Angiogenesis as a target in treating non-small cell lung cancer (NSCLC)

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HOT SPOT

- Lung cancer is the leading cause of cancer deaths in both women and men worldwide
- NSCLC accounts for approximately 85% of all lung cancer cases
- significant advancements have been made in the treatment of NSCLC over the last decade, but prognosis for advanced stage disease remains poor with median survival ranging between 10 and 13 months with first line treatment
- with an increased understanding of tumour biology and discovery of novel agents that target specific pathways such as angiogenesis, there is an opportunity to further improve the outcomes of patients with advanced NSCLC

Angiogenesis and cancer

- Angiogenesis is a pathological adaptation of a normal biologic process by tumour cells to gain survival advantage
- by altering the dynamic balance between proangiogenic and antiangiogenic factors, solid tumours attain the capacity to grow beyond a size that otherwise would be unsustainable with normal vasculature
- VEGF induces the proliferation, migration, and survival of vascular endothelial cells and stimulates the recruitment of bone marrow-derived endothelial progenitor cells to the new vessels
- there is a multitude of physiologic pro-angiogeneic factors including fibroblast growth factors (FGF), epidermal growth factors (EGF), matrix metalloproteinases (MMP), placental growth factor (PGF) and platelet-derived growth factor (PDGF)
- the most important proangiogenic factor is the vascular endothelial growth factor (VEGF), which drives the rate limiting step in both physiologic and pathologic new vessel formation
- VEGF has five isoforms - VEGF A, -B, -C, -D and -E
- VEGF has generally been used to refer to the VEGF A isoform
- the biologic action of VEGF is mediated through its interaction with surface VEGF receptors of which there are three members: VEGFR 1, -2 and -3

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VEGF and NSCLC

- VEGF expression has been observed in all forms of NSCLC, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma
- studies have shown that the degree of tumour-associated angiogenesis correlates with disease progression and serves as a marker of unfavourable survival outcome
- a recent study suggests a correlation between VEGF and nicotine, a carcinogen linked to lung cancer

Bevacizumab (Avastin) and NSCLC

- Anti-angiogenesis therapy is one of the most active areas of clinical investigation in NSCLC
- only intervention in the first-line treatment of advanced NSCLC that has led to a major improvement in survival outcomes (two months) in the last five years
- Avastin is a full humanized monoclonal antibody that binds VEGF-A
- Avastin results in a more mature vasculature that is thought to facilitate the delivery of chemotherapeutic agents by decreasing microvascular permeability and decreasing intra-tumoural pressure, which may explain why bevacizumab acts synergistically with cytotoxic or other targeted agents (Figure 1)

Bevacizumab in combination with chemotherapy

- **ECOG phase III study (E4599)** of carboplatin and paclitaxel (CP) with or without bevacizumab (15 mg/kg) was a pivotal study enrolling 878 patients with recurrent and advanced (stage IIIB and IV) NSCLC (Figure 1)
- patients were randomized to receive chemotherapy alone (n=444) or chemotherapy plus bevacizumab (n=434)
- patients without progressive disease (PD) after induction therapy in the CP+bev arm continued to receive bevacizumab until PD or unacceptable toxicity
- median overall survival (OS) of 12.3 months, 10.3 months in favour of bevacizumab (HR 0.79; 95% CI, 0.67 to 0.92; p=0.003)
- median progression-free survival (PFS) of 6.2 versus 4.5 months (HR=0.66; 95% CI, 0.57 to 0.77; p<0.001)
- response rate of 35% versus 15% (p<0.001) in favour of the bevacizumab containing arm

