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Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29)†

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Background: Sorafenib (S), a multitargeted tyrosine kinase inhibitor, is the standard of care for first-line systemic treatment of advanced hepatocellular carcinoma (HCC). Everolimus (E) is a potent inhibitor of mTOR, a pathway frequently activated in HCC. Preclinical data suggest that the combination S + E has additive effects compared with single-agent S.

Patients and methods: Patients with unresectable or metastatic HCC and Child-Pugh ≤7 liver dysfunction were randomized to receive daily S 800 mg alone or with E 5 mg until progression or unacceptable toxicity. The primary end point was progression-free survival at 12 weeks (PFS12). The secondary end points included response rate, PFS, time to progression (TTP), overall survival (OS), duration of disease stabilization (DDS), safety, and quality-of-life (QoL) assessments.

Results: A total of 106 patients were randomized: 46 patients received S and 60 patients received S + E. Ninety-three patients were assessable for the primary end point and 105 patients for the safety analysis. The PFS12 rate was 70% [95% confidence interval (CI) 54–83] and 68% (95% CI 53–81) in patients randomized to S and S + E, respectively. The RECIST (mRECIST) response rate was 0% (23%) in the S arm and 10% (35%) in the S + E arm. Median PFS (6.6 versus 5.7 months), TTP (7.6 versus 6.3 months), DDS (6.7 versus 6.7 months), and OS (10 versus 12 months) were similar in the S and S + E arms, respectively. Grade 3/4 adverse events occurred in 72% and 86% of patients in arm S and arm S + E, respectively. Patients had similar QoL scores over time, except for a greater worsening in physical well-being and mood in the arm S + E.

Conclusions: No evidence was found that S + E improves the efficacy compared with S alone. Combining 5 mg E with full-dose S is feasible, but more toxic than S alone. Further testing of this drug combination in molecularly unselected HCCs appears unwarranted.

ClinicalTrials.gov: NCT01005199.

Key words: hepatocellular carcinoma, sorafenib, everolimus, tyrosine kinase inhibitor

introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, with ~500 000 new cases per year globally. Sorafenib, an oral multitargeted tyrosine kinase inhibitor (TKI), has become the mainstay in the treatment of advanced-stage HCC based on two randomized, placebo-controlled phase III trials [1, 2]. Since the approval of sorafenib in HCC, several

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phase III clinical trials have failed to demonstrate superiority of other agents over sorafenib in the first-line setting or impact on outcome after sorafenib failure [3, 4]. At present, sorafenib remains the only approved systemic therapy for HCC.

HCC is characterized by complex molecular aberrations affecting multiple cellular signaling pathways [5, 6]. Therefore, combining therapies that target different major signaling pathways may improve the efficacy of first-line treatment over single-agent targeted therapies. Combination therapies may also reduce drug resistances following up-regulation of a secondary pathway in response to single-agent targeted therapies. The mTOR pathway is activated in a relevant proportion of HCC [7]. It plays an important role in angiogenesis, cell cycle progression, and proliferation of liver cancer cells. Everolimus, a rapamycin analog, inhibits the mTOR pathway and blocks tumor growth in xenograft models of human HCC [8]. The *in vivo* efficacy of everolimus was potentiated when combined with sorafenib in orthotopic models of human metastatic HCC, and this combination strongly inhibited the proliferation of HCC xenografts [8, 9]. In addition, everolimus administered alone and in combination with sorafenib induced apoptosis and decreased tumor angiogenesis. Accordingly, this combination appears to have significant advantages compared with single-agent sorafenib.

methods

This was a multicenter, open-label, randomized phase II trial. The objective of the trial was to investigate if the combination of sorafenib plus everolimus (arm S + E) can stop tumor progression, with a sorafenib monotherapy group (arm S) used to control selection bias.

eligibility criteria

Eligible patients had histo-, cyto-, or radiologically confirmed unresectable or metastatic HCC that was stage B or C according to the Barcelona Clinic Liver Cancer (BCLC) staging classification [10] and measurable according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. No prior therapies for HCC were allowed other than liver directed therapies (chemoembolization was limited to five treatments), provided that previously treated lesions remained separate from the target lesions measured for this trial. Other eligibility criteria included age ≥18 years, WHO performance status 0–1, Child-Pugh class A or mild Child-Pugh class B (≤7 points) liver dysfunction, adequate hematologic, hepatic, and renal function indicated by an absolute neutrophil count ≥1500/μl, platelets ≥75 000/μl, prothrombin time-international normalized ratio ≤2, serum ALT ≤ 5 × upper level of normal (ULN), and calculated creatinine clearance ≥40 ml/min according to the Cockcroft-Gault formula.

