JAMA Oncology | Original Investigation

# Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib

## The CheckMate 040 Randomized Clinical Trial

Thomas Yau, MD; Yoon-Koo Kang, MD; Tae-You Kim, MD; Anthony B. El-Khoueiry, MD; Armando Santoro, MD; Bruno Sangro, MD; Ignacio Melero, MD; Masatoshi Kudo, MD; Ming-Mo Hou, MD; Ana Matilla, MD; Francesco Tovoli, MD; Jennifer J. Knox, MD; Aiwu Ruth He, MD; Bassel F. El-Rayes, MD; Mirelis Acosta-Rivera, MD; Ho-Yeong Lim, MD; Jaclyn Neely, PhD; Yun Shen, PhD; Tami Wisniewski, MPH; Jeffrey Anderson, MD; Chiun Hsu, MD, PhD

**IMPORTANCE** Most patients with hepatocellular carcinoma (HCC) are diagnosed with advanced disease not eligible for potentially curative therapies; therefore, new treatment options are needed. Combining nivolumab with ipilimumab may improve clinical outcomes compared with nivolumab monotherapy.

**OBJECTIVE** To assess efficacy and safety of nivolumab plus ipilimumab in patients with advanced HCC who were previously treated with sorafenib.

**DESIGN, SETTING, AND PARTICIPANTS** CheckMate 040 is a multicenter, open-label, multicohort, phase 1/2 study. In the nivolumab plus ipilimumab cohort, patients were randomized between January 4 and September 26, 2016. Treatment group information was blinded after randomization. Median follow-up was 30.7 months. Data cutoff for this analysis was January 2019. Patients were recruited at 31 centers in 10 countries/territories in Asia, Europe, and North America. Eligible patients had advanced HCC (with/without hepatitis B or C) previously treated with sorafenib. A total of 148 patients were randomized (50 to arm A and 49 each to arms B and C).

**INTERVENTIONS** Patients were randomized 1:1:1 to either nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, administered every 3 weeks (4 doses), followed by nivolumab 240 mg every 2 weeks (arm A); nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, administered every 3 weeks (4 doses), followed by nivolumab 240 mg every 2 weeks (arm B); or nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (arm C).

**MAIN OUTCOMES AND MEASURES** Coprimary end points were safety, tolerability, and objective response rate. Duration of response was also measured (investigator assessed with the Response Evaluation Criteria in Solid Tumors v1.1).

**RESULTS** Of 148 total participants, 120 were male (81%). Median (IQR) age was 60 (52.5-66.5). At data cutoff (January 2019), the median follow-up was 30.7 months (IQR, 29.9-34.7). Investigator-assessed objective response rate was 32% (95% CI, 20%-47%) in arm A, 27% (95% CI, 15%-41%) in arm B, and 29% (95% CI, 17%-43%) in arm C. Median (range) duration of response was not reached (8.3-33.7+) in arm A and was 15.2 months (4.2-29.9+) in arm B and 21.7 months (2.8-32.7+) in arm C. Any-grade treatment-related adverse events were reported in 46 of 49 patients (94%) in arm A, 35 of 49 patients (71%) in arm B, and 38 of 48 patients (79%) in arm C; there was 1 treatment-related death (arm A; grade 5 pneumonitis).

**CONCLUSIONS AND RELEVANCE** In this randomized clinical trial, nivolumab plus ipilimumab had manageable safety, promising objective response rate, and durable responses. The arm A regimen (4 doses nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks then nivolumab 240 mg every 2 weeks) received accelerated approval in the US based on the results of this study.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT01658878

*JAMA Oncol*. doi:10.1001/jamaoncol.2020.4564
Published online October 1, 2020.

Visual Abstract

Supplemental content

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Thomas Yau, MD, Department of Medicine, University of Hong Kong, 102 Pok Fu Lam Rd, Hong Kong 999077, China (tyaucc@hku.hk).

Liver cancer is the fourth leading cause of cancer-related deaths worldwide; 75% to 85% of cases are hepatocellular carcinoma (HCC).[1] Most patients are diagnosed with advanced disease unsuitable for resection or transplantation; outcomes remain poor and new effective treatment options are needed. Multikinase inhibitors, including regorafenib, cabozantinib, and the monoclonal antibody ramucirumab, are approved for patients treated with sorafenib; pivotal phase 3 trials report median overall survival ranging from 8.5 to 10.6 months.[2-4]

The anti-programmed cell death 1 (anti-PD-1) checkpoint inhibitors nivolumab and pembrolizumab are approved in the United States and elsewhere as second-line therapy for HCC.[5,6] In CheckMate 040, nivolumab monotherapy demonstrated manageable safety, objective response rate (ORR) of 14%, duration of response of at least 12 months in 59% of patients, and promising long-term median survival of 15.1 months in patients with advanced HCC treated with sorafenib.[5,7] These results led to investigation of nivolumab combination therapies with the goal of durable responses in more patients. Programmed cell death protein 1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immune checkpoint inhibitors (eg, nivolumab and ipilimumab) promote antitumor immune responses by distinct and complementary mechanisms affecting different signaling pathways. Programmed cell death protein 1 contributes to T-cell exhaustion, mainly in the tumor microenvironment, and CTLA-4 inhibits activated and regulatory T cells in the lymphoid organs.[8,9] Nivolumab plus ipilimumab has proved effective in the treatment of other tumor types (eg, renal cell carcinoma, non–small cell lung cancer, melanoma, microsatellite instability–high/mismatch repair–deficient metastatic colorectal cancer).[10-13] The combination of nivolumab plus ipilimumab has recently been approved in the United States as second-line therapy for HCC.[14] We report the safety and efficacy of nivolumab plus ipilimumab in patients who are sorafenib refractory or sorafenib intolerant and have advanced HCC from CheckMate 040.

