ANTHONY EL-KHOUEIRY, MD

HEPATOCELLULAR CANCER: LATEST ADVANCES

RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

GRANT/RESEARCH SUPPORT: ASTRA ZENECA; ASTEX
CONSULTANT: GENENTECH, BAYER, ASTRA-ZENECA, EXELIXIS, EISAI, BMS, CYTOMX, PIERIS, MERCK

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The Medical Educator Consortium

14th Annual California Cancer Conference Consortium
August 10-12, 2018

Hepatocellular Cancer: Latest Advances

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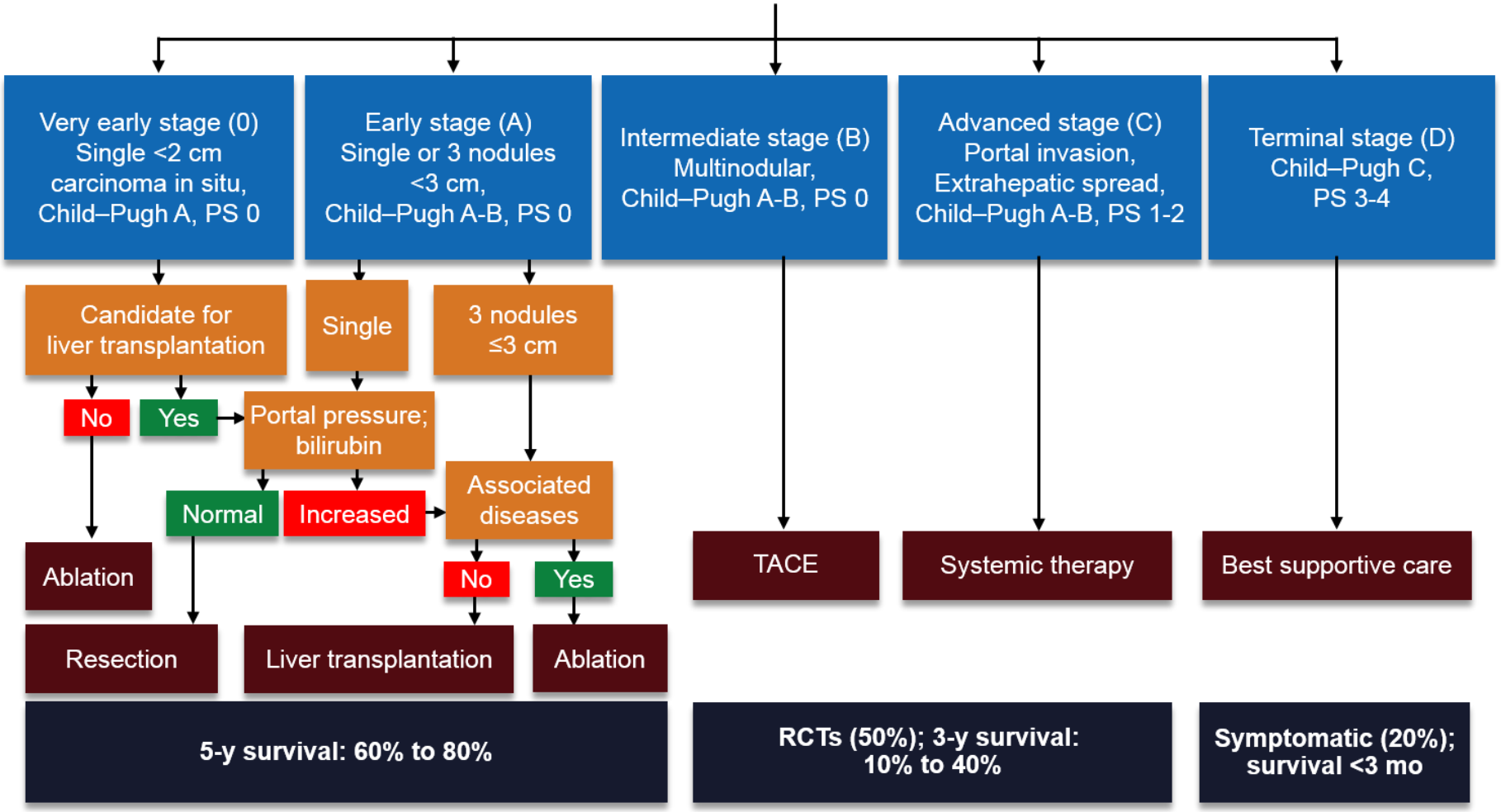
Norris Comprehensive Cancer Center

HCC: Barcelona Clinic Liver Cancer Staging

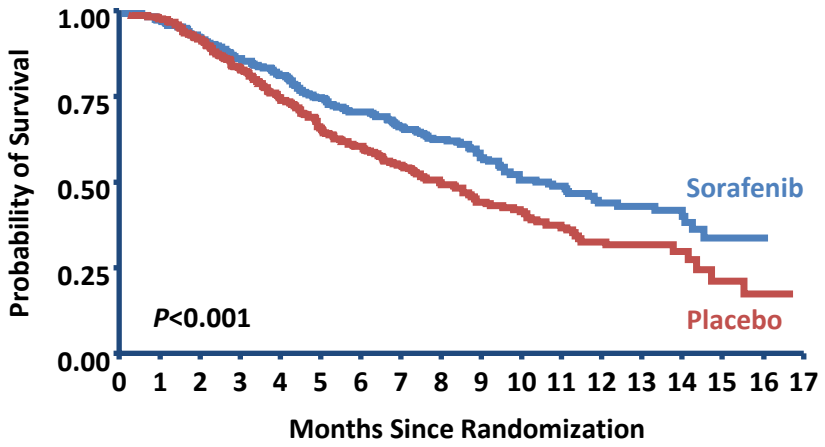


What is “advanced” HCC

- Clinical Trials Definition
  - Extrahepatic metastases
  - Vascular invasion
  - Not candidates for locoregional therapy options
- In practice
  - Extrahepatic metastases
  - Vascular invasion
    - Main vs. branch portal vein
  - Failure of liver directed therapies
    - No uniform definition
  - Liver limited disease BUT multifocal with large lesions

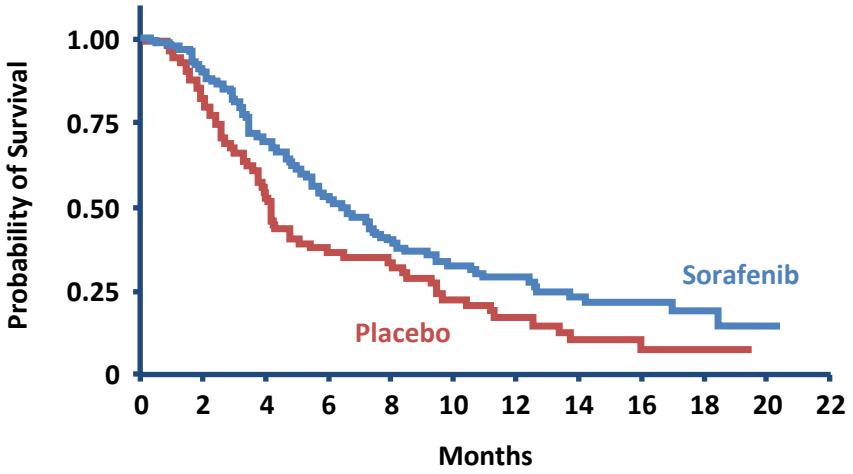
Treatment of Advanced HCC: 2007–2016

Sorafenib Outcomes in Western Patients[1]



	Sorafenib (n=299), %	Placebo (n=303), %
Best response by RECIST[2]*		
Complete response	0	0
Partial response	2.3	0.7
Stable disease	71	67
Progressive disease	18	24
Progression-free rate at 4 mo[2]	62	42

Sorafenib Outcomes in Asian Patients[2]



	Sorafenib (n=150)	Placebo (n=76)
Complete response	0 (0)	0 (0)
Partial response	5 (3.3)	1 (1.3)
Stable disease	81 (54.0)	21 (27.6)
Progressive disease	46 (30.7)	41 (54.0)
Not assessable	18 (12.0)	13 (17.1)

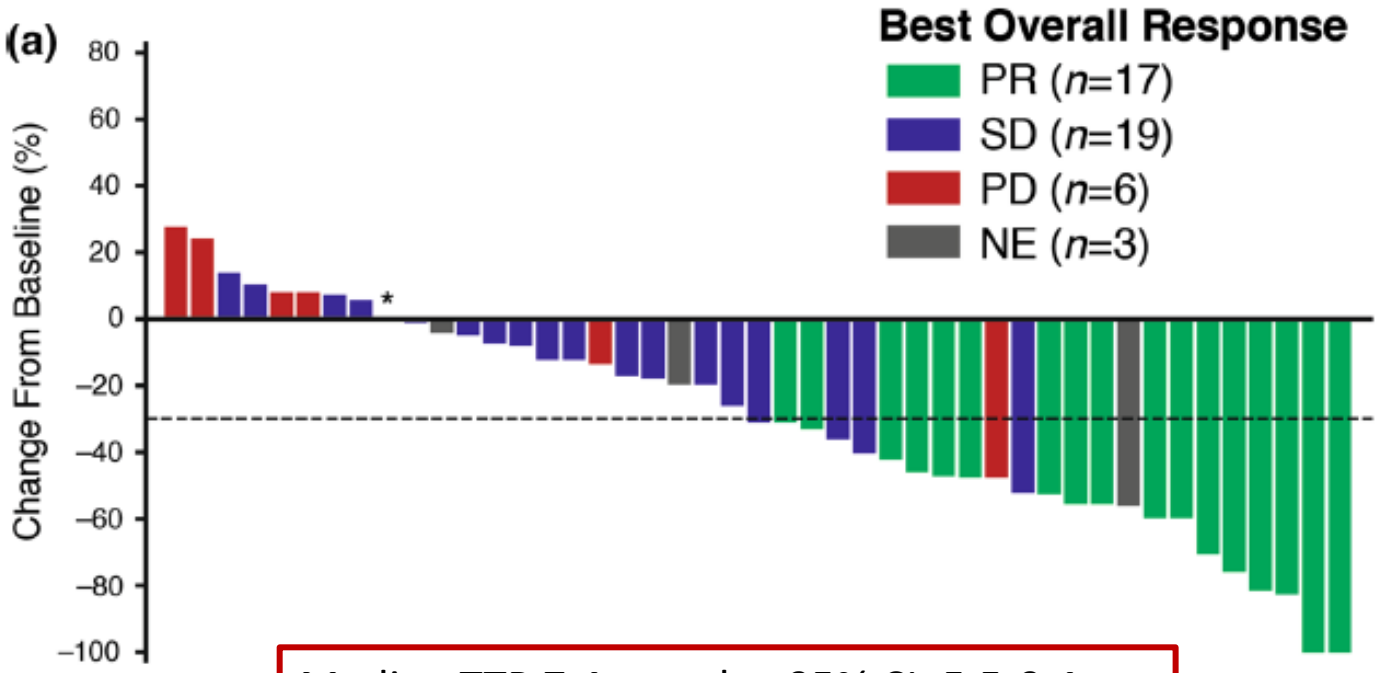
HCC=hepatocellular carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors.

1. Llovet JM et al. *N Engl J Med*. 2008;359(4):378-390. 2. Cheng AL et al. *Lancet Oncol*. 2009;10(1):25-34.

What's new in first line?

Lenvatinib in first line HCC

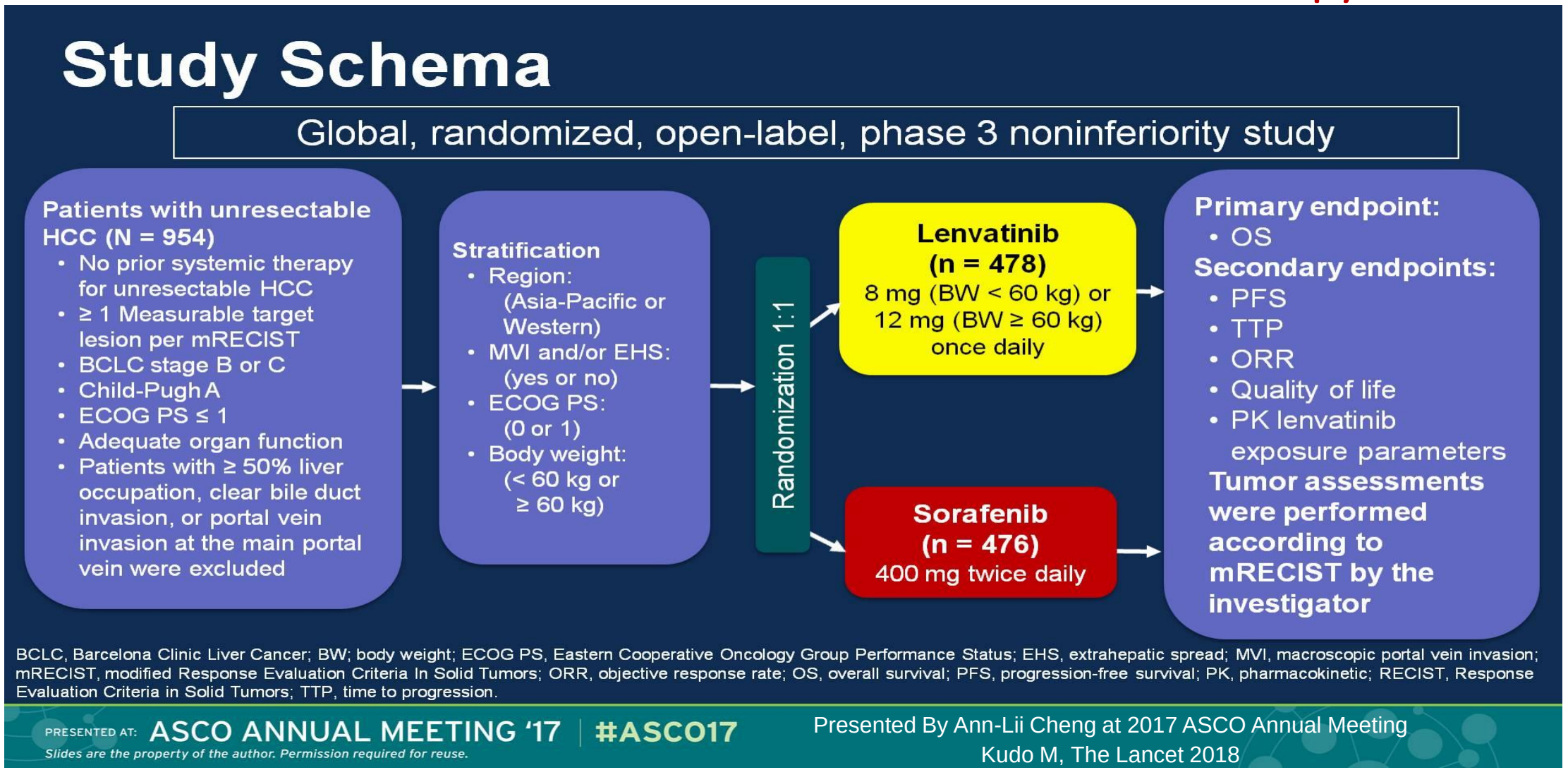
Lenvatinib targets:
VEGFR1 (FLT1),
VEGFR2 (KDR),
VEGFR3 (FLT4),
FGFR1, 2, 3, and 4
PDGFRα
KIT
RET



Median TTP 7.4 months; 95% CI: 5.5-9.4
Median OS 18.7 months; 95% CI: 12.7-25.1

Ikeda J et al, J Gastroenterol 2016

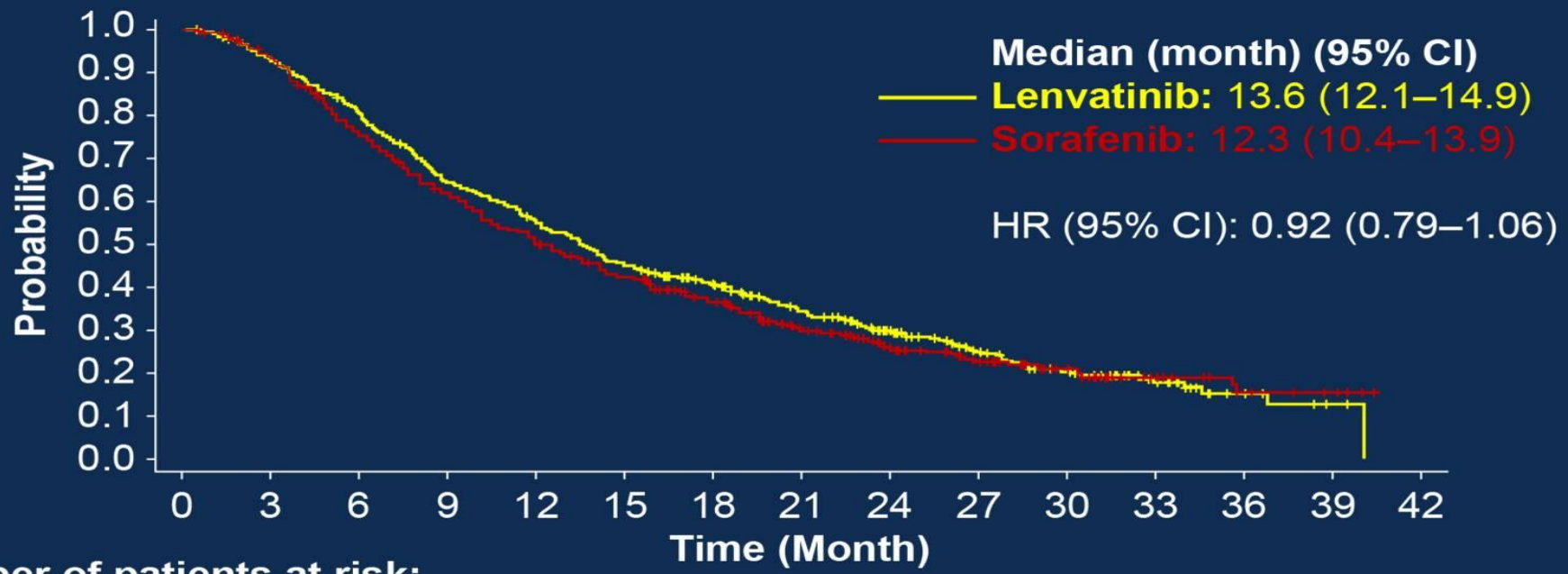
REFLECT Trial: Lenvatinib vs. Sorafenib as frontline therapy



