ANG 1005
A paclitaxel conjugate designed to cross the Blood Brain Barrier

TAT 2016
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I/We have no real or apparent conflicts of interest to report.
LRP1 mediates bidirectional transcytosis of amyloid-β across the blood-brain barrier
Angiochem’s ANG1005:
Novel, targeted taxane derivative leveraging the LRP-1 pathway to cross the BBB and enter cancer cells

Angiopep-2: *Binds to LRP-1 receptor*
Angiopep backbone accumulates in mouse brain parenchyma and meninges

Green = Angiopep Cy5.5 conjugate
Red = Vasculature Dextran Texas Red dye

Mouse study, 24 hours post-infusion
Autoradiography of paclitaxel and ANG1005 in a breast cancer brain metastasis model

4-6 wk MDA-MB-231BR Tumor in NuNu Mice

$^{125}\text{I}}$-ANG1005 and $^{14}\text{C}$-paclitaxel (30 min after i.v. injection)

$^{14}\text{C}$-Paclitaxel

- Normal Brain: 1.2* nCi/g
- Tumor: 1.6* nCi/g
- Tumor: 5.2* nCi/g
- Normal Brain: 0.82* nCi/g
- Tumor: 3.3* nCi/g

$^{125}\text{I}$ -ANG 1005

- Tumor: 24 nCi/g
- Tumor: 31 nCi/g
- Tumor: 35 nCi/g
- Normal Brain: 22 nCi/g

Average Normal Brain Concentration

$^{14}\text{C}$-Paclitaxel: 1.0 nCi/g

$^{125}\text{I}$-ANG 1005: 29 nCi/g

## ANG1005 has activity in brain metastases as seen in five clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase I Solid Tumors (CLN-02)</th>
<th>Phase II Breast Cancer (CP1005B016)</th>
<th>Phase II Lung Cancer (CP1005B017)</th>
<th>Phase II Breast Cancer NCI study</th>
<th>Phase II Breast Cancer (CLN-04)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/m²)</td>
<td>¥420</td>
<td>¥550</td>
<td>650</td>
<td>550</td>
<td>600</td>
</tr>
<tr>
<td>Sample Size</td>
<td>N=18</td>
<td>N=61</td>
<td>N=10</td>
<td>N=10</td>
<td>N=38</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>4 (22%)</td>
<td>14 (23%)</td>
<td>2 (20%)</td>
<td>2 (20%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>10 (56%)</td>
<td>35 (57%)</td>
<td>3 (30%)</td>
<td>7 (70%)</td>
<td>21 (55%)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>4 (22%)</td>
<td>12 (20%)</td>
<td>5 (50%)</td>
<td>1 (10%)</td>
<td>11 (29%)</td>
</tr>
</tbody>
</table>

- **Evaluable Patients Intracranial Best Response by MRI**
- **A cycle is drug day 1 IV every 21 days**
- **MRI is performed at baseline and every 2 cycles**
ANG1005 active against brain metastases in breast cancer patients, including patients who have received prior taxane treatment (PR 23%)
ANG1005 has activity at sites of extra-cranial disease in breast cancer patients including those who have received prior treatment with a taxane (PR 25%)

https://clinicaltrials.gov/ct2/show/NCT01480583

* Prior taxane
+ PD based on New lesion(s)/non-target lesions(s)
Primary Objective: Determine whether one cycle of therapy ANG1005 is associated with a significant change in FLT-PET uptake

NCI Sub-Study: Evaluation of $^{18}$F-FLT-PET Imaging

All patients underwent FLT PET/CT imaging before and after 1 cycle of ANG1005

Ang1005 administered intravenously at 550 mg/m$^2$ every 21 days until progression of intra-cranial disease or unacceptable toxicity

- $^{18}$F-FLT - Dose max: 5 mCi
MRI T1          FLT PET/CT

11/20/2012 (Baseline)

SUV\text{max} = 2.35
T:N = 11.75

MRI T1          FLT PET/CT

12/13/2012 (>Cycle 1)

SUV\text{max} = 0.78
T:N = 6.5

Percent change: SUV\text{max} = -66.8%
T:N = -44.7%
## NCI Sub-study of FLT-PET Imaging

