ATLAS OF MOLECULAR ONCOLOGY

Pharmacogenomics of Angiogenesis

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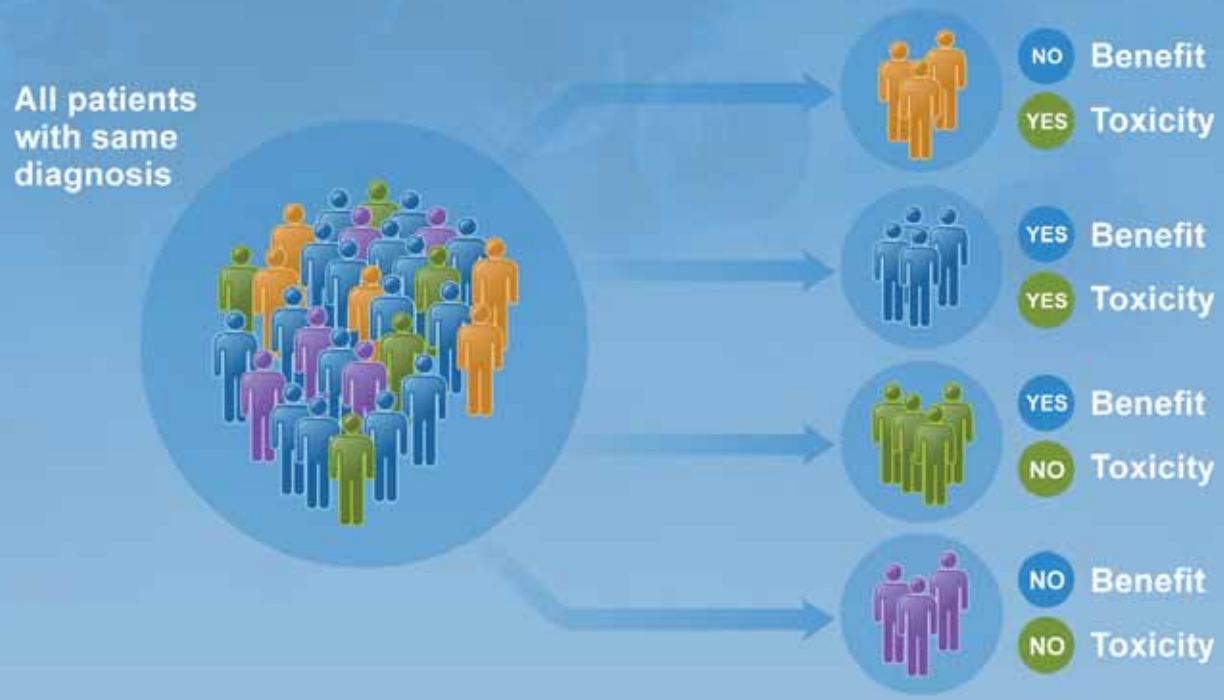
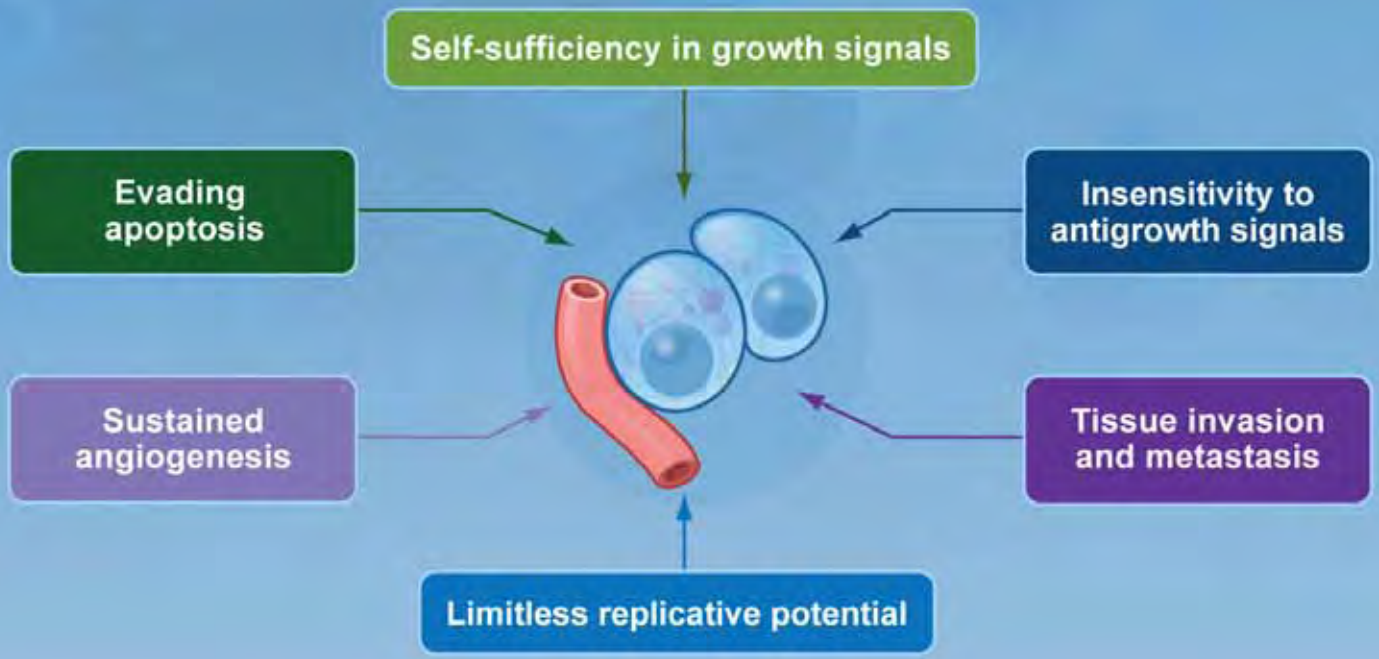
Overview: Pharmacogenetic Approach to Angiogenesis Biomarker Discovery