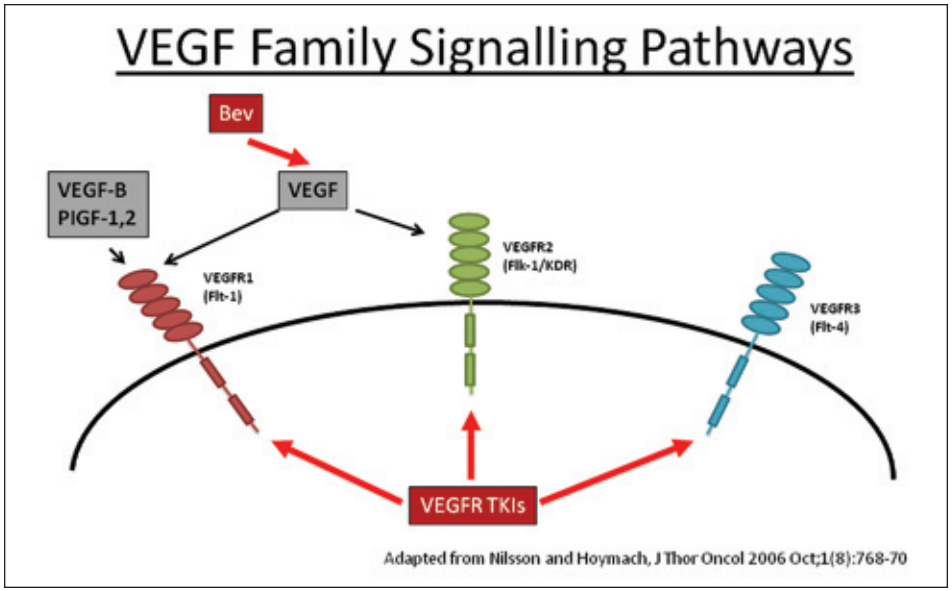

Figure 1.

- incidence of adverse events such as bleeding, hypertension, proteinuria, neutropenia, febrile neutropenia, thrombocytopenia, hyponatremia, rash and headache were significantly higher among the patients treated with bevacizumab ($p < 0.05$)
- 15 of the 17 treatment-related deaths were recorded in the bevacizumab arm
- despite the deaths, the survival benefit in the overall patient population clearly outweighed the added toxicity risk, which led to the approval of this regimen by the FDA and Health Canada in 2006 and European Medicines Agency (EMA) in 2007 (Figures 2 and 3)
- **AVAil (Avastin in lung cancer) trial** was a three-arm phase III randomized trial conducted in Europe that evaluated two different doses of bevacizumab (7.5 mg/kg and 15 mg/kg) in combination with a different chemotherapy cisplatin 80 mg/m^2 and gemcitabine 1250 mg/m^2
- a total of 1,043 patients were randomized to placebo (347), low-dose bevacizumab (n = 345) and high-dose bevacizumab (n = 351)
- PFS was 6.1, 6.5 and 6.7 months respectively in favour of the Avastin arms
- RR was 20%, 30% and 34%, again in favour of Avastin arms
- however, there was no OS benefit
- the reason for the failure of the AVAil to demonstrate a survival advantage has been ascribed to different factors including the use of a potentially more effective cisplatin combination chemotherapy regimen, the use of a three-arm trial design that was underpowered to detect a modest survival advantage and the lack of maintenance Avastin arm (Figure 4)
- Avastin has been studied with other chemotherapy combinations
- multiple phase II trials have established the safety and improved efficacy of bevacizumab when combined with other platinum doublets (carboplatin + docetaxel, carboplatin + pemetrexed)
- none have shown significant OS benefits, only PFS benefits

Targeting VEGF and EGFR

One treatment strategy being investigated is simultaneously targeting both VEGF and the epidermal growth factor receptor (EGFR).

- EGFR is an important stimulator of both tumour growth and angiogenesis in many cancer types, including NSCLC
- BETA Lung evaluated the anti-EGFR drug erlotinib (Tarceva®) with or without bevacizumab, as second-line therapy in NSCLC patients who had received no prior anti-VEGF or anti-EGFR therapy
- although patients who received the bevacizumab/erlotinib combination did not live longer compared with patients who got erlotinib alone, PFS time was doubled
- in a second phase III trial, called ATLAS, patients who were treated with bevacizumab and erlotinib following chemotherapy lived about a month longer (PFS) without their disease getting worse than patients who got bevacizumab alone. Overall survival time was not significantly improved

