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THE HEART OF MEDICAL EDUCATION

THE EXPANDING ROLE OF IMMUNOTHERAPY IN HCC:

COMBINING LOCOREGIONAL AND SYSTEMIC TREATMENTS IN INTERMEDIATE HCC

MICRO LEARNING

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DEVELOPED BY HCC CONNECT

This programme is developed by HCC CONNECT, an international group of experts in the field of hepatocellular carcinoma and brought to you alongside GI CONNECT, an international group of experts in the field of gastrointestinal oncology.

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THIS PROGRAMME HAS BEEN DEVELOPED BY A GROUP OF EXPERTS

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CLINICAL TAKEAWAYS

THE EXPANDING ROLE OF IMMUNOTHERAPY IN HEPATOCELLULAR CARCINOMA (HCC) – COMBINING LOCOREGIONAL AND SYSTEMIC TREATMENTS IN INTERMEDIATE HCC

- **Immuno-oncology therapy (IO) and IO combinations** are **transforming the landscape** for patients with advanced and intermediate HCC who are not candidates for local therapy, with 1st line options (IMbrave150, HIMALAYA, CheckMate 9DW) offering improved **long-term outcomes**, including 20% survival at 5-years in HIMALAYA
- **Intermediate-stage HCC** may benefit from **multimodal strategies**, **combining IO with locoregional therapies (LRTs)** to address both visible and invisible disease, enhancing immune response, and optimising tumour control
- **IO + LRT combinations**, such as TACE plus IO, show promise for patients with intermediate HCC, with positive trials like **EMERALD-1** and **LEAP-012** demonstrating **improved PFS and manageable safety profiles**, with ongoing evaluation of OS outcomes
- A **multidisciplinary approach** is crucial to determine which **patients with intermediate HCC may benefit from multimodal combinations**, requiring coordination among oncologists, hepatologists, interventional radiologists, radiation oncologists, and transplant surgeons

IO, immuno-oncology therapy; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolisation

BUILDING THE FOUNDATION

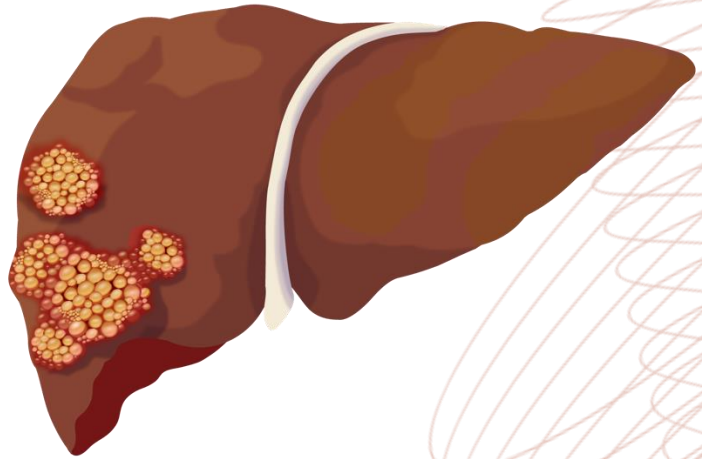
BACKGROUND ON HCC, STAGING, AND BALANCING CHALLENGES

HCC, hepatocellular carcinoma;

BACKGROUND

HEPATOCELLULAR CARCINOMA (HCC)[1]

- Liver cancer is the **sixth most prevalent cancer** globally and ranks as the third leading cause of cancer-related deaths, with HCC representing 75%-86% of primary liver cancer cases
- In the United States, HCC incidence and mortality rates rose between 1970 and 2010; however, incidence began declining in 2011, and mortality rates stabilised in 2013, with one study reporting an annual decrease of ~3% in subsequent years
- **Cirrhosis,** regardless of the underlying liver disease, is the **strongest risk factor** for HCC, affecting more than 80% of patients diagnosed with the disease
- Patients with cirrhosis have an **estimated 2% yearly risk** of developing HCC
  - Chronic viral hepatitis (HBV and HCV) remains a major risk factor for HCC in many regions; however, its impact is decreasing in areas due to HBV vaccination programmes and curative antiviral treatments for HCV
  - HCC related to alcohol and metabolic dysfunction-associated steatotic liver disease (MASLD) (previously known as NAFLD[2]) is now the leading cause of HCC in patients without cirrhosis



HBV/HCV, hepatitis B/C virus; NAFLD, non-alcoholic fatty liver disease

1. Singal AG, et al. Hepatology. 2023;78:1922-1965; 2. New Year, New Name: NAFLD becomes MASLD. Available at: https://www.aafp.org/pubs/afp/afp-community-blog/entry/new-year-new-name-nafld-becomes-masld.html (accessed January 2025)

HCC STAGING

INTERMEDIATE HCC IS COMPLEX AND HETEROGENEOUS

Patients with **intermediate HCC** exceed the Milan Criteria (UNOS T2) for early HCC:[1,2]

- One tumour <5 cm or up to three tumours <3 cm

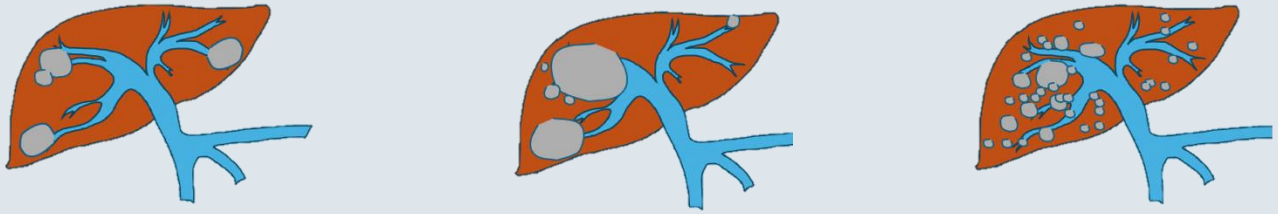
Intermediate HCC sub-stratification:

Up-to-7 criteria[3,4]

# of tumours + largest tumour size (in cm) ≤7

Liver transplantation may be considered if within the extended UCSF criteria[5,6]
In single tumours ≤8 cm, TARE can be an alternative option for patients who are unfavourable for resection[7]

BCLC-B[8] intermediate HCC – phenotype driven



• *Well defined nodules* • *Selectable* • *Within extended transplant criteria* • *Preserved portal flow*	• *Well defined nodules* • *Selectable* • *Out of extended transplant criteria* • *Preserved portal flow*	• *Non-selectable* • *Diffuse* • *Infiltrative* • *Out of extended transplant criteria*
LT may be considered	*TACE recommended*	*Systemic Therapy recommended*

Other sub-stratification criteria for intermediate HCC exist, such as Bolondi[9] and Kinki[10]

BCLC-B, Barcelona Clinic Liver Cancer Stage B; HCC, hepatocellular carcinoma; LT, liver transplant; TACE, transarterial chemoembolisation; TARE, transarterial radioembolization; UCSF, University of California, San Francisco; UNOS T2, United Network for Organ Sharing Tumour 2

Graphics kindly provided by Prof. Toskich

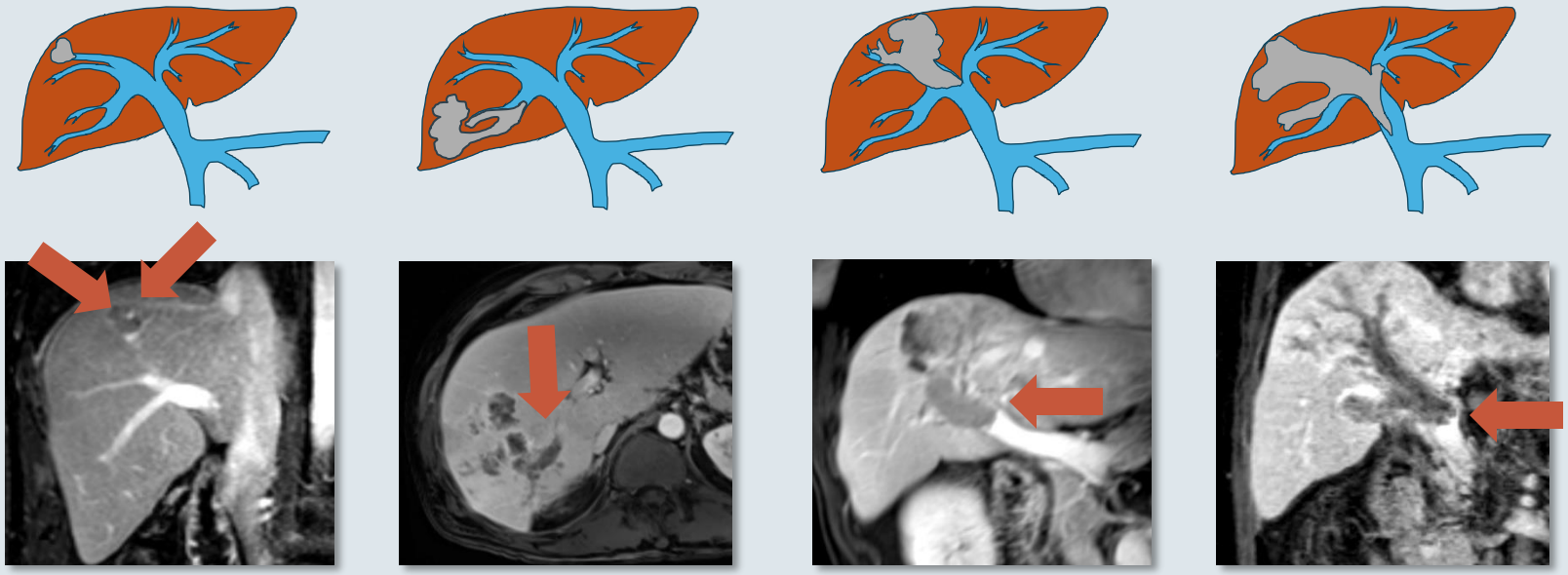
1. Famularo S, et al. HPB (Oxford). 2020;22:1349-1358; 2. Gundlach J-P et al. Z Gastroenterol. 2024;62:43-49; 3. Mazzaferro, et al. Lancet Oncology. 2009; 4. Chen H-Y, et al. J Formos Med Assoc. 2022;121:778-786; 5. Yao FY, et al. Am J Transplant. 2007;7:2587-2596; 6. Horwitz JK and Agopian VG. Curr Hepatol Rep. 2024;23:185-192. 7. Vogel A, et al. Ann Oncol. 2025 (article in press; https://doi.org/10.1016/j.annonc.2025.02.006); 8. Reig M, et al. J Hepatol. 2022;76:681-693; 9. Bolondi L, et al. Semin Liver Dis. 2012;32:348-359; 10. Kudo M, et al. Dig Dis. 2015;33:751-758

HCC STAGING

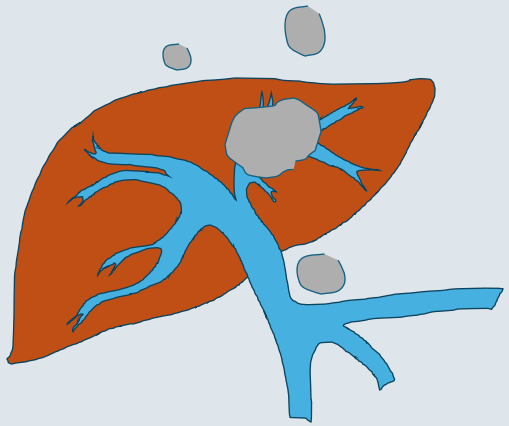
HETEROGENEITY AND SUBCLASSIFICATIONS ALSO APPLY TO ADVANCED HCC

- Patients with advanced HCC (BCLC-C) have vascular invasion and/or extrahepatic disease[1]
- Patients with advanced HCC are candidates for systemic therapy but can be candidates for local therapy depending on the level of vascular invasion, disease biology, and liver involvement[1,2]

Vascular invasion (LCSGJ)[2,a]



