

Angiogenesis

*Biomarkers profile and clinical factors in
selecting patients*

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Phase III Trial of Bevacizumab in Non-Squamous NSCLC: ECOG 4599

Eligibility:

- Non-squamous NSCLC
- No Hx of hemoptysis
- No CNS metastases
- No anti-coagulation
- Central tumors ELIGIBLE

Stratification Variables:

- RT vs no RT
- Stage IIIB or IV vs recurrent
- Wt loss <5% vs \geq 5%
- Measurable vs non-measurable

(PC)

Paclitaxel 200 mg/m²
Carboplatin AUC = 6
(q 3 weeks) x 6 cycles

No crossover to
bevacizumab
permitted

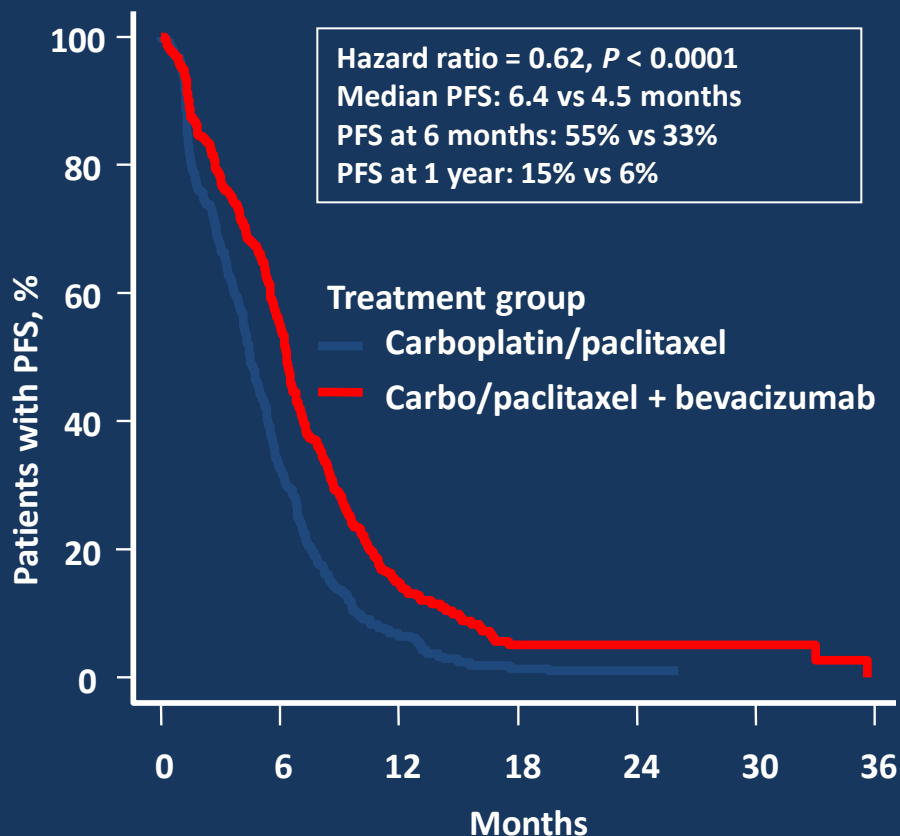
(PCB)

PC x 6 cycles
+
Bevacizumab
(15mg/kg q 3 wks) to PD

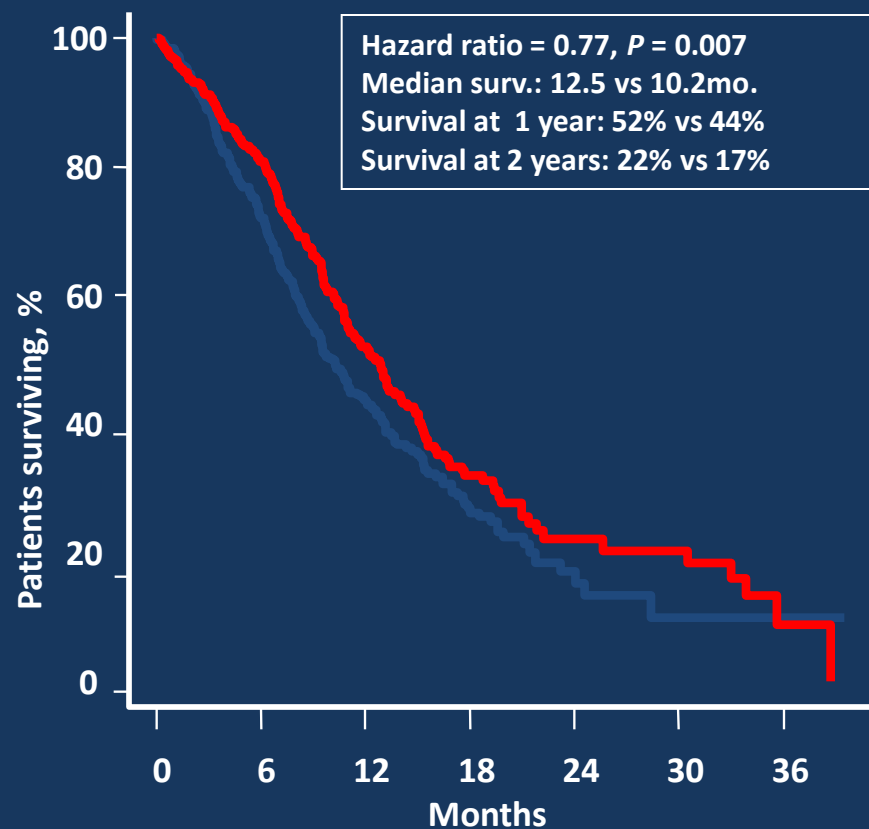
ECOG 4599: Carboplatin/Paclitaxel +/- Bevacizumab

