Current Readings: Window-of-Opportunity Trials for Thoracic Malignancies

Anne S. Tsao, MD

Recent major advances in metastatic non–small cell lung cancer have occurred with the identification of molecular biomarker targets and administration of novel agents with resulting improvement in clinical outcomes. In the early-stage setting, personalized therapy with novel agents and molecular profiling are being incorporated into neoadjuvant "window-of-opportunity" trials. These important studies enable biomarker research and an expedited analysis of the efficacy of the targeted agent. However, there are significant limitations to window-of-opportunity trials. The aim of this article is to review the current window-of-opportunity trials of neoadjuvant targeted agents for thoracic malignancies, discuss the benefits and limitations of these trials, and propose more optimal alternative trial end points. Neoadjuvant trials of resectable non–small cell lung cancer and mesothelioma that are ongoing or under development and relevant to thoracic surgeons are also discussed. The success of these trials will depend on a collaborative multidisciplinary effort, especially from the field of thoracic surgery.

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INTRODUCTION

Neoadjuvant chemotherapy is a common approach to managing resectable local or regionally advanced non–small cell lung cancer (NSCLC). Most neoadjuvant trials have used 4 cycles of platinum-doublet chemotherapy and, as a whole, have shown a 5% absolute survival benefit at 5 years.[1] The advantages and disadvantages to using neoadjuvant chemotherapy are listed in Table 1. Clinical trials using neoadjuvant chemotherapy or chemoradiotherapy have identified prognostic factors for improved survival after tumor resection.[2-5] Patients with superior survival outcomes include those who achieve a response to chemotherapy, whose disease is downstaged from N2, who have single-station N2 rather than multistation N2 disease, who achieve R0 resection, and who have a complete pathologic response.[2,4]

Department of Thoracic & Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

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Address reprint requests to Anne S. Tsao, MD, Department of Thoracic & Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 432, Houston, TX 77030. E-mail: astsao@mdanderson.org

Thus, it can be extrapolated that better systemic therapies may lead to increased downstaging and superior clinical outcomes. In the era of personalized therapy with novel agents and molecular profiling, designing studies—such as "window-of-opportunity" trials—that enable biomarker research and expedited analysis of whether the agents are efficacious are critically needed. This review article summarizes the current literature on 3 thoracic window-of-opportunity studies with novel targeted agents to illustrate the evolution of this type of trial design. The advantages and disadvantages of novel agent window-of-opportunity trials and alternative trial end points are discussed. Ongoing neoadjuvant studies with novel agents relevant to the thoracic surgical community are summarized. Window-of-opportunity studies with multidisciplinary effort, especially surgical support, are a necessary and vital component to move the field of thoracic oncology forward.

PHASE II STUDY OF PREOPERATIVE GEFITINIB IN CLINICAL STAGE I NON–SMALL CELL LUNG CANCER

Lara-Guerra H, Waddell T, Salvarrey M, et al: J Clin Oncol 27:6229-6236, 2009

Lara-Guerra et al[6] conducted a preoperative window-of-opportunity trial (Fig. 1) using gefitinib, an epidermal growth factor receptor (EGFR) tyrosine

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Table 1. Hypothetical Implications of Neoadjuvant Therapy

Advantages	Disadvantages
Gives patients time to quit using tobacco	Delays definitive procedure
Eliminates micrometastatic disease earlier	Interferes with surgery owing to the toxicity of chemotherapy
Allows higher dose chemotherapy (patients tolerate chemotherapy better before rather than after major surgery)	Creates staging ambiguity
May lead to downstaging of disease	Increases the risk of postoperative complications
Provides prognostic value (assessment of chemosensitivity)	

kinase inhibitor, and demonstrated that this type of trial design is feasible and safe for patients with early-stage resectable non–small cell lung cancer (NSCLC).

In this single-arm phase II study, Lara-Guerra et al[6] enrolled 36 patients with stage I resectable NSCLC and treated them with preoperative gefitinib (250 mg/d) for up to 28 days. Radiographic imaging results as determined using standard response evaluation criteria in solid tumors (RECIST) were obtained before and after preoperative gefitinib therapy. After 24-48 hours from the last dose of neoadjuvant gefitinib, patients underwent mediastinoscopy and surgical resection. The primary end point of the trial was overall response rate as determined by RECIST, and the secondary end points included the overall survival and progression-free survival rates. The translational studies included analysis of tumor tissue for EGFR by immunohistochemistry and fluorescent in situ hybridization, *EGFR* gene mutation, and serum levels for tumor growth factor α.

Among the 35 evaluable patients, 11% had a partial response, 81% stable disease, and 8% progression of disease as determined by RECIST after 28 days of gefitinib treatment. Tumors shrank in 15 (43%) patients, grew in 15 patients (43%), and did not change in size in 5 (14%) patients.

The only biomarker that predicted a clinical partial response was the presence of a sensitizing *EGFR* mutation (deletion exon 19 or L858 mutation). Among the patients with a *KRAS* mutation, there were no responders. No other biomarkers were predictive or prognostic, although in one case a patient with a high *EGFR* gene copy number as determined by fluorescent in situ hybridization and no *EGFR* mutation also demonstrated a partial response.

MOLECULAR CHARACTERISTICS PREDICT CLINICAL OUTCOMES: PROSPECTIVE TRIAL CORRELATING RESPONSE TO THE EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITOR GEFITINIB WITH THE PRESENCE OF SENSITIZING MUTATIONS IN THE TYROSINE BINDING DOMAIN OF THE EGFR GENE

Rizvi N, Rusch V, Pao W, et al: Clin Cancer Res 17:3500-3506, 2011

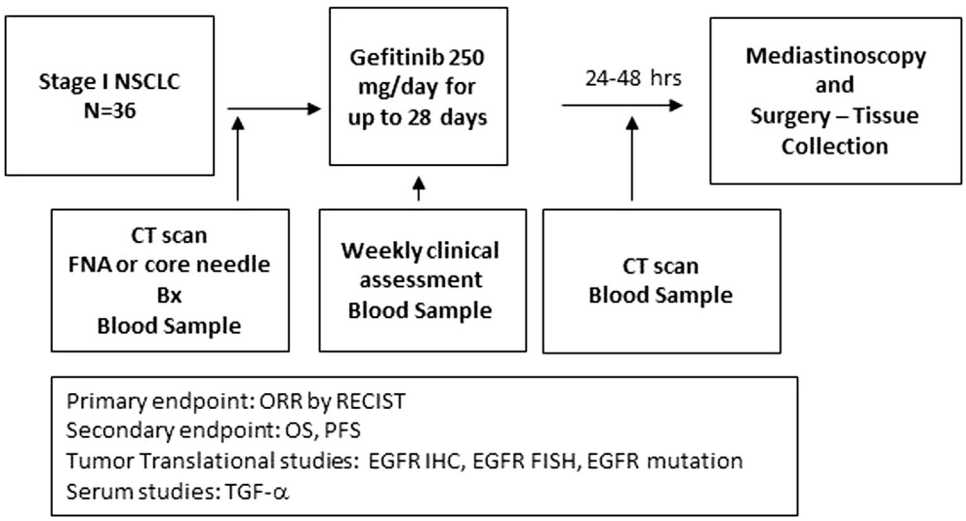

Figure 1. Phase II trial schema of preoperative gefitinib for patients with stage I resectable NSCLC.[6] FISH, fluorescent in situ hybridization; FNA, fine needle aspiration; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TGFα, transforming growth factor α.