Exclusion criteria included: known central nerve system metastases, a history of other primary malignancy within 5 years except for nonmelanomatous skin cancer or adequately treated *in situ* cervical cancer, prior organ transplantation, known fibrolamellar HCC or mixed cholangiocarcinoma/HCC, documented variceal hemorrhage within 3 months before registration, repeated paracentesis (>1 month), encephalopathy, active infection requiring i.v. antibiotics, requirement of anticoagulant therapy except for low-dose anticoagulants for the maintenance of patency of central venous access or prevention of deep vein thrombosis, current use or anticipated need for drugs that are known CYP3A4 inhibitors or inducers, prolongation of QTc >500 msec in screening electrocardiogram (ECG) or family history of long QT syndrome, and any serious underlying medical condition which could impair the patient to participate in the trial or to take oral medication. Institutional review boards at participating centers and health authorities approved the protocol. The study followed the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

randomization, dose feasibility evaluation, and treatment plan

Patients were randomly assigned at the ratio 46:60 to receive either sorafenib (arm S) or sorafenib and everolimus (arm S + E). Randomization was stratified according to ECOG performance status (0 versus 1), extrahepatic spread (yes versus no), and study site.

Treatment consisted of sorafenib 2 × 400 mg daily alone or with everolimus 5 mg daily. All drugs were given orally as a continuous, uninterrupted schedule until disease progression, unacceptable toxicity, or withdrawal of patient consent. The doses of sorafenib and everolimus were based on the results of a dose-escalation trial in patients with renal cell cancer and normal liver function [11]. The safety and tolerability of this drug combination in mildly hepatically impaired patients had not been investigated when this study protocol was developed.

We evaluated the dose feasibility of everolimus using the first nine assessable patients of the S + E arm. This evaluation appeared necessary to avoid an unexpectedly high number of grade 3/4 toxicities with the selected doses of sorafenib and everolimus, which might have jeopardized the successful conduct of the trial. Criteria for the dose feasibility evaluation included any grade 3/4 adverse events (AEs) occurring starting within the first 28 days of treatment or requiring a 2-week interruption of any study drug. If more than three patients out of the first nine patients fulfilled the criteria, the dose of everolimus was to be reduced to 2.5 mg daily for all further patients.

If grade 3/4 AEs occurred, the study drug treatment was interrupted until toxicities had resolved below grade 2 or discontinued after 3 weeks. For selected grade 2 AEs (sorafenib: hand–foot skin reaction >7 days, diarrhea, cardiac events; everolimus: hand–foot skin reaction >7 days, stomatitis, noninfectious pneumonitis) and reoccurring grade 3 AEs, the doses of sorafenib and everolimus were reduced by 50%. The best palliative and supportive care for disease-related symptoms was offered to all patients.

assessments

Tumor response was assessed using the RECIST version 1.1 [12] based on computerized tomography (CT) or magnetic resonance imaging (MRI) scans performed at baseline and every 6 weeks until week 18, and every 8 weeks thereafter during treatment administration. Objective responses (complete or partial) were confirmed after a minimum of 4 weeks. Original CT and MRI scans from baseline, weeks 6 and 12 assessment were reviewed for tumor response (RECIST), HCC-adapted RECIST criteria (mRECIST [13]) and Choi criteria [14] by two independent radiologists, blinded to the investigator's evaluation and the study arms.

A medical history, physical examination, routine blood and urine analysis, analysis of hepatitis B virus (HBV) DNA, hepatitis C virus (HCV) RNA, α-fetoprotein (AFP), and a pregnancy test for women aged <50 years, were carried out within 2 weeks of study entry. Clinical visits included assessment of AEs, serial laboratory testing including AFP, ECG, and physical examinations (once every 2 weeks). HBV DNA or HCV RNA was measured in case of progressive ALT elevation (≥5 × ULN or ≥3 × baseline value) in patients with chronic HBV/HCV infection, respectively. Patients were followed up every 2 months after treatment.

