HCC 2022

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Disclosures

- Bayer
- Taiho
- Pfizer
- Daichii
- AstraZeneca
- Merck
- Caris
- Indivumed

What a difference a decade makes….

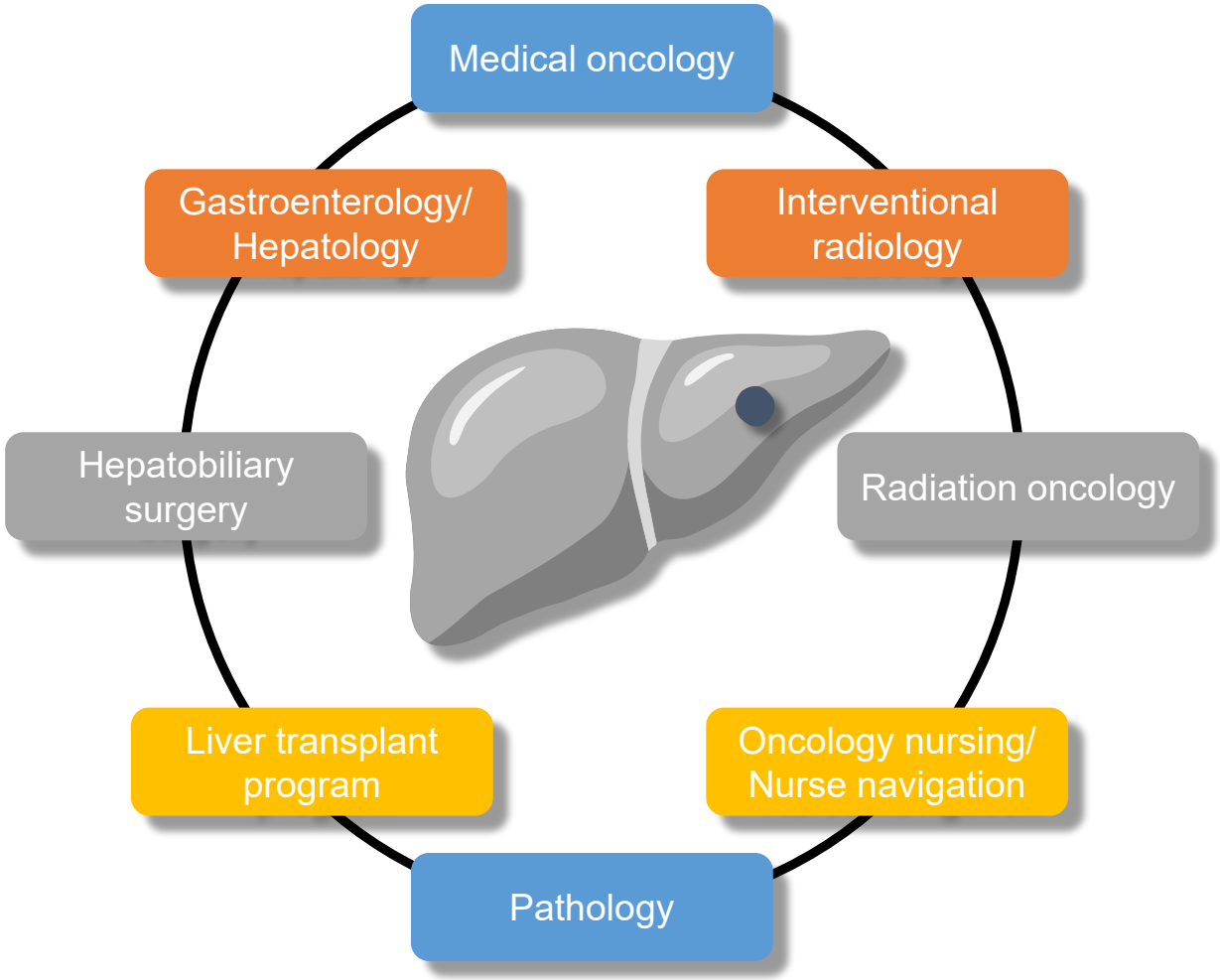
2010

- Cancer is clonal
- All cancer is the same
- Immune therapies will never work
- Gene testing for some
- Randomized phase 3 trials
- Microbiome is disgusting
- Cancer treatment is expensive
- We love our jobs

2020

- Cancer is polyclonal
- All cancer is different
- Immune therapies are miraculous
- Broad testing for many
- Small single arm trials
- Microbiome is beautiful
- Cancer treatment is more expensive
- Highest burnout and suicide in medicine

MDTs and MDCs Improve Survival, Impact Treatment Plans, Increase Early Detection and Curative Treatment Receipt for Patients With HCC[1-5]



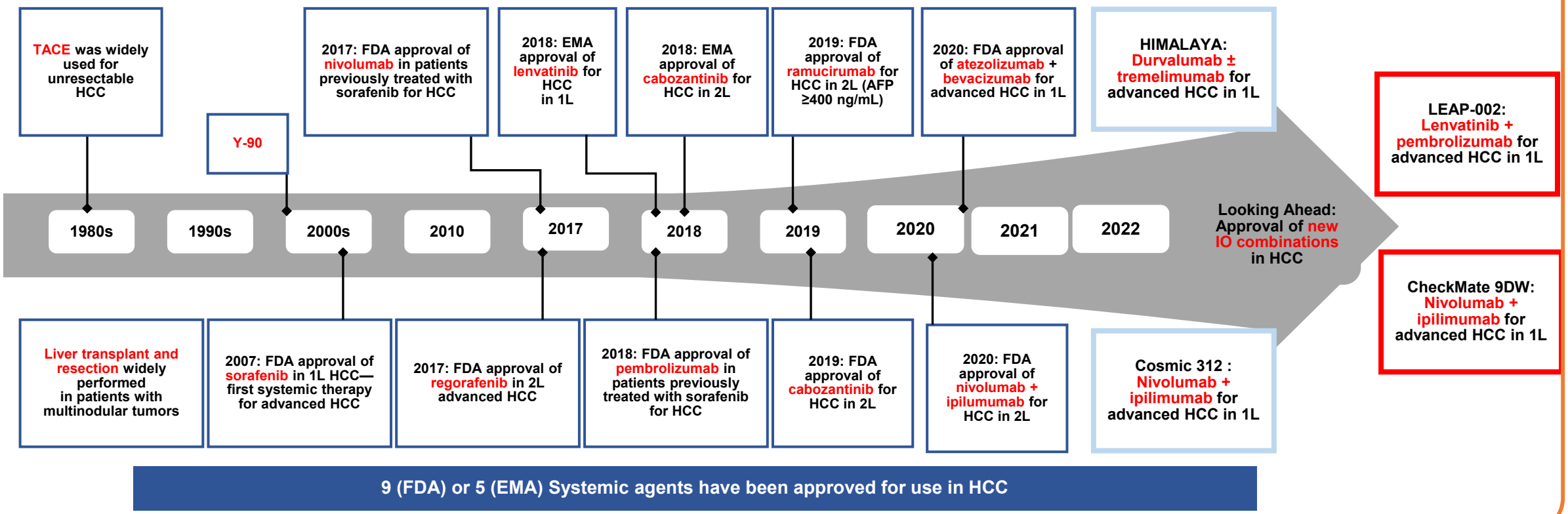
Study	Outcomes
Single day MDT conference (N = 6619)[1]	Improves survival
VA hospital or multispecialty evaluation (N = 3988)[2]	Increases tx receipt and improves survival
Single day MDT clinic and conference (N = 355)[3]	Improves early detection, curative tx, time to tx, and survival
Single day MDLC (N = 343)[4]	Changes imaging/ pathology interpretation and tx plan
MDTT for fluid referrals and joint conferences (N = 121)[5]	Improves early detection, curative tx, and survival

MDC, multidisciplinary clinic; MDLC, multidisciplinary liver clinic; MDT, multidisciplinary team; tx, treatment; VA, Veterans Affairs.

1. Sinn DH, et al. *PLoS One*. 2019;14(1):e0210730. 2. Serper M, et al. *Gastroenterology*. 2017;152(8):1954-1964. 3. Yopp AC, et al. *Ann Surg Oncol*. 2014;21(4):1287-1295. 4. Zhang J, et al. *Curr Oncol*. 2013;20(2):e123-e131. 5. Chang TT, et al. *HPB (Oxford)*. 2008;10(6):405-411.

History of Treatment Landscape in HCC

Treatment options were limited for unresectable HCC



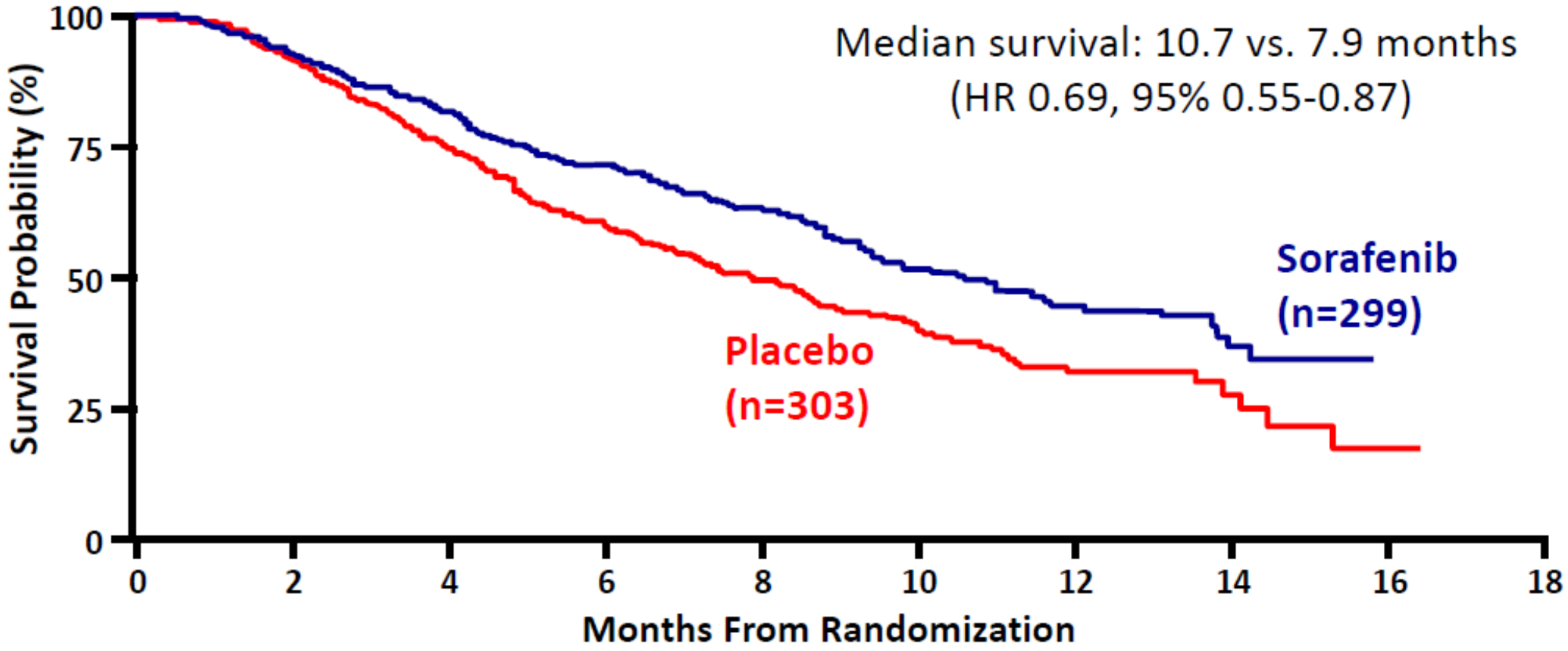
9 (FDA) or 5 (EMA) Systemic agents have been approved for use in HCC

2L, second line; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Consortium; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HR, hazard ratio; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NE, not estimable; ORR, overall response rate; OS, overall survival; PD, disease progression; TACE, transarterial chemoembolization; Y-90, Yttrium-90.

