be highly encouraged and supported in our thoracic oncology community.

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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?

Christopher G. Azzoli, MD,[a] and Thomas Ng, MD[b]

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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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of death (overall survival), which may be difficult to achieve in a population that generally lives longer.[6] In 2018, osimertinib supplanted erlotinib as the first-line drug of choice for patients with stage IV disease by improving overall survival compared with erlotinib or gefitinib.[7] An adjuvant study of up to 3 years of osimertinib is underway (ADAURA, NCT02511106) and initial reports are encouraging, possibly practice changing.

Adjuvant studies take many years to complete. Rapid progress in the development of new drugs for stage IV disease has elevated the importance of neoadjuvant studies, which have rapid, surrogate efficacy end points like pathologic response or downstaging. To minimize delay in curative therapy, neoadjuvant treatment is decidedly short, on the order of weeks. The ideal neoadjuvant therapy would confer survival benefit in short order.

Short, or even long, courses of drug therapy for lung cancer rarely result in complete pathologic responses, especially with TKIs. Major pathologic response (MPR) is a lower bar than complete pathologic response and is defined as 10% or less residual viable cancer cells after neoadjuvant drug therapy.[8,9] Mounting evidence suggests MPR can predict longer survival. Early results of several neoadjuvant studies of immune checkpoint inhibitors are reporting MPR rates of 15% to 80%, with greater rates observed using a combination chemotherapy + immune checkpoint inhibitor strategy.[10]

In this issue of the *Journal*, Zhang and colleagues[11] report the results of their phase II study of 42 days of gefitinib as preoperative therapy for patients with resectable stage II-IIIA (high-risk) lung cancer with *EGFR* mutation. The authors should be commended for their work in testing and caring for more than 200 patients to find the 28 patients who completed the study requirements. Eight patients (24%) demonstrated MPR, and those patients had dramatically longer disease-free survival and a strong trend toward improved overall survival. It should be noted that delivery of adjuvant cytotoxic chemotherapy was not specified in this study, but every patient received it. These data bolster confidence that MPR may prove to be a meaningful surrogate efficacy end point, even when measuring the benefit of TKIs, which almost never produce complete pathologic responses.

These data highlight the limits of MPR, especially when applied to a treatment that is effective in most patients and is most effective when delivered continuously. For example, should MPR with 42 days of preoperative therapy be used to encourage, or liberate a patient from years of continuous postoperative therapy, or liberate a patient from chemotherapy? In this sense, the lack of MPR in the neoadjuvant space is akin to lack of clearance of the *EGFR* mutation from blood in patients with stage IV disease—it is a bad omen during effective therapy, and currently without practical use outside of a clinical trial.[12,13]

The appeal of neoadjuvant treatment remains. But in order to routinely delay curative surgery, neoadjuvant therapy must prove itself to both save lives and meaningfully alter treatment decisions, such as sparing patients difficult, dangerous, expensive, or unnecessary postoperative therapies. Too few neoadjuvant studies factor this value into their design.

To date, we know that neoadjuvant combination chemotherapy only rarely interferes with successful surgery and improves overall survival just as well as adjuvant therapy.[14] Immune checkpoint inhibitors might actually work better when the cancer is still present in the body.[10] Rapid discovery of new drugs requires rapid platforms for testing in patients with high-risk, resectable disease. So, we know that neoadjuvant platforms are here to stay and will ultimately serve to validate surrogate biomarkers (like MPR) that can be used to direct both selection, and duration, of postoperative therapy. The work of Zhang and colleagues,[11] and ongoing adjuvant studies of EGFR TKIs, help move us toward a future in which neoadjuvant treatment will be a stich in time that truly justifies a delay from stiches.

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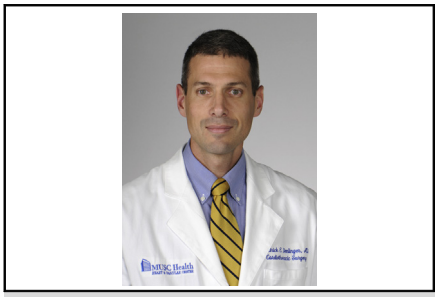
Commentary: Durable activity of a tyrosine kinase inhibitor in lung cancer

Chadrick E. Denlinger, MD



Chadrick E. Denlinger, MD

CENTRAL MESSAGE

Surgery for locally advanced lung cancers following neoadjuvant gefitinib appears safe with surprisingly optimistic long-term outcomes.

Lung cancer treatment has progressed dramatically in the past decade with the emergence of tyrosine kinase inhibitors (TKI) targeting specific growth factor receptors and immune checkpoint inhibitors. After identifying that growth factor mutations, rather than simple overexpression, was a critical factor for the efficacy of TKIs, some of these agents became the preferred treatment for lung cancers. Epithelial growth factor receptor (EGFR) inhibitors, such as gefitinib and other newer agents, have replaced cytotoxic agents as the principal treatment for advanced-stage lung cancers for patients with activating mutations of EGFR based on improved efficacy and better side effect profiles.[1] TKIs have a substantial influence on progression-free survival while overall survival rates remain similar to standard cytotoxic chemotherapy.[2] It is well understood that the long-term treatment efficacy of TKIs is limited by cancers developing new point mutations or alternative escape pathways leading to TKI resistance and cancer progression.[3] For this reason, TKIs are not currently indicated in any curative-intent treatment strategies.

Zhang and colleagues[4] pushed the envelope to determine the efficacy of using gefitinib as neoadjuvant therapy followed by surgical resection of locally advanced lung cancer harboring EGFR activating mutations.[4] Most importantly, the treatment protocol appears safe with short-term surgical outcomes that were comparable to other neoadjuvant treatment protocols. Indeed, there were no 90-day mortalities and the median operative blood loss was 100 mL. Loose correlations between clinical response and pathological response open the door for interpretation. However, the direct relationship between pathological response and both progression-free and overall survival are logical and correlate with well-established outcomes associated with neoadjuvant treatments.[5]

The overall survival rate of 66% is quite impressive for a cohort of stage II through IIIA patients even when considering that some reports suggest lung cancer patients with mutant EGFR have improved outcomes relative to EGFR wild-type patients.[6] This is particularly true when considering that 27 of 33 patients included in the survival analysis were diagnosed with stage IIIA disease. One concern for the unusually favorable results is the potential for selection bias, and this concern is accentuated by the exclusion in

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