Localized Potentially Operable CCA: What are the neoadjuvant options?

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Debate: TACE and Systemic Therapy
Combine or sequence?

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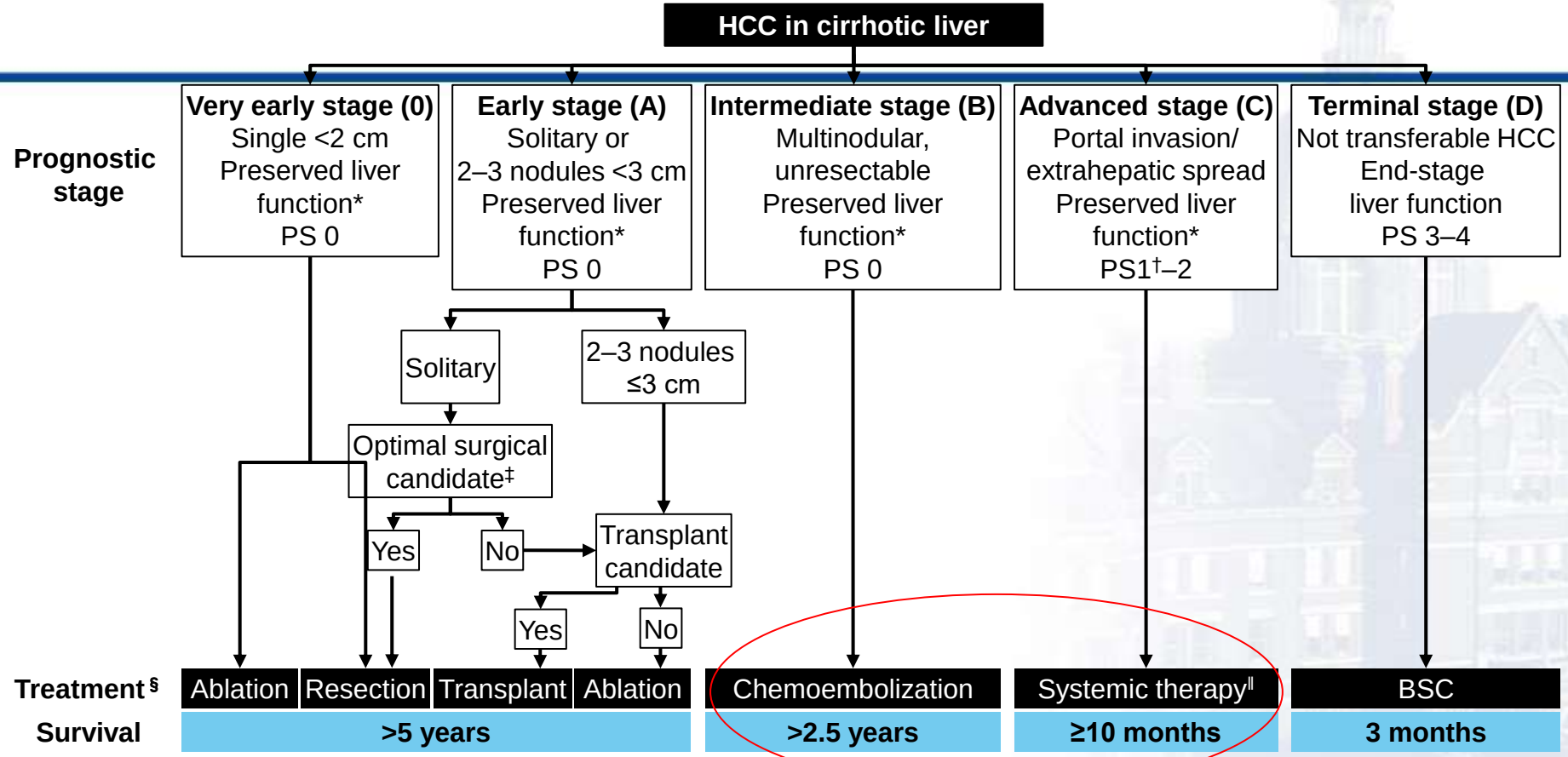
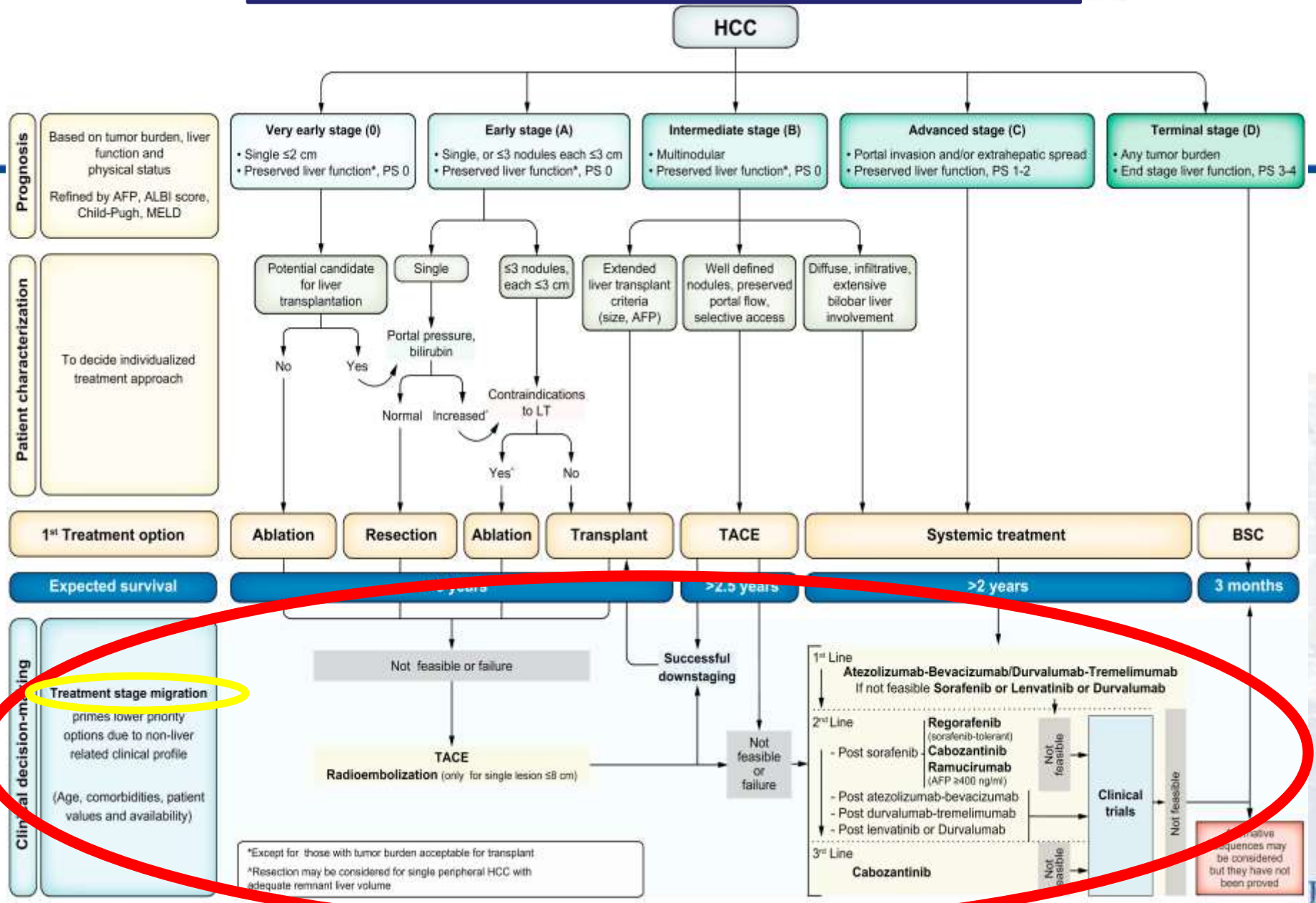
Modified BCLC staging system: LRT 2018



