

Brief Report: Combination of Osimertinib and Dacomitinib to Mitigate Primary and Acquired Resistance in *EGFR*-Mutant Lung Adenocarcinomas



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ABSTRACT

Purpose: Primary and acquired resistance to osimertinib remain significant challenges for patients with *EGFR*-mutant lung cancers. Acquired *EGFR* alterations such as *EGFR* T790M or C797S mediate resistance to *EGFR* tyrosine kinase inhibitors (TKI) and combination therapy with dual *EGFR* TKIs may prevent or reverse on-target resistance.

Patients and Methods: We conducted two prospective, phase I/II trials assessing combination osimertinib and dacomitinib to address on-target resistance in the primary and acquired resistance settings. In the initial therapy study, patients received dacomitinib and osimertinib in combination as initial therapy. In the acquired resistance trial, dacomitinib with or without osimertinib was administered to patients with *EGFR*-mutant lung cancers with disease progression on osimertinib alone and evidence of an acquired *EGFR* second-site mutation.

Results: Cutaneous toxicities occurred in 93% (any grade) of patients and diarrhea in 72% (any grade) with the combination. As initial therapy, the overall response to the combination was 73% [95% confidence interval (CI), 50%–88%]. No acquired secondary alterations in *EGFR* were observed in any patients at progression. In the acquired resistance setting, the overall response was 14% (95% CI, 1%–58%).

Conclusions: We observed no acquired secondary *EGFR* alterations with dual inhibition of *EGFR* as up-front treatment, but this regimen was associated with greater toxicity. The combination was not effective in reversing acquired resistance after development of a second-site acquired *EGFR* alteration. Our study highlights the need to develop better strategies to address on-target resistance in patients with *EGFR*-mutant lung cancers.

Introduction

Twenty percent of patients with metastatic lung adenocarcinomas have somatic activating mutations in the *EGFR* gene (1, 2). Osimertinib, a third generation *EGFR* tyrosine kinase inhibitor (TKI), is approved in the first-line setting in patients with *EGFR*-mutant lung cancers given the progression-free survival (PFS) and overall survival (OS) benefit observed over other *EGFR* TKIs (3, 4). Similar to earlier generation *EGFR* TKIs, responses to osimertinib are incomplete with

eventual disease progression. In up to 35% of cases in the later-line setting and 15% of cases in the first-line treatment setting, acquired alterations in *EGFR* such as C797S or G724S mutations mediate resistance to osimertinib (5). Similar to development of *EGFR* T790M after treatment with earlier generation *EGFR* TKIs, osimertinib binds to *EGFR* at C797, and a mutation at this location impedes drug binding. Interestingly, in the presence of the original *EGFR* activating mutation (i.e., exon 19 deletion or L858R) and *EGFR* C797S without *EGFR* T790M, cells retain sensitivity to first- and second-generation *EGFR* TKIs (6). Other reports also demonstrated that cells with acquired resistance via G724S were sensitive to earlier generation *EGFR* TKI afatinib (7, 8).

Dacomitinib is a pan-HER inhibitor with superiority over other earlier generation *EGFR* TKIs as initial treatment for *EGFR*-mutant lung cancers (9). With the aim of preventing on-target resistance to osimertinib, we designed a phase I study using evolutionary modeling-optimized dose levels of combination dacomitinib and osimertinib as first-line treatment for patients with *EGFR*-mutant lung cancer. The modeling and initial dose-finding experience from the phase II study were previously published (10). For patients with tumors resistant to osimertinib with acquired on-target *EGFR* alterations, we designed a phase I study of dacomitinib with or without osimertinib after progression on osimertinib. Dacomitinib monotherapy for unselected patients without acquired *EGFR* alterations after initial osimertinib treatment was also assessed and deemed ineffective in our prior report (11). Herein, we present a combined final report from these two phase I studies of combination osimertinib and dacomitinib in patients with *EGFR*-mutant lung cancers as a means to address on-target *EGFR*-mediated resistance.

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Translational Relevance

Primary and acquired resistance to osimertinib remain significant challenges for patients with *EGFR*-mutant lung cancers. We conducted two prospective, phase I/II trials assessing combination osimertinib and dacomitinib to address on-target resistance in the primary and acquired resistance settings. Combination osimertinib and dacomitinib was effective at preventing acquired secondary alterations in *EGFR*, but this treatment was associated with greater toxicity. Our study highlights the need to develop better strategies to address on-target resistance in patients with *EGFR*-mutant lung cancers.

