AdventHealth

HCC : *Immunotherapy & Beyond Review and Future Insights for Oncologist*

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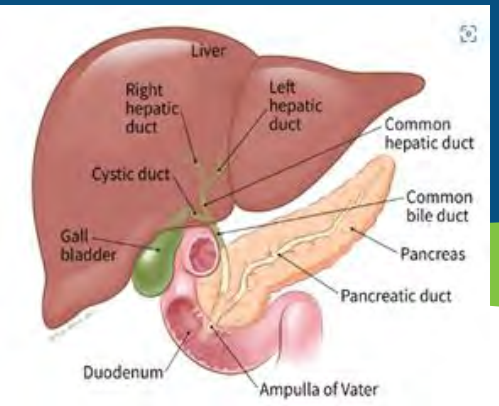
Associate Professor, School of Medicine University of Central Florida

Introduction

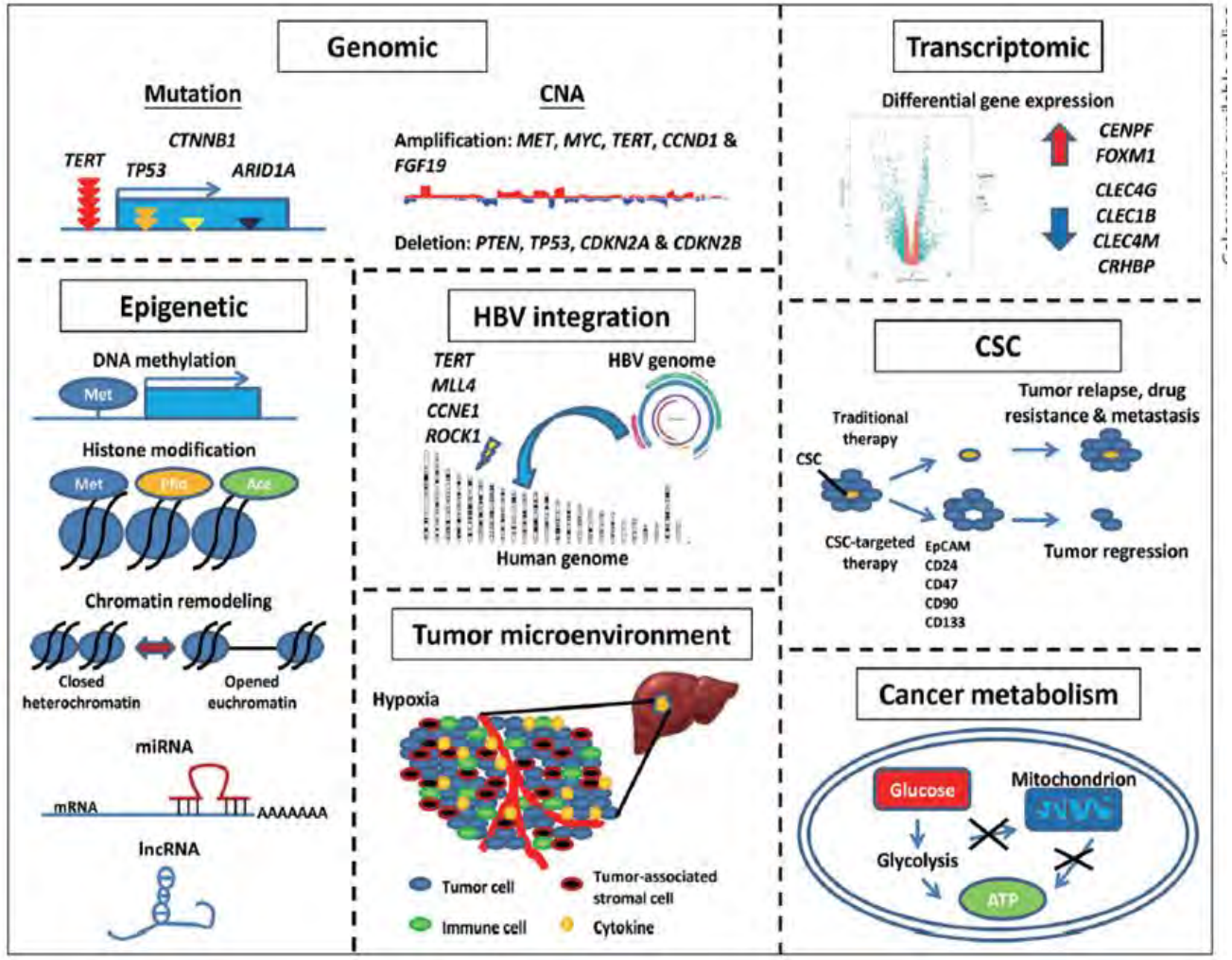


- In terms of HCC there is a global variation in the incidence , The complex etiology of the disease and its geographic distribution
- the American cancer society estimates for HCC cancer in the united states in 2023 :
  - About 41,210 new cases will be diagnosed, 29380 will loose the battle
  - The incidence has Tripled over last 4 decades
  - Estimated 5 year Survival is around to 20 % (5% in advanced HCC)
- A wide Heterogeneity in HCC:
  - Vital Hepatitis Related Ca Vs Non-Viral Cancer (NASH, Alcoholic Cirrhosis

Introduction

Patient Centered Care, Personalized treatment Options, Tumor Genomic Profiling

Key Events in Molecular Pathogenesis of HCC



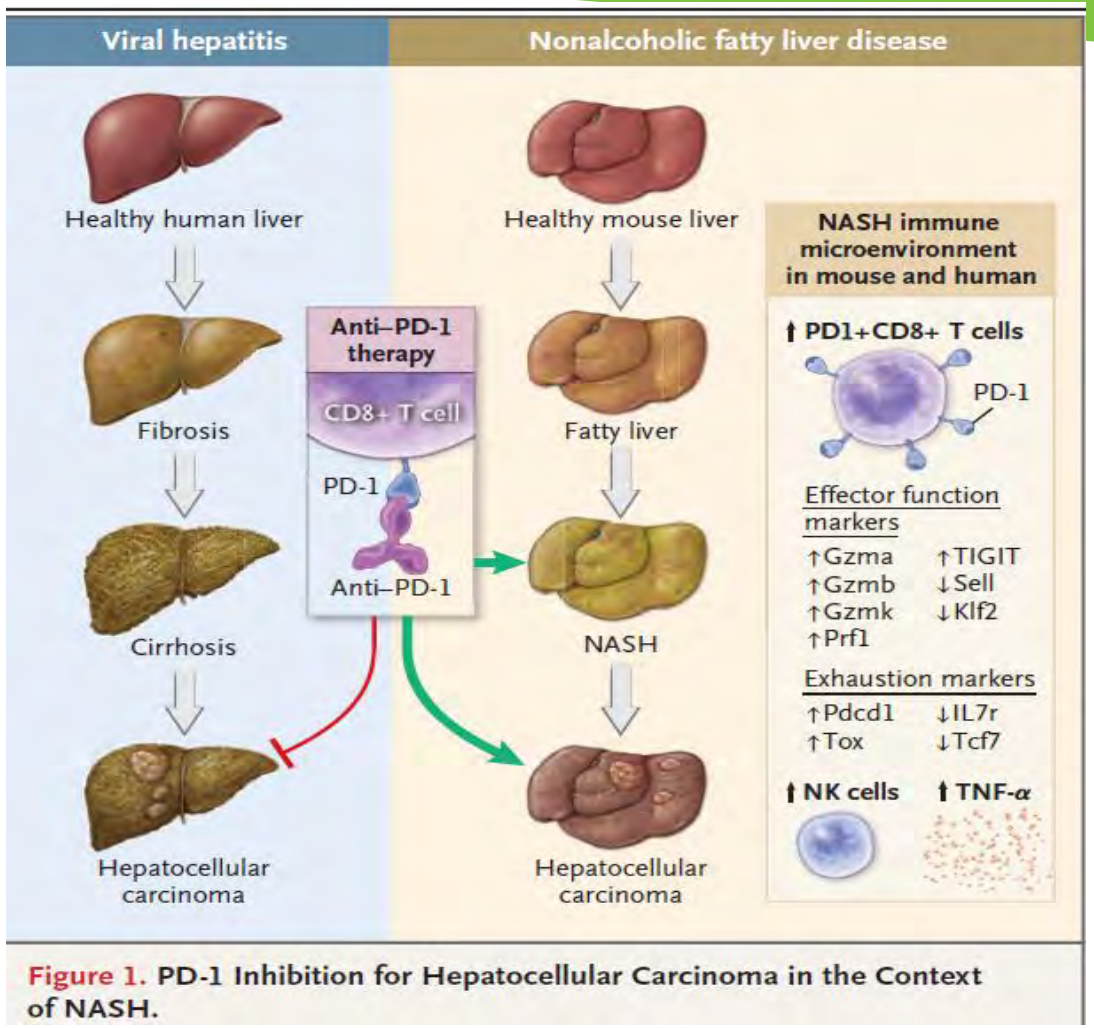


Figure 1. PD-1 Inhibition for Hepatocellular Carcinoma in the Context of NASH.

Treatment Options for HCC

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Hepatocellular Carcinoma

NCCN Guidelines Index
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CLINICAL PRESENTATION	TREATMENT[r,ll]	RESPONSE ASSESSMENT
Extrahepatic/metastatic disease; and deemed ineligible for resection, transplant, or locoregional therapy → Consider biopsy[p,r,s] (preferred) for histologic confirmation if not previously done	• Clinical trial • Systemic therapy[nn]	Assess for response and • Reconsider resection,[s] transplant, locoregional therapy or • Subsequent-line systemic therapy if progression on or after systemic therapy[nn]
	• Best supportive care[oo]	

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Hepatocellular Carcinoma

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PRINCIPLES OF SYSTEMIC THERAPY[a,b,c]

First-Line Systemic Therapy

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Atezolizumab + bevacizumab (category 1)[d,e,f,1] • Tremelimumab-actl + durvalumab (category 1)[e,2]	• Durvalumab (category 1)[e,2] • Lenvatinib (category 1)[3,4] • Sorafenib (category 1)[5,6] • Tislelizumab-jsgr (category 1)[e,7] • Pembrolizumab (category 2B)[e,8]	• For *NTRK* gene-fusion positive tumors: ‣ Repotrectinib (category 2B)[9]

Subsequent-Line Systemic Therapy if Disease Progression[g,h,i]

Options	Other Recommended Regimens	Useful in Certain Circumstances
• Cabozantinib (category 1)[12] • Regorafenib (category 1)[13] • Lenvatinib • Sorafenib	• Nivolumab + ipilimumab[e,j,14-16] • Pembrolizumab[e,k,l,m,17-19]	• Ramucirumab (AFP ≥400 ng/mL) (category 1)[20] • Nivolumab[e,k,l,21-24] • For MSI-H/dMMR tumors ‣ Dostarlimab-gxly (category 2B)[e,k,l,n,25] • For *RET* gene fusion-positive tumors: ‣ Selpercatinib (category 2B)[26]

IMbrave150: updated overall survival data from a global, randomized, open-label Phase III study of atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma

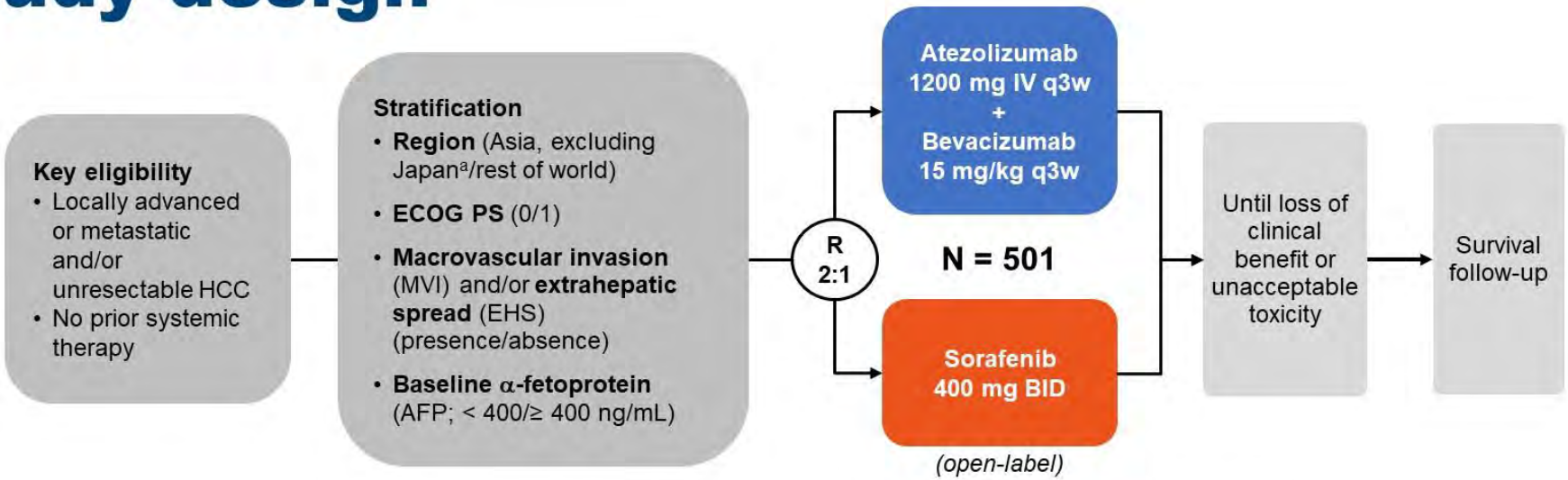
Finn RS,[1] Qin S,[2] Ikeda M,[3] Galle PR,[4] Ducreux M,[5] Kim T-Y,[6] Lim HY,[7] Kudo M,[8] Breder V,[9] Merle P,[10] Kaseb A,[11] Li D,[12] Verret W,[13] Shao H,[14] Liu J,[14] Li L,[14] Zhu AX,[15] Cheng AL[16]

[1]Jonsson Comprehensive Cancer Center, Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]People's Liberation Army Cancer Center, 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]Seoul National University College of Medicine, Seoul, Korea; [7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [8]Kindai University Faculty of Medicine, Osaka, Japan; [9]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [10]University 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]Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [16]National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan

PRESENTED AT: Gastrointestinal Cancers Symposium

#GI21

Study design



Primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary efficacy endpoints
- IRF-assessed ORR and DOR per RECIST 1.1
- IRF-assessed ORR and DOR per HCC mRECIST

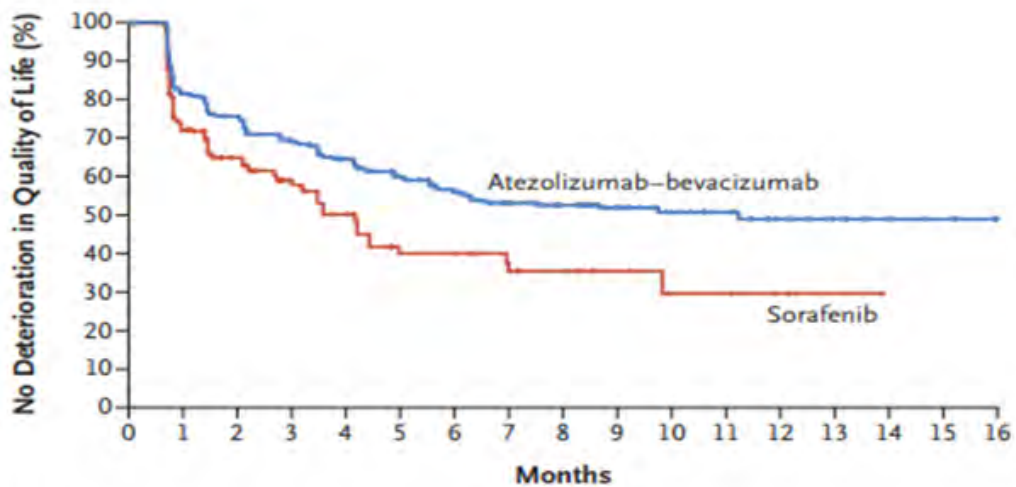
Chinese cohort:
137 Chinese patients who were included in the global study population/analysis +
57 additional Chinese patients who were enrolled in the China extension cohort and were not included in the global population/analysis

BID, twice a day; q3w, every 3 weeks; [a] Japan is included in rest of world.

