AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

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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Disclosure information

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I have the following relevant financial relationships to disclose:

Employee of: SingHealth, Duke-NUS Medical School

Consultant for: AUM Biosciences, BeiGene, Omega Therapeutics, Roche, and Sirtex

Speaker's bureau for: AstraZeneca, Bayer, Omega Therapeutics, Roche, and Worrell

Grant/research support from: Roche and Sirtex

Stockholder in: AVATAMED

Honoraria from: AstraZeneca, Bayer, Perspectum, Roche, Sirtex, and Worrell

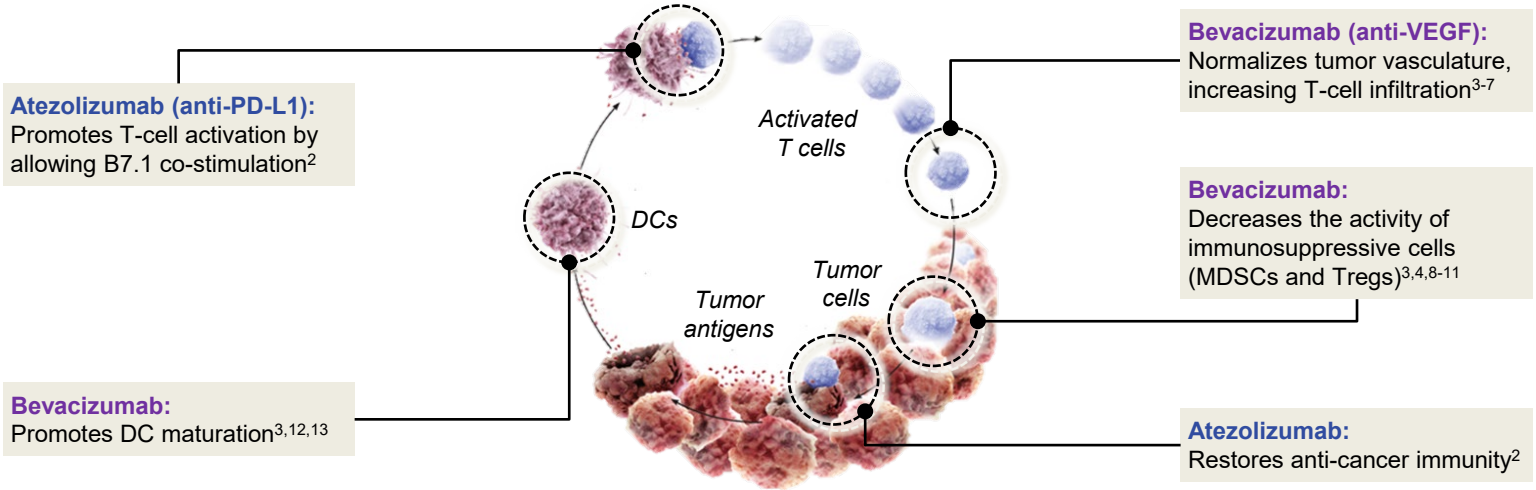
Background

- 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]
- 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[4,5]
- 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

1. Chan et al. J Hepatol 2018; 2. Lim et al. Br J Surg 2012; 3. Imamura et al. J Hepatol 2003; 4. Finn et al. NEJM 2020; 5. Cheng et al. J Hepatol 2022.

Mode of action of atezolizumab + bevacizumab

VEGF/PD-L1 blockade augments anti-cancer immune mechanisms relevant to postoperative HCC recurrence[1,2,a]



- Bevacizumab combined with atezolizumab can induce favorable immune modulation of the hepatic tumor microenvironment, thereby enhancing antitumor immunity
- These hypotheses on the mode of action of atezolizumab + bevacizumab were validated in the correlative biomarker analyses of the Phase 3 IMbrave150 study[14]

[a] Figure adapted from Chen and Mellman. Immunity 2013. DC, dendritic cell; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

1. Hack et al. Future Oncol 2020; 2. Chen, Mellman. Immunity 2013; 3. Hegde et al. Semin Cancer Biol 2017; 4. Wallin et al. Nat Commun 2016; 5. Goel et al. Physiol Rev 2011; 6. Motz et al. Nat Med 2014; 7. Hodi et al. Cancer Immunol Res 2014; 8. Gabrilovich et al. Nat Rev Immunol 2009; 9. Roland et al. PLoS One 2009; 10. Facciabene et al. Nature 2011; 11. Voron et al. J Exp Med 2015; 12. Gabrilovich et al. Nat Med 1996; 13. Oyama et al. J Immunol 1998; 14. Zhu et al. Nat Med 2022.

