Oncology Updates: Multidisciplinary Management of Hepatocellular Carcinoma

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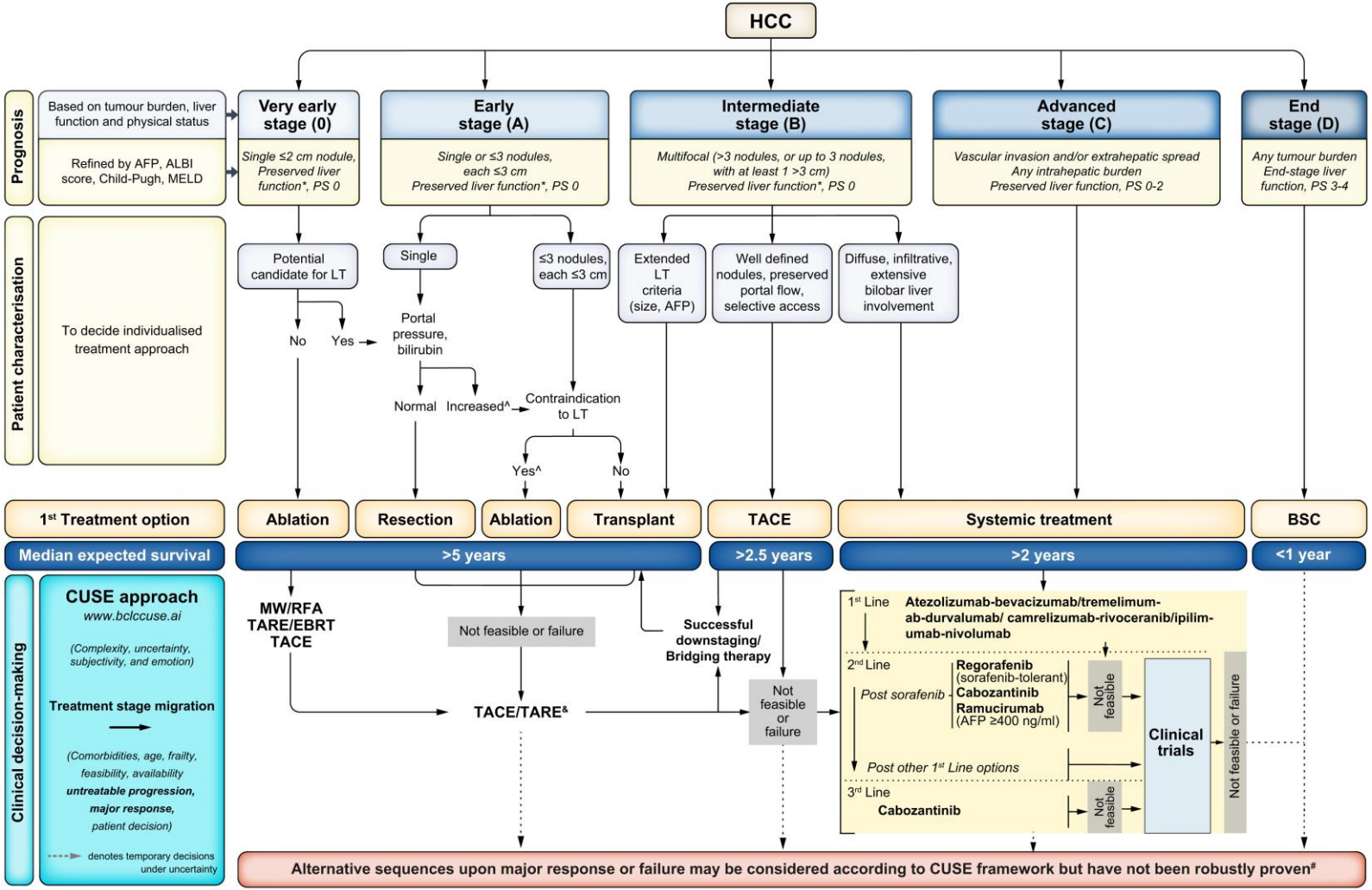
Disclosures

- Adam Burgoyne, MD, PhD has consulting relationships with AstraZeneca, Boston Scientific, Deciphera, Eisai, Exelixis, and Genentech; and contract research relationships with AstraZeneca, Boston Scientific, Cogent, Deciphera, Exelixis, Genentech, Jiangsu Hengrui, Merck, Replimune, Taiho, and Trisalus.
- I will be discussing non-FDA approved indications during my presentation.

Objectives

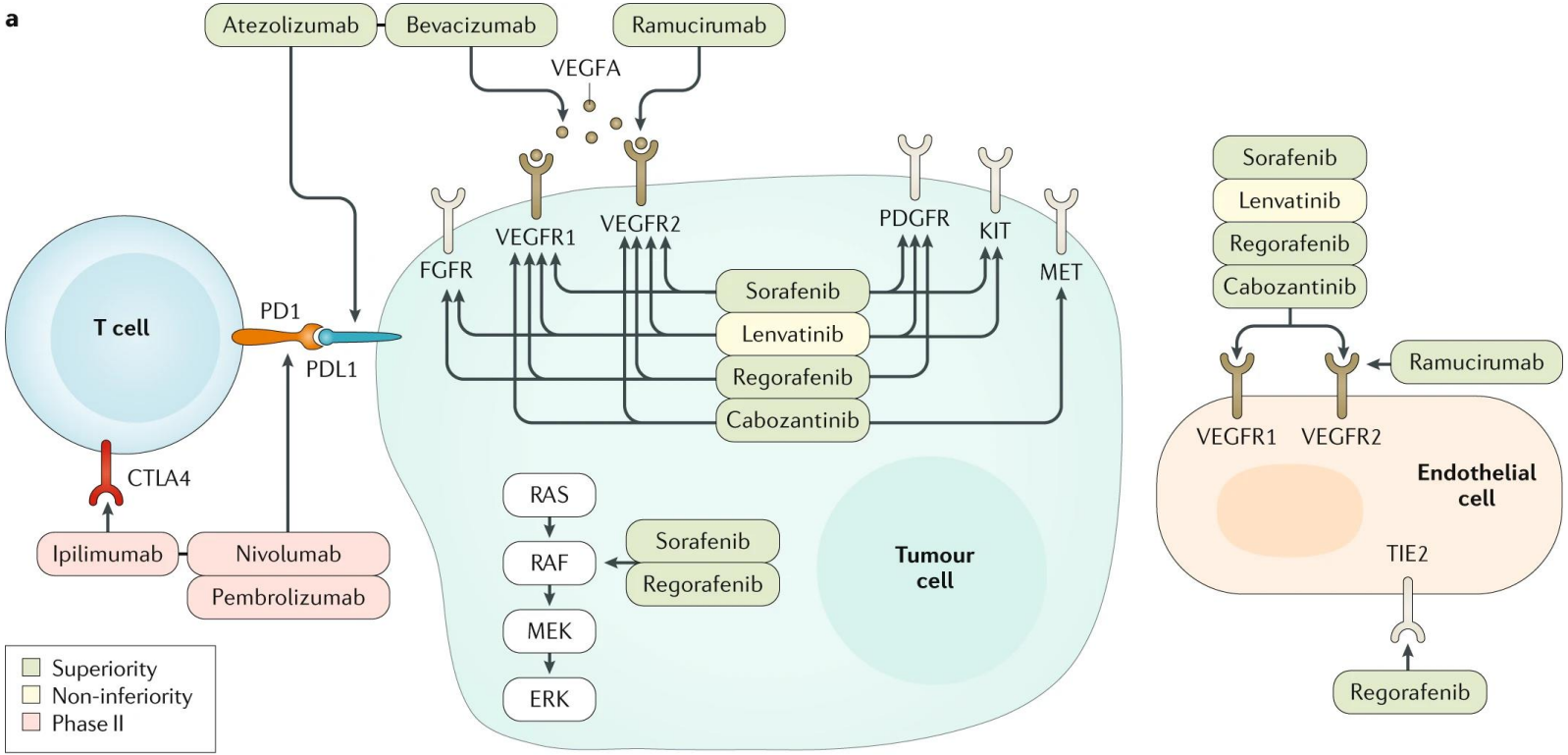
1. Learn systemic therapy options and emerging clinical trials for advanced stage HCC
2. Learn locoregional therapy options and emerging clinical trials for intermediate stage HCC
3. Learn combination (locoregional and systemic) therapies and ongoing clinical trials across HCC stages



Reig M et al. J Hepatol. 2025 Oct 27:S0168-8278(25)02571-1.

Advanced HCC Systemic Therapies

Therapeutic Targets in HCC



Llovet JM et al. Nat Rev Dis Primers. 2021 Jan 21;7(1):6.

