

New Frontiers in Antiangiogenic Therapy in NSCLC

6th Annual Atlanta Lung Cancer Symposium

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February 7, 2009



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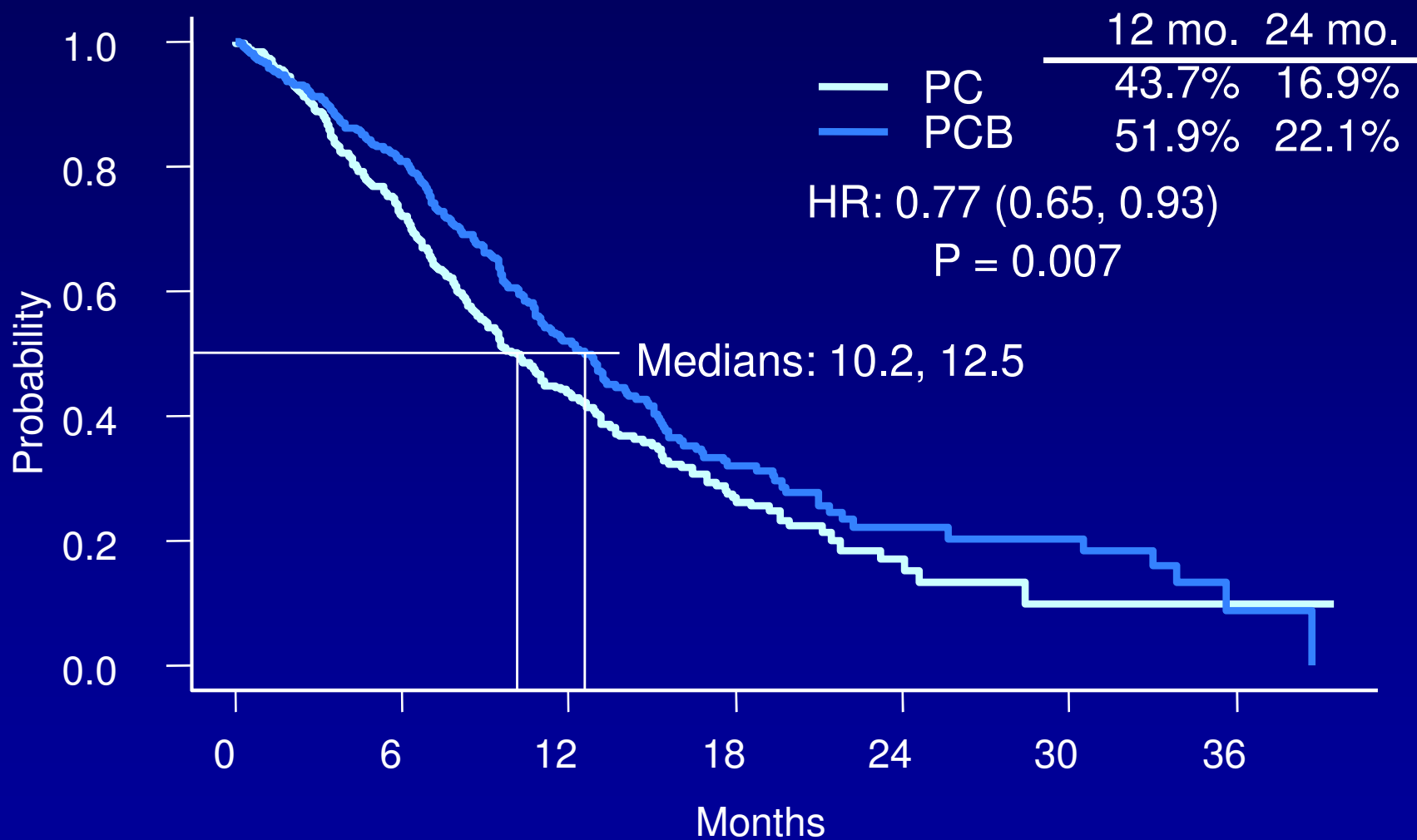
Disclosure

JVH has received research funding and served on advisory boards for AstraZeneca, Pfizer, and Glaxosmithkline, and served on advisory boards for Genentech.

Antiangiogenic agents for NSCLC in 2009: Current status

- Bevacizumab remains the only approved angiogenesis inhibitor for NSCLC
 - ECOG 4599: Overall survival improvement improves by 2.3 months with the addition of BV to PC
 - Recommended use currently limited to:
 - Advanced/metastatic disease
 - First line setting
 - Non-squamous histology
 - No CNS metastases
 - Concerns regarding those with poorly controlled HTN, TE disease
- This represents only a small fraction of total NSCLC patients!

ECOG 4599: Overall survival

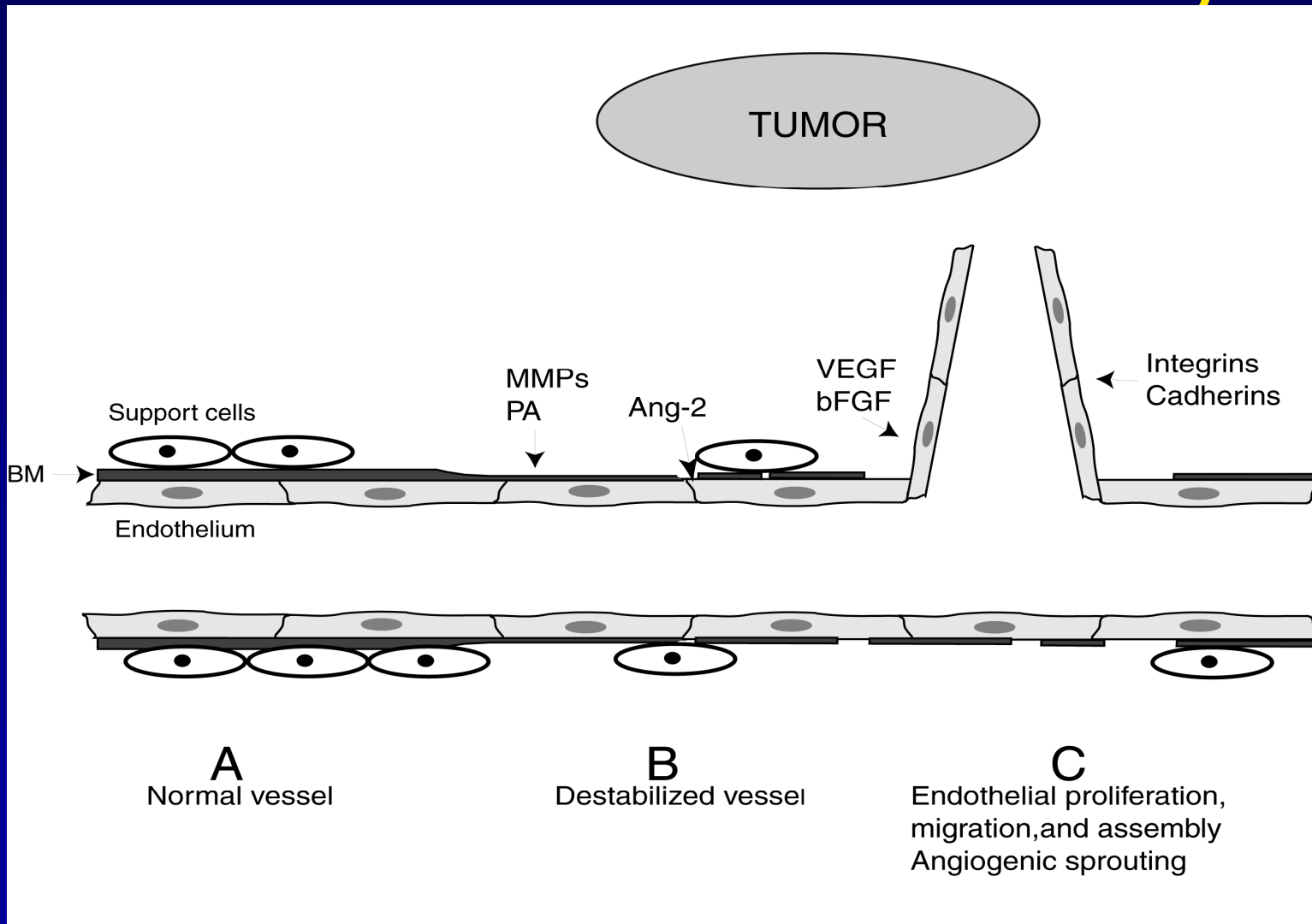


Sandler et al, NEJM, 2006

Where do we go from here?

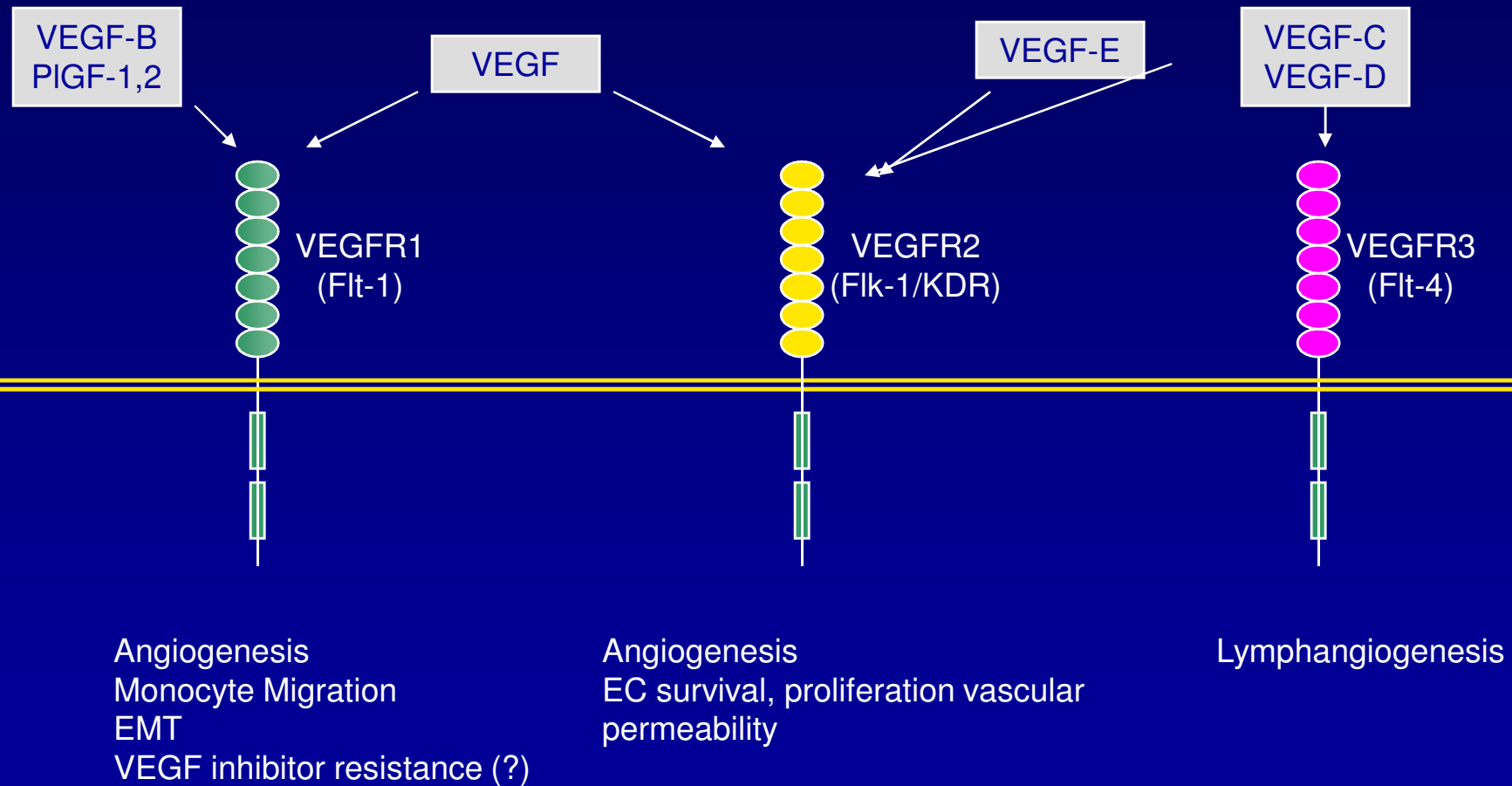
- Expanding bevacizumab use
 - New combinations
 - Additional NSCLC populations
- Different inhibitors of the VEGF pathway
 - New proteins
 - TKIs
- Drugs directed at new targets
 - bFGFR, Tie2, PDGFR, etc
- VDAs
- Identifying which patients are most likely to respond (or experience harm) using biomarkers