IMbrave050 study design

Patient Population
- Confirmed first diagnosis of HCC and had undergone curative resection or ablation
- Disease free
- Child-Pugh class A
- High risk of recurrence[a]
- No extrahepatic disease or macrovascular invasion (except Vp1/Vp2)
- ECOG PS 0 or 1

4-12 weeks

1 cycle of TACE, if indicated

R 1:1

12 months or 17 cycles

Atezolizumab 1200 mg q3w + bevacizumab 15 mg/kg q3w (n=334)

Active surveillance (n=334)

Recurrence[b] or unacceptable toxicity

Survival follow-up

Crossover permitted

Stratification
- Region (APAC excluding Japan vs rest of world)
- High-risk features and procedures:
  - Ablation
  - Resection, 1 risk feature, adjuvant TACE (yes vs no)
  - Resection, ≥2 risk features, adjuvant TACE (yes vs no)

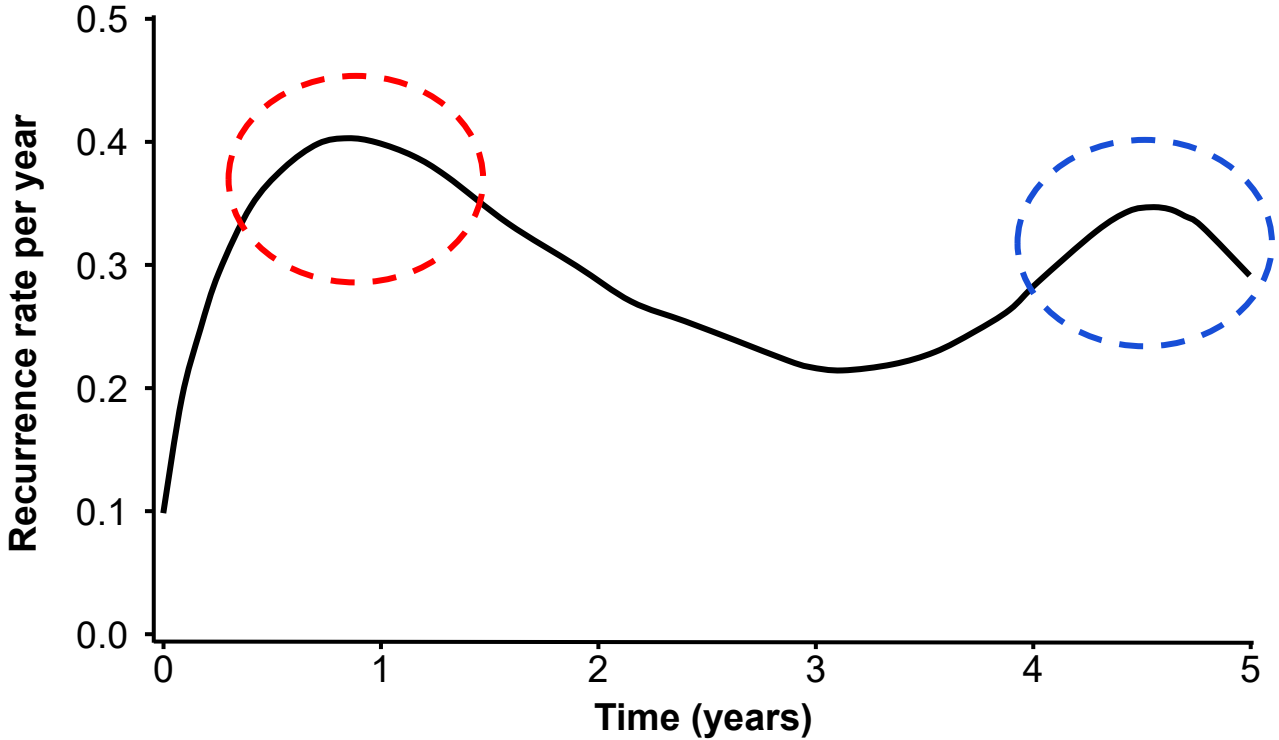
Primary endpoint
- Recurrence-free survival assessed by the independent review facility[b]

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.

