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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

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A B S T R A C T

Purpose
Expression of erbB2 and/or epidermal growth factor receptor (EGFR) is associated with biologic aggressiveness and poor prognosis in malignant salivary gland tumors (MSGTs). This phase II study was conducted to determine the antitumor activity of lapatinib, a dual inhibitor of EGFR and erbB2 tyrosine kinase activity, in MSGTs.

Patients and Methods
Patients with progressive, recurrent, or metastatic adenoid cystic carcinoma (ACC) immunohistochemically expressing at least 1+ EGFR and/or 2+ erbB2 were treated with lapatinib 1,500 mg daily, in a two-stage cohort. Patients with non-ACC MSGTs were treated as a separate single-stage cohort.

Results
Of 62 patients screened, 29 of 33 (88%) ACC and 28 of 29 (97%) non-ACC patients expressed EGFR and/or erbB2. Forty patients with progressive disease were enrolled onto the study. Among 19 assessable ACC patients, there were no objective responses, 15 patients (79%) had stable disease (SD), nine patients (47%) had SD ≥ 6 months, and four patients (21%) had progressive disease (PD). For 17 assessable non-ACC patients, there were no objective responses, eight patients (47%) had SD, four patients (24%) had SD ≥ 6 months, and nine patients (53%) had PD. The most frequent adverse events were grade 1 to 2 diarrhea, fatigue, and rash. Eight paired tumor biopsies for correlative studies were procured; results did not correlate with clinical outcome.

Conclusion
Although no responses were observed, lapatinib was well tolerated, with prolonged tumor stabilization of ≥ 6 months in 36% (95% CI, 21% to 54%) of assessable patients. The antitumor effects of lapatinib in MGSTs appear mainly cytostatic, hence evaluation of other molecular targeted agents, or combinations with lapatinib, may be considered. Continued efforts should be made to gain better understanding into the biology of this heterogeneous group of malignancies.

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INTRODUCTION

Malignant salivary gland tumors (MSGTs) account for less than 1% of all cancers, and 6% to 7% of cancers of the head and neck.[1-3] Adenoid cystic carcinoma histology (ACC) accounts for 11% and 41% of major and minor MSGTs, respectively. ACC is treated mainly with surgery and radiation; systemic therapy is reserved for the management of local recurrence no longer amenable to additional local therapy, and in the palliation of symptoms from metastases. Response rates to conventional chemotherapy are generally low, based on small institutional series, and are not clearly associated with any survival advantage.[4,5] Unlike ACC, non-ACC MSGTs are a heterogeneous group with distinct histologies and variable biologic behavior. Patients with recurrent or metastatic non-ACC MSGTs may achieve objective response rates ranging from 15% to 50% with conventional cytotoxic chemotherapy, but duration of response is typically limited to 6 to 9 months.[4,5] Given this, patients with progressive ACC and non-ACC MSGT are ideal candidates for trials of investigational new drugs.

Lapatinib is a dual inhibitor of the tyrosine kinase domains of the epidermal growth factor receptor (EGFR) and erbB2 by interfering with adenosine triphosphate binding, thus blocking autophosphory-lation and resultant downstream signaling activities, including cellular proliferation and survival.[6] In head and neck squamous cell cancers, EGFR expression predicts for poor disease-free and cause-specific survivals.[7] Overexpression of erbB2 is associated with biologic aggres-siveness and poor prognosis in MSGTs.[8-13] Clinicopathologic studies with limited sample sizes examining the expression of EGFR and erbB2 in MSGTs by immunohistochemistry (IHC) have reported wide variations in frequencies ranging from 0% to 85%[14-18] and 0% to 100%,[10,12,16,19-30] respectively.

This study aimed to evaluate the antitumor activity of lapatinib in recurrent and/or metastatic ACC and other MSGTs with documented IHC expression of EGFR and/or erbB2. We chose to study ACC and non-ACC MSGTs because of the paucity of effective palliative treat-ments available to both groups and the evidence for target expression in both histologic subtypes by IHC.

