



In Regard to “Activity of EGFR TKIs in Caucasian Patients With NSCLC Harboring Potentially Sensitive Uncommon EGFR Mutations”

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We have read with interest the article titled “Activity of EGFR TKIs in Caucasian Patients With NSCLC Harboring Potentially Sensitive Uncommon EGFR Mutations” by Passaro et al.¹ In their multicenter retrospective observational study on the activity of first- or second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in uncommon EGFR-mutated advanced non-small-cell lung cancer (NSCLC), 88 patients were enrolled during a 13-year period. Cohort B included 42 patients with exon 18 mutations and cohort A, 46 patients with complex mutations (co-occurring common mutations, classic with uncommon mutations or double uncommon mutations). In cohort B, 69% of the patients and in cohort A, 78.3% of the patients had received EGFR TKI as first-line treatment. In cohort B, the median progression-free survival (mPFS) was 8.3 months and the median overall survival (mOS) was 17.0 months. In contrast, in cohort A, the mPFS was 12.3 months and the mOS was 31.0 months, with, apparently, no detrimental effects resulting from the presence of exon 20 mutations in cohort A.

According to Passaro et al,¹ EGFR uncommon mutations can be considered potentially sensitive to first- and second-generation EGFR TKIs, as shown by the similar survival outcomes compared with the classic mutations. Also, patients with complex EGFR mutations seemed to have longer survival outcomes compared with those with exon 18-point mutations.

We would like to take this opportunity to report a case series of nonclassic EGFR mutations observed at the Oncology Unit of Careggi University Hospital in Florence, Italy. From January 2016

to June 2019, we treated 9 patients (7 men and 2 women) with a median age of 76 years (range, 64-81 years) with advanced or metastatic NSCLC with uncommon EGFR mutations. Two patients (group A) showed a complex mutation (1 with G719C/L861Q and 1 with G719C/S768I), and seven patients (group B) presented with a single EGFR uncommon mutation (Table 1). In group B, 5 patients had single exon 18-point mutations (3 with G719A, 1 with G719C, and 1 with G719S) and 2 patients had exon 20 S768I point mutation. Both group A and group B patients received afatinib (40 mg/d orally) as first-line treatment. The clinical and pathologic characteristics of the patients are summarized in Table 1.

For all patients, we have observed a mPFS of 6 months and a mOS of 9 months (Figure 1). At the time of data collection (November 2019), only 2 patients were still receiving treatment with afatinib, with 1 patient having an 8-month treatment duration and 1 patient a 17-month treatment duration. Both of these patients had a complex mutation and had experienced a partial response as the best objective response. In contrast, of the other 7 patients, 3 had had stable disease and 4 had experienced disease progression.

In our case series, the best survival outcomes were observed in patients with complex EGFR mutations treated with afatinib. This observation agrees with the study reported by Passaro et al¹ and with other previous data and reports.²⁻⁷

However, in our case series, the patients with exon 18 and exon 20 single mutations experienced little benefit from afatinib treatment and had the worst survival outcomes. The reported data, including the study by Passaro et al,¹ showed that exon 18 mutations seem to have partial sensitivity to EGFR TKIs. In particular, G719X mutations (exon 18) presented with comparable outcomes compared with common mutations.^{8,9} In the post hoc analysis of the 3 LUX-Lung trials, high afatinib activity was reported for patients with the uncommon EGFR mutations G719X and S768I (exon 20).¹⁰ However, this was not confirmed in our case series.

