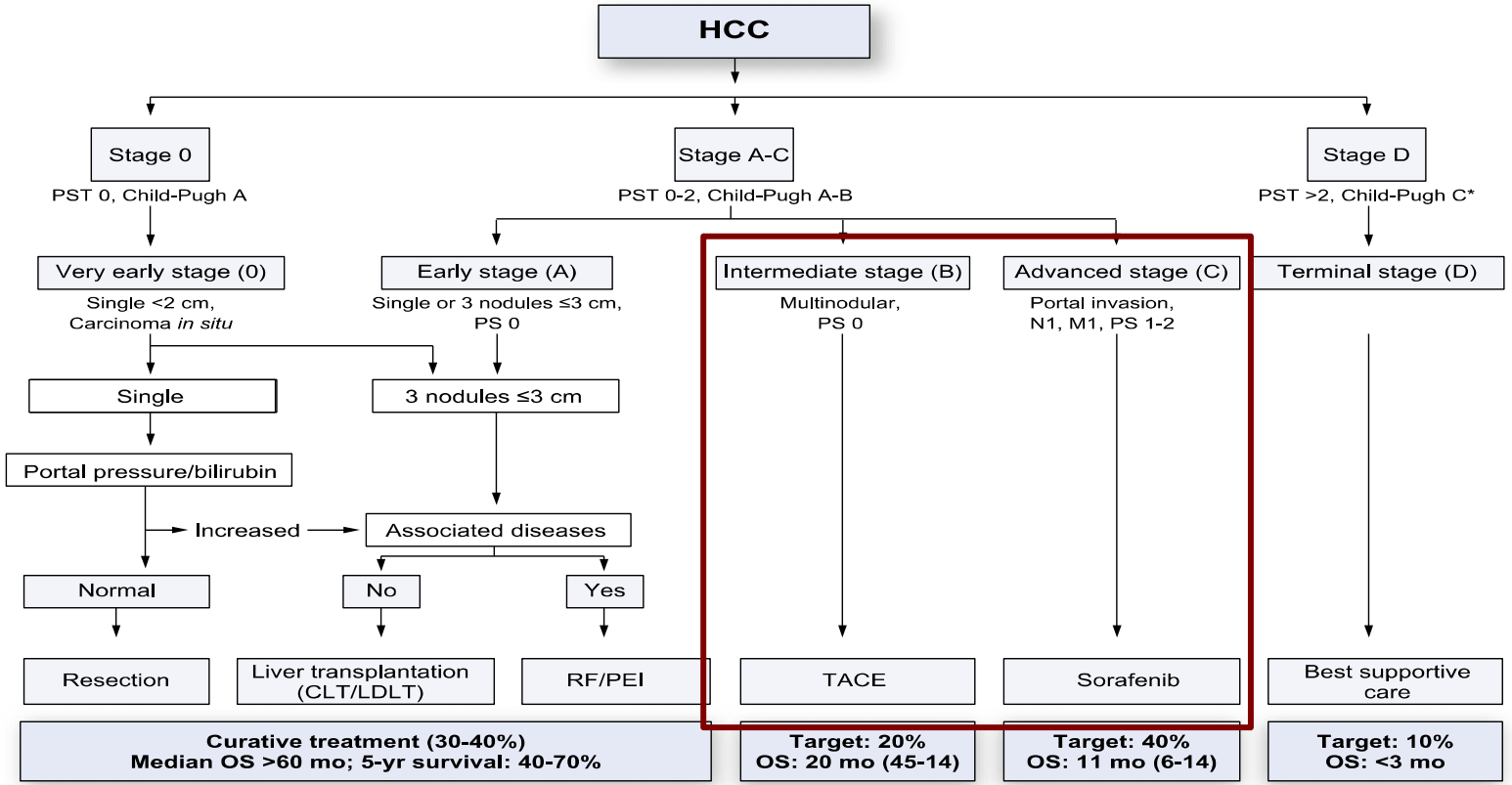
New Therapies in HCC

Bruno Sangro
Clínica Universidad de Navarra. IdISNA. CIBERehd.
Pamplona, Spain

PHC 2018 - www.aphc.info

EASL-EORTC Guidelines



EASL–EORTC Guidelines. J Hepatol. 2012;56:908-43.

Systemic Therapy of HCC

TREATMENT OF HEPATOCELLULAR CARCINOMA WITH ADRIAMYCIN

Preliminary Communication

CHARLES L. M. OLWENY, MMED,* TOM TOYA, MD†
EDWARD KATONGOLE-MBIDDE, MB, CHB,‡ JOSUA MUGERWA, MD,‡
SEBASTIAN K. KYALWAZI, FRCS(Ed),‖ AND HERMAN COHEN, PHD**

In a Phase II clinical trial, 14 patients with histologically proven primary hepatocellular carcinoma were treated with adriamycin administered intravenously at a dose of 75 mg/m² every 3 weeks. All 11 evaluable patients responded with 3 exhibiting complete tumor regression after two, three, and five courses of adriamycin respectively. The remission durations for these 3 were 3, 6, and 7 months, and their survivals were 8, 9, and 13 months, respectively. The median survival of the evaluable patients is 8 months (range 1–13 months). The side effects encountered included myelosuppression, anorexia, nausea, vomiting, and alopecia. Adriamycin seems to be an effective agent in hepatocellular carcinoma. Further trials are underway to test its true efficacy both singly and in combination with other drugs in the management of this tumor.

Cancer 36:1250–1257, 1975.

Table 1 | **Major recurrent molecular aberrations observed in advanced HCC**

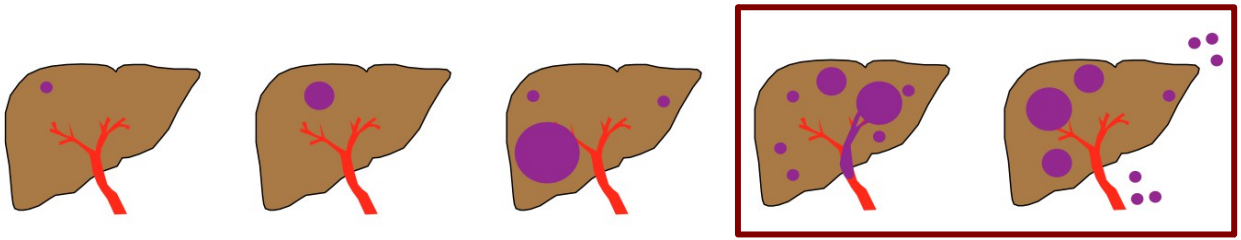
Pathway(s)	Gene(s)	Alteration	Frequency in HCC
Telomere maintenance	*TERT*	Promoter mutation	54–60%
		Amplification	5–6%
Cell cycle control	*TP53*	Mutation or deletion	12–48%
	RB1	Mutation or deletion	3–8%
	CCND1	Amplification	7%
	CDKN2A	Mutation or deletion	2–12%
WNT–β-catenin signalling	*CTNNB1*	Mutation	11–37%
	AXIN1	Mutation or deletion	5–15%
Oxidative stress	*NFE2L2*	Mutation	3–6%
	KEAP1	Mutation	2–8%
Angiogenesis	*VEGFA*	Amplification	3–7%

no clear oncogenic addiction loops reporting response to targeted therapies have been described

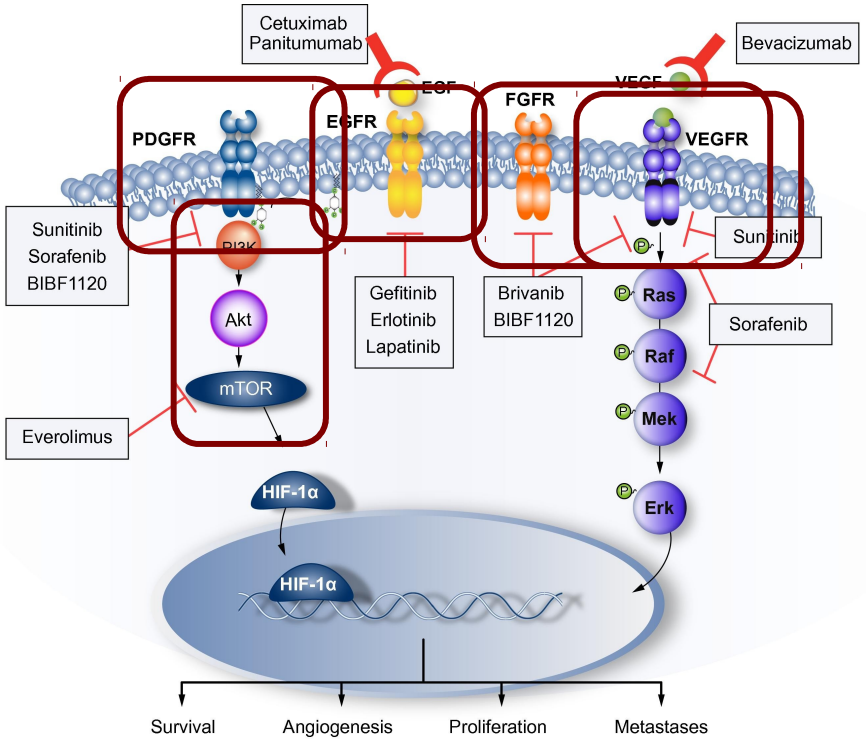
Olweny CLM, et al. Cancer 1975; 36: 1250-1257.