Finn RS, et al. *N Engl J Med* 2020.

ORIGINAL ARTICLE

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma



	Quality of Life — Median Time to Deterioration (95% CI)
	mo
Atezolizumab–Bevacizumab	11.2 (6.0–NE)
Sorafenib	3.6 (3.0–7.0)

Hazard ratio, 0.63 (95% CI, 0.46–0.85)

No. at Risk

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

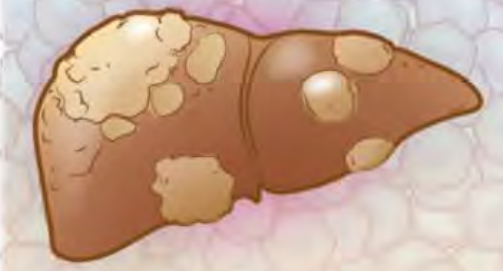
Figure 2. Kaplan–Meier Analysis of Time to Deterioration of Quality of Life.

Shown are Kaplan–Meier estimates of the time to deterioration in quality of life in the intention-to-treat population. Tick marks indicate censored data.

The NEW ENGLAND JOURNAL of MEDICINE

Atezolizumab + Bevacizumab for Hepatocellular Carcinoma

PHASE 3, OPEN-LABEL, MULTICENTER, RANDOMIZED TRIAL



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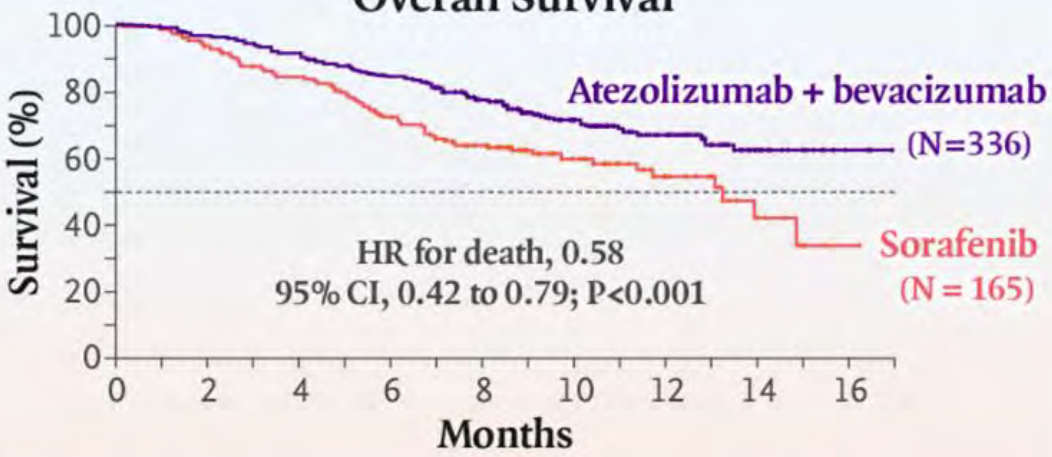
Patients with locally advanced hepatocellular carcinoma (metastatic, unresectable, or both)



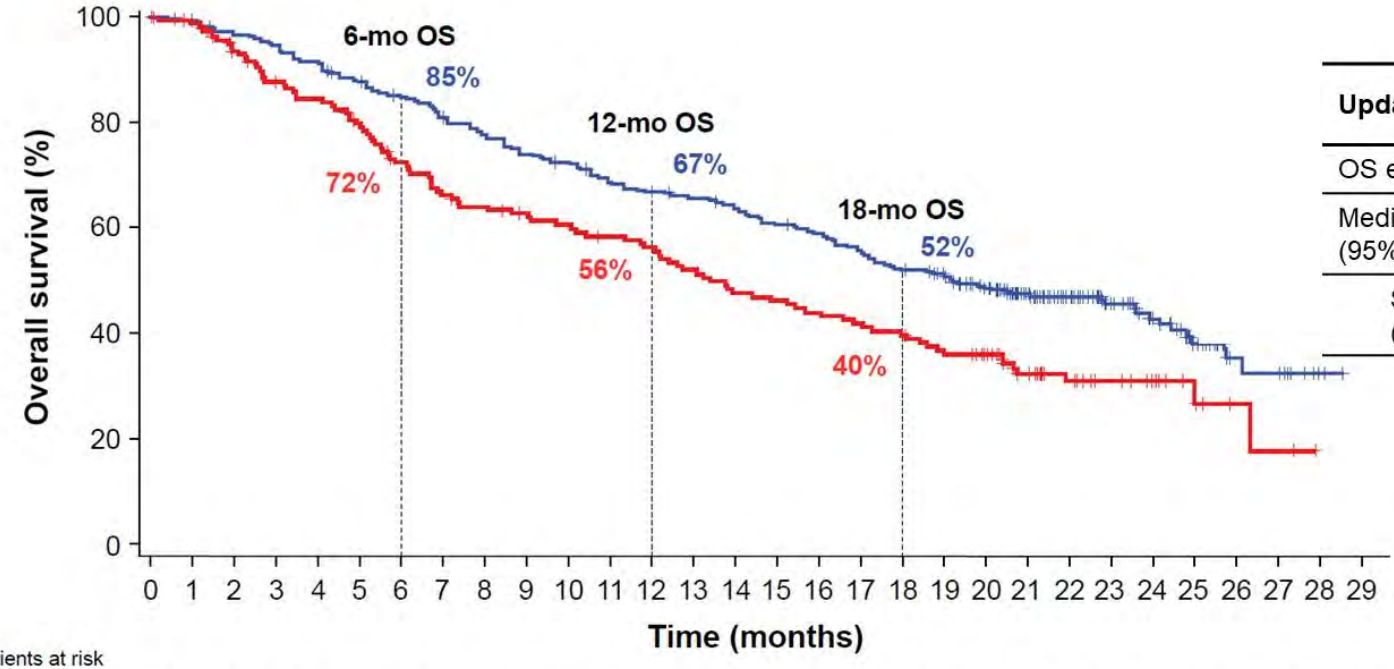
Median progression-free survival

Atezolizumab + bevacizumab	Sorafenib
6.8 Mo	4.3 Mo

HR for disease progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001

R.S. Finn et al. 10.1056/NEJMoa1915745

Updated OS



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

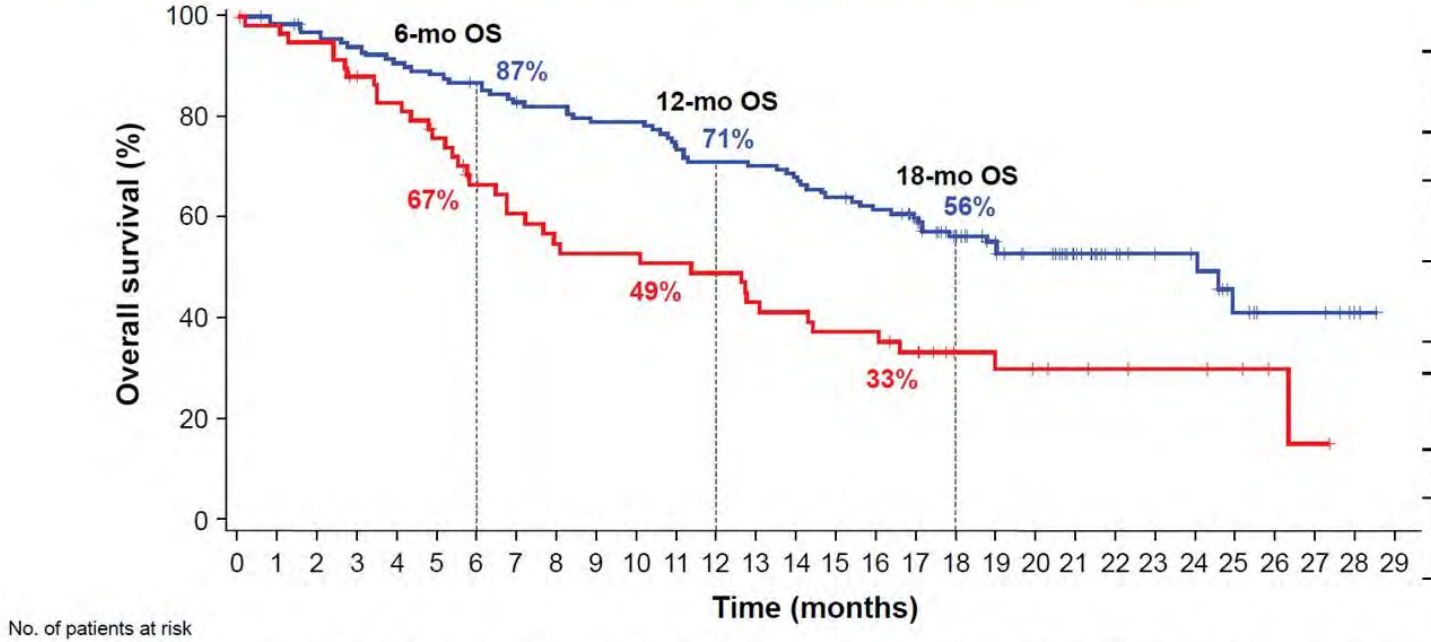
No. of patients at risk

Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.

[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

China cohort updated OS



Updated OS	Atezo + Bev (n = 133)	Sorafenib (n = 61)
OS events, n (%)	61 (46)	38 (62)
Median OS, mo (95% CI)	24.0 (17.1, NE)	11.4 (6.7, 16.1)
Stratified HR (95% CI)[a]	**0.53** (0.35, 0.80)	
Primary OS		
OS events, n (%)	26 (20)	25 (41)
Median OS, mo (95% CI)	**NE** (13.5, NE)	**11.4** (6.7, NE)
Stratified HR (95% CI)[a]	**0.44** (0.25, 0.76)	

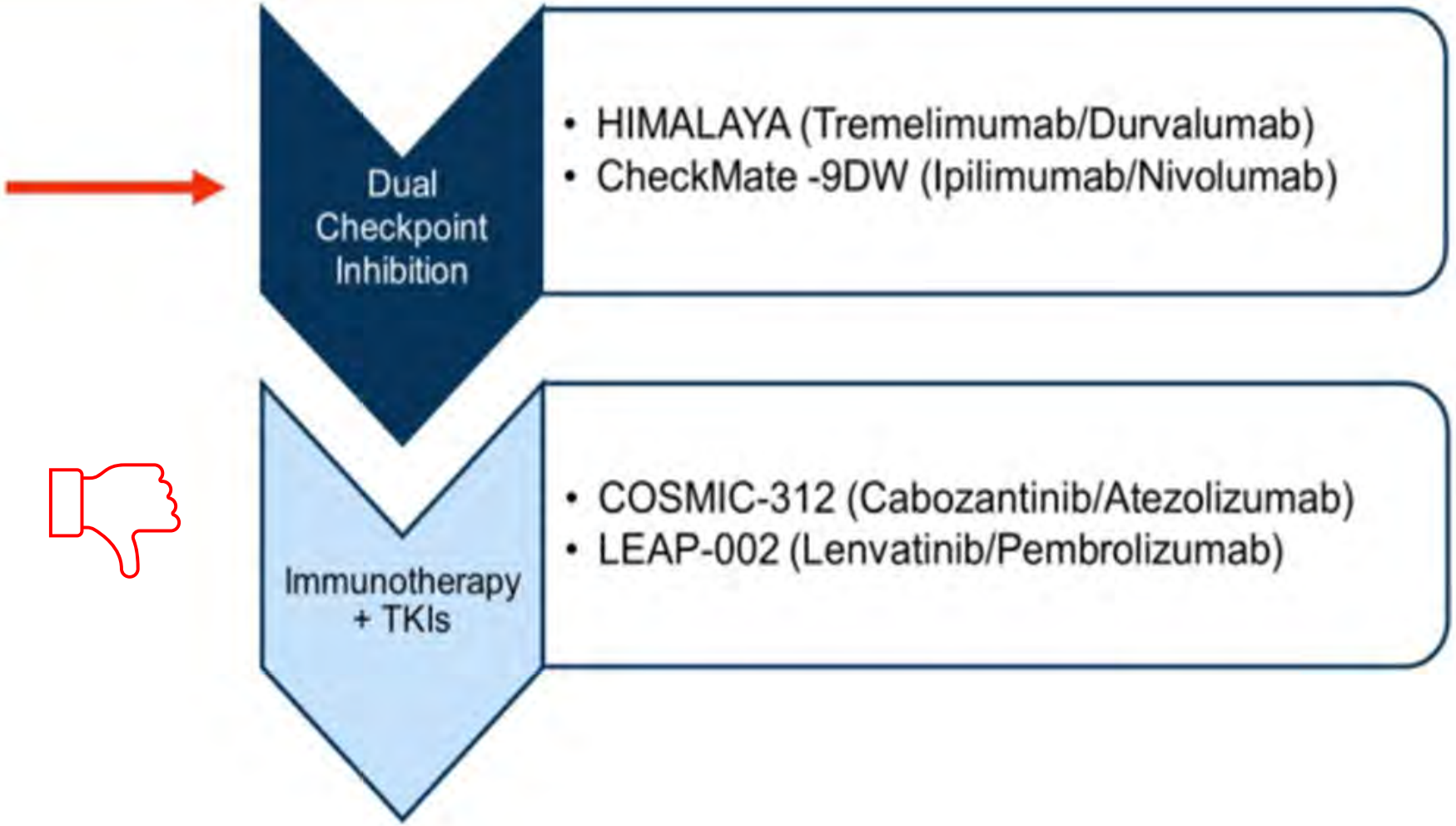
Clinical cutoff: August 31, 2020.

