

Clinical Update of Antiangiogenic Therapy for Lung, Kidney, Liver, and Gastrointestinal Stromal Cancers

Antiangiogenic therapies that disrupt key angiogenic growth factor signaling pathways are changing the treatment landscape of a number of common and deadly tumor types. These agents include bevacizumab (Avastin[®]; BV), a humanized monoclonal antibody for vascular endothelial growth factor (VEGF), and several small molecule tyrosine kinase inhibitors (TKIs) for receptors of VEGF and other key growth factors. Other angiogenesis inhibitors, either already FDA approved or in advanced clinical trials, include inhibitors of mammalian target of rapamycin (mTOR) and novel inhibitors of stem cell factor receptor (c-Kit), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR). Here, we look at some recent clinical research highlights of antiangiogenic therapies for the treatment of non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), and gastrointestinal stromal tumor (GIST).

Non-small Cell Lung Cancer (NSCLC)

Bevacizumab, a humanized anti-VEGF monoclonal antibody was FDA approved as front-line therapy for advanced NSCLC after it was found to significantly prolong overall survival (OS) when added to carboplatin and paclitaxel¹. A second phase 3 trial (AVAiL), conducted primarily in Europe, evaluated the addition either low- (7.5 mg/kg) or high-dose BV (15 mg/kg) to cisplatin and gemcitabine². Both median PFS and objective response rates were significantly increased for both the low- and high-dose BV arms relative to placebo, thus validating the use of BV with this chemotherapy doublet. The final OS data, however, showed no difference between the three arms (median OS, 13.1 mo., 13.6 mo., and 13.4 mo. for placebo, low-dose BV, and high-dose BV, respectively)³.

BV has also been evaluated in combination with pemetrexed disodium (Alتما[®]), a multi-targeted antifolate chemotherapy that in preclinical studies has shown synergy with antiangiogenic agents⁴. A single-stage phase 2 trial (SWOG N0426) was conducted in 48 NSCLC patients using BV (15 mg/kg) plus pemetrexed (500 mg/m²) as second-line therapy⁴. Although only 24 of 42 patients met the study's predefined

success criteria (≥ 26 of 42 patients progression free and on treatment at 3 months), the median PFS of 4.1 mo. is considered promising. An ongoing, randomized, open-label phase 3 trial is comparing BV plus pemetrexed and carboplatin to the current standard BV/carboplatin/paclitaxel regimen in patients with non-squamous, stage IV NSCLC⁵. This study also incorporates a maintenance phase of continuation of BV plus pemetrexed vs. BV alone.

Another antiangiogenic treatment strategy under investigation for NSCLC involves the use of VEGF inhibitors in combination with inhibitors of the epidermal growth factor receptor (EGFR), either with or without chemotherapy. One of the first studies to address this question was a randomized, placebo-controlled phase 3 trial (BETA-Lung) involving 636 stage IV NSCLC patients who had progressed on front-line chemotherapy⁶. Patients were randomized to receive the EGFR inhibitor erlotinib (Tarceva[®]) plus either BV or placebo. Although a significant increase in PFS was observed in the erlotinib/BV arm compared with placebo (3.4 mo. vs. 1.7 mo.; $P < 0.0001$), it did not translate into an improvement in OS, the trial's primary endpoint. More recently, results were presented from ATLAS, a randomized, placebo-controlled phase 3b trial of BV with or without erlotinib following treatment with BV plus a platinum-containing chemotherapy doublet⁷. The median PFS after randomization was 4.8 mo. for BV plus erlotinib vs. 3.7 mo. for erlotinib alone ($P = 0.0012$).

Promising efficacy results were also reported from a single-arm, phase 2 study (SWOG 0536) that combined front-line paclitaxel/carboplatin chemotherapy with both BV and cetuximab for up to 6 cycles, followed by BV plus cetuximab until disease progression⁸. This treatment regimen produced surprisingly high response and survival rates in treatment-naïve patients, with a 54% partial response (PR) rate, and PFS and OS times of 7.0 mo. and 14.0 mo., respectively. SWOG has since initiated a randomized phase 3 trial (SWOG 0819) of combination paclitaxel/carboplatin plus BV with or without cetuximab followed by maintenance therapy with BV with or without cetuximab⁹. The primary endpoint is OS, and researchers will also be comparing treatment efficacy according to tumor EGFR status.

