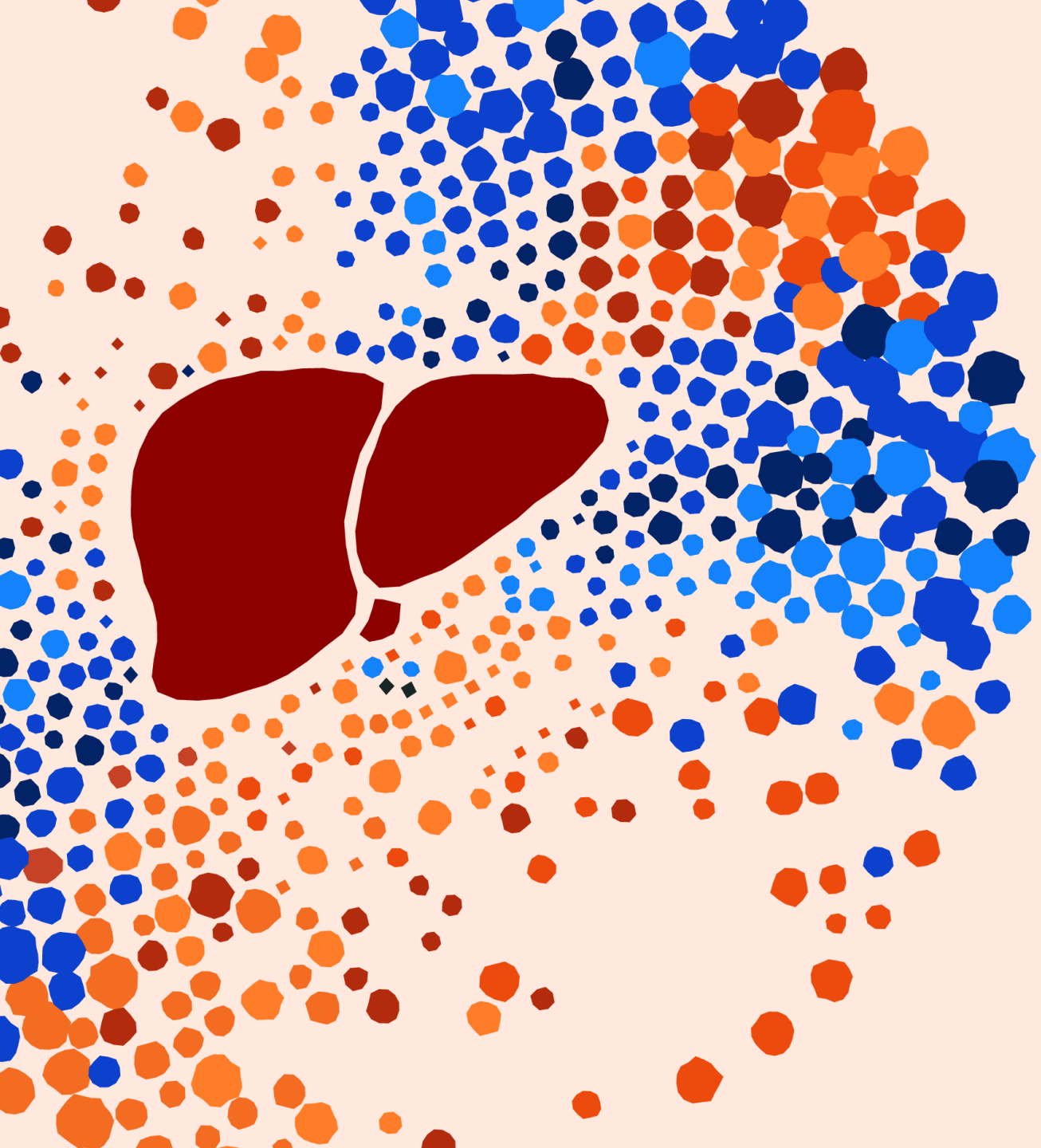

OneLiver

Roche

Expanding horizons in HCC: early detection and systemic treatment opportunities

EASL Liver Cancer Summit 2023

18:20–19:20 Friday 21 April

Disclaimer

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Disclosures

Lorenza Rimassa

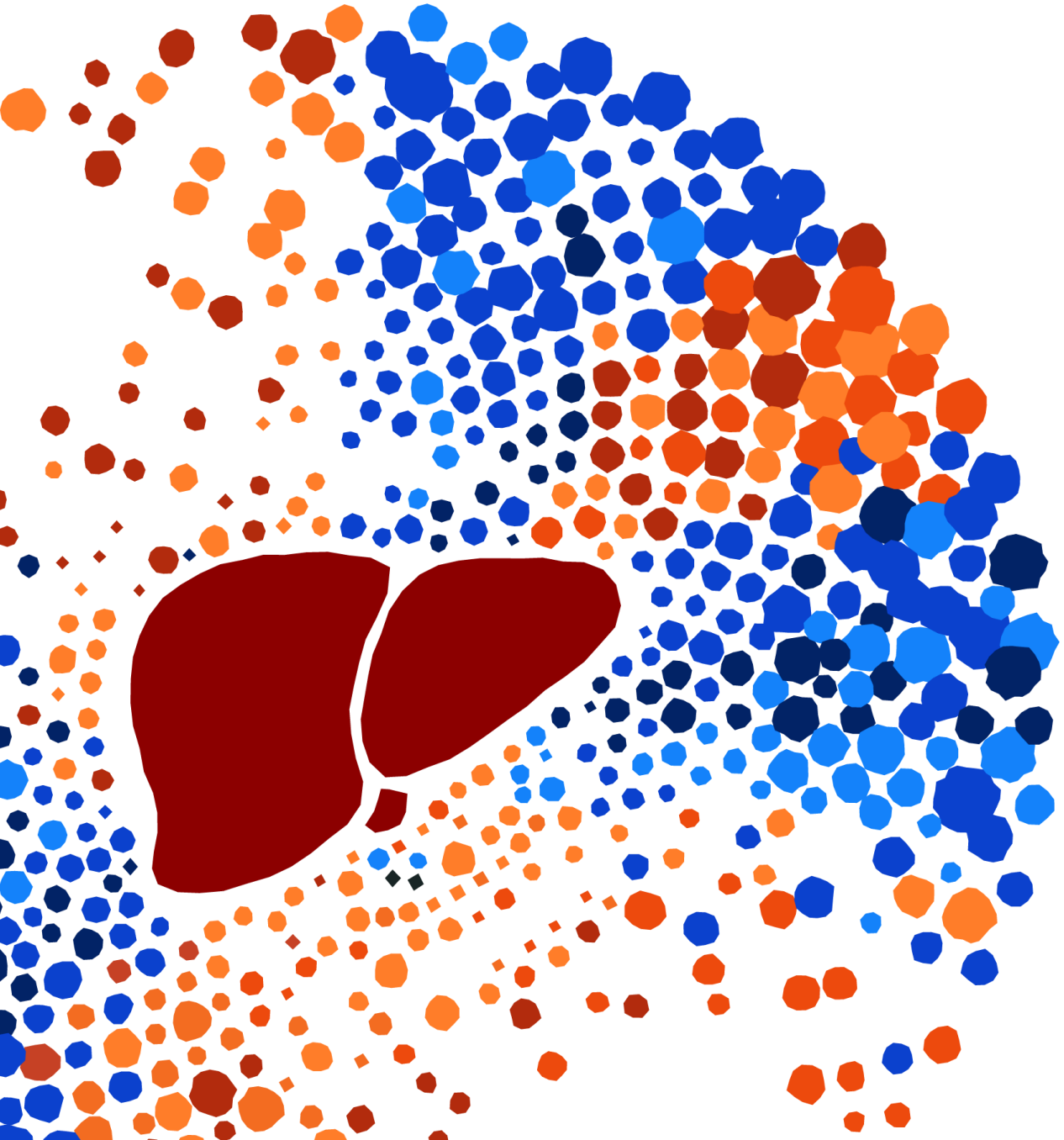
- **Consulting fees:** AstraZeneca, Basilea, Bayer, BMS, Celgene, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Lilly, MSD, Nerviano Medical Sciences, Roche, Sanofi, Taiho Oncology, Zymeworks
- **Lecture fees:** AstraZeneca, Bayer, Eisai, Gilead, Incyte, Ipsen, Merck Serono, Roche, Sanofi, Servier
- **Travel:** AstraZeneca
- **Institutional research funding:** Agios, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Zymeworks

Jörg Trojan

- **Consulting fees:** Amgen, AstraZeneca, Bayer, BMS, Eisai, Institute for Quality and Efficiency in Health Care (IQWiG), Ipsen, Merck Serono, MSD, Lilly Imclone, PCI Biotech, onkowissen.de, Roche, Servier
- **Lecture fees:** Amgen, Bayer, BMS, Daichi Sankyo, Eisai, Ipsen, Merck Serono, MSD, Lilly Imclone, Nationale Gesundheitsakademie, Roche, Servier, streamedup!
- **Travel:** Ipsen, Roche
- **Institutional research funding:** AstraZeneca, BMS, Ipsen, MSD, PCI Biotech, Roche

Pierce Chow

- **Personal Financial Interests - Advisory role**: Sirtex Medical, Ipsen, BMS, Oncosil, Bayer, New B Innovation, MSD, BTG Plc, Guerbet, Roche, AUM Bioscience, L.E.K. Consulting, AstraZeneca, Eisai, Genentech, IQVIA, Abbot, Omega Therapeutics, Synergy Research, Worrell
- **Research funding**: Sirtex Medical, Ipsen, IQVIA, New B Innovation, AMiLi, Perspecrum, MiRXES, Roche
- **Leadership roles**: Founding President, College of Clinician Scientists, Academy of Medicine Singapore; Protocol Chair, The Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group; Academic Vice Chair (Research), Surgery Academic Clinical Program, SingHealth-Duke-NUS Academic Medical Centre; Chief Medical Officer, AVATAMED PTE LTD



Welcome and introductions

Lorenza Rimassa

Expert Panel

Lorenza Rimassa

Associate Professor of Medical Oncology
Humanitas University and IRCCS Humanitas Research Hospital, Italy

Jörg Trojan

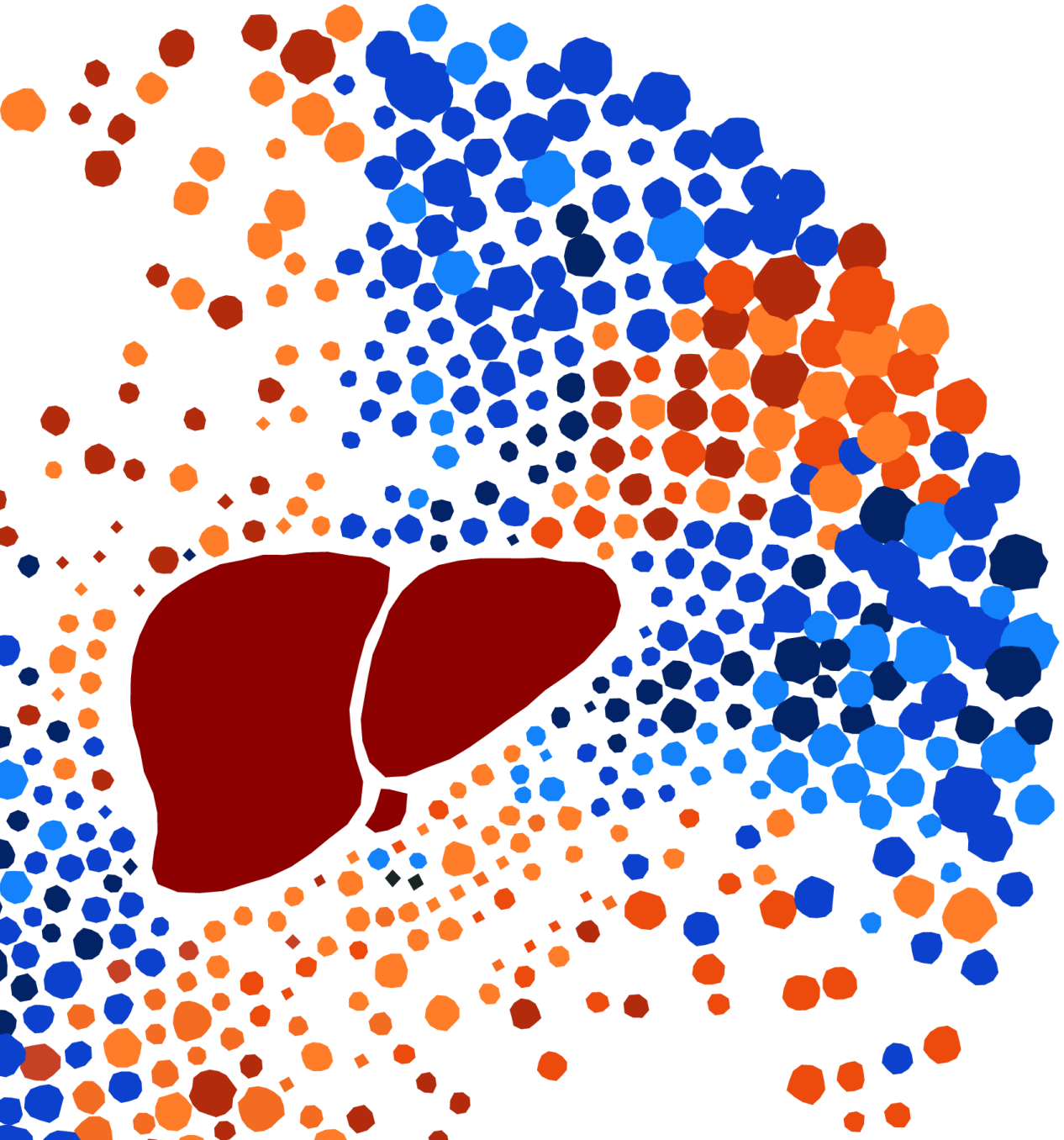
Professor of Medicine and Head of the Gastrointestinal Oncology Unit
University Hospital and Cancer Center, Frankfurt, Germany

Pierce Chow

Senior Consultant Surgeon, National Cancer Centre Singapore and
Professor and Program Director Duke-NUS Medical School, Singapore

Agenda

Time	Topic	Speaker
18:20–18:25	Welcome and introductions	Lorenza Rimassa
18:25–18:35	Where do we stand in clinical practice? Systemic HCC treatment today	Lorenza Rimassa
18:35–18:45	Improving patient survival and care: early HCC screening and diagnosis	Jörg Trojan
18:45–18:55	Evolving perspectives in the HCC treatment landscape	Pierce Chow
18:55–19:15	Q&A and panel discussion: insights into the patient journey	All faculty Moderator: Lorenza Rimassa
19:15–19:20	Summary and close	Lorenza Rimassa



Where do we stand in clinical practice? Systemic HCC treatment today

Lorenza Rimassa

Insights into the patient journey: a case study

Screening → Early-stage HCC → Intermediate-stage HCC → **Advanced-stage HCC**

1L treatment

- 62-year-old male patient with pre-existing autoimmune disorder (hypothyroidism) who undergoes regular blood tests to assess liver function
- Relapsed and progressed to advanced-stage HCC after previous locoregional treatment

Confirmed advanced-stage HCC

- **Child-Pugh A**
- **BCLC stage C**
- **ECOG PS 1**
- **AFP 356 ng/ml**

Patient characteristics:

- Compensated liver cirrhosis
- NASH
- BMI 32
- Arterial hypertension
- HBV–/HCV–
- Two tumours, both ≥ 5cm
- Spread to multiple lymph nodes
- Main portal invasion
- EHS

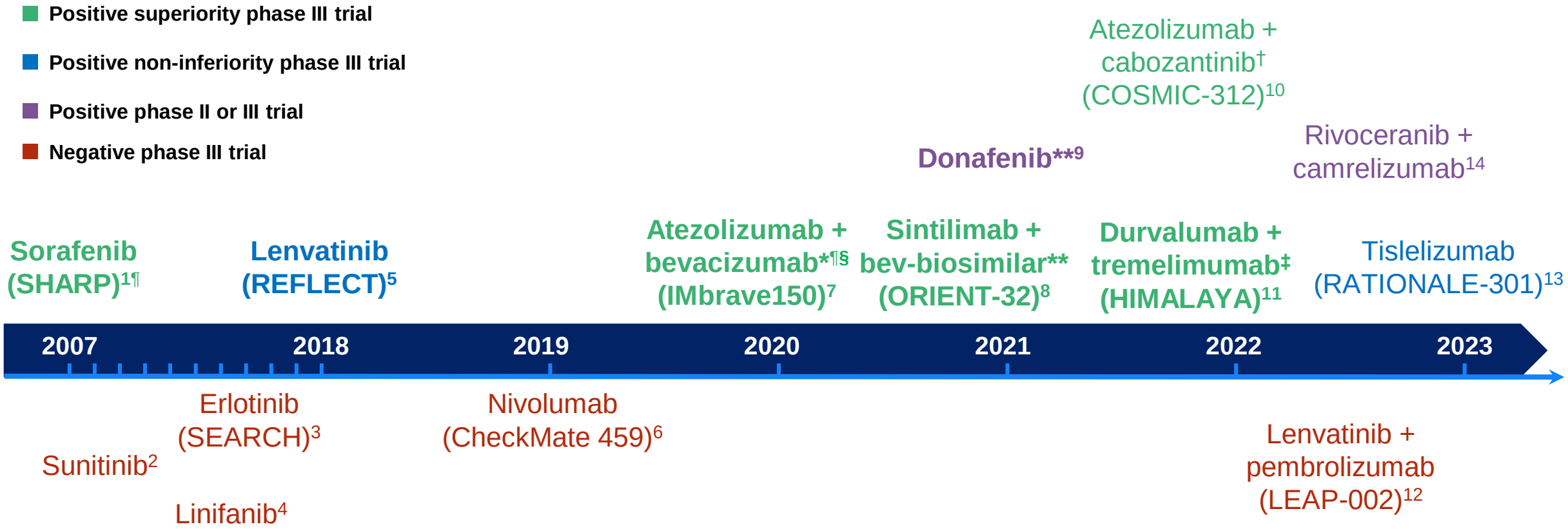
Fictional case study for the purposes of this presentation

What is the most important feature in the patient characteristics that you base your treatment decision on?

