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Efficacy and Safety of Atezolizumab plus Bevacizumab versus Sorafenib in Hepatocellular Carcinoma with Main Trunk and/or Contralateral Portal Vein Invasion in IMbrave150

Richard S. Finn[a] Peter R. Galle[b] Michel Ducreux[c] Ann-Lii Cheng[d] Norelle Reilly[e] Alan Nicholas[e] Sairy Hernandez[e] Ning Ma[e] Philippe Merle[f] Riad Salem[g] Daneng Li[h] Valeriy Breder[i]

[a]Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [b]University Medical Center Mainz, Mainz, Germany; [c]Paris-Saclay University, Gustave Roussy and INSERM-U1279, Collective Invasion, Villejuif, France; [d]National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan; [e]Genentech Inc, South San Francisco, CA, USA; [f]Croix-Rousse University Hospital, Lyon, France; [g]Northwestern University, Chicago, IL, USA; [h]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [i]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia

Keywords
Portal vein tumor thrombosis · Vp4 · High-risk prognostic factors · PD-L1 inhibitor · Immunotherapy

Abstract

Introduction: Atezolizumab plus bevacizumab significantly improved overall survival (OS) and progression-free survival (PFS) versus sorafenib in patients with unresectable hepatocellular carcinoma (HCC) in IMbrave150. Efficacy and safety in patient subpopulations with Vp4 portal vein tumor thrombosis (PVTT) and other high-risk prognostic factors are reported. ***Methods:*** IMbrave150 was a global, randomized (2:1), open-label, phase 3 study in systemic treatment–naive patients with unresectable HCC; OS and PFS were co-primary endpoints. Exploratory analyses compared the efficacy and safety of atezolizumab 1,200 mg plus bevacizumab 15 mg/kg every 3 weeks versus sorafenib 400 mg twice daily in patients (i) with and without Vp4 PVTT alone and (ii) with and without high-risk prognostic factors. ***Results:*** In patients with Vp4 PVTT, median OS was 7.6 months (95% CI: 6.0–13.9) with atezolizumab plus bevacizumab ($n = 48$) and 5.5 months (95% CI: 3.4–6.7) with sorafenib ($n = 25$; HR 0.62 [95% CI: 0.34–1.11]; descriptive $p = 0.104$). Median PFS in the respective arms was 5.4 months (95% CI: 3.6–6.9) and 2.8 months (95% CI: 1.5–5.3; HR 0.62 [95% CI: 0.35–1.09]; descriptive $p = 0.094$). In patients without Vp4, median OS was 21.1 months (95% CI: 18.0–24.6) with atezolizumab plus bevacizumab ($n = 288$) and 15.4 months (95% CI: 12.6–18.6) with sorafenib ($n = 140$; HR 0.67 [95% CI: 0.51–0.88]; descriptive $p = 0.003$). Median PFS in the respective arms was 7.1 months (95% CI: 6.1–9.6) and 4.7 months (95% CI: 4.2–6.1; HR 0.64 [95% CI: 0.51–0.81]; descriptive $p < 0.001$). The high-risk versus non–high-risk populations had similar outcome patterns. In the respective treatment arms, grade ≥3 treatment-related adverse events occurred in 43% and 48% of patients with Vp4 and 46% and 47% of patients without Vp4. ***Conclusion:*** Regardless of VP4 PVTT or other high-risk features of

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karger@karger.com
www.karger.com/lic

Correspondence to:
Richard S. Finn, rfinn@mednet.ucla.edu

unresectable HCC, which have often resulted in exclusion from other front-line trials, patients benefited from atezolizumab and bevacizumab versus sorafenib.

Introduction

Hepatocellular carcinoma (HCC) accounts for more than three-quarters of liver cancers [1]. An aggressive biological characteristic is the tendency to invade the portal vein, resulting in portal vein tumor thrombosis (PVTT) [1]. PVTT is one of the most common complications of HCC and is present in 10–40% of patients at diagnosis [2]. It is a very poor prognostic sign, and without intervention, the median overall survival (OS) in affected patients can be as short as 2–4 months [2].

The extent of PVTT can be classified according to the degree of tumor involvement in anatomical branches of the portal vein; classifications include Vp1 (thrombus distal to the second-order branches of the portal vein but no direct involvement), Vp2 (invasion of the second-order branches of the portal vein), Vp3 (thrombus in the first-order branch [i.e., right or left portal vein]), and Vp4 (thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe or both) (Fig. 1) [3]. PVTT, along with the extent of PVTT, Child-Pugh score, α-fetoprotein (AFP) level, and tumor size, are robust predictors of survival and death from HCC [4, 5].

For a decade, sorafenib was the global standard of care for front-line therapy for advanced HCC. However, in 2018, lenvatinib was approved as a first-line treatment after demonstrating noninferiority to sorafenib and improved secondary endpoints in the REFLECT trial [6]. In 2020, the primary analysis of the IMbrave150 study in patients with unresectable HCC showed atezolizumab plus bevacizumab to be the first regimen to improve OS in the first-line setting versus sorafenib (OS hazard ratio [HR] 0.58 [95% CI: 0.42–0.79]; $p < 0.001$) [7], and atezolizumab plus bevacizumab became a new global standard of care. Updated efficacy analyses of IMbrave150 after 15.6 months' follow-up demonstrated a median OS of 19.2 months versus 13.4 months with sorafenib (HR 0.66 [95% CI: 0.52–0.85]) [8]. The combination of atezolizumab and bevacizumab is well tolerated, even in older patients [9]. Evidence from a meta-analysis of current HCC therapies supported superior efficacy benefits with atezolizumab plus bevacizumab in patients with unresectable HCC versus other available tyrosine kinase inhibitors, immunotherapies, and locoregional treatment options [10].

Patients with high-risk prognostic indicators, which include PVTT as well as bile duct invasion and/or ≥50% liver involvement, have often been excluded from pivotal HCC trials due to their association with a poor prognosis and hemodynamic changes from increased portal vein pressure [11]. The REFLECT study excluded patients with ≥50% liver involvement, obvious invasion of the bile duct, or Vp4 PVTT [6]. The HIMALAYA study of durvalumab with or without tremelimumab versus sorafenib [12], the RATIONALE-301 study of tislelizumab versus sorafenib [13], and the LEAP-002 study of lenvatinib plus pembrolizumab versus lenvatinib [14] also excluded patients with Vp4 PVTT. In contrast to these studies, IMbrave150 included a broad population of patients, including those with high-risk features such as bile duct invasion, ≥50% liver involvement, and Vp4 PVTT [7]. The inclusion of patients with these characteristics in pivotal clinical trials, as in IMBrave150 and CARES-310 [15], makes the study population more representative of patients commonly encountered in clinical practice: study population representativeness should be a consideration when evaluating results from first-line trials.

We conducted exploratory analyses of IMbrave150 data to determine whether the clinical benefits and safety of atezolizumab plus bevacizumab observed in the intent-to-treat (ITT) population [7, 8] would differ between patients with unresectable HCC with and without Vp4 PVTT alone because Vp4 is the most common form of macrovascular invasion (MVI) related to HCC [16] and an exclusion criterion in many pivotal trials of advanced HCC [16, 17]. We also compared the safety and efficacy of treatment in patients with unresectable HCC with and without the previously mentioned high-risk prognostic factors, collectively.