- Response rate: 15% for CbP vs 35% for CbP+ bevacizumab

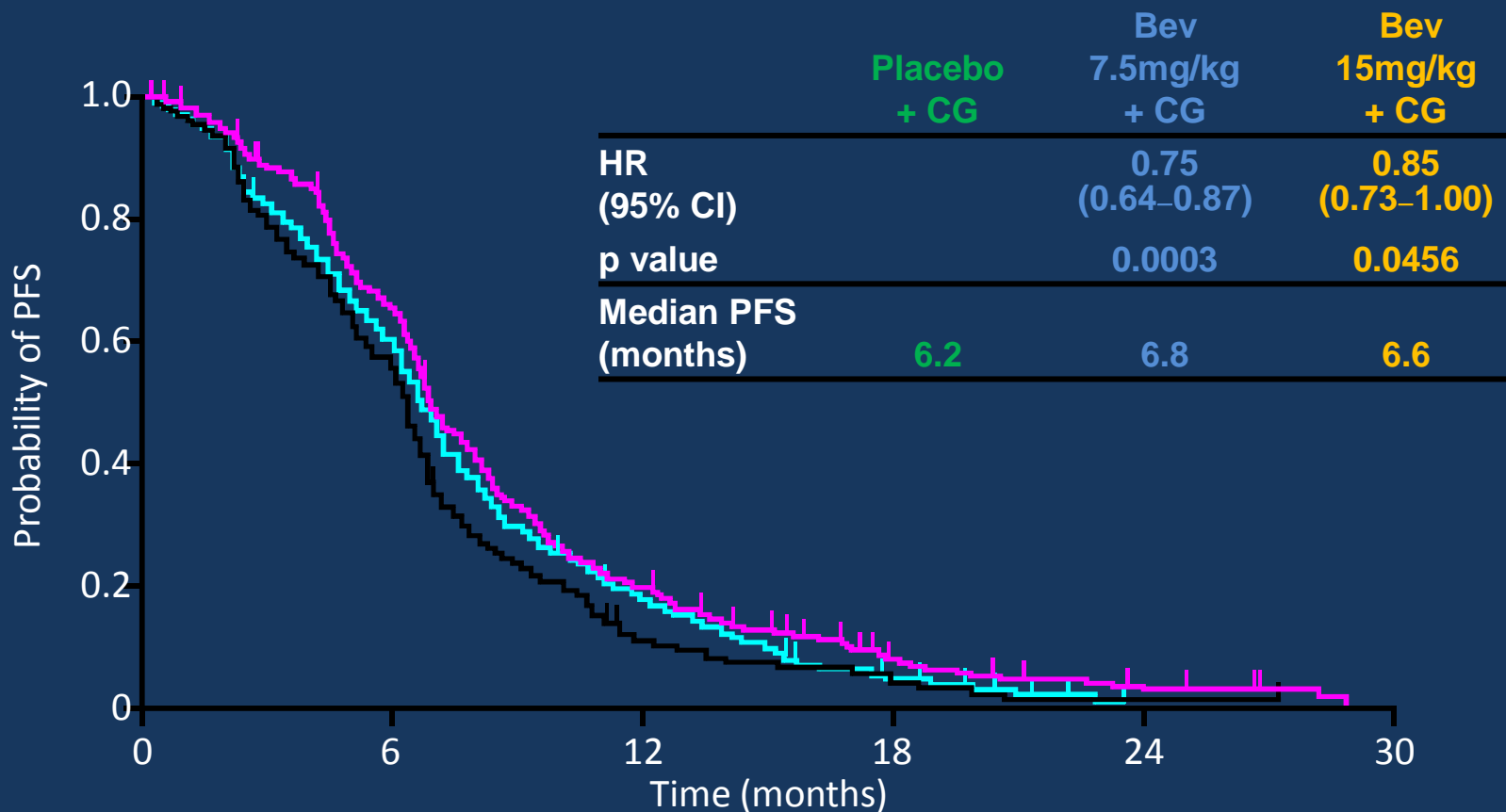
Progression-Free Survival



Overall Survival



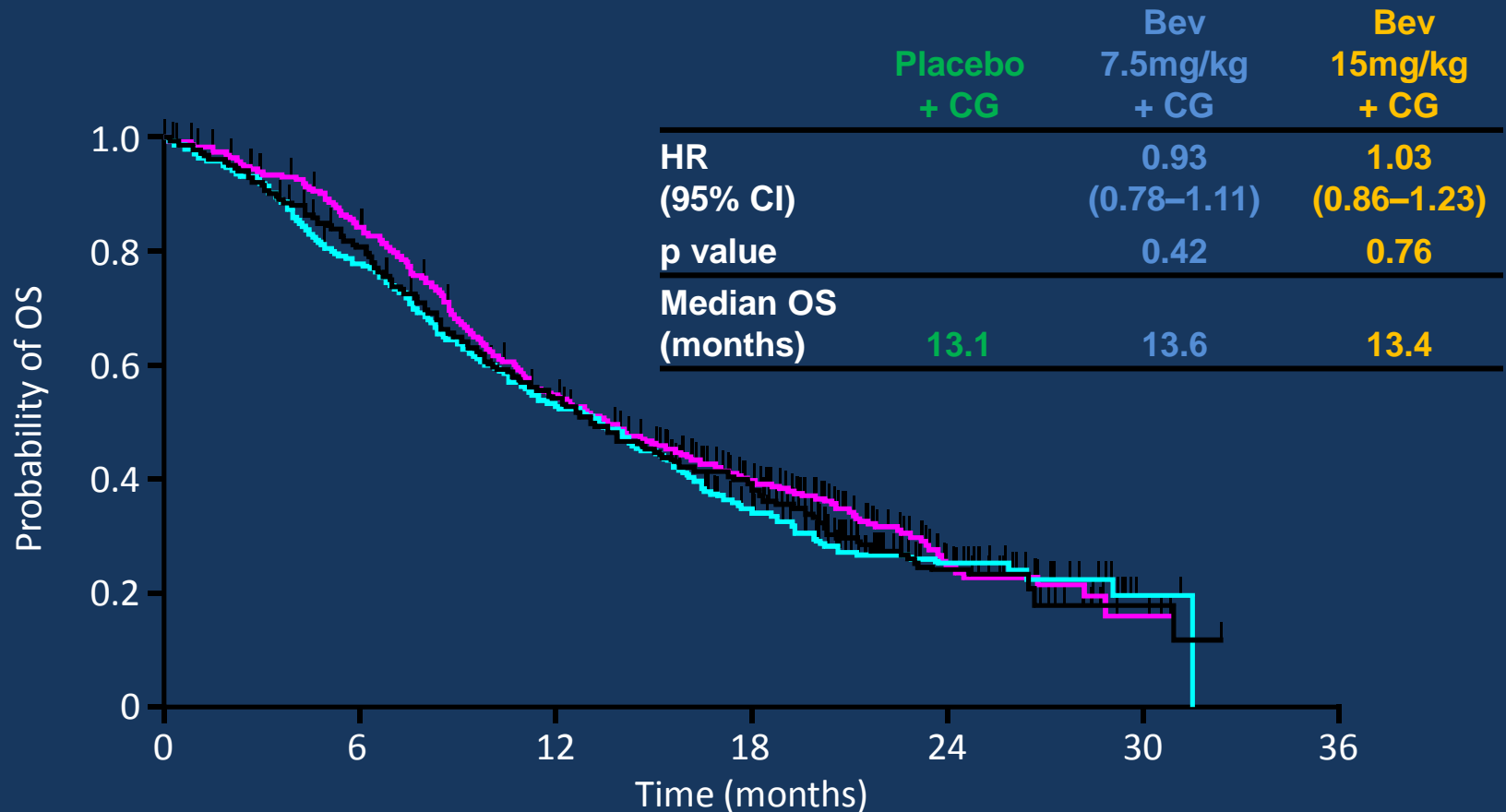
AVAiL: PFS (primary endpoint)



No. at risk

Placebo + CG	347	178	34	12	3	0
Bev 7.5mg/kg + CG	345	214	63	18	5	0
Bev 15mg/kg + CG	351	200	57	12	0	0

AVAiL: OS (secondary endpoint)



No. at risk	0	6	12	18	24	30	36
Placebo + CG	347	272	182	100	36	3	0
Bev 7.5mg/kg + CG	345	286	182	107	34	3	0
Bev 15mg/kg + CG	351	264	177	92	33	2	0

*ITT (intent-to-treat) population

Patient Selection Factors

How can we make the treatment better and safer

- Clinical Selection Factors
 - Sex
 - Age
 - Pulmonary hemorrhage
 - Histology
 - Central location and cavitations
 - Anti-coagulation
 - Brain metastases
 - Hypertension
- Biomarkers

Exploratory Subgroup Analyses E4599

- Subgroups analyzed
 - Stage
 - Weight loss
 - Prior RT
 - Race
 - PS
 - Age
 - Gender
- These were not pre-specified analyses
- Survival benefit was seen across all treatment subgroups except for gender

Efficacy by Sex

	Male	Female
OS (HR)	0.69 p=0.003	0.96 P=0.80
PFS (HR)	0.53 P=<0.0001	0.68 P=0.002
RR (%)	12.2 vs 23.5 p=0.006	7.4 vs 31.7 P<0.0001

Possible Explanations for Survival Differences by Gender?

- Use of second and third-line treatment
 - EGFR-TKI's
 - chemotherapy
- Imbalance in unmeasured baseline prognostic factors
 - Demographic
 - Molecular
- Statistical chance alone
- True difference

