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HCC CONNECT

HIGHLIGHTS FROM ESMO 2024
IO AND IO BASED TREATMENTS IN HCC

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SEPTEMBER 2024

ESMO, European Society for Medical Oncology; HCC, hepatocellular carcinoma; IO, immunotherapy

DEVELOPED BY HCC CONNECT

This programme is developed by HCC CONNECT, an international group of experts in the field of hepatocellular carcinoma.

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Acknowledgement and disclosures

AstraZeneca has provided a sponsorship grant towards this independent programme. The programme is therefore independent, the content is not influenced by the supporter and is under the sole responsibility of the experts.

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Expert disclosures:

- **Dr Richard Finn** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: AstraZeneca, Bayer, CStone, Eisai, Eli Lilly, Exelixis, Hengrui, Merck, Pfizer, Roche/Genentech

CLINICAL TAKEAWAYS

HIGHLIGHTS FROM ESMO 2024 - HCC

ABSTRACT 1:

- **HIMALAYA:** results from the extended follow-up set a new benchmark in unresectable HCC, with one in five patients alive with single tremelimumab regular interval durvalumab (STRIDE) at 5 years

ABSTRACT 2:

- **CheckMate 9DW:** further supports nivolumab + ipilimumab as a potential first-line treatment option for patients with unresectable HCC

ABSTRACT 3:

- **LEAP-012:** met its primary endpoint. Lenvatinib + pembrolizumab + TACE showed a statistically significant and clinically meaningful improvement in PFS and an early trend towards improvement in OS versus placebo + TACE in patients with intermediate HCC

ABSTRACT 4:

- **IMbrave050:** does not support atezolizumab + bevacizumab as an adjuvant therapy for all high-risk HCC

ESMO, European Society for Medical Oncology; HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; STRIDE, ; TACE, transarterial chemoembolisation

EDUCATIONAL OBJECTIVE

- Understand the latest practice-changing HCC data on IO and IO-based treatments from ESMO and how this could be implemented in clinical practice

ESMO, European Society for Medical Oncology; HCC, hepatocellular carcinoma; IO, immunotherapy

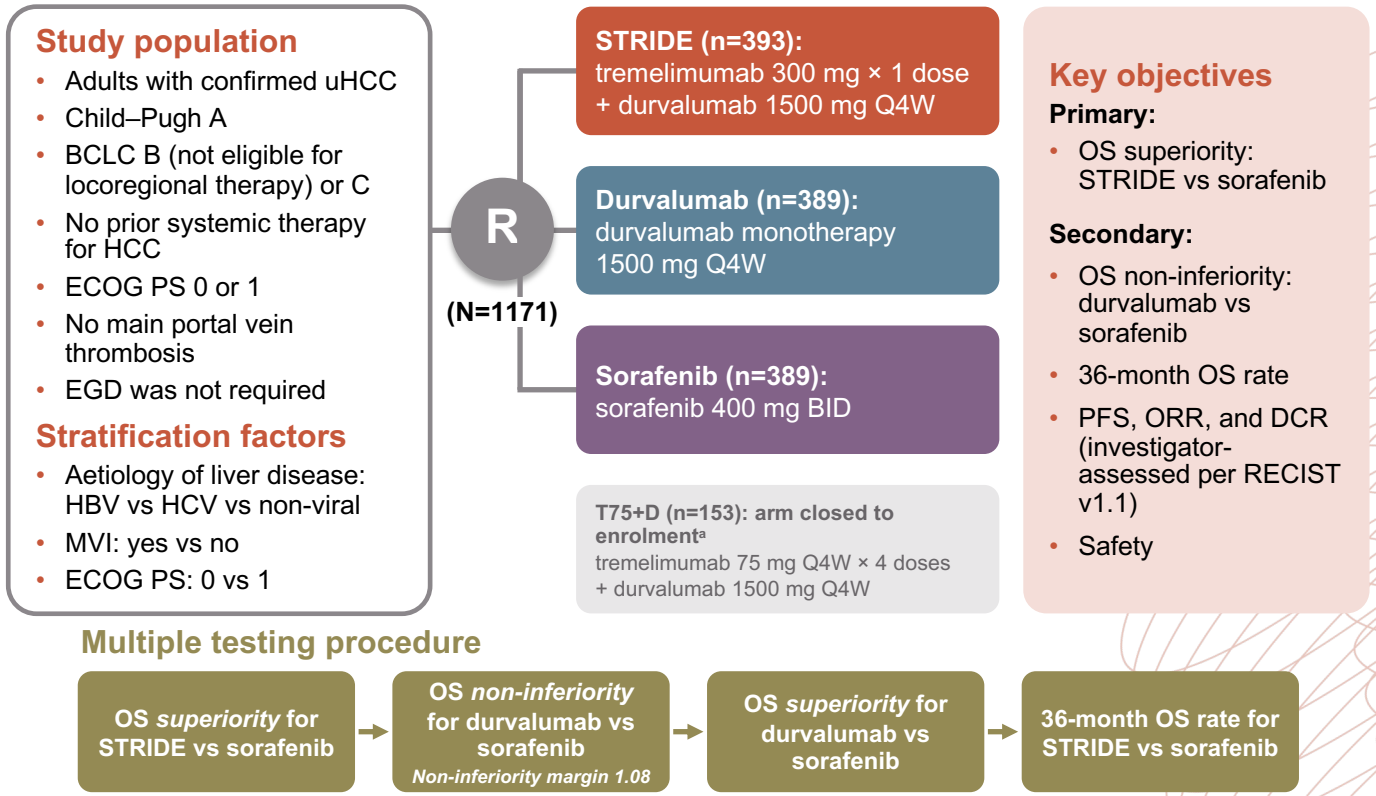
FIVE-YEAR OS AND OS BY TUMOUR RESPONSE MEASURES FROM THE PHASE 3 HIMALAYA STUDY OF TREMELIMUMAB PLUS DURVALUMAB IN uHCC

