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Update HCC: 2023 New Data and Abstracts From AASLD

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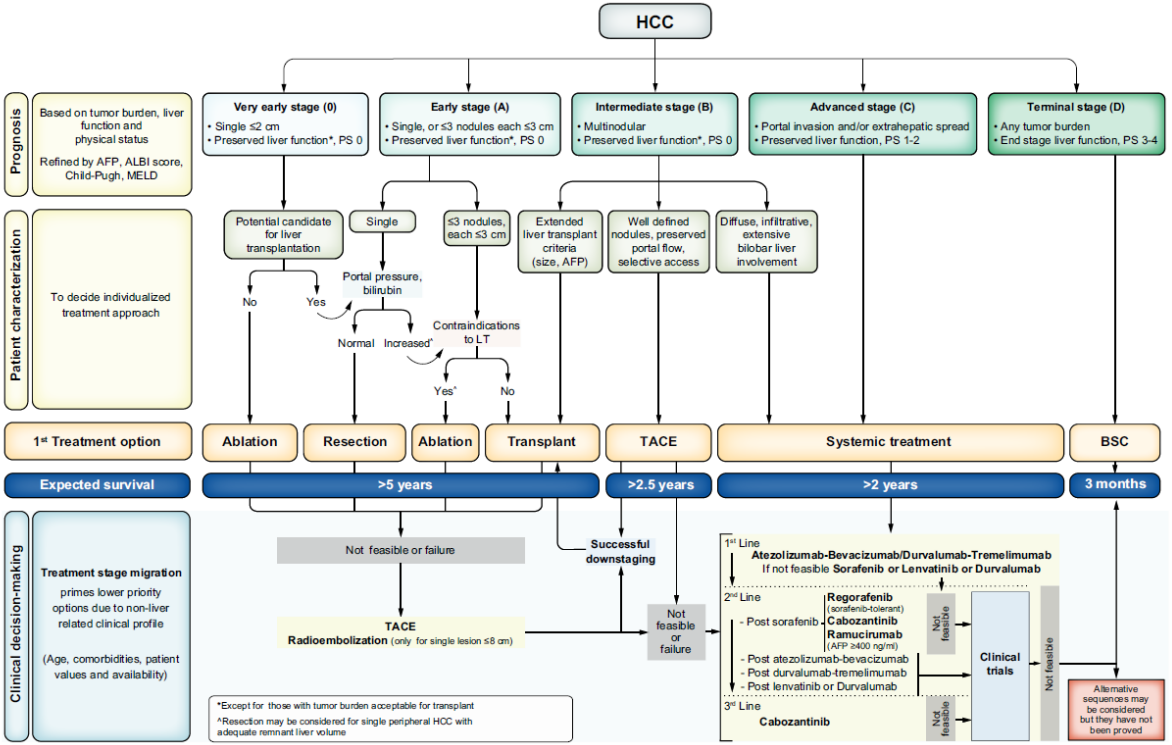
Disclosures

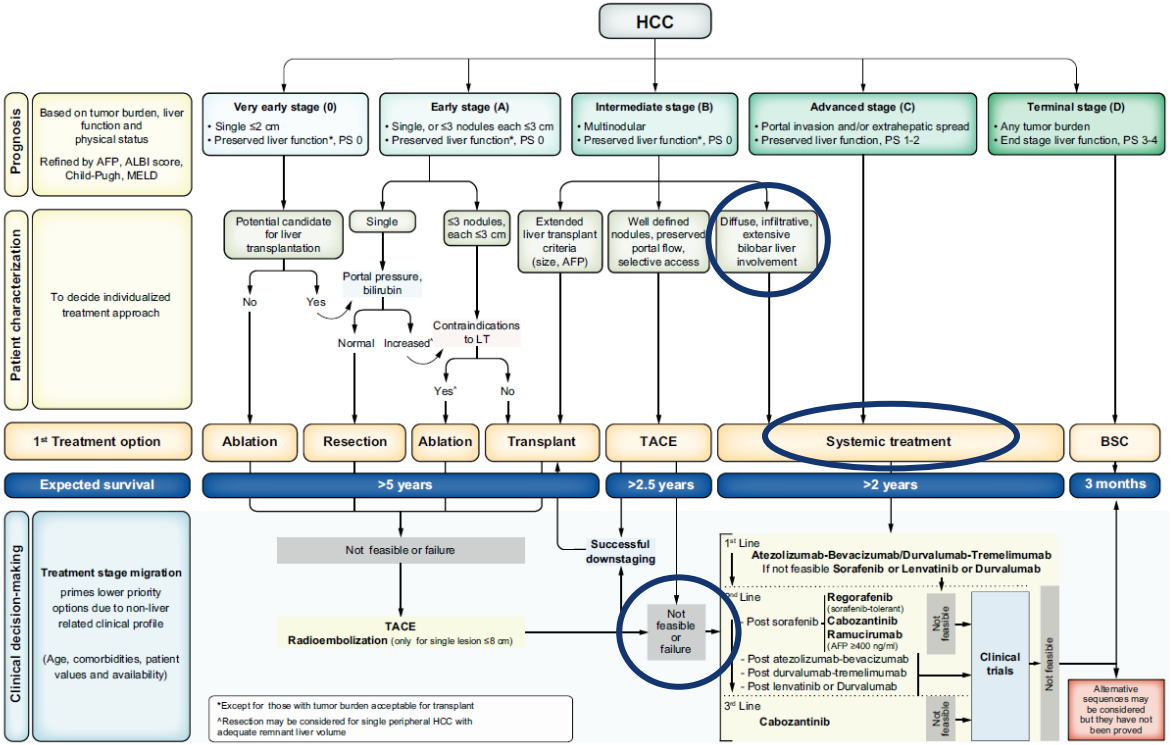
- Consultant: Astra Zeneca, C Stone, Bayer, Bristol Myers Squibb, Eisai, Eli-Lilly, Exilixis, Hengrui, Merck, Novartis, Pfizer, Roche/ Genentech

BCLC Management of HCC-2022



Reig M. *J Hep*. 2022.

BCLC Management of HCC-2022



Reig M. *J Hep*. 2022.

Positive Phase 3 Studies in Advanced HCC With Global Approvals

	SHARP	REFLECT	IMBRAVE 150	HIMALAYA
Control	Placebo	Sorafenib	Sorafenib	Sorafenib
Treatment Arm	Sorafenib	Lenvatinib	Atezo-bev	Durva-treme
VP4 included	Yes	No	Yes	No
HR OS	0.69	0.92 (Non-inf)	0.58	0.78
• mOS	10.7 mos	13.6 mos	19.2 mos	16.43 mos
HR PFS	0.58 (TTP)	0.66	0.59	0.90 (Not sig)
• mPFS	5.5 mos (TTP)	7.4 mos	6.9 mos	3.78 mos
ORR (RECIST)	2%	18.8 %	30%	20%
Reference	Llovet NEJM 2008	Kudo Lancet 2017	Finn NEJM 2020, Cheng J Hep 2022	Abou-Alfa NEJM Evidence 2022

FDA Approved Second Line Systemic Therapies

Study Name	Treatment	Median OS (mos)	Median PFS (mos)	ORR mRECIST;RECIST	Grade 3/4 TRAEs	Most common G3/4	D/C rate
RESORCE	Reografenib	10.6	3.1	11%/ 7%	50%	HTN 13% HFSR 13% Fatigue 13%	10%
CELESTIAL	Cabozantinib	10.2	5.2	NR/ 7%	68% (all cause)	HFSR 17% HTN 16% Increased ALT 12%	16%
REACH-2 (AFP≥400)	Ramucirumab	8.5	2.8	NR/ 5%	NR	HTN 8% Liver injury 4% Proteinuria 2%	11%
KEYNOTE 240/224 (accelerated approval)	Pembrolizumab	13.9	3.0	NR/ 18.3%	18.3	Increased AST 13% Increased Bili 7.5% Fatigue 2.5%	6.5%
CheckMate 040, arm A (accelerated approval)	Ipilimumab+ Nivolumab	22.8	3.9	34%/ 32%	53%	Pruritis 45% Rash 29% Diarrhea 24%	22%

Bruix. 2017; Abou-Alfa. 2018; Zhu. 2019; Finn. 2020; Zhu. 2018; Yau. 2020.
NR – not reported.

