Clinical Progress in Antiangiogenic Therapy for Lung Cancer

Cancer of the lung and bronchus remains the leading cause of cancer-related death for both men and women in the United States in 2014, with an estimated 224,210 new cases and 159,260 expected deaths.[1] In patients with newly-diagnosed non-small cell lung cancer (NSCLC), 40% of patients will have advanced, metastatic disease.[2] While platinum-based chemotherapy regimens can improve both survival time and the quality of life for patients with newly-diagnosed, advanced non-small cell lung cancer (NSCLC), most still develop progressive disease in the first six months of treatment. Because this poor prognosis remains despite progress in the treatment of lung cancer, newer therapies that disrupt critical growth factor/receptor signaling pathways that are involved in tumor angiogenesis and lymphangiogenesis have been being intensively researched for NSCLC. There are many known cellular proteins involved in tumor angiogenesis; the one that has been most extensively studied and clinically validated as a therapeutic target is vascular endothelial growth factor (VEGF).[3] VEGF induces the proliferation, migration, and survival of vascular endothelial cells and stimulates the recruitment of the bone marrow-derived endothelial progenitor cells to the new vessels. High expression levels of VEGF in the tumor microenvironment have been correlated with increased tumor vascular density, invasive behavior, and metastasis in NSCLC and other tumor types. VEGF binding and activation of VEGF receptor (VEGFR) lead to receptor dimerization, phosphorylation of key tyrosine residues on its intracellular tail, and activation of numerous downstream signaling pathways.[4] Two downstream activated pathways that play an important role in endothelial and tumor cell growth and survival are the Raf-MEK-Erk and phosphotidylinositol-3-kinase (PI3K)-Akt pathways (please refer to illustration). These pathways also mediate proangiogenic intracellular signaling initiated through other receptor tyrosine kinases, such as platelet derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR). Each member of these proangiogenic pathways represents potential targets for drug development and mechanisms of action for the treatment of cancer.

Clinical trials demonstrating the efficacy of antiangiogenic agents directed at the VEGF family of proteins and its group of receptors have accelerated the commercial drug development of VEGF inhibitors for cancer therapy. Bevacizumab, a fully human anti-VEGF monoclonal antibody, is approved for the treatment of colorectal cancer, renal cell carcinoma, NSCLC, and glioblastoma. Bevacizumab is the only angiogenesis inhibitor that has been approved for NSCLC after demonstrating its ability to significantly improve survival and response when combined with chemotherapy in phase 3 clinical trials.[5] Several newer agents that target proangiogenic signaling through VEGFR and other growth factors, such as tyrosine kinase inhibitors (TKIs), have also advanced into late stage clinical trials for NSCLC and yielded mixed results to date. Antiangiogenic agents with novel mechanisms of action are also being explored in NSCLC. The ongoing clinical research in the field also includes the assessment of potential biomarkers that could help identify the cancer patients who benefit most from antiangiogenic therapy.

Monoclonal Antibodies

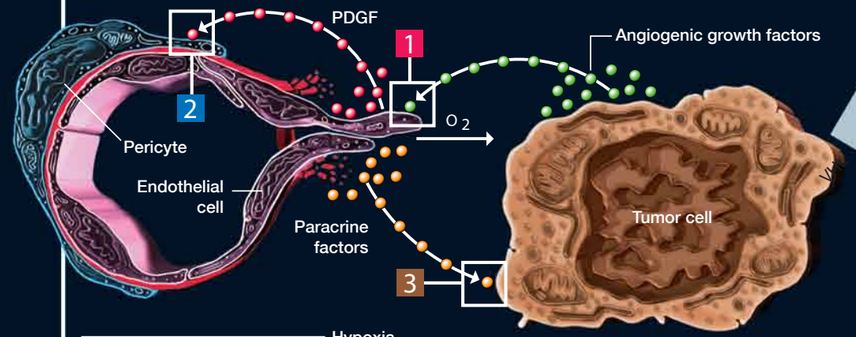
Bevacizumab

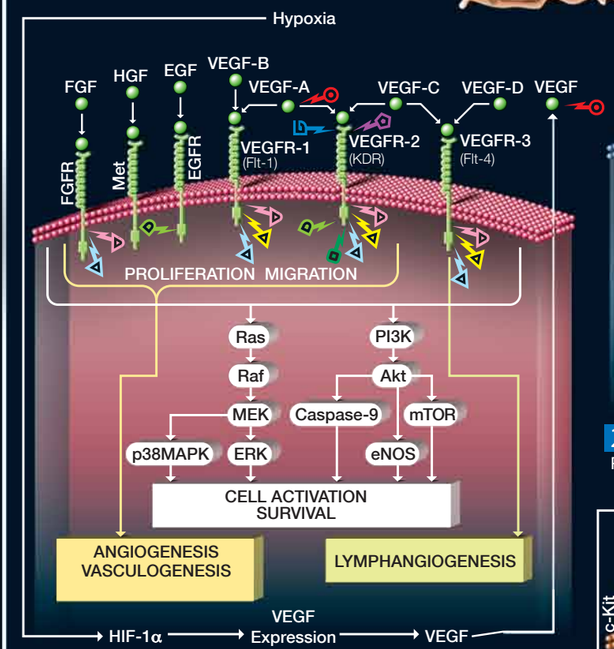
Bevacizumab (BV) was FDA approved for advanced nonsquamous NSCLC after data from two phase 3 trials demonstrated its superiority to first-line chemotherapy for treatment of advanced and metastatic NSCLC. Bevacizumab (15 mg/kg q3w) was found to prolong overall survival (OS) by about 2 months when added to first-line carboplatin/paclitaxel chemotherapy doublet in the landmark ECOG 4599 phase 3 clinical trial.[6] A second phase 3 trial (AVAiL), conducted primarily in Europe evaluated the addition of two different doses of BV, 7.5 mg/kg or 15 mg/kg q3w, to cisplatin/gemcitabine.[7] Both median progression-free survival (PFS) and the objective response rate (ORR) were significantly increased in patients who received either BV dose level in combination with chemotherapy compared to those who received placebo, thus validating the use of BV with this alternate chemotherapy combination. However, the final OS data from AVAiL revealed no significant difference between the 3 treatment groups.[8] A significant percentage (65%) of these patients received therapy after the study in each of the treatment arms; this may have influenced the OS results.

