Emerging Treatment Paradigms for EGFR-Mutant Lung Cancers Progressing on Osimertinib: A Review

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Since its approval in April 2018, osimertinib has been widely adopted as first-line therapy for patients with advanced EGFR-mutant non-small cell lung cancer (NSCLC). Understanding osimertinib resistance mechanisms and currently available treatment options are essential to selecting optimal second line therapy for patients whose disease progresses during front-line osimertinib. Using data compiled from 6 osimertinib-resistance series, we describe here the heterogeneous profile of EGFR-dependent and independent mechanisms of osimertinib treatment failure. We identified MET alterations (7%-24%), EGFR C797X (0%-29%), SCLC transformation (2%-15%), and oncogene fusions (1%-10%) as the most common mechanisms of resistance. This review provides an evidence-based, algorithmic approach to the evaluation and management of post-osimertinib progression as well as a compendium of active, enrolling clinical trials for this population.

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INTRODUCTION
Epidermal growth factor receptor (EGFR) mutations are the most common targetable driver mutations in lung cancer, found in 17%-61% of lung adenocarcinomas in various series, with the highest rates among Asian, female, and never-smoking patients.1,2 A series of landmark studies established first-generation (gefitinib, erlotinib) and second-generation (afatinib) EGFR tyrosine kinase inhibitors (TKIs) as the standard of care for newly diagnosed EGFR-mutant lung cancer on the basis of improved progression-free survival (PFS) compared with platinum-doublet chemotherapy.3-5 Recently, the third generation EGFR TKI osimertinib, originally developed to treat T790M-mediated resistance to first-generation TKIs,6 became the preferred first-line option, on the basis of findings from the randomized phase III FLAURA study7 in which osimertinib demonstrated improved PFS (median, 18.9 v 10.2 months) and overall survival (OS; median, 38.6 v 31.8 months) compared with first-generation TKIs, and improved control of CNS metastases.8,9 Because osimertinib has moved to the front-line setting, we are now increasingly faced with the challenge of selecting the next line of treatment for patients whose disease progresses on osimertinib. In this review, we summarize the current understanding of osimertinib resistance mechanisms and explore pragmatic treatment options for patients whose disease progresses on osimertinib.

EVALUATION OF PATIENTS WITH LUNG CANCER THAT PROGRESS ON OSIMERTINIB THERAPY
As described in prior reviews,10,11 acquired resistance to targeted therapies in lung cancer can present with a variety of clinical patterns, including indolent or rapid growth, oligoprogression, or widespread systemic progression. Osimertinib resistance is clinically similar; hence, we recommend thorough assessment of clinical symptoms and complete imaging of the chest, abdomen, pelvis, and CNS to fully evaluate the extent of osimertinib progression (Fig 1).

Slow, asymptomatic progression often does not require an immediate treatment change and many patients can safely continue osimertinib beyond initial radiographic progression. Although prospective data for postprogression osimertinib are limited, we can extrapolate from data supporting treatment beyond progression with first- and second-generation EGFR TKIs.12,13 Patients treated beyond progression should be monitored closely for new disease-related symptoms or more rapid or bulky tumor growth, which should prompt a change in treatment.

Adding locally ablative therapy to osimertinib can be considered for patients with oligoprogression. Findings from a study of 72 patients with EGFR-mutant non–small-cell lung cancer (NSCLC) that progressed on later-line osimertinib suggested a significant improvement in median OS (6.1 to 11.2 months; P = .02) with locally ablative therapy, recapitulating
data reported with other TKIs.\textsuperscript{14,15} Although this practice is generally well tolerated and may improve outcomes, selection bias could confound the degree of reported benefit, because patients with rapidly progressing disease are typically transitioned to next-line systemic therapy.

**EVALUATION FOR RESISTANCE MECHANISMS TO OSIMERTINIB**

When a change in systemic therapy is needed, treatment selection should be guided by the molecular mechanisms driving resistance whenever possible. Repeating a tissue biopsy remains the gold standard for assessment of osimertinib resistance mechanisms. To capture all potentially targetable osimertinib resistance mechanisms (discussed in detail in the next section), we recommend submitting tissue for histologic assessment, DNA next-generation sequencing (NGS), and an RNA-based fusion panel.\textit{MET} fluorescence in situ hybridization (FISH) is also recommended if NGS does not specifically assess for gene copy number gain.

If the sites of progressive disease cannot be safely accessed for tissue biopsy, circulating tumor DNA (ctDNA) analysis (also known as liquid biopsy) can be considered as a surrogate, keeping in mind several key limitations of this methodology. First, it is essential to acknowledge that not all cancers “shed” sufficient DNA to be detected by current ctDNA assays, sometimes limiting the sensitivity of this approach.\textsuperscript{16} Second, histologic transformations cannot be detected in liquid biopsy specimens, including small-cell or squamous cell transformation, which are important resistance mechanisms to osimertinib.\textsuperscript{17} Finally, it is essential to understand the specific characteristics of the ctDNA test used. In particular, gene amplifications and acquired oncogene fusions are not always reliably captured by current ctDNA assays. If ctDNA does not identify the founder \textit{EGFR} mutation or any resistance mechanisms, tissue biopsy should be reconsidered.

