Lung Cancer: Targets and Therapy

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CASE REPORT

Cis-oriented solvent-front EGFR G796S mutation in tissue and ctDNA in a patient progressing on osimertinib: a case report and review of the literature

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Abstract: Acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) is a universal event and limits clinical efficacy. The third-generation EGFR inhibitor osimertinib is active in EGFR-mutant/T790M positive non-small-cell lung cancer. Mechanisms of acquired resistance are emerging, and here we describe a *cis*-oriented solvent-front EGFR G796S mutation as the resistance mechanism observed in a progression biopsy and circulating tumor DNA (ctDNA) from a patient with initial response followed by progression on osimertinib. This is one of the earliest reports of a sole solvent-front tertiary EGFR mutation as a resistance mechanism to osimertinib. Our case suggests a monoclonal resistance mechanism. We review the importance of the solvent-front residues across TKIs and describe known osimertinib resistance mechanisms. We observe that nearly all clinical osimertinib-resistant tertiary EGFR mutations are oriented in *cis* with EGFR T790M. This case highlights the importance of mutations affecting EGFR kinase domains and supports the feasibility of broad panel ctDNA assays for detection of novel acquired resistance and tumor heterogeneity in routine clinical care.
Keywords: EGFR G796, lung cancer, ctDNA, resistance, osimertinib, T790M

Introduction

Acquired resistance to epidermal growth factor receptor (EGFR)-directed therapies is universal and can be partly predicted by tyrosine kinase inhibitor (TKI) structure and EGFR binding features. The third-generation irreversible EGFR inhibitor osimertinib is effective in EGFR T790M positive non-small-cell lung cancer (NSCLC).[1,2] The landscape of osimertinib resistance is evolving and highlighted by the acquired EGFR C797S mutation, which limits covalent binding.[3] Allelic orientation of osimertinib resistance mutations with respect to EGFR T790M may dictate the spectrum of resistant mutation treatment strategies, and here we report an EGFR solvent-front G796S mutation oriented in *cis* with T790M in an EGFR L858R-mutant NSCLC patient at progression on osimertinib.[4,5]

Case presentation

A 69-year-old Asian female never smoker presented in July 2014 with back and hip pain and was found to have a 4.4-cm left lower lobe mass, a right ischium bone metastasis and malignant adenopathy (Figure 1). CT-guided left lower lobe biopsy confirmed a poorly differentiated adenocarcinoma, and hotspot polymerase chain reaction (PCR) testing identified an activating EGFR L858R mutation but no EGFR T790M. The patient was

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begun on erlotinib 150 mg orally once daily. She achieved a good partial response and symptomatic improvement lasting 13 months, at which time a new left lower lobe lesion 1.8 × 1.3 cm as well as increased activity in her known bony disease was seen (Figure 1). A biopsy of the right pelvic mass was performed and was consistent with poorly differentiated adenocarcinoma. Additional hotspot molecular testing post-erlotinib confirmed the EGFR L858R mutation and was negative for EGFR T790M. However, a single-gene droplet-digital PCR test from circulating tumor DNA (ctDNA) performed after progression on erlotinib identified EGFR T790M, and the patient was transitioned to osimertinib in October 2015. She had symptomatic improvement and partial response lasting 12 months, at which point a new left pelvic mass with bony involvement was identified (Figure 1). A left pelvic mass core biopsy from the soft tissue component was subjected to comprehensive genomic profiling (FoundationOne®, Foundation Medicine, Cambridge, MA, USA), which identified the original EGFR L858R at a mutant allele frequency (MAF) of 50.52%, an EGFR T790M at 37.14%, an EGFR G796S at 38.69%, *EGFR* amplification at 16 predicted copies, and a low mutational burden (four mutations per DNA megabase). Overlapping sequencing reads spanning the T790M and G796S confirmed *cis* orientation (Figure 2A). A concurrent ctDNA assay (FoundationACT™, Foundation Medicine) detected the EGFR L858R (MAF 12.8%), EGFR T790M (MAF 11.2%), and the G796S (MAF 11.6%) without other putative resistance alterations (Table S1). Immunohistochemistry confirmed high PD-L1 expression at 70% by tumor proportion score (Dako 22C3 pharmDx, Agilent Technologies, Santa Clara, CA, USA). Additional genomic alterations are shown in Table S1, and no other putative drivers were detected. In the absence of available trials, she was transitioned to carboplatin plus pemetrexed and achieved stable disease after three cycles (Figure 1) followed by disease progression. Based on lack of standard therapies and high PD-L1 expression that patient was then enrolled in a clinical trial of pembrolizumab in combination with the oral IDO-1 inhibitor epacadostat (NCT02178722). She has achieved a radiographic partial response and remains on therapy, now 5 months in duration. The patient has provided written informed consent to have the case details and any accompanying images published.

