Original Article

Patients With Adenoid Cystic Carcinomas of the Salivary Glands Treated With Lenvatinib: Activity and Quality of Life

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BACKGROUND: The treatment of patients with recurrent and/or metastatic (R/M) salivary gland adenoid cystic carcinoma (ACC) remains an unmet need. **METHODS:** Patients with R/M disease with a history of clinical or symptomatic disease progression within 6 months and a maximum of 1 previous line of chemotherapy or a multiple kinase inhibitor received oral lenvatinib at a dose of 24 mg/day. The primary endpoint was the objective response rate; secondary endpoints included quality of life (QOL) (according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Items [EORTC QLQ-C30] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module Head and Neck Module [EORTC QLQ-H&N35]), progression-free survival and overall survival, duration of response, and toxicities. **RESULTS:** Twenty-eight patients with R/M ACC were enrolled. Among 26 evaluable patients, 3 partial responses (11.5%) were reported. Target lesion reductions between 23% to 28% were observed in 4 of 20 patients with stable disease. Treatment-related adverse events were frequent (all grades, 96%; grade≥3 in 50% of cases according to version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events). The dose of lenvatinib was reduced in 24 patients, whereas in 21 patients the dose was reduced within the first 12 weeks and 4 patients maintained the full dose throughout treatment. The QOL deteriorated between baseline and 6 months with regard to Fatigue and Dry Mouth. There was no evidence of changes in Swallowing and Physical Functioning. At a median follow-up of 29 months, 2 patients remained on treatment, 10 patients were off protocol for disease progression and were alive with disease, and 14 patients had died of disease progression. The median overall survival, progression-free survival, and duration of response were 27 months, 9.1 months, and 3.1 months, respectively. **CONCLUSIONS:** Lenvatinib appears to have modest activity in ACC. Toxicities are common but manageable and QOL was found to deteriorate in some domains. ***Cancer* 2020;126:1888-1894**. © *2020 American Cancer Society*.

KEYWORDS: adenoid cystic carcinoma, lenvatinib, quality of life, toxicity.

INTRODUCTION

Carcinomas of the salivary glands are rare, representing <1% of all head and neck cancers diagnosed in Europe, and include >20 histotypes.[1,2] Among these, adenoid cystic carcinoma (ACC) is characterized by a high frequency of local disease recurrence (16%-85%) despite aggressive multimodality treatments including surgery and radiotherapy. ACC demonstrates a slow and indolent growth pattern with extensive local infiltration and perineural invasion. In the head and neck region, it may diffuse through nerve routes to the skull base and cavities, causing disabling pain syndromes and poor quality of life (QOL).[3] Despite these features, the 5-year and 10-year survival may be prolonged, reported to be 69% and 46%, respectively.[4]

Palliative chemotherapy currently is provided to patients with symptomatic or rapidly progressing recurrent and/or metastatic (R/M) disease. It generally is associated with few responses, although an overall response rate of 25%

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has been reported.[5] To the best of our knowledge, chemotherapy has not been studied in phase 3 trials to date, and thus its effect on patient outcomes remains unknown.

ACC is characterized by a low mutational load,[6] with a wide mutational diversity involved in chromatin state regulators, DNA damage, and kinase signaling. Alterations in the *MYB* signaling pathway (65%) are considered to be a hallmark of ACC. Mutations have been identified in genes involved in the *FGF/IGF/PI3K* and *NOTCH* pathways in 30% and 15%, respectively, of cases.

Possible driving molecular inhibitors, such as *MYB* and *NOTCH1*, currently are under development.[7]

Agents such as imatinib,[8] gefitinib,[9] dovitinib,[10,11] regorafenib, and dasatinib have demonstrated no activity[8,9,12] or only weak activity (3%-6%).[10,11,13] Sorafenib, a multiple kinase inhibitor (MKI) (VEGFR1-3, PDGFR, RET, c-KIT, FLT3, and BRAF),[14,15] and axitinib (VEGFR1-3)[16] have shown some activity in patients with advanced ACC (overall response rates of 11% and 9%, respectively).