PATIENTS AND METHODS

Patient Eligibility

Patients ≥ 18 years of age with histologically or cytologically confirmed ACC or non-ACC MSGTs were potentially eligible if they had ≥ 1+ EGFR and/or ≥ 2+ erbB2 expressing tumors, determined by IHC. Patients were required have recurrent and/or metastatic disease not amenable to potentially curative surgery or radiotherapy, and documented disease progression within 6 months of study entry. Progressive disease (PD) was defined as a minimum of 20% increase in the sum of maximal diameters of measurable disease, the appearance of new lesions, or deterioration in clinical status. Patients were required to have measurable disease according to the Response Evaluation Criteria in Solid Tumors Committee (RECIST) criteria,[31] and may have had unlimited prior therapy up to 4 weeks before study enrollment. Other key eligibility criteria included Eastern Cooperative Oncology Group performance status ≤ 2; life expectancy of at least 12 weeks; normal organ and marrow function (total bilirubin within normal limits, AST and ALT ≤ 2.5× upper limit of normal, creatinine within normal limits or creatinine clearance ≥ 60 mL/min/1.73 m^2, leukocytes ≥ 3,000/μL, absolute neutrophil count ≥ 1,500/μL, and platelets ≥ 100,000/μL); and normal cardiac left ventricular ejection fraction (LVEF) by multiple-gated acquisition scan. Patients were required to undergo tumor biopsy once before (between days −7 and 0) and once during investigational therapy (between days 14 and 21) unless there was a medical contraindication. Patients were excluded if they had prior treatment with an EGFR or erbB2 inhibitor. Participants provided written informed consent before study enrollment; the study was approved by all local research ethics committees of participating centers.

Study Therapy and Dose Modifications

Study treatment consisted of lapatinib 1,500 mg orally once daily on an empty stomach. Lapatinib was supplied by the National Cancer Institute, Division of Cancer Treatment and Diagnosis, Cancer Therapy Evaluation Program. Cycle length was 28 days and treatment was continued until disease progression, unacceptable toxicity, patient refusal, or physician's decision to withdraw the patient. Patients were assessed for objective response, classified by RECIST,[31] every 8 weeks.

Toxicity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. For intolerable grade 2 or for grade 3 or 4 toxicity, lapatinib was withheld until the toxicity was grade ≤ 1 and then resumed at 1,500 mg/d for the first intolerable grade 2 toxicity, or 1,000 mg/d for subsequent intolerable grade 2 toxicity and any grade 3 or 4 toxicity. A second dose reduction to 750 mg/d was allowed. Necessity for a third dose reduction, persistent toxicity after 3 weeks off lapatinib, grade 3 or 4

interstitial pneumonitis, or left ventricular systolic dysfunction would man-date discontinuation of study therapy.

Archival Specimens

Histologies of all patients were reviewed centrally by a blinded patholo-gist (M.T.). Two (5%) discrepancies were identified when compared with original pathology reports.

Screening for EGFR and erbB2 expression, using archival paraffin sam-ples or fresh tumor biopsies, was measured by IHC. For EGFR, IHC was performed using a standard avidin-biotin technique. The incubation time was 1 hour with the primary mouse monoclonal antibody (clone 31G7, 1:50 dilution; Zymed Laboratories, South San Francisco, CA). For erbB2, the sec-tions were subjected to antigen retrieval by boiling in citrate buffer followed by incubation with the primary antibody (rabbit antip185/HER-2, Herceptest; DAKO AS, Copenhagen, Denmark). After sections were washed, they were incubated for 20 minutes each with biotinylated secondary antibody, followed by streptavidin– horseradish peroxidase using the Multi-Species Ultra Strepta-vidin Kit (Signet Laboratories, Dedham, MA). The slides were developed for 5 minutes using the NovaRed substrate kit (Vector Laboratories, Burlingame, CA), and then counterstained with Mayer's hematoxylin. Slides were scored on a 0 to 3+ scale: 0, staining in less than 10% of tumor cells or no staining; 1+, faint and partial membrane staining in ≥ 10% of tumor cells; 2+, weak to moderate complete membrane staining in ≥ 10% of tumor cells; or 3+, moderate to strong complete membrane staining in ≥ 10% of tumor cells.

Correlative Studies on Paired Tumor Specimens

Biomarkers related to EGFR and erbB2 and their associated pathways were analyzed in tumor tissues using a colorimetric IHC technique. Phosphor-ylation of EGFR activates downstream signaling pathways that include Ras-Raf–mitogen-activated protein kinase kinase extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase/Akt, and the signal transducer and activator of transcription-3 (STAT-3) pathways. Ki-67 is an index of cellular proliferation, p27 is a cell cycle regulatory protein, and insulin-like growth factor receptor-1 (IGFR-1) and STAT-3 are signaling proteins poten-tially involved in resistance to inhibition of the EGFR/erbB2 pathway. Phos-phorylation denotes the activation state of the cellular phosphoproteins under evaluation. Paired tumor biopsies were assessed by IHC for EGFR, phosphorylated (p) -EGFR, erbB2, p-erbB2, p-ERK, p-Akt, p27, Ki-67, IGFR-1, and p-STAT-3.