1. **Age**
2. **MVI**
3. **PD-L1 status**
4. **Cardiovascular comorbidities**
5. **Tumour load**

Progress has been made in 1L systemic treatment of HCC in recent years

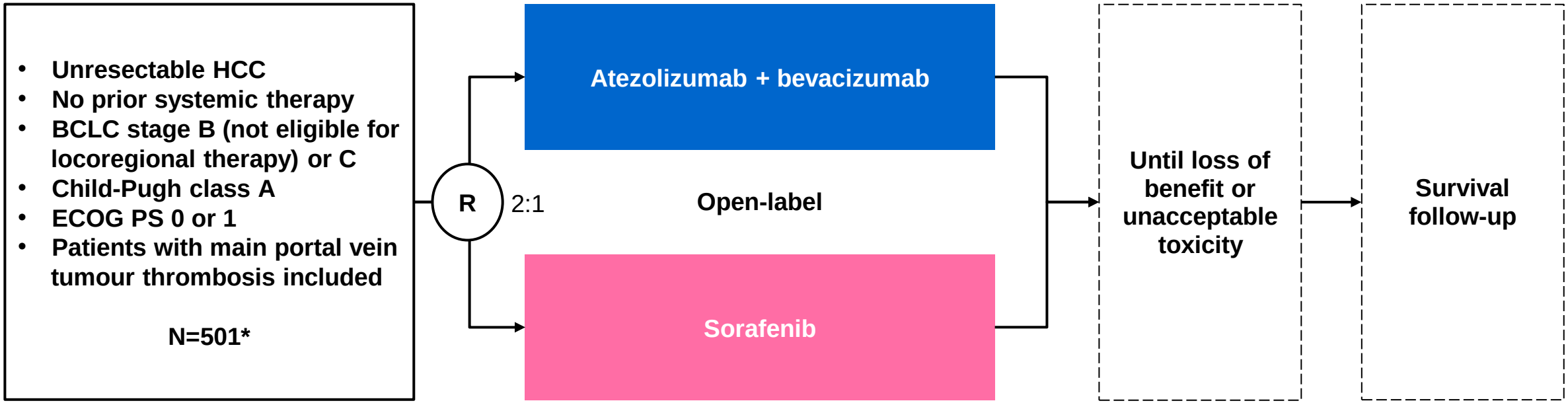
- **Positive superiority phase III trial**
- **Positive non-inferiority phase III trial**
- **Positive phase II or III trial**
- **Negative phase III trial**



*The TECENTRIQ® indication in combination with Bevacizumab is funded by the HNS for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have not received prior systemic therapy, with liver function (Child-Pugh stage A), an ECOG score of 0 or 1, in the absence of untreated or undertreated esophagogastric varices and in the absence of autoimmune diseases; **In China only; †The use of this product has EMA authorisation but is pending for obtaining funding conditions from HNS; ‡Does not currently have EMA authorisation; ¶The use of this product has EMA authorisation and funding conditions from the HNS; §The reflected information refers to the Avastin® data sheet. In case of administering another bevacizumab, the corresponding data sheet should be consulted; This slide has research data from products without EMA authorisation, with the only purpose of medical education; **Trials in bold supported an approval**

1. Llovet et al. N Engl J Med 2008; 2. Cheng et al. J Clin Oncol 2013
3. Zhu et al. J Clin Oncol 2015; 4. Cainap et al. J Clin Oncol 2015
5. Kudo et al. Lancet 2018; 6. Yau et al. Lancet Oncol 2022
7. Finn et al. N Engl J Med 2020; 8. Ren et al. Lancet Oncol 2021
9. Qin et al. J Clin Oncol 2021; 10. Kelley et al. Lancet Oncol 2022
11. Abou-Alfa et al. N Engl J Med Evidence 2022
12. Finn et al. ESMO 2022; 13. Qin et al. ESMO 2022 (LBA36)
14. Qin et al. ESMO 2022 (LBA35)

IMbrave150 (phase III): study design



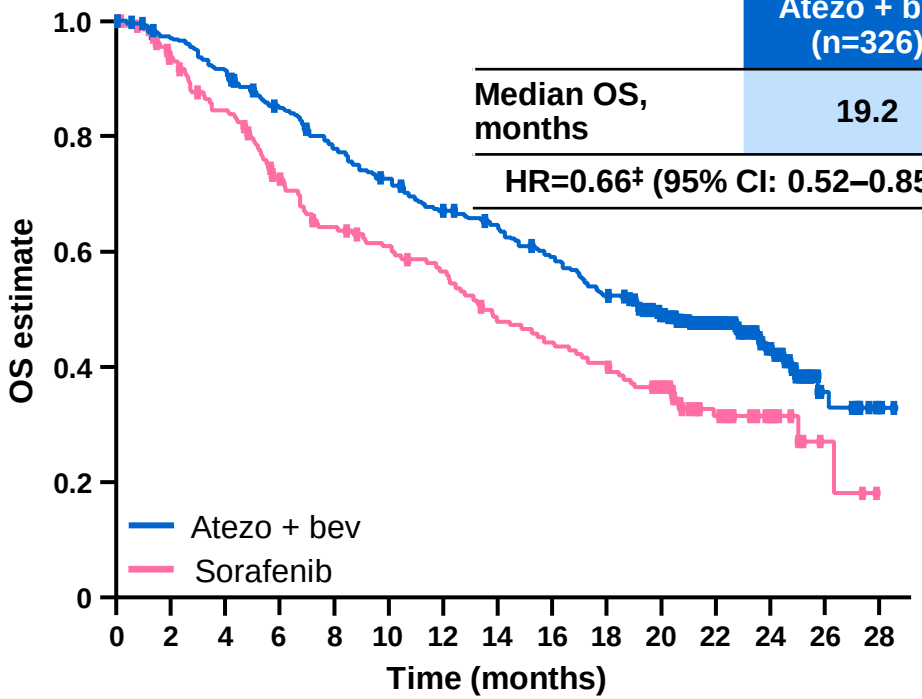
Stratification
- Region (Asia excluding Japan‡/RoW)
- ECOG PS (0 or 1)
- MVI and/or EHS (presence/absence)
- Baseline AFP (<400/≥400ng/mL)

Primary endpoints
- OS, PFS (IRF RECIST v1.1)

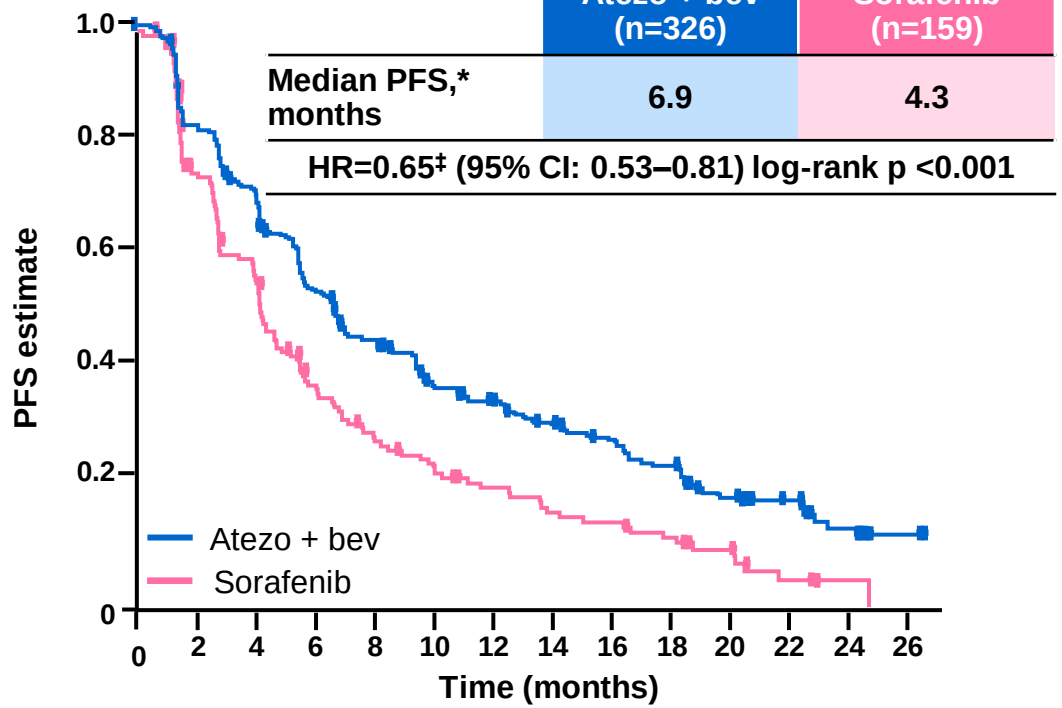
*There were an additional 57 Chinese patients in the China extension cohort who were not included in the global population/analysis; ‡Japan is included in RoW; AFP, α-fetaprotein

NCT03434379

IMbrave150 (phase III): efficacy



	Atezo + bev (n=326)	Sorafenib (n=159)
Median OS, months	19.2	13.4
HR=0.66‡ (95% CI: 0.52–0.85) log-rank p <0.001		



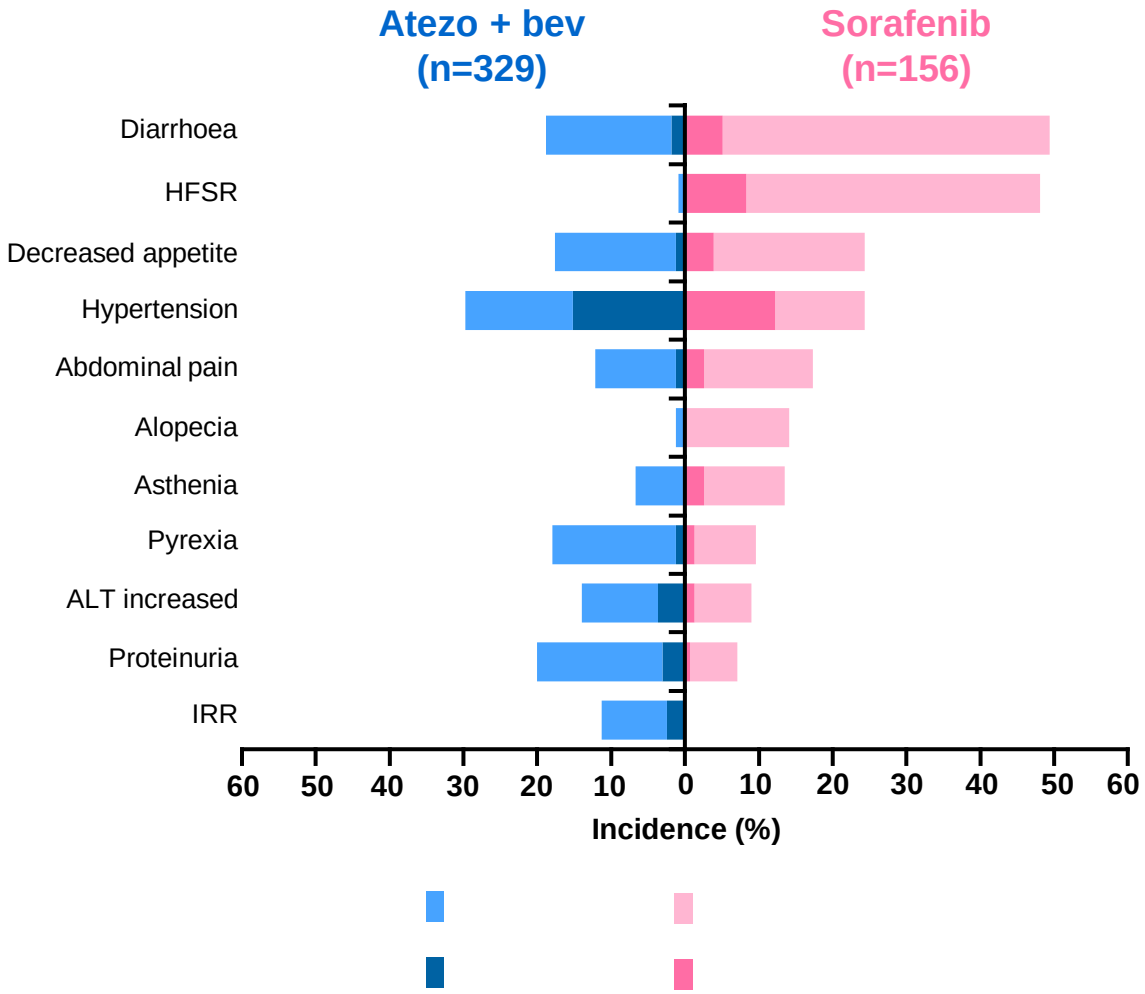
	Atezo + bev (n=326)	Sorafenib (n=159)
Median PFS,* months	6.9	4.3
HR=0.65‡ (95% CI: 0.53–0.81) log-rank p <0.001		

Clinical response: RECIST 1.1	Atezo + bev (n=326)	Sorafenib (n=159)
Confirmed ORR, n (%*; 95% CI) CR, n (%) PR, n (%)	97 (30; 25–35) 25 (8) 72 (22)	18 (11; 7–17) 1 (<1) 17 (11)
SD, n (%)	144 (44)	69 (43)
PD, n (%)	63 (19)	40 (25)
DCR, n (%)	241 (74)	87 (55)
Median DoR, (95% CI) months‡	18.1 (14.6–NE)	14.9 (4.9–17.0)

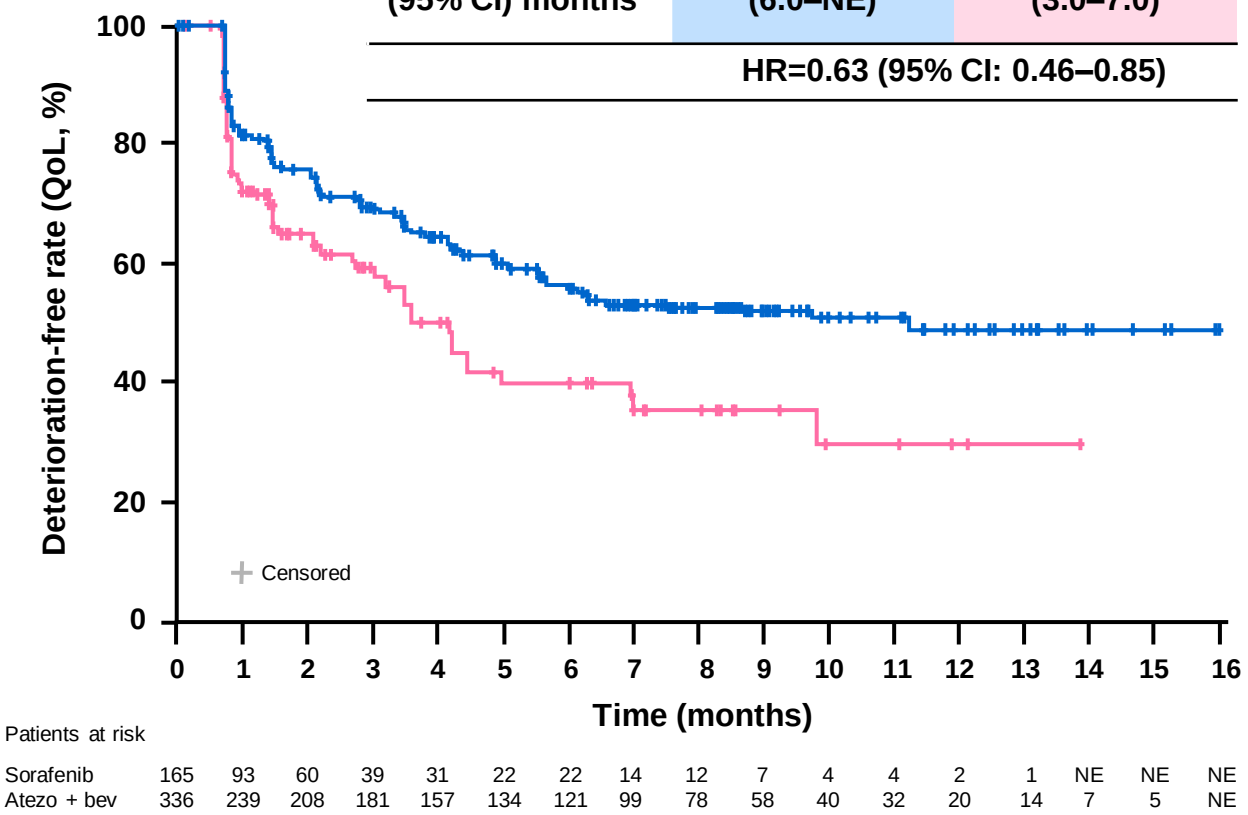
CCOD: 31 August 2020; median follow-up: 15.6 months; *IRF, RECIST v1.1; ‡Stratified: stratification factors included in the Cox model are geographic region (Asia excluding Japan vs RoW), AFP level (<400ng/mL vs ≥400ng/mL) at baseline and MVI and/or EHS (Yes vs No) per IxRS

Cheng et al. J Hepatol 2022

IMbrave150 (phase III): safety and HRQoL



	Atezo + bev (n=336)	Sorafenib (n=165)
Median TTD, (95% CI) months	11.2 (6.0–NE)	3.6 (3.0–7.0)
HR=0.63 (95% CI: 0.46–0.85)		



Patients at risk

Sorafenib	165	93	60	39	31	22	22	14	12	7	4	4	2	1	NE	NE	NE
Atezo + bev	336	239	208	181	157	134	121	99	78	58	40	32	20	14	7	5	NE