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

OS, overall survival; uHCC, unresectable hepatocellular carcinoma

HIMALAYA
BACKGROUND AND STUDY DESIGN

- Phase 3 HIMALAYA study in unresectable HCC[1]: **STRIDE significantly improved OS** versus sorafenib in the primary analysis[2] and demonstrated durable long-term survival with a 4-year OS rate of 25.2%[3]
- At ESMO 2024[4]:
  - The first **5-year OS** analysis in uHCC was reported
  - Survival by **multiple tumour response measures** was evaluated



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 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

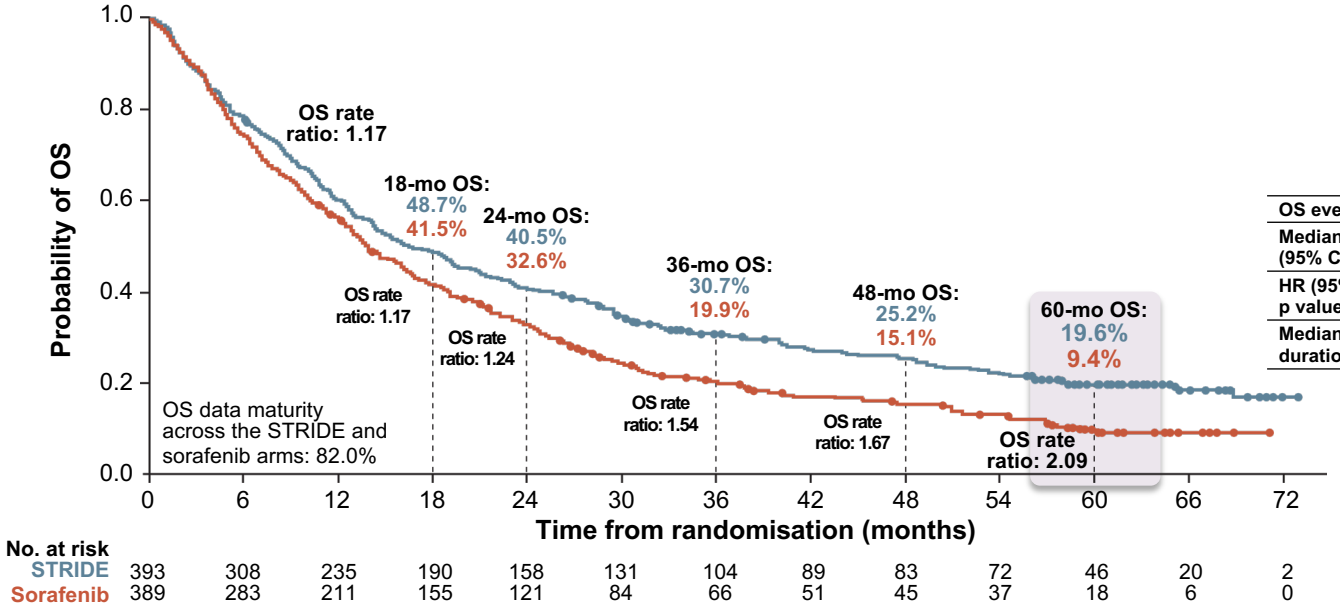
BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EGD, esophagogastroduodenoscopy; ESMO, European Society for Medical Oncology; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; 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 hepatocellular carcinoma

