is the central metabolic organ, and patients with liver cirrhosis and liver damage have abnormalities in energy metabolism,[22] we hypothesize that, with the improvement of HCC status (partial responses) caused by nivolumab treatment, there is an accompanying improvement in energy metabolism,

leading to a subsequent improvement in liver function and cirrhosis status. Both tumour burden and advanced cirrhosis might be at the core of patients with HCC reaching Child-Pugh B class. Poor liver function and ascites in patients with HCC with cirrhosis may be the result of either tumour involvement or advanced cirrhosis. For the former, tumour response should be followed by improved liver function and better prognosis (as shown in this cohort). For the latter, tumour response may only reduce the rate of liver function decline.

No new safety signals were observed in the current study, and the rate of discontinuation due to TRAEs was low. The safety profile of nivolumab in patients with Child-Pugh B class appears comparable to that observed in patients with Child-Pugh A class in other cohorts of the CheckMate 040 study. Only 2 patients (4%) had a TRAE leading to discontinuation in the Child-Pugh B cohort (grade 3 hepatic function abnormal [n = 1]; grade 2 hyperbilirubinemia plus grade 3 hypertransaminasemia [n = 1]). In the Child-Pugh A cohort of CheckMate 040, 15 patients (6%) discontinued treatment because of TRAEs. Importantly, hepatic TRAEs, select TRAEs, and IMAEs were not more frequent and were manageable. There were no treatment-related deaths, and no patients died while in response.

Indirect cross-trial comparisons suggest that patients with HCC and Child-Pugh B class treated with sorafenib or lenvatinib had more frequent and more severe AEs than patients in studies of nivolumab monotherapy.[11, 23] In the GIDEON observational study, the rate of TRAEs was comparable between sorafenib-treated patients with Child-Pugh A and B liver function status, although serious TRAEs were more common in patients with Child-Pugh B than Child-Pugh A class (14% *vs.* 9%, respectively).[11] In the phase 1 study of lenvatinib in patients with aHCC, 6 of 11 patients (55%) with Child-

Pugh B class had an SAE.[23] Only 2 nivolumab-treated patients (4%) had a serious TRAE. However, comparisons with historical data are challenging, as the populations may vary in proportions of patients with Child-Pugh B score, presence of extrahepatic metastases and/or vascular invasion, and previous or subsequent treatments.

Our study demonstrated stable HRQoL over time relative to baseline. This may serve as a benchmark for future HRQoL research assessing systemic treatment in this patient population, as, to the best of our knowledge, there are currently no comparable studies in the literature.

Limitations of this study include the noncomparative, open-label design with a small patient population, and the inclusion of both sorafenib-naïve and sorafenib-treated patients; a prospective randomized trial of nivolumab monotherapy may be needed to evaluate safety and efficacy more accurately in this patient population. Child-Pugh B HCC comprises a more heterogenous population than Child-Pugh A HCC, so inclusion of only patients with Child-Pugh B7 and B8 class HCC means that these data may not be extrapolated to patients with more severe liver dysfunction. Furthermore, exclusion criteria surrounding prior hepatic encephalopathy and treatment of ascites may have potentially impacted the findings. Direct comparisons cannot be made between patients with Child-Pugh B class HCC in the current analysis and patients with Child-Pugh A class in CheckMate 040 cohorts 1 and 2.

Conclusions

Nivolumab showed clinical activity and manageable safety in patients with Child-Pugh B class aHCC compared with historical data, suggesting that the use of nivolumab monotherapy in this patient population warrants further investigation. Stable liver function was observed in patients with clinical benefit based on Child-Pugh scores and

ALBI grade over time. Among responders, Child-Pugh scores improved over time, and all responders maintained stable ALBI grades for ≥6 months.