Materials and Methods

Study Design, Patients, and Procedures

IMbrave150 (NCT03434379) was a phase 3, randomized (2:1), open-label study of atezolizumab plus bevacizumab versus sorafenib in adults with locally advanced or metastatic and/or unresectable HCC. The study design, eligibility criteria, randomization, stratification factors (geographic region, AFP level, Eastern Cooperative Oncology Group performance status [ECOG PS], and MVI and/or extrahepatic spread), and study procedures have been previously described [7].

Patients received either 1,200 mg of atezolizumab plus 15 mg/kg of bevacizumab intravenously every 3 weeks or 400 mg of sorafenib orally twice daily until loss of clinical benefit or unacceptable toxicity; they could continue treatment past

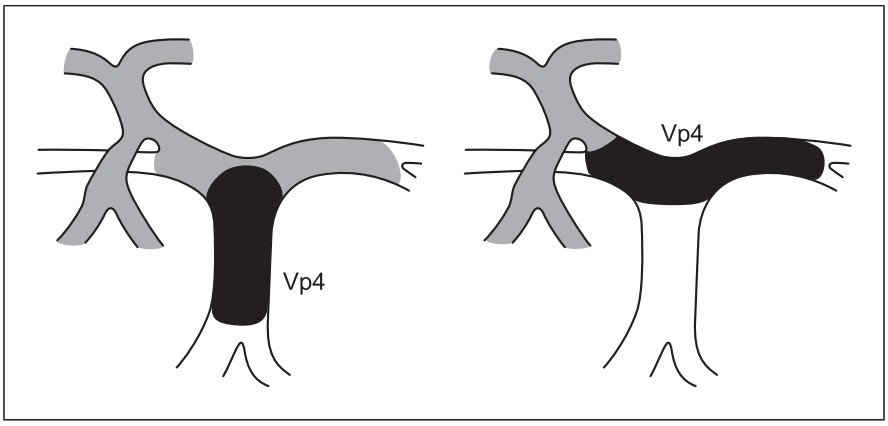


Fig. 1. Extent of Vp4 PVTT. Vp4 indicates the presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both). PVTT, portal vein tumor thrombosis.

progression if there was evidence of clinical benefit without unequivocal disease progression, as determined by the investigator. Protocol approval was obtained from the institutional review board (IRB) or ethics committee (EC) at each site. The first IRB approval for IMbrave150 was granted on December 19, 2017 from the City of Hope National Medical Center, Duarte, CA, USA (IRB No. 20172734; Western Institutional Review Board, Inc., Puyallup, WA, USA) [7, 8]. The full list of participating site and ECs can be found in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000539897).

Outcomes

The co-primary study endpoints were OS (time from randomization to death from any cause) and progression-free survival (PFS; time from randomization to the first occurrence of either disease progression per independent review facility–assessed Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 or death). Secondary endpoints included objective response rates (ORRs) per independent review facility–assessed RECIST 1.1, duration of response (DOR), and safety (adverse events [AEs] according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0).

These exploratory analyses of the updated data from the cutoff on August 31, 2020, were performed to compare the efficacy and safety of these 2 treatment regimens in (i) patients with and without Vp4 PVTT alone (termed the "Vp4" and "without Vp4" PVTT populations) and (ii) patients with and without high-risk prognostic factors (termed the "high-risk" and "non–high-risk" populations). High-risk factors were defined as HCC with Vp4 PVTT, bile duct invasion, and/or ≥50% liver involvement. The without-Vp4 population comprised the patients in the ITT population who did not have Vp4 at baseline but might have had another high-risk prognostic factor. The non–high-risk population comprised patients in the ITT group who had none of these risk factors.

Statistical Analyses

Confirmed response rates in these subgroups in patients with measurable disease at baseline were estimated, along with 95% CIs. The Kaplan-Meier method was used to estimate median OS, PFS, and DOR with 95% CIs in confirmed responders for each treatment arm. *p* values were calculated using a log-rank test. Time to onset of gastrointestinal (GI) bleeding events and median OS following the first GI bleeding event were similarly calculated post hoc in patients with and without VP4. To adjust for differences in baseline disease characteristics between treatment arms, multivariable Cox proportional hazard regression models for PFS and OS were conducted in patients with VP4, with treatment and ECOG (0 vs. 1), EHS (Yes vs. No), and AFP (<400 ng/mL vs. ≥400 ng/mL). An exploratory univariate analysis of high-risk prognostic factors for HCC was conducted to determine whether any 1 variable had a greater impact on outcomes than the others. Univariate Cox proportional hazards regression with each prognostic factor (Table 1) was used to estimate the HR and its 95% CI for PFS and OS separately within each arm. *p* values based on exploratory analyses were nominal and unadjusted for multiple comparisons.

Results

Study Population

The ITT population included 501 patients who were randomized to the atezolizumab plus bevacizumab (*n* = 336) or sorafenib (*n* = 165) arms. Overall, 101 patients had Vp4 PVTT, ≥50% liver involvement, and/or bile duct invasion and were included in the high-risk population: 64 (19%) in the atezolizumab plus bevacizumab arm and 37 (22%) in the sorafenib arm (Table 1). Seven patients (2%) in the atezolizumab plus bevacizumab arm and 3 (2%) in the sorafenib arm had bile duct invasion, and 18 (5%) and 13 (8%) in the respective arms had ≥50% liver invasion. Thirteen patients had 2 high-risk prognostic factors (Vp4 PVTT and ≥50% liver invasion): 9 (3%) in the atezolizumab plus bevacizumab arm and 4 (2%) in the sorafenib arm. None of the patients had 3 high-risk prognostic factors.

Seventy-three patients had Vp4 PVTT only and were included in the Vp4 population: 48 (14%) and 25 patients (15%) in the respective treatment arms. The median age was 60.0 years in the Vp4 population and 65.0 years in the

Table 1. HCC prognostic factors in the ITT population of IMbrave150

Characteristic, *n* (%)	ITT (*N* = 501)	
	atezolizumab + bevacizumab (*n* = 336)	sorafenib[a] (*n* = 165)
High-risk status[b]	64 (19)	37 (22)
Any PVTT	177 (53)	89 (54)
Vp1 PVTT	27 (8)	14 (8)
Vp2 PVTT	48 (14)	24 (15)
Vp3 PVTT	54 (16)	26 (16)
Vp4 PVTT	48 (14)	25 (15)
Liver involvement ≥50%	18 (5)	13 (8)
Bile duct invasion	7 (2)	3 (2)
Hepatic vein thrombus	27 (8)	12 (7)
Inferior vena cava thrombus	11 (3)	9 (5)

ITT, intent to treat; PVTT, portal vein tumor thrombosis. [a]One patient in the sorafenib arm had missing data for high-risk disease characteristics. [b]Defined as tumor invasion of the main trunk of the portal vein and/or the portal vein branch contralateral to the primarily involved lobe (Vp4 PVTT), bile duct invasion, and/or liver tumor burden ≥50.

without-Vp4 population. Compared with the without-Vp4 population, the Vp4 population included more patients with an AFP level of ≥400 ng/mL (60 vs. 33%), known varices at baseline (37 vs. 25%), and no prior locoregional therapy (74 vs. 47%), respectively. Within the Vp4 population, baseline characteristics were otherwise generally balanced between treatment arms, except among patients with an ECOG PS of 1, hepatitis B virus etiology, hepatitis C virus etiology, extrahepatic spread, varices, or AFP ≥400 ng/mL and those from Asia, where differences between the treatment groups were >10% (Table 2).

