

# PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

## Antiangiogenic Agents in Neoadjuvant Therapy

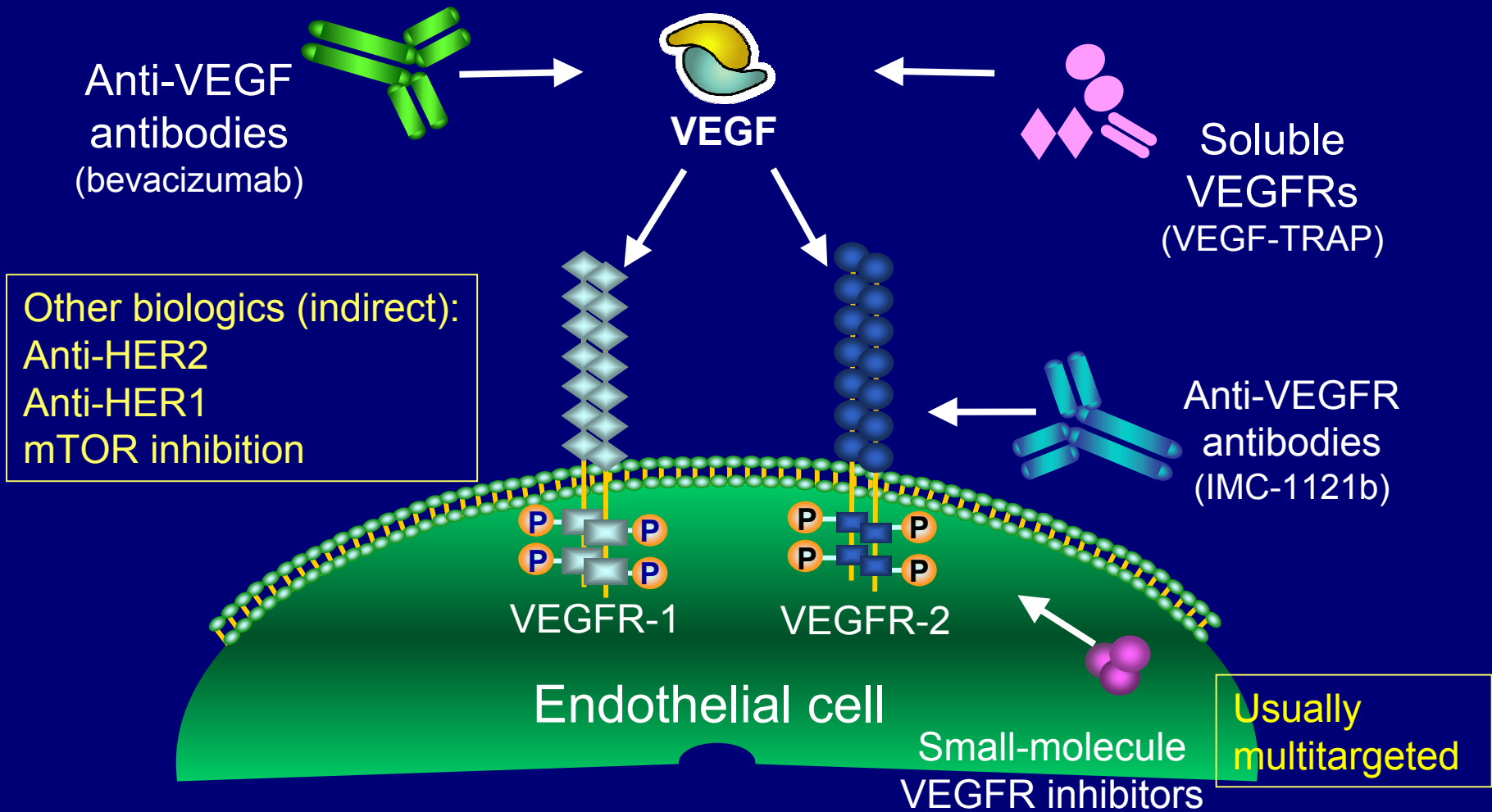
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Lineberger Comprehensive Cancer Center



# Agents Targeting the VEGF Pathway



Adapted from Podar and Anderson. *Blood*. 2005;105:1383.