1. NCCN Flash Update. Available at: https://www.nccn.org/about/news/ebulletin/ebulletindetail.aspx?ebulletinid=1219. Accessed September 23, 2020.

The 1st line treatment for patients with advance stage HCC

Sorafenib improves survival for advanced HCC

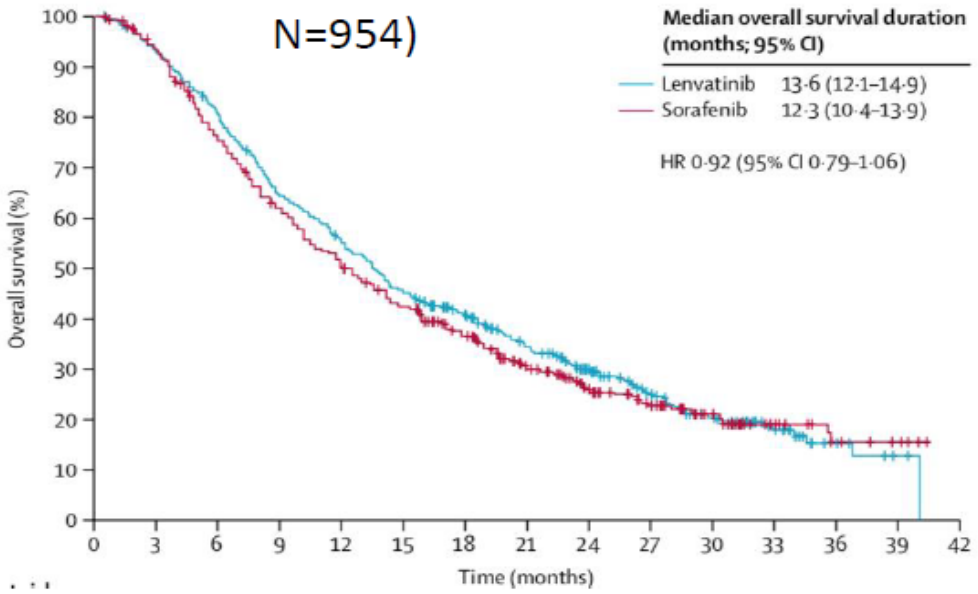


Llovet et al *NEJM* 2008

Several subsequent negative HCC trials

Drug	Treatment	Patients	Trial results
Sunitinib	1st line	1074	7.9 vs. 10.2 months
Brivanib	1st line	1150	9.5 vs. 9.9 months
Linafinib	1st line	1035	9.1 vs. 9.8 months
Erlotinib/sorafenib	1st line	720	9.5 vs. 8.5 months
Brivanib	2nd line	395	9.4 vs. 8.2 months
Everolimus	2nd line	546	7.6 vs. 7.3 months

Lenvatinib is non-inferior to sorafenib in OS but provides better response rates

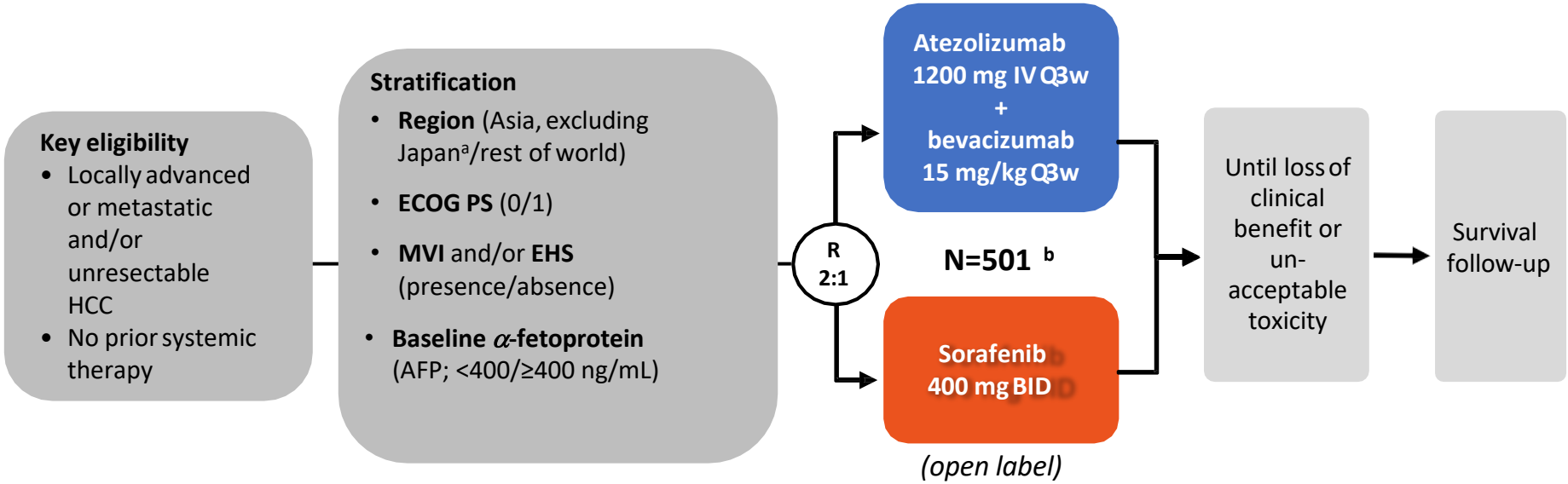


Response rates (mRECIST)

	Lenvantinib	Sorafenib
Response rate	41%	12%
Complete	2%	1%
Partial	38%	12%
Stable disease	33%	46%
Progressive disease	17%	32%
TTP (month)	7.4	3.7
	HR 0.60 (0.51 – 0.71)	

Kudo et al *Lancet* 2018

IMbrave150: Study Design



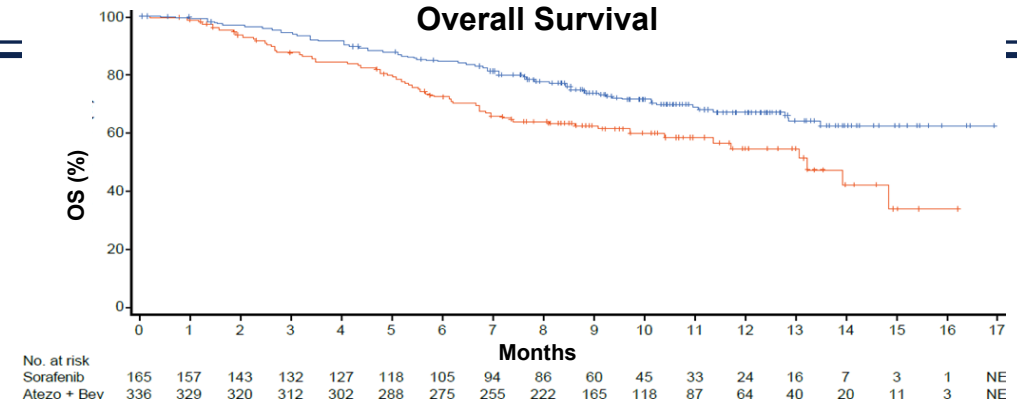
Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

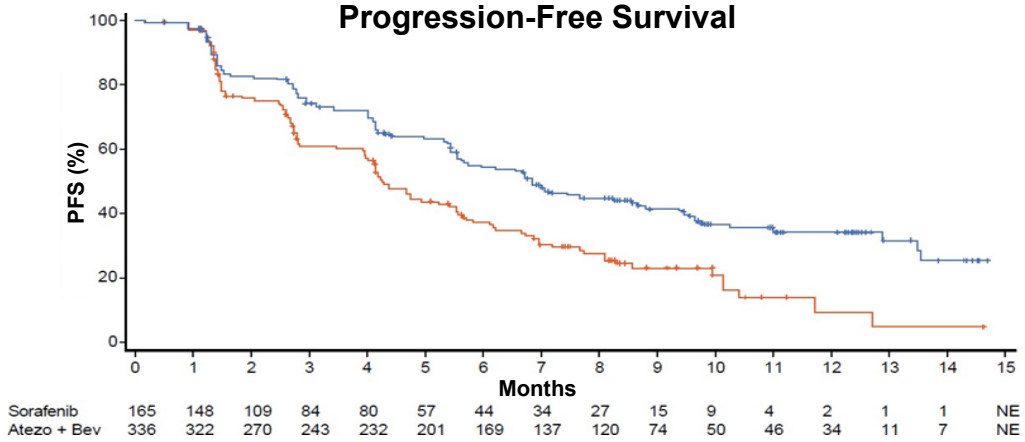
Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

[a]Japan is included in rest of world. [b]An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.
BID, twice daily; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; IRF, independent review facility; IV, intravenous; MVI, macrovascular invasion; ORR, objective response rate; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; R, randomized; RECIST, response evaluation criteria in solid tumors.
Cheng AL, et al. Presented at: ESMO Asia Congress; November 22-24, 2019; Singapore. Abstract LBA3.

IMbrave150: Atezolizumab + Bevacizumab Combination in 1L HCC

Significant Benefits in Both Coprimary Endpoints





	Median OS (95% CI), mo
Atezo + bev	NE
Sorafenib	13.2 (10.4–NE)
HR (95% CI)	0.58 (0.42–0.79) *P*=0.0006

Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

	Median PFS (95% CI), mo
Atezo + bev	6.8 (5.7–8.3)
Sorafenib	4.3 (4.0–5.6)
HR (95% CI)	0.59 (0.47–0.76) *P*<0.0001

Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

1
1

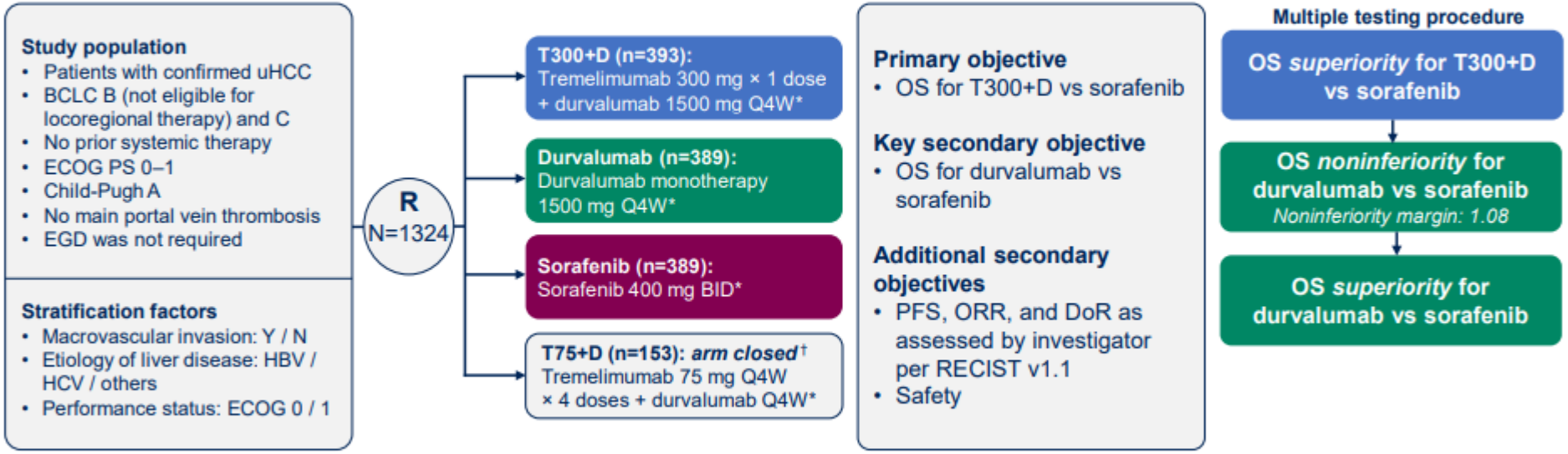
OS, overall survival; PFS, progression-free survival.