Symptom-related quality of life (QoL) was assessed within 2 weeks of study entry and every 2 weeks until week 12 with the 18-item subscale of the Functional Assessment of Cancer Therapy-Hepatobiliary Subscale (FACT-HS) [15]. Global QoL was assessed with linear analog self-assessment (range 0–100) indicators for physical well-being, mood, coping effort [16], functional performance, and overall treatment burden [17].

statistics

The primary end point, progression-free survival (PFS) at 12 weeks (PFS12), was defined as the patient being alive and without radiological evidence of tumor progression 12 weeks (±7 days) after trial registration. A PFS12 of ≤55% was considered uninteresting, and PFS12 ≥75% was considered promising, based on the results of the SHARP study [1]. According to Fleming and A' Hern [18] with 90% power and a 5% significance level, 50 assessable patients in the arm S + E were required. If more than 33 patients were progression-free at 12 weeks, the trial therapy was to be considered worthy of further investigation. The calibration arm S used 38 assessable patients based on a 95% confidence interval (CI) approach. To take 20% of nonassessable patients (no trial treatment or insufficient tumor assessments) into account, the arms were expanded to 60 and 46 patients, respectively.

AEs were graded using the Common Terminology Criteria for Adverse Event, version 3 (CTCAE v. 3.0) and summarized per patient. Secondary efficacy end points were disease stabilization (DS), defined as either a complete response, partial response (PR), or stable disease as the best response during therapy, and time to progression (TTP), PFS, duration of disease stabilization (DDS), and overall survival (OS). All patients who received at least one dose of trial medication were considered as evaluable for safety and secondary efficacy (safety population).

Patients' characteristics and treatment administration were based on the safety population. Time-to-event end points were analyzed using Kaplan–Meier methods. No formal comparisons between arms were planned. QoL was analyzed by a mixed-effect model for repeated measures with treatment arm as primary covariate.

Statistical analyses were carried out using SAS version 9.2 (SAS Institute, Inc., Cary, NC) and R version 3.0.1.

results

patient baseline characteristics and disposition

Between December 2009 and February 2013, 106 eligible patients were randomly assigned to arm S ($n = 46$) or to arm S + E ($n = 60$). One patient in the arm S + E did not receive study treatment and was excluded from the analysis. All other patients ($n = 105$) were assessable for the safety and secondary end point analyses. Ninety-three patients were assessable for the primary end point (Figure 1). The median follow-up time was 20 months. Baseline characteristics were balanced between the treatment arms (Table 1).

treatment administration

Patients received a median daily dose of 800 mg sorafenib in arm S and 773 mg sorafenib and 5 mg everolimus in arm S + E. The median duration of sorafenib treatment was 118 and 106 days in arms S and S + E, respectively, and the median duration of everolimus was 84 days. Sorafenib doses in arm S and arm S + E were interrupted in 34 (74%) and 49 (83%) patients, respectively, and were reduced in 21 (46%) and 33 (56%) patients, respectively. Everolimus doses were interrupted in 46 (78%) patients and were reduced in 24 (41%) patients. At the time of the analyses, two patients in each arm remained on treatment. The main reasons for treatment termination were progressive disease (arm S 64%; arm S + E 51%) and AEs (arm S 21%; arm S + E 28%).

safety

AEs are summarized in Table 2. The most common AEs were fatigue, diarrhea, and increase in bilirubin level. Grade 3/4 events occurred in 72% of patients in arm S and 88% in arm S + E, respectively. No patient experienced liver failure and there were no treatment-related deaths. Serious adverse events occurred in 14 (30%) patients in arm S and 28 (47%) patients in arm S + E. No patient had HCV activation in arm S, whereas 2 of 59 (3%) patients had HCV reactivation in arm S + E.

In the interim safety analysis, only one of nine patients in the arm S + E reported a dose feasibility AE (grade 3 diarrhea); therefore, it was decided to continue without dose modification.

efficacy

Thirty (70%; 95% CI 54% to 83%) patients were progression-free at 12 weeks in arm S and 34 (68%; 95% CI 53%–81%) in arm S + E. The median PFS was 6.6 months (95% CI 4.5–8.2) in arm S and 5.7 months (95% CI 4.5–6.8) in arm S + E. The median TTP was 7.6 months (95% CI 4.5–8.5) in arm S and 6.3