Frozen samples were embedded in Cryomatrix embedding resin (Thermo Shandon, Pittsburgh, PA) and 5-μm sections were prepared using a cryostat. Fixation, permeabilization, and staining for specific antigens were performed, as described previously.[32] Because of a lack of staining with frozen samples for p-EGFR, p-erbB2, and p-Akt, the samples were fixed in formalin and processed into paraffin blocks to retest for these three markers. Primary antibodies used for IHC are listed in Appendix Table A1 (online only).

Scoring was done similar to the archival specimens stained for EGFR and erbB2. For p27, cytoplasmic and nuclear staining was scored separately. p-ERK scoring was based on the percentage of tumor cells positive for cytoplasmic staining. Both Ki-67 and p-STAT-3 scoring were based on the percentage of tumor cells positive for nuclear staining.

Statistical Considerations

The primary objective of this study was to determine the objective re-sponse rate (complete responses and partial responses [PRs]) of lapatinib in ACC. Secondary objectives were to evaluate the duration of response; rate and duration of stable disease (SD); progression-free, median, and overall survival (OS) rates; and safety and tolerability of lapatinib in this population. A two-stage design was used for the ACC cohort, according to Simon.[33] The null hypothesis assumed that the response rate was less than 5% and the alternative hypothesis assumed that the response rate was at least 20%. The design allowed enrollment of 12 assessable patients in the first stage. If one response was observed, an additional 25 assessable patients were to be enrolled. Assessment of the activity of lapatinib in non-ACC MSGTs was exploratory without a predetermined study design, with up to 30 patients planned.

For correlative samples, descriptive statistics were used to summarize each marker outcome at pretreatment, during treatment, and any difference between the two. Wilcoxon signed rank test was used to assess statistically

significant changes in marker value from pre- to during-treatment biopsy. Fisher's exact tests assessed whether pretreatment marker values, or the change in marker value, predicted SD as best response. For this analysis, optimal splits of the marker were performed to maximize statistical power. Whisker plots and bar graphs were used to demonstrate marker values pre- and during-treatment. Cox proportional hazards regression methods assessed whether pretreatment marker values, or change in markers, were predictive of time to progression (TTP). No investigation of predictors of OS was conducted. All tests were two sided and exact *P* values are reported throughout.

RESULTS

Patients and Treatment

Between November 2004 and March 2006, 20 patients with ACC and 20 patients with non-ACC MSGTs were enrolled at seven centers in Canada and the United States. Fifty-seven (92%) of 62 screened patients were positive for EGFR and/or erbB2. Of the 57 patients, nine were found to be ineligible for the study and eight patients declined participation. Of 40 patients enrolled onto the study, 39 and 36 were assessable for toxicity and objective response, respectively. One non-ACC patient had rapidly progressive disease after enrollment, never received study drug, and was excluded from additional analysis. Three patients, one with ACC and two with non-ACC, were not assessable for response but were included in the toxicity analysis; one had evidence of brain metastasis within 7 days of starting study treatment, one had a prior active malignancy within 5 years of study entry (and was ineligible per protocol), and one was withdrawn from study after 7 days to be treated with a protocol-prohibited medication (proton pump inhibitor). Patient characteristics are listed in Table 1.

Response and Survival

Of 19 assessable ACC patients, four had PD within two cycles. Of the 15 patients with SD after two cycles of treatment, six patients experienced disease progression within four cycles, and seven patients experienced disease progression after 6, 7, 10, 13, 14, 20, and 21 cycles, respectively. For the remaining two patients, one patient with SD was removed from study after six cycles due to an asymptomatic decrease in LVEF, and one remains on treatment and has received 21 cycles of therapy.

Of 17 assessable non-ACC MSGT patients, one died at the end of cycle 2 due to disease progression/pneumonia before objective response evaluation, seven had PD within two cycles, and two with objective SD were taken off therapy after two cycles (one for symptomatic progression and one at the discretion of the local investigator). Of seven patients with SD after two cycles, three patients experienced disease progression before cycle 5, and four patients experienced disease progression after 6, 9, 10, and 20 cycles, respectively.

