Development of Rational Drug Combinations for Oncology Indications - An Industry Perspective

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Genentech Inc
Identify a biological feature (relatively) unique to cancer cells versus normal cells
  – Ex. Constitutively activated growth factor signaling pathway
Identify a drug-able target
Generate clinical candidates with acceptable preclinical pharmacology and toxicology
Assess human safety and PK
Assess clinical activity either as a single agent or in combination with standard of care (SOC) therapy in tumor type of highest interest
Limitations of developing targeted drugs “one target at a time”

• High failure rate due to
  – Lack of clinically meaningful single agent activity
  – Inability to combine with SOC therapy (ie. chemotherapy)

• Approved drugs may have only modest benefit
  – Pathway not fully suppressed
  – Biological process not fully suppressed (Ex. tumor angiogenesis)
  – Resistance pathways either pre-exist or are induced
  – Disease heterogeneity

• Value of the drug to patients and sponsor not fully realized
## Examples of Genentech Drug Combinations

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Drug</th>
<th>MOA</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarceva®</td>
<td>EGFR inhibitor</td>
<td>Avastin®</td>
<td>Anti-angiogenesis</td>
<td>Phase III negative</td>
</tr>
<tr>
<td>Tarceva®</td>
<td>EGFR inhibitor</td>
<td>MetMAb</td>
<td>Met inhibitor</td>
<td>Phase III</td>
</tr>
<tr>
<td>Herceptin®</td>
<td>HER2 Signaling</td>
<td>Pertuzumab</td>
<td>HER2 Signaling</td>
<td>Phase III</td>
</tr>
<tr>
<td>Rituxan®</td>
<td>ADCC</td>
<td>Navitoclax&lt;sup&gt;1&lt;/sup&gt;</td>
<td>BCL2 inhibitor</td>
<td>Phase II</td>
</tr>
<tr>
<td>Avastin®</td>
<td>Anti-angiogenesis</td>
<td>Anti-EGFL7</td>
<td>Anti-angiogenesis</td>
<td>Phase II</td>
</tr>
<tr>
<td>Avastin®</td>
<td>Anti-angiogenesis</td>
<td>Anti-NRP1</td>
<td>Anti-angiogenesis</td>
<td>Phase Ib terminated</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>RAF inhibitor</td>
<td>Yervoy&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Immunotherapy</td>
<td>Phase Ib</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>RAF inhibitor</td>
<td>GDC-0973</td>
<td>MEK inhibitor</td>
<td>Phase Ib</td>
</tr>
<tr>
<td>GDC-0941</td>
<td>PI3K inhibitor</td>
<td>GDC-0973</td>
<td>MEK inhibitor</td>
<td>Phase Ib</td>
</tr>
</tbody>
</table>

**FDA approved**  **NDA submitted**  
<sup>1</sup>co-development with Abbott  
<sup>2</sup>BMS
Strategies to enhance the anti-angiogenic activity of bevacizumab

- Bevacizumab: EC apoptosis, tumor regression/stasis
- Drugs that sensitize tumor vasculature to Bevacizumab (anti-NRP1)
- Vascular Maturation
- Other Angiogenic factors
- Drugs that prevent vascular recovery from Bevacizumab (anti-EGFL7)
# Anti-NRP1 Potentiates Bevacizumab-induced Proteinuria

- Proteinuria was not observed in the anti-NRP1 Phase I
- Phase Ib: Arm A - escalating doses anti-NRP1 with Bevacizumab
  - Arm B – escalating doses of anti-NRP1 with Bevacizumab/Taxol

## Table

<table>
<thead>
<tr>
<th>Cohort (mg/kg)</th>
<th>n</th>
<th>Grades 1-2 (n)</th>
<th>Grades 3-4 (n)</th>
<th>All Grades (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>67</td>
</tr>
<tr>
<td>24</td>
<td>7</td>
<td>2*</td>
<td>1</td>
<td>43</td>
</tr>
<tr>
<td>Subtotal %</td>
<td>14</td>
<td>29</td>
<td>7</td>
<td>36</td>
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<tr>
<td>12</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>16</td>
<td>5</td>
<td>1</td>
<td>1**</td>
<td>40</td>
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<tr>
<td>Subtotal %</td>
<td>10</td>
<td>30</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Total %</td>
<td></td>
<td>29</td>
<td>13</td>
<td>42</td>
</tr>
</tbody>
</table>

- Anti-NRP1 development terminated
- Anti-EGFL7 found to be safe and tolerable in a similar Phase Ib and has moved into Phase II testing with chemo/Avastin®

TAT, 2011 and Proc ASCO, 2011
NEOSPHERE – A randomized Phase II evaluating combination therapy targeting HER2

Patients with operable or locally advanced / inflammatory* HER2-positive BC

Chemo-naïve & primary tumors >2cm (N=417)

TH (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)

THP (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

HP (n=107)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

TP (n=96)
docetaxel (75→100 mg/m²)
pertuzumab (840→420 mg)

Study dosing: q3w x 4

SURGERY

• Primary endpoint: comparison of pCR rates
  TH vs THP
  TH vs HP
  THP vs TP

• Secondary endpoints:
  Clinical response
  DFS
  Breast conservation rate
  Biomarker evaluation

