EDITORIAL

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Update on afatinib-based combination regimens for the treatment of *EGFR* mutation-positive non-small-cell lung cancer

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“Further head-to-head trials with afatinib as a comparator are required, alongside careful analysis of patient subgroups, in order to precisely define which first-line EGFR-TKI will provide the best outcomes in specific patient populations as well as provide the most appropriate foundation for subsequent sequential treatment.”

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Over the last decade, the first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC) has been revolutionized by targeted therapies. Randomized Phase III trials of the EGFR-targeting tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib and afatinib have clearly shown that these agents are superior to first-line chemotherapy in terms of safety, progression-free survival (PFS) and overall response rate (ORR) [1]. As a result, all three EGFR-TKIs are considered to be current first-line standards of care for *EGFR* mutation-positive NSCLC.

While erlotinib and gefitinib are first-generation EGFR-TKIs that reversibly bind to and block EGFR signaling, second-generation afatinib has a broader and more potent spectrum of activity, irreversibly inhibiting signaling from all ErbB family receptor homodimers and heterodimers (EGFR/ErbB1, human EGFR 2/ErbB2, ErbB3 and ErbB4) [2,3]. The recent results of LUX-Lung 7 (NCT01466660),

the first randomized multicenter head-to-head study to compare first-line gefitinib with afatinib, suggest that first- and second-generation EGFR-TKIs are not interchangeable, and the broad and irreversible mechanism of action of afatinib may benefit clinical outcomes in treatment-naïve patients with *EGFR* mutation-positive NSCLC [4]. Afatinib was associated with improved efficacy across a range of clinically relevant end points compared with gefitinib in LUX-Lung 7, including median PFS (11.0 vs 10.9 months; HR: 0.73 [95% CI: 0.57–0.95]), time to treatment failure (13.7 vs 11.5 months; HR: 0.73 [95% CI: 0.58–0.92]) ORR (70 vs 56%; odds ratio: 1.87 [95% CI: 1.18–2.99]), while the rate of discontinuations due to treatment-related adverse events was comparable between agents [4]. Further head-to-head trials with afatinib as a comparator are required, alongside careful analysis of patient subgroups, in order to precisely define which first-line

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EGFR-TKI will provide the best outcomes in specific patient populations as well as provide the most appropriate foundation for subsequent sequential treatment.

Despite the initial clinical benefit observed with erlotinib, gefitinib and afatinib in *EGFR* mutation-positive NSCLC, most patients eventually experience disease progression. The development of third-generation EGFR-TKIs, such as osimertinib, has opened the door to the era of sequential EGFR-TKI therapy, at least in patients whose tumors harbor the *T790M* resistance mutation (50–60% of cases) [5]. *T790M*-positive tumors are exquisitely sensitive to osimertinib, with response rates of >60% [6,7]; thus, it is now considered second-line standard-of-care in this setting.

Nevertheless, there are two key areas of unmet medical need in the *EGFR* mutation-positive NSCLC field. First, there is currently a paucity of efficacious second-line treatment options in approximately 50% of patients who progress after first-line EGFR-TKIs but do not harbor the *T790M* mutation [8]. Mechanisms of resistance to first-line EGFR-TKIs in *EGFR* *T790M* mutation-negative patients, while poorly understood, are known to be heterogeneous and involve a number of different escape pathways [8]. Consequently, there is a rationale for the development of novel treatment combination regimens that target multiple aberrant pathways in patients with *T790M*-negative tumors. The second area of unmet need is the development of treatment options in patients with *T790M*-positive tumors following progression on osimertinib. Studies to date indicate that resistance mechanisms to third-generation TKIs are highly heterogeneous and vary from tumor to tumor. Mechanisms that have been identified include *EGFR*, human *EGFR* 2 or *MET* amplification, small-cell transformation and the acquisition of tertiary mutations in the *EGFR* gene such as *C797S* [5,9]. Furthermore, recent data indicate that such resistance mutations predominantly occur in *cis* with *T790M* which, in principle, will preclude the possibility of using first- or second-generation EGFR-TKIs following osimertinib in most cases [10]. This assertion has been substantiated in preclinical studies which show that cells resistant to third-generation EGFR-TKIs are cross-resistant to first-generation TKIs [5].

Given the heterogeneous nature of resistance mechanisms to third-generation TKIs, targeted treatment options have not been established and

are an area of active investigation. One approach is to use novel combination regimens to provide broader inhibition of intracellular pathways. Several trials are ongoing, including combinations using EGFR inhibitors as a backbone [9].

As we have previously reported [11], afatinib is a promising combination partner for anti-cancer therapies across a range of tumors, given its broad and irreversible inhibitory profile and low potential for drug–drug interactions [2]. Here, recent developments with afatinib-based combinations that may have particular promise in the areas of unmet need described above are discussed. Such regimens include combinations with EGFR monoclonal antibodies, such as cetuximab and nimotuzumab [12,13], IGF-signaling inhibitors, such as xentuzumab [14], chemotherapeutic agents including paclitaxel [15] and immune checkpoint inhibitors.

Afatinib plus EGFR antibodies

The notion of combining different ErbB-targeted agents such as afatinib and cetuximab to boost ErbB pathway inhibition in relapsed/resistant *EGFR* mutation-positive NSCLC is supported by the promising efficacy and tolerability observed with this combination in both preclinical and early-phase clinical studies. Afatinib plus cetuximab demonstrated encouraging antitumor activity in mouse models of human NSCLC [16] as well as a Phase Ib study of heavily pretreated patients with advanced solid tumors (NCT02020577) [17]. Most relevantly, in a Phase Ib study of 126 patients with advanced *EGFR* mutation-positive NSCLC with acquired resistance to first-line erlotinib or gefitinib (NCT01090011), afatinib plus cetuximab conferred an ORR of 29%, with similar response rates in patients harboring *T790M*-positive and -negative tumors (32 vs 25%). The median PFS in patients with *T790M*-positive and -negative tumors was 4.8 and 4.6 months, respectively [12].