Presented By Ann-Lii Cheng at 2017 ASCO Annual Meeting
Kudo M, The Lancet 2018

REFLECT Trial: Lenvatinib vs. Sorafenib as frontline therapy

Primary Endpoint: Kaplan-Meier Estimate of OS

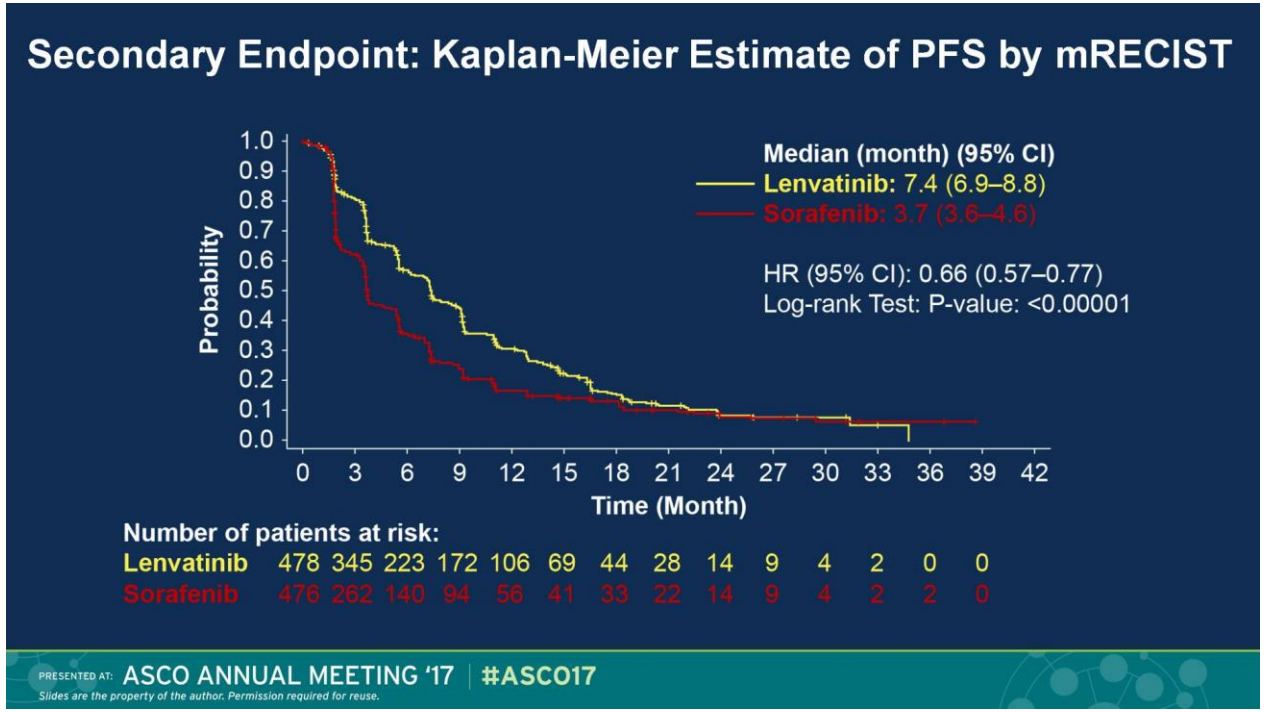


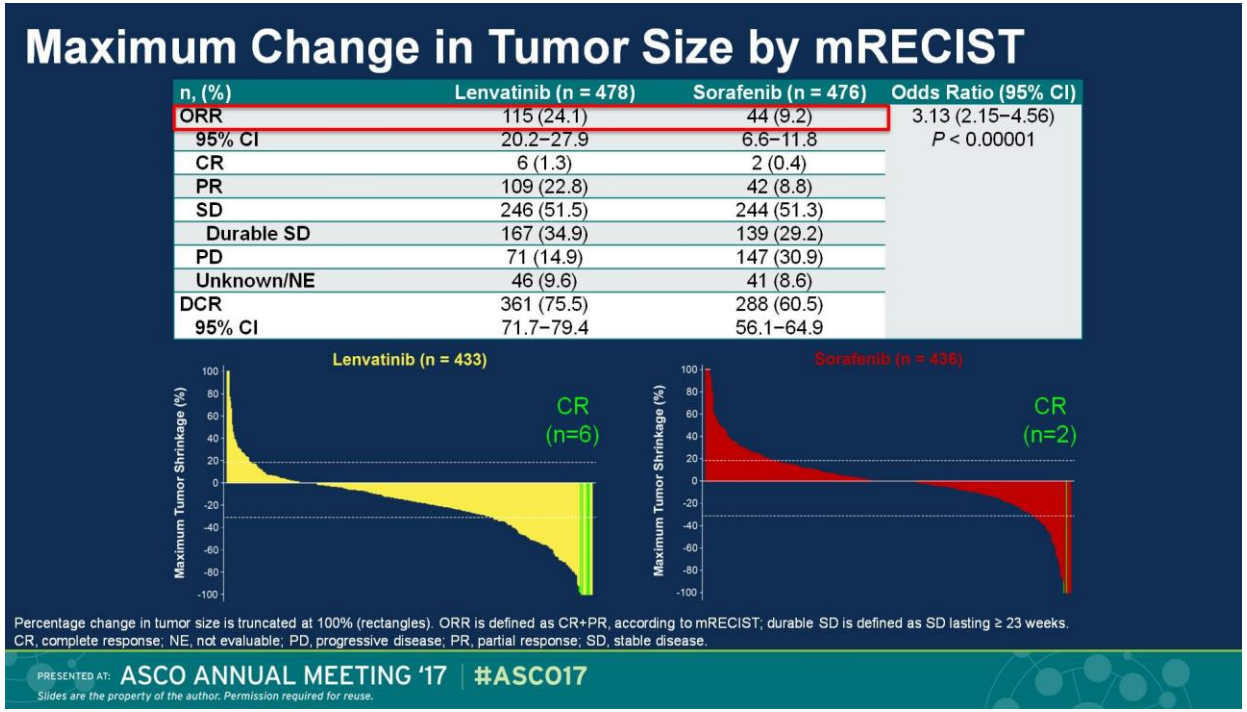
Number of patients at risk:

Lenvatinib	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
Sorafenib	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

Presented By Ann-Lii Cheng at 2017 ASCO Annual Meeting
Kudo M, The Lancet 2018

REFLECT Trial: Lenvatinib vs. Sorafenib as frontline therapy





ORR by RECIST 1.1 18.8% (95% CI 15.3-22.3

Kudo M et al, Lancet 2018

REFLECT Trial: Lenvatinib vs. Sorafenib as frontline therapy

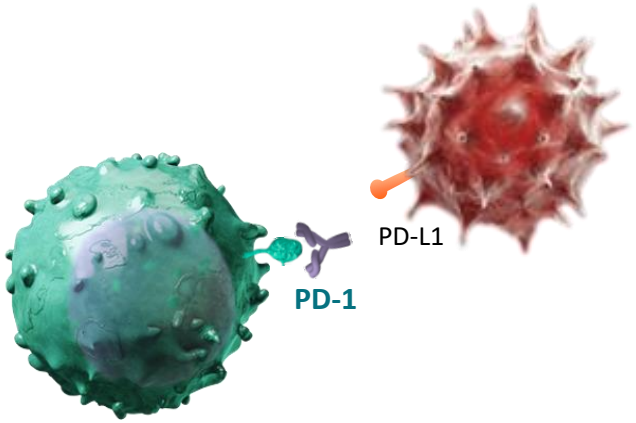
Most Frequent TEAEs (≥ 15%)

Adverse event, n (%)	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hypertension	201 (42)	111 (23)	144 (30)	68 (14)
Diarrhea	184 (39)	20 (4)	220 (46)	20 (4)
Decreased appetite	162 (34)	22 (5)	127 (27)	6 (1)
Decreased weight	147 (31)	36 (8)	106 (22)	14 (3)
Fatigue	141 (30)	18 (4)	119 (25)	17 (4)
Palmar-plantar erythrodysesthesia	128 (27)	14 (3)	249 (52)	54 (11)
Proteinuria	117 (25)	27 (6)	54 (11)	8 (2)
Dysphonia	113 (24)	1 (0)	57 (12)	0 (0)
Nausea	93 (20)	4 (1)	68 (14)	4 (1)
Decreased platelet count	87 (18)	26 (6)	58 (12)	16 (3)
Abdominal pain	81 (17)	8 (2)	87 (18)	13 (3)
Hypothyroidism	78 (16)	0 (0)	8 (2)	0 (0)
Vomiting	77 (16)	6 (1)	36 (8)	5 (1)
Constipation	76 (16)	3 (1)	52 (11)	0 (0)
Elevated aspartate aminotransferase	65 (14)	24 (5)	80 (17)	38 (8)
Rash	46 (10)	0 (0)	76 (16)	2 (0)
Alopecia	14 (3)	0 (N/A)	119 (25)	0 (N/A)

Presented By Ann-Lii Cheng at 2017 ASCO Annual Meeting
Kudo M, The Lancet 2018

Trial: NCT02576509

CHECKMATE-459: Phase III trial of nivolumab vs sorafenib in first-line advanced HCC patients[1]



Adapted from Mellman I et al 2011.[2]

Start Date: **November 2015**

Primary Endpoints: **TTP, OS**

Other Endpoints: **ORR, PFS, biomarkers**

Key Eligibility Criteria

N=726

- Advanced HCC not eligible for or progressive after surgical and/or locoregional therapies
- Child-Pugh A

R

Nivolumab

Sorafenib

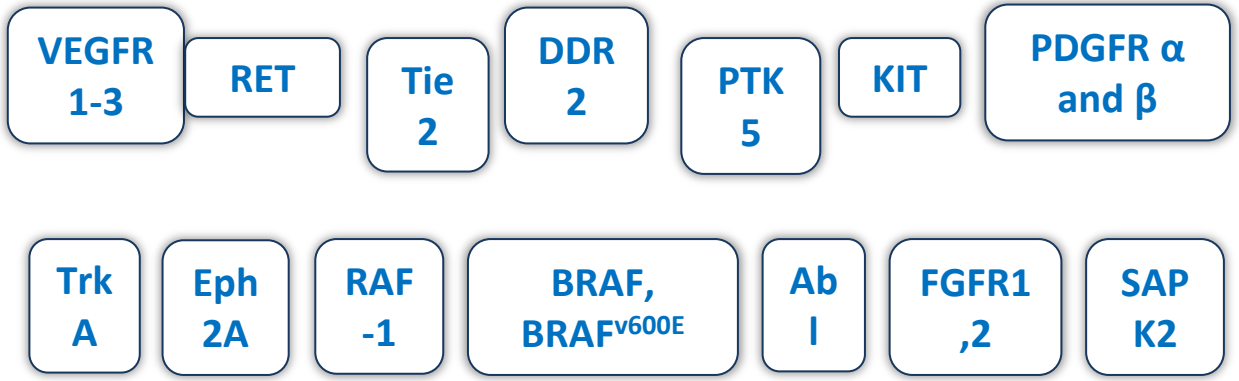
HCC, hepatocellular carcinoma; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; TTP, time to progression.

. **Mellman I et al. *Nature*. 2011;480(7378):480-489.**

What’s new in second line and beyond?

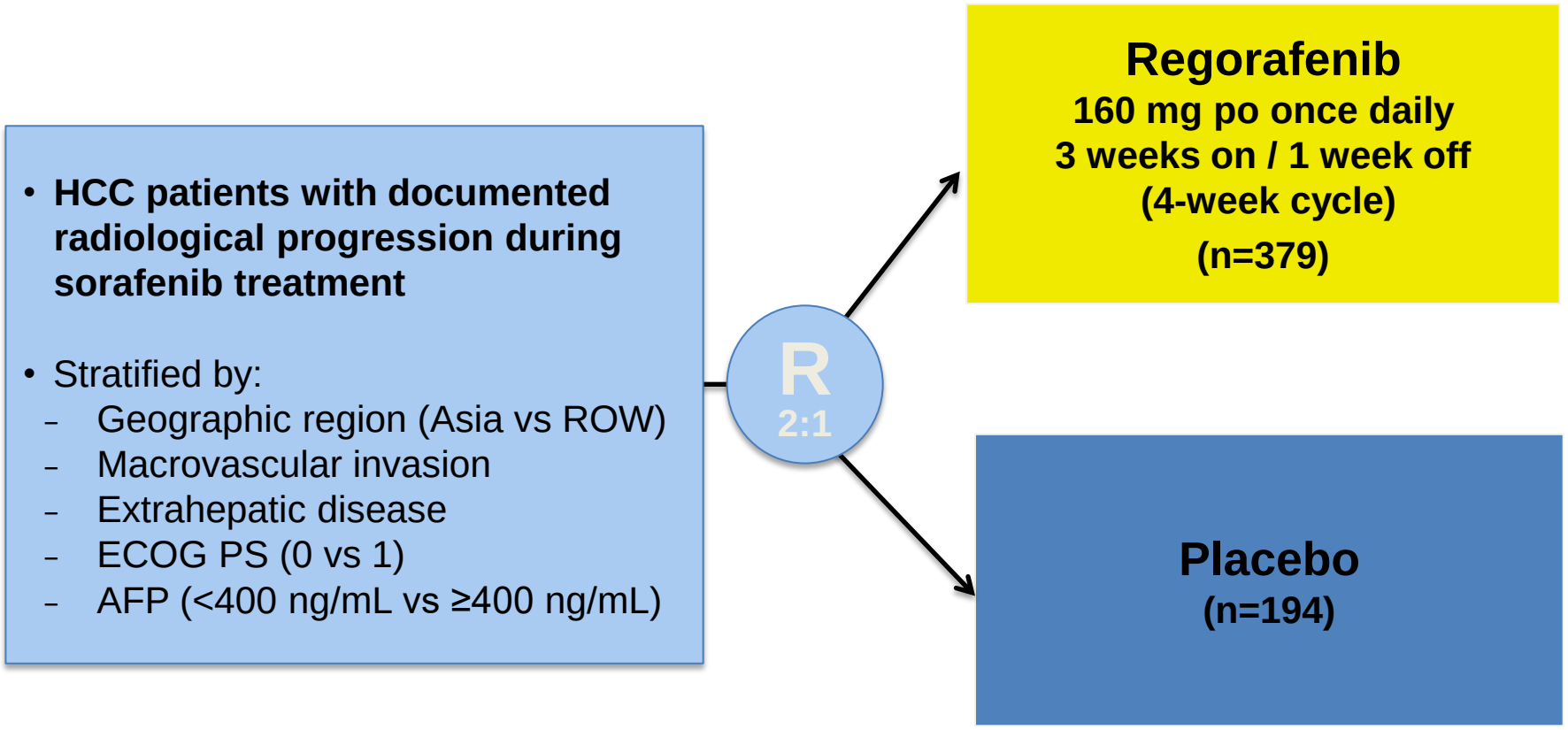
Regorafenib Mechanism of Action

- **Regorafenib is an oral inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes including angiogenesis, oncogenesis and maintenance of tumor microenvironment.**



Miuira K et al, *Expert Opin Drug Discov.* ***2014 Sep;9(9):1087-101***

RESORCE trial design



- 152 centers in 21 countries in North and South America, Europe, Australia, Asia
- All patients received best supportive care
- Treat until progression, unacceptable toxicity, or withdrawal

ROW, rest of the world; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein

Bruix J et al, Lancet 2017; 389: 56–66

Key inclusion criteria

- HCC confirmed by histological or cytological analysis, or diagnosed by non-invasive assessment per AASLD criteria in a patient with confirmed cirrhosis
- BCLC stage B or C patients who could not benefit from resection, local ablation, or chemoembolization
- Documented radiological progression during sorafenib
- Randomization within 10 weeks after the last sorafenib dose
- Tolerability of prior sorafenib, defined as receiving sorafenib ≥400 mg daily for at least 20 of the last 28 days of treatment
- ECOG PS 0/1
- Child-Pugh A liver function

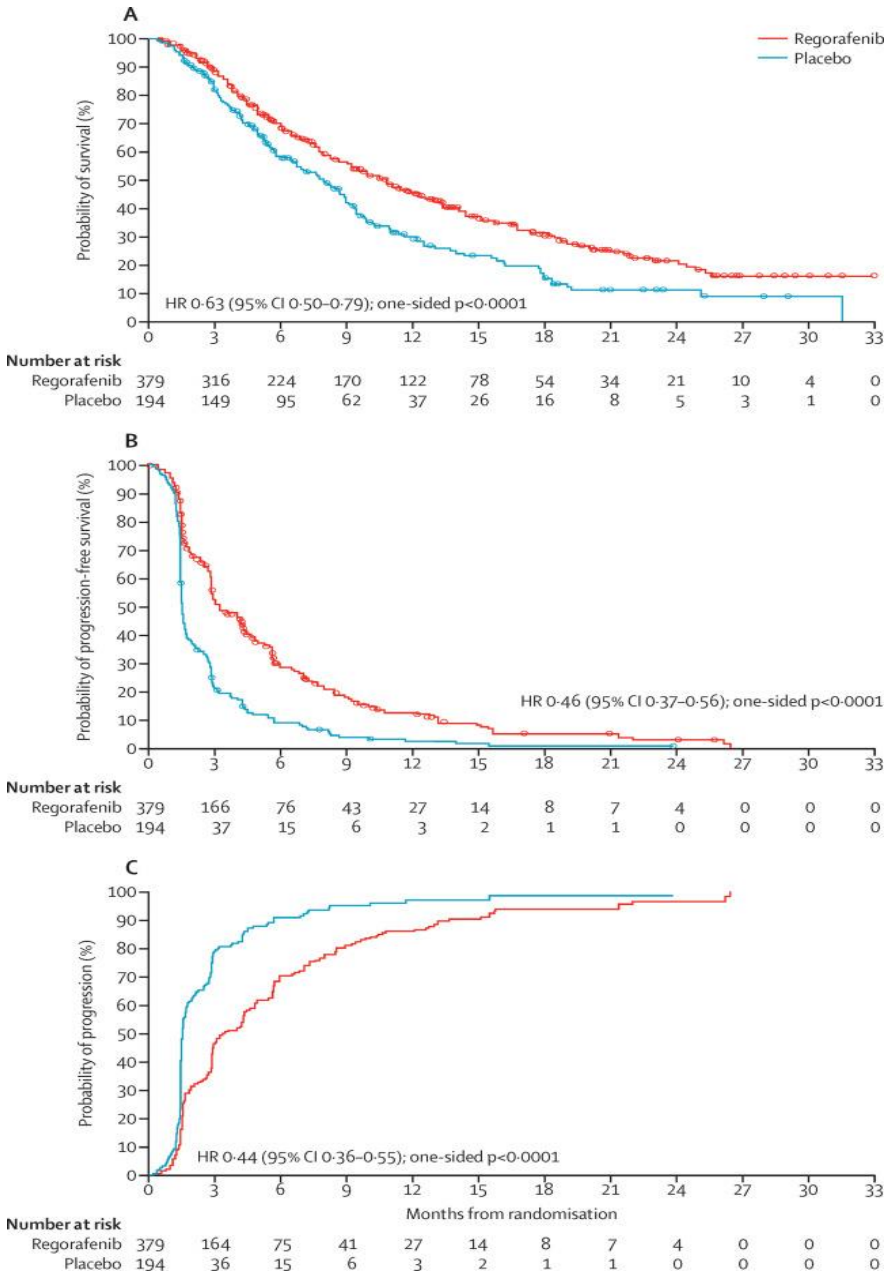
Bruix J et al, Lancet 2017; 389: 56–66

RESORCE efficacy

	Regorafenib n=379	**Placebo** n=194
Events	**232 (61%)**	140 (72%)
Censored	**147 (39%)**	54 (28%)
Median OS (95% CI)	**10.6 months (9.1, 12.1)**	7.8 months (6.3, 8.8)
HR 0.62 (95% CI: 0.50, 0.78)		
P<0.001 (2-sided)		

	Regorafenib n=379	**Placebo** n=194
Events	**291 (77%)**	181 (93%)
Censored	**88 (23%)**	13 (7%)
Median PFS (95% CI)	**3.1 months (2.8, 4.2)**	1.5 months (1.4, 1.6)
HR 0.46 (95% CI: 0.37, 0.56)		
P<0.001 (2-sided)		

