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## Angiogenesis and the Role of Avastin (Bevacizumab) in First Line Therapy for Advanced Non-Small Cell Lung Cancer (NSCLC)



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On cycle 18 of chemo/avastin, and counting



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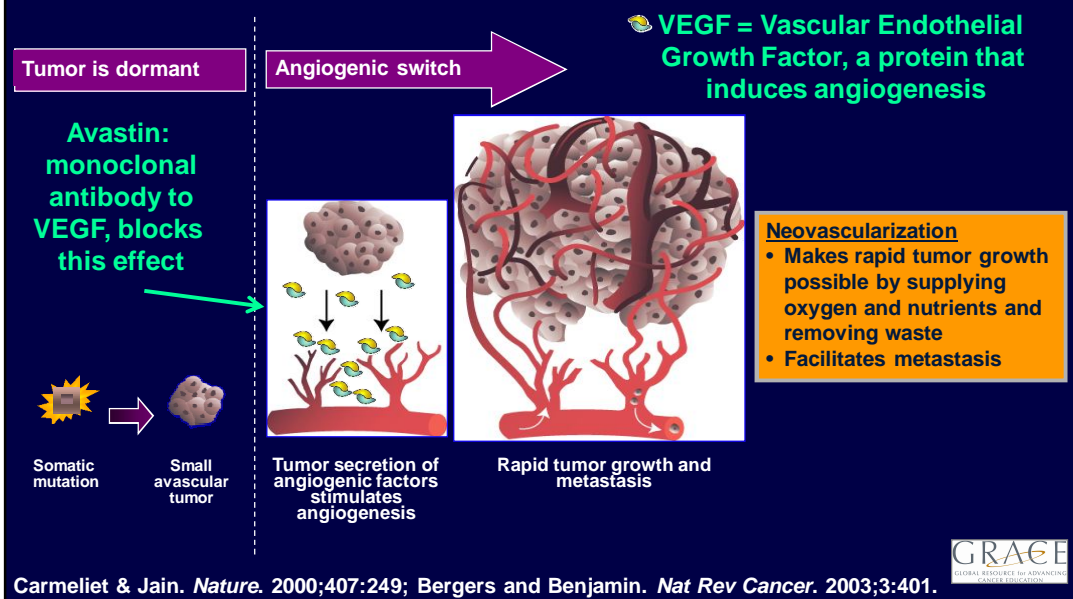


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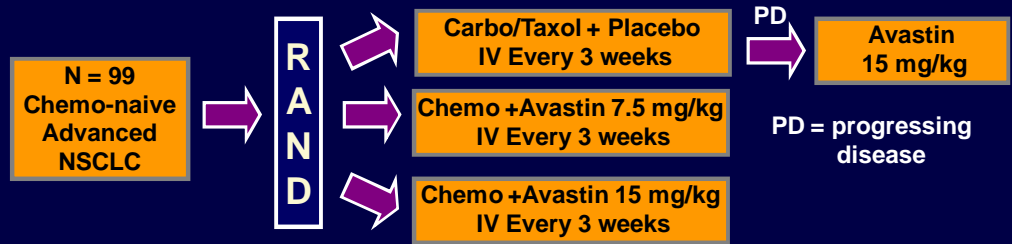
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## The Angiogenic Switch Is Necessary for Tumor Growth and Metastasis



## Phase II Study of Avastin (Bevacizumab) with Chemo in First Line Advanced NSCLC



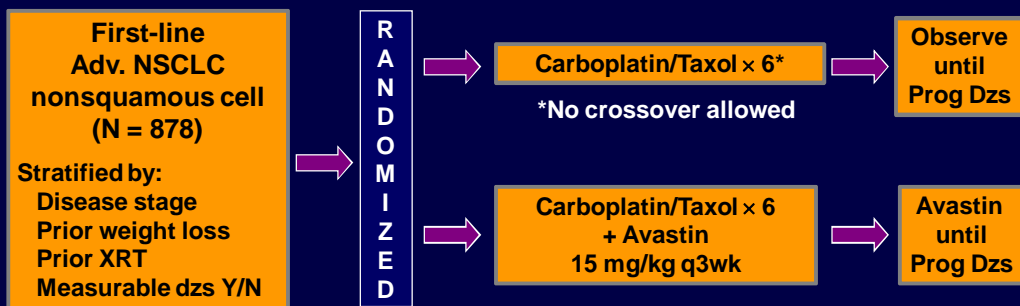
	Chemo Alone	Chemo/Avastin 7.5 mg/kg	Chemo/Avastin 15 mg/kg
Time to Prog	4.2 mo	4.3 mo	7.4 mo
Median Overall Surv.	14.9 mo	11.6 mo.	17.7 mo
Pulm Hemorrhage (# pts)	0	5	1

- Risk factors for bleeding: History of hemoptysis, squamous histology
- Squamous histology (4/13, 31%) vs. non-squamous NSCLC (2/53, 4%)