Data on vandetanib (ZD6474; Zactima[®]), a dual VEGFR/EGFR inhibitor, was recently reported from a trio of second-line phase 3 trials in advanced NSCLC. The first of these (ZEAL) compared vandetanib plus pemetrexed with pemetrexed alone¹⁰. Although an improvement in overall response was reported in the vandetanib arm (19.1% vs. 7.9%; $P < 0.001$), the study did not meet its primary endpoint of significantly prolonged PFS. In a second trial (ZEST), treatment with vandetanib failed to significantly prolong PFS vs. erlotinib, although it demonstrated equivalent efficacy in a preplanned non-inferiority analysis¹¹. There was, however, a higher frequency of grade 3/4 adverse events with vandetanib (50% vs. 40%). A third phase 3 trial (ZODIAC), which assessed the addition of vandetanib to docetaxel, did report a statistically significant increase in median PFS compared with docetaxel plus placebo (PFS, 4.0 mo. vs. 3.2 mo.; $P < 0.001$), while OS showed a modest, non-significant trend in favor of the vandetanib arm¹².

From the Editor-in-Chief



2009 brought continuing advancements in antiangiogenic cancer therapy. These included FDA approval of two additional antiangiogenic agents, bevacizumab and pazopanib, for advanced kidney cancer, bringing to six the total number of approved angiogenesis inhibitors for this tumor type. Two novel targeted agents, masitinib and nilotinib, have moved to phase 3 clinical trials for advanced gastrointestinal stromal tumors (GIST). In this issue of our ongoing CME series, Targeting Tumor Angiogenesis, we look at the most recent research highlights of antiangiogenic therapies for cancers of the lung, kidneys, liver, and GIST.

– William W. Li, M.D., President, The Angiogenesis Foundation

The manufacturer of vandetanib withdrew its regulatory submissions for NSCLC in both the U.S. and in Europe after comments from regulatory agencies indicated that approval for this indication was unlikely, based on the available phase 3 trial data. Results are pending from a fourth phase 3 trial (ZEPHYR) of vandetanib vs. placebo in NSCLC patients previously treated with an EGFR inhibitor.

Renal Cell Carcinoma (RCC)

Two new antiangiogenic agents, bevacizumab and pazopanib (Votrient™), were FDA approved in 2009 for the treatment of advanced RCC, becoming the fifth and sixth new therapies, respectively, to be approved for this tumor type since 2005. The approval of BV followed on results from AVOREN, the first of two randomized phase 3 trials conducted in previously untreated RCC patients. In the AVOREN trial, which compared BV plus interferon to interferon alone, the median PFS was 10.2 mo. vs. 5.4 mo. ($P < 0.0001$), and response rates were 30.6% vs. 12.4% ($P < 0.0001$), showing significant improvement with the combination therapy¹³. A second phase 3 trial (CALGB 90206) assigned 732 patients to receive open-label BV plus interferon or interferon monotherapy¹⁴. While OS data are still pending, both median PFS and response rates were significantly increased with BV—8.5 mo. vs. 5.2 mo. ($P < 0.0001$), and 25.5% vs. 13.1% ($P = 0.0001$).

Pazopanib, an inhibitor of VEGFR-1, -2, and -3, PDGFR, and c-Kit, was evaluated in a randomized, placebo-controlled phase 3 trial comprised of 233 treatment naïve and 202 cytokine-refractory RCC patients¹⁵. Median PFS was significantly prolonged in pazopanib-treated patients relative to placebo: 9.2 vs. 4.2 mo. ($P < 0.001$) in the overall study population, 7.4 vs. 4.2 mo ($P < 0.001$) in pretreated patients, and 11.1 vs. 2.8 mo. ($P < 0.0001$) in treatment-naïve patients. The objective response rates were 30% vs. 3%. Diarrhea and hypertension were the most common adverse events. Cardiotoxicity, as well as serious and, rarely, fatal liver toxicity has been reported in RCC patients receiving pazopanib. FDA labeling states that patients should be monitored with periodic electrocardiograms and blood tests to monitor electrolytes, and receive liver function tests every 4 weeks for at least the first 4 months of treatment, with periodic monitoring thereafter¹⁶.

