WORKSHOP ON FUTURE OPPORTUNITIES FOR THE COMBINATION BIOLOGICAL THERAPY OF CANCER

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INTERNATIONAL SOCIETY FOR THE BIOLOGICAL THERAPY OF CANCER
ORGANIZING COMMITTEE

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• Rachel Humphrey, MD-Bristol-Myers Squibb
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GOALS FOR THE DAY

Program Structure:
• Overview of 2006 Think-Tank
• State-of-the-Science Sessions
• Abstract Program
• Perspectives Presentations
• Breakout Sessions

Objectives:
• Review and define key scientific opportunities.
• Define central obstacles to progress.
• Articulate specific innovative solutions/novel approaches.
• Promote dialogue between academicians, industry and regulatory agencies and enhance shared capabilities.
• Facilitate communication regarding these issues between US, European and Asia-Pacific scientific communities.
MAJOR THEMES: LEADERSHIP PERSPECTIVES

• FDA extremely motivated to facilitate communication with scientific community and educate the respective stakeholders about process and guidelines that impact on the development of biologic combinations.

• Regulatory pathways may differ substantially based on nature of combination.

• FDA and investigator definitions of what constitutes a combination therapy may differ. May warrant additional dialogue between agency

• Organizational changes have resulted in role for both CDER and CBER in the regulation of biologics with coordination via the Office of Oncology Drug Products.

• Keen interest by the NCI in facilitating both investigation and rapid clinical translation of combination approaches for the treatment of cancer—"a paradigm shift from a search and destroy mode to a target and control approach” that selectively targets the biology of the host immune response and the tumor microenvironment.
MAJOR THEMES: LEADERSHIP PERSPECTIVES

• The NCI noted mechanisms to facilitate translational research
  - Translational Research Working Group (TRWG)
  - NCI-FDA Interagency Oncology Task Force (IOTF)
  - Developmental Therapeutics Program (DTP)
  - Cancer Therapeutics Evaluation Program (CTEP)
  - CCR-DCTD Early Therapeutics Program

• Both organizations (NCI and FDA) recognize the unique complexities
  that can impede the development of combinations and the importance of
  addressing these issues in a timely manner.
MAJOR THEMES: INVESTIGATOR PERSPECTIVES

• Dichotomy between “ideal” combination from a commercial drug development perspective and “reality” with biologic combinations.

• **Features of a “perfect” drug combination (early-stage development):**
  - Highly-predictive preclinical models
  - Predictable biomarkers of safety and efficacy
  - Demonstration of POC in phase I
  - Advantageous dose and schedule-finding in phase II

• **Features of a “perfect” drug combination (late-stage development):**
  - High signal-noise ration with predictable PK/PD
  - Established regulatory guidelines
  - Large numbers of patients with unmet medical need
  - Exclusive IP position with little competition
MAJOR THEMES: INVESTIGATOR PERSPECTIVES

• Features of a “nightmare” drug combination (early-stage):
  - Poorly-predictive preclinical models
  - Absence of predictable biomarkers of safety and efficacy
  - Absence of clinical or physiological signal in phase I
  - Disadvantageous dose and schedule-finding in phase II (small effect, expensive endpoints, need for large studies to achieve POC)

• Features of a “nightmare” drug combination (late-stage)
  - Low signal-noise ratio in phase III with unpredictable PK/PD, difficult to assess biologic effect.
  - Regulatory guidelines that are not well-defined.
  - Narrow target population.
  - Shared/disputed IP position with substantial competition
CHALLENGE:
Creation of “ideal” scientific, regulatory and commercial environment for the clinical development of biologic combinations.
MAJOR THEMES: INVESTIGATOR PERSPECTIVES

• Major specific challenges for development of combinations:
  - Access to Reagents
  - Patient Population
  - Regulatory Issues
  - Funding
ACCESS TO REAGENTS

• Combining agents difficult even in preclinical setting.
  - Intellectual Property
  - Liability
  - Contracting, MTA, CTA
  - Impact of toxicity from combination studies on registration

• Many single agents moth-balled prematurely due to “inactivity”.

• Need for additional funding to support DTP-RAID mechanism for synthesis of novel agents.

• Solutions
  - Enhance coordination of efforts between NCI, FDA and industry
  - IP template language shared by NCI, academia, industry
  - Incentives to industry for early access to drugs for combo studies
  - Increase role for CTEP in negotiating contracts for combinations
PATIENT POPULATION

- Treatments may be less effective in immunosuppressed patients with advanced disease and/or extensive pretreatment.

- Adjuvant treatments require surrogate markers or large randomized studies for assessment of clinical activity.

- Complex adjuvant treatments in patients who may be cured may be more difficult to justify in some settings.

- **Solutions:**
  - Improved animal models for preclinical studies
  - More informed correlative biomarker studies
  - More translational research funds from NCI, industry
REGULATORY ISSUES

• Evolving standards for regulation of biologic combinations.

• Costly to comply with standards for manufacturing and safety testing.

• Investigator often ends up holding the IND for IISPs
  -Inadequate training, funding and staff

• Solutions:
  -Tailor regulatory burden to disease severity
  -Increased support for RAID or alternative mechanism for production of reagents.
  -Consider unique study populations and designs
  -Focus on combinations with “targeted” biologic agents
FUNDING ISSUES

• Costs of holding/managing IND

• Need funding for correlative biomarker studies—costly

• Increasing funding pressure based on contracting federal funding sources.
THE GOOD NEWS!

• Exciting range of new options for combination therapy
  - Immunotherapy-Immunotherapy
  - Immunotherapy-Angiogenesis Inhibitors
  - Immunotherapy-Apoptosis Inducers
  - Immunotherapy-Chemotherapy
THE ROAD FORWARD

• Rationale for combination biological therapy of cancer.

• Convergence of interests seeking to enable the development of novel combinations.

• Coordination of resources and strategy will be essential to maximize impact on this issue.

• iSBTc well-suited as organization to address the issue based on translational focus of each group.