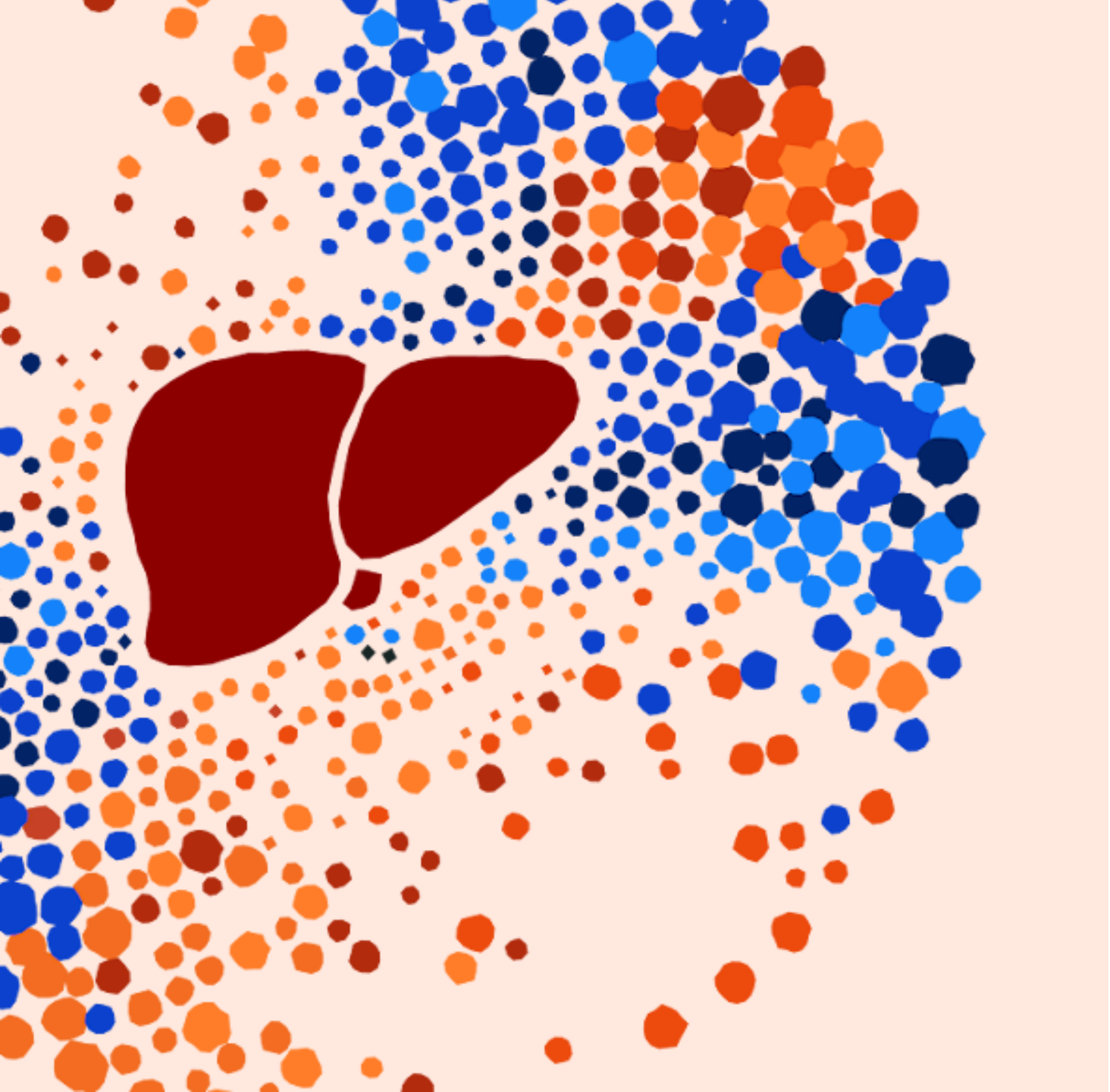
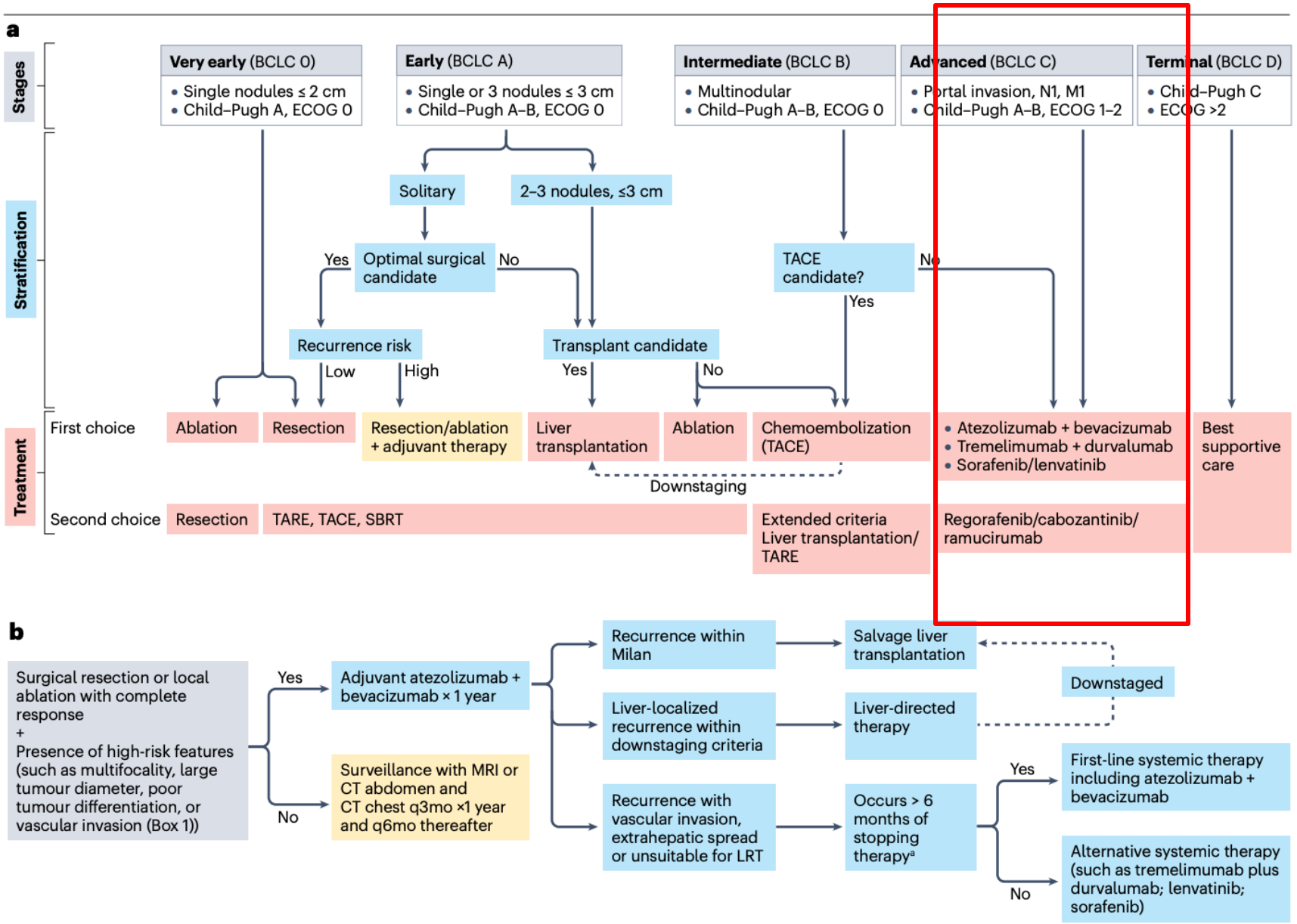


Systemic treatment in unresectable HCC

Dr Han Shuting
Medical Oncologist
National Cancer Centre Singapore

Still open discussion for (neo)adjuvant space



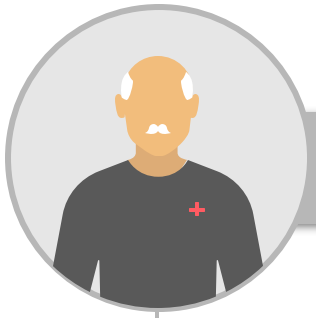
Llovet, J.M., Pinyol, R., Yarchoan, M. *et al.* Adjuvant and neoadjuvant immunotherapies in hepatocellular carcinoma. *Nat Rev Clin Oncol 2024*

Unresectable HCC is a heterogeneous disease and management is complex

Ranges from BCLC-B (low volume multifocal HCC) to extensive disease with EHS. Aetiology is also heterogenous

Factors leading to HCC development[1]

- HBV/HCV
- ALD
- MASLD
- Liver cirrhosis
- Male



Treatment considerations[2]

- Liver function
- Performance status, age
- Number/size of liver lesions
- Presence of varices/ascites (portal hypertension)
- Vascular invasion and/or EHS
- Comorbidities – cardiovascular/autoimmune risks
- Concomitant medications

ALD, alcoholic liver disease; EHS, extrahepatic spread; HBV, hepatitis B virus
HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease

1. Llovet et al. Nat Rev Dis Primers 2021; 2. Reig et al. J Hepatol 2022

Recommendations for 1L cancer immunotherapy in the HCC setting differ between regional guidelines

ASCO (2020)[1]

- Atezolizumab + bevacizumab is the preferred 1L regimen (Child-Pugh class A)

ESMO (2021 eUpdate)[3]

- Atezolizumab + bevacizumab is recommended as standard of care in 1L therapy

APASL (2017)[6†]

- No recommended cancer immunotherapy options at time of guideline publication

EASL (2021)[4]

- Atezolizumab + bevacizumab is recommended as 1L therapy
- If not feasible, sorafenib or lenvatinib

AASLD (2020 Consensus Conference)[2]

- Atezolizumab + bevacizumab is recommended as 1L therapy

BCLC (2022)[5]

- Atezolizumab + bevacizumab / durvalumab + tremelimumab* is recommended as 1L therapy for advanced-stage HCC
- If not feasible, sorafenib or lenvatinib or durvalumab

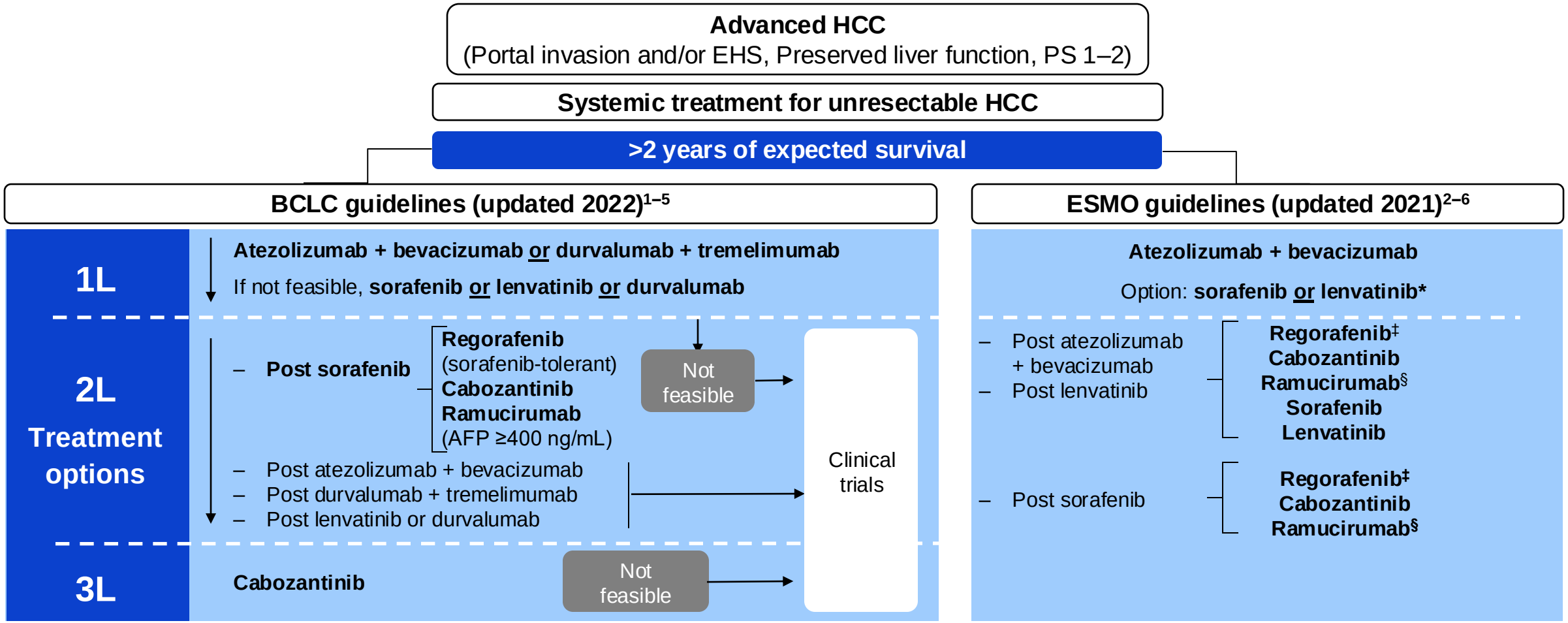
ILCA (2020)[7]