HFSR, hand-foot skin reaction

Finn et al. N Engl J Med 2020

HIMALAYA (phase III): efficacy and safety

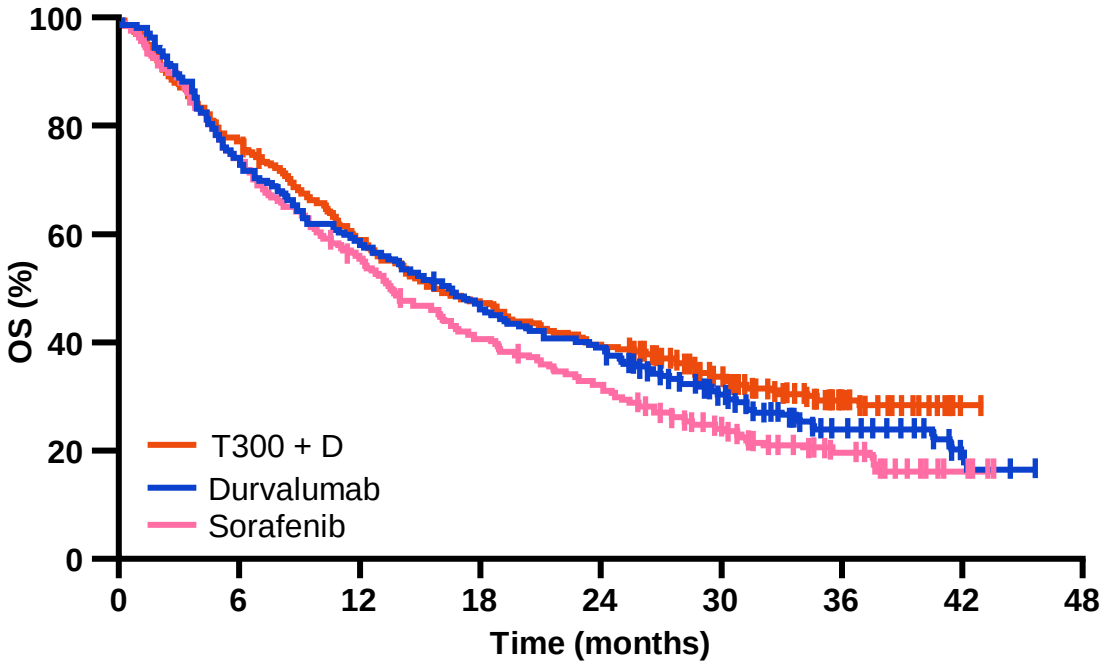
- Unresectable HCC
- No prior systemic therapy
- BCLC stage B (not eligible for LRT) or C
- Child-Pugh class A
- ECOG PS 0 or 1
- No tumour thrombus involving main trunk of portal vein

N=1171

R (1:1:1)

- Tremelimumab (T300) + durvalumab
- Durvalumab
- Sorafenib

Primary endpoint: OS for T300 + durvalumab vs sorafenib



	T300 + durvaulmab (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Median OS, (95% CI) months	16.43 (14.16–19.58)	16.56 (14.06–19.12)	13.77 (12.25–16.13)
HR vs sorafenib	0.78 (96.02% CI: 0.65–0.93)	0.86 (95.67% CI: 0.73–1.03)	–
Median PFS, (95% CI) months	3.8 (3.68–5.32)	3.7 (3.19–3.75)	4.1 (3.75–5.49)
HR (95% CI)	0.9 (0.77–1.05)	1.0 (0.88–1.19)	–
ORR (RECIST v1.1), %	20	17	5
DCR, %	60	55	61
Median DoR, months	22.34	16.82	18.43

Event, n (%)	T300 + durvalumab (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Any Grade 3/4 TRAE	196 (51)	144 (37)	196 (52)
imAEs requiring high-dose steroids	78 (20.1)	37 (9.5)	7 (1.9)
imAEs leading to treatment discontinuation	22 (5.7)	10 (2.6)	6 (1.6)

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

RATIONALE-301 (phase III): efficacy and safety

- Histologically confirmed HCC
- No prior systemic therapy
- BCLC stage C/B
- Child-Pugh class A
- ≥1 measurable lesion (RECIST v1.1)
- ECOG PS ≤1
- No tumour thrombus involving main trunk of portal vein or inferior vena cava

N=674

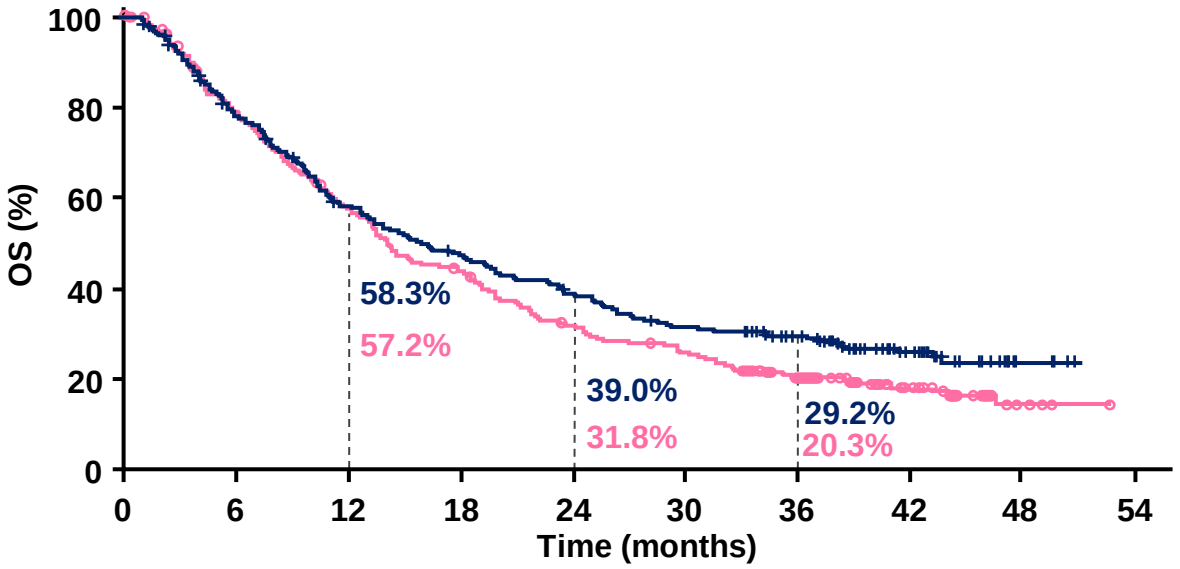
R 1:1

Tisleizumab

Sorafenib

Treatment until disease progression or intolerable toxicity

Primary endpoint: OS (ITT)
Secondary endpoints: ORR, PFS, DoR by BIRC per RECIST 1.1 and safety



	Tisleizumab (n=342)	Sorafenib (n=332)
Median OS, (95% CI) months	15.9 (13.2–19.7)	14.1 (12.6–17.4)
Stratified HR (95% CI)	0.85 (0.712–1.019)	
Median PFS, (95% CI) months	2.1 (2.1–3.5)	3.4 (2.2–4.1)
Stratified HR (95% CI)	1.11 (0.92–1.33)	
ORR n (%) [95% CI]	49 (14.3) [10.8–18.5]	18 (5.4) [3.2–8.4]
Median DoR, (95% CI) months	36.1 (16.8–NE)	11.0 (6.2–14.7)

Event, %	Tisleizumab (n=338)	Sorafenib (n=324)
Occurrence of Grade ≥3 TRAE	22.2	53.4
imAE requiring steroids	12.7	3.1
TRAE leading to discontinuation	6.2	10.2

Qin et al. ESMO 2022 (LBA36)

SHR-1210-III-310 (phase III): efficacy and safety

- Unresectable or metastatic HCC
- No prior systemic therapy
- BCLC stage C/B
- Child-Pugh class A
- ≥1 measurable lesion (RECIST v1.1)
- ECOG PS 0 or 1

N=543

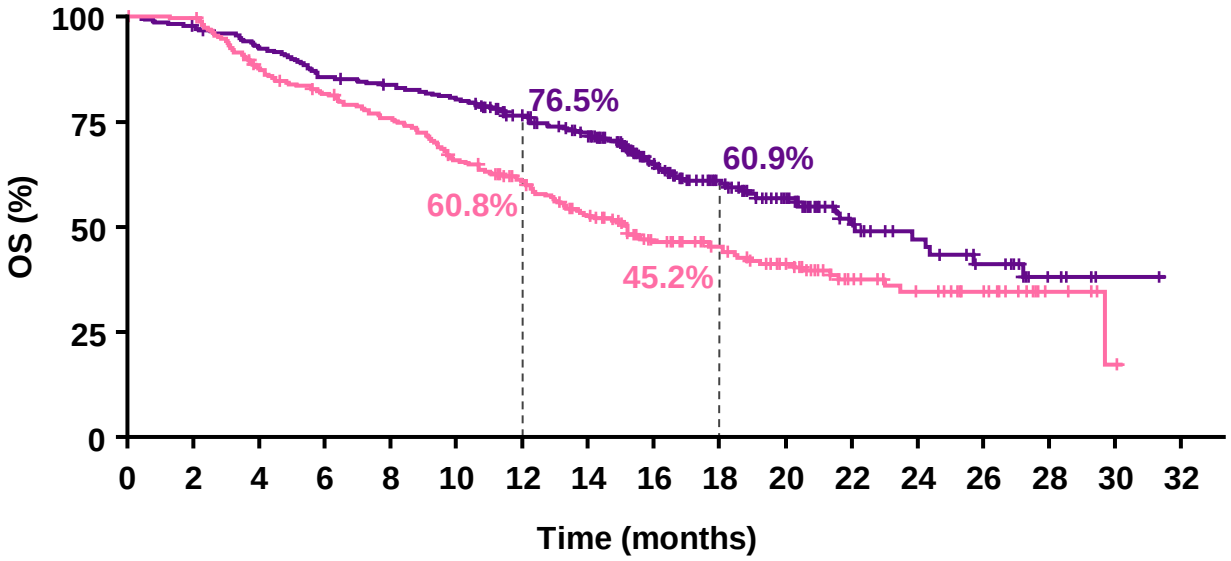
R 1:1

Camrelizumab + rivoceranib

Sorafenib

Treatment until loss of clinical benefits or intolerable toxicity

Primary endpoint: PFS, OS
Secondary endpoints: ORR



	Camrelizumab + rivocernaib (n=272)	Sorafenib (n=269)
Median OS, (95% CI) months	22.1 (19.1–27.2)	15.2 (13.0–18.5)
Stratified HR (95% CI)	0.62 (0.49–0.80), p<0.0001	
Median PFS, (95% CI) months	5.6 (5.5–6.3)	3.7 (2.8–3.7)
Stratified HR (95% CI)	0.52 (0.41–0.65), p<0.0001	

Safety, n (%)	Camrelizumab + rivocernaib (n=272)	Sorafenib (n=269)
Any grade 3/4 TRAE	219 (80.5)	140 (52.0)
TRAEs leading to dose modification or interruption of treatment	219 (80.5)	135 (50.2)

Qin et al. ESMO 2022 (LBA35)

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)

AASLD (2020 Consensus Conference)[2]

- Atezolizumab + bevacizumab is recommended as 1L therapy

ESMO (2021 eUpdate)[3]

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

EASL (2021)[4]

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

BCLC (2022)[5]

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

APASL (2017)[6¶]

- No recommended cancer immunotherapy options at time of guideline publication

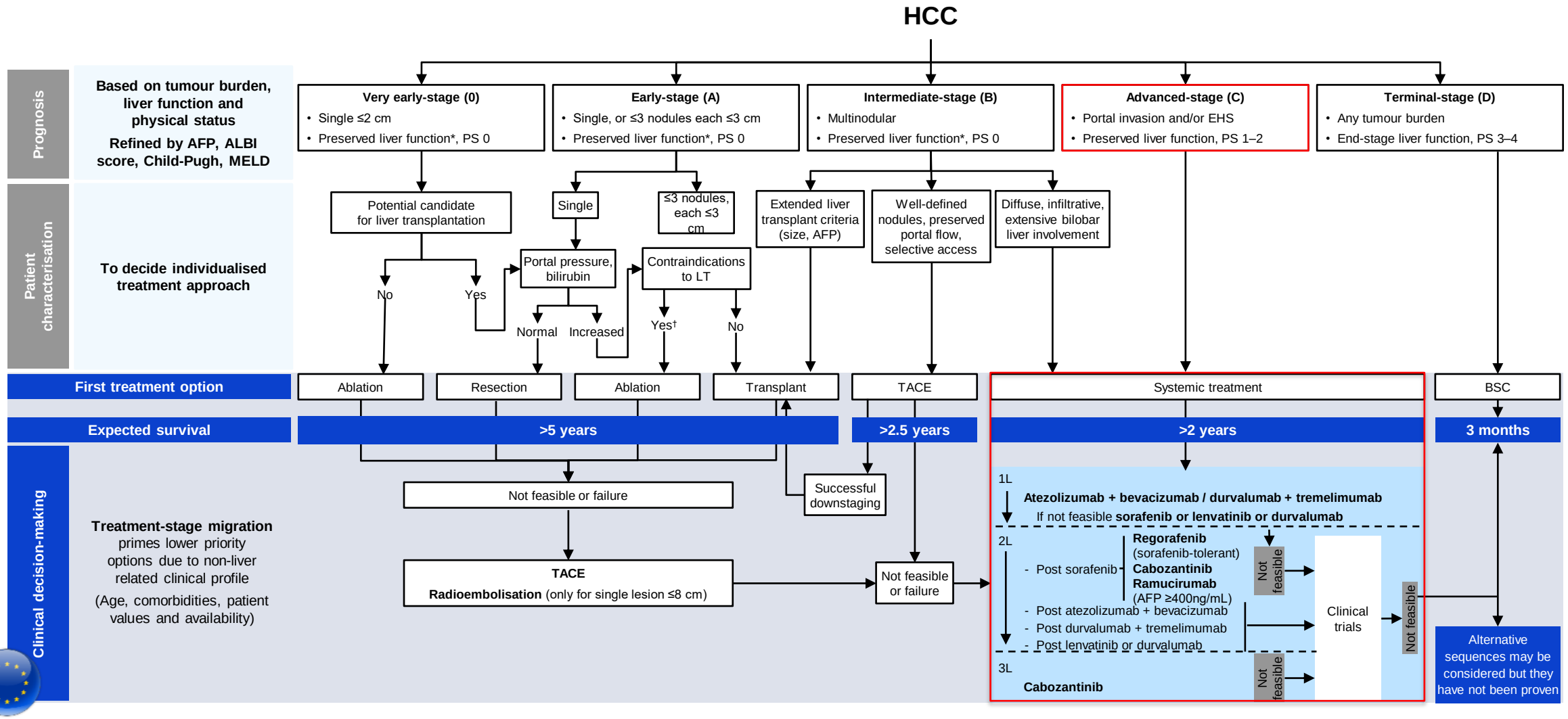
ILCA (2020)[7]

- 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

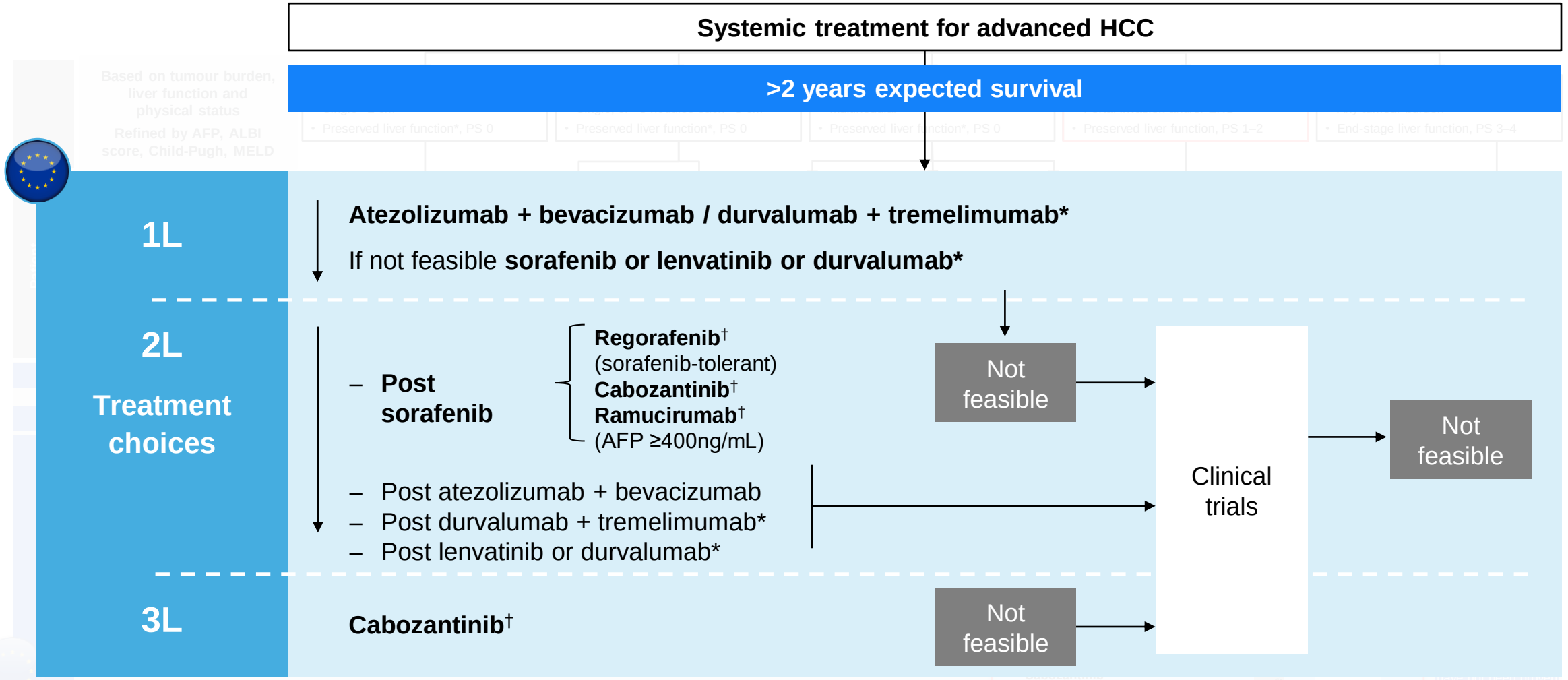
1. Gordan et al. J Clin Oncol 2020; 2. Llovet et al. Hepatology 2021
3. Vogel et al. Ann Oncol 2021; 4. Bruix et al. J Hepatol 2021
5. Reig et al. J Hepatol 2022; 6. Omata et al. Hepatol Int 2017
7. ILCA Systemic Therapy Guidance (last updated November 2020)

