Lessons learned from BATTLE-2 in the war on cancer: the use of Bayesian method in clinical trial design

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In the past decade, the therapeutic landscape for non-small cell lung cancer (NSCLC) has evolved considerably with the advent of targeted therapy. It has become the standard of care to match patients with relevant targeted therapeutics according to their molecular abnormalities (1). Treatment of patients with *EGFR*-mutant NSCLC with EGFR tyrosine kinase inhibitors (EGFR-TKIs) serves as the paradigm of precision medicine in lung cancer. In the U.S., three first- or second-generation EGFR-TKIs (erlotinib, gefitinib, afatinib) are available for use in the first-line treatment of *EGFR*-mutant NSCLC (2). Osimertinib, a third-generation EGFR-TKI, is approved by the U.S. Food and Drug Administration (FDA) for patients whose disease has progressed after an earlier generation EGFR-TKI and whose tumors have a secondary mutation (T790M) (2). The list of genetic aberrations for which effective targeted therapeutics are available includes ALK and ROS1 translocations (3,4), and continues to expand due to an improved understanding of the molecular pathogenesis of NSCLC. However, due to the ever-growing number of targeted therapeutics and their putative targets, the simultaneous development of a molecularly targeted agent and a predictive biomarker is not often achievable using data from traditional non-randomized early-phase clinical trials (5), which raises the need for innovative approaches to clinical trial design.

Accompanying this editorial is an article reporting the results of the BATTLE-2 (BATTLE-2 program: a biomarker-integrated approaches of targeted therapy study in previously treated patients with advanced non-small cell lung cancer) trial, which is a prospective, biopsy-mandated, biomarker-based phase II trial of patients with pretreated NSCLC (6). Designed based on the experiences and knowledge acquired from the BATTLE-1 trial (7), the BATTLE-2 trial aims to discover predictive biomarkers and assess efficacy for targeted therapeutics with an emphasis on *KRAS*-mutant NSCLC. The novel aspects of the BATTLE-2 trial include the incorporation of mandatory biopsies prior to initiating therapy to accurately analyze the biomarker status of an individual's tumor and the adoption of Bayesian-based adaptive randomization in the study design. The BATTLE-2 trial utilizes a two-stage design and the article reports the results from the first stage. In the first stage of the trial, stratified by *KRAS* mutation status, 200 patients were randomized to four arms: arm 1, erlotinib; arm 2, erlotinib+MK-2206 (AKT inhibitor); arm 3, MK2206+AZD6244 (MEK inhibitor); and arm 4, sorafenib. Patients who received EGFR-targeted therapy previously were randomized only to arms 2, 3, or 4. The first 70 patients were equally randomized to the four treatment arms. Subsequently, adaptive randomization, which was enabled by the use of Bayesian scheme, was employed to assign more patients to more effective therapies based on their *KRAS* mutation status. For example, if results from the

first 70 patients suggest that a certain treatment arm offers a higher 8-week disease control rate (DCR) as compared to other arms for *KRAS*-mutant NSCLC, the next study enrollee with *KRAS*-mutated NSCLC would have a higher chance of being assigned to that particular arm. The randomization ratio constantly changes throughout the study according to the accumulating data from the trial. During the first stage of the trial, tumor samples obtained at baseline were subjected to various tests including mutation analysis using next-generation sequencing (NGS) to identify promising prognostic and predictive biomarkers. The investigators intend to use the identified biomarkers and/or gene signatures to generate a refined predictive model for the second stage to improve the efficiency of the trial and validate the biomarkers.

After enrollment, patients underwent tumor assessments every two cycles (every 8 weeks). The primary outcome was the 8-week DCR, which is an unconventional surrogate end point. The overall outcomes are discouraging. The overall 8-week DCR was 48%. The overall 8-week DCRs were not statistically different when arms 2, 3, and 4 were compared to arm 1. The median progression-free survival (PFS) and overall survival (OS) were 2.0 and 6.5 months, respectively. There was no difference in PFS and OS among the four arms and also for *KRAS*-mutated *vs*. *KRAS*-wild type tumors. The only significant factor to predict OS was performance status and treatment assignment did not predict 8-week DCR, PFS, or OS. Patients with *KRAS* mutations had a worse prognosis if they were treated with an erlotinib containing treatment (arms 1 or 2), which is not surprising because it has been shown that KRAS mutations are a predictor of resistance to EGFR-TKIs (8). There were only 6 patients who achieved a partial response, suggesting the lack of antitumor activity of the treatments used in the BATTLE-2 trial. It is notable that a sorafenib sensitivity signature and an epithelial mesenchymal transition (EMT) signature were not predictive of outcomes, although patients with mesenchymal tumors had an OS benefit if they were treated with sorafenib, a finding that is largely hypothesis generating and needs validation in future studies.

