STATO DELL'ARTE SULL'EPATOCARCINOMA 2017-2018

Milano, 21 Settembre 2018

Update sulle altre linee di terapia sistemica dell'epatocarcinoma

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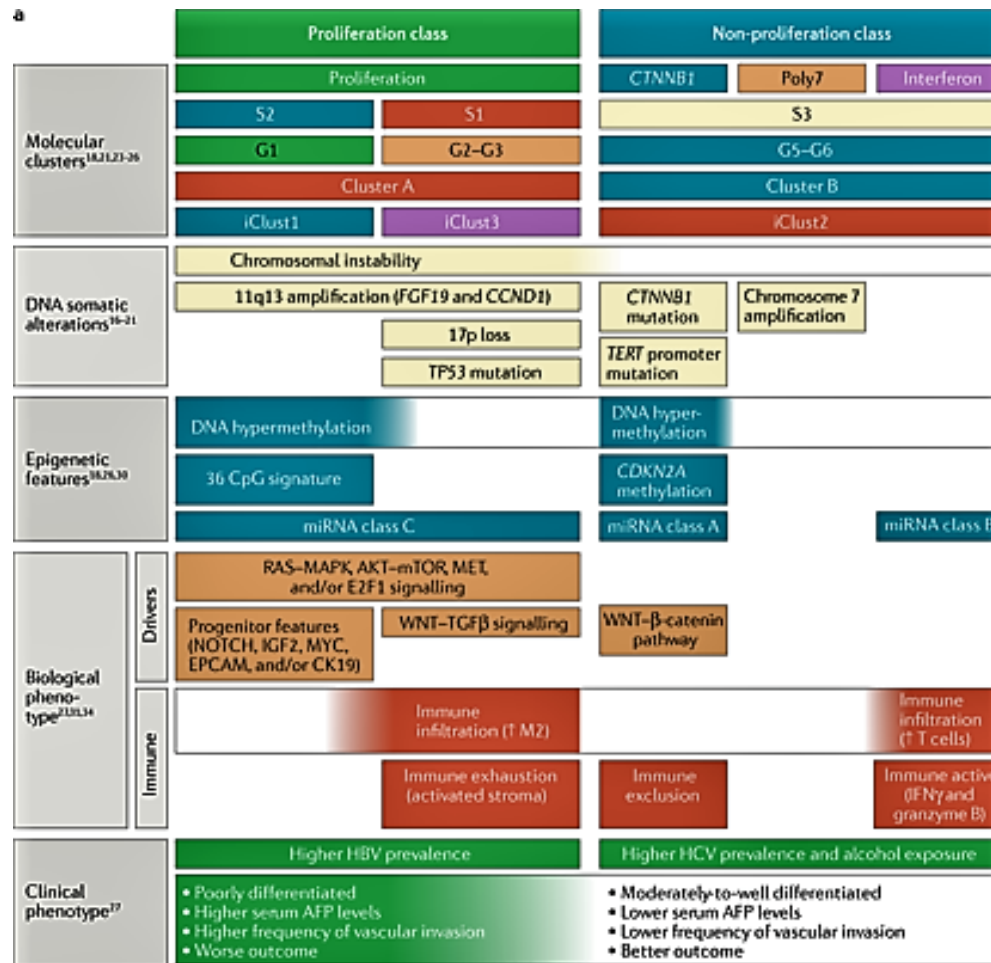Università degli Studi di Milano

Financial Disclosures

Dr. Angelo Sangiovanni

Grant and research support: Fusjrebio

Speaking and teaching: Bayer, Gilead Science, BMS, Janssen,

                             Abbvie, Tiziana, Novartis

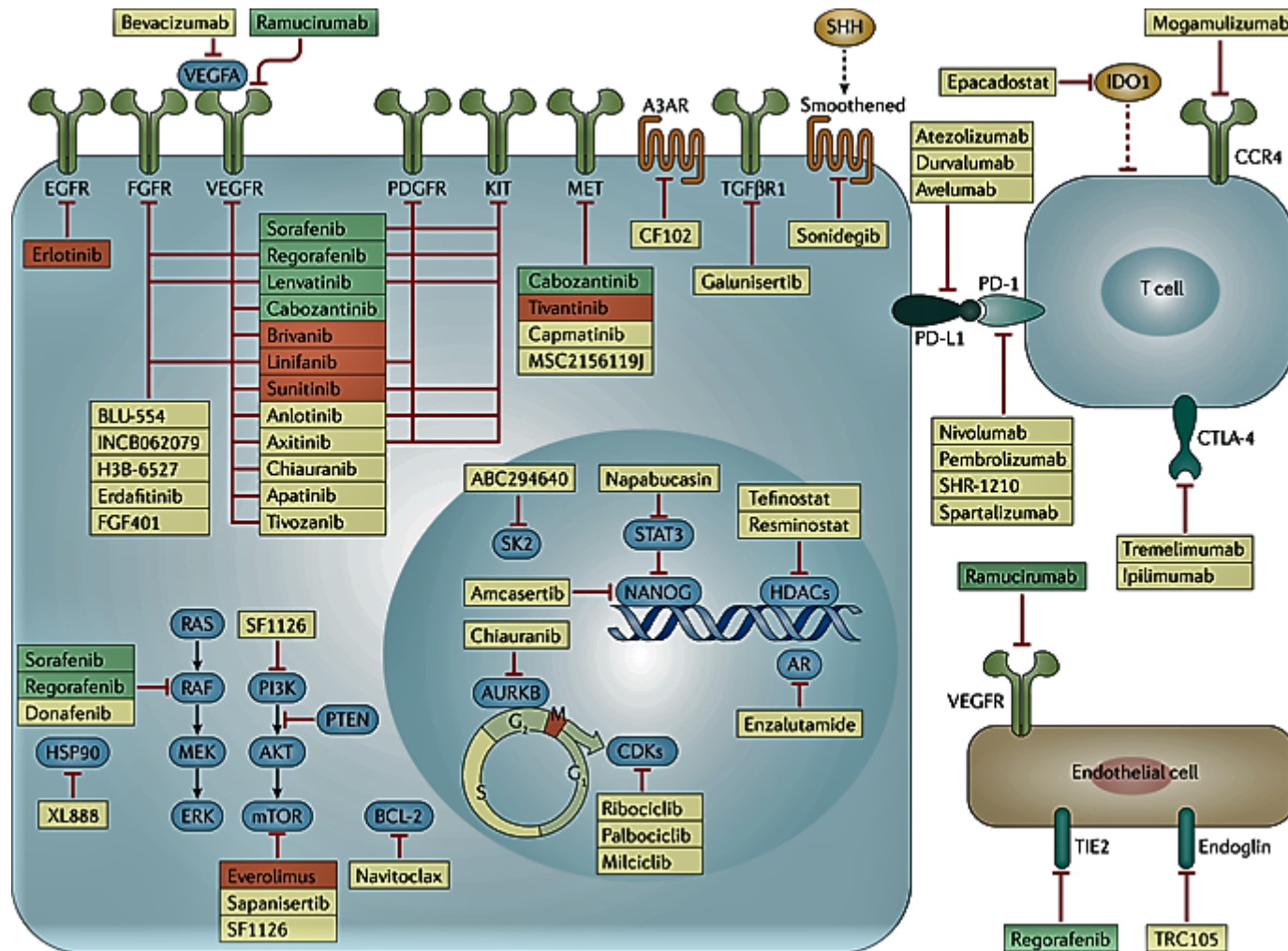# Molecular Therapies and Precision Medicine: Integreative Molecular Classification for HCC

Llovet JM et al, Nat Rev Clin Oncol, 2018

Molecular Therapies and Precision Medicine: Integreative Immunological Classification for HCC

Llovet JM et al, Nat Rev Clin Oncol, 2018

Molecular Targeted Therapies for HCC and Their Targeted Signalling Pathways

Timeline of Targeted Therapies that Succeeded and Failed in Phase 3 RCTs of HCC
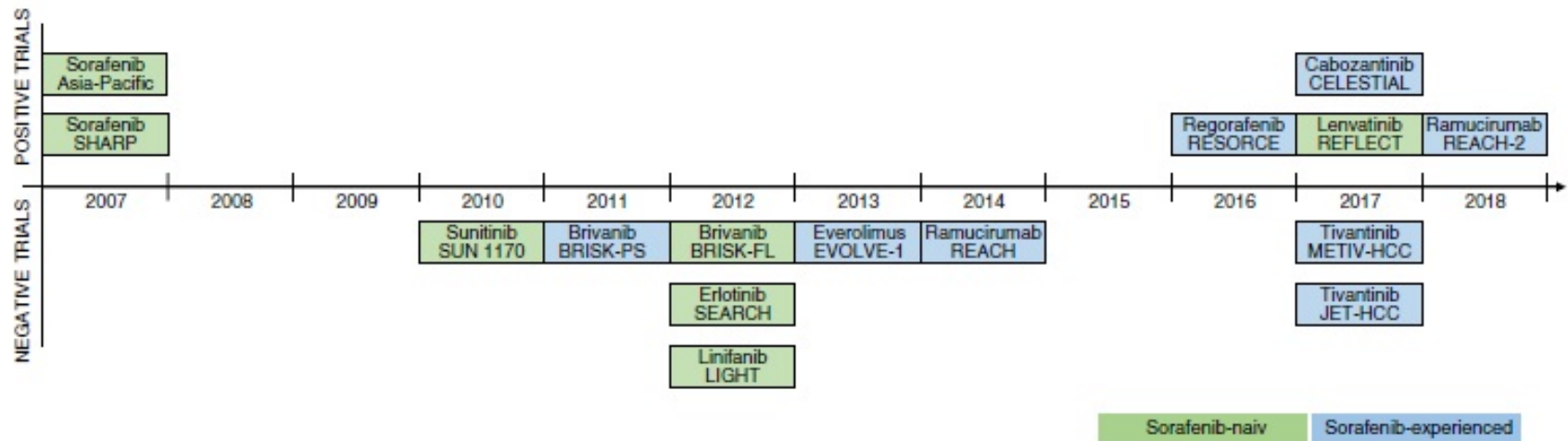
Outline

- ➢ First line therapy other than Sorafenib

    - ➢ Lenvatinib

- ➢ Second line therapy

    - ➢ Regorafenib

    - ➢ Cabozantinib

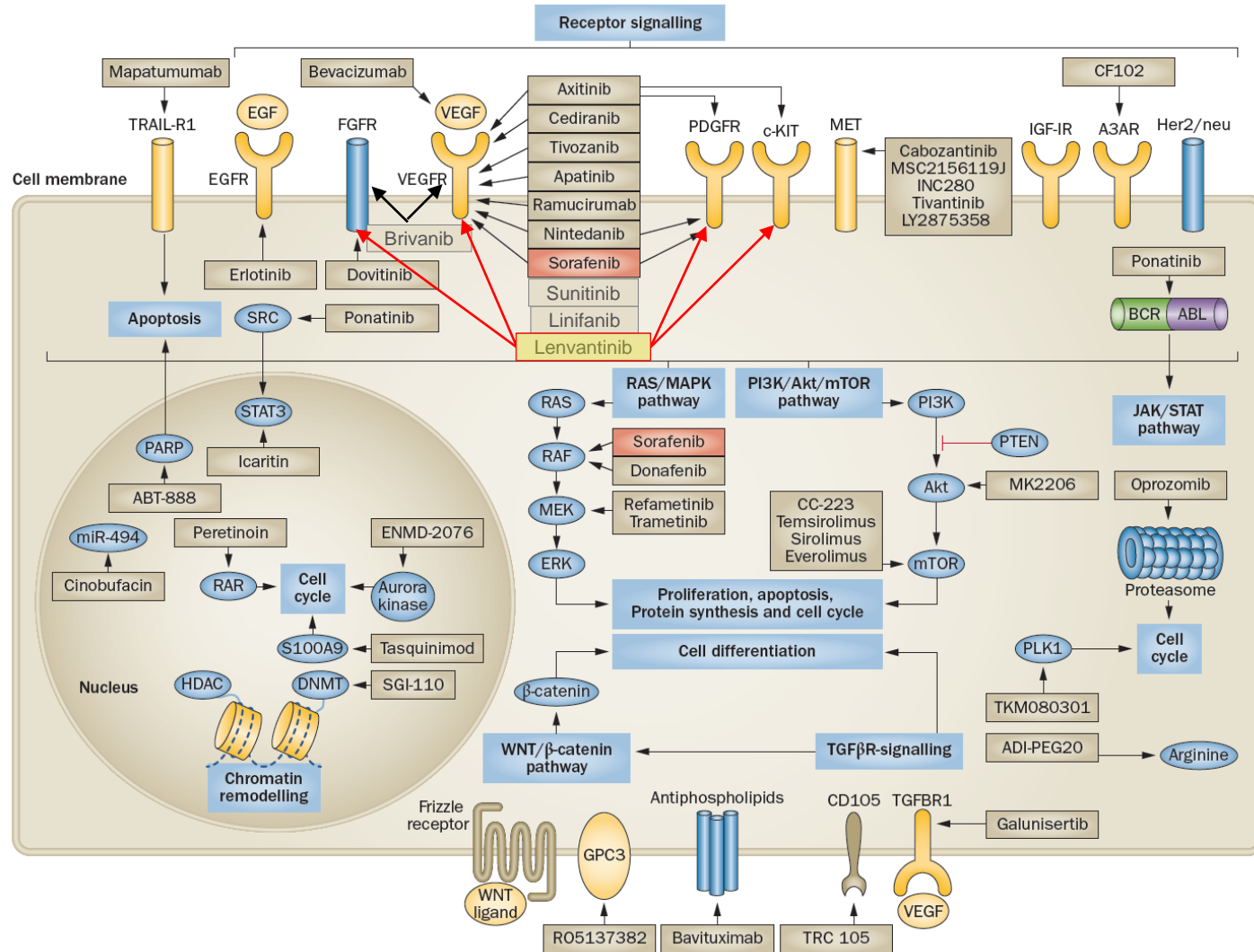   - ➢ Ramacirumab

    - ➢ Nivolumab

Outline

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    ➢ Ramacirumab

    ➢ Nivolumab

Molecular Targeted Therapies for HCC
Their Target Signalling Pathways

Phase 2 study of Lenvatinib (12mg) in Patients with Advanced Hepatocellular Carcinoma

46 pts, Japan 94%, CPT-A 98%; ECOG-PS 0 83%; PVI 11%; MTX 46%; BCLC-C 59%, prior SOR 13%.
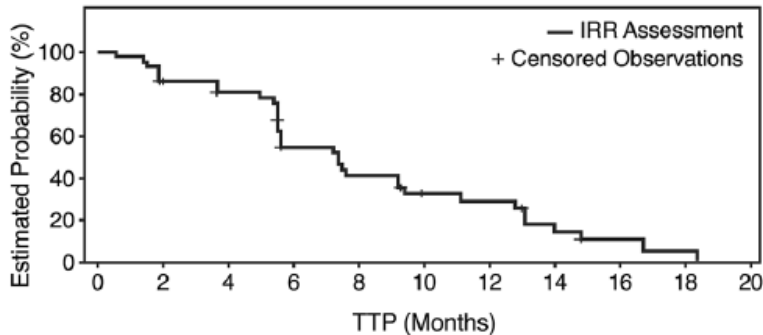
Median **TTP** was 7.4 months as assessed by an IRRC according to mRECIST criteria
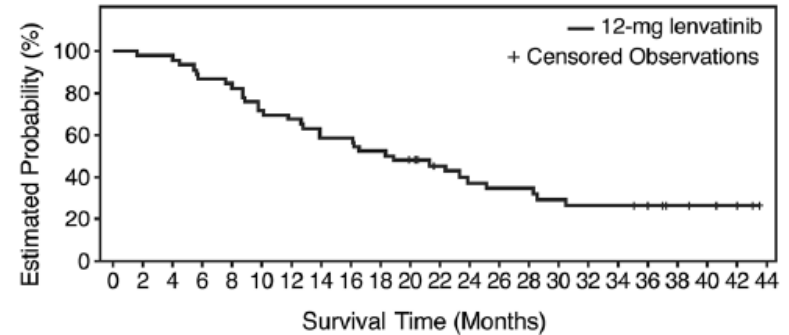
Median **OS** was 18.7 months.