Extrahepatic disease



[a] MRI scans and graphics kindly provided by Prof. Toskich

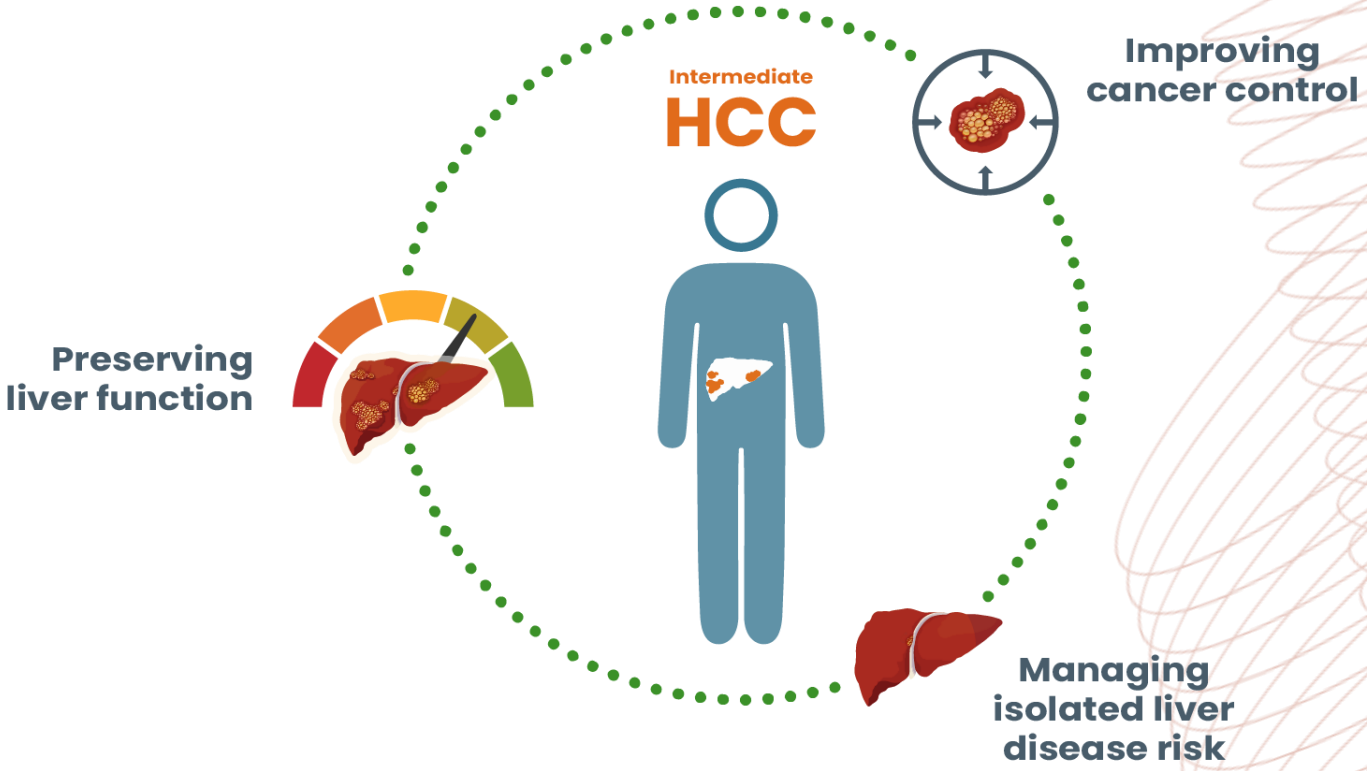
BCLC-C, Barcelona Clinic Liver Cancer Stage C; HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan; MRI, magnetic resonance imaging; Vp, vascular portal (classification)

1. Reig M, et al. J Hepatol. 2022;76:681-693; 2. Chan SL, et al. World J Gastroenterol. 2016;22:7289-7300

COMPETING HAZARDS IN THE TREATMENT OF HCC

PRIMARY CHALLENGES THAT MUST BE BALANCED

- Balancing the **hazards**
  - Treatment decisions in HCC require careful evaluation to optimise outcomes[1,2]
    - **Preserve liver function:** ensuring the patient's liver can tolerate the chosen therapy[1]
    - **Control cancer progression:** selecting the optimal treatment strategy to effectively target the cancer[1,2]
    - **Understand and manage isolated liver disease risk:** identifying the patient's hepatic substrate hazard, regardless of their cancer therapy, and ensuring comprehensive care[2]



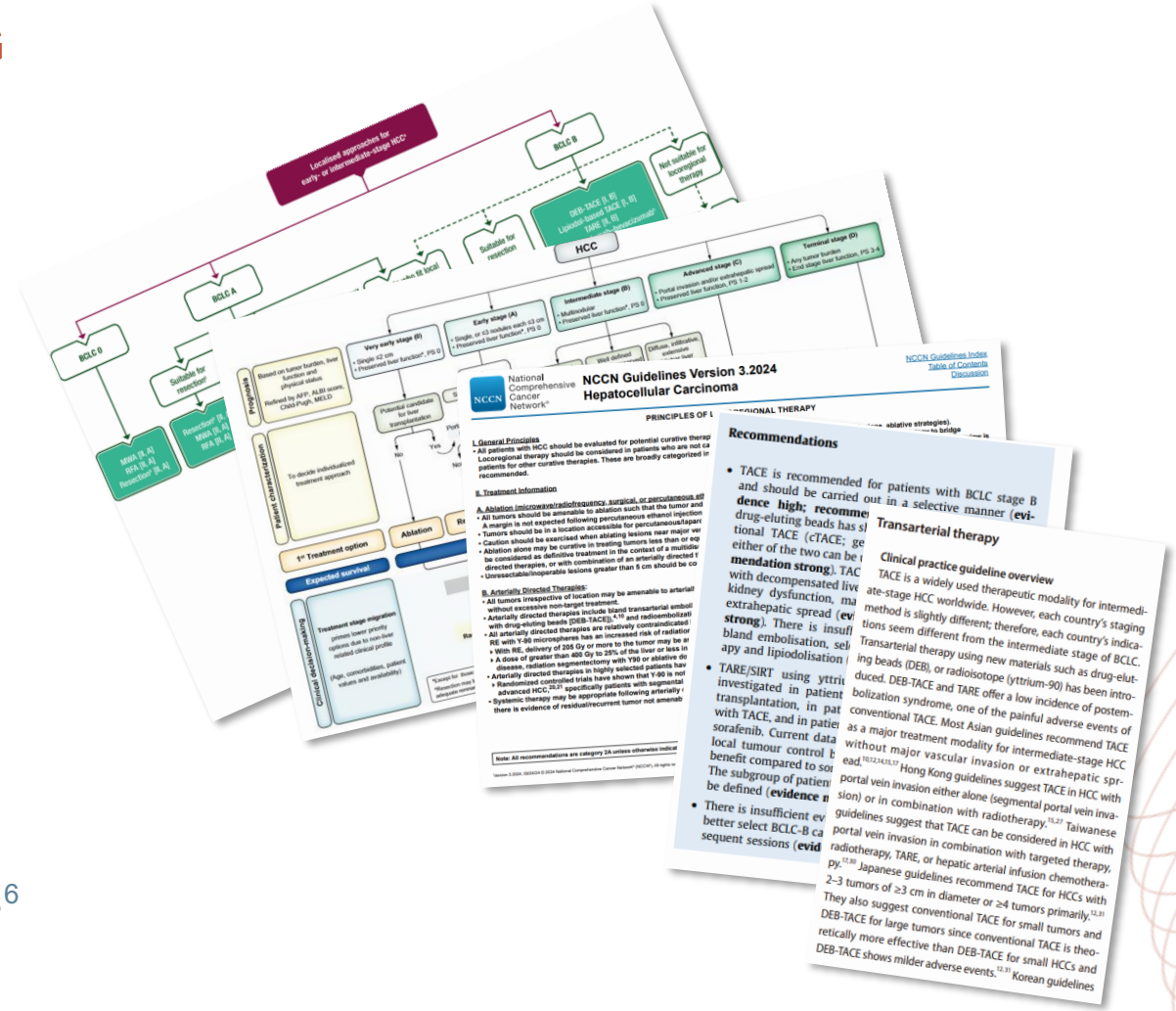
HCC, hepatocellular carcinoma

1. Devcic Z, et al. Semin Intervent Radiol. 2019;36:287-297; 2. Lurje I, et al. Int J Mol Sci. 2019;20:1465

HCC GUIDELINES

OVERVIEW FOR FURTHER READING

- BCLC guidelines[1]
  - More information HERE
- NCCN guidelines[2]
  - More information HERE
- AASLD Practice Guidance[3]
  - More information HERE
- ESMO Clinical Practice Guidelines[4]
  - More information HERE
- EASL Clinical Practice Guidelines[5,a]
  - More information HERE
- Overview of Asian Clinical Practice Guidelines[6]
  - More information HERE



[a] Guidelines need updating

AASLD, ;American Association for the Study of Liver Diseases; BCLC, Barcelona Clinic Liver Cancer (algorithm); EASL, European Association for the Study of the Liver; ESMO, European Society for Medical Oncology; HCC, hepatocellular carcinoma; NCCN, National Comprehensive Cancer Network

1. Reig M, et al. J Hepatol. 2022;76:681-693; 2. NCCN Clinical Practice Guidelines in Oncology. Hepatocellular Carcinoma (Version 4.2024). Available here (accessed January 2025); 3. Singal AG, et al. Hepatology. 2023;78:1922-1965; 4. Vogel A, et al. Ann Oncol. 2025 (article in press; https://doi.org/10.1016/j.annonc.2025.02.006); 5. EASL Guidelines. Management of hepatocellular carcinoma. Available here (accessed January 2025); 6. Cho Y, et al. Clin Mol Hepatol. 2023;29:252-262

STANDALONE THERAPIES FOR HCC

LRT AND IO-BASED SYSTEMIC THERAPIES

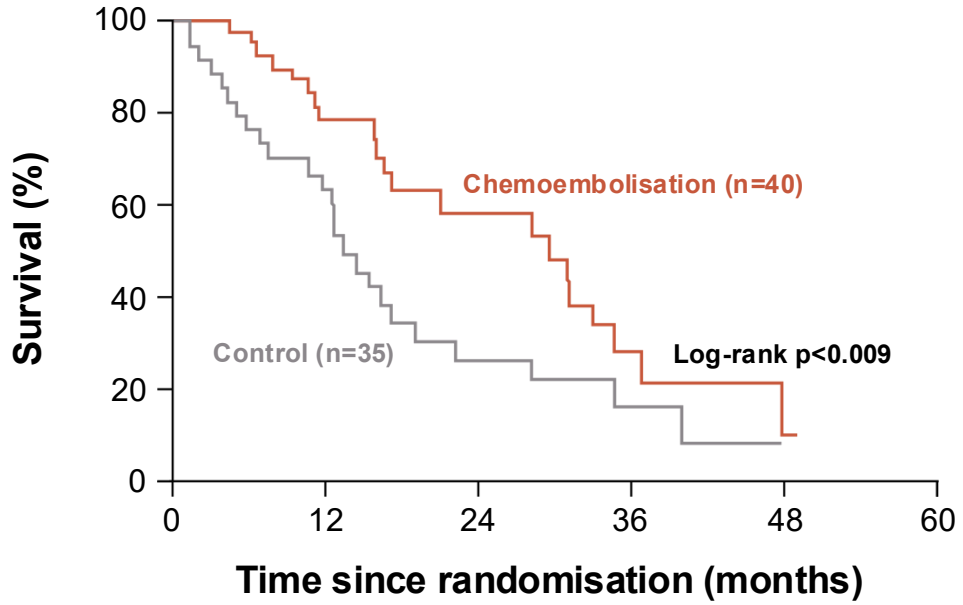
HCC; hepatocellular carcinoma; IO, immuno-oncology therapy; LRT, locoregional therapy

LOCOREGIONAL THERAPIES STANDALONE EVIDENCE

BENCHMARK STUDIES SUPPORTING TRANSARTERIAL CHEMOEMBOLISATION (TACE) AS STANDARD OF CARE

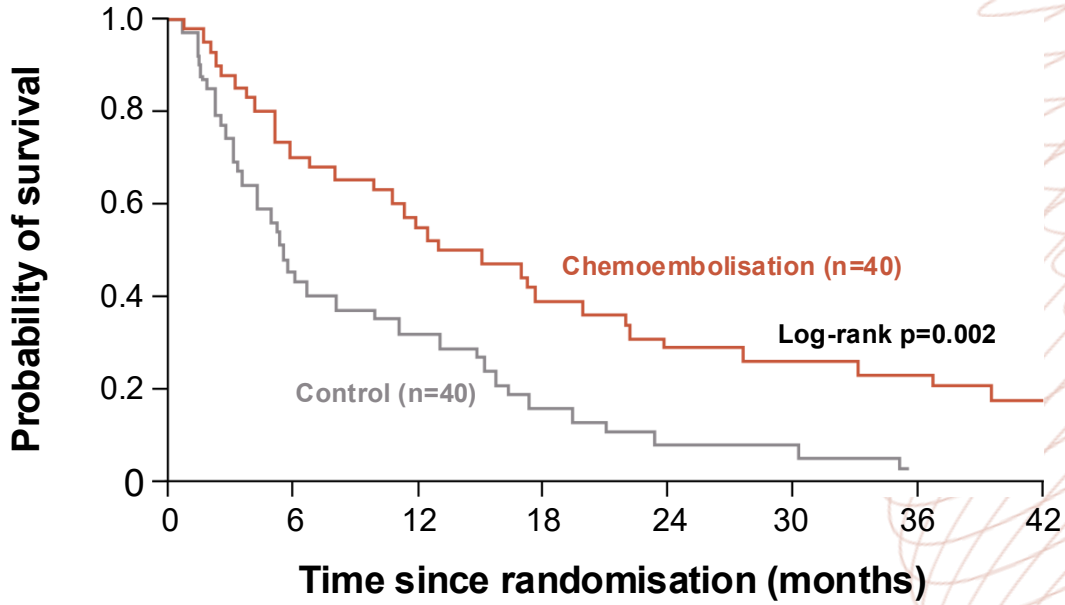
- Significant improvements in survival for patients with unresectable HCC

PROBABILITY OF SURVIVAL[1]



Patients at risk					
Chemoembolisation	40	29	14	4	2
Control	35	19	7	3	0

PROBABILITY OF SURVIVAL[2]



Patients at risk							
Chemoembolisation	40	29	22	16	12	10	10
Control	39	17	12	7	4	3	1

