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A Phase II Study of Dovitinib in Patients with Recurrent or Metastatic Adenoid Cystic Carcinoma

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Abstract

Purpose: Genetic and preclinical studies have implicated FGFR signaling in the pathogenesis of adenoid cystic carcinoma (ACC). Dovitinib, a suppressor of FGFR activity, may be active in ACC.

Experimental Design: In a two-stage phase II study, 35 patients with progressive ACC were treated with dovitinib 500 mg orally for 5 of 7 days continuously. The primary endpoints were objective response rate and change in tumor growth rate. Progression-free survival, overall survival, metabolic response, biomarker, and quality of life were secondary endpoints.

Results: Of 34 evaluable patients, 2 (6%) had a partial response and 22 (65%) had stable disease >4 months. Median PFS was 8.2 months and OS was 20.6 months. The slope of the overall TGR fell from 1.95 to 0.63 on treatment ($P < 0.001$). Toxicity was moderate; 63% of patients developed grade 3–4 toxicity, 94% required dose modifications, and 21% stopped treatment early. An early metabolic response based on ^{18}FDG-PET scans was seen in 3 of 15 patients but did not correlate with RECIST response. *MYB* gene translocation was observed and significantly correlated with overexpression of MYB but did not correlate with FGFR1 phosphorylation or clinical response to dovitinib.

Conclusions: Dovitinib produced few objective responses in patients with ACC but did suppress the TGR with a PFS that compares favorably with those reported with other targeted agents. Future studies of more potent and selective FGFR inhibitors in biomarker-selected patients will be required to determine whether FGFR signaling is a valid therapeutic target in ACC. *Clin Cancer Res; 23(15); 4138–45. ©2017 AACR.*

Introduction

Adenoid cystic carcinomas (ACC) are rare malignancies that afflict 1,200 individuals per year in the United States. The most common primary sites are the salivary gland and other regions in the head and neck, but they may also arise in the skin, breast, and uterus (1). Localized ACCs are usually treated with surgery and/or radiotherapy, but local and distant recurrences are frequent due to the tumor's propensity for perineural infiltration and to metastasize to the lung. Although the median survival for patients with metastatic ACC is about 4 years, the disease often becomes more aggressive later in the course, such that the median survival for patients whose disease had progressed within the previous 6 months is in the range of 18 to 20 months (1–4). Unfortunately, there is no effective systemic treatment for advanced ACC, as standard cytotoxic chemotherapy agents produce tumor response rates in the range of 5% to 15% without a clear impact on patient survival (5–7). Targeted agents, including cetuximab, erlotinib, gefitinib, vorinostat, and others, have also shown limited activity against ACCs (3, 4, 8, 9). One potential target, the tyrosine kinase receptor KIT, is overexpressed in the majority of these tumors, but treatment of ACC patients with the KIT inhibitor, imatinib, produced no or little clinical benefit (10–12). Similarly, the multikinase inhibitors sunitinib and sorafenib, whose targets include VEGFR and PDGFR, rarely cause objective responses, although they may confer a modest improvement in progression-free survival (PFS; refs. 3, 4).

Genetic analyses have shown that ACCs frequently acquire chromosomal translocations such as t(6;9)(q22–23;p23–24) that result in the overexpression of the oncogenic transcription factors MYB or MYBL1 (13–19). The relevance of MYB to the pathogenesis of ACCs is supported by the observation that inhibition of its transcriptional regulatory functions by the BET domain inhibitor JQ1 suppresses the growth of lower grade ACCs propagated as primary xenografts (15). An alternative is to target downstream effectors of MYB, which may include the FGFRs. Among the potential consequences of MYB overexpression appears to be upregulation of FGFR2 and its ligand FGF2, perhaps related to MYB DNA-binding sites that are located near the corresponding genes (15, 17, 20). This, perhaps in conjunction with elevated FGFR1 expression, could result in autocrine receptor signaling and promote tumor growth (21). This scenario is consistent with proteomic studies of primary ACC xenografts that detected spontaneous phosphorylation of peptides derived from the carboxy

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Translational Relevance

FGFR signaling in adenoid cystic carcinoma (ACC) is believed to be upregulated by recurring *MYB:NFIB* translocations seen in the majority of ACC tumor samples or uncommon mutations in components of the FGFR signaling pathway. Dovitinib, a multikinase inhibitor that suppresses FGFR 1–3 signaling, reduces growth of some ACC xenografts. This article describes an open-label, phase II study of the efficacy of dovitinib treatment for patients with recently progressive tumors. Clinical response rate was low, but disease stabilization was common. Dovitinib also induced a significant decrease in tumor growth rate as measured by change point analysis. Analysis of a subset of tumors showed that *MYB:NFIB* translocations correlated significantly with increased MYB expression. FGFR1 phosphorylation was frequent but did not correlate with MYB expression or with clinical endpoints. Although dovitinib has some activity against ACC, additional studies of FGFR-specific inhibitors in biomarker-selected patients along with companion pharmacodynamic studies are needed to determine whether FGFR signaling is a valid therapeutic target in ACC.

terminus of FGFR1 (22). In addition, 4% to 12% of ACCs harbor mutations that are predicted to activate or enhance FGFR signaling independently of MYB overexpression (16, 19). A role for FGFR signaling in the pathogenesis of ACC is further supported by the observation that inhibitors of the receptor kinase can suppress the growth of primary ACC xenografts (23).