Response category	Investigator assessment (mRECIST), $n = 46$	IRRC assessment (mRECIST), $n = 46$
Best response, n (%)		
Complete response	0 (0)	0 (0)
Partial response	17 (37)	17 (37)
Stable disease	21 (46)	19 (41)
Progressive disease	5 (11)	6 (13)
Not evaluable	3 (7)	4 (9)
Objective response rate, n (%)	17 (37)	17 (37)
Disease control rate, n (%)	38 (83)	36 (78)

IRRC independent radiologic review committee, *mRECIST* modified response evaluation criteria in solid tumors

Ikeda K et al, J Gastroenterol 2017

Phase 2 study of Lenvatinib (12mg) in Patients with Advanced Hepatocellular Carcinoma

Adverse event	Any grade, n = 46	Grade 3, n = 46	Grade 4, n = 46
Hypertension	35 (76.1)	25 (54.3)	0
Palmar-plantar erythrodysesthesia syndrome	30 (65.2)	4 (8.7)	0
Decreased appetite	28 (60.9)	1 (2.2)	0
Proteinuria	28 (60.9)	9 (19.6)	0
Fatigue	25 (54.3)	0	0
Diarrhea	20 (43.5)	6 (13.0)	0
Constipation	19 (41.3)	0	0
Nausea	17 (37.0)	1 (2.2)	0
Dysphonia	17 (37.0)	0	0
Thrombocytopenia	16 (34.8)	9 (19.6)	1 (2.2)
Peripheral edema	16 (34.8)	0	0
Decreased weight	14 (30.4)	2 (4.3)	0
Neutropenia	13 (28.3)	2 (4.3)	0
Nasopharyngitis	13 (28.3)	0	0
Rash	13 (28.3)	0	0
Increased blood thyroid-stimulating hormone level	12 (26.1)	0	0
Back pain	11 (23.9)	0	0
Stomatitis	11 (23.9)	0	0
Vomiting	11 (23.9)	1 (2.2)	0
Pyrexia	10 (21.7)	0	0
Hypothyroidism	10 (21.7)	0	0
Insomnia	10 (21.7)	0	0

Hepatic encephalopathy was the most common SAE (5 pts, 11%)

Dose reduction occurred frequently and early in the course of treatment: 74% pts required a dose reduction and 10% withdrawal due to AEs

(a)

Patients with dose reduction/drug withdrawal — Patients without dose reduction/drug withdrawal (Body Weight (kg))

Ikeda K et al, J Gastroenterol 2017

Phase 3 Trial Lenvatinib vs Sorafenib in First-Line Treatment of Patients with Unresectable HCC

Multicenter   Open-Label   <u>Non inferiority</u>: Efficacy and Safety

Primary Outcome: Overall survival

Secondary Outcomes: **PFS**, TTP, ORR, HRQoL, Plasma PK Lenvatinib
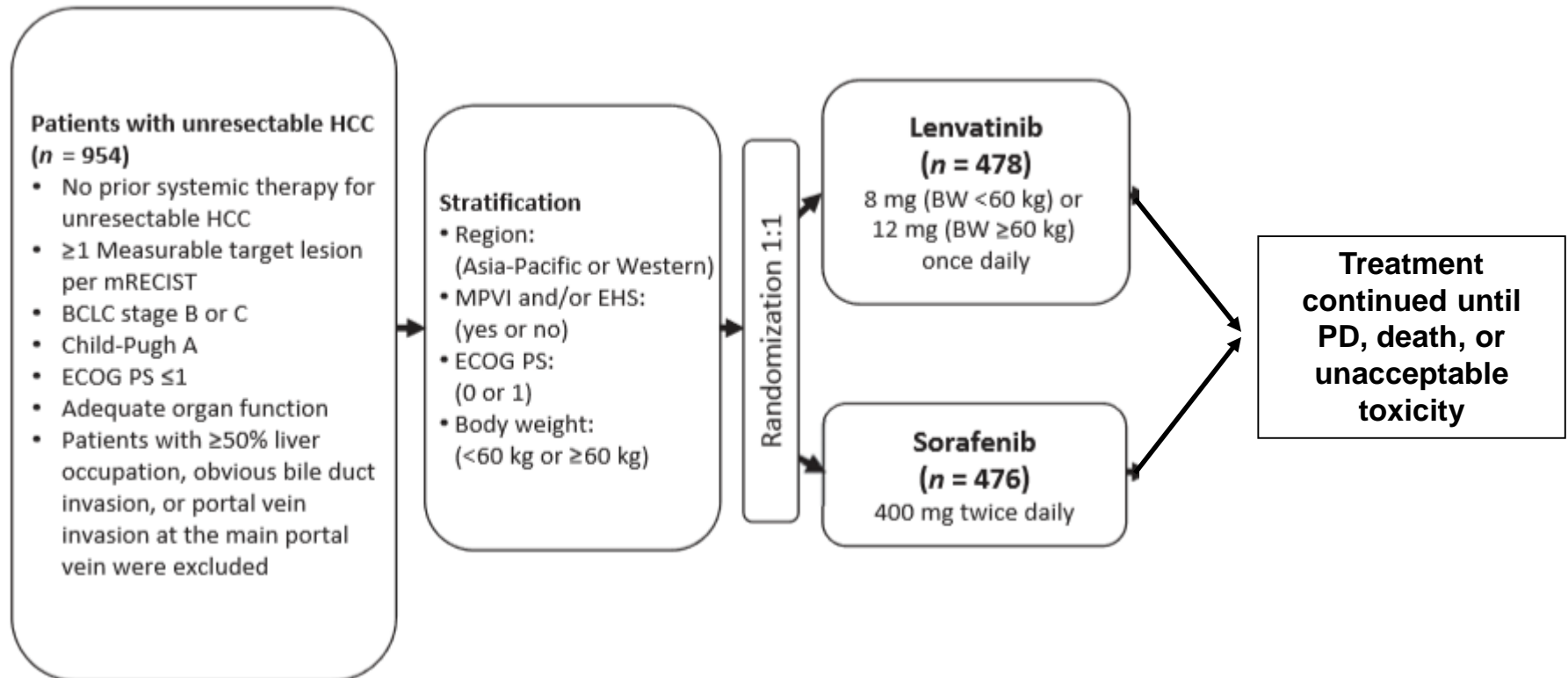
Lenvantinib vs Sorafenib in First-Line Treatment of Patients with Advanced HCC: Phase 3 Non-Inferiority trial

Kudo M et al, Lancet 2018
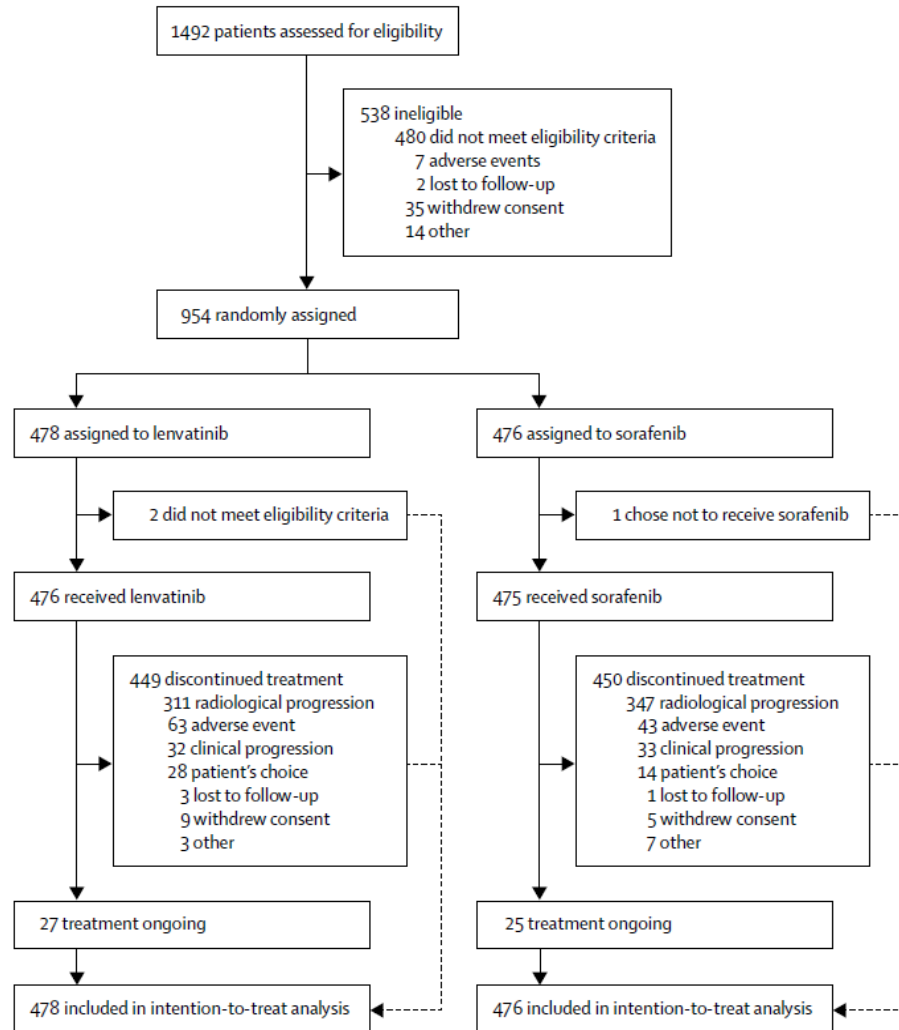
Lenvantinib vs Sorafenib in First-Line Treatment of Patients with Advanced HCC: Overall Survival Outcomes
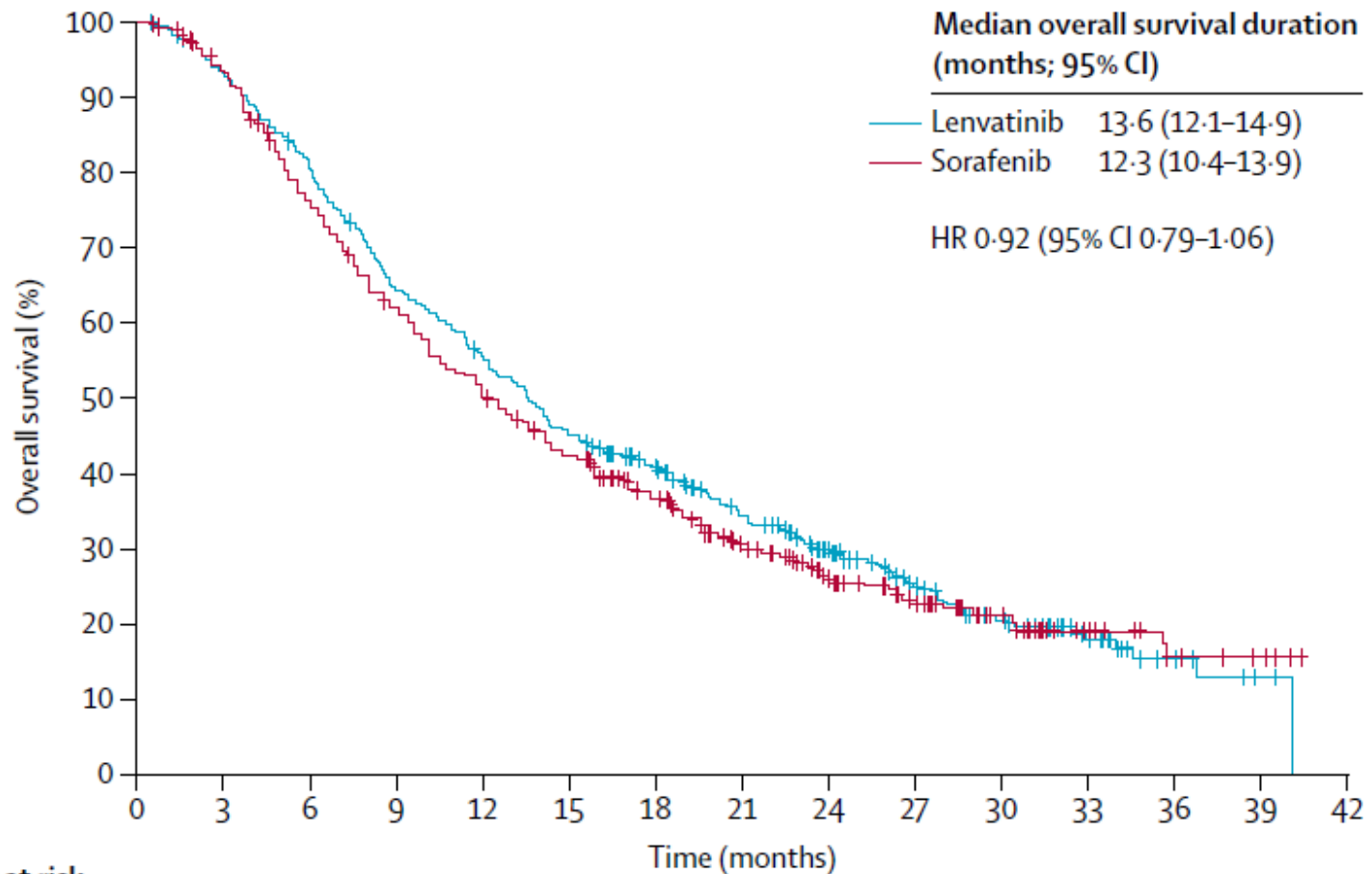
Kudo M et al, Lancet 2018

Lenvantinib vs Sorafenib in First-Line Treatment of Patients with Advanced HCC: Progression-Free Survival Outcomes