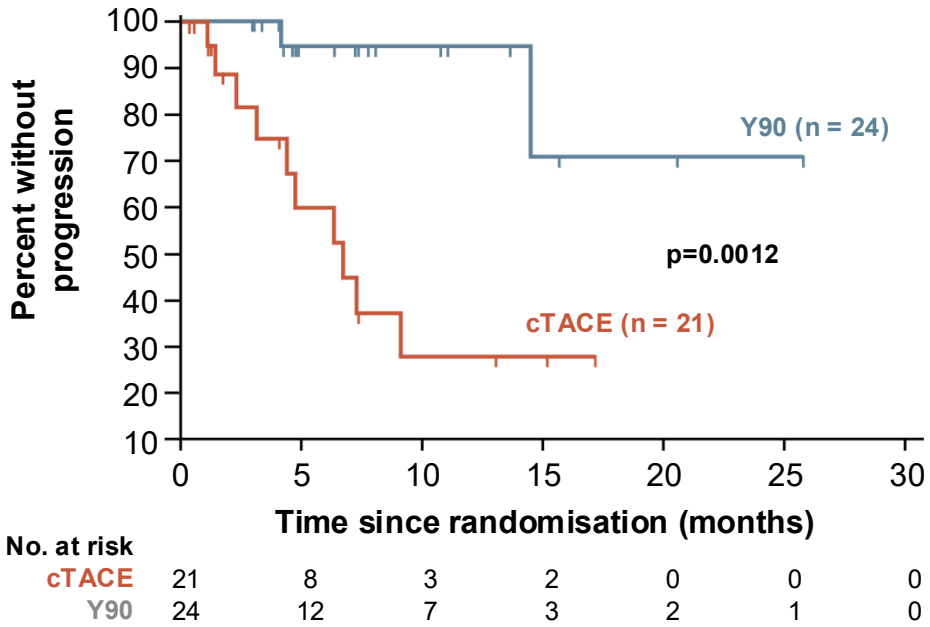
HCC, hepatocellular carcinoma;

1. Llovet JM, et al. Lancet. 2002;359:1734-1739; 2. Lo CM. Hepatology. 2002;35:1164-1171

LOCOREGIONAL THERAPIES: STANDALONE EVIDENCE

Y90 TRANSARTERIAL RADIOEMBOLISATION (TARE) COMPARED TO TACE

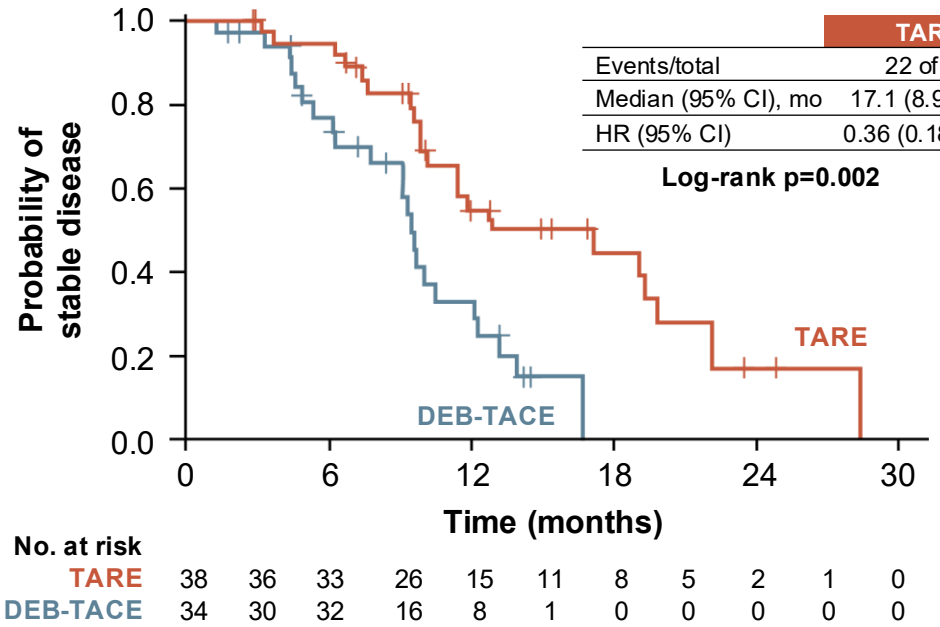
TTP IN INTENTION-TO-TREAT GROUP[1]



No. at risk							
cTACE	21	8	3	2	0	0	0
Y90	24	12	7	3	2	1	0

- Unilobar 67%, bilobar 33% (BCLC not reported)
- Y90 prolongs TTP when compared with cTACE for early intermediate stage HCC

TTP IN INTENTION-TO-TREAT GROUP[2]



	TARE	DEB-TACE
Events/total	22 of 38	23 of 34
Median (95% CI), mo	17.1 (8.9-25.4)	9.5 (8.8-10.2)
HR (95% CI)	0.36 (0.18-0.70)	Reference

No. at risk											
TARE	38	36	33	26	15	11	8	5	2	1	0
DEB-TACE	34	30	32	16	8	1	0	0	0	0	0

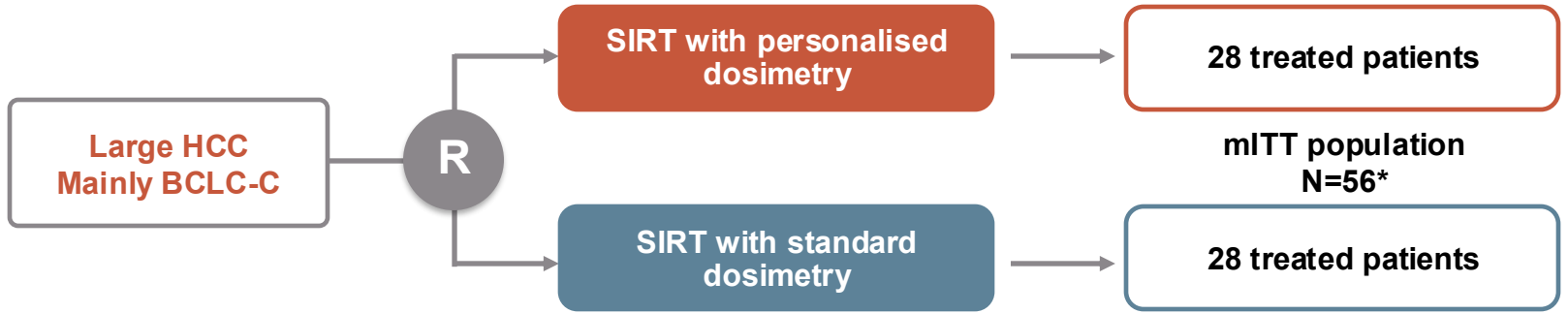
- BCLC A 18%, unilobar 50%, bilobar 50%
- Median TTP was 17.1 mo for TARE vs 9.5 mo for DEB-TACE (HR, 0.36; 95% CI: 0.18, 0.70; p=0.002)
- Median overall survival was 30.2 mo after TARE and 15.6 mo after DEB-TACE (HR, 0.48; 95% CI: 0.28, 0.82; p=0.006)

CI, confidence interval; cTACE, conventional TACE; DEB-TACE; drug-eluting bead TACE; HCC, hepatocellular carcinoma; HR, hazard ratio; mo, months; OS, overall survival; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation; TTP, time to overall tumour progression; Y90, yttrium 90

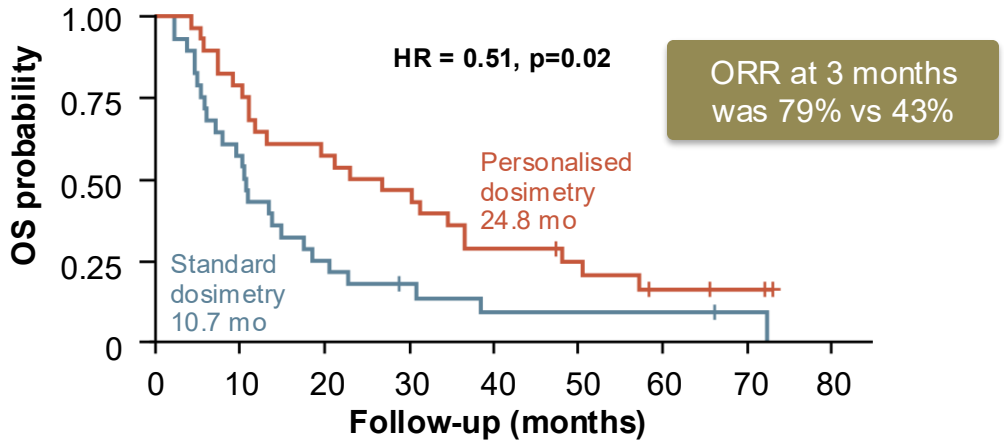
1. Salem R, et al. Gastroenterology. 2016;151:1155-1163.e2; 2. Dhondt E, et al. Radiology. 2022;303:699-710

LOCOREGIONAL THERAPIES: STANDALONE EVIDENCE

TARE FOR ADVANCED HCC – DOSISPHERE-01 PHASE 2



MEDIAN OVERALL SURVIVAL



ORR at 3 months was 79% vs 43%

OVERALL SURVIVAL RATES

OS rate (%)	2 years	3 years	5 years
Personalised vs. standard dosimetry	50.0 vs. 17.8	35.7 vs. 13.3	16.4 vs. 8.9
Tumour dose ≥205 Gy vs. <205 Gy	48.5 vs. 13.3	35.7 vs. 13.3	18.3 vs. 6.7
Resected vs. not resected	81.8 vs. 22.2	63.6 vs. 15.0	**53.0** vs. 2.5

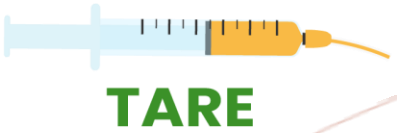
Patients with advanced HCC treated with personalized TARE dosimetry have a median OS of 24.8 months and half of them are alive at 5 years if downstaged to resection

BCLC-C, Barcelona Clinic Liver Cancer Stage C; HCC, hepatocellular carcinoma; HR, hazard ratio; mITT, modified intent-to-treat population; mo, months; OS, overall survival; ORR, objective response rate; **The study was designed for 254 patients, and stopped preliminary due to a predetermined efficacy criterion*

Garin E, et al. J Nucl Med. 2024;65:264-269

LOCOREGIONAL THERAPIES IN INTERMEDIATE HCC

SUMMARY: ACHIEVED RESULTS FOR TACE AND TARE (Y90)



- **TACE (Transarterial Chemoembolisation):**
  - Historically, TACE has been the standard of care for unresectable HCC[1,2]
  - It offers a favourable response rate and is generally well-tolerated[3] but has limitations, including a shorter time to progression[4] and a lack of the ablative capability seen with TARE[5]
  - While it has the most supporting evidence, TACE usage is declining,[6] especially in the USA, where TARE and systemic therapies are increasingly favoured[7-9]
- **TARE (Transarterial Radioembolisation):**
  - TARE is frequently used for patients with more localised disease (BCLC stage A)[10,11] and as an ablative treatment for larger tumours or those with macrovascular invasion[12,13]
  - In the USA, TARE is now the most common bridging therapy for liver transplant candidates[9]
  - Its use in combination with IO regimens shows promise and is being investigated with multiple ongoing trials[14,15]
  - TARE may have a unique mechanism of action by modulating the immune microenvironment,[16] distinct from TACE
  - TARE can induce liver remnant hypertrophy and enable resection[17]

BCLC-A, Barcelona Clinic Liver Cancer Stage A; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation; USA, United States of America; Y90, yttrium 90

1. Gao H, et al. BMJ Support Palliat Care. 2023;14(e2):e003870; 2. ASCO Daily News. EMERALD-1 Trial Shows PFS Benefit With Addition of Durvalumab/Bevacizumab to TACE in Unresectable, Embolization-Eligible HCC. Available here (accessed January 2025); 3. Kotsifa E, et al. J Pers Med. 2022;12:436; 4. Brown AM, et al. Cancer Med. 2023;12:2590-2599; 5. Young S and Golzarian J. AJR Am J Roentgenol. 2020;215:223-234; 6. Pelizzaro F, et al. Fron Oncol. 2022;12:822507; 7. Ahn JC, et al. J Nucl Med. 2021;62:1692-1701; 8. Coffman-D'Annibale K, et al. Carcinogenesis. 2023;44:537-548; 9. Expert input; 10. Badar W, et al. Oncologist. 2024;29:117-122; 11. Guiu B, et al. Cardiovasc Intervent Radio. 2022;45:1599-1607; 12. Kim J, et al. J Nucl Med. 2022;63:1215-1222; 13. Garin E, et al. J Nucl Med. 2024;65:264-269; 14. Clinicaltrials.gov: NCT03040099 15. ClinicalTrials.gov: NCT05063565;16. Chew V, et al. Gut. 2019;68:335-346; 17. Entezari, P., RadioGraphics. 2022;42:2166-2183;

LRT VS SYSTEMIC TREATMENT STUDIES

REASONS WHY WE SEE MORE PHASE 3 STUDIES FOR SYSTEMIC TREATMENTS

- Randomising patients to a procedural arm versus a non-procedural arm raises ethical concerns when Phase 2 results show efficacy and safety of the procedure
- Local treatments require resources and expertise that may not be available in all centres
- Perceived lack of standardisation in LRT
- Funding for LRT studies can be limited
- Post-progression options confound OS analyses for earlier-stage disease treatments
- Not all patients who are candidates for local therapy are referred for treatment
- Systemic therapy trials are often designed for later-stage disease and enrol quickly
- LRT studies can take a long time to enrol in which there may be a change in SoC at the time of completion
- Similarly, there are limited Phase 3 data for surgical studies

