Phase II trial of sorafenib in advanced salivary adenoid cystic carcinoma of the head and neck

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ABSTRACT: *Background.* There is a need to improve the systemic treatment of advanced adenoid cystic carcinoma (ACC). Response rates to chemotherapy are poor and preliminary investigations of molecularly targeted agents have been disappointing. In this study, we evaluate sorafenib, an oral multikinase inhibitor, which has an attractive targeting profile for this disease.

Methods. In a single-arm phase II trial, patients with unresectable locally recurrent and/or metastatic ACC were treated with sorafenib 400 mg bid.

Results. Twenty-three patients, median age 51 years, were recruited from 2009 to 2011. Median progression-free survival (PFS) and overall survival (OS) were 11.3 and 19.6 months, respectively. PFS at 6 and 12 months were 69.3% and 46.2%, respectively. Sorafenib was only reasonably well tolerated, and 13 patients (57%) experienced grade 3 toxicity.

Conclusion. Sorafenib showed modest activity in ACC with a 12-month PFS of 46.2%. Sorafenib 400 mg bid was associated with significant toxicity and, taken together with limited effectiveness, cannot be enthusiastically recommended for further evaluation. © 2013 Wiley Periodicals, Inc. *Head Neck* 00: 000–000, 2013

KEY WORDS: trial, sorafenib, adenoid cystic carcinoma

INTRODUCTION

Adenoid cystic carcinoma (ACC) is rare and represents only 1% of head and neck malignancies.[1] It accounts for approximately 25% of salivary gland carcinomas.[2] Primary treatment is usually surgical excision and postoperative radiotherapy.[3] Despite this combined approach, the disease is characterized by an indolent and progressive course, often with local recurrence and distant spread many years after treatment.[3,4] Prognostic factors include patient sex, tumor site, size, histological pattern, and perineural invasion.[3]

The incidence of disease relapse is dependent on the length of the patient's follow-up.[4] Only 10% to 20% of patients remain disease-free at 15 years and 35% to 50% of patients develop distant metastases, with the lungs as the most common site.[4,5] Median survival from diagnosis of metastatic disease is approximately 2 to 3 years, but, in some patients, the disease will progress very slowly over many years.[1,5,6] Objective response rates to cytotoxic chemotherapy are variable and often poor, in the range of 25% to 33% for combination therapy and duration of response approximately 5 to 13 months.[1] However, symptomatic response rates are generally greater and chemotherapy is often reserved for those with symptomatic or rapidly progressive disease.[1,5]

The limited effectiveness of cytotoxic chemotherapy has encouraged research into understanding the molecular biology of the disease and development of targeted therapies. Identification that the transmembrane protein tyrosine kinase c-kit is overexpressed in ACC led to investigation of the receptor antagonist imatinib.[7–9] However, results were disappointing without clear evidence of clinical benefit, perhaps because of low prevalence of c-kit activating mutations in ACC.[10–12] Vascular endothelial growth factor receptor (VEGFR) is both highly expressed and associated with recurrent and metastatic disease in ACC.[10,13] However, sunitinib, which is a multitargeted small molecule inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3, as well as c-kit, platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), RET, and FMS-like tyrosine kinase 3 showed limited activity in a phase II trial of recurrent or metastatic ACC with no objective responses, but there was prolonged stabilization of disease

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(defined as $\geq$6 months) in 62% of patients.[14] Other agents, whose targets include epidermal growth factor and hormone receptors, have also been tested but not found beneficial.[1,5]

Sorafenib inhibits the serine/threonine kinases c-Raf and b-Raf as well as VEGFR-2, VEGFR-3, PDGFR-β, FMS-like tyrosine kinase 3, c-kit, and p38α (a member of the mitogen-activated protein kinase family).[15,16] It has been shown to improve progression-free survival (PFS) and overall survival (OS) in advanced renal clear cell and hepatocellular carcinomas with a manageable toxicity profile.[17,18] Aberrant RAF-MEK-ERK signaling is implicated in the growth and survival of tumors.[19] There is a putative role for targeting angiogenesis in ACC,[10,14] and a case report describing clinical benefit of sorafenib in a patient with advanced ACC and lung metastases.[20] We report the results of a phase II trial to investigate the effectiveness and tolerability of sorafenib in treatment of locally recurrent or metastatic ACC not amenable to surgery or curative radiotherapy.

