Strategies to Complement VEGF Targeted Therapy

Targeted Anti-Cancer Therapeutics Meeting, Paris March 2011

Amy Peterson, MD
Associate Group Medical Director
Early Clinical Development, Genentech

Disclosures:

I am a full time employee of Genentech

Bevacizumab is an important treatment option in multiple indications

Indication	FL	SL	Phase III Studies
CRC	✪	✪	Positive: AVF2107, N016966, E3200
MBC	✪	★	Positive: E2100, AVADO, Ribbon-1, Ribbon-2 Negative: 2119
Lung	✪		Positive: E4599, AVAiL (PFS) Pendng: Pointbreak, AVAPERL Negative: AVAiL-on OS, BeTa (2L)
RCC†	✪		Positive: CALGB 90206, AVOREN
GBM	⊙	✪	Positive: PhII Av v Av/CPT-11 Pending: AVAglio (2013)
Ovarian	★	★	Positive: GOG218, ICON7, OCEANS

†RCC label in US does not specify line of Rx

Key	
✪	US Approval
★	Positive P3 data
⊙	P3 results pending

BUT…
there is room for improvement

Combination Targeted Therapy With Sorafenib and Bevacizumab Results in Enhanced Toxicity and Antitumor Activity

Nilofer S. Azad, Edwin M. Posadas, Virginia E. Kwitkowski, Seth M. Steinberg, Lokesh Jain, Christina M. Annunziata, Lori Minasian, Gisele Sarosy, Herbert L. Kotz, Ahalya Premkumar, Liang Cao, Deborah McNally, Catherine Chow, Helen X. Chen, John J. Wright, William D. Figg, and Elise C. Kohn

Challenges and Pitfalls of Combining Targeted Agents in Phase I Studies

Stephen A. Cannistra, *Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA*

A Phase I Study of Sunitinib plus Bevacizumab in Advanced Solid Tumors

[1] Matthew M. Cooney,[2] Paul Elson,[1] Allison Tyler,[1] Kristi Beatty,[2]
,[1] R.M. Bukowski,[1] G. Thomas Budd,[1] Pierre Triozzi,[1]
len X. Chen,[3] Afshin Dowlati,[2] and Robert Dreicer[1]

Phase I Trial of Bevacizumab Plus Escalated Doses of Sunitinib in Patients With Metastatic Renal Cell Carcinoma

Darren R. Feldman, Michael S. Baum, Michelle S. Ginsberg, Hani Hassoun, Carlos D. Flombaum, Susanne Velasco, Patricia Fischer, Ellen Ronnen, Nicole Ishill, Sujata Patil, and Robert J. Motzer

Or is there?

From Theoretical Synergy to Clinical Supra-Additive Toxicity

VOLUME 27 · NUMBER 9 · MARCH 20 2009
JOURNAL OF CLINICAL ONCOLOGY

Jean-Charles Soria and Christophe Massard, *Université Paris XI, Service des Innovations Thérapeutiques Précoces,*

Table 1. Efficacy and Toxicity in Selected Trials Testing Bevacizumab, Sunitinib, and Sorafenib in RCC

Result	Sunitinib	Sorafenib	BVZ	BVZ	Sunitinib + BVZ	Sorafenib + BVZ	Sutent + BVZ
First author	Motzer et al[2]	Escudier et al[3]	Escudier et al[4]	Rini[5]	Feldman[7]	Azad[23]	Cooney[24]
Trial phase	III	III	III	III	I	I	I
No. of patients	750	903	649	732	26	39	38
Experimental arms	Sunitinib *v* IFN	Sorafenib *v* placebo	BVZ + IFN *v* IFN	BVZ + IFN *v* IFN	Sutent + BVZ	Sorafenib + BVZ	Sutent + BVZ
Line of therapy	First line	Post-cytokine	First line	First line	First line for 88% of patients	Any	Any
RR, %	31% *v* 6%	10% *v* 2%	31% *v* 13%	25 *v* 13%	52%	18%	25%
CR, %	0% *v* 0%	< 1% *v* 0%	1% *v* 2%	NA	4%	0%	0%
PR, %	31% *v* 6%	10% *v* 2%	30% *v* 11%	NA	48%	18%	25%
SD, %	48% *v* 49%	74% *v* 53%	46 *v* 50%	NA	36%	41%	46%
PFS, months	11 *v* 5	5,5 *v* 2,8	10,2 *v* 5,4	8,5 *v* 5,2		NA	NA
Grade 3/4 AE							
Hypertension	8 *v* 1%	4% *v* <1%	3% *v* <1%	10 *v* 0%	60%	33%	25%
Proteinuria	NA	NA	7 *v* 0%	15 *v* 1%	36%	5%	NA
Thrombocytopenia	8 *v* 0%	NA	2 *v* <1%	2 *v* 1%	24%	3%	8%
TMA	NA	NA	NA	NA	8%	NA	NA
RCC patients	100%	100%	100%	100%	100%	7%	16%

Abbreviations: RCC, renal cell carcinoma; BVZ, bevacizumab; IFN, interferon; RR, response rate; CR, complete response; PR, partial response; SD, stable disease; PFS, progression-free survival; NA, not available; AE, adverse event; TMA, thrombotic microangiopathy.

Evolving clinical landscape provides challenge in developing bevacizumab based combinations

- The importance of **dose duration** becoming more clear (GOG-218, ICON7)
  - Primary EP of PFS met with 1 year Maintenance in 1L Ovarian CA

- Is there a rationale for **treatment beyond "progression"**?
  - Does RECIST PD means resistance to vascular inhibition?
  - BRITE and ARIES registry data supportive of treatment beyond progression
    - This is not a first—5FU in CRC, Platinum-sensitive OvCa, hormonal therapy in BrCa in ProsCa
  - ML18147is a Phase III randomized study in CRC testing bev beyond PD (BBP)
    - If positive, how will change the way we use RECIST
    - Ir RECIST is used for immuno-modulatory agents,