Immune Checkpoint Inhibitors

Immunotherapy Combinations: Targets

Drug	HCC Dosing	Targets
Atezolizumab **Bevacizumab**	1200mg IV q3weeks 15mg/kg IV q3weeks	PD-L1 VEGF
Tremelimumab **Durvalumab**	300mg IV x 1 dose 1500mg IV q4weeks	CTLA-4 PD-L1
Ipilimumab **Nivolumab**	3mg/kg IV q3weeks x 4 doses 1mg/kg IV q3weeks x 4 doses 480mg IV q4weeks thereafter	CTLA-4 PD-1

Finn RS et al. N Engl J Med. 2020 May 14;382(20):1894-1905.
Abou-Alfa GK et al. NEJM Evid. 2022;1(8).
Yau T et al. Lancet. 2025 May 24;405(10492):1851-1864.

1st Line Systemic Therapy:
Atezolizumab plus Bevacizumab

IMbrave150: phase 3, randomized, multicenter, open-label trial

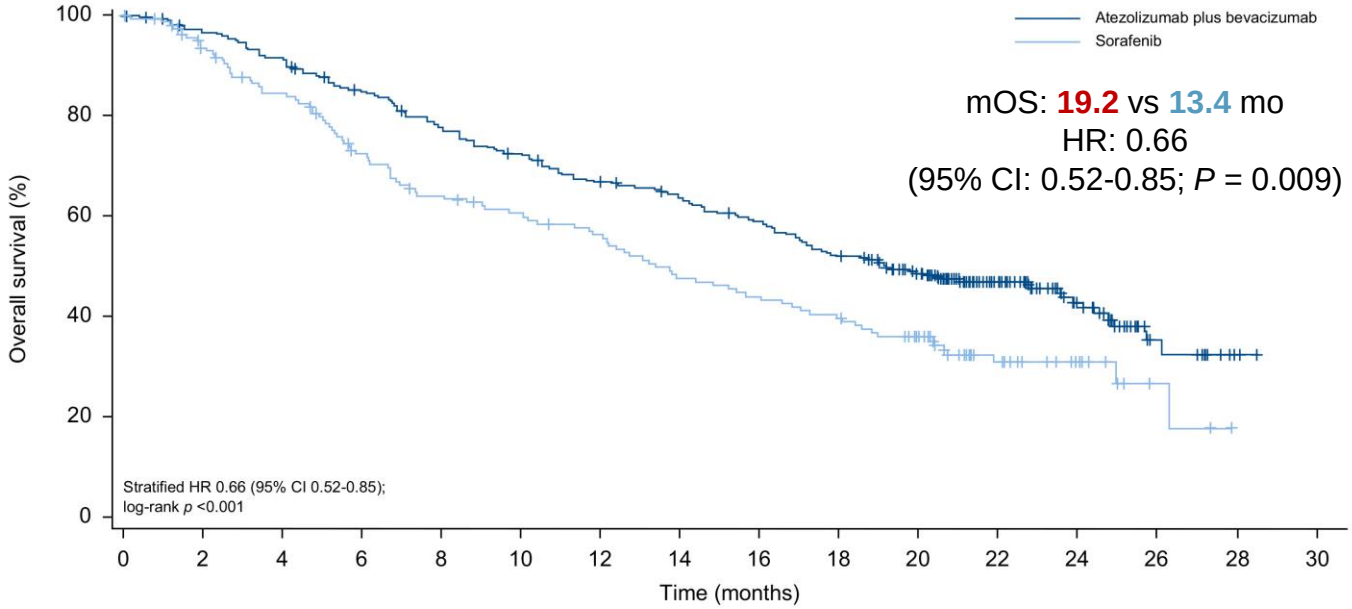
501 patients at 111 sites in 17 countries

POPULATION	RANDOMIZATION/ STRATIFICATION	INTERVENTION	ENDPOINTS
Advanced HCC No prior systemic therapy Child Pugh A ECOG ≤ 1	Asia vs ROW ECOG 0 vs 1 ± MVI/EHS AFP </≥ 400	1:2 Atezolizumab 1200mg IV Bevacizumab 15mg/kg IV q3weeks Sorafenib 400mg PO BID	**Co-Primary:** OS, PFS **Key Secondary:** ORR RECIST v1.1 ORR mRECIST

Finn RS et al. N Engl J Med. 2020 May 14;382(20):1894-1905.

IMbrave150 Co-Primary Endpoints: OS

A

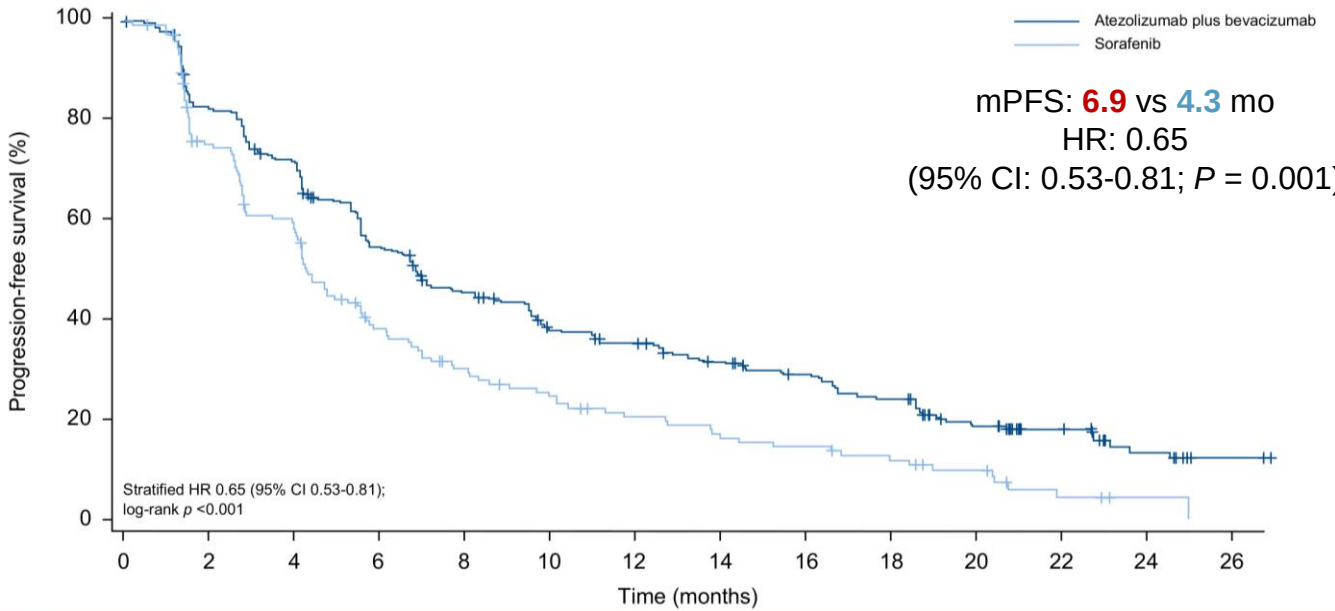


N° at risk (number censored)																
Atezolizumab plus bevacizumab	336 (0)	320 (6)	302 (6)	276 (10)	252 (11)	233 (12)	214 (14)	202 (16)	186 (17)	164 (17)	134 (37)	80 (87)	42 (120)	12 (145)	2 (154)	0 (156)
Sorafenib	165 (0)	144 (11)	128 (13)	106 (17)	92 (19)	85 (21)	78 (22)	66 (22)	61 (22)	55 (22)	44 (28)	24 (43)	12 (55)	3 (63)	0 (65)	0 (65)

Finn RS et al. N Engl J Med. 2020 May 14;382(20):1894-1905.
Cheng AL et al. J Hepatol. 2021 Dec 10:S0168-8278(21)02241-8.

IMbrave150 Co-Primary Endpoints: PFS

B



mPFS: **6.9** vs **4.3** mo
HR: 0.65
(95% CI: 0.53-0.81; *P* = 0.001)

N° at risk (number censored)														
Atezolizumab plus bevacizumab	336 (0)	271 (8)	234 (10)	174 (14)	141 (19)	113 (24)	102 (27)	88 (31)	77 (35)	64 (35)	41 (45)	25 (60)	12 (68)	3 (76)
Sorafenib	165 (0)	110 (18)	84 (19)	52 (23)	39 (25)	31 (26)	24 (28)	19 (28)	17 (28)	13 (29)	9 (31)	3 (33)	1 (35)	0 (35)