Discussion

The median progression-free survival (PFS) for first-line erlotinib in EGFR-mutant NSCLC is roughly 10 months from the EURTAC (Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer) trial.[6] Among patients who develop EGFR T790M-mediated resis-

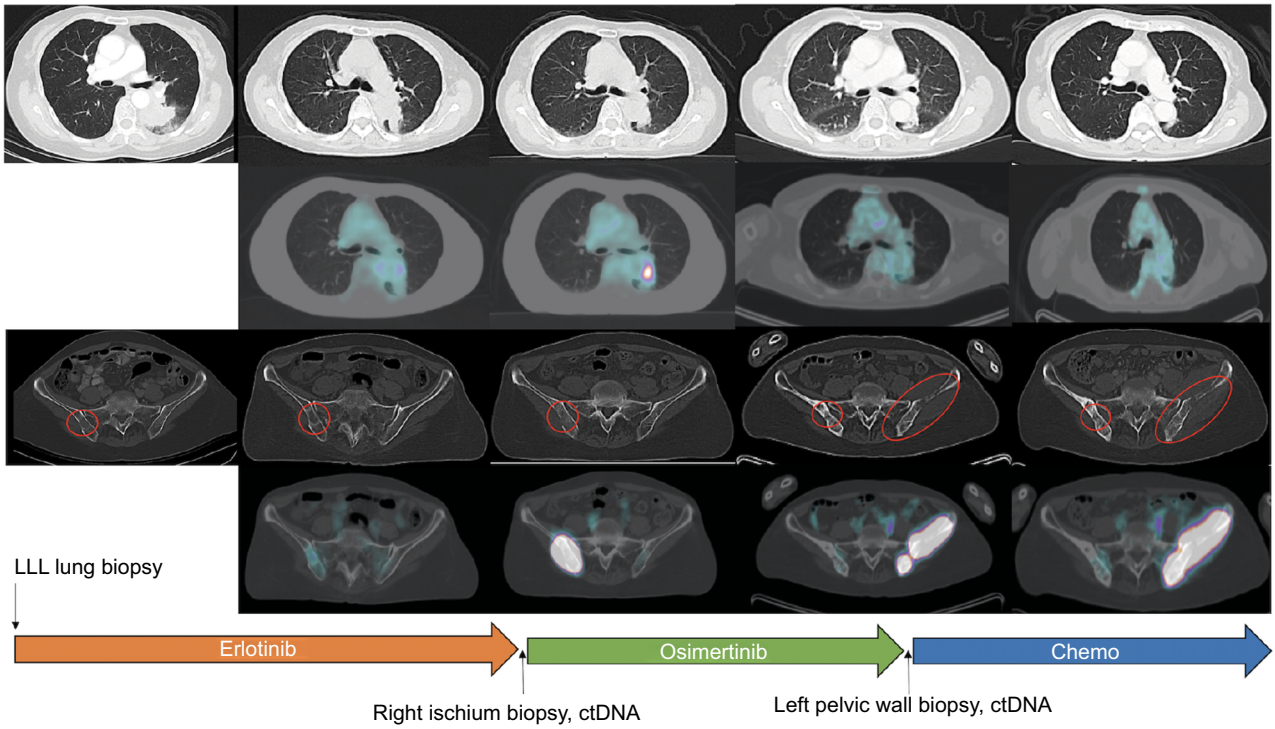

Figure 1 Radiographic response followed by progression in a EGFR L858R NSCLC with response to first-line erlotinib and second-line osimertinib.
Notes: Arrows depict treatment timeline events, and red circles denote bony lesions.
Abbreviations: ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; LLL, left lower lobe; NSCLC, non-small-cell lung cancer.