### Key Points

**Question** Does adding ipilimumab to nivolumab improve clinical outcomes for patients with advanced hepatocellular carcinoma previously treated with sorafenib?

**Findings** In the CheckMate 040 randomized clinical trial of nivolumab plus ipilimumab in patients with advanced hepatocellular cancer previously treated with sorafenib, patients were randomized 1:1:1 to 3 different treatment arms to evaluate different dosing regimens. Investigator-assessed objective response rate was greater than 30% across treatment arms, and the combination of nivolumab plus ipilimumab led to high overall survival rates and had a manageable safety profile.

**Meaning** The manageable safety profile and promising response rates observed in this study support further investigation of nivolumab plus ipilimumab as a treatment option for this patient population.

## Methods

### Study Design

CheckMate 040 is a multicenter, open-label, multicohort, phase 1/2 randomized clinical trial. For this cohort, patients were recruited from 31 centers in 10 countries/territories in Asia, Europe, and North America. The 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. The report was prepared according to the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. All patients provided written informed consent to participate based on the principles of the Declaration of Helsinki. The Trial Protocol is available in Supplement 1.

### Patients

Eligible patients were 18 years or older with histologically confirmed advanced HCC (not eligible for surgical/locoregional therapies or with disease progression after or intolerance of sorafenib) and Child-Pugh liver function class A. Patients were required to have an Eastern Cooperative Oncology Group performance status score of 1 or less and at least 1 untreated target lesion that could be measured in 1 dimension according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[15]

Eligible patients had HCC with or without hepatitis B virus (HBV) infection or hepatitis C virus (HCV) infection. Patients who had active coinfection with HBV and HCV, or HBV and hepatitis D virus, were not eligible. Hepatitis infection definition and additional eligibility criteria are in the eMethods in Supplement 2.

Race and ethnicity (United States only) were recorded based on the patient's best description at enrollment. This was an important consideration because HCC prevalence, incidence, cause, and mortality vary by race and ethnicity, which has potential implications for tumor control and survival.[16-18]

### Randomization and Masking

Blocked randomization was performed using the Interactive Voice Response System (IVRS) without stratification. Investigators called the IVRS to enroll participants and receive participants' treatment randomizations. Random allocation was implemented by the IVRS, a centralized automated third-party system, using a sequentially numbered list generated by the Randomization Information Management System. This ensured that the sequentially numbered list was concealed until treatment allocation was completed.

Patients were randomized to 1 of 3 dosing arms by 2-stage enrollment. For each dosing arm, 12 patients were enrolled for a safety and tolerability assessment at week 13, and subsequent patients were enrolled after completing the safety assessment. Treatment group information was blinded in the database after randomization.

### Procedures

Patients were randomized 1:1:1 into 3 dosing arms. Arm A was treated with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks (4 doses). Arm B was treated with nivolumab

3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks (4 doses). Both arm A and arm B regimens were followed by nivolumab 240 mg intravenously every 2 weeks. Arm C was treated with nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks. Tumors were assessed by computed tomography or magnetic resonance imaging at baseline and every 6 weeks until 48 weeks; thereafter, tumors were assessed every 12 weeks until disease progression. Treatment was permitted beyond initial investigator-assessed RECIST version 1.1 progression with a repeated evaluation at the next tumor assessment visit (6 or 12 weeks). Treatment continued until unacceptable toxic effects emerged, disease progressed as defined by RECIST version 1.1, or consent was withdrawn. Treatment interruptions were permitted to manage adverse events.

### Outcomes

The key objective was to evaluate the safety and tolerability, ORR, and durability of response of combinations of nivolumab and ipilimumab. The coprimary end points were safety and tolerability, and ORR was assessed by investigators per RECIST version 1.1. Secondary and exploratory efficacy end points included ORR, disease control rate, and duration of response, assessed by blinded independent central review (BICR) per RECIST version 1.1, ORR per modified RECIST, and overall survival. Definitions are in the eAppendix in Supplement 2. Additional end points included response stratified by programmed cell death ligand 1 (PD-L1) expression. Tumor biopsies collected at baseline, either fresh or archival, were used retrospectively to analyze tumor PD-L1 expression by immunohistochemistry using the PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako, Agilent Technologies ).[5] Investigators assessed safety continuously for up to 100 days after the last dose or until all treatment-related adverse events were resolved to baseline levels or deemed irreversible by investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Additional safety criteria are listed in the eAppendix in Supplement 2. We assessed patient-reported health status using the 3-level version of the European Quality of Life 5 Dimensions questionnaire (EQ-5D-3L; described in the eAppendix in Supplement 2).

### Statistical Analyses

Objective response rate, complete response rate, and disease control rate with corresponding 2-sided 95% CIs were estimated using the Clopper-Pearson method. Kaplan-Meier methods were used to estimate medians and 95% CIs for duration of response, overall survival, and progression-free survival. Survival outcomes were calculated from date of randomization. The study was not powered to detect differences between the 3 treatment arms. See eMethods and eTable 1 in Supplement 2 for sample size information.

All analyses were performed using the intent-to-treat population, comprising all randomized patients, except for exposure and safety analyses, which were evaluated in randomized patients who received at least 1 dose of the study drug. Patient-reported outcomes were evaluated using descriptive analyses in patients with both a valid baseline and at least 1 postbaseline assessment. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute). CheckMate 040 is registered with ClinicalTrials.gov (NCT01658878).