**Reported Mechanisms of Resistance to Osimertinib**

Understanding mechanisms of acquired resistance to osimertinib and other third-generation EGFR inhibitors has been an area of active investigation since these drugs first
TABLE 1. Reported Mechanisms of Resistance to Osimertinib Arranged by Series

<table>
<thead>
<tr>
<th>Mechanism of Resistance</th>
<th>Piotrowska&lt;sup&gt;20&lt;/sup&gt; (n = 41)</th>
<th>Oxnard&lt;sup&gt;21&lt;/sup&gt; (n = 41)</th>
<th>Le&lt;sup&gt;15&lt;/sup&gt; (n = 42)</th>
<th>Papadimitrakopoulou&lt;sup&gt;22&lt;/sup&gt; (n = 73)</th>
<th>Ramalingam&lt;sup&gt;23&lt;/sup&gt; (n = 91)</th>
<th>Schoenfeld&lt;sup&gt;17&lt;/sup&gt; (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients who received osimertinib</td>
<td>3L (n = 24)</td>
<td>2L (n = 41)</td>
<td>1L (n = 6)</td>
<td>2L (n = 73; AURA3 progressors)</td>
<td>1L (n = 91; FLAURA progressors)</td>
<td>1L (n = 27)</td>
</tr>
<tr>
<td>Specimen</td>
<td>Tissue and/or plasma</td>
<td>Tissue and/or plasma</td>
<td>Plasma only</td>
<td>Plasma only</td>
<td>Tissue only</td>
<td>Tissue only</td>
</tr>
<tr>
<td>T790M lost, %</td>
<td>66</td>
<td>68</td>
<td>53</td>
<td>49</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>MET alteration, %</td>
<td>24</td>
<td>10</td>
<td>14</td>
<td>19</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>C797X, %</td>
<td>29</td>
<td>22</td>
<td>21</td>
<td>15</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>SCLC, %</td>
<td>6</td>
<td>15</td>
<td>2</td>
<td>N/R (ctDNA)</td>
<td>N/R (ctDNA)</td>
<td>4</td>
</tr>
<tr>
<td>Fusions detected in each series, %&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

Abbreviations: 1L, 2L, 3L, first, second, and third line of therapy, respectively; ctDNA, circulating tumor DNA; N/A, not applicable; N/R, not reported.

*pSpecific fusions detected in each series are indicated in the final row; other key findings of each study are provided in Appendix Table A1.

entered the clinic in 2013.<sup>18,19</sup> Because of the historical sequence of osimertinib approvals (initially as a second-line therapy guided by T790M status and, 2 years later, as an up-front treatment), the majority of osimertinib-resistant series published to date have focused primarily on patients treated in the second- or later-line setting.<sup>15,20-22</sup> Initial reports of resistance to first-line osimertinib are now emerging<sup>17,23</sup> and appear to be generally consistent, though more time is needed before this can be stated with confidence. Although an extensive list of potential osimertinib resistance mechanisms has been identified (Appendix Table A1; online only), in this review, we focus our discussion on the most frequent and clinically actionable mechanisms (Table 1; Fig 2).

The 6 largest series of osimertinib-resistant cases to date examined mechanisms of resistance using paired tissue and/or liquid biopsy specimens.<sup>15,17,20-23</sup> Although these studies are the primary focus of this discussion, several key limitations must be acknowledged. These series are limited in size, many represent single-institutional cohorts, and some, particularly those examining first-line osimertinib resistance, may be biased toward patients with early disease progression. Longer follow-up and prospective, multi-institutional studies, such as the ongoing ELIOS trial (ClinicalTrials.gov identifier: NCT03239340),<sup>24</sup> will be required to gain a more complete picture of osimertinib resistance.

Similar to acquired resistance to prior EGFR TKIs, resistance to osimertinib can be broadly categorized as on-target resistance (ie, alterations or mutations in EGFR), upregulation of bypass signaling pathways, and histologic transformations. Although this review is limited to the most common, well-characterized, and potentially actionable resistance mechanisms, many other putative mechanisms have also been identified. These include acquired mutations in the RAS-MAPK signaling pathway and cell-cycle genes,<sup>15,23</sup> genomic instability,<sup>25</sup> transcriptional reprogramming,<sup>26</sup> epigenetic changes,<sup>27</sup> and epithelial-to-mesenchymal transition among others (Appendix Table A1).<sup>28</sup> These alterations may be critical to understanding the complex biology of osimertinib treatment failure and remain an area of active investigation, but their therapeutic implications have not yet been defined.