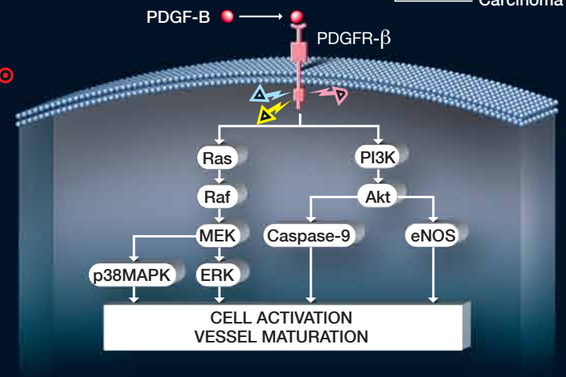
The continuation of BV after the completion of standard therapy has been evaluated in patients with advanced non-squamous NSCLC. The ARIES study, an observational cohort study of patients receiving chemotherapy plus BV as front-line therapy for advanced NSCLC, was the first large, prospective analysis of BV use in the clinical setting. The ARIES results suggested that BV use in the treatment of advanced NSCLC was safe and effective in all patient subgroups and that BV treatment after first-line therapy could have a role in managing disease.[9] An update of the ARIES trial supported this concept, as a time-dependent analysis indicated that post-progression OS increased by approximately 4% for each additional 21- day interval of cumulative BV exposure.[10] As a result of the ARIES data, a randomized phase 3b trial is being conducted evaluating the safety and efficacy of standard treatment with or without continuous BV beyond disease progression, AvaALL (MO22097). In AvaALL, patients who have progressive disease after first-line therapy with BV/platinum-containing chemotherapy doublet and at least two cycles of BV monotherapy will be randomized to treatment with chemotherapy (physician's choice)

Targeting Cells and Pathways in Lung Cancer

During tumor angiogenesis, endothelial cells recruit pericytes to stabilize blood vessels perfusing tumors. Endothelial cells also provide paracrine factors to tumor cells which, in turn, release growth factors that sustain angiogenesis. Key pathways in each cell can be targeted for therapy.

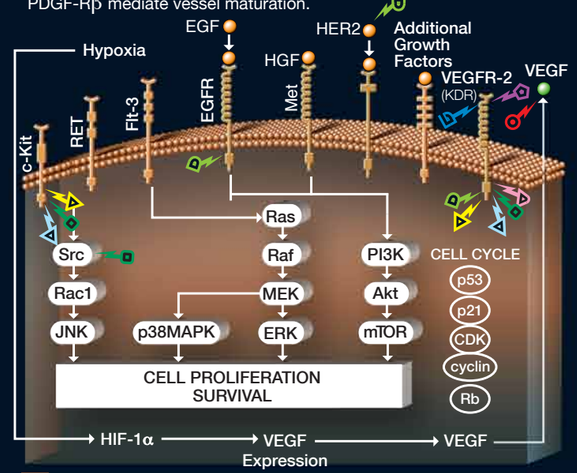






1 ENDOTHELIAL CELLThe vascular endothelial growth factor (VEGF) family (A-D) binds to receptors VEGF-R1, VEGF-R2, VEGF-R3, activating signal transduction to promote angiogenesis,vasculogenesis, and lymphangiogenesis.

2 PERICYTE Platelet-derived growth factor (PDGF) and its receptor PDGF-Rβ mediate vessel maturation.



3 TUMOR CELL Multiple growth factors and receptors activate signal transduction and cell cycle pathways to stimulate tumor cell growth.

Targeted Agents

(Targets shown in diagram above and to the right)

- Bevacizumab
- Endostar
- Ramucirumab
- Nintedanib
- Pazopanib
- Motesanib
- KD019
- Apatinib

