The treatment of advanced hepatocellular carcinoma in 2017

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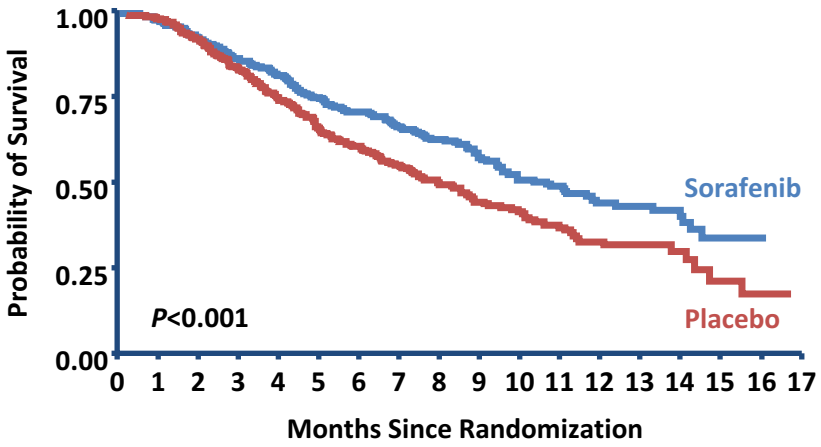
Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP
Consulting Agreements	Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation, CytomX Therapeutics, Genentech BioOncology, Transgene

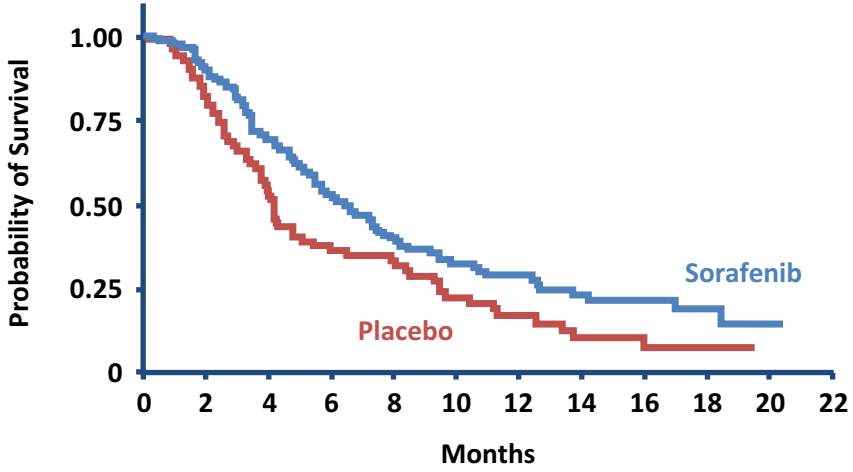
Treatment of Advanced HCC: 2007–2016

Sorafenib Outcomes in Western Patients[1]



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

The Challenge: first-line randomized phase 3 trials

Phase 3	Target(s)	TTP (months)	OS (months)
Sunitinib vs. Sorafenib (Cheng AL et al)	VEGFRs, PDGFRs, c-kit, (Flt) 3, RET	4.1 vs. 3.8 HR=1.13 (95% CI, 0.98–1.31); P=0.16	7.9 vs. 10.2 HR=1.30 (95% CI, 1.13–1.50); two-sided $p<0.0014$
Brivanib vs. Sorafenib (Johnson et al)	VEGFR2, FGFR	4.2 vs 4.1 HR 1.01 (95% CI, 0.88-1.16)	9.5 vs. 9.9 HR, 1.06; 95% CI, 0.93–1.22; p<0.373
Linifanib vs. Sorafenib (Cainap et al)	VEGFR and PDGFR	5.4 vs. 4 HR= 0.76 (95% CI, 0.64–0.89); $P < 0.001$	9.1 vs. 9.8 HR = 1.04 (95% CI, 0.89–1.22); P=NS
Sorafenib+Erlotinib Vs. Sorafenib+placebo (Zhu A et al)	VEGFR1,2,3, Ras, Raf, EGFR	3.2 vs 4 HR = 1.14 (95% CI, 0.94–1.36) $P = 0.91$	9.5 vs. 8.5 HR = 0.93 (95% CI, 0.78–1.1); $P = 0.2$
Doxorubicin+Sorafenib vs. Sorafenib CALGB 80802 (Abou-Alfa GK et al)	VEGFR1,2, PDFG, Ras, Raf	3.6 vs. 3.2 HR = 0.90, (95% CI 0.72-1.2)	9.3 vs. 10.5 HR= 1.06 (95% CI 0.8-1.4)

