Society for Immunotherapy of Cancer

SITC Immunotherapy Resistance Committee Update

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Massachusetts General Hospital

Problem Statement

- The majority of patients treated with immune checkpoint inhibitors (ICI) experience *de novo* progression or acquired resistance
- Clinical trials of novel therapies and combinations are currently being designed to address the clinical challenge of treating ICI-resistant patients
- Uniform definitions of PD-(L)1 inhibitor resistance are needed to standardize enrollment of patients in order to better enable effective comparisons among regimens and treatment approaches
- There is a current lack of comprehensive clinical trial data sets available to effectively assess clinical PD-(L)1 resistance

What is needed to define resistance?

1) **Adequate exposure**
    a) # doses?
    b) Duration of therapy?
2) **Confirmation of disease progression**
    a) Repeat imaging necessary?
    b) If so, what is the optimal interval (e.g. 2, 4, 6 weeks)?
3) **Does treatment setting requires individual definitions?**
    a) Primary resistance
    b) Secondary resistance
    c) Resistance after stopping therapy
        a) Does timing post-exposure matter?
        b) Does reason for discontinuation matter?

Willingness to accept a 5% ”false progression rate”

SITC Anti-PD-1/PD-L1 Resistance Workshop

Embassy Suites Atlanta at Centennial Olympic Park
Legacy E & F

April 1, 2019
7:00 – 11:00 am

Workshop Goal

Convene stakeholders from across the field of cancer immunotherapy to generate consensus definitions for three scenarios of PD-(L)1 inhibitor resistance:

1) Primary Resistance
2) Secondary Resistance
3) Resistance after Stopping Therapy

