See Article page 434.

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 colleagues¹ 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 colleagues² 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 colleagues⁴ report that among 492 patients in 2 neoadjuvant 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 colleagues⁷ 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 colleagues⁸ 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 colleagues¹ 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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Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication March 9, 2020; revisions received March 9, 2020; accepted for publication March 9, 2020; available ahead of print March 31, 2020.

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J Thorac Cardiovasc Surg 2021;161:443-4

0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2020.03.055>

be highly encouraged and supported in our thoracic oncology community.

References

1. Zhang Y, Fu F, Hu H, Shengping W, Li Y, Hu H, et al. Gefitinib as neoadjuvant therapy for resectable stage II-III non-small cell lung cancer: a phase II study. *J Thorac Cardiovasc Surg*. 2021;161:434-42.e2.
2. Hellmann MD, Chaft JE, William WN Jr, Rusch V, Pisters KM, Kalhor N, et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. *Lancet Oncol*. 2014;15:e42-50.
3. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med*. 1989;8:431-40.
4. Mouillet G, Monnet E, Milleron B, Puyraveau M, Quoix E, David P, et al. Pathologic complete response to preoperative chemotherapy predicts cure in early-stage non-small-cell lung cancer: combined analysis of two IFCT randomized trials. *J Thorac Oncol*. 2012;7:841-9.
5. Rusch VW, Giroux DJ, Kraut MJ, Crowley J, Hazuka M, Johnson D, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Thorac Cardiovasc Surg*. 2001;121:472-83.
6. Rusch VW, Giroux DJ, Kraut MJ, Crowley J, Hazuka M, Winton T, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Clin Oncol*. 2007;25:313-8.
7. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73:2680-6.
8. Davies AR, Gossage JA, Zylstra J, Mattsson F, Lagergren J, Maisiey N, et al. Tumor stage after neoadjuvant chemotherapy determines survival after surgery for adenocarcinoma of the esophagus and esophagogastric junction. *J Clin Oncol*. 2014;32:2983-90.

See Article page 434.

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

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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

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CENTRAL MESSAGE

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

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Disclosures: The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication April 4, 2020; revisions received April 4, 2020; accepted for publication April 6, 2020; available ahead of print April 18, 2020.

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J Thorac Cardiovasc Surg 2021;161:444-6

0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2020.04.028>

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-III *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