18as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2023

Madrid, 22 y 23 de noviembre de 2023

Actualización del tratamiento del hepatocarcinoma

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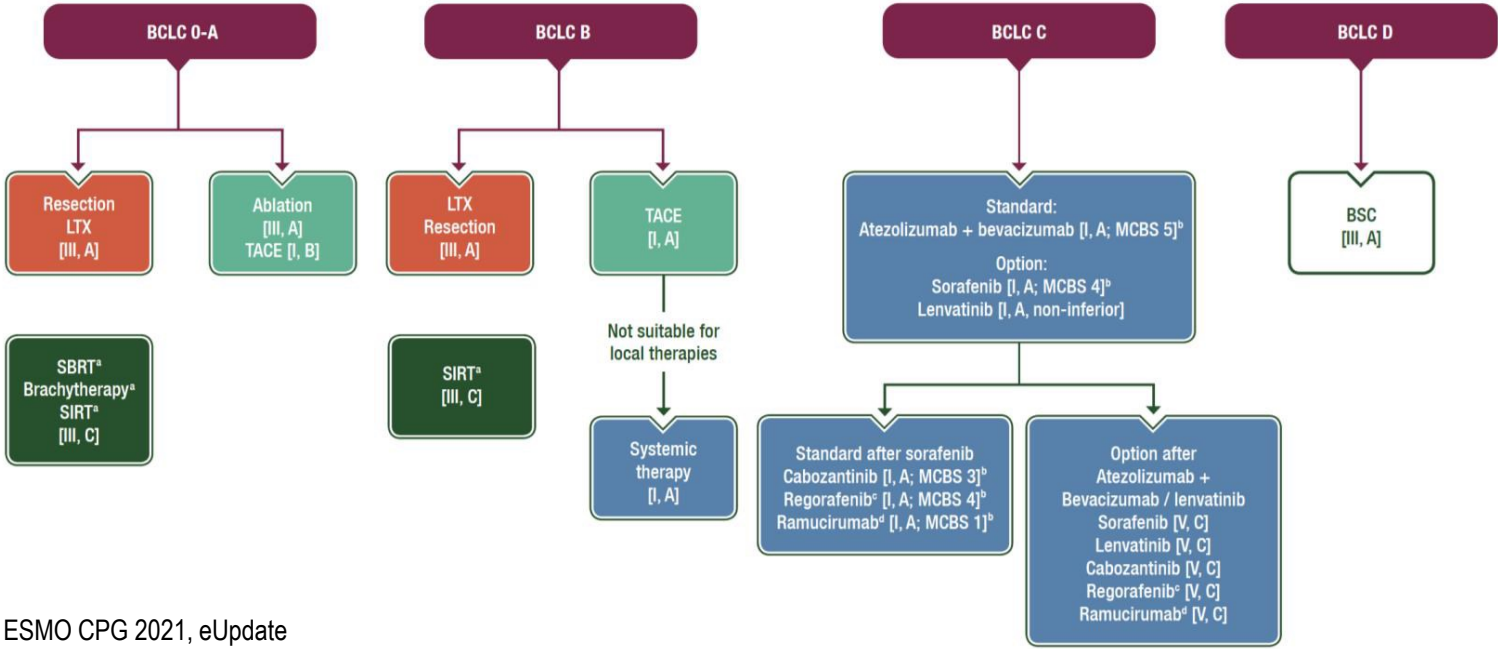
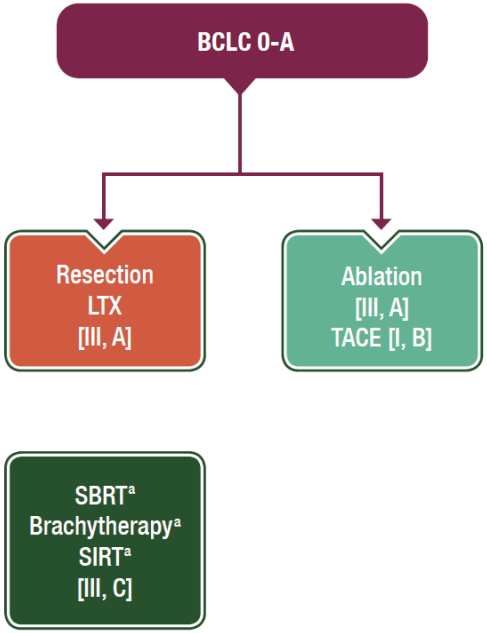
ESMO CLINICAL PRACTICE GUIDELINE HCC

IO based combinations move to earlier stages



Vogel et al. ESMO CPG 2021, eUpdate

What is on the horizon in early stage?



- **KEYNOTE-937**:

  Pembrolizumab vs placebo

- **IMbrave050**

  Atezolizumab + Bevacizumab vs placebo

- **CHECKMATE-9DX:**

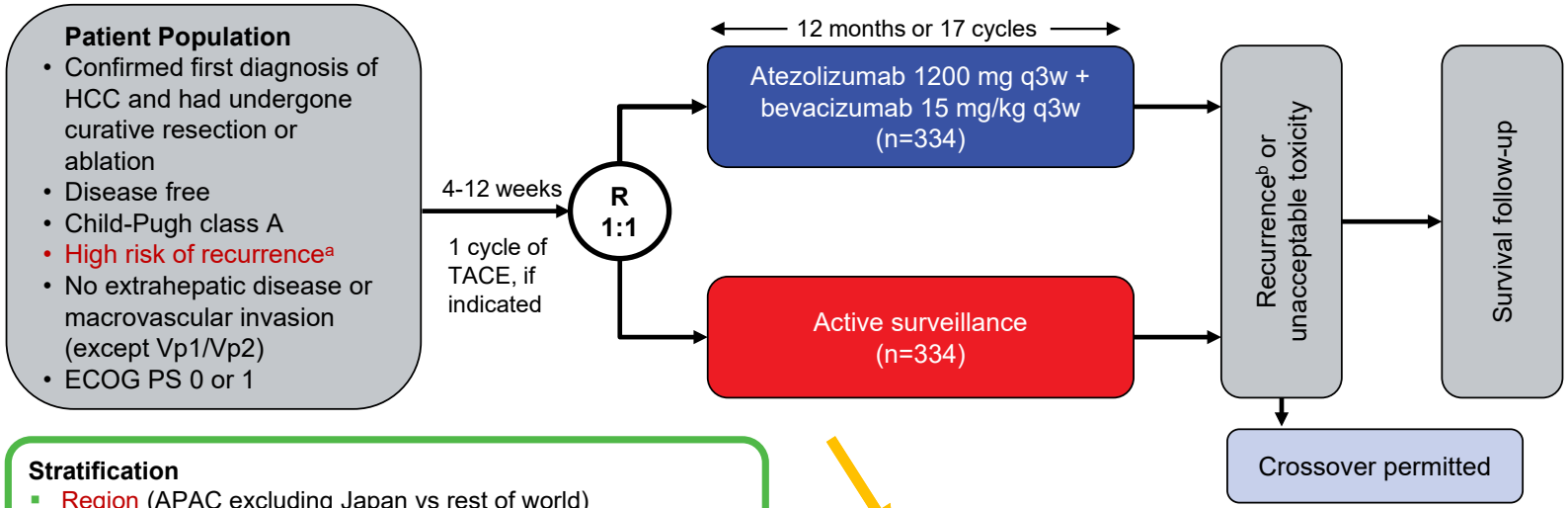
  Nivolumab vs placebo

- **EMERALD-2:**

  Durvalumab/Bevacizumab vs placebo

Modified from Vogel et al. ESMO CPG 2021, eUpdate

IMbrave050 study design

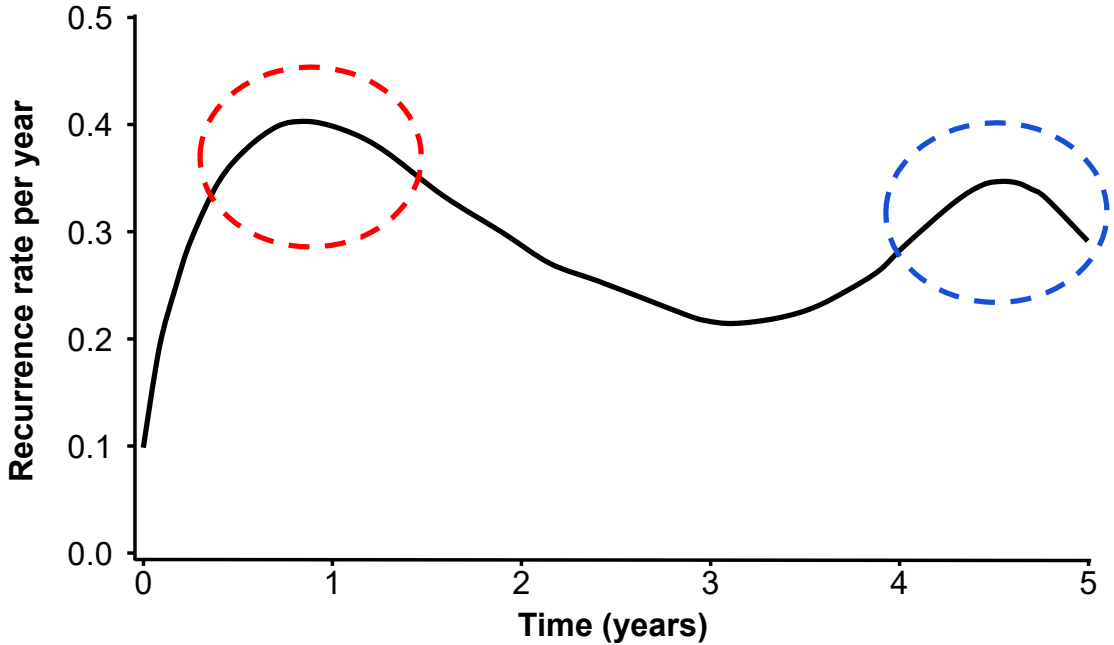


ClinicalTrials.gov, NCT04102098. ECOG PS; Eastern Cooperative Oncology Group performance status; Q3W, every three weeks; R, randomization; TACE, transarterial chemoembolization.

[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.

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.

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]		
[redacted]	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

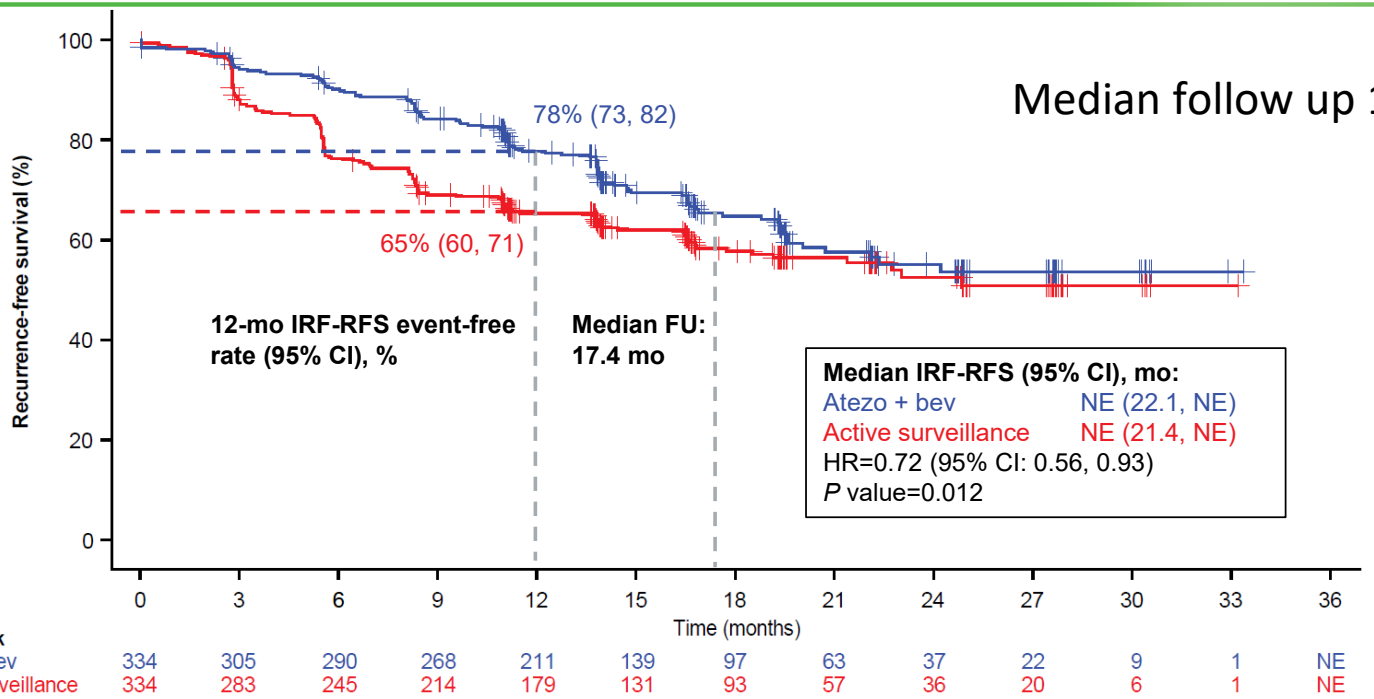
Characteristic	Atezo + bev (n=334)	Active surveillance (n=334)
Resection, n (%)	293 (87.7)	292 (87.4)
Longest diameter of the largest tumor at diagnosis, median (range), cm[a]	5.3 (1.0-18.0)	5.9 (1.1-25.0)
Tumors, n (%)		
1	266 (90.8)	260 (89.0)
2	20 (6.8)	29 (9.9)
3	4 (1.4)	2 (0.7)
4+	3 (1.0)	1 (0.3)
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)

Solitary tumor 526 patients (90%)