We have historically considered resistance mechanisms to be mutually exclusive, but recent studies suggest resistant tumors can display significant heterogeneity.<sup>29,30</sup> Indeed, a key limitation of tissue biopsies is that they sample only a single site of disease and thus may underestimate cancer heterogeneity. A liquid biopsy specimen, on the other hand, can be used to detect ctDNA shed from multiple sites of disease and can potentially identify multiple putative resistance mechanisms from separate but coexistent tumoral subclones.<sup>29</sup> In the clinic, this scenario poses a challenge because it is difficult to discern which subclone is the dominant driver of resistance and should be selected as the therapeutic target. For patients with multiple resistance mechanisms identified, the allelic fraction may provide some insight into the relative abundance of each subclone, but in many such cases, a nontargeted treatment strategy such as chemotherapy may be the best therapeutic...
approach. Some data suggest the presence of co-occurring putative resistance mechanisms in a progression biopsy specimen may have negative prognostic value and may predict inferior response to the actionable alteration.

**Acquired Resistance Mutations in EGFR**

Point mutations of the cysteine residue at position 797 in EGFR were predicted to drive resistance to osimertinib and other third-generation EGFR inhibitors in preclinical models, and were one of the earliest resistance mechanisms identified in patients with progressing disease. C797 is the covalent binding site for irreversible TKIs such as osimertinib and afatinib, and acquired mutations at this residue interfere with drug-protein binding. The incidence of EGFR C797X mutations is as high as 28% post-osimertinib therapy in some series, but notably lower (7%) within the plasma samples from the first-line FLAURA trial. Likewise, Schoenfeld et al did not observe any C797X mutations in their series of tissue biopsy specimens after first-line osimertinib, and on-target resistance was rare. This could be related to the relatively short follow-up in their study (median time on first-line osimertinib, 13.6 months), creating a biased sample overrepresenting early progressors. The on-target resistance mechanism T790M is more common among those with longer time to resistance while being treated with first-generation EGFR TKIs. Hence, the frequency of on-target resistance mechanisms including C797X mutations may increase with longer follow-up, though it is also possible that the biology of cancers treated with osimertinib as their initial TKI may be distinct from those treated in later lines of therapy.

Although optimal strategies for targeting C797S have not yet been defined, multiple potential therapies have emerged. Recently, responses in C797S-positive patients have been reported across a variety of phase I studies, though these results are limited by small numbers and should be interpreted with caution. Seven of 21 patients with EGFR C797S responded to the bispecific EGFR/MET antibody JNJ-61186372 (often abbreviated JNJ-372) in a phase I study. In another phase I trial, osimertinib and necitumumab (an EGFR monoclonal antibody) led to 2 responses among 4 C797S-positive patients. Finally, U3-1402, a novel antibody-drug conjugate targeting HER3, induced partial responses in 2 of 3 patients with C797S in an early report. All 3 approaches are being explored further in ongoing clinical trials, which should be considered for C797S-positive patients (Table 2). In addition, the multiarm ORCHARD study will investigate the efficacy of combined gefitinib and osimertinib in patients in whom the C797S mutation develops after first-line osimertinib.

Several other strategies have not yet reached the clinic but may be considerations in the future for C797S. Preclinical studies and a case report have shown the combination of the ALK/EGFR TKI brigatinib and an anti-EGFR antibody (cetuximab or panitumumab) inhibits -mutant cell lines expressing both T790M and C797S. Allosteric EGFR inhibitors (meaning they bind EGFR at a site other than the tyrosine kinase domain) have shown activity against C797S triple mutants in preclinical models, and additional preclinical data suggest these drugs may have synergy with osimertinib. A future phase I/II trial of the fourth-generation EGFR inhibitor BBT-176 was also recently
announced. Currently, our approach to patients with \( EGFR \) C797X mutations is to consider clinical trials such as JNJ-372, osimertinib/necitumumab, U3-1402, ORCHARD, or others. If patients cannot access a clinical trial, we generally use standard chemotherapy.

Other less-common \( EGFR \) point mutations associated with osimertinib resistance include G724S, L792H, and G769R. To our knowledge, there are no published reports of targeted treatment strategies to address these tertiary \( EGFR \) mutations, though preclinical studies suggest afatinib may have some activity against G724S mutations.

Finally, \( EGFR \) amplification is also a common finding in osimertinib resistance, though its clinical significance remains unknown. In ORCHARD, patients with acquired \( EGFR \) amplification and no other actionable targets will be enrolled in a biomarker-matched arm of osimertinib and necitumumab to evaluate the role of targeting this finding. Other treatment strategies that can be considered for

