Atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150

Ann-Lii Cheng,[1] Shukui Qin,[2] Masafumi Ikeda,[3] Peter R. Galle,[4] Michel Ducreux,[5] Andrew X. Zhu,[6] Tae-You Kim,[7] Masatoshi Kudo,[8] Valeriy Breder,[9] Philippe Merle,[10] Ahmed Kaseb,[11] Daneng Li,[12] Wendy Verret,[13] Derek-Zhen Xu,[14] Sairy Hernandez,[13] Juan Liu,[14] Chen Huang,[14] Sohail Mulla,[15] Ho Yeong Lim,[16] Richard S. Finn[17]

[1]National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan; [2]People's Liberation Army Cancer Center, Jinling Hospital, Nanjing, People's Republic of China; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]University Medical Center Mainz, Mainz, Germany; [5]Gustave Roussy Cancer Center, Villejuif, France; [6]Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [7]Seoul National University College of Medicine, Seoul, Korea; [8]Kindai University Faculty of Medicine, Osaka, Japan; [9]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Hospital La Croix-Rousse, Lyon, France; [11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [13]Genentech, Inc., South San Francisco, CA, USA; [14]Roche Product Development, Shanghai, People's Republic of China; [15]Hoffmann-La Roche Limited, Mississauga, ON, Canada; [16]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [17]Jonsson Comprehensive Cancer Center, Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Disclosures

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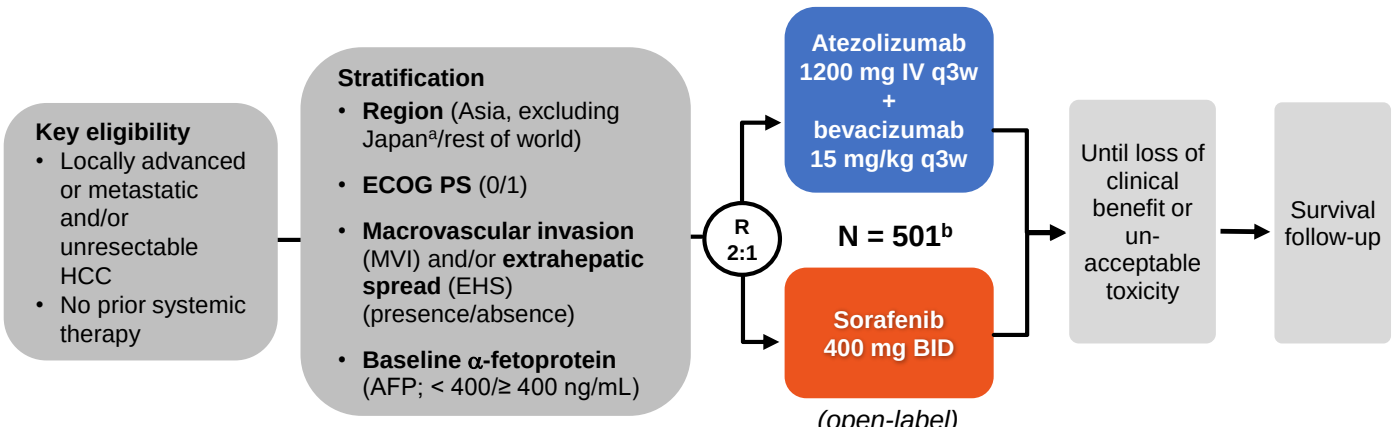
- F. Hoffmann-La Roche, Ltd, sponsored the study and was involved in study design, analysis and interpretation of results and development of this report

Background

- Multikinase inhibitors sorafenib and lenvatinib are the preferred first-line systemic treatments for unresectable hepatocellular carcinoma (HCC)[1-7]
  - While these agents have had modest effects on overall survival, they are both associated with considerable side effects
  - With sorafenib, the median overall survival ranges from ≈ 12 to 14 months; however, no treatment has demonstrated a statistically significant and clinical meaningful improvement in overall survival beyond sorafenib in over a decade
- A Phase 1b study (NCT02715531) of atezolizumab (anti–PD-L1) + bevacizumab (anti-VEGF) in patients with advanced HCC demonstrated a tolerable safety profile and promising antitumour activity, with an objective response rate of 36% and a median progression-free survival of 7.3 months[8-9]
- Here we report the results of IMbrave150, a global, open-label, Phase 3, randomised study of atezolizumab + bevacizumab vs sorafenib in patients with unresectable HCC who have not received prior systemic therapy

