National Cancer Institute

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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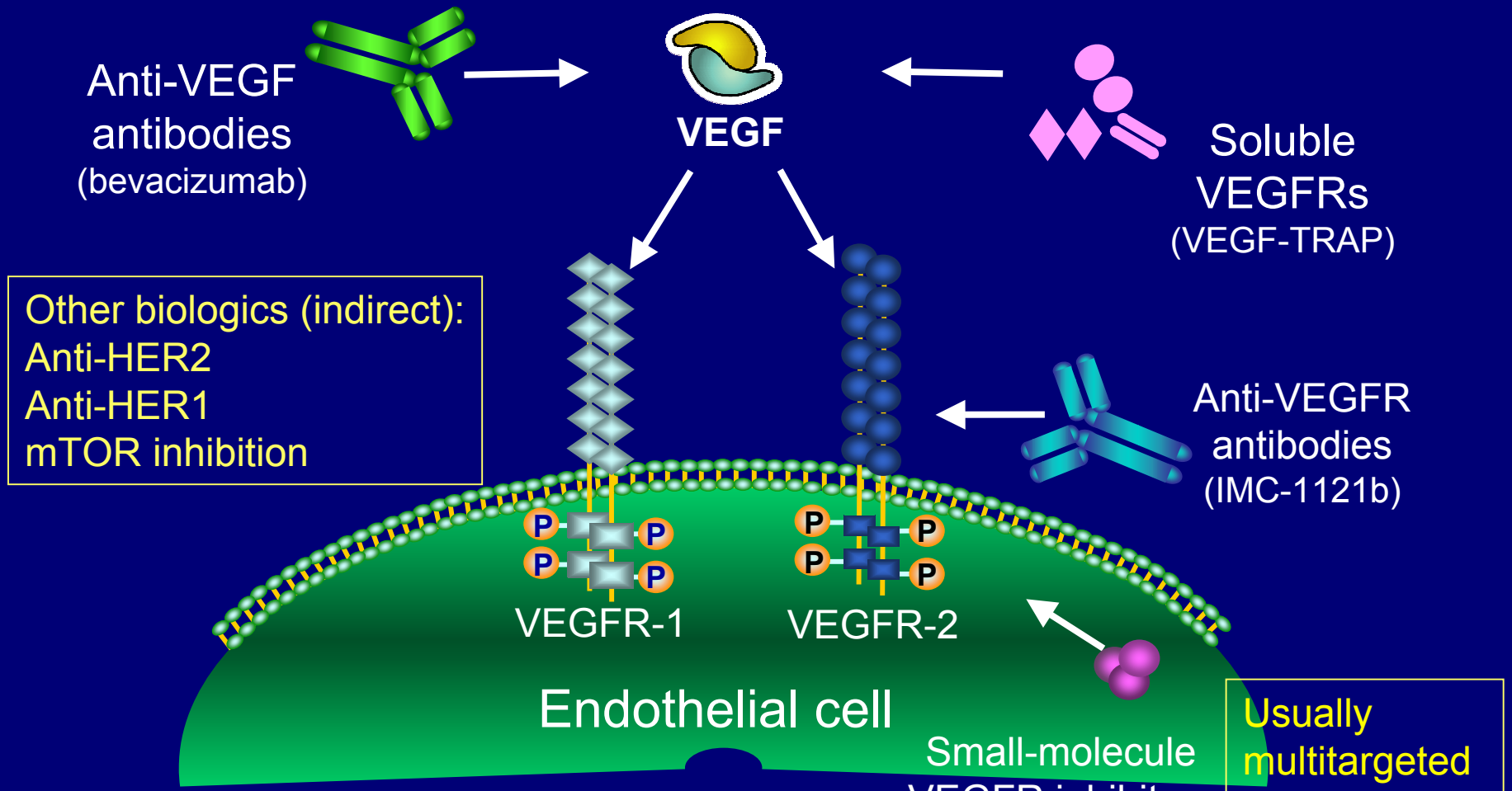
National Institutes of Health

