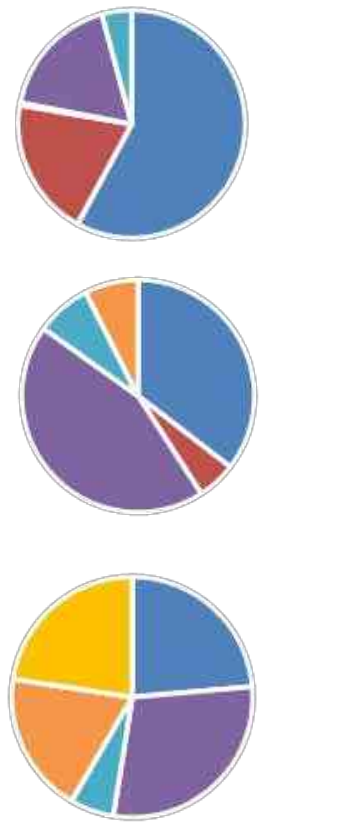
Can Immunotherapies Enhance Surgical Outcomes in HCC?

Real-world data from APAC INSIGHT Registry

Between Jan 2013 – Dec 2019, 2,533 HCC patients were recruited from 9 countries in Asia Pacific

- 1,052 in retrospective cohort and 1,481 in prospective cohort
- Australia, New Zealand, Korea, Taiwan, Hong Kong, Japan, China, Thailand and Singapore

Distribution of patients by BCLC Stage receiving surgical resection

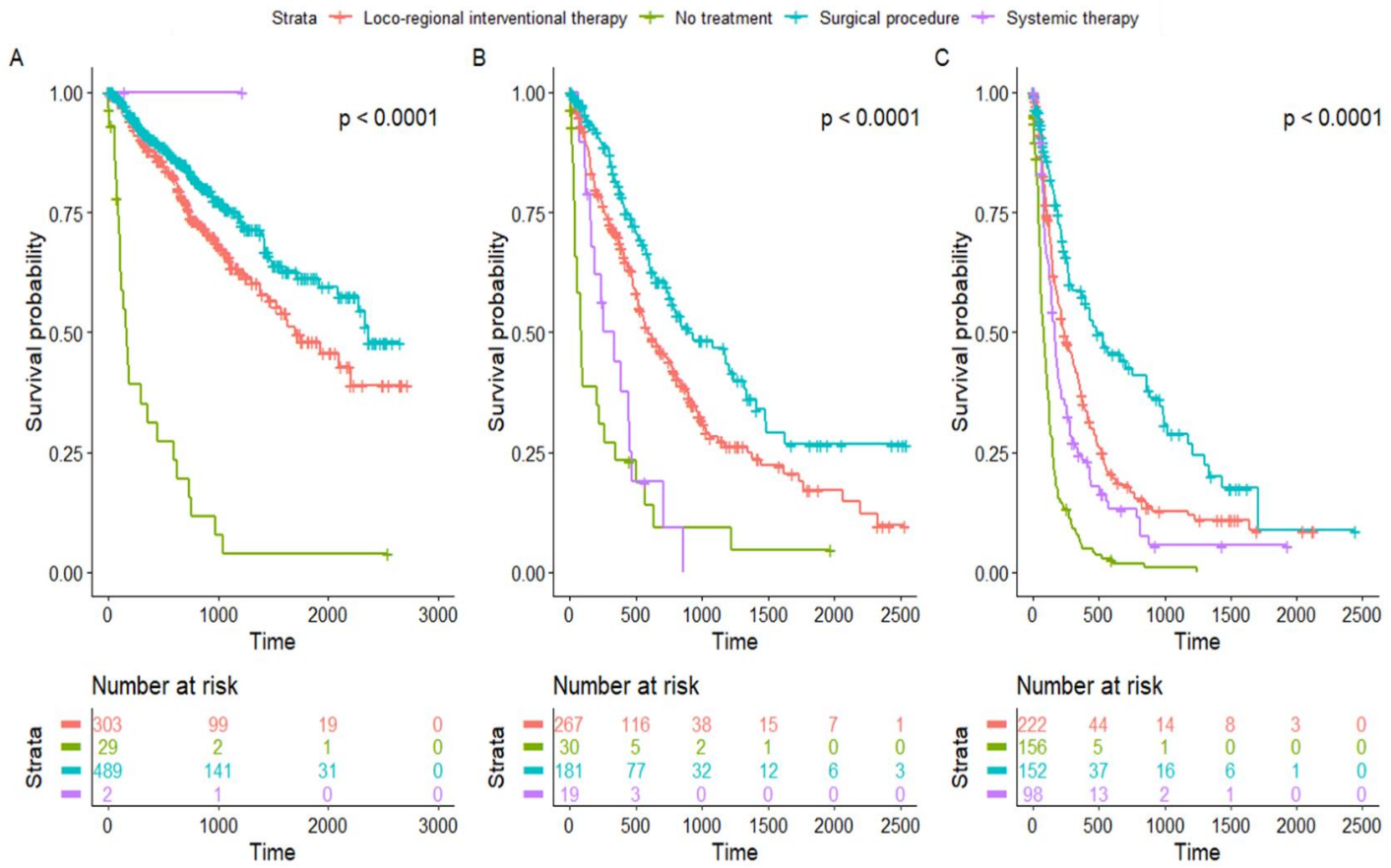


BCLC 0/A
506/825 patients 61.3%

BCLC B
190/494 patients 38.5%

BCLC C
164/657 patients 25.0%

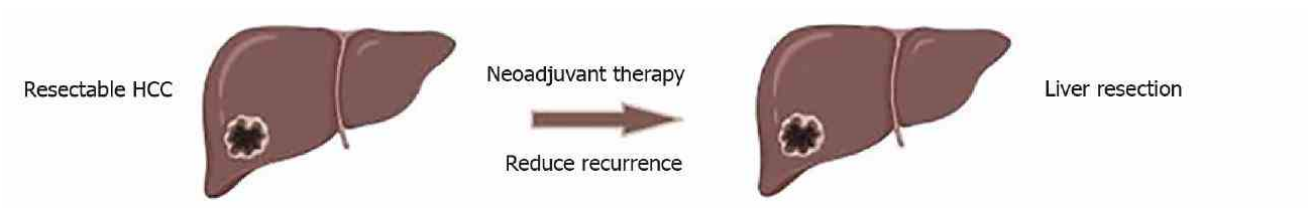
Survival outcomes across all stages of HCC stratified based on modality

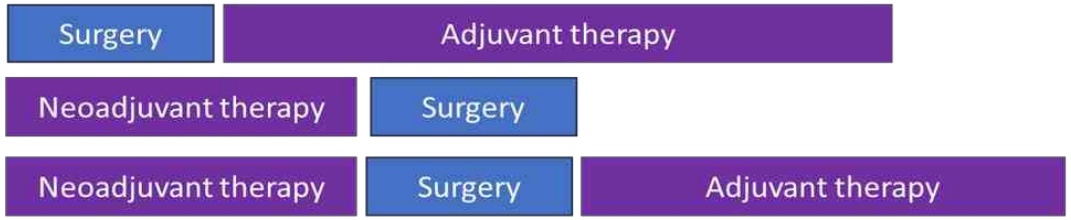


Chow et al. Liver Cancer. 2023.

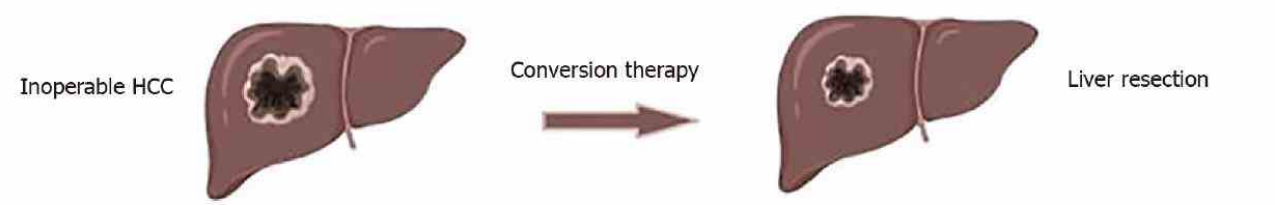
How can immunotherapies potentially enhance surgical outcomes in HCC?

Adjuvant /neoadjuvant therapy: Reduce recurrence in resectable HCC

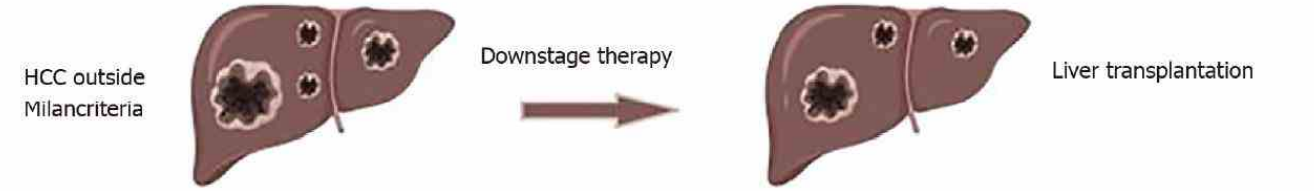




Conversion therapy: Inoperable HCC to resectable HCC



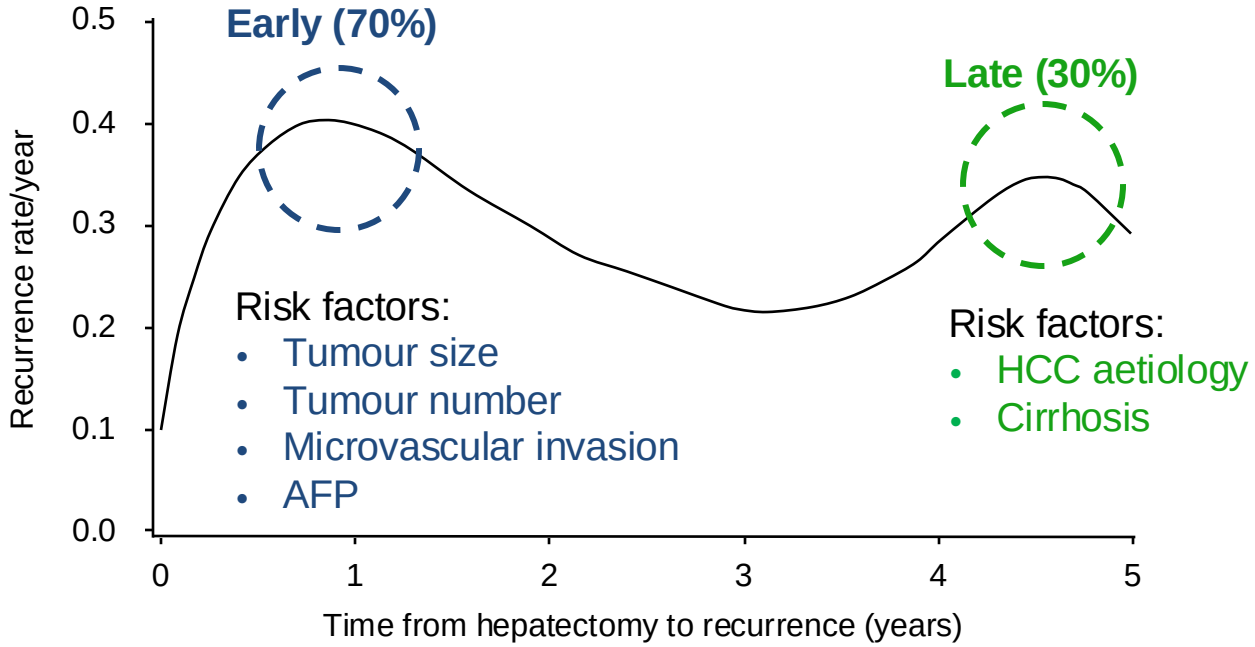
Bridging/downstaging: Liver transplantation

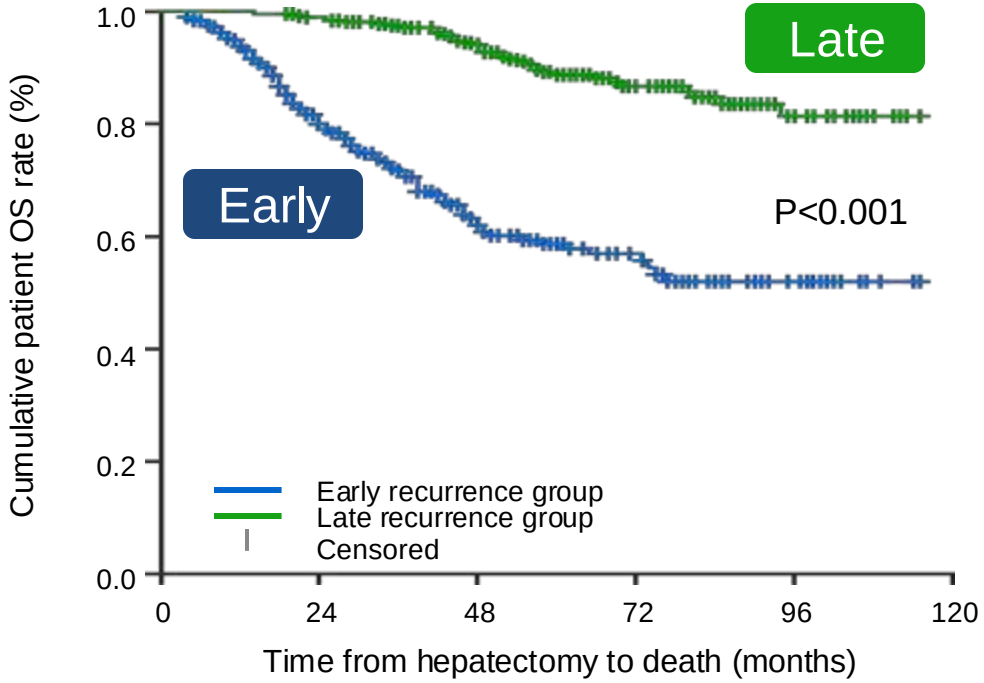


Adapted from Xu et al. World Journal of Gastrointestinal Surgery. 2021.