1. NCCN Clinical Practice Guidelines. V2.2019; 2. Vogel A, et al. *Ann Onc* 2019; 3. Cheng AL, et al. *Lancet Oncol* 2009; 4. Kudo M, et al. *Lancet* 2018; 5. Llovet JM, et al. *N Engl J Med* 2008; 6. Boige V, et al. *Oncologist* 2012; 7. Finn RS, et al. *Expert Rev Anticancer* 2009; 8. Lee MS, et al. ESMO 2019; 9. Hsu C-H, et al. ESMO Asia 2019.

IMbrave150 study design

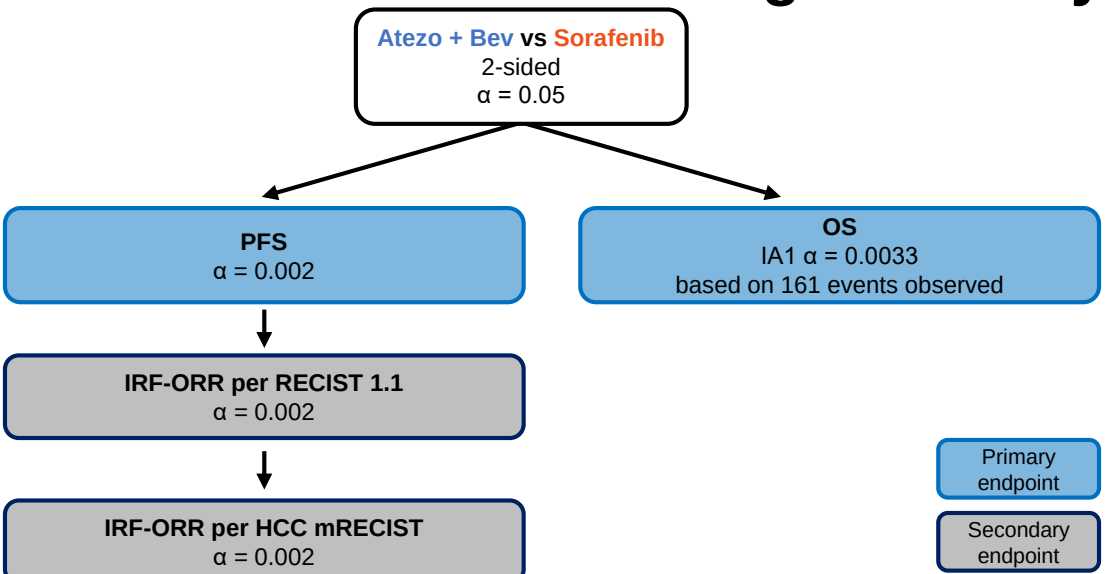


Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

IMbrave150 statistical testing hierarchy



IA, interim analysis.
Alpha recycling per graphical method was designed but not shown because all endpoints passed at their initially allocated alpha.