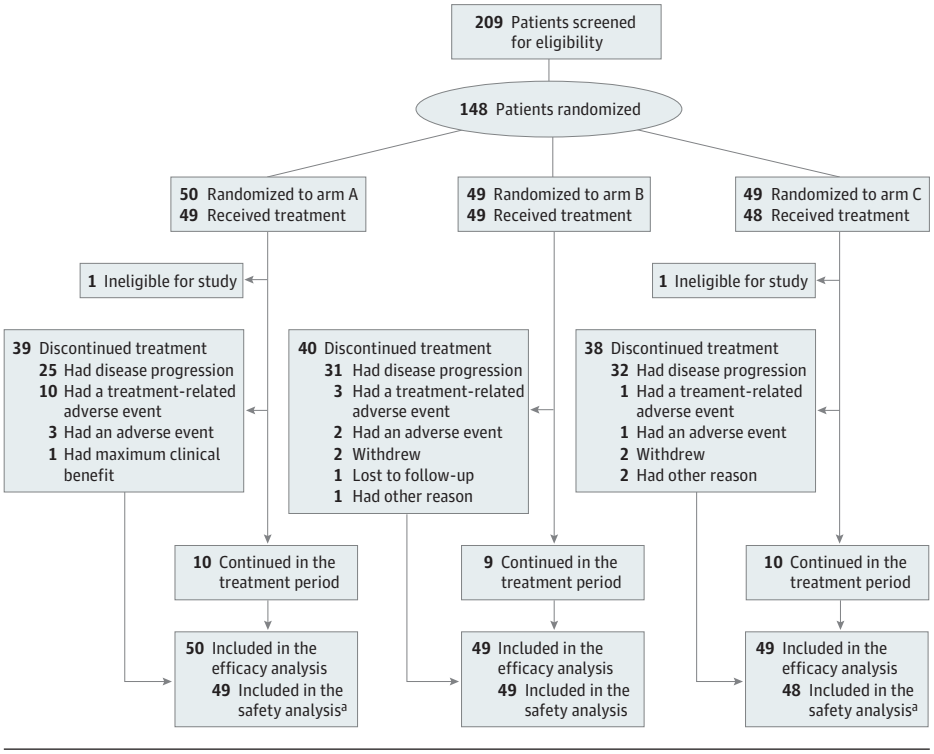
## Results

Between January 4 and September 26, 2016, a total of 148 patients with advanced HCC were randomized across 3 dosing arms. Of all participants, 120 were male (81%). Median (interquartile range [IQR]) age was 60 (52.5-66.5). All randomized patients were included in efficacy analyses, and 146 treated patients were included in safety and drug exposure analyses (**Figure 1**). At data cutoff (January 2019), the median follow-up was 30.7 months (IQR, 29.9-34.7). Baseline demographics and clinical characteristics were generally comparable across treatment arms (eTable 2 in Supplement 2). A high proportion of patients had poor prognostic features and HBV-related HCC, and 9% had at least 3 prior systemic therapies. Overall, 146 of 148 patients received prior sorafenib therapy (99%); 84% discontinued sorafenib because of disease progression and 14% because of toxic effects (by investigator assessment).

In arms A, B, and C, investigator-assessed ORR was 32%, 27%, and 29%, and median duration of response was not reached, 15.2 months, and 21.7 months, respectively (**Table**). Objective response rate by BICR per RECIST version 1.1 was 32% in arm A, 31% in arm B, and 31% in arm C. A total of 7 patients had a complete response by BICR, 4 patients in arm A and 3 patients in arm B. Duration of response, median time to response, and disease control rate were similar across treatment arms. All responses occurred early in treatment (eFigure 1 in Supplement 2). Responses were observed regardless of baseline etiology and PD-L1 status (eTable 3 in Supplement 2).

We observed substantial reductions in tumor burden in all treatment arms (eFigure 2 in Supplement 2), and several responders exhibited deep responses (eFigure 3 in Supplement 2). Median overall survival was 22.8 months (95% CI, 9.4-not reached) in arm A vs 12.5 months (95% CI, 7.6-16.4) in arm B and 12.7 months (95% CI, 7.4-33.0) in arm C (**Figure 2**A; eTable 4 in Supplement 2). In arm A, the 12-month overall survival rate was 61% (95% CI, 46%-73%) and the 24-month overall survival rate was 48% (95% CI, 34%-61%). Response conferred a survival benefit in the overall population; the median overall survival of patients with complete/partial response was not reached at data cutoff (95% CI, 33.0-not evaluable) vs 14.5 months (95% CI, 8.4-29.6) for patients with stable disease and 8.3 months (95% CI, 6.6-10.8) for patients with progressive disease (Figure 2B; eTable 5 in Supplement 2). When evaluated by baseline etiology, the median overall survival of patients who were HBV/HCV uninfected, HBV infected, or HCV infected in arm A was 22.2 months, 22.8 months, and 14.9 months; in arm B, 11.8 months, 12.1 months, and 16.1 months; and in arm C, 7.4 months, 9.6 months, and 33.0 months, respectively (eTable 3 in Supplement 2), although small subgroups limit comparisons. In each arm, median overall survival by baseline PD-L1 status was comparable.

Figure 1. Enrollment, Randomization, and Outcomes




[a] The 2 patients who did not receive treatment were excluded from the safety analysis.

Table. Response, Disease Control, and Durability

| Characteristic | No. (%) | | |
|---|---|---|---|
| | Arm A[a] (n = 50) | Arm B[b] (n = 49) | Arm C[c] (n = 49) |
| Response by investigator assessment using RECIST v1.1 | | | |
| Objective response rate, No. (%) [95% CI] | 16 (32) [20 to 47] | 13 (27) [15 to 41] | 14 (29) [17 to 43] |
| Duration of response, median (range), mo | NE (8.3 to 33.7+) | 15.2 (4.2 to 29.9+) | 21.7 (2.8 to 32.7+) |
| Response by BICR using RECIST v1.1 | | | |
| Objective response rate, No. (%) [95% CI][d] | 16 (32) [20 to 47] | 15 (31) [18 to 45] | 15 (31) [18 to 45] |
| Best overall response | | | |
| Complete response | 4 (8) | 3 (6) | 0 |
| Partial response | 12 (24) | 12 (24) | 15 (31) |
| Stable disease[e] | 9 (18) | 5 (10) | 9 (18) |
| Progressive disease | 20 (40) | 24 (49) | 21 (43) |
| Unable to determine[f] | 3 (6) | 4 (8) | 4 (8) |
| Disease control rate[g] | 27 (54) | 21 (43) | 24 (49) |
| Duration of response, median (range), mo[h] | 17.5 (4.6 to 30.5+) | 22.2 (4.2 to 29.9+) | 16.6 (4.1+ to 32.0+) |
| Duration of response of ≥24 mo[h] | 5 (31) | 4 (27) | 5 (33) |
| Time to response, median (IQR), mo[h] | 2.0 (1.3 to 2.7) | 2.6 (1.3 to 4.0) | 2.7 (1.3 to 2.8) |
| Response by BICR using mRECIST | | | |
| Objective response rate, No. (%) [95% CI][d] | 17 (34) [21 to 49] | 16 (33) [20 to 48] | 15 (31) [18 to 45] |