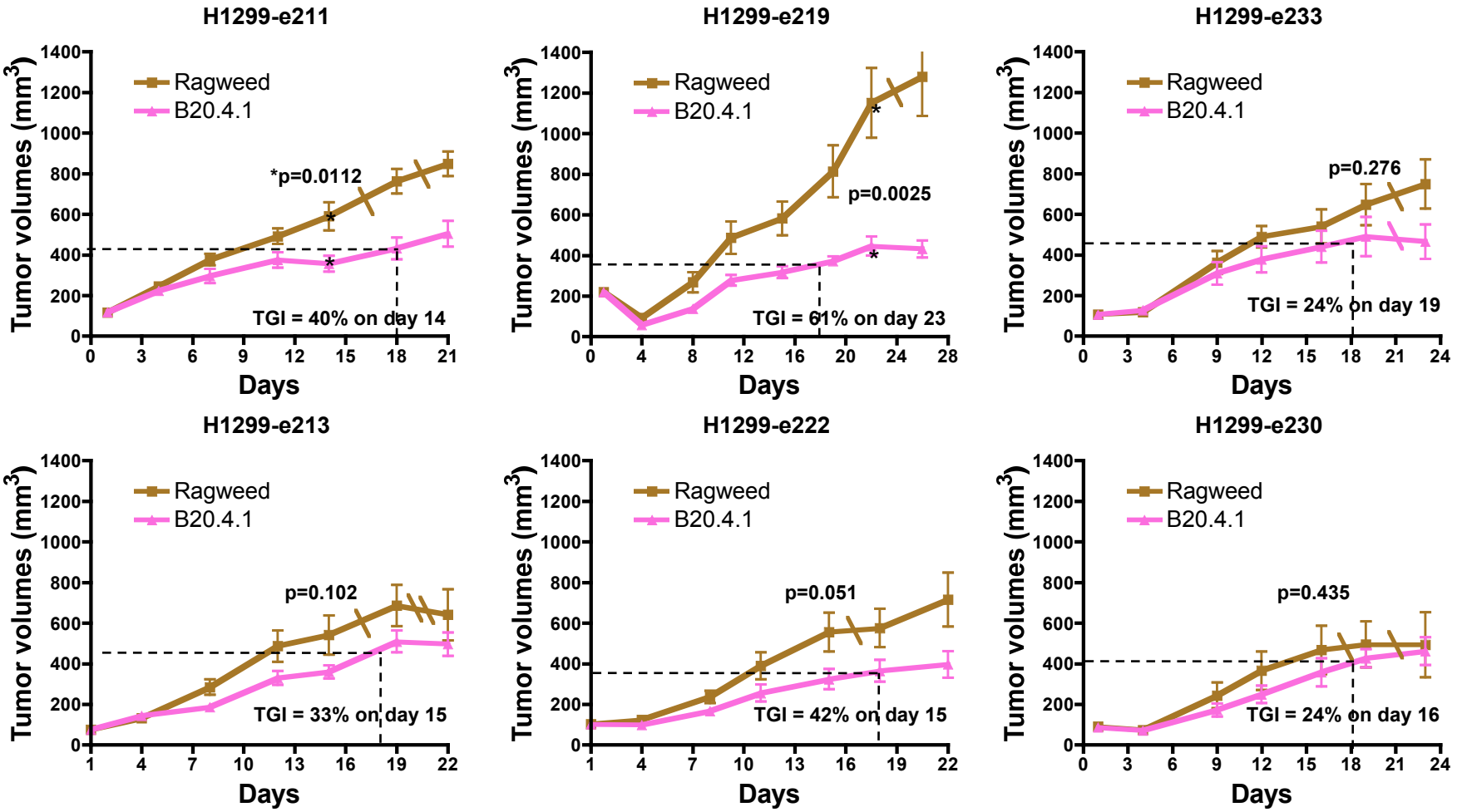
- Indications suitable for evaluating bevacizumab based combos will shift
  - Ovarian 1L and/or 2L (OCEANS), GBM 1L or 2L, MBC (1L, 2L, at all?)

- Identification of a predictive diagnostic for bevacizumab will impact the way we analyze bev-based combos
  - Will the combination work better in patients who derive the most benefit from bev? Or
  - In those who derive the least benefit?

Indication selection and development planning of molecules targeting anti-angiogenesis must take these changes into account

‘Reproducibility’ of VEGF inhibition in a single xenograft model highlights preclinical hurdles

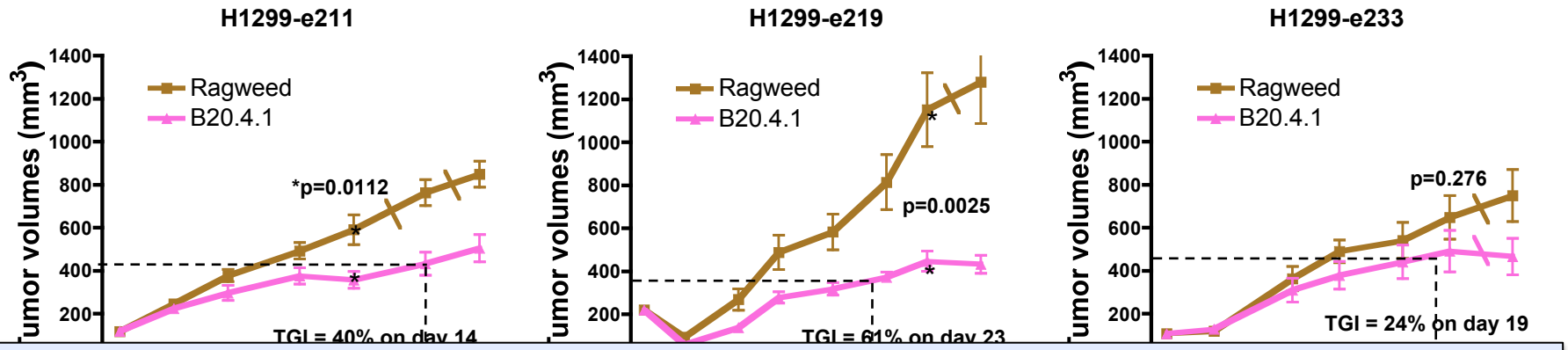
TGI (p<0.05) in 2 of 6 despite fairly consistent pattern with B20 in all



 Ragweed (control MAb) or B20.4.1 dosed at 5mg/kg/2xweek. *New Molecular Entities

‘Reproducibility’ of VEGF inhibition in a single xenograft model highlights preclinical hurdles

TGI (p<0.05) in 2 of 6 despite fairly consistent pattern with B20 in all



Successful development of molecules cannot focus singularly on preclinical efficacy studies.
Rather must
focus on Biology, Mechanism of Action (MOA) and Pharmacodynamics (PD) to inform clinical development

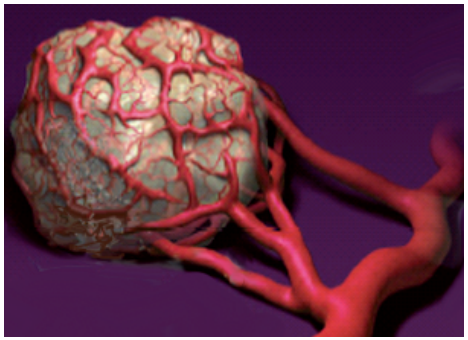
Weilan Ye Ragweed (control MAb) or B20.4.1 dosed at 5mg/kg/2xweek.