Patients and Methods

Both trials were conducted after approval of the institutional review board at Memorial Sloan Kettering Cancer Center according to the Declarations of Helsinki. All patients provided written informed consent prior to participation.

Study designs

Dacomitinib with osimertinib as initial therapy

The initial therapy (first-line trial) was a phase II study in patients with *EGFR*-mutant lung cancers without prior *EGFR* TKI treatment (NCT03810807). The primary objective was to determine the maximum tolerated dose of the combination of osimertinib and dacomitinib. Secondary objectives were to measure best overall response, PFS and OS.

Dacomitinib with and without osimertinib after disease progression on osimertinib

The second trial was a prospective phase I/II trial in patients with *EGFR*-mutant lung cancers with disease progression on initial

osimertinib (NCT03755102). We report on patients that received combination osimertinib and dacomitinib or single-agent dacomitinib with acquired second-site alterations in *EGFR* prior to study enrollment. The primary objective was to determine the overall response rate of osimertinib and dacomitinib after progression on osimertinib. Secondary objectives were to measure PFS and OS. This study was initially designed as evaluation of single-agent dacomitinib in all patients after progression on osimertinib. Given the lack of efficacy observed for dacomitinib alone in unselected patients after an interim analysis, the protocol was amended to evaluate the role of combination osimertinib and dacomitinib after progression on osimertinib in only patients with acquired second-site *EGFR* alterations. The first 10 patients enrolled in this study who received dacomitinib alone were published previously (11). The dose-finding experience for the initial study was also published previously (10).

Patients and inclusion criteria

Patients treated on study had stage IV or recurrent lung cancers with a somatic activating mutation in *EGFR*. For the initial therapy trial, no prior *EGFR* TKI therapy was permitted. For the acquired resistance trial, patients demonstrated radiologic progression during treatment with initial osimertinib and were required to have had a repeat biopsy after osimertinib progression that identified an acquired *EGFR* mutation in addition to the original *EGFR* sensitizing mutation.

Study assessment

Treatment cycles were 4 weeks in duration. Patients were assessed after 2 weeks for the first cycle and every 4 weeks subsequently. Toxicity was graded according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE). Response to therapy was assessed by imaging every 8 weeks with response evaluated per RECIST 1.1.

Table 1. Baseline characteristics.

Characteristic	Initial therapy study Dacomitinib and osimertinib N = 22 ^a	Acquired resistance study Dacomitinib ± osimertinib for acquired resistance to Osimertinib with second-site <i>EGFR</i> mutations N = 7 ^a
Age	65 (59, 73)	67 (49, 71)
Gender		
F	15 (68%)	1 (14%)
Smoking		
Former	12 (55%)	3 (43%)
Never	10 (45%)	4 (57%)
Smoking (pack years)	2.2 (0–10)	0 (0, 22)
KPS		
≥90	16 (73%)	6 (86%)
80	6 (27%)	1 (14%)
<i>EGFR</i> sensitizing mutation prior to enrollment		
Exon 19 deletion	13 (59%)	5 (71%)
L858R	7 (32%)	2 (29%)
L858R, E709A, L861Q	1 (4.5%)	0
<i>EGFR</i> acquired second-site mutation prior to enrollment		
C797S	NA	2 (29%)
G724S	NA	3 (42%)
C797S, L718Q, L718V	NA	1 (14%)
Treatment		
Osimertinib + dacomitinib	22 (100%)	5 (71%)
Dacomitinib alone	0	2 (29%)

^aMedian interquartile range (IQR); n (%).

Statistical analysis

Safety and tolerability were summarized using descriptive statistics and CTCAE version 5 grading. Response rates were calculated using binomial proportions and exact 95% confidence intervals (CI). PFS was estimated using the Kaplan–Meier method and defined as the time from start of study treatment until progression or death. OS was estimated using the Kaplan–Meier method and defined as the time from start of study treatment until death.

Next-generation sequencing

Patients with available pre- and post-treatment tumor specimens underwent next-generation sequencing with MSK-IMPACT; cell-free DNA from peripheral blood was interrogated with MSK-ACCESS as described previously (12).

Data availability statement

Data will be made available upon reasonable request to the corresponding author.