New subset data were also recently presented from TARGET, a landmark randomized, placebo-controlled phase 3 trial of sorafenib (Nexavar®) in patients with advanced RCC. A subanalysis from a minority of treatment-naïve patients enrolled in TARGET (sorafenib: $n = 77$; placebo: $n = 84$) found similar PFS times vs. placebo (5.8 mo. vs. 2.8 mo.; HR, 0.48) to those previously reported for patients who had received prior cytokine therapy (5.5 vs. 2.7 mo., $P < 0.001$)¹⁷. A separate analysis retrospectively evaluated the incidence of brain metastases among 139 patients in TARGET (sorafenib: $n = 70$; placebo: $n = 69$)¹⁸. After a median of 12.5 mo. follow-up, the overall incidence of brain metastases were 3% and 12% in patients treated with sorafenib and placebo, respectively ($P = 0.04$). It is unclear whether sorafenib may suppress the development of brain metastases by inhibiting angiogenesis or by another process, and further study is required in this area¹⁸.

Numerous ongoing phase 3 clinical trials are evaluating and comparing antiangiogenic agents in various combinations and sequences for the treatment of advanced RCC. Temezirolimus, an mTOR inhibitor, is being combined with BV and compared against BV plus interferon as front-line therapy in a randomized, open label, phase 3b trial (INTORACT)¹⁹. Another open-label, front-line phase 3 trial is comparing sequential therapy with sorafenib followed by sunitinib (Sutent®) vs. sunitinib followed by sorafenib after progression or toxicity on the first agent²⁰. Pazopanib is being compared in a head-to-head trial (COMPARZ) to sunitinib in previously untreated patients with advanced RCC²¹. Two other VEGFR TKIs, axitinib (AG-013736) and tivozanib (AV-951), are also in phase 3 trials in advanced RCC: axitinib vs. sorafenib in two separate front- and second-line studies^{22, 23}, and tivozanib, and inhibitor

of VEGFR-1, -2, and -3, vs. sorafenib in either treatment-naïve or cytokine-refractory patients (TIVO-1)²⁴.

In the adjuvant RCC treatment setting, sorafenib and sunitinib are being evaluated in three separate phase 3 trials in patients with resected RCC at risk for recurrence: ASSURE, a three-arm trial comparing sorafenib, sunitinib, and placebo, with 1 year of treatment and 9 years of planned follow up²⁵, SORCE (sorafenib twice daily for 1 or 3 years, or placebo)²⁶, and S-TRAC (sunitinib 50 mg/day for 1 year vs. placebo)²⁷.

Hepatocellular Carcinoma (HCC)

The inherent hypervascularity of liver cancer makes it a logical target for antiangiogenic therapy. The efficacy of sorafenib in advanced HCC has now been demonstrated by two placebo-controlled phase 3 trials: the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial²⁸, and a second trial involving HCC patients from the Asia-Pacific region²⁹. Although patients in the Asia-Pacific trial had more advanced disease than those in the SHARP trial, both trials were conducted primarily in patients with Child-Pugh A cirrhosis and good performance status. In SHARP, median OS was 10.7 mo. for sorafenib compared with 7.9 mo. for placebo ($P = 0.00058$; HR 0.69), while in the Asia-Pacific trial, median OS was 6.5 mo. vs. 4.2 mo. ($P = 0.014$). The most common side effects of sorafenib therapy were hand-foot skin reaction and diarrhea, leading to dose reductions in approximately 7-12% of patients, but rarely to discontinuation of treatment. Sorafenib is also being evaluated in combination with erlotinib in front-line HCC in a randomized phase 3 trial³⁰, as well as in the adjuvant treatment setting. The phase 3 adjuvant trial (STORM) is comparing sorafenib (400 mg twice daily) with placebo in HCC patients at moderate to high risk for recurrence following surgical resection or local ablation³¹.

Two recent phase 2 studies, published around the same time, provide important new data on the use of sunitinib for HCC. The first trial, conducted at centers in France and Asia, enrolled 37 patients with advanced HCC to receive sunitinib 50 mg/day for 4 weeks on therapy followed by two weeks off (4/2 dosing schedule)³². Although the median time-to-progression (TTP) in this study (5.3 mo.) was similar to that of sorafenib in the SHARP trial (5.5 mo.), there was considerable toxicity, leading to dose reductions and discontinuation of therapy in 43% of patients. Furthermore, there were 4 treatment-related deaths (10.8%) related to liver failure, thrombocytopenia, and variceal bleeding. Based on these findings, the authors discourage further evaluation of sunitinib for advanced HCC at the 50 mg dose. Results from the second phase 2 trial indicate that sunitinib at 37.5 mg (4/2 dosing schedule) is better tolerated while providing a similar PFS time (4.1 mo.) relative to the 50 mg dose³³. Meanwhile, an ongoing randomized, open-label phase 3 trial is comparing sorafenib to continuous dosing of sunitinib 37.5 mg/day in advanced HCC.