MATERIALS AND METHODS

Patient selection

Eligible patients were aged $\geq$18 years with histologically confirmed ACC of the head and neck with unresectable locally recurrent and/or metastatic disease. Any number of prior therapies were allowed, including chemotherapy, other molecularly targeted agents, radiofrequency ablation, and radiotherapy. However, patients must have completed radiotherapy or any systemic treatment more than 3 or 4 weeks before enrollment, respectively.

Other eligibility criteria included: presence of at least 1 unidimensional measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) committee criteria[21]; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1[22]; adequate bone marrow reserve (plt $\geq 100 \times 10^9$/l; Hb $\geq$100 g/l; absolute neutrophil count $\geq 1.5 \times 10^9$/l), liver function (bilirubin $\leq 1.5 \times$ ULN; ALT/AST $\leq 2.5 \times$ ULN [$\leq 5 \times$ ULN for patients with liver metastases]; AlkPhos $\leq 4 \times$ ULN, PT, and APTT $< 1.5 \times$ ULN), and renal function (Cr $\leq 1.5 \times$ ULN).

Exclusion criteria included: history of serious cardiac disease, including active coronary artery disease, New York Heart Association class III or IV congestive heart failure, cardiac arrhythmias requiring anti-arrhythmic therapy (although digoxin or beta blockers were permitted); thrombotic or embolic events within the past 6 months; serious nonhealing wound, ulcer, or bone fracture; history of organ allograft; seizure disorder; active clinically serious infection (Common Terminology Criteria for Adverse Events [CTCAE] grade $>$2); patients undergoing renal dialysis; known brain metastases; other cancer within 5 years before the start of study treatment except cervical carcinoma in situ; treated basal cell carcinoma; or superficial bladder cancer.

Patients gave written informed consent before enrollment. The study was registered with European Union Drug Regulating Authorities Clinical Trials (number: 2008-000066-22) and approved by South Manchester Research Ethics Committee (REC number: 08/H1003/5).

Study treatment

The study treatment was delivered as an out-patient and consisted of sorafenib 400 mg twice daily, taken orally on a continuous schedule. Treatment was discontinued at disease progression, if there was unacceptable toxicity, or on patient withdrawal.

Toxicity assessment and dose reductions

Toxicity was assessed and graded using the CTCAE, version 3.0. For grade 2 toxicity, sorafenib was withheld until this had resolved to $\leq$ grade 1 and then restarted at the same dose. If the same grade 2 toxicity recurred, sorafenib was withheld until the toxicity had resolved to $\leq$ grade 1 and then restarted with a dose reduction to 600 mg daily. If this occurred again, then sorafenib was interrupted as before and when restarted there was a further dose reduction to 400 mg daily; on further occurrence, sorafenib was discontinued. If the patient experienced grade 3 or 4 toxicity, sorafenib was withheld until the toxicity resolved to $\leq$ grade 1 and then restarted with a dose reduction to 600 mg daily. If this occurred again, then sorafenib was interrupted as before and when restarted there was a further dose reduction to 400 mg daily; on further occurrence, sorafenib was discontinued. If for any reason interruption of sorafenib was for $\geq$21 days, the treatment was discontinued.

Assessment of response

Patients were followed up weekly for the first 4 weeks of study, every 2 weeks for the second 4 weeks, and at least 6 weekly until discontinuation of sorafenib and then for a further 6 months thereafter. Response to treatment was evaluated radiologically, using MRI/CT for locally recurrent disease and/or CT for sites of metastatic disease at intervals of 4 months or on clinical suspicion of progressive disease, and classified according to RECIST 1.1 criteria.[21] Patients with known lung metastases additionally underwent 2 monthly plain chest radiograph evaluation.

Statistical considerations

The primary purpose of this study was to determine PFS at 12 months in sorafenib-treated patients with advanced salivary ACC. Secondary purposes were to measure response rate (complete and partial responses), time to progression (TTP), OS, and to characterize the toxicity profile of sorafenib in this patient group. To determine the number of patients, the null hypothesis was that 10% or less of patients will not have progressed or died at 12 months. The alternative hypothesis was that the progression-free rate would be $\geq$40% at 12 months. Twenty-one patients were required to reject the null hypothesis (alpha = 2.5%; beta = 10%). If among these 21 evaluable patients, 6 or more were progression-free at 12 months, then the hypothesis that $p \leq 10\%$ would be rejected. If fewer than 6 patients were progression-free, then the hypothesis that $p \geq 40\%$ would be rejected (one sample Fleming design). In addition, it was assumed that 5% of the enrolled patients may not be valid for analysis and the sample size determined was 23 patients. PFS and

TABLE 1. Baseline patient characteristics.

