Perioperative ctDNA-Based MRD Detection in NSCLC—Response

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We appreciate Yu and colleagues for their interest in our study and we would like to give our reply to their concerns.

In LUNGCA-1 study, a total of 330 patients with resected tumor tissues and preoperative blood samples available were included in prognostic analysis, and all but one of these 330 patients had at least one available plasma sample at postoperative 3 days and/or 1 month (1). Thus, preoperative circulating tumor DNA (ctDNA) and postoperative ctDNA-based molecular residual disease (MRD) analysis was done for 330 and 329 patients respectively, as reflected in the number of patients in both Fig. 1 and detailed sample information listed in Supplementary Table S5. LUNGCA-1 study was aimed at evaluating the potential of ctDNA-based MRD during perioperative period for predicting disease relapse and identifying patients who may potentially benefit from adjuvant therapy, and throughout the entire article, there was no mentioning of ctDNA testing after adjuvant therapy.

We designed two postoperative blood collection timepoints for ctDNA-based MRD detection. We found that the amount of cell-free DNA increased significantly at 3 days after surgery, and then dropped at postoperative 1 month. ctDNA status at postoperative 3 days was significantly associated with recurrence-free survival ($P < 0.001$), although with lower prognostic value than ctDNA status at postoperative 1 month (HR: 8.6 vs. 14.3). Among 5 patients whose ctDNA was positive at postoperative 3 days but negative at the other two perioperative timepoints, 4 (80.0%) experienced disease relapse, and the only one who remained disease free had received adjuvant therapy and had a relatively short follow-up (437 days) at the time of data lockdown. Therefore, ctDNA at 3 days after surgery proved to be useful in complementing MRD analysis at postoperative 1 month by increasing detection sensitivity without sacrificing specificity.

The current LUNGCA-1 study focused on the association of postoperative MRD detection with disease relapse. The clinical relevance of preoperative ctDNA concentration was not a concern of the published paper and therefore not reported. The criteria for determining ctDNA status had been clearly described in the paragraph "Next-generation sequencing and ctDNA analysis" of the Materials and Methods section, as well as the Supplementary Methods. Disease relapse included locoregional recurrence and distant metastases after surgery, which was determined by radiological methods and/or biopsy.

Authors' Disclosures

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