Targeting Tumor Angiogenesis

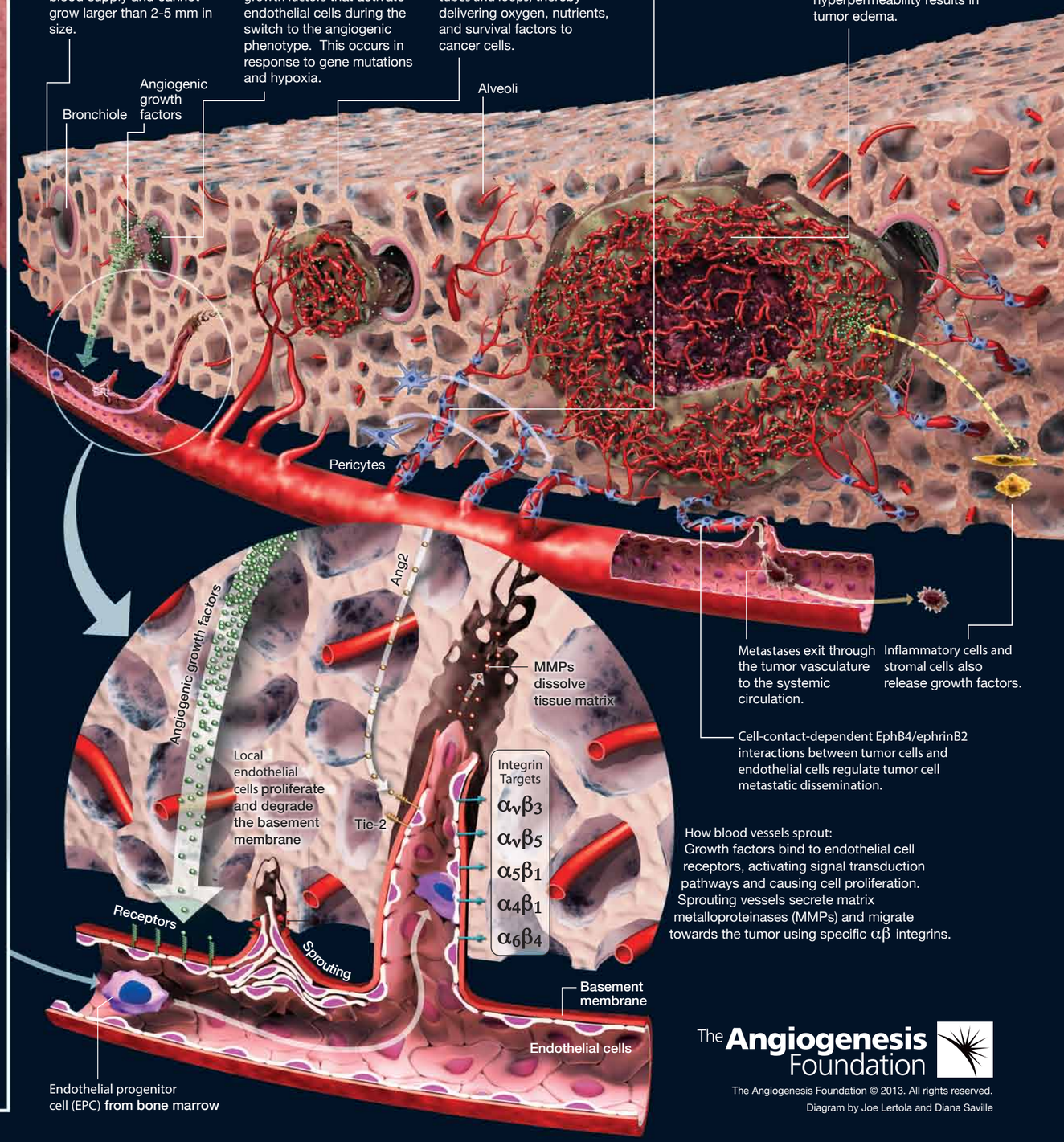
1 Incipient cancers lack a blood supply and cannot grow larger than 2-5 mm in size.

2 Cancer cells release growth factors that activate endothelial cells during the switch to the angiogenic phenotype. This occurs in response to gene mutations and hypoxia.

3 Angiogenic vessels form tubes and loops, thereby delivering oxygen, nutrients, and survival factors to cancer cells.

4 Vessels mature as pericytes are recruited by endothelial cells to stabilize new capillaries.

5 Unabated angiogenesis enables tumor expansion and local invasion. Abnormal blood flow leads to central hypoxia. Vessel hyperpermeability results in tumor edema.



Metastases exit through the tumor vasculature to the systemic circulation.

Inflammatory cells and stromal cells also release growth factors.

Cell-contact-dependent EphB4/ephrinB2 interactions between tumor cells and endothelial cells regulate tumor cell metastatic dissemination.

How blood vessels sprout:
Growth factors bind to endothelial cell receptors, activating signal transduction pathways and causing cell proliferation. Sprouting vessels secrete matrix metalloproteinases (MMPs) and migrate towards the tumor using specific αβ integrins.

The Angiogenesis Foundation

Diagram by Joe Lertola and Diana Saville

± BV (7.5 or 15 mg/kg);[11] the estimated completion date for this study is 2016.[12] Along these lines, a phase 4 study has been implemented to evaluate the effect of the cumulative exposure to BV after induction therapy. A time-dependent analysis of this trial, the SAiL (MO19390) study, has indicated that continuous BV post-induction (post-IP) until disease progression prolongs OS.[13] The hazard ratio for OS, which indicates the benefit from BV, decreased by approximately 7% with each post-IP additional 21-day interval of cumulative exposure. Indeed, patients who achieved eight post-IP BV cycles experienced a substantially increased benefit from BV treatment than those who received only one post-IP BV cycle (HR 0.46 and HR 0.91, respectively).

