Novedades en Hepatocarcinoma

21st November 2024

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1. Early-disease
2. Intermediate stage
3. Advanced disease

1. **Early-disease**
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BCLC 2022 Updated Guidelines

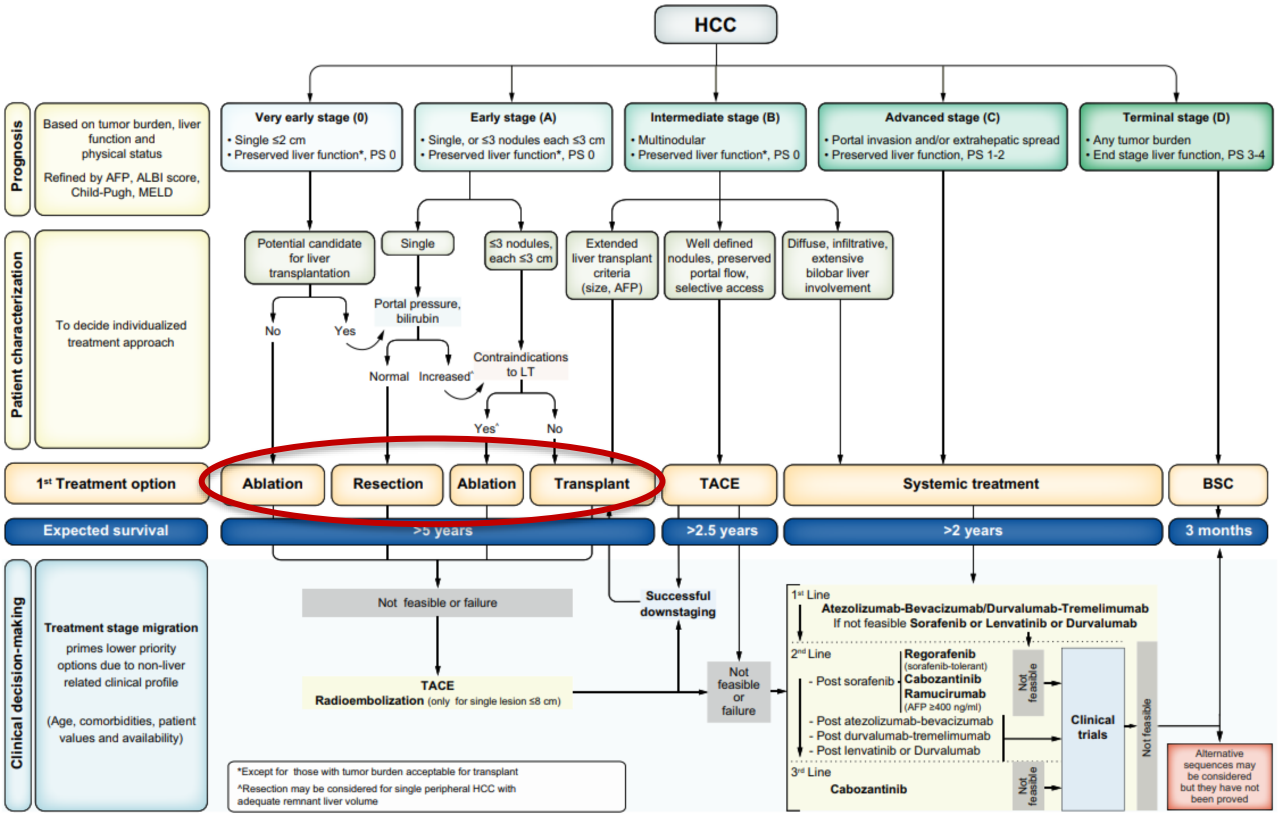
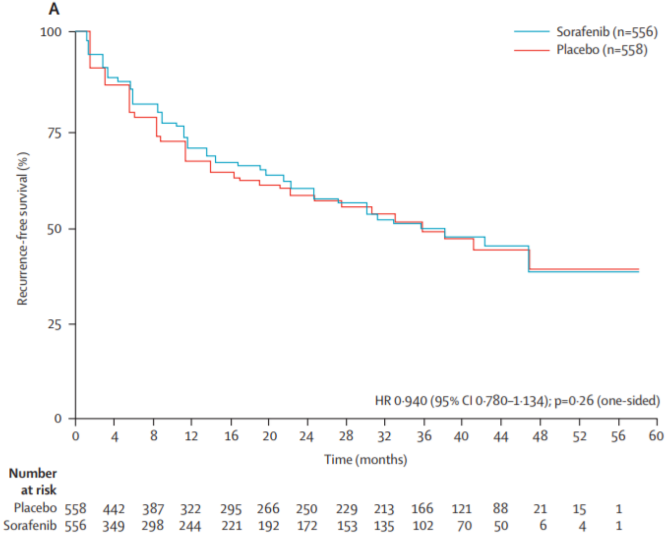


Fig. 1. BCLC staging and treatment strategy in 2022. The BCLC system establishes a prognosis in accordance with the 5 stages that are linked to first-line treatment recommendation. The expected outcome expressed as median survival of each tumour stage according to the available scientific evidence. Individualised clinical decision-making, according to the available data on November 15, 2021, is defined

Reig J of Hepatol 2022

Adjuvant treatment

- **No adjuvant** treatment for HCC
  - STORM study: no benefit of sorafenib vs observation (recurrence-free survival)

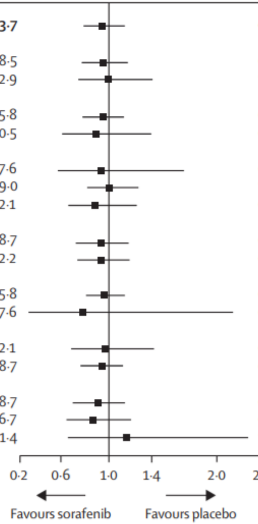


THE LANCET Oncology

ARTICLES | VOLUME 16, ISSUE 13, P1344-1354, OCTOBER 01, 2015

Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial

	Sorafenib n	Sorafenib Median RFS (months)	Placebo n	Placebo Median RFS (months)	HR (95% CI)
All patients (ITT)	**556**	**33·3**	**558**	**33·7**	**0·940 (0·780–1·134)**
Age					
<65 years	383	38·5	361	38·5	0·942 (0·752–1·179)
≥65 years	173	27·8	197	32·9	1·007 (0·722–1·405)
Sex					
Male	451	33·1	461	35·8	0·951 (0·777–1·165)
Female	105	33·3	97	30·5	0·887 (0·564–1·396)
Region					
Americas	60	38·5	60	27·6	0·931 (0·513–1·691)
Asia-Pacific	330	38·5	330	39·0	1·006 (0·792–1·277)
Europe	166	24·8	168	22·1	0·871 (0·617–1·230)
Risk					
Intermediate risk	298	41·7	308	38·7	0·926 (0·710–1·209)
High risk	258	24·9	250	22·2	0·933 (0·721–1·207)
Child-Pugh status					
Child-Pugh A	541	33·3	538	35·8	0·954 (0·791–1·152)
Child-Pugh B	15	NE	20	27·6	0·760 (0·270–2·141)
Type of treatment					
Local ablation	106	19·6	108	22·1	0·970 (0·656–1·434)
Surgical resection	450	41·7	450	38·7	0·937 (0·759–1·156)
Cause of HCC					
Hepatitis B	282	41·7	264	38·7	0·900 (0·695–1·166)
Hepatitis C	119	25·5	151	16·7	0·849 (0·601–1·199)
Alcohol use	47	30·1	45	41·4	1·183 (0·614–2·280)



Interpretation

Our data indicate that sorafenib is not an effective intervention in the adjuvant setting for hepatocellular carcinoma following resection or ablation.

Bruix et al, Lancet Oncol 2015

Adjuvant treatment – IMBRAVE-050

Adjuvant AtezoBev x12 months vs observation (n= 668)

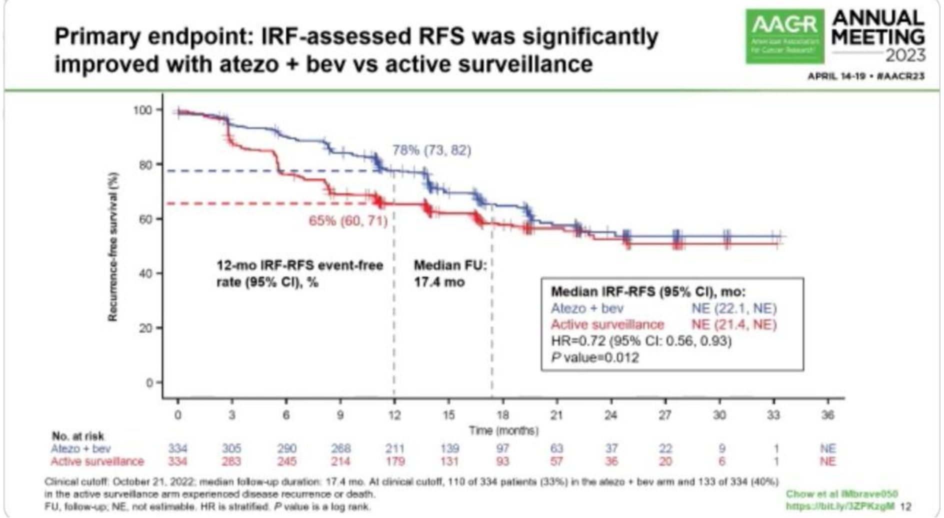
AACR ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

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.

Chow et al IMbrave050
https://bit.ly/3ZPKzgM 7



OS data immature

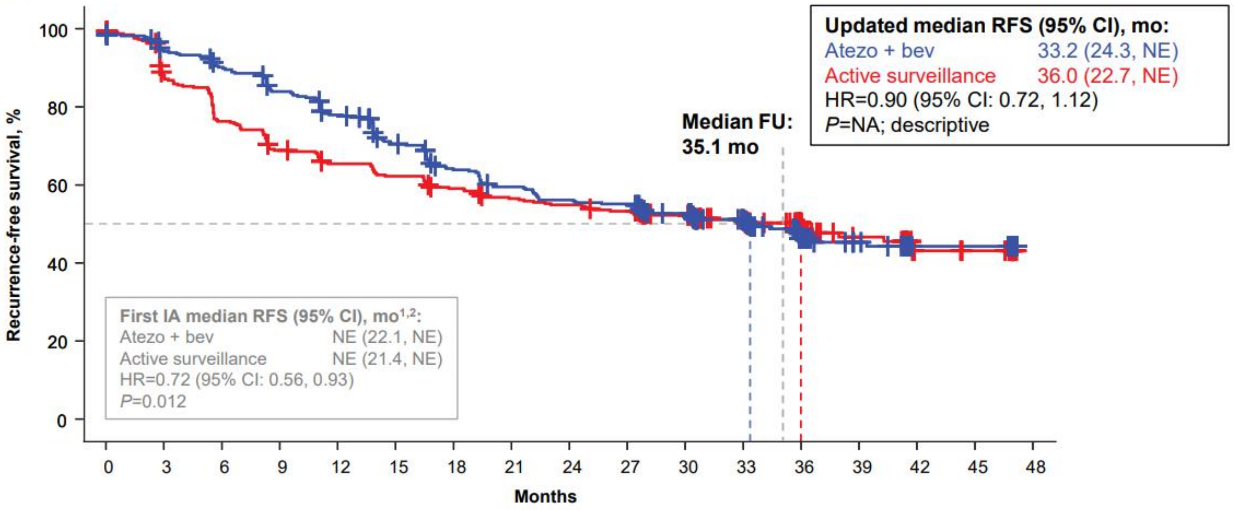
Grade 5 tox: 1.8%

Chow et al, AACR 2023

IMBRAVE-050 (ESMO 2024 results updated)

Early RFS benefit was not maintained with longer follow-up

BARCELONA 2024 ESMO congress



No. at risk																	
Atezo + bev	334	305	290	268	245	216	191	177	167	164	147	123	62	45	18	18	NE
Active surveillance	334	285	247	221	207	197	185	175	170	164	145	124	63	42	16	14	NE

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. At clinical cutoff, 162 of 334 patients (49%) in the atezo + bev arm and 164 of 334 (49%) in the active surveillance arm experienced disease recurrence or death. HRs are stratified. *P* values are log rank.
FU, follow-up; NA, not applicable; NE, not estimable. 1. Qin et al. Lancet 2023. 2. Chow et al. AACR 2023 [abstract CT003].

