Phase II Clinical and Exploratory Biomarker Study of Dacomitinib in Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of Head and Neck

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Abstract

Purpose: The goals of this study were to investigate the clinical activity, safety, and biomarkers of dacomitinib, an irreversible tyrosine kinase inhibitor of EGFR, HER2, and HER4, in recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN).

Experimental Design: Patients were eligible if the diseases were not amenable to curative treatment and had progressed on platinum-based chemotherapy, and were treated with dacomitinib 45 mg/day. The primary endpoint was objective response rate by RECIST1v1.1. Exploratory analysis included the characterization of somatic mutation, gene copy number, gene expression, p16INK4A expression by IHC, and investigation of their relationship with clinical outcomes.

Results: Forty-eight patients were evaluable for efficacy and toxicity. Ten patients (20.8%) had partial responses and 31 patients (65%) had stable diseases. The median progression-free survival (PFS) and overall survival (OS) were 3.9 months [95% confidence interval (CI), 2.9–5.0] and 6.6 months (95% CI, 5.4–10.3). Adverse events were mostly grade 1–2. Mutations in the PI3K pathway (PIK3CA, PTEN) and high expression of inflammatory cytokines (IL6, IL8, IL1A, IL1B, IL4, and TNF) were significantly associated with shorter PFS (2.9 vs. 4.9 months without mutations, P = 0.013; 2.8 vs. 9.9 months with low expression, P = 0.004). Those harboring PI3K pathway mutations or high inflammatory cytokine expression had shorter median OS (6.1 vs. 12.5 months lacking PI3K pathway mutations and with low inflammatory cytokine expression, P = 0.005).

Conclusions: Dacomitinib demonstrated clinical efficacy with manageable toxicity in platinum-failed R/M-SCCHN patients. Screening of PI3K pathway mutation and inflammatory cytokine expression may help identify which R/M-SCCHN patients are likely to gain benefit from dacomitinib. Clin Cancer Res; 21(3): 544–52. ©2014 AACR.

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is the seventh most common cancer worldwide (1). Although locally advanced disease is potentially curable with combined-modality therapy, 50% to 60% of patients developed locoregional or distant recurrence in 2 years (2). The prognosis of recurrent...
and/or metastatic SCCHN (R/M-SCCHN) is very poor, with a median survival of 6 to 10 months (3, 4). Platinum-based combination chemotherapy achieved modest response rates of 21% to 36% and failed to improve overall survival (OS) compared with single-agent chemotherapies (5).

The EGFR is a proto-oncogene regulating cell proliferation, angiogenesis, and metastasis. EGFR is almost universally expressed in SCCHN (6), and its overexpression is correlated with poor prognosis (7, 8). In this context, biologic agents targeting EGFR have been extensively studied in SCCHN (9–11). The current strategies for EGFR-targeted therapies in the treatment of R/M-SCCHN include EGFR-specific mAbs and small-molecule EGFR tyrosine kinase inhibitors (EGFR-TKI).

Cetuximab, a chimeric anti-EGFR mAb, was approved for the treatment of R/M-SCCHN as a single agent or in combination with chemotherapy (9, 10). The addition of cetuximab to platinum-based combination chemotherapy significantly improved objective response rate (ORR), progression-free survival (PFS), and OS compared with chemotherapy alone (9). Cetuximab as a monotherapy showed modest activity with ORR of 13% in R/M-SCCHN that progressed on platinum therapy (10).

Gefitinib and erlotinib are EGFR-TKIs that selectively block EGFR signaling through competitive reversible binding at the EGFR-TK domain. In R/M-SCCHN, gefitinib or erlotinib showed relatively low ORR of 1.4% to 10.6% with median OS of 5.5 to 8.1 months (12, 13). In a phase III study, gefitinib did not improve OS compared with methotrexate in R/M-SCCHN (13).

Clearly, only a minority of patients with R/M-SCCHN respond to EGFR inhibitors. To maximize the clinical potential of EGFR inhibitors, there is an urgent need to identify molecular predictors of the efficacy of EGFR inhibitors. In an earlier study, patients with SCCHN with high EGFR gene copy number showed higher ORR to erlotinib therapy than patients with low EGFR gene copy number. However, high EGFR gene copy number or EGFR overexpression failed to predict greater benefit from cetuximab combined with chemotherapy in R/M-SCCHN (14, 15). Recently, p16 status, a surrogate marker for human papilloma virus, has been suggested as a molecular predictor for panitumumab in combination with platinum combination for R/M-SCCHN (14, 15). Recently, p16 status, a surrogate marker for human papilloma virus, has been suggested as a molecular predictor for panitumumab in combination with platinum combination for R/M-SCCHN (14, 15).