Patient characteristics	No. of patients, $n = 23$
Age, y	
Median (range)	51 (36–73)
Sex	
Female	16
Male	7
ECOG Performance Status	
0	4
1	19
Prior treatment	
Surgery, primary	18
Radical radiotherapy, primary	7
Adjuvant radiotherapy, locoregional	14
Palliative radiotherapy, distant metastases	2
Palliative cytotoxic chemotherapy	10
Imatinib	7
Radiofrequency ablation, distant metastases	1
Number of prior systemic treatment regimens	
0	13
1	4
2	4
3	1
4	1
Status at enrollment	
Progressive disease	19
Stable disease	4
Site of disease	
Locally advanced only	4
Locally advanced and distant metastases	4
Distant metastases only	15
Site of distant metastases	
Lung	17
Liver	9
Renal	1
Peritoneum	1
Bone	6
(Locally advanced with intracranial spread)	(4)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

OS estimates were calculated using the Kaplan–Meier method.

RESULTS

Between September 2009 and March 2011, 23 patients were recruited at The Christie NHS Foundation Trust, Manchester, United Kingdom. Table 1 shows baseline patient characteristics and Table 2 shows the best radiological response, duration of stable disease, and reason for discontinuation of sorafenib. Individual patient data for baseline characteristics, TTP, OS, best radiological response, and reason for study discontinuation are shown in Table 3. Figure 1 is a waterfall plot demonstrating the best radiological response by the sum of unidimensional marker lesions. Kaplan–Meier estimates for PFS and OS are illustrated in Figures 2 and 3, respectively. Toxicities reported by maximum CTCAE grade are shown in Table 4.

Baseline characteristics

Twenty-three patients, 16 women and 7 men, were recruited. Median age was 51 years (range, 36–73 years) and median ECOG performance status was 1 (19 of 23 patients). Fifteen patients (65%) had distant metastases only, 4 patients (17%) had locally advanced and distant disease, and 4 patients (17%) had locally advanced and unresectable disease only. Of 23 patients, 13 (57%) had received no previous systemic therapy, 10 (43%) had palliative cytotoxic chemotherapy, and 7 (30%) had imatinib, a molecular-targeted therapy.

Survival and response to treatment

Median PFS and OS were 11.3 (95% confidence interval [CI], 8.9–13.7) and 19.6 (CI, 12.4–26.8) months, respectively (Figures 2 and 3). PFS and OS at 6 months were 69.3% (CI, 46.1–84.1) and 82.6% (CI, 60.1–93.1), and at 12 months were 46.2% (CI, 25.1–65.0) and 73.9% (CI, 50.8–87.4), respectively (Figures 2 and 3). Radiological response was not evaluable in 4 patients (17%) because of early discontinuation of sorafenib (Table 3). In 3 patients, this was due to toxicity or deterioration in performance status and in 1 patient it was a subdural empyema, thought unrelated to sorafenib. In terms of RECIST-defined best radiological response,[21] 2 patients (11%) demonstrated a partial response (PR), 13 (68%) had stable disease, and 4 (21%) had progressive disease (Tables 2 and 3; Figure 1). Both patients with PR showed reduction in disease at the primary site with stable disease elsewhere. Stable disease at 6 and 12 months was seen in 68% and 42% of patients, respectively. On retrospective evaluation, at enrollment, 4 of 23 patients did not show radiological evidence of disease progression. Of these, none demonstrated a PR and 1 of 4 had stable disease at 6 months (Table 3).

Toxicity

The median duration of sorafenib treatment was 11.8 months. However, it was only reasonably well tolerated and 13 patients (57%) experienced grade 3 toxicity. There were 25 grade 3 events (Table 4). The most common grade 3 toxicities were fatigue, weight loss, hand foot syndrome, abdominal pain, and deranged liver function

TABLE 2. Best radiological response, duration of stable disease, and reason for sorafenib discontinuation.

