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.

KEYWORDS: cetuximab ■ chemotherapy ■ EGF receptor ■ erlotinib ■ gefitinib ■ non-small-cell lung cancer ■ radiotherapy

Bruno R Bastos[†] & Rogerio C Lilenbaum[1]

[1]Mount Sinai Cancer Center, 4306 Alton Road, Miami Beach, FL 33140, USA
[†]Author for correspondence: Cleveland Clinic Florida, Department of Hematology & Oncology, 2950 Cleveland Clinic Boulevard, Weston, FL 33331, USA
Tel.: +1 954 659 5840
Fax: +1 954 659 5833
bastosb@ccf.org

Recently, with the better understanding of the biology of lung cancer, novel molecular targeted agents have emerged as one of the tools to improve survival and care for patients with non-small-cell lung cancer (NSCLC). Preclinical data have indicated that some targeted agents may be synergistic when combined with chemotherapy. Erlotinib and gefitinib are oral agents that inhibit the intracellular tyrosine kinase domain of the EGF receptor (EGFR). Erlotinib has been demonstrated in a randomized Phase III trial to improve overall survival and progression-free survival (PFS) of patients with metastatic NSCLC in the second- or third-line setting when compared with placebo [1]. Recent Phase III clinical studies have demonstrated that patients with NSCLC whose tumors harbor an *EGFR* mutation (exon 19 and 21) have achieved average response rates of 73.7% with the use of single-agent EGFR tyrosine kinase inhibitors (TKIs) in the first-line setting [2]. Recent data from the Optimal trial revealed that the use of single-agent erlotinib as a first line therapy in EGFR mutant lung cancer patients may also improve overall survival when compared with patients receiveing chemotherapy; data revealed an impressive threefold higher PFS in *EGFR* mutant patients treated with erlotinib upfront compared with carboplatin/gemcitabine [3].

Owing to the low toxicity profile associated with target agents as compared with cytotoxic chemotherapy, the combination of targeted agents has been explored. There are several combination trials that have investigated the use of erlotinib or gefitinib in combination with chemotherapy. Other combination trials have explored the use of the chimeric monoclonal antibody cetuximab and chemotherapy. Cetuximab is a chimeric human–murine monocloncal IgG1 antibody against the extracellular domain of EGFR.

This article provides an overview of the published clinical trials that incorporated the use of EGFR inhibitors 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.

Clinical trials combining EGFR 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 versus chemotherapy alone. Unfortunately, these robust Phase III randomized clinical trials have failed to demonstrate a survival advantage with the use of EGFR TKI in combination with chemotherapy.

Each of these studies was designed based on the knowledge that both gefitinib and erlotinib have demonstrated antitumor activity in patients with refractory, advanced NSCLC, with only modest toxicity, and on the premise that these

future medicine part of fsg

Table 1. Results of Phase III trials combining chemotherapy and EGF receptor tyrosine kinase inhibitor.

Study	Treatment	Number of patients	Odds ratio (%)	Time to progression (months)	Mean survival (months)	1-year survival (%)	Ref.
INTACT-1	P–Gem	363	47.2	6.0	10.9	44	[27]
	P–Gem + ↓G	365	51.2	5.8	9.9	41	
	P–Gem + ↑G	365	50.3	5.5	9.9	43	
INTACT-2	Cb–Pac	345	28.7	5.0	9.9	42	[28]
	Cb–Pac + ↓G	345	30.4	5.3	9.8	41	
	Cb–Pac + ↑G	347	30.0	4.6	8.7	37	
TALENT	P–Gem	536	29.9	5.7	10.3	42	[29]
	P–Gem + E	533	31.5	5.5	10.0	41	
TRIBUTE	Cb–Pac	533	19.3	4.9	10.5	44	[30]
	Cb–Pac + E	526	21.5	5.1	10.6	47	

↓: 250 mg; ↑: 500 mg; Cb: Carboplatin; E: Erlotinib; G: Gefitinib; Gem: Gemcitabine; INTACT: Iressa® NSCLC Trial Assessing Combination Treatment; P: Cisplatin; Pac: Paclitaxel; TALENT: Tarceva® Lung Cancer Investigation; TRIBUTE: Tarceva Responses in Conjunction with Paclitaxel and Carboplatin.
Reproduced with permission from [31].

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

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, statiscally 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 [14]. 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 downregulated 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/m^2), 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/m^2 then 250 mg/m^2 intravenously weekly) followed by maintenance cetuximab (250 mg/m^2 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.

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.

No writing assistance was utilized in the production of this manuscript.

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.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Shepherd FA, Rodrigues Pereira J, Ciuleanu T *et al.*: Erlotinib in previously treated non-small-cell lung cancer. *N. Engl. J. Med.* 353(2), 123–132 (2005).

2 Mok TS, Wu YL, Thongprasert S *et al.*: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N. Engl. J. Med.* 361(10), 947–957 (2009).

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

3 Zhou C: Optimal trial. Presented at: *35th Congress of the European Society for Medical Oncology (ESMO).* Milan, Italy 8–12 October 2010.

4 Janne PA, Wang XF, Socinski MA *et al.*: Randomized Phase II trial of erlotinib (E) alone or in combination with carboplatin/paclitaxel (CP) in never or light former smokers with advanced lung adenocarcinoma: CALGB 30406.*J. Clin. Oncol.* 28(Suppl. 15) (2010) (Abstract 7503).

▪▪ **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.**

5 Ciardiello F, Tortora G: EGFR antagonists in cancer treatment. *N. Engl. J. Med.* 358(11), 1160–1174 (2008).

6 Mellstedt H: Monoclonal antibodies in human cancer. *Drugs Today (Barc).* 39(Suppl. C), 1–16 (2003).

7 Morgensztern D, Govindan R: Is there a role for cetuximab in non-small-cell lung cancer? *Clin. Cancer Res.* 13(15 Pt 2), S4602–S4605 (2007).