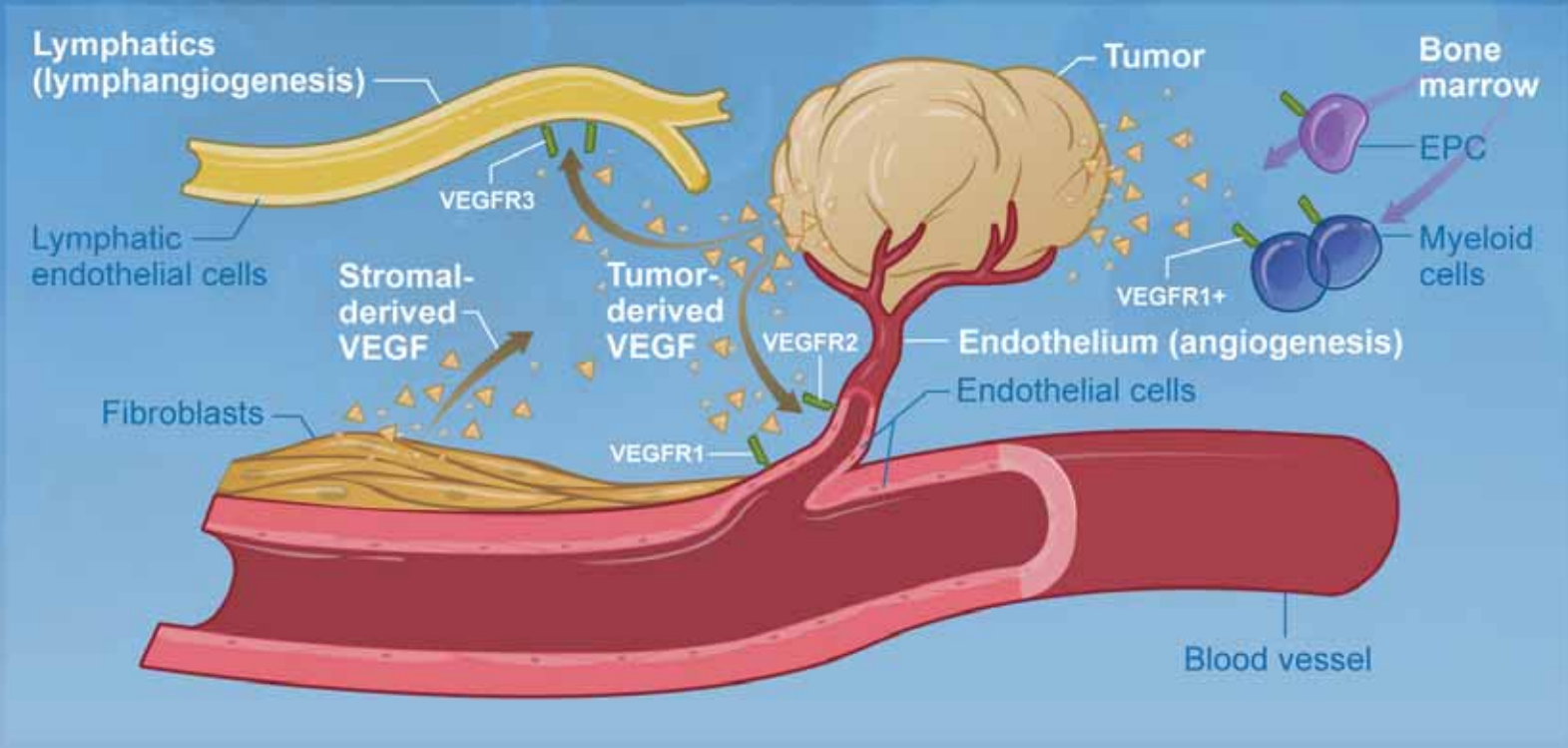
Source: With permission from Walgren et al. *JCO* 2005; 23:7342-7349

Hallmarks of Malignancy: A Biomarker Rich Environment?



Source: *Cell,* Vol. 2, Hanahan D, Weinberg RA, The Hallmarks of Cancer, 57-70, 2000

Angiogenesis is Critical for Tumor Proliferation

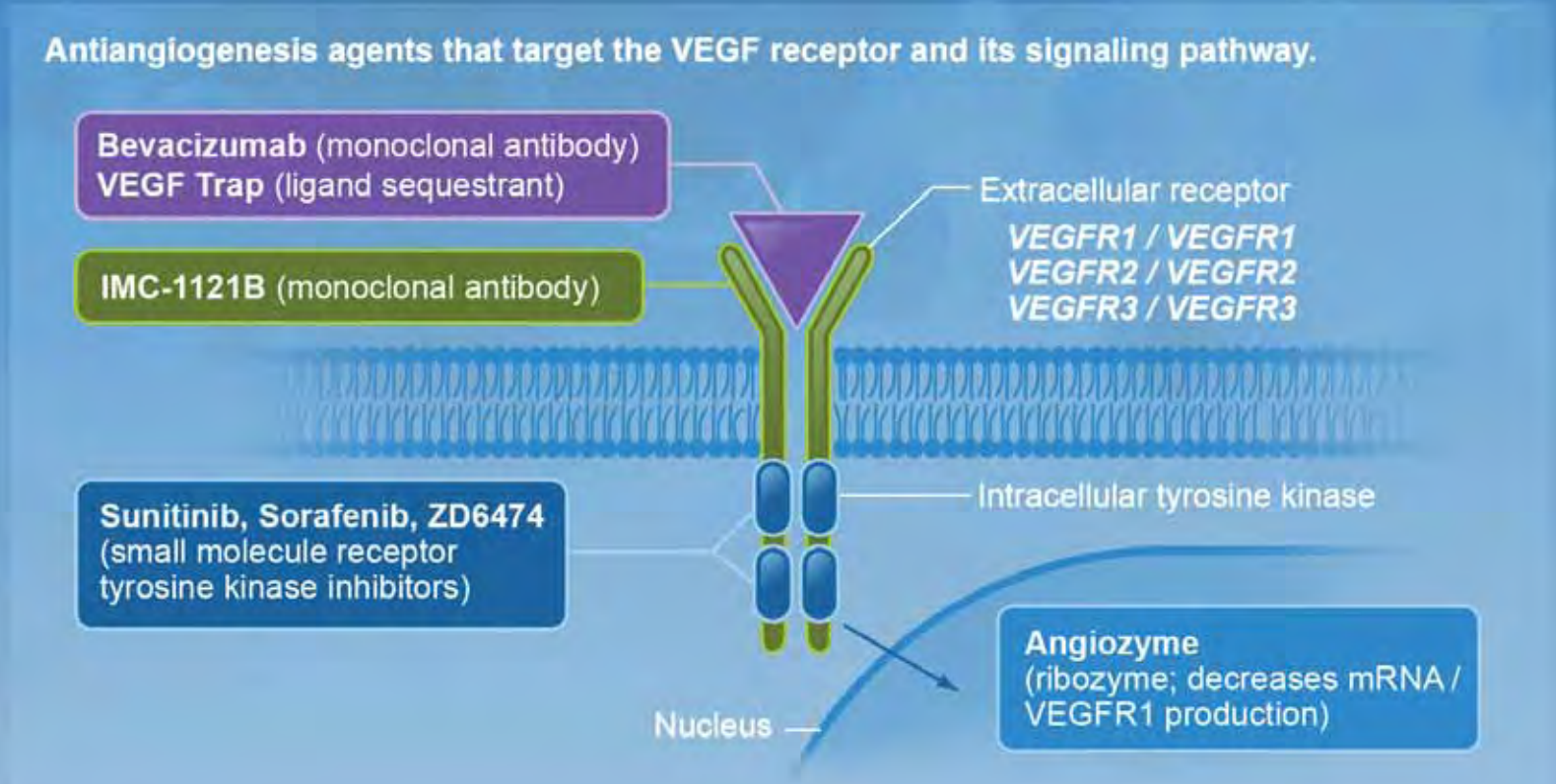


Source: With permission from Hicklin et al, *JCO*, 2005: 23, 1011

Evidence for Angiogenic Role in Tumor Pathogenesis

- Increased MVD associated with advanced stage & poor outcomes in multiple malignancies
- High pro-angiogenic factor tumor expression correlated with poor clinical outcome in malignancy
- Inhibition of angiogenesis successful in MULTIPLE tumor types

Multiple Targets to Inhibit Angiogenesis



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VEGF SNPs Associated with Outcome

VEGF Allele	Trial	Association
-2578A	E2100 (phase III breast)	Improved OS
-1498C	E2100	More HTN
-1154A (tagSNP)	E2100	Improved OS
-634G	E2100	More HTN
	E4599 (phase III lung)	Improved OS
	RCCA (axitinib)	More HTN
VEGF -2578A, -1498C, -1154A, and -634G A alleles are in L.D.		

