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Society for Immunotherapy of Cancer (SITC) checkpoint inhibitor resistance definitions: efforts to harmonize terminology and accelerate immuno-oncology drug development

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ABSTRACT

The need for solid clinical definitions of resistance to programmed death 1 or its ligand (PD-(L)1) inhibitors for clinical trial design was identified as a priority by the Society for Immunotherapy of Cancer (SITC). Broad consensus efforts have provided definitions for primary and secondary resistance and resistance after stopping therapy for both single-agent PD-(L)1 inhibitors and associated combinations. Validation of SITC's definitions is critical and requires field-wide data sharing and collaboration. Here, in this commentary, we detail current utility and incorporation of SITC's definitions and discuss the next steps both the society and the field must take to further advance immuno-oncology drug development.

INTRODUCTION

Immunotherapy has been a standard treatment for some malignancies dating back to the 1980s. However, the modern era of immunotherapy with immune checkpoint inhibitors (ICIs) began in earnest with development of ipilimumab, a monoclonal antibody against cytotoxic T lymphocyte-associated antigen-4, and was revolutionized with the clinical introduction of antibodies against the programmed death receptor 1 (PD-1) and its ligand, PD-L1.[1] While other immunotherapeutic approaches are being developed, ICIs remain foundational, especially in combination with other drugs. Despite this progress, most patients treated with immunotherapy either do not respond or develop therapeutic resistance after initial clinical benefit. Moreover, biomarkers that predict benefit from immunotherapy are suboptimal, and there is a great need to develop optimized approaches for prescribing immunotherapy.

Improved understanding of immunotherapy resistance mechanisms in concert with advancements in drug and assay development are needed, as are close collaborations between industry, academia, funding agencies, and regulatory bodies. To accomplish these goals, a widely accepted definition of ICI resistance is necessary. For example, post-resistance treatment strategies will require clinical trial enrollment of patients with similarly defined resistant disease; in the absence of clear definitions of resistance, drug development in this space may be suboptimal. This commentary focuses on efforts led by the Society for Immunotherapy of Cancer (SITC) towards harmonizing ICI resistance definitions and amplifying their importance. Tables summarizing the definitions of resistance to combinations of more than one ICI, combinations with targeted therapies or combinations with chemotherapy are provided in the online supplemental materials.

SITC immunotherapy resistance definitions

SITC held a workshop in 2019 to develop single-agent ICI resistance definitions towards providing framework for future rational combination development. This workshop involved three distinct components—creation of clinical definitions of primary resistance to PD-(L)1 inhibitors, secondary resistance definitions, and resistance definitions for situations where treatment was stopped in either the adjuvant or metastatic setting. A white paper describing the consensus was published in the *Journal of ImmunoTherapy of Cancer* (JITC) in 2020.[2]

In 2021, a similar endeavor to define resistance to combinations with a PD-(L)1 backbone commenced. The SITC Immunotherapy Resistance Committee similarly identified experts with diverse backgrounds and employment. Given the multitude of approved regimens and the diversity of partnering drugs,

the workshop and its participants were divided into three subgroups, one focusing on combinations of immuno-oncology (IO) agents with PD-(L)1 inhibitors, the second on anti-PD-(L)1 with targeted therapies, and the third on anti-PD-(L)1 with cytotoxic chemotherapy. Subgroups met to discuss definitions of primary resistance, secondary resistance and tumor growth while off therapy. Consensus statements from these efforts were recently published in JITC.[3–5] Of note, each of the three immunotherapy combination manuscripts and the initial manuscript on resistance to anti-PD-1 monotherapy address tumor growth on or after adjuvant therapy and growth during or after neoadjuvant therapy, as these drugs are now being increasingly used in earlier stages of disease.

Current usage of SITC resistance definitions

Retrospective analyses

SITC's resistance definitions have been used within retrospective analyses. Current definitions provide clear delineation between patients with primary/secondary resistance allowing investigators to ask key questions about relationships between pretreatment factors that may correlate with clinical resistance. Such studies may ultimately provide insight into resistance mechanisms. For example, SITC's definitions were incorporated into a retrospective clinical and radiologic review of patients with melanoma treated with single-agent anti-PD-1 at two institutions, analyzed by blinded radiographic review. Investigators, using prior primary or secondary resistance definitions,[2] showed that primary resistance correlated with poorer outcomes at time of progression and that secondary resistance were more likely to present as oligo-progression.[6] The different clinical manifestations seen support the notion that the biology driving primary and secondary resistance may be distinct, and that SITC's definitions can assist in future, similar studies.

