



Liquid biopsy guided precision therapy for lung cancers

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Comment on: Wang Z, Cheng Y, An T, *et al.* Detection of EGFR mutations in plasma circulating tumour DNA as a selection criterion for first-line gefitinib treatment in patients with advanced lung adenocarcinoma (BENEFIT): a phase 2, single-arm, multicentre clinical trial. *Lancet Respir Med* 2018;6:681-90.

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Wang *et al.* reported results of the BENEFIT trial sponsored by Chinese Thoracic Oncology Group (CTONG) in *Lancet Respiratory Medicine*, the first clinical trial conducted using circulating tumor DNA (ctDNA) for patient selection (1). In this multicenter, single-arm, phase 2 trial, patients with advanced lung adenocarcinoma received first-line gefitinib therapy when *EGFR* activating mutations were detected by droplet digital polymerase chain reaction (ddPCR) in ctDNA. The primary endpoint was the proportion achieving an objective response according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary endpoints included median progression-free survival (PFS) and safety. A total of 188 patients with *EGFR* mutations detected in ctDNA were enrolled and received gefitinib; 183 patients were evaluable for the primary efficacy analysis, having undergone at least one post-baseline radiographic assessment. The objective response was 72.1% (95% CI: 65.0–78.5%) and median PFS was 9.5 months (95% CI: 9.07–11.04 months). Furthermore, among 167 patients with serial blood samples drawn during gefitinib therapy, clearance of their *EGFR* mutations in ctDNA by the 8th week of treatment was observed in 147 (88%) patients. Median PFS was significantly longer in these patients than in the other 20 patients who had persistence of their *EGFR* mutations in ctDNA [11.0 *vs.* 2.1 months, hazard ratio (HR), 0.14, 95% CI: 0.08–0.23, *P*<0.001]. The authors also reported three genomic subsets of patients defined by next-generation

sequencing (NGS) of pre-treatment ctDNA with a 168-gene panel: *EGFR* mutation alone, *EGFR* mutation with co-altered tumor-suppressor genes, and *EGFR* mutation with co-altered putative oncogenes. In total, 97 (54%) patients harbored mutations in the *TP53*, *RB1*, or *PTEN* tumor-suppressor genes. Several putative oncogenes apart from *EGFR* activating mutations, including mutations in *MET*, *ERBB2*, *KRAS*, *BRAF*, *RET*, *ROS1*, or *EGFR* T790M, were observed in 24 (13%) patients. The Median PFS of the three groups was 13.2 months (*EGFR* along), 9.3 months (*EGFR* + tumor suppressor), and 4.7 months (*EGFR* + co-altered oncogene), respectively.

Robust evidence from several phase III randomized clinical trials has shown that *EGFR* tyrosine kinase inhibitors (TKIs) prolong PFS and improve the quality of life (QoL) when given as first-line therapy for advanced *EGFR* mutant non-small cell lung cancer (NSCLC) patients (2). Based on these trials (3–6), gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib were approved by the U.S. Food and Drug Administration (FDA) as the first-line therapy for advanced NSCLC patients harboring *EGFR* mutations detected in tumor tissue. Companion diagnostic tests performed in tumor tissue for *EGFR* mutations have also been approved by FDA (7). Tumor testing does, however, have limitations, including accessibility (site of biopsy, temporal expediency), inter-tumoral heterogeneity, and the increasingly complex demands for tissue utilization.

Liquid biopsy using ctDNA is an approach proposed

more recently for the detection of oncogenic alterations in blood, cerebrospinal fluid (CSF), or urine through the use of sensitive technologies such as ddPCR, NGS (8). Liquid biopsies have the advantage of overcoming some of the drawbacks associated with tumor biopsies. Blood samples are relatively easy to obtain from patients. Plasma ctDNA may better capture the total landscape of oncogenic alterations found across all tumor sites. Currently, the Cobas *EGFR* mutation test v2 from Roche is the only ctDNA platform approved by FDA as a companion diagnostic test for the detection of *EGFR* exon 19 deletions, exon 21 L858R mutations, and exon 20 T790M mutation (7,9). Several commercially available liquid biopsy platforms based on NGS technology have been analytically validated, with sensitivities, specificities, false negative rates, false positive rates, positive predictive values, and negative predictive values noted in comparison with tissue (10,11). The specificity of ctDNA is generally high while the sensitivity varies between different platforms. However, these data have not yet led to the incorporation of ctDNA into routine clinical practice (12). The BENEFIT trial adds to the general body of knowledge by prospectively selecting advanced non-small cell lung cancer patients for EGFR-TKI therapy based on ctDNA testing, demonstrating that doing so yields similar clinical efficacy as when patients are selected by tumor testing.

Importantly, the BENEFIT trial also found other factors associated with PFS benefit. Longer PFS was observed in the patients who cleared their *EGFR* mutations from the blood by the 8th week of treatment. This likely represents a surrogate for tumor response to gefitinib, a surrogate for depth of response that BENEFIT shows correlated with significantly longer PFS in a way that might be less clear from radiographic assessment alone. The data raises the possibility that early intervention in reaction to ctDNA clearance, or lack thereof, of an *EGFR* mutation might alter the prognosis of patients, creating new strategies for future trials.

Heterogeneity in the co-alterations found in ctDNA in the BENEFIT trial provides further evidence that other genomic factors likely modulate response to EGFR-TKIs. The ease of performing ctDNA testing provides a more facile platform to utilize this information in a more personalized fashion to optimize treatment, both upfront as well as over time as alterations emerge or recede. Some attempts have been made to do this. Most generally, combining targeted drugs with chemotherapy and/or bevacizumab is a strategy that has shown promise (13,14).

Today, tissue biopsy for histopathology diagnosis remains the gold standard for testing purposes. The implementation of liquid biopsy may change the clinical diagnostic workflow. Liquid biopsy can be an expressway to obtaining the molecular profile of the tumor and can provide data that complements or augments radiographic interpretation of response. The BENEFIT trial affirms both benefits associated with ctDNA testing, helping to point the way forward to new diagnostic paradigms and trial designs as we seek to optimize therapies for our patients.

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Footnote

Conflicts of Interest: Chongrui Xu—Consulting: Boehringer Ingelheim; Honoraria: AstraZeneca, Boehringer Ingelheim, Lilly, MSD, Novartis, Pfizer, Roche. Michael Offin—Consulting: PharmaMar. Paul K. Paik—Honorarium: Celgene, Takeda, Abbvie, Lilly Advisory Board: Celgene, Lilly, Abbvie; IDSMC: Takeda. Bob T. Li—Consulting/advisory board: Biosceptre International, Roche/Genentech, Thermo-Fisher Scientific, Mersana Therapeutics, Guardant Health, Hengrui Therapeutics.

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