- Atezolizumab + bevacizumab is recommended as 1L therapy
- If not feasible, sorafenib or lenvatinib

*On 15 December 2022, the EMA's CHMP adopted a positive opinion for durvalumab + tremelimumab as first-line treatment for adults with advanced or unresectable HCC; †Patients not amenable to surgical resection, liver transplantation, LRT or TACE, in patients with good performance status and Child-Pugh class A liver function

1. Gordan et al. J Clin Oncol 2020; 2. Llovet et al. Hepatology 2021
3. Vogel et al. Ann Oncol 2021; 4. Bruix et al. J Hepatol 2021
5. Reig et al. J Hepatol 2022; 6. Omata et al. Hepatol Int 2017
7. ILCA Systemic Therapy Guidance (last updated November 2020)

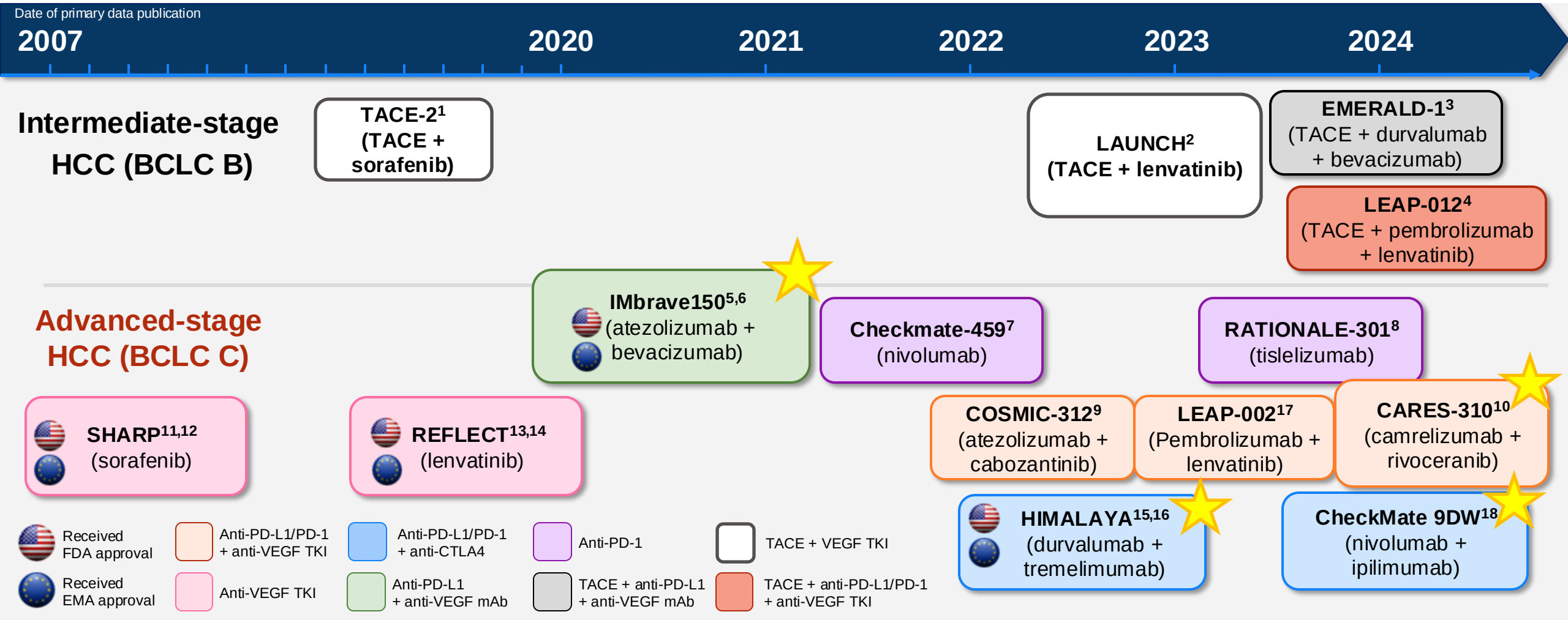
BCLC and ESMO guidelines for treating unresectable HCC[1,2]



*Non-inferiority to sorafenib established, no evaluable benefit; ‡Not recommended in TKI-naïve patients
§Only recommended in patients with AFP ≥400ng/mL
1/2/3L, first/second/third-line; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer
TKI, tyrosine kinase inhibitor

1. Reig et al. J Hepatol 2022; 2. Atezolizumab SmPC
3. Durvalumab SmPC; 4. Sorafenib SmPC; 5. Lenvatinib SmPC; 6. Vogel et al. Ann Oncol 2021

Recent phase III trials in advanced HCC



PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1
TACE, transarterial chemoembolisation; VEGF, vascular endothelial growth factor

1. Meyer et al Lancet Gastro Hep 2017 2. Peng et al JCO 2023 2. Lencioni et al. J Clin Oncol 2024; 3.Llovet et al. ESMO 2024 4. Galle et al. ASCO 2024 5. Finn et al. N Engl J Med 2020; 6. Atezolizumab SmPC 7. Yau et al Lancet Oncol 2022 8. Qin et al. JAMA Oncol 2023; 9. Kelley et al. Lancet Oncol 2022; 10. Qin et al. Lancet 2023; 11. Llovet et al. N Engl J Med 2008 12. Sorafenib SmPC; 13. Yamashita et al. J Gastroenterol 2020; 14. Lenvatinib SmPC; 15. Abou-Alfa et al. N Engl J Med 2022 16. Durvalumab SmPC; 17. Llovet et al. Lancet Oncol 2023 18 Galle et al ASCO 2024

HR of 0.66 for OS
HR of 0.65 for PFS

IMbrave150 (phase III): efficacy[1]

- Unresectable HCC
- No prior systemic therapy
- BCLC stage B (ineligible for LRT) or BCLC stage C
- Child-Pugh class A
- ECOG PS 0 or 1
- Patients with main portal vein tumour thrombosis included

N=501*

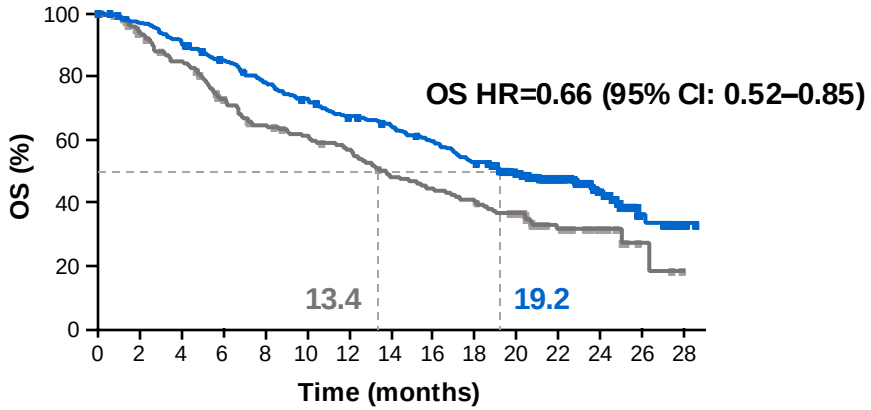
R 2:1

Atezolizumab + bevacizumab

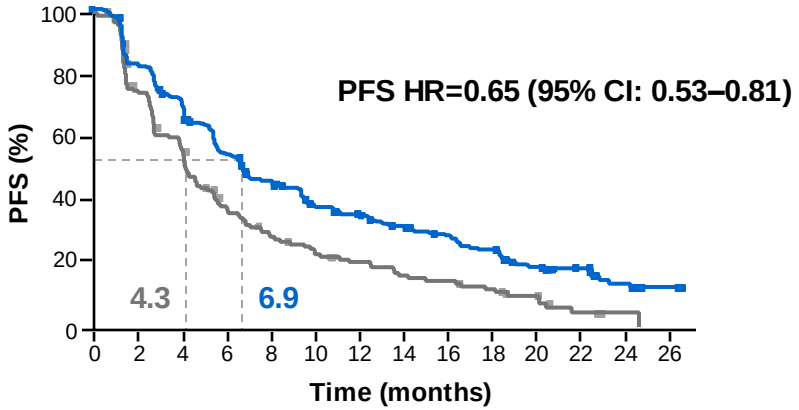
Open label

Sorafenib

Primary endpoint: OS



Primary endpoint: PFS



Response rates

ORR: 30% vs 11%

CR: 8% vs <1%

DCR: 74% vs 55%

Stratification factors for randomisation included: MVI and/or EHS (presence/absence); baseline AFP; (<400/≥400ng/mL); region (Asia excluding Japan/RoW including Japan); ECOG PS (0 or 1). *There were an additional 57 Chinese patients in the China extension cohort who were not included in the global population/analysis[2]
LRT, locoregional therapy; MVI, microvascular invasion; RoW, rest of world

1. Cheng et al. J Hepatol 2022
2. Qin et al. Liver Cancer 2021
NCT03434379

Well tolerated overall

IMbrave150: Safety and HRQoL

Primary analysis	Atezolizumab + bevacizumab (n=329)	Sorafenib (n=156)
All grade AEs, n (%) Grade 3–4	323 (98) 186 (57)	154 (99) 86 (55)
AEs leading to treatment discontinuation, n (%)	51 (16)	16 (10)

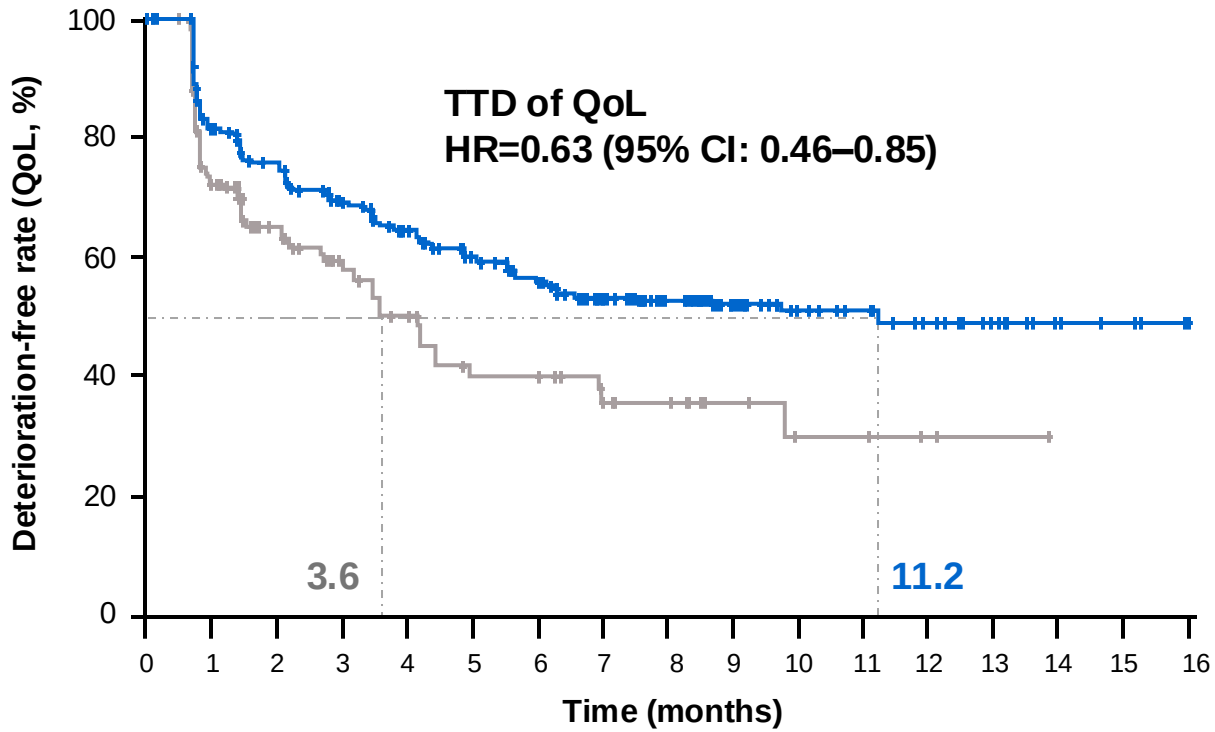
The most frequently reported Grade 3–4 TRAEs in the

Atezolizumab + bevacizumab group were:
- **Hypertension** (n=34, **10%**)
- **AST increase** (n=14, **4%**)
- **Proteinuria** (n=9, **3%**)

Sorafenib group were:
- **Hypertension** (n=14, **9%**)
- **PPE syndrome** (n=13, **8%**)
- **Diarrhoea** and **decreased appetite** (each n=6, **4%**)