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

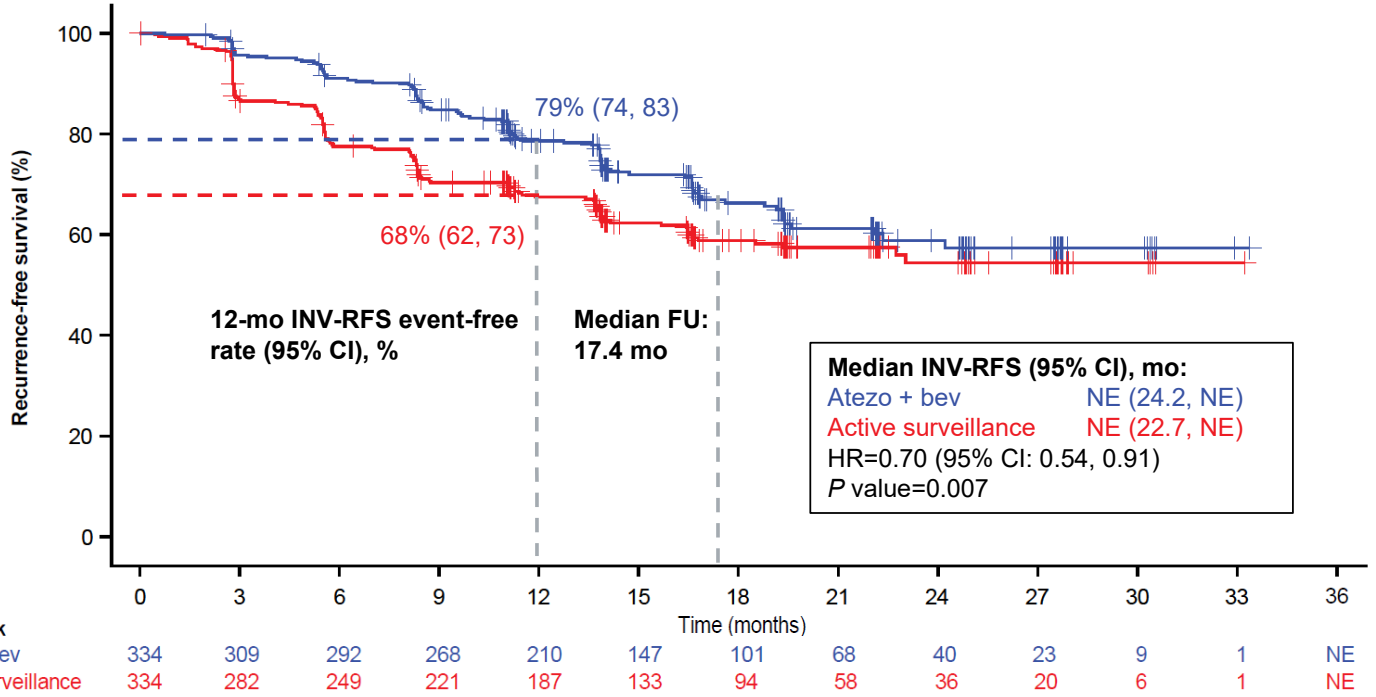
Median follow up 17.4 months



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.

Chow et al IMbrave050
https://bit.ly/3ZPKzgM

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



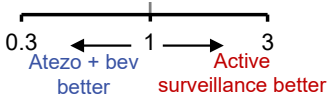
No. at risk													
Atezo + bev	334	309	292	268	210	147	101	68	40	23	9	1	NE
Active surveillance	334	282	249	221	187	133	94	58	36	20	6	1	NE

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.

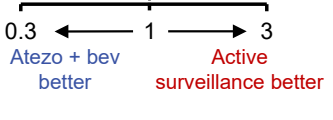
Chow et al IMbrave050
https://bit.ly/3ZPKzgM

IRF-assessed RFS subgroups

Baseline risk factors	No. of patients	Unstratified HR (95% CI)
All patients	668	0.74 (0.57, 0.95)
[illegible]	427	0.80 (0.58, 1.08)
[illegible]	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-[illegible]	294	0.82 (0.55, 1.20)
PD-[illegible]	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)
[illegible] 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)



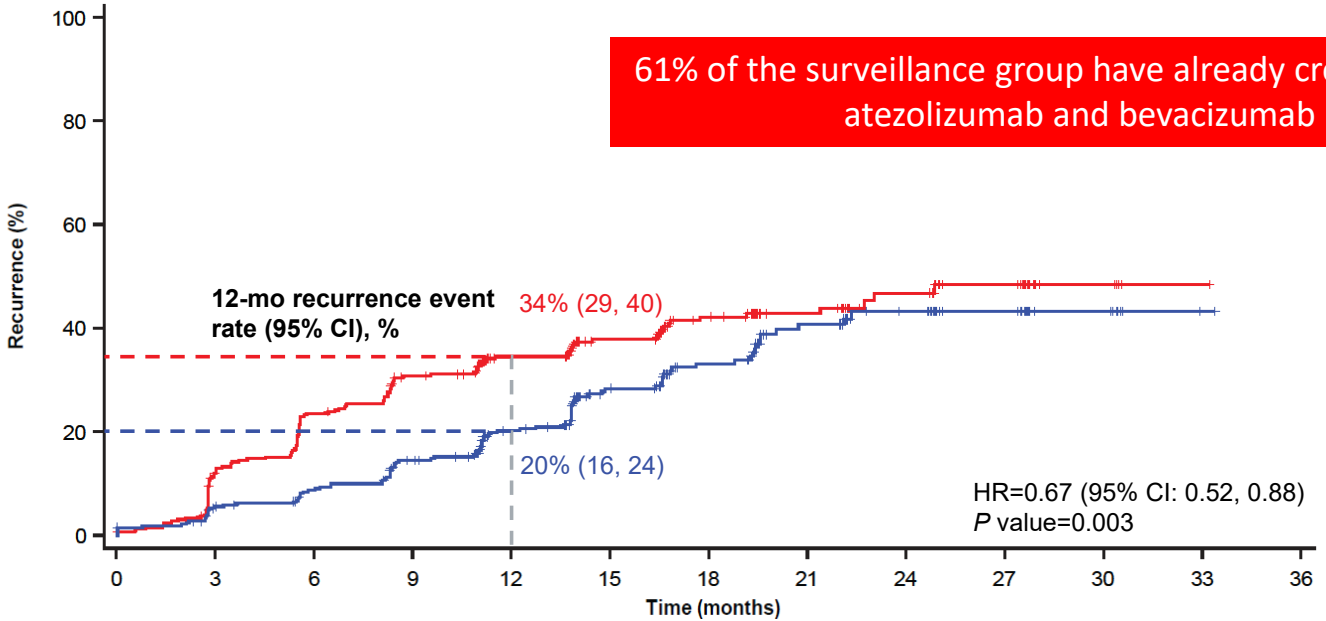
Baseline risk factors	No. of patients	Unstratified HR (95% CI)
Hepatitis B etiology	416	0.87 (0.63, 1.20)
Hepatitis C etiology	72	0.65 (0.30, 1.40)
Non-viral etiology	83	0.70 (0.34, 1.42)
Unknown etiology	97	0.45 (0.23, 0.89)
Resection	585	0.75 (0.58, 0.98)
Ablation	83	0.61 (0.26, 1.41)
In patients who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

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

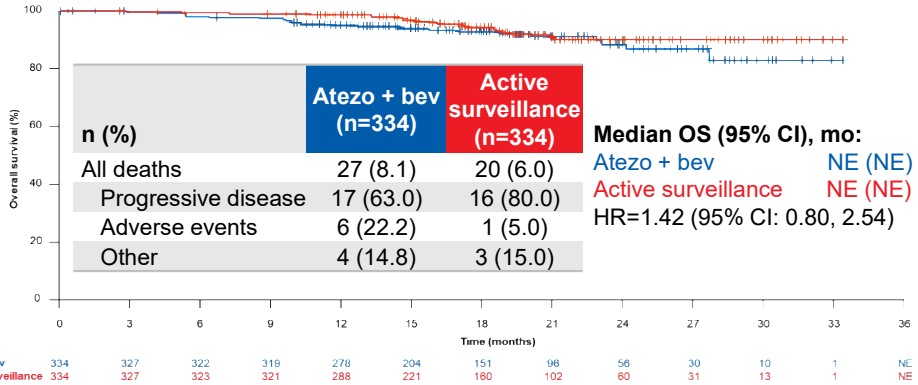
61% of the surveillance group have already crossed over to atezolizumab and bevacizumab