Kudo M et al, Lancet 2018
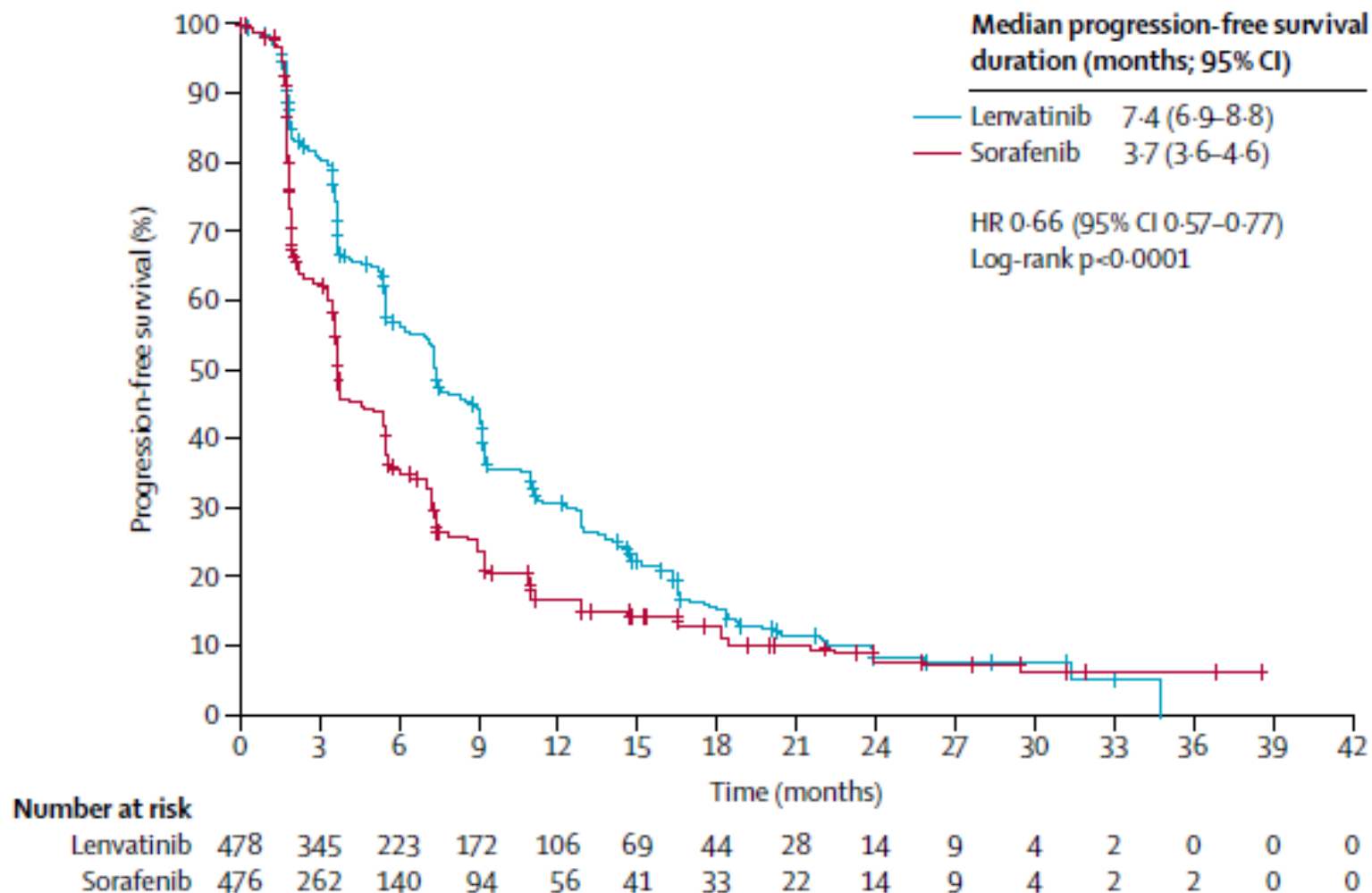
Lenvantinib vs Sorafenib in First-Line Treatment of Patients with Advanced HCC: Efficacy Measures

	Lenvatinib (n=478)	Sorafenib (n=476)	Effect size (95% CI)	p value
Investigator review according to mRECIST				
Overall survival (months)	13·6 (12·1–14·9)	12·3 (10·4–13·9)	HR 0·92 (0·79–1·06)	··
Progression-free survival (months)	7·4 (6·9–8·8)	3·7 (3·6–4·6)	HR 0·66 (0·57–0·77)	<0·0001
Time to progression (months)	8·9 (7·4–9·2)	3·7 (3·6–5·4)	HR 0·63 (0·53–0·73)	<0·0001
Objective response (%, 95% CI)	115 (24·1%, 20·2–27·9)	44 (9·2%, 6·6–11·8)	OR 3·13 (2·15–4·56)	<0·0001
Complete response	6 (1%)	2 (<1%)	··	··
Partial response	109 (23%)	42 (9%)	··	··
Stable disease	246 (51%)	244 (51%)	··	··
Durable stable disease lasting ≥23 weeks	167 (35%)	139 (29%)	··	··
Progressive disease	71 (15%)	147 (31%)	··	··
Unknown or not evaluable	46 (10%)	41 (9%)	··	··
Disease control rate (%, 95% CI)	361 (75·5%, 71·7–79·4)	288 (60·5%, 56·1–64·9)	··	··

Phase 3 trial Lenvatinib vs Sorafenib in First-Line Treatment of Patients with Unresectable HCC

	Lenvatinib (n=476)	Sorafenib (n=475)
Total treatment-emergent adverse events	470 (99%)	472 (99%)
Total treatment-related treatment-emergent adverse events	447 (94%)	452 (95%)
Treatment-emergent adverse events of grade ≥3	357 (75%)	316 (67%)
Treatment-related treatment-emergent adverse events of grade ≥3	270 (57%)	231 (49%)
Serious treatment-emergent adverse events	205 (43%)	144 (30%)
Serious treatment-related treatment-emergent adverse events	84 (18%)	48 (10%)

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  - ➢ Ramacirumab

  - ➢ Nivolumab

Molecular Targeted Therapies for HCC
Their Target Signalling Pathways

Modified form: Llovet JM et al, Nat Rev Clin Oncol 2015
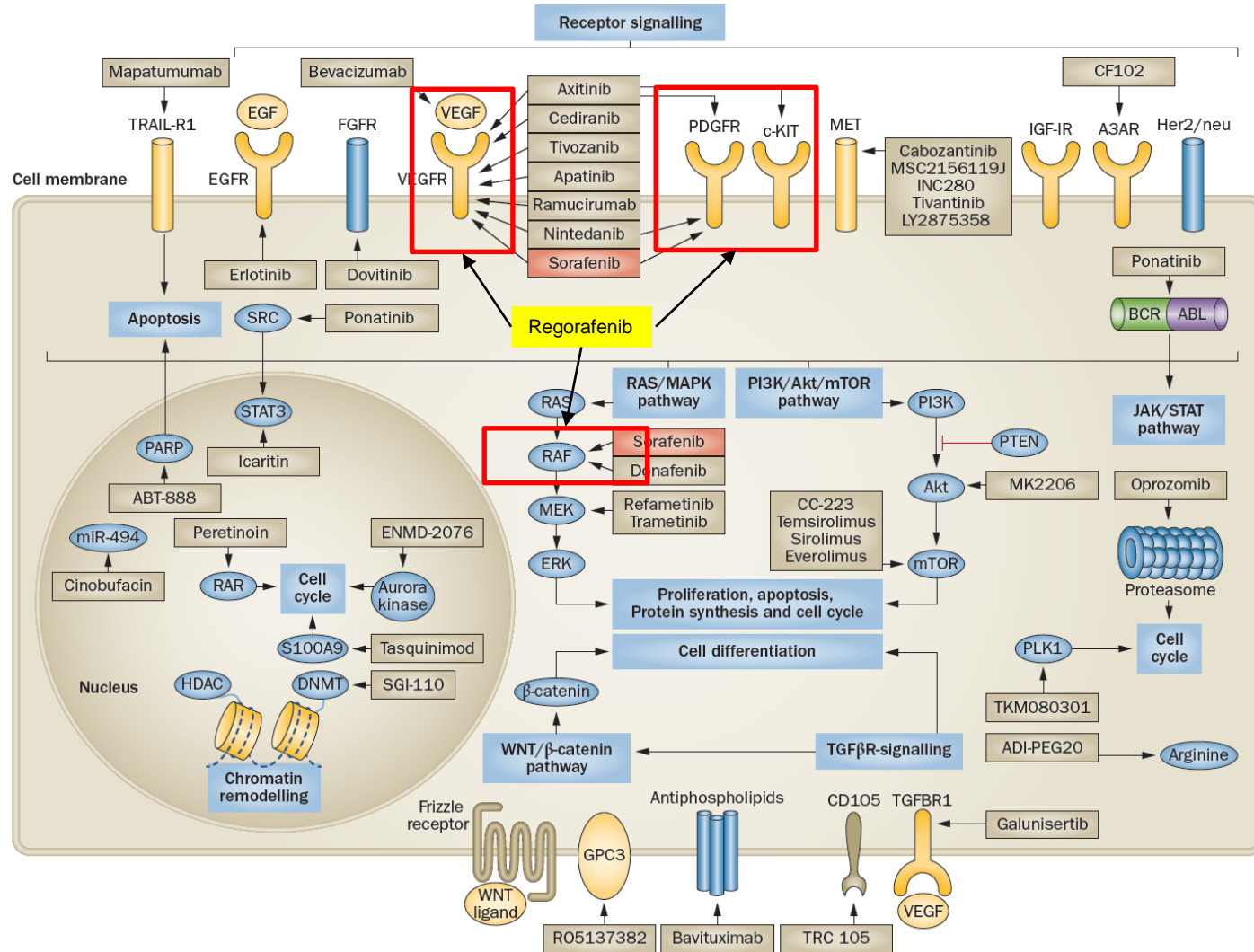
Regorafenib as Second-Line Treatment in Advanced HCC: Open-Label Phase 2 Study

OS: 13.8 mos (95% C.I. 9.3-18.3)
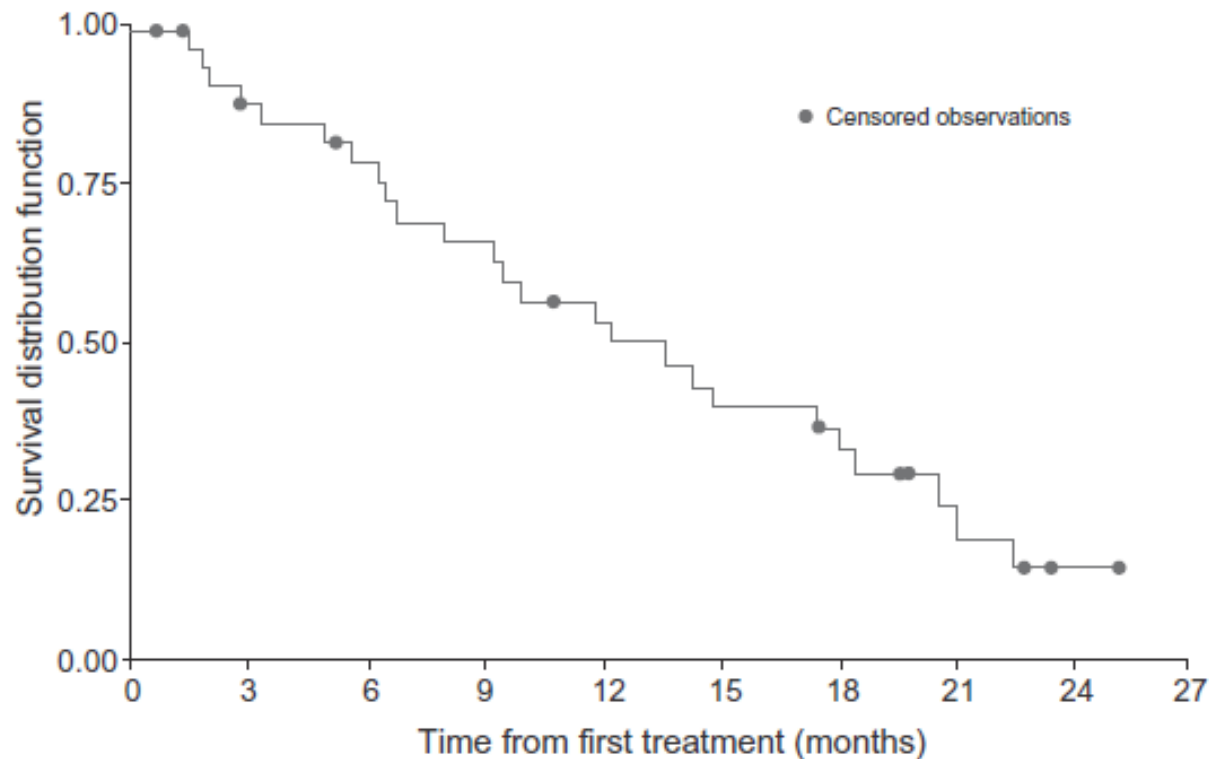
Bruix J, et al. Eur J Cancer, 2013

Regorafenib as Second-Line Treatment in Advanced HCC: Drug-Related Adverse Events: Phase 2 Study

	Any grade	Grade $\geqslant 3$
	n (%)	n (%)
Any adverse event	35 (97)	21 (58)
Diarrhoea	19 (53)	2 (6)
Fatigue	19 (53)	6 (17)
Hand–foot skin reaction	19 (53)	5 (14)
Hypothyroidism	15 (42)	0
Anorexia	13 (36)	0
Hypertension	13 (36)	1 (3)
Nausea	12 (33)	0
Voice changes	10 (28)	0
Constipation	9 (25)	0
Headache	7 (19)	0
Weight loss	7 (19)	0
Proteinuria	6 (17)	1 (3)
Oral mucositis	5 (14)	1 (3)
Vomiting	5 (14)	0
Abdominal pain	4 (11)	1 (3)
Anaemia	4 (11)	1 (3)
Fever	4 (11)	0
Hyperbilirubinaemia	4 (11)	2 (6)
Hyperthyroidism	4 (11)	1 (3)
Mood alteration, depression	4 (11)	0
Hypophosphataemia	2 (6)	2 (6)

Bruix J, et al. Eur J Cancer, 2013

Phase 3 RESORCE: Regorafenib in HCC After Progression on Sorafenib

In Phase II trial, the median OS was 13.8 months, and the efficacy was mainly based on disease stabilization with a disease control rate of 72%.

