WORKSHOP ON FUTURE OPPORTUNITIES FOR THE COMBINATION BIOLOGICAL THERAPY OF CANCER

NOVEMBER 1, 2007
BOSTON, MASSACHUSETTS

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INTERNATIONAL SOCIETY
FOR THE
BIOLOGICAL THERAPY OF CANCER

ORGANIZING COMMITTEE

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- Thomas Gajewski, MD, PhD-University of Chicago
- Rachel Humphrey, MD-Bristol-Myers Squibb
- Hy Levitsky, MD-Johns Hopkins University
- Jon Wigginton, MD-Merck Research Laboratories

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.**

- **<u>Solutions</u>**
  - **-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.


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