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

Overall survival was highly immature

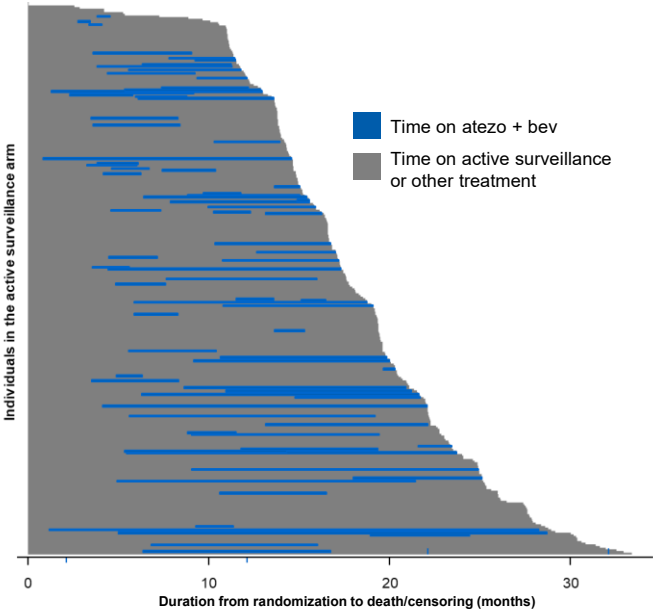
- **OS is highly immature, with a 7% event-patient ratio (n=47).** There were:
  - 7 more deaths in the atezo + bev arm (27 vs 20)
  - Similar number of deaths due to HCC recurrence
  - 3 COVID-19-related deaths within 1 year of randomization, all in the atezo + bev arm
- Patients in the active surveillance 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.

Chow et al IMbrave050
https://bit.ly/3ZPKzgM

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
[illegible]; 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.

Chow et al IMbrave050
https://bit.ly/3ZPKzgM

[illegible] treatment group by preferred term

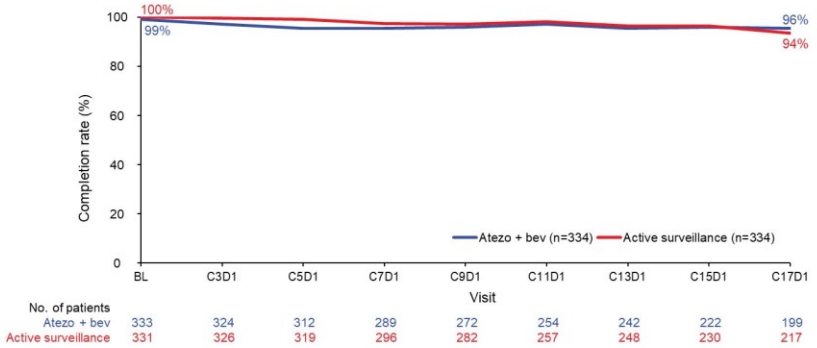
Event, n (%)	Atezo + bev (n=332)		Active surveillance (n=330)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Proteinuria	154 (46.4)	29 (8.7)	12 (3.6)	0
Hypertension	127 (38.3)	61 (18.4)	10 (3.0)	3 (0.9)
Platelet count decreased	66 (19.9)	15 (4.5)	22 (6.7)	4 (1.2)
Aspartate aminotransferase increased	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.

Efficacy, safety and patient-reported outcomes from the Phase III IMbrave050 trial of adjuvant atezolizumab + bevacizumab vs active surveillance in patients with hepatocellular carcinoma at high risk of disease recurrence following resection or ablation

Masatoshi Kudo,[1] Minshan Chen,[2] Pierce Chow,[3] Ahmed Kaseb,[4] Han Chu Lee,[5] Adam Yopp,[6] Lars Becker,[7] Sairy Hernandez,[8] Bruno Kovic,[9] Qinshu Lian,[8] Ning Ma,[8] Chun Wu,[10] Shukui Qin,[11] Ann-Lii Cheng[12]

IL42–EORTC QLQ-C30 completion rates



No. of patients									
Atezo + bev	333	324	312	289	272	254	242	222	199
Active surveillance	331	326	319	296	282	257	248	230	217

- IL42–EORTC-C30 completion rates remained >93% in both arms from baseline through Cycle 17 of treatment or surveillance[a]
- Interpretation of analyses focused on data through Cycle 17, when over half of the population in each arm remained in the study

[a]Includes responses with ≥1 question completed.
Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.

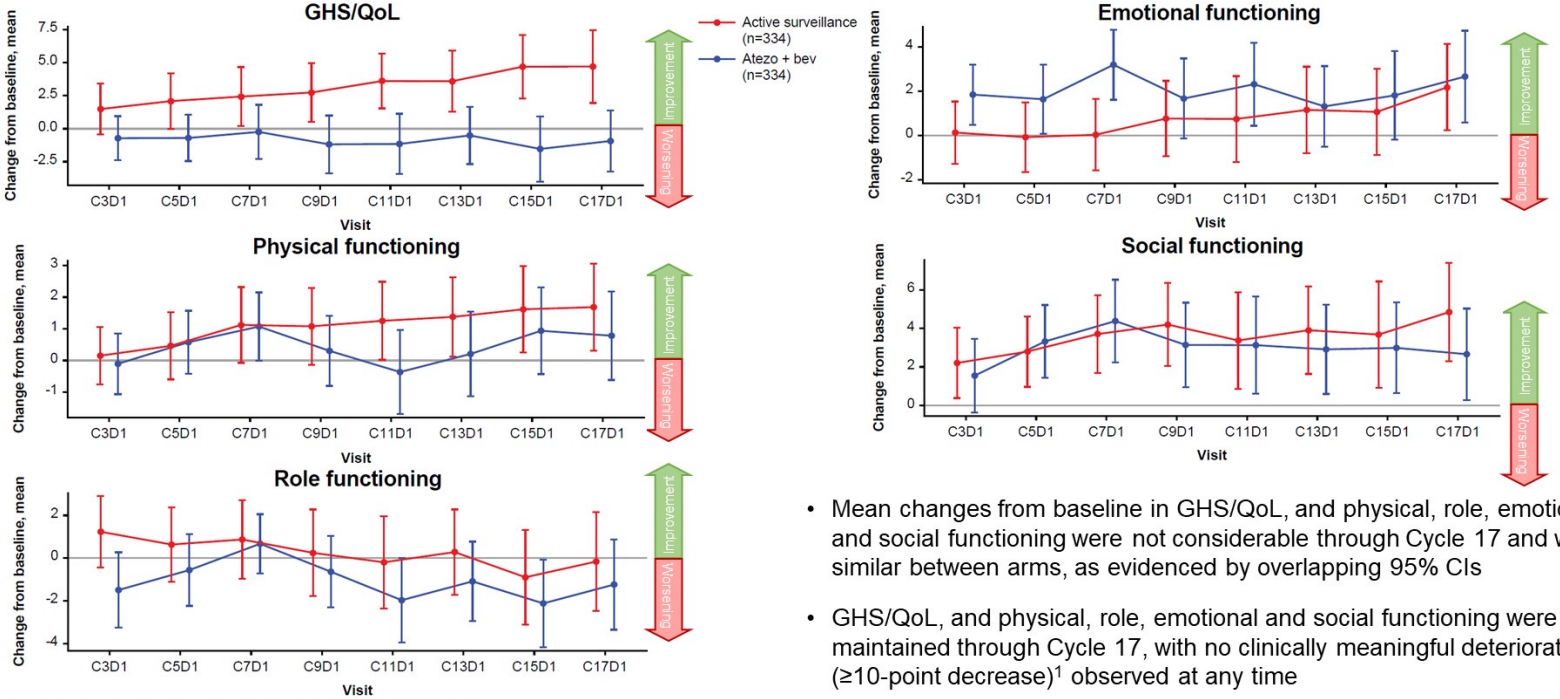
IL42–EORTC QLQ-C30 baseline scale scores