For patients who undergo resection, early recurrence of disease (within 2 years) can significantly impact OS

Resection is specifically indicated for BCLC stage 0/A HCC[1]; however, patients with BCLC stage B/C are often referred for resection and many have clinical features that increase the risk of HCC recurrence[2,3]

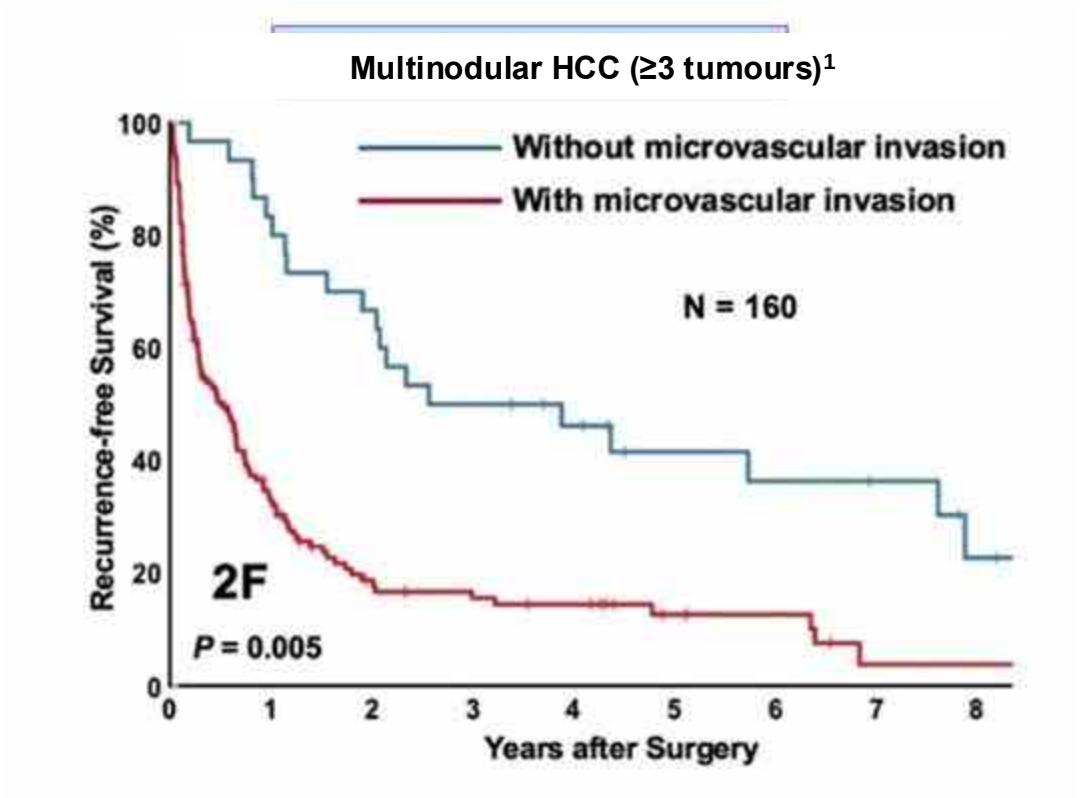


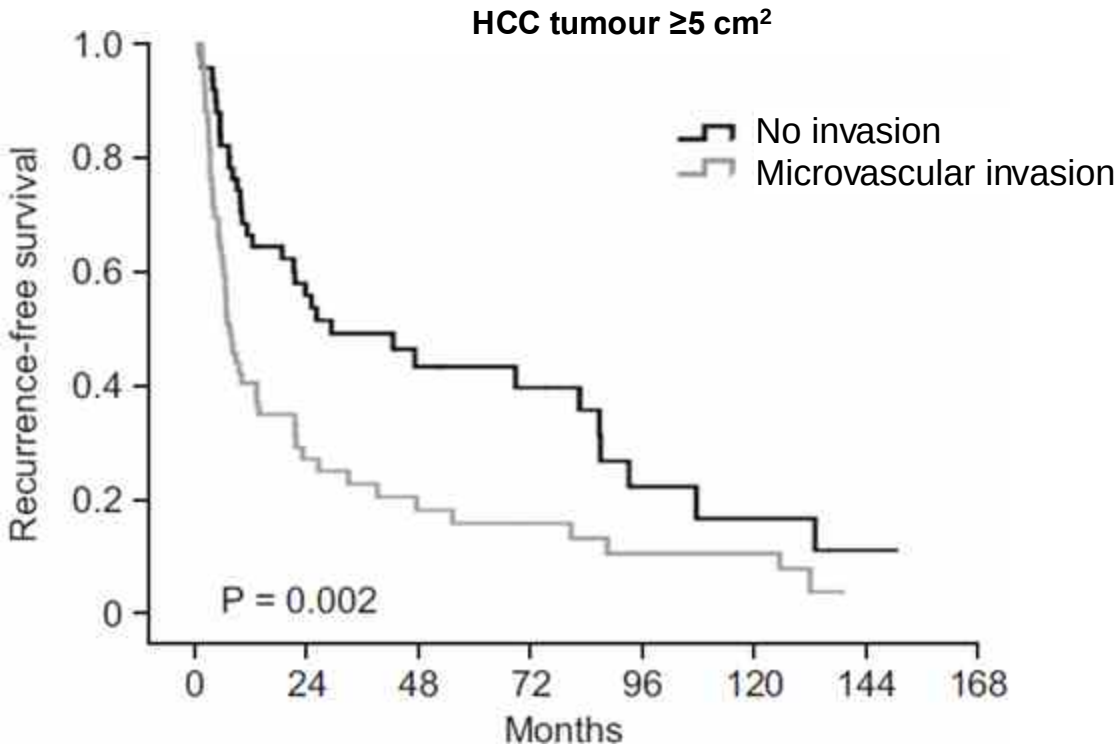


Adjuvant treatment may overcome the risk of early HCC recurrence and improve patient prognosis; however, there are currently no approved agents in this setting for HCC – this represents an urgent unmet need[6]

1. Reig et al. J Hepatol 2022; 2. Guo et al. Cancer Manag Res 2018; 3. Torzilli et al. Arch Surg 2008
4. Imamura et al. I J of Hepatology 2003; 5. Jung et al. J Gastrointest Surg 2019; 6. Hack et al. Future Oncol 2020.

Alongside tumour size/number, microvascular invasion may be a critical risk factor for early recurrence following resection[1–3*]





Vascular invasion has previously been associated with increased tumour size and number,[1] but these data suggest microvascular invasion is an independent negative prognostic marker in both multinodular and large HCC

*There are no validated criteria used to define high-risk patients following surgical resection

1. Li et al. Eur J Surg Oncol 2019; 2. Noh et al. Ann Surg Treat Res 2016;
3. Pawlik et al. Liver Transpl 2005.

QMH Experience

ORIGINAL ARTICLE

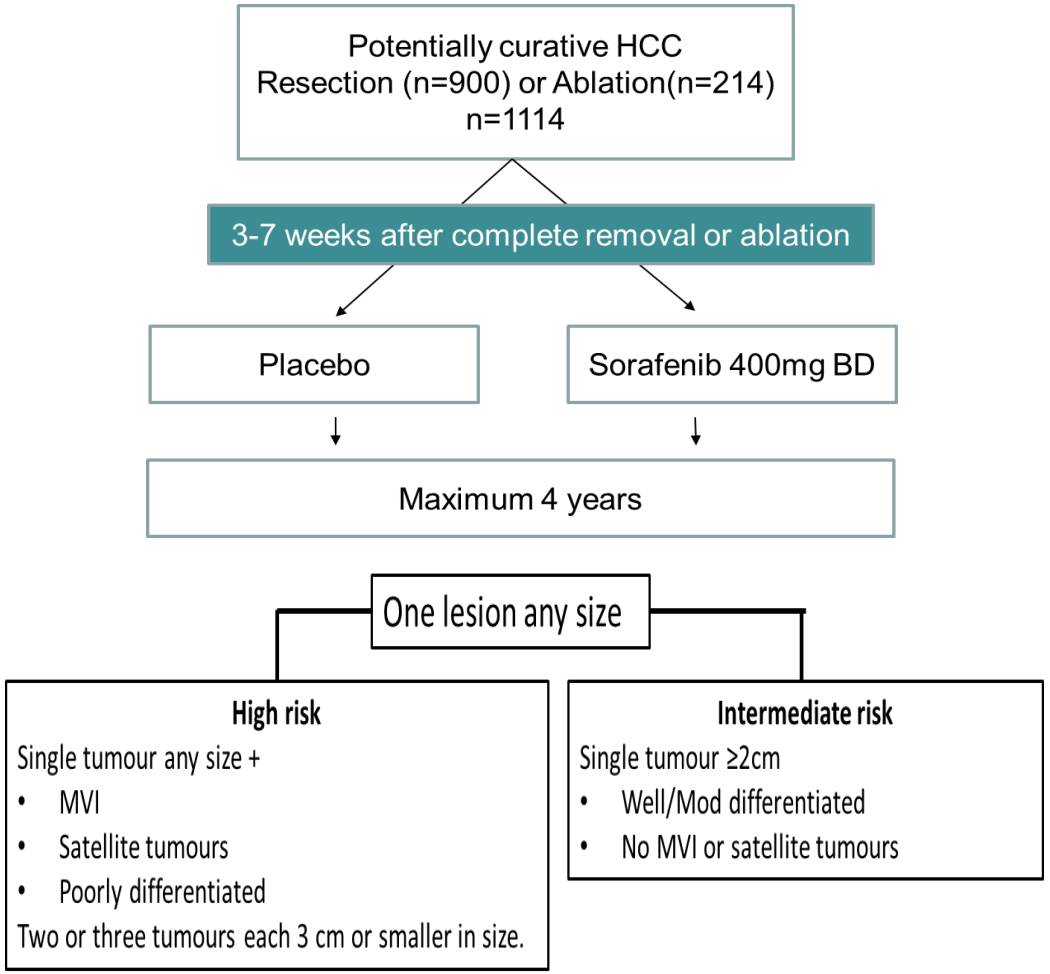
Evaluation of the seventh edition of the American Joint Committee on Cancer tumour–node–metastasis (TNM) staging system for patients undergoing curative resection of hepatocellular carcinoma: implications for the development of a refined staging system

Factors	P	Hazard ratio	95% confidence interval
Albumin	0.017	0.978	0.961 – 0.996
Platelet count	< 0.001	0.998	0.996 – 0.999
Tumour > 5 cm	0.003	1.037	1.012 – 1.061
Bilobar HCC	0.035	1.304	1.019 – 1.670
Symptomatic HCC	0.004	1.355	1.099 – 1.670
Multiple tumours	< 0.001	1.633	1.349 – 1.976
Microvascular invasion	< 0.001	1.910	1.592 – 2.291

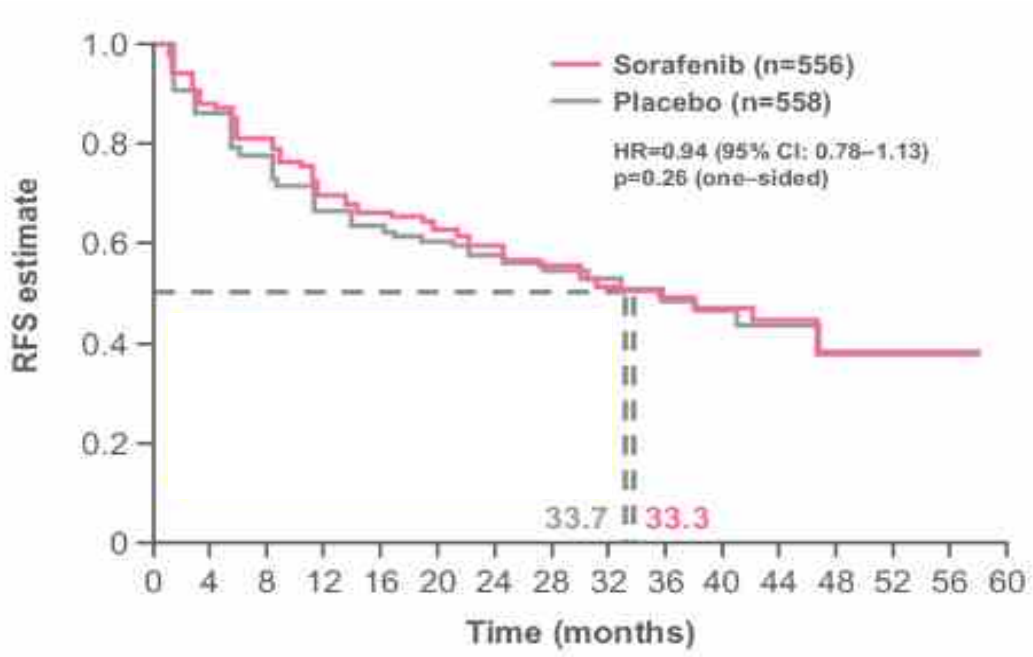
Chan AC, Fan ST, Lo CM et al. HPB 2013

STORM: Adjuvant sorafenib vs placebo failed to demonstrate an RFS benefit

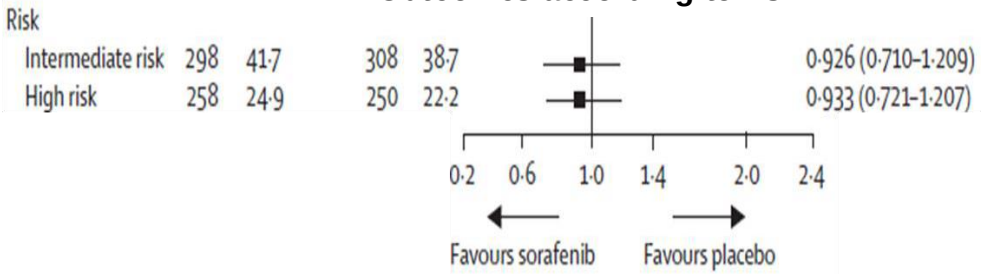
- Phase 3, randomised, double-blind, placebo-controlled study in 28 countries (APAC: 59%; EU: 30%; America: 11%)
- Indication for resection/ablation based on BCLC/EASL, excluded patients with small solitary HCC, AFP >400 ng/L
- Vast majority of patients randomised had solitary, low volume HCC



Median recurrence free survival ~33 months



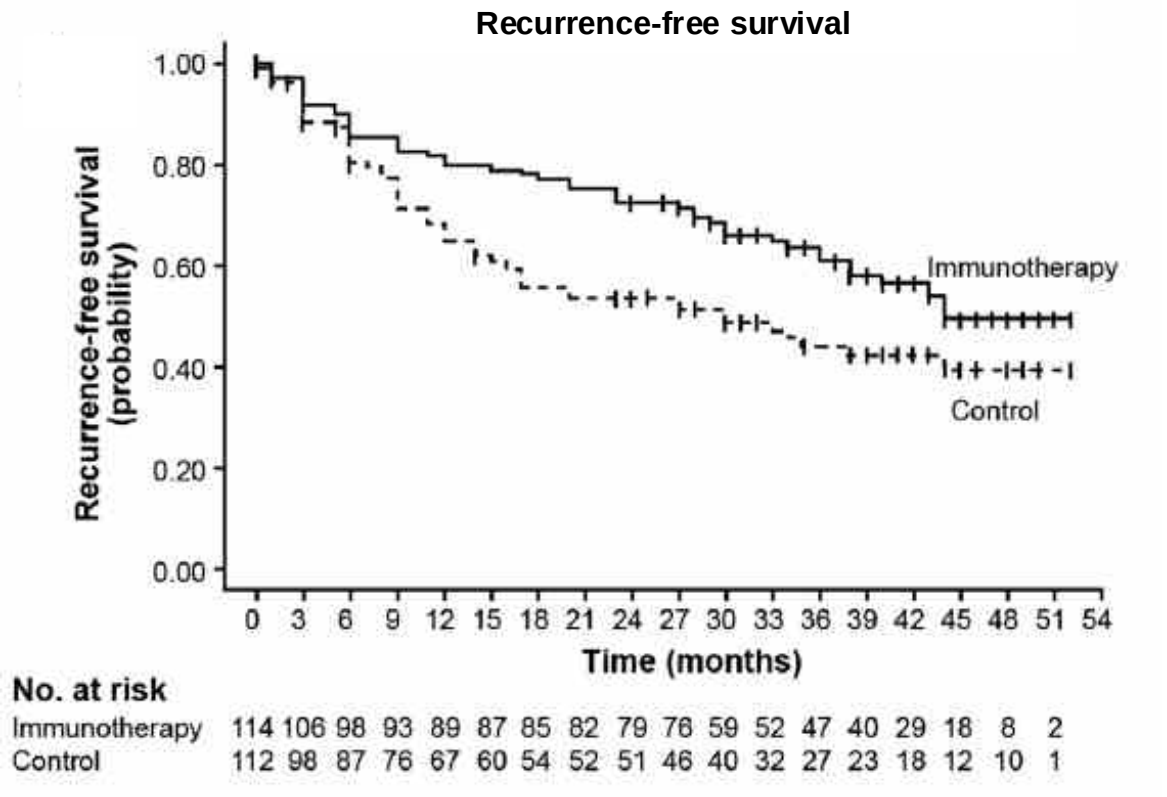
Outcomes according to risk

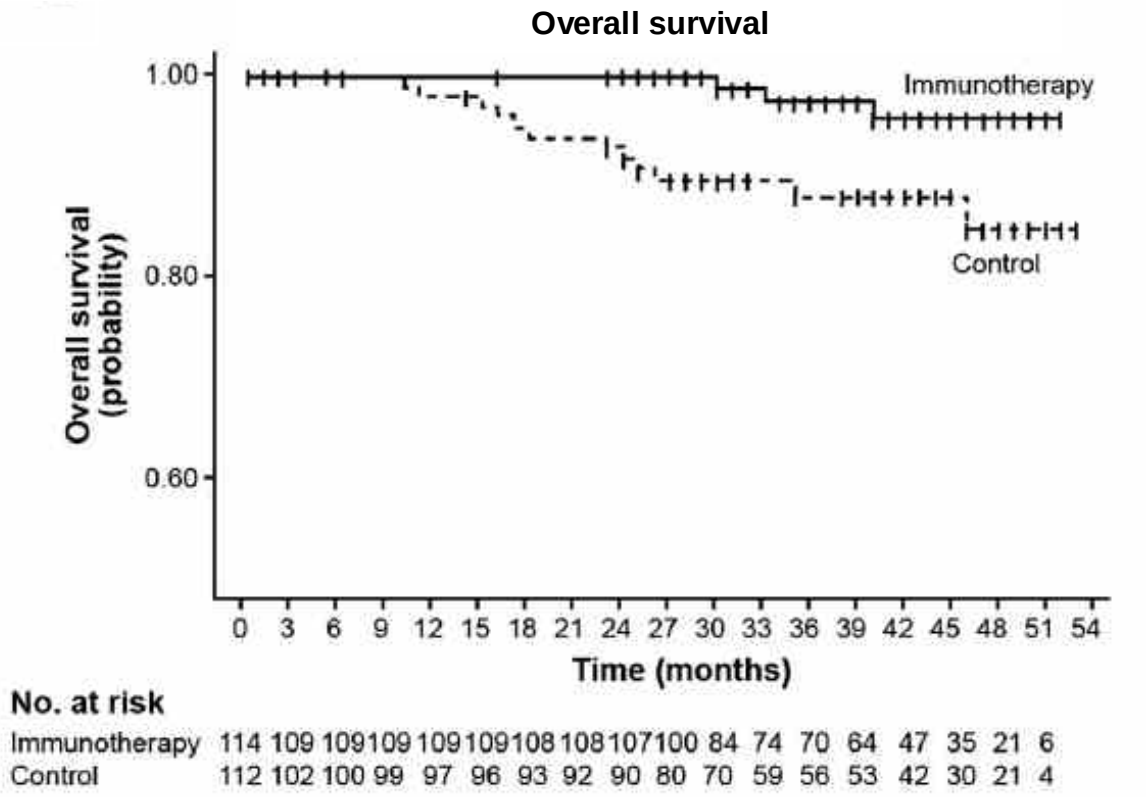


Bruix J et al. Lancet Oncol. 2015.