Randomized, double-blind phase III trial

Randomized 2:1

4-wk cycles

| Pts with BCLC stage B or C HCC; **documented PD on sorafenib ≥ 20 days at ≥ 400 mg/day**; Child-Pugh A liver function; ECOG PS 0-1 (N = 573) |

Regorafenib + BSC
160 mg PO daily Wks 1-3
(n = 379)

Placebo + BSC
PO daily Wks 1-3
(n = 194)

All pts treated until PD, death, or unacceptable toxicity
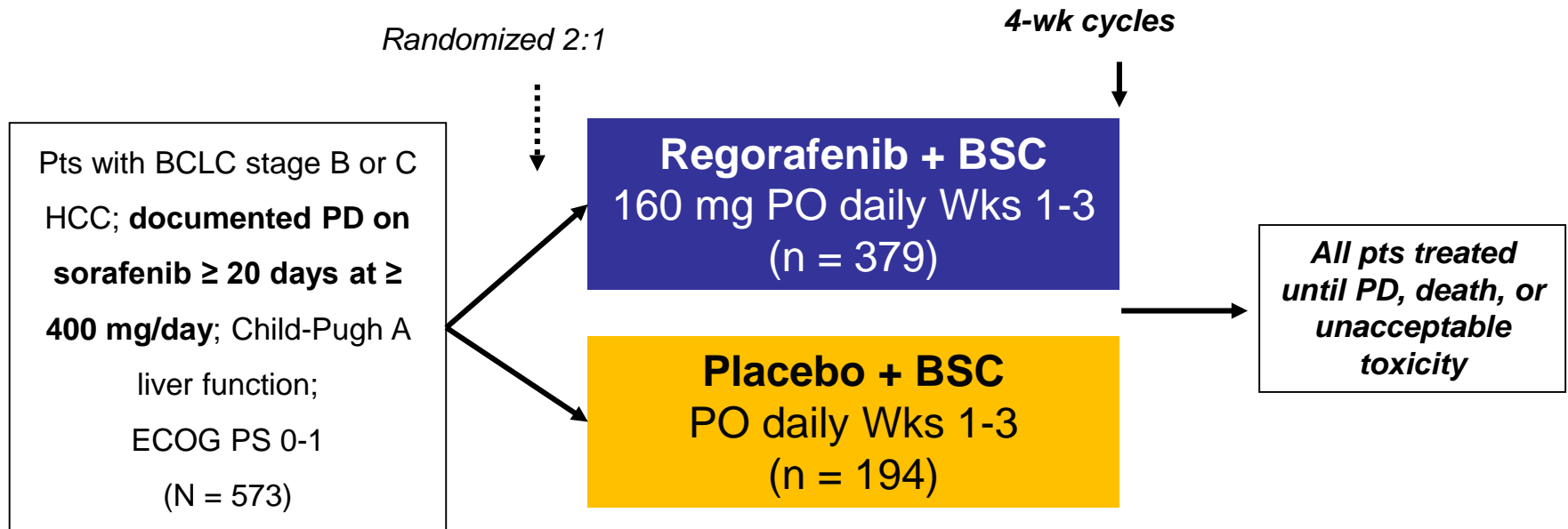
Primary endpoint: OS (ITT)

Secondary endpoints: PFS, TTP, RR, DCR

Regorafenib as Second-Line Treatment in Advanced HCC: RESORCE Phase 3 trial

843 patients assessed for eligibility

270 ineligible, primary reason
- 238 screen failure
- 22 withdrawal by patient
- 7 adverse event
- 2 death
- 1 therapeutic procedure required

573 randomised

379 assigned to regorafenib
- 374 received regorafenib
- 5 did not receive regorafenib

194 assigned to placebo
- 193 received placebo
- 1 did not receive placebo

309 discontinued treatment, primary reason
- 149 progressive disease, radiological progression
- 21 progressive disease, clinical progression
- 56 adverse event associated with disease progression
- 47 adverse event not associated with disease progression
- 1 adverse event
- 5 death
- 26 withdrawal by patient
- 2 non-compliance with study drug
- 1 physician decision
- 1 protocol violation

183 discontinued treatment, primary reason
- 119 progressive disease, radiological progression
- 14 progressive disease, clinical progression
- 1 progressive disease*
- 28 adverse event associated with disease progression
- 12 adverse event not associated with disease progression
- 3 protocol violation
- 5 withdrawal by patient
- 1 other

65 treatment ongoing

10 treatment ongoing

379 included in intention-to-treat analysis

194 included in intention-to-treat analysis

Bruix J, et al. Lancet 2016

RESORCE Efficacy
of Regorafenib vs Placebo: OS

Endpoint	Regorafenib (n = 379)	Placebo (n = 194)
Median OS, mos	10.6	7.8

38% reduction in risk of death (HR: 0.62; 95% CI: 0.50-0.78; $p < .001$)

Number at risk

Regorafenib	379	316	224	170	122	78	54	34	21	10	4	0
Placebo	194	149	95	62	37	26	16	8	5	3	1	0

ORR: 11% *vs* 4% (*p*=0.0047)

Bruix J, et al. Lancet 2016

RESORCE
Efficacy of Regorafenib vs Placebo: DFS

Endpoint	Regorafenib (n = 379)	Placebo (n = 194)
Median DFS, mos	3.1	1.5

HR 0·46 (95% CI 0·37–0·56); one-sided p<0·0001

Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33
Regorafenib	379	166	76	43	27	14	8	7	4	0	0	0
Placebo	194	37	15	6	3	2	1	1	0	0	0	0

Bruix J, et al. Lancet 2016

RESORCE
Tumor Response Regorafenib vs Placebo

	Regorafenib (n=379)	Placebo (n=194)
Best overall response*		
Complete response	2 (1%; <1–2)	0
Partial response	38 (10%; 7–14)	8 (4%; 2–8)
Stable disease	206 (54%; 49–59)	62 (32%; 26–39)
Non-complete response/ non-progressive disease	1 (<1%; 0–2)	0
Progressive disease	86 (23%; 19–27)	108 (56%; 48–63)
Not evaluable	19 (5%; 3–8)	8 (4%; 2–8)]
Not assessed	27 (7%; 5–10)	8 (4%; 2–8)
Clinical progression†	86 (23%; 19–27)	40 (21%; 15–27)
Objective response (complete response + partial response)*	40 (11%)‡	8 (4%)‡
Disease control*	247 (65%)§	70 (36%)§

Data are n (%; 95% CI). *Based on radiological review using modified Response Evaluation Criteria in Solid Tumors for HCC (mRECIST).[22] †Defined as worsening of ECOG performance status or symptomatic deterioration including increase in liver function tests. ‡One-sided p=0·0047. §One-sided p<0·0001.

Bruix J, et al. Lancet 2016

RESORCE
Treatment-Emergent Drug-Related Adverse Events

	Treatment-emergent drug-related					
	Regorafenib (n=374)			Placebo (n=193)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any adverse event	346 (93%)	173 (46%)	14 (4%)	100 (52%)	31 (16%)	1 (1%)
Hand–foot skin reaction	196 (52%)	47 (13%)	NA	13 (7%)	1 (1%)	NA
Diarrhoea	125 (33%)	9 (2%)	0	18 (9%)	0	0
Fatigue	110 (29%)	24 (6%)	NA	37 (19%)	3 (2%)	NA
Hypertension	87 (23%)	48 (13%)	1 (<1%)	9 (5%)	6 (3%)	0
Anorexia	88 (24%)	10 (3%)	0	12 (6%)	0	0
Increased blood bilirubin	70 (19%)	24 (6%)	1 (<1%)	7 (4%)	4 (2%)	0
Abdominal pain	34 (9%)	5 (1%)	NA	5 (3%)	0	NA
Increased AST	48 (13%)	16 (4%)	3 (1%)	15 (8%)	9 (5%)	1 (1%)
Nausea	40 (11%)	1 (<1%)	NA	13 (7%)	0	NA
Ascites	8 (2%)	3 (1%)	0	1 (1%)	1 (1%)	0
Anaemia	23 (6%)	5 (1%)	1 (<1%)	2 (1%)	1 (1%)	0
Increased ALT	29 (8%)	6 (2%)	2 (1%)	8 (4%)	2 (1%)	0
General disorders and administration site conditions, other	8 (2%)	5 (1%)	0	2 (1%)	1 (1%)	0
Weight loss	27 (7%)	4 (1%)	NA	3 (2%)	0	NA
Oral mucositis	42 (11%)	4 (1%)	0	5 (3%)	1 (1%)	0
Thrombocytopenia	19 (5%)	7 (2%)	1 (<1%)	2 (1%)	0	0
Hoarseness	34 (9%)	0	NA	0	0	NA

Bruix J, et al. Lancet 2016

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Molecular Targeted Therapies for HCC
Their Target Signalling Pathways
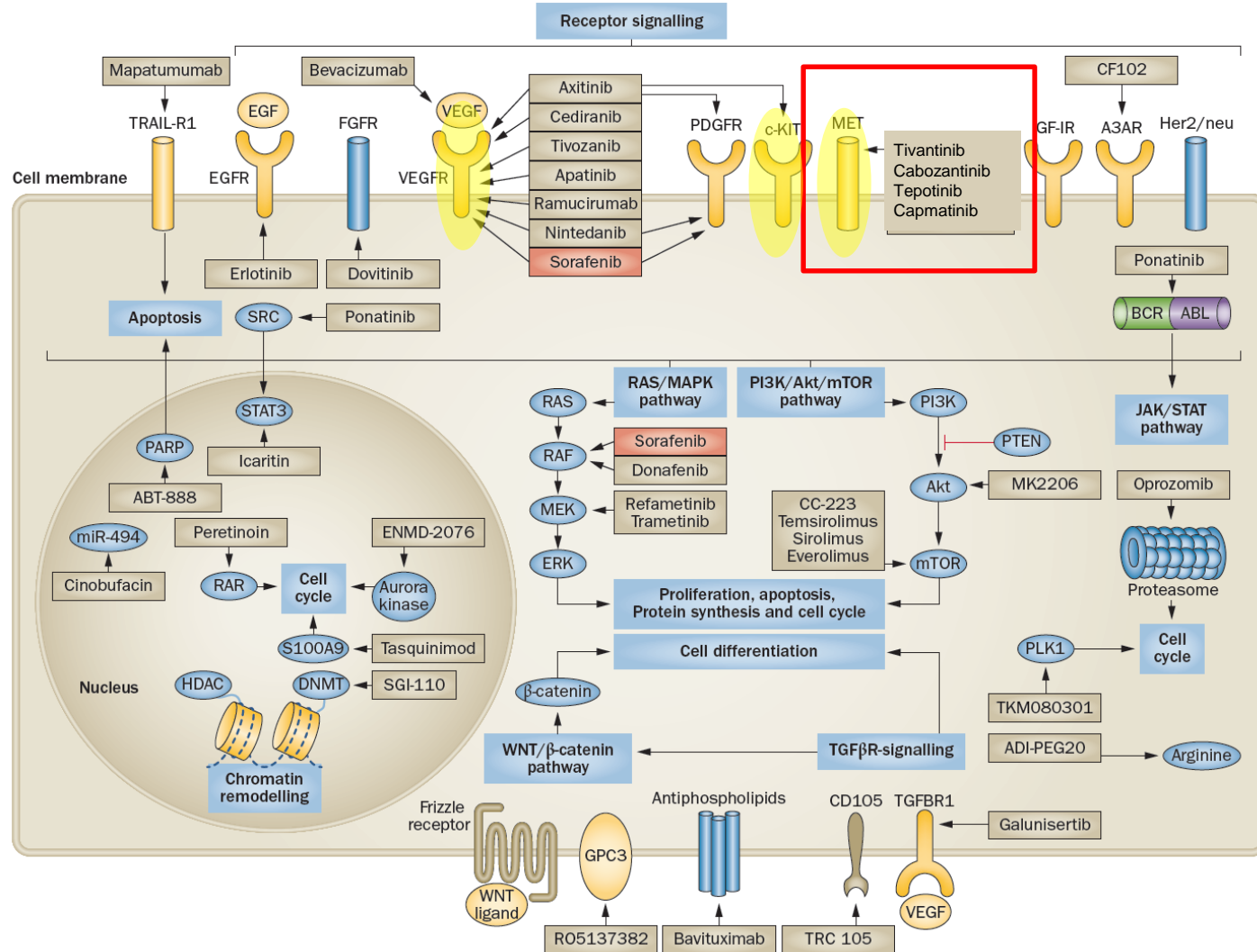
Cabozantinib in HCC: Phase 2 Placebo-Controlled Randomized Discontinuation Study

The RDT enrolled 526 patients across nine tumor-type cohorts. 41 patients with HCC enrolled from the US, Belgium, and Taiwan
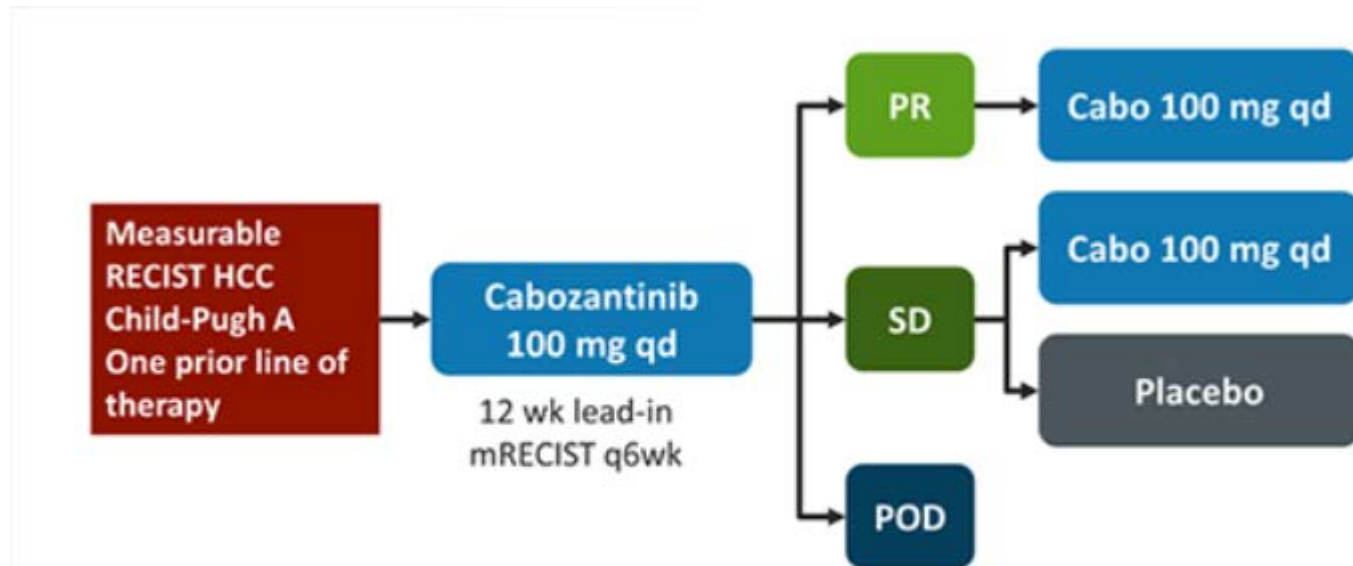
- ✓ The primary end point of the lead-in stage was objective response rate (ORR) at week 12.
- ✓ The primary end point of the randomized stage was progression-free survival (PFS).

