Antiangiogenic Agents in Neoadjuvant Therapy

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Agents Targeting the VEGF Pathway

- Anti-VEGF antibodies (bevacizumab)
- VEGF
- Soluble VEGFRs (VEGF-TRAP)
- Other biologics (indirect):
  - Anti-HER2
  - Anti-HER1
  - mTOR inhibition
- VEGFR-1
- VEGFR-2
- Small-molecule VEGFR inhibitors (PTK787, SU11248, ZD6474, BAY 43-9006, AG013736)

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

Angiogenesis inhibitor

Abnormal environment, Direct effects

Chemotherapy

VEGFR1, 2

cancer cell
Metronomic Chemotherapy + VEGF-targeted Therapy

Kerbel, R. S. J Clin Oncol; 19:45s-51s 2001
Bevacizumab/AT in Inflammatory Breast Cancer

N=21
(20 IBC)

Bevacizumab 15mg/kg q3w
cycle 1-7

AT (50/75)
cycle 2-7

(4 wks)

RT
Bevacizumab
X 8 cycles
Endocrine Rx prn

DCE-MRI
Tumor Biopsy

Wedam et al, JCO 2006
## Bev/AT in IBC
### Patient/Tumor Characteristics

<table>
<thead>
<tr>
<th></th>
<th>N=21</th>
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<tbody>
<tr>
<td>Median age</td>
<td>50</td>
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<tr>
<td>Stage:</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>17</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
</tr>
<tr>
<td>Grade 3</td>
<td>12</td>
</tr>
<tr>
<td>ER +</td>
<td>9</td>
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<tr>
<td>HER2 +</td>
<td>4</td>
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<tr>
<td>Skin biopsy +</td>
<td>12</td>
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</table>

*Wedam et al, JCO 2006*
## Bev / AT in IBC: Toxicity

<table>
<thead>
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<tr>
<td>Hypertension (gr 3)</td>
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<tr>
<td>Bleeding (gr 1)</td>
<td>5</td>
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<tr>
<td>LVEF ↓ (asymptomatic)</td>
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<tr>
<td>Mean ↓ LVEF</td>
<td>-6.2%</td>
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<tr>
<td>Wound complications:</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
</tr>
<tr>
<td>Prolonged seroma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2)</td>
</tr>
<tr>
<td>Incision separation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>Prolonged closure</td>
<td></td>
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</table>

* 8 came off protocol before surgery

*Wedam et al, JCO 2006*

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**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

<table>
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<tr>
<td>CR</td>
<td>0</td>
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<tr>
<td>PR</td>
<td>14 (67%)</td>
</tr>
<tr>
<td>SD</td>
<td>5</td>
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<tr>
<td>PD</td>
<td>2</td>
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<tr>
<td>pCR</td>
<td>1 (of 13)</td>
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</table>

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

Randomized Phase II
N=49
Stage III-IV Unresectable

Weekly docetaxel x 16

(4 wks)

AC x 4
RT Endocrine Rx prn

MRI
Plasma (bFGF, VEGF)
MUGA
Tumor Biopsy*

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?

  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

• 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

Chow and Eckhardt, JCO 2007

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Imatinib</th>
<th>GW 786034</th>
<th>PTZ787</th>
<th>ZD6474</th>
<th>AG 013736</th>
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<td>0.04</td>
<td>0.04</td>
<td>&lt;0.001</td>
<td>0.03</td>
<td>0.2-1.3</td>
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<td>0.02-0.10</td>
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<td>VEGFR1</td>
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<td>0.08</td>
<td>1.6</td>
<td>&lt;0.001</td>
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<td>0.58</td>
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<td>PDGFRαα</td>
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<td>C-kit</td>
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<td>0.07</td>
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<td>C-met</td>
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<td>IGFR1R</td>
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<td>&gt;200</td>
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<td>&gt;100</td>
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<tr>
<td>CSF1R</td>
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<td>Raf-1</td>
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<td>0.006</td>
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CALGB 40603

N=400
Stage II-III
“Triple Negative”

Paclitaxel
Carboplatin
No carboplatin

Paclitaxel
Carboplatin
No carboplatin

Bevacizumab

Breast imaging
Blood
MUGA
Tumor Biopsy*

Breast imaging
Blood
MUGA

Dose-dense AC
RT prn

Surgery
NSABP B-40

N=1200
Stage II-III
Not HER2+

Docetaxel alone
+ Capecitabine
+ Gemcitabine

Docetaxel alone
+ Capecitabine
+ Gemcitabine

Bevacizumab (through cy 2 AC)

Breast imaging
Serum
Blood (DNA, proteomics)
MUGA
Tumor Biopsy (required)

AC

Surgery

Bevacizumab x 30 wks

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

“Never, ever, think outside the box.”