International Society for the Biological Therapy of Cancer
"Combination Therapy for Cancer: Opportunities and Obstacles for Future Development"

Clinical Trial Design and Development of Combinations

Breakout 2

July 29, 2006

Questions for Today

- Role for phase 0 or pilot studies in triaging targeted therapies (single agent or *combinations*) based on observed translational/biological effects
- Defining biologic activity for early phase studies?
- Defining clinical benefit for late phase studies?
  - WHO? RECIST? Do these conventional approaches apply?
  - Response after initial progression
- Optimal clinical setting?
  - Minimal residual disease?

- Absence or weak single-agent activity
  - How to structure *combinations,* defining contribution of component
- Issues specific to *combinations* with immunotherapy
  - Potential for antagonism
  - Timing of regimen components
- Exclusion of patients with underlying autoimmunity and/or those who are likely to experience immune-mediated events: is this appropriate?
  - The use of patient enrichment strategies – increasing importance

"Combination"

- "Multi-component therapy is not the same as combination therapy" (Raj Puri; July 29, 2006, 11am)
- For today's discussion, "combination" is any coordinated administration of therapeutic agents
  - "Contribution of components" may need to be defined for US or EU registration
  - E.g. CTLA-4 *plus* vaccine
- "Regulatory" definition (as per Dr. Puri):
  - "combination product" – two agents that are only administered together
    - "contribution of components" may not be required
  - E.g. 5FU/levamisole; vaccine/adjuvant

Phase 0 Studies for Single agents and/or Combinations of Interest (1)

- Rationale
  - Exploratory study to gauge the biological effect of certain targeted or biological therapy with a few patients and limited dosing
    - Antibodies, small molecules, growth conditions for adoptive cell transfer, TKIs,
    - E.g. tumor biopsy where you quantify Th1 response, imaging endpoints
    - Answers the question: which single agent or combination to move forward into development?
  - Low or "effective" single dose
  - Look for targeted biological effect
  - May be appropriate in some clinical settings where low single dose and/or limited may give you enough information to proceed
  - ***Clinical data*** has a clear advantage over ***animal models*** (e.g. toxicity)

Phase 0 Studies for Single agents and/or Combinations of Interest (2)

- Difference between phase 0 and phase I
  - Focused, single dose evaluation of PD only
- Disadvantage
  - May be misleading conclusions with limited data
  - Does it really replace a formal phase I with multiple patients per cohort, multiple doses and escalating cohorts?
- FDA guidance:
  - Currently: this is not applied to multiple vaccine regimens, gene vectors or cells.
    - Internal discussions and interagency (NCI/CTEP) underway.
    - It's only used for small molecules only (sub-treatment dose, single dose, for PK or PD only to show the biological effect.

Small Pilot Studies for Single agents of Interest

- Rationale
  - Exploratory FIH study to gauge the biological effect of certain targeted with a few patients and limited dosing
    - Answers the question: which combination partner to proceed
  - Look for targeted biological effect that serves your combination needs
  - May be appropriate in some clinical settings where low single dose may give you enough information
  - ***Clinical data*** has a clear advantage over ***animal models*** (e.g. toxicity)

Defining Clinical Benefit

- "Second wave" of clinical benefit (e.g. clear benefit preceded by initial progression)
- Key questions:
  - When should patients be switched over to other therapies?
  - How to interpret the activity of "next" treatment whose activity reflects latent benefit from the previous immunotherapy?
- Examples from GIST –
  - Redefine "response", "progression", "meaningful endpoint"
  - PET scan or other imaging approach to define benefit
- Trials should give the option to remain on drug after "progression"
- Definition of response must include the "late responders"
- "Re-set" the baseline at a fixed timepoint (e.g. 6 weeks)?
- Important: distinguish patient management from clinical design elements that add flexibility to the definition of benefit
- May be judged on a cancer by cancer basis

Enrichment Strategies

- Probably not best for phase I
  - Potentially excludes sensitive patients
- Optimally started with hypothesis-generating clinical data in-hand
  - E.g. her-2 neu + for herceptin

Optimal Clinical Setting

- Treat as early as possible before tumor-specific resistance develops
  - Novel trial designs (with smaller numbers of patients) are needed
  - Meaningful biomarkers are key (e.g. bcr/abl)
- Key questions:
  - It remains unclear the best clinical setting
  - Prior to chemotherapy "poisoning"?
  - When the tumor is still in place?
  - Adjuvant? Widely metastatic disease?
  - Cancer stem-cell settings?
  - Neo-adjuvant?