Sorafenib in HCC

- Consistent effect in the advanced stage (HR: 0,69)
  - SHARP and AP trials; 828 patients randomised.
- No significant effect in combination with TACE in the intermediate stage
  - SPACE and TACE-2 trials; 601 patients randomised
- No significant effect as an adjuvant therapy post-resection or ablation in the early stages
  - STORM trial; 1,114 patients randomised



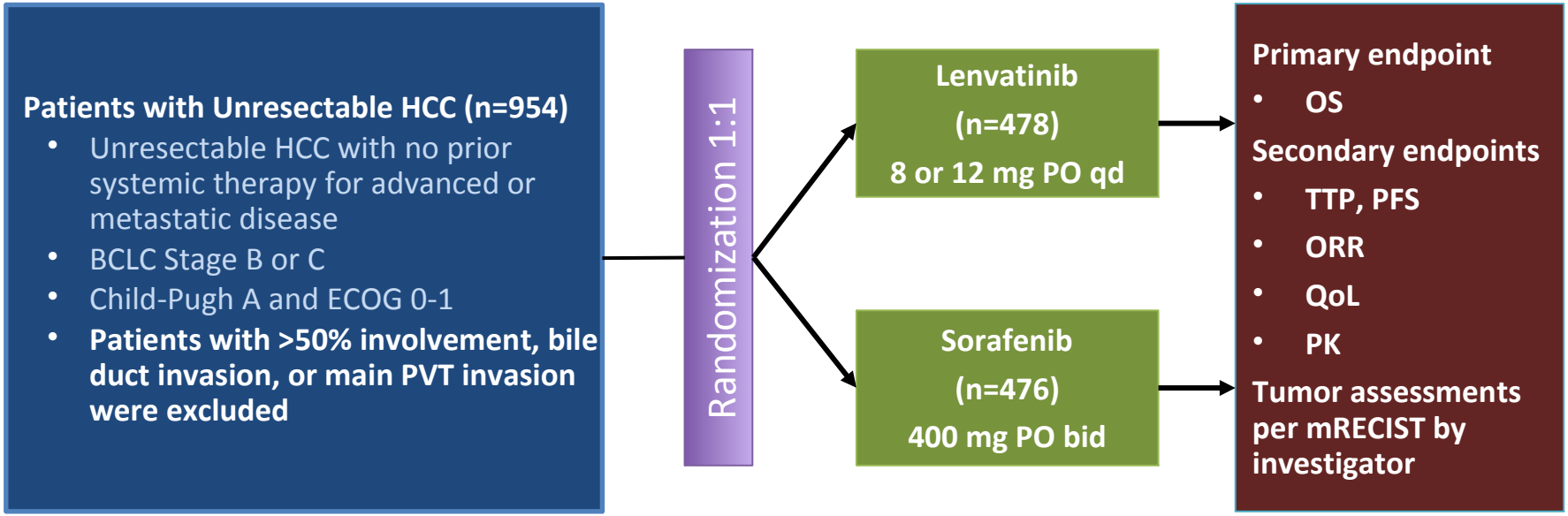
Targeted agents beyond Sorafenib



- **Sunitinib**: p 3 Trial halted for futility
- **Brivanib**: failed in 3 settings
  - 2L vs. Placebo
  - First line vs. Sorafenib
  - Combination with TACE vs. Placebo
- **Erlotinib**: no benefit in Sor combo
- **Everolimus**: no benefit in 2 settings
  - 2L vs. Placebo
  - 1L in combination with Sorafenib

Faivre S, et al. Lancet Oncol 2008; Llovet JM, et al. J Clin Oncol 31:3509-3516. Zhu A, et al. J Clin Oncol. 2015;33:559. Zhu A, et al. JAMA. 2014;312:57. Koeberle D, et al. Ann Oncol. 2016;27:856

Lenvatinib: the REFLECT Trial



- Open-label design
- The primary endpoint (OS) was first tested for noninferiority then for superiority.

Kudo M, et al. Presented at ASCO 2017

Lenvatinib: the REFLECT Trial

Characteristic	Lenvatinib	Sorafenib
Mean age (y)	61.3	61.2
Male Sex, %	85	84
A-P Region, %	**67**	**67**
Hepatitis B, %	**53**	**48**
MVI or EHD, %	69	71
ECOG 0, %	64	63
Child A, %	99	99
BCLC C, %	78	81

<u>Overall Survival, median (95%CI)</u>

- Lenvatinib: 13.6 (12.1-14.9)
- Sorafenib: 12.3 (10.4-13.9)

- HR (95%CI): 0.92 (0.79-1.06)

- Higher TRAE G≥3 and SAEs

Kudo M, et al. Presented at ASCO 2017

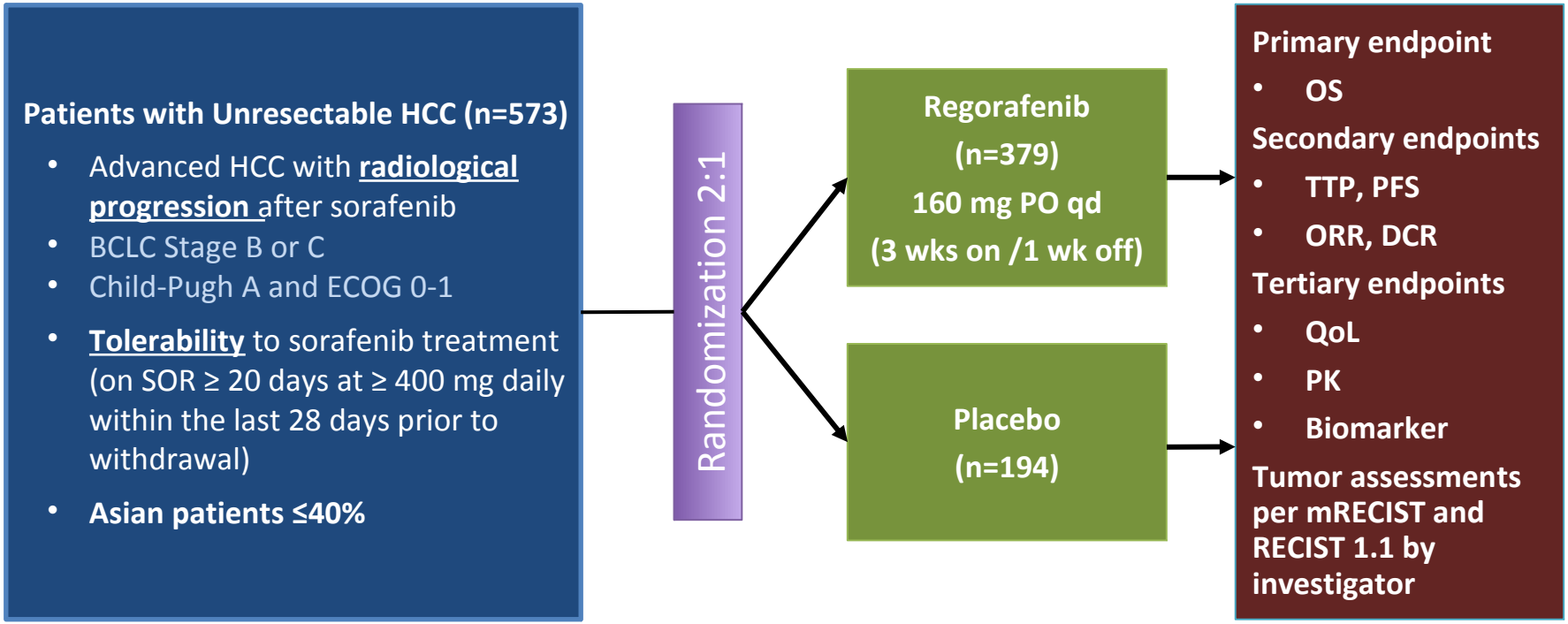
Phase 3 Trials Comparing SIRT and Sorafenib

Trial	SIRVENIB (Asia-Pacific)	SARAH (France)
Target Population	BCLC B or BCLC C without EHD, ECOG 0 – 1, Child-Pugh A or B7	
	Without > 2 prior intraarterial therapies	**Failed after 2 sessions of TACE**
Patients assessed	489 (360 randomized 1:1)	496 (467 randomized 1:1)
Population treated	**HBV** was the most frequent etiology Most patients were BCLC-B	**Alcohol** was the most frequent etiology **34-32% had main trunk PVI**
Not receiving assigned Tx	**28% in SIRT arm,** 9% in Sorafenib arm	**26% in SIRT arm,** 7% in Sorafenib arm
Primary Endpoint (MOS)	**8.8 mo (SIRT) vs. 10 mo (SOR)**	**8.0 mo (SIRT) vs. 9.9 mo (SOR)**
Relevant secondary endpoints	Response Rate (PP): 23.1% (SIRT)vs. 1.9% (SOR), p<0.001. Patients with ≥1 TRAE grade ≥3: 13.1% (SIRT) vs 37.7% (SOR), p< 0.001	Response Rate (PP): 19% (SIRT) vs. 11.6% (SOR), p=0.042. Patients with ≥1 TRAE grade ≥3: 40% (SIRT) vs 63% (SOR), p< 0.001