BCLC B: large heterogeneous group with varying tumor burdens, liver function (Child-Pugh A/B) and liver disease causes
Not all get benefit from TACE, and that some may benefit from other treatments
Advanced stage, similar heterogeneous

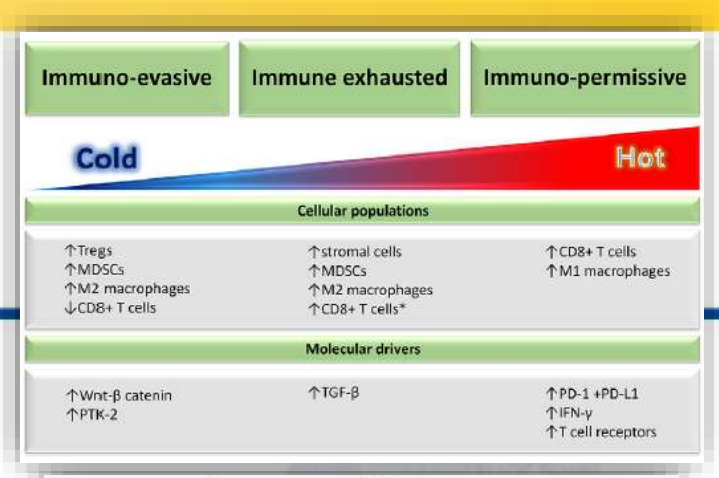
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

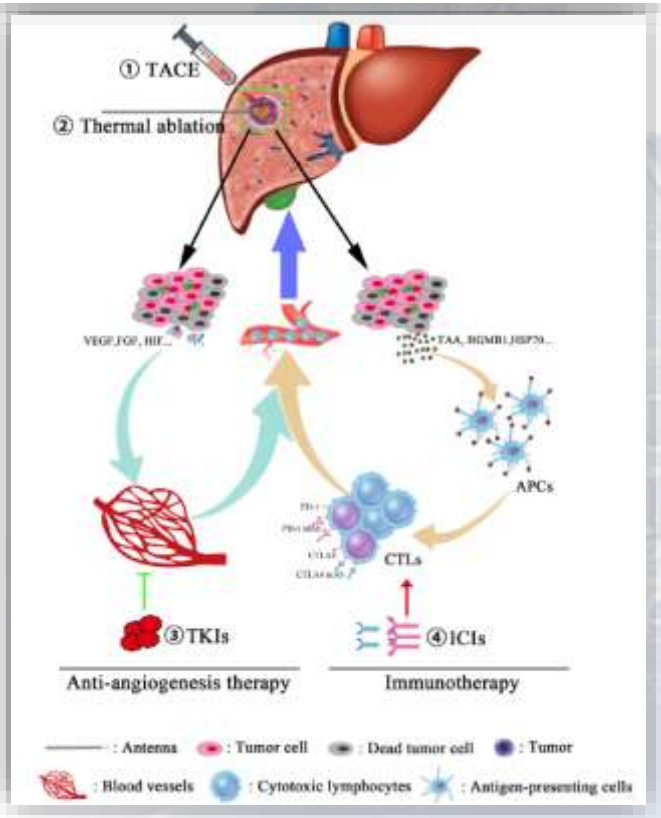
BCLC staging and treatment strategy in 2022



