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# Clinical Benefit of Tyrosine Kinase Inhibitors in Advanced Lung Cancer with *EGFR*-G719A and Other Uncommon *EGFR* Mutations

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

## Abstract

The optimal management of advanced non-small cell lung cancer (NSCLC) with noncanonical epidermal growth factor receptor (*EGFR*) mutations (i.e., exon 19 deletion and exon 21 L858R) is constrained by the heterogeneous behavior of individual uncommon mutations and limited prospective clinical data in this setting. Despite encouraging results with osimertinib from a recently published phase II trial from South Korea, afatinib remains the only currently approved drug for patients with tumors harboring uncommon *EGFR* mutations (i.e., S768I, L861Q, and/or G719X). When used at the standard dose of 40 mg daily, afatinib is associated with significant rates of treatment-related adverse events, leading to frequent dose reductions and treatment discontinuations. We report a case of a woman with advanced NSCLC harboring *EGFR*-G719A mutation treated with afatinib (at an off-label pulse dose strategy that merits further evaluation in prospective studies) with sustained partial response for 20 months with manageable expected toxicities. Subsequent disease progression was mediated by off-target pan-EGFR inhibitor (including osimertinib)–resistant *KRAS* mutation and not by acquisition of *EGFR*-T790M. We further present the current state of evidence in the literature behind use of first-, second-, and third-generation tyrosine kinase inhibitors and summarize the evolving spectrum of activity ascribed to osimertinib (and newer *EGFR* inhibitors with a more favorable therapeutic window and intracranial penetration) in this population of patients with advanced NSCLC and uncommon *EGFR* mutations. ***The Oncologist*** 2021;26:281–287

## Key Points

- Uncommon EGFR mutations characterize a heterogeneous group of patients with advanced non-small cell lung cancer (NSCLC).
- Afatinib is the only currently U.S. Food and Drug Administration–approved drug for management of advanced NSCLC with uncommon *EGFR* mutations (S768I, L861Q, and/or G719X).
- Afatinib treatment at 40 mg daily is associated with high rates of adverse events and dose reductions; alternative strategies including pulse intermittent dosing should be evaluated prospectively.
- Osimertinib (with favorable safety profile and intracranial penetration) has shown promising results in this population in a phase II trial from South Korea; additional trials are ongoing.

## Introduction

The discovery of sensitizing mutations in the epidermal growth factor receptor (*EGFR*) gene and their antagonism with tyrosine kinase inhibitors (TKIs) has transformed the therapeutic landscape of advanced non-small cell lung cancer (NSCLC) and kickstarted the era of precision oncology [1, 2]. First-generation (gefitinib and erlotinib), second-generation (afatinib and dacomitinib), and subsequently third-generation (osimertinib) *EGFR* inhibitors have all been approved for first-line treatment of advanced NSCLC harboring the two most common *EGFR* mutations (exon 19 deletion and exon 21 L858R), which account for 80% + of all *EGFR*-positive lung cancers [3, 4]. Other less common but consistently occurring *EGFR* mutations in exons 18–21 are well established in NSCLC: exon 18 indels, G719X, exon 19 insertions, exon 20 S786I, exon

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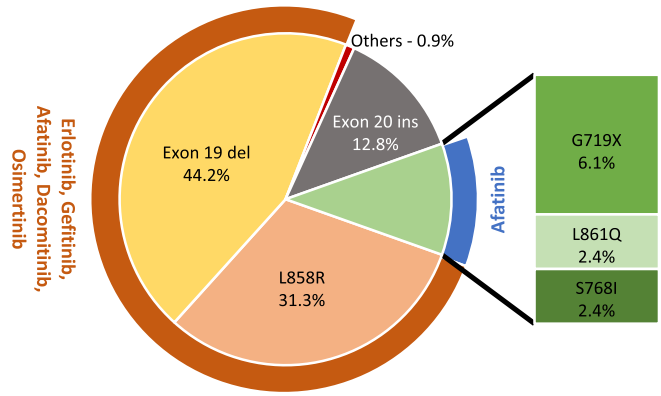
**A**