Results

Patients

Patient characteristics are presented in Table 1. From August 2019 to May 2020, 22 patients were enrolled on the initial therapy study and

treated with the combination of osimertinib and dacomitinib. From February 2019 to October 2021, 7 patients were enrolled on the acquired resistance study and treated with either the combination osimertinib and dacomitinib (*n* = 5) or dacomitinib alone (*n* = 2). For the initial therapy study, 14 patients discontinued study treatment due to progression, 2 due to toxicity, 2 withdrew consent, and 5 patients remain on study. For the acquired resistance study, 6 patients discontinued study treatment due to progression, and 1 patient continues on study.

Safety and tolerability

All patients were evaluable for toxicity. Findings from the phase I dose escalation to identify the recommended phase II dose (RP2D) for combination therapy were published previously (10). Data regarding dose reductions are included in Supplementary Figs. S1 and S2. The dose escalation identified osimertinib 80 mg daily and dacomitinib 30 mg daily to be the RP2D. Among 16 patients in the first-line trial treated at the RP2D, 10 patients (63%) required dose reductions (Supplementary Fig. S1). Among 5 patients in the second-line trial treated at the RP2D, 1 patient required a dose reduction (20%; Supplementary Fig. S2).

The most frequent treatment-related all grade adverse events (>10%) to the combination were rash (93%), diarrhea (72%), dry skin (66%), mucositis (55%), weight loss (31%), and fatigue (31%; Supplementary Table S1). There were 2 patients with grade 3