Agents Targeting the VEGF Pathway

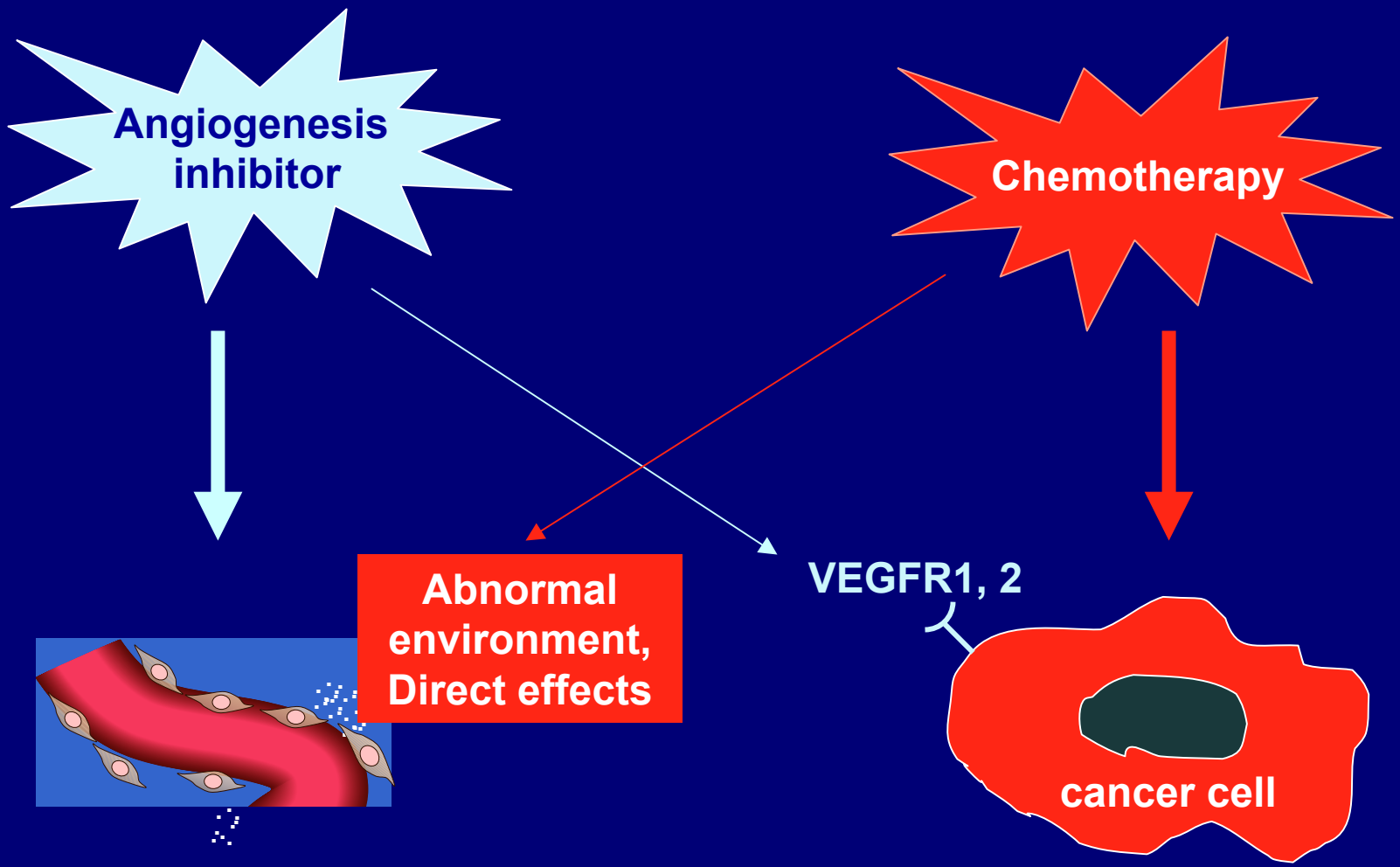


Adapted from Podar and Anderson. *Blood.* 2005;105:1383.

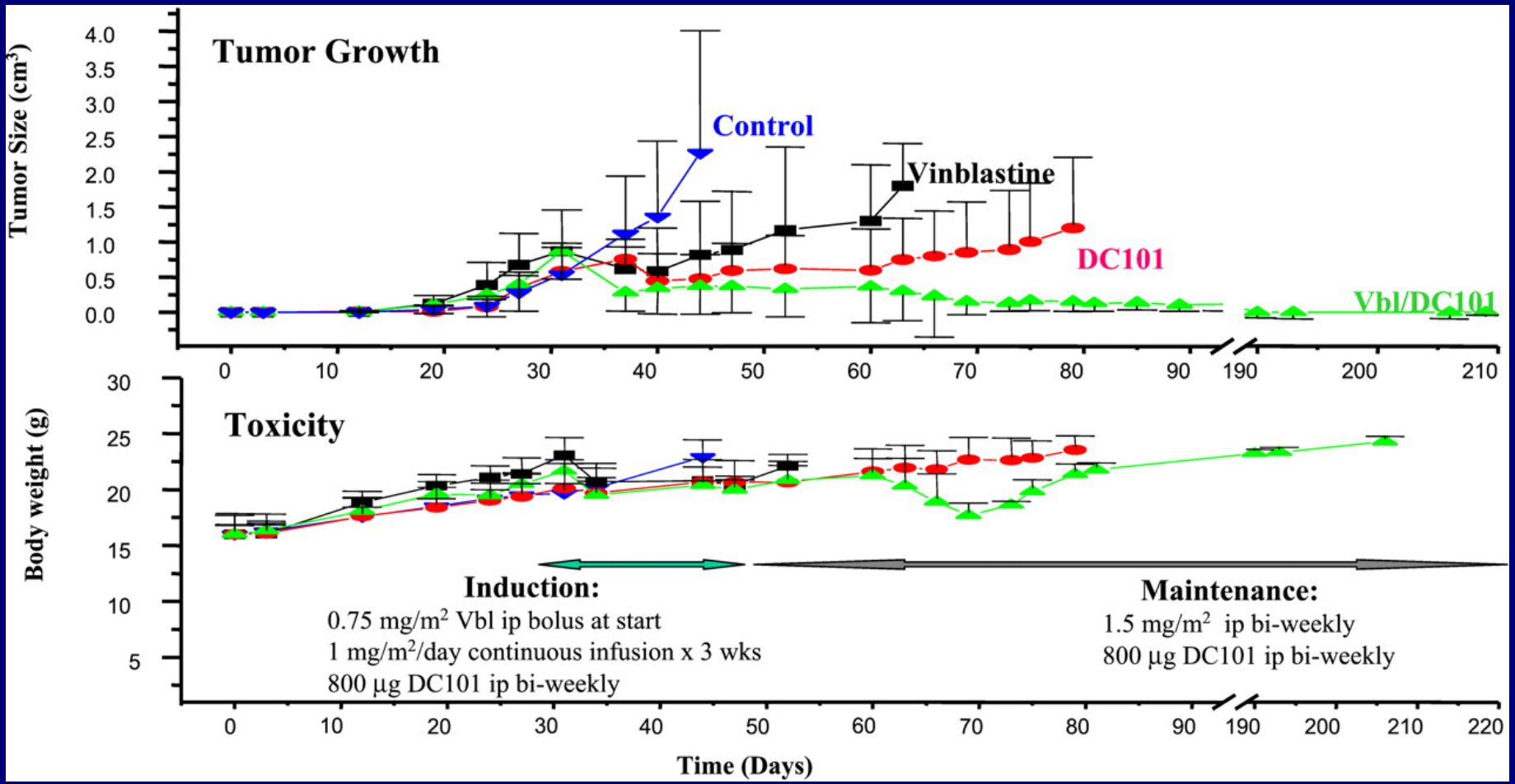
Rationale / Issues Regarding Antiangiogenics in the Neoadjuvant Setting

