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Nivolumab in Sorafenib-Naive and -Experienced Patients With Advanced Hepatocellular Carcinoma: CheckMate 040 Study

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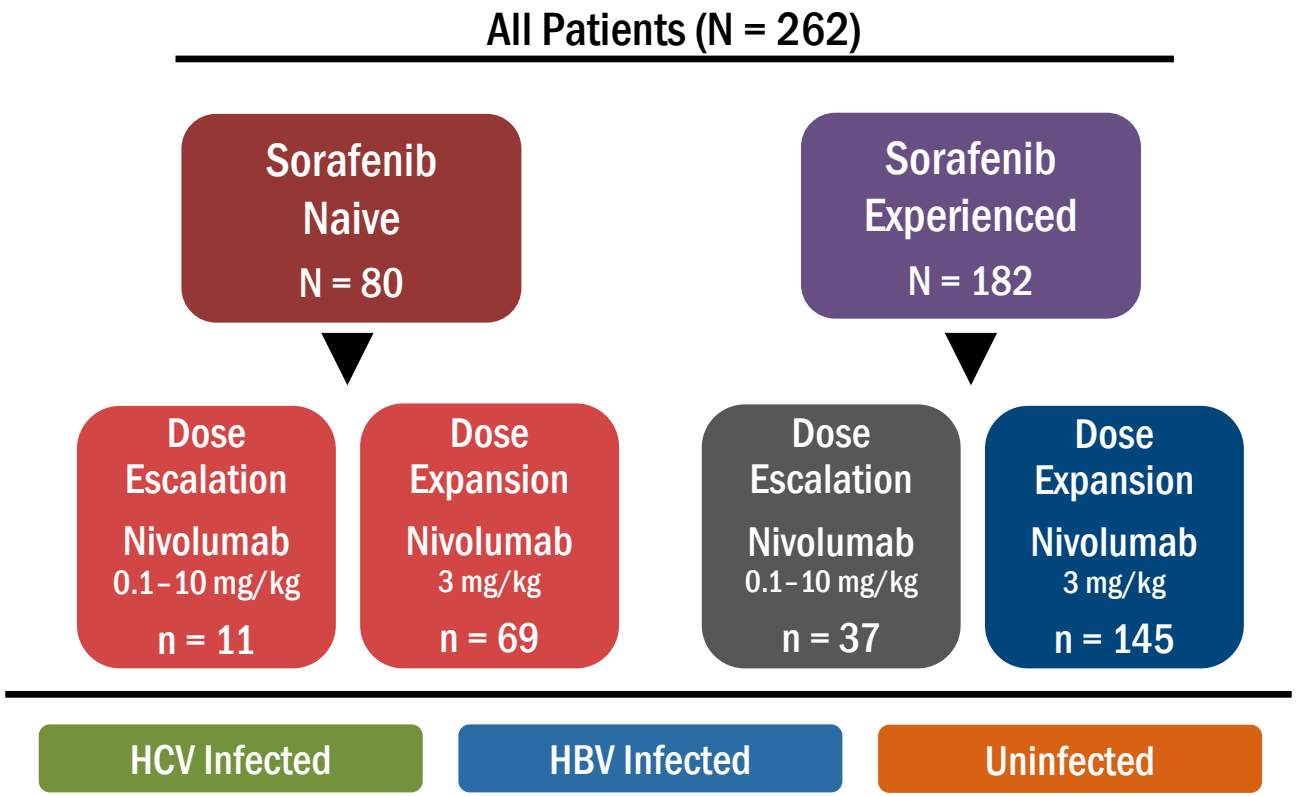
Background

- Treatment with the multikinase inhibitor sorafenib is currently the only first-line systemic therapy option for patients with advanced HCC[1]
  - A large majority of patients progress on first-line sorafenib[2]
  - Regorafenib, recently approved as a second-line therapy, provided a median overall survival of 10.6 months in a phase 3 trial[3]
- Nivolumab is a fully human IgG4 monoclonal antibody inhibitor of the PD-1 receptor that restores T-cell–mediated antitumor activity
- CheckMate 040 (NCT01658878) is a phase 1/2 multicohort of study of nivolumab in patients with advanced HCC, and has demonstrated:
  - Substantial tumor reductions and objective response rates (ORRs) of 15%–20% irrespective of line of therapy[4]
  - Disease control rates of 58% in the dose-escalation phase and 64% in the dose-expansion phase[4]
  - Objective responses were observed regardless of PD-L1 expression (PD-L1 ≥ 1%: ORR 26% [9/34]; PD-L1 < 1%: ORR 19% [26/140])[4]
- Sorafenib-naive and -experienced patients in the CheckMate 040 study have been assessed with extended follow-up