- Mean scores at baseline in both arms were high and similar

Baseline scale score, mean (SD)	Atezo + Bev (n=334)	Active surveillance (n=334)	General population[1]
GHS/QoL	**81.2** (16.7)	**79.1** (18.6)	**71.2** (22.4)
Physical functioning	**92.4** (10.7)	**92.1** (11.3)	**89.8** (16.2)
Role functioning	**92.7** (13.9)	**92.1** (15.4)	**84.7** (25.4)
Emotional functioning	**88.8** (14.9)	**88.8** (15.4)	**76.3** (22.8)
Social functioning	**88.2** (17.7)	**87.3** (19.0)	**87.5** (22.9)

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.
1. Scott et al. *EORTC QLQ-C30 Reference Values*. EORTC Quality of Life Group; 2008.

Change from baseline in IL42–EORTC QLQ-C30 scales



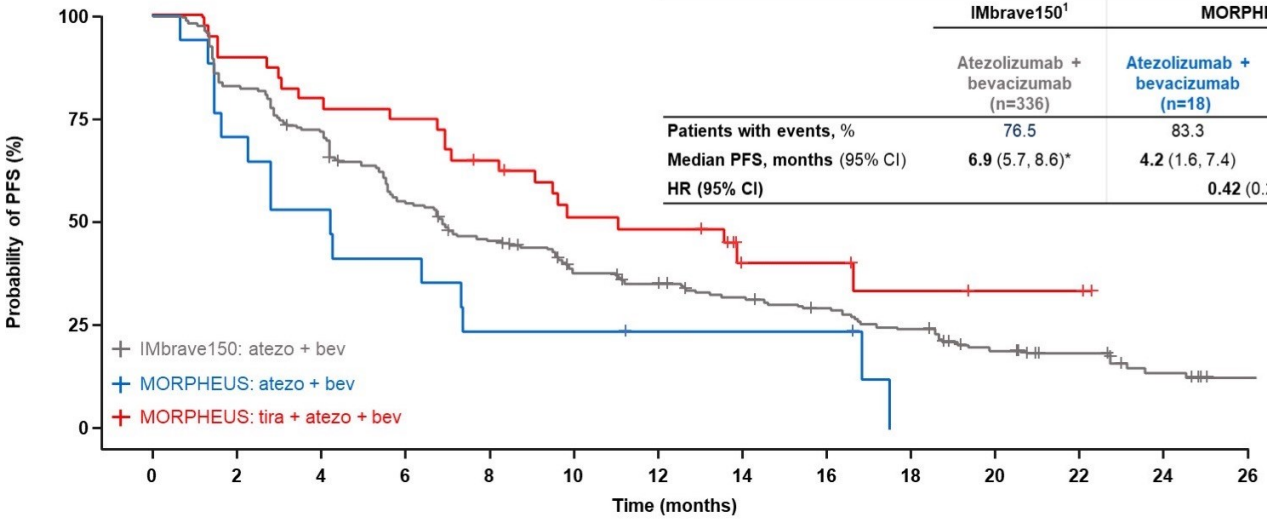
- Mean changes from baseline in GHS/QoL, and physical, role, emotional and social functioning were not considerable through Cycle 17 and were similar between arms, as evidenced by overlapping 95% CIs
- GHS/QoL, and physical, role, emotional and social functioning were maintained through Cycle 17, with no clinically meaningful deterioration (≥10-point decrease)[1] observed at any time

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

1. Osoba et al. J Clin Oncol 1998;16:139-44.

- PRO analysis showed that patients started the trial with high baseline scores in both arms for health-related QoL and physical, role, emotional and social functioning, and did not experience any clinically meaningful deterioration at any time during the treatment period
- Health-related QoL and functioning scores between atezo+bev and active surveillance were comparable throughout treatment

Investigator-assessed PFS per RECIST v1.1



	IMbrave150[1]	MORPHEUS-liver	
	Atezolizumab + bevacizumab (n=336)	Atezolizumab + bevacizumab (n=18)	Tiragolumab + atezolizumab + bevacizumab (n=40)
Patients with events, %	76.5	83.3	57.5
Median PFS, months (95% CI)	**6.9** (5.7, 8.6)*	**4.2** (1.6, 7.4)	**11.1** (8.2, NE)
HR (95% CI)		**0.42** (0.22, 0.82)	

IMbrave150: atezo + bev	336	271	234	174	141	113	102	88	77	64	41	25	12	3
MORPHEUS: atezo + bev	18	12	9	7	4	4	3	3	3	0	0	0	0	0
MORPHEUS: tira + atezo + bev	40	36	32	30	25	17	16	7	7	5	2	2	0	0

Efficacy evaluable population. Data cut-off: 28 November 2022
*Independent-review facility assessed PFS

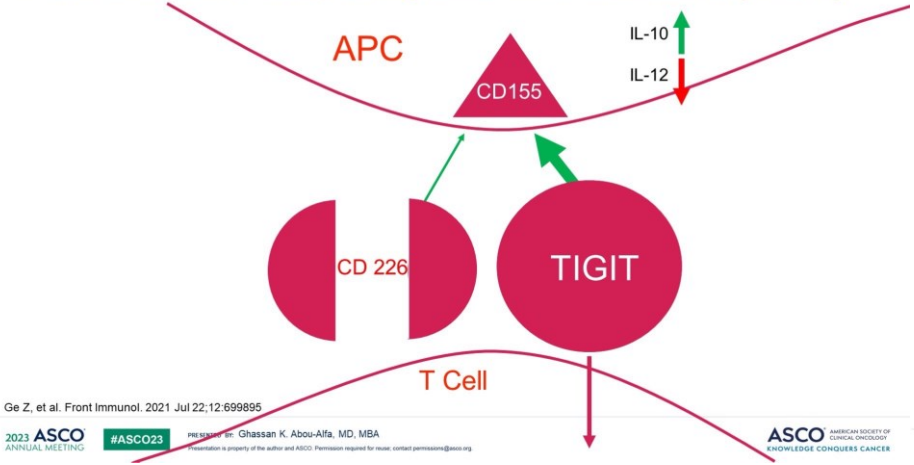
1. Cheng et al. J Hepatol 2022; NCT03434379

PRESENTED BY: Richard S. Finn, MD

Anti-TIGIT in HCC

ASCO 2023

T cell Immunoreceptor Ig and ITIM domains (TIGIT)