- 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

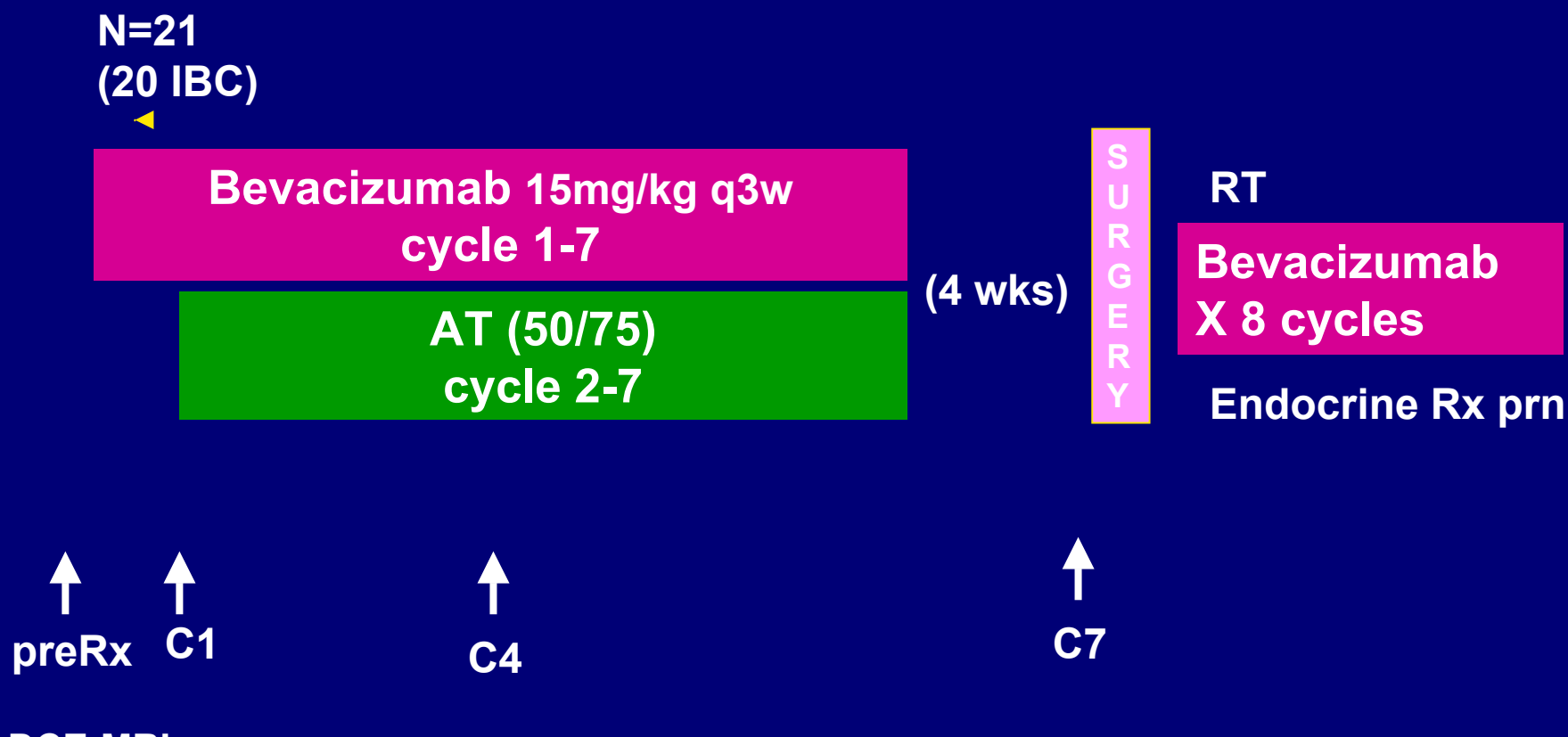


Metronomic Chemotherapy + VEGF-targeted Therapy



Kerbel, R. S. J Clin Oncol; 19:45s-51s 2001

Bevacizumab/AT in Inflammatory Breast Cancer



Wedam et al, JCO 2006

Bev/AT in IBC
Patient/Tumor Characteristics

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