Cheng AL, et al. *J Clin Oncol.* 2013;31:4067–75
Johnson PJ et al. *J Clin Oncol*. 2013;31:3517-24
Cainap C et al. *J Clin Oncol.* 2015 Jan 10;33(2):172-9
Zhu A et al. *J Clin Oncol.* 2015 Feb 20;33(6):559-66
Abou-Alfa GK et al. *J Clin Oncol 34,* 2016 (suppl 4S; abstr 192*)*

Lenvatinib (LEN) in first line HCC

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

- Pts with unresectable HCC
- No prior systemic therapy

→ Lenvatinib N=478

→ Sorafenib N=476

Non-inferiority
Primary endpoint OS

Most common LEN TEAEs were hypertension (42%), diarrhea (39%), decreased appetite (34%), decreased weight (31%), and fatigue (30%).

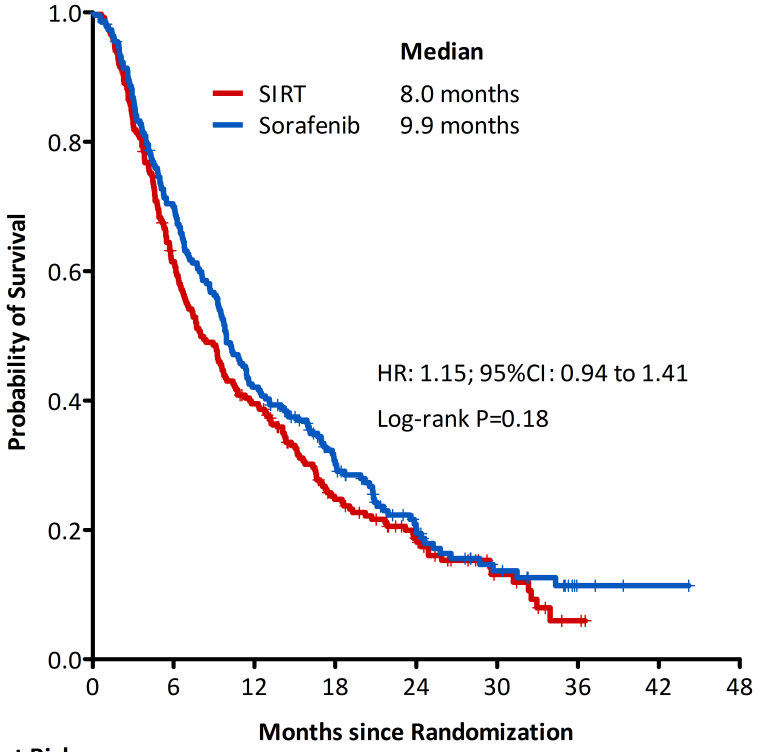
Outcomes	LEN	SOR	HR
Median OS, mos (95% CI)	13.6 (12.1–14.9)	12.3 (10.4–13.9)	0.92 (0.79–1.06)
Median PFS, mos (95% CI)*	7.4 (6.9–8.8)	3.7 (3.6–4.6)	0.66 (0.57–0.77)
Median TTP, mos (95% CI)*	8.9 (7.4–9.2)	3.7 (3.6–5.4)	0.63 (0.53–0.73)
ORR, n (%)*	115 (24)	44 (9)	