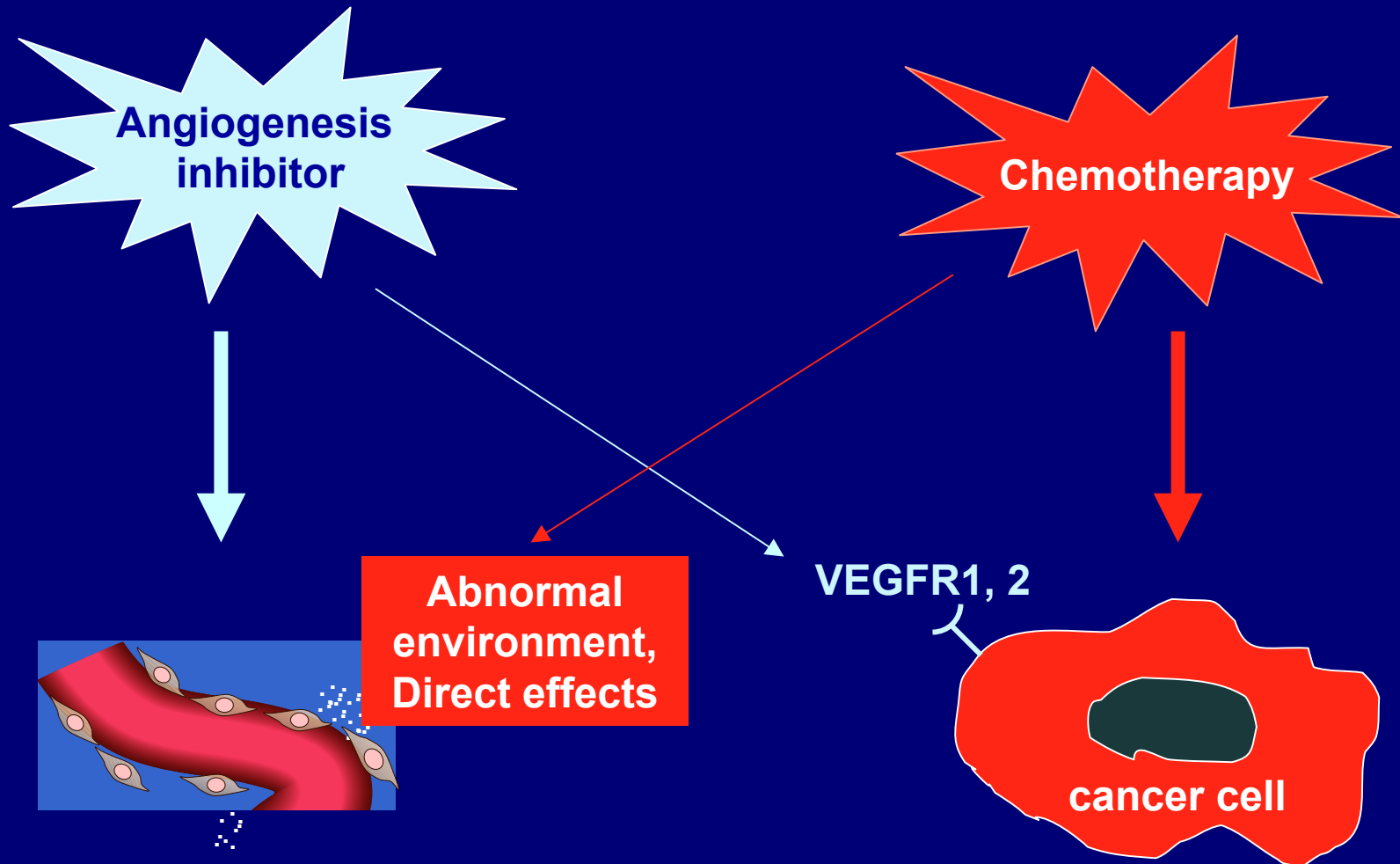
(PTK787, SU11248, ZD6474, BAY 43-9006, AG013736)