HRQoL: TTD of QoL

Atezolizumab + bevacizumab (n=336) *vs* ***sorafenib (n=165)***



HRQoL, health-related quality of life; PPE, palmar-plantar erythrodysesthesia; QoL, quality of life; TRAE, treatment-related AE; TTD, time to deterioration

Finn et al. N Engl J Med 2020

OS HR 0.78, PFS HR no sig

HIMALAYA (phase III): efficacy

- Unresectable HCC
- No prior systemic therapy
- BCLC stage B (not eligible for LRT) or C
- Child-Pugh class A
- ECOG PS 0 or 1
- No tumour thrombus involving main trunk of portal vein

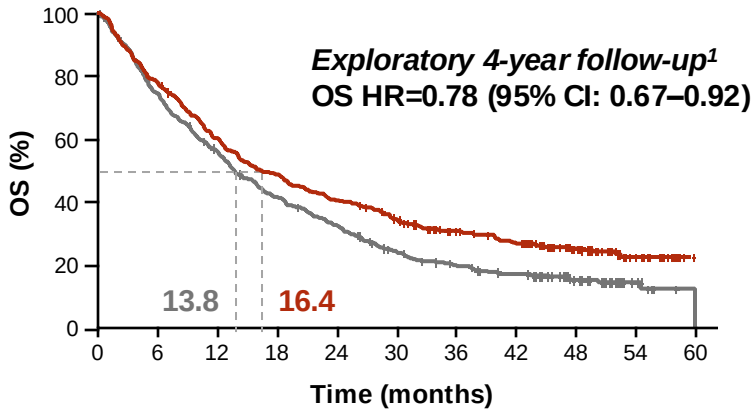
N=1171

R 1:1:1

- **Tremelimumab + durvalumab**
- **Durvalumab**
- **Sorafenib**

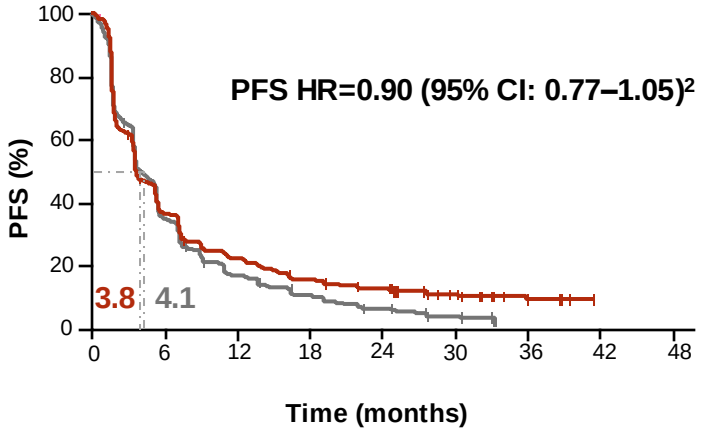
Primary endpoint: OS[1]

Tremelimumab + durvalumab vs sorafenib



Secondary endpoint: PFS[2]

Tremelimumab + durvalumab vs sorafenib



Response rates[2]

ORR: 20% vs 17%

CR: 3% vs 2%

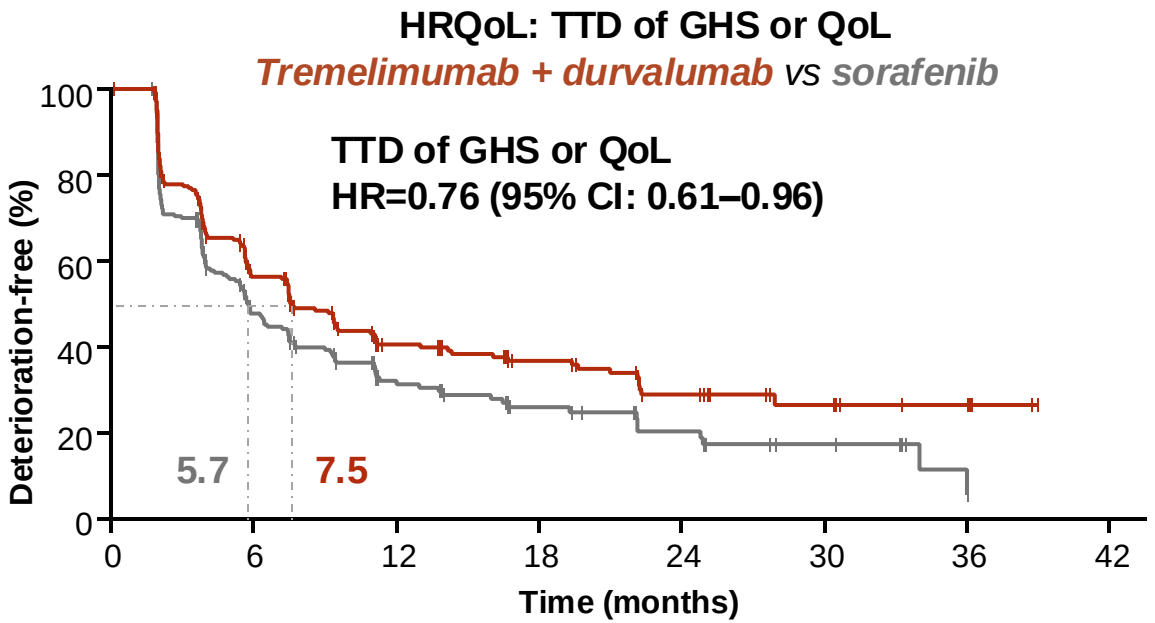
DCR: 60% vs 55%

1. Sangro et al. ESMO GI 2023; 2. Abou-Alfa et al. N Engl J Med Evid 2022
NCT03298451

imAE higher in doublet IO arm

HIMALAYA: safety and HRQoL

Primary analysis	Tremelimumab + durvalumab (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
Grade 3–4 AEs, n (%)	196 (51)	144 (37)	196 (52)
AEs leading to treatment discontinuation, n (%)	53 (14)	32 (8)	63 (17)
imAEs, n (%)	139 (36)	64 (17)	30 (8)
imAEs requiring high-dose steroids*, n (%)	78 (20)	37 (10)	7 (2)
imAEs leading to treatment discontinuation, n (%)	22 (6)	10 (3)	6 (2)



The most frequently reported Grade 3–4 TRAEs in the

Tremelimumab + durvalumab group were:
- **Lipase increase** (n=17, **4%**)
- **Diarrhoea** (n=13, **3%**)
- **Amylase increase** (n=10, **3%**)

Durvalumab group were:
- **AST increase** (n=9, **2%**)
- **Lipase increase** (n=8, **2%**)
- **ALT increase** and **diarrhoea** (n=5, **1%**)

Sorafenib group were:
- **PPE syndrome** (n=33, **9%**)
- **Hypertension** (n=20, **5%**)
- **Diarrhoea** (n=15, **4%**)

*The most frequently reported were hepatic events (n=55), diarrhoea/colitis (n=22), dermatitis/rash (n=20) and pancreatic events (n=9)
GHS, global health status; imAE, immune-mediated adverse event

Abou-Alfa et al. N Engl J Med Evid 2022

Good ORR but did not translate to PFS. OS is sig HR 0.79 cf lenva/sorafenib

CheckMate 9DW (phase III): efficacy

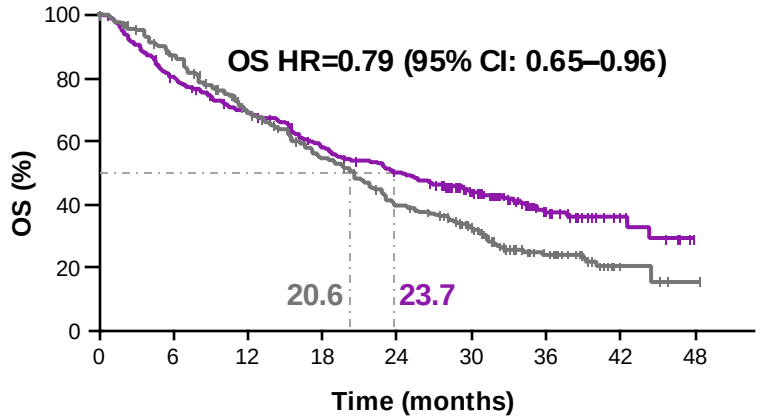
- Unresectable HCC
- No prior systemic therapy
- Child-Pugh class A
- ECOG PS 0 or 1
- No main portal vein invasion (Vp4)

N=668

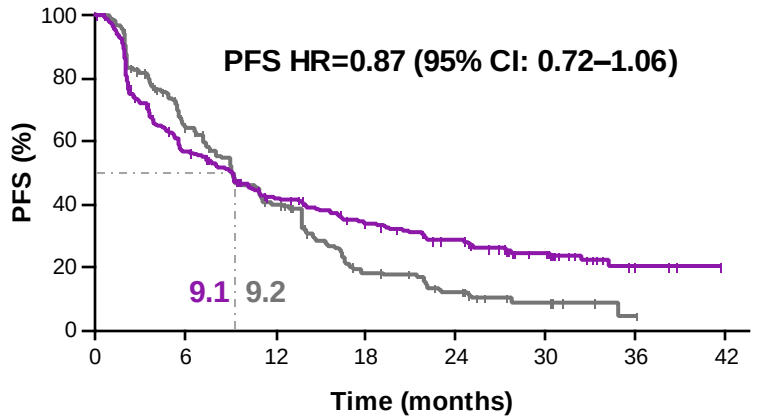
R 1:1

- **Nivolumab + ipilimumab***
- **Lenvatinib or sorafenib**

Primary endpoint: OS



Key exploratory endpoint: PFS per BICR



Response rates

ORR: 36% vs 13%

CR: 7% vs 2%

*Nivolumab + ipilimumab is given for up to 4 cycles Q3W, then nivolumab monotherapy is given Q4W until disease progression, unacceptable toxicity, withdrawal of consent and for a maximum of 2 years
BICR, blinded independent central review

Galle et al. ASCO 2024

imAEs are significant

CheckMate 9DW (phase III): safety and HRQoL

Primary analysis	Nivolumab + ipilimumab (n=332)	Lenvatinib or sorafenib (n=325)
Grade 3–4 TRAEs, n (%)	137 (41)	138 (42)
TRAEs leading to discontinuation, n (%)	59 (18)	34 (10)
imAEs, n (%)	191 (58)	–
imAEs requiring high-dose steroids*, n (%)	96 (29)	–
imAEs leading to treatment discontinuation, n (%)	42 (13)	–

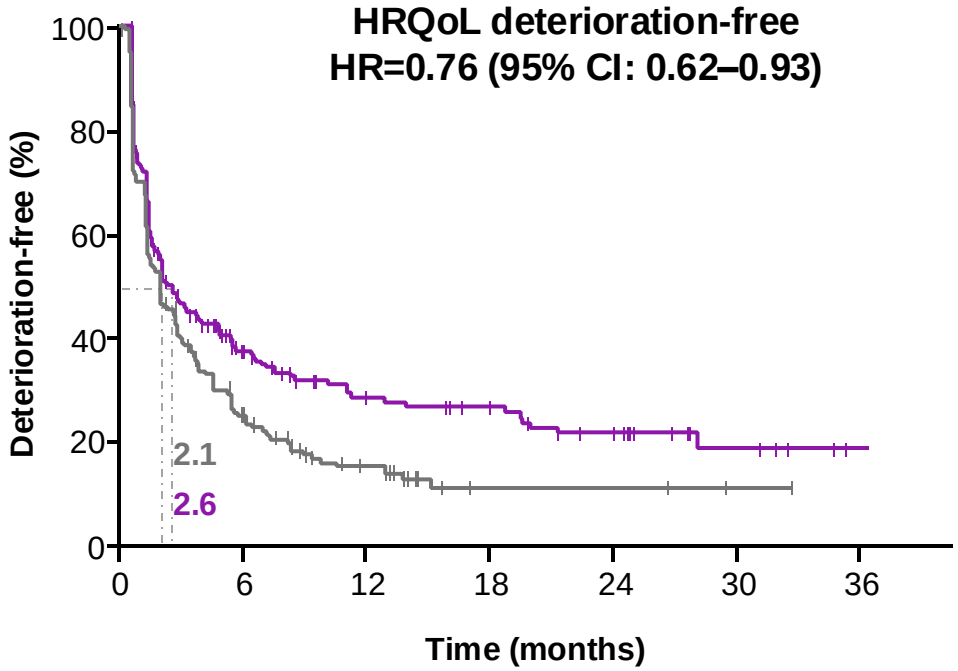
The most frequently reported Grade 3–4 TRAEs in the

Nivolumab + ipilimumab group were:
- **AST increase** (**6%**)
- **ALT increase** (**5%**)
- **Lipase increase** (**5%**)

Lenvatinib or sorafenib group were:
- **Hypertension** (**12%**)
- **Proteinuria** (**5%**)
- **Diarrhoea** and **PPE syndrome** (**3%**)