Chow P, et al. Presented at ASCO 2017

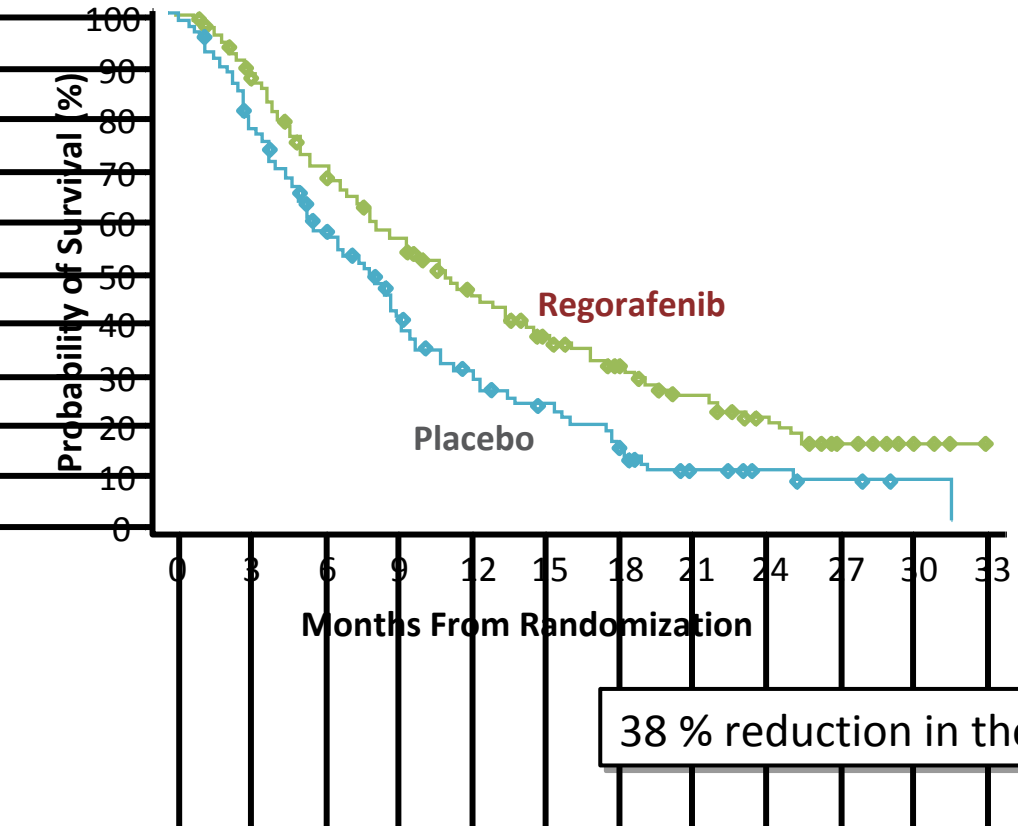
Vilgrain V, et al. Presented at EASL 2017

Regorafenib: the RESORCE trial



Bruix J et al. Lancet. 2017;389:56-66

Regorafenib: the RESORCE trial

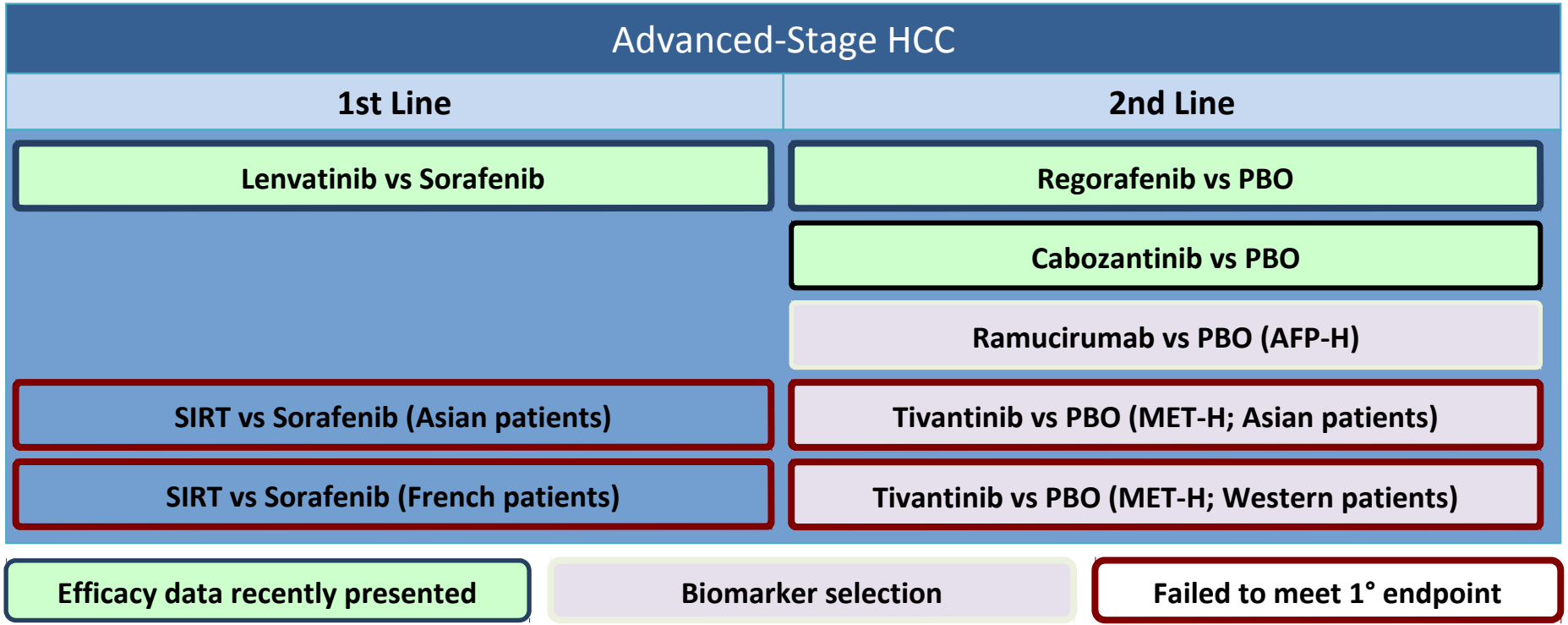


	Regorafenib	Placebo
mOS, mo (95% CI)	10.6 (9.1–12.1)	7.8 (6.3–8.8)
HR (95% CI)	0.63 (0.50, 0.79) *P*<0.0001	
HBV		
mOS, mo (95% CI)	8.8 (7.3–13.3)	5.3 (4.2–8.8)
HR (95% CI)	0.58 (0.41–0.82) *P*=0.0009	
HCV		
mOS, mo (95% CI)	10.9 (7.4–15.5)	8.8 (5.7–9.7)
HR (95% CI)	0.79 (0.49–1.26) *P*=0.1583	

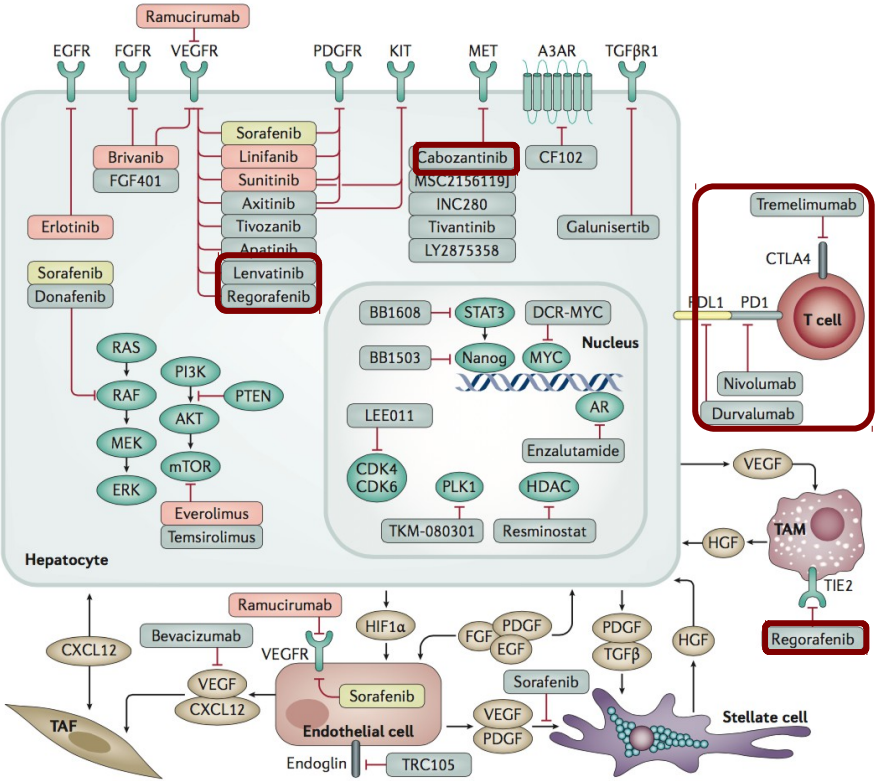
38 % reduction in the risk of death

Bruix J et al. Lancet. 2017;389:56-66.