### TABLE 2. Current, Open Studies for Patients Whose Cancer Is Progressing on Osimertinib

<table>
<thead>
<tr>
<th>Category</th>
<th>Study Name/Sponsor</th>
<th>NCT Identifier*</th>
<th>Phase</th>
<th>Treatment Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker driven</td>
<td>ORCHARD/AstraZeneca</td>
<td>NCT03944772</td>
<td>II</td>
<td>MET amp/mut → osimertinib + savolitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( EGF ) C797X → osimertinib + gefitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( EGF ) amp → osimertinib + necitumumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No biomarker → various</td>
</tr>
<tr>
<td></td>
<td>SAVANNAH/AstraZeneca</td>
<td>NCT03778229</td>
<td>II</td>
<td>Osimertinib + savolitinib (MET TKI)</td>
</tr>
<tr>
<td></td>
<td>EMD Serono</td>
<td>NCT03940703</td>
<td>II</td>
<td>Osimertinib + tepotinib (MET TKI)</td>
</tr>
<tr>
<td></td>
<td>Netherlands Cancer Institute/Roche/AstraZeneca</td>
<td>NCT03784599</td>
<td>II</td>
<td>Osimertinib + TDM-1 (trastuzumab-entansine)</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Checkmate 722/Bristol Myers Squibb</td>
<td>NCT02864251</td>
<td>III</td>
<td>Platinum/pemetrexed ± nivolumab</td>
</tr>
<tr>
<td></td>
<td>KEYNOTE-789/Merck</td>
<td>NCT03515837</td>
<td>III</td>
<td>Platinum/pemetrexed ± pembrolizum</td>
</tr>
<tr>
<td></td>
<td>MGH/Bristol Myers Squibb</td>
<td>NCT03256136</td>
<td>II</td>
<td>Platinum/pemetrexed + nivolumab/hippurumab/nivolumab</td>
</tr>
<tr>
<td>Other</td>
<td>Fox Chase/NCCN</td>
<td>NCT03786692</td>
<td>II</td>
<td>Carboplatin/pemetrexed/bevacizum + atezolizumab</td>
</tr>
<tr>
<td></td>
<td>Duke University</td>
<td>NCT04099836</td>
<td>II</td>
<td>Atezolizumab + bevacizumab</td>
</tr>
<tr>
<td></td>
<td>MedImmune</td>
<td>NCT03381274</td>
<td>Ib/Ii</td>
<td>Arm A: osimertinib + oleclumab (MEDI9447; CD73 monoclonal antibody)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arm B: oleclumab + AZD4635 (A2aR antagonist)</td>
</tr>
<tr>
<td></td>
<td>NCI[29]</td>
<td>NCT02496663</td>
<td>I</td>
<td>Osimertinib + necitumumab</td>
</tr>
<tr>
<td></td>
<td>MGH/DFCI; Tesaro</td>
<td>NCT03891615</td>
<td>I</td>
<td>Osimertinib + niraparib (PARP inhibitor)</td>
</tr>
<tr>
<td></td>
<td>Ascentage Pharma</td>
<td>NCT04001777</td>
<td>Ib</td>
<td>Osimertinib + APG-1252 (Bcl-2 inhibitor)</td>
</tr>
<tr>
<td></td>
<td>EATON/University of Cologne</td>
<td>NCT03516214</td>
<td>I</td>
<td>EGF816 (third-generation ( EGF ) inhibitor) + trametinib (MEK inhibitor)</td>
</tr>
<tr>
<td></td>
<td>G1 Therapeutics</td>
<td>NCT03455829</td>
<td>Ib/Ii</td>
<td>Osimertinib + G1T38 (CDK4/6 inhibitor)</td>
</tr>
<tr>
<td></td>
<td>JACKPOT1/Dizal (Jiangsu)</td>
<td>NCT03450330</td>
<td>I/Ii</td>
<td>AZD4205 (JAK inhibitor) + osimertinib</td>
</tr>
<tr>
<td></td>
<td>NCI</td>
<td>NCT02759835</td>
<td>I</td>
<td>Osimertinib + locally ablative therapy</td>
</tr>
<tr>
<td></td>
<td>NCI</td>
<td>NCT02520778</td>
<td>Ib</td>
<td>Osimertinib + navitoclax (Bcl-2 inhibitor)</td>
</tr>
<tr>
<td></td>
<td>Janssen[21]</td>
<td>NCT02609776</td>
<td>I</td>
<td>JNJ-61186372 (bisppecific ( EGF ) and ( cMET ) antibody); JNJ-372 + lazertinib (third-generation ( EGF ) TKI)</td>
</tr>
<tr>
<td></td>
<td>AbbVie</td>
<td>NCT02099068</td>
<td>I/Ib</td>
<td>Osimertinib + telsituzumab vedotin (c( MET ) ADC)</td>
</tr>
<tr>
<td></td>
<td>Daiichi Sankyo[21]</td>
<td>NCT03260491</td>
<td>I</td>
<td>U3-1402 (HER3 ADC)</td>
</tr>
<tr>
<td></td>
<td>Vanderbilt-Ingram Cancer Center</td>
<td>NCT03054038</td>
<td>I</td>
<td>Aflatinib + necitumumab</td>
</tr>
<tr>
<td></td>
<td>University of California, San Francisco/ Takeda</td>
<td>NCT04085315</td>
<td>I/Ib</td>
<td>Osimertinib + alisertib (aurora A kinase inhibitor)</td>
</tr>
<tr>
<td></td>
<td>Advaxis</td>
<td>NCT03847519</td>
<td>I/Ii</td>
<td>ADXS-503 (novel antigen delivery construct) ± pembrolizumab</td>
</tr>
</tbody>
</table>

Abbreviations: ADC, antibody-drug conjugate; amp, amplification; DFCI, Dana-Farber Cancer Institute; MGH, Massachusetts General Hospital; mut, mutation; NCI, National Cancer Institute; NCCN, National Comprehensive Cancer Network; TKI, tyrosine kinase inhibitor.