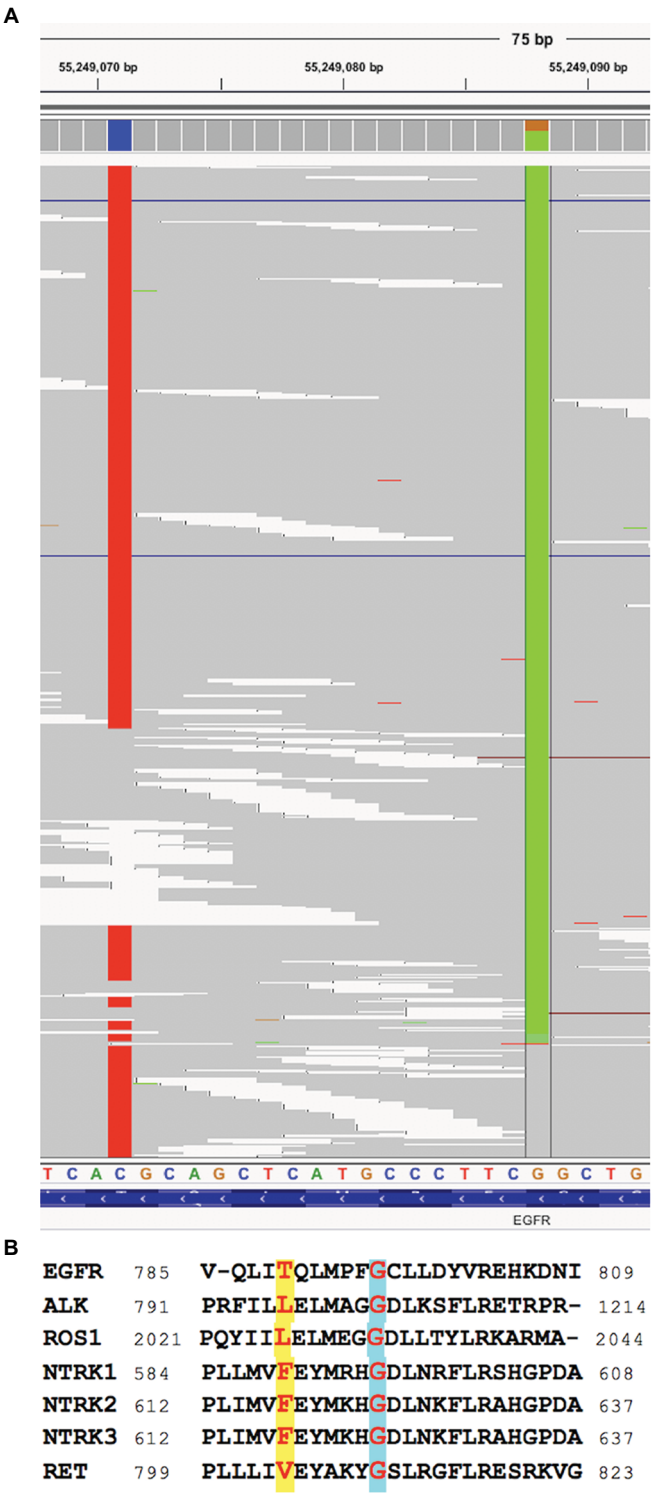

Figure 2 (A) Integrated genomics viewer highlighting the presence of a C>T at codon 790 (EGFR T790M) mutation (red) oriented in *cis* with a G>A at codon 796 (EGFR G796S) mutation (green). Overlapping reads spanning the T790M and G796S indicate *cis* orientation on the same allele. **(B)** The RTK sequence alignments across relevant TKIs with the gatekeeper residue highlighted in yellow and the relevant solvent-front residue in teal.
Abbreviations: EGFR, epidermal growth factor receptor; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor.

