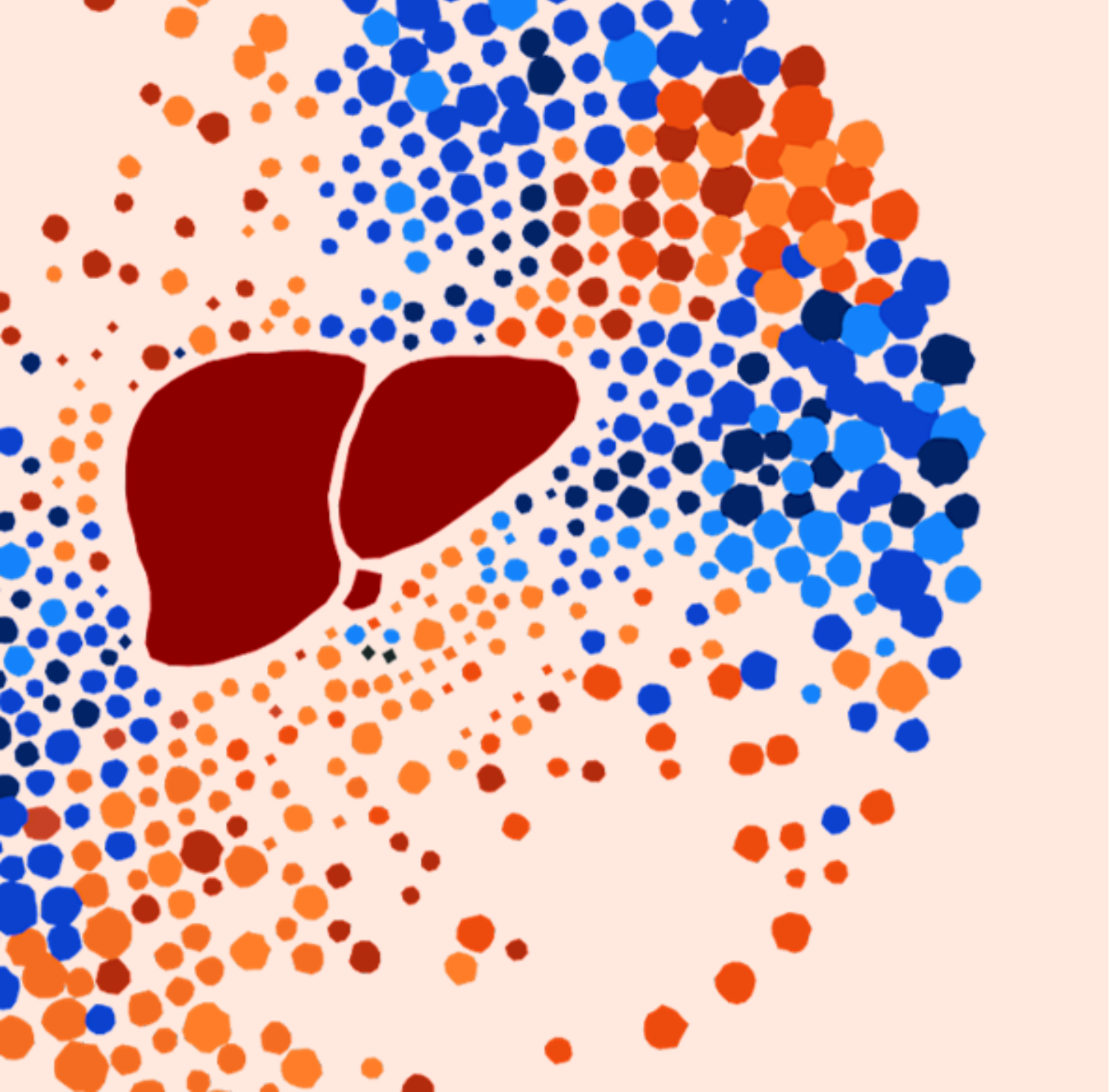

HCC illuminated: Exploring future frontiers with systemic immunotherapies

ESMO Asia Industry Satellite Symposium 2023

16:00 – 17:00 SGT
Friday, 1st December 2023

This is a non-promotional meeting intended for HCPs only.
It may include scientific information about investigational compounds that are not approved or valid in your jurisdiction.
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Disclosures

Han Chong Toh

- **Consulting fees:** AstraZeneca, Roche
- **Travel support :** Roche
- **Speakers bureau :** Roche, Eisai, AstraZeneca, MSD, Merck

Ann-Lii Cheng

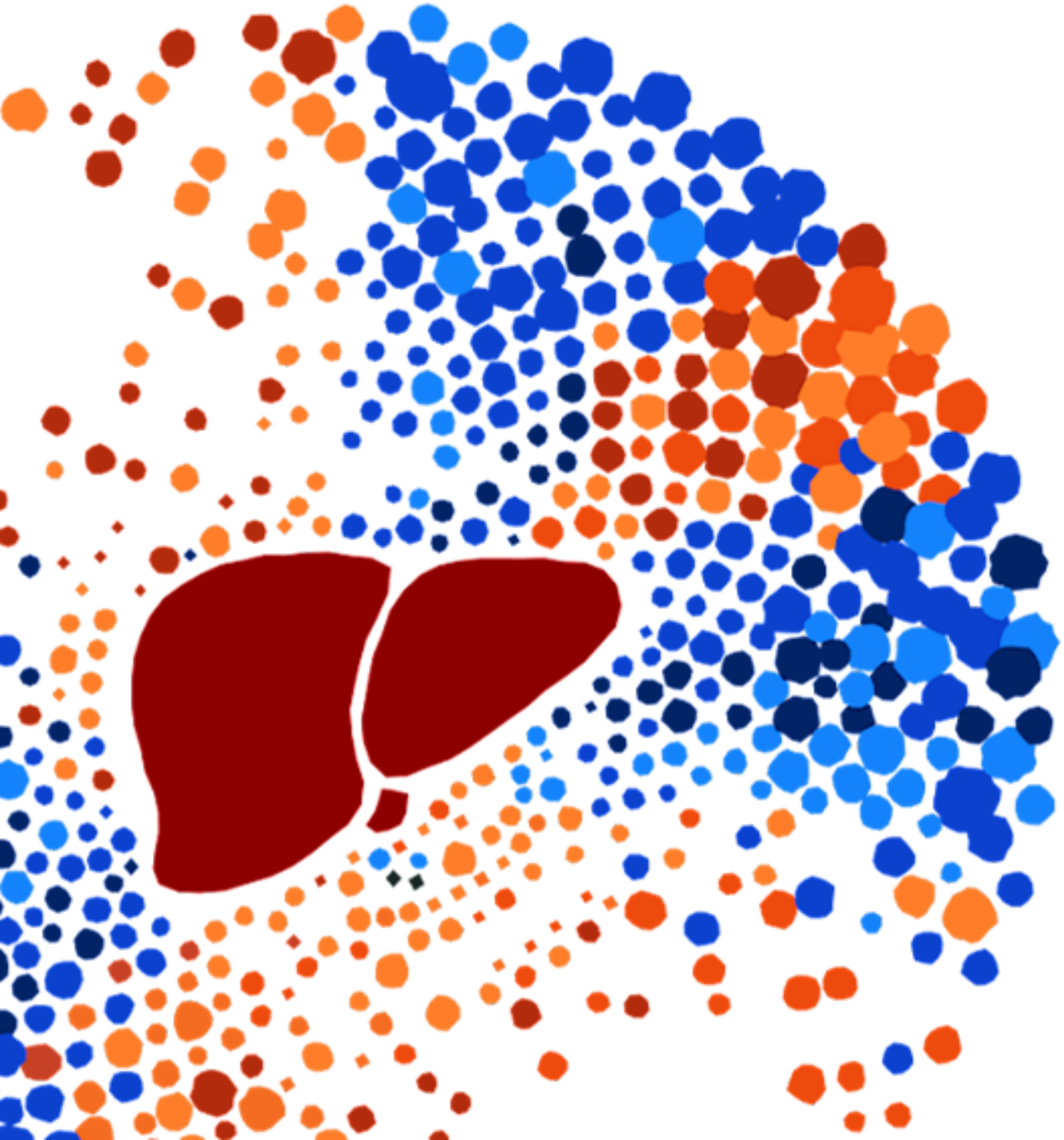
- **Consulting fees:** AstraZeneca, Bristol-Myers Squibb, Eisai, Ono Pharmaceutical, IPSEN Innovation, Bayer Healthcare, Merck Sharp Dohme, Roche/Genentech, BeiGene, EXELIXIS Ltd., F. Hoffmann–La Roche, Omega Therapeutics, Inc., AbbVie Inc., and IQVIA
- **Travel support:** Bayer Yakuhin, Ltd., Eisai, Roche/Genentech, Chugai Pharmaceutical, and IQVIA
- **Speakers bureau:** Bayer Yakuhin, Ltd., Novartis, Eisai, Ono Pharmaceutical and Amgen Taiwan

Hui-Chuan Sun

- **Speaker Fees:** AstraZeneca, Bayer, BeiGene, Eisai, Hengrui, Innovent, MSD, Roche, TopAlliance, and Zelgen
- **Research Funding:** Eisai, Innovent, Roche, MSD

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, Abbott, Omega Therapeutics, Synergy Research, Worrell
- **Research funding**: Sirtex Medical, IPSEN, IQVIA, New B Innovation, AMiLi, Perspectum, 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 opening remarks

Han Chong Toh

Expert Faculty

Han Chong Toh (Chair)

Deputy CEO (Strategic Partnerships), National Cancer Center Singapore, and Professor, Duke-NUS Medical School, Singapore

Ann-Lii Cheng

Chair Professor, National Taiwan University and President Emeritus, National Taiwan University Cancer Center, Taipei, Taiwan

Hui-Chuan Sun

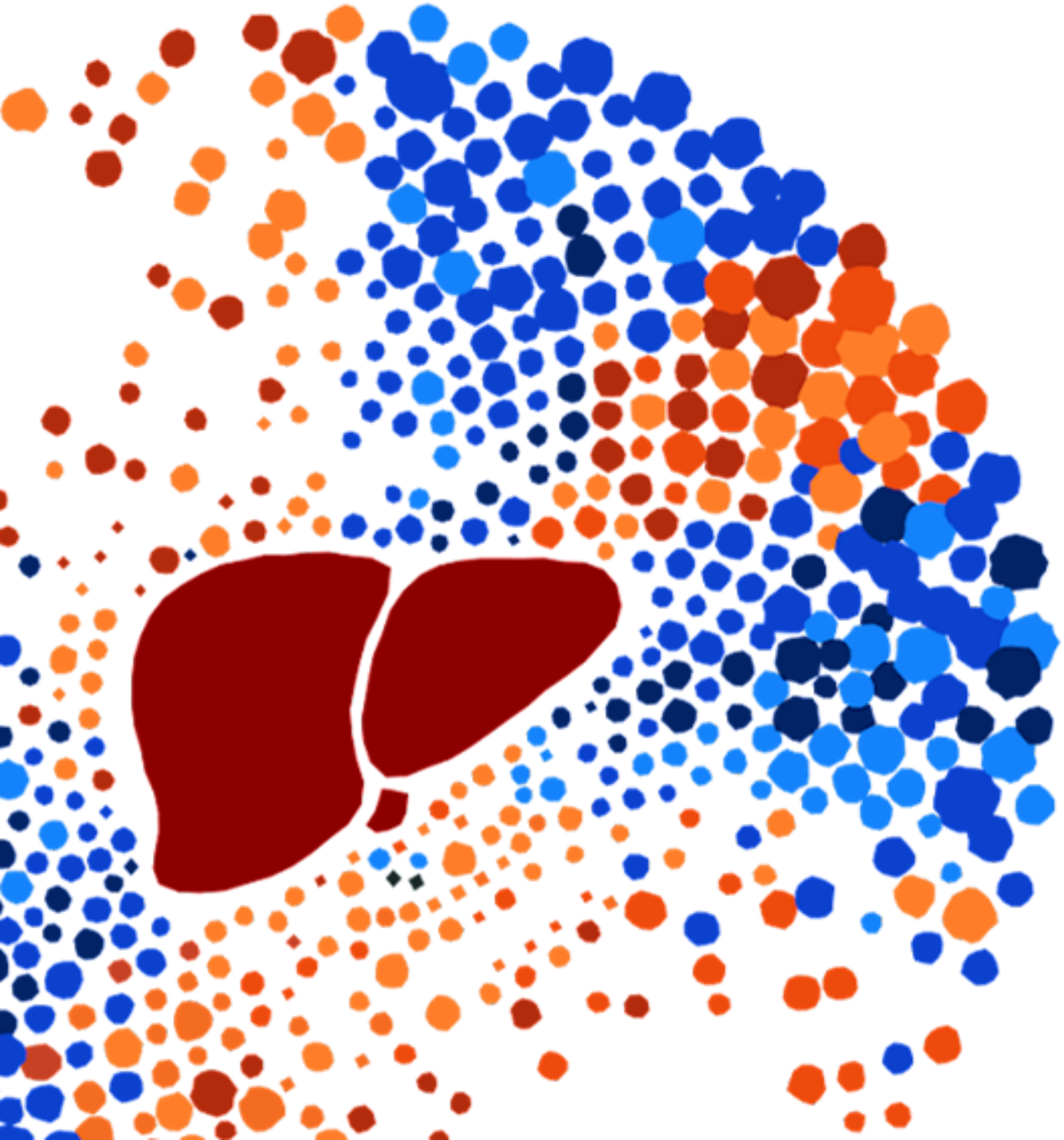
Deputy Medical Director, Liver Cancer Research Institute, Fudan University and Department of Liver Surgery, Zhongshan Hospital, Shanghai, China

Pierce Chow

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

Agenda

Time	Topic	Speaker
16:00 – 16:05	**Welcome and opening remarks**	Han Chong Toh
16:05 – 16:25	**Plenary presentation: Expanding role of systemic immunotherapy in the management of HCC**	Ann-Lii Cheng
16:25 – 16:40	**Case discussion: Systemic therapy, locoregional therapy or both?**	Hui-Chuan Sun
16:40 – 16:55	**Case discussion: Adjuvant therapy in HCC, who and how?**	Pierce Chow
16:55 – 17:00	**Audience Q&A and closing remarks**	Han Chong Toh



Plenary presentation: Expanding role of systemic immunotherapy in the management of HCC

Ann-Lii Cheng

Expanding Role of Systemic Immunotherapy in the Management of HCC

Roche Symposium, Dec. 1, 2023, Singapore

Ann-Lii Cheng, M.D., Ph.D.

National Taiwan University Cancer Center, Taipei, Taiwan.

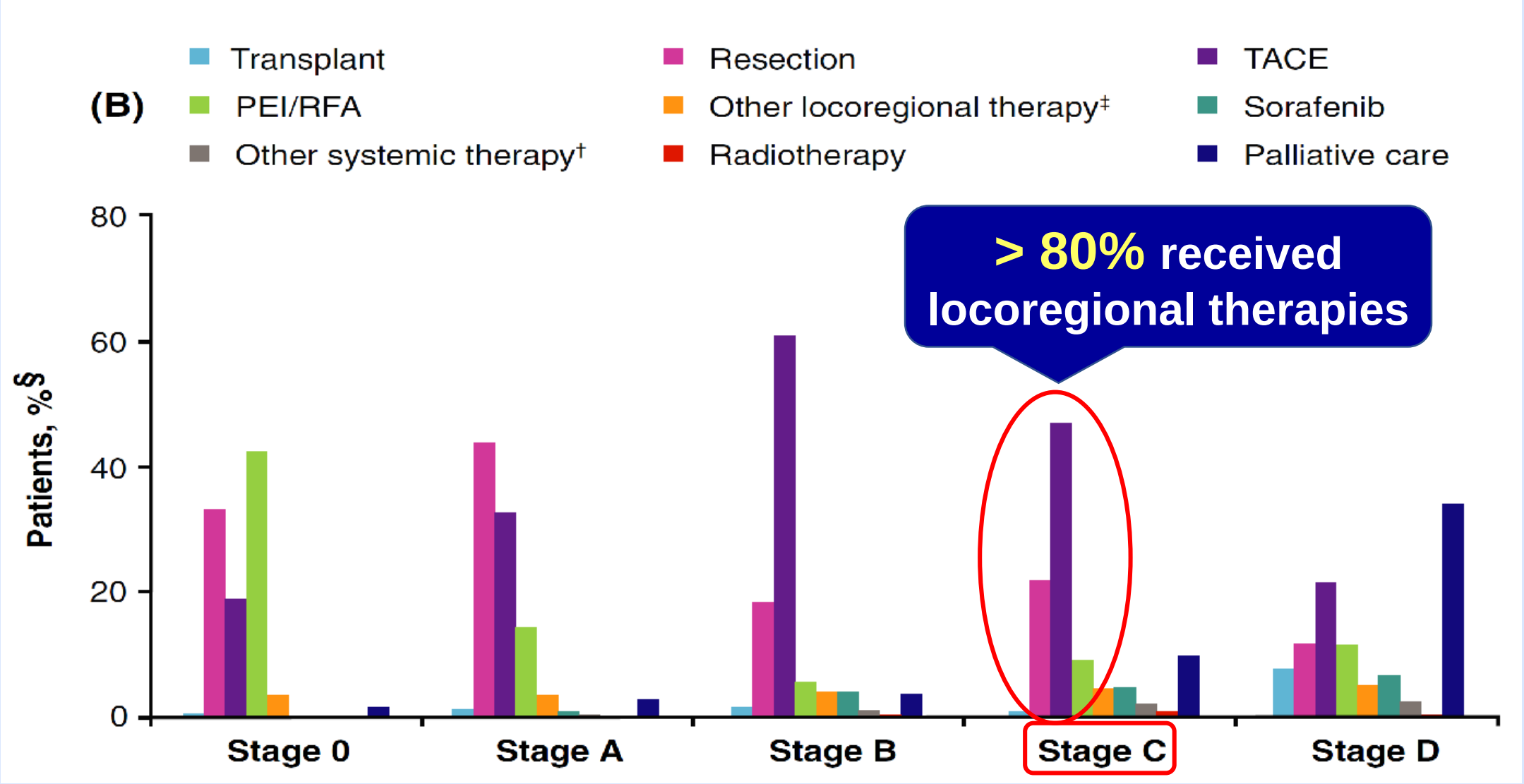
Atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150

Ann-Lii Cheng,[1] Shukui Qin,[2] Masafumi Ikeda,[3] Peter R. Galle,[4] Michel Ducreux,[5] Andrew X. Zhu,[6] Tae-You Kim,[7] Masatoshi Kudo,[8] Valeriy Breder,[9] Philippe Merle,[10] Ahmed Kaseb,[11] Daneng Li,[12] Wendy Verret,[13] Derek-Zhen Xu,[14] Sairy Hernandez,[13] Juan Liu,[14] Chen Huang,[14] Sohail Mulla,[15] Ho Yeong Lim,[16] Richard S. Finn[17]

[1]National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan; [2]People's Liberation Army Cancer Center, Jinling Hospital, Nanjing, People's Republic of China; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]University Medical Center Mainz, Mainz, Germany; [5]Gustave Roussy Cancer Center, Villejuif, France; [6]Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [7]Seoul National University College of Medicine, Seoul, Korea; [8]Kindai University Faculty of Medicine, Osaka, Japan; [9]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Hospital La Croix-Rousse, Lyon, France;
[11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [13]Genentech, Inc., South San Francisco, CA, USA; [14]Roche Product Development, Shanghai, People's Republic of China; [15]Hoffmann-La Roche Limited, Mississauga, ON, Canada; [16]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [17]Jonsson Comprehensive Cancer Center, Geffen School of Medicine at UCLA, Los Angeles, CA, USA

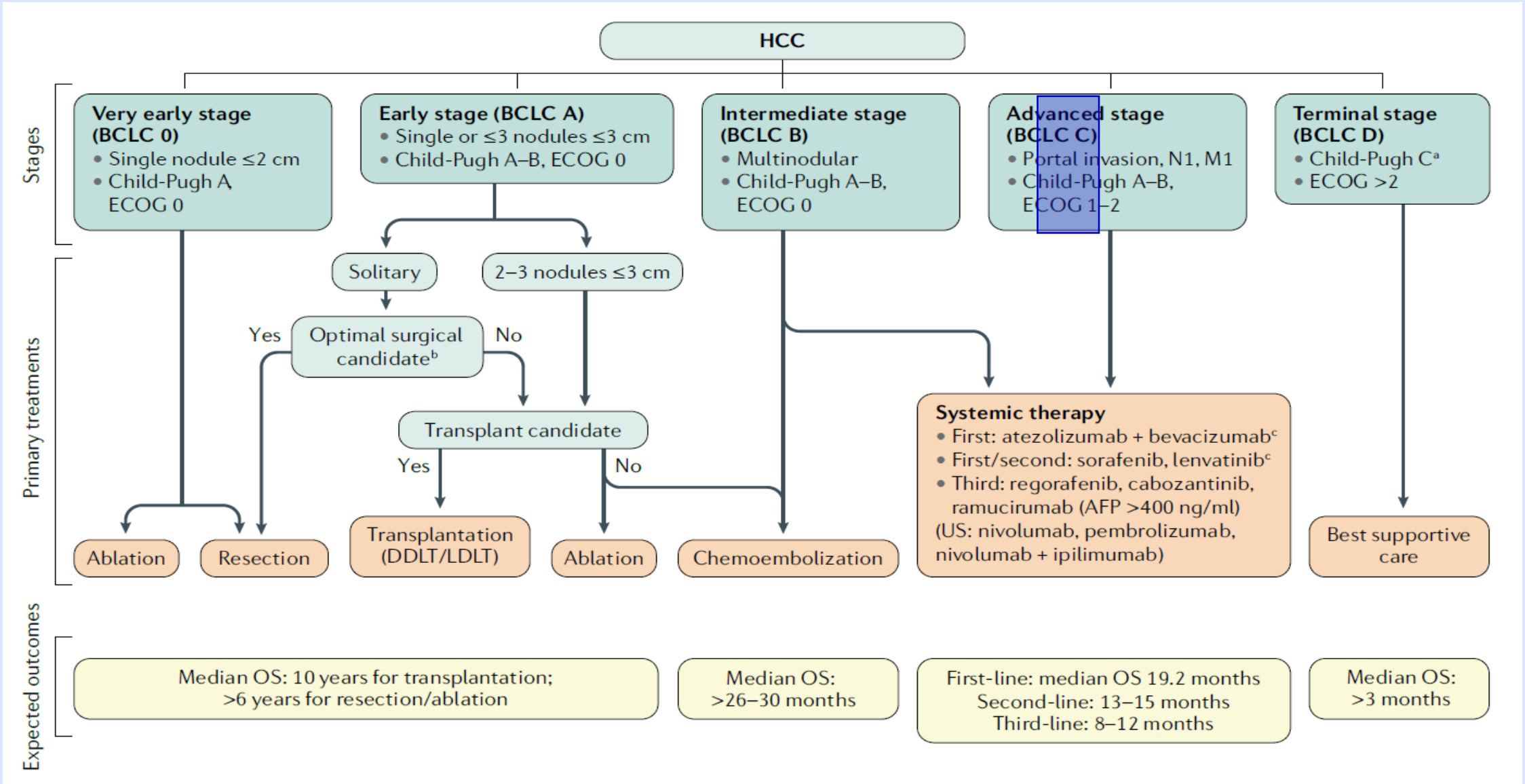
Real World Practice : 18031 patients from around the world

First HCC treatment -- BRIDGE Study



Park JW, et al. Liver Int. 2015; 35(9): 2155–2216.

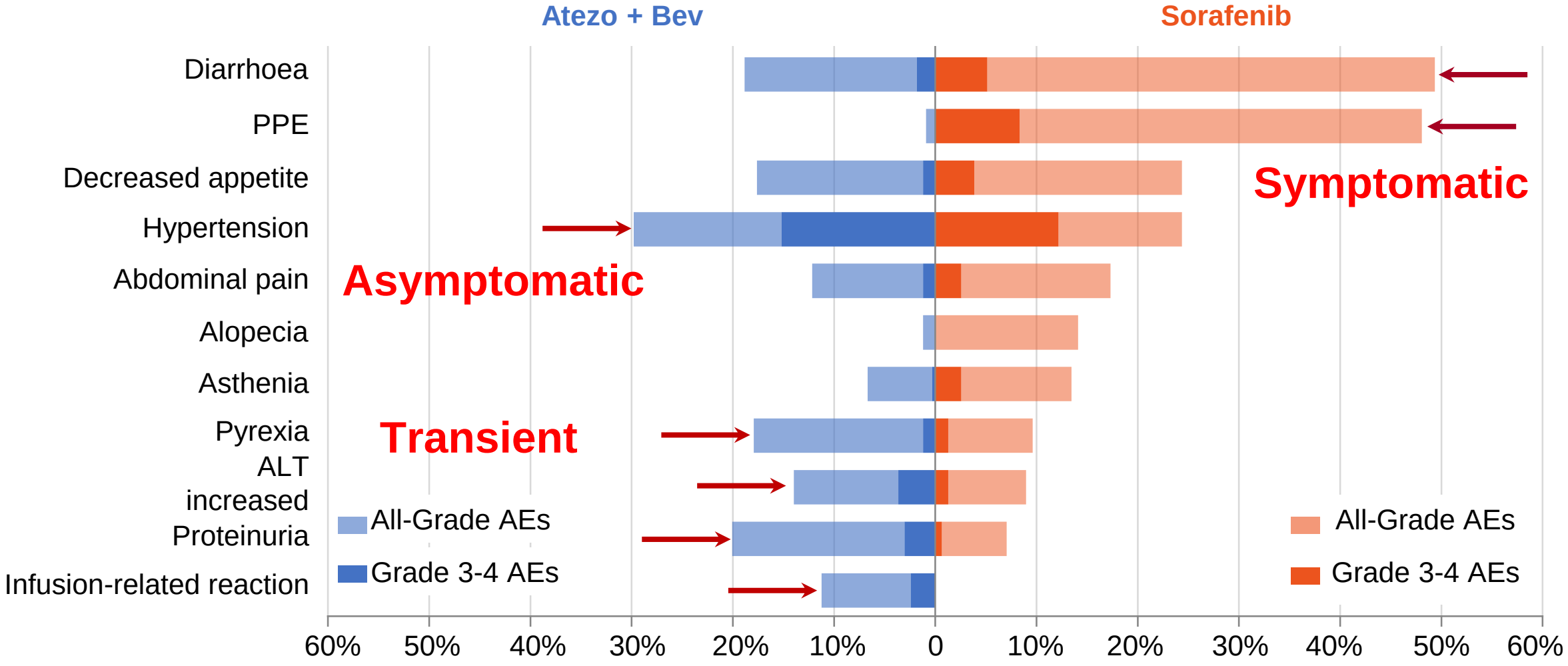
Evolving Treatment Strategy for Locally-advanced HCC



Llovet JM et al. Nat Rev Dis Primers. 2021;7(1):6.

