Combination of Molecularly Targeted Agents (MTAs)

- Clinical Perspectives

Helen Chen, M.D.
Investigational Drug Branch
Cancer Therapy Program (CTEP)
NCI

For IOM discussion, June, 2011

Cancer targets and available agents – opportunities for combination studies (a partial list)

- **Approved agents**
  - Estrogen /androgen receptors
  - BCR-ABL (Imatinib, dasatinib, nilotinib)
  - C-KIT (Imatinib)
  - EGFR (Gefitinib, Erlotinib, Cetuximab, Panitumumab)
  - HER2 amplification (lapatinib, Trastuzumab)
  - PDGF mutation – Imatinib
  - mTOR (temsirolimus, everolimus)
  - VEGF (Bevacizumab, sunitinib, sorafenib, pazopanib)
  - Proteosome (Bortezomib)
  - HDAC (vorinostat)
  - Methylation (azacytidine)
  - CTLA-4 (ipilimumab)

- **Validated targets with Investigational agents**
  - PARP – BRCA deficient tumors
  - Hedgehog (PATCH mutation) - basal cell ca
  - JAK2 - myelofibrosis
  - EML4-ALK - crizotinib
  - BRAFV600E – melanoma
  - MEK

- **Emerging targets/agents**
  - AKT
  - TOR1/2
  - P13K
  - C-MET/HGF
  - IGF-1R
  - BCL-2 family
  - TRAIL
  - STAT
  - SRC
  - CK2, Ron, Axl
  - “Stem cell” targets
  - ....

Challenges in combining two or more NMEs:
IP, Regulatory, and Scientific
Outline of discussion – Scientific issues

• **General consideration**
  – Identifying and prioritizing combinations for clinical testing

• **Clinical experience**
  – Toxicity and efficacy

• **Challenges and critical gaps**

---

Which combination?
- rationale and hypothesis

• **Derived from high throughput screening:**
  - Genomic tools: e.g. siRNA library + agent of interest
  - Unbiased binary drug combination screen: e.g. “COMBO-Plate”; CombinatoRx

• **Mechanism based experiments:**
  – Maximize inhibition of a critical target
    – e.g. VEGFR + VEGF; Her2 TKIs and Abs
  – Maximize inhibition of a pathway (linearly):
    – e.g. Her2 + mTOR
  – Block parallel pathways/cellular process
    – e.g. *antiangiogenic + antitumor;
  – Overcome resistance/escape mechanisms:
    – e.g. IGF-1R + mTOR; BRAFV600-MEK; MEK- AKT/PI3K; AKT –RTK
    – HDACi + Proteosome inhibitor
    – Many others…
Prioritization for clinical evaluation amongst many possible combinations

Factors to consider (no set of criteria will fit all):

• Most essential: credentials of the individual agents
  – Adequate PK and safety of each agent
  – Evidence of clinical activity, and/or target engagement in patients

• Level of clinical validation of the individual targets
  – Biological activity in the indication to be treated

• Strength of preclinical POP for the combination (esp. important if only one or neither agent was clinically active)
  – Tested at clinically relevant doses/exposures?
  – Degree of therapeutic enhancement? (growth inhibition $\rightarrow$ cell kill)
  – Consistent results in multiple models?
    • Or molecular contexts of synergism identified?

Examples of NME combination trials in the pilot project 2003 (VEGF, EGFR, mTOR)

- ECOG 2804 (BeST) RCC (VEGF, mTOR)
  - Bevacizumab
  - Bevacizumab + Sorafenib
  - Bevacizumab + CCI-779
  - CCI-779 + Sorafenib

- NABTC 05-052 GBM (VEGF, mTOR, EGFR)
  - Sorafenib + CCI-779
  - Sorafenib + erlotinib
  - Erlotinib + CCI-779

- SWOG-0438 Melanoma (VEGF, mTOR, raf/raf)
  - Sorafenib + CCI-779
  - Sorafenib + tipifarnib

 Trials based on best available knowledge and strong rationale

However,

- Limited knowledge about the optimal dose/schedule
- No patient selection markers

Investigational agents supplied by respective CRADA partners

Phase I, followed by Randomized phase II design

Mandatory baseline tissue collection and central banking

Central depository of imaging data (DCE-MRI)
To date, hundreds of target agent combination trials have been conducted, for various targets, and agents ....