Abbreviations: BICR, blinded independent central review; IQR, interquartile range; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RECIST, Response Evaluation Criteria in Solid Tumors.

[a] Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks.

[b] Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks.

[c] Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks.

[d] Defined as complete response plus partial response.

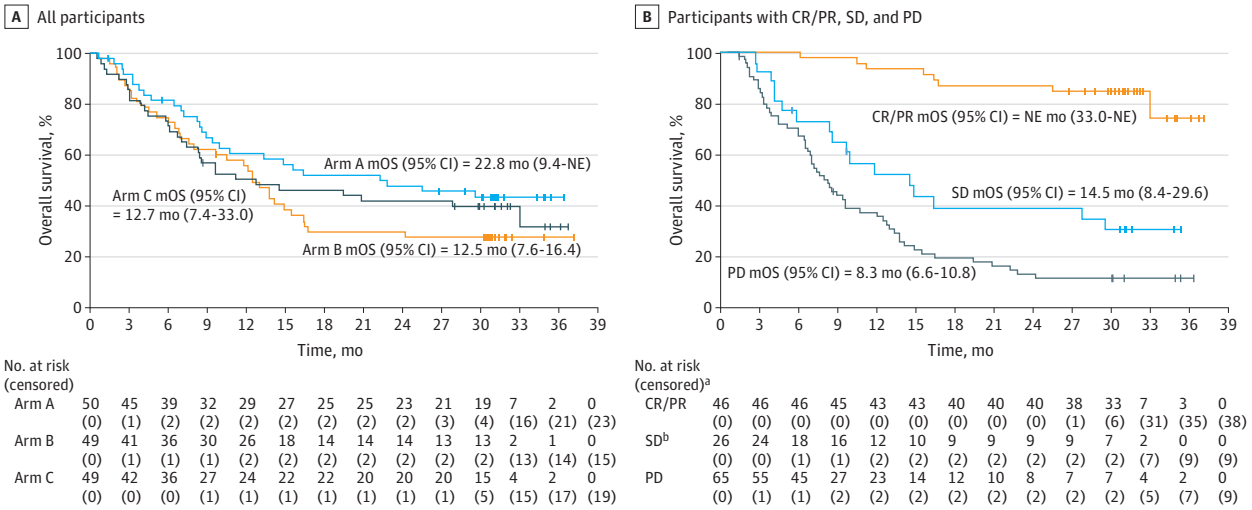
[e] Stable disease does not include 2 patients in arm A and 1 patient in arm B who were reported as noncomplete response/nonprogressive disease and did not meet the definition of stable disease by BICR.

[f] These patients were not scanned; therefore, best overall response could not be determined.

[g] Defined as complete response plus partial response plus stable disease plus noncomplete response/nonprogressive disease.

[h] Patients with a complete response or partial response.

Figure 2. Kaplan-Meier Analysis of Median Overall Survival




No. at risk (censored)

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arm A | 50 (0) | 45 (1) | 39 (2) | 32 (2) | 29 (2) | 27 (2) | 25 (2) | 25 (2) | 23 (2) | 21 (3) | 19 (4) | 7 (16) | 2 (21) | 0 (23) |
| Arm B | 49 (0) | 41 (1) | 36 (1) | 30 (1) | 26 (2) | 18 (2) | 14 (2) | 14 (2) | 14 (2) | 13 (2) | 13 (2) | 2 (13) | 1 (14) | 0 (15) |
| Arm C | 49 (0) | 42 (0) | 36 (0) | 27 (1) | 24 (1) | 22 (1) | 22 (1) | 20 (1) | 20 (1) | 20 (1) | 15 (5) | 4 (15) | 2 (17) | 0 (19) |

No. at risk (censored)[a]

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CR/PR | 46 (0) | 46 (0) | 46 (0) | 45 (0) | 43 (0) | 43 (0) | 40 (0) | 40 (0) | 40 (0) | 38 (1) | 33 (6) | 7 (31) | 3 (35) | 0 (38) |
| SD[b] | 26 (0) | 24 (0) | 18 (1) | 16 (1) | 12 (2) | 10 (2) | 9 (2) | 9 (2) | 9 (2) | 9 (2) | 7 (2) | 2 (7) | 0 (9) | 0 (9) |
| PD | 65 (0) | 55 (1) | 45 (1) | 27 (2) | 23 (2) | 14 (2) | 12 (2) | 10 (2) | 8 (2) | 7 (2) | 7 (2) | 4 (5) | 2 (7) | 0 (9) |

A, survival by treatment arm; B, overall population survival stratified by best overall response. CR indicates complete response; mOS, median overall survival; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Eleven patients overall did not have a scan; therefore, best overall response could not be determined.

[b] Stable disease was reported as noncomplete response/nonprogressive disease in 2 patients in arm A and 1 patient in arm B. These were patients who only had nontarget lesions at baseline and did not meet the definition of stable disease by blinded independent central review.