Although no objective responses were observed (Table 1), a subset of patients had a reduction in measurable disease (Fig 1). When analyzed together, 13 patients had documented SD ≥ 6 months (Table 2). For these patients, the mean TTP before initiating therapy was 3 months, with a range of 2 to 6 months.

For all patients, the median follow-up duration, OS, and progression-free survival (PFS) was 15.8 months, not reached, and 3.4 months (95% CI, 2.1 to 5.3 months), respectively. For ACC, the median OS duration and 6-month OS rate were not reached and 90.0% (95% CI, 77.8% to 100%), respectively, whereas the median PFS duration and 6-month PFS rate were 3.5 months (95% CI, 3.1 to 12.7 months) and 35.0% (95% CI, 19.3% to 63.6%) respectively. For

Table 1. Patient Characteristics for Both ACC and Non-ACC Cohorts

Characteristic	ACC No. of Patients	ACC %	Non-ACC No. of Patients	Non-ACC %
No. of patients	20	100	19	100
Age, years				
Median	52		64	
Range	38-72		45-80	
Sex				
Male	12	60	16	84
Female	8	40	3	16
Performance status				
0	8	40	10	53
1	11	55	9	47
2	1	5	0	
Disease status at study entry				
Locoregionally recurrent	3	15	4	21
Metastatic	15	75	13	68
Both	2	10	2	11
Histology				
ACC	20	100	0	
Adenocarcinoma	0		7	35
Large/salivary duct carcinoma	0		4	20
Squamous cell carcinoma	0		3	15
Undifferentiated carcinoma	0		3	15
Mucoepidermoid carcinoma	0		2	10
Acinic cell carcinoma	0		1	5
IHC results				
EGFR positive/erbB2 positive	1	5	8	40
EGFR positive /erbB2 negative	19	95	12	60
EGFR-positive scores				
0	0		0	
1+	5	25	3	15
2+	10	50	6	30
3+	5	25	11	55
erbB2-positive scores				
0	13	65	7	35
1+	6	30	5	25
2+	1	5	3	15
3+	0		5	25
No. of prior regimens				
0	11	55	9	47
1	4	20	3	16
2	4	20	5	26
3	1	5	2	11
Prior therapy				
Chemotherapy	9	45	10	53
Radiation	18	90	17	89
Target/nontarget lesions				
Median	3/1		4/1	
Range	1-6/0-5		1-9/0-10	
Lung	16/13		13/11	
Liver	2/1		3/2	
Nodes	4/1		7/4	
Abdomen	0/1		0/0	
Other	5/1		4/4	
Best response to lapatinib treatment				
PR	0		0	
SD ≥ 6 months	9	45	4	21
SD < 6 months	6	30	4	21
PD	4	20	9	47
NA	1	5	2	11

Abbreviations: ACC, adenoid cystic carcinoma; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; PR, partial response; SD, stable disease; PD, progressive disease; NA, not assessable.
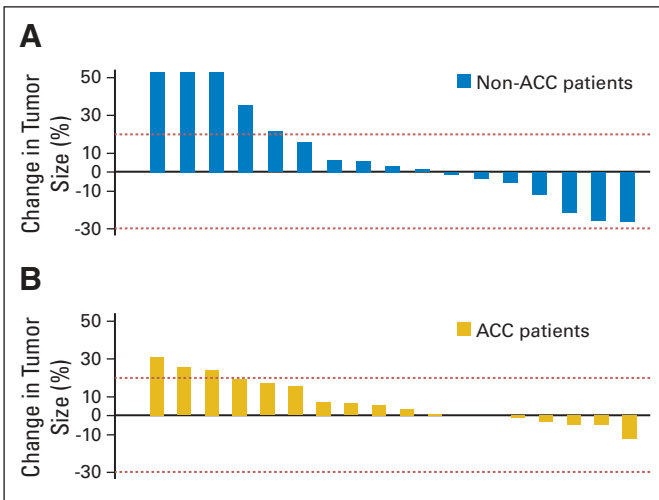
Fig 1. Maximal percentage of tumor reduction for target lesions by Response Evaluation Criteria in Solid Tumors Committee (RECIST). Percentages are calculated using the summed unidimensional measurements of target lesions per RECIST.