Sorafenib	No. of patients	P %
Best response	$N = 19$	
CR	0/19	0
PR	2/19	11
SD	13/19	68
PD	4/19	21
(Not evaluable)	(4/23)	(17)
Duration of SD	$N = 19$	
SD $\geq$6 mo	13/19	68
SD $\geq$12 mo	8/19	42
Reason for discontinuation	$N = 23$	
PD	15	65
Toxicity	7	30
Intercurrent illness (unrelated)	1	4

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

TABLE 3. Individual patient data for baseline characteristics, response to treatment, and reason for sorafenib discontinuation.

Sex	Age, y	ECOG PS	Sites of disease*	Status at enrollment	Prior systemic therapy	TTP, mo	OS, mo	Best response (RECIST)	Reason for sorafenib discontinuation
F	58	1	2, 3, 6	PD	Yes	NA	6.7	NE	Toxicity (decline ECOG PS)
M	44	1	2, 3, 4	PD	Yes	22.2	33.2	SD	PD
F	46	1	2	PD	Yes	10.7	18.8	SD	PD
F	64	1	2, 3	PD	Yes	NA	15.2	NE	Toxicity (nausea)
M	68	1	1, 2	PD	Yes	12.9	23.3	PR	PD
F	47	1	1, 2	PD	No	NA	17.5	SD	Toxicity (fatigue, diarrhea)
F	36	1	2, 3, 5	PD	Yes	10.8	30.7	SD	PD
M	55	1	2	PD	Yes	11.1	27.7	SD	PD
F	45	1	1, 7	PD	Yes	NA	3.6	NE	Intercurrent illness (subdural empyema)
F	51	0	2, 3	PD	No	5.9	8.1	SD	PD
M	69	1	3, 6	PD	No	3.3	4.6	PD	PD
F	49	1	1, 2, 3, 6, 7	PD	No	11.3	NA	SD	PD
F	63	1	2, 3, 6	PD	No	14.3	18.7	SD	PD
M	62	1	6	PD	No	3.4	18.4	PD	PD
F	59	1	2	SD	No	NA	19.6	SD	Toxicity (fatigue)
M	45	0	1, 7	SD	No	NA	2.9	NE	Toxicity (decline ECOG PS)
F	39	0	2, 3	SD	No	NA	NA	SD	Toxicity (cutaneous ulceration)†
F	73	1	1, 2	PD	No	12.9	NA	PR	PD
F	61	1	2	PD	Yes	30.2	NA	SD	PD
F	70	1	1	PD	No	NA	NA	SD	Toxicity (anorexia, weight loss)
F	45	1	2	SD	Yes	3.7	NA	PD	PD
F	38	1	1, 7	PD	No	2.6	4.0	PD	PD
M	50	0	2, 6	PD	No	23.9	NA	SD	PD

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale; TTP, time to progression; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; PD, progressive disease; NA, not applicable; NE, not evaluable; SD, stable disease; PR, partial response.
* Local = 1, lung = 2, liver = 3, renal = 4, peritoneum = 5, bone = 6, and intracranial = 7.
† Discontinuation because of suspected toxicity, subsequently found unrelated to the study drug.

tests (Table 4). A dose reduction was required in 74% of patients (12 of 23 patients were reduced to 600 mg and 5 of 23 to 400 mg) and only 6 of 23 patients did not receive this. Dose intensity, defined as the sum of the total intended dose divided by the sum of the actual total dose received for each patient (including dose reductions, planned treatment interruptions, and reported missed doses) expressed as median and mean percentages was 77% and 79%, respectively.

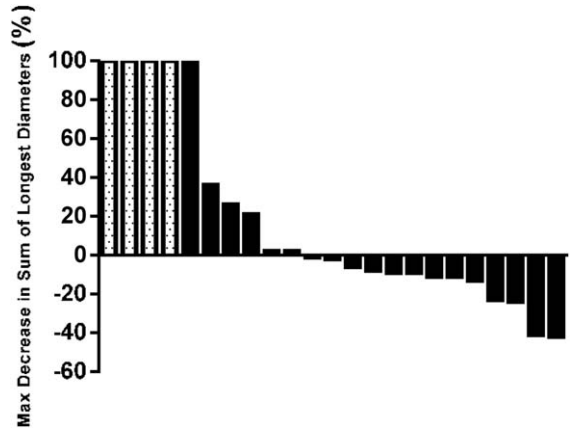

FIGURE 1. Waterfall plot to show maximum decrease in sum of longest dimensions of target lesions. One patient at first radiological evaluation experienced progression as a result of new lesions and this is represented as a 100% increase. Response was not evaluable in 4 patients because of early discontinuation of sorafenib, illustrated as dotted bars.

