



# FDA Approval Summary: Atezolizumab Plus Bevacizumab for the Treatment of Patients with Advanced Unresectable or Metastatic Hepatocellular Carcinoma

Sandra J. Casak<sup>1</sup>, Martha Donoghue<sup>1</sup>, Lola Fashoyin-Aje<sup>1</sup>, Xiaoping Jiang<sup>1</sup>, Lisa Rodriguez<sup>1</sup>, Yuan-Li Shen<sup>1</sup>, Yuan Xu<sup>1</sup>, Xiling Jiang<sup>1</sup>, Jiang Liu<sup>1</sup>, Hong Zhao<sup>1</sup>, William F. Pierce<sup>1</sup>, Shubhangi Mehta<sup>1</sup>, Kirsten B. Goldberg<sup>1,2</sup>, Marc R. Theoret<sup>1,2</sup>, Paul G. Kluetz<sup>1,2</sup>, Richard Pazdur<sup>1,2</sup>, and Steven J. Lemery<sup>1</sup>

## ABSTRACT

On May 29, 2020, the FDA approved atezolizumab for use in combination with bevacizumab, for the treatment of adult patients with unresectable locally advanced or metastatic hepatocellular carcinoma (HCC) with no prior systemic treatment. The approval was based on data from Study IMbrave150, which randomly allocated (2:1) patients to receive either atezolizumab plus bevacizumab (atezolizumab-bevacizumab) or sorafenib. Overall survival (OS) and independently assessed progression-free survival (PFS) in the intent-to-treat population were the primary endpoints. At the time of the primary analysis, the estimated median OS could not be estimated in the atezolizumab-bevacizumab arm and was 13.2 months in the sorafenib arm [HR, 0.58; 95% confidence interval (CI), 0.42–0.79]. The estimated median PFS was 6.8 months (95% CI, 5.8–8.3) and 4.3 months (95% CI, 4.0–5.6) in the atezolizumab-bevacizumab and sorafenib arms,

respectively. Adverse reactions occurring in >20% of patients receiving atezolizumab-bevacizumab were hypertension, fatigue/asthenia, and proteinuria. Adverse reactions occurring in >20% of patients receiving sorafenib were palmar-plantar erythrodysesthesia, diarrhea, hypertension, and decreased appetite. Hemorrhage was reported more frequently in patients receiving atezolizumab-bevacizumab (25%) than in patients receiving sorafenib (17%). An evaluation for the presence of varices is recommended within 6 months of initiation of atezolizumab-bevacizumab in patients with HCC. Approval of atezolizumab-bevacizumab is likely to change the treatment paradigm for HCC, given that treatment with atezolizumab-bevacizumab resulted in improved OS and PFS compared with sorafenib, an accepted standard of care for first-line treatment of patients with unresectable HCC.

See related commentary by Castet et al., p. 1827

## Introduction

It is estimated that in 2020, 42,810 adults in the United States will be diagnosed with primary liver cancer and 30,160 deaths from this disease will occur (1). At diagnosis most patients have advanced disease with only 44% of patients having early-stage disease (2), which may be curable by surgery, ablation, or liver transplantation. With currently available treatment options, the 5-year overall survival (OS) for patients with locally advanced or metastatic hepatocellular carcinoma (HCC) is estimated to be around 12% and 2.5%, respectively (2).

Atezolizumab (Tecentriq, Genentech Inc.) is a humanized monoclonal IgG1 antibody that binds to programmed death-ligand 1 (PD-L1) and blocks its interactions with the PD-1 and B7.1 receptors, both of which function as inhibitory receptors expressed on T cells. Blockade of PD-L1 binding (checkpoint inhibition) increases the magnitude of tumor-specific T-cell responses. Atezolizumab is approved for

various indications and settings in the treatment of bladder cancer, lung cancer, and breast cancer. Bevacizumab (Avastin, Genentech Inc.) is a humanized monoclonal IgG1 antibody that binds the VEGF ligand and inhibits angiogenesis. It is approved for various indications and settings in the treatment of colorectal cancer, lung cancer, glioblastoma, renal cancer, cervical cancer, and ovarian cancer.