[a] Stratification factors included in the Cox model are AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per IxRS.

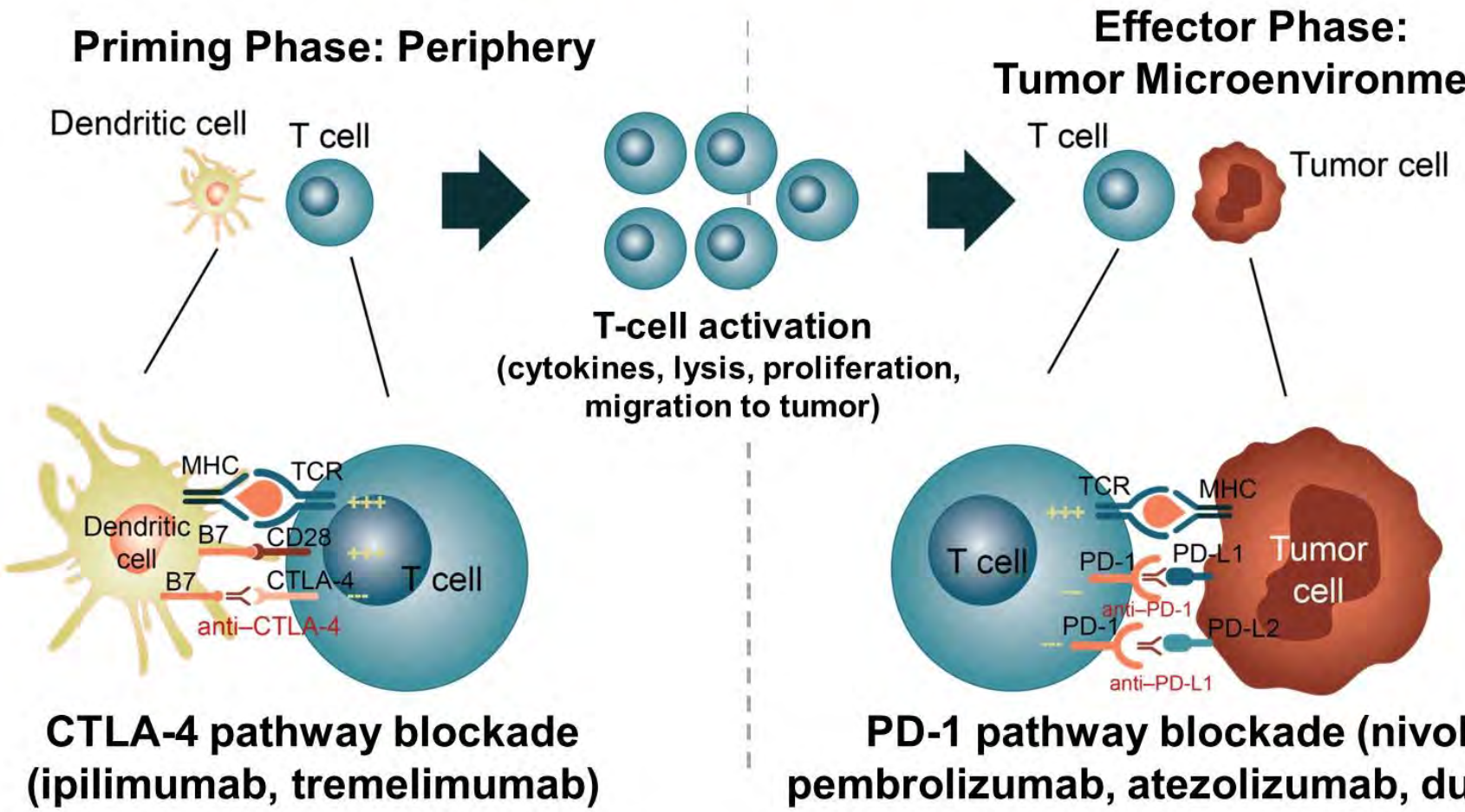
Conclusions

- With an additional 12 months of follow-up, atezolizumab + bevacizumab continued to demonstrate a consistent clinically meaningful treatment benefit vs sorafenib
  - Median OS: 19.2 mo vs 13.4 mo; HR = 0.66 (95% CI: 0.52, 0.85)
  - Median PFS per IRF-assessed RECIST 1.1: 6.9 mo vs 4.3 mo; HR = 0.65 (95% CI: 0.53, 0.81)
  - ORR / CR per RECIST 1.1: 30% / 8% vs 11% / < 1%
  - ORR / CR per HCC mRECIST: 35% / 12% vs 14% / 3%
- The safety and tolerability profile of atezolizumab + bevacizumab remains consistent with the known safety profiles of each individual drug and the underlying disease
- Atezolizumab + bevacizumab provides the longest overall survival seen in a front-line Phase III study in advanced HCC, confirming this combination as the standard of care for previously untreated, unresectable HCC

Combination Therapy in HCC

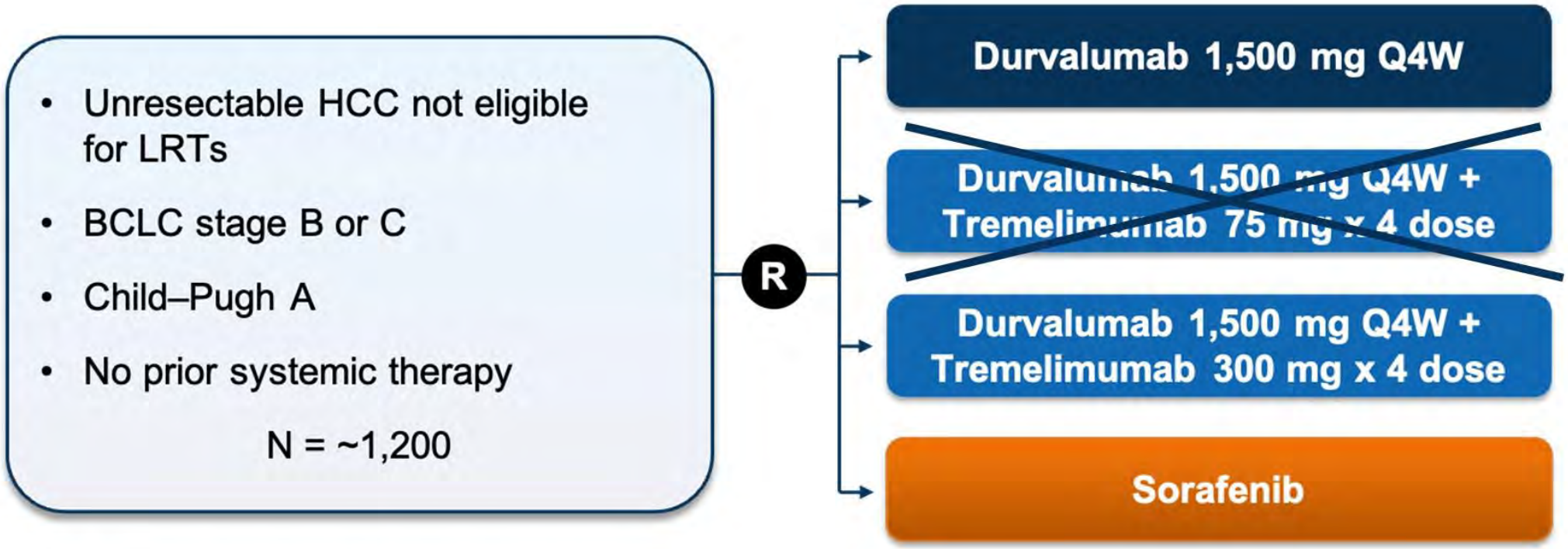


Immuno-Oncology: Blocking CTLA-4 and PD-1 Pathways With Monoclonal Antibodies[1]



1. Wolchock J et al. 2013 American Society of Clinical Oncology Annual Meeting (ASCO 2013). Abstract 9012.

Phase 3 HIMALAYA Trial: First-Line Durvalumab Plus Tremelimumab Versus Sorafenib[1]

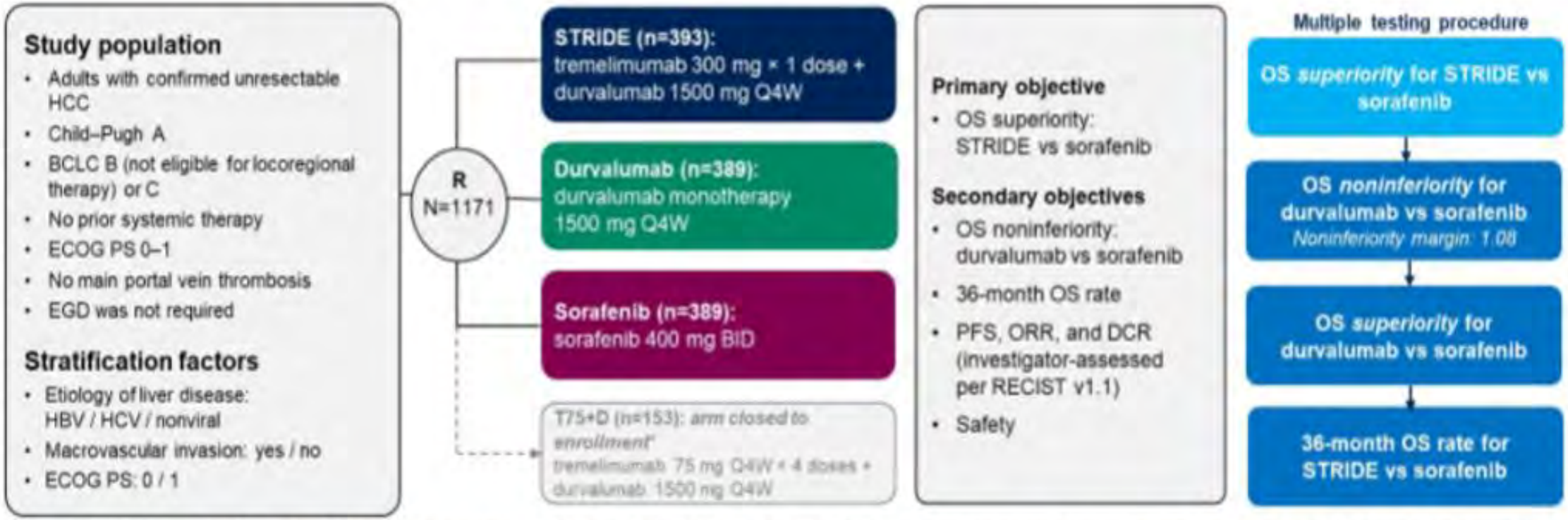


- **Primary endpoint:** OS
- **Other endpoints:** TTP, PFS, ORR, DCR, DOR, and QOL

1. https://clinicaltrials.gov/ct2/show/NCT03298451.