IMbrave150 Study Design

Key eligibility

- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy
- ECOG PS 0-1
- Child-Pugh class A liver function

Stratification

- **Region** (Asia excluding Japan[a]/Rest of world)
- **ECOG** (0/1)
- **Macrovascular invasion** and/or **extrahepatic spread** (Presence/Absence)
- **Baseline AFP** (<400/≥400 ng/mL)

R 2:1

N = 501

Atezolizumab 1200 mg IV q3w + Bevacizumab 15 mg/kg q3w

Sorafenib 400 mg bid

(open-label)

Until loss of clinical benefit or un-acceptable toxicity[b]

Survival follow-up

Co-primary endpoints

- OS
- IRF-assessed PFS per RECIST 1.1

Secondary endpoints included:

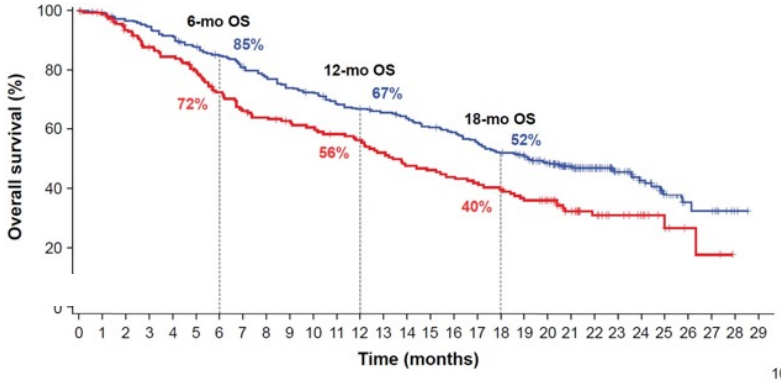
- IRF-assessed ORR, DOR per RECIST 1.1 and HCC mRECIST[b]
- PROs: TTD[c] of QOL, physical and role functioning (EORTC QLQ-C30)
- Safety and tolerability assessed based on the nature, frequency and severity of AEs per NCI CTCAE version 4.0

[a] Japan is included in rest of world. [b] Tumor assessment by computed tomography or magnetic resonance imaging was done at baseline and every 6 weeks until 54 weeks, then every 9 weeks thereafter.
[c] Time from randomization to first decrease from baseline of ≥ 10 points maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.
AFP, α-fetoprotein; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer; IRF, independent review facility; mRECIST, modified RECIST; NCI, National Cancer Institute; PRO, patient-reported outcomes; QOL, quality of life; TTD, time to deterioration.
Finn et al. *New Engl J Med.* 2020

IMbrave150 Trial

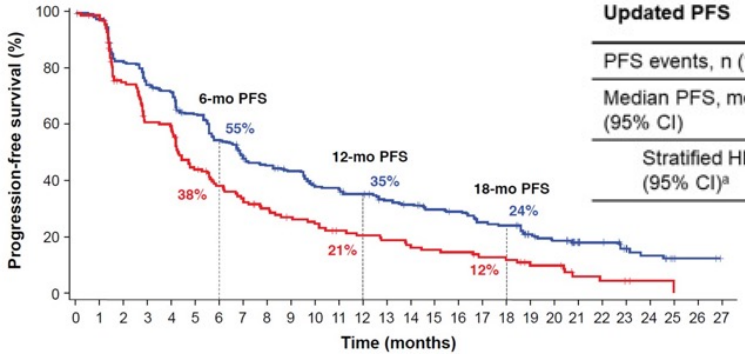
Key Efficacy Data: Updated OS and PFS

- Primary analysis OS/PFS HR: 0.58/0.59 (median follow-up: 8.6 mo)



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

- Median follow-up: 15.6 mo



Updated PFS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	**6.9** (5.7, 8.6)	**4.3** (4.0, 5.6)
Stratified HR (95% CI)[a]	**0.65** (0.53, 0.81) *P* = 0.0001[b]	

Finn RS et al. *NEJM*. 2020; Finn RS et al. *ASCO GI*. 2021.

Updated Response and Duration of Response

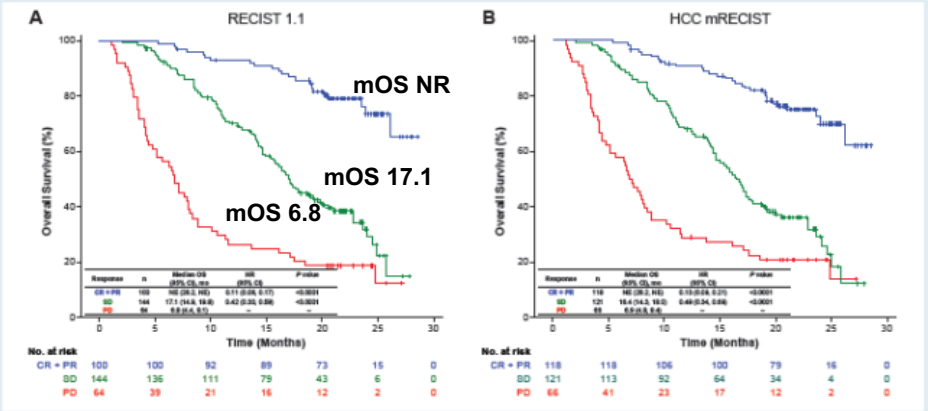
	Updated analysis[a]			
	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**	**35 (30, 41)**	**14 (9, 20)**
CR, n (%)	25 (8)	1 (< 1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DOR (95% CI), mo[b]	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**	**16.3 (13.1, 21.4)**	**12.6 (6.1, 17.7)**

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. DCR, disease control rate.
[a] Only patients with measurable disease at baseline were included in the analysis of ORR.
[b] Only confirmed responders were included in the analysis of ORR and DOR.
Cheng AL. *J Hep*. 2022.

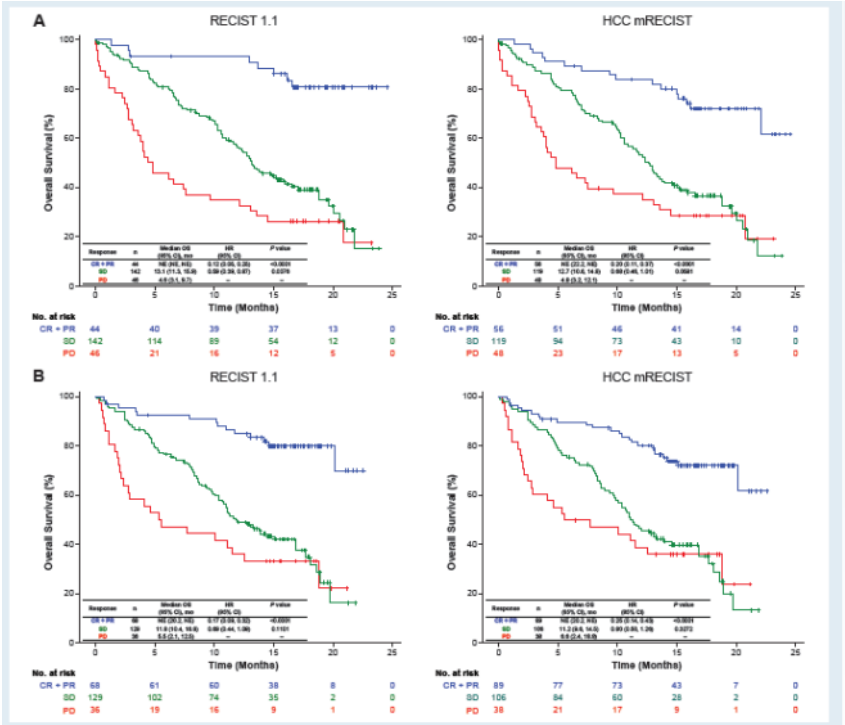
Best Response and OS From ImBrave 150

- OS by BOR per RECIST 1.1 and HCC mRECIST is shown in Figure 2

Figure 2. OS in Patients (Atezolizumab + Bevacizumab Arm) With Confirmed Response vs SD vs PD per (A) RECIST 1.1 and (B) HCC mRECIST



CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

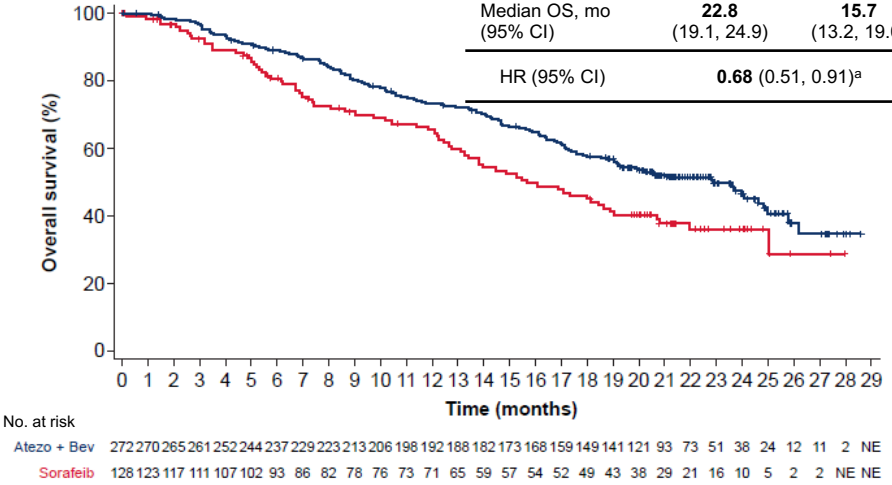


Ducreux et al. ASCO. 2021.