Bruix J et al, Lancet 2017; 389: 56–66

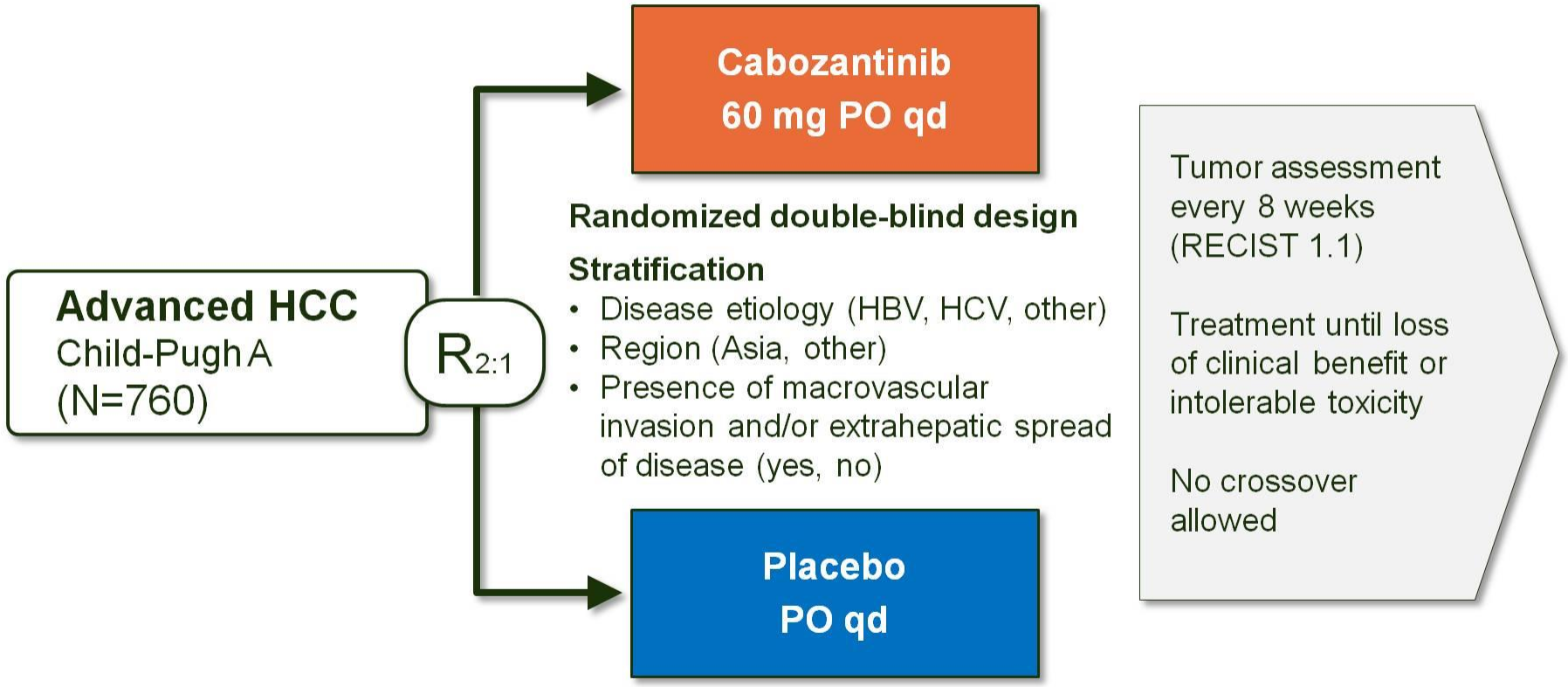


Exploratory Analysis: Survival with the sequence of Sorafenib and Regorefanib

	Regorafenib	Placebo
Time from start of prior sorafenib treatment to death on RESORCE study drug		
All patients		
n	374	193
Median, months (95% CI)	26.0 (22.6, 28.1)	19.2 (16.3, 22.8)
Asia		
n	143	73
Median, months (95% CI)	21.5 (19.6, 27.8)	15.6 (12.2, 24.9)
Rest of the world		
n	231	120
Median, months (95% CI)	26.8 (23.3, 28.9)	19.9 (17.5, 25.9)

Finn R et al. GI Cancers Symposium 2017

CELESTIAL Study Design



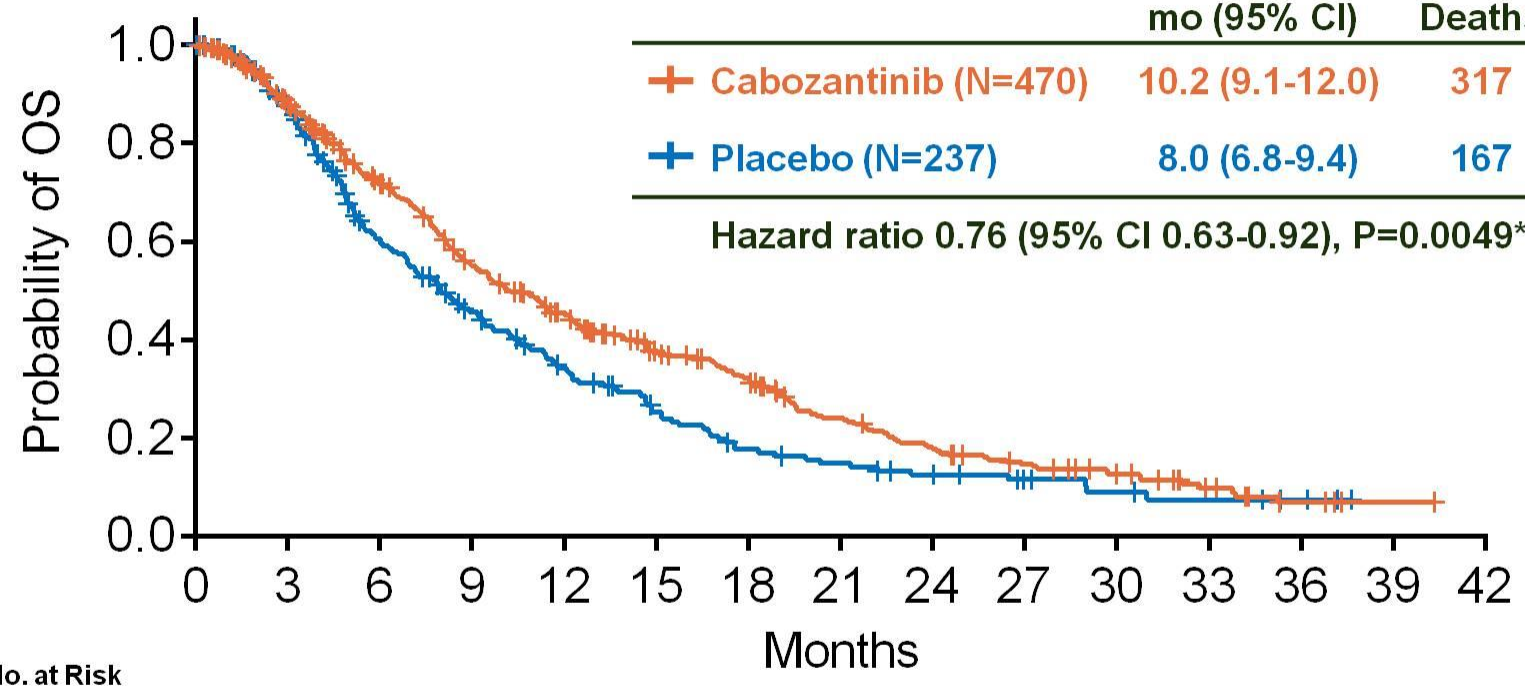
Abou Alfa G et al, NEJM 2018

Key Eligibility Criteria

- Pathologic diagnosis of HCC not amenable to curative treatment
- Child-Pugh score A
- Received prior sorafenib
- Progressed following at least one prior systemic treatment for HCC
- Received up to two prior systemic regimens for advanced HCC
- ECOG performance status 0 or 1
- No uncontrolled hypertension, defined as sustained BP > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment

Abou Alfa G et al, NEJM 2018

Overall Survival



No. at Risk

Cabozantinib	470	382	281	206	159	116	93	63	44	31	22	12	4	1	0
Placebo	237	190	117	82	57	37	25	20	15	10	7	5	3	0	0

*Critical p-value ≤ 0.021 for second interim analysis

Abou Alfa G et al, NEJM 2018

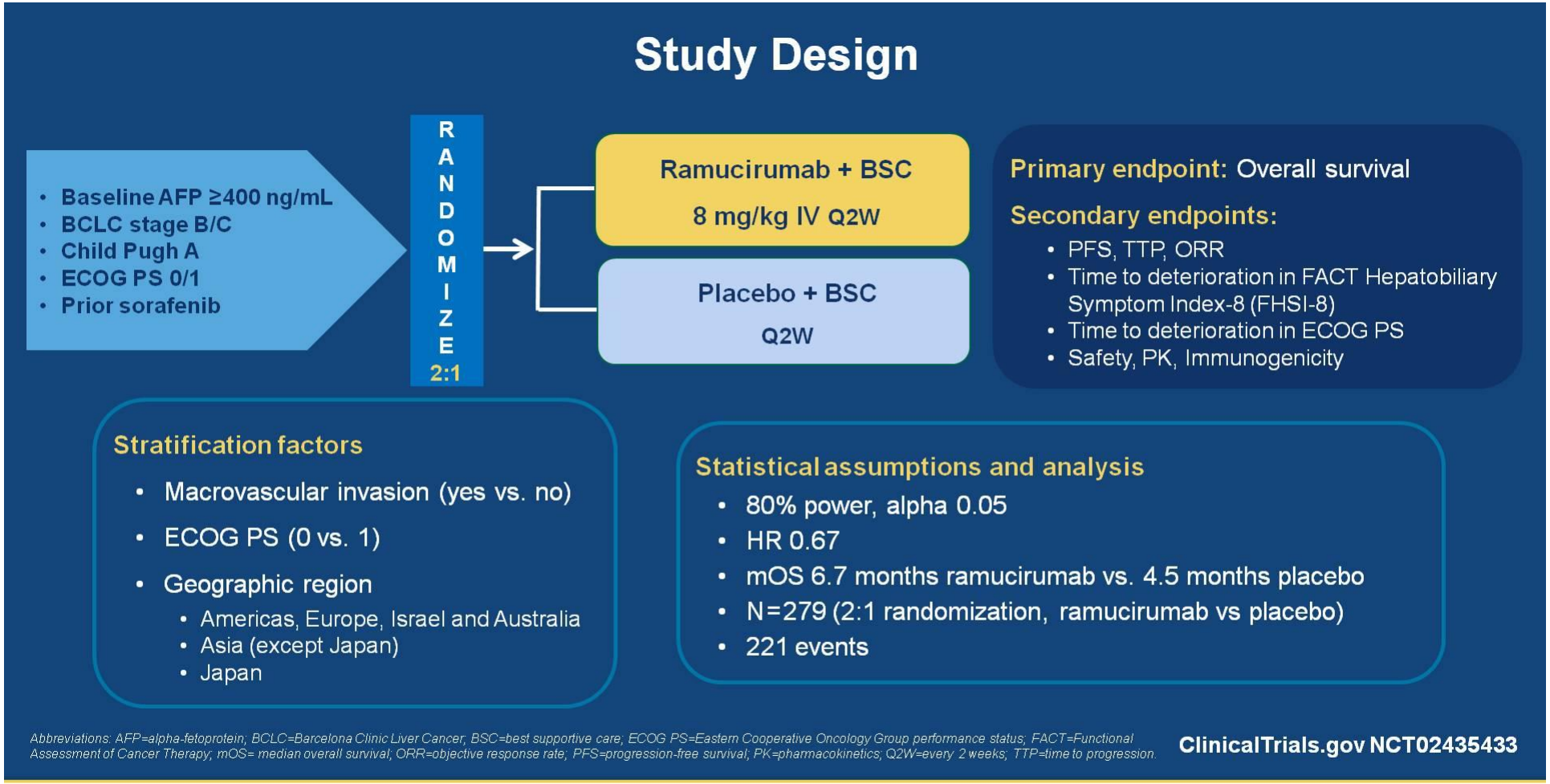
REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib

Andrew X. Zhu[1], Yoon-Koo Kang[2], Chia-Jui Yen[3], Richard S. Finn[4], Peter R. Galle[5], Josep M. Llovet[6], Eric Assenat[7], Giovanni Brandi[8], Ho Yeong Lim[9], Marc Pracht[10], Kun-Ming Rau[11], Philippe Merle[12], Kenta Motomura[13], Izumi Ohno[14], Bruno Daniele[15], Dong Bok Shin[16], Guido Gerken[17], Paolo B. Abada[18], Yanzhi Hsu[19], Masatoshi Kudo[20], for the REACH-2 study investigators

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Andrew Zhu, MD, PhD
Massachusetts General Hospital Cancer Center, Harvard Medical School

REACH 2: Ramucirumab vs. placebo in HCC patients with AFP ≥ 400



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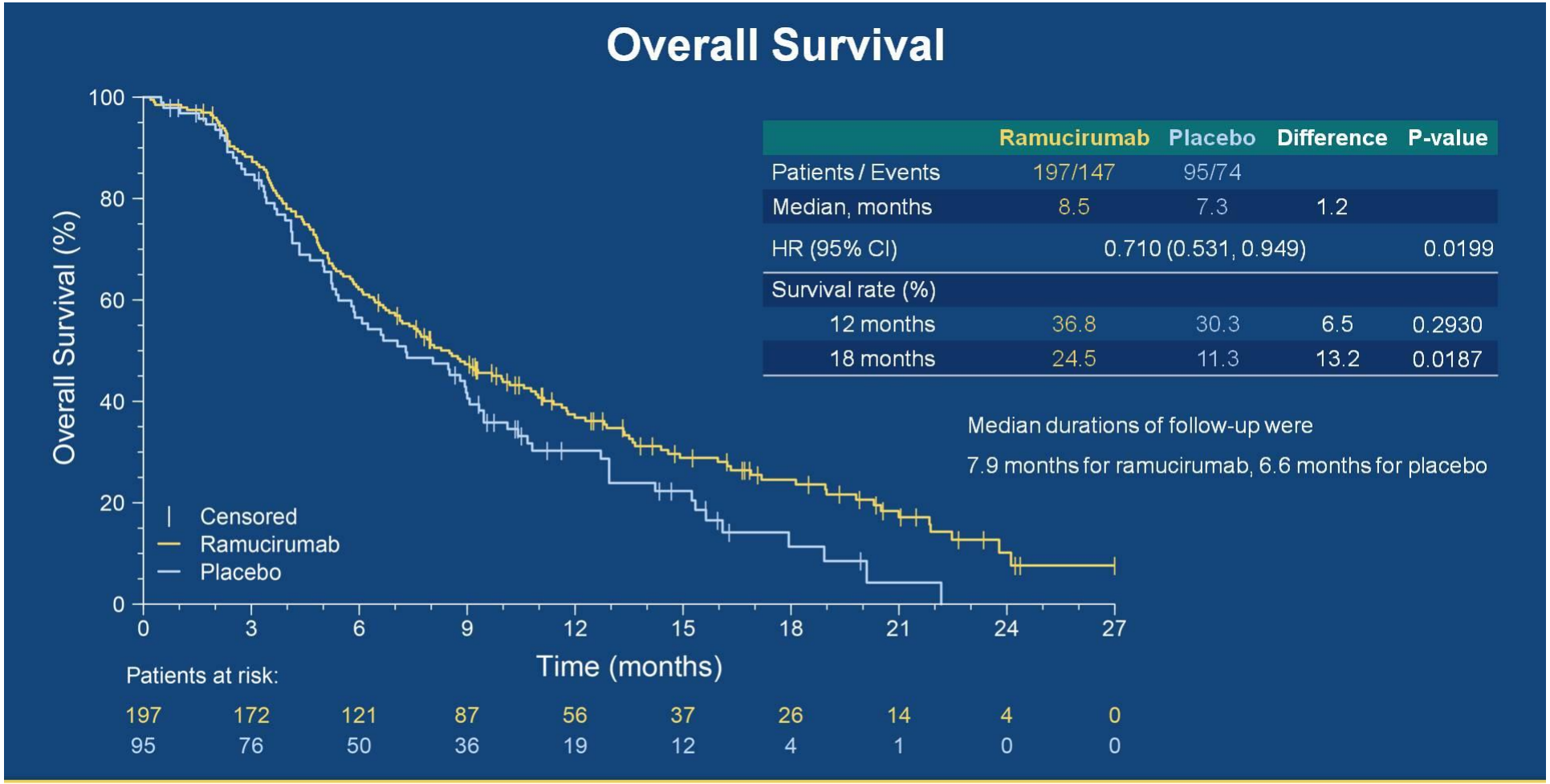
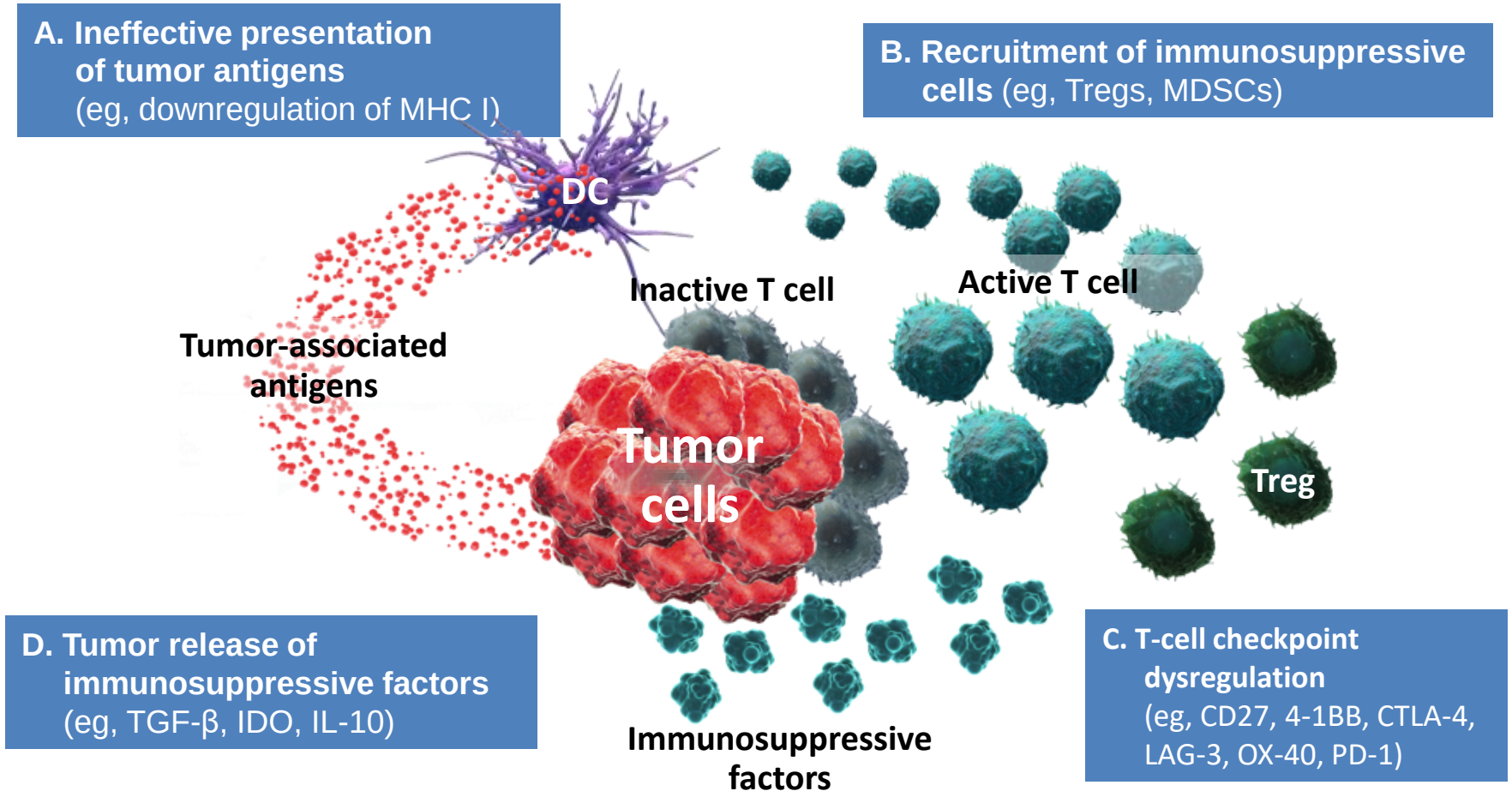
REACH 2: Ramucirumab vs. placebo in HCC patients with AFP ≥ 400



