RESEARCH LETTER

Osimertinib Responses After Disease Progression in Patients Who Had Been Receiving Rociletinib

Third-generation EGFR tyrosine kinase inhibitors (TKIs) that block activating EGFR mutations and the T790M resistance mutation yield marked responses among patients with EGFR mutation–positive lung cancer and acquired resistance to initial TKIs.1,2 Osimertinib (formerly AZD9291) was recently approved by the US Food and Drug Administration, and rociletinib (formerly CO-1686) is under regulatory consideration. Little is known about using third-generation EGFR inhibitors sequentially.

Methods | This cohort includes all patients exposed to more than 1 third-generation EGFR TKI at our center. Patients were enrolled in the TIGER-X phase 1/2 trial of rociletinib (NCT01526928) and subsequently on the AURA phase 1/2 trial of osimertinib (NCT01802632).1,2 Each study required screening biopsy specimens to assess T790M status; depending on enrollment date, T790M-positive status may not have been required. We report both prospectively assessed responses, where independent target lesions were chosen for each study, and retrospective longitudinal responses, which were measured across both therapies using consistent target lesions for patients who transitioned directly from rociletinib to osimertinib. While eligibility criteria for AURA allowed prior treatment with other third-generation TKIs, the TIGER-X trial did not. This project was approved by our institutional review board (IRB). Specific written informed consent for this retrospective analysis was waived by the IRB. No financial compensation was provided to patients.

Results | We treated 9 EGFR-mutant patients with rociletinib and subsequent osimertinib (Table). Seven had documented T790M-positive status prior to treatment with rociletinib, and 8 were T790M-positive prior to treatment with osimertinib. Rociletinib was discontinued for progressive disease (PD) in all. Six transitioned directly from rociletinib to osimertinib (patients 1-6); 3 had intervening therapies. Rociletinib doses ranged from 500 to 1000 mg twice daily; 6 patients required dose reductions. Osimertinib was administered at 80 or 160 mg daily; no dose reductions were necessary.

The best responses to rociletinib in the TIGER-X trial included 2 partial responses (PRs), 3 patients with stable disease (SD), and 4 with PD; the median progression-free survival (PFS) was 75 days (95% CI, 39-149 days). The best responses to osimertinib in the AURA trial included 3 patients with PR, 4 with SD, and 2 with PD; the median PFS was 208 days (95% CI, 41-208 days). Among 6 patients who transitioned directly from rociletinib to osimertinib (patients 1-6), retrospective longitudinal response measurements show that despite acquired resistance to rociletinib, all derived clinical benefit from osimertinib with either prolonged SD or PR (Figure). Among the 4 with PD while taking rociletinib, 2 also had refractory disease to osimertinib (patients 8 and 9) and 2 had prolonged SD of 208 days and 375 days or more (patients 6 and 7, respectively).

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>Rociletinib Dose (mg BID), Initial/Final</th>
<th>Best Response to Rociletiniba</th>
<th>PFS Rociletinib, d</th>
<th>T790M Status Pre-osimertinib</th>
<th>Osimertinib Dose, mg QD</th>
<th>Best Response to Osimertinibb</th>
<th>PFS Osimertinib, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>500/375</td>
<td>~35%, PR</td>
<td>313</td>
<td>T790M+</td>
<td>160</td>
<td>~16%, SD</td>
<td>207c</td>
</tr>
<tr>
<td>2/F</td>
<td>750/250</td>
<td>~50%, PR</td>
<td>251</td>
<td>T790M+</td>
<td>160</td>
<td>~47%, PR</td>
<td>41</td>
</tr>
<tr>
<td>3/F</td>
<td>750/375</td>
<td>~25%, SD</td>
<td>149</td>
<td>T790M+</td>
<td>80</td>
<td>~35%, PR</td>
<td>334c</td>
</tr>
<tr>
<td>4/M</td>
<td>625/500</td>
<td>~11%, SD</td>
<td>75c</td>
<td>T790M+</td>
<td>160</td>
<td>~52%, PR</td>
<td>202c</td>
</tr>
<tr>
<td>5/M</td>
<td>750/500</td>
<td>~21%, SD</td>
<td>125c</td>
<td>T790 wild-typec</td>
<td>160</td>
<td>~15%, SD</td>
<td>208c</td>
</tr>
<tr>
<td>6/M</td>
<td>750/375</td>
<td>~31%, PD (new CNS lesions)</td>
<td>39c</td>
<td>T790M+</td>
<td>80</td>
<td>~29%, SD</td>
<td>375c</td>
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<tr>
<td>7/F</td>
<td>500/500</td>
<td>0%, PD (new CNS lesions)</td>
<td>39</td>
<td>T790M+</td>
<td>160</td>
<td>~3%, SD</td>
<td>208c</td>
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<tr>
<td>8/F</td>
<td>500/500</td>
<td>+41%, PD</td>
<td>28</td>
<td>T790M+</td>
<td>160</td>
<td>0%, PD (new lung nodules)</td>
<td>20</td>
</tr>
<tr>
<td>9/M</td>
<td>1000/1000</td>
<td>+30%, PD</td>
<td>NSQ</td>
<td>80</td>
<td>+7%, PD (new lung nodules)</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily; CNS, central nervous system; NSQ, insufficient material for genotyping; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; SD, stable disease; +, positive.