Comprehensive molecular profiling, including somatic mutations, DNA copy number, and mRNA expression, may provide further opportunities to characterize a subset of patients who benefit the most from EGFR inhibitors.

Dacomitinib (PF-00299804) is a second-generation irreversible TKI of members of EGFR family, including EGFR, ErbB2, and ErbB4 (16). A phase I study determined the dose of 45 mg/d for clinical use. Dacomitinib significantly abrogates growth of SCCHN cells that are resistant to cetuximab (17).

The purpose of this study was to investigate the clinical activity, safety, and predictive biomarkers of dacomitinib in heavily treated R/M-SCCHN.

Materials and Methods

Study design

This was a multicenter, phase II study of dacomitinib monotherapy in patients with R/M-SCCHN who had progressed on platinum-based chemotherapy or was considered platinum intolerant (ClinicalTrials.gov Identifier: NCT01449201). The primary objective was to evaluate the ORR. Secondary objective was to evaluate the clinical benefit (CB; PFS ≥ 4 months on dacomitinib), PFS, OS, and the safety profile of dacomitinib therapy. Exploratory objectives were to evaluate whether tumor somatic mutations, copy number change, or gene expression is correlated with clinical outcomes.

All patients provided informed consent. The study was conducted in accordance with the Helsinki Declaration.

Study population

Patients with histologically confirmed R/M-SCCHN were enrolled. Patients were at least the age of 18 years, had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 to 2, had at least one measurable disease, had documented platinum administration or ECOG-PS2 were allowed to enter the study at the physician’s discretion.

Patients were excluded if patients had received ≥ 3 lines of palliative chemotherapy for R/M-SCCHN, had nasopharyngeal cancer, or had symptomatic brain metastases. Previous treatments with EGFR mAbs were allowed.

Treatment

Patients received continuous treatment with oral dacomitinib 45 mg once daily until disease progression, death, or unacceptable adverse events (AE). Treatment cycles were 28 days long. Drug doses were withheld and/or reduced for intolerable grade 2 or grade 3/4 toxic effects. A maximum of two dose-level reductions were permitted (30 mg then 15 mg). Patients who could not resume treatment after a 3-week delay were discontinued from the study.

Patient assessment

Response evaluations were defined according to RECIST 1.1 guidelines (18). Radiographic imaging was conducted at week 4, and every 8 weeks thereafter until disease progression or when clinically indicated. If a patient was documented as having a complete response (CR) or a partial response (PR), a confirmatory evaluation was performed after 4 weeks.

Safety assessments included physical examinations, documentation of AEs, and laboratory measurements on day 1 of each.
cycle. AEs were graded according to the Common Terminology Criteria for Adverse Events version 4.0 (19).

Exploratory biomarker analyses
Fresh or archival tumor tissues were collected at baseline for biomarker analysis, which included the characterization of somatic mutations using the Ion Torrent AmpliSeq Cancer Hotspot Panel v2 (CHPv2), a next-generation sequencing assay identifying multiple somatic mutations [2,800 Catalogue Of Somatic Mutations In Cancer (COSMIC) mutations from 50 genes]; gene copy number using Nanostring nCounter Cancer Copy Number Variation Assay (86 genes); gene expression using Nanostring nCounter Human Cancer Reference Kit (230 genes; Supplementary Table S1). The Nanostring method allows direct measurement of actual levels of RNAs with no need for target amplification. The sensitivity and specificity of the AmpliSeq CHPv2 and nCounter system have been previously validated (20, 21). Genomic DNA and mRNA were extracted from paraffin-embedded tumor blocks or fresh-frozen tissues using standard extraction procedures.

Methods for gene set analysis, IHC, FISH, and ELISA are described in the Supplementary Information.