tance, the median PFS for osimertinib is 10.1 months in the AURA3 trial, with the largest proportion developing EGFR C797S-mediated resistance based on limited study.[1,3] The importance of the covalent binding residue (EGFR C797) was highlighted by ibrutinib resistance mutations at the analogous cysteine residue C481 (C481S) in Bruton's tyrosine kinase (BTK).[7] With increasing clinical use of osimertinib, several additional resistance alterations have been described, the

Table 1 Currently described resistance mechanisms to the third-generation EGFR tyrosine kinase inhibitor osimertinib

Resistance mechanism	Original EGFR mutation	Resistance category	Preclinical or clinical	Concurrent T790M	Orientation to T790M	Reference
EGFR G796SR/S/D	L858R	Solvent front	Clinical	Yes	*Cis*	13, 20
EGFR L792H/F	Exon 19 del	Hinge pocket	Clinical	Yes	*Cis*	5, 9
EGFR P794S	Exon 19 del	Structural TK change	Clinical	Yes	*Cis*	5
EGFR F795C	L858R	Structural TK change	Clinical	Yes	NR	28
EGFR C797S/G	L858R, Exon 19 del	Binding interference	Preclinical, clinical	Yes	*Cis* and *Trans*	3, 4, 9, 12, 24
EGFR L844V[a]	Exon 19 del, L858R	Steric hindrance	Preclinical	Yes	*Trans*	9
EGFR L718Q/V[a]	Exon 19 del, L858R	Steric hindrance	Preclinical, clinical	Yes	*Trans*	9, 10, 20
SCLC Transformation	Exon 19 del	EMT	Clinical	Yes	N/A	29–31
T790M loss/outgrowth T790M-Clone	L858R	Clonal divergence	Clinical	No	N/A	32
BRAF V600E	L858R	Bypass tract	Preclinical, Clinical	Yes	N/A	33
MET amplification	Exon 19 del, L858R	Bypass tract	Preclinical, clinical	Yes	N/A	32, 34, 35
HER2 amplification	Exon 19 del	Bypass tract	Clinical	Yes	N/A	32, 36
SFK/FAK signaling	N/A	Bypass tract	Preclinical	N/A	N/A	37
Multiple concurrent mechanisms	Exon 19 del, L858R	Multiple	Clinical	Yes	N/A	28

Notes: Representative references are included. [a]Denotes variable sensitivity to osimertinib in preclinical models.[8]
Abbreviations: del, deletion; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; N/A, not applicable; NR, not reported; SCLC, small-cell lung cancer; TK, tyrosine kinase.

majority related to acquired changes affecting inhibitor binding (Table 1). Tertiary mutations affecting the EGFR solvent-front (G796S/R), hinge region (L792H/F), osimertinib covalent binding residue (C797S/G), and residues predicted to decrease affinity through steric interaction (L718Q/V, L844V) are described, and triple mutants (EGFR activating/T790M/tertiary EGFR) appear resistant to all third-generation EGFR TKIs.[3–5,8–11] It is anticipated that the majority of clinically observed osimertinib-resistant tertiary mutations will occur in *cis* with the EGFR T790M. However, a recent report suggested *trans*-oriented T790M and C797S exists, and in fact may be sensitive to combination erlotinib and osimertinib, as would be predicted preclinically.[4,12] Non-target-modifying resistance alterations, broadly defined as bypass track activation (*MET*, *ERBB2*, *EGFR* amplification), histologic transformation to small-cell lung cancer (SCLC), and clonal divergence of T790M-cells, have been observed, and ongoing experience will clarify relative frequencies (Table 1).

