ORIGINAL ARTICLE

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

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ABSTRACT

BACKGROUND

The combination of atezolizumab and bevacizumab showed encouraging antitumor activity and safety in a phase 1b trial involving patients with unresectable hepatocellular carcinoma.

METHODS

In a global, open-label, phase 3 trial, patients with unresectable hepatocellular carcinoma who had not previously received systemic treatment were randomly assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib until unacceptable toxic effects occurred or there was a loss of clinical benefit. The coprimary end points were overall survival and progression-free survival in the intention-to-treat population, as assessed at an independent review facility according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).

RESULTS

The intention-to-treat population included 336 patients in the atezolizumab–bevacizumab group and 165 patients in the sorafenib group. At the time of the primary analysis (August 29, 2019), the hazard ratio for death with atezolizumab–bevacizumab as compared with sorafenib was 0.58 (95% confidence interval [CI], 0.42 to 0.79; P<0.001). Overall survival at 12 months was 67.2% (95% CI, 61.3 to 73.1) with atezolizumab–bevacizumab and 54.6% (95% CI, 45.2 to 64.0) with sorafenib. Median progression-free survival was 6.8 months (95% CI, 5.7 to 8.3) and 4.3 months (95% CI, 4.0 to 5.6) in the respective groups (hazard ratio for disease progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001). Grade 3 or 4 adverse events occurred in 56.5% of 329 patients who received at least one dose of atezolizumab–bevacizumab and in 55.1% of 156 patients who received at least one dose of sorafenib. Grade 3 or 4 hypertension occurred in 15.2% of patients in the atezolizumab–bevacizumab group; however, other high-grade toxic effects were infrequent.

CONCLUSIONS

In patients with unresectable hepatocellular carcinoma, atezolizumab combined with bevacizumab resulted in better overall and progression-free survival outcomes than sorafenib. (Funded by F. Hoffmann–La Roche/Genentech; ClinicalTrials.gov number, NCT03434379.)

Hepatocellular carcinoma is a common cancer worldwide and a leading cause of cancer-related death.[1] Although early-stage disease may be curable by resection, liver transplantation, or ablation,[2] most patients present with unresectable disease and have a poor prognosis.[2]

The multikinase inhibitors sorafenib and lenvatinib are the approved first-line systemic treatments for unresectable hepatocellular carcinoma on the basis of studies showing modestly longer survival with sorafenib than with placebo[3] and noninferiority of lenvatinib to sorafenib.[4] Both are associated with considerable side effects that impair quality of life.

Programmed death 1 (PD-1) inhibitors have shown promising clinical activity as second-line treatment for hepatocellular carcinoma in phase 1/2 studies.[5,6] However, despite being associated with response rates in the range of 15 to 20% in phase 3 studies of single-agent treatment in first- and second-line settings, they did not significantly improve overall survival.[7,8]

Several active intrinsic immune-evasion pathways, including overexpression of vascular endothelial growth factor (VEGF), have been linked to the development and progression of liver cancer.[9,10] Anti-VEGF therapies reduce VEGF-mediated immunosuppression within the tumor and its microenvironment[11-13] and may enhance anti–PD-1 and anti–programmed death ligand 1 (PD-L1) efficacy by reversing VEGF-mediated immunosuppression and promoting T-cell infiltration in tumors.[14,15]

Several cancer immunotherapies that target the PD-L1–PD-1 pathway (i.e., checkpoint inhibitors) are currently being evaluated in patients with hepatocellular carcinoma.[16] Atezolizumab selectively targets PD-L1 to prevent interaction with receptors PD-1 and B7-1, thus reversing T-cell suppression.[17] Bevacizumab is a monoclonal antibody that targets VEGF,[18] inhibits angiogenesis and tumor growth,[19] and showed response rates of 13 to 14% in single-agent phase 2 studies in patients with advanced liver cancer.[16,20-22] A phase 1b study of atezolizumab plus bevacizumab in patients with untreated unresectable hepatocellular carcinoma showed an acceptable side-effect profile and promising antitumor activity, with an objective response rate of 36% and a median progression-free survival of 7 months.[23] We conducted IMbrave150, a global, multicenter, open-label, phase 3 randomized trial, to determine the safety and efficacy of atezolizumab plus bevacizumab as compared with sorafenib in patients with unresectable hepatocellular carcinoma who had not previously received systemic therapy.

