Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): results of phase 1/2 dose escalation and expansion

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Running title: 040 HCC Dose Escalation and Expansion

SUMMARY

Background

For patients with advanced hepatocellular carcinoma (HCC), sorafenib is currently the only approved drug, and outcomes remain poor. We assessed the safety and efficacy of nivolumab, a programmed death-1 (PD-1) immune checkpoint inhibitor, in patients with advanced HCC with or without chronic viral hepatitis.

Methods

CheckMate 040 (NCT01658878) is a phase 1/2, open-label, dose study of nivolumab in sorafenib-naive or -treated patients with or without hepatitis C or B viral infection. Patients received nivolumab 0·1–10 mg/kg Q2W in the dose-escalation phase (3+3 design) or nivolumab 3 mg/kg Q2W in the dose-expansion phase in uninfected sorafenib naive/intolerant, uninfected sorafenib progressor, HCV-infected, and HBV-infected cohorts. Primary endpoints for the escalation and expansion phases were safety/tolerability and objective response rate (ORR), respectively. Overall, 202/262 patients completed treatment; follow-up is ongoing.

Findings

Since November 26, 2012, 262 patients have been treated in CheckMate 040 dose-escalation or -expansion phases. During dose escalation, nivolumab demonstrated a manageable safety profile, including acceptable tolerability. Rates of treatment-related AEs did not correlate with dose and no maximum tolerated dose was reached; nivolumab 3 mg/kg was chosen for dose expansion. The ORR by RECIST v1·1 was 20% (95% CI 15–26) in patients treated with nivolumab 3 mg/kg in the dose-expansion phase (ORR was 15% [95% CI 6–28] in the dose-escalation phase); disease control rate was 64% (95% CI 58–71). Durable objective responses were

observed across etiologies, were not associated with tumour cell programmed death-ligand 1 (PD-L1) expression, and occurred irrespective of prior sorafenib treatment. The 9-month overall survival rate in the dose-expansion phase was 74% (95% CI 67–79).

Interpretation

Nivolumab had a manageable safety profile and no new signals were observed in patients with advanced HCC. Durable objective responses and long-lasting disease stabilisations demonstrated the potential of nivolumab in advanced HCC.

Funding

Bristol-Myers Squibb.

Research in context

Evidence before this study

Patients with advanced hepatocellular carcinoma (HCC) who have tumours that are not amenable to surgical resection or local treatment have few effective treatment options. While treatment with multikinase inhibitors sorafenib or regorafenib provides some overall survival (OS) benefit in treatment-naive patients and sorafenib progressors, respectively, there remains an unmet need in many patients. Chronic inflammatory conditions in the liver such as cirrhosis and viral hepatitis result in some degree of immunosuppression within the HCC tumour microenvironment, making immune checkpoints attractive therapeutic targets. We searched PubMed from September 1, 2010 to September 1, 2016 for articles using search terms "advanced HCC" and "immunotherapy OR immune checkpoint AND HCC." Non-English articles, review articles, and meta-analysis references were excluded. We identified one relevant phase 1 clinical trial from 2013 evaluating the cytotoxic T-lymphocyte antigen (CTLA-4) checkpoint inhibitor tremelimumab in a small cohort of patients with advanced HCC who were infected with hepatitis C virus (HCV), which reported a manageable safety profile as well as preliminary evidence of antitumour and antiviral activity. Several preclinical studies have provided evidence in support of immunotherapeutic approaches for HCC, including the immunogenicity of transformed hepatocytes and immunosuppressive tumour microenvironments containing infiltrating lymphocytes. However, evidence demonstrating the utility of immune checkpoint inhibitors in the treatment of patients with advanced HCC has been very limited. As early as 2010, reports have demonstrated that PD-1 inhibitors can be potent immuno-oncology agents in patients with metastatic melanoma, providing rationale for immune checkpoint therapies in

multiple other malignancies. When the CheckMate 040 trial began in 2012, several trials of nivolumab in metastatic tumour settings were ongoing. In patients with HCC, it was uncertain whether liver-related toxicities from immune checkpoint inhibitors would be impacted by concomitant HCV or hepatitis B virus (HBV) infection.

Added value of this study

This is the first report of a PD-1 checkpoint inhibitor in patients with advanced HCC. The CheckMate 040 trial is a prospective, noncomparative, phase 1/2 dose study of nivolumab that assessed safety and clinical benefit across multiple HCC etiologies, including patients with HCV or HBV infection. The efficacy of nivolumab monotherapy was evaluated as a first- and second-line treatment in patients who were naive to or intolerant of sorafenib and those with prior disease progression on sorafenib, respectively.

Implications of all the available evidence

Since the CheckMate 040 trial began, nivolumab has been approved in the United States and European Union for the treatment of melanoma, refractory non-small cell lung cancer, advanced renal cell carcinoma, and Hodgkin lymphoma and squamous cell carcinoma of the head and neck (only in the United States). Studies have demonstrated that nivolumab monotherapy provides improved OS and clinical benefit in these approved indications. In this study in patients with advanced HCC, nivolumab demonstrated encouraging objective response rates and OS. The safety profile of nivolumab was manageable, and no new safety signals were observed. These findings support further investigation of nivolumab as a treatment option for

patients with advanced HCC; a phase 3 randomised study of nivolumab monotherapy compared with sorafenib is underway.

