Editorial

Respecting your elders: osimertinib demonstrates preferential activity in elderly patients with T790M positive non-small cell lung cancers

Hiromichi Ebi[1,2,3], Sosipatros Boikos[4], Anthony C. Faber[5]

[1]Division of Molecular Therapeutics, Aichi Cancer Center Research Institute, Nagoya, Japan; [2]Precision Medicine Center, Aichi Cancer Center, Nagoya, Japan; [3]Division of Advanced Cancer Therapeutics, Nagoya University Graduate School of Medicine, Nagoya, Japan; [4]Department of Medicine, VCU School of Medicine, Richmond, VA, USA; [5]Philips Institute for Oral Health Research, VCU School of Dentistry and Massey Cancer Center, Richmond, VA, USA

Correspondence to: Anthony C. Faber. Philips Institute for Oral Health Research, VCU School of Dentistry and Massey Cancer Center, Richmond, VA 23298, USA. Email: acfaber@vcu.edu.

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Ever since Lynch *et al*. identified that some non-small cell lung cancers (NSCLCs) responded to the EGFR inhibitors gefitinib and erlotinib, and this could be correlated to activating mutations in EGFR, one of the great success stories in the era of targeted therapies was born. However, enthusiasm was disrupted by the realization that patients invariably become resistant to these drugs, which are reversible small-molecule competitive inhibitors of ATP to EGFR. The discovery that *T790M* mutations were often associated with acquired resistance to gefitinib and erlotinib, and did so by preventing their binding to EGFR, led to a search for next generation inhibitors that could overcome this limitation (1-4).

Osimertinib was developed by AstraZeneca as an irreversible ATP competitor for EGFR, blocking EGFR enzyme activity even when EGFR is mutated at T790M (5,6).

A key clinical trial, AURA3, demonstrated that osimertinib was superior to doublet platinum chemotherapy in advanced *EGFR* mutant NSCLC patients whom acquired the T790M mutation (7).

Even prior to the development of osimertinib, it was reported that other mutations in EGFR could alter the ability of irreversible EGFR inhibitors to block EGFR, such as mutations at residue 797 (8). Interestingly though, unlike T790M, C797S does not appear to be present in naïve *EGFR* mutant NSCLC patients (9). This is interesting as it eliminates a potential confounding factor when studying the responses of EGFR mutant *T790M* patients to osimertinib.

In this study, Kato et al. (10), in a modest number of patients with lung cancers that progressed on earlier generation EGFR inhibitors through acquisition of a *T790M* mutation, analyzed the responses of elderly patients (defined as 65 years of age or greater) to osimertinib compared to their younger counterparts. These authors report that elderly patients benefited greater both in progression-free survival (PFS) (6.4 months for elderly and 3.5 months for younger patients) and overall survival (OS) (19.4 *vs.* 5.3 months). While these data may appear surprising at first blush, these data fit with the emerging clinical evidence of an advantage of elderly patients with *T790* mutations treated with osimertinib following progression on earlier generation EGFR inhibitors. Nakao and colleagues (11) demonstrated that in 36 elderly patients (defined as 75 years of age or older) with *EGFR T790M* mutant NSCLC that progressed on first or second generation EGFR inhibitors, objective response rate (ORR) was 58.3%, which is comparable to historical responses in younger patients. Similarly, Hida and colleagues (12) demonstrated that in 19 elderly NSCLC patients, again defined as 75 years of age or older, with *T790M* mutations and that failed earlier generation EGFR inhibitor therapy, PFS was superior compared to 58 non-elderly patients with

the same tumor characteristics (T790M) and treatment history.

In addition to these studies, the efficacy demonstrated in elderly NSCLC patients was also not inferior to younger patients in the large AURA 2 study; however, this study reported similar response of the elderly and not a superior response: In the subgroup analysis of AURA2 study, the response rate for the patients older than 65 was 70% (95% CI: 60–79%), which was comparable to patients younger than 65 (RR: 71%, 95% CI: 61–79%) (13).

Over 70% of NSCLC patients are 65 and over at the time of diagnosis, making the question of how to treat elderly patients particularly relevant. These data from these three smaller studies (including this current one) demonstrating good tolerability and excellent responses (at least at the level of their younger counterparts and possibly even better) also seem particularly important in light of the overall picture: elderly patients receive chemotherapy less for metastatic NSCLC than their younger counterparts and have more toxicities with chemotherapy (14,15). In addition, adding radiotherapy to chemotherapy does not provide benefit for locally advanced NSCLC patients 70 years of age or older as it does for their younger counterparts (16). Impressively, osimertinib has demonstrated safety in large studies outside of clinical trials, across more than 3,000 patients with T790M mutant lung cancer, asserting its safety profile (17). This advantage over chemotherapy-related toxicities likely contributes to the ability of osimertinib to induce preferential activity in the elderly. In line with this, results of the AURA3 study (7) demonstrated that patients older than 65 showed greater benefit from osimertinib compared to platinum-pemetrexed chemotherapy, as the latter regimen can be particularly toxic to elderly patients (HR 0.38; 95% CI: 0.28–0.54 in patients with younger than 65, and HR:0.34; 95% CI: 0.23–0.50 in patients older than 65, respectively).

This study therefore serves to begin to answer an important question in a large patient population. Namely, elderly patients with EGFR mutant T790M NSCLCs benefit not only like their younger counterparts, but to a greater extent, while maintaining a good toxicity profile. The shortcomings of the study are a small sample size (31 patients total, 23 elderly and 8 non-elderly), which will require larger patient populations to confirm these interesting data. Also, significantly higher incidence of CNS metastasis could affect the shorter survival in younger patients demonstrated in this study.

Nonetheless, these data add to the growing understanding that osimertinib is a very effective and tolerable drug in elderly patients with *T790M EGFR* mutant NSCLC and is yet another strong piece of clinical evidence of the immense utility of targeted therapies in lung cancer, even in diverse populations of patients with varying degrees of co-morbidities.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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