Are we making any progress at all in the treatment of advanced hepatocellular carcinoma?

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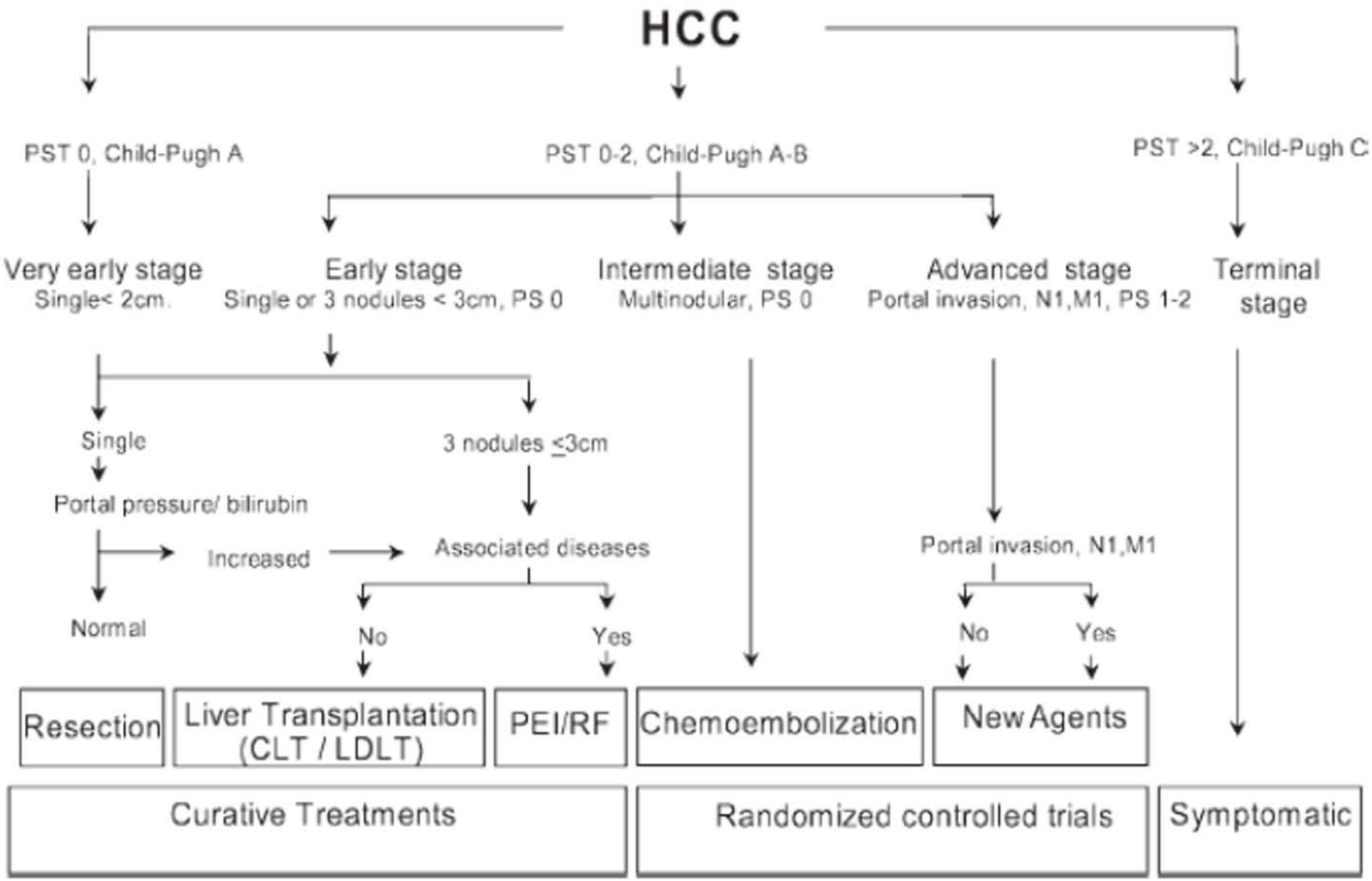
DISCLOSURES

Advisory Committee	Amgen Inc, Bayer HealthCare Pharmaceuticals, Genentech BioOncology