Wedam et al, JCO 2006

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)

*** 8 came off protocol before surgery**

Wedam et al, JCO 2006

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"

Bev / AT in IBC: Efficacy

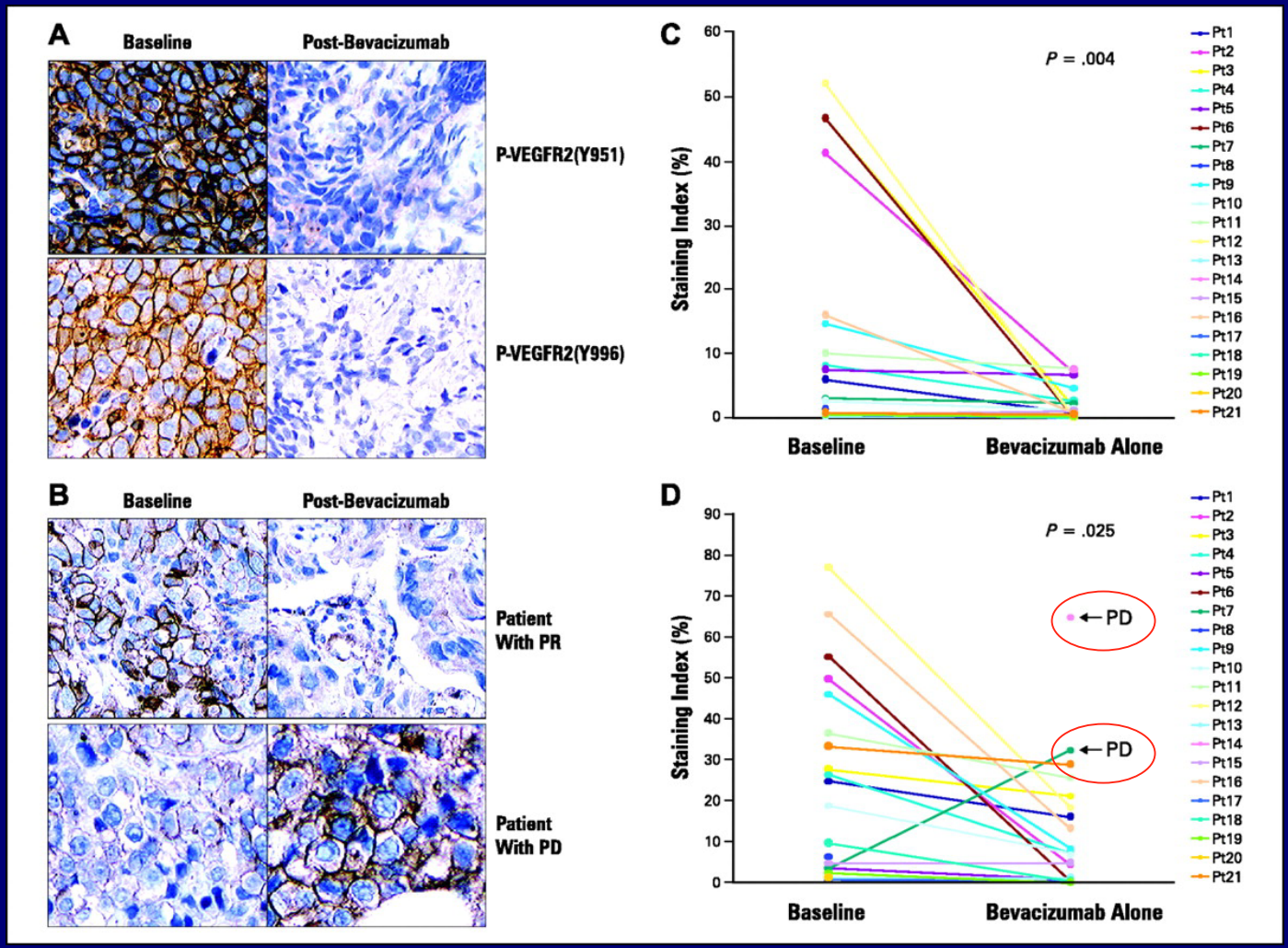
	N=21
Clinical RR	
CR	**0**
PR	**14 (67%)**
SD	**5**
PD	**2**
pCR	**1 (of 13)**