Acknowledgments

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Abbreviations: AE, adverse event; AFP, alpha-fetoprotein; aHCC, advanced hepatocellular carcinoma; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; EQ-5D, European Quality of Life 5 Dimensions questionnaire; EQ-5D-3L, 3-level version of the EQ-5D; FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary; HRQoL, health-related quality of life; IMAE, immune-mediated adverse events; IQR, interquartile range; LS, least squares; MELD-Na, model for end-stage liver disease – sodium; MMRM, mixed model with repeated measures; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NLR, neutrophil-to-lymphocyte ratio; NR, not reported; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome;

RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SD, stable disease; TRAE, treatment-related adverse event; TTP, time to progression; TTR, time to response.

Data sharing

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

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Table 1: Patient demographics and baseline characteristics

	Child-Pugh B			Child-Pugh A*
	Sorafenib naive (n = 25)	**Sorafenib treated (n = 24)**	**All patients (N = 49)**	**Cohorts 1 and 2 (N = 262)**
Age, years				
Median	68	66.5	67	63
Range	40–77	47–78	40–78	19–83
IQR	66–70	61–74	62–72	56–70
BCLC stage, n (%)				
A	1 (4)	1 (4)	2 (4)	3 (1)
B	3 (12)	5 (21)	8 (16)	24 (9)
C	19 (76)	17 (71)	36 (73)	234 (89)
D	2 (8)	1 (4)	3 (6)	NR
Extrahepatic metastases, n (%)	8 (32)	12 (50)	20 (41)	178 (68)
Vascular invasion, n (%)	8 (32)	6 (25)	14 (29)	82 (31)
HCC aetiology,† n (%)				
HBV infected	5 (20)	3 (13)	8 (16)	66 (25)
HCV infected	8 (32)	13 (54)	21 (43)†	60 (23)
Uninfected	12 (48)	8 (33)	20 (41)	136 (52)
Child-Pugh score,‡ n (%)				
6	1 (4)	0	1 (2)	68 (26)
7	17 (68)	20 (83)	37 (76)	4 (2)

8	7 (28)	4 (17)	11 (22)	0
AFP ≥400 µg/L, n (%)	10 (40)	9 (38)	19 (39)	94 (36)
ALBI grade, n (%)				
I	0	0	0	125 (48)
II	23 (92)	21 (88)	44 (90)	137 (52)
III	2 (8)	3 (13)	5 (10)	0
ALBI score				
Median	–1.7	–1.7	–1.7	–2.6
Range	–2.6 to –1.1	–2.4 to –1.0	–2.6 to –1.0	–3.6 to –1.4
IQR	–2.1 to –1.6	–1.8 to –1.5	–1.9 to –1.5	–2.9 to –2.3
Prior sorafenib treatment				
Sorafenib naive	25 (100)	–	25 (51)	80 (31)
Sorafenib treated[§]	–	24 (100)	24 (49)	182 (69)
Disease progression	–	16 (67)	16 (33)	135 (74)
Toxicity	–	7 (29)	7 (14)	39 (21)
Completed treatment	–	1 (4)	1 (2)	2 (1)
Other	–	2 (8)	2 (4)	6 (3)

BCLC, Barcelona Clinic Liver Cancer; IQR, interquartile range; NR, not reported.

*Data from CheckMate 040 cohorts 1 and 2, in which almost all patients (98%) had Child-Pugh A class, are presented for indirect comparison.

[†]Among the 21 patients infected with HCV, viral load data were available for 19; HCV RNA was detected in 17 of these patients.

[‡]One patient in the Child-Pugh B cohort had Child-Pugh A6 class; the patient had Child-Pugh B7 class prior to allocation that improved to A6 on the day of the first treatment dose.

[§]Patient may have had multiple reasons for sorafenib discontinuation.