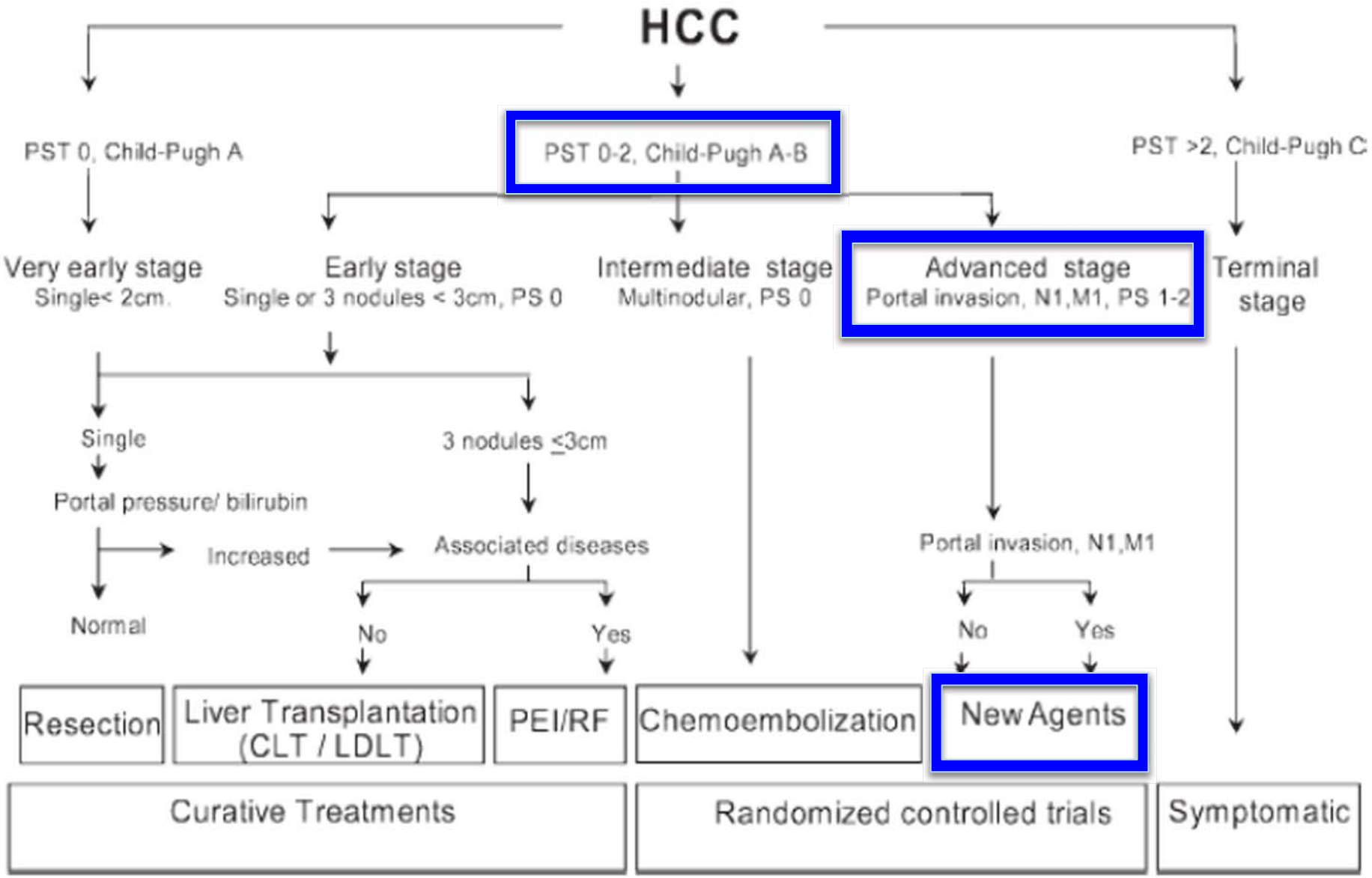
INTRODUCTION

- Most HCC is diagnosed at advanced stage (ie, unresectable/non-transplantable)
- Therapeutic choices for advanced HCC depend on tumor and liver characteristics