Lenvatinib is a second-generation MKI with a strong antiangiogenic effect that recently was found to demonstrate a promising response rate of 15.6% in a phase 2 trial of 32 patients with ACC.[17] In the current study, we have reported a second phase 2 study regarding treatment with lenvatinib in patients with R/M ACC. The study was conducted in Europe at a single institution at which we investigated the patients' treatment-related QOL.

MATERIALS AND METHODS

Patients

The current study was a prospective, single-arm, phase 2 trial performed at the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, Italy, and examining lenvatinib at a dose of 24 mg daily administered to patients with R/M ACC until disease progression or unacceptable toxicity occurred. Details regarding eligibility criteria, treatment schedule, response assessments, and serious adverse events (SAEs) are reported in the Supporting Information. All patients provided written informed consent. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by the local ethics committee (ClinicalTrials.gov identifier NCT02860936).

QOL Assessments

QOL was measured at each course of treatment from baseline until disease progression using validated questionnaires (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Items [EORTC QLQ-C30] and the EORTC Quality of Life Questionnaire–Core Module Head and Neck Module [EORTC QLQ-H&N35). The EORTC QLQ-C30 is a 30-item, cancer-specific questionnaire that often has been used for patients with head and neck cancer.[18-21] The head and neck–specific EORTC QLQ-H&N35 module contains 35 items that can be condensed into 7 multi-item and 11 single-item scales. Both questionnaires result in scales that score from 0 to 100. For the function scales, a score of 100 indicates perfect QOL, whereas for the symptom scales it would indicate a heavy burden. A difference of 10 points is considered to approximately indicate minimal important clinical differences.[22]

Health status was measured using the EuroQol (European Quality of Life) Five Dimension Five Level Scale (EQ-5D-5L). Patients indicate the level of problems they have (from none to severe) regarding 5 dimensions (mobility, self-care, usual activities, pain and/or discomfort, and anxiety and/or depression). A value (utility) can be assigned to each health profile. We used Spanish value sets because to the best of our knowledge Italian ones are not yet available for the EQ-5D-5L (www.euroqol.org). A value of 1 represents excellent health, whereas a value of 0 indicates health equal to death. Negative values represent health worse than death. In addition to this, the patients rate their subjective health on that day using a visual analogue scale (with 0 indicating worst imaginable health and 100 indicating best imaginable health).

QOL: Statistical Analysis

Details regarding the statistical methods of the entire clinical trial are reported in the Supporting Information. We defined the following QOL domains a priori to be of primary interest for this study: Physical Functioning, Global Quality of Life, Fatigue, Swallowing, and Dry Mouth.

Progression-free survival (PFS) was measured as the interval between the initiation of treatment and disease progression or death from any cause. Overall survival (OS) was calculated as the interval between the initiation of treatment and death from any cause. For each endpoint, time was censored at the date of the last follow-up assessment in patients who were event free. Survival curves were estimated using the Kaplan-Meier method.

The relative dose intensity, defined as the ratio of drug dose delivered (in mg/days) to the planned dose intensity (in mg/days), was calculated for each patient at 12 weeks and at the completion of treatment. The relative dose intensity was expressed as a percentage.

The scales of the EORTC QOL questionnaires were constructed according to the EORTC guidelines[23] by summation and then transformed from 0 to 100. Unless at least approximately one-half of the items of a certain scale were available, no score was computed for that scale. These scores were calculated for baseline (t1), 3 months (t3), 6 months (t6), 9 months (t9), and 12 months (t12).

For all scales of the EORTC QLQ-C30 and EORTC QLQ-H&N35, we calculated the mean per time point plus the standard deviation. We further calculated the delta (Δ) between t1 and t6 as well as between t1 and t12 per patient (pairwise comparison). For the primary QOL endpoints (Swallowing, Dry Mouth, Physical Functioning, Fatigue, and Global Quality of Life), we performed Wilcoxon signed-rank tests to compare scores between t1 and t6 as well as t1 and t12.

For t1, t3, t6, t9, and t12, the mean subjective health and the usefulness were calculated plus the standard deviation. We compared both scores with the Italian norms.[24]

RESULTS

Patient Characteristics

From June 2015 to August 2017, a total of 28 patients were enrolled. Patient characteristics are listed in Supporting Table 1. The majority of patients (85%) had been treated previously for R/M disease. The heterogeneous management received at the time of disease recurrence highlights the lack of a standard approach. Approximately 21% of patients (6 of 28 patients) had extensive local disease with skull base involvement and/or disease close to the internal carotid artery. Two patients died before first disease reassessment due to rapid disease progression and were replaced by 2 other evaluable patients.