Promising results were reported from a phase II study that combined chemotherapy

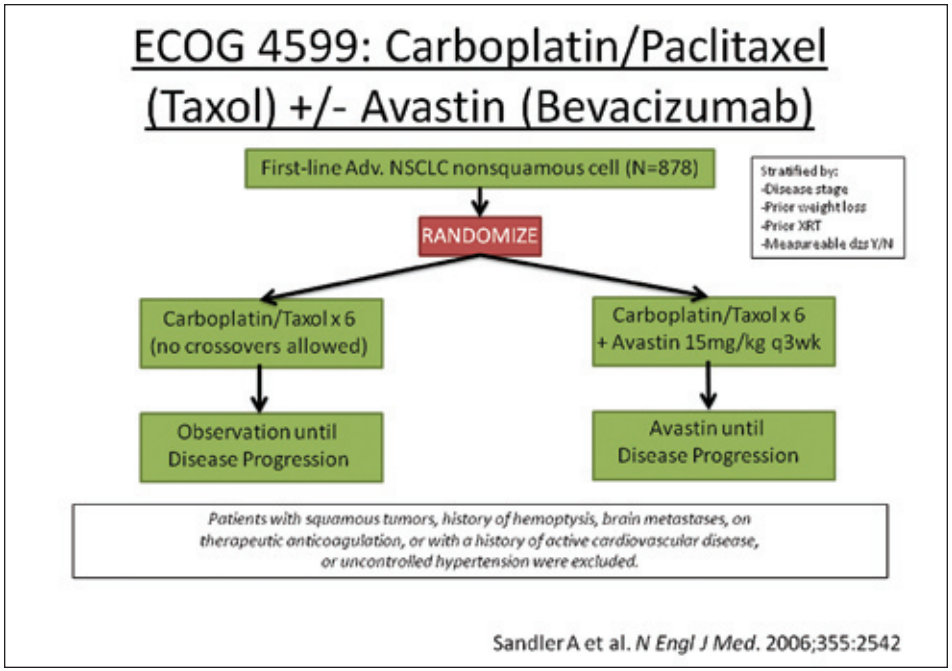

Figure 2.

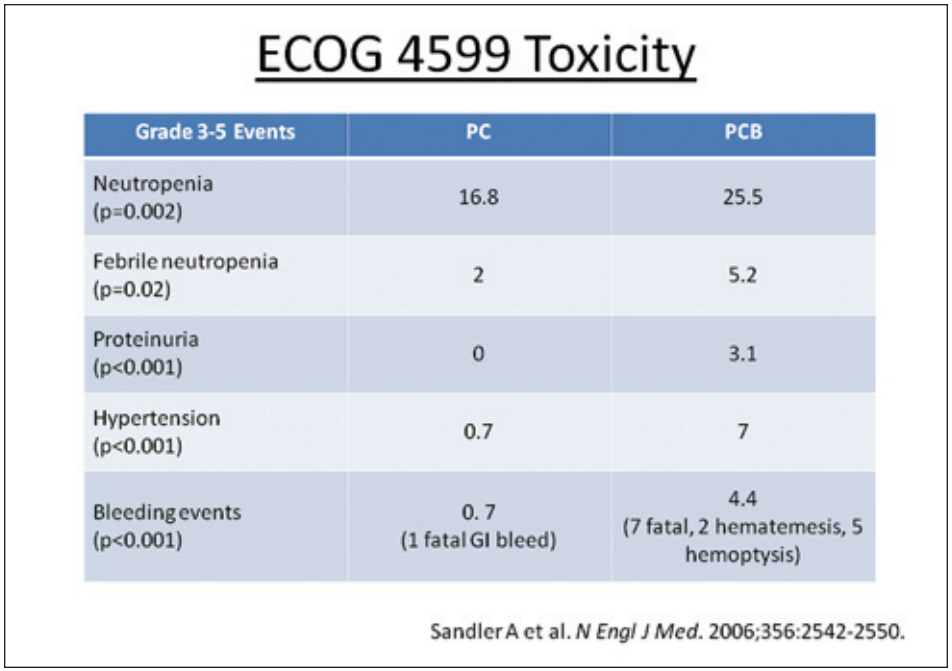

Figure 3.

with both bevacizumab and the anti-EGFR antibody agent cetuximab (Erbitux®).

- 54% of patients had at least partial tumour shrinkage, PFS and OS times were about seven months and 14 months, respectively
- a phase III trial using this treatment approach is forthcoming

New agents in development

A number of new antiangiogenic agents are in development for NSCLC. Please see Table 1 (page 4).