E4599 and Elderly Subset: Results

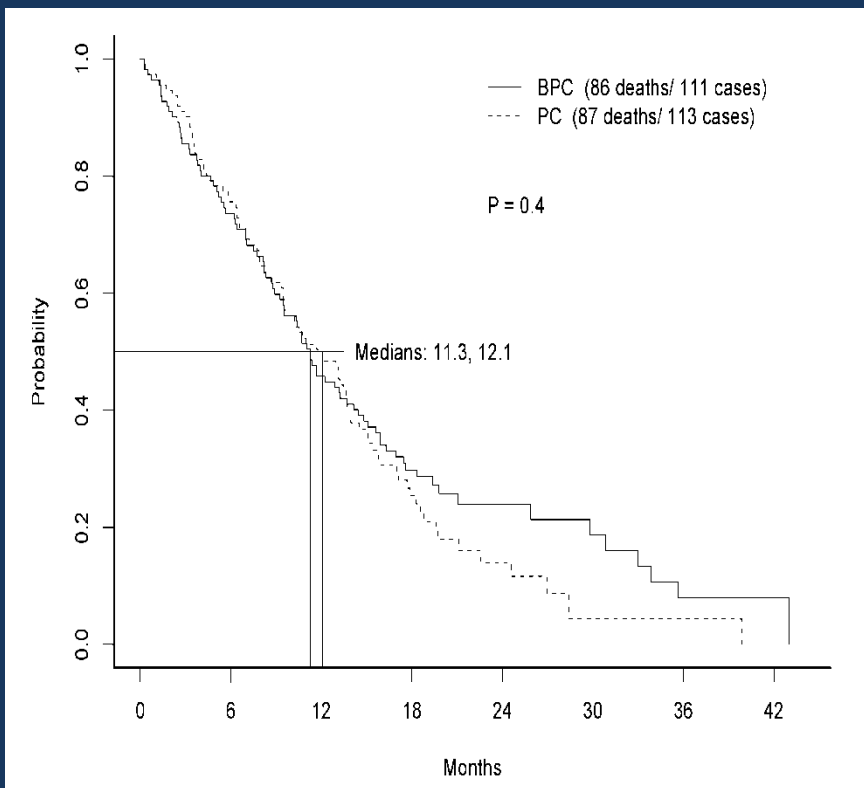
- Eligible cases = 850 (PC : n=433; PCB : n=417)
- ≥ 70 years: n=224 (26%)
- ≥ 80 years: 1.6%
- Median age:
 - Non-elderly: 63 years
 - Elderly: 74 years
- Median number of cycles of therapy for patients ≥ 70 yrs
 - PC : 5 cycles
 - PCB : 7 cycles

Efficacy

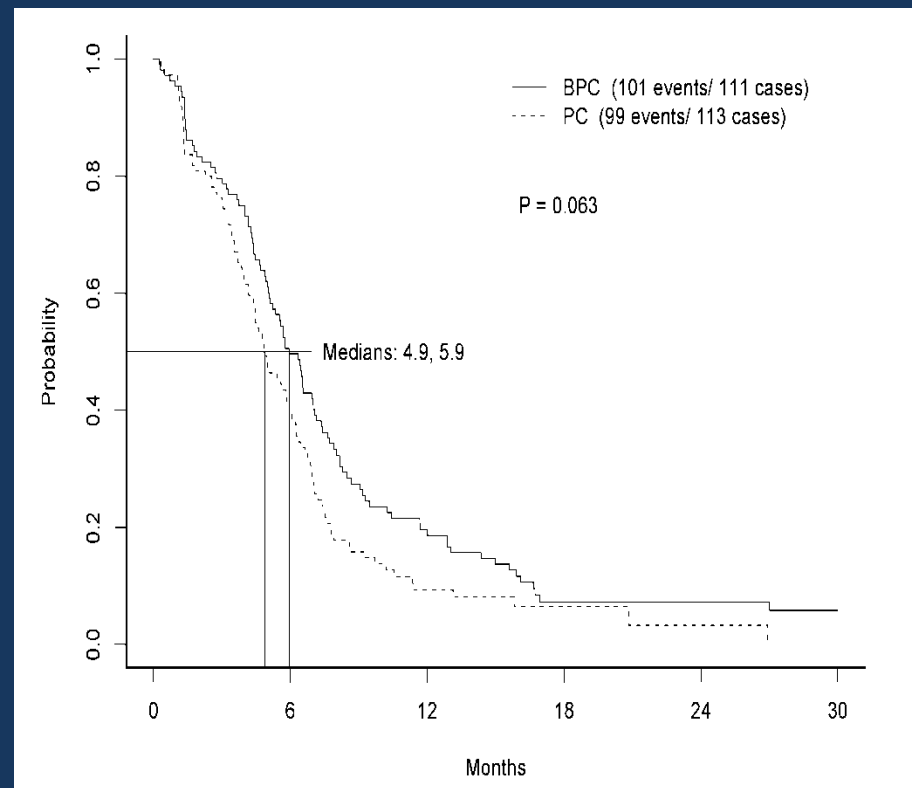
	Elderly		Non-Elderly	
	PC	PCB	PC	PCB
CR+PR	17%	29%	14%	36%
SD	50%	39%	50%	39%
Median PFS	4.9 m	5.9 m P=0.063	4.4 m	6.2 m P<0.001
1-Yr Survival	50%	46%	42%	53%
Median survival	12.1 m	11.3 m P = 0.4	9.6 m	12.8 m P = 0.0027