*P< 0.00001

Cheng AL et al, ASCO 2017

Y90 radioembolization vs. sorafenib
The SARAH trial

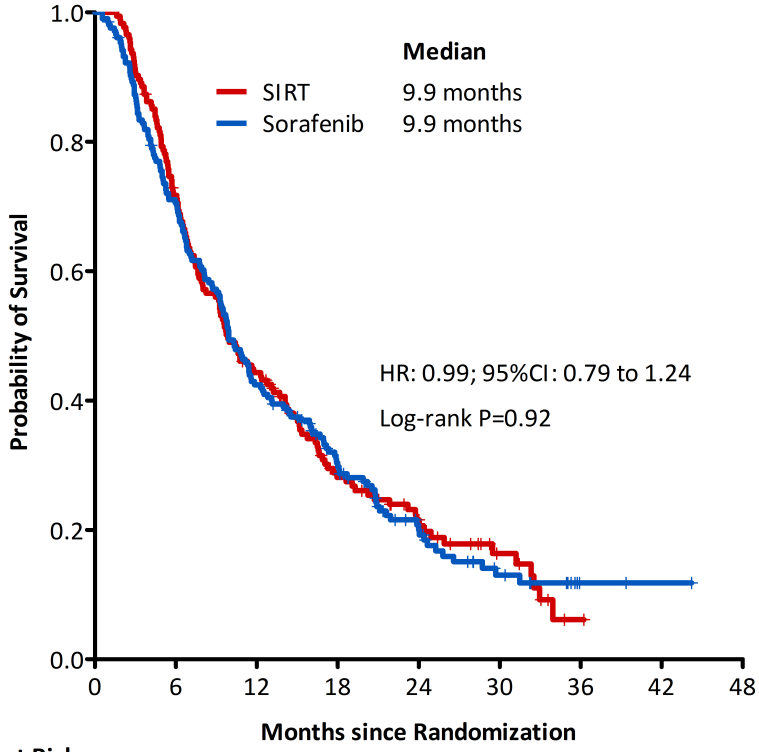
Intention to treat population
N=459



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

Vilgrain V, Bouattour M, et al, EASL 2017

Tolerance and safety

SARAH

	SIRT	Sorafenib
Nb of patients with AE (%)	173 (76.5%)	203 (94.0%)
Median nb of AEs/patient	5	10

Treatment-related AES	SIRT Nb of patients (≥G 3)	Sorafenib Nb of patients (≥G 3))
Fatigue	94 (20)	140 (41)
Weight loss	14 (0)	46 (6)
Alopecia	0 (0)	35 (0)
Hand foot skin reaction	1(1)	45 (12)
Pruritus	7 (1)	19 (1)
Diarrhea	29 (3)	146 (30)
Abdominal pain	46 (6)	63 (14)
Hypertension	6 (0)	28 (5)

VilgrainV, Bouattour M, et al, EASL 2017

The Challenge: second line randomized trials

Phase 3	Target(s)	TTP or PFS (months)	OS (months)
Ramucirumab vs. placebo (Zhu A et al)	IgG1 Ab to VEGFR2	2.8 vs. 2.1 HR 0.63 P<0.0001	9.2 vs 7.6 HR 0·87 [95% CI 0·72–1·05]; p=0·14
Brivanib vs. placebo (Llovet J et al)	VEGFR2 and FGFR	4.2 vs. 2.7 HR = 0.56 (95% CI, 0.42–0.78); *P* = 0.001	9.4 vs. 8.2 HR = 0.89 (95% CI, 0.69–1.15); *P* = 0.33
Everolimus vs. placebo (Zhu A et al)	mTOR	3 vs 2.6 HR = 0.93 (95% CI, 0.75–1.15); P: NA	7.6 versus 7.3 HR = 1.05 (95% CI, 0.86–1.27) *P* = 0.67
METIV-HCC Tivantinib vs. BSC (Rimassa L et al)	MET (biomarker selection trial)	2.1 vs. 2.0 HR = 0.96 (0.75-1.22), P = 0.72	8.4 vs. 9.1 m HR = 0.97 (0.75-1.25) P = 0.81

BSC = best supportive care

Zhu A et al. Lancet Oncol. 2015 Jul;16(7):859-70
Llovet J et al. J Clin Oncol, 31 (28) (2013):3509-16
Zhu A et al. ASCO Meeting Abstracts, 32 (3_suppl) (2014)
Rimassa L et al. ASCO annual meeting 2017

RESORCE trial design

- Patients with HCC 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)

- 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

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

Baseline characteristics

	Regorafenib (n=379)	**Placebo** (n=194)
BCLC stage, A / B / C	0.3% / 14% / 86%	0% / 11% / 89%
Child-Pugh class*		
A	98%	97%
B	1%	3%
Macrovascular invasion (MVI)	29%	28%
Extrahepatic disease (EHD)	70%	76%
MVI and/or EHD	80%	84%
Alpha-fetoprotein ≥400 ng/mL	43%	45%
Cirrhosis present†	75%	74%

*Child-Pugh class was missing in 1 patient (0.3%) in the regorafenib group
†Investigator assessment based on medical history
BCLC, Barcelona Clinic Liver Cancer