- Agents w/o selection markers
  - EGFR (in EGFR WT)
  - mTOR
  - VEGF
  - Proteosome (Bortezomib)
  - HDAC (vorinostat)
  - CTLA4
  - PARP
  - IGF-1R
  - BCL-2 family
  - SRC
  - SHH (in paracrine mechanisms)
  - NOTCH

- Agents with candidates of selection markers
  - AKT
  - P13K
  - C-MET/HGF
  - MEK
  - C-MET
  - ...

- Agents with known predictive markers
  - HER2 (amplification)
  - BRAFV600E
  - EGFR (mutation)...
  - BCR-ABL; PDGFRA (mutation)

Sponsored by industry, academia or NCI

Recent combination studies (a select list)

| IGF-1R + MEK | MEK + mTOR | EGFR/HER2 + mTOR |
| MEK + mTOR | MEK + AKT | HER2 + AKT |

Clinical experience

- Tolerability and efficacy
- Challenges
Example 1 – VEGF + mTOR

• Preclinical data supports the hypothesis

(an HCC models)

• Clinical agents available and individually active

<table>
<thead>
<tr>
<th>mTOR inhibitors</th>
<th>VEGF/VEGFR inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temsirolimus; Everolimus; Deforolimus</td>
<td>Bevacizumab; Sorafenib; Sunitinib; ..... others</td>
</tr>
</tbody>
</table>

Active in:
- RCC; Endometrial ca; Neuroendocrine ca
- .....Lymphoma

Active in:
- RCC; Endometrial ca; Neuroendocrine ca
- .....HCC, Ovarian ca

*Similar results in ovarian, RCC and pancreatic ca models

Tolerability

<table>
<thead>
<tr>
<th>VEGFR TKI + mTOR i</th>
<th>MTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib + Temsirolimus</td>
<td>Not tolerable despite dose reduction</td>
</tr>
<tr>
<td>Sorafenib + Temsirolimus</td>
<td>50% dose↓ (sorafenib)</td>
</tr>
<tr>
<td>Sorafenib + Everolimus</td>
<td>75% dose↓ (everolimus)</td>
</tr>
</tbody>
</table>

DLT:
- G3 hand and foot syndrome
- G3 cytopenia

- G3 renal dysfunction
- G3 rash
- G3 typhitis

Enhancement in efficacy?

Sorafenib + CCI-779 (Phase II)
- GMB – not active - RR: 0%; 6m PFS: 0%
- Melanoma – not active - RR: 0%; 6m PFS: 0%
- RCC – pending (BeST trial)
Bevacizumab + CCI-779

Phase I
(Merchan et al, ASCO 2007)

MTD = Full doses of both agents

Phase 2

Prolonged therapy not well tolerated
– ↑G3-4 toxicities (proteinuria; fistula, etc)

Enhanced Activity?
(TORAVA trial, Escudier et al, ASCO 2010)

<table>
<thead>
<tr>
<th></th>
<th>Temsirolimus/Bevacizumab (n = 88)</th>
<th>Sunitinib (n = 42)</th>
<th>Bevacizumab/Interferon (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>28%</td>
<td>24%</td>
<td>36%</td>
</tr>
<tr>
<td>mPFS</td>
<td>8.2 m</td>
<td>8.2m</td>
<td>16.8m</td>
</tr>
<tr>
<td>Median Rx duration</td>
<td>4.7 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off-Rx w/o PD</td>
<td>50.0%</td>
<td>11.9%</td>
<td>30.0%</td>
</tr>
</tbody>
</table>

- ↑ ORR over historical single agent data; however, no clinical benefit over SOC
- Inadequate duration of therapy? Inappropriate discontinuation rules?