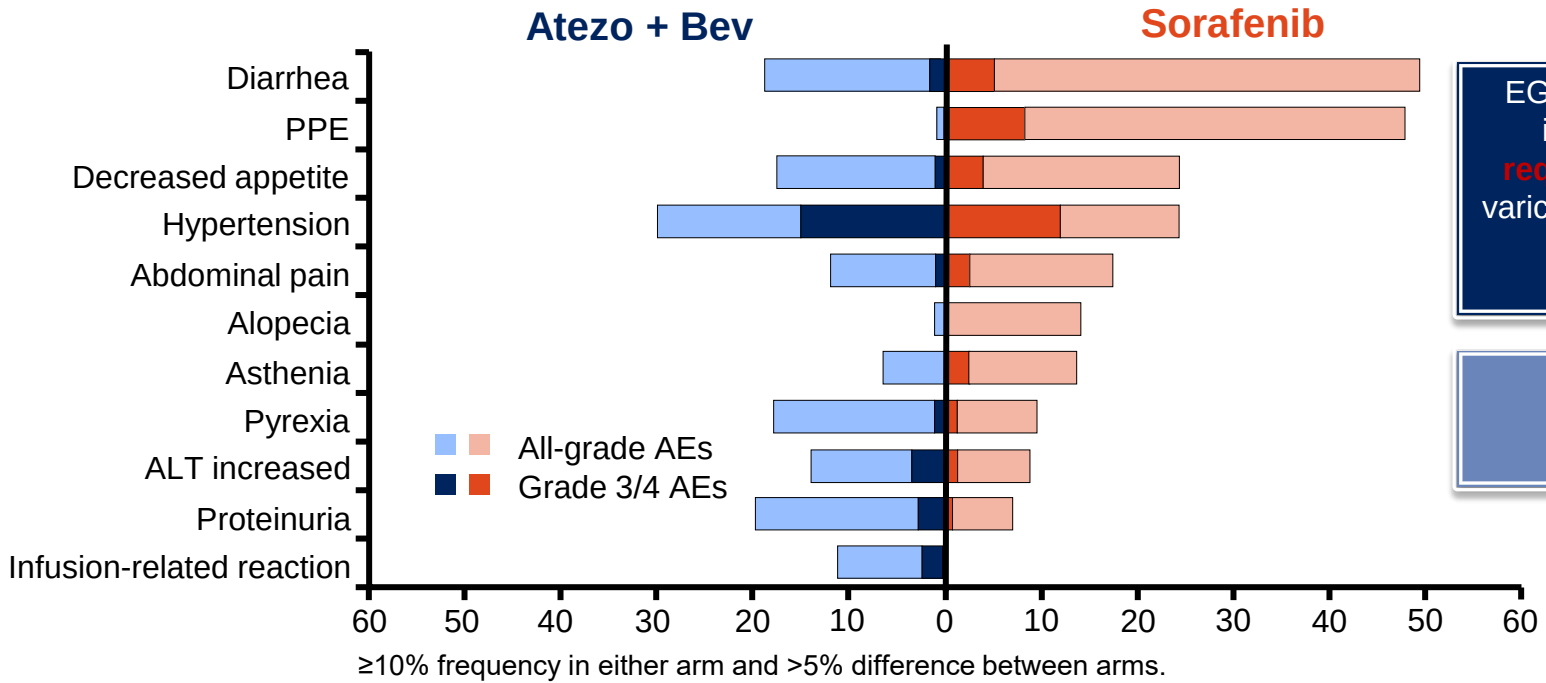
Finn RS et al. N Engl J Med. 2020 May 14;382(20):1894-1905.
Cheng AL et al. J Hepatol. 2021 Dec 10:S0168-8278(21)02241-8.

IMbrave150: Response Rates

Outcome	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR,% (95% CI)	30 (32-35)	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, mo (95% CI)	18.1 (14.6-NE)	14.9 (4.9-17.0)	16.3 (13.1-21.4)	12.6 (6.1-17.7)

Finn RS et al. N Engl J Med. 2020 May 14;382(20):1894-1905.
Cheng AL et al. J Hepatol. 2021 Dec 10:S0168-8278(21)02241-8.

IMbrave150: Safety



EGD within 6 months of initiating treatment **required** to evaluate for varices; varices of any size according to local standards of care

UGIB rates:
7% atezo + bev
4.5% sorafenib

Finn RS et al. N Engl J Med. 2020 May 14;382(20):1894-1905.
Cheng AL et al. J Hepatol. 2021 Dec 10:S0168-8278(21)02241-8.

Dual Immune Checkpoint Blockade

STRIDE

- **S**ingle **T**remelimumab *(anti-CTLA4)*
- **R**egular **I**nterval **D**urvalumab *(anti-PDL1)*

1st Line Systemic Therapy:
Durvalumab plus Tremelimumab

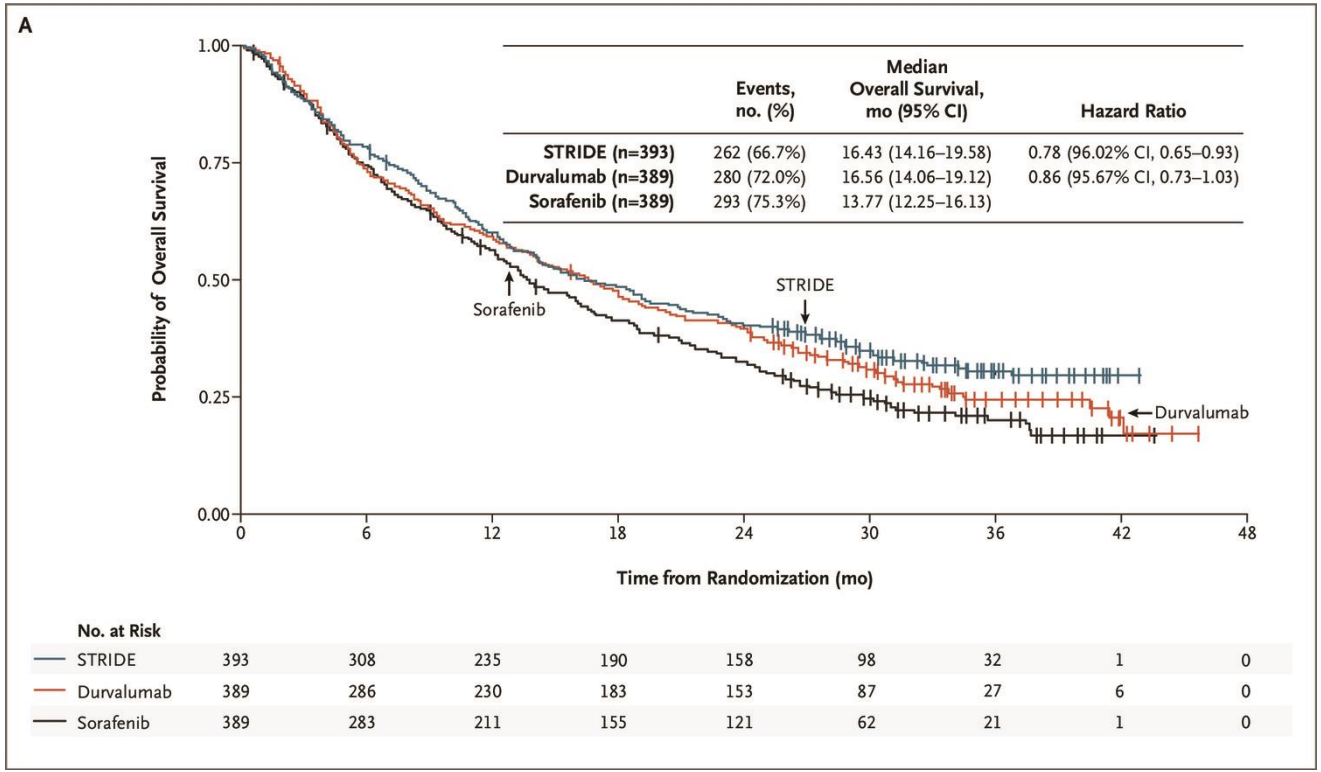
HIMALAYA: phase 3, randomized, multicenter, open-label trial

1324 patients at 181 sites in 16 countries

POPULATION	RANDOMIZATION/ STRATIFICATION	INTERVENTION	ENDPOINTS
Advanced HCC No prior systemic therapy Child Pugh A ECOG ≤ 1 No main PVT EGD not required	HBV/HCV/other ECOG 0 vs 1 ± MVI	1:1:1 Tremelimumab 300mg x1 Durvalumab 1500mg IV q4weeks Durvalumab 1500mg IV q4weeks Sorafenib 400mg PO BID	**Primary:** OS (STRIDE vs sorafenib) **Key Secondary:** OS (durva vs sorafenib) **Other Secondary:** PFS, ORR, DoR

Abou-Alfa GK et al. NEJM Evid. 2022;1(8).

HIMALAYA Primary Endpoint: OS



Abou-Alfa GK et al. NEJM Evid. 2022;1(8).

HIMALAYA: Response Rates

Table 2. Response Outcomes in the Intent-to-Treat Population (Confirmed).*

Parameter	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Response — no. (%)			
Objective†	79 (20.1)	66 (17.0)	20 (5.1)
Complete	12 (3.1)	6 (1.5)	0
Partial	67 (17.0)	60 (15.4)	20 (5.1)
Stable disease — no. (%)	157 (39.9)	147 (37.8)	216 (55.5)
Disease control rate — %	236 (60.1)	213 (54.8)	236 (60.7)
Duration of response — mo‡			
Median	22.34	16.82	18.43
IQR	8.54–NR	7.43–NR	6.51–25.99
Time to response — mo			
Median	2.17	2.09	3.78
95% CI	(1.84–3.98)	(1.87–3.98)	(1.89–8.44)

Abou-Alfa GK et al. NEJM Evid. 2022;1(8).