Yopp et al. IMbrave050 update https://ter.li/q4cyl1

Yopp et al, ESMO 2024

IMBRAVE-050 (ESMO 2024 results updated)

RFS was consistent across clinically relevant subgroups

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Baseline risk factors	No. of patients	Unstratified HR (95% CI)
All patients	668	0.91 (0.73, 1.13)
<65 years old	427	0.98 (0.75, 1.28)
≥65 years old	241	0.78 (0.54, 1.13)
Male	555	0.91 (0.72, 1.15)
Female	113	0.96 (0.53, 1.73)
Asian	545	0.90 (0.70, 1.15)
White	78	0.79 (0.42, 1.48)
Other race	45	1.32 (0.61, 2.86)
ECOG PS 0	527	0.84 (0.65, 1.07)
ECOG PS 1	141	1.19 (0.75, 1.88)
PD-L1 ≥1%	294	0.98 (0.70, 1.37)
PD-L1 <1%	269	0.73 (0.53, 1.02)
Unknown PD-L1	105	1.39 (0.78, 2.49)
1 high-risk feature[a]	312	0.85 (0.60, 1.22)
>1 high-risk features[a]	273	0.94 (0.69, 1.27)
BCLC 0/A	572	0.92 (0.73, 1.18)
BCLC B	56	0.78 (0.39, 1.56)
BCLC C	40	0.99 (0.47, 2.11)

0.3 ← 1 → 3

Atezo + bev better | Active surveillance better

Baseline risk factors	No. of patients	Unstratified HR (95% CI)
Hepatitis B etiology	418	0.96 (0.72, 1.27)
Hepatitis C etiology	72	1.04 (0.55, 1.99)
Non-viral etiology	86	0.91 (0.50, 1.64)
Unknown etiology	92	0.64 (0.36, 1.13)
Resection	585	0.89 (0.71, 1.12)
Ablation	83	1.04 (0.55, 1.97)
In patients who underwent resection:		
1 tumour	526	0.91 (0.71, 1.17)
>1 tumours	59	0.75 (0.39, 1.45)
Tumour size >5 cm	327	0.84 (0.64, 1.12)
Tumour size ≤5 cm	258	1.10 (0.73, 1.65)
mVI present	358	0.96 (0.72, 1.28)
mVI absent	227	0.78 (0.53, 1.15)
Poor tumour differentiation	244	0.83 (0.58, 1.17)
No poor tumour differentiation	341	0.94 (0.69, 1.28)
Received TACE	67	1.20 (0.62, 2.31)
Did not receive TACE	518	0.86 (0.67, 1.10)
Within up-to-7 criteria	302	1.01 (0.70, 1.46)
Outside up-to-7 criteria	283	0.84 (0.62, 1.13)

0.3 ← 1 → 3

Atezo + bev better | Active surveillance better

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo.
[a] Patients who underwent ablation were categorized as NA.

Yopp et al. IMbrave050 update https://ter.li/q4cyl1

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Yopp et al, ESMO 2024

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IMBRAVE-050 (ESMO 2024 results updated)

Updated OS remained immature but showed numerical improvement from the first IA

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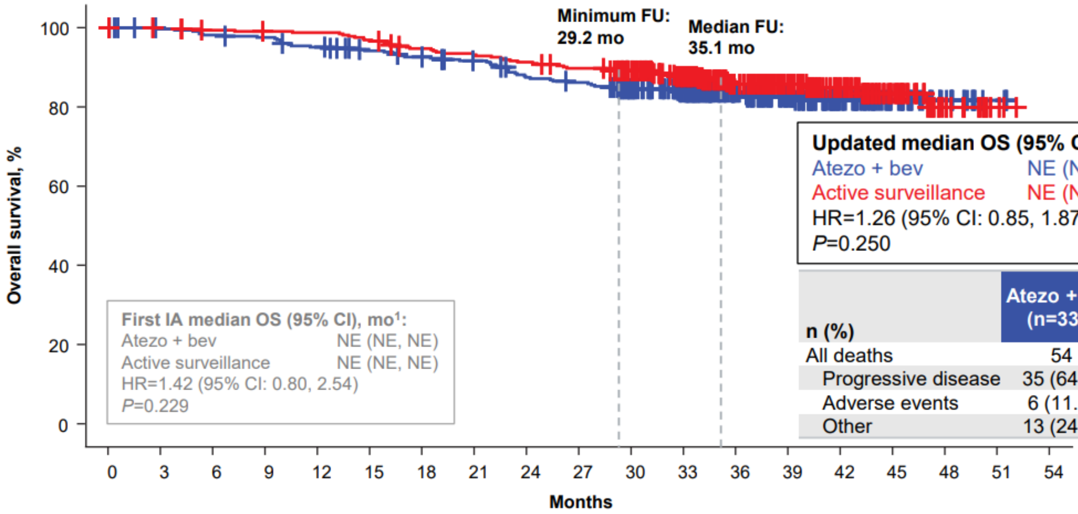

n (%)	Atezo + bev (n=334)	Active surveillance (n=334)
All deaths	54	46
Progressive disease	35 (64.8)	35 (76.1)
Adverse events	6 (11.1)	2 (4.3)
Other	13 (24.1)	9 (19.6)

No. at risk																			
Atezo + bev	334	327	322	319	310	301	294	286	271	266	243	206	142	101	60	34	16	3	NE
Active surveillance	334	327	323	321	320	314	304	299	293	286	266	226	157	108	71	38	15	3	NE

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. HRs are stratified. *P* values are log rank.
1. Qin et al. Lancet 2023.

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

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Yopp et al, ESMO 2024

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IMBRAVE-050 (ESMO 2024 results updated)

Conclusions

- IMbrave050 was the first Phase 3 study to demonstrate that an adjuvant immunotherapy-based regimen could delay recurrence following curative intent resection or ablation at the prespecified IA[1]
- In this updated analysis, initial RFS benefit with atezolizumab + bevacizumab vs active surveillance was not sustained over time (HR, 0.90; 95% CI: 0.72, 1.12)
  - Post hoc analyses showed a pronounced delaying of recurrence with atezolizumab plus bevacizumab within the first 12 months after resection with curative intent in some patients
- OS continued to be immature at the updated IA, with >80% of patients alive in both arms after 2 years
  - Updated OS HR was >1 (HR, 1.26; 95% CI: 0.85, 1.87), that showed numerical improvement with atezolizumab + bevacizumab vs active surveillance between the first and second IA[1]
- The safety profile of adjuvant atezolizumab + bevacizumab remained manageable and consistent with that of each agent and with the underlying HCC; no new safety concerns were observed
- The benefit-risk profile based on this updated analysis does not support atezolizumab + bevacizumab as an adjuvant therapy for all patients with high-risk HCC; efficacy follow-up for OS will continue
- These results will inform ongoing and future approaches to improve outcomes for patients with early HCC

1. Qin et al. Lancet 2023.

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

Yopp et al, ESMO 2024

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BCLC 2022 Updated Guidelines

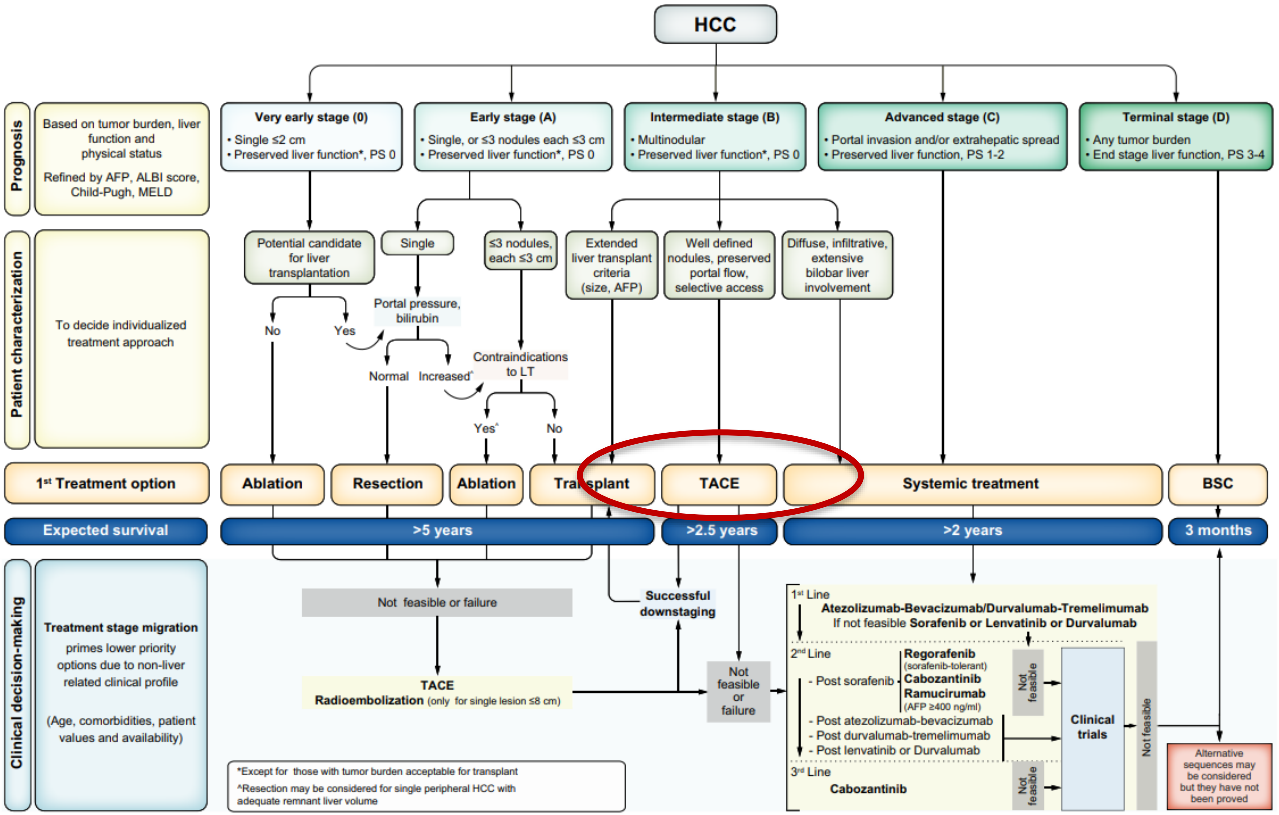

Fig. 1. BCLC staging and treatment strategy in 2022. The BCLC system establishes a prognosis in accordance with the 5 stages that are linked to first-line treatment recommendation. The expected outcome expressed as median survival of each tumour stage according to the available scientific evidence. Individualised clinical decision-making, according to the available data on November 15, 2021, is defined

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EMERALD-1 study design

EMERALD-1 was a global, double-blind, placebo-controlled Phase 3 study

Study population*
- Adults with confirmed HCC
- Not amenable to curative therapy, e.g. surgical resection, ablation, transplantation
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG PS 0 or 1
- Measurable disease per mRECIST
- Excludes Vp3 and Vp4
- No prior systemic therapy or TACE†

Stratification factors
- TACE modality (DEB-TACE vs cTACE)
- Geographical region (Japan vs Asia [excluding Japan] vs other)
- Portal vein invasion (Vp1 or Vp2+ / -Vp1 vs none)

R 1:1:1
N=616

Arm A: Durvalumab‡ (1500 mg Q4W) **+ TACE§** → **Durvalumab** (1120 mg Q3W) **+ placebo** for bevacizumab (Q3W)

Arm B: Durvalumab† (1500 mg Q4W) **+ TACE§** → **Durvalumab** (1120 mg Q3W) **+ bevacizumab** (15 mg/kg Q3W)

Arm C: Placebo for durvalumab (Q4W) **+ TACE§** → **Placebo** for durvalumab (Q3W) **+ placebo** for bevacizumab (Q3W)

Primary endpoint:
- PFS‖ for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary endpoints:
- PFS for Arm A vs Arm C
- OS
- QoL

Other secondary endpoints:
- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomization. †Prior use of TACE or TAE is acceptable if it was used as part of therapy with curative intent, but not if it was used as the sole modality in curative therapy. ‡Durvalumab / placebo started ≥7 days after TACE. §DEB-TACE or cTACE. Participants will receive up to 4 TACE procedures within the 16 weeks following Day 1 of their first TACE procedure. ‖Only new lesions consistent with progression that were not eligible for TACE occurring prior to the first on study imaging at 12 weeks were considered progression events; standard mRECIST progression criteria were used after the 12-week imaging.
BICR, blinded independent central review; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead-transarterial chemoembolization; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W / Q4W, every 3 / 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TAE, transarterial embolization; TTP, time to progression.

EMERALD-1

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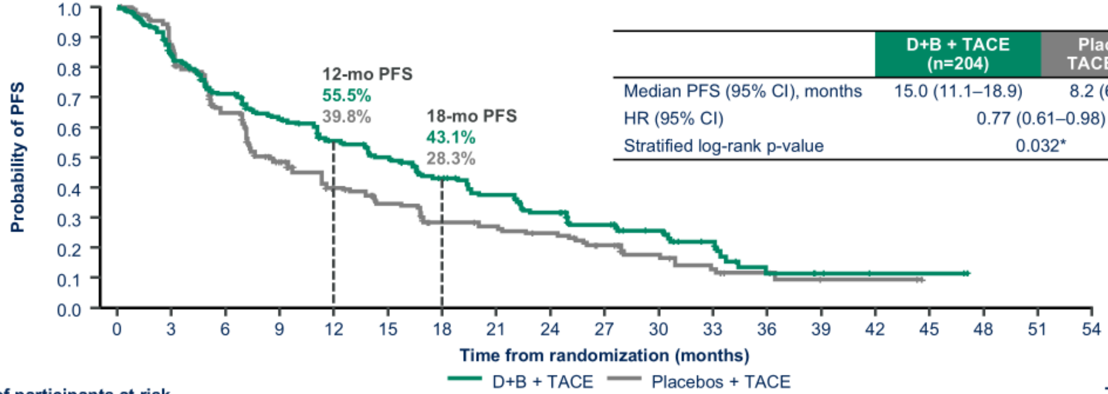
PFS with D+B + TACE versus placebos + TACE: primary endpoint

Median PFS was improved by 6.8 months with D+B + TACE versus placebos + TACE



	D+B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	

No. of participants at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	Total events
D+B + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0	136
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	149

Median (range) duration of follow-up in censored participants, D+B + TACE 16.7 (0.03–47.1) months, Placebos + TACE 10.3 (0.03–44.3) months. **Median (95% CI) duration of follow-up** in all participants using the reverse Kaplan-Meier method, D+B + TACE 22.2 (16.7–27.3) months, Placebos + TACE 26.3 (16.7–30.4) months. PFS was assessed by BICR (RECIST v1.1)

*The threshold of significance for this analysis was 0.0435 based on the α spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.