Sources: Schneider, *JCO* 2008; Zhang, ASCO:abstr# 8032, 2009; Kim ASCO:abstr# 5005, 2009

Pharmacogenetic Approach to Angiogenesis Biomarker Discovery

Essential Ingredients*:*

- **Genetic variability must have potential for biologic impact**
- **Genetic variability must exist in drug disposition or destination**
  - **Metabolizing enzymes/transporters/targets**
- **Drug evaluated must be heterogeneous in outcome**
  - **Mix of success and toxicity**
- **Variability must be frequent**
  - **Generalizability of results**

Source: Walgren et al. *JCO* 2005; 23:7342-7349

Genetic Variability Impacts Angiogenesis: Brief Summary

- **Epidemiologic Data:**
  - **Variable risk & prognosis in multiple conditions where angiogenesis is important: risk/prognosis in multiple malignancies, retinopathy, nephropathy, pre-eclampsia, recurrent pregnancy loss, vasculopathy**
  - **Mostly VEGF, HIF1, & NOS**
  - **Limitations: Conflicting data, single gene/SNP approach, & clinical variables often ignored**

Genetic Variability Impacts Angiogenesis: Brief Summary

- Variability may associate with site of metastasis
  - VEGF-1498 CC more common in visceral (vs. bone) mets
- VEGFR-1 promoter SNP associated with differential induction by p53: (Menendez, PNAS 2006)
- Variability in complement factor H may affect treatment outcome in macular degeneration (?biomarker): (Brantley, Ophthalmology 2007)
  - CC genotype had inferior outcome in visual acuity with intravitreal bevacizumab

Genetic Variability Impacts Angiogenesis: Brief Summary

- NOT level 1 evidence: body of data strongly suggests variability is biologically important
- Breast cancer angiogenesis as a model

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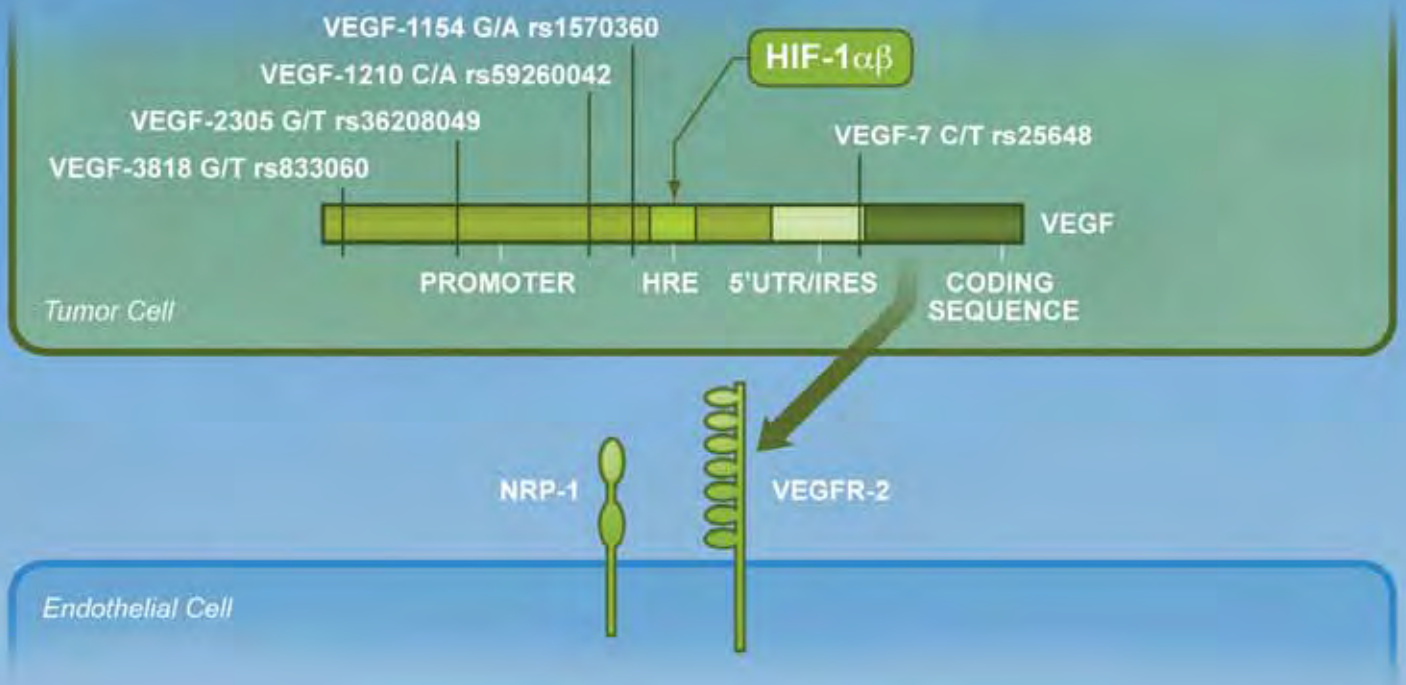
Excellent Genetic Variability in Angiogenesis Drug Targets



Source: Reprinted with permission from Schneider et al, *CCR* 15, 5297; 2009;15:5297 fig 1