Treatment Response and Follow-Up

At the time of data analysis (June 3, 2019), the median duration of follow-up was 29 months (95% CI, 22-47 months). Among the 26 patients who were evaluable for response, 3 patients achieved a partial response (11.5%), 20 patients had stable disease, and 3 patients experienced disease progression as their best response. No complete response was observed. Target lesion shrinkage between 23% and 28% was observed in 4 of 20 patients with stable disease (see Supporting Fig. 1). Clinical benefit (partial response and stable disease maintained for ≥6 months) was reported in 17 patients (65.4%). The median PFS and duration of response were 9.1 months (95% CI, 5.5-13.8 months) and 3.1 months (range, 1.8-30.7 months), respectively. The median OS was 27 months (95% CI, 12-45 months). The median time to response according to Response Evaluation Criteria in Solid Tumours (RECIST) was 5.4 months (range, 1.7-11 months).

Safety and Tolerability

Nearly all patients (96%) experienced at least 1 treatment-related AE (see Supporting Table 2). The median duration of treatment for the study population was 9.1 months (range, 2.4-36.1 months). Grade 3 AEs (grading was performed according to version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events) occurred in approximately one-half of patients, whereas no grade 4 and grade 5 toxicities were observed.

As of June 3, 2019, treatment with lenvatinib still was ongoing in 2 patients, whereas 14 patients had died of progressive disease. Disease progression was the main cause of treatment discontinuation, occurring in approximately 88% of patients. Conversely, 1 patient discontinued treatment for unsustainable toxicity despite dose reductions (grade 2 asthenia and weight loss).

SAEs and Dose Reductions

Eleven SAEs were reported among 10 patients; 6 were considered to be drug related (hypertension, ischemic attack, acute cholecystitis, tubular interstitial nephritis,[23] and 1 episode of gastrointestinal and renal toxicity with dehydration and related asthenia) and a symptomatic myocardial infarction also was observed. The median time to the appearance of any SAE was 9.6 months (range, 0.4-29 months). Hypertension was the earliest reported SAE at 0.4 months.

In 2 responding patients (see Supporting Fig. 2), tumor shrinkage was complicated by the formation of an oral fistula that required the placement of a gastrostomy tube.

The starting dose of lenvatinib was 24 mg. Dose reductions were required for 24 patients. Four patients maintained the full dose for a median of 1.7 months (range, 1.0-2.8 months). The first dose reduction occurred within 12 weeks from the initiation of therapy in approximately 88% of patients (21 of 24 patients) and the median dose intensity was 69% (range, 35%-82%), with no difference noted between responders and nonresponders.

Quality of Life

QOL questionnaires were completed by 25 patients at t1. During follow-up, the questionnaires were completed by