Steps in tumor angiogenesis: VEGF is not the whole story!



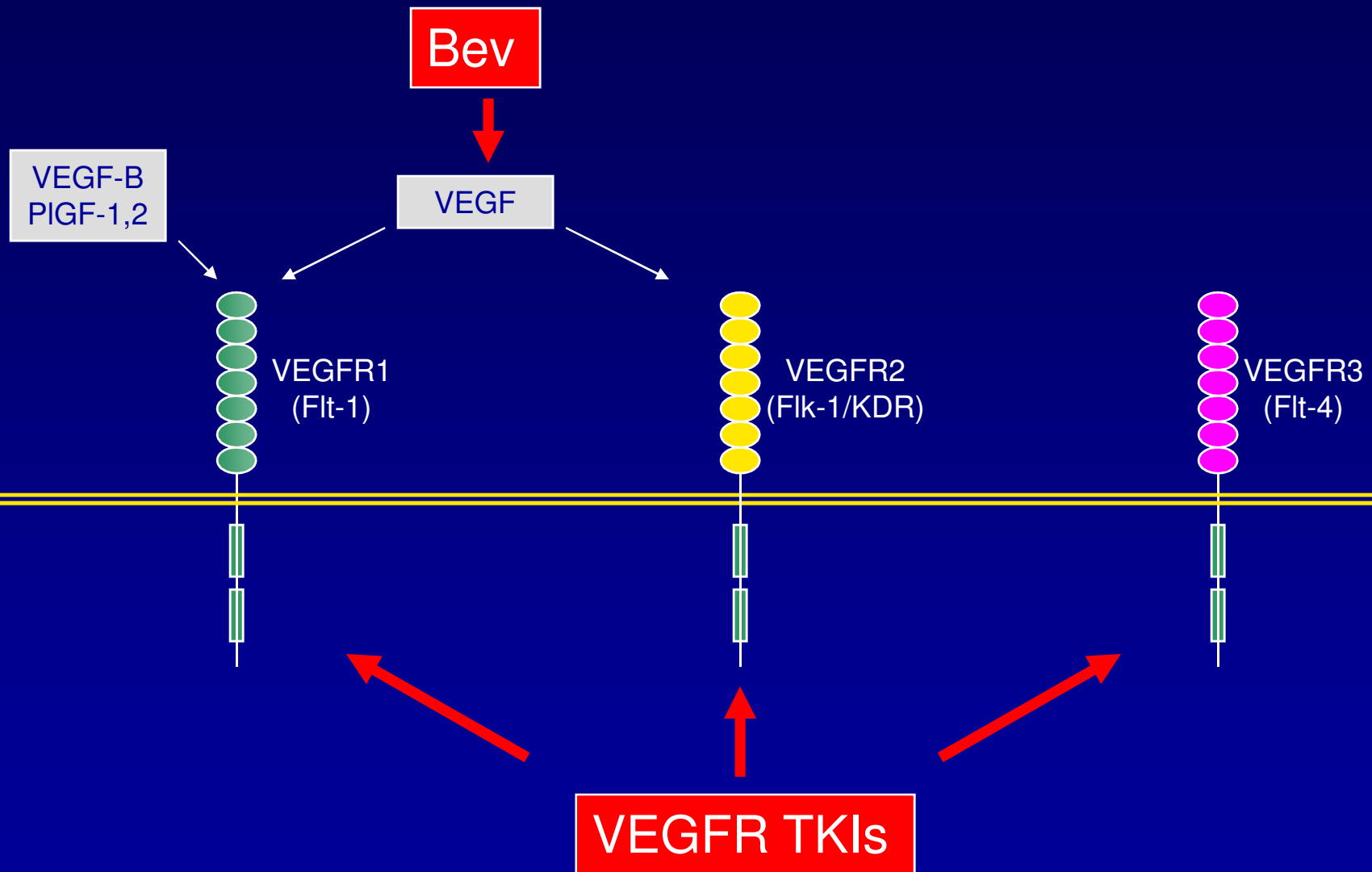
Adapted from Heymach, JV.(2001) Curr Opin Oncol, 13(4) 261-269

VEGF family signaling pathways



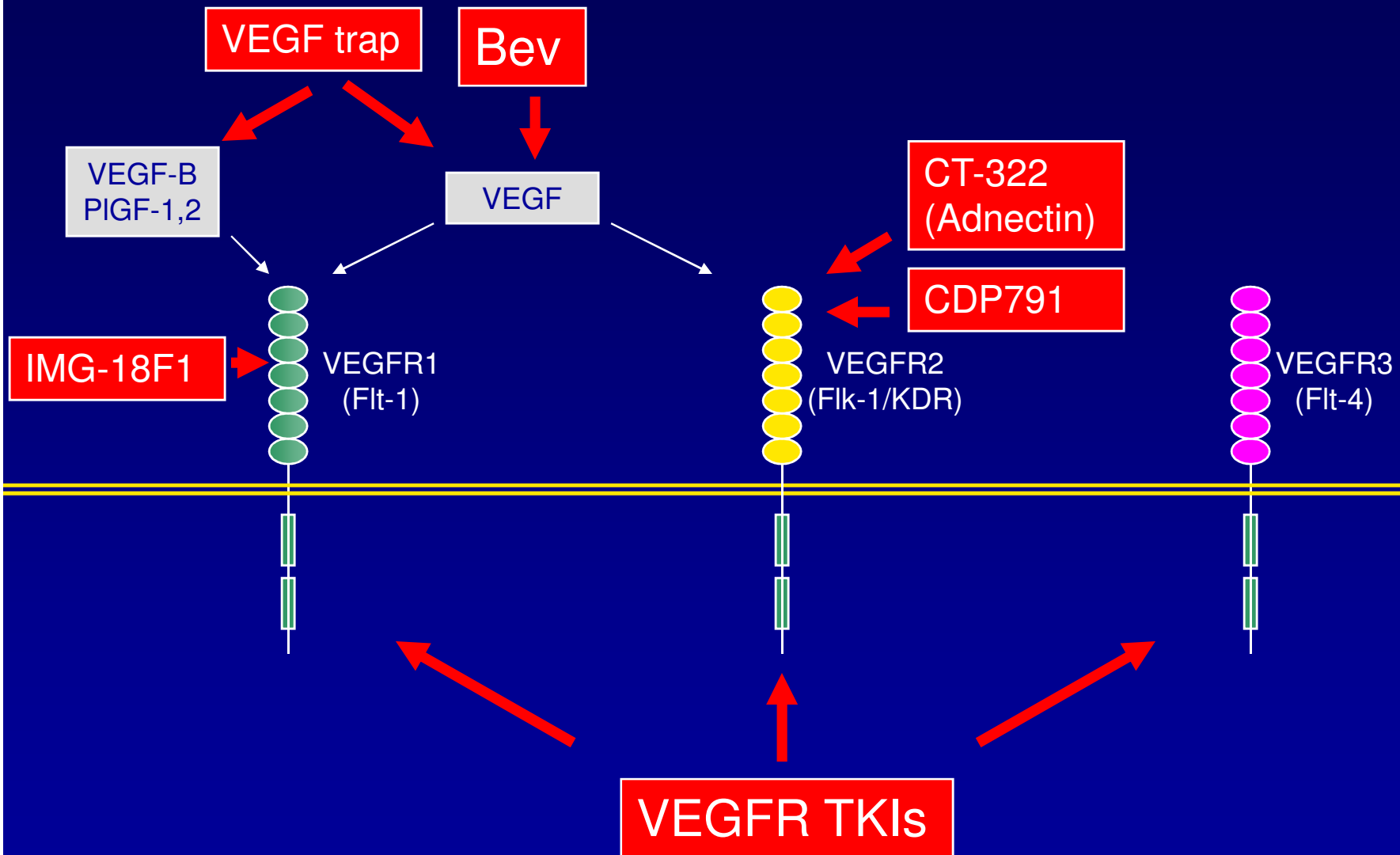
Adapted from Nilsson and Heymach, J Thor Oncol 2006 Oct;1(8):768-70

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VEGF family signaling pathways



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Antibodies and other proteins targeting VEGF signaling