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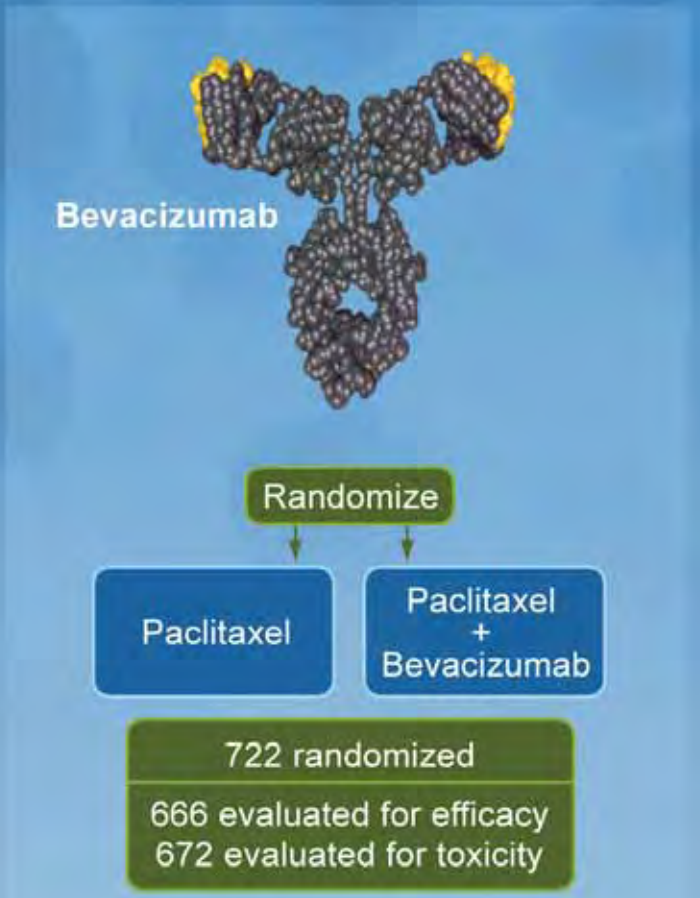
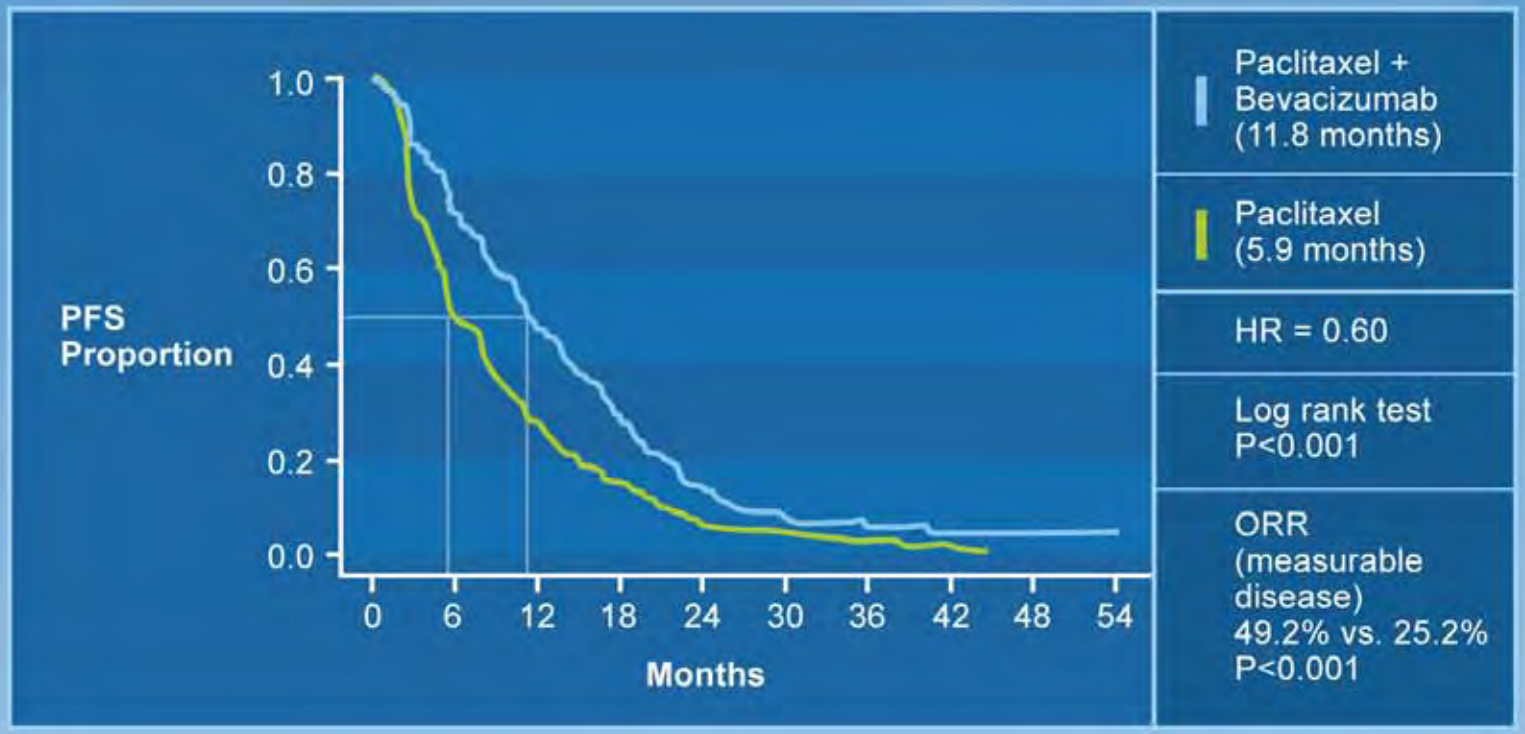
Bevacizumab in Breast Cancer (E2100)

Stratify:

- **DFI ≤ 24 mos. vs. > 24 mos.**
- **<3 vs. ≥3 metastatic sites**
- **Adjuvant chemotherapy: yes vs. no**
- **ER+ vs. ER- vs. ER unknown**