Phase 3 Trials of Targeted Therapy for Advanced HCC



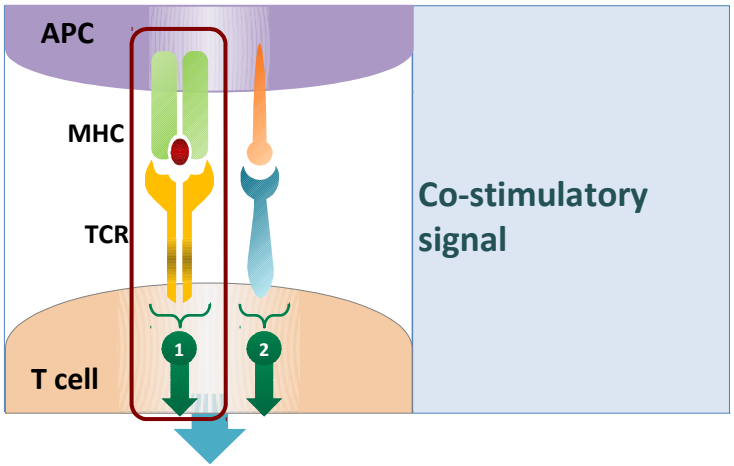
Targeted Therapies for HCC

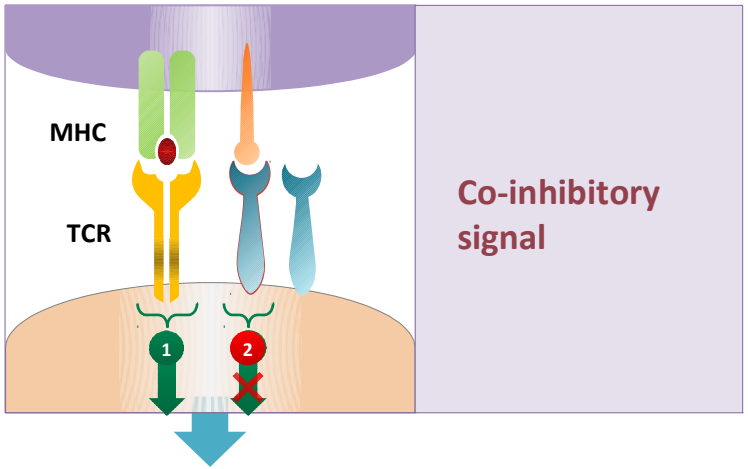


Llovet JM, et al. Nat Rev Dis Primers. 2016 Apr 14;2:16018. doi: 10.1038/nrdp.2016.18.

Activation and Inhibition of T Cells

T-cell response is regulated by a balance between co-stimulatory and co-inhibitory signals, also referred to as “checkpoint” pathways1,2



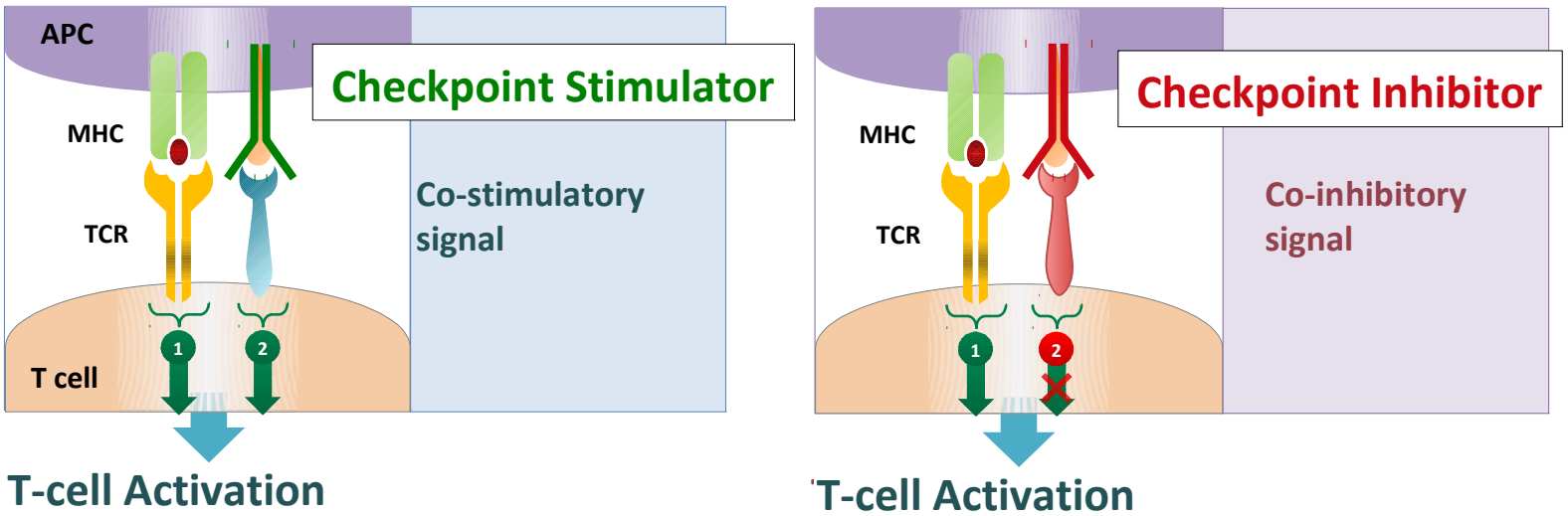


APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264. 2. Weber J. *Semin Oncol.* 2010;37(5):430-439.

Activation and Inhibition of T Cells

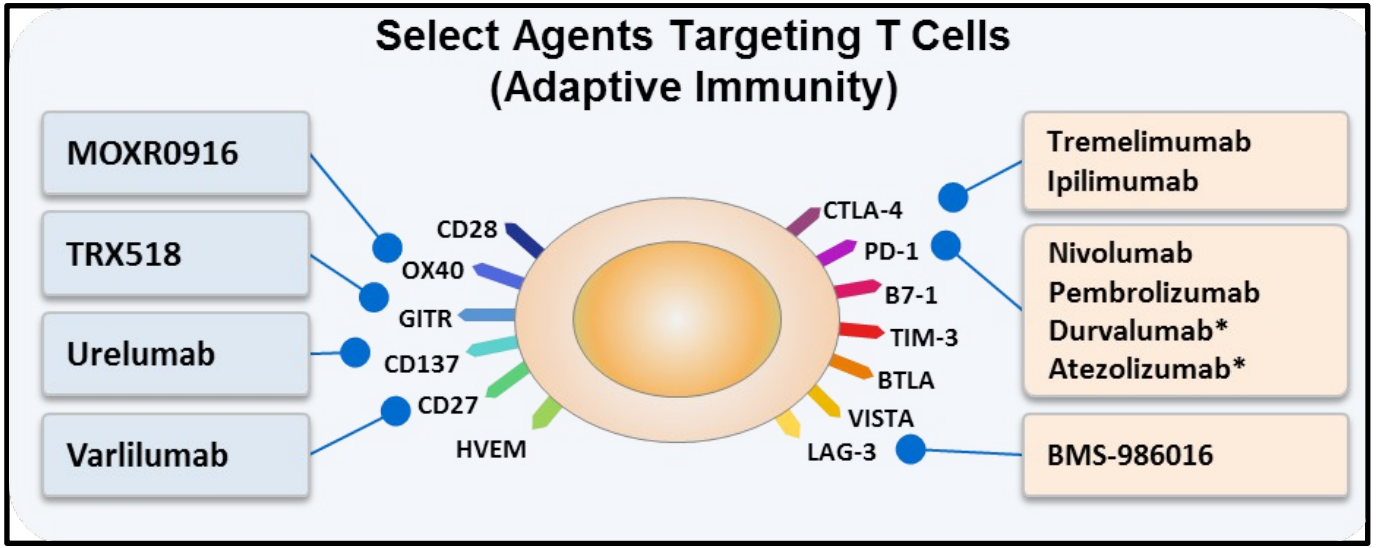
T-cell response is regulated by a balance between co-stimulatory and co-inhibitory signals, also referred to as “checkpoint” pathways1,2



APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264. 2. Weber J. *Semin Oncol.* 2010;37(5):430-439.