Cheng AL, et al. Presented at: ESMO Asia Congress; November 22-24, 2019; Singapore. Abstract LBA3.

Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma- HIMALAYA

HIMALAYA study design

HIMALAYA was an open-label, multicenter, global, Phase 3 trial



*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

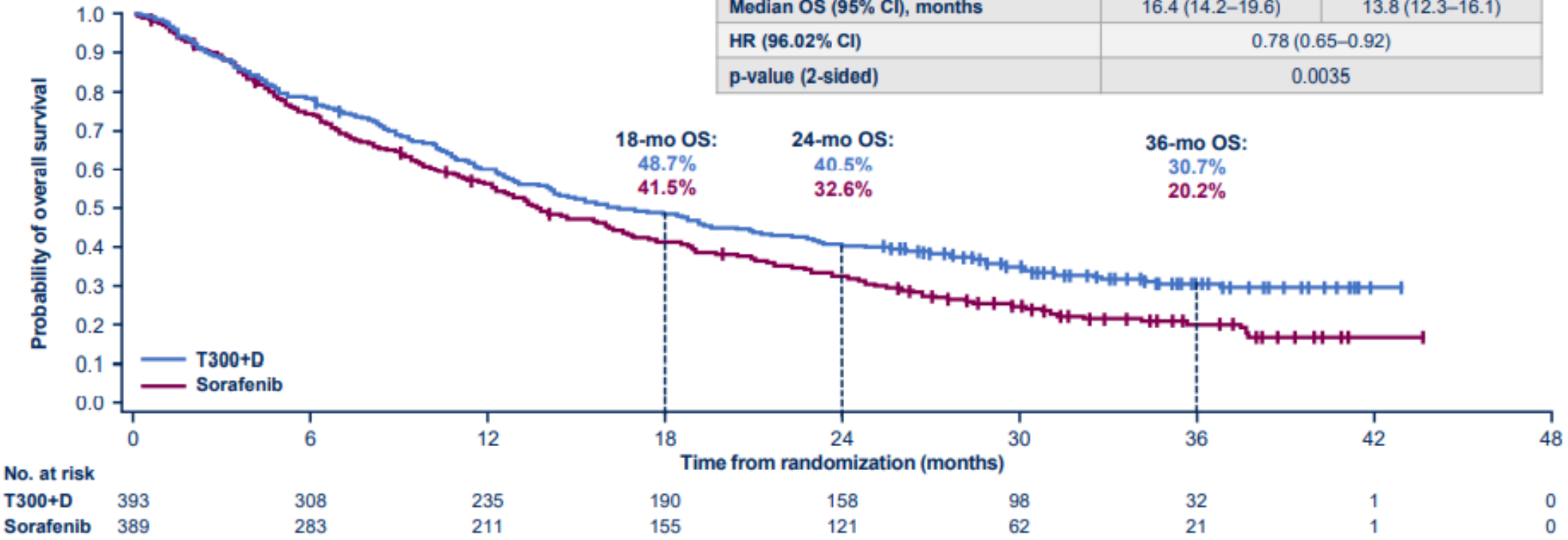
BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks.

Published June 6, 2022 NEJM Evidence
DOI:https://doi.org/10.1056/EVIDoa2100070

PRESENTED BY: Ghassan K Abou-Alfa, MD, MBA

Primary objective: overall survival for T300+D vs sorafenib

	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	



No. at risk									
T300+D	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 33.10 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.

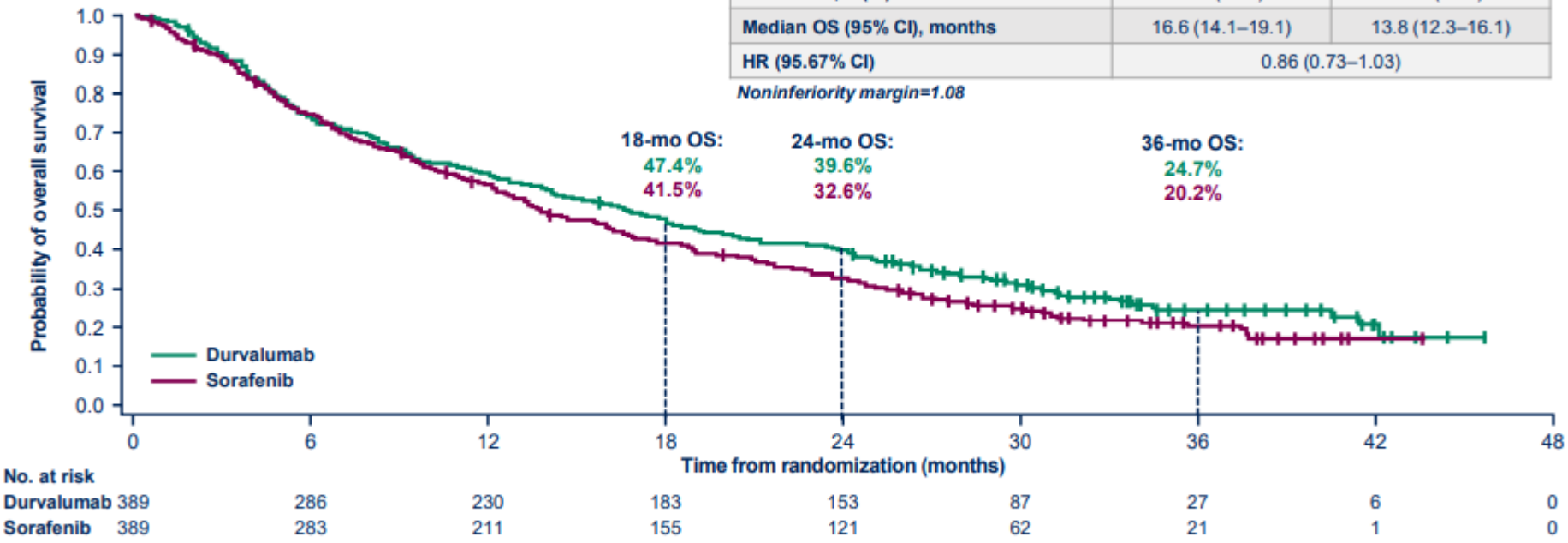
CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

PRESENTED BY: Ghassan K Abou-Alfa, MD, MBA

Secondary objective: overall survival for durvalumab vs sorafenib

	Durvalumab (n=389)	Sorafenib (n=389)
OS events, n (%)	280 (72.0)	293 (75.3)
Median OS (95% CI), months	16.6 (14.1–19.1)	13.8 (12.3–16.1)
HR (95.67% CI)	0.86 (0.73–1.03)	

Noninferiority margin=1.08



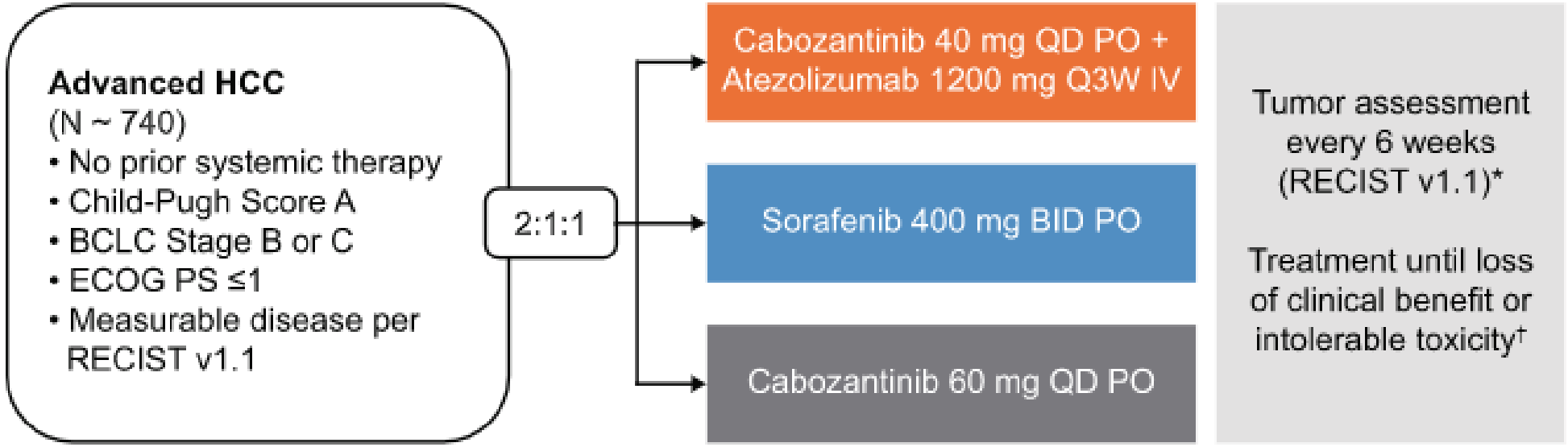
No. at risk								
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 32.56 (95% CI, 31.57–33.71) months for durvalumab and 32.23 (95% CI, 30.42–33.71) months for sorafenib.
CI, confidence interval; HR, hazard ratio; NI, noninferiority; OS, overall survival.

