

A Phase I Clinical Trial and Independent Patient-Derived Xenograft Study of Combined Targeted Treatment with Dacomitinib and Figitumumab in Advanced Solid Tumors

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Abstract

Purpose: This phase I, open-label, single-arm trial assessed the safety and tolerability of dacomitinib–figitumumab combination therapy in patients with advanced solid tumors.

Experimental Design: A standard 3 + 3 dose escalation/descalation design was utilized. Starting doses were figitumumab 20 mg/kg administered intravenously once every 3 weeks and dacomitinib 30 mg administered orally once daily. We also performed an independent study of the combination in patient-derived xenograft (avatar mouse) models of adenoid cystic carcinoma.

Results: Of the 74 patients enrolled, the most common malignancies were non–small cell lung cancer (24.3%) and colorectal cancer (14.9%). The most common treatment-related adverse events in the 71 patients who received treatment across five dose levels were diarrhea (59.2%), mucosal inflammation (47.9%), and fatigue and acneiform dermatitis (45.1% each). The most common dose-limiting toxicity was mucosal inflammation. Dosing schedules of dacomitinib 10 or 15 mg

daily plus figitumumab 20 mg/kg every 3 weeks after a figitumumab loading dose were tolerated by patients over multiple cycles and considered recommended doses for further evaluation. Objective responses were seen in patients with adenoid cystic carcinoma, ovarian carcinoma, and salivary gland cancer. Pharmacokinetic analysis did not show any significant drug–drug interaction. In the adenoid cystic carcinoma xenograft model, figitumumab exerted significant antitumor activity, whereas dacomitinib did not. Figitumumab-sensitive tumors showed downregulation of genes in the insulin-like growth factor receptor 1 pathway.

Conclusions: Dacomitinib–figitumumab combination therapy was tolerable with significant dose reductions of both agents to less than the recommended single-agent phase II dose of each drug. Preliminary clinical activity was demonstrated in the potential target tumor adenoid cystic carcinoma. *Clin Cancer Res*; 23(5); 1–9. ©2016 AACR.

See related commentary by Sundar et al., p. 1123

Introduction

The members of the human epidermal growth factor receptor (HER) family comprise HER1/EGFR, HER2, and HER4 tyrosine kinases and the kinase-null HER3. HER family members act together via heterodimerization and homodimerization to enable downstream signaling pathways modulating a range of cellular activities including growth, proliferation, differentiation, and migration (1, 2). The role of HER1, HER2, and HER3 in many

cancer types is well-documented. This includes overexpression or aberrant function of HER receptors, as noted in lung, breast, head and neck, colorectal, and other malignancies (3). Reversible EGFR tyrosine kinase inhibitors such as erlotinib and gefitinib selectively target HER1/EGFR, just one of the members of the HER family (1). Dacomitinib (PF-00299804) is an orally bioavailable, potent, highly selective, irreversible small-molecule inhibitor of HER1/EGFR, HER2, and HER4 tyrosine kinases that has demonstrated antitumor activity in both gefitinib-sensitive and gefitinib-resistant preclinical non–small cell lung cancer (NSCLC) models (4, 5). Dacomitinib has shown promising clinical anticancer activity in patients with NSCLC that progressed following prior chemotherapy (6) as well as first-line in patients with advanced NSCLC with an *EGFR*-activating mutation (7).

Insulin-like growth factors (IGF) and their receptors are important components of lung cancer signaling pathways (8). IGF receptor 1 (IGF-1R) is often overexpressed in NSCLC and can mediate the proliferation of lung cancer cell lines (8). In addition, acquired resistance to EGFR tyrosine kinase inhibitors in lung cancer cell lines is associated with enhanced dependency on IGF-1R signaling (9–11). Indeed, in NSCLC cells, erlotinib can induce EGFR/IGF-1R heterodimerization, which transmits a survival signal through IGF-1R and its downstream mediators and increases the synthesis of EGFR and

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Translational Relevance

Evidence supports cross-talk between the insulin-like growth factor receptor 1 (IGF-1R) and epidermal growth factor receptor (EGFR) pathways, with resistance to EGFR inhibition mediated by IGF-1R and vice versa. This suggests that combination of targeted inhibitors of these pathways might improve patient outcome. We conducted a phase I trial to assess the safety, tolerability, and preliminary efficacy of the combination of the EGFR inhibitor dacomitinib and the anti-IGF-1R antibody figitumumab in patients with advanced malignant solid tumors. Dacomitinib–figitumumab combination therapy was found to be challenging, with significant dose reductions of both agents to less than the recommended single-agent phase II dose required for each drug. Preliminary clinical activity was demonstrated in adenoid cystic carcinoma. Because of multiple pathways involved in tumorigenesis and disease resistance, concurrent development of investigational drugs is a rational approach to treatment.

antiapoptotic survivin proteins (11). In one study, IGF-1R expression was found to be a biomarker for intrinsic resistance to gefitinib in NSCLC cell lines and patients, although its role in this resistance was questioned (12).

IGF-1R has also been implicated in the development of colorectal cancer (13, 14), and it has been suggested that cross-talk between the EGFR and IGF-1R signaling pathways may be a mechanism by which colorectal cancer cells develop resistance to EGFR tyrosine kinase inhibitors (15). Indeed, preclinical evidence suggests that gefitinib can induce downstream activation of the Akt and MAPK pathways in colorectal cancer cell lines by triggering phosphorylation of IGF-1R or heterodimerization of EGFR and IGF-1R (15). In a separate study, combined downregulation of both EGFR and IGF-1R in colorectal cancer cell lines was shown to decrease cell proliferation and induce apoptosis more effectively than downregulation of either receptor alone (16). Evidence is therefore accumulating that signaling interplay, or cross-talk, occurs between the IGF-1R and EGFR pathways with resistance to EGFR inhibition mediated by IGF-1R and vice versa (9), suggesting that rational combination of targeted inhibitors of these pathways might improve patient outcome.