**B** Preclinical *in vitro* data of *EGFR* inhibitors in Ba/F3 cells expressing following *EGFR* mutations

| EGFR mutation | First generation (Erlotinib) | | Second generation (Afatinib) | | Third generation (Osimertinib) | |
|---|---|---|---|---|---|---|
| | Sensitivity ($IC_{50}$ < 500 nmol/L) | Selectivity (SI WT/Mutant >3) | Sensitivity ($IC_{50}$ < 500 nmol/L) | Selectivity (SI WT/Mutant >3) | Sensitivity ($IC_{50}$ < 500 nmol/L) | Selectivity (SI WT/Mutant >3) |
| **Common mutations** | | | | | | |
| Exon 19 Del 19 | Yes | Yes | Yes | Yes | Yes | Yes |
| Exon 21 L858R | Yes | Yes | Yes | No | Yes | Yes |
| | | | | | | |
| **Uncommon mutations** | | | | | | |
| Exon 18 G719X | Yes | Yes | Yes | Yes | Yes | Yes |
| Compound G719A + T790M | No | NA | Yes | No | Yes | Yes |
| Exon 21 L861Q | No | NA | Yes | No | Yes | Yes |
| Compound L861Q + T790M | No | NA | Yes | No | Yes | Yes |
| Compound S7681+V769L | No | NA | Yes | Yes | Yes | Yes |
| Exon 20 insertions[a] | No | NA | Yes | No | Yes | No[b] |

**Figure 1.** Uncommon *EGFR* mutations. **(A):** Frequency of individual mutations in *EGFR*-mutated lung cancer calculated from [5]. Others include EGFR fusions, exon 19 insertion, and exon 18–25 kinase domain duplication. Note: Drugs listed in orange and blue are approved for classic and uncommon *EGFR* mutations, respectively. **(B):** Preclinical data on in vitro sensitivity of *EGFR* inhibitors in Ba/F3 cells expressing *EGFR* mutations. The content of the data is adapted from original research data of our group's prior publication, as detailed in reference [6].
Abbreviations: del, deletion; $IC_{50}$, half maximal inhibitory concentration; NA, not applicable; SI, selectivity index; WT, wild type.

21 L861Q, exon 20 insertions, compound mutations, exon 18–25 kinase domain duplications, and rearrangements (*EGFR-RAD51* and *EFFR-PURB*) (Fig. 1); however most clinical trials have excluded these subsets [3, 5].

Afatinib is currently the only U.S. Food and Drug Administration–approved agent for use against these non-canonical *EGFR* mutations (i.e., S768I, L861Q, and/or G719X). However, its use in real-world settings is tempered by significant mucocutaneous toxicities, often necessitating dose reductions and/or treatment interruption/discontinuation at the approved dose of 40 mg daily. Here, we describe a case of a patient with advanced NSCLC with an uncommon *EGFR* mutation who was treated with pulse dose weekly afatinib with durable and tolerable disease control and review the relevant literature.

## Patient Story

A 66-year-old woman of Chinese ethnicity with no history of tobacco exposure was found to have a right lower lobe (RLL) lung mass on a chest radiograph. She had intermittent dry cough but no other respiratory or systemic symptoms. Further evaluation with computed tomography (CT) of the chest and positron emission tomography (PET)/CT showed the RLL lung mass with right hilar adenopathy and additional pulmonary and bony metastases (Fig. 2). Magnetic resonance imaging of the brain showed no evidence of intracranial metastases. Fine needle aspiration of the RLL lung mass and level 7 lymph node showed adenocarcinoma of lung origin, also confirmed on left iliac biopsy and thus establishing stage IVB lung adenocarcinoma.

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Comprehensive tumor genomic profiling (FoundationOne CDx, Foundation Medicine, Cambridge, MA) of the tumor showed presence of *EGFR*-G719A and S720F mutations; additional noted alterations included *TP53*-Q331* (pathogenic per the Catalogue of Somatic Mutations database); amplification of *EGFR*, *NFKBIA*, and *NKX2-1* genes; loss of *CDKN2A*, *CDKN2B*, and *MTAP* genes; microsatellite stable status; and tumor mutational burden of six mutations per megabase.

*EGFR*-G719X mutation in exon 18 is one of the more frequent mutations in the diverse group of uncommon *EGFR* mutations seen in NSCLC (Fig. 1). It is a point mutation that results in substitution of the amino acid glycine at position 719 with other amino acids—alanine (G719A in our patient's

