Strategies to Develop Combinations of Investigational Agents

Janet E. Dancey MD
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment Diagnosis
Obstacles/Challenges

• Intellectual Property and Data Sharing
  – Agreement of companies AND investigators, institutions
• Risk
• Regulatory (for registration)
  – Safety and efficacy of the agents
• Scientific and medical
  – Mechanism, pharmacology, activity, safety,
• Additional considerations
  – Selection markers for the right therapy for right patient
  – Multiple potential combination of multiple targeted agents against multiple pathways and cellular processes
Combination Studies: IP and Risk

• Evaluation of investigational agent combinations may lead to IP

• Evaluation of investigational agents may be viewed as higher risk for adverse outcomes given the limited knowledge of safety and efficacy
NCI/CTEP Goal: Facilitating Early Combinations

- Overcome barriers: risk aversion, IP, regulatory
- Support early proof of principle (POP) trials with correlative studies
- Identify appropriate molecular contexts for improved efficacy
NCI/CTEP Approaches to IP issues in combining investigational agents from different sponsors

• NCI/CTEP holds collaborative development agreements with > 80 industry partners for > 100 IND agents

• NCI/CTEP has clinical trial agreements with academic institutions, consortia and cooperative groups

• Template agreement language for between NCI, Industry and Investigator
  - Access to data by all parties who provided agents in combination
  - Ability to use the data for scientific and regulatory purposes consistent with development of the single agent
  - IP option: Each collaborator receives fully paid, Non-exclusive, royalty-free licenses to any inventions from the combination studies

Website: [http://CTEP.cancer.gov/industry/ipo.html](http://CTEP.cancer.gov/industry/ipo.html)
Industry-NCI/CTEP-Investigator Agreements

Common Data Sharing and IP Option Agreement Language

Collaborative Agreement

Funding Agreement or MTA (for non-clinical studies)

Collaborator A
Investigational Agent A
Collaborator B
Investigational Agent B
NCI/DCTD

• Agreements cover multiple trials/studies of mutual interest
• Accepted by collaborators.
  – 105 trials combining investigational agents
  – 75 investigational agent combinations MTAs
Investigational Agent Combinations Activated Per Year

* vaccines not included
Combinations: Regulatory Issues

• Safety:
  – Non-clinical studies needed to support combination development depends on information available with each agent
    • Toxicology, pharmacology
  – Non-clinical toxicology for combination may/may not be required
    • Agents have been tested in clinic
    • Agents toxicity

• Efficacy:
  – “…Requirement to show the contribution of each component of a fixed combination regimen”
  – Generally obtained in clinical studies
  – May be supported by compelling non-clinical data
    Examples: High-dose IL-2 + LAK cells
                5-Fluorouracil and Leucovorin

Requires early discussion with regulatory authorities
Combinations: Scientific Issues

- Target selection
- Agent selection
- Patient selection
- Dose and schedule
- Clinical trial design and endpoints
Combinations: Scientific Issues

• Incomplete understanding of individual agents
  – Mechanisms of action, sensitivity, resistance
• Incomplete understanding of human tumors
  – Molecular and biological characterizations
• Limitation of preclinical models
  – Correlation with human tumor characteristics
  – Correlation with human pharmacology and toxicity
• Limitation of clinical trial methodology
  – Means to measure and compare anti-tumor effect and clinical benefit
  – Biomarker assays for patient samples
Non-Clinical Studies

• Needs/uses
  – Understand mechanism of action
  – Evaluate the effects of dose and schedule
  – Develop useful biomarkers
  – Prioritize drugs and drug combinations
Limitations in Predictive Value of Non-clinical Models

- Intrinsic difference between models and cancers in patients
- Limited number of models may not reflect heterogeneity in patients
- Doses used in models may not reflect clinical practice
- Endpoints may not be clinically relevant
- Control/comparator may not be clinically relevant
Improving Non-clinical Testing of Combinations

Systematic effort:
- Molecular characterization of human tumors and non-clinical models

Experiments for specific combinations
- Test in multiple tumor models
- Test clinically relevant doses/concentrations
  - Single agent control at full dose for comparison with combination
- Interpret results in the molecular contexts of the models
  - Synergism or antagonism? In what model and why?
  - Sequence effect? In what model and why?
Which Targets?