The high-risk population (Vp4 PVTT, ≥50% liver involvement, and/or bile duct invasion) had a median age of 61 years compared with 65 years in the non–high-risk population and included more patients with no prior locoregional therapy (68 vs. 47%), AFP ≥400 ng/mL (53 vs. 33%), and more extensive disease (median sum of target lesion diameters 99 mm vs. 69.1 mm). Baseline demographic and disease characteristics in the high-risk and the non–high-risk populations are shown by treatment arm for comparison with the Vp4 and without-Vp4 populations, respectively, in online supplementary Table 2. Baseline characteristics were generally balanced between treatment arms in the high-risk population, except that the atezolizumab plus bevacizumab arm included 18% fewer patients from Asia, 14% more patients who had varices, and 13% fewer patients with hepatitis B virus etiology than the sorafenib arm.

Efficacy in the Vp4 versus Without-Vp4 Populations

In patients with Vp4 PVTT, the median OS was 7.6 months (95% CI: 6.0–13.9) in the atezolizumab plus bevacizumab arm and 5.5 months (95% CI: 3.4–6.7) in the sorafenib arm (HR 0.62 [95% CI: 0.34–1.11]; descriptive $p = 0.104$) (Fig. 2a). In patients without Vp4, the median OS was 21.1 months (95% CI: 18.0–24.6) in the atezolizumab plus bevacizumab arm and 15.4 months (95% CI: 12.6–18.6) in the sorafenib arm (HR 0.67 [95% CI: 0.51–0.88]; descriptive $p = 0.003$).

In the Vp4 population, the median PFS was 5.4 months (95% CI: 3.6–6.9) in the atezolizumab plus bevacizumab arm and 2.8 months (95% CI: 1.5–5.3) in the sorafenib arm (HR 0.62 [95% CI: 0.35–1.09]; descriptive $p = 0.094$) (Fig. 2b). In the without-Vp4 population, the median PFS was 7.1 months (95% CI: 6.1–9.6) in the atezolizumab plus bevacizumab arm and 4.7 months (95% CI: 4.2–6.1) in the sorafenib arm (HR 0.64 [95% CI: 0.51–0.81]; descriptive $p < 0.001$).

To account for differences in baseline disease characteristics observed between treatment arms, multivariable Cox proportional hazard regression models for PFS and OS were conducted by treatment in VP4 patients, adjusted for baseline ECOG, EHS, and AFP. The results showed that the treatment HRs and 95% CIs for OS and PFS were almost identical to the unadjusted models (online suppl. Table 3).

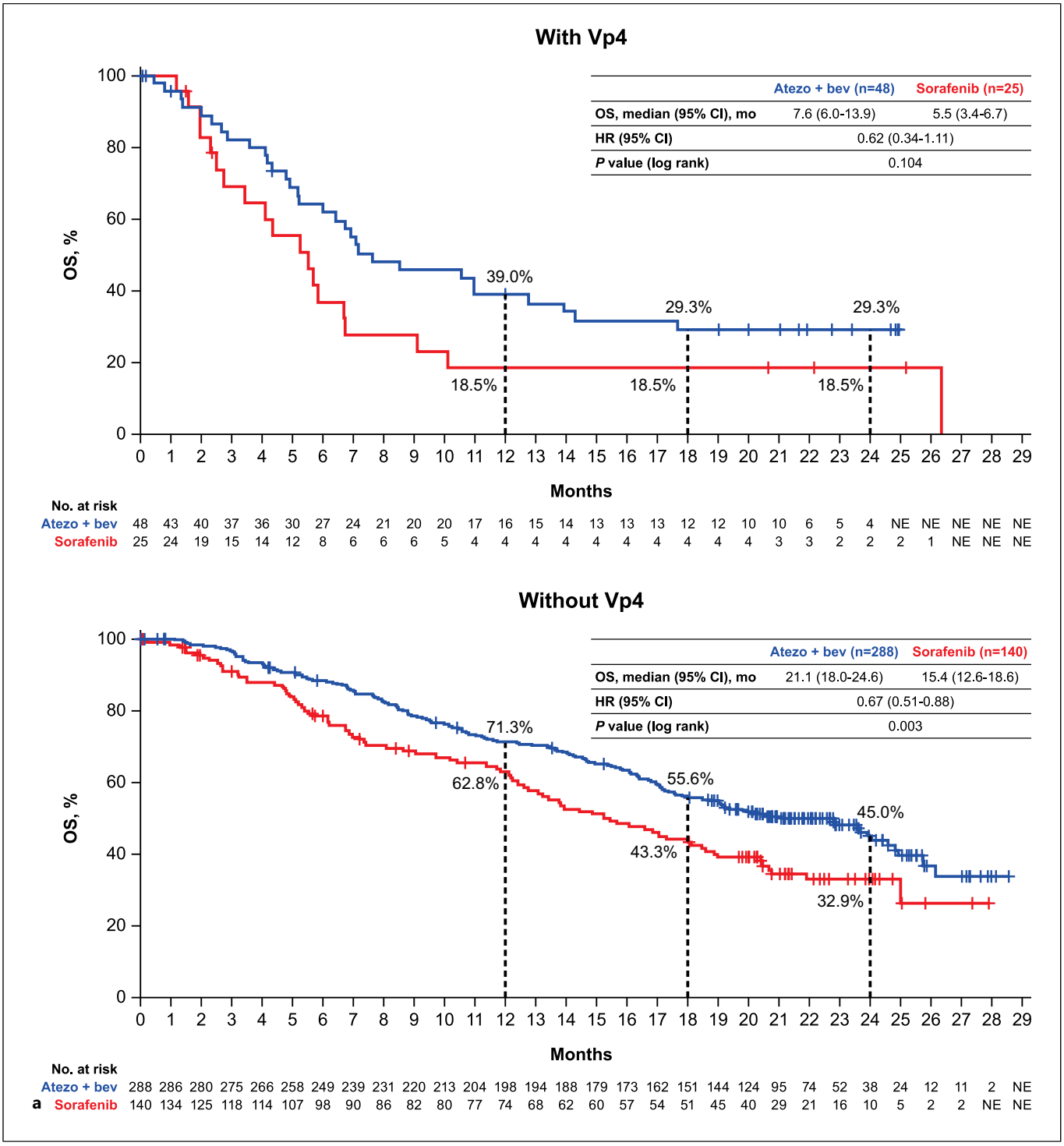
The ORR in the Vp4 population included 2 complete responses (CRs) and 9 partial responses (PRs) in the atezolizumab plus bevacizumab arm (ORR 23% [95% CI:

Table 2. Baseline and disease characteristics by treatment arm of patients with and without Vp4 in the ITT population