Safety[a]

≥ 10% frequency of AEs in either arm and > 5% difference between arms

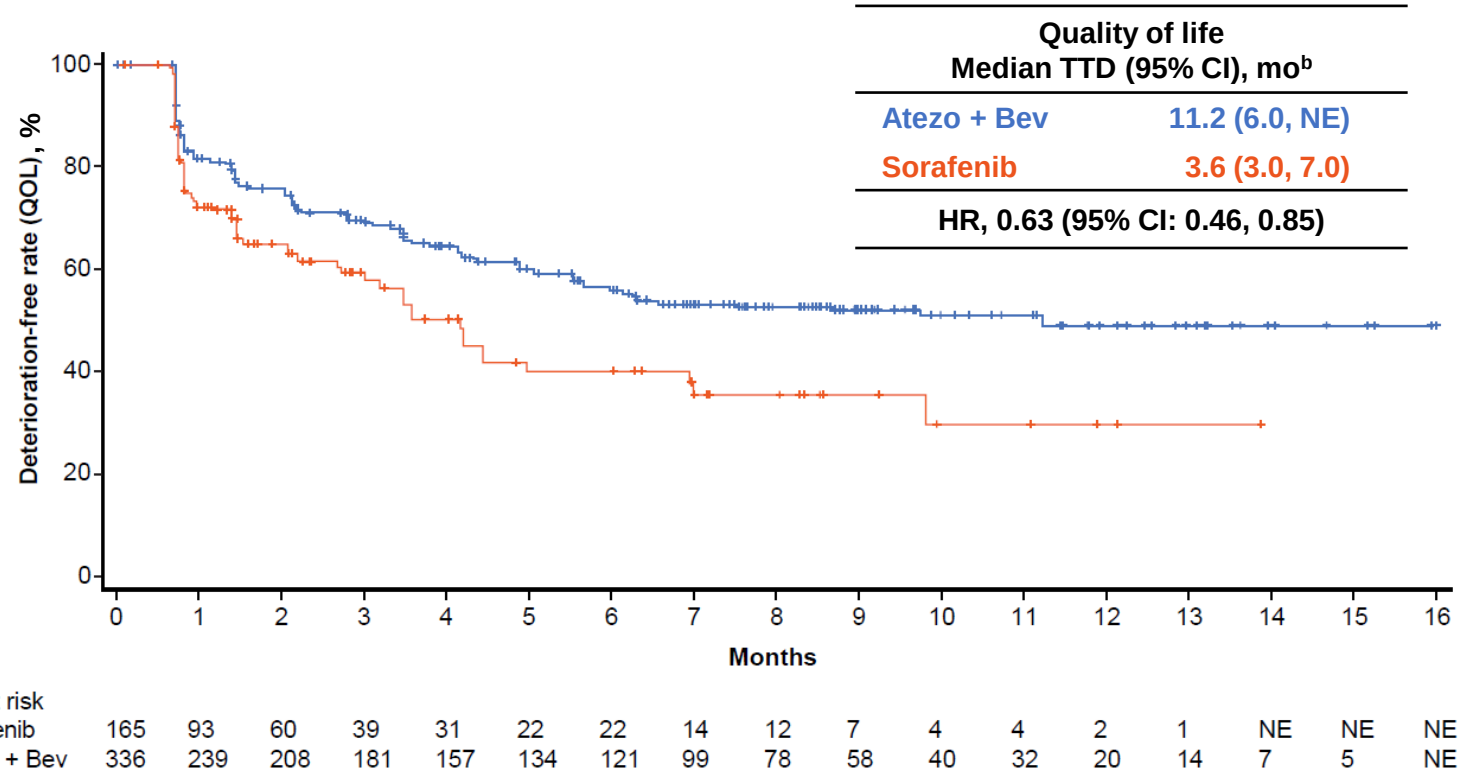


AE, adverse event, ALT, alanine aminotransferase; PPE, palmar-plantar erythrodysaesthesia.

[a] Safety-evaluable population.

Patient-reported outcomes[a]

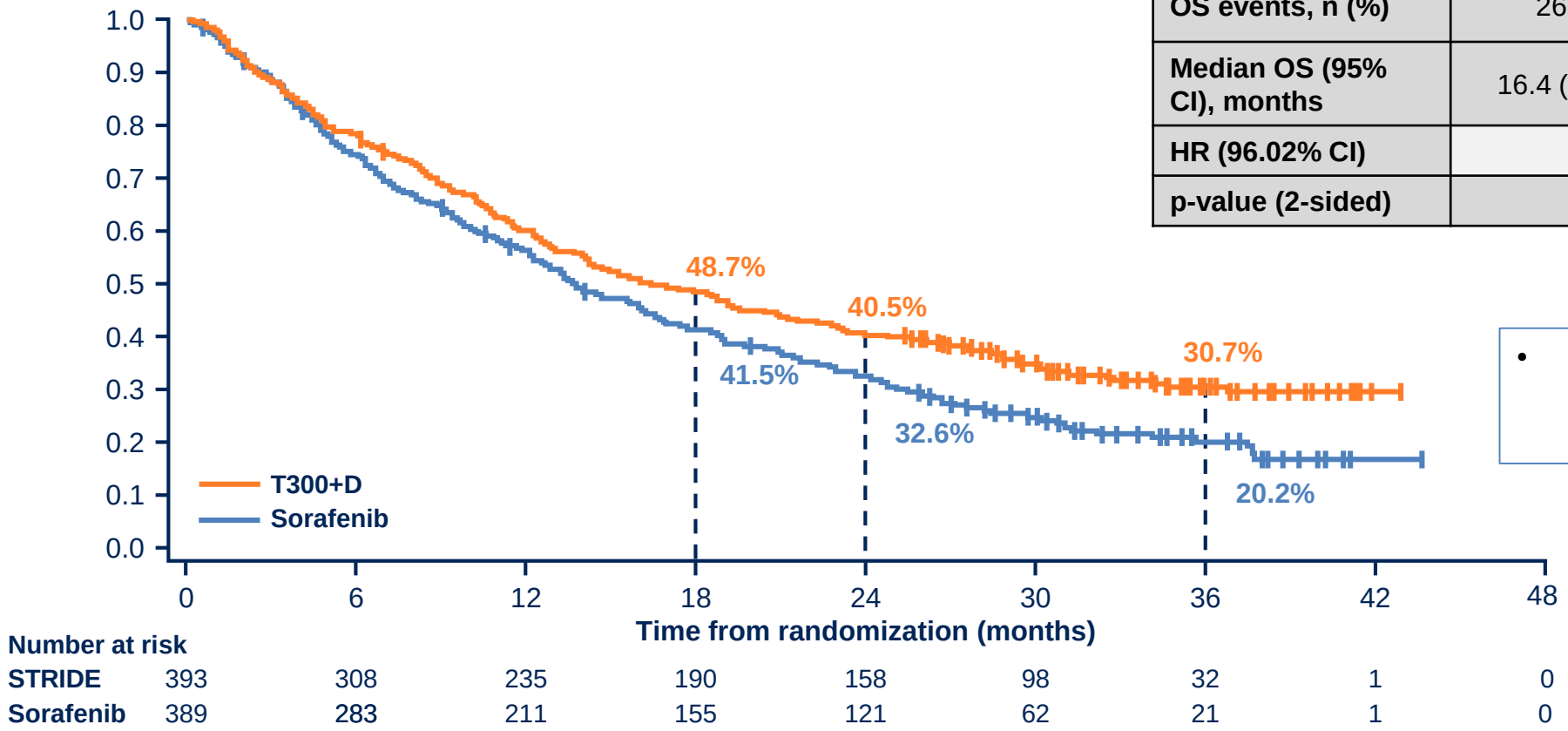
- Atezolizumab + bevacizumab delayed the time to deterioration of patient-reported quality of life compared with sorafenib



EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire for Cancer; TTD, time to deterioration.
[a] Pre-specified secondary endpoint that was not formally tested; EORTC QLQ-C30 administered every 3 weeks on treatment and every 3 months after treatment discontinuation or progression. [b] Time to deterioration defined as first decrease from baseline of ≥ 10 points[1] in the patient-reported health-related global health status/quality of life (GHS/QoL) scale of the EORTC QLQ-C30 maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.
1. Osoba D, et al. *J Clin Oncol.* 1998.
Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

HIMALAYA : Primary Endpoint – OS for T300+D vs Sorafenib[a]

	T300+D n=393	Sorafenib n=389
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI), months	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (96.02% CI)	0.78 (0.65, 0.92)	
p-value (2-sided)	0.0035	



Number at risk

STRIDE	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

- **HIMALAYA met its primary endpoint: the T300+D regimen was superior to sorafenib for OS**

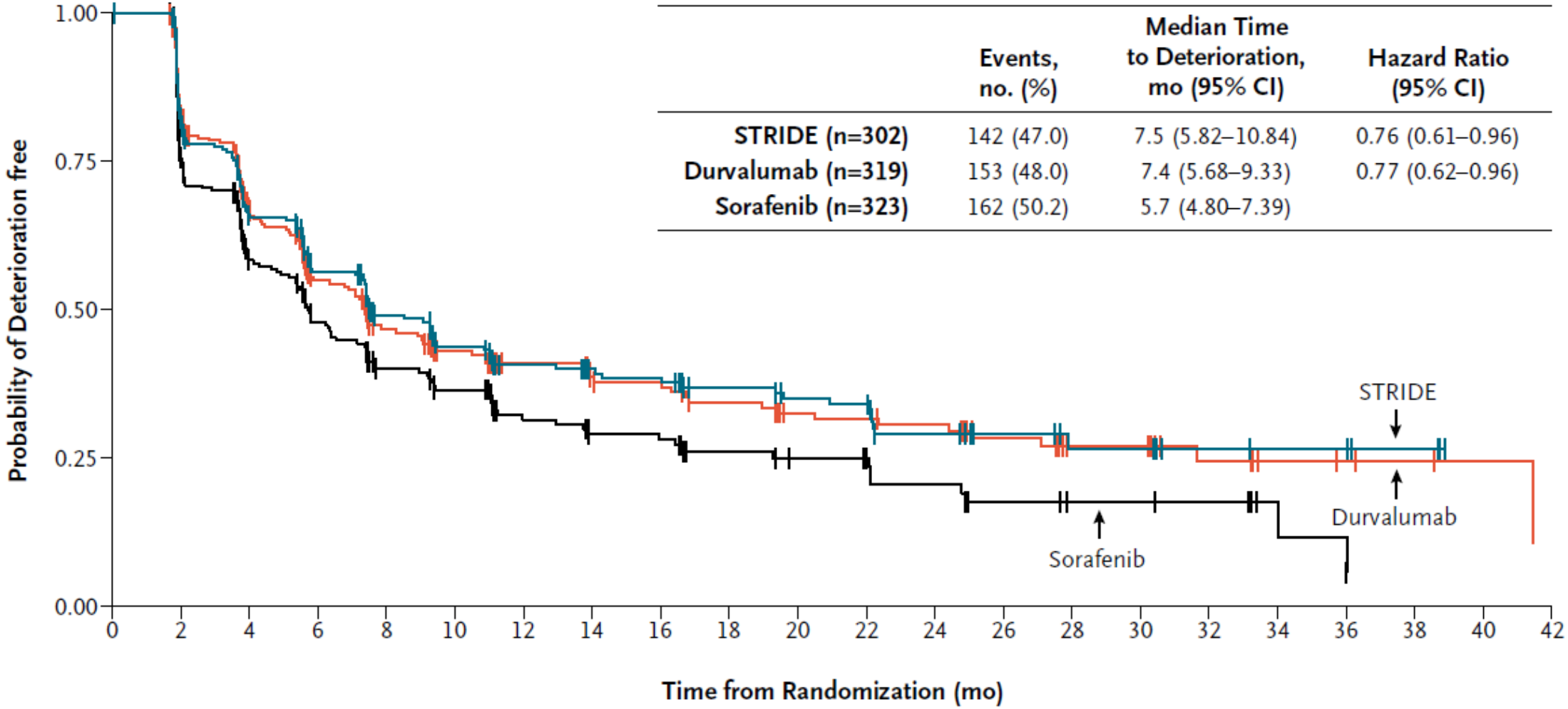
[a]Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; PD-L1, programmed cell death ligand-1; OS, overall survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; Q4W, every 4 weeks; vs, versus.

Abou-Alfa GK et al. ASCO GI 2022.
Abou-Alfa GK et al. NEJM Evid. 2022;1(8).

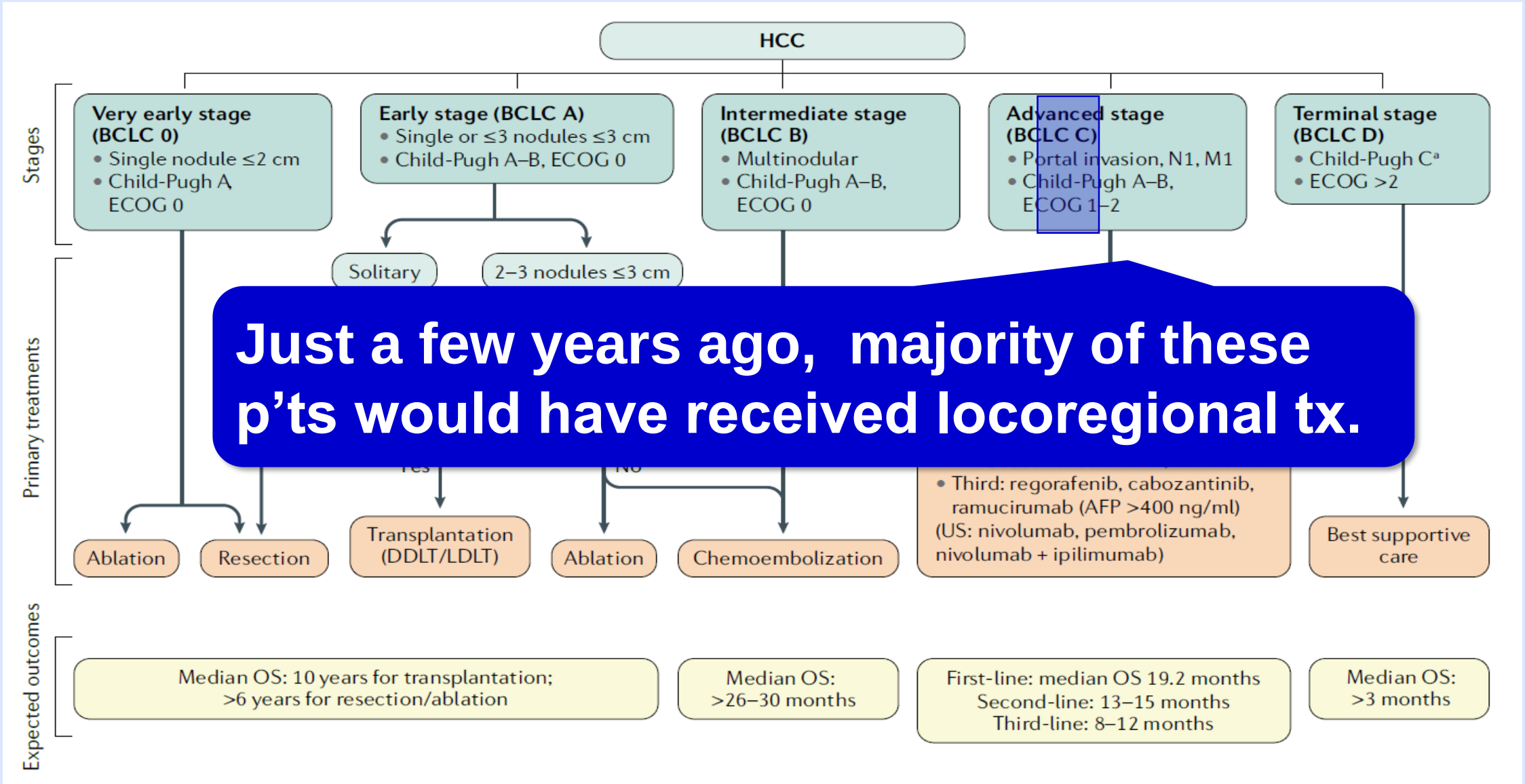
HIMALAYA : Time to Deterioration of Global Health Status or Quality of Life (EORTC QLQ-C30)

	Events, no. (%)	Median Time to Deterioration, mo (95% CI)	Hazard Ratio (95% CI)
STRIDE (n=302)	142 (47.0)	7.5 (5.82–10.84)	0.76 (0.61–0.96)
Durvalumab (n=319)	153 (48.0)	7.4 (5.68–9.33)	0.77 (0.62–0.96)
Sorafenib (n=323)	162 (50.2)	5.7 (4.80–7.39)	



Abou-Alfa GK et al. NEJM Evid. 2022;1(8).

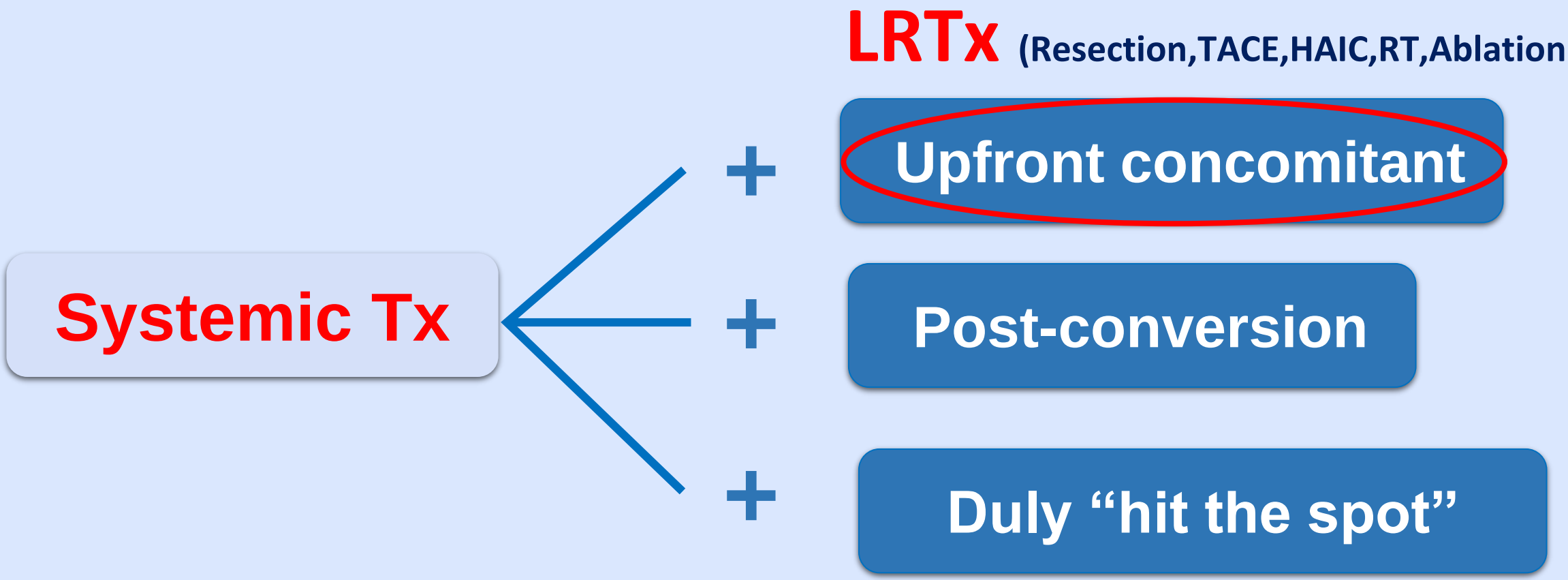
Evolving Treatment Strategy for Locally-advanced HCC



Just a few years ago, majority of these p'ts would have received locoregional tx.

Llovet JM et al. Nat Rev Dis Primers. 2021;7(1):6.

Versatile SysTx / LRTx in BCLC-C



Lenvatinib plus TACE versus lenvatinib alone as 1L treatment for advanced HCC: phase III, randomized (LAUNCH study)

- N=336, **BCLC-C (with TACEable primary lesions)**
- Single lesion size < 10cm
  Number of lesions < 10
  Tumor burden < 50%
- Primary endpoint = OS

TACE to all TACEable

	LEN-TACE	LEN	P
ORR (RECIST1.1) (CR)	45.9% (0.6%)	20.8% (0.6%)	<0.001
mOS	17.8m	11.5m	<0.001
mPFS	10.6m	6.4m	<0.001

Peng ZW et al. J Clin Oncol. 2023;41(1):117–127.

Sorafenib plus FOLFOX-HAIC vs Sorafenib for HCC with Portal Vein Invasion — A randomized trial

N = 247

FOLFOX-HAIC
Oxa 85 mg/m^2, D1 5-FU bolus 400mg/m^2 ,then 2400 mg/m^2, 46hrs Leucovorin 400mg/m^2, D1

Results:

	mOS(m)	PFS(m)	RR(%)
HAIC + Sor	13.4	7.0	40.8
Sor	7.1	2.6	2.5
P	<0.001	<0.001	<0.001

He M et al. JAMA Oncol. 2019;5(7):953–960.

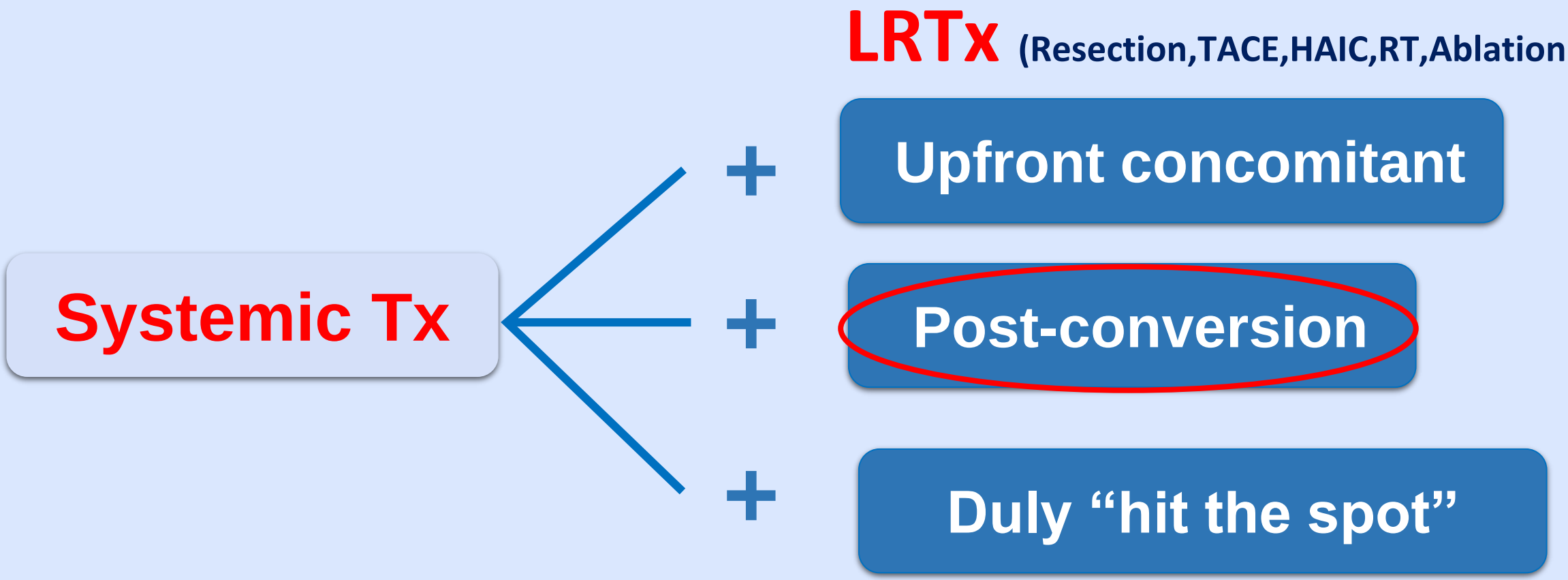
Adding Radiation to Systemic Therapy Extends OS for Advanced Liver Cancer (Phase III NRG/RTOG 1112 study)

- N = 177, not suitable for resection or locoregional Tx
- SBRT+Sorafenib vs Sorafenib
- OS 15.8 vs 12.3 months (P=0.042, adjusted)

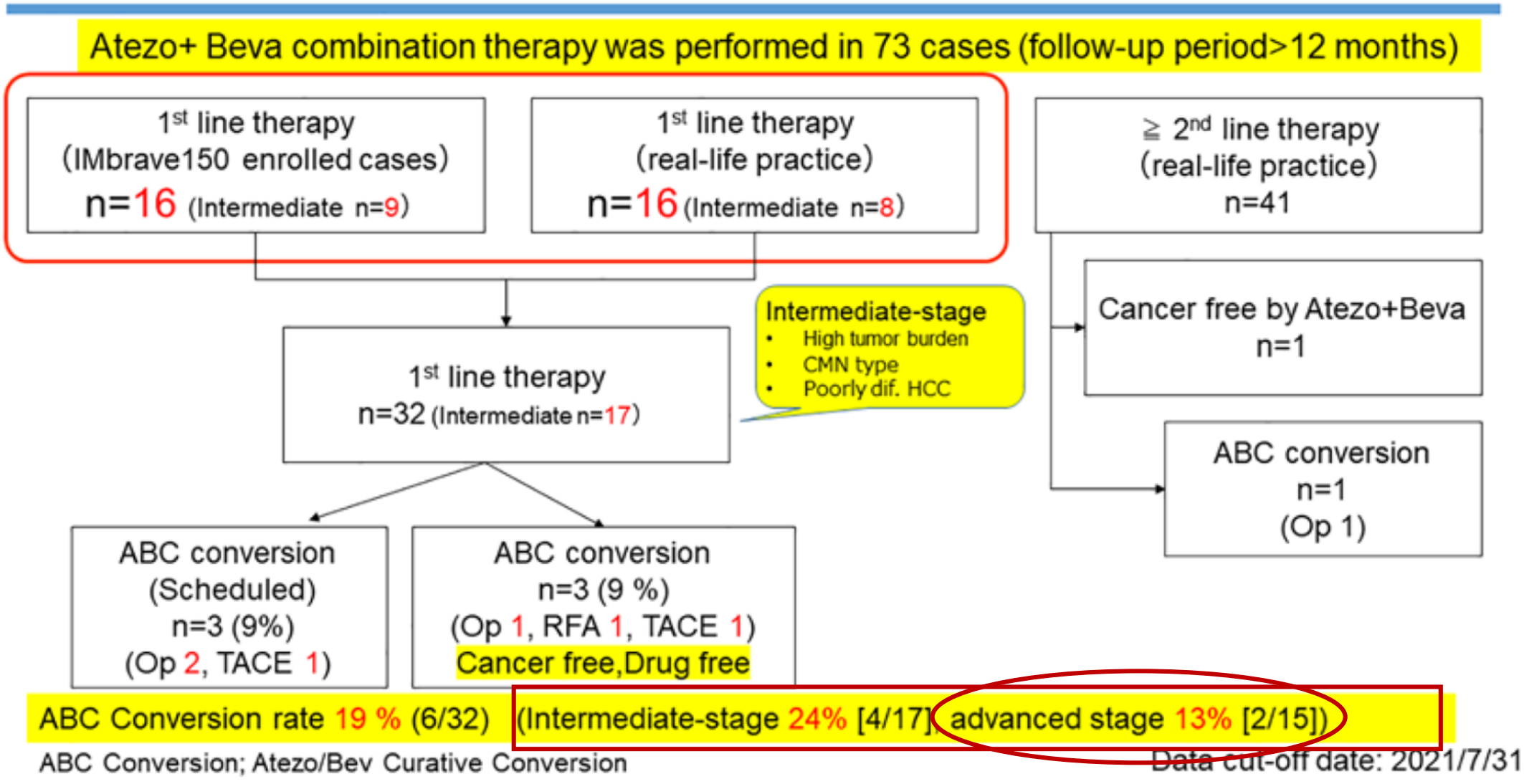
  PFS 9.2 vs 5.5 months (P < 0.001)

Dawson L et al. ASTRO 2022.