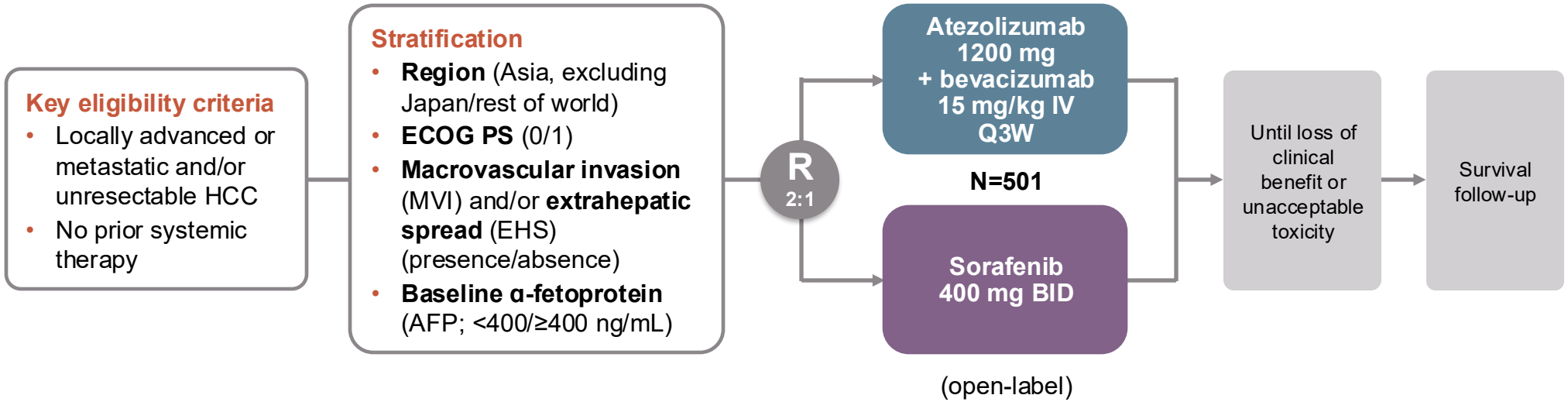
Getting data for locoregional therapies is not the same as getting data for systemic treatments

Expert input

BCLC, Barcelona Clinic Liver Cancer (algorithm); OS, overall survival; LRT, locoregional therapy; SoC, standard of care

ATEZOLIZUMAB + BEVACIZUMAB (IMbrave150)

STUDY DESIGN



Primary endpoints

- OS
- IRF-assessed PFS per RECIST 1.1

Secondary efficacy endpoints

- IRF-assessed ORR and DoR per RECIST 1.1
- IRF-assessed ORR and DoR per HCC mRECIST

BID, twice daily; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IO, immuno-oncology; IRF, independent review facility; IV, intravenous; (m)RECIST, (modified) Response Evaluation Criteria in Solid Tumours; Q3W, every 3 weeks; R, randomisation; ORR, objective response rate; OS, overall survival

Finn RS, et al. N Engl J Med. 2020;382:1894-1905;

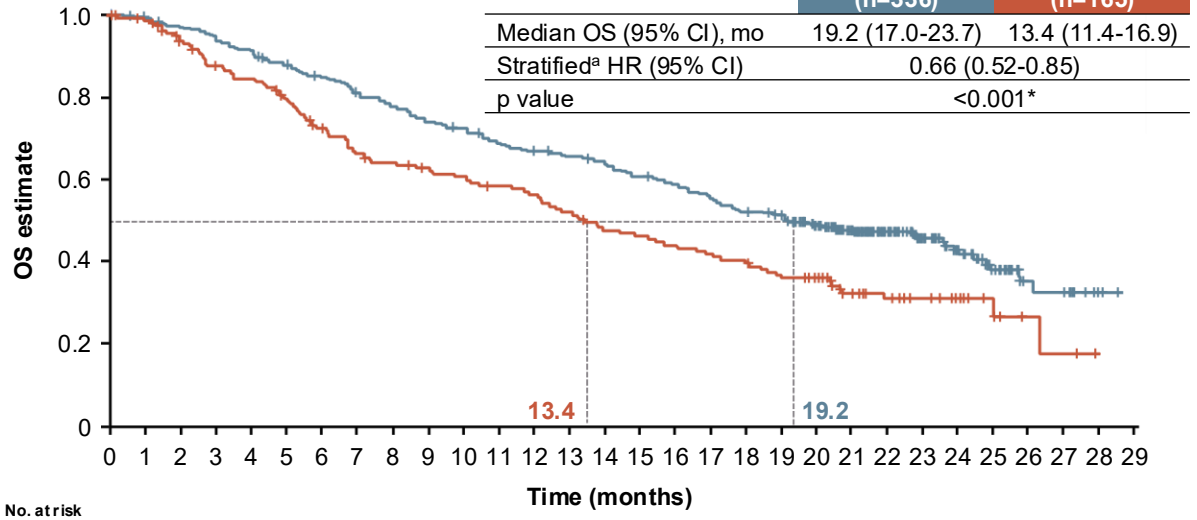
ATEZOLIZUMAB + BEVACIZUMAB (IMbrave150)

RESULTS: OS AND PFS BENEFIT VERSUS SORAFENIB (UPDATED)

- With additional 12 months of follow-up, atezolizumab + bevacizumab continued to demonstrate a consistent clinically meaningful treatment benefit vs sorafenib

OVERALL SURVIVAL

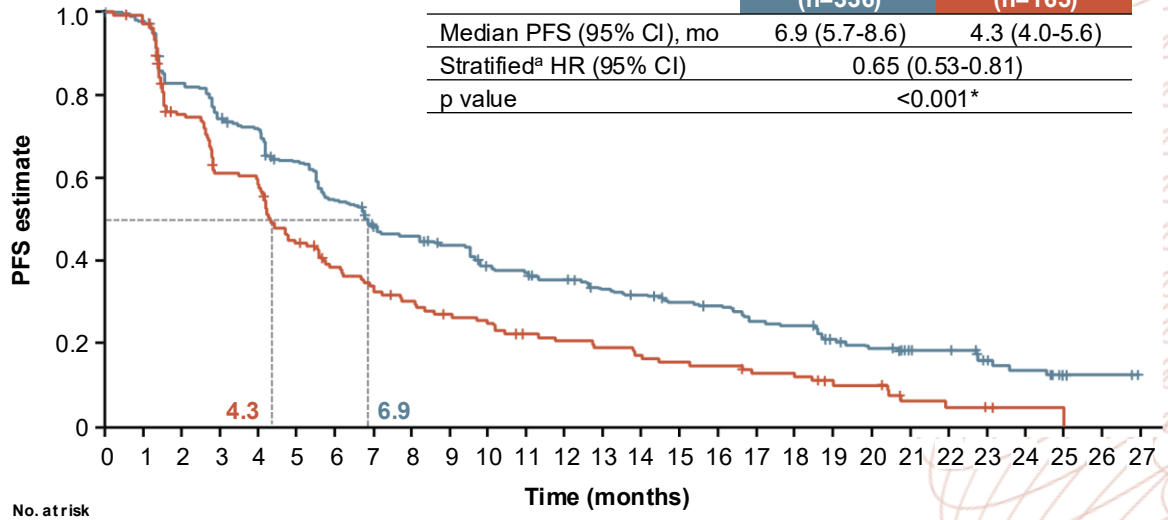
	Atezo + bev (n=336)	Sorafenib (n=165)
Median OS (95% CI), mo	19.2 (17.0-23.7)	13.4 (11.4-16.9)
Stratified[a] HR (95% CI)	0.66 (0.52-0.85)	
p value	<0.001*	



No. at risk (censored)																
Atezo + bev	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)

PROGRESSION FREE SURVIVAL

	Atezo + bev (n=336)	Sorafenib (n=165)
Median PFS (95% CI), mo	6.9 (5.7-8.6)	4.3 (4.0-5.6)
Stratified[a] HR (95% CI)	0.65 (0.53-0.81)	
p value	<0.001*	



No. at risk (censored)																
Atezo + bev	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)		

[a] Stratification factors included are geographic region (Asia excluding Japan vs RoW), AFP level (<400 ng/mL vs ≥400 ng/mL) at baseline, and MVI and/or EHS (yes vs no) per IxRS;
* p value for descriptive purposes only
atezo, atezolizumab; AFP, alpha fetoprotein; bev, bevacizumab; CI, confidence interval; EHS, extrahepatic spread; HR, hazard ratio; IO, immuno-oncology; IxRS, interactive voice/web response system; mo, months; MVI, macrovascular invasion; PFS, progression free survival; OS, overal survival; RoW, rest of world;
Cheng A-L, et al. J Hepatol. 2022;76:862-873

ATEZOLIZUMAB + BEVACIZUMAB (IMbrave150)

SUMMARY

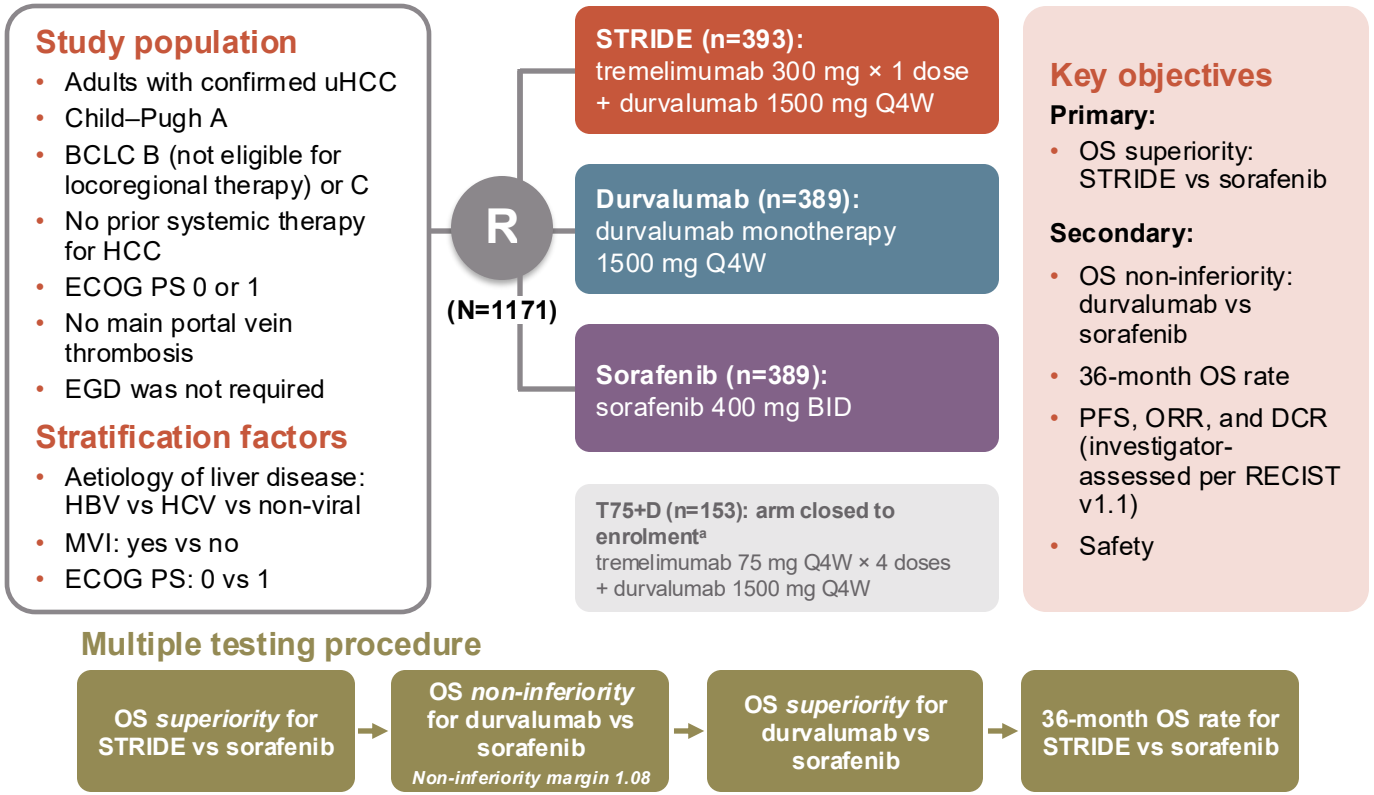
- Atezolizumab + bevacizumab continued to demonstrate a consistent **clinically meaningful treatment benefit** vs sorafenib at 12 months additional follow-up
- The safety and tolerability of atezolizumab + bevacizumab remains consistent with the known safety profiles of each individual drug and the underlying disease
- The combination is the **standard of care** for previously untreated, unresectable HCC

HCC, hepatocellular carcinoma; IO, immuno-oncology

Finn RS, et al. N Engl J Med. 2020;382:1894-1905; Cheng A-L, et al. J Hepatol. 2022;76:862-873

DURVALUMAB + TREMELIMUMAB (HIMALAYA)

STUDY DESIGN



Treatment continued until unacceptable toxicity, or any discontinuation criteria were met. Participants with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria in the setting of progressive disease could continue treatment