Overall Survival

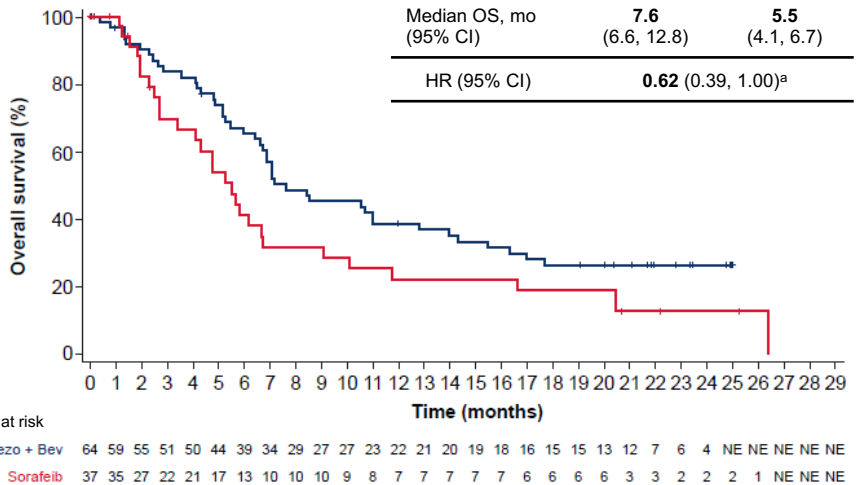
Non–high-risk patients

	Atezo + Bev (n=272)	Sorafenib (n=128)
OS events, n (%)	136 (50)	71 (55)
Median OS, mo (95% CI)	**22.8** (19.1, 24.9)	**15.7** (13.2, 19.0)
HR (95% CI)	**0.68** (0.51, 0.91)[a]	



High-risk patients

	Atezo + Bev (n=64)	Sorafenib (n=37)
OS events, n (%)	44 (69)	29 (78)
Median OS, mo (95% CI)	**7.6** (6.6, 12.8)	**5.5** (4.1, 6.7)
HR (95% CI)	**0.62** (0.39, 1.00)[a]	

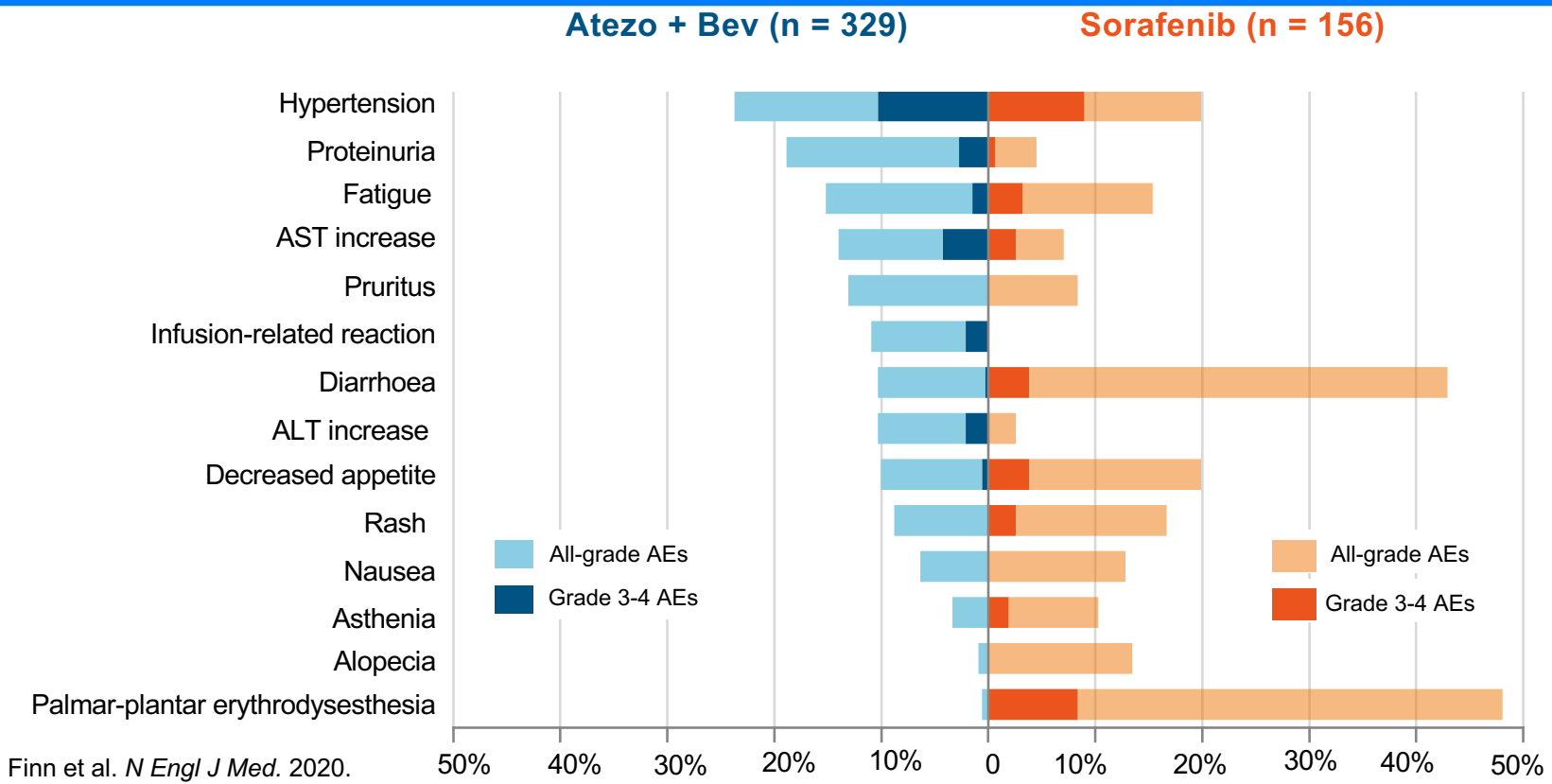


Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. NE, not evaluable.

[a] OS analysis is descriptive.

Finn RS. IMbrave150 high-risk patients [abs #5080]; https://bit.ly/3vjRqjk.

TRAEs: ≥ 10% Any Grade in Either Arm



Finn et al. *N Engl J Med.* 2020.

Bleeding Events

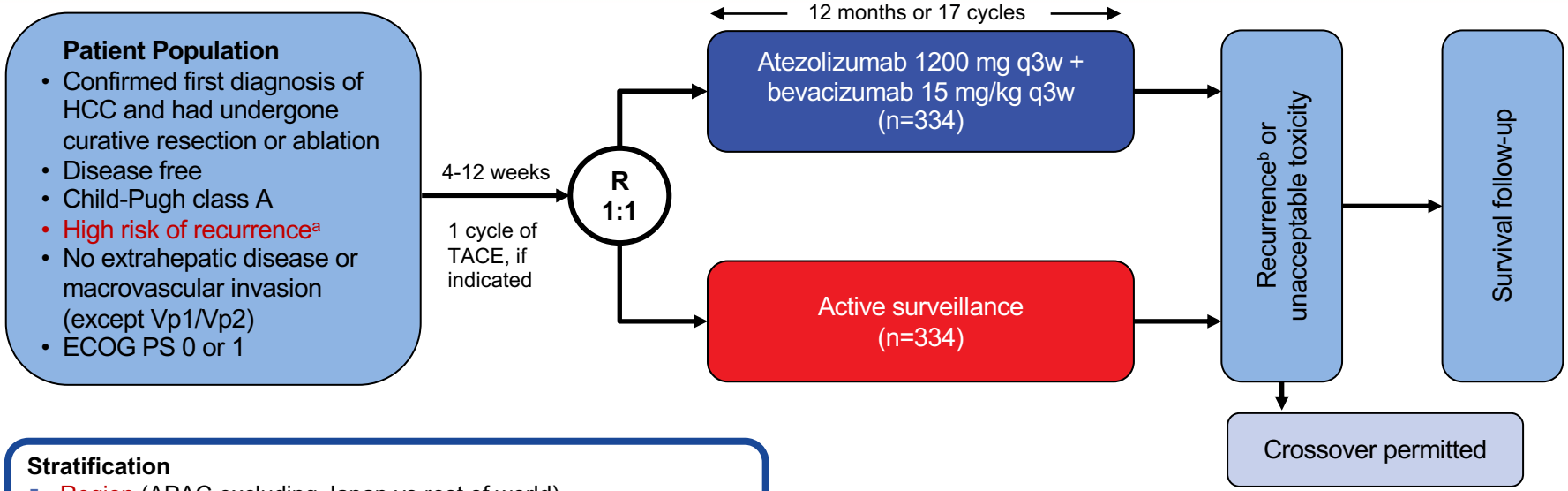
All-cause AESIs by medical concept and preferred term, n (%)[a]	Atezo + Bev (n = 329)		Sorafenib (n = 156)	
	All grade	Grade 3-4	All grade	Grade 3-4
Bleeding/haemorrhage	83 (25.2)	21 (6.4)	27 (17.3)	9 (5.8)
Bleeding events in > 1% of either group				
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Haematuria	10 (3.0)	1 (0.3)	0	0
Gingival bleeding	9 (2.7)	0	0	0
Oesophageal varices haemorrhage	8 (2.4)	6 (1.8)	1 (0.6)	1 (0.6)
Gastrointestinal haemorrhage	8 (2.4)	4 (1.2)	3 (1.9)	3 (1.9)
Rectal haemorrhage	5 (1.5)	1 (0.3)	3 (1.9)	0
Upper gastrointestinal haemorrhage	4 (1.2)	2 (0.6)	2 (1.3)	2 (1.3)
Haemoptysis	3 (0.9)	0	5 (3.2)	0
Peritoneal haemorrhage	0	0	2 (1.3)	1 (0.6)

SAEs ≥ 2% in Either Arm

n (%)	Atezo + Bev (n = 329)			Sorafenib (n = 156)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
Gastrointestinal haemorrhage	8 (2.4)	4 (1.2)	3 (0.9)	3 (1.9)	3 (1.9)	0
Oesophageal varices haemorrhage	8 (2.4)	6 (1.8)	1 (0.3)	1 (0.6)	1 (0.6)	0
Pyrexia	7 (2.1)	3 (0.9)	0	2 (1.3)	1 (0.6)	0

Finn et al. *N Engl J Med.* 2020.