INTRODUCTION

Worldwide, liver cancer accounts for more than 850,000 new cancer cases annually, and approximately 90% of these are hepatocellular carcinoma (HCC).[1, 2] Chronic infection with hepatitis C or B viruses (HCV or HBV) is the leading cause of HCC.[3] HCC is often diagnosed at advanced stages of disease for which highly effective therapies are lacking. At present, sorafenib, a small-molecule multikinase inhibitor is the only evidence-based systemic treatment option for patients with advanced HCC.[2, 4] In treatment-naive patients with advanced HCC, the median overall survival (OS) was 10·7 months in those treated with sorafenib and 7·9 months in those who received placebo (hazard ratio [HR] in the sorafenib-treated group, 0·69; 95% CI 0·55 to 0·87; p<0·001).[5, 6] In selected patients who tolerated sorafenib but progressed while on therapy, another multikinase inhibitor, regorafenib, was reported to provide an OS benefit compared with placebo (10·6 versus 7·8 months [HR 0·62; 95% CI 0·50 to 0·78; p<0·001]).[7]

Immunotherapies that inhibit the programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) immune checkpoint interaction have demonstrated substantial survival benefit in a fraction of patients with metastatic carcinomas of multiple tissue origins.[8-11] The presence of tumour-infiltrating lymphocytes (TILs) expressing PD-1 in HCC lesions and correlation with outcome suggest that immunotherapeutic approaches may be useful.[12-15]

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that disrupts PD-1 immune checkpoint signaling and thereby restores the antitumour activity of otherwise suppressed effector T cells. CheckMate 040 is an ongoing, global, phase 1/2 study of nivolumab in sorafenib-naive and -treated patients with advanced HCC with or without chronic viral

hepatitis. In this first report of a PD-1 checkpoint inhibitor for the treatment of advanced HCC, we detail nivolumab safety and efficacy results from the dose-escalation and -expansion phases of CheckMate 040.

METHODS

Study design and participants

CheckMate 040 is a multicentre, noncomparative, open-label, phase 1/2 study in patients with advanced HCC with or without chronic viral hepatitis (HCV or HBV) evaluating the safety and efficacy of nivolumab as a monotherapy. The dose-escalation phase was conducted at 7 sites in 4 countries (including United States, Spain, Hong Kong, and Singapore) and the dose-expansion phase was conducted at 39 sites in 11 countries (including Canada, United Kingdom, Germany, Italy, Japan, Korea, and Taiwan in addition to the original countries involved in dose escalation).

Eligible patients were ≥18 years old with histologically confirmed advanced HCC (not amenable to curative surgery or local treatment); use of archival tissue samples was allowed. Fresh tumour biopsy was required at baseline if there was no other record of histological diagnosis. Patients in the dose-escalation phase and patients in the HCV- and HBV-infected cohorts of the expansion phase included those whose disease progressed while receiving at least one prior line of systemic therapy, including sorafenib, or who were intolerant of or refused sorafenib treatment. Patients were also required to have Child-Pugh scores of ≤7 (Child-Pugh A or B7) and ≤6 (Child-Pugh A) at screening for the dose-escalation and -expansion phases, respectively, and

an ECOG performance status of ≤1. HBV-infected patients were required to be receiving effective antiviral therapy and have a viral load <100 IU/mL at screening; antiviral therapy was not required for HCV-infected patients. Prior treatment with an agent targeting T-cell costimulation or checkpoint pathways (including those targeting PD-1, PD-L1 or -L2, CD137, or cytotoxic T-lymphocyte antigen [CTLA-4]) was excluded. Additional eligibility criteria are provided in the Supplementary Appendix. All patients provided written informed consent, and the study protocol and amendments were approved by each site's institutional review board or independent ethics committee.

Procedures

Patients received intravenous nivolumab every 2 weeks (Q2W). In the dose-escalation phase, patients were enrolled into three cohorts based on HCC etiology (uninfected, HCV infected, and HBV infected). Across these cohorts, sequential patient groups (of up to six patients per dose level for doses 0·1–3·0 mg/kg; up to 13 patients for 10 mg/kg) received the following doses of nivolumab: 0·1 mg/kg (HBV-infected patients only), 0·3 mg/kg, 1·0 mg/kg, 3·0 mg/kg, or 10 mg/kg (uninfected patients only) in a 3+3 design with the intention of determining the maximum-tolerated dose (MTD). Dose-limiting toxicities (DLTs) were determined based on the incidence and intensity of adverse events (AEs) occurring up to 2 weeks following the third nivolumab dose. Patients were treated until a confirmed complete response (CR) was achieved (dose-escalation phase only) or until disease progression or unacceptable toxicity occurred.

Safety assessments were performed continuously during treatment and up to 100 days following the last dose or until all treatment-related AEs were resolved to baseline or deemed

irreversible by the investigator; AEs were evaluated using the National Cancer Institute CTCAE v4·03. Patients were followed up for survival every 3 months.

Tumour response was determined by investigator assessment using RECIST v1·1 for key study endpoints.[16] Exploratory endpoints included tumour assessments by mRECIST (evaluated by blinded-independent central review; BICR). RECIST v1·1 was used for assessment of the primary endpoint because it is well established and provides a more conservative estimation of response than mRECIST. Assessment by RECIST v1·1 also allows for comparisons of response data with pivotal studies in patients with HCC (eg, sorafenib/SHARP trial). mRECIST has not been prospectively validated and has not been evaluated for immuno-oncology therapies. Tumour biopsies collected at baseline were retrospectively used for analysis of PD-L1 expression by immunohistochemistry. Details on tumour assessments and measurement of tumour PD-L1 expression are described in the Supplementary Appendix. In HCV- and HBV-infected patients, HCV RNA and HBV surface antigen (HBsAg), respectively, were measured from patient sera at baseline and on treatment. Serum anti-HBs levels were also measured.