Cabozantinib in HCC: Phase 2 Placebo-Controlled Randomized Discontinuation Study

The week 12 ORR was 5%
The week 12 DCR was 66%
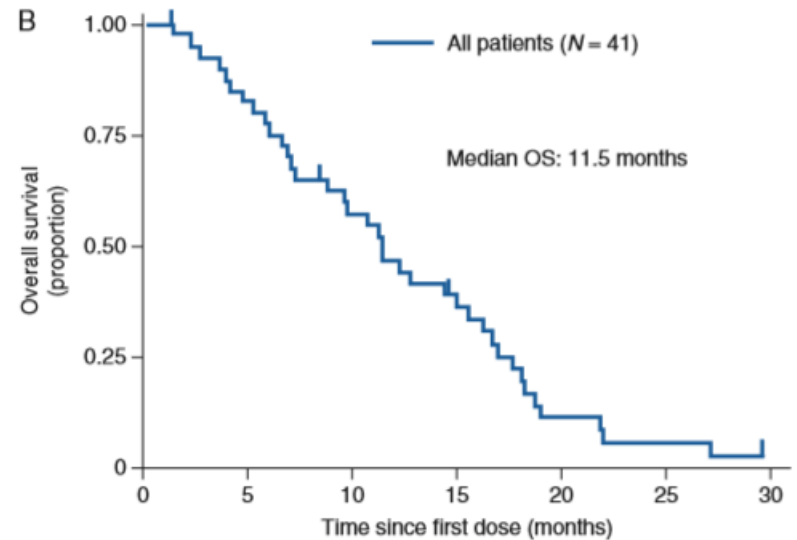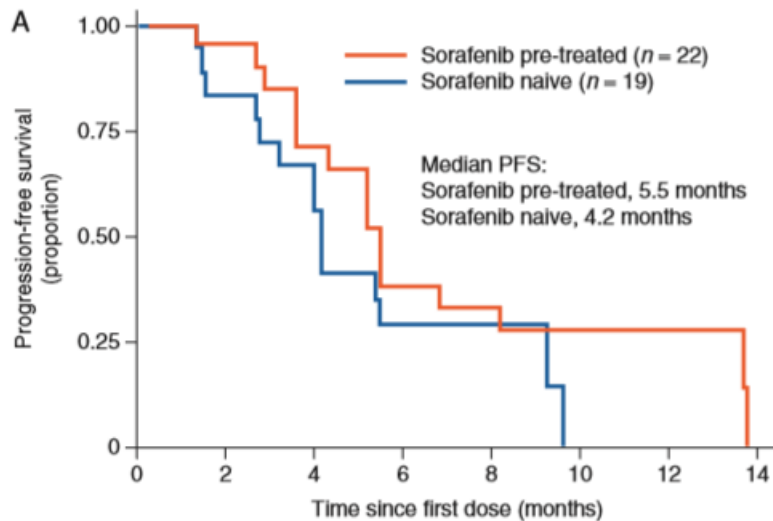
22 (54%) patients with SD at week12 were randomized.

Median PFS was 2.5 mos with cabozantinib and 1.4 mos with placebo, ns.

Cabozantinib in HCC: Phase 2 Placebo-Controlled Randomized Discontinuation Study

Adverse event[a]	All grades (n = 41) Patients, n (%)	Grade ≥3 (n = 41)
Any adverse event	41 (100)	35 (85)
Diarrhea	26 (63)	8 (20)
Hand-foot syndrome	23 (56)	6 (15)
Fatigue	23 (56)	1 (2)
Thrombocytopenia	15 (37)	6 (15)
Nausea	15 (37)	1 (2)
Vomiting	15 (37)	1 (2)
Decreased appetite	12 (29)	0 (0)
Aspartate aminotransferase increased	11 (27)	4 (10)
Hypertension	10 (24)	4 (10)
Rash	10 (24)	0 (0)
Asthenia	9 (22)	3 (7)
Weight decreased	9 (22)	1 (2)
Constipation	9 (22)	0 (0)
Hair color changes	9 (22)	0 (0)

Starting daily dose 100 mg.

Dose reductions in 59% for AEs.

The median average daily dose was 66 mg/day

Median time to first dose reduction 39.5 days.

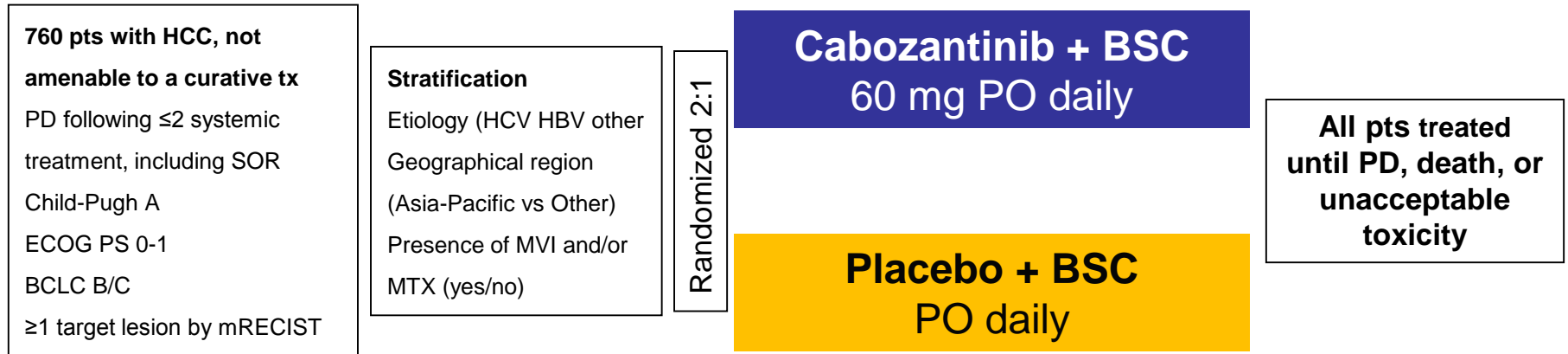Even with dose reductions, patients maintained disease control as shown by the high DCR at week 12.

Starting dose in Phase 3 Trial 60 mg daily

Cabozantinib in HCC: Phase 3 Randomized Double-Blind Placebo-Controlled Trial

Primary endpoint: OS

Secondary endpoints: ORR, PFS

Exploratory endpoints: patient-reported outcomes, biomarkers and safety.

760 pts with HCC, not amenable to a curative tx
PD following ≤2 systemic treatment, including SOR
Child-Pugh A
ECOG PS 0-1
BCLC B/C
≥1 target lesion by mRECIST

Stratification
Etiology (HCV HBV other
Geographical region (Asia-Pacific vs Other)
Presence of MVI and/or MTX (yes/no)

Randomized 2:1

Cabozantinib + BSC
60 mg PO daily

Placebo + BSC
PO daily

All pts treated until PD, death, or unacceptable toxicity

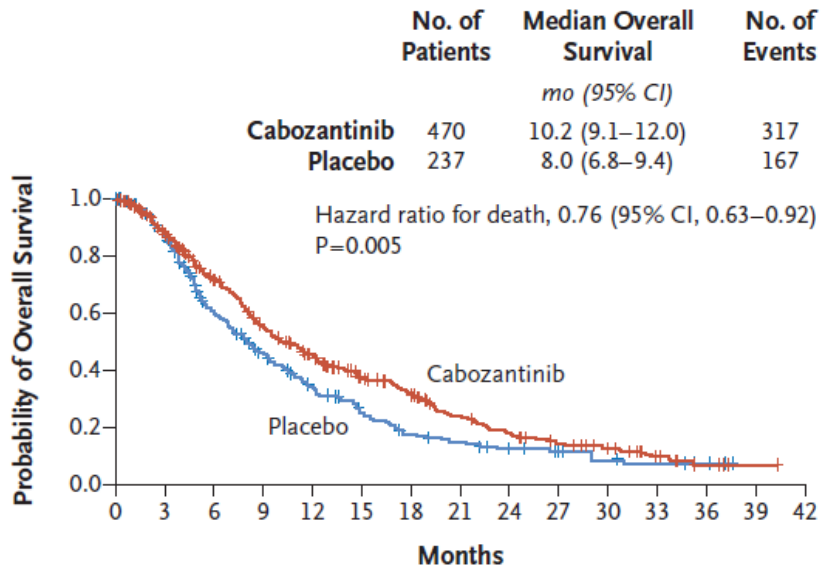Assumed median OS of 8.2 months for the placebo arm.

A total of 621 events provide the study with 90% power to detect a 32% increase in OS (HR = 0.76). Two interim analyses were planned to be conducted at 50% and 75% of the planned events.

# Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma: CELESTIAL Study

Abou-Alfa GK et al, N Engl J Med, 2018
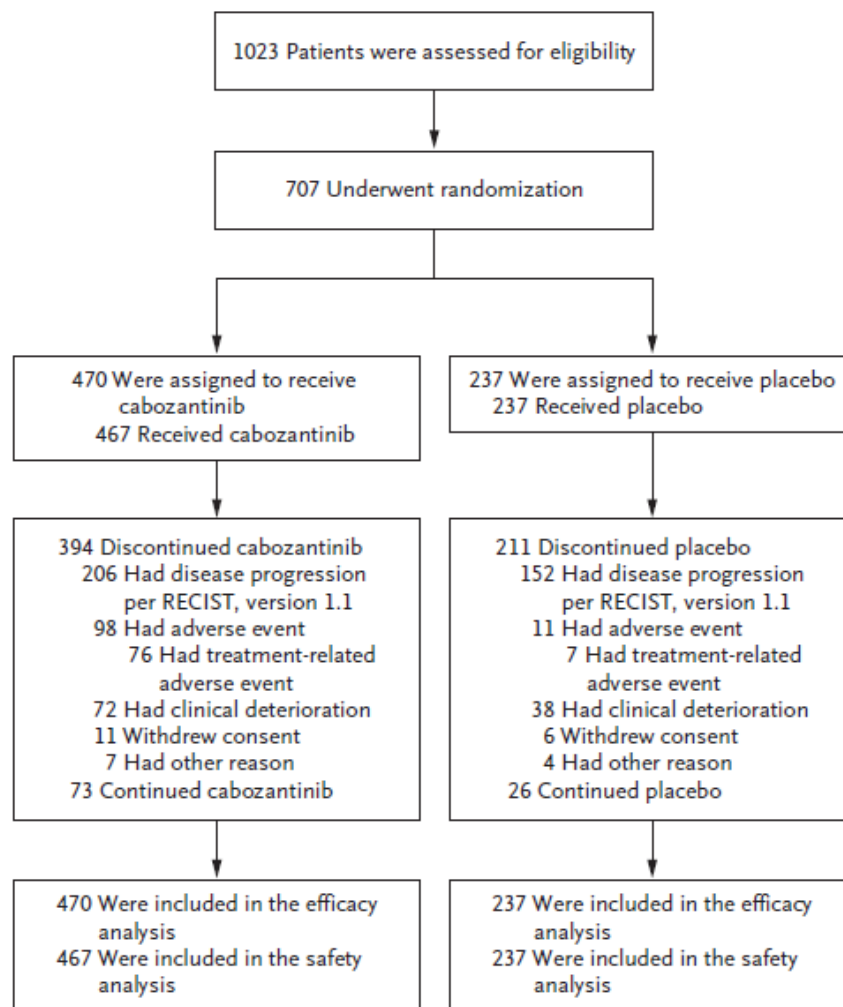
Overall Survival and Progression-Free Survival: CELESTIAL Study

Overall Survival

	No. of Patients	Median Overall Survival mo (95% CI)	No. of Events
Cabozantinib	470	10.2 (9.1–12.0)	317
Placebo	237	8.0 (6.8–9.4)	167

Hazard ratio for death, 0.76 (95% CI, 0.63–0.92)
P=0.005

Progression-free Survival

	No. of Patients	Median Progression-free Survival mo (95% CI)	No. of Events
Cabozantinib	470	5.2 (4.0–5.5)	349
Placebo	237	1.9 (1.9–1.9)	205

Hazard ratio for disease progression or death, 0.44 (95% CI, 0.36–0.52)
P<0.001

No. at Risk

Cabozantinib	470	328	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
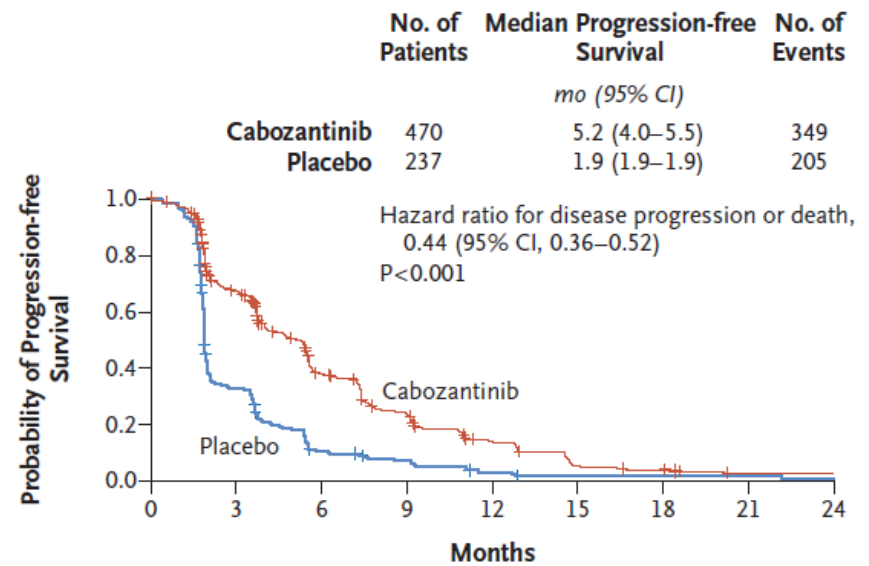
No. at Risk

Cabozantinib	470	266	131	80	39	15	10	3	3
Placebo	237	70	21	13	5	2	2	2	1

Adverse Events: CELESTIAL Study

Event	Cabozantinib (N=467)			Placebo (N=237)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	460 (99)	270 (58)	46 (10)	219 (92)	80 (34)	6 (3)
Diarrhea	251 (54)	45 (10)	1 (<1)	44 (19)	4 (2)	0
Decreased appetite	225 (48)	27 (6)	0	43 (18)	1 (<1)	0
Palmar–plantar erythrodysesthesia	217 (46)	79 (17)	0	12 (5)	0	0
Fatigue	212 (45)	49 (10)	0	70 (30)	10 (4)	0
Nausea	147 (31)	10 (2)	0	42 (18)	4 (2)	0
Hypertension	137 (29)	73 (16)	1 (<1)	14 (6)	4 (2)	0
Increase in aspartate aminotransferase level	105 (22)	51 (11)	4 (1)	27 (11)	15 (6)	1 (<1)
Asthenia	102 (22)	31 (7)	1 (<1)	18 (8)	4 (2)	0
Abdominal pain	83 (18)	7 (1)	1 (<1)	60 (25)	10 (4)	0
Weight loss	81 (17)	5 (1)	0	14 (6)	0	0
Increase in alanine aminotransferase level	80 (17)	23 (5)	0	13 (5)	5 (2)	0
Mucosal inflammation	65 (14)	8 (2)	0	5 (2)	1 (<1)	0
Pyrexia	64 (14)	0	0	24 (10)	1 (<1)	0
Upper abdominal pain	63 (13)	3 (1)	0	31 (13)	0	0