IMbrave050 Study Design



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

Panel: Criteria for high risk of hepatocellular carcinoma recurrence by curative treatment

Resection

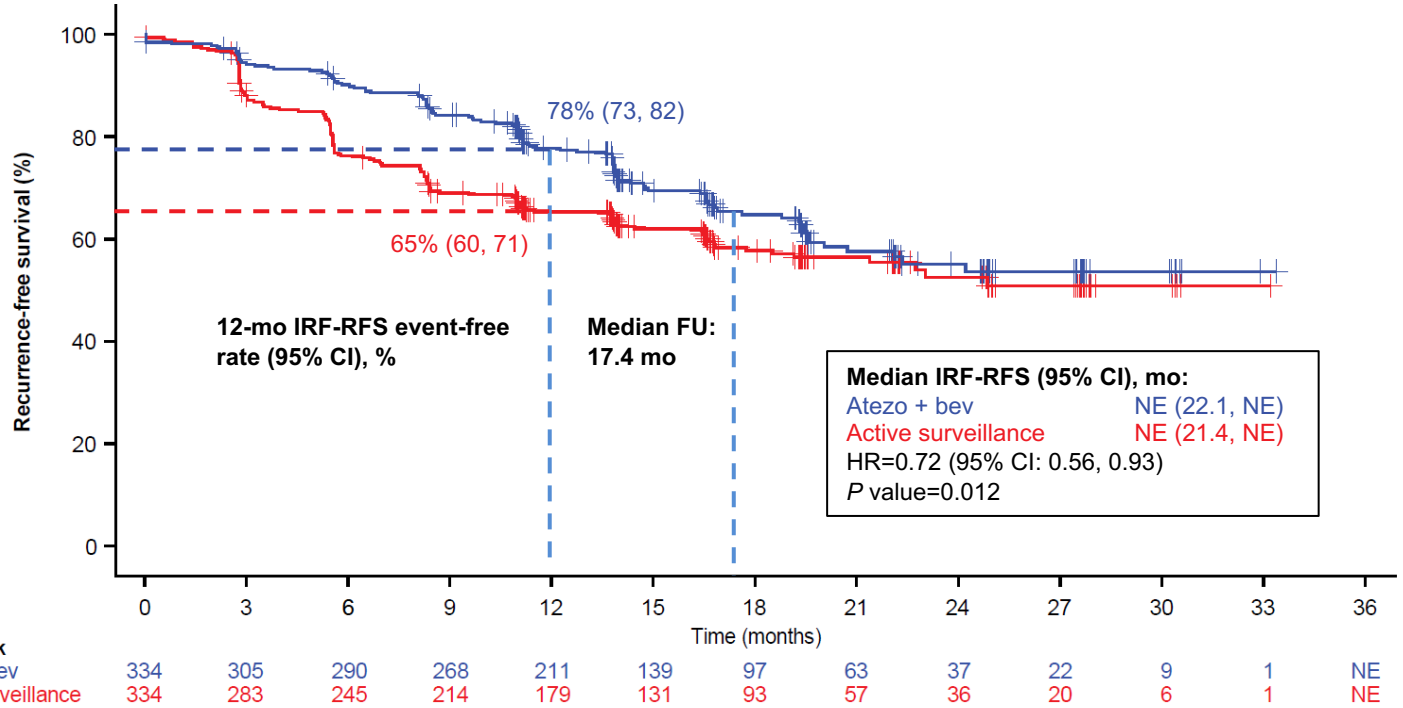
- Up to three tumours, with largest tumour >5 cm regardless of vascular invasion (microvascular invasion or segmental portal vein invasion—Vp1 or Vp2), or poor tumour differentiation (grade 3 or 4)*
- Four or more tumours, with largest tumour ≤5 cm regardless of vascular invasion (microvascular invasion or segmental portal vein invasion—Vp1 or Vp2), or poor tumour differentiation (grade 3 or 4)*
- Up to three tumours, with largest tumour ≤5 cm with vascular invasion (microvascular invasion or segmental portal vein invasion—Vp1 or Vp2), with or without poor tumour differentiation (grade 3 or 4)*

Ablation†

- Single tumour >2 cm but ≤5 cm
- Multiple tumours (up to four tumours), all ≤5 cm

Vp1=segmental portal vein invasion. Vp2=right anterior or posterior portal vein.
*In cases in which a patient has evidence of mixed tumour differentiation, the worst differentiation status rather than the predominant differentiation status should be used to characterise high-risk criteria. †Ablation must be radiofrequency ablation or microwave ablation.

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

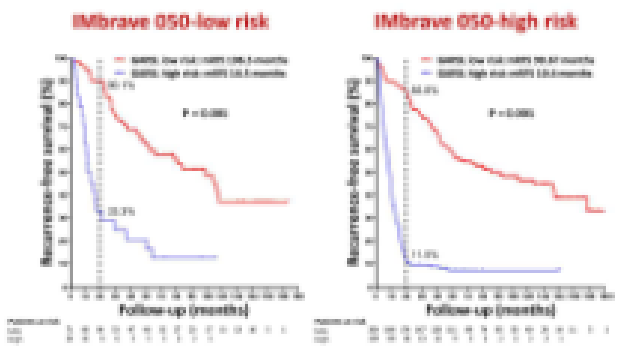
89 | COMPARISON OF RECURRENCE PREDICTION MODELS AND IMBRAVE 050 CRITERIA TO SELECT PATIENTS FOR ADJUVANT IMMUNOTHERAPY AFTER CURATIVE RESECTION OF HEPATOCELLULAR CARCINOMA

I-Cheng Lee[1,2], Hao-Cyuan Chu[2], Shinn-Ying Ho[2], Gar-Yang Chau[3], Ming-Chih Hou[1] and Yi-Hsiang Huang[1,2], (1)Taipei Veterans General Hospital, (2)National Yang Ming Chiao Tung University, (3)Taipei Veterans General Hospital Department Surgery

Discriminative value of AI-derived GARSL model for the risk of recurrence in IMbrave 050-low and -high risk groups

	GARSL-post model	
IMbrave050 criteria	Low risk	High risk
All patient (n=488)	280 (58)	203 (42)
Low risk (n=95)	71 (74.7)	24 (25.3)
High risk (n=368)	204 (56.2)	159 (43.8)
Group 1 (n=199)	90 (45.7)	107 (54.3)
Group 2 (n=1)	0 (0)	1 (100)
Group 3 (n=168)	114 (69.5)	49 (30.1)
Beyond criteria (n=25)	5 (20)	20 (80)

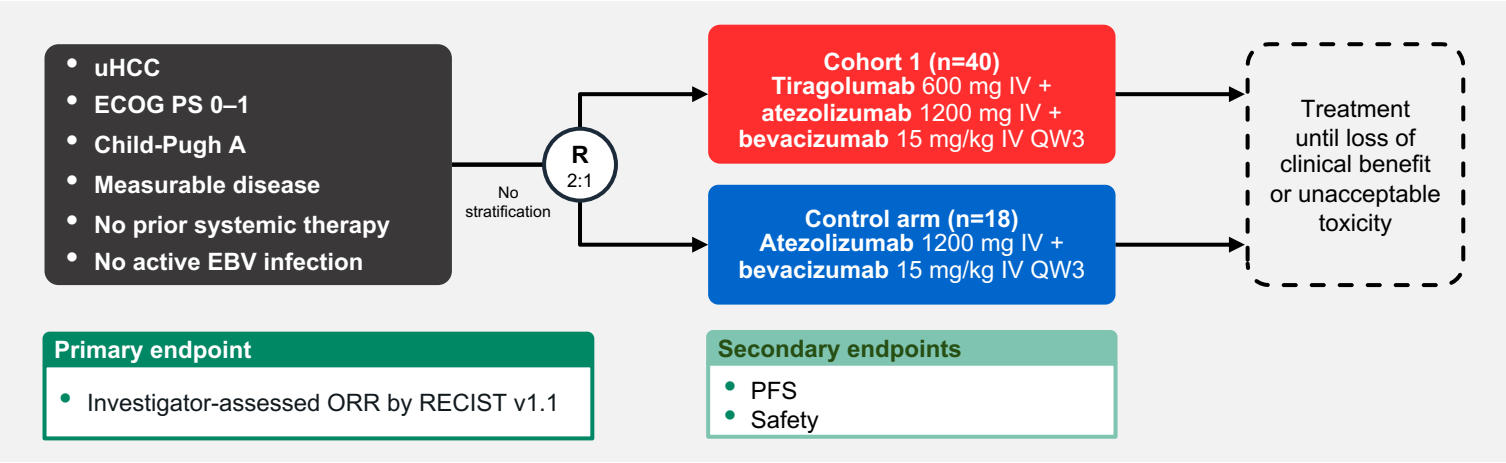
RFS stratified by GARSL-postoperative model



- 483 patients with available CT radiomic data were included for GARSL model analysis

