Cancer Immunotherapy Clinical Trials: Concepts & Challenges &Proposed Solutions

April 4-5, 2013

National Institutes of Health Campus
(Masur Auditorium)
Bethesda, MD

Howard Streicher

Senior Investigator

NCI DCTD CTEP IDB

Recent clinical successes have validated the immune system may achieve meaningful antitumor effects BUT challenge existing concepts

- Activity of monoclonal antibodies to CTLA-4, PD-1, PDL1 and PDL-2… (Hoos, Hodi Session 3)
  - Immune system was dynamic, actively suppressed not inert or ignorant
  - Overall Survival essential- develops over time including durable survival plateau (4year OS 20% vs 9% for DTIC)
  - Responses may be late, occur after progression
  - Many tumor types can be immunogenic
  - Toxicity immunologically mediated– not dose related possibly related to benefit
  - Antigenic targets, mechanism, and optimal treatment are not identified
  - Continued room for expanding the scope duration of benefit
- Vaccines Provenge (PAP+GM-CSF) ;

  ProstVac- Phase 3 trials Schlom, Fojo

Complex but interconnected

- Adoptive cell transfer- TIL
  - **Established that anti-tumor activity existing in tumor infiltrates**
  - **Capable of high rates of response against against large bulky tumors**
- TCR, CAR – T cell effectors identify single epitope targets

  BiSpecific Antibodies- blinitumumab CD19- critical targeting

  Monoclonal-DAC antibody conjugates
- Cytokines- IL-2
  - IL 2 with peptide vaccine vs IL 2 had an overall PFS and OS advantage Schwartzentrubber
  - IL 2 with ipilimumab had a 25% 5 year survival and less toxicity than ipi alone

Conclusions

- **Recent success has redefined Tumor Immunology- It is not Immunity**
- Many more new agents and combinations to be tested than can be done
- Clinical trials stand between the experimental goals of “translational science” and establishing “effective or best practice objectives” for treating patients

Drug Development is Inefficient

- The current system is inefficient, creates a bottle neck, doesn't use all available information
- Phase 1 generally uninformative and (necessary) but useless - toxicity does not limit efficacy not dose defining
- Phase 2 Typically not reliable predicting activity
- Phase 3 Although designed as definitive are incomplete and often misleading especially regarding the control groups and appropriate use of sequential treatment and combinations

Immunotherapies are at a tipping point

- Changing from tumor immunology as immune deficiency, attempts to non-specifically stimulating immune responses, to immunizing with specific tumor antigens to breaking tolerance, to expanding an active endogenous immune response by removing suppression**. Current trials are defining new concepts** that will shape our thinking for future clinical trials.
- In the ongoing discussion of clinical trials as a public health resource , genomics, large data bases, and interactivity – centered on "targeted, personalized, or precision" medicine **immunotherapy is rarely included.**

General Objectives

- How should we emend the current phase 1.2.3 trial designs and objectives
- How are immunotherapy trials similar to or different from chemotherapy and targeted therapy
- What are we learning and how do we make decisions about activity and efficacy
- What new concepts are emerging that will shape future trials
- How can we best organize and support/ pay for these efforts

REGULATORY ISSUES

- FDA at AACR 2013 Every Day
  - 3:00 p.m.-5:00 p.m. Regulatory Science and Policy Session
  - Monday A Conversation on Oncology Drug Development: An International Regulatory Perspective from the United States, the European Union, and Canada

    Richard Pazdur, Chairperson
- Regulatory standards are an essential part of the clinical trials system
- It is up to us to set the bar and therefore determine objectives for clinical trials

Organization – Five Sessions

- Goal is to focus on (speakers asked to orient to) on clinical trials issues arising from their work
- Panel Discussions to raise and discuss important clinical trials issues in more detail **Encourage ACTIVE PARTICIPATION--** specific examples and experiences
- Conference summary and continued discussion among individuals and groups -
- SiTC web site
- Encourage challenges to status quo, “conventional wisdom”, and the convenience of necessity

- --

Almost uniformly lack reference to immunotherapy in discussing clinical trials across cancer treatments

- Numerous Articles –
  - Clinical Trials for Targeted Agents – generally not cytotoxic
  - Exploit molecular data
  - Patient selection
  - Tumor Types and clinical stages e.g. Early, adjuvant, metastatic
  - Tumor heterogeneity and “steminess”
  - Biomarkers
  - Surrogate end points
  - Proof of principle studies based on mechanism of action and targeted effect
  - Call for electronic records and data mining , standardization of assays

Immune Activity is Active and Dynamic But Suppressed

- CTLA-4 melanoma, RCC, ovarian cancer
  - Patterns of Activity Differ from cytotoxic chemotherapy Responses are Delayed may occur after initial disease progression

  (Marshall JCO 2000)
  - Modest ORR and PFS advantages
  - OS advantage develops with time; likely plateau effect -
  - Combinations may greatly enhance OS
  - Toxicity is autoimmune inflammatory related
    - Continue treatment past progression defined criteria
    - Use OS as the primary end point

Unique challenges

- Many types of immunotherapy
  - Some rely on “active” stimulation, expansion
  - Some on “passive” or adoptive transfer which use immunologic mechanism

Is there anything new under the sun?

Recent clinical successes have validated the longstanding idea that therapeutic manipulation of the immune system may achieve meaningful antitumor effects understanding that this is a dynamic active process

Re examine the idea of endogenous antitumor immunity and what identifies an immunogenic tumor , tolerance, the nature of cancer antigens, the role of vaccines, cellular adoptive therapies , cytokines, immune regulation-- immune suppression, microenvironment and tumor-promoting inflammation immunomodulatory effects of cancer treatment, emerging technologies and clinical investigations. End points patient selection and biomarkers. (adapted from *AACR Cancer Immunology Research* Dranoff)

Critical Question
General

- What pre-clinical and early clinical data is needed to initiate trials and make choices
- Impact of Recent Studies
- How do we do Combination Studies
- What biomarkers would support these studies
- How do we organize the intellectual and functional aspects of research

2

What are the right controls- standard of care?

What are criteria for patient selection

How do we choose targeted therapies for these patients

Which diseases and stages

Can we do precision medicine with immunotherapy

Delving into somatic variation in sporadic melanoma

Walia Pigment Cell Melanoma Res
2012 March ; 25(2): 155–170