HIMALAYA study design

HIMALAYA is an open-label, multicenter, global, Phase 3 trial[1]

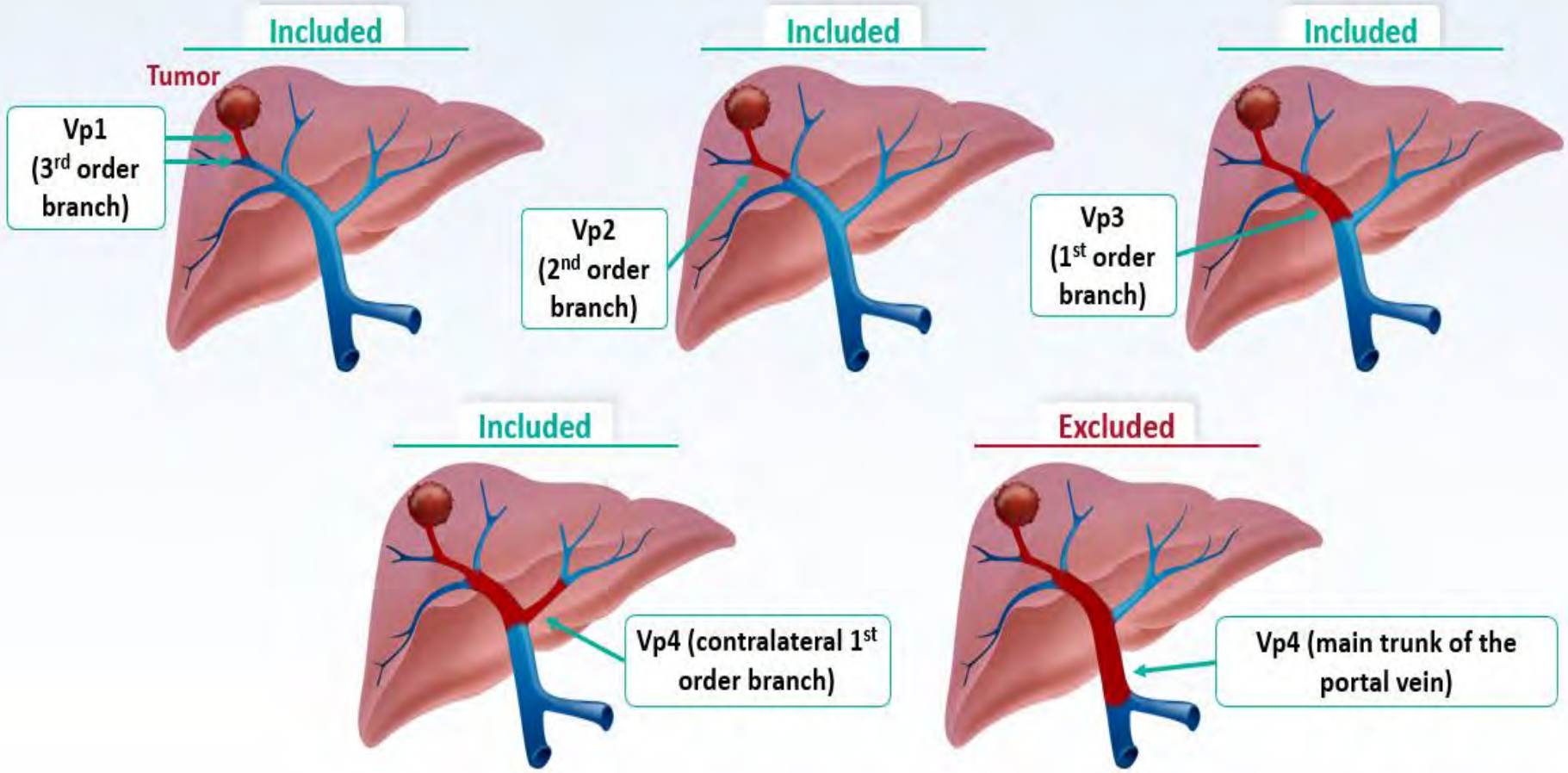


*The T75+D arm was closed to enrollment following a preplanned analysis of a Phase 2 study. Participants randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

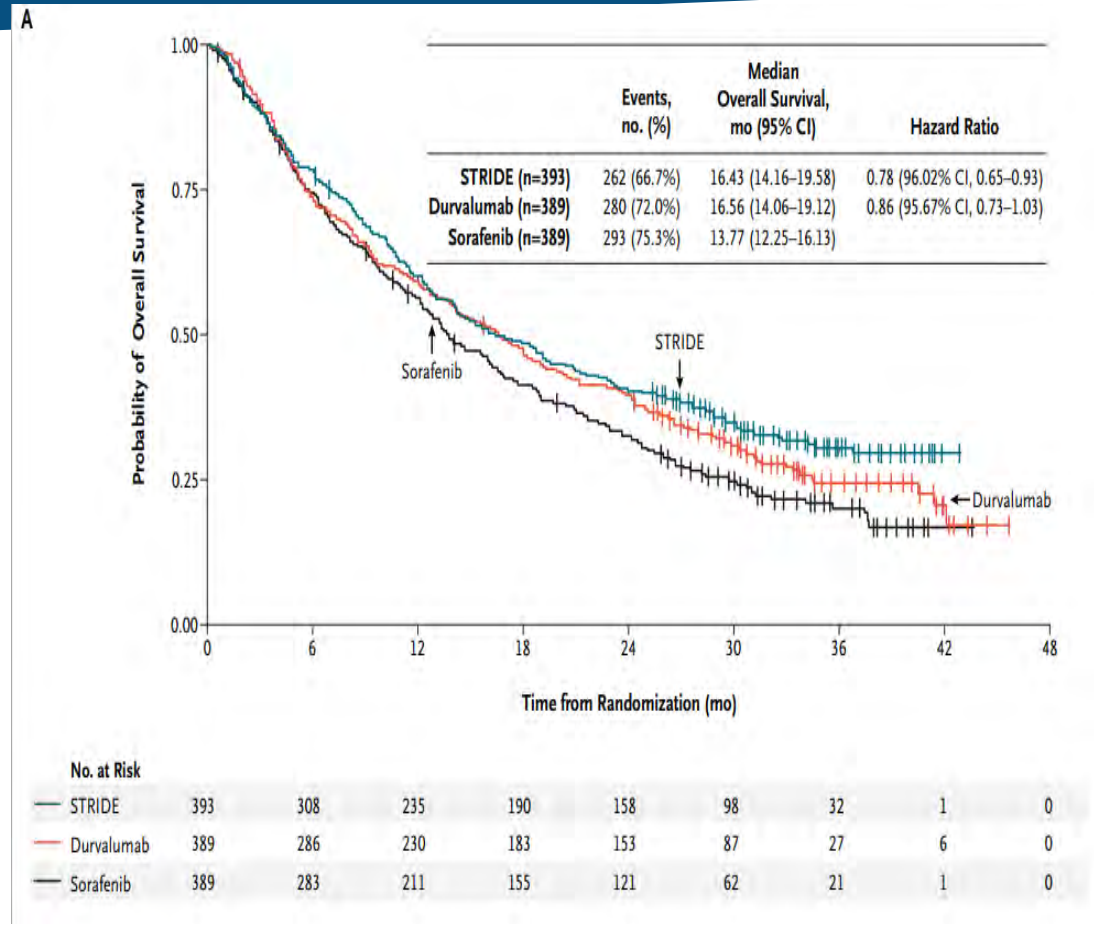
BCLC, Barcelona Clinic Liver Cancer; BID, twice a day; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EGD, esophagogastroduodenoscopy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q4W, every 4 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; T75+D, tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W.

1. Abou-Alfa GK, *et al. NEJM Evid* 2022;1:EVIDoa2100070.

Portal Vein Tumor Thrombosis Selection Criteria for the HIMALAYA Study[1,2]



Himalaya Trial



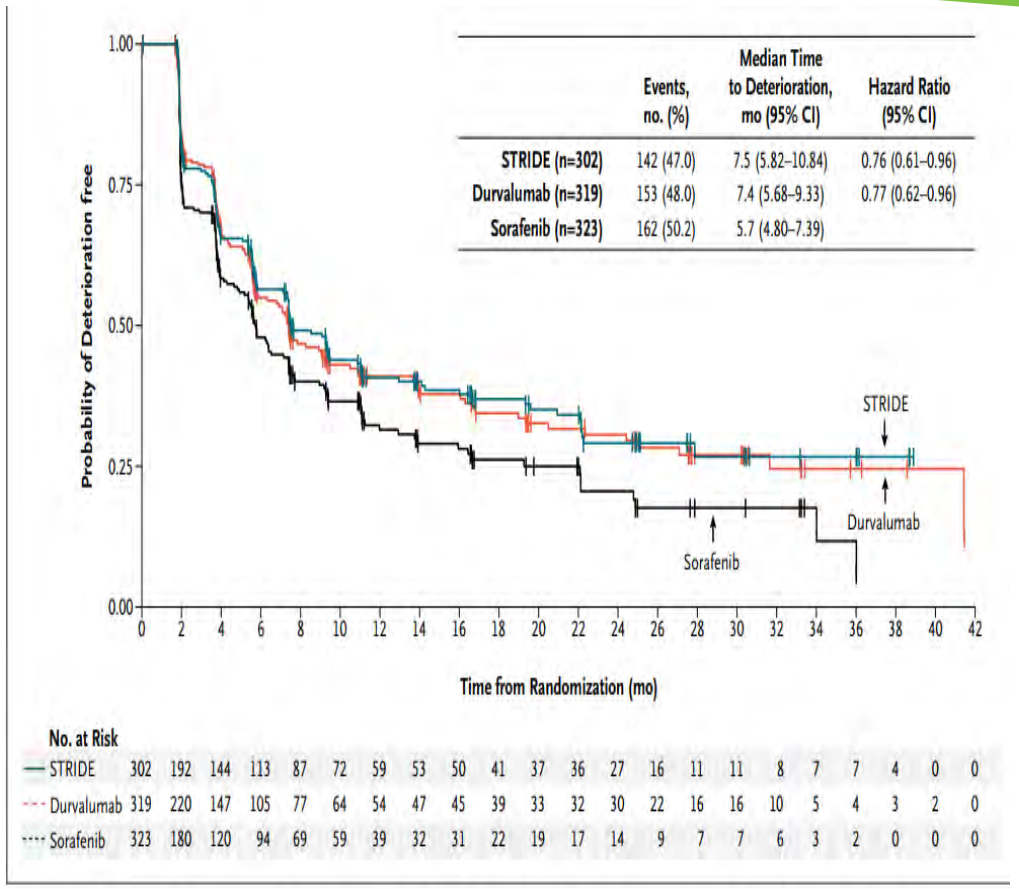
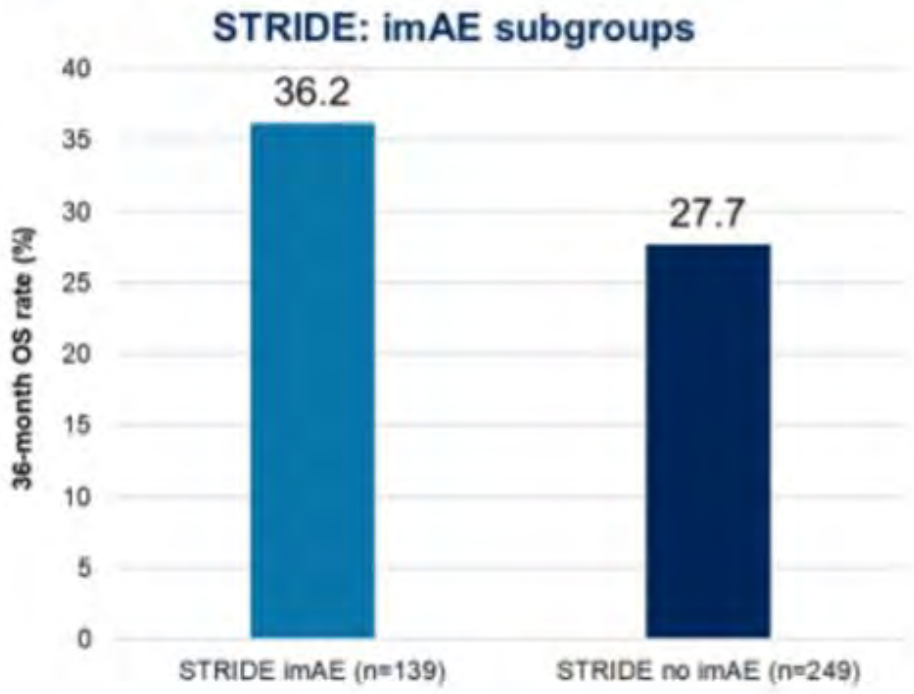
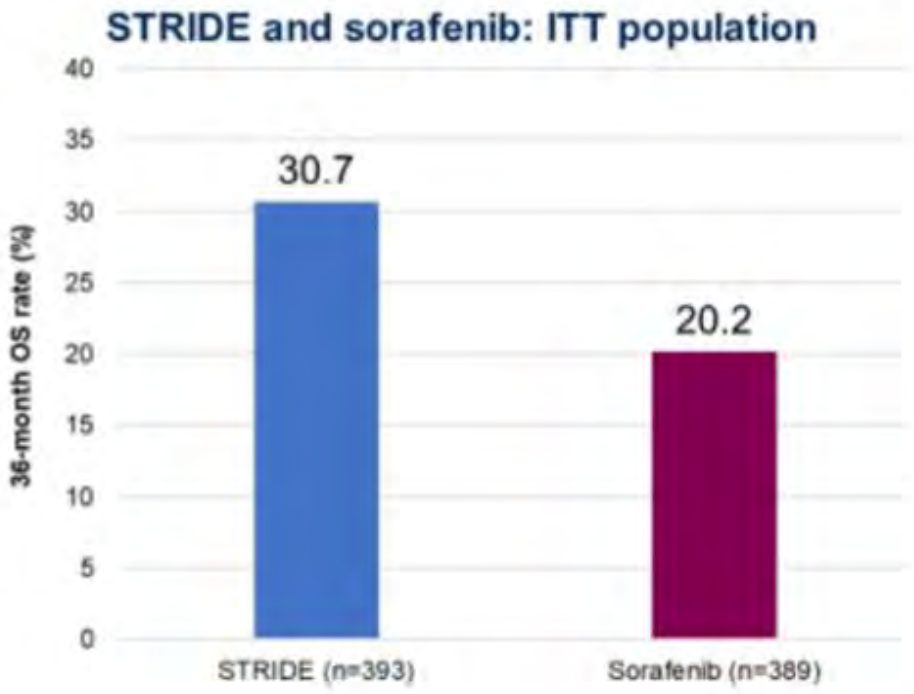


Figure 2. Time to Deterioration of Global Health Status or Quality of Life According to EORTC QLQ-C30 Scores.

Landmark 36-month OS rates for STRIDE in imAE subgroups

OS rates at 36 months were higher with STRIDE than with sorafenib (ITT population) irrespective of imAE occurrence



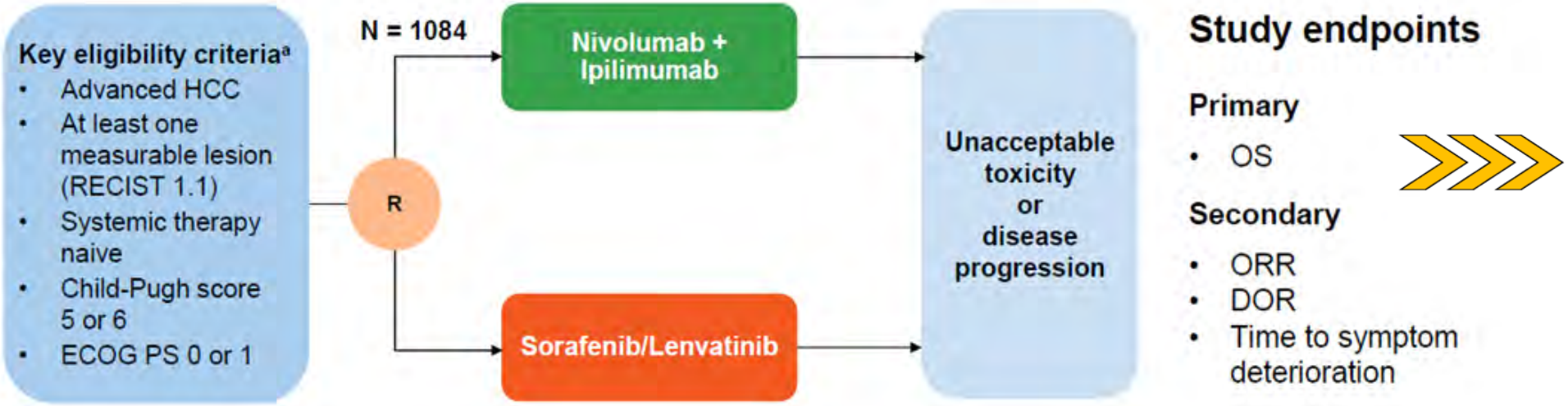


imAE, immune-mediated adverse event; ITT, intent-to-treat; OS, overall survival.

