NATIONAL ACADEMIES Sciences Engineering Medicine

SESSION 6

Reflections on the Workshop and Next Steps to Overcome Resistance to Immune Modulator Therapies for Cancer Treatment

MODERATORS

George Weiner and Scott Lippman

PANELISTS

Session 1: Samir Khleif and Tom Curran

Session 2: Gideon Blumenthal and Marc Theoret

Session 3: Kimryn Rathmell and Chris Boshoff

Session 4: Nancy Davidson and Julie Gralow

Session 5: Roy Herbst and Hedvig Hricak

NATIONAL CANCER POLICY FORUM

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

ADDRESSING RESISTANCE IN THE DEVELOPMENT OF CANCER IMMUNE MODULATOR THERAPEUTICS

SESSION 6 PANEL DISCUSSION

Reflections on the Workshop and Next Steps to Overcome Resistance to Immune Modulator Therapies for Cancer Treatment

SESSION MODERATORS

George Weiner, Holden Comprehensive Cancer Center, University of Iowa
Scott Lippman, Moores Cancer Center, University of California, San Diego

PANELISTS:

Session 1 Moderators: Samir N. Khleif and Tom Curran

Session 2 Moderators: Gideon Blumenthal and Marc Theoret

Session 3 Moderators: Kimryn Rathmell and Chris Boshoff (virtual)

Session 4 Moderators: Nancy Davidson and Julie Gralow

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NATIONAL ACADEMIES *Sciences Engineering Medicine*

SESSION 1
CRITERIA TO MOVE SINGLE AGENTS INTO CLINICAL TRIALS

KEY ISSUES IDENTIFIED BY SESSION SPEAKERS

1. Only 2 of the many single agents made it to the clinic - What is missing in determining success of a single agent?

2. The transition form a single immunotherapeutic agent to a combination treatment is not clear – what is the most efficient way to move single agents into combination, administration (dose and sequence).

3. Despite the thousands of clinical trials testing combination, very had shown any success very - How to select the winning combination?

1. Data Sharing needs to be significantly improved including corporate clinical trial data.

1. T Cell exhaustion and additional degradation of immune response in relapsed patients

SESSION 1
CRITERIA TO MOVE SINGLE AGENTS INTO CLINICAL TRIALS

POLICY OPPORTUNITIES TO ADVANCE PROGRESS

- Opportunity 1-2
  1. Identifying a detailed MOA, MOResp and MOResit in appropriate clinical models
  2. Identifying & confirming MOA through phase I POM trials –
  3. Next fork of decision making – Single agent vs. combination
  4. Determine the potential use in combination through proper testing with appropriate pre-clinical models – sensitive and resistant
  5. Consider unconventional clinical trial design paths including single arm rescue

  Opportunity 2

  Need widespread adoption of data standards- some best practices are available
  Big data approaches need big data to work on- model on genomic consortia, modeling, real time data, AI, machine learning
  Critical to develop relevant biomarkers to determine if an agent is active on the target in tumors in Phase I/II even if no biological response otherwise can’t advance to combination therapy

  Opportunity 3
  Use immunotherapies up front or in adjuvant setting as early as possible in disease course

SESSION 3
CURRENT CHALLENGES AND OPPORTUNITIES: BIOMARKERS AND SURROGATE ENDPOINTS

KEY ISSUES IDENTIFIED BY SESSION SPEAKERS

- Issue 1: The host immune system. What is normal? What is abnormal?
- Issue 2: What does the immune system need to render functional antitumor activity?
- Issue 3: How do we get a holistic view of the tumor immune environment?
- Issue 4: Do we have the right imaging tools to effectively represent cancer/response?
- Issue 5: How do we get imaging tools into the clinical arena more quickly?
- Issue 6: How does the evolution of the tumor genome (timing of 9p21 deletion) correspond to resistance?
- Issue 7: Need for effective industry/academic partnerships.
- Issue 8: How can we streamline the process of validating surrogate biomarkers?
- Issue 9: How can we leverage shared databases to increase statistical rigor for surrogate endpoints?
- Issue 10: Accelerating surrogate marker implementation in adaptive or other trial designs.
- Issue 11: ctDNA implementation for drug development or as a surrogate endpoint.