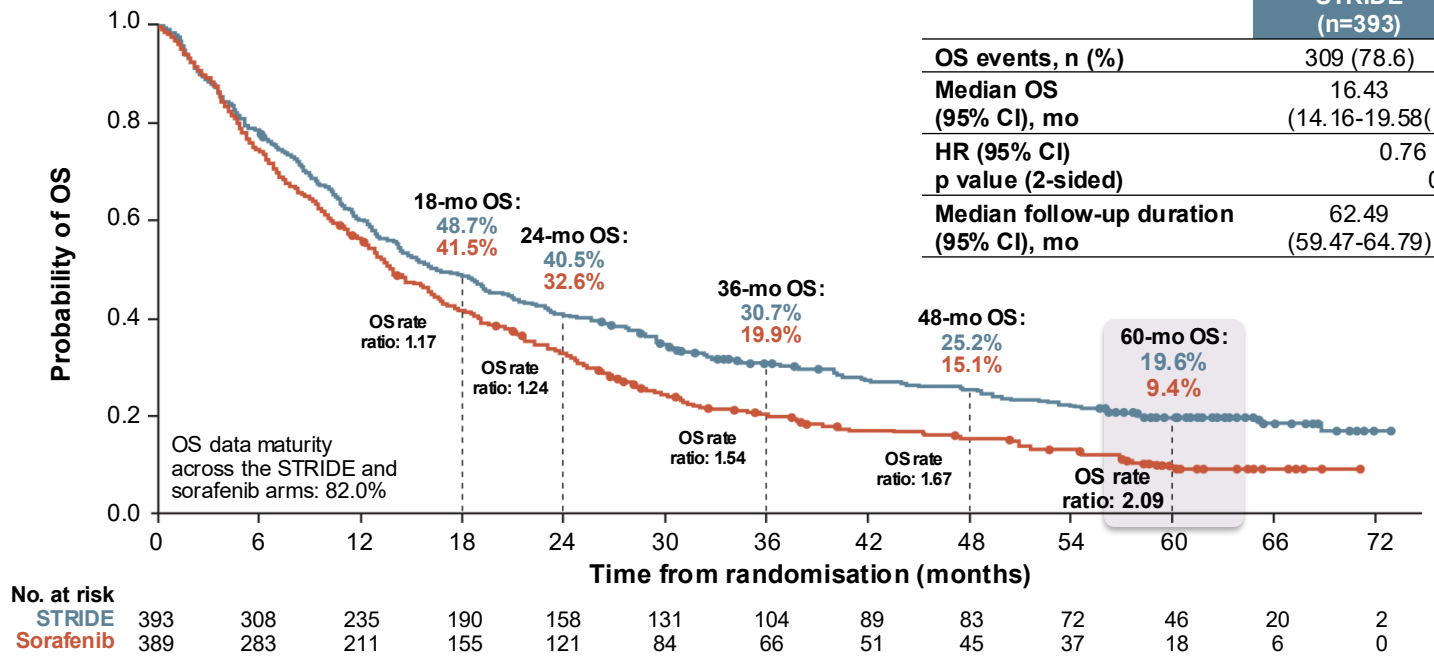
[a] The T75+D arm (75 mg of tremelimumab Q4W for four doses plus 1500 mg of durvalumab Q4W) was closed following a preplanned analysis of a Phase 2 study. Participants randomised to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation

BCLC-B/C, Barcelona Clinic Liver Cancer Stage B/C; BID, twice daily; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EGD, esophagogastroduodenoscopy; HBV/HCV, hepatitis B/C virus; HCC, hepatocellular carcinoma; IO, immuno-oncology; MVI, macrovascular invasion; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q4W, every 4 weeks; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; STRIDE, single tremelimumab regular interval durvalumab; uHCC, unresectable HCC

Abou-Alfa GK, et al. NEJM Evid. 2022;1:EVIDoa2100070; Rimassa L, et al. ESMO 2024. Abstract #947MO

DURVALUMAB + TREMELIMUMAB (HIMALAYA)

RESULTS: STRIDE DEMONSTRATED A SUSTAINED OS BENEFIT AT 5 YEARS



	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) p value (2-sided)	0.76 (0.65-0.89) 0.0008	
Median follow-up duration (95% CI), mo	62.49 (59.47-64.79)	59.86 (58.32-61.54)

- There were no additional serious safety events
- OS benefit with STRIDE was enhanced in participants experiencing disease control (OS rates of 28.7% for STRIDE vs 12.7 for sorafenib at 5 years)

OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment aetiology, ECOG PS, and MVI. Updated analysis data cutoff: March 1, 2024

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IO, immuno-oncology; mo, months; MVI, macrovascular invasion; OS, overall survival; STRIDE, single tremelimumab regular interval durvalumab

Rimassa L, et al. ESMO 2024. Abstract #947MO. Oral presentation

DURVALUMAB + TREMELIMUMAB (HIMALAYA)

SUMMARY

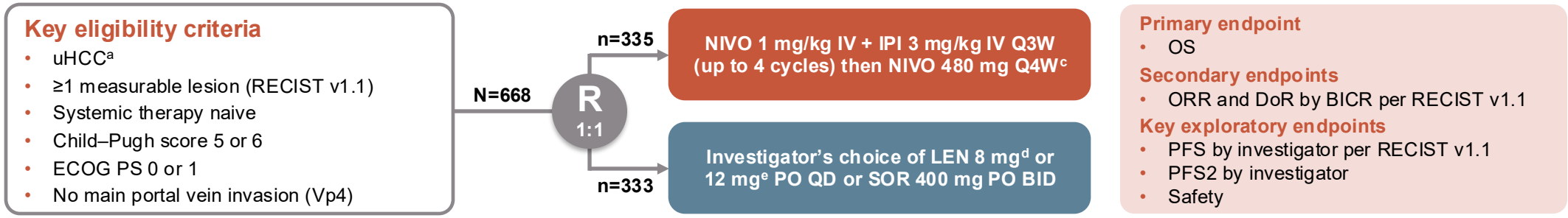
- STRIDE demonstrated an **unprecedented 5-year survival rate**
  - There were no additional serious treatment-related adverse events (TRAEs) in the extended follow-up
- The results set a new benchmark in uHCC, with **one in five patients alive** with **STRIDE** at 5 years

IO, immuno-oncology; STRIDE, single tremelimumab regular interval durvalumab

Rimassa L, et al. ESMO 2024. Abstract #947MO

NIVOLUMAB + IPILIMUMAB (CheckMate 9DW)

STUDY DESIGN



Stratification factors

- Aetiology (HBV vs HCV vs uninfected)[b]
- MVI/EHS (present vs absent)
- AFP (<400 vs ≥400 ng/mL)

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 or SOR:
275 (85%) received LEN and 50 (15%) received SOR

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

[a] Disease not eligible for, or progressive disease after, curative surgical and/or locoregional therapies; [b] Based on central lab serology results for stratification purpose; [c] Minimum of 1 dose of nivolumab + ipilimumab is required before proceeding to nivolumab monotherapy; [d] If body weight <60 kg; [e] If body weight ≥60 kg; [f] Time between randomisation date and cutoff date

AFP, alpha-fetoprotein; BICR, blinded independent central review; BID, twice daily; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HBV/HCV, hepatitis B/C virus; IO, immuno-oncology; IPI, ipilimumab; IV, intravenous; LEN, lenvatinib; MVI, macrovascular invasion; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second PFS; PO, oral; Q3W, every 3 weeks; Q4W, every 4 weeks; QD, once daily; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; SOR, sorafenib; uHCC, unresectable hepatocellular carcinoma; Vp, vascular portal (classification)

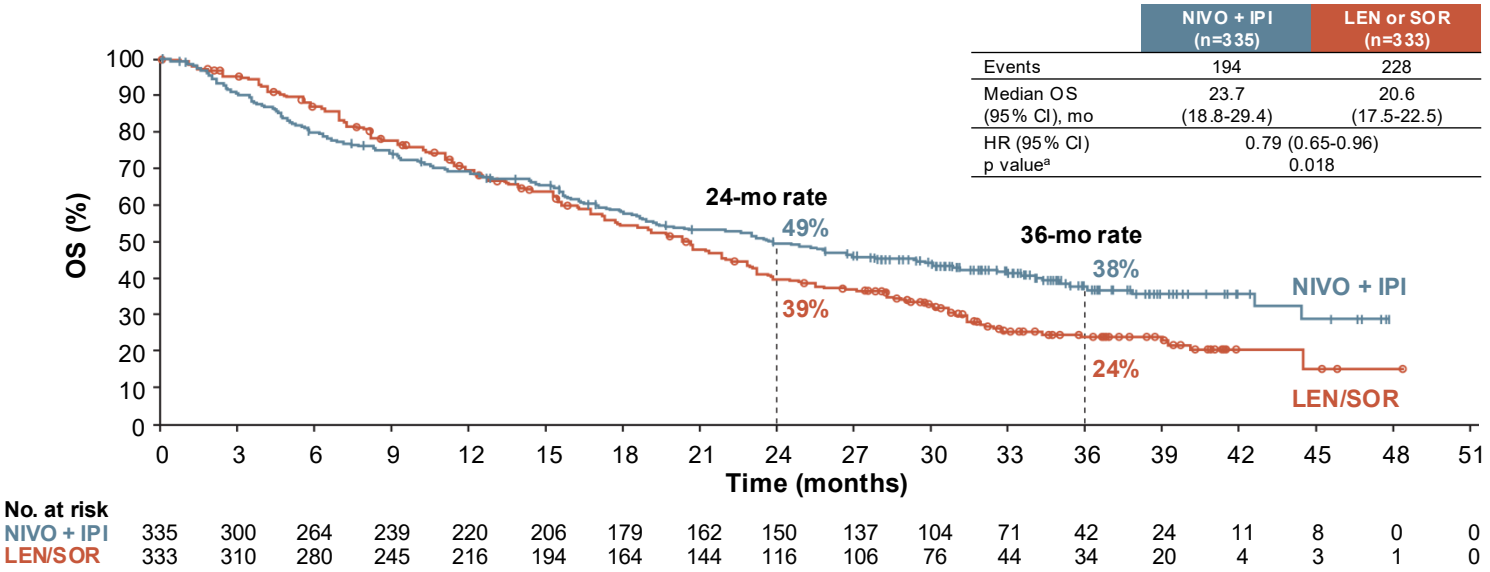
ClinicalTrials.gov: NCT04039607; Decaens T, et al. ESMO 2024. Abstract #965MO. Oral presentation

NIVOLUMAB + IPILIMUMAB (CheckMate 9DW)

RESULTS: PRIMARY ENDPOINT WAS MET

- There was a statistically significant and clinically meaningful OS benefit with nivolumab + ipilimumab versus lenvatinib or sorafenib

OS



TRAEs

All treated patients, n (%)	Nivolumab + ipilimumab (n=332)			Lenvatinib or sorafenib (n=325)		
	Any grade	Grade 3 or 4	Any grade leading to D/C	Any grade	Grade 3 or 4	Any grade leading to D/C
Any TRAEs[b]	278 (84)	137 (41)	59 (18)	297 (91)	138 (42)	34 (10)
Treatment-related hepatic events						
Hepatobiliary disorders	44 (13)	35 (11)	15 (5)	15 (5)	10 (3)	4 (1)
Hepatobiliary investigations[c]						
AST increased	65 (20)	20 (6)	4 (1)	27 (8)	2 (<1)	1 (<1)
ALT increased	63 (19)	16 (5)	3 (<1)	19 (6)	3 (<1)	0
Bilirubin increased	14 (4)	1 (<1)	1 (<1)	23 (7)	5 (2)	1 (<1)
Treatment-related deaths[d]	12 (4)[e]			3 (<1)[f]		

Median OS is estimated using Kaplan–Meier methodology. HR and 95% CI from stratified Cox proportional hazards model. HR is nivolumab + ipilimumab over lenvatinib or sorafenib. Symbols represent censored observations

[a] Two-sided p value from stratified log-rank test. Boundary for statistical significance: p≤0.0257; [b] Includes events reported between first dose and 30 days after the last dose of study therapy; [c] Reported in ≥5% of patients; [d] Treatment-related deaths were reported irrespective of timeframe; [e] TRAEs leading to death included immune-mediated hepatitis (n=4), hepatic failure (n=3), and hepatic insufficiency, decompensated cirrhosis, diarrhoea-colitis, autoimmune haemolytic anaemia, and dysautonomia (n=1 each). In the nivolumab + ipilimumab arm, 2 patients with hepatic-related causes of death died at least 90 days after the last dose of study treatment. Furthermore, disease progression per BICR was confirmed in 1 patient (with hepatic failure as cause of death) and was suspected by imaging test in 3 additional patients (2 with immune-mediated hepatitis as cause of death and one with hepatic cirrhosis as cause of death); [f] TRAEs leading to death included hepatorenal syndrome, ischaemic stroke, and acute kidney injury (n = 1 each)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BICR, blinded independent central review; CI, confidence interval; D/C, discontinuation; HR, hazard ratio; IO, immuno-oncology; IPI, ipilimumab; LEN, lenvatinib; NIVO, nivolumab; mo, months; OS, overall survival; SOR, sorafenib; TRAE, treatment-related adverse event

Decaens T, et al. ESMO 2024. Abstract #965MO. Oral presentation

NIVOLUMAB + IPILIMUMAB (CheckMate 9DW)