Presented By Andrew Zhu at 2018 ASCO Annual Meeting

Tumors Use Complex, Overlapping Mechanisms to Evade and Suppress the Immune System

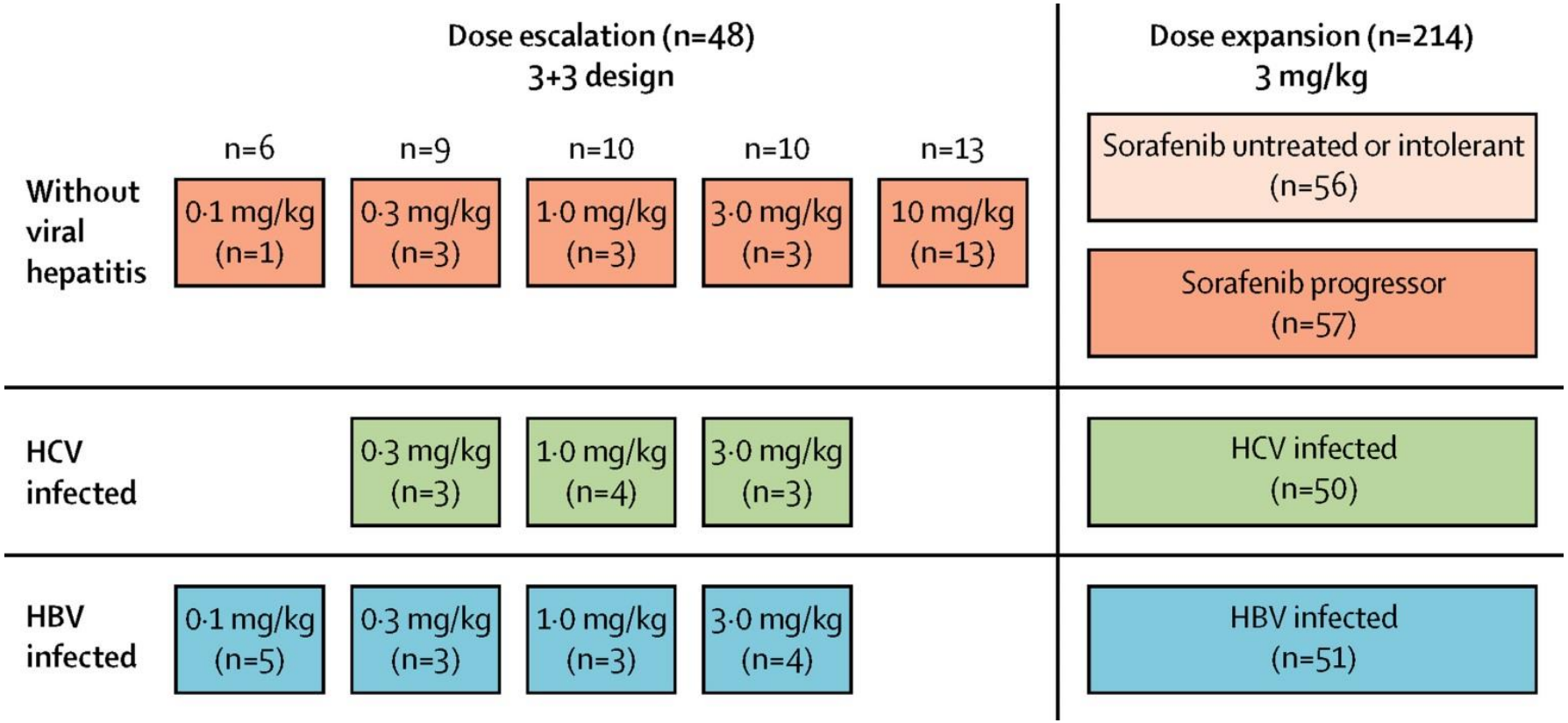


CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte antigen-4; DC, dendritic cell; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; LAG-3, lymphocyte activation gene-3; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; PD-1, programmed death receptor-1; TGF-β, transforming growth factor beta; TIM-3, T cell immunoglobulin and mucin domain-3; Treg, regulatory T cell.

Vesely MD et al. Ann Rev Immunol. 2011;29:235-271.
Mellman I et al. Nature. 2011;480(7378):480-489.

Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

*Anthony B El-Khoueiry,*Bruno Sangro,*Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan, Theodore H Welling 3rd, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely, Hao Tang, Homa B Dastani, Ignacio Melero*



El-Khoueiry A et al, Lancet, online April 2017

Baseline Characteristics

Patients, n (%)	Dose Escalation (N = 48)	Dose Expansion (N = 214)	All Patients (N = 262)
Age, median (range), years	62 (22–83)	64 (56–70)	63 (19–83)
Male	36 (75)	171 (80)	207 (79)
Race			
White	28 (58)	105 (49)	133 (51)
Asian	18 (38)	101 (47)	119 (45)
Black/other	2 (4)	8 (4)	10 (4)
Extrahepatic metastases	34 (71)	144 (67)	178 (68)
Vascular invasion	19 (40)	63 (29)	82 (31)
Child-Pugh score			
5	41 (85)	149 (70)	190 (73)
6	7 (15)	61 (29)	68 (26)
> 6	0	4 (2)	4 (2)
AFP ≥ 400 μg/L[a]	15 (31)	79 (37)	94 (36)
Prior treatment			
Surgical resection	36 (75)	128 (60)	164 (63)
Radiotherapy[b]	10 (21)	41 (19)	51 (19)
Local treatment for HCC[c]	24 (50)	117 (55)	141 (54)
Systemic therapy experienced	40 (83)	159 (74)	199 (76)
Sorafenib	37 (77)	145 (68)	182 (69)
Systemic therapy naive	8 (17)	55 (26)	63 (24)

[a] Baseline α-fetoprotein (AFP) levels not reported in 10 patients; [b] Internal or external; [c] Includes transcatheter arterial chemoembolization, transcatheter embolization.

El-Khoueiry A et al, Lancet, online April 2017

Dose expansion: treatment related adverse events

	Uninfected (n = 112)		HCV (n = 51)		HBV (n = 51)		Total (N = 214)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Patients with any TRAE, n (%)	72 (64)	21 (19)	37 (73)	15 (29)	30 (59)	3 (6)	139 (65)	39 (18)
Symptomatic TRAEs reported in > 4% of all patients								
Fatigue	31 (28)	2 (2)	7 (14)	0	7 (14)	0	45 (21)	2 (1)
Pruritus	11 (10)	0	11 (22)	0	11 (22)	0	33 (15)	0
Rash	12 (11)	1 (1)	8 (16)	0	6 (12)	0	26 (12)	1 (0.5)
Diarrhea	16 (14)	2 (2)	3 (6)	0	1 (2)	1 (2)	20 (9)	3 (1)
Nausea	8 (7)	0	6 (12)	0	0	0	14 (7)	0
Decreased appetite	5 (5)	0	2 (4)	0	3 (6)	0	10 (5)	0
Dry mouth	5 (4)	0	1 (2)	0	2 (4)	0	8 (4)	0
Laboratory-value TRAEs reported in > 4% of all patients								
ALT increased	6 (5)	2 (2)	7 (14)	4 (8)	2 (4)	0	15 (7)	6 (3)
AST increased	7 (6)	3 (3)	6 (12)	6 (12)	0	0	13 (6)	9 (4)
Platelet count decreased	4 (4)	1 (1)	3 (6)	2 (4)	5 (10)	1 (2)	8 (4)	3 (1)
Anemia	2 (2)	0	3 (6)	1 (2)	3 (6)	0	8 (4)	1 (0.5)

El-Khoueiry A et al, Lancet, online April 2017

Checkmate 040: Nivolumab efficacy

	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Objective response*	13 (23%; 13 to 36)	12 (21%; 11 to 34)	10 (20%; 10 to 34)	7 (14%; 6 to 26)	42 (20%; 15 to 26)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
Stable disease	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
Progressive disease	13 (23%)	18 (32%)	14 (28%)	23 (45%)	68 (32%)
Not evaluable	1 (2%)	4 (7%)	3 (6%)	0	8 (4%)
Duration of response*					
KM median	8·4 (8·3 to NE)	NR	9·9 (4·5 to 9·9)	NR	9·9 (8·3 to NE)
Ongoing, n/N (%)	8/13 (62%)	7/12 (58%)	8/10 (80%)	5/7 (71%)	28/42 (67%)
Disease control*	42 (75%; 62 to 86)	35 (61%; 48 to 74)	33 (66%; 51 to 79)	28 (55%; 40 to 69)	138 (64%; 58 to 71)
Disease control with stable disease for ≥6 months	22 (39%; 27 to 53)	22 (39%; 26 to 52)	17 (34; 21 to 49)	18 (35%; 22 to 50)	79 (37%; 30 to 44)
Overall survival					
6 months	89% (77 to 95)	75% (62 to 85)	85% (72 to 93)	84% (71 to 92)	83% (78 to 88)
9 months	82% (68 to 90)	63% (49 to 74)	81% (66 to 90)	70% (55 to 81)	74% (67 to 79)
KM median	NR	13·2 (8·6 to NE)	NR	NR	NR
Progression-free survival*					
KM median	5·4 (3·9 to 8·5)	4·0 (2·6 to 6·7)	4·0 (2·6 to 5·7)	4·0 (1·3 to 4·1)	4·0 (2·9 to 5·4)

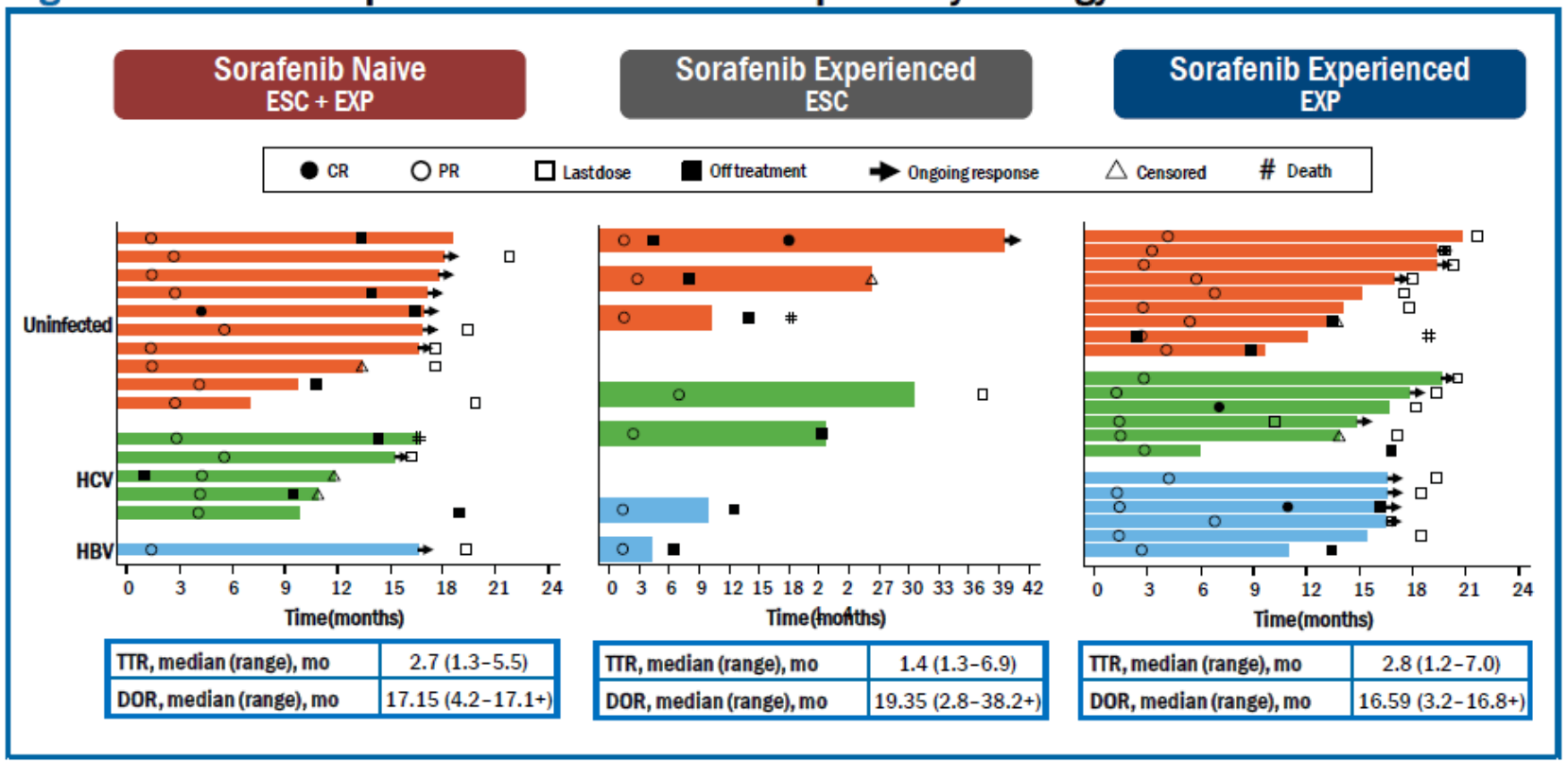
Unless otherwise indicated, data are n (%; 95% CI); n (%); months (95% CI); or % (95% CI). HCV=hepatitis C virus. HBV=hepatitis B virus. KM=Kaplan-Meier estimate. NR=not reached. NE=not estimable. RECIST=Response Evaluation Criteria In Solid Tumors. *Determined by investigator assessment using RECIST version 1.1.

***Table 4*: Nivolumab efficacy in the dose-expansion phase**

El-Khoueiry A et al, Lancet, online April 2017

Time to response and duration of response

Figure 2. Time to Response and Duration of Response by Etiology

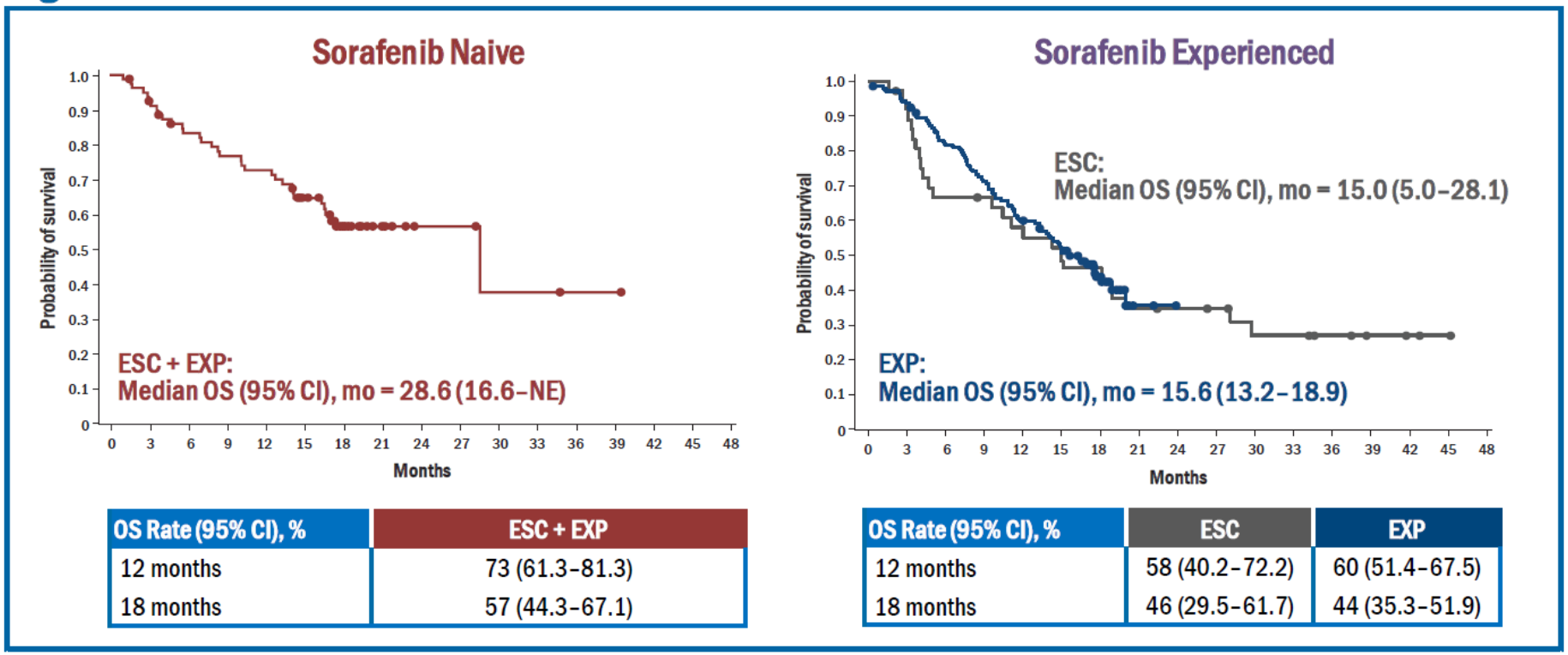


Tumor response assessed by BICR using RECIST v1.1. TTR, time to response; DOR, duration of response.