METHODS

PATIENTS

Eligible patients were 18 years of age or older and had locally advanced metastatic or unresectable hepatocellular carcinoma (or both), with the diagnosis confirmed by histologic or cytologic analysis or clinical features according to the American Association for the Study of Liver Diseases criteria for patients with cirrhosis.[24] Eligible patients had not previously received systemic therapy for liver cancer and had measurable disease, as defined by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), that was not amenable to curative or locoregional therapies or that had progressed thereafter; a performance status score of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (scores range from 0 to 5, with higher numbers reflecting greater disability); an A classification on the Child–Pugh liver function scale (a three-category scale [A, B, or C], with C indicating the most severe compromise of liver function); and adequate hematologic and organ function.

Among the key exclusion criteria were a history of autoimmune disease, coinfection with hepatitis B or hepatitis C virus, and untreated or incompletely treated esophageal or gastric varices (assessed with esophagogastroduodenoscopy and treated according to local clinical practice) with bleeding or high risk of bleeding. Full eligibility criteria are provided in the trial protocol, available with the full text of this article at NEJM.org.

OVERSIGHT

F. Hoffmann–La Roche/Genentech sponsored the trial, provided the trial drugs, and collaborated with an academic steering committee on the trial design and on the collection, analysis, and interpretation of the data. IMbrave150 was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. All patients gave written

informed consent. Protocol approval was obtained from the institutional review board or ethics committee at each site. An independent data monitoring committee reviewed unmasked safety and trial conduct data approximately every 6 months. All drafts of the manuscript were prepared by the authors, with editorial assistance funded by the sponsor. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

TRIAL DESIGN AND INTERVENTIONS

In this open-label, phase 3 trial, patients were randomly assigned in a 2:1 ratio to receive atezolizumab plus bevacizumab or sorafenib. Randomization was performed through an interactive voice-response or Web-response system in permuted blocks, stratified by geographic region (Asia excluding Japan vs. the rest of the world), macrovascular invasion or extrahepatic spread of disease (presence vs. absence), baseline alpha-fetoprotein level (<400 vs. ≥400 ng per milliliter), and ECOG performance status (0 vs. 1).

Patients assigned to the atezolizumab–bevacizumab group received 1200 mg of atezolizumab plus 15 mg per kilogram of body weight of bevacizumab intravenously every 3 weeks; patients assigned to the sorafenib group received 400 mg of sorafenib orally twice daily. Patients received their assigned drugs until unacceptable toxic effects occurred or there was loss of clinical benefit. Patients could continue treatment beyond disease progression if the investigator observed evidence of clinical benefit and if symptoms and signs indicating unequivocal disease progression were absent. Dose modifications were not permitted in the atezolizumab–bevacizumab group but were allowed in the sorafenib group. Patients who transiently or permanently discontinued either atezolizumab or bevacizumab because of an adverse event were allowed to continue taking single-agent therapy as long as the investigator determined that there was clinical benefit.

ASSESSMENTS

Tumors were assessed by computed tomography or magnetic resonance imaging at baseline and every 6 weeks until week 54 and then every 9 weeks thereafter. (Assessments and patient-reported outcomes are described in detail in the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org.)

Safety was continuously evaluated by vital signs and clinical laboratory test results and assessment of the incidence and severity of adverse events according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 4.0. Patient-reported outcomes were evaluated with the use of the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire for cancer (EORTC QLQ–C30).

END POINTS

The coprimary end points were overall survival (the time from randomization to death from any cause) and progression-free survival (the time from randomization to disease progression according to RECIST 1.1, as assessed at an independent review facility, or death from any cause, whichever occurred first). Secondary end points included the objective response rate (the percentage of patients with a confirmed complete or partial response) and the duration of response (the time from first documented complete or partial response to disease progression or death) according to investigator-assessed and independently-assessed RECIST 1.1 and hepatocellular carcinoma–specific modified RECIST (mRECIST)[25] criteria; and the time to deterioration of quality of life, physical functioning, and role functioning, as reported by the patient, with deterioration defined as a decrease from baseline of 10 points or more on the EORTC QLQ–C30 maintained for two consecutive assessments or a decrease of 10 points or more in one assessment followed by death from any cause within 3 weeks. Safety and side-effect profiles were assessed on the basis of the nature, frequency, and severity of adverse events, according to NCI Common Terminology Criteria for Adverse Events, version 4.0. The full list of end points is described in the protocol.