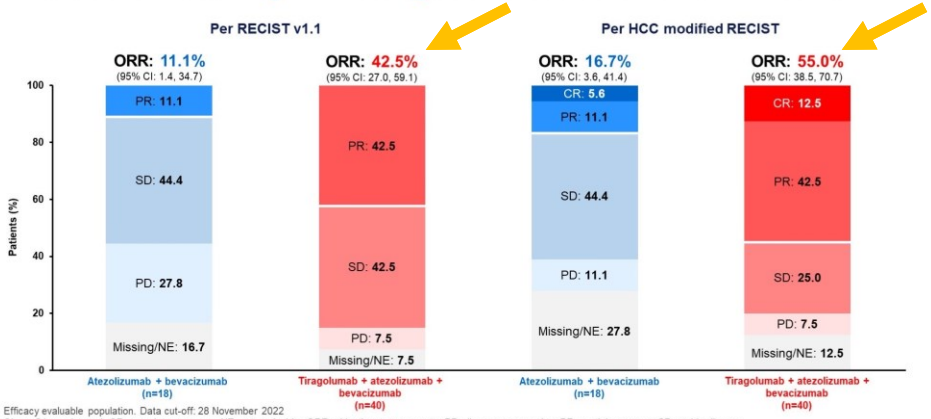


Ge Z, et al. Front Immunol. 2021 Jul 22;12:699895

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Ghassan K. Abou-Alfa, MD, MBA

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Antitumor activity: investigator-assessed confirmed ORR



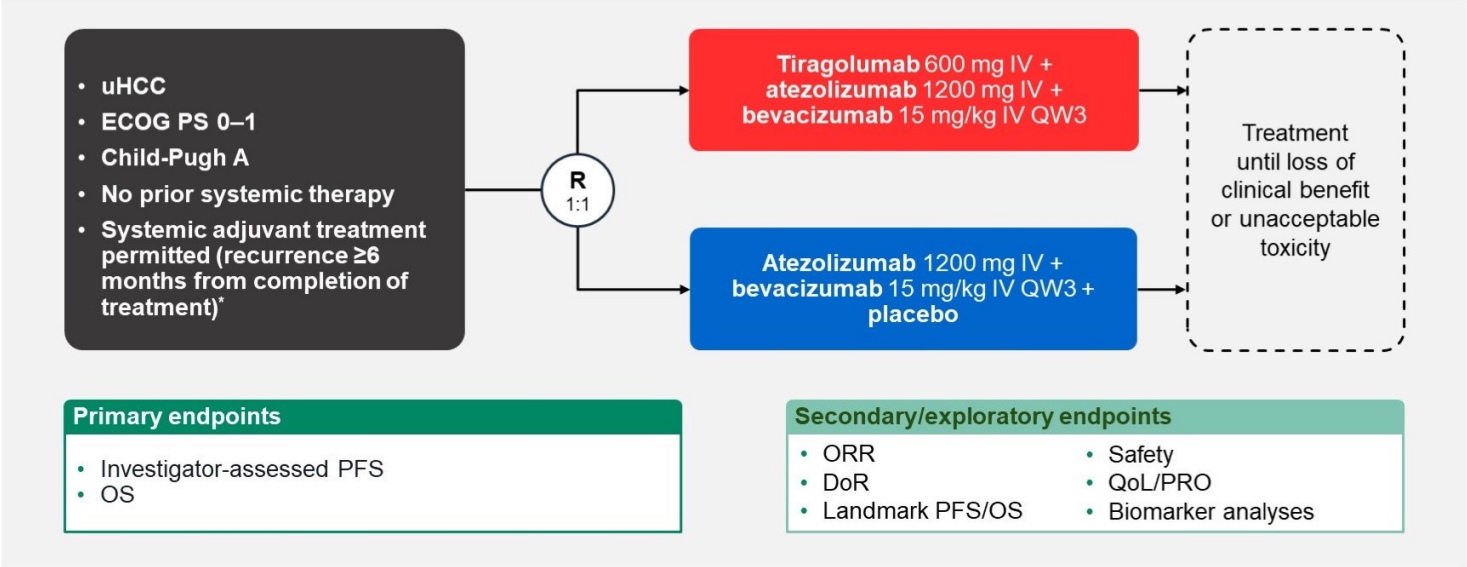
Efficacy evaluable population. Data cut-off: 28 November 2022

CI, confidence interval; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, disease progression; PR, partial response; SD, stable disease

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Richard S. Finn, MD

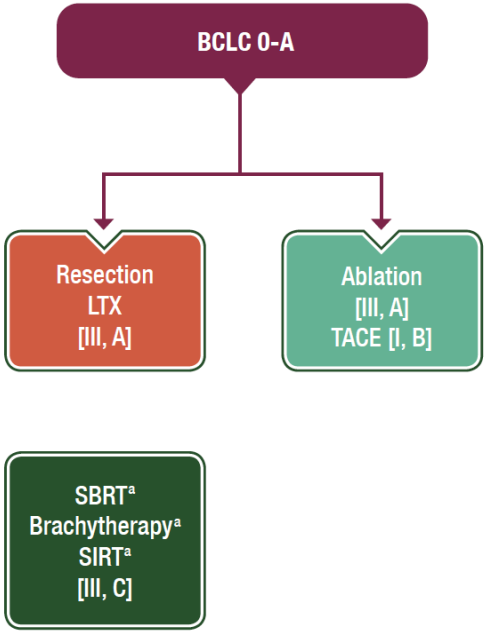
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

IMbrave152/SKYSCRAPER-14: a phase III, double-blind, placebo-controlled, randomized, global study



*Allows for adjuvant atezolizumab + bevacizumab which may be approved during the course of the study
DoR, duration of response; OS, overall survival; PRO, patient reported outcomes; QoL, quality of life

What is on the horizon in early stage?



EN BREVE MÁS DATOS…

- **KEYNOTE-937**:

  Pembrolizumab vs placebo

- **IMbrave050**

  Atezolizumab + Bevacizumab vs placebo

- **CHECKMATE-9DX:**

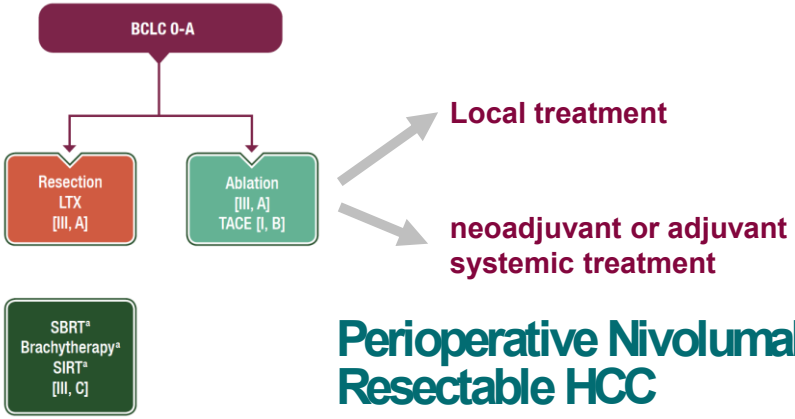
  Nivolumab vs placebo

- **EMERALD-2:**

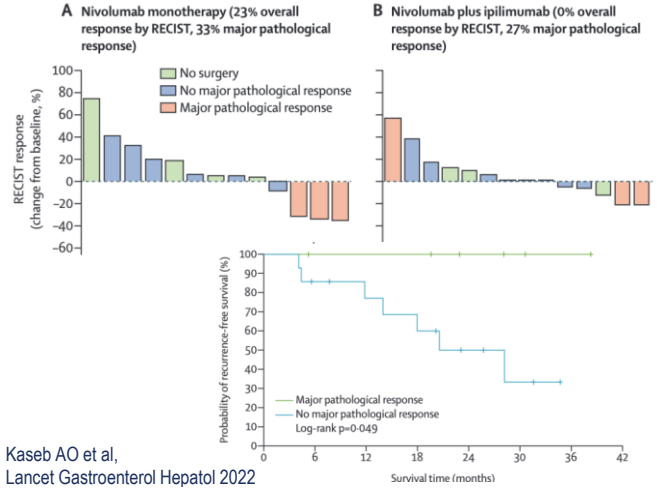
  Durvalumab/Bevacizumab vs placebo

Modified from Vogel et al. ESMO CPG 2021, eUpdate

What is on the horizon in early stage?