	With Vp4 (*n* = 73)		Without Vp4 (*n* = 428)	
	atezolizumab + bevacizumab (*n* = 48)	sorafenib (*n* = 25)	atezolizumab + bevacizumab (*n* = 288)	sorafenib (*n* = 140)
Age				
Median (range), years	61 (26–85)	59 (33–82)	64 (27–88)	67 (34–87)
≥65 years, *n* (%)	18 (38)	8 (32)	143 (50)	83 (59)
Male, *n* (%)	43 (90)	21 (84)	234 (81)	116 (83)
Race, *n* (%)				
Asian	24 (50)	13 (52)	164 (57)	83 (59)
White	22 (46)	10 (40)	101 (35)	42 (30)
Black	1 (2)	1 (4)	5 (2)	3 (2)
Native American	0	0	0	1 (1)
Unknown	1 (2)	1 (4)	18 (6)	11 (8)
Geographic region, *n* (%)[a]				
Asia (excluding Japan)	15 (31)	12 (48)	118 (41)	56 (40)
Rest of world	33 (69)	13 (52)	170 (59)	84 (60)
ECOG PS, *n* (%)[a]				
0	25 (52)	10 (40)	184 (64)	93 (66)
1	23 (48)	15 (60)	104 (36)	47 (34)
Etiology of HCC, *n* (%)				
Hepatitis B virus	21 (44)	17 (68)	143 (50)	59 (42)
Hepatitis C virus	16 (33)	4 (16)	56 (19)	32 (23)
Nonviral	11 (23)	4 (16)	89 (31)	49 (35)
EHS, *n* (%)[a]	29 (60)	12 (48)	183 (64)	81 (58)
Child-Pugh score, *n* (%)				
A5	24 (50)	14 (56)	215 (75)	107 (76)
A6	23 (48)	11 (44)	71 (25)	33 (24)
B7	1 (2)	0	0[b]	0
SLD, median (range), mm[c]	89.2 (10.0–254.8)	106.0 (39.2–248.0)	71.6 (10.0–321.0)	75.0 (10.0–312.0)[d]
Metastatic sites, *n* (%)				
0	30 (63)	16 (64)	147 (51)	81 (58)
1	17 (35)	7 (28)	114 (40)	46 (33)
2	1 (2)	2 (8)	25 (9)	12 (9)
3	0	0	2 (1)	1 (1)
AFP level ≥400 ng/mL, *n* (%)[a]	26 (54)	18 (72)	100 (35)	43 (31)
Varices, *n* (%)	21 (44)	6 (24)	68 (24)	37 (26)
Prior locoregional therapy, *n* (%)	12 (25)	7 (28)	149 (52)	78 (56)

AFP, α-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; ITT, intent to treat; SLD, sum of longest diameters. [a]Per electronic case report form, not interactive voice/web response system. [b]Two patients had missing data. [c]Per investigator. [d]One patient had missing data.

12–38]) compared with 1 CR and 2 PRs in the sorafenib arm (ORR 13% [95% CI: 3–34]) (Table 3). The median DOR was not estimable (NE; 95% CI: 15.5 months-NE) in the atezolizumab plus bevacizumab arm and NE (95% CI: 3.9 months-NE) in the sorafenib arm. In the without-Vp4 population, 23 CRs and 63 PRs were observed in the atezolizumab plus bevacizumab arm (ORR 31% [95% CI: 25–37]) compared with 0 CRs and 15 PRs (ORR 11% [95% CI: 6–18]) in the sorafenib arm. The median DOR in the without-Vp4 population was 18.1 months (95% CI: 14.2-NE) in the atezolizumab plus bevacizumab arm and 12.6 months (95% CI: 4.9–16.5) in the sorafenib arm.



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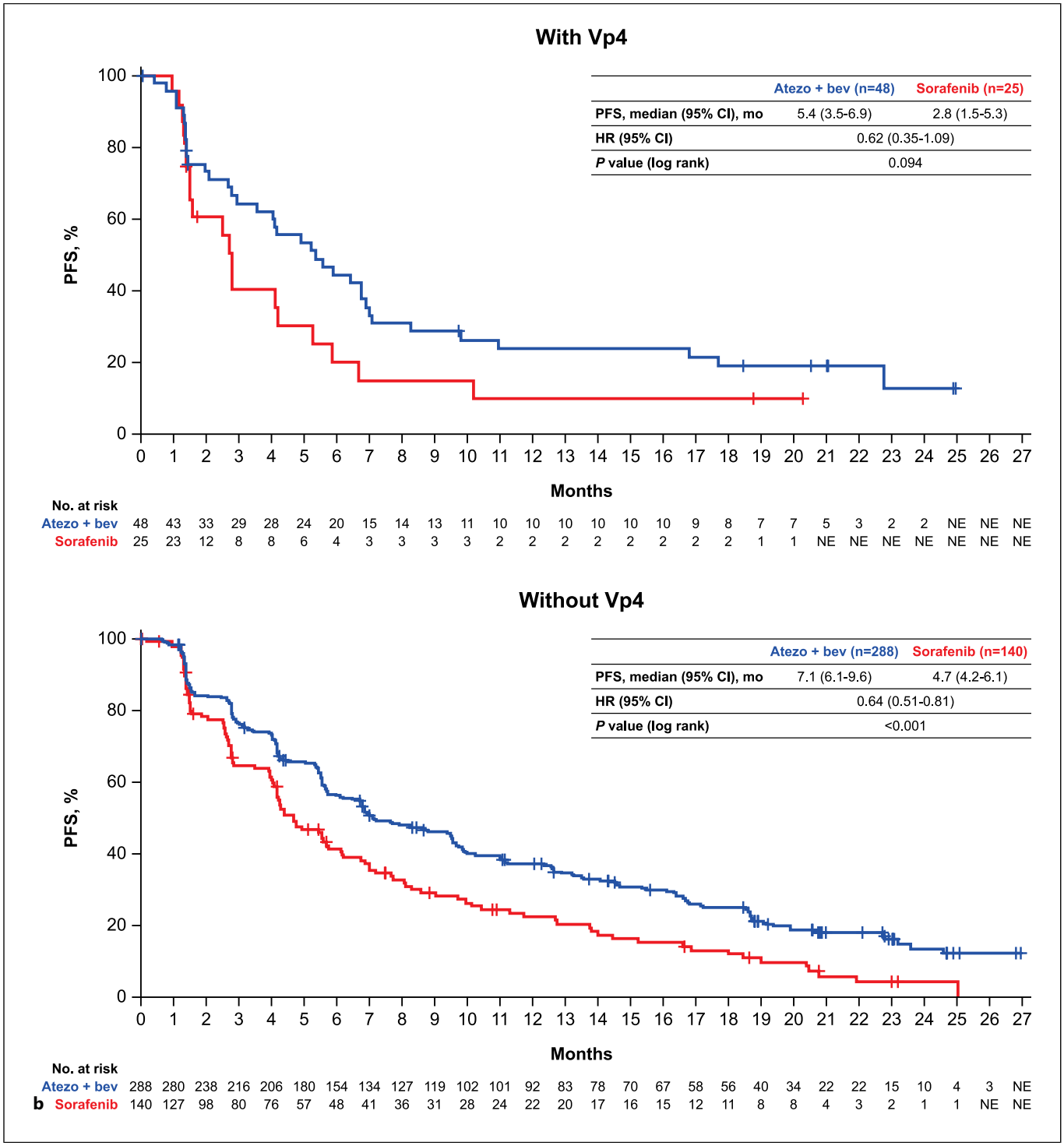

b

Fig. 2. a, **b** OS and PFS in patients with and without Vp4 PVTT. The vertical dashed lines represent 12-, 18-, and 24-month landmark analyses. atezo, atezolizumab; bev, bevacizumab; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival; PVTT, portal vein tumor thrombosis.