HIMALAYA: Safety

Event, n (%)	T300+D (n=388)		Durvalumab (n=388)		Sorafenib (n=374)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients with hepatic SMQ TRAE	66 (17.0)	27 (7.0)	55 (14.2)	20 (5.2)	46 (12.3)	18 (4.8)
Patients with hemorrhage SMQ TRAE	7 (1.8)	2 (0.5)	3 (0.8)	0	18 (4.8)	6 (1.6)
Alanine aminotransferase increased	18 (4.6)	4 (1.0)	22 (5.7)	5 (1.3)	8 (2.1)	3 (0.8)
Aspartate aminotransferase increased	22 (5.7)	9 (2.3)	25 (6.4)	9 (2.3)	10 (2.7)	6 (1.6)
Blood bilirubin increased	6 (1.5)	1 (0.3)	6 (1.5)	0	10 (2.7)	2 (0.5)
Ascites	1 (0.3)	0	0	0	2 (0.5)	0
Hepatic encephalopathy	0	0	0	0	2 (0.5)	1 (0.3)
International normalized ratio increased	4 (1.0)	1 (0.3)	0	0	0	0
Esophageal varices hemorrhage	0	0	0	0	0	0

New front-line option for advanced HCC patients that have higher risk of **bleeding** with VEGF-sparing regimen

Abou-Alfa GK et al. NEJM Evid. 2022;1(8).

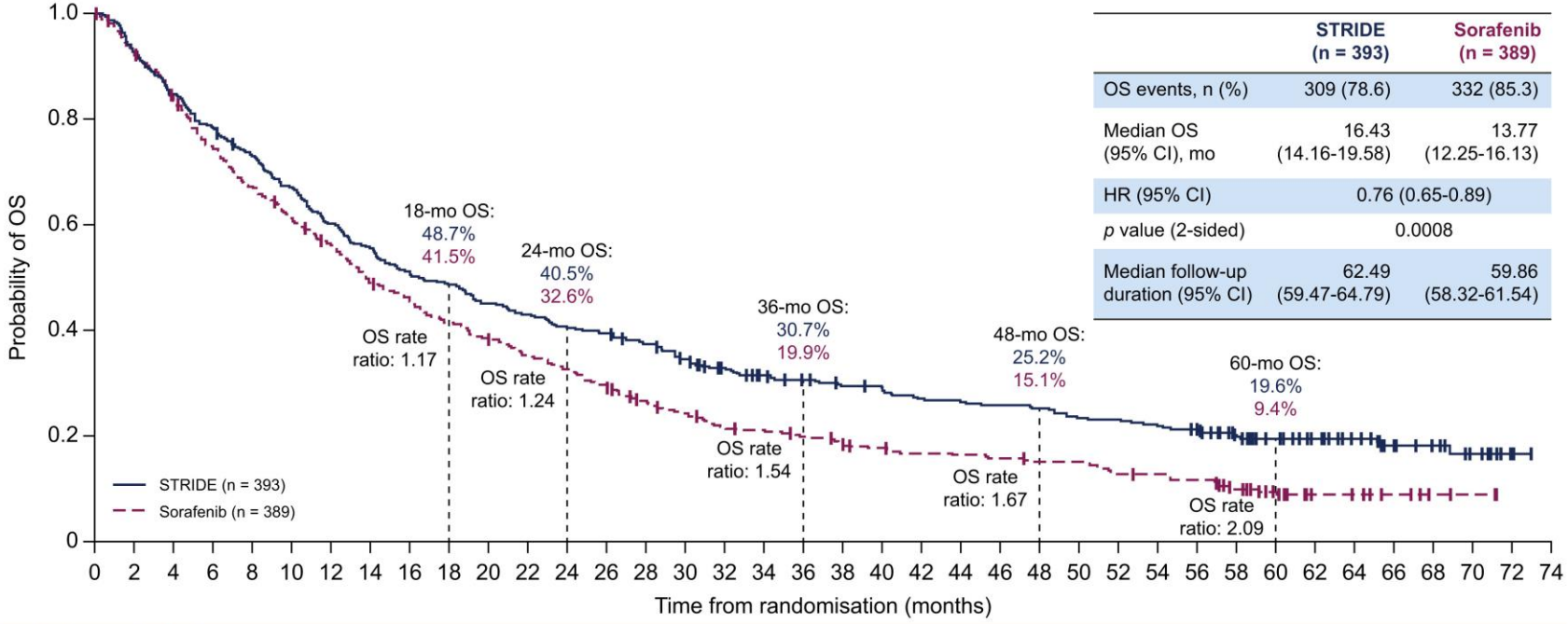
HIMALAYA: Safety

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

CheckMate-040 study with ipilimumab/nivolumab had **53% grade 3 TRAEs**; STRIDE regimen has improved safety profile

Abou-Alfa GK et al. NEJM Evid. 2022;1(8).

HIMALAYA: 5-Year OS Update



	STRIDE (n = 393)	Sorafenib (n = 389)
OS events, n (%)	309 (78.6)	332 (85.3)
Median OS (95% CI), mo	16.43 (14.16-19.58)	13.77 (12.25-16.13)
HR (95% CI)	0.76 (0.65-0.89)	
p value (2-sided)	0.0008	
Median follow-up duration (95% CI)	62.49 (59.47-64.79)	59.86 (58.32-61.54)

No. of participants at risk																																					
STRIDE	393	365	333	308	285	262	235	217	197	190	176	168	158	154	144	131	118	110	104	98	95	89	87	85	83	77	76	72	68	56	46	40	32	20	15	9	2	0
Sorafenib	389	356	319	283	255	231	211	183	170	155	142	131	121	108	93	84	74	71	66	58	55	51	50	48	45	45	38	37	34	25	18	10	9	6	3	2	0	0

Rimassa L et al. J Hepatol. 2025 Apr 11:S0168-8278(25)00226-0.

1st Line Systemic Therapy:
Ipilimumab plus Nivolumab

CheckMate 9DW: phase 3, randomized, multicenter, open-label trial

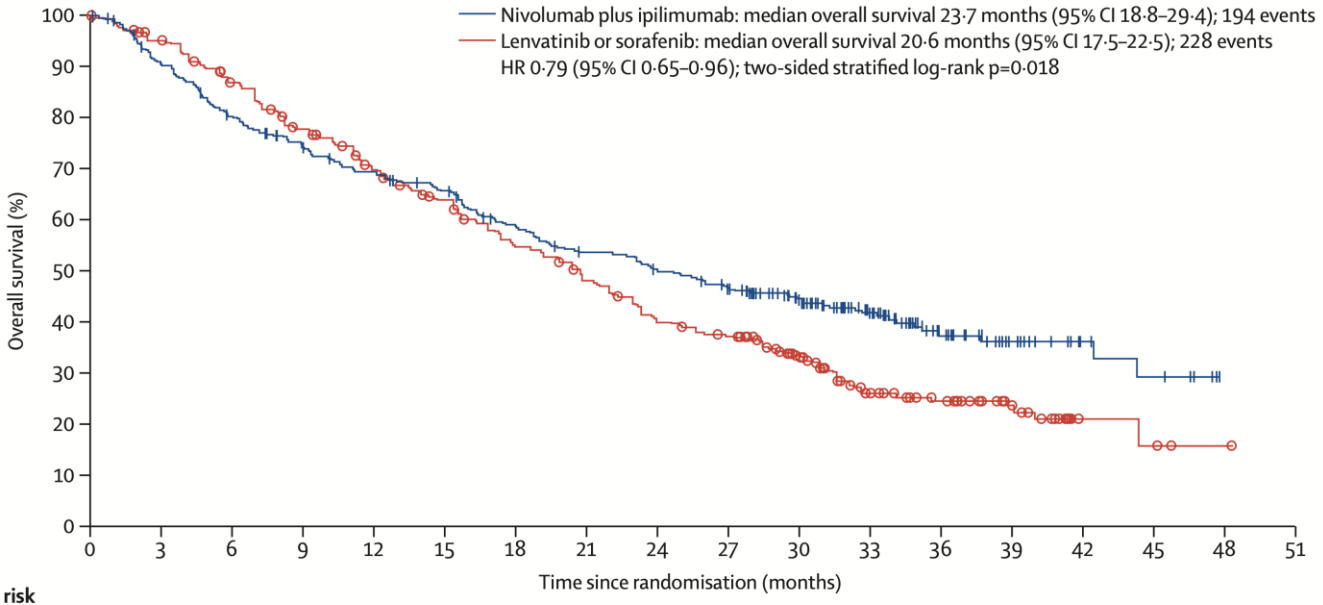
668 patients at 163 sites in 25 countries

POPULATION	RANDOMIZATION/ STRATIFICATION	INTERVENTION	ENDPOINTS
Advanced HCC No prior systemic therapy Child Pugh A ECOG ≤ 1 No main PVT EGD not required	HBV/HCV/non-viral ± MVI/EHS AFP </≥ 400	1:1 Ipilimumab 3mg/kg IV Nivolumab 1mg/kg IV* q3weeks x 4 **then 480mg IV q4weeks* Sorafenib 400mg PO BID OR Lenvatinib 8/12mg PO daily	**Primary:** OS **Key Secondary:** ORR RECIST v1.1 DOR RECIST v1.1

Yau T et al. Lancet. 2025 May 24;405(10492):1851-1864.