*All studies are active and enrolling.*
patients with EGFR amplification include JNJ-372 and a clinical trial of afatinib/cetuximab (Table 2).

**Acquired MET Amplification**

The most common bypass pathway seen in patients with osimertinib-resistant cancer is cMET amplification. Although this finding was rare (approximately 5%) in patients whose disease progressed on first- or second-generation TKIs,50-54 MET copy number alterations are seen in 10%-24% of patients with disease progressing on osimertinib.15,17,20-23 Assessment for MET amplification by NGS or FISH should be performed on all biopsies performed to determine osimertinib resistance to identify patients who may benefit from combined MET and EGFR inhibition.

The TATTON study, which investigated the combination of osimertinib and the MET TKI savolitinib, represents the largest current data set for this strategy. Patients were selected on the basis of MET-amplification, defined as either MET gene copy number $\geq 5$ or MET:CEP7 $\geq 2.2$. Among 48 patients with MET-amplified disease progression on a third-generation TKI, the objective response rate to osimertinib/savolitinib was 30%, with a median duration of response of 7.9 months.49 The combination is under additional investigation in the SAVANNAH (Table 2) and ORCHARD (Table 2) studies.

Similarly, responses to and tolerance of osimertinib and crizotinib have also been reported in individual patients with acquired MET amplification or MET exon 14 skipping mutations after osimertinib therapy,50-54 and off-label use of this combination can be considered for patients unable to access a MET/EGFR TKI trial. Finally, responses among MET-amplified patients were also seen with JNJ-372, the bispecific MET/EGFR antibody discussed in the previous section (Table 2).34 Importantly, it remains to be seen whether an antibody-based approach would be effective after disease progression in patients with MET amplification receiving MET/EGFR TKI combinations.

**Other Bypass Pathways: Fusions**

Several groups have identified acquired fusions in RET, ALK, BRAF, FGFR3, and other oncogenes upon disease progression while receiving osimertinib therapy. Although rare, such fusion events appear to activate bypass signaling pathways and drive resistance. Like the MET bypass pathway, combining EGFR inhibition with an inhibitor of the altered fusion protein is an emerging treatment strategy, and several case reports have demonstrated efficacy across a variety of fusions.

We found that engineering a CCDC6-RET fusion into an EGFR-mutant cell line resulted in resistance to EGFR TKI monotherapy but sensitivity to combined RET/EGFR inhibition.20 Two patients (1 acquired CCDC6-RET after second-line osimertinib and the other acquired NCOA4-RET after afatinib therapy) were then treated with osimertinib and pralsetinib (BLU-667), and both had confirmed partial responses. A third patient developed CCDC6-RET fusion after afatinib and demonstrated disease control with osimertinib and caboazinib therapies. Similarly, Lu et al found acquired RET rearrangements in 6 of 57 patients (11%) whose disease progressed on osimertinib. One of 3 patients treated with osimertinib and caboazinib in this series derived benefit.

Offin et al56 reported 2 cases of acquired EML4-ALK fusion after osimertinib (detected by ctDNA and tissue-based FISH), both of which benefitted clinically from combination EGFR and ALK TKIs (alectinib or crizotinib). Zhou et al57 reported an acquired STRN-ALK fusion detected by NGS after osimertinib therapy, which responded to gefitinib plus crizotinib. Similarly, an acquired G0PC-ROS1 rearrangement was described in a patient with EGFR exon 19 deletion whose disease progressed on osimertinib therapy and subsequently had a partial response to osimertinib plus crizotinib.58 Finally, we reported a response to osimertinib and the MEK inhibitor trametinib in a patient with an acquired AGK-BRAF fusion after osimertinib therapy.59 In this case, the osimertinib/trametinib combination had significant toxicity and the patient ultimately discontinued treatment because of a radiographically detected colonic microperforation, which emphasizes that not all TKI combinations will be tolerable and should ideally be assessed in prospective clinical trials.

Although clinical experience in treating all these bypass track mutations remains anecdotal, a clear pattern is emerging that suggests acquired fusions are a recurrent and targetable mechanism of resistance to osimertinib and should be included in molecular analyses at progression. Importantly, NGS may not always detect fusions, and RNA-based fusion panels should be performed. Going forward, multiarm trials such as ORCHARD may present an opportunity to prospectively validate both safety and efficacy of TKI combinations for these rare but recurrent fusions.

