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Epidermal Growth Factor Receptor Inhibitors and Antiangiogenic Agents for the Treatment of Non-Small Cell Lung Cancer

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Abstract

Non-small cell lung cancer (NSCLC) is a major global health problem and represents the leading cause of cancer-related deaths worldwide. The majority of patients with NSCLC are diagnosed with advanced-stage disease, and the prognosis for such patients is poor. The currently approved cytotoxic chemotherapy is associated with substantial limitations in both efficacy and safety. The availability of agents targeted against the epidermal growth factor receptor (EGFR), as well as the antiangiogenic agent bevacizumab, have provided some clinical benefit. Nonetheless, the efficacy of these agents is also inadequate, and resistance has emerged as a clinical problem. Numerous novel targeted therapies are now in clinical development and may have potential for overcoming the limitations associated with currently available agents. In this article we review clinical data for molecular-targeted therapies in NSCLC, with emphasis on EGFR inhibitors and antiangiogenic agents.

In 2008, it is estimated that non-small cell lung cancer (NSCLC) will account for 80% of the anticipated 214,990 new cases and 161,890 deaths from lung cancer in the United States (1). Two thirds of patients with NSCLC present with advanced disease and have an average survival of 8 to 10 months when treated with standard chemotherapy (2). Novel strategies are thus required to improve patient outcomes. In this article we discuss the current status of the clinical testing of molecularly targeted therapies, focusing on epidermal growth factor receptor (EGFR) inhibitors and antiangiogenic agents for the treatment of patients with NSCLC.

Inhibition of the EGFR Pathway

The EGFR is a receptor tyrosine kinase (TK) of the ErbB/HER family. Ligand binding to EGFR induces receptor homo- or hetero-dimerization with other ErbB family members or with other extracellular receptors (e.g., insulin-like growth factor-1 receptor or MET; ref. 3). Receptor activation signals key downstream pathways that regulate cell proliferation, differentiation, and survival (4–6). EGFR overexpression has been reported in 50% to 80% of NSCLCs (7–10). Aberrant EGFR expression can lead to tumor development. Agents

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Disclosure of Potential Conflicts of Interest

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targeting the EGFR pathway have shown activity and continue to be evaluated in patients with NSCLC.

Monoclonal antibodies to the EGFR pathway

Cetuximab is a human murine chimeric immunoglobulin G (IgG)1 antibody that binds to EGFR and affects ligand-induced phosphorylation and receptor degradation (11). IgG1 antibodies also activate the complement pathway and mediate antibody-dependent cellular cytotoxicity. In a phase II trial of previously treated NSCLC patients, single agent cetuximab had activity similar to that reported with pemetrexed, erlotinib, or docetaxel (Table 1; refs. 12–25).

Phase II trials evaluating the addition of cetuximab to platinum- based chemotherapy in patients with advanced NSCLC have yielded favorable results (14, 16, 26, 27). In one phase II trial (LUCAS), patients with chemotherapy-naïve advanced NSCLC who had 1% EGFR positive cells as measured by immunohistochemistry (IHC) were randomized to receive chemotherapy with cisplatin-vinorelbine plus cetuximab or chemotherapy alone. A higher response rate (RR) and a nonsignificant trend toward improved progression-free survival (PFS) and overall survival (OS) was associated with the patients who received cetuximab (16). These findings led to a randomized phase III trial (FLEX) evaluating cisplatin-vinorelbine with or without cetuximab in 1,125 patients with advanced NSCLC and at least one EGFR positive cell by IHC (17). The low requirement for EGFR positivity allowed 85% (1,442 of 1,688) of screened patients to be eligible. There was no difference in PFS but a significant improvement in RR and OS (primary end point) in the patients receiving cetuximab compared with placebo, 11.3 versus 10.1 months [hazard ratio (HR), 0.871; $P=0.044$]. A prespecified subgroup analysis showed no improvement in OS among Asian patients. However, fewer patients receiving cetuximab received poststudy treatment with EGFR TK inhibitors (TKIs). Further, there was a significant improvement in OS among Caucasian patients receiving cetuximab (HR, 0.803; $P=0.003$).

Translational Relevance

Lung cancer is the leading cause of cancer-related mortality in North America. NSCLC accounts for 80% to 85% of all new cases. Two thirds of patients are diagnosed with advanced disease at the time of diagnosis. These patients have a median survival of approximately 8 to 10 months when treated with standard platinum based chemotherapy. There has been considerable interest in developing novel therapeutic agents that target aberrant pathways involved in cell growth and metastases. The well-established role of angiogenesis and the epidermal growth factor receptor (EGFR) pathway in the pathogenesis of lung cancer has led to the rationale development of agents that selectively target these pathways. There are a few agents currently approved for the treatment of NSCLC and a multitude of new agents in clinical development. In this article we review these agents with an emphasis on their mechanism of action, clinical activity and mechanisms of resistance.

In a second phase III trial, BMS-099, 676 advanced NSCLC patients with no required EGFR testing were randomized to carboplatin-paclitaxel or docetaxel with or without cetuximab. This study did not meet its primary end point of PFS by an independent review committee (IRCC) (HR 0.90; $P=0.23$), although there was a significant improvement in response as determined by an IRCC (16% versus 17%) and PFS as determined by investigators (28). OS was 9.7 months for cetuximab-treated patients compared with 8.4 months for chemotherapy alone [HR 0.89, 95% confidence interval (CI) = 0.75–1.05, $P=0.17$] (29).

Two other monoclonal antibodies to the EGFR, panitumumab, a fully human monoclonal IgG2 antibody to the EGFR (25), and matuzumab, a humanized IgG1 monoclonal antibody to the EGFR (19), have shown limited success in patients with NSCLC. This latter agent has recently been halted in development following disappointing results in colon cancer patients.

Currently, cetuximab seems to be the only monoclonal antibody to EGFR that has shown benefit (albeit modest) in a subset of patients with NSCLC. Hirsch and colleagues reported a preferential benefit for treatment with cetuximab in patients who were EGFR positive as determined by fluorescence *in situ* hybridization (FISH; ref. 30). In addition colorectal cancer patients, with tumors that harbor the KRAS mutation do not benefit from treatment with cetuximab (31). Prospective studies are needed to further define the use of cetuximab in biomarker-enriched NSCLC patients, although a retrospective analysis of tissue samples from FLEX and BMS-099 may also provide useful information.

Reversible EGFR TKIs

Erlotinib and gefitinib inhibit EGFR signaling by binding to the intracellular TK domain, suppressing receptor phosphorylation and downstream signaling (32, 33). These agents were the first EGFR-targeted therapies to be approved for the second-or third-line treatment of patients with advanced NSCLC (Table 2; refs. 34–36). Two randomized phase III trials evaluated monotherapy with EGFR TKIs in patients with previously treated NSCLC (37, 38). Trial BR.21 found a significant improvement in OS among patients who were given erlotinib compared with placebo ($P < 0.001$; ref. 37), whereas the ISEL trial found no difference in OS between patients who received gefitinib compared with placebo ($P = 0.087$; ref. 38).