Patient-reported health status in the dose-expansion phase was evaluated using the three-level version of the European Quality of Life–5 Dimensions utility index (EQ-5D-3L) and visual analogue scale (EQ-5D-VAS).[17] Patients completed the EQ-5D-3L at baseline and every 6 weeks through week 25 while on treatment. The analysis population included those who had a baseline EQ-5D-3L assessment and at least one post-baseline assessment. Additional details on the methodology for assessing patient-reported outcomes are provided in the Supplementary Appendix.

Outcomes

The primary endpoint of the dose-escalation phase was safety and tolerability based on incidence of AEs, serious AEs, AEs leading to discontinuation, and deaths. The primary endpoint of the dose-expansion phase was objective response rate (ORR). Key secondary endpoints included ORR (dose-escalation phase only), CR rate, disease control rate (DCR), duration of response (DOR), time to response, time to progression (TTP), progression-free survival (PFS), OS, OS rate, and response stratified by PD-L1 expression. Additionally, patient-reported quality of life measures were an exploratory endpoint.

Statistical analyses

Descriptive statistics were used to characterise safety analyses performed in all treated patients and to characterise patient-reported quality of life outcomes in patients treated in the dose-expansion phase. The Clopper-Pearson and conventional Wald methods were used to estimate the 95% CIs for ORR and patient-reported outcomes, respectively, and Kaplan-Meier methodology was used to determine medians and 95% CIs for DOR and OS. Sample sizes for each dose in the dose-escalation phase (3–13 patients) were determined based on observed toxicities, not statistical considerations. For the dose-expansion phase, sample sizes of approximately 50 treated patients per cohort were chosen to provide a better estimation of efficacy. With a minimum of 50 patients, the lower bound of the 95% CI for a hypothetical response rate of 20% would be 10%.

Role of the funding source

The study was designed by the authors in collaboration with the sponsor (Bristol-Myers Squibb). The authors and sponsor were responsible for data collection, and the sponsor was responsible for data analysis. The authors and sponsor were involved in data interpretation, development of the report, and the decision to submit.

RESULTS

Dose-escalation phase

The cutoff date for this analysis was August 8, 2016. Between November 26, 2012, and the cutoff date, 262 patients with advanced HCC with or without HCV or HBV infection were treated in the dose-escalation phase (n=48) or dose-expansion phase of (n=214) of CheckMate 040 (Figure 1). Nivolumab monotherapy doses were 0·1–10 mg/kg Q2W in the dose-escalation phase, and cohorts included patients without viral hepatitis (n=23), patients with HCV infection (n=10), and patients with HBV infection (n=15). Across these three cohorts, six patients were assigned to nivolumab 0·1 mg/kg, nine patients to 0·3 mg/kg, 10 patients to 1 mg/kg, 10 patients to 3 mg/kg, and 13 patients to 10 mg/kg Q2W. Only patients in the uninfected cohort were assigned to the maximum dose of 10 mg/kg.

Patient demographics, baseline disease characteristics, and prior treatments are presented in Table 1. The overall median age was 62 years (IQR [55–69]; Table 1). Patients were heavily pretreated, and 37 of 48 patients (77%) had prior treatment with sorafenib. Extrahepatic metastases and vascular invasion were present in 34 patients (71%) and 19 patients (40%),

respectively. In the dose-escalation phase, all patients were reported as Child-Pugh class A with Child-Pugh scores of 5 or 6 at baseline.

In the dose-escalation phase, 46 of 48 patients (96%) discontinued treatment; 42 (88%) discontinued due to disease progression (Table 2). Two patients (4%; both uninfected) discontinued after achieving a CR (per study protocol) and entered the follow-up period. Other reasons for discontinuation included study drug–related toxicity (n=1) or AEs unrelated to treatment (n=1). Among patients who discontinued nivolumab because of disease progression, 23 (48%) were treated with a subsequent therapy (Table S1). At the time of data cutoff, two of the 48 patients in the dose-escalation phase were continuing treatment with nivolumab.

One DLT of grade 2 hepatic impairment was reported in a patient in the uninfected cohort who received 10 mg/kg; this DLT resolved within 7 days. An MTD was not reached. Grade 3/4 treatment-related AEs occurred in 12 of 48 patients (25%; Table 3). Treatment-related AEs that occurred in >10% of patients were rash (n=11; 23%), aspartate aminotransferase (AST) increase (n=10; 21%), alanine aminotransferase (ALT) increase (n=7; 15%), lipase increase (n=10; 21%), amylase increase (n=9; 19%), and pruritus (n=9; 19%). Treatment-related serious AEs were reported in three patients (6%; pemphigoid [n=1], adrenal insufficiency [n=1], liver disorder [n=1]). Grade 3/4 select AEs, those with a potential inflammatory mechanism requiring more frequent monitoring, were adrenal insufficiency (n=1), diarrhea (n=1), hepatitis (n=2), infusion hypersensitivity (n=1), and acute kidney injury (n=1; Table S2). One uninfected patient who received nivolumab 3 mg/kg discontinued due to treatment-related ALT and AST increases without concomitant changes in liver function. Overall, 30 of 48 patients in the dose-escalation

phase died, and no deaths were determined to be related to nivolumab therapy.