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

Decreased DCE-MRI seen, did not correlate with response

Wedam et al, JCO 2006

Bevacizumab:
In Vivo Effect on Phosphorylated VEGFR2



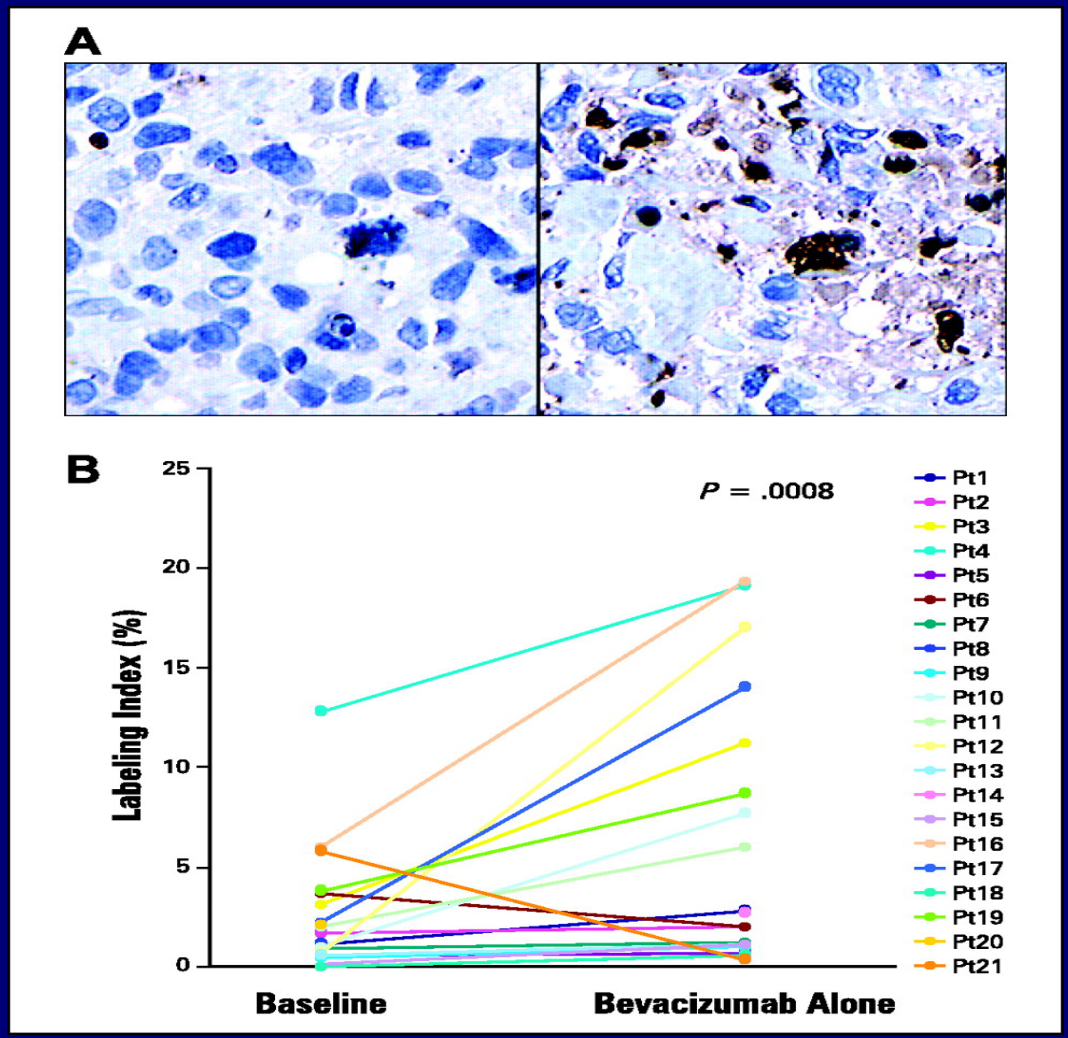
↓ p-VEGFR2 with single agent bev

Persisted during chemo

No change VEGF, VEGFR2

Wedam et al, JCO 2006

Bevacizumab: Effect on Apoptosis



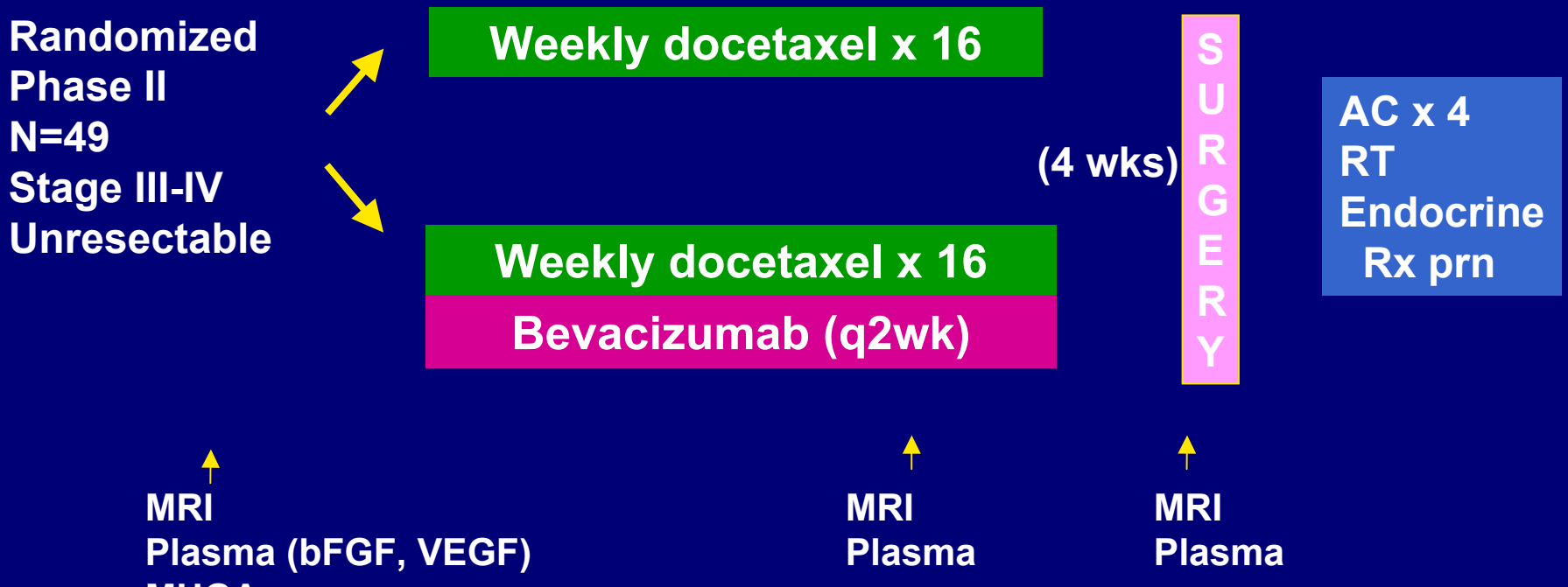
↑ Apoptosis (~129%)

Persisted (~75%) during chemo