Methods

Figure 1. CheckMate 040 Study Design



- Median follow-up was 16.4 months in sorafenib-naive patients and 14.3 months and 14.9 months in sorafenib-experienced patients in the dose-escalation (ESC) and -expansion (EXP) phases, respectively

Study Endpoints

Primary

- Safety and tolerability (ESC)
- ORR (EXP)[a]

Secondary

- ORR (ESC)[a]
- Disease control rate
- Time to response
- Duration of response
- Overall survival

Other

- Biomarker assessments

ESC, dose-escalation phase; EXP, dose-expansion phase. [a] Using RECIST v1.1.

Methods

Assessments

- Tumor imaging (CT or MRI) every 6 weeks
- Tumor response was determined by blinded independent central review (BICR) and investigator assessment using RECIST v1.1, and also by BICR using modified RECIST (mRECIST)
- Tumor-cell PD-1 ligand 1 (PD-L1) expression was retrospectively assessed using biopsies (archival or fresh) collected at baseline

Eligibility Criteria

- Inclusion criteria included histologically confirmed advanced HCC not amenable to curative resection, and progression on 1 prior line of systemic therapy or intolerance or refusal of sorafenib
- For HBV-infected patients, viral load < 100 IU/mL and concomitant effective antiviral therapy was required
- Additional eligibility criteria have been described previously[4]

Results

Patients

- Demographics and baseline characteristics of sorafenib-naive patients and -experienced patients were comparable (**Table 1)**; prior sorafenib treatment characteristics are shown in **Table 2**
- Overall, patients were heavily pretreated, and extrahepatic metastases were present in the majority of patients regardless of prior therapy

Table 1. Baseline Characteristics

Patients	Sorafenib Naive ESC + EXP N = 80	Sorafenib Experienced ESC N = 37	Sorafenib Experienced EXP N = 145
Age, median (range), yr	65 (20–83)	58 (22–79)	63 (19–81)
Male, n (%)	68 (85)	27 (73)	112 (77)
Race, n (%)			
White	46 (58)	20 (54)	67 (46)
Asian	28 (35)	16 (43)	75 (52)
Black/other	6 (8)	1 (3)	3 (2)
BCLC stage, n (%)			
B	7 (9)	3 (8)	14 (10)
C	72 (90)	33 (89)	129 (89)
Extrahepatic metastases, n (%)	49 (61)	26 (70)	103 (71)
Vascular invasion, n (%)	27 (34)	14 (38)	41 (28)

Results

Table 1. Baseline Characteristics (cont)

Patients	Sorafenib Naive ESC + EXP N = 80	Sorafenib Experienced ESC N = 37	Sorafenib Experienced EXP N = 145
HCC etiology, n (%)			
HCV infected	25 (31)	5 (14)	30 (21)
HBV infected	8 (10)	15 (41)	43 (30)
Uninfected	47 (59)	17 (46)	72 (50)
Child-Pugh score, n (%)			
5	58 (73)	34 (92)	97 (67)
6	20 (25)	3 (8)	46 (32)
> 6	2 (3)	0	2 (1)
AFP ≥ 400 μg/L, n (%)[a]	27 (34)	12 (32)	55 (38)
PD-L1—expressing tumor cells, n (%)			
≥ 1%	11 (14)	9 (24)	25 (17)
< 1%	56 (70)	26 (70)	102 (70)
Unable to determine	13 (16)	2 (5)	18 (12)
Prior treatments, n (%)			
Surgical resection	42 (53)	27 (73)	95 (66)
Radiotherapy	6 (8)	9 (24)	36 (25)
Local treatment for HCC	37 (46)	19 (51)	85 (59)
Time from initial HCC diagnosis to nivolumab start, median (range), yr	0.8 (0.1–10.3)	1.8 (0.4–11.8)	2.2 (0.0–24.6)

AFP, alpha-fetoprotein. [a] Nine patients did not have baseline AFP values available.