The overall ORR was 15% (95% CI 6–28; Table S3) in the dose-escalation phase, including three CRs and four partial responses (PRs). Responses occurred early in treatment; of the seven patients who achieved an objective response, five responded within 3 months of treatment initiation (Figure 2). The DCR was 58% (95% CI 43–72) and the median TTP was 3·4 months (95% CI 1·6–6·9). The median DOR was 17 months (95% CI 6–24) and the 6- and 9-month OS rates were both 66% (95% CI 51–78). Median OS for patients in the dose-escalation phase was 15·0 months (95% CI 9·6–20·2).

Dose-expansion phase

Based on results from the dose-escalation phase and from studies of nivolumab in other tumour types, a dose of 3 mg/kg was selected for the dose-expansion phase.[18] A total of 214 patients with advanced HCC were treated in the dose-expansion phase in four cohorts: HCV/HBV-uninfected patients who were sorafenib naive or intolerant (n=56) or who had progression on sorafenib (n=57) or patients with HCV (n=50) or HBV (n=51) infection (Figure 1). Patients enrolled in the dose-expansion phase had comparable demographics and baseline disease characteristics to those in the dose-escalation phase (Table 1). Overall, 145 of 214 patients (68%) had prior sorafenib treatment.

As of August 8, 2016, 58 of 214 patients (27%) enrolled in the dose-expansion phase were continuing treatment. Disease progression was the most common reason for discontinuation, occurring in 132 of 214 patients (62%). Eight patients (4%) discontinued after experiencing

study drug toxicity. Other reasons for discontinuation are provided in Table 2.

An objective response was observed in 42 patients (20%; 95% CI 15–26) who received nivolumab 3 mg/kg Q2W in the dose-expansion phase (Table 4). Objective responses included three CRs and 39 PRs. Stable disease was observed in 96 patients (45%), and disease control was observed in 138 patients (64%). Among patients with at least one post-baseline target lesion assessment (n=206), substantial reductions in tumour burden were observed in all cohorts (Figure 3a). Maximal changes in tumour burden are shown in Figure 3b. The majority of the objective responses (29/42; 69%) occurred before 3 months, similar to the time-to-response profile observed in the dose-escalation phase (Figure 2). Of the 42 patients with a response, 28 patients had ongoing responses at the time of data cutoff. The median DOR was 9·9 months (95% CI 8·3–not estimable [NE]). Most disease stabilisations lasted ≥6 months as reported in 79 of 138 patients (57%) with disease control. In the dose-expansion phase, the median TTP was 4·1 months (95% CI 3·7–5·5). The 6- and 9-month OS rates with nivolumab 3 mg/kg in patients in the dose-expansion phase were 83% (95% CI 78–88) and 74% (95% CI 67–79), respectively (Table 4). The 6- and 9-month PFS rates were 37% (95% CI 30–43) and 28% (95% CI 22–35), respectively.

Objective responses occurred in 13 of 56 uninfected sorafenib-naive or -intolerant patients (23%) and 12 of 57 uninfected sorafenib progressors (21%; Table 4); 15 responses were ongoing. The three CRs in the dose-expansion phase occurred in two uninfected patients who had progression on sorafenib therapy and one HBV-infected patient (who had prior sorafenib treatment). The DCRs were 75% (42/56 patients) in the uninfected sorafenib-naive or

-intolerant cohort and 61% (35/57 patients) in the uninfected sorafenib progressor cohort. The 6-month OS rate in uninfected patients was 89% (95% CI 77–95) in the sorafenib-naive or -intolerant cohort (48 at risk) and 75% (95% CI 62–85) in the sorafenib progressor cohort (43 at risk; Table 4). The median OS in the uninfected sorafenib progressor cohort was 13·2 months (95% CI 8·6–NE); medians were not reached in the other dose-expansion cohorts.

ORRs were 20% and 14% in the HCV-infected cohort (10 of 50 patients) and HBV-infected cohort (7 of 51 patients), respectively (Table 4); 13 responses were ongoing. The HCV-infected cohort had a DCR of 66% (33/50 patients), and the HBV-infected cohort had a DCR of 55% (28/51 patients). The 6-month OS rates were 85% (95% CI 72–93) in the HCV-infected cohort (38 at risk) and 84% (95% CI 71–92) in the HBV-infected cohort (43 at risk). Nivolumab demonstrated limited antiviral activity. The kinetics of HCV RNA levels over time were assessed in HCV-infected patients with advanced HCC, and no patient achieved a sustained virologic response >24 weeks. Some HCV-infected patients experienced transient reductions in HCV RNA. No patients had reactivation of HBV, and no instances of anti-HBs seroconversion were noted among HBV-infected patients.

In the dose-expansion phase, ORR was analysed using mRECIST by BICR in the 145 patients who had prior sorafenib treatment (irrespective of HCC etiology); under these criteria an ORR of 19% (27/145 patients) was observed, including 5 patients with a CR (Table S5).

The overall safety profile of nivolumab in patients in the dose-expansion phase was comparable to that observed in the dose-escalation phase. Frequencies of patients with grade 3/4 treatment-related AEs and treatment-related serious AEs overall were 19% (n=40) and 4%

(n=9), respectively (Table S4). Rates of symptomatic treatment-related AEs were comparable in the uninfected and HCV- or HBV-infected cohorts. AEs led to discontinuation in 24 patients, and there were no treatment-related deaths.

As a secondary endpoint, PD-L1 expression levels were retrospectively assessed as a potential biomarker for nivolumab therapy in the 174 of 214 patients with available data in the dose-expansion phase. Membrane expression of PD-L1 on ≥1% of tumour cells was observed in 34 of 174 patients (20%) at baseline; 140 patients (80%) had PD-L1 on <1% of tumour cells (Table 5). Objective responses were achieved by nine of 34 patients (26%; 95% CI 13–44) with PD-L1 on ≥1% of tumour cells and by 26 of 140 patients with PD-L1 on <1% of tumour cells (19%; 95% CI 13–26).

