Keynote Lecture

Adjuvant molecularly targeted therapy—epidermal growth factor tyrosine kinase inhibition and beyond

Joel W. Neal[1], Lecia V. Sequist[2]

[1]Stanford Cancer Institute, Stanford University, USA; [2]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA
Corresponding to: Joel W. Neal, MD, PhD, Assistant Professor of Medicine (Oncology). Stanford Cancer Center, 875 Blake Wilbur Drive, CC 2220, Stanford, CA 94305-5826, USA. Email: jwneal@stanford.edu.

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Introduction

In stage IV non-small cell lung cancer (NSCLC), DNA molecular testing for mutations in epidermal growth factor receptor (*EGFR*) and gene rearrangements of anaplastic lymphoma kinase (*ALK*) has become the new standard of care. This is based on the unprecedented efficacy of small molecule EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib against *EGFR* mutant NSCLC (1,2), and the ALK TKI crizotinib against ALK positive NSCLC (3). While these highly active drugs should conceptually be effective as a component of the curative treatment of earlier stage NSCLC, the presently available evidence is minimal as pivotal studies are either underway or still in development. This article reviews current evidence about the use of adjuvant therapy for molecular targets in NSCLC, in particular regarding the use of EGFR TKIs in the treatment of early stage NSCLC harboring EGFR mutations (*Video 1*).

Video 1 Adjuvant molecularly targeted therapy—epidermal growth factor tyrosine kinase inhibition and beyond

Retrospective studies regarding adjuvant gefitinib and erlotinib

In 2004, activating *EGFR* mutations were identified as a key biomarker of sensitivity to the EGFR-TKIs gefitinib and erlotinib (4-6). Based on the observed cytotoxicity of these agents upon cell lines, and the availability of EGFR TKIs by prescription for the treatment of stage IV NSCLC, some physicians began to use these drugs in patients with early stage disease. Memorial Sloan Kettering performed a retrospective analysis of 167 patients with stage I-III *EGFR* mutant NSCLC and compared a cohort of 56 patients who received neoadjuvant or adjuvant EGFR TKI to a separate cohort of 111 patients who did not receive TKI (7). In a multivariate analysis that adjusted for stage and treatment with adjuvant chemotherapy, patients who received an EGFR-TKI had a 2-year disease free survival (DFS) rate of 89%, as compared with 72% for patients not treated with TKI (P=0.06), suggesting possible benefit and supporting the need for prospective research. The 2-year overall survival was ≥90% in both groups, and was not statistically different.

In another retrospective study from Memorial, 22 patients who recurred after adjuvant EGFR TKI treatment were identified, of whom 11 were retreated with TKI and 8 responded for a median duration of 10 months (8). In this study, the resistance mutation T790M was only identified in tumors from patients who were either in the midst of

adjuvant EGFR TKI therapy or less than 6 months from completion. This suggests that, similar to estrogen-receptor positive breast cancer treated with adjuvant tamoxifen (9), longer duration of an active adjuvant therapy may potentially be beneficial, and that adjuvant TKI therapy may not be increasing cure rates, but may simply be delaying recurrences.

Adjuvant gefitinib

Over 10 years ago, two large randomized trials were designed to test EGFR TKIs in early stage NSCLC (not molecularly-selected patients)—one involving chemoradiation followed by gefitinib in stage III NSCLC (SWOG S0023), and the other with adjuvant gefitinib in stage I-III NSCLC. Unfortunately, in 2005, the large ISEL trial of second line gefitinib in unselected stage IV NSCLC failed to meet its overall survival endpoint, which prematurely disrupted enrollment in both early stage trials (10).

The phase III S0023 study enrolled a total of 243 patients with stage III NSCLC expected to receive concurrent chemotherapy and radiation and randomized them to outback gefitinib for up to 5 years or placebo (11). An unplanned interim analysis in 2005 at the time of the ISEL read-out demonstrated a signal of harm for gefitinib, with a median survival time of 23 months for patients receiving gefitinib, and 35 months for patients who received placebo (P=0.013). A subset analysis to look for potential benefit, or at least lack of harm, in patients with *EGFR* mutation-positive disease could not be retrospectively performed. Based on this study, EGFR-TKI therapy after combined chemoradiation is not recommended outside of a clinical trial.