Bimodal recurrence after HCC resection



- Recurrence rate after resection peaks at around **1 year**, then gradually decreases over the next 2 years.[1] Current consensus is that these recurrences are from **micro-metastases**
- A second lower postoperative recurrence peak occurs at **4-5 years**[1]
- The second peak is currently understood to be due to **de novo tumors** associated with underlying liver disease[2]

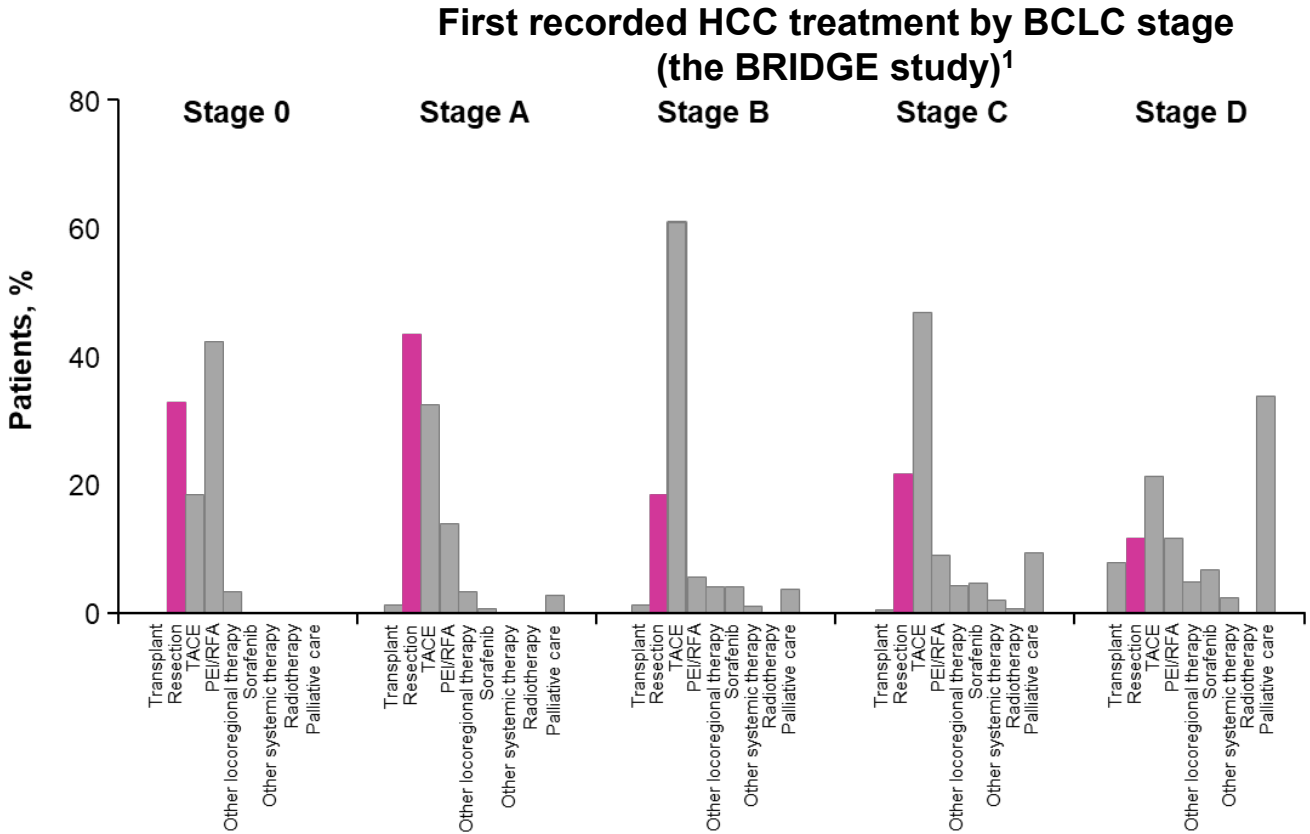
1. Imamura et al. J Hepatol 2003. 2. Yao et al. Ann Surg Oncol 2022.

