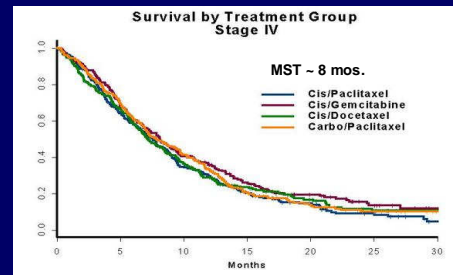


New Advances on Non-Small Cell Lung Cancer Management with Anti-VEGF and EGFR TKI

Alan Sandler, M.D.
Vanderbilt-Ingram Cancer Center

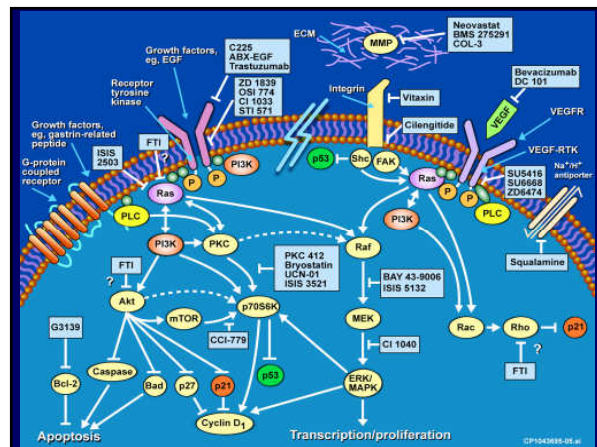
Have We Approached the Ceiling for Chemotherapy in Advanced NSCLC?



Schiller et al., NEJM 2002

Targeted Therapy in Oncology

- Goals
 - Identify **agents** that target tumor-specific molecules, thus sparing normal cells
 - Increased specificity leads to decreased toxicity
 - Identify ideal drug **target**
 - Drives tumor growth
 - Turns on key mechanisms of cancer progression
 - Reversible by inhibition with agent
 - Dispensable in normal cells
 - Target measurable in tumor tissue



Phase III Trial of Bevacizumab in Non-Squamous NSCLC: ECOG 4599 N=855 (eligible)

Eligibility:

- Non-squamous NSCLC
- No Hx of hemoptysis
- No CNS metastases

Stratification Variables:

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

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

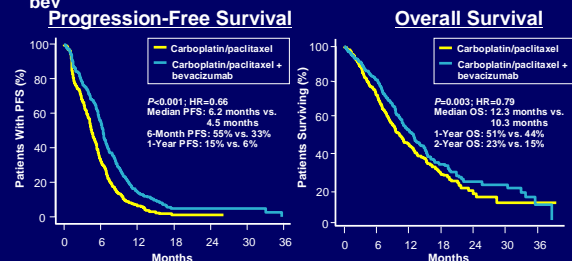
No crossover to Bevacizumab permitted

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

Sandler, et al New Engl J Med Dec 2006

Carboplatin/Paclitaxel +/- Bevacizumab: Key Clinical Outcomes

- Response rate: 15% for carbo/paclitaxel vs. 35% for chemo + bev



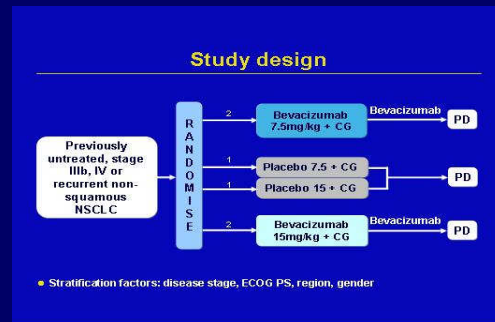
Sandler et al. N Engl J Med. 2006;355:2542

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%	

Sandler, et al New Engl J Med Dec 2006

Avail Trial Avastin in Lung Cancer



Manegold, C et al ASCO 2007

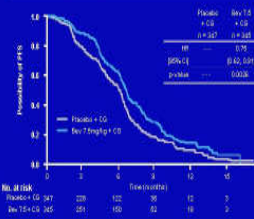
Tumor response and response duration (patients with measurable disease at baseline)