STATISTICAL ANALYSIS

We estimated that a sample size of 480 patients, targeting 312 deaths, would provide 80% power to detect a hazard ratio for overall survival of 0.71 favoring atezolizumab–bevacizumab over sorafenib using a log-rank test at a two-sided 0.048 significance level. The two-sided signifi-

cance level for progression-free survival was 0.002. The overall type I error (0.05) was controlled through the use of a graphical approach[26,27] (see the protocol and the Supplementary Methods and Fig. S1 in the Supplementary Appendix). Independently-assessed objective response rates, according to RECIST 1.1 and hepatocellular carcinoma–specific mRECIST, were also part of the statistical testing hierarchy.

One analysis of progression-free survival, two interim analyses, and a final analysis of overall survival were planned. The primary analysis was to be conducted after approximately 308 occurrences of disease progression or death, and the first interim analysis of overall survival was planned to occur at the same time. By August 29, 2019, a total of 306 instances of disease progression or death, including 161 deaths, had occurred. On the basis of the observed number of deaths, the multiplicity-adjusted, two-sided alpha level for the first interim analysis of overall survival was 0.0033.

Efficacy was assessed in all patients who had been randomly assigned to treatment (the intention-to-treat population). Both overall and progression-free survival were compared between treatment groups with the use of a stratified log-rank test, and hazard ratios for disease progression or death were estimated with a stratified Cox proportional-hazards model. Kaplan–Meier analysis was applied to overall and progression-free survival, duration of response (in patients who had confirmed response), and time to deterioration for patient-reported outcomes. Confirmed response rates were compared between treatment groups with the stratified Cochran–Mantel–Haenszel test. The randomization stratification factors were applied to all stratified efficacy analyses except ECOG performance status. Patients included in safety evaluations were those who had received at least one dose of trial treatment.

RESULTS

PATIENTS AND TREATMENT

Between March 15, 2018, and January 30, 2019, a total of 501 patients at 111 sites in 17 countries (Table S1) were randomly assigned to receive atezolizumab plus bevacizumab (336 patients) or sorafenib (165 patients) and were included in the intention-to-treat population (Fig. S2). Baseline characteristics were generally well balanced between treatment groups (Table 1, and Table S2). Follow-up therapies are summarized in Table S3.

EFFICACY

As of the date of clinical data cutoff (August 29, 2019), the median duration of follow-up was 8.6 months (8.9 months in the atezolizumab–bevacizumab group and 8.1 months in the sorafenib group). A total of 96 patients (28.6%) in the atezolizumab–bevacizumab group and 65 (39.4%) in the sorafenib group died (stratified hazard ratio for death, 0.58; 95% confidence interval [CI], 0.42 to 0.79; P<0.001) (Fig. 1A). Overall survival was significantly longer with atezolizumab–bevacizumab; the estimated rates of survival at 6 months and 12 months were 84.8% (95% CI, 80.9 to 88.7) and 67.2% (95% CI, 61.3 to 73.1), respectively, in the atezolizumab–bevacizumab group and 72.2% (95% CI, 65.1 to 79.4) and 54.6% (95% CI, 45.2 to 64.0) in the sorafenib group.

A total of 197 patients (58.6%) receiving atezolizumab–bevacizumab and 109 patients (66.1%) receiving sorafenib had disease progression or died. Progression-free survival was significantly longer with atezolizumab–bevacizumab than with sorafenib (median, 6.8 months [95% CI, 5.7 to 8.3] vs. 4.3 months [95% CI, 4.0 to 5.6]; stratified hazard ratio for progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001) (Fig. 1B). Progression-free survival at 6 months was 54.5% in the atezolizumab–bevacizumab group and 37.2% in the sorafenib group.

Given that results for progression-free survival were statistically significant, objective response rates were sequentially tested (Table 2). The confirmed objective response rates were 27.3% (95% CI, 22.5 to 32.5) with atezolizumab–bevacizumab and 11.9% (95% CI, 7.4 to 18.0) with sorafenib, according to independent assessment with RECIST 1.1 (P<0.001), and 33.2% (95% CI, 28.1 to 38.6) and 13.3% (95% CI, 8.4 to 19.6), respectively, according to hepatocellular carcinoma–specific mRECIST (P<0.001). Eighteen patients (5.5%) in the atezolizumab–bevacizumab group, as compared with no patients in the sorafenib treatment group, had a complete response. The disease control rate (objective response plus stable disease) was 73.6% with atezolizumab–bevacizu-