Crocenzi T et al, J Clin Oncol 35, 2017 (suppl; abstr 4013)

Survival update based on sorafenib exposure

Figure 4. Overall Survival



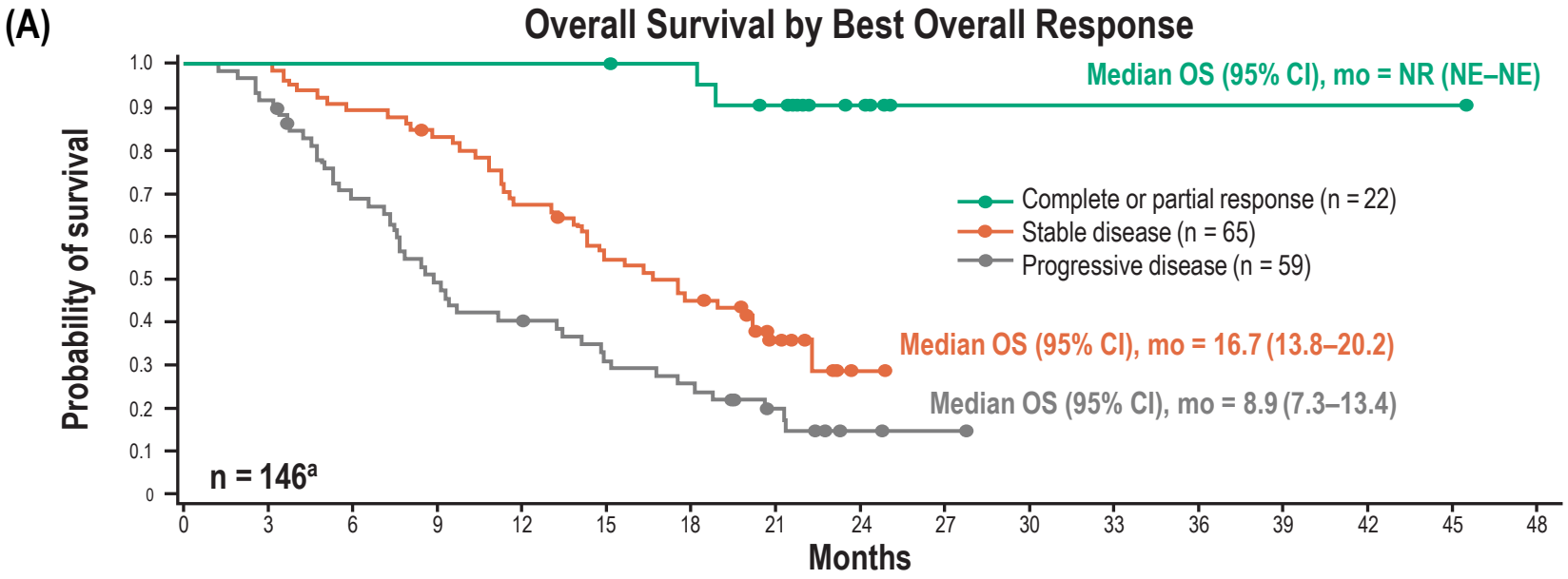
OS Rate (95% CI), %	ESC + EXP
12 months	73 (61.3–81.3)
18 months	57 (44.3–67.1)

OS Rate (95% CI), %	ESC	EXP
12 months	58 (40.2–72.2)	60 (51.4–67.5)
18 months	46 (29.5–61.7)	44 (35.3–51.9)

Kaplan-Meier method; closed circles denote censored patients.

Crocenzi T et al, J Clin Oncol 35, 2017 (suppl; abstr 4013)

Checkmate 040: Overall survival analyzed by best overall response or change in target lesion size

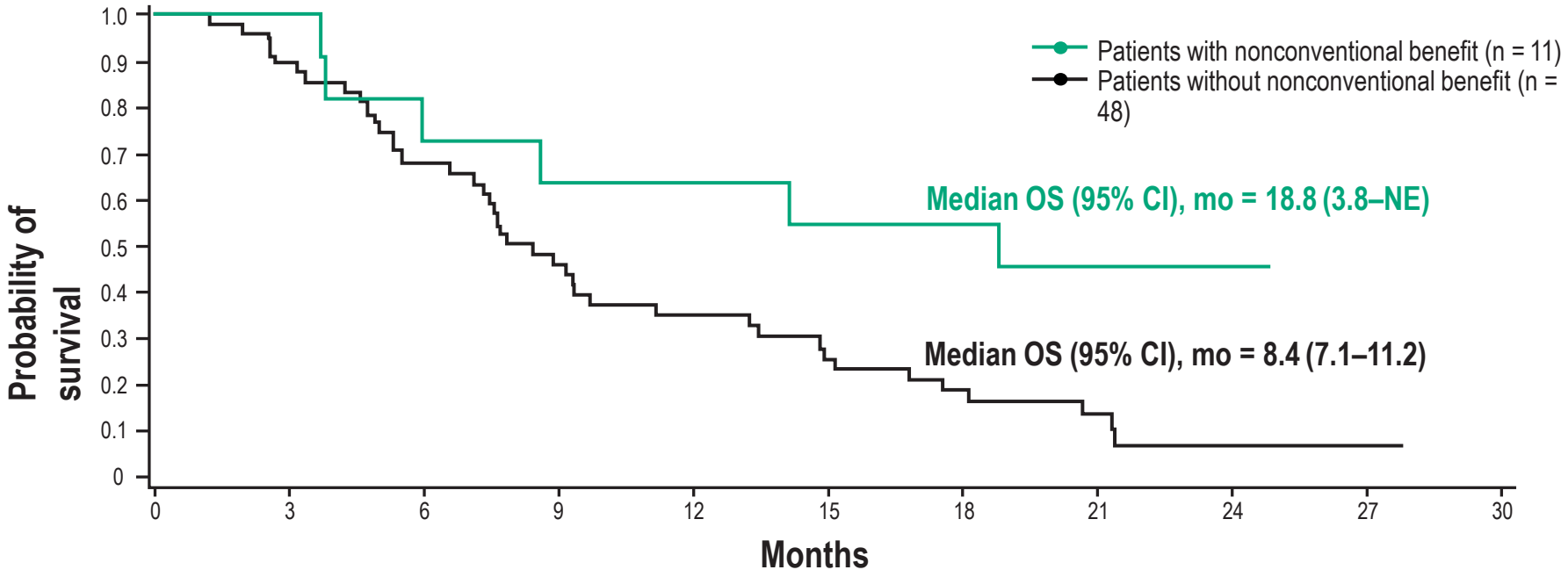


OS rate (95% CI), %	Complete/partial response n = 22	Stable disease n = 65	Progressive disease n = 59
12 month	100 (100–100)	67 (55–77)	41 (28–53)
18 month	100 (100–100)	45 (33–57)	26 (15–38)

[a]Best overall response was unable to be determined in 8 patients

El-Khoueiry A et al, GI Cancers Symposium, 2018

Checkmate 040: Overall survival analyzed by nonconventional benefit in patients with a best overall response of progressive disease



El-Khoueiry A et al, GI Cancers Symposium, 2018

Keynote 224: Pembrolizumab in advanced HCC

Study Design

- Key eligibility criteria
  - ≥18 y
  - Pathologically confirmed HCC
  - Progression on or intolerance to sorafenib treatment
  - Child Pugh class A
  - ECOG PS 0-1
  - BCLC Stage C or B disease
  - Predicted life expectancy >3 mo

→ **Pembrolizumab** 200 mg Q3W for 2y or until PD, intolerable toxicity, withdrawal of consent or investigator decision → **Survival follow-up**

- Response assessed Q9W
- Primary endpoint: ORR (RECIST v1.1, central review)
- Secondary endpoint: DOR, DCR, PFS, OS. and safetv and tolerabilitv

Zhu A et al, Lancet Oncol 2018

Anti-tumor Activity

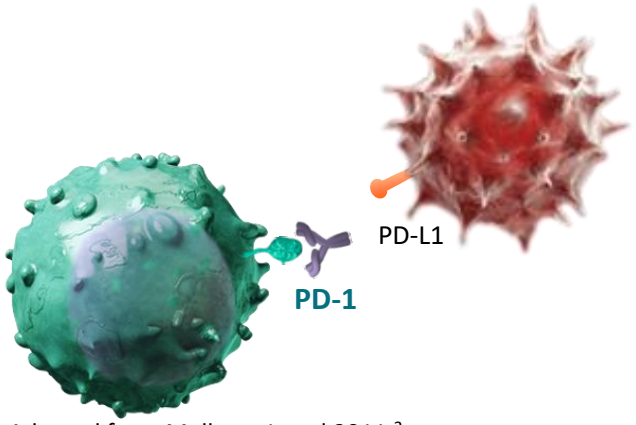
Response†	Total N=104 n (%)	95% CI‡
ORR (CR+PR)	17 (16.3)	9.8 - 24.9
Disease control (CR+PR+SD)	64 (61.5)	51.5 - 70.9
Best overall response		
CR	1 (1.0)	0.0 - 5.2
PR	16 (15.4)	9.1- 23.8
SD	47 (45.2)	35.4 - 55.3
PD	34 (32.7)	23.8 - 42.6
No Assessment§	6 (5.8)	2.1-12.1

†Confirmed best response by independent central review per RECIST v1.1. ‡Based on binomial exact confidence interval method. §Subjects who had a baseline assessment by investigator review or central radiology but no post-baseline assessment on the data cutoff date including discontinuing or death before the first post-baseline scan. Data cutoff date: Aug 24, 2017.

Zhu A et al, Lancet Oncol 2018

Trial: NCT02702401

KEYNOTE-240: Phase III trial of pembrolizumab vs best supportive care as a 2L therapy in prior systemically treated advanced HCC patients[1]



Adapted from Mellman I et al 2011.[2]

Start Date: May 2016

Primary Endpoints: PFS, OS

Other Endpoints: ORR, DCR, TTP, DOR

Key Eligibility Criteria

N=408

- Histo- or cytologically confirmed advanced HCC
- BCLC Stage B or C, not amenable to locoregional therapy or refractory to locoregional therapy
- Child-Pugh A
- Untreated HCV or >4 weeks of successful HCV treatment
- Has not had prior systemic therapy for HCC other than sorafenib

R

Pembrolizumab + Best Supportive Care

Placebo + Best Supportive Care

2L, second line; BCLC, Barcelona Clinic for Liver Cancer; DCR, disease control rate; DOR, duration of response; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TTP, time to progression.

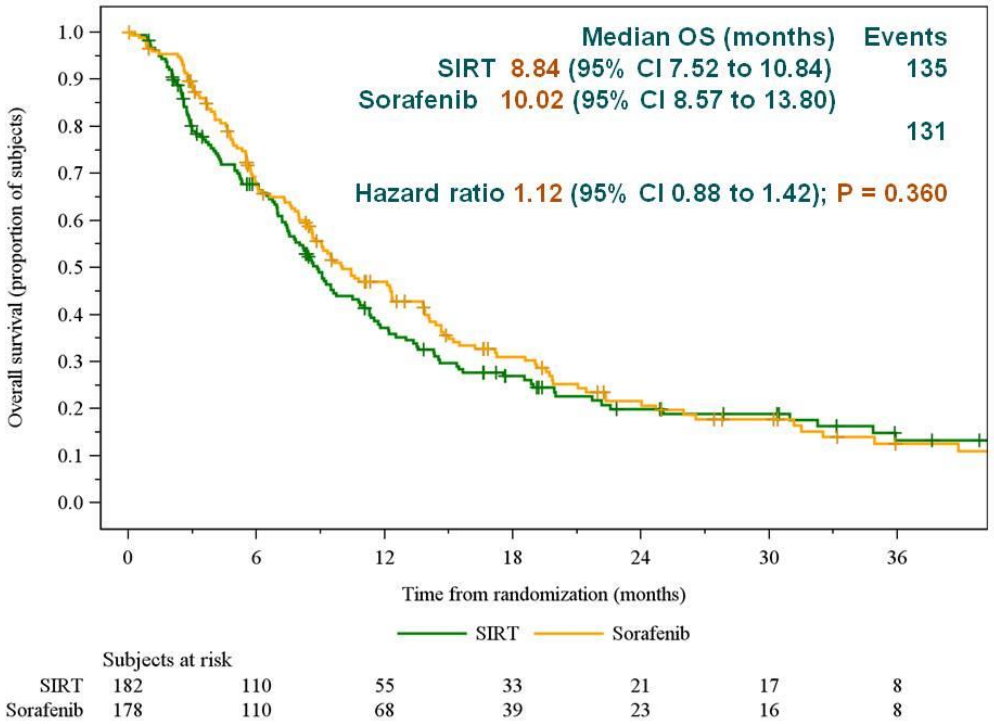
1. **Clinicaltrials.gov. NCT02702401. Accessed July 29, 2016.**
2. **Mellman I et al. *Nature*. 2011;480(7378):480-489.**

