Combining EGF receptor inhibitors with chemotherapy or chemoradiotherapy in patients with non-small-cell lung cancer

The use of EGF receptor inhibitors has recently been incorporated into the armamentarium of agents available to treat patients with non-small-cell lung cancer. Their use in combination with chemotherapy and radiotherapy has been investigated in Phase II and III trials. The use of EGF receptor tyrosine kinase inhibitors in combination with chemotherapy has been somewhat disappointing, whereas the use of anti-EGF receptor monoclonal cetuximab in combination with chemotherapy has provided mixed results. The use of cetuximab in combination with chemotherapy and radiotherapy in patients with locally advanced disease has generated encouraging results in Phase II trials, and Phase III trials are currently ongoing. The identification of molecular biomarkers to predict benefit is a work in progress.

Clinical trials combining EGF inhibitors plus chemotherapy & radiotherapy in locally advanced NSCLC

The results of the Iressa® NSCLC Trial Assessing Combination Treatment (INTACT) I, and II, and Tarceva® Responses in Conjunction with Paclitaxel and Carboplatin (TRIBUTE), Tarceva Lung Cancer Investigation (TALENT) trials are well known (Table 1). These four large clinical trials investigated the use of EGFR TKI in combination with chemotherapy; in addition, this article also discusses ideas regarding how to better incorporate the use of EGFR inhibitors along with chemotherapy, aiming to improve the overall survival of patients with lung cancer.
drugs could enhance the cytotoxic effects of standard chemotherapy agents as demonstrated in preclinical studies.

It was widely anticipated that combining EGFR TKI with standard chemotherapy would improve patient outcomes in advanced NSCLC compared with chemotherapy alone. However, these trials failed to meet their primary end point and demonstrated that the combination of EGFR with chemotherapy in a nonselected population of patients should not be further developed.

The subset analysis of the TRIBUTE trial has demonstrated that nonsmokers experienced improved overall survival in the erlotinib/chemotherapy arm. This observation prompted the development of the Phase II Cancer and Leukemia Group B (CALGB) 30406. In this trial, chemotherapy-naive, never smokers or former light smokers with advanced NSCLC were randomized to erlotinib alone or to erlotinib, carboplatin and taxol. Recently, the data from the randomized Phase II trial, CALGB 30406 was presented.[4]

The results demonstrated similar efficacy in both arms but less toxicity in the single-agent erlotinib arm. As expected, patients with EGFR mutation were most likely to benefit from the use of erlotinib, and their outcomes were similar whether or not chemotherapy was used.

**Clinical trials combining chemotherapy & cetuximab**

Cetuximab is an anti-EGFR monoclonal antibody that binds to the extracellular domain of EGFR when it is in the inactive configuration, competes for receptor binding by occluding the ligand-binding region and, thereby, blocks ligand-induced EGFR tyrosine kinase activation.[5] It is pertinent to highlight some of the differences between cetuximab and the TKIs that may have implications for their future use in clinical practice. Similar to other antibodies, it is possible that cetuximab stimulates antibody-dependent cell-mediated cytotoxicity, which may contribute to its antitumor effects.[6]

There are preclinical data indicating the synergistic effect of cetuximab when used in combination with chemotherapy or radiotherapy, which also suggested that the addition of cetuximab could overcome chemotherapy resistance.[7] This observation launched several clinical trials to explore this strategy. As a single agent, cetuximab has a marginal effect in advanced NSCLC.[8] Encouraging results from Phase II trials that explored the combination of Cetuximab plus chemotherapy have demonstrated partial responses ranging from 26 to 37% and median survival time ranging from 7 to 11 months.[9–12]

These results have led to the development of two large Phase III trials, which have been recently published.

The First-Line Erbitux in Lung Cancer (FLEX) trial randomized 1125 patients with EGFR-positive tumors by immunohistochemistry to chemotherapy plus cetuximab (n = 557) or chemotherapy alone (n = 568).[13] Patients given chemotherapy plus cetuximab survived longer than those in the chemotherapy-alone group (median survival: 11.3 months vs 10.1 months; hazard ratio for death: 0.871; 95% CI: 0.762–0.996; p = 0.044). The main cetuximab-related adverse event was an acne-like rash (57 out of 548 patients, grade 3). Interestingly, the hazard ratio (85% CI) for death on the basis of prespecified subgroup analysis of the intention-to-treat

<table>
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<tr>
<th>Study</th>
<th>Treatment</th>
<th>Number of patients</th>
<th>Odds ratio (%)</th>
<th>Time to progression (months)</th>
<th>Mean survival (months)</th>
<th>1-year survival (%)</th>
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EGF receptor inhibitors in patients with non-small-cell lung cancer

Population was 0.80 (0.69–0.93) in Caucasians and 1.18 (0.73–1.90) in Asians, demonstrating a significant difference (p = 0.011) based on the ethnic origin of the group. Therefore, the FLEX trial has demonstrated a modest improvement in overall survival, statistically reaching its end point. The data has suggested that the addition of cetuximab may generate the highest benefit in Caucasians and may be detrimental in the Asian population.