PRESENTED BY: Ghassan K Abou-Alfa, MD, MBA

Durvalumab is recommended on NCCN guideline

COSMIC-312: Cabozantinib Plus Atezolizumab Improves Progression-Free Survival in Advanced Hepatocellular Carcinoma ESMO Asia 2021



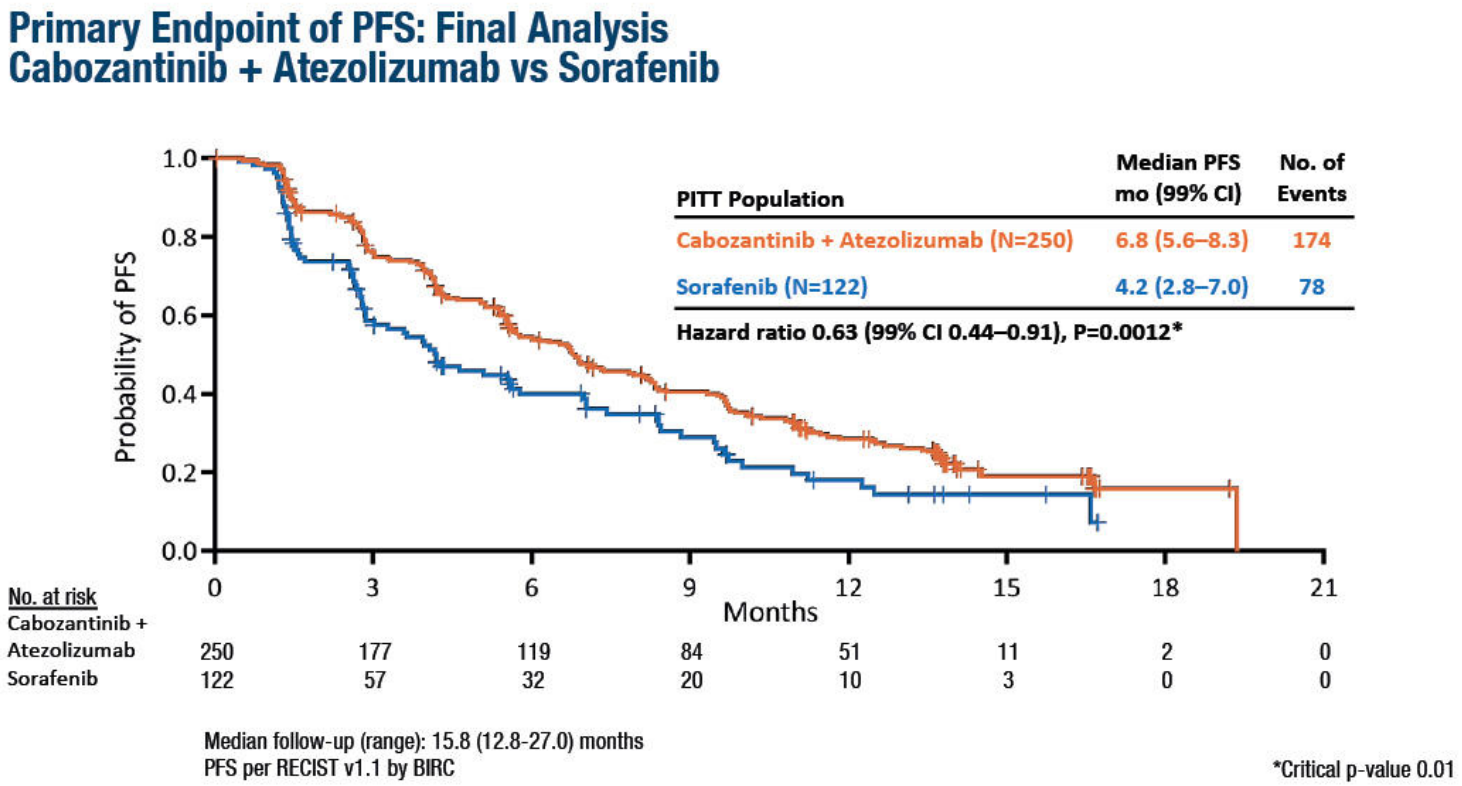
Stratification
- Disease etiology (HBV, HCV, other)
- Region (Asia, other)
- Presence of extrahepatic disease and/or macrovascular invasion (yes/no)

Primary Endpoints
- PFS and OS of cabozantinib plus atezolizumab vs sorafenib

Secondary Endpoint
- PFS of single-agent cabozantinib vs sorafenib

*Every 6 weeks for the first 48 weeks then every 12 weeks thereafter
†Patients may be treated beyond progression if there is a clinical benefit in the opinion of the investigator.

Primary Study Objectives: PFS – HR 0.63

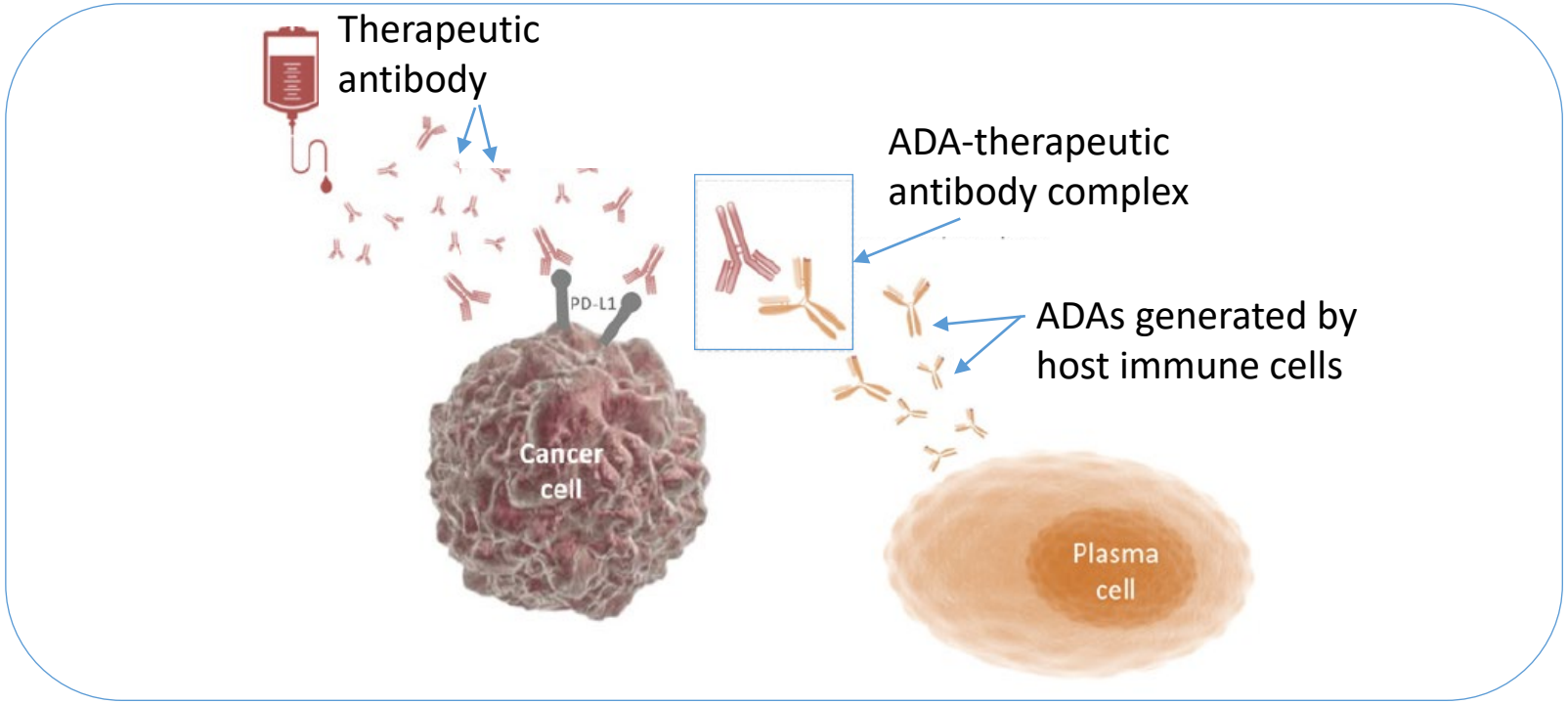


Primary Study Objectives: OS- HR 0.90

Median overall survival was 15.4 months with cabozantinib/atezolizumab and 15.5 months with sorafenib (HR = 0.90; *P* = .438).

Impact of ADAs in Cancer

- Systemic administration of humanized monoclonal antibodies can induce production of ADAs in patients with HCC[1]
- ADAs may cause loss of drug activity via mechanisms including[2]:
  - Blockade of the drug target binding (neutralizing antibodies)
  - Increasing the clearance of the ADA-drug complex



ADA, antidrug antibodies; HCC, hepatocellular carcinoma.

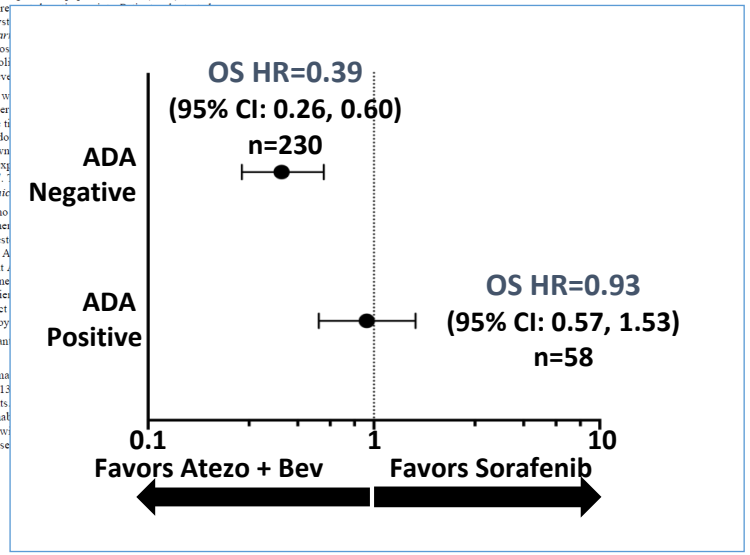
1. Chon HJ, et al. Presented at: ASCO Annual Meeting; June 3-7, 2022; Chicago, IL. 2. Enrico D, et al. *Clin Cancer Res*. 2020;26(4):787-792.

ADAs May Affect the Efficacy of Atezolizumab + Bevacizumab in HCC

ADA Information in the Atezolizumab PI[1]

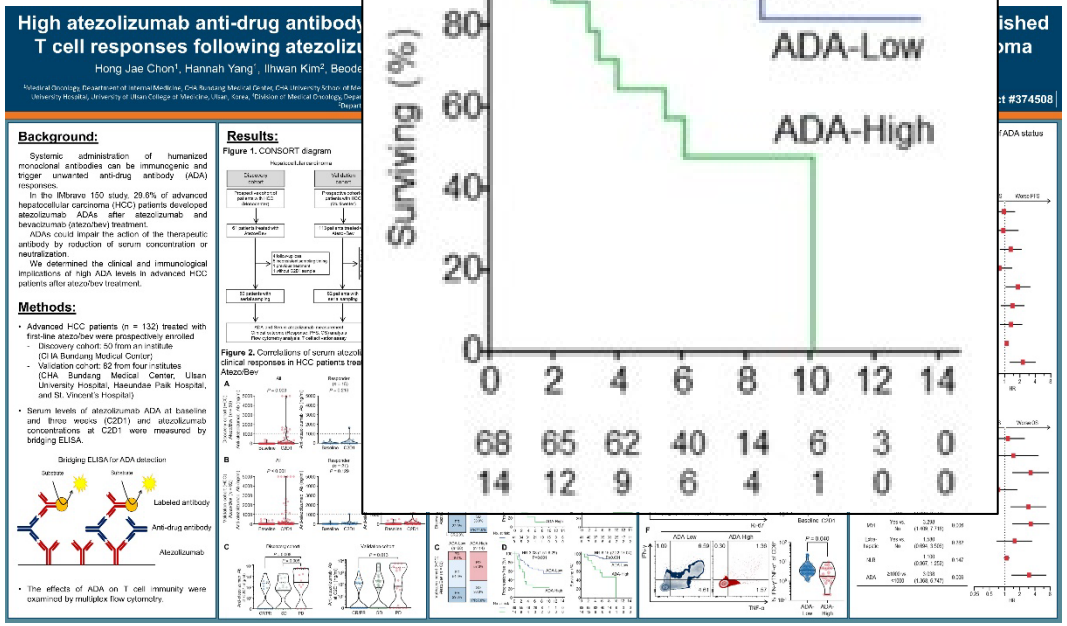
28% (n=88/315) of ADA-evaluable patients with HCC who received atezolizumab and bevacizumab in IMbrave150 tested positive for treatment-emergent ADA at one or more post-dose time points