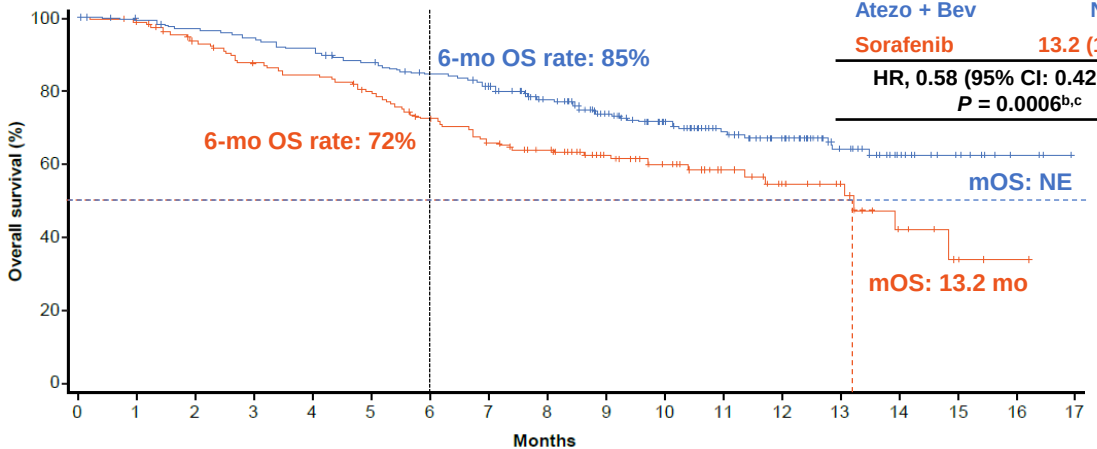
IMbrave150 baseline characteristics (ITT)

Characteristic	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median age (range), years	64 (26-88)	66 (33-87)
Sex, male, n (%)	277 (82)	137 (83)
Region, n (%)		
Asia (excluding Japan[a])	133 (40)	68 (41)
Rest of world	203 (60)	97 (59)
ECOG PS 1, n (%)	127 (38)	62 (38)
Child-Pugh class, n (%)		
A | B	333 (99) | 1 (< 1)	165 (100) | 0
BCLC staging at study entry, n (%)		
A | B | C	8 (2) | 52 (15) | 276 (82)	6 (4) | 26 (16) | 133 (81)
Aetiology of HCC, n (%)		
HBV | HCV | Non-viral	164 (49) | 72 (21) | 100 (30)	76 (46) | 36 (22) | 53 (32)
AFP ≥ 400 ng/mL, n (%)	126 (38)	61 (37)
EHS, n (%)	212 (63)	93 (56)
MVI, n (%)	129 (38)	71 (43)
EHS and/or MVI, n (%)	258 (77)	120 (73)
Prior TACE, n (%)	130 (39)	70 (42)
Prior radiotherapy, n (%)	34 (10)	17 (10)

[a] Japan is included in rest of world.

OS: co-primary endpoint

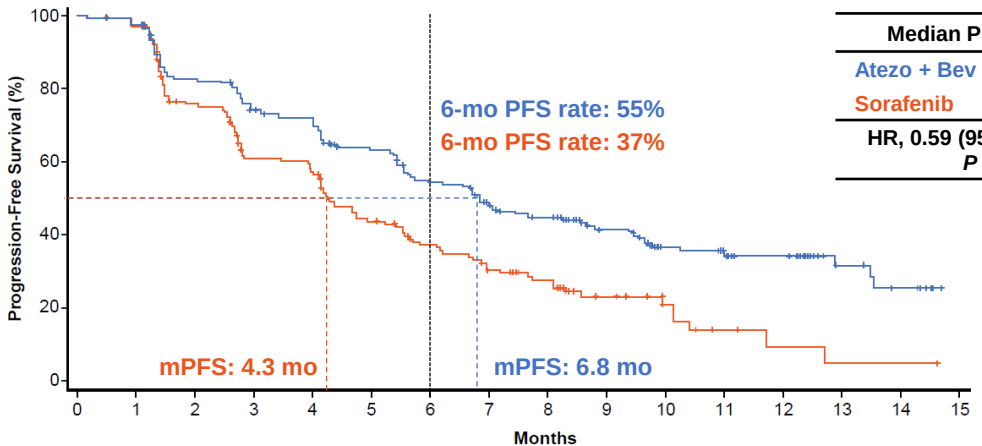
Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b]	
P = 0.0006[b,c]	



No. at risk																		
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

NE, not estimable. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Confirmed PFS[a]: co-primary endpoint



