IMbrave050: Phase 3 study of adjuvant atezolizumab + bevacizumab versus active surveillance in patients with hepatocellular carcinoma at high risk of disease recurrence following resection or ablation

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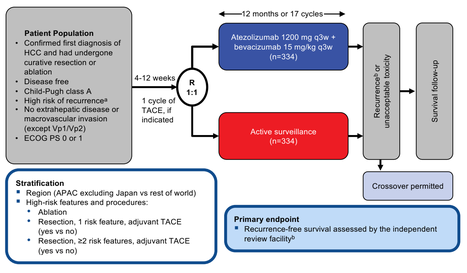
BACKGROUND

- Currently, no standard of care exists in the adjuvant setting for hepatocellular carcinoma (HCC) following resection or ablation with curative intent
- The risk of postoperative recurrence is high, with a reported 63% recurrence rate at 5 years. This rate is even higher in patients with high-risk features (e.g., large tumor size, multiple tumors, poor tumor differentiation, or vascular invasion)[1,2]
  - Recurrence occurs in a bimodal pattern, with most events appearing within 2 years of resection or ablation followed by a second wave at 4-5 years[1,3]
- VEGF/PD-L1 blockade augments anti-cancer immune mechanisms relevant to postoperative HCC recurrence[4]
- The Phase 3 IMbrave150 study demonstrated statistically significant and clinically meaningful improvement in progression-free survival, overall survival and objective response rate with atezolizumab (atezo) + bevacizumab (bev) compared with sorafenib in the first-line unresectable HCC setting, establishing atezo + bev as a standard of care[5,6]
- Here we report the results of IMbrave050, a global, open-label, Phase 3, randomized study of atezo + bev vs active surveillance in patients at high risk of disease recurrence following resection or ablation with curative intent

METHODS

Figure 1. IMbrave050 Study Design



ClinicalTrials.gov, NCT04102098. ECOG PS; Eastern Cooperative Oncology Group performance status; Q3W, every three weeks; R, randomization; TACE, transarterial chemoembolization.
[a]High-risk features include: tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion (Vp1/Vp2), or Grade 3/4 pathology.
[b]Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1.

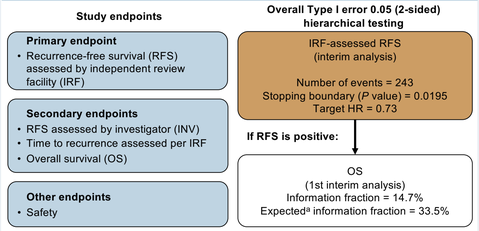
Figure 2. High-risk criteria by curative treatment

Curative treatment	Criteria for high risk of HCC recurrence
Resection	▪ ≤3 tumors, with largest tumor >5 cm regardless of vascular invasion,[a] or poor tumor differentiation (Grade 3 or 4) ▪ ≥4 tumors, with largest tumor ≤5 cm regardless of vascular invasion,[a] or poor tumor differentiation (Grade 3 or 4) ▪ ≤3 tumors, with largest tumor ≤5 cm with vascular invasion,[a] and/or poor tumor differentiation (Grade 3 or 4)
Ablation[b]	▪ 1 tumor >2 cm but ≤5 cm ▪ Multiple tumors (≤4 tumors), all ≤5 cm

[a]Microvascular invasion or minor macrovascular portal vein invasion of the portal vein—Vp1/Vp2.
[b]Ablation must be radiofrequency ablation or microwave ablation.

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.

Figure 3. Study endpoints and testing hierarchy



[a]Per protocol.