Adjuvant autologous cytokine induced killer cells demonstrated a significant RFS benefit

- Multicentre, randomised, open-label, phase 3 trial in Korea
- Post-surgical resection, RFA, or percutaneous ethanol injection
- 2 arms: Immunotherapy (injection of 6.4 × 10^9 autologous CIK cells, 16 times during 60 weeks) or no adjuvant (control)





Median RFS **44 mo vs 30 mo**

HR=0.63 (95% CI: 0.43–0.94)

p=0.010

Median OS **Not reached**

HR=0.21 (95% CI: 0.06–0.75)

p = 0.008

Lee JH et al. Gastroenterology. 2015.

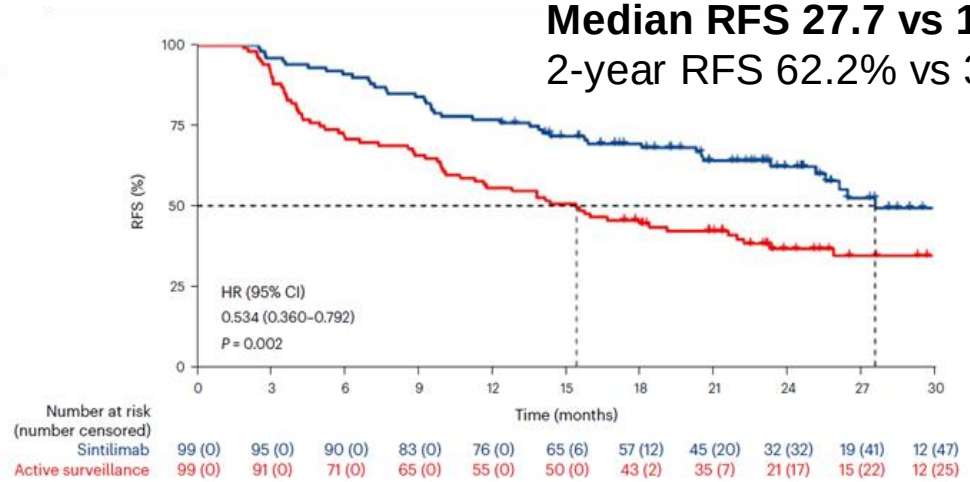
Adjuvant Sintilimab (PD-1 Inhibitor) vs active surveillance demonstrated RFS benefit

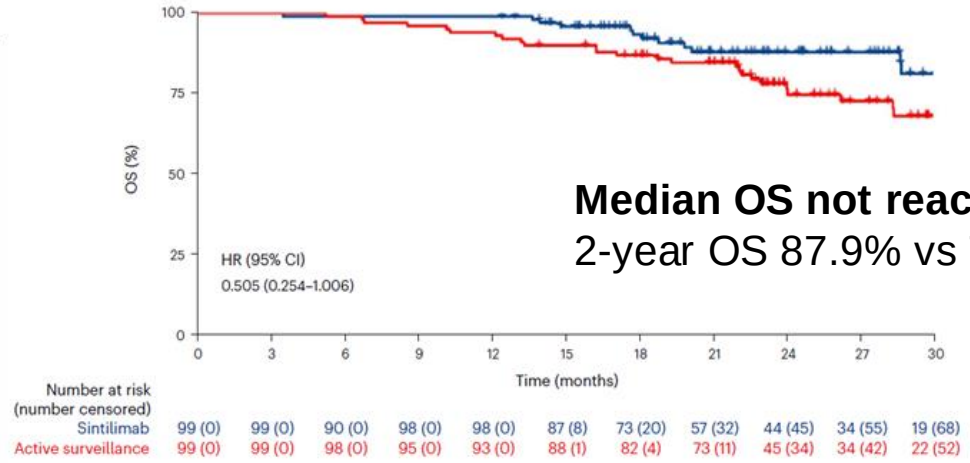
- Open-label, randomised, phase 2 trial with 198 patients from 6 Chinese hospitals
- Majority HCC of CHB aetiology with microvascular invasion

Baseline patient characteristics

Characteristics	Active surveillance group (*n*=99)	Sintilimab group (*n*=99)
Age (years), median (IQR)	54.0 (49.0–61.0)	53.0 (48.0–61.0)
Sex, *n* (%)		
Male	83 (83.8)	85 (85.9)
Female	16 (16.2)	14 (14.1)
Etiology, *n* (%)		
Hepatitis B	75 (75.8)	70 (70.7)
Hepatitis C	2 (2.0)	3 (3.0)
Other	22 (22.2)	26 (26.3)
Heavy drinking, *n* (%)		
Yes	21 (21.2)	30 (30.3)
No	78 (78.8)	69 (69.7)
Cirrhosis, *n* (%)		
With	56 (56.6)	44 (44.4)
Without	43 (43.4)	55 (55.6)
Tumor size, *n* (%)		
>5 cm	51 (51.5)	58 (58.6)
≤5 cm	48 (48.5)	41 (41.4)
Tumor number, *n* (%)		
3	4 (4.0)	2 (2.0)
2	9 (9.1)	10 (10.1)
1	86 (86.9)	87 (87.9)
MVI grade, *n* (%)		
High-risk	50 (50.5)	40 (40.4)
Low-risk	49 (49.5)	59 (59.6)

Median RFS 27.7 vs 15.5 mo
2-year RFS 62.2% vs 36.6%





Median OS not reached
2-year OS 87.9% vs 78.0%

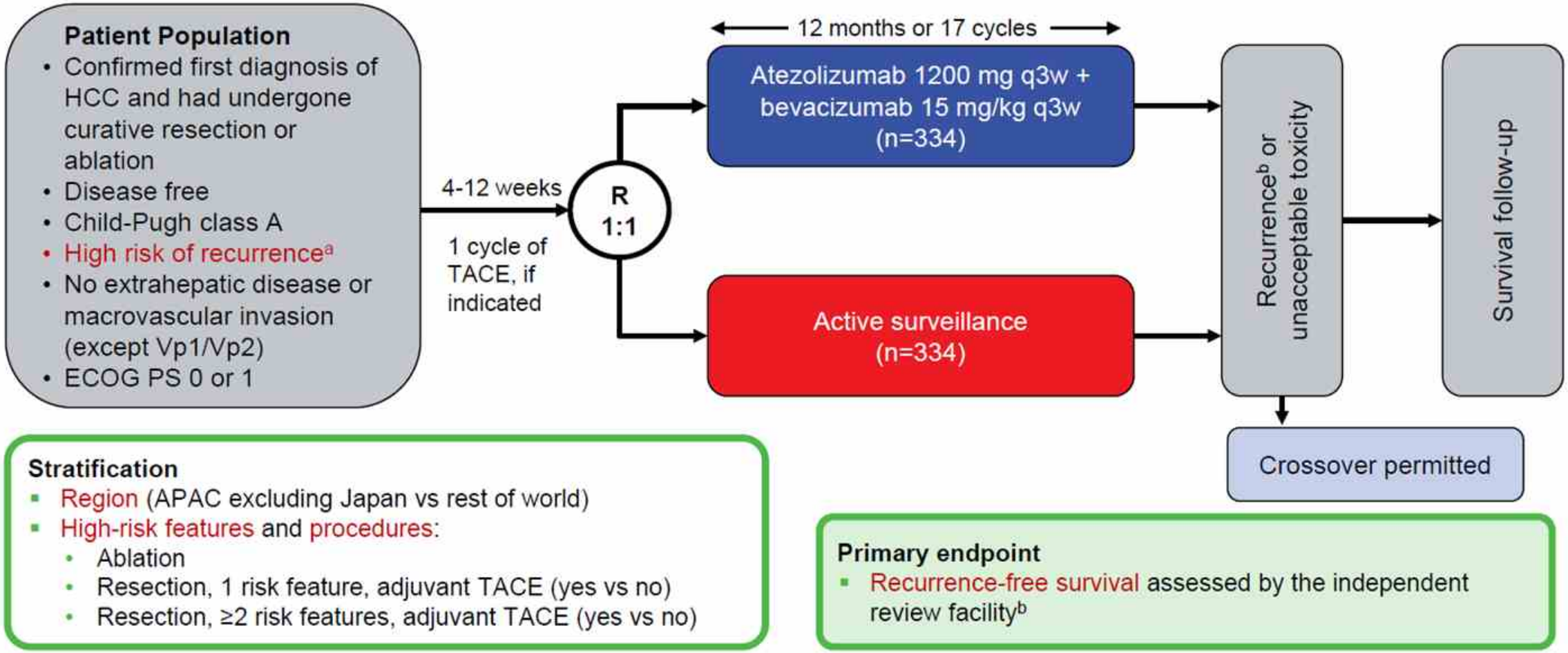
Wang K et al. Nat Med. 2024.

Phase 3 Global Adjuvant Immunotherapy Trials in HCC

Trial no	Sponsor	n	Centers	Eligibility	Therapy 1	Therapy 2	Primary Endpoint	Start	End	Status	Protocol Chair
NCT03867084 (KEYNOTE-937)	Merck Sharp & Dohme Corp.	950	193 sites	• Complete radiological response ≥4 weeks after complete surgical resection/ablation • Randomization within 12 weeks of the date of surgical resection or local ablation	Pembrolizumab at 200 mg on Day 1 of each 21-day cycle for up to 17 cycles.	Placebo on Day 1 of each 21-day cycle for up to 17 cycles.	RFS (up to 6 years) OS	May 28, 2019	Oct 31, 2027	Active, Not Recruiting	MSD
NCT04102098 (IMbrave050)	Hoffmann-La Roche	662	173 sites	1st diagnosis of HCC and curative resection or ablation (RFA or MVA) • No MVI/EHS • ECOG status of 0-1 • Child-Pugh A	Atezolizumab 1200mg and Bevacizumab 15mg/kg will be administered on Day 1 of each 21-day cycle.	Nil. Active surveillance.	RFS (Up to 39 months)	Dec 31, 2019	Jul 16, 2027	Active, Not Recruiting	Clinical Trials, Hoffmann-La Roche
NCT03383458 (CheckMate 9DX)	Bristol-Myers Squibb	530	218 sites	Resection or ablation • ECOG status of 0-1 • Child Pugh score of 5-6 • No tumor metastasis or co-existing malignant disease	Nivolumab – specified dose on specified days.	Placebo – specified dose on specified days.	RFS (Up to 49 months)	Dec 18, 2017	Dec 16, 2025	Active, Not Recruiting	BMS

Trial no	Sponsor	n	Centers	Eligibility	Therapy 1	Therapy 2	Therapy 3	Primary Endpoint	Start	End	Status	Protocol Chair
NCT03847428 (EMERALD-2)	Astrazeneca	888	182 sites	Resection / ablation • Histologically confirmed HCC and has completed curative therapy • ECOG status of 0-1 • Child Pugh score of 5-6 • No evidence of metastasis, macrovascular invasion or co-existing disease	Durvalumab 1120mg (Q3W) and Bevacizumab 15mg/kg (Q3W).	Durvalumab 1120mg (Q3W) + Bevacizumab placebo (Q3W).	Durvalumab placebo (Q3W) + Bevacizumab placebo (Q3W).	RFS (Up to 49 months)	Apr 29 2019	May 29 2026	Active, Not Recruiting	Jia Fan and Jennifer Knox

IMbrave 050 Study design



ClinicalTrials.gov, NCT04102098. ECOG PS; Eastern Cooperative Oncology Group performance status; Q3W, every three weeks; R, randomization; TACE, transarterial chemoembolization.

[a] **High-risk features** include: tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion Vp1/Vp2, or Grade 3/4 pathology.

[b] Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1.

Qin S et al. Lancet. 2023.

High-risk criteria by curative treatment

Curative treatment	Criteria for high risk of HCC recurrence
Resection	▪ ≤3 tumors, with **largest tumor >5 cm** regardless of vascular invasion,[a] or poor tumor differentiation (Grade 3 or 4) ▪ **≥4 tumors**, with largest tumor ≤5 cm regardless of vascular invasion,[a] or poor tumor differentiation (Grade 3 or 4) ▪ ≤3 tumors, with largest tumor ≤5 cm with **vascular invasion**,[a] and/or **poor tumor differentiation** (Grade 3 or 4)
Ablation[b]	▪ 1 tumor >2 cm but ≤5 cm ▪ Multiple tumors (≤4 tumors), all ≤5 cm

[a] Microvascular invasion or minor macrovascular portal vein invasion of the portal vein—Vp1/Vp2.
[b] Ablation must be radiofrequency ablation or microwave ablation.

Qin S et al. Lancet. 2023.