The subset of patients who were ADA-positive by week 6 (20%; 58/288) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 6



ASCO 2022: Prospective Korean Study of Clinical Outcomes by ADA Status[2]

N=132 patients treated with first-line atezolizumab + bevacizumab

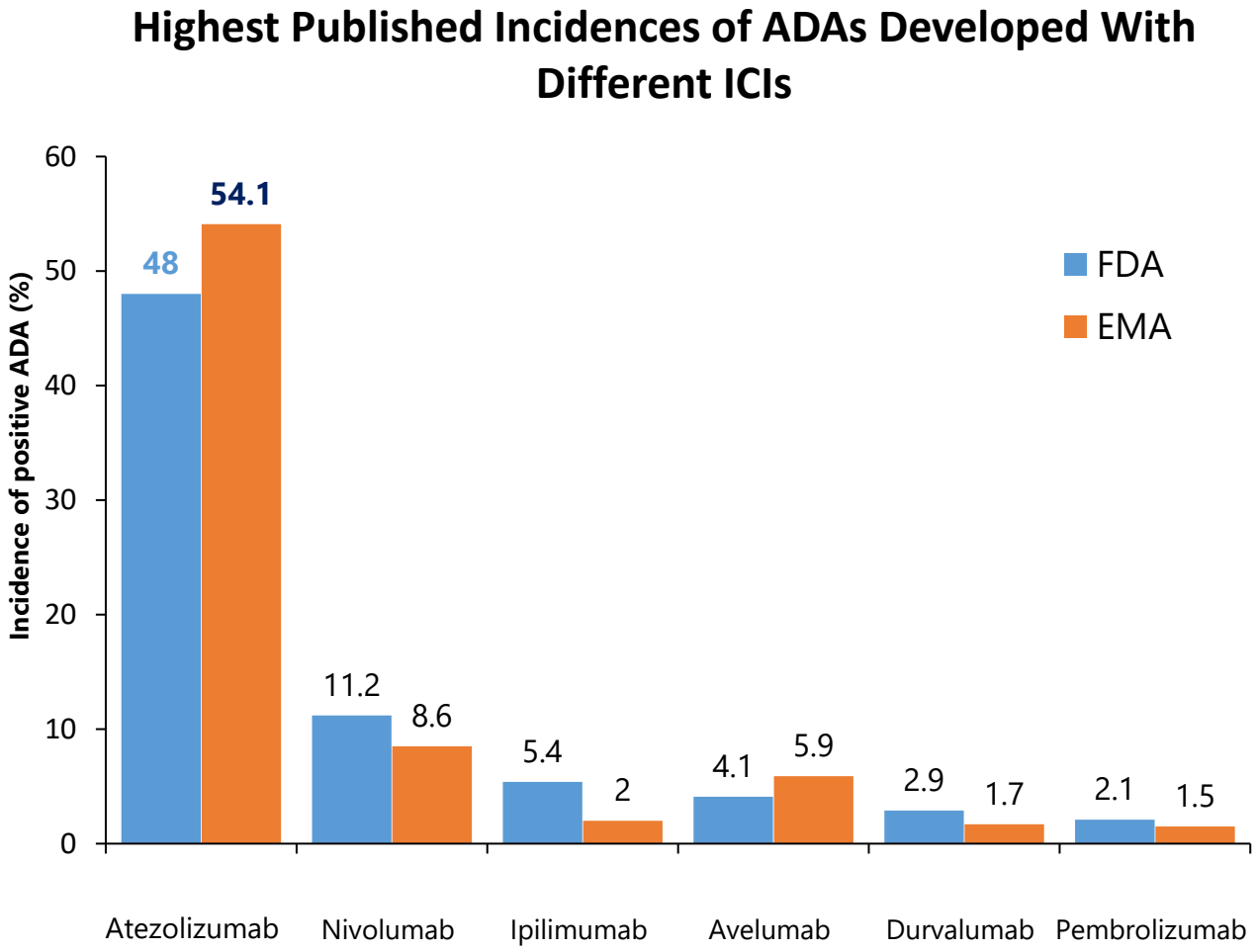


ADAs to durvalumab were observed in 9 (3.1%) and 7 (2.5%) of patients receiving STRIDE or durva monotherapy, respectively, in the HIMALAYA trial[3]

ADA, anti-drug antibody; HR, hazard ratio; PI, prescribing information.

1. Atezolizumab [Prescribing Information]. South San Francisco, CA: Genentech, Inc; 2021. 2. Chon HJ, et al. Presented at: ASCO Annual Meeting; June 3-7, 2022; Chicago, IL. 3. Abou-Alfa GK, et al. *NEJM Evid*. 2022;0(0):EVIDoa2100070.

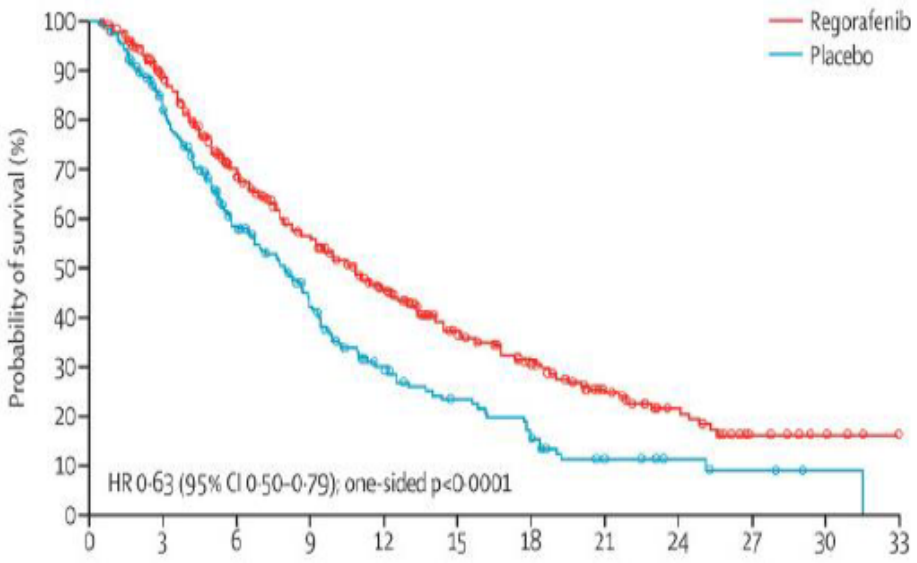
ADA Incidence By Immunotherapeutic Agent



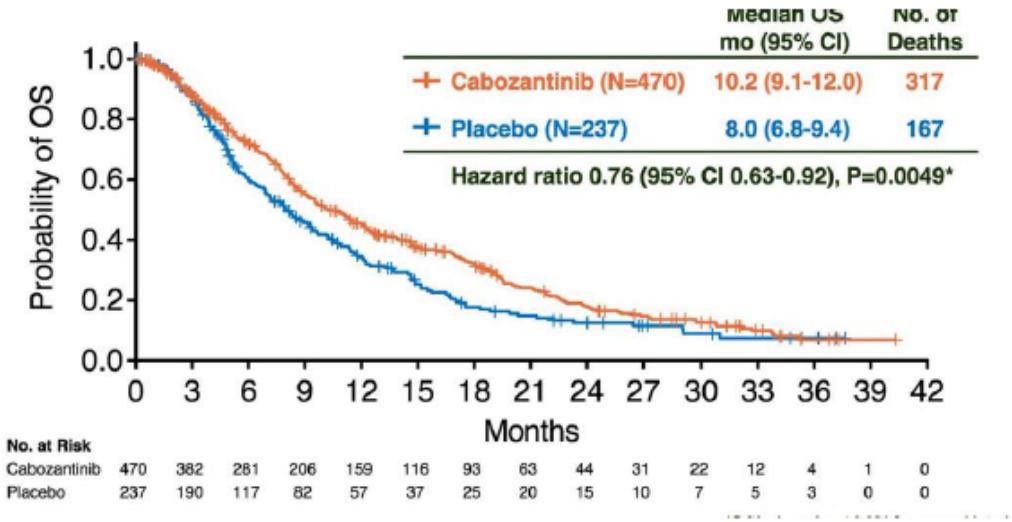
EMA, European Medicines Agency; FDA, US Food and Drug Administration; ICI, immune checkpoint inhibitor.
Enrico D, et al. *Clin Cancer Res*. 2020;26(4):787-792.

The Subsequent lines of therapy in HCC patients who progressed or not tolerating 1st line therapy

New agents can improve survival as 2nd line therapy for advanced HCC

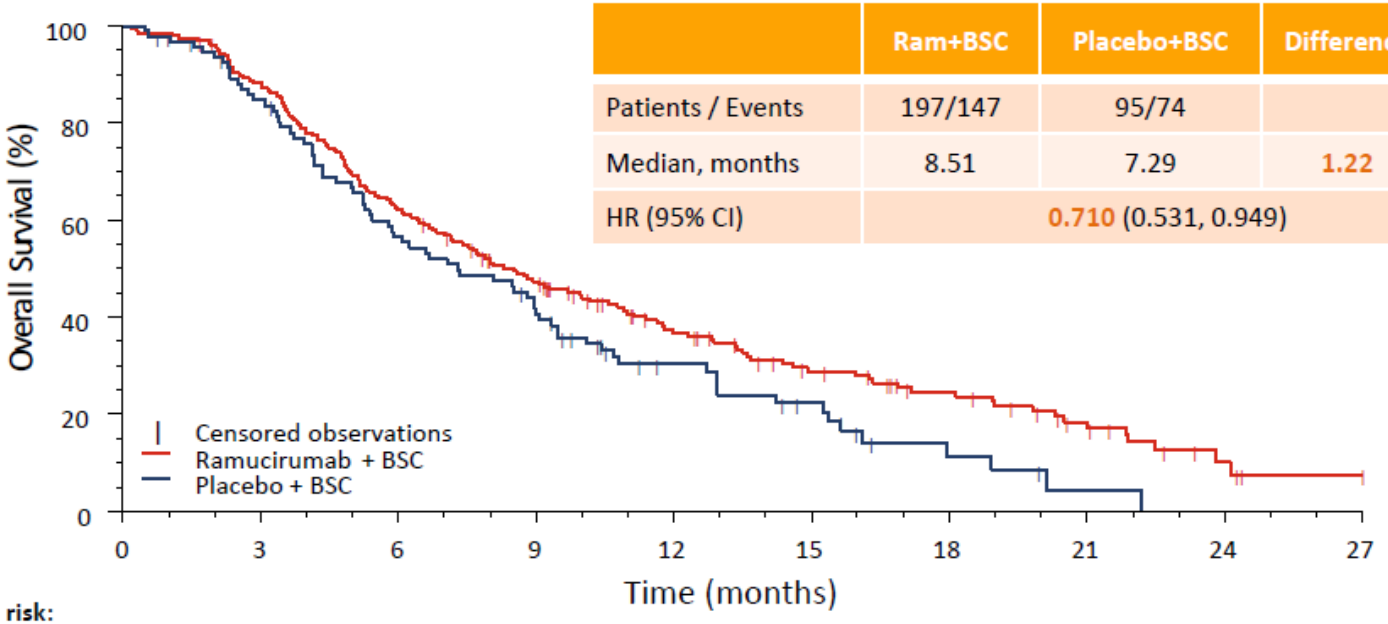


Median survival: 10.6 vs. 7.8 months
(HR 0.63, 95% 0.50-0.79)