B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; HR, hazard ratio; mo, months, PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.

Lencioni et al, ASCO-GI 2024

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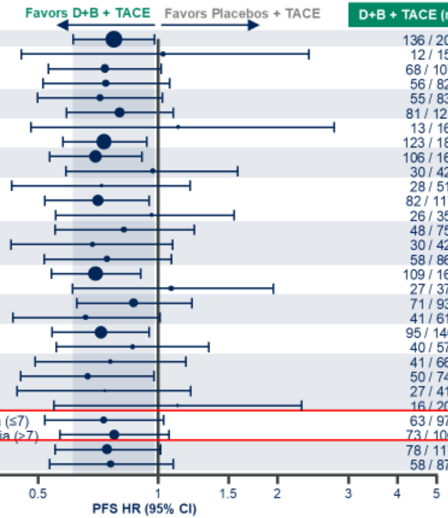
PFS with D+B + TACE versus placebos + TACE in key subgroups

PFS benefit with D+B + TACE was generally consistent across subgroups



		D+B + TACE (n=204), n / N (%)	Placebos + TACE (n=205), n / N (%)	HR (95% CI)
All participants:		136 / 204 (66.7%)	149 / 205 (72.7%)	0.77 (0.61–0.98)
Geographical region	Japan	12 / 15 (80.0%)	11 / 15 (73.3%)	1.03 (0.45–2.39)
	Asia non-Japan	68 / 107 (63.6%)	77 / 107 (72.0%)	0.74 (0.53–1.02)
	Other	56 / 82 (68.3%)	61 / 83 (73.5%)	0.74 (0.51–1.07)
TACE technique	DEB-TACE	55 / 83 (66.3%)	67 / 85 (78.8%)	0.71 (0.50–1.02)
	cTACE	81 / 121 (66.9%)	82 / 120 (68.3%)	0.80 (0.59–1.09)
Portal vein invasion	Vp1 or Vp2+ / -Vp1	13 / 16 (81.3%)	10 / 13 (76.9%)	1.12 (0.48–2.76)
	None	123 / 188 (65.4%)	139 / 192 (72.4%)	0.73 (0.57–0.93)
Sex	Male	106 / 162 (65.4%)	116 / 163 (71.2%)	0.70 (0.53–0.91)
	Female	30 / 42 (71.4%)	33 / 42 (78.6%)	0.96 (0.58–1.58)
BCLC stage	A	28 / 51 (54.9%)	31 / 49 (63.3%)	0.72 (0.43–1.21)
	B	82 / 117 (70.1%)	91 / 122 (74.6%)	0.71 (0.52–0.95)
	C	26 / 35 (74.3%)	25 / 31 (80.6%)	0.96 (0.55–1.68)
Etiology of liver disease*	HBV	48 / 75 (64.0%)	48 / 74 (64.9%)	0.82 (0.55–1.23)
	HCV	30 / 42 (71.4%)	44 / 54 (81.5%)	0.68 (0.43–1.09)
	Non-viral	58 / 86 (67.4%)	57 / 76 (75.0%)	0.74 (0.51–1.08)
Screening ECOG PS	0	109 / 167 (65.3%)	128 / 175 (73.1%)	0.70 (0.54–0.90)
	1	27 / 37 (73.0%)	21 / 30 (70.0%)	1.08 (0.61–1.94)
Baseline PD-L1†	<1%	71 / 93 (76.3%)	67 / 88 (76.1%)	0.87 (0.62–1.21)
	≥1%	41 / 61 (67.2%)	47 / 64 (73.4%)	0.66 (0.43–1.01)
AFP	≤400 ng/mL	95 / 146 (65.1%)	107 / 150 (71.3%)	0.72 (0.54–0.94)
	>400 ng/mL	40 / 57 (70.2%)	42 / 55 (76.4%)	0.86 (0.56–1.33)
HAP score	A	41 / 66 (62.1%)	41 / 64 (64.1%)	0.76 (0.49–1.17)
	B	50 / 74 (67.6%)	56 / 75 (74.7%)	0.66 (0.45–0.98)
	C	27 / 41 (65.9%)	37 / 48 (77.1%)	0.73 (0.44–1.21)
	D	16 / 20 (80.0%)	15 / 18 (83.3%)	1.12 (0.55–2.29)
Tumor burden at baseline	Within up-to 7 criteria (≤7)	63 / 97 (64.9%)	68 / 102 (66.7%)	0.73 (0.52–1.03)
	Beyond up-to-7 criteria (>7)	73 / 106 (68.9%)	81 / 103 (78.6%)	0.78 (0.56–1.07)
ALBI at baseline	Grade 1	78 / 117 (66.7%)	87 / 126 (69.0%)	0.74 (0.55–1.01)
	Grade ≥2	58 / 87 (66.7%)	62 / 79 (78.5%)	0.76 (0.53–1.09)

Size of circles are proportional to the number of events.
*One participant in each arm had both HBV and HCV. Neither of these participants experienced a PFS event. †Baseline PD-L1 TAP expression.
AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; B, bevacizumab; BCLC, Barcelona Clinical Liver Cancer; CI, confidence interval; cTACE, conventional transarterial chemoembolization; D, durvalumab; DEB-TACE, drug-eluting bead-transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; HAP, hepatoma arterial-embolization prognostic; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PS, performance status; TACE, transarterial chemoembolization; TAP, tumor area positivity.

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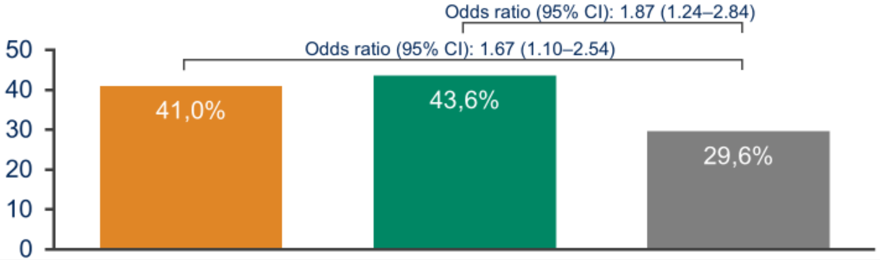
ORR using BICR per RECIST v1.1

ORR was improved with both D + TACE and D+B + TACE versus placebos + TACE



	D + TACE (n=207)	D+B + TACE (n=204)	Placebos + TACE (n=205)
Participants with measurable disease at baseline	205	202	203
Confirmed response,* n (%)	84 (41.0)	88 (43.6)	60 (29.6)
Complete response, n (%)	3 (1.5)	6 (3.0)	5 (2.5)
Partial response, n (%)	81 (39.5)	82 (40.6)	55 (27.1)
Stable disease ≥20 weeks, n (%)	42 (20.5)	45 (22.3)	63 (31.0)
Median duration of response, (LQ–UQ) months	14.0 (6.9–30.7)	22.1 (11.2–30.3)	16.4 (6.3–26.3)

*Responses included confirmed complete or partial response.
B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; LQ, lower quartile; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; UQ, upper quartile.

Lencioni et al, ASCO-GI 2024

Safety: summary

AEs were consistent with the known safety profiles of durvalumab, bevacizumab, and TACE

	D + TACE (n=232)*	D+B + TACE (n=154)*	Placebos + TACE (n=200)*
Any AE, n (%)	**215 (92.7)**	**151 (98.1)**	**186 (93.0)**
Possibly related to study treatment	117 (50.4)	124 (80.5)	90 (45.0)
Possibly provoked by TACE	101 (43.5)	78 (50.6)	95 (47.5)
SAEs (including AEs with outcome of death), n (%)	**84 (36.2)**	**74 (48.1)**	**62 (31.0)**
Possibly related to any treatment	13 (5.6)	30 (19.5)	10 (5.0)
Any AE of max CTCAE Grade 3 or 4, n (%)	**64 (27.6)**	**70 (45.5)**	**46 (23.0)**
Any AE possibly related to study treatment of max CTCAE Grade 3 or 4 , n (%)	**15 (6.5)**	**41 (26.6)**	**12 (6.0)**
Any AE possibly provoked by TACE of max CTCAE Grade 3 or 4, n (%)	**21 (9.1)**	**13 (8.4)**	**17 (8.5)**
Any AE with outcome of death, n (%)	**21 (9.1)**	**16 (10.4)**	**11 (5.5)**
Possibly related to study treatment	3 (1.3)	0	3 (1.5)
Possibly related to durvalumab / placebo	2 (0.9)	0	1 (0.5)
Possibly related to bevacizumab / placebo	1 (0.4)	0	2 (1.0)
AE leading to discontinuation, n (%)	**28 (12.1)**	**38 (24.7)**	**14 (7.0)**
Possibly related to study treatment	8 (3.4)	13 (8.4)	6 (3.0)
Possibly related to durvalumab / placebo	6 (2.6)	7 (4.5)	3 (1.5)
Possibly related to bevacizumab / placebo	3 (1.3)	9 (5.8)	4 (2.0)
Possibly provoked by TACE	2 (0.9)	0	2 (1)

*Safety analysis set: all randomized patients who received any amount of study treatment (i.e. durvalumab, bevacizumab, or placebo) regardless of arm randomized to.
AE, adverse event; B, bevacizumab; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab; NA, not applicable; SAE, serious adverse event; TACE, transarterial chemoembolization.

LEAP-012 Study Design (NCT04246177)

Key Eligibility Criteria

- Confirmed HCC not amenable to curative treatment
- ≥1 measurable HCC lesion per RECIST v1.1
- All lesions treatable with TACE in 1 or 2 sessions
- No portal vein thrombosis or extrahepatic disease
- Child-Pugh liver class A
- ECOG PS of 0 or 1

R
1:1

Lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) PO QD
+
Pembrolizumab 400 mg IV Q6W (up to 2 years)
+
TACE[b]

Placebo PO QD +
Placebo IV Q6W (up to 2 years)
+
TACE[b]

Stratification Factors

- Study site
- Alpha fetoprotein (≤400 ng/mL vs >400 ng/mL)
- ECOG PS (0 vs 1)
- ALBI grade (1 vs 2 or 3)
- Tumor burden score[1,a] (≤6 vs >6 but ≤12 vs >12)

End Points

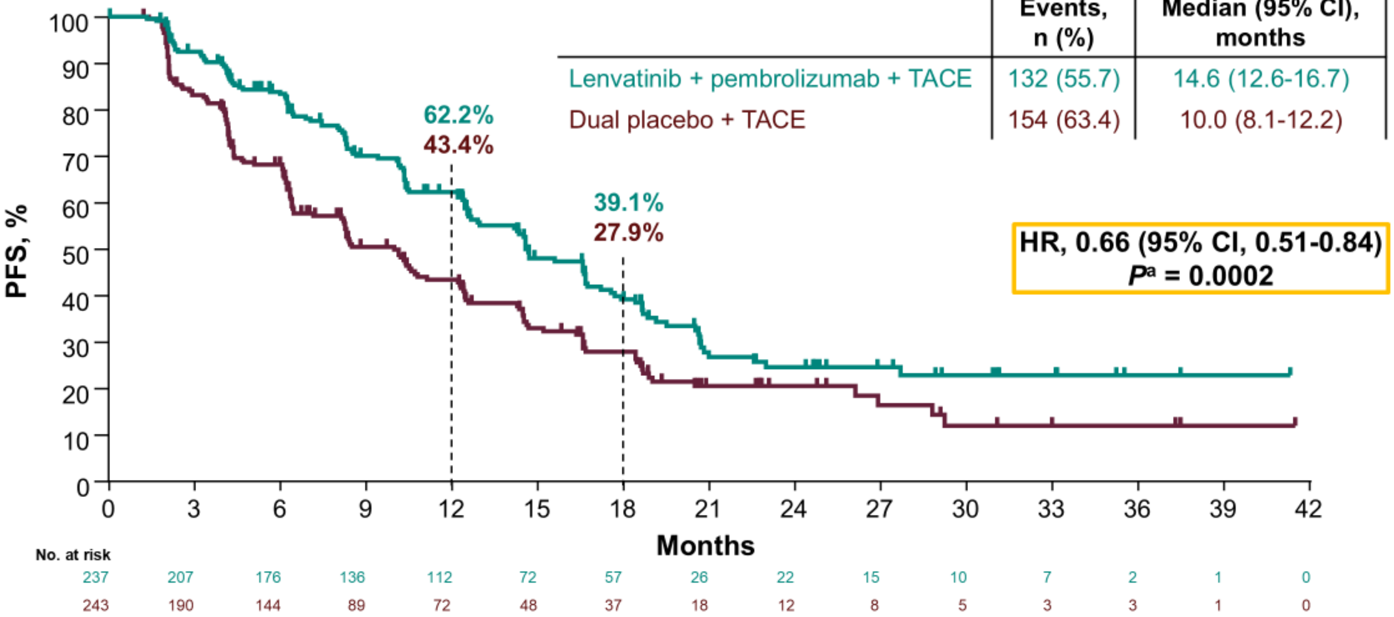
- Primary: PFS[c] and OS
  - IA1 is the final analysis for PFS
  - Initial alpha of 0.025 (1-sided) allocated to PFS; passed to OS if PFS is statistically significant
- Secondary: ORR,[c,d] DOR,[c,d] DCR,[c,d] TTP,[c,d] PFS,[d] and safety

1. Wang Q et al. *J Hepatol.* 2019;70:893-903.

[a]Largest tumor in centimeters + number of tumors. [b]2-4 weeks after the start of systemic therapy with a maximum of 2 treatments per tumor (4 total) and no more than 1 treatment per month.
[c]Per RECIST v1.1 by BICR. [d]Per mRECIST by BICR.