Results

Table 2. Prior Sorafenib Treatment Characteristics

Parameter	Sorafenib Experienced ESC N = 37	Sorafenib Experienced EXP N = 145
Duration of sorafenib therapy, median (range), mo	3.88 (0.0–13.5)	3.75 (0.1–48.1)
Sorafenib intolerance, n (%)[a]	1 (3)	12 (8)
Sorafenib progression, n (%)[a]	33 (89)	132 (91)
Time from progression to nivolumab start, median (range), mo	5.22 (0.4–80.3)	2.53 (0.1–56.4)
Time from sorafenib start to nivolumab start, median (range), mo	9.17 (0.8–82.3)	8.71 (1.2–70.5)
Time from sorafenib discontinuation to nivolumab start, median (range), mo	3.48 (0.5–80.4)	2.17 (0.1–44.7)

[a] Four sorafenib-experienced patients were neither intolerant of sorafenib nor were they progressors.

Results

- The majority of treatment discontinuations were due to disease progression (**Table 3**)
- Treatment beyond disease progression was allowed at the investigator's discretion if the patient was experiencing clinical benefit and was tolerant of nivolumab
  - 34 sorafenib-naive patients (43%) were treated beyond progression, and 21 (57%) and 78 (54%) sorafenib-experienced patients were treated beyond progression in the dose-escalation and -expansion phases, respectively

Table 3. Patient Disposition

Patients, n (%)	Sorafenib Naive ESC + EXP N = 80	Sorafenib Experienced ESC N = 37	Sorafenib Experienced EXP N = 145
Continuing treatment	10 (13)	2 (5)	24 (17)
Not continuing treatment	70 (88)	35 (95)	121 (83)
Reasons for discontinuation			
Complete response	0	2 (5)	NA[a]
Disease progression	56 (70)	32 (86)	107 (74)
Study drug toxicity	7 (9)	1 (3)	5 (3)
Unrelated AE	5 (6)	0	3 (2)
Other[b]	2 (3)	0	5 (3)
Death	0	0	1 (1)

NA, not applicable. [a] Complete response was not a protocol-defined reason for discontinuation in the dose-expansion phase; [b] Includes patient request, withdrawal of consent, and other reasons.

Results

Efficacy

- Disease control rates (BICR) were 54% in sorafenib-naive patients and 55% in all sorafenib-experienced patients (**Table 4**)