HRQoL: TTD

Nivolumab + ipilimumab *vs* ***lenvatinib or sorafenib***



Nivolumab + ipilimumab is given for up to 4 cycles Q3W, then nivolumab monotherapy is given Q4W until disease progression, unacceptable toxicity, withdrawal of consent and for a maximum of 2 years. *The most frequently reported were hepatitis (n=56), diarrhoea/colitis (n=27), rash (n=10) and pneumonitis (n=6)

Galle et al. ASCO 2024

Summary of Key Phase III trials in advanced HCC

		Atezolizumab + Bevacizumab IMbrave150[1]	Durvalumab + Tremelimumab HIMALAYA[2]	Durvalumab mono HIMALAYA[2]	Nivolumab + Ipilimumab CheckMate-9DW[3]
Demographics	BCLC B	15%	20%	21%	27%
	PS 0/1	62%/38%	62%/38%	61%/39%	70%/30%
	HBV / HCV / Non-viral	49% / 21% / 30%	31% / 28% / 41%	31% / 27% / 42%	34% / 27% / 37%
	MVI / EHS / Either	38% / 63% / 77%	26% / 53% / NR	24% / 55% / NR	23% / 56% / 66%
	MVI Vp4	14%	excluded	excluded	excluded
Efficacy	mOS (months)	19.2 vs 13.4 (HR=0.66)	16.4 vs 13.8 (HR=0.78)	16.6 vs 13.8 (HR=0.86)*	23.7 vs 20.6 (HR=0.79)
	mPFS (months)	6.9 (HR=0.65)	3.78 (HR=0.90)*	3.65 (HR=1.02)*	9.1 (HR=0.87)*
	ORR	30.0%	20.1%	17.0%	36.0%
	DCR	74%	60%	55%	68%
	mFollow-Up (range)	15.6 (N/A)	33.2 (31.74 to 34.53)	32.6 (31.57 to 33.71)	35.2 (26.8-48.9)
Safety	Treatment Duration	8.4mo (Atezo) / 7.0mo (Bev)	5.5mo	5.5mo	4.7mo
	TRAE Rate	86%	76%	52%	84%
	Gr3+ TRAE rate	43%	26%	13%	41%
	Gr5 TRAEs	1.8%	2.3%	0%	3.6%
	AEs leading to disc	22%	14%	8%	13%
	Corticosteroid use	12%	20%**	10%**	29%**

*Not statistically significant** High-dose steroid only (overall rate unknown)
Data from different trials are presented for informational purposes only, and are not intended for cross-trial comparison. Each trial's results should be interpreted independently, as methodologies and populations vary.

1. Cheng et al. J Hepatol 2022.
2. 2. Abou-Alfa et al. N Engl J Med Evid 2022.
3. Galle et al. ASCO 2024.

As more treatment options become available, answering key questions and alleviating concerns from patients remains a priority

Am I receiving the best possible therapy available?

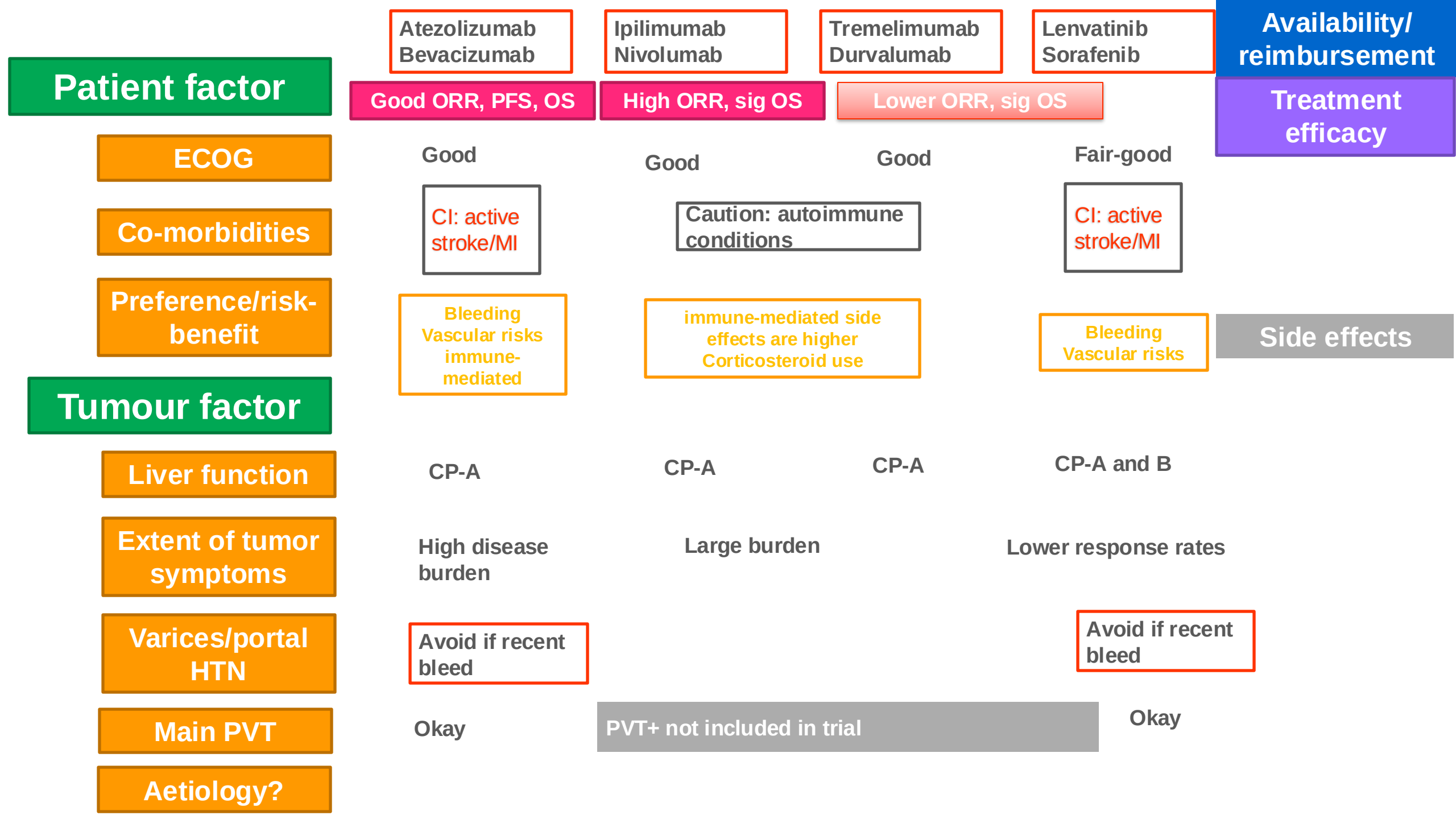
What are the severe side effects that I'm willing to risk?

What changes can I expect from this therapy?

Can I afford the treatment and how long does it go on for?

How will I feel when I start this new therapy?

How long will I live? Is there still a chance of cure?


Atezolizumab
Bevacizumab
Ipilimumab
Nivolumab
Tremelimumab
Durvalumab
Lenvatinib
Sorafenib
Availability/ reimbursement
Patient factor
Good ORR, PFS, OS
High ORR, sig OS
Lower ORR, sig OS
Treatment efficacy
ECOG
Good
Good
Good
Fair-good
Co-morbidities
CI: active stroke/MI
Caution: autoimmune conditions
CI: active stroke/MI
Preference/risk-benefit
Bleeding
Vascular risks
immune-mediated
immune-mediated side effects are higher
Corticosteroid use
Bleeding
Vascular risks
Side effects
Tumour factor
Liver function
CP-A
CP-A
CP-A
CP-A and B
Extent of tumor symptoms
High disease burden
Large burden
Lower response rates
Varices/portal HTN
Avoid if recent bleed
Avoid if recent bleed
Main PVT
Okay
PVT+ not included in trial
Okay
Aetiology?

Real-world data are important to inform treatment decisions[1-6]

Clinical trials

- **Trusted** mechanism of evidence generation
- **Clear hypothesis** and high internal validity
- Homogeneous patient population; controlled environment
- 'Fixed' and **somewhat inflexible** experimental conditions
- Basis for **standard treatment guidelines** that inform **clinical decisions**

Real world

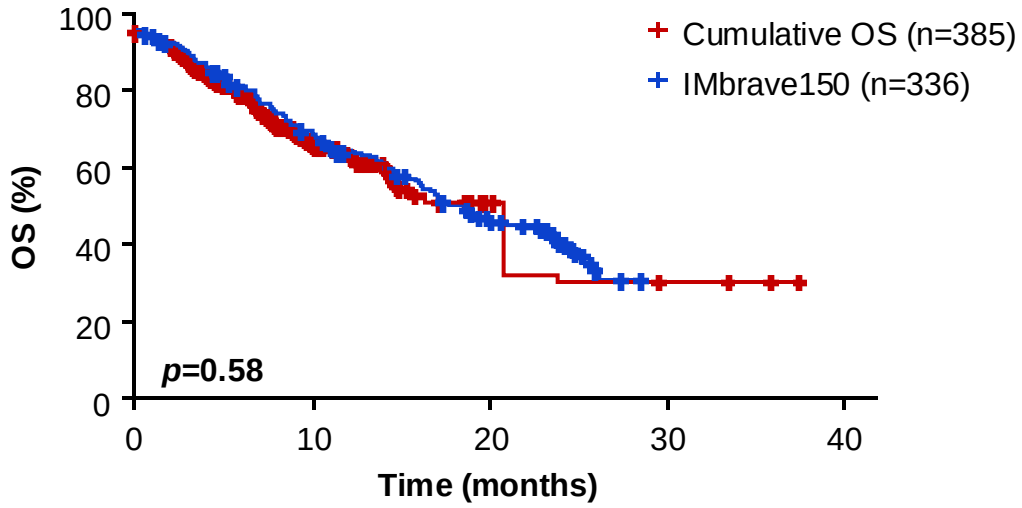
- **Representativeness** of routine clinical care
- **Supports** a wide variety of **clinical decisions**, where evidence from large clinical trials is scarce
- **Supports regulatory approval**
- **Complexity** – potential limitations based on confounding and bias possibilities
- Need for **extrapolation**
- Adoption not pervasive

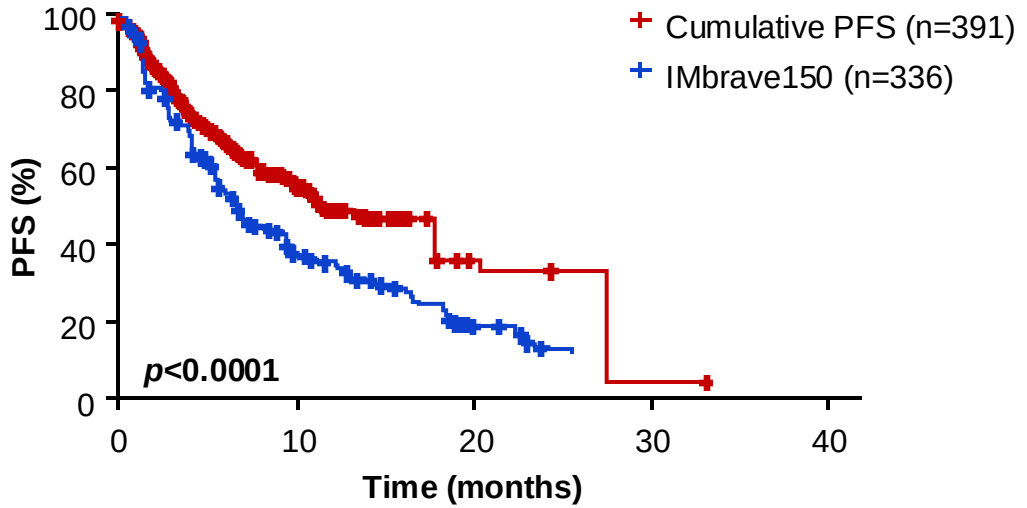
RWE, real-world evidence

1. Blonde et al. Adv Ther 2018; 2. Katkade et al. J Multidiscip Healthc 2018; 3. Kim et al. J Korean Med Sci 2018
4. Chodankar. Perspect Clin Res 2021; 5. Liu & Panagiotakos. BMC Med Res Methodol 2022; 6. Zisis et al. J Pharm Pharm Sci 2024

A systematic review and meta-analysis on atezolizumab + bevacizumab in advanced HCC compared RWD with IMbrave150 (N=2,179)

Comparison of RWD in patients with Child-Pugh A disease compared with IMbrave150





No significant difference (p=0.58) was found in the median OS between real-world patients (20.9 months) and IMbrave150 (19.2 months)

Median PFS was significantly longer (p<0.001) in real-world patients (11.8 months) compared with IMbrave150 (6.9 months)

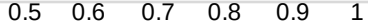
In an exploratory analysis, the pooled 24-month OS (including 4 studies) and PFS (including 3 studies) was 39% (95%CI 31-49; I_2=90%) and 25%, respectively