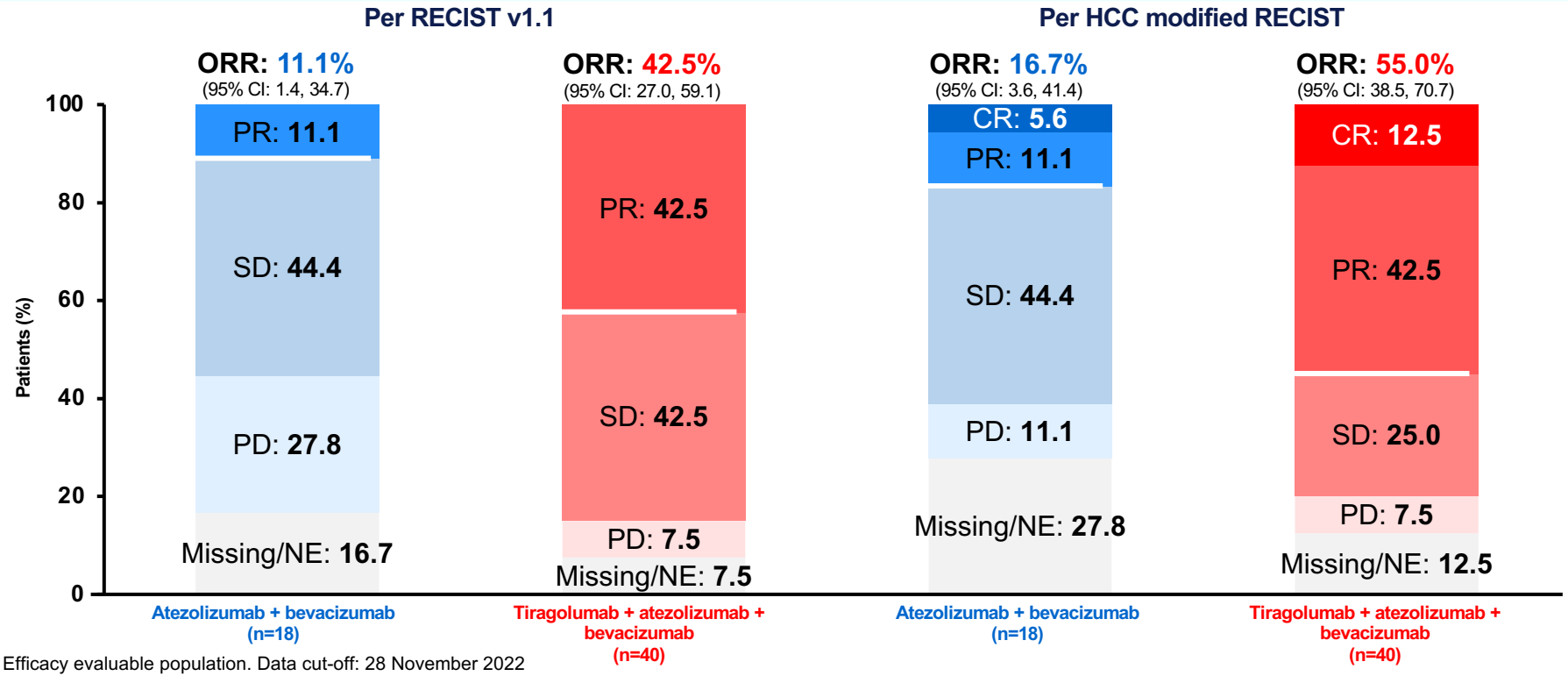
MORPHEUS-Liver: A Phase Ib/II, Open-Label, Multicenter, Randomized Study

- MORPHEUS-Liver is an umbrella study evaluating multiple immunotherapy-based treatment combinations in participants with uHCC who have not yet received prior systemic therapy
- Cohort 1 investigated the addition of tiragolumab to atezolizumab + bevacizumab



Q3W, every 3 weeks; EBV, Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status.
IV, intravenous; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.
Richard S. Finn, MD.
NCT04524871.

Antitumor Activity: Investigator-Assessed Confirmed ORR

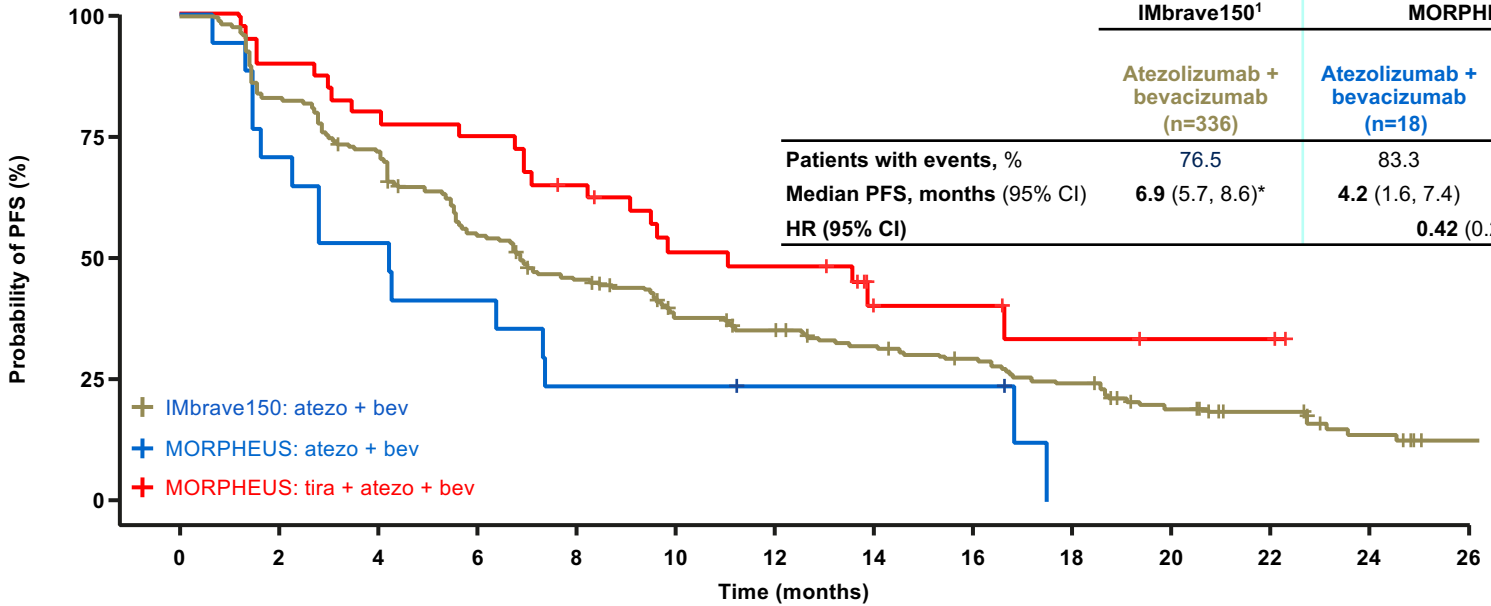


Efficacy evaluable population. Data cut-off: 28 November 2022

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

Richard S. Finn, MD.

Investigator-Assessed PFS per RECIST v1.1

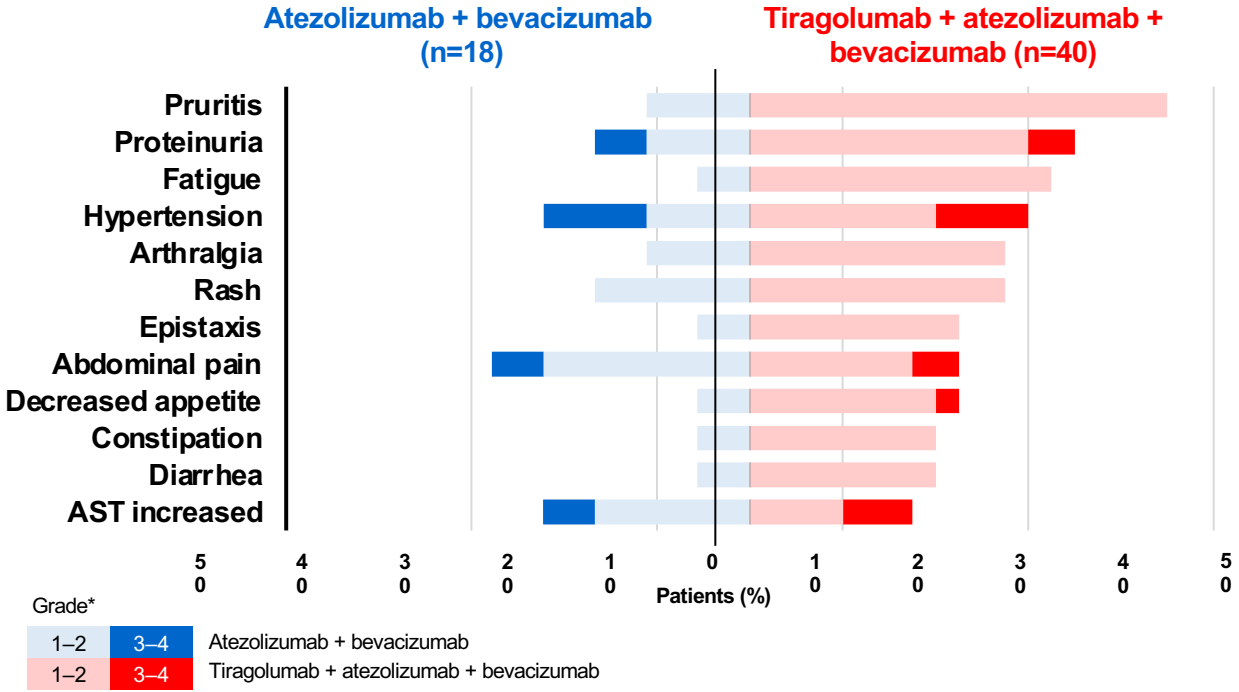


	IMbrave150[1]	MORPHEUS-liver	
	Atezolizumab + bevacizumab (n=336)	Atezolizumab + bevacizumab (n=18)	Tiragolumab + atezolizumab + bevacizumab (n=40)
Patients with events, %	76.5	83.3	57.5
Median PFS, months (95% CI)	**6.9** (5.7, 8.6)*	**4.2** (1.6, 7.4)	**11.1** (8.2, NE)
HR (95% CI)		**0.42** (0.22, 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
Richard S. Finn, MD; 1. Cheng et al. *J Hepatol*. 2022; NCT03434379.