Bevacizumab Significantly Improved PFS



Source: With permission from Miller et al. *NEJM* 357:2666; 2007

Bevacizumab Increased Grade 3/4 Toxicity

Likely related to duration of taxane exposure

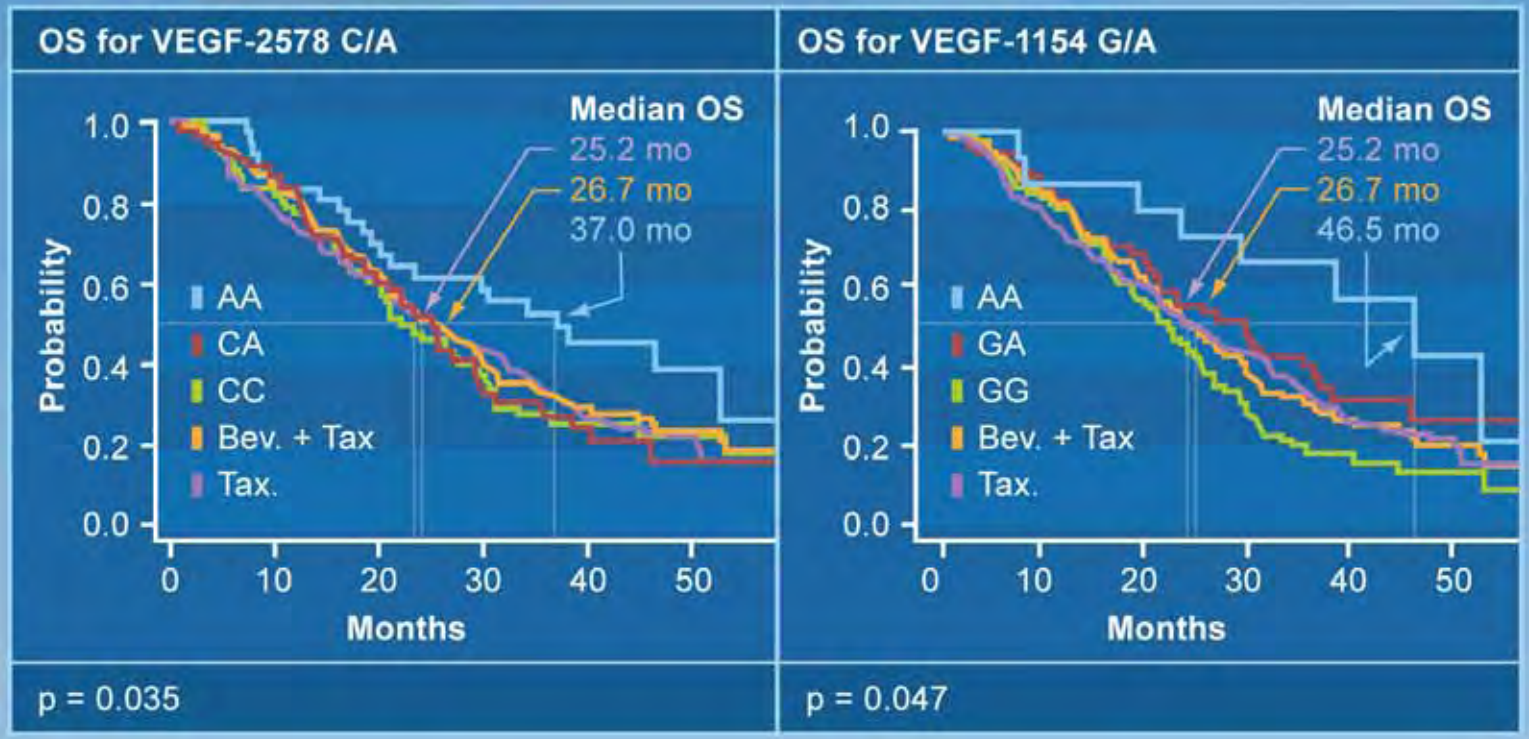
Serious and bevacizumab induced, but rare

Serious, frequent, and clearly bevacizumab induced

Toxicity	P (%)	P + B (%)	p-value
Infection	2.9	9.3	<0.001
Fatigue	4.9	9.1	0.04
Neuropathy	17.7	23.5	0.05
CNS ischemia	0	1.9	0.02
Headache	0	2.2	0.008
Proteinuria	0	3.5	<0.001
Hypertension	0	14.8	<0.001

Source: Miller et al. *NEJM* 357:2666; 2007

VEGF-2578 AA and -1154 AA Genotypes in Combination Arm Outperformed Control in E2100



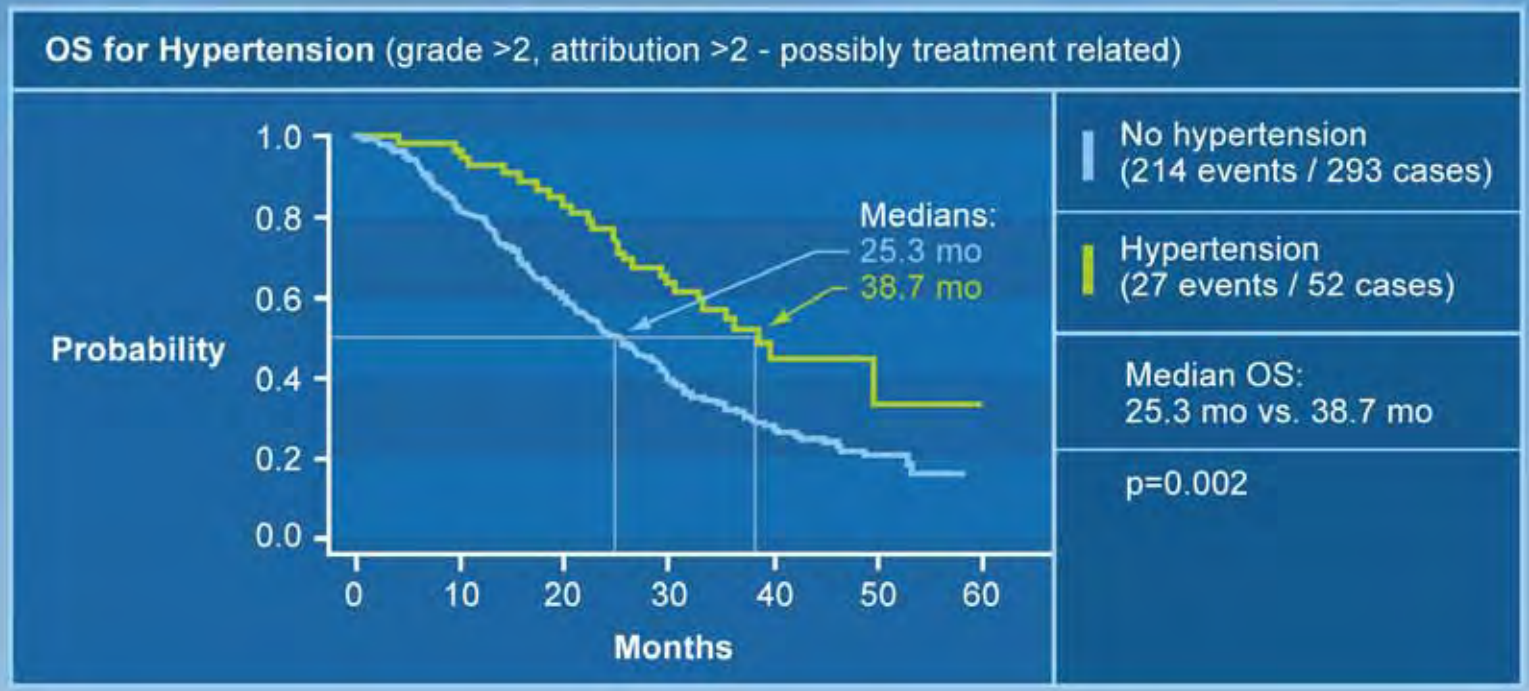
Source: With permission from Schneider et al; *JCO*; 26, 2008: 4672-4678

Genetic Variability of VEGF Predicts Clinically Significant Hypertension in E2100

SNP	Percent Grade 3/4 Hypertension (no./%) by Genotype	p-value
VEGF-634	CC=0% (n=27, 15.3%) vs. GC=22% (n=82, 46.3%) vs. GG=19% (n=68, 38.4%)	0.013
	CC vs. GC+GG	**0.005**
VEGF-1498	TT=8% (n=60, 33.9%) vs. CT=22% (n=82, 46.3%) vs. CC=23% (n=35, 19.8%)	0.056
	TT vs. CC+CT	**0.022**

