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Adaptive BATTLE trial uses biomarkers to guide lung cancer treatment

A pioneering Phase II trial reported at the American Association for Cancer Research 2010 annual meeting (abstract number LB-1) is the first to demonstrate the use of multiple biomarkers to guide the treatment of patients with non-small cell lung cancer (NSCLC).

"The BATTLE [biomarker-integrated approaches of targeted therapy for lung cancer elimination] study has demonstrated that it is feasible (using fresh tissue biopsies) to identify groups of patients with NSCLC who are more likely to benefit from a specific agent(s)," says Roy Herbst, University of Texas MD Anderson Cancer Center, USA, the co-principal investigator on the trial.

"The BATTLE trial represents an important model for future genotype-driven studies of targeted therapies in lung cancer," says William Pao, Director of Personalized Cancer Medicine at Vanderbilt University, Tennessee, USA. "A major strength of the BATTLE study was that pretreatment biopsies were obtained from all patients in the study, which yielded sufficient material for molecular analysis."

Notably, the BATTLE trial incorporated an adaptive design to use information about how patients enrolled initially were responding to treatment within a given biomarker group to guide the treatment selected for patients that were subsequently enrolled.

Patients participating in the study were tested for 11 potential biomarkers, which included mutations in epidermal growth factor receptor (*EGFR*) and *KRAS*; copy number of *EGFR* and *cyclin D1*; and expression of vascular endothelial growth factor receptor (*VEGFR*). The initial group of patients was randomized to receive erlotinib (Tarceva; Roche), sorafenib (Nexavar; Onyx/Bayer), vandetanib or erlotinib plus bexarotene (Targretin; Eisai). Then, once enough baseline results had been collected, the data from this group were used to assign the remaining patients to the treatment arms most likely to result in the best outcome based on their tumour type. The primary end point was disease control at 8 weeks.

Key findings of the study showed that patients with *KRAS* mutations tended to respond better to sorafenib relative to the other three regimens, whereas patients with *EGFR* mutations responded better to erlotinib. The erlotinib and bexarotene combination worked best in patients that were positive for *cyclin D1* or had *EGFR* copy number amplifications, and increases in *VEGFR2* expression correlated with a good response to vandetanib.

However, Herbst cautions that these early data need to be validated in larger confirmatory studies, and that the precise mechanisms of the link between the biomarker and the drug effect need to be more closely investigated.

Several of these biomarkers are likely to be taken forward in more definitive conventional Phase III randomized studies, using the same or other anticancer agents. It is also planned that these biopsy samples (that are correlated with patient outcome) will be used to explore the genomic and proteomic predictors of drug response.

Herbst also notes that lessons learned from the adaptive trial design should make future iterations more effective. "When the current trial was designed in 2004, we used the best information available, but some of the chosen biomarkers turned out to be less selective in discriminating the group. In our next study (BATTLE-2), we are only going to predetermine one or two markers at most before the trial begins, and instead observe and learn in real time what the most predictive and discriminating markers could be. Additionally, we hope to begin the adaptive randomization earlier."

Moreover, Herbst hopes that the biomarkers identified in the BATTLE study might be beneficial when using the drugs in other cancers that have similar molecular characteristics. "The initial medical treatment of localized malignant disease (using surgery and/or radiation therapy) is likely to be based on its site of origin, but metastatic disease that has spread from the primary site is, in most cases, the reason for mortality from cancer. So, I expect that in the next few years we will begin to explore treating more tumours based on genotype and molecular classifiers, no matter what the original site of origin." However, Pao cautions: "Currently, we're assuming that a mutation found in one cancer will be associated with the same sensitivity (or resistance) to a specific therapy in another cancer. Only time will tell if this is the case."