The median (IQR) treatment duration was longest in arm A (5.1 months [2.1-19.5]) vs arm B (2.3 months [0.7-13.8]) and arm C (4.0 months [1.2-17.8]). Disease progression was the most common reason for treatment discontinuation (arm A, 51% of patients; arms B and C, 69% of patients). The percentage of patients discontinuing the treatment regimen because of study drug toxic effects was highest in arm A (22%) vs arm B (6%) and arm C (2%).

Any-grade treatment-related adverse events were observed in 46 patients (94%) in arm A, 35 patients (71%) in arm B, and 38 patients (79%) in arm C (eTable 6 in Supplement 2). Although arm A had higher rates of treatment-related adverse events than arms B and C, the types of events were similar across arms, and no new safety signals were observed. The types of events in patients with and without HBV or HCV infection were also generally comparable across treatment arms (eTable 7 in Supplement 2). Virologic breakthrough, conservatively defined as a 1-log increase in HBV DNA or HCV RNA from baseline, was observed in 7 of 82 HBV-infected patients (9%) and 4 of 39 HCV-infected patients (10%) overall. Changes in viral kinetics were not associated with treatment-related significant hepatic adverse events. Investigator-reported, any-grade treatment-related adverse events led to discontinuation of either drug in 9 patients (18%) in arm A, 3 patients (6%) in arm B, and 1 patient (2%) in arm C. Among them, 5 patients in arm A, 2 patients in arm B, and 1 patient in arm C had grade 3-4 treatment-related adverse events. Within 100 days of the final dose of study drug, 1 patient from arm A died of a serious treatment-related adverse event (grade 5 pneumonitis).

Arm A had higher rates of immune-mediated adverse events and immune-mediated adverse events leading to discontinuation compared with arms B and C (eTable 6 in Supplement 2). eFigure 4 in Supplement 2 summarizes the time to onset and time to resolution of any-grade immune-mediated adverse events. The median (IQR) time to onset of hepatic events was 5.6 weeks (3.4-9.3) for arm A, 8.1 weeks (3.0-11.0) for arm B, and 5.9 weeks (3.6-8.6) for arm C. The proportion of hepatic events (median [IQR] time to resolution) that resolved was 9 out of 10 (90%; 6.6 weeks [2.0-15.0]) in arm A, 5 out of 6 (83%; 7.9 weeks [6.7-10.9]) in arm B, and 2 out of 3 (67%; 6.1 weeks [3.9-not evaluable]) in arm C. In arms A, B, and C, of the 10, 6, and 3 patients who had a hepatic immune-mediated adverse event, 7, 3, and 2 received high-dose glucocorticoids (≥40 mg of prednisone per day or equivalent) for a median (IQR) of 2 weeks (0.9-7.0), 1 week (0.6-1.1), and 3 weeks (2.0-3.0), respectively. None of these patients received additional immunosuppressive therapy. For all immune-mediated adverse events, standard treatment management algorithms were used, as specified by the Trial Protocol. Of patients who were rechallenged with nivolumab or ipilimumab after experiencing an immune-mediated adverse event in any category, no patients experienced a recurrence of the event after rechallenge (eTable 8 in Supplement 2).

Descriptive analyses indicated a trend for improvement in each arm based on both EQ-5D visual analogue scale and utility index, with some scores reaching general population standards. Patients in arm A experienced greater benefit compared with patients in arms B and C based on the mixed-model repeated-measures analyses. Patients in arm A had improvement in both visual analogue scale (2.1 [SE, 2.6]) and utility index (UK, 0.033 [0.031]; US, 0.027 [0.023]) scores, whereas patients in arms B and C had improvement in visual analogue scale (1.2 [2.3]), but a slight decrease in utility index (UK, -0.016 [0.029]; US, -0.011 [0.021]) overall. The mean dif-

ference between groups favored arm A overall and at most individual time points.

## Discussion

To our knowledge, this is the first report of nivolumab-ipilimumab combination therapy in the treatment of advanced HCC. Nivolumab plus ipilimumab provided a robust clinical benefit in patients treated with sorafenib, with high ORRs (by BICR per RECIST version 1.1) of 16 out of 50 (32%) in arm A, 15 out of 49 (31%) in arm B, and 15 out of 49 (31%) in arm C (7 patients had complete responses). Patients in arm A had the highest complete response rate, most promising median overall survival of 22.8 months, and 12-month survival rates of 61%, 24-month survival rates of 48%, and 30-month overall survival rates of 44%, with improvement in health status relative to the other 2 arms. The higher overall survival observed in arm A vs arms B and C may be due to the higher starting dose of ipilimumab in arm A; however, this study was not powered to detect differences between treatment arms. Across all arms, patients with the best overall response of complete/partial response had substantially improved median overall survival compared with those who had stable disease or progressive disease, underscoring the importance of achieving a response with treatment.

Nivolumab monotherapy demonstrated a median overall survival of 15.1 months and an ORR of 14% in patients who were sorafenib refractory and had advanced HCC.[7] A phase 2 study[6] of the PD-1 inhibitor pembrolizumab reported median overall survival of 12.9 months and an ORR of 17%, and a recent phase 3 study[19] of pembrolizumab monotherapy showed median overall survival of 13.9 months and an ORR of 18% in patients treated with sorafenib. Although comparisons are indirect, our results suggest that nivolumab plus ipilimumab may provide improved efficacy in terms of ORR, and, potentially, survival in arm A relative to anti-PD-L1 monotherapy.