Proc SABCS, 2010
Pertuzumab increased pCR when added to trastuzumab/docetaxel

Proc SABCS, 2010

H, trastuzumab; P, pertuzumab; T, docetaxel
### Data supporting an erlotinib plus anti-MET Ab (MetMAb) combination in NSCLC

**In vitro**

<table>
<thead>
<tr>
<th>NSCLC cell line</th>
<th>Treatment</th>
<th>Erlotinib IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H596</td>
<td>–</td>
<td>0.508, &gt;10</td>
</tr>
<tr>
<td>H596</td>
<td>MetMAb</td>
<td>0.997</td>
</tr>
</tbody>
</table>

H596: Met-Exon14Δ, EGFR WT cell line

**In vivo mouse model**

<table>
<thead>
<tr>
<th>Day</th>
<th>Placebo</th>
<th>Erlotinib</th>
<th>MetMAb</th>
<th>MetMAb + erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
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<td>56</td>
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</tr>
<tr>
<td>63</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Clinical**

MET gene amplification is associated with EGFR-TKI resistance in EGFR mutant NSCLC *(Engelman et al., Science 2007)*

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Proc ASCO, 2011
MetMAb plus erlotinib in Met Dx+ patients

**PFS: HR=0.53**

<table>
<thead>
<tr>
<th></th>
<th>Placebo + erlotinib</th>
<th>MetMAb + erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (mo)</td>
<td>1.5</td>
<td>2.9</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.53 (0.28–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>27</td>
<td>20</td>
</tr>
</tbody>
</table>

**OS: HR=0.37**

<table>
<thead>
<tr>
<th></th>
<th>Placebo + erlotinib</th>
<th>MetMAb + erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (mo)</td>
<td>3.8</td>
<td>12.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.37 (0.19–0.72)</td>
<td>0.002</td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>26</td>
<td>16</td>
</tr>
</tbody>
</table>

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**Proc ASCO, 2011**
Scientific Rationale

- Pathways downstream of validated oncology drug targets (HER2, EGFR, KIT)
- Prominent mutational activation in multiple tumor types
- Extensive pathway cross-talk leading to primary or acquired resistance to single agent/single pathway therapy
Combined effects of PI3Ki and MEKi on markers of pathway signaling, cell cycle, and apoptosis

**Pathway Inhibition**

1xEC$_{50}$

- GDC-0973 = 0.05 μM
- GDC-0941 = 2.5 μM

- GDC-0973
- GDC-0941
- p-ERK1/2
- p-AKT(T308)
- pPRAS40(T246)
- p-S6(S235/236)
- p-S6(S240/244)
- S6

**Cell cycle**

1xEC$_{50}$

- GDC-0973 = 0.3 μM
- GDC-0941 = 2.5 μM

- p-ERK1/2
- p-AKT(T308)
- cyclin D1
- p27Kip1
- actin/GAPDH

**Apoptosis**

1xEC$_{50}$

- GDC-0973 = 0.05 μM
- GDC-0941 = 2.5 μM

- BimEL(23kD)
- BimS(12kD)
- BimL(15kD)
- actin/GAPDH

*888MEL BRAFV600E*  
Proc ASCO, 2011
Daily (and intermittent) dosing of GDC-0973 and GDC-0941 results in combination efficacy in xenografts

**Vehicle, GDC-0973, GDC-0941, Combination**

**A375**
BRAF\textsuperscript{V600E}
Melanoma

6 CR (n=10.grp)
2 PRs, 8 CRs

**NCI-H2122**
KRAS\textsuperscript{G12C}
NSCLC

**DLD-1**
KRAS\textsuperscript{G13D}
CRC

**A2058**
BRAF\textsuperscript{V600E}
PTEN\textsuperscript{null}
Melanoma

Proc ASCO, 2011
Phase Ib Study of GDC-0973 and GDC-0941 - Dose Escalation Cohorts

21/7 MEKi Dosing

Intermittent MEKi Dosing

Dose Escalation Schema

<table>
<thead>
<tr>
<th>GDC-0973 (mg)</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD 21/7</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>6a</td>
</tr>
<tr>
<td>GDC-0941 (mg)</td>
<td>80</td>
<td>100</td>
<td>130</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GDC-0973 (mg)</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD 21/7</td>
<td></td>
</tr>
</tbody>
</table>

| GDC-0941 (mg) | 130 | 180 | ...
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>QD 21/7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3+3 study design
PK sample collection
Serial FDG-PET scans
Tumor assessments q8 weeks
Archival tumor tissue collection

Proc ASCO, 2011
Example of anti-tumor activity in K-RAS mutant endometrial cancer

125 mg GDC-0973 intermittent + 130 mg GDC-0941 21/7

Proc ASCO, 2011
Summary and Conclusions

- Rational combination strategies have started to yield promising results in the clinic.
- Success requires a strong scientific rationale and pharmacologically compatible molecules.
- Early Phase Ib testing of combinations is feasible and recommended.
- Efficiently identifying an optimal dose and schedule for combinations of small molecules is challenging.
- Biomarkers (predictive and pharmacodynamic) for the combination should be strongly considered.
- Enhanced toxicity (either additive or synergistic) will derail some combinations.
- Direct collaboration between sponsors is happening at early stages of drug development to rapidly evaluate promising drug combinations.