Versatile SysTx / LRTx in BCLC-C

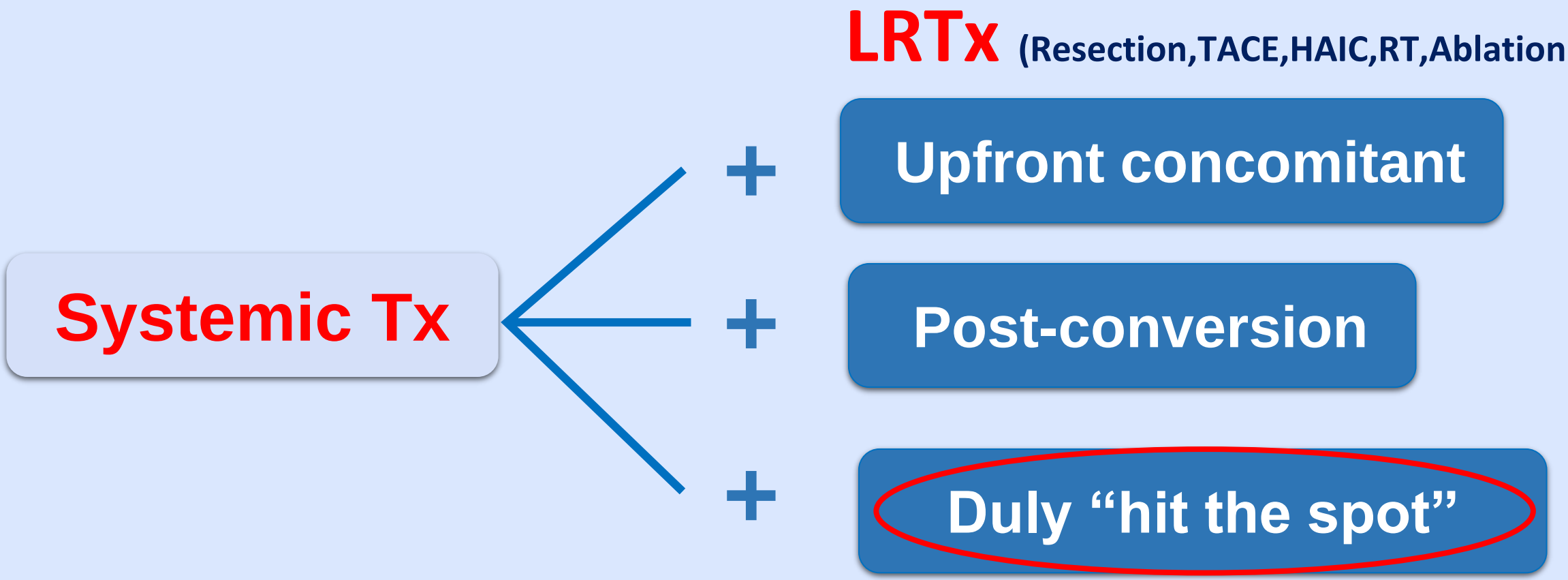


Atezolizumab+Bevacizumab Curative Conversion Therapy (ABC Conversion Therapy)



Kudo M, Liver Cancer 2021;10:539–544.
Kudo M, KanTanSui 2021;83(3):475–483.

Versatile SysTx / LRTx in BCLC-C

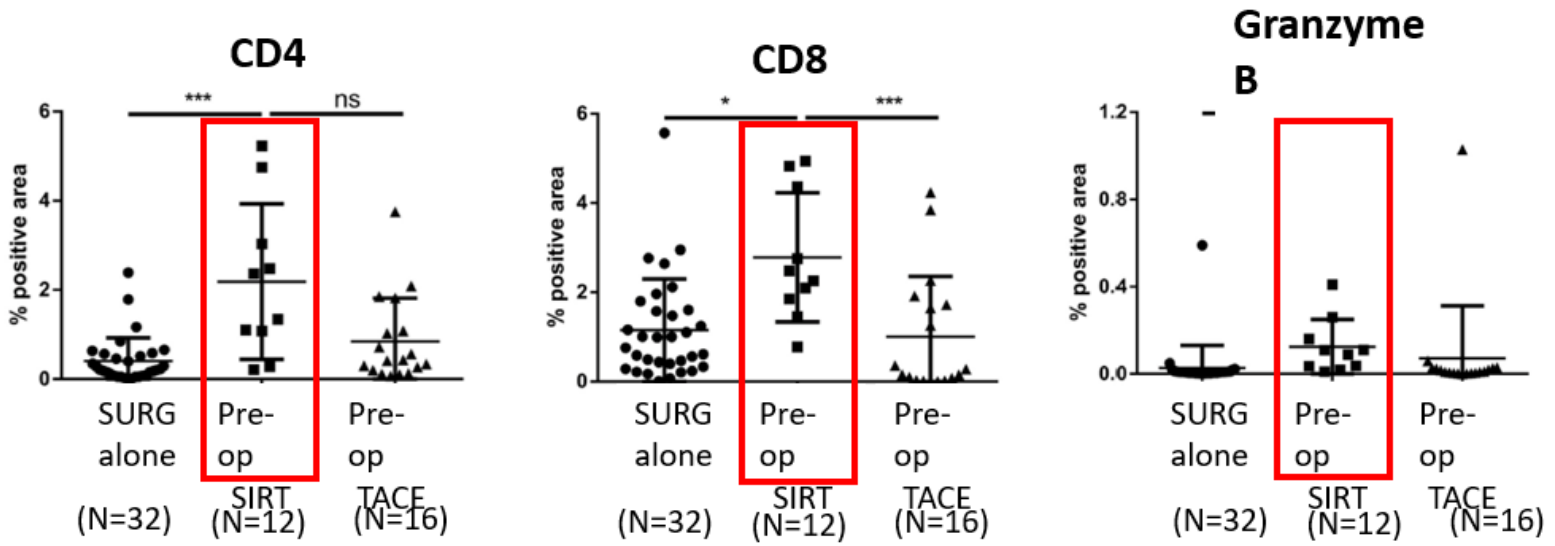


CR

Immune Elimination

SIRT increased T cell recruitment and CD8 T cell activation

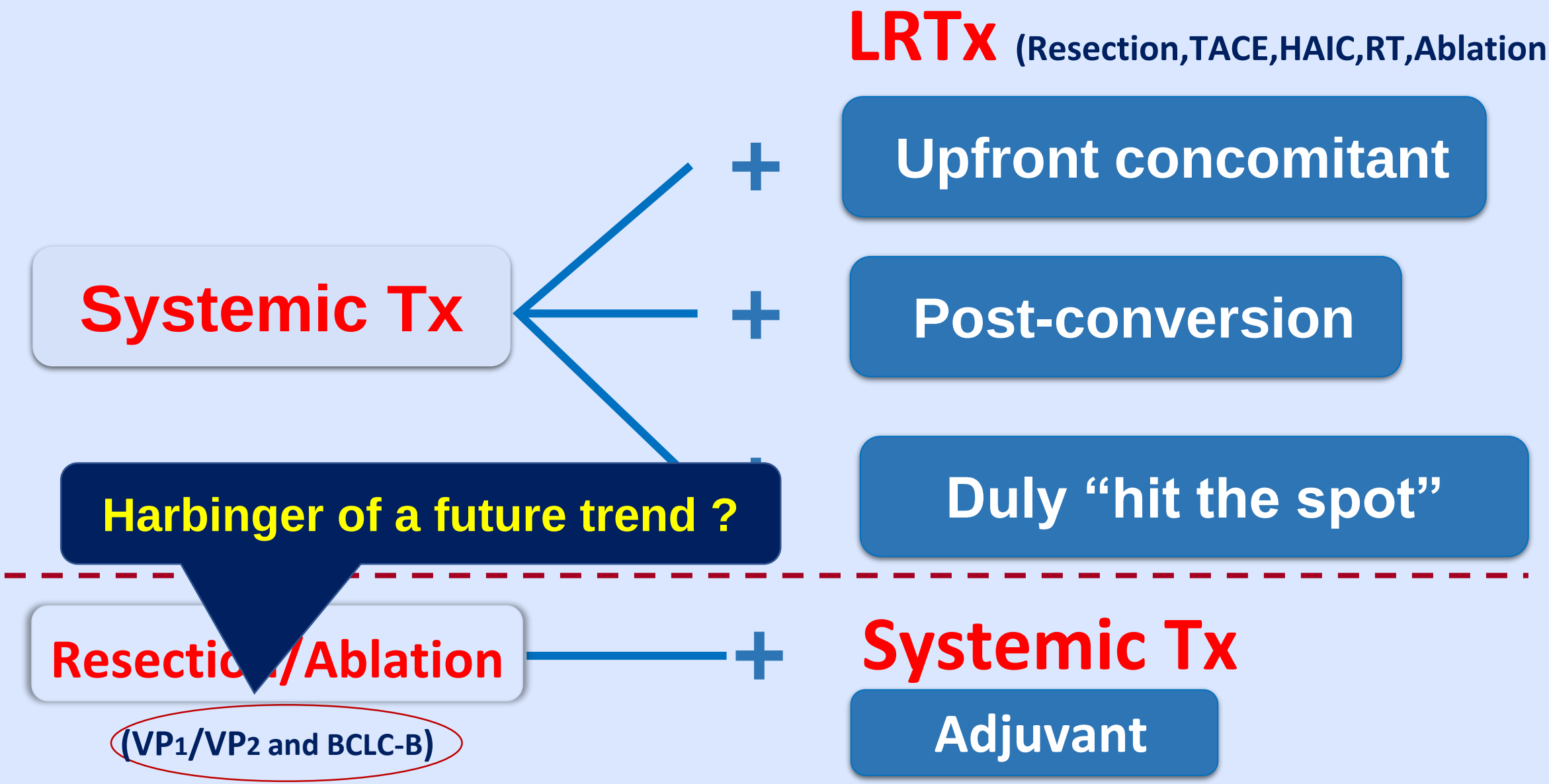
IHC analysis of hepatectomy specimens with or without pre-operative SIRT or TACE



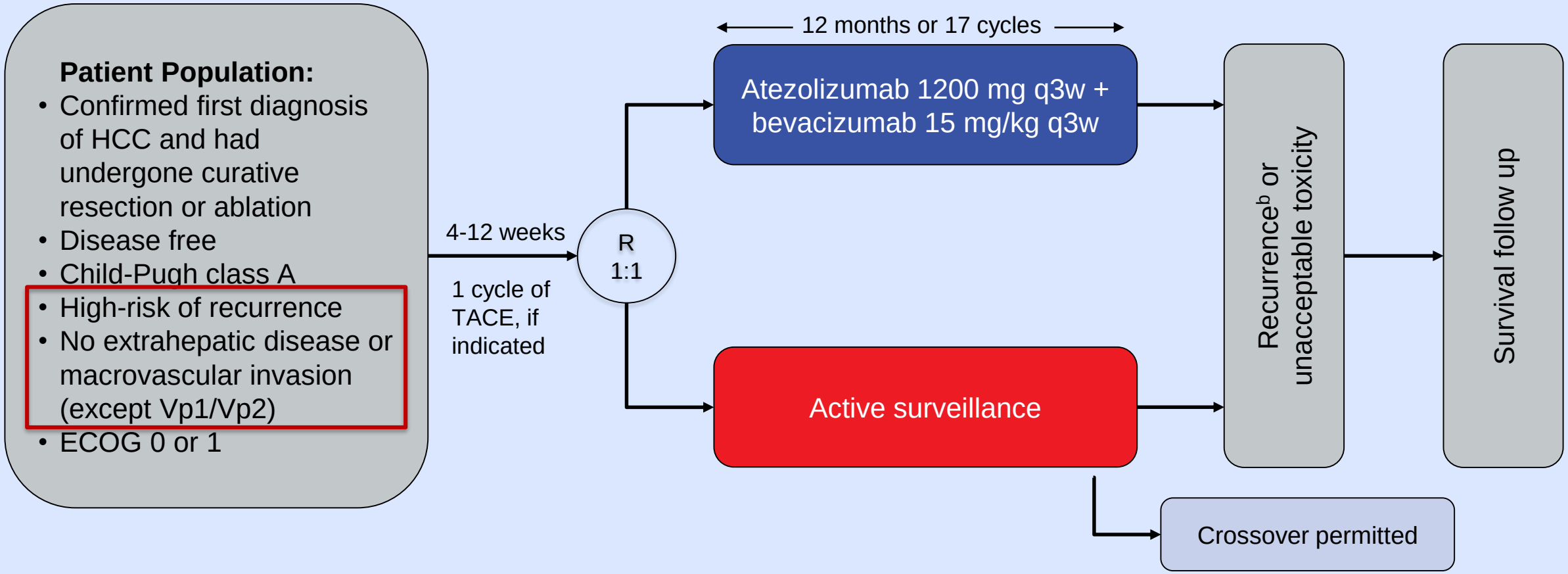
Craciun et al. BMC Cancer 2020;20:135

- **Destroy escaping clones.**
- **Push immune balance toward tumor elimination.**

Versatile SysTx / LRTx in BCLC-C

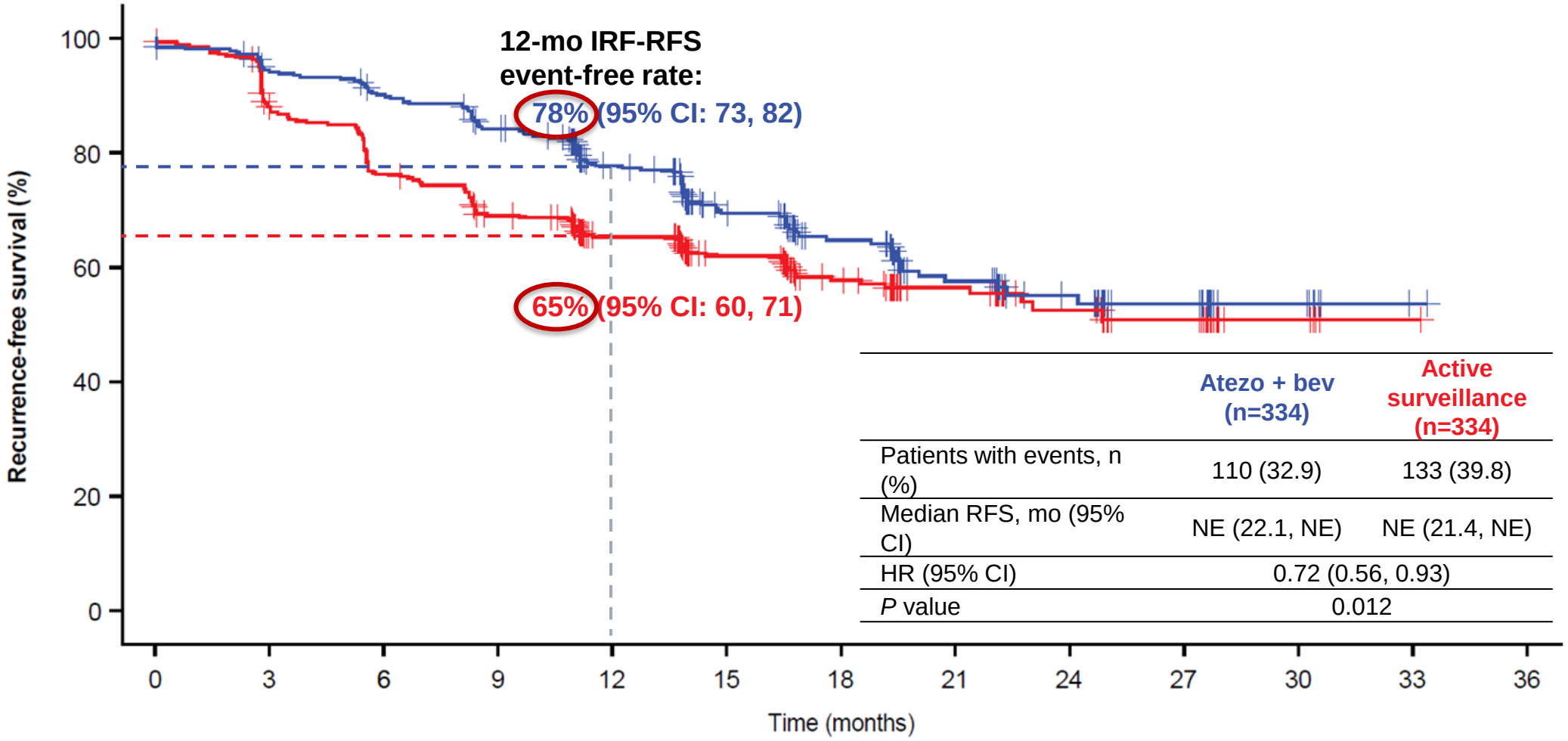


IMbrave050 Study Design



Qin S et al. Lancet. 2023;402(10415):1835–1847.

Primary Endpoint: IRF-assessed RFS



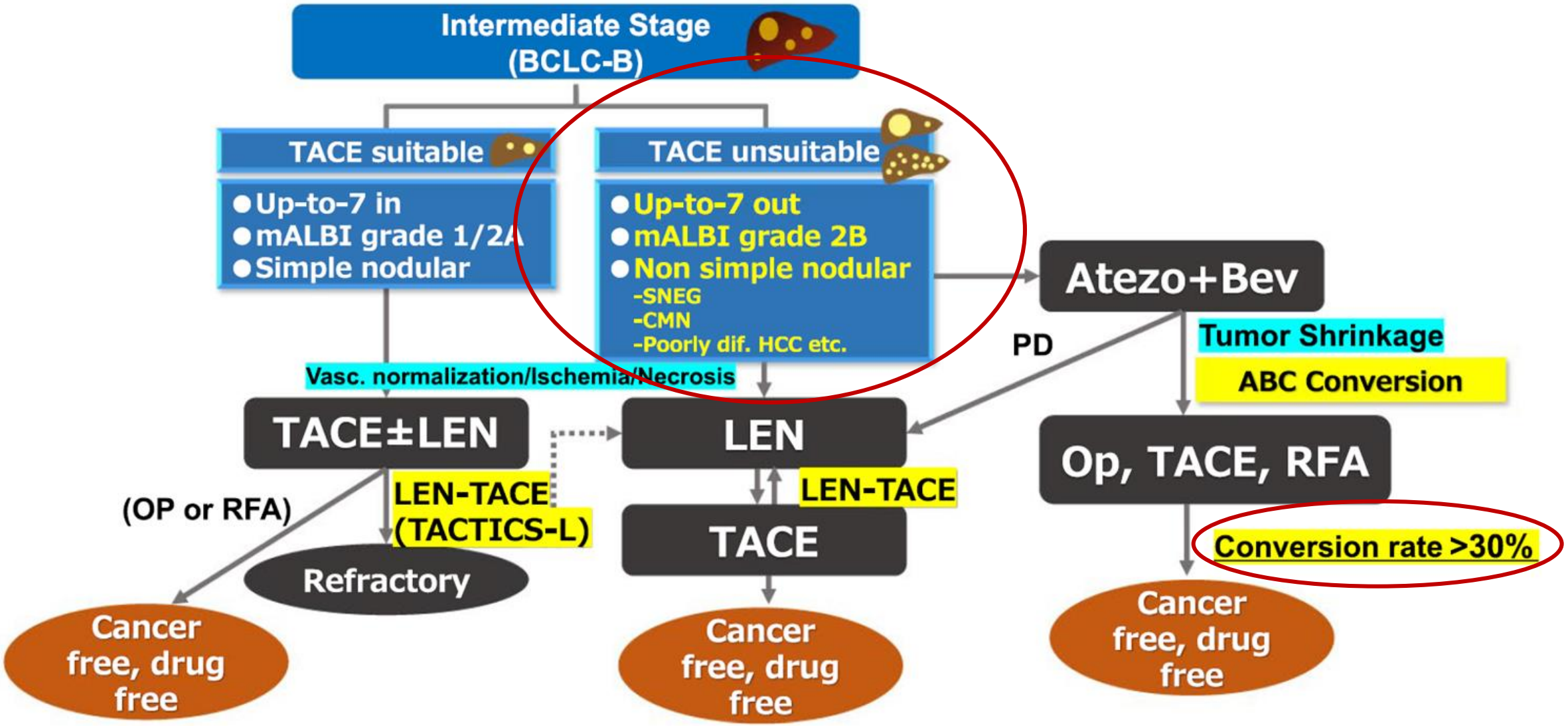
	Atezo + bev (n=334)	Active surveillance (n=334)
Patients with events, n (%)	110 (32.9)	133 (39.8)
Median RFS, mo (95% CI)	NE (22.1, NE)	NE (21.4, NE)
HR (95% CI)	0.72 (0.56, 0.93)	
P value	0.012	

Qin S et al. Lancet. 2023;402(10415):1835–1847.

Intermediate-stage HCC

Effective systemic therapy discourages low-yield LRTx.

Treatment Strategy of Intermediate-stage HCC



Kudo M. Int J Clin Oncol. 2022;27(7):1110–1119.

To treat more intermediate-stage HCC with upfront systemic therapy alone ?