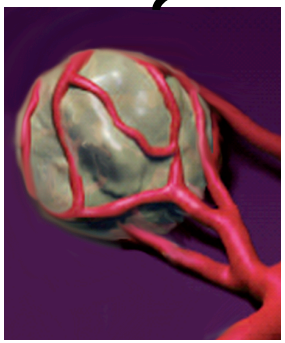
*New Molecular Entities

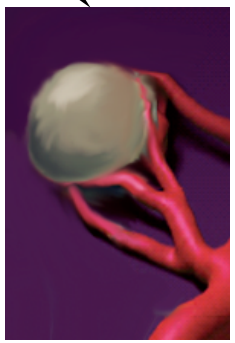
Broad Mechanisms that could augment anti-VEGF therapy

Avastin® +/- Chemo:
EC apoptosis, tumor regression/stasis

NMEs* that sensitize tumor vasculature to Avastin® and/or Chemo **(aNRP1)**



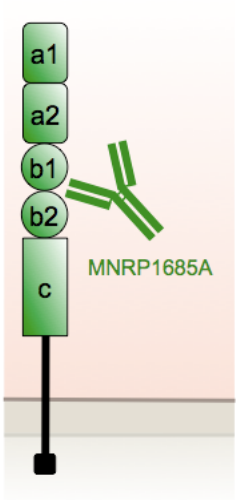


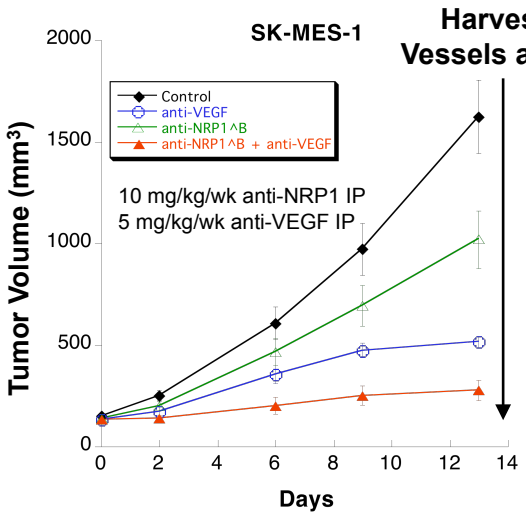


Continuous Rx with NME may not be required, but may be beneficial.

*New Molecular Entities

MNRP1685A Ab (Anti-NRP1) MOA and imaging as potential PD marker



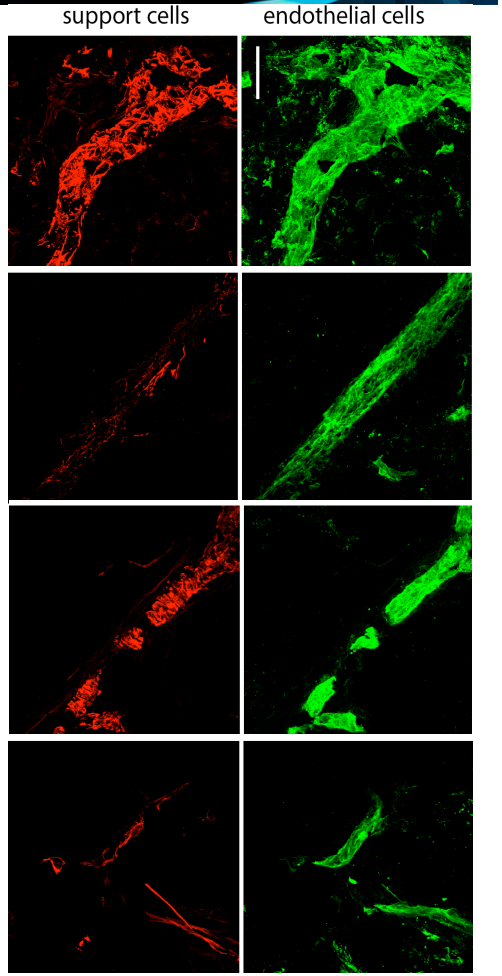


Control
Wide vessels
SCs loosely associated

Anti-NRP1
Wide vessels
Minimal SC staining

Anti-VEGF
Thin vessels
SCs tightly associated

Anti-NRP1 + anti-VEGF
Thin vessels
Minimal SC staining



Red:anti-aSMA for pericyte
Green: PECAN, ICAM, MECA32 combination stain for vessel

Neuropilin-1 (NRP1)
- Multi-domain receptor, no tyrosine kinase activity-VEGF co-receptor
- Ligands include VEGF family members and semaphorins
- Necessary for blood vessel maturation
- Expressed on endothelial and support cells

MNRP1685A
- Phage-derived, recombinant human antibody
- Binds NRP1 with high affinity at b1 and b2 domains
- Clinical activity as single-agent considered very unlikely

Anil Bagri

9

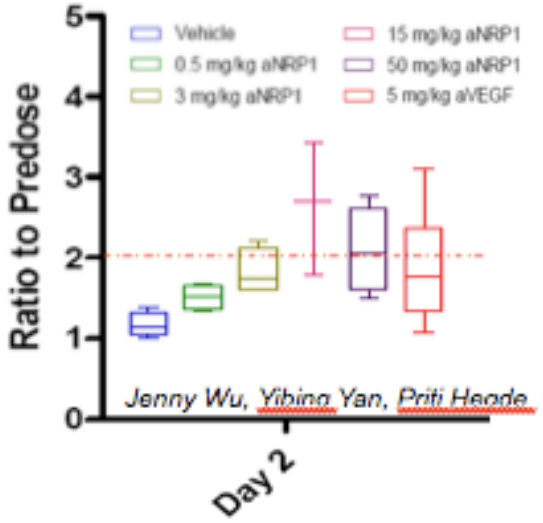
PlGF as PD Marker for NRP1 Pathway Inhibition