Is there a role for liver directed therapy in patients with advanced HCC

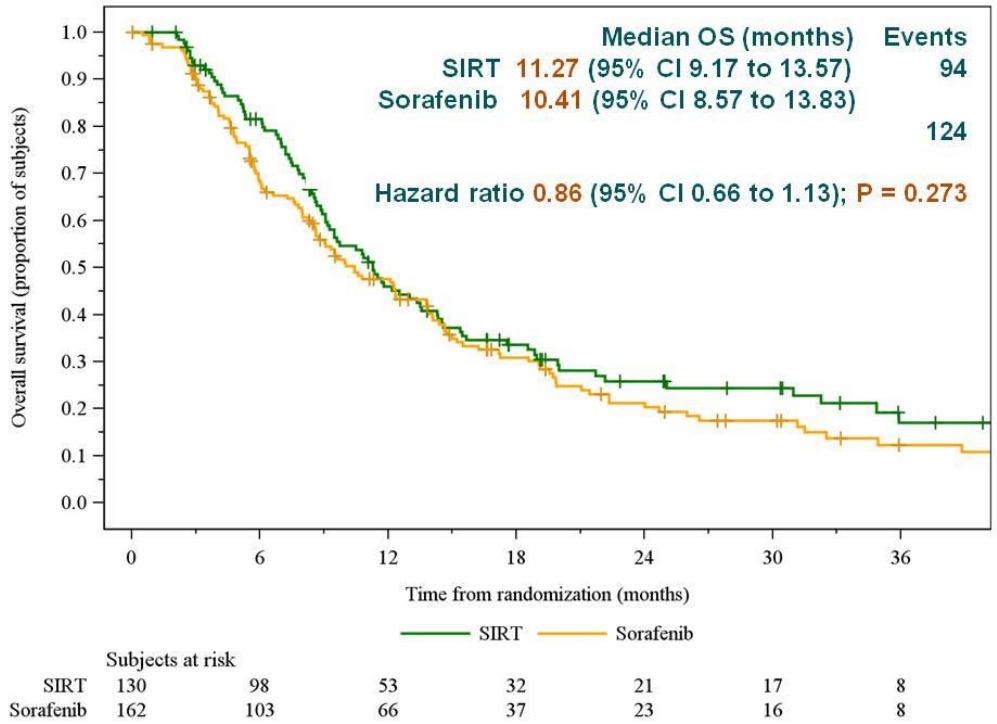
The SIRveNIB study: SIRT vs Sorafenib

Efficacy: Overall Survival

- **Intent-to-treat population**

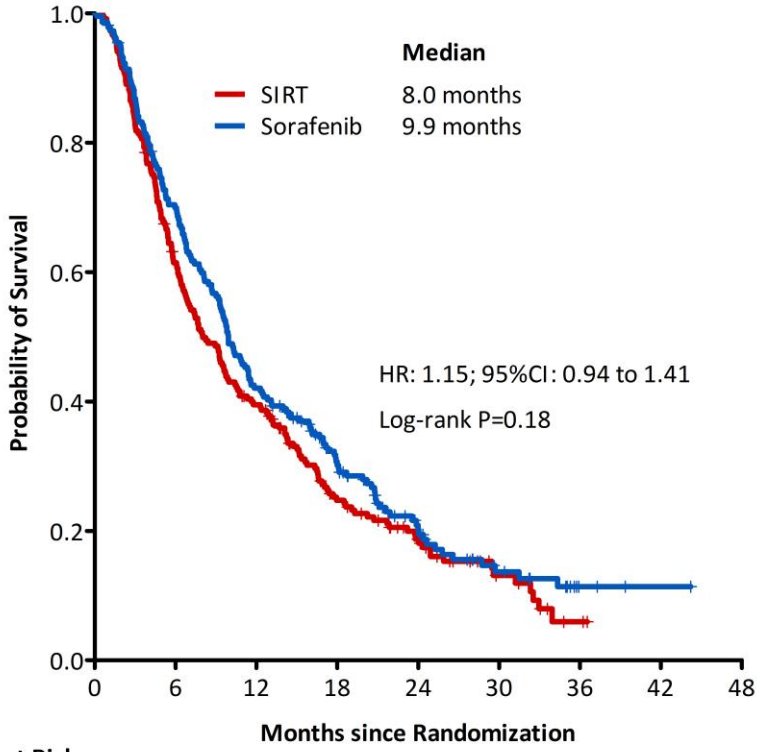


- **Treated population**



The SARAH Trial: Y90 radioembolization vs. sorafenib

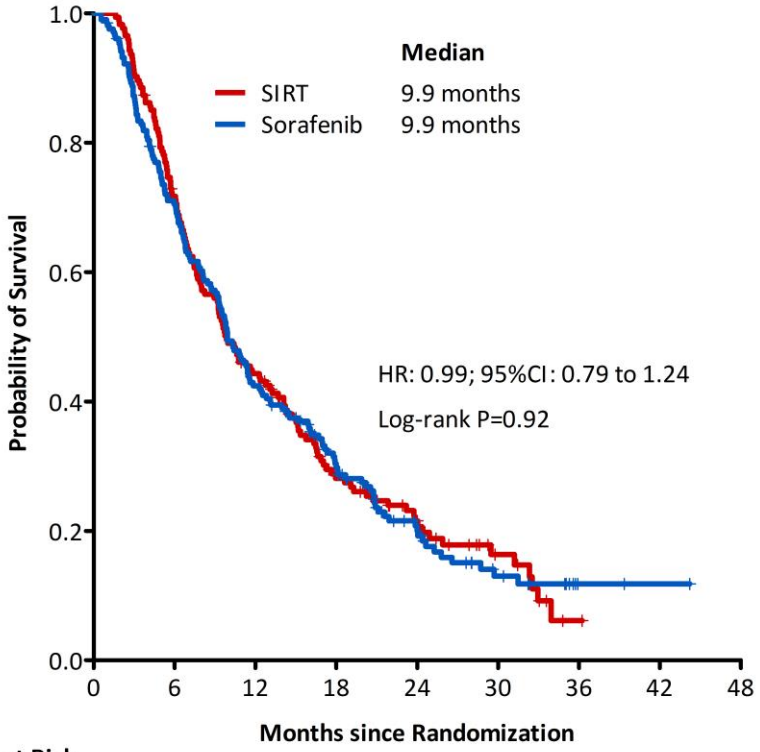
Intention to treat population
N=459



No. at Risk

SIRT	237	143	90	49	30	11	2	0	
Sorafenib	222	153	92	57	28	14	3	1	0

Per-protocol population
N=380

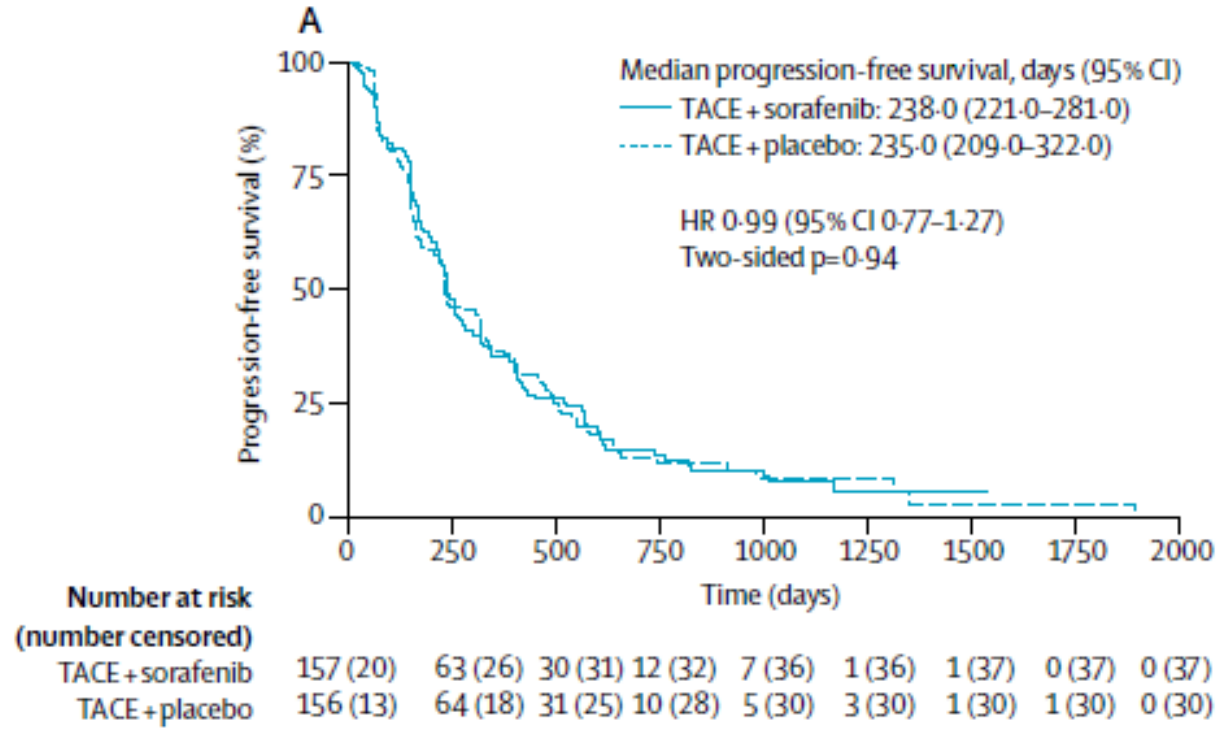


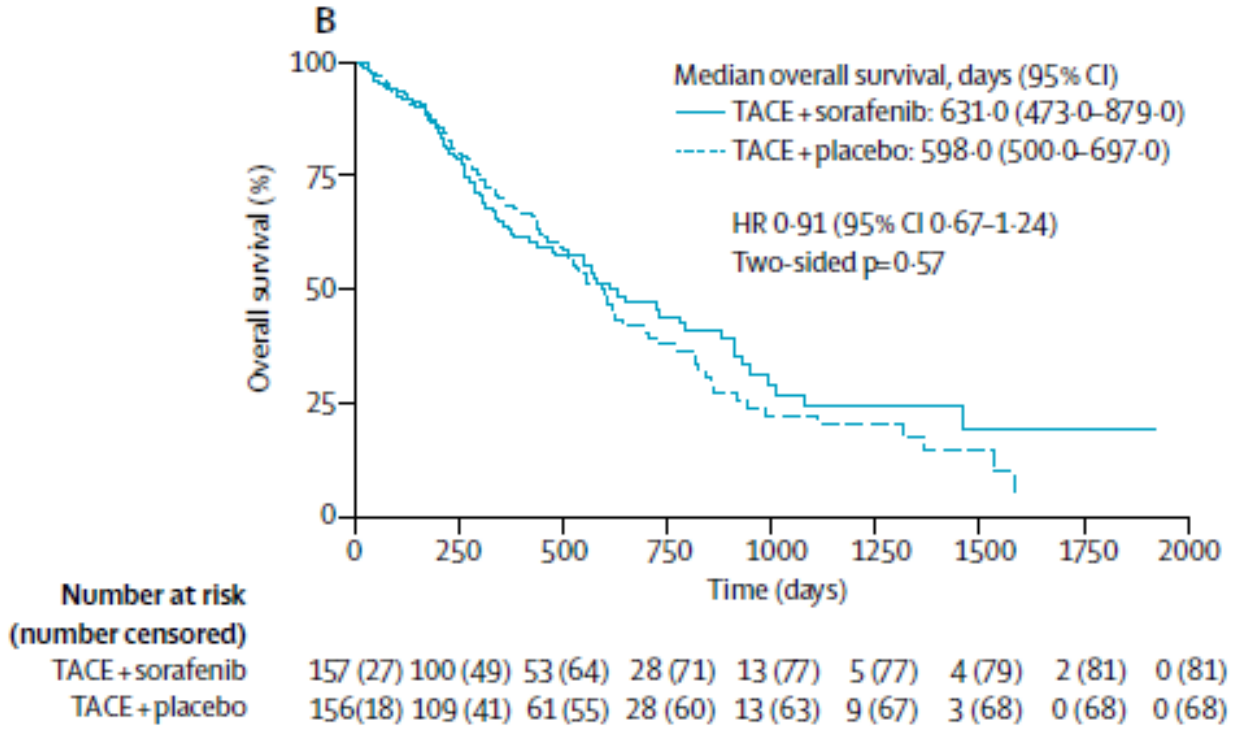
No. at Risk

SIRT	174	123	75	41	26	10	1	0	
Sorafenib	206	143	86	54	26	12	2	1	0

VilgrainV, Bouattour M, et al, EASL 2017

What about liver directed+systemic? TACE 2 results

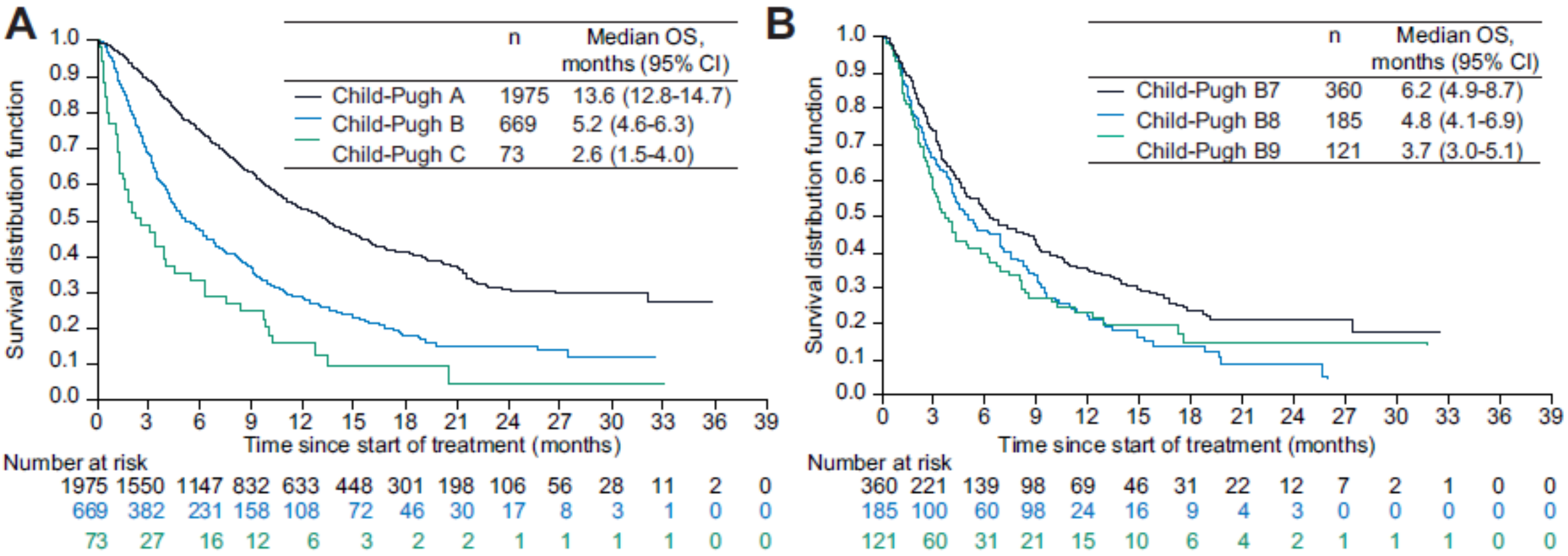




Meyer T, Lancet Gastroenterol Hepatol 2017

Should we treat patients beyond child pugh A?

The impact of cirrhosis



Marrero J, J of Hepatology 65, 2016

Safety of Sorafenib in child pugh B cirrhosis

Table 3. Overall safety profile of sorafenib by Child-Pugh score.

n (%)	Child-Pugh score[a,b]					
	A (<7) (n = 1968)	B7 (n = 359)	B8 (n = 182)	B9 (n = 122)	B (7-9)[c] (n = 666)	C (>9) (n = 74)
AEs (all grades)	1653 (84)	313 (87)	166 (91)	109 (89)	590 (89)	68 (92)
Drug-related AEs (all grades)	1349 (69)	240 (67)	114 (63)	74 (61)	429 (64)	29 (39)
Serious AEs[d]	708 (36)	192 (54)	126 (69)	82 (67)	402 (60)	52 (70)
Drug-related serious AEs	174 (9)	48 (13)	28 (15)	18 (15)	94 (14)	2 (3)
All grade 3 or 4 AEs	638 (33)	109 (30)	57 (31)	44 (36)	210 (32)	13 (18)
Drug-related grade 3 or 4 AEs	503 (26)	79 (22)	41 (23)	26 (21)	146 (22)	8 (11)
Deaths[e]	349 (18)	113 (31)	78 (43)	46 (38)	239 (36)	38 (51)

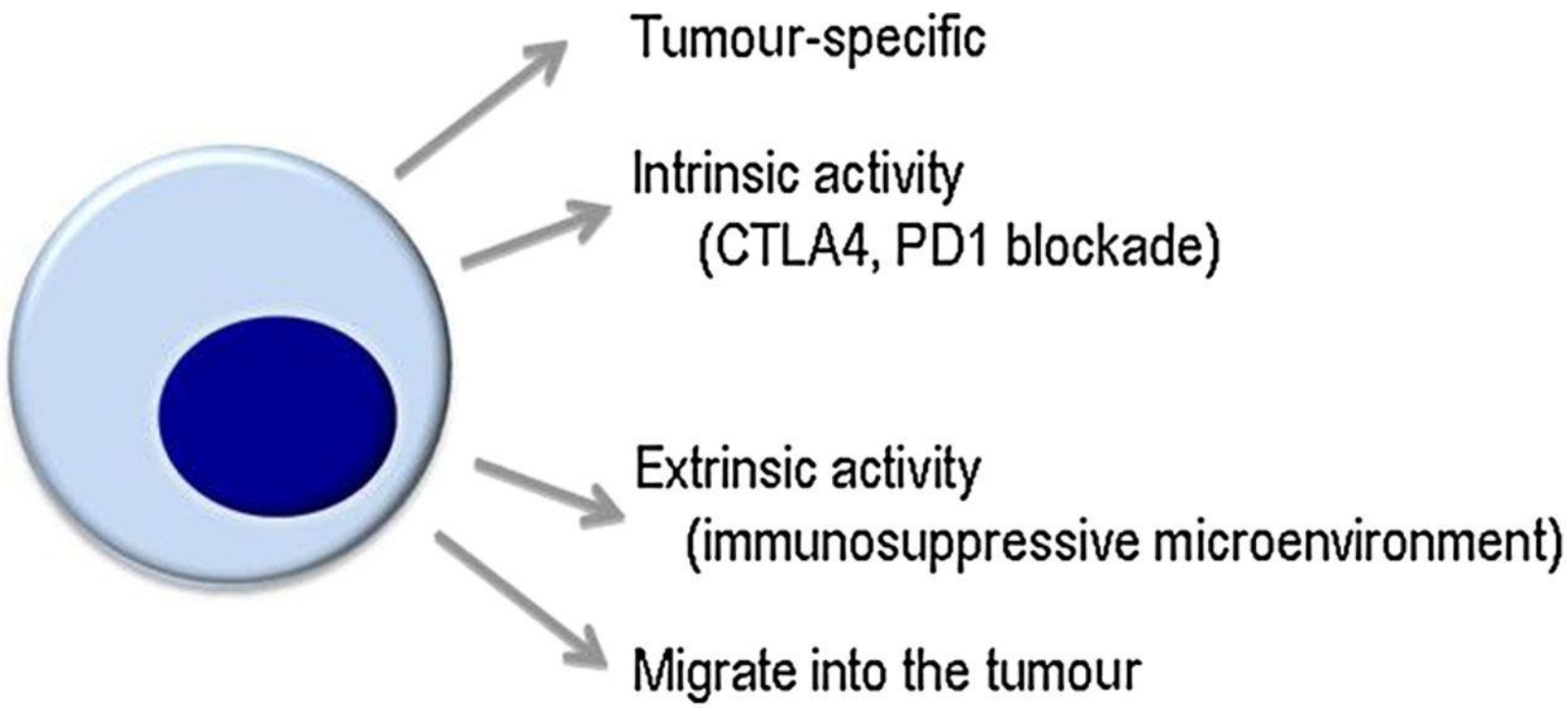
Table 4. Incidence of adverse events and drug-related adverse events occurring in ⩾10% of patients by Child-Pugh score.

n (%)	Child-Pugh score[a,b]											
	A (<7) (n = 1968)		B7 (n = 359)		B8 (n = 182)		B9 (n = 122)		B (7-9)[c] (n = 666)		C (>9) (n = 74)	
	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE
Diarrhea	616 (31)	556 (28)	112 (31)	98 (27)	52 (29)	48 (26)	31 (25)	23 (19)	196 (29)	170 (26)	13 (18)	8 (11)
Hand-foot skin reaction	636 (32)	626 (32)	70 (20)	70 (20)	29 (16)	29 (16)	14 (11)	14 (11)	116 (17)	113 (17)	4 (5)	4 (5)
Fatigue	440 (22)	311 (16)	98 (27)	56 (16)	43 (24)	22 (12)	30 (25)	17 (14)	171 (26)	95 (14)	15 (20)	10 (14)
Anorexia	285 (15)	209 (11)	57 (16)	30 (8)	29 (16)	11 (6)	14 (11)	8 (7)	100 (15)	49 (7)	10 (14)	5 (7)
Abdomen pain	224 (11)	62 (3)	63 (18)	26 (7)	31 (17)	8 (4)	23 (19)	6 (5)	118 (18)	24 (4)	13 (18)	4 (5)
Liver dysfunction[d]	203 (10)	36 (2)	46 (13)	10 (3)	43 (24)	7 (4)	30 (25)	2 (2)	120 (18)	19 (3)	16 (22)	0
Rash/desquamation	258 (13)	238 (12)	41 (11)	35 (10)	17 (9)	15 (8)	8 (7)	7 (6)	66 (10)	57 (9)	4 (5)	3 (4)
Nausea	167 (8)	106 (5)	42 (12)	28 (8)	19 (10)	8 (4)	9 (7)	5 (4)	70 (11)	41 (6)	9 (12)	7 (9)
Hypertension	243 (12)	215 (11)	21 (6)	18 (5)	7 (4)	7 (4)	3 (2)	3 (2)	31 (5)	28 (4)	0	0

Marrero J, J of Hepatology 65, 2016

Future Directions

How do we expand the benefit of immunotherapy to more patients with hepatocellular carcinoma? .



Tim F Greten et al. Gut 2015;64:842-848

GUT

Combination of PD-1/PDL-1 and CTLA4 antibodies

- **Phase I/II of durvalumab and tremelimumab**
  - 40 pts enrolled (11 HBV+, 9 HCV+, 20 uninfected)
  - 30% had no prior systemic therapy
  - 93% Child Pugh Class A
  - Most common (≥15%) treatment-related AEs: fatigue (20%), increased ALT (18%), pruritus (18%), and increased AST (15%).

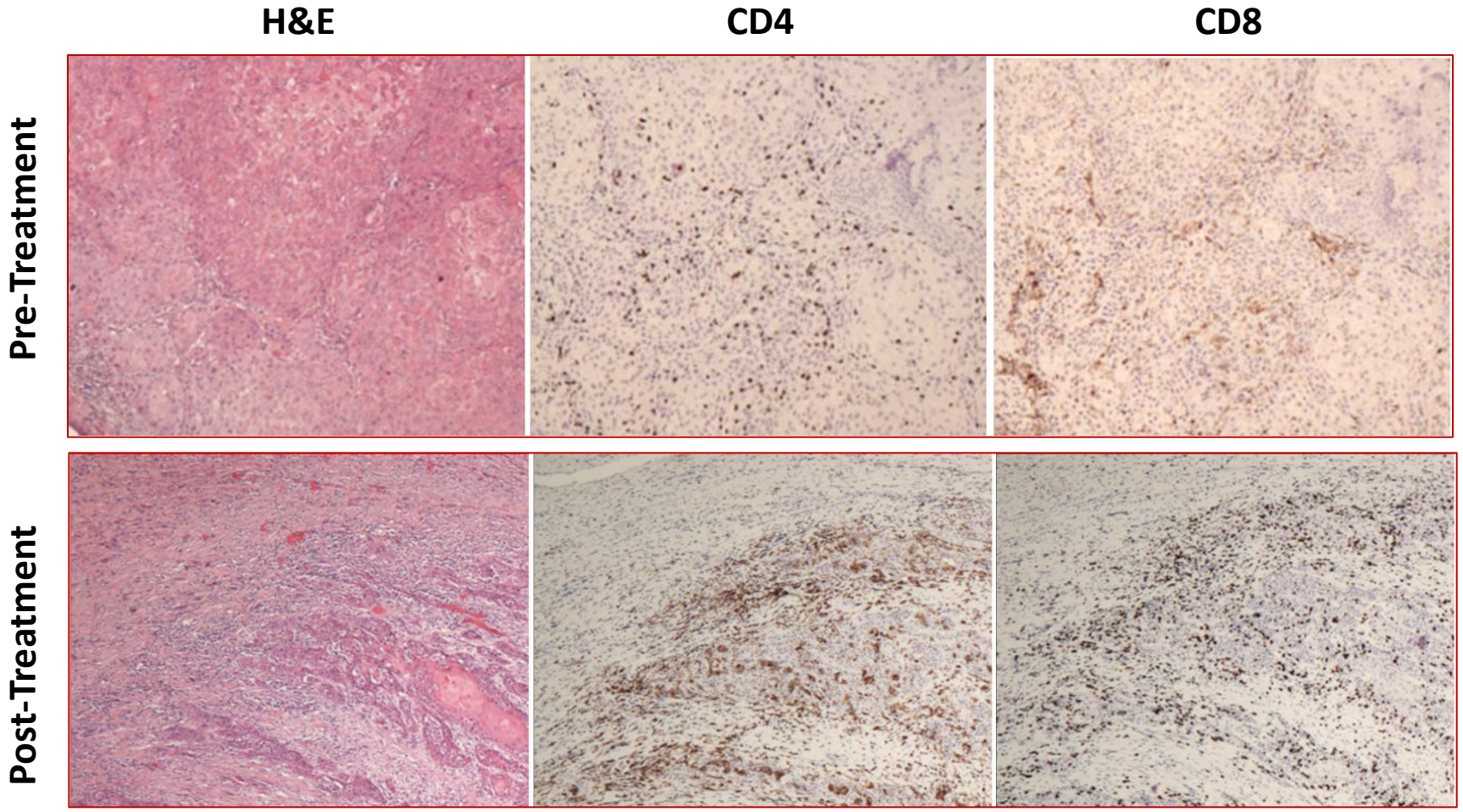
Investigator-assessed response	HBV+ (N = 11)	HCV+ (N = 9)	Uninfected (N = 20)	All (N = 40)
Confirmed ORR (all PR), % (95% CI)	0 (0.0–28.5)	11.1 (0.3–48.2)	30.0 (11.9–54.3)	17.5 (7.3–32.8)
CR + PR (confirmed + unconfirmed), % (95% CI)	9.1 (0.2–41.3)	11.1 (0.3–48.2)	40.0 (19.1–63.9)	25.0 (12.7–41.2)
CR + PR + SD ≥16 weeks (DCR16), % (95% CI)	45.5 (16.7–76.6)	44.4 (13.7–78.8)	70.0 (45.7–88.1)	57.5 (40.9–73.0)