Baseline characteristics were balanced across arms

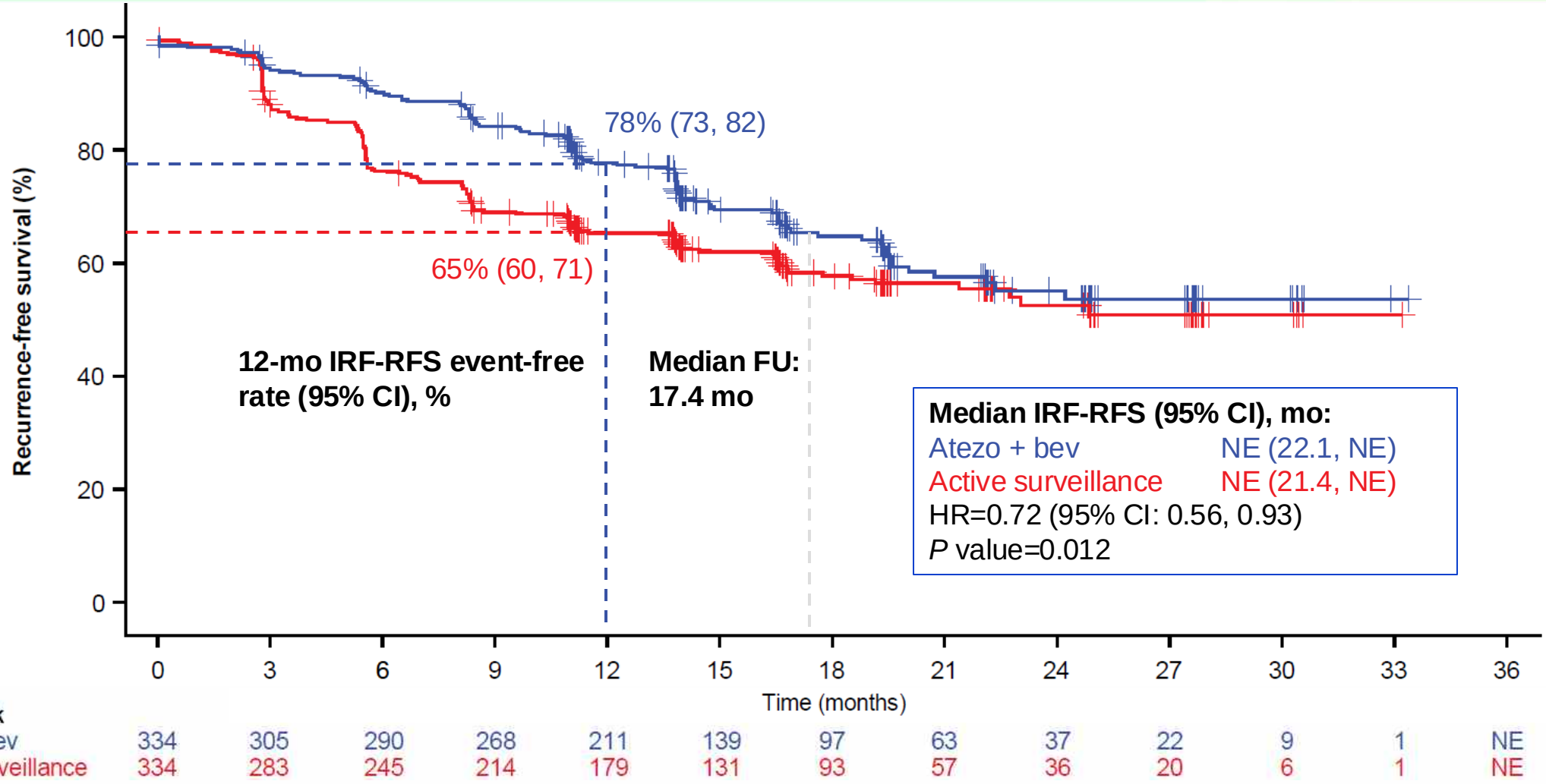
Characteristic	Atezo + bev (n=334)	Active surveillance (n=334)
Median age (range), years	60 (19-89)	59 (23-85)
Male sex, n (%)	277 (82.9)	278 (83.2)
Ethnicity, n (%) Asian | White | Other	276 (82.6) | 35 (10.5) | 23 (6.9)	269 (80.5) | 41 (12.3) | 24 (7.2)
Geographic region, n (%) Asia Pacific excluding Japan | Rest of world	237 (71.0) | 97 (29.0)	238 (71.3) | 96 (28.7)
ECOG PS score, n (%) 0 | 1	258 (77.2) | 76 (22.8)	269 (80.5) | 65 (19.5)
PD-L1 status, n (%)[a,b] ≥1% | <1%	154 (54.0) | 131 (46.0)	140 (50.4) | 138 (49.6)
Etiology, n (%) Hepatitis B | Hepatitis C | Non viral | Unknown	210 (62.9) | 34 (10.2) | 45 (13.5) | 45 (13.5)	208 (62.3) | 38 (11.4) | 41 (12.3) | 47 (14.1)
BCLC stage, n (%) 0 | A | B | C	2 (0.6) | 286 (85.6) | 25 (7.5) | 21 (6.3)	3 (0.9) | 281 (84.1) | 31 (9.3) | 19 (5.7)

Characteristic	Atezo + bev (n=334)	Active surveillance (n=334)
Resection, n	293	292
Longest diameter of largest tumour, median (range), cm	5.3 (1.0-18.0)	5.9 (1.1-25.0)
Tumours, n (%) 1 | >1	266 (90.8) | 27 (9.2)	260 (89.0) | 32 (11.0)
Adjuvant TACE following resection, n (%)	33 (11.3)	34 (11.6)
Any tumours >5 cm, n (%)	152 (51.9)	175 (59.9)
mVI present, n (%)	179 (61.1)	176 (60.3)
Minor MVI (Vp1/Vp2) present, n (%)	21 (7.2)	17 (5.8)
Poor tumour differentiation (Grade 3 or 4), n (%)	124 (42.3)	120 (41.1)
Outside up-to-7 criteria, n (%)	135 (46.1)	148 (50.7)
Ablation, n	41	42
Longest diameter of largest tumour, median (range), cm	2.5 (1.2-4.6)	2.6 (1.5-4.6)
Tumours, n (%) 1 | >1	29 (70.7) | 12 (29.3)	31 (73.8) | 11 (26.2)

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. Minor changes to baseline characteristics have been made following the IA. BCLC, Barcelona Clinic Liver Cancer; mVI, microvascular invasion; MVI, macrovascular invasion. [a] n=285 for atezo + bev and 278 for active surveillance. [b] PD-L1 expression is defined as the total percentage of the tumour area covered by tumour and immune cells stained for PD-L1 using the SP263 immunohistochemistry assay (VENTANA).

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

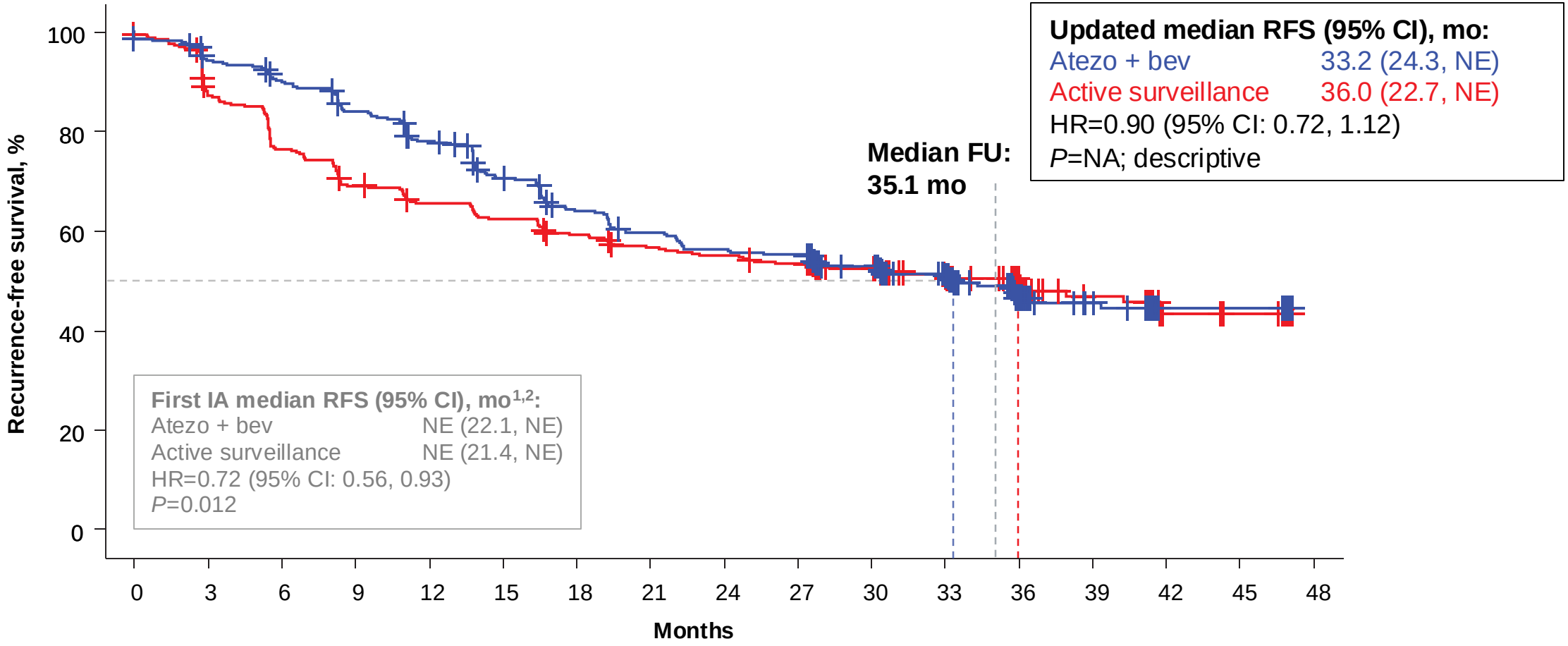
Primary endpoint: RFS from first IA



Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 110 of 334 patients (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death.
FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log rank.

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

Early RFS benefit was not maintained with longer follow-up



No. at risk

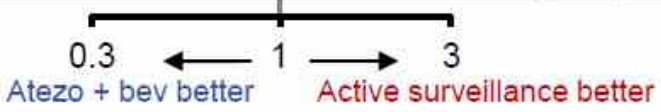
Atezo + bev	334	305	290	268	245	216	191	177	167	164	147	123	62	45	18	18	NE
Active surveillance	334	285	247	221	207	197	185	175	170	164	145	124	63	42	16	14	NE

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

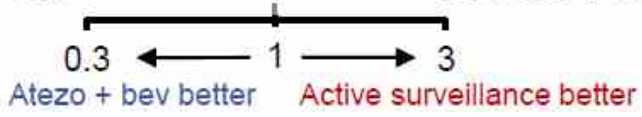
Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

Subgroup analysis for RFS

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



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



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IMbrave050 update
https://ter.li/q4cyl1

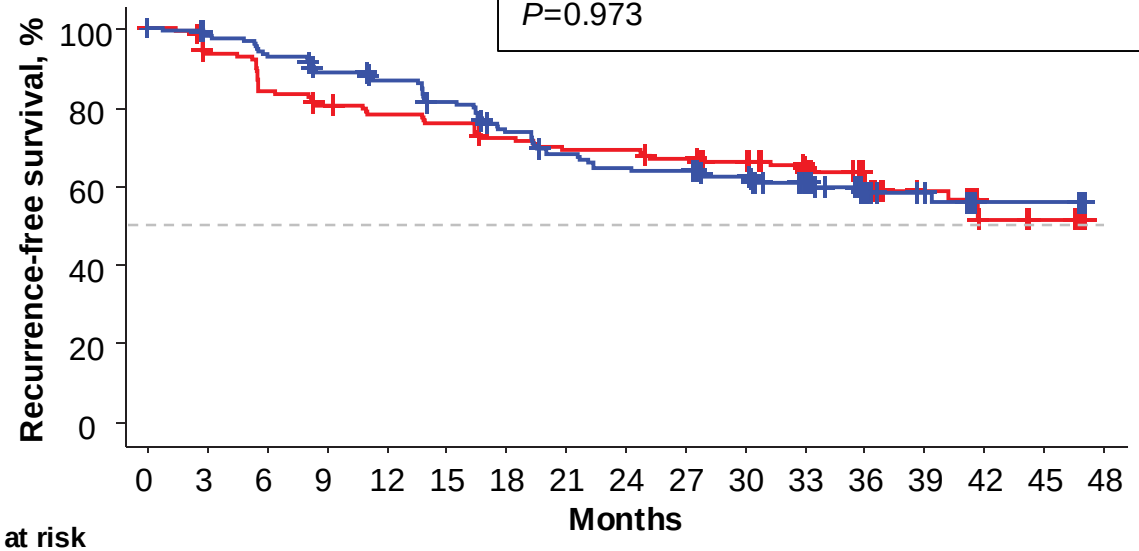
Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo.

[a] Patients who underwent ablation were categorized as NA.

RFS among resection patients was numerically better in those who were outside up-to-7 criteria

Within up-to-7 criteria

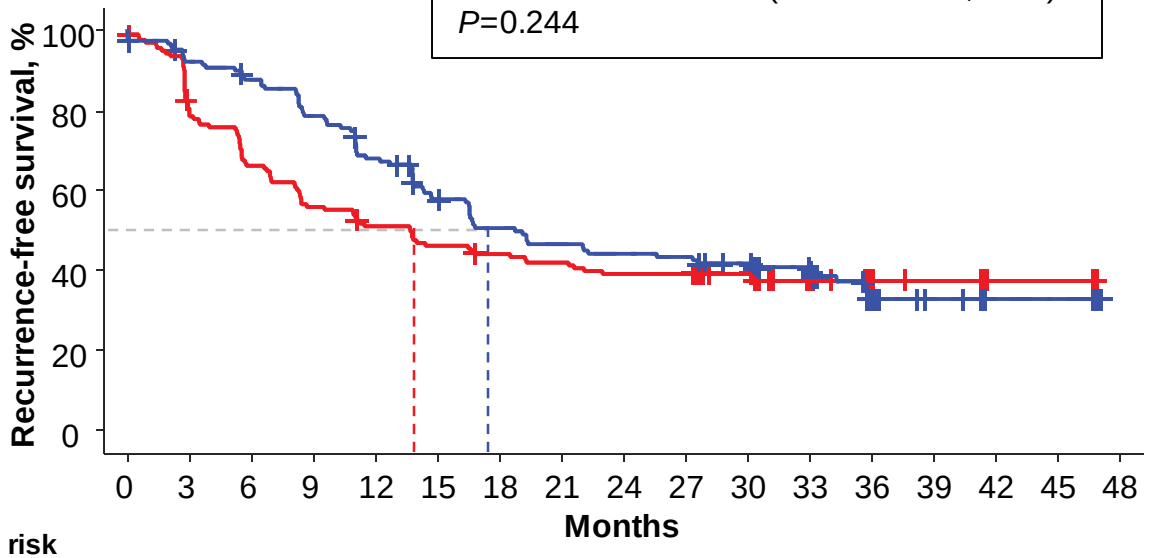
Post hoc median RFS (95% CI), mo:
Atezo + bev NE (35.9, NE)
Active surveillance NE (36.1, NE)
Unstratified HR=1.01 (95% CI: 0.70, 1.46)
P=0.973



No. at risk																	
Atezo + bev	158	148	141	132	127	118	105	96	91	90	84	70	35	26	7	7	NE
Active surveillance	144	128	115	109	105	102	96	92	92	88	83	75	42	27	9	7	NE

Outside up-to-7 criteria

Post hoc median RFS (95% CI), mo:
Atezo + bev 16.9 (14.7,27.6)
Active surveillance 13.7 (8.4,19.4)
Unstratified HR=0.84 (95% CI: 0.62, 1.13)
P=0.244

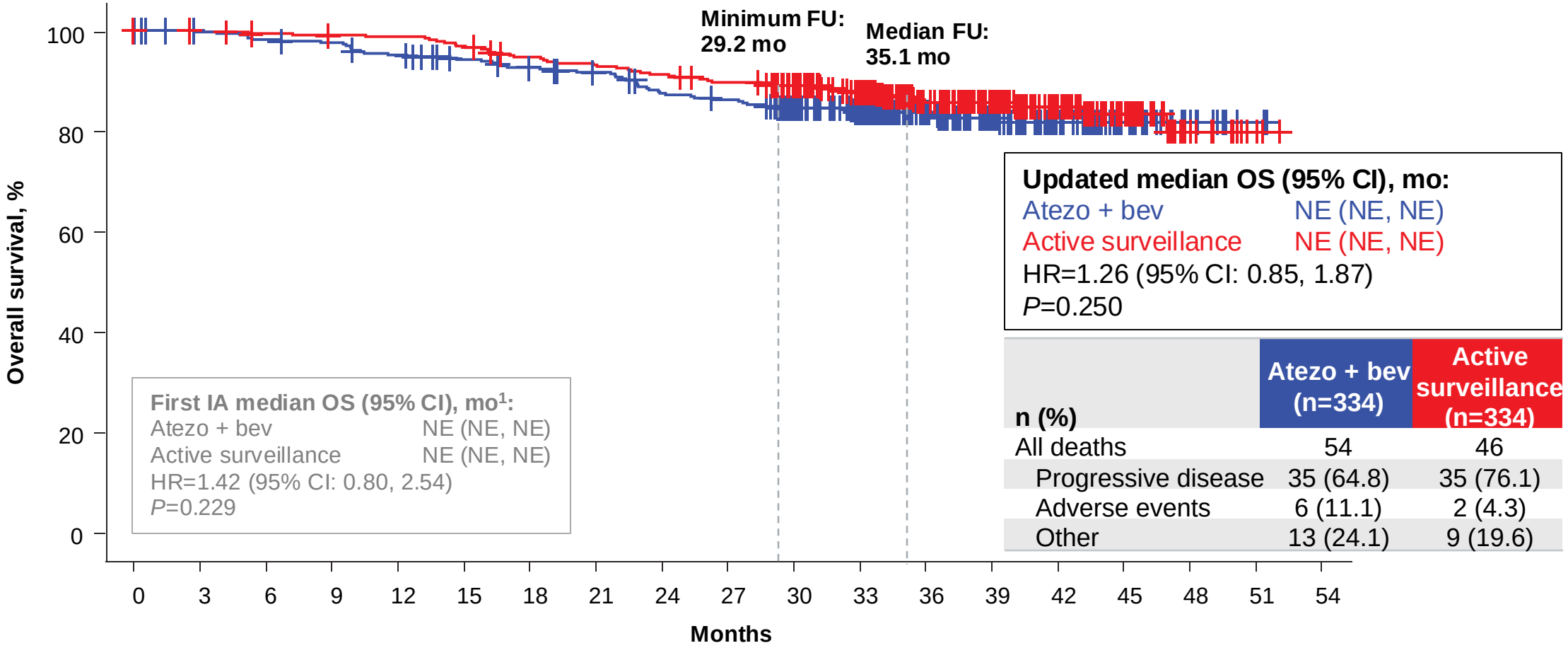


No. at risk																	
Atezo + bev	135	122	115	103	88	72	62	57	54	53	46	39	18	11	7	7	NE
Active surveillance	148	117	96	81	73	66	62	59	55	55	45	35	11	9	5	5	NE

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo.