Progression-Free Survival per RECIST v1.1 by BICR

	Events, n (%)	Median (95% CI), months
Lenvatinib + pembrolizumab + TACE	132 (55.7)	14.6 (12.6-16.7)
Dual placebo + TACE	154 (63.4)	10.0 (8.1-12.2)

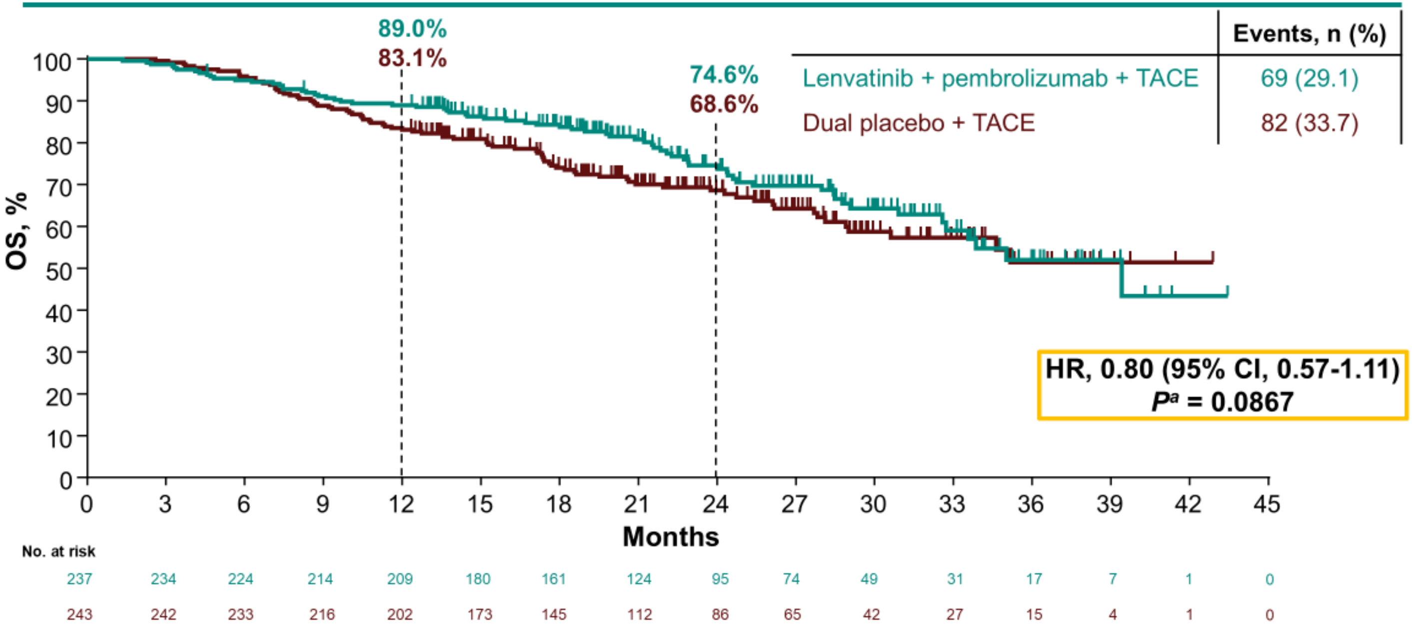


[a]One-sided P from re-randomization test; threshold P = 0.025. Data cutoff date for IA1: January 30, 2024.

Llovet et al, ESMO 2024

LEAP-012

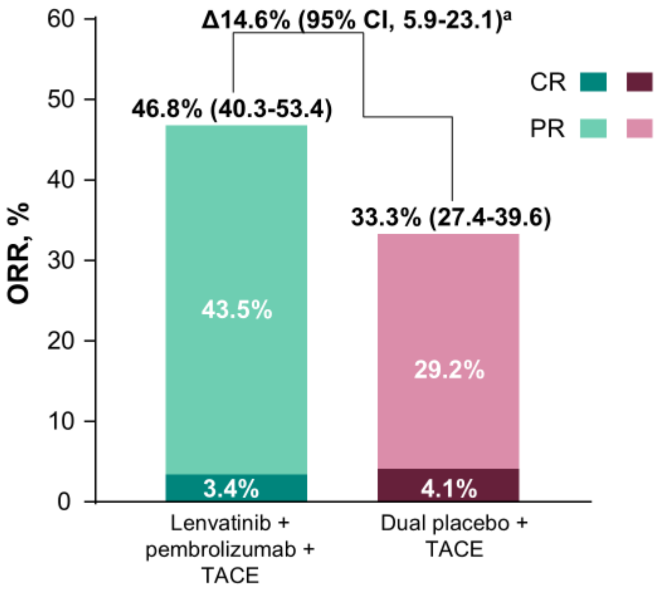
Overall Survival



[a]One-sided *P* from re-randomization test; threshold *P* = 0.025. Data cutoff date for IA1: January 30, 2024.

Llovet et al, ESMO 2024

Objective Response Rate per RECIST v1.1 by BICR

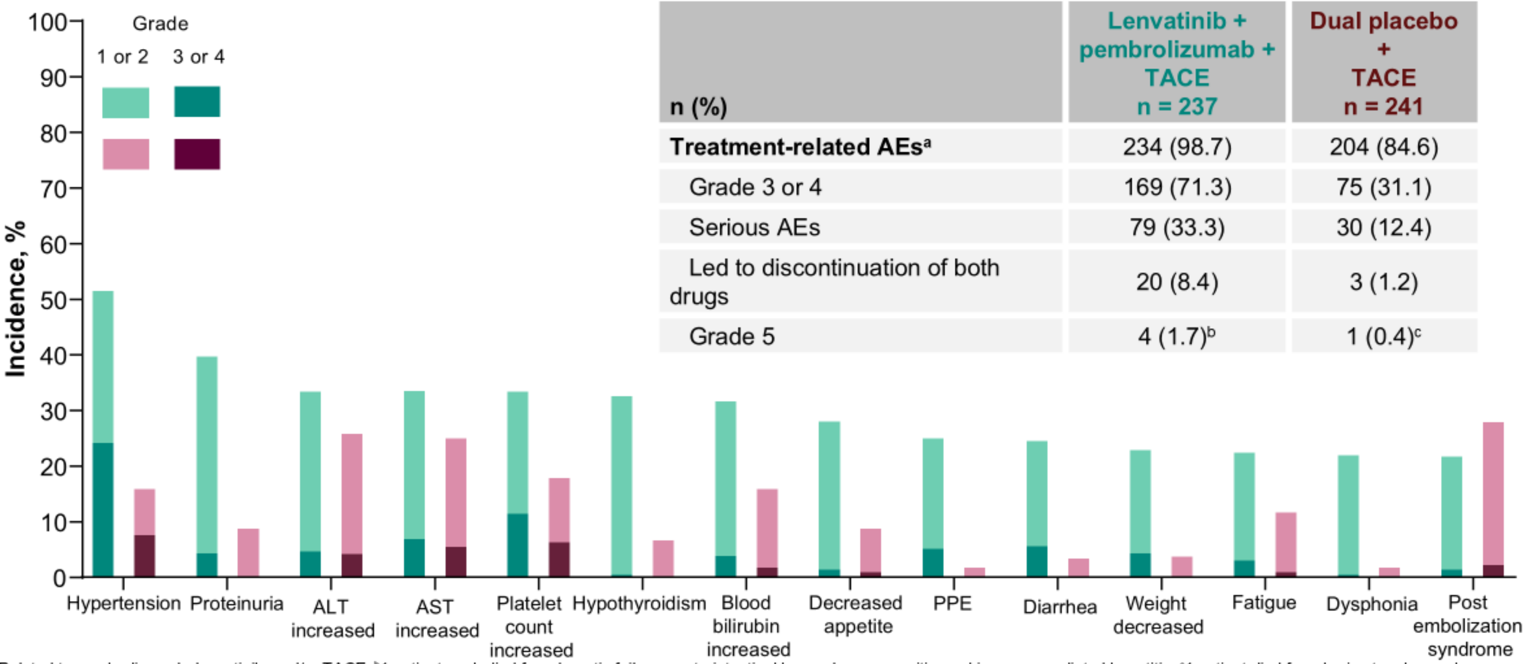


	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 243
Best overall response, % (95% CI)[b,c]		
Complete response	3.4 (1.5-6.5)	4.1 (2.0-7.4)
Partial response	43.5 (37.1-50.0)	29.2 (23.6-35.4)
Stable disease	42.6 (36.2-49.2)	48.1 (41.7-54.6)
Progressive disease	6.8 (3.9-10.7)	14.8 (10.6-19.9)
Duration of response, median (range), months	12.6 (1.3+ to 39.1+)	10.7 (2.0+ to 39.5+)
Disease control rate	89.5 (84.8-93.1)	81.5 (76.0-86.2)

[a]Estimated from stratified analysis. [b]Patients with insufficient data for assessment of response: 2.1% in the lenvatinib + pembrolizumab + TACE group and 1.6% in the dual placebo + TACE group. [c]Patients without postbaseline assessments: 1.7% in the lenvatinib + pembrolizumab + TACE group and 2.1% in the dual placebo + TACE group. Data cutoff date for IA1: January 30, 2024.

Llovet et al, ESMO 2024

Most Common Treatment-Related Adverse Events[a] (≥25%)



n (%)	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 241
Treatment-related AEs[a]	234 (98.7)	204 (84.6)
Grade 3 or 4	169 (71.3)	75 (31.1)
Serious AEs	79 (33.3)	30 (12.4)
Led to discontinuation of both drugs	20 (8.4)	3 (1.2)
Grade 5	4 (1.7)[b]	1 (0.4)[c]

[a]Related to pembrolizumab, lenvatinib, and/or TACE. [b]1 patient each died from hepatic failure, gastrointestinal hemorrhage, myositis, and immune-mediated hepatitis. [c]1 patient died from brain stem hemorrhage. Data cutoff date for IA1: January 30, 2024.

Llovet et al, ESMO 2024

LEAP-012 vs EMERALD-1

LEAP-012 vs EMERALD-1

Observations with CURRENT data

*BASELINE CHARACTERISTICS: more VHB, BCLC-A, ALBI1 in LEAP-012

	Lenvatinib + pembrolizumab + TACE n = 237		Lenvatinib + pembrolizumab + TACE n = 237
Age, median (range), yrs	65.0 (31-87)	Child-Pugh score A5	204 (86.1)
Age, ≥65 yrs	128 (54.0)	BCLC stage[d]	
Sex, male	192 (81.0)	A	80 (33.8)
Geographic region, Asia (without Japan)	135 (57.0)	B	135 (57.0)
ECOG PS 0	216 (91.1)	C	21 (8.9)
HBV status – positive[a]	153 (64.6)	ALBI grade 1[e]	171 (72.2)
HCV status – positive[b]	42 (17.7)	Tumor burden score[1,f]	
Viral etiology[c]	179 (75.5)	≤6	112 (47.3)
Alcohol etiology	107 (45.1)	>6 and ≤12	120 (50.6)
AFP ≤400 ng/mL	200 (84.4)	>12	5 (2.1)

		D+B + TACE (n=204)*
Age (years)	Median	64.5
Sex, n (%)	Male	162 (79.4)
Geographical region, n (%)	Japan	15 (7.4)
	Asia (non-Japan)	107 (52.4)
	Others	82 (40.1)
TACE modality, n (%)	DEB-TACE	84 (41.2)
	cTACE	119 (58.3)
Etiology of liver disease, n (%)	HBV	75 (36.8)
	HCV	42 (20.6)
	Non-viral	86 (42.2)
BCLC stage, n (%)	A	51 (25.0)
	B	117 (57.4)
	C	35 (17.2)
Portal vein invasion, n (%)	No	188 (92.2)
	Yes	16 (7.8)
Screening ECOG PS, n (%)	0	167 (81.9)
	1	37 (18.1)
Baseline PD-L1[†], n (%)	High (≥1%)	61 (29.9)
	Low (<1%)	93 (45.6)
	Unknown	50 (24.5)
Child-Pugh score, n (%)	A	200 (98.0)
	B	4 (2.0)
ALBI at baseline, n (%)	Grade 1	117 (57.4)
	Grade ≥2	87 (42.6)
Tumor burden at baseline, n (%)	Within up-to 7 criteria (≤7)	97 (47.5)
	Beyond up-to-7 criteria (>7)	106 (52.0)
HAP score, n (%)	A	66 (32.4)
	B	74 (36.3)
	C	41 (20.1)
	D	20 (9.8)
	Missing	3 (1.5)

Lenvioni et al ASCO GI 2024; Llovet et al ESMO 2024

LEAP-012 vs EMERALD-1

Observations with CURRENT data

*Both have PFS benefit

- HR 0.66 (LEAP-012) vs 0.77 (EMERALD-1)
- ▲ Median PFS (months): 4.6 (LEAP-012) vs 6.8 (EMERALD-1)

*Curves separate earlier in LEAP-012

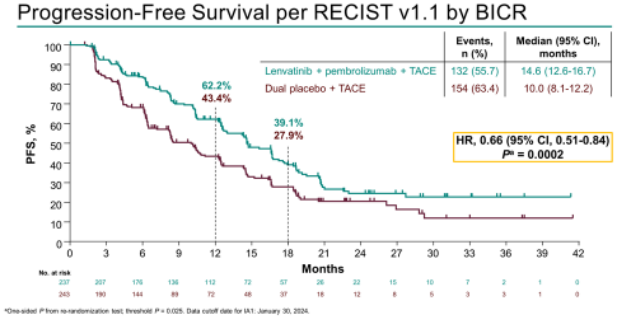
*ORR benefit in LEAP-012 and EMERALD-1

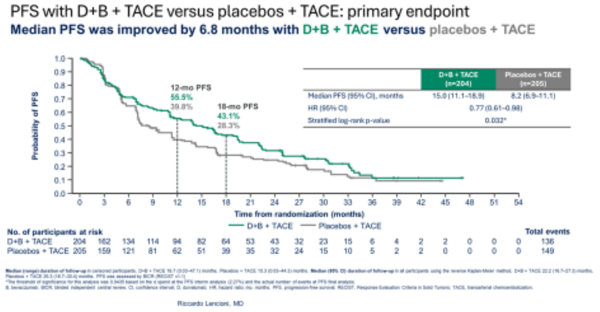
*EMERALD-1 showed discrepancies between PFS and TTP (no TTP data in LEAP-012)

*Toxicity does not seem to be an issue - higher rate of discontinuation due to AEs (both 8.4% (LEAP-012) vs any/both 24.7% (EMERALD-1))

*Impact on OS?