Immune Checkpoint Inhibition

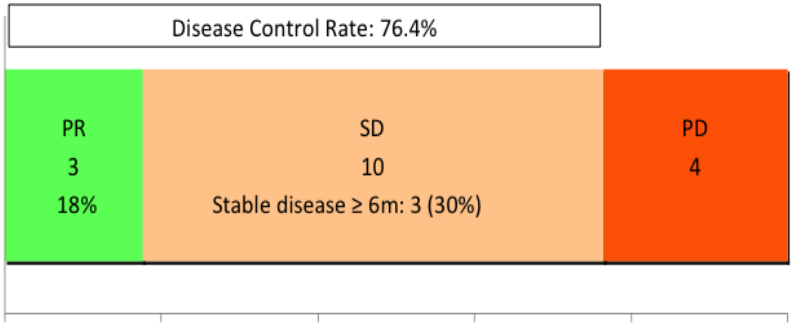


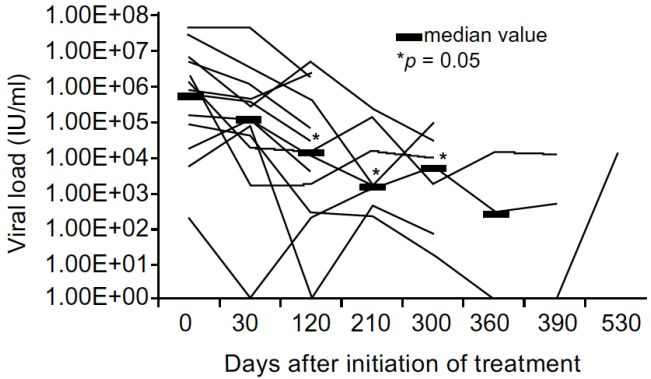
Checkpoint inhibitors have had a major impact on the treatment of multiple cancer types, leading to approvals in 9 cancer types: Melanoma, NSCLC, Renal cell carcinoma, Merkel cell carcinoma, Bladder cancer, SCCHN, Hodgkin's lymphoma, MSI-high tumors, **Hepatocellular carcinoma**

Pardoll DM. *Nat Rev Cancer*. 2012;12:252-64. Mellman I et al. *Nature*. 2011;480:480-9.

Tremelimumab in HCC

- IIT, multicentric, single arm phase 2 trial
- **Advanced HCC + chronic HCV infection**
- Main endpoint: **tumor response**
- Sample size: **20 patients**
- **Tremelimumab**: 15 mg/kg IV q 90 days

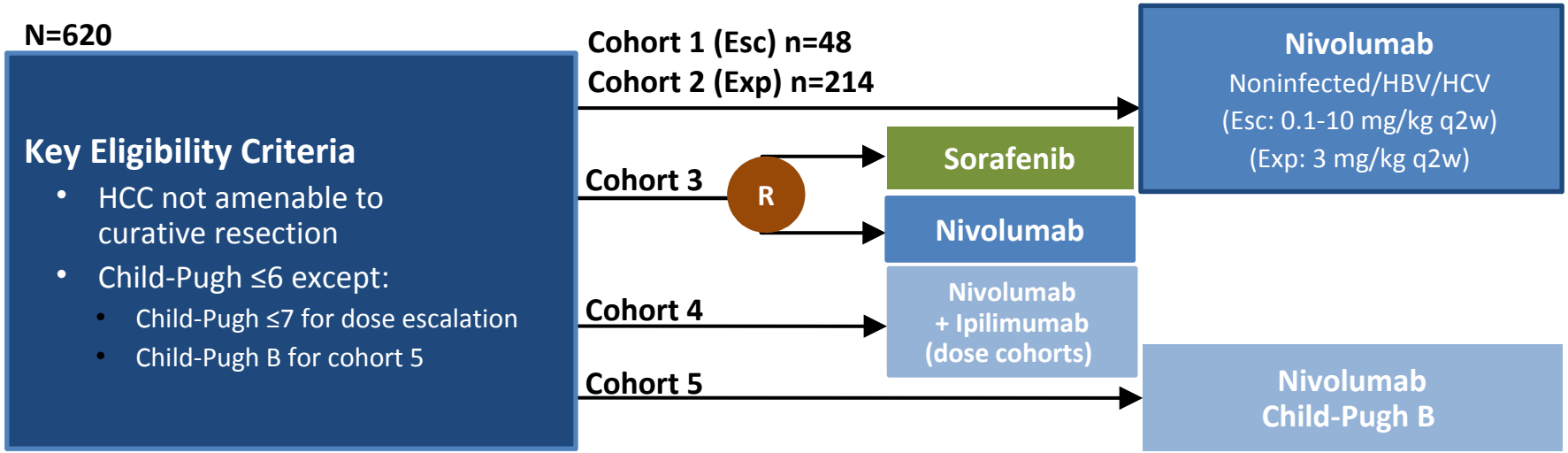




Antiviral effect not related not antitumor activity

Sangro B, et al. J Hepatol 2013, 59:81

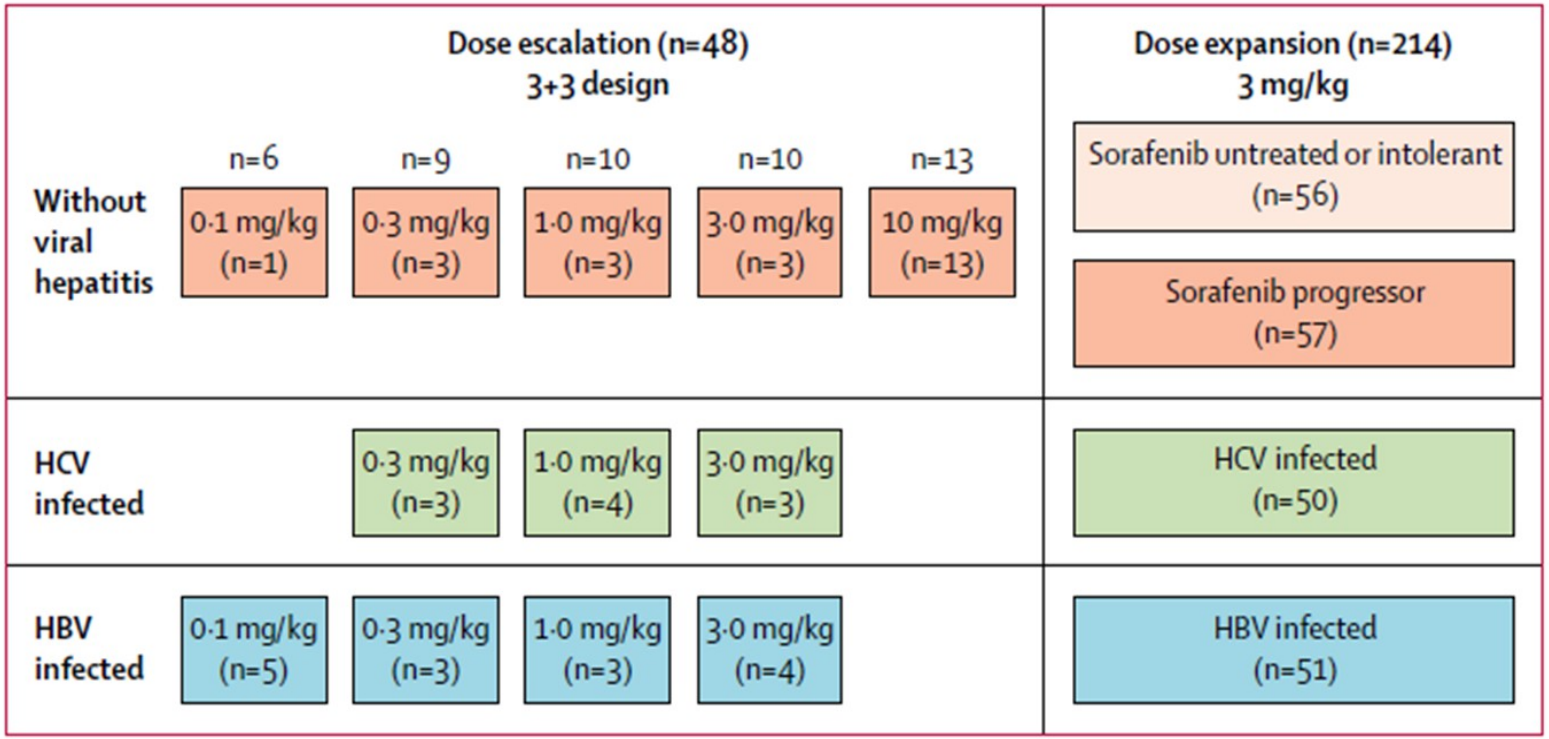
Nivolumab in HCC - CHECKMATE 040 Trial



- **Primary Endpoints (Cohorts 1&2):** Safety and tolerability, ORR
- **Location:** Multinational
- **Status:** Ongoing, recruiting

Clinicaltrials.gov. NCT01658878. Accessed February, 27 2017.