# Rationale / Issues Regarding Antiangiogenics in the Neoadjuvant Setting

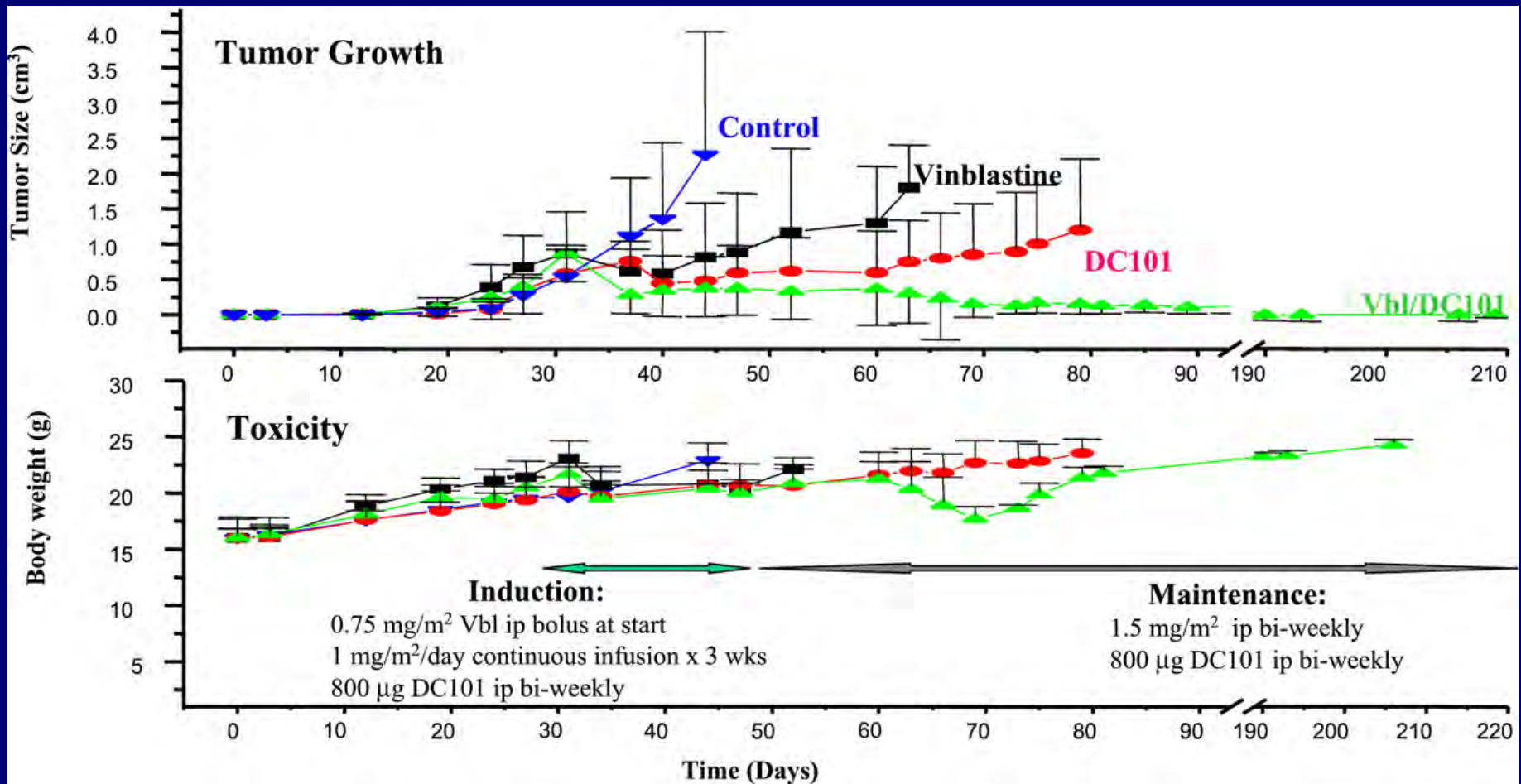
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- Augmented response in Stage IV
- Broad applicability
- Non-crossresistance with existing multimodality therapy
- Wound healing
- Large tumor - normalizing existing vessels
- Biologic discordance b/w primary and micrometastases?
- Adjuvant vs neoadjuvant timing?
- Selection?

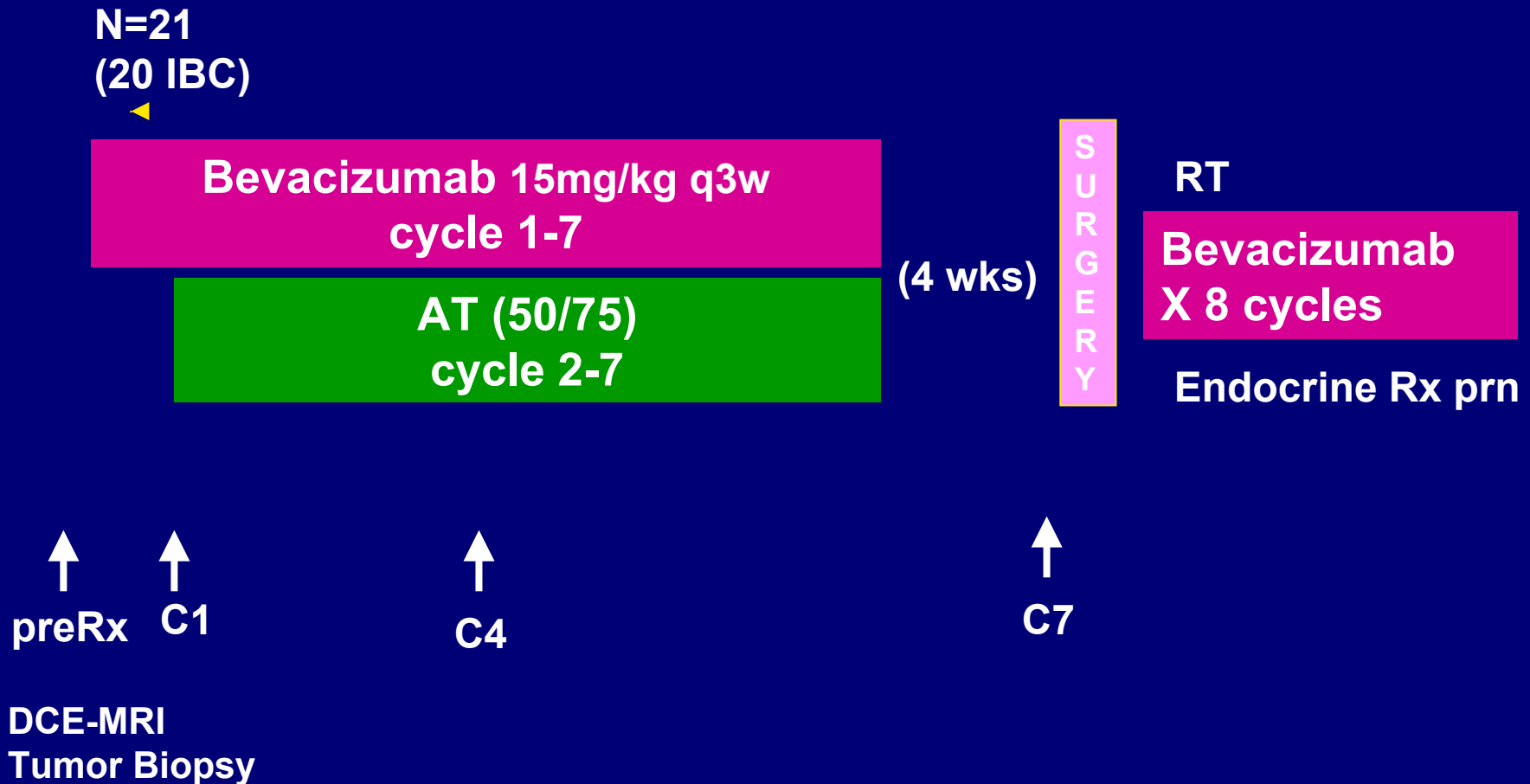
# Antiangiogenesis Agents and Synergy with Chemotherapy