Bruix et al *Lancet* 2017

REACH 2 study



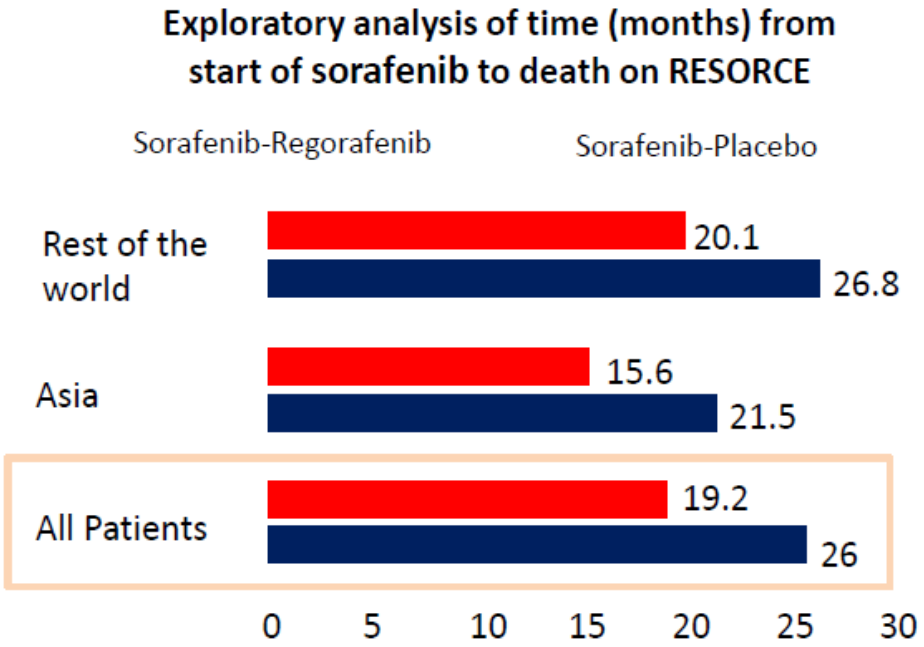
	Ram+BSC	Placebo+BSC	Difference	P-value
Patients / Events	197/147	95/74		
Median, months	8.51	7.29	1.22	
HR (95% CI)	0.710 (0.531, 0.949)			0.0199

Patients at risk:

Ram + BSC	197	172	121	87	56	37	26	14	4	0
Placebo + BSC	95	76	50	36	19	12	4	1	0	0

BSC, best-supportive care; CI, confidence interval; HR, hazard ratio; Ram, ramucirumab
Zhu AX, et al. Lancet Oncol 2019;20:282-96

Sequential therapy can provide prolonged survival

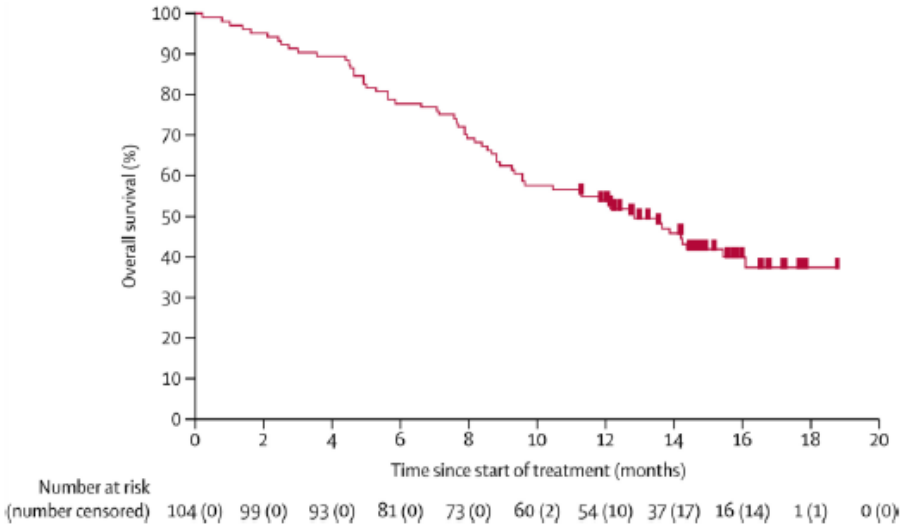


Survival	Sorafenib-regorafenib (n-379)	Sorafenib-placebo (n=194)
6 months	97%	97%
12 months	82%	76%
24 months	53%	42%
36 months	31%	20%
48 months	19%	12%
60 months	16%	3%
72 months	10%	3%

Finn et al *J Hepatology* 2018

Pembrolizumab leads to durable responses and likely meaningful survival as shown in a phase I study

Best Response	Patients (n=104)
Objective response Complete Partial	17.3% 1% 16.3%
Stable disease	44.2%
Progression	32.7%



- Most common grade 3-4 TRAEs were increased AST (7%), increased ALT (4%), fatigue (4%)
- One death due to ulcerative esophagitis attributed to treatment

Zhu et al *ASCO* 2018

However, phase III study Keynote 240 did not meet primary study endpoint
- Pembrolizumab did not show **significant** OS improvement over placebo treatment.

Pembrolizumab Plus Best Supportive Care Versus Placebo Plus Best Supportive Care as Second-line Therapy in Patients in Asia With Advanced Hepatocellular Carcinoma: Phase 3 KEYNOTE-394 Study

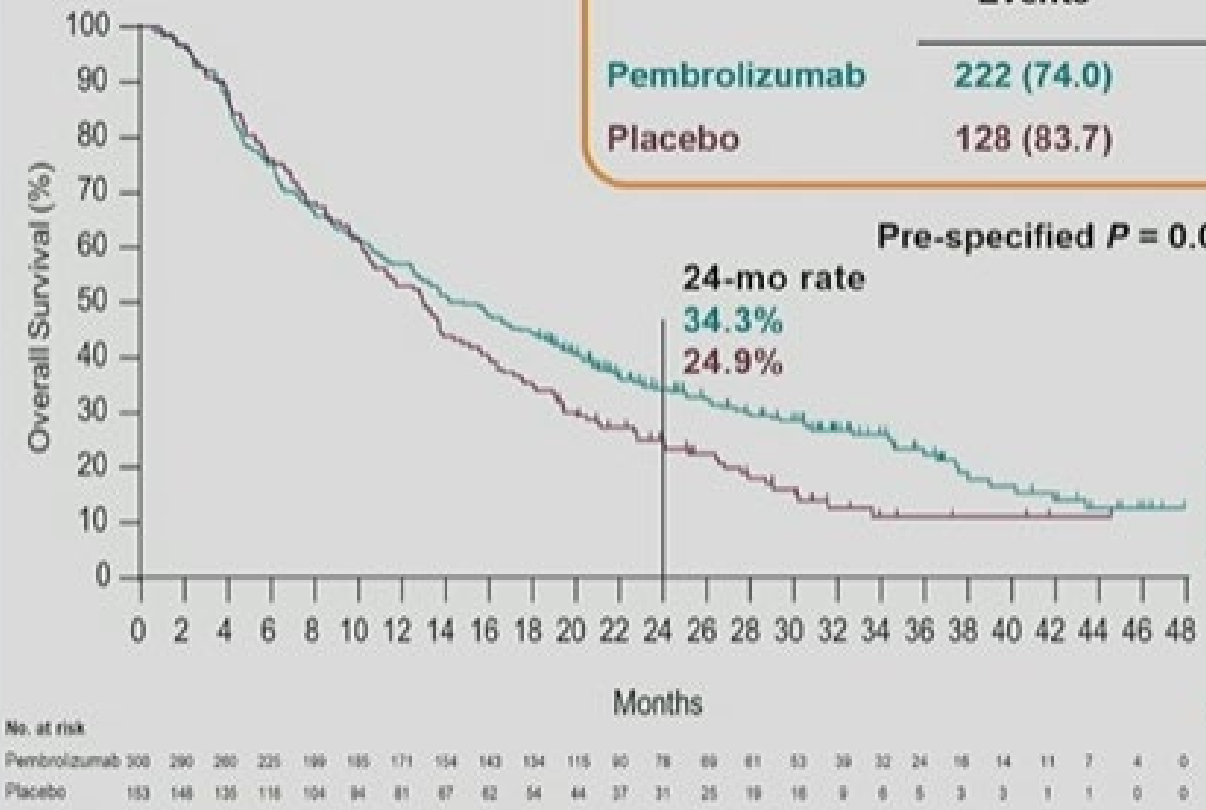
Shukui Qin, MD[1]; Zhendong Chen, MD[2]; Weijia Fang, MD[3]; Zhenggang Ren, MD[4]; Ruocai Xu, MD[5]; Baek-Yeol Ryoo, MD[6]; Zhiqiang Meng, MD[7]; Yuxian Bai, MD[8]; Xiaoming Chen, MD[9,10]; Xiufeng Liu, MD[1]; Juxiang Xiao, MD[11]; Gwo Fuang Ho, MRCP, MBChB[12]; Yimin Mao, MD[13]; Xin Wang, MD[14]; Jieer Ying, MD[15]; Jianfeng Li, MD[16]; Wen Yan Zhong, PhD[17]; Yu Zhou, MD[17]; Abby B. Siegel, MD[18]; Chunyi Hao, MD[19]

[1]Jinling Hospital, Nanjing University of Chinese Medicine, Nanjing, China; [2]The Second Affiliated Hospital of Anhui Medical University, Hefei, China; [3]The First Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China; [4]Zhongshan Hospital, Fudan University, Shanghai, China; [5]Hunan Cancer Hospital, Changsha, China; [6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [7]Fudan University Shanghai Cancer Center, Shanghai, China; [8]Harbin Medical University Cancer Hospital, Harbin, China; [9]Guangdong Provincial People's Hospital, Guangzhou, China;[10]Guangdong Academy of Medical Science, Guangzhou, China; [11]The First Affiliated Hospital of Xi'An Jiaotong University, Xi'an, China; [12]University Malaya Medical Centre, Kuala Lumpur, Malaysia; [13]Shanghai Jiaotong University School of Medicine, Renji Hospital, Shanghai, China; [14]West China Hospital of Sichuan University, Chengdu, China; [15]Cancer Hospital of The University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China; [16]MSD China, Beijing, China; [17]MSD China, Shanghai, China; [18]Merck & Co., Inc., Kenilworth, NJ, USA; [19]Peking University Cancer Hospital, Beijing, China

Overall Survival

	Events	OS, median (95% CI), mo	HR (95% CI)	*P*[a]
Pembrolizumab	222 (74.0)	14.6 (12.6-18.0)	0.79 (0.63-0.99)	*0.0180*
Placebo	128 (83.7)	13.0 (10.5-15.1)		