Fig 2. Survival and time to progression for patients with adenoid cystic carcinoma (ACC) and non-ACC malignant salivary gland tumors treated with lapatinib.
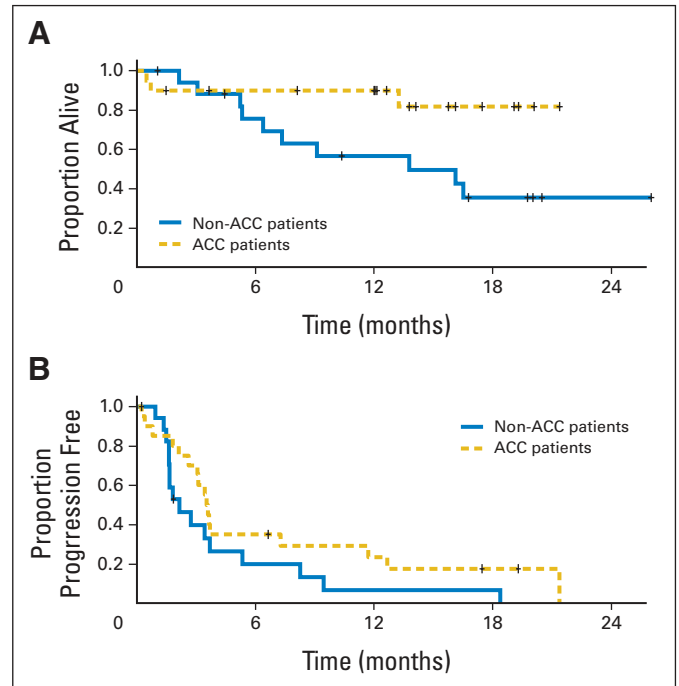
non-ACC, the median OS duration and 6-month OS rate were 13.8 months (95% CI, 7.3 to not reached) and 69.3% (95% CI, 50.1% to 95.9%), respectively, whereas the median PFS duration and 6-month PFS rate were 2.1 months (95% CI, 1.6 to 8.3 months) and 19.9% (95% CI, 7.3% to 54.0% months), respectively (Fig 2).

Correlative Studies

Archival specimens. The percentage of assessable patients with SD $\geq$ 6 months in subgroups based on EGFR or erbB2 expression in archival specimens suggested a positive correlation as follows: 1+ to 2+ EGFR (seven of 23; 30%) versus 3+ EGFR (six of 13; 46%); 0 to 2+ erbB2 (10 of 32; 31%) versus 3+ erbB2 (three of four; 75%). Interestingly, three of three patients (100%) with 3+ EGFR and 3+ erbB2 staining in archival tumor specimens had SD $\geq$ 6 months (Table 2).

Table 2. Characteristics for Patients With Stable Disease Beyond 6 Months

Histology	No. of Cycles	EGFR	erbB2	Prior TTP (months)
ACC	21	2+	0	3
ACC	6	1+	0	3
ACC	6	3+	1+	3
ACC	21	3+	1+	3
ACC	7	2+	1+	3
ACC	19	1+	0	6
ACC	10	2+	1+	2
ACC	14	2+	0	4
ACC	13	3+	0	3
Undifferentiated carcinoma	6	1+	1+	3
Adenocarcinoma	20	3+	3+	3
Squamous cell carcinoma	9	3+	3+	5
Undifferentiated carcinoma	10	3+	3+	6

Abbreviations: ACC, adenoid cystic carcinoma; EGFR, epidermal growth factor receptor; TTP, time to progression.

Paired Tumor Biopsies

Pretreatment and during-treatment biopsies were taken from 22 and 16 patients, respectively. Only eight patients had sufficient tumor cells on microscopic evaluation in both samples (Fig 3). A trend toward decreased p-Akt, decreased Ki-67, and increased p-STAT-3 was observed, but small numbers precluded any conclusions. There were no statistically significant associations between marker assessment and clinical outcome, nor were they of predictive value.

Toxicity

Lapatinib was tolerated well by most patients (Table 3). The majority of adverse events were grade 1 to 2 in intensity. Two grade 4 adverse events occurred: a secondary malignancy (laryngeal cancer) and laryngeal edema. Neither was believed to be related to lapatinib. Three patients died while on study, two as a result of disease progression, and one as a result of an intercurrent pneumonia.