Statistical rationale for study design and statistical analysis
A Fleming’s one-stage design was used to test the null hypothesis ($P_0$) with a 5% significance level that the ORR is $\leq 5\%$ versus the alternative hypothesis ($P_1$) that the ORR is $\geq 15\%$. Forty-four response-evaluable patients were required to provide 80% power to reject $P_0$ when the true ORR is 15%. Allowing for a 10% loss to follow-up rate, it is anticipated that the total sample size is 49.

PFS was defined as the time from the first day of chemotherapy until the first disease progression or death from any cause. OS was defined as the time from the first day of chemotherapy to death from any cause. PFS and OS were summarized using the Kaplan–Meier method.

For the predictive biomarker analysis, we define PFS $\geq$ 4 months on dacomitinib as CB, because most salvage therapies with either cytotoxics or EGFR inhibitors in R/M-SCCHN have shown PFS of approximately 2 months (22, 23). The association of biomarkers with clinical outcomes was analyzed using a two-tailed Fisher exact test and a log-rank test, respectively. $P$ value $\leq 0.05$ was considered significant. The significance was adjusted for the multiple tests when appropriate. Bonferroni correction for survival analysis and FDR for gene expression analysis was performed using R version 3.0.1. A detailed method for corrected $P$ value calculation is described in the Supplementary Information.

Results
Patient characteristics
From January 2012 to March 2013, a total of 49 patients were enrolled (Supplementary Fig. S1). One patient with external auditory canal cancer was incorrectly enrolled and excluded for the further analysis. Patient demographics are listed in Table 1. The majority of patients were male and ECOG-PS 0 or 1. The median age was 60.5 years. Approximately half of the patients had both locoregional and distant disease in at least three organ sites. Only 5 patients (10%) received dacomitinib as the first-line systemic therapy because of ECOG-PS2 ($n = 3$) or borderline renal function ($n = 2$). Almost two thirds (67%) of patients had received all treatment modalities before enrollment. Five patients (10%) had received cetuximab as either definitive setting or palliative setting.

Efficacy and treatment delivery
Forty-eight patients were evaluated for response (Table 2). Overall, 20.8% of patients (10 of 48) had PR, 65% (31 of 48) had SD, and 13% (6 of 48) had PD as a best response. The waterfall plots of maximum percentage changes from baseline for 45 patients with follow-up images available are shown in Fig. 1. The median duration of treatment was 15.6 weeks (interquartile range, 11.2–24.8 weeks). Reasons for treatment discontinuation were disease progression ($n = 46, 96\%$), patient withdrawal ($n = 1, 2\%$), and unacceptable toxicity ($n = 1, 2\%;$ pneumonia). Eleven patients (23%) subsequently received CB as second-line therapy (Table 2).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, $n$ (%)</th>
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<tr>
<td><strong>Primary site</strong></td>
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<tr>
<td>Oral cavity</td>
<td>18 (37)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Larynx</td>
<td>9 (19)</td>
</tr>
<tr>
<td>Maxillary sinus</td>
<td>2 (4)</td>
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<tr>
<td><strong>Disease status at study entry</strong></td>
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</tr>
<tr>
<td>Localoregional</td>
<td>15 (31)</td>
</tr>
<tr>
<td>Distant</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Both</td>
<td>22 (46)</td>
</tr>
<tr>
<td><strong>Number of involved disease sites</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (15)</td>
</tr>
<tr>
<td>2</td>
<td>17 (35)</td>
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<tr>
<td>3</td>
<td>24 (50)</td>
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<tr>
<td><strong>No. of prior chemotherapy regimens</strong></td>
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<tr>
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<td>5 (10)</td>
</tr>
<tr>
<td>1</td>
<td>25 (52)</td>
</tr>
<tr>
<td>$\geq$ 2</td>
<td>18 (38)</td>
</tr>
</tbody>
</table>

Abbreviations: PF, cisplatin and 5-fluourouracil; DP, docetaxel and cisplatin; TPF, docetaxel, cisplatin and fluorouracil; RT, radiotherapy; CT, chemotherapy.
<table>
<thead>
<tr>
<th><strong>Previous chemotherapy regimen</strong></th>
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<tr>
<td>Platinum based</td>
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<tr>
<td>Cisplatin alone</td>
<td>20 (42)</td>
</tr>
<tr>
<td>PF regimen</td>
<td>15 (31)</td>
</tr>
<tr>
<td>DP regimen</td>
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<tr>
<td>TPF regimen</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>5 (10)</td>
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<tr>
<td>Prior treatment</td>
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<tr>
<td>None</td>
<td>2 (4)</td>
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<tr>
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<td>3 (6)</td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Surgery + CT</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Radiation + CT</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Surgery + RT + CT</td>
<td>32 (67)</td>
</tr>
</tbody>
</table>
received BKM120, a pan-PI3K inhibitor after progression on dacomitinib.