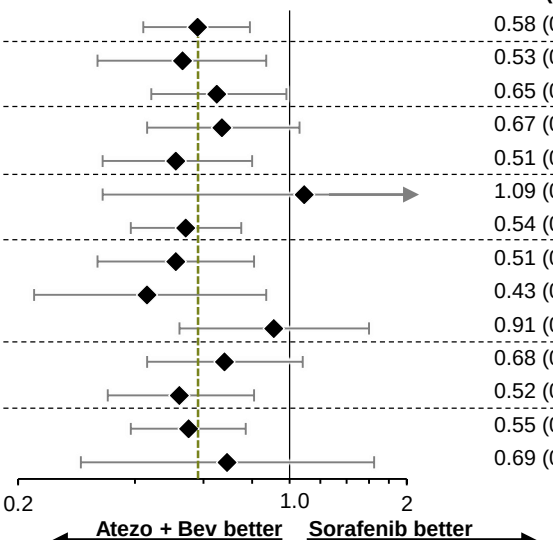
No. at risk															
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE

Median PFS (95% CI), mo[b]	
Atezo + Bev	6.8 (5.7, 8.3)
Sorafenib	4.3 (4.0, 5.6)
HR, 0.59 (95% CI: 0.47, 0.76)[c,d] *P* < 0.0001[d]	

[a] Assessed by IRF per RECIST 1.1. [b] 197 patients (59%) in the Atezo + Bev arm vs 109 (66%) in the sorafenib arm had an event. [c] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [d] The 2-sided *P* value boundary is 0.002. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

OS subgroups

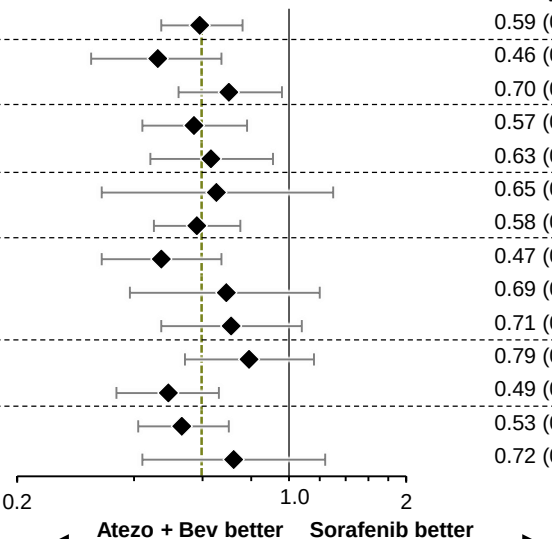
Characteristic (n)	Atezo + Bev mOS, mo (n = 336)	Sorafenib mOS, mo (n = 165)	HR (95% CI)[a]
All patients (501)	NE	13.2	0.58 (0.42, 0.79)
Asia (excluding Japan[b]) (201)	NE	13.1	0.53 (0.32, 0.87)
Rest of world (300)	NE	13.2	0.65 (0.44, 0.98)
ECOG PS 0 (312)	NE	13.9	0.67 (0.43, 1.06)
ECOG PS 1 (189)	NE	7.4	0.51 (0.33, 0.80)
BCLC stage B[c] (78)	NE	14.9	1.09 (0.33, 3.53)
BCLC stage C[c] (409)	NE	11.4	0.54 (0.39, 0.75)
HBV HCC (240)	NE	13.9	0.51 (0.32, 0.81)
HCV HCC (108)	NE	13.1	0.43 (0.22, 0.87)
Non-viral HCC (153)	NE	14.9	0.91 (0.52, 1.60)
AFP ≥ 400 ng/mL (187)	12.8	9.1	0.68 (0.43, 1.08)
AFP < 400 ng/mL (314)	NE	13.9	0.52 (0.34, 0.81)
EHS and/or MVI (378)	NE	10.4	0.55 (0.39, 0.77)
No EHS and MVI (123)	NE	14.9	0.69 (0.29, 1.65)



NE, not estimable.
[a] Unstratified HR shown for all characteristics except for "All patients," where stratified HR is shown. [b] Japan is included in rest of world.
[c] BCLC stage A not shown, as there were only 14 patients; thus, estimation is not meaningful.
Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