MNRP1685A

Plasma PlGF as a marker of VEGFR pathway inhibition for Anti-NRP1

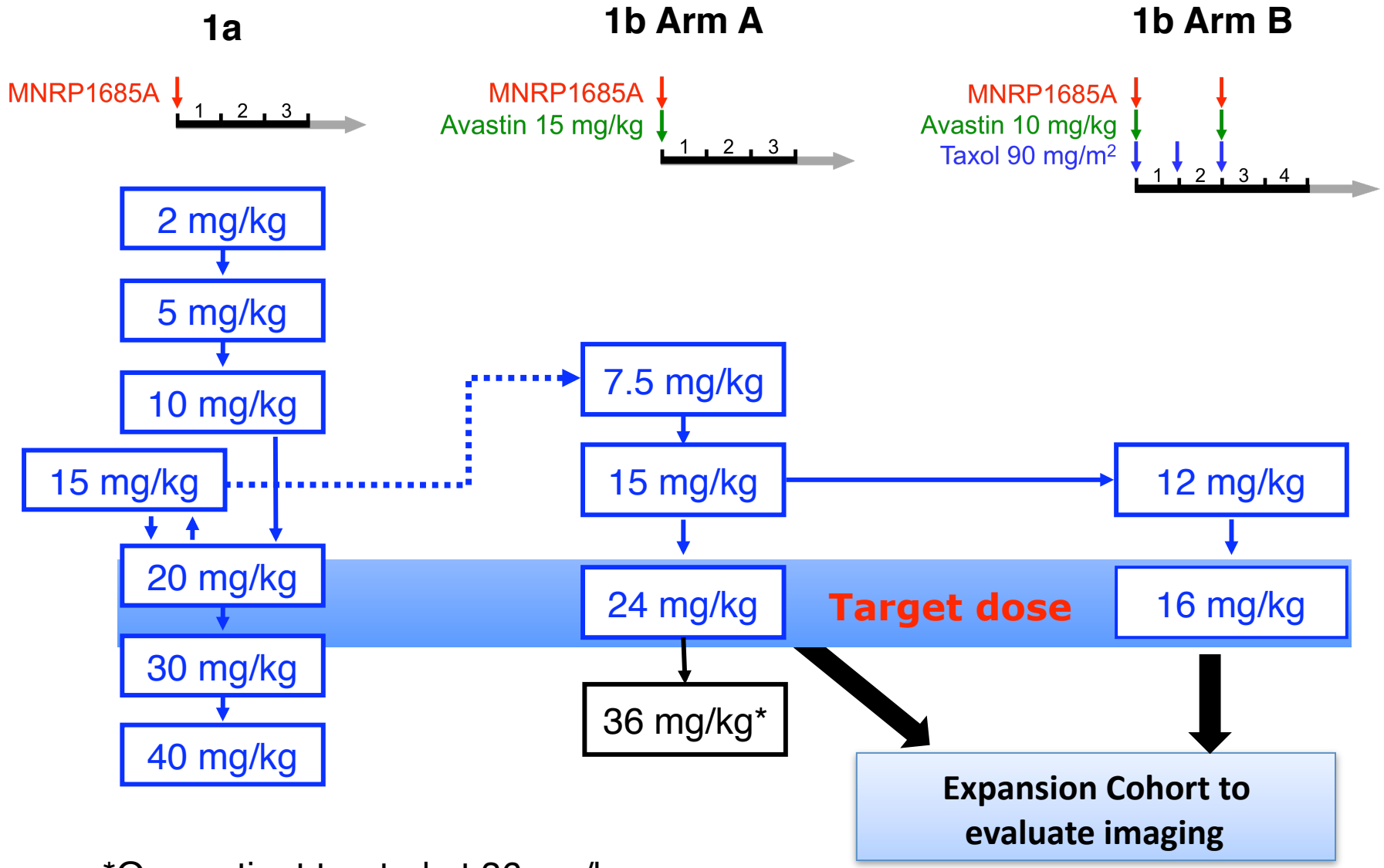
- PlGF is a ligand for NRP1, anti-NRP1 blocks PlGF binding to the receptor
- PlGF is a systemic marker of VEGFR1/R2 pathway inhibition
- PlGF elevation does not correlate with anti-tumor activity for bevacizumab
- Bevacizumab results in ~1.8x elevation in PlGF (<10% have PlGF >2x)

Treatment with anti-NRP1 results in induction of circulating PlGF in Cynomolgous monkeys



Goal: Achieve dose that => sustained elevation of PlGF (>1.8x) in Phase I

Anti-NRP1 Phase I and Ib Studies



*One patient treated at 36 mg/kg

PIGF modulation in Anti-NRP1 Phase Ib PLGF

MNRP1685A

Clinical Projection for linear range PK:

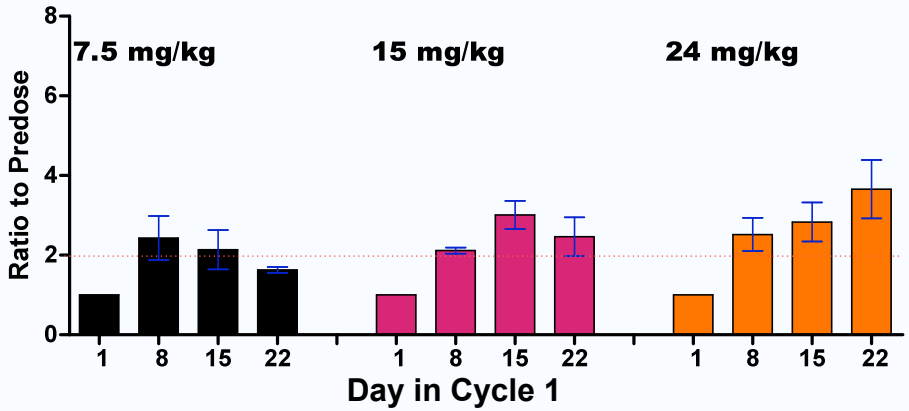
≥15mg/kg q2w

or

≥24mg/kg q3wk

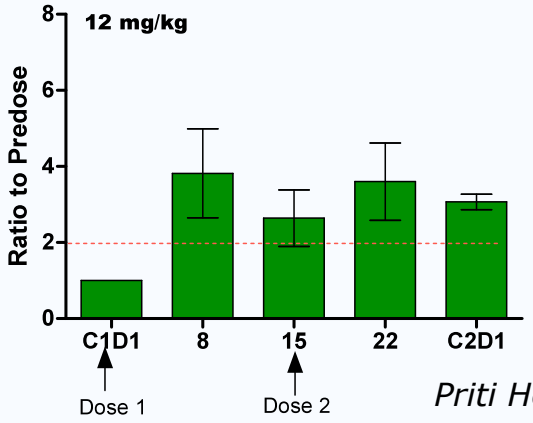
Anti-NRP1 + Bev, q3w

Sustained combination activity of biomarker observed from 15mg/kg (Phase IB: Arm A)



Anti-NRP1 + Bev + Taxol q2w

Sustained combination biomarker activity observed at 12 mg/kg (Phase IB:Arm B)



Priti Hegde

12

Proteinuria on anti-NRP1 Phase Ib

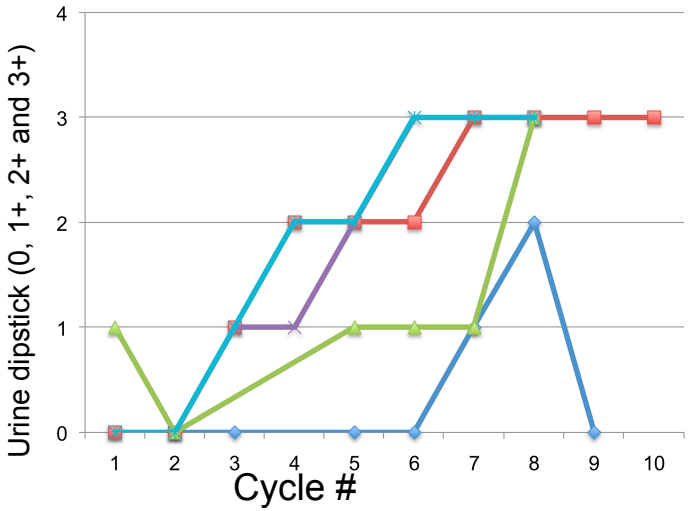
Data as of Jan 2011

	Cohort (mg/kg)	n	Grades 1-2 (n)	Grades 3-4 (n)	All Grades (%)
Arm A	15	3	2	0	67
	24	7	2*	1	43
	Subtotal %	**14**	**29**	**7**	**36**
Arm B	12	5	2	1	60
	16	5	1	1**	40
	Subtotal %	**10**	**30**	**20**	**50**
	Total %		**29**	**13**	**42**

* 1 of which was Gr1, ** Gr4

Data as of Jan 2011

New ≥2+ urine dipstick (Grade ≥2) in 5/5 of patients on study for ≥6 cycles



New onset or worsening proteinuria was not observed in Phase 1a

- Based on protocol-specified assessment by urine protein creatinine ratio

Background Rate for Gr3 Proteinuria on bev	Probability Observing by Chance
1.0-3.2%	**0.1-2.8%**