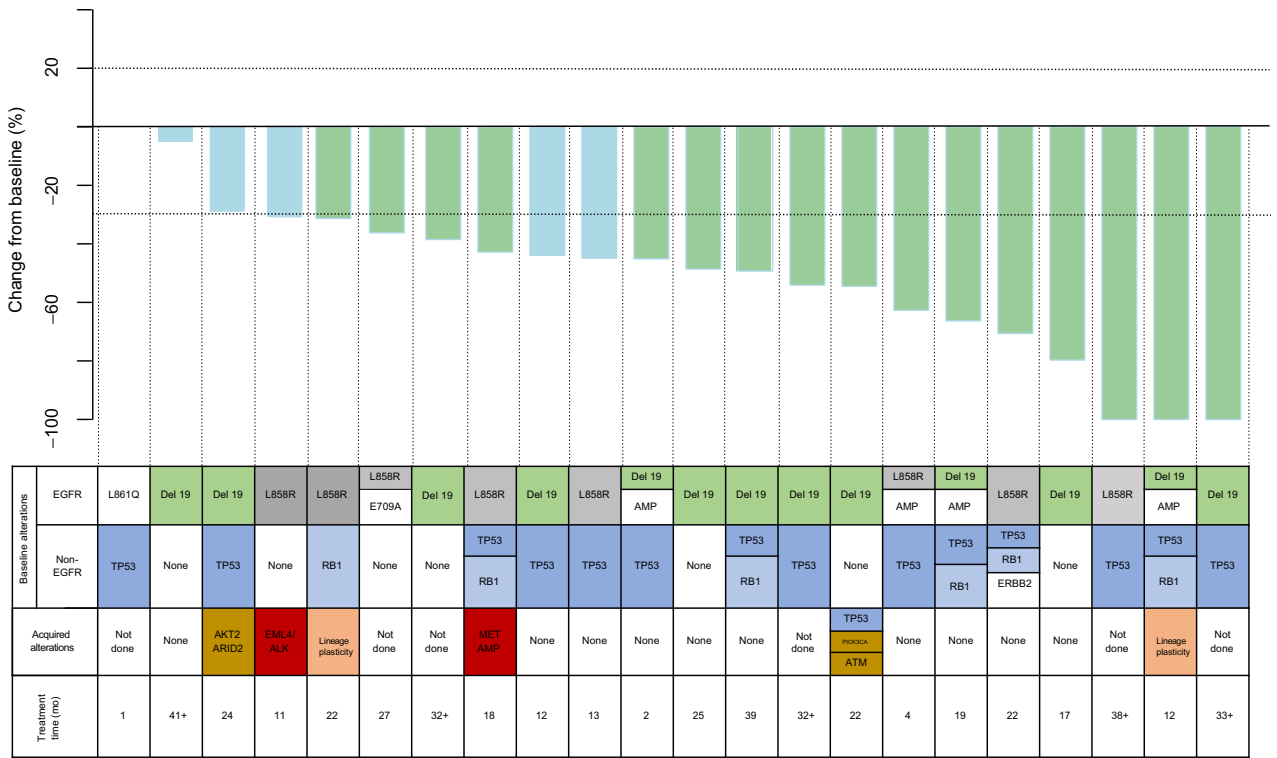


Figure 1. Efficacy of initial therapy of Dacomitinib and Osimertinib and Pretreatment/Posttreatment Genomic Analysis. Waterfall plot demonstrating best response of target lesions measured by RECIST 1.1. Only alterations with known prognostic or therapeutic relevance are shown in the figure. None found; samples underwent sequencing; however, no genomic alterations were found. Not done; genomic sequencing not done. First column; patient withdrew from study before target lesions could be evaluated. Green indicates confirmed partial response. Plus sign in treatment time section indicates patient is still on treatment.

diarrhea (7%), 3 patients with grade 3 mucositis (10%), and 2 patients with grade 3 anorexia/weight loss (7%). There were no grade 4 or 5 events.

Efficacy

For the initial therapy study, all patients had baseline and on-treatment radiologic assessments except one (withdrew before first assessment due to toxicity). Fifteen patients had a confirmed partial response, and one patient had a confirmed complete response, for an ORR rate of 73% (95% CI, 50%–88%; **Fig. 1**). Median PFS is 20.3 months (Supplementary Fig. S3A) and median OS is 36.1 months (Supplementary Fig. S3B). For the acquired resistance study, all patients had baseline and on-treatment radiologic assessment except

one (died before first assessment). One patient had a confirmed partial response, for an ORR rate of 14% (95% CI, 1%–58%; **Fig. 2**). Median PFS is 5.6 months (Supplementary Fig. S4A) and median OS is 26.1 months (Supplementary Fig. S4B).

Genomic analyses

All patients had pretreatment biopsy samples. The main correlative objective of the first-line study was to determine the frequency of acquired on-target second-site *EGFR* mutations with the combination of osimertinib and dacomitinib. Among 16 patients with post-osimertinib biopsy samples, none developed an acquired second-site mutations in *EGFR* (0% observed rate; 95% CI, 50%–88%). As for other acquired mechanisms of resistance, 1 patient developed an