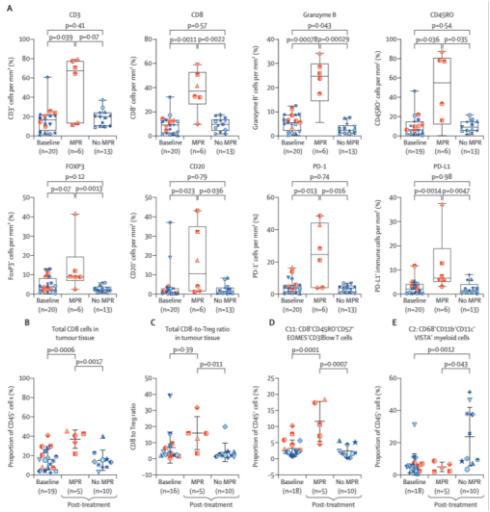


Perioperative Nivolumab vs Nivolumab+Ipilimumab in Resectable HCC

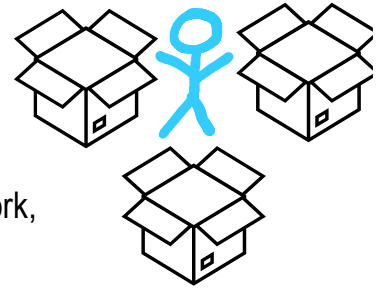


Kaseb AO et al,
Lancet Gastroenterol Hepatol 2022

Biomarker: Immune cell density box plots

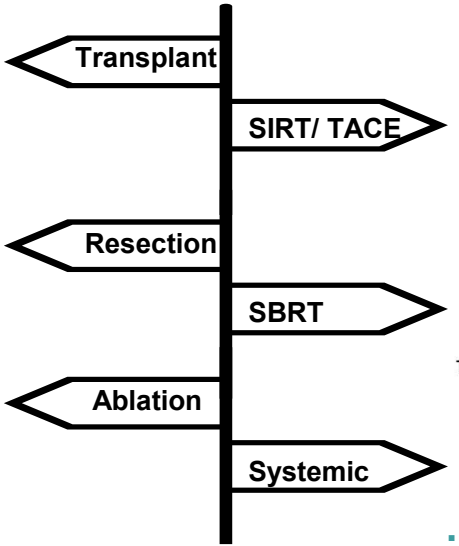


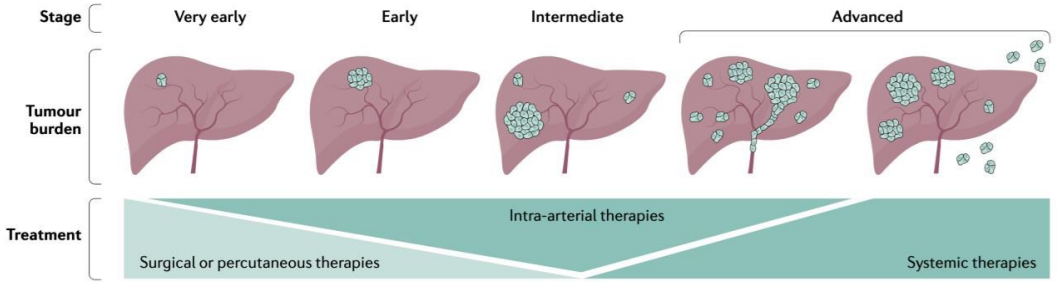
Stage BCLC B patients are a heterogeneous population: Challenge for care givers



We have options….

Existing categories define a therapeutic framework, but do not allow for extrapolation to single therapeutic options.

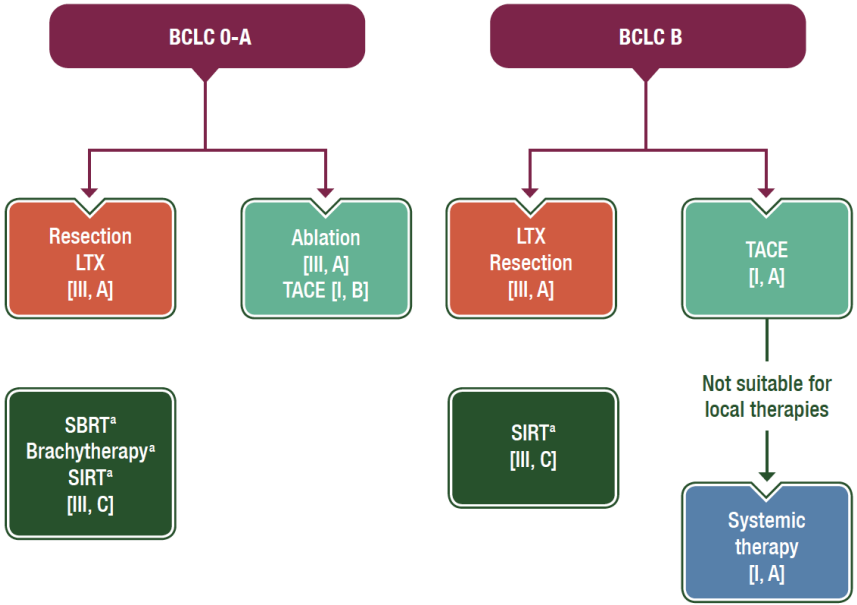




Sangro et al, Nat. Rev. Gastroenterol & Hepatol 2021

…but what is the best option?

What is on the horizon in intermediate stage?