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

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



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

No. at risk

Atezo + bev	334	327	322	319	310	301	294	286	271	266	243	206	142	101	60	34	16	3	NE
Active surveillance	334	327	323	321	320	314	304	299	293	286	266	226	157	108	71	38	15	3	NE

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

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

Recurrence patterns

BARCELONA 2024 ESMO congress

First post-baseline unequivocal recurrence

	Atezo + bev (n=334)	Active surveillance (n=334)
Patients with recurrence, n	141	160
Location of recurrence, n (%)		
Intrahepatic only	103 (73.0)	109 (68.1)
Extrahepatic only	35 (24.8)	44 (27.5)
Both intra- and extrahepatic	3 (2.1)	7 (4.4)
Outside Milan criteria, n (%)		
Yes	51 (36.2)	67 (41.9)
No	89 (63.1)	89 (55.6)
NA[a]	1 (0.7)	4 (2.5)
Outside up-to-7 criteria, n (%)		
Yes	51 (36.2)	67 (41.9)
No	89 (63.1)	89 (55.6)
NA[a]	1 (0.7)	4 (2.5)

Patients with intrahepatic recurrence (regardless of extrahepatic recurrence)

	Atezo + bev (n=334)	Active surveillance (n=334)
Intrahepatic recurrence, n	106	116
Macrovascular invasion, n (%)		
Yes	14 (13.2)	15 (12.9)
No	92 (86.8)	100 (86.2)
Not evaluable	0	1 (0.9)
Tumour liver lobe invasion, n (%)		
Unilobar	99 (93.4)	110 (94.8)
Bilobar	7 (6.6)	6 (5.2)

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. [a] Patients were considered NA for Milan and up-to-7 criteria if they did not have extrahepatic spread or MVI and had ≥1 non-measurable lesion.

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

First post-recurrence treatment

	Atezo + bev (n=147)	Active surveillance (n=156)
Curative intent, n (%)	49 (33.3)	59 (37.8)
Resection	28 (19.0)	28 (17.9)
Radiofrequency ablation	17 (11.6)	17 (10.9)
Microwave ablation	4 (2.7)	13 (8.3)
Other	0	1 (0.6)
Locoregional, n (%)	45 (30.6)	18 (11.5)
Embolisation	32 (21.8)	13 (8.3)
Radiation	13 (8.8)	5 (3.2)
Systemic therapy, n (%)	33 (22.4)	72 (46.2)
Atezolizumab + bevacizumab	3 (2.0)	61 (39.1)
Immunotherapy	2 (1.4)	2 (1.3)
Immunotherapy + TKI/immunotherapy + VEGF(R) mAb	11 (7.5)	2 (1.3)
Other	4 (2.7)	1 (0.6)
TKI	12 (8.2)	6 (3.8)
VEGF(R) mAb	1 (0.7)	0

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. Recurrence was assessed by the investigator. For the active surveillance arm, resection/radiofrequency ablation/microwave ablation received at crossover screening and crossover atezo + bev treatment, whichever was the first, was included. mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor; VEGF(R), vascular endothelial growth factor (receptor).

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

Overall safety trend was the same as the first IA

	Atezo + bev (n=332)	Active surveillance (n=330)
Treatment duration, median, mo	Atezo: 11.1 Bev: 11.0	NA
Patients with ≥1 AE, n (%)	326 (98.2)	208 (63.0)
Treatment-related AE	295 (88.9)	NA
Grade 3/4 AE, n (%)	141 (42.5)	46 (13.9)
Treatment-related Grade 3/4 AE	120 (36.1)	NA
Serious AE, n (%)	83 (25.0)	34 (10.3)
Treatment-related serious AE	45 (13.6)	NA
Grade 5 AE, n (%)	6 (1.8)	1 (0.3)
Treatment-related Grade 5 AE	2 (0.6)[a]	NA
AE leading to dose interruption of any study treatment, n (%)	158 (47.6)	NA
AE leading to withdrawal from any study treatment, n (%)	62 (18.7)	NA

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. In safety-evaluable patients. No additional Grade 5 AEs occurred in the atezo + bev arm since the first IA. AE, adverse event. [a] Oesophageal varices haemorrhage and ischaemic stroke; 1 was related to atezo and bev and the other was related to bev only.

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

AE of any grade with an incidence rate of ≥10% in either treatment group by preferred term

Event, n (%)	Atezo + bev (n=332)		Active surveillance (n=330)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Proteinuria	154 (46.4)	29 (8.7)	12 (3.6)	0
Hypertension	127 (38.3)	61 (18.4)	10 (3.0)	3 (0.9)
Platelet count decreased	66 (19.9)	15 (4.5)	22 (6.7)	4 (1.2)
Aspartate aminotransferase increased	52 (15.7)	3 (0.9)	18 (5.5)	2 (0.6)
Alanine aminotransferase increased	47 (14.2)	2 (0.6)	18 (5.5)	3 (0.9)
Hypothyroidism	47 (14.2)	0	1 (0.3)	0
Arthralgia	40 (12.0)	1 (0.3)	8 (2.4)	1 (0.3)
Pruritus	40 (12.0)	1 (0.3)	3 (0.9)	0
Rash	40 (12.0)	0	1 (0.3)	0
Blood bilirubin increased	34 (10.2)	1 (0.3)	23 (7.0)	1 (0.3)
Pyrexia	34 (10.2)	0	7 (2.1)	0

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. In safety-evaluable patients.

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

What have we learned, and questions raised?

What is the ideal duration of adjuvant therapy?

- 1 year or longer?

Should we expect improvement in RFS to result in improved OS?

- Crossover
- Second tumor – bimodal relapse curve

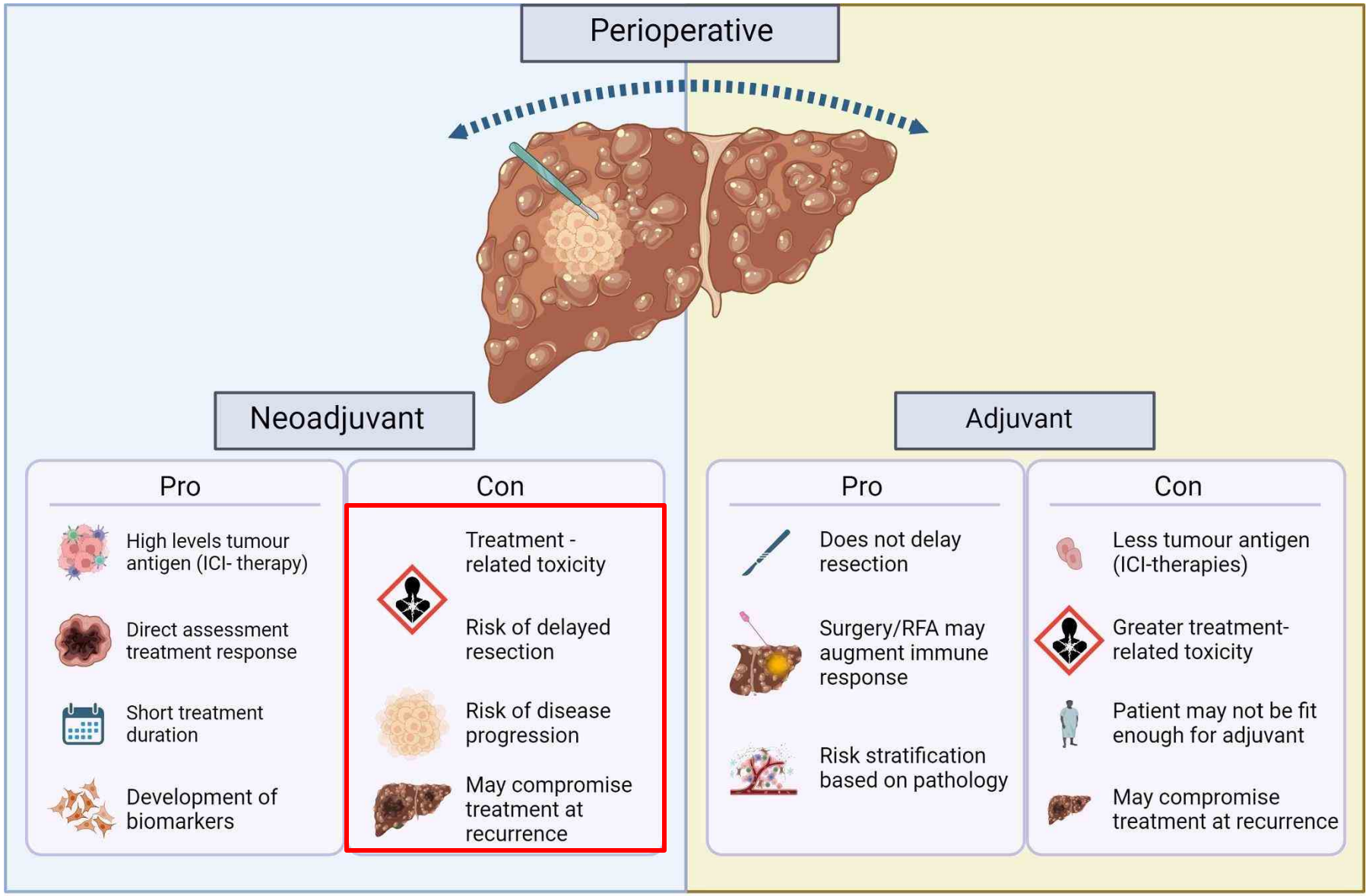
How do we select patients likely to benefit from adjuvant therapy?

- Predictive biomarkers
- High-risk features (e.g., beyond up-to-7)

Future Directions…

- Neoadjuvant/peri-operative approaches?

Pros and cons of neoadjuvant vs adjuvant approaches



Vogel A. Hepatology. 2023.

Advantages and disadvantages of approaches to perioperative treatment in HCC

	Adjuvant (resectable)	Neoadjuvant (resectable)	Downstaging/ conversion	Transplant neoadjuvant/ downstaging
Rationale	Reduce recurrences and improve OS	Reduce recurrences and improve OS Improve surgical outcomes	Improve chance for curative resection Limit extent of surgery	Improve chances for transplant/cure
Advantages	RFA and surgery may augment immune response No delay of resection Histology-informed patient selection	Tumor in situ Generate diverse immune response Faster endpoints, eg, MPR Translational research	Downstage to resectability Treats micrometastatic disease	May improve outcomes in high-risk patients
Disadvantages		Toxicity Delay of surgery		Toxicity Graft rejection

Abbreviations: MPR, major pathologic response; OS, overall survival; RFA, radiofrequency ablation.

Vogel A. Hepatology. 2023.

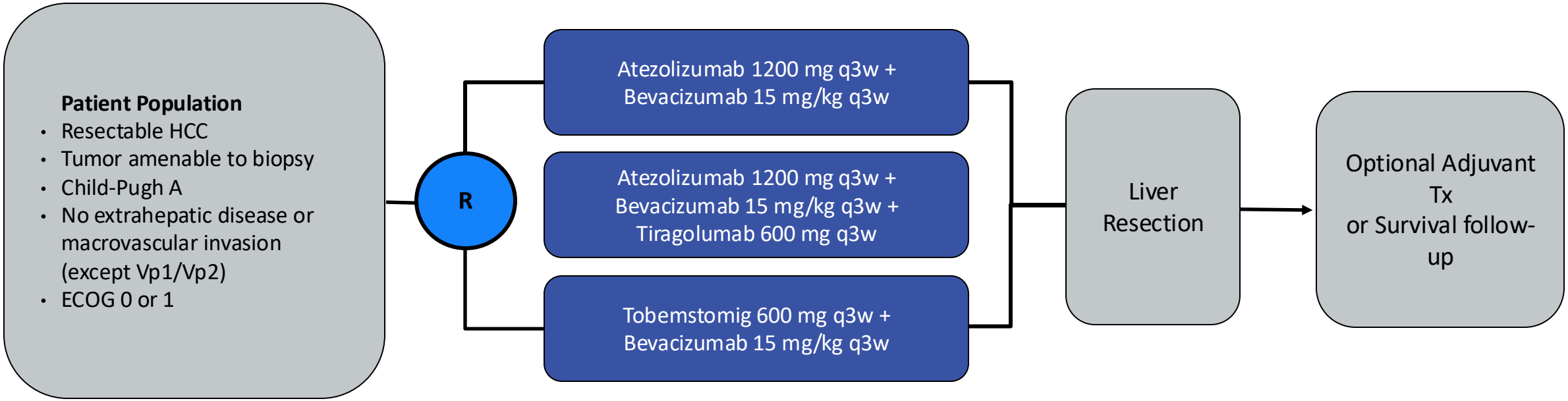
Published or present neoadjuvant trials of ICI/ICI combinations in resectable or potentially resectable HCC

Trial/NCT	Phase	Treatment arms	N	1°EP	Adjuvant	MPR definition	MPR, n (%)	pCR[a], n (%)	ORR	Dropout rate[b]	Surgical delays, (n/%)
Marron et al[14] NCT03916627	2	Cemiplimab	21	MPR	6 mo	>70%	4/20 (20%)	3/20 (15%)	3/20 (15%)	1/21 (5%)	1 (5.8%)
Kaseb et al[15] NCT03222076	2	Nivolumab vs. Nivolumab/ Ipilimumab	27	Safety/tolerability	2 y	>70%	3/9 (33%) 3/11 (27%)	2/9 (22%) 3/11 (27%)	3/13 (23%) 0/11(0%)	7/27 (26%)	0
Xia et al[16] NCT04297202	2	Camrelizumab/Apatinib	18	ORR MPR	6 mo	>90%	3/17 (18%)	1/17 (6%)	3/18 (17%)	1/18 (6%)	0
Ho et al[17] NCT03299946	1	Cabozantinib/Nivolumab	15	Safety/tolerability	No	>90%	5/12 (42%)	1/12 (8%)	1/14 (7%)	3/15 (20%)	0
PRIME-HCC NCT03682276	1b/2	Ipilimumab/Nivolumab	26	Delay to surgery/safety	No	>70%	8/19 (42%)	6/19 (32%)	6/23 (26%)	1/20 (0.5)	1 (4%)
Shi et al[18] NCT03867370	1b/2	Toripalimab vs Toripalimab/ Lenvatinib	16	MPR	48 wk	>50%	2/8 (25%) 1/8 (13%)	1/16 (6%)	NA	0/16 (0%)	0

Vogel A. Hepatology. 2023.