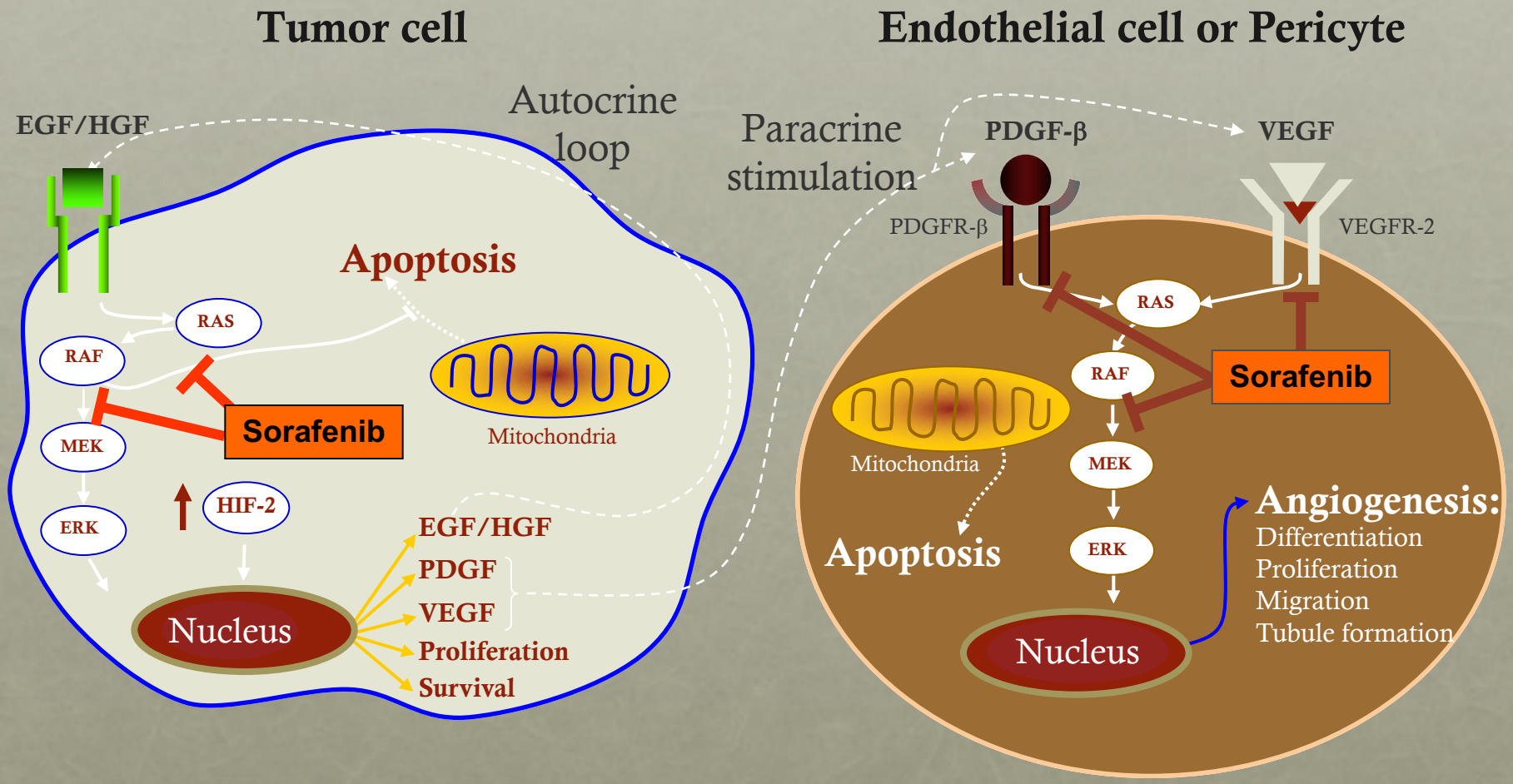
BCLC Algorithm



BCLC Algorithm- Advanced

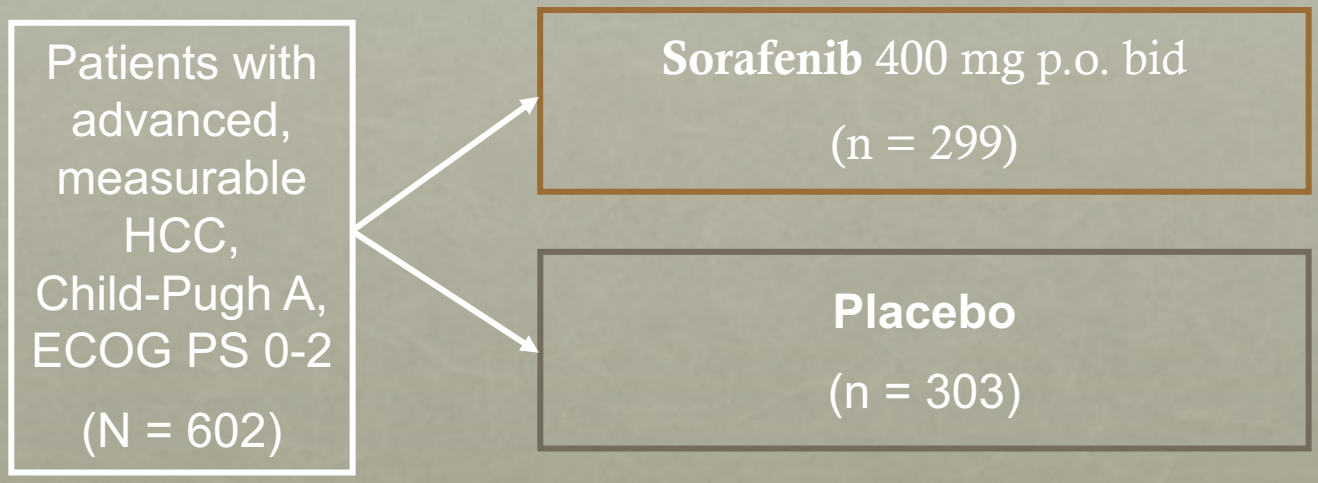


Sorafenib MOA



Wilhelm S et al. *Cancer Res.* 2004;64:7099-7109.