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.

Resection is frequently used as first treatment for HCC with high-risk factors for recurrence



- Globally, treatment practices include surgical resection for **high-risk patients** like those enrolled in IMbrave050

1. Park et al. Liver Int 2015.

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Study endpoints and testing hierarchy

Study endpoints

Primary endpoint

- Recurrence-free survival (RFS) assessed by independent review facility (IRF)

Secondary endpoints

- RFS assessed by investigator (INV)
- Time to recurrence assessed per IRF
- Overall survival (OS)

Other endpoints

- Safety

Overall Type I error 0.05 (2-sided) hierarchical testing

IRF-assessed RFS
(interim analysis)

Number of events = 243
Stopping boundary (*P* value) = 0.0195
Target HR = 0.73

If RFS is positive:

OS
(1st interim analysis)
Information fraction = 14.7%
Expected[a] information fraction = 33.5%

[a] Per protocol.

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)

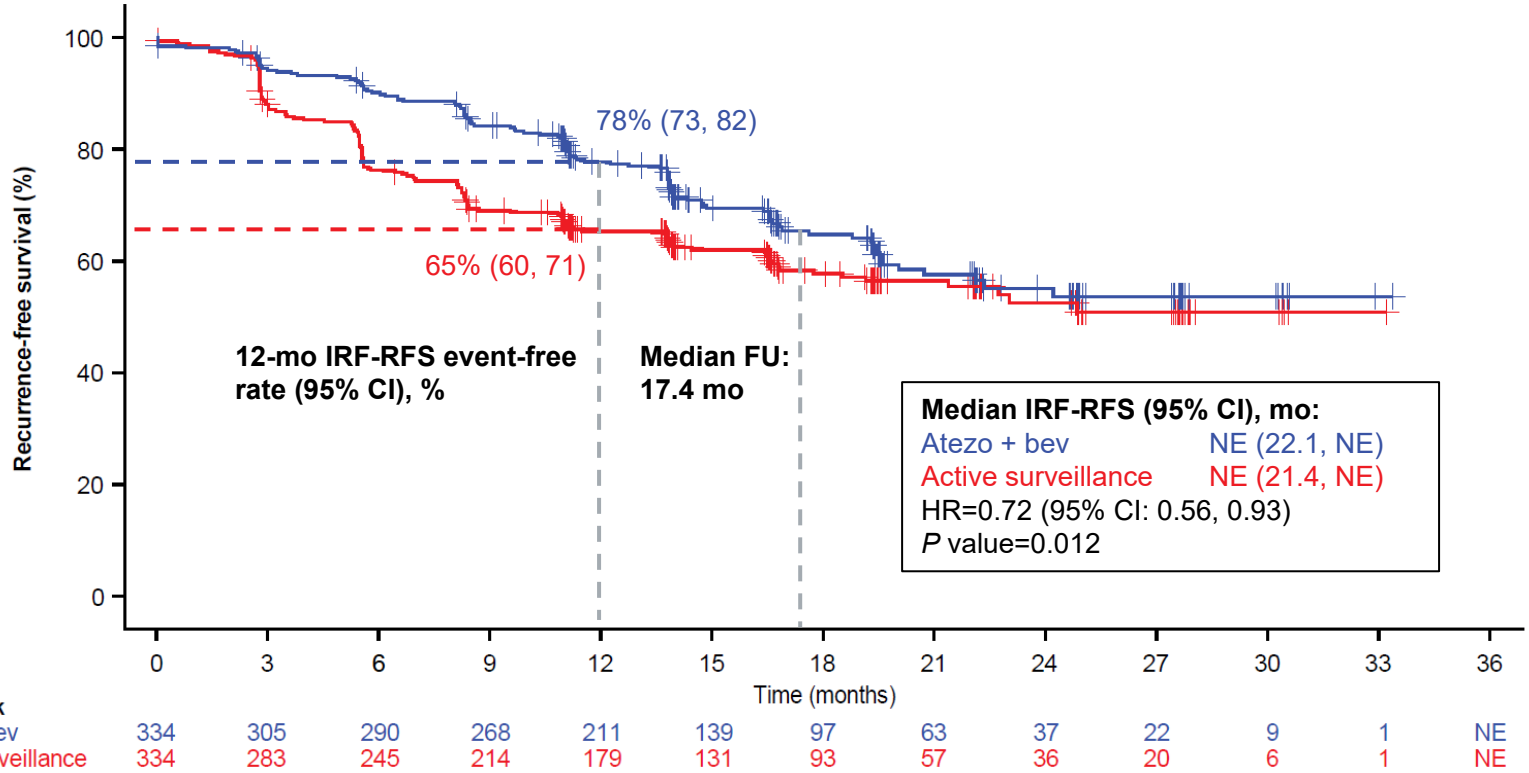
Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. BCLC; Barcelona Clinic Liver Cancer.
[a] n=285 for atezo + bev and 279 for active surveillance. [b] PD-L1 expression is defined as the total percentage of the tumor area covered by tumor and immune cells stained for PD-L1 using the SP263 immunohistochemistry assay (VENTANA).