SESSION 3
CURRENT CHALLENGES AND OPPORTUNITIES: BIOMARKERS AND SURROGATE ENDPOINTS

POLICY OPPORTUNITIES TO ADVANCE PROGRESS

- Opportunity 1: Application of immune-PET for treatment stratification, accelerating the implementation of immune-PET in the clinic, translating animal models with human data.
- Opportunity 2: Create an integrated “Immune atlas” to better characterize the range of immune system response behaviors in diseased and normal state.
- Opportunity 3: Create pathway to support collaboration of academia with industry and health authorities for sharing databases to accelerate surrogate biomarker development.
- Opportunity 4: Harmonizing tissue-based biomarkers to be applicable across drugs and disease states.

SESSION 4
CURRENT CHALLENGES AND OPPORTUNITIES: THE ROLE OF DATA AND COMPUTATIONAL TOOLS

KEY ISSUES IDENTIFIED BY SESSION SPEAKERS

- Issue 1: Better characterization of immunotherapy resistance and response, and immune-related adverse events, is needed
- Issue 2: Lack of standardization in data nomenclature
- Issue 3: Issues with quality of data, quantity of data, missing data
- Issue 4: Barriers with respect to data security, data sharing, patient protection, regulatory issues
- Issue 5: Limited communication between researchers, clinicians, patients, and other relevant stakeholders

POLICY OPPORTUNITIES TO ADVANCE PROGRESS

- Opportunity 1: Advanced computing tools and quantum molecular models could advance immunotherapy development
- Opportunity 2: Single cell data could facilitate understanding of immunotherapy resistance/response
- Opportunity 3: Standardize data nomenclature, structured data included in EHRs, and define critical data elements
  - example: MCODE (Minimum common Oncology Data Elements) www.mCODEinitiative.org, https://health.mitre.org/mcode/
- Opportunity 4: Improve machine learning/natural language processing for unstructured data
- Opportunity 5: Incentivize data sharing and communication
- Opportunity 6: Train the next generation of investigators to be fluent in biology/medicine and computational/data science

SESSION 5
CRITERIA TO ASSESS CANCER IMMUNOTHERAPY COMBINATIONS IN EARLY-PHASE CLINICAL TRIALS

KEY ISSUES IDENTIFIED BY SESSION SPEAKERS

- Negative clinical trial results can have dramatic repercussions on the entire field, threatens novel immunotherapy development
- Biomarkers in many different contexts crucial to development—patient selection, immune response, outcome
- Phase 1—Interpret the data, do not extrapolate
- Single arm trials of combination therapies can be problematic, randomized designs are needed, especially early on
- The importance of collaboration, public-private partnerships, and multidisciplinary team science
- Regulatory considerations
    - Opportunities to demonstrate contribution of effect for a combination therapy, early FDA communication to identify potential strategies for meeting regulatory requirement

POLICY OPPORTUNITIES TO ADVANCE PROGRESS

- Incentivize collaboration and facilitate public-private partnerships for combinations
- Enable broad patient access and improve diversity in immunotherapy clinical trials
- Consider opportunities to improve clinical trial design: did drug fail or did the trial not evaluate it intelligently?
  - Biomarker development & validation strategies for selection of multiplex combination biomarkers
  - Leverage new methodologies, such as ex vivo & in vivo functional diagnostics
  - Incorporating pharmacodynamics
  - Biologically effective dose, randomized dose finding
  - Identify patients who do not benefit from current standard of care to triage to first-line investigational therapies
  - Add novel agents to standard-of-care in the context of suboptimal response
  - Use on-therapy immunologic response to guide addition of novel agents