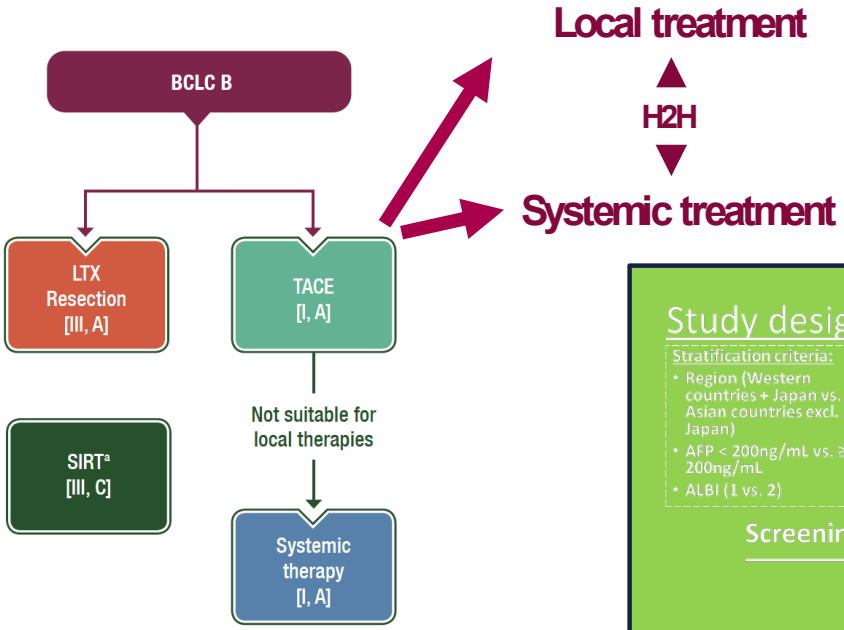
Local treatment

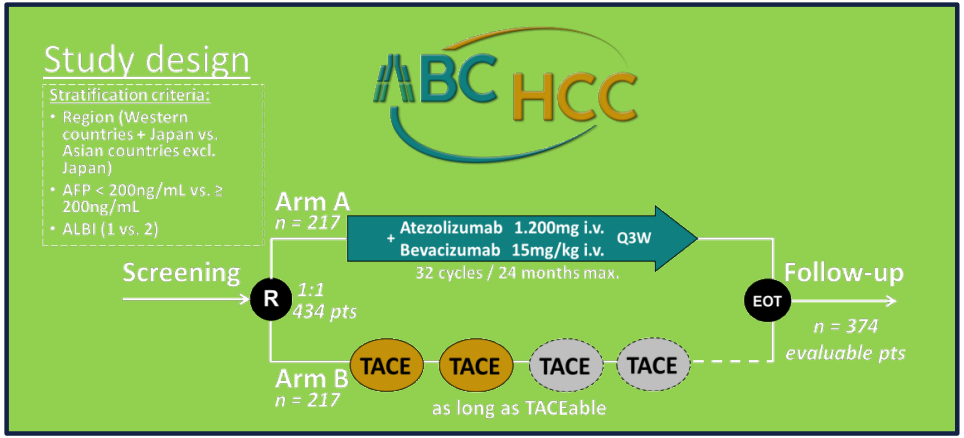
Systemic treatment

Combination

- No positive phase-III Studies so far

Local vs. systemic Head-to-tead





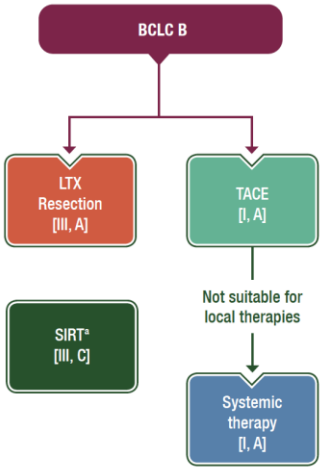
Modified from Vogel et al. ESMO CPG 2021, eUpdate

MADRID 2023 ESMO congress

Arndt Vogel

On the Horizon: TACE / IO combinations

Phase III, Intermediate stage HCC



- **TACE-3:**

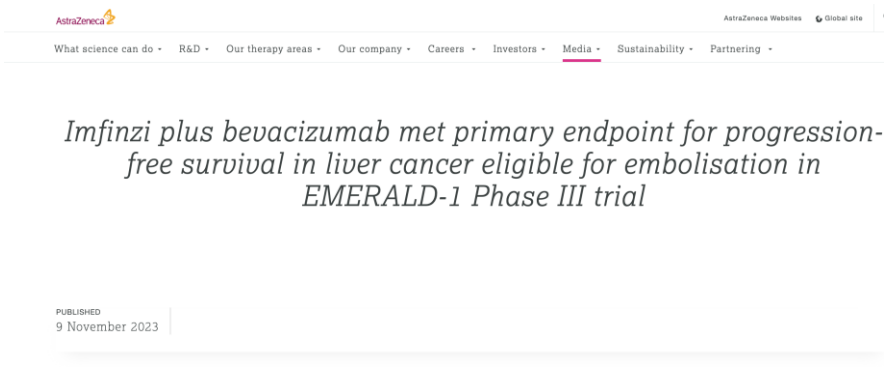
  TACE ± Nivolumab
- **TALENTACE:**

  TACE ± Atezolizumab + Bevacizumab
- **EMERALD-1:**

  TACE ± Durvalumab + Bevacizumab
- **LEAP-012:**

  TACE ± Pembrolizumab + Lenvatinib
- **EMERALD-3:**

  TACE ± Durvalumab/Tremelimumab ± Lenvatinib


AstraZeneca

AstraZeneca Websites · Global site

What science can do · R&D · Our therapy areas · Our company · Careers · Investors · Media · Sustainability · Partnering

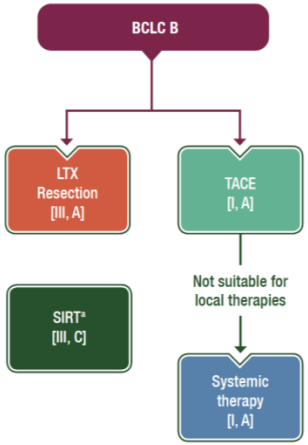
Imfinzi plus bevacizumab met primary endpoint for progression-free survival in liver cancer eligible for embolisation in EMERALD-1 Phase III trial

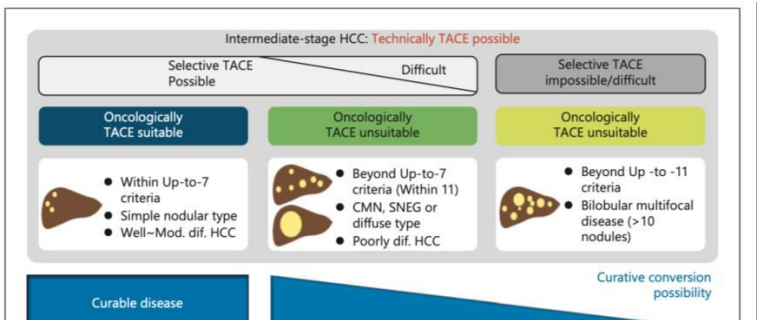
PUBLISHED
9 November 2023

First global Phase III trial to show improved clinical outcome for systemic therapy in combination with transarterial chemoembolisation (TACE) in this setting

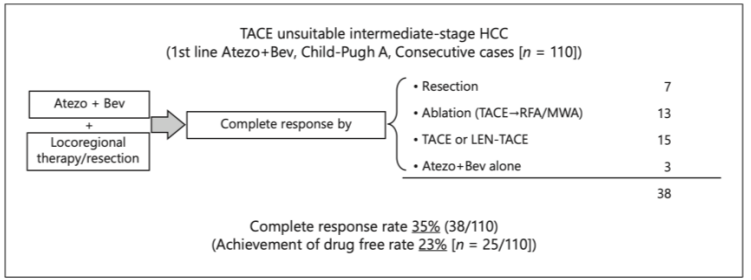
New avenues?

PROOF-OF-CONCEPT: "CURATIVE" CONVERSION





SYSTEMIC THERAPY → **LOCOREGIONAL OR SURGERY**



Kudo et al Liver Cancer 2023

Muchas gracias por la atención

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