Molecular characterization of tumors has become integral in the management of advanced non-small cell lung cancer (NSCLC) (1). Over the last decade, major evolution in understanding the role of biomarkers has shaped the current management strategies of NSCLC. Molecularly targeted therapies have now become the preferred initial therapy for NSCLC patients with tumors containing epidermal growth factor receptor (EGFR) mutations, as well as translocations of the anaplastic lymphoma kinase (ALK) gene and c-ros oncogene 1 (ROSI) (2–4). These successes have driven the goal to further personalize treatment decisions in NSCLC. Trials such as the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) evaluated the feasibility of repeat tumor biopsy at the time of disease progression in order to direct further treatment, based on tumor molecular profile (5). The BATTLE trial demonstrated an 8-week disease control rate (DCR) of 46%. Biomarker analysis showed a higher DCR in patients with EGFR wild type (WT) and KRAS mutated tumors, randomized to sorafenib (6).

The BATTLE-2 trial recently reported by Papadimitrakopoulou et al. in the Journal of Clinical Oncology, further developed the concept of biomarker driven therapy in patients with previously treated advanced NSCLC (7). Two hundred and seventy four good performance status patients with previously treated stage IV NSCLC underwent fresh tumor biopsies at the time of disease progression. Molecular profiling was undertaken to determine EGFR, KRAS and ALK status as well as mRNA and DNA sequencing. Two hundred patients, with EGFR WT, or ALK negative tumors, were stratified by KRAS status and adaptively randomized to erlotinib (erl), erlotinib and the AKT inhibitor MK-2206, MK-2206 and the MEK inhibitor AZD-6244, or sorafenib. The primary outcome was 8-week DCR. Secondary outcomes included progression-free survival (PFS), overall survival (OS) and toxicity rates. Exploratory outcomes examined efficacy according to tumor biomarker profiles.

There were 186 patients eligible for analysis of the primary outcome. The overall 8-week DCR was 48% and there were no differences between the treatment arms (erl 32%, erl + MK-2206 50%, MK-2206 + AZD6244 47%, sorafenib 54%). The median PFS was 2.0 months (95% CI, 1.9–2.8 months) and median OS was 6.5 months (95% CI, 5.1–7.6 months) and similarly there were no differences between treatment arms. KRAS mutations were present in 27% of patients and were not associated with 8-week DCR, PFS or OS.

Exploratory biomarker analyses demonstrated a significant qualitative interaction between KRAS mutation status and erlotinib therapy for PFS. Additionally, KRAS WT patients had a better OS when treated with erlotinib compared to other treatments (9.0 vs. 5.1 months, HR, 0.66; 95% CI, 0.45–0.97; P=0.03), whereas no difference was observed among KRAS mutated patients (6.0 vs. 7.5 months, HR, 1.26; 95% CI, 0.65–2.46; P=0.50). Analysis of the epithelial-mesenchymal transition (EMT) gene signature demonstrated no difference in overall PFS between epithelial and mesenchymal tumors. However, improved PFS was observed in patients with mesenchymal signature who received the MEK inhibitor (P=0.04) and patients with mesenchymal tumors had better OS compared with patients with epithelial tumors (log-rank test, P=0.02). This effect was greatest in patients with KRAS mutated tumors who...
received sorafenib (log-rank test, P=0.01).

At face value, BATTLE-2 is a negative trial. Not only were there no significant differences observed between the randomized groups in primary or secondary outcomes, but the observed PFS and OS results are almost identical to the results from the BR.21 randomized trial of erlotinib versus best supportive care in pretreated NSCLC patients (8). Toxicity associated with the experimental arms was generally greater than erlotinib alone. Patients in all three experimental arms experienced more fatigue than patients randomized to erlotinib alone. Hyperglycemia occurred more commonly in patients receiving MK-2206, although grade 3 hyperglycemia was uncommon. These and other differences in toxicity were reflected in higher rates of treatment discontinuation (14–15% vs. 9%) and requirement for dose reduction (39–43% vs. 18%) that were observed for the experimental arms compared with erlotinib alone.