Phase III SHARP Trial: Sorafenib vs Placebo in Advanced HCC

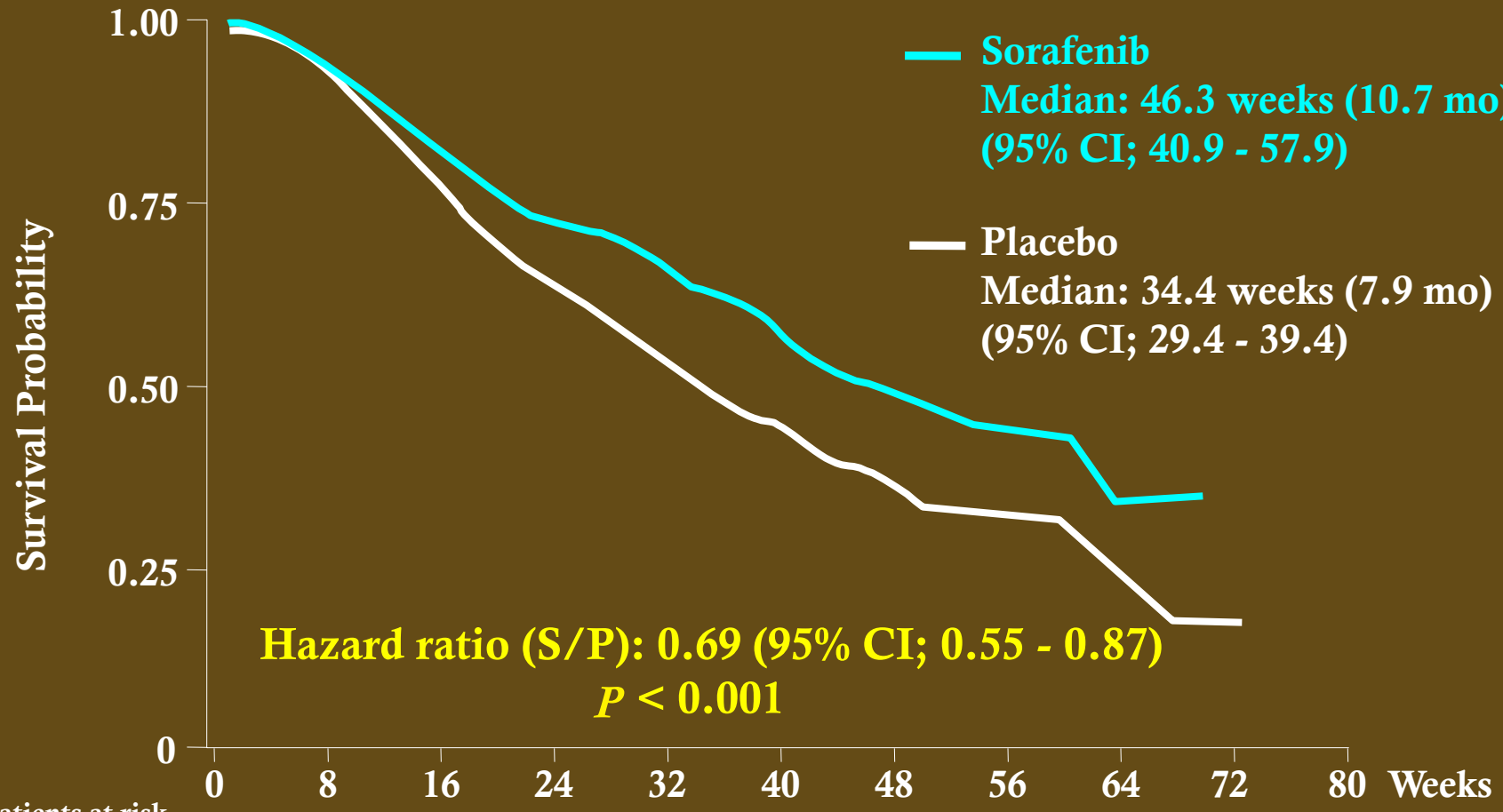


- Primary endpoints: OS and time to symptomatic progression
- Secondary endpoints: radiologic progression, disease control rate, and AEs

AEs=adverse events; ECOG=Eastern Cooperative Oncology Group; OS=overall survival; PS=performance status.

Llovet. *N Engl J Med*. 2008;359:378.