No change Ki67, MVD

Wedam et al, JCO 2006

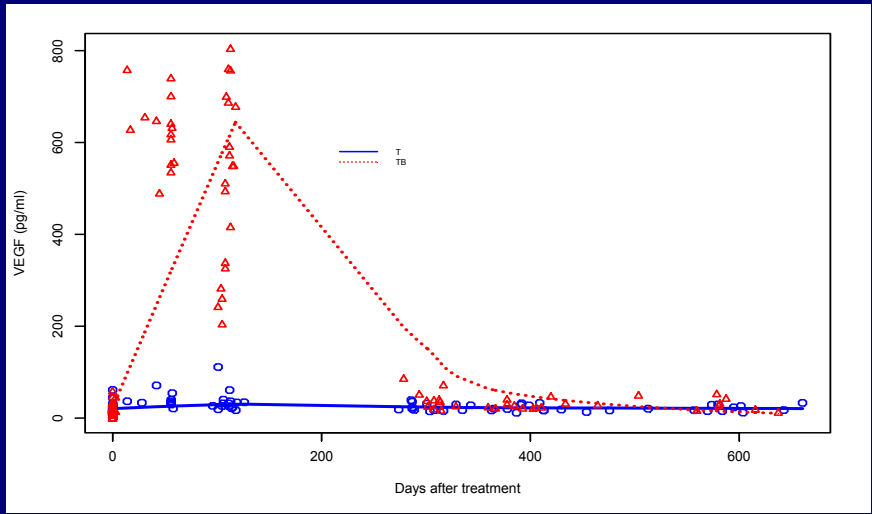
CWRU 3100



Lyons et al, ASCO 06

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

Lyons et al, ASCO 06

Relationship of Neoadjuvant Response to Outcome

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

Micromet?

Macromet?

Prevention trial: can angiogenic switching be prevented?

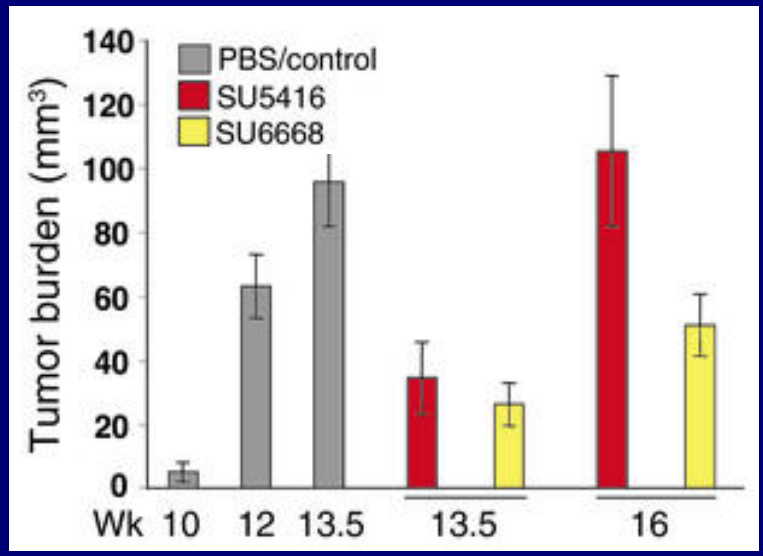
Intervention trial: can tumor progression be slowed or stopped?