Clinical features known to correlate with response to EGFR TKI treatment include gender, smoking status, adenocarcinoma histology, and Asian ethnicity (34–37, 39). Molecular predictors of response have also been identified, and comprehensive reviews that focus on EGFR mutations in lung cancer are available (40, 41). Mutations in the kinase domain of EGFR correlate with response and improved survival with EGFR TKI treatment (8, 42–46). The point mutation in exon 21 (L858R) and the deletion at exon 19 account for 80% to 95% of EGFR mutations in NSCLC (47). High EGFR gene copy number as detected by FISH, and protein overexpression as determined by IHC, has also been associated with improved RRs and survival (48–50). KRAS mutations are a negative predictor of benefit from TKIs (51). In addition, most patients on EGFR TKIs eventually develop resistance, most commonly due to an exon 20-point mutation (T790M; refs. 52, 53). Recently reported results from an open label, first-line, phase III study of gefitinib versus carboplatin-paclitaxel in East Asian patients who were never or light smokers with advanced NSCLC (IPASS), indicated that gefitinib was favored over chemotherapy in patients testing positive for EGFR mutations (HR 0.48, 95% CI 0.36–0.64; $P < 0.0001$), whereas chemotherapy was favored in patients testing negative (HR 2.85, 95% CI 2.05–3.98; $P < 0.0001$; ref. 54).

Four randomized phase III trials evaluated erlotinib or gefitinib in combination with standard chemotherapy with disappointing results (55–58). Subgroup analyses from the TRIBUTE trial identified a benefit in nonsmokers treated with erlotinib and chemotherapy compared with placebo (57). These results led to the RADIANT trial, which is evaluating adjuvant chemotherapy with or without erlotinib in nonsmokers with EGFR-positive NSCLC. Lapatinib, a dual reversible inhibitor with a high affinity for EGFR and HER2 (59), has been investigated in patients with NSCLC and also produced disappointing results (60–62).

Irreversible dual EGFR/HER2 receptor TKIs

A new generation of dual irreversible EGFR/HER2 inhibitors that may be effective in patients with resistance to reversible EGFR TKIs are under development. These agents form a covalent bond with CYS-733 in EGFR (63). In preclinical studies, several such agents showed activity against tumors overexpressing EGFR or harboring the T790M mutation (64, 65). Resistance may also develop less frequently with irreversible EGFR TKIs than with reversible inhibitors (66). An additional advantage may be the dual inhibition of EGFR and HER2, which blocks cooperative signaling between these two receptors and has been shown to result in improved antitumor activity in preclinical models (67, 68). The clinical goals for patients treated with irreversible TKIs include activity after failure with reversible TKI therapy and a more prolonged PFS compared with reversible TKIs in therapy-naïve patients.

BIBW 2992 is an irreversible dual inhibitor of EGFR and HER2. Preliminary results of a phase I trial showed two partial responses (PRs) among 26 women with lung adenocarcinomas (69). The agent was well tolerated, with primary toxicities being rash and diarrhea. A phase II trial of previously treated patients with NSCLC with known activating EGFR mutations is currently ongoing (70). Additionally, a randomized phase III trial is underway comparing BIBW 2992 to placebo in patients with NSCLC with acquired resistance to gefitinib or erlotinib.

HKI-272 is an irreversible inhibitor of EGFR and HER2 that has been shown to inhibit the growth of cells that express EGFR or HER2, including cells with the T790 mutation (65). In a phase I trial involving 73 patients with tumors expressing EGFR or HER2, stable disease (SD) was reported in 42% of 16 NSCLC patients all of whom had initially responded to erlotinib or gefitinib. However, phase II studies in NSCLC patients are not planned at this time.

PF299804 is an irreversible inhibitor of EGFR, HER2, and HER4. Preclinical studies showed growth inhibition of cell lines expressing EGFR activating mutations and T790 mutations supporting further development of the compound for patients who develop acquired resistance to gefitinib or erlotinib (71). Phase I trials of PF299804 in patients with NSCLC are underway.

Angiogenesis Inhibitors

Angiogenesis is a fundamental step in tumor growth and metastases (72, 73). Vascular endothelial growth factor (VEGF) is the central mediator of angiogenesis and its expression has been found to correlate with new vessel formation, disease-free survival, and OS in NSCLC patients (74–76). Given its important role in tumor development, angiogenesis is a rationale therapeutic target in NSCLC patients (77, 78).

Bevacizumab

Bevacizumab is a monoclonal antibody with a high affinity for VEGF (79, 80). A randomized phase II trial found the addition of bevacizumab to carboplatin-paclitaxel improved RR and time to progression compared with chemotherapy alone in patients with advanced NSCLC (Table 3; ref. 81). There was also a nonsignificant improvement in OS. In this trial, patients whose tumors were squamous cell histology were found to be at greater risk for developing hemoptysis. On the basis of the results of this trial, the Eastern Cooperative Oncology Group (ECOG) conducted a phase III trial (E4599) comparing carboplatin-paclitaxel with and without bevacizumab in 878 patients with advanced nonsquamous NSCLC (82). The results indicated a significant improvement in RR ($P < 0.001$), PFS (HR, 0.66; $P < 0.001$), and OS (HR, 0.79; $P = 0.003$) among bevacizumab-treated patients.

A second randomized phase III trial (AVAiL), compared cisplatin-gemcitabine with or without bevacizumab, 7.5 or 15 mg/kg, in 1,043 patients with advanced NSCLC (Table 3; ref. 83). Following the results of the ECOG trial, the primary end point of AVAiL was amended from OS to PFS. Although the AVAiL trial was not powered to compare the two bevacizumab doses directly, efficacy and safety data were similar for both doses. There was a significant improvement in PFS and RR at both doses of bevacizumab with no difference in OS (84). The difference in OS between E4599 and AVAiL may be explained by preclinical findings showing paclitaxel induces circulating endothelial progenitor cells (CEPs) whereas gemcitabine does not, and that the addition of an anti-VEGFR2 antibody acts synergistically only in combination with CEP-mobilizing chemotherapeutic agents (85). Although bevacizumab is directed against the VEGF ligand rather than the receptor, the disappointing OS findings in AVAiL may have resulted from the lack of CEP mobilization with gemcitabine.

Patients with brain metastases were initially excluded from trials with bevacizumab because of the catastrophic potential associated with intracranial hemorrhage. Several large trials, ATLAS, ARIES, and PASSPORT have included patients with brain metastases and have not found them to be at increased risk of central nervous system hemorrhage (86, 87). However, these trials are ongoing and more mature data are required.

Small-molecule inhibitors of angiogenic growth factors and their receptors

Sorafenib is an oral multi-kinase inhibitor that targets VEGFR2 and 3, platelet-derived growth factor- β (PDGFR- β) RAF, stem cell factor receptor (c-KIT), and fms-like TK-3 (FLT-3; refs. 88–90). Of note, it has been suggested that the combined blockade of PDGFR- and VEGFR2-mediated signaling may induce greater inhibition of angiogenesis (91).

ECOG conducted the largest trial of single agent sorafenib in patients with previously treated NSCLC (E2501) (Table 4; ref. 92). In this trial, patients received two cycles of sorafenib with those patients who responded continuing on treatment whereas those patients who had SD were randomized to sorafenib or placebo. The primary end point of the study was the proportion of patients with disease control [SD, PR, complete response (CR)] 2 months following randomization. A total of 107 patients with SD were randomized and 83 were assessable for response. A significantly higher number of sorafenib-treated patients had disease control as compared with placebo ($P = 0.01$). Median PFS was also significantly longer ($P = 0.009$), and there was a trend toward improvement in OS.

Sorafenib has also been evaluated in combination with chemotherapy (Table 4; refs. 93, 94). The phase III ESCAPE trial, which randomized 926 untreated patients with advanced NSCLC to receive carboplatin-paclitaxel with or without sorafenib, found no difference in RR, PFS (HR, 1.0; $P = 0.514$), or OS (HR, 1.16; $P = 0.930$) between treatment groups. In a subset analysis, patients with squamous cell histology seemed to do poorly when treated with sorafenib (94). The NExUS study, a second phase III trial, is currently under way to evaluate cisplatin-gemcitabine with sorafenib. Based on the data from the ESCAPE trial, patients with squamous cell histology are no longer eligible for enrollment in NExUS.