Dovitinib (TKI258) is a multityrosine kinase inhibitor that not only inhibits the VEGFR, PDGFR, c-Kit, CSF-1R, RET, TrkA, and FLT3 receptor kinases, but also FGFRs 1–3 (IC_{50} of 10 nmol/L; refs. 24, 25). This contrasts with sorafenib and sunitinib that have similar activity against the VEGFRs and other shared targets but have only weak activity against the FGFRs (IC_{50} = 580 and 880 nmol/L, respectively). Given that *MYB* gene alterations are found in the majority of ACCs and may drive autocrine activation of FGFRs, we postulated that the ability of dovitinib to inhibit signaling by these receptors would result in a high tumor response rate in patients with advanced and progressive tumors. To test this hypothesis, we conducted a phase II study of dovitinib in patients whose tumors had progressed in the past 6 months. Objective tumor response was set as the primary endpoint, but we also measured alterations in the tumor growth rate (TGR) as determined by change point analysis to detect more subtle antitumor drug effects that may be clinically relevant. Other secondary endpoints included estimation of the PFS, overall survival (OS) and clinical benefit rate, evaluation of the adverse events, and descriptions of the early metabolic response rate, changes in quality of life (QOL), and correlation between biomarkers and clinical outcome.

Materials and Methods

Patients

Eligible patients were 18 years of age or older with a diagnosis of ACC confirmed by expert review (Drs. C.A. Moskaluk and H. Frierson). All patients had unresectable and/or metastatic measurable disease with evidence of progression within the previous 6 months based on imaging and RECIST 2.0 criteria. All patients were required to submit remote pretreatment cross-sectional films (minimum of 3 months prior to baseline film) to calculate the pretreatment TGR. Up to five target lesions were chosen from scans 3 to 6 months prior to enrollment and assessed by a radiologist. There was no limit on the number of prior therapies, but patients must not have had chemotherapy, radiotherapy, surgery, or investigational treatments in the previous 4 weeks. Other eligibility criteria were as follows: ECOG performance status of 0 to 2, life expectancy of at least 16 weeks, neutrophil count $\geq$1,500/μL, platelet count $\geq$100,000/μL, hemoglobin >9 g/dL, total bilirubin $\leq$1.5× upper limit of normal (ULN), AST and/or ALT $\leq$3× ULN, creatinine $\leq$1.5× ULN or creatinine clearance $\geq$30 mL/minute, absence of brain metastases, no other active malignancy in the past 3 years (adequately treated cervical carcinoma *in situ* and nonmelanoma skin cancers excepted), no serious medical conditions, left ventricular ejection fraction >45%, and absence of uncontrolled hypertension, malabsorption, cirrhosis, warfarin therapy, pregnancy, and active breastfeeding. Referring hospitals were asked to submit tissue blocks for biomarker analysis. This study was approved by the University of Virginia Institutional Review Board for Health Sciences Research, and patients signed informed consent before study entry.

Study design and treatment

This was a modified two-step phase II clinical trial in which patients were treated with dovitinib (supplied by Novartis Pharmaceuticals Corporation) at a starting dose of 500 mg taken orally for 5 days on and 2 days off; cycle length was 28 days. Treatment was continued until disease progression, unacceptable toxicity, patient refusal, or at the physician's discretion. Dose reductions and delays were allowed as per protocol. Toxicity was graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. For intolerable grade 2, or for grade 3 or 4 toxicity, dovitinib was withheld until the toxicity returned to grade 1 or baseline, and the dose was reduced to 400 mg at the same schedule. If the toxicity recurred, the drug was stopped again until the toxicity returned to grade 1 or baseline, and the dose was reduced to 300 mg. For asymptomatic grade 3 hypertension, hyperlipidemia, or cytopenias, dovitinib was withheld until the toxicity resolved to grade 1 and then resumed at the same dose or decreased one dose level at physician discretion. If the grade 3 or 4 toxicity recurred, the drug was withheld until recovery to grade 1, and the dose was again reduced. For a third recurrence of any grade 3 or 4 toxicity, the drug was discontinued. Patients were also taken off treatment if the interruption for toxicity lasted longer than 21 days without recovery to grade 1 or baseline or if they developed a grade 4 toxicity that was judged to be life threatening.

Statistical analyses

The primary endpoints were objective tumor response rate [ORR; complete (CR) and partial responses (PR)] and drug-induced changes in the TGR using the change point method (26). Tumor response was determined by RECIST 1.1 criteria from CT or magnetic resonance images obtained at 2, 4, and 8 months then every 4 cycles until progression. The modified two-stage trial design incorporated the alternative hypothesis that dovitinib would produce an ORR of at least 18% as compared with 1%, with approximate power of 90% and a one-sided type I

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error rate of 5%. The first stage allowed the study to be terminated for drug inactivity if no responses were seen in the first 16 patients. If at least one objective response was observed, 5 additional patients would be enrolled. If $\geq$2 of the 21 patients experienced an objective response, a subsequent protocol amendment recommended the recruitment of 14 additional evaluable patients to more precisely evaluate the change in the TGR. The two stage design was chosen to allow an early "go or no go" decision to minimize patient exposure to dovitinib.

For change point analysis, piecewise linear models of tumor growth were fit to describe a patient's tumor growth profile while on treatment compared with their pretreatment profile (using up to five index lesions from prebaseline films). A preliminary analysis of data from 5 untreated ACC patients allowed us to estimate the variance and power to detect reductions in slopes using change point analysis. In each model, we allowed for one change point, one slope measured from −6 months to time 0 (TG0) compared with the slope (TG1) for the period from study entry to a minimum of 4 months after the start of treatment (time 0 to time 4 months). The effect of treatment on tumor growth was assessed by measuring the change in slope between the pre- and posttreatment periods. Using the estimated variance of change in tumor growth from studies of untreated patients (data not shown), we designed this study to detect a change in the TGR. With a total of 35 patients, there would be 80% power to detect an absolute reduction of 0.62 in the slope of the line that represents the tumor growth rate.