PRESENTED BY: George Lau, MD, FRCP, FAASLD

CheckMate 9DW Study Design

A Randomized, Open Label, Phase 3 Study of Nivolumab in Combination With Ipilimumab Compared to Sorafenib or Lenvatinib as First-Line Treatment in Participants With Advanced Hepatocellular Carcinoma

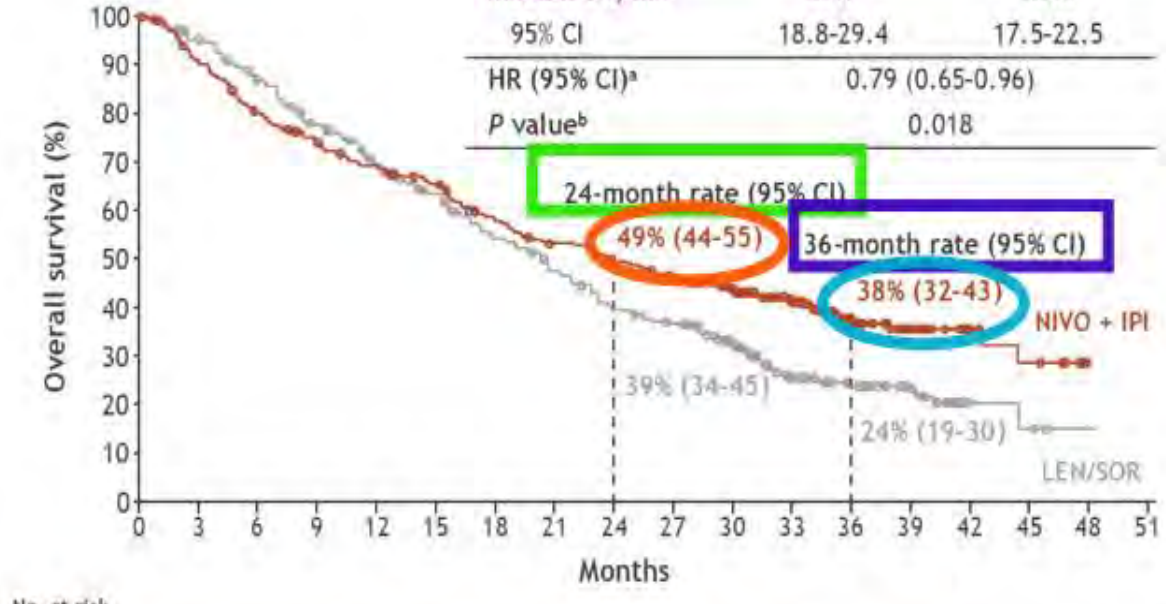


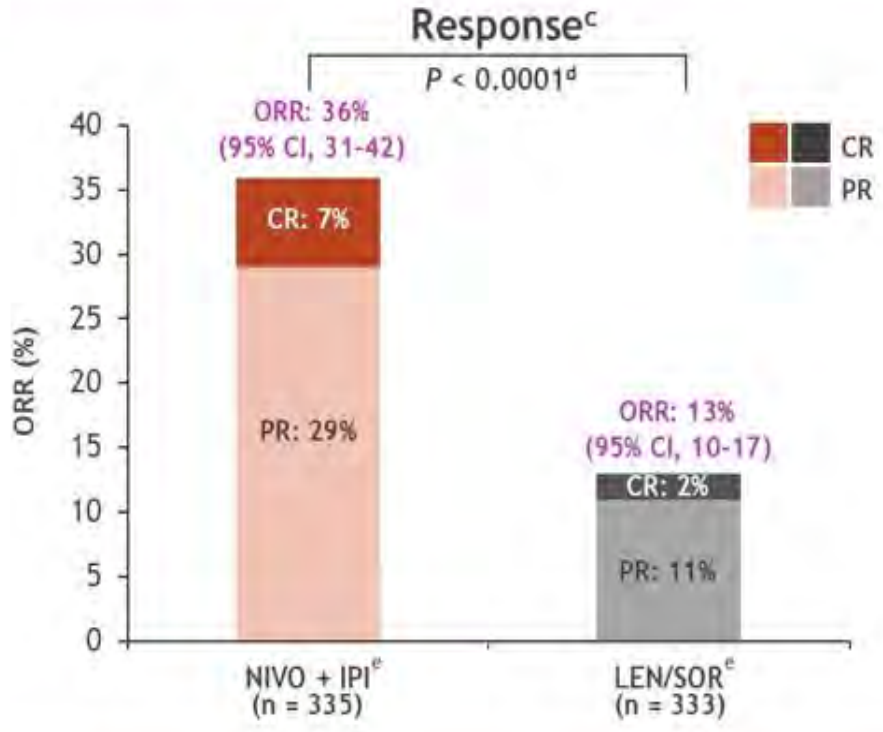
Start date: September 2019
Estimated study completion date: September 2023
Estimated primary completion date: September 2023
Status: Recruiting
Study sponsor: Bristol-Myers Squibb

[a]ClinicalTrials.gov. NCT04039607.

Overall survival, response, and duration of response

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



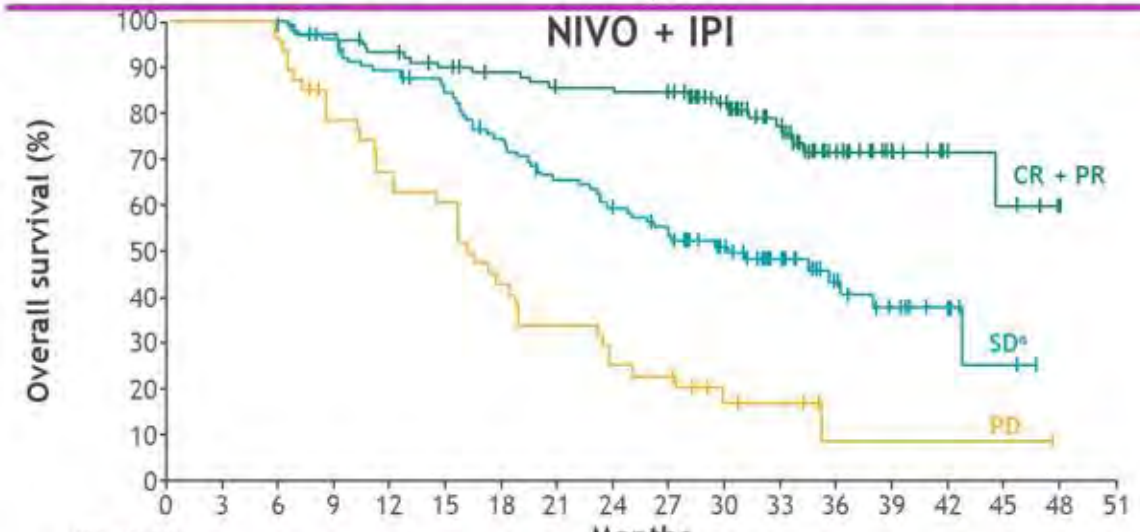


Median TTR (range),[f] mo	2.2 (1.1-11.6)	3.7 (0.6-11.2)
Median DOR (95% CI),[f] mo	30.4 (21.2-NE)	12.9 (10.2-31.2)

- Statistically significant and clinically meaningful OS benefit with NIVO + IPI vs LEN/SOR, with higher OS rates at 24 and 36 months
- Statistically significant and clinically meaningful improvement in ORR by BICR[c] with NIVO + IPI vs LEN/SOR, with a higher CR rate and durable responses

Median (range) follow-up, 35.2 (26.8-48.9) months. [a]HR and 95% CI from stratified Cox proportional hazard model. Symbols represent censored observations. [b]Two-sided *P* value from stratified log-rank test. Boundary for statistical significance: *P* value ≤ 0.0257. [c]Assessed by BICR based on RECIST v1.1. [d]Two-sided *P* value from stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: *P* value ≤ 0.025. [e]Percentage with BOR of SD (includes non-CR/non-PD, which refers to patients with persistence of 1 or more non-target lesion[s]): NIVO + IPI, 32%; LEN/SOR, 62%. Percentage with BOR of PD: NIVO + IPI, 20%; LEN/SOR,

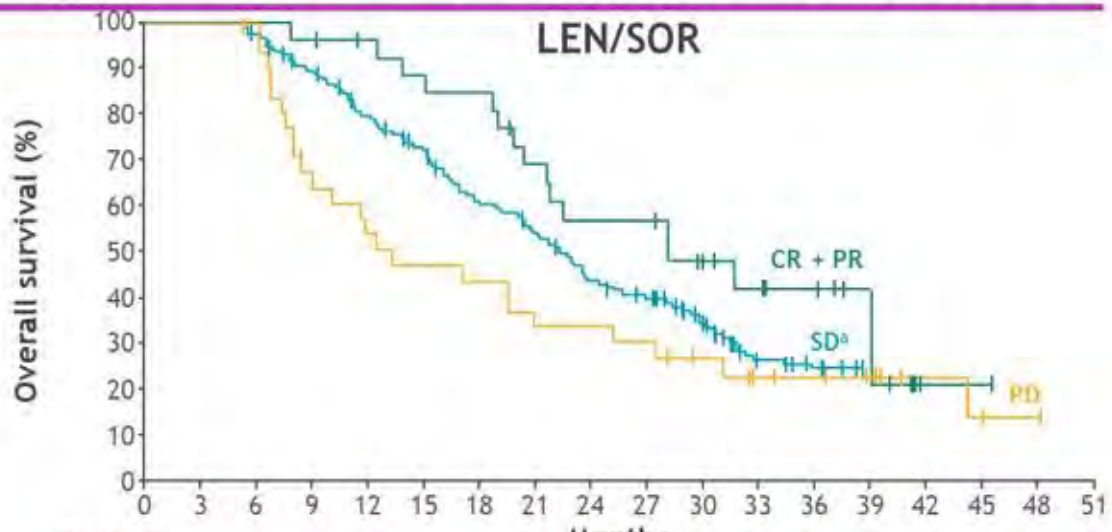
Overall survival by best overall response at 24-week landmark



No. at risk

CR/PR	101	101	101	95	91	86	82	78	77	76	59	41	25	12	6	5	0	0
SD[a]	105	105	103	98	92	85	72	64	57	49	38	25	15	10	4	2	0	0
PD	47	47	45	35	28	27	19	15	11	10	5	4	1	1	1	1	0	0

NIVO + IPI	CR + PR (n = 101)	SD[a] (n = 105)	PD (n = 47)
Events	24	56	38
Median OS, mo	NR	30.0	16.0
95% CI	44.4-NE	23.5-37.8	12.0-18.7
HR (95% CI), CR+PR vs PD	0.14 (0.08-0.24)		
HR (95% CI), SD[a] vs PD	0.40 (0.26-0.60)		



No. at risk

CR/PR	28	28	28	27	25	23	22	17	14	14	10	7	5	2	1	1	0	0
SD[a]	212	212	205	186	162	146	120	107	84	76	55	31	24	15	3	2	1	0
PD	31	31	31	20	17	14	13	11	10	9	6	3	2	1	0	0	0	0

LEN/SOR	CR + PR (n = 28)	SD[a] (n = 212)	PD (n = 31)
Events	15	115	28
Median OS, mo	28.3	22.5	13.5
95% CI	20.6-NE	20.5-24.8	8.7-25.3
HR (95% CI), CR+PR vs PD	0.45 (0.23-0.86)		
HR (95% CI), SD[a] vs PD	0.69 (0.45-1.08)		

- In both treatment arms, objective response by BICR[b] was associated with improved OS outcomes
  - NIVO + IPI: The HR for CR or PR versus PD was 0.14 and for SD versus PD was 0.40
  - LEN/SOR: The HR for CR or PR versus PD was 0.45 and for SD versus PD was 0.69

Median (range) follow-up, 35.2 (26.8-48.9) months. Symbols represent censored observations. [a]Includes non-CR/non-PD. Non-CR/non-PD refers to patients with persistence of 1 or more non-target lesion(s). [b]Based on RECIST v1.1.