Manfredi et al. EASL 2024

Systematic review and meta-analysis of RWD on atezolizumab + bevacizumab in advanced HCC

Pooled 6-month OS rate

Study	Events	Total	Proportion	95% CI	Weight
Kulkarni	45	67	0.67	(0.55–0.77)	9.2%
Himmelsbach	45	66	0.68	(0.56–0.78)	9.1%
Charonpongsuntorn	23	30	0.77	(0.59–0.89)	6.5%
Kim	67	86	0.78	(0.68–0.86)	9.1%
Chon	94	121	0.78	(0.70–0.84)	9.8%
Su	36	46	0.78	(0.64–0.88)	7.6%
Fulgenzi	246	296	0.83	(0.78–0.87)	10.7%
Persano	708	823	0.86	(0.83–0.88)	11.3%
Maesaka	60	69	0.87	(0.77–0.93)	7.6%
Tanaka	326	370	0.88	(0.84–0.91)	10.6%
Niizeki	150	161	0.93	(0.88–0.96)	8.4%
Random effects model		**2135**	**0.82**	**(0.76–0.86)**	**100%**
Prediction interval				**(0.59–0.93)**	



Heterogeneity: I^2=80%, τ^2=0.23, p<0.01

Pooled 6-month PFS rate

Study	Events	Total	Proportion	95% CI	Weight
Su	22	46	0.47	(0.33–0.61)	5.9%
Chon	59	120	0.49	(0.40–0.58)	10.6%
Kim	42	86	0.49	(0.39–0.59)	8.9%
Sho	22	43	0.52	(0.37–0.66)	5.7%
Fulgenzi	162	294	0.55	(0.49–0.61)	14.9%
Himmelsbach	38	66	0.58	(0.46–0.69)	7.5%
Maesaka	40	69	0.58	(0.46–0.69)	7.7%
Charonpongsuntorn	18	30	0.60	(0.42–0.76)	4.2%
Niizeki	100	161	0.62	(0.54–0.69)	11.9%
Tanaka	237	371	0.64	(0.59–0.69)	15.6%
Kulkarni	45	67	0.67	(0.55–0.77)	7.1%
Random effects model		**1353**	**0.57**	**(0.53–0.61)**	**100%**
Prediction interval				**(0.45–0.68)**	

Heterogeneity: I^2=49%, τ^2=0.03, p=0.03

The pooled 6- and 12-month OS rates were 82% (95% CI: 76–86; I^2=80%) and 65% (95% CI: 60–70; I^2=70%), respectively

The pooled 6- and 12-month PFS rates were 57% (95% CI: 53–61; I^2=49%) and 35% (95% CI: 31–39, I^2=60%), respectively

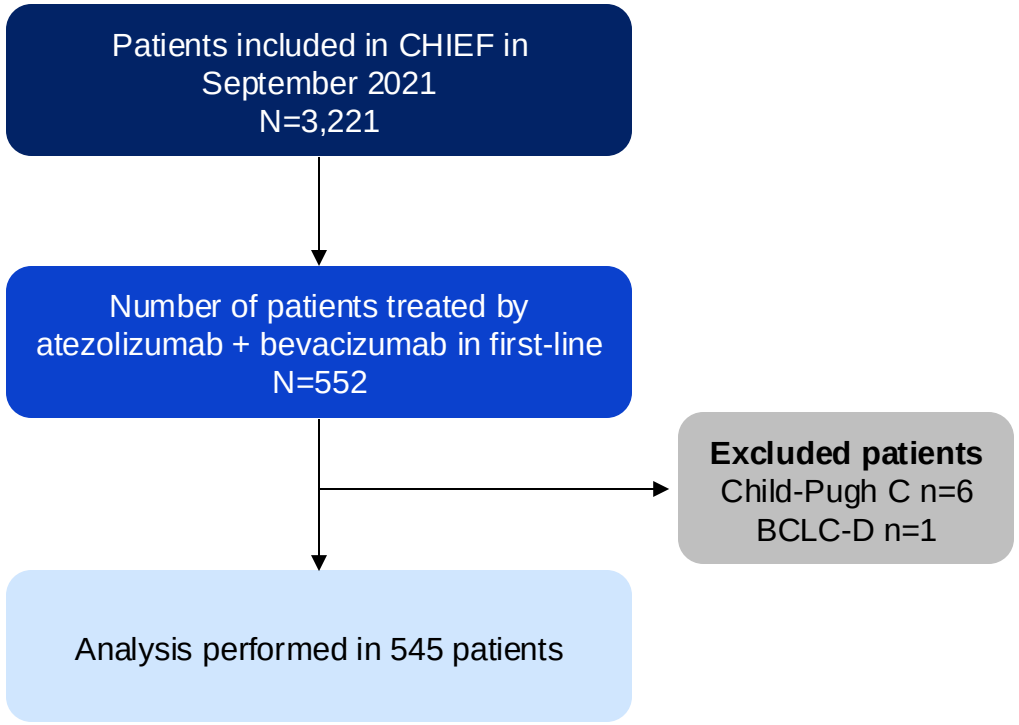
Pooled ORR: 32% (95%CI: 29–35%, I^2=50%) | Pooled DCR: 78% (95%CI: 73–81%, I^2=63%)

In an exploratory analysis, the pooled 24-month OS (including 4 studies) and PFS (including 3 studies) was 39% (95%CI 31–49; I^2=90%) and 25%, respectively

Note: Forest plot lines represent the 95% CI for the respective 6-month OS and PFS rates for each study
The size of squares represents the weight of each study; the diamond represents the pooled effect

Manfredi et al. EASL 2024

CHIEF is a prospective, multicentre study of patients treated with atezolizumab + bevacizumab in the first-line setting



Baseline characteristics

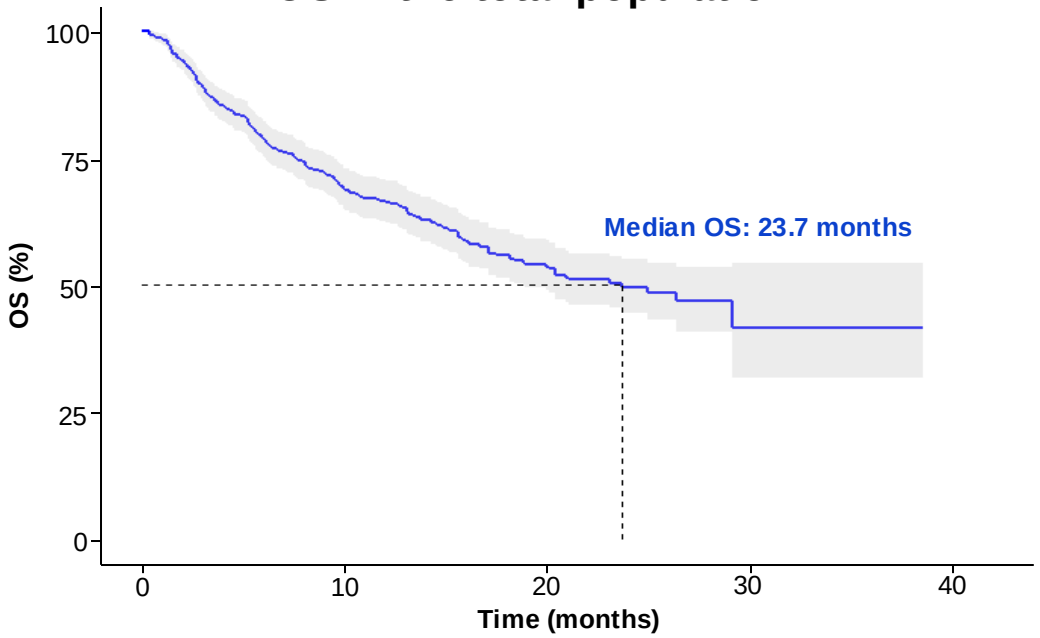
Characteristic		Whole cohort (N=545)
Patient characteristics	Female, %	14
	Age, years	68 (62–75)
Liver function	Chronic alcohol consumption only, %	30
	Viral infection only, %	16
	MASLD only, %	14
	Mixed etiologies with at least alcohol / viral infection, %	58 / 27
	Child-Pugh A, %	81
	MELD score	10 (7–11)
	ALBI grade 1 / 2 / 3, %	31 / 64 / 5
	Presence of esophageal varices, %	65
	Large size esophageal varices, %	22
	Ascites , %	8
HCC characteristics	BCLC A / B / C, %	5 / 28 / 67
	Multinodular HCC, %	32
	Infiltrative HCC, %	21
	Vascular invasion, %	47
	Extrahepatic spread, %	14
	AFP, ng/mL	63 (7–721)
	AFP >400 ng/mL, %	32

AFP, alpha-fetoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end stage liver disease

Allaire et al. EASL 2024

CHIEF: Overall Survival

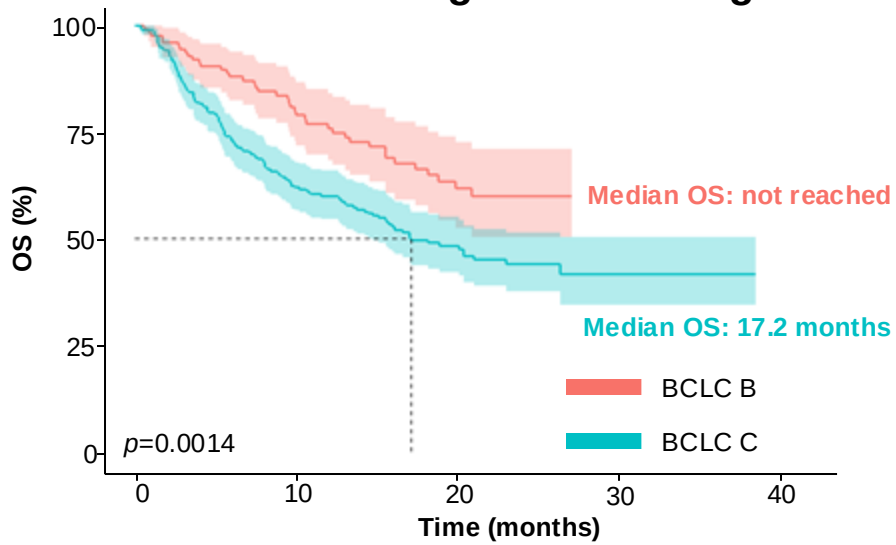
OS in the total population



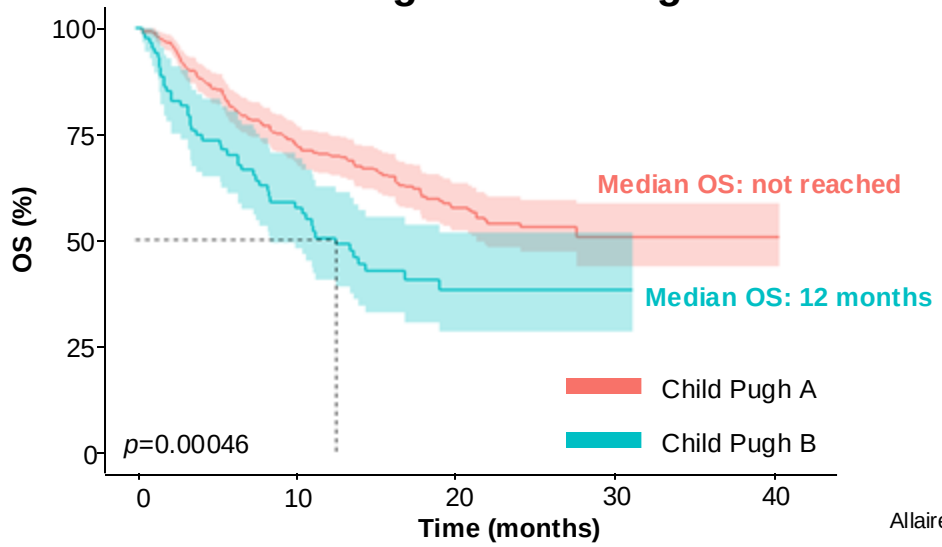
Predictive factors of mortality

	Multivariate analysis	
	HR	*p* value
Oesophageal varices	1.44	0.11
Child-Pugh B	**1.66**	**0.05**
BCLC-B	0.66	0.18
Vascular invasion	1.38	0.20
Creatinine	1.01	0.86

