

Strategies to Develop Combinations of Investigational Agents

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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

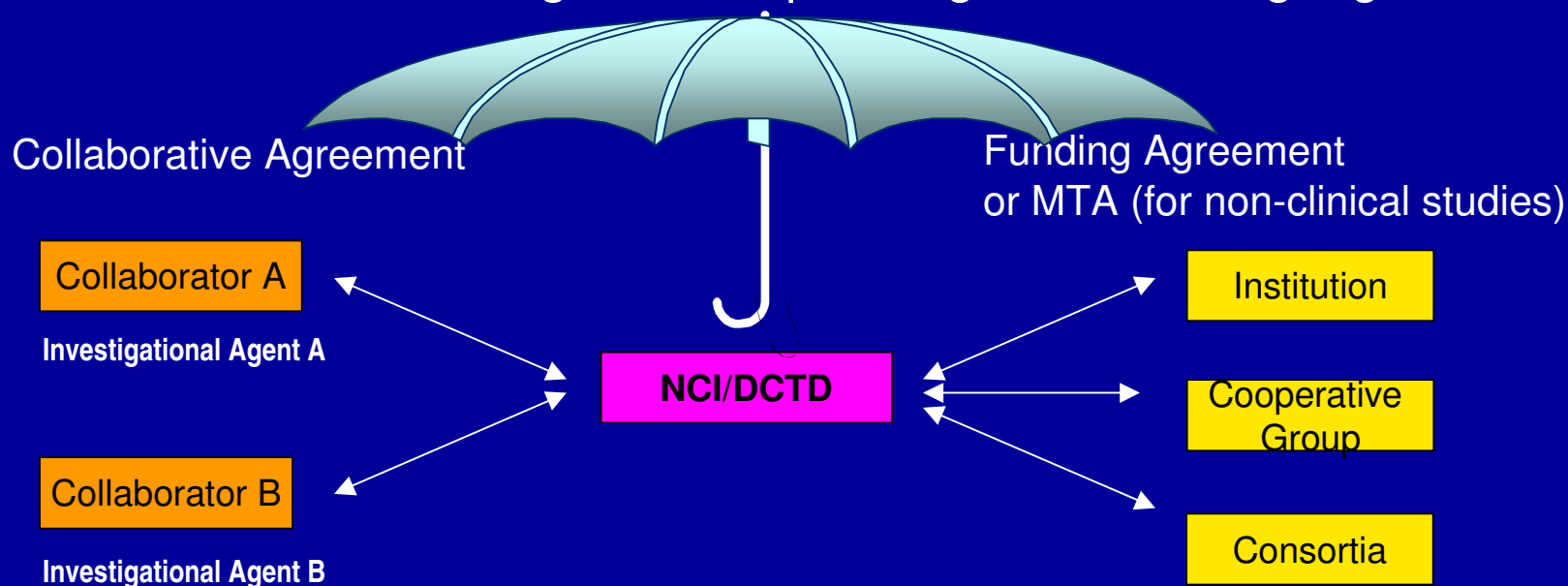
NCI/CTEP Approaches to IP issues in combining investigational agents from different sponsors

- 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>

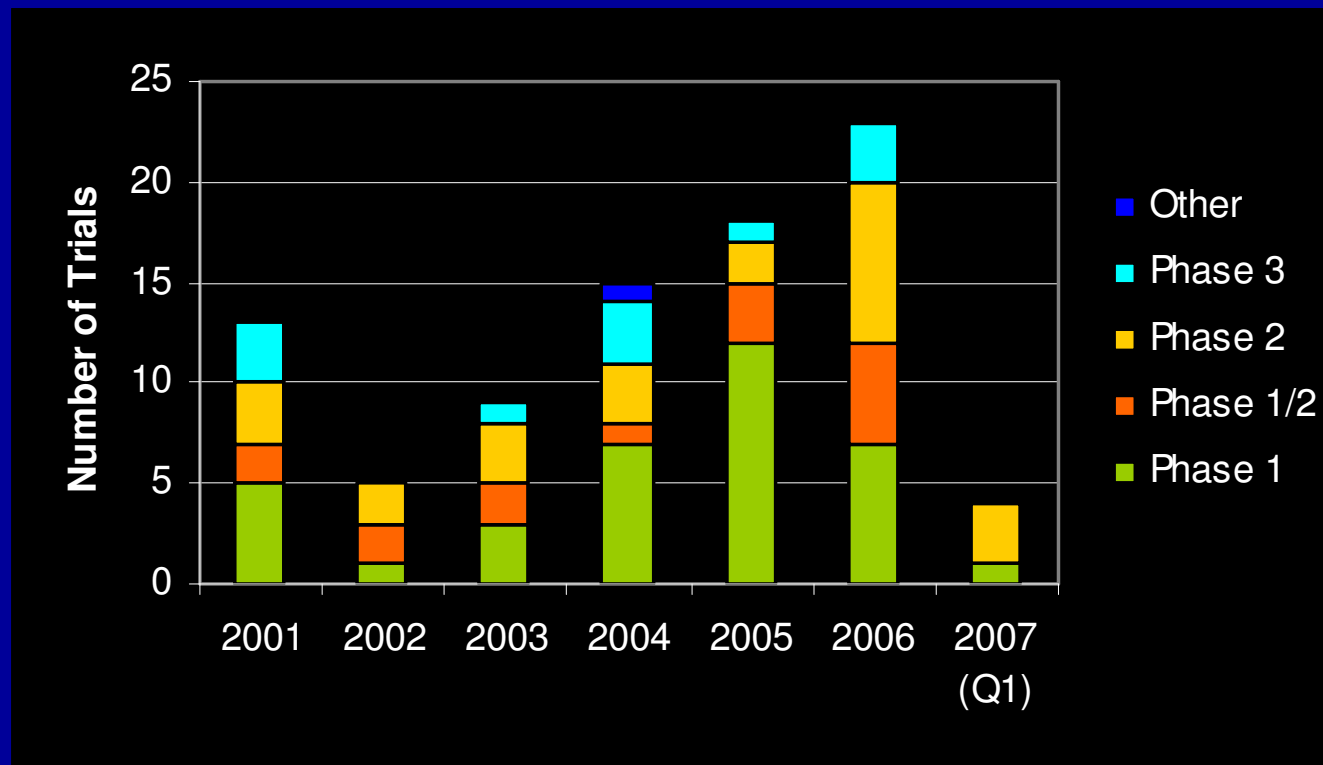
Industry-NCI/CTEP-Investigator Agreements