Rainer Brachmann, Mason Shih

anti-NRP1 Clinical development

MNRP1685A

The safety profile of aNRP1 plus bevacizumab **at the current recommended doses and schedule** is not acceptable for continued clinical development

Acknowledgments

We thank the patients who participated in the studies and their families, as well as the following contributors:

University of Colorado Cancer Center (Phase 1a and 1b)
Colin Weekes, MD
Sarah Eppers
Sarah Rippke

START, San Antonio (Phase 1a and 1b)
Amita Patnaik, MD
Jim Agnew
Danielle Mutz

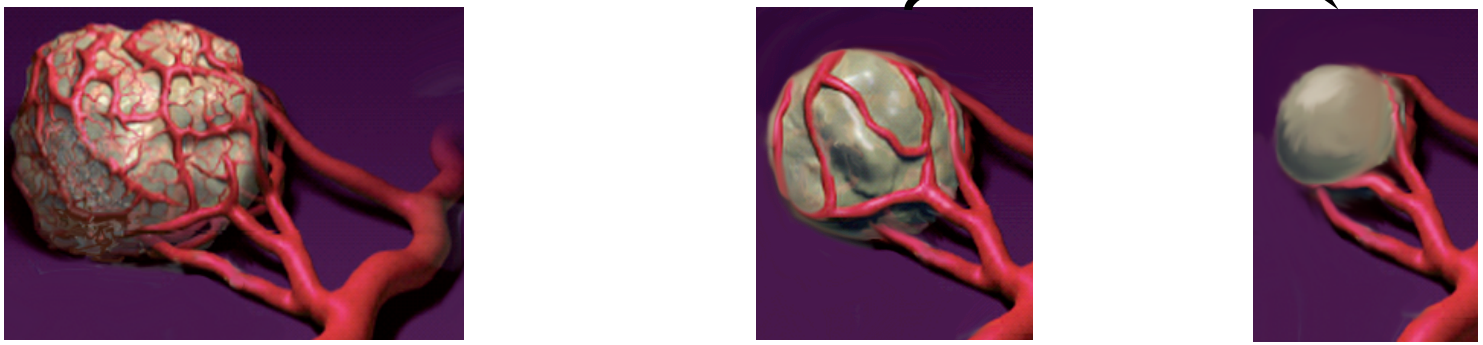
Karmanos Cancer Center, Detroit (Phase 1b)
Patricia LoRusso, MD
Lindsay Casetta

Genentech
Anil Bagri, MD, PhD
Paul Boche
Shumei Chi
Jakob Dupont, MD
Rashell Kinard
Jessica Li
Benny Luu
Amy Peterson, MD
Rosario Roverso
KP Smith
Douglas Thieu
Ryan Watts, PhD
Yibing Yan, PhD

Broad Mechanisms that could augment anti-VEGF therapy

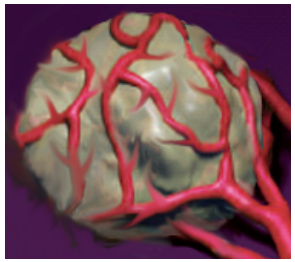
Avastin® +/- Chemo:
EC apoptosis, tumor regression/stasis

NMEs* that sensitize tumor vasculature to Avastin® and/or Chemo **(aNRP1)**



Other Angiogenic factors

Vascular Maturation



NMEs* that prevent vascular recovery from Avastin® and/or Chemo **(aEGFL**7)

Continuous Rx with NME is desirable

*New Molecular Entities

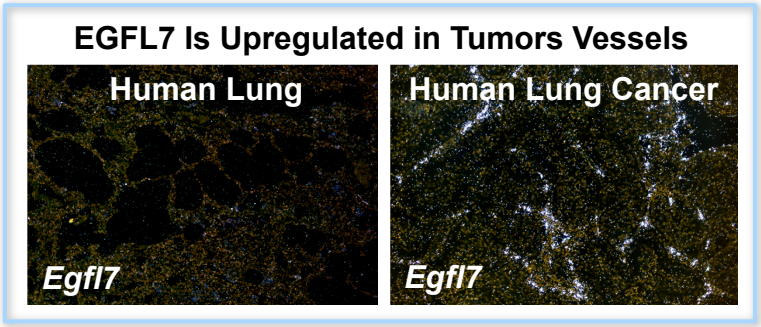
MEGF0444A (Anti-EGFL7): MOA

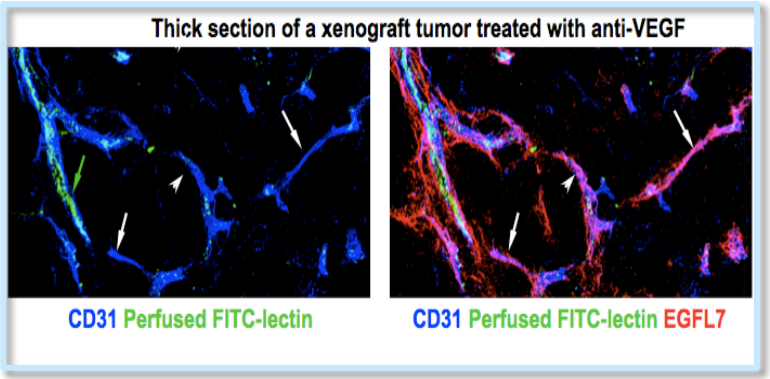
EGFL7

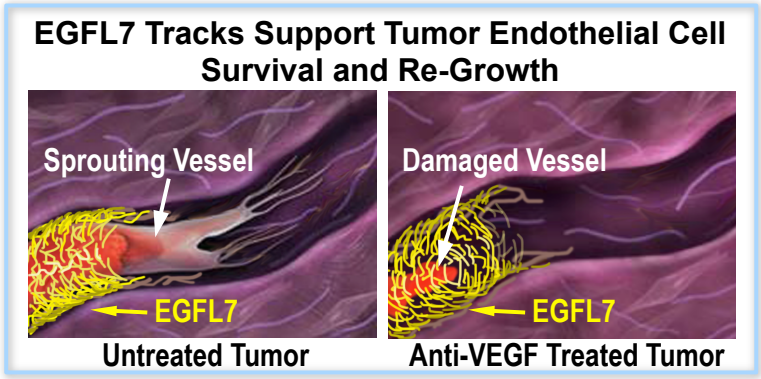
- EGFL7 is a tumor-enriched vascular extracellular matrix (ECM) protein that supports endothelial cell survival, particularly under stress
- EGFL7 forms peri-vascular tracks that regulate blood vessel formation
- EGFL7 tracks persist along tumor blood vessels damaged by anti-angiogenic therapy; these tracks may protect the surviving endothelial cells and thus enable them to rebuild new vessels

Drug candidate: anti-EGFL7 MAb MEGF0444A

- Blocks interaction between endothelial cells and EGFL7
- Demonstrates *tumor-selective anti-vascular* and *anti-angiogenic* activity
- Inhibits tumor vascular *re-growth* following anti-VEGF treatment