Table 3. Best confirmed overall response per IRF-assessed RECIST 1.1 by Vp4 PVTT status in patients with measurable disease at baseline

	With Vp4 (n = 70)		Without Vp4 (n = 415)	
	atezolizumab + bevacizumab (n = 47)	sorafenib (n = 23)	atezolizumab + bevacizumab (n = 279)	sorafenib (n = 136)
Confirmed ORR, n (%) [95% CI]	11 (23) [12–38]	3 (13) [3–34]	86 (31) [25–37]	15 (11) [6–18]
CR, n (%)	2 (4)	1 (4)	23 (8)	0
PR, n (%)	9 (19)	2 (9)	63 (23)	15 (11)
SD, n (%)	16 (34)	5 (22)	128 (46)	64 (47)
PD, n (%)	12 (26)	9 (39)	51 (18)	31 (23)
NE, n (%)	1 (2)	3 (13)	7 (3)	11 (8)
Missing, n (%)	7 (15)	3 (13)	7 (3)	15 (11)
DOR, median (95% CI), months	NE (15.6-NE)	NE (3.9-NE)	18.1 (14.2-NE)	12.6 (4.9–16.5)

CR, complete response; DOR, duration of response; IRF, independent review facility; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; PVTT, portal vein tumor thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Table 4. Safety summary by Vp4 status in the safety population

n (%)[a]	With Vp4 (n = 67)		Without Vp4 (n = 418)	
	atezolizumab + bevacizumab (n = 44)	sorafenib (n = 23)	atezolizumab + bevacizumab (n = 285)	sorafenib (n = 133)
Treatment duration, median (range), months	Atezo: 5.5 (0–25) Bev: 4.7 (0–25)	1.4 (0–21)	Atezo: 8.9 (0–28) Bev: 7.6 (0–28)	2.8 (0–25)
Any-grade AEs	42 (95)	23 (100)	280 (98)	131 (98)
Treatment-related AEs	37 (84)	22 (96)	247 (87)	126 (95)
Grade 3/4 AEs	26 (59)	13 (57)	181 (64)	76 (57)
Treatment-related grade 3/4 AEs	18 (41)	11 (48)	125 (44)	61 (46)
Grade 5 AEs	8 (18)	2 (9)	15 (5)	7 (5)
Treatment-related grade 5 AEs	1 (2)[b]	0	5 (2)[c]	1 (1)[d]
Serious AEs	25 (57)	9 (39)	135 (47)	42 (32)
Treatment-related serious AEs	11 (25)	5 (22)	65 (23)	20 (15)
Any-grade GI bleeding events	10 (23)	0	24 (8)	6 (5)
Grade ≥3 GI bleeding events	9 (20)	0	19 (7)	6 (5)
AEs leading to withdrawal from any study treatment component	11 (25)	2 (9)	61 (21)	16 (12)
AEs leading to dose modification/ interruption of any study treatment	26 (59)	17 (74)	169 (59)	80 (60)
Grade 5 AEs occurring in ≥2 patients in any group, n (%)				
Pneumonia	0	0	2 (1)	0
Hepatic cirrhosis	0	0	1 (<1)	2 (2)
GI hemorrhage	2 (5)	0	1 (<1)	0
Esophageal varices hemorrhage	2 (5)	0	0	0

AE, adverse event; GI, gastrointestinal. [a]Number of patients with ≥1 event. [b]Gastric ulcer perforation. [c]Abnormal hepatic function, liver injury, GI hemorrhage, pneumonia, and subarachnoid hemorrhage. [d]Hepatic cirrhosis.

Among 24 patients with Vp4 who had IRF-assessed disease progression (PD), 63% had EHS at baseline and 100% had BCLC C disease. Of these, 15 (63%) were subsequently treated with atezolizumab, 2 (8%) received other anticancer therapies, and 7 (30%) received no treatment after PD.

Efficacy in the High-Risk versus Non–High-Risk Populations

The median OS in the high-risk population (Vp4 portal vein invasion, ≥50% liver involvement, and/or bile duct invasion) was 7.6 months (95% CI: 6.6–12.8) with atezolizumab plus bevacizumab and 5.5 months (95% CI: 4.1–6.7) with sorafenib (HR for survival 0.62 [95% CI: 0.39–1.00]; descriptive $p = 0.049$) (online suppl. Fig. 1A). In the non–high-risk population, the median OS was 22.8 months (95% CI: 19.1–24.9) with atezolizumab plus bevacizumab and 15.7 months (95% CI: 13.2–19.0) with sorafenib (HR for survival 0.68 [95% CI: 0.51–0.91]; descriptive $p = 0.009$).

The median PFS in the high-risk population was 5.4 months (95% CI: 4.0–6.9) in the atezolizumab plus bevacizumab arm and 2.8 months (95% CI: 2.5–5.3) in the sorafenib arm (HR 0.74 [95% CI: 0.47–1.17]; descriptive $p = 0.197$) (online suppl. Fig. 1B). In the non–high-risk population, the median PFS was 7.2 months (95% CI: 6.5–9.6) with atezolizumab plus bevacizumab and 4.4 months (95% CI: 4.0–5.8) with sorafenib (HR 0.61 [95% CI: 0.48–0.78]; descriptive $p < 0.001$).

Five CRs and 11 PRs occurred in the atezolizumab plus bevacizumab arm of the high-risk population (ORR 25% [95% CI: 15–38]) compared with 1 CR and 4 PRs in the sorafenib arm (ORR 14% [95% CI: 5–30]) (online suppl Table 4). The median DOR was 16.3 months (95% CI: 13.5-NE) in the atezolizumab plus bevacizumab arm and 16.5 months (95% CI: 3.9-NE) in the sorafenib arm. In the non–high-risk population, 20 CRs and 61 PRs occurred in the atezolizumab plus bevacizumab arm (ORR 31% [95% CI: 25–37]) compared with 0 CRs and 13 PRs in the sorafenib arm (ORR 10% [95% CI: 6–17]). The median DOR in the non–high-risk population was 19.0 months (95% CI: 14.6-NE) in the atezolizumab plus bevacizumab arm and 12.6 months (95% CI: 4.9–17.0) in the sorafenib arm.

Prognostic Factors for OS and PFS

Univariate log-rank analysis indicated that, with the exception of bile duct invasion, each individual prognostic factor evaluated (i.e., high-risk disease status as defined in this analysis, as well as Vp1, Vp2, Vp3, and Vp4 PVTT, ≥50% liver involvement, hepatic vein thrombus, and inferior vena cava thrombus) significantly impacted OS in patients treated with atezolizumab plus bevacizumab ($p < 0.01$) (online suppl. Table 5). Of these factors, inferior vena cava thrombus had the greatest impact on OS and PFS in patients in the atezolizumab plus bevacizumab arm (HR 4.05 and 2.02, respectively). In the sorafenib arm, the following factors significantly impacted OS ($p < 0.05$): high-risk disease status as defined in this analysis, Vp3 PVTT, Vp4 PVTT, ≥50% liver involvement, and hepatic vein thrombus.