OS according to BCLC stage



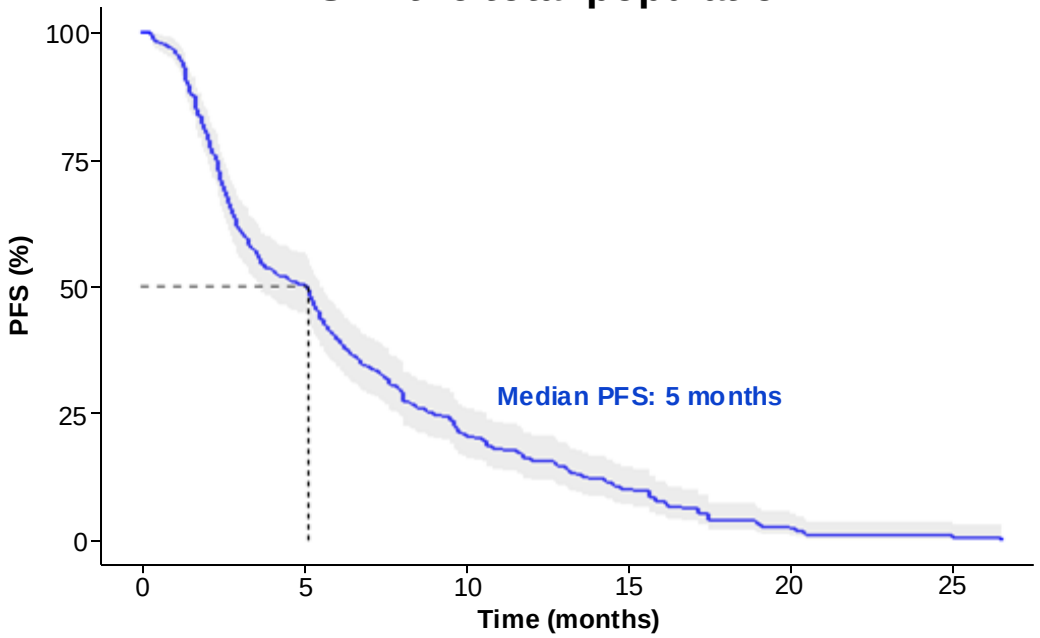
OS according to Child-Pugh score



Allaire et al. EASL 2024

CHIEF: Progression Free Survival

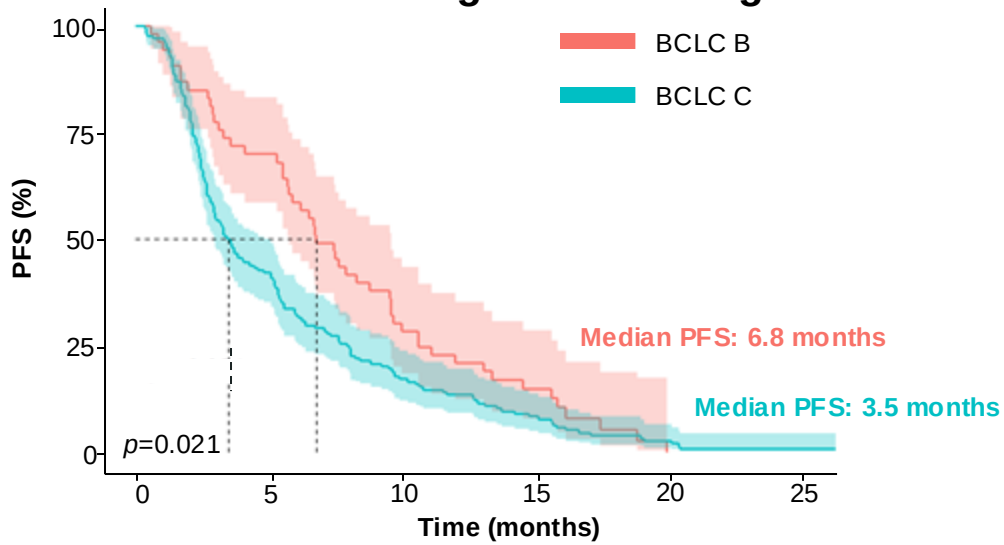
PFS in the total population



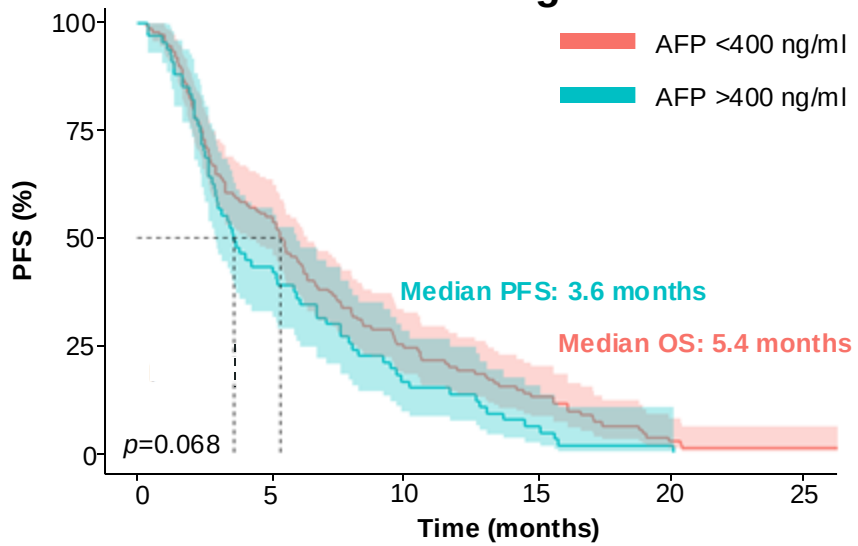
Predictive factors of progression

	Multivariate analysis	
	HR	*p* value
Alcohol consumption	1.331	0.21
BCLC-B	1.246	0.25
AFP	**1**	**0.01**
Bilirubin	0.99	0.10

PFS according to BCLC stage



PFS according to AFP



Allaire et al. EASL 2024

Real-world data: clinical activity of atezolizumab + bevacizumab in patients with Child-Pugh B disease[1]

Data from selected real-world studies of first-line atezolizumab + bevacizumab in patients with Child-Pugh B disease

	Child-Pugh B disease							Child-Pugh B7 disease	
Study	**D'Alessio et al. 2022[2]**	**de Castro et al. 2022[3]**	**Tanaka et al. 2022[4]**	**Vithayathil et al. 2022[5]**	**Kulkarni et al. 2023[6]**	**Cheon et al. 2023[7]**	**Allaire et al. 2024[8]**	**Tanaka et al. 2022[4]**	**Cheon et al. 2023[7]**
Region(s)	Asia/USA/Europe	Germany/Austria	Japan	Asia/USA/Europe	India	South Korea	France	Japan	South Korea
No. of patients	48	35	30	44	36	36	91	21	24
Median age, years	69*	67‡§	74	68*	–	61	68*	74*	61*
ECOG PS 0–1, %	98*	67‡	93	97*	–	86	–	93*	86*
mOS, months	6.7	6.8	6.4	5.9–6.2	9.0	7.7	12	7.3	7.7
mPFS, months	3.4	–	6.0	3.3–3.7	8.0	3.0	–	6.3	3.0
ORR, %	21.0	–	25.0	–	40.6	11.1	–	–	12.5

when used in first-line therapy for patients with unresected HCC and Child-Pugh B disease[1]

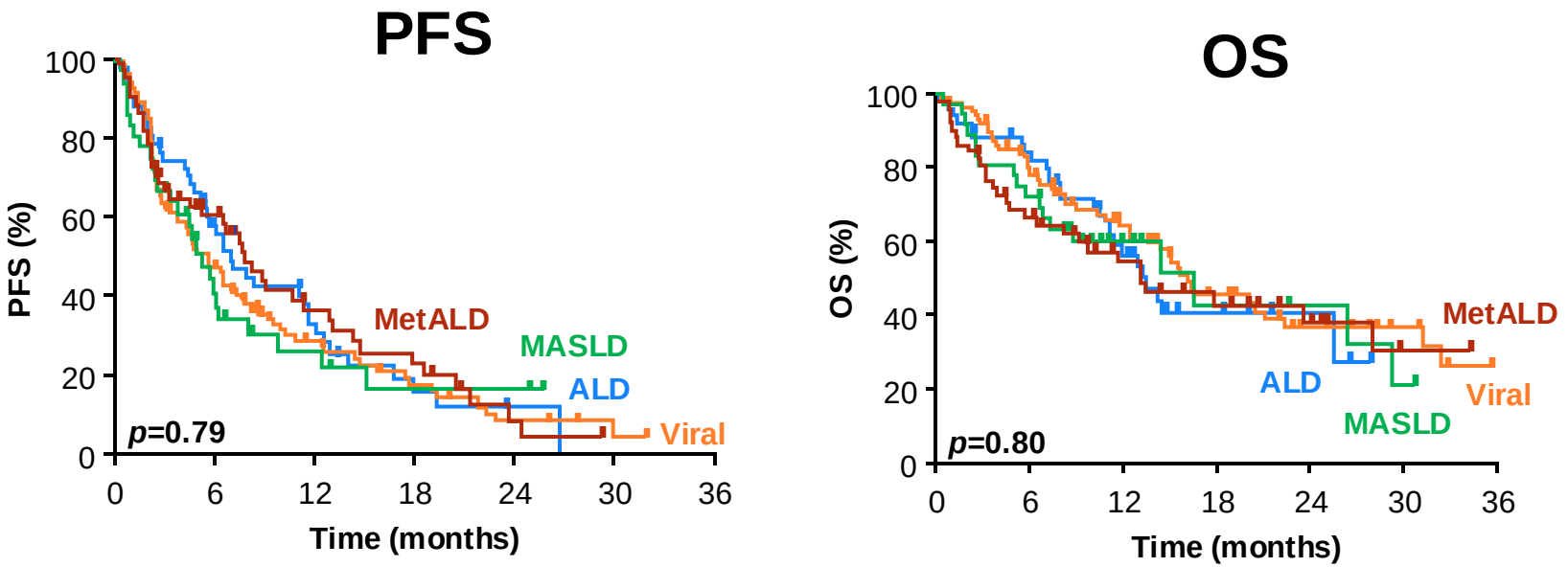
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommendation for atezolizumab + bevacizumab as an NCCN Category 1 preferred first-line systemic regimen for certain patients with unresectable HCC is regardless of Child-Pugh status[9]

*Overall population
‡IMbrave-OUT cohort
§ Mean age

1. Kulkarni et al. eClinical Medicine 2023; 2. D'Alessio et al. Hepatology 2022; 3 de Castro et al. Ther Adv Med Oncol 2022; 4. Tanaka et al. Hepatol Res 2022; 5. Vithayathil et al. Liver Int 2022
6. Kulkarni et al. J Clin Exp Hepatol 2023; 7. Cheon et al. Ther Adv Med Oncol 2023; 8. Allaire et al. EASL 2024; 9. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatocellular Carcinoma Version 3.2024.© National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed 2 October 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way

Does aetiology affect survival outcomes?

Retrospective, multicentre study of 295 patients from France[1]



Network meta-analysis of 9 studies and 3,897 patients
There was a generally consistent efficacy benefit across aetiologies[2]

Phase III studies of first-line immunotherapy in HCC have also **not shown any clear association** between liver **aetiology and response**[3]

No major impact from aetiology?

1. Copil et al. Liver Int 2024; 2. Vogel et al. Liver Cancer 2021; 3. Meyer et al. J Hepatol 2023

How do we select the optimal systemic therapy for our patients – side effect profile

Patient aged 72

- 4-month history of general malaise, 3kg weight loss, and right upper abdominal pain
- Lifetime non-smoker, non-drinker, no previously diagnosed liver disease, non-viral etiology (MASLD)
- BCLC-C HCC with PVT and lung metastases, CP-A
- ECOG PS 1, BMI 28

Medical history

- 10 years ago received single stenting for **ischaemic heart disease**, no further cardiac symptoms
- Hypertension
- **Autoimmune thyroiditis**
- Type 2 diabetes mellitus without end organ damage