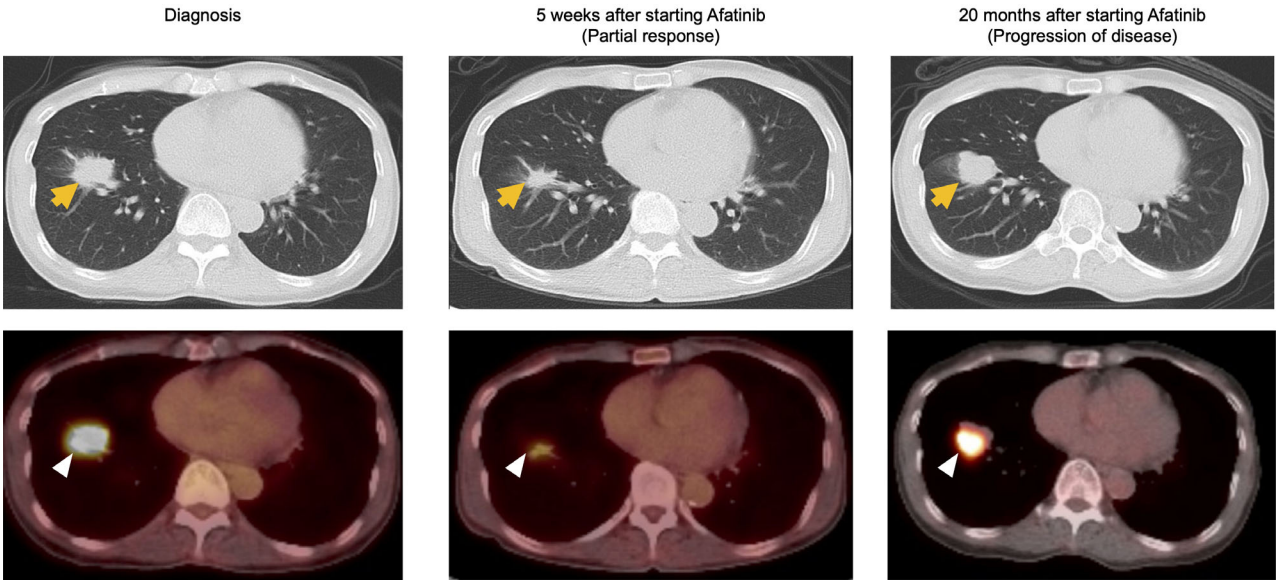


**Figure 2.** Radiographic findings from diagnosis, and response-assessment at 5 weeks and 20 months after initiation of pulse dose afatinib. Yellow arrows represent lung findings on computed tomography chest and white arrowheads represent fluorodeoxyglucose-avid areas on positron emission tomography scan.

**Table 1.** Major studies of *EGFR* inhibitors in patients with advanced non-small cell lung cancer with uncommon *EGFR* mutations[a]

| | First generation | | Second generation | | | Third generation |
|---|---|---|---|---|---|---|
| **EGFR-TKIs** | **Gefitinib** | | **Afatinib** | | | **Osimertinib** |
| Type of study | Prospective Phase II single arm [7] | Prospective Post hoc analysis of phase III randomized trial [8] | Prospective Post hoc pooled analysis of three (phase II + phase III) trials [36] | Prospective Subgroup analysis of single-arm phase IIIb trial [40][b] | Prospective Pooled data from clinical trials and real world [41] TKI naïve/ pretreated | Prospective Phase II single arm [49] |
| *n* | 7 | 5 | 38 | 67 | 110 / 32 | 36 |
| ORR (%) | 0% | 20% | 71.1% (95% CI, 54.1–84.6) | Not reported | 60% / 25% | 50% (95% CI, 33–67) |
| Median PFS | Not reported | 2.2 months (range, 0.5–10.6) | 10.7 months (95% CI, 5.6–14.7) | 9.1 months (95% CI, 5.6–13.6) | Not reported | 8.2 months (95% CI, 5.9–10.5) |
| Median OS | Not reported | 11.9 months (range, 5.8–22.6) | 19.4 months (95% CI, 16.4–26.9) | Not reported | Not reported | Not reached |

[a]Retrospective studies have been summarized in supplemental online Table 1.
[b]Included patients with *EGFR* exon 20 insertions and T790M mutation.
Abbreviations: CI, confidence interval; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

case), serine (G719D), or cysteine (G719C)—leading to constitutive activation of the EGFR receptor. S720F is another deleterious mutation in exon 18 that leads to substitution of serine with phenylalanine at position 720. Evaluation in mostly observational studies has yielded inconsistent results regarding the clinical activity of first-generation *EGFR* TKIs in these patients, at least in part because of the simultaneous grouping of patients with molecularly heterogeneous tumors (preclinical data by our group reviewed in Fig. 1 [6], major studies reviewed in Table 1 [7, 8] and Table 2 [7–10], and additional studies reviewed in supplemental online Table 1 [11–28]). Preclinical experiments and computational analysis by other groups have suggested augmented sensitivity of *EGFR*-G719A to afatinib compared with first- and third-generation TKIs [29, 30]. Similar preclinical results were reported for *EGFR*-S768I and other exon 18 (E709K and exon 18 deletion) mutations, whereas L861Q mutations are sensitive to both afatinib and osimertinib [29, 31]. Retrospective clinical studies in patients with advanced NSCLC with uncommon *EGFR* mutations have suggested improved progression-free survival (PFS) on treatment with afatinib compared with first-generation TKIs (supplemental online Table 1) [32–35].