The BATTLE-2 investigators at the University of Texas MD Anderson Cancer Center and Yale Cancer Center are to be lauded for testing the novel idea of designing a clinical trial using Bayesian-based adaptive design (more specifically adaptive randomization) and proving the feasibility of incorporating mandatory research biopsies into the study design. The use of adaptive randomization, at least theoretically, ensures that more patients are assigned to more effective treatments. Also, from our own experience of conducting a phase II basket trial of multiple targeted agents in patients with NSCLC at the National Cancer Institute (9), we have learned the importance of acquiring adequate tumor tissue for molecular analysis prior to treatment initiation. From these perspectives, we regard the BATTLE-2 trial as a major step toward our goal of improving the study design of clinical trials of molecularly targeted agents. However, many questions arise from the design and findings of the BATTLE-2 trial and answering these questions may help us better our ability to design future clinical trials of targeted therapeutics.

Perhaps, one of the biggest questions is about under which circumstances the Bayesian-based adaptive clinical trial design will contribute to the faster identification of a molecularly targeted agent and a predictive biomarker pair. While often touted as a better strategy than the traditional non-randomized clinical design in developing biomarkers and assessing therapies simultaneously, the adaptive randomization method is potentially less efficient than a fixed randomization approach when there is only one experimental arm (10). Even when there are multiple experimental arms, alternative non-Bayesian strategies such as multi-arm multi-stage design with stopping rules may provide better efficiency if none of the experimental agents is effective (11). More importantly, when a biologically well-defined target and a potent targeted agent exist, the traditional early phase clinical design may be a more straightforward approach to obtain approval as we have seen in the cases of osimertinib for T790M-positive NSCLC and crizotinib for ALK-rearranged NSCLC (12). Little experience in utilizing this novel study design is available and more research to define the role of Bayesian-based study design is needed.

Overall outcomes of the BATTLE-2 trial were not encouraging and the composition of the treatment arms deserves further evaluation. The investigators excluded patients with *EGFR* mutations, but two out of fours arms contained erlotinib. A series of studies have demonstrated that *EGFR* mutations are the strongest factor to predict benefit from EGFR-TKIs (13,14); the fact that there was no objective response observed in patients treated with erlotinib containing regimens (arms 1 and 2) confirms this observation. The BATTLE-2 trial used adaptive randomization, but not other features of adaptive approaches such as incorporating or removing treatment arms based on accumulating knowledge from the trial itself

or the literature, unlike the I-SPY2 trial, another trial with outcome adaptive randomization (12,15). Although fewer patients were assigned to the erlotinib containing arms due to the use of adaptive randomization, 32% of the patients still received an erlotinib-containing treatment, which probably would have contributed to the disappointing study outcomes.

At the same time, the BATTLE-2 trial demonstrates the elusive nature of *KRAS* mutation as a target. As one of the most frequently mutated genes in lung cancer, it is detected in 20–30% of patients with lung adenocarcinomas (16). Mutant KRAS proteins are insensitive to GTPase-activating proteins (GAP) and thus stay in the active, GTP-bound form, resulting in the activation of downstream signaling pathways such as the MEK/ERK and PI3K/AKT pathways (16). KRAS mutations portend a poor prognosis (17,18), but there exists no targeted therapy that has been shown to be effective for KRAS-mutated NSCLC. Because RAS proteins have a high affinity for GTP/GDP and does not have pockets to which small-molecule inhibitors can bind (19), efforts to directly target mutant KRAS have been challenging. As a result, previous strategies have attempted to exploit post-translational modifications of RAS proteins or inhibit RAS downstream signaling pathways for the treatment of *KRAS*-mutant NSCLC. However, clinical trials utilizing inhibitors of farnesyl protein transferase or downstream effector molecules such as MEK have not led to satisfactory outcomes and no biomarkers that predict responses to therapy have been identified in these trials (20-23). Novel approaches are needed for the treatment of patients with KRAS-mutated NSCLC given the unsatisfactory efficacy and poor tolerability of combination targeted therapy. One potential strategy is to combine a targeted therapeutic such as a MEK inhibitor with immunotherapy, which is supported by a recent study suggesting that the efficacy of selumetinib is potentially reduced by an increase in immune checkpoint receptors on T-regulatory cells and $CD8^+$ T cells (24).

In summary, the successful completion of the first-stage of the BATTLE-2 trial provided proof that analyzing tumor samples in real time is not a remote possibility. More studies using Bayesian methods will likely be a bigger part of our future efforts to efficiently identify effective treatments and concurrently discover promising biomarkers, but further research is required to better understand in what clinical contexts the Bayesian-based adaptive clinical trial design works the best. Lastly, we need novel approaches to target the untargetable, the *KRAS* mutation.

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Footnote

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

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