Table 4. Best Overall Response With Nivolumab

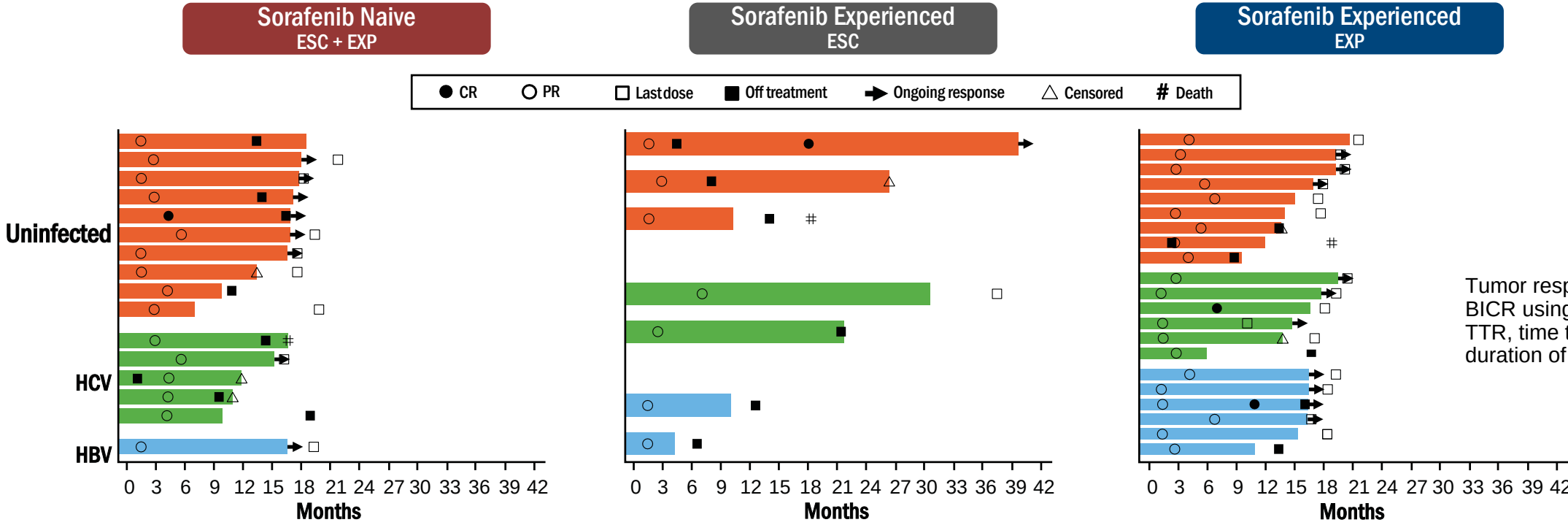
Patients, n (%)	Sorafenib Naive ESC + EXP N = 80		Sorafenib Experienced ESC N = 37		Sorafenib Experienced EXP N = 145	
	BICR	INV	BICR	INV	BICR	INV
Objective response using RECIST v1.1	**16 (20)**	**18 (23)**	**7 (19)**	**6 (16)**	**21 (14)**	**28 (19)**
Complete response	1 (1)	1 (1)	1 (3)	3 (8)	2 (1)	4 (3)
Partial response	15 (19)	17 (21)	6 (16)	3 (8)	19 (13)	24 (17)
Stable disease[a]	27 (34)	32 (40)	13 (35)	15 (41)	60 (41)	65 (45)
Progressive disease	32 (40)	26 (33)	13 (35)	12 (32)	56 (39)	47 (32)
Not evaluable	5 (6)	4 (5)	4 (11)	4 (11)	8 (6)	5 (3)
Objective response using mRECIST	**19 (24)**	**NA**	**8 (22)**	**NA**	**27 (19)**	**NA**

BICR, blinded independent central review; INV, investigator assessment; mRECIST, modified RECIST; NA, not applicable. [a] Includes 2 sorafenib-naive patients and 1 sorafenib-experienced (ESC) patient who had a best overall response reported as non-CR/non-PD by BICR.

Results

- The majority of objective responses in sorafenib-naive (56% [9/16]) or sorafenib-experienced patients (64% [18/28]) occurred in ≤ 3 months (**Figure 2**)
- Responses were ongoing in 50% (8/16) of sorafenib-naive patients and 39% (11/28) of all sorafenib-experienced patients

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



TTR, median (range), mo	2.7 (1.3–5.5)
DOR, median (range), mo	17.15 (4.2–17.1+)

TTR, median (range), mo	1.4 (1.3–6.9)
DOR, median (range), mo	19.35 (2.8–38.2+)

TTR, median (range), mo	2.8 (1.2–7.0)
DOR, median (range), mo	16.59 (3.2–16.8+)

- Disease control of ≥ 6 months was achieved in 34% of sorafenib-naive patients and 27% of all sorafenib-experienced patients

Results

- Objective responses were observed irrespective of sorafenib treatment status (**Figure 3**)
- Responses occurred across HCC etiologies and baseline tumor-cell PD-L1 expression status