With a median follow-up of 8.4 months, median PFS and OS were 3.9 months (95% CI 2.9–5.0) and 6.6 months (95% CI 5.4–10.3). ECOG-PS 2 was significantly associated with shorter OS (2.9 vs 8.8 months with ECOG-PS 0 or 1, \(P < 0.01\)) with a trend toward shorter PFS (2.9 vs 3.9 months with ECOG-PS 0 or 1, \(P = 0.06\)). Prior cetuximab treatment was also significantly associated with shorter PFS (2.8 vs. 3.9 months without cetuximab, \(P = 0.04\)), but was not associated with OS (6.4 vs. 8.2 months without cetuximab, \(P = 0.42\)). There was no significant difference in ORR, PFS, and OS according to other clinical factors such as age, primary site, smoking history, or the number of prior chemotherapy.

Safety

Forty-eight patients were assessed for treatment-related AEs (Table 3). AEs were mostly grade 1 to 2 and easily manageable. The most common AEs were paronychia (65%) and diarrhea (52%). Treatment-related grade 3 AEs occurred in 6 patients. At least one dose interruption and reduction due to treatment-related AEs occurred in 24 patients (50%) and 9 (19%).

Detection of somatic aberrations

Biomarker results were available in 33 (somatic mutation; Fig. 2A), 20 (gene expression; Fig. 2B), 31 (DNA copy number; Fig. 2C), and 34 patients (serum IL6 concentration; Fig. 2D).

Analysis of target-capture sequencing data identified a total of 58 point mutations, insertion, or deletions, previously implicated in COSMIC database (Supplementary Table S2; ref. 24). Median sequencing depth in target regions was 730X. The frequency of somatic mutations was illustrated in Fig. 2A. TP53 was the most frequently altered gene (58%) followed by CDKN2A (15%) and PIK3CA (15%). The PI3K pathway (PIK3CA, PTEN, and AKT1) mutations were frequently observed (8/33, 24%) and mutations in this pathway seemed to be mutually exclusive, except in one patient.

Gene expression profiling revealed that genes involved in inflammatory responses, such as TNF, IL1, IL4, IL6, IL8, secretory type II phospholipase A2 (PLA2G2A), and prostaglandin-endoperoxide synthase-2 (PTGS2, also known as COX2), were differentially expressed between patients with CB (n = 8) and non-CB (n = 12; \(P < 0.001\), FDR = 0.006; Supplementary Tables S3 and S4). Hierarchical cluster analysis demonstrated that 20 tumors could be classified into two clusters, each with distinctive expression pattern of inflammatory genes (Fig. 2B). All patients with non-CB on dacomitinib belonged to cluster 1 with overexpression of inflammatory genes. Gene set analysis revealed that gene sets of inflammatory cytokines/mediators were significantly associated with cluster 1 (Supplementary Table S4). Three (15%) among 20 patients had both PI3K pathway mutations and overexpression of inflammatory cytokines.

Frequent DNA copy number alterations were observed in genes related to cell cycle (CDKN2A, CCND1, CDK4, CDK6), cell differentiation (DCUN1D1), receptor tyrosine kinase (FGFR1, EGFR, ERBB2), and proliferation (PIK3CA; Fig. 2C and Supplementary Table S5).

Association of biomarkers with clinical outcomes

Kaplan–Meier curves of Median PFS (3.9 months) and OS (6.6 months) were in Fig. 3A. The frequency of somatic mutations in PIK3CA (ES45K, ES42K), PTEN (D326N, A120T, D107N, splice variant exon 3 c.165-1G>C), or AKT1 (D44G) was significantly higher in the non-CB patients (39% vs. 7% with CB patients; \(P = 0.046\); Bonferroni-adjusted \(P = 0.231\); Fig. 2A). Patients with these somatic mutations were significantly associated with shorter PFS (2.9 vs 4.9 months without PI3K pathway mutations; \(P = 0.013\); Bonferroni-adjusted \(P = 0.063\); Fig. 3B). OS was not different according to PI3K pathway mutations (Fig. 3B). Patients...
without PIK3CA/PTEN/AKT1 mutation had unusually long durations of response (5.3, 6.1, 6.4, 6.8, 14.4, and 19.9 months). There is no objective response (PR or CR) in patients with PI3K pathway mutations.