SUMMARY

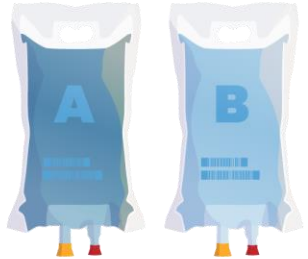
- Nivolumab + ipilimumab demonstrated statistically significant OS benefit versus lenvatinib or sorafenib, with higher ORR and durable responses, in patients with previously untreated uHCC[1]
- Safety was manageable and consistent with the established safety profile of the regimen
  - Most treatment-related hepatic events were grade 1 / 2 laboratory abnormalities
  - The majority of the immune-mediated adverse events were grade 1 / 2 and did not result in treatment discontinuation
- Results further **support nivolumab + ipilimumab as a 1st line treatment option** for patients with uHCC[2]

IO, immuno-oncology; OS, overall survival; ORR, objective response rate; OS, overall survival; uHCC, unresectable HCC

1. Decaens T, et al. ESMO 2024. Abstract #965MO. Oral presentation 2. Nivolumab Plus Ipilimumab Receives EC Approval for First-Line Unresectable HCC. Available here (accessed March 2025)

IO-BASED THERAPIES FOR UNRESECTABLE HCC

SUMMARY: ACHIEVED RESULTS FOR IO-BASED STANDALONE THERAPIES



IO-based combination

- Atezolizumab + bevacizumab is an IO-based combination approved for 1st line treatment for patients with unresectable HCC[1]
  - ORR 30%, mOS 19.2 months[2]
- Durvalumab + tremelimumab (STRIDE) is a dual IO combination approved for 1st line treatment for patients with unresectable HCC[3]
  - 20% survival rate at 5 years.[4]
  - Among the 5-year survival, some patients had stable disease while treated with the STRIDE regimen
- Nivolumab + ipilimumab is a dual IO combination and received EC approval for 1st line treatment for patients with unresectable HCC[6]
  - ORR 36%,[5] mOS 23.7 months[5], median duration of response >30 months[5]
- IO and IO-based therapies are generally well-tolerated and immune-related adverse events can be managed with steroids[3-5]

IO and IO-based combinations have revolutionised the systemic treatment of unresectable HCC

HCC, hepatocellular carcinoma; IO, immuno-oncology; mOS; median overall survival; ORR, objective response rate; STRIDE; Single Tremelimumab Regular Interval Durvalumab

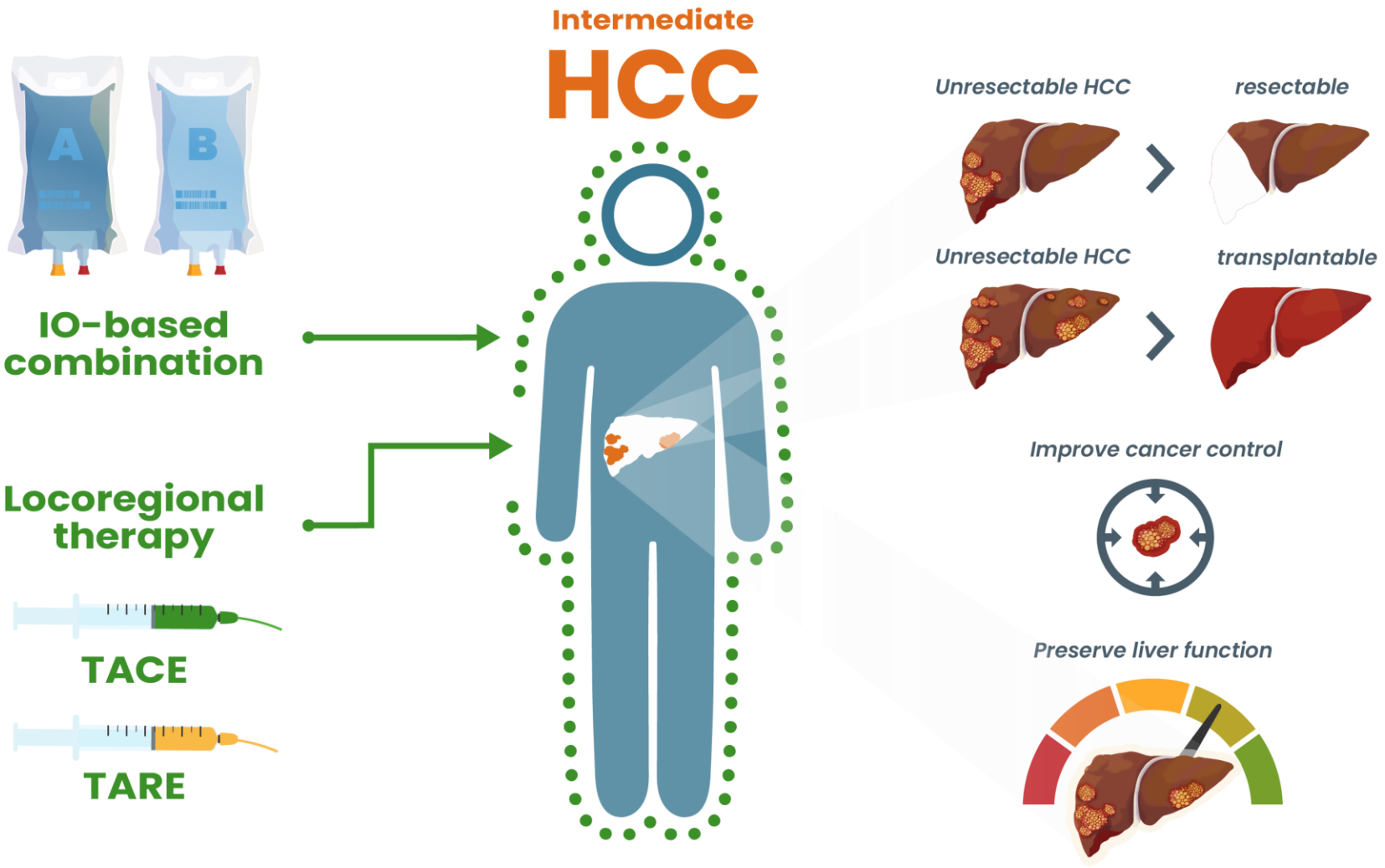
1. Jain A, et al. World J Hepatol. 2021;13:1132-1142; 2. Cheng A-L, et al. J Hepatol. 2022;76:862-873; 3. Fujii Y, et al. Oncology. 2024. doi: 10.1159/000542517 (Online ahead of print); 4. Rimassa L, et al. ESMO 2024. Abstract #947MO. Oral presentation; 5. Decaens T, et al. ESMO 2024. Abstract #965MO. Oral presentation; 6. Nivolumab Plus Ipilimumab Receives EC Approval for First-Line Unresectable HCC. Available here (accessed March 2025)

THE EXPANDING ROLE OF IO-BASED COMBINATIONS IN INTERMEDIATE HCC

Exploring IO in combination with LRT

HCC, hepatocellular carcinoma; IO, immuno-oncology; LRT, locoregional therapy;

EXPLORING IO-BASED TREATMENTS COMBINED WITH LRT



HCC, hepatocellular carcinoma; IO, immuno-oncology; LRT, locoregional therapy; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation;

EXPLORING IO-BASED TREATMENTS COMBINED WITH LRT

STRENGTHS OF ONE THERAPY MITIGATE WEAKNESSES OF THE OTHER

Overview of the contemporary and potential use of Y90 and IO across the BCLC spectrum

Contemporary clinical use						
Y90-RE ICI +/– anti-VEGF						
	A – Early	**B – Intermediate**			**C – Advanced**	
BCLC Stage	**Solitary, 3 up to 3 cm**	**Extended transplant**	**Well-defined tumours**	**Infiltrative, bilobar**	**Vascular invasion**	**Extrahepatic metastasis**
Y90-RE limitations potentially addressed with ICI	Out of field progression			Narrow therapeutic index		
	Watershed regions					
			Complete tumour coverage			
			Microsatellite disease			
ICI limitations potentially addressed with Y-90-RE			Low response rates (<30%)			
			Tolerability and candidacy of full ICI regimens			
			Immunologically cold tumours and microenvironments			
Potential combination treatment strategies	High-risk biology: Y90-RE primary, ICI adjuvant	Y90-RE primary, ICI adjuvant	Y90-RE primary, ICI adjuvant	ICI primary, Y90-RE adjuvant	If Vp1-Vp2: Y90-RE primary, ICI adjuvant	ICI primary, Y90-RE adjuvant
Advantages of combination	Less malignant subclone selection, unaddressed microscopic disease, cancer vaccine?			Increase ORR, immune modulation, downstage to resection, FLR hypertrophy		
Disadvantages of combination	Need for ICI washout in peri-transplant setting, additional adverse event profile			Hepatic decompensation risk, limiting efficacy of ICIs		

The **combination of** locoregional therapies and IO-based treatments could improve local and systemic control of the disease

BCLC, Barcelona Clinic Liver Cancer (algorithm); FLR, future liver remnant; ICI, immune checkpoint inhibitor; IO, immuno-oncology; LRT, locoregional therapy; ORR, overall response rate; RE, radioembolisation; VEGF, vascular endothelial growth factor; Vp, vascular portal (classification); Y90, yttrium 90

Malone CD, et al. J Vasc Interv Radiol. 2024;S1051-0443(24)00718-8

EXPLORING IO-BASED TREATMENTS COMBINED WITH LRT IN HCC

SYNERGISTIC EFFECTS VS ADDITIVE EFFECTS

- **Synergy** refers to a therapy combination that is more efficacious than the sum of its individual parts
  - LRT can enhance the release of tumour antigens and modify the tumour immune microenvironment. This may synergise with IO to strengthen the anti-tumour immune response, which in turn improves local therapy outcomes
- **Additive** refers to a therapy combination that is efficacious up to the sum of its individual parts:
  - If a combination of locoregional and systemic treatment is used, it must generally demonstrate outcomes that surpass the results achieved in the individual trials of each approach
- A deep dive into tumour characteristics is needed for **proper patient selection** and **treatment design**
  - Identifying which patient presentation and tumour phenotypes benefit from the treatment intensification of combination IO and LRT is a critical next step for more universal adoption
  - There may be some patients who are interested in the potential benefit of combination prior to maturation of these data due to clinically observed durable effects in select cases

HCC, hepatocellular carcinoma; IO, immuno-oncology; LRT, locoregional therapy;
Malone CD, et al. J Vasc Interv Radiol. 2024;S1051-0443(24)00718-8; Expert input;

EXPLORING IO-BASED TREATMENTS COMBINED WITH LRT

WHAT WOULD BE THE MAIN TREATMENT MODALITY IN INTERMEDIATE HCC?

- Locoregional therapies as **primary therapy**:
  1. **Locoregional therapy** targets and optimises the definitive treatment of visible disease
  2. **IO-based treatment** addresses presumed invisible disease and enhances systemic antitumour immune response
- **Considerations**
  - Therapeutic goals:
    - **Downstaging / bridge to curative treatment** may favour locoregional therapy as the main treatment modality
    - **Systemic control** may favour IO-based therapy as the main treatment modality
  - Disease load:
    - **Earlier stages (intermediate) / limited amount of disease** may favour locoregional therapy first
    - **More extensive disease** may favour IO-based therapy first
  - Liver reserve:
    - Locoregional therapy is appropriate for good liver reserve
    - IO-based therapy can be considered when local therapy may cause liver dysfunction

- Efficacy of the combination of therapies is likely optimised when given in “relatively close proximity”
- There is insufficient evidence to declare one sequencing strategy universally better than others

HCC, hepatocellular carcinoma; IO, immuno-oncology; LRT, locoregional therapy

Williamson CW, et al. Cancer. 2021;127:1553-67 and expert input

IO-BASED TREATMENTS COMBINED WITH LRT

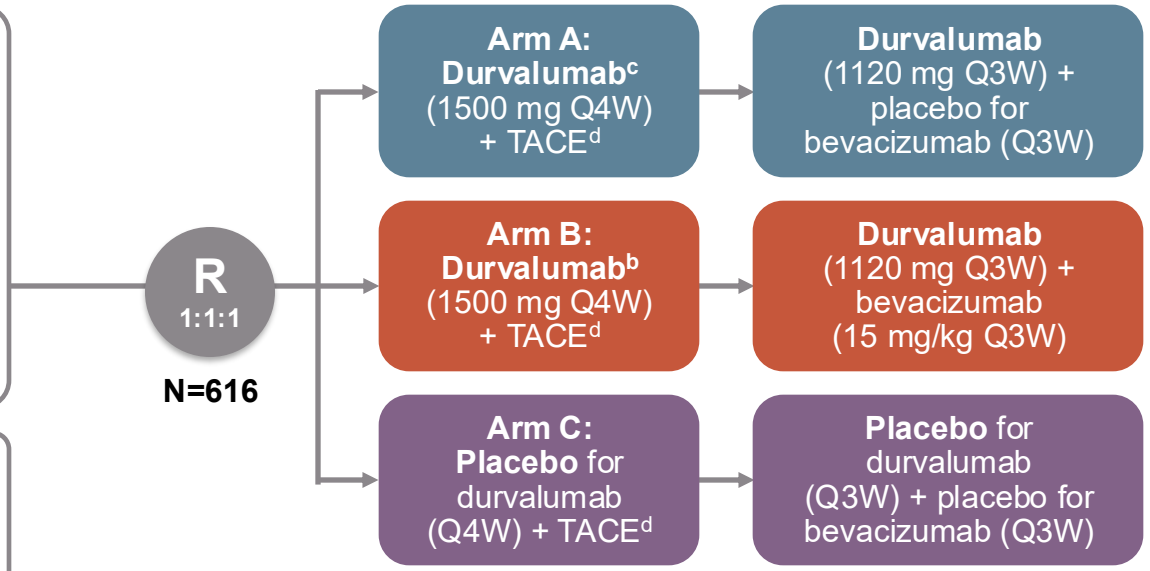
EMERALD-1: STUDY DESIGN

Study population[a]