Source: Schneider et al; *JCO*; 26, 2008: 4672-4678

Grade 3/4 Hypertension Associated with Improved Median OS in E2100



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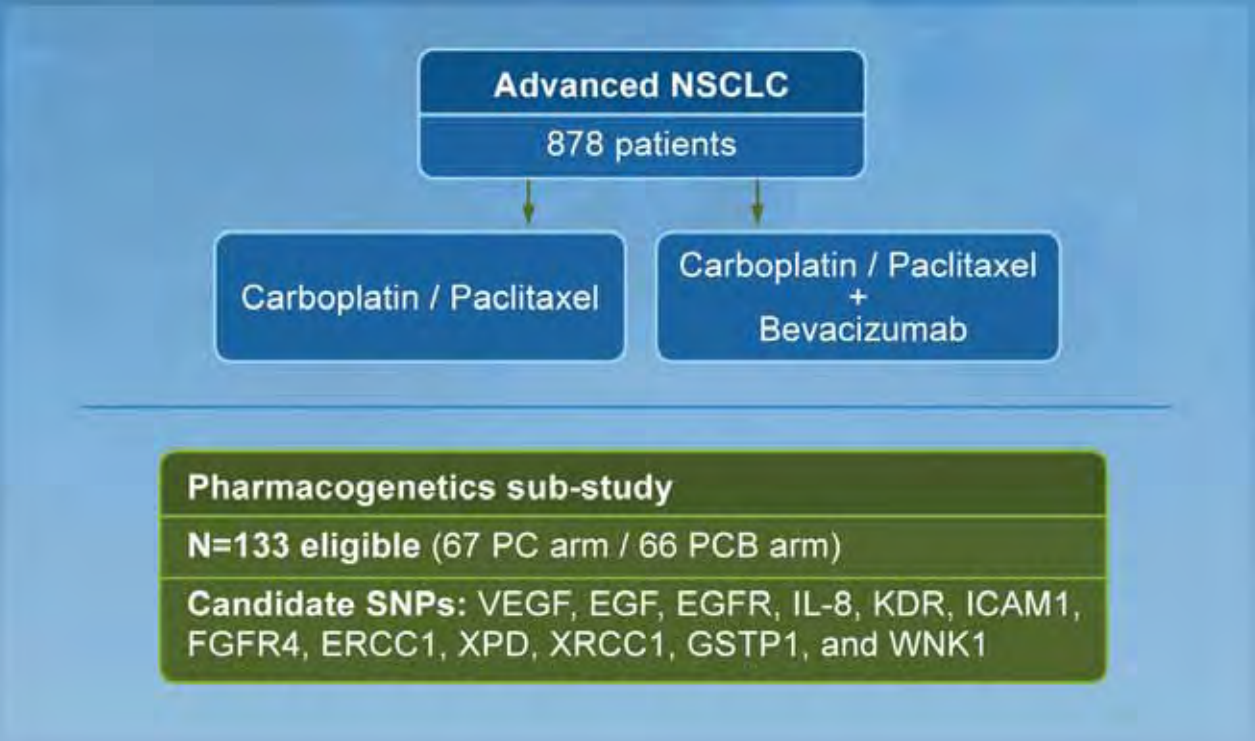
Hypertension Association with Survival

Trial	Anti-VEGF	Definition of HTN	Association
E2100 (breast: phase III)	Bevacizumab	CTC grade 3/4	Improved OS
E4599 (lung: phase III)	Bevacizumab	CTC any grade and > 150/100	Improved OS and PFS
NCIC BR24 (lung: randomized phase II)	Cediranib	New HTN or worsening grade HTN	Improved RR and PFS
Axitinib Meta-analysis	Axitinib	dBP > 90 mm Hg	Improved OS

Sources: Schneider *JCO* 2008; Dahlberg *ASCO*: abstr #8042, 2009, Goodwin *ASCO*: abstr #3527, 2009; Rini *ASCO*: abstr #3543, 2008

E4599 Lung Cancer Trial

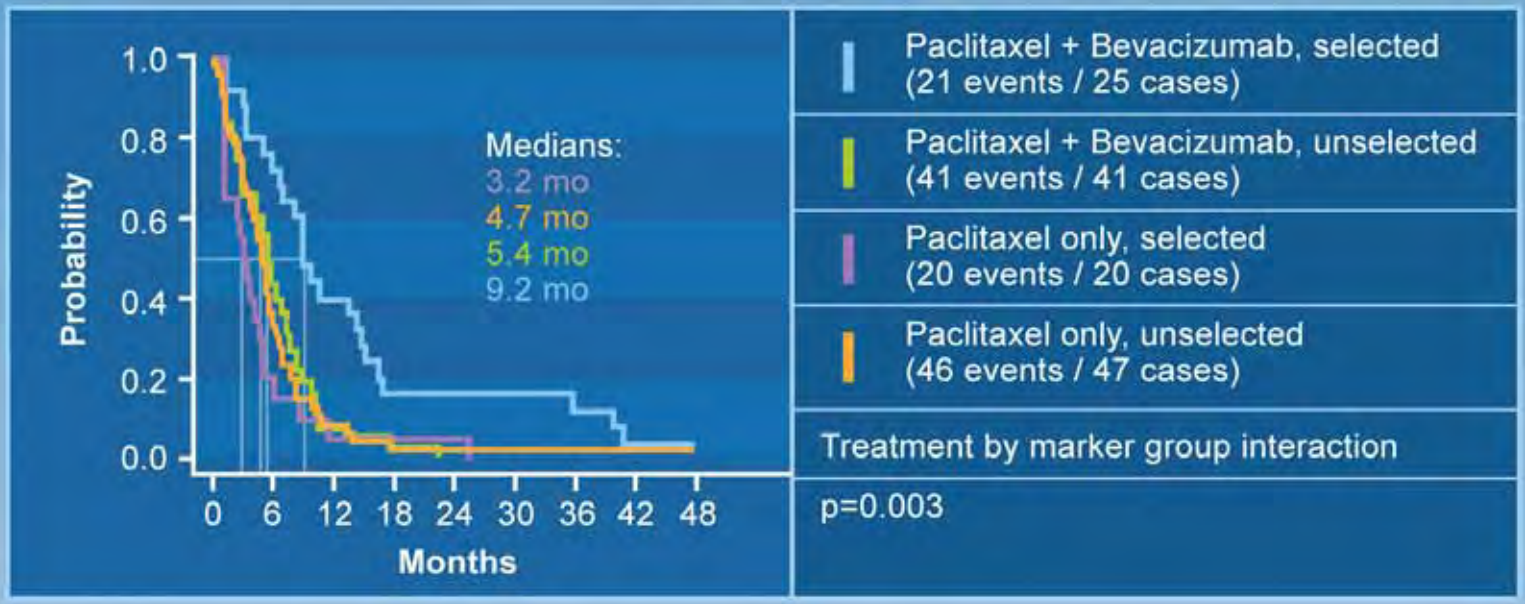


E4599 Results

- **Median OS:**
  - **PC arm=10.3 months (95% CI: 8.2-15.6)**
  - **BPC arm=13.0 months (95% CI: 10.2-16.6)**
- **Median PFS:**
  - **PC arm=4.6 months (95% CI: 3.6-5.6)**
  - **BPC arm=6.5 months (95% CI: 5.4-8.3)**
- **Treatment by genotype interactions tested for in a multivariable model:**
  - **Gender**
  - **PS (0 or 1)**
  - **Stage (IIIB/IV vs. recurrent)**
  - **Adrenal mets, liver mets, and bone mets**