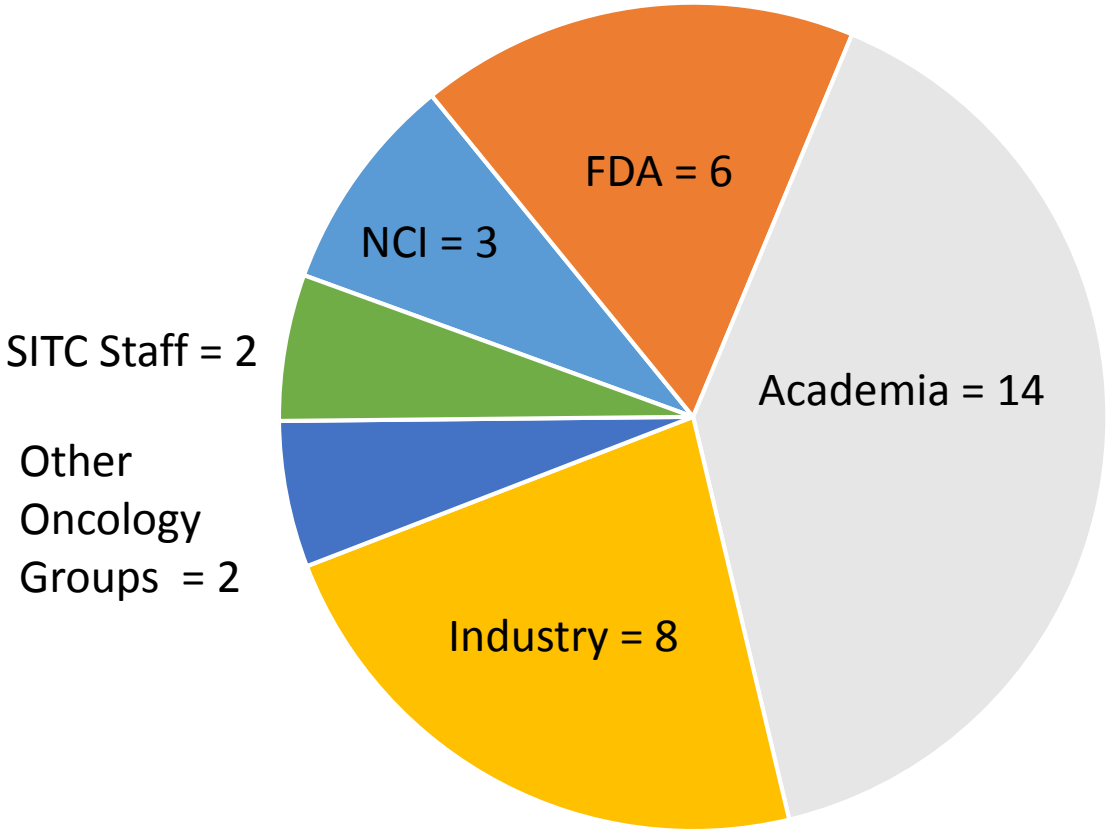
Committee Leadership

Ryan Sullivan, MD
Massachusetts General Hospital

Harriet Kluger, MD
Yale School of Medicine

Hussein Tawbi, MD, PhD
MD Anderson Cancer Center

Immunotherapy Resistance Workshop Attendees



Total Workshop Attendees: 36

Industry Representatives

AstraZeneca
Bristol-Myers Squibb
CytomX Therapeutics
Genentech
Merck

Other Oncology Groups

Cancer Research Institute
Parker Institute for Cancer Immunotherapy

Workshop Outputs

Primary Resistance – Consensus Definitions

Resistance Phenotype	Drug Exposure Requirement	Best response	Confirmatory Scan for PD Requirement	Confirmatory Scan Time Frame
Primary Resistance	≥ 6 Weeks	PD; SD for < 6 months*	Yes**	At least 4 weeks after initial disease progression***

***Indolent tumor types might require modification of the timeframe**

****Other than when tumor growth is very rapid and patients are deteriorating clinically**

*****Per RECIST**

Workshop Outputs

Primary Resistance – Key Caveats

- Not applicable to patients who discontinued treatment due to adverse events and have subsequent disease progression.

- Time frames for confirmatory scans may be dependent on tumor histology.

- The extent and location of tumor growth on PD-(L)1 inhibitors might define variable biologic entities (e.g. oligometastatic disease, lymph node only progression).

- More data is needed:
  - Further interrogation of databases from large clinical trials may serve to determine the true frequency of late responses after initial progression, using this definition of primary resistance, with the understanding that this might vary between drugs and tumor types.

Workshop Outputs

Secondary Resistance – Consensus Definitions

Resistance Phenotype	Drug Exposure Requirement	Best response	Confirmatory Scan for PD Requirement	Confirmatory Scan Time Frame
Secondary Resistance	≥ 6 Months	CR, PR, or SD for > 6 months*	Yes**	At least 4 weeks after disease progression***

***Indolent tumor types might require modification of the timeframe**

****Other than when tumor growth is very rapid and patients are deteriorating clinically**

*****Per RECIST**

Workshop Outputs

Secondary Resistance – Key Caveats

- Not applicable to patients who discontinued treatment due to adverse events and have subsequent disease progression.
- A ‘gray zone’ exists between the above definitions of primary and secondary resistance. For simplification and clinical trial eligibility, the taskforce defines these patients as having primary resistance seeing that resistance developed within six months.
- The consensus was that this definition would be generally applicable to solid tumors in the context of PD-(L)1 inhibitor therapy; but appreciate that may not be applicable to all tumor types.
- Exceptions might be necessary for tumors that tend to be more indolent.
- These recommendations are not based on empiric data from clinical trials, patient registries, or previous studies investigating treatment beyond progression and/or treatment after relapse.

Workshop Outputs

Adjuvant and Neoadjuvant Setting

Adjuvant Therapy	Drug Exposure Duration Prior to PD	Confirmatory Biopsy Requirement*
Primary Resistance	< 12 weeks	Yes
Secondary Resistance	≥ 12 Weeks	Yes

***In this setting, a confirmatory biopsy would supplant a confirmatory scan**

Neoadjuvant Therapy		
Major Pathological Response	Yes	No
Resistance Definition Recommendation	Follow Secondary Resistance Definitions	Follow Primary Resistance Definitions

Workshop Outputs

Treatment Discontinuation Setting

Stopped Therapy (CR/PR/end of study)	Drug Exposure Duration Prior to PD	Confirmatory Biopsy Requirement*
Primary Resistance	NA	NA
Secondary Resistance	≥ 12 Weeks	Yes

***In this setting, a confirmatory biopsy would supplant a confirmatory scan**

Stopped Therapy for toxicity		
Major Pathological Response	Yes	No
Resistance Definition Recommendation	Follow Secondary Resistance Definitions	Follow Primary Resistance Definitions

Future Action Items to Refine Immunotherapy Resistance Definition (as Identified by the Taskforce)

1) Identify rate of pseudoprogression with described definitions using large clinical trial databases

2) Characterize long-term clinical outcomes of patients with PR/SD < 6 months

3) Collect and analyze data concerning patients with primary/secondary resistant tumors retreated with PD-(L)1 inhibitors

4) Define resistance for individual drugs

5) Define resistance for distinct tumor types

Future Action Items to Refine Immunotherapy Resistance Definition (as Identified by the Taskforce)

1) Identify rate of pseudoprogression with described definitions using large clinical trial databases

2)

3) retreated with PD-(L)1 inhibitors

4) Define resistance for individual drugs

5) Define resistance for distinct tumor types

Newly formed SITC Immunotherapy Resistance Committee
Co-chairs – Kluger, Tawbi, Sullivan