- 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[b]

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)



Endpoints

Primary:

- PFS[e] for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary:

- PFS for Arm A vs Arm C
- OS
- QoL

Other secondary:

- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR and TTP using investigator and BICR per ***mRECIST***

[a] Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomisation; [b] 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; [c] Durvalumab/placebo started ≥7 days after TACE; [d] DEB-TACE or cTACE, Participants will receive up to 4 TACE procedures within the 16 weeks following Day 1 of their first TACE procedure; [e] 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 was used after the 12-week imaging

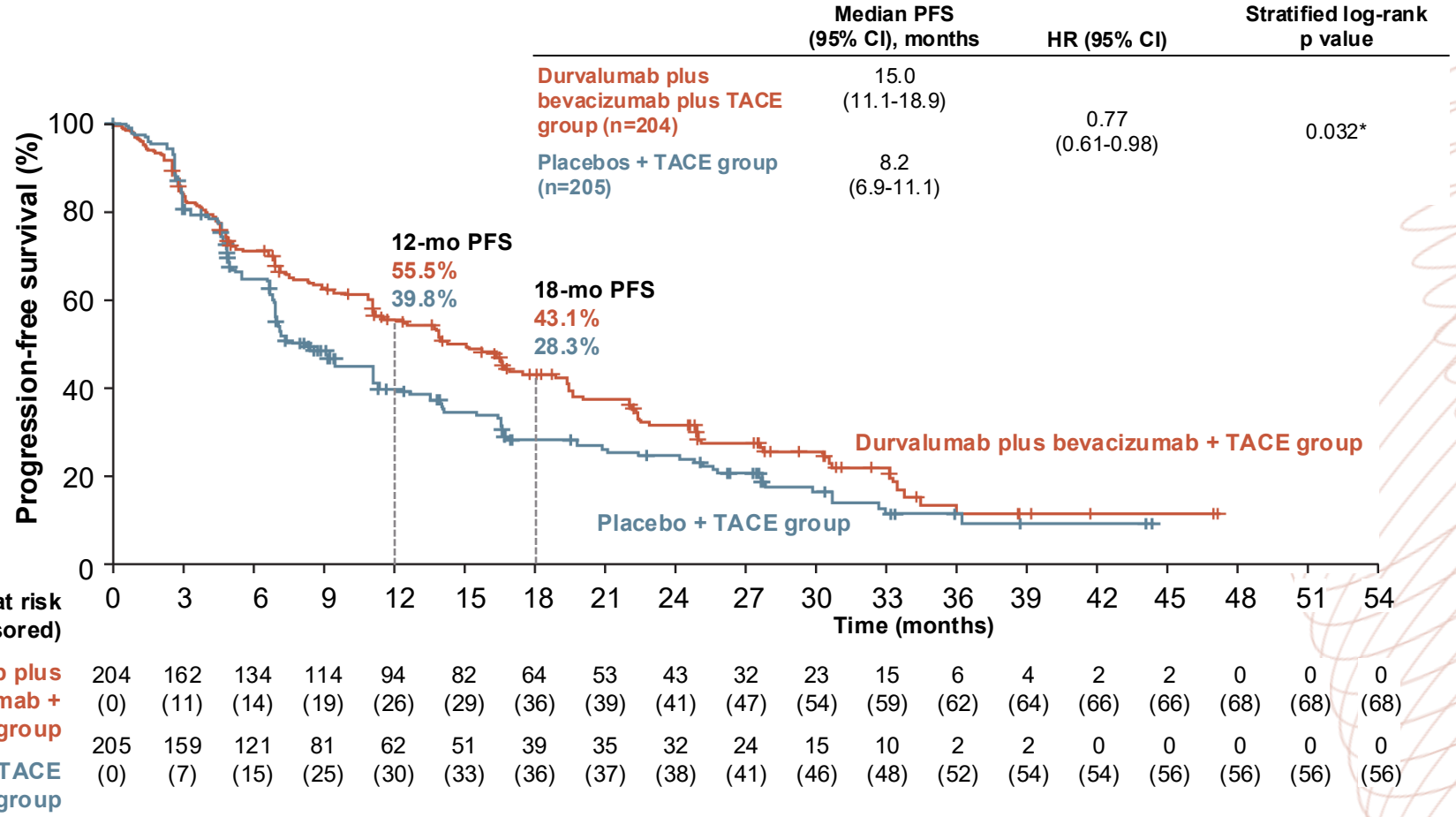
BICR, blinded independent central review, cTACE, conventional TACE; DEB-TACE, drug-eluting TACE; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IO, immuno-oncology; LRT, locoregional therapy; (m)RECIST, (modified) Response Evaluation Criteria in Solid Tumours; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W/Q4W, every 3/4 weeks; QoL, quality of life; R, randomisation; TACE, transarterial chemoembolisation; TAE, transarterial embolisation; TTP, time to progression; Vp, vascular portal (classification)

Lencioni R, et al. J Clin Oncol. 2024;42(3 suppl)LBA432. DOI:10.1200/JCO.2024.42.3_suppl.LBA432; Sangro B, et al. Lancet. 2025;405:216-232

IO-BASED TREATMENTS COMBINED WITH LRT

EMERALD-1: RESULTS – PRIMARY ENDPOINT WAS MET

- Median PFS was improved with durvalumab + bevacizumab + TACE versus placebos + TACE
- No new safety signals were identified
- Patients continue to be followed for OS



* Threshold of significance: 0.044

CI, confidence interval; HR, hazard ratio; LRT, locoregional; IO, immuno-oncology; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolisation

Sangro B, et al. Lancet. 2025;405:216-232

IO-BASED TREATMENTS COMBINED WITH LRT

EMERALD-1: SUMMARY

- EMERALD-1 met its primary endpoint:
  - Median PFS was 15.0 months with D+B+TACE and 8.2 months with placebo + TACE
  - PFS HR was 0.77, p=0.032
- PFS benefit with D+B+TACE was generally consistent across key clinical subgroups.
- The safety profile was manageable and consistent with the known safety profile of TACE, durvalumab and bevacizumab in unresectable HCC

Durvalumab + bevacizumab + TACE has the potential to set a new standard of care

B, bevacizumab; D, durvalumab; HCC, hepatocellular carcinoma; HR, hazard ratio; IO, immuno-oncology; LRT, locoregional therapy; PFS, progression-free survival; TACE, transarterial chemoembolisation

Sangro B, et al. Lancet. 2025;405:216-232

IO-BASED TREATMENTS COMBINED WITH LRT

LEAP-012 – BACKGROUND AND STUDY DESIGN[1,2]

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 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]

Endpoints

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

- Secondary: ORR,[c,d] DoR,[c,d] TTP,[c,d] PFS,[d] and safety

Stratification factors

- Study site
- AFP (≤400 ng/mL vs >400 ng/mL)
- ECOG PS (0 vs 1)
- Albumin-bilirubin grade (1 vs 2 or 3)
- Tumour burden score[1,a] (≤6 vs >6 but ≤12 vs >12)

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

AFP, alpha fetoprotein; BICR, blinded independent central review; BW, body weight; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IA1, interim analysis 1; IO, immuno-oncology; IV, intravenous; LRT, locoregional therapy; (m)RECIST, (modified) RECIST; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; Q6W, every 6 weeks; QD, once daily; R, randomised; TACE, transarterial chemoembolisation; TTP, time to progression

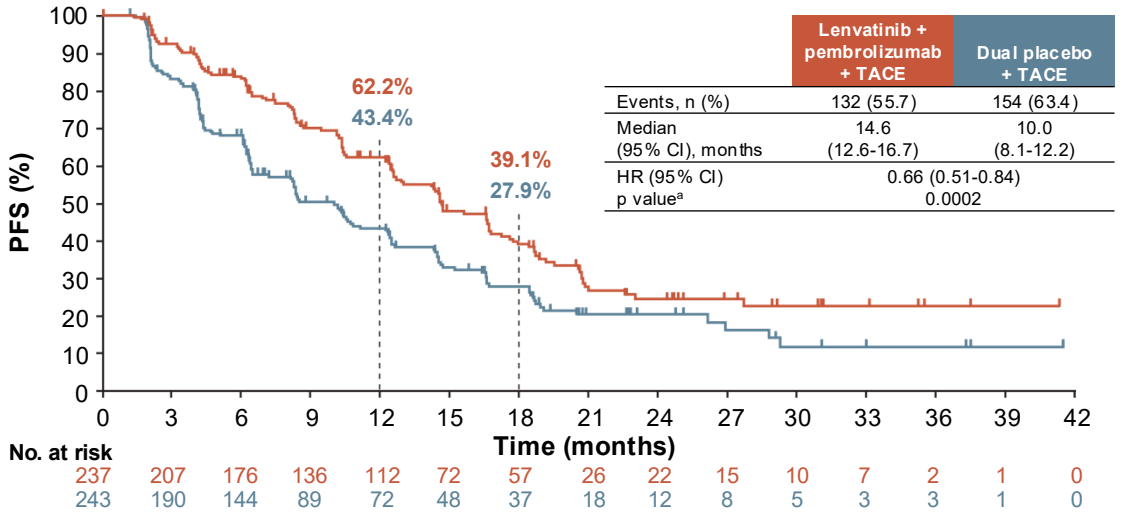
1. ClinicalTrials.gov: NCT04246177; 2. Wang Q, et al. J Hepatol. 2019;70:893-903; 3. Llovet J, et al. ESMO 2024. Abstract #LBA3. Oral presentation

IO-BASED TREATMENTS COMBINED WITH LRT

LEAP-012 – RESULTS: PRIMARY ENDPOINT IN PFS WAS MET

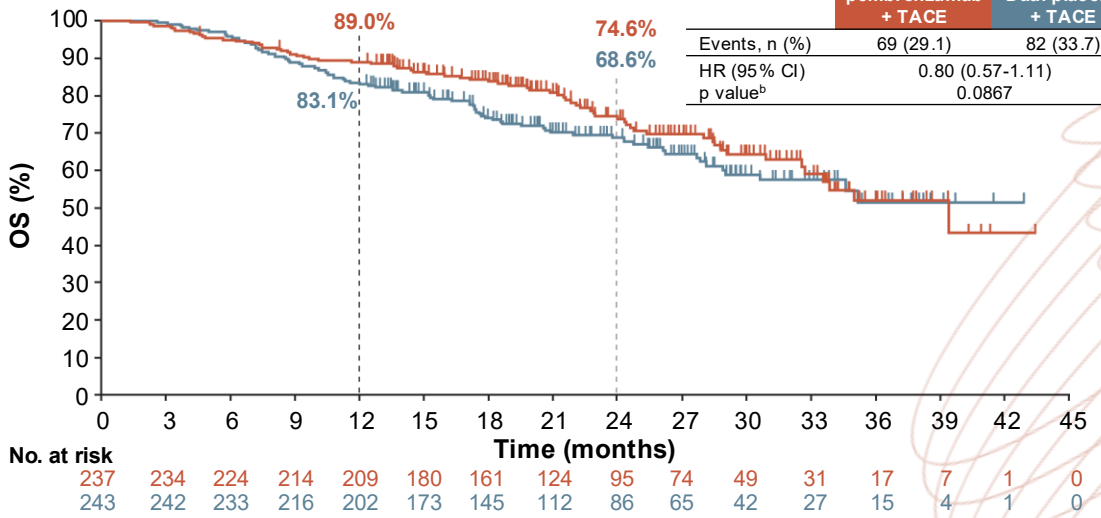
- There was a clinically meaningful and statistically significant improvement in PFS for patients with intermediate-stage HCC who received lenvatinib + pembrolizumab + TACE versus dual placebo + TACE

PFS PER RECIST V1.1 BY BICR



	Lenvatinib + pembrolizumab + TACE	Dual placebo + TACE
Events, n (%)	132 (55.7)	154 (63.4)
Median (95% CI), months	14.6 (12.6-16.7)	10.0 (8.1-12.2)
HR (95% CI)	0.66 (0.51-0.84)	
p value[a]	0.0002	

OS



	Lenvatinib + pembrolizumab + TACE	Dual placebo + TACE
Events, n (%)	69 (29.1)	82 (33.7)
HR (95% CI)	0.80 (0.57-1.11)	
p value[b]	0.0867	

- Although immature, a favourable OS trend was observed
- The safety profile of lenvatinib + pembrolizumab, in combination with TACE, was manageable and consistent with known safety profiles

Data cutoff date for IA1: January 30, 2024; [a] One-sided p value from re-randomisation test; threshold p=0.025; [b] One-sided p from re-randomisation test; threshold p=0.0012

BICR, blinded independent central review; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; IA1, interim analysis 1; IO, immuno-oncology; LRT, locoregional therapy; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; TACE, transarterial chemoembolisation

Llovet J, et al. ESMO 2024. Abstract #LBA3. Oral presentation; Kudo M, et al. Lancet. 2025;405:203-215