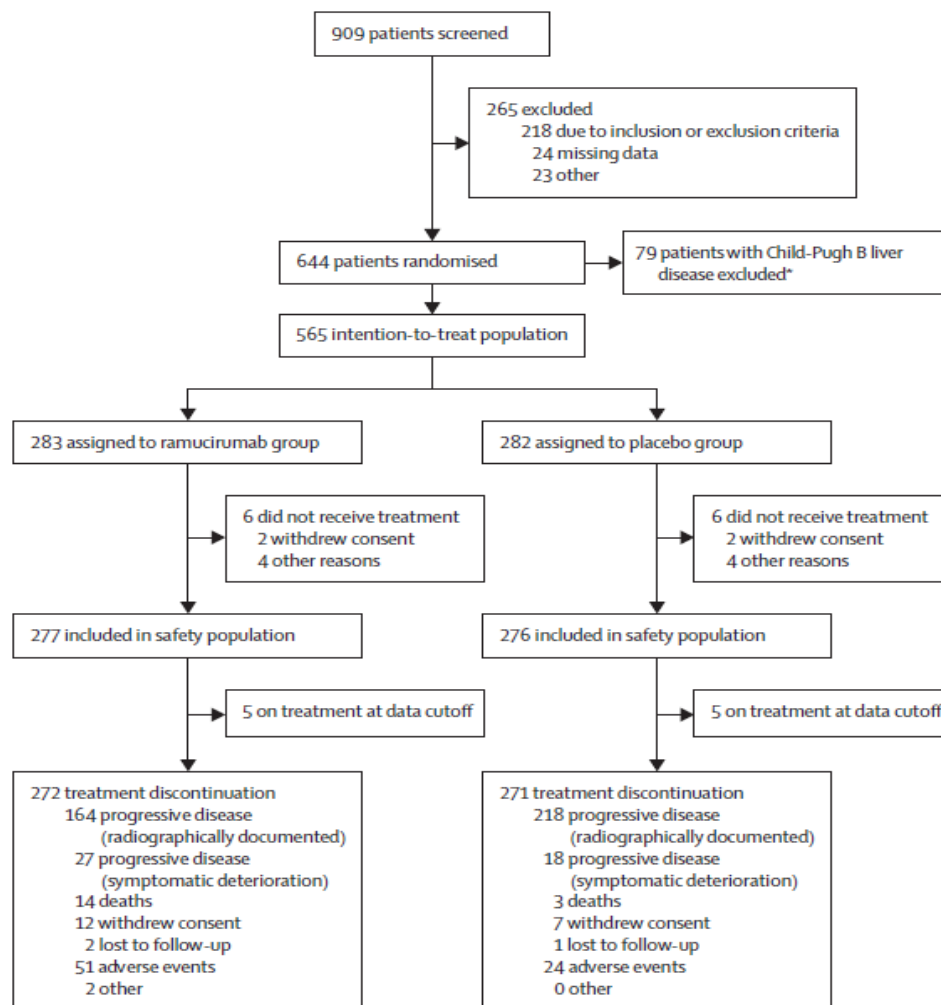*Modified from Abou-Alfa GK et al, N Engl J Med, 2018*

Outline

- First line therapy other than Sorafenib

  - Lenvatinib

- Second line therapy

  - Regorafenib

  - Cabozantinib

  - Ramacirumab

  - Nivolumab

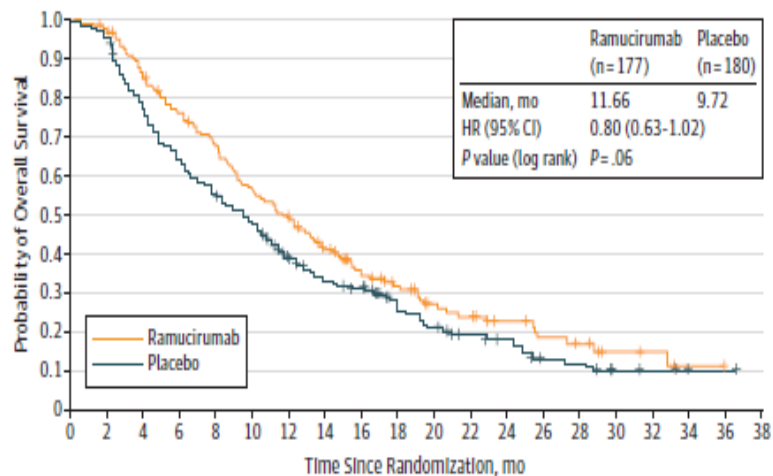# Molecular Targeted Therapies for HCC
Their Target Signalling Pathways
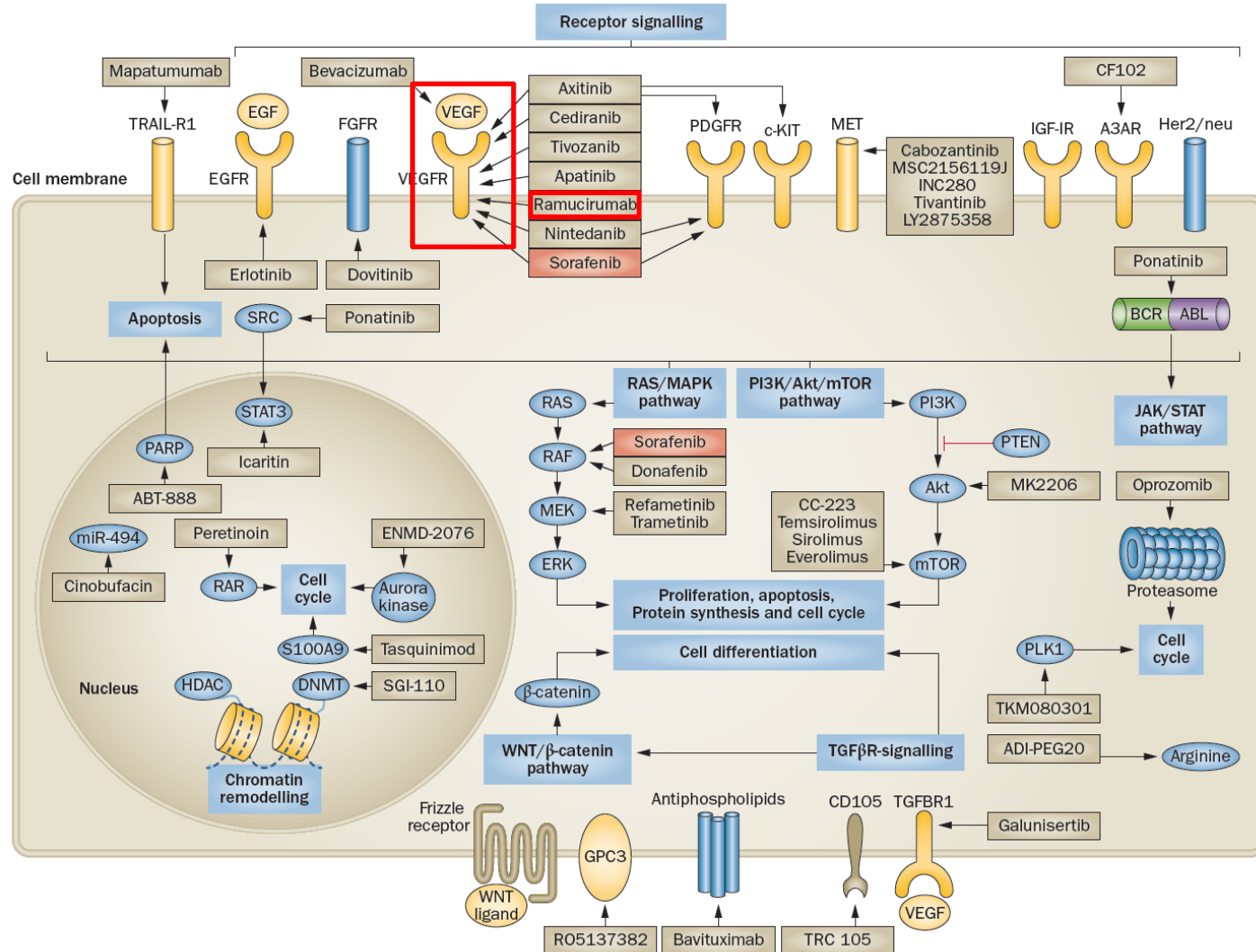
Ramucirumab as Second-Line Treatment in Advanced HCC: Adverse Events: CELESTIAL Study

Zhu AX et al, JAMA Oncol, 2017

Ramucirumab as Second-Line Treatment in Advanced HCC: Subanalysis according to C-P Score and Serum AFP Value

Overall survival for all randomized patients in Child-Pugh A5

Overall survival for all randomized patients in Child-Pugh A5 and AFP > 400ng/ml

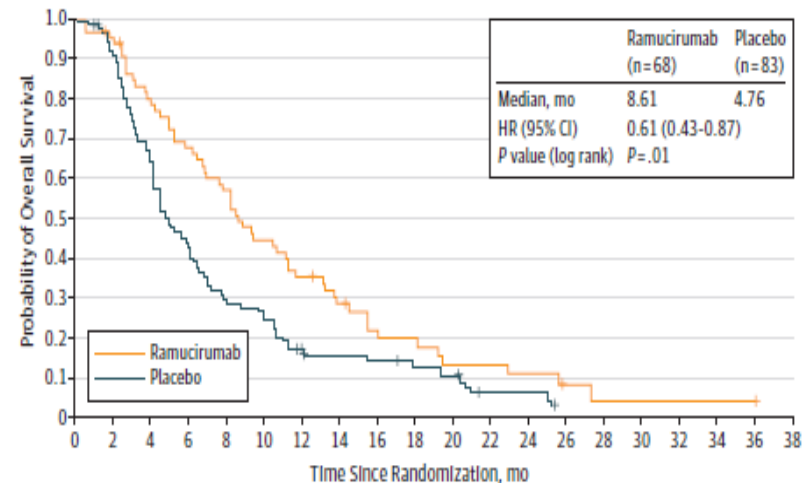*Zhu AX et al, JAMA Oncol, 2017*

Ramucirumab as Second-Line Treatment in Advanced HCC: Subanalysis According to C-P Score and Serum AFP Value
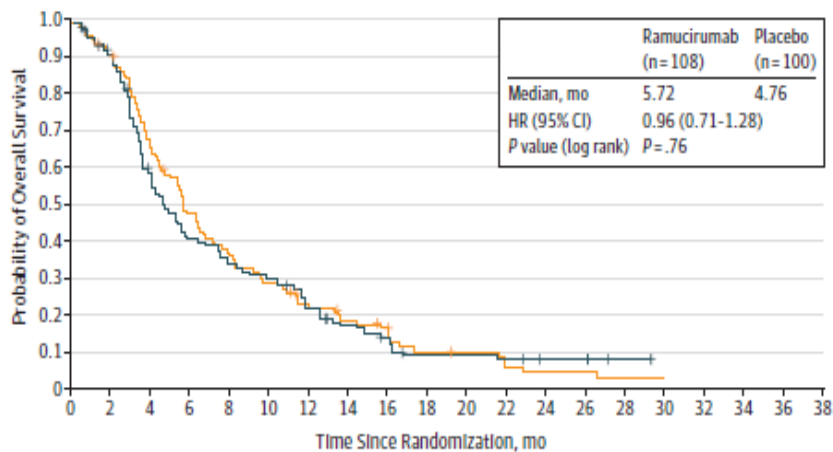
Overall survival for all randomized patients in Child-Pugh A6

Overall survival for all randomized patients in Child-Pugh A6 and AFP > 400ng/ml
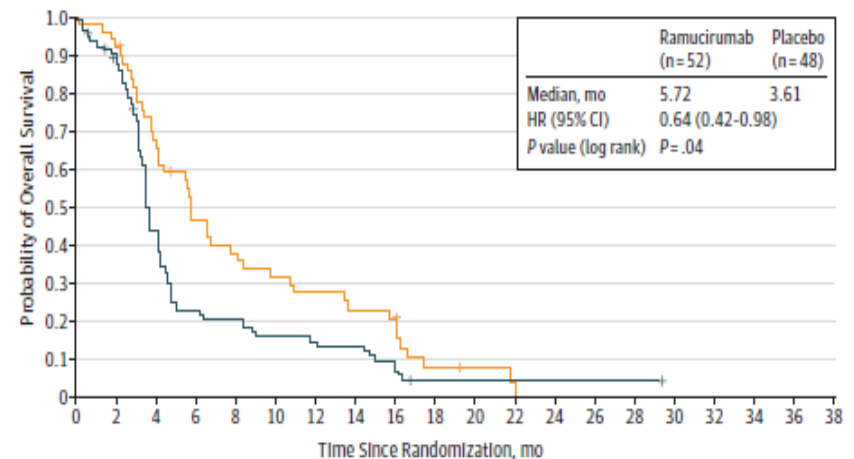
Outline

➢ First line therapy other than Sorafenib

      ➢ Lenvatinib

➢ Second line therapy

      ➢ Regorafenib

      ➢ Cabozantinib

      ➢ Ramacirumab

      ➢ Nivolumab

How the Immune System Is Unleashed by Check-point Inhibitors

Immune checkpoints: co-inhibitory molecules that interrupt the immune response to avoid over-activation of T cells

Shih K et al. Drugs. 2014;74(17):1993-2013. 2. Trojan J, Waidmann O. J Hepatol 2016;3:31-36
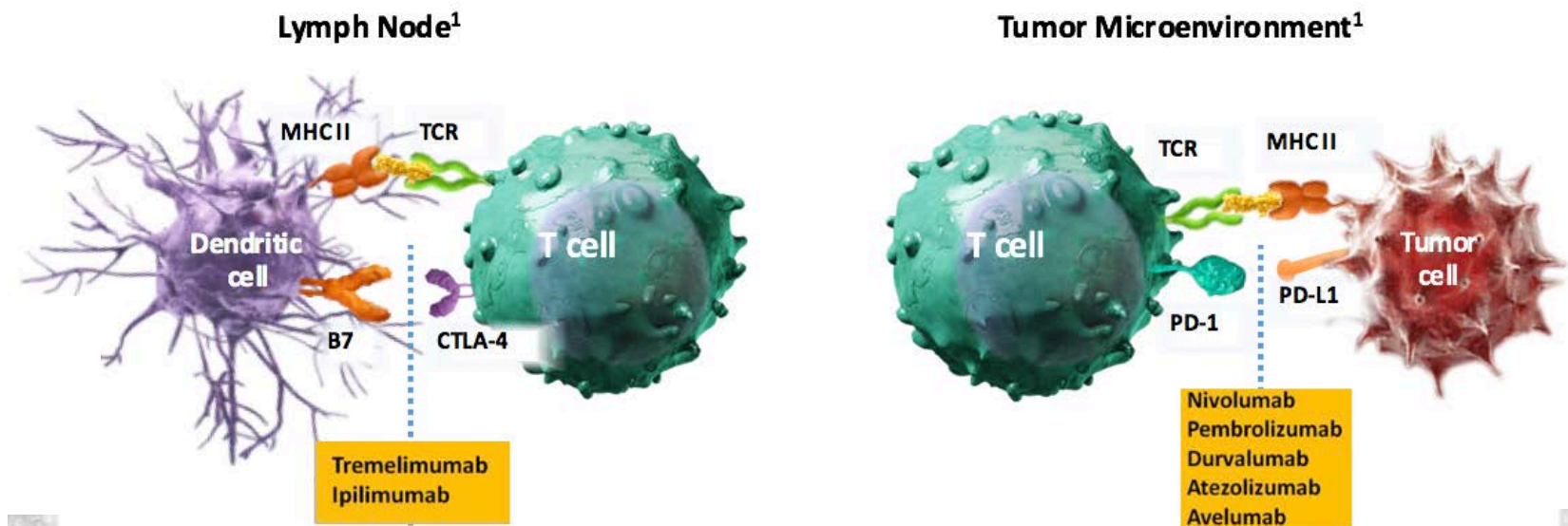
Immune Check-point Inibition by Nivolumab

➢ HBV and HCV infections are associated with manifestations of immune suppression, including upregulation of programmed death-1 (PD-1) receptor, T-cell exhaustion, and spontaneous apoptosis of immune cells.