Unlike most of the landmark trials that established the use of currently available *EGFR* TKIs, the LUX-Lung clinical trials have allowed enrollment of patients with these less common *EGFR* mutations. A post hoc pooled analysis of the

**Table 2.** Major studies of *EGFR* inhibitors in patients with advanced non-small cell lung cancer with selected uncommon *EGFR* mutations

| | First generation | | | Second generation | | | Third generation |
|---|---|---|---|---|---|---|---|
| **EGFR-TKIs** | **Erlotinib/ gefitinib** | **Gefitinib** | | **Afatinib** | | **Neratinib** | **Osimertinib** |
| Type of study | Retrospective pooled [9, 10] | Prospective phase II single arm [7] | Prospective Post hoc analysis of phase III randomized trial [8] | Prospective Post hoc pooled analysis of three (phase II + phase III) trials [36] | Prospective Pooled data from clinical trials and real world [41] TKI naïve/ pretreated | Prospective Subgroup analysis of single-arm phase II trial [50] | Prospective phase II single arm [49] |
| ***EGFR*-G719X[a] mutations** | | | | | | | |
| *n* | 142 [9] | 1 | 3 | 18 | 55 / 19 | 4 | 19 |
| ORR (%) | 35.2% | 0% | 0% | 77.8% (95% CI, 52.4–93.6) | 63.4% / 10.5% | 75% | 53% (95% CI, 28–77) |
| Median PFS | Not reported | Not reported | 1.8 months (range, 0.5–2.2) | 13.8 months (95% CI, 6.8–NE) | Not reported | 52.7 weeks (90% CI, 25.6–57.0) | 8.2 months (95% CI, 6.2–10.2) |
| Median OS | Not reported | Not reported | 7.9 months (range, 5.8–11.9) | 26.9 months (95% CI, 16.4–NE) | Not reported | Not reported | Not reported |
| ***EGFR*-L861Q[a] mutations** | | | | | | | |
| *n* | 70 [9] | 1 | 2 | 16 | 47 / 11 | | 9 |
| ORR (%) | 38.6% | 0% | 50% | 56.3% (95% CI, 29.9–80.2) | 59.6% / 45.5% | | 78% (95% CI, 44–100) |
| Median PFS | Not reported | Not reported | 8.5 months (range, 6.4–10.6) | 8.2 months (95% CI, 4.5–16.6) | Not reported | | 15.2 months (95% CI, 1.3–29.1) |
| Median OS | Not reported | Not reported | 17.3 months (range, 12–22.6) | 17.1 months (95% CI, 15.3–21.6) | Not reported | | |
| ***EGFR*-S786I[a] mutations** | | | | | | | |
| *n* | 33 [10] | | | 8 | 8 / 2 | | 8 |
| ORR (%) | 45.4%[b] | | | 100% (95% CI, 63.1–100) | 62.5% / 50% | | 38% (95% CI, 0–81) |
| Median PFS | Not reported | | | 14.7 months (95% CI, 2.6–NE) | Not reported | | 12.3 months (95% CI, 0–28.8) |
| Median OS | Not reported | | | NE (95% CI, 3.4–NE) | Not reported | | Not reported |