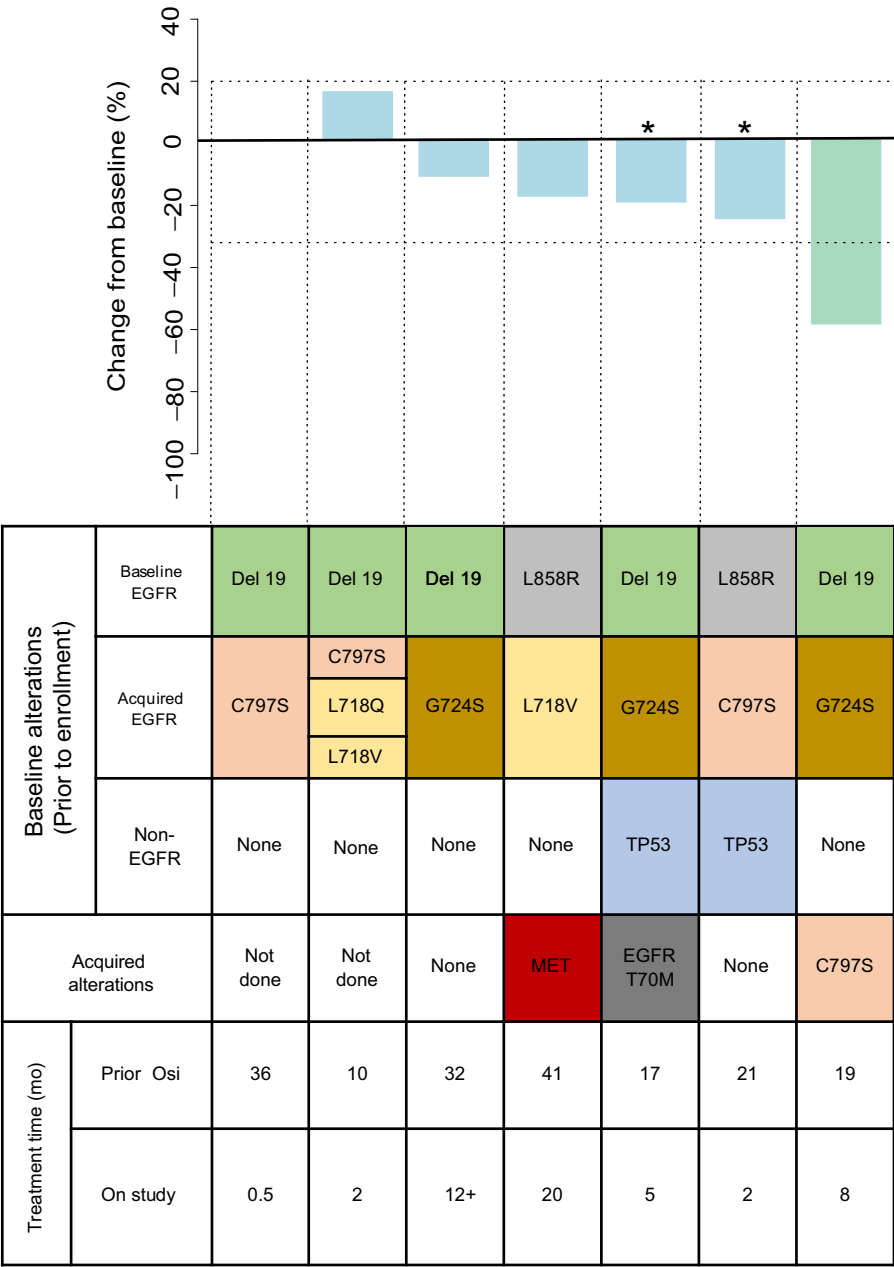


Figure 2. Efficacy of Dacomitinib ± Osimertinib after acquired resistance to Osimertinib and Pretreatment/Posttreatment Genomic Analysis. Waterfall plot demonstrating best response of target lesions measured by RECIST 1.1. Only alterations with known prognostic or therapeutic relevance shown in the figure. None found; samples underwent sequencing; however, no genomic alterations were found. Not done; genomic sequencing not done. First column; patient withdrew from study before target lesions could be evaluated. *Indicates patient received dacomitinib monotherapy. Green indicates confirmed partial response. Plus sign in treatment time section indicates patient is still on treatment.

EML4/ALK fusion, 1 developed a *MET* amplification, 1 acquired mutations in *PIK3CA*^{E545K} and *ATM*^{E2272}, and 1 developed mutations in *AKT2*^{E17K} and *ARID2*. One patient underwent small cell transformation and another patient large cell neuroendocrine transformation (Fig. 1). In the acquired resistance study, the only patient with a confirmed partial response to the combination of osimertinib and dacomitinib had a baseline EGFR G724S, with a variant allele frequency (VAF) ratio (acquired EGFR/initial sensitizing EGFR mutation) of 61%. Of the 3 patients that were on therapy for ≥ 6 months, 2 had baseline G724S mutations. The individual that remained on osimertinib and dacomitinib for the longest (20 months) had an acquired EGFR alteration in L718V with a VAF of 88%. Four patients had post-study treatment samples. The patient with a confirmed PR acquired an EGFR C797S alteration. One patient developed a *MET*^{D1228N} activating mutation on treatment (Fig. 2).

Discussion

We report a combined analysis of two distinct clinical trials combining dacomitinib with osimertinib in patients with EGFR-mutant lung adenocarcinomas. As an initial therapy, we sought to prevent the development of a second-site acquired EGFR alteration(s) and delay progression on combination treatment. In patients with acquired second-site EGFR mutations and resistance to osimertinib, we sought to reverse on-target resistance. As initial combined treatment, we detected no acquired second-site EGFR alterations, demonstrating that dual inhibition of EGFR may be effective at preventing second-site acquired alterations to EGFR. However, 4 patients in the first-line study developed acquired resistance to EGFR including in secondary pathways such as *MET* and *EML4/ALK*, further underpinning the need to prevent the development of these acquired bypass mechanisms. The median PFS of 20.1 months for the combination was not substantially different from the 18.9 months observed with osimertinib alone (3) and there was substantial added toxicity attributed to dual inhibition of EGFR.