Outcomes with nivolumab plus ipilimumab compare favorably with results of other approved second-line targeted therapies. Pivotal trials of the multikinase inhibitors regorafenib and cabozantinib in patients treated with sorafenib demonstrated median overall survival of 10.6 months and 10.2 months, and ORR of 11% and 4%, respectively.[2,4] In patients with baseline α-fetoprotein levels of at least 400 µg/L, ramucirumab showed a median overall survival of 8.5 months and an ORR of 5%.[3]

The results of this study are consistent with the PD-1/PD-L1 and CTLA-4 pathways having distinct but complementary roles in negatively regulating immune activity.[20] These results confirm that HCC is sensitive to CTLA-4 blockade, as previously suggested in small single-arm trials of tremelimumab.[21,22] These results suggest that increased ipilimumab doses may translate into higher durable responses and improved survival in patients with advanced HCC. Nivolumab-ipilimumab combination trials in advanced melanoma, recurrent small cell lung cancer, and metastatic renal cell carcinoma have also shown some improved responses with higher ipilimumab doses and, where reported, improved overall survival.[23-25]

In this study, responses occurred regardless of HCC etiology or PD-L1 expression. However, because this study was not powered to detect differences between etiologies or PD-L1 status, larger studies are required to draw conclusions on these factors.

This study reported higher rates of adverse events with nivolumab and ipilimumab regimens than have previously been reported with nivolumab monotherapy.[5] However, the safety profile was consistent in presentation and management with that of nivolumab and ipilimumab monotherapy. The safety profile was also consistent with studies investigating nivolumab and ipilimumab in the treatment of other tumor types.[10-12,23,26] In patients with advanced melanoma treated with nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg), 248 of 448 (55.4%) had grade 3 or 4 treatment-related adverse events, and 186 (41.5%) had grade 3 or 4 treatment-related select adverse events.[26] Patients in arm A reported the highest rates of adverse events, immune-mediated adverse events, and discontinuation due to study drug toxic effects. Most immune-mediated adverse events resolved across treatment arms, including hepatic events (occurring in 10 of 49 [20%] patients in arm A, with 90% resolving using protocol-specified management algorithms). The frequency of virologic breakthrough in patients with chronic HBV infection on suppressive antiviral therapy and patients with chronic HCV infection was consistent with reports in the literature in the absence of immuno-oncology therapy.[27-30] Overall, the adverse events were consistent with those previously identified in other tumor types and were effectively managed with established treatment algorithms, and there was a compelling overall survival benefit in patients receiving nivolumab plus ipilimumab. Furthermore, encouraging patient-reported health status results were observed for all arms, particularly arm A, despite higher rates of adverse events in this arm.

### Limitations

Limitations of this study include (1) its design as an open-label phase 1/2 study in a relatively small patient population; (2) its lack of a comparator arm, particularly a nivolumab monotherapy arm; and (3) its lack of patient stratification (owing to small population), with potential prognostic factors not necessarily balanced across the 3 arms. However, the patient cohort was not a highly selected population and included high-risk patients in general who were heavily pretreated with high frequency of extrahepatic spread and elevated α-fetoprotein levels. New larger, randomized, active comparator-controlled clinical studies are being initiated to investigate the efficacy benefits.

## Conclusions

For patients with advanced HCC previously treated with sorafenib, nivolumab-ipilimumab regimens had manageable safety profiles and durable responses with high ORRs. Overall survival rates were promising, especially for arm A. Based on the results of this study, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks followed by nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks received accelerated approval in the United States as a second-line therapy for HCC. Investigation of this combination is under way as first-line therapy in patients with HCC (NCT04039607).

## ARTICLE INFORMATION

**Accepted for Publication:** July 17, 2020.

**Published Online:** October 1, 2020. doi:10.1001/jamaoncol.2020.4564



**Author Affiliations:** Department of Medicine, University of Hong Kong, Hong Kong, China (Yau); Asan Medical Center, Department of Oncology, University of Ulsan, Seoul, South Korea (Kang); Department of Internal Medicine, Seoul National University, Seoul, South Korea (Kim); Norris Comprehensive Cancer Center, Division of Medical Oncology/Hematology, University of Southern California, Los Angeles, California (El-Khoueiry); Humanitas Clinical and Research Center, Department of Medical Oncology, Humanitas University, Rozzano, Italy (Santoro); Department of Internal Medicine, Clinica Universidad de Navarra, Instituto de Investigación Sanitaria de Navarra, and Centro de Investigacion Biomedica en Red de Enfermedades Hepaticas y Digestivas, Pamplona, Spain (Sangro); Department of Immunology and Immunotherapy, Clinica Universidad de Navarra and Centro de Investigación Biomédica en Red de Cáncer, Pamplona, Spain (Melero); Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan (Kudo); Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Taipei, Taiwan (Hou); Department of Medicine, Servicio de Digestivo, Hospital General Universitario Gregorio Marañón, Centro de Investigacion Biomedica en Red de Enfermedades Hepaticas y Digestivas, Madrid, Spain (Matilla); Department of Medical & Surgical Sciences, University of Bologna, Bologna, Italy (Tovoli); Cancer Clinical Research Unit, Princess Margaret Cancer Centre, Toronto, Ontario, Canada (Knox); Division of Hematology/Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC (Ruth He); Department of Hematology, Emory University Winship Cancer Institute, Atlanta, Georgia (El-Rayes); Department of Hematology and Oncology, Fundacion de Investigacion, San Juan, Puerto Rico (Acosta-Rivera); Samsung Medical Center, Department of Hematology and Oncology, Sungkyunkwan University School of Medicine, Seoul, South Korea (Lim); Department of Immuno-Oncology, Biomarkers, and Translational Medicine, Bristol Myers Squibb, Princeton, New Jersey (Neely); Department of Immuno-Oncology, Oncology, and Immunology, Bristol Myers Squibb, Princeton, New Jersey (Shen); Department of Clinical Research, Bristol Myers Squibb, Princeton, New Jersey (Wisniewski, Anderson); Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan (Hsu).