In the atezolizumab plus bevacizumab arm, PFS was significantly ($p < 0.05$) impacted by high-risk disease status as defined in this analysis, as well as by Vp2, Vp3, and Vp4 PVTT and ≥50% liver involvement (online suppl. Table 6). In the sorafenib arm, PFS was significantly impacted by ≥50% liver involvement ($p < 0.05$).

Safety in the Vp4 versus Without-Vp4 Populations

The median treatment durations in the Vp4 population were 5.5 months (atezolizumab), 4.7 months (bevacizumab), and 1.4 months (sorafenib) (Table 4). In the non-Vp4 population, the median treatment durations were 8.9 months (atezolizumab), 7.6 months (bevacizumab), and 2.8 months (sorafenib).

When comparing the safety profile of atezolizumab plus bevacizumab with that of sorafenib in the Vp4 population, a lower incidence of any-grade treatment-related AEs (TRAEs) was observed in the atezolizumab plus bevacizumab arm (84 vs. 96% with sorafenib; Table 4). The incidence of grade 3/4 TRAEs was also lower with atezolizumab plus bevacizumab (41 vs. 48% with sorafenib; Table 4). When comparing the safety of atezolizumab plus bevacizumab between patients with and without Vp4, the incidence of all-grade variceal bleeding (gastric varices, esophageal varices, and anorectal varices hemorrhage) was higher in patients with Vp4 PVTT at baseline ($n = 6$ [14%]) than in those without ($n = 7$ [2%]) (online suppl. Table 7). GI bleeding events in the Vp4 population occurred more frequently in the atezolizumab plus bevacizumab arm ($n = 10$ [23%] vs. 0 in the sorafenib arm) (Table 4). In the Vp4 population, the median time to onset of the first GI bleeding event was 4.8 months (range, 1.5–17.3) for any-grade events in the atezolizumab plus bevacizumab arm and 4.7 months (range, 1.5–17.3) for grade ≥3 events (online suppl. Table 8). The median OS following the first any-grade GI bleeding event was 3.3 months (IQR, 0.4–6.7) in the atezolizumab plus bevacizumab arm and 3.2 months (IQR, 0.4–6.7) after the first grade ≥3 bleeding event.

In the without-Vp4 population, GI bleeding events occurred at similar rates in the atezolizumab plus bevacizumab and sorafenib arms ($n = 24$ [8%] vs. $n = 6$ [5%]; Table 4). The median time to onset of the first GI bleeding event was 7.5 months (range, 0.3–24.2) for any-grade

events in the atezolizumab plus bevacizumab arm and 7.3 months (range, 0.3–24.2) for grade ≥3 events. In the sorafenib arm, the median time to onset of the first GI bleeding event was shorter: 4.5 months (range, 0.6–9.6) for any-grade and grade ≥3 GI bleeding events. The median OS following the first any-grade GI bleeding event in the atezolizumab plus bevacizumab arm was 8.2 months (IQR, 2.8-NE); 8.2 months (IQR, 2.1-NE) after the first grade ≥3 bleeding event. In the sorafenib arm, the median OS after the first GI bleeding event was again shorter: 3.9 months (IQR, 1.7–5.8) after the first any-grade and grade ≥3 GI bleeding event.

In the atezolizumab plus bevacizumab arm, a grade 5 TRAE occurred in 1 patient (2%) in the Vp4 population (Table 4); the death was attributed to a gastric ulcer perforation that was considered related to bevacizumab. In the non-Vp4 population, grade 5 TRAEs occurred in 5 patients (2%) treated with atezolizumab plus bevacizumab (abnormal hepatic function, liver injury, GI hemorrhage, pneumonia, and subarachnoid hemorrhage) and 1 patient (1%) treated with sorafenib (hepatic cirrhosis).

Safety in High-Risk versus Non–High-Risk Populations

In the high-risk population (patients with Vp4 PVTT, ≥50% liver involvement, and/or bile duct invasion), the respective median durations of treatment with atezolizumab, bevacizumab, and sorafenib were 4.9, 4.8, and 1.4 months, and in the non–high-risk population, they were 9.0, 7.6, and 2.8 months (online suppl. Table 9). The incidence of any-grade TRAEs was lower in the atezolizumab plus bevacizumab arm (78%) than in the sorafenib arm (97%) of the high-risk population (online suppl. Table 9). The incidence of grade 3/4 TRAEs was also lower with atezolizumab plus bevacizumab (35%) than with sorafenib (49%). When comparing the safety of atezolizumab plus bevacizumab between patients with and without high-risk prognostic factors, a lower incidence of grade 3/4 TRAEs was seen with atezolizumab plus bevacizumab in the high-risk population than in the non–high-risk population (35 vs. 45%, respectively; online suppl. Table 9). The incidence of any-cause grade 5 AEs was higher with atezolizumab plus bevacizumab in the high-risk population than in the non–high-risk population (in 10 [17%] vs. 13 patients [5%], respectively). However, the incidence of grade 5 TRAEs with atezolizumab plus bevacizumab was the same in the high-risk (1 patient [2%]) and non–high-risk populations (5 patients [2%]) (online suppl. Table 9). Five of 10 grade 5 AEs in the atezolizumab plus bevacizumab arm in the high-risk population were upper GI hemorrhage events: GI hemorrhage in 2 patients, esophageal varices hemorrhage in 2 patients, and gastric ulcer perforation in 1 patient. All 5 of these patients had Vp4 PVTT. Only the gastric ulcer perforation was considered by the investigator to be treatment related (bevacizumab). One grade 5 GI hemorrhage occurred in the non–high-risk population in a patient who had Vp3 PVTT and was in the atezolizumab plus bevacizumab arm. AEs leading to discontinuation of atezolizumab plus bevacizumab were similar between patients in the high-risk (22%) and non–high-risk populations (20%) (online suppl. Table 9).

Discussion

Patients with high-risk HCC prognostic factors such as Vp4 PVTT, ≥50% liver involvement, and/or bile duct invasion have a poor prognosis. They are often excluded from pivotal HCC clinical trials and lack clinically meaningful treatment options. This exploratory analysis was conducted to determine the safety and efficacy of atezolizumab plus bevacizumab in these patient groups with high-risk HCC in IMbrave150.