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)		

	mRECIST		RECIST 1.1	
	Regorafenib n=379	Placebo n=194	Regorafenib n=379	Placebo n=194
Response rate	10.6%	4.1%	6.6%	2.6%
	P=0.01 (2-sided)		*P*=0.04 (2-sided)	
Disease control rate	65.2%	36.1%	65.7%	34.5%
	P<0.001 (2-sided)		*P*<0.001 (2-sided)	

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

Treatment-emergent grade 3 or 4 adverse events occurring in at least 5% of patients in either group

	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

AST, aspartate aminotransferase; HFSR, hand-foot skin reaction; NA, not applicable
NCI-CTCAE v4.03

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

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

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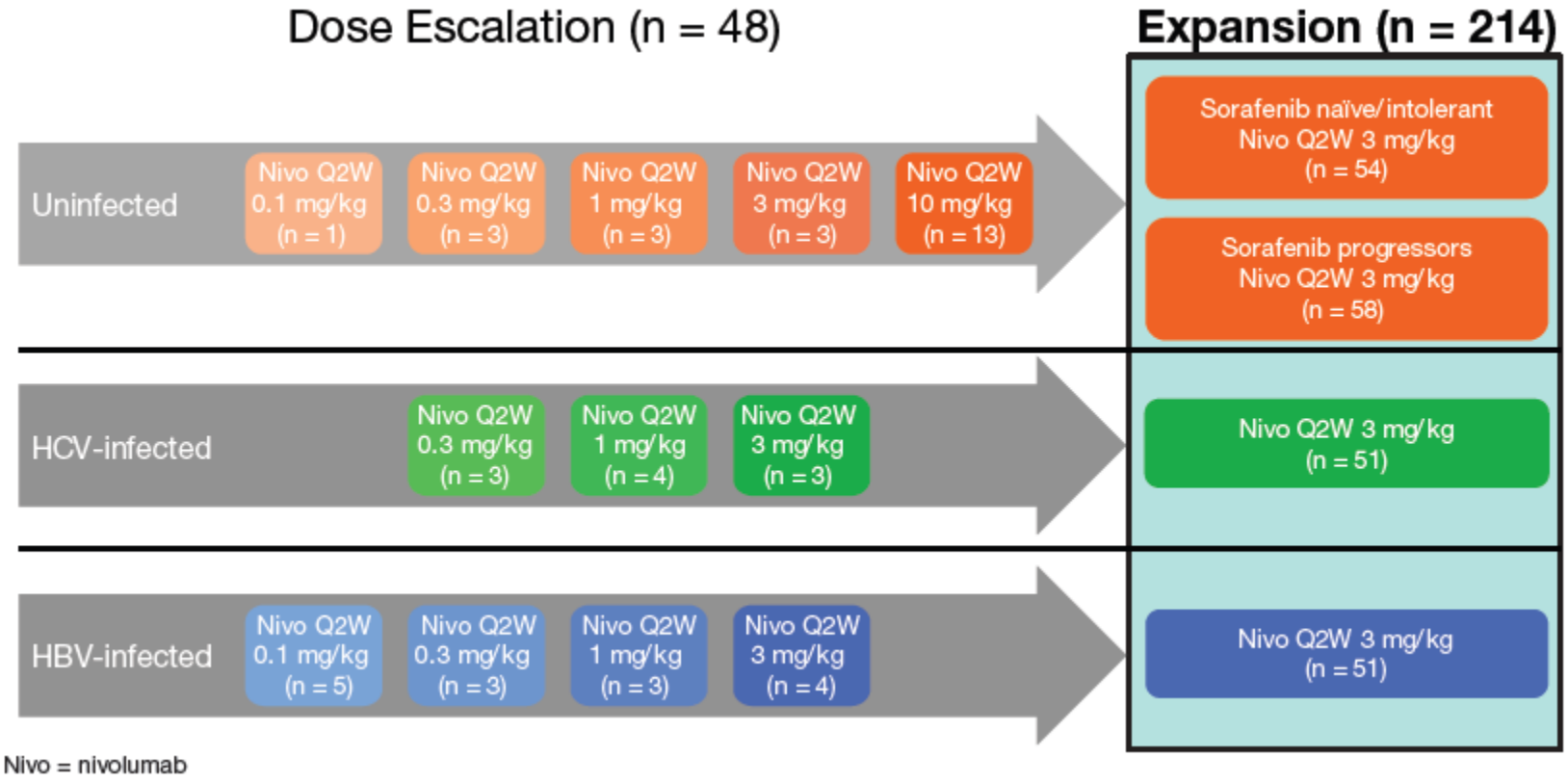