Overall Survival



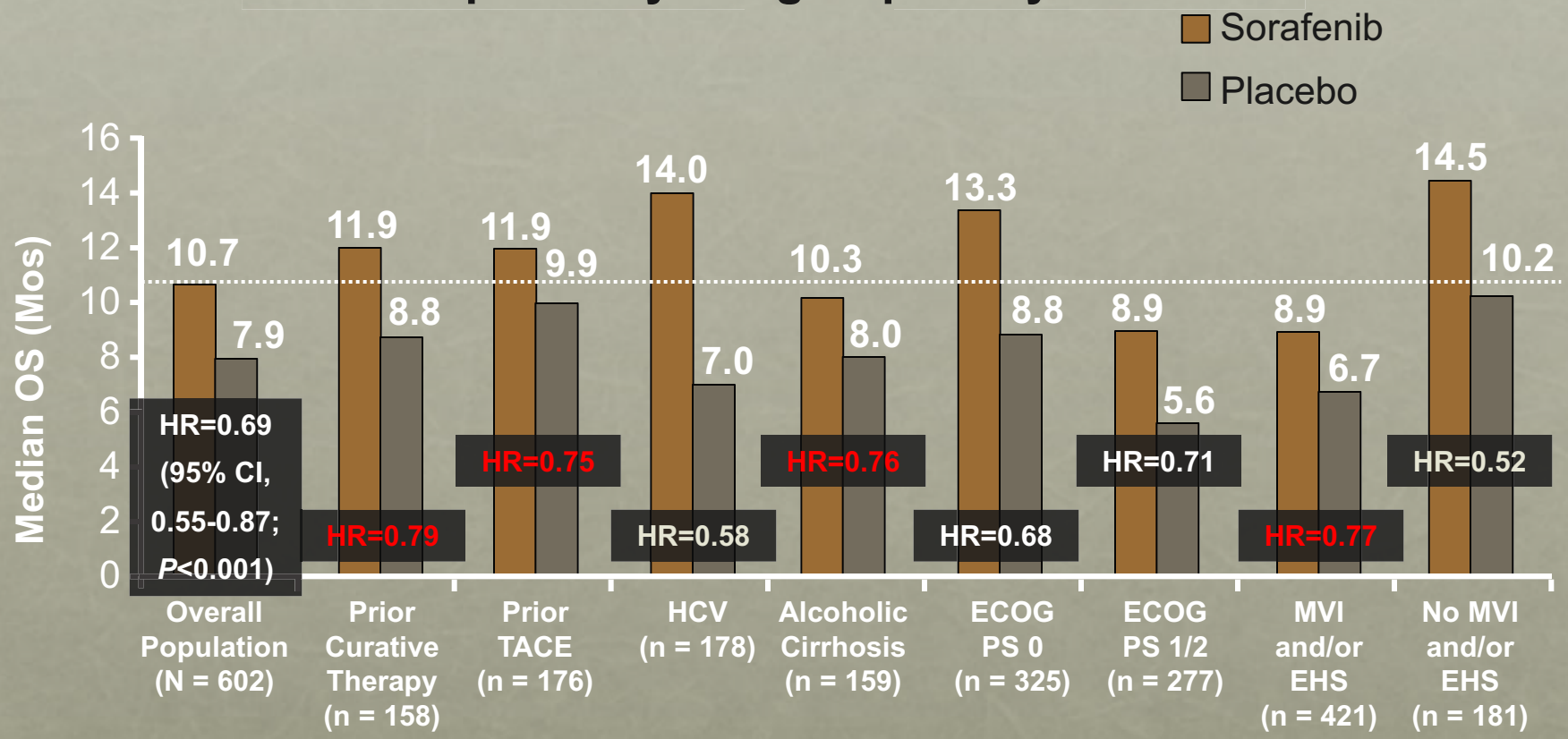
Patients at risk

Sorafenib:	299	274	241	205	161	108	67	35	12	0	0
Placebo:	303	276	224	179	126	78	47	25	7	2	0

Llovet JM, et al. *N Engl J Med.* 2008;359: 378-390

YEARS THEN PASSED….

Phase III SHARP Trial: Subgroup Analysis



EHS = extrahepatic spread; HCV = hepatitis C virus; MVI = macroscopic vascular invasion.

Llovet. *N Engl J Med*. 2008;359:378; Galle. *EASL*. 2008; Bolondi. *ASCO GI*. 2008 (abstr 129); Craxi. *ASCO*. 2008. (abstr 15591); Raoul. *ASCO*. 2008. (abstr 4587); Sherman. *ASCO*. 2008 (abstr 4584).

REGORAFENIB

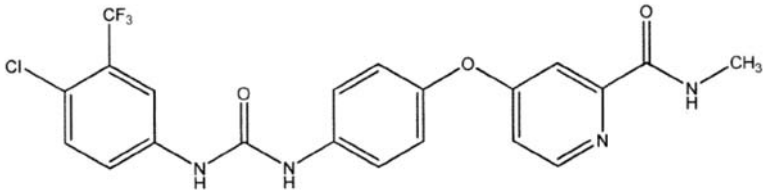


Figure 2: Sorafenib

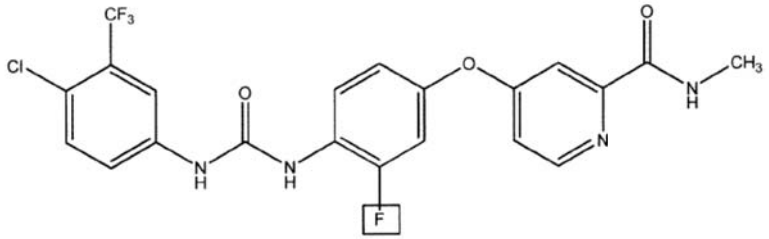


Figure 3: Fluoro-Sorafenib

Biochemical activity of regorafenib and sorafenib

	Mean IC_{50} (nM) ± SD	
Biological target	Regorafenib	Sorafenib
VEGFR-1	13 ± 0.4	–
Murine VEGFR-2	4.2 ± 1.6	15 ± 6
Murine VEGFR-3	46 ± 10	20 ± 6
TIE2	311 ± 46	–
PDGFR-β	22 ± 3	57 ± 20
Flt-3	–	58 ± 20
FGFR-1	202 ± 18	580 ± 100
KIT	7 ± 2	68 ± 21
RET	1.5 ± 0.7	–
RAF-1	2.5 ± 0.6	6 ± 3
BRAF	28 ± 10	22 ± 6
BRAF V600E	19 ± 6	38 ± 9

IC 50 half maximal inhibitory concentration

Target Oncol. 2015; 10(2): 199–213.

REGORAFENIB IN HCC

- HCC patients with documented radiological progression during sorafenib treatment

- Stratified by:
  - Geographic region (Asia vs ROW)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (<400 ng/mL vs ≥400 ng/mL)

R
2:1

Regorafenib
160 mg po once daily
3 weeks on / 1 week off
(4-week cycle)
(n=379)

Placebo
(n=194)