BCLC staging is the foundation of the treatment algorithm for HCC



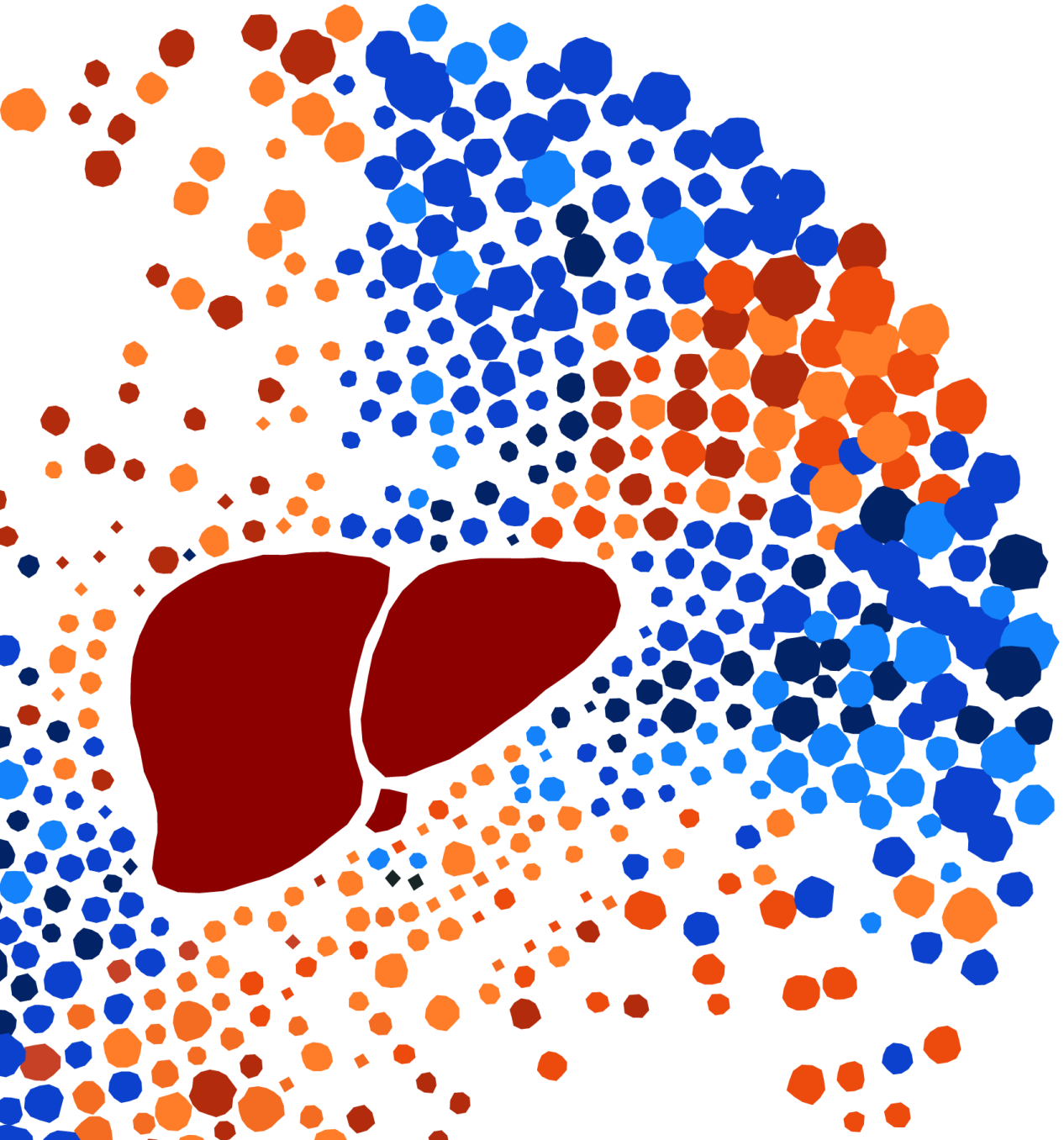
*Except for those with tumour burden acceptable for transplant
†Resection may be considered for single peripheral HCC with adequate remnant liver volume

BCLC staging is the foundation of the treatment algorithm for HCC



*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; †The use of this product has EMA authorisation but is pending for obtaining funding conditions from HNS

Reig et al. J Hepatol 2022; Copyright (2023), with permission from Elsevier



Improving patient survival and care: early HCC screening and diagnosis

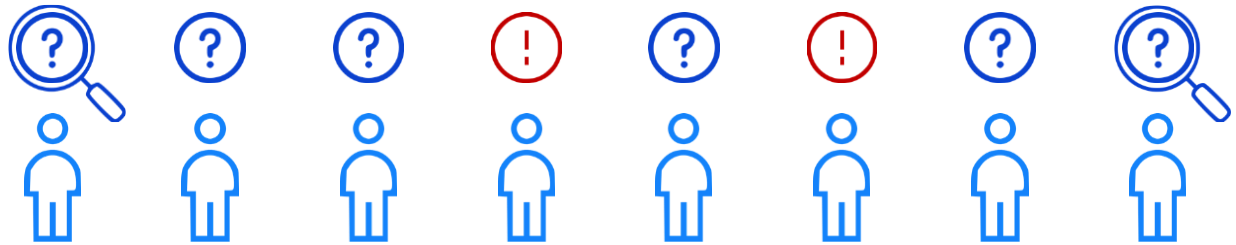
Jörg Trojan

What is your current preferred choice of surveillance method?

1. US
2. US & AFP
3. US & algorithms
4. GALAD alone
5. GAAD alone

HCC diagnosis is often made too late

Early-stage HCC is asymptomatic



Surveillance of at-risk population

Early stage | **Late stage**

Only 13% diagnosed and treated early

5-year survival rate: **40–70%**[1,2]

20% of patients fulfil resection criteria

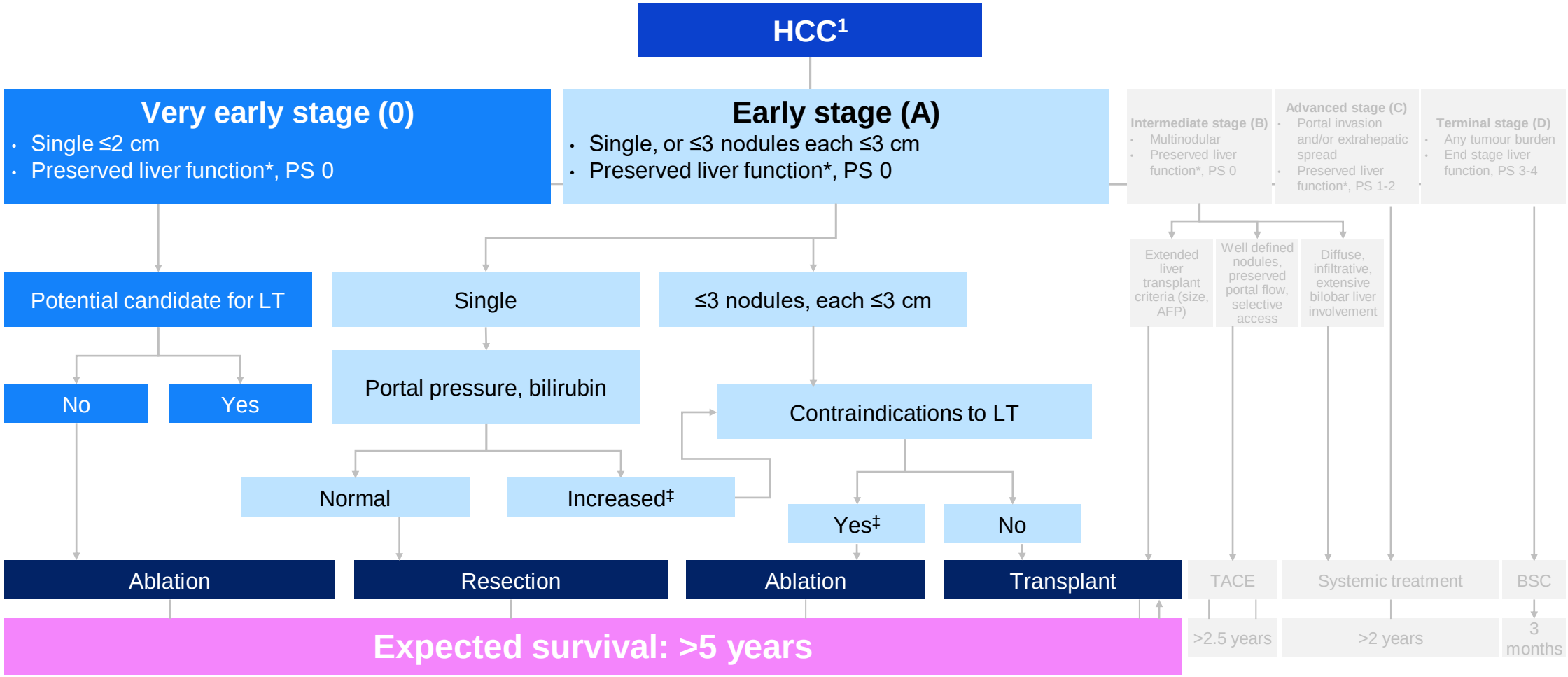
5-year survival rate: **<5%**[1]

Because **early-stage HCC gives no symptoms**, screening of population at risk plays crucial role in HCC treatment

Identify high-risk groups → **Regular testing ~6 months** → **37% decrease in HCC mortality by biannual screening** [3,4]

1. El-Serag et al. Ther Adv Gastroenterol 2011; 2. Kao et al. Medicine 2015
3. Wu and Qin. Chin Clin Oncol 2013; 4. Zhang et al. J Cancer Res Clin Oncol 2004

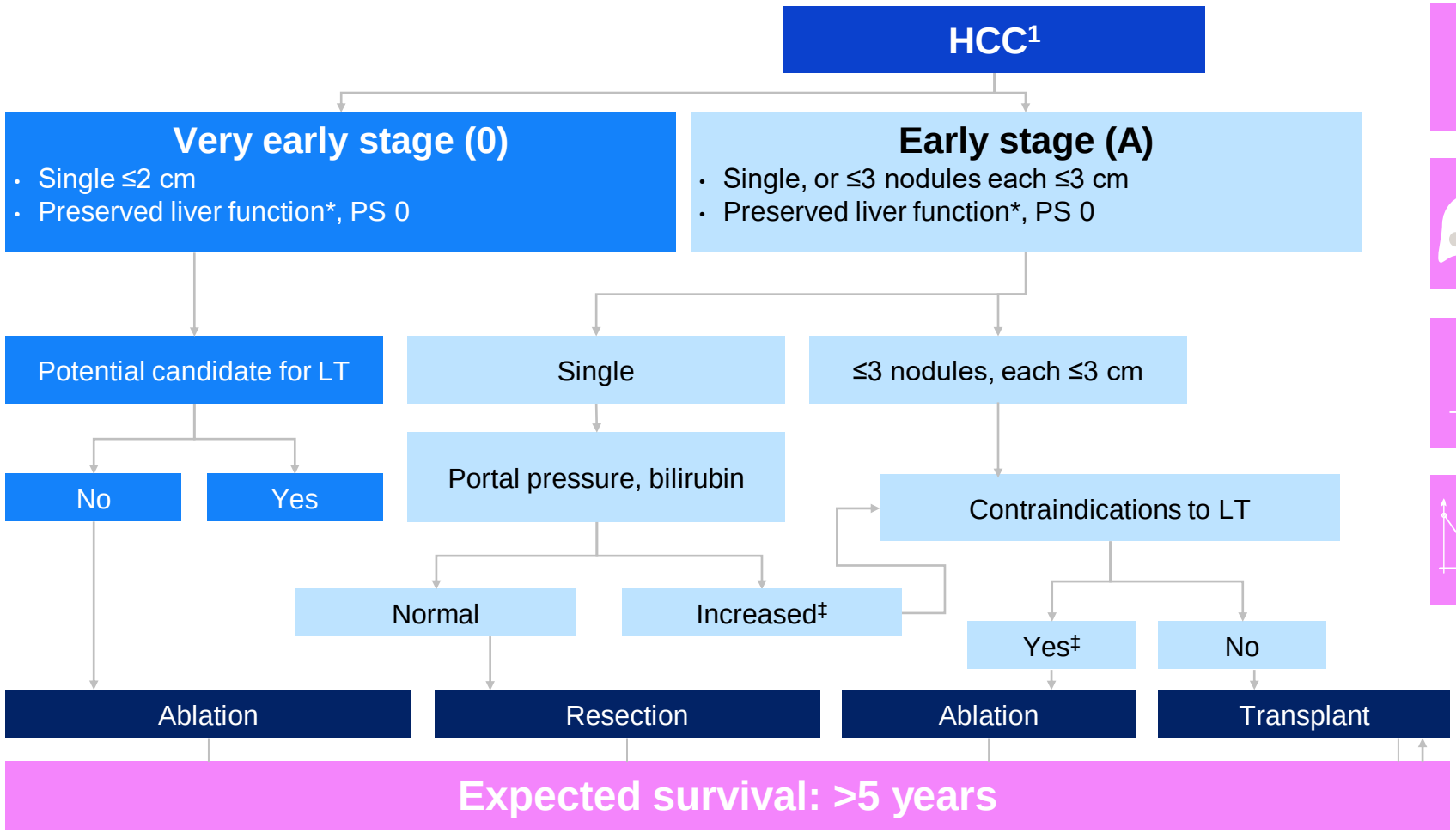
Diagnosing HCC at earlier stages is critical so more patients can benefit from potentially curative therapies



*Except for those with tumour burden acceptable for transplant
‡Resection may be considered for single peripheral HCC with adequate remnant liver volume

1. Reig et al. J Hepatol 2022; Copyright (2023), with permission from Elsevier

HCC surveillance is associated with improved early detection, use of curative treatment and longer OS



Surveillance is associated with[2]

Early-stage detection:
OR 1.86
(95% CI: 1.73–1.98)

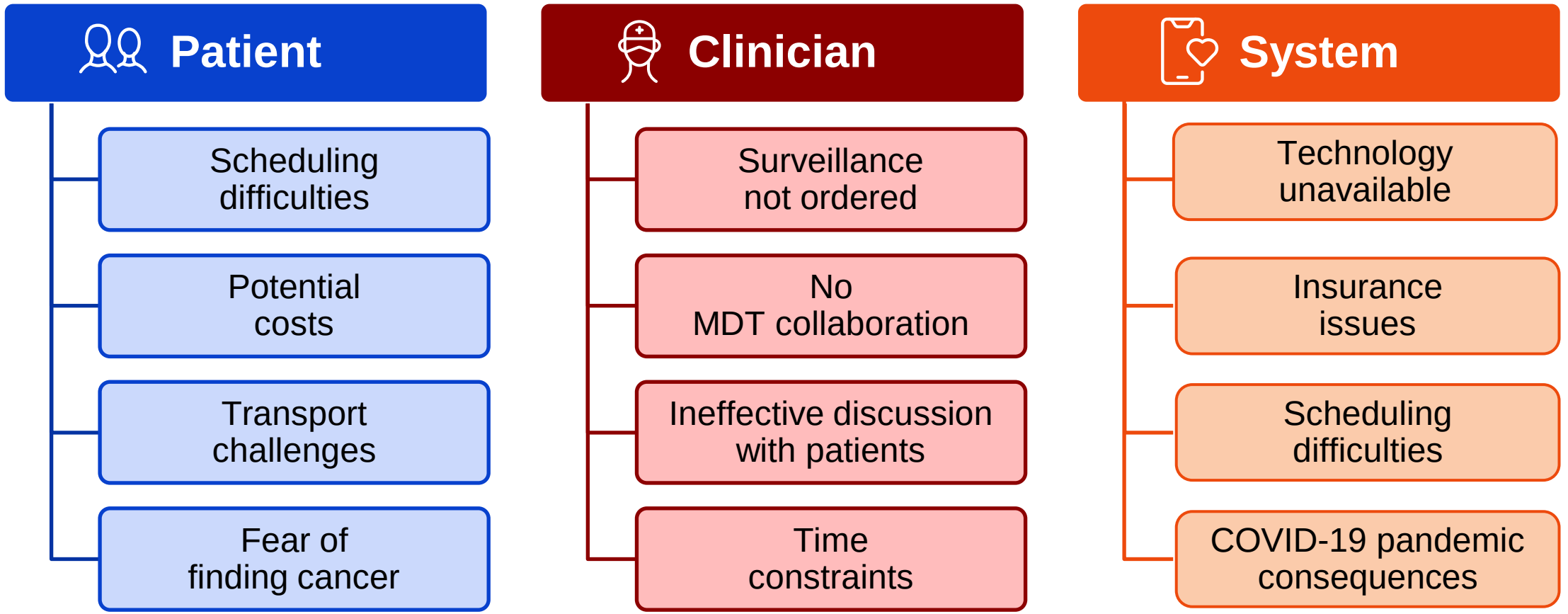
Use of curative therapy:
OR 1.83
(95% CI: 1.69–1.97)

OS:
HR 0.67
(95% CI: 0.61–0.72)

*Except for those with tumour burden acceptable for transplant
‡Resection may be considered for single peripheral HCC with adequate remnant liver volume

1. Reig et al. J Hepatol 2022; Copyright (2023), with permission from Elsevier

Barriers to HCC surveillance can be related to the patient, clinician or broader healthcare system



1. Parikh et al. JAMA Netw Open 2022
2. Farvardin et al. Hepatology 2017
3. Beal et al. ASCO GI 2022 (Abstract 404)

Traditional surveillance techniques such as ultrasound and AFP profiling have limited sensitivity for early-stage HCC[1,2]

There is an unmet need for specific and sensitive surveillance modalities that can detect HCC in at-risk patients as early as possible[2]