Our case adds to the emerging resistance literature, and the lack of a detected concurrent C797S adds strong support to the suggestion that G796S is mediating osimertinib resistance in our patient. Additional support is observed in an osimertinib-resistant case with both EGFR G796S and G796R mutations.[13] Orthogonal support from other oncogenic receptor tyrosine kinases (RTKs) is suggested, and we note that the EGFR G796S is analogous to the confirmed solvent-front resistance mutations ALK G1202R, ROS1 G2032R, TRKA G595R, and TRKC G623R (Figure 2B).[14–17] Broadly, solvent-front resistance mutations often cause direct steric hindrance to inhibitor binding and/or destabilize the favorable electrostatic interactions between the inhibitor and its respective binding site.[18] Critically, there is a need to functionally validate clinically observed solvent-front EGFR mutations, and we acknowledge a paucity of structural and functional data surrounding EGFR codon 796.

The emergence of ct DNA assays offers potential for monitoring and serial noninvasive tumor assessment, which may overcome issues with inter- and intratumoral heterogeneity.[19] The tissue and ctDNA concordance observed in our case supports a likely monoclonal resistance in which the *cis*-oriented T790M/G796S containing clones drive the clinical progression. As would be expected, the mutant allele frequencies for the T790M and G796R are nearly identical by both tissue and ctDNA assays, and this patient would not be expected to respond to any currently available EGFR inhibitors. Although more data is needed, the MAF % is an important difference between our case and a recently reported EGFR G796D mutation mediating resistance to osimertinib.[20] In the case reported by Zheng et al,[20] the EGFR L858R MAF at pre-gefitinib sample (4.28%) also contained a G796D at MAF 0.61% but no EGFR T790M. At progression on gefitinib, the T790M was detected at MAF of 1.85%, but at progression on osimertinib, the T790M and L858R mutation were undetectable, and the EGFR G796D MAF had increased to 1.9%. This pattern could also be explained by more polyclonal resistance in which a preexisting population of EGFR G796D+ (without concurrent EGFR L858R or T790M) increased during osimertinib therapy. The overlapping reads observed in our case offer a more convincing argument that an acquired G796S developed in cells harboring the original L858R and acquired T790M alterations and is the driver of resistance. A larger experience

with resistance to 3rd generation TKIs and ctDNA data will be required to understand the clinical implications of these differences.

Triple mutants (EGFR activating/T790M/tertiary EGFR) represent a major clinical challenge, and an iterative process of resistance assessment at each progression (ctDNA, tissue, or both) is critical.[21,22] It is known that a proportion of TKI-naïve EGFR-mutant NSCLC harbor concurrent T790M, and investigation is ongoing into how first-line osimertinib affects the resistance patterns in these patients (AZENT Trial, NCT02841579).[23] Ongoing combinatorial approaches combining osimertinib and bevacizumab (BOOSTER phase II, NCT03133546), dasatinib, and gefitinib are geared to delay/prevent resistance and will be eagerly awaited. The fourth-generation EGFR mutant-selective allosteric non-ATP competitive inhibitor EAI045 binds in the inactive EGFR kinase conformation (type II) and has demonstrated activity in the L858R/T790M/C797S models, partly because the C797 residue is distant from the allosteric binding pocket.[24] Importantly, Jia et al[24] demonstrated synergistic activity and marked tumor reduction of EAI045 with the EGFR-dimer disrupting antibody cetuximab in L858R/T790M/C797S mice.[25] Structural studies with compound Go6976, a potent protein kinase C (PKC) inhibitor that also binds preferentially to EGFR T790M, bound to EGFR T790M/C797S support the idea that non-ATP competitive inhibitors may be preferential to overcome the presence of C797S.[26] Whether a similar strategy is applicable to the G796S solvent-front alteration observed in our patient is unstudied. Overall, the optimal approach to EGFR tertiary mutation positive (EGFRm3+) tumors remains an unknown, and we anticipate combination approaches will be needed.