Table 1. Patient Characteristics at Baseline.*

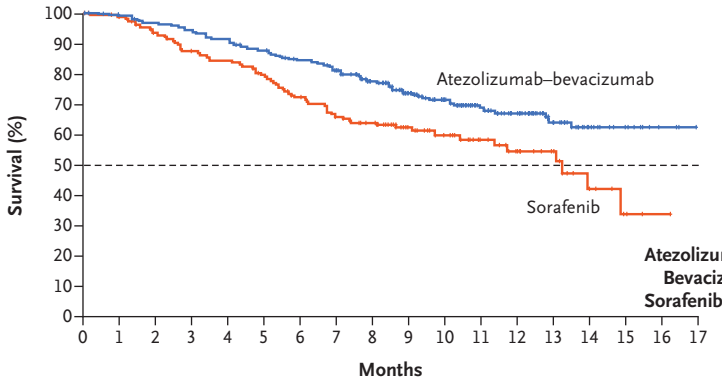
Variable	Atezolizumab–Bevacizumab (N=336)	Sorafenib (N=165)
Median age (IQR) — yr	64 (56–71)	66 (59–71)
Male sex — no. (%)	277 (82)	137 (83)
Geographic region — no. (%)		
Asia, excluding Japan	133 (40)	68 (41)
Rest of the world†	203 (60)	97 (59)
ECOG performance status score — no. (%)‡		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
Child–Pugh classification — no./total no. (%)§		
A5	239/333 (72)	121/165 (73)
A6	94/333 (28)	44/165 (27)
Barcelona Clinic liver cancer stage — no. (%)¶		
A	8 (2)	6 (4)
B	52 (15)	26 (16)
C	276 (82)	133 (81)
Alpha-fetoprotein ≥400 ng per milliliter — no. (%)	126 (38)	61 (37)
Presence of macrovascular invasion, extrahepatic spread, or both — no. (%)	258 (77)	120 (73)
Macrovascular invasion	129 (38)	71 (43)
Extrahepatic spread	212 (63)	93 (56)
Varices — no. (%)		
Present at baseline	88 (26)	43 (26)
Treated at baseline	36 (11)	23 (14)
Cause of hepatocellular carcinoma — no. (%)		
Hepatitis B	164 (49)	76 (46)
Hepatitis C	72 (21)	36 (22)
Nonviral‖	100 (30)	53 (32)
Prior local therapy for hepatocellular carcinoma — no. (%)	161 (48)	85 (52)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† The rest of the world includes the United States, Australia, New Zealand, and Japan.
‡ Eastern Cooperative Oncology Group (ECOG) scores range from 0 to 5, with higher numbers reflecting greater disability.
§ The Child–Pugh liver function scale is a three-category scale (A, with scores of 5 or 6, indicating good hepatic function; B, with scores of 7 to 9, indicating moderately impaired hepatic function; or C, with scores of 10 to 15, indicating advanced hepatic dysfunction). Classification is determined by scoring according to the presence and severity of five clinical measures of liver disease (encephalopathy, ascites, bilirubin levels, albumin levels, and prolonged prothrombin time). Data shown reflect patients in Class A with scores of 5 or 6 and thus good hepatic function. Precise numeric scores for two patients in the atezolizumab–bevacizumab group who were in Class A on the Child–Pugh scale were not available. Data are not included for one patient in the atezolizumab–bevacizumab group whose classification was B7.
¶ The Barcelona Clinic liver cancer staging system ranks hepatocellular carcinoma in 5 stages, beginning at 0 (very early stage) and progressing from A (early stage) to D (terminal stage).
‖ Nonviral causes include alcohol, other, and unknown non-hepatitis B and C causes.

mab and 55.3% with sorafenib (Table 2). Investigator-assessed progression-free survival and objective response rates are summarized in Table S4.

The estimated percentage of patients with duration of response longer than 6 months was 87.6% in the atezolizumab–bevacizumab group and 59.1% in the sorafenib group. We observed

A Overall Survival



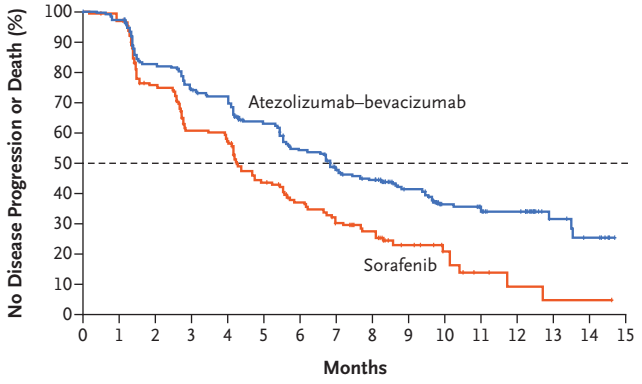
	No. of Events/ No. of Patients (%)	Median Overall Survival (95% CI)	Overall Survival at 6 Mo
		mo	%
Atezolizumab–Bevacizumab	96/336 (28.6)	NE	84.8
Sorafenib	65/165 (39.4)	13.2 (10.4–NE)	72.2