Efficacy of BV with platinum doublet chemotherapy for non-squamous NSCLC

AVAIL vs. 4599

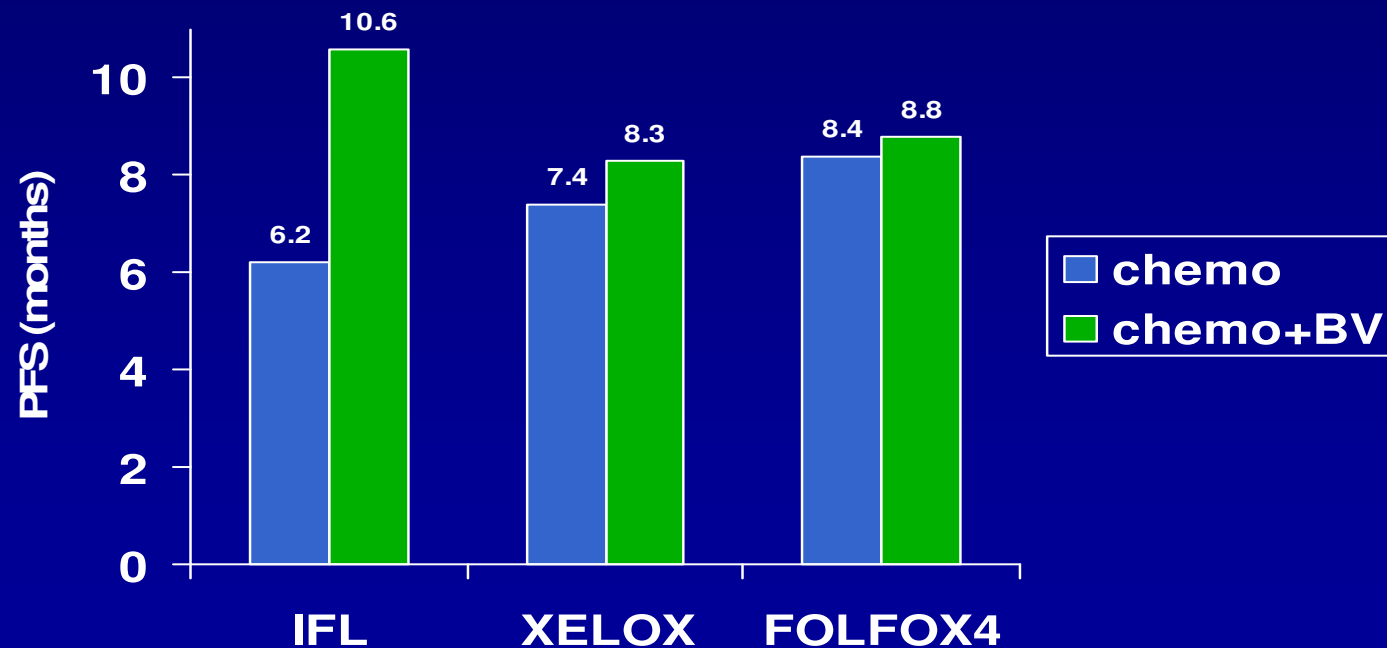
	G/P	G/P/7.5	G/P/15	C/P	C/P/15
# pts	347	345	351	433	417
RR	20%	34%*	30%*	15%	35%*
PFS	6.1	6.7*	6.5*	4.5	6.2*
OS		NS**	NS**	10.3	12.3*

* $P < 0.05$

Manegold et al, ASCO 2007; Sandler et al, NEJM, 2006; Lynch, ASCO 2007;
 **Genentech press release, April 20, 2008.

Does the chemo partner for BV matter? PFS in phase III trials of chemotherapy +/- BV for first-line mCRC

	IFL	XELOX*	FOLFOX*
HR	0.54	0.77	0.89
P value	<0.001	0.0026	0.18
N	813	700	700



Hurwitz et al. *N Engl J Med.* 2004;350:2335, *subgroup analyses from N016966 trial, Saltz et al. ASCO GI, 2007.
Abstract 238. Updated from oral presentation. Courtesy of L. Ellis. .

BV combinations

- Pemetrexed (Adjei et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 8080)) in 2nd/3rd line
 - median PFS 4.1m, 50% DCR encouraging
 - Pem/carboplatin for first line (Patel et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 8044))
 - ORR 49%, acceptable toxicity profile
 - Pac/carbo, gem/carbo, doc/carbo +/- erlo (ATLAS) (Plikoff *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 8079))
 - No unexpected safety events
 - Docetaxel/gemcitabine (Ansari et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 19077))
 - 3/17 with GI perforation (GIP), 2 deaths attributed
 - Study closed due to GIP
- Most but not all combinations seem to have acceptable safety profile.

Preliminary results of phase III trial comparing bevacizumab and erlotinib vs erlotinib (BeTa)

(Herbst et al, Chicago Multidisciplinary Symposium, 2008)

- N = 636; peripheral squamous, treated CNS mets allowed
- Did not prolong OS (primary endpoint)

	E	B+E	HR	<i>P</i>
OS (m)	9.2	9.3	.97 (0.80-1.18)	NS
PFS (m)	1.7	3.4	.62 (.52-.75)	
ORR (%)	6.2	12.6		0.006

Interim analysis of phase III ATLAS study

(Press release, Roche, Feb. 3, 2009)

- Erlotinib+BV vs BV as maintenance after first line chemo+BV (N = 1,157)
- Stopped early because of significant improvement in PFS at interim analysis

BV in NSCLC patients with CNS metastases and anticoagulation

- BV in pts with brain metastases (Akerley et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 8043))
 - 91 patients with treated CNS mets, with standard therapy
 - No CNS bleeds during treatment; 1 Gr 2 bleed post-progression
 - 7 Gr 3-5 CNS events
 - 1 Gr 3 leukoencephalopathy
 - BV in pts with anticoagulation (Griesinger et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 8049))
 - 87 patients on anticoagulation, 15 with bleeding events (17%) comparable to those not on anticoagulation
 - No grade 3 or greater bleeding events
 - Observational cohort of pts treated with BV (ARIES study) (Lynch et al, *J Clin Oncol* 26: 2008 (May 20b suppl; abstr 8077))
 - 621 of planned 2000 pts enrolled in “real-world” setting, multiple regimens used (PC, Doc/carboplatin, etc)
 - Pts with CNS mets, anticoagulation, PS2
 - Low rates of Gr $\frac{3}{4}$ bleeding, thromboembolic events, RPLS, etc.
- **Growing evidence that BV may be safe for those with CNS metastases and anticoagulation**

VEGF trap (Aflibercept)

- Soluble decoy receptor with EC domains of VEGFR1,2 fused to FC domain
 - Binds VEGF and PlGF
- Monotherapy activity and tolerable safety profile in platinum- and erlotinib-resistant NSCLC
(Massarelli et al, *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 7627)
- Phase I with doc/cis (Freyer et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 14539))
- Phase III testing with docetaxel ongoing

Other proteins targeting VEGF/VEGFR pathways

- VEGFR-1 mAb IMC-18F1
 - Phase I: no significant safety concerns reported
(Krishnamurthi *et al*, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 14630))
- CT322: Adnectin protein targeting VEGFR2
 - Phase I shows AE profile and rise in plasma VEGF consistent with VEGF pathway blockade
(Sweeney *et al*, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 3523))

TKIs targeting VEGFR and other
angiogenic RTKs (angiokinase inhibitors)

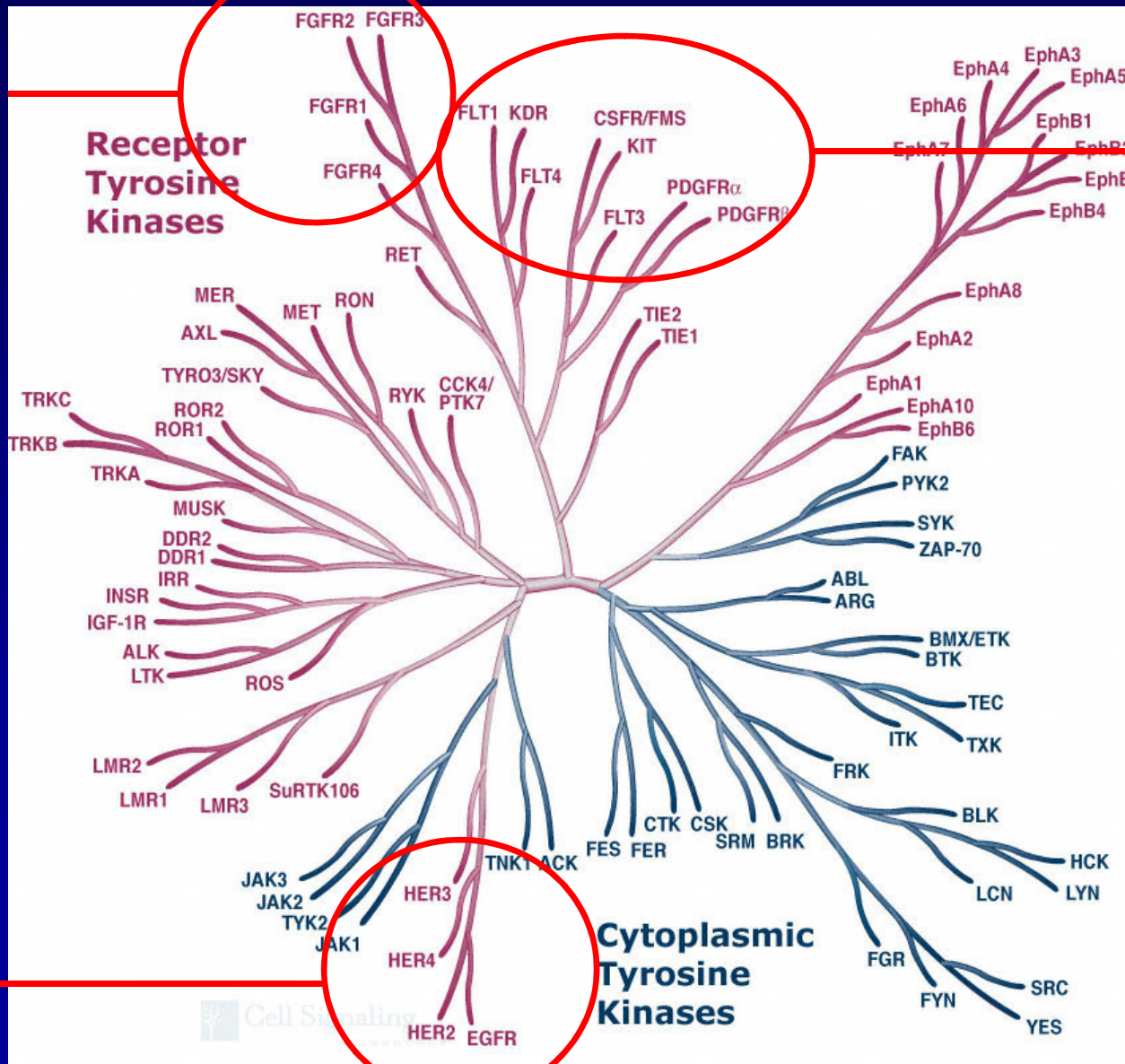
Possible benefits from VEGFR TKIs vs antibodies

- Oral dosing, more flexible dosing
- Potency and pharmacokinetics
 - **improved degree or duration of inhibition of key targets.
 - Continuous target coverage probably preferable
 - Target inhibition in tumor probably not complete even for “potent” TKIs such as sunitinib
- Differences in toxicity (?)
- TKIs are multitargeted (a.k.a. “dirty”)
 - Is that a good thing?

Tyrosine kinases within the kinome

FGFR 1,2,3,4

Receptor Tyrosine Kinases



VEGFR 1,2,3
Flt3
KIT
CSFR/FMS
PDGFR

EGFR
Her2
Her3
Her4

Cytoplasmic Tyrosine Kinases

From Cell Signaling

Characteristics of selected VEGFR TKIs being tested for NSCLC

Drug	Half-life (hr)	IC ₅₀ (nM)*					Other
		VEGFR-1	VEGFR-2	VEGFR-3	PDGFR	KIT	
Sunitinib	44		9	17	8	10	RET
Sorafenib	~27	-	90	20		68	B-Raf, RET
Vandetanib	~120	1600	40	110			EGFR, RET
AZD2171	13-35	5	< 1	< 3		2	
AMG 706	5-7	2	3	6	8	84	RET
AG013736	2-5	1.2	0.25	0.29			
Vatalinib	3-6	54	39	195	567	364	
BIBF1120		21	21	13	59		FGFR-1/3
Others: pazopanib, ABT869, OSI930, XL647, etc.							