[a]Includes patients with compound *EGFR* mutations involving the particular mutation.
[b]Calculated by excluding patients who received either afatinib or whose tumors had *EGFR* exon 19 deletion/L858R mutation in addition to S768I.
Abbreviations: CI, confidence interval; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials evaluated the clinical activity of afatinib in TKI-naïve stage IIIB–IV lung-adenocarcinomas with uncommon EGFR mutations [36]. Whereas LUX-Lung 2 was a nonrandomized single-arm phase II trial, LUX-Lung 3 (global) and LUX-Lung 6 (Asia) were randomized phase III trials that compared afatinib with chemotherapy control arms [37–39]. Thirty-eight patients with noncanonical *EGFR* alterations were classified into one of the three groups: point mutations or duplications in in exons 18–21 (group 1); de novo T790M mutations alone or in combination with other mutations (group 2); or exon 20 insertions (group 3). Objective response rate (ORR) for group 1 was 71.1% (95% confidence interval [CI], 54.1–84.6), median PFS was 10.7 months (95% CI, 5.6–14.7), and median overall survival (OS) was 19.4 months (95% CI, 16.4–26.9) (Table 1). Analysis for individual mutations showed that ORR for patients with tumors harboring G719X mutation was 77.8% (95% CI, 52.4–93.6), median PFS was 13.8 months (95% CI, 6.8, not estimable), and median OS was 26.9 months (95% CI, 16.4, not estimable) (Table 2). In January 2018, this led to the approval of afatinib in advanced NSCLC harboring alterations in these less common subgroups (S768I, L861Q, and/or G719X). Further data supporting the activity of afatinib in these cohorts have

also been published (Table 1, Table 2, supplemental online Table 1) [40–43].

Daily dosing of afatinib at 40–50 mg in clinical trials has been associated with significant rates of treatment discontinuations and dose reductions because of treatment-related adverse events (TRAEs). The most common toxicities involve the gastrointestinal tract (diarrhea), mucosa (oral mucositis), and skin (rash/acneiform dermatitis, dry skin, pruritus, paronychia) and are related to the simultaneous inhibition of wild-type (WT) *EGFR* [44]. The rates of treatment discontinuation because of TRAEs have ranged from 3.8% to 12% across numerous studies [37–40]. Dose reductions to less than 40 mg daily have been required in up to 50% of study participants in these trials. A combined analysis evaluating the impact of afatinib dose reductions in the LUX trials included 5.7% and 9.1% patients with uncommon *EGFR* mutations, respectively [45]. Although this study showed similar PFS for patients with dose reductions within the first 6 months compared with those without, it was limited by small subgroup sizes and the post hoc nature of the analysis.

Osimertinib is now the standard-of-care first-line treatment option for patients with advanced NSCLC with common *EGFR* mutations in the U.S. and many other countries in view of brisk and durable systemic and intracranial efficacy with a favorable toxicity profile [46, 47]. In contrast to the first-generation *EGFR* inhibitors, osimertinib has low avidity for the *EGFR* WT receptor [48]. The activity of osimertinib against patients with uncommon *EGFR* mutations was first observed in the phase I/II AURA study, in which two of ten patients had responses in their tumors after progression on a prior EGFR TKI [48]. A recently published multicenter, open-label, single-arm phase II trial from South Korea evaluated the clinical activity and safety of osimertinib in 36 *EGFR* TKI–naïve patients with metastatic or recurrent NSCLC harboring mutations other than exon 19 deletion, L858R/T790M mutations, and exon 20 insertions (Table 1) [49]. Nineteen (53%), nine (25%), eight (22%), and four (11%) patients had tumors with *EGFR*-G719X, L861Q, S768I, and other mutations in the *EGFR* gene, respectively. Investigator-assessed ORR was 50% (95% CI, 33–67), with median duration of response 11.2 months (95% CI, 7.7–14.7 months), disease control rate 89% (95% CI, 78–100), and median PFS 8.2 months (95% CI, 5.9–10.5); median OS was not reached. Intracranial ORR was 40%, with responses seen in two of five evaluable patients. Subgroup analysis revealed ORR of 53% (95% CI, 28–77) and median PFS of 8.2 months (95% CI, 6.2–10.2) in patients with G719X mutations (Table 2). The safety profile was as expected from prior studies, with rash, pruritus, anorexia, diarrhea, and dyspnea as the most common but nonsevere adverse events. Dose reduction was required in only one patient, whereas no patient (0%) discontinued therapy because of TRAEs. The shortcomings of cross-trial comparisons notwithstanding, the comparative efficacy of osimertinib as compared with afatinib and neratinib is summarized in Table 1 (for all uncommon *EGFR* mutations) and Table 2 (for G719X, S768I, and L861Q mutations) [36, 40, 41, 49, 50].

In light of concern for high rates of adverse events and dose reductions with standard dose afatinib, we include discussions regarding an alternative off-label strategy of intermittent pulsatile dosing of afatinib at 280 mg weekly while making shared management decisions with patients. This strategy was previously reported by our group in a small cohort of patients with *ERBB2* exon 20 insertion–mutated lung adenocarcinoma [44]. In this study, partial responses were seen in two of three patients, with exceptional response in one; there was minimal diarrhea and no reported rash [44]. The biologic rationale behind this intermittent pulsatile dosing approach is to achieve adequate pharmacodynamic inhibition and intracranial penetration while avoiding toxicities incurred by daily continuous inhibition of WT EGFR, as evaluated previously with pulsatile administration of erlotinib [51–53].