- Promising (LEAP-012) vs Not available yet (EMERALD-1)





Lenvioni et al ASCO GI 2024; Llovet et al ESMO 2024

BARCELONA 2024 ESMO congress

Dr Angela Lamarca (@DrAngelaLamarca)
Invited Discussant LBA3

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Lamarca, LBA3 invited discussant, personal opinion

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1. Early-disease
2. Intermediate stage
3. **Advanced disease**

BCLC 2022 Updated Guidelines

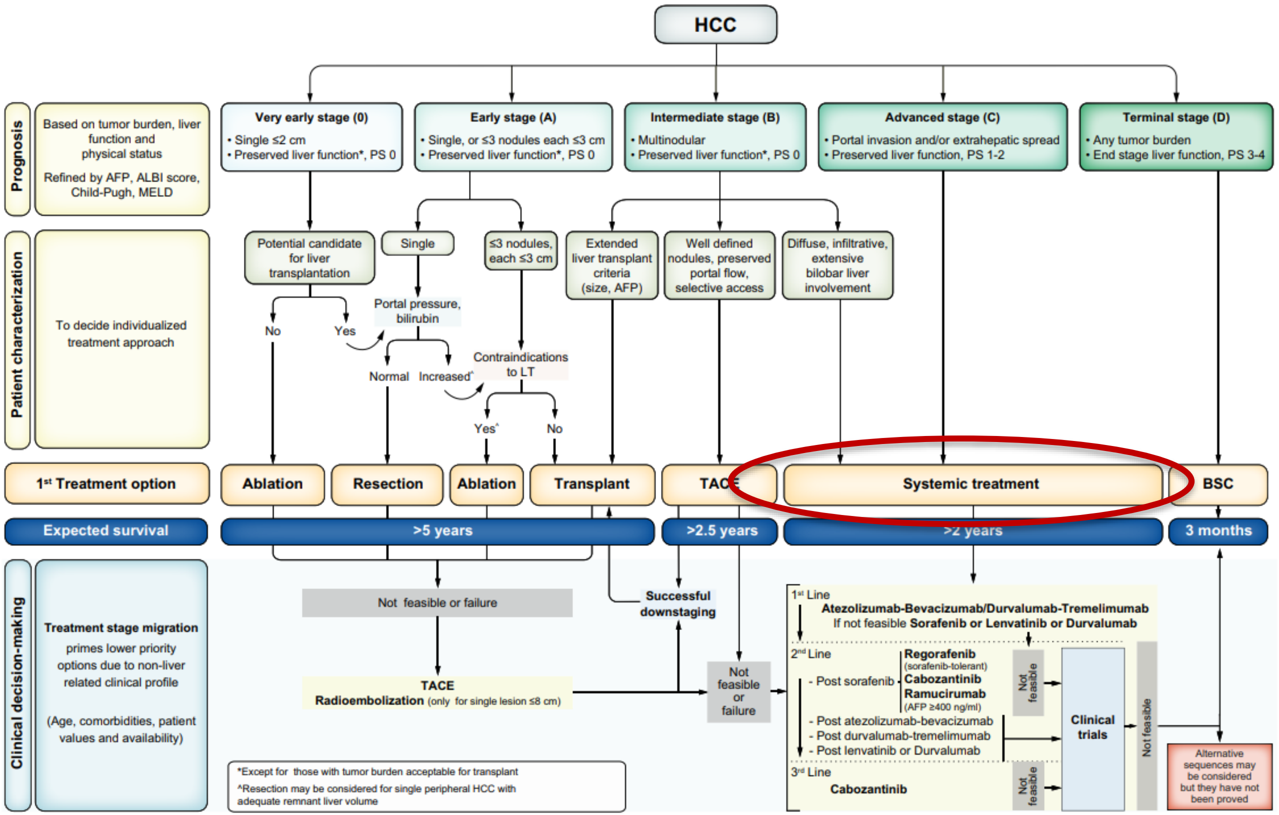
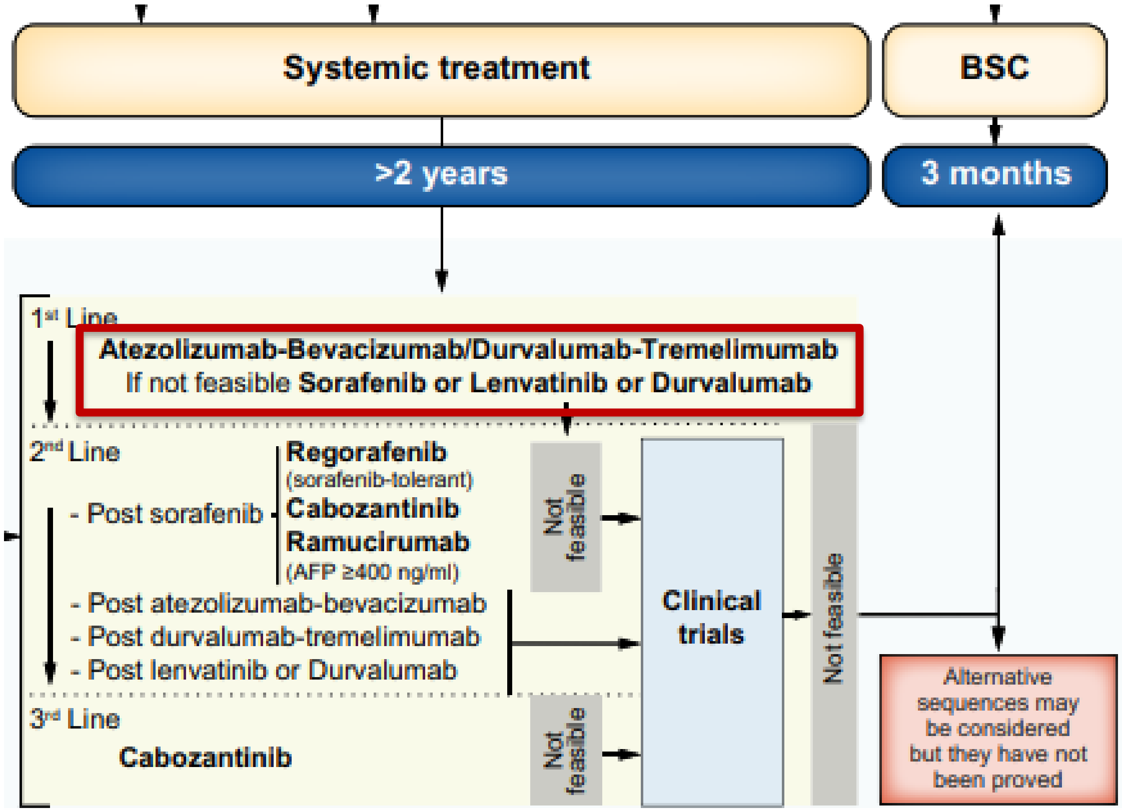


Fig. 1. BCLC staging and treatment strategy in 2022. The BCLC system establishes a prognosis in accordance with the 5 stages that are linked to first-line treatment recommendation. The expected outcome expressed as median survival of each tumour stage according to the available scientific evidence. Individualised clinical decision-making, according to the available data on November 15, 2021, is defined

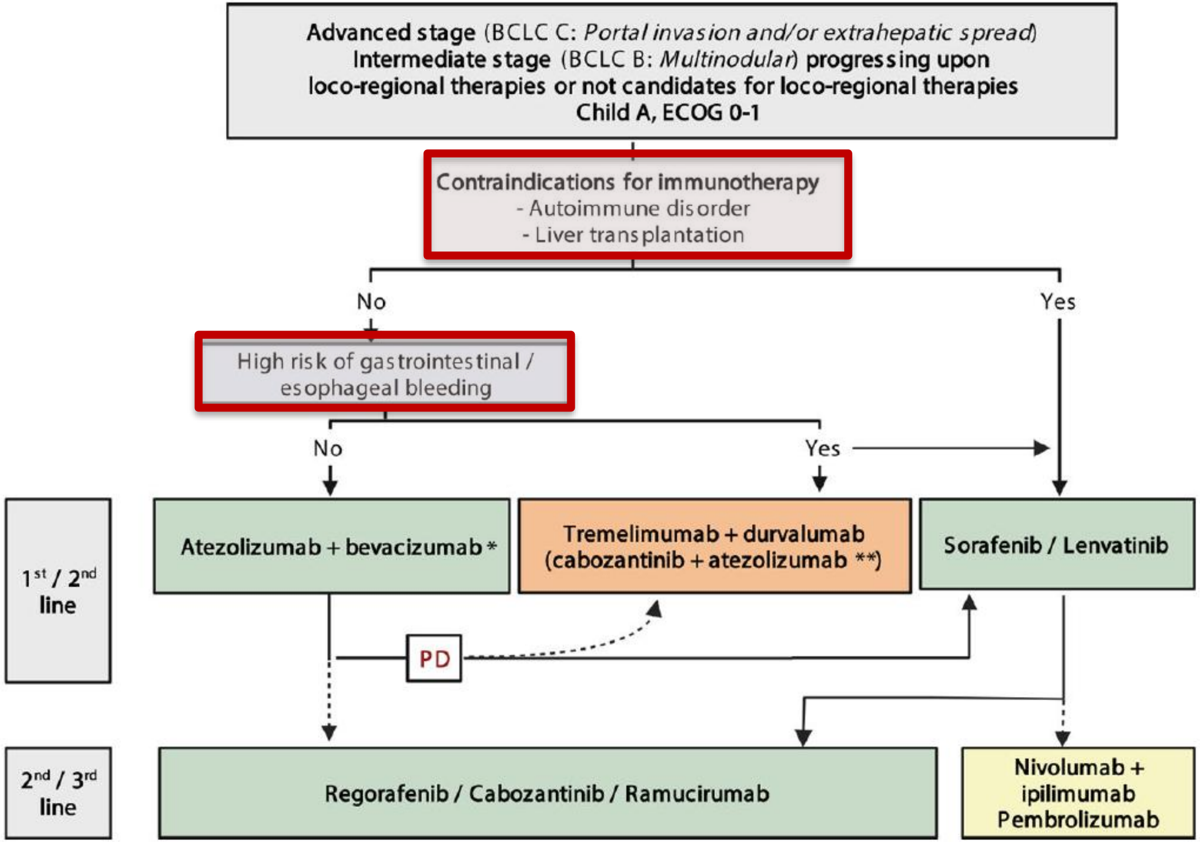
Reig J of Hepatol 2022

BCLC 2022 Updated Guidelines



Reig J of Hepatol 2022

Real Life Clinical Practice



Lovet et al, Nat Cancer. 2022

CHECKMATE-9DW: IpiNivo vs Sorafenib/Lenvatinib

CheckMate 9DW study design

- CheckMate 9DW is a global, phase 3, randomized, open-label study of NIVO in combination with IPI compared with LEN or SOR as 1L treatment in patients with unresectable HCC[a]

Key eligibility criteria
- Unresectable HCC[b]
- At least 1 measurable lesion (RECIST v1.1)
- Systemic therapy naive
- Child-Pugh score 5 or 6
- ECOG PS 0 or 1
- No main portal vein invasion (Vp4)

N = 668

R 1:1

n = 335: NIVO 1 mg/kg IV + IPI 3 mg/kg IV Q3W (up to 4 cycles) then NIVO 480 mg Q4W[d]

n = 333: Investigator's choice of LEN 8 mg[e] or 12 mg[f] PO QD or SOR 400 mg PO BID

Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO + IPI arm only)

Among 325 patients treated with LEN/SOR: 275 (85%) received LEN and 50 (15%) received SOR

Primary endpoint:
- OS

Secondary endpoints:
- ORR and DOR by BICR per RECIST v1.1
- Time to symptom deterioration[g]

Key exploratory endpoints:
- PFS by BICR per RECIST v1.1
- Safety

Stratification factors:
- Etiology (HBV vs HCV vs uninfected)[c]
- MVI/EHS (present vs absent)
- AFP (< 400 vs ≥ 400 ng/mL)

- At data cutoff (January 31, 2024), median (range) follow-up[h] was 35.2 (26.8-48.9) months

[a]ClinicalTrials.gov: NCT04039607. [b]Disease not eligible for, or progressive disease after, curative surgical and/or locoregional therapies. [c]Based on central lab serology results for stratification purpose of NIVO + IPI is required before proceeding to NIVO monotherapy. [e]If body weight < 60 kg. [f]If body weight ≥ 60 kg. [g]HCS subscale score of the FACT-Hep. [h]Time between randomization date and cutoff

Baseline characteristics

All randomized	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Median age (range), years	65 (20-86)	66 (20-89)
≥ 65 years	173 (52)	184 (55)
Male, n (%)	271 (81)	277 (83)
Region, n (%)		
Asia	133 (40)	147 (44)
North America/Europe	144 (43)	145 (44)
Rest of the world	58 (17)	41 (12)
Etiology, n (%)[a,b]		
HBV	114 (34)	115 (35)
HCV	90 (27)	96 (29)
Uninfected	124 (37)	119 (36)
Child-Pugh score, n (%)[c]		
5	254 (76)	263 (79)
6	72 (21)	58 (17)
ECOG PS 1, n (%)[d]	102 (30)	89 (27)
BCLC stage, n (%)[e]		
≤ B	89 (27)	88 (26)
C	246 (73)	242 (73)
MVI/EHS, n (%)[b]		
MVI	77 (23)	92 (28)
EHS	188 (56)	172 (52)
MVI/EHS	221 (66)	217 (65)
AFP ≥ 400 ng/ml, n (%)	108 (32)	113 (34)
Prior locoregional therapy, n (%)	142 (42)	158 (47)

[a]7 patients in the NIVO + IPI arm and 3 patients in the LEN/SOR arm were reported as having both HBV and HCV as risk factors for HCC; these patients did not have active co-infection with HBV and HCV. [b]Per CRF.
[c]Score ≥ 7: NIVO + IPI, n = 9; LEN/SOR, n = 11. Not reported: LEN/SOR, n = 1. [d]Not reported: LEN/SOR, n = 1. [e]Unknown: LEN/SOR, n = 3.