Common (≥20%) Adverse Events

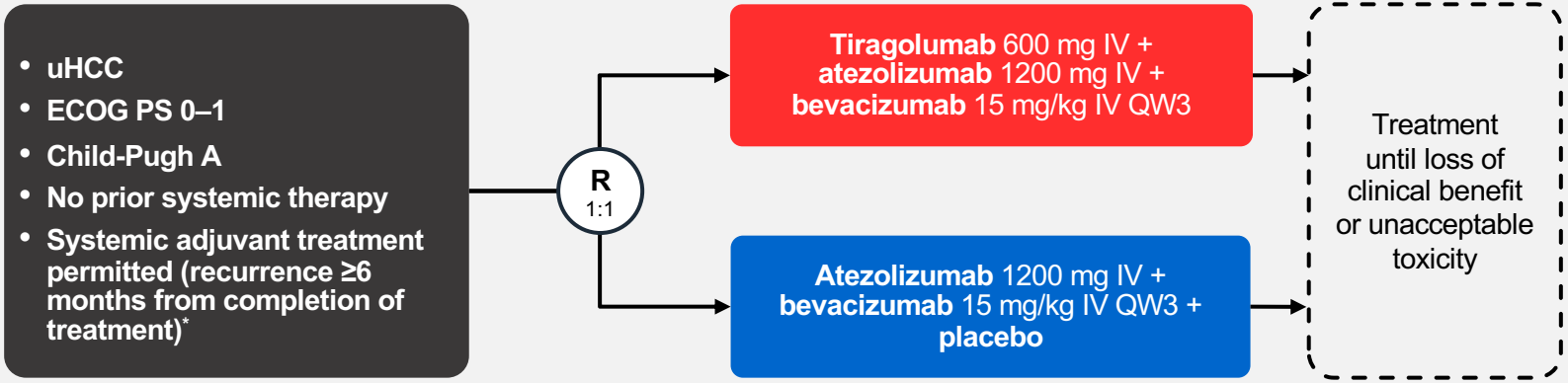


Treatment exposure

	Atezolizumab + bevacizumab (n=18)		Tiragolumab + atezolizumab + bevacizumab (n=40)		
	Atezo	Bev	Tira	Atezo	Bev
Median treatment duration, days	128.0	137.0	284.5	284.5	274.0
Median number of cycles, n	7.0	7.5	14.5	14.5	14.0

Safety evaluable population. Data cut-off: 28 November 2022 (median duration of safety follow-up: atezolizumab + bevacizumab, 5.5. months; tiragolumab + atezolizumab + bevacizumab, 10.3 months)
*No Grade 5 AEs were reported; AST, aspartate aminotransferase
Richard S. Finn, MD.

IMbrave152/SKYSCRAPER-14: A Phase III, Double-Blind, Placebo-Controlled, Randomized, Global Study



Primary endpoints

- Investigator-assessed PFS
- OS

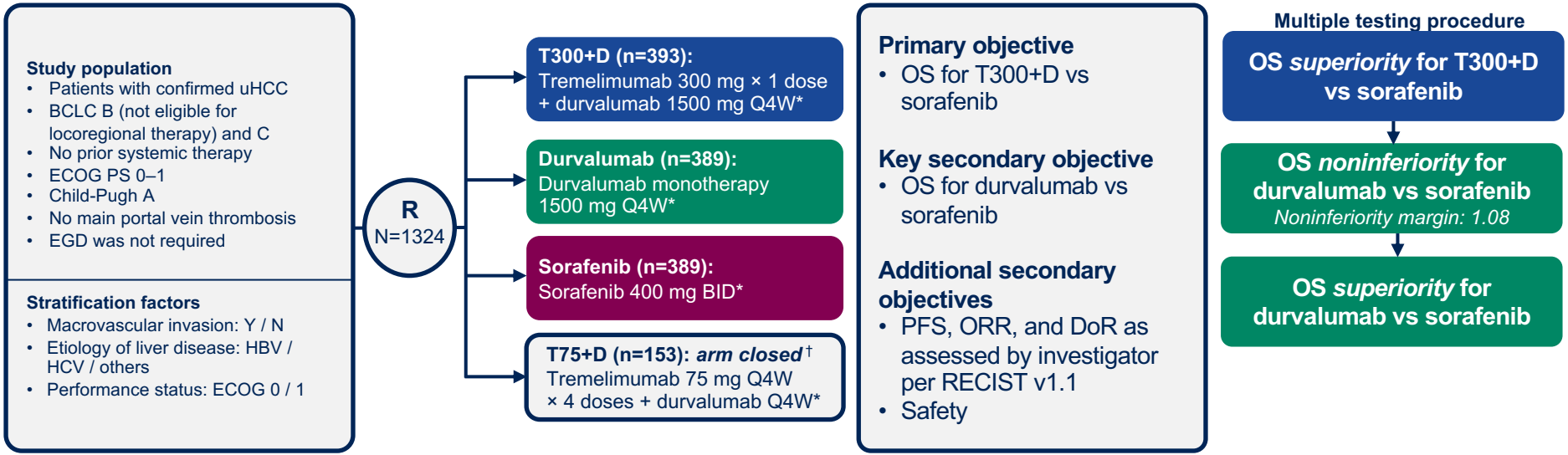
Secondary/exploratory endpoints

- ORR
- DoR
- Landmark PFS/OS
- Safety
- QoL/PRO
- Biomarker analyses

*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.
Richard S. Finn, MD.

HIMALAYA Study Design

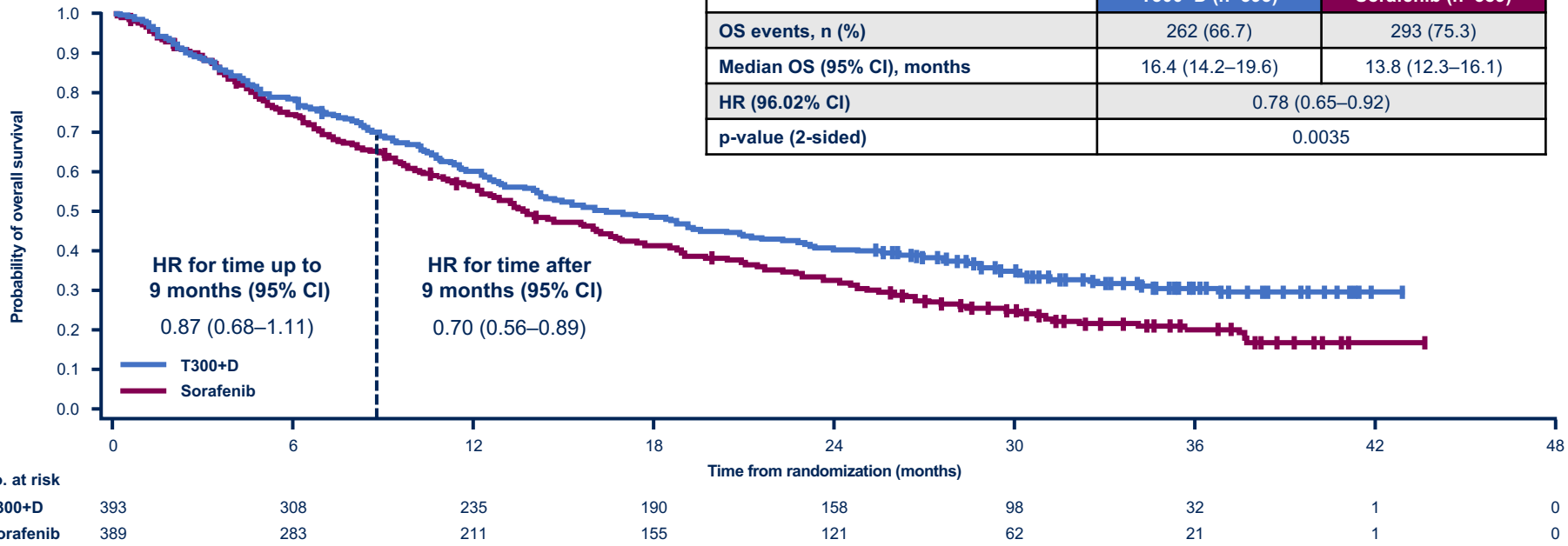
HIMALAYA was an open-label, multicenter, global, Phase 3 trial



*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.
BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks.
Ghassan K Abou-Alfa, MD, MBA.

Primary Objective: Overall Survival for T300+D vs Sorafenib

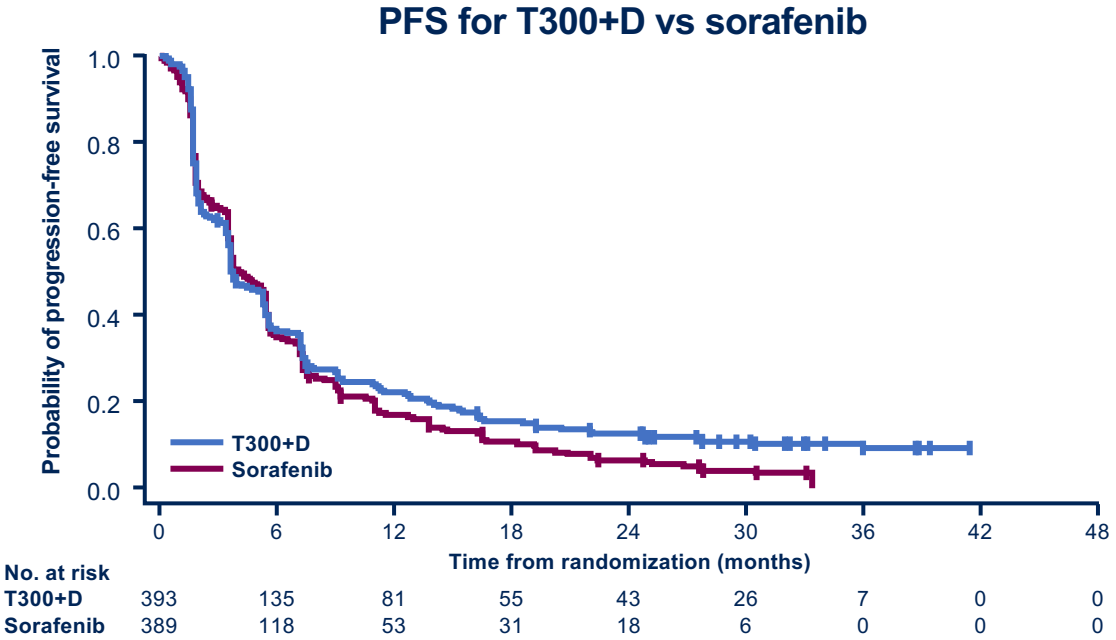
	T300+D (n=393)	Sorafenib (n=389)
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI), months	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (96.02% CI)	0.78 (0.65–0.92)	
p-value (2-sided)	0.0035	



No. at risk									
T300+D	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.
CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.
Ghassan K Abou-Alfa, MD, MBA.