Sunitinib (SU11248) is a multitargeted, small-molecule inhibitor of VEGFR1, 2, and 3, PDGFR- α and - β , FLT3, c-KIT, and the receptor encoded by the *ret* proto-oncogene (RET, rearranged during transfection; ref. 95). Phase II trials of single-agent sunitinib yielded favorable results (Table 4; refs. 96, 97). Sunitinib in combination with cisplatin-gemcitabine was evaluated in a phase I study in untreated patients with advanced NSCLC (Table 4) and 37.5 mg was recommended with this chemotherapy regimen (98). Further combination studies are ongoing.

BIBF 1120 is an oral angiokinase inhibitor targeting VEGFR1, 2, and 3, PDGFR- α and - β , and fibroblast growth factor receptor (FGFR) 1, 2, and 3. Casanovas and colleagues showed that resistance to anti-VEGF treatment can arise through the secretion of alternative ligands, in particular, FGF (99). Thus, it has been postulated that the triple VEGF/PDGF/FGF inhibitory properties of BIBF 1120 may overcome such resistance and afford prolonged response to treatment (100). A randomized phase II trial compared two doses of BIBF 1120 (150 and 250 mg twice daily) in previously treated NSCLC patients (Table 4; ref. 101). Preliminary results showed no objective responses and similar SD and PFS rates between treatment groups. In a phase I trial of BIBF 1120 combined with pemetrexed in previously treated NSCLC patients there was one CR and two PRs and eight SD among 20 evaluable patients (Table 4; ref. 102). Phase III trials evaluating BIBF 1120 in combination with chemotherapy for patients with advanced NSCLC are ongoing.

Several other antiangiogenic TKIs are also in early clinical development, including cediranib, axitinib, and AE-941. Results from clinical trials with these agents are summarized in Table 4 (103–105). Of note, the National Cancer Institute of Canada recently closed a trial of carboplatin-paclitaxel with or without cediranib because of excess toxicities in the cediranib treatment group.

Dual EGFR and VEGFR Inhibition

VEGFR and EGFR share common downstream signaling pathways (106). The inhibition of VEGFR is believed to contribute to the mechanism of action of agents targeting EGFR (107). Increased VEGFR activity is one mechanism via which tumors develop resistance to EGFR inhibitors (108). Dual EGFR-VEGFR inhibition has been shown to have additive effects and may help overcome resistance to EGFR inhibition (106).

Several studies have evaluated the combination of bevacizumab and erlotinib (Table 5; refs. 109–111). A promising phase I–II trial of bevacizumab plus erlotinib in advanced NSCLC patients (109) led to a randomized phase II trial in 120 patients with recurrent or refractory NSCLC in which chemotherapy alone (docetaxel or pemetrexed) was compared with chemotherapy plus bevacizumab or bevacizumab plus erlotinib (110). The RR was highest for patients who received bevacizumab plus erlotinib. The median PFS, OS, and 1-year survival rates were lowest in the patients who received chemotherapy alone and comparable in the two groups who received bevacizumab. Available tissue samples (<10% of patients) were tested for EGFR by IHC and FISH, as well as EGFR and k-Ras mutations. FISH-negative patients treated with erlotinib-bevacizumab had prolonged PFS (110). A phase III trial compared erlotinib plus bevacizumab to erlotinib alone in patients who had progressed after first-line chemotherapy (BETA; ref. 112). There was no difference in OS (9.3 versus 9.2 months). However, biomarker analysis may identify subgroups of patients who would benefit from this regimen given the impressive doubling of RR and PFS in the erlotinib-bevacizumab treatment group. A second phase III trial comparing maintenance erlotinib plus bevacizumab to maintenance bevacizumab alone in patients who had disease control following four cycles of upfront platinum based chemotherapy has met its primary end point of PFS with final results expected shortly.

Combination treatment with antiangiogenic TKIs and EGFR TKIs is also being tested in clinical studies. A phase I trial of 31 patients with advanced NSCLC evaluated the combination of sorafenib and gefitinib (Table 5; ref. 113). One patient achieved a PR and 20 had SD. The combination of sunitinib plus erlotinib compared with erlotinib alone in previously treated NSCLC patients is currently being evaluated in a phase III trial.

Vandetanib (AZD6474) is a single agent that blocks VEGFR2, 3, RET, and EGFR (114, 115). Vandetanib has shown growth inhibition in tumors resistant to EGFR inhibitors (116).

In a phase II trial in which vandetanib was administered to 53 Japanese patients, the RR was 13.2% and the time to progression was 2 to 3 months (117). A randomized phase II trial of 168 patients with previously treated NSCLC compared single-agent vandetanib to gefitinib and found a higher RR and PFS for vandetanib (Table 5; ref. 118). However, OS did not differ significantly between treatment arms. Two randomized phase III trials comparing vandetanib with erlotinib (ZEST) or placebo (ZEPHYR) in previously treated NSCLC are currently accruing.

Several studies have also evaluated vandetanib in combination with chemotherapy in patients with advanced NSCLC (Table 5; refs. 119, 120). A phase II randomized trial reported a higher RR but no difference in OS times when docetaxel combined with vandetanib was compared with docetaxel alone (119). The results of this study led to two phase III trials comparing chemotherapy with docetaxel (ZODIAC) or pemetrexed (ZEAL) with or without vandetanib in the same patient population. ZODIAC met its primary endpoint, improvement in PFS and both trials reported an improvement in RR with a trend toward improvement in OS when vandetanib was combined with chemotherapy compared with chemotherapy alone. A phase II trial randomized 181 untreated patients with advanced NSCLC to one of three treatments: vandetanib alone, paclitaxel and carboplatin, or vandetanib plus paclitaxel and carboplatin and reported no difference in RR, PFS, or OS between treatment arms (120, 121).

XL647 targets EGFR, HER2, VEGFR2, and EphB4. Two phase I studies of XL647 reported SD in an approximately two thirds of patients (122, 123). Preliminary results of a trial involving 23 patients with NSCLC treated with XL647 who relapsed after achieving an initial benefit from erlotinib or gefitinib showed one patient with a PR and seven patients with SD (Table 5; ref. 124). A second trial administered XL647 to 41 chemotherapy-naïve patients with NSCLC meeting at least one of the eligibility criteria: Asian ethnicity, female gender, and minimal (<15 pack-years) or no smoking history (Table 5; ref. 125). Among assessable patients, the PR rate was 28%, and 36% of patients had SD for 3 months. EGFR mutations were detected in 70% of patients who had a PR. Phase II studies with XL647 in patients with NSCLC are ongoing.

AEE788 is dual EGFR-VEGFR inhibitor with activity against EGFR, HER2, and VEGFR2 (126). It was found to inhibit the growth of NSCLCs *in vivo* with similar efficacy to a two-drug combination of an ErbB and VEGFR inhibitor. This agent has recently entered phase I clinical testing.