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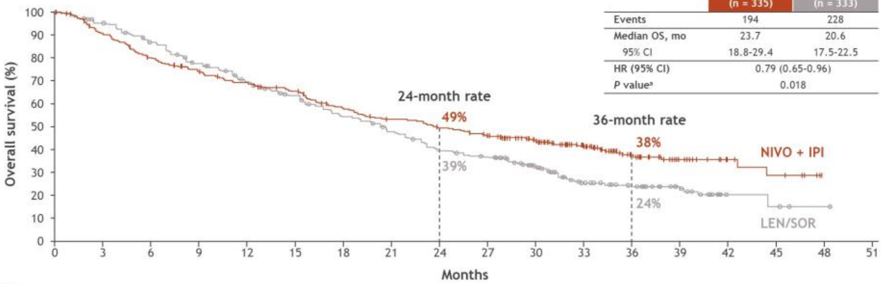
CHECKMATE-9DW: IpiNivo vs Sorafenib/Lenvatinib

Overall survival

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	194	228
Median OS, mo	23.7	20.6
95% CI	18.8-29.4	17.5-22.5
HR (95% CI)	0.79 (0.65-0.96)	
P value[a]	0.018	



No. at risk

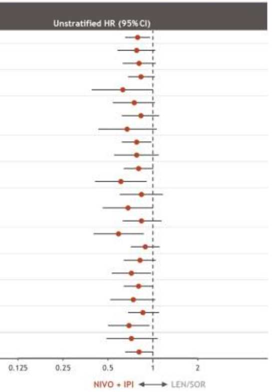
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
NIVO + IPI	335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
LEN/SOR	333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

- Statistically significant and clinically meaningful OS benefit with NIVO + IPI vs LEN/SOR
  - Longer median OS and long-term survival benefit with higher OS rates at 24 and 36 months

Median (range) follow-up, 35.2 (26.8-48.9) months. Median OS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a]Two-sided *P* value from stratified log-rank test. Boundary for statistical significance: *P* value ≤ 0.0257.

Overall survival subgroup analysis

Category	Subgroup	Median OS, mo NIVO + IPI	Median OS, mo LEN/SOR	Unstratified HR
Overall (N = 668)		23.7	20.6	0.79
Age, years	< 65 (n = 311)	26.8	22.7	0.78
	≥ 65 (n = 357)	18.8	18.2	0.81
Sex	Male (n = 548)	23.0	21.1	0.83
	Female (n = 120)	26.9	17.3	0.63
Region	Asia (n = 280)	34.0	22.5	0.75
	North America/Europe (n = 289)	22.9	19.8	0.83
	Rest of world (n = 99)	18.8	12.4	0.67
ECOG PS[a]	0 (n = 476)	27.9	22.5	0.78
	1 (n = 191)	16.4	15.3	0.78
Child-Pugh score[b]	5 (n = 517)	27.9	23.2	0.80
	6 (n = 130)	18.3	10.3	0.61
Etiology[c,d]	HBV (n = 229)	23.5	22.3	0.84
	HCV (n = 186)	33.0	17.8	0.68
	Uninfected (n = 243)	19.3	18.4	0.84
MVI[c]	Yes (n = 169)	22.9	15.4	0.59
	No (n = 499)	23.9	21.9	0.89
EHS[c]	Yes (n = 360)	18.7	16.6	0.82
	No (n = 308)	33.5	22.5	0.72
MVI/EHS[c]	Yes (n = 438)	19.4	17.7	0.80
	No (n = 230)	33.5	23.0	0.74
Baseline AFP, ng/ml	< 400 (n = 447)	25.9	23.8	0.86
	≥ 400 (n = 221)	16.4	12.1	0.69
BCLC at baseline[e]	≤ B (n = 177)	33.5	27.1	0.72
	C (n = 488)	20.3	17.8	0.81



Median (range) follow-up, 35.2 (26.8-48.9) months. HRs and 95% CIs from unstratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. HR is not computed for subset categories with 10 or less patients per treatment arm. [a]Not reported, n = 1. [b]Score ≥ 7, n = 20; not reported, n = 1. [c]Per CRF. [d]Reported as having both HBV and HCV as risk factors for HCC, n = 10; these patients did not have active co-infection with HBV and HCV. [e]Unknown, n = 3.

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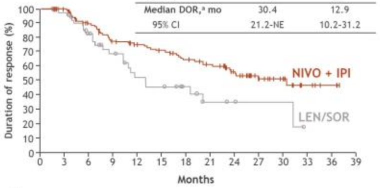
CHECKMATE-9DW: IpiNivo vs Sorafenib/Lenvatinib

Response and duration of response

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
ORR,[a] %	36	13
95% CI	31-42	10-17
P value[b]	< 0.0001	
Best overall response,[a] %		
Complete response	7	2
Partial response	29	11
Stable disease[c]	32	62
Progressive disease	20	14
Not evaluable	12	11
Median TTR (range),[a] mo	2.2 (1.1-11.6)	3.7 (0.6-11.2)

Duration of response

	NIVO + IPI (n = 121)[d]	LEN/SOR (n = 44)[d]
Events	48	22
Median DOR,[a] mo	30.4	12.9
95% CI	21.2-NE	10.2-31.2



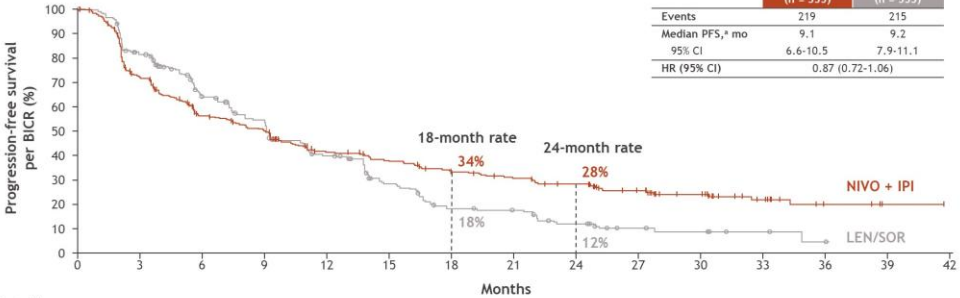
No. at risk														
NIVO + IPI	121	116	97	81	74	67	59	52	39	22	14	6	3	0
LEN/SOR	44	42	31	23	16	13	9	4	3	2	2	0	0	0

- Statistically significant and clinically meaningful improvement in ORR with NIVO + IPI vs LEN/SOR, with a higher complete response rate (7% vs 2%, respectively) and durable responses

Median (range) follow-up, 35.2 (26.8-48.9) months. Symbols represent censored observations. [a]Assessed by BICR based on RECIST v1.1. [b]Two sided *P* value from stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: *P* value ≤ 0.025. [c]Includes non-CR/non-PD: NIVO + IPI, n = 6 (2%); LEN/SOR, n = 7 (2%). Non-CR/non-PD refers to patients with persistence of one or more non-target lesion(s). [d]Number of confirmed responders.

Progression-free survival

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	219	215
Median PFS,[a] mo	9.1	9.2
95% CI	6.6-10.5	7.9-11.1
HR (95% CI)	0.87 (0.72-1.06)	



No. at risk															
NIVO + IPI	335	224	160	140	103	92	78	69	61	45	29	16	6	1	0
LEN/SOR	333	242	164	131	82	52	30	26	16	8	6	3	1	0	0

- Numerically higher PFS rates with NIVO + IPI vs LEN/SOR at 18 and 24 months

Median (range) follow-up, 35.2 (26.8-48.9) months. Median PFS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a]Assessed by BICR based on RECIST v1.1.

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CHECKMATE-9DW: IpiNivo vs Sorafenib/Lenvatinib

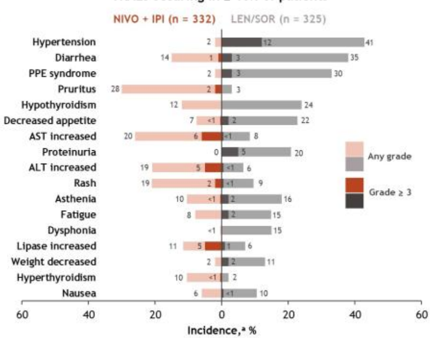
CheckMate 9DW

Treatment-related adverse events

All treated patients, n (%)	NIVO + IPI (n = 332)	LEN/SOR (n = 325)
Median (range) duration of treatment, mo	4.7 (< 1 to 24.4)	6.9 (< 1 to 45.8)

All treated patients, n (%)	NIVO + IPI (n = 332) Any grade	NIVO + IPI (n = 332) Grade 3/4	LEN/SOR (n = 325) Any grade	LEN/SOR (n = 325) Grade 3/4
TRAEs[a]				
Any TRAEs	278 (84)	137 (41)	297 (91)	138 (42)
Serious TRAEs	94 (28)	83 (25)	47 (14)	42 (13)
TRAEs leading to discontinuation	59 (18)	44 (13)	34 (10)	21 (6)
Treatment-related deaths[b]	12 (4)[c]		3 (< 1)[d]	

TRAEs occuring in ≥ 10% of patients



[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Treatment-related deaths were reported regardless of time frame. [c]TRAEs leading to death in the NIVO + IPI arm included immune-mediated hepatitis (n = 4), hepatic failure (n = 3), hepatic insufficiency (n = 1), decompensated cirrhosis (n = 1), diarrhea-colitis (n = 1), autoimmune hemolytic anemia (n = 1), and dysautonomia (n = 1). [d]TRAEs leading to death in the LEN/SOR arm included hepatorenal syndrome (n = 1), ischemic stroke (n = 1), and acute kidney injury (n = 1).

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CheckMate 9DW

Immune-mediated adverse events

All treated patients, n (%)	NIVO + IPI (n = 332) Any grade	Grade 3/4	Received high-dose steroids	Leading to discontinuation
Patients with IMAEs[a]	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
Diarrhea/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

- The majority of IMAEs were grade 1 or 2, were manageable, and did not result in treatment discontinuation

[a]IMAEs 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

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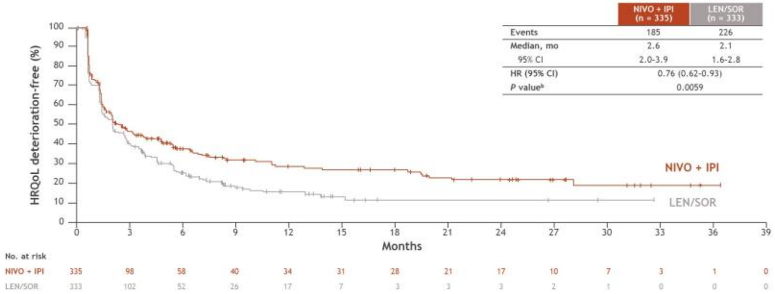
CheckMate 9DW

Time to first symptom deterioration of HCS[a] score



- NIVO + IPI resulted in a statistically significant reduced risk (24%) of symptom deterioration vs LEN/SOR

Median (range) follow-up, 35.2 (26.8-48.9) months. Symbols represent censored observations. Median time to first symptom deterioration is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. [a]HCS subscale score of the FACT-Hep. [b]Two-sided *P* value from stratified log-rank test. Boundary for statistical significance: *P* value ≤ 0.0197.