	Placebo + CG n = 324	Bevacizumab 7.5mg/kg + CG n = 323	Bevacizumab 15mg/kg + CG n = 332
Response rate (%)	20	34 p < 0.0001	30 p = 0.0017
Duration of response			
Median (months)	4.7	6.1	6.1
[95% CI]	[4.6, 5.6]	[5.1, 7.0]	[5.0, 6.6]

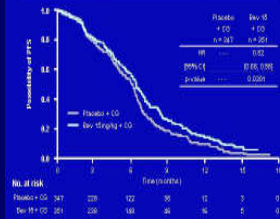
Manegold, C et al ASCO 2007

Results

PFS: primary analysis (ITT) of bevacizumab 7.5mg/kg vs pooled placebo



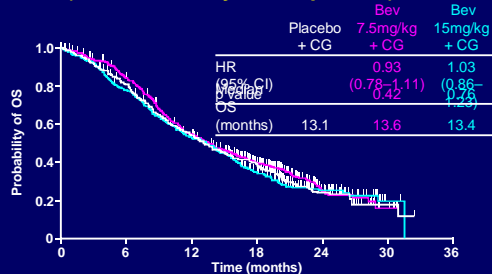
PFS: primary analysis (ITT) of bevacizumab 15mg/kg vs pooled placebo



*Toxicity was similar to that of E4599

Manegold, C et al ASCO 2007

AVAIL: Overall Survival (secondary endpoint)



No. at risk
Placebo + CG 347 272 182 100 36 3 0
Bev 7.5mg/kg + CG 345 268 182 107 34 3 0
Bev 15mg/kg + CG 351 264 177 92 33 2 0
*ITT (intent-to-treat) population

Future Directions

- Bevacizumab in “high-risk” patients – trials are ongoing
 - Squamous cell histology
 - Previously treated brain metastases
- Bevacizumab in earlier stage disease
 - Stage III - with chemotherapy/radiation
 - Adjuvant therapy – E1505
- Combination with other targeted agents
 - Bevacizumab plus erlotinib

E1505: Phase III Adjuvant Chemotherapy ± Bevacizumab

Principal investigator: Heather Wakelee

Eligibility

- Resected IB (> 4 cm) –IIIA
 - ≥ lobectomy
 - No previous chemotherapy
 - No planned XRT
 - No CVA/TIA
 - No ATE in 12 months
- N = 1500

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Chemotherapy* x 4 cycles

Chemotherapy* x 4 cycles + bevacizumab x 1 year

*Specified regimens

- Cisplatin and docetaxel
- Cisplatin and vinorelbine
- Cisplatin and gemcitabine

Primary endpoint: overall survival

Secondary endpoints: disease-free survival, safety [bleeding and arterial thromboembolic events (ATEs)]

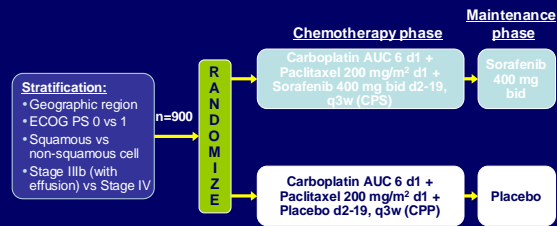
Oral VEGF-TKI's

Agent	Target/MOA	Company
ZD6474	VEGFR-2, EGFR	AstraZeneca
Sunitinib	VEGFR-1/2, PDGFR, Kit, FLT-3	Sugen/Pfizer Inc
Sorafenib	VEGFR-2/3, FLT-3, Kit	Onyx/Bayer
Vatalanib	VEGFR-1/2/3, PDGFR, Kit	Novartis
AG013736	VEGFR-1/2, PDGFR, Kit	Pfizer Inc
AMG 706	VEGFR, PDGFR, Kit, Ret	Amgen
AEE-788	VEGFR, EGFR, erb	Novartis