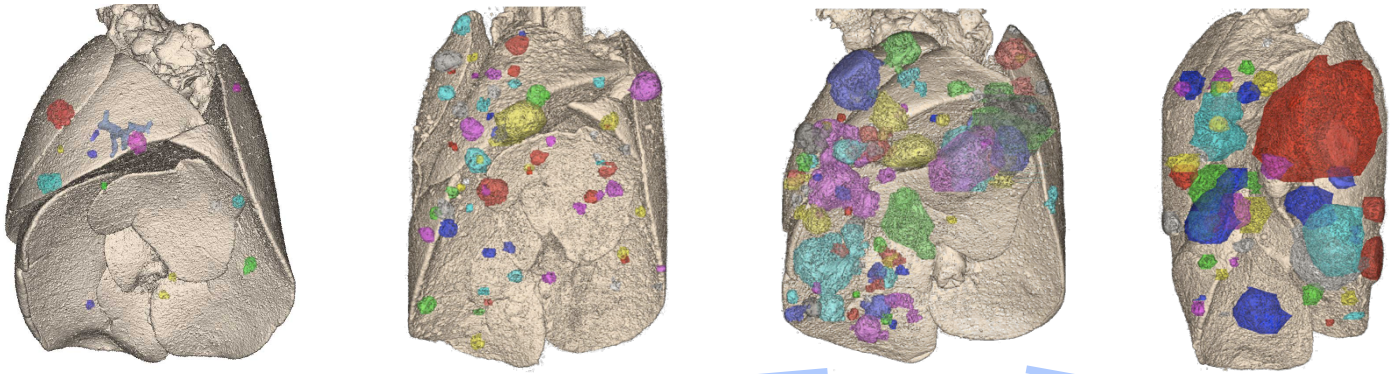
MicroCT Detection & Quantitation of NSCLC Genetically Engineered Mouse Models (GEMMs)

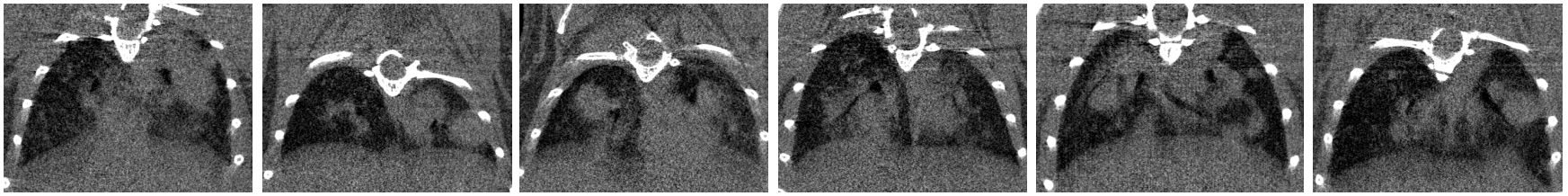
Ad-FIC delivery

8 wks **12 wks** **16 wks** **20 wks**

Rx begins

K-ras^{G12D}; p53$^{Ft/Ft}$

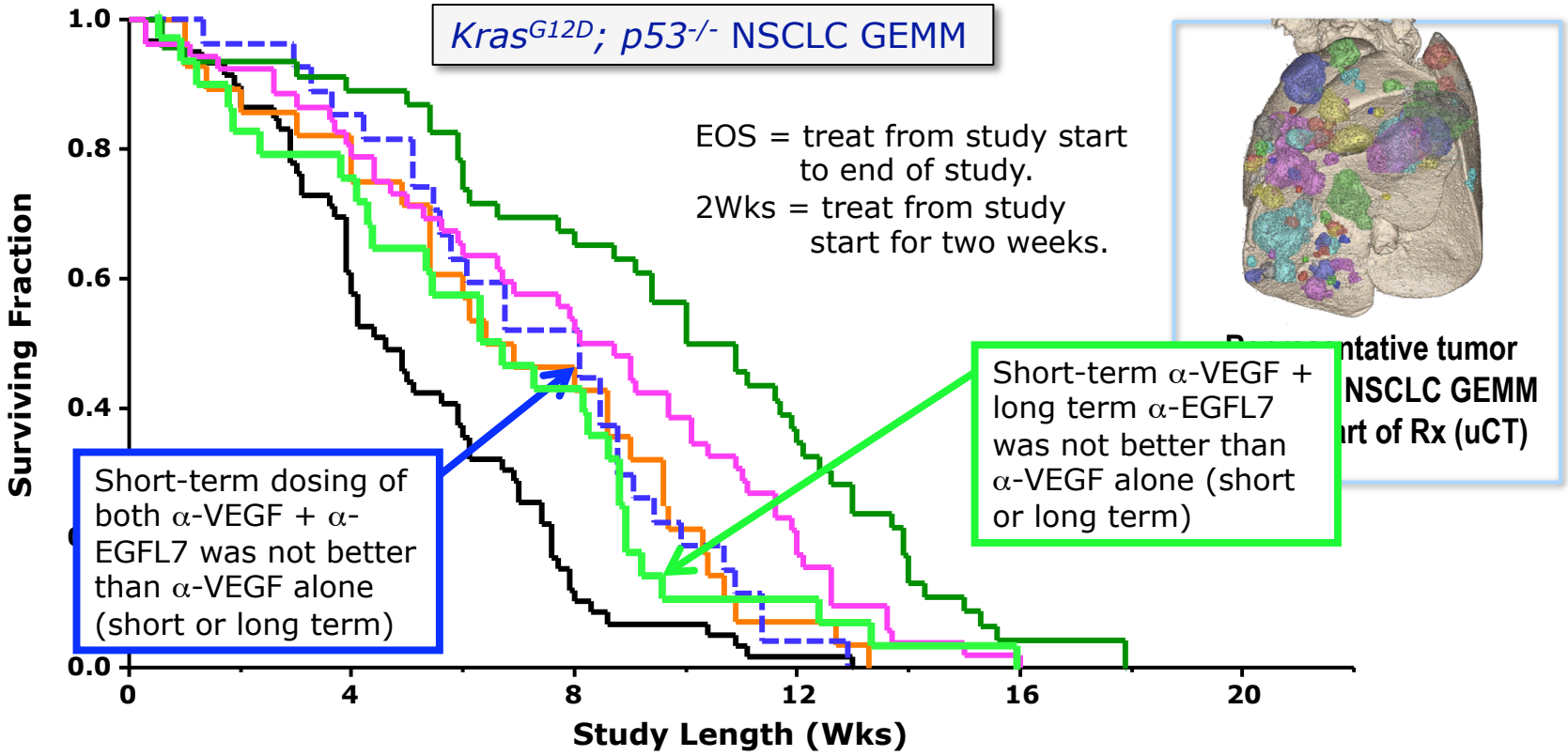




(Serial CT scans of a mouse at 16 weeks post tumor initiation)

Continued a-EGFL7 + a-VEGF provides maximum OS benefit in a NSCLC GEMM model

MEGF0444A



ntative tumor
NSCLC GEMM
rt of Rx (uCT)