BeST trial (CTEP) and Phase 3 trial results pending

MTD of MTA combinations

<table>
<thead>
<tr>
<th></th>
<th>MTD (cycle 1-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR + mTOR i</td>
<td>Bevacizumab + CCI-779 Full dose</td>
</tr>
<tr>
<td></td>
<td>Sunitinib + CCI-779 Not tolerable</td>
</tr>
<tr>
<td></td>
<td>Sorafenib + CCI-779 Dose reduction ↓ (sorafenib)</td>
</tr>
<tr>
<td>EGFR + mTOR</td>
<td>Erlotinib + CCI-779 Dose reduction ↓</td>
</tr>
<tr>
<td>IGF-1R + mTOR</td>
<td>IMC-A12 + CCI-779 Dose reduction ↓ / Full dose</td>
</tr>
<tr>
<td>VEGF + VEGFR</td>
<td>Bevacizumab + Sorafenib Dose reduction ↓↓ (&gt; 50%↓)</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab + Sutent Not tolerable</td>
</tr>
<tr>
<td>EGFR + MEK</td>
<td>Erlotinib + AZD 6244 Dose reduction ↓</td>
</tr>
<tr>
<td>MEK + AKT</td>
<td>AZD 6244 + MK2066 Dose reduction ↓↓</td>
</tr>
<tr>
<td>EGFR + c-MET</td>
<td>Erlotinib + MetMab Full dose</td>
</tr>
<tr>
<td>EGFR + VEGF</td>
<td>Erlotinib + Bevacizumab Full dose</td>
</tr>
<tr>
<td></td>
<td>Erlotinib + Sorafenib Full dose</td>
</tr>
</tbody>
</table>

- Agents with higher specificity more “combinable”
- Combinations targeting the same pathways or “nodal signals” less tolerable
- MTD based on cycle 1-2 did not always predict feasibility of longer therapy
### MTA combinations with promising activity

#### Maximizing inhibition of the same target

<table>
<thead>
<tr>
<th>Target Combination</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 Ab + TKI Trastuzumab + Lapatinib</td>
<td>Breast ca → phase 3 (PFS)</td>
</tr>
<tr>
<td>VEGF + VEGFR Bevacizumab + Sorafenib</td>
<td>RCC, Ovarian ca (phase I)</td>
</tr>
<tr>
<td>EGFR Ab + TKI Gefitinib + Cetuximab</td>
<td>NSCLC (pilot phase II)</td>
</tr>
</tbody>
</table>

#### Inhibition of parallel pathways

<table>
<thead>
<tr>
<th>Target Combination</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF + EGFR BV + Erlotinib</td>
<td>NSCLC → in phase 3 (PFS)</td>
</tr>
<tr>
<td>EGFR + c-MET Erlotinib + MetMab</td>
<td>NSCLC (c-MET IHC+)</td>
</tr>
</tbody>
</table>

#### Other

<table>
<thead>
<tr>
<th>Target Combination</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1R + mTOR IMC-A12 + Temsirolimus</td>
<td>Ewing sarcoma (phase I)</td>
</tr>
<tr>
<td>PI3K + MEK GDC + GDC</td>
<td>Phase I</td>
</tr>
<tr>
<td>BRAF + MEK GSK + GSK</td>
<td>Melanoma</td>
</tr>
</tbody>
</table>

*Many still awaiting confirmatory trials*

- Agents with clinical activities individually more likely to show additive efficacy when combined

### Combinations of MTAs that “failed” in clinical trials

<table>
<thead>
<tr>
<th>Targets</th>
<th>Combinations</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF + EGFR</td>
<td>BV + Chemotherapy + Panitumumab</td>
<td>Colon* → worse PFS and OS</td>
</tr>
<tr>
<td></td>
<td>BV + Erlotinib</td>
<td>Pancreatic, RCC, breast</td>
</tr>
<tr>
<td></td>
<td>Erlotinib + Sorafenib</td>
<td>GBM</td>
</tr>
<tr>
<td>VEGF + PDGF</td>
<td>BV + Imatinib</td>
<td>RCC</td>
</tr>
<tr>
<td>mTOR + Estrogen</td>
<td>CCI-779 + Aromatase inhibitor</td>
<td>Breast*</td>
</tr>
<tr>
<td>mTOR + ImmunoRx</td>
<td>CCI-779 + INFα</td>
<td>RCC*</td>
</tr>
<tr>
<td>mTOR + EGFR</td>
<td>CCI-779 + Erlotinib</td>
<td>GBM</td>
</tr>
<tr>
<td>mTOR + VEGF</td>
<td>CCI-779 + Sorafenib</td>
<td>GBM, Melanoma</td>
</tr>
</tbody>
</table>