Medication

- **Aspirin**, amlodipine, metformin, gliclazide, levothyroxine sodium

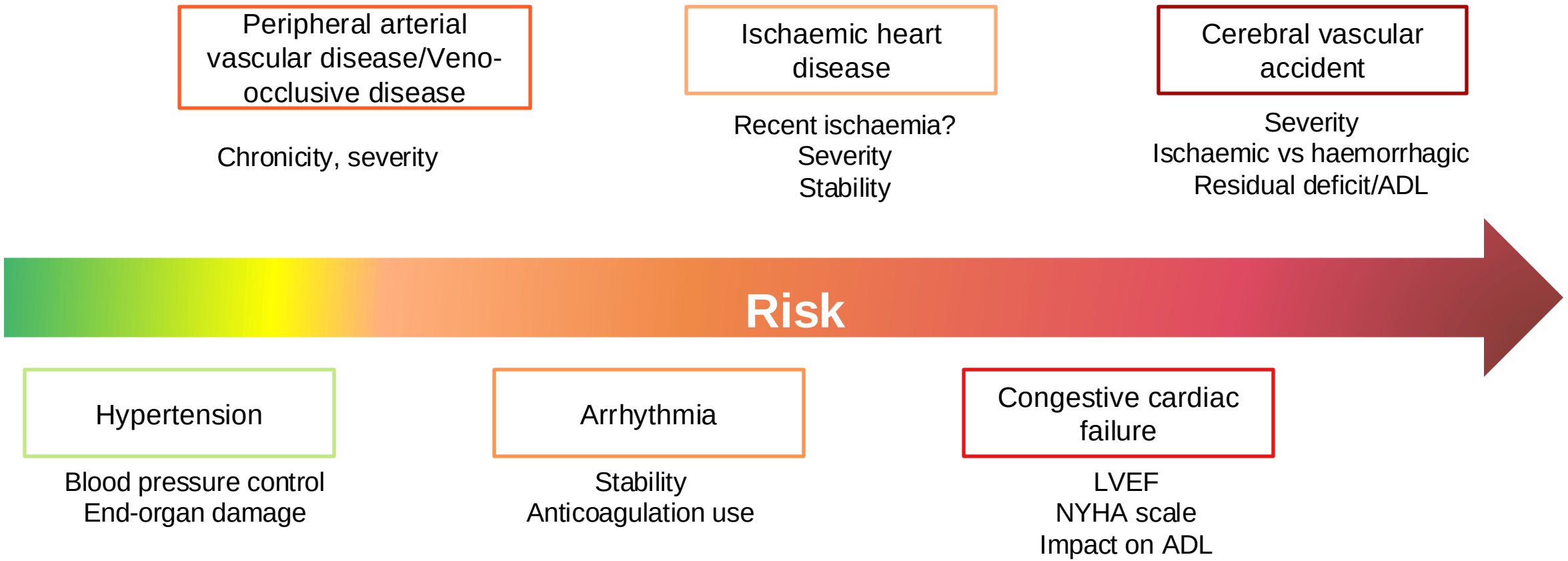
Cardiovascular risk

Bleeding risk

Immune-related

Fictitious clinical case for the purpose of this presentation

Cardiovascular disease



ADL, activities of daily living; AF, atrial fibrillation; LVEF, left ventricular ejection fraction
NYHA, New York Heart Association
Fictitious clinical case for the purpose of this presentation

Meta-analysis: Cardiovascular toxicity of bevacizumab

Risk ratios for adverse events for different follow-up times†

Follow-up time	11–14 months	21–24 months	>24 months
Arterial adverse events	0.86 (0.63–1.18); p=0.35	1.44 (0.85–2.44); p=0.18	2.40 (1.64–3.52); p<0.001*
Cardiac ischaemia	1.75 (0.86–3.54); p=0.12	4.02 (1.14–14.15); p=0.03*	5.16 (0.91–29.33); p=0.06
Cerebral ischaemia	1.00 (0.29–3.43); p=1.0	3.63 (0.85–15.45); p=0.08	12.39 (1.62–94.49); p=0.02*
Venous adverse events	1.26 (0.95–1.67); p=0.12	1.06 (0.74–1.51); p=0.75	1.37 (1.11–1.68); p=0.03*
Bleeding	2.26 (1.74–2.95); p<0.001*	2.84 (1.98–4.06); p<0.001*	2.96 (2.46–3.56); p<0.001*
Arterial hypertension	4.06 (2.52–6.54); p<0.001*	4.30 (2.59–7.14); p<0.001*	4.81 (3.10–7.46); p=0.001*

Cardiovascular Toxicity

- Time-dependant
- Often late effect

→

- Survivorship
- Requirement for long-term awareness/surveillance

*Statistically significant data; †No patients with HCC were included in this meta-analysis
Data are expressed as risk ratio (95% CI), p value

Totzeck et al. J Am Heart Assoc 2017

Considerations in patients with CV disease/risk factors

CV disease/risk factors are frequent in patients with HCC[1]: it is important to distinguish absolute from relative contraindications to anti-angiogenic therapy

Anti-angiogenic therapy

- Baseline assessment: type, severity, stability of cardiovascular status. Number of anti-hypertensives/concomitant medicines
- On-treatment review: BP targets DBP <85–90 mmHg
- Stable heart disease vs recent cardiovascular events/ongoing ischaemia
- NYHA classification
- Find partner cardiologist to help treat patient if concerned

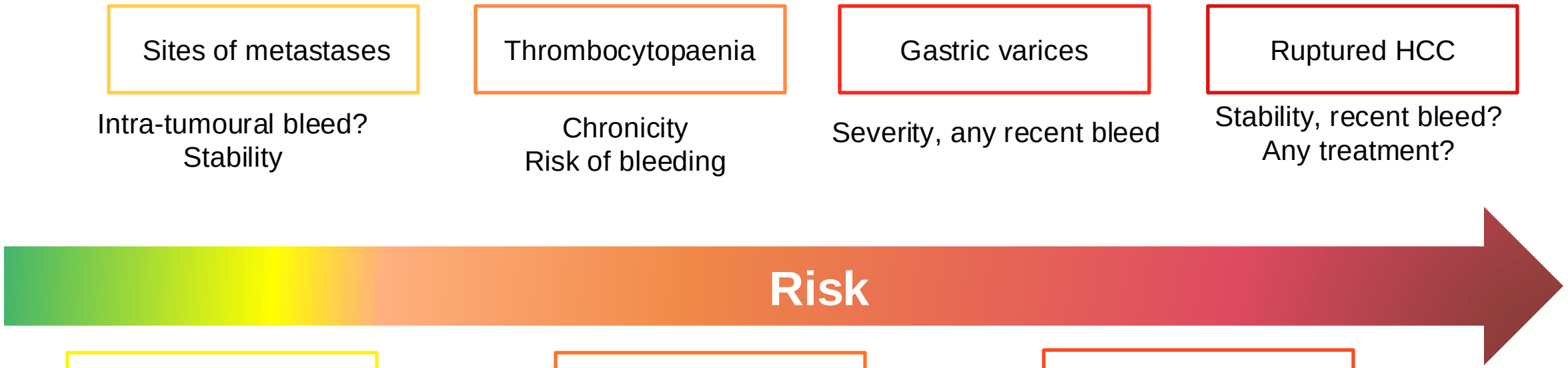
Immune checkpoint inhibitors

- Checkpoint inhibitors could be considered a potential treatment option for patients with cardiovascular disease unsuitable for anti-angiogenics, though specific data are lacking[1]

DBP, diastolic blood pressure

1. Rimassa et al. J Hepatol 2021
2. Rimassa et al. Cancer Treatment Rev 2019

Bleeding


Sites of metastases
Intra-tumoural bleed?
Stability
Thrombocytopaenia
Chronicity
Risk of bleeding
Gastric varices
Severity, any recent bleed
Ruptured HCC
Stability, recent bleed?
Any treatment?
Risk
Stable oesophageal varices
Adequacy of control
Banding
Severity
Anticoagulation
Underlying indication
Risk of bleeding
Relative contraindication
Recent UBGIT bleed
Contraindication for Bev

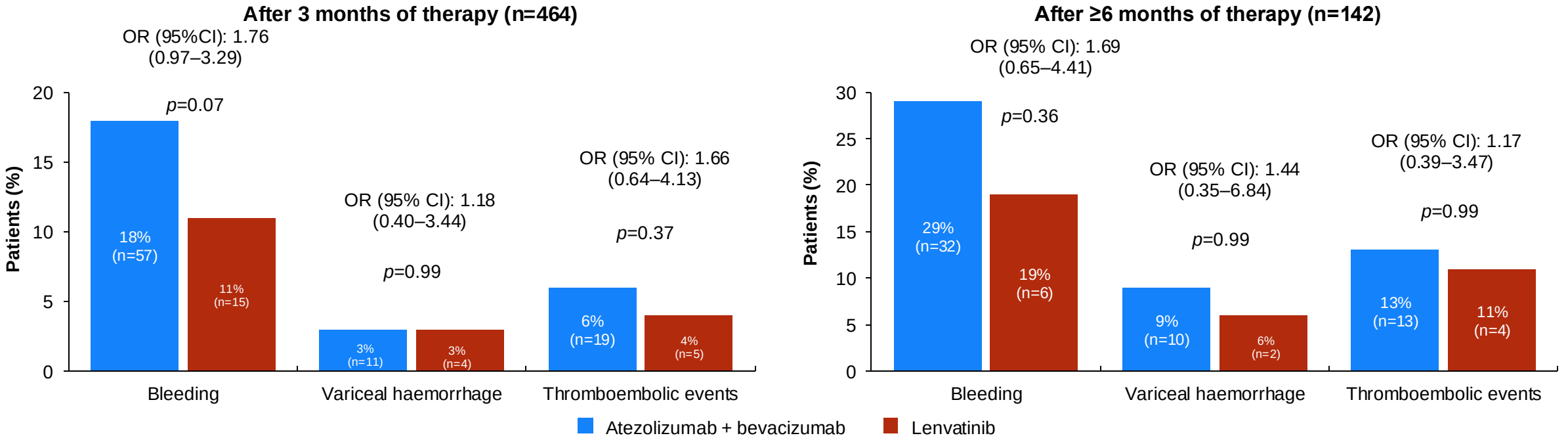
IMbrave150 included patients who had a higher risk of bleeding at baseline

	IMbrave150 - non-Vp4-patients[1] Atezo + Bev (n = 285)	IMbrave150 - Vp4-patients[1] Atezo + Bev (n = 44)	HIMALAYA[2] Durva + Treme (n = 388)
Patients with MVI Vp4	**14 %[3]**		**excluded**
Bleedings prior to study inclusion	Pt. with bleeding from esophageal and/or gastric varices in the **6 months before enrolment** excluded		Pt. with active GI hemorrhage or GI hemorrhage occurring in the **12 months before enrolment** excluded
Bleedings events grade 3 - 4	28 (**9%**)[4]		15 (**3,9%**)[5]
Systemic steroid use	12%[6] (any dose)		20%[7] (**high-dose** steroid use)
Oesophageal varices haemorrhage	Any grade: 3 (1%)[1]	Any grade: 6 (14%)[1]	1 (0,3%)[5]
	Grade 3/4: 2 (1%)[1]	Grade 3/4: 4 (9%)[1]	*data on the grade of bleeding n.a.*
	Grade 5: 0[1]	Grade 5: 2 (5%)[1]	
Gastrointestinal haemorrhage	Any grade: 7 (2%)[1]	Any grade: 3 (7%)[1]	7 (1,8%)[5]
	Grade 3/4: 5 (2%)[1]	Grade 3/4: 1 (2%)[1]	*data on the grade of bleeding n.a.*
	Grade 5: 1 (<1%)[1]	Grade 5: 2 (5%)[1]	
Upper gastrointestinal haemorrhage	Any grade: 4 (1%)[1]	Any grade: 3 (7%)[1]	7 (1,8%)[5]
	Grade 3/4: 2 (1%)[1]	Grade 3/4: 1 (2%)[1]	*data on the grade of bleeding n.a.*

1. Cheng et al. J Hepatol 2022.
2. 2. Abou-Alfa et al. N Engl J Med Evid 2022.

Bleeding rates with atezolizumab + bevacizumab may be similar to lenvatinib

A **real-world analysis** in 464 patients in Germany and Austria found **no difference in bleeding rates** between **atezolizumab + bevacizumab**, and **lenvatinib**



Safety considerations relating to bleeding may not be helpful in guiding treatment decisions

A subgroup analysis suggested that variceal bleeding in patients receiving atezolizumab + bevacizumab (n=18) did not appear to be related to disease progression, poor liver function or a lack of prophylaxis for portal hypertension

Khaled et al. JHEP Rep 2024

Considerations in patients with a higher risk of bleeding

Risk of bleeding can be increased by anticoagulation, antiplatelet therapy or low platelet count

Anti-angiogenic agent

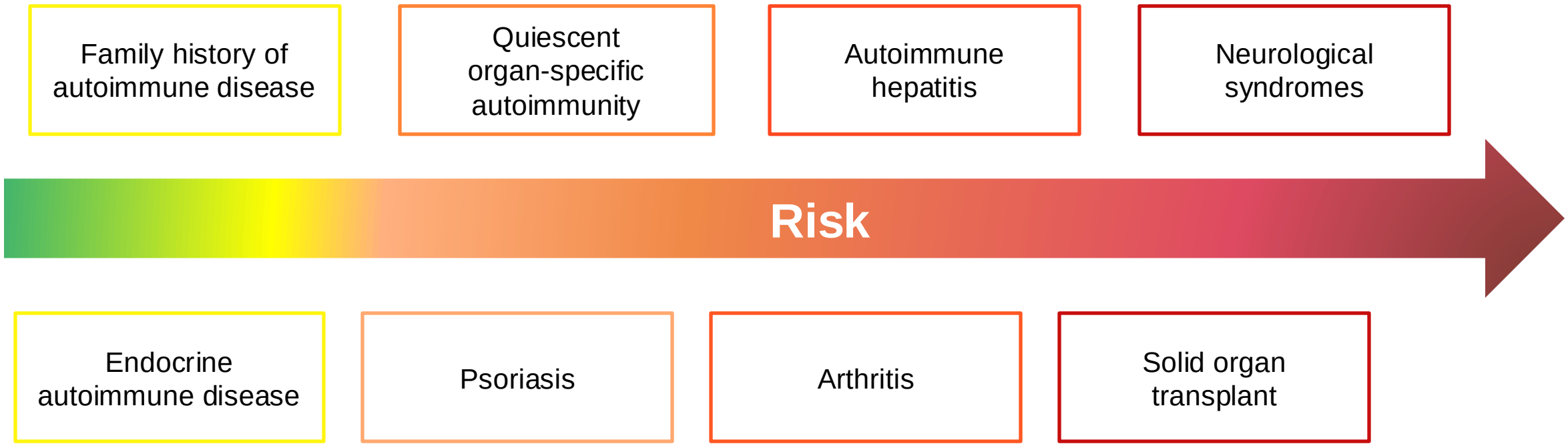
- Assessing the bleeding risk (OGD) and treating varices adequately is strongly recommended before initiating bevacizumab[1,2]
- Epistaxis and gingival bleeding are also common with anti-angiogenic agents, but can be minor and may not require medical attention[3]

EGD, esophagogastroduodenoscopy

1. Finn et al. New Engl J Med 2020; 2. Bruix et al. J Hepatol 2021
3. Rimassa et al. J Hepatol 2021

Autoimmune risk factors (more of concern for doublet IO)

- Active vs chronic/controlled
- Severity of autoimmune condition
- Organ involvement



Considerations in patients with autoimmune disease

Autoimmune disorders range from those with very good prognosis (such as hypothyroidism) to those with potentially life-threatening complications (such as lupus)

Anti-angiogenic agents

- In the absence of contraindications, anti-angiogenic agents can be used in these patients

Immune checkpoint inhibitors

- Cancer immunotherapy should be used with caution in these patients, depending on the severity of the autoimmune disease and the need for immune-suppressive therapy

Rimassa et al. J Hepatol. 2021

Which patients are not eligible for atezolizumab + bevacizumab?