Phase IIIb, randomized, open-label trial of Atezo-Bev vs TACE in intermediate-stage HCC with high disease burden

(IKF002-ABC-HCC study)

ClinicalTrials.gov NCT04803994

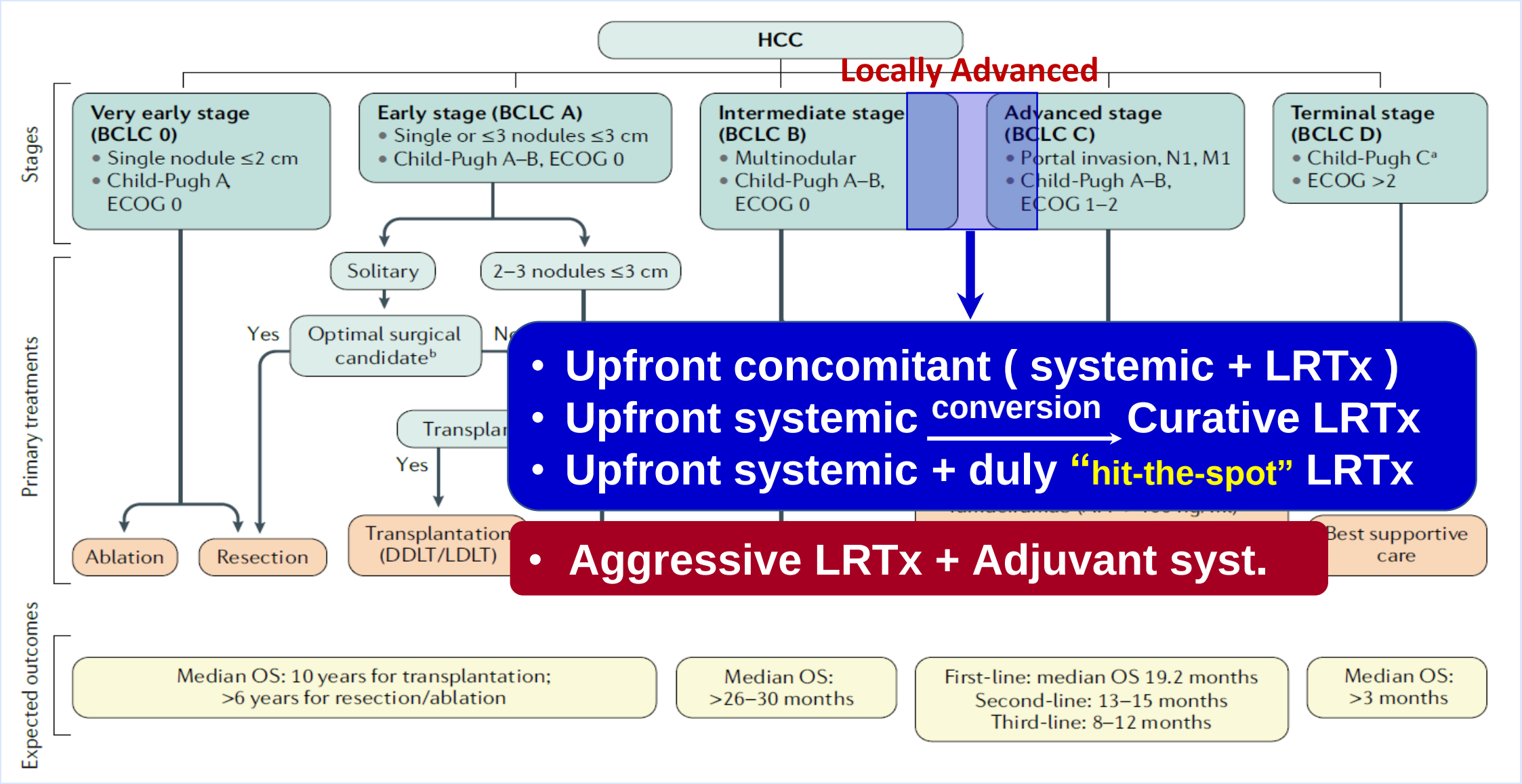
Phase III, randomized, open-label trial of Regorafenib plus Pembrolizumab vs TACE in intermediate-stage HCC with beyond Up-to-7 criteria

(REPLACE study)

ClinicalTrials.gov NCT04777851

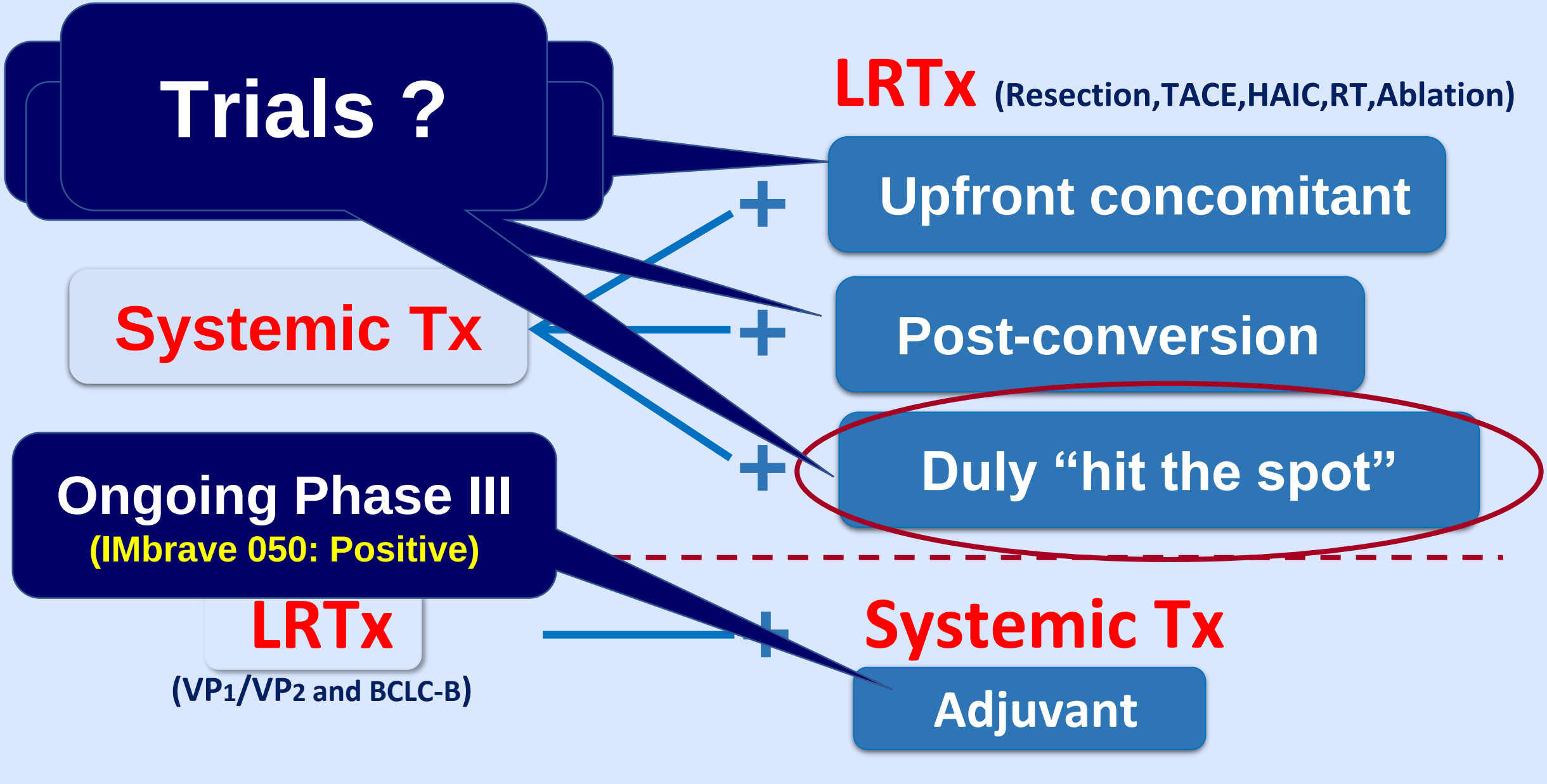
All locally advanced (non-metastatic BCLC-C and TACE-unsuitable BCLC-B) are treated by a similar strategy.

Evolving Treatment Strategy for Locally-advanced HCC



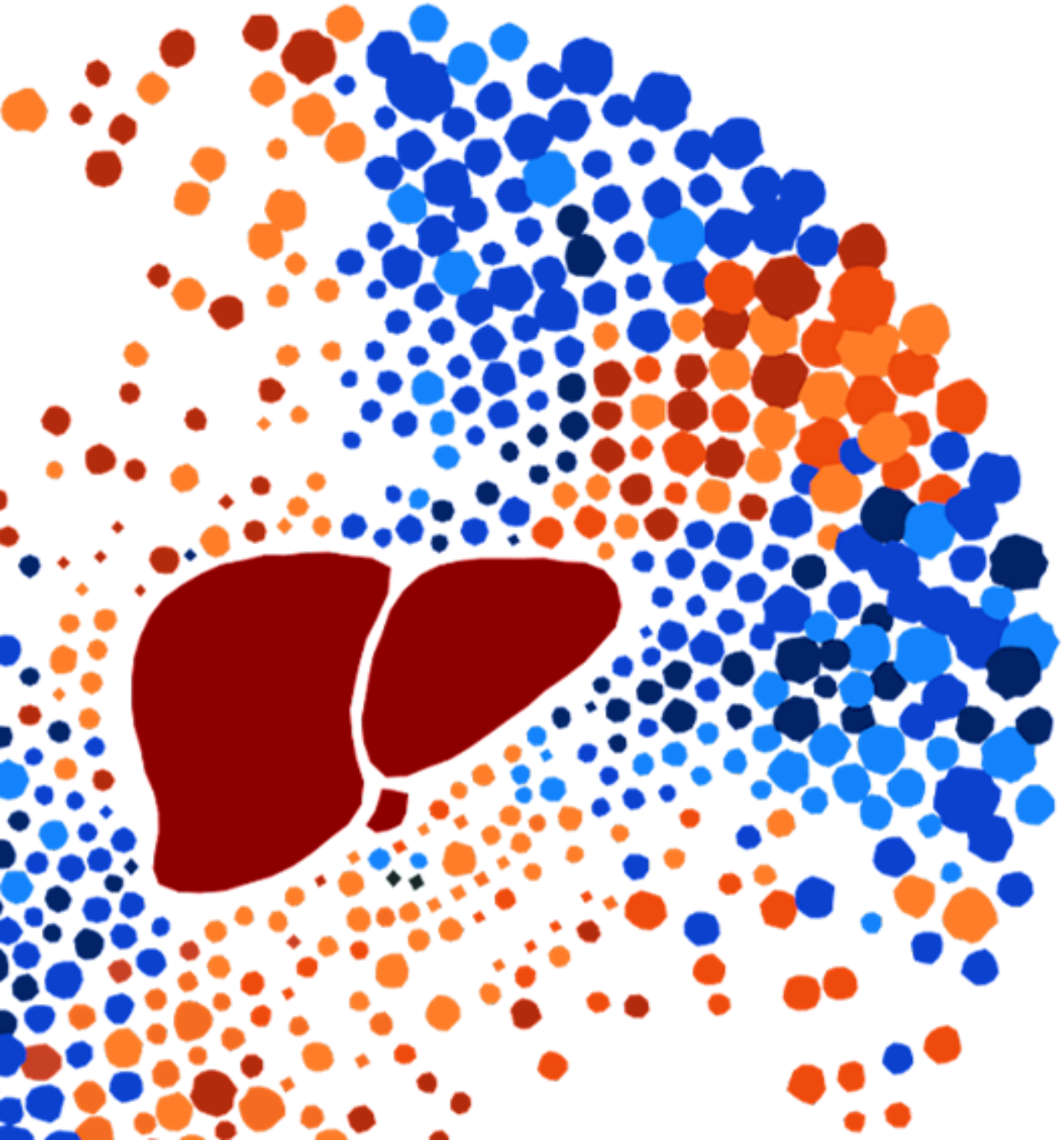
Llovet JM et al. Nat Rev Dis Primers. 2021;7(1):6.

Versatile SysTx / LRTx in Locally-Advanced HCC



Summary

- **Effective systemic immunotherapy is changing our practice in the majority of HCC patients.**
- **Sophisticated planning are necessary for the treatment of locally advanced HCC.**
- **Search for solid evidence for each of the possible systemic + locoregional therapy is mandatory.**



Case discussion: Systemic therapy, locoregional therapy or both?

Hui-Chuan Sun

Please participate in the polling!

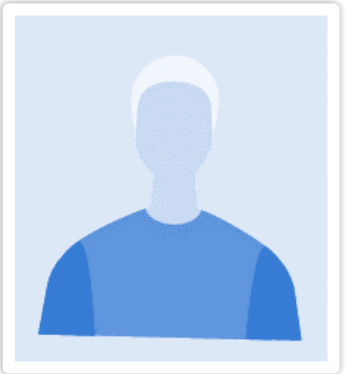
Scan the QR code to join directly

OR

go to
https://esmoasia23.cnf.io/
and
tap the session titled
"Roche - HCC illuminated: Exploring future frontiers with systemic immunotherapies"

Patient Disease Characteristics: May 2021

Male Patient aged 34



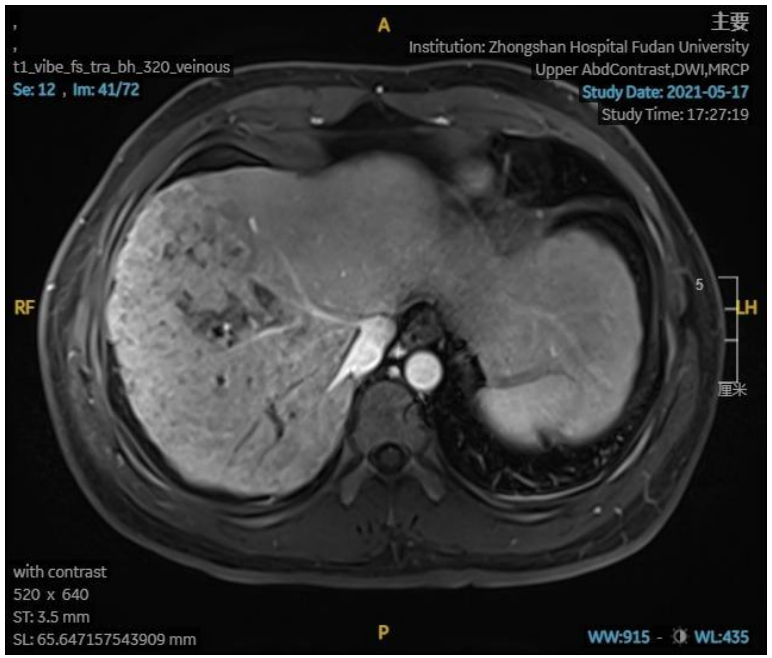
- Had been infected with hepatitis B virus, antiviral therapy with entecavir for half a year
- **Liver function:** Child-Pugh class was A5
- **AFP:** 7481 ng/ mL
- **PIVKA-II:** 53348 mAU/ mL
- **MRI:** Invasive liver cancer in the right lobe of the liver, about 15 cm in diameter, tumor thrombus in the right branch of the portal vein (VP3 PVTT)

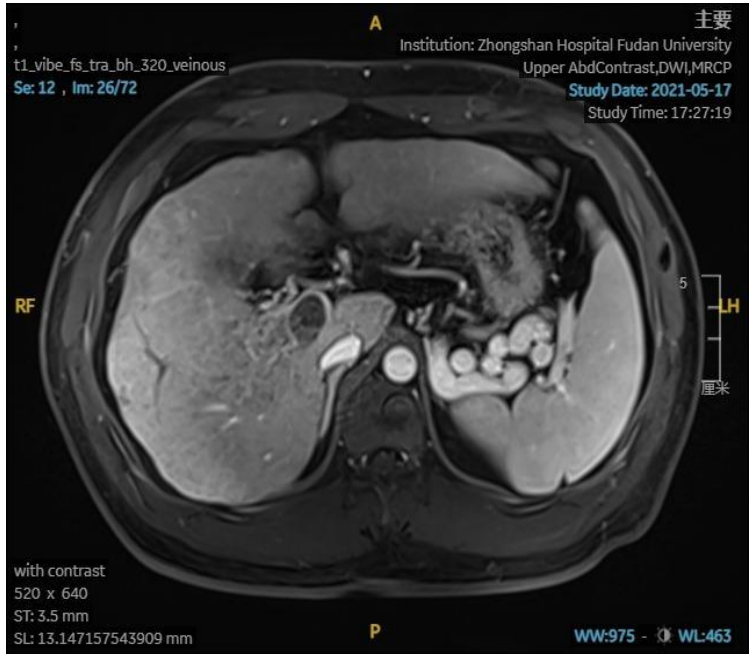
Diagnosis: Hepatocellular Carcinoma, BCLC Stage C (PVTT)

Case study provided by Prof. Sun for the purposes of this presentation.
AFP, alpha fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; PVTT, portal vein tumor thrombosis; MRI, magnetic resonance imaging.

MRI Image at Baseline: 17 May 2021

Invasive liver cancer in the right lobe of the liver, about 15 cm in diameter; tumor thrombus in the right branch of the portal vein (VP3 PVTT)

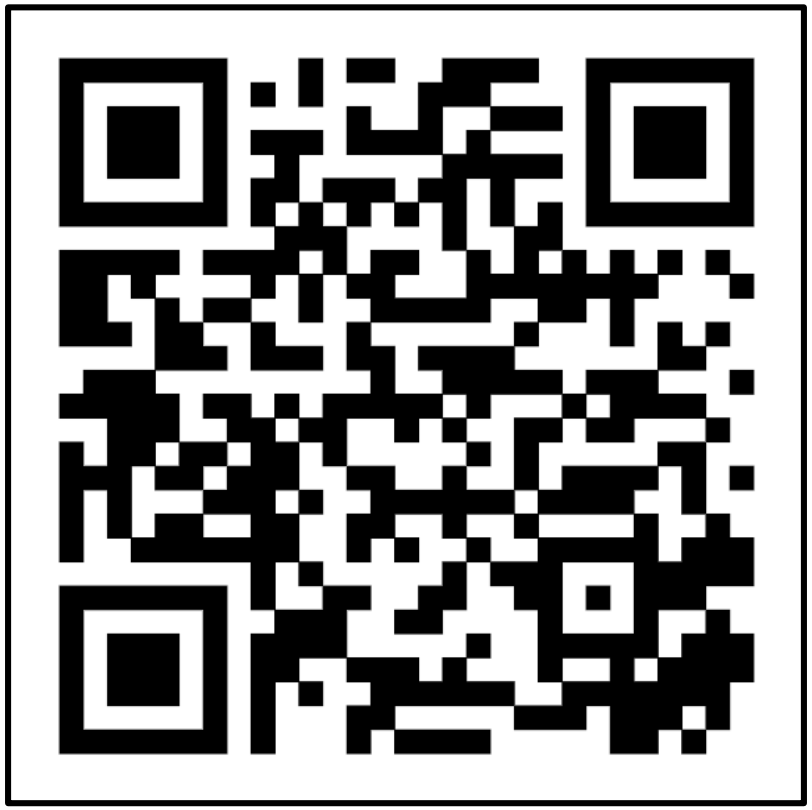




Case study provided by Prof. Sun for the purposes of this presentation.
PVTT, portal vein tumor thrombosis; MRI, magnetic resonance imaging.

What would be your initial treatment of choice for this patient?

1. **Anti-PD-1/PD-L1 + anti-VEGF**
2. **Anti-PD-1/PD-L1 + anti-CTLA-4**
3. **TKI monotherapy**
4. **Locoregional therapy (TACE/TARE/SIRT with Y-90)**
5. **Combination of locoregional & systemic therapy**



Polling options may include treatments that are not approved in your jurisdiction and should not be considered as a recommendation that the product can be employed for indications other than those authorized.
SIRT, selective internal radiation therapy; TKI, tyrosine kinase inhibitor; TARE, transarterial radioembolization; TACE, transarterial chemoembolization.

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: What would be your initial treatment of choice for this patient?

The development of immunotherapy has driven a change in overall strategies for HCC and provided new ideas for combination/conversion therapy

Outcome of Phase III Study on Advanced First Line Treatment of HCC

2020 | 2021 | 2022

		Atezolizumab + bevacizumab[1-3]	Sintilimab + bevacizumab[4]	Durvalumab + Tremelimumab[8]	Camrelizumab + Rivoceranib[5]	Pembrolizumab + Lenvatinib[6]	Cabozantinib + Atezolizumab[7]
Study		IMbrave150	ORIENT-32	HIMALAYA	SHR-1210-III-310	LEAP-002	COSMIC-312
Patients (n)		336	380	393	272	395	432
mOS (mo.)		19.2	NE	16.4	22.1	21.2	15.4
mPFS (mo.)		6.9	4.6	3.78	5.6	8.2	6.8
RECIST 1.1	ORR (%)	**30**	21	20.1	25.4	26.1	11
	CR (%)	**8**	0	3.1	1.1	1.5	<1
	PD (%)	**19**	27	39.9	16.2	12.2	14
	mDoR (mo)	**18.1**	NE	22.34	14.8	16.6	10.6
	TTR	**2.8**	/	2.17	1.9	/	4.0
≥3 grade TRAE	Any grade	**45%**	35.3%	25.8%	80.9%	62.5%	76%
	AST	**7.0%**	<3%	2.3%	16.5%	22.0%	9%
	ALT	**3.6%**	<2%	1.0%	12.9%	19.2%	9%

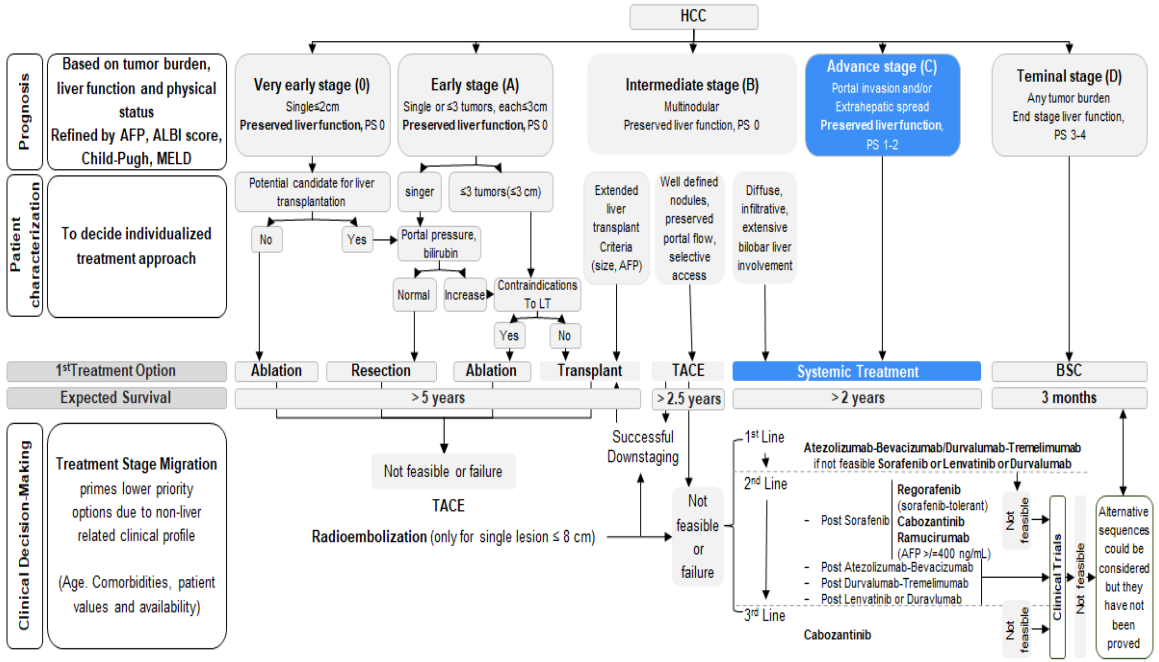
* LEAP-002 and COSMIC-312 are negative results, and different studies have heterogeneity. The data is not of comparative significance and is for reference only.

AST, Aspartate transaminase; ALT, Alanine transaminase; PFS; progression free survival; mo; months; mDoR, median duration of response; ORR, overall response rate; CR, complete response; PD, partial disease; TTR, time to response; TRAE; treatment-related adverse event

1. Finn RS et al. ASCO GI 2021. Abstract #267.
2. Finn RS et al. J Clin Oncol 2020;38(26):2960–2970.
3. Finn RS et al. New Engl J Med 2020;382(20):1894–1905.
4. Ren Z et al. Lancet Oncol. 2021;22(7):977–990.
5. Qin S et al. ESMO 2022. Abstract #LBA35.
6. Finn RS et al. ESMO 2022. Abstract #LBA34
7. Kelley RK et al. Lancet Oncol. 2022;23(8):995–1008.
8. Abou-Alfa GK et al. ASCO GI 2022. Abstract #TPS379.

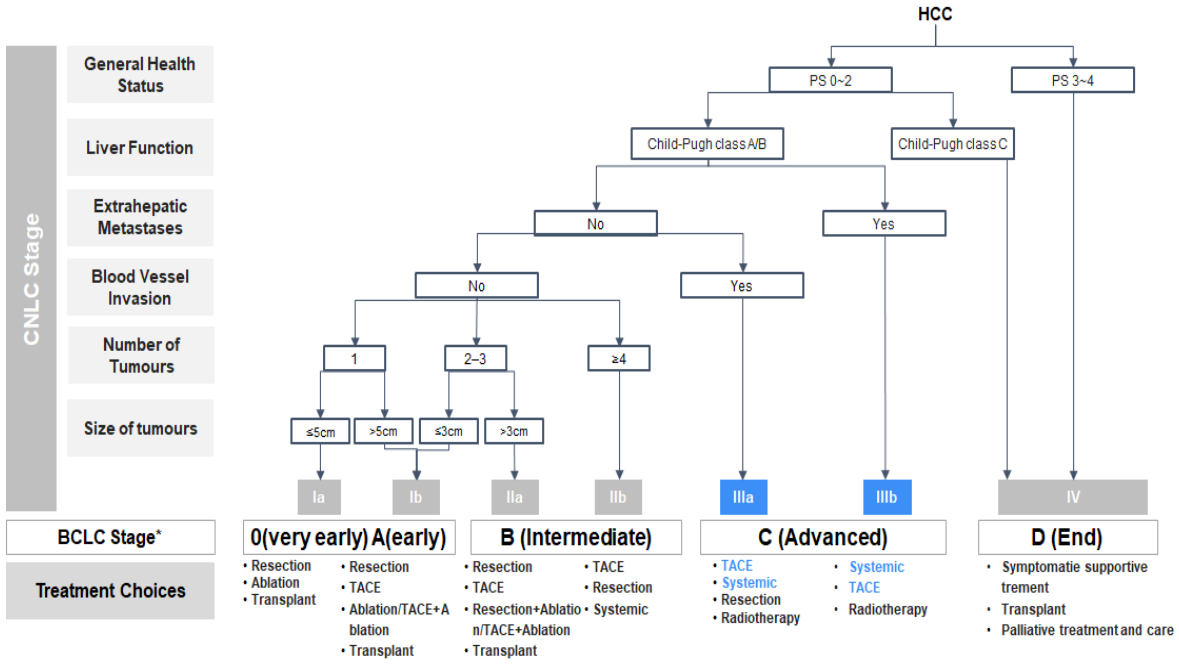
For advanced liver cancer with BCLC stage C, there are differences in treatment recommendations between Chinese and international guidelines

BCLC Strategy for prognosis prediction and treatment recommendation: The 2022 update[1]



The preferred option for HCC patients with BCLC stage C is systemic therapy

"Primary Liver Cancer Diagnosis and Treatment Guidelines" 2022 Edition, China[2]



For HCC patients with CNLC Stage IIIa-IIIb (BCLC stage C), locoregional therapy or systemic therapy is recommended.