Other important studies in NSCLC are evaluating BV in combination with alternate chemotherapy agents in the front-line setting. Pemetrexed, a multi-targeted antifolate chemotherapy, produced superior survival outcomes in combination with cisplatin versus cisplatin plus gemcitabine in patients with previously untreated NSCLC.[14] In a phase 2 first-line study assessing a potential role for BV in NSCLC, BV added to pemetrexed/carboplatin, followed by pemetrexed/BV maintenance therapy, produced a median PFS and OS of 7.8 months and 14.1 months, respectively.[15] There were no treatment related deaths in this study, and the rate of serious toxicity was minimal. Based on these encouraging results, two randomized phase 3 trials investigating BV/pemetrexed-containing regimens, PointBreak and AVAPERL1, were initiated. Published results of PointBreak, a randomized, open-label phase 3 trial comparing pemetrexed/BV plus carboplatin followed by pemetrexed/BV maintenance (Arm A) and paclitaxel/carboplatin/BV followed by BV maintenance (Arm B) as first-line therapy for patients with advanced NSCLC, revealed that the primary endpoint, OS, was not reached.[16] A total of 939 patients were randomized between the two treatment arms and maintenance therapy was continued until disease progression. Although median OS was comparable between Arm A and Arm B (12.6 vs. 13.4 months; HR 1.00, P = 0.949), a modest but significant increase in median PFS was found for Arm A (6.0 vs. 5.6 months; HR 0.83, P = 0.012). Toxicity profiles associated with treatment regimens differed. Significantly more drug-related grade 3/4 anemia (14.5% vs. 2.7%), thrombocytopenia (23.3% vs. 5.6%), and fatigue (10.9% vs. 5.0%) were found for Arm A, while a significantly greater incidence of grade 3/4 neutropenia (40.6% vs. 25.8%), febrile neutropenia (4.1% vs. 1.4%), and sensory neuropathy (4.1% vs. 0) was found for Arm B. Notwithstanding, the rate of discontinuation due to serious adverse events (2.7% vs. 3.6%), adverse events (10.4% vs. 9.0%), and drug-related deaths from adverse events (1.8% vs. 2.3%) were comparable for Arms A and B, respectively.

In contrast, preliminary results from AVAPERL, an open-label phase 3 trial conducted primarily in Europe reported at the 2011 European Society for Medical Oncology, indicated the trial met its primary endpoint, PFS, and were a bit more encouraging regarding the use of cisplatin/pemetrexed/BV as maintenance therapy in patients with advanced NSCLC.[17] In updated results for AVAPERL,[18] 376 patients with no progressive disease after 1 line of cisplatin/pemetrexed/BV therapy were randomized to BV (7.5 mg q3w) maintenance therapy with or without pemetrexed until disease progression. Median PFS was prolonged in patients who received maintenance therapy with BV/pemetrexed compared to BV alone (10.2 vs. 6.6 months; HR 0.5, P < 0.001). The OS for the BV arm was also improved (19.8 v 15.9 m, HR 0.88 [0.64-1.22], p = 0.032). Adverse events in the trial were consistent with those observed in previous BV and pemetrexed clinical studies and manageable. With an increase in OS of almost 4 months, these results indicated that BV/pemetrexed is a potential option for maintenance treatment of advanced or metastatic NSCLC.

Another combination treatment strategy under investigation in patients with NSCLC includes agents targeting VEGF and the epidermal growth factor receptor (EGFR), an important angiogenesis- and tumor-promoting target involved in the development of NSCLC. EGFR-activating mutations occur in approximately 10% of Western and up to 50% of Asian NSCLC patients, with higher EGFR mutation frequency seen in non-smokers, women, and in mucinous adenocarcinoma.[19] In this tumor type, clinical investigators have been motivated by the potential for benefit from targeting two pathways known to play a large role in its development, growth and survival. An initial study evaluating this therapeutic strategy was a randomized, placebo-controlled phase 3 trial (BeTa) comparing the efficacy of erlotinib/BV and erlotinib/placebo in 636 patients with recurrent or refractory NSCLC after failing first-line chemotherapy.[20] The trial did not meet its primary endpoint, OS (9.3 vs. 9.2 months; HR 0.97, P = 0.7583), although a statistically significant increase in median PFS was observed in patients who had received erlotinib/BV (3.4 vs. 1.7 months; HR 0.62, P < 0.0001). Of note, 20 patients in the erlotinib/BV group suffered grade 5 adverse events, including 2 thromboembolic events, compared with 14 patients in the erlotinib/placebo group.

In a similar placebo-controlled phase 3b trial, the ATLAS study, investigators compared BV/erlotinib and BV/placebo following induction therapy with a platinum-containing chemotherapy doublet/BV in patients with advanced NSCLC.[21] A total of 768 patients who lacked progressive disease after induction therapy were randomized to receive BV/erlotinib or BV/placebo. ATLAS met its primary endpoint, PFS, which demonstrated a significant improvement in median PFS (4.8 vs. 3.7 months; HR 0.722, P = 0.0012) for patients who received BV/erlotinib. The median OS times from random assignment were 13.3 and 14.4 months with bevacizumab/placebo and bevacizumab/erlotinib, respectively (HR, 0.92; 95% CI, 0.70 to 1.21; P = 0.5341) which did not meet the level of statistical significance.[22] Biomarker analysis indicated that the combination was most active in patient subsets who had EGFR fluorescent in situ hybridization- (FISH)-positive (HR = 0.66), EGFR mutated (HR = 0.44), and KRAS wild-type (HR = 0.67) tumors.[23]