PFS subgroups

Characteristic (n)	Atezo + Bev mPFS, mo (n = 336)	Sorafenib mPFS, mo (n = 165)	HR (95% CI)[a]
All patients (501)	6.8	4.3	0.59 (0.47, 0.76)
Asia (excluding Japan[b]) (201)	7.7	2.8	0.46 (0.31, 0.67)
Rest of world (300)	6.7	4.9	0.70 (0.52, 0.96)
ECOG PS 0 (312)	7.9	4.8	0.57 (0.42, 0.78)
ECOG PS 1 (189)	5.6	4.0	0.63 (0.44, 0.91)
BCLC stage B[c] (78)	NE	8.6	0.65 (0.33, 1.30)
BCLC stage C[c] (409)	6.4	4.1	0.58 (0.45, 0.75)
HBV HCC (240)	6.7	2.8	0.47 (0.33, 0.67)
HCV HCC (108)	8.3	5.8	0.69 (0.39, 1.20)
Non-viral HCC (153)	7.1	5.6	0.71 (0.47, 1.08)
AFP ≥ 400 ng/mL (187)	5.2	4.1	0.79 (0.54, 1.16)
AFP < 400 ng/mL (314)	8.3	4.4	0.49 (0.36, 0.66)
EHS and/or MVI (378)	6.1	4.0	0.53 (0.41, 0.70)
No EHS and MVI (123)	9.9	8.6	0.72 (0.42, 1.24)



NE, not estimable.
[a] Unstratified HR shown for all characteristics except for "All patients," where stratified HR is shown. [b] Japan is included in rest of world.
[c] BCLC stage A not shown, as there were only 14 patients; thus, estimation is not meaningful.
Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Response rate and duration of response

	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)[a]	Sorafenib (n = 158)
Confirmed ORR, n **(%)** (95% CI)	89 **(27)** (23, 33)	19 **(12)** (7, 18)	108 **(33)** (28, 39)	21 **(13)** (8, 20)
CR	18 (6)	0	33 (10)	3 (2)
PR	71 (22)	19 (12)	75 (23)	18 (11)
Stratified *P* value[b]	**< 0.0001**		**< 0.0001**	
SD, n (%)	151 (46)	69 (43)	127 (39)	66 (42)
PD, n (%)	64 (20)	39 (25)	66 (20)	40 (25)
DCR, n (%)	240 (74)	88 (55)	235 (72)	87 (55)
Ongoing response, n (%)[c]	77 (87)	13 (68)	84 (78)	13 (62)
Median DOR, months (95% CI)	NE	6.3 (4.7, NE)	NE	6.3 (4.9, NE)
Event-free rate at 6 months, n (%)	88	59	82	63

[a] IRF HCC mRECIST–evaluable population was based on patients who presented with measurable disease at baseline per HCC mRECIST criteria.
[b] Stratification factors included geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] Denominator is patients with confirmed CR/PR. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