Progression-Free Survival



	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
PFS events, n (%)	335 (85.2)	345 (88.7)	327 (84.1)
Median PFS (95% CI), months	3.78 (3.68–5.32)	3.65 (3.19–3.75)	4.07 (3.75–5.49)
PFS HR* (95% CI)	0.90 (0.77–1.05)	1.02 (0.88–1.19)	–
Progression-free at DCO, n (%)	49 (12.5)	32 (8.2)	19 (4.9)
Median TTP (95% CI), months	5.42 (3.81–5.62)	3.75 (3.68–5.42)	5.55 (5.13–5.75)
Treated ≥1 cycle beyond progression, n (%)†	182 (46.9)	188 (48.5)	134 (34.4)

*Versus sorafenib. †Percent calculated from total patients in the safety analysis set: T300+D, N=388; durvalumab, N=388, sorafenib, n=374.
CI, confidence interval; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTP, time to progression.
Ghassan K Abou-Alfa, MD, MBA.

Tumor Response

	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* n (%)	**79 (20.1)**	**66 (17.0)**	**20 (5.1)**
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD,† n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, %	60.1	54.8	60.7
Median DoR,‡ months 25th percentile 75th percentile	22.34 8.54 NR	16.82 7.43 NR	18.43 6.51 25.99
Median TTR (95% CI), months	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Remaining in response,‡ % 6 months 12 months	 82.3 65.8	 81.8 57.8	 78.9 63.2

*By investigator assessment according to RECIST v1.1. Responses are confirmed. †Defined as neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD. ‡Calculated using Kaplan-Meier technique.

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTR, time to response.

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Safety and Tolerability

Event, n (%)	T300+D (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
Any AE	378 (97.4)	345 (88.9)	357 (95.5)
Any TRAE*	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3/4 AE	196 (50.5)	144 (37.1)	196 (52.4)
Any grade 3/4 TRAE	100 (25.8)	50 (12.9)	138 (36.9)
Any serious TRAE	68 (17.5)	32 (8.2)	35 (9.4)
Any TRAE leading to death	9 (2.3)†	0	3 (0.8)‡
Any TRAE leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)

Includes AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy.
*Treatment-related was as assessed by investigator. †Nervous system disorder (n=1), acute respiratory distress syndrome (n=1), hepatitis (n=1), myocarditis (n=1), immune-mediated hepatitis (n=2), pneumonitis (n=1), hepatic failure (n=1), myasthenia gravis (n=1). ‡Hematuria (n=1), cerebral hematoma (n=1), hepatic failure (n=1).
AE, adverse event; SMQ, Standardized MedDRA Query; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TRAE, treatment-related adverse event.
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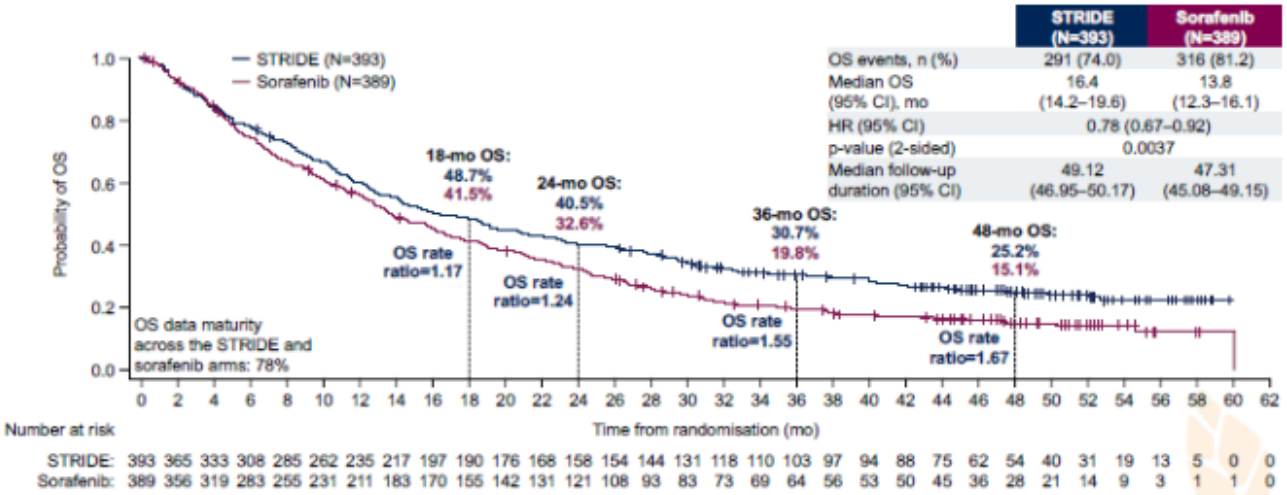
Immune-Mediated Adverse Events

Event, n (%)	T300+D (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
Patients with immune-mediated event	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (6.4)	37 (9.5)	10 (2.6)
Hepatic events	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)	26 (6.7)	17 (4.4)	25 (6.4)	5 (1.3)
Diarrhea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)
Pancreatic events	9 (2.3)	7 (1.8)	7 (1.8)	0	2 (0.5)	1 (0.3)	2 (0.5)	0
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0	6 (1.5)	3 (0.8)	3 (0.8)	0
Hyperthyroid events	18 (4.6)	1 (0.3)	2 (0.5)	0	4 (1.0)	0	0	0
Hypothyroid events	42 (10.8)	0	1 (0.3)	0	19 (4.9)	0	0	0
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Renal events	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)	0	0	0	0

Includes adverse events with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy. Patients may have had >1 event. Events include those that occurred in ≥1% of patients in either treatment arm.
T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.
Ghassan K Abou-Alfa, MD, MBA.

Four-year updated overall survival for STRIDE versus sorafenib

STRIDE demonstrated an unprecedented one in four survival rate at 4 years



	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	291 (74.0)	316 (81.2)
Median OS (95% CI), mo	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (95% CI)	0.78 (0.67–0.92)	
p-value (2-sided)	0.0037	
Median follow-up duration (95% CI)	49.12 (46.95–50.17)	47.31 (45.08–49.15)

Number at risk

STRIDE:	393	365	333	308	285	262	235	217	197	190	176	168	158	154	144	131	118	110	103	97	94	88	75	62	54	40	31	19	13	5	0	0
Sorafenib:	389	356	319	283	255	231	211	183	170	155	142	131	121	108	93	83	73	69	64	56	53	50	45	36	28	21	14	9	3	1	1	0

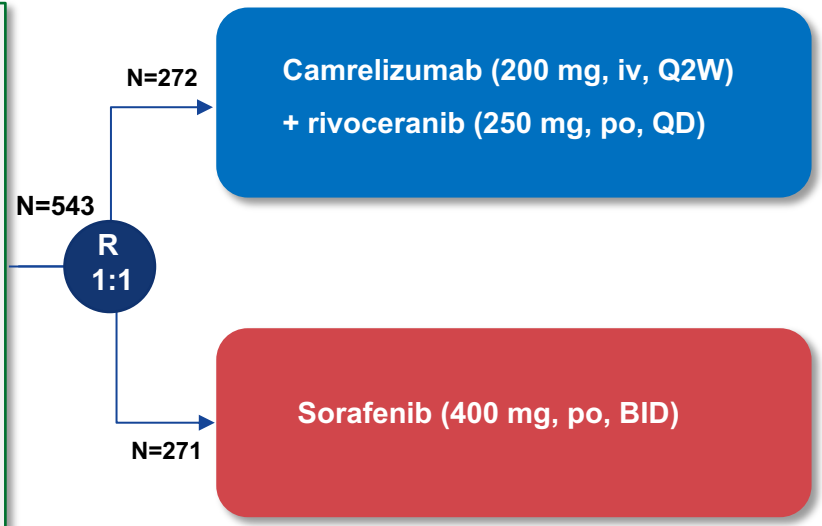
OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG PS and MVI. The 36-mo OS rate had a nominal 2-sided p-value of 0.0036.
Updated analysis data cut-off: 23 January 2023.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mo, month; MVI, macrovascular invasion; OS, overall survival; PS, performance status.

Sangro. ESMO GI 2023; Abou-Alfa. AASLD 2023.