Secondary objectives were to estimate PFS, the clinical benefit rate (CR + PR + stable disease >4 months), OS, and to determine the adverse event profile. Exploratory analyses included evaluation of early metabolic tumor response rate (day 12), changes in QOL, and biomarker studies. Early metabolic responses were defined as 25% reduction in the maximal standard uptake (SUV) of 18F-fluorodeoxyglucose (^{18}FDG) on PET scans done on day 12 as compared with pretreatment values (27). QOL outcomes were monitored by the FACT-G questionnaires at each clinic visit. The biomarker studies looked for potential correlations between *MYB:NFIB* chromosomal translocation and the expression of c-MYB, phosphorylated FGFR1, and clinical endpoints (Supplementary Data).

Results

Between February 2012 and December 2013, 65 patients were screened and 38 patients were consented (Table 1). Thirty-four patients were evaluable for response and 35 for toxicity. Two patients signed consent but were never treated (financial burden for one and pneumonia for another). The median number of completed cycles was 8 (range, 0–20). Twenty-two patients came off study due to progressive tumor, 8 because of toxicity, 3 due to withdrawals, one due to disease-related adverse event, and one due to death.

Clinical responses and stable disease were observed in treated patients

Partial tumor responses were observed in 2 patients, including one with a CR of the measurable tracheal lesion without changes in nonmeasurable bone metastases (Table 2). The other experienced a 32% decrease in RECIST measurements at 2 months, primarily due to marked regression of the largest lung metastasis and also a dramatic decrease in cancer pain. However, although this response was apparent on the follow-up scan 4 months later, the appearance of a new ground glass area made this an unconfirmed response by standard RECIST criteria (unclear whether pneumonia vs. tumor per radiologist). Given the extent of the initial response and the relatively long interval between scans, we chose to list this case as a response but denote it as unconfirmed. Overall, 14 patients (41%) experienced any degree of tumor regression at any point (Fig. 1). In addition, dovitinib significantly suppressed the TGR (Fig. 2). Prior to treatment, the slope of the line representing TGR was 1.95, which dropped to 0.63 after four cycles of dovitinib ($P < 0.001$). In an unplanned analysis, we noted that beyond 4 months, the slope increased to 1.06 but remained significantly lower than the pretreatment level ($P < 0.001$). This suggested the emergence of partial drug resistance with an ongoing drug effect at least up until the time treatment was stopped, the consequence of the frequent dose reductions of dovitinib, and/or the influence of drug-independent events. Given the low rate of clinical responses, no robust association of TGR with outcome (OR, PFS, or OS) was observed in an exploratory analysis. It is noted that the two partial responders had relatively steep TGRs prior to treatment but so did some nonresponders. It is noteworthy that half of the patients (49%) on this trial had prior systemic therapies (Table 1) for ACC (possibly owing to the lack of effective therapies for ACC). Of the participants, 37% (13/35) had a prior systemic therapy in the 6 months prior to enrollment.

Table 1. Characteristics of 35 patients with ACC

Characteristics	Median (range)
Age, years	56 (28–75)
	Patients, *n* (%)
Gender	
Female	18 (51)
Male	17 (49)
Ethnicity	
Hispanic or Latino	3 (9)
Non-Hispanic	32 (91)
Race	
Asian	1 (3)
Black or African American	2 (6)
More than one race	1 (3)
White	30 (86)
Other	1 (3)
ECOG performance status	
0	12 (34)
1	21 (60)
2	2 (6)
Primary site	
Parotid gland	10 (29)
Minor salivary gland	12 (34)
Other oronasopharyngeal site	8 (23)
Trachea	3 (9)
Bartholin's gland	1 (3)
Lacrimal	1 (3)
Number of prior systemic regimens	
0	18 (51)
1	9 (26)
2	4 (11)
3	1 (3)
4 or more	3 (9)
Metastatic sites (multiple possible)	
Lung	32 (91)
Liver	15 (43)
Bone	16 (46)
Kidney or spleen	4 (11)
Soft tissue	11 (31)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

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Table 2. Summary of responses and reasons for removal from study

Best response	*n* = 34 (%; 95% CI)	Reason off study
PR/UcPR	2 (5.9; 0.7–19.7)	Progression (1) AEs (1)
Stable 2 month scan	9 (26.5; 12.9–44.4)	Early death (1) Progression (3) AEs (4) Withdrawal (1)
Stable ≥ 4 months	22 (64.7; 46.5–80.3)	Progression (18) AEs (2) Withdrawal (2)
Failure/death	1 (2.9; 0.1–15.3)	AE
PR/uPR + SD4	24 (70.6; 52.5–84.9)	

Abbreviation: AE, adverse events.

At the last follow-up, 15 patients have died and 20 patients remain alive. The median PFS for the entire group (Fig. 3) was 8.2 months [90% confidence interval (CI), 7.3–11.0] with a median OS of 20.6 months (90% CI, 17.6–unmet). Of 34 evaluable patients, all but one had stable or responsive disease at 2 months, whereas the clinical benefit rate (CR + PR + stable disease ≥4 months) was 70.6%.

In an exploratory study, 15 patients underwent PET imaging with ^{18}FDG before and 12 days after starting treatment to determine whether FGFR inhibition alters tumor glucose metabolism and whether metabolic tumor response correlates with subsequent clinical outcome (27–29). Three patients (20%) had metabolic responses with no discernable changes in tumor size. Overall, the tumor SUV decreased in 8 patients and increased in 6. However, there was no apparent association between metabolic response and other study endpoints (Supplementary Table S4).