*Biochemical IC₅₀ values were determined using slightly different methods between the studies and are not directly comparable.

Adapted from Lee and Heymach, Clin Lung Ca 2006

Wedge SR, *Cancer Res* 62:4645-55, 2002; Mendel DB, *Clin Cancer Res* 9:327-37, 2003; Wilhelm SM, *Cancer Res* 64:7099-109, 2004; Hess-Stumpo *ChemBioChem* 2005

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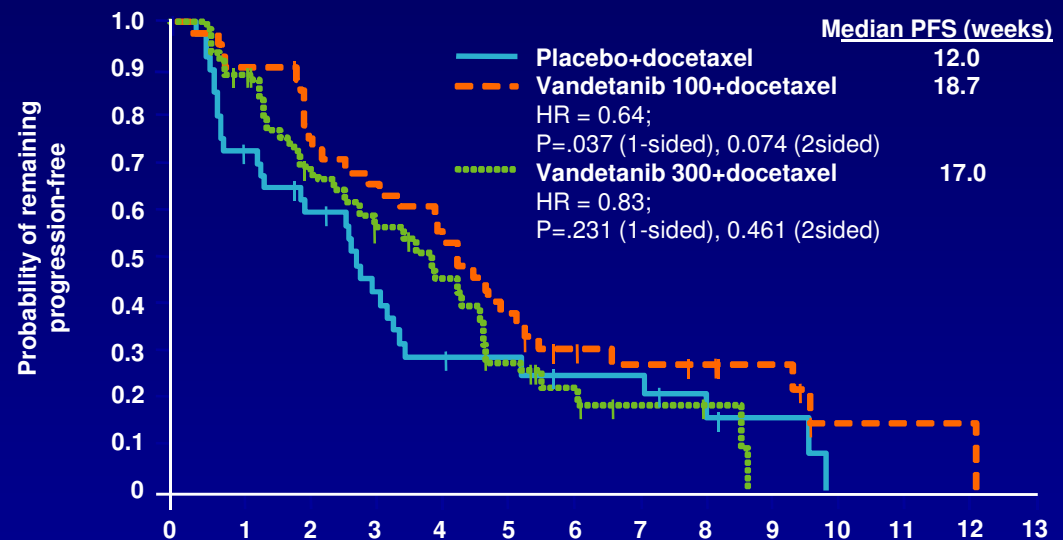
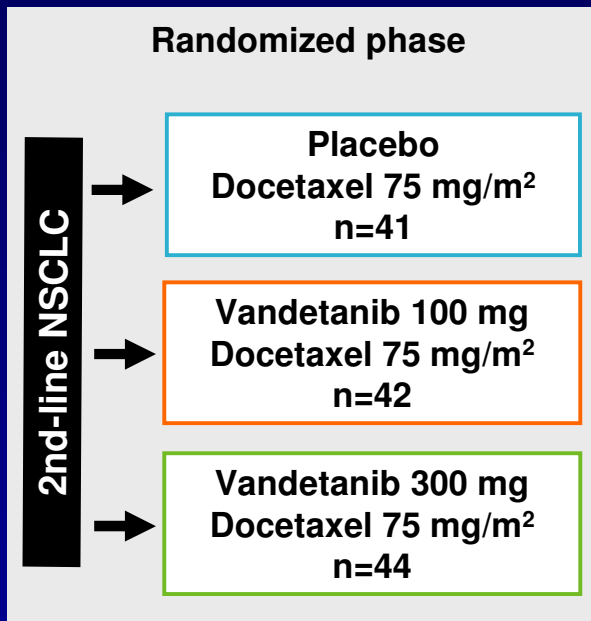
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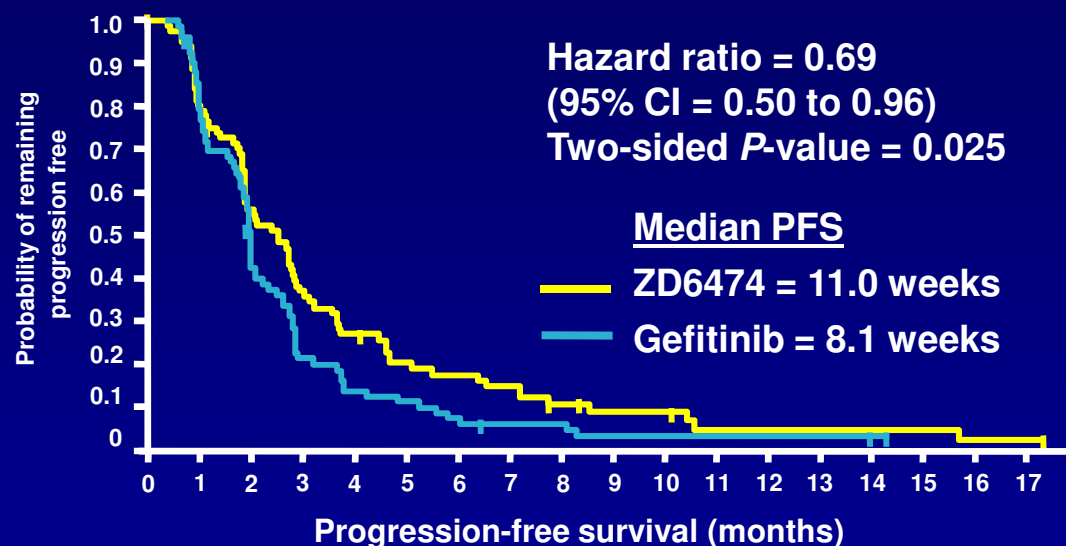
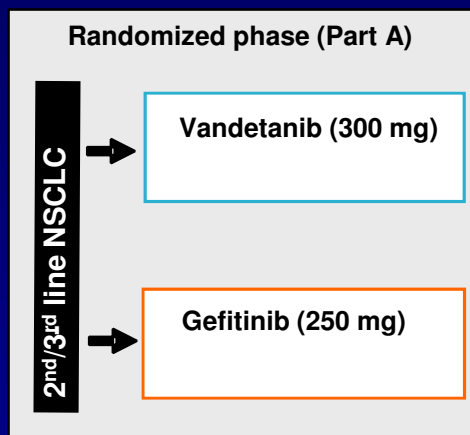
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Phase II, randomized study of vandetanib (ZD6474) with docetaxel (100 or 300 mg) for previously treated NSCLC (Trial 6)



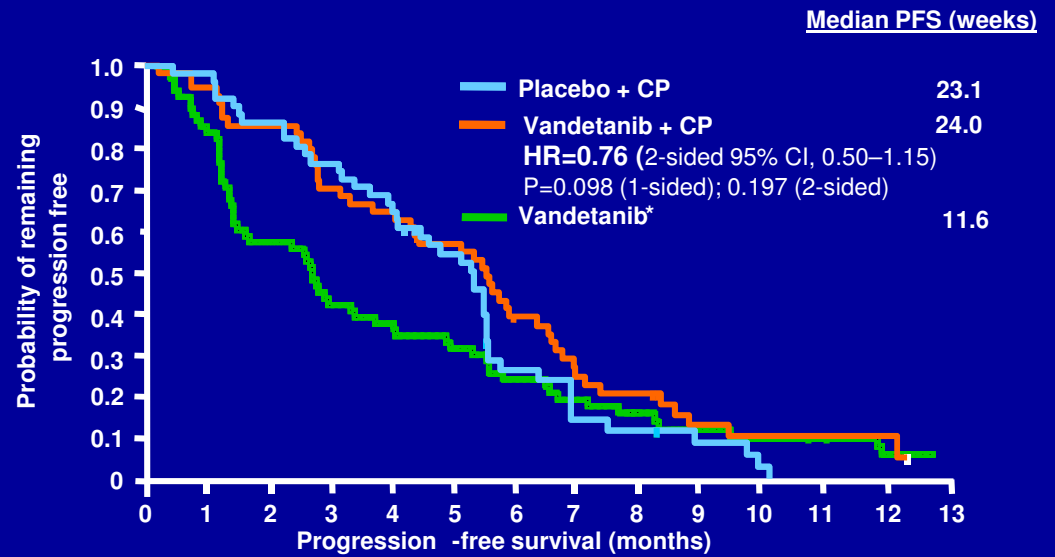
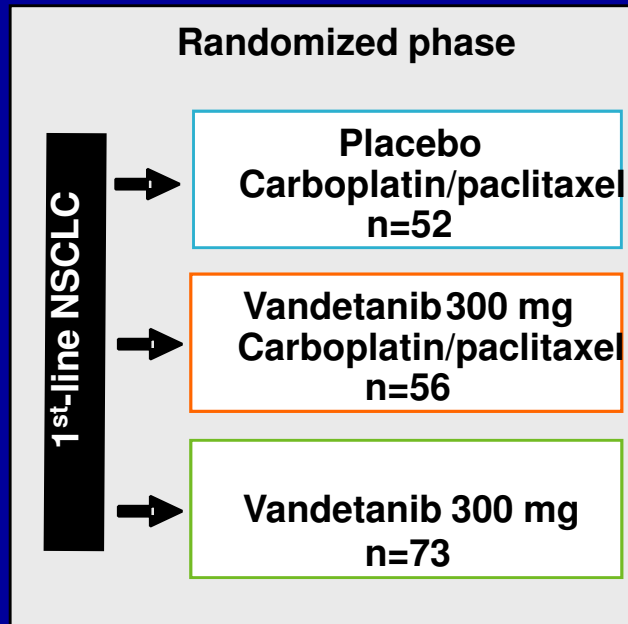
- Second/third line; 127 patients randomized
- Primary endpoint was met – vandetanib 100 mg + doc prolonged PFS vs Doc (HR = 0.64; 1-sided $P = 0.037$, 2-sided 0.074)

Vandetanib vs gefitinib as 2nd/3rd-line treatment for NSCLC (Trial 003)



- Second/third line; 168 patients randomized
- Primary endpoint was met – vandetanib prolonged PFS vs gefitinib (HR = 0.69, 95% CI: 0.50–0.96; 1-sided *P* = 0.013)

Phase II, randomized, partially-blinded, study of vandetanib (ZD6474) alone or with CP vs CP for first-line NSCLC (Trial 7)



Vandetanib for NSCLC

- Achieved primary endpoint of prolongation in PFS in three randomized phase II studies
 - vs erlotinib
 - + doc (100 or 300 mg) vs doc.
 - Trend towards greater benefit in 100 mg arm, females.
 - + CP vs CP (monotherapy inferior)
 - Trend towards greater benefit in females