Ph Ib/II MORPHEUS neo-HCC: Study Design (Study Ongoing)

A study evaluating the efficacy and safety of **neoadjuvant immunotherapy** combinations in patients with surgically resectable hepatocellular carcinoma



Primary endpoint

- Major pathological response

Secondary endpoints

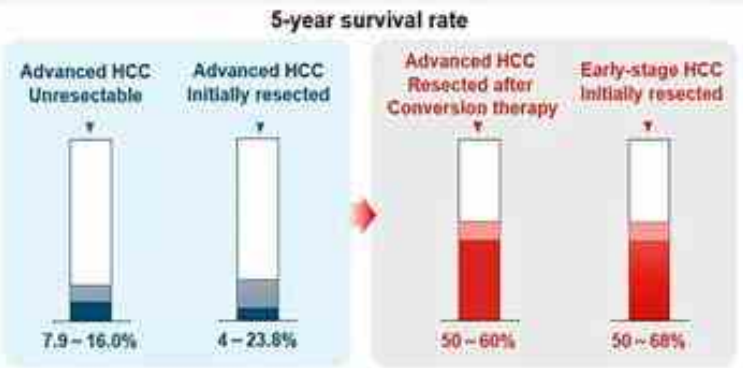
- Pathological complete response (pCR)
- Relapse-free survival (RFS)
- Event-free survival (EFS)
- Overall survival (OS)
- OS rate at 24 months
- Overall Response Rate (ORR)
- Proportion of participants downstaged to within Milan criteria
- R0 resection rate

NCT05908786

Emergence of treatment paradigm in advanced unresectable HCC with conversion therapy

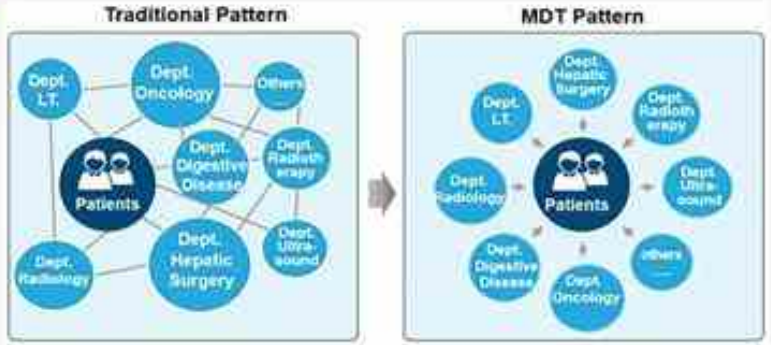
Current Status of Conversion Therapy

- Advanced HCC poses survival challenges
- Effective tumor downstaging brings surgical opportunities for uHCC patients
- Diverse combined conversion approaches show remarkable and promising results
- Lack of guidelines or standard protocols



Multi Disciplinary Team (MDT Model)

- Establishment of a stable MDT
- Convenient communication channels
- Comprehensively evaluation
- Timely decision-making or adjustment of treatment strategies



Short-term goal

Curative-intent Resection

Ultimate goal

High-quality Long-term Survival

Wang et al. Cancer Science. 2024.

In China, HCC conversion therapy has made significant progress in recent years

1990s

Studies reported 5-year survival rates of 50-60% in patients undergoing 'conversion and resection', **preliminarily demonstrating the benefit of conversion therapy**[1]

2019

Conversion therapy was **first listed as one of the treatment options for unresectable HCC by Chinese guidelines**[2]

2021

The **Chinese expert consensus on conversion therapy** for hepatocellular carcinoma was published[3]

Review Article

Chinese expert consensus on conversion therapy for hepatocellular carcinoma (2021 edition)

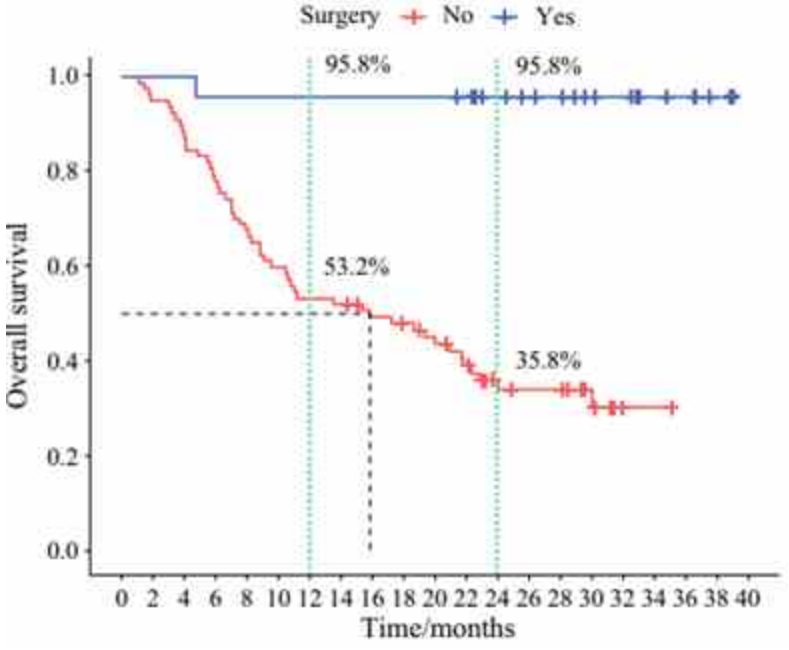
Hui-Chuan Sun[1], Jian Zhou[1], Zheng Wang[1], Xiufeng Liu[2], Qing Xie[3], Weidong Jia[4], Ming Zhao[5], Xinyu Bi[6], Gong Li[7], Xueli Bai[8], Yuan Ji[9], Li Xu[10], Xiao-Dong Zhu[1], Dousheng Bai[11], Yajin Chen[12], Yongjun Chen[13], Chaoliu Dai[14], Rongping Guo[15], Wenzhi Guo[16], Chunyi Hao[17], Tao Huang[18], Zhiyong Huang[19], Deyu Li[20], Gang Li[21], Tao Li[22], Xiangcheng Li[23], Guangming Li[24], Xiao Liang[25], Jingfeng Liu[26], Fubao Liu[27], Shichun Lu[28], Zheng Lu[29], Weifu Lv[30], Yilei Mao[31], Guoliang Shao[32], Yinghong Shi[1,33], Tianqiang Song[34], Guang Tan[35], Yunqiang Tang[36], Kaishan Tao[37], Chidan Wan[38], Guangyi Wang[39], Lu Wang[40], Shunxiang Wang[41], Tianfu Wen[42], Baocai Xing[43], Bangde Xiang[44], Sheng Yan[45], Dinghua Yang[46], Guowen Yin[47], Tao Yin[48], Zhenyu Yin[49], Zhengping Yu[50], Bixiang Zhang[19], Jialin Zhang[51], Shuijun Zhang[52], Ti Zhang[53], Yamin Zhang[54], Yubao Zhang[55], Aibin Zhang[56], Haitao Zhao[57], Ledu Zhou[58], Wu Zhang[59], Zhenyu Zhu[60], Shukui Qin[61], Feng Shen[62], Xiujun Cai[63], Gaojun Teng[64], Jianqiang Cai[65], Minshan Chen[66], Qiang Li[67], Lianxin Liu[68], Weilin Wang[69], Tingbo Liang[70], Jiahong Dong[71], Xiaoping Chen[19], Xuehao Wang[72], Shusen Zheng[73], Jia Fan[1]; Alliance of Liver Cancer Conversion Therapy, Committee of Liver Cancer of the Chinese Anti-Cancer Association

1. Chen X et al. Front Oncol. 2021.
2. Zhou J et al. Liver Cancer 2020.
3. Sun HC et al. Hepatobiliary Surg Nutr. 2022.

Conversion surgery is associated with better survival benefit than palliative care or upfront surgery in patients with intermediate/advanced-stage HCC

OS with conversion-surgery was significantly better than non-surgical palliative care[1]

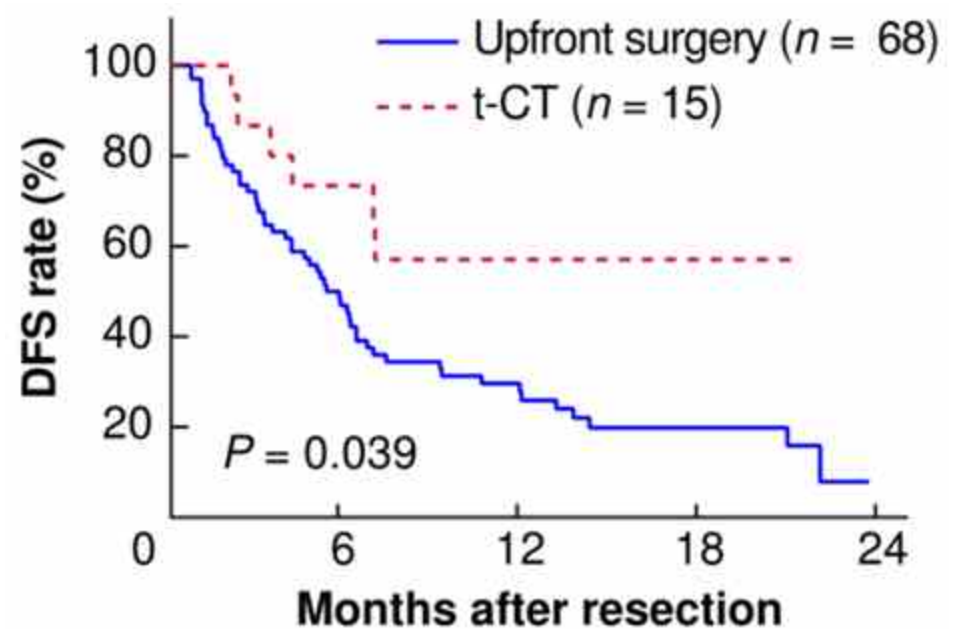
24-month survival rates were 95.8% vs 35.8% for patients who underwent vs did not undergo conversion surgery



- Study enrolled 101 patients who received combined TKI/anti-PD-1 antibodies as 1L treatment for initially uHCC, including 24 patients (23.8%) who underwent R0 resection after initiation of systemic therapy

The DFS of conversion-surgery was significantly higher than upfront surgery[2]

mDFS was not reached vs 5.4 months for patients with conversion-surgery vs upfront surgery



- 30 patients with initially uHCC receiving triple combination therapy (t-CT) were enrolled, 15 of whom underwent conversion-surgery

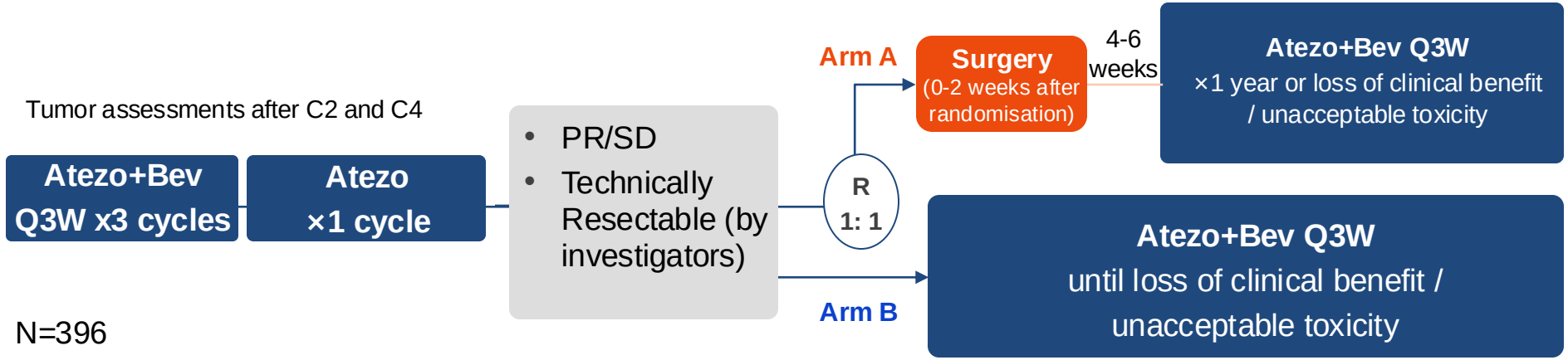
1. Zhu XD et al. Ann Surg Oncol. 2023.
2. Qu WF et al. BJS Open. 2022.

TALENTop IIS: Hepatic Resection with Peri-operative Atezo/Bev in HCC Patients with MVI

- A multicentre, randomised, open-label study evaluating the efficacy and safety of hepatic resection for HCC with macrovascular invasion after initial atezolizumab plus bevacizumab therapy

Patient Population

- ECOG 0-1
- Confirmed diagnosis of HCC
- No prior anti-tumour therapies
- ≥1 measurable lesion
- MVI(+)
- EHS(-)
- Remnant liver volume (RLV%) ≥ 25%
- Child-Pugh A



N=396

Primary endpoint: Time-to-treatment failure (TTF) (IRF-RECIST v1.1)

- Defined as the time from randomization to the first documented treatment failure (i.e., local recurrence or progression, EHS, or death from any cause)

Dose: Atezo 1200mg Q3W IV
Bev 15mg/kg Q3W IV

Secondary endpoint:

- OS (the time from randomisation to death)
- TTF (INV-RECIST v1.1, IRF/INV-mRECIST)
- ORR (Induction and arm B)
- TTEHS (the time from randomisation to EHS)
- RFS (Arm A)
- R0 rate (Arm A)
- pCR rate (Arm A)
- Safety

Stratification factors:

- Target lesion shrinkage vs non-shrinkage
- ECOG PS 0 vs 1

PR: partial response; SD: stable disease; Q3W: once every 3 weeks; MVI: macrovascular invasion; PVTT: portal vein tumor thrombosis; EHS: extrahepatic spread; IV: intravenous; INV: investigator; IRF: Independent review facility; RFS: recurrence-free surviva; pCR: pathological complete regression; TTEHS: time to EHS after randomization; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

https://www.clinicaltrials.gov. NCT04649489

TALENTop IIS Update: Conversion response and prognostic factors

From Apr 2021 to Dec 2022, 201 patients were enrolled and entered induction phase and completed induction phase therapy of atezo/bev at cut-off date (Apr 2023). Treatment efficacy in induction phase is analysed. Study is ongoing.

Baseline clinical characteristics of enrolled patients

Characteristic	n=201
Age, years	
Median (Range)	55 (26–78)
Aetiology (%)	
HBV	187 (93)
Vessel characteristic (%)	
MVI	201(100)
PVTT	191 (95)
Vp classification, n (%)	
Vp1	3 (1.5)
Vp2	37 (18.4)
Vp3	108 (53.7)
Vp4	43 (21.4)
Tumour size by IRF (mm)	
Mean	100
Range	26-231

Tumour response of enrolled patients

n=201	RECIST1.1, n (%)	mRECIST
ORR,%	38 (18.9)	47 (23.4)
PR	38 (18.9)	46 (22.9)
SD	106 (52.7)	97 (48.3)
DCR,%	71.6	144 (71.7)

In univariate logistic regression, the following clinical measures were associated with randomization (i.e. high viability for conversion):

VP1-2 PVTT
AFP <400 ng/mL
NLR (neutrophil-to-lymphocyte ratio) <2.63
Tumor diameter <100 mm

Of 201 patients, **73 patients (36.3%) were evaluated as suitable for R0 resection and randomized**. Atezo/bev showed high response rate and conversion rate in the HCC patients with MVI, suggesting a promising conversion strategy in this population.

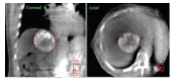
Wang et al. ESMO ASIA 2023.

