Editorial Commentary

What the future holds: BBT-176, beyond third-generation EGFR tyrosine kinase inhibitors

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Lung cancer holds the record in terms of cancer-related mortality in the world; non-small cell lung cancer (NSCLC) is the most frequent subtype (1). For many years, platinum-based chemotherapy has represented the only therapeutic strategy for advanced NSCLC patients although with a poor survival benefit (2). In the last decade, some NSCLC oncogenic drivers were discovered, and consequently, new targeted drugs were developed providing an impressive amelioration of overall survival (OS) for selected patients. The epidermal growth factor receptor (EGFR) gene mutations are the most important oncogenic drivers (1). In fact, several EGFR-tyrosine kinase inhibitors (EGFR-TKIs) became standard therapies for NSCLC patients with activating EGFR gene mutations. The EGFR gene encodes for a membrane tyrosine kinase receptor whose stimulation leads to the activation of various downstream signaling pathways that regulate cellular proliferation, survival, and apoptosis (3). To be specific, EGFR exons 18 to 24 encode the tyrosine kinase domain of the receptor. The constitutive EGFR activation of the receptor is due to specific mutations to EGFR exons 18, 19, 20, and 21 leading to cell proliferation (4). Globally, EGFR mutations regard 10–15% of Caucasian and 30–50% of Asian NSCLC patients, more frequently women, non-smokers, and with adenocarcinoma histotype (5). Exon 19 deletion, and exon 21 L858R point mutation are the most common EGFR mutations corresponding to 85–90% of cases; they usually confer sensitivity to EGFR-TKIs treatment. The remaining mutations are called uncommon and include rare EGFR mutations and complex EGFR mutations, accounting for 10–15%; they have variable predictive values (6). In addition, it is not rare to find a combination of EGFR mutations (1).

All generations of EGFR-TKIs have greatly changed the prognosis of EGFR-activating mutant NSCLC patients with. Osimertinib is a third-generation EGFR inhibitor that received its first approval for NSCLC patients who progressed during treatment with first- or second-generation EGFR inhibitors because of the occurrence of EGFR T790M-mediated resistance. Nowadays, osimertinib is the first-line therapy for advanced NSCLC patients with EGFR-activating mutations following the results of the FLAURA trial that demonstrated the superiority of this drug in terms of OS compared to previous generations of EGFR-TKIs (7). Moreover, osimertinib is actually indicated in the adjuvant setting for a period of treatment of 3 years based on the favorable data of the ADAURA trial (8).

However, the clinical efficacy of osimertinib is limited due to the occurrence of acquired resistance, usually related to the development of EGFR C797S mutation [10–25% in second-line, 7% in first-line settings (1,9)]. It corresponds to a tertiary point mutation, consisting of substitution of

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the cysteine with serine within the adenosine triphosphate (ATP)-binding site. This change prevents the constitution of the covalent bond of osimertininb to mutant EGFR (1). Moreover, this mutation is responsible for cross-resistance to all other third-generation EGFR TKIs, such as narzartinib and rociletinib because of their similar binding models (10).

Several options are being evaluated to challenge the acquired resistance to osimertinib such as catalytic kinase inhibitors with enhanced coverage (for example, BBT-176) and, allosteric kinase inhibitors (for example, JBJ-09-063) (11-13). Actually, no approved targeted therapies are available after progression on a third-generation EGFR-TKI. Thus, these patients are candidates only to chemotherapy. In fact, immunotherapy did not provide important survival benefit for oncogene-addicted NSCLC. Therefore, the development of a next-generation EGFR-TKI, able to overcome C797S mutation-related resistance is an urgent need.

Lim *et al.* developed a novel oral, reversible, fourth-generation EGFR-TKI, called BBT-176, that was developed with the aim to inhibit triple-mutant EGFR L858R/T790M/C797S and 19Del/T790M/C797S. In particular, the authors employed recombinant EGFR proteins, and Ba/F3 cell lines, patient-derived cells and patient-derived xenografts expressing mutant EGFRs to evaluate, both *in vitro* and *in vivo*, the inhibitory activity and the anticancer action of BBT-176. Preclinical data from engineered Ba/F3 cells and cell-derived xenografts harboring the EGFR 19Del/T790M/C797S mutation demonstrated significant antitumor activities of BBT-176 across single-, double-, and triple-mutant models (14). These preclinical findings led to the clinical evaluation of BBT-176 (NCT04820023) as single agent for the treatment of EGFR-mutant NSCLC patients who were already treated with an EGFR-TKI or more. In this regard, the authors reported two cases of patients who obtained tumor shrinkage. Liquid biopsies were also performed for both patients to analyze circulating tumor DNA (ctDNA) and non-EGFR mechanisms of acquired resistance were not found. On these bases, it is impossible to define if BBT-176 is also active against tumors with this type of acquired resistance mechanism (14).

In addition, Lim *et al.* performed an N-ethyl-N-nitrosourea (ENU) mutagenesis screen to identify those resistance mechanisms that might reduce BBT-176 activity. ENU is a potent mutagen that induces the highest mutation frequency of any known chemical or physical agent (15). ENU mutagenesis screen is a method greatly employed for finding potential mutants of secondary resistance (16). Through this technique, the authors have previously discovered clinically relevant mutations driving resistance to EGFR, KRAS, HER2, and MET inhibitors and suggested therapeutic strategies to overcome them (17,18). However, in this experiment, they did not identify EGFR resistance mutations to BBT-176, suggesting that the resistance to this drug is not probably due to genomic point mutations in EGFR; therefore, the increased EGFR homo- or hetero dimerization might be responsible for the enhanced EGFR signaling (14). Previous preclinical data reported that cetuximab can strongly enhance EGFR-TKI activity against C797S mutants by decreasing EGFR expression or remodeling of EGFR protein conformation. On these bases, the authors also analyzed cetuximab plus BBT-176 in EGFR 19Del/T790M/C797S cell clones with resistance to BBT-176 showing a significant improvement of BBT-176 activity. However, despite the interesting results this combination was not clinically tested due to the expected overlapping toxicities. Furthermore, the authors tested BBT-176 in combination with osimertinib without evidence of synergistic antiproliferation activity against BBT-176-resistant clones of EGFR 19Del/T790M/C797S and 19Del/C797S mutants (14).

To note, this study also analyzed an interesting and emerging area that regards ctDNA and its clinical application (14,19). In detail, a correlation between objective and ctDNA responses was observed.

However, although the study showed promising early clinical data for BBT-176, some issues remain still to be solved. In fact, despite the encouraging results of efficacy in a small patient population, the dose-finding study of BBT-176 is still ongoing to determine the pharmacological dosage that may provide the best activity but with a safe profile of toxicity. In this regard, the authors have already designed an expansion phase of the clinical trial as soon as the optimal dosing schedule is determined. In our opinion, the ongoing clinical study with BBT-176 will clarify the potential role of this drug in the treatment of patients with triple-mutant EGFR L858R/T790M/C797S and 19Del/T790M/C797S.

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