QOL as assessed by FACT-G questionnaires is summarized in Supplementary Fig. S2. In modeling overall QOL, there was a significant association between overall QOL and time to treatment failure, where higher scores of QOL were associated with a smaller instantaneous hazard of end of treatment ($P = 0.073$). Time is the only significant covariate in the model, where there is an average decrease in QOL of 1.2 points for each additional month in the study ($P = 0.014$). The subset of patients who experienced pain relief while on dovitinib generally had the least decline in FACT-G scores, but there was no correlation with objective tumor response or PFS. Notably, overall QOL scores trend lower over time, suggesting either morbidity from disease progression or cumulative toxicity from treatment or a combination.

MYB gene rearrangements and exome sequencing results

Tumor samples from a subset of patients were available for biomarker and genetic testing. Tissue samples were frequently insufficient or had been depleted by prior pathologic studies during clinical analyses of this rare tumor type. Serial biopsies were not pursued for safety considerations; in many patients, this would require lung biopsies. Of the 15 tested tumors, 10 had *MYB* gene rearrangements as determined by the break-apart FISH assay. Despite the limited sample sizes, we found significant associations between *MYB* translocation and higher MYB expression ($P = 0.021$) as determined by IHC; however, there was no apparent association with FGFR1 phosphorylation ($P = 0.99$) or clinical endpoints. Nine tumor samples yielded DNA suitable for exome sequence analysis of the Foundation One gene panel. This revealed gene mutations previously reported to be altered in ACCs but no alterations in the FGF or FGFR genes (Supplementary Table S4).

Toxicity

Dovitinib was generally tolerable, although dose reductions were required in all but 2 patients and 8 stopped treatment due to toxicity, most often due to fatigue and anorexia. Grade 1 and 2 toxicities that were seen in more than 50% of patients

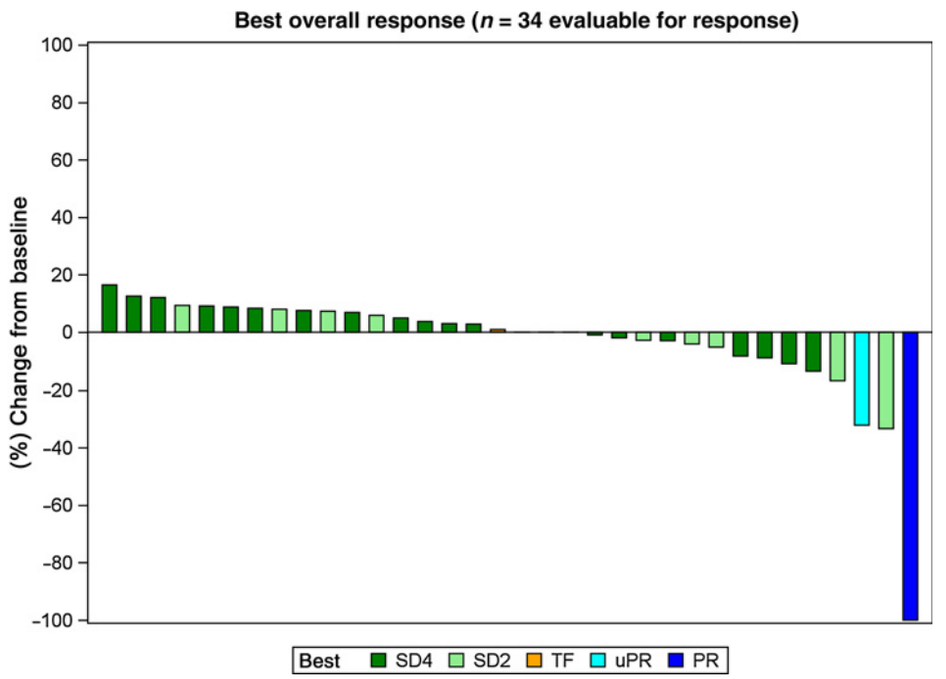

Figure 1.
Response to treatment. Maximum percentage change from baseline in target lesions. SD4, stable disease at 4-month assessment; SD2, stable disease at 2-month assessment; TF, a patient with stable disease who died while on study; uPR, unconfirmed PR. PR, confirmed PR.

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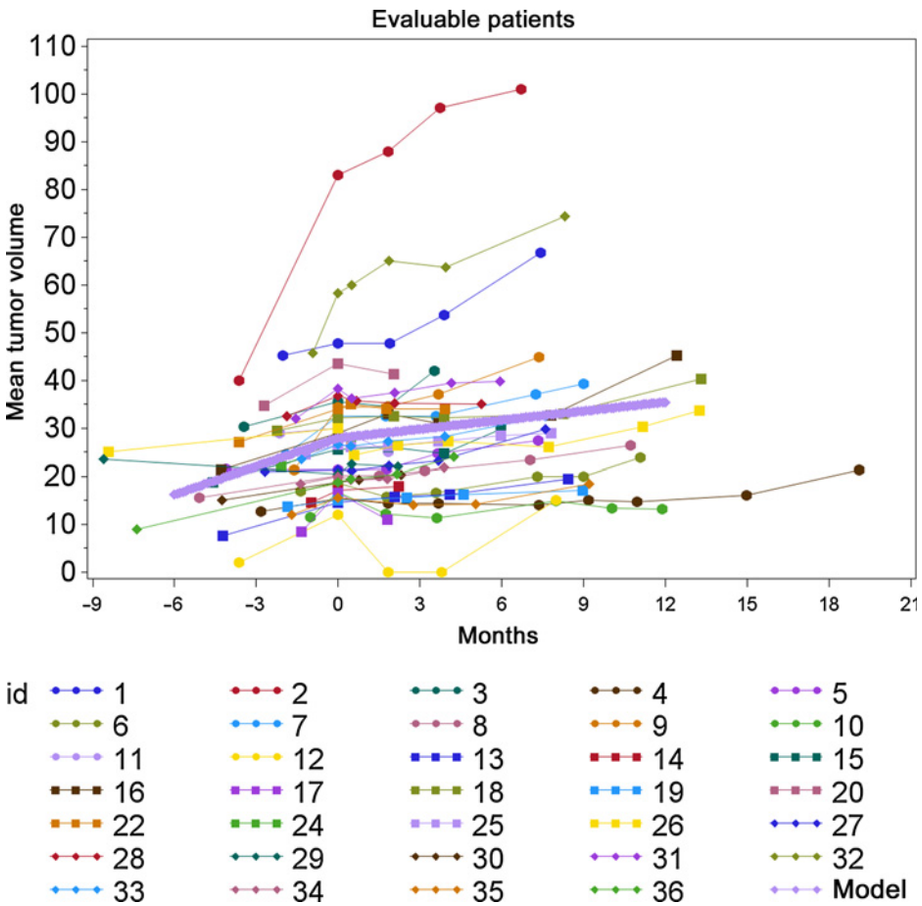