1. ClinicalTrials.gov: NCT03298451; 2. Abou-Alfa GK, et al. NEJM Evid. 2022;1:EVIDoa2100070; 3. Sangro B, et al. Ann Oncol. 2024;35:448-57; 4. Rimassa L, et al. ESMO 2024. Abstract #947MO. Oral presentation

HIMALAYA

RESULTS: STRIDE DEMONSTRATED A SUSTAINED OS BENEFIT

- STRIDE demonstrated a sustained OS benefit versus sorafenib 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)
- More participants treated with STRIDE than sorafenib had deep responses (>50%)

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; mo, month(s); MVI, macrovascular invasion; OS, overall survival; STRIDE, single tremelimumab regular interval durvalumab

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

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 improved OS outcomes observed across **multiple tumour response evaluations** provide novel insights on the clinical benefit of dual immune checkpoint inhibition **beyond conventional response measures**
- The results set a new benchmark in uHCC, with **one in five patients alive** with **STRIDE** at 5 years

Clinical perspective

- HIMALAYA presents the longest follow-up to date in Phase 3 studies in uHCC
- Conventional response measures may not fully capture the benefits of STRIDE
- Data support that STRIDE is a live-prolonging regimen

OS, overall survival; STRIDE, single tremelimumab regular interval durvalumab; uHCC, unresectable hepatocellular carcinoma

Rimassa L, et al. ESMO 2024. Abstract #947MO. Oral presentation; Harding J. ESMO 2024. Invited discussant for Abstracts #965MO and #947MO

NIVOLUMAB PLUS IPILIMUMAB VS LENVATINIB OR SORAFENIB AS FIRST-LINE TREATMENT FOR uHCC: EXPANDED ANALYSES FROM CheckMate 9DW

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

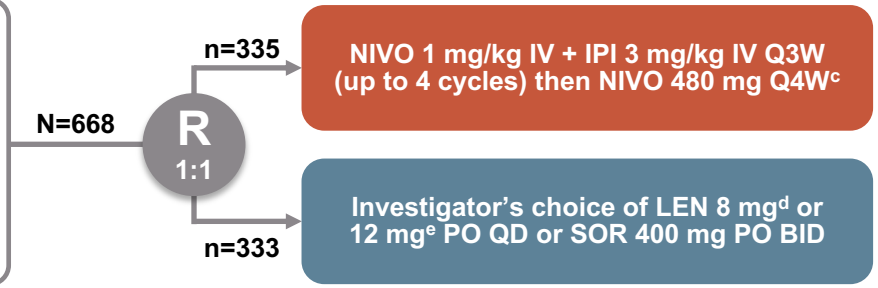
uHCC, unresectable hepatocellular carcinoma

CheckMate 9DW
BACKGROUND AND STUDY DESIGN

- Phase 3 CheckMate 9DW in uHCC[1]: first-line **nivolumab + ipilimumab** demonstrated significant and clinically meaningful **OS benefit** versus lenvatinib/sorafenib
- At ESMO 2024[2]: additional exploratory analyses from a preplanned interim analysis (IA) were presented

Key eligibility criteria
- uHCC[a]
- ≥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)

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

Primary endpoint
- OS

Secondary endpoints
- ORR and DOR by BICR per RECIST v1.1

Key exploratory endpoints
- PFS by investigator per RECIST v1.1
- PFS2 by investigator
- Safety

At data cutoff (January 31, 2024), the median follow-upf 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; ESMO, European Society for Medical Oncology; HBV, hepatitis B virus; HCV, hepatitis C virus; IPI, ipilimumab; IV, intravenous; LEN, lenvatinib; MVI, macrovascular invasion; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; 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