Patient-reported outcomes

Among patients in the dose-expansion phase who were on treatment at the data cutoff, the EQ-5D-3L completion rate exceeded 90% at each time point through week 25. EQ-5D-3L index scores (mean; 95% CI) were stable while on treatment with no significant changes from baseline (0·856; 0·827–0·884) to week 25 (0·829; 0·786–0·872). EQ-5D-VAS scores (mean; 95% CI) were also stable, with no significant changes from baseline (73·0; 69·0–77·1) to week 25 (75·4; 70·0– 80·9). Comparable results were observed in patients who had prior sorafenib treatment. For this patient subpopulation, there was no appreciable change in EQ-5D-3L scores (mean; 95% CI) from baseline (0·853; 0·816–0·889) through week 25 (0·825; 0·773–0·877). Likewise, EQ-5D-VAS scores (mean; 95% CI) were stable from baseline (73·9; 69·2–78·6) through week 25 (75·8; 69·3–82·4).

DISCUSSION

Prior studies of first-line sorafenib and second-line regorafenib targeted therapies have shown response rates of 2%–3% and 7%, respectively.[5-7] In this study, nivolumab demonstrated substantial tumour reductions and ORRs of 15%–20% across first- and second-line therapy settings. Notably, the DCRs in the dose-escalation and -expansion phases were 58% and 64%, respectively, which may have a positive impact on OS rates. Baseline tumour cell PD-L1 status did not have an apparent impact on response rates. Median DORs observed in both phases of the study (as high as 17 months in the dose-escalation phase) suggest that in the treatment of patients with advanced HCC, nivolumab may offer durable responses where other existing therapies have not.[5, 6] Median OS relative to sorafenib was encouraging in a patient population enriched in patients with metastatic disease and with prior sorafenib experience.[19, 20]

In the dose-escalation phase, the safety profile of nivolumab in HCC was consistent with that observed in other tumour types.[9, 10, 21-24] All previous studies of PD-1 inhibitors have excluded patients with chronic viral hepatitis. Hepatic safety events in virally infected patients with HCC treated with a CTLA-4 checkpoint inhibitor have been reported.[25] Therefore, in an abundance of caution, viral etiologies were evaluated in this study in separate cohorts to identify any unique safety signals. No new nivolumab safety signals were noted. Overall, safety findings from the dose-escalation phase were consistent with those in a larger group of patients from the dose-expansion phase.

The comparable ORR results in patients who were naive to or intolerant of sorafenib and in patients with prior progression on sorafenib suggests that nivolumab efficacy is not affected by prior sorafenib treatment status. In addition to potentially supporting nivolumab as a viable second-line therapy for patients with disease progression on multikinase inhibitors (as demonstrated with a median OS of >13 months in uninfected patients with prior progression on sorafenib), an ORR of 23% and a 9-month OS rate of 74% in untreated patients supports the investigation of nivolumab as a first-line therapy for patients with advanced HCC. This study was not powered for statistical comparisons between patients who were infected with HCV or HBV, or who were uninfected; however responses were observed irrespective of HCC etiology. Treatment with nivolumab was associated with stable patient-reported outcomes, including indicators of health status and quality of life, irrespective of prior sorafenib treatment.

A limitation of the phase 1 dose-escalation and phase 2 dose-expansion studies of CheckMate 040 is the lack of randomised control arms. A subsequent randomised cohort-expansion phase of CheckMate 040 (currently ongoing) is evaluating nivolumab compared with sorafenib in the first-line setting. Although objective responses occurred regardless of PD-L1 expression on tumour cells (using a 1% PD-L1 expression level), future studies will need to evaluate the expression of PD-1 and PD-L1 on TILs as potentially valuable biomarkers. It is possible that inhibition of PD-L1 expressed by non-tumour cells could contribute to the efficacy of nivolumab in patients who lack PD-L1 expression on tumour cells. Although PD-L1 is not yet established as a consistently reliable biomarker across tumour types or lines of therapy, it is also possible that in a larger patient population, patients who have a higher proportion of tumour cells expressing PD-L1 may achieve greater benefit. An in-depth characterisation of tumour-infiltrating T-cell

and macrophage subsets, including their expression of PD-1 and PD-L1, could be important for future biomarker assessments in patients with advanced HCC. Additionally, for more meaningful median OS results in the dose-expansion patient cohorts, longer follow-up will be needed.

Results from subsequent comparative, randomised phases of CheckMate 040 will further inform the therapeutic potential of nivolumab in patients with advanced HCC who currently have few treatment options. Nivolumab may provide favourable efficacy with a good safety profile in the context of currently available targeted therapies. A phase 3 randomised study of nivolumab monotherapy compared with sorafenib in the first-line setting is currently recruiting patients (NCT02576509).

Contributors

AB El-Khoueiry, B Sangro, TS Crocenzi, TH Welling, III, J Anderson, C dela Cruz, and I Melero conceived and designed the study. AB El-Khoueiry, B Sangro, T Yau, TS Crocenzi, M Kudo, C Hsu, T-Y Kim, S-P Choo, J Trojan, TH Welling, III, T Meyer, Y-K Kang, W Yeo, A Chopra, and I Melero recruited patients and collected the data. J Anderson, C dela Cruz, L Lang, J Neely, H Tang, and HB Dastani analysed the data. All authors interpreted the data and were involved in development, review, and approval of the manuscript.