Overall Survival and PFS For Elderly: PC vs. PCB

Overall Survival



Progression-Free Survival



Toxicity on PCB Arm: Elderly vs. Non-Elderly

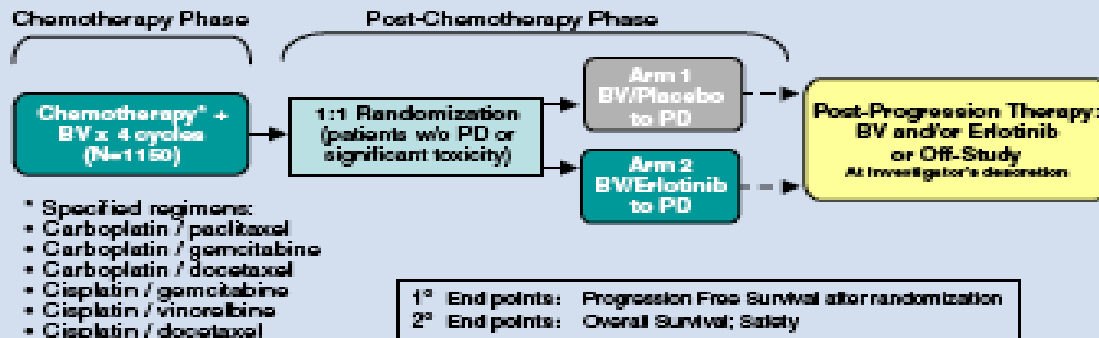
Grade 3/4	≥ 70 yrs	< 70 yrs	P
Neutropenia	34%	22%	0.02
Melena/GI Bleed	3.5%	0.9%	0.005
Proteinuria	7.9%	1.3%	0.001
Muscle weakness	7.8%	2.2%	0.02
Motor neuropathy	3.5%	0.6%	0.05
Dizziness	7.9%	1.6%	0.003
Worst Grade	87%	70%	< 0.001

ARIES: Toxicity in Elderly versus Non-Elderly Avastin-Treated Patients

Patients With Grade ≥ 3 Bleeding Events, N (%)	<70 Years N=1174	≥ 70 Years N=584	≥ 80 Years N=121
All Grade 3-5 Bleeding Events	40 (3.4)	17 (2.9)	2 (1.7)
Pulmonary Hemorrhage	10 (0.9)	2 (0.3)	0
GI Bleeding	13 (1.1)	7 (1.2)	1 (0.8)
CNS Hemorrhage	2 (0.2)	0	0
Epistaxis	5 (0.4)	1 (0.2)	0
Arterial Thromboembolic Events	14 (1.2)	15 (2.6)	5 (4.1)
Other Bleeding Events	12 (1.0)	7 (1.2)	1 (0.8)

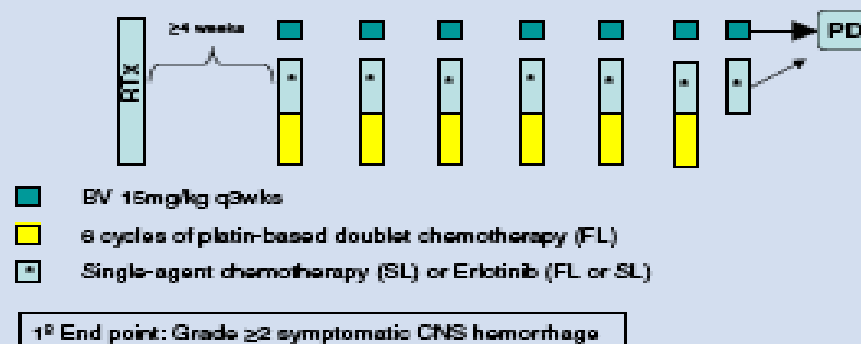
Treated Brain Metastases: PASSPORT & ATLAS

A. ATLAS Phase III Study



B. PASSPORT Phase II Study

- FL of SL NSCLC (n=100)
- Bv start ≥4 weeks post-RTx (WBRT or stereotactic RTx)



Abbreviations: WBRT=whole brain radiotherapy; PD=progressive disease; BV=bevacizumab; FL=first-line treatment; SL=second-line treatment.

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The ATLAS study is on-going at several U.S. and ex-U.S. sites, and the PASSPORT study is on-going at several U.S. sites.

Low Overall Incidence of Cerebral Hemorrhage in Patients With CNS Metastases

- Two prospective studies, PASSPORT and ATLAS
 - Patients with pretreated CNS metastases (whole-brain radiation therapy/neurosurgery) included
 - 131 patients with CNS mets/846 patients in total at interim

Cerebral hemorrhage	PASSPORT (n=106)	ATLAS (n=25)	All (n=131)
All grades, n (%)	0	1 (4)	1 (0.8)
Grade 2, n (%)	0	1 (4)	1 (0.8)

