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Commentary: Drawing the target after shooting the arrow: The importance of trial design

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CENTRAL MESSAGE

Major pathological response after neoadjuvant therapy for lung cancer is associated with improved long-term survival. Pathological response should be the primary end point in neoadjuvant trial design.

Zhang and colleagues[1] report a phase 2 neoadjuvant trial with the tyrosine kinase inhibitor gefitinib followed by resection for exon 19 deletion and exon 21 L858R mutant stage II through IIIA lung adenocarcinoma. The primary end point was radiological objective response rate (ORR). A secondary end point was major pathological response (MPR) ($\leq$10% viable tumor). They noted 2-year disease-free survival of 87.5% versus 52.4% with or without MPR, respectively. ORR did not correlate with survival or pathological response. The authors should be commended for designing, executing, and reporting a neoadjuvant surgical trial.

Hellmann and colleagues[2] argue that neoadjuvant trials are more effective than adjuvant trials in shortening the time to results. Adjuvant trials require years because patients must be followed for recurrences or death. In contrast, neoadjuvant trials obtain response data at surgical resection that is a surrogate for survival. For a surrogate to be meaningful, treatment must be associated with the surrogate, the surrogate must be associated with the outcome, and the surrogate must explain the effect on the outcome.[3] Fortunately, pathological response meets these criteria with minor revisions noted by Hellmann and colleagues.[2]

The importance of pathological response in thoracic oncology has been known for years. Mouillet and colleagues[4] report that among 492 patients in 2 neoajuvant trials for resectable lung cancer, 8.3% achieved a pathological complete response with 5-year overall survival of 80%. In Intergroup Trial 0160, Rusch and colleagues[5,6] reported that pathological response was the most important predictor of survival after neoadjuvant chemoradiotherapy and resection for pancoast tumors. They noted median survival that was not reached versus 30 months with pathological complete response versus residual disease, respectively. In 1994, Mandard and colleagues[7] reported that pathological tumor response grade was the only predictor of survival on multivariable analysis among patients with esophageal cancer who received neoadjuvant chemoradiotherapy. In 2014, Davies and colleagues[8] reported that the downstaging after neoadjuvant therapy is the most important determinant of survival in esophageal cancer regardless of the initial clinical stage. These results support that pathological assessment after neoadjuvant therapy is a valuable surrogate for survival in patients with thoracic cancers.

Zhang and colleagues[1] report that the secondary end point, MPR, was associated with improved DFS as opposed to the primary end point, ORR. This findings highlight the importance of trial design because radiological assessment does not necessarily correlate with treatment response. Pathological response rates should be the primary end points for most if not all neoadjuvant trials. As a corollary, pretreatment pathological confirmation is critical for primary tumor as well as adenopathy. As the authors state, "Future clinical trials of neoadjuvant therapy may consider…pathological evaluation as a surrogate end point." Given the importance for patients with lung cancer as well as other thoracic cancers, neoadjuvant trials such as this one should

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Commentary: Preoperative gefitinib for stage II-III non–small cell lung cancer with *EGFR* mutation: A stich in time, or delay from stiches?

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CENTRAL MESSAGE

In this phase 2 study, 42 days of gefitinib produced a major pathologic response in 1of 4 patients with stage II-IIIA *EGFR* mutant lung cancer, which was associated with longer disease-free survival.

Resected lung cancers with activating/sensitizing *EGFR* mutations have improved overall survival compared with wildtype EGFR, which may be due to favorable disease biology, treatment with EGFR tyrosine kinase inhibitors (TKIs) at recurrence, or both.[1] There is great interest in developing EGFR TKIs as adjuvant therapy for resected lung cancers with *EGFR* mutation. Published adjuvant and neoadjuvant studies demonstrate that TKIs delay recurrence compared with chemotherapy or no therapy, raising the question of the value of continuous therapy versus treatment at recurrence.[2-5]

The National Cancer Institute's ongoing Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST, NCT02193282) is randomizing patients with resected stage IB-IIIA *EGFR* mutant lung cancer to 2 years of postoperative erlotinib versus observation. The study opened in 2014, is anticipated to complete accrual in 2021, and is powered to detect a 30% reduction in the risk

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