- **Phase I/II of nivolumab and ipilumumab ongoing (Checkmate 040)**

Kelley RK et al, J Clin Oncol 35, 2017 (suppl; abstr 4073)

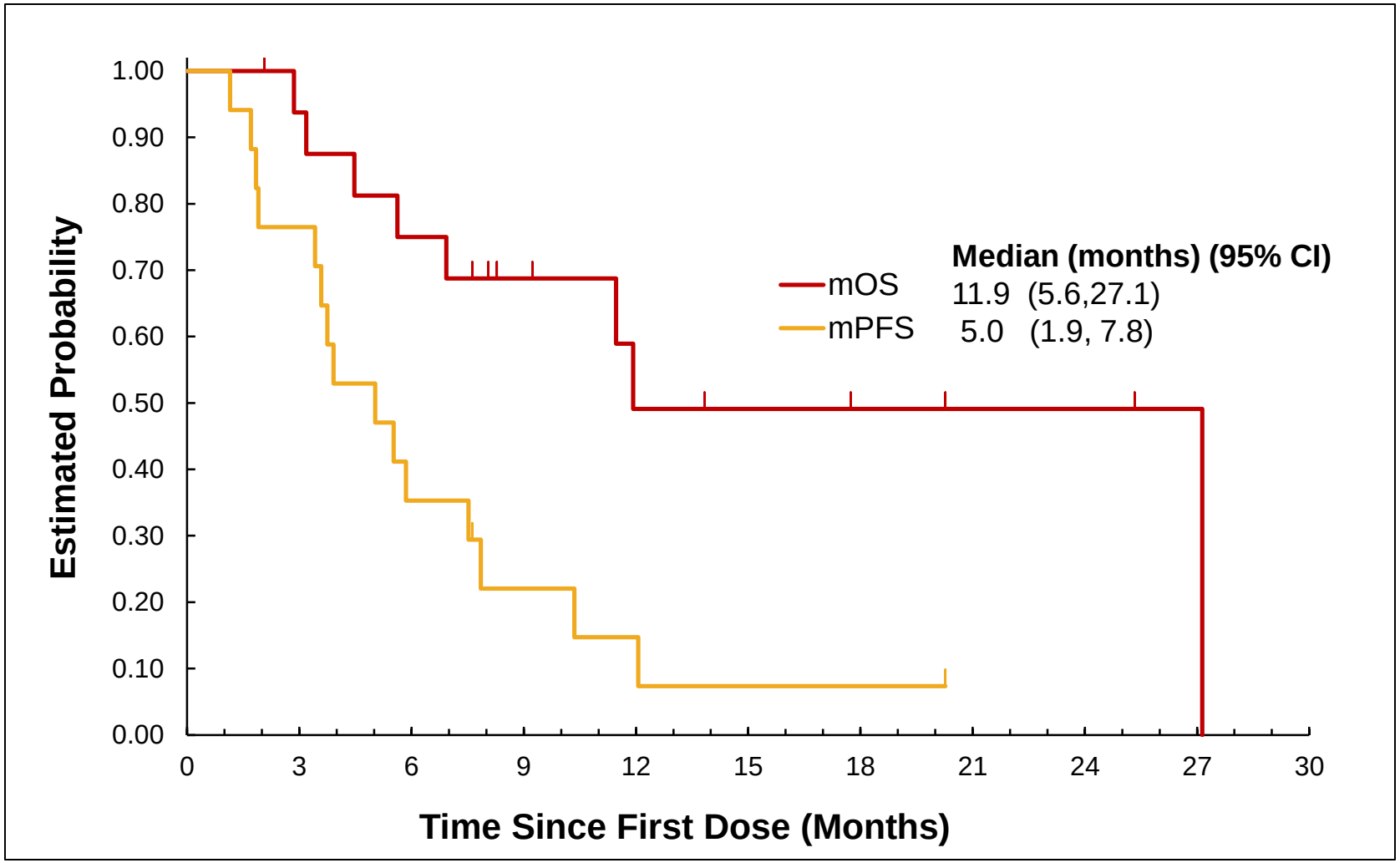
USC: First-in-Human study of sEphB4-HSA in advanced solid tumors

sEphB4-HSA promotes CD4 and CD8 infiltration in the tumor



- Pre and post treatment tissue samples from 12 patients were evaluated.
- On therapy, 6 patients showed marked increase in CD4, CD8, CD3 cell infiltration.

sEphB4-HSA single agent expansion in HCC

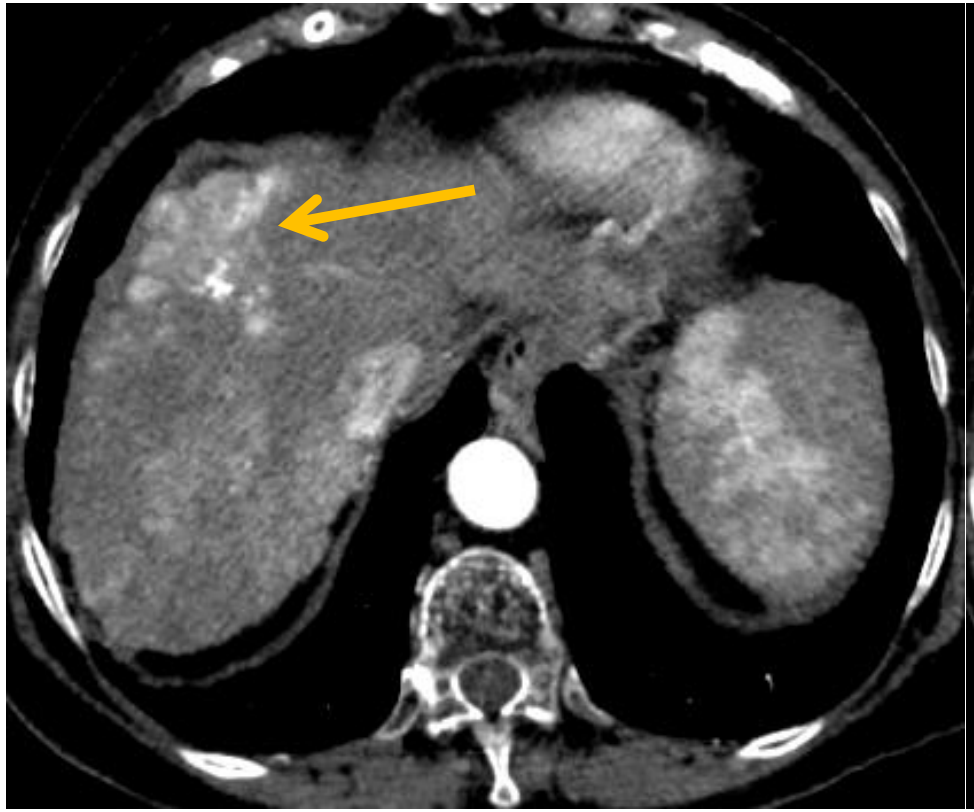


Thomas J et al, ASCO GI 2018

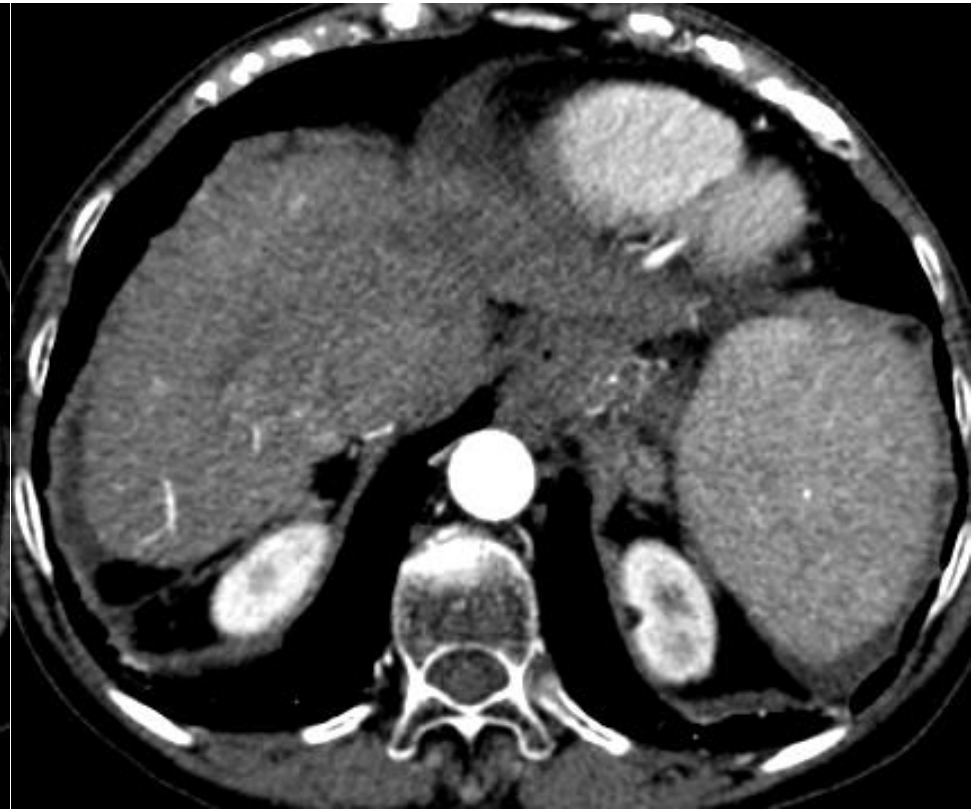
Hepatocellular Carcinoma: Partial Remission

Patient: FN 77F **Best Response on sEphB4-HSA:** Partial Remission at 5 months
sEphB4-HSA Status: Currently on sEphB4-HSA; Treatment duration – 5+ months
Current Status: On therapy

Regimen #	Treatment (History)	Treatment Duration	Best overall response
1	TACE	15 months	PR
2	Anti-PD1 Antibody Therapy (Nivolumab)	5 months	SD



8-26-15
5.4 cm arterially enhancing mass



8-17-16
Not present

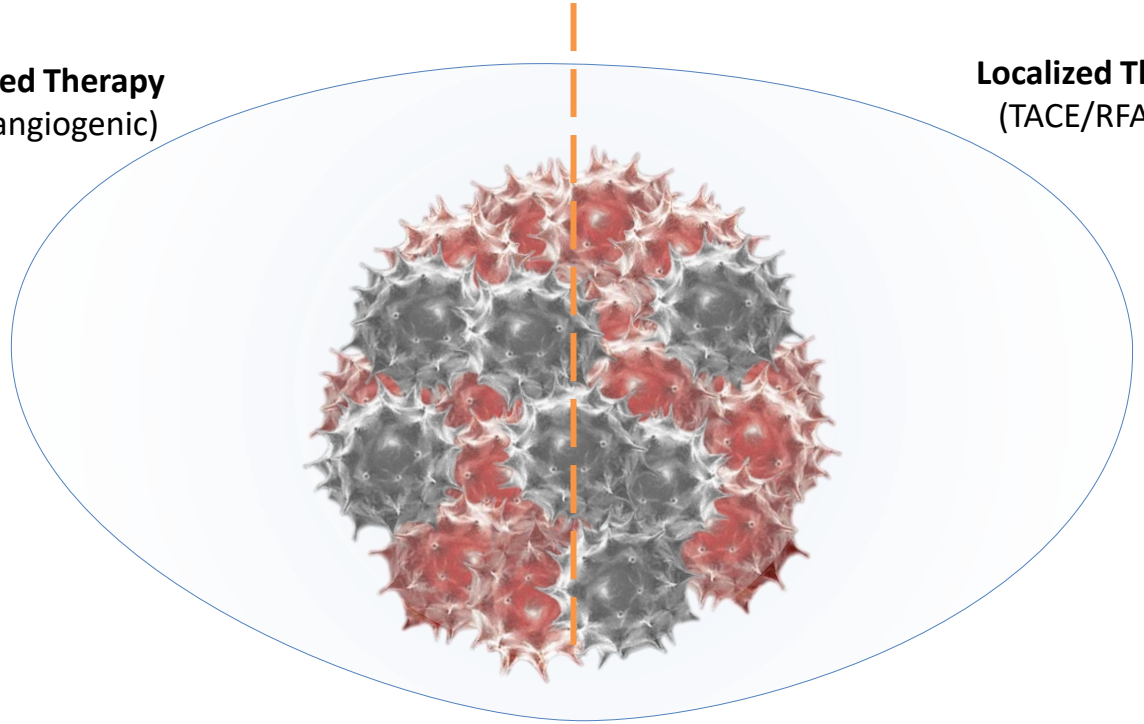
Rationale Behind Combination Approaches

Targeted Therapy
(anti-angiogenic)

Targeted therapy induces:
- Hypoxia
- ↓ Treg population
- ↓ MDSC
- ↑PD-L1 expression
- Enhanced T cell tumor infiltration and activation

Localized Therapy
(TACE/RFA/PEI)

Localized therapy induces:
- High antigen load
- Damage to liver cells
- Tumor-specific T-cell response



Tumor Microenvironment

I-O, immuno-oncology; PD-L1, programmed death-ligand 1; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter arterial embolization; Treg, regulatory T cell.

1. *Chen Y et al. Hepatology. 2015;61(5):1591-1602.*
2. *Greten et al. Rev Recent Clin Trial. 2008*
3. **Hedge PS, Semin Cancer Biol 2017**

A phase Ib trial of Lenvatinib and Pembrolizumab in patients with HCC

Table 2. Summary of TEAEs (Safety Analysis set)

Parameter, n (%)	LEN + PEM		
	Part 1 (n = 6)	Part 2 (n = 24)	Overall (N = 30)
TEAEs	6 (100.0)	24 (100.0)	30 (100.0)
Treatment-related TEAEs	6 (100.0)	22 (91.7)	28 (93.3)
TEAEs ≥ grade 3	5 (83.3)	13 (54.2)	18 (60.0)
Serious AEs	2 (33.3)	6 (25.0)	8 (26.7)
Fatal AEs[a]	0	3 (12.5)	3 (10.0)
Dose modifications			
LEN or PEM dose interruptions due to TEAEs	5 (83.3)	13 (54.2)	18 (60.0)
LEN dose reductions due to TEAEs	5 (83.3)	13 (54.2)	18 (60.0)
Discontinuation of LEN or PEM due to TEAE(s)[b]	0	5 (20.8)	5 (16.7)

[a]Acute respiratory distress syndrome (n = 1); intestinal perforation (n = 1); bacterial peritonitis (n = 1)

Table 4. Summary of Tumor Response (Investigator Assessment by mRECIST; Efficacy Analysis set[a])

Parameter, n (%)	LEN + PEM		
	Part 1 (n = 6)	Part 2 (n = 20)	Overall (n = 26)
BOR, n (%)			
CR[b]	0	1 (5.0)	1 (3.8)
PR[c]	4 (66.7)	6 (30.0)	10 (38.5)
SD	2 (33.3)	13 (65.0)	15 (57.7)
PD	0	0	0
ORR (including unconfirmed responses), n (%)	4 (66.7)	7 (35.0)	11 (42.3)
95% CI	22.3, 95.7	15.4, 59.2	23.4, 63.1
ORR (excluding unconfirmed responses), n (%)	3 (50.0)	4 (20.0)	7 (26.9)
95% CI	11.8, 88.2	5.7, 43.7	11.6, 47.8

[a]Patients with post-evaluable tumor assessment; [b]0 CR confirmed; [c]7 PR confirmed.

Ikeda M et al, ASCO 2018

A phase Ib of Atezolizumab and Bevacizumab in advanced HCC

Table 2. Safety Summary

Adverse Events	Safety-Evaluable Population (N = 43)
Any grade, n (%)	42 (98%)
Treatment-related	35 (81%)
Grade 3-4, n (%)	15 (35%)
Treatment-related	12 (28%)
Grade 5, n (%)[a]	2 (5%)
Treatment-related	0
Serious AE, n (%)	11 (26%)
Treatment-related[b]	3 (7%)
AESI with atezolizumab, any grade, n (%)	25 (58%)
AESI with bevacizumab, any grade, n (%)	26 (61%)

AE, adverse event; AESI, adverse event of special interest.
[a] Cardiac arrest (day 154, unrelated), bacterial peritonitis (day 141, unrelated); [b] Autoimmune encephalitis (day 127, related to atezolizumab), mental status change (day 198, related to atezolizumab), intra-abdominal hemorrhage (day 4, related to bevacizumab) and jugular vein thrombosis (day 215, related to bevacizumab). Autoimmune encephalitis and mental status change occurred in the same patient.