AFP, alpha fetoprotein; HCC, hepatocellular carcinoma

1. Tzartzeva et al. Gastroenterology 2018; 2. Ahn et al. Hepatoma Res 2022

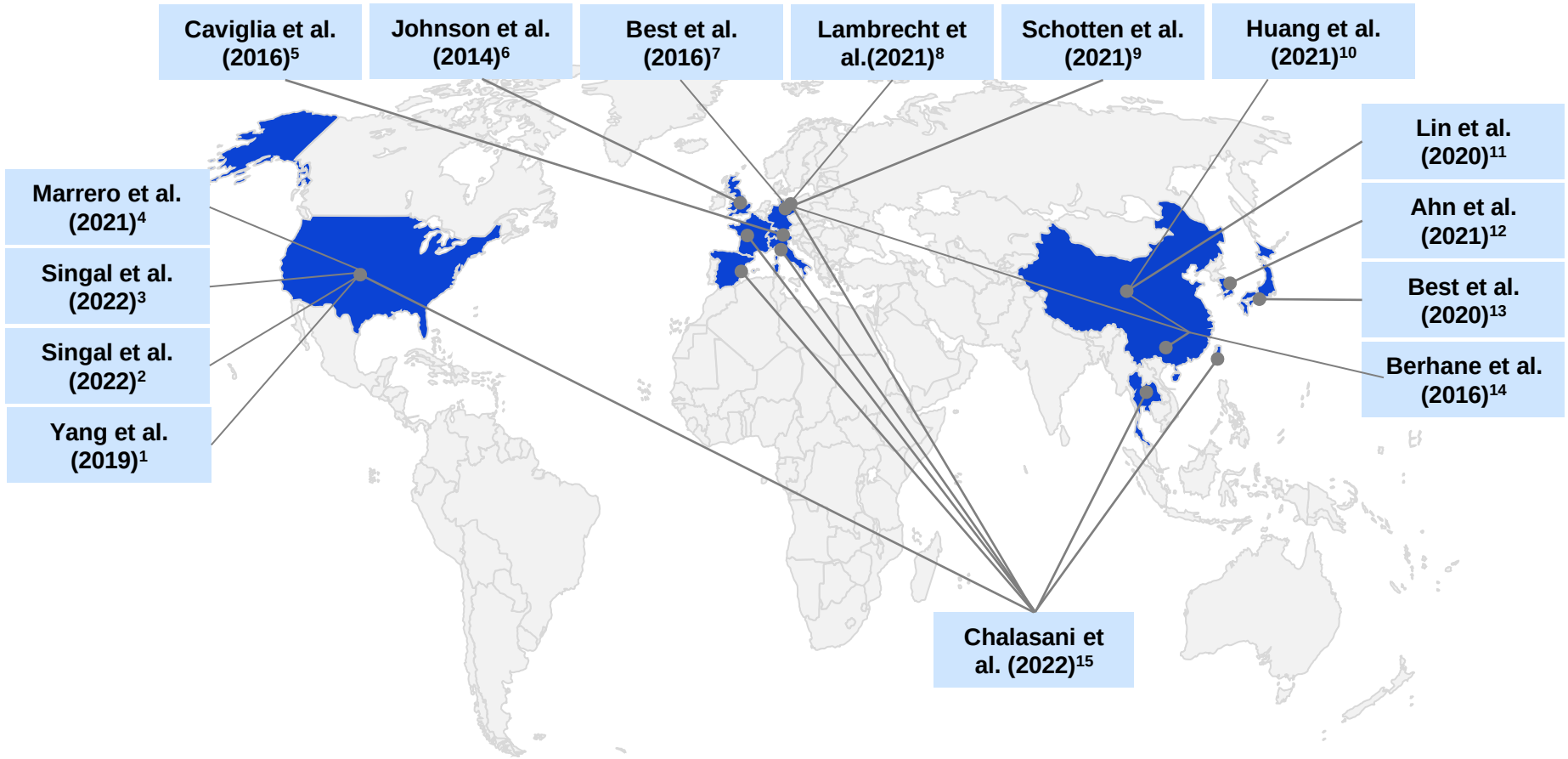
Published GALAD evidence generated in independent cohorts since 2014

AFP
Alpha-fetoprotein

AFP-L3
Alpha-fetoprotein Isoform

PIVKA II
Protein Induced by Vitamin K Antagonist-II

GALAD
Gender,
Age,
AFP-L3,
AFP,
DCP (PIVKA-II)



1. Yang et al. Cancer Epidemiol Biomarkers Prev 2019; 2. Singal et al. Hepatology 2022
3. Singal et al. Clin Gastroenterol Hepatol 2022; 4. Marrero et al. Hepatology 2021 5. Caviglia et al. Hepatol Res 2016
6. Johnson et al. Cancer Epidemiol Biomarkers Prev 2014; 7. Best et al. Z Gastroenterol 2016
8. Lambrecht et al. J Clin Med 2021; 9. Schotten et al. Pharmaceutials 2021; 10. Huang et al. Liver International 2021
11. Lin et al. Hepatol Commun 2022; 12. Ahn et al. Hepatoma Res 2022; 13. Best et al. Clin Gastroenterol Hepatol 2020
14. Berhane et al. Clin Gastroenterol Hepatol 2016; 15. Chalasani et al. Clin Gastroenterol Hepatol 2022

Elecsys® GAAD score has shown strong clinical performance for detection of HCC in its early stages

GAAD:
Gender
Age
AFP
DCP (PIVKA-II)

GAAD cut-off: **2.57**

	Elecsys® GAAD		Elecsys® AFP assay	
	All HCC (N=156)	**Early-stage (n=71)**	**All HCC (N=156)**	**Early-stage (n=71)**
Sensitivity, (95% CI)	**86.5 (80.2–91.5)**	**78.9 (67.6–87.7)**	**52.6 (44.4–60.6)**	**38.0 (26.8–50.3)**
Specificity, (95% CI)	**91.4 (86.7–94.8)**	**91.4 (86.7–94.8)**	**98.1 (95.2–99.5)**	**98.1 (95.2–99.5)**

Abnormal DCP (PIVKA-II) is a liver-specific protein produced when HCC is present and acts as tumour marker for HCC

GAAD is a fully automated in vitro diagnostics platform[1]

GAAD performed better than the Elecsys® AFP assay alone for detecting HCC[2]

GAAD showed strong clinical performance for early HCC detection[2]

GAAD differentiated HCC from chronic liver disease regardless of aetiology[2]

AFP, alpha fetoprotein; PIVKA-II, protein induced by vitamin K absence-II

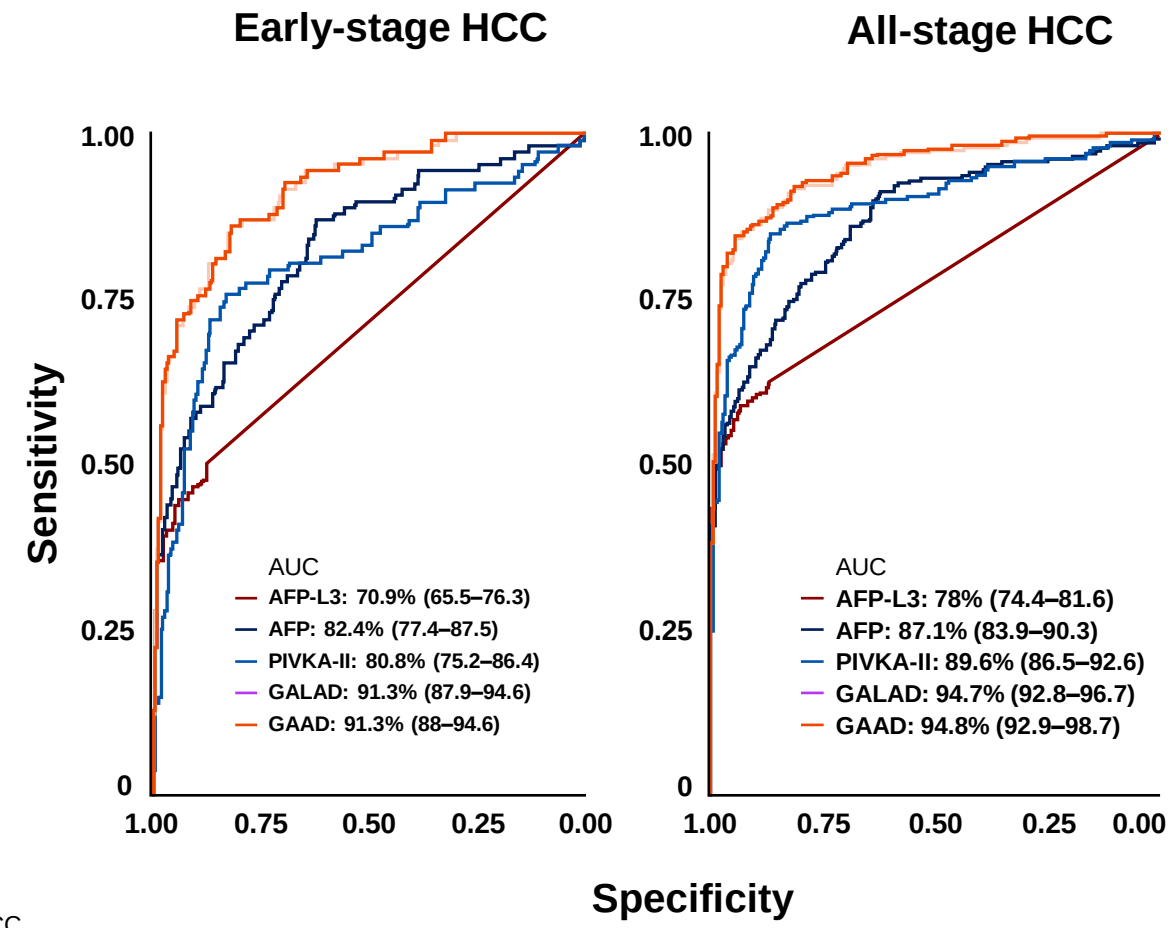
1. Elecsys® GAAD Method Sheet. Reference: 09342192001
2. Chan et al. ISHVLD GHS 2021

GALAD vs GAAD

- A comparison of the Elecsys® GALAD and Elecsys® GAAD algorithms for differentiating HCC from benign chronic liver disease showed that the algorithms had a similar clinical performance
- Both algorithms were superior to individual biomarkers alone

		Early-stage HCC	All-stage HCC
GALAD	Sensitivity, %	73.8	85.8
	Specificity, %	90.8	90.8
GAAD	Sensitivity, %	72.9	85.0
	Specificity, %	92.2	92.2

ROC curves for GALAD and GAAD algorithms and biomarker assays for discriminating between HCC and liver disease



AFP, alpha-fetoprotein; AFP-L3, Lens culinaris-agglutinin-reactive fraction of AFP; AUC, area under the curve; HCC, hepatocellular carcinoma; PIVKA-II, protein induced by vitamin K absence-II; ROC, receiver operating characteristic

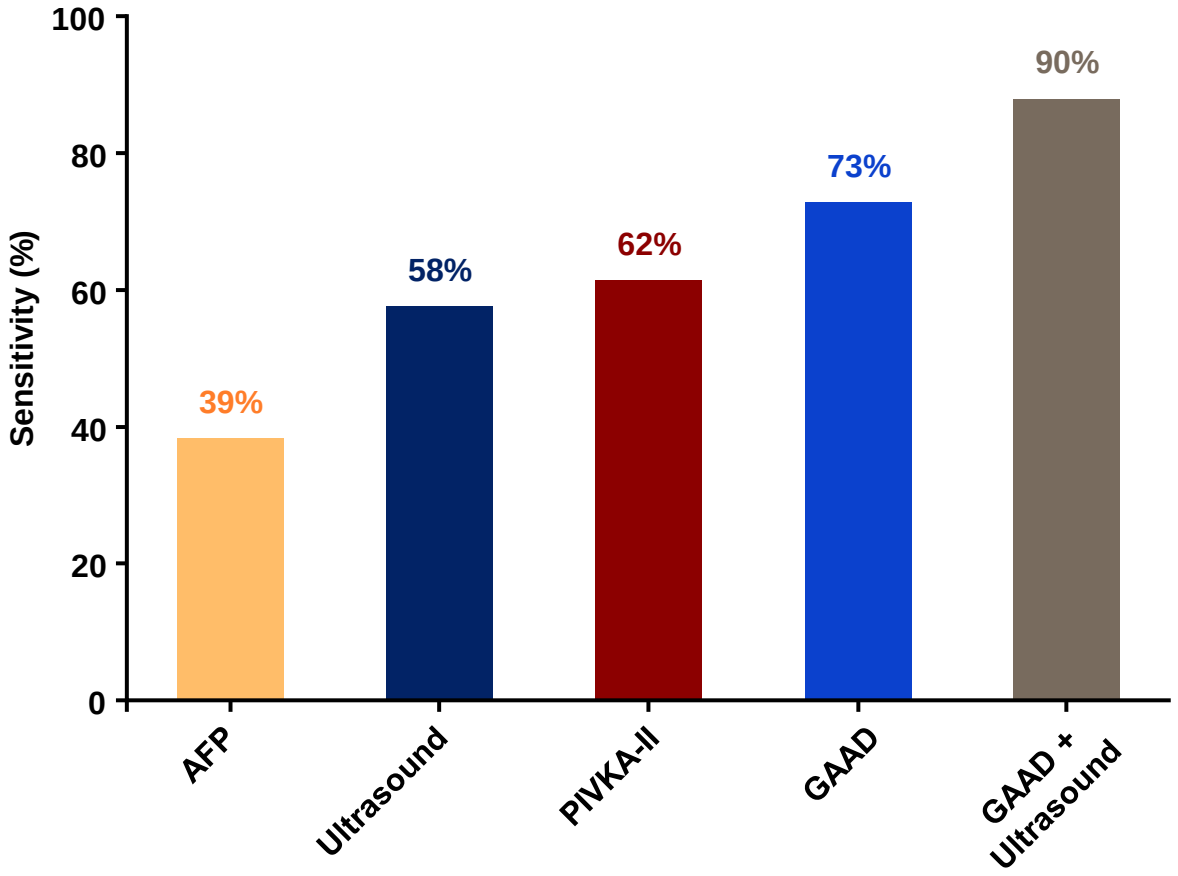
Chan et al. EASL ILC 2022

Sensitivity of GAAD compared with clinical biomarkers and ultrasound has been investigated in patients with HCC

HCC all stages

	SEN, %	SPE, %	AUROC	P value
Non-liver cirrhosis				
AFP >20 ng/mL	28.6	98.4	0.78	<0.001
PIVKA-II >28.4 ng/mL	66.7	98.1	0.94	<0.001
GAAD score >2.57	71.4	96.8	0.87	<0.001
GAAD score >2.57 plus US	100	96.8		<0.001
Liver chirrosis				
AFP >20 ng/mL	53.1	91.7	0.76	<0.001
PIVKA-II >28.4 ng/mL	71.9	80.0	0.87	<0.001
GAAD score >2.57 plus US	87.5	83.3		<0.001
GAAD score >2.57	81.3	83.3	0.90	<0.001

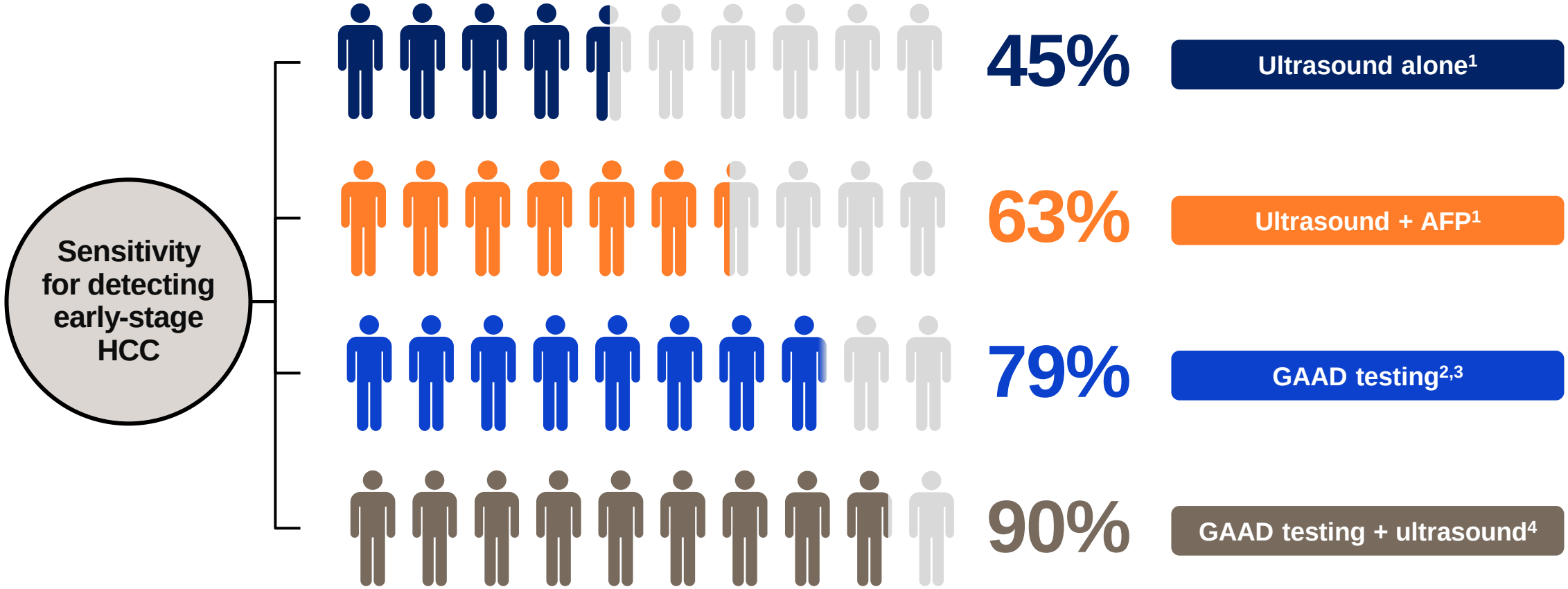
Early-stage HCC



AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; PIVKA-II: Protein induced by Vitamin K absence-II

Huang et al. APASL 2022 STC on HCC

GAAD testing combined with ultrasound has demonstrated improved sensitivity for detecting early-stage HCC compared with other surveillance techniques



AFP, alpha fetoprotein

1. Tzartzeva et al. Gastroenterology 2018; 2. Elecsys® GAAD Method Sheet. Reference: 09342192001
3. Chan et al. ISHVLD GHS 2021; 4. Huang et al. APASL 2022 STC on HCC