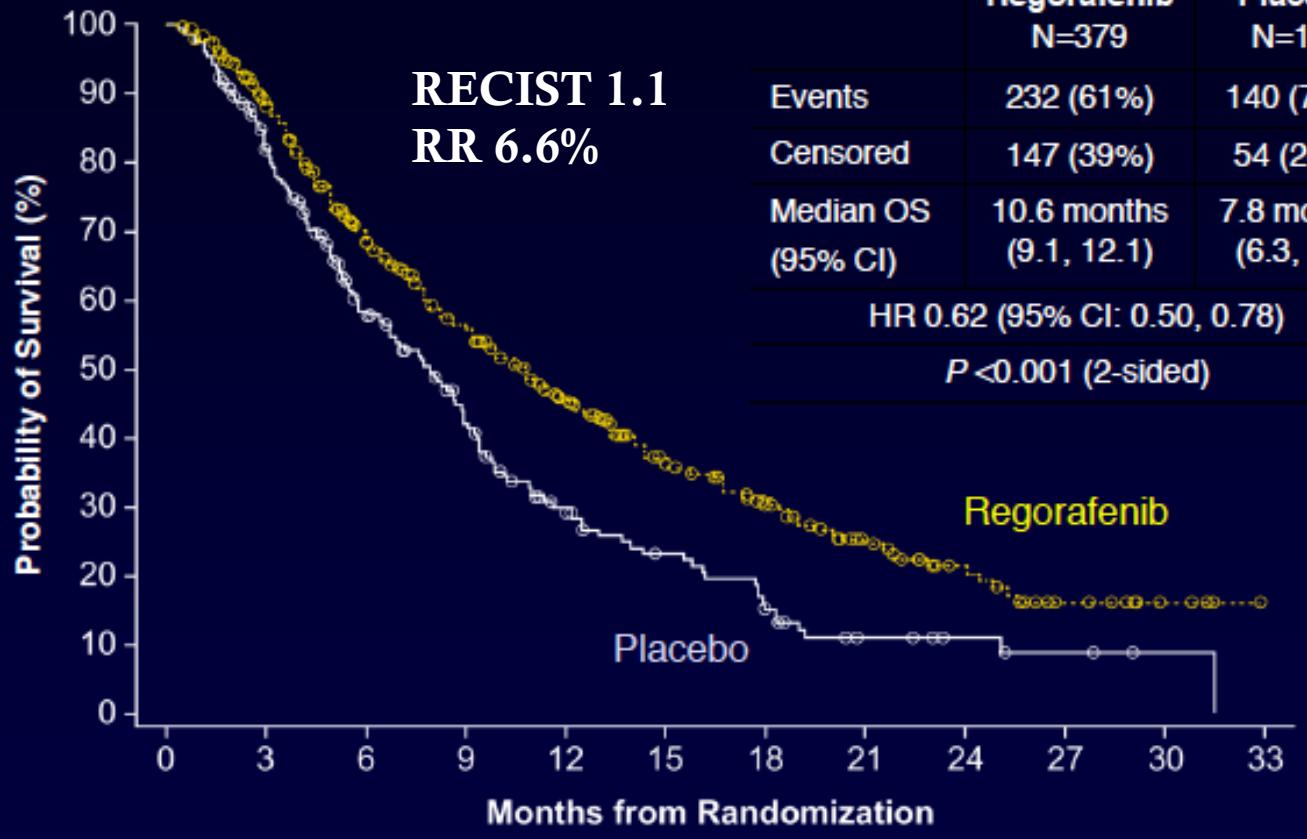
Bruix J et al, ESMO World GI Congress, 2016 Abstract LBA03

REGO ADVERSE EVENTS

	Treatment-emergent						Drug-related treatment-emergent					
	Regorafenib n=374			Placebo n=193			Regorafenib n=374			Placebo n=193		
	Any grade	Gr 3	Gr 4	Any grade	Gr 3	Gr 4	Any grade	Gr 3	Gr 4	Any grade	Gr 3	Gr 4
HFSR	53%	13%	NA	8%	1%	NA	52%	13%	NA	7%	1%	NA
Fatigue	41%	9%	NA	32%	5%	NA	30%	6%	NA	19%	2%	NA
Hypertension	31%	15%	<1%	6%	5%	0	23%	13%	<1%	5%	3%	0
Bilirubin increased	29%	10%	1%	18%	8%	3%	19%	6%	<1%	4%	2%	0
AST increased	25%	10%	1%	20%	10%	2%	13%	4%	1%	8%	5%	1%
Ascites	16%	4%	0	16%	6%	0	2%	1%	0	1%	1%	0
Anemia	16%	4%	1%	11%	5%	1%	6%	1%	<1%	1%	1%	0
Hypophosphatemia	10%	8%	1%	2%	2%	0	6%	4%	1%	1%	1%	0
Lipase increased	7%	5%	2%	3%	2%	0	5%	4%	<1%	2%	1%	0

Bruix J et al, ESMO World GI Congress, 2016 Abstract LBA03

OVERALL SURVIVAL



	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)		