Table 4. Best Overall Response (BOR)

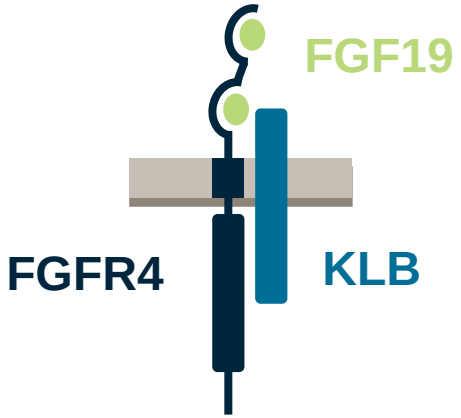
BOR	INV-Assessed per RECIST v1.1 (n = 23)	IRF-Assessed per RECIST v1.1 (n = 23)
ORR, n (%)	14 (61%)	15 (65%)
CR	0	1 (4%)
PR	14 (61%)	14 (61%)
SD	5 (22%)	7 (30%)
PD	4 (17%)	1 (4%)
DCR, n (%)		
CR + PR + SD	19 (83%)	22 (96%)
CR + PR + SD ≥ 6 mo	15 (65%)	16 (70%)

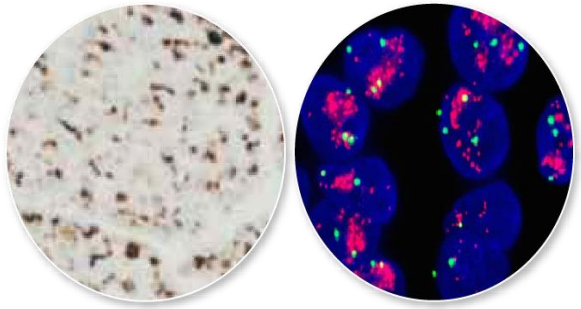
BOR, best overall response; CR, complete response; DCR, disease control rate; INV, investigator; IRF, independent review facility; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

- Figure 3 displays the change in tumor burden over time in response to atezolizumab + bevacizumab treatment

Stein S et al, ASCO 2018

BLU-554: first-in-human study



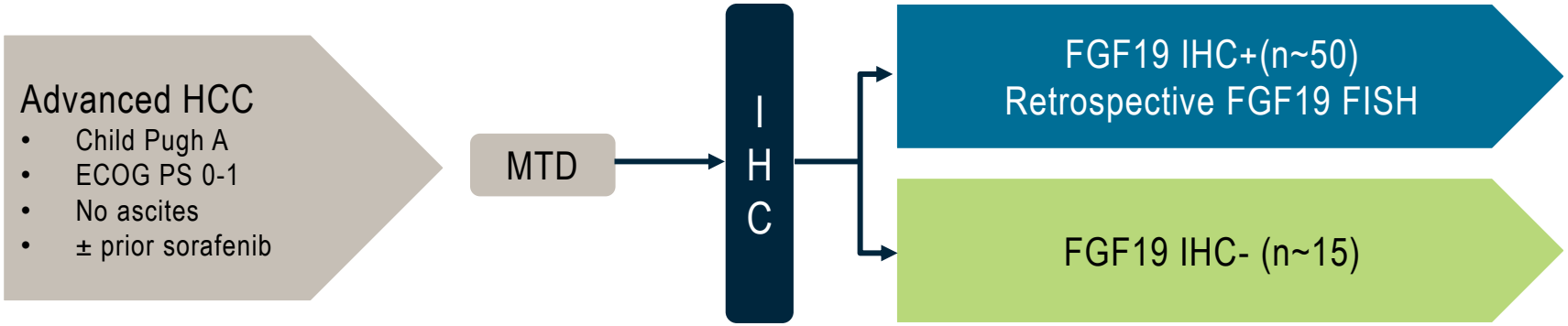


FGF19 IHC+
~30% HCC

FGF19 FISH+
~7% HCC

Part 1: Dose escalation – completed

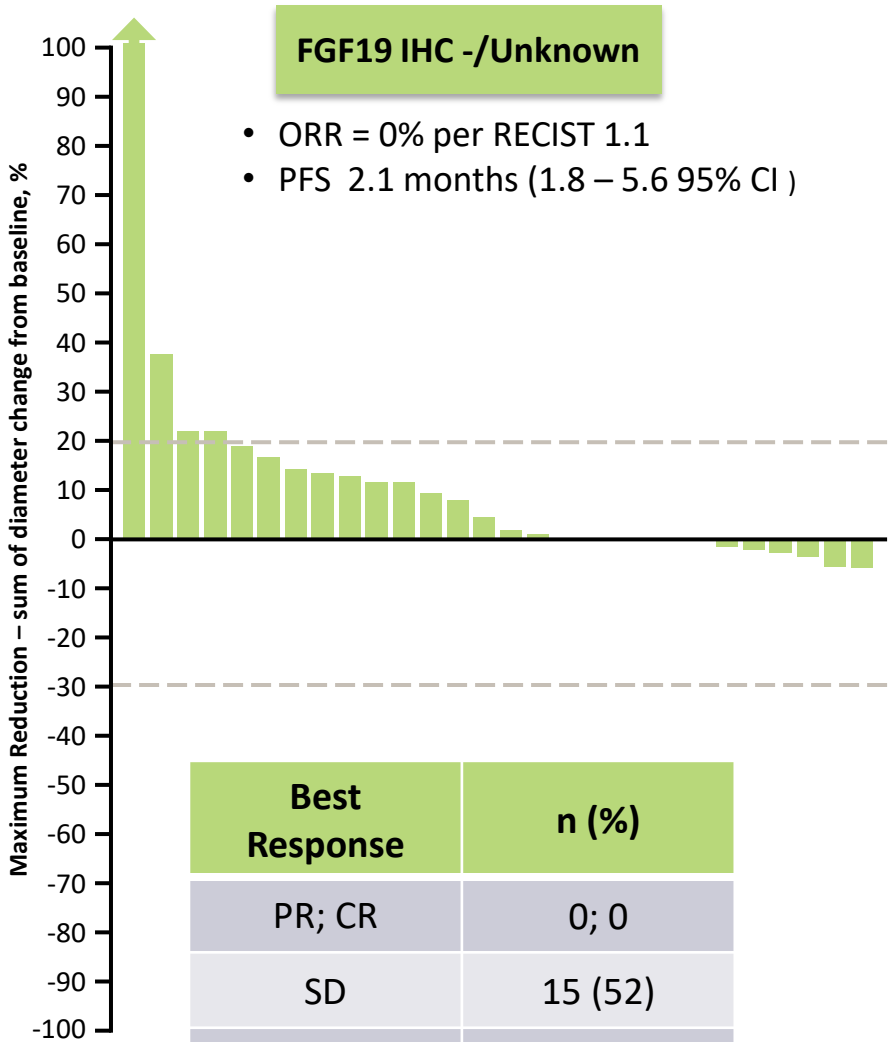
Part 2: Dose expansion – enrolling



- 3+3 dose escalation (140-900 mg PO QD)
- 600 mg established as MTD

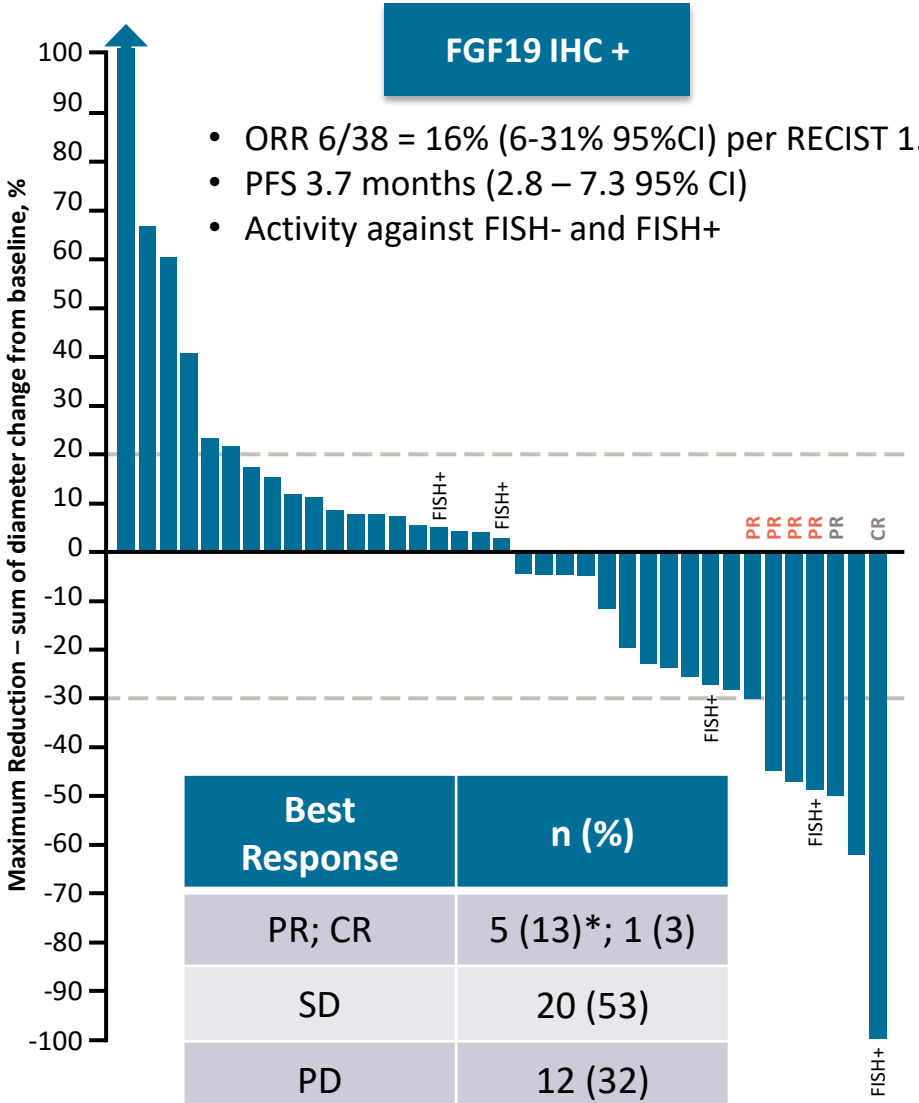
Kim R et al, ESMO 2017

IHC-positivity enriches for radiographic tumor reduction and response



- ORR = 0% per RECIST 1.1
- PFS 2.1 months (1.8 – 5.6 95% CI)

Best Response	n (%)
PR; CR	0; 0
SD	15 (52)
PD	14 (48)



- ORR 6/38 = 16% (6-31% 95%CI) per RECIST 1.1
- PFS 3.7 months (2.8 – 7.3 95% CI)
- Activity against FISH- and FISH+

Best Response	n (%)
PR; CR	5 (13)*; 1 (3)
SD	20 (53)
PD	12 (32)

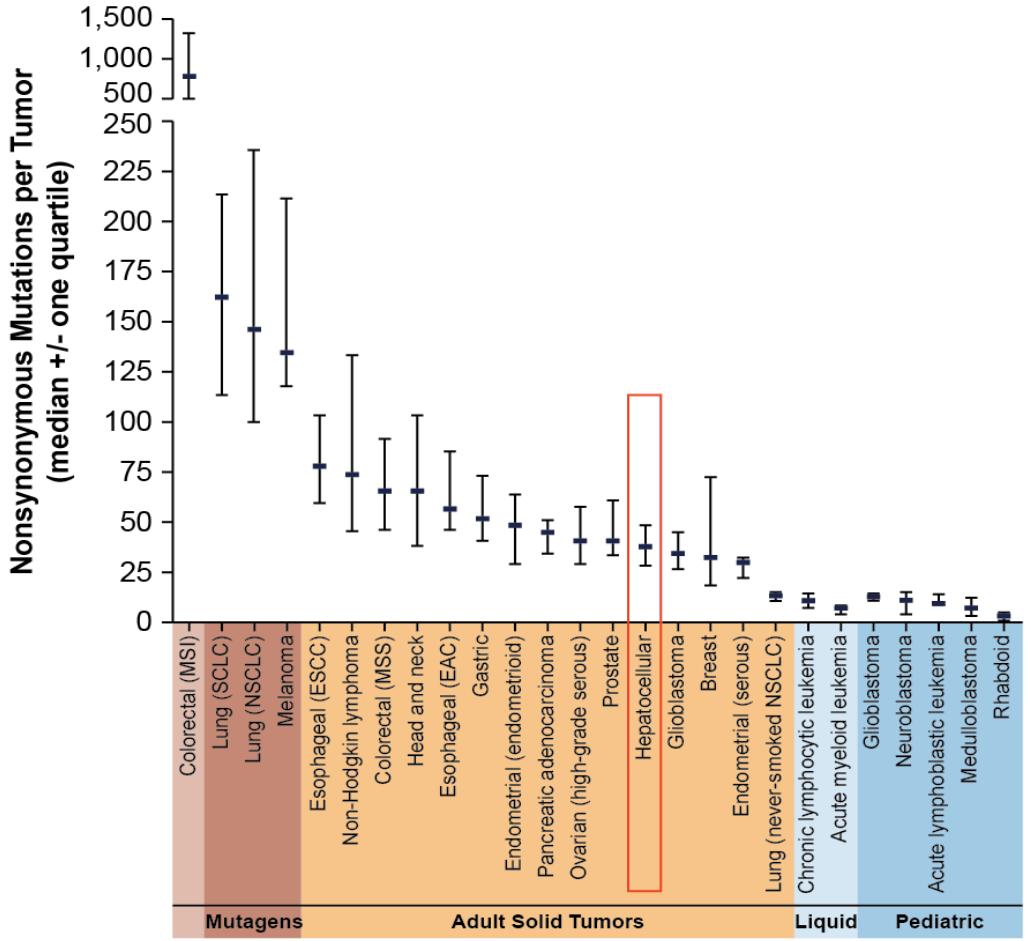
*4 confirmed PR; 1 PR/1 CR, unconfirmed
Data are preliminary as of data cut off: 18 August 2017
CR, complete response; ORR, overall response rate; PFS, progression-free survival;

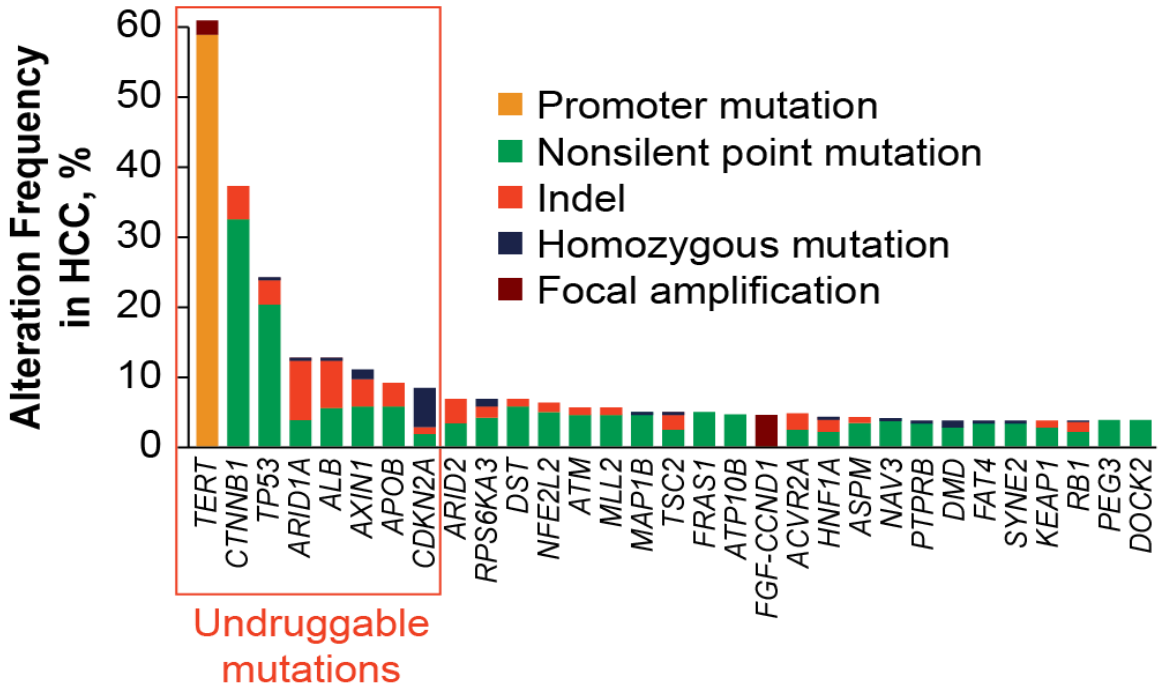
Kim R et al, ESMO 2017

A new reality for patients with advanced HCC

First line	Second line	Third line
Sorafenib	Regorefanib	
Lenvatinib	Nivolumab	Nivolumab
	Cabozantinib	Cabozantinib
	Ramucirumab	
Ongoing phase 3 of Nivolumab versus Sorafenib	Ongoing phase 3 of Pembrolizumab versus BSC	

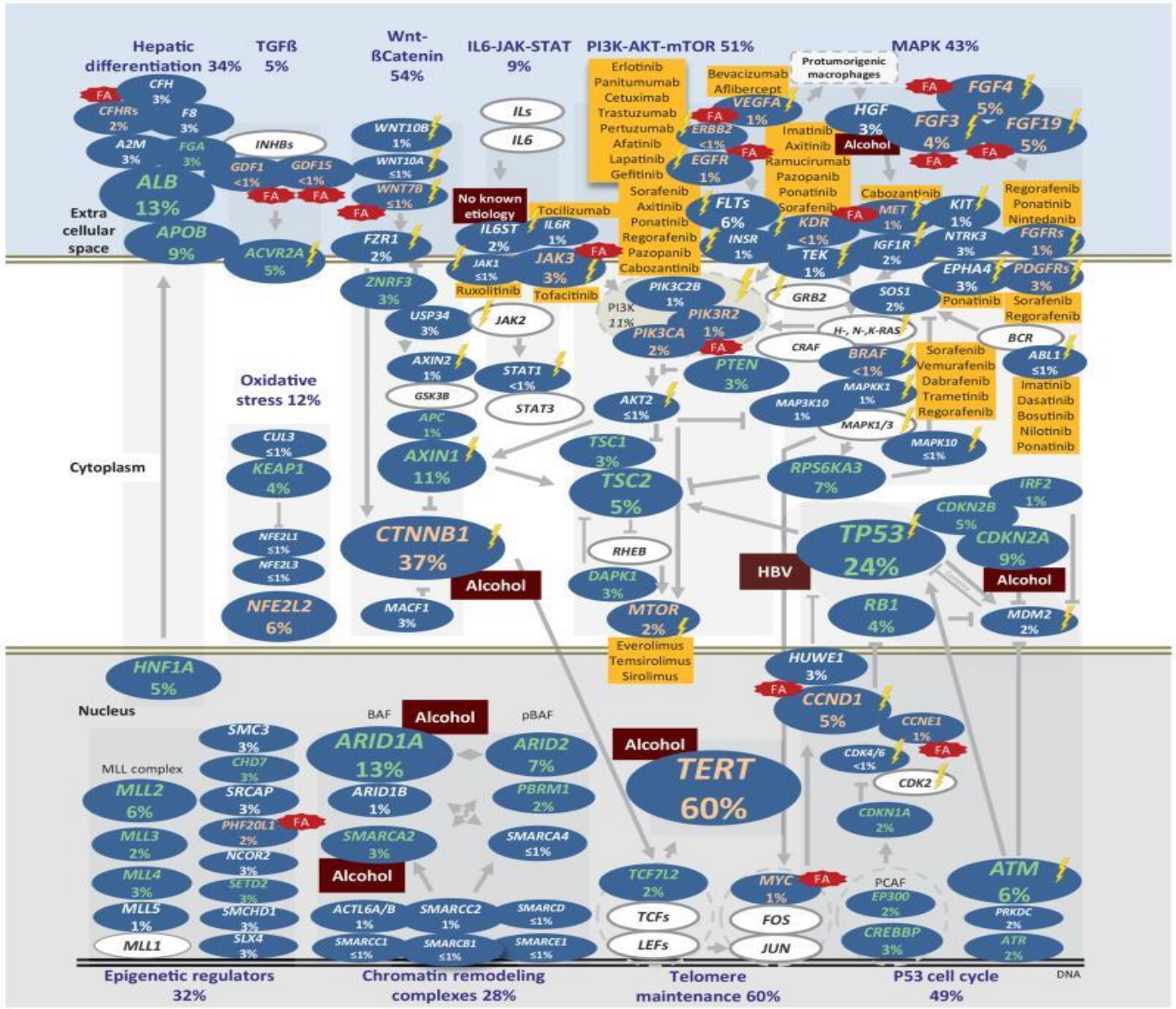
Mutational landscape of HCC





Vogelstein B et al. Science. 2013;339:1546-1558. 2. Schulze K et al. Nat Genet. 2015;47:505-511

Challenges ahead



Schulze K et al, nature Genetics 2015

Summary and conclusions

- Lenvatinib is non-inferior to Sorafenib in first line HCC treatment
- Regorefanib, Cabozantinib, Ramucirumab have shown activity post sorafenib

- Immunotherapy has shown activity in HCC
  - Checkpoint inhibitors (Nivolumab, Pembrolizumab)
  - Looking forward to phase 3 trial results
  - CIK

- Targeting molecular subtypes is feasible and shows preliminary efficacy
  - FGF19

Summary and conclusions

- Areas of active investigation
  - Immunotherapy combinations
  - Immunotherapy + non-immunotherapy combinations
    - Emerging data from checkpoint inhibitor plus TKI or Bevacizumab intriguing

- Challenges:
  - Optimal sequencing strategies
  - Biomarkers development for patient selection and prognostication
  - Expanding the benefit of immunotherapy to special HCC populations (Child Pugh B)
  - Incorporation into earlier stages of disease
    - Locoregional combinations
    - Adjuvant/neo-adjuvant

- A new era for the treatment of hepatocellular carcinoma