Figure 3. Best Change in Target Lesion From Baseline

HCC Etiology

Sorafenib Naive
ESC + EXP

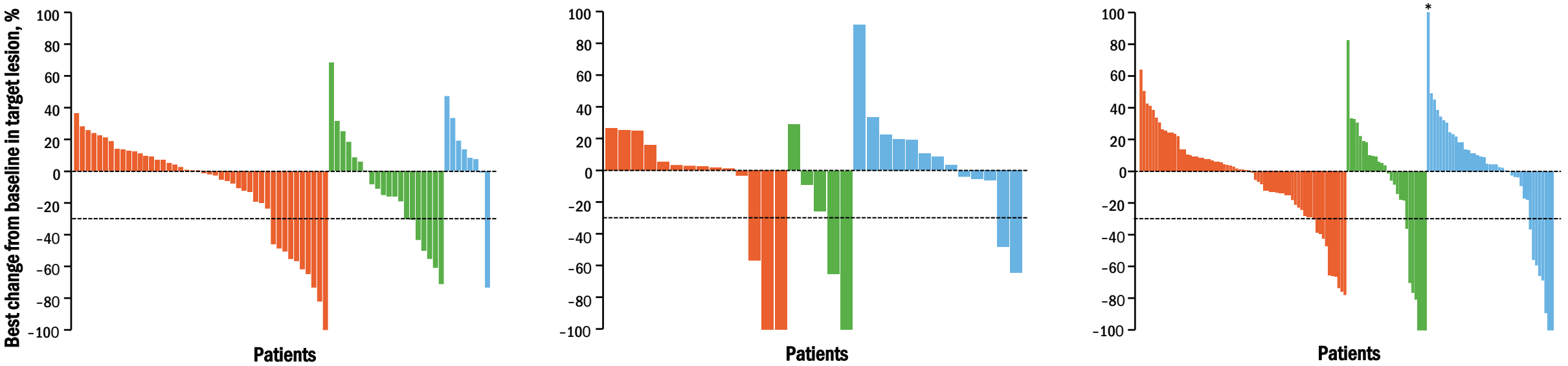
	Uninfected	HCV	HBV
ORR, n/N (%)	10/47 (21)	5/25 (20)	1/8 (13)

Sorafenib Experienced
ESC

	Uninfected	HCV	HBV
ORR, n/N (%)	3/17 (18)	2/5 (40)	2/15 (13)

Sorafenib Experienced
EXP

	Uninfected	HCV	HBV
ORR, n/N (%)	9/72 (13)	6/30 (20)	6/43 (14)



Tumor response assessed by BICR using RECIST v1.1; plots include patients who were evaluable for tumor response and had at least one post-baseline target lesion assessment (sorafenib naive, n = 72; sorafenib experienced (ESC), n = 32; and sorafenib experienced (EXP), n = 135). * Percent change truncated to 100%.

Results

Figure 3. Best Change in Target Lesion From Baseline (cont)

Tumor-cell PD-L1 Expression

Sorafenib Naive
ESC + EXP

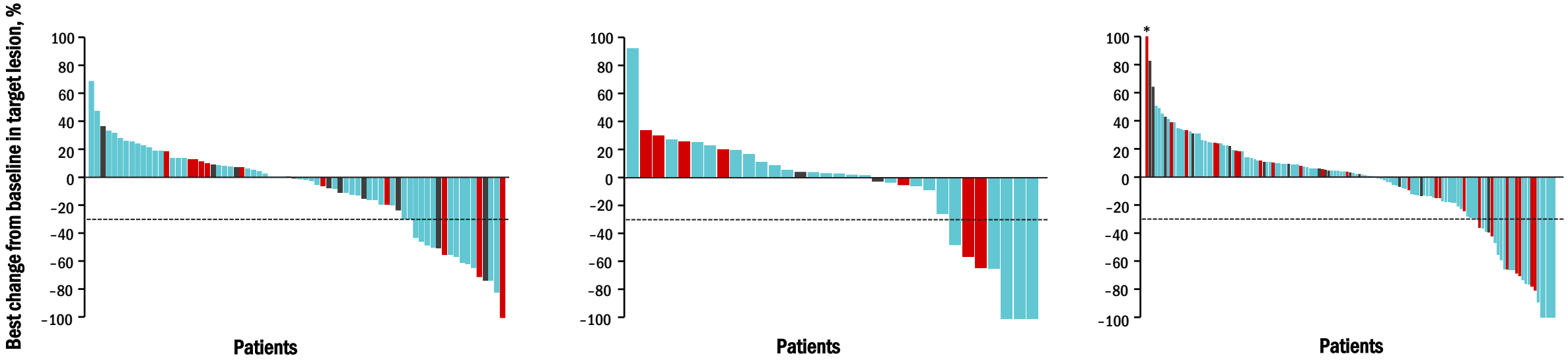
	PD-L1⁺	PD-L1⁻	UTD
ORR, n/N (%)	3/11 (27)	11/56 (20)	2/13 (15)

Sorafenib Experienced
ESC

	PD-L1⁺	PD-L1⁻	UTD
ORR, n/N (%)	2/9 (22)	5/26 (19)	0/2 (0)

Sorafenib Experienced
EXP

	PD-L1⁺	PD-L1⁻	UTD
ORR, n/N (%)	7/25 (28)	13/102 (13)	1/18 (6)