RESULTS

Table 1. Baseline characteristics were balanced across treatment arms

Characteristic	Atezo + bev (n=334)	Active surveillance (n=334)
Median age (range), years	60 (19-89)	59 (23-85)
Male sex, n (%)	277 (82.9)	278 (83.2)
Ethnicity, n (%)		
Asian	276 (82.6)	269 (80.5)
White	35 (10.5)	41 (12.3)
Other	23 (6.9)	24 (7.2)
Geographic region, n (%)		
Asia Pacific excluding Japan | rest of world	237 (71.0) | 97 (29.0)	238 (71.3) | 96 (28.7)
ECOG PS score, n (%)		
0 | 1	258 (77.2) | 76 (22.8)	269 (80.5) | 65 (19.5)
PD-L1 status, n (%)[a,b]		
≥1% | <1%	154 (54.0) | 131 (46.0)	140 (50.2) | 139 (49.8)
Etiology, n (%)		
Hepatitis B	209 (62.6)	207 (62.0)
Hepatitis C	34 (10.2)	38 (11.4)
Non viral | unknown	45 (13.5) | 46 (13.8)	38 (11.4) | 51 (15.3)
BCLC stage at diagnosis, n (%)		
0	2 (0.6)	3 (0.9)
A	287 (85.9)	277 (82.9)
B	25 (7.5)	32 (9.6)
C	20 (6.0)	22 (6.6)

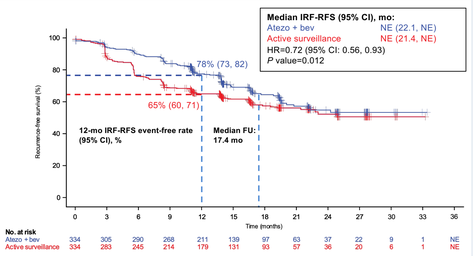
BCLC; Barcelona Clinic Liver Cancer.
[a]n=285 for atezo + bev and 279 for active surveillance. [b]PD-L1 expression is defined as the total percentage of the tumor area covered by tumor and immune cells stained for PD-L1 using the SP263 immunohistochemistry assay (VENTANA).

Table 2. Baseline characteristics—curative procedures

Characteristic	Atezo + bev (n=334)	Active surveillance (n=334)
Resection, n (%)	293 (87.7)	292 (87.4)
Longest diameter of the largest tumor at diagnosis, median (range), cm[a]	5.3 (1.0-18.0)	5.9 (1.1-25.0)
Tumors, n (%)		
1	266 (90.8)	260 (89.0)
2	20 (6.8)	29 (9.9)
3	4 (1.4)	2 (0.7)
4+	3 (1.0)	1 (0.3)
Adjuvant TACE following resection, n (%)	32 (10.9)	34 (11.6)
Any tumors >5 cm, n (%)	152 (51.9)	175 (59.9)
Microvascular invasion present, n (%)	178 (60.8)	176 (60.3)
Minor macrovascular invasion (Vp1/Vp2) present, n (%)	22 (7.5)	17 (5.8)
Poor tumor differentiation (Grade 3 or 4), n (%)	124 (42.3)	121 (41.4)
Ablation, n (%)	41 (12.3)	42 (12.6)
Longest diameter of the largest tumor at diagnosis, median (range), cm	2.5 (1.2-4.6)	2.6 (1.5-4.6)
Tumors, n (%)		
1	29 (70.7)	31 (73.8)
2	11 (26.8)	8 (19.0)
3	1 (2.4)	3 (7.1)

[a]1 patient in the atezo + bev arm was excluded from the calculation due to data entry error.

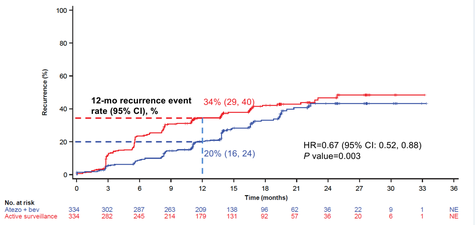
Figure 4. Primary endpoint: IRF-assessed RFS was significantly improved with atezo + bev vs active surveillance



FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log rank.

- At clinical cutoff, 110 of 334 (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death
- A 28% reduction in risk of recurrence was observed with atezo + bev

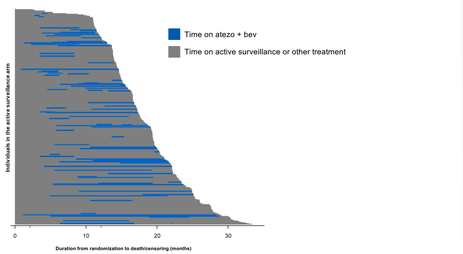
Figure 5. IRF-assessed disease recurrence was 33% lower in the atezo + bev group than the active surveillance group



HR is stratified. *P* value is a log rank.