Inhibition of angiogenesis with VEGF-targeting tyrosine kinases, like sorafenib, lenvatinib, cabozantinib, and regorafenib, as well as ramucirumab, a mAb targeting the VEGFR2, has been a relatively successful strategy resulting in the approval of these drugs for the first- or second-line treatment of HCC based on studies demonstrating modest improvements in survival in randomized clinical trials. Early studies with bevacizumab showed activity in advanced HCC, with reported response rates of 13% to 14% in two single-agent studies (3, 4). Checkpoint inhibition in patients with previously treated HCC with nivolumab (5), pembrolizumab (6), and the combination nivolumab/ipilimumab (7) led to overall response rates (ORR; as per RECIST) of 14%, 17%, and 33% respectively, characterized by long durability; however, the reported results of randomized trials have not verified the treatment benefit based on these response rates to date (8, 9). The VEGF pathway plays a role in exerting and maintaining an immunosuppressive tumor microenvironment (10). Blocking this pathway may increase intratumoral T-cell recruitment and therefore, be synergistic with checkpoint inhibition.

The authors summarize the FDA's review of data supporting the approval of atezolizumab in combination with bevacizumab for the treatment of patients with locally advanced or metastatic HCC. The investigators' analyses and interpretation of the data have been previously published (11, 12).

<sup>1</sup>Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland. <sup>2</sup>Oncology Center of Excellence, U.S. Food and Drug Administration, Silver Spring, Maryland.

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**Corresponding Author:** Sandra J. Casak, United States Food and Drug Administration, 10993 New Hampshire Ave blg 22 #2387, Silver Spring, MD 20993. Phone: 301-796-3812; Fax: 301-796-3220; E-mail: sandra.casak@fda.hhs.gov

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## Clinical Trial Design

IMbrave150 (NCT03434379) was an open-label, randomized (2:1) two-arm trial in patients with locally advanced or metastatic HCC who had not received prior systemic therapy. Eligible patients had measurable disease that was not amenable to curative or locoregional treatment at the time of enrollment, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, Child–Pugh A score, and adequate hematologic and organ function. Patients with hepatitis B and C coinfection, untreated or incompletely treated esophageal or gastric varices with bleeding or high risk of bleeding [as per esophagogastroduodenoscopy (EGD) assessment within 6 months prior to initiation of study treatment], moderate or severe ascites, history of hepatic encephalopathy, and who otherwise did not meet criteria to receive atezolizumab and bevacizumab, were excluded. Randomization was stratified by geographic region (Asia, excluding Japan vs. the rest of the world), macrovascular invasion or extrahepatic spread of disease (presence vs. absence), alpha fetoprotein level (<400 vs. ≥400 ng/mL), and ECOG PS (0 vs. 1). Patients received either atezolizumab 1,200 mg and bevacizumab 15 mg/kg via intravenous infusion on day 1 of every 21-day cycle or sorafenib 400 mg twice daily. Treatment was administered until intolerable toxicity or disease progression. Disease response and progression were measured at baseline and every 6 weeks, until week 54, and every 9 weeks thereafter. The primary endpoints were OS and independently assessed progression-free survival (PFS) in the intent-to-treat (ITT) population. Key secondary endpoints were independently and investigator-assessed ORR, as well as duration of response using RECIST 1.1 (13) and RECIST modified for HCC (mRECIST; ref. 14).

With a planned sample size of 480 patients with 312 events (deaths), the study had 80% power to detect an HR of 0.71 for OS using a log-rank test at a two-sided significance level of 0.048 (median improvement vs. control of 4.9 months) and 97% power to detect an HR of 0.55 in PFS (median improvement vs. control of 3.3 months) using a log-rank test at a two-sided significance level of 0.002. One analysis of PFS, two interim OS analyses, and one final OS analysis were planned. The two-sided alpha allocated for the first interim analysis of OS was 0.0033.

The efficacy analyses were conducted in the ITT population, defined as all patients who were randomly assigned to treatment. The stratified log-rank test was used to compare OS and PFS between arms and the Cox proportional hazard model was used to estimate the HRs. Kaplan–Meier method was applied to summarize OS, PFS, and duration of response. The Cochran–Mantel–Haenszel test was used to compare

ORR. Safety was analyzed in patients who received at least one dose of study treatment.