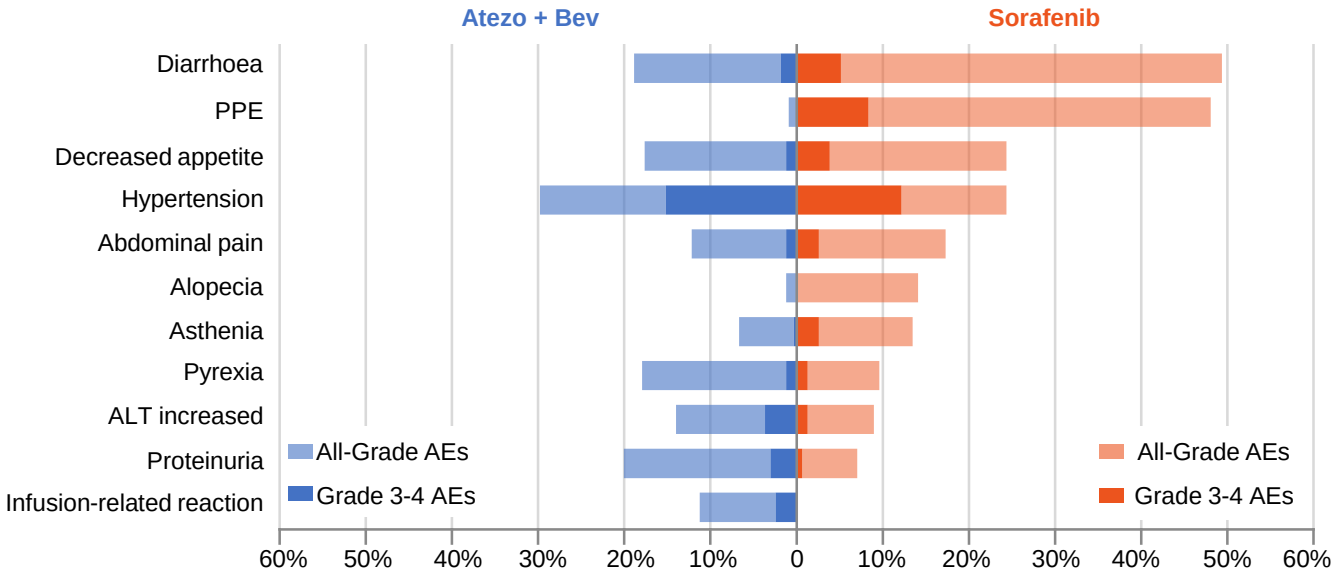
Safety summary[a]

Characteristic	Atezo + Bev (n = 329)	Sorafenib (n = 156)
Treatment duration, median, mo	**Atezo = 7.4; Bev = 6.9**	**2.8**
All-Grade AEs, any cause, n (%)	323 (98)	154 (99)
Treatment-related all-Grade AEs	276 (84)	147 (94)
Grade 3-4 AE , n (%)[b]	186 (57)	86 (55)
Treatment-related Grade 3-4 AE[b]	117 (36)	71 (46)
Serious adverse event, n (%)	125 (38)	48 (31)
Treatment-related SAE	56 (17)	24 (15)
Grade 5 AE, n (%)	15 (5)	9 (6)
Treatment-related Grade 5 AE	6 (2)	1 (< 1)
AE leading to withdrawal from any component, n (%)	51 (16)	16 (10)
AE leading to withdrawal from both components	23 (7)	16 (10)
AE leading to dose interruption of any study treatment, n (%)	163 (50)	64 (41)
AE leading to dose modification of sorafenib, n (%)[c]	0	58 (37)

[a] Safety-evaluable population. [b] Highest grade experienced.
[c] No dose modification allowed for Atezo + Bev arm.

Safety[a]

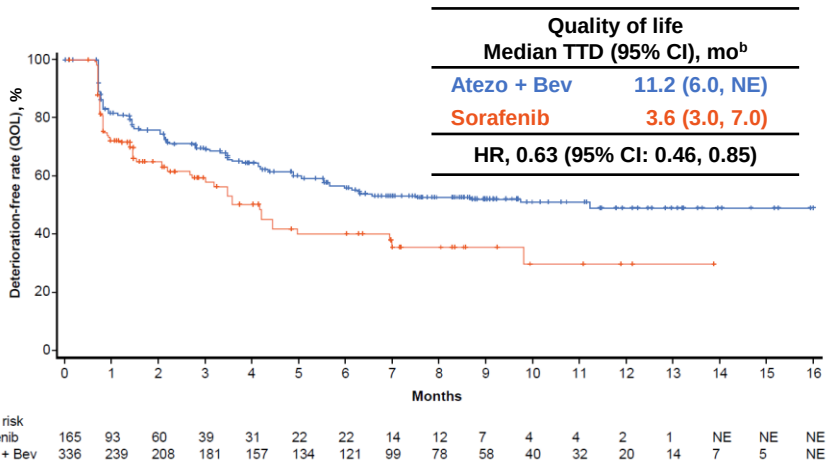
≥ 10% frequency of AEs in either arm and > 5% difference between arms



PPE, palmar-plantar erythrodysaesthesia.
[a] Safety-evaluable population.