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

Bruix J, et al. Presented at World Congress on Gastrointestinal Cancer 2016

Abstract LBA 101

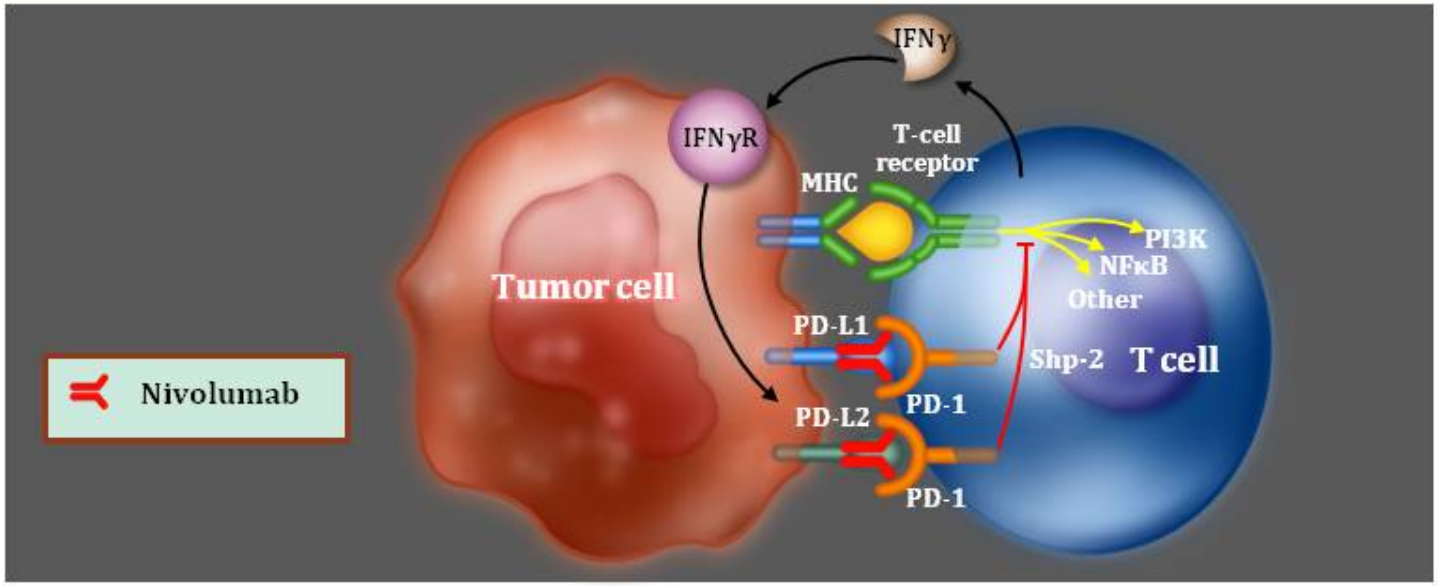
Phase 1/2 Safety and Antitumor Activity of Nivolumab in Patients With Advanced Hepatocellular Carcinoma (HCC): CA209-040

Anthony B. El-Khoueiry,[1] Ignacio Melero,[2] Todd S. Crocenzi,[3] Theodore H. Welling III,[4] Thomas Yau,[5] Winnie Yeo,[5] Akhil Chopra,[6] Joseph F. Grosso,[7] Lixin Lang,[7] Jeffrey Anderson,[7] Christine dela Cruz,[7] Bruno Sangro[2]

[1]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [2]Clinica Universidad de Navarra and CIBERehd, Pamplona, Spain; [3]Providence Cancer Center, Portland, OR, USA; [4]University of Michigan, Ann Arbor, MI, USA; [5]University of Hong Kong, China; [6]Johns Hopkins Singapore International Medical Centre, Singapore; [7]Bristol-Myers Squibb, Princeton, NJ, USA

PRESENTED AT: ASCO Annual '15 Meeting

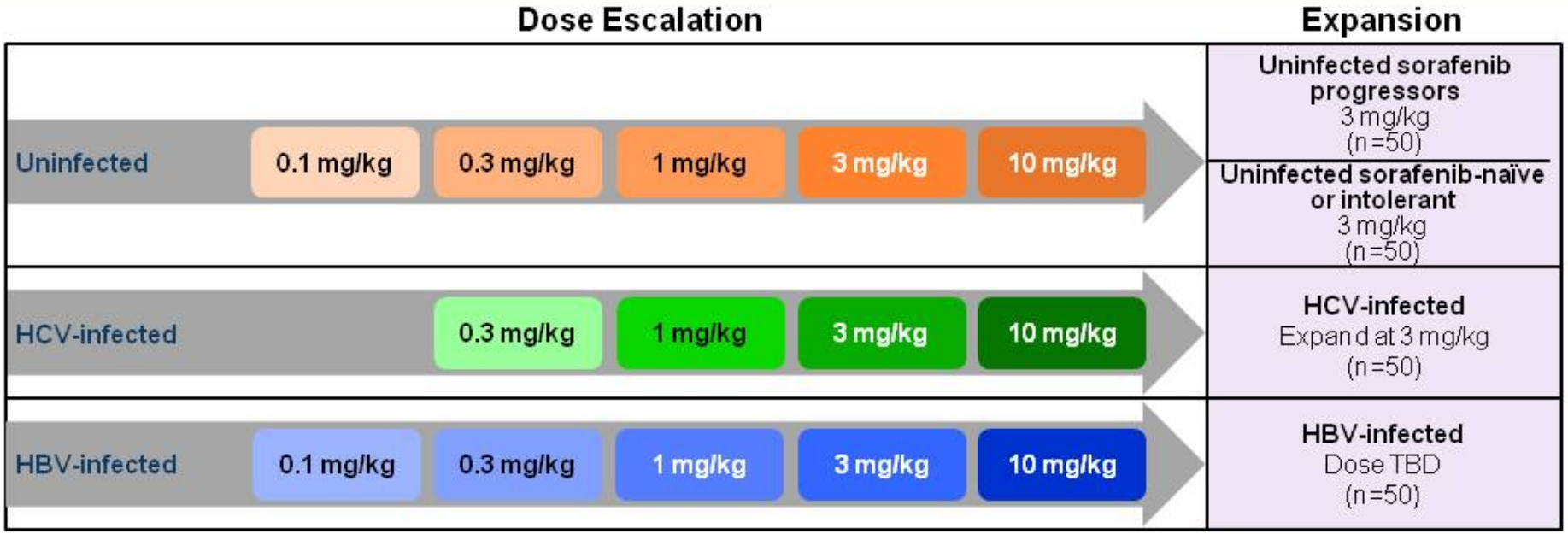
Nivolumab and Immune Checkpoint Inhibition



- Nivolumab is a fully human IgG4 anti-PD-1 monoclonal antibody that selectively blocks the interaction between PD-1 and PD-L1/PD-L2,[1] restoring T-cell immune activity directed against the tumor cell