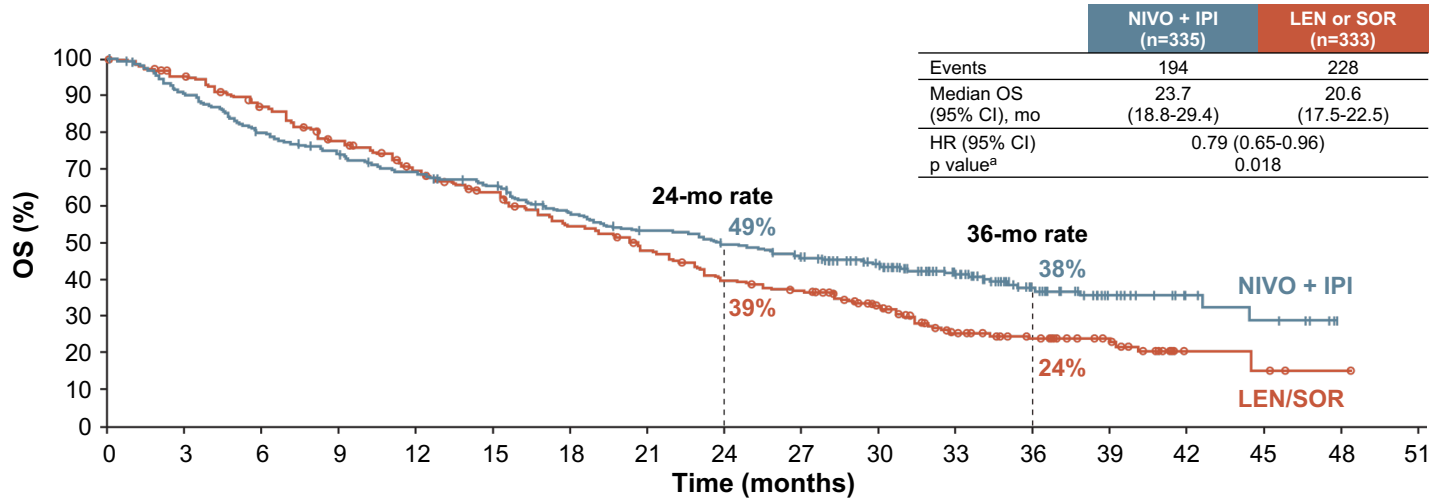
1. ClinicalTrials.gov: NCT04039607; 2. Decaens T, et al. ESMO 2024. Abstract #965MO. Oral presentation

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



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

No. at risk																	
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

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; CI, confidence interval; D/C, discontinuation; HR, hazard ratio; IPI, ipilimumab; LEN, lenvatinib; NIVO, nivolumab; mo, month(s); OS, overall survival; SOR, sorafenib; TRAE, treatment-related adverse event

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

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
- Results further **support nivolumab + ipilimumab as a potential first-line treatment option** for patients with uHCC

Clinical perspective[2]

- CheckMate 9DW confirms the efficacy of dual CTLA4 and PD1/PD-L-1 blockade in treatment-naive advanced HCC
- Waiting for the 5-year follow-up data
- Nivolumab + ipilimumab is likely to become a standard-of-care treatment option in the future

CTL4A, cytotoxic T-lymphocyte associated protein 4; HCC, hepatocellular carcinoma; ORR, objective response rate; OS, overall survival; PD1, programmed death 1; PD-L1, programmed death ligand 1; ORR, objective response rate; OS, overall survival; uHCC, unresectable HCC

1. Decaens T, et al. ESMO 2024. Abstract #965MO. Oral presentation; 2. Harding J. ESMO 2024. Invited discussant for Abstracts #965MO and #947MO

TACE WITH OR WITHOUT LENVATINIB + PEMBROLIZUMAB FOR INTERMEDIATE-STAGE HCC: PHASE 3 LEAP-012 STUDY

Llovet J, et al. ESMO 2024. Abstract #LBA3. Oral presentation

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolisation

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

- TACE remains standard of care for patients with intermediate-stage HCC
- At ESMO 2024[3]: results from the Phase 3 LEAP-012 were presented, **evaluating lenvatinib + pembrolizumab + TACE versus placebo + TACE** in intermediate-stage HCC

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; ESMO, European Society for Medical Oncology; HCC, hepatocellular carcinoma; IA1, interim analysis 1; IV, intravenous; mRECIST, modified RECIST; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; Q6W, every 6 weeks; QD, once daily; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; TACE, transarterial chemoembolisation; TTP, time to progression