Safety issues of antiangiogenesis therapy in NSCLC

- Avastin is contraindicated in:
  - patients with squamous histology
  - untreated brain metastases
  - presence of hemoptysis
- VEGF inhibition may be associated with hypertension, impaired wound healing and, infrequently, gastrointestinal perforations, fistula formation, thromboembolic complications, and reversible posterior leukoencephalopathy
- Antiangiogenic therapies are rarely used in combination with radiation because of the danger of tracheoesophageal fistulas when these agents are combined with chest radiation
- Side effects from sunitinib or sorafenib therapy may include diarrhea, fatigue, nausea, stomatitis, hypertension, and mucosal inflammation
  - have also been associated with a number of dermatological toxicities, including hand-foot skin reaction and rash (primarily sorafenib), hair depigmentation (sunitinib), and subungual splinter hemorrhages (both agents)
  - Sunitinib has been associated with both pulmonary and cerebral hemorrhage
  - Sunitinib requires the monitoring for the development of hypothyroidism, reduced left ventricular ejection fraction (LVEF), and QT interval prolongation

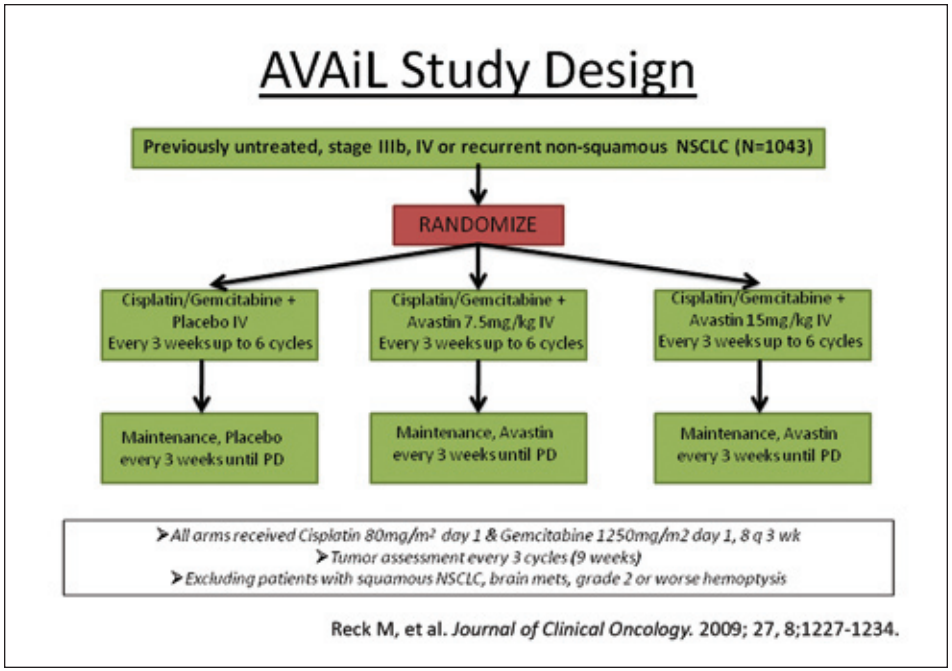

Figure 4.

Potential biomarkers for anti-VEGF therapy in NSCLC

- numerous studies have suggested **the development of hypertension** could be a marker of clinical response to BV therapy
- ECOG 4,599 trial included an analysis of the clinical course of patients who developed hypertension (defined as BP >150/100 at baseline or at the end of cycle 1 or an increase of >20 mmHg in diastolic BP between these two time points) during treatment
- the median OS among patients in the BV/chemotherapy arm who developed high blood pressure was 15.9 months (95% CI, 13.4 to 20.3 months) compared with 11.5 months for patients who did not have hypertension (95% CI, 10.4 to 13.4 months)
- ECOG 4,599 trial also analyzed the **expression of several single nucleotide polymorphisms (SNPs)** as marker of response to BV therapy
- results indicated that specific germ line polymorphisms were associated with improved response rates in the BV treatment arm
- patients with these polymorphisms had a 44% response rate to BV therapy versus 16% among patients without these specific SNPs

The role of Avastin in clinical practice

- greater than 70% of patients would **be ineligible** for frontline therapy with a bevacizumab-containing regimen based on the presence of one or more exclusion criteria employed in the E4599 trial
- the exclusion criteria were: poor performance status, brain metastasis, therapeutic anticoagulation, squamous histology, hemoptysis