Promising efficacy results have been reported from a single arm phase 2 study (SWOG 0536) that combined front-line paclitaxel/carboplatin chemotherapy with BV and the anti-EGFR monoclonal antibody cetuximab for up to 6 cycles, followed by BV plus cetuximab alone until disease progression. The trial met its primary endpoint, the frequency and severity of grade 4 hemorrhagic toxicities, and grade 4 or above hemorrhage was 2%. This treatment regimen produced surprisingly high response and survival rates in treatment-naïve patients, with a 56% PR and 77% disease control rates.[24] The median PFS was 7 months, with a 57% one-year survival rate and a median OS of 15 months. The findings of this study led to the initiation of a randomized phase 3 trial (SWOG 0819) with 2 treatment arms: the comparator arm receive paclitaxel/carboplatin with or without BV followed by maintenance BV therapy, and the treatment arm receive paclitaxel/carboplatin with or without BV plus cetuximab, followed by maintenance BV therapy with or without cetuximab.[25] The primary endpoints of the trial are the OS and PFS of EGFR FISH-positive patients, and the predictive value of therapy based on EGFR FISH and KRAS mutation status will also be explored. Results are expected in 2017.

Smaller, preliminary studies have also looked at BV in combination with other medications to treat advanced NSCLC. A phase 2 study was conducted to evaluate the efficacy and safety of docetaxel and BV in patients with previously-treated NSCLC.[26] These patients were treated with D (60 mg/m^2) and B (15 mg/kg) on day 1, repeated q3w until progressive disease or unacceptable toxicity. The primary endpoint was RR. The response rate and disease control rate were 66.7% and 96%, respectively. After a median follow-up of 12.7 months, the median PFS was 7.9 months. Another study looked at BV and weekly paclitaxel as a fourth line or beyond therapy in advanced NSCLC.[27] The median progression-free survival and overall survival were 6.4 months and 9.6 months, respectively. The researchers found prolonged responses in a patient who had received bevacizumab as part of first-line chemotherapy and in another one who harbored an ALK rearrangement. The researchers for both of these phase 2 studies suggested that these combinations might require further study.

Ramucirumab

Ramucirumab, a fully human IgG1 monoclonal antibody that inhibits signaling due to its binding specificity for the extracellular domain of VEGFR-2, initially showed promising anti-tumor activity as a single agent in phase 1 studies in heavily pretreated patients with multiple tumor types.[28] Recently reported phase 2 trials have confirmed the utility of ramucirumab in patients with advanced NSCLC. First, an open label phase 2 study of ramucirumab in combination with paclitaxel and carboplatin followed by maintenance ramucirumab found a 6-month PFS rate, the primary endpoint, of 62.5 % and a median PFS of 7.9 months.[29] Investigators also reported an overall disease control rate (CR+ PR + SD) of 90%. The most frequently observed grade 3 adverse events were neutropenia (13%), thrombocytopenia (10%), fatigue (8%), and febrile neutropenia (8%). A double-blind, randomized phase 3 trial of docetaxel plus ramucirumab compared to docetaxel plus placebo in second line therapy for stage IV NSCLC (REVEL) is currently underway.[30] Eligible patients had disease progression on a prior platinum-based line of therapy; the primary outcome measure was OS, and secondary outcomes include PFS, ORR, and disease control rate. Early results from this study with over 1200 participants have shown a statistically significant improvement in overall survival in the ramucirumab plus docetaxel arm compared to placebo plus docetaxel. This trial also found a statistically significant improvement in PFS in the ramucirumab arm compared to the control arm.[31] The specific data will be presented at a future scientific meeting and will be presented to regulatory agencies in 2014.

Tyrosine Kinase Inhibitors in Phase 3 Trials

Although many antiangiogenic tyrosine kinase inhibitors have reached late stage clinical development in advanced NSCLC, success in meeting phase 3 clinical trial primary endpoints has been elusive. The most recent inhibitors that are in phase 3 development include nintedanib, pazopanib, and KD019, all of which inhibit angiogenesis by blocking the action of VEGF receptor signaling as well as other targets.

Nintedanib

Nintedanib (formerly BIBF 1120) is a tyrosine kinase inhibitor that suppresses the signaling function of VEGFR1-3, FGFR, and PDGFR.[32] Findings of phase 1 analysis of BIBF 1120 in combination with pemetrexed in patients with advanced NSCLC who had failed one previous platinum-containing therapeutic line indicated that the combination was tolerable and had promising efficacy signals.[33] One patient achieved a complete response and 50% had stable disease. Based on this promising data, a double-blind phase 2 study was initiated to assess the efficacy and safety of nintedanib monotherapy at two dose levels, 150 mg twice daily or 250 mg twice daily, in patients with advanced disease who had failed two previous lines of therapy.[34] The investigators found no superiority of nintedanib 250 mg over nintedanib 150 mg based on PFS (53 vs. 48 days, respectively) and the median PFS for all patients was 6.9 weeks. Overall median OS was 21.9 weeks, with a trend towards prolonged survival in patients who received the higher dose (29.7 vs. 20.6 weeks; HR 0.69, P = 0.21). One patient achieved a partial response, while 46% of all patients had stable disease. The most common grade 3 treatment-related adverse events were nausea (6.8%), diarrhea (8.2%), and increases in alanine aminotransferase (9.6%) and gamma glutamyl transferase (4.1%). The investigators noted that efficacy was comparable between the 150 mg and 250 mg dose-levels with the exception that the one partial response occurred in the 250 mg cohort, but that grade 3 adverse events occurred at a higher rate in these patients as well. Two large phase 3 trials have been implemented to evaluate nintedanib in combination with other agents as second-line therapy for patients with advanced NSCLC. The LUME-Lung 1 trial[35] that compared the efficacy and safety of nintedanib/docetaxel to placebo/docetaxel in squamous and non-squamous cell NSCLC found that PFS was significantly improved in the nintedanib/docetaxel group compared with the placebo/docetaxel group (median 3.4 months vs 2.7 months; HR 0.79, p= 0.0019). The OS was significantly improved for patients with adenocarcinoma histology with a median OS of 12.6 months vs 10.3 months; HR 0.83, p = 0.0359) and in the subgroup of patients with adenocarcinoma and fast-growing tumors (who progressed within 9 months of starting therapy) at 10.9 vs 7.9 months (P = 0.0073). Grade 3 or worse adverse events that were more common in the docetaxel plus nintedanib group than in the docetaxel plus placebo group were diarrhea, reversible increases in alanine aminotransferase, and reversible increases in aspartate aminotransferase. The LUME-Lung 2 trial compared nintedanib/pemetrexed to placebo/pemetrexed in non-squamous cell NSCLC; while enrollment was stopped early due to futility, an ITT analysis showed that PFS favored the nintedanib-treated area (4.4 vs 3.6, p = 0.04). No difference in OS or RR was found.[36] There was no increase in serious adverse events or in grade 5 adverse events with nintedanib/pemetrexed. The addition of nintedanib did result in a higher incidence of ≥G3 elevated ALT and AST levels and diarrhea. The approval application for this medication has been submitted to the regulatory agency in Europe and will be submitted in the US.