Toxicity of Small Molecular Agents

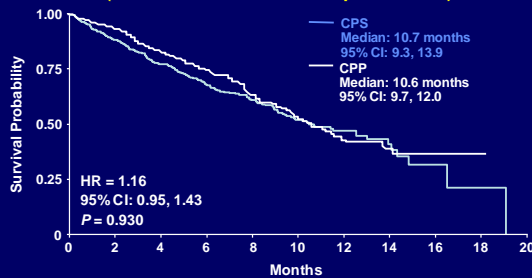
1. All these agents seem to produce either cavitation and/or bleeding.
 - Clearly a class effect
 - Seems limited to primary lung cancer
 - More studies are needed to better assess risks and potential therapeutic interventions
2. Hypertension.
 - Due to INOS effect
 - Usually treatable with medications
3. Other unique toxicities (especially with the multitargeted agents).
 - Rash
 - Hand-Foot Syndrome
 - Fatigue
 - Slightly Increased Neutropenia (effect of VEGF on lymphoid cells)

ESCAPE Trial Study Design



Scagliotti, et al ASCO 2008

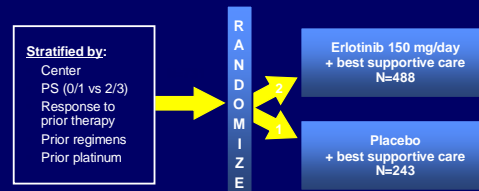
Overall Survival (Intent-to-Treat Population)



Patients at Risk

Months	0	2	4	6	8	10	12	14	16	18	20
CPS	464	406	268	155	86	47	16	7	1	1	
CPP	462	426	377	300	157	83	34	13	5	1	

BR.21: Treatment Schema



- Erlotinib should be taken at least 1 hour before or 2 hours after food
- Primary endpoint: Improvement in overall survival of 33%
- Secondary endpoints include PFS, ORR, duration of response, QOL, and safety

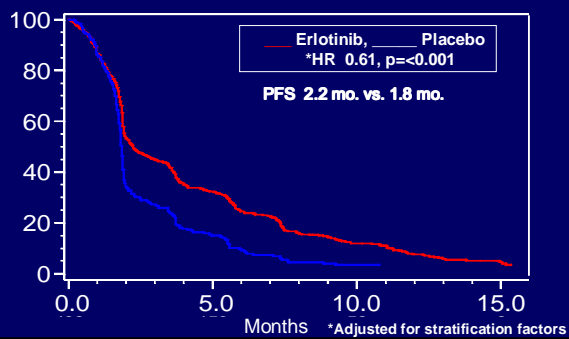
BR.21 Patient Characteristics

Characteristic	Tarceva N = 488	Placebo N = 243
Median age (years)	62	59
% Female	35	34
% PS 0:1	13 : 52	14 : 54
% PS 2:3	26 : 9	23 : 9
% Adenocarcinoma	50	49
% Prior regimens 1:2:3	50 : 49 : 1	50 : 49 : 1
% Response to prior chemo		
CR/PR	40	40
SD	39	39
PD	21	21
% Measurable disease	88	87

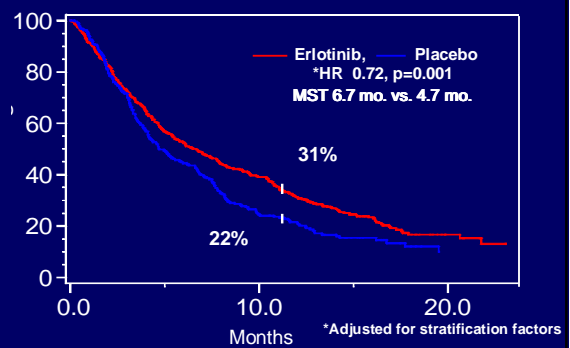
NCIC CTG BR.21: Best Response (N=638)

	Erlotinib (N=427)	Placebo (N=211)
Complete response	1%	<1%
Partial response	8%	<1%
Stable disease	35%	27%
Progression	38%	57%
Inevaluable / Not assessed	18%	15%
Response duration	7.9 mo (95% CI 5.7-10.6)	3.7 mo (95% CI 2.9-4.4)