HTN Analysis

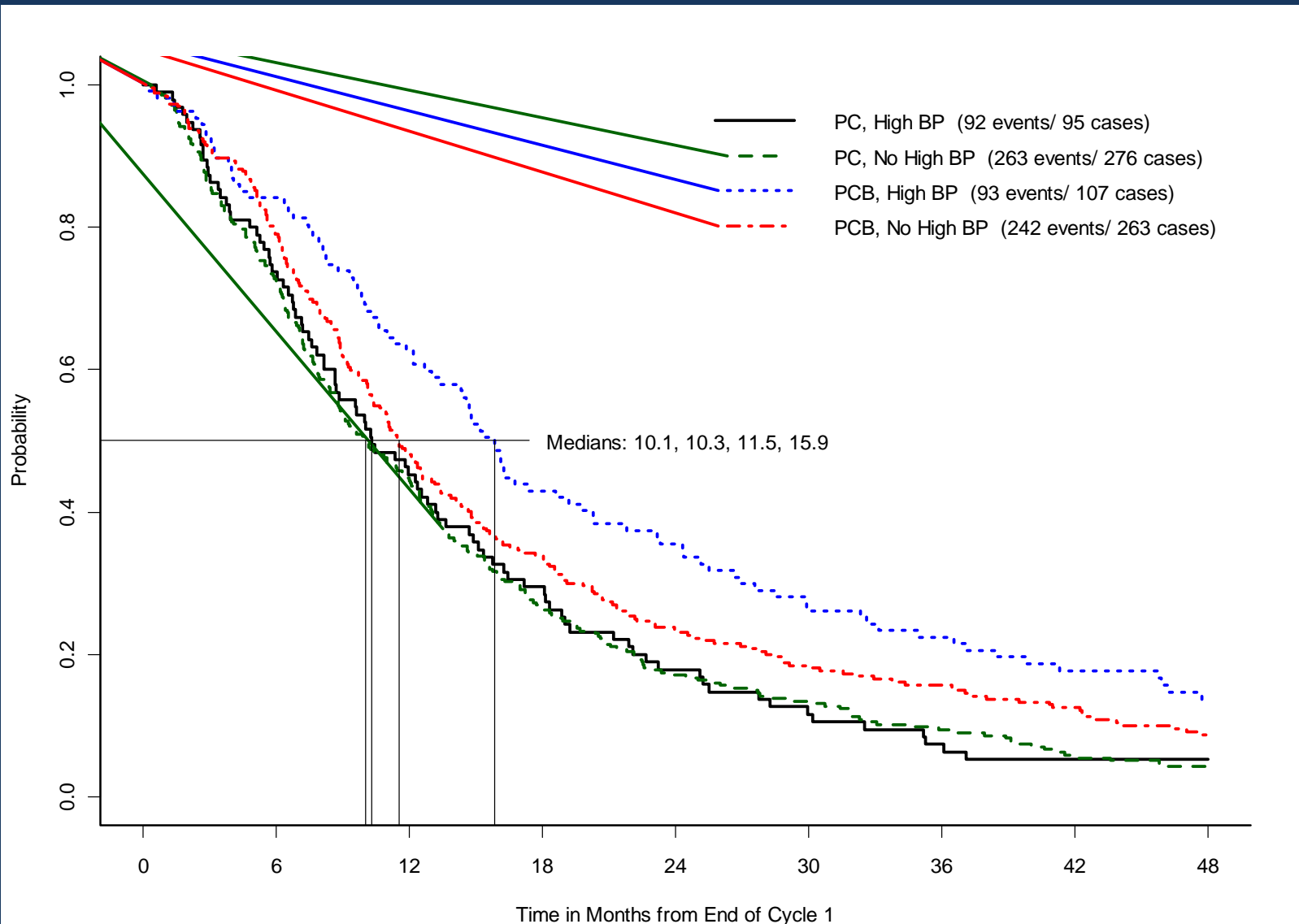
Background

- Antagonism of VEGF decreases nitric oxide production
- Leads to constriction of the vasculature and a reduction in sodium ion renal excretion
- Cause of increased blood pressure
- Hypertension may also be a consequence a depletion of the arterioles and capillaries, caused by the inhibition of angiogenic growth factors

Adjusted hazard ratios

- N = 741 of 850 eligible patients (370 on the PCB arm, 371 on the PC arm)
 - 106 patients missing BP measurements at baseline or at the end of cycle 1
 - three other patients who died or progressed before the landmark time at the end of cycle 1.
- High Blood Pressure - $>150/100$ at any previous time or > 20 mm Hg for diastolic at any time
 - PCB, High Blood pressure by the end of cycle 1
 - ◆ OS: 0.65 (0.51-0.82), $p=0.0002$
 - ◆ PFS: 0.60 (0.48-0.75), $p<0.0001$
 - PCB, No High Blood pressure by the end of cycle 1
 - ◆ OS: 0.85 (0.72-1.00), $p=0.05$
 - ◆ PFS: 0.68 (0.58-0.80), $p<0.0001$

Landmark analysis: overall survival



Biomarkers

HYPOTHESIS & CANDIDATE GENE POLYMORPHISMS

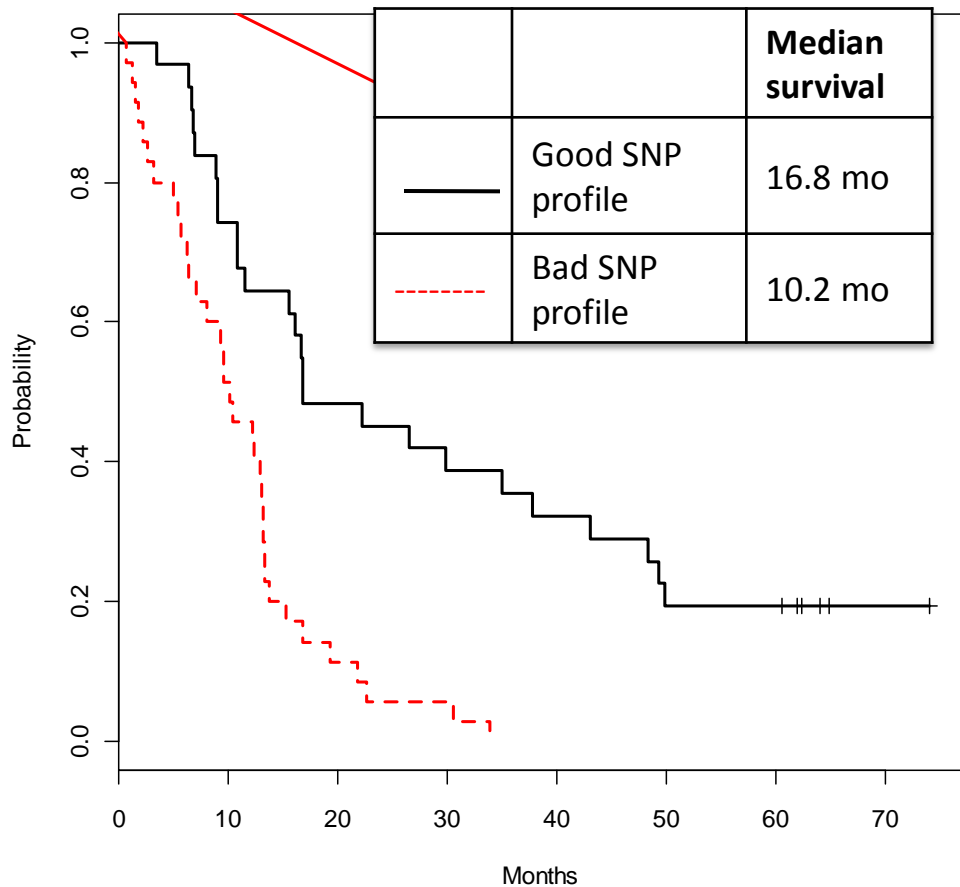
Clinical outcome for patients with advanced NSCLC may be predicted by SNPs:

- Angiogenesis pathway:
VEGF C+936T, VEGF G-634C, VEGF C-1498T, VEGF G-1154A, ICAM1 T469C, FGFR4 G388A, EGF A-61G, EGFR G497A, IL8 T-251A, CXCR2 C+785T, COX2 G-765C
- DNA repair pathway:
ERCC1 C118T, ERCC1 3'UTR C/A, XPD A751C, XPD C156A, XRCC1 G-399A, GSTP1 A105G, KDR T/A
- WNK1 rs11064560 T/G; WNK1 rs2158501 G/A

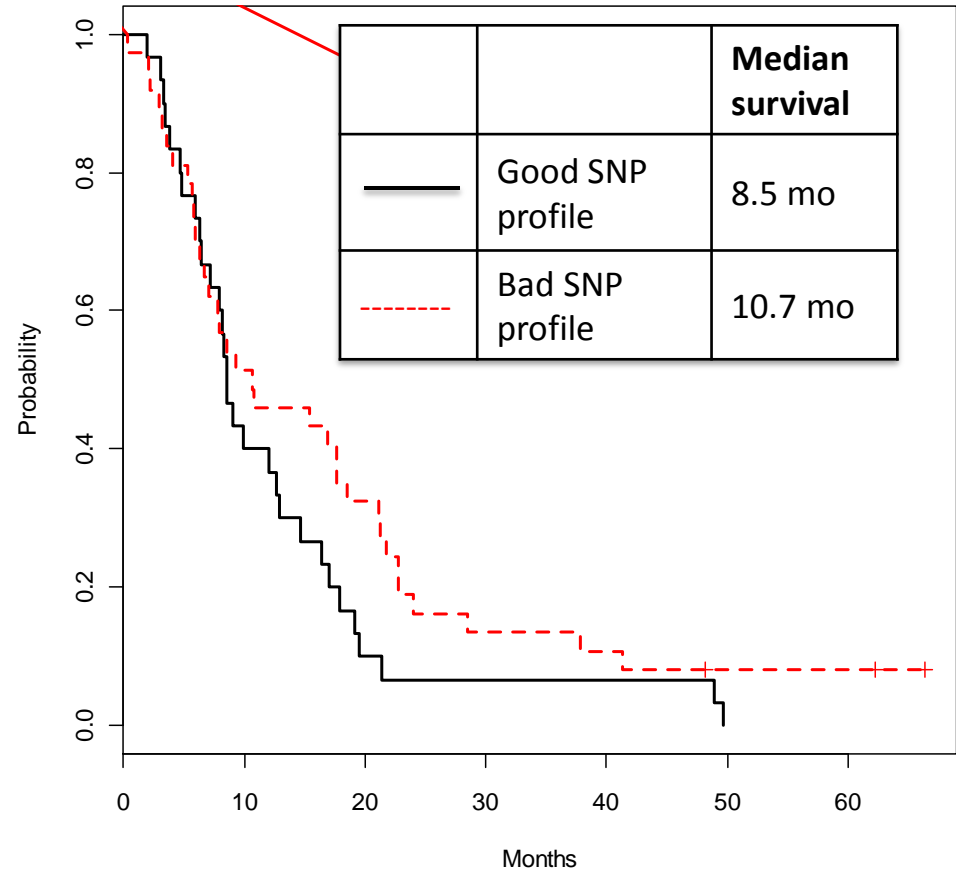


4599 Survival by SNP profile

Carbo/Paclitaxel + Bev



Carbo/Paclitaxel



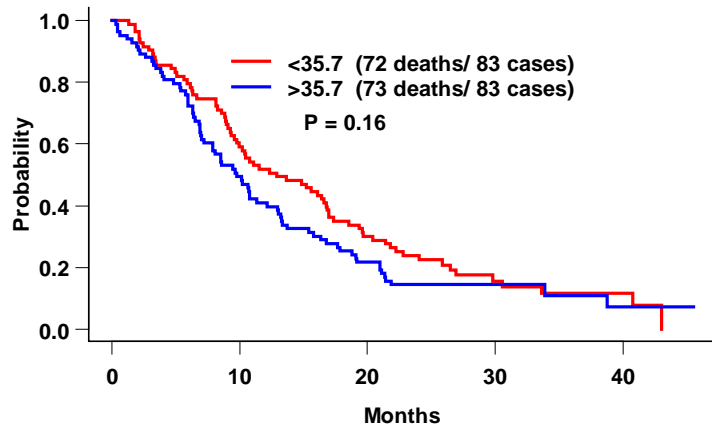
Laboratory Correlates

E4599

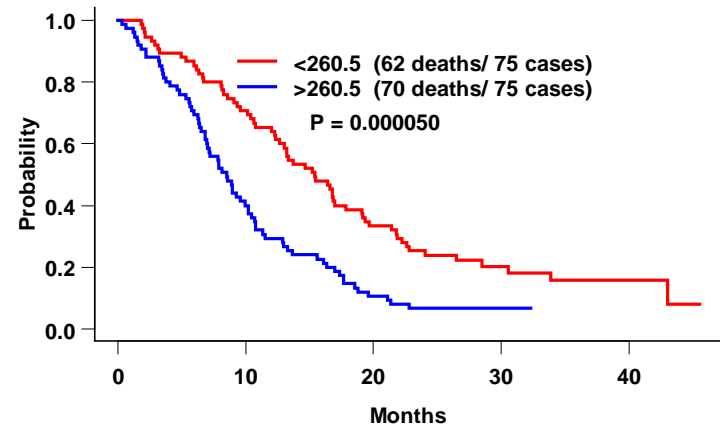
- E-Selectin: (Endothelial Leukocyte Adhesion Molecule-1)
 - 115 kDa, transmembrane glycoprotein
 - Expressed only on endothelial cells and only after activation by inflammatory cytokines
 - Rationale: Elevated levels of E-Selectin is seen in disorders characterized by endothelial cell apoptosis and malignancies
- ICAM-1: (CD54 – Intercellular Adhesion Molecule-1)
 - 90 kDa type-1 transmembrane glycoprotein adhesion molecule
 - Expressed on endothelial, epithelial, lymphocytes, monocytes, hepatocytes and hematopoietic cells