Table 2: Patient disposition

Patients, n (%)	Child-Pugh B			Child-Pugh A*
	Sorafenib naive (n = 25)	Sorafenib treated (n = 24)	All patients (N = 49)	Cohorts 1 and 2 (N = 262)
Continuing treatment	1 (4)	1 (4)	2 (4)	12 (5)
Not continuing treatment	24 (96)	23 (96)	47 (96)	250 (95)
Reasons for discontinuation				
Disease progression	22 (88)	16 (67)	38 (78)	211 (81)
Study-drug toxicity	0	2 (8)	2 (4)	15 (6)
Death	0	2 (8)	2 (4)	0
Unrelated AE	1 (4)	2 (8)	3 (6)	8 (3)
Patient request to discontinue	1 (4)	0	1 (2)	8 (3)
Lost to follow-up	0	1 (4)	1 (2)	0
Follow-up, months				
Median	16.1	16.3	16.3	30.0
Range	11.0–21.6	12.2–22.5	11.0–22.5	26.7–62.2
IQR	14.0–18.9	14.0–17.7	14.0–18.4	29.3–32.8
Treatment duration, months				
Median	2.3	2.9	2.3	5.0
Range	0.0–14.7	0.0–15.9	0.0–15.9	0.0–49.3
IQR	0.9–6.3	1.3–8.6	1.0–8.3	2.3–11.1

Any subsequent therapy	5 (20)	5 (21)	10 (20)	136 (52)
Radiotherapy	0	2 (8)	2 (4)	56 (21)
Surgery[†]	0	2 (8)	2 (4)	24 (9)
Systemic therapy	4 (16)	2 (8)	6 (12)	91 (35)
Intra-arterial therapy	3 (12)	0	3 (6)	49 (19)

*Data from CheckMate 040 cohorts 1 and 2, in which almost all patients (98%) had Child-Pugh A class, are presented for indirect comparison.

[†]One patient underwent a laminectomy, and the other patient underwent partial hepatectomy.

Table 3: Response, disease control, and durability by investigator assessment

	Child-Pugh B			Child-Pugh A*
	Sorafenib naive (n = 25)	Sorafenib treated (n = 24)	All patients (N = 49)	Cohorts 1 and 2 (N = 262)
Objective response using RECIST v1.1, n (%)	3 (12)	3 (13)	6 (12)	53 (20)
95% CI	3–31	3–32	5–25	16–26
BOR				
Complete response, n (%) [95% CI]	0 [0–14]	0 [0–14]	0 [0–7]	8 (3) [1–6]
Partial response, n (%) [95% CI]	3 (12) [3–31]	3 (13) [3–32]	6 (12) [5–25]	45 (17) [13–22]
Stable disease, n (%)	12 (48)	9 (38)	21 (43)	107 (41)
Progressive disease, n (%)	7 (28)	8 (33)	15 (31)	88 (34)
Unable to determine, n (%)	3 (12)	4 (17)	7 (14)	14 (5)
DCR, n (%) [95% CI]	15 (60) [39–79]	12 (50) [29–71]	27 (55) [40–69]	160 (61) [55–67]
Time to response, months				
Median	2.7	1.4	2.7	2.7
Range	2.7–10.3	1.2–4.2	1.2–10.3	1.2–16.4
IQR	2.7–10.3	1.2–4.2	1.4–4.2	1.4–4.1
Median duration of response, months	9.8	9.9	9.9	12.4
Range	1.4+ to 9.9	4.2+ to 9.9	1.4+ to 9.9	2.8 to 51.1+
95% CI	9.7–9.9	Not applicable	9.7–9.9	9.4–18.7

*Data from CheckMate 040 cohorts 1 and 2, in which almost all patients (98%) had Child-Pugh A class, are presented for indirect comparison.