DISCUSSION

Patients with locally advanced recurrent and/or metastatic ACC are incurable.[1] The disease shows a

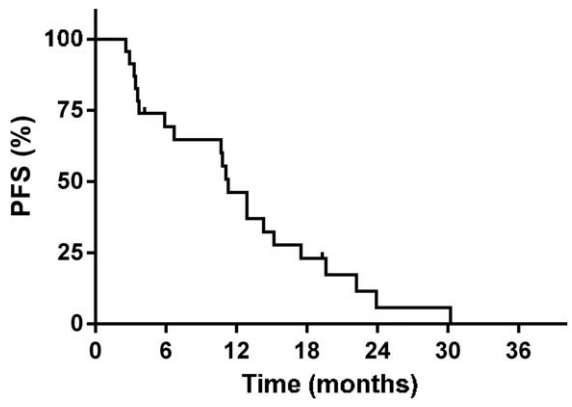

FIGURE 2. Kaplan–Meier estimation to show progression-free survival (PFS). Alive patients who stopped sorafenib because of toxicity are censored at the time of study drug discontinuation.

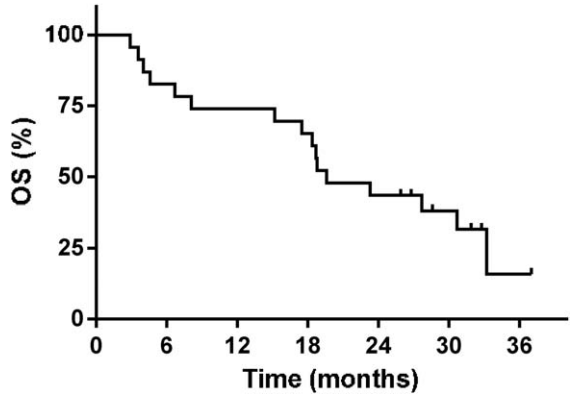

FIGURE 3. Kaplan–Meier estimation to show overall survival (OS). Alive patients are censored at the time of analysis.

variable natural history, often characterized by slow progression.[3,5] There is a limited role for cytotoxic chemotherapy, with relatively poor objective or sustained responses.[1] Consequently, there have been a number of trials investigating effectiveness of molecularly targeted agents. However, to date, these have shown disappointing objective responses and survival outcomes, as summarized in Table 5.[7–9,14,23–25] We report the results of a phase II trial of sorafenib, an oral multikinase inhibitor, in treatment of advanced ACC.

The primary endpoint of this trial was to determine PFS at 12 months, which was seen in 46.2% of patients (CI, 25.1–65.0). Of interest, because sorafenib targets multiple pathways (proliferative, apoptotic, and angiogenic), it may be more effective when combined with chemotherapy agents that have a complementary mechanism of action.[26] Indeed, there are early clinical studies demonstrating promising results in use of sorafenib combined with a range of chemotherapy agents in a number of solid tumors.[26]

Interpretation of RECIST-defined radiological response[21] in ACC is confounded by the often indolent nature of disease progression. This is compounded by investigation of molecularly targeted agents, in which the predominant mode of action may be cytostatic rather than cytotoxic.[14] Despite this, 2 of 19 patients demonstrated a PR, which compares favorably to other trials of targeted agents (Table 5). However, this comparison should be interpreted with caution as the response was observed at the primary site with stable disease elsewhere. Nonetheless, in an ongoing phase II trial of sorafenib in salivary gland carcinomas, 2 of 19 patients with ACC also showed a PR.[14,27] A prolonged period of stable disease defined as $\geq$6 months,[14,23] may be of clinical benefit.[9,24]This was observed in 68% of assessable patients (Tables 2 and 3). This is comparable to a phase II study of sunitinib, superior to trials with imatinib alone or epidermal growth

TABLE 4. Toxicity reported by maximum Common Terminology Criteria for Adverse Events grade, version 3.0.