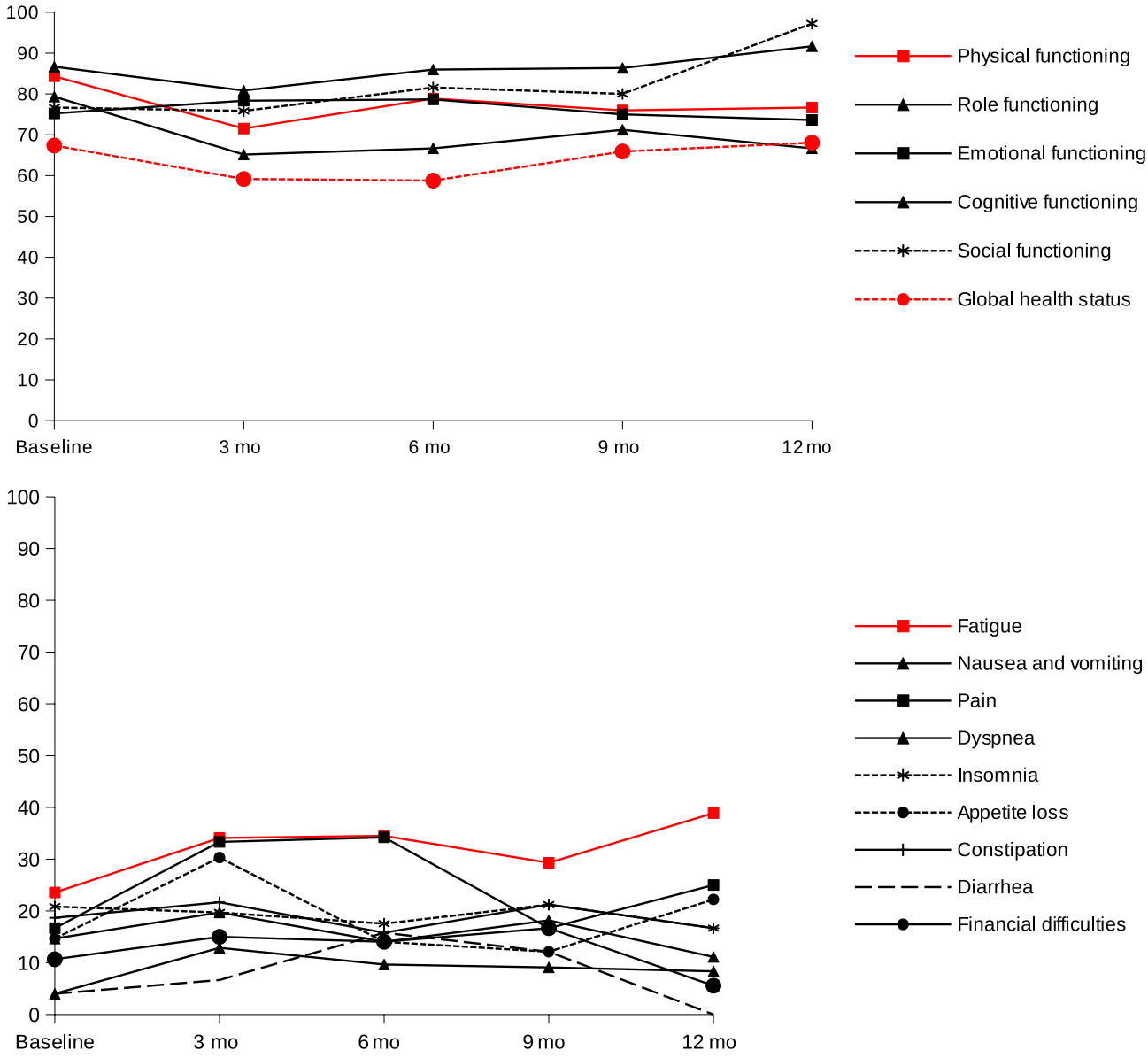

Figure 1. Changes in general quality of life between baseline and 12 months were >10 points for the domains of Physical Functioning, Role Functioning, Social Functioning, Global Health, Fatigue, Pain, and Appetite Loss.

22 patients at t3, 19 patients at t6, 11 patients at t9, and 6 patients at t12.

Changes in general QOL between baseline and t6 were >10 points for Role Functioning, Global Health, Fatigue, Pain, and Diarrhea. Changes between baseline and t12 were >10 points for Physical Functioning, Role Functioning, Social Functioning, Global Health, Fatigue, Pain, and Appetite Loss (Fig. 1). There was evidence of deterioration in Global Quality of Life between t1 and t6 (Δ, 13 points; $P = .03$) and weak evidence between t1 and t12 (Δ, 18 points; $P = .06$). Fatigue increased considerably between t1 and t6 (Δ, 18 points; $P = .005$) and also between t1 and t12 (Δ, 32 points; $P = .07$). All these changes were deteriorations. There was no evidence of changes in Physical Functioning between t1 and t6 (Δ, 8 points; $P = .10$) and between t1 and t12 (Δ, 14 points; $P = .17$).