Overexpression of inflammatory cytokines/mediators was significantly associated with shorter PFS (2.8 vs. 9.9 months with low inflammatory cytokine expression; \( P = 0.004 \); Bonferroni-adjusted \( P = 0.016 \)) and shorter OS (6.1 vs. 20.3 months with low inflammatory cytokine expression; \( P = 0.014 \); Bonferroni-adjusted \( P = 0.056 \)), respectively (Fig. 3C). Patients with low inflammatory cytokine expression also tended to have higher ORR (40% vs. 13% with high expression; \( P = 0.25 \)), with unusually long durations of response (5.2, 5.8, 9.9, 14.4, and 19.9 months). Overall, patients who harbor PIK3CA/PTEN/AKT1 mutation or inflammatory cytokine overexpression were significantly associated with shorter PFS (2.9 vs. 6.1 months; \( P = 0.001 \); Bonferroni-adjusted \( P = 0.02 \)) and shorter OS (6.1 vs. 12.5 months; \( P = 0.005 \); Bonferroni-adjusted \( P = 0.1 \); Fig. 3D). p16 positivity was not associated with PFS, but had a trend toward better OS (Supplementary Fig. S2).

Patients with gene amplifications of receptor tyrosine kinases tended to have shorter PFS (1.0, 1.2, 2.1, and 2.9 months; Fig. 2C). A representative case of FGFR1 amplification was illustrated using FISH (Supplementary Fig. S3).

Serum IL6 level was measured in 34 patients at baseline and 14 days after the start of dacomitinib (Fig. 2D). There was no difference in baseline IL6 level between patients with CB and non-CB (\( P = 0.986 \)). At day 14, however, there was a reduction of IL6 concentration compared with baseline only in patients with CB (\( P = 0.055 \)). Furthermore, serum IL6 concentration was significantly lower in patients with CB, compared with patients with non-CB at day 14 (\( P = 0.048 \)).

### Discussion

In our study, characterization of somatic mutation, DNA copy number, and gene expression was performed by high-throughput sequencing and digital count technology. Overall, this comprehensive biomarker analysis identified that the screening for PI3K pathway alteration and/or inflammatory gene expression could help identify subgroups that most likely benefit from dacomitinib in R/M-SCCHN. Although our findings need to be validated in future randomized trials, our study demonstrated the applicability of a multiomics approach for identification of novel biomarkers in the clinical trial setting of refractory R/M-SCCHN.

Compared with previous studies with single-agent EGFR inhibitors (10, 12, 13), patients enrolled in our study had noticeably more clinical factors associated with poor prognosis; 38% of patients had progressive disease after two prior chemotherapy regimens, 67% of patients had previously received all standard treatment modalities, and 50% of patients had at least three involved disease sites. In this population with poor prognosis, dacomitinib demonstrated encouraging clinical activity (confirmed ORR, 20.8%; PFS, 3.9 months). Our data compare favorably with the limited activity of cetuximab as a single agent in R/M-SCCHN (ORR 13%; time to progression of 70 days; ref. 10).

Our data suggest that assessment of PI3K pathway mutation may be used to guide therapy for R/M-SCCHN. The PI3K pathway has been reported to be the most frequently mutated oncogenic pathway in SCCHN (25). In our study, the frequency of PI3K pathway mutations was 24% (8 of 33 evaluable patients), which was comparable with those from the previous reports (25–28). Most of the PI3K pathway mutations were mutually exclusive, supporting an oncogenic role of the PI3K pathway in SCCHN. Oncogenic activation of the PI3K pathway contributes to resistance to EGFR inhibition in SCCHN preclinical models (29).

