Editorial Commentary

The shifting paradigm of biomarker-driven care in advanced non-small cell lung cancer (NSCLC)

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Provenance: This is an invited article commissioned by the Section Editor Hengrui Liang (Department of Thoracic Surgery, Guangzhou Medical University, Guangzhou, China).

Comment on: Herbst RS, Redman MW, Kim ES, *et al.* Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): a randomised, phase 3 study. Lancet Oncol 2018;19:101-14.

Submitted Apr 04, 2019. Accepted for publication Apr 08, 2019.

doi: 10.21037/tlcr.2019.04.04

View this article at: http://dx.doi.org/10.21037/tlcr.2019.04.04

There will be an estimated 228,150 new cases of lung cancer in the U.S. and approximately 2.1 million cases worldwide in 2019. In 2018, it is estimated that 1.76 million people worldwide died from lung cancer (1,2). Most people with lung cancer have locally advanced or metastatic disease at the time of diagnosis, and thus, the improvement of systemic therapies for this population is of critical importance (3).

The treatment of metastatic non-small cell lung cancer (NSCLC) has evolved over the last eight decades, since the advent of chemotherapy. Initial attempts failed to improve outcomes in this patient population due to a variety of factors, including the limited efficacy and significant toxicity of the drugs that were deployed in an older patient population with significant co-morbidities and poor performance status. Clinical trials in the 1970s evaluated alkylating agents such as cyclophosphamide, vinca alkaloids such as vindesine, vincristine, and vinblastine, and the folate antagonists including methotrexate (3-5). In the 1980s, investigations of cisplatin, the anthracyclines such as doxorubicin, and the topoisomerase inhibitor etoposide took place in the treatment of patients with lung cancer (6). Many early trials used these chemotherapeutics as single agents, demonstrating only modest activity. Subsequent efforts moved toward the use of combination treatments that demonstrated some improved efficacy at the price of considerable increased toxicity. Over time, the data evolved to show that cisplatin-based chemotherapy regimens were the most consistently active; however, because of their considerable toxicity, consensus on their use remained controversial in many parts of the world even into the mid-1990s. In 1995, a meta-analysis from the Non-Small Cell Lung Cancer Collaborative Group indicated a statistically significant advantage in survival for cisplatin-based chemotherapy over best supportive care alone with an advantage of approximately 10% at one year (7). In the 1990s, many trials compared cisplatin alone *vs.* cisplatin with newer agents such as taxanes, gemcitabine, newer vinca alkaloids such as vinorelbine, or irinotecan. These trials demonstrated improvements with doublet regimens over single agent cisplatin, but trials comparing different doublets showed similar efficacy regardless of the platinum partner (8).

These early advances were modest, but offered some improvement in survival times for patients. All of these advances in systemic treatment for advanced NSCLC were observed in trials with similar designs. As a result, modest but slowly progressive improvements in survival times, generally in the order of weeks to a few months, compared with best supportive care were observed. In addition, all trials were conducted in unselected populations of patients with the diagnosis of NSCLC, regardless of tumor characteristics or specific histology. None of these trials has demonstrated universal efficacy in all patients, and no reliable biomarker was available to distinguish those patients who would benefit from those who would not. Attempts to identify predictive biomarkers for chemotherapy were undertaken, resulting in the emergence

of modestly predictive biomarkers for several classes of chemotherapeutic agents. In NSCLC trials, one of the best studied biomarkers was ERCC1 as a predictive biomarker for cisplatin (9,10). Additional biomarkers such as beta-tubulin levels to predict benefit to taxanes, topoisomerase II levels to predict the benefit of topoisomerase II inhibitors, the anthracyclines and etoposide, and thymidylate synthase overexpression as a marker for pemetrexed resistance have also been studied (11-13). While many of these biomarkers have shown some ability to predict responses to specific chemotherapy agents, the results have largely been inconsistent and none of these biomarkers has been integrated into routine clinical practice.

Much of the progress in the development of predictive biomarkers has been realized since the introduction of molecularly targeted therapies. Initial trials with gefitinib in unselected patients suggested benefit in certain patient subsets such as women, adenocarcinoma histology, patients of Asian origin, and light or never smokers. These retrospective observations led to prospective trials which enriched for this subset of patients and ultimately to the discovery of epidermal growth factor receptor (*EGFR*) gene mutations as a predictive biomarker for the EGFR tyrosine kinase inhibitor class (14). This was the first example of a predictive biomarker strong enough to influence routine clinical practice, and its identification revolutionized the treatment of patients with *EGFR*-mutated NSCLC beginning in 2004. Since that time, a number of other biomarkers have been identified with similar impacts on clinical practice. Biomarker-driven FDA-approved therapies in NSCLC now exist for translocations in both anaplastic lymphoma kinase (*ALK*) and *ROS1* as well as mutations in *BRAF* V600E. Active therapies have also been identified for *MET* exon 14 alterations, *RET* translocations, and *HER-2* mutations, though these are still undergoing investigation and some are awaiting FDA approval. These advances have dramatically changed the landscape of treatment for patients with adenocarcinoma of the lung and have spared a number of patients from receiving ineffective therapies. Response rates in enriched populations are reported in the 60–90% range and prospective randomized trials have indicated the improved efficacy of these molecularly targeted agents compared with empiric chemotherapy regimens.