Head and neck–specific QOL deteriorated between t1 and t6 by >10 points in the domains of Sexuality, Dry Mouth, Sticky Saliva, Coughing, and Weight Gain (Fig. 2). Between t1 and t12, there also were some improvements: the domains of Senses and Problems

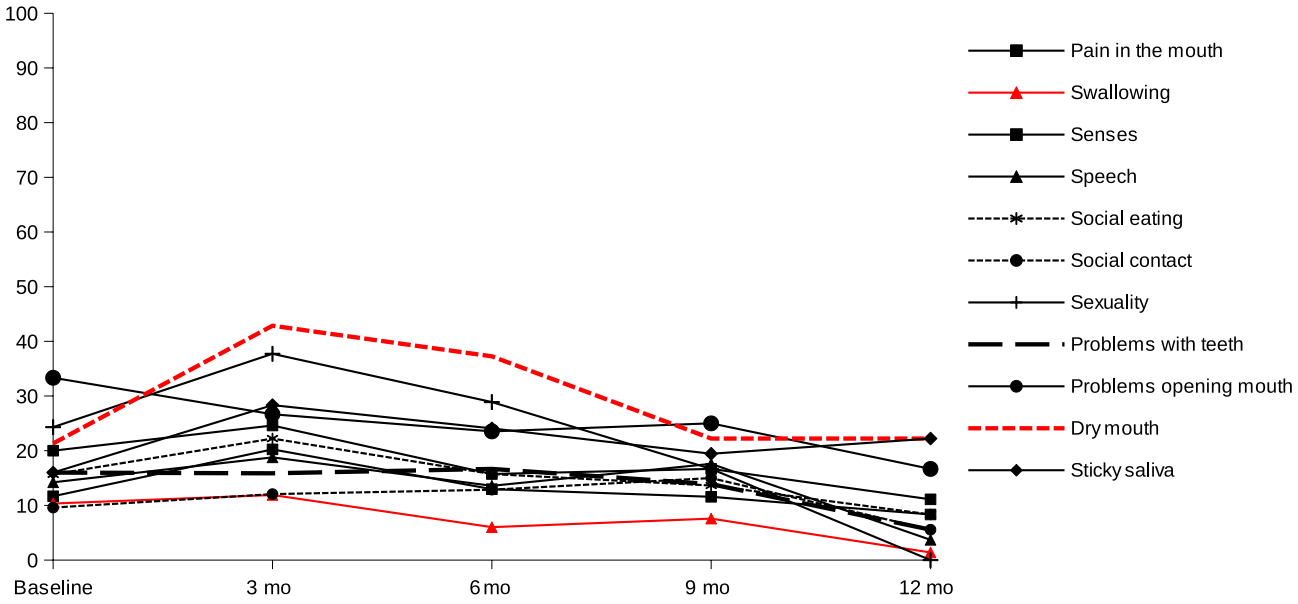

Figure 2. Changes in head and neck–specific quality of life between baseline and 6 months of >10 points were noted for the domains of Sexuality, Dry Mouth, Sticky Saliva, Coughing, and Weight Gain.

Opening Mouth decreased by >10 points. However, the domains of Dry Mouth, Sticky Saliva, Feeling Ill, Use of Painkillers, and Weight Loss deteriorated by >10 points. It is interesting to note that all these comparisons were only descriptive. We performed statistical tests only for the primary QOL endpoints. There was no evidence of changes in Swallowing between t1 and t6 (Δ, 0.5 points; $P = .66$) or between t1 and t12 (Δ, 1 point; $P = .32$). Dry Mouth worsened between t1 and t6 (Δ, 19 points; $P = .03$) but there was no clear evidence of changes between t1 and t12 (Δ, 11 points; $P = .16$). Details are reported in Supporting Tables 3 and 4.

Health Status

Mean self-rated health was 67.3 at t1, 62.3 at t3, 62.3 at t6, 66.4 at t9, and 63.3 at t12. The utilities derived from the health profiles ranged from 0.7 (at t3) to 0.9 (at t9) (see Supporting Table 5). Compared with the general Italian population, the health status was found to be decreased at all time points (see Supporting Fig. 3).

DISCUSSION

The current study met its primary objective by demonstrating the activity of lenvatinib in patients with R/M ACC of the salivary glands.