CheckMate 9DW Primary Endpoint: OS

A



Number at risk (number censored)																	
Nivolumab plus ipilimumab	335 (0)	300 (3)	264 (5)	239 (9)	220 (11)	206 (15)	179 (19)	162 (21)	150 (22)	137 (24)	104 (51)	71 (79)	42 (103)	24 (119)	11 (132)	8 (133)	0 (141)	0 (141)
Lenvatinib or sorafenib	333 (0)	310 (7)	280 (11)	245 (15)	216 (20)	194 (23)	164 (25)	144 (27)	116 (28)	106 (31)	76 (48)	44 (67)	34 (75)	20 (88)	4 (102)	3 (102)	1 (104)	0 (105)

Yau T et al. Lancet. 2025 May 24;405(10492):1851-1864.

CheckMate 9DW: Response Rates

	Nivolumab plus ipilimumab group (n=335)	Lenvatinib or sorafenib group (n=333)
Objective response rate* (%; 95% CI)	121 (36%; 31–42)	44 (13%; 10–17)
Best overall response†		
Complete response	23 (7%)	6 (2%)
Partial response	98 (29%)	38 (11%)
Stable disease‡	108 (32%)	205 (62%)
Progressive disease	67 (20%)	47 (14%)
Could not be evaluated§	39 (12%)	37 (11%)
Median duration of response (95% CI), months¶	30·4 (21·2–NE)	12·9 (10·2–31·2)
Patients with duration of response (%; 95% CI)¶		
≥24 months	55% (44–64)	35% (17–53)
≥36 months	47% (34–59)	NA
Median time to response (IQR), months‖	2·2 (2·1–3·8)	3·7 (2·1–5·6)

Yau T et al. Lancet. 2025 May 24;405(10492):1851-1864.

CheckMate 9DW: Safety

***Table S11*: Immune-mediated adverse events in all treated patients in the nivolumab plus ipilimumab group**

Event*	Nivolumab plus ipilimumab (n=332)			
	Any grade	Grade 3–4	Received high-dose steroids	Leading to discontinuation
Any immune-mediated adverse event	191 (58%)	93 (28%)	96 (29%)	42 (13%)
Hepatitis	63 (19%)	51 (15%)	56 (17%)	19 (6%)
Hypothyroidism/thyroiditis	62 (19%)	1 (<1%)	2 (<1%)	0
Rash	51 (15%)	14 (4%)	10 (3%)	1 (<1%)
Hyperthyroidism	36 (11%)	2 (< 1%)	3 (<1%)	0
Diarrhoea/colitis	28 (8%)	15 (5%)	27 (8%)	9 (3%)
Adrenal insufficiency	18 (5%)	6 (2%)	2 (<1%)	4 (1%)
Hypophysitis	9 (3%)	4 (1%)	3 (<1%)	4 (1%)
Pneumonitis	7 (2%)	3 (<1%)	6 (2%)	3 (<1%)
Nephritis and renal dysfunction	5 (2%)	3 (<1%)	3 (<1%)	2 (<1%)
Hypersensitivity	4 (1%)	0	3 (<1%)	0
Diabetes mellitus	2 (<1%)	2 (<1%)	0	0

Data are n (%). *Immune-mediated adverse events are specific events considered as potential immune-mediated events by investigator, occurring within 100 days after the last dose of study treatment, regardless of causality, and, with the exception of endocrine events, are treated with immune-modulating medication.

Yau T et al. Lancet. 2025 May 24;405(10492):1851-1864.

Tyrosine Kinase Inhibitors

Tyrosine Kinase Inhibitors: Targets

Drug	HCC Dosing	Targets
Sorafenib	400mg PO BID	**VEGFR**, PDGFR B/C-RAF
Lenvatinib	12mg PO daily (≥60 kg) 8mg PO daily (<60 kg)	**VEGFR**, PDGFR, RET, KIT, FGFR
Regorafenib	160mg PO daily days 1-21 q28days	**VEGFR**, PDGFR, RET, KIT, FGFR, TIE2 B/C-RAF
Cabozantinib	60mg PO daily	**VEGFR**, RET, KIT, TIE2, C-MET, AXL

Llovet JM et al. N Engl J Med. 2008 Jul 24;359(4):378-90.
Cheng AL et al. Lancet Oncol. 2009 Jan;10(1):25-34.
Kudo M et al. Lancet. 2018 Feb 9. pii:S0140-6736(18)30207-1.
Bruix J et al. Lancet. 2017 Jan 7;389(10064):56-66.
Abou-Alfa GK et al. N Engl J Med. 2018 Jul 5;379(1):54-63.

Tyrosine Kinase Inhibitors: Efficacy

Drug	Trial	Line	Phase	Comparison	ORR (%)*	SD (%)*	mOS (mos)
Sorafenib	SHARP Asia-Pacific	1st 1st	III III	Placebo Placebo	2 3	71 54	10.7 vs 7.9 6.5 vs 4.2
Lenvatinib	REFLECT	1st	III	Sorafenib *(non-inferiority)*	19 vs 7	54 vs 53	13.6 vs 12.3
Regorafenib	RESORCE	2nd	III	Placebo	11	54	10.6 vs 7.8
Cabozantinib	CELESTIAL	2nd	III	Placebo	4	60	10.2 vs 8.0

**Assessed by RECIST v1.0 or v1.1*

Llovet JM et al. N Engl J Med. 2008 Jul 24;359(4):378-90.
Cheng AL et al. Lancet Oncol. 2009 Jan;10(1):25-34.
Kudo M et al. Lancet. 2018 Feb 9. pii:S0140-6736(18)30207-1.
Bruix J et al. Lancet. 2017 Jan 7;389(10064):56-66.
Abou-Alfa GK et al. N Engl J Med. 2018 Jul 5;379(1):54-63.

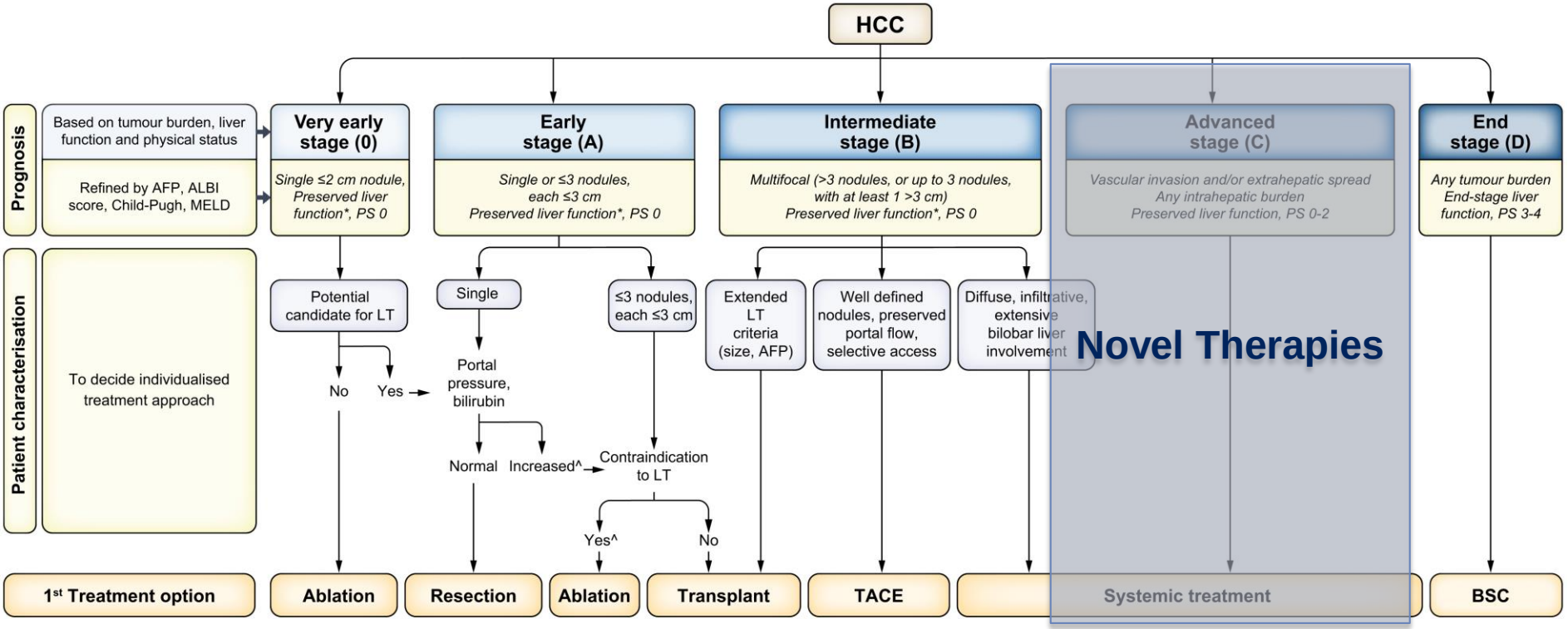
Tyrosine Kinase Inhibitors: Toxicity

Drug	Toxicity
Sorafenib	Fatigue, Anorexia, Weight loss, Alopecia, Nausea, Diarrhea Hand-foot syndrome, Rash Hypertension, Voice changes
Lenvatinib	Fatigue, Anorexia, **Weight loss, Alopecia,** Nausea, Diarrhea, Abdominal pain **Hand-foot syndrome,** Rash **Hypertension, Proteinuria, Voice changes, Hypothyroidism**
Regorafenib	Fatigue, Anorexia, Weight loss, Fever, Oral mucositis, Vomiting, Diarrhea Hand-foot syndrome Hypertension, Hoarseness, Thrombocytopenia, Hypophosphatemia
Cabozantinib	Fatigue, Decreased appetite, Weight loss, Asthenia, Mucositis, Nausea, Diarrhea Hand-foot syndrome Hypertension, Dysphonia, Dysgeusia, Thrombocytopenia