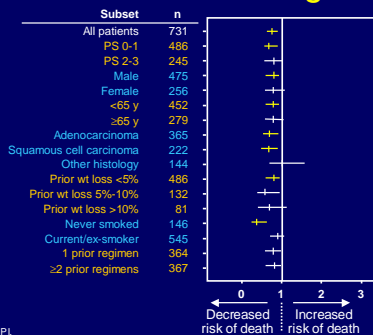
BR.21 Progression Free Survival



BR.21 Overall Survival



BR.21 Exploratory Study: Survival Across Subgroups

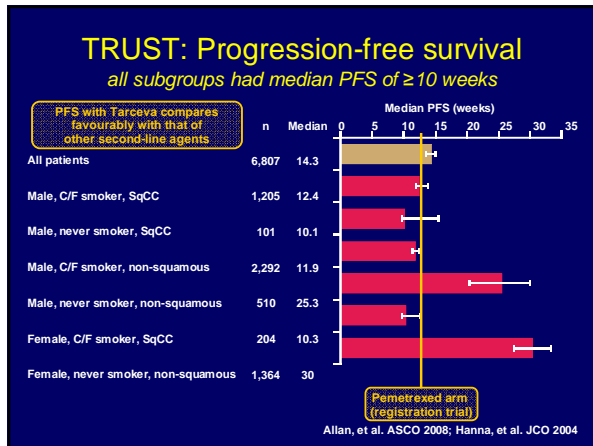


Tarceva (erlotinib) PL

TRUST: Phase IV trial of Tarceva in 'real-life' clinical practice

Previously treated (or unsuitable to receive chemotherapy/radiotherapy) stage IIIB/IV NSCLC (n≈7,000) → Tarceva 150mg/day

- Phase IV, open-label, non-randomised, multicentre study
- Tarceva administered until disease progression or unacceptable levels of toxicity



Phase III Trial Results

	RR (%)	TTP (mo.)	MST (mo.)
Docetaxel	9.1/7.6	3.5	#7.9/8.0
Pemetrexed	8.8	3.4	#8.3
Gefitinib	8.2/9.1	NA	*5.6/7.6
Erlotinib	9.0	2.2	*6.7

#included ~12% PS-2 patients
*included PS-3 patients

Hanna et al. *J Clin Oncol*. 2004;22:1589-1597; Shepherd et al. *N Engl J Med*. 2005;353:123-132.
Thatcher et al. *Lancet*. 2005;368:1527-1537.
Douillard et al. 12th World Conference on Lung Cancer. Abstract #PRS-02

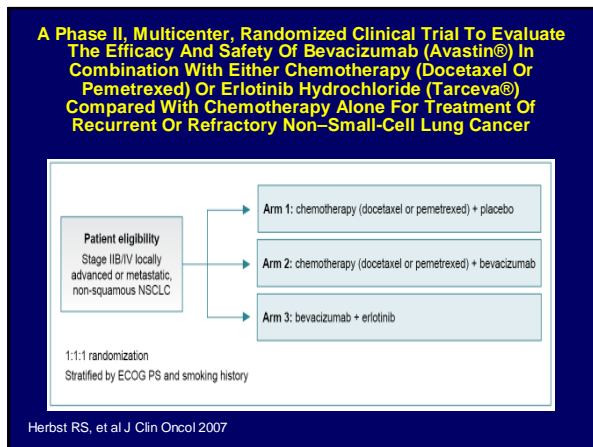
Multi-Targeted Approaches

Multiple agents
versus
Single agents with multiple targets

MDACC/Vanderbilt Trial of Erlotinib + Bevacizumab in Refractory, Advanced NSCLC

Endpoints: Safety, dose, tissue endpoints for BOTH agents
Goal: Ultimately combine with chemotherapy in 1st line rx