This phase I trial assessed the safety and tolerability of the combination of dacomitinib and figitumumab in patients with advanced malignant solid tumors and evaluated preliminary efficacy in two expansion cohorts of patients with advanced NSCLC and advanced solid malignancies, with the objective of recommending a phase II dosing regimen (RP2D). Figitumumab (CP-751,871) is a fully human IgG2 mAb that specifically binds to IGF-1R, inhibiting binding of the IGF-1 ligand and downstream receptor signaling, and causing downregulation of the receptor in cells (17). During this work, we also aimed to test the activity of figitumumab and dacomitinib, both alone and in combination, in a set of avatar mouse models of adenoid cystic carcinoma. Avatars (also known as patient-derived xenograft models) are essentially personalized mouse models developed by transplanting fragments of tumor tissue from a patient into immunocompromised mice. These murine avatars offer a mirror image of the human cancer, allowing drug activity and biomarker profiles to be tested in individual cancers in tandem with the patient's clinical

course of disease (18). Used alongside clinical trials, this is known as a co-clinical trial approach. The goals of these studies were to investigate individual drug efficacy as well as to search for biomarkers of activity.

Materials and Methods

Patient population

Patients with a histologically or cytologically confirmed malignant solid tumor and advanced disease unresponsive or no longer responsive to prior standard treatment, age 18 years or over, and Eastern Cooperative Oncology Group performance status (ECOG PS) 0/1 were eligible. An expansion cohort at the maximum tolerated dose (MTD) enrolled patients with advanced NSCLC previously treated with a platinum-based chemotherapy regimen and no more than three prior chemotherapy regimens for advanced disease, including adjuvant treatment if relapse had occurred within 12 months of initiation, and with ECOG PS 0 to 2.

Exclusion criteria included chemotherapy, radiotherapy, or surgery within 2 weeks or investigational or immune-based treatment within 4 weeks of study entry, prior treatment with figitumumab or any agent that targets the IGF-1R signaling pathway, and uncontrolled or significant cardiovascular disease. Patients with histologic or cytologic evidence of small cell or carcinoid lung cancer and those who received prior dacomitinib or any agent that targets the EGFR or HER2 signaling pathways were excluded in the NSCLC expansion cohort. Details and additional inclusion/exclusion criteria are available online.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guideline on Good Clinical Practice, and applicable local regulatory requirements and laws. All patients, or their legally acceptable representative, provided written informed consent before any study-specific activities were performed. Investigators obtained prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents from the Institutional Review Board/Independent Ethics Committee.

Trial design and treatment

This was a multicenter, nonrandomized, open-label, single-arm phase I trial. Patients were enrolled at four centers in the United States, Spain, and France. Cohorts of at least 3 patients were planned at each dose level in a standard dose escalation/desescalation design to determine the MTD, with no intrapatient dose escalation permitted. Dose escalation to the next dose level occurred following evaluation of safety and tolerability during the first treatment cycle in the first 3 evaluable patients enrolled at a dose level. If no dose-limiting toxicity (DLT) was observed in the first 3 patients evaluable for safety, the dose was escalated for the next cohort. If there was one DLT among the first 3 patients, an additional 3 patients were enrolled at the same dose level. If two DLTs were observed in up to 6 patients, dosing at that level was stopped and dose finding continued below this dose level.

The starting dose of figitumumab was 20 mg/kg administered intravenously once every 3 weeks, whereas the starting dose of dacomitinib was 30 mg orally, administered once daily on an empty stomach (2 hours before or after food intake). These starting doses were selected based on the safety and tolerability of each drug from ongoing studies, with reduction in dacomitinib

Table 1. Combination-regimen dose levels

Planned dose level	Dacomitinib dose (mg orally every day)	Figitumumab (mg/kg i.v. every 3 weeks)	Patients enrolled (n)	DLTs observed
Original protocol starting dose				
D1	30 + LD	20 + LD	2	Yes
Protocol amendment starting dose ^a				
D1a	30	20 + LD	3	Yes
Planned dose-reduction levels				
D-1a	20	20 + LD	11	Yes
D-1b ^b	10	20 + LD	25	No
D-1c	20	10 + LD	8	Yes
D-1d ^b	15	20 + LD	25	Yes
Planned dose-escalation level ^c				
D2 ^c	45	20 + LD	0	-

Abbreviations: D, dose level; DLT, dose-limiting toxicity; LD, loading dose.

^aD1 included loading doses for both dacomitinib and figitumumab; the dacomitinib loading dose was omitted in all subsequent dose levels.

^bRecommended dose levels for further evaluation in expansion cohorts.

^cCriteria for dose escalation were not achieved in the study, and no patients were recruited to the planned D2 dose level.

from the recommended phase II dose for monotherapy of 45 to 30 mg daily in the initial cohort. A loading dose of figitumumab, consisting of administration of two consecutive once-daily infusions on days 1 and 2 of cycle 1, was used to expedite achievement of steady-state drug levels. The original protocol also included a dacomitinib loading schedule of twice-daily dosing on days 1 to 3 of cycle 1, followed by once-daily dosing from cycle 1, day 4. Following development of DLTs in 3 of the first 5 patients, the study was amended to omit the dacomitinib loading dose. The planned combination-regimen dose levels are shown in Table 1.

The highest tolerated dose regimen was declared the MTD. If more than 6 patients were enrolled at a dose level, the MTD was defined as the highest dose level at which less than 33% of patients (e.g., ≤ 2 of 7–9 patients) experienced DLTs in cycle 1. Once the MTD was defined, two expansion cohorts were opened for enrollment to gather additional safety data on patients with advanced solid malignancies (expansion cohort A) and advanced NSCLC (expansion cohort B) and help determine the RP2D. A total of 12 to 18 patients evaluable for at least two cycles were enrolled into each dose regimen of each expansion cohort.

Treatment was discontinued in the event of progression of disease, unacceptable toxicity (including toxicity resulting in treatment delay for more than 21 days), protocol noncompliance, or patient withdrawal.

Study endpoints and assessments

The primary endpoint was the overall safety profile, characterized by type, frequency, severity, timing, and relationship to trial treatment of adverse events (AE) and laboratory abnormalities. Safety was assessed by monitoring AEs during the trial (from initiation of study treatment until at least 28 days after the last dose of dacomitinib and until 150 days after the last dose of figitumumab) by clinical laboratory tests, recording vital signs, 12-lead electrocardiography, echocardiography if appropriate, and performance status. AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI CTCAE v 3.0). DLT was defined as any of the following occurring during cycle 1 when considered related to study treatment: CTCAE grade 3 or 4 hematologic toxicity or grade 3 or 4 nonhematologic toxicity despite optimal supportive care and/or prophylaxis, or any recurrent or persistent grade 2 toxicity considered intolerable by the patient, which resulted in an unacceptable treatment delay (more than 2 weeks for dacomitinib and

3 weeks for figitumumab) despite optimal supportive care and/or prophylaxis. Grade 3 or 4 laboratory abnormalities not considered clinically severe (e.g., hypomagnesemia, hypophosphatemia, gamma-glutamyl transferase elevation, or asymptomatic hyperglycemia) by the investigator or sponsor were not considered DLTs.