Patients with PI3K pathway mutations had a significantly shorter PFS, compared with patients without these mutations. A similar finding has recently been reported in patients with breast cancer treated with lapatinib combined with letrozole (30). Given the controversial prognostic impact of PI3K pathway mutation in various malignancies (31–33), a significantly longer PFS and durable objective response in our patients without PI3K pathway mutations are most likely due to the favorable therapeutic effect of dacomitinib. Upon progression, 11 patients (23%) were enrolled into a phase II trial of BKM120 and one patient who had a PFS of 2.3 months to dacomitinib showed a PR to BKM120. Expectedly, a subsequent therapy with potential efficacy in patients with PI3K pathway mutations might influence OS in our study.

Inflammation in the tumor microenvironment plays a critical role in tumor cell survival, angiogenesis, and resistance to anticancer therapy (34). In our study, overexpression of inflammatory genes contributed to resistance to dacomitinib. The overexpression of inflammatory cytokines/mediators can alter responses to dacomitinib via multiple mechanisms. These include induction of epithelial-to-mesenchymal transition (EMT; ref. 35), suppression of antitumor immunity (36, 37), reprogramming of protumoral microenvironment (36, 38), and upregulation of growth and survival pathway (39–43). IL1β modulates Snail and thereby downregulates E-cadherin expression in SCCHN, suggesting the role of inflammation on the induction of EMT (35). IL4 plays a key role in humoral and adaptive immunity and mediates...
immune evasion of cancer cells in the tumor microenvironment (36). IL8 signaling was shown to transactivate EGFR, promoting proliferation and survival of cancer cells through the PI3K/MAPK pathway (39). In addition to its role in angiogenesis, IL8 induces a chemotactic infiltration of neutrophils into the tumor site, thereby generating protumoral microenvironment (38). Secretion of inflammatory cytokines has been known to constitutively activate NF-κB and STAT3, which directly regulate numerous genes, such as Bcl-2, cyclin D1, and c-myc, which have been associated with cell survival and chemoresistance (37, 40, 42, 44). TNF was reported to mediate constitutive activation of NF-κB in SCCHN cells (40). IL6 is a key downstream target of NF-κB and is a potent activator of STAT3 as well (45). Inhibition of PLA2G2A, a rate-limiting enzyme in tumor-stimulating eicosanoid production, reduced cell proliferation and NF-κB activity in non–small cell lung cancer (41). In addition, PLA2G2A induced proliferation of...
Figure 3. Kaplan–Meier estimates of PFS and OS according to PIK3CA/PTEN/AKT1 mutation or inflammatory gene expression. A, PFS and OS (N = 48); B, PFS and OS according to PIK3CA/PTEN/AKT1 mutation status (N = 33); C, PFS and OS by inflammatory gene expression (N = 20); D, PFS and OS according to PIK3CA/PTEN/AKT1 mutation or inflammatory gene expression (N = 33).
astrocytoma via activation of EGFR, suggesting its potential role in resistance to EGFR inhibitors (46).

IL6 has been known to induce resistance to anticancer therapy in different types of cancer (43, 45). To complement IL6 overexpression (26-fold) in local tumor microenvironment, we compared the concentrations of plasma IL6 in patients with CB and non-CB on dacomitinib. Despite similar IL6 concentrations at baseline between two groups, its concentration at day 14 of dacomitinib was significantly higher in non-CB patients than in CB patients. This may suggest that IL6 induced by dacomitinib from tumor or stromal cells promoted resistance to dacomitinib in non-CB patients. This is in accordance with our previous report that dacomitinib induced STAT3 activation via autocrine IL6 production, promoting de novo resistance to dacomitinib (43).

It will be important to determine usefulness of plasma IL6 detection for monitoring therapeutic response to EGFR inhibitors in the future study.

Combination strategies targeting the PI3K pathway or inflammatory pathway can be a potential therapeutic option to overcome resistance and enhance efficacy of dacomitinib in R/M-SCCHN. Several agents targeting the PI3K pathway (e.g., BYL719, XL147; refs. 47, 48), inflammatory cytokines/mediators (e.g., nxolutinib; ref. 49), or COX-2 pathway (e.g., celecoxib; ref. 50) in combination with EGFR inhibitors are under active investigation.

In conclusion, dacomitinib demonstrated promising efficacy with manageable toxicity in platinum-failed R/M-SCCHN patients. Screening of PI3K pathway mutation and expression of inflammatory mediators may help identify patients with R/M-SCCHN most likely benefit from dacomitinib.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

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