➢ Blockade of the cytotoxic T-lymphocyte antigen-4 receptor by monoclonal antibodies has shown encouraging activity in patients with HCC and HCV infection.

➢ Nivolumab is a fully human IgG4 monoclonal antibody to the PD-1 receptor, blocking the interaction with PD-L1/PD-L2 and restoring T-cell–mediated antitumor activity

Nivolumab in Advanced HCC: Open-Label, Non-Comparative, Phase 1/2 Dose Escalation and Expansion Trial

Patients received intravenous nivolumab every 2 weeks.

El-Khoueiry AB, et al. Lancet 2017

Nivolumab in Advanced HCC: Open-Label, Non-Comparative, Phase 1/2 Dose Escalation and Expansion Trial

	Escalation phase				Expansion phase				
	Uninfected (n=23)	HCV infected (n=10)	HBV infected (n=15)	All patients (n=48)	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Median age (years)	61 (54–72)	67 (60–74)	62 (46–66)	62 (55–69)	66 (59–71)	65 (60–71)	65 (61–73)	55 (42–66)	64 (56–70)
≥65 years	8 (35%)	6 (60%)	6 (40%)	20 (42%)	33 (59%)	29 (51%)	25 (50%)	13 (25%)	100 (47%)
Sex									
Female	6 (26%)	4 (40%)	2 (13%)	12 (25%)	8 (14%)	15 (26%)	8 (16%)	12 (24%)	43 (20%)
Male	17 (74%)	6 (60%)	13 (87%)	36 (75%)	48 (86%)	42 (74%)	42 (84%)	39 (76%)	171 (80%)
Race									
White	19 (83%)	8 (80%)	1 (7%)	28 (58%)	38 (68%)	34 (60%)	29 (58%)	4 (8%)	105 (49%)
Asian	2 (9%)	2 (20%)	14 (93%)	18 (38%)	16 (29%)	22 (39%)	18 (36%)	45 (88%)	101 (47%)
Black	2 (9%)	0	0	2 (4%)	1 (2%)	1 (2%)	2 (4%)	2 (4%)	6 (3%)
Other	0	0	0	0	1 (2%)	0	1 (2%)	0	2 (1%)
ECOG performance status 1*	9 (39%)	4 (40%)	6 (40%)	19 (40%)	16 (29%)	22 (39%)	15 (30%)	24 (47%)	77 (36%)
Extrahepatic metastases	16 (70%)	6 (60%)	12 (80%)	34 (71%)	36 (64%)	41 (72%)	25 (50%)	42 (82%)	144 (67%)
Vascular invasion	8 (35%)	5 (50%)	6 (40%)	19 (40%)	13 (23%)	18 (32%)	17 (34%)	15 (29%)	63 (29%)
Child-Pugh score									
5	19 (83%)	8 (80%)	14 (93%)	41 (85%)	43 (77%)	37 (65%)	27 (54%)	42 (82%)	149 (70%)
6	4 (17%)	2 (20%)	1 (7%)	7 (15%)	12 (21%)	20 (35%)	20 (40%)	9 (18%)	61 (29%)
7–9	0	0	0	0	1 (2%)	0	3 (6%)	0	4 (2%)
α-fetoprotein ≥400 µg/L†	6 (26%)	3 (30%)	6 (40%)	15 (31%)	15 (27%)	22 (39%)	17 (34%)	25 (49%)	79 (37%)
Previous treatment									
Surgical resection	15 (65%)	8 (80%)	13 (87%)	36 (75%)	34 (61%)	36 (63%)	18 (36%)	40 (78%)	128 (60%)
Radiotherapy‡	6 (26%)	2 (20%)	2 (13%)	10 (21%)	9 (16%)	17 (30%)	4 (8%)	11 (22%)	41 (19%)
Local treatment for HCC§	8 (35%)	6 (60%)	10 (67%)	24 (50%)	24 (43%)	28 (49%)	25 (50%)	40 (78%)	117 (55%)
Systemic therapy	19 (83%)	6 (60%)	15 (100%)	40 (83%)	23 (41%)	57 (100%)	32 (64%)	47 (92%)	159 (74%)
Sorafenib¶	17 (74%)	5 (50%)	15 (100%)	37 (77%)	15 (27%)	57 (100%)	30 (60%)	43 (84%)	145 (68%)

Nivolumab in Advanced HCC: Open-Label, Non-Comparative, Phase 1/2 Dose Escalation and Expansion Trial

Safety and tolerability of nivolumab in the dose-escalation phase

	0·1 mg/kg (n=6)		0·3 mg/kg (n=9)		1 mg/kg (n=10)		3 mg/kg (n=10)		10 mg/kg (n=13)		All patients (n=48)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related serious AEs	1 (17%)*	1 (17%)*	1 (11%)†	1 (11%)†	0	0	0	0	1 (8%)‡	0	3 (6%)	2 (4%)
AEs leading to discontinuation	0	0	1 (11%)§	1 (11%)§	0	0	1 (10%)¶	1 (10%)¶	1 (8%)‖	1 (8%)‖	3 (6%)	3 (6%)
Treatment-related deaths	0	0	0	0	0	0	0	0	0	0	0	0
Patients with a treatment-related AE	4 (67%)	2 (33%)	8 (89%)	3 (33%)	8 (80%)	5 (50%)	9 (90%)	2 (20%)	11 (85%)	0	40 (83%)	12 (25%)
Treatment-related AEs**												
Rash	1 (17%)	0	2 (22%)	0	2 (20%)	0	2 (20%)	0	4 (31%)	0	11 (23%)	0
Pruritus	2 (33%)	0	3 (33%)	0	0	0	1 (10%)	0	3 (23%)	0	9 (19%)	0
Diarrhoea	0	0	3 (33%)	0	0	0	1 (10%)	0	1 (8%)	0	5 (10%)	0
Decreased appetite	1 (17%)	0	2 (22%)	0	1 (10%)	0	0	0	1 (8%)	0	5 (10%)	0
Fatigue	1 (17%)	1 (17%)	2 (22%)	0	1 (10%)	0	0	0	0	0	4 (8%)	1 (2%)
Asthenia	0	0	1 (11%)	0	0	0	1 (10%)	0	1 (8%)	0	3 (6%)	0
Weight decreased	0	0	1 (11%)	0	0	0	0	0	2 (15%)	0	3 (6%)	0
Nausea	0	0	1 (11%)	0	0	0	1 (10%)	0	1 (8%)	0	3 (6%)	0
Dry mouth	0	0	1 (11%)	0	1 (10%)	0	0	0	1 (8%)	0	3 (6%)	0
Laboratory treatment-related AEs**												
AST increase	0	0	2 (22%)	2 (22%)	3 (30%)	2 (20%)	1 (10%)	1 (10%)	4 (31%)	0	10 (21%)	5 (10%)
ALT increase	0	0	2 (22%)	2 (22%)	1 (10%)	0	2 (20%)	1 (10%)	2 (15%)	0	7 (15%)	3 (6%)
Lipase increase	1 (17%)	1 (17%)	1 (11%)	0	4 (40%)	4 (40%)	2 (20%)	1 (10%)	2 (15%)	0	10 (21%)	6 (13%)
Amylase increase	1 (17%)	0	0	0	4 (40%)	1 (10%)	2 (20%)	1 (10%)	2 (15%)	0	9 (19%)	2 (4%)
Anaemia	0	0	1 (11%)	0	1 (10%)	1 (10%)	0	0	2 (15%)	0	4 (8%)	1 (2%)
Hypoalbuminaemia	0	0	1 (11%)	0	1 (10%)	0	0	0	1 (8%)	0	3 (6%)	0
Hyponatraemia	0	0	0	0	2 (20%)	0	0	0	1 (8%)	0	3 (6%)	0

Nivolumab in Advanced HCC: Open-Label, Non-Comparative, Phase 1/2 Dose Escalation and Expansion Trial

Nivolumab efficacy in the dose-expansion phase

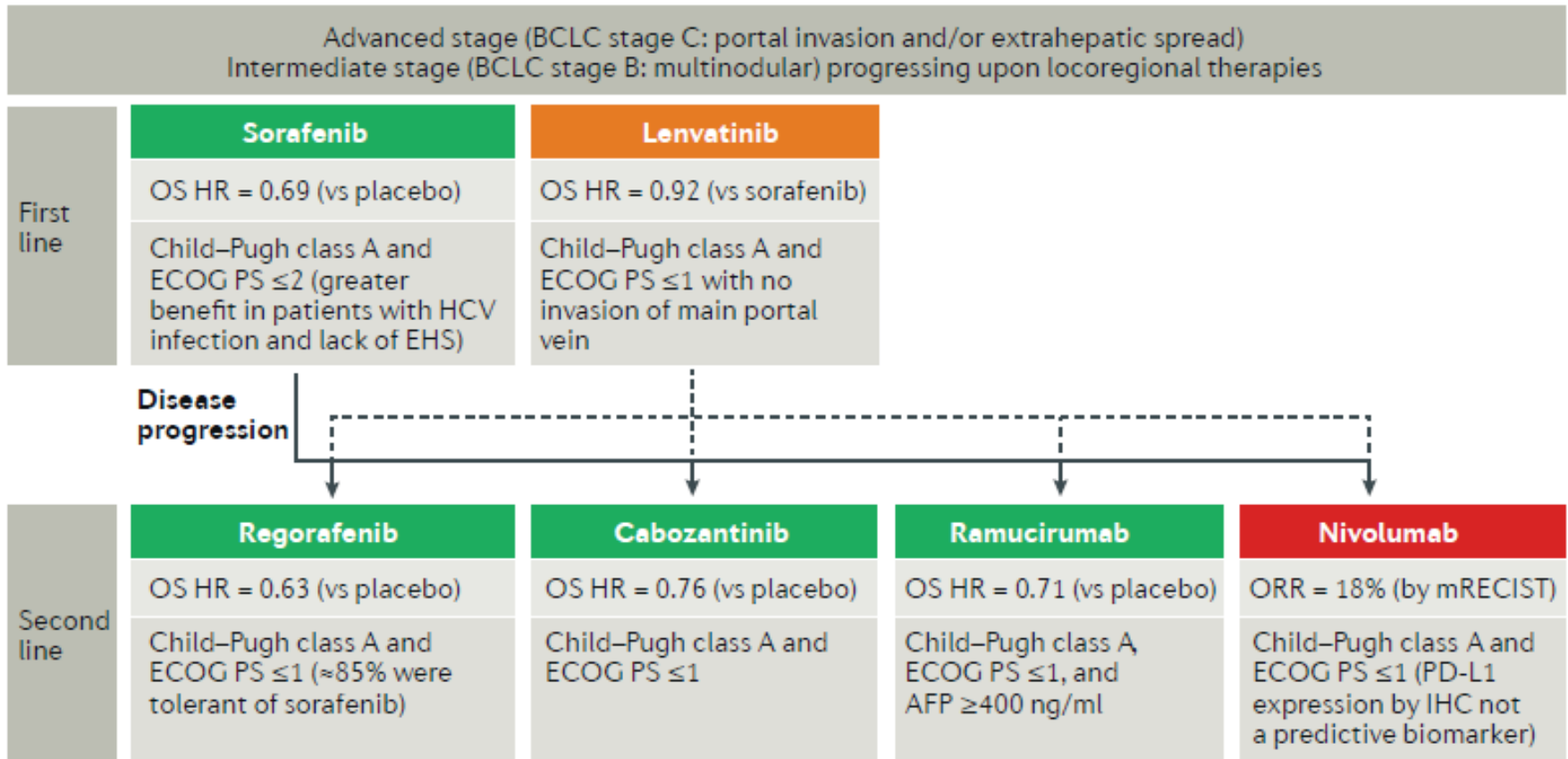|	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Objective response*	13 (23%; 13 to 36)	12 (21%; 11 to 34)	10 (20%; 10 to 34)	7 (14%; 6 to 26)	42 (20%; 15 to 26)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response	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					

This signs of efficacy were consistent with the more recently reported median OS of 28.6 months (95%CI 16.6–NE) in the population naive to sorafenib, and 15.6 months (95%CI 13.2–18.9) in the much larger population exposed to sorafenib (90% sorafenib progressors).

El-Khoueiry AB, et al. Lancet 2017 and Crocenzi TS et al, J Clin Oncol. 2017;35(suppl).

Nivolumab in Advanced HCC: Open-Label, Non-Comparative, Phase 1/2 dose Escalation and Expansion Trial

	Escalation phase (n=44)*	Expansion phase (n=174)*
PD-L1 ≥1%†	11 (25%)	34 (20%)
Objective response	3/11 (27%; 6–61)	9/34 (26%; 13–44)
Complete response	1 (9%)	1 (3%)
Partial response	2 (18%)	8 (24%)
Stable disease	0	16 (47%)
Progressive disease	7 (64%)	9 (26%)
Not determined	1 (9%)	0
PD-L1 <1%†	33 (75%)	140 (80%)
Objective response	4/33 (12%; 3–28)	26/140 (19%; 13–26)
Complete response	2 (6%)	2 (1%)
Partial response	2 (6%)	24 (17%)
Stable disease	19 (58%)	62 (44%)
Progressive disease	8 (24%)	46 (33%)
Not determined	2 (6%)	6 (4%)

ORR occurred in this study regardless of PD-L1 expression on tumour cells (1% of tumour cells expressing PD-L1 as cutoff).