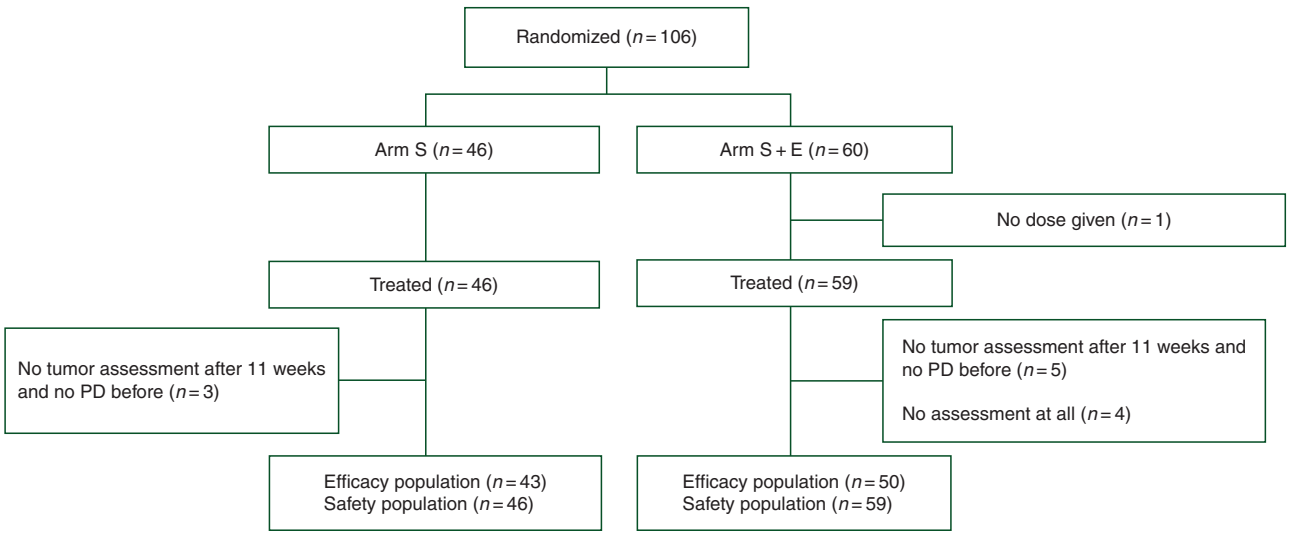

Figure 1. Consort flow diagram.

Table 1. Baseline patient and disease characteristics

	Arm			
	S ($N = 46$)		S + E ($N = 59$)	
	n	%	*n*	%
Median age (years) (range)	65 (39–82)		66 (32–83)	
Male	40	87	48	81
ECOG performance status				
0	33	72	35	59
1	13	28	24	41
Etiology				
Hepatitis B	8	17	10	17
Hepatitis C	13	28	17	29
Alcohol abuse	27	59	25	42
BCLC stage				
B	14	30	15	25
C	32	70	44	75
Child-Pugh score				
5/6	37	80	50	85
7	9	20	9	15
Portal vein invasion	16	35	16	27
Extrahepatic disease	26	57	32	54
Previous local treatment				
TACE	8	17	9	15
TAE	–	–	3	5
PEI	–	–	2	3
Radiofrequency ablation	1	2	3	5
Liver resection	2	4	8	14
Radiotherapy	–	–	2	3
Liver function parameter				
Median albumin (g/l) (range)	39 (20–54)		39 (28–55)	
Median bilirubin (μmol/l) (range)	17 (5–51)		16 (4–46)	
Median INR (range)	1.1 (1.0–1.5)		1.1 (0.9–2.0)	
AFP ≥1.5 × ULN	34	74	33	56
Median AFP (ng/ml)[a] (range)	350 (25–639 116)		350 (10–99 615)	

AFP, α-fetoprotein; ECOG, Eastern Cooperative Group; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization;,TAE, transarterial embolization; PEI, percutaneous ethanol injection; INR, international normalized ratio; ULN, upper level of normal.
[a]In patients with AFP ≥1.5 × ULN.

months (95% CI 4.7–9.2) in arm S + E (Figure 2). The median OS was 10 months (95% CI 7.9–14.3) in arm S and 12 months (95% CI 9.9–17.9) in arm S + E. No patient in the arm S and six patients in arm S + E achieved a PR as the best response during treatment according to RECIST. Within patients in the safety population having at least one tumor assessment ($n = 46$ for arm S and $n = 55$ for arm S + E), 80% and 84% of them achieved DS in the arm S and arm S + E, respectively. The median DDS was 6.7 months in both arms. Three patients in arm S and four patients in arm S + E received systemic second-line treatment.