PHASE III TRIALS OF ZD6474 (VANDETANIB) IN 2 ND + LINE NSCLC		
Study	Population	status
Monotherapy		
ZD6474 (300) vs erlotinib	Platinum-refractory	enrolling
ZD6474 (300) vs placebo	Previously treated with EGFR inhibitor	enrolling
Combination with chemotherapy		
ZD6474 (100)+ doc vs doc	Platinum-refractory	enrolling
ZD6474 (100) + pem vs pem	Platinum-refractory	Planned 2007

Randomized phase III studies of vandetanib for NSCLC: preliminary results

(press release Nov. 19, 2008)

- ZODIAC (V100+DOC vs DOC; N = 1391)
 - Achieved primary endpoint of prolongation in PFS; trend towards prolonged OS
- ZEAL (V100+PEM vs PEM; N = 534)
 - Prolonged PFS, did not achieve statistical endpoint
- ZEST (V300 vs erlotinib); N = 1240)
 - Did not meet the primary objective of prolonged PFS but showed equivalent efficacy for PFS and OS in a pre-planned non-inferiority analysis

Sorafenib in relapsed NSCLC: E2501

Schiller et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 8014)

- Randomized discontinuation design
- Patients with SD for 2 months on sorafenib randomized to sorafenib or placebo (step 2).
- PFS in step 2:
 - Sora: 3.6 months
 - Placebo: 1.9 months ($P = 0.01$)

Phase III trial of sorafenib, carboplatin and paclitaxel (ESCAPE)

- N = 900+ first line patients
- Stopped at planned interim analysis
- DMC concluded that it would not meet primary endpt of improved OS
- Higher mortality observed in patients with squamous cell carcinoma

Sunitinib Shows Single-agent Activity in Pretreated Patients with Recurrent NSCLC

	4/2 schedule ¹ n (%) (N = 63)	CD schedule ² n (%) (N = 47)
Best response, n (%)		
OBJECTIVE RESPONSE RATE*	7 (11.1)	1 (2.1)
	95% CI (4.6–21.6)	95% CI (0.1–11.3)
Partial response	7 (11.1)	1 (2.1)
Stable disease [†]	18 (28.6)	9 (19.1)
Progressive disease	23 (36.5)	24 (51.1)
Not evaluable [‡]	9 (14.3)	13 (27.7)
Median duration of response, weeks (range)	21.2 (4.4+–36.3+) [§]	24.4 [¶]

CD schedule followed the 4/2 schedule

*Rate of complete response + partial response

[†]Stable disease ≥8 weeks

[‡]Patients for whom scans were not evaluable or missing

[§]One patient with ongoing tumor response at 36.3 weeks

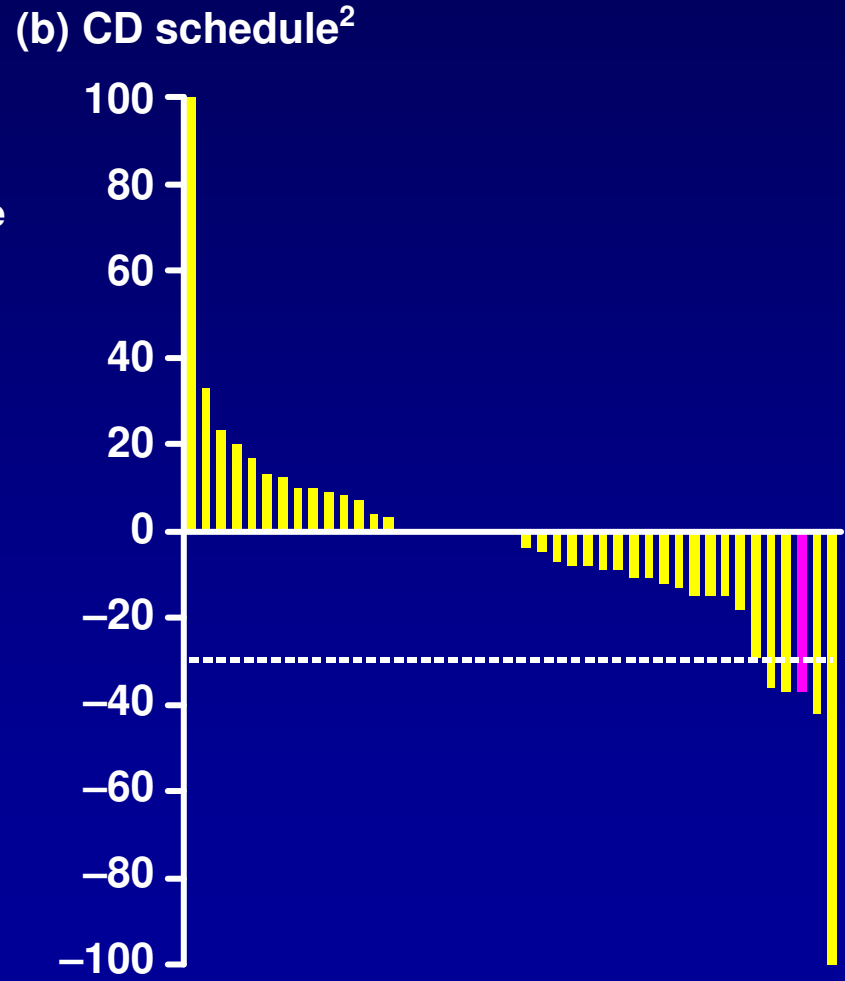
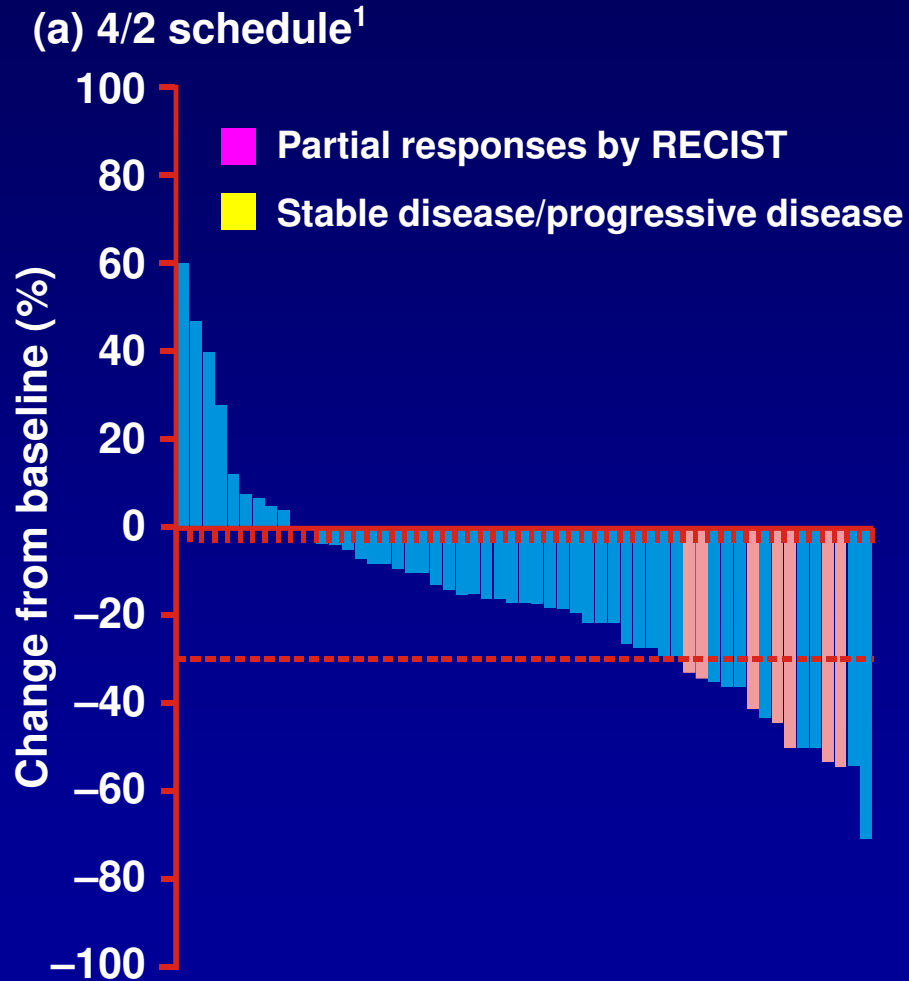
[¶]No data range (n=1 patient)

¹Socinski et al. *J Clin Oncol* 26:650-6, 2008

²Govindan et al. Poster presented at ECCO, Sept 2007

Slide courtesy of M. Socinsky

Previously treated NSCLC patients treated with sunitinib: reductions in tumor volume



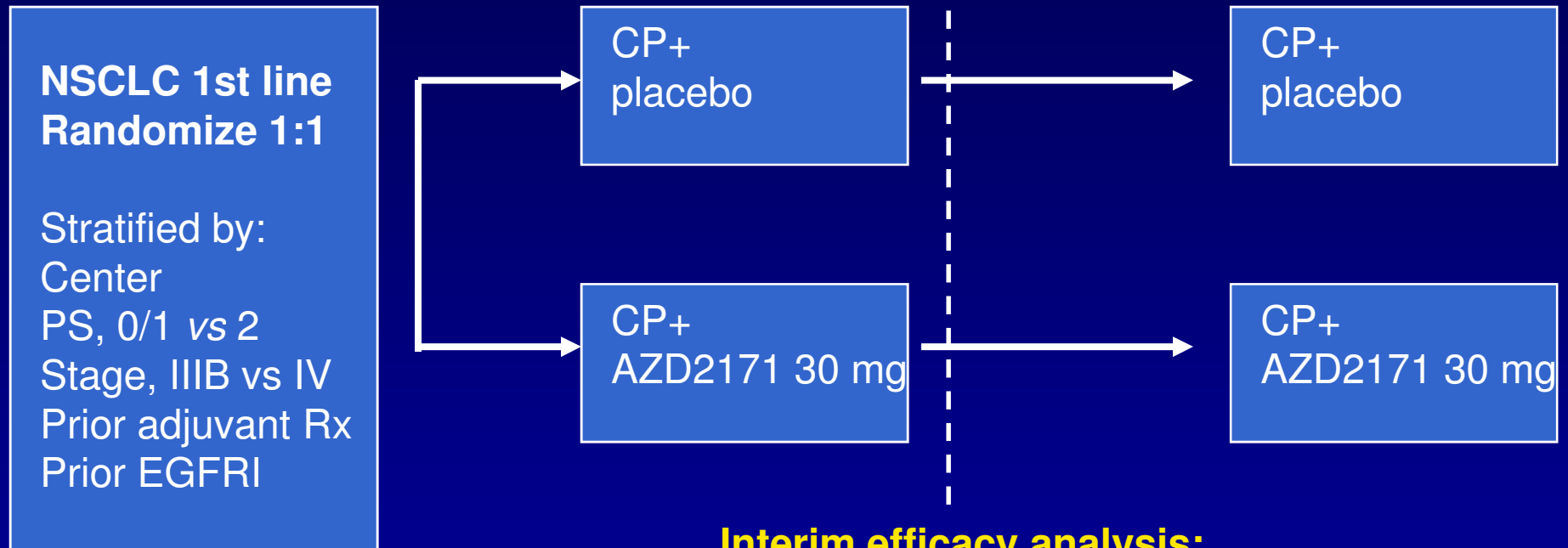
Slide courtesy of M. Socinski

¹Socinski et al. *J Clin Oncol* 26:650-6, 2008

²Govindan et al. Poster presented at ECCO, Sept 2007

Phase II/III study of AZD2171 in combination with carboplatin/paclitaxel for advanced NSCLC