Cardiovascular risk

- Severe uncontrolled hypertension with end-organ damage
- Recent ischaemic/haemorrhagic cardiovascular event

Bleeding risk

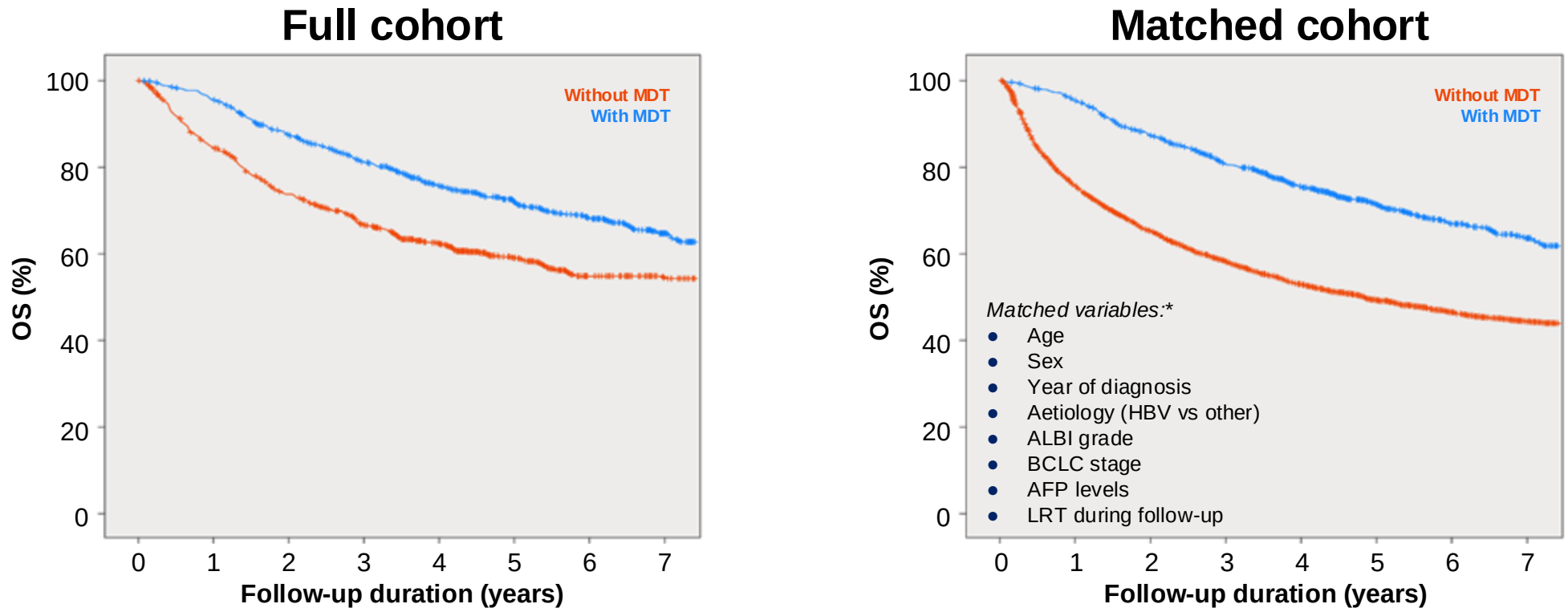
- Ruptured HCC at presentation
- Intra-tumoural bleeding
- Recurrent and/or uncontrolled variceal bleeding despite optimal endoscopic/medical management

Autoimmune

- Solid tumour organ transplant recipients
- Organ- or life-threatening autoimmune disease

Optimal Management of HCC Requires Strong MDT Collaboration

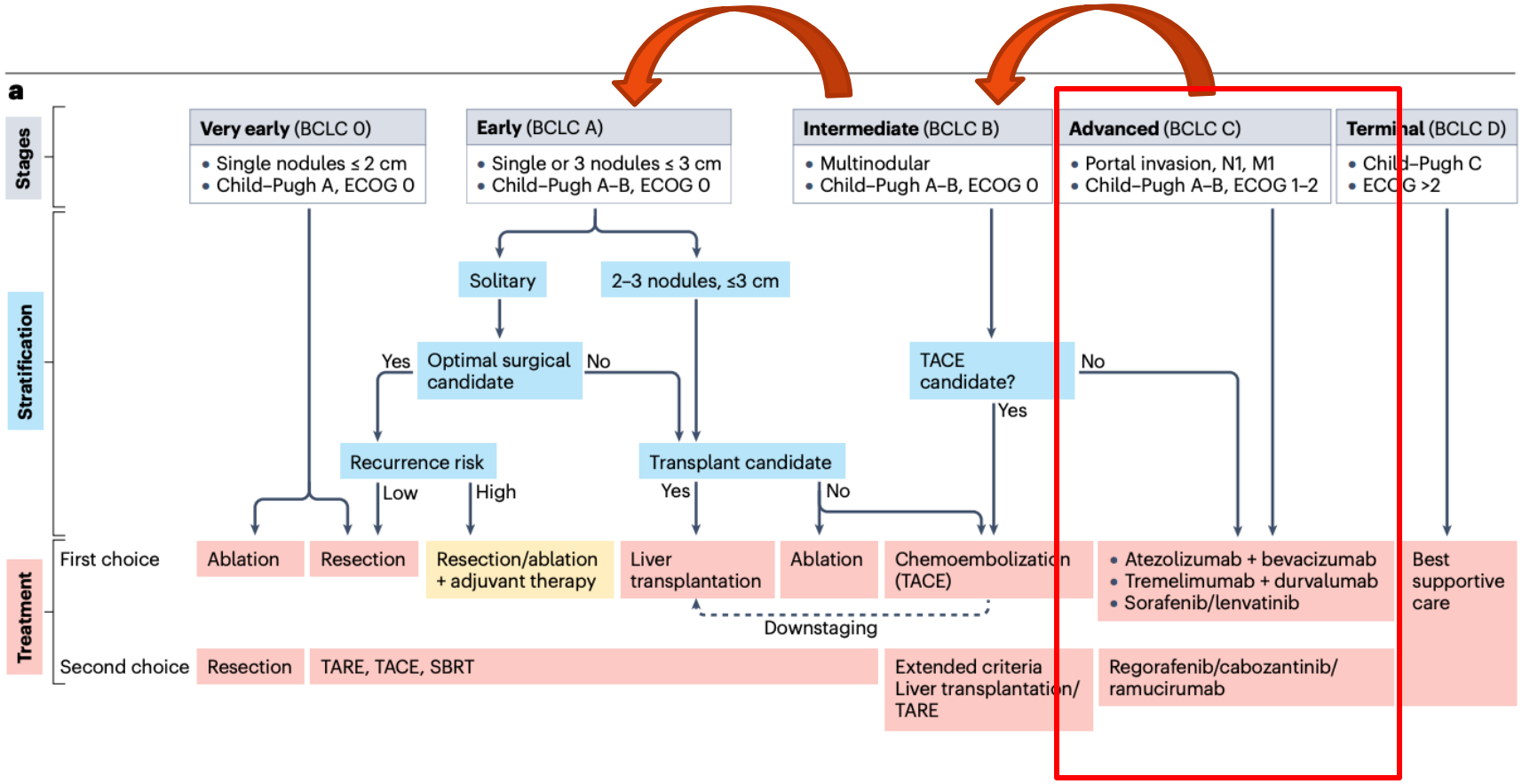
Retrospective study based on **prospective HCC registry** for patients with **BCLC 0 to D**

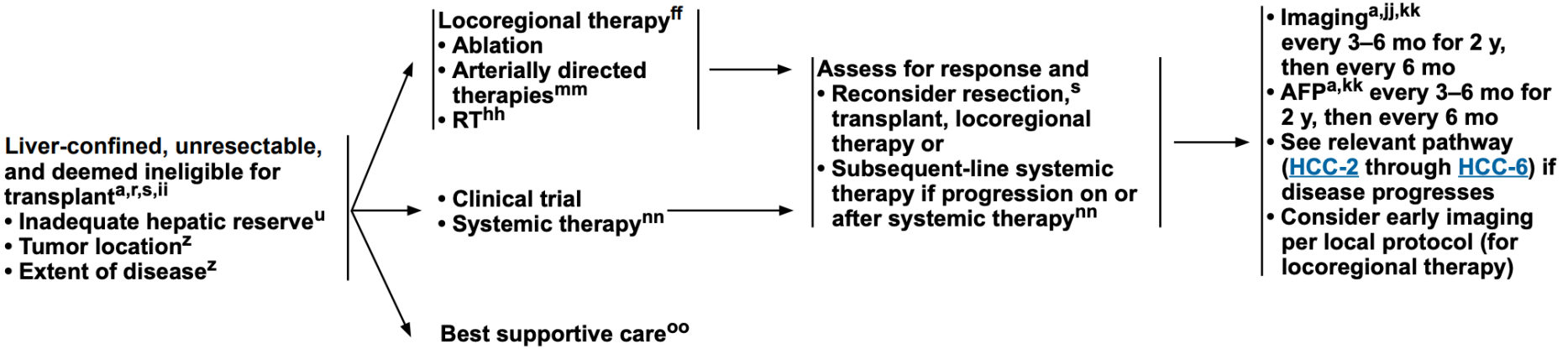


This is a retrospective cohort study based on a prospective HCC registry that has recorded clinical characteristics, tumour characteristics, and treatment information of newly diagnosed HCC patients from 2005 to 2013 at Samsung Medical Centre, Seoul, South Korea. Patients included presented with HCC at different stages (BCLC A to D) and were managed with different treatment approaches *Age groups, sex, year of diagnosis (2005–2007, 2008–2010, and 2011–2013), aetiology (HBV vs other), ALBI Grade (1, 2, and 3), BCLC stage (0, A, B, C, and D), AFP levels (<200 and ≥200 mg/dL), and LRT during follow-up were exactly matched between patients with MDT management and patients without MDT management in a 1:1 ratio

ALBI, albumin-bilirubin

Sinn et al. PLOS ONE 2019





Treatment intent in view of good disease control rate

- For those BCLC-B not suitable for LCT → for the good responders, can revisit LCT/surgery/ transplant possibly?
- For BCLC-C, depending on response and EHS, still can consider some LCT
- Up-and-coming: combining systemic and locoregional therapy early for BCLC-B, neoadjuvant approach?

These are my own systemic treatment considerations (always discuss at MDT first)

1. Liver function, BCLC stage and performance score of patient → CP-B borderline but fit, can discuss, CP-C and unfit for BSC

2. If fit, CP-A → atezo/bev is still my first choice unless if:
   - OGD shows significant untreated varices or recent bleed/BGIT
   - Severe heart failure (HYHA >2), recent stroke/MI and uncontrolled hypertension

3. If no PVT and strong contraindication to bevacizumab (then I may consider treme/durva or possibly ipi/nivo) → single agent PD1 may not have strong role unless want to lower risk of irAE?

   If pt has significant autoimmune disease then:
   - lenvatinib or sorafenib are still reasonable alternatives for first line

Aim for downstaging for BCLC-B, and good durable disease control for BCLC-C (response rate and durable control both important)

Second line: class of drug not tried in first line (also depends on reimbursement options)
Clinical trials where available

With thanks to Roche for the slides

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