Patient-reported outcomes[a]

- Atezolizumab + bevacizumab delayed the time to deterioration of patient-reported quality of life compared with sorafenib



EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire for Cancer; TTD, time to deterioration.
[a] Pre-specified secondary endpoint that was not formally tested; EORTC QLQ-C30 administered every 3 weeks on treatment and every 3 months after treatment discontinuation or progression. [b] Time to deterioration defined as first decrease from baseline of ≥ 10 points[1] in the patient-reported health-related global health status/quality of life (GHS/QoL) scale of the EORTC QLQ-C30 maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.
1. Osoba D, et al. *J Clin Oncol*. 1998.
Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

IMbrave150 conclusions

- IMbrave150 demonstrated statistically significant and clinically meaningful improvement with atezolizumab + bevacizumab over sorafenib for OS and IRF-assessed PFS per RECIST 1.1
  - OS HR, 0.58 (95% CI: 0.42, 0.79); *P* = 0.0006
  - IRF-PFS HR, 0.59 (95% CI: 0.47, 0.76); *P* < 0.0001

  Co-primary endpoints in ITT population
- PFS and OS benefits were generally consistent across subgroups
- Statistically significant and clinically meaningful improvements were seen in ORR and responses were durable with atezolizumab + bevacizumab
- The safety and tolerability profile of atezolizumab + bevacizumab was in line with the known safety profiles of each individual component and the underlying disease
- Treatment with atezolizumab + bevacizumab resulted in a clinically meaningful delay in deterioration of patient-reported quality of life vs sorafenib
- Atezolizumab + bevacizumab should be considered a practice-changing treatment for patients with unresectable HCC who have not received prior systemic therapy

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Investigator list

R. Anty
T. Aramaki
R. Asghari
J. Asselah
E. Assenat
J.-H. Baek
Y. Bai
A. Baron
B. Bencsikova
T. Berg
V. Breder
V. Broadbridge
J.-P. Bronowicki
A. Burgoyne
W. Cance
B. Cao
H. Castel
S. Cattan
A. Cencelewicz
L. Chan
Y. Chao
M. Chen
X. Chen
A.-L. Cheng
Y. Cheng
V. Chiu
H.-J. Choi
A. Cubillo Gracian
F. Dayyani
F. Di Fiore
M. Ducreux
J. Evans
W. Fang
J. Feliu Batlle
Y.-H. Feng
R. Finn
G. Frassineti
D. Germano
R. Gerolami Santandrea
R. Goel
P. Gold
K. Gu
S. Gu
Y. Guo
A. Hagihara
A.-R. He
Y. He
H. Hidaka
S. Hige
R. Hubner
P. Hudziec
J.-E. Hwang
M. Ikeda
E. Janczewska
A. Kandulski
A. Kaseb
N. Kato
P. Kavan
R. Kim
T.-Y. Kim
H. Koga
M. Kudo
M. Kundranda
D. Li
W. Li
H.-Y. Lim
D. Lin
L. Lipton
T. Macarulla Mercade
G. Masi
B. Melichar
Z. Meng
P. Merle
T. Meyer
T. Müller
M. Nguimpi Tambou
K. Ogawa
N. Oza
H. Pan
R. Pazo Cid
S. Qin
Z. Ren
P. Ross
P. Rozanowski
B.-Y. Ryoo
R. Salgia
J. Samol
J. Sastre Valera
G. Scagliotti
M. Scartozzi
J. Suga
M. Tanaka
H.-C. Toh
Y. Touchefeu
N. Trikalinos
J. Trojan
K. Tsuchiya
A. Vogel
N. Volkov
B. Wang
W. Wang
H. Wege
M. Wieczorek-Rutkowska
M. Wörns
J. Wu
B. Xing
T. Yamashita
T.-S. Yang
T. Yau
C.-J. Yen
J. Ying
X. Yuan
V. Zagonel
A. Zekry
H. Zhao
A. Zhu