Immuno-oncology combined with LRT

- 2022 BCLC HCC Update, introduction of <u>Stage migration</u>
- Embolization causes hypoxia overexpression of VEGF
- Synergistic benefits of LRT for immunotherapy
- Despite positive trials, IO alone limited by ORR 20-40%, eventually disease progression or failure to respond
- Underlying resistance mechanisms multifactorial
- LRT target and alter the tumor microenvironment by local tumor destruction
- enhance exposure of tumor antigens by priming and converting immunosuppressive tumor microenvironment toward more potent T-cell response
- Supports coordinated sequencing and combination





Li X, et al. Locoregional Combined With Systemic Therapies for Advanced HCC: An Inevitable Trend of Rapid Development. Front Mol Biosci. 2021 Apr 13;8:635243
Greten TF, et al. Combined locoregional-immunotherapy for liver cancer. J Hepatol. 2019 May;70(5):999-1007
Bitar R, et al. Interventional Oncology Meets Immuno-oncology: Combination Therapies for Hepatocellular Carcinoma. Radiology. 2024 Nov;313(2):e232875

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Current combination trials with LRT: many varying sequencing- between LRT and IO

Table 1 Ongoing studies evaluating the efficac

Clinical trials	Start date	Number of patients
NCT01853618	May 2, 2013	61
NCT02821754	July 5, 2016	90
NCT03033446	December 2016	40
NCT03203304	August 25, 2017	50
NCT03482102	May 14, 2018	70
NCT03638141	May, 2019	30
NCT03572582	June 14, 2018	49
NCT02837029	July, 2016	35
NCT03939975	May 1, 2019	50
NCT03316872	February 15, 2018	30
NCT03099564	March 28, 2017	30
NCT03397654	January 28, 2018	26
NCT03259867	July 1, 2017	80

TACE, transcatheter arterial chemoembolization; *PEIT*, percutaneous ethanol injection therapy; *C* programmed death-ligand 1; *DCs*, dendritic cells;

Recent Important Clinical Trials Advocating for the Integration of Immunotherapy and LRT in the Treatment of HCC

Trial Registration No. and Name	Phase	Cancer	LRT	Treatment Regimen	Status and Results	End Points
NCT03298451 (HIMALAYA)	3	Advanced-stage HCC	None	Durvalumab + tremelimumab vs sorafenib	Ongoing with results; positive	A loading dose of 300 mg CTLA-4 inhibitor followed by subsequent cycles of PD-L1 inhibitor demonstrated increased OS in comparison with sorafenib (30.7% vs 24.7% at 36 months); median PFS was not significantly different (to be completed August 2027)
NCT03434379 (IMbrave150)	3	Advanced-stage HCC	None	Atezolizumab + bevacizumab vs sorafenib	Complete; positive	PD-L1 inhibitor + VEGF inhibitor improved OS in comparison with sorafenib (67.2% vs 54.6% at 12 months); median PFS was also increased (6.8 vs 4.3 months) (completed November 2022)
NCT04102098 (IMbrave050)	3	BCLC 0/A with high risk of recurrence	Ablation/ resection	Atezolizumab + bevacizumab + ablation/resection	Ongoing with results; negative	The addition of PD-L1 inhibitor + VEGF inhibitor after curative resection or ablation in patients with high risk of recurrence appeared to delay recurrence within the first 12 months of intervention; while initial analysis suggested RFS to be superior with the addition of systemic therapy, updated analysis demonstrates this benefit was not sustained (33.2 vs 36.0 months); this study remains ongoing to obtain OS data (to be completed July 2027)
NCT03847428 (EMERALD-2)	3	Early HCC	Ablation/ resection	Durvalumab (with or without bevacizumab) + ablation/ resection	Ongoing	This study aims to assess whether the addition of adjuvant PD-L1 inhibitor (with or without VEGF inhibitor) will improve RFS and OS in patients after curative ablation/resection (to be completed August 2025)

Greten TF, et al. Combined locoregi
Bitar R, et al. Interventional Oncology Meets Immuno-oncology: Combination Therapies for Hepatocellular Carcinoma. Radiology. 2024 Nov;313(2):e232875.

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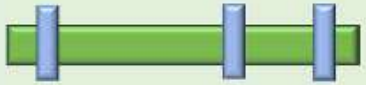
Immuno-oncology combined with LRT

Therapy Sequence	Ablation	Embolization	Implications
Sequential 	NCT04102098 (IMbrave 050) • ablation → atezolizumab + bevacizumab every 3 weeks initiated 4-12 weeks after ablation (or resection)	NCT03778957 (EMERALD-1) • TACE → durvalumab every 4 weeks → 2 weeks after the last TACE, durvalumab + bevacizumab every 3 weeks	• Emphasizes safety and minimizes risks for adverse events between LRT and immunotherapy • Limited synergy due to lacking overlap of TME effects with focus on additive effects
Interrupted 	NCT03630640 (NIVOLEP) • nivolumab every 2 weeks for two cycles → IRE → Nivolumab every 4 weeks for 12 months	NCT02821754 • durvalumab + tremelimumab every 4 weeks for up to 4 doses → TACE on ~ Day 36	• Primes TME with immunotherapy to enhance immunologic effect of LRT while eradicating residual disease • Interrupts regimen of immunotherapy to increase patient safety and reduce adverse events
Continuous 	None underway	NCT01853618 • tremelimumab every 4 weeks for 6 doses → every 12 weeks for 2 years. • TACE on Day 36 (however may be repeated at months 3, 7, 13, and every 6 months thereafter)	• Maximizes therapeutic potency of both LRT and neoadjuvant + adjuvant immunotherapy • Highest chance for synergy • Increased risk for adverse events

- LRT target and alter the tumor microenvironment by local tumor destruction
- enhance exposure of tumor antigens by priming and converting immunosuppressive tumor microenvironment toward more potent T-cell response
- Supports coordinated sequencing; recent positive trials