Pre-specified *P* = 0.0193 required for statistical significance

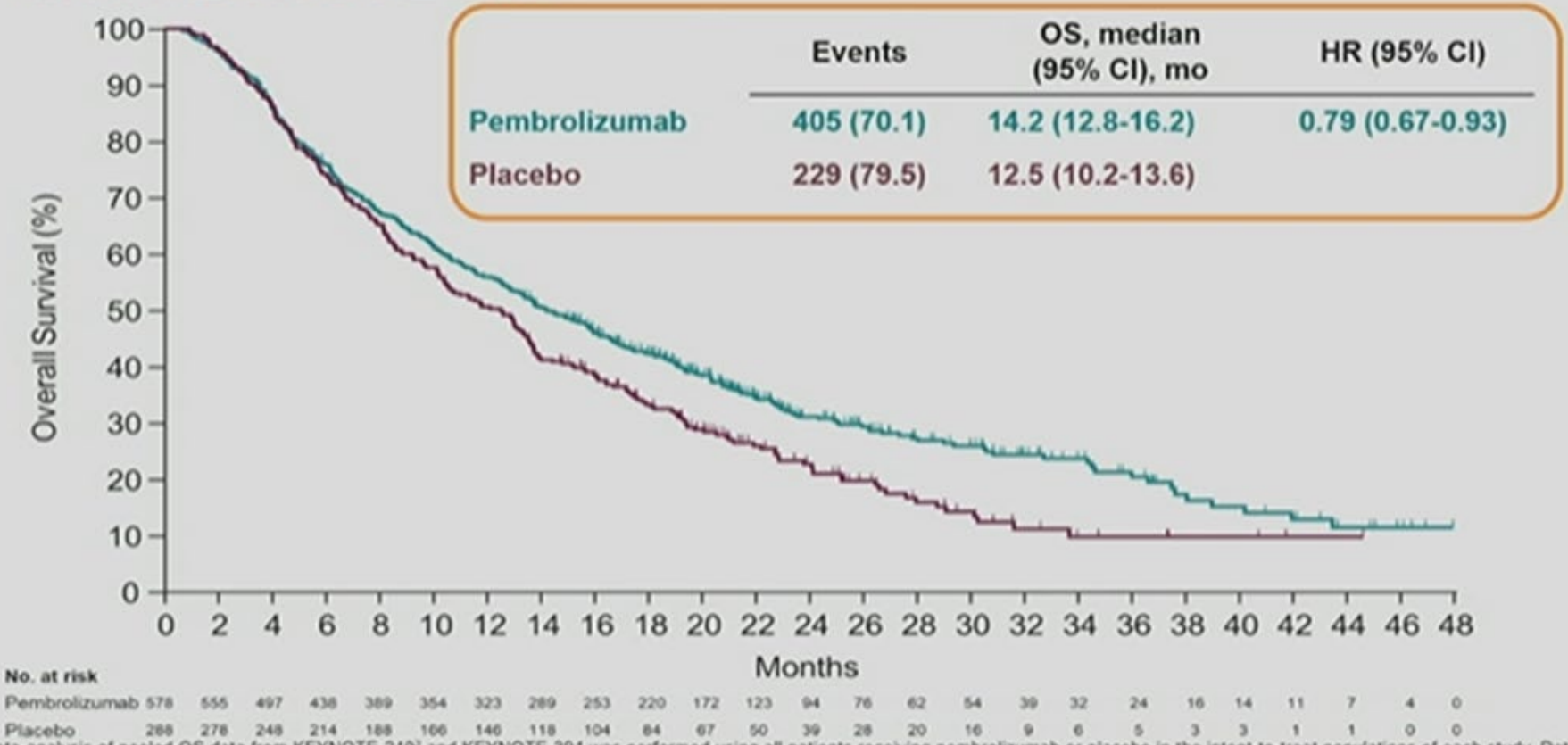


Post-Study Systemic Anticancer Therapy

	Pembrolizumab n = 300	Placebo n = 153
Any post-study systemic anticancer therapy	152 (50.7)	102 (66.7)
PD-1 inhibitor or PD-L1 inhibitor[b]	62 (20.7)	43 (28.1)

[a]One-sided *P* for testing difference. Data cutoff: June 30, 2021 (final analysis). [b]Includes both with/without prior exposure to other post-study systemic anticancer therapies.

Overall Survival Based on Meta-Analysis of KEYNOTE-394 and KEYNOTE-240



	Events	OS, median (95% CI), mo	HR (95% CI)
Pembrolizumab	405 (70.1)	14.2 (12.8-16.2)	0.79 (0.67-0.93)
Placebo	229 (79.5)	12.5 (10.2-13.6)	

No. at risk

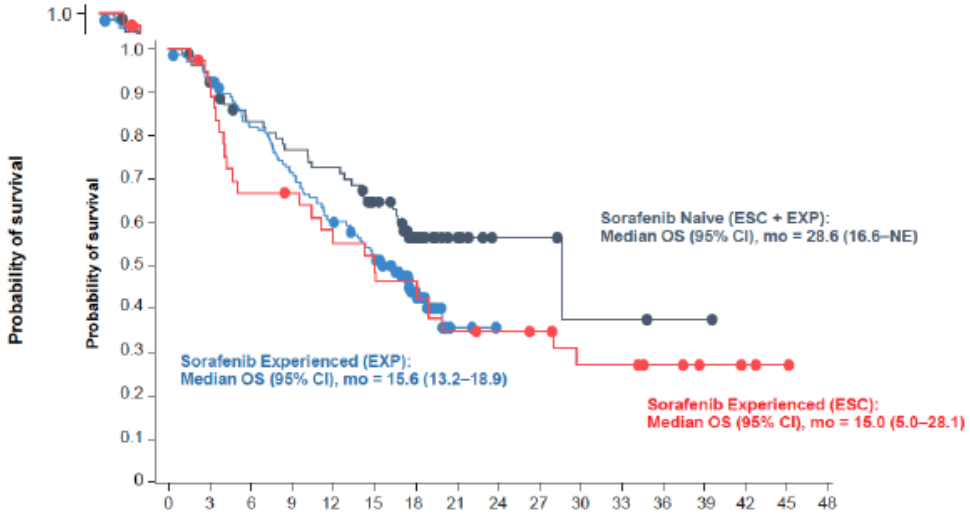
Pembrolizumab	578	555	497	438	389	354	323	289	253	220	172	123	94	76	62	54	39	32	24	16	14	11	7	4	0
Placebo	288	278	248	214	188	166	146	118	104	84	67	50	39	28	20	16	9	6	5	3	3	1	1	0	0

Meta-analysis of pooled OS data from KEYNOTE-240[2] and KEYNOTE-394 was performed using all patients receiving pembrolizumab or placebo in the intent-to-treat populations of each study. Data cutoff: KEYNOTE-240: January 2, 2019 (final analysis; Finn RS et al. *J Clin Oncol* 2020;38:193-202); KEYNOTE-394: June 30, 2021 (final analysis).

Met Primary Study Objective

Nivolumab leads to durable responses and likely meaningful survival – as shown in a phase I study

	SOR naïve	SOR experienc
Objective response	20%	15%
Complete	1%	1%
Partial	19%	14%
Stable disease	31%	38%
Progression	40%	37%



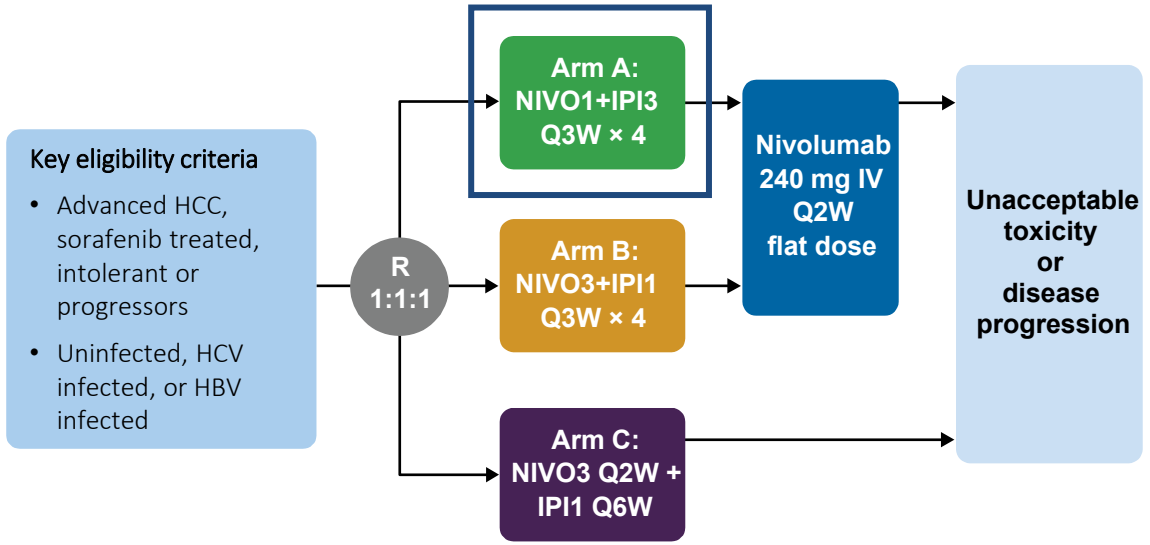
Tumor response is durable!
Median duration of response 16.6 months, with 55% having response > 12 months

Lack of predictive biomarker for response:
No difference in response by tumor PDL1 expression. MSI high rare (<2%) in HCC

El-Khoueiry et al *Lancet* 2017

However, phase III study Checkmate 459 did not meet primary study endpoint
- Nivolumab did not show **significant** OS improvement over Sorafenib treatment.

Figure 1. CheckMate 040 NIVO+IPI combination cohort study design



Primary endpoints

- Safety and tolerability using NCI CTCAE v4.0
- ORR and DOR based on investigator assessment[a]

Secondary endpoints

- DCR
- PFS
- OS
- TTP
- TTR

Other key endpoints

- BOR and ORR based on BICR-assessed tumor response[a]

[a]Using RECIST v1.1.
Minimum follow-up at time of data cutoff: 28 months.
BICR, blinded independent central review; BOR, best overall response; DCR, disease control rate; DOR, duration of response; IPI1, ipilimumab 1 mg/kg; IV, intravenous; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NIVO3, nivolumab 3 mg/kg; PFS, progression-free survival; R, randomization; TTP, time to progression; TTR, time to response.