# Metronomic Chemotherapy + VEGF-targeted Therapy



# Bevacizumab/AT in Inflammatory Breast Cancer



# Bev/AT in IBC

## Patient/Tumor Characteristics

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		N=21
Median age		50
Stage:	III	17
	IV	4
Grade 3		12
ER +		9
HER2 +		4
Skin biopsy +		12

# Bev / AT in IBC: Toxicity

	N=21*
Hypertension (gr 3)	8
Bleeding (gr 1)	5
LVEF ↓ (asymptomatic)	2
Mean ↓ LVEF	-6.2%
Wound complications:	9
Prolonged seroma	(2)
Incision separation	(2)
Prolonged closure	(1)

**Wound healing complications:  
~2% in mCRC trials**

“...Do not initiate therapy within 28 days of major surgery and only following complete healing of the incision. Bevacizumab should be discontinued prior to elective surgery and the estimated half-life (20 days) should be considered”

\* 8 came off protocol before surgery

*Wedam et al, JCO 2006*



# Bev / AT in IBC: Efficacy

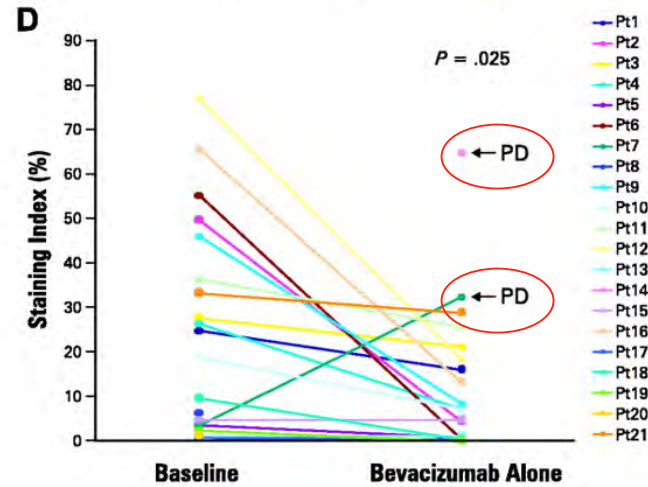
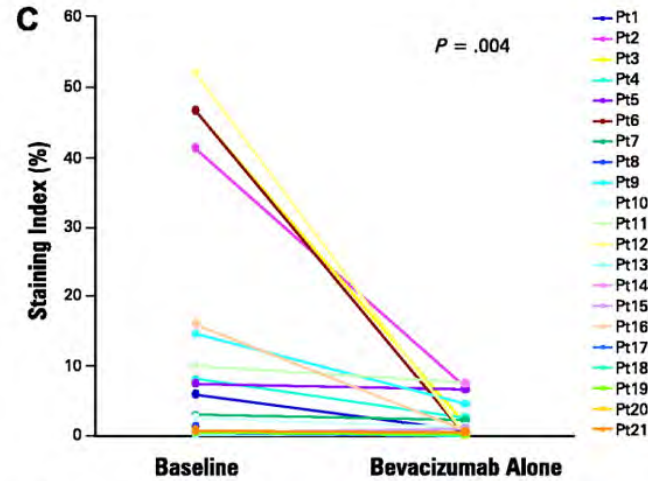
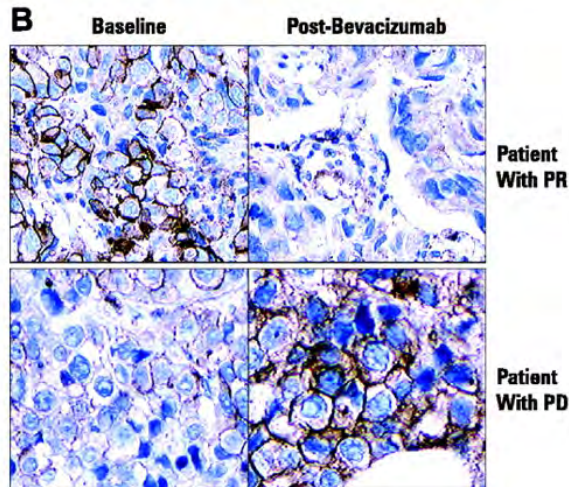
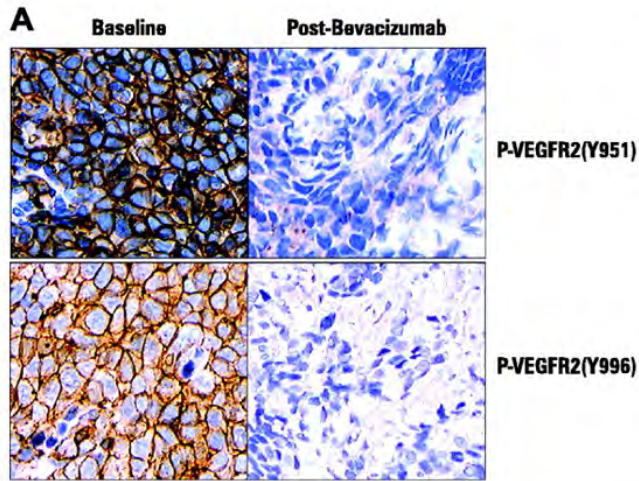
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		N=21
Clinical RR	CR	0
	PR	14 (67%)
	SD	5
	PD	2
pCR		1 (of 13)