(NCIC CTG BR.24, chairs Laurie and Goss)



**Interim efficacy analysis;
If HR < 1.33 for PFS, trial terminated***

*The study will not continue into phase III following efficacy and tolerability analysis by the DSMB. Although "evidence of clinical activity seen, there appeared to be an imbalance in toxicity..." (AZ press release, Feb 27, 2008)

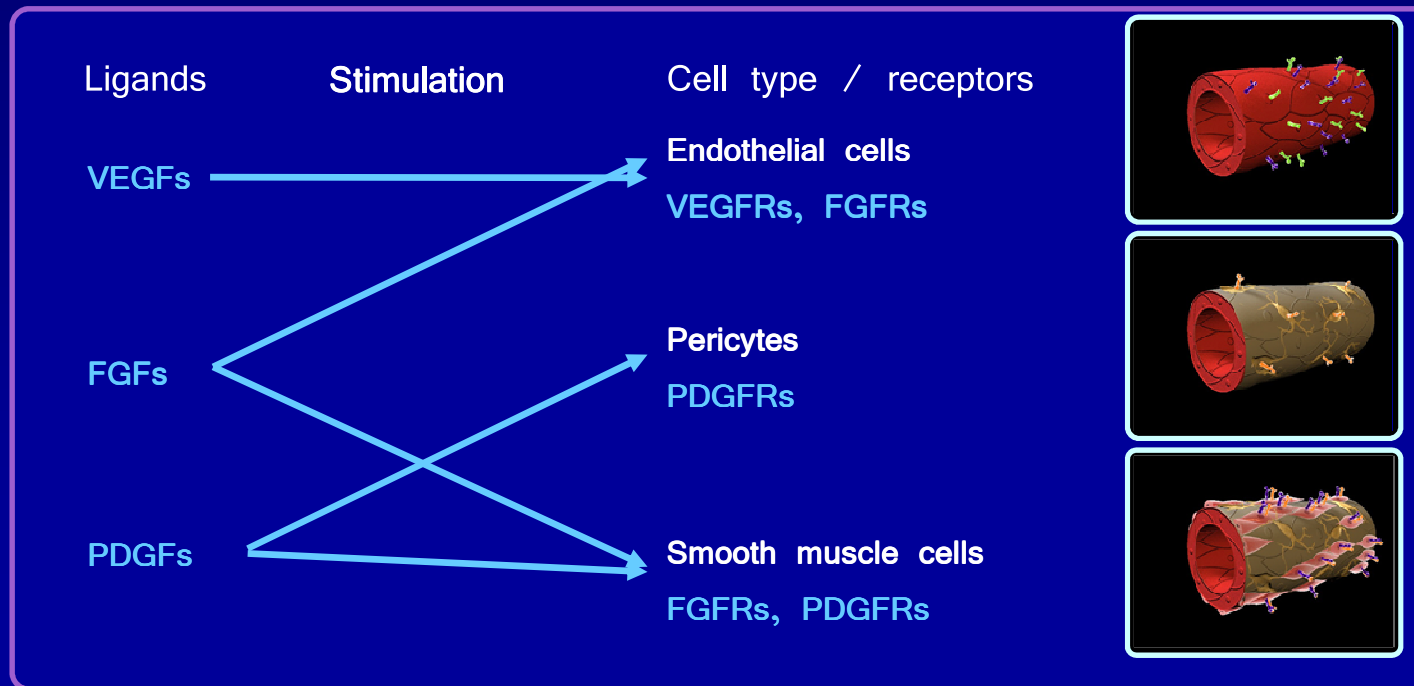
XL647 for NSCLC

- Inhibits VEGFR2, EGFR, Her2
 - Activity in tumors with EGFR T790M secondary mutations
- Patients with acquired resistance to EGFR TKIs (Miller et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 8028))
- Patients enriched for EGFR mutations (Rizvi et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 8053))
 - Antitumor activity observed in 28%, all 8 with EGFR mutations had shrinkage

BIBF 1120

VEGFR, PDGFR, FGFR inhibitor

	VEGFR 1 / 2 / 3	PDGFR α / β	FGFR 1 / 3	HUVEC / HSMEC proliferation
IC ₅₀ /EC ₅₀ (nM)	24 / 21 / 13	59 / 60	69 / 137	9 / 12



FGF receptor inhibitors

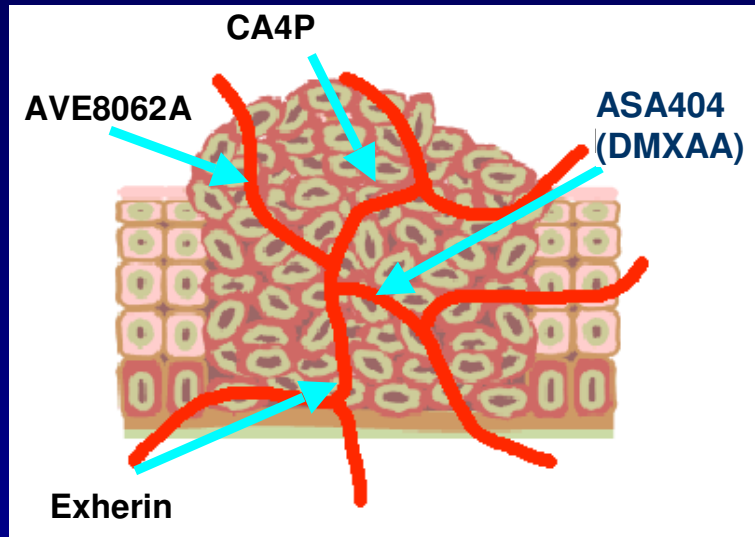
- BIBF1120
 - Under investigation as monotherapy and in combination with carbo/pac for NSCLC
- Brivanib
 - a dual inhibitor of VEGFR and FGFRs
 - Phase I reported (Platero et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 3506)
 - Higher tumor FGF2+ associated with improved clinical outcome with treatment

Other targets

- Angiopoietin/Tie-2 pathway
 - AMG386; angiopoietin1/2-neutralizing peptide-Fc fusion protein (peptibody)
 - Tie-1/2 TKIs and receptor-bodies in development
- Neuropilin/Sema
 - VEGF coreceptor, also involved in axonal guidance.

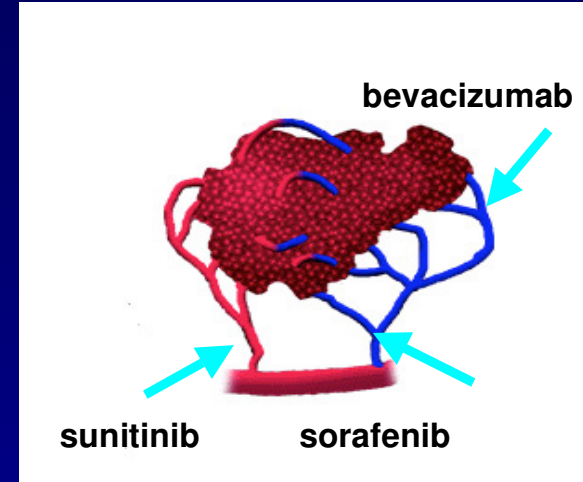
VDA vs Antiangiogenic Agents

VDA



- Large solid tumors—
established blood vessels
- Causes vessel occlusion
and necrosis
- Major effect on central part
of tumor

Antiangiogenic Agents*



- Smaller solid tumors—
new blood vessels
- Inhibits endothelial
proliferation and
migration
- Major effect on
peripheral part of tumor

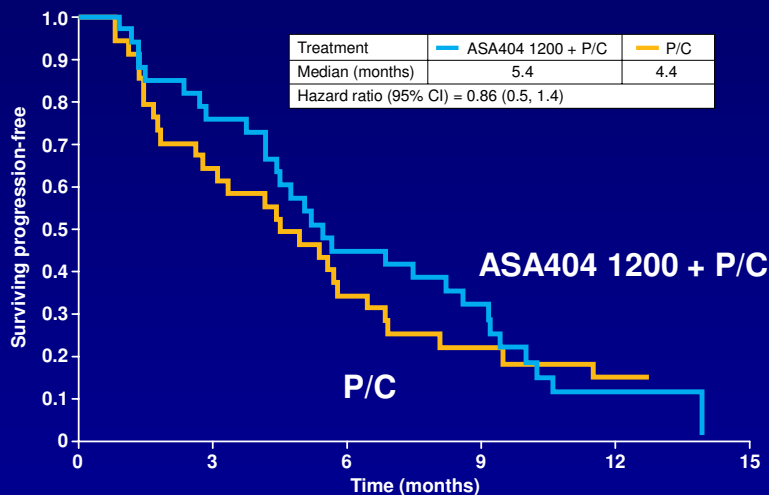
*Bevacizumab (Avastin®); sunitinib (Sutent®); sorafenib (Nexavar®).
Kelland. *Curr Cancer Ther Rev.* 2005;1:1-9. Slide courtesy of J. West.

ASA404 in NSCLC

- VDA with proposed dual mechanism of activity (direct anti-endothelial, TNF and NO effects)
- Encouraging activity with CP in first-line NSCLC
- No hemoptysis or other safety concerns observed in squam or non-squam pts (McKeage et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 8072))
 - 101 pts reported from phase II studies
- Phase III pending

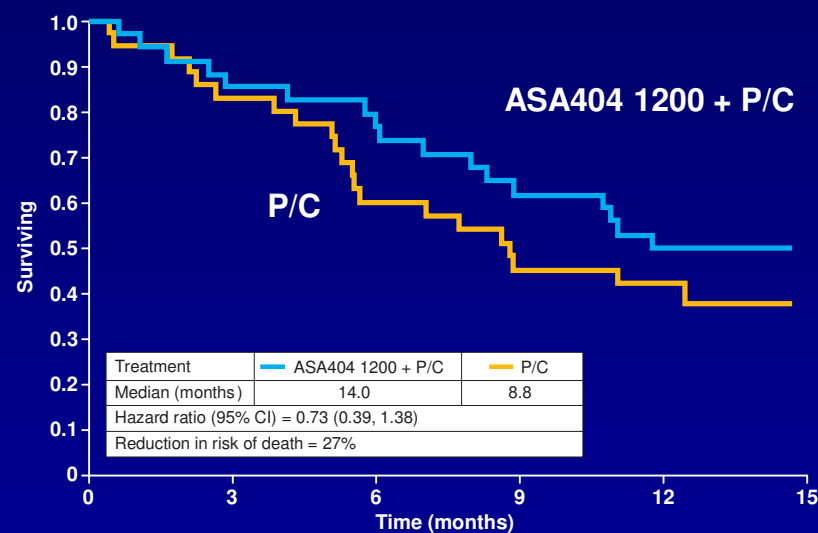
ASA404 + Paclitaxel/Carboplatin (P/C) in First-Line Therapy of Advanced NSCLC

Progression-Free Survival



Patients at risk		0	3	6	9	12	15
ASA404 1200 + P/C	34	24	14	9	3		
P/C	36	21	11	6	4		

Overall Survival



Patients at risk		0	3	6	9	12	15
ASA404 1200 + P/C	34	29	27	21	17	3	
P/C	36	29	21	15	14	1	

*Investigator determined.