IO-BASED TREATMENTS COMBINED WITH LRT

LEAP-012 – SUMMARY

- LEAP-012 met its primary endpoint
  - **Lenvatinib + pembrolizumab + TACE** showed a statistically significant and clinically meaningful **improvement in PFS** versus double placebo + TACE in patients with intermediate-stage HCC
  - There was an **early trend toward improvement in OS** versus placebo + TACE in patients with intermediate-stage HCC
    - OS will be retested in future analyses
- The adverse event profile was consistent with known safety profiles of lenvatinib, pembrolizumab, and TACE
  - No new safety signals were identified

Lenvatinib + pembrolizumab + TACE may be accepted as a new standard of care in intermediate HCC

HCC, hepatocellular carcinoma; IO, immuno-oncology; LRT, locoregional therapy; OS, overall survival; PFS, progression free survival; TACE, transarterial chemoembolisation

Llovet J, et al. ESMO 2024. Abstract #LBA3. Oral presentation; Kudo M, et al. Lancet. 2025;405:203-215

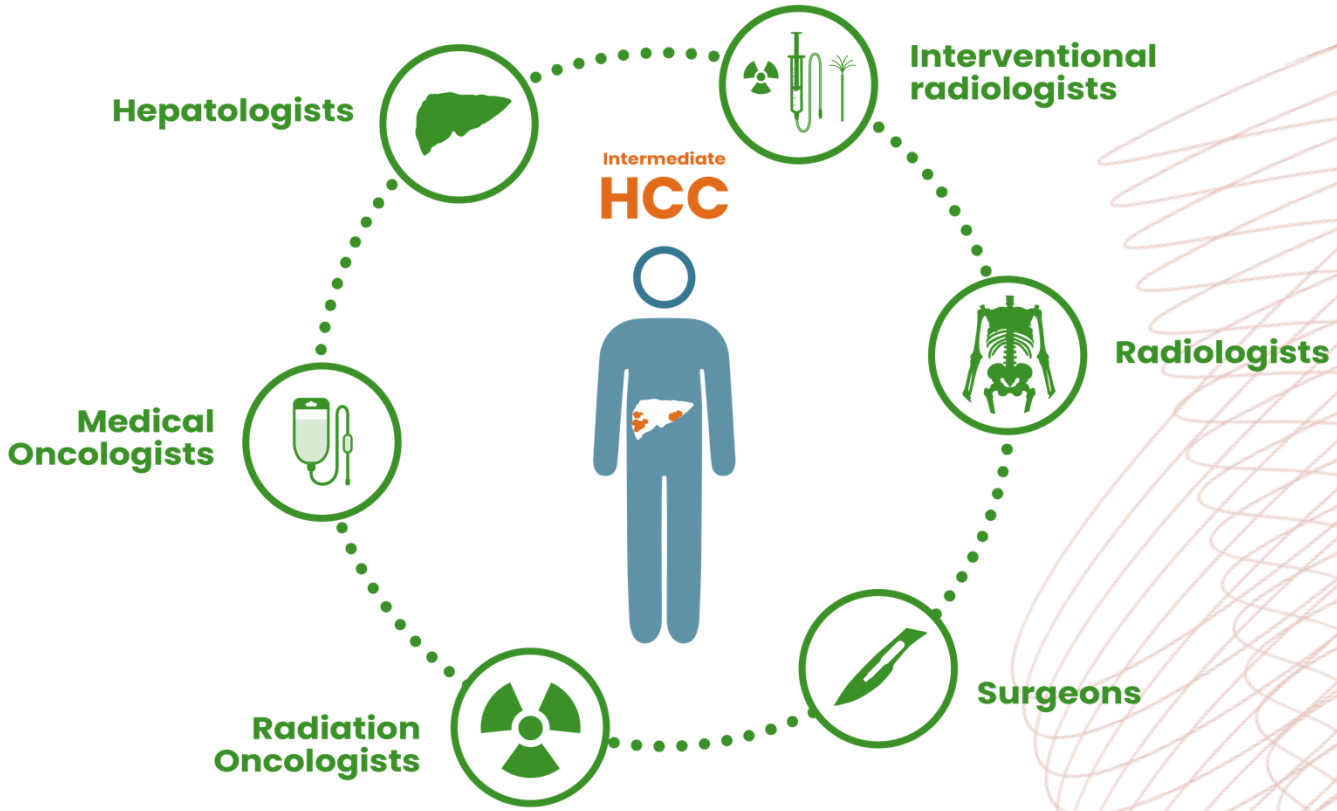
MDT AND MULTIMODAL TREATMENT IN HCC

HCC, hepatocellular carcinoma; MDT, multidisciplinary team

MULTIDISCIPLINARY TEAM APPROACH FOR HCC

CONSIDERATIONS AND BEST PRACTICES

- **HCC care is complex**, and requires liver care and HCC treatment, which makes nuanced specialist assessment crucial[1]
  - Programmatic, **multidisciplinary clinical practice,** through the course of treatment, is best[1]
- **MDT care is tailored to individual patient needs** and provides optimal outcomes[1]
  - Guidelines provide a foundation, but **cannot capture all patient nuances**[2]
  - Each specialty **optimises its role**, achieving more than a single specialist[1,3]
  - **Patient needs** must always remain the **top priority**[4]



HCC, hepatocellular carcinoma; MDT, multidisciplinary team

1. Oh JH and Sinn DH. J Liver Cancer. 2024;24:47-56; 2. Matsumoto MM, et al. Cardiovasc Intervent Radiol. 2021;44:1070-1080; 3. Naugler WE, et al. Clin Gastroenterol Hepatol. 2015;13:827-835; 4. Suddle A, et al. Gut. 2024;73:1235-1268

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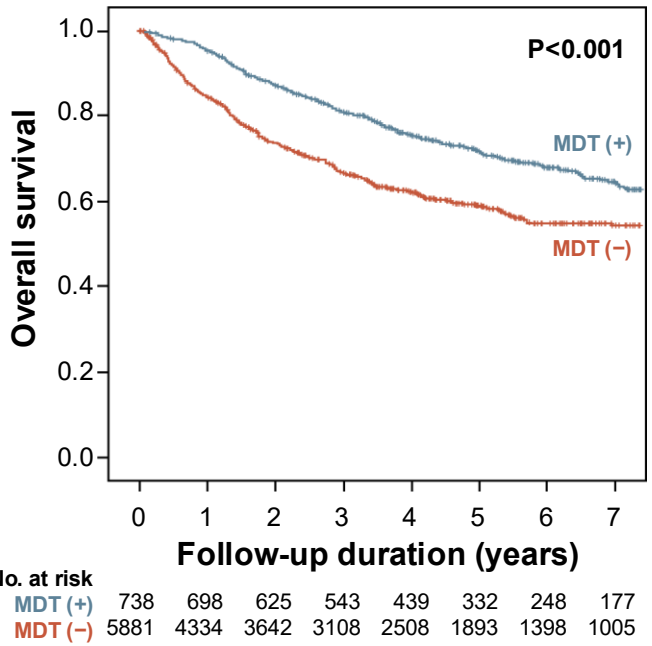
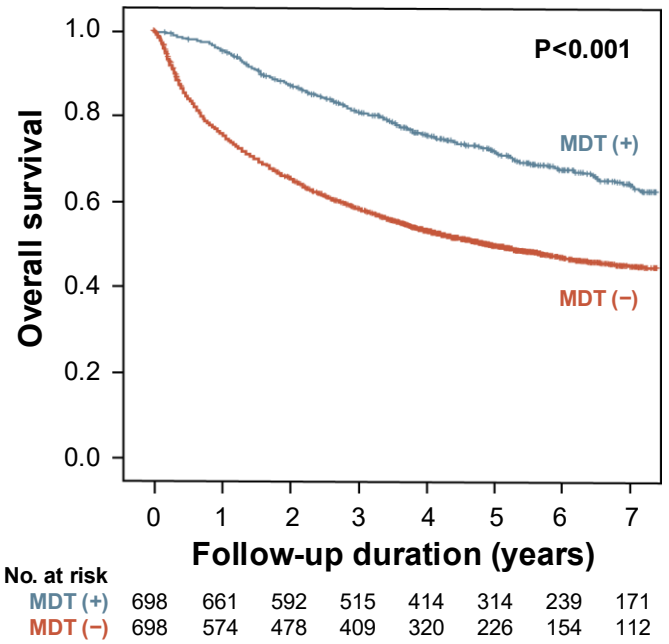
KEY TO OFFER OPTIMAL TREATMENT OPTIONS TO EACH PATIENT

OS entire cohort[1]



No. at risk								
MDT (+)	738	698	625	543	439	332	248	177
MDT (−)	5881	4334	3642	3108	2508	1893	1398	1005

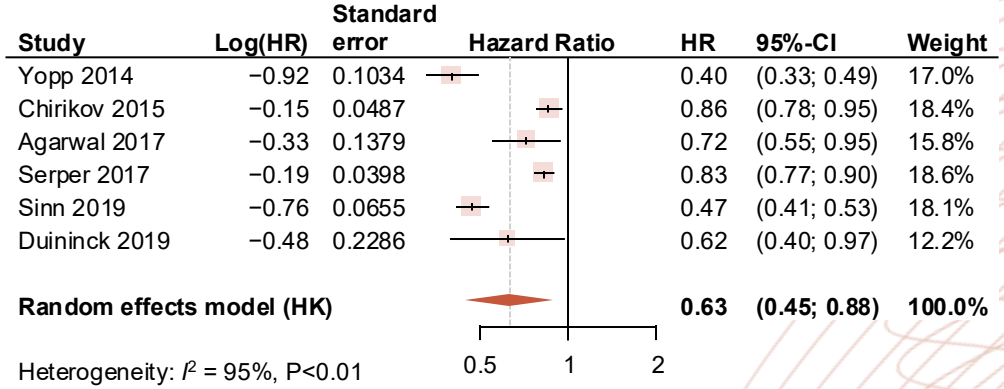
OS Exactly Matched cohort[1]



No. at risk								
MDT (+)	698	661	592	515	414	314	239	171
MDT (−)	698	574	478	409	320	226	154	112

5 year OS rate 71.4% MDT vs 58.7% non-MDT (P<0.001)
MDT management benefit particularly significant in patients with ALBI 2 and 3 – BCLC B and C – AFP > 200 ng/mL

Association between multidisciplinary care and overall survival[2]



Multidisciplinary care was significantly associated with improved survival

HCC, hepatocellular carcinoma; IO, immunotherapy; MDT, multidisciplinary team

Sinn DH, et al. PLOS ONE 2019; 2. Dahan et al. Hepatology Communications, 2023

MULTIDISCIPLINARY TEAM APPROACH FOR HCC
CONSIDERATIONS AND BEST PRACTICES

- **Optimizing therapy while preserving liver function** is critical for long-term survival of patients[1]
  - The MDT discussion plays a crucial role in the best treatment approach to optimize treatment opportunities at each stage of disease while managing liver function[1-3]
- **The oncologic intent** should be clearly defined for each patient[2,4]
  - The MDT composition may vary based on the oncologic intent[4]
    - **Curative intent:** Eradicate all known disease[4]
    - **Palliative intent:** Improve survival, focus on QoL, disease control, symptom relief, etc.[2,5] If these patients demonstrate durable response, they may be considered for curative intent[4]
- A **full window of opportunity** and exploration of treatment options within the MDT ensures the best possible outcomes[4]
  - The MDT allows for the agile **reassessment** of patients for modifying the care plan based on treatment response[4]

MDT, multidisciplinary team; QoL, quality of life

1. Naugler WE, et al. Clin Gastroenterol Hepatol. 2015;13:827-835; 2. Suddle A, et al. Gut. 2024;73:1235-1268; 3. Oh JH and Sinn DH. J Liver Cancer. 2024;24:47-56; 4. Miguet M, et al. J Visc Surg. 2019;156:217-227; 5. Woodrell CD, et al. Clin Ther. 2018;40:512-525

CONCLUSIONS

CONCLUSIONS

THE EXPANDING ROLE OF IMMUNOTHERAPY IN HEPATOCELLULAR CARCINOMA (HCC) – COMBINING LOCOREGIONAL AND SYSTEMIC TREATMENTS IN INTERMEDIATE HCC

- **IO and IO combinations for advanced and intermediate HCC**
  - IO and IO combinations are integrated into the 1st line treatment for unresectable HCC
- **Scientific rationale for IO in intermediate-stage HCC**
  - Intermediate-stage HCC is heterogeneous. LRT is the current SoC, but there are some patients who will be poor candidates.
  - Multimodal approaches combining IO with LRT could potentially target both visible and invisible disease, particularly in more challenging disease presentations
- **Efficacy and safety of IO + LRT combinations**
  - Combining IO with TACE shows promising outcomes in terms of safety and efficacy vs TACE alone
    - EMERALD-1 and LEAP-012 both meet their primary endpoints of PFS
    - Patients continue to be followed for OS data
  - Safety profiles were manageable and consistent with the known safety profiles of each treatment
- **Multidisciplinary team coordination for optimal treatment**
  - Collaboration among oncologists, hepatologists, interventional radiologists, transplant surgeons, and radiation oncologists is essential for effective treatment planning, sequencing and comprehensive patient care

IO, immuno-oncology; LRT, locoregional therapy; OS, overall survival; PFS, progression free survival; SoC, standard of care; TACE, transarterial chemoembolisation

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