Li X, et al. Locoregional Combined With Systemic Therapies for Advanced HCC: An Inevitable Trend of Rapid Development. Front Mol Biosci. 2021 Apr 13;8:635243
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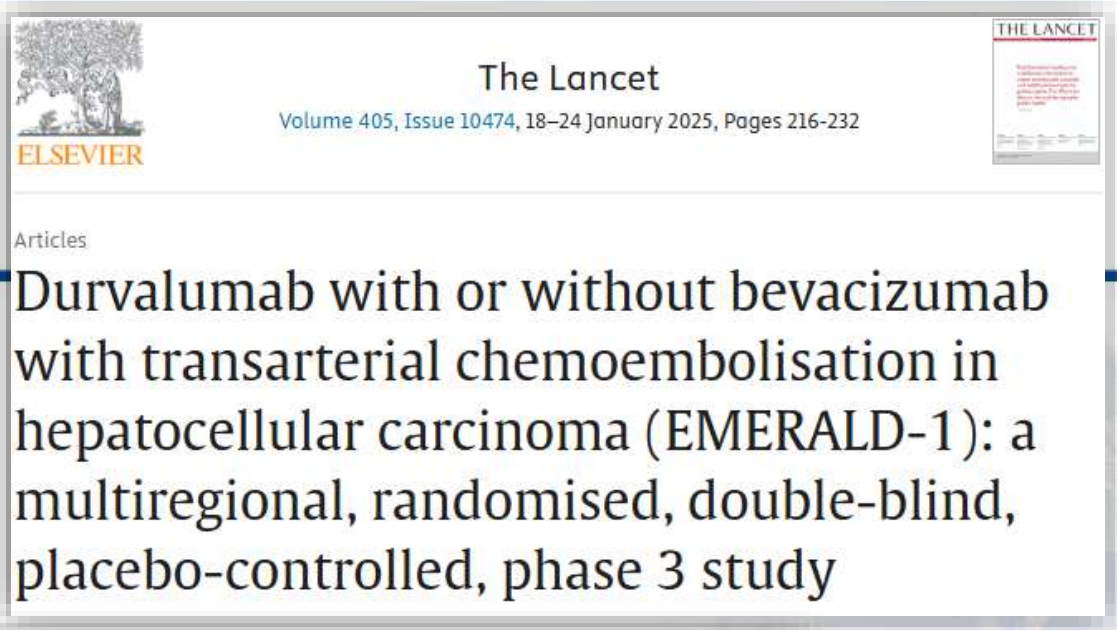
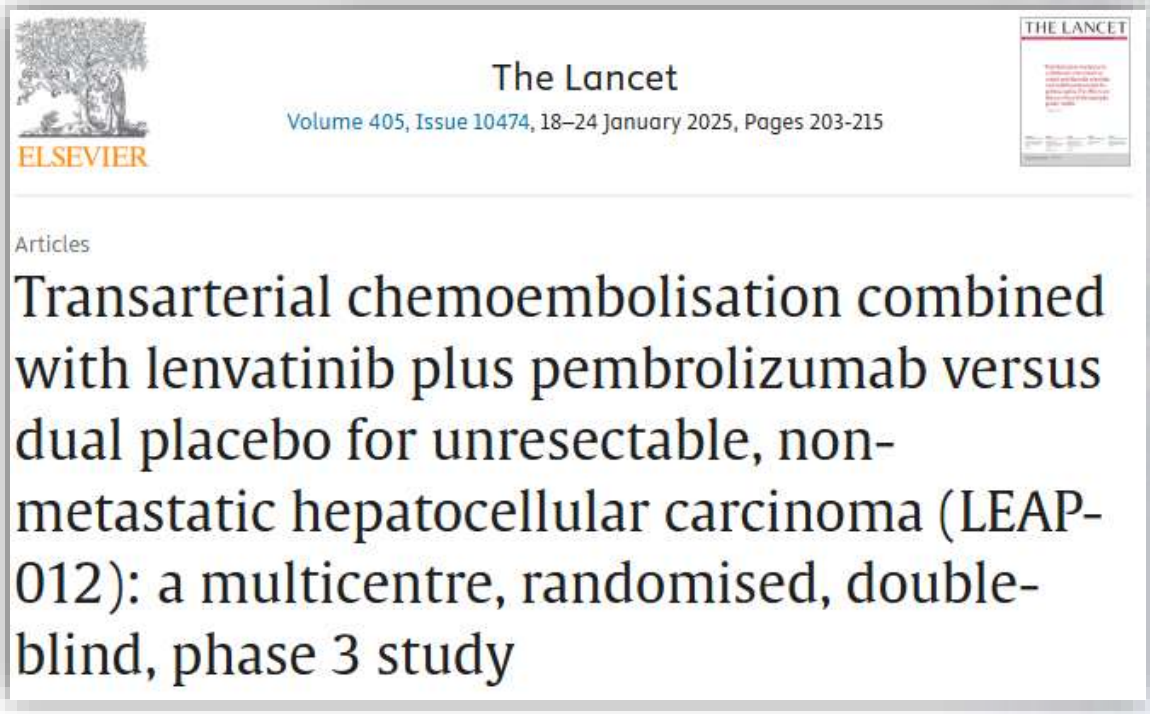
Current combination trials with LRT: many varying sequencing- between LRT and IO