- Patients in the active surveillance arm were allowed to cross over to receive atezo + bev either directly after IRF-confirmed recurrence or following a second resection or ablation
  - Of the 133 patients with an RFS event during active surveillance, 81 (61%) crossed over to atezo + bev

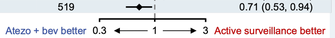
Figure 6. Time on different treatments for patients in the active surveillance arm



NE, not estimable. HR is stratified.

Figure 7. IRF-assessed RFS subgroups

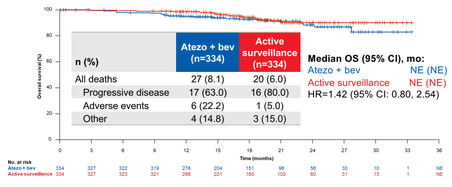
Baseline risk factors	No. of patients	Unstratified HR (95% CI)
All patients	668	0.74 (0.57, 0.95)
<65 years old	427	0.80 (0.58, 1.08)
≥65 years old	241	0.64 (0.41, 1.00)
Male	555	0.74 (0.56, 0.98)
Female	113	0.73 (0.38, 1.40)
Asian	545	0.75 (0.56, 0.99)
White	78	0.59 (0.28, 1.25)
Other race	45	0.91 (0.36, 2.29)
ECOG PS 0	527	0.65 (0.48, 0.87)
ECOG PS 1	141	1.13 (0.67, 1.91)
PD-L1 ≥1%	294	0.82 (0.55, 1.20)
PD-L1 <1%	270	0.62 (0.43, 0.91)
Unknown PD-L1	104	0.82 (0.39, 1.71)
1 high-risk feature[a]	311	0.74 (0.48, 1.14)
≥2 high-risk features[a]	274	0.77 (0.55, 1.08)
BCLC 0/A	569	0.78 (0.59, 1.04)
BCLC B	57	0.44 (0.18, 1.08)
BCLC C	42	0.73 (0.31, 1.73)
Hepatitis B etiology	416	0.87 (0.63, 1.20)
Hepatitis C etiology	72	0.65 (0.30, 1.40)
Non-viral etiology	83	0.70 (0.34, 1.42)
Unknown etiology	97	0.45 (0.23, 0.89)
Resection	585	0.75 (0.58, 0.98)
Ablation	83	0.61 (0.26, 1.41)
In patients who underwent resection		
1 tumor	526	0.77 (0.58, 1.03)
>1 tumors	59	0.60 (0.28, 1.27)
Tumor size >5 cm	327	0.66 (0.48, 0.91)
Tumor size ≤5 cm	258	1.06 (0.65, 1.74)
mVI present	354	0.79 (0.56, 1.10)
mVI absent	231	0.69 (0.45, 1.06)
Poor tumor differentiation	245	0.76 (0.51, 1.12)
No poor tumor differentiation	340	0.74 (0.52, 1.07)
Received TACE	66	1.21 (0.57, 2.59)
Did not receive TACE	519	0.71 (0.53, 0.94)



mVI, microvascular invasion.
[a]Patients who underwent ablation were categorized as "not applicable."

- OS is highly immature, with a 7% event-patient ratio (n=47). There were:
  - 7 more deaths in the atezo + bev arm (27 vs 20)
  - Similar number of deaths due to HCC recurrence
  - 3 COVID-19-related deaths within 1 year of randomization, all in the atezo + bev arm
- Patients in the active surveillance arm were allowed to cross over to receive atezo + bev either directly after IRF-confirmed recurrence or following a second resection or ablation
  - Of the 133 patients with an RFS event during active surveillance, 81 (61%) crossed over to atezo + bev

Figure 8. Overall survival was highly immature



NE, not estimable. HR is stratified.