## Results

### Efficacy

A total of 501 patients were randomized between the two arms (336 to atezolizumab-bevacizumab and 165 to sorafenib). Baseline demographics and disease characteristics for patients in the ITT population were balanced (Table 1). The study enrolled 10 patients (2%) across both arms who identified as Black or African American.

At the first prespecified interim analysis of survival (data cutoff, 29 August 2019), 306 PFS events and 161 deaths were observed. With a median follow-up duration of 8.6 months, IMbrave150 demonstrated a clinically meaningful and statistically significant improvement in OS, with an HR of 0.58 [95% confidence interval (CI), 0.42–0.79;  $P < 0.001$ ]; the estimated median OS difference could not be calculated [not estimable (NE) vs. 13.2 months in the sorafenib arm; Fig. 1]. A statistically significant improvement in PFS was also demonstrated, with an HR of 0.59 (95% CI, 0.47–0.76;  $P < 0.001$ ); the estimated median PFS was 6.8 months (95% CI, 5.8–8.3) versus 4.3 months (95% CI, 4.0–5.6) in the atezolizumab-bevacizumab and sorafenib arms, respectively (Fig. 2).

In the ITT population, the independently assessed ORR per RECIST was 27.7% (95% CI, 23.0%–32.8%) in the atezolizumab-bevacizumab arm versus 11.5% (95% CI, 7.1%–17.4%) in the sorafenib arm; ORR per mRECIST was 33.3% (95% CI, 28.3%–38.7%) in the atezolizumab-bevacizumab arm versus 12.7% (95% CI, 8.1%–18.8%) in the sorafenib arm. The median response duration could not be estimated in the atezolizumab-bevacizumab arm and was estimated at 6.3 months (95% CI, 4.7, NE) in the sorafenib arm (both per RECIST 1.1 and mRECIST). Efficacy analyses are summarized in Table 2.

The overall treatment effect was generally consistent across subgroups, with the exception of a subset of patients (20%) in whom antidrug antibodies (ADA) against atezolizumab were detected by week 6. In an exploratory analysis, the OS HR was 0.93 (95% CI, 0.57–1.53) comparing the ADA-positive subgroup of the atezolizumab-bevacizumab arm with sorafenib, and was 0.39 (95% CI, 0.26–0.60) comparing the ADA-negative subgroup with sorafenib.