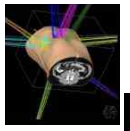
Sequential transarterial chemobolization and stereotactic radiotherapy followed by immunotherapy (START-FIT)

A novel tri-modality strategy

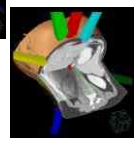
HKU Med

TACE
(Tumor lipoidal staining facilitates SBRT planning)





SBRT
- Direct anti-tumor effect



Immunotherapy

Patient centered care
- Only 1 episode of hospital stay for TACE
- SBRT – daily visits for 5 days
- IO – day center
- *No* incision
- *No* anaesthesia
- **6 months – a well-defined treatment endpoint for patients**

Sequential transarterial chemoembolisation and stereotactic body radiotherapy followed by immunotherapy as conversion therapy for patients with locally advanced, unresectable hepatocellular carcinoma (START-FIT): a single-arm, phase 2 trial

Chi Leung Chiang, Keith Wan Hang Chiu, Kenneth Sik Kwan Chan, Francis Ann Shing Lee, James Chun Bong Li, Catherine Wing Suet Wan, Wing Chiu Dai, Tai Chung Lam, Wengi Chen, Natalie Sean Man Wong, Andy Lai Yin Cheung, Venus Wan Yan Lee, Vince Wing Hang Lau, Aya El Helali, Kwan Man, Feng Ming (Spring) Kong, Chung Mau Lo, Albert Chi-Yan Chan**

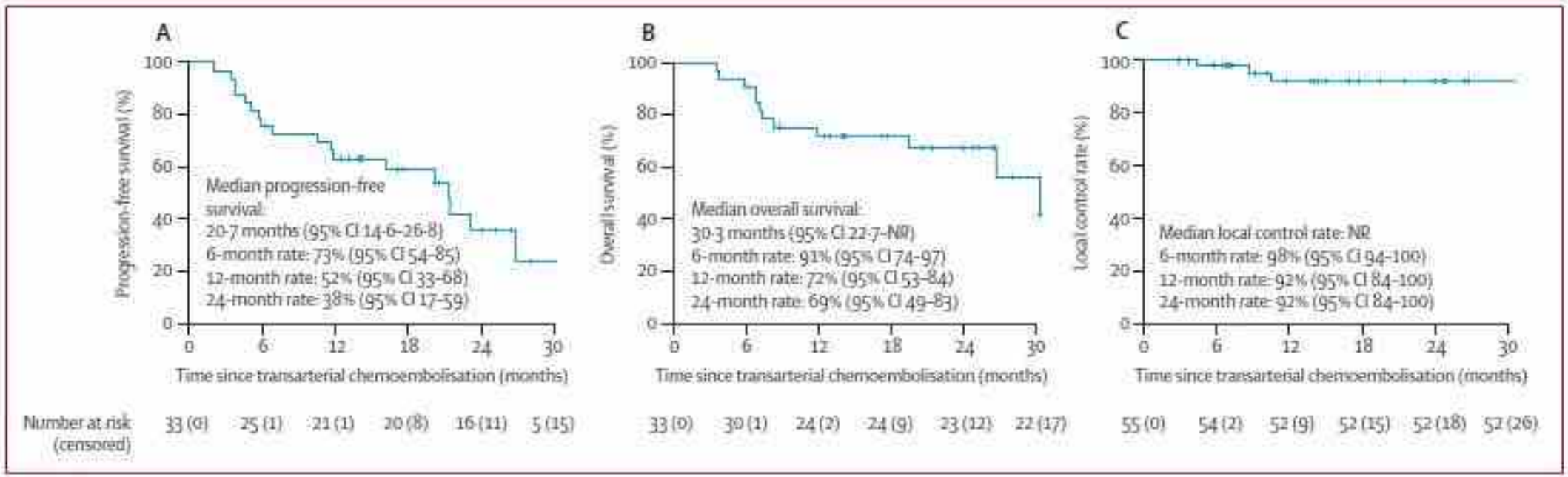
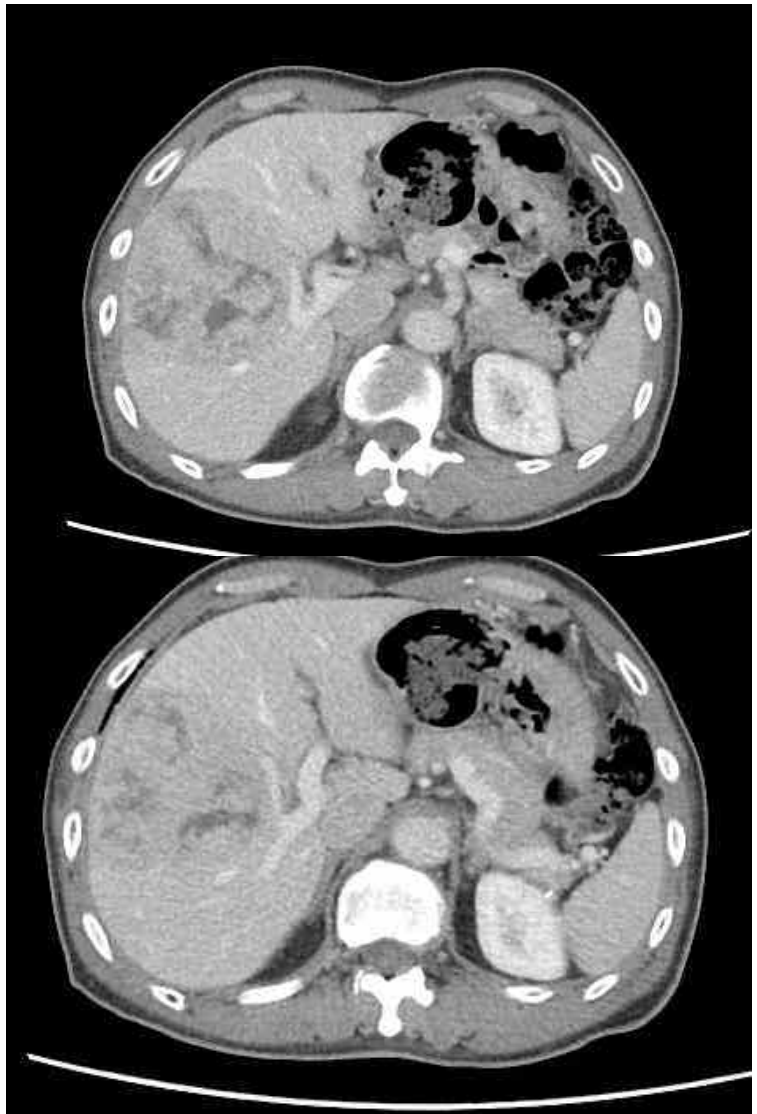


Figure 3: **Survival outcomes and local control**

(A) Progression-free survival, per patient (n=33). (B) Overall survival, per patient (n=33). (C) Local control, per lesion (n=55). NR=not reached.

Chiang CL….Chan AC. Lancet Gastro & Hepatol 2023 Feb

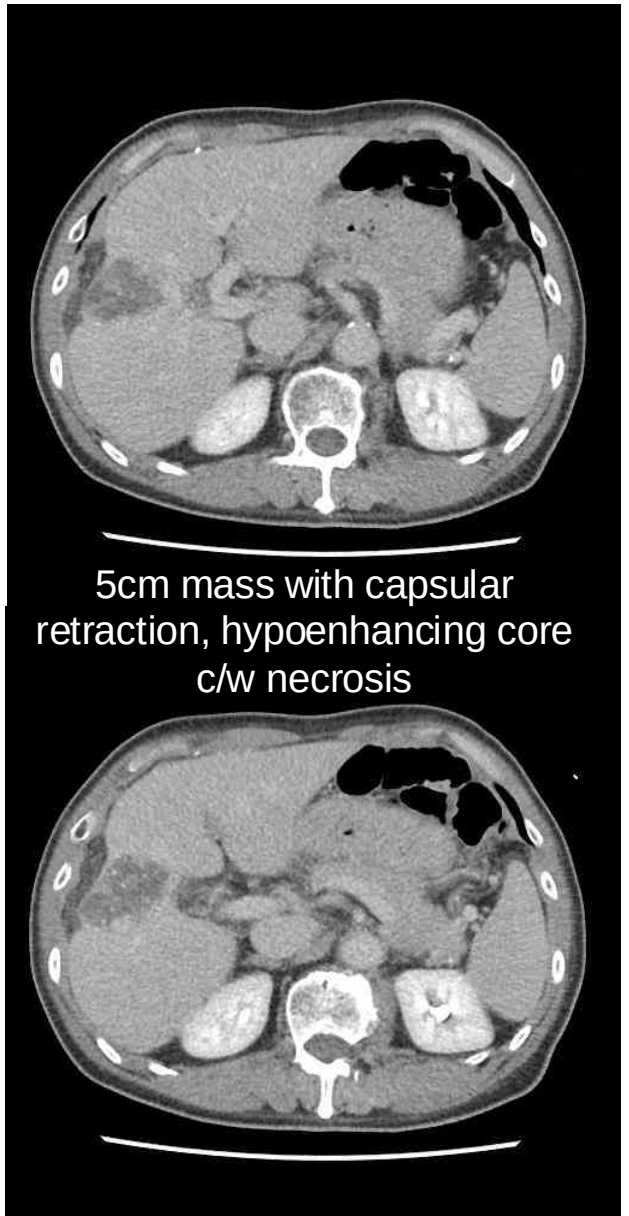
M/70, STEMI 2021 with PCI, AF
Non-B, Non-C HCC – 10.6x7.6x8.7 cm
ICG 20.2%, LFT normal, Plt 142x109/L,



Inoperable due to small left liver and borderline ICG

TACE x 1 24.5.2023
SBRT (5Gy x 5) 26-30.6.2023
Atezo + Bev 24.7.2024 Q3W x 11 cycles