a Best response is measured by Response Evaluation Criteria in Solid Tumors (RECIST) as percentage of tumor shrinkage and categorized as partial response, stable disease, and progressive disease. Note that assigned target lesions may have been different across the 2 trials for each patient.

b Denotes patients who continued on therapy beyond RECIST progression for ongoing clinical benefit, as was allowed on both the TIGER-X and AURA trials.

c Denotes that progression has not yet occurred.

d Denotes a sample that had discordant T790M results—wild-type on local testing and T790M centrally at the sponsor.

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We also observed central nervous system (CNS) responses to osimertinib among 3 patients who developed new brain metastases on rociletinib (patients 1, 5, and 6). None of these CNS lesions underwent radiation.

Discussion | The clinically significant benefit from osimertinib among our patients implies that rociletinib progression may be due to incomplete target inhibition, which can be overcome by osimertinib, including within CNS metastases. Indeed, excluding 2 patients with disease that was highly refractory to both drugs, the remainder of our cohort had good outcomes on osimertinib, either PRs or stability for 7 to 12 or more months following disease progression on rociletinib.

A significant proportion of osimertinib-resistant cancers develop the C797S resistance mutation at the covalent binding site used by both drugs, but this mutation has not been identified in rociletinib resistance. Indeed, the lack of a bona fide EGFR resistance mutation post-rociletinib is reminiscent of most crizotinib-resistant ALK-rearranged cancers, which lack ALK mutations and are sensitive to the more potent ALK TKI ceritinib.

Our cohort is small, and further research is needed, including exploration of the effects of rociletinib dose and post-rociletinib T790M status. T790M persisted post-rociletinib in most of this cohort, which differs from the expected 50% rate of T790M loss because T790M positivity was typically required to enroll in the AURA trial. Nevertheless, the observation that patients whose disease progresses while taking rociletinib who maintain T790M-positive status can subsequently respond to osimertinib is immediately relevant for this patients. This cohort, taken together with recent data on acquired resistance to these drugs, suggests that osimertinib may be more potent than rociletinib at clinical doses. Further studies are needed to determine optimal sequencing of third-generation EGFR TKIs.

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Author Contributions: Dr Sequist had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Sequist, Piotrowska, Engelman.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Sequist.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Sequist, Digumarthy.

Obtained funding: Sequist.

Administrative, technical, or material support: Sequist, Engelman.

Study supervision: Sequist, Engelman.

Conflict of Interest Disclosures: Dr Sequist reports consulting relationships with Clovis Oncology, AstraZeneca, Boehringer-Ingelheim, Merrimack Pharmaceuticals, Novartis, Taiho, and Ariad. Dr Piotrowska reports a consulting relationship with Clovis Oncology. Dr Heist reports consulting relationships with Boehringer-Ingelheim and research funding from GSK, Sanofi, AbbVie, Novartis, Roche, Incyte, Celgene, Mirati, Peregrine, Exelixis, Millenium, and Debi. Dr Shaw reports honoraria from Pfizer, Novartis, and Roche/Genentech; consulting relationships with Pfizer, Novartis, Genentech, EMD Serono, Roche, Ariad, Ignyta, Blueprint Medicines, and Daiichi Sankyo. Dr. Engelman reports a stock/ownership interest in Gatekeeper Pharmaceuticals, which is prosecuting a patent on T790M inhibitors and has licensed that IP; consulting relationships with Novartis, Sanofi, Genentech, Clovis Oncology, and AstraZeneca; and research funding from Novartis and AstraZeneca. No other disclosures are reported.