**Histologic Transformations**

Histologic transformations have been reported in up to 15% of patients with disease progressing on first-line osimertinib17 and highlight the critical role of tissue biopsy at progression. Small-cell transformation has been well described in EGFR-mutant cancers and occurs in approximately 3%-5% of patients whose cancer progresses on first- and second-generation EGFR TKIs.28,48 Most published series suggest SCLC transformation occurs at a similar frequency among patients whose disease progresses on osimertinib.20,21 Similar to de novo SCLC, SCLC transformations among EGFR-mutant NSCLC have been strongly associated with loss of RB1- and TP53-mediated tumor suppression and loss of EGFR signaling.60,61 It is important to note that the mere presence of RB1 and TP53 mutations in an EGFR-mutant cancer does not necessarily indicate that a SCLC transformation has occurred, but it is
clear that EGFR-mutant NSCLCs with baseline TP53 and/or RFI comutations are at increased risk of SCLC transformation during their disease course. Because this high-risk group of patients often has detectable TP53 and/or RFI mutations even before SCLC transformation has occurred, plasma ctDNA testing cannot be used to screen for transformation, and tissue biopsies must be performed. In practice, detection of RFI and TP53 mutations via ctDNA should raise the index of suspicion of potential SCLC transformation and tissue biopsy should be strongly considered, particularly in patients with rapid disease progression.

When SCLC transformation occurs, we recommend treatment with platinum/etoposide chemotherapy, as in de novo SCLC. In a retrospective series of 58 EGFR-mutant, SCLC-transformed cancers, 54% of patients had a clinical response to platinum/etoposide. Median survival from the time of transformation was 10.9 months (95% CI, 8.0 to 13.7 months). Notably, none of 17 patients treated with immunotherapy (nivolumab monotherapy or combination ipilimumab/nivolumab) responded, but due to the timing of the patients studied, none received immunotherapy with concurrent chemotherapy (as in IMpower133 and CASPIAN). The role of chemoinmunotherapy in EGFR-positive patients with SCLC transformation is unknown at this time.

Another question for patients with SCLC-transformed EGFR is whether to continue osimertinib (or another EGFR TKI) with or after chemotherapy. Although the transformed SCLC clone is likely insensitive to EGFR inhibition, resistant subclones can be heterogenous and adenocarcinoma can re-emerge after SCLC transformation, providing a clinical rationale to consider continuing the TKI with or after platinum/etoposide. Importantly, when disease in patients with SCLC transformation progresses again in the future, it is optimal (if feasible) to repeat tissue sampling to determine which clone is driving progression and guide subsequent therapy.

Transformations from adenocarcinoma to squamous cell carcinoma have also been described among patients with cancer that progressed on osimertinib and other EGFR TKIs. This phenomenon and its implications for subsequent therapy are under study, but histology should likely be taken into consideration when selecting chemotherapy for these patients.

**POSTPROGRESSION CHEMOTHERAPY**

We recommend consideration of clinical trials, if possible, for patients who do not have a targetable resistance mechanism identified when their cancer progresses on osimertinib. For example, the ORCHARD trial has both biomarker-matched and nonmatched treatment arms for patients whose disease progresses on first-line osimertinib, and will provide important data regarding optimal second-line treatment strategies. For those who cannot access clinical trials, histology-driven, platinum-based chemotherapy remains the standard of care.

There is a paucity of data about whether to continue osimertinib when initiating chemotherapy after front-line osimertinib. The phase III IMPRESS study assessed the benefit of continuing gefitinib or placebo in combination with second-line, platinum-based chemotherapy and showed no improvement in PFS or OS. However, results from 3 more recent phase III studies have suggested there could be significant OS benefits to combining chemotherapy with gefitinib in the front-line setting. While we await data from the randomized FLAURA2 study (ClinicalTrials.gov identifier: NCT04035486), which will compare first-line osimertinib with osimertinib plus chemotherapy, and the randomized COMPEL study (ClinicalTrials.gov identifier pending) of continued osimertinib or placebo with chemotherapy after front-line osimertinib (with CNS-specific outcomes), it remains unclear if the results of IMPRESS should be extrapolated to patients with disease that progresses on front-line osimertinib. In contrast to gefitinib in the IMPRESS study, in our experience, the excellent CNS penetration of osimertinib frequently results in durable control of brain metastases, even in the face of systemic progression. Thus, particularly for patients with baseline brain metastases that remain controlled on osimertinib at the time of systemic progression, we consider continuing osimertinib with second-line, platinum-based chemotherapy. Retrospective data suggest osimertinib can be safely combined with carboplatin/ pemetrexed and many other chemotherapy regimens.