 - Rationale: Elevated levels seen in a variety of malignancies and alterations seen with vascular targeting and antiangiogenic agents
- VEGF and b-FGF: well-known angiogenic factors

Baseline Marker and Survival

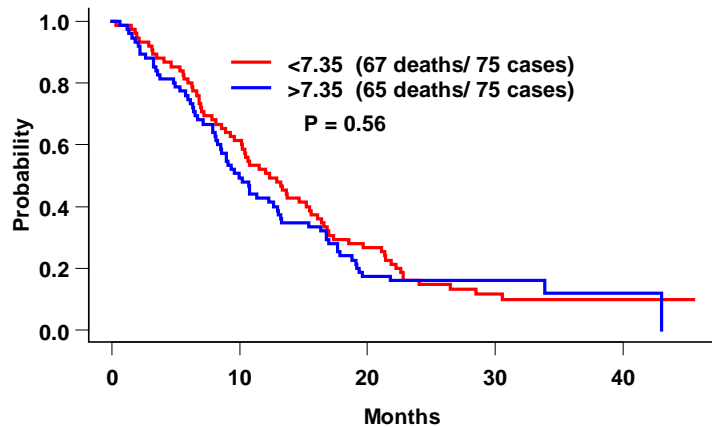
Survival by Baseline VEGF



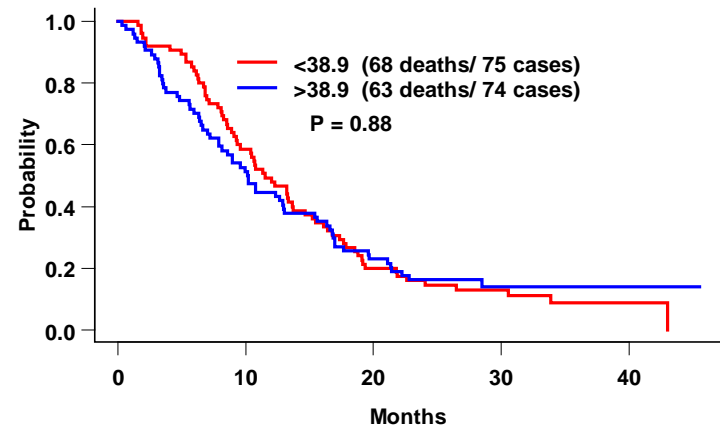
Survival by Baseline ICAM



Survival by Baseline bFGF



Survival by Baseline E-Selectin



Patient Selection Factors

Conclusions

- Clinical Selection Factors
 - Sex – women appear to benefit (RR and PFS)
 - Age – elderly appear to benefit with improved RR and PFS (trend)
 - Pulmonary hemorrhage
 - Histology – non-squamous cell only
 - Central location and cavitations – no clear association
 - Anti-coagulation - acceptable
 - Brain metastases - previously treated acceptable
 - Hypertension – may predict outcome with bevacizumab (and other VEGF-TKI's)
- Biomarkers
 - No markers available yet

Grade 3 – 5 Non-Hematologic Toxicity

	CP (N = 441)	BvCP (N = 427)	P Value
Hemorrhage	1.1	4.7	0.001
Hemoptysis	0.5%	2.1%	
CNS	0.2%	0.7%	
GI	0.5%	1.2%	
Other [†]	0.2%	1.2%	
Hypertension	0.7%	7.7%	<0.001
Proteinuria	---	3.1%	<0.001
Venous thromb	3.2%	5.6%	
Arterial thromb	1.6%	2.8%	