Pazopanib

Pazopanib, an oral angiogenesis inhibitor, specifically targets the action of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, FGFR, and c-Kit.[37] Pazopanib has been approved by the FDA for the treatment of renal cell carcinoma and soft tissue sarcoma, and was found to be tolerable in a phase 1 study in patients with various tumor types.[38] The European Organization for Research and Treatment of Cancer

(EORTC) is conducting an ongoing phase 2/3 trial of pazopanib vs. placebo as maintenance therapy in patients with stage IIIB-IV NSCLC (squamous and nonsquamous cell histology) who have not progressed after first-line chemotherapy. The primary endpoint is OS and results are expected in 2015.[39]

KD019

KD019 (formerly XL647) is a small molecule tyrosine kinase inhibitor that targets EGFR, VEGFR2, HER2, and Ephrin type-B receptor 4 (EphB4).[40] In a phase 1 dose escalation clinical trial of KD019 in patients with advanced solid cancers, 1 patient with NSCLC had a partial response and 3 NSCLC patients had stable disease.[41] Diarrhea was a dose-limiting adverse event. Based upon additional preclinical studies, the single agent activity of KD019 was studied in phase 2 trial in patients with advanced NSCLC who were resistant to erlotinib or gefitinib, and/or patients with a documented EGFR T790M mutation.[42] About 50% of patients who develop resistance to EGFR inhibitors have the EGFR T790M mutation. Of 33 evaluable patients, there was one partial response, resulting in a response rate of 3%. For patients who had EGFR T790M mutations, the PFS was significantly worse. A second phase 2 trial was conducted in treatment naïve patients with EGFR mutations or in patients with one or more of the following criteria: being Asian, female, or no smoking history.[43] Forty-one patients were enrolled in the study, most eligible because of non-smoking status. The response rate was 20% and PFS was 5.3 months for the entire cohort. In the 14 patients with mutated EGFR, the response rate was 57% and the PFS was 9.3 months.

Common adverse events included diarrhea, nausea, and fatigue. A double-blind, randomized, phase 3 trial of KD019 vs erlotinib in patients with advanced NSCLC who have progressed after first or second line chemotherapy, excluding prior EGFR TKIs is currently underway.[44] The primary endpoint of that trial is OS, and the secondary endpoints include PFS and response rate.

Angiogenesis Inhibitors and NSCLC in Asia

Research has found that there are ethnic differences with regard to survival outcomes, mutation rates, and response rates between Asians and Caucasians with advanced NSCLC treated with systemic therapies.[45] Hematological toxicities from various chemotherapies occur more frequently in Asians than in Caucasians. Asians have higher rates of EGFR mutations and respond better to EGFR inhibitors compared to Caucasians, but also have a higher incidence of interstitial lung disease as a side effect to EGFR inhibitors. Pharmacogenomic differences across ethnic groups in metabolizing enzymes and transporters influence the frequencies of toxicities of anticancer drugs. Contrasting diet, lifestyle, and medical care between East and West may also contribute to this "pharmacoethnicity" that exists in NSCLC treatments and outcomes.

Endostar

In 2005, China's State Food and Drug Administration (SFDA) approved endostar (rh-endostatin), a novel recombinant human endostatin, for the treatment of NSCLC.[46] Endostar has multiple mechanisms of action, includes targeting endothelial cell VEGFR-2 signaling in capillaries inside and surrounding tumors.[47] Although results from rigorous, randomized controlled phase 3 clinical trials have not been published, a meta-analysis of 15 published phase 3 clinical trials of endostar in combination with platinum-based chemotherapy compared to treatment with platinum-based chemotherapy alone included 1953 patients.[48] The overall response rate (14.7% improvement) and disease control rate (13.5% improvement) of endostar plus platinum based chemotherapy vs. platinum based chemotherapy alone were both significantly higher ($P < 0.00001$). Five of the trials could be used to analyze one year survival rates, which increased by 10.1% when endostar in combination with platinum based chemotherapy was compared vs. treatment with platinum based chemotherapy alone (55.4% and 45.3%, respectively). The most common adverse events included hematological reactions, diarrhea, hepatic toxicity, and nausea/vomiting, mostly grade 1 and 2. Additional data from rigorous, randomized controlled phase 3 clinical trials is required to fully evaluate the efficacy of endostar.