Funding/Support: The prospective clinical trials on which these patients were treated were funded by Clovis Oncology (TIGER-X) and AstraZeneca (AURA). Financial support for the research team was provided by Lungevity, Lungstrong, Targeting a Cure for Lung Cancer, Be a Piece of the Solution, and the National Cancer Institute (2R01CA137008).

Role of the Funder/Sponsor: Neither sponsor was involved in the design and conduct of this study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank our patients and the lung cancer research staff at Massachusetts General Hospital, including Lisa Stober, RN, Ally Wanat, RN, Coleen Rizzo, Linnea Fulton, Jennifer Logan, NP, Kelly Goodwin, NP, Jennifer Nunes, Allison Charles, Ben Drapkin, MD, PhD, Jennifer Temel, MD, and Mari Mino-Kenudson, MD, for their help with data collection, analysis and manuscript preparation. None of these colleagues received financial compensation for their collaboration.


Figure. Longitudinal Response for Each Patient Who Transitioned Directly From Rociletinib to Osimertinib

Tumor burden is measured via the sum of the longest diameters of all the target lesions, as per the Response Evaluation Criteria In Solid Tumors (RECIST) method. Pt indicates patient.
Prevalence of Nonrecommended Screening for Prostate Cancer and Breast Cancer in the United States: A Nationwide Survey Analysis

Existing guidelines acknowledge the risks of overdiagnosis and overtreatment associated with early detection of prostate cancer and breast cancer and recommend against screening for these tumors in individuals with limited life expectancy.\textsuperscript{1,2} The cost to the US health care system related to overdiagnosis may be as high as $1.2 billion annually.\textsuperscript{3} That finding, combined with the aging population and an expected surge of older individuals with prostate cancer and breast cancer in upcoming years,\textsuperscript{4} indicates that a contemporary nationwide and state-by-state assessment of the prevalence of nonrecommended screening for prostate cancer and breast cancer is essential and timely.

**Methods** | All individuals responding to the Behavioral Risk Factors Surveillance System survey conducted between January and December 2012 who were 65 years or older and residing in the United States or District of Columbia were included. The median combined response rate was 45.2%, comparable with that in similar surveys.\textsuperscript{5} The primary outcome was nonrecommended screening, defined as receipt of prostate-specific antigen (PSA) testing or mammography in individuals with a life expectancy of less than 10 years.\textsuperscript{6} This cutoff was chosen based on previous reports.\textsuperscript{1,2} Receipt of PSA testing was coded as performed if men answered yes to the question, “Have you ever had a PSA test?” and answered “Within the past year” to the question, “How long has it been since you had your last PSA test?” Receipt of mammography was coded as performed if women answered yes to the question, “Have you ever had a mammogram?” and “Within the past year” to the question, “How long has it been since you had your last mammogram?” Men who underwent PSA testing owing to a previous diagnosis of prostate cancer were excluded. Those previously diagnosed with breast cancer or prostate cancer were also excluded. A total of 149,514 individuals were identified (weighted n = 43,586,000).

For all point estimates, 95% CIs and \( P \) values were calculated using the Complex Samples Package for SPSS (SPSS, Inc). The prevalence of self-reported screening in the past year was estimated for 2012 and quantified for each state. With the state as the unit of analysis, Pearson correlation coefficient was used to test the association between nonrecommended screenings for prostate cancer and breast cancer. Complex sample multivariable logistic regression models assessed the odds of nonrecommended screening for prostate cancer and breast cancer.

All statistical analyses were performed using SPSS, version 21, and the R statistical package (R Foundation for Statistical Computing), with a 2-sided significance set at \( P < .05 \). Data analysis was conducted from July 27, 2014, to October 30, 2015. Henry Ford Hospital Institutional Review Board approval was waived in accordance with institutional regulation when dealing with deidentified, previously collected data.