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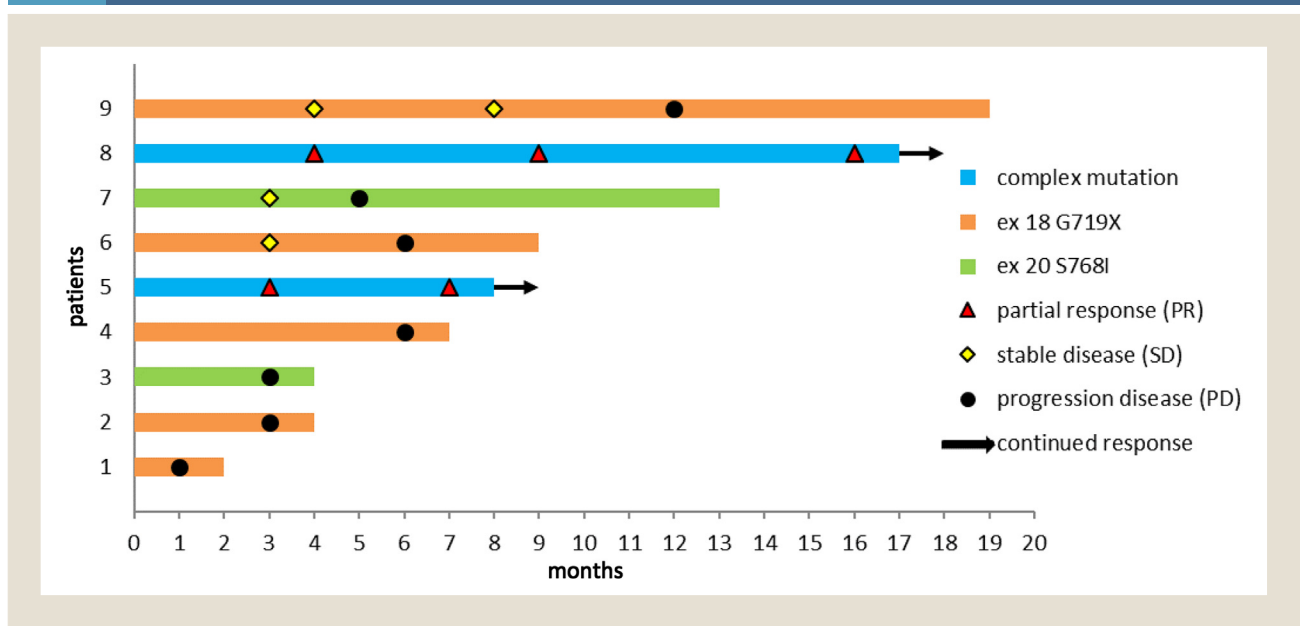
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Table 1 Clinical and Pathologic Characteristics

Pt. No.	Age, y	Sex	Heavy Smoker	ECOG PS	Stage	EGFR Mutation	Best Response	mPFS, mo	mOS, mo
1	76	Male	Yes	1	IVB	ex18 G719C	PD	1	2
2	66	Male	Yes	1	IVA	ex18 G719A	PD	3	4
3	78	Male	Yes	0	IIIC	ex20 S768I	PD	3	4
4	64	Female	Yes	0	IVA	ex18 G719A	PD	6	7
5	81	Female	No	0	IIIC	ex18 G719C/ ex21 L861Q	RP	≥8	≥8
6	68	Male	Yes	0	IVA	ex18 G719A	SD	6	9
7	77	Male	Yes	0	IVB	ex20 S768I	SD	5	13
8	80	Male	Yes	1	IVA	ex18 G719C/ ex20 S768I	RP	≥17	≥17
9	72	Male	Yes	0	IVB	ex18 G719S	SD	12	19

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; mOS = median overall survival; mPFS = median progression-free survival; PD = progressive disease; PR = partial response; PS = performance status; Pt. No. = patient number; SD = stable disease.

Figure 1 Patient Response to Afatinib Stratified by Uncommon Epidermal Growth Factor Receptor Mutation Subtype



Our series had some differences from the study by Passaro et al.¹ First, the number of patients included in our study was limited. Second, our series included older patients with an inverse male/female ratio, and almost all were heavy smokers (8 of 9). Another difference is that in the study by Passaro et al,¹ the second-generation EGFR TKI afatinib was used as first-line treatment in 15 patients, 11 with complex mutations and 4 with exon 18-point mutations. Our overall interpretation of the different results reported by Passaro et al¹ is that EGFR nonclassic mutations are a wide and heterogeneous group of genetic alterations with different biologic and clinical significance and, consequently, have different sensitivity to first- and second-generation EGFR TKIs. Currently, the reported data on the efficacy of EGFR TKIs in rare mutations are available for second-generation EGFR TKI afatinib and all have derived from retrospective or post hoc analyses. To date, few

preclinical data are available on the efficacy of the third-generation TKI osimertinib for EGFR uncommon mutations. Some ongoing trials are testing the role of osimertinib (alone or in combination) and have shown promising activity in patients with nonclassic mutations.^{11,12} Recently Cho et al¹³ reported favorable activity of osimertinib in patients with NSCLC with uncommon EGFR mutations in a multicenter phase II study.

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