8 Hanna N, Lilenbaum R, Ansari R *et al.*: Phase II trial of cetuximab in patients with previously treated non-small-cell lung cancer. *J. Clin. Oncol.* 24(33), 5253–5258 (2006).

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

9 Thienelt CD, Bunn PA Jr, Hanna N *et al.*: Multicenter Phase I/II study of cetuximab with paclitaxel and carboplatin in untreated patients with stage IV non-small-cell lung cancer. *J. Clin. Oncol.* 23(34), 8786–8793 (2005).

10 Robert F, Blumenschein G, Herbst RS *et al.*: Phase I/IIa study of cetuximab with gemcitabine plus carboplatin in patients with chemotherapy-naive advanced non-small-cell lung cancer. *J. Clin. Oncol.* 23(36), 9089–9096 (2005).

11 Rosell R, Robinet G, Szczesna A *et al.*: Randomized Phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer. *Ann. Oncol.* 19(2), 362–369 (2008).

12 Kelly K, Herbst RS, Crowley JJ *et al.*: Concurrent chemotherapy plus cetuximab or chemotherapy followed by cetuximab in advanced non-small-cell lung cancer (NSCLC): a randomized Phase II selectional trial SWOG 0342. *Proc. Am. Soc. Clin. Oncol.* 24(Suppl. 18), 7545 (2007).

13 Pirker R, Pereira JR, Szczesna A *et al.*: Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised Phase III trial. *Lancet* 373(9674), 1525–1531 (2009).

▪▪ **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.**

14 Lynch TJ, Patel T, Dreisbach L *et al.*: Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter Phase III trial BMS099. *J. Clin. Oncol.* 28(6), 911–917 (2010).

15 Khambata-Ford S, Harbison CT, Hart LL *et al.*: Analysis of potential predictive markers of cetuximab benefit in BMS099, a Phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer. *J. Clin. Oncol.* 28(6), 918–927 (2010).

16 Provencio M, Sanchez A, Garrido P, Valcarcel F: New molecular targeted therapies integrated with radiation therapy in lung cancer. *Clin. Lung Cancer* 11(2), 91–97 (2010).

17 Saleh MN, Raisch KP, Stackhouse MA *et al.*: Combined modality therapy of A431 human epidermoid cancer using anti-EGFR antibody C225 and radiation. *Cancer Biother. Radiopharm.* 14(6), 451–463 (1999).

18 Huang SM, Bock JM, Harari PM: Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. *Cancer Res.* 59(8), 1935–1940 (1999).

19 Milas L, Mason K, Hunter N *et al.*: *In vivo* enhancement of tumor radioresponse by C225 antiepidermal growth factor receptor antibody. *Clin. Cancer Res.* 6(2), 701–708 (2000).

20 Blumenschein GR, Paulus R: A Phase II study of cetuximab (C225) in combination with chemoradiation (CRT) in patients (PTS) with stage IIIA/B non-small-cell lung cancer (NSCLC): a report of the 2 year and median survival (MS) for the RTOG 0324 trial. *J. Clin. Oncol.* 26(Suppl.) (2008) (Abstract 7516).

21 Govindan R, Bogart J, Wang D *et al.*: A Phase II study of pemetrexed, carboplatin and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: CALGB 30407 – early evaluation of feasibility and toxicity. *J. Clin. Oncol.* 26(Suppl. 26) (2008) (Abstract 7518).

▪▪ **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 curently ongoing.**

22 Kelly K, Chansky K, Gaspar LE *et al.*: Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J. Clin. Oncol.* 26(15), 2450–2456 (2008).

23 Davies AM, Ho C, Lara PN Jr, Mack P, Gumerlock PH, Gandara DR: Pharmacodynamic separation of epidermal growth factor receptor tyrosine kinase inhibitors and chemotherapy in non-small-cell lung cancer. *Clin. Lung Cancer* 7(6), 385–388 (2006).

24 Jung YD, Mansfield PF, Akagi M *et al.*: Effects of combination anti-vascular endothelial growth factor receptor and anti-epidermal growth factor receptor therapies on the growth of gastric cancer in a nude mouse model. *Eur. J. Cancer* 38(8), 1133–1140 (2002).

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

monoclonal antibody in combination with vascular endothelial growth factor antisense oligonucleotide in human GEO colon cancer cells. *Clin. Cancer Res.* 6(9), 3739–3747 (2000).

26 Gandara D, Kim ES, Herbst RS *et al.*: Carboplatin, paclitaxel, cetuximab and bevacizumab followed by cetuximab and bevacizumab maintanance in advanced NSCLC, a SWOG Phase II study. *J. Clin. Oncol.* 27(Suppl. 15) (2009) (Abstract 8015).

27 Giaccone G, Herbst RS, Manegold C *et al.*: Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a Phase III trial – INTACT 1. *J. Clin. Oncol.* 22(5), 777–784 (2004).

28 Herbst RS, Giaccone G, Schiller JH *et al.*: Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a Phase III trial – INTACT 2. *J. Clin. Oncol.* 22(5), 785–794 (2004).

29 Gatzemeier U, Pluzanska A, Szczesna A *et al.*: Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. *J. Clin. Oncol.* 25(12), 1545–1552 (2007).

30 Herbst RS, Prager D, Hermann R *et al.*: TRIBUTE: a Phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J. Clin. Oncol.* 23(25), 5892–5899 (2005).

31 Johnson DH: Targeted therapies in combination with chemotherapy in non-small cell lung cancer. *Clin. Cancer Res.* 12(14 Pt 2), 4451s–4457s (2006).