Conclusion

Despite advances in our knowledge of tumor biology and our ability to develop therapies that more precisely affect the target of interest, only modest improvements have been made in the treatment of patients with NSCLC. Agents that inhibit the EGFR, VEGF pathway, or both, have shown benefit in the treatment of patients with NSCLC in phase III trials. These agents are particularly appealing given their unique toxicity profile compared with that of chemotherapeutic agents in patients with comorbid illnesses. There are no proven biomarkers of antiangiogenic therapy in patients with NSCLC. Despite EGFR overexpression in a large number of NSCLC patients, only approximately 10% of patients respond to anti-EGFR therapy. This may in part be due to limitations in study designs or methods currently employed to measure EGFR. As previously discussed, patients with EGFR amplification and/or mutations have prolonged PFS when treated with EGFR-directed therapy. It will be important to ensure that future studies are designed appropriately, and that consistent, reproducible mechanisms for measuring EGFR expression/mutations are identified. To achieve this goal, larger randomized phase III studies are needed. The

increased sophistication of preclinical models and the enrollment of patients in clinical trials that include measurements of biomarkers will help identify patients who are likely to benefit from therapy, as well as further define mechanisms of resistance to therapy.

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References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin.* 2008; 58:71–96. [PubMed: 18287387]
2. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med.* 2002; 346:92–98. [PubMed: 11784875]
3. Earp HS, Dawson TL, Li X, et al. Heterodimerization and functional interaction between EGF receptor family members: a new signaling paradigm with implications for breast cancer research. *Breast Cancer Res Treat.* 1995; 35:115–132. [PubMed: 7612898]
4. Herbst RS, Bunn PA Jr. Targeting the epidermal growth factor receptor in non-small cell lung cancer. *Clin Cancer Res.* 2003; 9:5813–5824. [PubMed: 14676101]
5. Baselga J, Arteaga CL. Critical update and emerging trends in epidermal growth factor receptor targeting in cancer. *J Clin Oncol.* 2005; 23:2445–2459. [PubMed: 15753456]
6. Hubbard SR, Miller WT. Receptor tyrosine kinases: mechanisms of activation and signaling. *Curr Opin Cell Biol.* 2007; 19:117–123. [PubMed: 17306972]
7. Li AR, Chitale D, Riely GJ, et al. EGFR mutations in lung adenocarcinomas: clinical testing experience and relationship to EGFR gene copy number and immunohistochemical expression. *J Mol Diagn.* 2008; 10:242–248. [PubMed: 18403609]
8. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med.* 2004; 350:2129–2139. [PubMed: 15118073]
9. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A.* 2004; 101:13306–13311. [PubMed: 15329413]
10. Sakurada A, Shepherd FA, Tsao MS. Epidermal growth factor receptor tyrosine kinase inhibitors in lung cancer: impact of primary or secondary mutations. *Clin Lung Cancer.* 2006; 7:S138–S144. [PubMed: 16764754]
11. Goldstein NI, Prewett M, Zuklys K, et al. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. *Clin Cancer Res.* 1995; 1:1311–1318. [PubMed: 9815926]
12. 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.* 2006; 24:5253–5258. [PubMed: 17114658]
13. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol.* 2004; 22:1589–1597. [PubMed: 15117980]
14. Thienelt CD, Bunn PA Jr, Hanna N. 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.* 2005; 23:8786–8793. [PubMed: 16246975]
15. Blumenschein G Jr, Sandler A, O'Rourke T. Safety and pharmacokinetics (PK) of AMG 706, panitumumab, and carboplatin/paclitaxel (CP) for the treatment of patients (pts) with advanced non-small cell lung cancer (NSCLC). *ASCO Meeting Abstracts.* 2006; 24:7119.

16. 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.* 2008; 19:362–369. [PubMed: 17947225]
17. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomized phase III trial. *Lancet.* 2009; 373:1525–1531. [PubMed: 19410716]
18. Herbst RS, Davies AM, Natale RB, et al. Efficacy and safety of single-agent pertuzumab, a human epidermal receptor dimerization inhibitor, in patients with non small cell lung cancer. *Clin Cancer Res.* 2007; 13:6175–6181. [PubMed: 17947484]
19. Kollmannsberger C, Schittenhelm M, Honecker F, et al. A phase I study of the humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody EMD 72000 (matuzumab) in combination with paclitaxel in patients with EGFR-positive advanced non-small-cell lung cancer (NSCLC). *Ann Oncol.* 2006; 17:1007–1013. [PubMed: 16533873]
20. Clamon G, Herndon J, Kern J, et al. Lack of trastuzumab activity in nonsmall cell lung carcinoma with overexpression of erb-B2: 39810: a phase II trial of cancer and leukemia group B. *Cancer.* 2005; 103:1670–1675. [PubMed: 15751020]
21. Krug LM, Miller VA, Patel J, et al. Randomized phase II study of weekly docetaxel plus trastuzumab versus weekly paclitaxel plus trastuzumab in patients with previously untreated advanced non-small cell lung carcinoma. *Cancer.* 2005; 104:2149–2155. [PubMed: 16208701]
22. Langer CJ, Stephenson P, Thor A, et al. Trastuzumab in the treatment of advanced nonsmall-cell lung cancer: is there a role? Focus on Eastern Cooperative Oncology Group study 2598. *J Clin Oncol.* 2004; 22:1180–1187. [PubMed: 14981103]
23. Zinner RG, Glisson BS, Fossella FV, et al. Trastuzumab in combination with cisplatin and gemcitabine in patients with Her2-overexpressing, untreated, advanced non-small cell lung cancer: report of a phase II trial and findings regarding optimal identification of patients with Her2-overexpressing disease. *Lung Cancer.* 2004; 44:99–110. [PubMed: 15013588]
24. Gatzemeier U, Groth G, Butts C, et al. Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. *Ann Oncol.* 2004; 15:19–27. [PubMed: 14679114]
25. Crawford J, Sandler AB, Hammond LA, et al. ABX-EGF in combination with paclitaxel and carboplatin for advanced non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2004; 22:7083.
26. Robert F, Blumenschein G, Herbst RS, et al. Phase I/IIa study of cetuximab with gemcitabine plus carboplatin in patients with chemotherapy-naïve advanced non-small-cell lung cancer. *J Clin Oncol.* 2005; 23:9089–9096. [PubMed: 16301597]
27. Olsen CC, Paulus R, Komaki R, et al. RTOG 0324: A phase II study of cetuximab (C225) in combination with chemoradiation (CRT) in patients with stage IIIA/B non-small cell lung cancer (NSCLC)-association between EGFR gene copy number and patients outcomes. *J Clin Oncol.* 2008; 26:7607.
28. Lynch TJ, Patel T, Dreisbach L, et al. A randomized multicenter phase III study of cetuximab (erbitux) in combination with taxane/carboplatin versus taxane/carboplatin alone as first-line treatment for patients with advanced/metastatic non-small cell lung cancer (NSCLC) [abstract B3–03]. *J Thorac Oncol.* 2007; 2:S340–S341.
29. Lynch TJ, Patel T, Dreisbach L, et al. Overall survival (OS)-results from the phase III trial BMS 099: cetuximab + taxane/carboplatin as first-line treatment for advanced NSCLC. *J Thorac Oncol.* 2008; 3:S305.
30. Hirsch FR, Herbst RS, Olsen C, et al. Increased EGFR gene copy number detected by fluorescent *in situ* hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy. *J Clin Oncol.* 2008; 26:3351–3357. [PubMed: 18612151]
31. Van Cutsem E, Lang I, D'Haens G, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: the CRYSTAL experience. *J Clin Oncol.* 2008; 26:2.
32. Ciardiello F, Caputo R, Bianco R, et al. Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. *Clin Cancer Res.* 2000; 6:2053–2063. [PubMed: 10815932]