Stratified hazard ratio for death, 0.58 (95% CI, 0.42–0.79)
P<0.001

No. at Risk

Atezolizumab–bevacizumab	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

B Survival without Disease Progression



	No. of Events/ No. of Patients (%)	Median Progression-free Survival (95% CI)	Progression-free Survival at 6 Mo
		mo	%
Atezolizumab–Bevacizumab	197/336 (58.6)	6.8 (5.7–8.3)	54.5
Sorafenib	109/165 (66.1)	4.3 (4.0–5.6)	37.2

Stratified hazard ratio for progression or death, 0.59 (95% CI, 0.47–0.76)
P<0.001

No. at Risk

Atezolizumab–bevacizumab	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE

Figure 1. Kaplan–Meier Analysis of Overall and Progression-free Survival.

Shown are Kaplan–Meier estimates of overall survival (Panel A) and progression-free survival (Panel B), as assessed at an independent review facility according to Response Evaluation Criteria in Solid Tumors, version 1.1, for patients in the intention-to-treat population. Stratified hazard ratios for progression or death are reported, along with P values. The two-sided P-value boundary calculated on the basis of 161 deaths is 0.0033. Randomization was performed through an interactive voice-response or Web-response system, and factors included in the stratified P value and Cox model were geographic region (Asia [excluding Japan] vs. the rest of the world), alpha-fetoprotein level at baseline (<400 ng per milliliter vs. ≥400 ng per milliliter), and macrovascular invasion, extrahepatic spread, or both (yes vs. no). Tick marks indicate censored data. CI denotes confidence interval, and NE could not be evaluated.

similar durations of response using hepatocellular carcinoma–specific mRECIST (Table 2). The overall survival benefit and progression-free survival benefit with atezolizumab–bevacizumab as compared with sorafenib were generally consistent across the clinically relevant subgroups analyzed (Fig. S3).

For patient-reported outcomes, compliance with the EORTC QLQ-C30 questionnaire (defined as completion of at least one question) in the intention-to-treat population was at least 93% from baseline until treatment cycle 17 (56 patients at week 51), and was at least 80% thereafter until treatment was discontinued. Treatment

Table 2. Secondary Efficacy Outcomes.*

Variable	RECIST 1.1			HCC-Specific mRECIST		
	Atezolizumab–Bevacizumab (N=326)	Sorafenib (N=159)	Difference (P Value)†	Atezolizumab–Bevacizumab (N=325)	Sorafenib (N=158)	Difference (P Value)†
Confirmed objective response — no. (% [95% CI])‡	89 (27.3 [22.5–32.5])	19 (11.9 [7.4–18.0])	15.4 (<0.001)	108 (33.2 [28.1–38.6])	21 (13.3 [8.4–19.6])	19.9 (<0.001)
Complete response — no. (%)	18 (5.5)	0		33 (10.2)	3 (1.9)	
Partial response — no. (%)	71 (21.8)	19 (11.9)		75 (23.1)	18 (11.4)	
Stable disease — no. (%)	151 (46.3)	69 (43.4)		127 (39.1)	66 (41.8)	
Disease control rate — no. (%)§	240 (73.6)	88 (55.3)		235 (72.3)	87 (55.1)	
Progressive disease — no. (%)	64 (19.6)	39 (24.5)		66 (20.3)	40 (25.3)	
Could not be evaluated — no. (%)	8 (2.5)	14 (8.8)		10 (3.1)	14 (8.9)	
Data missing — no. (%)	14 (4.3)	18 (11.3)		14 (4.3)	17 (10.8)	
Ongoing objective response at data cutoff — no./total no. (%)	77/89 (86.5)	13/19 (68.4)		84/108 (77.8)	13/21 (61.9)	

* Included are patients who presented with measurable disease according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), and according to hepatocellular carcinoma (HCC)–specific modified RECIST (mRECIST), as assessed at an independent review facility. CI denotes confidence interval.