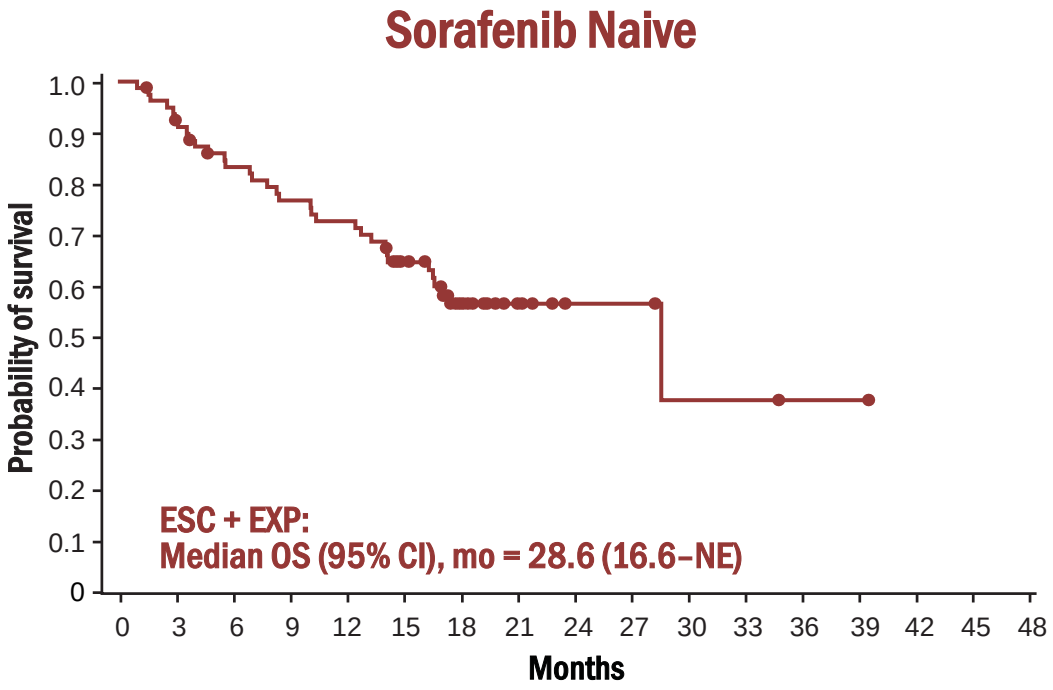


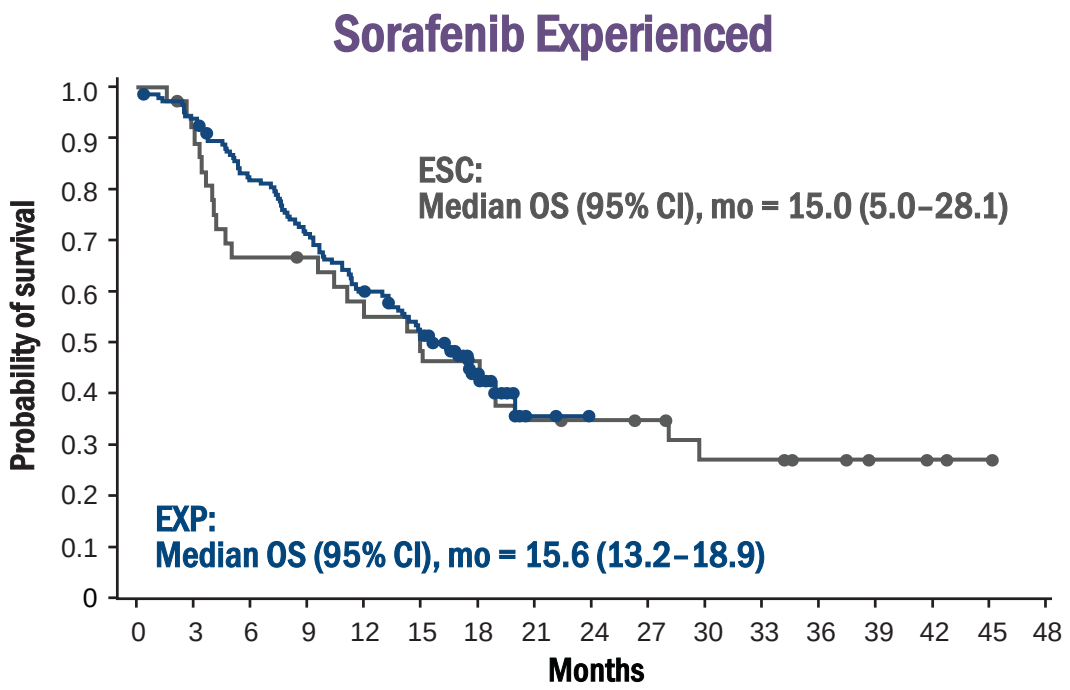
Tumor response assessed by BICR using RECIST v1.1; plots include patients who were evaluable for tumor response and had at least one post-baseline target lesion assessment (sorafenib naive, n = 72; sorafenib experienced (ESC), n = 32; and sorafenib experienced (EXP), n = 135). PD-L1⁺, ≥ 1% tumor cells expressing PD-L1; PD-L1⁻, < 1% tumor cells expressing PD-L1; UTD, unable to determine PD-L1 expression. * Percent change truncated to 100%.