**At 27m, 1-yr PFS 77%, 2-yr PFS 53%**

**Decreased DCE-MRI seen, did not correlate with response**

# Bevacizumab: In Vivo Effect on Phosphorylated VEGFR2

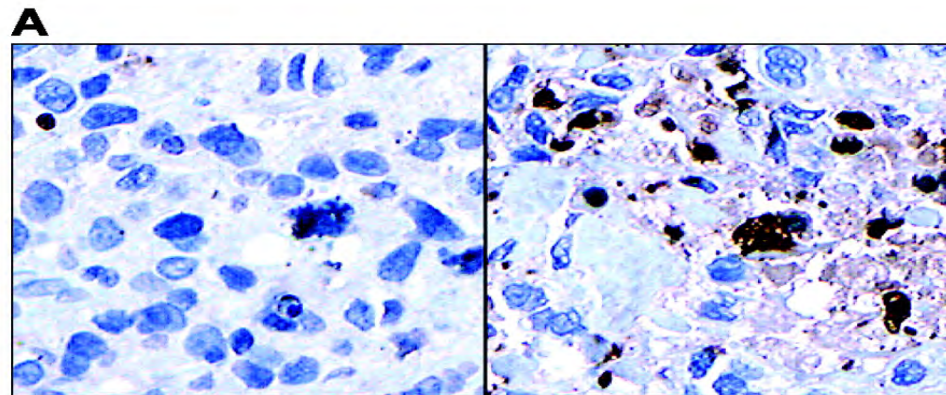


↓ p-VEGFR2  
with single  
agent bev

Persisted  
during  
chemo

No change  
VEGF,  
VEGFR2

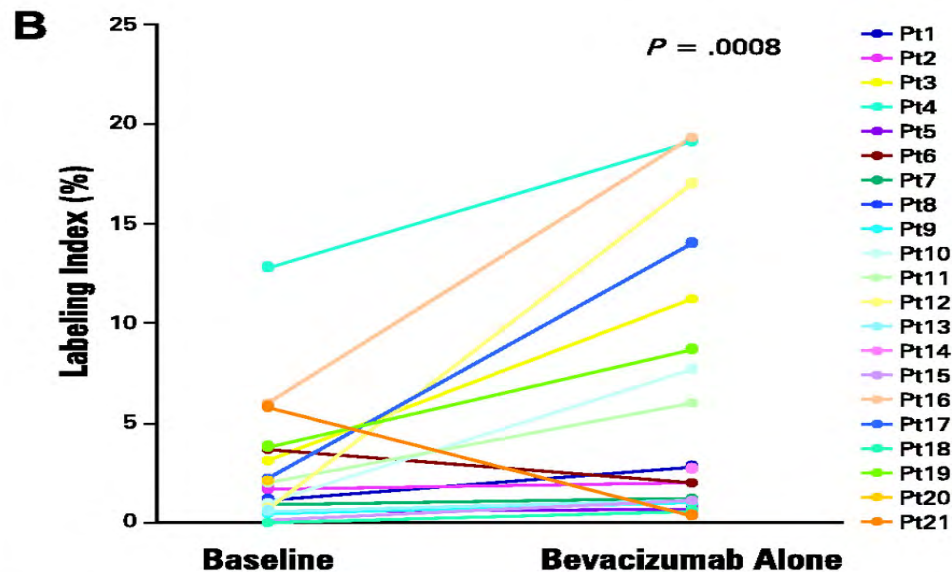
# Bevacizumab: Effect on Apoptosis



↑ Apoptosis (~129%)