† The difference is the between-group difference (atezolizumab–bevacizumab minus sorafenib) in the percentage of patients with confirmed response, expressed in percentage points. The P value was derived from a Cochran–Mantel–Haenszel test. Randomization, which was performed through an interactive voice-response or Web-response system, included as stratification factors geographic region (Asia excluding Japan vs. the rest of the world), alpha-fetoprotein level (<400 ng per milliliter vs. ≥400 ng per milliliter) at baseline, and macrovascular invasion, extrahepatic spread, or both (yes vs. no).

‡ Confirmed objective response was defined as a response (complete or partial) seen at two consecutive tumor assessments at least 28 days apart.

§ The control rate is the sum of complete response, partial response, and stable disease.

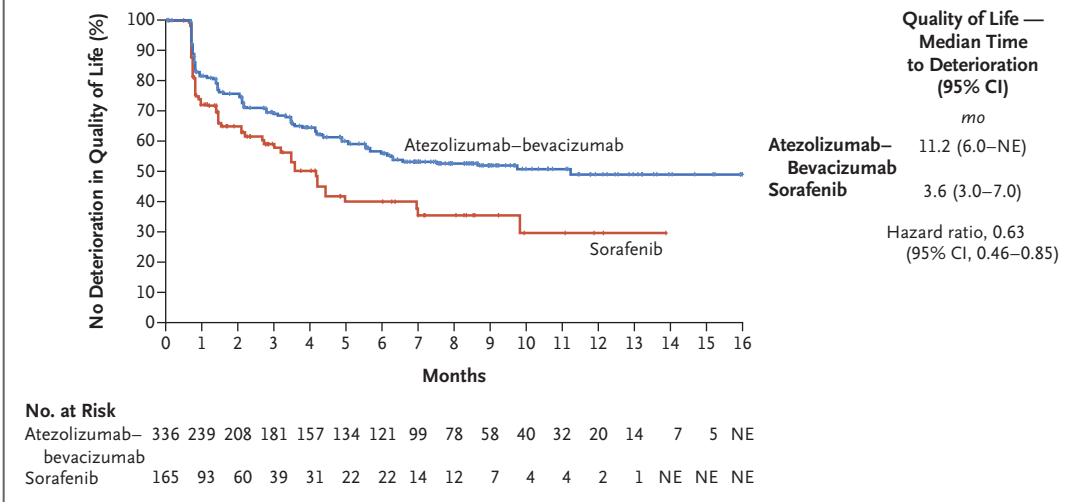


Figure 2. Kaplan–Meier Analysis of Time to Deterioration of Quality of Life.

Shown are Kaplan–Meier estimates of the time to deterioration in quality of life in the intention-to-treat population. Tick marks indicate censored data.

with atezolizumab–bevacizumab delayed deterioration of patient-reported quality of life (median time to deterioration, 11.2 months with atezolizumab–bevacizumab vs. 3.6 months with sorafenib; hazard ratio, 0.63; 95% CI, 0.46 to 0.85) (Fig. 2), physical functioning (median time to deterioration, 13.1 months vs. 4.9 months; hazard ratio, 0.53; 95% CI, 0.39 to 0.73), and role functioning (median time to deterioration, 9.1 months vs. 3.6 months; hazard ratio, 0.62; 95% CI, 0.46 to 0.84) (Fig. S4).

SAFETY

A total of 485 patients received at least one dose of trial treatment (329 received atezolizumab–bevacizumab and 156 received sorafenib) and were included in safety analyses. The median duration of treatment was 7.4 months with atezolizumab, 6.9 months with bevacizumab, and 2.8 months with sorafenib. The mean (±SD) dose intensity was 95±7% for atezolizumab, 93±10% for bevacizumab, and 84±20% for sorafenib; the respective median dose intensities were 98% (range, 54 to 104), 97% (range, 44 to 104), and 96% (range, 27 to 100).

Adverse events of any grade regardless of causality were reported by 323 patients (98.2%) who received atezolizumab–bevacizumab and by 154 patients (98.7%) who received sorafenib (Tables 3 and 4, and Table S5). Grade 5 events occurred in 15 patients (4.6%) in the atezolizumab–bevacizumab group and in 9 patients (5.8%) in the sorafenib group. Serious adverse events occurred more frequently with atezolizumab–bevacizumab (125 patients [38.0%]) than with sorafenib (48 patients [30.8%]). No specific events were responsible for the increased incidence of serious adverse events in the atezolizumab–bevacizumab group. No serious adverse events with a difference between the treatment groups of 2% or more were noted. The most common grade 3 or 4 event with atezolizumab–bevacizumab was hypertension (15.2%), a finding consistent with the known safety profile of bevacizumab. Treatment-related events that occurred in at least 10% of patients (or grade 3 or 4 events that occurred in ≥2%) are listed in Table S6. The percentage of patients who discontinued any treatment component because of adverse events was 15.5% in the atezolizumab–bevacizumab group (7% discontinued both components) and 10.3% in the sorafenib group (Table 3). Adverse events leading to dose modification or interruption occurred in 49.5% of patients who were receiving atezolizumab–bevacizumab and in 60.9% who were receiving sorafenib (Table 3). (Adverse events leading to treatment discontinuation and all-cause adverse events of special interest in patients receiving atezolizumab or bevacizumab are listed in Table S7 and Table S8, respectively.)