correlative studies

Change in tumor size and density, assessed by the independent reviewer based on CT scans at baseline and 6 and 12 weeks after treatment initiation according to the mRECIST and Choi criteria, was available in 45 and 55 patients (6-week assessment) and in 34 and 39 patients (12-week assessment) in arm S and arm S + E, respectively. Supplementary Table S1, available at *Annals of Oncology* online, shows the best objective response during therapy, as determined by RECIST, mRECIST, and Choi criteria. Best relative change in lesion size according to mRECIST is shown in supplementary Figure S1, available at *Annals of Oncology* online.

Sixty-seven (64%) patients had elevated baseline AFP levels, of which nine patients in arm S and 16 patients in arm S + E showed a decrease of at least 50% at any stage during treatment administration.

quality of life

The FACT-HS score was similar over time in both treatment groups. The odds of having a clinically relevant improvement in the FACT-HS score (a change of ≥5 points) was higher in patients in arm S compared with those in arm S + E [odds ratio with 95% CI 3.2 (1.0–10.9); $P = 0.03$]. No clinically relevant improvement at any time point was reported by 23 patients receiving S, and by 35 patients receiving S + E, respectively. Patients in arm S + E reported worse scores for global QoL indicators over time compared with those in arm S. Significant differences in change from baseline for physical well-being ($P = 0.02$) and

Table 2. Adverse events according to CTCAE v. 3.0 by patients[a]

	Arm					
	S ($N = 46$)			S + E ($N = 59$)		
	All grades, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	All Grades, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Any event	46 (100)	26 (63)	4 (9)	59 (100)	38 (66)	13 (22)
Anemia	1 (2)	1 (2)	–	5 (8)	2 (3)	1 (2)
Neutropenia	1 (2)	1 (2)	–	5 (8)	5 (8)	–
Thrombocytopenia	4 (9)	1 (2)	–	15 (25)	10 (17)	1 (2)
Bilirubin	24 (52)	5 (11)	–	20 (34)	8 (14)	–
ALAT	19 (41)	2 (4)	–	26 (44)	4 (7)	–
Diarrhea	22 (48)	7 (15)	–	38 (64)	12 (20)	–
Mucositis	5 (11)	1 (2)	–	10 (17)	3 (5)	–
Pneumonitis	–	–	–	3 (5)	2 (3)	–
Fatigue	34 (74)	11 (24)	1 (2)	39 (66)	14 (24)	3 (5)
Hand–foot syndrome	15 (33)	3 (7)	–	17 (29)	5 (8)	–
Rash	11 (24)	1 (2)	–	16 (27)	–	–
Anorexia/weight loss	27 (59)	–	–	33 (56)	11 (19)	–
Hemorrhages	4 (9)	1 (2)	–	13 (22)	5 (9)	2 (3)
Hyperglycemia	–	–	–	18 (21)	5 (9)	5 (9)

[a]Worst observed grade per patient per event type.

CTCAE, Common Terminology Criteria for Adverse Events; ALAT, alanine aminotransferase.

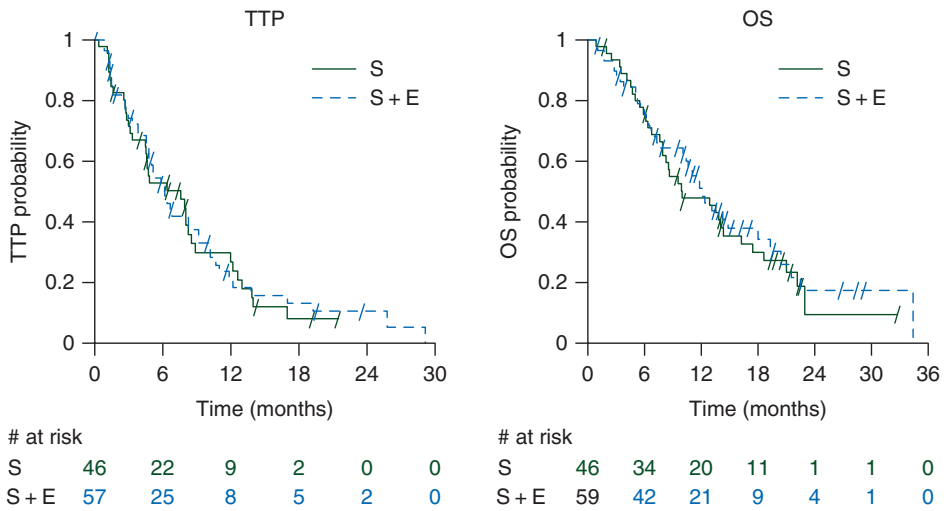

Figure 2. TTP and OS curves.