## Patient Update

After an informed discussion of known risks and benefits, the patient started on first-line afatinib at an off-label dose of 280 mg weekly (afatinib 40 mg $\times$ 7 tablets taken once weekly). She experienced Common Terminology Criteria for Adverse Events grade 2 oral mucositis, grade 1 diarrhea, grade 1 acneiform rash, and grade 2 paronychia. Topical dexamethasone use for oral mucositis was complicated by oral candidiasis and led to treatment interruption for 1 week. After resuming treatment, the patient had no recurrence of oral mucositis. Nonbloody diarrhea occurred predictably 3 days after each weekly dose and lasted for no more than 1 day. Cutaneous adverse events were managed successfully with topical steroids along with dermatology consultation. No dose reductions were needed.

PET/CT scan done 5 weeks after initiating afatinib showed a partial response using RECIST version 1.1 (Fig. 2) that lasted for 20 months. Ultimately, the patient developed new symptomatic bony lesions, intrathoracic progression, and new intracranial metastases (Fig. 2). Repeat tissue biopsy did not reveal histologic transformation to small cell carcinoma. Circulating tumor DNA evaluation showed a new *KRAS*-G12V mutation and did not show new mutations in the *EGFR* gene in addition to the known G719A and S720F mutations, revealing acquired resistance without *EGFR*-T790M or C797S. Her treatment was next transitioned to carboplatin and pemetrexed. However, because of rapid progression of systemic disease on chemotherapy after two cycles, treatment was switched to third-line osimertinib (at 80 mg/day) that was associated with progressive disease as best response. Tissue biopsy while on osimertinib therapy confirmed the presence of the original *EGFR* mutation profile along with the *KRAS*-G12V mutation, confirming the latter as the mechanism of resistance to EGFR-targeted therapy. She, unfortunately, continued to clinically decline and died approximately 27 months from the start of first-line afatinib treatment.

## Conclusion

Patients with uncommon *EGFR* mutations represent a heterogeneous group with the possibility for benefit with existing TKIs. It is prudent to consider preclinical data, computational analysis, and available prospective/retrospective data in determining optimal therapies for these patients. Moreover, with expanding use of comprehensive genomic

profiling platforms and potential for more sensitive detection of noncanonical *EGFR* alterations, it is becoming increasingly relevant to avoid exclusion of these patients from new and upcoming trials in this domain. We report here an off-label strategy of intermittent pulse dose afatinib with clinically meaningful benefit and manageable toxicities. It is imperative to rigorously and prospectively evaluate such strategies vis-à-vis emerging data for *EGFR*-T790M active and central nervous system–penetrant osimertinib (phase II trial from South Korea [49] and ongoing phase II clinical trial in the U.S., NCT03434418) for the optimal management of these patients. We believe that future reporting of on-target and off-target mechanisms of resistance to EGFR TKI monotherapy for *EGFR*-G719X and other uncommon *EGFR*-mutated NSCLC will help define unmet needs for future therapeutic advances.

## Glossary of Genomic Terms and Nomenclature

***CDKN2A*:** cyclin dependent kinase inhibitor 2A

***CDKN2B*:** cyclin dependent kinase inhibitor 2B

***EGFR*:** epidermal growth factor receptor

***MTAP*:** methylthioadenosine phosphorylase

***NFKBIA*:** nuclear factor-kappa-B–inhibitor alpha

***NKX2-1*:** NK2 homeobox 1

***TP53*:** tumor protein p53

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## Disclosures

**Deepa Rangachari:** DynaMed, Advance Medical/TelaDoc (C/A), Bristol-Meyer Squibb, Novocure, Abvvie/Stemcentrx (RF); **Paul A. VanderLaan:** Gala Therapeutics, Foundation Medicine, Caris Life Sciences, Flatiron Health, Intuitive Surgical, Clearview Healthcare Partners (C/A); **Daniel B. Costa:** Takeda/Millennium Pharmaceuticals, AstraZeneca, Pfizer (C/A, H, RF—institutional), Merck Sharp & Dohme, Merrimack Pharmaceuticals, Bristol-Myers Squibb, Clovis Oncology, Spectrum Pharmaceuticals, Tesaro (other—nonfinancial institutional research support). The other authors indicated no financial relationships.

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