Have adjuvant tyrosine kinase inhibitors lost their shine?

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Abstract: Despite broad advances in molecularly targeted therapies, lung cancer remains the leading cause of cancer related mortality in the United States. Epidermal growth factor receptor (EGFR) mutations occur in approximately 17% of advanced non-small cell lung cancer (NSCLC) in the US population. The remarkable efficacy of small-molecule EGFR tyrosine kinase inhibitors (TKIs) in this unique subset of patients has revolutionized the therapeutic approach to lung cancer. The success of these agents in the metastatic setting leads to the logical question of what role these drugs may have in the adjuvant setting for patients with earlier stage disease. RADIANT, an international randomized, double-blind, placebo controlled phase III study in patients with completely resected stage IB to IIIA NSLC whose tumors expressed EGFR by IHC and EGFR amplification by FISH, attempted to answer the question of whether erlotinib would improve disease free survival and overall survival in the adjuvant setting. While RADIANT does not conclude for or against adjuvant use of EGFR-TKIs, all data points towards benefit in a selected population. As clinicians, we must continue to enroll to potentially practice changing therapeutic neoadjuvant and adjuvant chemotherapy studies internationally.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR); tyrosine kinase inhibitor (TKI); adjuvant; erlotinib; gefitinib; afatinib

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Despite broad advances in molecularly targeted therapies, lung cancer remains the leading cause of cancer related mortality in the United States (1). The 5-year overall survival for patients with resectable stage I–IIIA non-small cell lung cancer (NSCLC) is 60% (2). Historically, clinical trials have shown a significant survival benefit in patients treated with adjuvant cisplatin-doublet chemotherapy. The Lung Adjuvant Cisplatin Evaluation pooled analysis of five large clinical trials showed a 5.4% benefit in overall survival in patients who received cisplatin-based chemotherapy (3). In the International Association for the Study of Lung Cancer (IASLC) staging project, the 5-year overall survival ranged from 73% in pathologic stage IA disease and 36% in pathologic stage IIB disease (4). While the recently reported ECOG 1505 study, a phase III randomized trial of adjuvant chemotherapy with or without bevacizumab showed a numerically improved median overall survival in all patients relative to historic adjuvant studies, this is presumably due to stage migration, early detection and improved surgical techniques, as the intervention itself was negative (5).

Epidermal growth factor receptor (EGFR) mutations occur in approximately 17% of advanced NSCLC in the United States population (6) and at a higher frequency in South East Asia (7). The remarkable efficacy of small-molecule EGFR tyrosine kinase inhibitors (TKIs) in this unique subset of patients has revolutionized the therapeutic approach to lung cancer. Erlotinib, a small molecule TKI of EGFR has proven efficacy in the treatment of advanced stage IV NSCLC. TKI therapy was initially approved for use in an unselected and previously treated patient population (8). Around the time of approval, multiple correlative analyses detected an activating mutation in *EGFR* as the predictive biomarker of response to EGFR TKIs. Subsequently, marked clinical activity of EGFR TKIs was demonstrated in patients with metastatic disease whose tumors harbor an EGFR exon 19 deletion or exon

21 L858R-activating mutations (9). A definitive study in an *EGFR* wildtype patient population, TAILOR, confirmed that chemotherapy is superior to erlotinib in the absence of an *EGFR* sensitizing mutation (10). Erlotinib, gefitinib, and afatinib, are now FDA approved for the treatment of NSCLC with *EGFR* mutation. The success of these agents in the metastatic setting leads to the logical question of what role these drugs may have in the adjuvant setting for patients with earlier stage disease. The use of EGFR TKI therapy in the adjuvant setting for non-metastatic EGFR-mutated lung cancer remains controversial as there is no conclusive prospective data to support its use or lack thereof, even after the publication of the much anticipated RADIANT study, as it was performed without molecular selection.

The first large randomized controlled trials to evaluate the use of TKIs in the adjuvant setting were performed over ten years ago in an unselected patient population. SWOG S2003 a phase III trial enrolled 672 patients with unresectable, locally advanced, stage III NSCLC receiving definitive chemotherapy and radiation. Patients who had no evidence of disease progression were randomized to gefitinib 250 mg daily versus placebo. An interim analysis demonstrated inferior survival for those receiving gefitinib and the study was closed early (11). The CALGB phase II study of chemoradiotherapy and gefitinib in an unselected patient population showed no benefit in overall survival as well (12). These results prompted the premature closure of the National Cancer Institute of Canada, phase III, randomized controlled double blinded BR.19 trial of adjuvant gefitinib in unselected patients with stage IB–IIIA resected disease. The study accrued only half of the planned patients and the median duration of therapy was less than 6 months. Fifteen patients had activating EGFR mutations of whom 7 received gefitinib and 8 received placebo (13). This was an underpowered study that was terminated early as it was not enriched for the relevant patient population. This data has no clinical utility.