Common Data Sharing and IP Option Agreement Language



- 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

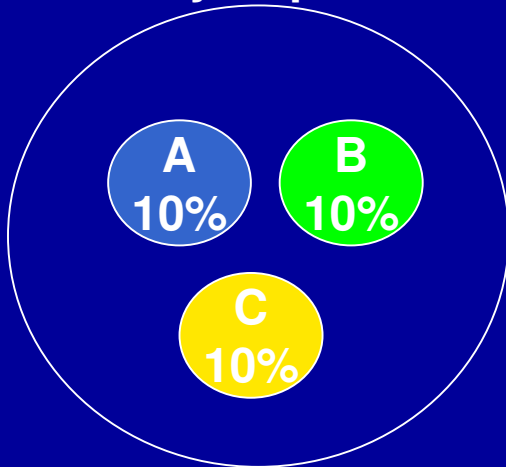
- **Individual targeted agents are usually tested in unselected patients**
 - Success (or failure) of a trial depended on the average outcome of the population, often without knowledge of who benefited to what extent
- **For combination regimens tested in unselected patients, same problem but more complicated ...**

Which Patients?

Possible Outcomes with Combinations in Unselected patients

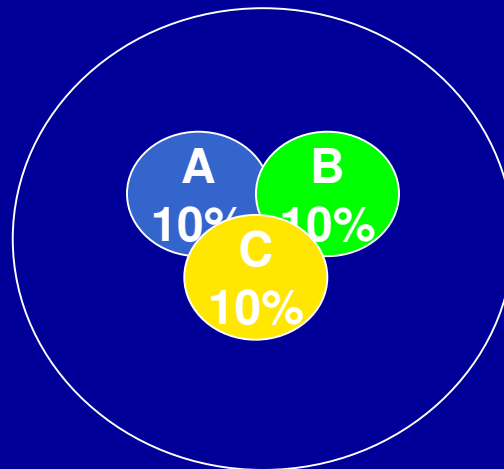
If a portion of patients within group benefit from each agent.
A combination of the agents may have additive, antagonist or synergistic outcome

Study Population



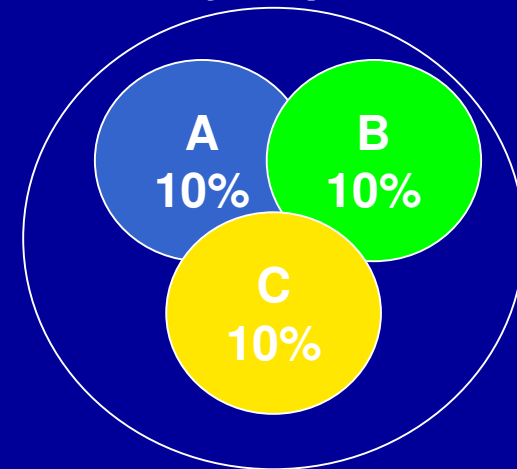
$A+B+C = 30\%$
Patients benefiting
only from 1 agent

Study Population



$A+B+C < 30\%$
Unfavorable interaction
Overlap of sensitivities
Cannot exclude possible
benefit in subset