Incorporation into novel clinical trial protocols

Identifying novel treatment options for patients with primary or secondary ICI resistance is critical. Two National Cancer Institute (NCI)-sponsored trials through SWOG Cancer Research Network highlight the importance of incorporating resistance definitions for both trial design and interpretability. First, S1616 (NCT03033576) was designed for patients with advanced, primarily PD-(L)1-resistant melanoma and excluded those with secondary resistance per SITC's definitions, and its results are applicable to a specific group of patients. Trials lacking clear definitions may result in ambiguous results. For example, S1607 (NCT02965716), which evaluates the combination of talimogene laherparepvec and pembrolizumab in patients with advanced melanoma who have progressed following prior anti-PD-1 therapy, with or without an initial response, had a broader population than S1616 and, as such, its results may be confounded by initial response. This serves as an example where stratification by resistance subgroups would help interpretability of results and guide future drug development.

Increasing opportunities to enroll relapsed patients exist as PD-(L)1 inhibitors gain more approvals. For example, a recent trial (NCT03141684) was designed to enroll patients with alveolar soft part sarcoma (ASPS) who developed resistance to atezolizumab to crossover to atezolizumab with bevacizumab. However, this trial also highlights limitations of SITC's definitions, as they may be restrictive for rare diseases like ASPS. As such, it is important that current definitions be treated as recommendations where conditions change according to disease, histology, patient populations, and unmet medical need, until increased data availability and validation allow for refinement and optimization.

Incorporation into translational immunotherapeutic efforts

A cross-disciplinary workshop that included the Parker Institute for Cancer Immunotherapy, the Cancer Research Institute, and SITC serves as an example of the utility of SITC's definitions in developing a mechanistic framework for key biological processes that influence antitumor immunity. The workshop highlighted how biomarker data would have limited utility for informing treatment in future studies in the absence of uniform resistance definitions.[7] Instead, SITC's initial work enables molecular analysis of patient populations that are more clinically uniform for a deeper understanding of immune resistance and ultimately should provide data sets that can be leveraged across studies and reveal biological complexity associated with clinical outcomes. SITC's newly developed combination resistance definitions will provide a critical framework for homogeneous biomarker data and allow for data aggregation across combination studies.

Challenges facing standardized IO resistance definition usage

While SITC's efforts serve as an excellent starting point, harmonization of clinical PD-(L)1 resistance definitions faces challenges in widespread adoption. First, increased visibility and dissemination to the IO drug development community is necessary. Clinical investigators need to be made more acutely aware of those definitions and educated on their use, potentially through presentations at workshops and educational meetings.

Importantly, SITC's definitions were developed as a consensus among experts based on their vast clinical experience rather than real-world and/or clinical trial data. The next challenge is to correlate definitions to clinical outcomes through application against patient-level data, ideally from existing clinical trials. Unfortunately, there remains a paucity of randomized studies in the second-line setting that can take advantage of the generated definitions and stratify accordingly. In addition, the field requires precompetitive data sharing mechanisms that will allow efforts such as these to be validated and used for the benefit of all stakeholders.

Finally, added pressure from the US Food and Drug Administration (FDA) to apply the above approaches would be helpful. An opportunity to collect necessary

data for validation may exist within the growing acceptance of externally-augmented clinical trial designs. One might imagine the development of a Consolidated Standards of Reporting Trials-diagram-like requirement in journals detailing the PD-(L)1 resistance cohorting of patients in IO drug development.

Future SITC efforts towards supporting standardized IO resistance definition usage

SITC will take a proactive approach to educate and disseminate the current definitions. Communications will highlight that while these efforts were SITC-organized, they are not and should not remain SITC-specific and should serve as a tool for the field. These definitions may also encourage and support translational studies that investigate immunotherapeutic resistance based on clinical phenotypes. As such, SITC's definitions serve as a foundation for institutions/pharma to share data in a derisked manner as they support future drug development in a non-biased, precompetitive way.

It is critical that SITC encourages broad incorporation of definitions when stakeholders design clinical trials. SITC will need to engage key stakeholders such as FDA, industry, cooperative clinical trial groups, patient advocacy organizations and others to increase definition awareness and usage. We propose live programing detailing the importance of these definitions and allowing for a dialog on how best to implement them. Such programing should include discussion on key scientific questions, including whether distinct immunotherapies require unique definitions of resistance or if certain diseases require modified definitions. We must also determine how SITC's definitions correlate with widely accepted regulatory end points, including overall survival, progression-free survival, overall response rate, and quality of life metrics.

SITC's resistance definitions also serve as a critical resource for biomarker development. Current definitions can assist in evaluating the relationship between assay outputs, ascertained resistance profiles, and ultimately help personalize patient selection. However, lack of data sharing in this arena serves as a barrier for progress. Work by the SITC Biomarkers Committee outlined both conceptual and practical challenges to data sharing.[8] Solutions for addressing these barriers include striving for realistic goals and culture shifts as they relate to data sharing. Engaging with key stakeholders using the recommendations from the SITC Biomarkers Committee in concert with SITC resistance definitions may help in gaining access to data supporting both efforts, which is drastically needed for future IO drug development.