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)

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.
[a] 1 patient in the atezo + bev arm was excluded from the calculation due to data entry error.

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



Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 110 of 334 patients (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death.
FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log rank.

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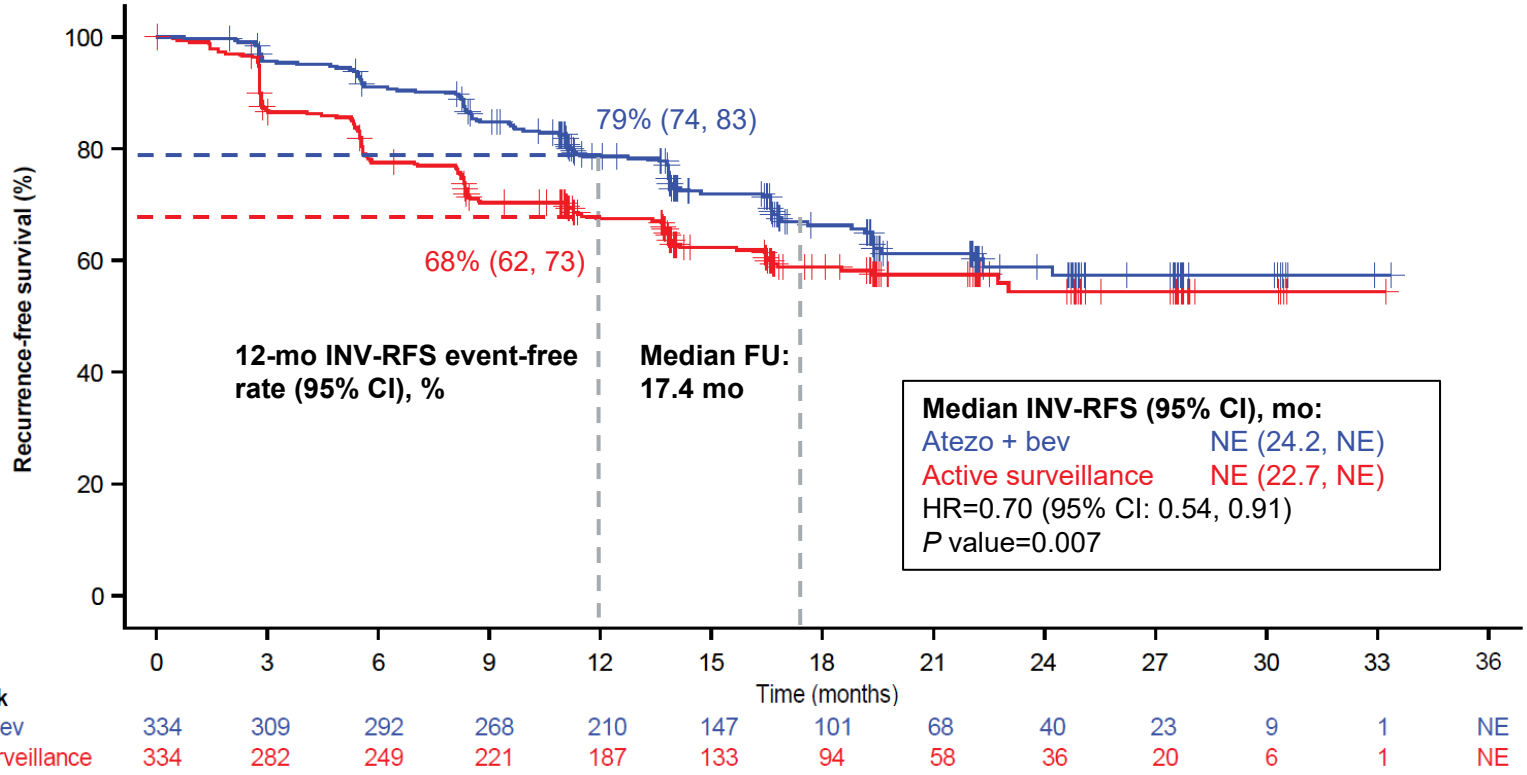