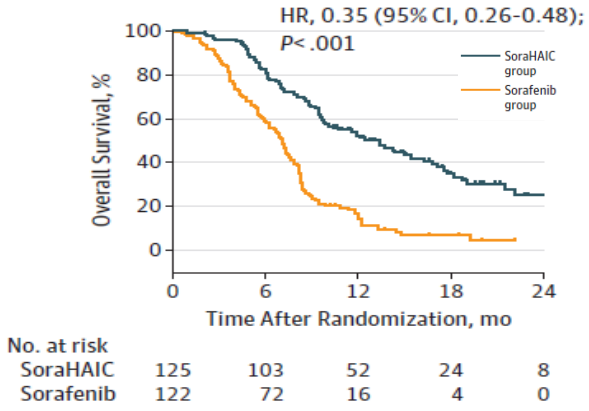
*Corresponding BCLC stage has been added for ease of comparison.

1. Reig M, et al. J Hepatol. 2022;76(3):681–693.
2. Zhou J, et al. Liver Cancer. 2023;12(5):405–444. "Primary Liver Cancer Diagnosis and Treatment Guidelines" 2022 Edition, National Health Commission of the People's Republic of China

Two Phase III studies demonstrated that the combination strategy significantly improved PFS and OS in patients with advanced HCC and increased the rate of curative surgical resection

Sorafenib + HAIC vs Sorafenib[1]

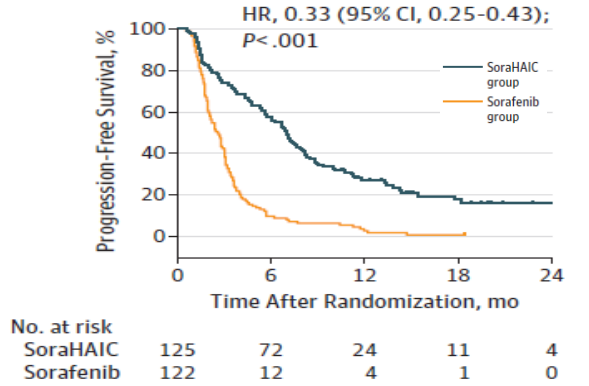
OS



	mOS, Months (95% CI)
Sorafenib	7.13 (6.28-7.98)
SoraHAIC	**13.37 (10.27-16.46)**

HR=0.35(0.26-0.48)
P<0.001

PFS



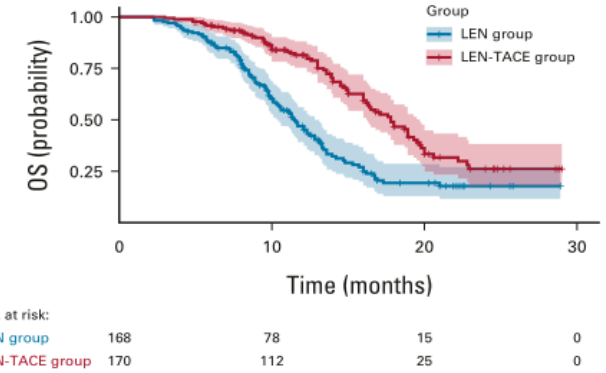
	mPFS, Months (95% CI)
Sorafenib	2.6 (2.15-3.05)
SoraHAIC	**7.03 (6.05-8.02)**

HR=0.33(0.25-0.43)
P<0.001

Curative Surgical Resection: SoraHAIC vs Sorafenib = 12.8% (16/125) VS. 0.8% (1/122)

LAUNCH: TACE + Lenvatinib vs Lenvatinib[2]

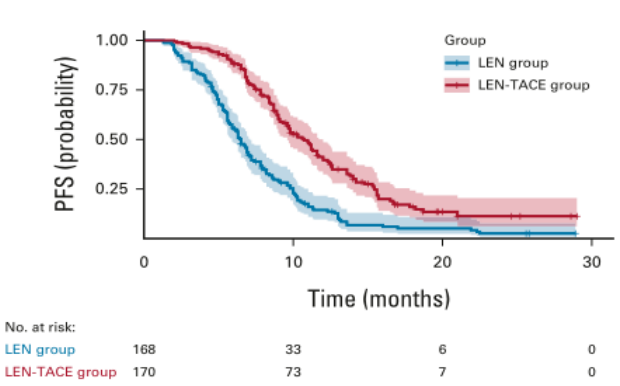
OS



	mOS, Months (95%CI)
LEN	11.5 (10.3-12.7)
LEN-TACE	**17.8 (16.1-19.5)**

HR=0.45(0.33-0.61)
P<0.001

PFS



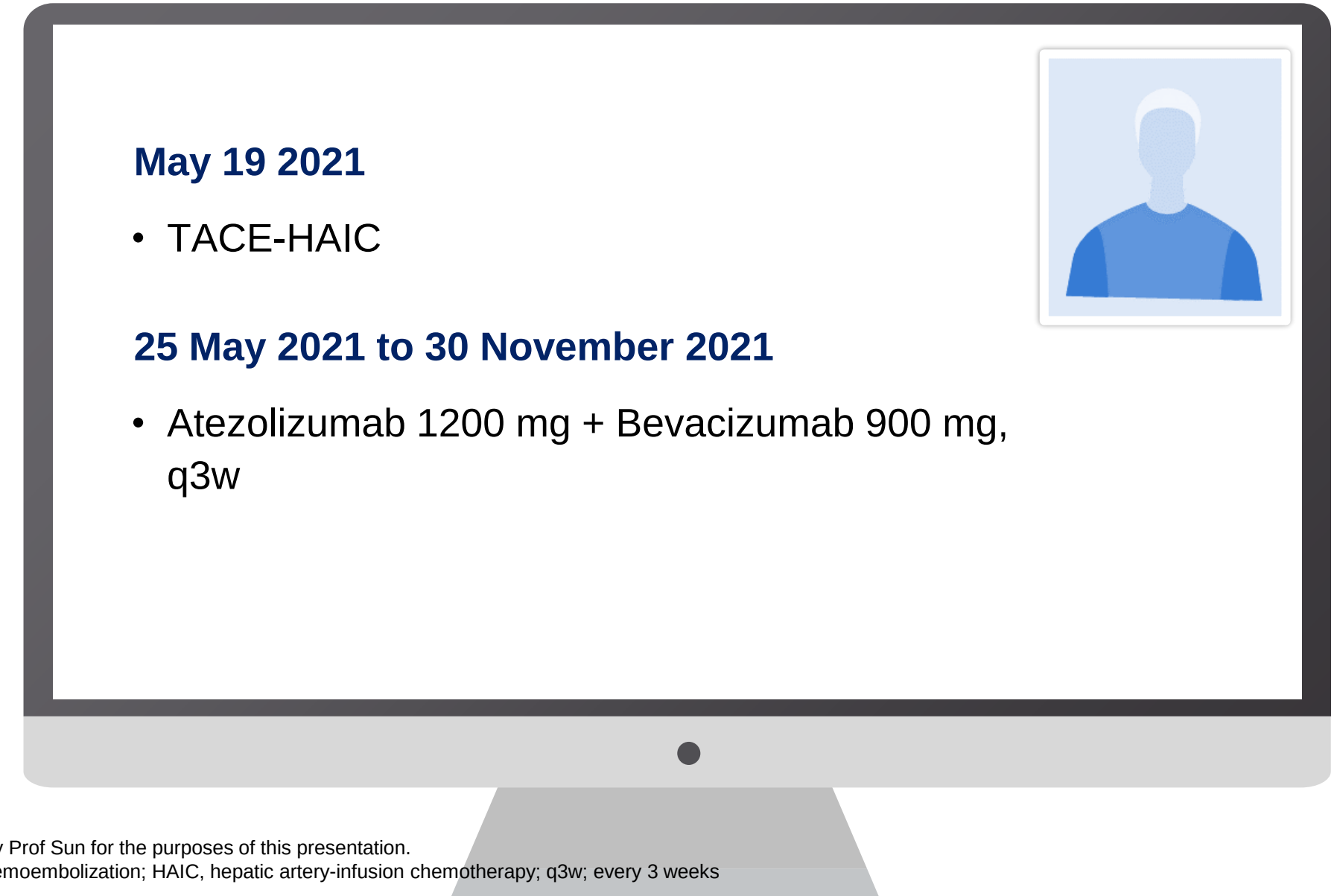
	mPFS, Months (95% CI)
LEN	6.4 (5.8-7.0)
LEN-TACE	**10.6 (9.5-11.7)**

HR=0.43(0.34-0.55)
P<0.001

Curative Surgical Resection: LEN-TACE vs LEN = 15.3% (26/170) VS. 1.8% (3/168)

1. He M et al. JAMA Oncol. 2019;5(7):953–960. 2. Peng Z et al. J Clin Oncol. 2023;41(1):117–127.
PFS, progression free survival, OS, overall survival, HAIC, hepatic artery-infusion chemotherapy, HR, hazard ratio.

Treatment Option: May 2021 to November 2021



May 19 2021

- TACE-HAIC

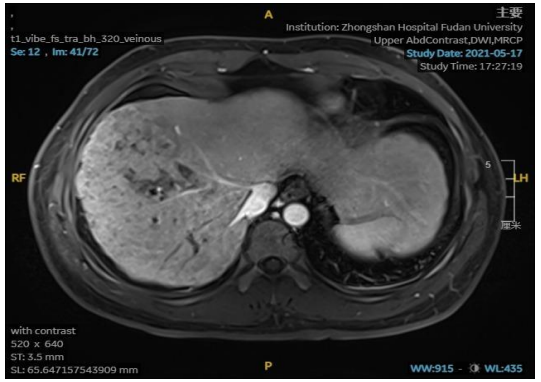
25 May 2021 to 30 November 2021

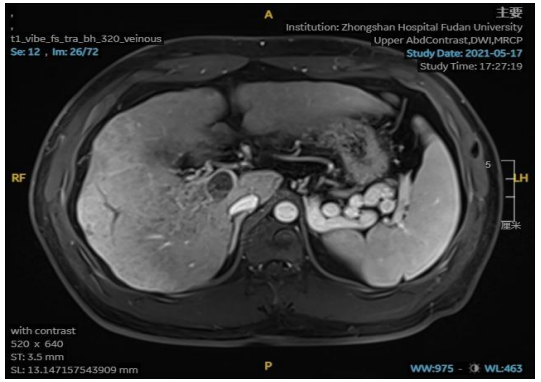
- Atezolizumab 1200 mg + Bevacizumab 900 mg, q3w

Case study provided by Prof Sun for the purposes of this presentation.
TACE, transarterial chemoembolization; HAIC, hepatic artery-infusion chemotherapy; q3w; every 3 weeks

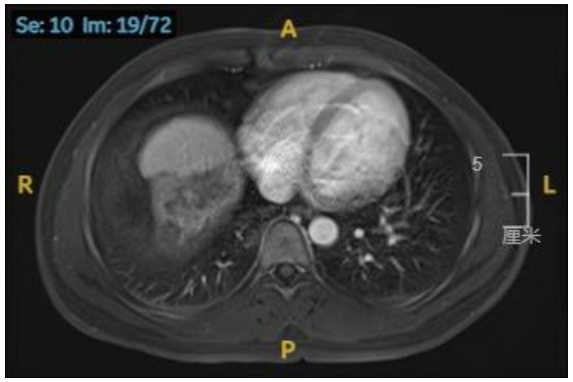
Efficacy Assessment: After 7.2 months of treatment

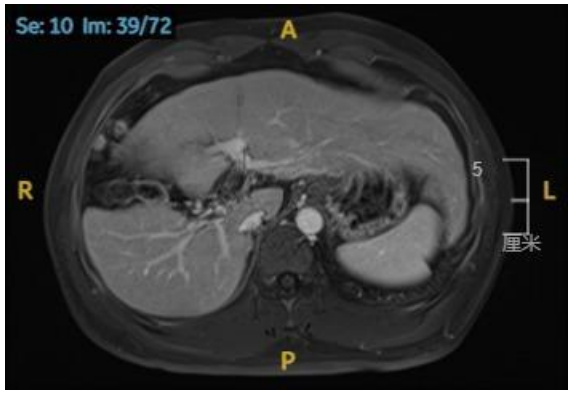
17 May 2021
Baseline

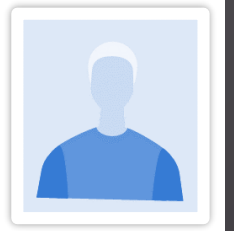




20 Dec 2021
After approx. 7.2 months of treatment







- **Liver function: Child-Pugh class was A5**
- **ECOG PS: 0**

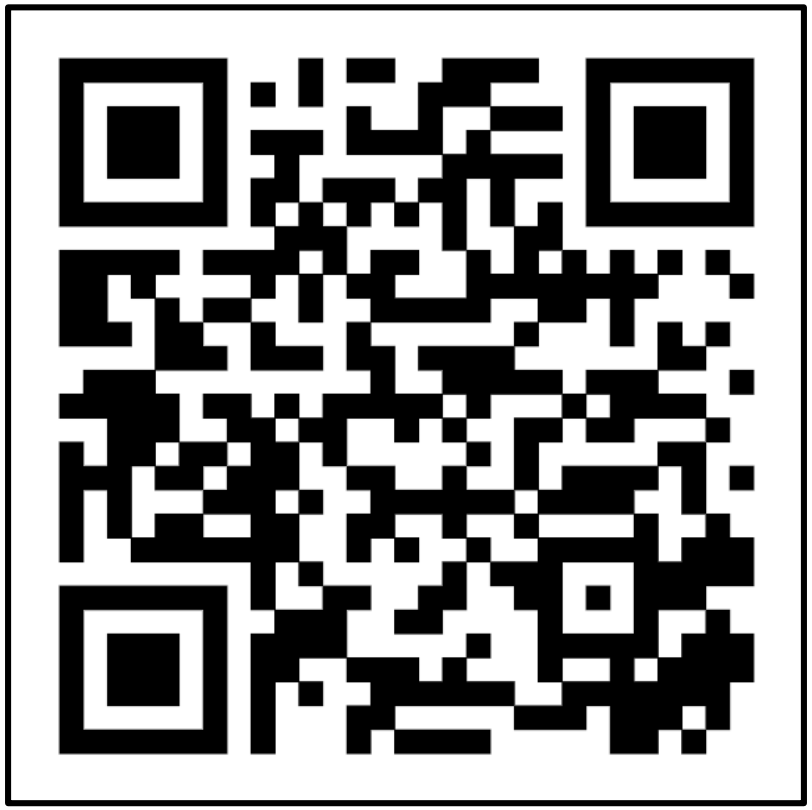
Tumor thrombus necrosis, tumor downstaging?

Partial Response (RECIST v1.1 & mRECIST criteria)

Case study provided by Prof Sun for the purposes of this presentation.
RECIST, Response evaluation criteria in solid tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors

What would be your next treatment for this patient?

1. **Resection**
2. **Ablation**
3. **Anti-PD-1/PD-L1 + anti-VEGF**
4. **Locoregional therapy (TACE/TARE/SIRT with Y-90)**



Polling options may include treatments that are not approved in your jurisdiction and should not be considered as a recommendation that the product can be employed for indications other than those authorized.
SIRT, selective internal radiation therapy; TARE, transarterial radioembolization; TACE, transarterial chemoembolization.

Live Content Slide

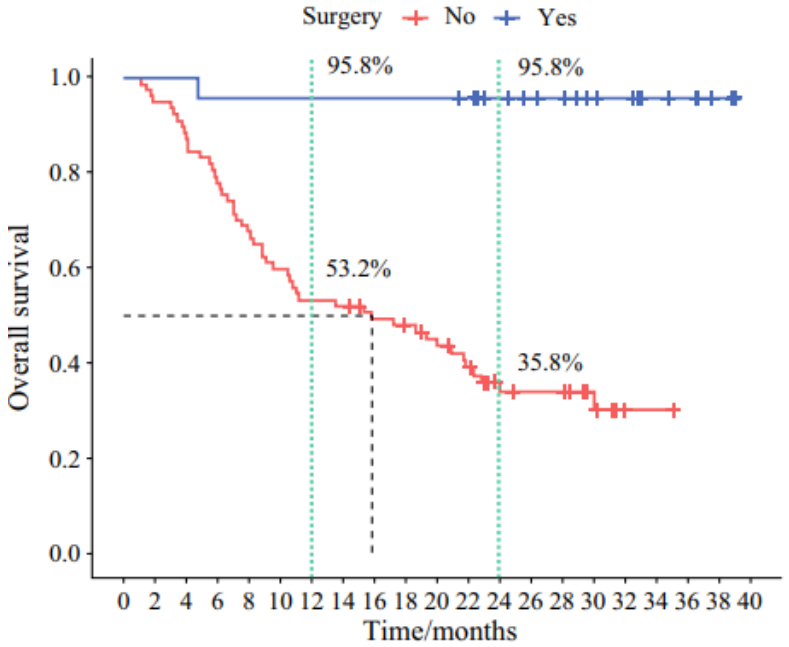
When playing as a slideshow, this slide will display live content

Poll: What would be your next treatment for this patient?

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

The survival of conversion-surgery was significantly better than non-surgical palliative care

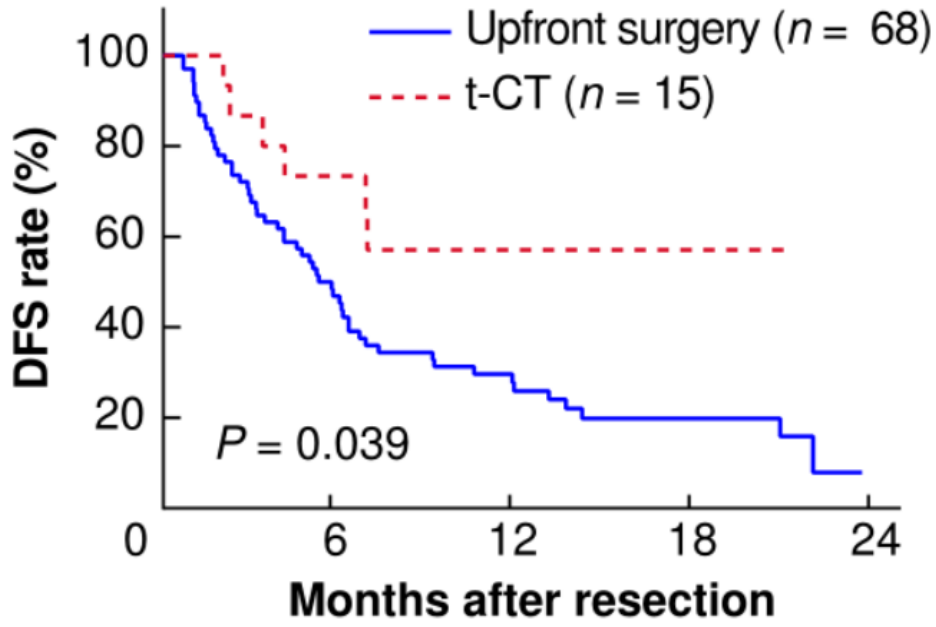
24-month survival rates were 95.8% vs 35.8% for patients who underwent vs did not undergo conversion surgery



- The 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

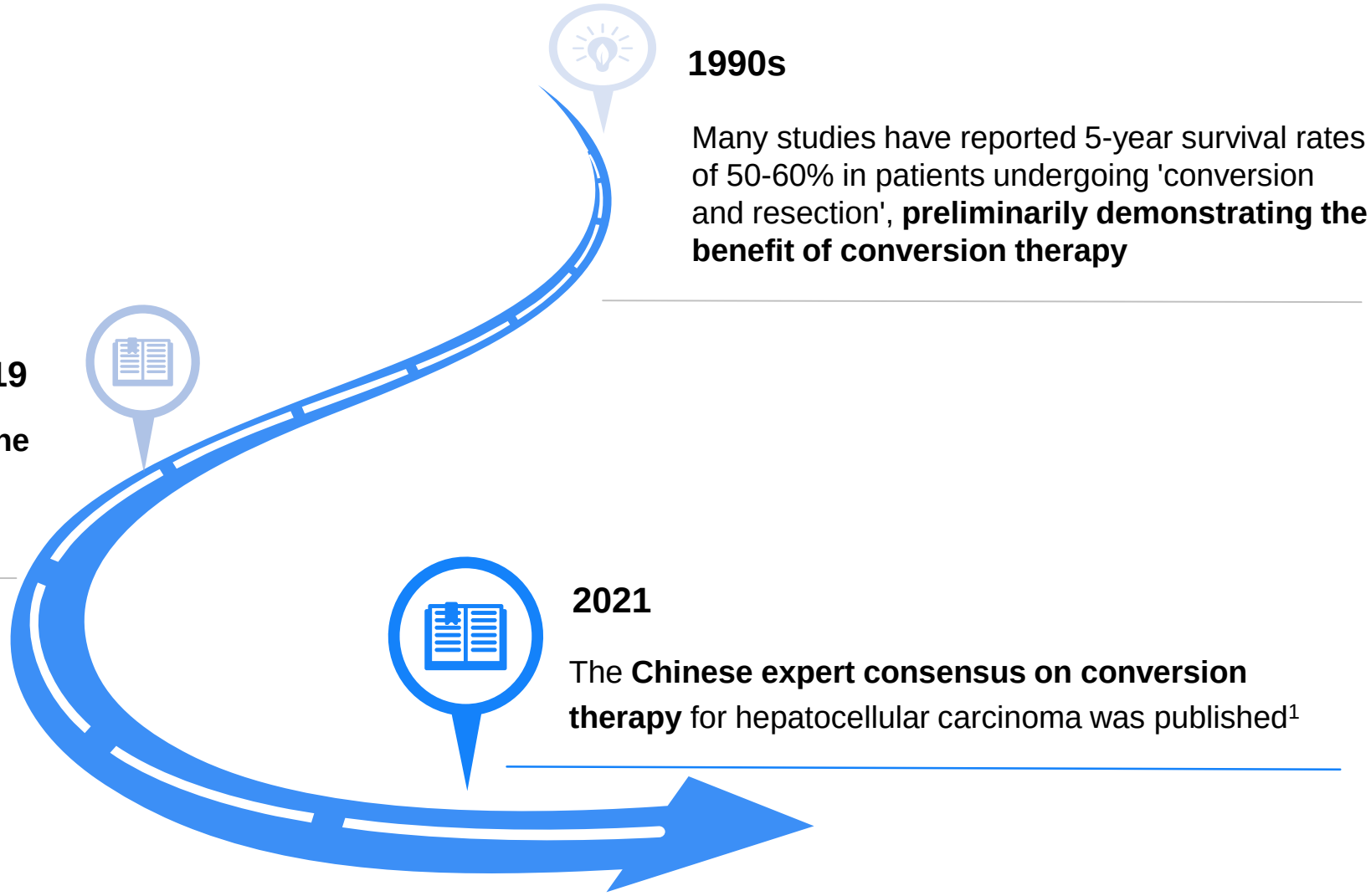
mDFS was not reached vs 5.4 months for patients with conversion-surgery vs upfront surgery



- 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;30(5):2782–2790.
2. Qu WF et al. BJS Open. 2022;6(5):zrac114.

HCC conversion therapy has made great progress in recent years after long-term development



1990s

Many studies have reported 5-year survival rates of 50-60% in patients undergoing 'conversion and resection', **preliminarily demonstrating the benefit of conversion therapy**

2019

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

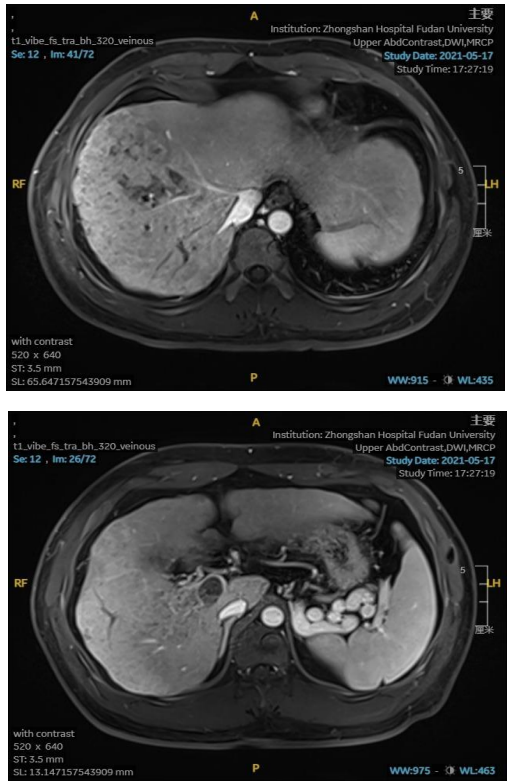
2021

The **Chinese expert consensus on conversion therapy** for hepatocellular carcinoma was published[1]

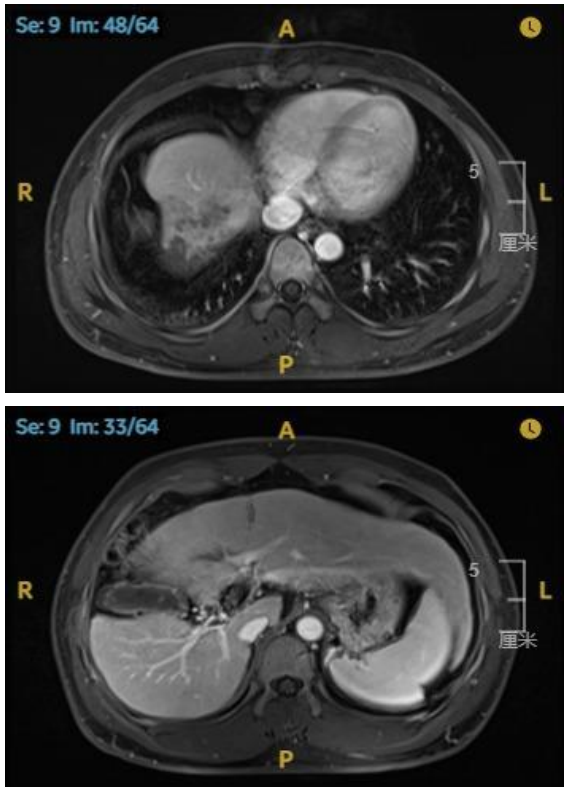
1. Sun HC et al. Hepatobiliary Surg Nutr. 2022;11(2):227–252.