Figure 2.

Change point analysis plot. This figure demonstrates the assessment of tumor growth kinetics based on prestudy and on-study measurements of the sum of the longest diameters of target lesions. The measurements at month zero are the on-study scans. Up to 3 prestudy scans were evaluated up to 9 months prior to study enrollment. The tumor diameter sums are shown for 34 patients. The thick blue line is the summary change point analysis line as modeled using piecewise linear models of tumor growth allowing for one inflection point for the pre- and posttreatment periods. The component of the summary line for the slope of tumor growth rate pretreatment was 1.95. The slope of that blue summary line posttreatment was 0.63 ($P < 0.001$). Repeated measures model results:

Label	Estimate	SE	t-value	Pr>|t|
Pre slope	1.95	0.29	6.71	<0.001
Post slope	0.63	0.18	3.41	<0.001
Post – Pre	−1.32	0.35	−3.77	<0.001

included fatigue, nausea, diarrhea, anorexia, and acneiform rash (Supplementary Table S3). Hyperphosphatemia was not observed. Grade 3 or higher toxicity was observed in 63% of the patients, including 9 with hypertriglyceridemia (Table 3). One patient with locally recurrent stage III ACC of the parotid developed central necrosis of tumor after 2 months of therapy but died from pneumonia while on study.

Discussion

This study revealed that dovitinib has demonstrable but limited antitumor activity in patients with recently progressed ACC. Although the ORR (6%) was not sufficient to reject the null hypothesis, dovitinib significantly suppressed the overall TGR as determined by change point analysis. Consistent with this, about 40% of the patients had some reduction in tumor volume, and 65% had stable disease for greater than 4 months. We also observed that 3 of 15 evaluable patients had early metabolic responses as determined by ^{18}FDG PET imaging. Although a high proportion (43%) of our patients had liver involvement, an adverse prognostic factor, the median PFS (8.2 months) and OS (21 months) compared favorably with those reported for ACC patients treated with other kinase inhibitors. For instance, median PFS for patients treated with cetuximab, lapatinib, imatinib, or regorafenib in phase II studies is in the range of 2.5 to 6 months, whereas the values for those given sunitinib or sorafenib were 7.2 and 11.3 months, respectively (3, 4, 8, 12, 16). The prolonged PFS in the sorafenib study may reflect the inclusion of patients without evidence of recent tumor progression; also, despite the reported PFS, the OS (19.6 months) was similar to that seen in our dovitinib-treated patients (4). The antitumor effects of dovitinib were achieved at

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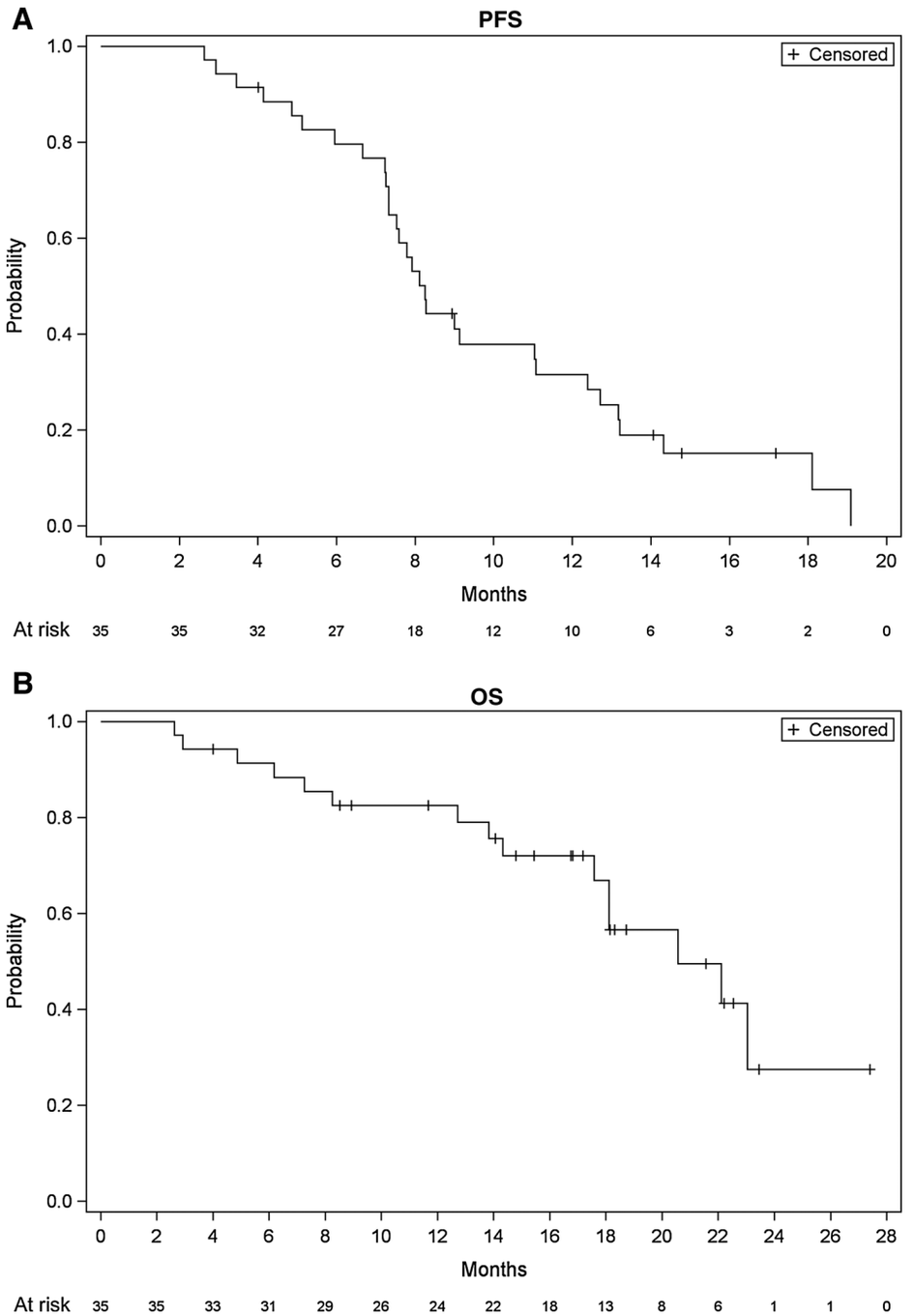