Nivolumab in HCC - Checkmate 040 Trial



El-Khoueiry A, Sangro B, Lau T, et al. Lancet 2017;389: 2492

Nivolumab in HCC - Checkmate 040 Trial

Best Overall Response by Blinded Independent Central Review

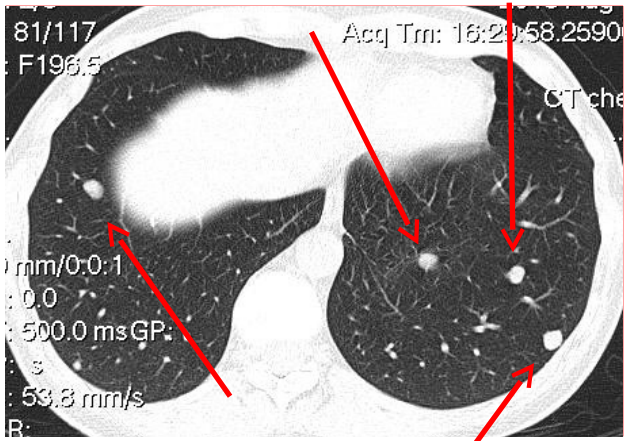
Patients, n (%)	Sorafenib Naive ESC + EXP n = 80a	Sorafenib Experienced ESC n = 37a	Sorafenib Experienced EXP n = 145
Objective response using RECIST v1.1	**16 (20)**	**7 (19)**	**21 (14)**
Complete response	1 (1)	1 (3)	2 (1)
Partial response	15 (19)	6 (16)	19 (13)
Stable disease	25 (31)	12 (32)	60 (41)
Progressive disease	32 (40)	13 (35)	56 (39)
Not evaluable	5 (6)	4 (11)	8 (6)

a Two sorafenib-naive patients and 1 sorafenib-experienced (ESC) patient had a best overall response reported as non-CR/non-PD by BICR.

- Disease control rates were 54% in SOR-naive patients and 55% in all SOR-experienced patients
- Median duration of response: 17 months. Median survival not reached among responders

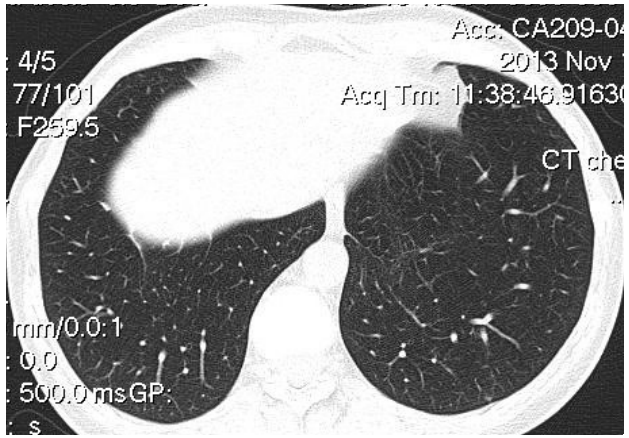
Sangro B, et al. Presented at AASLD 2017

Nivolumab in HCC - Checkmate 040 Trial



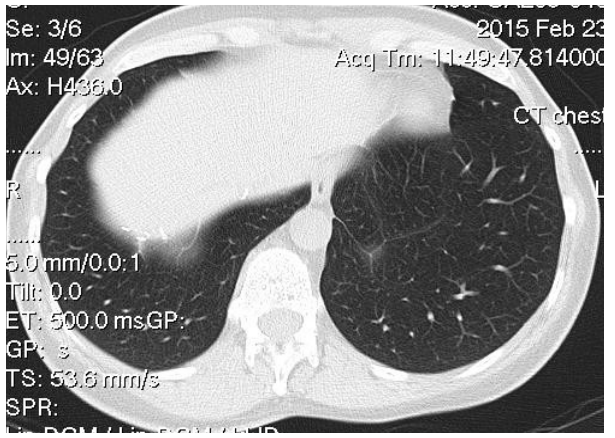
Baseline

Multiple bilateral lung lesions



Week 12

Complete response

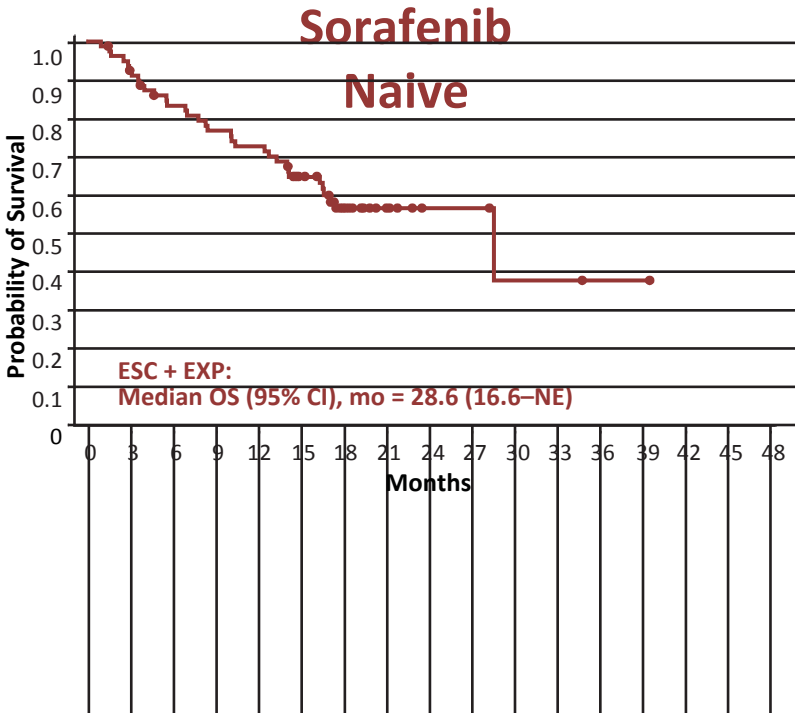


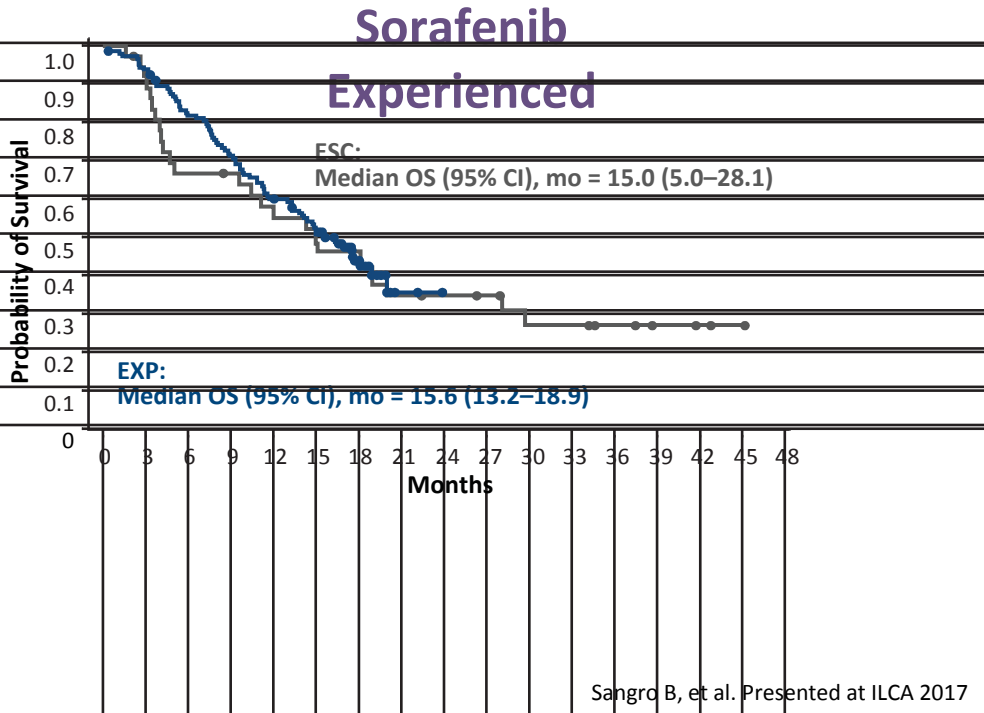
Week 78

Nivolumab discontinued at Week 18; CR maintained
>23 months after last dose

Sangro B, et al. Presented at AASLD 2016.