Tyrosine Kinase Inhibitors in development in Asia

The two tyrosine kinase inhibitors are currently being evaluated in Phase 3 clinical trials exclusively in Asian countries: Apatinib in China and Motesanib in Japan, Hong Kong, South Korea and Taiwan.

Apatinib

Apatinib (YN968D1) is a small molecule VEGFR-2 TKI that also mildly inhibits c-Kit and c-SRC and is undergoing clinical development in China.[49] In a phase 1 dose escalation study of apatinib in 37 evaluable, heavily pretreated patients with advanced solid cancers, 7 patients had partial responses (18.9%), and 24 patients had stable disease (64.9%), resulting in disease control rate of 83.8% at 8 weeks.[50] Adverse events included hypertension, proteinuria, and hand and foot syndrome. A placebo-controlled phase 2 trial of third-line apatinib was conducted in advanced NSCLC patients. Prior lines of therapy could include EGFR TKIs but not anti-VEGF therapy.[51] For the apatinib arm, PFS was 4.7 months vs. 1.9 months for placebo group ($p < 0.0001$). The response rate (12.2% vs. 0%) ($P = 0.0158$) and disease control rate (68.9% vs. 24.4%) ($P < 0.0001$) were both significantly better in the apatinib arm than in the placebo arm. Hypertension, proteinuria, and hand-foot syndrome were again the most common adverse events, and were generally mild. A randomized, double blind, placebo controlled phase 3 study of apatinib vs. placebo in patients who had previously received (EGFR) TKIs and at least second line chemotherapy is ongoing.[52] The primary endpoint is PFS, and the secondary endpoints include OS and response rate.

Motesanib

Motesanib (development code: AMG 706) is a TKI that inhibits VEGFR-1, -2, -3, PDGFRs, and c-kit.[53] Motesanib combined with carboplatin/paclitaxel vs. carboplatin/paclitaxel alone was evaluated in a first-line, international, randomized, placebo-controlled, double-blind phase 3 clinical trial (MONET1) in 1,090 patients with advanced nonsquamous NSCLC.[54] Analysis of the entire trial population demonstrated that the trial did not meet its primary endpoint, median OS, which increased nonsignificantly from 11.0 months to 13.0 months, respectively, for the carboplatin/paclitaxel alone arm vs motesanib plus carboplatin/paclitaxel arm ($P = 0.14$). However, a subgroup analysis of the 227 Asian patients in the trial (from Japan, S. Korea, Philippines, Hong Kong, Taiwan, and Singapore) indicated that median OS was significantly increased when motesanib was added to carboplatin/paclitaxel, from 14.5 months to 20.9 months, respectively ($P < 0.05$).[55] Progression free survival (5.3 months to 7.0 months, ($P < 0.001$)) and response rate (27% to 62%, ($P< 0.001$)) also increased when motesanib was added to carboplatin/paclitaxel. Grade 3 or higher adverse events seen more often in the motesanib arm were neutropenia and hypertension. As a result of this subgroup analysis, a phase 3 clinical trial has been initiated in Japan, Hong Kong, South Korea and Taiwan, evaluating motesanib combined with carboplatin/paclitaxel vs. carboplatin/paclitaxel alone in patients with advanced non-squamous NSCLC.[56] The primary endpoint of the trial is PFS.

Biomarkers

As antiangiogenic therapies become incorporated into standard first- and second-line treatment regimens for NSCLC, scientists have begun to search for biomarkers, either clinical or genetic, that could help identify which patients are most likely to respond to these agents. Testing tumor samples for EGFR mutation status has become standard practice for predicting response to EGFR inhibitors, as patients with drug-sensitive EGFR mutations are significantly more likely to respond to treatment with EGFR TKIs than those without them, although EGFR testing remains underutilized.[57] While there are no clinically validated predictive biomarkers for antiangiogenic therapy at this time, there have been some intriguing findings. ECOG 4599 (BV plus carboplatin/paclitaxel vs. carboplatin/paclitaxel alone) included an analysis of several potential predictive genetic markers of response to antiangiogenic therapy.[58] Clinical outcomes in 133 patients enrolled in the trial were compared against expression of several single nucleotide polymorphisms (SNPs), and results indicated that specific germ line polymorphisms were associated with improved response rates in the BV treatment arm. Germ line polymorphisms in IL-8, VEGF, and ICAM1, specifically, were associated with improved response in patients who received BV. Patients with these polymorphisms had a 44% response rate to BV therapy versus 16% among patients without these specific SNPs. Tests for treatment effects indicated statistically significant differences in response according to genotype ($P < 0.05$). For instance, patients with VEGF, ICAM1, and WNK1 polymorphisms experienced superior outcomes in OS. Patients with specific ICAM1, EGF A-61G, and CXCR2 and C785T polymorphisms had greater PFS benefit from BV than those without these polymorphisms. Although exploratory, these preliminary results suggest germ lines SNPs in the angiogenesis pathway may predict response.