Regression trial: can tumor growth be stabilized or regressed and can survival be extended?

Hanahan D, SABCS 06

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

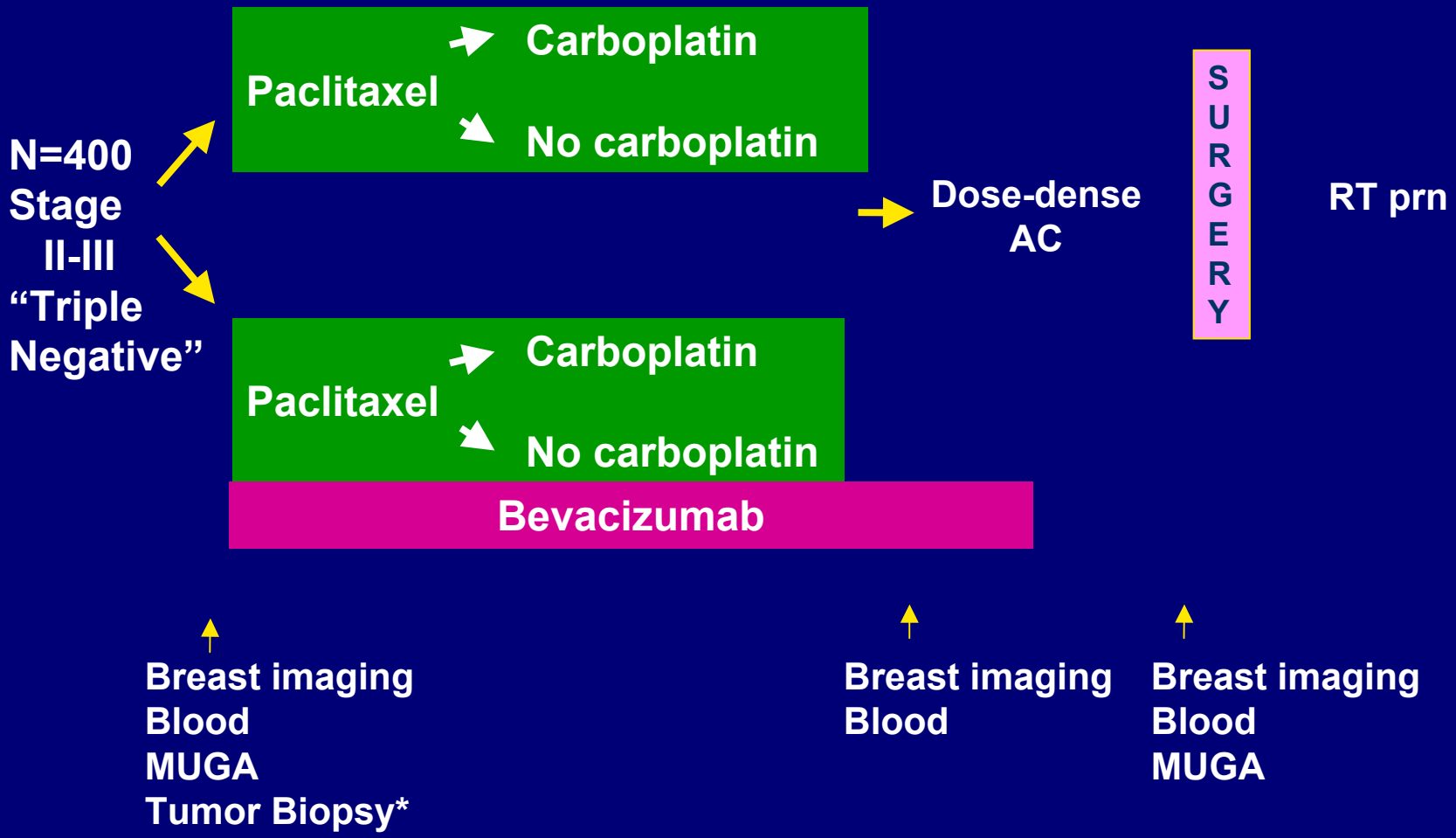
If true, are primary tumor measurements useful?