Table 4: Summary of TRAEs

n (%)‡	Child-Pugh B*						Child-Pugh A†	
	Sorafenib naive (n = 25)		Sorafenib treated (n = 24)		All patients (N = 49)		Cohorts 1 and 2 (N = 262)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
TOTAL	11 (44)	4 (16)	14 (58)	8 (33)	25 (51)	12 (24)	206 (79)	59 (23)
Skin and subcutaneous tissue disorders	8 (32)	2 (8)	3 (13)	0	11 (22)	2 (4)	103 (39)	6 (2)
Pruritus	5 (20)	0	1 (4)	0	6 (12)	0	56 (21)	1 (0.4)
General disorders	2 (8)	0	5 (21)	0	7 (14)	0	84 (32)	4 (2)
Asthenia	0	0	3 (13)	0	3 (6)	0	5 (2)	0
Blood and lymphatic system disorders	3 (12)	1 (4)	2 (8)	0	5 (10)	1 (2)	23 (9)	6 (2)
Gastrointestinal disorders	3 (12)	1 (4)	2 (8)	1 (4)	5 (10)	2 (4)	91 (35)	7 (3)
Metabolism and nutrition disorders	1 (4)	0	3 (13)	1 (4)	4 (8)	1 (2)	39 (15)	7 (3)
Nervous system disorders	2 (8)	0	1 (4)	0	3 (6)	0	22 (8)	0
Infections and infestations	1 (4)	0	1 (4)	0	2 (4)	0	5 (2)	0
Musculoskeletal and	1 (4)	0	1 (4)	0	2 (4)	0	30	1 (0.4)

connective tissue disorders							(11)	
Endocrine disorders	0	0	1 (4)	0	1 (2)	0	17 (7)	1 (0.4)
Eye disorders	0	0	1 (4)	0	1 (2)	0	5 (2)	0
Vascular disorders	1 (4)	0	0	0	1 (2)	0	7 (3)	0
Investigations[§]	1 (4)	0	5 (21)	4 (17)	6 (12)	4 (8)	74 (28)	37 (14)
Amylase increased	0	0	2 (8)	2 (8)	2 (4)	2 (4)	21 (8)	8 (3)
Aspartate aminotransferase increased	0	0	2 (8)	2 (8)	2 (4)	2 (4)	27 (10)	15 (6)
Lipase increased	1 (4)	0	1 (4)	1 (4)	2 (4)	1 (2)	19 (7)	15 (6)
Alanine aminotransferase increased	0	0	1 (4)	0	1 (2)	0	26 (10)	10 (4)
Liver function test increased	0	0	1 (4)	0	1 (2)	0	1 (0.4)	1 (0.4)
Hepatobiliary disorders[‖]	0	0	3 (13)	3 (13)	3 (6)	3 (6)	7 (3)	1 (0.4)
Hypertransaminasemia	0	0	2 (8)	2 (8)	2 (4)	2 (4)	2 (1)	0
Hepatic function abnormal	0	0	1 (4)	1 (4)	1 (2)	1 (2)	NR	NR
Hyperbilirubinemia	0	0	1 (4)	0	1 (2)	0	3 (1)	0

*Includes all system organ classes and individual any-grade events reported in ≥5% of patients in the Child-Pugh B cohort, unless otherwise noted.

[†]Data from CheckMate 040 cohorts 1 and 2, in which almost all patients (98%) had Child-Pugh A class, are presented for indirect comparison.

[‡]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 all investigations reported in patients in the Child-Pugh B cohort.

[‖]Includes all hepatobiliary disorders reported in patients in the Child-Pugh B cohort.

Table 5: Summary of IMAEs

	Child-Pugh B						Child-Pugh A*	
	Sorafenib naive n = 25		Sorafenib treated n = 24		All patients N = 49		Cohorts 1 and 2 N = 262	
n (%)	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Hepatitis	0	0	1 (4)	1 (4)	1 (2)	1 (2)	14 (5)	12 (5)
Aspartate aminotransferase increased	0	0			1 (2)	1 (2)	6 (2)	6 (2)
Rash	3 (12)	1 (4)	2 (8)	0	5 (10)	1 (2)	36 (14)	3 (1)
Pneumonitis	0	0	0	0	0	0	3 (1)	2 (1)
Diarrhoea/colitis	0	0	0	0	0	0	8 (3)	2 (1)
Adrenal insufficiency	0	0	0	0	0	0	3 (1)	0
Hypothyroidism/thyroiditis	0	0	0	0	0	0	1 (0.4)	0
Thyroiditis	0	0	0	0	0	0	1 (0.4)	0
Hypersensitivity	0	0	0	0	0	0	4 (2)	0

IMAEs are specific events considered as potential immune-mediated events by investigator occurring within 100 days of last dose, regardless of causality, treated with immune-modulating medication.