The future

- patient selection is important for the optimal use of these agents
- it is highly desirable that predictive markers of response and/or toxicity be established to assist in the optimal selection of patients
- the presence of significant squamous differentiation on histologic evaluation remains the only established marker that predicts for increased risk of bleeding complications
- use of anti-VEGF as second- or third-line therapy or in the adjuvant setting remains to be determined
- to date, trials with most antiangiogenesis agents continue to show mixed results with modest benefits only

References

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Table 1. Anti- Angiogenic Drugs Under Investigation in NSCLC				
Name of drug	**Mechanism of action**	**Studies**	**Population**	**Results**
Motesanib	an oral angiogenesis inhibitor by targeting VEGFR -1, -2, and -3	MONET1 a randomized, placebo-controlled phase III trial of Motesanib for advanced NSCLC randomized to receive Carboplatin/ Paclitaxel plus either Motesanib (125 mg once daily; Arm A) or placebo (Arm B)	untreated patients with non-squamous NSCLC	Median PFS was 5.6 mos vs. 5.4 mos in favour of the motesanib arm (P=0.0006). Overall RR were 40% and 26% for the two arms, respectively (P<0.0001)
Ramucirumab	antibody against VEGFR-2	a phase II study	Pretreated patients	10 of 15 lung cancer patients (67%) saw tumour shrinkage
		a phase III trial is enrolling—patients will be randomly assigned to treatment with the chemotherapy drug Docetaxel, either with or without Ramucirumab		pending
BIBF 1120	an investigational triple angiokinase inhibitor that targets FGRF, PDGFR and VEGFR	phase III trials LUME lung 1—second line Docetaxel +/- BIBF1120 LUME lung 2—second line Pemetrexed +/- BIBF1120)	for NSCLC for patients who have relapsed or progressed on front line therapy	pending
Aflibercept	VEGF Trap is a soluble recombinant fusion molecule combining portions of the extracellular domains of human VEGF receptors-1 and -2 fused to the Fc segment of human immunoglobulin IgG1	VITAL phase III studies with Docetaxel in a multinational randomized study	failed one platinum-based line of therapy	pending
		phase II study in combination with Cisplatin and Pemetrexed		pending
VEGF Receptor Tyrosine Kinases Inhibitors: targeting the receptor tyrosine kinase activity of the VEGF receptor				
Sorafenib (oral agent)	targets threonine kinases c-Raf and b-Raf, the VEGFRs 1, 2 and 3, PDGRF, the proto-oncogene RET and c-KIT	phase II studies—Sorafenib 400 mg po bid • most frequent grade 3 treatment-related adverse events were hand-foot syndrome and hypertension • study in first line treatment	previously treated with not more than two regimens	produced no objective responses • 59% SD, median PFS was 2.7 mos and median OS was 6.7 mos failed to show any benefit and was closed prematurely
		phase II trial of Erlotinib +/- Sorafenib	previously treated with up to two prior chemotherapeutic regimens	showed improvement in PFS , even in squamous histology subset
		trials with Sorafenib with Carbo and Paclitaxel	first line treatment	suggested negative results due to interaction of Sorafenib with the pharmacokinetics of chemotherapeutic regimen
		NEXUS trial—Sorafenib + Cisplatin + Gemcitabine		Pending
Sunitinib (oral agent)	oral agent that inhibits VEGFR, PDGFR, c-KIT and RET	phase II studies	second or third line therapy	PFS 3 months OS 9 months
Vandetanib (Zactima)	multi-targeted TKI with potent activity against VEGFR-2, VEGFR-3, EGFR and RET	ZEST trial—Vandetanib vs. Erlotinib	salvage therapy in NSCLC who have progressed on frontline chemotherapy	no difference in RR or PFS or OS
		ZODIAC study—Vandetanib (100mg) combined with Docetaxel vs. Docetaxel alone		ORR was 17% vs. 10% p<0.001 but no difference in OS
		ZEPHYR—comparing Vandetanib to BSC in those who have progressed on chemo and EGFR inhibitors	pending	
Vascular Disrupting Agents				
Vadimezan DMXAA (5,6 dimethylxanthenone-4-acetic acid)	• selectively target newly formed tumour-associated blood vessels • shown to promote apoptosis of tumour blood vessel endothelial cells, resulting in the breakdown of tumour vasculature and hemorrhagic tumour necrosis	ATTRACT-1 phase II trial		failed to show benefit interim analysis resulting in early termination of the trial and discontinuation of the clinical development program in NSCLC