Results

- Long-term survival was observed across sorafenib-naive and -experienced cohorts (**Figure 4**)

Figure 4. Overall Survival With Nivolumab





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.

Results

Safety

- Overall safety profile of nivolumab was similar to that in other tumor types, with no new safety signals (**Table 5**)
- In the dose-escalation phase, 1 dose-limiting toxicity was reported (grade 2 hepatic impairment), and no maximum tolerated dose was reached
- One sorafenib-experienced (EXP) patient died due to study-drug toxicity (pneumonitis)

Table 5. Treatment-related AEs With Nivolumab

n (%)	Sorafenib Naive ESC + EXP N = 80		Sorafenib Experienced ESC + EXP N = 182	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Patients with any treatment-related AE	62 (78)	23 (29)	141 (77)	32 (18)
Treatment-related AEs (≥ 5%)[a]				
Fatigue	16 (20)	0	40 (22)	4 (2)
Pruritus	19 (24)	0	37 (20)	1 (1)
Rash	13 (16)	1 (1)	33 (18)	1 (1)
Diarrhea	10 (13)	1 (1)	26 (14)	2 (1)
Nausea	7 (9)	0	14 (8)	0
Decreased appetite	4 (5)	0	12 (7)	1 (1)
Anemia	4 (5)	0	9 (5)	1 (1)
Dry mouth	6 (8)	0	10 (5)	0

[a] Reported in ≥ 5% of all patients (N = 262), any grade.

Results

Table 5. Treatment-related AEs With Nivolumab (cont)

n (%)	Sorafenib Naive ESC + EXP N = 80		Sorafenib Experienced ESC + EXP N = 182	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Laboratory treatment-related AEs (≥ 5%)[a]				
ALT increased	9 (11)	4 (5)	16 (9)	5 (3)
AST increased	10 (13)	7 (9)	16 (9)	7 (4)
Blood bilirubin increased[b]	3 (4)	1 (1)	4 (2)	0
Lipase increased	6 (8)	6 (8)	12 (7)	8 (4)
Amylase increased	9 (11)	5 (6)	10 (5)	2 (1)

[a] Reported in ≥ 5% of all patients (N = 262), any grade; [b] Blood bilirubin increases were reported in < 5% of all patients.

Authors' Conclusions

- Nivolumab demonstrated clinically meaningful efficacy across etiologies in sorafenib-naive and -experienced patients with extended follow-up:
  - Early responses: 56% (sorafenib naive) and 64% (all sorafenib experienced) of responses occurred before 3 months
  - Durable responses: median DORs of 17 months (sorafenib naive) and 19 months (all sorafenib experienced)
  - Long-term survival: 18-month OS rates of 57% (sorafenib naive) and 44% (all sorafenib experienced)
- Safety profiles of nivolumab in sorafenib-naive and -experienced patients were consistent with what has been observed with nivolumab in other tumor types
  - No new safety signals were observed
- A phase 3 randomized study of nivolumab compared with sorafenib in systemic treatment–naive patients with advanced HCC is ongoing (CheckMate 459; ClinicalTrials.gov NCT02576509)

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