By contrast, the Bristol-Myers Squibb (BMS)-099 trial, did not reach its primary end point [44]. The trial, which did not require EGFR staining, randomized 676 chemotherapy-naive patients with stage IIIB (pleural effusion) or stage IV NSCLC to carboplatin/taxane (docetaxel or paclitaxel) versus cetuximab with carboplatin/taxane, and failed to reach a statistically significant difference in PFS. There was a nonsignificant improvement in response rate and a trend toward improved survival favoring cetuximab. From a histological standpoint, the subset of patients with squamous cell carcinoma histology may derive benefit from the use of cetuximab. In the BMS-099 trial, a subset analysis indicated a hazard ratio of 0.70 for PFS in the cetuximab arm compared with an overall hazard ratio for all patients of 0.871, clearly favoring the cetuximab arm.

From a molecular standpoint, the EGFR copy number, EGFR and KRAS mutation status of patients participating in the BMS-099 study has been published [15]. The data demonstrated absolutely no difference in the PFS or overall survival benefit for cetuximab on the basis of EGFR copy number or mutation status. These results were almost identical to those reported for the FLEX trial. Unlike colon cancer, the KRAS mutation status had no predictive value in either BMS-099 or FLEX. This appears to be related to the observation that, in lung cancer, the downstream target pathway of the EGFR activation through the PI3K–MAPK cascade is non-RAS dependent, as opposed to RAS-dependent PI3K activation in colon cancer, where cetuximab has been demonstrated to have no efficacy in the KRAS mutant cancer population. This is a fascinating area of research and further studies to differentiate the role of RAS with regard to EGFR signaling in NSCLC and colorectal cancer are required.

Clinical trials combining EGFR TKI plus chemotherapy & radiotherapy in locally advanced NSCLC

Radiation activates EGFR signaling, leading to radioresistance by inducing cell proliferation and enhanced DNA repair [16]. Several preclinical models have demonstrated synergistic activity when cetuximab was combined with radiation therapy [17-19]. Some Phase II trials have evaluated the safety and efficacy of synchronous cetuximab, chemotherapy and radiation therapy with promising results.

Phase II results from Radiation Therapy Oncology Group (RTOG) 0324 [20], a trial which combined cetuximab with conventional (63 Gy) chemoradiation (carboplatin/taxol) in patients with locally advanced NSCLC, met planned safety and efficacy end points. Although the toxicity was equivalent to that reported for conventional chemoradiation, there was an improvement in median survival to 22.7 months, the highest observed in RTOG trials in stage III disease. The results from RTOG 0324 led to a Phase III trial (RTOG 0617), which is currently evaluating the addition of cetuximab to chemotherapy along with either conventional (60 Gy) chemoradiation or high-dose radiation (74 Gy).

The CALGB B30407 trial [21], a Phase II study, evaluated the combination of carboplatin and pemetrexed during concurrent radiation therapy (70 Gy over 7 weeks), with or without the addition of cetuximab, followed by four cycles of consolidation therapy with pemetrexed. Preliminary data has been published for 99 randomized patients. The most common histological type was adenocarcinoma (in 46% of patients in the chemoradiotherapy arm and 41% in the chemoradiotherapy plus cetuximab arm). With a median follow-up of 17 months, the response rate was 73% in the chemoradiotherapy arm versus 71% in the cetuximab arm; median survival was 22.3 months in the chemoradiotherapy arm versus 18.7 in the cetuximab arm. Therefore, in this Phase II trial, the addition of cetuximab to chemotherapy and thoracic radiotherapy did not appear to yield better results.

The Southwestern Oncology Group (SWOG) study, S0023, has investigated the sequential use of EGFR TKI in inoperable stage III NSCLC with the use of gefitinib versus placebo after completion of definitive chemoradiotherapy plus consolidation docetaxel [22]. The rationale for the study is mainly related to the possibility of a negative interaction with the use of EGFR TKI in combination with chemotherapy, since EGFR TKI induces G1 cell cycle arrest [23]. Unfortunately, the use of gefitinib did not improve survival and has perhaps been associated with decreased survival. The results from S0023 did not indicate survival improvement with the use of gefitinib. In fact, the patients who received gefitinib had decreased overall survival.
The CALGB 30605 trial is also exploring concomitantly administered erlotinib with thoracic radiotherapy in patients with poor performance status after induction chemotherapy.

**EGFR inhibitors in combination with bevacizumab & chemotherapy**

Combining targeted agents that block multiple signaling pathways may reveal a very useful therapeutic approach leading to better outcomes. EGFR and VEGF share common downstream signaling pathways. They exert effects directly and indirectly on tumor cells, and combining drugs that target these molecules may confer additional clinical benefit. VEGF is also down-regulated by EGFR inhibition and a recent study suggested that blockade of VEGF may also inhibit EGFR autocrine signaling. Therefore, the dual blockade of these molecular targets may produce synergistic cytostatic effects. Preclinical studies have investigated the synergistic antitumor activity of combined anti-EGFR and anti-VEGF agents [24,25].

