Going into BATTLE: umbrella and basket clinical trials to accelerate the study of biomarker-based therapies

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With the recognition that tumor molecular phenotypes may predict response to targeted therapies, a number of national multi-center umbrella and basket trials have been initiated in recent years. Umbrella trials enroll patients with a single tumor type, defined by primary anatomic site, and assign various treatments according to the molecular characterization of each case. Conversely, basket trials enroll patients with multiple tumor types, restricting eligibility according to biomarker status. Examples of both models abound, including the Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis (I SPY) trials in breast cancer (1), Lung Master Protocol (Lung MAP) trial in advanced squamous lung cancer (2), Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) in surgically resected non-small cell lung cancer (NSCLC) (3), Lung Cancer Mutation Consortium (LCMC)-associated trials in advanced lung adenocarcinoma (4), the National Cancer Institute (NCI)-Molecular Analysis for Therapy Choice (NCI MATCH) Trial (5), and the Targeted Agent and Profiling Utilization Registry (TAPUR) (6), sponsored by the American Society of Clinical Oncology (ASCO) in previously treated advanced solid tumors.

These efforts require tremendous resources and coordination, and they would not be undertaken without an earlier generation of studies that demonstrated feasibility. Chief among these earlier trials is the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) program, a prospective, biopsy-mandated, biomarker-based, adaptive randomized clinical trial platform for patients with advanced NSCLC (7,8). Recognizing that archival tumor tissue from the time of diagnosis may not accurately reflect the current biomarker status of the tumor, the BATTLE trials pioneered the use of real-time biopsies and biomarker analysis to assign patients to specific treatment cohorts. Despite concerns over the willingness of patients with metastatic lung cancer to undergo yet another round of invasive procedures, as well as the associated risks, the BATTLE trials demonstrated this approach to be highly doable.

The BATTLE trials also pioneered the use of adaptive randomization, which permits efficient pairing of biomarkers and therapeutic agents and assigns patients to the treatment with the greatest potential benefit on the basis of cumulative data (9). For instance, in BATTLE-2, the first 70 patients underwent equal randomization to 1 of 4 treatment arms: (I) the epidermal growth factor receptor (EGFR) inhibitor erlotinib; (II) erlotinib plus the AKT inhibitor MK-2206; (III) the MEK inhibitor AZD6244 plus MK-2206; and (IV) the multi-targeted [RAF/MEK/ERK pathway, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR)] kinase inhibitor sofafenib. Subsequently, adaptive randomization incorporating 8-week disease

control status [previously shown to correlate with overall survival (10)], *KRAS* mutation status and treatment was used to calculate and continuously update the posterior probability of efficacy for each treatment arm. This process, in turn, was designed to allow more patients to be assigned to effective therapies and fewer patients to be assigned to less effective therapies.

BATTLE-2 capitalized on the experience and knowledge gained during and after BATTLE-1, including the promising clinical effect of sorafenib and preliminary efficacy of MEK and AKT inhibitors, including in mutant *KRAS* tumors (11-17). Despite these advantages, BATTLE-2 made only modest inroads into the thorny challenge of pre-treated advanced NSCLC. The 8-week disease control rate was 48%, comparable to that observed in BATTLE-1. Overall, there was no significant association between 8-week disease control rate and *KRAS* mutation status. As might be expected, performance status predicted outcomes. Consistent with results from earlier trials of EGFR inhibitors (18,19), patients with *KRAS* mutant tumors had significantly longer PFS if treated with therapy that did not contain erlotinib (P=0.04).

Ultimately, the trial failed to identify any new promising treatments or predictive biomarkers. The use of EGFR inhibitors remains largely confined to patients with tumors harboring classic activating *EGFR* mutations (20,21). The search for effective treatments for *KRAS* mutant tumors—the second most common genomic alteration in human cancer following *p53* mutations—continues apace, with efforts focusing on inhibition of effector pathways, inhibition of post-translational modification, synthetic lethality, and development of direct KRAS G12C inhibitors (17,22,23).

That the BATTLE-2 trial already seems somewhat outdated is testament to the incredible, unprecedented pace of discovery and advances in lung cancer and other malignancies. Multiplex, next-generation sequencing now provides simultaneous analysis of hundreds of cancer-related genes using similar quantities of tissue, within a similar time frame, and at comparable cost as those of single-gene assays such as Sanger sequencing (24). Particularly for patients with lung cancer, for whom biopsy of the primary site requires an invasive procedure and conveys risk of pneumothorax, the emergence of blood- and urine-based tumor genomic assays represents a major advantage. These platforms analyze circulating or cell-free tumor DNA and provide a spectrum, sensitivity, and specificity of genomic analysis comparable to that of tissue testing (25). Finally, the emergence of immunotherapy-based regimens, which have improved efficacy and tolerability compared to conventional chemotherapy, has revolutionized the treatment of advanced NSCLC (26-29). How these new drugs are best integrated into precision medicine remains to be seen.

Despite these seismic shifts in the lung cancer landscape, the BATTLE trials have not lost relevance. The willingness of patients to undergo additional testing and await results before treatment, the ability to perform complex biomarker testing with rapid result turnaround, and the coordination and conduct of trials with dynamic designs remain key concepts as we continue the war on cancer, one battle at a time.

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Footnote

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