mood ($P = 0.02$) were observed between groups (see supplementary Figure S2, available at *Annals of Oncology* online), with patients in arm S + E reporting a greater worsening until 12 weeks. Of note, baseline scores for mood were worse in arm S and remained lower over time.

discussion

Despite preclinical models [10–13] and evidence for single-agent activity of everolimus [19], the combination of sorafenib plus everolimus was not superior to sorafenib alone in the first-line treatment of HCC patients. Many reasons may have contributed to this finding.

First, dose adjustments are usually required when combining two TKIs. In our trial, we explored the full dose of sorafenib and half of the regular monotherapy dose of everolimus (5 mg daily). The target doses appeared feasible although many grade 3/4 AEs led to treatment discontinuation. Severe AEs, mainly hematological toxicity and anorexia, were more frequent in the S + E arm. Dose-limiting thrombocytopenia was not observed, contrary to a phase I trial of the same drug combination in advanced HCC [20]. This may reflect differences in the patient cohorts between trials: we included patients with mild Child-Pugh class B liver (≤7 points) dysfunction in our trial. Furthermore, in the phase I trial, the majority of patients were of Asian origin and had hepatitis B. QoL was similar for both treatments during the 12 weeks, yet patients receiving sorafenib plus everolimus reported a greater worsening in physical well-being and mood than those receiving sorafenib alone. However, the greater decline in mood for the combined

treatment has to be interpreted with caution, as patients on Sorafenib alone had worse baseline scores.

Second, the result for the primary end point of our trial, PFS12 strictly defined according to radiological criteria, was higher than anticipated in both arms. Concordantly, TTP was considerably longer than in previously reported randomized first-line trials [4], even with comparable patient populations. This might have masked the effects of sorafenib plus everolimus in this parallel-group randomized phased II trial. While objective response favored the combination treatment, this did not translate into a prolongation of TTP or OS, as shown previously in other HCC trials.

Third, a role of mTOR inhibition in the treatment of unselected patients with HCC has not yet been established. The recently reported phase III EVOLVE-1 trial failed to demonstrate a benefit of everolimus in patients in whom sorafenib treatment failed [21]. A way forward might be to assess dual mTOR inhibition in HCC. This may overcome the limitation of everolimus, which only blocks one of the complementary components of the mTOR pathway (mTORC1) [22].

It remains speculative, whether the everolimus dose used in our trial is effective enough to control HCC. Sequencing treatments with full doses, as it is standard of care in renal cell carcinoma, may be a better approach. In HCC however, only a minor proportion of patients is available for systemic second-line treatment. In addition, no evidenced-based systemic treatment has been established after sorafenib progression.

In summary, we found no evidence that adding everolimus to sorafenib improves clinical efficacy compared with sorafenib alone in patients with advanced HCC. Further testing of this drug combination in molecularly unselected HCCs seems unwarranted.

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disclosure

DK reports advisory board member of Merck; JFD reports advisory board member of Abbvie, Bayer, BMS, Gilead Science, Janssen Cilag, Merck, Novartis, and Sillagen and grants and personal fees from Abbvie, Bayer, Gilead Science, Novartis, Roche; PS declares consultant or advisory role for Roche, Celgene, Sanofi, and Takeda; MP-R acts as speaker, member of advisory boards, steering committees for Bayer, advisor for Novartis, advisor and speaker for Lilly, advisor and steering committee member for Arqle-Daiichi, advisor for SillaJen and Boehringer-Ingelheim, and received grant support from Bayer and Arqle; ADW gave scientific advice to Amgen, Roche, Celgene, Merck Serono, Taiho, and Lilly and lectured for Taiho-sponsored symposia; GB reports advisory board member of Novartis, Bayer, Roche, Janssen, Lilly, Pfizer, Nordic Pharma. All remaining authors have declared no conflicts of interest.

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