33. Grunwald V, Hidalgo M. Development of the epidermal growth factor receptor inhibitor Tarceva (OSI-774). *Adv Exp Med Biol.* 2003; 532:235–246. [PubMed: 12908562]
34. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (the IDEAL 1 trial) [corrected]. *J Clin Oncol.* 2003; 21:2237–2246. [PubMed: 12748244]
35. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAM A.* 2003; 290:2149–2158.
36. Perez-Soler R, Chachoua A, Hammond LA, et al. Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. *J Clin Oncol.* 2004; 22:3238–3247. [PubMed: 15310767]
37. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med.* 2005; 353:123–132. [PubMed: 16014882]
38. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet.* 2005; 366:1527–1537. [PubMed: 16257339]
39. Miller VA, Kris MG, Shah N, et al. Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. *J Clin Oncol.* 2004; 22:1103–1109. [PubMed: 15020612]
40. Eberhard DA, Giaccone G, Johnson BE. Biomarkers of response to epidermal growth factor receptor inhibitors in Non-Small-Cell Lung Cancer Working Group: standardization for use in the clinical trial setting. *J Clin Oncol.* 2008; 26:983–994. [PubMed: 18281673]
41. Janne PA, Engelman JA, Johnson BE. Epidermal growth factor receptor mutations in non-small-cell lung cancer: implications for treatment and tumor biology. *J Clin Oncol.* 2005; 23:3227–3234. [PubMed: 15886310]
42. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science.* 2004; 304:1497–1500. [PubMed: 15118125]
43. Cortes-Funes H, Gomez C, Rosell R, et al. Epidermal growth factor receptor activating mutations in Spanish gefitinib-treated non-small-cell lung cancer patients. *Ann Oncol.* 2005; 16:1081–1086. [PubMed: 15851406]
44. Han SW, Kim TY, Hwang PG, et al. Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small cell lung cancer patients treated with gefitinib. *J Clin Oncol.* 2005; 23:2493–2501. [PubMed: 15710947]
45. Mitsudomi T, Kosaka T, Endoh H, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small cell lung cancer with postoperative recurrence. *J Clin Oncol.* 2005; 23:2513–2520. [PubMed: 15738541]
46. Takano T, Ohe Y, Sakamoto H, et al. Epidermal growth factor receptor gene mutations and increased copy number predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. *J Clin Oncol.* 2005; 23:6829–6837. [PubMed: 15998907]
47. Riely GJ, Pao W, Pham D, et al. Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. *Clin Cancer Res.* 2006; 12:839–844. [PubMed: 16467097]
48. Hirsch FR, Varella-Garcia M, Bunn PA Jr. Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol.* 2006; 24:5034–5042. [PubMed: 17075123]
49. Zhu CQ, da Cunha Santos G, Ding K, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol.* 2008; 26:4268–4275. [PubMed: 18626007]
50. Cappuzzo F, Hirsch FR, Rossi E, et al. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. *J Natl Cancer Inst.* 2005; 97:643–655. [PubMed: 15870435]
51. Riely GJ, Marks J, Pao W. KRAS mutations in non-small cell lung cancer. *Proc Am Thorac Soc.* 2009; 6:201–205. [PubMed: 19349489]

52. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2005; 352:786–792. [PubMed: 15728811]
53. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med*. 2005; 2:e73. [PubMed: 15737014]
54. Mok, T.; Wu, Y-L.; Thongprasert, S., et al. Phase III, randomised, open-label first-line study of gefitinib vs carboplatin/paclitaxel in clinically selected patients with advanced non-small cell lung cancer [abstract 1]. European Society for Medical Oncology (ESMO); 33rd ESMO Conference; IPASS; Stockholm, Sweden. 2008.
55. 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*. 2004; 22:777–784. [PubMed: 14990632]
56. 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*. 2004; 22:785–794. [PubMed: 14990633]
57. 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*. 2005; 23:5892–5899. [PubMed: 16043829]
58. 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*. 2007; 25:1545–1552. [PubMed: 17442998]
59. Rusnak DW, Lackey K, Affleck K, et al. The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumor-derived cell lines *in vitro* and *in vivo*. *Mol Cancer Ther*. 2001; 1:85–94. [PubMed: 12467226]
60. Burris HA III, Hurwitz HI, Dees EC, et al. Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. *J Clin Oncol*. 2005; 23:5305–5313. [PubMed: 15955900]
61. Smylie M, Blumenschein GR Jr, Dowlati A, et al. A phase II multicenter trial comparing two schedules of lapatinib (LAP) as first or second line monotherapy in subjects with advanced or metastatic non-small cell lung cancer (NSCLC) with either bronchioloalveolar carcinoma (BAC) or no smoking history. *J Clin Oncol*. 2007; 25:7611.
62. LoRusso PM, Jones SF, Koch KM, et al. Phase I and pharmacokinetic study of lapatinib and docetaxel in patients with advanced cancer. *J Clin Oncol*. 2008; 26:3051–3056. [PubMed: 18565892]
63. Yun CH, Mengwasser KE, Toms AV, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci U S A*. 2008; 105:2070–2075. [PubMed: 18227510]
64. Riely GJ. Second-generation epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. *J Thorac Oncol*. 2008; 3:S146–S149. [PubMed: 18520300]
65. Rabindran SK, Discafani CM, Rosfjord EC, et al. Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. *Cancer Res*. 2004; 64:3958–3965. [PubMed: 15173008]
66. Kwak EL, Sordella R, Bell DW, et al. Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib. *Proc Natl Acad Sci U S A*. 2005; 102:7665–7670. [PubMed: 15897464]
67. Britten CD. Targeting ErbB receptor signaling: a pan-ErbB approach to cancer. *Mol Cancer Ther*. 2004; 3:1335–1342. [PubMed: 15486201]
68. Ye D, Mendelsohn J, Fan Z. Augmentation of a humanized anti-HER2 mAb 4D5 induced growth inhibition by a human-mouse chimeric anti-EGF receptor mAb C225. *Oncogene*. 1999; 18:731–738. [PubMed: 9989823]