Persisted (~75%)  
during chemo

No change Ki67, MVD



# CWRU 3100

Randomized  
Phase II  
N=49  
Stage III-IV  
Unresectable



Weekly docetaxel x 16

Weekly docetaxel x 16

Bevacizumab (q2wk)

(4 wks)

S  
U  
R  
G  
E  
R  
Y

AC x 4  
RT  
Endocrine  
Rx prn

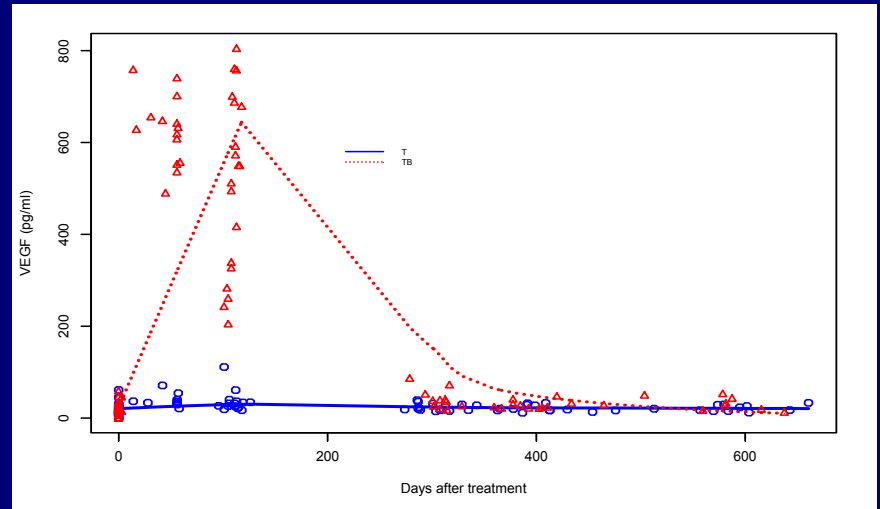
↑  
MRI  
Plasma (bFGF, VEGF)  
MUGA  
Tumor Biopsy\*

↑  
MRI  
Plasma

↑  
MRI  
Plasma

# CWRU 3100: Results

- **N=49 (24 BD, 25 D)**
- **Efficacy – no overt difference**
  - 7 (14%) cCR
  - 32 (65%) cPR
  - 5 (10%) NR
  - 5 (10%) PD
- **Toxicity**
  - No significant differences
  - Wound healing complications:
    - 5 BD, 3 D



**Serum VEGF in BD arm ↑ then ↓**

**No other differences between arms in plasma bFGF, VCAM-1, E-selectin**

# Relationship of Neoadjuvant Response to Outcome

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- **Response to conventional cytotoxics:**  
Primary (macrometastasis) response ~ DFS (micrometastasis)
- **Is this true in antiangiogenesis?**

**Prevention trial:** can angiogenic switching be prevented?

Micromet?

**Intervention trial:**

can tumor progression be slowed or stopped?

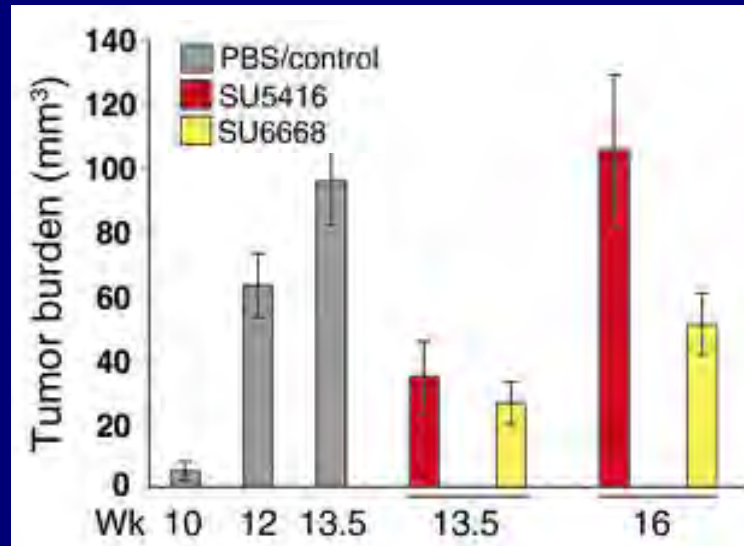
Macromet?

**Regression trial:**

can tumor growth be stabilized or regressed and can survival be extended?