PFS Classifying Patients by the SNPs that Selected Patients for Superior PFS

(VEGF634 GG and IL8-251 TT ≠ TT, VEGF634 GG and IL8-251 TT and ICAM469 TT)



Source: With permission from Zhang W et al. *Proc ASCO* 2009 Abstract 8032

E4599: OS Classifying Patients by the SNPs that Selected Patients for Superior OS

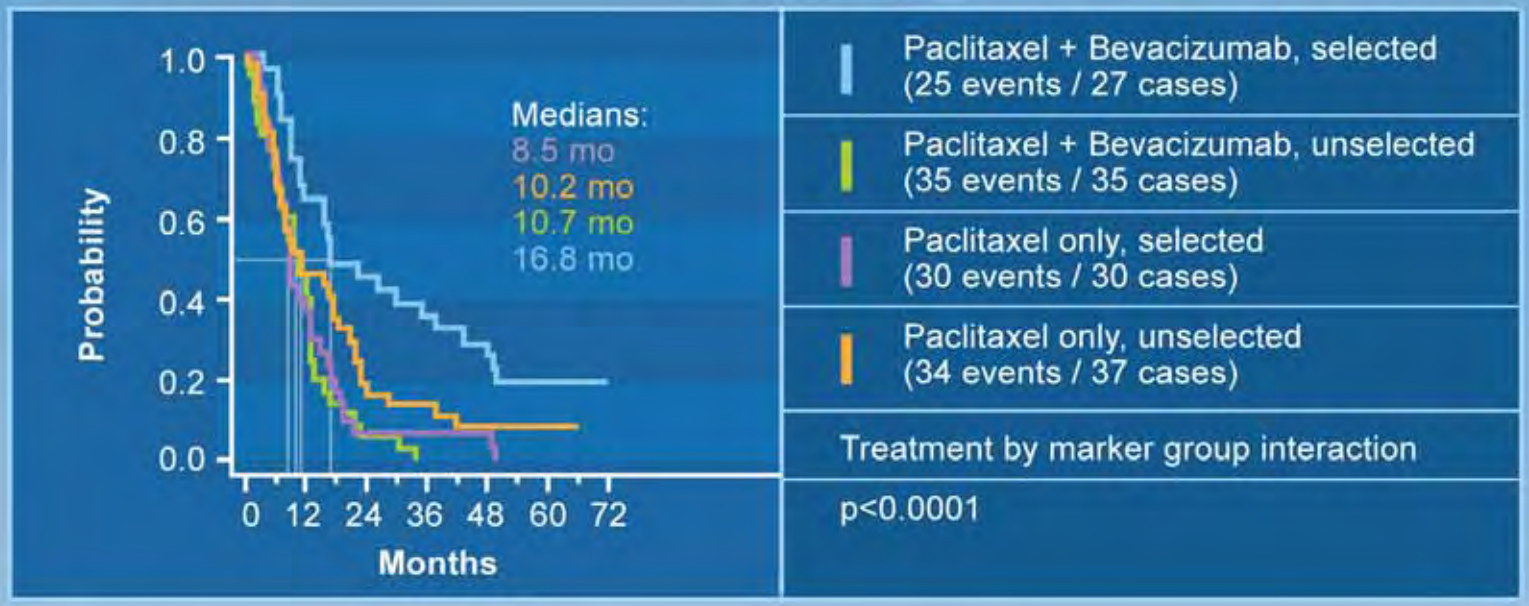
(ICAM469 TT and VEGF634 GG, ICAM469 ≠ TT and IL8-251 ≠ TT)

- **Hypothesis: SNPs involved in angiogenesis pathway (VEGF, EGF, EGFR, IL-8, KDR, ICAM1, FGFR4), DNA repair pathway (ERCC1, XPD, XRCC1, GSTP1) and WNK1 will predict clinical outcome in a subset of patients enrolled on E4599.**

	Bad SNPs	Good SNPs
Chemo alone	8.5	10.2
Chemo + Bevacizumab	10.7	16.8

E4599: OS Classifying Patients by the SNPs that Selected Patients for Superior OS

(ICAM469 TT and VEGF634 GG, ICAM469 ≠ TT and IL8-251 ≠ TT)



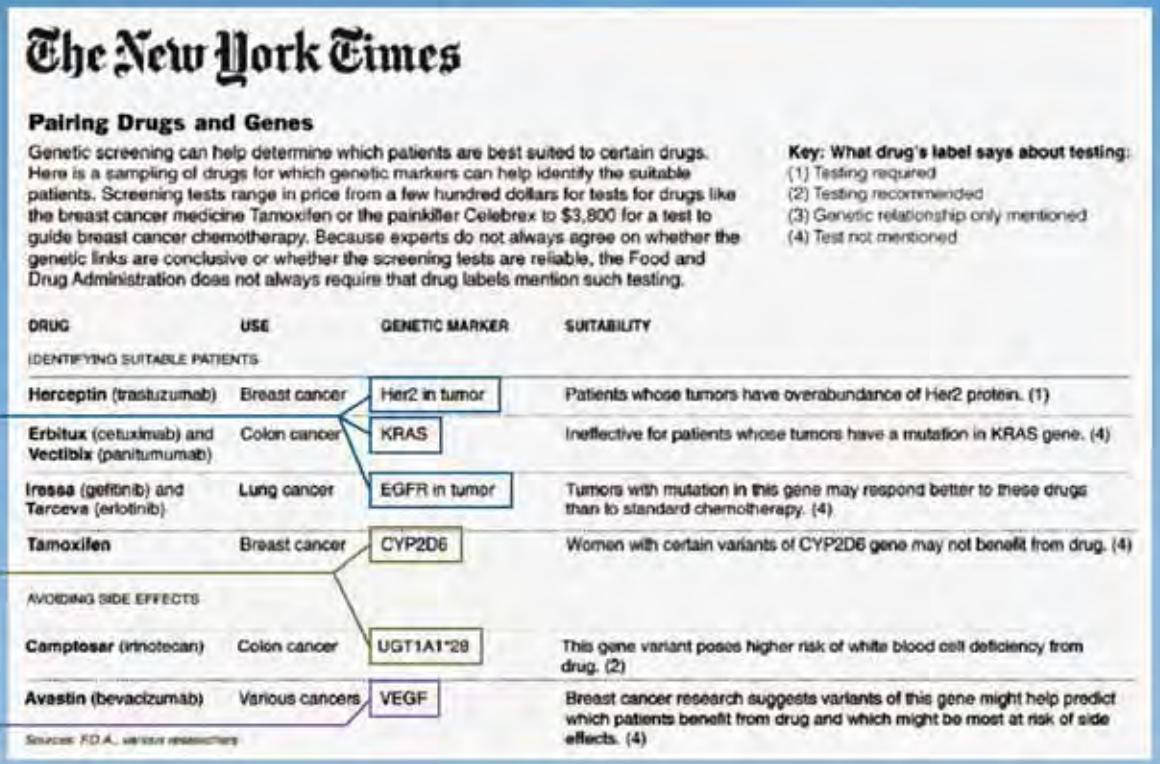
Source: With permission from Zhang W et al. *Proc ASCO* 2009 Abstract 8032