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Hormone Receptor Status</th>
<th># Cycles Received</th>
<th>Response</th>
<th>Best MRI Response</th>
<th>% FLT-PET/CT Decrease (Week 3 SUV\text{max})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ER-/PgR-/HER2-</td>
<td>2</td>
<td>SD</td>
<td>-5%</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>ER-/PgR-/HER2+</td>
<td>6</td>
<td>SD</td>
<td>-20%</td>
<td>-11%</td>
</tr>
<tr>
<td>3</td>
<td>ER-/PgR-/HER2+</td>
<td>8</td>
<td>SD</td>
<td>-3%</td>
<td>-6%</td>
</tr>
<tr>
<td>4</td>
<td>ER+/PgR+/HER2-</td>
<td>6</td>
<td>SD</td>
<td>-25%</td>
<td>-33%</td>
</tr>
<tr>
<td>5</td>
<td>ER-/PgR-/HER2-</td>
<td>6</td>
<td>PR</td>
<td>-62%</td>
<td>-68%</td>
</tr>
<tr>
<td>6</td>
<td>ER-/PgR-/HER2-</td>
<td>3</td>
<td>PD</td>
<td>-15%</td>
<td>28%</td>
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<tr>
<td>7</td>
<td>ER+/PgR+/HER2+</td>
<td>18</td>
<td>PR</td>
<td>-59%</td>
<td>-51%</td>
</tr>
<tr>
<td>8</td>
<td>ER+/PR+/HER2+</td>
<td>7</td>
<td>SD</td>
<td>-22%</td>
<td>-38%</td>
</tr>
<tr>
<td>9</td>
<td>ER-/PgR+/HER2+</td>
<td>4</td>
<td>SD</td>
<td>+5%</td>
<td>-7%</td>
</tr>
<tr>
<td>10</td>
<td>ER-/PgR-/HER2-</td>
<td>3</td>
<td>SD</td>
<td>-10%</td>
<td>-18%</td>
</tr>
</tbody>
</table>

**Median**
- -17.5%  
- -14%
NCI Pt #007

• 56-year old female
• 1997: Diagnosis of HER2+ breast cancer
• 2011: Relapsed with brain metastases
• Prior Therapy: Surgery, Adriamycin/Cyclophosphamide, Tamoxifen, Taxol/Capecitabine, Taxol/Carboplatin/Herceptin, Herceptin, Lapatinib/Herceptin, Capecitabine, Lapatinib/Capecitabine, WBRT
• Main symptoms at baseline: Gait disturbance and headache – both improved after 1st ANG1005 treatment

Baseline  >2 Cycles (Week 6)  32% decrease  >4 Cycles (Week 12)  43% decrease
• Best Response: 56% decrease
• Plateau in response after Cycle 9
• Stable through Cycle 18
FLT-PET and MRI: A Comparison

Best Response on MRI (Target lesion only)

Percent Change Median \( \text{SUV}_{\text{max}} \) (Target + Non-target Lesions)

Spearman Correlation
\[ r^2 = 0.7939 \ (p = 0.0088) \]
FLT-PET and MRI: A Comparison

Spearman Correlation
$r^2 = 0.6364$ (p = 0.0002)
Conclusion:
FLT-PET imaging appears to provide a second assessment method that complements and could improve MRI evaluation of CNS response; could give an early index of response
Kaplan-Meier Estimates of Survival
~ Patients with Leptomeningeal Carcinomatosis

MD Anderson
LC Treated since 2005
HER2+ = 25 weeks
HER2- = 10.4 weeks

LC Treated with ANG1005
HER2+: 38.9 weeks
HER2-: 29.9 weeks

HER2+ Median Survival (95% CI): 38.9 weeks (23.3wks-NE)
HER2- Median Survival (95% CI): 29.9 weeks (5.9-34.6wks)

Betty Lawrence, Angiochem; Ken Hess, MD Anderson
ANG 1005

1. The therapy of CNS metastases and leptomeningeal disease has remained largely unchanged for the past three decades.
2. The incidence of CNS metastases is increasing worldwide and that agents to treat this complication of cancer must be developed.
3. Not a novel cytotoxic but an established one with a known, broad spectrum of activity against the most common tumor histologies that metastasize to the CNS.
4. Treats disease outside the CNS.
5. Well-tolerated, and like paclitaxel can be expected to combine well with other agents.
Acknowledgements

NCI Study Team:

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