A phase III randomized, double-blind, placebo-controlled trial of the epidermal growth factor receptor inhibitor gefitinib in completely resected stage IB-IIIA non-small cell lung cancer (NSCLC): NCIC CTG BR.19

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Background

- Platinum-based adjuvant chemotherapy in completely resected NSCLC had demonstrated a modest survival benefit of 5% at 5 years when this study was initiated.
- EGFR expression in NSCLC has been correlated with aggressive morphology and poor response to chemotherapy (Pavelic, Anticancer Res, 1993). Several small molecule and antibody based targeted agents have been developed directed against elements of the EGFR pathway.
- Gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, showed good activity in previously treated advanced NSCLC, leading to its approval by the FDA. Furthermore, it appeared to be well tolerated.
- Given the apparently marginal benefit from adjuvant chemotherapy, and the activity and tolerability of oral gefitinib, an adjuvant study comparing gefitinib to placebo after complete resection of NSCLC was initiated, and the results are presented here:

Methods

- Eligibility criteria:
  - Patients with completely resected Stage IB-IIIA NSCLC
  - Complete mediastinal lymph node dissection
  - Post-operative radiation and chemotherapy allowed
  - Patients were stratified by sex, stage, histology, and post-op radiation.
In January 2003 the protocol was amended to allow for adjuvant chemotherapy, and this became an additional stratification factor.

Pts were then randomized on a 1:1 basis to gefitinib (250 mg daily for 2 years) or placebo.

Primary endpoint: Overall survival (OS)

Secondary endpoints: Disease free survival (DFS), toxicity.

Other study goals included establishing a tumor bank, and determining the prognostic and predictive significance of the following biomarkers:

- KRAS mutation status
- EGFR gene expression (by FISH)
- EGFR mutation status

This study was powered to detect a HR of 1.33, requiring enrollment of 1160 patients

Results

The study closed prematurely in April 2005 after an interim analysis demonstrated worse survival in patients receiving gefitinib compared to placebo.

- 503 patients had been enrolled.
  - All were taken off the study drug at that time; average time on study drug was 5 months.
  - Follow-up continued until all patients had been followed for 4 years.

Arms were well-balanced in terms of gender, race, histology (60% adenocarcinoma in both), and smoking history (89% had smoking history in both)

The arms were also balanced in terms of performance status, stage, and adjuvant chemotherapy

20% of patients in this study received adjuvant chemotherapy.

Primary outcome: no significant difference was demonstrated in OS with the addition of gefitinib, although there was a trend towards improved survival in the placebo arm

Secondary outcomes:

- No significant difference in disease-free survival was demonstrated
  - On multivariate analysis, only age >65 and tumor size > 4 cm were associated with worse survival, although there was a trend towards gefitinib being associated with worse outcomes
  - Toxicity: Very few Grade 3 and 4 adverse events were encountered, and these were more frequent in the placebo arm

Biomarker analysis:
• 27% of all tumors harbored KRAS mutations, 41% had high EGFR copy number by FISH, and 21% harbored EGFR mutations (these patients were more likely to be Stage II, never smokers, and of Asian ethnicity)

• KRAS mutation status and EGFR copy number by FISH were neither prognostic nor predictive of gefitinib benefit in terms of OS.

• Unlike findings in patients with advanced disease, sensitizing EGFR mutation status was neither prognostic nor predictive of response to gefitinib.

Author’s Conclusions

• Gefitinib was well tolerated.

• The study was under-powered due to early closure after interim analysis, and confounded by the fact that patients were on the drug for a short median time of 5 months

• Gefitinib did not improve OS or DFS in patients with completely resected early stage NSCLC

• KRAS mutation status and EGFR copy number and mutations status were neither prognostic nor predictive of response to gefitinib

• There is no demonstrable benefit to targeted agents in the adjuvant setting for NSCLC; therefore adjuvant chemotherapy remains the standard of care.

• The authors note that we await the results of RADIANT trial, evaluating the role of adjuvant erlotinib in NSCLC.

Clinical Implications

• There are several limitations of this study, which the authors readily acknowledge:

• The standard of care is now to deliver adjuvant cisplatin doublet based chemotherapy in most patients with Stage IB-IIIA NSCLC after complete resection, so the placebo and treatment arms in this study are no longer relevant (only 20% patients received adjuvant chemo in this trial).

• In addition, the group of patients enrolled was quite heterogenous, as were the treatments delivered.

• The study is underpowered in terms of the number of patients enrolled;

• The median time that patients were on the study drug was only 5 months, leading some investigators to propose that abrupt withdrawal of EGFR inhibition may have led to borderline worse outcomes in the gefitinib arm compared to placebo alone.

• Based on the results of this negative study, adjuvant chemotherapy, as opposed to targeted therapies, remains the standard of care for adjuvant treatment in good performance status patients with completely resected NSCLC.

• The results presented here are valuable, and provide answers to some clinical and biological questions regarding the role of targeted therapies in NSCLC.

• Additionally, this study may reveal insights into promising targets for future development of targeted therapeutics:

• The tumor bank can be analyzed for both known and novel biomarkers that are prognostic of outcomes in this subset of patients, which may help guide the development of novel targeted agents, and further characterize which patients are likely to benefit from pre-existing targeted agents.