Johnson, J Clin Oncol 2004



## ECOG 4599: Carboplatin/Paclitaxel (Taxol) +/- Avastin (Bevacizumab)



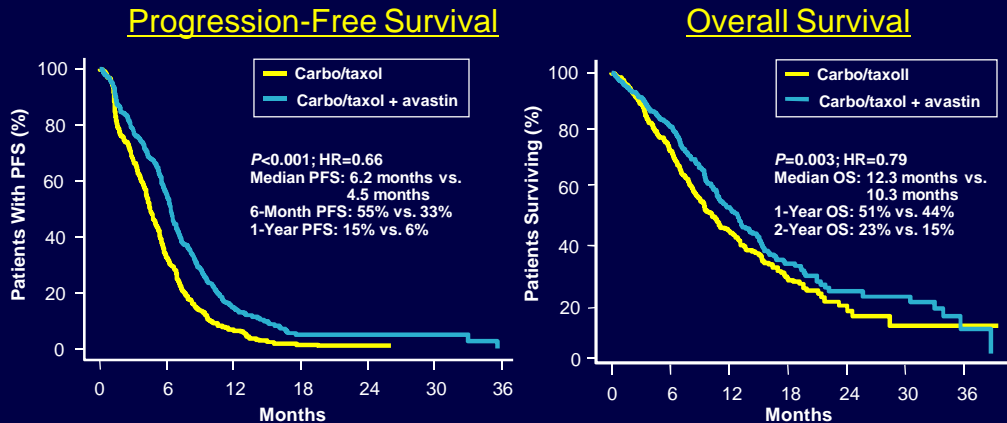
- This trial excluded patients with squamous tumors, history of hemoptysis, brain metastases, on therapeutic anticoagulation, or with a history of active cardiovascular disease or uncontrolled hypertension

Sandler et al. *N Engl J Med.* 2006;355:2542.



## Carbo/Taxol +/- Avastin (Bevacizumab): Key Clinical Outcomes

- Response rate: 15% for carbo/taxol vs. 35% for same chemo + avastin



HR=hazard ratio; OS=overall survival; PFS=progression-free survival.

Sandler et al. *N Engl J Med.* 2006;355:2542; Sandler et al. *ASCO.* 2005 (abstr 4).



## Carboplatin/Paclitaxel +/- Avastin: Toxicity and Treatment-Related Deaths

Toxicity	Carbo/Taxol Alone (N=427)	Carbo/Taxol + Avastin (Bevacizumab) (N=420)	P Value
<b>Hematologic (grade 4)</b>			
Neutropenia	16.8%	25.5%	0.002
Thrombocytopenia	0.2%	1.6%	0.04
Anemia	0.9%	0%	NS
<b>Nonhematologic (grade ≥3)</b>			
Hemorrhage	0.7%	4.4%	<0.001
Hypertension	0.7%	7.0%	<0.001
Venous Thrombosis	3.0%	3.8%	NS
Arterial Thrombosis	1.0%	1.9%	NS

### Treatment-Related Deaths:

- 15 with chemo/avastin vs. 2 with chemo alone
- 5 cases of hemoptysis with chemo/avastin vs. 0 with chemo alone

Sandler et al. *N Engl J Med.* 2006;355:2542; Sandler et al. *ASCO.* 2005 (abstr 4).



## Toxicity on Chemo/Avastin in Elderly vs. Non-Elderly Patients

<u>Grade 3/4</u>	<u>&gt; 70 yrs</u>	<u>&lt; 70 yrs</u>	<u>P value</u>
Neutropenia (Gr 4)	34%	22%	0.02
GI Bleed	3.5%	0.9%	0.005
Proteinuria	7.9%	1.3%	0.001
Muscle weakness	7.8%	2.2%	0.02
Motor neuropathy	3.5%	0.6%	0.05
Dizziness	7.9%	1.6%	0.003
Worst Grade	87%	70%	< 0.001
Treatment-Related Deaths	6.3%	2.6%	0.08

Ramalingam, J Clin Oncol 2008



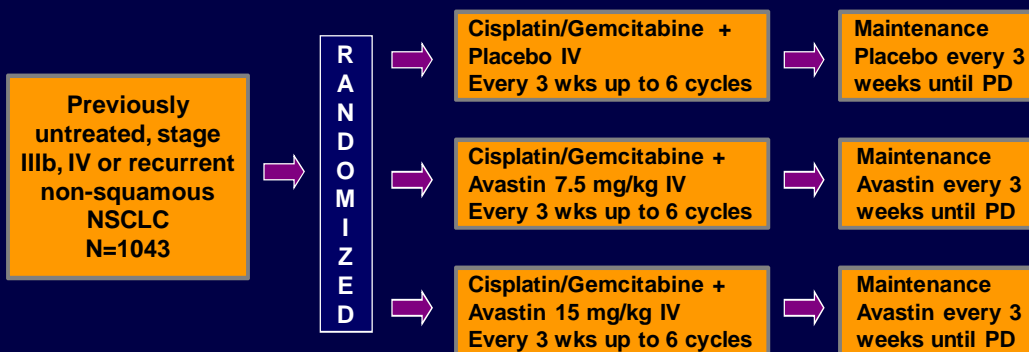
## Efficacy Endpoints on ECOG 4599: Elderly vs. Non-Elderly Patients