Evaluation of antitumor activity was based on objective tumor assessments by investigator review of computed tomography or magnetic resonance imaging scans using Response Evaluation Criteria in Solid Tumors version 1.0. Tumor assessments were performed at baseline and at the end of every other 3-week treatment cycle or when progressive disease was suspected.

Blood samples for the evaluation of plasma pharmacokinetic parameters of dacomitinib and figitumumab were collected at the MTD level only, including both expansion cohorts at dose levels D-1b and D-1d, prior to dosing and at various time points post-dosing on day 1 of cycle 2 and prior to dosing on day 1 of cycles 3 and 4. Samples were collected at baseline from available NSCLC tumor tissue for evaluation of *KRAS* mutation and *EGFR* mutation/amplification status in the MTD NSCLC expansion cohort.

Statistical design and analyses

As the primary purpose of this study was to determine the safety and tolerability of this drug combination and the RP2D, no specific statistical hypothesis with regard to safety, pharmacokinetics, and efficacy was planned. Descriptive statistics were used to summarize all patient characteristics, treatment administration/compliance, efficacy endpoints, safety, and pharmacokinetic parameters.

Plasma samples were analyzed for dacomitinib concentrations at Alta Analytical Laboratory, El Dorado Hills, CA, using a validated, sensitive analytical assay and a specific high-performance liquid chromatography tandem mass spectrometric method in compliance with Pfizer standard operating procedures. Pharmacokinetic parameters were calculated using the eNCA version 2.2 software package (Pfizer Inc.).

Mouse treatment studies

Adenoid cystic carcinoma tumors (ACCX5M1, ACCX6, ACCX9, ACCX11, ACCX14, and ACCX16; ArrayExpress accession no. E-GEOD-36820) for implantation into avatar mice were obtained, established, and propagated at the University of Virginia (Charlottesville, VA) according to the methods described by Moskaluk

and colleagues (19) and kindly provided by the Adenoid Cystic Carcinoma Research Foundation (ACCRF; Needham, MA) for these studies; cell lines were confirmed as authentic and reconfirmed by short tandem repeat analysis. Preclinical studies were conducted at START (South Texas Accelerated Research Therapeutics, San Antonio, TX) under International Animal Care and Use Committee–approved protocols. Briefly, tumor fragments from host mice were harvested and implanted subcutaneously into immune-deficient mice. Animals were matched by tumor volume (TV) and randomized to control, figitumumab (20 mg/kg i.v. once weekly for 4 weeks), dacomitinib (7.5 mg/kg orally once daily for 4 weeks), and the combination (5 or 10 mice per group). TV and animal weight data were collected electronically using a digital caliper and scale; tumor dimensions were converted to volume using the formula $TV (\text{mm}^3) = \text{width}^2 (\text{mm}^2) \times \text{length} (\text{mm}) \times 0.52$. Endpoints were a mean control TV of approximately 1 to 2 cm^3 ; change in TV of each group was compared with the control. Statistical analysis was performed using a two-way analysis of variance (ANOVA), followed by the Dunnett multiple comparisons test.

Biological studies

DNA extracted from adenoid cystic carcinoma models was used for Sequenom MassARRAY somatic mutation profiling using a customized primer panel (Supplementary Table S1). Gene expression data were available for all six tumors (five hybridized using Human Genome U133 Plus 2.0 Array and one using Human Genome U133A Array, both platforms from Affymetrix). We used a frozen multiarray analysis (FRMA) method for preprocessing (because it allows analysis of microarrays individually or in small batches) and then combined the data for analysis (20). After preprocessing, both platforms were combined keeping the common probes. The genes from all arrays were annotated using genome version Ensembl 63. On the basis of the results of mouse treatment studies, adenoid cystic carcinoma tumor models were divided into a responder group (tumor growth inhibition with $P < 0.05$ for figitumumab versus control; ACCX5M1, ACCX11, and ACCX14) and a nonresponder group (ACCX6, ACCX9, and ACCX16). We used the Limma package to test for differential expression at baseline in responders versus nonresponders (21). We ranked all genes according to their T statistic and performed gene-set enrichment analysis (GSEA) using the GseaPreranked tool of the GSEA software package (22). GSEA analysis was performed with the default parameters using an IGF-1R signature gene set and was focused on figitumumab (23).

Results

Patient characteristics and disposition

A total of 74 patients (43 male and 31 female) were enrolled, and 71 patients received treatment across five dose levels between August 2008 and August 2011. Three patients (1 each in D–1a, D–1b, and D–1c) were enrolled but never treated—2 patients due to abnormal baseline laboratory values and 1 patient due to worsening ECOG PS. Tumor tissue was available from 6 patients with NSCLC in expansion cohort B, from which three different *KRAS* mutations and no instances of *HER* mutation or amplification were identified; no correlations with efficacy were made given the small number of samples. In the dosing cohorts D–1b and D–1d, 8 and 7 patients with NSCLC were enrolled, respectively. Combination-regimen dose levels and patient characteristics are summarized in Tables 1 and 2.

Safety and tolerability

Safety and tolerability were assessed in the 71 patients who were enrolled and received study treatment. Two patients were enrolled at the initial starting dose level D1 (dacomitinib 30 mg daily and figitumumab 20 mg/kg every 3 weeks plus loading doses for both). One patient experienced two DLTs (grade 3 mucosal inflammation and grade 3 fatigue). The second patient developed grade 3 mucosal inflammation in cycle 2. Following protocol amendment to remove the dacomitinib loading dose and to allow evaluation of lower starting doses of dacomitinib and figitumumab, the study continued with 3 patients enrolled at dose level D1a. Two of the 3 patients (66.7%) enrolled experienced a DLT (grade 3 diarrhea and grade 3 mucosal inflammation), and this dose level was not explored further. All dose cohorts reported a DLT except dose level D–1b (dacomitinib 10 mg and figitumumab 20 mg/kg i.v. every 3 weeks plus figitumumab loading dose; Table 3).

Dose cohorts D–1b and D–1d (dacomitinib 15 mg daily and figitumumab 20 mg/kg i.v. every 3 weeks plus figitumumab loading dose) were tolerated by patients over multiple cycles. These schedules were therefore considered the RP2Ds for any further exploration of this combination.