Although limited by a single patient observation, it is worth noting our patient responded to the combination of pembrolizumab and epacadostat. Data has been mixed, but it has been suggested that EGFR-mutant NSCLC are less responsive to immune checkpoint inhibitor therapies despite the 14% rate of >50% PD-L1 positivity seen in post-EGFR-TKI treated specimens.[27] Whether or not PD-L1 expression continues to increase after serial lines of TKI therapy (our patient was tested after osimertinib progression) and how this impacts on immunotherapy sensitivity is unknown. Further, our patient was treated with a novel immunotherapy combination, and whether or not this can overcome the lower response rates seen in EGFR-mutant cases is unknown.

Conclusion

Here we confirm that the EGFR solvent-front G796S mutation confers clinical resistance to osimertinib without the occurrence of C79S or L792 mutations, and is oriented in *cis* with T790M, consistent with observations of other tertiary EGFR mutations. As endorsed by the National Comprehensive Cancer Network (NCCN) guidelines for NSCLC, comprehensive genomic profiling is critical to detect novel mutations with therapeutic implications, and serial testing is supported by our case.

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Disclosure

Samuel J Klempner has received honoraria from Foundation Medicine, Inc. through participation in speaker bureau activities. Pareen Mehta has no disclosures. Alexa B Schrock and Siraj M Ali are employees of Foundation Medicine, Inc. and own stocks in Foundation Medicine, Inc. Sai-Hong Ignatius Ou has received speaking and adviser honorarium from Astra Zeneca. The authors report no other conflicts of interest in this work.

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Supplementary material

Table S1 Complete list of genomic alterations detected in concurrent tissue and blood analyses at the time of progression on osimertinib in a patient with EGFR L858R NSCLC

Genomic alteration	Tissue MAF	ctDNA MAF	Additional genomic information
EGFR L858R	50.52%	12.8%	N/A
EGFR T790M	37.14%	11.2%	N/A
EGFR G796S	38.69%	11.6%	N/A
EGFR amplification	N/A	ND	16 copies predicted
TP53 R273H	25.8%	3.0%	N/A
TP53 V311	62.24%	ND	N/A
BCOR V1456fs*12	5.75%	N/A	N/A
ERRFI1 L96fs*26	8.66%	N/A	N/A
LZTR1 Y136*	49.75%	N/A	N/A
MYC amplification	N/A	ND	7 copies predicted
BRAF amplification	N/A	ND	10 copies predicted
KEL amplification	N/A	N/A	10 copies predicted
CDK2NA loss	N/A	N/A	N/A
CDKN2B loss	N/A	N/A	N/A
KRAS A146S	ND	1.2%	N/A
Variants of unknown significance			
AR S176R	Detected	N/A	N/A
CARD11 amplification	Detected	N/A	N/A
EZH2 amplification	Detected	N/A	N/A
FLCN F188I	Detected	N/A	N/A
IKZF1 S364W	Detected	N/A	N/A
IKZF1 amplification	Detected	N/A	N/A
INHBA amplification	Detected	N/A	N/A
INPP4B amplification	Detected	N/A	N/A
KMT2C amplification	Detected	N/A	N/A
MLL2 Q3745_H3746insQ	Detected	N/A	N/A
MSH2 L530I	Detected	N/A	N/A
PMS2 amplification	Detected	N/A	N/A
RAC1 amplification	Detected	N/A	N/A
SPTA1 R1387H	Detected	N/A	N/A
TET2 Q321del	Detected	N/A	N/A
BRCA2 A2351P	ND	Detected	N/A
ERBB2 R487G	ND	Detected	N/A
TSC1 A84T	Detected	N/A	N/A
Microsatellite stable	Detected	N/A	N/A

Notes: Note that MAF for tissue and ctDNA cannot be directly compared. For complete gene panels for tissue and ctDNA testing, please refer to Foundation Medicine technical specifications.

Abbreviations: ctDNA, circulating tumor DNA; del, deletion; EGFR, epidermal growth factor receptor; MAF, mutant allele frequency; N/A, not applicable; ND, not detected; NSCLC, non-small-cell lung cancer.