Now eligible for S4/5 wedge resection

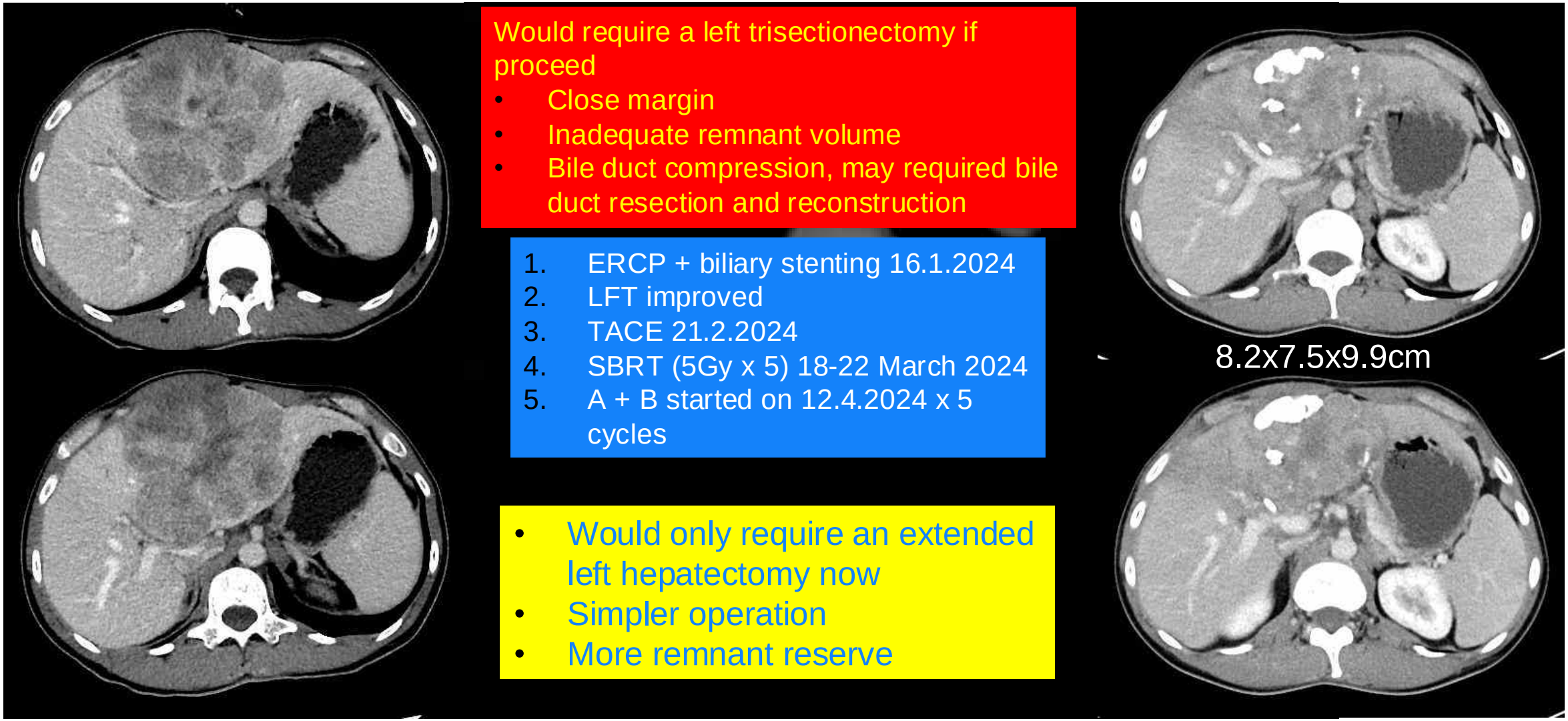


5cm mass with capsular retraction, hypoenhancing core c/w necrosis

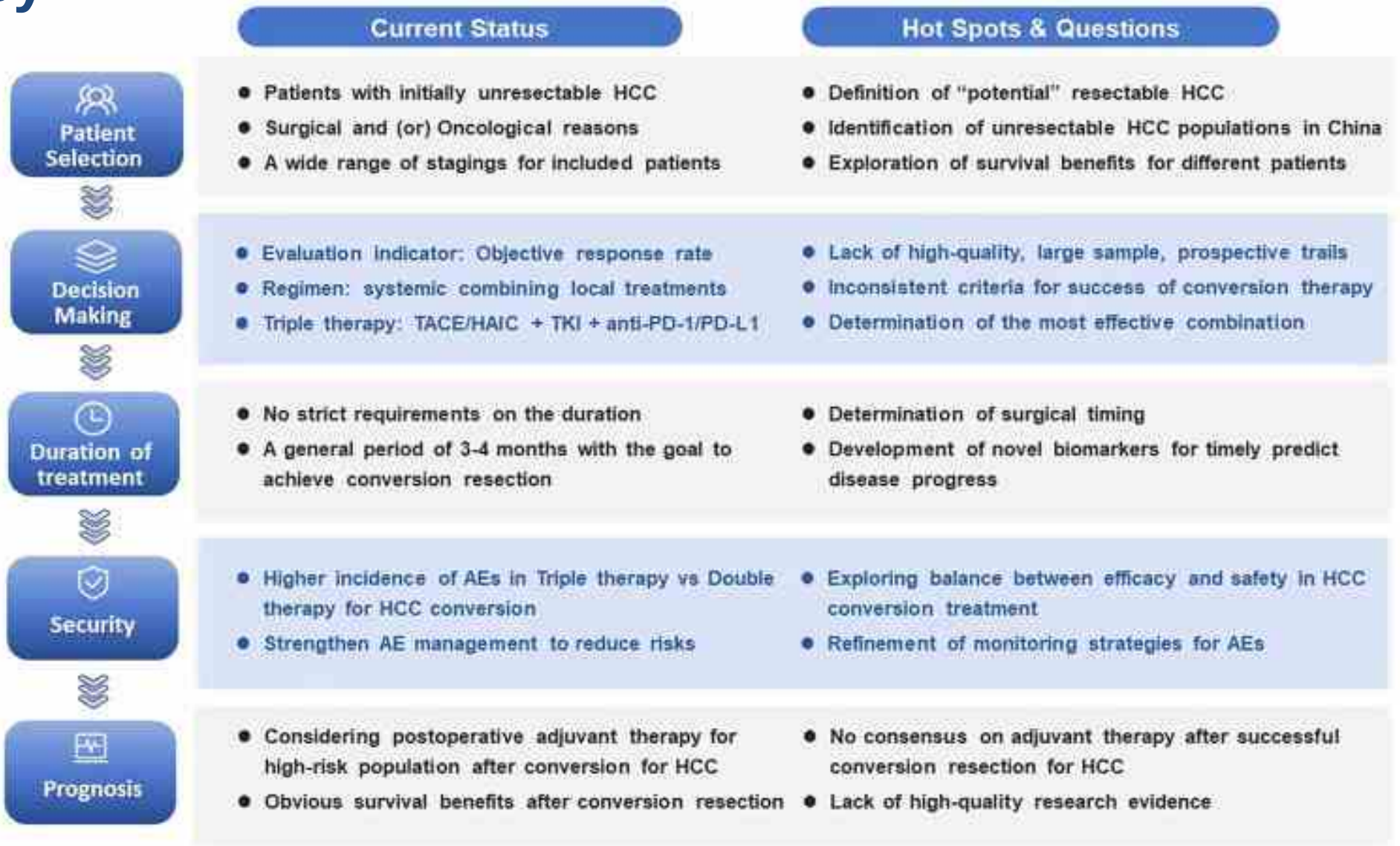
M/36, Good past health

HBV-HCC 11.8x8.7x11.3 cm

Bilirubin 10 umol/L, ALP 305 u/L, GGT 238 u/L, AST 298 u/L

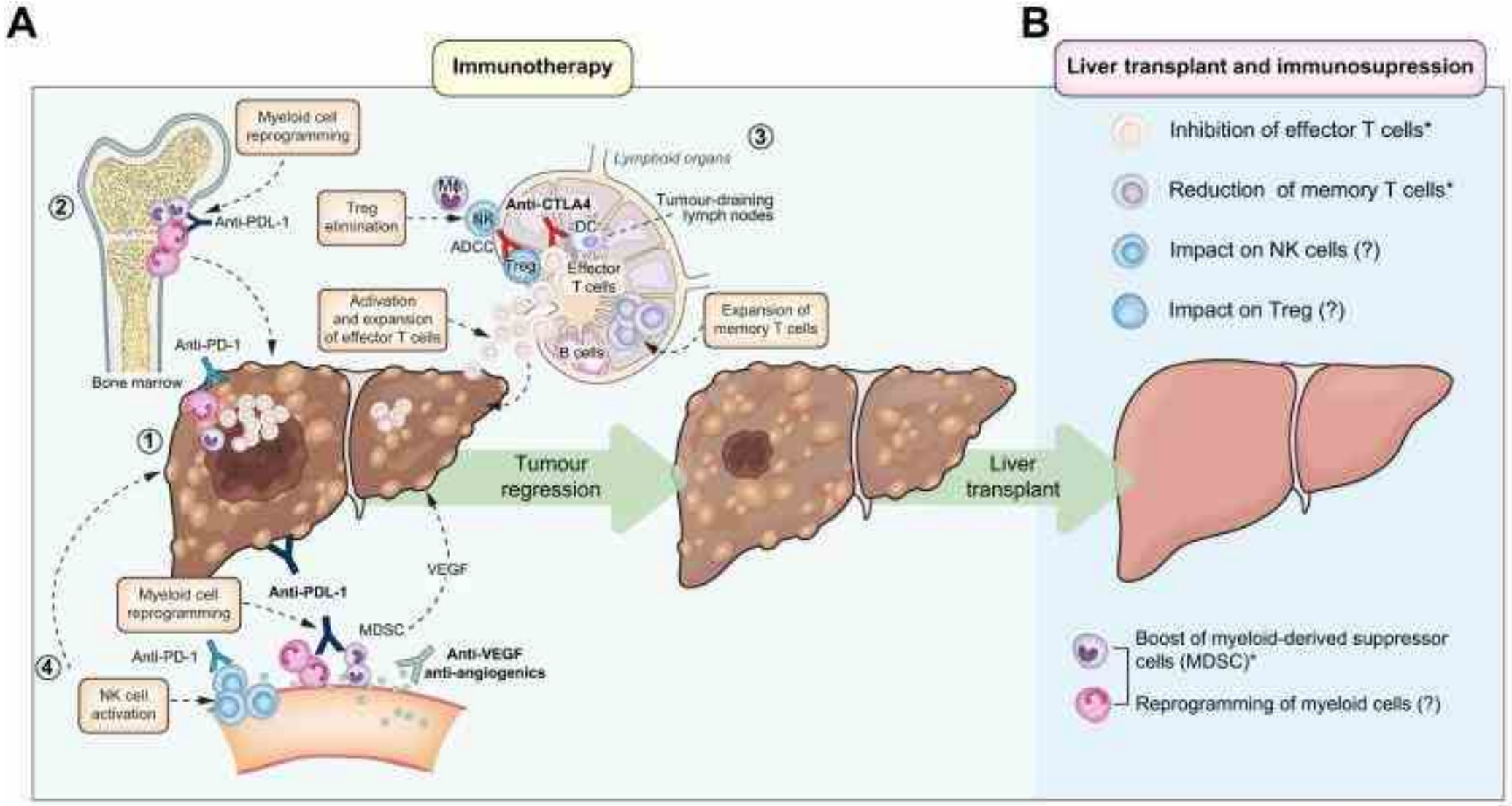


Current status and questions to be answered with conversion therapy



Wang et al. Cancer Science. 2024.

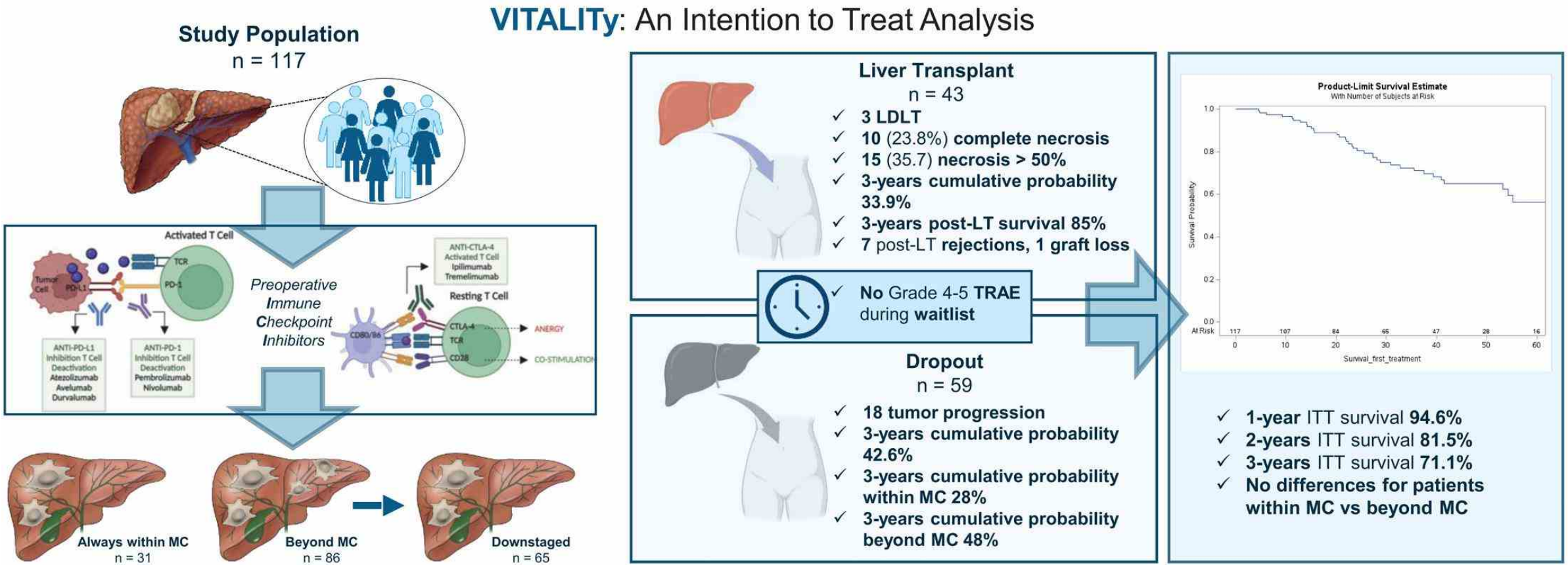
Challenge of pre-transplant immunotherapy and post-transplant immunosuppression



Mazzaferro et al. J Hepatol. 2024.

VITALITy: Validate Immunotherapy for HCC pre-Liver Transplant

- First, multicenter US study (2016 to 2023) to evaluate immune checkpoint inhibitors pre-LT
- High **downstaging percentage (76%)** and **survival rates (3-yr ITT OS 71%)**

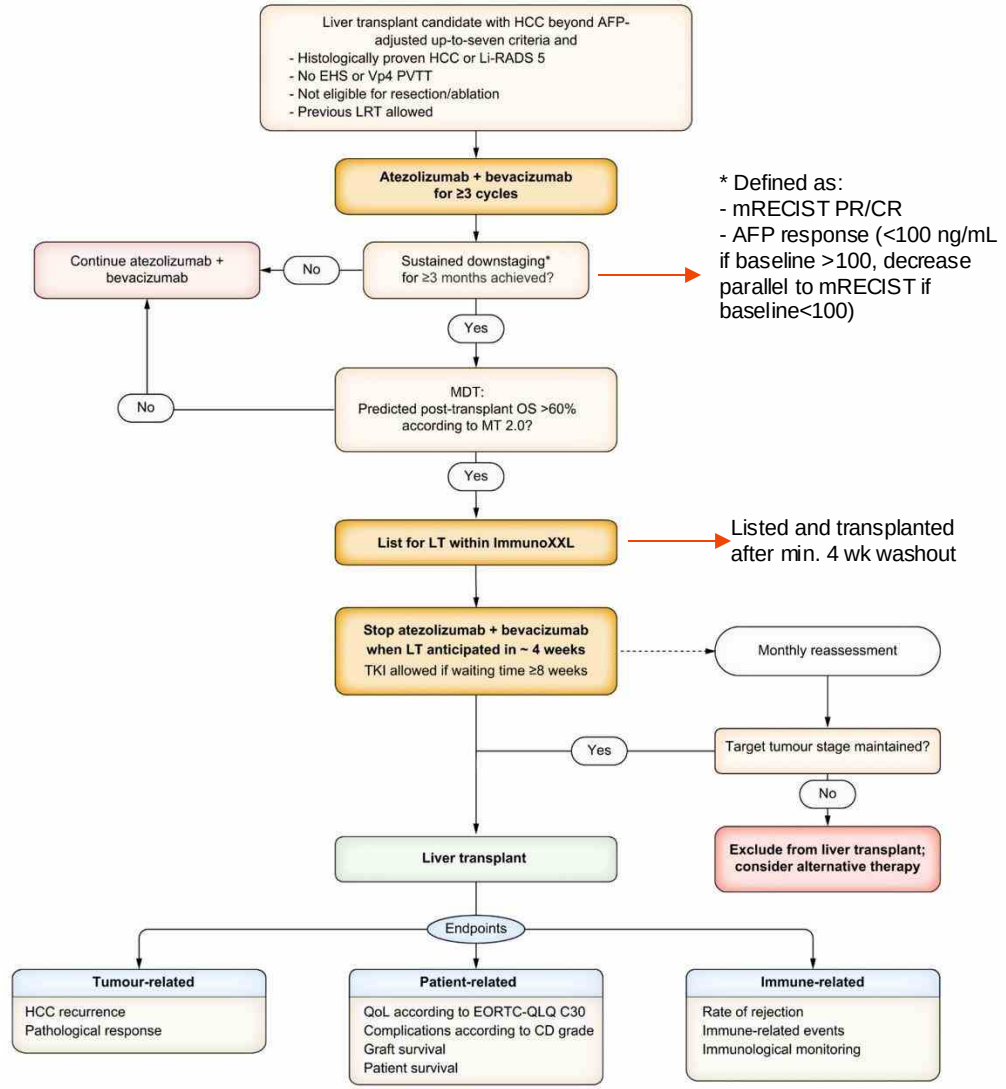


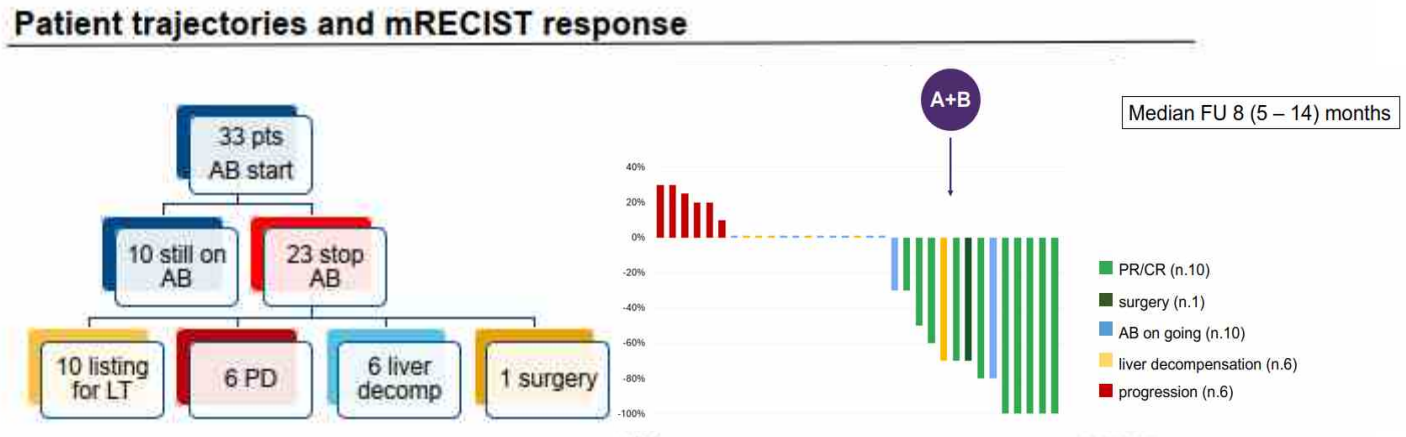
Study also highlights the potential efficacy of combining LRT with ICI. This strategy could be beneficial for high-risk patients, including those requiring downstaging or with elevated AFP levels despite LRTs.

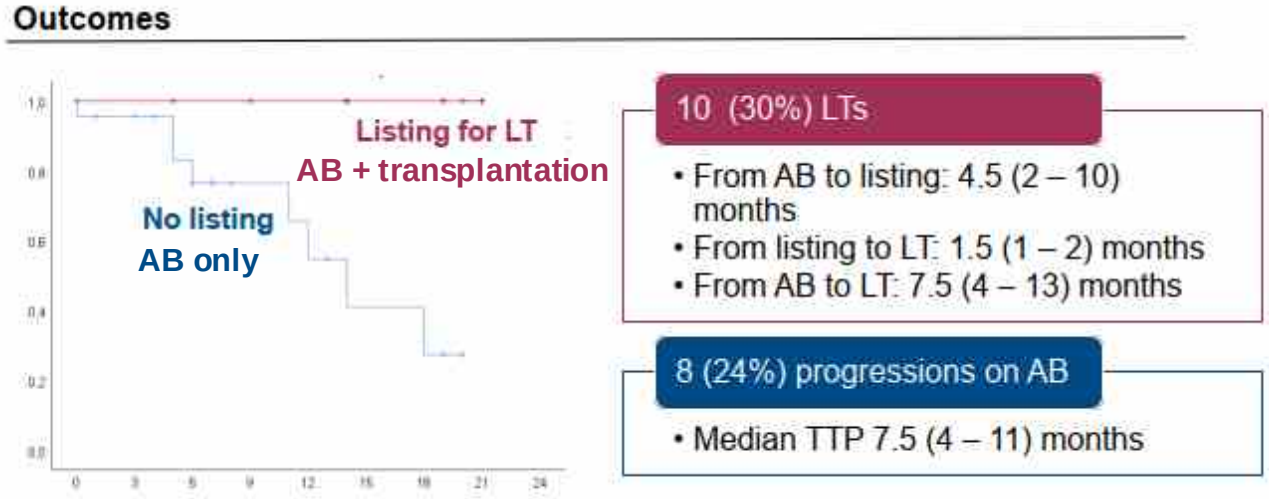
Tabrizian et al. J Hepatol. 2024.

ImmunoXXL: ITT analysis of atezo-bev for downstaging in HCC

- Observational, prospective, single-arm multicenter study evaluating LT in HCC with partial/complete and sustained (>3 months) response to atezo+bev (i.e. achieving >=60% post-transplant survival according to the Metroticket 2.0 calculator)
- A minimum washout period of 30 days prior to LT is required







Mazzaferro et al. EASL. 2024.

Conclusion

- Surgical resection is a common treatment option in APAC. However, clinical outcomes of surgical resection in HCC remains poor with high recurrence rates.

- IMbrave050 was the first Phase 3 study to demonstrate that an adjuvant immunotherapy-based regimen could delay recurrence following curative intent resection or ablation at the pre-specified IA. While initial RFS benefit with was not sustained over time, questions still remain on optimal duration and patient selection for adjuvant therapy.

- A number of early peri-operative trials also suggest that combination immunotherapies may be useful towards conversion and expanding eligibility for liver transplantation (downstaging) in select high-risk patients.

- A multidisciplinary, collaborative approach is essential to tailor individualized treatment plans and establish the most appropriate treatment sequence.