**Author Contributions:** Dr Yau had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Yau, El-Khoueiry, Sangro, Melero, Lim, Anderson.
*Acquisition, analysis, or interpretation of data:* Yau, Kang, Kim, El-Khoueiry, Santoro, Melero, Kudo, Hou, Matilla, Tovoli, Knox, Ruth He, El-Rayes, Acosta-Rivera, Lim, Neely, Shen, Wisniewski, Anderson, Hsu.
*Drafting of the manuscript:* Yau, El-Khoueiry, Santoro, Melero, El-Rayes, Lim, Shen, Wisniewski, Anderson, Hsu.
*Critical revision of the manuscript for important intellectual content:* Yau, Kang, Kim, El-Khoueiry, Sangro, Melero, Kudo, Hou, Matilla, Tovoli, Knox, Ruth He, El-Rayes, Acosta-Rivera, Lim, Neely, Wisniewski, Anderson, Hsu.
*Statistical analysis:* Yau, Lim, Shen, Anderson.
*Administrative, technical, or material support:* Yau, Hou, Knox, El-Rayes, Acosta-Rivera, Lim, Neely, Wisniewski, Hsu.
*Supervision:* Yau, Kim, El-Khoueiry, Melero, Kudo, Hou, Ruth He, El-Rayes, Lim, Anderson, Hsu.

**Conflict of Interest Disclosures:** Dr Yau reported receiving personal fees from Bristol Myers Squibb during the conduct of the study; and grants and personal fees from Bristol Myers Squibb, personal fees from Merck Sharp & Dohme Oncology, Exelixis, Ipsen, and AstraZeneca outside the submitted work. Dr Kang reported personal fees from Bristol Myers Squibb, ALX Oncology, Novartis, and Surface Oncology outside the submitted work. Dr El-Khoueiry reported grants and nonfinancial support from Bristol Myers Squibb during the conduct of the study; personal fees from Bristol Myers Squibb, Bayer, Eisai Co, Merck, Roche/Genentech, Exelixis, AstraZeneca, Agenus, EMD Serono, Zymeworks, Agios, QED Therapeutics, Cytomx, Pieris, and Target PharmaSolutions outside the submitted work. Dr Santoro reported other support from Bristol Myers Squibb, Laboratoires Servier, Gilead Sciences, Pfizer, Eisai Co, Bayer, Merck Sharp & Dohme, ArQule Inc, Sanofi, Takeda, Bristol Myers Squibb, Roche, AbbVie, Amgen, Celgene, Laboratoires Servier, Gilead Sciences, AstraZeneca, Pfizer, Eli Lilly, Sandoz, and Novartis outside the submitted work. Dr Sangro reported personal fees from AstraZeneca, Adaptimmune Limited, Bayer, H3 Biomedicine, Ipsen, Eli Lilly, Roche/Genentech, and BTG; and grants and personal fees from Bristol Myers Squibb and Sirtex Medical outside the submitted work. Dr Melero reported personal fees from Bayer, Servier, Numab, Pieris, and Merck Sharp & Dohme, and grants and personal fees from Bristol Myers Squibb, Roche, Bioncotech, Alligator, AstraZeneca, and Merck Serono during the conduct of the study. Dr Kudo reported grants and other support from Eisai; other support from Bayer, Merck Sharp & Dohme, Bristol Myers Squibb, Roche, and Ono Pharmaceutical; grants from Gilead Sciences, Taiho Pharmaceutical, Sumitomo Dainippon Pharma, Takeda Pharmaceutical Company, Otsuka Pharmaceutical, EA Pharma Co, and AbbVie outside the submitted work. Dr Matilla reported personal fees from Bristol Myers Squibb during the conduct of the study, and personal fees from Bristol Myers Squibb, Bayer, Boston Scientific, Terumo, and Eisai outside the submitted work. Dr Tovoli reported personal fees and nonfinancial support from Bayer AG and personal fees from LaForce outside the submitted work. Dr Knox reported grants from Ipsen and grants and personal fees from AstraZeneca, Merck, and F. Hoffman-La Roche outside the submitted work. Dr El-Rayes reported grants and personal fees from Bristol Myers Squibb during the conduct of the study; grants and personal fees from Merck, grants from Boston Biomedical, Pfizer, Novartis, MedImmune, Xencor, EUSA Pharma, grants and other support from Exilixis, and other support from Erytech, Incyte, Bayer, and Adaptimmune outside the submitted work. Dr Neely reported personal fees from Bristol Myers Squibb outside the submitted work. Dr Shen reported being an employee of Bristol Myers Squibb. Dr Wisniewski reported other support from Bristol Myers Squibb during the conduct of the study; other suport from Bristol Myers Squibb outside the submitted work; and stock ownership in Bristol Myers Squibb as an employee of the company. Dr Anderson reported other support from Bristol Myers Squibb during the conduct of the study and other support from Bristol Myers Squibb outside the submitted work. Dr Hsu reported grants and personal fees from Bristol Myers Squibb and Ono Pharmaceutical during the conduct of the study; grants from Roche and Ipsen, and personal fees from AstraZeneca, Bayer, Eisai, Eli Lilly, Ipsen, Merck Serono, Merck Sharp & Dohme, Novartis, Roche, and TTY Biopharm outside the submitted work. No other disclosures were reported.

**Funding/Support:** This study was supported by Bristol Myers Squibb (Princeton, New Jersey) and Ono Pharmaceutical (Osaka, Japan).

**Role of the Funder/Sponsor:** The authors designed the study in collaboration with the funder (Bristol Myers Squibb). The funder gathered and analyzed the data with the authors.

**Meeting Presentation:** Presented in part at the American Society of Clinical Oncology; Chicago, Illinois; May 31-June 4, 2019.