Pairing Drugs and Genes

Mutational variability

Metabolizing enzyme SNPs

Host Target SNPs



The New York Times

Pairing Drugs and Genes

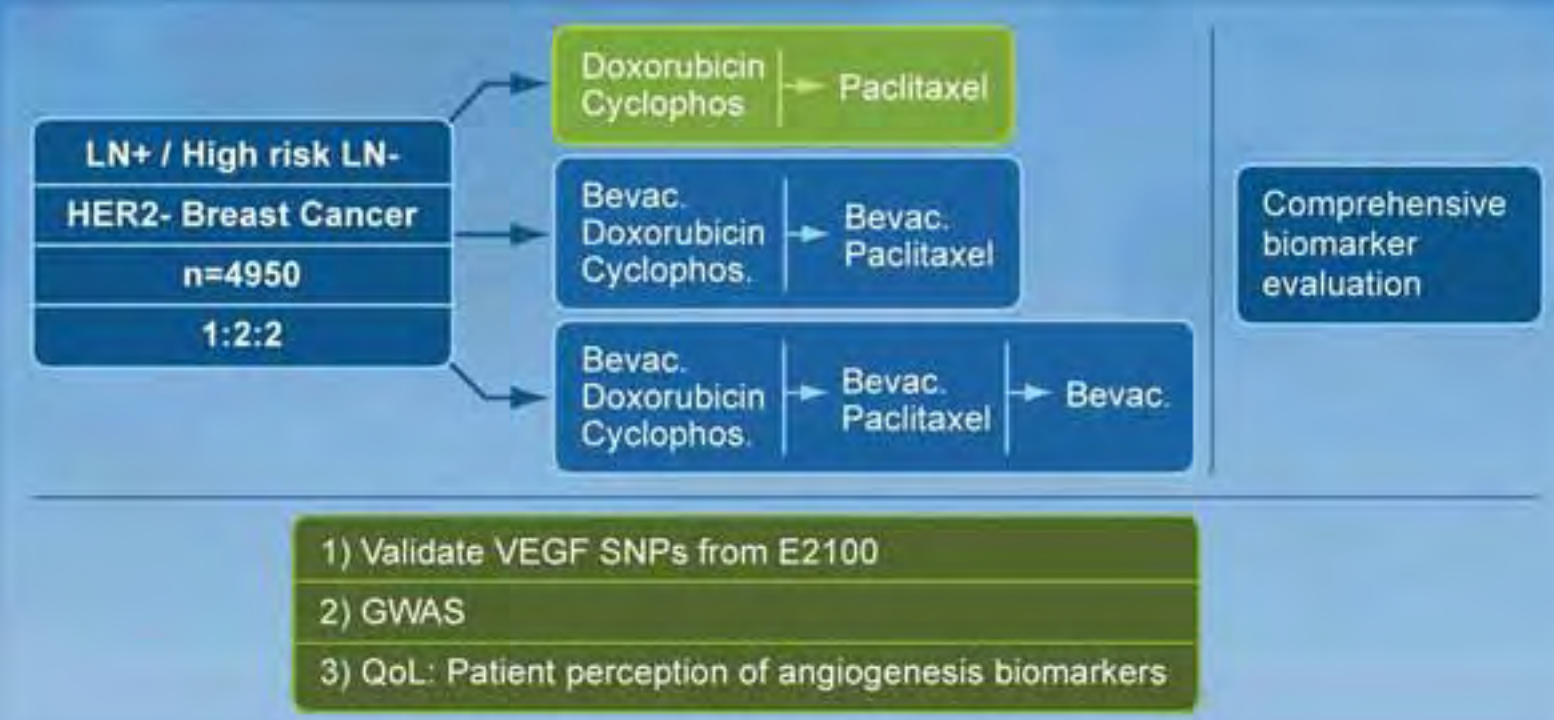
Genetic screening can help determine which patients are best suited to certain drugs. Here is a sampling of drugs for which genetic markers can help identify the suitable patients. Screening tests range in price from a few hundred dollars for tests for drugs like the breast cancer medicine Tamoxifen or the painkiller Celebrex to $3,800 for a test to guide breast cancer chemotherapy. Because experts do not always agree on whether the genetic links are conclusive or whether the screening tests are reliable, the Food and Drug Administration does not always require that drug labels mention such testing.

Key: What drug's label says about testing:
(1) Testing required
(2) Testing recommended
(3) Genetic relationship only mentioned
(4) Test not mentioned

DRUG	USE	GENETIC MARKER	SUITABILITY
IDENTIFYING SUITABLE PATIENTS			
Herceptin (trastuzumab)	Breast cancer	Her2 in tumor	Patients whose tumors have overabundance of Her2 protein. (1)
Erbitux (cetuximab) and **Vectibix** (panitumumab)	Colon cancer	KRAS	Ineffective for patients whose tumors have a mutation in KRAS gene. (4)
Iressa (gefitinib) and **Tarceva** (erlotinib)	Lung cancer	EGFR in tumor	Tumors with mutation in this gene may respond better to these drugs than to standard chemotherapy. (4)
Tamoxifen	Breast cancer	CYP2D6	Women with certain variants of CYP2D6 gene may not benefit from drug. (4)
AVOIDING SIDE EFFECTS			
Camptosar (irinotecan)	Colon cancer	UGT1A1*28	This gene variant poses higher risk of white blood cell deficiency from drug. (2)
Avastin (bevacizumab)	Various cancers	VEGF	Breast cancer research suggests variants of this gene might help predict which patients benefit from drug and which might be most at risk of side effects. (4)

Sources: F.D.A., various researchers

Comprehensive Analysis of Genetic Variability in E5103



Conclusions

- **Pharmacogenetics (biomarkers)**
  - **Improves therapeutic index**
  - **Leads to drug discovery**
  - **Benefits patients**

Conclusions

- Angiogenesis
  - Hallmark of malignancy
  - Inhibition effective in multiple tumor types
  - Therapeutic heterogeneity – biomarkers needed
    - Early work suggests germline genetic variability might be important
    - Validation and further understanding of molecular biology essential

"Host Hallmark"