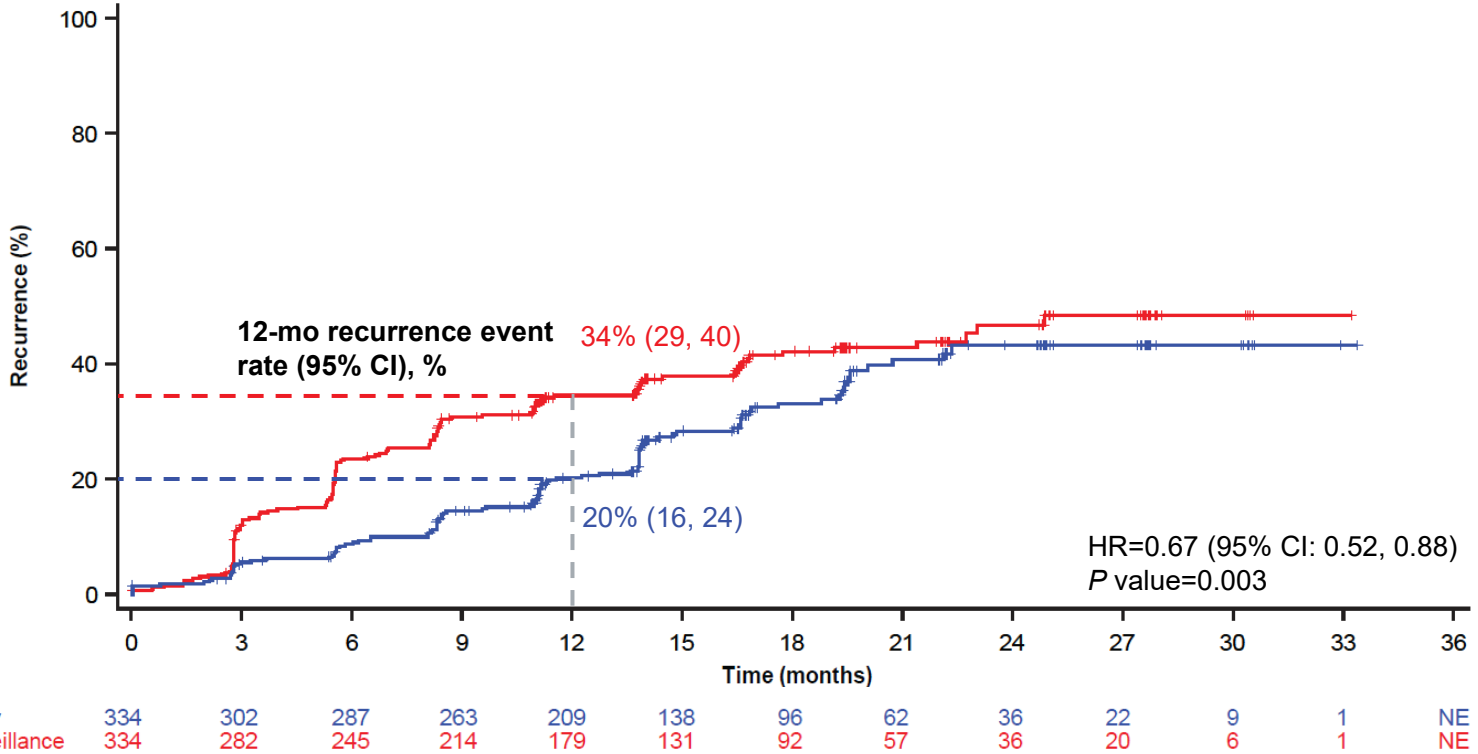
INV-assessed RFS results were consistent with those of IRF-assessed RFS



No. at risk													
Atezo + bev	334	309	292	268	210	147	101	68	40	23	9	1	NE
Active surveillance	334	282	249	221	187	133	94	58	36	20	6	1	NE

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 103 of 334 patients (31%) in the atezo + bev arm and 128 of 334 (38%) in the active surveillance arm experienced disease recurrence or death.
HR is stratified. *P* value is a log rank.