Preoperative Assessment: After approx. 7.8 months of treatment

17 May 2021
Baseline



6 Jan 2022
After approx. 7.8 months of treatment

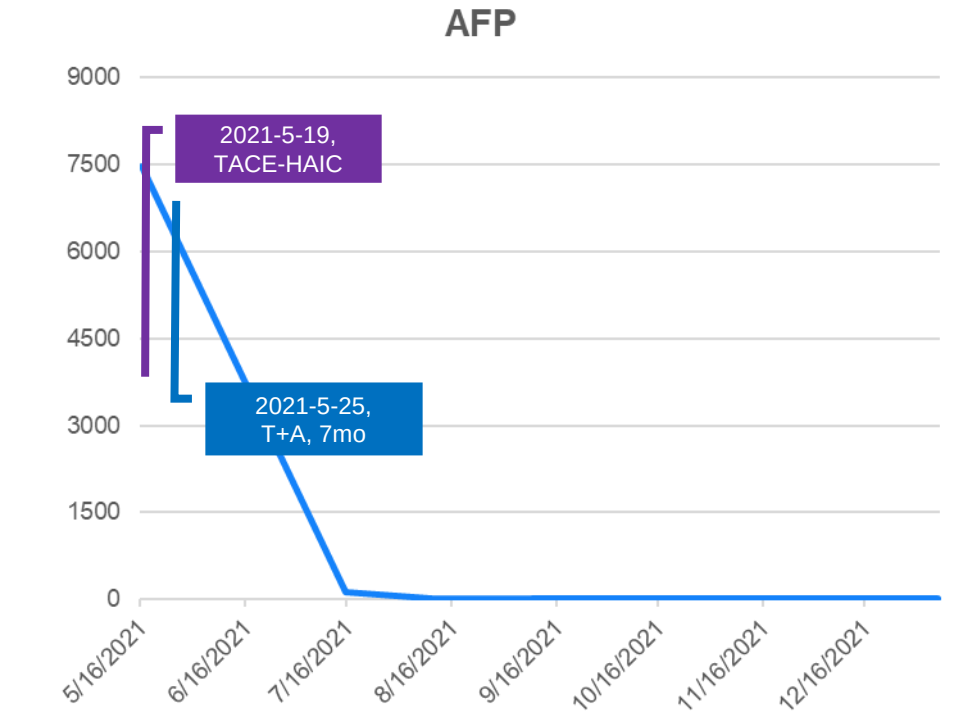


- **Liver function: Child-Pugh class was A5**
- **ECOG PS: 0**

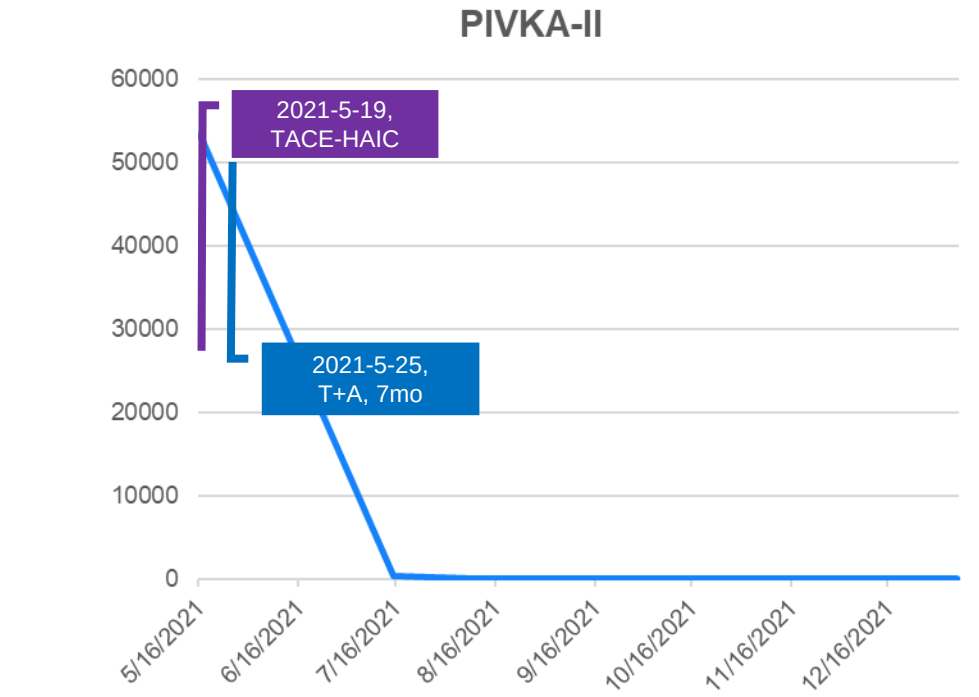
Efficacy Assessment: PR Ongoing (RECIST v1.1 & mRECIST criteria)

Case study provided by Prof. Sun for the purposes of this presentation.
AFP, alpha fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

Tumor marker changes during preoperative treatment



	5/16/2021	7/15/2021	8/10/2021	9/8/2021	10/6/2021	11/2/2021	11/30/2021	1/6/2022
AFP	7481	128	28.3	10.4	10.8	11.6	14.7	16.6

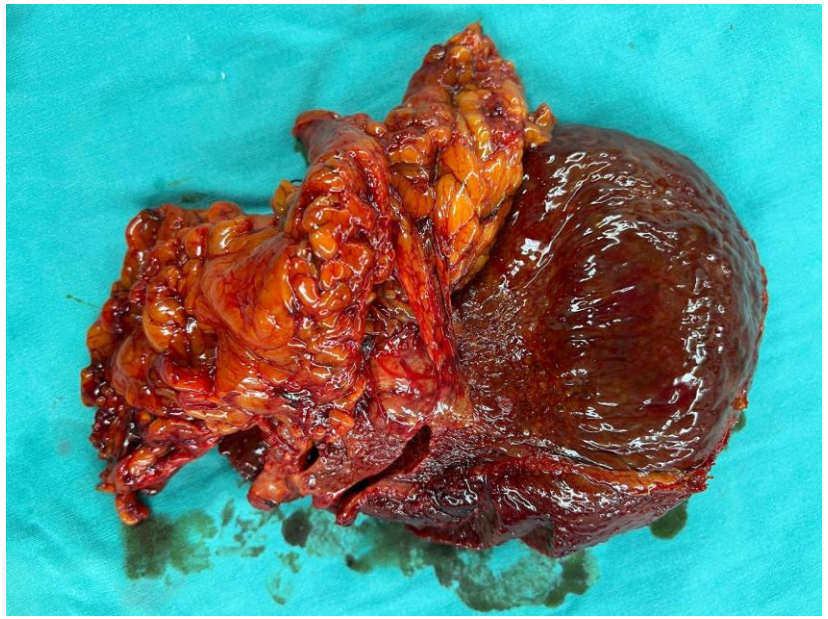


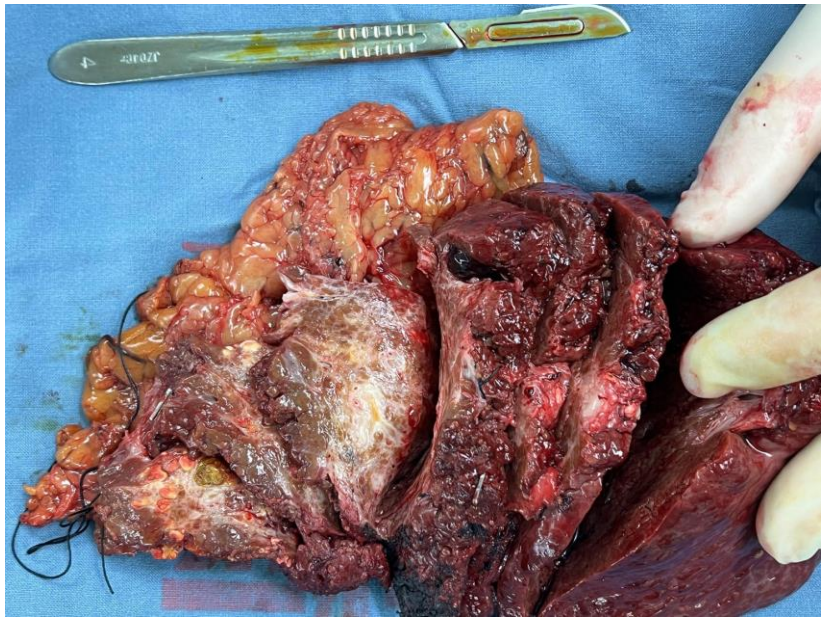
	5/16/2021	7/15/2021	8/10/2021	9/8/2021	10/6/2021	11/2/2021	11/30/2021	1/6/2022
PIVKA-II	53348	489	109	117	135	68	107	113

Case study provided by Prof. Sun for the purposes of this presentation.
AFP, alpha fetoprotein; PIVKA-II, protein induced by vitamin K absence-II.

Surgical Resection: 13 January 2022

Right hepatic lobectomy + resection of portal vein tumor thrombus
Pathology: HCC, major pathological response



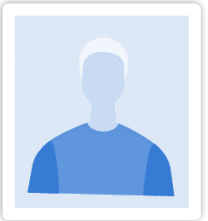


Case study provided by Prof. Sun for the purposes of this presentation.
HCC, hepatocellular carcinoma

Postoperative Treatment and Assessment

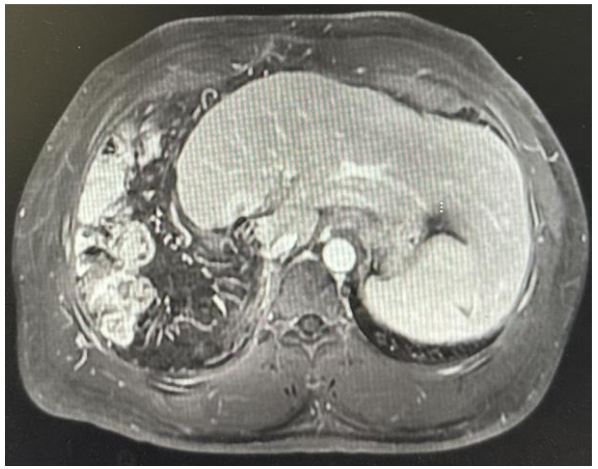
February 2022 to January 2023

- Adjuvant treatment with atezolizumab + bevacizumab



February 2023

- Atezolizumab + bevacizumab therapy was withdrawn for observation



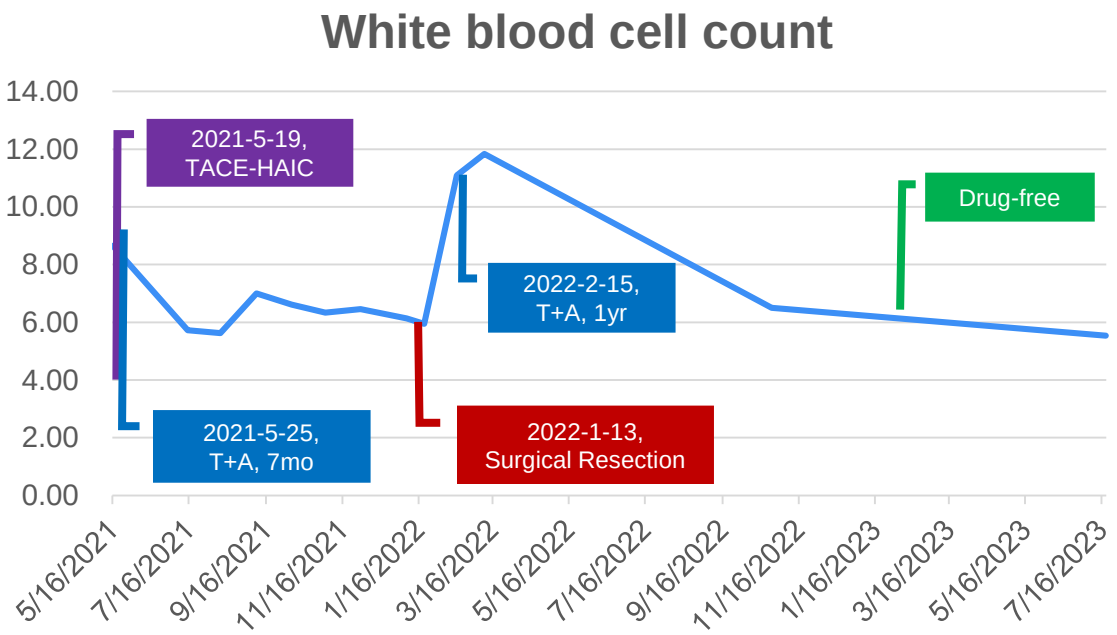
19 Jul 2023

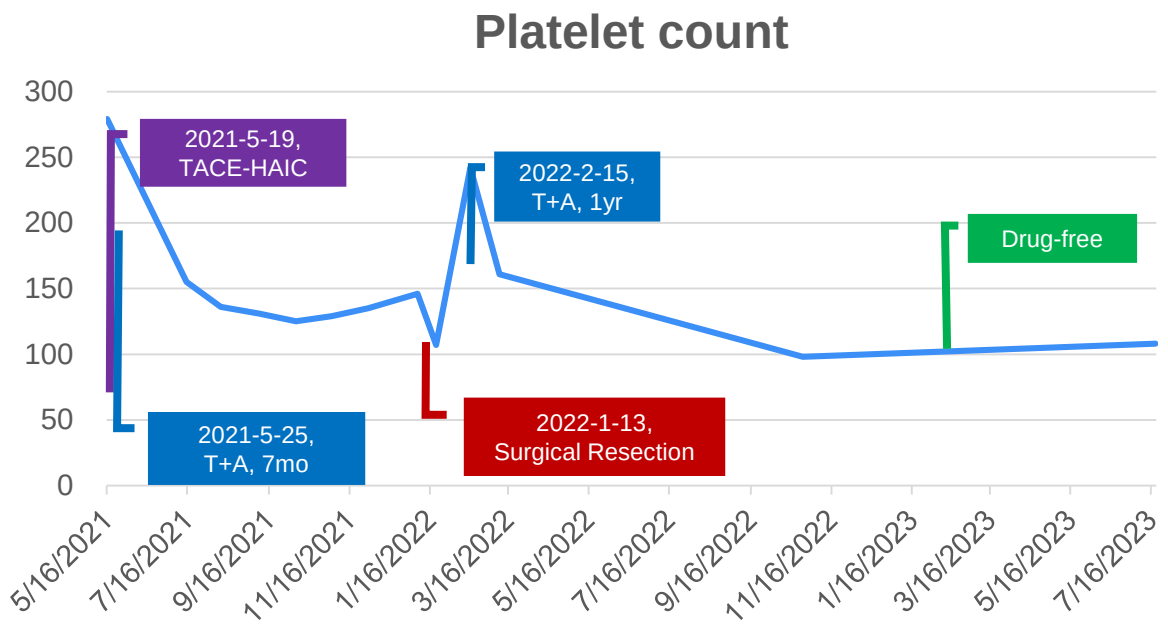
- **MRI:** No tumor recurrence
- **AFP:** 2.1 ng/mL
- **PIVKA-II:** 2.2 mAU/mL

Case study provided by Prof. Sun for the purposes of this presentation.
AFP, alpha fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; MRI, magnetic resonance imaging.

Safety

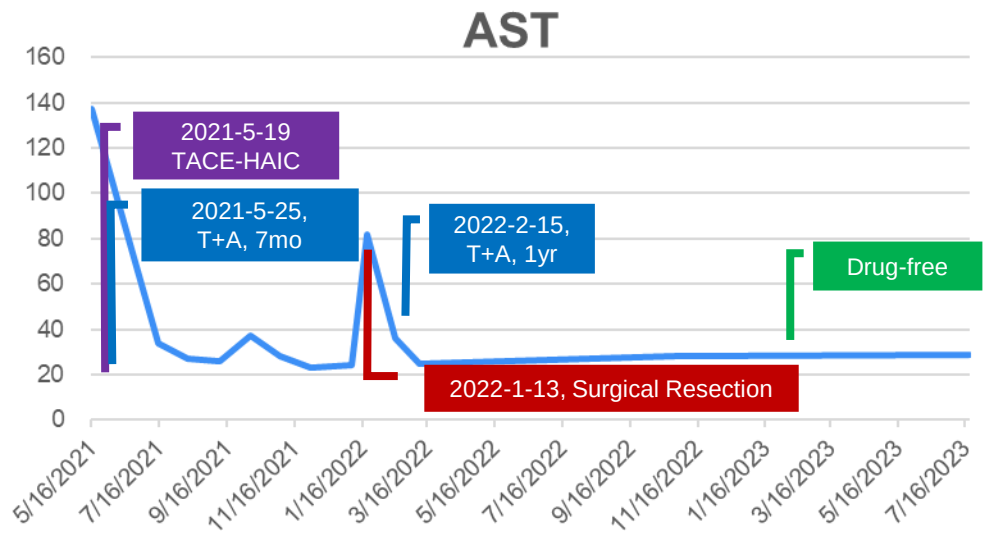
- During the perioperative period, only Grade 1 or 2 adverse events occurred;
- There were no Grade 3 or higher complications after surgical resection.

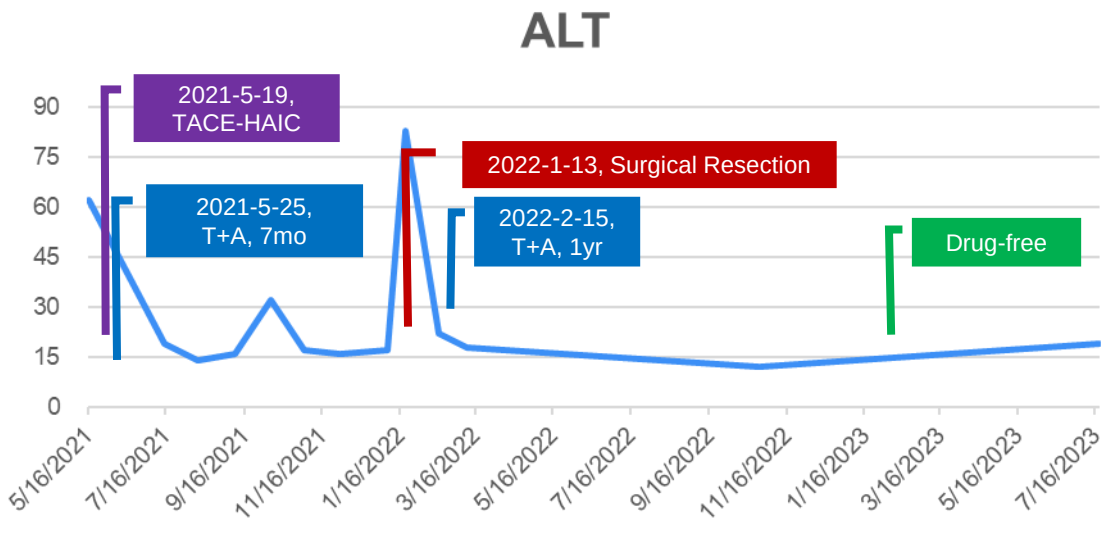


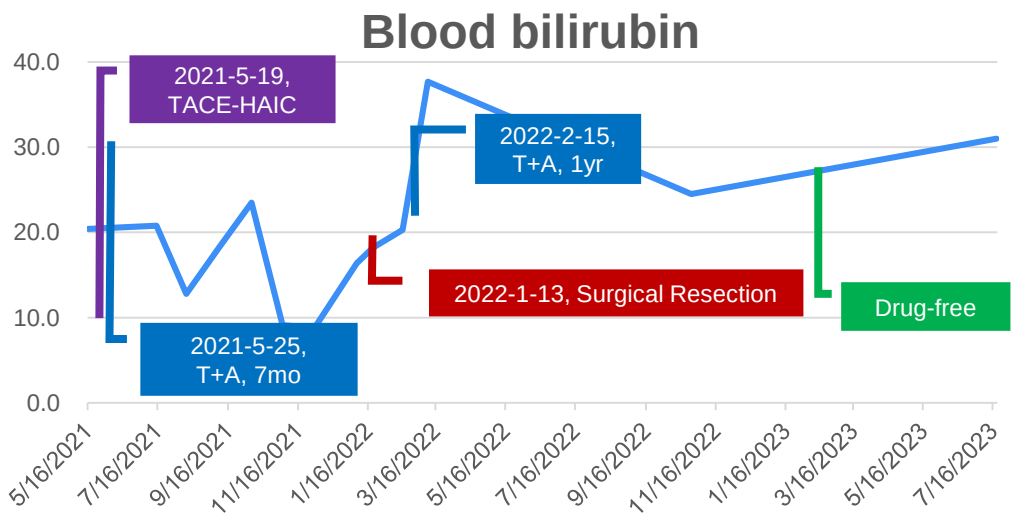


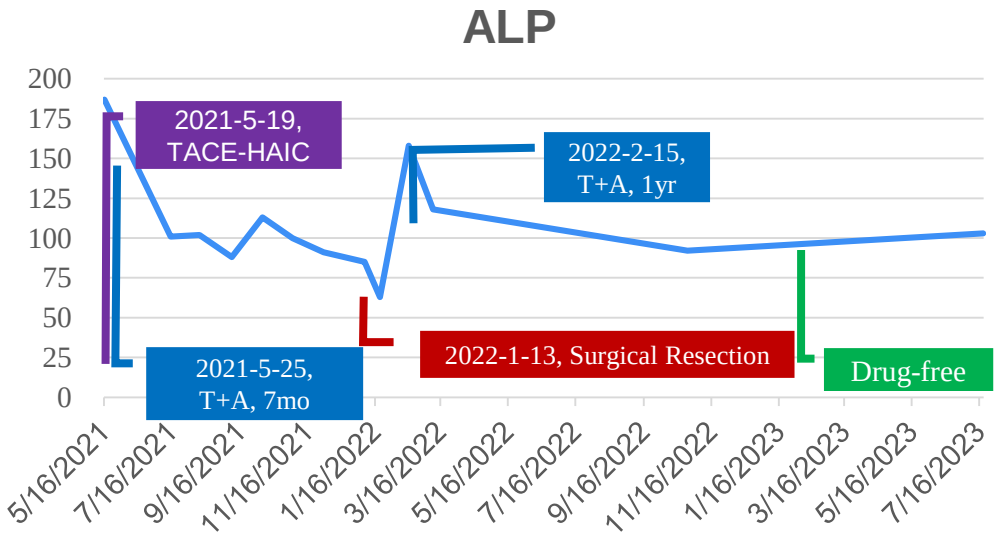
Case study provided by Prof. Sun for the purposes of this presentation.
AST, Aspartate transaminase; ALT, Alanine transaminase; ALP, Alkaline phosphatase.

Safety





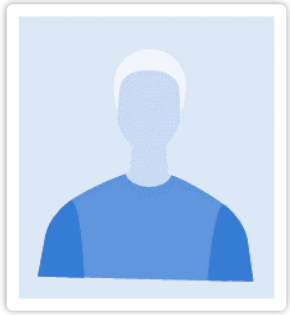




Case study provided by Prof. Sun for the purposes of this presentation.
AST, Aspartate transaminase; ALT, Alanine transaminase; ALP, Alkaline phosphatase.