	<u>Elderly (&gt; 70)</u>		<u>Non-Elderly (&lt; 70)</u>	
	<u>Chemo</u>	<u>Chemo/Avastin</u>	<u>Chemo</u>	<u>Chemo/Avastin</u>
Response Rate	17%	29%	14%	36%
Median PFS	4.9 mo	5.9 mo P=0.063	4.4 mo	6.2 mo P<0.001
1-Yr Survival	50%	46%	42%	53%
Median survival	12.1 mo	11.3 mo P = 0.4	9.6 m	12.8 mo P = 0.0027

Ramalingam, J Clin Oncol., 2008



## AVAiL Study design

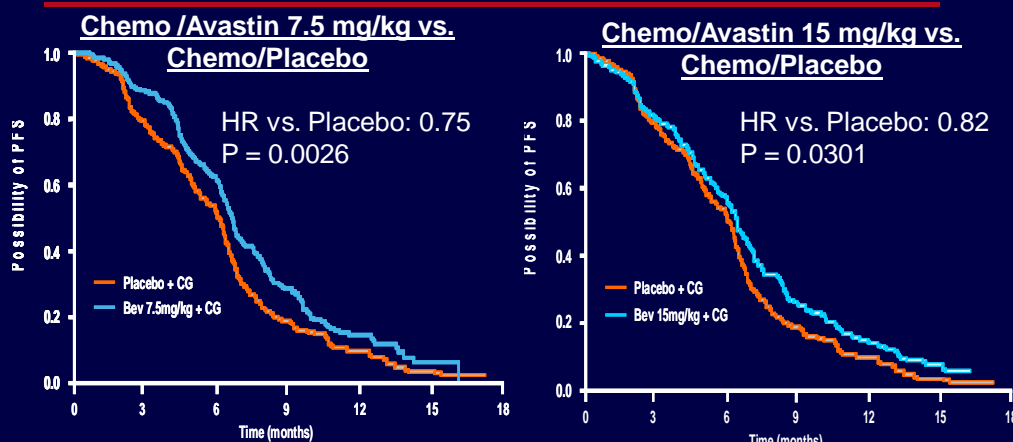


- All Arms received Cisplatin 80 mg/m<sup>2</sup> day 1 & Gemcitabine 1250 mg/m<sup>2</sup> day 1,8 q 3 wk
- Tumor assessment every 3 cycles (9 weeks)
- Excluding patients with squamous NSCLC, brain mets, grade 2 or worse hemoptysis.

Manegold, Proc of ASCO 2007,A#7514; ESMO, 2008



## AVAiL Trial: Efficacy



	<u>Chemo/Placebo</u>	<u>Chemo/ Avastin 7.5 mg/kg</u>	<u>Chemo/ Avastin 15 mg/kg</u>
Median Overall Surv	13.1 mo.	13.6 mo.	13.4 mo.

Manegold, Proc of ASCO 2007,A#7514; ESMO, 2008



## AVAiL Safety: Severe (Gr ≥3) AEs with ≥2% difference between arms

	<u>Chemo/ Placebo (N = 327)</u>	<u>Chemo/ Avastin 15 mg/kg (N = 330)</u>	<u>Chemo/ Avastin 15 mg/kg (N = 329)</u>
Neutropenia* (low neutrophil count)	32%	40%	36%
Thrombocytopenia (low platelets)	23%	27%	23%
Anemia	14%	10%	10%
Asthenia (fatigue)	3%	5%	5%
Vomiting	4%	7%	9%
Hypertension	2%	6%	9%
Epistaxis (nosebleeds)	<1%	2%	3%

\*Febrile neutropenia

1%

2%

2%



## Avastin (Bevacizumab) with Chemo for First Line Treatment of Advanced NSCLC

- Angiogenesis is an important factor in NSCLC
- A limited subset of patients have been eligible for clinical trials that include avastin
  - Tumor not predominantly squamous
  - No brain metastases
  - No history of hemoptysis
  - Not on full dose blood thinners
- Carbo/taxol + avastin x 6 cycles, followed by avastin alone as “maintenance therapy” associated with a significant improvement in overall survival (difference in median OS = two months) vs. chemo alone
- Cisplatin/gem + avastin (low or high dose) vs. chemo/placebo demonstrates significant improvement in PFS at either avastin dose, no improvement in OS
- Open questions: why different in 2 trials? Right dose? Value of maintenance avastin, if any...



## Questions and Comments?

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