Figure 3.
Patient survival data. **A,** PFS. **B,** OS.

the expense of moderate toxicity, as dose reductions were required in almost all patients, and one in five stopped treatment due to adverse effects. That dovitinib has limited activity against ACC is supported by a recently reported trial in which only one of 32 treated ACC patients responded to this drug, although 69% did exhibit minor responses (30).

The results of our trial leave open the question of whether or not FGFR is an appropriate therapeutic target in ACC. We had postulated that FGFR signaling acted downstream of the frequently acquired *MYB* gene mutations, and inhibition of this signaling would produce at least a moderate objective tumor response rate. This was not observed; however, treatment was associated with a reduction in TGR and a favorable PFS. Because dovitinib is a multikinase inhibitor, we cannot determine whether the observed antitumor effects were due to inhibition of signaling by the FGFR or other target receptors, or a combinatorial effect. In this regard, sunitinib and sorafenib, which lack activity against FGFRs, nonetheless confer PFS or OS similar to that seen in our dovitinib-treated patients. Thus, the similarities in clinical outcome seen with these three

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Table 3. Grade 3/4 toxicities believed to be possibly, probably, or definitely related to dovitinib

Toxicity (grade 3 or 4)	Number
Anemia	1
Constipation	1
Diarrhea	1
Mucositis	1
Nausea/vomiting	1
Stomach pain	2
Fatigue	1
Urinary tract infection	1
Transaminitis	1
GGT elevation	4
Dehydration	1
Neutropenia	1
Hypertriglyceridemia	9
Anxiety	1
Thromboembolic event	1
Hypertension	1
Pain	2
Acneiform rash	1

Abbreviation: GGT, gamma-glutamyltransferase.

kinase inhibitors may stem from suppression of shared targets, such as the VEGFRs.

One possible explanation for the low ORR of ACCs to dovitinib is failure of the drug to adequately suppress oncogenic FGFR signaling in tumor tissues. Although dovitinib has been shown to increase the blood levels of FGF23, a biomarker of systemic FGFR inhibition, the drug produces little or no hyperphosphatemia, which is a marker of more robust receptor inhibition (31–33). That dovitinib may not produce sufficient FGFR suppression *in vivo* is supported by phase II studies of patients with bladder cancer who were treated with dovitinib or the more potent and specific FGFR inhibitor BGJ398. Dovitinib produced only one response in 54 treated patients and none in 12 patients whose tumors harbored FGFR3 gene mutations (34). In contrast, BGJ398 caused hyperphosphatemia in up to one half of the treated patients and an ORR of 36% in those whose tumors contained FGFR gene alterations (31). Thus, it is possible that the more potent and specific FGFR inhibitors, such as BGJ398, may be more effective than dovitinib in the treatment of ACC.

Another explanation for the few objective responses in our study is that the FGFRs are not major drivers of tumorigenesis in the majority of ACCs, irrespective of *MYB* gene status. In the ancillary studies, we found that 10 of the 15 tumors that were studied contained detectable *MYB* gene rearrangements, and this correlated with higher MYB expression as determined by IHC. However, in this limited sampling, there was no apparent association between *MYB* mutation or expression and the level of FGFR1 phosphorylation ($P = 0.99$) or clinical outcome. This suggests that *MYB* translocation is not tightly associated with FGFR1 activation and therefore may not be a reliable marker of sensitivity to FGFR inhibitors. However, our observations do not exclude the possibility that the response rate to dovitinib would be much higher in the small subset of ACC patients with tumors that contain activating mutations in the FGFR or FGF genes (16, 19).

This study did confirm that change point analysis of TGR of ACCs is feasible and capable of detecting statistically significant reductions in the TGR following within 4 months of initiating drug treatment. However, additional studies will be needed to determine the degree of TGR suppression required to confer a true clinical benefit. Once established, the specified reduction in TGR could be used as an early endpoint in trials of ACC designed to identify agents likely to be clinically effective. In this regard, reductions in the TGR (measured by a distinct method) were linked to improved OS in patients with renal cancer treated with kinase inhibitors and with favorable PFS in patients entered into a series of phase I trials (35–37).