Summary of IO based Rx Options for HCC

	IMbrave150 Atezo/Bev	HIMALAYA Durva/Treme	CheckMate 9DW Nivo/Ipi	CARES-310 Camre/Rivo
Median OS	19m Vs 13.4m	16.4m Vs 13.8	23.7m Vs 20.6m	22.8 m Vs 15.2m
ORR	30% Vs 11%	20.1% Vs 5.1%	36% Vs 13%	26.8% Vs 5.9 %
Median DOR	18.1 m Vs 14.9m	22.34 m Vs 18.43m	30.4m Vs 12.9m	17.5m Vs 9.2m
OS rate				
18- Mo	52% Vs 40%	48.7% Vs 41.5%	-----	-----
24- Mo	-----	40.5% Vs 32.6%	49% Vs 39%	49.0% Vs 32.6%
36-Mo	-----	30.7% Vs 19.8%	38% Vs 24%	37.7% Vs 24.8%
48-Mo	-----	25.2% Vs 15.1%	------	-----

Is There Role of IO in the Adjuvant Setting in HCC

Ongoing Phase 3 Trials of Adjuvant Immunotherapy[1-4]

- High risk for HCC recurrence after resection or ablation
- Child–Pugh class A

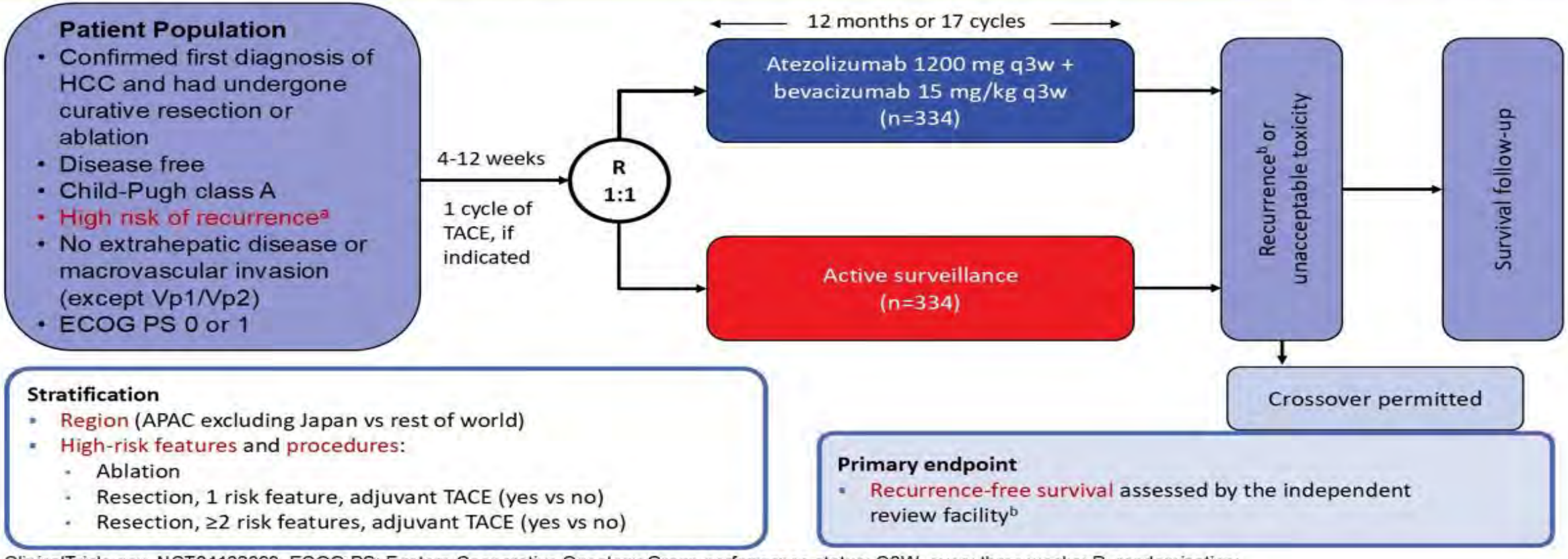
EMERALD-2	CheckMate-9DX	IMbrave050	KEYNOTE-937
• Durvalumab ± bevacizumab + vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Nivolumab vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Atezolizumab + bevacizumab vs active surveillance • ECOG PS 0-1 • Primary endpoint: RFS	• Pembrolizumab vs placebo • ECOG PS 0 • AFP <400 ng/mL • Primary endpoint: RFS and OS

1. https://clinicaltrials.gov/ct2/show/NCT03383458. 2. https://clinicaltrials.gov/ct2/show/NCT03867084. 3. https://clinicaltrials.gov/ct2/show/NCT03847428. 4. https://clinicaltrials.gov/ct2/show/NCT04102098.

Adjuvant Therapy for HCC

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

IMbrave050 study design



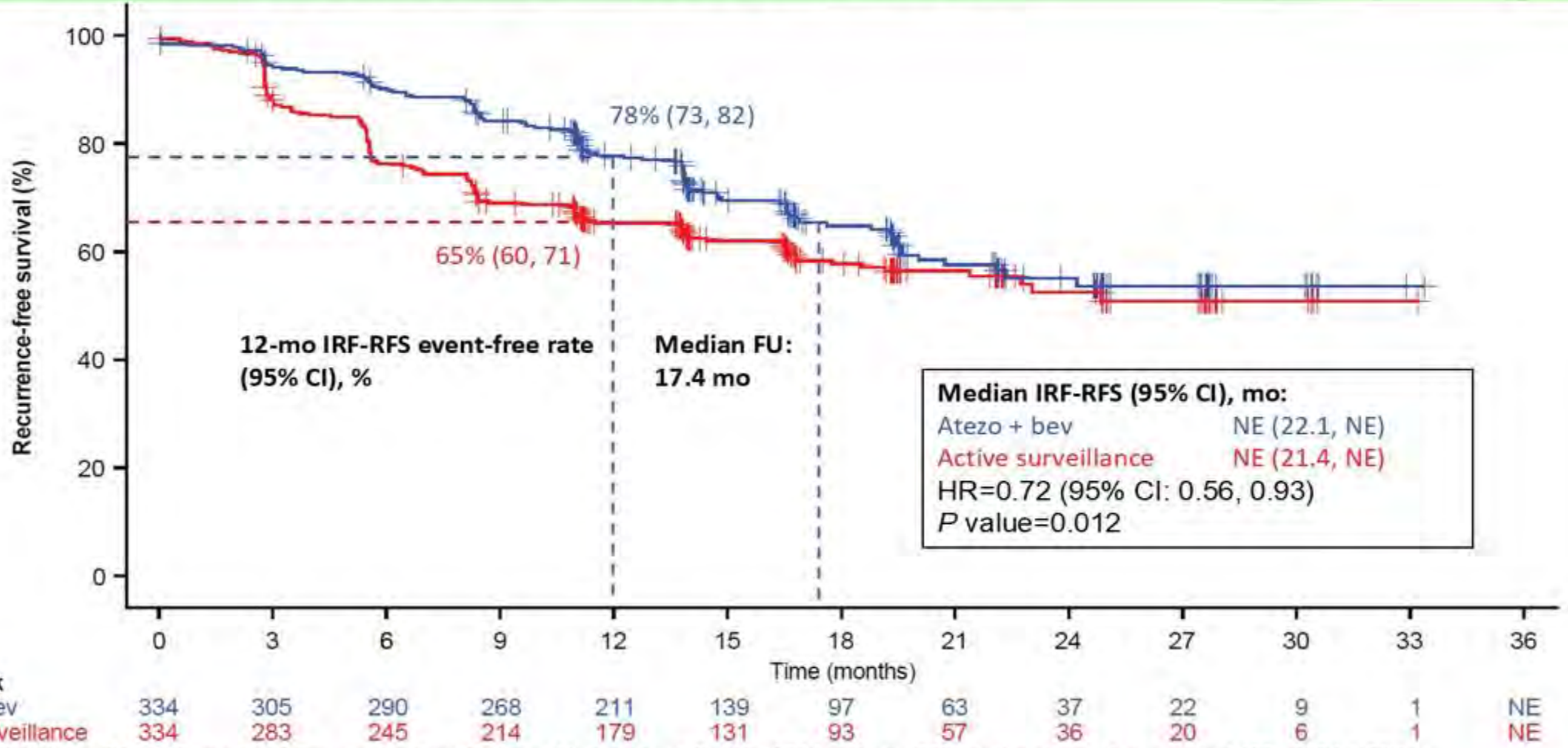
ClinicalTrials.gov, NCT04102098. ECOG PS; Eastern Cooperative Oncology Group performance status; Q3W, every three weeks; R, randomization; TACE, transarterial chemoembolization.

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

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

Qin Lancet 2023

Primary endpoint: IRF-assessed RFS was significantly improved with atezo + bev vs active surveillance



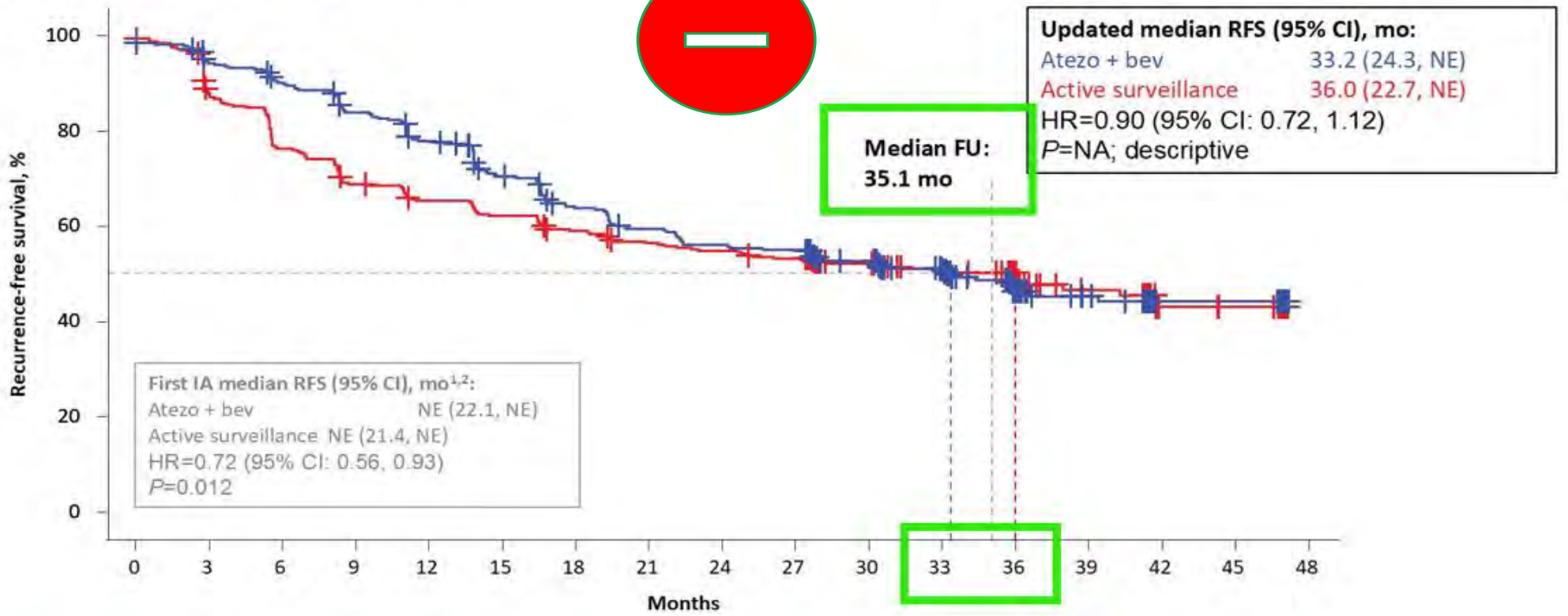
No. at risk													
Atezo + bev	334	305	290	268	211	139	97	63	37	22	9	1	NE
Active surveillance	334	283	245	214	179	131	93	57	36	20	6	1	NE

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 110 of 334 patients (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death.

FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log rank.

Qin Lancet 2023

Early RFS benefit was not maintained with longer follow-up



No. at risk																	
Atezo + bev	334	305	290	268	245	216	191	177	167	164	147	123	62	45	18	18	NE
Active surveillance	334	285	247	221	207	197	185	175	170	164	145	124	63	42	16	14	NE

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

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

ASCO Gastrointestinal Cancers Symposium

EMERALD-1: a Phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization

Riccardo Lencioni*[1], Masatoshi Kudo[2], Joseph Erinjeri[3], Shukui Qin[4], Zhenggang Ren[5], Stephen L Chan[6], Yasuaki Arai[7], Jeong Heo[8], Anh Mai[9], Jose Escobar[10], Yamil Alonso Lopez Chuken[11], Jung-Hwan Yoon[12], Won Young Tak[13], Tanita Suttichaimongkol[14], Mohamed Bouattour[15], Shi-Ming Lin[16], Magdalena Żotkiewicz[17], Stephanie Udoye[18], Gordon J Cohen[18], **Bruno Sangro***[19]

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Co-principal investigators

EMERALD-1 study design

EMERALD-1 was a global, double-blind, placebo-controlled Phase 3 study

Study population*
- Adults with confirmed HCC
- Not amenable to curative therapy, e.g. surgical resection, ablation, transplantation
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG PS 0 or 1
- Measurable disease per mRECIST
- Excludes Vp3 and Vp4
- No prior systemic therapy or TACE†

Stratification factors
- TACE modality (DEB-TACE vs cTACE)
- Geographical region (Japan vs Asia [excluding Japan] vs other)
- Portal vein invasion (Vp1 or Vp2+ / -Vp1 vs none)

R 1:1:1
N=616

- **Arm A: Durvalumab‡** (1500 mg Q4W) **+ TACE§** → **Durvalumab** (1120 mg Q3W) **+ placebo** for bevacizumab (Q3W)
- **Arm B: Durvalumab†** (1500 mg Q4W) **+ TACE§** → **Durvalumab** (1120 mg Q3W) **+ bevacizumab** (15 mg/kg Q3W)
- **Arm C: Placebo** for durvalumab (Q4W) **+ TACE§** → **Placebo** for durvalumab (Q3W) **+ placebo** for bevacizumab (Q3W)

Primary endpoint:
- PFS‖ for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary endpoints:
- PFS for Arm A vs Arm C
- OS
- QoL

Other secondary endpoints:
- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

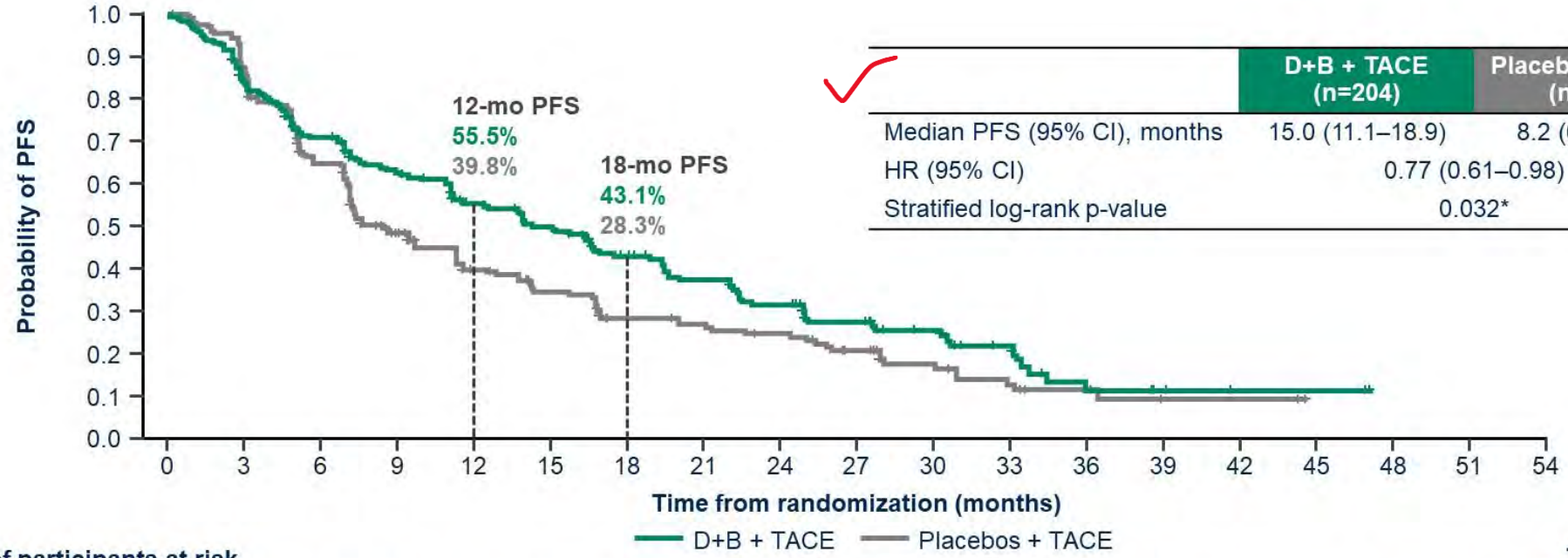
*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomization. †Prior use of TACE or TAE is acceptable if it was used as part of therapy with curative intent, but not if it was used as the sole modality in curative therapy. ‡Durvalumab / placebo started ≥7 days after TACE. §DEB-TACE or cTACE. Participants will receive up to 4 TACE procedures within the 16 weeks following Day 1 of their first TACE procedure. ‖Only new lesions consistent with progression that were not eligible for TACE occurring prior to the first on study imaging at 12 weeks were considered progression events; standard mRECIST progression criteria were used after the 12-week imaging.