	# mice	Median OS (wks)	*P* Values	HR
Control	**59**	**4.6**	**-**	**-**
α-VEGF (2 Wks) + α-Ragweed (2 Wks)	**27**	**8.0**		
α-VEGF (2 Wks) + α-EGFL7 (2 Wks)	**28**	**6.9**		
α-VEGF (EOS) + α-Ragweed (EOS)	**52**	**8.1**	**-**	**-**
α-VEGF (EOS) + 1.0 mpk α-EGFL7 (EOS)	**46**	**10.9**	**0.0164***	**0.55**
α-VEGF (2 Wks) + α-EGFL7 (EOS)	**28**			

*p ≤ 0.05 (log-rank test)

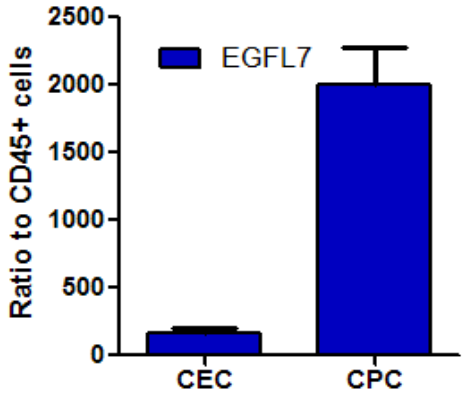
Lima, Molina, Hamilton, Long, Barck, Cao, Bou-Reslan, Carano, Nannini, Ye, & Johnson

CPCs: a PD marker for a-EGFL7

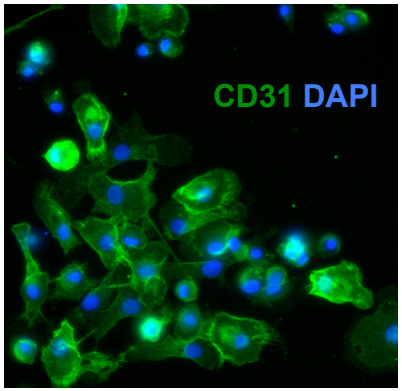
MEGF0444A

Circulating Progenitor Cells (CPCs): $CD34^{Hi}CD31^{Low}$ $CD45^{low}$, Circulate in blood (<0.1%), express high levels of EGFL7, and have a defined role in tumor angiogenesis

EGFL7 mRNA

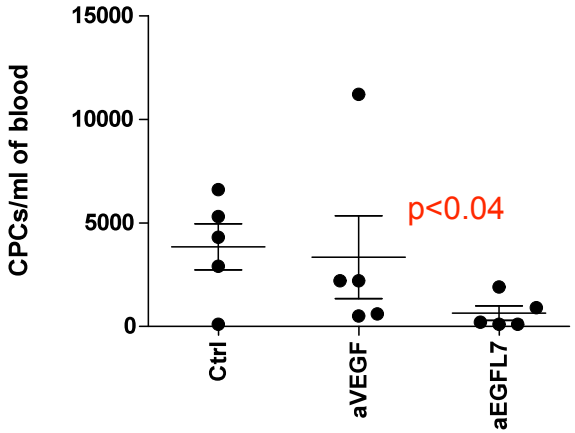


CPCs differentiate into endothelial cells

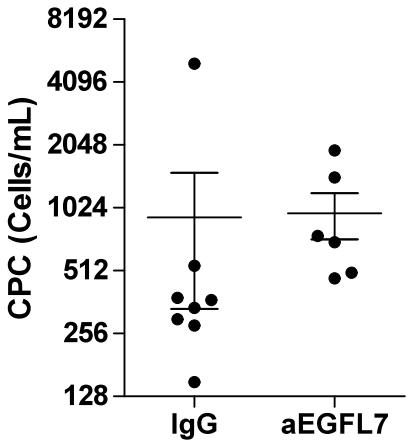


cells also express vWF and CD105

CPCs in MDA-MB231 models (Day 19)



CPCs in MV522 model

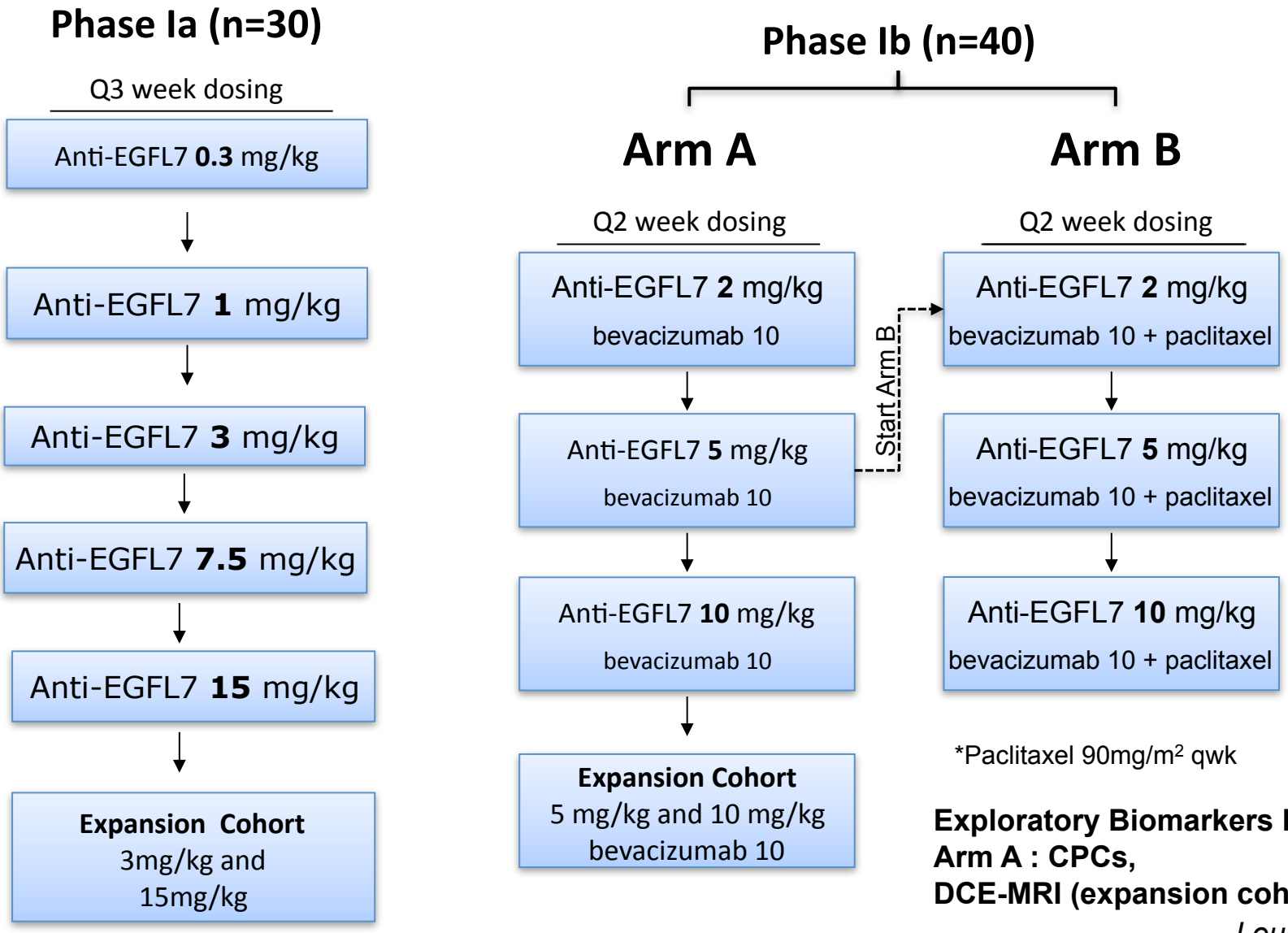


- Anti-EGFL7 shows delayed reduction in CPCs in tumor bearing mice
  - Ab mediated clearance of CPCs unlikely
  - Possible altered mobilization or reduced half-life in circulation
- Anti-EGFL7 does not affect CPCs in non-tumor bearing mice
  - Effect is not systemic
- Anti-VEGF does not affect CPCs at delayed time points (day 14 onwards)