Trial Registration No. and Name	Phase	Cancer	LRT	Treatment Regimen	Status and Results	End Points
NCT03778957 (EMERALD-1)	3	Unresectable HCC	TACE	Durvalumab (with or without bevacizumab) + TACE vs TACE alone	Ongoing with results; positive	PD-L1 inhibitor + VEGF inhibitor when added to TACE improved PFS in comparison with TACE alone in nonresectable HCC (15.0 vs 8.2 months); to be completed August 2026
NCT05301842 (EMERALD-3)	3	Unresectable HCC	TACE	Durvalumab + tremelimumab with or without lenvatinib + TACE	Ongoing	This study aims to assess whether the addition of dual ICI + RTK inhibitor + TACE will improve PFS (to be completed February 2027)
NCT04712643 (TALENTACE)	3	Unresectable HCC	TACE	Atezolizumab + bevacizumab + TACE vs TACE alone	Ongoing	This study aims to assess if PD-L1 inhibitor + VEGF inhibitor when added to TACE can improve PFS and OS (to be completed February 2029)
NCT04803994 (ABC-HCC)	3	Intermediate HCC	TACE	Atezolizumab + bevacizumab vs TACE	Ongoing	This study aims to assess if PD-L1 inhibitor + VEGF can outperform TACE in intermediate HCC in regard to PFS and OS (to be completed April 2025)
NCT03380130 (NASIR-HCC)	2	Unresectable HCC	TARE	TARE + nivolumab	Complete; positive	The addition of PD-1 inhibitor demonstrated an acceptable safety profile, and median OS was notable at 20.9 months for locally advanced HCC (completed November 2020)
NCT05063565 (ROWAN)	2	Unresectable HCC	TARE	Durvalumab + tremelimumab + TARE	Ongoing	This study investigates safety and ORR in patients who undergo radioembolization with dual ICI therapy (to be completed June 2027)

Greten TF, et al. Combined locoregional-immunotherapy for liver cancer. J Hepatol. 2019 May;70(5):999-1007
Bitar R, et al. Interventional Oncology Meets Immuno-oncology: Combination Therapies for Hepatocellular Carcinoma. Radiology. 2024 Nov;313(2):e232875.

Positive RCT's TACE combined with IO: 2025





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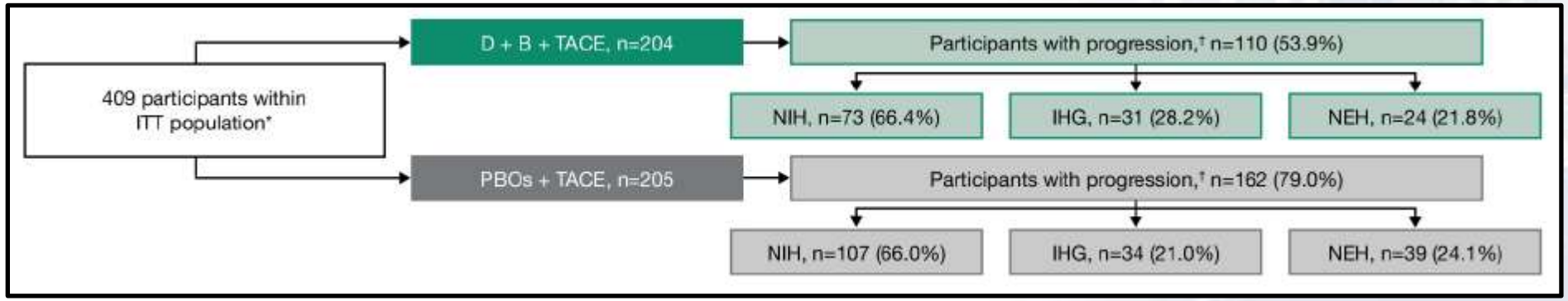
Durvalumab with or without bevacizumab with transarterial chemoembolisation in hepatocellular carcinoma (EMERALD-1): a multiregional, randomised, double-blind, placebo-controlled, phase 3 study

- TACE eligible patients, adding durvalumab, with or without bevacizumab, might improve PFS
- Multiregional, RCT, 157 centers, 18 countries, confirmed HCC not amenable to curative therapy (e.g. surgical resection, ablation)
- No extrahepatic disease, Child-Pugh A to B7, ECOG PS 0/1
- Excludes Vp3 and Vp4 (included Vp1 and 2)
- TACE modality (DEB-TACE vs cTACE)