Consistent with the primary [7] and updated results [8] in the IMbrave150 ITT population, clinical benefit was seen with atezolizumab plus bevacizumab across all efficacy parameters (OS, PFS, and ORR) versus sorafenib, irrespective of whether the patients had baseline Vp4 PVTT only or several high-risk HCC prognostic factors. The difference between treatments was not statistically significant in patients with VP4 PVTT; however, the clear separation between treatment arms in the OS and PFS Kaplan-Meier curves indicated that both the Vp4 and high-risk populations derived greater benefit from atezolizumab plus bevacizumab than sorafenib. Overall, the HRs for survival between the different treatments were similar among all risk populations analyzed (0.62 in patients with Vp4 PVTT and 0.67 in patients without Vp4; 0.62 in the high-risk population and 0.68 in the non–high-risk population) and were comparable to the OS HR of 0.66 in the ITT population at the updated analysis [8]. The same clinical benefits were observed with atezolizumab plus bevacizumab after adjustments for imbalances in baseline disease characteristics between treatment arms in the Vp4 PVTT group. Of note, patients in the atezolizumab plus bevacizumab arm who had HCC without Vp4 PVTT had numerically longer OS than those in the ITT population (median, 21.1 vs. 19.2 months in the ITT population).

The non–high-risk population, which showed a median OS of 22.8 months in the atezolizumab plus bevacizumab arm and 15.7 months in the sorafenib arm in

this exploratory analysis, had inclusion criteria similar to those in REFLECT, in which the median OS was 13.6 months with lenvatinib versus 12.3 months with sorafenib (HR 0.92 [95% CI: 0.79–1.06]) [6]. In HIMALAYA, which excluded patients with Vp4 PVTT but not bile duct or ≥50% liver involvement, the median OS was 16.4 months with tremelimumab plus durvalumab and 13.8 months with sorafenib (HR 0.78 [95% CI: 0.65–0.92]; $p = 0.009$) after 16 months' follow-up [12]. In RATIONALE-301, which excluded patients with Vp4 PVTT and inferior vena cava thrombus, the median OS was 15.9 months with tislelizumab and 14.1 months with sorafenib (HR 0.85 [95% CI: 0.712–1.019]) [13]. Although direct between-study comparisons cannot be made due to differences in study designs and study population characteristics, the comparative OS outcomes in REFLECT, HIMALAYA, and RATIONALE-301 differed from those in the non–high-risk and without-Vp4 populations of IMbrave150, in which 7.1-month and 5.4-month OS increases, respectively, were seen with atezolizumab plus bevacizumab versus sorafenib. LEAP-002 excluded patients with Vp4, but two-thirds of the study population had extrahepatic spread and MVI [14]. The median OS was 21.2 months with lenvatinib plus pembrolizumab and 19.0 months with lenvatinib. These OS outcomes were similar to those in the IMbrave150 non-Vp4 population, supporting our finding that even patients with some high-risk HCC factors derive benefit from treatment. Furthermore, the CARES-310 study of camrelizumab plus rivoceranib versus sorafenib [15], which also included patients with Vp4 tumor invasion, demonstrated similar outcomes, indicating that targeting the PD-1/PD-L1 and VEGF pathways in the first line improves survival in patients with high-risk unresectable HCC.

As expected, the patients with baseline Vp4 and/or other high-risk factors generally had less prognostically favorable baseline characteristics, such as an ECOG PS of 1, Child-Pugh A score of 6, viral etiology, greater sum of target lesion diameters, and AFP level of ≥400 ng/mL, than the rest of the ITT population who did not have these high-risk factors. The AE profiles were consistent with the known safety profile of each drug and the complications associated with underlying liver disease and advanced liver cancer. As expected, given the overlap between the Vp4 and high-risk populations, the severity and incidences of AEs in the atezolizumab plus bevacizumab arms were very similar between these populations. The safety data were also generally comparable between the Vp4 and without-Vp4 populations and between the high-risk and non–high-risk populations. However, higher incidences of esophageal varices hemorrhage, GI hemorrhage, and upper GI hemorrhage events were seen in patients with versus without high-risk factors and Vp4. This finding is not surprising given that patients with PVTT, and Vp4 in particular, are generally at greater risk of variceal bleeding, given the increased portal hypertension and rapid growth of collateral vessels caused by PVTT [18]. In a matched case-control study of patients with HCC with and without PVTT, the incidence of esophageal bleeding was 8% versus 6%, respectively, over 43 months, with acute variceal bleeding occurring in 5% of patients with PVTT, almost all of whom had existing high-risk varices [18]. In a real-world study of patients treated with first-line atezolizumab plus bevacizumab in routine clinical practice, the incidence of bleeding events was 14%, with grade ≥3 bleeding events occurring in 6% of patients [19]. Among the patients who underwent baseline esophagogastroduodenoscopy, the investigators found no association between the presence of baseline PVTT or varices and development of bleeding events of any grade [19]. They noted that systematic pretreatment screening (as done in IMbrave150) and timely introduction of prophylaxis were effective in preventing bleeding events and recommended this as part of routine clinical practice [19]. Inferences about bleeding risks in studies of other regimens that do not include patients with a high risk for these events remain inconclusive as a result of limited to no data in this population.

The median time to onset of the first grade ≥3 GI bleeding event was shorter in the atezolizumab plus bevacizumab arm in patients with Vp4 PVTT (4.7 months) than in patients without Vp4 (7.3 months). This was as expected, given that patients with Vp4 would be at greater risk of portal hypertension, which in turn may have put them at greater risk of bleeding while on bevacizumab. The median OS after these first events was 3.2 months (IQR, 0.4–6.7) and 7.3 months (IQR, 0.3–24.2) in patients with and without Vp4 PVTT, respectively. However, in the without-Vp4 population, the median time to onset of any-grade GI bleeding was longer in the atezolizumab plus bevacizumab arm (7.3 months) than in the sorafenib arm (4.5 months). In fact, the median time to GI bleeding onset in the sorafenib arm appeared similar to that in patients with Vp4 in the atezolizumab plus bevacizumab arm (4.8 months). Notably, in patients without Vp4, time to bleeding and survival among the few patients who did have GI bleeding was greater in patients treated with atezolizumab plus bevacizumab (median OS 8.2 months [IQR, 2.9-NE]) than those treated with sorafenib (3.9 months [IQR, 1.7–5.8]). Small patient numbers preclude firm conclusions, but one possibility is that this finding may be due to

better tumor control in the atezolizumab plus bevacizumab arm because in patients without Vp4, the bleeding risk could be partly related to overall disease burden and control.

In a previous analysis in the IMbrave150 ITT population, the median time to onset of the first grade ≥3 GI bleeding events and OS thereafter in atezolizumab- plus bevacizumab-treated patients with varices at baseline was 5.9 months (range, 0.3–24.2) and 3.3 months (IQR, 1.3-NE), respectively [20]. In patients without varices at baseline, the median time to the first grade ≥3 GI bleeding event was 7.9 months (range, 2.0–21.0) and the median OS after this event was 6.7 months (IQR, 3.0–8.2). However, an analysis of OS by baseline varices in the IMbrave150 ITT population showed that the median OS in the atezolizumab arm was 17.7 months (95% CI: 14.3–23.9) in patients with baseline varices and 19.9 months (95% CI: 17.1–24.6) in those without baseline varices [20]. Furthermore, although withholding bevacizumab in patients with variceal bleeding might have been expected to impact survival, another exploratory analysis of IMbrave150 showed that OS and PFS were similar between patients who skipped bevacizumab due to bevacizumab-related AEs of special interest and those who did not (OS HR 1.04 [95% CI: 0.64–1.69] and PFS HR 1.07 [95% CI: 0.74–1.55]) [21].