All 71 patients experienced treatment-emergent AEs, with 97.2% experiencing treatment-related AEs. Overall, the most common treatment-related AEs were diarrhea (59.2%), mucosal inflammation (47.9%), and fatigue and dermatitis acneiform (45.1% each). Grade 3 or 4 treatment-related AEs were reported in 35.2% of patients. The only grade 5 treatment-related AE reported was a single patient from dosing cohort D–1a who had grade 5 disease progression reported as a treatment-related AE. Five of 69 (7.0%) and 6 of 69 (8.7%) patients who discontinued dacomitinib and figitumumab, respectively, did so due to treatment-related AEs. Overall, 18.3% of patients had treatment temporarily interrupted, and 8.5% of patients had a dose reduction because of treatment-related AEs. AEs resulting in dose modifications were predominantly gastrointestinal (stomatitis, mucosal inflammation, and diarrhea) and fatigue. There were 31 deaths on study, all of which were attributed to the disease under study.

At the RP2Ds [D–1b ($n = 25$) and D–1d ($n = 12$)], treatment-related grade 3 to 5 toxicities were very infrequent and consisted of grade 3 decreased appetite, fatigue, and bone pain in 1 patient (4%), each at D–1b, and grade 3 fatigue (3 patients, 12%), diarrhea (2 patients, 8%), diabetes mellitus and neutropenia (each 1 patient, 4%), mucosal inflammation (1 patient, 4%), hyponatremia (1 patient, 4%), and asthenia (1 patient, 4%) and grade 4 hyperuricemia/blood uric acid increased (2 patients, 8%) at D–1d.

Efficacy

The best overall response (BOR) was assessed in the 61 response-evaluable patients who received at least one dose of study medication, had an adequate baseline tumor assessment, and had at least one on-study tumor assessment. Among the 61 response-evaluable patients, there were three partial responses (PR), and 22 patients had a BOR of stable disease (SD); no complete responses were observed (Fig. 1). One PR was observed at dose level D–1d (dacomitinib 15 mg and figitumumab 20 mg/kg plus figitumumab loading dose; an RP2D) in a patient with adenoid cystic carcinoma who continued on study treatment for more than 1.5 years. Two PRs were observed

Table 2. Patient characteristics

Characteristic	Starting dose levels ^a		Dose de-escalation levels				Total (N = 74)
	D1 Daco30 + LD/ Fig120 (n = 2)	D1a Daco30/ Fig120 (n = 3)	D-1a Daco20/ Fig120 (n = 11)	D-1b ^b Daco10/ Fig120 (n = 25)	D-1c Daco20/ Fig110 (n = 8)	D-1d ^b Daco15/ Fig120 (n = 25)	
Median age, years (range)	70.5 (54-87)	60.0 (47-75)	64.0 (48-75)	55.0 (18-74)	60.5 (47-73)	59.0 (26-75)	59.0 (18-87)
Gender, n (%)							
Male	1 (50.0)	1 (33.3)	3 (27.3)	18 (72.0)	5 (62.5)	15 (60.0)	43 (58.1)
Female	1 (50.0)	2 (66.7)	8 (72.7)	7 (28.0)	3 (37.5)	10 (40.0)	31 (41.9)
Race/ethnicity, n (%)							
Caucasian	2 (100.0)	3 (100.0)	10 (90.9)	25 (100.0)	6 (75.0)	25 (100.0)	71 (95.9)
Black	0	0	1 (9.1)	0	0	0	1 (1.4)
Other ^c	0	0	0	0	2 (25.0)	0	2 (2.7)
ECOG performance status, n (%)							
0	1 (50.0)	2 (66.7)	7 (63.6)	14 (56.0)	2 (25.0)	13 (52.0)	39 (52.7)
1	1 (50.0)	1 (33.3)	4 (36.4)	9 (36.0)	6 (75.0)	11 (44.0)	32 (43.2)
2	0	0	0	2 (8.0)	0	1 (4.0)	3 (4.1)
Prior systemic treatment regimens, n (%)							
0	0	0	1 (9.1)	0	0	0	1 (1.4)
1	0	0	0	2 (8.0)	1 (12.5)	7 (28.0)	10 (13.5)
2	0	0	1 (9.1)	8 (32.0)	1 (12.5)	4 (16.0)	14 (18.9)
3	1 (50.0)	2 (66.7)	0	5 (20.0)	2 (25.0)	8 (32.0)	18 (24.3)
>3	1 (50.0)	1 (33.3)	9 (81.8)	9 (36.0)	3 (37.5)	6 (24.0)	29 (39.2)
Not reported	0	0	0	1 (4.0)	1 (12.5)	0	2 (2.7)
Time since diagnosis, n [duration, range (years)]							
Breast cancer	0	1 (6.2)	0	2 (4.0-11.6)	1 (36.7)	1 (4.1)	5 (4.0-36.7)
Colorectal cancer	1 (8.0)	0	6 (1.0-5.9)	2 (2.8-4.4)	2 (2.0-2.2)	0	11 (1.0-8.0)
NSCLC	0	0	1 (1.4)	8 (0.3-10.8)	2 (0.8-1.9)	7 (0.2-2.3)	18 (0.2-10.8)
Other tumors ^d	1 (4.9)	2 (0.8-2.5)	4 (1.4-13.5)	13 (0.6-12.3)	3 (2.4-8.5)	17 (0.4-11.5)	40 (0.4-13.5)

Abbreviations: Daco, dacomitinib; ECOG, Eastern Cooperative Oncology Group; Fig1, figitumumab; LD, loading dose; NSCLC, non-small cell lung cancer.

^aD1 included loading doses for both dacomitinib and figitumumab; the dacomitinib loading dose was omitted from D1a and subsequent dose levels.

^bRecommended dose levels for further evaluation in expansion cohorts. These dose-level groups together (D-1b and D-1d) included patients with advanced solid tumors in expansion cohort A and patients with NSCLC in expansion cohort B.

^cHispanic (n = 1) and Arab (n = 1).