**IMMUNOTHERAPY**

PD(L1) inhibitor (IO) monotherapy has little activity in EGFR-mutant NSCLC. Although our experience suggests outcomes appear equally poor when IO is used in later lines of treatment, with response rates of < 10% and median duration of treatment < 1 month regardless of PD-L1 status, recent data from the IMMUNOTARGET registry suggest higher PD-L1 may predict benefit from IO in EGFR-mutant NSCLC. However, on the basis of the totality of current data and our local experience, we rarely use IO monotherapy for patients with EGFR mutation, preferring instead clinical trials and/or chemotherapy whenever possible, particularly for patients with PD-L1–low tumors (the majority).

For patients with an EGFR mutation whose disease progresses on osimertinib and who move to second-line chemotherapy, the role of combination chemoinmunotherapy is not well understood, because patients with EGFR mutation were excluded entirely from the KEYNOTE-189 study and composed only a small portion of patients in the IMpower150 and IMpower130 studies. IMpower150, which demonstrated both PFS and OS benefits when adding atezolizumab to carboplatin/paclitaxel and bevacizumab (ABC), is the
only chemoimmunotherapy trial to demonstrate a benefit thus far in patients with EGFR mutation, though only 59 patients with known EGFR-sensitizing mutations were included among 802 patients in the study. Furthermore, the benefit of adding atezolizumab for treatment of cancer in patients with EGFR mutation was only seen in the 4-drug ABCP arm of IMpower150 and not in the arm that compared carboplatin, paclitaxel, and atezolizumab with chemotherapy alone nor in the IMpower130 trial, which assessed carboplatin and nab-paclitaxel with or without atezolizumab. These results raise the possibility that both a PD-L1 inhibitor and antiangiogenesis agent are required to improve on chemotherapy for patients with EGFR-positive disease. Additional studies are ongoing to determine the role of antiangiogenesis agents and immunotherapy together with chemotherapy in EGFR-positive disease (Table 2).

Notably, emerging data suggest toxicities may be more frequent when patients receive an EGFR TKI after immunotherapy. Although prior studies have shown rates of pneumonitis as high as 38% in patients who received concurrent osimertinib and durvalumab, sequential TKI use after immunotherapy also appears to increase this risk. A recent retrospective series suggested up to 24% incidence of severe, immune-related adverse events, particularly pneumonitis, when patients initiated osimertinib within 3 months of receiving treatment with an immune checkpoint inhibitor. Thus, osimertinib should be used with great caution in patients recently treated with immunotherapy.

**PATIENTS WITH BRAIN METASTASES**

One final group that bears special consideration is the significant subset of patients with EGFR-mutant lung cancers with CNS metastases. CNS disease is common in this population; approximately 20% of patients in the FLAURA trial had CNS metastases at presentation, and osimertinib’s strong CNS penetration has likely contributed to the drug’s success. Among patients with brain metastases in FLAURA, osimertinib improved PFS to 15.2 months (95% CI, 12.1 to 21.4), compared with 9.6 months (95% CI, 7.0 to 12.4) on the first-generation TKIs. The BLOOM trial also showed that osimertinib is active in patients with leptomeningeal disease (LMD). Patients with LMD received osimertinib 160 mg once daily, and 23 of 32 patients had radiographic disease stabilization or improvement on 12-week imaging, and 7 of 8 patients had clinical improvement in symptomatic LMD at 12-week neurologic assessment.

In patients with CNS progression on osimertinib, full restaging is essential to confirm whether concurrent systemic progression is present. If extracranial progression is confirmed, tissue and/or liquid biopsy should be pursued to guide further therapy, as outlined earlier in this review. For patients with CNS-only progression, liquid biopsy specimens are often unrevealing and brain biopsy may be a high-risk procedure. Lumbar puncture for CSF sampling is typically considered only for patients with symptoms concerning for leptomeningeal involvement, and even in these cases, there are few data about the accuracy of molecular analyses of CSF. Unfortunately, even if actionable alterations are detected, patients with active CNS metastases are often ineligible for clinical trials, potentially limiting opportunities for targeted therapy.

Although the BLOOM trial used osimertinib at 160 mg daily, rather than the standard dose of 80 mg, patients in the trial were osimertinib naive and the benefit may have been related to the introduction of osimertinib rather than the higher dose. For patients who have been compliant with osimertinib 80 mg, there is a lack of data about whether dose escalation to 160 mg at the time of CNS progression would be sufficient to induce CNS response. If a dose-escalation strategy is pursued, we recommend careful monitoring for neurologic symptoms and short-interval imaging. More commonly, we consider local ablative therapy (radiation and/or surgery) with continued osimertinib for oligoprogression. If multifocal or rapid CNS progression is seen, we favor transitioning to an alternative systemic therapy with known intracranial penetration, if possible. Platinum doublets with known intracranial penetration, like carboplatin/pemetrexed, with or without bevacizumab are particularly attractive in this context. For patients with asymptomatic, multifocal CNS progression who would require whole-brain radiation therapy to encompass their metastases, we generally defer radiation for a short trial of change in systemic therapy to avoid the long-term cognitive toxicities of radiation in the event of rapid CNS response to the systemic therapy.