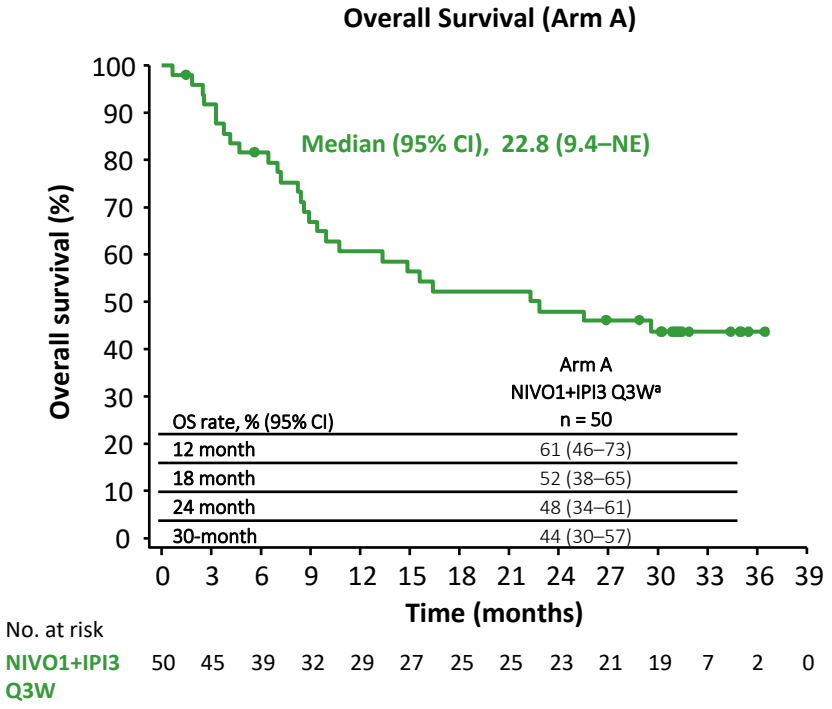
Response, Disease Control, and Durability

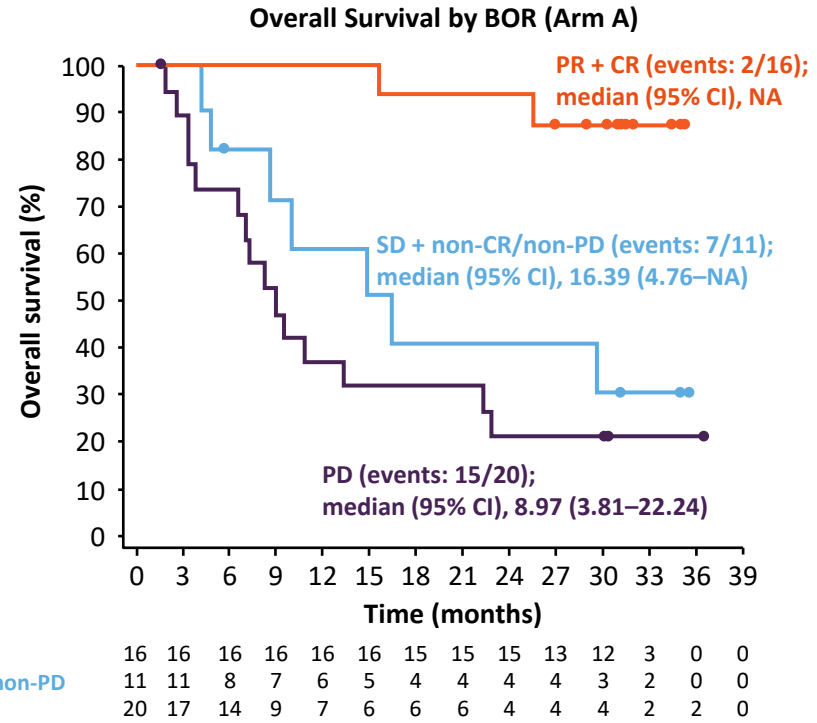
	Arm A NIVO1+IPI3 Q3W n = 50[a]
ORR by BICR using RECIST v1.1,[b] n (%)	16 (32)
BOR, n (%)	
CR	4 (8)
PR	12 (24)
SD	9 (18)
PD	20 (40)
Unable to determine	3 (6)
DCR,[c] n (%)	27 (54)
Median TTR (range),[d] months	2.0 (1.1–12.8)
Median DOR (range), [d] months	17.5 (4.6 to 30.5+)

- Four patients had a CR and the DCR (CR + PR + SD + non-CR/non-PD) was >50%

[a]NIVO1/ IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose; [b]Defined as CR + PR; [c]Defined as CR + PR + SD + non-CR/non-PD; [d]Patients with CR or PR.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
Yau T, et al. Presented at the American Society of Clinical Oncology Annual Meeting 2019; May 31–June 4, 2019; Chicago, IL. Poster 4012.

Overall Survival





- Median OS was 22.8 months, with an OS rate of 44% through 30 months

- Median OS for patients with PR + CR (2/16 events) was not reached

[a]NIVO1/ IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose.
mo, month; NA, not achieved; NE, not estimable.

Summary

First Line

1. Bevacizumab + Atezolizumab (IMBRAVE 150) 2020
2. Lenvatinib (REFLECT) 2018
3. Sorafenib (SHARP) 2007
4. Durvalumab 2022 (NCCN)
5. Durvalumab + Tremelimumab (pending FDA approval)

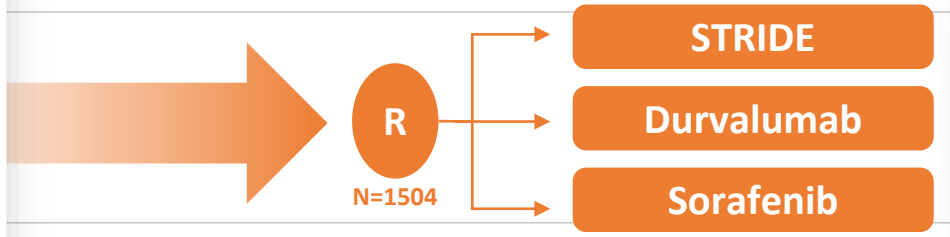
Subsequent lines:

1. Regorafenib 2017
2. Cabozantinib 2019
3. Ramucirumab 2019
4. Pembrolizumab 2018
5. Nivolumab + Ipilimumab 2020

Immunotherapy-Based Regimens on the Horizon for Advanced HCC

HIMALAYA[1]

Patient Population
- BCLC Stage B (not eligible for LRT) or Stage C
- Child-Pugh Class A



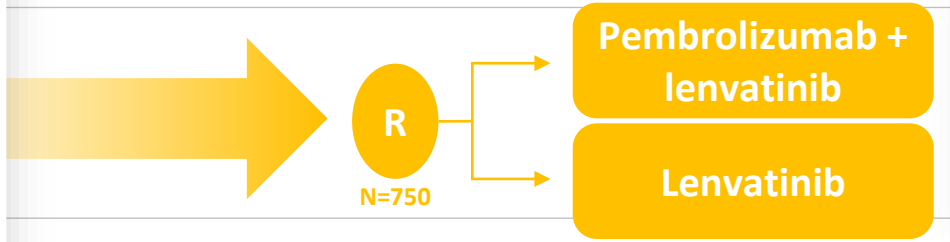
1EP: OS *(STRIDE vs sorafenib)*

2EPs: TTP, PFS, ORR, DCR, DoR

STRIDE = **S**ingle **T**remelimumab **R**egular **I**nterval **D**urvalumab

LEAP-002[2]

Patient Population
- BCLC Stage C; BCLC Stage B, not amenable to LRT or curative treatment
- Child-Pugh Class A

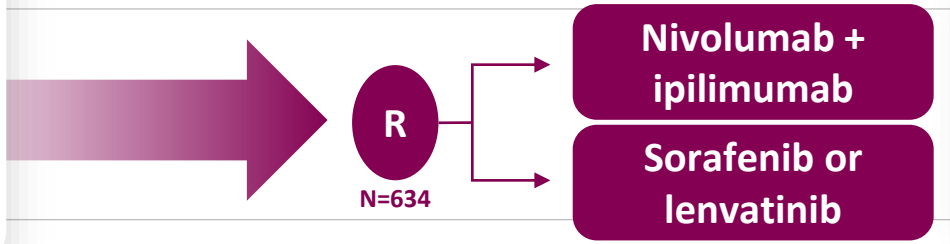


1EP: PFS, OS

2EPs: ORR, DoR, DCR, TTP, safety

CheckMate 9DW[3]

Patient Population
- Child-Pugh score 5 or 6
- Excluded active BMs or leptomeningeal metastases

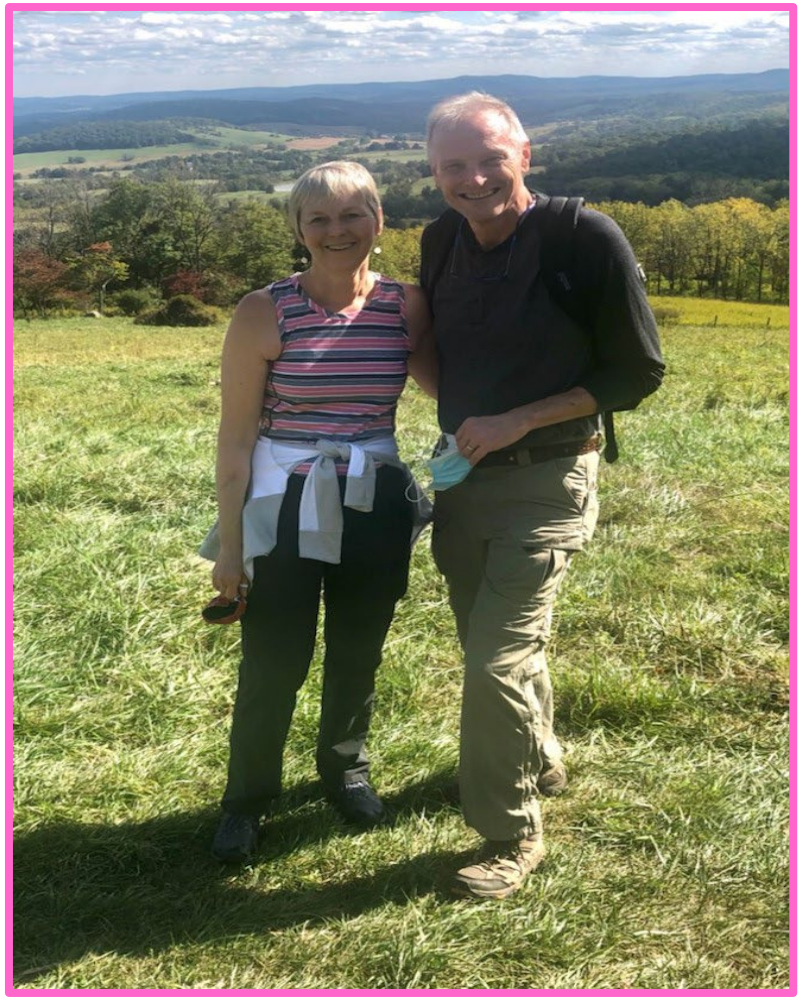


1EP: OS

2EPs: ORR, DoR, TTSD

1EP, primary endpoint; 2EP, secondary endpoint; BCLC, Barcelona Clinic Liver Cancer; BM, brain metastases; DCR, disease control rate; DoR, duration of response; HCC, hepatocellular carcinoma; LRT, locoregional therapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TTP, time to disease progression; TTSD, time to symptom deterioration.

1. ClinicalTrials.gov. NCT03298451. Accessed March 28, 2022. https://clinicaltrials.gov/ct2/show/NCT03298451. 2. ClinicalTrials.gov. NCT03713593. Accessed March 28, 2022. https://clinicaltrials.gov/ct2/show/NCT03713593. 3. ClinicalTrials.gov. NCT04039607. Accessed March 28, 2022. https://clinicaltrials.gov/ct2/show/NCT04039607.



Dr. John and Liza Marshall. Off Our Chests – A Candid Tour Through the World of Cancer.