Editorial

Precision medicine in lung cancer: the battle continues

Saiama N. Waqar, Daniel Morgensztern

Division of Medical Oncology, Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO, USA

Correspondence to: Daniel Morgensztern, M.D. Associate Professor of Medicine, Division of Oncology, Washington University School of Medicine, 660 S. Euclid, Box 8056, St Louis, MO 63110, USA. Email: dmorgens@dom.wustl.edu.

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Lung cancer remains the leading cause of cancer-related mortality in the United States, with approximately 160,000 estimated deaths in 2016 (1). Non-small cell lung cancer (NSCLC) accounts for 87% of lung cancers, and 40% of patients have metastatic disease at presentation (2,3). Chemotherapy, the standard treatment of metastatic lung cancer, results in a modest survival benefit compared to best supportive care, and has reached a plateau with no meaningful differences among the many platinum-based regimens used (4).

The approval of the small molecule tyrosine kinase inhibitors (TKIs) of *epidermal growth factor receptor* (*EGFR*) marked the beginning of the era of targeted therapies in lung cancer. Since then, the understanding of markers for response to EGFR TKI has evolved from clinical variables, such as female gender, Asian ethnicity, never-smoker status and adenocarcinoma histology, to genetic markers for response, namely activating mutations in the *EGFR* tyrosine kinase domain, including the most frequent exon 19 deletions, and exon 21 L858R mutations (5). Prospective studies conducted in patients with activating *EGFR* mutations consistently demonstrated improved progression-free survival (PFS) with first line EGFR TKI therapy over platinum-doublet chemotherapy, with erlotinib, gefitinib and afatinib approved by the Federal Drug Administration (FDA), based on the benefit demonstrated in randomized clinical trials (6-9).

The discovery of the *echinoderm microtubule-associated protein-like 4* (*EML4*)-*anaplastic lymphoma kinase* (*ALK*) gene fusions as oncogenic drivers in lung cancer in 2007 marked another therapeutic advance in the treatment of lung cancer (10). The serendipitous finding of activity of the *MET* inhibitor crizotinib in this molecular subset led to an expansion cohort of patients with ALK positive NSCLC treated with crizotinib (11). Subsequent clinical trials demonstrated PFS superiority of crizotinib over both front-line and second-line chemotherapy in patients with *ALK* positive NSCLC, leading to its approval in 2011 (12,13).

Despite the initial therapeutic benefit from molecularly targeted agents in *EGFR*-mutant and *ALK* positive NSCLC, patients eventually develop disease progression. Tissue specimens obtained from re-biopsy in patients with *EGFR*-mutant NSCLC at the time of disease progression have shown histologic changes such as differentiation into small cell lung cancer (14). At the molecular level, the most common mechanism of resistance is the *EGFR* T790M resistance mutation, which is seen in approximately 50% of cases (14). This finding has led to the development of third generation mutant specific EGFR TKI's to target T790M. Osimertinib is the first agent in this class to be granted accelerated approval by the FDA for the treatment of *EGFR* T790M positive NSCLC in 2015 based on the impressive results from the phase 2 trial (15).

Similarly re-biopsies in *ALK*-positive NSCLC have provided information on the mechanisms of crizotinib resistance. *ALK* kinase domain mutations, including L1196M, C1156Y and G1202R among others, have been observed in approximately a third of patients (16). The activity of next generation ALK inhibitors such ceritinib and alectinib may depend on the secondary *ALK* mutations. While both ceritinib and alectinib are active against L1196M, only alectinib has activity against C1156Y and neither is active against G1202R (17,18). Although the sequencing of these agents is still being investigated in clinical trials, it is possible that resistance mutations identified on repeated biopsies may influence the treatment choice.

The Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial

evaluated utility of targeted therapies in refractory lung cancer, with a unique trial design of biopsy-mandated prospective adaptively randomized therapy, based on tissue biomarker status (19). A total of 255 pre-treated patients with NSCLC were randomized to agents that were promising at the time of study design in 2005, including erlotinib, vandetanib, erlotinib plus bexarotene, and sorafenib. Patients were assigned based on testing results for *EGFR* mutation or copy number, *KRAS* or *BRAF* mutation, VEGF or VEGFR-2 expression and RXRs, cyclin D1 expression or *CCND1* copy number on study-related core biopsy specimens. The primary endpoint of the study was 8-week disease control rate (DCR), which was noted to be 46% overall, and as high as 79% in patients with *KRAS* or *BRAF* mutations treated with sorafenib. Importantly, this study showed the feasibility of performing re-biopsies on patients in real time and assigning patients to treatment accordingly, as well as the utility of 8-week DCR being used as a surrogate for overall survival (OS). Some of the study limitations included the selection of biomarkers associated with limited predictive value such as RXR and grouping markers such as *EGFR* mutation and copy number by FISH, which have distinct predictive value.

The BATTLE-2 study was developed based on the experience from the previous study, following the umbrella design with adaptive random assignment of therapy and performed in two stages (20). Nevertheless, there was a specific focus on optimizing treatments for *KRAS* mutant NSCLC, one of the most common driver mutations for which there is no specific therapy. Since there are already established treatment options for *EGFR* mutation and *ALK* translocations, patient harboring these alterations were excluded from the study. In the initial stage of the study (stage 1), 200 patients were assigned to study treatment by adaptive random assignment. Based on the discovery markers found in the initial stage, an additional 200 patients were assigned to one of the treatment arms in the stage 2. The four treatment arms were erlotinib alone (arm 1), erlotinib in combination with an AKT inhibitor MK-2206 (arm 2), MK-2206 in combination with a MEK inhibitor AZD6233 (arm 3), and sorafenib (arm 4). Patients were stratified by *KRAS* mutation status. Two hundred patients, including 27% with *KRAS* mutated tumors, were adaptively randomly assigned to the 4 treatment arms. The primary endpoint of DCR at 8 weeks was achieved by 48% of patients. The overall response rate was 3%, with median PFS of 2 months (95% CI: 1.9–2.8 months), which was not statistically different among the four treatment groups. For patients with *KRAS* mutant NSCLC, the DCR was 20%, 25%, 62% and 44% for arms 1, 2, 3 and 4 respectively, while in patients with *KRAS* wild-type tumors, the DCR was 36%, 57%, 49% and 47% for arms 1, 2, 3 and 4 respectively.

Although the BATTLE-2 study did not show a better strategy in patients with *KRAS* mutant NSCLC, it demonstrated the feasibility of re-biopsy and use of an umbrella protocol to assign patients to a particular treatment based on molecular profile. Unlike basket studies, which are based on the hypothesis that the presence of a molecular marker predicts response to therapy independent of tumor histology, and are designed to test a single drug in patients with a single gene alteration regardless of the primary tumor, umbrella studies are designed to test the impact of different drugs on different mutations in a single type of cancer (21). The rationale for the umbrella trials is to facilitate screening and accrual, since a large number of patients can be screened in the same study for multiple and often low prevalence biomarkers for which individual studies would otherwise require a large number of screened patients to achieve the target accrual. In addition to the BATTLE, there are several ongoing umbrella trials in NSCLC including the Lung Cancer Mutation Consortium (LCMC) for adenocarcinoma, the lung Master Protocol (Lung-MAP) for squamous lung cancer, and the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) in the adjuvant setting (22,23). The main objective of these trials is to facilitate the pathway towards rapid test and approval for promising novel therapies in the case of LCMC and Lung-MAP or the testing of approved drugs for metastatic disease in the adjuvant setting in the case of ALCHEMIST.

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Footnote

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