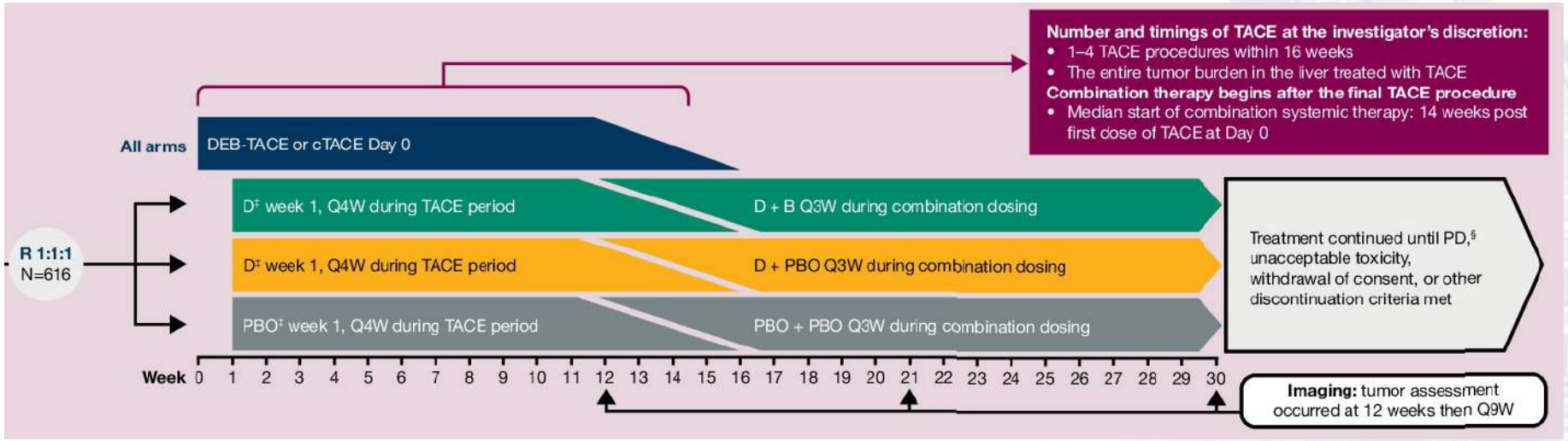


Sangro B, Lencioni R et al; EMERALD-1 Investigators. Durvalumab with or without bevacizumab with transarterial chemoembolisation in hepatocellular carcinoma (EMERALD-1): a multiregional, randomised, double-blind, placebo-controlled, phase 3 study. Lancet. 2025 Jan 18;405(10474):216-232.

JOHNS HOPKINS MEDICINE

Durvalumab with or without bevacizumab with transarterial chemoembolisation in hepatocellular carcinoma (EMERALD-1): a multiregional, randomised, double-blind, placebo-controlled, phase 3 study

- 3 arms: TACE, with dura, with dura/ beva
- Systemic therapy started after TACE, 14 weeks, all lesions targeted



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- PVT included, mostly Intermediate stage, but also A's and C's
- Higher tumor burden within the D+B+TACE arm PBOs+TACE (up-to-7 criteria)
- More participants with BCLC stage C in PBOs+TACE arm compared with the D+B +TACE arm

	New intrahepatic lesion		Intrahepatic growth		New extrahepatic lesion	
n (%)	D + B + TACE (n=73)	PBOs + TACE (n=107)	D + B + TACE (n=31)	PBOs + TACE (n=34)	D + B + TACE (n=24)	PBOs + TACE (n=39)
BCLC stage						
A	21 (28.8)	29 (27.1)	8 (25.8)	5 (14.7)	8 (33.3)	6 (15.4)
B	46 (63.0)	62 (57.9)	19 (61.3)	21 (61.8)	10 (41.7)	22 (56.4)
C	6 (8.2)	14 (13.1)	4 (12.9)	8 (23.5)	6 (25.0)	11 (28.2)
Missing	0	2 (1.9)	0	0	0	0
PVMI present	4 (5.5)	5 (4.7)	2 (6.5)	4 (11.8)	4 (16.7)	3 (7.7)
Baseline tumor burden						
≤7*	40 (54.8)	62 (57.9)	9 (29.0)	17 (50.0)	10 (41.7)	18 (46.2)
>7*	33 (45.2)	45 (42.1)	22 (71.0)	17 (50.0)	14 (58.3)	21 (53.8)

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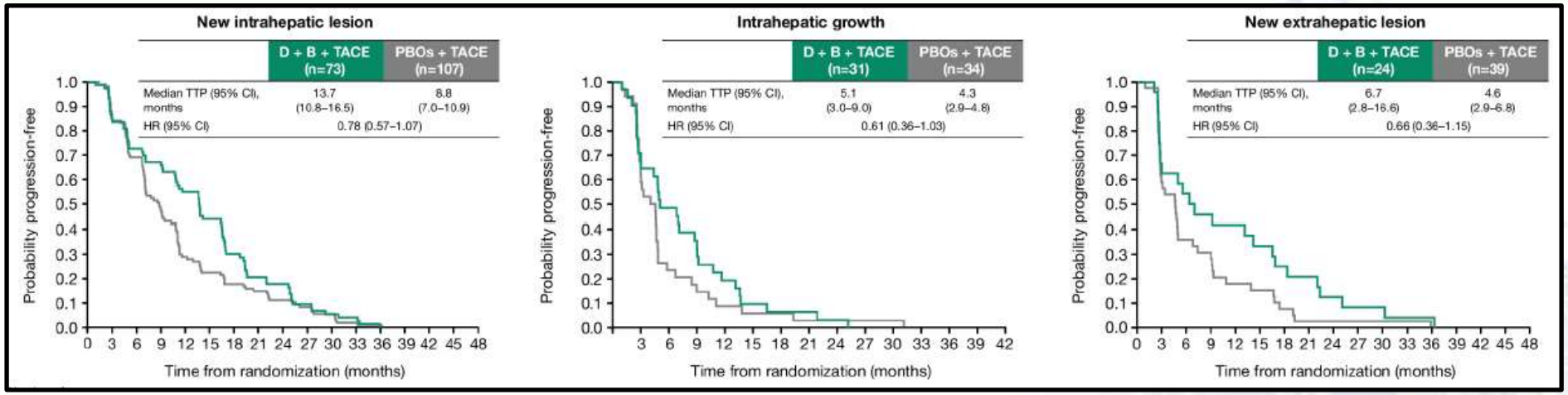


As of data cutoff (9/11/23) median follow-up was 27·9 months (95% CI 27·4–30·4)

Median PFS 15.0 months (95% CI 11·1–18·9) with durva plus beva plus TACE, HR 0.77