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

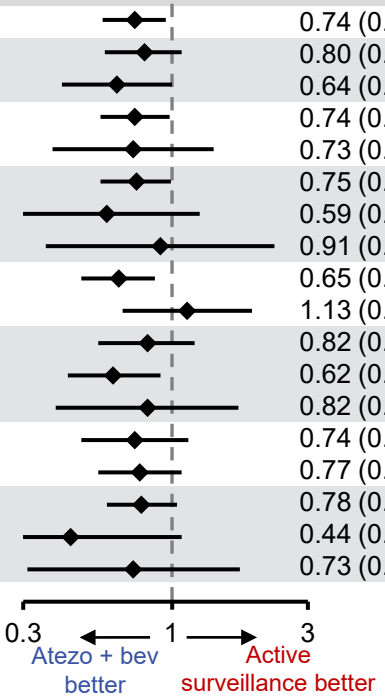


No. at risk													
Atezo + bev	334	302	287	263	209	138	96	62	36	22	9	1	NE
Active surveillance	334	282	245	214	179	131	92	57	36	20	6	1	NE

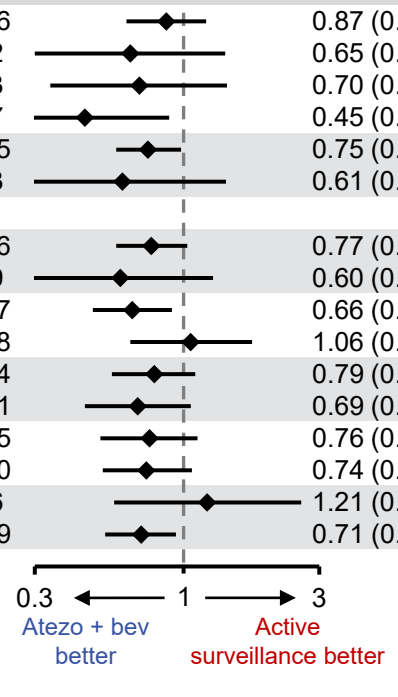
Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.
HR is stratified. *P* value is a log rank.

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)



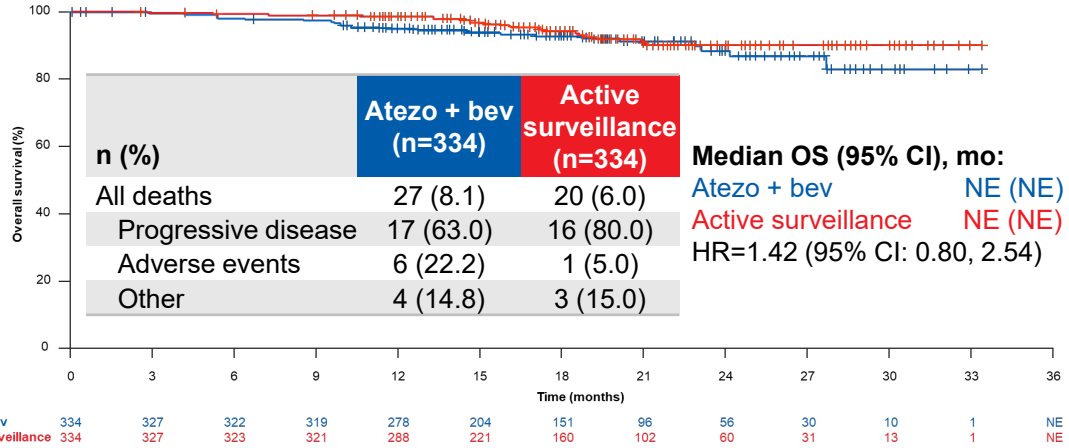
Baseline risk factors	No. of patients	Unstratified HR (95% CI)
Hepatitis B etiology	416	0.87 (0.63, 1.20)
Hepatitis C etiology	72	0.65 (0.30, 1.40)
Non-viral etiology	83	0.70 (0.34, 1.42)
Unknown etiology	97	0.45 (0.23, 0.89)
Resection	585	0.75 (0.58, 0.98)
Ablation	83	0.61 (0.26, 1.41)
In patients who 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)



Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.
mVI, microvascular invasion. [a] Patients who underwent ablation were categorized as "not applicable."