TTP = time to tumor progression.

Von Pawel et al. EORTC-NCI-AACR 2006.

Thalidomide

- Phase III trials in NSCLC and SCLC show no survival improvement (Lee et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 8045))
- NSCLC trial: 722 patients, stage IIIb/IV
 - Gem/carbo \pm thalidomide
 - Median OS 8.4 m thalidomide arm vs 8.9 m placebo, HR 1.11
 - Increased thrombotic events (RR 1.68)
- SCLC trial
 - Etoposide/carboplatin \pm thalidomide
 - Median OS 10.2 m thalidomide vs 10.5 control, HR 1.10

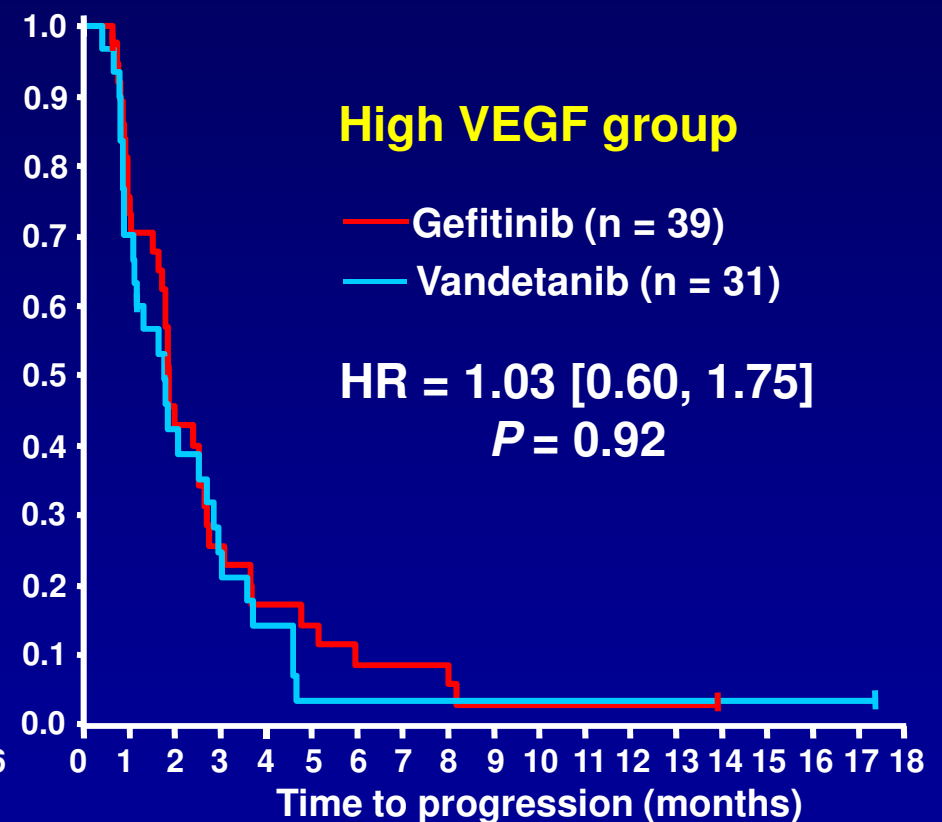
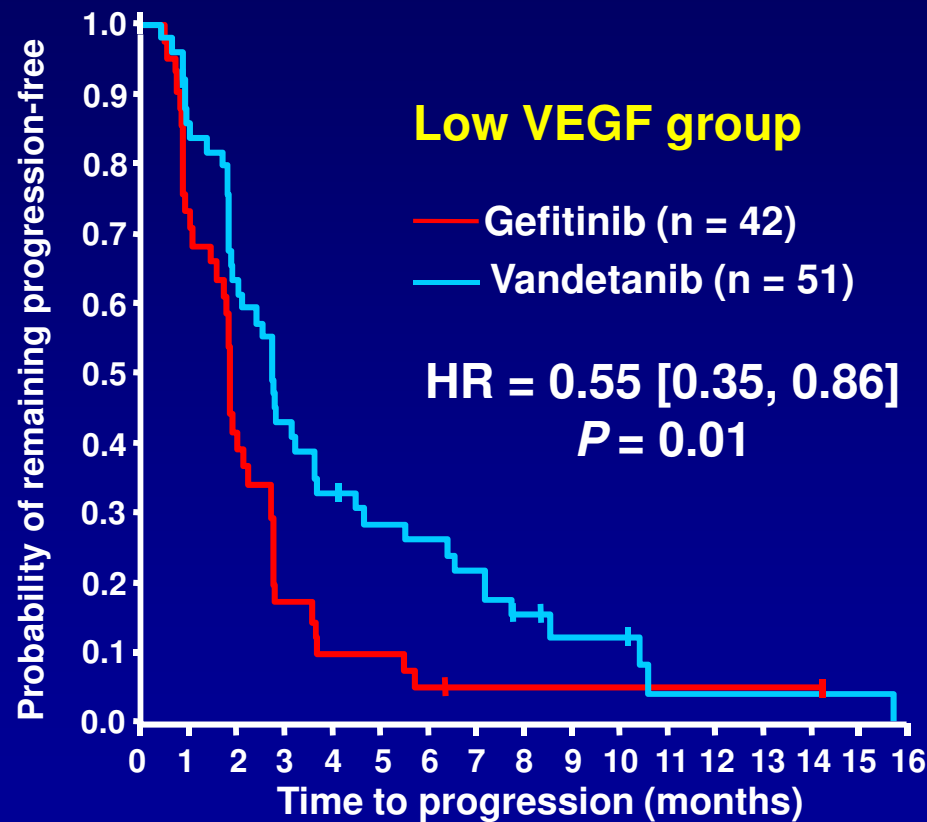
Biomarkers for VEGF pathway inhibitors

Blood-Based Biomarkers in E4599

- ELISA (plasma) for VEGF at baseline (n = 166) and for E-selectin, ICAM-1 and bFGF at baseline and week 7 (n = 150)
- Predictive markers:
 - High baseline VEGF levels associated with higher RR with addition of Bev to CP (test for treatment by factor interaction, $P = 0.04$)
 - Stability of E-selectin from baseline to week 7 predictive of OS benefit from addition of Bev to CP (treatment x factor $P = 0.05$)
 - Low baseline ICAM-1 predictive of PFS benefit from addition of Bev to CP (treatment x factor $P = 0.04$).

VEGF as a potential predictive marker for PFS benefit for vandetanib

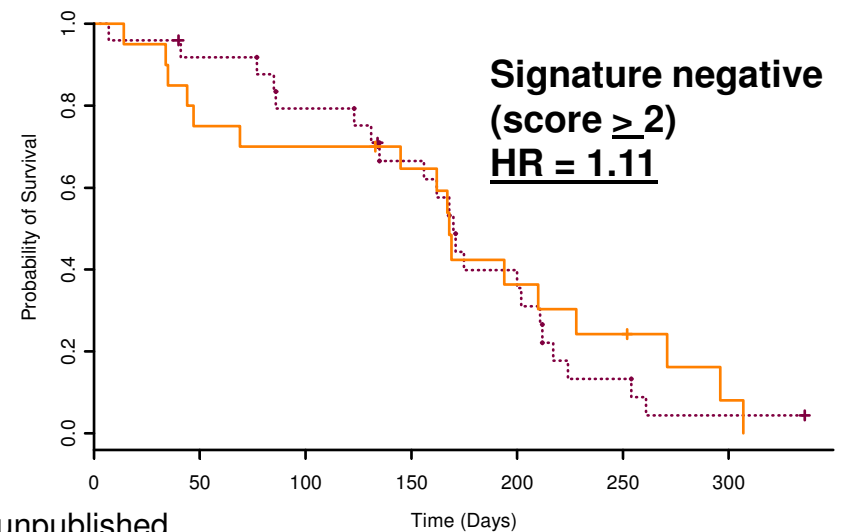
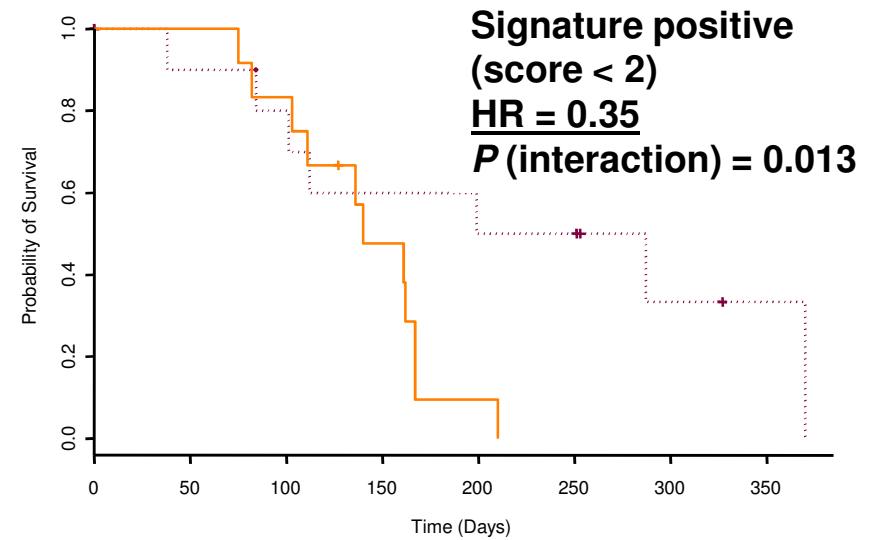
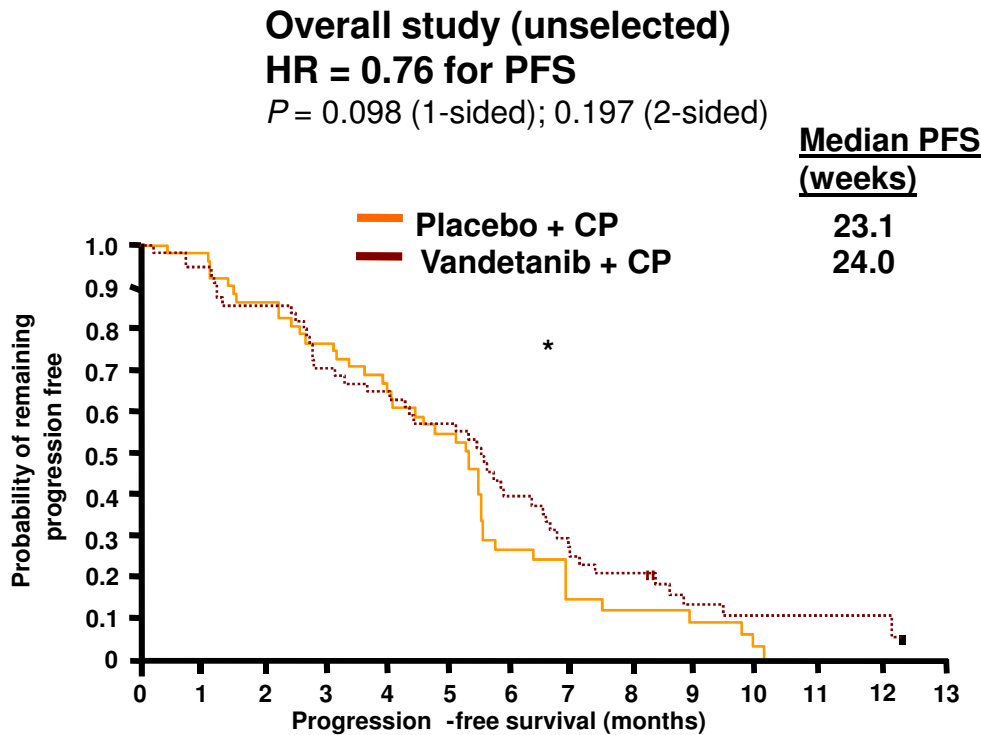
Vandetanib 300 mg vs gefitinib 250 mg (low and high VEGF)