Safety

BV is presently contraindicated in NSCLC patients with squamous cell histology because of an increased risk of fatal pulmonary hemorrhage, which occurred in patients with this histology in a randomized phase 2 trial.[59] A consensus report from an expert panel concluded that certain factors, specifically central tumor location, tumor cavitation, histology, concomitant anticoagulation therapy and age, can reliably predict patients who are at risk for developing pulmonary hemorrhage, and that the majority of the bleeding events can be resolved or improved without interruption/discontinuation of bevacizumab.[60, 61]

In addition to these NSCLC-specific safety concerns, VEGF inhibition in general may be associated with hypertension, impaired wound healing, and, infrequently, gastrointestinal perforation, fistula formation, thromboembolic complications, and very rarely, reversible posterior leukoencephalopathy. Side effects associated with VEGFR TKIs include diarrhea, fatigue, nausea, stomatitis, hypertension, mucosal inflammation, and with some TKIs (apatinib) dermatological toxicities, notably hand and foot skin reaction.

Future Directions

Bevacizumab combined with paclitaxel/carboplatin is currently standard first-line therapy for BV-eligible stage IV lung cancer patients. Oncologists treating lung cancer patients await the results of a completed phase 3 trial that will determine whether pemetrexed combined with BV and carboplatin could be an effective alternative regimen to carboplatin/paclitaxel. Several other targeted treatments have been recently approved; several of these agents have treatment benefits for patients with specific biomarkers. However, a number of targeted antiangiogenic agents in development for NSCLC have led to disappointing results, but multiple therapies with novel mechanisms of action remain in clinical development. In addition, investigators continue to search for predictive markers for BV and other antiangiogenic agents that, when clinically validated, will greatly impact and guide treatment decisions.

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ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through Joint Providership of New York Medical College and the Angiogenesis Foundation. New York Medical College is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION

New York Medical College designates this enduring material for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Credit will be awarded to those who complete this activity according to the instructions and achieve a score of 70% or better on the post activity examination. A certificate of credit will be available for download to those who successfully complete the examination.

RELEASE AND EXPIRATION

Date of original release:
June 13, 2014

Date of expiration:
June 12, 2015

CME Course Code: 2014LUNG

TARGET AUDIENCE

Practicing oncologists, pulmonologists, and primary care physicians in the U.S., researchers and medical students.

HEALTHCARE GAP

In the United States alone, more than 228,190 new cases of lung cancer are estimated to have be diagnosed in 2013, and an estimated 159,480 have died from this disease. Approximately 85% of lung cancers are a variety called non-small cell lung cancer (NSCLC), which are actually a number of tumor subtypes that originate in lung epithelial cells. The outlook for people with lung cancer that has spread (metastasized) to other organs of the body is almost uniformly grim: most patients with metastatic disease treated with standard chemotherapy survive for less than one year. Because of this poor prognosis, there is an urgent need for better treatments.

PROGRAM LEARNING OBJECTIVES

At the completion of this activity, participants should be able to:

• Summarize the current clinical progress of targeted therapies in the management of metastatic lung cancer in early and late stage clinical trials.

• Explain current clinical challenges in the management of metastatic lung cancer.

• Interpret the outcome data from recent well-designed scientific and clinical studies of protocols studying new-targeted therapies.

• Integrate side effect management into the long term management of patients with metastatic lung cancer.

• Assess treatment options, efficacy data, and side effect management with members of the cancer treatment team, as well as cancer patients and their family members.

ACTIVITY GOAL

This activity is designed to address the following ABMS / IOM competencies:

• Patient Care and Medical Knowledge

METHOD OF PARTICIPATION

There are no fees for participating in and receiving credit for this online educational activity. The participant should, in order, read the objectives and faculty disclosures, review the educational content, answer the multiple-choice post-test and complete the evaluation. This program is available in PDF format accessible from the Angiogenesis Foundation's website (http://www.angio.org) in the CME section. A print version is also available; for more information contact outreach@angio.org. After reviewing the material, CME credits are available through the Angiogenesis Foundation's website (http://www.cmeonline.org) by selecting the name of the program (registration required). Course code: 2014LUNG

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COURSE FACULTY

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Dartmouth Medical College

DISCLOSURE

New York Medical College asks all individuals involved in the development and presentation of Continuing Medical Education (CME) activities to disclose all relationships with commercial interests. This information is disclosed to CME activity participants. New York Medical College has procedures to resolve apparent conflicts of interest. In addition, faculty members are asked to disclose when any unapproved use of pharmaceuticals and devices is being discussed.

William W. Li, M.D.

President, the Angiogenesis Foundation, Editor-in-Chief

Dr. Li has nothing to disclose with regard to commercial interests.

TOPICS AND EDUCATIONAL CONTENT

Emerging Concepts in Targeted Therapy for Non-Small Cell Lung Cancer:

• Clinical Progress in Antiangiogenic Therapy for Lung Cancer

• Monoclonal Antibodies

• Tyrosine Kinase Inhibitors in Phase 3 Trials

•Angiogenesis Inhibitors and NSCLC in Asia

• Biomarkers

• Safety

• Future Directions

SYSTEM REQUIREMENTS

This educational program is available as a mobile application and a PDF file. The mobile application can be run on any iOS or Android device. To view and print PDF files, you must have Adobe Reader installed on your computer. Most computers already have this software installed. If yours does not, you can download Adobe Reader free from the Adobe Web site: http://www.adobe.com.

For questions about this program, please contact the Angiogenesis Foundation at 617-401-2779 or outreach@angio.org.