Brivanib, a novel TKI of VEGFR and FGFR, has shown modest activity for advanced HCC. Results were recently reported from a two-cohort phase 2 study involving both patients who had received no prior therapy (cohort A; $n = 45$), or had progressed on prior therapy with sorafenib or thalidomide (cohort B; $n = 32$)³⁴. Median TTP was 2.8 mo. in cohort A, and 2.0 mo. in cohort B, and 49% and 43% of patients in the two groups, respectively, had a > 50% reduction of alpha fetoprotein levels during therapy. Brivanib is being evaluated in two randomized phase 3 trials in advanced HCC, both as front-line therapy vs. sorafenib or placebo (BRISK FL)³⁵, and in combination with best supportive care vs. placebo in patients who failed prior therapy with sorafenib³⁶.

Gastrointestinal Stromal Tumor (GIST)

Interim results of a randomized, placebo-controlled, phase 3 study of sunitinib 50 mg/day on a 4/2 dosing schedule demonstrated significant efficacy in patients with advanced GIST after disease progression or

intolerance to imatinib³⁷. Median time to tumor progression in the trial was 27.3 weeks for sunitinib compared with 6.4 weeks for placebo ($P < 0.0001$), leading to international approval of sunitinib for this indication. A recent open-label phase 2 trial evaluated continuous daily dosing of sunitinib (37.5 mg/day) in 61 patients with imatinib resistant/intolerant GIST³⁸. Clinical benefit was observed in 32 of 60 patients (53%), including 8 who achieved objective partial responses. The tolerability profile was similar to that seen with intermittent sunitinib dosing.

Masitinib (AB1010), a novel TKI of c-Kit, PDGFR, and FGFR-3, was recently evaluated in 30 imatinib-naïve patients with inoperable, locally advanced or metastatic GIST³⁹. After a median follow-up of 23.7 mo., 7% of patients had a complete response (CR), 43% PR, and 47% stable disease (SD) as their best response. Median PFS was 27.2 mo. with a PFS rate of 68.8% at 1 year. A randomized, open-label, comparative phase 3 trial is underway to evaluate masitinib (7.5 mg/day) or imatinib (400 or 600 mg/day) as front-line treatment in patients with recurrent, locally advanced, or metastatic GIST⁴⁰.

Sorafenib has demonstrated clinical activity as a third-line agent in GIST patients who failed prior therapy with both imatinib and sunitinib. In a recent 26-patient phase 2 study in this treatment setting, sorafenib produced a median PFS of 5.3 mo. and OS of 13.0 mo.⁴¹. Most recently, sorafenib was evaluated in 32 GIST patients in Europe who had failed three prior TKIs (imatinib, sunitinib, and nilotinib)⁴². At a median follow-up of 22 weeks, median PFS was 20 weeks, and median OS was 42 weeks. Nineteen percent and 44% of patients achieved PR and SD, respectively.

Nilotinib, a second generation TKI of c-Kit, PDGFR, and BCR-ABL currently approved to treat certain forms of imatinib-refractory leukemia, has shown some activity in advanced, treatment-resistant GIST. In a retrospective analysis conducted in 52 European patients with advanced GIST resistant to both imatinib and sunitinib, nilotinib (400 mg twice daily) produced 5 responses (10%), disease stabilization in 19 patients (37%), and a median TTP of approximately 3 months⁴³. Phase 3 trials are now underway of nilotinib in both front- and second-line treatment settings in advanced GIST.

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CME REQUIREMENTS

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RELEASE AND EXPIRATION

Release date is March 15, 2010. Expiration is March 15, 2011.

INTENDED AUDIENCE

Practicing oncologists in the U.S.

EDUCATIONAL OBJECTIVES

At the conclusion of this educational activity, clinicians will be able to:

- Describe the rationale for antiangiogenic therapy for cancer.
- Identify the molecular targets of both biologic and small molecule agents.
- Review the most recent clinical data regarding the safety and efficacy of antiangiogenic agents in the treatment of non-small cell lung cancer, renal cell carcinoma, hepatocellular carcinoma, and gastrointestinal stromal tumor.

METHOD OF PARTICIPATION

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FACULTY

William W. Li, M.D.,
President and Medical Director, the
Angiogenesis Foundation

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