The SWOG 0536 trial evaluated the combination of carboplatin, paclitaxel, cetuximab and bevacizumab followed by cetuximab and bevacizumab in a Phase II study as a first-line treatment [26]. Patients (performance status 0–1) with advanced nonsquamous NSCLC who had received no prior chemotherapy were treated with paclitaxel (200 mg/m²), carboplatin (area under the curve of 6), bevacizumab (15 mg/kg) intravenously every 3 weeks, as well as with up to six cycles of cetuximab (400 mg/m² then 250 mg/m² intravenously weekly) followed by maintenance cetuximab (250 mg/m² intravenously weekly) plus bevacizumab (15 mg/kg intravenously every 3 weeks). The primary end point was to evaluate the frequency and severity of hemorrhage toxicities. The incidence of severe pulmonary hemorrhage rate was 2%; the overall response was 53%, with a PFS of 7 months and overall survival of 14 months. The study met its end point and a randomized Phase III trial (SWOG 0819) is ongoing.

**Future perspective**

Recent data have not yet demonstrated a benefit in the use of chemotherapy in combination with EGFR inhibitors.

The use of cetuximab in combination with chemotherapy and thoracic radiotherapy has revealed intriguing results. Data from large Phase III ongoing clinic trials are expected.

An open discussion regarding the cost of the use of EGFR monoclonal antibodies in combination with chemotherapy should be conducted when considering the application of the FLEX regimen into current clinical practice.

Future efforts should focus on identifying molecular drivers of the individual tumors, in order to generate positive clinical trials to benefit patients with lung cancer, such as EGFR mutations. Therefore, routine molecular testing for EGFR, KRAS and ALK mutations in patients with NSCLC cancer should be considered.

**Executive summary**

- The results of the Iressa® NSCLC Trial Assessing Combination Treatment (INTACT) I and II, and Tarceva® Responses in Conjunction with Paclitaxel and Carboplatin (TRIBUTE) and Tarceva Lung Cancer Investigation (TALENT) trials, which investigated the combination of chemotherapy and EGF receptor tyrosine kinase inhibitors trials have failed to demonstrate a survival advantage with the use of EGF receptor tyrosine kinase inhibitors in combination with chemotherapy.
- The First-Line Erbitux in Lung Cancer (FLEX) trial, which investigated the use of cetuximab in combination with chemotherapy has demonstrated a modest improvement in overall survival, statistically reaching its end point. The data have suggested that the addition of cetuximab may generate the highest benefit in Caucasians and may be detrimental in Asians. The Bristol-Myers Squibb (BMS)-0999 trial, on the other hand, failed to demonstrate a statistically significant difference in progression-free survival in patients who received cetuximab in combination with chemotherapy.
- The use of cetuximab in combination with chemotherapy and thoracic radiotherapy has been investigated in Phase II clinical trials in patients with locally advanced non-small-cell lung cancer with mixed results. The Radiation Therapy Oncology Group (RTOG) 0324 trial demonstrated a median survival of 22.7 months, the highest observed in RTOG trials in stage III disease. Cancer and Leukemia Group B (CALGB) 30407, a randomized Phase II study, demonstrated that the addition of cetuximab to chemotherapy and thoracic radiotherapy did not appear to yield better results.
- A Phase II clinical trial has demonstrated impressive response rates with the use of chemotherapy plus cetuximab and bevacizumab in patients with stage IV non-small-cell lung cancer, a Phase III clinical trial to explore the double VEGF/EGF receptor blockade in combination with chemotherapy is planned.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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**Bibliography**

Papers of special note have been highlighted as:
* of interest
** of considerable interest


**Phase III trial that demonstrated** improvement in progression-free survival in patients with EGF receptor (EGFR) mutant lung cancer treated with gefitinib versus chemotherapy.


**Randomized Phase II trial that demonstrated a 32-month overall survival in patients with EGFR mutant lung cancer treated with erlotinib as the first-line of therapy as compared with chemotherapy plus erlotinib. In addition, it demonstrated that the addition of chemotherapy to erlotinib does not add any benefit in progression-free survival and overall survival.**


* Presents the data of the single-agent activity of cetuximab in non-small-cell carcinoma.


**Large Phase III clinical trial that has shown improvement in overall survival in patients who received cetuximab in combination with chemotherapy. The hazard ratio was more favorable in Caucasians and in patients with tumors of squamous cell histology.**


**This Phase II data has generated the highest observed median overall survival in patients with locally advanced non-small-cell lung cancer of 22.7 months. This led to the development of Radiation Therapy Oncology Group (RTOG) 0617, a Phase III clinical trial that is currently ongoing.**


25. Ciardiello F, Bianco R, Damiano V et al.: Antiangiogenic and antitumor activity of anti-epidermal growth factor receptor C225...