Two patients with ACC had an asymptomatic reduction in LVEF from baseline of at least 10%. One had a baseline LVEF of 76% that decreased to 60%, 44%, and 55% after two, four, and six cycles, respectively. A second patient had a baseline LVEF of 62% that decreased to 51% after two cycles; LVEF values on the subsequent 11 evaluations ranged from 54% to 65%.

DISCUSSION

Salivary gland cancers are a heterogeneous group with varied natural history, aggressiveness, and prognosis. Given that EGFR or ErB2 status may be linked to a poor prognosis, lapatinib, an inhibitor against these targets, may benefit a group of patients with MSGT. Although no objective responses were observed, prolonged SD beyond 6 months
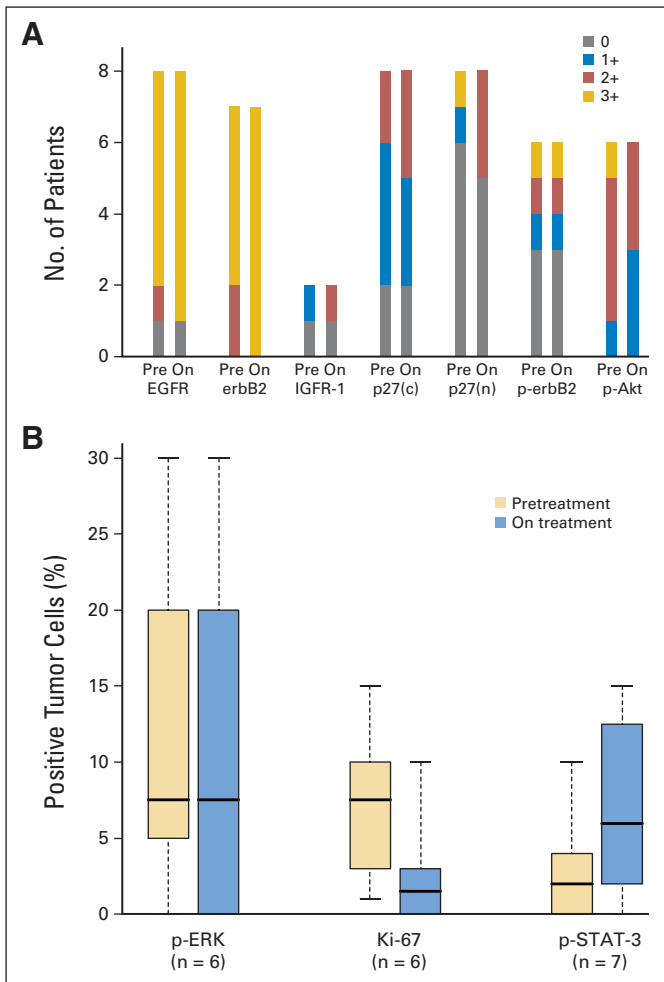
Fig 3. Pretreatment (pre) and during-treatment (on) tumor biopsies from the eight paired samples available for assessment. (A) Bar graphs illustrate marker values for epidermal growth factor receptor (EGFR), erbB2, insulin-like growth factor receptor-1 (IGFR-1), p27, phosphorylated (p-) erbB2, p-Akt. (B) Whisker plots illustrate marker values for extracellular signal-regulated kinase (p-ERK), Ki-67, and signal transducer and activator of transcription-3 (p-STAT-3). Staining was poor for p-EGFR and thus this marker was not included in (B).

Table 3. Toxicities Considered at Least Possibly Related to Lapatinib

Toxicity	No. of Patients (n = 39)	%	Worst Grade, Any Patient	No. of Cycles (n = 233)	%	No. of Cycles With Grade 3 or 4 Toxicity (n = 233)
Nonhematologic						
Diarrhea	24	62	2	103	44	0
Rash (acneiform)	19	49	2	67	29	0
Fatigue	16	41	3	86	37	1
Nausea	11	28	1	52	22	0
Dry skin	8	21	1	33	14	0
Pruritus	5	13	1	31	13	0
ALT	5	13	2	17	7	0
AST	5	13	2	17	7	0
Mucositis	5	13	1	17	7	0
Hyperglycemia	5	13	2	9	4	0
Headache	4	10	3	26	11	19
Creatinine	4	10	1	13	6	0
Dysgeusia	4	10	2	13	6	0
Vomiting	4	10	2	5	2	0
Alopecia	3	8	1	25	11	0
Rash (desquamation)	3	8	2	10	4	0
Dyspepsia	3	8	2	9	4	0
Pain	3	8	2	5	2	0
Hematologic						
Anemia	5	13	1	21	9	0
Leukopenia	4	10	1	6	3	0
Neutropenia	4	10	2	6	3	0
Lymphopenia	3	8	2	14	6	0
Thrombocytopenia	2	5	1	10	4	0

was observed in 13 (36%) of 36 assessable patients with PD before starting therapy.