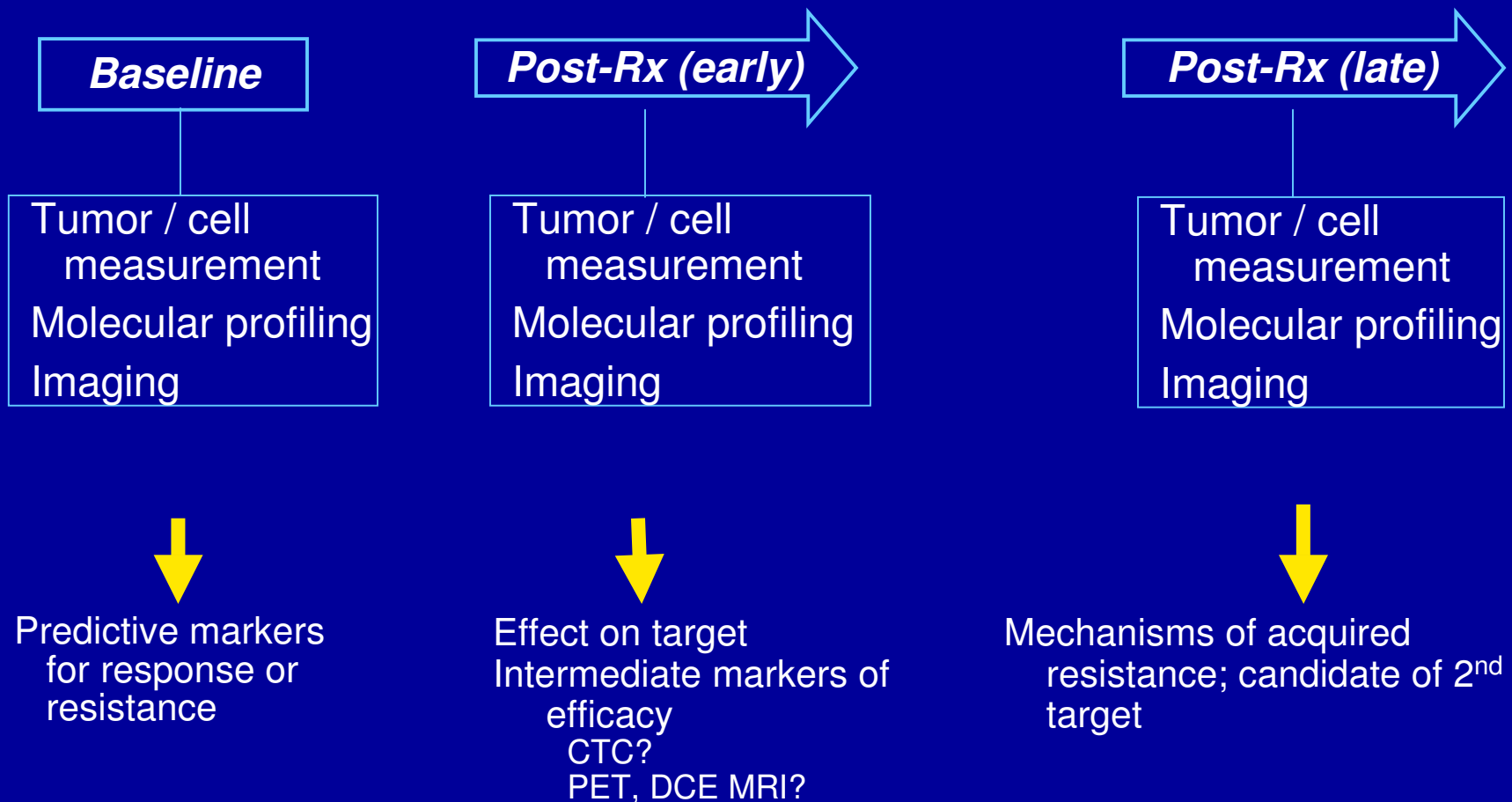
Study Population



$A+B+C > 30\%$
(or there are cures)
True synergy

Comprehensive approach to correlative studies

Cell lines, animal models, patients



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
 - $\frac{1}{2}$ dose A + $\frac{1}{2}$ dose B
 - $\frac{1}{4}$ 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

	Single Agent Data (Historical)		Phase 1 Combination Clinical Trials	Reference
Ovarian Cancer	sorafenib •RR: 4%	bevacizumab •RR: 18 %	bevacizumab + sorafenib • RR: 6/14 (29%)	Azad et al., ASCO 2006
Renal Cancer	sorafenib •RR: 2%	bevacizumab •RR: 10%	bevacizumab + sorafenib •RR: 14/34 (41%)	Sosman et al., ASCO 2007
Renal Cancer	temsirolimus •RR: 7%	bevacizumab •RR: 10%	bevacizumab + temsirolimus RR 8/12 (67%)	Merchan et al., ASCO 2007

* 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

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