References

1.Chan et al. *J Hepatol* 2018; 2. Lim et al. *Br J Surg* 2012; 3. Imamura et al. *J Hepatol* 2003; 4. Hack et al. *Future Oncol* 2020; 5. Finn et al. *NEJM* 2020; 6. Cheng et al. *J Hepatol* 2022. 7. Roche, data on file.

Table 4. Safety summary

	Atezo + bev (n=332)	Active[a] surveillance (n=330)	IMbrave150[5,7] (n=329)
Treatment duration, median, mo	Atezo: 11.1 Bev: 11.0	NA	Atezo: 7.4 Bev: 6.9
Patients with ≥1 AE, n (%)	326 (98.2)	205 (62.1)	323 (98.2)
Treatment-related AE	293 (88.3)	NA	276 (83.9)
Grade 3/4 AE, n (%)	136 (41.0)	44 (13.3)	186 (56.5)
Treatment-related Grade 3/4 AE	116 (34.9)	NA	117 (35.6)
Serious AE, n (%)	80 (24.1)	34 (10.3)	125 (38.0)
Treatment-related serious AE	44 (13.3)	NA	56 (17.0)
Grade 5 AE, n (%)	6 (1.8)	1 (0.3)[c]	15 (4.6)
Treatment-related Grade 5 AE	2 (0.6)[b]	NA	6 (1.8)
AE leading to dose interruption of any study treatment, n (%)	155 (46.7)	NA	163 (49.5)
AE leading to withdrawal from any study treatment, n (%)	63 (19.0)	NA	51 (15.5)

In safety-evaluable patients. AE, adverse event. NA, not available.
[a] All safety data for the surveillance arm are from evaluations prior to crossover. [b]Esophageal varices hemorrhage and ischemic stroke. 1 was related to atezo and bev and the other was related to bev only.
[c]Esophageal varices hemorrhage.

Table 5. AE of any grade with an incidence rate of ≥10% in either treatment group by preferred term

Event, n (%)	Atezo + bev (n=332)		Active surveillance[a] (n=330)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Proteinuria	154 (46.4)	29 (8.7)	12 (3.6)	0
Hypertension	127 (38.3)	61 (18.4)	10 (3.0)	3 (0.9)
Platelet count decreased	66 (19.9)	15 (4.5)	22 (6.7)	4 (1.2)
Aspartate aminotransferase increased	52 (15.7)	3 (0.9)	18 (5.5)	2 (0.6)
Alanine aminotransferase increased	47 (14.2)	2 (0.6)	18 (5.5)	3 (0.9)
Hypothyroidism	47 (14.2)	0	1 (0.3)	0
Arthralgia	40 (12.0)	1 (0.3)	8 (2.4)	1 (0.3)
Pruritus	40 (12.0)	1 (0.3)	3 (0.9)	0
Rash	40 (12.0)	0	1 (0.3)	0
Blood bilirubin increased	34 (10.2)	1 (0.3)	23 (7.0)	1 (0.3)
Pyrexia	34 (10.2)	0	7 (2.1)	0

In safety-evaluable patients. [a] All safety data for the surveillance arm are from evaluations prior to crossover.

CONCLUSIONS

- IMbrave050 is the first Phase 3 study of adjuvant treatment for HCC to demonstrate RFS improvement following curative intent resection or ablation
- At the prespecified interim analysis, adjuvant atezolizumab + bevacizumab met its primary endpoint and showed a statistically significant and clinically meaningful improvement in IRF-assessed RFS vs active surveillance in patients with a high risk of HCC recurrence (HR, 0.72; 95% CI: 0.56, 0.93; *P*=0.012)
  - Similar improvement in INV-assessed RFS was also observed
- RFS benefit with atezolizumab + bevacizumab was generally consistent across key clinical subgroups
- At the time of this prespecified interim analysis, OS was highly immature compared with assumptions made in the protocol; longer follow-up for OS is needed
- The safety profile of adjuvant atezolizumab + bevacizumab was generally consistent with that of each agent and with the underlying disease
- Atezolizumab + bevacizumab may be a practice-changing adjuvant treatment option for patients with high-risk HCC that may change the clinical indications for surgical resection

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Disclosures

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