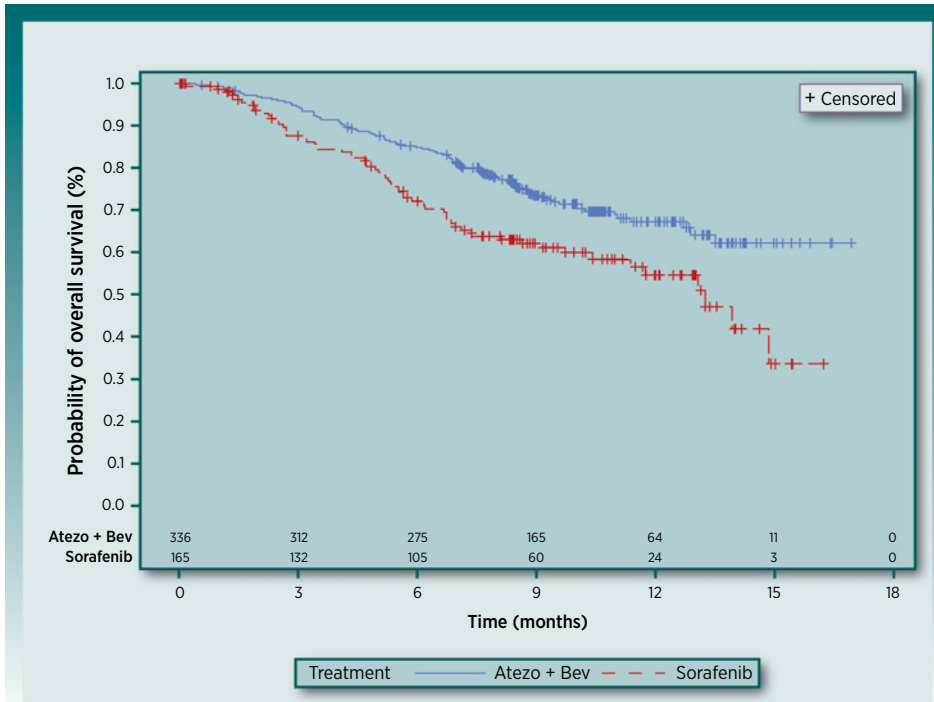
### Safety

The safety analysis was based on 485 patients who received at least one dose of atezolizumab-bevacizumab ( $n = 329$ ) or sorafenib ( $n = 156$ ). The most common treatment-emergent adverse events (TEAE,

**Table 1.** Study IMbrave150: baseline demographics and disease characteristics.

	Atezolizumab-bevacizumab (N = 336)	Sorafenib (N = 165)
Median age, years (range)	64 (26–88)	66 (33–87)
Male sex, n (%)	277 (82%)	137 (83%)
Asian country (excluding Japan)	133 (40%)	68 (41%)
ECOG PS 0/1, n (%)	209 (62%)/127 (38%)	103 (62%)/62 (37%)
BCLC, n (%)	276 (82%)	133 (81%)
Hepatitis B/C, n (%)	164 (49%)/72 (21%)	76 (46%)/36 (22%)
EHS and/or MVI	258 (77%)	120 (73%)
Child Pugh A5/A6, n (%)	239 (72%)/94 (28%)	121 (73%)/44 (27%)
AFP ≥ 400 ng/mL	126 (38%)	61 (37%)
Varices at enrollment	88 (26%)	43 (26%)

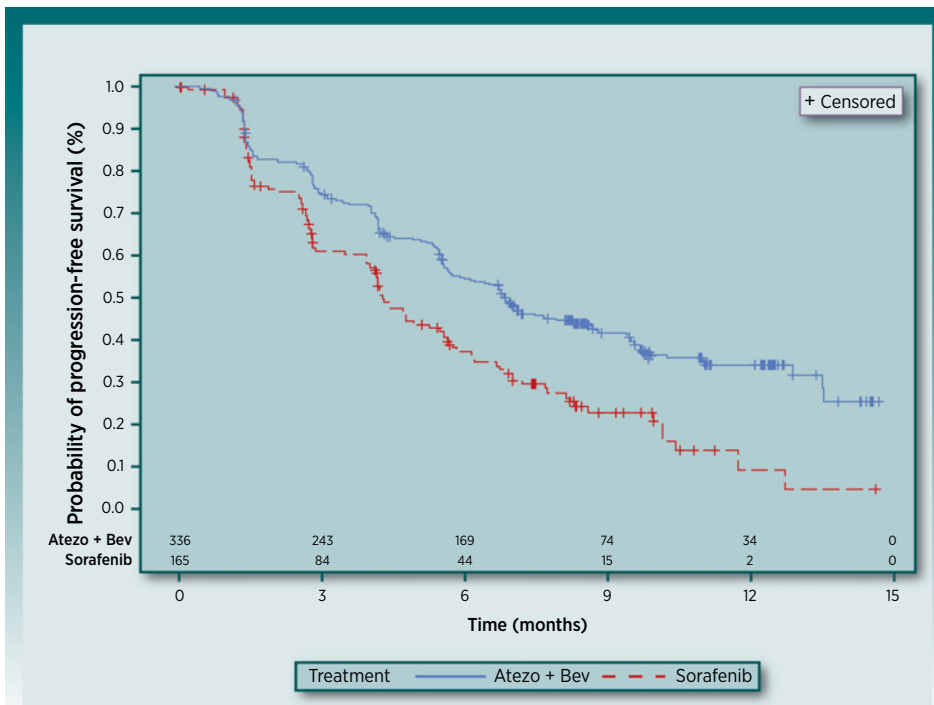
Abbreviations: AFP, alpha-feto protein; BCLC, Barcelona Clinic Liver Cancer; EHS, extra hepatic disease; MVI, macrovascular invasion.