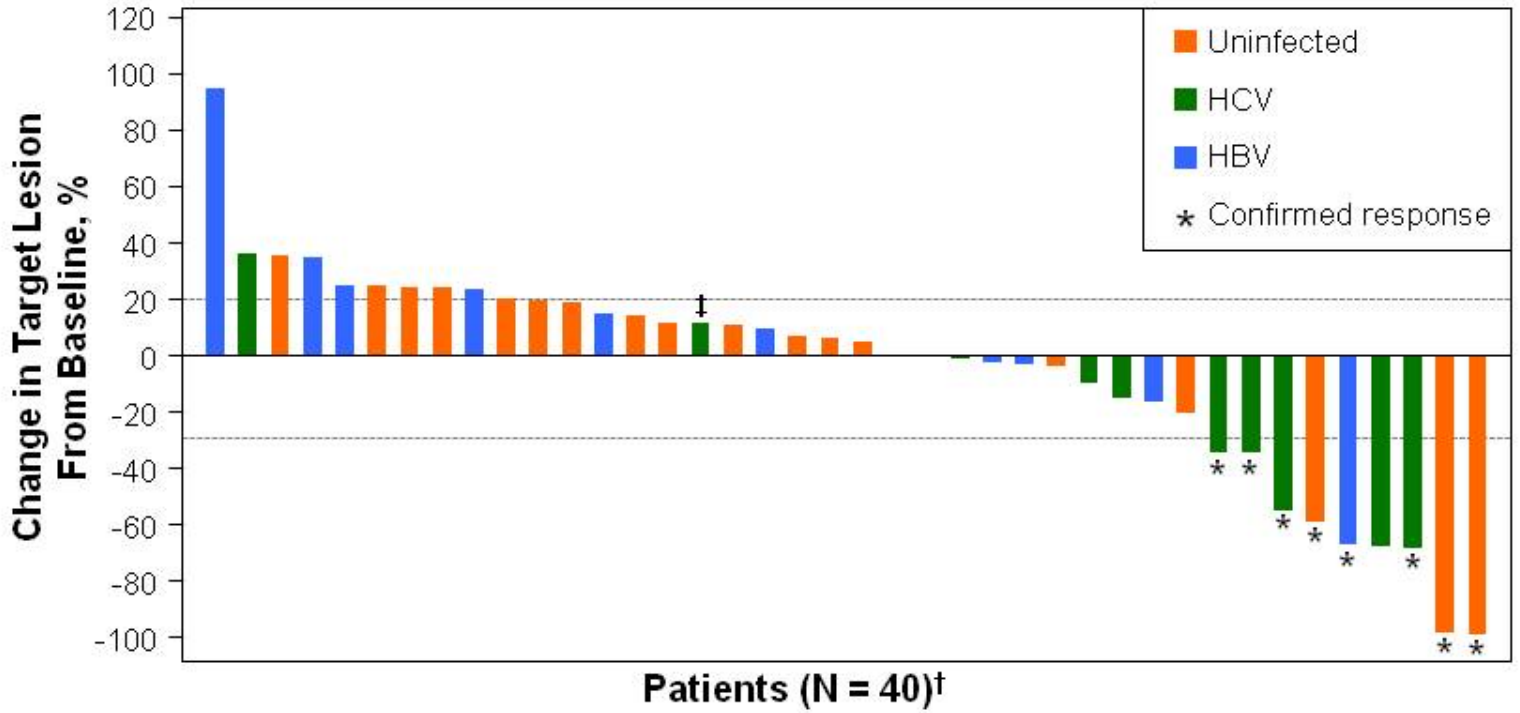
1. Topalian SL, et al. *N Engl J Med*. 2012;366:2443-2454

Study Design



- Patients received nivolumab Q2W for up to 2 years (maximum of 48 doses), depending on response
  - Imaging for disease assessment performed every 6 weeks
- A 3+3 design was used in the phase 1 dose escalation phase
- Here, we report interim results from the ongoing dose escalation phase and part of the expansion phase

Maximal Change in Target Lesions From Baseline



†2 uninfected patients not shown: 1 had disease progression before the first assessment; 1 had a maximal change of +23%
‡Patient with resolved HCV infection

Treatment-Related Adverse Events

	Total (N=47)		
	Any Grade	Grade 3	Grade 4
Patients with any treatment-related adverse event, n (%)	**32 (68)**	**8 (17)**	**1 (2)**
Treatment-related adverse events reported in ≥5% of patients			
AST increased	9 (19)	5 (11)	0
Lipase increased	8 (17)	3 (6)	1 (2)
Rash	8 (17)	0	0
ALT increased	7 (15)	4 (9)	0
Amylase increased	7 (15)	0	0
Pruritus	6 (13)	0	0
Hypoalbuminemia	4 (9)	0	0
Anemia	3 (6)	1 (2)	0
Fatigue	3 (6)	1 (2)	0
Asthenia	3 (6)	0	0
Diarrhea	3 (6)	0	0
Hyponatremia	3 (6)	0	0

- There were no grade 5 treatment-related AEs

WHAT ELSE IS OUT THERE?

- Awaiting results of lenvatinib phase III trial (versus sorafenib)
- cMET inhibition for cMET + (amplified, overexpressing?) HCC
- Combination immunotherapy strategies
- Strategies based on molecular characterization (FGFR, CDK4/6, etc.)