Herbst R, et al. *J Clin Oncol* 2005



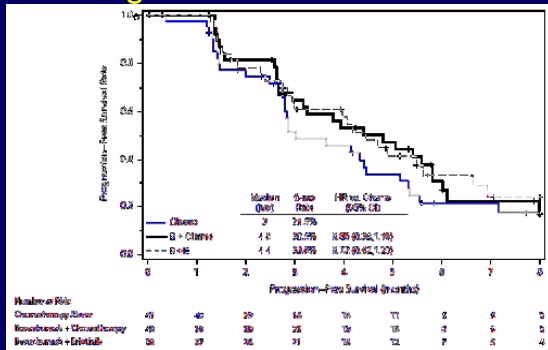
Efficacy and Safety Summary

	Chemotherapy Alone (n=41)	Bevacizumab + Chemo (n=40)	Bevacizumab + Erlotinib (n=39)
PFS			
Median, mo	3.0	4.8	4.4
Adjusted Hazard Ratio* (95% CI)	NA	0.66 (0.39, 1.16)	0.72 (0.42, 1.23)
Overall Survival			
6-month rate, %	62.4	72.1	79.3
Response Rate, n (%)			
CR/PR	5 (12.2)	5 (12.5)	7 (17.9)
CR/PR/SD	18 (39.0)	21 (52.5)	20 (51.3)
*Adjusted by randomization stratification factors (ECOG PS, smoking history)			
	Chemotherapy Alone (n=41)	Bevacizumab + Chemo (n=40)	Bevacizumab + Erlotinib (n=39)
Drug discontinuation due to AE, n (%)	10 (24)	10 (25)	4 (10)
SAEs, n (%)	22 (54)	16 (40)	13 (33)
Grade 3 Drug-related AEs	2 (5)	3 (8)	1 (3)
Pulmonary Hemorrhage (grade 3-5)	0	2 (5)	1 (3)

*Proteomics pending

Herbst RS, et al *J Clin Oncol* 2007

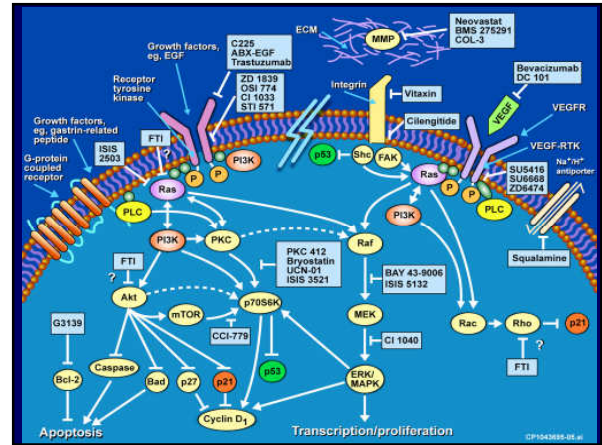
Progression-Free Survival



Herbst RS, et al J Clin Oncol 2007

Summary

- The monoclonal antibody, bevacizumab, most advanced in clinical development
- Paclitaxel/carboplatin + bevacizumab considered ECOG reference regimen based on ECOG 4599
- Bevacizumab being investigated in other settings
 - Early stage disease (adjuvant and neoadjuvant)
 - Brain metastases, squamous cell histology
 - Safety being established in other settings and in combination with other regimens, including other targeted agents
- The multi-targeted VEGF inhibitors appear promising in phase II trials and are being studied in phase III trials but with one negative trial with sorafenib



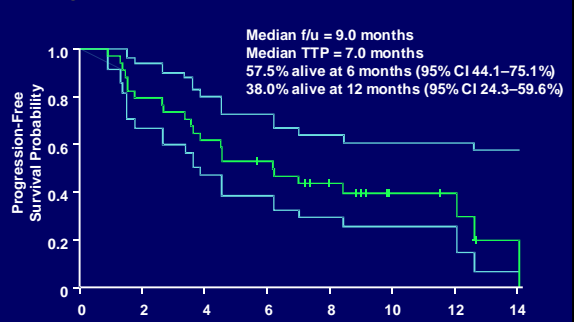
Overall Antitumor Activity Ph I/II*

Parameter	No. of Patients (%)
Complete Response	0 (0)
Partial Response	8 (20)
Stable Disease	26 (65)
Progressive Disease	6 (15)

*RECIST criteria (n = 40)

Herbst R, et al. J Clin Oncol 2005

Progression-Free Survival: Phase II*



f/u, follow up; TTP, time to progression
Herbst RS et al. J Clin Oncol. 2005;23:2544.