In summary, we found that dovitinib has limited but demonstrable antitumor activity against ACCs. However, it is not clear whether these limitations are related to inability of the drug to adequately suppress oncogenic FGFR signaling or the fact that FGFRs are not valid therapeutic targets in the majority of tumors. These issues can be clarified by additional preclinical studies to confirm that MYB gene translocation is associated with autocrine FGFR signaling. If so, this would justify a follow-up phase II trial of a potent FGFR-specific inhibitor along with companion genetic and pharmacodynamic studies to verify that most tumors contain *MYB* mutations and that FGFR signaling is effectively suppressed. In addition, a trial of FGFR inhibitors for the treatment of the 4% to 12% of ACCs with *FGFR* or *FGF* gene mutations is also appropriate. However, because of their rarity, these tumors would probably be best studied in the context of a "basket trial," which enrolls patients with different types of tumors that contain similar *FGFR* gene alterations.

Disclosure of Potential Conflicts of Interest

P.M. Dillon reports receiving other commercial research support from Novartis Pharmaceuticals. G.R. Petroni is a consultant/advisory board member for NeuroHabilitation Corp. C.A. Moskaluk reports receiving commercial research grants from Philips. C.Y. Thomas is a consultant/advisory board member for Novartis. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P.M. Dillon, C.A. Moskaluk, P.M. Fracasso, M.G. Douvas, S. Zaja-Milatovic, C.Y. Thomas

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.M. Dillon, G.R. Petroni, B.J. Horton, C.A. Moskaluk, M.G. Douvas, N. Varhegyi, C.Y. Thomas

Writing, review, and/or revision of the manuscript: P.M. Dillon, G.R. Petroni, B.J. Horton, C.A. Moskaluk, P.M. Fracasso, C.Y. Thomas

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P.M. Dillon, C.A. Moskaluk, C.Y. Thomas

