IMPRESS is impressing

“EGF receptor-tyrosine kinase inhibitors should be used as long as possible until patients get dramatic progression, then the treatment must be switched to chemotherapy alone.”

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The discovery of *EGFR* mutations in patients with NSCLC has dramatically changed the treatment of NSCLC in recent years. Deletions in exon 19 and the L858R point mutation on exon 21 are the most common mutations which occurred in the tyrosine kinase domain of the *EGFR* gene [1].

Several randomized prospective trials have demonstrated that first-line EGF receptor-tyrosine kinase inhibitors (TKIs) in patients with activating *EGFR* mutations significantly improved the response rate and prolonged progression-free survival (PFS) compared with standard platinum-based chemotherapy [2–7]. However, most patients would inevitably experience disease progression after approximately 10–15 months of TKIs treatment, which is referred to acquired resistance [8].

Treatment subsequent to acquired resistance EGFR-TKI failure is challenging. Clinicians often choose to discontinue TKI and switch to cytotoxic therapies [9]. According to the results of a prospective trial carried out in 2007, patients who had developed acquired resistance have resulted in symptomatic progression in tumor growth and symptoms after premature

discontinuation of EGFR TKIs (gefitinib or erlotinib). Furthermore, after restarting erlotinib or gefitinib, patients may still regain benefit which suggests that some tumor cells remain sensitive to EGFR blockade. A randomized trial was recommended in this study to assess the value of continuing erlotinib or gefitinib after development of acquired resistance [10].

Here comes the question: which kind of treatment strategies should we administer to our patients at the time of RECIST-assessed disease progression on EGFR-TKI? Is it appropriate for us to discontinue using TKIs immediately?

At the European Society for Medical Oncology Congress 2014, two relevant studies – the IMPRESS and ASPIRATION trials have been presented.

The IMPRESS trial performed in Europe and Asia was the first randomized Phase III study comparing the continuation of gefitinib with standard chemotherapy and with pemetrexed and cisplatin versus chemotherapy plus placebo. The primary end point was PFS. In total, 265 patients diagnosed with locally advanced or metastatic NSCLC with an activating *EGFR* mutation who received gefitinib as first-line

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therapy were enrolled in total, 133 in gefitinib plus chemo arm and 132 in the other. The response rate was not different: about 31 versus 34%. The primary end point, the median overall PFS, was the same 5.4 months. The hazard ratio had no statistical significance either. Besides, the overall survival data were still immature [11].

In the further analysis, we have got the message that more patients in the placebo group had a better response to first-line gefitinib (76% in the placebo group vs 68% in the gefitinib group). Besides in the placebo group, there were fewer patients under 65 years of age who had brain metastases (23 vs 33% on gefitinib). In addition, the poststudy treatment was different in the two groups, with more patients in the placebo group going on to receive chemotherapy (12.9 vs 3.8% on gefitinib) and/or a TKI (33.3% on placebo vs 22.6% on gefitinib).

Based on the IMPRESS study data, once a patient has shown progression after first-line treatment of TKIs, clinicians should switch to chemotherapeutic regimens instead of continuing with TKIs combined with chemotherapy. However, the ASPIRATION trial seemed to tell us a slightly different story.

The ASPIRATION study was the first prospective study designed to investigate into the effects of continuing TKIs in treatment beyond progression. In total, 207 patients with exon 18–21 mutations (except T790M) were enrolled and 93 of them continued treatment after progression at last. The results have demonstrated that continuing erlotinib post-RECIST PD resulted in an additional PFS of 3.1 months, from 11.0 to 14.1 months without any safety signals [12].

However, there are still some comments about this result. It seemed like that researchers were selecting the best subgroup of patients to be treated with EGFR-TKI. In fact, the selection of patients continuing TKI is a natural process rather than a standard process in the ASPIRATION trial. Patients who were good at the RECIST progression point suggested they were still responding and could have benefited from the drug, so they continued using TKIs and got an extra 3.1 months eventually [13].

The ASPIRATION trial told us that continuing TKIs could get a benefit of 3.1 months while the IMPRESS trial suggested us to choose chemotherapy after progression. Thus, what has caused these two different results? Furthermore, it was a pity that in the IMPRESS trial there was

not a control group in which patients continued TKIs alone after progression. So here comes the question: which strategy on Earth should we pick after progression?

Let us focus on the first question. Patients who continued TKIs were in good physical condition at the RECIST progression point in the ASPIRATION trial. Maybe the different status that patients had at the RECIST progression could be the cause of the differences in results. Regardless, we think that the RECIST criteria are a little strict. For example, a 20% increase in the diameter of the tumor is defined as progression, but this may not yet signify clinical progression. As suggested by the data from the ASPIRATION study, some tumor clones may be starting to become resistant to the TKI, but others are still responsive, and there is still some benefit to be derived from continuing with the TKI. So the tumor progression exists heterogeneity and the assessment could be complicated. Since RECIST criteria were developed for gauging the effects of chemotherapy, and they could not reflect the diversity of failure in patients with EGFR-TKI treatment, here is another debate about what is really meant by ‘progression of disease’ in EGFR-TKI failure treatment: how can we address the patients who are suitable for continuation of TKI?

Based on the duration of disease control, evolution of tumor burden and clinical symptoms, regardless of genotype profile, Yang *et al.* in 2013 reported that diversity of EGFR-TKI-acquired resistance could be divided into three modes – dramatic progression, gradual progression and local progression. Unfortunately, the reported data have not explored the potential molecular mechanism of diverse TKI failure modes. Mixed response induced by tumor heterogeneity or secondary gene variations may be a possible reason [14].

According to the study results, continuation of EGFR-TKI plus local intervention is an appropriate choice for patients demonstrating strictly localized lesions in clinical practice. For those with gradual progression, continuation of EGFR-TKI would be an optimal treatment strategy after failure. The standard of care should remain doublet chemotherapy alone for gradual progression patients.

Based on the available data, we suggest that strategies for clinical management should be made according to different EGFR-TKI failure modes. EGFR-TKI should be used as long as

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