^dAdenoid cystic carcinoma, adrenocortical carcinoma, bronchial carcinoma, bronchioalveolar carcinoma, colon cancer, desmoplastic small round cell tumor, Ewing sarcoma, gastric cancer, gastroesophageal cancer, gingival cancer, lung adenocarcinoma, malignant lung neoplasm, malignant hepatic neoplasm, malignant melanoma, neuroendocrine carcinoma, esophageal carcinoma, ovarian cancer, pancreatic carcinoma, pancreatic neuroendocrine tumor, penis carcinoma, prostate cancer, salivary gland cancer, and testicular leiomyosarcoma.

at dose level D-1a (dacomitinib 20 mg and figitumumab 20 mg/kg plus figitumumab loading dose)—one in a patient with ovarian carcinoma and one in a patient with salivary gland cancer. This dose level was above the RP2D. The patient with salivary gland cancer discontinued figitumumab approximately 5 months after starting the study due to mitral valve incompetence and continued on single-agent dacomitinib until discontinuation due to progressive disease at approximately 21 months from study start. Multiple dacomitinib dose interruptions were required due to the presence of AEs, and the dacomitinib dose was reduced to 10 mg at cycle 3 due to grade

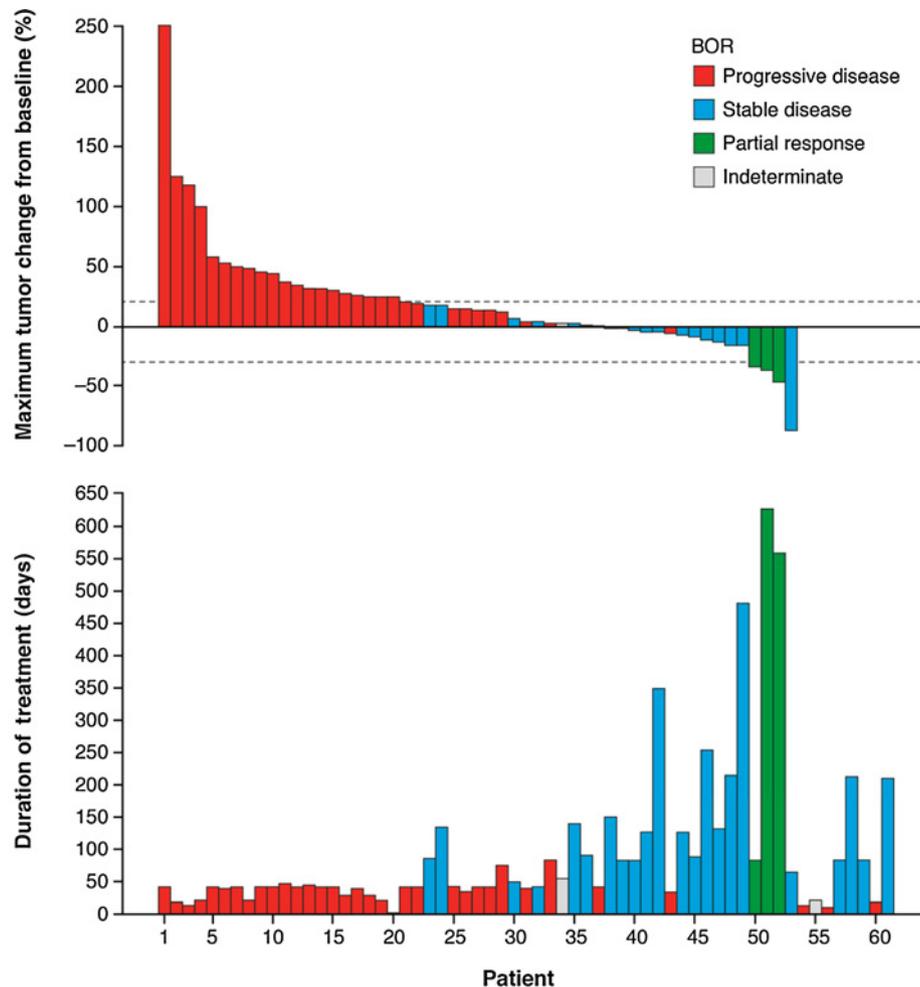
1 constipation, grade 1 mucosal inflammation, grade 1 restless leg syndrome, and grade 1 dry skin. The patient experienced no DLTs and had one serious adverse event (SAE; failed suicide attempt). The patient with ovarian carcinoma was treated for four cycles before discontinuing both dacomitinib and figitumumab due to withdrawal of consent. This patient experienced no DLTs and no SAEs, and no dose reductions were required. Multiple dacomitinib dose interruptions were required due to grade 2 exfoliative rash related to dacomitinib, grade 3 palmar-plantar erythrodysesthesia syndrome related to dacomitinib and figitumumab, and grade 2 pruritus related to dacomitinib.

Table 3. DLTs

Dose level	Dacomitinib dose (mg every day)	Figitumumab dose (mg/kg every 3 weeks)	Evaluable for safety (n)	Patients with DLTs (n)	DLTs (n)	Events
D1	30 + LD	20 + LD	2	1	2	Fatigue (n = 1) Mucosal inflammation (n = 1)
D1a	30	20 + LD	3	2	2	Diarrhea (n = 1) Mucosal inflammation (n = 1)
D-1a	20	20 + LD	10	1	1	Mucosal inflammation (n = 1)
D-1b ^a	10	20 + LD	24	0	0	No DLTs reported
D-1c	20	10 + LD	7	2	2	Mucosal inflammation (n = 2)
D-1d ^a	15	20 + LD	25	3	3	Hyperuricemia (n = 1) Neutropenia (n = 1) Fatigue (n = 1)

Abbreviation: DLT, dose-limiting toxicity; LD, loading dose.

^aRecommended dose levels for further evaluation in expansion cohorts.

**Figure 1.**

Summary of best overall responses (BOR) and duration of treatment among 61 response-evaluative patients who received at least one dose of study medication. Each bar represents an individual patient's maximum reduction in target lesion size (top) or duration of treatment (bottom). Colors indicate patients' BORs per Response Evaluation Criteria in Solid Tumors (RECIST). Dotted lines at -30% and 20% indicate RECIST-defined cutoffs for partial response and stable disease, respectively. Tumor data were unavailable for 8 patients, 4 patients with nontarget lesions only had stable disease, 3 had progressive disease due to new lesions, and 1 was indeterminate. Note that all response-evaluative patients are presented in the plot, notwithstanding their heterogeneous primary diagnoses and varied treatment dose levels. Therefore, strong caution is advised in the interpretation of the plot.