Summary

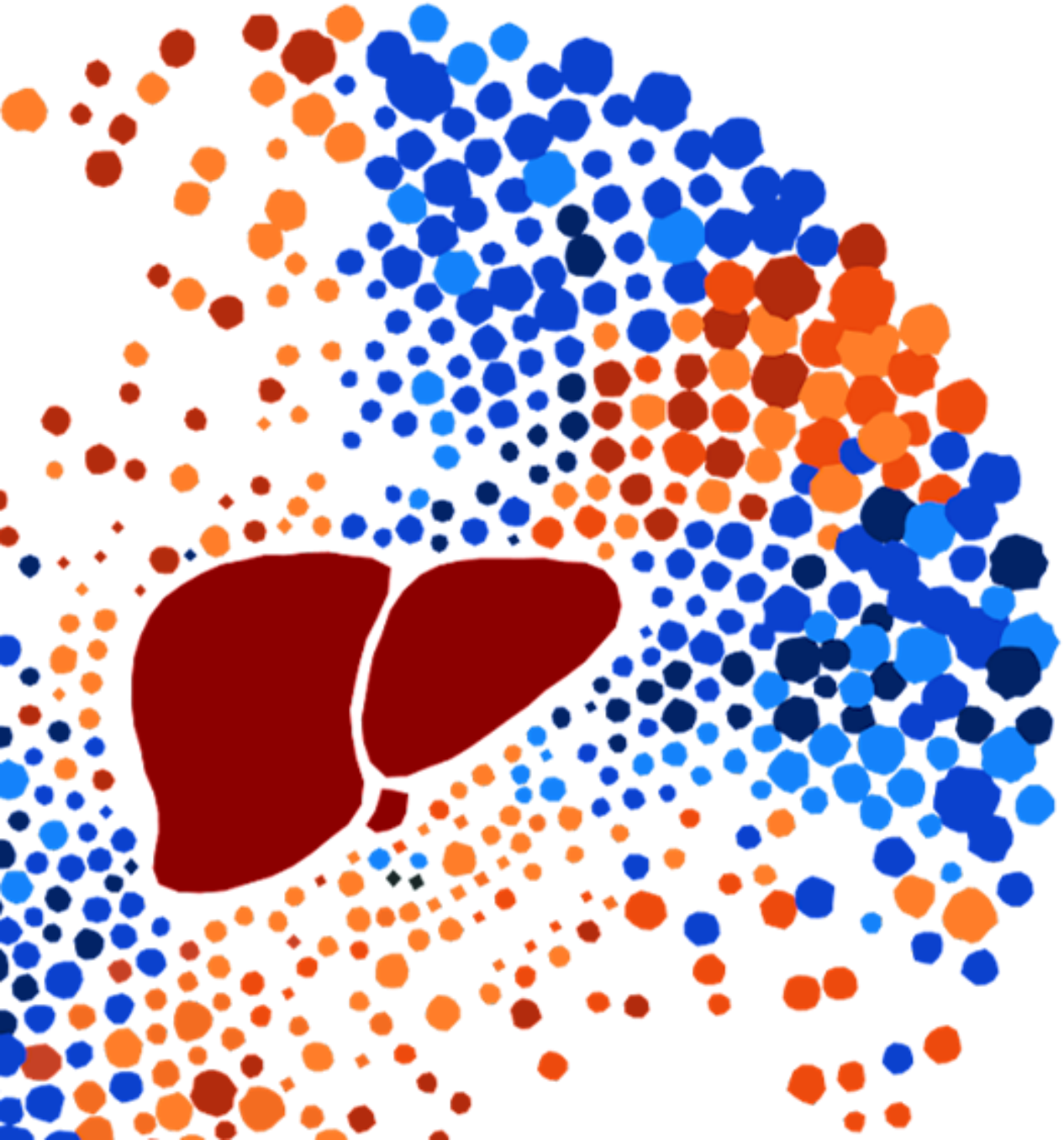
Male patient, with hepatitis B virus infection



- BCLC-C stage HCC, PVTT VP3, w/o extrahepatic metastasis
- TACE-HAIC was used once, followed by atezo + bev continuous treatment for 7 months
- Partial response per RECIST v1.1 & mRECIST
- surgical resection and the pathology was MPR
- Atezo + bev adjuvant therapy for one year, remains tumor free in 1.5 years
- No serious adverse events and liver function

OS >2.4 years, DFS >1.5 years, drug-free >9 mo

Case study provided by Prof Sun for the purposes of this presentation.
atezo, atezolizumab; bev, bevacizumab; DFS, disease-free survival; HAIC, hepatic artery-infusion chemotherapy; OS, overall survival; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MPR, major pathologic response; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; .



Case discussion: Adjuvant therapy, who and how?

Pierce Chow

Please participate in the polling!

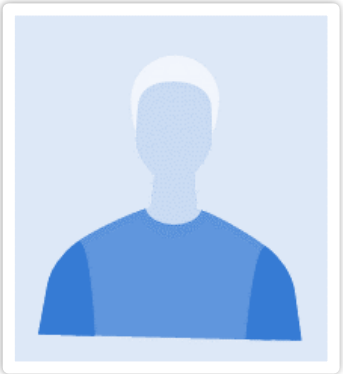
Scan the QR code to join directly

OR

go to
https://esmoasia23.cnf.io/
and
tap the session titled
"Roche - HCC illuminated: Exploring future frontiers with systemic immunotherapies"

Patient History

64- year-old gentleman, retired banker



- Known case of chronic Hep B, on Tenofovir
- Background liver cirrhosis and fatty liver
- With family history of Hep B +ve HCC

Oct Year 1 : On 6-monthly HCC surveillance program

- **US abdomen:** no suspicious lesion
- **AFP:** normal

Feb Year 2 : Visit 2

- **US abdomen:** hepatic steatosis; no suspicious lesion
- **AFP:** normal (2.7 ug/L)

Aug Year 2 : Visit 3

- **US abdomen:** no suspicious lesion
- **AFP:** 24.4 ug/L elevated up trending

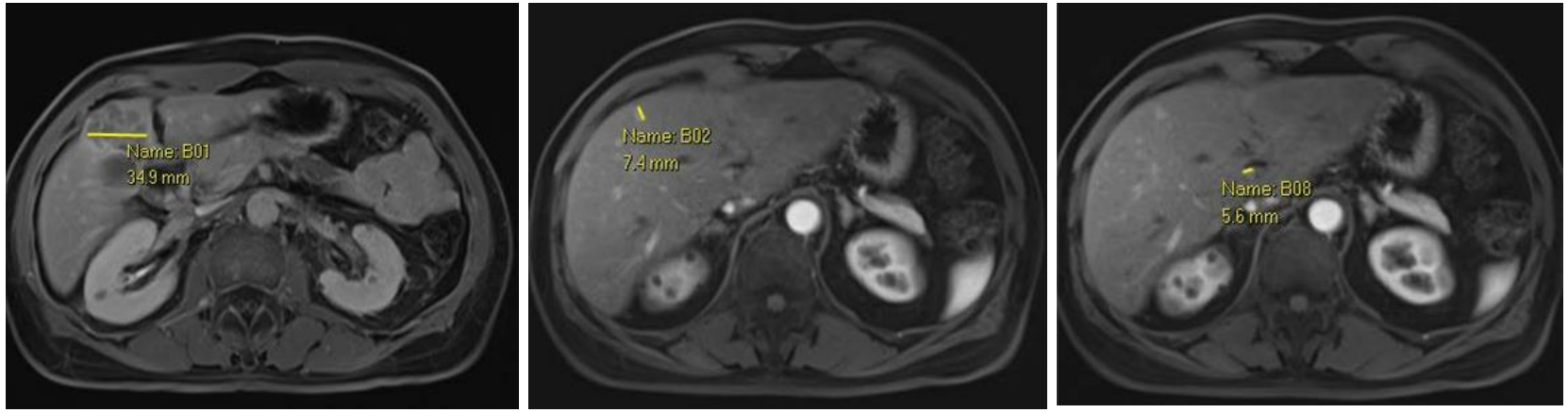
Case study provided by Prof. Chow for the purposes of this presentation.
AFP; alpha fetoprotein; Hep B; hepatitis B; US; ultrasound.

Investigation: August Year 2

MRI Liver was performed with Gadovist for further assessment

August Year 2

- **3.5cm Seg 4b/5** and **0.7cm Seg 8** lesions are suspicious for multifocal HCC
- 0.6cm Caudate enhancement indeterminate
- No extra-hepatic metastases



Case study provided by Prof. Chow for the purposes of this presentation.
PVTT, portal vein tumor thrombosis; MRI, magnetic resonance imaging.

Investigation: September Year 2

Case was discussed in the Comprehensive Liver Cancer Clinic, NCCS MDT discussion

- **Recommendation:** MRI with Primovist to adequately evaluate all the liver lesions including caudate lobe lesion

MRI Primovist:

- Seg 4B/5 HCC increase from 3.5 to 3.9cm, Seg 4A/8 HCC stable at 0.7cm.
- Caudate lobe lesion was not seen, likely perfusion anomalies.

Blood tests

- **AFP:** 24.4
- **LFT:** Normal
- **Child Pugh A**
- **ICG** @ 15min 15.0%

Liver Function Test		
Protein Total, serum	*	74
Albumin, serum	*	41
Bilirubin Total, serum	*	11
Alkaline Phosphatase, serum	*	94
Alanine Transaminase, serum	*	15
Aspartate Transaminase, serum	*	21
Routine		
Gamma-Glutamyl Transferase, serum	*	31
Special		
Alphafoeto Protein, serum	* ↑	24.4

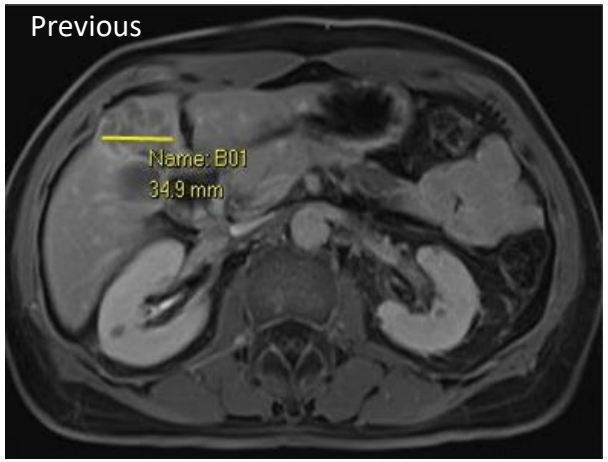
Case study provided by Prof. Chow for the purposes of this presentation.

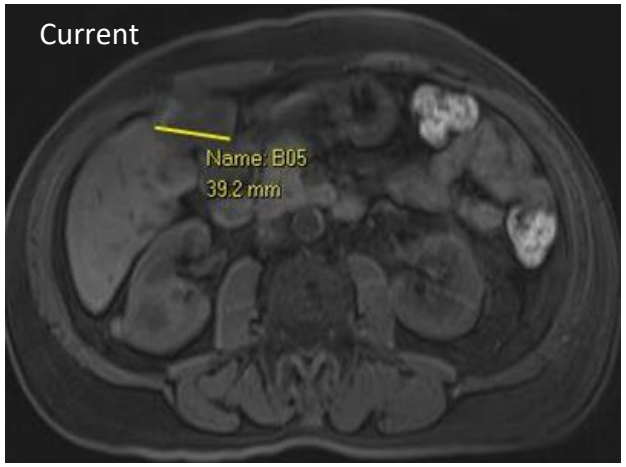
AFP, alpha fetoprotein; ICG, indocyanine green; LFT, liver function test; PVTT, portal vein tumor thrombosis; MRI, magnetic resonance imaging;

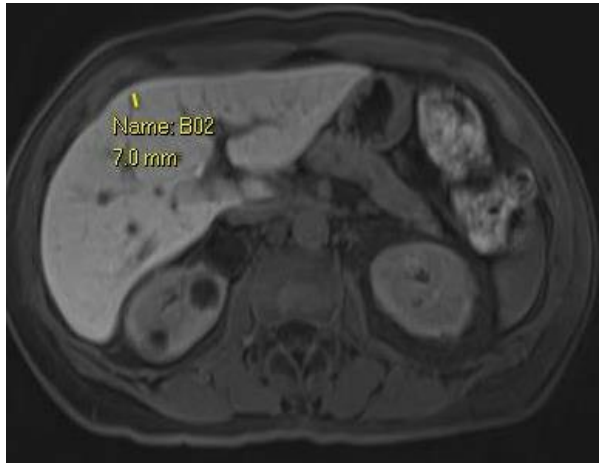
Investigation: September Year 2

MRI Primovist:

- Seg 4B/5 HCC increase from 3.5 to 3.9cm, Seg 4A/8 HCC stable at 0.7cm.
- Caudate lobe lesion was not seen, likely perfusion anomalies.



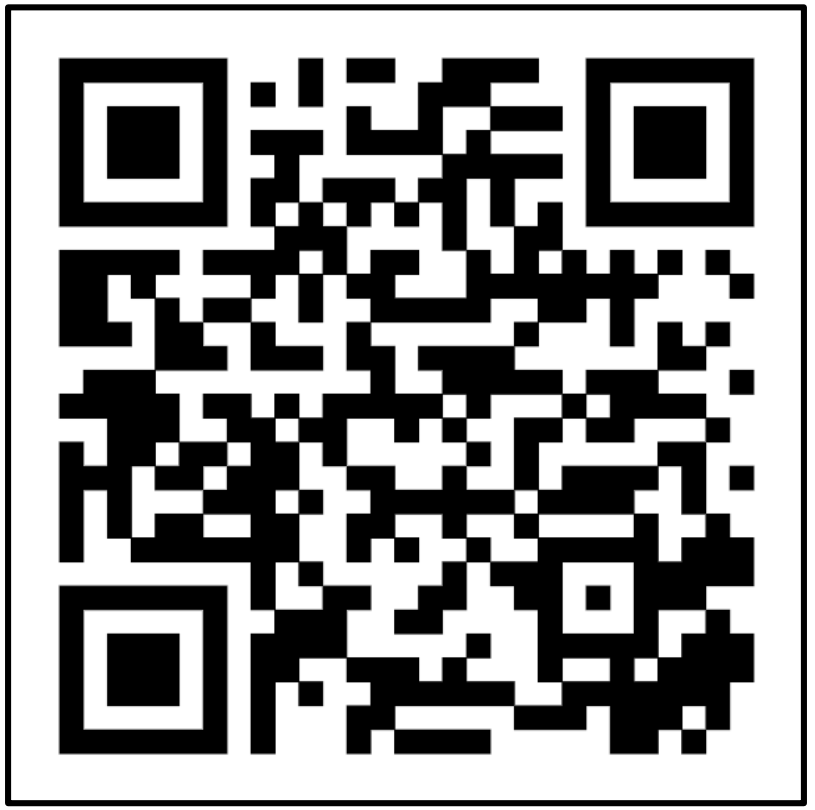




Case study provided by Prof Chow for the purposes of this presentation.
MRI, magnetic resonance imaging

What would be your initial treatment of choice for this patient?

1. **Resection of 3.9cm Seg 4b/5 + RFA of 0.7cm Seg 8 lesions**
2. **RFA/MWA of both lesions**
3. **TACE + RFA**
4. **SIRT with Y-90 + RFA**
5. **Liver transplantation**
6. **Systemic therapy**



Polling options may include treatments that are not approved in your jurisdiction and should not be considered as a recommendation that the product can be employed for indications other than those authorized.
RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; TKI, tyrosine kinase inhibitor; TACE, transarterial chemoembolization; MWA, microwave ablation.

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: What would be your initial treatment of choice for this patient?

Management and Follow-up: October Year 2

October Year 2

- **Surgical resection** of Seg 4b/5 HCC
- Segment 4A/8 7mm lesion : interventional radiologist unable to locate identify the lesion by intra-op CEUS
- Also unable to locate with intra-op ICG localization

Histology:

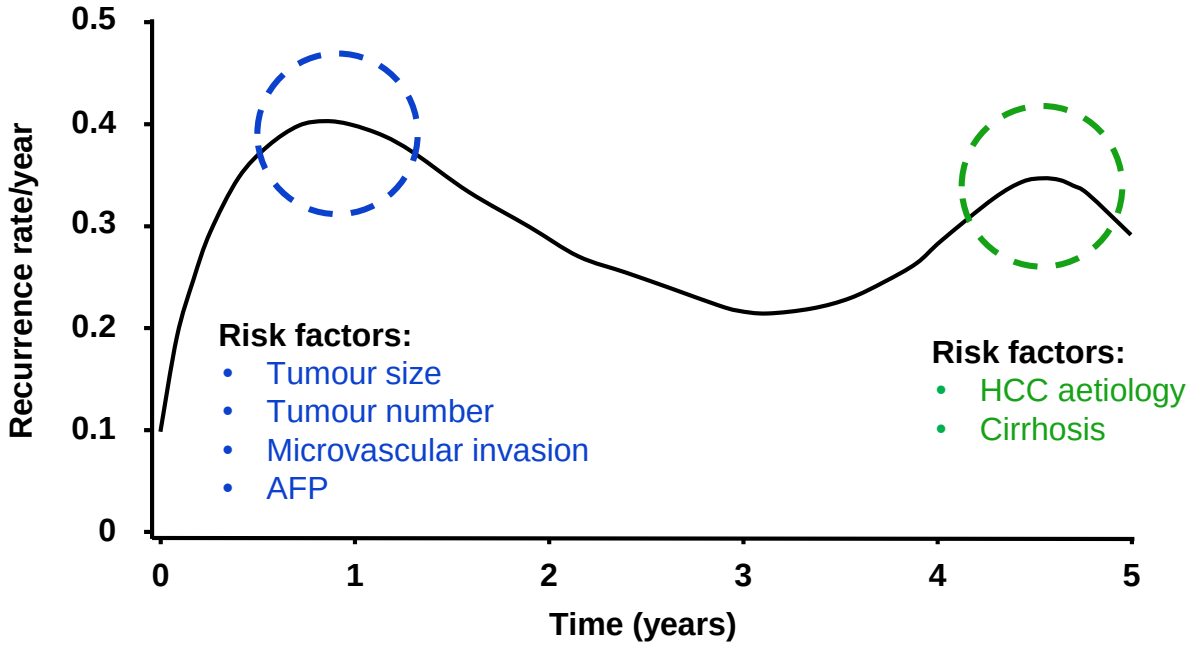
- Poorly differentiated (Edmondson grade 3) HCC
- 5.2cm in maximum dimension
- Microvascular invasion (pT2)
- Margins clear (R0 resection)

```
DIAGNOSIS
   (A) Liver, segment 4B and 5 tumour; wedge resection:
   Poorly differentiated (Edmondson grade 3) hepatocellular carcinoma (HCC);
    - measures 5.2cm in maximum dimension,
    - with vascular invasion (pT2),
    - 0.3cm away from hepatic resection margin,
    - background cirrhosis with chronic hepatitis B clinically.
```

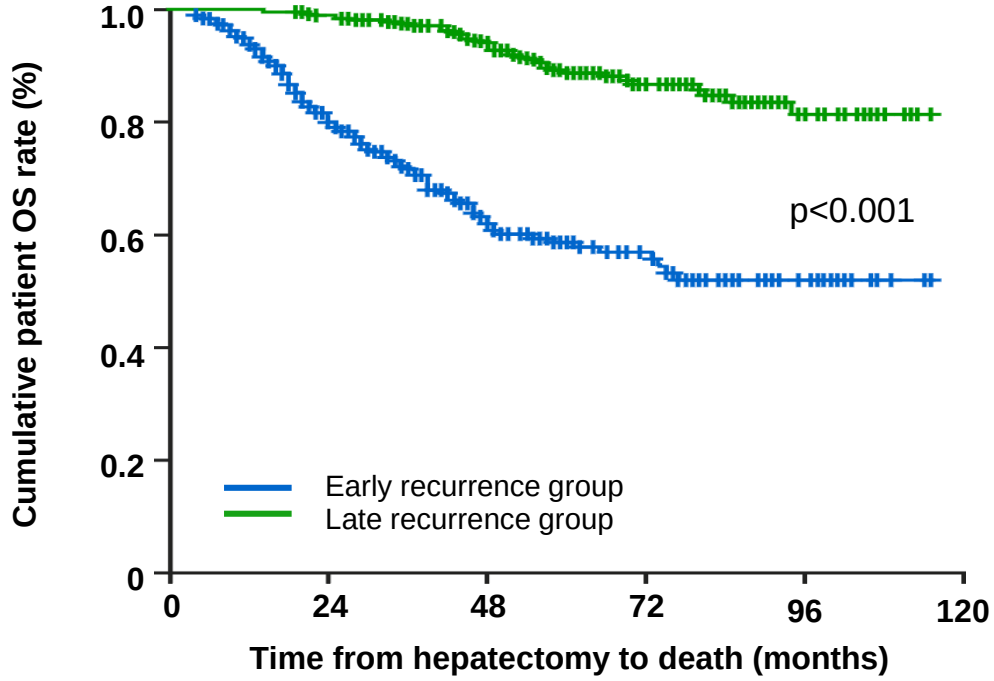
Case study provided by Prof. Chow for the purposes of this presentation.
CEUS, contrast enhanced ultrasound; ICG, indocyanine green; PVTT, portal vein tumor thrombosis; MRI, magnetic resonance imaging.

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

Estimated recurrence rate of HCC over time post-hepatectomy[1]



Cumulative patient survival rate post-hepatectomy[2]



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, representing an urgent unmet need[3]

1. Imamura et al. J Hepatol 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; 16(15):975–989.

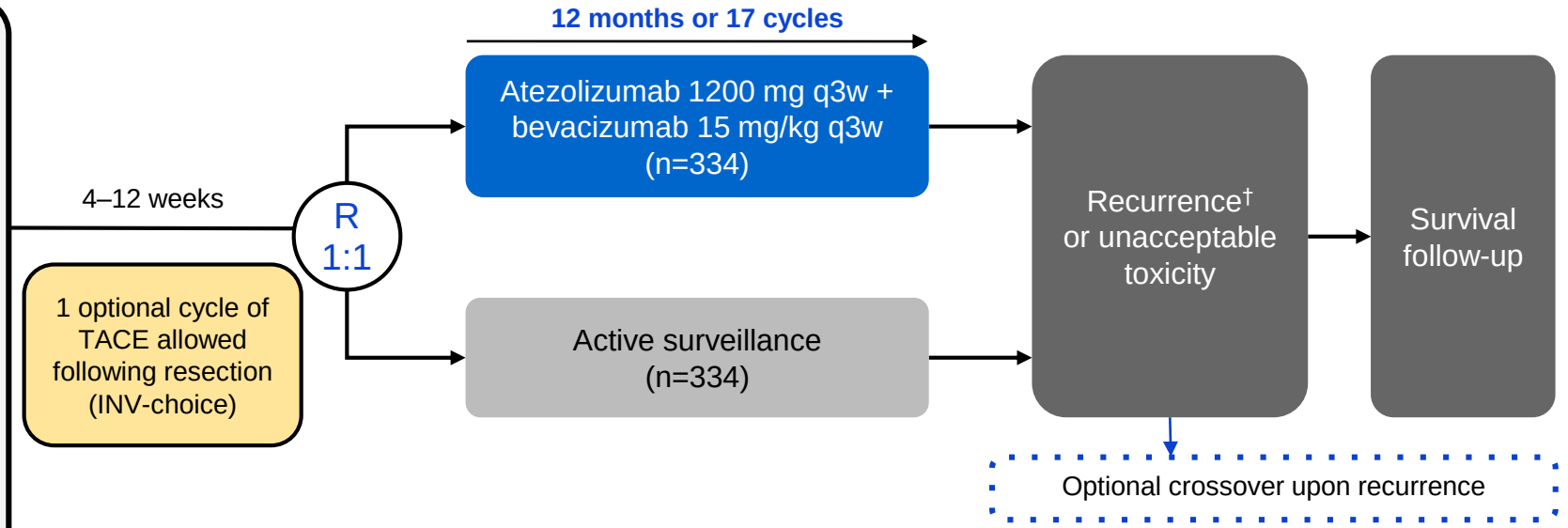
IMbrave050: study design[1]

Phase III, multicenter, randomized, open-label study

Key eligibility criteria:

- Confirmed first diagnosis of HCC who have undergone curative resection or ablation (complete resection or RFA/MWA)
  - R0 on pathology report (resection)
  - CR by imaging (ablation)
- Child-Pugh A
- High risk of recurrence*
- No extrahepatic spread or macrovascular invasion (except Vp1/Vp2)
- ECOG 0/1

(N=668)



Stratification:
- Region (APAC excl Japan vs RoW+Japan)
- High-risk features and procedures:
  - Ablation
  - Resection, 1 risk feature, adjuvant TACE (yes vs no)
  - Resection, 2+ risk features, adjuvant TACE (yes vs no)

Primary endpoint

- IRF-assessed RFS

Secondary endpoints

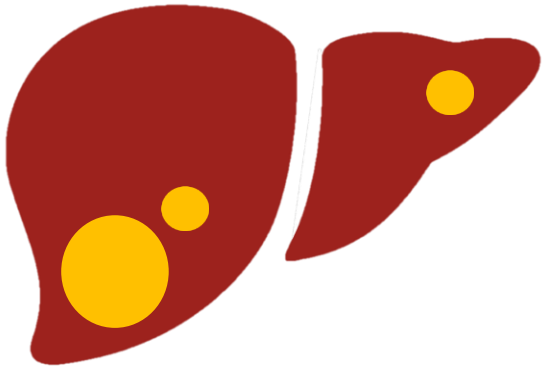
- OS
- INV-assessed RFS
- RFS and OS according to PD-L1 status
- Time to recurrence
- Time to EHS and/or MVI
- Safety

*High-risk features include: Tumor > 5 cm, >3 tumors, microvascular invasion, minor MVI (Vp1/Vp2) or G3/4 pathology.
†Per EASL criteria for intrahepatic lesions or RECIST for extrahepatic lesions.
ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; IRF, independent review facility; INV, investigator; MWA, microwave ablation; MVI, macrovascular invasion; OS, overall survival; PD-L1, programmed death-ligand 1; q3w, once every 3 weeks; RFA, radiofrequency ablation; RFS, recurrence-free survival; RoW, rest of the world; TACE, transarterial chemoembolization

1. Qin S et al. Lancet. 2023;402(10415):1835–1847.

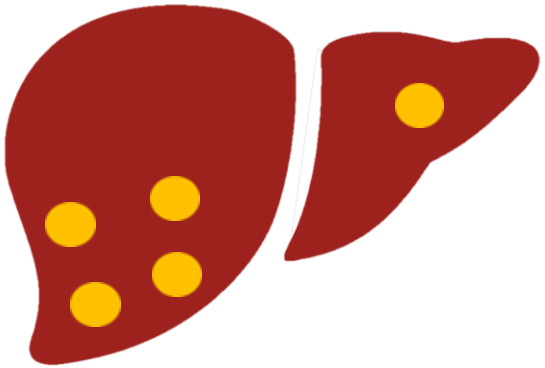
IMbrave050: Definition of ‘high-risk of early recurrence’ after resection[1]