Favors sorafenib
Favors lenvatinib

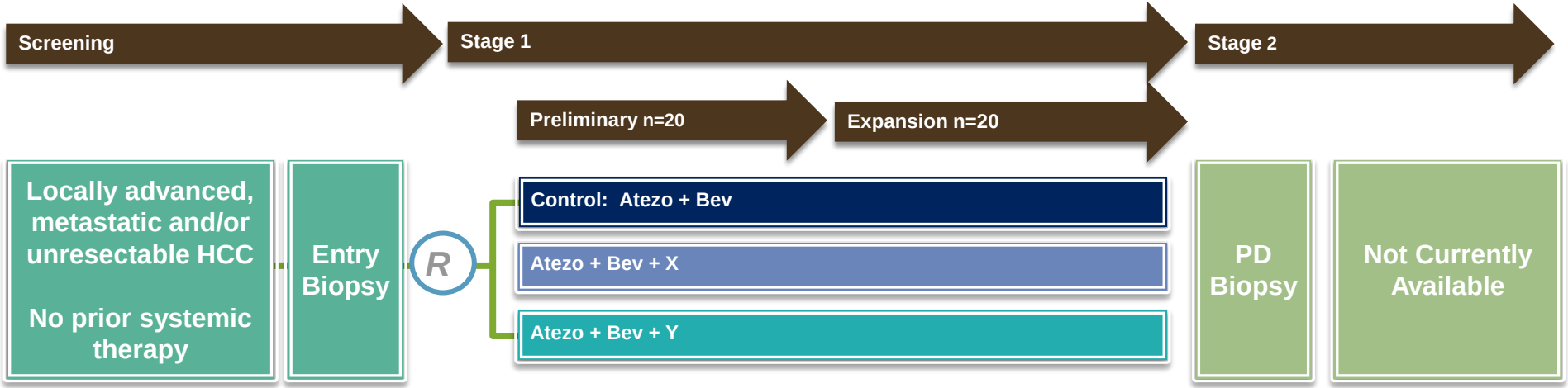
Llovet JM et al. N Engl J Med. 2008 Jul 24;359(4):378-90.
Cheng AL et al. Lancet Oncol. 2009 Jan;10(1):25-34.
Kudo M et al. Lancet. 2018 Feb 9. pii:S0140-6736(18)30207-1.
Bruix J et al. Lancet. 2017 Jan 7;389(10064):56-66.
Abou-Alfa GK et al. N Engl J Med. 2018 Jul 5;379(1):54-63.

Future Directions: Advanced Stage



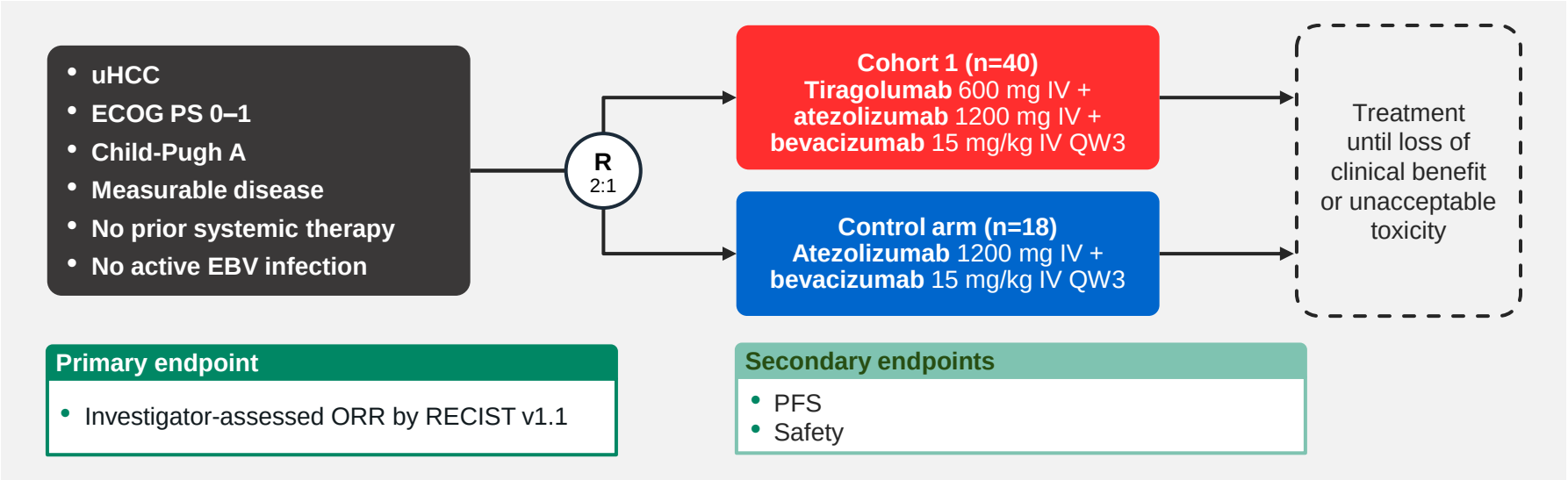
Reig M et al. J Hepatol. 2025 Oct 27:S0168-8278(25)02571-1.