Declaration of interests

AB El-Khoueiry has received research support from Astex; has received personal fees from Merrimack; and has served as an advisor for Bristol-Myers Squibb, AstraZeneca, Bayer, Genentech, and Novartis. B Sangro has received speaking and consulting fees from Bristol-Myers Squibb and Bayer; and consulting fees from AstraZeneca, Transgene, and Adaptimmune. T Yau has received speaking fees and research support from Bristol-Myers Squibb; and has served as an advisor to Bristol-Myers Squibb. TS Crocenzi has received research support from Bristol-Myers Squibb. S-P Choo has received speaking fees from Bristol-Myers Squibb. J Trojan has received speaking and consulting fees from Bristol-Myers Squibb and Bayer. T Meyer has served as a consultant for Bristol-Myers Squibb, Bayer, Ipsen, and Eisai. Y-K Kang has received consulting fees from Bristol-Myers Squibb, Ono Pharmaceutical Co, Bayer, Blueprint, AstraZeneca, Pfizer, Dicerna, and Mirna. W Yeo has received research support from Bristol-Myers Squibb; and has served as an advisor to Bristol-Myers Squibb. A Chopra has received research support and personal fees from Bristol-Myers Squibb, Bayer, Astellas, MSD, and Boehringer Ingelheim; and has received personal fees from Jannsen Oncology, Bayer, Lilly,

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FIGURE LEGENDS

Figure 1. Trial design

In the dose-escalation phase, patients were assigned to nivolumab doses of 0·1, 0·3, 1, 3, or 10 mg/kg Q2W in a 3+3 trial design that included HCV- (n=10) and HBV- (n=15) infected and uninfected (n=23) cohorts. A sentinel dosing strategy was used for the first HBV-infected cohort (0·1 mg/kg), in which treatment initiation was separated by 2 weeks for each patient in the cohort to mitigate safety concerns. In the dose-expansion phase, patients were assigned to nivolumab 3 mg/kg Q2W; cohorts included uninfected sorafenib-naive or -intolerant patients (n=56), uninfected sorafenib progressors (n=57), HCV-infected (n=50), and HBV-infected (n=51) patients.

HCV, hepatitis C virus; HBV, hepatitis B virus; Q2W, every 2 weeks.

Figure 2. Time to response and DOR

DORs (months) to nivolumab are displayed for the 49 patients who achieved a CR or PR in the dose-escalation (top) or -expansion (bottom) phases. Sorafenib-naive and -treated patients are represented by green and blue bars, respectively. Open circles, first PR; closed circles, first CR; open triangles, censored; closed triangles, censored with ongoing response; open square, last dose of nivolumab; closed square, last dose of nivolumab when patient ended treatment; hashtag, patient death.

HCV, hepatitis C virus; HBV, hepatitis B virus; DOR, duration of response; CR, complete response; PR, partial response.

Figure 3. Change in tumour burden

Percent change in tumour lesion size from baseline over time (A) and maximum percent change in tumour lesion size from baseline (B) are displayed by patient cohort for evaluable patients in the dose-expansion phase (n=206). Treatment response was evaluated by Response Evaluation Criteria in Solid Tumours (RECIST) v1·1. Panel A: (+), first occurrence of new lesion; closed circle, patient off treatment; closed triangle, CR or PR; open square, percent change truncated to 100%. Panel (B): light orange, uninfected sorafenib-naive or -intolerant patients; dark orange, uninfected sorafenib progressors; green, HCV-infected patients; blue, HBV-infected patients. HCV, hepatitis C virus; HBV, hepatitis B virus; CR, complete response; PR, partial response.

TABLES

Table 1. Patient demographics, baseline characteristics, and prior treatment

	Escalation Phase				Expansion Phase				
Parameter	Uninfected (n=23)	HCV Infected (n=10)	HBV Infected (n=15)	All Patients (N=48)	Uninfected Naive/Intol (n=56)	Uninfected Progressor (n=57)	HCV Infected (n=50)	HBV Infected (n=51)	All Patients (N=214)
Median age (IQR), years	61 (54–72)	67 (60–74)	62 (46–66)	62 (55–69)	66 (59–71)	65 (60–71)	65 (61–73)	55 (42–66)	64 (56–70)
≥65 years, n (%)	8 (35)	6 (60)	6 (40)	20 (42)	33 (59)	29 (51)	25 (50)	13 (25)	100 (47)
Male, n (%)	17 (74)	6 (60)	13 (87)	36 (75)	48 (86)	42 (74)	42 (84)	39 (76)	171 (80)
Race, n (%)									
White	19 (83)	8 (80)	1 (7)	28 (58)	38 (68)	34 (60)	29 (58)	4 (8)	105 (49)
Asian	2 (9)	2 (20)	14 (93)	18 (38)	16 (29)	22 (39)	18 (36)	45 (88)	101 (47)
Black	2 (9)	0	0	2 (4)	1 (2)	1 (2)	2 (4)	2 (4)	6 (3)
Other	0	0	0	0	1 (2)	0	1 (2)	0	2 (1)
ECOG performance status 1, n (%)[a]	9 (39)	4 (40)	6 (40)	19 (40)	16 (29)	22 (39)	15 (30)	24 (47)	77 (36)
Extrahepatic metastases, n (%)	16 (70)	6 (60)	12 (80)	34 (71)	36 (64)	41 (72)	25 (50)	42 (82)	144 (67)
Vascular invasion, n (%)	8 (35)	5 (50)	6 (40)	19 (40)	13 (23)	18 (32)	17 (34)	15 (29)	63 (29)
Child-Pugh score, n (%)									
5	19 (83)	8 (80)	14 (93)	41 (85)	43 (77)	37 (65)	27 (54)	42 (82)	149 (70)
6	4 (17)	2 (20)	1 (7)	7 (15)	12 (21)	20 (35)	20 (40)	9 (18)	61 (29)
7–9	0	0	0	0	1 (2)	0	3 (6)	0	4 (2)
Alpha-fetoprotein ≥400 μg/L, n (%)[a]	6 (26)	3 (30)	6 (40)	15 (31)	15 (27)	22 (39)	17 (34)	25 (49)	79 (37)
Prior treatment, n (%)									
Surgical resection	15 (65)	8 (80)	13 (87)	36 (75)	34 (61)	36 (63)	18 (36)	40 (78)	128 (60)
Radiotherapy[b]	6 (26)	2 (20)	2 (13)	10 (21)	9 (16)	17 (30)	4 (8)	11 (22)	41 (19)
Local treatment for HCC[c]	8 (35)	6 (60)	10 (67)	24 (50)	24 (43)	28 (49)	25 (50)	40 (78)	117 (55)
Systemic therapy	19 (83)	6 (60)	15 (100)	40 (83)	23 (41)	57 (100)	32 (64)	47 (92)	159 (74)