69. Shaw H, Plummer R, Vidal L, et al. A phase I dose escalation study of BIBW 2992, an irreversible dual EGFR/HER2 receptor tyrosine kinase inhibitor, in patients with advanced solid tumours. *J Clin Oncol.* 2006; 24:3027.
70. Yang C, Shih J, Chao T, et al. Use of BIBW 2992, a novel irreversible EGFR/HER2 TKI, to induce regression in patients with adenocarcinoma of the lung and activating EGFR mutations: preliminary results of a single-arm phase II clinical trial. *J Clin Oncol.* 2008; 26:8026.
71. Engelman JA, Zejnullahu K, Gale CM, et al. PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to gefitinib. *Cancer Res.* 2007; 67:11924–11932. [PubMed: 18089823]
72. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med.* 1971; 285:1182–1186. [PubMed: 4938153]
73. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell.* 1996; 86:353–364. [PubMed: 8756718]
74. Fontanini G, Faviana P, Lucchi M, et al. A high vascular count and overexpression of vascular endothelial growth factor are associated with unfavourable prognosis in operated small cell lung carcinoma. *Br J Cancer.* 2002; 86:558–563. [PubMed: 11870537]
75. Fontanini G, Vignati S, Boldrini L, et al. Vascular endothelial growth factor is associated with neovascularization and influences progression of non-small cell lung carcinoma. *Clin Cancer Res.* 1997; 3:861–865. [PubMed: 9815760]
76. Imoto H, Osaki T, Taga S, et al. Vascular endothelial growth factor expression in non-small-cell lung cancer: prognostic significance in squamous cell carcinoma. *J Thorac Cardiovasc Surg.* 1998; 115:1007–1014. [PubMed: 9605068]
77. Kerbel RS. Antiangiogenic therapy: a universal chemosensitization strategy for cancer? *Science.* 2006; 312:1171–1175. [PubMed: 16728631]
78. Baluk P, Hashizume H, McDonald DM. Cellular abnormalities of blood vessels as targets in cancer. *Curr Opin Genet Dev.* 2005; 15:102–111. [PubMed: 15661540]
79. Ferrara N, Hillan KJ, Gerber HP, et al. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat Rev Drug Discov.* 2004; 3:391–400. [PubMed: 15136787]
80. Presta LG, Chen H, O'Connor SJ, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res.* 1997; 57:4593–4599. [PubMed: 9377574]
81. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol.* 2004; 22:2184–2191. [PubMed: 15169807]
82. Sandler A, Gray R, Perry MC, et al. Paclitaxelcarboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006; 355:2542–2550. [PubMed: 17167137]
83. Manegold C, von Pawel J, Zatloukal P, et al. Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): BO17704 [abstract LBA7514]. *J Clin Oncol.* 2007; 25
84. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. *J Clin Oncol.* 2009; 27:1227–1234. [PubMed: 19188680]
85. Shaked Y, Henke E, Roodhart JM, et al. Rapid chemotherapy-induced acute endothelial progenitor cell mobilization: implications for antiangiogenic drugs as chemosensitizing agents. *Cancer Cell.* 2008; 14:263–273. [PubMed: 18772115]
86. Lynch TJ, Brahmer J, Fischbach N, et al. Preliminary treatment patterns and safety outcomes for non-small cell lung cancer (NSCLC) from ARIES, a bevacizumab treatment observational cohort study (OCS). *J Clin Oncol.* 2008; 26:8077.
87. Akerley WL, Langer CJ, Oh Y, et al. Acceptable safety of bevacizumab therapy in patients with brain metastases due to non-small cell lung cancer. *J Clin Oncol.* 2008; 26:8043.
88. Ahmad T, Eisen T. Kinase inhibition with BAY 43–9006 in renal cell carcinoma. *Clin Cancer Res.* 2004; 10:6388S–6392S. [PubMed: 15448036]

89. Wilhelm SM, Carter C, Tang L, et al. BAY 43–9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res.* 2004; 64:7099–7109. [PubMed: 15466206]
90. Murphy DA, Makonnen S, Lassoued W, et al. Inhibition of tumor endothelial ERK activation, angiogenesis, and tumor growth by sorafenib (BAY43–9006). *Am J Pathol.* 2006; 169:1875–1885. [PubMed: 17071608]
91. Cabebe E, Wakelee H. Role of anti-angiogenesis agents in treating NSCLC: focus on bevacizumab and VEGFR tyrosine kinase inhibitors. *Curr Treat Options Oncol.* 2007; 8:15–27. [PubMed: 17634832]
92. Schiller JH, Lee JW, Hanna NH, et al. A randomized discontinuation phase II study of sorafenib versus placebo in patients with non-small cell lung cancer who have failed at least two prior chemotherapy regimens: E2501. *J Clin Oncol.* 2008; 26:8014.
93. Schiller JH, Flaherty KT, Redlinger M, et al. Sorafenib combined with carboplatin/paclitaxel for advanced non-small cell lung cancer: A phase I subset analysis. *J Clin Oncol.* 2006; 24:7194.
94. Scagliotti, G.; Von Pawel, J.; Reck, M., et al. Phase III trial comparing carboplatin and paclitaxel with or without sorafenib in chemo-naïve patients with stage IIIB (with effusion) or IV non-small cell lung cancer. Presented at the 1st IASLC-ESMO European Lung Cancer Conference; Geneva (Switzerland). 2008.
95. Abrams TJ, Lee LB, Murray LJ, et al. SU11248 inhibits KIT and platelet-derived growth factor receptor β in preclinical models of human small cell lung cancer. *Mol Cancer Ther.* 2003; 2:471–478. [PubMed: 12748309]
96. Socinski MA, Novello S, Brahmer JR, et al. Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. *J Clin Oncol.* 2008; 26:650–656. [PubMed: 18235126]
97. Brahmer JR, Govindan R, Novello S, et al. Efficacy and safety of continuous daily sunitinib dosing in previously treated advanced non-small cell lung cancer (NSCLC): Results from a phase II study. *J Clin Oncol.* 2007; 25:7542.
98. Reck M, Frickhofen N, Gatzemeier U, et al. A phase I dose escalation study of sunitinib in combination with gemcitabine + cisplatin for advanced non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2007; 25:18057.
99. Casanovas O, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell.* 2005; 8:299–309. [PubMed: 16226705]
100. Hilberg F, Roth GJ, Krssak M, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res.* 2008; 68:4774–4782. [PubMed: 18559524]
101. von Pawel J, Kaiser R, Eschbach C, et al. A double-blind phase II study of BIBF 1,120 in patients suffering from relapsed advanced nonsmall cell lung cancer (NSCLC). *J Clin Oncol.* 2007; 25:7635.
102. Hanna N, Ellis P, Stopfer P, et al. A phase I study of continuous oral treatment with the triple angiokinase inhibitor BIBF 1120 together with pemetrexed in previously treated patients with non-small cell lung cancer: P3–091. *J Thorac Oncol.* 2007; 2:S717–S718.
103. Laurie SA, Gauthier I, Arnold A, et al. Phase I and pharmacokinetic study of daily oral AZD2171, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with carboplatin and paclitaxel in patients with advanced non-small-cell lung cancer: the National Cancer Institute of Canada clinical trials group. *J Clin Oncol.* 2008; 26:1871–1878. [PubMed: 18398152]
104. Schiller JH, Larson T, Ou SI, et al. Efficacy and safety of axitinib (AG-013736; AG) in patients (pts) with advanced non-small cell lung cancer (NSCLC): a phase II trial. *J Clin Oncol.* 2007; 25:7507.
105. Latreille J, Batist G, Laberge F, et al. Phase I/II trial of the safety and efficacy of AE-941 (Neovastat) in the treatment of non-small-cell lung cancer. *Clin Lung Cancer.* 2003; 4:231–236. [PubMed: 14624712]