MORPHEUS: Adaptive Phase 1b/2 Trial



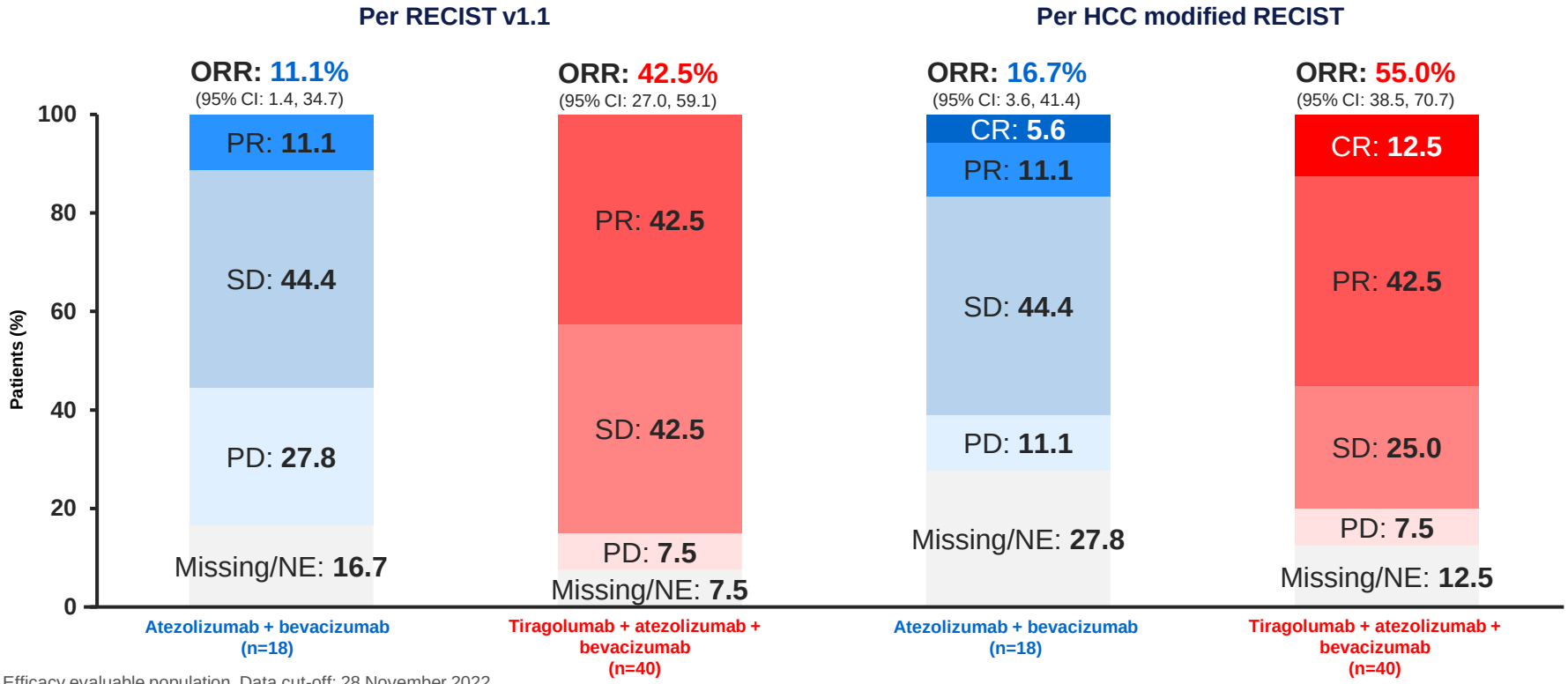
NCT04524871

MORPHEUS: Tiragolumab Arm



Finn RS et al. 2023 ASCO

MORPHEUS: Tiragolumab Arm

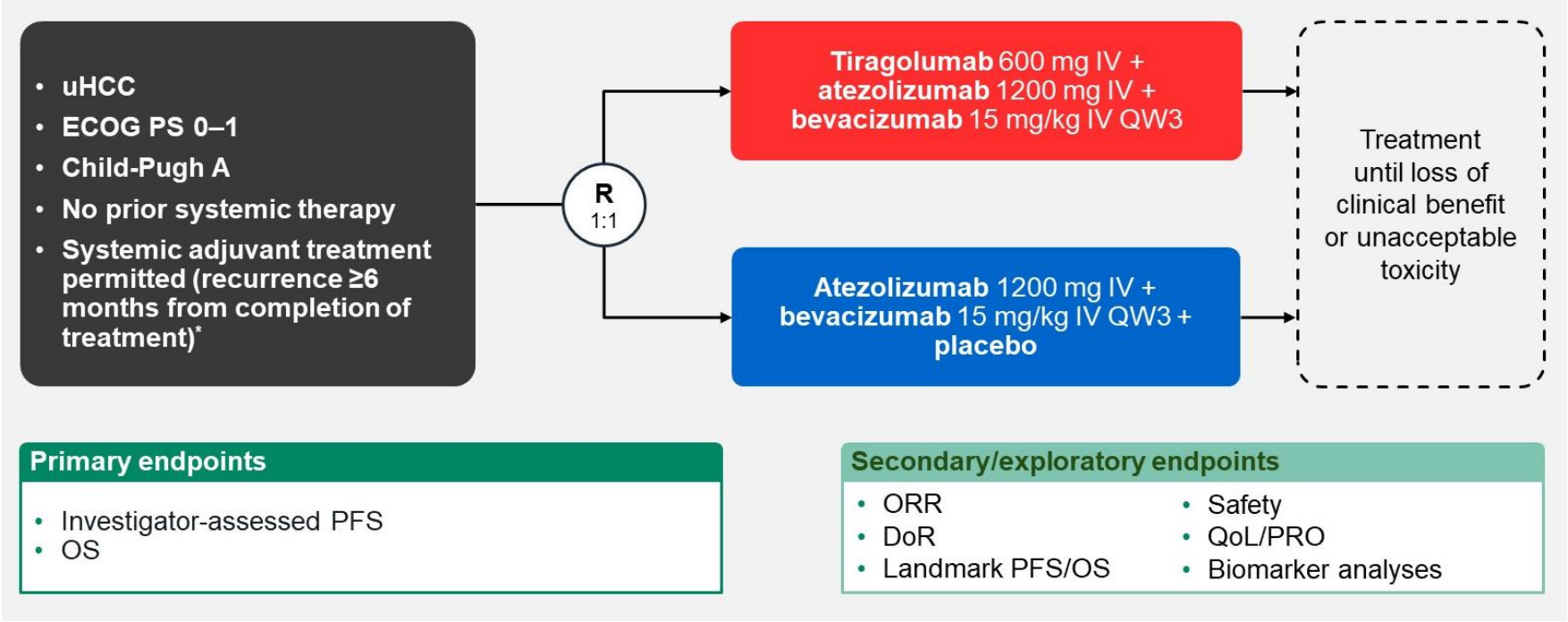


Efficacy evaluable population. Data cut-off: 28 November 2022

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

Finn RS et al. 2023 ASCO

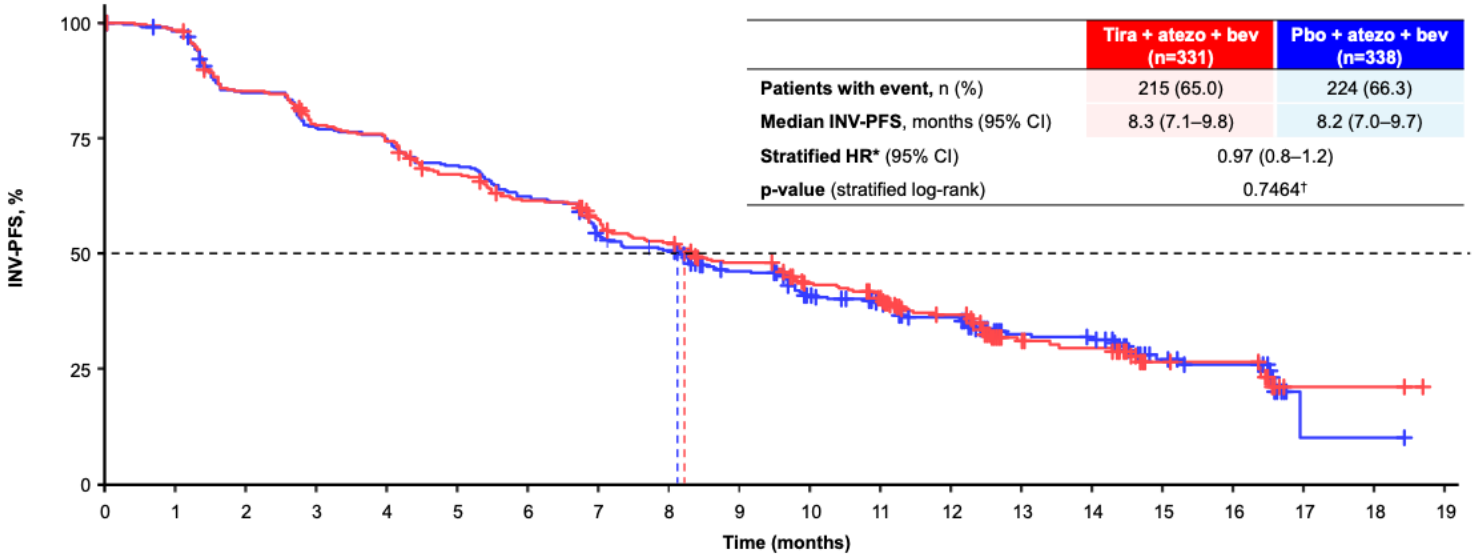
IMbrave152/SKYSCRAPER-14



Finn RS et al. 2023 ASCO

IMbrave152/SKYSCRAPER-14

Primary endpoint: INV-PFS per RECIST v1.1



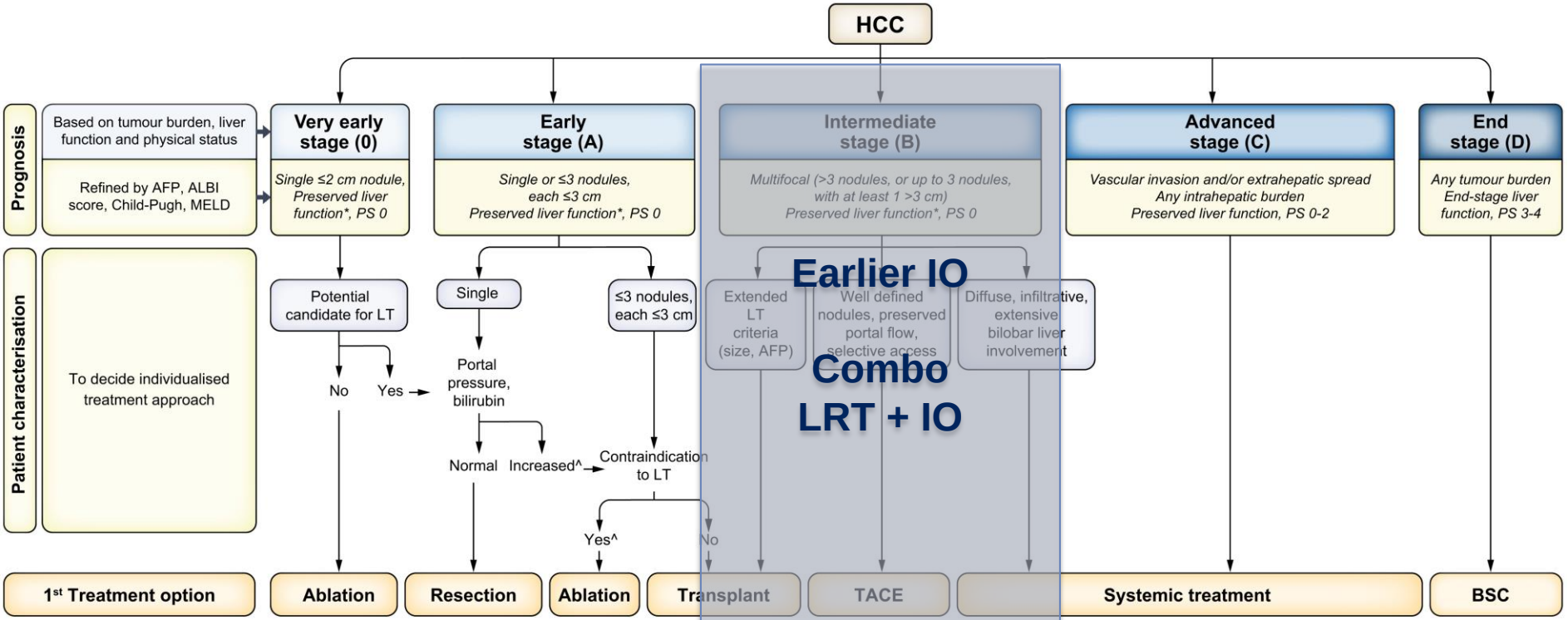
	Tira + atezo + bev (n=331)	Pbo + atezo + bev (n=338)
Patients with event, n (%)	215 (65.0)	224 (66.3)
Median INV-PFS, months (95% CI)	8.3 (7.1–9.8)	8.2 (7.0–9.7)
Stratified HR* (95% CI)	0.97 (0.8–1.2)	
p-value (stratified log-rank)	0.7464†	