**Figure 1.** IMbrave150, Kaplan-Meier curves of OS. Atezo, atezolizumab; bev, bevacizumab.

>15%) in the combination arm were hypertension (30%), fatigue/asthenia (20%), proteinuria (20%), diarrhea (19%), pruritus (19%), decreased appetite (18%), and fever (18%); and in the sorafenib arm, TEAEs >15% were diarrhea (49%), palmar-plantar erythrodysesthesia (48%), hypertension (24%), decreased appetite (24%), fatigue/asthenia (19%), abdominal pain (17%), rash (17%), and nausea (16%).

The most common grade 3–4 TEAEs occurring in  $\geq 4\%$  of patients in the combination arm were hypertension (15%) and fatigue/asthenia (7%); and in the sorafenib arm, grade 3–4 TEAEs occurring in  $\geq 4\%$  were hypertension (12%), palmar-plantar erythrodysesthesia (8%), fatigue/asthenia (7%), diarrhea (5%), decreased appetite (4%), and hypophosphatemia (4%).



**Figure 2.** IMbrave150, Kaplan-Meier curves of PFS. Atezo, atezolizumab; bev, bevacizumab.

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**Table 2.** Study IMbrave150: efficacy results.

	Atezolizumab-bevacizumab (N = 336)	Sorafenib (N = 165)
OS		
Number of deaths (%)	96 (29%)	65 (39%)
Median OS in months (95% CI)	NE (NE-NE)	13.2 (10.4,NE)
HR <sup>a</sup> (95% CI), P <sup>b</sup>		0.58 (0.42-0.79), 0.0006 <sup>2</sup>
PFS <sup>c</sup>		
Number of events (%)	197 (59%)	109 (66%)
Median PFS in months (95% CI)	6.8 (5.8-8.3)	4.3 (4.0-5.6)
HR <sup>a</sup> (95% CI), P		0.59 (0.47-0.76), <0.0001
Overall response rate <sup>c, e</sup> (ORR), RECIST 1.1		
Number of responders (%) (95% CI)	93 (28%), (23%-33%)	19 (12%), (7%-17%)
P <sup>d</sup>		<0.0001
Complete responses, n (%)	22 (7%)	0
Partial responses, n (%)	71 (21%)	19 (12%)
Median duration of response, months (95% CI)	NE (NE-NE)	6.3 (4.7, NE)
Range, months	(1.3+–13.4+)	(1.4+–9.1+)
ORR <sup>c, e</sup> , mRECIST		
Number of responders (%) (95% CI)	112 (33%), (28–39)	21 (13%), (8–19)
P		<0.0001
Complete responses, n (%)	37 (11%)	3 (1.8%)
Partial responses, n (%)	75 (22%)	18 (11%)
Median duration of response, months (95% CI)	NE (NE-NE)	6.3 (4.9 NE)
Range, months	(1.3+–13.4+)	(1.4+–9.1+)

Note: RECIST 1.1, refs. 15, 16.

Abbreviations: N/A, not applicable; NE, not estimable.

<sup>a</sup>Stratified by geographic region (Asia, excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL).

<sup>b</sup>On the basis of two-sided stratified log-rank test; compared to significance level 0.004 (two-sided), based on 161/312 = 52% information using the OBF method.

<sup>c</sup>Per independent radiology review.

<sup>d</sup>On the basis of two-sided Cochran–Mantel–Haenszel test.

<sup>e</sup>Confirmed responses, +, denotes a censored value.

Hemorrhagic events were more common in the atezolizumab-bevacizumab arm (25% vs. 17%), and epistaxis, hematuria, and gingival bleeding were the most frequent events (grades 1–2 in all, but 2 patients). **Table 3** lists grade 3–4 hemorrhagic events. Laboratory abnormalities were common in both arms; grade 3–4 events that occurred in ≥2% of patients in the atezolizumab-bevacizumab arm were increased alanine aminotransferase (8%), decreased sodium (13%), increased glucose (9%), and decreased platelets (7%).

Fatal TEAEs were reported in 5% and 6% of patients in the atezolizumab-bevacizumab and sorafenib arms, respectively. The leading causes of death were hemorrhage, five (1.5%, four gastrointestinal and one subarachnoid) in the atezolizumab-bevacizumab arm versus one (0.6%, peritoneal) in the sorafenib arm; and infection, four (1.2%) in the atezolizumab-bevacizumab arm versus one (0.6%) in the sorafenib arm.