	Maximum CTCAE grade			
Toxicity	1	2	3	4
Nausea	14	1	0	0
Vomiting	7	1	0	0
Gastric disturbance	7	0	0	0
Constipation	3	1	1	0
Diarrhea	13	3	2	0
Anorexia	7	3	1	0
Weight loss	4	4	3	0
Dysphagia	2	1	1	0
Oral mucositis	4	1	0	0
Fatigue	7	10	5	0
Rash	11	4	2	0
Hand foot syndrome	11	3	3	0
Peripheral neuropathy	4	0	0	0
Tinnitus	3	0	0	0
Hypertension	3	0	0	0
Bleeding	0	1	0	0
Abdominal pain	5	1	3	0
Alopecia	7	0	0	0
Low mood	0	3	0	0
Anemia	0	1	0	0
Neutropenia	0	0	1	0
Deranged liver function tests	0	0	3	0

Abbreviation: Common Terminology Criteria for Adverse Events.

TABLE 5. Phase II studies of targeted agents in advanced adenoid cystic carcinoma.

Study	Study drug(s)	No. of patients	PD required at enrollment	Best response, no. (%)		SD for $\geq$6 mo	SD for $\geq$12 mo	Median PFS, mo	Median OS, mo
				PR	SD				
Hotte et al[7]	Imatinib	16	No	0/15	9/15 (60)	2/15 (13)	2/15 (13)	2.3	6.9
Ghosal et al[9]	Imatinib and cisplatin	28	Yes	3/28 (11)	19/28 (68)	22/28 (79)	16/28 (57)	16 (from graph)	35
Pfeffer et al[8]	Imatinib	10	No	0/10	7/10 (70)	2/10 (20)	1/10 (10)	NA	NA
Agulnik et al[23]	Lapatinib	20	Yes	0/19	15/19 (79)	9/19 (47)	5/19 (26)	3.5	Not reached
Locati et al[24]	Cetuximab	23	No	0/23	20/23 (87)	12/23 (52)	NA	6.0 (TTP)	NA
Argiris et al[25]	Bortezomib (with doxorubicin on progression)	24	Yes	0/21	15/21 (71)	Median SD = 4.2 mo	NA	6.4	21
Chau et al[14]	Sunitinib	14	Yes	0/13	11/13 (85)	8/13 (62)	NA	7.2 (TTP)	18.7
Current study	Sorafenib	23	No	2/19 (11)	13/19 (68)	13/19 (68)	8/19 (42)	11.3	19.6

Abbreviations: PD, progressive disease; PR, partial response; SD, stable disease; PFS, progression-free survival; OS, overall survival; NA, not applicable; TTP, time to progression.

factor receptor targeted therapies, and inferior to a combination of cisplatin and imatinib (Table 5).[7–9,14,23,24]

A potential criticism of this study is that radiological evidence of progressive disease was not a requirement at enrollment. On retrospective evaluation, 4 of 23 patients had stable disease on commencing sorafenib. Of these, none demonstrated an objective response and only 1 of 4 showed stable disease for >6 months. Therefore, this seems to have had minimal confounding influence on differentiating activity of the study drug from inherently indolent disease. In support of this, at inclusion 19 patients (83%) had evidence of disease progression and of the 16 of 19 patients with evaluable disease, 12 (75%) showed stable disease at 6 months (Table 3).

Sorafenib was only reasonably well tolerated. Most patients (17 of 23) required a dose reduction and 13 (57%) experienced grade 3 toxicity. This is higher than seen in previous trials of sorafenib in renal cell carcinoma and hepatocellular carcinoma and in a phase II study of head and neck squamous cell carcinoma.[17,18,28] This may partly be explained by the longer median duration of treatment in this study.

In summary, we demonstrate modest activity of sorafenib in advanced ACC with a 12-month PFS of 46.2% and evidence of disease stabilization in some two thirds of patients. However, sorafenib 400 mg twice daily was associated with significant toxicity. When considered together with limited effectiveness, single agent sorafenib cannot be enthusiastically recommended for further evaluation. Future scheduling and dose-finding studies of sorafenib combined with chemotherapy in treatment of advanced ACC may be warranted.

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