10.0 months (9·0–12·7) with TACE plus durva, HR 0.94

8·2 months (6·9–11·1) with placebo TACE

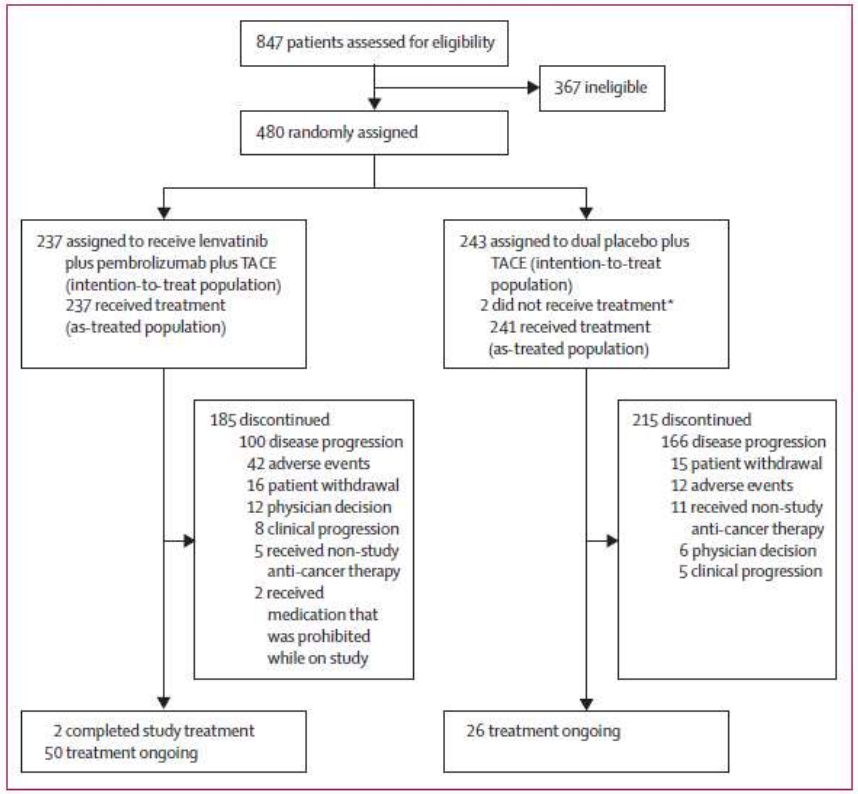
AE's: hypertension [6%] anemia, durvalumab and placebo [4%] and post-embolisation syndrome [4%]

Sangro B, Lencioni R et al; EMERALD-1 Investigators. Durvalumab with or without bevacizumab with transarterial chemoembolisation in hepatocellular carcinoma (EMERALD-1): a multiregional, randomised, double-blind, placebo-controlled, phase 3 study. Lancet. 2025 Jan 18;405(10474):216-232.

JOHNS HOPKINS MEDICINE

TACE combined with lenvatinib plus pembrolizumab versus dual placebo for unresectable, non-metastatic hepatocellular carcinoma (LEAP-012): a multicentre, randomised, double-blind, phase 3 study

- Aim: TACE plus lenvatinib and pembrolizumab
  versus TACE plus dual placebo
- patients with non-metastatic HCC, not amenable to curative treatment, but with tumors amenable to TACE
- multicenter, randomized, double-blind, phase 3 study (LEAP-012)
  137 sites in 33 countries
- Primary endpoints were PFS and OS
- First interim analysis, final for PFS



Kudo M, Llovet JM et al; LEAP-012 investigators. Transarterial chemoembolisation combined with lenvatinib plus pembrolizumab versus dual placebo for unresectable, non-metastatic hepatocellular carcinoma (LEAP-012): a multicentre, randomised, double-blind, phase 3 study. Lancet. 2025 Jan 18;405(10474):203-215.

JOHNS HOPKINS MEDICINE

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	Lenvatinib plus pembrolizumab plus TACE (n=237)	Placebo plus TACE (n=243)
Age, years		
Median	65 (57-72)	66 (59-73)
<65	109 (46%)	106 (44%)
≥65	128 (54%)	137 (56%)
Sex		
Female	45 (19%)	37 (15%)
Male	192 (81%)	206 (85%)
ECOG performance status score		
0	216 (91%)	213 (88%)
1	21 (9%)	30 (12%)
Aetiology‡		
HCV	42 (18%)	39 (16%)
HBV	153 (65%)	144 (59%)
Alcohol	107 (45%)	112 (46%)
Non-viral	54 (23%)	75 (31%)
α-Fetoprotein level at screening		
≤400 ng/mL	200 (84%)	203 (84%)
>400 ng/mL	37 (16%)	40 (16%)
BCLC stage§		
0	1 (<1%)	0
A	80 (34%)	68 (28%)
B	135 (57%)	146 (60%)
C	21 (9%)	29 (12%)
Child-Pugh A score points¶		
5	204 (86%)	217 (89%)
6	33 (14%)	26 (11%)
Albumin-bilirubin grade‖		
1	171 (72%)	174 (72%)
2	65 (27%)	69 (28%)
Missing	1 (<1%)	0
Tumour burden score**		
≤6	112 (47%)	116 (48%)
>6 to ≤12	120 (51%)	117 (48%)
>12	5 (2%)	10 (4%)

- Matched; Hep B's and C's and non virals
- included BCLC A's and C's

Kudo M, Llovet JM et al, LEAP-012 Investigators. Transarterial chemoembolisation combined with lenvatinib plus pembrolizumab versus dual placebo for unresectable, non-metastatic hepatocellular carcinoma (LEAP-012): a multicentre, randomised, double-blind, phase 3 study. Lancet. 2025 Jan 18;405(10474):203-215.