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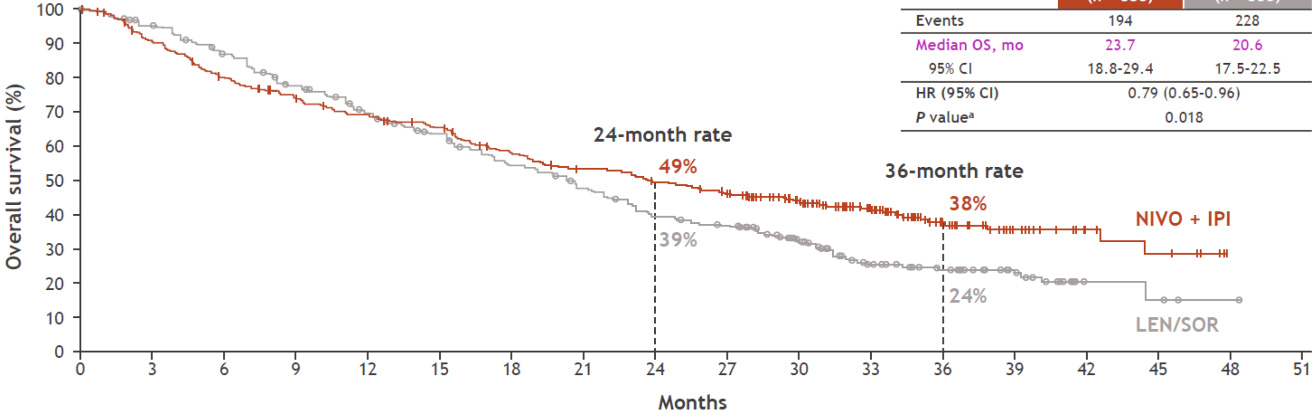
Galle et al, ASCO 2024

CheckMate 9DW 2024 ESMO Update

Overall survival

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	194	228
Median OS, mo	23.7	20.6
95% CI	18.8-29.4	17.5-22.5
HR (95% CI)	0.79 (0.65-0.96)	
P value[a]	0.018	



No. at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
NIVO + IPI	335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
LEN/SOR	333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

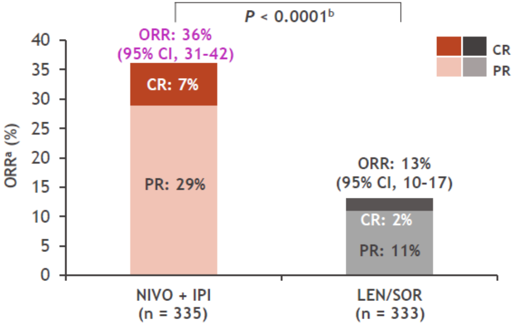
- Statistically significant and clinically meaningful OS benefit with NIVO + IPI vs LEN/SOR
  - Longer median OS and long-term survival benefit with higher OS rates at 24 and 36 months

Median OS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a]Two-sided *P* value from stratified log-rank test. Boundary for statistical significance: *P* value ≤ 0.0257.

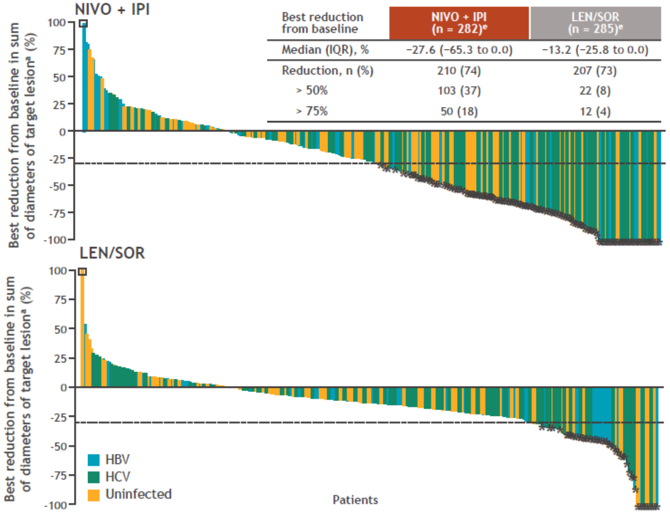
Decaens et al, ESMO 2024

CheckMate 9DW 2024 ESMO Update

Objective response



	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Best overall response,[a] %		
SD[c]	32	62
PD	20	14
Not evaluable	12	11
Median TTR (range),[a,d] mo	2.2 (1.1-11.6)	3.7 (0.6-11.2)
Median DOR (95% CI),[a,d] mo	30.4 (21.2-NE)	12.9 (10.2-31.2)



Best reduction from baseline	NIVO + IPI (n = 282)[e]	LEN/SOR (n = 285)[e]
Median (IQR), %	−27.6 (−65.3 to 0.0)	−13.2 (−25.8 to 0.0)
Reduction, n (%)	210 (74)	207 (73)
> 50%	103 (37)	22 (8)
> 75%	50 (18)	12 (4)

- Statistically significant and clinically meaningful improvement in ORR with NIVO + IPI vs LEN/SOR, with a higher complete response rate (7% vs 2%, respectively) and durable responses
- Responses with NIVO + IPI were observed regardless of etiology

[a]Assessed by BICR based on RECIST v1.1. [b]Two-sided *P* value from stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: *P* value ≤ 0.025. [c]Includes non-CR/non-PD: NIVO + IPI, n = 6 (2%); LEN/SOR, n = 7 (2%). Non-CR/non-PD refers to patients with persistence of 1 or more non-target lesion(s). [d]In confirmed responders (NIVO + IPI: n = 121; LEN/SOR: n = 44). [e]Response evaluable patients defined as those with a best overall response of CR, PR, SD, non-CR/non-PD, or PD; target lesion(s) assessed at baseline; and ≥ 1 on-study assessment of all baseline target lesion(s). Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1. Asterisk symbol, responders; square symbol, percent change truncated to 100%. Ten patients with HBV-HCV coinfections were categorized to HCV.

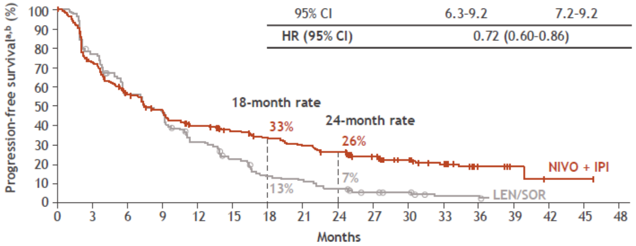
Decaens et al, ESMO 2024

CheckMate 9DW 2024 ESMO Update

PFS and PFS2 per investigator

Progression-free survival

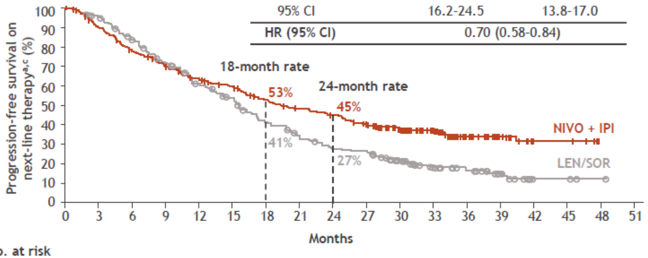
	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	242	281
Median PFS,[a,b] mo	7.5	7.5
95% CI	6.3-9.2	7.2-9.2
HR (95% CI)	0.72 (0.60-0.86)	



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
NIVO + IPI	335	236	173	143	114	101	89	78	69	53	35	23	9	3	1	1	0
LEN/SOR	333	243	170	140	88	62	34	28	18	11	8	3	2	0	0	0	0

Progression-free survival on next-line therapy (PFS2)

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	206	257
Median PFS2,[a,c] mo	19.3	15.4
95% CI	16.2-24.5	13.8-17.0
HR (95% CI)	0.70 (0.58-0.84)	



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
NIVO + IPI	335	298	256	228	205	189	163	148	136	120	90	61	33	18	6	6	0	0
LEN/SOR	333	310	269	229	190	162	124	101	80	76	50	32	25	13	3	3	1	0

- Numerically higher PFS[b] rates with NIVO + IPI vs LEN/SOR at 18 and 24 months
- PFS2[c] favored NIVO + IPI over LEN/SOR with a 30% reduction in the risk of death or disease progression on subsequent systemic therapy
- Subsequent systemic anticancer therapies were received by 38% vs 52% of patients in the NIVO + IPI vs LEN/SOR arm; subsequent immunotherapies were received by 13% vs 35% of patients, respectively

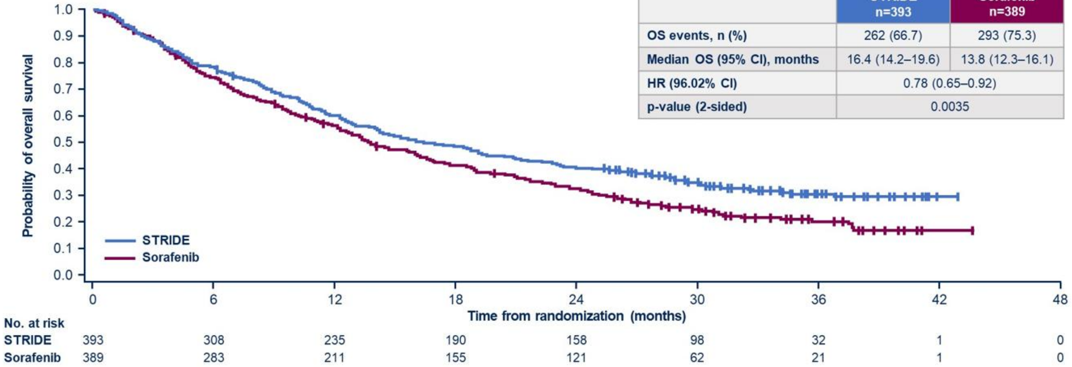
[a]Assessed by investigator based on RECIST v1.1. [b]Time from randomization to first documented radiological progression or death. [c]Time from randomization to documented progression (radiological or clinical) after next-line of therapy (i.e. subsequent systemic anticancer therapy) or death or to the start of second next-line systemic therapy.

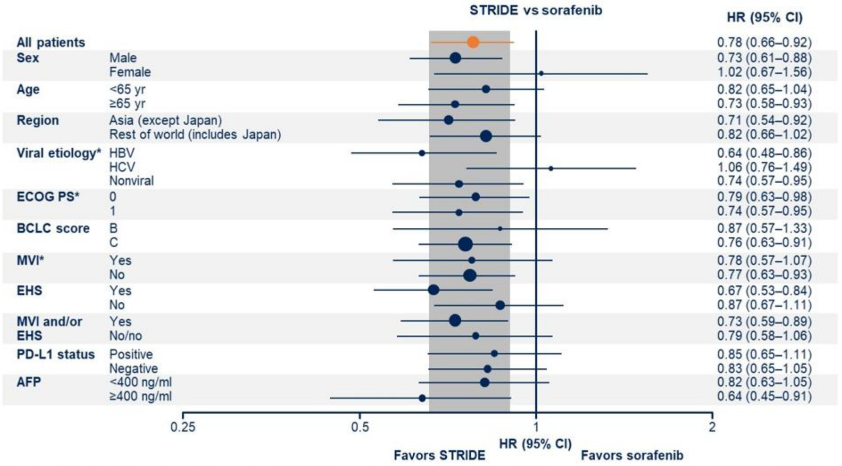
Decaens et al, ESMO 2024

HIMALAYA: Durvalumab + Tremelimumab vs Sorafenib

Primary objective: overall survival for STRIDE vs sorafenib

	STRIDE 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	





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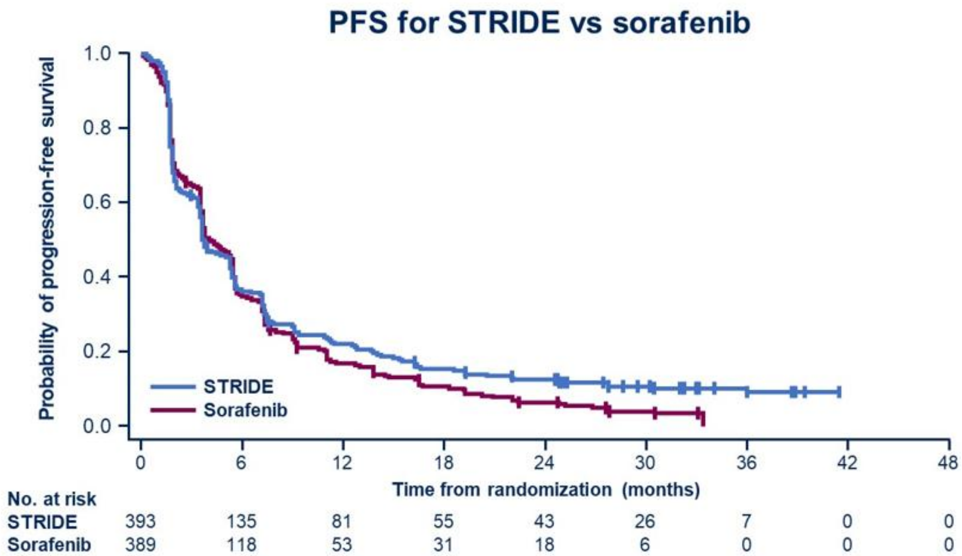
Abou-Alfa et al, ASCO GI 2022; Abou-Alfa et al, NEJM Evidence 2022

HIMALAYA: Durvalumab + Tremelimumab vs Sorafenib

Progression-free survival



Summary of PFS

	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Median TTP (95% CI), months	5.42 (3.81–5.62)	3.75 (3.68–5.42)	5.55 (5.13–5.75)
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)	–

*Versus sorafenib.

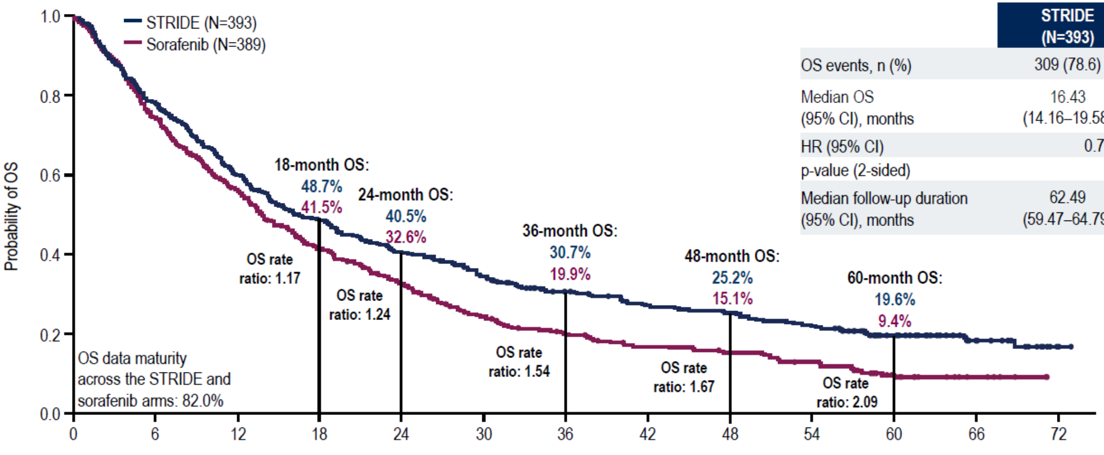
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TTP, time to progression.