The checkpoint inhibitors, anti-programmed death-1 (PD-1) and anti-programmed death ligand-1 (PD-L1) antibodies, have revolutionized the treatment of NSCLC over the last decade. These immunotherapy agents have the potential to achieve durable clinical responses and are commonly well tolerated in comparison to chemotherapy. However, they are expensive, do not work in all patients, and have the potential of causing severe and sometimes life-threatening immune-related complications. While these agents are approved in unselected patient populations with NSCLC, biomarkers have emerged that predict response to these agents. The most promising biomarker for the PD-1 and PD-L1 inhibitors are PD-L1 tumor proportion score (TPS) and tumor mutational burden (TMB). PD-L1 TPS has been shown in a phase III clinical trial to predict which patients may respond better to pembrolizumab than platinum-based chemotherapy. Those with a PD-L1 TPS of $\geqslant$50% had higher response rates, longer progression free survival (PFS), and improved overall survival (OS) when treated with pembrolizumab alone compared with a platinum-containing doublet regimen (15). Furthermore, other trials have shown the predictive ability of intermediate or high TMB to predict responses and improved PFS, independent of PD-L1 TPS status, with checkpoint inhibitors (16). Neither of these biomarkers is perfectly predictive of response to checkpoint inhibitors, however, and research in this area continues, including attempts to predict biomarkers of resistance.

A recently published trial in *Lancet Oncology* by Herbst *et al.* is an excellent example of correlative research helping to elucidate new biomarkers and facilitate proper patient selection for systemic therapies in NSCLC. This trial, "Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): a randomised, phase 3 study," was a large open-label study conducted by the Southwestern Oncology Group (SWOG). Patients were randomized 1:1 to receive carboplatin plus paclitaxel (control) or carboplatin plus paclitaxel plus cetuximab. Bevacizumab could be added to either regimen at the discretion of the treating physician if the patient had no contraindications, and the two arms were stratified by bevacizumab administration. All patients underwent EGFR testing by FISH analysis which was considered positive if tumors harbored four or more copies of EGFR in 40% or more of cells or if they showed EGFR amplification. The co-primary endpoints of the study were PFS in the EGFR FISH-positive patients and OS in the entire patient population. The investigators reported no difference in PFS between the cetuximab-containing and control arms for patients demonstrating EGFR FISH-positivity (5.4 *vs.* 4.8 months, HR 0.92, P=0.40). Furthermore, median OS for the entire study population did not differ for those

treated with cetuximab *vs.* those on the control arm (10.9 *vs.* 9.2 months, HR 0.93, P=0.22). However, there was a pre-specified subgroup analysis of EGFR FISH-positive patients with squamous histology. This analysis showed improved OS in patients treated with the cetuximab combination (HR 0.58, P=0.0071) and a trend towards improved PFS in this subset of patients, although the result did not reach statistical significance (HR 0.68, P=0.055). In the EGFR FISH-negative subgroup with squamous cell histology, there was no difference in either PFS or OS, and there was no difference in patients with non-squamous histology regardless of EGFR FISH status. The conclusions of the authors were that although this study did not meet its primary endpoints, the improved OS noted in the EGFR FISH-positive squamous cell carcinoma subgroup was encouraging and may warrant further evaluation of anti-EGFR antibodies in this subpopulation.

The authors should be congratulated for completing this large trial and applauded for the addition of such a robust correlative biomarker analysis. Success with targeted therapies in lung cancer depends upon predictive biomarkers. Otherwise, the use of these agents in unselected populations underappreciates the impressive efficacy in subsets of patients. In the absence of predictive biomarkers, highly active agents in small subsets of patients may be missed, resulting in the abandonment of development of potentially useful drugs. The SWOG investigators planned this biomarker subset analysis of patients with squamous cell lung cancer with FISH positivity after previous clinical trials, including FLEX and SQUIRE, had demonstrated improved patient outcomes with the addition of EGFR monoclonal antibodies, especially in patients with squamous cell histology (17,18). Closer analysis of these trials and others suggests that the benefit may be highest in those with high EGFR protein expression, and because of this, the authors selected EGFR FISH-positivity as a promising biomarker in this study. The inclusion of this particular biomarker is both intriguing and rational in light of previous evidence, and we agree that the improvement in OS for this particular subgroup is encouraging.

The era of biomarker discovery is well underway. While initial attempts in discovering predictive biomarkers for chemotherapeutics did not result in their implementation into routine use in clinical practice, it is clearly evident that newer efforts have. These predictive biomarkers include mutations in EGFR, HER-2, BRAF, and MET as well as translocations in ALK, ROS-1, RET, and NTRK. Furthermore, PD-L1 TPS and TMB are excellent biomarkers predictive of response to the PD-1 and PD-L1 inhibitors. As research continues, we are able to elucidate more specificity in these biomarkers. For example, not all EGFR mutations predict for response to the currently FDA approved EGFR tyrosine kinase inhibitors. MET mutations in exon 14 predict response to MET tyrosine kinase inhibitors, but MET amplification has demonstrated mixed results to predict response. Certain ALK mutations are acquired mechanisms of resistance to ALK tyrosine kinase inhibitors. Active research is ongoing to understand the details of the mutations, mechanisms of resistance, and individual pharmacogenomic profiles. Much work still needs to be done, but the insights gained thus far, encourage this continued exploration and hold the promise of delivering personalized therapies to all patients with NSCLC.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Durm G, Hanna N. The shifting paradigm of biomarker-driven care in advanced non-small cell lung cancer (NSCLC). Transl Lung Cancer Res 2019;8(4):539-542. doi: 10.21037/tlcr.2019.04.04