Three partial responses were observed (11.5%) and target lesion reductions between 23% and 28% were noted among 4 of 20 patients with stable disease. The median PFS of 9 months was comparable to that previously reported in trials in which antiangiogenic agents were administered, ranging from 5.7[16] to 8.9 months,[15] but far from the median PFS of 17.5 months reported with lenvatinib.[17] This could be related to different characteristics of the enrolled patients, including 28% of patients with locoregional disease recurrence[17] versus 39% in the current study and 21.9% of ACCs originating from a primary site other than the salivary glands (eg, skin, breast, or lacrimal gland). Tumor shrinkage usually occurred rapidly and was found to be already present at the time of the first radiological evaluation at 8 weeks. We did not observe any difference with regard to the activity of lenvatinib in patients with locoregional disease or distant metastases.

Treatment toxicities were frequent (96% of cases) but manageable with dose reductions or interruptions. The spectrum of toxicities was in keeping with that of other studies in which lenvatinib was administered at the same dosage, except for asthenia and stomatitis, which were more common in the current study population whereas hypertension, nausea, and diarrhea were less frequent.[25] Slight differences in the occurrence of MKI-related side effects in different diseases have been shown. Although toxic events generally appear early during treatment, SAEs may manifest later (median, 9.6 months), suggesting that accurate clinical monitoring should be maintained during the entire treatment period.

The use of antiangiogenic agents represents a potential challenge in patients with head and neck cancer. Both patients with primary head and neck cancer as well as those with local disease recurrence are potentially at risk of hemorrhages due to spontaneous tumor bleeding, vascular erosions, or surgical or irradiation complications.[26] In the patient population in the current study, approximately 35% of patients experienced a local disease recurrence in the head and neck area (89% of which occurred within a previously irradiated field), and no bleeding event occurred in patients with intracranial disease extension or disease close to major blood vessels.

These patients generally experience few symptoms, and have a prolonged life expectancy despite the presence of R/M disease. In this scenario, there is major concern regarding the use of MKIs that may commonly induce side effects in an otherwise poorly symptomatic population. Within this context, even low-grade (grade 1 to grade 2) side effects might cause patients' QOL to deteriorate. It is interesting to note that there was no evidence that swallowing did deteriorate during the first year of treatment with lenvatinib (although this also could be due to the fact that the sample size in the current study was too small to detect any effects). However, patients reported more problems with dry mouth after 6 months. They also complained more about fatigue and judged their QOL in general to be worse. Both dry mouth and fatigue might be drug-related side effects.

We are aware of the limitations of the current study. The current study was not a randomized trial and the activity of lenvatinib in patients with R/M ACC could be overestimated. Moreover, the sample size was small, making it difficult to detect smaller effects of the drug on QOL. Finding no significant differences does not necessarily mean that there were no differences. Instead, the differences may not have been large enough to be detected against random variance. In addition, no translational analyses were performed on tissue samples to correlate the activity of lenvatinib with the genomic profiling, even if it appears to be irrelevant for patient selection.[17] Conversely, to the best of our knowledge, no molecular predictive markers have been identified in thyroid and liver cancers, for which lenvatinib has been approved.

To our knowledge, lenvatinib represents the most active antiangiogenic agent for use in patients with R/M ACC. It can be considered safe, although the toxicities noted in the current study were not negligible. Data are promising and further randomized trials investigating lenvatinib in patients with ACC are warranted.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Conceptualization: **Laura D. Locati** and **Lisa F. Licitra**. Data curation: All authors. Formal analysis: **Susanne Singer**, **Luigi Mariani**, and **Salvatore Lo Vullo**. Funding acquisition: **Laura D. Locati** and **Lisa F. Licitra**. Investigation: All authors. Methodology: **Susanne Singer**, **Luigi Mariani**, and **Salvatore Lo Vullo**. Project administration: **Laura D. Locati** and **Lisa F. Licitra**. Resources: **Laura D. Locati** and **Lisa F. Licitra**. Software: **Susanne Singer**, **Luigi Mariani**, and **Salvatore Lo Vullo**. Supervision: **Laura D. Locati** and **Lisa F. Licitra**. Validation: All authors. Visualization: All authors. Writing–original draft: **Laura D. Locati**, **Donata Galbiati**, and **Lisa F. Licitra**. Writing–review and editing: All authors. Editing: All authors.

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