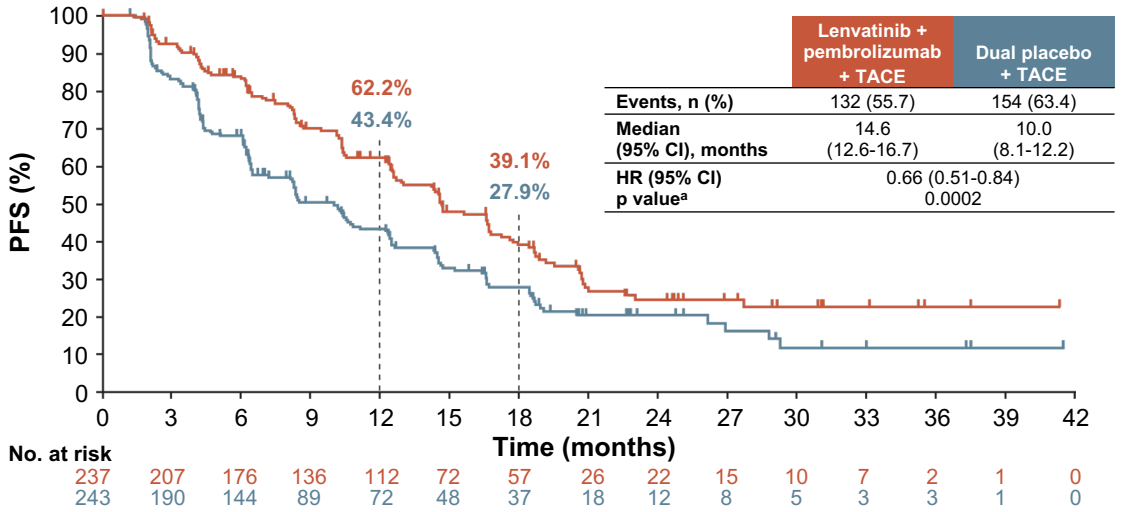
1. ClinicalTrials.gov: NCT04246177; 2. Wang Q, et al. J Hepatol. 2019;70:893-903; 3. Llovet J, et al. ESMO 2024. Abstract #LBA3. Oral presentation

LEAP-012

RESULTS: PRIMARY ENDPOINT IN PFS WAS MET

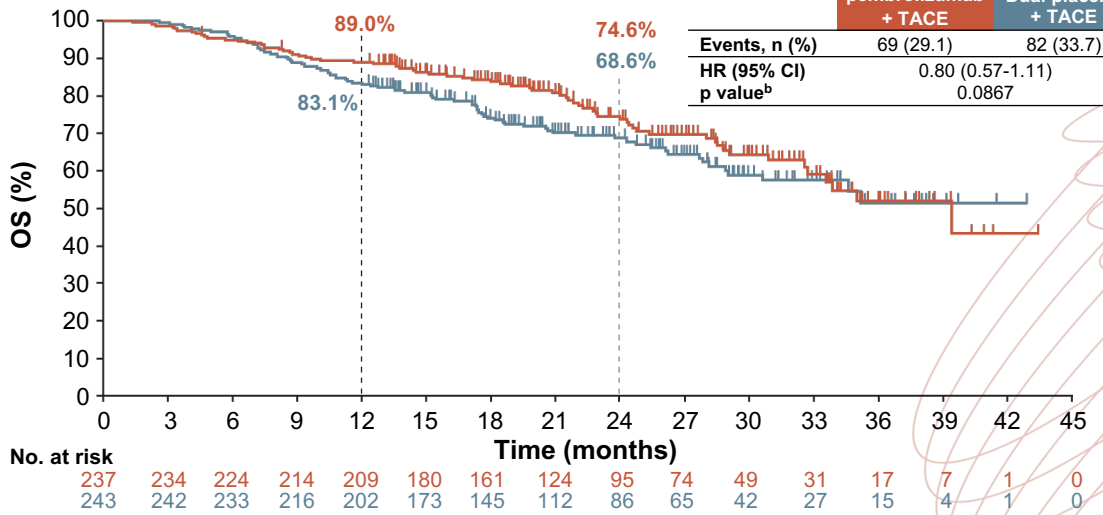
- There was a clinically meaningful and statistically significant improvement in PFS for patients with intermediate-stage HCC who received lenvatinib + pembrolizumab + TACE versus dual placebo + TACE

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; 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

LEAP-012
SUMMARY[1]