Overall survival was highly immature

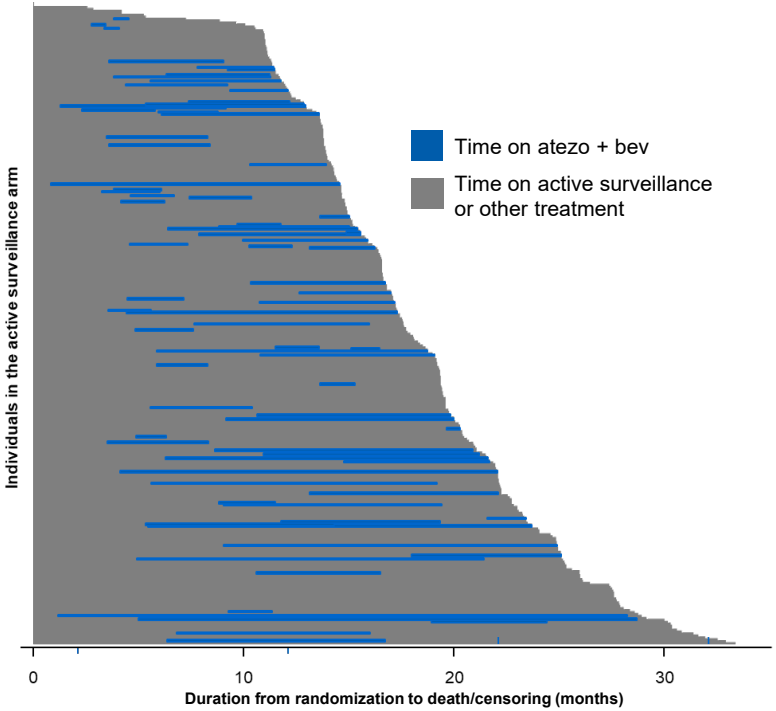
- **OS is highly immature, with a 7% event-patient ratio (n=47).** There were:
  - 7 more deaths in the atezo + bev arm (27 vs 20)
  - Similar number of deaths due to HCC recurrence
  - 3 COVID-19-related deaths within 1 year of randomization, all in the atezo + bev arm
- Patients in the active surveillance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



n (%)	Atezo + bev (n=334)	Active surveillance (n=334)
All deaths	27 (8.1)	20 (6.0)
Progressive disease	17 (63.0)	16 (80.0)
Adverse events	6 (22.2)	1 (5.0)
Other	4 (14.8)	3 (15.0)

Median OS (95% CI), mo:
Atezo + bev NE (NE)
Active surveillance NE (NE)
HR=1.42 (95% CI: 0.80, 2.54)

Of the 133 patients with an RFS event during active surveillance, **81 (61%) crossed over to atezo + bev**



Clinical cutoff: October 21, 2022. Median follow-up duration: 17.4 mo. NE, not estimable. HR is stratified.

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Safety summary

	Atezo + bev (n=332)	Active surveillance (n=330)	IMbrave150[1,2] (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)	15 (4.6)
Treatment-related Grade 5 AE	2 (0.6)[a]	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)

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. In safety-evaluable patients. AE, adverse event. NA, not available.
[a] Esophageal varices hemorrhage and ischemic stroke; 1 was related to atezo and bev and the other was related to bev only.
1. Finn et al. NEJM 2020. 2. Data on file.

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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 (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

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

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**

Acknowledgments

- The patients and their families
- The investigators and clinical study sites
- This study was sponsored by F. Hoffmann-La Roche Ltd
- This oral presentation was developed by the authors with medical writing assistance provided by Bena Lim, PhD, of Nucleus Global and funded by F. Hoffmann-La Roche Ltd