The longer exposure to atezolizumab plus bevacizumab in the non–high-risk population most likely accounted for the increase in treatment-related grade 3/4 AEs compared with the high-risk population. However, the incidence of deaths related to atezolizumab plus bevacizumab was the same (2%) in the Vp4 and high-risk populations.

The inclusion of patients with poor prognosis in the IMbrave150 study population is a study strength because it permitted evaluation of the efficacy and safety of a new standard-of-care treatment combination in patients with high-risk HCC, who are often excluded from phase 3 trials. In clinical practice, this population is difficult to treat successfully; therefore, these phase 3 data are important because they highlight and inform the unmet needs of this population. This analysis showed that the OS, PFS, and ORR benefits they derived with atezolizumab plus bevacizumab were consistent with those in the ITT population. These findings also revealed information about the group of patients with VP4 PVTT, who are at greatest risk of severe GI bleeding, but are not typically included in HCC trials. The analysis in these populations, which included post hoc analyses of prognostic factors that impacted OS and PFS in each treatment group, was limited by its exploratory nature. The relatively small number of patients in the Vp4 and high-risk populations was another limitation. Because RECIST 1.1 does not explicitly include measurement of PVTT, further analyses of PRs and CRs, in terms of PVTT or target lesion resolution on imaging scans, would be required before considering downstaging to liver transplant.

In summary, these exploratory analyses showed that atezolizumab plus bevacizumab demonstrated a numeric survival benefit versus sorafenib in patients with unresectable HCC not only with Vp4 PVTT alone but also with other high-risk prognostic factors. Patients who had HCC without high-risk prognostic factors benefited from substantially prolonged OS with atezolizumab plus bevacizumab versus sorafenib. The incidence of all-grade and grade 3/4 TRAEs was lower with atezolizumab plus bevacizumab than sorafenib in the Vp4 PVTT and high-risk populations. In patients with Vp4 and high-risk HCC, the incidence of treatment-unrelated deaths was higher in the atezolizumab plus bevacizumab arms than in the sorafenib arms; this was driven to some extent by bleeding events, but these populations still benefited from prolonged OS compared with sorafenib treatment.

Considering the totality of the efficacy and safety evidence, the risk-benefit ratio remains in favor of atezolizumab plus bevacizumab regardless of Vp4 invasion and other high-risk HCC features. The survival benefit obtained with atezolizumab plus bevacizumab versus sorafenib confirms this combination as the standard of care for a broad population of patients with previously untreated unresectable HCC.

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Statement of Ethics

IMbrave150 was carried out in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. Protocol approval was obtained from the IRB or EC at each site. The first IRB approval for IMbrave150 was granted on December 19, 2017, from the City of Hope National Medical Center, Duarte, CA, USA (IRB No. 20172734; Western Institutional Review Board, Inc. Puyallup, WA, USA), in addition to multiple other EC/IRB approvals obtained across all participating sites in the different countries of enrollment. An independent data monitoring committee reviewed unmasked safety and trial conduct data

approximately every 6 months until study unblinding. The study sponsor supplied the study drugs and collaborated with academic authors on the study design, data collection, data analysis, and data interpretation. All patients gave written informed consent to participate in the study.

Conflict of Interest Statement

Richard S. Finn reports receiving consulting fees from AstraZeneca, Bayer, CStone Pharmaceuticals, Eisai, Eli Lilly, Exelixis, F. Hoffmann-La Roche Hengrui, Merck, and Pfizer; research funding to institution from Adaptimmune, Bristol Myers Squibb, Eisai, Eli Lilly, Merck, Pfizer, and F. Hoffmann-La Roche Ltd; and is an Editorial Board Member of *Liver Cancer*. Peter R. Galle reports receiving consulting fees from Adaptimmune, AstraZeneca, Bayer, Boston Scientific, Bristol Myers Squibb, Eisai, Eli Lilly, F. Hoffmann-La Roche Ltd., Guerbet, Ipsen, Merck Sharp and Dohme, and Sirtex Medical; honoraria from Adaptimmune, AstraZeneca, Bayer, Boston Scientific, Bristol Myers Squibb, Eisai, Eli Lilly, F. Hoffmann-La Roche Ltd., Guerbet, Ipsen, Merck Sharp and Dohme, and Sirtex Medical; advisory fees from Adaptimmune, AstraZeneca, Bayer, Boston Scientific, Bristol Myers Squibb, Eisai, Eli Lilly, F. Hoffmann-La Roche Ltd., Guerbet, Ipsen, Merck Sharp and Dohme, and Sirtex Medical; and research funding to institution from Bayer and F. Hoffmann-La Roche Ltd. Michel Ducreux reports receiving honoraria, consulting fees, or advisory fees to self from Amgen, AstraZeneca, Bayer, Eli Lilly, F. Hoffmann-La Roche Ltd., Ipsen, Merck Serono, Pierre Fabre, and Servier; travel support from Bayer, Eli Lilly, F. Hoffmann-La Roche Ltd., Ipsen, Merck Sharp & Dohme, and Servier; speaker bureau participation for Amgen, Bayer, Eli Lilly, F. Hoffmann-La Roche Ltd., Ipsen, and Merck Serono; and research funding to institution from Bayer and F. Hoffmann-La Roche Ltd. Ann-Lii Cheng reports receiving research funding to institution from F. Hoffmann-La Roche Ltd. Alan Nicholas is an employee and stockholder of Roche/Genentech. Philippe Merle has had a consulting or advisory role for Bayer, Ipsen, Lilly, Eisai, AstraZeneca, Bristol Myers Squibb, and MSD; received institutional research funding from Ipsen; and travel and accommodation expenses from Bayer and Ipsen. Riad Salem is a consultant for Boston Scientific, Eisai, Genentech, Cook, Sirtex and AstraZeneca. Daneng Li has received honoraria and advisory/consultancy fees from AstraZeneca, Ipsen, Eisai, Exelixis, Coherus, Genentech, QED, Merck, Adagene, Delcath, Servier, Sumitomo, Transthera, and TerSera; and received institutional research funding from Brooklyn Immunotherapeutics and AstraZeneca. Valeriy Breder has received advisory/consultancy fees from F. Hoffmann-La Roche, MSD, Eisai, Bristol Myers Squibb, and Ipsen; and travel and accommodation expenses from F. Hoffmann-La Roche, MSD, Eisai, Bristol Myers Squibb, and Bayer. Ning Ma is an employee and stockholder of Roche/Genentech. Sairy Hernandez is an employee and stockholder of Roche/Genentech.

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Author Contributions

Richard S. Finn, Valeriy Breder, and Riad Salem contributed to conceptualization, methodology, investigation, resources, data curation, writing – review and editing, visualization, and supervision. Peter R. Galle, Michel Ducreux, Ann-Lii Cheng, Philippe Merle, and Daneng Li contributed to conceptualization, validation, investigation, and writing – review and editing. Norelle Reilly, Alan Nicholas, Sairy Hernandez, and Ning Ma contributed to conceptualization, formal analysis, methodology, resources, writing – review and editing, and visualization.

Data Availability Statement

The data that support the findings of this study are not publicly available to ensure patient privacy. Qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli, available at https://vivli.org/ourmember/roche/. For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://go.roche.com/data_sharing.

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