Table 3. Adverse Events from Any Cause.

Variable	Atezolizumab–Bevacizumab (N=329)	Sorafenib (N=156)
	number (percent)	
Patients with an adverse event from any cause	323 (98.2)	154 (98.7)
Grade 3 or 4 event*	186 (56.5)	86 (55.1)
Grade 5 event†	15 (4.6)	9 (5.8)
Serious adverse event	125 (38.0)	48 (30.8)
Adverse event leading to withdrawal from any trial drug	51 (15.5)	16 (10.3)
Withdrawal from atezolizumab–bevacizumab	23 (7.0)	—
Adverse event leading to dose modification or interruption of any trial drug	163 (49.5)	95 (60.9)
Dose interruption of any trial treatment	163 (49.5)	64 (41.0)
Dose modification of sorafenib	—	58 (37.2)

* Numbers represent the highest grades assigned.
† Grade 5 events in the atezolizumab–bevacizumab group included gastrointestinal hemorrhage (in 3 patients), pneumonia (in 2 patients), empyema, gastric ulcer perforation, abnormal hepatic function, liver injury, multiple-organ dysfunction syndrome, esophageal varices hemorrhage, subarachnoid hemorrhage, respiratory distress, sepsis, and cardiac arrest (in 1 patient each); grade 5 events in the sorafenib group included death (in 2 patients), hepatic cirrhosis (in 2 patients), cardiac arrest, cardiac failure, general physical health deterioration, hepatitis E, and peritoneal hemorrhage (in 1 patient each).

DISCUSSION

The IMbrave150 trial showed significantly better overall survival and progression-free survival outcomes with atezolizumab plus bevacizumab than with sorafenib in patients with unresectable hepatocellular carcinoma who had received no previous systemic treatment. This benefit was generally consistent across clinical subgroups and confirms previous phase 1b findings that showed the clinical benefit of targeting both angiogenesis and PD-L1 signaling in unresectable liver cancer.[23] The early separation of the Kaplan–Meier curves for overall survival was maintained over time despite a higher proportion of patients in the sorafenib group receiving subsequent systemic therapy, including immunotherapy. In addition, the trial population included a subgroup of particularly high-risk patients. Approximately 40% of patients had macrovascular invasion. The trial also included patients who had macrovascular invasion of the main portal trunk or the portal vein branch contralateral to the primarily involved lobe, bile duct invasion, or at least 50% hepatic involvement (or any combination of these three features) — patients who were excluded from other contemporary phase 3 trials of treatment for hepatocellular carcinoma.[4,7]

The 42% lower hazard of death and the significantly longer overall survival with atezolizumab–bevacizumab than with sorafenib in the IMbrave150 trial is underpinned by a 2.5-month increase in median progression-free survival, a corresponding 41% decrease in the hazard of disease progression or death, and a response rate of 27.3%, as well as the fact that 88% of patients who had a response (complete or partial) continued to have a response at 6 months. Furthermore, in the atezolizumab–bevacizumab group, the median time to deterioration in quality of life and functioning was markedly longer than the median progression-free survival, but this difference was not observed in the sorafenib group. The median duration of sorafenib treatment (2.8 months) was consistent with the median progression-free survival as assessed by the investigators (Table S4), because treatment decisions were made by the investigators according to their assessments of tumor responses.

The spectrum, incidence, and severity of adverse events observed with the combination of atezolizumab and bevacizumab were consistent with the known safety profile of each agent and the underlying disease. Approximately 15% of patients in the atezolizumab–bevacizumab group discontinued treatment owing to adverse events,

Table 4. Adverse Events with an Incidence of More Than 10% in Either Group.