Recent trials of targeted therapies in patients with advanced ACC have reported variable results. Imatinib (which inhibits the c-KIT tyrosine kinase) and gefitinib (which inhibits the EGFR tyrosine kinase) have been evaluated.[34-40] Four phase II studies and two case reports have evaluated imatinib in 45 patients with ACC. Three reported responses have been documented.[34,40] Although disease stabilization was documented in studies of imatinib and gefitinib, disease progression as a criterion for study entry was not typically required, and therefore stabilization may in fact reflect the relatively indolent natural course of the disease. The largest of these trials, reported previously by our group,[39] evaluated the use of imatinib in 16 patients. The median TTP on that study was 2.3 months compared with 3.5 months for the ACC patients reported in the present trial. Although direct comparisons across two different studies are not valid, they may be of exploratory value in a rare disease such as ACC. This caveat notwithstanding, it would seem that treatment with lapatinib may be

associated with a more prolonged TTP than treatment with imatinib. Of note, in contrast to our prior study with imatinib, our current study with lapatinib enrolled only patients with documented PD. Disease stabilization may represent more meaningful biologic activity in such a patient population.

In addition to imatinib and gefitinib, other targeted agents have been investigated in this disease. A phase II study of trastuzumab in patients with advanced or metastatic MSGTs confirmed one PR and an overall median TTP of 4.2 months.[41] A phase II trial of bortezomib in patients with incurable ACC reported a median PFS of 8.5 months in patients with PD within 9 months of study entry.[42] In a phase I trial of axitinib (AG-013736), a potent small molecule tyrosine kinase inhibitor of all known vascular endothelial growth factor receptors, platelet-derived growth factor receptor beta, and c-KIT, one patient with ACC experienced a PR.[43]

Identifying relevant proliferation and antiapoptosis survival pathways in malignant cells may inform therapeutic options based on tumor biology rather than histology alone. Preclinical data have shown the effects of lapatinib on human tumor cell lines.[44] Although inhibition of EGFR resulted preferentially in cell growth arrest, inhibition of erbB2 yielded both growth arrest and cell death. In a phase I study of lapatinib, all patients achieving PR had tumors that overexpressed erbB2, whereas pretreatment EGFR status did not discriminate between responders and nonresponders.[45] In this regard, it is of interest that among our patients with non-ACC MSGTs, all three patients with 3+ coexpressions of EGFR and erbB2 achieved SD ≥ 6 months. This observation may suggest greater therapeutic effect when there is a high degree of marker expression. Given that only one

patient with ACC expressed erbB2 at high levels in our study, conclusions based on marker status for those patients are impossible. Despite our desire to identify biologic pathways that might predict or correlate with response, too few viable samples were procured. The challenge of producing meaningful correlative study data is likely a reflection of both technical issues and heterogeneity across patients. Most of the patients on this study had lung metastases, for example, that are often difficult to biopsy safely with adequate tissue acquisition. The choice of tissue fixation is also critical in the demonstration and evaluation of protein expression by IHC.[46] Our results may have been affected negatively by the use of fresh frozen as opposed to formalin-fixed specimens, as others have reported previously.[46]

Stage I of the ACC protocol over-accrued patients because of the overwhelming interest of investigators and patients participating in this trial. Given that no objective responses were seen in either cohort, the second stage of the ACC arm did not open and the non-ACC arm was also terminated. Although there were no objective responses, a significant rate of disease stabilization seen in a group of patients with PD at study entry is of clinical relevance. The antitumor activity of lapatinib in MSGTs is believed to be primarily cytostatic. With this in mind, additional evaluation of molecular targeted therapies in this disease optimally would be performed using a novel study design with progression-based rather than response-based end points, as well as mandating assessment of disease progression by RECIST within 6 months of study entry. This study illustrates further that clinical trials in MSGTs can accrue successfully based on collaborative efforts by multiple groups.

AUTHOR CONTRIBUTIONS

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Acknowledgment

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).