- 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

Clinical perspective[2]

- Lenvatinib + pembrolizumab + TACE may be accepted as a new standard of care in intermediate HCC
- It is expected that systemic therapies will move to earlier disease stages shortly

HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression free survival; TACE, transarterial chemoembolisation

1. Llovet J, et al. ESMO 2024. Abstract #LBA3. Oral presentation; 2. Lamarca A. ESMO 2024. Invited discussant for Abstract #LBA3

UPDATED EFFICACY AND SAFETY DATA FROM IMbrave050: PHASE 3 STUDY OF ADJUVANT ATEZOLIZUMAB + BEVACIZUMAB VERSUS ACTIVE SURVEILLANCE IN PATIENTS WITH RESECTED OR ABLATED HIGH-RISK HCC

Yopp A, et al. ESMO 2024. Abstract #LBA39. Oral presentation

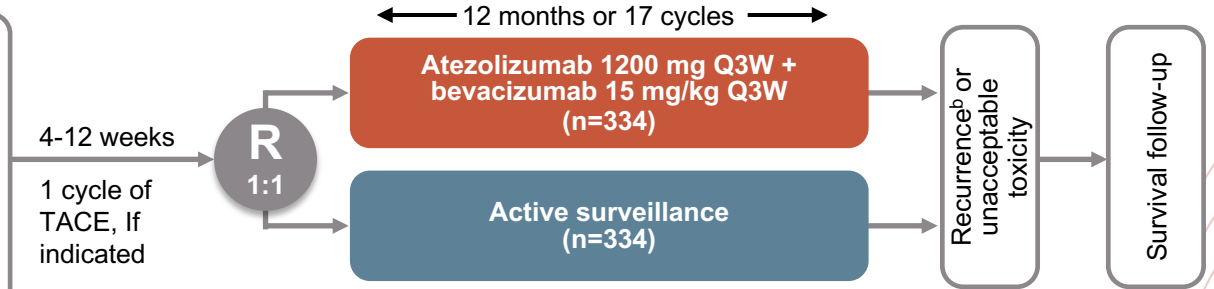
HCC, hepatocellular carcinoma

IMbrave050
BACKGROUND AND STUDY DESIGN

- Phase 3 IMbrave050[1]: at the pre-specified IA IMbrave050 met its primary endpoint of improved independent review facility (IRF)-assessed recurrence-free survival (RFS) in patients with high-risk HCC. OS was immature
- At ESMO 2024[2]: updated analyses were presented for atezolizumab + bevacizumab versus active surveillance for patients with high-risk HCC

Patient population
- Confirmed first diagnosis of HCC and had undergone curative resection or ablation
- Disease free
- Child–Pugh liver class A
- High risk of recurrence[a]
- No extrahepatic disease or MVI (except Vp1/Vp2)
- ECOG PS of 0 or 1

Stratification factors
- Region (Asia–Pacific excluding Japan vs rest of world)
- High-risk features and procedures:
  - Ablation
  - Resection, 1 risk feature, adjuvant TACE (yes vs no)
  - Resection, ≥2 risk features, adjuvant TACE (yes vs no)



[a] High-risk features include: tumour >5 cm, >3 tumours, microvascular invasion, minor MVI Vp1/Vp2, or grade 3/4 pathology; [b] Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1