Month:	0	2	4	6	8	10	12	14	15
At risk:	93	48	20	14	7	5	2	2	1

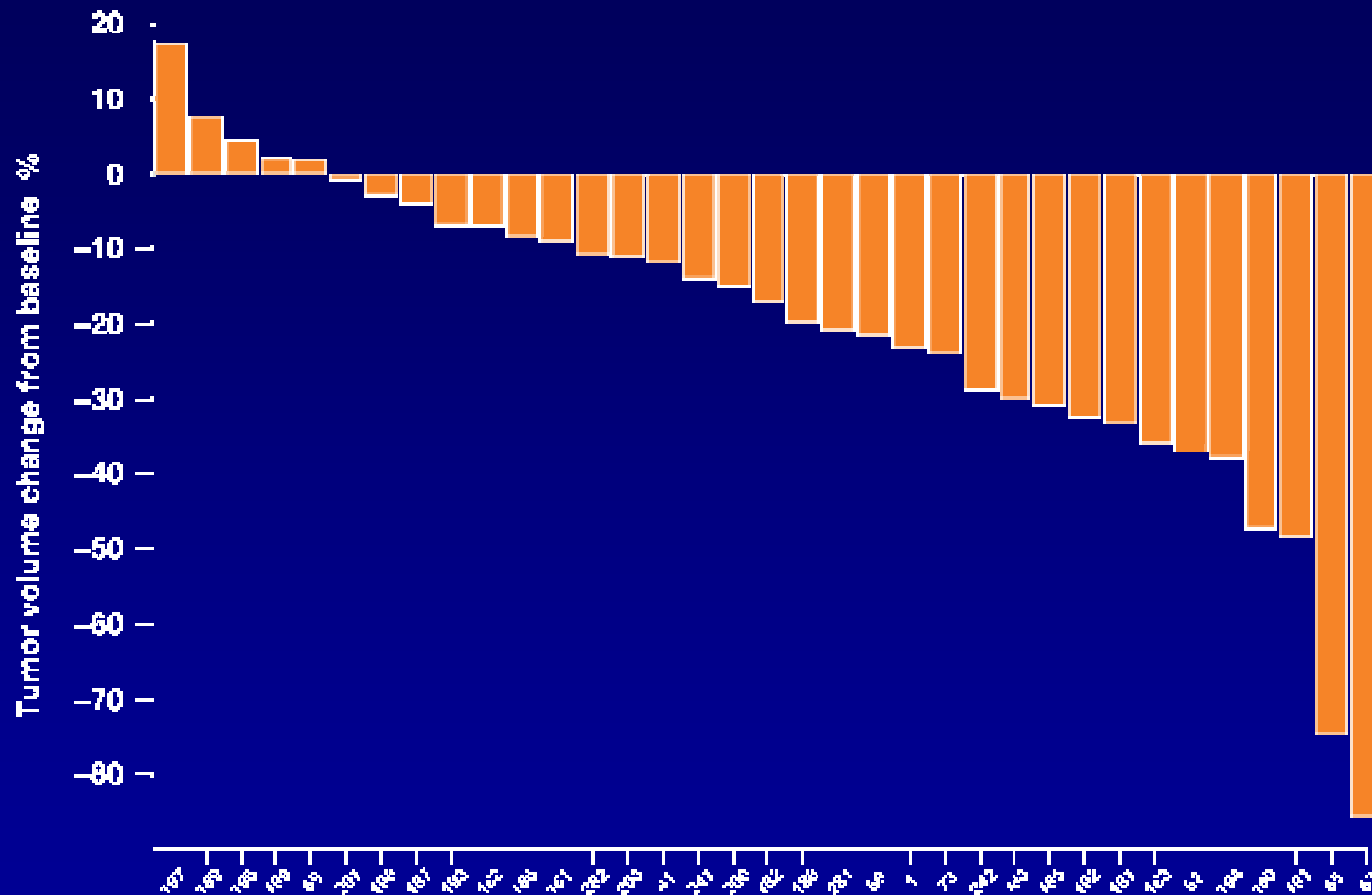
Month:	0	2	4	6	8	10	12	14	16
At risk:	70	28	10	4	4	2	2	1	1

Cytokine and angiogenic factor (CAF) signatures identify groups that have different PFS benefit from VCP compared to CP (5 marker signature)



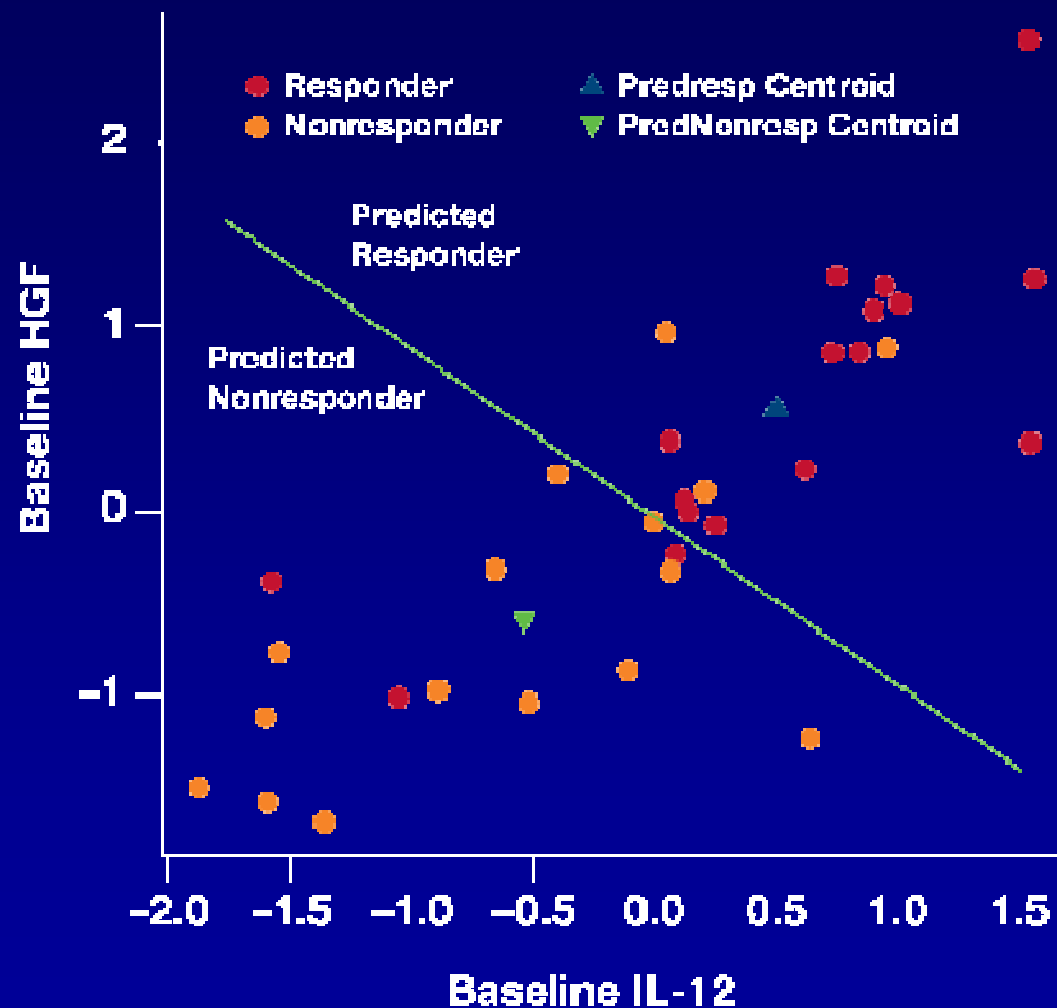
Pre-operative pazopanib in NSCLC

Altorki et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 7557)



- Thirty (85.7%) patients achieved a reduction in tumor volume after pazopanib treatment
 - Tumor volume changes ranged from -86% to +17%

Cytokine classifier for predicting response to pazopanib in NSCLC



Nikolinakos et al, *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 7568)

Summary

- Trials continue to yield mixed results, modest benefits although “batting average” higher than historical averages
- Many new promising TKIs in development
- Moving beyond VEGF blockade will require:
 - New targets being explored and rational combinations developed early
 - New types of agents (eg. MABs)

Phase III trials of VEGF pathway inhibitors in NSCLC: the scorecard

Trial	Setting	Treatment	Control	1° endpoint	Achieved 1°?	Other
ECOG4599	1 st	BV+CP	CP	OS	Yes	Improved PFS, ORR
AVAiL	1 st	BV+GC	GC	PFS	Yes	OS not sig improved
ATLAS	1 st (maint)	BV+E	BV	OS	Yes	N/A
ESCAPE	1 st	Sora+CP	CP	OS	No	Stopped at interim
BR24	1 st	AZD2171+CP	CP	OS	No	Stopped at interim (phase II part)

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BR24	1 st	AZD2171+CP	CP	OS	No	Stopped at interim (phase II part)
ZODIAC	2 nd +	Van+Doc	Doc	PFS	Yes	OS not sig improved
ZEAL	2 nd +	Van+Pem	Pem	PFS	No	OS not sig improved
ZEST	2 nd +	Van	E	PFS	No	Non-inferior to E
BeTa	2 nd +	BV+E	E	OS	No	PFS improved

Summary

- Trials continue to yield mixed results, modest benefits although “batting average” higher than historical averages
- Many new promising TKIs in development
- Moving beyond VEGF blockade will require:
 - New targets being explored and rational combinations developed early.
 - New types of agents e.g. VDAs
 - Biomarkers for identifying patients likely to respond or develop resistance.