Sorafenib[e]	17 (74)	5 (50)	15 (100)	37 (77)	15 (27)	57 (100)	30 (60)	43 (84)	145 (68)

HCV, hepatitis C virus; HBV, hepatitis B virus; Intol, intolerant; HCC, hepatocellular carcinoma.

[a] Eastern Cooperative Oncology Group; all patients had a baseline ECOG performance status of 0 or 1.

[b] Baseline alpha-fetoprotein levels were not available for 10 patients; dose escalation (n=1), dose expansion (n=9).

[c] Internal or external, and could include radioembolisation.

[d] Includes transcatheter arterial chemoembolisation, transcatheter embolisation.

[e] Reasons for prior treatment failure with sorafenib therapy included disease progression (165/262; 63%) and sorafenib intolerance (13/262; 5%); 4/262 patients (2%) experienced sorafenib treatment failure due to other reasons.

Table 2. Patient disposition

	Escalation Phase				Expansion Phase				
Patients, n (%)	Uninfected (n=23)	HCV Infected (n=10)	HBV Infected (n=15)	All Patients (N=48)	Uninfected Naive/Intol (n=56)	Uninfected Progressor (n=57)	HCV Infected (n=50)	HBV Infected (n=51)	All Patients (N=214)
Continuing treatment	1 (4)	1 (10)	0	2 (4)	20 (36)	10 (18)	14 (28)	14 (27)	58 (27)
Discontinued treatment	22 (96)	9 (90)	15 (100)	46 (96)	36 (64)	47 (82)	36 (72)	37 (73)	156 (73)
Disease progression	18 (78)	9 (90)	15 (100)	42 (88)	29 (52)	42 (74)	24 (48)	37 (73)	132 (62)
Study drug toxicity	1 (4)	0	0	1 (2)	4 (7)	0	4 (8)	0	8 (4)
Unrelated AE	1 (4)	0	0	1 (2)	0	4 (7)	4 (8)	0	8 (4)
Patient decision[a]	0	0	0	0	2 (4)	1 (2)	3 (6)	0	6 (3)
Complete response	2 (9)	0	0	2 (4)	0	0	0	0	0
Other/not reported	0	0	0	0	1 (2)	0	1 (2)	0	2 (1)

HCV, hepatitis C virus; HBV, hepatitis B virus; Intol, intolerant; AE, adverse event.

[a] Includes patients who withdrew consent.

Table 3. Safety and tolerability of nivolumab in the dose-escalation phase

	0·1 mg/kg (n=6)		0·3 mg/kg (n=9)		1 mg/kg (n=10)		3 mg/kg (n=10)		10 mg/kg (n=13)		All Patients (N=48)	
Patients, n (%)	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Treatment-related serious AEs	1 (17)[a]	1 (17)[a]	1 (11)[b]	1 (11)[b]	0	0	0	0	1 (8)[c]	0	3 (6)	2 (4)
AEs leading to discontinuation	0	0	1 (11)[d]	1 (11)[d]	0	0	1 (10)[e]	1 (10)[e]	1 (8)[f]	1 (8)[f]	3 (6)	3 (6)
Treatment-related deaths	0	0	0	0	0	0	0	0	0	0	0	0
Patients with a treatment-related AE	4 (67)	2 (33)	8 (89)	3 (33)	8 (80)	5 (50)	9 (90)	2 (20)	11 (85)	0	40 (83)	12 (25)
Treatment-related AEs[g]												
Rash	1 (17)	0	2 (22)	0	2 (20)	0	2 (20)	0	4 (31)	0	11 (23)	0
Pruritus	2 (33)	0	3 (33)	0	0	0	1 (10)	0	3 (23)	0	9 (19)	0
Diarrhea	0	0	3 (33)	0	0	0	1 (10)	0	1 (8)	0	5 (10)	0
Decreased appetite	1 (17)	0	2 (22)	0	1 (10)	0	0	0	1 (8)	0	5 (10)	0
Fatigue	1 (17)	1 (17)	2 (22)	0	1 (10)	0	0	0	0	0	4 (8)	1 (2)
Asthenia	0	0	1 (11)	0	0	0	1 (10)	0	1 (8)	0	3 (6)	0
Weight decreased	0	0	1 (11)	0	0	0	0	0	2 (15)	0	3 (6)	0
Nausea	0	0	1 (11)	0	0	0	1 (10)	0	1 (8)	0	3 (6)	0
Dry mouth	0	0	1 (11)	0	1 (10)	0	0	0	1 (8)	0	3 (6)	0
Laboratory treatment-related AEs[g]												
AST increase	0	0	2 (22)	2 (22)	3 (30)	2 (20)	1 (10)	1 (10)	4 (31)	0	10 (21)	5 (10)
ALT increase	0	0	2 (22)	2 (22)	1 (10)	0	2 (20)	1 (10)	2 (15)	0	7 (15)	3 (6)
Lipase increase	1 (17)	1 (17)	1 (11)	0	4 (40)	4 (40)	2 (20)	1 (10)	2 (15)	0	10 (21)	6 (13)
Amylase increase	1 (17)	0	0	0	4 (40)	1 (10)	2 (20)	1 (10)	2 (15)	0	9 (19)	2 (4)
Anemia	0	0	1 (11)	0	1 (10)	1 (10)	0	0	2 (15)	0	4 (8)	1 (2)
Hypoalbuminemia	0	0	1 (11)	0	1 (10)	0	0	0	1 (8)	0	3 (6)	0
Hyponatremia	0	0	0	0	2 (20)	0	0	0	1 (8)	0	3 (6)	0

AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a] Pemphigoid (n=1); [b] Adrenal insufficiency (n=1); [c] Liver disorder (n=1); [d] Malignant neoplasm progression (n=1); [e] Grade 3 ALT increase (n=1), grade 2 AST increase; [f] Grade 3 blood bilirubin increase (n=1); [g] Treatment-related AEs reported in ≥5% of all patients, any grade.

Table 4. Nivolumab efficacy in the dose-expansion phase

Parameter	Uninfected Naive/Intol (n=56)	Uninfected Progressor (n=57)	HCV Infected (n=50)	HBV Infected (n=51)	All Patients (N=214)
Objective response, n (%) [95% CI][a]	13 (23) [13, 36]	12 (21) [11, 34]	10 (20) [10, 34]	7 (14) [6, 26]	42 (20) [15, 26]
Complete response, n (%)	0	2 (4)	0	1 (2)	3 (1)
Partial response, n (%)	13 (23)	10 (18)	10 (20)	6 (12)	39 (18)
Stable disease, n (%)	29 (52)	23 (40)	23 (46)	21 (41)	96 (45)
Progressive disease, n (%)	13 (23)	18 (32)	14 (28)	23 (45)	68 (32)
Not evaluable, n (%)	1 (2)	4 (7)	3 (6)	0	8 (4)
Duration of response[a]					
KM median, months [95% CI]	8·4 [8·3, NE]	NR	9·9 [4·5, 9·9]	NR	9·9 [8·3, NE]
Ongoing response, n/N (%)	8/13 (62)	7/12 (58)	8/10 (80)	5/7 (71)	28/42 (67)
Disease control, n (%) [95% CI][a]	42 (75) [62, 86]	35 (61) [48, 74]	33 (66) [51, 79]	28 (55) [40, 69]	138 (64) [58, 71]
Disease control with stable disease for ≥6 months	22 (39) [27, 53]	22 (39) [26, 52]	17 (34) [21, 49]	18 (35) [22, 50]	79 (37) [30, 44]
Overall survival					
6-month overall survival, % [95% CI]	89 [77, 95]	75 [62, 85]	85 [72, 93]	84 [71, 92]	83 [78, 88]
9-month overall survival, % [95% CI]	82 [68, 90]	63 [49, 74]	81 [66, 90]	70 [55, 81]	74 [67, 79]
KM median overall survival, months [95% CI]	NR	13·2 [8·6, NE]	NR	NR	NR
Progression-free survival					
KM median progression-free survival, months [95% CI]	5·4 [3·9, 8·5]	4·0 [2·6, 6·7]	4·0 [2·6, 5·7]	4·0 [1·3, 4·1]	4·0 [2·9, 5·4]

Intol, intolerant; HCV, hepatitis C virus; HBV, hepatitis B virus; KM, Kaplan-Meier estimate; NR, not reached; NE, not estimable; RECIST, Response Evaluation Criteria In Solid Tumours.

[a] Determined by investigator assessment using RECIST v1·1.

Table 5. PD-L1 expression on tumour cells and response

Parameter	Escalation Phase (N=44)[a]	Expansion Phase (N=174)[a]
PD-L1 ≥1%, N (%)[b]	11 (25)	34 (20)
Objective response, n/N (%) [95% CI]	3/11 (27) [6, 61]	9/34 (26) [13, 44]
Complete response, n (%)	1 (9)	1 (3)
Partial response, n (%)	2 (18)	8 (24)
Stable disease, n (%)	0	16 (47)
Progressive disease, n (%)	7 (64)	9 (26)
Not determined, n (%)	1 (9)	0
PD-L1 <1%, N (%)[b]	33 (75)	140 (80)
Objective response, n/N (%) [95% CI]	4/33 (12) [3, 28]	26/140 (19) [13, 26]
Complete response, n (%)	2 (6)	2 (1)
Partial response, n (%)	2 (6)	24 (17)
Stable disease, n (%)	19 (58)	62 (44)
Progressive disease, n (%)	8 (24)	46 (33)
Not determined, n (%)	2 (6)	6 (4)

PD-L1, programmed death-ligand 1.

[a] Four patients in the dose-escalation phase and 40 patients in the dose-expansion phase did not have tumour PD-L1 expression data available.

[b] PD-L1 membrane expression on tumour cells.