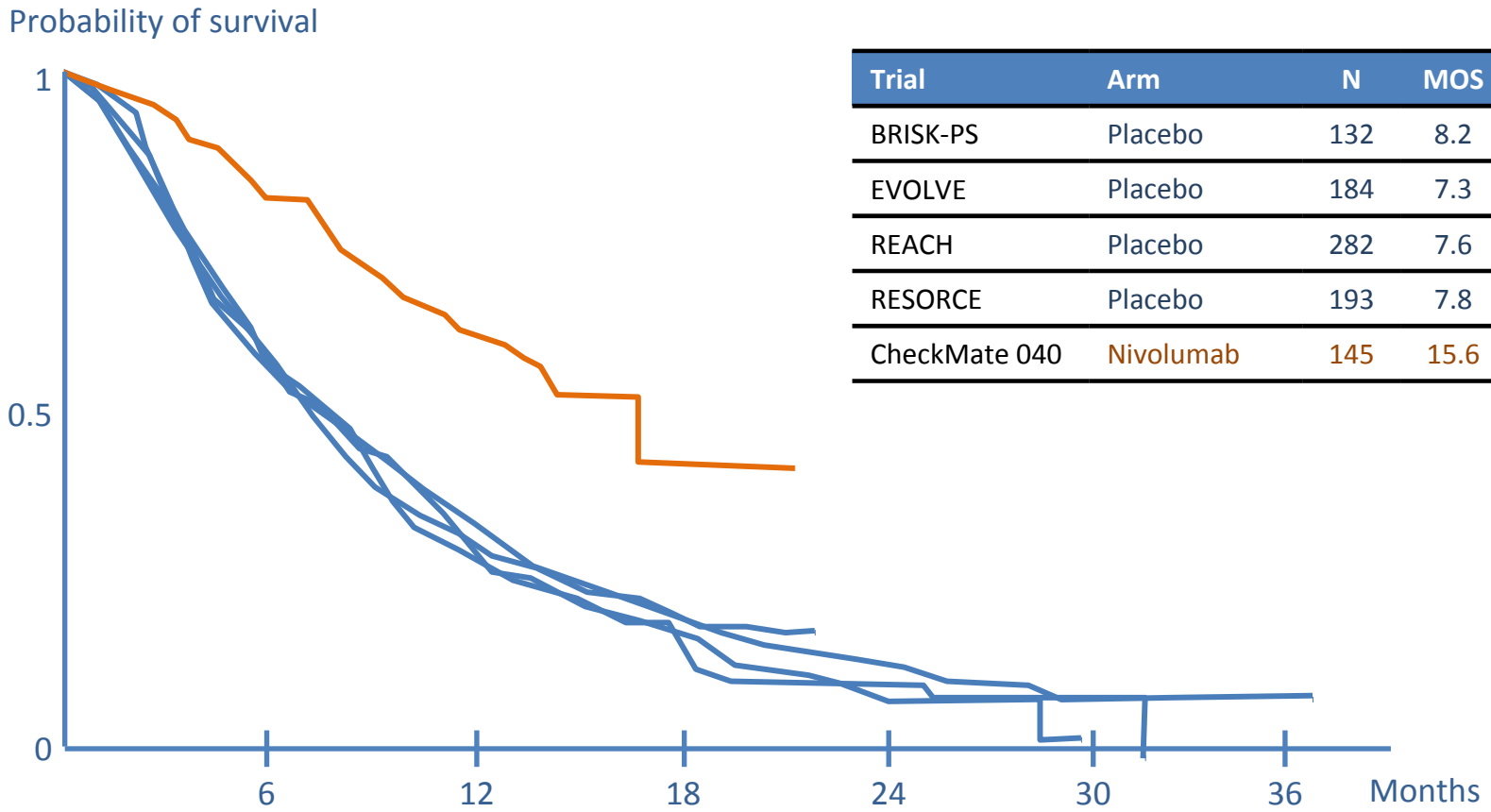
Nivolumab in HCC - Checkmate 040 Trial





Sangro B, et al. Presented at ILCA 2017

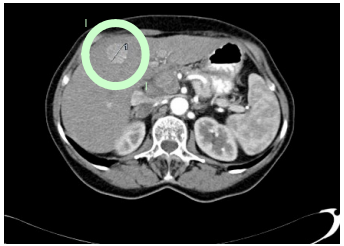
Survival of Advanced HCC in 2L p3 Trials



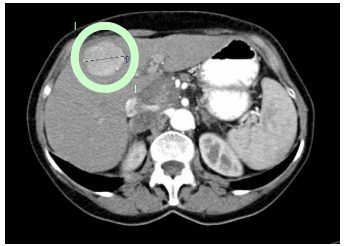
Trial	Arm	N	MOS	95%CI
BRISK-PS	Placebo	132	8.2	NR
EVOLVE	Placebo	184	7.3	6.3-8.7
REACH	Placebo	282	7.6	6.0-9.3
RESORCE	Placebo	193	7.8	6.3-8.8
CheckMate 040	Nivolumab	145	15.6	13.2-18.8

Special Patterns of Response to I-O Agents

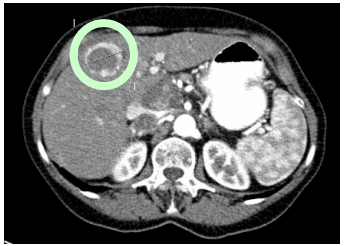
- Sustained stabilization
- Response after initial progression



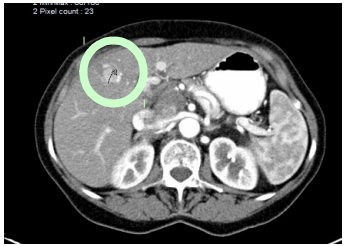
Baseline



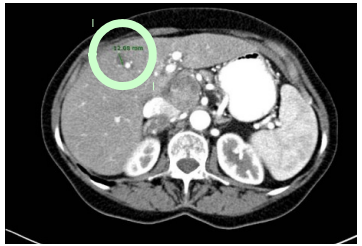
Post 3 cycles



Post 4 cycles



Post 6 cycles



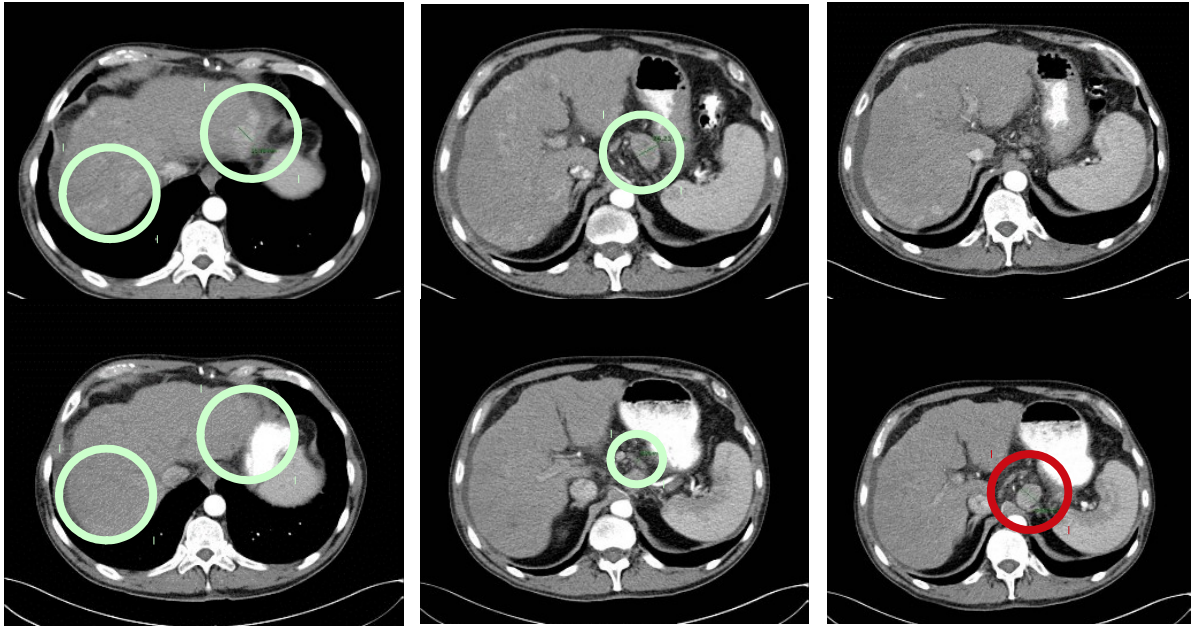
Post 8 cycles

Special Patterns of Response to I-O Agents

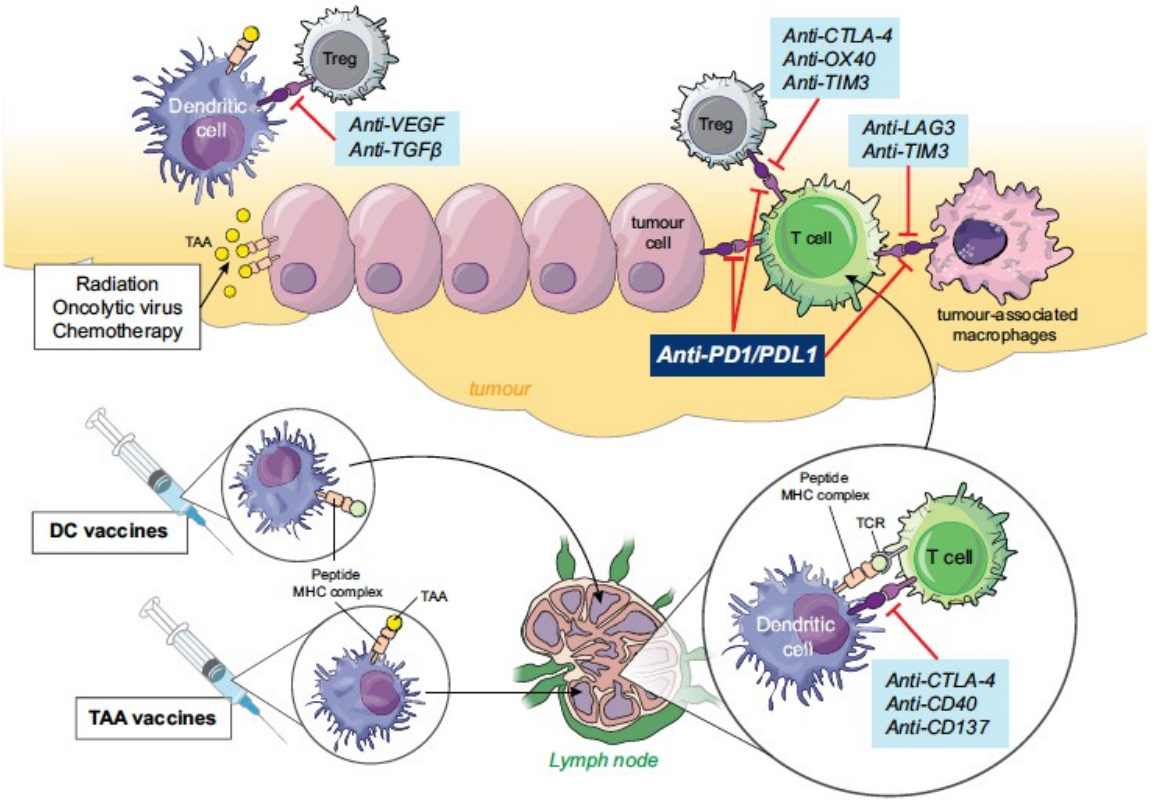
- Sustained stabilization
- Response after initial progression
- Response/control in the presence of new lesions
- Heterogenous response