* Combinations failed, even though individual agents were active in the same clinical setting

---

**What went wrong?**

- Wrong hypothesis? Incomplete understanding of the biology
- Inadequate dose or duration of therapy?
- Wrong patient population or lack of patient selection?
The dose and schedule question

*If reduction of drug exposure is necessary for a combination...*

- **What would be the optimal dose ratio?**
  - \( \frac{1}{2} \) dose of A + \( \frac{1}{2} \) dose of B
  - \( \frac{1}{4} \) dose of A + Full dose of B
  - Full dose of A + \( \frac{1}{4} \) dose of B

- **Is intermittent exposure sufficient or better?**

**Need to known ...**

- **Preclinical** –
  - Optimal schedule/doses
  - PD/PK required for synergism; surrogate marker of cytotoxicity
- **Clinical** –
  - PD/PK at the chosen and deliverable doses
  - May need to test more than one dose/schedule (with clinical and PD endpoints)

Patient selection issues

- **A given combination can be synergistic or antagonist in different molecular contexts. Patient selection is key to ...**
  - Improving trial efficacy
  - Avoiding unnecessary drug exposure or negative outcomes

- **If a combination requires significant dose reduction, therapeutic window may still (only) exist in selected patients ...**
  - If the tumor is exquisitely sensitive to the agent
    - e.g. EGFR TKIs in EGFR mutant NSCLC (*MTD may not be necessary*)
  - If *the* molecular context is associated with synergism
    - True synergism may confer better efficacy despite dose reduction

**... how to find these pts?**
Issues with tumor biology
-- Experience of IGF-1R and mTOR combination

Phase 1 trial IMC-A12 + Temsirolimus (Naing, LoRusso, ASCO 2011)

- Expansion cohort for EWS (n=17)
  - ORR: 2/17 (12%)
    - 1CR (16m+) in pt with prior IGF-1R mab failure
  - PFS: 5/17 (29%) at 5 months

There are more escape mechanisms!

- AKT inhibition can induce activation of an array of RTKs
  - HER3, InR, EGFR, FGFR, EGFR, …
  - Which RTK is responsible for escape depends on different cell lines and underlying molecular makeup

Further studies may identify which RTK should be inhibited in which patients

However, other escape pathways may emerge!
Optimizing the patient outcome – therapeutic goals and strategies

- Search for combinations that are truly synthetically lethal to tumor cells:
  - Intensive, short course (sustained response or cure)

- If tumor control requires continuous therapy, consider
  - “lighter” dose or regimen that can be tolerated up to tumor progression
  - Sequential rather than concurrent use of active components

- Incorporate agents that act beyond the tumor molecular complexity
  - Active immunotherapy (vaccine, anti-CTLA4, PD-1 …)
  - Other modalities

What have we learned about combinations among MTAs

- Adverse effects on normal tissues may limit the spectrum and degree/duration of combined target inhibitions

- Efficacy results have been variable, with (modest) successes and notable failures – preclinical data not easy to translate

- **Identifying the optimal dose/schedule and the right patients may improve the therapeutic index and outcome**
Filling the Gaps

- **Systematic preclinical studies across diverse molecular backgrounds**
  - Identify molecular contexts predictive of synergism or antagonism

- **In-depth studies on individual agents and their combinations**
  - Define molecular effects on targets; surrogate markers of biological activity

- **Models for toxicity studies**
  - Predict risk, explore mechanism and mitigation strategy

- **Systematic effort in biomarkers infrastructure**
  - Marker discovery, assay development; assay performance

- **Resource and tools to facilitate biomarker incorporation in clinical trials**

Acknowledgement

- **NCI/DCTC**
  - James Doroshow, M.D., Director, DCTD
  - Sherry Ansher, Ph.D., RAB, CTEP
  - Jeff Abrams, M.D., Associate Director, CTEP
  - James Zwiebel, M.D., Chief, IDB
  - Michaele Christian, MD (former CTEP Associate director)

- **Investigators**

- **Industry Collaborators**