The median duration of exposure to atezolizumab was 7.4 months (range, 0–16 months) and to bevacizumab was 6.9 months (range, 0–16 months). Atezolizumab treatment was permanently discontinued because of toxicity in 28 (9%) patients and bevacizumab was discontinued because of toxicity in 48 (15%) patients. The most common adverse reactions leading to discontinuation of atezolizumab were hemorrhagic events (1.2%), increased transaminases or bilirubin (1.2%), infusion-related reaction/cytokine release syndrome (0.9%), and autoimmune hepatitis (0.6%). The most common adverse reactions leading to bevacizumab discontinuation were hemorrhagic events (4.9%) and increased transaminases or bilirubin (0.9%). Sor-

afenib was permanently discontinued because of toxicity in 10% of patients, mostly related to liver or skin toxicities.

## Regulatory Considerations

This is the first FDA approval demonstrating an improvement in survival for immunotherapy in HCC. Sorafenib was approved in 2007 on the basis of a survival benefit and lenvatinib was approved in 2018 on the basis of noninferiority of survival and improved PFS when compared with sorafenib. IMbrave150 showed significantly better OS in patients receiving atezolizumab-bevacizumab compared with patients receiving sorafenib. The study results, in a population of patients with high-risk features (75% patients had baseline macrovascular invasion or extrahepatic spread), are robust and consistent across subgroups of patients. The combination also resulted in a statistically significant improvement in PFS and an improvement in ORR.

The FDA review of the application also considered the results of a single-arm cohort from Study GO30140 (arm A) that enrolled 104 patients with metastatic HCC and no had prior systemic therapy treatment with atezolizumab in combination with bevacizumab. Arm A of Study GO30140, which was included in the applications to provide supportive evidence of efficacy, demonstrated an independently assessed ORR of 35.6% (95% CI, 26.4%–45.6%; RECIST 1.1), with 11.5% of patients with complete response.

A separate randomized (1:1) component of Study GO30140 (arm F), which randomized 119 patients, favored the atezolizumab-

**Table 3.** Study IMbrave150: hemorrhage/bleeding events with at least one grade 3–4 event.

Adverse event (preferred term)	Atezolizumab-bevacizumab N = 329; n (%)		Sorafenib N = 156; n (%)	
	All grades	Grades 3–4	All grades	Grades 3–4
Epistaxis	34 (10)	0	7 (4)	1 (1)
Hematuria	10 (3)	1 (<1)	0	0
Gastrointestinal hemorrhage	8 (2)	4 (1)	3 (2)	3 (2)
Rectal hemorrhage	5 (2)	1 (<1)	3 (2)	0
Esophageal varices hemorrhage	8 (2)	6 (2)	1	1 (1)
Upper gastrointestinal hemorrhage	4 (1)	2 (1)	2 (1)	2 (1)
Esophageal hemorrhage	3 (1)	2 (1)	0	0
Hematemesis	2 (1)	2 (1)	0	0
Hemorrhage	2 (1)	1 (<1)	0	0
Gastric varices hemorrhage	1 (0)	1 (<1)	1 (1)	1 (1)
Gastric ulcer hemorrhage	0	0	1 (1)	1 (1)
Peritoneal hemorrhage	0	0	2 (1)	1 (1)
Bleeding varicose vein	1 (1)	1 (<1)	0	0
Large intestinal hemorrhage	1	1 (<1)	0	0
Pulmonary hemorrhage	1	1 (<1)	0	0

bevacizumab combination over single-agent atezolizumab on PFS [HR, 0.55 (95% CI, 0.34–0.88)]; these results provided support for the use of bevacizumab as part of the combination regimen.

The median length of treatment in IMbrave150 was more than double in the atezolizumab-bevacizumab arm compared with the sorafenib arm (7.4 vs. 2.8 months). Although the safety profile of adverse events observed with the atezolizumab-bevacizumab combination was consistent with the known safety profile of each agent, consideration should be given to the bleeding risk. The IMbrave150 protocol required an EGD assessment within 6 months of enrollment. Patients with untreated or incompletely treated varices with bleeding, or high risk of bleeding were excluded from enrollment in the study.