Tumor size



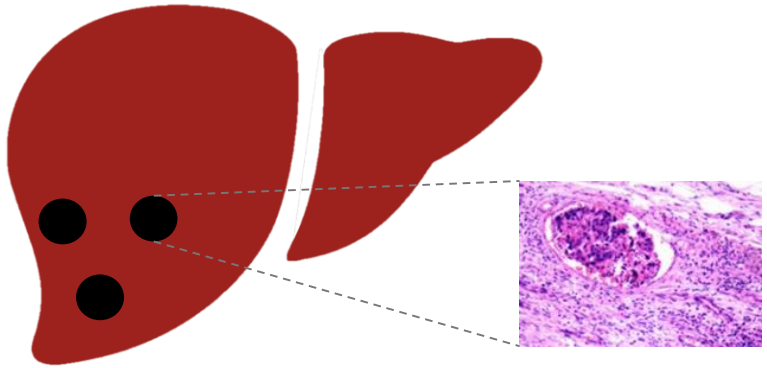
Largest tumor >5 cm
AND
≤3 tumors

Multiplicity



≥4 tumors
AND
largest tumor ≤5 cm

Clinicopathology

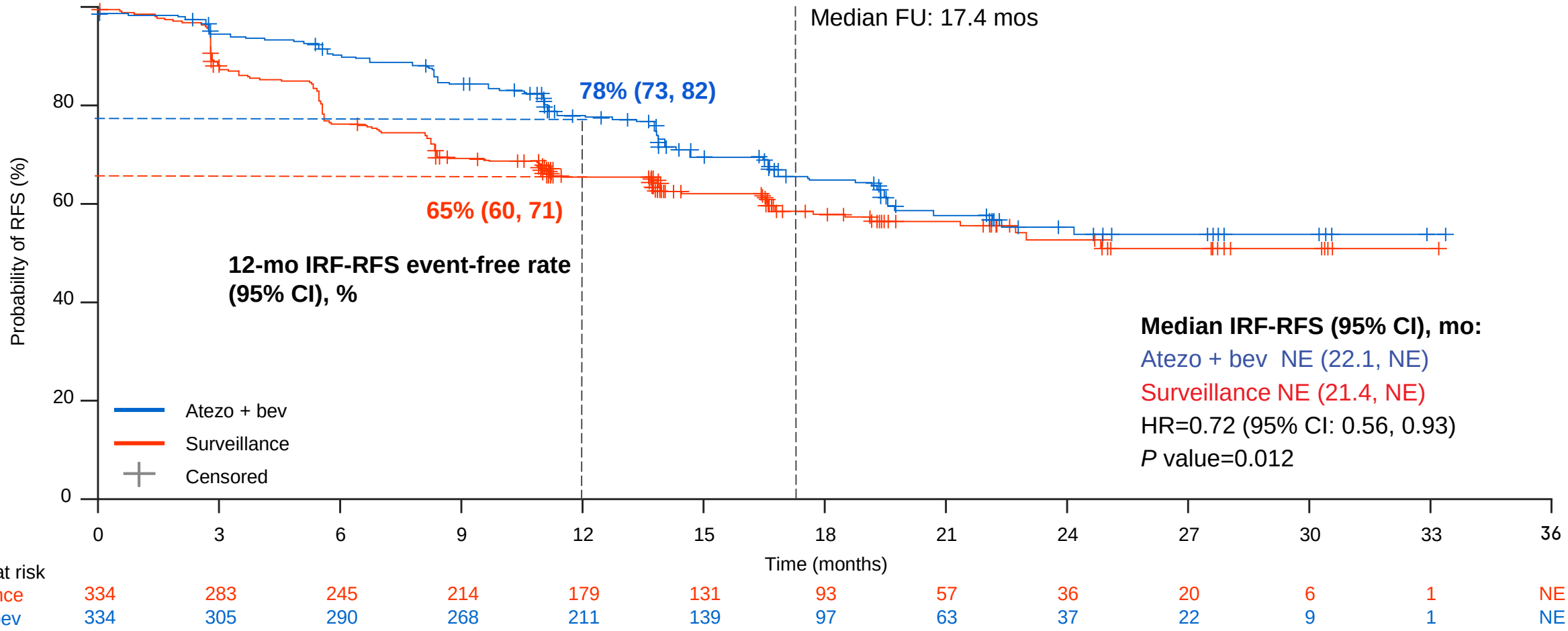


Vascular invasion* and/or poor tumor differentiation (Gr 3/4)
AND
largest tumor ≤5 cm
AND
≤3 tumors

*Microvascular invasion or minor macrovascular portal vein invasion of the portal vein—Vp1/Vp2.
Criteria based on published literature and feedback from clinical practice.
1. Qin S et al. Lancet. 2023;402(10415):1835–1847.

IMbrave050: IRF-assessed RFS[1]

Primary endpoint



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

CCOD: 21 October 2022. Minimum follow-up time: 10.8 months; 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

.1. Qin S et al. Lancet. 2023;402(10415):1835–1847.

What would be your post-surgery strategy?

1. **Close follow-up**

2. **Adjuvant immunotherapy (anti-PD-1/PD-L1 + anti-VEGF)**

Polling options may include treatments that are not approved in your jurisdiction and should not be considered as a recommendation that the product can be employed for indications other than those authorized.

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: What would be your post-surgery strategy?

Post-operation Follow-up: February Year 3

February Year 3 (3 months post-op)

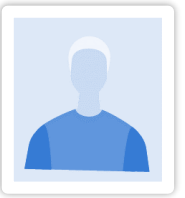
- **MRI Liver Primovist:** New innumerable bilobar hepatic lesions suspicious for multifocal HCC recurrence. For example:
- Largest Seg 8 (1.5 cm)
- Seg 7 (1.1 cm)
- Seg 2 (1.2 cm)

CT Thorax : lungs clear

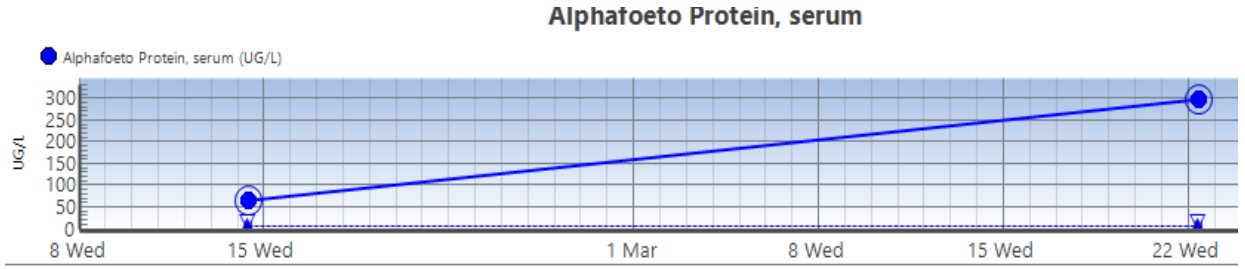
Bloods:

AFP uptrend elevated

13.2 → 63 → 298



Liver Function Test		
Protein Total, serum	*	74
Albumin, serum	* ↓	36
Bilirubin Total, serum	*	23
Alkaline Phosphatase, serum	* ↑	170
Alanine Transaminase, serum	*	28
Aspartate Transaminase, serum	* ↑	64
Special		
Alphafoeto Protein, serum	* ↑	298

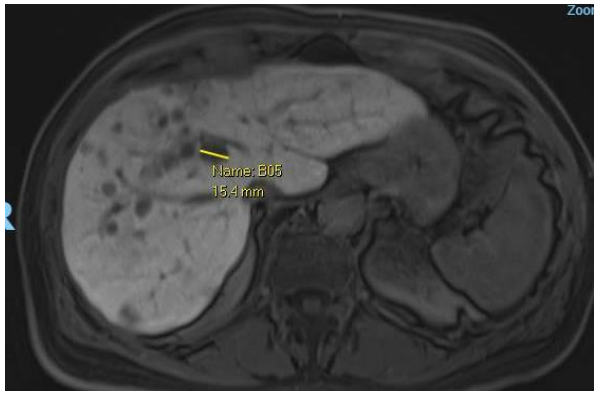


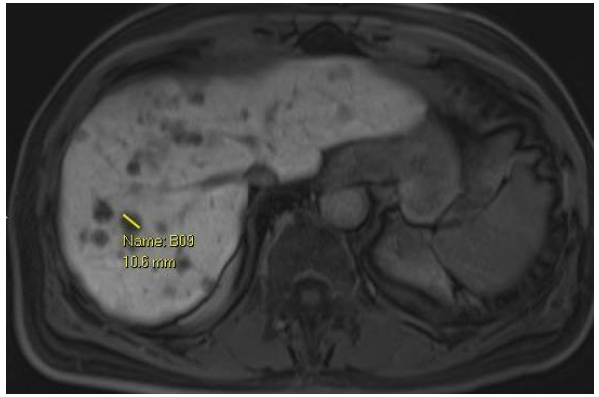
Case study provided by Prof. Chow for the purposes of this presentation.
AFP, alpha fetoprotein; CT, computerized tomography; MRI, magnetic resonance imaging.

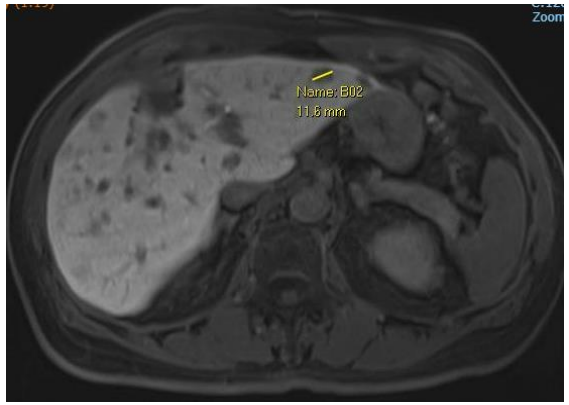
Post-operation Follow-up: February Year 3

February Year 3 (3 months post-op)

- **MRI Liver Primovist:** New innumerable bilobar hepatic lesions suspicious for multifocal HCC recurrence. For example:
- Largest Seg 8 (1.5 cm)
- Seg 7 (1.1 cm)
- Seg 2 (1.2 cm)
- No extra-hepatic metastases



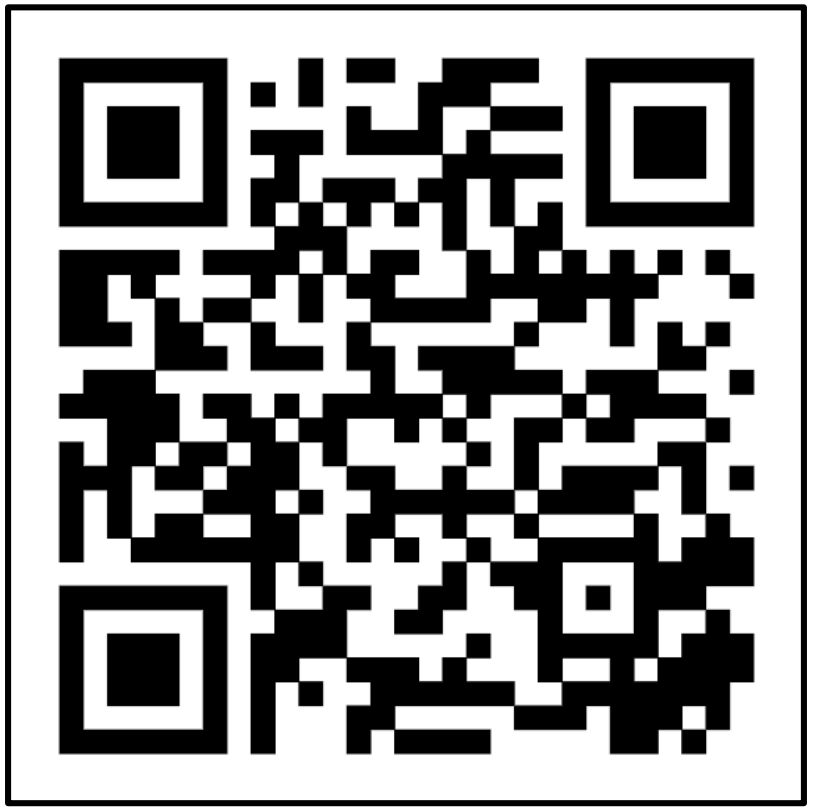




Case study provided by Prof Chow for the purposes of this presentation.
MRI, magnetic resonance imaging.

What would be your treatment option for this patient?

1. **TACE**
2. **SIRT with Y-90**
3. **Anti-PD-1/PD-L1 + anti-VEGF**
4. **Anti-PD-1/PD-L1 + anti-CTLA-4**
5. **TKI monotherapy**



Polling options may include treatments that are not approved in your jurisdiction and should not be considered as a recommendation that the product can be employed for indications other than those authorized.
SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor.

Live Content Slide

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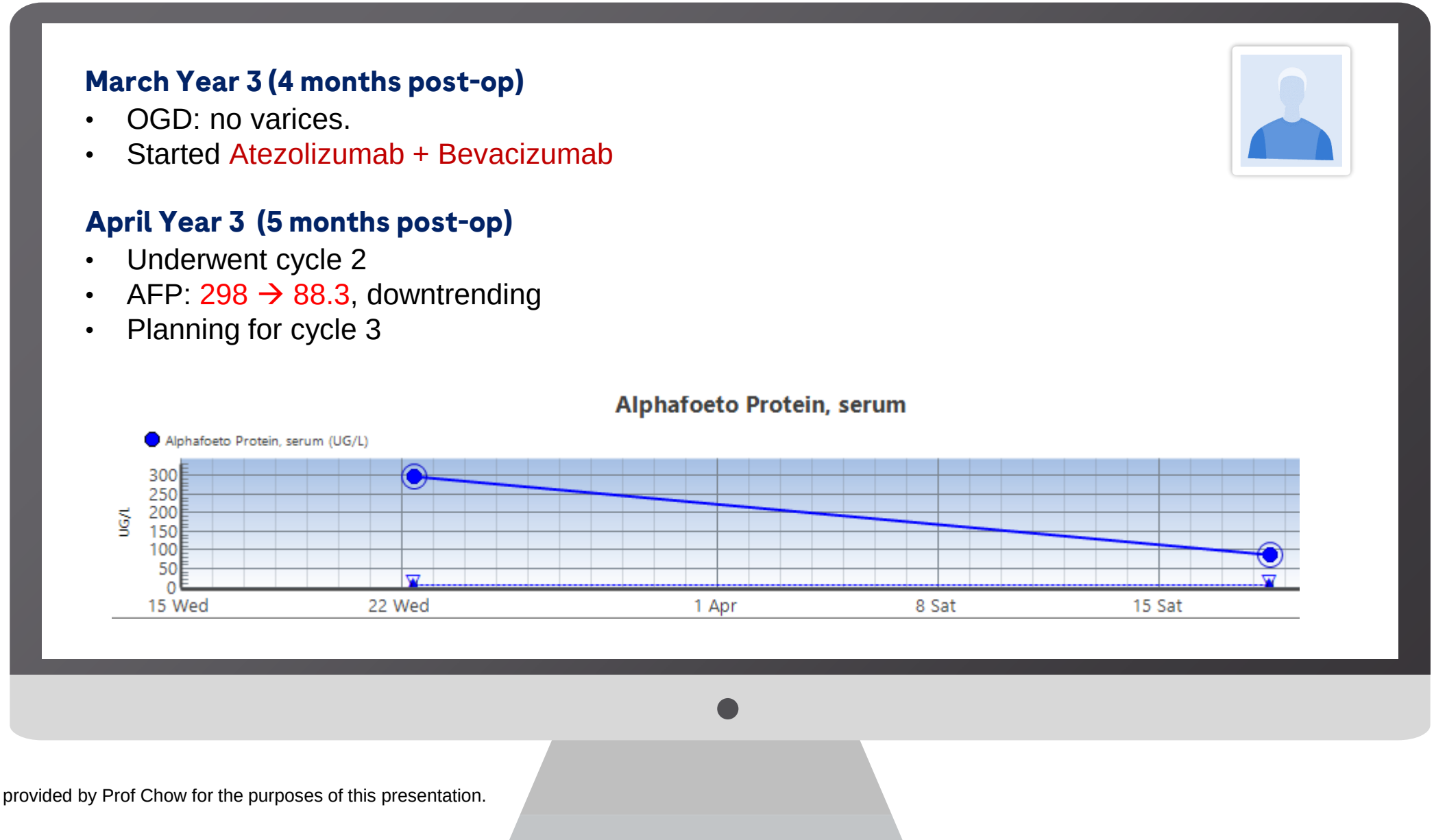
Poll: What would be your treatment option for this patient?

Post-operation Follow-up: February Year 3



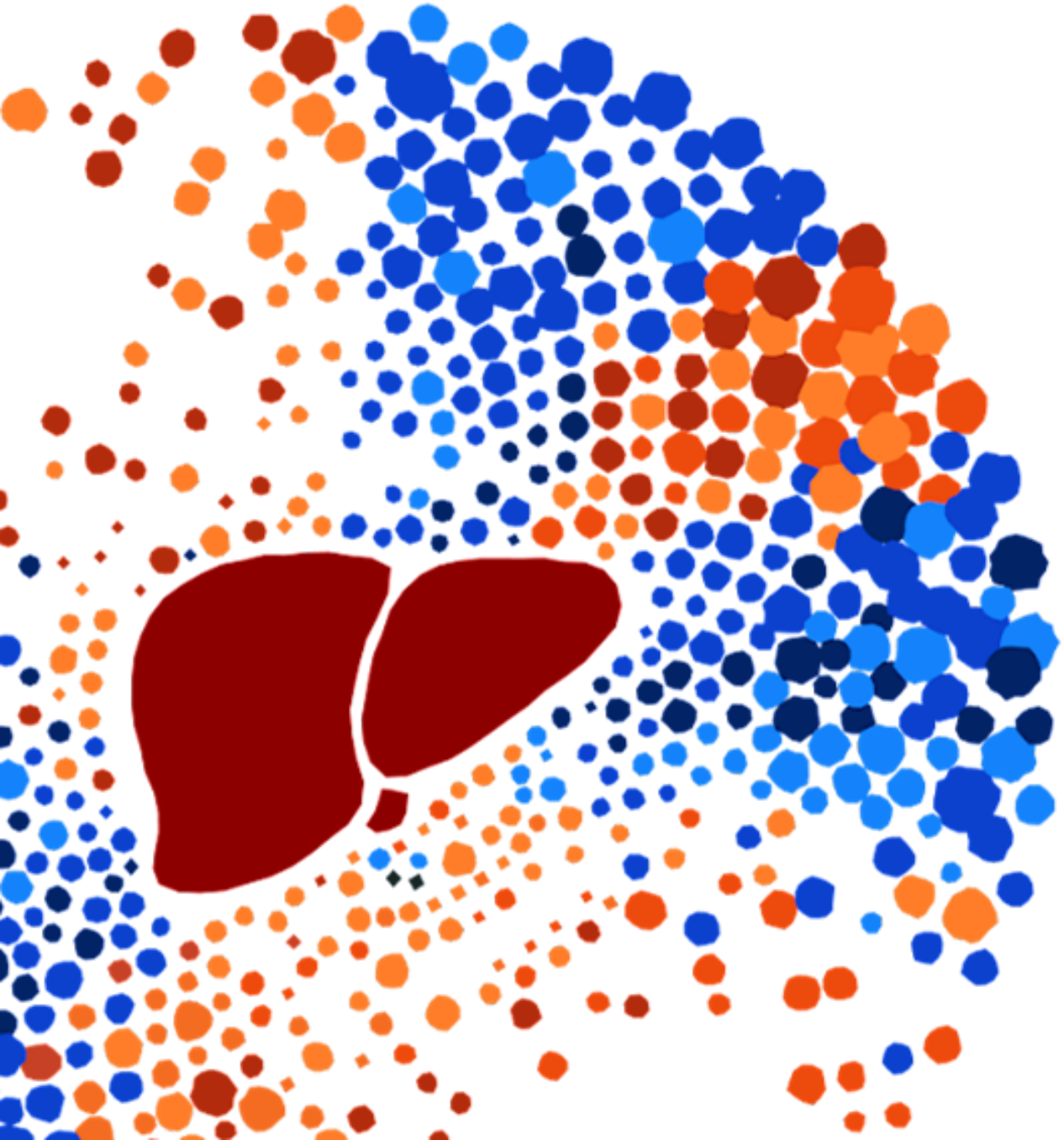
March Year 3 (4 months post-op)

- OGD: no varices.
- Started Atezolizumab + Bevacizumab

April Year 3 (5 months post-op)

- Underwent cycle 2
- AFP: 298 → 88.3, downtrending
- Planning for cycle 3

Case study provided by Prof Chow for the purposes of this presentation.



Audience Q&A / Closing Remarks

Han Chong Toh

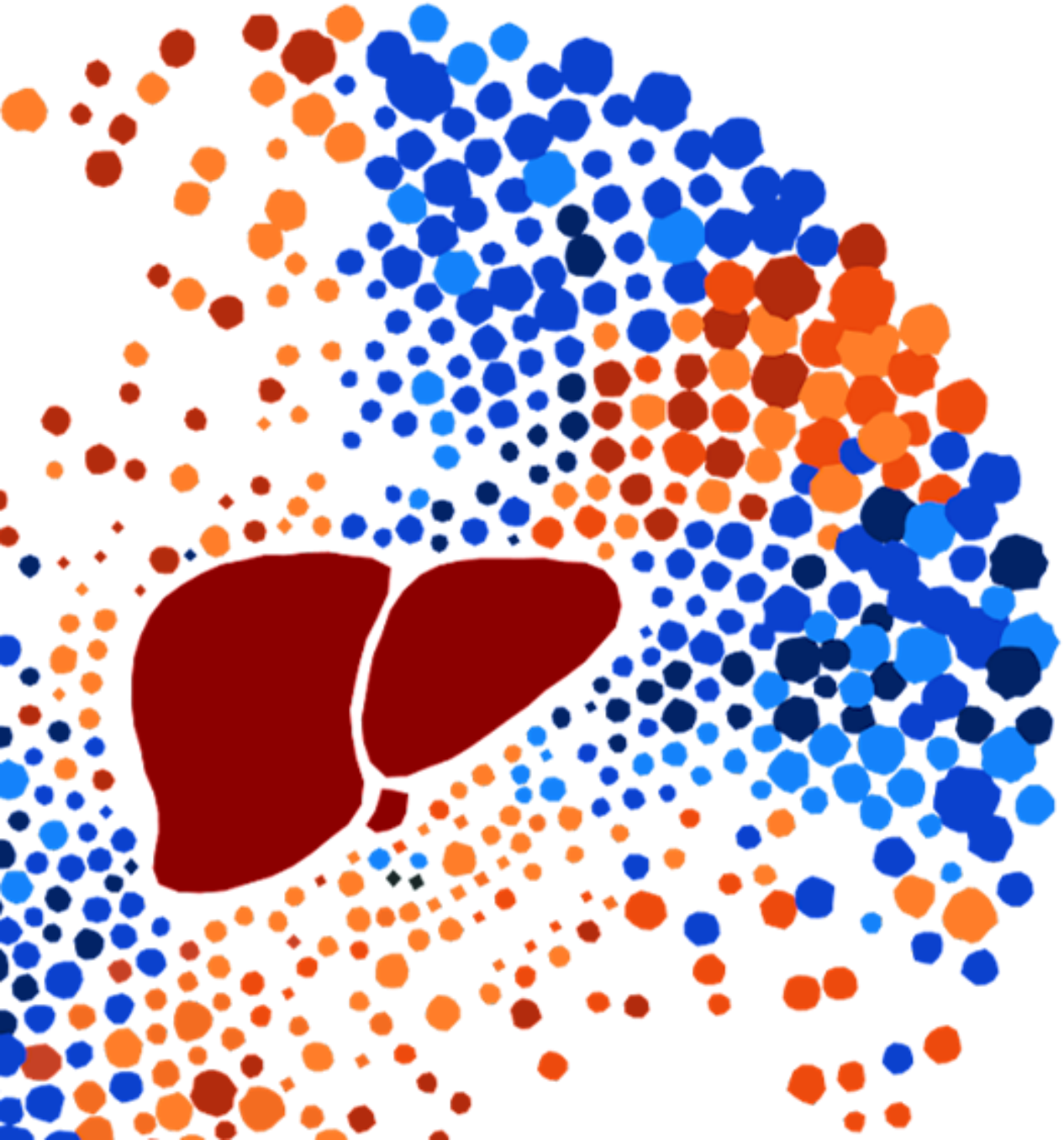
Key summary points

Combination immunotherapies, including atezolizumab and bevacizumab, have demonstrated **high response rates** and are now considered **standard of care** for patients with unresectable HCC. The role of immunotherapies continues to expand. Treatment decisions are likely to become more complex, requiring **MDT support**.

Most HCC patients are diagnosed at an advanced stage. **Downstaging conversion therapy** may provide patients with an opportunity for curative treatment (resection/ablation) and **prolong survival time for patients with advanced HCC**.

For **patients with HCC eligible for curative intent treatment**, surgical interventions remain the best opportunity for cure. However, **recurrent disease** still poses a **significant risk**. The **positive results of IMBrave050** has shown that immunotherapy can be an **efficacious adjuvant therapy in HCC**.

Research is ongoing to determine whether **combining systemic immunotherapy with locoregional therapy** can provide a better prognosis with minimal side effects for patients with HCC.



Come join us at our Roche Booth!

HCC “Meet The Expert”

17:15 – 18:00 SGT

Booth C101

Hui-Chuan Sun

Pierce Chow

Thank you for joining us!

Feedback

We aim to continuously improve your experience at our symposia, please provide your feedback using our evaluation form.