Given the complexity of combination drug dosing, employing an evolutionary modeling approach has the potential to incorporate tumor heterogeneity and intersubject variability of plasma drug concentrations to predict tumor evolution using different combination dosing regimens. Despite this strategy to inform dosing, dual inhibition of EGFR proved too toxic in this setting. As a single-agent, dacomitinib has significant toxicity (66% of patients require dose reduction with dacomitinib monotherapy) and therefore the combination of osimertinib and dacomitinib was limited by the toxicities of single-agent dacomitinib (13). There have been efforts to combine osimertinib with other earlier generation EGFR inhibitors such as afatinib, however this combination was also toxic and demonstrated limited efficacy (14). A different study combined osimertinib with gefitinib as first-line treatment, with 30% requiring ultimate discontinuation of one or both study drugs (15). These different studies highlight the challenge of dual EGFR inhibition therapies, especially in the first-line setting where the duration of treatment is long. Furthermore, the combination of osimertinib and dacomitinib did not successfully reverse resistance with acquired EGFR second-site mutations post-osimertinib, reinforcing the challenge of trying to reverse on-target resistance with combination therapy. Given the small number of patients enrolled in the second-line trial, no firm conclusions can be drawn about the efficacy of combination osimertinib and dacomitinib in

the acquired resistance setting; however, the limited response and high toxicity did not justify studying this combination further especially in light of 4th generation EGFR inhibitors that target acquired EGFR alterations currently in clinical development (NCT05256290).

Significant heterogeneity exists among EGFR-mutant lung cancers (2), and risk factors such as concurrent alterations (*TP53*, *RB1*) or lack of ctDNA clearance might identify patients who may particularly benefit from treatment escalation with combination therapies up front. The patients that appeared to benefit most from therapy in the later-line setting largely had more clonal resistance alterations with higher variant allele frequencies. Our two studies highlight the need to develop better initial treatments to better eradicate persister cells from which resistance ultimately emerges, for example using antibody-drug conjugates in combination with EGFR inhibition, or up-front combinations of EGFR inhibitors with chemotherapy (16, 17).

Authors' Disclosures

A. Elkrif reports grants from Canadian Institute of Health Research, Detweiler Travelling Fellowship - Royal College of Physicians and Surgeons of Canada, and Henry R. Shibata Fellowship - Cedar's Cancer Foundation during the conduct of the study. K.A. Moses reports grants from Pfizer during the conduct of the study. I.R. Preeshagul reports other support from Pfizer, AstraZeneca, G1 Therapeutics, Jazz pharmaceuticals, Novartis, Lab Corp, and Blue print Medicine outside the submitted work. P.K. Paik reports personal fees from Takeda, Mirati, Xencor, Crown Bio, and Novartis and personal fees and other support from EMD Serono outside the submitted work. M. Ladanyi reports grants from Pfizer during the conduct of the study; personal fees from AstraZeneca outside the submitted work. M.G. Kris reports personal fees from BerGenBio, Merus, Pfizer and Daiichi-Sankyo; personal fees and nonfinancial support from AstraZeneca; and nonfinancial support from Genentech/Roche during the conduct of the study. G.J. Riely reports grants from Pfizer during the conduct of the study; grants from Novartis, Roche, Mirati, Takeda, Pfizer, and Merck outside the submitted work. F. Michor is a cofounder of and has equity in Harbinger Health, has equity in Zephyr AI, and serves as a consultant for Harbinger Health, Zephyr AI, and Red Cell Partners; F. Michor declares that none of these relationships are directly or indirectly related to the content of this manuscript. H.A. Yu reports other support from Pfizer during the conduct of the study; other support from AstraZeneca, Cullinan, Daiichi, Novartis, ERASCA, C4 Therapeutics, Blueprint Medicine, Janssen, Black Diamond, and AbbVie outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

A. Elkrif: Conceptualization, data curation, software, formal analysis, visualization, methodology, writing—original draft, writing—review and editing. A. Makhnin: Resources, data curation, software, methodology, project administration, writing—review and editing. K.A. Moses: Resources, data curation, investigation, writing—review and editing. L.S. Ahn: Resources, data curation, investigation, writing—review and editing. I.R. Preeshagul: Investigation, writing—review and editing. A.N. Iqbal: Investigation, writing—review and editing. S.A. Hayes: Resources, data curation, writing—review and editing. A.J. Plodkowski: Resources, data curation, writing—review and editing. P.K. Paik: Resources, investigation, writing—review and editing. M. Ladanyi: Resources, supervision, writing—original draft, writing—review and editing. M.G. Kris: Supervision, investigation, writing—review and editing. G.J. Riely: Resources, investigation, writing—review and editing. F. Michor: Conceptualization, resources, funding acquisition, investigation, writing—review and editing. H.A. Yu: Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, validation, investigation, methodology, writing—original draft, writing—review and editing.

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Note

Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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