New blood vessel formation (angiogenesis) is essential for the processes of tumor growth, invasion, and metastatic dissemination, and agents that inhibit this pathway, such as bevacizumab, have proven anticancer activity. Interactions between tumor- and stroma-produced vascular endothelial growth factor (VEGF) ligands (particularly VEGF-A) and receptors (particularly VEGF receptor [VEGFR] 2) are central to angiogenesis and vessel permeability. VEGF-A also interacts with VEGFR1 expressed on endothelial cells, macrophage-lineage cells, and some tumor cells, assisting in angiogenesis and promoting direct tumor growth, metastasis, and inflammation. VEGFR3 is critical for lymphangiogenesis and inflammation. VEGFR3 is critical for lymphangiogenesis. Targeting the VEGF pathway inhibits vasculogenesis and tumor progression and is also thought to transiently normalize the tumor vascular supply, resulting in improved drug delivery when used in combination regimens. Drugs targeting the VEGF pathway were discussed at the 9th annual targeted therapies meeting in Santa Monica and are described below.

VEGF Ligand Blockers

Dr. Alan Sandler discussed Bevacizumab (Avastin), a humanized monoclonal antibody to circulating VEGF isoforms thus reducing circulating VEGF to undetectable levels. Two large phase III trials with the compound in combination with first-line chemotherapy have been presented. E4599 combined bevacizumab with carboplatin and paclitaxel (C + P) and found an improved RR (35% versus 15%), progression-free survival (PFS, 6.2 versus 4.5 months) and overall survival (OS, 12.3 versus 10.3 months). Bevacizumab increased hematologic toxicities, febrile neutropenia, hypertension, and proteinuria with 15 treatment-related deaths including five from pulmonary hemorrhage (PH). Among predictive markers studied, only low level of intercellular adhesion molecule correlated with better overall and 1-year survival. A European/Canadian phase III (AVAIL) combination of cisplatin/gemcitabine with 7.5 or 15 mg/kg of (B) or placebo had no improvement in OS but equivalent increase in RR and PFS at both doses (34.1/30.4 versus 20.1%) and (6.7/6.5 versus 6.1 months), when compared with placebo. Safety data were similar for both doses. In newer data, no intracranial hemorrhage occurred in 83 patients with pretreated brain metastases while on the ATLAS and PASSPORT studies. Retrospective evaluation identified baseline cavitation but not central tumor location to be associated with severe PH in patients treated with C + P + B. ECOG 1505 is a phase III randomized trial of bevacizumab versus placebo with standard chemotherapy doublets in the adjuvant setting.

Dr. Natasha Leighl discussed Afibercept (VEGF Trap/AVE0005) a recombinant fusion protein of extracellular domain portions from human VEGFR1 and 2 combined with the Fc of human IgG. This acts as a soluble VEGF receptor “trapping” VEGF from the circulation. Some single agent activity at 4 mg/kg every 2 weeks was seen, with expected VEGF related toxicity including two of 96 patients with PH in a phase II study in platinum- and erlotinib-resistant adenocarcinoma. Ongoing trials include a second-line phase III combination with docetaxel and a phase I/II combination with pemetrexed and cisplatin.

VEGFR2 Receptor Blockers

Dr. Ross Camidge discussed Ramucirumab (IMC-1121B), a fully human IgG1 monoclonal antibody, that binds VEGFR-2 and blocks VEGF ligand binding. The drug was well tolerated on weekly and biweekly schedules in phase I trials. Mechanism-related dose-limiting toxicities were hypertension, proteinuria, telangiectasia, and DVT. Patients who do not have lung cancer were studied in phase I, but encouraging single agent activity was seen in other malignancies. Ramucirumab is currently in a phase II clinical trial with C + P.

Dr. Leila Alland discussed Adnectin (CT-322), a fibronectin-based small protein, that blocks VEGF-R2 interaction with three of its ligands VEGF (A, C, and D). In phase I, it was well tolerated at weekly doses of 1 and 2 mg/kg with manageable VEGF pathway-related toxicity (HTN and proteinuria) and no cutaneous toxicity and no fatigue > G2. A phase II chemotherapy combination trial is planned.

Oral Small-Molecule Tyrosine Kinase Inhibitors

Dr. Amir Onn discussed Vandetanib (Zactima, ZD6474), an inhibitor of VEGFR2/3, RET, and less potently of EGFR. In second-line phase III trials, vandetanib improved PFS and quality of life in patients on docetaxel (ZODIAC trial) and improved RR and quality of life but not PFS in patients on pemetrexed (ZELAZ trial). As a single agent, it was equivalent to standard dose erlotinib on the ZEST trial. The ZEPHYR study of vandetanib monotherapy versus placebo in patients...
with prior anti-EGFR exposure is ongoing. Most common toxicities included rash, diarrhea, and hypertension.

Dr. Glenwood Goss discussed Cediranib (Recentin, AZD 2171) a highly potent daily pan-VEGFR, c-KIT, and PDGFR inhibitor. The randomized phase II Canadian trial BR.24 of C + P ± cediranib had to be amended to reduce dose from 45 to 30 mg because of excessive diarrhea, neutropenia, and dehydration. Despite an improvement in OR from 20 to 41% and a trend toward improvement in PFS, the study had to be discontinued because of disproportionate increased death rate in the cediranib arm even at the 30 mg dose (11.5% versus 2% \( p = 0.002 \)). All subgroups and histologies benefited except for patients with >5% wt loss, poor performance, and low albumin at enrollment. A randomized phase II/III trial BR.29 of C + P ± 20 mg/d of cediranib with preplanned early safety analysis was started.