BICR, blinded independent central review; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead-transarterial chemoembolization; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W / Q4W, every 3 / 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TAE, transarterial embolization; TTP, time to progression.

PRESENTED BY: Riccardo Lencioni, MD

PFS with D+B + TACE versus placebos + TACE: primary endpoint

Median PFS was improved by 6.8 months with D+B + TACE versus placebos + TACE



	D+B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	

No. of participants at risk

																			Total events
D+B + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0	136
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	149

Median (range) duration of follow-up in censored participants, D+B + TACE 16.7 (0.03–47.1) months, Placebos + TACE 10.3 (0.03–44.3) months. **Median (95% CI) duration of follow-up** in all participants using the reverse Kaplan-Meier method, D+B + TACE 22.2 (16.7–27.3) months, Placebos + TACE 26.3 (16.7–30.4) months. PFS was assessed by BICR (RECIST v1.1)

*The threshold of significance for this analysis was 0.0435 based on the α spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.

B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; HR, hazard ratio; mo, months, PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.

PRESENTED BY: Riccardo Lencioni, MD

Conclusions

- **EMERALD-1 met the primary endpoint** and is the **first, global Phase 3 study** to demonstrate a statistically significant and clinically meaningful improvement in PFS with an immunotherapy and TACE-based regimen in unresectable HCC eligible for embolization
  - **Median PFS was 15.0 months with D+B + TACE and 8.2 months with placebos + TACE**
  - **PFS HR was 0.77, p=0.032**
- PFS benefit with D+B + TACE was generally consistent across key clinical subgroups
- The **safety profile was manageable** and consistent with the known safety profiles of TACE, durvalumab, and bevacizumab in unresectable HCC

Durvalumab plus **bevacizumab** in combination with **TACE** has the potential to set a new standard of care in **unresectable HCC eligible for embolization**

B, bevacizumab; D, durvalumab; HCC, hepatocellular carcinoma; HR, hazard ratio; PFS, progression-free survival; TACE, transarterial chemoembolization.

ASCO Gastrointestinal Cancers Symposium

Adjuvant Radiotherapy After CuratIve ReSEction of Hepatocellular Carcinoma with Narrow Margin (<1 cm): A Phase 2, Multicenter, Randomized Controlled Trial (RAISE)

Ming KUANG[1,2], Zhenwei PENG[2], Zebin Chen[1], Shunli Shen[1], Bin Li[3]

[1]Center of Hepato-Pancreato-Biliary Surgery, First Affiliated Hospital, Sun Yat-sen University, China

[2]Cancer center, First Affiliated Hospital, Sun Yat-senUniversity, China

[3]Clinical Trials Unit, First Affiliated Hospital, Sun Yat-senUniversity, China

PRESENTED BY: Professor Ming Kuang

Schematic Diagram

- Primary HCC underwent R0 resection and pathological confirmation.
- Largest resection margin <1 cm.
- Enhanced CT or MRI 4-6 weeks after resection found no tumor.
- ECOG PS ≤1.
- Child-Pugh score 5-7.
- Satisfactory blood, liver, and kidney function parameters.

Randomization 1:1

Stratification factors:
- **MVI（+ vs -）**
- **Tumor size（≤5cm vs >5cm)**

Adjuvant RT group (n=74)
IMRT; 50Gy/25F

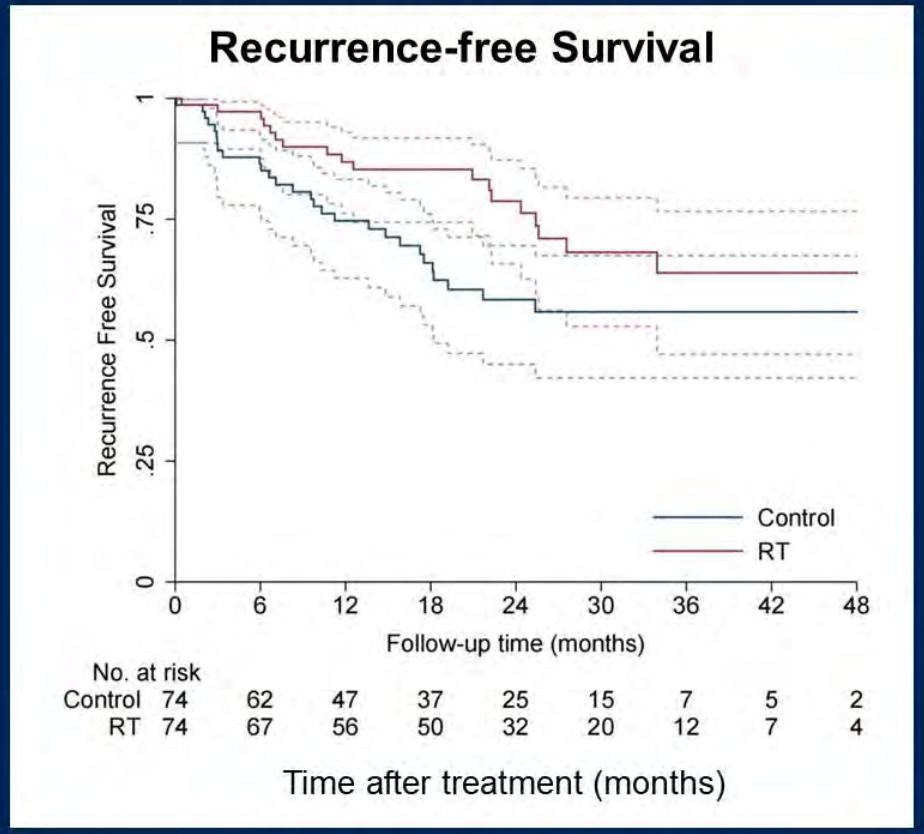
The control group (n=74)
Follow-up

Primary outcome:
- **Recurrence Free**
- **Survival**

Secondary outcome:
- **Time To Recurrence**
- **Overall Survival,**
- **Safety**

HCC, Hepatocellular carcinoma; MVI, Microvascular invasion; IMRT, Intensity-modulated radiotherapy

Survival Outcome



	No. of Events/ No. of Patients	12-month RFS, % (95% CI)	24-month RFS, % (95% CI)
RT	16/74(21.6%)	86.9 (76.3 to 93.0)	78.7 (65.8 to 87.3)
Control	27/74(36.5%)	74.7 (62.8 to 83.3)	58.4 (45.1 to 69.6)

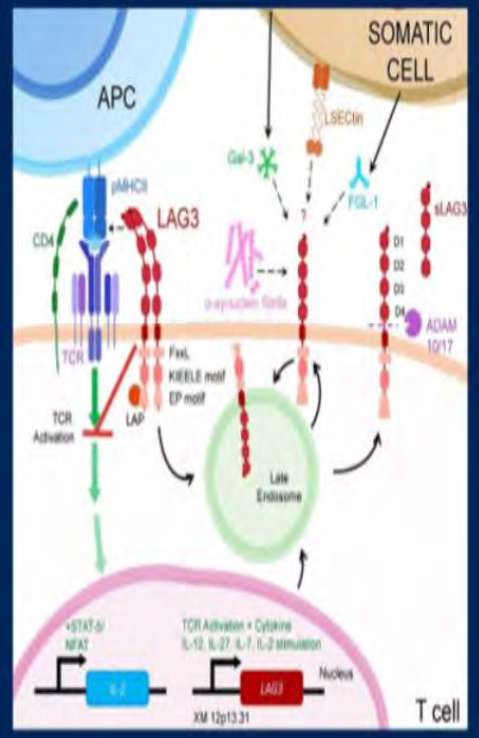
- The median follow-up period was 29.4 months
- The 2-year RFS was 78.74% vs 58.39%

  Stratified Hazard ratio, 0.55 (95% CI, 0.30 to 0.99), Stratified Log-rank *P* = 0.043

Future Pathways in HCC

Novel pathways: LAG-3

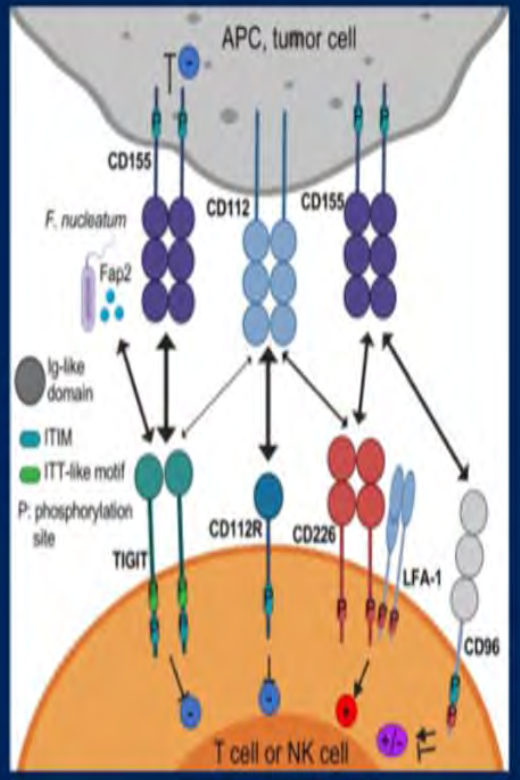
- LAG-3 (CD223) is a cell surface molecule expressed on activated CD4 and CD8 T cells, regulatory T cells (Tregs), NK cells, B cells and plasmacytoid dendritic cells (DCs)
- CITRINO study (NCT03250832): encelimab (TSR-033) with dostarlimab, bevacizumab and chemotherapy in CRC
  - pending results



Graydon et al, Frontiers in Immunology, 2021

TIGIT

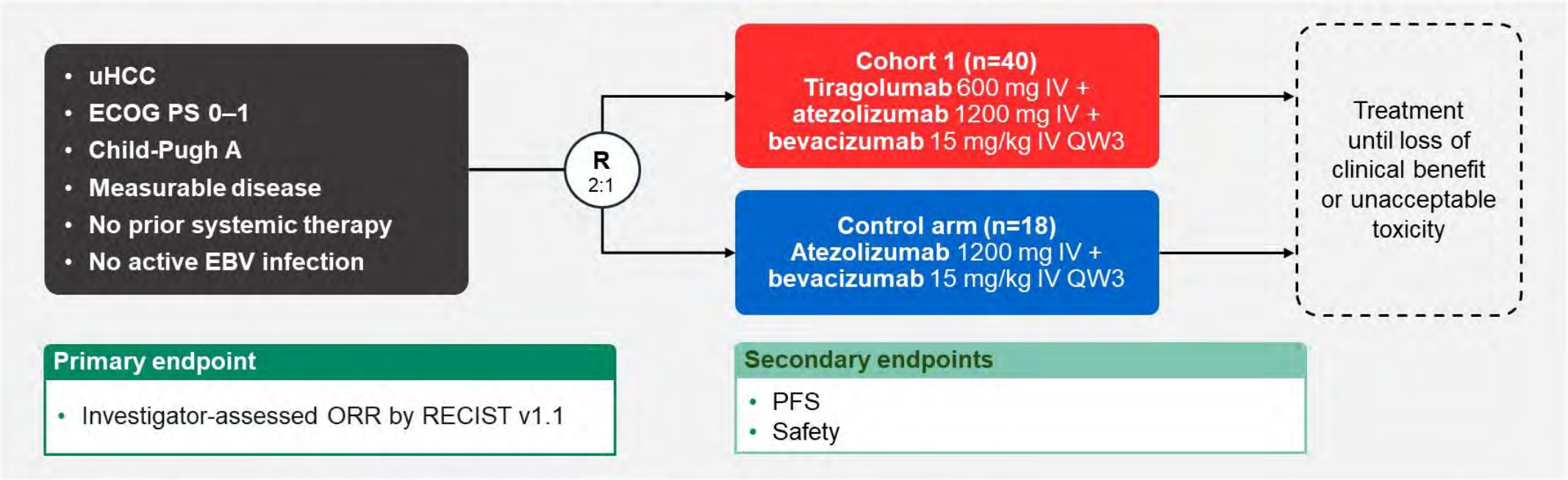
- TIGIT a member of the Ig super family and an immune inhibitory receptor, plays a key role in the suppression of T-cell proliferation and activation
- Promising early data in combination with PD-L1 inhibitors in patient with esophageal cancer
- Ongoing trials in combination with atezolizumab, chemotherapy and targeted therapies in upper GI and colorectal cancers
- AEs: rash, hepatitis, pancreatitis, hypophysitis, diabetes and hypothyroidism (all 5%).