The combination of afatinib with another EGFR-directed antibody, nimotuzumab, has also shown promising activity in patients with *EGFR* mutation-positive NSCLC who have developed resistance to erlotinib or gefitinib. In a recent Phase Ib/II study (NCT01861223), afatinib plus nimotuzumab conferred an ORR of 23% and median PFS of 4.0 months (95% CI: 2.3–5.7 months) [13]. In the subgroup of 27 patients categorized according to *T790M* mutation status, the ORR was 18 versus 33% and the median PFS was 3.7 versus 2.8 months

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for *T790M*-positive versus *T790M*-negative patients, respectively. An ongoing Phase I study is assessing the combination of afatinib and the *EGFR* monoclonal antibody necitumumab in patients with *EGFR T790M* mutation-negative NSCLC who have progressed on a first-generation *EGFR*-TKI as well as in patients with *EGFR T790M* mutation-positive NSCLC who have progressed on a third-generation *EGFR*-TKI (NCT03054038) [18].

These promising data with cetuximab and nimotuzumab remain to be confirmed by Phase III randomized studies. The mechanism of action of afatinib plus *EGFR* antibodies remains unknown, but appears to necessitate broad ErbB inhibition as no overall responses have been observed in trials of cetuximab in combination with erlotinib or gefitinib [19,20]

Afatinib plus IGF-1R inhibitors

IGF-1R signaling is known to play a critical role in the development and progression of various tumors, and has been implicated in acquired resistance to a variety of anticancer therapies, including *EGFR*-TKIs [21,22]. Although clinical studies of IGF-1R-targeted monotherapies have been largely disappointing to date, recent pre-clinical studies suggest that combination therapy with afatinib may help to overcome acquired resistance to *EGFR*-TKIs and thus potentially improve treatment outcomes in patients with *EGFR* mutation-positive NSCLC [23]. For example, combined treatment with an IGF-1R inhibitor and afatinib resulted in synergistic tumor growth inhibition in a mouse xenograft model of *EGFR* mutation-positive NSCLC.

An ongoing Phase Ib trial is assessing the combination of afatinib and xentuzumab (BI 836845), a humanized monoclonal antibody that binds to IGF-1/IGF-2, in patients with *EGFR* mutation-positive NSCLC with progression following a prior *EGFR*-TKI (NCT02191891) [14]. To date, this has proven to be a feasible combination which has demonstrated a manageable safety profile consisting of predominantly grade 1 and 2 adverse events commonly associated with afatinib. Encouraging activity has also been observed at the recommended Phase II dose of xentuzumab 1000 mg/week IV + oral afatinib 40 mg/day; 1 of the 12 patients with advanced NSCLC had a partial response and a further 10 patients had stable disease. The expansion part of the study is currently recruiting patients with NSCLC

harboring sensitive *EGFR* mutations and acquired resistance to afatinib, in the absence of *T790M* mutation [14].

Afatinib plus paclitaxel

A recent randomized Phase III study, LUX-Lung 5 (NCT01085136), assessed the efficacy and tolerability of paclitaxel added to afatinib in heavily pretreated NSCLC patients who had progressed following ≥ 1 line of chemotherapy, and whose tumors had progressed following initial disease control (≥ 12 weeks) on erlotinib or gefitinib and subsequently on afatinib monotherapy [15]. Compared with single-agent chemotherapy alone, paclitaxel plus afatinib significantly improved PFS (median 5.6 vs 2.8 months; $p = 0.003$) and ORR (32.1 vs 13.2%; $p = 0.005$) in this late-line treatment setting, while treatment-related adverse events were consistent with those previously reported for each agent.

The investigators concluded that LUX-Lung 5 was the first prospective study to support the concept of maintaining ErbB targeting beyond formal disease progression in oncogene-addicted NSCLC, and added that the combination of afatinib plus paclitaxel warrants consideration in patients with *EGFR T790M* mutation-negative NSCLC who have progressed on a first-generation *EGFR*-TKI [15]. In contrast to LUX-Lung 5, recent studies have demonstrated that continued exposure to erlotinib plus chemotherapy [24] or gefitinib plus chemotherapy [25] in heavily pretreated patients progressing after first-line therapy with an *EGFR*-TKI did not confer any additional clinical benefit, and increased toxicity versus chemotherapy alone.

Afatinib plus immune checkpoint inhibitors

The clinical success of programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 checkpoint inhibitors has generated numerous clinical studies exploring the application of these therapeutics in combinations with existing and experimental agents. Preclinical evidence suggests that activation of the oncogenic *EGFR* pathway enhances susceptibility of lung tumors to PD-1 blockade in mouse models [26], suggesting that the combination of PD-1 inhibitors with *EGFR*-TKIs may be a promising therapeutic strategy [27]. To date, however, the initial clinical studies of immunotherapies plus *EGFR*-TKIs have all been associated with

a relatively high incidence of treatment-related toxicities, leading to study termination in several cases [27]. Afatinib plus pembrolizumab, a PD-1 inhibitor, is being assessed in an ongoing Phase I/Ib study in patients with advanced/metastatic NSCLC with *EGFR* activating mutations who have progressive disease on erlotinib (NCT02364609) [28].

Conclusion

Afatinib holds promise as a therapeutic combination partner, especially in patients with limited treatment options such as those with *EGFR* T790M mutation-negative NSCLC that are resistant to first-line *EGFR*-TKIs or those with *EGFR* T790M mutation-positive NSCLC with acquired resistance to osimertinib.

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