However, the biomarker analyses from BATTLE-2 provide some reason for thought about this trial. While KRAS mutational status did not influence the primary study outcomes, patients with KRAS mutated NSCLC appeared to benefit less from therapy with erlotinib. These findings are in contrast with a pooled analysis of four trials of an EGFR TKI versus placebo, which failed to demonstrate differences in OS in KRAS mutated versus WT NSCLC patients randomized to an EGFR TKI (9). However, the type of KRAS mutation appeared to be predictive of efficacy from an EGFR TKI. Further exploration of the types of KRAS mutations among patients in the BATTLE-2 trial should be encouraged. Promising results have been seen from the addition of a MEK inhibitor, selumetinib, to docetaxel chemotherapy among patients with KRAS mutated NSCLC (10). Disappointingly and despite preclinical models suggesting activity in KRAS mutated lung cancer, the combination of MEK and AKT inhibition in this study did not improve outcomes compared with erlotinib alone. These results highlight the need for more research and improved treatment options for patients with KRAS mutated NSCLC (11,12).

The results of BATTLE-2 also highlight EMT as a potential predictive biomarker. In vitro studies demonstrate that EGFR addicted cell lines undergoing EMT become resistant to erlotinib (13). BATTLE researchers demonstrated the clinical importance of these findings. EMT expression correlated with erlotinib sensitivity in the BATTLE trial (14). The results of BATTLE-2 also suggest that cancers with mesenchymal expression may have improved outcomes with MEK inhibition, or sorafenib therapy. In an integrated analysis of three large databases that included data from BATTLE-1, EMT was highly associated with an inflammatory tumor microenvironment in lung adenocarcinoma. This association showed elevation in multiple immune checkpoint targetable molecules, regardless of the mutation burden (15). While BATTLE-2 did not set out to study abnormalities in immune pathways, evaluation of the EMT gene signature among patients undergoing immune checkpoint inhibitor therapy may further help define the patient population who benefits from immune directed therapy.

There are some limitations to the BATTLE-2 trial. Biomarker profiling may not be appropriate in all patients. Nearly 7% of patients suffered a pneumothorax from the biopsy procedure. Approximately one in four patients undergoing biopsy for molecular profiling did not proceed onto the randomized trial. There is a real risk that some patients might decline in condition awaiting the results of the molecular profiling. These risks would likely increase if this approach was generalized to a broader community. These findings highlight the need for further research into molecular profiling of lung cancers using circulating tumor cells (CTCs) and cell-free circulating tumor DNA (ctDNA), known as liquid biopsy (16). These techniques have been successful in identifying EGFR mutations and resistance mechanisms, although the technology needs to be validated in broad based molecularly profiling (17).

The BATTLE series of trials have been pioneering trials in this field. In the BATTLE trials, molecular profiling was conducted prospectively, although the predictive effect of this analysis on patient outcomes was evaluated at the study conclusion. More recently, an umbrella or basket approach has been utilized, in which the results of molecular profiling is used to feed patients into a series of clinical trials based on the specific molecular profile of the tumor. The Lung Master Protocol [(Lung-MAP), S1400] is one such example (18). This trial uses next generation sequencing of squamous cancers to assign patients into molecularly defined sub-studies of different investigational agents as second-line therapy. These designs will become increasingly important in the evaluation of molecularly defined subsets of NSCLC, both in early stage and advanced disease.

BATTLE-2 was a negative trial that does not change current practice. However, the lessons from BATTLE-2 should be used to inform for future research and clinical trials. Repeat biopsy for molecular analysis at the time of tumor progression proved feasible in most patients,
although these findings might not generalize to larger populations and greater number of institutions. Caution should be exercised in waiting for molecular testing in patients at risk of rapid disease progression. However, further exploration of the EMT gene signature developed in the BATTLE trials seems warranted. Further research is also needed to examine the interplay between molecularly guided therapy and immune therapy in these previously treated patients.

**Acknowledgements**

None.

**Footnote**

*Provenance:* This is an invited Commentary commissioned by Section Editor Wei Xu (Division of Respiratory Disease, Department of Geriatrics, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

*Conflicts of Interest:* Dr. P Ellis has received honoraria for speaking from Boehringer-Ingelheim, Pfizer and Novartis. Dr. A Al Farsi has no conflicts of interest to declare.


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