106. Tabernero J. The role of VEGF and EGFR inhibition: implications for combining anti-VEGF and anti-EGFR agents. *Mol Cancer Res.* 2007; 5:203–220. [PubMed: 17374728]
107. Ellis LM. Epidermal growth factor receptor in tumor angiogenesis. *Hematol Oncol Clin North Am.* 2004; 18:1007–1021. [PubMed: 15474332]
108. Vallbohmer D, Zhang W, Gordon M, et al. Molecular determinants of cetuximab efficacy. *J Clin Oncol.* 2005; 23:3536–3544. [PubMed: 15908664]
109. Herbst RS, Johnson DH, Mininberg E, et al. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. *J Clin Oncol.* 2005; 23:2544–2555. [PubMed: 15753462]
110. Herbst RS, O'Neill VJ, Fehrenbacher L, et al. Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer. *J Clin Oncol.* 2007; 25:4743–4750. [PubMed: 17909199]
111. Faoro L, Cohen EE, Govindan R, et al. Phase II trial of sequential bevacizumab (B), erlotinib (E) and chemotherapy for first line treatment of clinical stage IIIB or IV non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2008; 26:19130.
112. Hainsworth J, Herbst R. A phase III, multicenter, placebo-controlled, double-blind, randomized clinical trial to evaluate the efficacy of bevacizumab (Avastin) in combination with erlotinib (Tarceva) compared with erlotinib alone for treatment of advanced non-small cell lung cancer after failure of standard first-line chemotherapy (β) [abstract LBA1]. *J Thorac Oncol.* 2008; 3 S4:S302.
113. Adjei AA, Molina JR, Mandrekar S, et al. Phase I trial of sorafenib in combination with gefitinib in patients with refractory or recurrent non-small cell lung cancer. *Clin Cancer Res.* 2007; 13:2684–2689. [PubMed: 17473200]
114. Carlomagno F, Vitagliano D, Guida T, et al. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. *Cancer Res.* 2002; 62:7284–7290. [PubMed: 12499271]
115. Wedge SR, Ogilvie DJ, Dukes M, et al. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res.* 2002; 62:4645–4655. [PubMed: 12183421]
116. Ciardiello F, Bianco R, Caputo R, et al. Antitumor activity of ZD6474, a vascular endothelial growth factor receptor tyrosine kinase inhibitor, in human cancer cells with acquired resistance to antiepidermal growth factor receptor therapy. *Clin Cancer Res.* 2004; 10:784–793. [PubMed: 14760102]
117. Kiura K, Nakagawa K, Shinkai T, et al. A randomized, double-blind, phase IIa dose-finding study of vandetanib (ZD6474) in Japanese patients with non-small cell lung cancer. *J Thorac Oncol.* 2008; 3:386–393. [PubMed: 18379357]
118. Natale RB, Bodkin D, Govindan R, et al. ZD6474 versus gefitinib in patients with advanced NSCLC: Final results from a two-part, double-blind, randomized phase II trial. *J Clin Oncol.* 2006; 24:7000.
119. Heymach JV, Johnson BE, Prager D, et al. Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non small-cell lung cancer. *J Clin Oncol.* 2007; 25:4270–4277. [PubMed: 17878479]
120. Heymach J, Paz-Ares L, De Braud F, et al. Randomized phase II study of vandetanib (VAN) alone or in combination with carboplatin and paclitaxel (CP) as first-line treatment for advanced non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2007; 25:7544.
121. Johnson BE, Ma P, West H, et al. Preliminary phase II safety evaluation of ZD6474, in combination with carboplatin and paclitaxel, as 1st-line treatment in patients with NSCLC. *J Clin Oncol.* 2005; 23:7102.
122. Wakelee HA, Adjei AA, Halsey J, et al. A phase I dose-escalation and pharmacokinetic (PK) study of a novel spectrum selective kinase inhibitor, XL647, in patients with advanced solid malignancies (ASM). *J Clin Oncol.* 2006; 24:3044.

123. Wakelee HA, Fehling JM, Molina JR, et al. A phase I study of XL647, an EGFR, HER2, VEGFR2 inhibitor, administered orally daily to patients (pts) with advanced solid malignancies (ASM). *J Clin Oncol.* 2008; 26:3528.
124. Miller VA, Wakelee HA, Lara PN, et al. Activity and tolerance of XL647 in NSCLC patients with acquired resistance to EGFR-TKIs: Preliminary results of a phase II trial. *J Clin Oncol.* 2008; 26:8028.
125. Rizvi NA, Kris MG, Miller VA, et al. Activity of XL647 in clinically selected NSCLC patients (pts) enriched for the presence of EGFR mutations. Result from phase 2. *J Clin Oncol.* 2008; 26:8053.
126. Traxler P, Allegrini PR, Brandt R, et al. AEE788: a dual family epidermal growth factor receptor/ ErbB2 and vascular endothelial growth factor receptor tyrosine kinase inhibitor with antitumor and antiangiogenic activity. *Cancer Res.* 2004; 64:4931–4941. [PubMed: 15256466]

Table 1

Summary of trials with antibodies directed against EGFR and HER2

Trial	Phase	Treatment	N	RR, %	OS, mo
Hanna et al. (12)	II	Cetuximab 400 mg/m ² week 1 then 250 mg/m ² per week	66	5	8.9
Thienelt et al. (14)	I-II	Cetuximab 400 mg/m ² then carboplatin AUC6 day 1 + paclitaxel 200 mg/m ² day 1 every 3 wk + cetuximab 250 mg/m ² per week	31	26	11
Blumenschien et al. (15)	I-II	Carboplatin AUC 6 + paclitaxel 200 mg/m ² day 1 gemcitabine 1,000 mg/m ² days 1 and 8 every 3 wk + cetuximab 400 mg/m ² week 1 then 250 mg/m ² per week	35	29	10.2
Rosell (LUCAS) et al. (16)	II	Cisplatin 80 mg/m ² day 1 + vinorelbine 25 mg/m ² days 1 and 8 every 3 weeks	43	28	7.3
		Cisplatin 80 mg/m ² day 1 + vinorelbine 25 mg/m ² days 1 and 8 + cetuximab 400 mg/m ² then 250 mg/m ² per week	43	35	8.3
Pirker et al. (17) (FLEX)	III	Cisplatin 80 mg/m ² day 1 + vinorelbine 25 mg/m ² days 1 and 8 every 3 wk	568	29	10.1
		Cisplatin 80 mg/m ² day 1 + vinorelbine 25 mg/m ² days 1 and 8 + cetuximab 400 mg/m ² then 250 mg/m ² per week	557	36	11.3
Lynch (BMS 099) et al. (29)	III	Carboplatin AUC 6 + Paclitaxel 225 mg/m ² or docetaxel 75 mg/m ² day 1 every 3 wk	338	17	8.4
		Carboplatin AUC 6 + Paclitaxel 225 mg/m ² or docetaxel 75 mg/m ² day 1 every 3 wk + cetuximab 400 mg/m ² then 250 mg/m ² per week	338	26	9.7
Herbst et al. (18)	II	Pertuzumab 840 mg/m ² then 420 mg/m ² every 3 wk	43	0	NR
Kollmannsberger et al. (19)	I	Matuzumab 100–800 mg/m ² + paclitaxel 175 mg/m ² every 3 wk	18	22	NR
Clamon et al. (20)	II	Trastuzumab 4 mg/m ² then 2 mg/m ² every 3 wk	22	5	~5
Krug et al. (21)	II	Paclitaxel 90 mg/m ² for 6 of 8 weeks + trastuzumab 4 mg/m ² then 2 mg/m ² per week	30	32	14.3
		Docetaxel 35 mg/m ² for 6 of 8 weeks + trastuzumab 4 mg/m ² then 2 mg/m ² per week	34	23	16.2
Langer et al. (22)	II	Carboplatin AUC 6 + paclitaxel 225 mg/m ² + trastuzumab 4 mg/m ² then 2 mg/m ² per week	53	25	10.1
Zimmer et al. (23)	II	Cisplatin 75 mg/m ² day 1 + gemcitabine 1,250 mg/m ² days 1 and 8 every 3 wk + trastuzumab 4 mg/kg day 1 and 2 mg/kg weekly thereafter; following six 21-d cycles, weekly trastuzumab maintenance	21	38	Not reached at follow up (>16.2)
Gatzemeier et al. (24)	II	Cisplatin 75 mg/m ² day 1 + gemcitabine 1,250 mg/m ² days 1 and 8 every 3 wk	50	41	NR
		Cisplatin 75 mg/m ² day 1 + gemcitabine 1,250 mg/m ² days 1 and 8 every 3 wk + trastuzumab 4 mg/m ² then 2 mg/m ² per week	51	36	12.2
Crawford et al. (25)	II	Carboplatin AUC 6 + paclitaxel 225 mg/m ² + panitumumab 1–2.5 mg/m ² every 3 wk	19	26	NR

Abbreviations: AUC, area under the curve; NR, not reported.