Twenty-two (36.1%) of the 61 response-evaluative patients had a BOR of SD, of whom 8 had NSCLC, 3 Ewing sarcoma, 2 adenoid cystic carcinoma, 2 colorectal carcinoma, 2 pancreatic carcinoma, and 1 each lung adenocarcinoma, malignant lung neoplasm, esophageal carcinoma, prostate cancer, and salivary gland carcinoma. Of the 23 response-evaluative patients in D-1b, there were 8 (34.8%) SD and 15 (65.2%) PD. Of the 23 response-evaluative patients in D1-d, there was 1 (4.3%) PR, 12 (52.2%) SD, 9 (39.1%) PD, and 1 (4.3%) indeterminate response. Across the study, there were 3 patients enrolled with adenoid cystic carcinoma and 2 patients with salivary gland carcinoma. Of these 5 patients, 2 achieved a PR as BOR [1 at dose level D-1d (dacomitinib 15 mg and figitumumab 20 mg/kg plus figitumumab loading dose) and 1 at dose level D-1a (dacomitinib 20 mg and figitumumab 20 mg/kg plus figitumumab loading dose)]. The efficacy results should be interpreted with caution because of the small sample size and variety of primary diagnoses and histologic classifications of these patients.

Mouse treatment studies

The results from the avatar mouse models of adenoid cystic carcinoma are shown in Fig. 2A. As compared with control, single-agent dacomitinib was only effective against tumor ACCX11. In contrast, figitumumab demonstrated statistically

significant growth inhibition against three of the six tumor models. The combined treatment demonstrated statistically significant growth inhibition against four of the six tumor models and appeared to be superior to figitumumab only in tumor ACCX6. However, data for exposure in mouse models were not collected, and without equivalent or comparable exposures, it is difficult to compare clinical and animal model effects.

Biological studies

Analysis of genomic mutations using the Sequenom MassARRAY panel (Supplementary Table S1) did not reveal any mutations in the tested genes. Tumors responding to figitumumab showed lower expression at baseline of genes involved in the IGF-1R pathway after a GSEA (Fig. 2B). The IGF-1R gene signature was enriched in the nonresponders model, suggesting that IGF-1R transcriptional activity is decreased in tumors that respond to figitumumab.

Pharmacokinetic analyses

Pharmacokinetic parameters for dacomitinib, such as apparent oral clearance (CL/F), dose-normalized maximal plasma concentration (C_{max}), and area under the concentration-time curve over the dosing interval (AUC_{tau}) were observed to be similar between

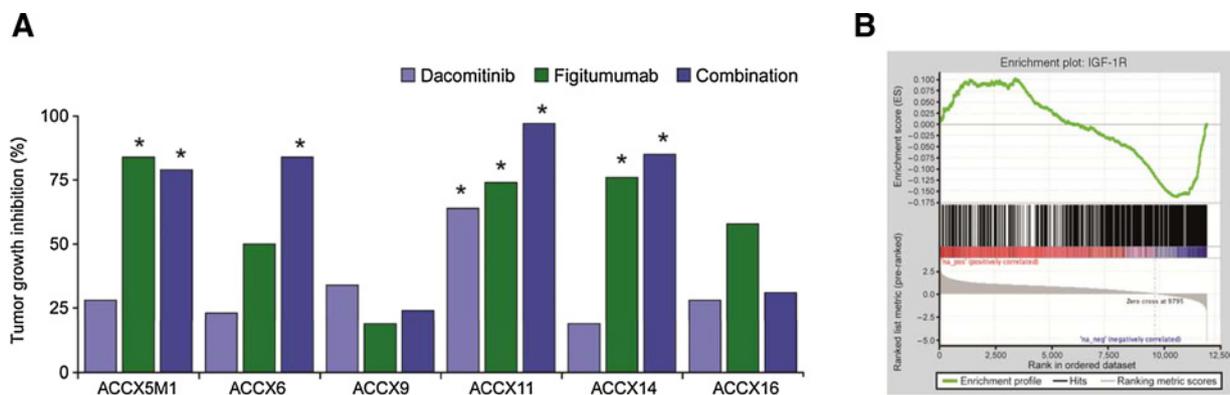


Figure 2.

Activity of figitumumab and dacomitinib in avatar mouse models of adenoid cystic carcinoma. **A**, Tumor growth inhibition effects of indicated treatments versus control (* $P < 0.05$, indicating treatment-sensitive cell lines). **B**, Gene-set enrichment analysis plot at baseline. Enrichment plot of IGF-1R signature showing downregulation of signature genes in models responding to figitumumab.

the dacomitinib 10-mg (D-1b) and 15-mg (D-1d) dose groups when dosed with figitumumab (20 mg/kg i.v. every 3 weeks plus figitumumab loading dose; Supplementary Figs. S1 and S2). Furthermore, in the presence of figitumumab at the 20-mg/kg dose plus figitumumab loading dose, dacomitinib appeared to have a higher clearance and hence lower plasma exposure when compared with parameters observed in historical studies with similar patient populations with dacomitinib as monotherapy (Supplementary Figs. S3 and S4; refs. 24–26). Pharmacokinetic parameters for patients considered to be dose compliant (i.e., having received consecutive doses for ≥ 14 days) are summarized and presented in Supplementary Figs. S3 and S4. A total of 11 and 13 patients were considered to be dose compliant for determining pharmacokinetic parameters in the D-1b and D-1d cohorts, respectively.

Discussion

The primary objective of this study was to evaluate the safety and tolerability of dacomitinib when administered in combination with figitumumab and to determine the MTD of this combination. Two dosing schedules were found to be tolerable over multiple cycles (dacomitinib 10 mg daily with figitumumab 20 mg/kg i.v. every 3 weeks plus figitumumab loading dose, and dacomitinib 15 mg daily with figitumumab 20 mg/kg i.v. every 3 weeks plus figitumumab loading dose) and were considered recommended doses for further exploration of this combination. Indeed, the combination was tolerable only with reduction of dacomitinib to less than the 45-mg daily RP2D as monotherapy (24). Although these dose reductions are consistent with treatment modifications in other dacomitinib studies, it is possible that the tumor responses observed in this study were primarily derived from figitumumab rather than dacomitinib. However, it should be noted that in the first-in-human phase I study of dacomitinib, a PR was observed in a patient with NSCLC who received dacomitinib at a dose of 16 mg daily (24).