Insights into the patient journey: a case study

Screening | Early-stage HCC | Intermediate-stage HCC | Advanced-stage HCC

Surveillance

- 62-year-old male patient with pre-existing autoimmune disorder (hypothyroidism) who undergoes regular blood tests to assess liver function
- Asymptomatic for HCC but has characteristics considered high-risk for HCC

Patient monitored regularly every 6 months

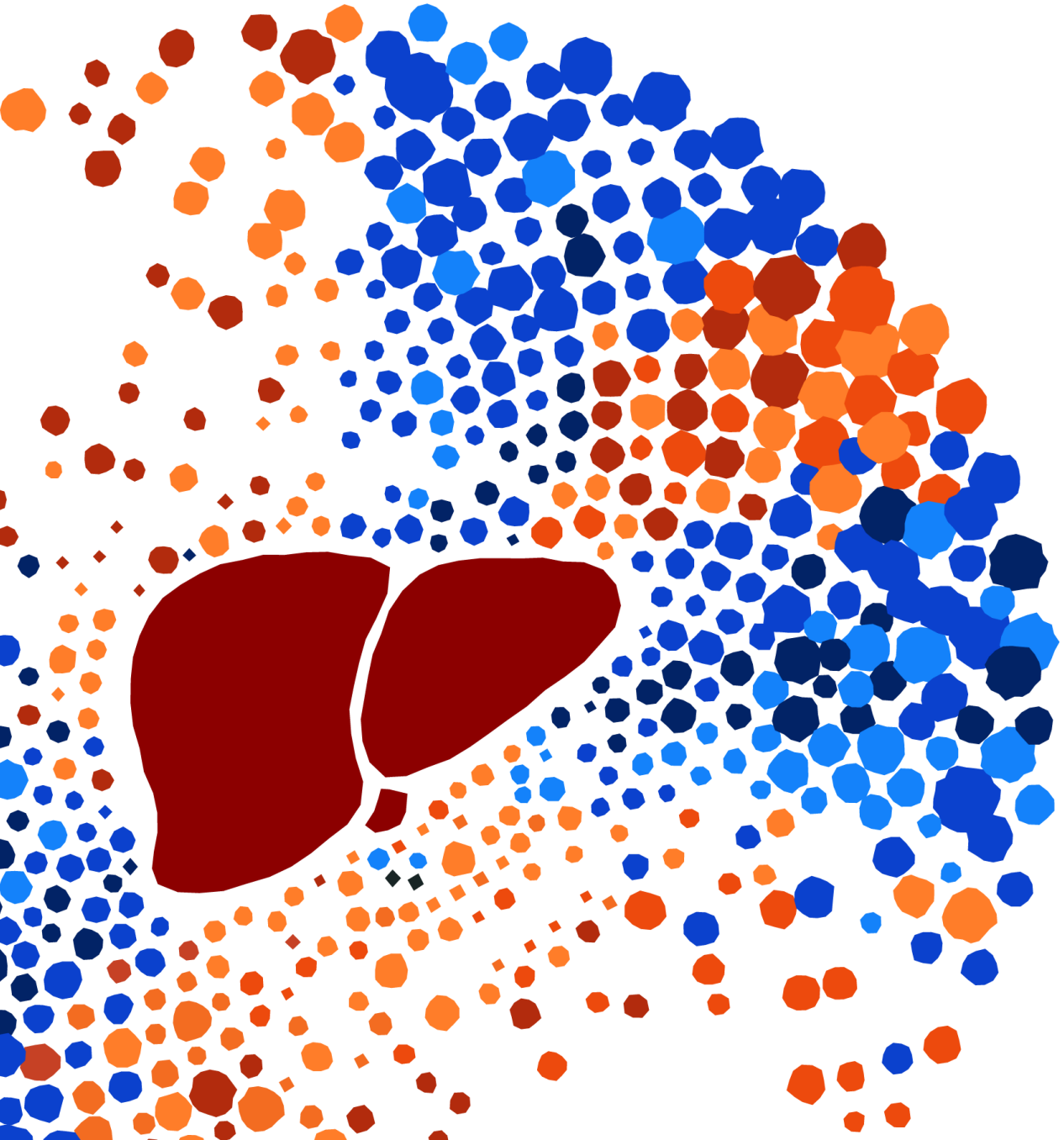
Patient characteristics:

- Liver cirrhosis
- NAFLD
- BMI 32
- Arterial hypertension
- HBV–/HCV–
- FIB4 score >3.5
- Liver enzymes slightly elevated

Fictional case study for the purposes of this presentation

Which choice of surveillance would you use for this patient?

1. US
2. US & AFP
3. US & algorithms
4. GALAD alone
5. GAAD alone



Evolving perspectives in the HCC treatment landscape

Pierce Chow

Insights into the patient journey: a case study

Screening | **Early-stage HCC** | Intermediate-stage HCC | Advanced-stage HCC

Diagnosis

- 62-year-old male patient with pre-existing autoimmune disorder (hypothyroidism) who undergoes regular blood tests to assess liver function
- Asymptomatic for HCC but has characteristics considered high-risk for HCC
- Diagnostic work-up performed including imaging, blood tests and biopsy
- Surveillance with ultrasound not conclusive; GAAD score shows value of 4.05; referred to MR which shows 5.1 cm LI-RADS 5 lesion in left liver lobe

Confirmed early-stage HCC

- Child-Pugh class A
- BCLC stage A
- ECOG PS 0
- AFP 15.2 ng/ml
- PIVKA II 23 ng/ml

Patient characteristics:

- Compensated liver cirrhosis
- NASH
- BMI 32
- Arterial hypertension
- HBV–/HCV–
- Single tumour 5.1 cm

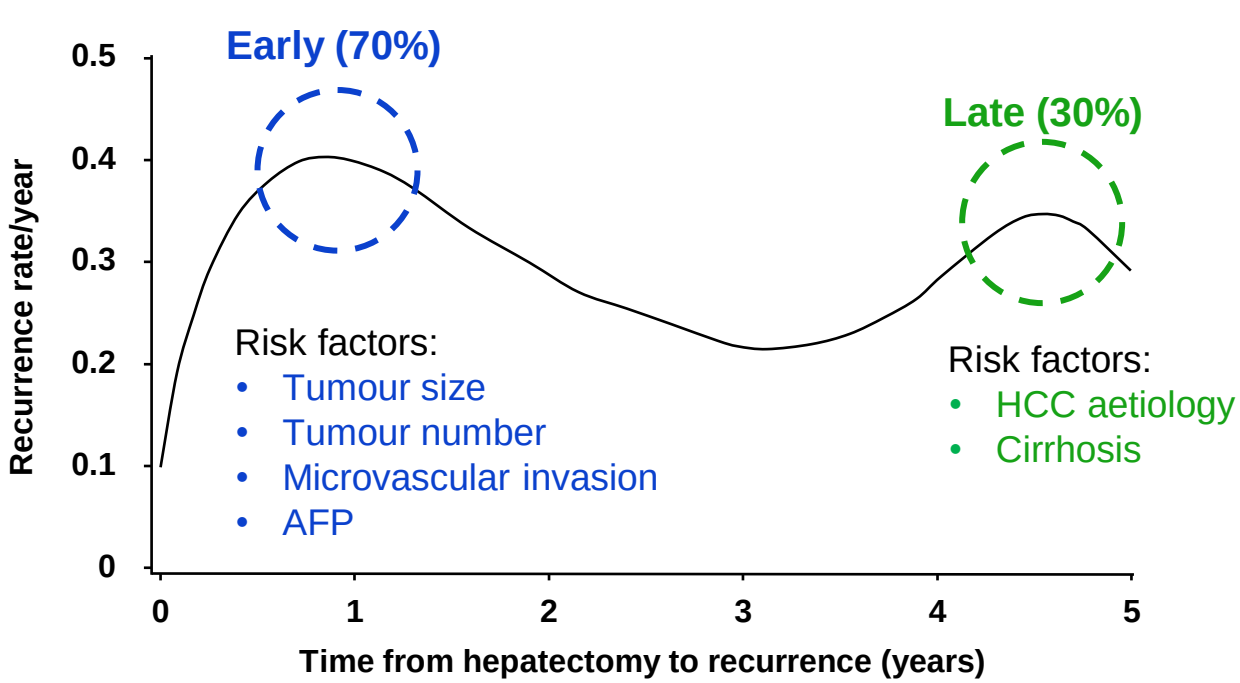
Fictional case study for the purposes of this presentation

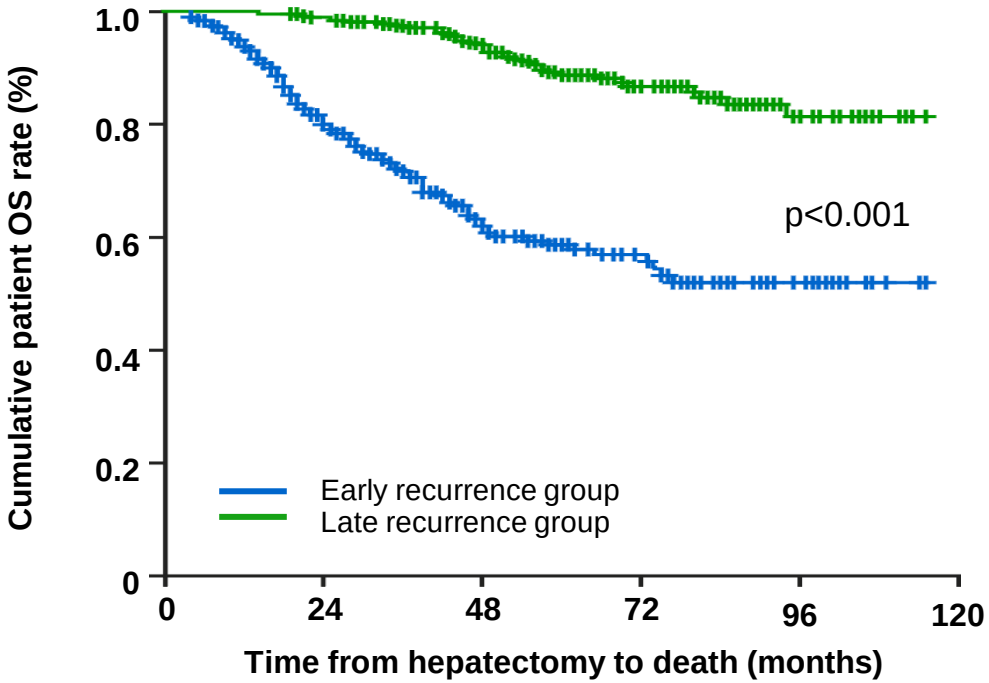
There are still unmet needs across the HCC treatment spectrum

	BCLC stage				
	0	A	B	C	D
Description	Very early	Early	Intermediate	Advanced	End-stage
ECOG PS	0	0	0	1/2	3/4
Child-Pugh class	A	A/B	A/B	A/B	C
Tumour stage	Single nodule ≤2 cm	Single tumour or ≤3 nodules each ≤3 cm	Large multinodular	Vascular invasion or EHS	Any
Unmet need	**Developing adjuvant therapy to prevent recurrence**		**Systemic therapies, alone or combined with LRT, to enhance efficacy**	**How to sequence systemic treatment beyond the 1L setting in order to prolong survival**	

EHS, extrahepatic spread; LRT, locoregional therapy

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



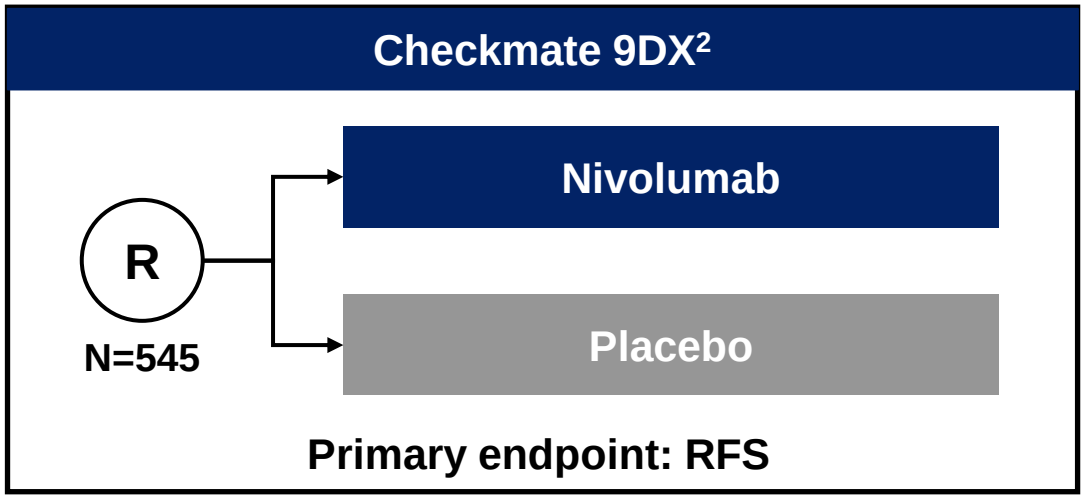


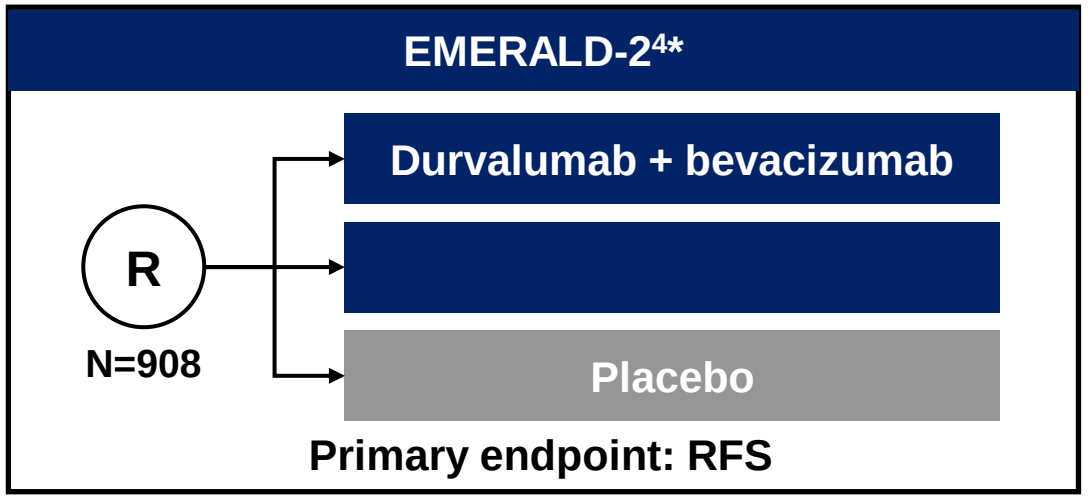
Adjuvant treatment may overcome the risk of early HCC recurrence and improve patient prognosis; however, there are currently no approved agents in this setting for HCC – this represents an urgent unmet need[3]

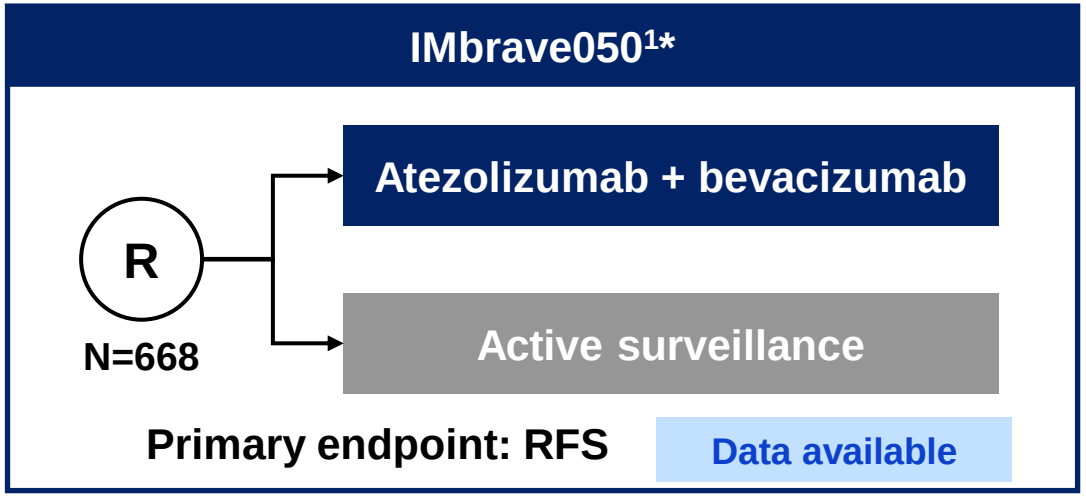
AFP, alpha fetoprotein

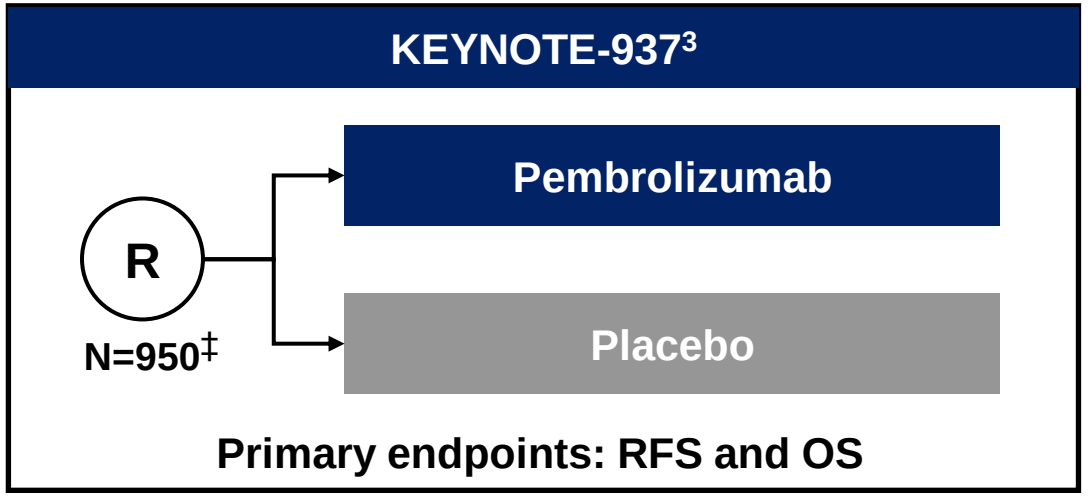
1. Imamura et al. I J of Hepatology 2003; Copyright (2023), with permission from Elsevier
2. Jung et al. J Gastrointest Surg 2019; Copyright (2023), with permission from Springer; 3. Hack et al. Future Oncol 2020