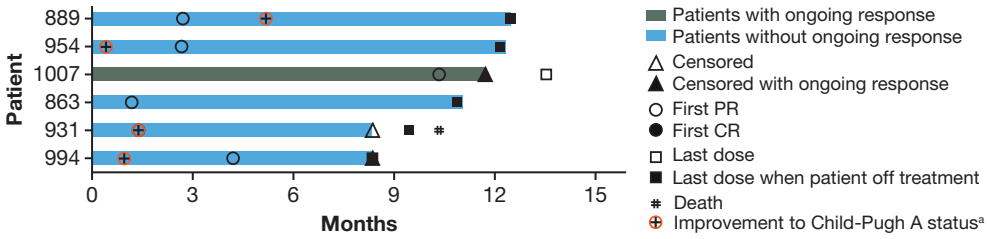
*Data from CheckMate 040 cohorts 1 and 2, in which almost all patients (98%) had Child-Pugh A class, are presented for indirect comparison.

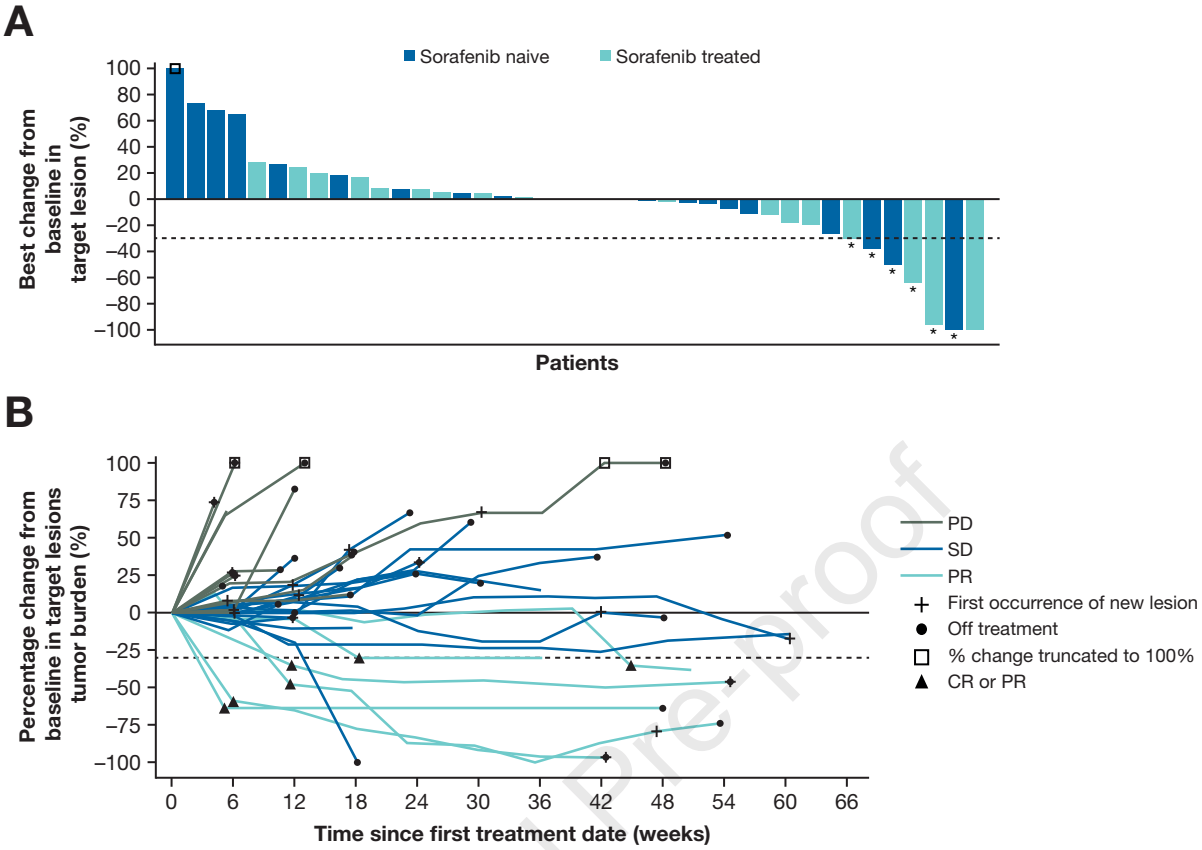
Figure Legends

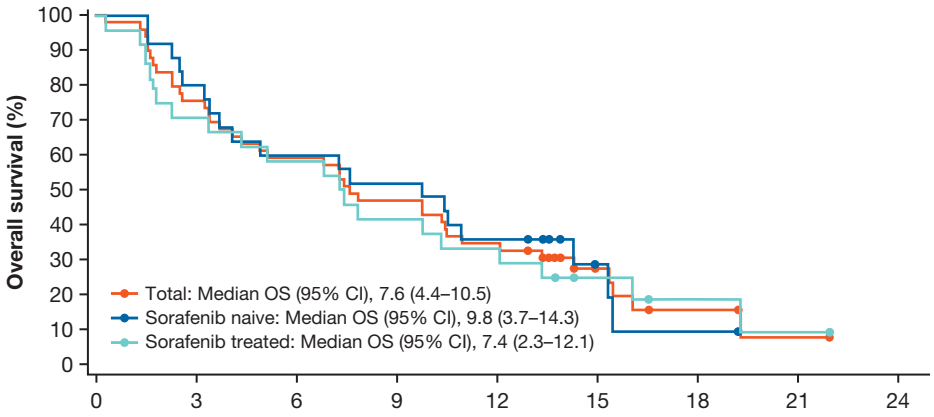
Fig. 1: Characterization of response per investigator assessment (TTR and DOR). Bar indicates time to progression; horizontal axis origin corresponds to first dosing date. *Improvement to Child-Pugh A class represents the first timepoint at which patient improved from Child-Pugh B to Child-Pugh A class and maintained for ≥6 months.

Fig. 2. Change in target lesion and tumour burden. (A) Best change in target lesion per investigator assessment. (B) Tumour burden change per investigator assessment. Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1. Response evaluable: patients with i) a BOR of CR, PR, SD, or PD; ii) target lesion(s) assessed at baseline; and iii) at least 1 on-study timepoint with all baseline target lesion(s) assessed. 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 RECIST v1.1. *Confirmed response per investigator assessment.

Fig. 3: Overall survival.







No. at risk									
Total	49 (0)	37 (0)	29 (0)	23 (0)	17 (0)	7(7)	3 (8)	1 (9)	0 (10)
Sorafenib naive	25 (0)	20 (0)	15 (0)	13 (0)	9 (0)	3 (5)	1 (5)	0 (6)	0 (6)
Sorafenib treated	24 (0)	17 (0)	14 (0)	10 (0)	8 (0)	4 (2)	2 (3)	1 (3)	0 (4)

Highlights:

- This is the first report, to our knowledge, of immune checkpoint inhibitor therapy in patients with advanced hepatocellular carcinoma (aHCC) and Child-Pugh B liver function status
- Median overall survival (OS) with nivolumab was longer than the historical OS rate for patients treated with sorafenib (7.6 months vs 2.5–5.4 months, respectively)
- Clinically meaningful stabilisation of liver function was observed, as evidenced by maintained or improved Child-Pugh scores and albumin-bilirubin scores
- Nivolumab had a favourable safety profile with manageable toxicities when used in patients with Child-Pugh B aHCC, and was comparable to that seen in patients with Child-Pugh A HCC