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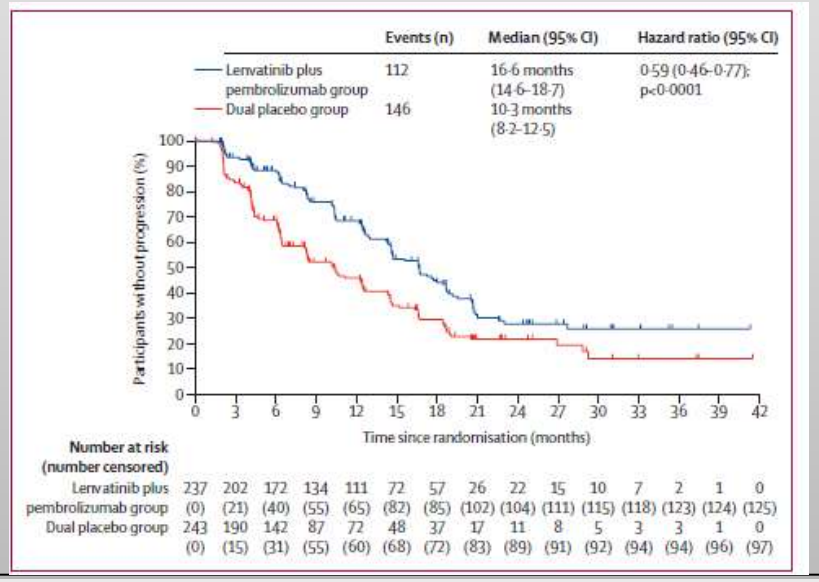
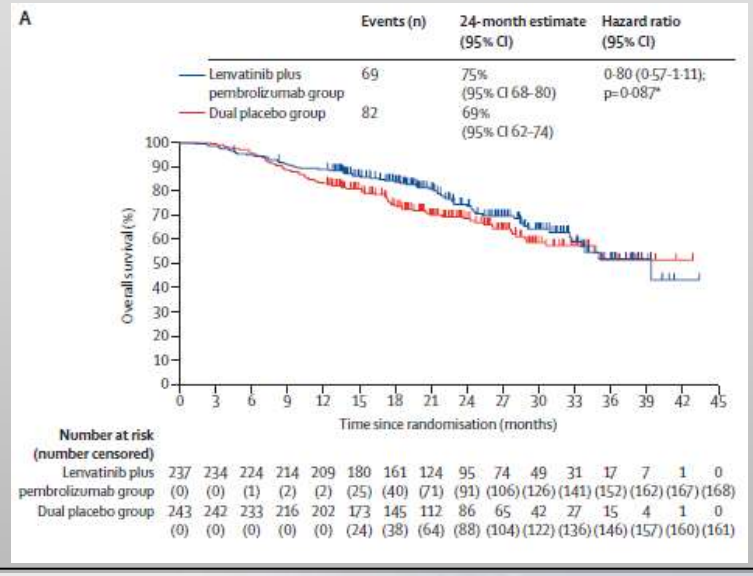
- Median PFS was 14.6 months (combination) vs 10 months TACE only
- (hazard ratio [HR] 0·66 [95% CI 0·51–0·84]; one-sided p=0·0002)
- OS rate (24-month) 75% (95% CI 68–80) in combo
- 69% (62–74) in TACE group (HR 0·80, p=0·087)





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TACE combined with lenvatinib plus pembrolizumab versus dual placebo for unresectable, non-metastatic hepatocellular carcinoma (LEAP-012): a multicentre, randomised, double-blind, phase 3 study

- Grade 3 or worse treatment-related adverse events hypertension (57 [24%] vs 18 [7%]) and platelet 27 [11%] vs 15 [6%]
- Deaths occurred in four (2%) combo group (hepatic failure, gastrointestinal hemorrhage, myositis, and immune-mediated hepatitis) and
  one (<1%) in the TACE placebo group (due to brain stem hemorrhage)

- Conclusion: TACE plus lenvatinib plus pembro showed significant, clinically meaningful improvement in PFS in patients with unresectable, non-metastatic HCC vs TACE plus placebo
- Improvement in OS encouraging, but longer follow-up is necessary

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Meeting Abstract: 2025 ASCO Gastrointestinal Cancers Symposium

FREE ACCESS | Hepatobiliary Cancer | January 27, 2025

Concurrent transarterial chemoembolization plus atezolizumab and bevacizumab in unresectable hepatocellular carcinoma: Interim analysis from a multicenter real-world study (CHANCE 023).

Authors: Rong Yan, Haidong Zhu, Jian Lu, and Gao-Jun Teng | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 43, Number 4_suppl • https://doi.org/10.1200/JCO.2025.43.4_suppl.542

- Other studies but not controlled trials (Japan, China)

Article | Open access | Published: 08 February 2023

Transarterial chemoembolization with PD-(L)1 inhibitors plus molecular targeted therapies for hepatocellular carcinoma (CHANCE001)

Hai-Dong Zhu, Hai-Liang Li, Ming-Sheng Huang, Wei-Zhu Yang, Guo-Wen Yin, Bin-Yan Zhong, Jun-Hui Sun, Zhi-Cheng Jin, Jian-Jian Chen, Nai-Jian Ge, Wen-Bin Ding, Wen-Hui Li, Jin-Hua Huang, Wei Mu, Shan-Zhi Gu, Jia-Ping Li, Hui Zhao, Shu-Wei Wen, Yan-Ming Lei, Yu-Sheng Song, Chun-Wang Yuan, Wei-Dong Wang, Ming Huang, Wei Zhao, for the CHANCE001 Investigators + Show authors

Signal Transduction and Targeted Therapy **8**, Article number: 58 (2023) | Cite this article

Liver Cancer

Research Article

Liver Cancer
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Published online: February 7, 2023

Achievement of Complete Response and Drug-Free Status by Atezolizumab plus Bevacizumab Combined with or without Curative Conversion in Patients with Transarterial Chemoembolization-Unsuitable, Intermediate-Stage Hepatocellular Carcinoma: A Multicenter Proof-Of-Concept Study

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Take Home Messages

- Rapid number of systemic therapies plus TACE very encouraging
- Recent publication of 2 positive RCT's with TACE combined with IO
- Selection of best patients? BCLC B? C?
- Criteria: up-to-7?
- Achieve better results than TACE or IO alone
- Combination is better

THANK YOU!

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Discussion

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