In conclusion, currently available data regarding management of patients whose cancer progresses on osimertinib are presented in this review and illustrate the heterogeneity of resistance mechanisms and the guiding concepts for clinical care. Although additional research is needed to more clearly delineate the optimal treatments for each resistance mechanism, there are a number of options already available today and this review is meant to serve as a practical guide for post-osimertinib progression.
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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Emerging Treatment Paradigms for EGFR-Mutant Lung Cancers Progressing on Osimertinib: A Review

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## TABLE A1. Other Putative Resistance Mechanisms by Osimertinib-Resistance Series

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Cases</th>
<th>Other Identified Putative Resistance Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piotrowska20 (2018)</td>
<td>(n = 41)</td>
<td>BRAF(^{\text{amp}}), CCND2(^{\text{amp}}), CCNE1(^{\text{m/amp}}), CCND3(^{\text{amp}}), CKD4/6(^{\text{amp}}), DAXX(^{\text{amp}}), EGFR(^{\text{amp}}), ERBB2(^{\text{amp}}), FGFR1(^{\text{amp}}), KRAS(^{\text{amp}}), MDM2(^{\text{amp}}), MYC(^{\text{amp}}), NKX2-1(^{\text{m/amp}}), APC(^{\text{m}}), AR(^{\text{m}}), AR1A(^{\text{m}}), ATRX(^{\text{m}}), BRCA1/2(^{\text{m}}), CIC(^{\text{m}}), CDKN2A(^{\text{m}}), CLKN2(^{\text{m}}), CTNNB1(^{\text{m}}), DAXX(^{\text{m}}), DDX3X(^{\text{m}}), EZH2(^{\text{m}}), FBXW7(^{\text{m}}), FGFR2(^{\text{m}}), GNAS(^{\text{m}}), HNF1A(^{\text{m}}), JAK2(^{\text{m}}), MAP3K1(^{\text{m}}), MSH6(^{\text{m}}), MTOR(^{\text{m}})</td>
</tr>
<tr>
<td>Oxnard21 (2018)</td>
<td>(n = 41)</td>
<td>TP53(^{\text{m}}), RB1(^{\text{m}}), PIK3CA(^{\text{m}}), RAF(^{\text{m}}), BRAF(^{\text{f}}), FGFR3(^{\text{m}}), KRAS(^{\text{m}}), SCLC(^{\text{t}})</td>
</tr>
<tr>
<td>Le15 (2018)</td>
<td>(n = 42)</td>
<td>EGFR(^{\text{amp}}), ERRB2(^{\text{amp}}), TP53(^{\text{m}}), FGFR1(^{\text{m/amp}}), KRAS(^{\text{m/amp}}) or BRAF(^{\text{m/amp}}), PIK3CA(^{\text{m/amp}}), BRCA(^{\text{m}}), SMARCB1/SMAD4(^{\text{m}}), ARID1A/B(^{\text{m}}), NOTCH1/2(^{\text{m}}), MDM2(^{\text{m}}), MYC(^{\text{m}}), JAK2(^{\text{m}}), GNAS(^{\text{m}}), CTNNB1(^{\text{m}}), APC(^{\text{m}}), ATM(^{\text{m}}), cell-cycle gene alterations (CDK4/6(^{\text{m/amp}}), CCND/E1(^{\text{m/amp}}), CDKN2A(^{\text{m}}))</td>
</tr>
<tr>
<td>Papadimitrakopoulou22 (2018)</td>
<td>(n = 73)</td>
<td>HER2(^{\text{m}}), PIK3CA(^{\text{m}}), RAF(^{\text{m}}), KRAS(^{\text{m}}), SCLC(^{\text{t}}), cell-cycle gene alterations</td>
</tr>
<tr>
<td>Ramalingam23 (2018)</td>
<td>(n = 91)</td>
<td>HER2(^{\text{m}}), HER2(^{\text{m}}), PIK3CA(^{\text{m}}), RAS(^{\text{m}}), RAF(^{\text{m}}), KRAS(^{\text{m}}), CCND(^{\text{amp}}), CCNE1(^{\text{amp}}), CDK4/6(^{\text{amp}})</td>
</tr>
<tr>
<td>Schoenfeld17 (2019)</td>
<td>(n = 71)</td>
<td>EGFR(^{\text{m}}), HER2(^{\text{amp}}), KRAS(^{\text{m}}), BRAF(^{\text{f}}), HER2(^{\text{m}}), BRAF(^{\text{f}}), SCC(^{\text{c}}), SCLC(^{\text{t}})</td>
</tr>
</tbody>
</table>

Abbreviations: \(^{\text{amp}}\), amplification; \(^{\text{f}}\), fusion; \(^{\text{m}}\), mutation; \(^{\text{m/amp}}\), mutation and/or amplification; \(^{\text{t}}\), transformation.