Nivo = nivolumab

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 (19–83)	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

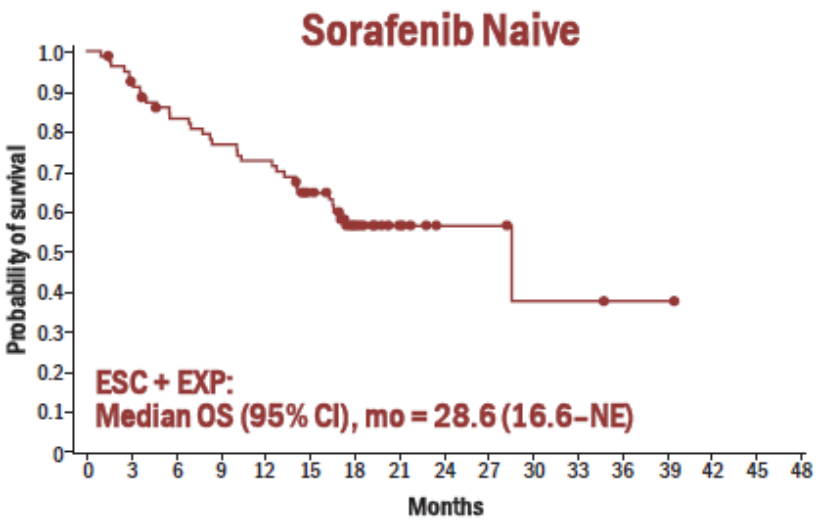
	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Objective response*	13 (23%; 13 to 36)	12 (21%; 11 to 34)	10 (20%; 10 to 34)	7 (14%; 6 to 26)	42 (20%; 15 to 26)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response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

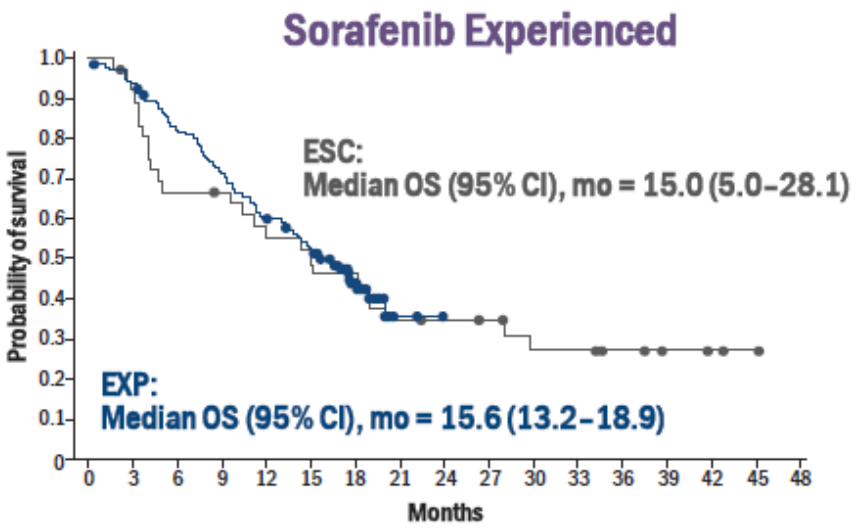
Unless otherwise indicated, data are n (%; 95% CI); n (%); months (95% CI); or % (95% CI). HCV=hepatitis C virus. HBV=hepatitis B virus. KM=Kaplan-Meier estimate. NR=not reached. NE=not estimable. RECIST=Response Evaluation Criteria In Solid Tumors. *Determined by investigator assessment using RECIST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

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

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

Nivolumab efficacy based on sorafenib exposure in checkmate 040





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.

Median duration of response
- Sorafenib naïve: 17.1 months (4.2-17.1+)
- Sorafenib experienced: 16.59 months (3.2-16.8+)

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

A new reality for patients with advanced HCC

First line	Second line	Third line
Sorafenib Lenvatinib?	Regorafenib Ongoing phase 3 of Cabozantinib vs. placebo	
Immunotherapy? Ongoing phase 3 of Nivolumab versus Sorafenib	Immunotherapy? Ongoing phase 3 of Pembrolizumab versus BSC	