FDA also considered the effects of ADA formation during the review of the application. Overall, 28% of 315 evaluable patients developed ADAs at one or more timepoints during the study. An exploratory analysis to assess the impact of ADA formation on OS, compared patients with early ADA formation (i.e., by week 6) with ADA-negative patients; the results of this analysis suggests a reduced effect on OS compared with ADA-negative patients [HR of ADA-positive patients vs. sorafenib was 0.93 (95% CI, 0.57–1.53)]. Consistent results were observed in sensitivity analyses adjusting for the effects of various prognostic factors (15). There is currently no known method to predict who may develop ADAs, and no FDA-approved commercial test to identify patients who may develop ADA during treatment with Tecentriq. Furthermore, to date, data are not available to guide treatment decisions in patients who develop ADAs. Importantly, to provide guidance on this issue, Genentech is performing an overall assessment of the effects of ADAs (including neutralizing antibodies) in various conditions of use as part of post marketing commitments for a prior approval in patients with non-small cell lung cancer.

Results of Study IMbrave150 will likely lead to a change in the treatment paradigm for the first-line treatment of patients with HCC, with atezolizumab-bevacizumab likely being selected as the preferred standard of care for patients who are eligible to receive the combination. Prior to the approval of atezolizumab-bevacizumab, nivolumab and pembrolizumab received accelerated approval for use as single agents in the second-line setting following sorafenib. In the trials that supported these approvals, patients had received prior treatment with single-agent kinase inhibitors. Clinical trials to address important

questions regarding the optimal sequencing of therapies in patients who progress on or following treatment with atezolizumab-bevacizumab are needed. We also acknowledge, however, that the treatment landscape may further change if other immunotherapy strategies are successful in clinical trials in the first-line setting in HCC.

Important limitations of the IMbrave150 trial and Study GO30140 include the selection of patients with relatively conserved liver function and lower bleeding risk in the study populations, compared with the broader HCC population; therefore, insufficient data exist to provide guidance on safety or efficacy in patient populations not studied (e.g., with more compromised liver function). Given the risk of bleeding in patients with advanced HCC, FDA revised the hemorrhage Warning in the Avastin U.S. Prescribing Information (16) to recommend that patients with HCC be evaluated for the presence of esophageal varices within 6 months of initiation of Avastin in patients with HCC. In addition, only 10 of 501 patients (2%) in IMbrave150 identified as Black or African American, a finding that is consistent with trials supporting other approvals for HCC. Given that age-adjusted incidence and mortality of HCC are higher in Black patients compared with White patients in the United States (17), increased efforts are needed to enroll a more representative patient population in future clinical trials.

## Conclusions

In summary, the combination of atezolizumab-bevacizumab for the treatment of patients with metastatic HCC has a favorable benefit-risk profile, with a meaningful improvement in survival demonstrated in Study IMbrave150. Although no new safety signals were detected, use of bevacizumab may increase the risk of bleeding in patients with HCC, who should be screened for the presence of esophageal varices or other risk factors for serious bleeding prior to treatment with atezolizumab-bevacizumab. Overall, the safety profile of the combination is acceptable given the demonstrated benefits in patients with metastatic HCC, in properly selected patients.

The combination of atezolizumab-bevacizumab for the first-line treatment of HCC was approved on May 29, 2020. The applications were reviewed under various programs designed to expedite the review of applications for patients with cancer including the Real-Time Oncology program entailing early receipt of datasets prior to

application submission; Assessment Aid (a voluntary review template submission from the applicant to facilitate FDA's assessment); and Project Orbis, under which FDA reviewed the atezolizumab application in collaboration with Singapore's Health Science Authority, Health Canada, and Australia's Therapeutic Goods Administration. Although collaboration under Project Orbis fostered discussion of issues pertinent to the review of the atezolizumab application, the application review was ongoing in Singapore, Canada, and Australia at the time that FDA approved the application.

### Authors' Disclosures

No disclosures were reported.

### Disclaimer

The Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose.

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