Event	Atezolizumab–Bevacizumab (N=329)		Sorafenib (N=156)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number (percent)			
Hypertension	98 (29.8)	50 (15.2)	38 (24.4)	19 (12.2)
Fatigue	67 (20.4)	8 (2.4)	29 (18.6)	5 (3.2)
Proteinuria	66 (20.1)	10 (3.0)	11 (7.1)	1 (0.6)
Aspartate aminotransferase increase	64 (19.5)	23 (7.0)	26 (16.7)	8 (5.1)
Pruritus	64 (19.5)	0	15 (9.6)	0
Diarrhea	62 (18.8)	6 (1.8)	77 (49.4)	8 (5.1)
Decreased appetite	58 (17.6)	4 (1.2)	38 (24.4)	6 (3.8)
Pyrexia	59 (17.9)	4 (1.2)	15 (9.6)	2 (1.3)
Alanine aminotransferase increase	46 (14.0)	12 (3.6)	14 (9.0)	2 (1.3)
Constipation	44 (13.4)	0	22 (14.1)	0
Blood bilirubin increase	43 (13.1)	8 (2.4)	22 (14.1)	10 (6.4)
Rash	41 (12.5)	0	27 (17.3)	4 (2.6)
Abdominal pain	40 (12.2)	4 (1.2)	27 (17.3)	4 (2.6)
Nausea	40 (12.2)	1 (0.3)	25 (16.0)	1 (0.6)
Cough	39 (11.9)	0	15 (9.6)	1 (0.6)
Infusion-related reaction	37 (11.2)	8 (2.4)	0	0
Weight decrease	37 (11.2)	0	15 (9.6)	1 (0.6)
Platelet count decrease	35 (10.6)	11 (3.3)	18 (11.5)	2 (1.3)
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Asthenia	22 (6.7)	1 (0.3)	21 (13.5)	4 (2.6)
Alopecia	4 (1.2)	0	22 (14.1)	0
Palmar–plantar erythrodysesthesia syndrome	3 (0.9)	0	75 (48.1)	13 (8.3)

as compared with 10% of patients in the sorafenib group. Gastrointestinal disorders were the most common reason for discontinuation in the atezolizumab–bevacizumab group, as expected in patients with liver cancer and underlying cirrhosis. Bleeding (including fatal events) is a known adverse reaction to bevacizumab, and upper gastrointestinal bleeding is a common and life-threatening complication in patients with cirrhosis and hepatocellular carcinoma. In this trial, patients had to be evaluated for the presence of varices before enrollment, and varices of any size were assessed and treated as needed according to local standards of care. Overall, the incidence of upper gastrointestinal bleeding observed in the atezolizumab–bevacizumab group was 7% (as compared with 4.5% in the sorafenib group), which is consistent with historical data in other trials of bevacizumab for hepatocellular carcinoma.[20,21]

Previous studies of single-agent checkpoint inhibitors failed to show a survival benefit in patients with hepatocellular carcinoma.[7,8] The randomized portion of the phase 1b study GO30140 showed significantly better progression-free survival outcomes with atezolizumab plus bevacizumab than with monotherapy with atezolizumab,[23] which suggests that both atezolizumab and bevacizumab contribute to the overall treatment benefit of the combination in patients with hepatocellular carcinoma.

In patients with previously untreated metastatic renal cell carcinoma, PD-L1 positivity has been shown to be associated with longer pro-

gression-free survival in patients who receive the combination of atezolizumab and bevacizumab than in patients who receive sunitinib.[28] However, the predictive value of PD-L1 status for the efficacy of PD-L1 and PD-1 inhibitors or combination therapies has not been clearly shown in the case of hepatocellular carcinoma.[5,8,23] Further tissue or blood-based biomarker analyses (or both) will need to be conducted to identify biomarkers of response and to determine the patients who would benefit most from atezolizumab–bevacizumab therapy.

The trial has several limitations. The open-label design was used to spare patients from two placebo infusions. To minimize the potential bias associated with the open-label design, a blinded independent review of imaging for progression-free survival was selected for the coprimary end point. The trial was conducted in a patient population that had preserved liver function (Child–Pugh class A) and a decreased risk of variceal bleeding. The safety of the combination in a broader population warrants further study.

In conclusion, treatment with atezolizumab plus bevacizumab was associated with significantly better overall survival and progression-free survival outcomes than sorafenib in patients with advanced unresectable hepatocellular carcinoma not previously treated with systemic therapy. Serious toxic effects were noted in 38% of the patients who received the combination therapy; however, no new or unexpected toxic effects were observed. The combination therapy also resulted in a longer time to deterioration of patient-reported quality of life and functioning than sorafenib.

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APPENDIX

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