RADIANT, an international randomized, double-blind, placebo controlled phase III study in patients with completely resected stage IB to IIIA NSLC whose tumors expressed EGFR by IHC and EGFR amplification by FISH, attempted to answer the question of whether erlotinib would improve disease free survival and overall survival in the adjuvant setting (14). Nine hundred and seventy three patients were randomized and assigned 2:1 to erlotinib 150 mg once per day or placebo for 2 years. The primary endpoint was disease free survival and secondary endpoints included overall survival. The trial design was justified by the hypothesis that EGFR expression by IHC as well as *EGFR* gene copy number would predict EGFR-TKI benefit. RADIANT began accrual in November of 2007, after the publications demonstrating that EGFR mutations confer sensitivity to erlotinib and gefitinib (15). As expected, the study's primary endpoint of median disease-free survival was not significantly different at 48.2 months for placebo versus 50.0 months for erlotinib (HR 0.90; P=0.32). Of note, the median duration of treatment was noticeably shorter with erlotinib than placebo, 11.9 versus 21.9 months, which is likely attributed to the known side effects of erlotinib, particularly at full dose 150 mg daily (Tarceva package insert). The overall survival data were immature, with a median follow up of 47 months at the time of publication. A subset analysis of 161 patients with more sensitizing EGFR mutations, deletion 19 or exon 21 L858R, representing 16% of the overall patients, showed an impressive disease free survival advantage in the erlotinib group when compared with placebo; 46.4 versus 28.5 months (HR 0.61; P=0.04). Although this subset analysis was positive, it was underpowered and due to the hierarchical testing procedure which dictated that if the primary endpoint was not met all subsequent endpoints would be invalid, the result was not considered meaningful. Median overall survival in the subset analysis was also not reached, with 22 events in the placebo arm and 13 events in the erlotinib arm (HR 1.09; P=0.81). Overall, the study results are compelling although not definitive and should not change current practice. This was valiant and forward thinking attempt to move EGFR TKIs to the curative setting, however with the wrong biomarker and an underpowered EGFR positive cohort.

Given the disproportionate drug discontinuation rate in the erlotinib arm, the optimal duration of adjuvant targeted therapy, if any, remains an active area of inquiry. In a high risk population of patients with resected stage IIIA-N2 EGFR-mutant adenocarcinomas, patients received adjuvant carboplatin + pemetrexed × 4 cycles followed by either 6 months of gefitinib or observation. This study met its primary endpoint of DFS with a median DFS of 79% in the gefitinib arm versus 54% in the chemotherapy only group (16). This small phase II study was not powered to demonstrate an OS advantage. While a quick look at this intriguing data would perhaps support a short course of therapy in resected high risk patients, though the DFS curves begin to fall at the same rate as the observation curves about a year after drug discontinuation.

The SELECT trial, a multicenter, single arm, phase II study of adjuvant erlotinib in resected stage IA–IIIA EGFR mutant NSCLC who completed adjuvant therapy readdressed the question at hand. The reported DFS was 89% versus the historical control of 76% (17). Although again encouraging, this was a single arm study and due to possible selection bias conclusions regarding true benefit cannot be reached. Furthermore, there was an alarming drop off in disease free survival at 3 years. A follow-up study at the SELECT institutions, NCT01746251, is studying the duration of therapy question, randomizing patients to 3 months versus 2 years of afatinib after completion of standard adjuvant therapy.

There are ongoing international efforts attempting to answer the question of utility of adjuvant EGFR TKIs. NCT02518802 is a Chinese Phase III trial of cisplatin + pemetrexed with and without gefitinib as adjuvant therapy in patients with stage II–IIIA, EGFR mutant NSCLC is currently enrolling patients with an estimated completion date of January 2018, with the primary endpoint of DFS. Perhaps more progressive, there are two alternative trial designs (NCT01405079 and NCT01410214) that will compare gefitinib or erlotinib, respectively to vinorelbine + cisplatin with the primary endpoint of DFS. This is a step away from chemotherapy that has not yet been widely accepted in Europe or the Americas.

In the US, NCT02193282 National Cancer Institute Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials or (ALCHEMIST) will enroll patients with EGFR-sensitizing mutations and randomize to erlotinib versus placebo with a primary endpoint of overall survival. This will ultimately answer the gold standard clinical question of survival in the adjuvant space. Unfortunately the results will not be available for many years still, and will perhaps be irrelevant pending completion of NCT02511106, an ongoing randomized phase III study of the 3rd generation EGFR TKI osimertinib, although again powered for a DFS endpoint.

In summary, while available randomized phase III data are inconclusive, all EGFR-selected studies and subsets point to an improvement in DFS at the cost of toxicity. To date, no randomized clinical trial has shown a benefit in overall survival with the use of EGFR-TKI directed therapy in the adjuvant setting. Disease free survival has been proposed to serve the role of a valid surrogate endpoint for overall survival in studies of adjuvant therapy in patients with resected NSCLC (18), though the single definitive study design ongoing in the US will require us to await an overall survival primary endpoint. While RADIANT does not conclude for or against adjuvant use of EGFR-TKIs, all data points towards benefit in a selected population. As clinicians, we must continue to enroll to potentially practice changing therapeutic neoadjuvant and adjuvant chemotherapy studies internationally, though stay alert to the evolving data and modify active studies, if possible, when predictive biomarkers become available.

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Footnote

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