El-Khoueiry AB, et al. Lancet 2017

Treatment Strategy for Advanced HCC

Advanced stage (BCLC stage C: portal invasion and/or extrahepatic spread)
Intermediate stage (BCLC stage B: multinodular) progressing upon locoregional therapies

First line

Sorafenib	Lenvatinib
OS HR = 0.69 (vs placebo)	OS HR = 0.92 (vs sorafenib)
Child–Pugh class A and ECOG PS ≤2 (greater benefit in patients with HCV infection and lack of EHS)	Child–Pugh class A and ECOG PS ≤1 with no invasion of main portal vein

Disease progression

Second line

Regorafenib	Cabozantinib	Ramucirumab	Nivolumab
OS HR = 0.63 (vs placebo)	OS HR = 0.76 (vs placebo)	OS HR = 0.71 (vs placebo)	ORR = 18% (by mRECIST)
Child–Pugh class A and ECOG PS ≤1 (≈85% were tolerant of sorafenib)	Child–Pugh class A and ECOG PS ≤1	Child–Pugh class A, ECOG PS ≤1, and AFP ≥400 ng/ml	Child–Pugh class A and ECOG PS ≤1 (PD-L1 expression by IHC not a predictive biomarker)

Llovet JM et al, Nat Rev Clin Oncol, 2018

Next Step: Targeted Therapy Combination

| Targeted therapy combinations						
Atezolizumab + bevacizumab	PD-L1 and VEGFA	Advanced; first line	None	III	OS	NCT03434379
Galunisertib + nivolumab	TGFβR1 and PD-1	Advanced; second line	AFP > 200 ng/ml	I–II	MTD	NCT02423343
Apatinib + SHR-1210	VEGFR2 and PD-1	Advanced; second line	None	I–II	OS	NCT02942329
Spartalizumab ± capmatinib	PD-1 and MET	Advanced; second line	None	I–II	DLTs	NCT02795429
FGF401 ± spartalizumab	FGFR4 and PD-1	Advanced; second line	FGFR4+ and KLB+	I–I	DLTs	NCT02325739
Pembrolizumab + lenvatinib	PD-1 plus VEGFR2 and VEGFR3	Advanced; second line	None	I	DLTs	NCT03006926
Regorafenib + pembrolizumab	VEGFRs, FGFRs, KIT, PDGFRs, and RAF plus PD-1	Advanced; first line	None	I	AEs	NCT03347292
Cabozantinib + nivolumab	MET and VEGFRs plus PD-1	Neoadjuvant	None	I	AEs	NCT03299946
Avelumab + axitinib	PD-L1 plus VEGFRs, KIT, and PDGFRs	Advanced; first line	None	I	AEs	NCT03289533
Ramucirumab + durvalumab	VEGFR2 and PD-L1	Advanced; second line	AFP > 1.5 × ULN	I	DLTs	NCT02572687
XL888 + pembrolizumab	HSP90 and PD-1	Advanced; second line	None	I	RP2D	NCT03095781
Navitoclax + sorafenib	BCL-2 plus VEGFRs, KIT, PDGFRs, and RAF	Advanced; second line	None	I	MTD	NCT02143401

Challenges Remain

➢ Improving pre-clinical testing of novel drugs (oncogenic addiction loop, oncogenic drivers, signaling pathways),combo and adjuvant therapy.

➢ Expanding 2nd line therapies beyond patients who tolerate sorafenib .

➢ Biomarkers to predict treatment response and early detection.

➢ Integrating cost-benefit and QoL analysis in clinical trials.

Dose finding of Lenvatinib in Subjects with Advanced HCC Based on Population Pharmacokinetic and Exposure-Response Analysis

Tamai T et al, J Clin Pharmacol 2017

Dose finding of Lenvatinib in subjects with advanced HCC based on population pharmacokinetic and exposure-response analysis

Tamai T et al J Clin Pharmacol 2017
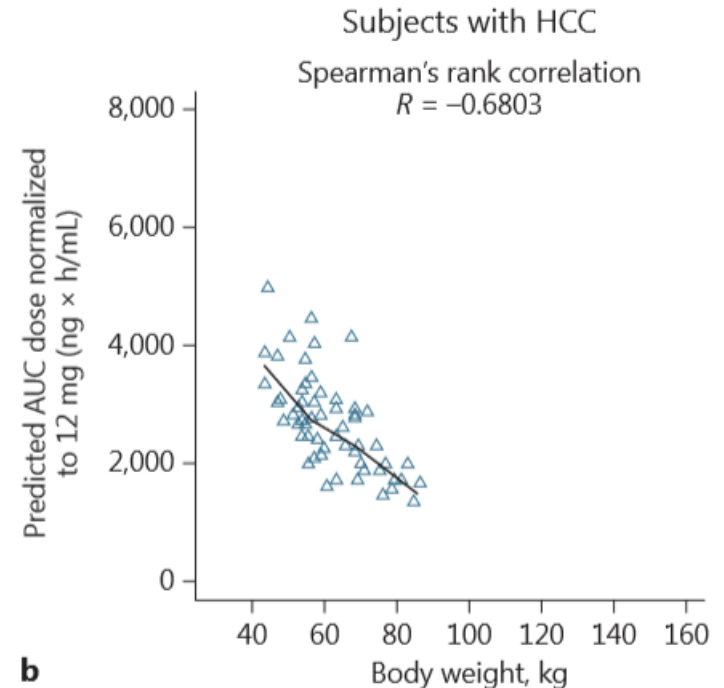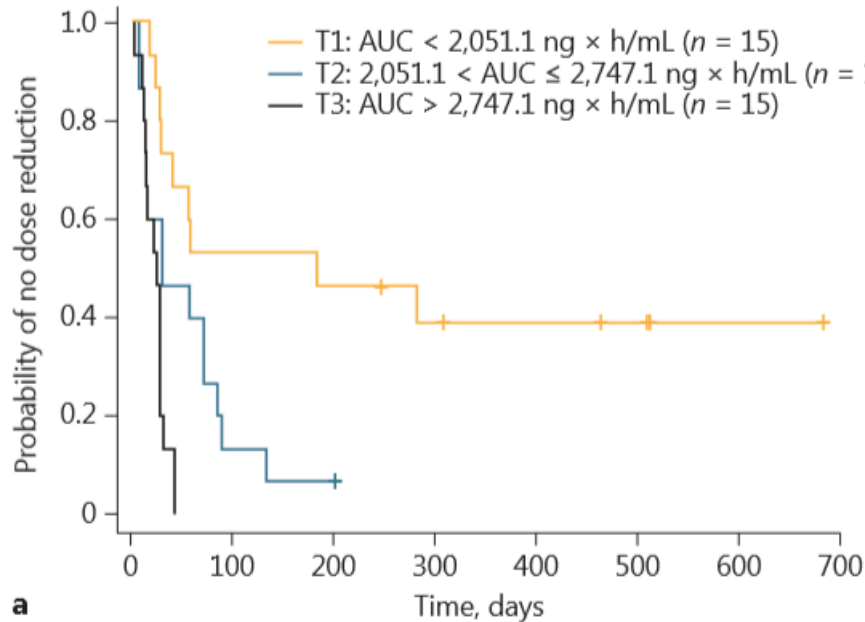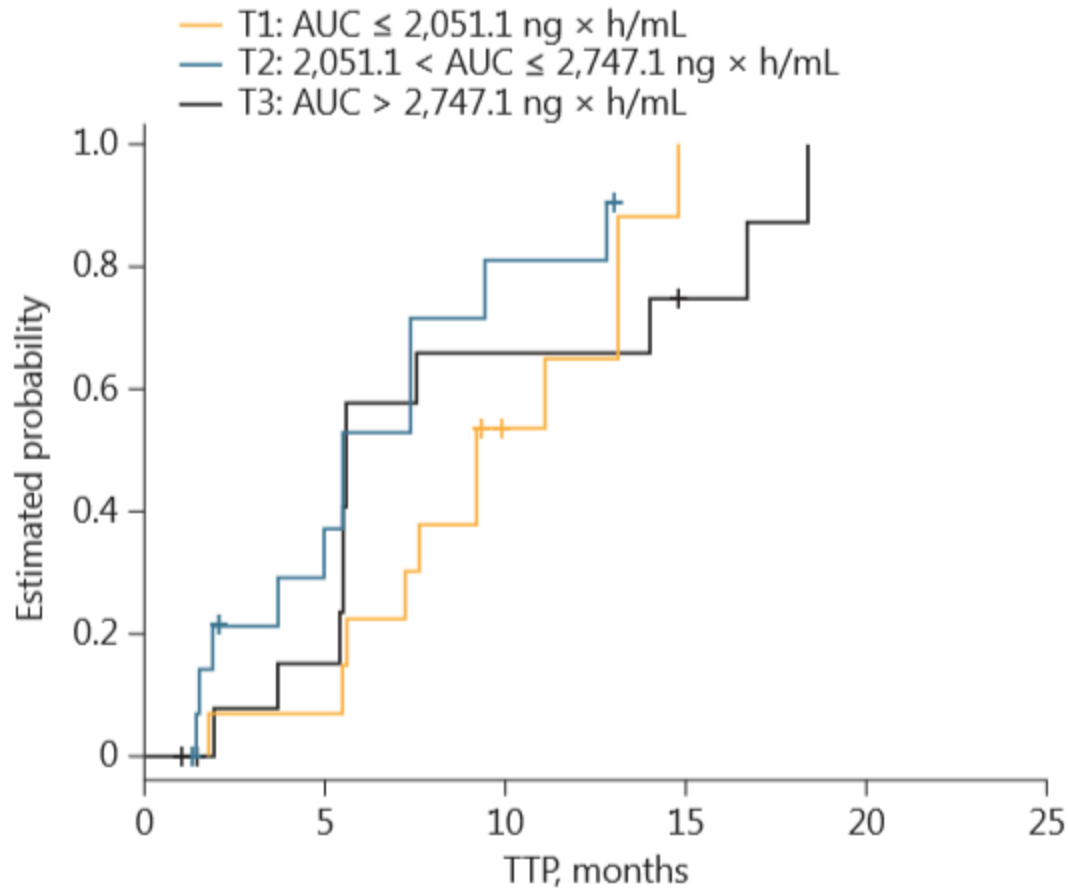
CELESTIAL Phase 3 Study:
Overall Survival Analyses

Up to 2 interim analyses were planned:

✓ IA #1 (planned at 50% information fraction)

      Data cut-off Jun 15, 2016

      Included 51.7% of total required deaths

      IDMC recommended study proceed without modification

✓ IA #2 (planned at 75% information fraction)

      Data cut-off Jun 1, 2017

      Included 78% of total required deaths

      IDMC recommended study stop for efficacy

Global phase 3 CELESTIAL trial met its primary endpoint of OS, with cabozantinib providing a statistically significant and clinically meaningful improvement in median OS _vs_ placebo in patients with advanced HCC.

Nivolumab in Advanced HCC: Open-Label, Non-Comparative, Phase 1/2 Dose Escalation and Expansion Trial

Time to response and duration of response

El-Khoueiry AB, et al. Lancet 2017
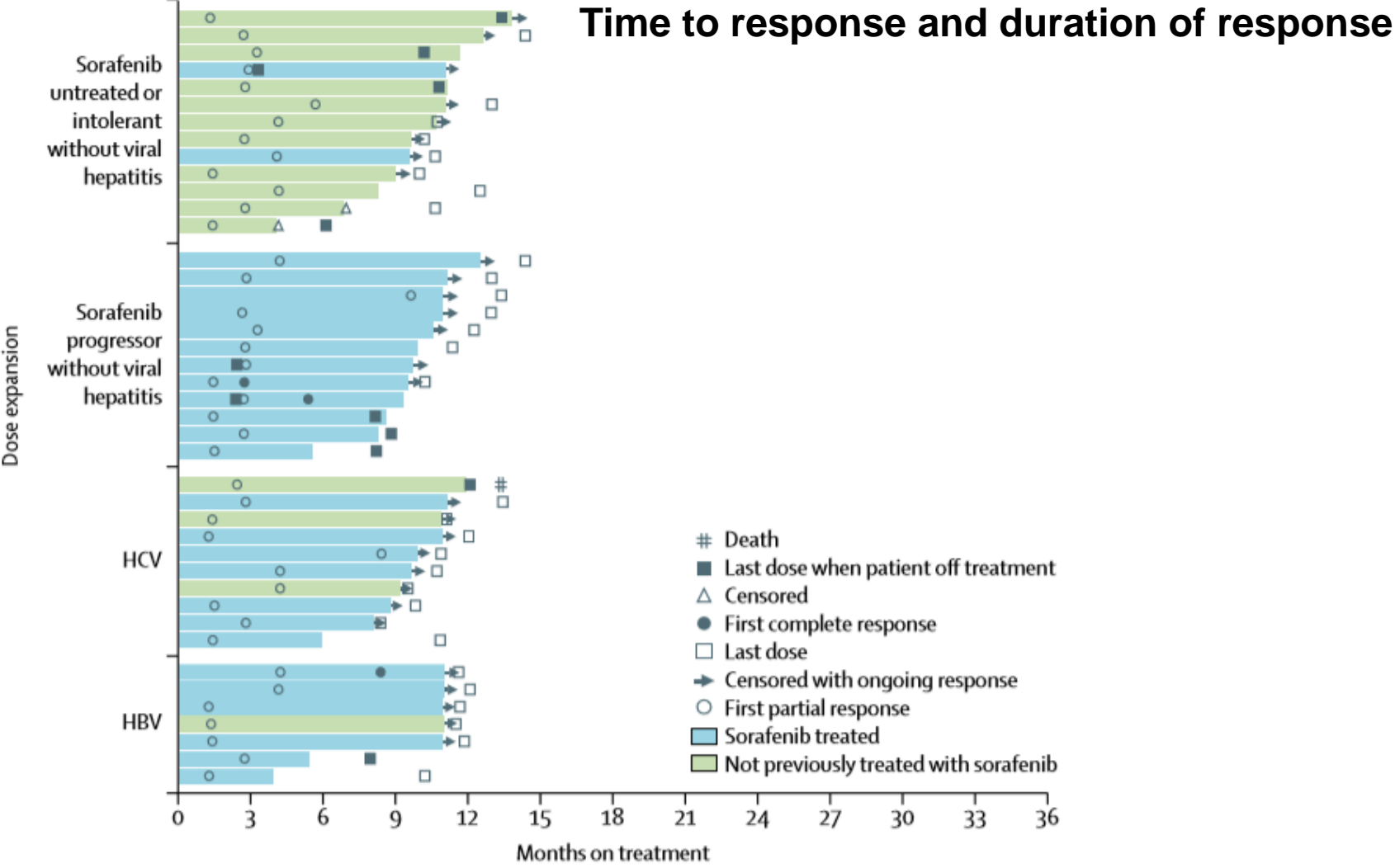
Nivolumab in Advanced HCC

The FDA has granted an accelerated approval to nivolumab for the treatment of patients with HCC following prior sorafenib, regardless of PD-L1 status.

The approval is based on 154 patients enrolled in the phase I/II CheckMate-040 trial, in which the overall response rate (ORR) by blinded independent central review (BICR) was 18.2% per mRECIST criteria for patients who had previously been treated with sorafenib. Additionally, 3.2% of patients experienced a complete response. The ORR by RECIST 1.1 was 14.3% with nivolumab and the response duration ranged from 3.2 to 38.2+ months.

A phase III randomized trial of nivolumab versus sorafenib has been launched in the frontline setting, with an enrollment goal of 726 patients. The estimated primary completion date is October 2018 (NCT02576509).