Patients at risk:

Tira + atezo + bev	331	321	276	250	239	213	192	175	159	142	122	110	85	42	38	18	17	3	3	0
Pbo + atezo + bev	338	326	279	254	246	227	205	174	162	136	112	98	87	54	51	26	22	1	1	0

Finn RS et al. 2025 ESMO

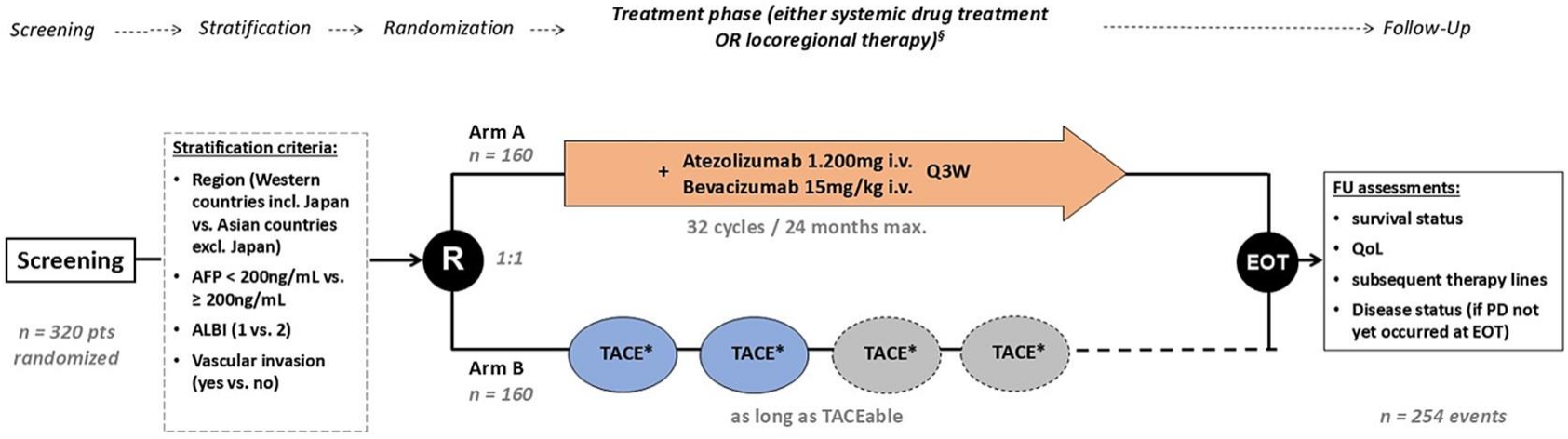
Future Directions: Intermediate Stage



Reig M et al. J Hepatol. 2025 Oct 27:S0168-8278(25)02571-1.

IKF-035/ABC-HCC Study Design

an international, randomized, multicenter, open-label, investigator-initiated phase 3b trial



§ Patients will be treated until loss of clinical benefit, development of unacceptable toxicity, participant request, or withdrawal of consent (whatever first).

* Both conventional TACE (cTACE) and drug-eluting beads (DEB-TACE) approaches are accepted. However, each study site is required to maintain consistency in the TACE procedure and the use of doxorubicin or epirubicin as a chemoembolization agent throughout the study duration.

Key Eligibility Criteria

Main Inclusion Criteria

- Intermediate stage HCC - not amenable to curative surgery, liver transplantation or curative ablation BUT disease amenable to TACE (minimal vascular invasion Vp1/Vp2 allowed)
- No massive multinodular pattern preventing adequate TACE
- No extrahepatic disease
- Child-Pugh-Score A or B7
- Performance Status ECOG 0-1
- No presence of untreated or incompletely treated varices with bleeding or high-risk for bleeding
- Absence of other severe comorbidities

Main Exclusion Criteria

- Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
- Previous treatment with atezolizumab or bevacizumab or a programmed death 1 (PD1), programmed death-ligand (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, or any form of cancer immunotherapy for HCC
- Clinically meaningful ascites, defined as ascites requiring nonpharmacologic intervention
- Known hypersensitivity to any of the study drugs

Primary endpoint

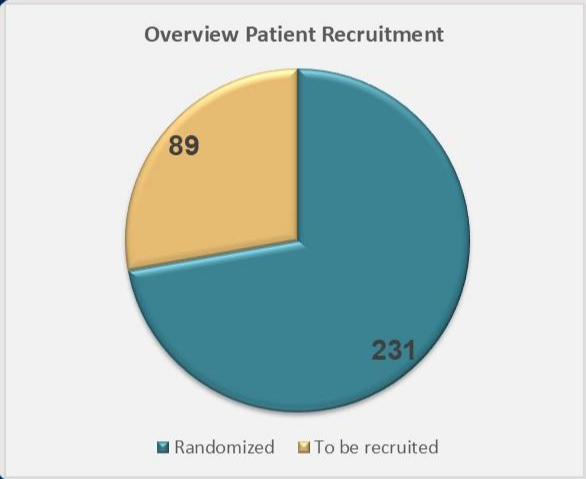
allowing a fair comparison between two modalities (systemic Tx vs. locoregional Tx)

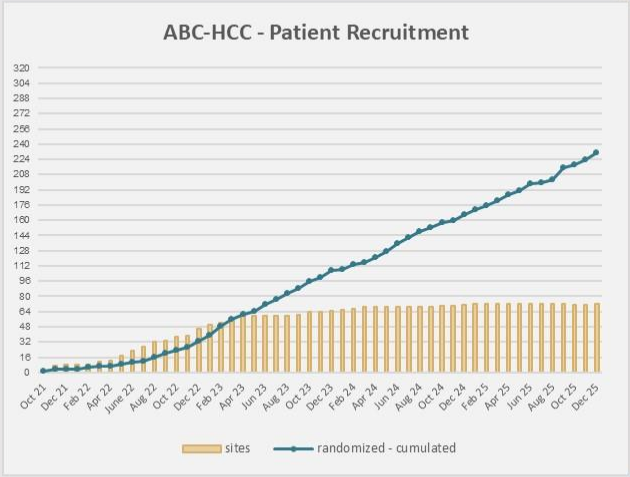
Time to failure of treatment strategy (TTFS)

Failure of strategy =	Arm A (Atezo/Bev)	Arm B (TACE)
1st condition →	radiologic progession	radiologic progression or stable disease
2nd condition →	**AND any of the following:** ▪ the loss of clinical benefit OR – Progression at critical anatomical sites – Development of symptoms and signs (including laboratory values) unequivocal progression of disease – Decline in ECOG performance status attributed to disease progression – No evidence of clinical benefit as assessed by the investigator ▪ unacceptable toxicity OR ▪ liver function deterioration OR ▪ therapy not further applicable for other reasons	

Current Status

Patient number: n=320 (planned)
Study sites: ~ 70 study sites
Countries: Germany, Spain, France, Italy, Austria, Japan, and India
Current recruitment: 231/320 patients (Dec-2025)



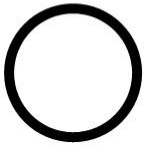


Interim Analyses

Interim Analysis: at two timepoints for efficacy/futility of TTFS

- 1st IA at 33% of information time (n=85 events)
  - **Reached**
  - Data cut-off: 13-Jun-2025 (100 events considered)

- 2nd IA at 66% of information time (planned at n=169 events)
  - Expected Q3 2026



Disclaimer:

Data at interim analyses is still premature and based on site specific reporting.

Data cleaning is still in progress. Slight changes at final analysis are possible!

Time to Failure of Treatment Strategy (TTFS)