Chauvin et al Journal for Immunotherapy of Cancer, 2020

MORPHEUS-Liver: Phase Ib/II, Open-label, Multicenter, Randomized Trial

- MORPHEUS-Liver is an umbrella study evaluating multiple immunotherapy-based treatment combinations in participants with uHCC who have not yet received prior systemic therapy
- Cohort 1 investigated the addition of tiragolumab to atezolizumab + bevacizumab

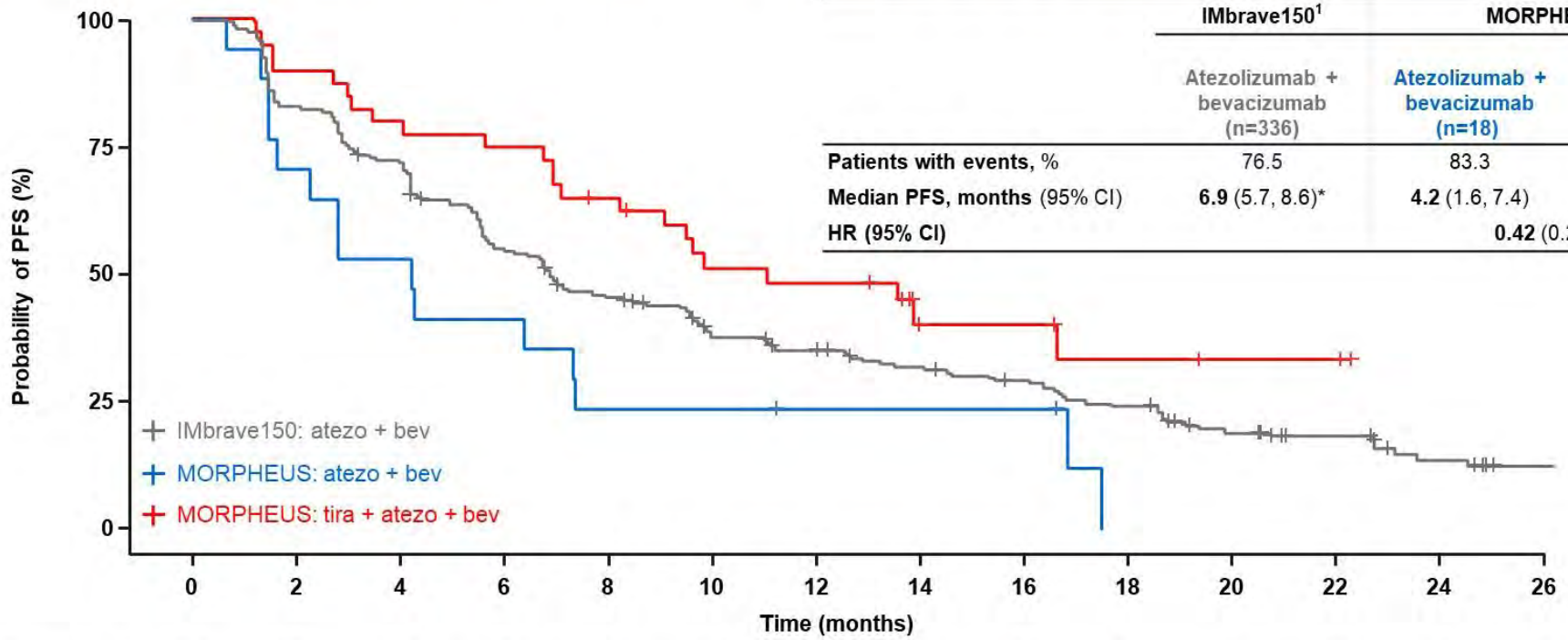


Q3W, every 3 weeks; EBV, Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status
IV, intravenous; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors

NCT04524871

PRESENTED BY: Richard S. Finn, MD

Investigator-assessed PFS per RECIST v1.1



	IMbrave150[1]	MORPHEUS-liver	
	Atezolizumab + bevacizumab (n=336)	Atezolizumab + bevacizumab (n=18)	Tiragolumab + atezolizumab + bevacizumab (n=40)
Patients with events, %	76.5	83.3	57.5
Median PFS, months (95% CI)	**6.9** (5.7, 8.6)*	**4.2** (1.6, 7.4)	**11.1** (8.2, NE)
HR (95% CI)		**0.42** (0.22, 0.82)	

IMbrave150: atezo + bev	336	271	234	174	141	113	102	88	77	64	41	25	12	3
MORPHEUS: atezo + bev	18	12	9	7	4	4	3	3	3	0	0	0	0	0
MORPHEUS: tira + atezo + bev	40	36	32	30	25	17	16	7	7	5	2	2	0	0

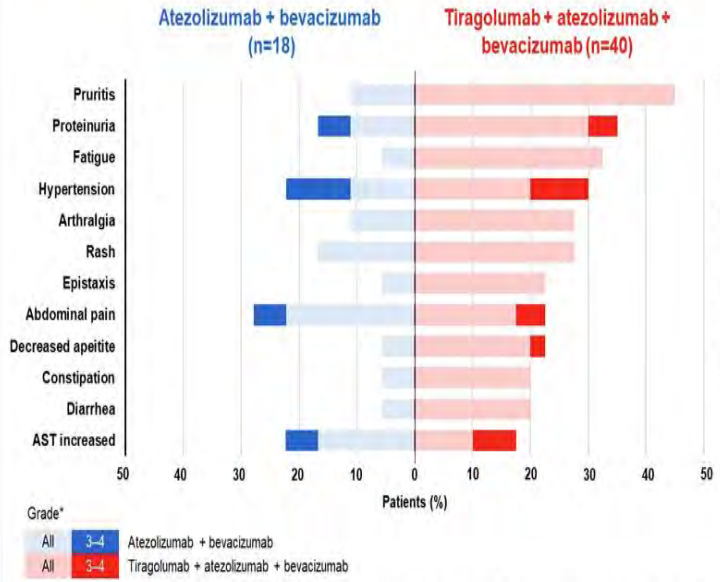
Efficacy evaluable population. Data cut-off: 28 November 2022
*Independent-review facility assessed PFS

1. Cheng et al. J Hepatol 2022; NCT03434379

PRESENTED BY: Richard S. Finn, MD

Future Pathways in HCC

Common (≥20%) Adverse Events



Treatment exposure

	Atezolizumab + bevacizumab (n=18)		Tiragolumab + atezolizumab + bevacizumab (n=40)		
	Atezo	Bev	Tira	Atezo	Bev
Median treatment duration, days	128.0	137.0	284.5	284.5	274.0
Median number of cycles, n	7.0	7.5	14.5	14.5	14.0

Safety evaluable population. Data cut-off: 28 November 2022 (median duration of safety follow-up: atezolizumab + bevacizumab, 5.5. months; tiragolumab + atezolizumab + bevacizumab, 10.3 months)
*No Grade 5 AEs were reported
AST, aspartate aminotransferase

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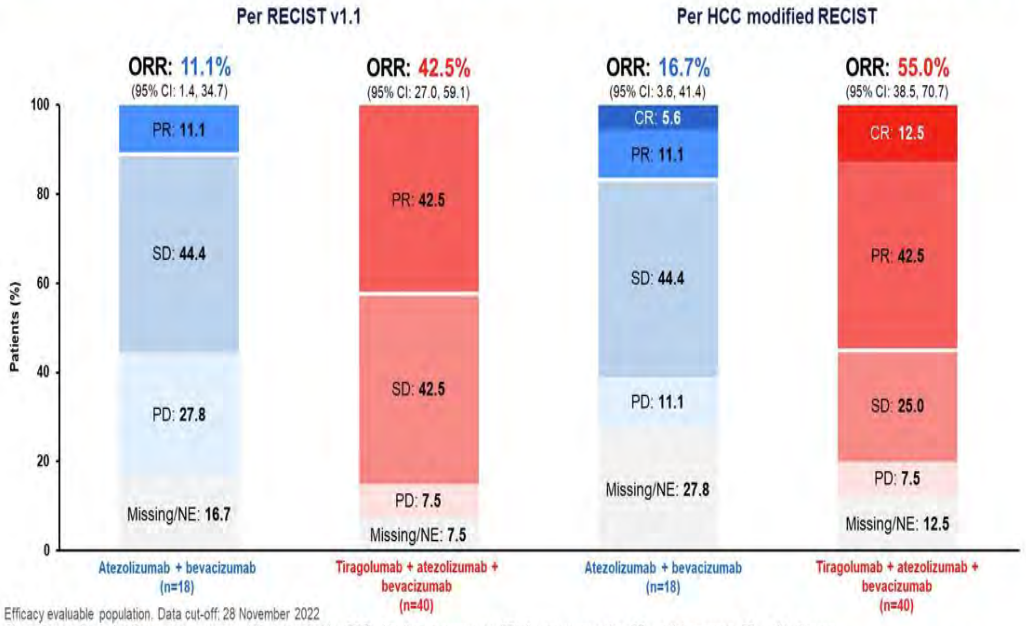
Antitumor activity: investigator-assessed confirmed ORR



Efficacy evaluable population. Data cut-off: 28 November 2022
CI, confidence interval; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, disease progression; PR, partial response; SD, stable disease

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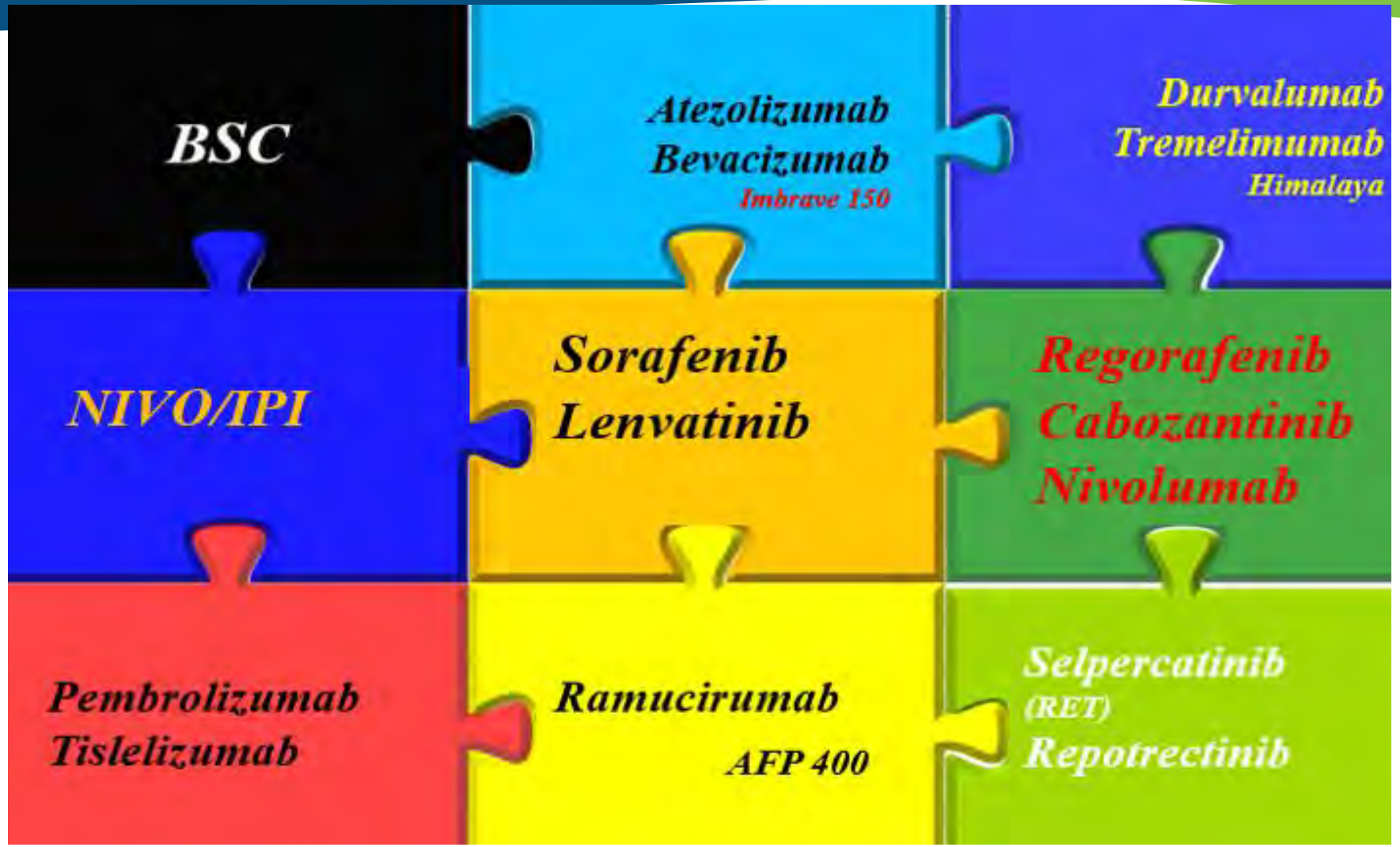
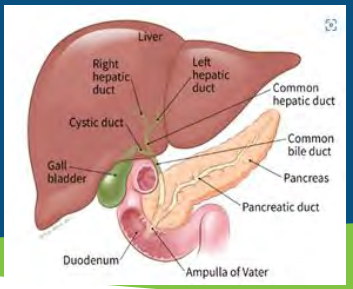
New Landscape Puzzle for HCC



Conclusion



- HCC remains challenging CA with high mortality , 5-year survival 20-25%, Heterogenous disease, based on etiology and Geographic distribution.
- Management of HCC Requires Multidisciplinary approach with Hepatology, Liver Surgery, Radiation Oncology and Interventional Radiology teams.
- Pivotal change in the landscape making a great impact on survival, Quality of life:
  - Targeted Rx and Combination IO: Med Survival 19m- 24m and 2 year OS up to 50%
  - Integrating IO with Liver Directed Rx : Emerald-1 and Emerald Y90
- Targeting New pathways :
  - LAG-3, TIGIT
  - Bispecific AB inhibiting PD1/CTLA4: Cadonilimab