Baseline

After 2 courses



Improving the Effect of PD-1/PD-L1 Blockade



Greten T, Sangro B, et al. J Hepatol 2017

Ongoing Clinical Trials Testing IO Agents in HCC

Anti-PD-1/PD-L1 agent	Combining agent	Mechanism of action	Patients	Population	NCT
Combinations with other immunotherapies					
Nivolumab	Ipilimumab	anti-CTLA4	620 *	HCC	01658878
Durvalumab	Tremelimumab	anti-CTLA4	144	HCC	02519348
Nivolumab	Pexavec	GMCSF-armed oncolytic virus	30	HCC	03071094
Combinations with antiangiogenics					
Durvalumab	Ramucirumab	anti-VEGFR2 mAb	114	HCC +	02572687
Pembrolizumab	Lenvatinib	TKI	30	HCC	03006926
Pembrolizumab	Nintedanib	TKI	18	HCC +	02856425
SHR-1210	Apatinib	TKI	30	HCC +	02942329
PDR001	Sorafenib	TKI	50	HCC	02988440

HCC+: HCC and other histologies

Ongoing Clinical Trials Testing IO Agents in HCC

Anti-PD-1/PD-L1 agent	Combining agent	Mechanism of action	Patients	Population	NCT
Combinations with other targeted agents					
Nivolumab	Galunisertib	TGF-beta inhibitor	75	HCC	02423343
Nivolumab	CC-122	Pleiotropic pathway modifier	50	HCC	02859324
Pembrolizumab	XL888	Hsp90 inhibitor	50	HCC +	03095781
PDR001	INC280	c-met inhibitor	108	HCC	02474537
PDR001	FGF401	FGFR4 inhibitor	238	HCC	02325739
Combinations with locoregional therapies					
Nivolumab	TACE	Ischemia	14	HCC	03143270
Nivolumab	Y90	Beta radiation	40	HCC	03033446
Nivolumab	Y90	Beta radiation	35	HCC	02837029
Pembrolizumab	Y90	Beta radiation	30	HCC	03099564

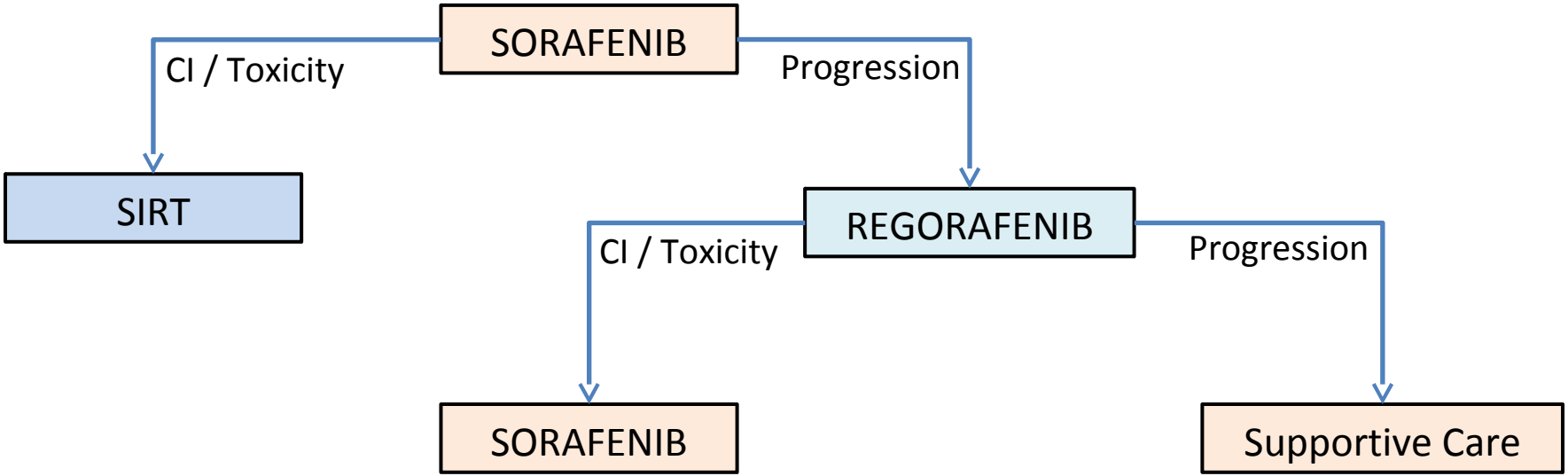
HCC+: HCC and other histologies

1st Line Clinical Trials in Advanced HCC

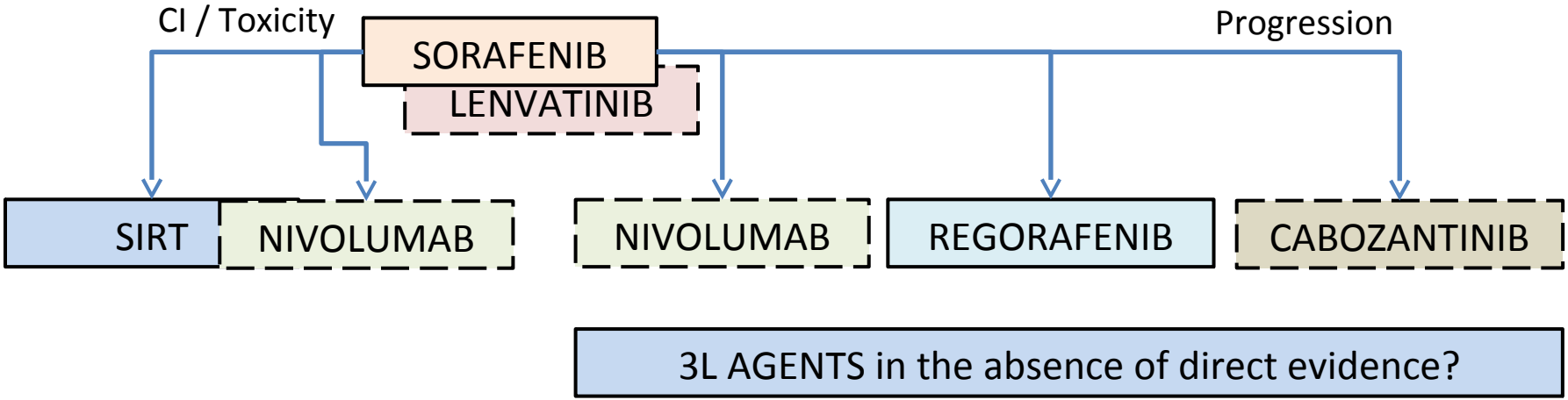
Acronym	Agents	No. Patients	Completion Date
SORAMIC	SIRT + Sorafenib vs. Sorafenib	665	2017
STOP-HCC	SIRT + Sorafenib vs. Sorafenib	400	2018
CheckMate-459	Nivolumab vs. Sorafenib	726	2018
Himalaya	Durvalumab + Tremelimumab vs. Durvalumab vs. Sorafenib	1200	2020

NCT02576509; NCT03298451; NCT01126645; NCT01556490

Systemic Therapy of HCC 2017



Systemic Therapy of HCC 2018?



Take Home Messages

- Patients with advanced HCC now may benefit from a broader spectrum of systemic targeted therapies
  - Sorafenib (and Lenvatinib?) and eventually SIRT in 1L patients
  - Regorafenib, Cabozantinib and Nivolumab in 2L patients

- Efforts now should focus on
  - Combination of systemic therapies (with strong rationale).
  - Combination with intraarterial therapies (TACE and SIRT) for intermediate stage patients
  - Adjuvant therapy for early stage patients

The International Liver Cancer Association Announces its 12th Annual Conference

SAVE THE DATE ILCA 2018

14–16 September 2018
London, United Kingdom

ILCA
International Liver Cancer Association

PRIMING KNOWLEDGE
IN LIVER CANCER
ACROSS DISCIPLINES

The international multidisciplinary forum for liver cancer experts around the latest innovations in research and care

www.ilca2018.org

Abstract submissions open in January 2018