Study supervision: P.M. Dillon, P.M. Fracasso, C.Y. Thomas

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References

1. Sessions RHL, Forastiere A. Tumors of the salivary glands and paragangliomas. In: Devita VT, Hellman S, Rosenberg SA, editors. Principles and practice of oncology. Philadelphia, PA: Lippincott-Raven Publishers; 2000.
2. Argiris A, Ghebremichael M, Burtness B, Axelrod RS, Deconti RC, Forastiere AA. A phase 2 trial of bortezomib followed by the addition of doxorubicin at progression in patients with recurrent or metastatic adenoid cystic carcinoma of the head and neck: a trial of the Eastern Cooperative Oncology Group (E1303). Cancer 2011; 117:3374–82.
3. Chau NG, Hotte SJ, Chen EX, Chin SF, Turner S, Wang L, et al. A phase II study of sunitinib in recurrent and/or metastatic adenoid cystic carcinoma (ACC) of the salivary glands: current progress and challenges in evaluating molecularly targeted agents in ACC. Ann Oncol 2012;23: 1562–70.
4. Thomson DJ, Silva P, Denton K, Bonington S, Mak SK, Swindell R, et al. Phase II trial of sorafenib in advanced salivary adenoid cystic carcinoma of the head and neck. Head Neck 2015;37:182–7.
5. Dillon PM, Chakraborty S, Moskaluk CA, Joshi PJ, Thomas CY. Adenoid cystic carcinoma: a review of recent advances, molecular targets and clinical trials. Head Neck 2016;38:620–7.
6. Vermorken JB, Verweij J, De Mulder PH, Cognetti F, Clavel M, Rodenhuis S, et al. Epirubicin in patients with advanced or recurrent adenoid cystic carcinoma of the head and neck: a phase II study of the EORTC Head and Neck Cancer Cooperative Group. Ann Oncol 1993;4:785–8.
7. Papaspyrou G, Hoch S, Rinaldo A, Rodrigo JP, Takes RP, van HC, et al. Chemotherapy and targeted therapy in adenoid cystic carcinoma of the head and neck: a review. Head Neck 2011;33:905–11.
8. Agulnik M, Cohen EW, Cohen RB, Chen EX, Vokes EE, Hotte SJ, et al. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. J Clin Oncol 2007;25:3978–84.
9. Goncalves P, Kummar S, Siu LL, Hansen AR, Savvides P, Sukari A, et al. A phase II study of suberoylanilide hydroxamic acid (SAHA) in subjects with locally advanced, recurrent, or metastatic adenoid cystic carcinoma (ACC). J Clin Oncol 31, 2013(suppl; abstr 6045).
10. Ghosal N, Mais K, Shenjere P, Julyan P, Hastings D, Ward T, et al. Phase II study of cisplatin and imatinib in advanced salivary adenoid cystic carcinoma. Br J Oral Maxillofac Surg 2011;49:510–5.
11. Holst VA, Marshall CE, Moskaluk CA, Frierson HF Jr. KIT protein expression and analysis of c-kit gene mutation in adenoid cystic carcinoma. Mod Pathol 1999;12:956–60.
12. Hotte SJ, Winquist EW, Lamont E, MacKenzie M, Vokes E, Chen EX, et al. Imatinib mesylate in patients with adenoid cystic cancers of the salivary glands expressing c-kit: a Princess Margaret Hospital phase II consortium study. J Clin Oncol 2005;23:585–90.
13. Brayer KJ, Frerich CA, Kang H, Ness SA. Recurrent fusions in MYB and MYBL1 define a common, transcription factor-driven oncogenic pathway in salivary gland adenoid cystic carcinoma. Cancer Discov 2016; 6:176–87.
14. Brill LB, Kanner WA, Fehr A, Andren Y, Moskaluk CA, Loning T, et al. Analysis of MYB expression and MYB-NFIB gene fusions in adenoid cystic carcinoma and other salivary neoplasms. Mod Pathol 2011; 24:1169–76.
15. Drier Y, Cotton MJ, Williamson KE, Gillespie SM, Ryan RJ, Kluk MJ, et al. An oncogenic MYB feedback loop drives alternate cell fates in adenoid cystic carcinoma. Nat Genet 2016;48:265–72.
16. Ho AH, Sherman EJ, Baxi SS, Haque S, Ni A, Antonescu CR, et al. Phase II study of regorafenib in progressive, recurrent/metastatic adenoid cystic carcinoma. J Clin Oncol 34, 2016 (suppl; abstr 6096).
17. Persson M, Andren Y, Mark J, Horlings HM, Persson F, Stenman G. Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck. Proc Natl Acad Sci U S A 2009;106:18740–4.
18. Persson M, Andren Y, Moskaluk CA, Frierson HF Jr, Cooke SL, Futreal PA, et al. Clinically significant copy number alterations and complex rearrangements of MYB and NFIB in head and neck adenoid cystic carcinoma. Genes Chromosomes Cancer 2012;51:805–17.
19. Stephens PJ, Davies HR, Mitani Y, Van LP, Shlien A, Tarpey PS, et al. Whole exome sequencing of adenoid cystic carcinoma. J Clin Invest 2013; 123:2965–8.
20. Miglarese MR, Halaban R, Gibson NW. Regulation of fibroblast growth factor 2 expression in melanoma cells by the c-MYB proto-oncoprotein. Cell Growth Differ 1997;8:1199–210.
21. Myoken Y, Myoken Y, Okamoto T, Sato JD, Kan M, McKeehan WL, et al. Immunohistochemical study of overexpression of fibroblast growth factor-1 (FGF-1), FGF-2, and FGF receptor-1 in human malignant salivary gland tumours. J Pathol 1996;178:429–36.
22. Moskaluk CA, Baras AS, Mancuso SA, Fan H, Davidson RJ, Dirks DC, et al. Development and characterization of xenograft model systems for adenoid cystic carcinoma. Lab Invest 2011;91:1480–90.
23. Frierson HF Jr, Moskaluk CA. Mutation signature of adenoid cystic carcinoma: evidence for transcriptional and epigenetic reprogramming. J Clin Invest 2013;123:2783–5.
24. Chase A, Grand FH, Cross NC. Activity of TKI258 against primary cells and cell lines with FGFR1 fusion genes associated with the 8p11 myeloproliferative syndrome. Blood 2007;110:3729–34.
25. Lee SH, Lopes de Menezes D, Vora J, Harris A, Ye H, Nordahl L, et al. *In vivo* target modulation and biological activity of CHIR-258, a multitargeted growth factor receptor kinase inhibitor, in colon cancer models. Clin Cancer Res 2005;11:3633–41.
26. Milella M. Optimizing clinical benefit with targeted treatment in mRCC: "Tumor growth rate" as an alternative clinical endpoint. Crit Rev Oncol Hematol 2016;102:73–81.
27. Dos Anjos RF, Dos Anjos DA, Vieira DL, Leite AF, Figueiredo PT, de Melo NS. Effectiveness of FDG-PET/CT for evaluating early response to induction chemotherapy in head and neck squamous cell carcinoma: A systematic review. Medicine 2016;95:e4450.
28. Rojas JM, Matsen ME, Mundinger TO, Morton GJ, Stefanovski D, Bergman RN, et al. Glucose intolerance induced by blockade of central FGF receptors is linked to an acute stress response. Mol Metab 2015;4:561–8.
29. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
30. Keam B, Kim SB, Shin SH, Cho BC, Lee KW, Kim MK, et al. Phase 2 study of dovitinib in patients with metastatic or unresectable adenoid cystic carcinoma. Cancer 2015;121:2612–7.
31. Pal SK, Rosenberg JE, Keam B, Wolf J, Berger R, Dittrich C, et al. Efficacy of BGJ398, a fibroblast growth factor receptor (FGFR) 1-3 inhibitor, in patients (pts) with previously treated advanced/metastatic urothelial carcinoma (mUC) with *FGFR3* alterations. J Clin Oncol 34, 2016(suppl; abstr 4517).
32. Escudier B, Grunwald V, Ravaud A, Ou YC, Castellano D, Lin CC, et al. Phase II results of Dovitinib (TKI258) in patients with metastatic renal cell cancer. Clin Cancer Res 2014;20:3012–22.
33. Yanochko GM, Vitsky A, Heyen JR, Hirakawa B, Lam JL, May J, et al. Pan-FGFR inhibition leads to blockade of FGF23 signaling, soft tissue mineralization, and cardiovascular dysfunction. Toxicol Sci 2013;135: 451–64.
34. Milkowski M, Dittrich C, Martinez ID, Jagdev S, Millard FE, Sweeney C. Final results of a multicenter, open-label phase II trial of dovitinib (TKI258) in patients with advanced urothelial carcinoma with either mutated or nonmutated *FGFR3*. J Clin Oncol 31, 2013 (suppl 6; abstr 255).
35. Ferte C, Koscielny S, Albiges L, Rocher L, Soria JC, Iacovelli R, et al. Tumor growth rate provides useful information to evaluate sorafenib and everolimus treatment in metastatic renal cell carcinoma patients: an integrated analysis of the TARGET and RECORD phase 3 trial data. Eur Urol 2014;65:713–20.
36. Ferte C, Fernandez M, Hollebecque A, Koscielny S, Levy A, Massard C, et al. Tumor growth rate is an early indicator of antitumor drug activity in phase I clinical trials. Clin Cancer Res 2014;20:246–52.
37. Stein WD, Wilkerson J, Kim ST, Huang X, Motzer RJ, Fojo AT, et al. Analyzing the pivotal trial that compared sunitinib and IFN-alpha in renal cell carcinoma, using a method that assesses tumor regression and growth. Clin Cancer Res 2012;18:2374–81.

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