Preface

Special issue on personalized therapy in lung cancer

Targeted therapy and immunotherapy are so inspiring when updates in personalized medicine in lung cancer come into mind. We hope the hot topics listed in this issue of *Translational Lung Cancer Research* (*TLCR*) journal will be quite encouraging and appealing to you.

First of all, how to identify resistant mechanisms of tyrosine kinase inhibitors (TKIs) is fairly critical for targeted therapy. Some new generations of tyrosine kinase inhibitors have brought out promising results. For epidermal growth factor receptor (EGFR)-TKIs, AZD9291 and CO-1686, the third generation of small molecule inhibitors, have been proven to be more effective to tumors with T790M resistant mutation than previous generations of EGFR-TKIs in clinical trials.

Although great improvement has been achieved among this particular subgroup of advanced non-small cell lung cancer (NSCLC), patients treated with new generations of EGFR-TKI therapy still fail to obtain long-term remission or cure. One of the most important rationales is that T790M mutation is not the only mechanism leading to resistance, despite of high incidence rate of up to 50%. MET activating pathway is another mechanism causing resistance to anti-EGFR therapies. Other than well-known successful stories like new generations of EGFR-TKIs, there seems to be a lack of ideal targeting biomarkers for MET-positive patients. MET-Lung, the phase III clinical trial presented a frustrating result and there was no efficacy evidence from the addition of onartuzumab to erlotinib regimen. Despite the negative results, several meaningful lessons from this trial can contribute to further studies of MET pathway. MET activating pathway is not only the leading cause of resistance to EGFR-TKIs but also a potential tumor-driver of the 'METoma' which is defined as *de novo* MET. Therefore, it is quite pivotal to detect precise biomarkers and identify appropriate subgroups of patients. For example, INC280, a small molecule, is a MET inhibitor which can inhibit phosphorylation of c-MET and its downstream molecules. In the phase IB/II study targeting at patients with EGFR-mutant NSCLC, which was presented at ASCO Annual Meeting 2014 by Dr. Wu *et al.*, patients with c-MET positive expression showed effective response if treated with combination of INC280 and gefitinib when disease progressed after EGFR-TKI regimens. Therefore, it is quite convincing to apply dual MET/EGFR inhibitors to patients with EGFR mutations and MET positive expressions to overcome the resistance to EGFR-TKIs.

Thirdly, for patients with ALK-rearranged lung cancer, crizotinib is the best choice for the first-line setting, but acquired resistances will inevitably occur. Although ceritinib (LDK378) and alectinib, the second generation ALK-inhibitors, are effective to tumors with resistance to crizotinib, patients suffered from intolerable adverse events. Even half of the patients had to reduce doses, so we need to pay more attention to the safety profile and figure out resolutions. It is more important and imperative to identify appropriate subgroups of patients with specific mutations who are eligible to receive second generation of ALK inhibitors.

In the REVEL trial, Ramucirumab, a monoclonal antibody to VEGFR-2, could improve overall survival in combination with docetaxel compared with docetaxel alone in the second-line setting of NSCLC, especially for patients with squamous cell lung cancer. Differing from small molecular inhibitors, angiogenesis agents play an important role in tumor growth and survival. But it remains hurdles to identify reliable predictive biomarkers to select patients who are more likely to benefit from anti-angiogenic therapies. In the SQUIRE trial, necitumumab, a humanized IgG1 monoclonal antibody against EGFR, could improve overall survival when combined with gemcitabine/cisplatin versus gemcitabine/cisplatin alone for patients with squamous cell lung cancer. The result is totally different from the previous INSPIRE clinical trial which showed that the combination of necitumumab with cisplatin/pemetrexed failed to demonstrate survival priority over cisplatin/pemetrexed for patients with non-squamous histology. Except for chemotherapy, no other effective regimens are available for squamous cell lung cancer, although it is the second largest part of lung cancer. So the result of SQUIRE gives us more encouragement in patients with squamous cell lung cancer.

Despite the impressive activity of targeted therapy, durable response is uncommon and tumors tend to develop resistance to treatment within months. Thus, it is urgent to develop novel modalities of treatment for advanced lung cancer. Immunotherapy initiated from the 19th century, earlier than targeted therapy, but in that pre-checkpoint blockade era lung cancer had been considered a poorly immunogenic tumor and results of it had been generally disappointing. Fortunately for us, tremendous changes have occurred to the landscape of immunotherapy for lung cancer in recent years. For example, immune checkpoint

inhibitors, Nivolumab, MEDI4736, and MK-3475, which target programmed death 1 (PD-1) or its ligand (PD-L1), have resulted in impressive and durable anti-tumor activity, as well as special safety monitoring and management algorithm different from conventional treatment. Although immune checkpoint blockade may predominate in a bright future of treating advanced lung cancer, there is still a long way to go for PD-L1 expression in tumor cells and tumor environment, methodology of detecting PD-L1, selecting patients for anti-PD-1/PD-L1 therapies and so on. Besides, it is also necessary to identify eligible patients who are more likely to benefit from immunotherapy, and conduct large-scale trials directly comparing efficacy and safety of immune checkpoint inhibitors with platinum-based doublet chemotherapy.

In conclusion, targeted therapy and immunotherapy are not the ending of lung cancer treatment. Although obstacles are overwhelming along with fighting with lung cancers, current researches have manifested certain success and researchers should spare no efforts to identify effective regimens to overcome refractory diseases with more confidence and courage. We acknowledge all the investigators in producing the outlook.

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doi: 10.3978/j.issn.2218-6751.2014.12.03

View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2014.12.03

Disclosure: The authors declare no conflict of interest.

Cite this article as: Zhang N, Zhong WZ, Wu YL. Special issue on personalized therapy in lung cancer. Transl Lung Cancer Res 2014;3(6):358-359. doi: 10.3978/j.issn.2218-6751.2014.12.03