Table 2

Summary of trials with EGFR TKIs

Trial	Phase	Treatment	N	RR, %	OS, mo
Fukuoka et al. (34)	II	Gefitinib 250 mg/day	104	18	7.6
Kris et al. (35)	II	Gefitinib 500 mg/day	106	19	8.0
		Gefitinib 250 mg/day	102	12	7.0
		Gefitinib 500 mg/day	114	9	6.0
		Erlotinib 150 mg/day	57	12	8.4
Perez-Soler et al. (36)	II	Placebo	563	1	5.1
Thatcher et al. (38)	III	Gefitinib 250 mg/day	1129	8	5.6
		Placebo	243	<1	4.7
Shepherd et al. (37)	III	Erlotinib 150 mg/day	488	9	6.7
Giaccone et al. (55)	III	Cisplatin 80 mg/m ² day 1 + gemcitabine 1,250 mg/m ² days 1 and 8 every 3 wk	363	45	10.9
		Cisplatin 80 mg/m ² + gemcitabine 1,250 mg/m ² + gefitinib 250 mg/day	365	50	9.9
		Cisplatin 80 mg/m ² + gemcitabine 1,250 mg/m ² + gefitinib 500 mg/day	365	50	9.9
Herbst et al. (56)	III	Carboplatin AUC 6 + paclitaxel 225 mg/m ² every 3 wk	345	29	9.9
		Carboplatin AUC 6 + paclitaxel 225 mg/m ² + gefitinib 250 mg/day	345	30	9.8
		Carboplatin AUC 6 + paclitaxel 225 mg/m ² + gefitinib 500 mg/day	347	30	8.7
Herbst et al. (57)	III	Carboplatin AUC 6 + paclitaxel 225 mg/m ² every 3 wk	533	19	10.5
		Carboplatin AUC 6 + paclitaxel 225 mg/m ² + erlotinib 150 mg/day	526	22	10.6
		Cisplatin 80 mg/m ² day 1 + gemcitabine 1,250 mg/m ² days 1 and 8 every 3 wk	579	30	10.3
Gatzemeier et al. (58)	III	Cisplatin 80 mg/m ² + gemcitabine 1,250 mg/m ² + erlotinib 150 mg/day	580	32	10.0
Smylie et al. (61)	II	Lapatinib 1,500 mg/day or 500 mg twice daily	131	1.5	NR

Abbreviations: AUC, area under the curve; NR, not reported.

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Table 3

Summary of key trials with bevacizumab

Trial	Phase	Treatment	N	RR, %	OS, mo
Johnson et al. (81)	II	Carboplatin AUC 6 + paclitaxel 200 mg/m ² every 3 wk	32	19	14.9
		Carboplatin AUC 6 + paclitaxel 200 mg/m ² + bevacizumab 7.5 mg/kg	35	28	11.6
		Carboplatin AUC 6 + paclitaxel 200 mg/m ² + bevacizumab 15 mg/kg	32	35	17.7
Sandler et al. (82)	III	Carboplatin AUC 6 + paclitaxel 200 mg/m ²	427	35	10.3
		Carboplatin AUC 6 + paclitaxel 200 mg/m ² + bevacizumab 15 mg/kg	440	15	12.3
Manegold et al. (83)	III	Cisplatin 80 mg/m ² day 1 + gemcitabine 1250 mg/m ² days 1 and 8 every 3 wk	347	20	
		Cisplatin 80 mg/m ² day 1 + gemcitabine 1250 mg/m ² + bevacizumab 7.5 mg/kg	345	34	NR
		Cisplatin 80 mg/m ² day 1 + gemcitabine 1250 mg/m ² + bevacizumab 15 mg/kg	351	30	

Abbreviations: AUC, area under the curve; NR, not reported.

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Table 4

Summary of trials with antiangiogenic TKIs

Trial	Phase	Treatment	N	RR, %	OS, mo
Schiller et al. (92)	II	Sorafenib 400 mg twice daily	51	2	11.9
		Placebo	32	3	9.0
Schiller et al. (93)	I–II	Carboplatin AUC 6 + paclitaxel 225 mg/m ² day 1 + sorafenib 400 mg twice daily days 2–18 every 3 wk	15	29	NR
Scagliotti et al. (94)	III	Carboplatin AUC 6 + paclitaxel 225 mg/m ² day 1 every 3 wk	462	24	10.7
		Carboplatin AUC 6 + paclitaxel 225 mg/m ² day 1 + sorafenib 400 mg twice daily	464	30	10.6
Hanna et al. (102)	I	Pemetrexed 500 mg/m ² + BIBF 1120 100–200 mg twice daily	26	15	NR
von Pawel et al. (101)	II	BIBF 1120 150 or 250 mg twice daily	73	0	NR
Socinski et al. (96)	II	Sunitinib 50 mg/day	63	11	5.4
Brahmer et al. (97)	II	Sunitinib 37.5 mg/day	47	2	8.6
Reck et al. (98)	I	Cisplatin 80 mg/m ² day 1 + gemcitabine 1000 or 1250 mg/m ² days 1 and 8 every 3 wk + sunitinib 37.5 or 50 mg/day	13	23	NR
Laurie et al. (103)	I	Carboplatin AUC 6 + paclitaxel 200 mg/m ² day 1 every 3 wk + cediranib 30 or 45 mg/day	20	45	NR
Schiller et al. (104)	II	Axitinib 5 mg twice daily	32	9	12.8
Latreille et al. (105)	I	AE-941 30, 60, 120, or 240 mL/day	80	0	2.6 mL/kg per day: 4.6 >2.6 mL/kg per day: 6.1

Abbreviations: AUC, area under the curve; NR, not reported.

Table 5

Summary of trials of dual EGFR/Antiangiogenic therapy

Trial	Phase	Treatment	N	RR, %	OS, mo
Herbst et al. (109)	I/II	Erlotinib + bevacizumab 15 mg/kg	40	20	12.6
Herbst et al. (110)	II	Docetaxel or pemetrexed	41	12	8.6
		Docetaxel or pemetrexed + bevacizumab 15 mg/kg	40	13	12.6
		Erlotinib + bevacizumab 15 mg/kg	39	18	13.7
Faoro et al. (111)	II	Erlotinib + bevacizumab 15 mg/kg	30	12	NR
		Carboplatin AUC6 + paclitaxel 200 mg/m ² every 3 wk + bevacizumab 15 mg/kg	37	21	NR
Adjei et al. (113)	I	Gefitinib 250 mg + sorafenib 200–400 mg twice daily	31	3	NR
Kiura et al. (117)	II	Vandetanib 100 mg/day	17	17	NR
		Vandetanib 200 mg/day	18	6	
		Vandetanib 300 mg/day	18	17	
		Vandetanib 300 mg/day	83	8	6.1
Natale et al. (118)	II	Gefitinib 250 mg/day	85	1	7.4
		Docetaxel 75 mg/m ² every 3 wk	41	12	13.4
Heymach et al. (119)	II	Docetaxel 75 mg/m ² + vandetanib 100 mg/day	44	26	13.1
		Docetaxel 75 mg/m ² + vandetanib 300 mg/day	42	18	7.9
		Carboplatin AUC 6 + paclitaxel 225 mg/m ² every 3 wk	52	25	
Heymach et al. (120)	II	Carboplatin AUC 6 + paclitaxel 225 mg/m ² + vandetanib 300 mg/day	56	32	NR
		Vandetanib 300 mg/day	73	7	
Miller et al. (124)	II	XL647 300 mg/day	23	4	NR
Rizvi et al. (125)	II	XL647 350 mg/day on an intermittent regimen (days 1–5 of each 14-day cycle)	41	28	NR

Abbreviations: AUC, area under the curve; NR, not reported.