Phase III research is ongoing for adjuvant HCC global trials





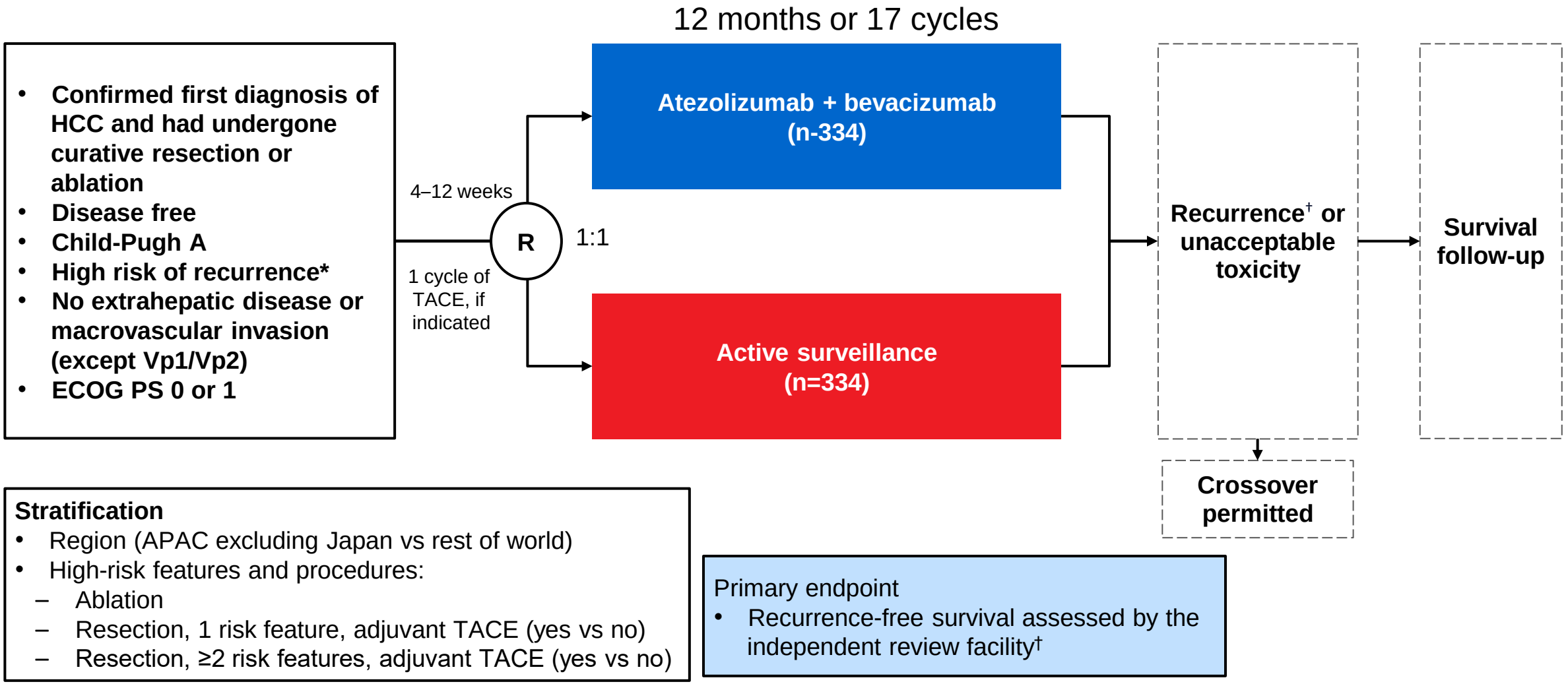




Information based on clinicaltrials.gov (accessed March 2023)
*Optional round of TACE after curative intervention allowed; ‡Estimated enrollment

1. NCT04102098; 2. NCT03383458
3. NCT03867084 4. NCT03847428

IMbrave050 (phase III): study design

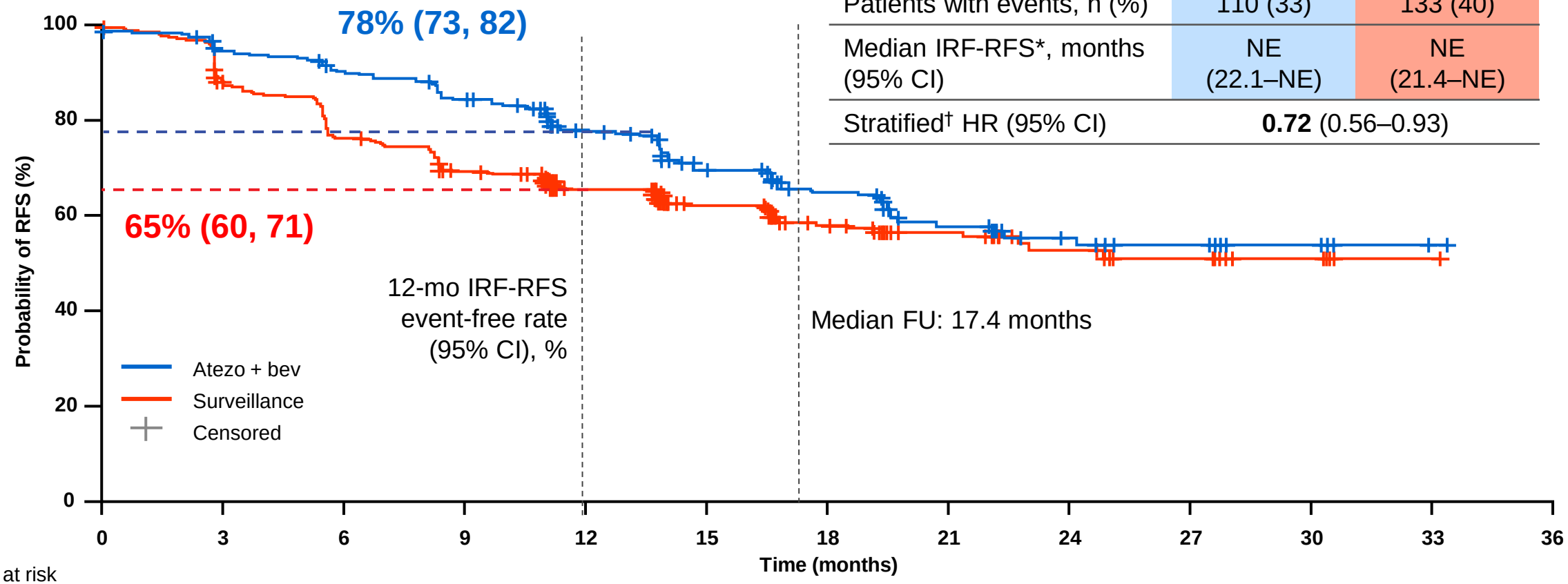


*High-risk features include: tumour >5 cm, >3 tumours, microvascular invasion, minor macrovascular invasion Vp1/Vp2, or Grade 3/4 pathology
†Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1

Chow et al. EASL LCS 2023 (also presented at AACR 2023)

IMbrave050 (phase III): RFS

	Atezo + bev (n=334)	Active surveillance (n=334)
Patients with events, n (%)	110 (33)	133 (40)
Median IRF-RFS*, months (95% CI)	NE (22.1–NE)	NE (21.4–NE)
Stratified† HR (95% CI)	**0.72** (0.56–0.93)	



Patients at risk													
Surveillance	334	283	245	214	179	131	93	57	36	20	6	1	NE
Atezo + bev	334	305	290	268	211	139	97	63	37	22	9	1	NE

*RFS after randomisation, defined as the time from randomisation to the first documented occurrence of intrahepatic HCC (according to EASL criteria) or extrahepatic HCC (according to RECIST 1.1) as determined by an IRF, or death from any cause (whichever occurs first)
†Stratification factors: region; high-risk features and procedures. CCOD: 21 October 2022. median follow-up time: 17.4 months; CI, confidence interval; HR, hazard ratio; INV, investigator; IRF, independent review facility; NE, not estimable; RFS, recurrence-free survival

Chow et al. EASL LCS 2023 (also presented at AACR 2023)

IMbrave050 (phase III): safety summary

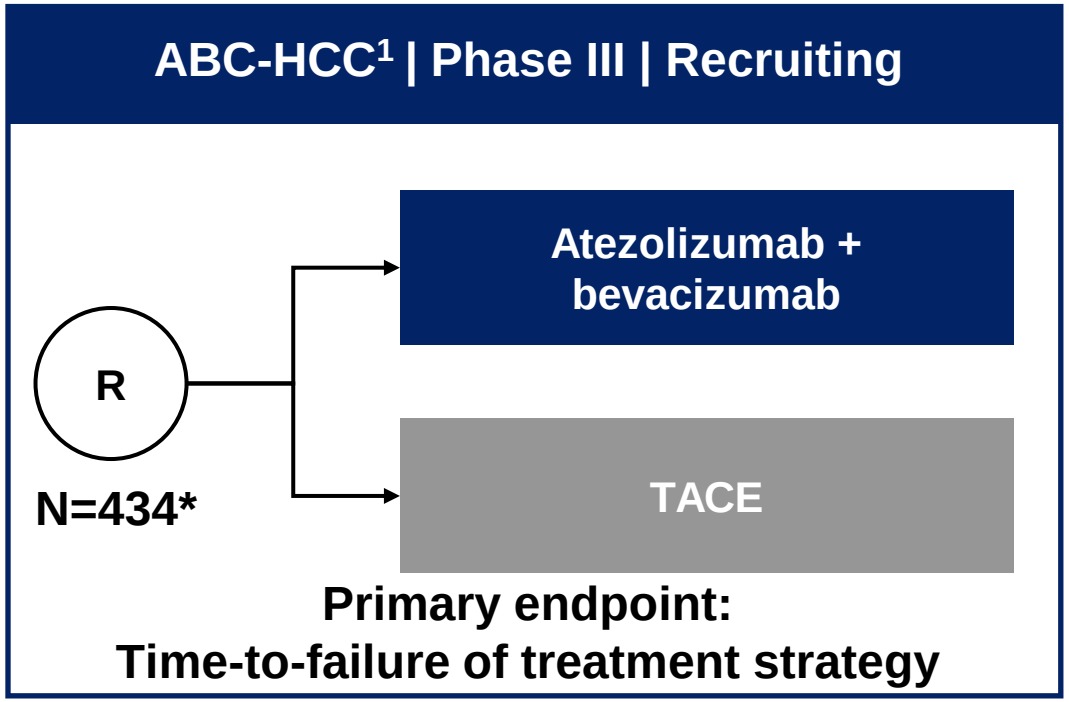
	Atezo + bev (n=332)	Active surveillance (n=330)	IMbrave150[2,3] (n=329)
Treatment duration, median, months	Atezo: 11.1 Bev: 11.0	NA	Atezo: 7.4 Bev: 6.9
Patients with ≥1 AE, n (%)	326 (98.2)	205 (62.1)	323 (98.2)
Treatment-related AE	293 (88.3)	NA	276 (83.9)
Grade 3/4 AE, n (%)	136 (41.0)	44 (13.3)	186 (56.5)
Treatment-related Grade 3/4 AE	116 (34.9)	NA	117 (35.6)
Serious AE, n (%)	80 (24.1)	34 (10.3)	125 (38.0)
Treatment-related serious AE	44 (13.3)	NA	56 (17.0)
Grade 5 AE, n (%)	6 (1.8)	1 (0.3)	15 (4.6)
Treatment-related Grade 5 AE	2 (0.6)*	NA	6 (1.8)
AE leading to dose interruption of any study treatment, n (%)	155 (46.7)	NA	163 (49.5)
AE leading to withdrawal from any study treatment, n (%)	63 (19.0)	NA	51 (15.5)

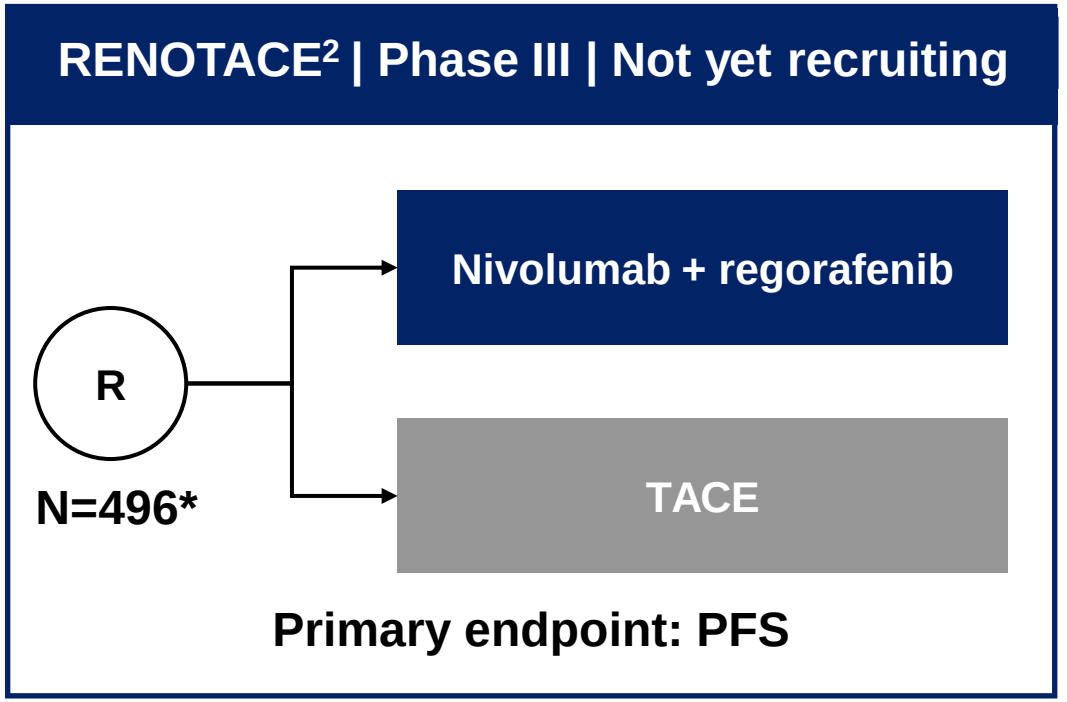
Clinical cutoff: 21 October 2022; median follow-up duration: 17.4 months. In safety-evaluable patients. AE, adverse event. NA, not available;
*Oesophageal varices haemorrhage and ischemic stroke; 1 was related to atezo and bev and the other was related to bev only

1. Chow et al. EASL LCS 2023 (also presented at AACR 2023)
2. Finn et al. N Engl J Med 2020; 3. Data on file

Key ongoing trials in intermediate-stage HCC

Systemic therapy vs TACE





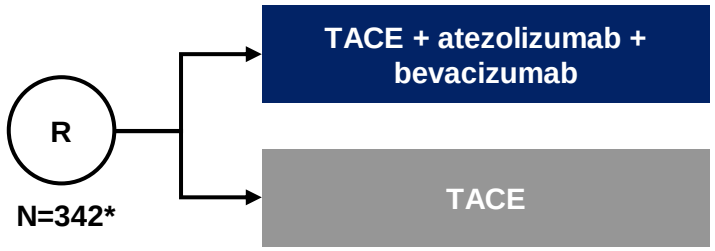
Information based on clinicaltrials.gov (accessed March 2023)
*Estimated enrollment

1. NCT04803994; 2. NCT04777851

Key ongoing trials in intermediate-stage HCC

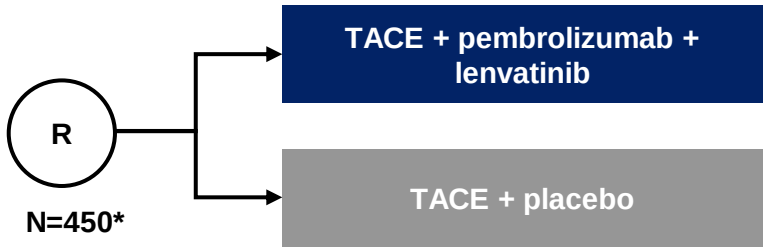
TACE + systemic therapy vs TACE

TALENTACE[1] | Phase III | Recruiting



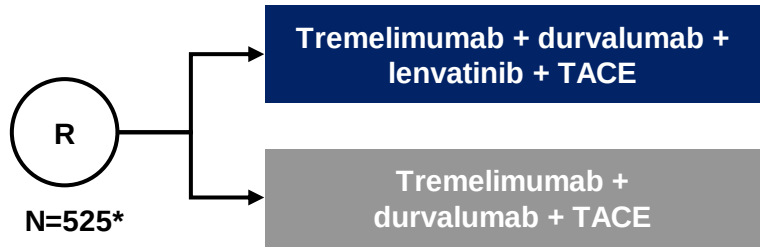
Primary endpoints: TACE PFS and OS

LEAP-012[2]| Phase III | Active, not recruiting



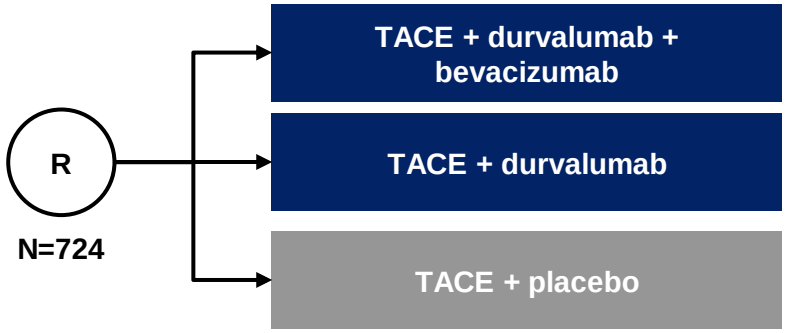
Primary endpoints: PFS and OS

EMERALD-3[3]| Phase III | Recruiting



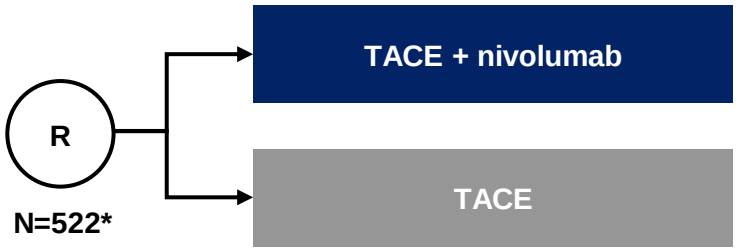
Primary endpoint: PFS

EMERALD-1[4] | Phase III | Active, not recruiting



Primary endpoint: PFS

TACE-3[5] | Phase II/III | Recruiting



Primary endpoints: OS and time to TACE progression

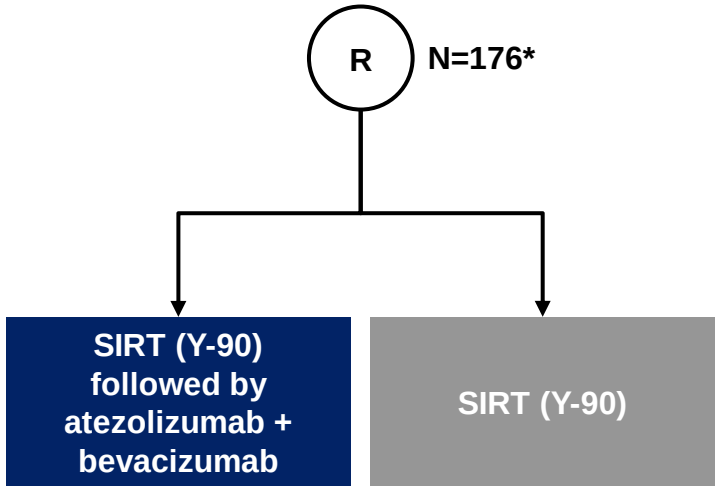
Information based on clinicaltrials.gov (accessed March 2023)
*Estimated enrollment