Although the overall AE profile in this study was similar to that observed for dacomitinib and figitumumab as monotherapies (24, 27, 28), increased frequencies of higher grade upper and lower gastrointestinal AEs led to dose de-escalation of figitumu-

mab to achieve a tolerable dose to be considered for the expansion cohorts. The apparent potentiation of toxicity does not appear to be due to any drug–drug interaction leading to increase of dacomitinib exposure in the presence of figitumumab at the 20-mg/kg dose. In fact, there appears to be a higher clearance of dacomitinib in the presence of figitumumab, resulting in lower plasma exposure than expected, compared with historical dacomitinib pharmacokinetic data when given as a monotherapy (Supplementary Figs. S1 and S2).

Although sample sizes among patients with individual tumor types and dose groups in our study were too small to draw any meaningful conclusions regarding efficacy of the dacomitinib and figitumumab combination, evidence of antitumor activity was observed in some patients. Three patients achieved PRs as their BORs, and 22 patients across all dose levels had a BOR of SD. One-quarter of patients treated at the RP2Ds achieved sustained, meaningful control of their disease for more than 4 months. Two of the PRs achieved were among 5 patients with adenoid cystic carcinoma or salivary gland cancer, which is in line with recent descriptions of EGFR family members (HER1 and HER2) found to be overexpressed in salivary gland carcinoma (29), although specific molecular abnormalities in adenoid cystic carcinoma are unknown. However, recurrent mutations have been identified in the FGF/IGF/PI3K pathway in adenoid cystic carcinoma tumor samples (30), and in a previous phase Ib study, one patient with adenoid cystic carcinoma who received the IGF-1R mAb R1507 plus sorafenib had a response of greater than 1 year (31).

As previously reported (18), we had identified figitumumab as an active agent against an avatar mouse model developed from a patient with adenoid cystic carcinoma, prompting the enrollment of that patient in this study with a favorable response. To gain additional insights into the potential activity of dacomitinib and figitumumab in adenoid cystic carcinoma, we enrolled additional patients with adenoid cystic carcinoma in the trial and performed, in collaboration with the ACCRF, a co-clinical trial in a collection of patient-derived xenograft models of adenoid cystic carcinoma. These studies aimed to evaluate the contribution of each agent alone as well as to explore potential biomarkers of activity. The results of these studies have shown that only modest regression (statistically significant in one of the six models) was seen with

single-agent dacomitinib, whereas single-agent figitumumab demonstrated statistically significant ($P < 0.05$) tumor growth inhibition in three of the six models, and the combination of figitumumab and dacomitinib was active in four of the six models. These results suggest that IGF-1R is a relevant target in adenoid cystic carcinoma tumorigenesis, with figitumumab being more effective than dacomitinib; indeed, the combination was not clearly superior to figitumumab alone. Interestingly, tumors sensitive to IGF-1R blockade exhibited downregulation of the IGF pathway at the transcriptional level, whereas the IGF-1R gene signature was enriched in nonresponders. These results are perhaps surprising, as it may have been expected that tumors with higher activation of the IGF-1R pathway would have been more sensitive to figitumumab. However, it is possible that this result is due to a saturation effect, whereby figitumumab is unable to block the IGF-1R pathway in tumors with higher pathway activation. Further research is required to understand this observation. Based on these data, future clinical trials in patients with adenoid cystic carcinoma should explore figitumumab as an IGF pathway inhibitor alone, in addition to the combination with dacomitinib, as this agent can be as effective and less toxic. Overall, data from this study suggest that there may be potential clinical benefit from this combination in advanced adenoid cystic carcinoma, as well as highlighting the potential relevance of individual patient translational oncology data to patient outcome in investigational drug trials.

The efficacy results of the combination treatment observed in this study occurred even with the need to reduce the dose of both drugs, including dacomitinib. The need to de-escalate the doses of dacomitinib and figitumumab appears to be due to potent inhibition of the parallel HER and IGF pathways rather than an increase in exposure of dacomitinib in the presence of figitumumab.

Disclosure of Potential Conflicts of Interest

J.-C. Soria is a consultant/advisory board member for Pfizer. A.W. Tolcher is an employee of Symphogen, and is a consultant/advisory board member for Akebia, AP Pharma, Arqule, Asana, Ascentage, Astex, Bayer Schering Pharma, Bicycle Therapeutics, Bind, Blend Therapeutics, Boehringer Ingelheim, Celator, Dicerna, Eli Lilly, Endocyte, Genmab, Heron, Idea Pharma, Ignyta, Janssen,

Johnson & Johnson, LiquidNet, Median, MedImmune, Mersana, Merus, Nano-biotix, OncoMed, Pharmacyclics, Pierre Fabre, Proximagen, Upsher-Smith, Valent, and Zymeworks. R. Millham holds ownership interest (including patents) in Pfizer. M. Hidalgo reports receiving commercial research grants from and is a consultant/advisory board member for Pfizer. No potential conflicts of interest were disclosed by the other authors.

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References

- Britten CD. Targeting ErbB receptor signaling: a pan-ErbB approach to cancer. *Mol Cancer Ther* 2004;3:1335-42.
- Mendelsohn J, Baselga J. Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer. *J Clin Oncol* 2003; 21:2787-99.
- Salomon DS, Brandt R, Ciardiello F, Normanno N. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol* 1995;19:183-232.
- Engelman JA, Zejnullahu K, Gale CM, Lifshits E, Gonzales AJ, Shimamura T, et al. PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with *EGFR* and *ERBB2* mutations that are resistant to gefitinib. *Cancer Res* 2007;67:11924-32.
- Gonzales AJ, Hook KE, Althaus IW, Ellis PA, Trachet E, Delaney AM, et al. Antitumor activity and pharmacokinetic properties of PF-00299804, a second-generation irreversible pan-erbB receptor tyrosine kinase inhibitor. *Mol Cancer Ther* 2008;7:1880-9.
- Ramalingam SS, Blackhall F, Krzakowski M, Barrios CH, Park K, Bover I, et al. Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2012;30:3337-44.
- Jänne PA, Ou S-HI, Kim D-W, Oxnard GR, Martins R, Kris MG, et al. Dacomitinib as first-line treatment in patients with clinically or molecularly selected advanced non-small-cell lung cancer: a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2014;15:1433-41.
- Kato T, Hayama S, Yamabuki T, Ishikawa N, Miyamoto M, Ito T, et al. Increased expression of insulin-like growth factor-II messenger RNA-binding protein 1 is associated with tumor progression in patients with lung cancer. *Clin Cancer Res* 2007;13:434-42.
- Jones HE, Gee JM, Hutcheson IR, Knowlden JM, Barrow D, Nicholson RL. Growth factor receptor interplay and resistance in cancer. *Endocr Relat Cancer* 2006;13(Suppl. 1):S45-51.
- Suda K, Mizuuchi H, Sato K, Takemoto T, Iwasaki T, Mitsudomi T. The insulin-like growth factor 1 receptor causes acquired resistance to erlotinib in lung cancer cells with the wild-type epidermal growth factor receptor. *Int J Cancer* 2014;135:1002-6.
- Morgillo F, Woo JK, Kim ES, Hong WK, Lee HY. Heterodimerization of insulin-like growth factor receptor/epidermal growth factor receptor and induction of survivin expression counteract the antitumor action of erlotinib. *Cancer Res* 2006;66:10100-11.
- Peled N, Wynes MW, Ikeda N, Ohira T, Yoshida K, Qian J, et al. Insulin-like growth factor-1 receptor (IGF-1R) as a biomarker for resistance to the