# Anti-VEGF: Differential Effects on Early and Late Stage Tumors

Transgenic mouse model pancreatic Ca



Bergers et al, JCI 03

- Anti-VEGF works early, not late
- Better effects of anti-VEGF and anti-pericyte
- ? Additional proangiogenic factors
- ? Importance of pericytes
- May be reason for “escape” in stage IV

If true, are primary tumor measurements useful?

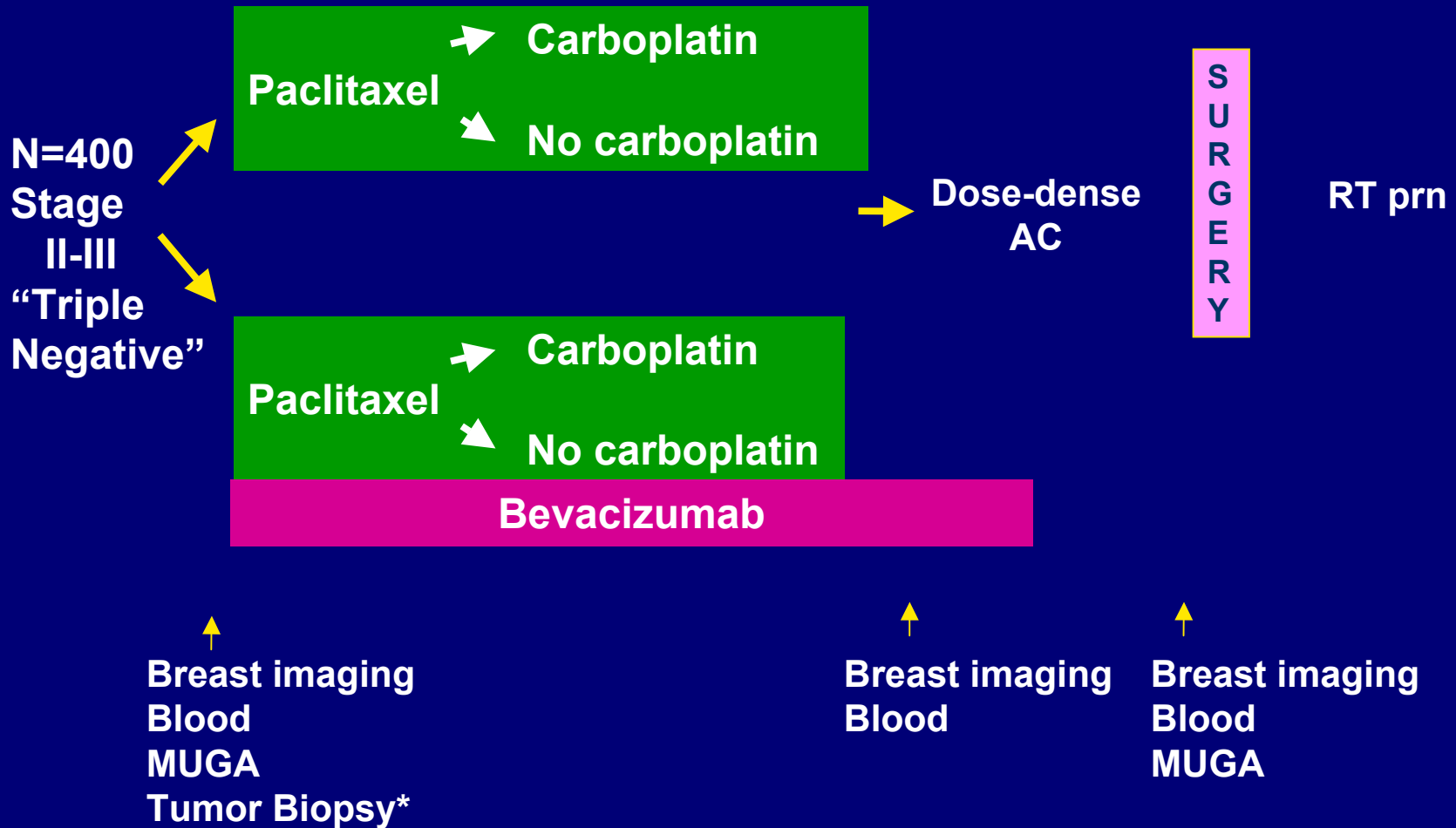


# Antiangiogenic Agents: Varying Kinase Specificities

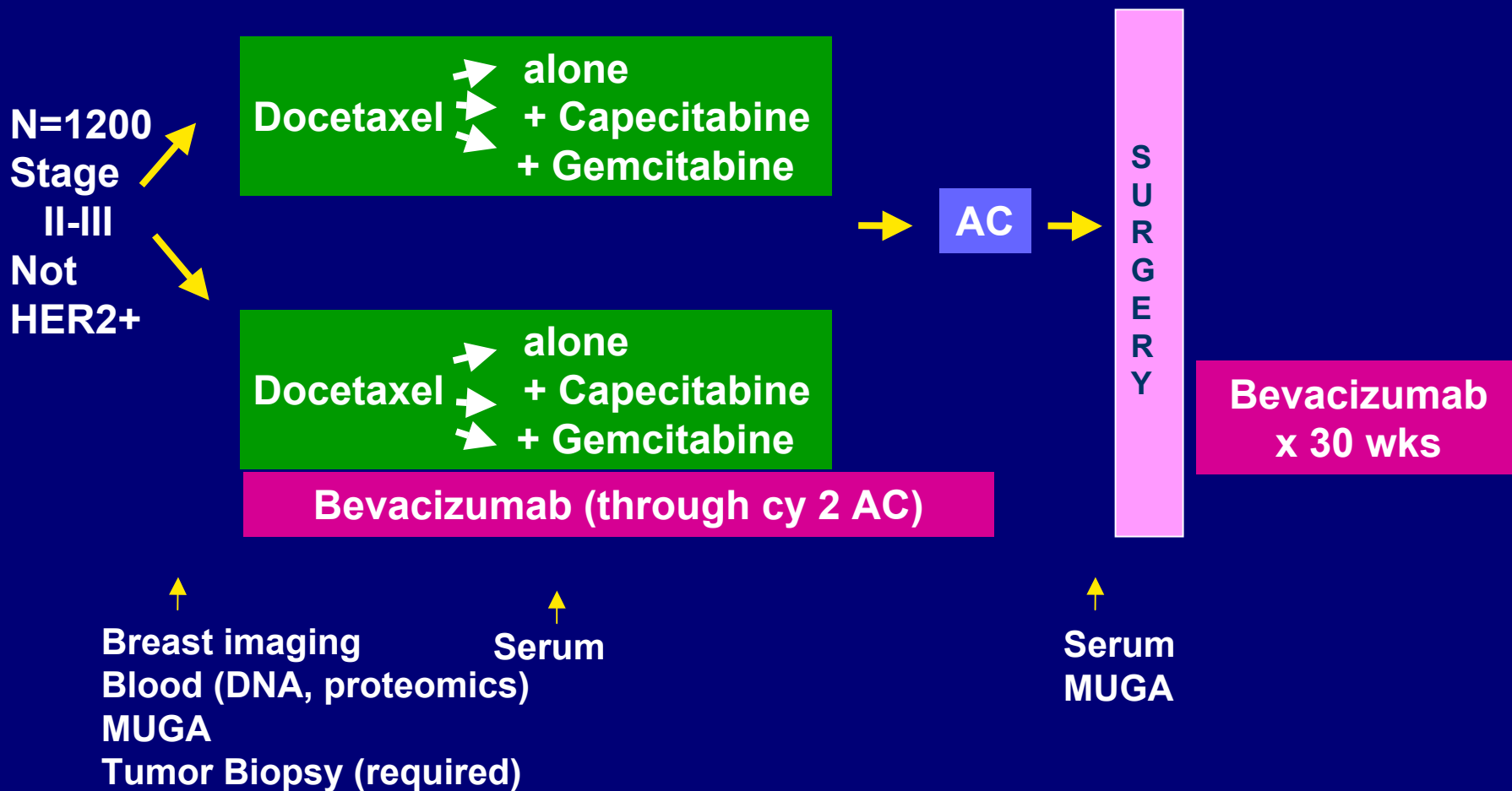
	Imatinib	GW 786034	PTZ787	ZD6474	AG 013736	BAY 43-9006	SU5416	SU6668	sunitinib
VEGFR2	-	0.05-<0.001	0.04	0.04	<0.001	0.03	0.2-1.3	3.9	0.004
VEGFR3	-	0.03	0.62-0.66	0.11	<0.001	0.02-0.10	-	-	-
VEGFR1	-	0.01	0.08	1.6	<0.001	-	<0.001	-	-
PDGFR $\beta$	0.10	0.08	0.58	1.1	<0.001	0.06-0.08	0.5-30	0.1	0.04
PDGFR $\alpha$	0.10-1.0	0.07	-	-	-	-	-	-	0.04
C-kit	0.1	0.07	0.73	>20	0.002	0.07	0.10-0.45	0.29	0.001-0.01
Flt3	10	-	-	-	-	0.02-0.06	-	-	0.008-0.01
FGFR1	-	0.72	-	3.6	-	0.58	4.2	3.8	0.88
EGFR	-	-	-	0.5	0	>100	-	>100	>10
C-met	37	-	-	-	-	>100	>10	>10	4
IGFR1R	-	-	-	>200	-	>100	>10	>10	2.4
CSF1R	-	-	1.4	-	-	-	-	-	0.05-0.1
Raf-1	-	-	-	-	-	0.006	-	-	-



# CALGB 40603



# NSABP B-40



# Summary

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- VEGF-targeting added to chemotherapy works in Stage IV
- Large neoadjuvant studies in progress
- Issues to bear in mind:
  - Selection (all settings!)
  - Wound healing
  - Assumptions about neoadjuvant model

# Thank you