- Primary (or both) targets should be relevant
- 2nd target may be selected to
  - Maximize inhibition of the same target
    - E.g. VEGFR + VEGF
  - Maximize pathway inhibition through vertical targeting:
    - E.g. Her-2 + mTOR
  - Block parallel pathways and cellular process
    - E.g. VEGF + EGFR
  - Overcome resistance mechanism(s)
Which Agents?

• Selected agents
  – Non-clinical studies for activity, safety and pharmacology
    • Very important if one/both agents/targets are not clinically active or validated
  – Clinical Studies
    • Acceptable pharmacology and safety
    • Evidence of antitumor activity, and/or effect on target (clinical activity may be absent)
  – Preferred:
    • Minimal PK interactions or overlapping toxicities
    • MOA and patient selection criteria are known
Issues in Clinical Trial Design

• Patient population
• Dose and schedule
• Trial design
• Endpoints
Which Patients?

- **Importance of patient selection and predictive markers:**
  - Efficient drug development
    - Enrich the patient population for a given therapy
  - Rational patient care:
    - Select the right therapy for a given patient

*However*

- **Individual targeted agents are usually tested in unselected patients**
  - Success (or failure) of a trial depended on the average outcome of the population, often without knowledge of who benefited to what extent

- **For combination regimens tested in unselected patients, same problem but more complicated ...**
Which Patients? Possible Outcomes with Combinations in Unselected patients

If a portion of patients within group benefit from each agent. A combination of the agents may have additive, antagonist or synergistic outcome.
Comprehensive approach to correlative studies
Cell lines, animal models, patients

**Baseline**
- Tumor / cell measurement
- Molecular profiling
- Imaging

**Post-Rx (early)**
- Tumor / cell measurement
- Molecular profiling
- Imaging

**Post-Rx (late)**
- Tumor / cell measurement
- Molecular profiling
- Imaging

- Predictive markers for response or resistance
- Effect on target
- Intermediate markers of efficacy
  - CTC? PET, DCE MRI?
- Mechanisms of acquired resistance; candidate of 2nd target
Dose/Schedule

• Sequence/schedule effects may be context/model dependent

• Best doses/schedule of combination may not be those of the individual agents

• Dose/schedule modifications for safety/tolerability may lead to multiple possible permutations
  – Would combination still do better than single agents at full doses given consecutively?
  – Different dose/schedule recommendations
    • ½ dose A + ½ dose B
    • ¼ dose A + full dose B
Combination Trial Design: Multi-arm Testing with Control

- Randomized phase 2 trials give better estimate of effect of combination

- Multiple experimental arms with concurrent control may improve efficiency of evaluation

  - ECOG 2804: Randomized trial in RCC
    - 90/arm targeting 50% increase in PFS
      - bevacizumab
      - bevacizumab + sorafenib
      - bevacizumab + temsirolimus
      - sorafenib + temsirolimus
    - Non-definitive screening comparison of combinations against bevacizumab and pick-the-winner(s) among the winning combinations
### Preliminary Efficacy Results

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Single Agent Data (Historical)</th>
<th>Phase 1 Combination Clinical Trials</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sorafenib: RR: 2%</td>
<td>bevacizumab: RR: 10%</td>
<td>bevacizumab + sorafenib: RR: 14/34 (41%)</td>
</tr>
<tr>
<td><strong>Renal Cancer</strong></td>
<td>temsirolimus: RR: 7%</td>
<td>bevacizumab: RR: 10%</td>
<td>bevacizumab + temsirolimus: RR 8/12 (67%)</td>
</tr>
</tbody>
</table>

* Agents individually active in these settings
Summary

- Significant legal, regulatory, scientific challenges
- These may be overcome by:
  - Common agreements
  - Systematic evaluation of targets/agents in predictive non-clinical models
    - Target/agent/sequence
    - Predictive biomarkers
  - Clinical trials designs to assess multiple combinations with control
  - Assessment of effect on target and evaluation of markers of sensitivity/resistance to individual agents/combinations
- Combinations should be appealing to clinicians and patients
- *Result should be more efficient identification of highly effective therapies*
Acknowledgements

• NCI colleagues:
  – Sherry Ansher
  – Helen Chen
  – Michaele Christian

• Industry and Academic Investigators