- tyrosine kinase inhibitor gefitinib in non-small cell lung cancer. *Cell Oncol* 2013;36:277–88.
13. Shan HB, Zhang R, Li Y, Xu G-L, Luo G-Y, Gao X-Y, et al. Expression of IGF-1R in colorectal polyps and its role in colorectal carcinogenesis. *Technol Cancer Res Treat* 2011;10:381–9.
 14. Zhang R, Xu G-L, Li Y, He L-J, Chen L-M, Wang G-B, et al. The role of insulin-like growth factor 1 and its receptor in the formation and development of colorectal carcinoma. *J Int Med Res* 2013;41:1228–35.
 15. Yang L, Li J, Ran L, Pan F, Zhao X, Ding Z, et al. Phosphorylated insulin-like growth factor 1 receptor is implicated in resistance to the cytostatic effect of gefitinib in colorectal cancer cells. *J Gastrointest Surg* 2011;15:942–57.
 16. Kaulfuß S, Burfeind P, Gaedcke J, Scharf J-G. Dual silencing of insulin-like growth factor-I receptor and epidermal growth factor receptor in colorectal cancer cells is associated with decreased proliferation and enhanced apoptosis. *Mol Cancer Ther* 2009;8:821–33.
 17. Cohen BD, Baker DA, Soderstrom C, Tkalecic G, Rossi AM, Miller PE, et al. Combination therapy enhances the inhibition of tumor growth with the fully human anti-type 1 insulin-like growth factor receptor monoclonal antibody CP-751,871. *Clin Cancer Res* 2005;11:2063–73.
 18. Morelli MP, Calvo E, Ordoñez E, Wick MJ, Viqueira BR, Lopez-Casas PP, et al. Prioritizing phase I treatment options through preclinical testing on personalized tumorgraft. *J Clin Oncol* 2012;30:e45–8.
 19. 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.
 20. McCall MN, Bolstad BM, Irizarry RA. Frozen robust multiarray analysis (fRMA). *Biostatistics* 2010;11:242–53.
 21. Smith FI, Qu Q, Hong SJ, Kim KS, Gilmartin TJ, Head SR. Gene expression profiling of mouse postnatal cerebellar development using oligonucleotide microarrays designed to detect differences in glycoconjugate expression. *Gene Expr Patterns* 2005;5:740–9.
 22. Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A* 2005;102:15545–50.
 23. Creighton CJ, Casa A, Lazard Z, Huang S, Tsimelzon A, Hilsenbeck SG, et al. Insulin-like growth factor-I activates gene transcription programs strongly associated with poor breast cancer prognosis. *J Clin Oncol* 2008;26:4078–85.
 24. Jänne PA, Boss DS, Camidge DR, Britten CD, Engelman JA, Garon EB, et al. Phase I dose-escalation study of the pan-HER inhibitor, PF299804, in patients with advanced malignant solid tumors. *Clin Cancer Res* 2011;17:1131–9.
 25. Takahashi T, Boku N, Murakami H, Naito T, Tsuya A, Nakamura Y, et al. Phase I and pharmacokinetic study of dacomitinib (PF-00299804), an oral irreversible, small molecule inhibitor of human epidermal growth factor receptor-1, -2, and -4 tyrosine kinases, in Japanese patients with advanced solid tumors. *Invest New Drugs* 2012;30:2352–63.
 26. Park K, Cho BC, Kim D-W, Ahn M-J, Lee S-Y, Gernhardt D, et al. Safety and efficacy of dacomitinib in Korean patients with KRAS wild-type advanced non-small-cell lung cancer refractory to chemotherapy and erlotinib or gefitinib: a phase I/II trial. *J Thorac Oncol* 2014;9:1523–31.
 27. Ramalingam SS, Jänne PA, Mok T, O'Byrne K, Boyer MJ, Von Pawel J, et al. Dacomitinib versus erlotinib in patients with advanced-stage, previously treated non-small-cell lung cancer (ARCHER 1009): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2014;15:1369–78.
 28. Haluska P, Shaw HM, Batzel GN, Yin D, Molina JR, Molife LR, et al. Phase I dose escalation study of the anti-insulin-like growth factor-I receptor monoclonal antibody CP-751,871 in patients with refractory solid tumors. *Clin Cancer Res* 2007;13:5834–40.
 29. Senft E, Lemound J, Stucki-Koch A, Gellrich NC, Kreipe H, Hussein K. Expression of cyclin-dependent kinase inhibitor 2A 16, tumour protein 53 and epidermal growth factor receptor in salivary gland carcinomas is not associated with oncogenic virus infection. *Int J Oral Sci* 2015;7:18–22.
 30. Ho AS, Kannan K, Roy DM, Morris LGT, Ganly I, Katabi N, et al. The mutational landscape of adenoid cystic carcinoma. *Nat Genet* 2013;45:791–8.
 31. Mahadevan D, Sutton GR, Arteta-Bulos R, Bowden CJ, Miller PJ, Swart RE, et al. Phase 1b study of safety, tolerability and efficacy of R1507, a monoclonal antibody to IGF-1R in combination with multiple standard oncology regimens in patients with advanced solid malignancies. *Cancer Chemother Pharmacol* 2014;73:467–73.

Clinical Cancer Research

A Phase I Clinical Trial and Independent Patient-Derived Xenograft Study of Combined Targeted Treatment with Dacomitinib and Figitumumab in Advanced Solid Tumors

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