In the phase III BR.19 study, patients with stage IB-IIIA NSCLC were randomized, following surgical resection and optional adjuvant chemotherapy, to 2 years of adjuvant gefitinib or equivalent placebo. Of a planned 1,160 patients, enrollment stopped at 503 in 2005 based on the negative ISEL trial and S0023 interim report. All patients were taken off of their assigned therapy. The analysis reported in 2010 demonstrated no difference between the groups, but a trend toward harm with gefitinib was observed for both disease free and overall survival (12). In the subgroup analysis of patients with *EGFR* mutant NSCLC, 40 patients treated with placebo had a numerically, but not significantly, improved overall survival compared with 36 patients who received adjuvant gefitinib. However, given the small numbers of patients and the shorter-than-planned 5 months median duration of adjuvant TKI, firm conclusions regarding the efficacy of adjuvant TKIs for *EGFR* mutant NSCLC should not be based on this trial.

At ASCO 2013, a relatively small Chinese trial was presented in which 60 patients with primarily resected stage IIIA-N2 NSCLC were treated with either 4 cycles of adjuvant carboplatin and pemetrexed, or the same chemotherapy followed by 6 months of gefitinib (13). Unlike the S0023 and BR.19 trials, no patients received radiation, and all patients had tumors with sensitizing *EGFR* mutations. An improvement was observed for the gefitinib arm versus the control arm for median DFS (39.8 *vs.* 27.0 mo, P=0.014, HR 0.37) and a trend toward improved median overall survival was noted (41.6 *vs.* 32.6 mo, P=0.066, HR 0.37). While this study is small, it does suggest benefit for an *EGFR* mutant population with adjuvant gefitinib treatment.

Adjuvant erlotinib—SELECT and RADIANT

Following FDA approval for erlotinib in the second line treatment of stage IV NSCLC based on the BR.21 trial (14), the potential efficacy of erlotinib in the adjuvant setting became an important question. The RADIANT trial is an ongoing phase III trial which targeted 945 patients with stage I-IIIA NSCLC whose tumors have EGFR protein expression by immunohistochemistry (IHC), or increased *EGFR* gene copy number by fluorescence in situ hybridization (FISH) (15). Following surgical resection and optional adjuvant chemotherapy, patients were randomized 2:1 to erlotinib for 2 years or placebo. The biomarker analysis presented early demonstrated an *EGFR* mutation positive rate of about 17%, suggesting that approximately 40 patients will be on the control arm and 80 on the erlotinib arm (16). The initial results of this trial, including a biomarker based outcome analysis, are expected soon.

During the time the large RADIANT trial became underway, increasing evidence suggested that *EGFR* mutation status was a bigger determinant of response to EGFR TKI than either EGFR protein expression or *EGFR* gene amplification. Therefore, we initiated a single arm phase II trial with 2 years of adjuvant erlotinib following surgery for stage I-IIIA surgically resected *EGFR* mutant NSCLC patients, dubbed the SELECT (Surgically resected *EGFR* mutant Lung cancer with adjuvant Erlotinib Cancer Treatment) trial (17). Following primary surgical resection, patients received standard-of-care adjuvant chemotherapy and/or radiation at the discretion of their treating physician, followed by adjuvant erlotinib at 150 mg po daily. A report

at ASCO 2012 of the first 36 enrolled patients demonstrated that the majority were able to tolerate 2 years of adjuvant treatment, though some required dose reductions. Only two patients recurred before two years (one during adjuvant erlotinib, and one following early discontinuation), for an observed 2-year DFS of 94%. An additional 10 patients recurred after 2 years and most still were responsive to subsequent EGFR TKI therapy. This trial was subsequently expanded to 100 patients total and has been completely enrolled, with results for the entire study population expected in another 1-2 years.

Future directions/conclusions

Based on the mixed results of existing trials, there are plans for larger phase III trial to further establish the magnitude of benefit, and potential risk, of adjuvant TKI in molecularly selected subgroups of patients. In the United States, the NCI and cooperative oncology groups are designing randomized placebo-controlled phase III trials that add adjuvant TKI to standard therapy regimens: one with adjuvant EGFR TKI in surgically resected *EGFR* mutant NSCLC (n=410), and another with adjuvant crizotinib in resected ALK-positive NSCLC (n=336) (18). Randomized trials that test substitution of EGFR-TKI with adjuvant chemotherapy are also ongoing in Asia, including the WJOG6410L trial in Japan (19) and the ADJUVANT trial in China (20), each of which are randomizing more than 200 patients between adjuvant cisplatin/vinorelbine and adjuvant gefitinib for stage II-III patients after resection. If these phase III trials show promise of efficacy, the next generation of TKIs, with their expanded spectrum of activity, may present additional opportunity for improvement. Furthermore, some fundamental biological questions, such as whether these agents are cytotoxic against micrometastatic disease or simply cytostatic, will require ongoing long-term follow up, and potentially investigating extended durations of treatment.

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