Dr. Paul Bunn discussed BIBF 1120 a potent triple inhibitor of VEGFR1/2/3, fibroblastic growth factor (1/2/3), and PDGFR(α/β). Most common toxicities presented included nausea, vomiting, diarrhea, increase in liver enzymes but no hand-foot syndrome, myelosuppression, or HTN. In 57 patients, single agent BIBF 1120 given beyond first line had 3.5% OR, 59% DCR, 12-week PFS, and 38-week OS. Two phase III trials (LUME-lung 1 and 2) are recruiting for second line trial of BIBF 1120 200 mg twice a day with docetaxel or pemetrexed, respectively.

Dr. Karen Kelly discussed AV-951 a potent highly selective pan-VEGF (1/2/3) inhibitor with a prolonged half-life. With 4 weeks on 2 weeks off dosing in phase I, common G1/2 toxicities were nausea/vomiting, diarrhea, hoarseness, rash, myalgias, and dose-dependent hypertension. DLTs were proteinuria, intracranial bleeding, and ataxia at mg and two cases of reversible transaminis in 1.5 mg/d. One patient with NSCLC had prolonged disease stability for 9 months. A phase Ib/Ila single agent study of 1 to 1.5 mg daily is ongoing.

Dr. Heather Wakelee discussed XL647, a multikinase inhibitor, with activity against VEGFR-2, HER2, EphB4, and EGFR. In a phase II first-line trial, patients with known sensitizing EGFR mutations or clinically favorable characteristics (Asian, female, and never smokers) received 350 mg PO daily 5/14 days of XL647 with a 26% partial response (PR) rate (7/10 EGFRmut [+]). On phase II trial, patients with progression after PR or prolonged SD on erlotinib/gefitinib or with a known T790M mutation received 300 mg PO daily continuously with 1/39 PR (exon 19 del) and 19 of 39 SDs. Activity was not seen in patients with T790M mutations. Mostly, G1/2 AEs included diarrhea, rash, fatigue, nausea, hypertension, anorexia, and reversible QTc prolongation with one patient with pneumonitis.

Dr. Joan Schiller discussed three tyrosine kinase inhibitors described below. Axitinib (AG-013736) is a potent inhibitor of all three VEGF receptors, PDGFR-β, and c-KIT. In a phase II trial, single-agent axitinib gave a PFS of 9.2 months, OS of 14.8 months, and 77.8% 1-year survival in nine patients treated first line and PFS of 3.8 months, OS of 15.5 months, and 1-year survival of 56.5% in 23 patients treated beyond first line. Two phase II first-line clinical trials of chemotherapy with axitinib are ongoing: one comparing axitinib to bevacizumab together with standard dose of C + P and continued as maintenance and a second single-arm study of cisplatinum + gemcitabine and axitinib in patients with squamous histology.

Sunitinib (Sutent) is a less selective multityrosine kinase inhibitor of VEGF, Kit, FLT3, PDGFR, and Raf. It had 29% SD and 1% PR when used alone continuously in the second-line phase II trial leading to mPFS of 12 weeks, mOS of 23.4 weeks and 1-year survival of 20%. Higher response rates were seen in earlier trials of intermittent dosing. Three trials are ongoing: phase II CALGB 30704 randomizes patients to second-line sunitinib or pemetrexed with or without sunitinib; phase III CALGB 30607 looks at sunitinib maintenance after four cycles of chemotherapy; and a third trial randomizes previously treated patients to erlotinib ± sunitinib (phase III).

Sorafenib (Nexavar) is a less selective multikinase inhibitor of PDGFR-β, Raf, c-KIT, FLT3 and all VEGFRs. In ESCAPE (a phase III first-line trial with C + P), the addition of sorafenib did not affect PFS (hazard ratio [HR] 1.0) or OS (HR 1.16, not significant) in the overall population but had a detrimental effect on mOS in the squamous histology subgroup (8.9 versus 13.6 months). In the phase II (E2501) randomized discontinuation study, 400 mg twice a day of sorafenib improved PFS rates (after 2 months run in phase of sorafenib) compared with placebo (3.6 versus 2.0 months, HR 2.16, \( p = 0.009 \)) with a trend toward improvement in OS (11.9 versus 9.0 months, HR 1.5, \( p = 0.18 \)). There is an ongoing phase I study of C + P + Bevacizumab+ sorafenib, the phase III NEXUS study of first-line cisplatin, gemcitabine with sorafenib, or placebo has met its accrual goal, a phase II second-line pemetrexed ± sorafenib is accruing, a phase II second or third-line erlotinib ± sorafenib is accruing, and a phase III sorafenib versus placebo trial in third/fourth line setting is in development.

**SUMMARY AND FUTURE DIRECTIONS**

There is abundant proof of activity of VEGF inhibition in NSCLC, but overall results seem modest with only small increases in activity when used in combination with chemotherapy and sometimes at the expense of significant toxicity. Single agent activity may be mostly limited to less selective tyrosine kinase inhibitors. Because there are subgroups of patients with dramatic benefit and prolonged disease stability with VEGF inhibition, it is of high priority to find reliable biomarkers able to identify them. Future studies are expected to further clarify the mode of action of VEGF inhibitors and help select compounds with better benefit to toxicity ratio.

**REFERENCES**