Antiangiogenic Agents: Varying Kinase Specificities

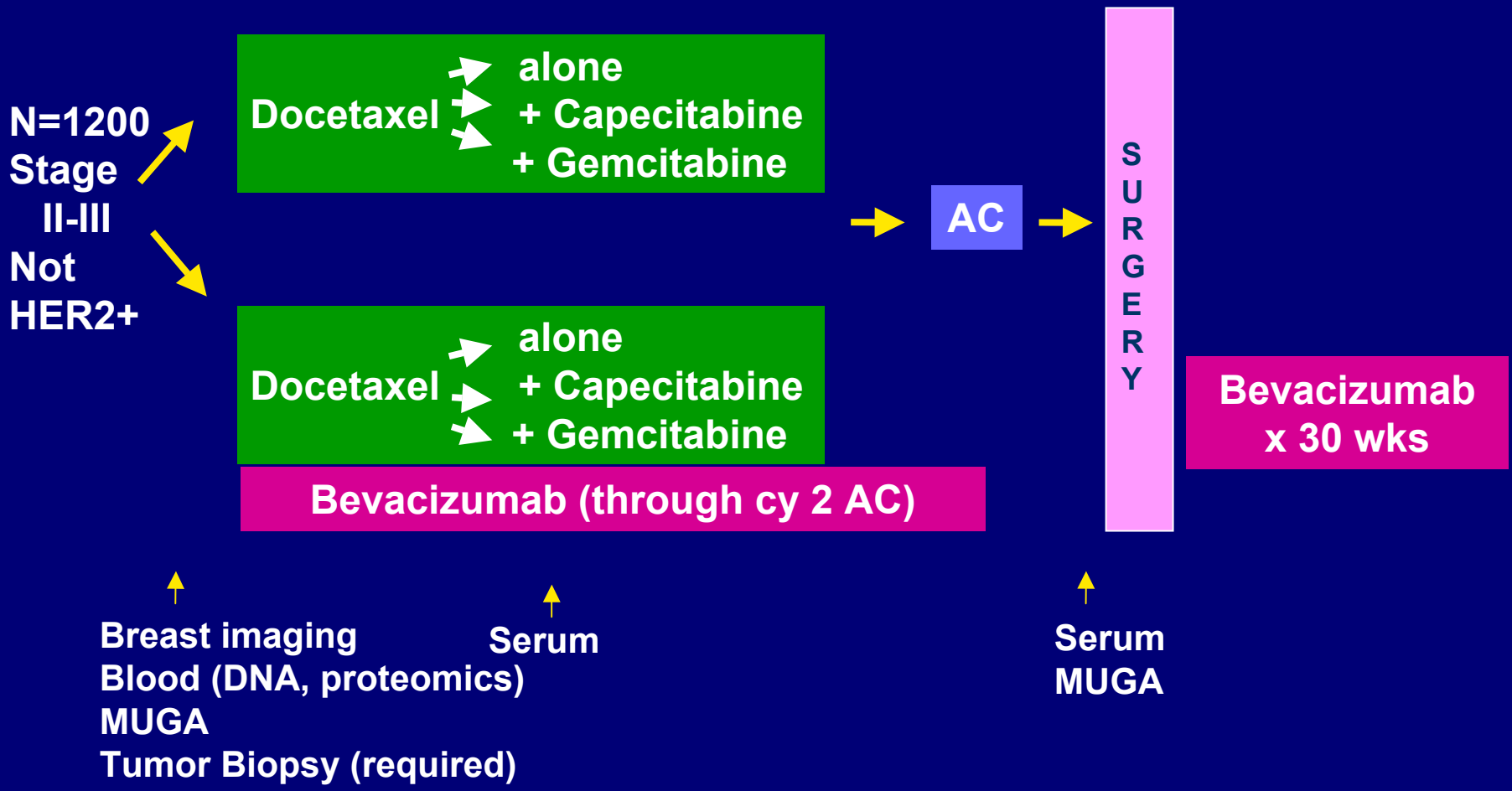
	Imatinib	GW 786034	PTZ787	ZD6474	AG 013736	BAY 43-9006	SU5416	SU6668	sunitinib
VEGFR2	-	0.05-<0.001	0.04	0.04	<0.001	0.03	0.2-1.3	3.9	0.004
VEGFR3	-	0.03	0.62-0.66	0.11	<0.001	0.02-0.10	-	-	-
VEGFR1	-	0.01	0.08	1.6	<0.001	-	<0.001	-	-
PDGFRβ	0.10	0.08	0.58	1.1	<0.001	0.06-0.08	0.5-30	0.1	0.04
PDGFRα	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	-	-	-

Chow and Eckhardt, JCO 2007

CALGB 40603


N=400
Stage
II-III
"Triple
Negative"
Paclitaxel
Carboplatin
No carboplatin
Paclitaxel
Carboplatin
No carboplatin
Bevacizumab
Dose-dense
AC
SURGERY
RT prn
Breast imaging
Blood
MUGA
Tumor Biopsy*
Breast imaging
Blood
Breast imaging
Blood
MUGA

NSABP B-40


N=1200
Stage
II-III
Not
HER2+
Docetaxel
alone
+ Capecitabine
+ Gemcitabine
Docetaxel
alone
+ Capecitabine
+ Gemcitabine
Bevacizumab (through cy 2 AC)
AC
SURGERY
Bevacizumab
x 30 wks
Breast imaging
Blood (DNA, proteomics)
MUGA
Tumor Biopsy (required)
Serum
Serum
MUGA

Summary

- 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