CONCLUSION

SITC's efforts in forming uniform resistance definitions serve as an excellent first step in the next frontier of immunotherapy trials—targeting the resistant population. Tables summarizing the definitions are provided in the online supplemental materials. The panel acknowledges the shortcomings of these definitions, primarily due to lack of validation using high-quality clinical data. The Committee hopes that the field can come together along SITC's example towards sharing necessary data in precompetitive mechanisms to broaden and validate resistance definitions as immunotherapies evolve, while introducing novel, life-changing treatment options for patients with cancer.

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Supplementary Figure 1: SITC ICI Monotherapy Resistance Definitions

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

Definitions of Primary and Secondary Resistance for ICI Monotherapy[2]

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***
Secondary Resistance	≥ 6 Months	CR, PR, 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 RECIST1.1

Definitions of Adjuvant Therapy Resistance for ICI Monotherapy[2]

Adjuvant Therapy	Timing of Last Dose Prior to PD	Confirmatory Biopsy Requirement*
Primary Resistance/ Early Relapse	< 12 weeks	Yes
Late Relapse	≥ 12 Weeks	Yes

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

Definitions of Neoadjuvant Therapy Resistance for ICI Monotherapy[2]

Major Pathological Response	Yes	No
Resistance Definition Recommendations	Follow Secondary Resistance Definitions	Follow Primary Resistance Definitions

Definitions of Resistance after Discontinuing Treatment with ICI Monotherapy[2]

Stopped Therapy (CR/PR/end of study/other social rationale)	Duration of time after last dose of PD-(L)1 Inhibitor	Confirmatory Scan Requirement
Primary Resistance	No CR/PR prior to discontinuation	No
Secondary Resistance	Prior CR/PR and ≤ 12 Weeks from last dose	Yes
Late Progression	Prior CR/PR and >12 weeks from last dose	Yes

Supplementary Figure 2: SITC ICI Combination Resistance Definitions

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

Definitions of Primary Resistance for ICI Combinations

Treatment combination	Exposure requirement	Best response	Confirmatory scan requirement
IO-Chemotherapy[3]*	6–8 weeks**	PD ≤ 6 months***	Not required
IO-Targeted[4]	8−12 weeks**** (at least 2 cycles of ICI component)	PD or SD < 6 months	Not required
IO-IO[5]	12 weeks and/or a minimum of 2 cycles of both drugs	PD or SD < 6 months	At least 4 weeks after PD, if clinically feasible

***For patients that experience recurrent disease after stopping therapy for reasons other than toxicity, no uniform clinical definitions of resistance applicable across disease states could be described
**For rapidly progressing disease, any exposure is adequate
****Timing of RECIST progression regardless of best response
*****In the absence of toxicity or progression while on treatment

Secondary Resistance for ICI Combinations

Treatment combination	Exposure requirement	Best response	Confirmatory scan requirement
IO-Chemotherapy[3]*	> 6 months	PD > 6 months**	Not required
IO-Targeted[4]	> 6 months	CR, PR, or SD ≥ 6 months	Not required
IO-IO[5]	> 6 months	CR, PR, or SD ≥ 6 months***	At least 4 weeks after PD, if clinically feasible

***For patients that experience recurrent disease after stopping therapy for reasons other than toxicity, no uniform clinical definitions of resistance applicable across disease states could be described
****Timing of RECIST progression regardless of best response
*****For aggressive tumors such as mesothelioma and NSCLC, 3 months is required

Resistance for ICI Combinations in the Adjuvant Setting

Treatment combination	Exposure requirement	Best response
IO-Chemotherapy[3]*	Undefined	Undefined
IO-Targeted[4]	A minimum of 6 weeks to adjuvant therapy completion	Recurrence < 12 weeks after the last administered dose
IO-IO[5]	Completion of regimen	≤ 12 weeks or recurrence on therapy after the last administered dose**

*Definitions could not be agreed upon given current data availability

**Primary resistance is deemed undeterminable if progression occurs > 12 weeks after the last administered dose

Resistance for ICI Combinations in the Neoadjuvant Setting

Treatment combination	Exposure requirement	Best response
IO-Chemotherapy[3]*	Undefined	Undefined
IO-Targeted[4]	Minimum of 6 weeks	< 50% tumor death in resection specimen
IO-IO[5]**	Completion of regimen	≤ 12 weeks or recurrence on therapy after the last administered dose***

*Definitions could not be agreed upon given current data availability

**Definitions are only applied in scenarios where postoperative therapy is not applied and major pathologic response was achieved. Resistance cannot be determined if major pathologic response is absent

***Primary resistance is deemed undeterminable if progression occurs > 12 weeks after the last administered dose