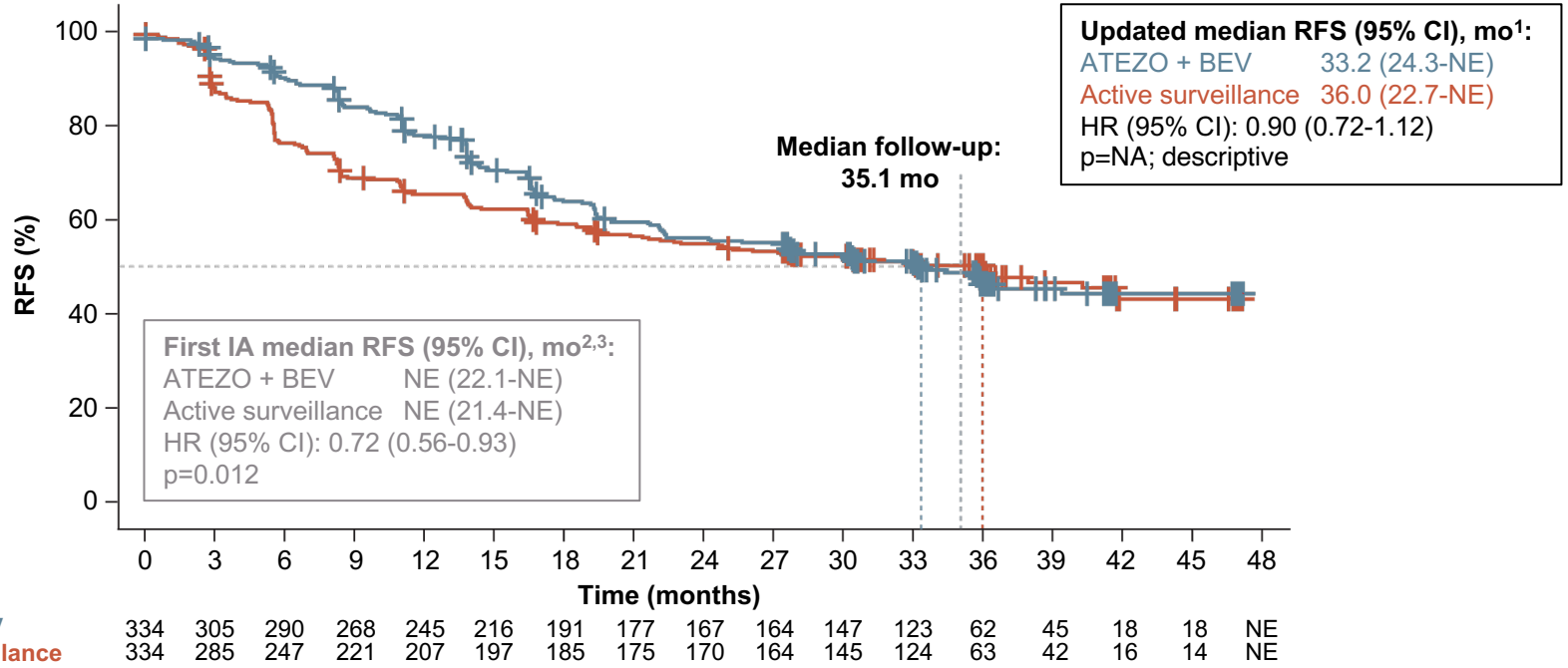
ClinicalTrials.gov: NCT04102098. EASL, European Association for the Study of the Liver; ECOG PS, Eastern Cooperative Oncology Group performance status; ESMO, European Society for Medical Oncology; HCC, hepatocellular carcinoma; IA, interim analysis; MVI, macrovascular invasion; OS, overall survival; Q3W, every 3 weeks; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; TACE, transarterial chemoembolisation

1. Qin S, et al. Lancet. 2023;402:1835-47; 2. Yopp A, et al. ESMO 2024. Abstract #LBA39. Oral presentation

IMbrave050

RESULTS: PRIMARY ENDPOINT OF RFS WAS NOT MET

- Early RFS benefit with atezolizumab + bevacizumab versus active surveillance was **not maintained** at follow-up[1]
- No new safety concerns were seen[1]



Clinical cutoff: May 3, 2024; median follow-up: 35.1 months. At clinical cutoff, 162 of 334 (49%) patients in the atezolizumab + bevacizumab arm and 164 of 334 (49%) in the active-surveillance arm experienced disease recurrence or death. HRs are stratified. p values are log rank

ATEZO, atezolizumab; BEV, bevacizumab; CI, confidence interval; HR, hazard ratio; IA, interim analysis; mo, months; NA, not applicable; NE, not estimable; RFS, recurrence-free survival; RFS, recurrence-free survival

1. Yopp A, et al. ESMO 2024. Abstract #LBA39. Oral presentation; 2. Qin S, et al. Lancet. 2023;402:1835-47; 3. Chow P, et al. AACR 2023. Abstract #CT003

IMbrave050
SUMMARY

- Initial RFS benefit with atezolizumab + bevacizumab versus active surveillance **was not sustained**
- Safety profile of atezolizumab + bevacizumab remained manageable and consistent with each agent and underlying HCC
- **Results do not support atezolizumab + bevacizumab as an adjuvant therapy for all high-risk HCC**
  - Efficacy follow-up for OS will continue

HCC, hepatocellular carcinoma; RFS, recurrence-free survival

Yopp A, et al. ESMO 2024. Abstract #LBA39. Oral presentation

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