1. NCT04712643; 2. NCT04246177; 3. NCT05301842
4. NCT03778957; 5. NCT04268888

Key ongoing trials in intermediate-stage HCC

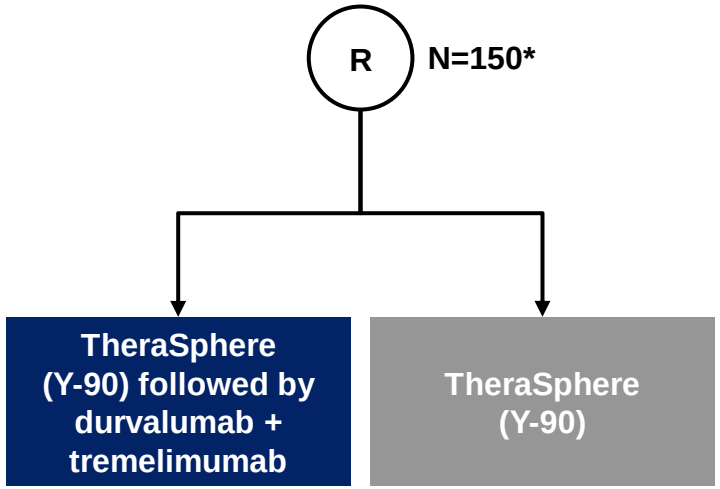
Y90 + immunotherapy

STRATUM[1] | Phase II | Recruiting



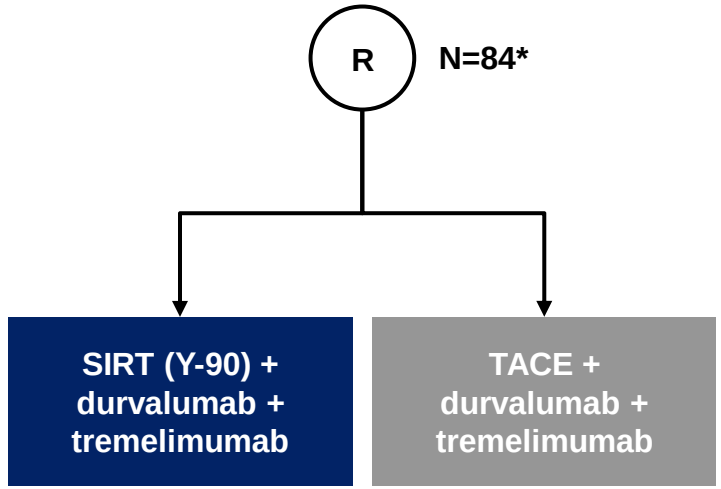
Primary endpoint: BORR

ROWAN[2] | Phase II | Paused†



Primary endpoint: ORR and DoR

NCT04522544[3] | Phase II | Recruiting



Primary endpoint: ORR

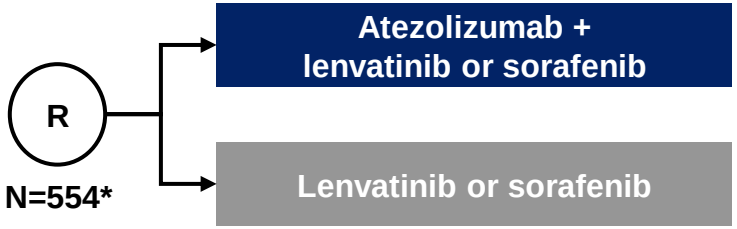
Information based on clinicaltrials.gov (accessed March 2023)
*Estimated enrollment

1. NCT05377034; 2. NCT05063565; 3. NCT04522544

Current ongoing studies addressing treatment sequencing in HCC

IMbrave251[1]

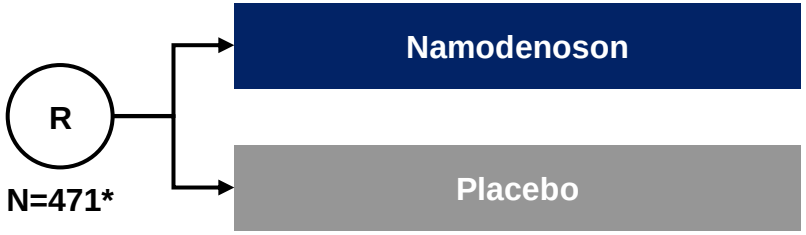
Progressive disease following prior atezolizumab + bevacizumab treatment (≥ 4 cycles)



Primary endpoint: OS

LIVERATION[2]

HCC has progressed on at least 1, but no more than 2, prior systemic treatment regimens



Primary endpoint: OS

POLARIS2021-001[3]

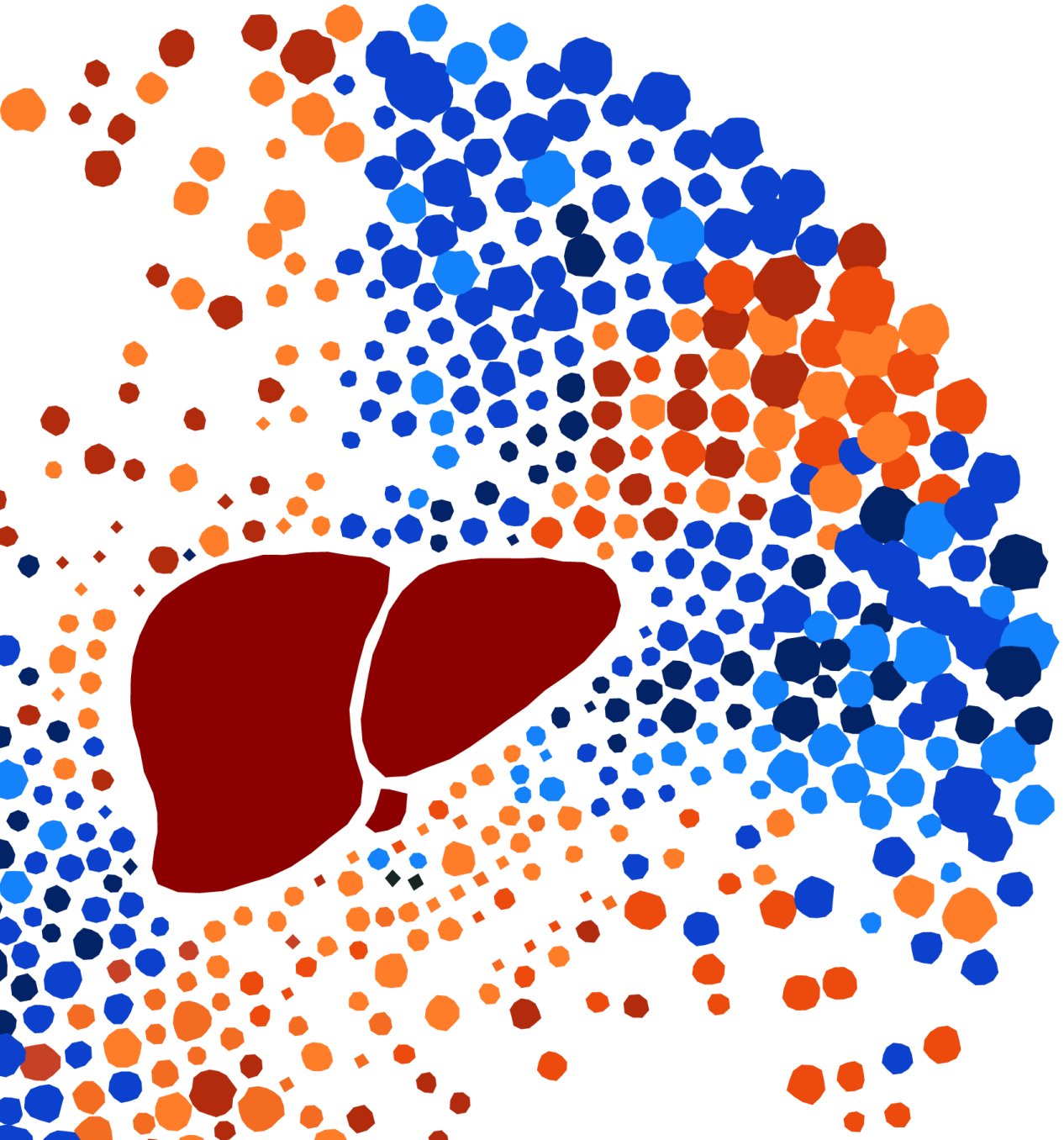
Prior treatment with at least 1 systemic agent for Child-Pugh A

Child-Pugh B7 without prior systemic treatment may be enrolled, if they are not eligible for any approved systemic therapies

Primary endpoint: OS

Information based on clinicaltrials.gov (accessed March 2023)
*Estimated enrollment

1. NCT04770896; 2. NCT05201404; 3. NCT05317819



Q&A and panel discussion: insights into the patient journey

All faculty

Moderated by Lorenza Rimassa

Insights into the patient journey: a case study

Screening | Early-stage HCC | Intermediate-stage HCC | Advanced-stage HCC

Surveillance

- 62-year-old male patient with pre-existing autoimmune disorder (hypothyroidism) who undergoes regular blood tests to assess liver function
- Asymptomatic for HCC but has characteristics considered high-risk for HCC

Patient monitored regularly every 6 months

Patient characteristics:

- Liver cirrhosis
- NAFLD
- BMI 32
- Arterial hypertension
- HBV–/HCV–
- FIB4 score >3.5
- Liver enzymes slightly elevated

Fictional case study for the purposes of this presentation

What barriers to screening and surveillance do you see in your clinic?

1. Cost
2. Scheduling difficulties
3. Technology unavailable
4. No MTD collaboration
5. Lack of awareness
6. Other

Insights into the patient journey: a case study

Screening | **Early-stage HCC** | Intermediate-stage HCC | Advanced-stage HCC

Diagnosis

- 62-year-old male patient with pre-existing autoimmune disorder (hypothyroidism) who undergoes regular blood tests to assess liver function
- Asymptomatic for HCC but has characteristics considered high-risk for HCC
- Diagnostic work-up performed including imaging, blood tests and biopsy
- Surveillance with ultrasound not conclusive; GAAD score shows value of 4.05; referred to MR which shows 5.1 cm LI-RADS 5 lesion in left liver lobe

Confirmed early-stage HCC

- Child-Pugh class A
- BCLC stage A
- ECOG PS 0
- AFP 15.2 ng/ml
- PIVKA II 23 ng/ml

Patient characteristics:

- Compensated liver cirrhosis
- NASH
- BMI 32
- Arterial hypertension
- HBV–/HCV–
- Single tumour 5.1 cm

Fictional case study for the purposes of this presentation

What would be your treatment of choice for this patient?

1. Resection
2. Ablation (RFA/MWA)
3. TACE
4. TARE
5. Transplant

Insights into the patient journey: a case study

Screening | Early-stage HCC | **Intermediate-stage HCC** | Advanced-stage HCC

Loco-regional and systemic treatment options

- 62-year-old male patient with pre-existing autoimmune disorder who undergoes regular blood tests to assess liver function

Confirmed intermediate-stage HCC

- Child-Pugh A
- BCLC stage B
- ECOG PS 1
- AF 15.2 ng/ml

Patient characteristics:

- Compensated liver cirrhosis
- NASH
- BMI 32
- Arterial hypertension
- HBV–/HBC–
- Bilobar disease
- Two tumours, both ≥5 cm
- Preserved portal vein flow

Fictional case study for the purposes of this presentation

What do you consider when initiating systemic therapy over TACE?

1. **Tumour burden exceeds "up to seven" criteria**
2. **Bilobar tumour**
3. **Response to TACE**
4. **High number of nodules**
5. **Other**

Insights into the patient journey: a case study

Screening → Early-stage HCC → Intermediate-stage HCC → **Advanced-stage HCC**

1L treatment

- 62-year-old male patient with pre-existing autoimmune disorder (hypothyroidism) who undergoes regular blood tests to assess liver function
- Relapsed and progressed to advanced-stage HCC after previous locoregional treatment

Confirmed advanced-stage HCC

- **Child-Pugh A**
- **BCLC stage C**
- **ECOG PS 1**
- **AFP 356 ng/ml**

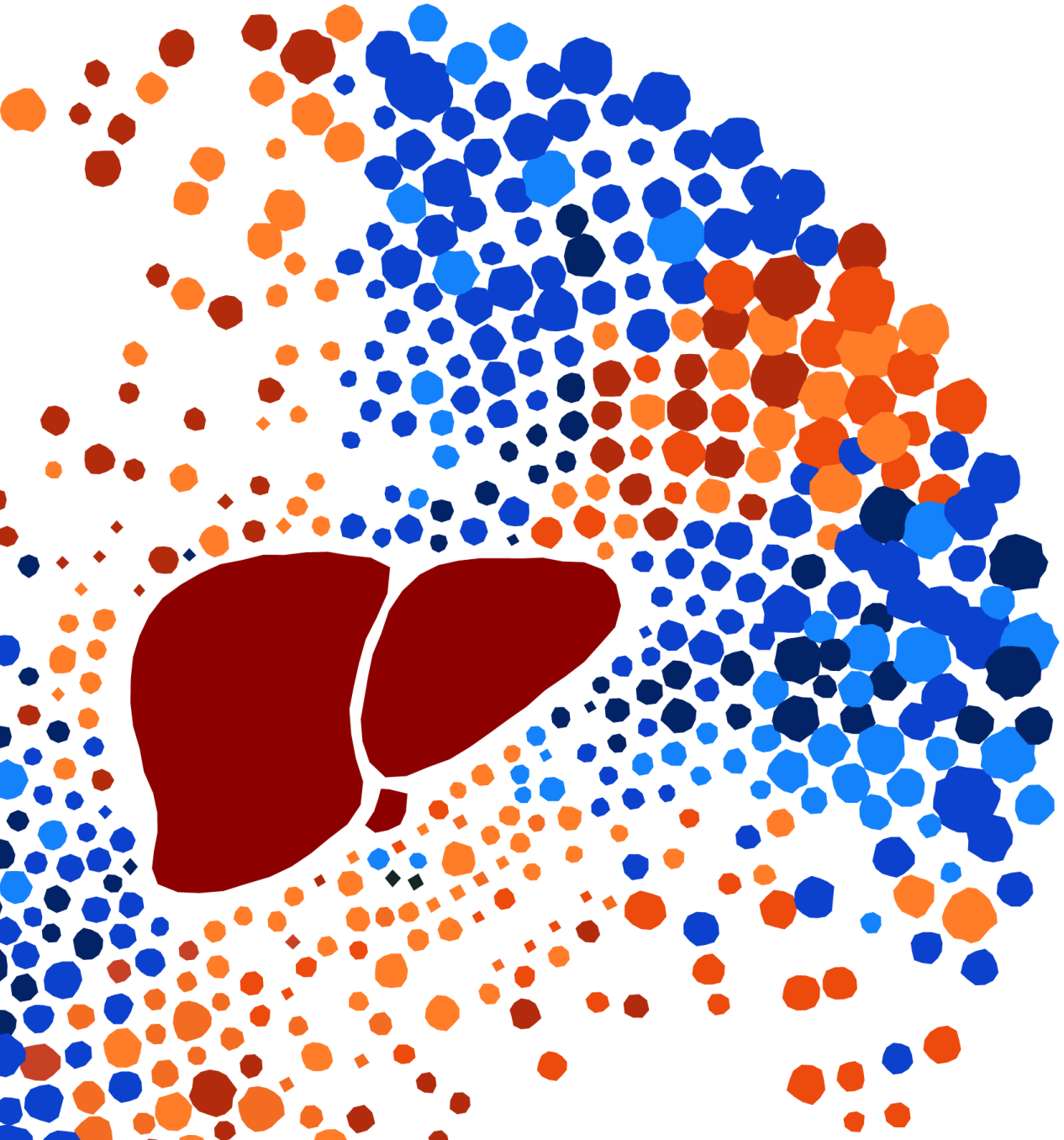
Patient characteristics:

- Compensated liver cirrhosis
- NASH
- BMI 32
- Arterial hypertension
- HBV–/HCV–
- Two tumours, both ≥ 5cm
- Spread to multiple lymph nodes
- Main portal invasion
- EHS

Fictional case study for the purposes of this presentation

What is the most important feature in the patient characteristics that you base your treatment decision on?

1. **Age**
2. **MVI**
3. **PD-L1 status**
4. **Cardiovascular comorbidities**
5. **Tumour load**



Summary and close

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