Priti Hegde

Anti-EGFL7 Phase I Design in Patients with advanced solid tumors

MEGF0444A

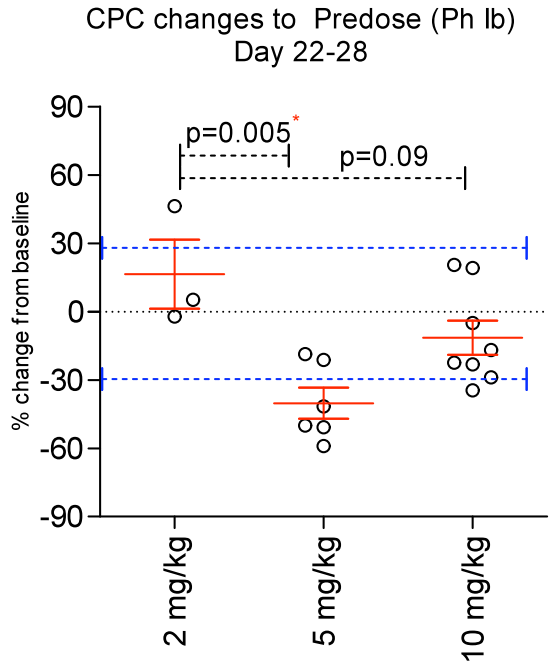


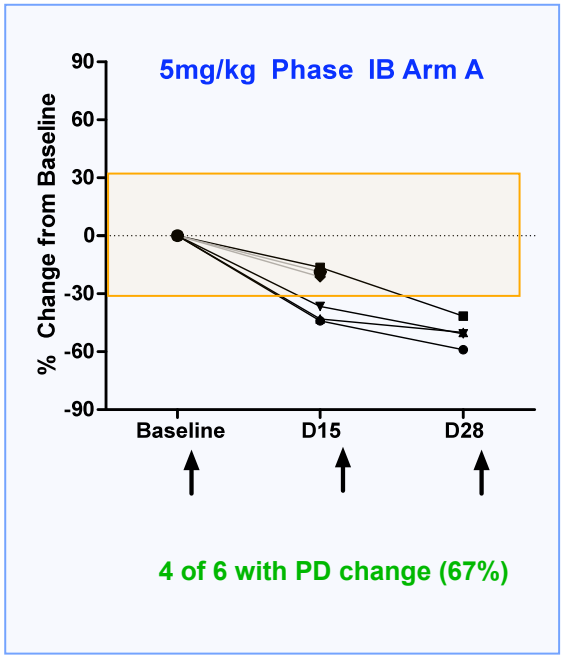
*Paclitaxel 90mg/m^2 qwk

Exploratory Biomarkers Ph Ia and Ph Ib
Arm A : CPCs,
DCE-MRI (expansion cohorts)

CPC modulation observed with ≥5 mg/kg of anti-EGFL7

MEGF0444A





- 40-60% reduction in CPCs in combination with bevacizumab
- CPC changes do not correlate with baseline numbers of CPCs
- Biomarker modulation did not correlate with response

Priti Hegde

Clinical activity observed in anti-EGFL7 Phase Ib

MEGF0444A

Phase Ib Anti-Tumor Activity	Prior Treatment	aEGFL7/Avastin N=22	aEGFL7/Avastin/ Paclitaxel # N=18
Cancer Type	Regimen: Months on Tx	Best response; time on treatment (as of Feb 2011)	
Ovarian Ca	CarboPac: 4mo Topotecan: 4mo GemCis: 4mo LY573636: 11mo	**cPR**; 6mo*	
Head and Neck	Doce/cetux/XRT: 5mo Carbo/doce: 4mo TRC102/pem: 13mo	**uPR**; 7.5+mo	
Renal Ca	Sunitinib/aCTLA4: 13mo Sorafenib: 10mo aSpingosine-1-P: 5mo	cMR; 9+mo*	
Ovarian	Carbo/pac: 5mo Cis/pac: 4mo		**cPR**; 6mo
Transitional Cell	Adj CarboGemx4: 10mo		**cPR**; 6.5+mo
Breast Cancer	Adj Xeloda/XRT: 2mo Femara: 36mo Faslodex: 3mo		**cPR**; 5+mo
NSCLC	Crizotinib: 12 mo CarbGem: 7 mo HSP90 INH: 1.5 mo		uMR (29.7% decrease); 3.4+mo

c=confirmed response $\geq$ 4 weeks after initial response; u=unconfirmed response

*Patients with CPC changes. # CPCs were not analyzed in this group.

Rate of Avastin®-associated AEs in anti-EGFL7 Phase Ib

MEGF0444A

Adverse Event	Phase Ia n (%)	Phase Ib n (%)
Hypertension		
Any	0 (0)	3 (12.5)
Grade ≥3	0 (0)	2 (8.3)
Proteinuria		
Any	2 (6.7)[1]	1 (4.1)[2]
Grade ≥3	0 (0)	0 (0)

[1] In 1 subject dipstick 3+ resolved to undetectable in 1 week; in a second subject dipstick 2+ was also present at screening

[2] Dipstick 1+ at study completion visit, event not reported as an AE

As of Jan 2011, there were no Gr≥3 ATE, GIP, Pulm Hemorrhage

Phase II plans with anti-EGFL7 currently include NSCLC and CRC

Anti-EGFL7 Acknowledgements

Premier Oncology, California

Lee Rosen
Isett Laux

Pinnacle Oncology and Hematology

Michael Gordon
Jane Wittner
Kallie Hazell

UCSF

Pamela Munster
Anne Reinert
Paula Fiermonte
Kristin Johansing

gRED Early Development

Dan Chen
Eric Wakshull
Heejo Baek
Jeff Douglas
Jessica Li
Junko Aimi
KP Smith
Louie Naumovski
Mark Velligan
Olivia Huang
Shuang Bai

gRED Research

Anthony Lima
Leisa Johnson
Mallika Singh
Rick Carano
Stacey Yeung
Tanya Smyczek
Weilan Ye

Thank you to the patients for participating in the trial and agreeing to provide tissue for biomarker analysis

Genentech
A Member of the Roche Group


Thank you!
Targeted Anti-Cancer Therapeutics
Meeting, Paris March 2011
Amy Peterson, MD
Associate Group Medical Director
Early Clinical Development, Genentech