**Data Sharing Statement:** See Supplement 3.

**Additional Contributions:** The authors would like to thank the patients who participated in this trial and their families; the investigators, study coordinators, study teams, and nurses who assisted; and Dako, an Agilent Technologies company, for collaborative development of the PD-L1 IHC 28-8 pharmDx assay. We acknowledge Christine Dela Cruz, MD, MHScM, for her contributions to the CheckMate 040 study, including study design, protocol development, and analysis and interpretation of data, while she was an employee of Bristol Myers Squibb. We acknowledge Steve Blum, MBA, MA, and Gwilym Thompson, PhD, employees of Bristol Myers Squibb, for their analysis and interpretation of patient-reported outcomes data; we also thank Fiona Taylor, MBiochem, Christine Yip, MPP, and Rachel Lawrence, CStat, from Adelphi Values, a consulting firm that received payment from Bristol Myers Squibb to conduct patient-reported outcome analyses for Bristol Myers Squibb, for the support provided in the analysis of the patient-reported outcomes data. Writing and editorial assistance was provided by Emily Bruce, PhD, of Parexel International (Waltham, Massachusetts), funded by Bristol Myers Squibb.

## REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492

**2**. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002

**3**. Zhu AX, Kang YK, Yen CJ, et al; REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(2):282-296. doi:10.1016/S1470-2045(18)30937-9

**4**. Bruix J, Qin S, Merle P, et al; RESORCE investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10064):56-66. doi:10.1016/S0140-6736(16)32453-9

**5**. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492-2502. doi:10.1016/S0140-6736(17)31046-2

**6**. Zhu AX, Finn RS, Edeline J, et al; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol*. 2018;19(7):940-952. doi:10.1016/S1470-2045(18)30351-6

**7**. El-Khoueiry AB, Melero I, Yau T, et al Impact of antitumor activity on survival outcomes, and nonconventional benefit, with nivolumab in patients with advanced hepatocellular carcinoma: subanalyses of CheckMate-040. Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 18-20, 2018; San Francisco, CA.

**8**. Das R, Verma R, Sznol M, et al. Combination therapy with anti-CTLA-4 and anti-PD-1 leads to distinct immunologic changes in vivo. *J Immunol*. 2015;194(3):950-959. doi:10.4049/jimmunol.1401686

**9**. Melero I, Berman DM, Aznar MA, Korman AJ, Pérez Gracia JL, Haanen J. Evolving synergistic combinations of targeted immunotherapies to combat cancer. *Nat Rev Cancer*. 2015;15(8):457-472. doi:10.1038/nrc3973

**10**. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non–small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol*. 2017;18(1):31-41. doi:10.1016/S1470-2045(16)30624-6

**11**. Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. *Lancet Oncol*. 2016;17(11):1558-1568. doi:10.1016/S1470-2045(16)30366-7

**12**. Motzer RJ, Tannir NM, McDermott DF, et al; CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378(14):1277-1290. doi:10.1056/NEJMoa1712126

**13**. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol*. 2018;36(8):773-779. doi:10.1200/JCO.2017.76.9901

**14**. Opdivo. Package insert. Bristol Myers Squibb; 2020..

**15**. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026

**16**. Jones PD, Diaz C, Wang D, Gonzalez-Diaz J, Martin P, Kobetz E. The impact of race on survival after hepatocellular carcinoma in a diverse american population. *Dig Dis Sci*. 2018;63(2):515-528. doi:10.1007/s10620-017-4869-3

**17**. Pinheiro PS, Medina HN, Callahan KE, et al. The association between etiology of hepatocellular carcinoma and race-ethnicity in Florida. *Liver Int*. 2020;40(5):1201-1210. doi:10.1111/liv.14409

**18**. Rich NE, Hester C, Odewole M, et al. Racial and ethnic differences in presentation and outcomes of hepatocellular carcinoma. *Clin Gastroenterol Hepatol*. 2019;17(3):551-559.e1. doi:10.1016/j.cgh.2018.05.039

**19**. Finn RS, Ryoo B-Y, Merle P, et al Results of KEYNOTE-240: phase 3 study of pembrolizumab (pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). *J Clin Oncol*. 2019;37(15 suppl):4004. doi:10.1200/JCO.2019.37.15_suppl.4004

**20**. Kyi C, Postow MA. Immune checkpoint inhibitor combinations in solid tumors: opportunities and challenges. *Immunotherapy*. 2016;8(7):821-837. doi:10.2217/imt-2016-0002

**21**. Duffy AG, Ulahannan SV, Makorova-Rusher O, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J Hepatol*. 2017;66(3):545-551. doi:10.1016/j.jhep.2016.10.029

**22**. Sangro B, Gomez-Martin C, de la Mata M, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. *J Hepatol*. 2013;59(1):81-88. doi:10.1016/j.jhep.2013.02.022

**23**. Hammers HJ, Plimack ER, Infante JR, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. *J Clin Oncol*. 2017;35(34):3851-3858. doi:10.1200/JCO.2016.72.1985

**24**. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17(7):883-895. doi:10.1016/S1470-2045(16)30098-5

**25**. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369(2):122-133. doi:10.1056/NEJMoa1302369

**26**. Sznol M, Ferrucci PF, Hogg D, et al. Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. *J Clin Oncol*. 2017;35(34):3815-3822. doi:10.1200/JCO.2016.72.1167

**27**. Boyd A, Gozlan J, Maylin S, et al. Persistent viremia in human immunodeficiency virus/hepatitis B coinfected patients undergoing long-term tenofovir: virological and clinical implications. *Hepatology*. 2014;60(2):497-507. doi:10.1002/hep.27182

**28**. Kuramoto IK, Moriya T, Schoening V, Holland PV. Fluctuation of serum HCV-RNA levels in untreated blood donors with chronic hepatitis C virus infection. *J Viral Hepat*. 2002;9(1):36-42. doi:10.1046/j.1365-2893.2002.00333.x

**29**. Park JW, Kwak KM, Kim SE, et al. Comparison of the long-term efficacy between entecavir and tenofovir in treatment-naïve chronic hepatitis B patients. *BMC Gastroenterol*. 2017;17(1):39. doi:10.1186/s12876-017-0596-7

**30**. Zhu AX, Kudo M, Assenat E, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. *JAMA*. 2014;312(1):57-67. doi:10.1001/jama.2014.7189