Abou-Alfa et al, ASCO GI 2022; Abou-Alfa et al, NEJM Evidence 2022

HIMALAYA 2024 ESMO Update (5-year OS)

Five-year updated OS for STRIDE versus sorafenib

STRIDE demonstrated a sustained OS benefit versus sorafenib, with OS rates of 19.6% versus 9.4% at 5 years and the OS rate ratios for STRIDE versus sorafenib increasing over time



No. of participants at risk

	0	6	12	18	24	30	36	42	48	54	60	66	72
STRIDE:	393	308	235	190	158	131	104	89	83	72	46	20	2
Sorafenib:	389	283	211	155	121	84	66	51	45	37	18	6	0

	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	309 (78.6)	332 (85.3)
Median OS (95% CI), months	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), months	62.49 (59.47–64.79)	59.86 (58.32–61.54)

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OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG PS and MVI. Updated analysis data cut-off: 01 March 2024.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MVI, macrovascular invasion; OS, overall survival; PS, performance status; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

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Rimassa et al, ESMO 2024

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HIMALAYA 2024 ESMO Update (5-year OS)

Five-year OS by disease control for STRIDE versus sorafenib

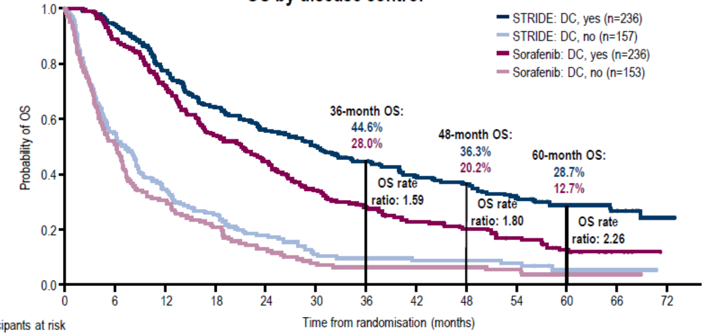
OS benefit with STRIDE was enhanced in participants experiencing disease control per RECIST v1.1, with OS rates of 28.7% for STRIDE and 12.7% for sorafenib at 5-years and the OS rate ratios for STRIDE versus sorafenib increasing over time

Best objective response (RECIST v1.1)

	Full analysis set[1]		eLTS† (≥48 months)	
	STRIDE (n=393)	Sorafenib (n=389)	STRIDE (n=83)	Sorafenib (n=45)
BOR, n (%)				
CR	12 (3.1)	0	10 (12.0)	0
PR	67 (17.0)	20 (5.1)	41 (49.4)	7 (15.6)
SD	157 (39.9)	216 (55.5)	23 (27.7)	30 (66.7)
PD	141 (35.9)	118 (30.3)	8 (9.6)	6 (13.3)
NE	16 (4.1)	35 (9.0)	1 (1.2)	2 (4.4)
Median TTR (IQR), months	2.17 (1.84–3.98)	3.78 (1.89–8.44)	2.10 (1.84–3.94)	5.49 (1.64–11.01)
Median DoR (IQR), months	22.34 (8.54–NR)	18.43 (6.51–25.99)	NR (20.50–NR)	NR (8.31–NR)
DCR*, n (%)	**236 (60.1)**	**236 (60.7)**	**74 (89.2)**	**37 (82.2)**

eLTS included participants regardless of response

OS by disease control*



No. of participants at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
STRIDE: DC, yes	236	222	181	150	130	116	93	80	74	64	43	19	2
STRIDE: DC, no	157	86	54	40	28	15	11	9	9	8	3	1	0
Sorafenib: DC, yes	236	209	167	125	102	73	57	43	37	30	17	5	0
Sorafenib: DC, no	153	74	44	30	19	11	9	8	8	7	1	1	0

Responses were based on investigator assessment according to RECIST v1.1. Responses were confirmed. Response data for both the full analysis set and eLTS were from the primary analysis (data cut-off: 27 August 2021). Updated analysis data cut-off: 01 March 2024.
*Disease control was defined as CR, PR or SD. †eLTS were defined as participants surviving ≥48 months beyond randomisation.
BOR, best objective response; CR, complete response; DC, disease control; DCR, disease control rate; DoR, duration of response; eLTS, extended long-term survivors; IQR, interquartile range; NE, not evaluable; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TTR, time to response.

1. Abou-Alfa GK, et al. *NEJM Evid* 2022;1(8):EVIDoa2100070.

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Rimassa et al, ESMO 2024

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Cell Therapy in HCC: CAR-T

2024 ASCO ANNUAL MEETING

Phase I study of C-CAR031, a GPC3-specific TGFβRIIDN armored autologous CAR-T, in patients with advanced hepatocellular carcinoma (HCC)

Qi Zhang[1,2], Qihan Fu[1,2], Wanyue Cao[1,2], Hongkan Wang[1,2], Xingyuan Xu[1,2], Jiaqi Huang[3], Andy Zou[3], Judy Zhu[3], Hui Wan[3], Yihong Yao[3], Eric Tu[4], John Stone[5], Attilio Bondanza[5], Benedetto Farsaci[4], Tingbo Liang[1,2].

[1]Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [2]Zhejiang Clinical Research Center of Hepatobiliary and Pancreatic Diseases, Hangzhou, China; [3]AbelZeta Pharma, Inc., Shanghai, China; [4]AstraZeneca, Gaithersburg, MD; [5]AstraZeneca, Cambridge, United Kingdom

Speaker: Qi Zhang, MD

C-CAR031 Study Design

A phase I, open-label, dose escalation and expansion study conducted in China

Primary Objectives:
- Safety and Tolerability (incidence and severity of TEAEs including DLTs)

Secondary Objectives:
- Investigator-assessed ORR, DCR, DoR, PFS per RECIST v1.1, and OS

Key Eligibility Criteria:
- 18-75 years of age
- Histologically confirmed GPC3+ HCC
- BCLC B/C, Child-Pugh A
- Relapsed/progressed/intolerant to HCC systemic therapies (≥1 line)
- No active CNS involvement

Screening → Apheresis → Bridging Therapy (as needed) → Lymphodepletion Cy (500 mg/m²) + Flu (25 mg/m²) → C-CAR031 Infusion → Assessments & FLUP

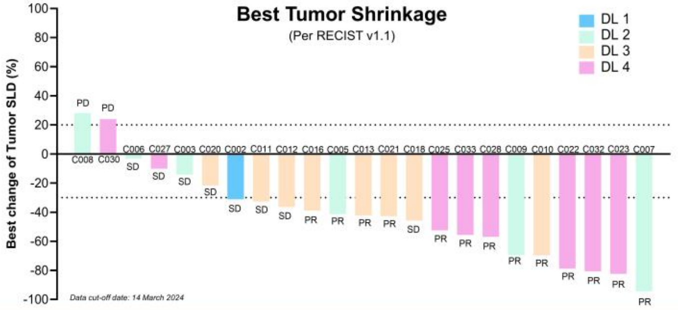
Screened (N=87) → Infused (N=24) → Safety Analysis Set (N=24) → Efficacy Analysis Set* (N=23)

Cut-off Date: 14 March, 2024

*. One patient (at DL3) who had major protocol deviation was not included for PK/PD and efficacy analysis.

TEAE, Treatment Emergent Adverse Event; DLT, Dose Limiting Toxicity; ORR, Objective Response Rate; DCR, Disease Control Rate; DoR, Duration of Response; PFS, Progression Free Survival; OS, Overall Survival; CNS, Central Nervous System; Cy, Cyclophosphamide; Flu, Fludarabine; FLUP, follow-up

C-CAR031 Showed Encouraging Tumor Responses in Late Line HCC



ORR (all confirmed PR)
- **56.5%** overall
- **75.0%** at DL 4

DCR
- **91.3%** overall

Tumor Size Reductions
- **42.2%** median target lesion reductions (range: -28.1% to 94.4%)

C-CAR031 Showed Favorable Safety Profile

Most patients experienced Grade 1/2 CRS

Adverse Events	N=24 n (%)
TRAEs[1]	24 (100)
• Grade 3/4	9 (37.5)
• Grade 5	0
SAE[2]	5 (20.8)
AESI	22 (91.7)
• CRS*	22 (91.7)
• Grade 3	**1 (4.2)**
• ICANS*	0

CRS	DL 1 N=1	DL 2 N=6	DL 3 N=9	DL 4 N=8	Overall N=24
*CRS, n (%)	1 (100)	5 (83.3)	8 (88.9)	8 (100)	22 (91.7)
• Grade 1/2	1 (100)	5 (83.3)	8 (88.9)	7 (87.5)	21 (87.5)
• Grade 3	0	0	0	**1 (12.5)**	**1 (4.2)**
Median Days to Onset, d (range)	7 (7, 7)	3 (2, 3)	3 (2, 4)	2 (1, 3)	**3 (1, 7)**
Median Days to Resolution, d (range)	4 (4, 4)	6 (4, 8)	3 (2, 6)	5 (3, 8)	**4 (2, 8)**
Treated with					
• Tocilizumab, n (%)	0	4 (66.7)	6 (66.7)	7 (87.5)	17 (70.8)
• Corticosteroids, n (%)	0	2 (33.3)	1 (11.1)	1 (12.5)	4 (16.7)

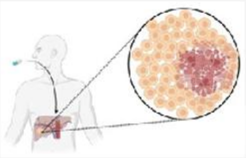
TRAE, treatment-related adverse event; SAE, serious adverse event; AESI, adverse event of special interest; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome

[1]. Defined as C-CAR031 related; [2]. Only 2 cases were C-CAR031 related; *, CRS/ICANS were graded per ASTCT Consensus (2019)

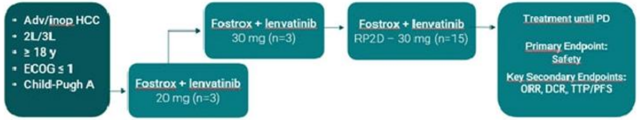
Zhang et al, ASCO 2024

MIV-818 FOSTROX (+ Lenvatinib) – 2/3 Line HCC

Background: Treatments in advanced HCC post 1L progression show limited clinical benefit and new effective and tolerable options are needed. Fostrox is a type of new smart chemotherapy, with an orally administered prodrug, based on the nucleoside analog troxacitabine. With a liver targeted approach, fostrox achieves 100-fold higher liver exposure to the active metabolite versus IV troxacitabine (in rat), leading to effective and selective cytotoxicity in liver tumors, while minimizing systemic exposure. Fostrox is in clinical development in combination with lenvatinib in patients with advanced HCC who progressed on prior treatment (NCT03781934).



Study design



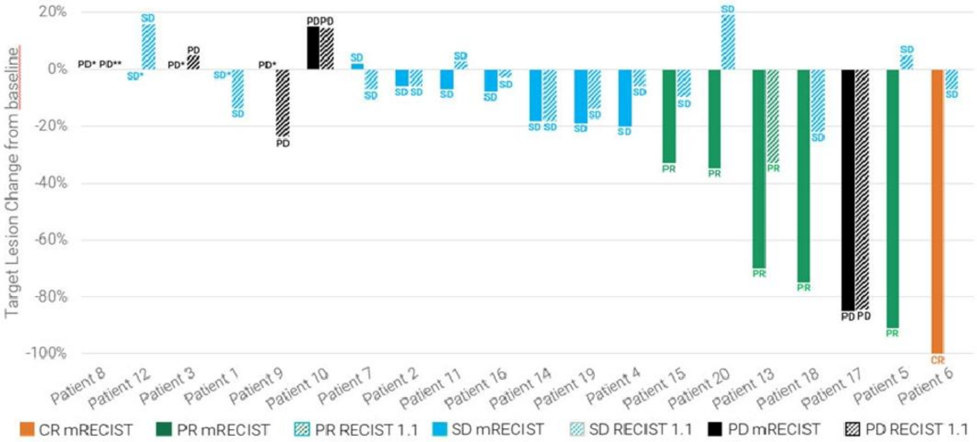
Imaging assessment with CT/MRI every 6 weeks

Objectives:
- Primary: safety and tolerability
- Key secondary: ORR (RECIST v1.1 and mRECIST), DCR, PFS
- Exploratory: PK/PD effects of fostrox in combination with lenvatinib

Dosing:
- Fostrox: oral, QD for 5 days/21 days cycle
- Lenvatinib: oral, 8 or 12 mg QD according to weight

Enrollment:
- 15 sites in the UK, Spain and South Korea

Central review - best response RECIST 1.1 and mRECIST



Data cut-off Sept 2023
* patients lacking contrast enhancement in arterial phase and could not be evaluated with mRECIST where 3 had PD in NTL.
** patient number 8 had no measurable TL with central RECIST 1.1

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Reig et al, ASCO GI 2024

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1. Early-disease – no role of adjuvant

2. Intermediate stage – systemic to be combinaed with TACE

3. Advanced disease – CTLA-4 stablished; new options coming

Thank you for your attention

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