Study Design

Key eligibility criteria

- Unresectable or metastatic HCC
- BCLC Stage B (unsuitable for radical surgery and/or locoregional treatment) or C
- No prior systemic therapy
- ECOG PS 0 or 1
- Child-Pugh A
- At least one measurable lesion per RECIST v1.1



Treatment until loss of clinical benefits* or intolerable toxicity

Stratification factors

- MVI and/or EHS (yes *vs.* no)
- Geographical region (Asia *vs.* non-Asia)
- Baseline serum AFP (<400 *vs.* ≥ 400 ng/mL)

Primary endpoints

- PFS‡
- OS

Key secondary endpoint

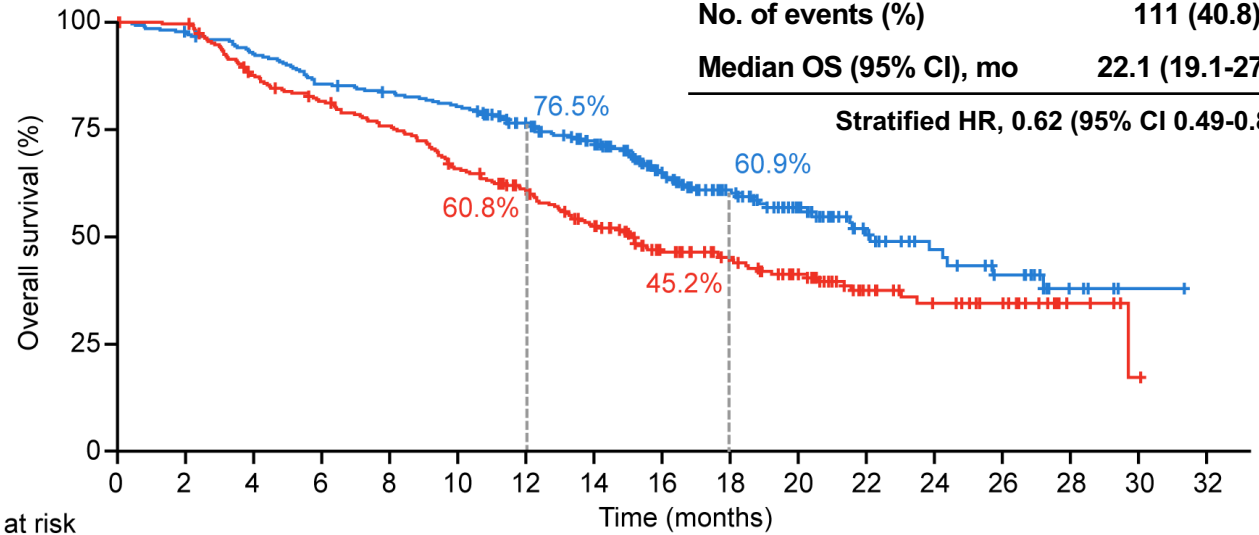
- ORR‡

* Treatment beyond progression allowed if there was evidence of clinical benefits per investigator. ‡ By BIRC per RECIST v1.1. AFP=alpha-fetoprotein; BCLC=Barcelona Clinic Liver Cancer; BIRC=blinded independent review committee; ECOG PS=Eastern Cooperative Oncology Group performance status; EHS=extrahepatic spread; MVI=macrovascular invasion.

Primary Endpoint: OS (ITT Population)

	Camrelizumab + rivoceranib	Sorafenib
No. of events (%)	111 (40.8)	151 (55.7)
Median OS (95% CI), mo	22.1 (19.1-27.2)	15.2 (13.0-18.5)

Stratified HR, 0.62 (95% CI 0.49-0.80)*, *p* <0.0001†



No. at risk																	
Camrelizumab+ rivoceranib	272	265	250	231	224	215	190	165	118	80	57	34	25	18	5	1	0
Sorafenib	271	268	232	214	198	171	149	124	91	70	53	31	22	17	5	1	0

*Stratified Cox proportional hazards model. †One-sided based on the stratified log-rank test. The stratification factors were the randomization strata. Data cutoff: Feb. 8, 2022; median follow-up: 14.5 mo.

Safety Summary

	Camrelizumab + rivoceranib (N=272)	Sorafenib (N=269)
Median exposure of treatment (IQR), mo		
Camrelizumab	**6.9 (3.6-13.4)**	**–**
Rivoceranib/sorafenib	**6.5 (3.4-11.9)**	**3.8 (1.9-7.4)**
Any TRAE*	**265 (97.4)**	**249 (92.6)**
Grade 3/4	**219 (80.5)**	**140 (52.0)**
Grade 5	**1 (0.4)†**	**1 (0.4)‡**
Serious TRAE	**66 (24.3)**	**16 (5.9)**
TRAEs leading to dose modification or interruption of any treatment component	**219 (80.5)**	**135 (50.2)**
TRAEs leading to discontinuation of any treatment component	**66 (24.3)**	**12 (4.5)**
TRAEs leading to discontinuation of all treatment components	**10 (3.7)**	**12 (4.5)**

Data are n (%) or otherwise indicated. *Causality to treatment was determined by the investigator. †Multiple organ dysfunction syndrome; ‡Respiratory failure and circulatory collapse. Data cutoff: Feb. 8, 2022. TRAE=treatment-related adverse event.

Ongoing Phase 3 Trials of Adjuvant Immunotherapy[1-4]

- High risk for HCC recurrence after resection or ablation
- Child–Pugh class A

EMERALD-2	CheckMate-9DX	IMbrave050	KEYNOTE-937
• Durvalumab ± bevacizumab + vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Nivolumab vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Atezolizumab + bevacizumab vs active surveillance • ECOG PS 0-1 • Primary endpoint: RFS	• Pembrolizumab vs placebo • ECOG PS 0 • AFP <400 ng/mL • Primary endpoint: RFS and OS

1. https://clinicaltrials.gov/ct2/show/NCT03383458; 2. https://clinicaltrials.gov/ct2/show/NCT03867084;
3. https://clinicaltrials.gov/ct2/show/NCT03847428; 4. https://clinicaltrials.gov/ct2/show/NCT04102098.

Ongoing Phase 3 Trials of Immunotherapy With LRT[1-4]

- Unsuitable for curative therapy (eg, surgical resection, ablation, transplantation)
- Disease amenable to TACE; no metastasis

EMERALD-1	CheckMate -74W	LEAP-012	TACE-3
• Durvalumab ± bevacizumab + TACE vs TACE + placebo • Child–Pugh A-B7 • ECOG PS 0 or 1 • Primary endpoint: PFS	• Nivolumab ± ipilimumab + TACE vs TACE + placebo • ECOG PS 0-1 • Primary endpoint: OS and TTTP	• Pembrolizumab + lenvatinib + TACE vs TACE + placebo • Primary endpoint: PFS and OS	• Nivolumab + TACE vs TACE • Child-Pugh A • ECOG PS 0-1 • Primary endpoint: OS and TTTP

1. https://clinicaltrials.gov/ct2/show/NCT03778957; 2. https://clinicaltrials.gov/ct2/show/NCT04246177;
3. https://clinicaltrials.gov/ct2/show/NCT04268888; 4. https://clinicaltrials.gov/ct2/show/NCT03905967.

Ongoing Phase 3 Trials of Immunotherapy With LRT[1-4]

- Unsuitable for curative therapy (eg, surgical resection, ablation [illegible]ation)
- Disease amenable to TACE; no metastasis

Press Release: November 9 2023, EMERALD-1 met its primary end-point

EMERALD-1	CheckMate	LEAP-012	TACE-3
• Durvalumab ± bevacizumab + TACE vs TACE placebo • Child–Pugh A-B7 • ECOG PS 0 or 1 • Primary endpoint: PFS	• [illegible]umab ± ipilimumab + TACE vs TACE + placebo • ECOG PS 0-1 • Primary endpoint: OS and TTTP	• Pembrolizumab + lenvatinib + TACE vs TACE + placebo • Primary endpoint: PFS and OS	• Nivolumab + TACE vs TACE • Child-Pugh A • ECOG PS 0-1 • Primary endpoint: OS and TTTP

1. https://clinicaltrials.gov/ct2/show/NCT03778957; 2. https://clinicaltrials.gov/ct2/show/NCT04246177;
3. https://clinicaltrials.gov/ct2/show/NCT04268888; 4. https://clinicaltrials.gov/ct2/show/NCT03905967.

Also From AASLD 2023

- **190: Campani et al**. Evaluated the utility of cell free DNA as pharmacodynamic marker in HCC
  - cfDNA correlated with disease burden, response, were able to detect mutations
- **1727A: Li et al.** Multi-center study of utility of auto-antibodies in ICI related high grade hepatitis
  - ANA, SMA have moderate and low sensitivity for diagnosis but ANA + had faster resolution of ALT, SMA slower, SMA associated with improved OS
  - IgG and anti-LKM1 no utility
- **1733A: Ennin et al.** Evaluated risk of hepatotxicity with ICI
  - Higher risk than sorafenib, highest with ipi-nivo, higher with autoimmune disorders
- **4022A: Chuma et al** Serum biomarkers and response to atezo-bev
  - No mutations, but elevated serum levels of Lag-3 and CXCL-9 better response

Also From AASLD 2023

- **4120: Yip etal:** Evaluated risk of HBV reactivation with IO treatment
  - Found patients do have increased risk of HBV reactivation, increased risk if prior TACE and not on NA prophylaxis
- **1085: Cui et al.** Impact of tacrolimus exposure and cancer mortality post OLT
  - No impact of tacrolimus exposure on the development and outcome of cancers post OLT

Conclusions:

- We have made tremendous progress in improving the survival of patients with advanced HCC
- The introduction of IO in the front-line setting is practice changing
- Not every patient will be a candidate for IO combinations
  - Consider TKIs or single agent IO
- IO based regimens are now showing efficacy in early stage HCC
  - Post-resection
  - In combination with LRT/ TACE
- Ongoing studies will help delineate optimal sequencing, new combinations, and management strategies ultimately improving outcomes for our patients

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