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Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce

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ABSTRACT

As the field of cancer immunotherapy continues to advance at a fast pace, treatment approaches and drug development are evolving rapidly to maximize patient benefit. New agents are commonly evaluated for activity in patients who had previously received a programmed death receptor 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitor as standard of care or in an investigational study. However, because of the kinetics and patterns of response to PD-1/PD-L1 blockade, and the lack of consistency in the clinical definitions of resistance to therapy, the design of clinical trials of new agents and interpretation of results remains an important challenge. To address this unmet need, the Society for Immunotherapy of Cancer convened a multistakeholder taskforce—consisting of experts in cancer immunotherapy from academia, industry, and government—to generate consensus clinical definitions for resistance to PD-(L)1 inhibitors in three distinct scenarios: primary resistance, secondary resistance, and progression after treatment discontinuation. The taskforce generated consensus on several key issues such as the timeframes that delineate each type of resistance, the necessity for confirmatory scans, and identified caveats for each specific resistance classification. The goal of this effort is to provide guidance for clinical trial design and to support analyses of emerging molecular and cellular data surrounding mechanisms of resistance.

INTRODUCTION

Cancer immunotherapy utilizes the immune system to mount an antitumor effect—most commonly through activation of tumor antigen-specific T cells—and includes multiple modalities including cell therapies, vaccines, and monoclonal antibodies that target immune checkpoints.[1 2] Specifically, immune checkpoint inhibitors (ICIs) have rapidly altered the treatment paradigm for cancer patients, across multiple settings and indications, primarily by providing durable clinical benefit—defined as tumor response or prolonged stable disease (SD), as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, lasting 6 months or greater[3]—to an increased number of patients compared with chemotherapy and radiation. Nevertheless, a majority of patients have disease that exhibits either no clinical response or response followed by progression to inhibitors of the programmed death receptor 1 (PD-1) or its major ligand programmed death-ligand 1 (PD-L1).[2] As such, the development of effective immunotherapies following PD-(L)1 inhibition for "ICI-resistant" populations across treatment settings and scenarios represents a significant challenge and a pressing priority for the field of oncology.

Resistance to PD-(L)1 inhibitors is clinically complex and can present at various time points during treatment, including immediately after treatment initiation (primary resistance), weeks or months after evidence of initial clinical benefit (secondary resistance), or after treatment has been halted for a variety of reasons. Due to this complexity and the rapid advancement of immunotherapy into the clinic, uniform definitions of PD-(L)1 inhibitor resistance have not yet been developed. While there have been initial efforts to characterize primary resistance and delayed progression following treatment with PD-(L)1 inhibitors in patients with unresectable or metastatic melanoma,[4] limited data are available that would allow for generation

of uniform resistance definitions applicable to multiple diseases across the above scenarios. Uniform definitions validated by comprehensive data sets would greatly benefit drug development by supporting standardized clinical trial enrollment and appropriate comparisons among novel regimens and treatment approaches in post-PD-(L)1 clinical trials.

In the absence of the necessary, compete clinical trial data sets, expert-driven consensus definitions of resistance have provided significant value in multiple disease settings. For example, consensus definitions of resistance concerning anti-epidermal growth factor receptor (EGFR) agents in lung cancer, as well as endocrine treatment in breast cancer, have greatly benefited patients by enabling pooled analyses and rendering research findings more easily understood, subsequently expediting the advancement of novel therapeutics into the clinic.[5 6]

Recognizing the unmet need within the field for PD-(L)1 inhibitor resistance definitions, as well as understanding that clinical trial data concerning PD-(L)1 inhibitor resistance are limited and not comprehensive, the Society for Immunotherapy of Cancer (SITC) established a taskforce to develop expert consensus definitions for the clinical phenotypes of PD-(L)1 inhibitor resistance, including clinical definitions of primary resistance, secondary resistance, and resistance that develops after discontinuation of therapy. This initiative aims to provide consistency in investigations of the clinical and biological manifestations of ICI resistance, as well as to establish a drug development framework that better estimates the therapeutic efficacy of novel agents administered alone or in combination with PD-(L)1 inhibitors after prior PD-(L)1 treatment. Furthermore, as many clinical trials are not currently designed to consistently collect comprehensive data on ICI resistance, the taskforce worked to identify areas of opportunity within future clinical trials to refine the developed PD-(L)1 resistance definitions by promoting data collection and sharing and to assist future efforts for other clinical settings and/or modalities.

METHODS

SITC formed the Immunotherapy Resistance Taskforce by convening a number of stakeholders—including representatives from academia, industry, government agencies, and other oncology-focused societies—in order to generate expert consensus definitions concerning resistance to PD-1 and PD-L1 inhibitors. A full taskforce roster can be found in the online supplementary materials.

To initiate discussions, leadership of the SITC Immunotherapy Resistance Taskforce distributed a survey to taskforce membership characterizing foundational concepts on clinical definitions for PD-(L)1 inhibitor resistance. Taskforce members were surveyed regarding three clinical scenarios for PD-(L)1 inhibitor resistance: primary resistance, secondary resistance, and progression after treatment discontinuation. It was decided that at this time, this effort would not focus on the development of definitions for resistance to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors or other immunotherapies.

In April 2019, the taskforce held an in-person workshop in Atlanta, Georgia to discuss the final survey results and develop consensus definitions for the three resistance scenarios. In all, 35 taskforce members attended the meeting and were split into three working groups. The meeting primarily consisted of working group discussions on each of the three resistance scenarios, and subsequent whole group (taskforce) discussions to form general consensus definitions. Initial results from this meeting were compiled into a summary report in the form of minutes, which were distributed to taskforce membership and served as the basis to generate this manuscript. All taskforce participants reviewed the consensus definitions and approved the final manuscript, yet there was not uniform agreement on every issue. For this reason, caveats to the consensus definitions are detailed next in an effort to capture the breadth of the conversation and scenarios where the definitions may not perfectly fit.

MAIN TEXT

General comments on consensus definitions

Overall, taskforce members agreed that the goal of this effort was to generate consensus definitions about PD-(L)1 inhibitor clinical resistance that would be most applicable for aspects of drug development and clinical trial design. The taskforce agreed that their efforts should not be aimed at generating treatment recommendations, and that the best clinical judgment should supplant any of the following recommendations as necessary.

An initial discussion topic among members of the taskforce concerned separation of clinical PD-(L)1 resistance scenarios. The taskforce recognized that an increasing number of clinical trials are being designed to address PD-(L)1 inhibitor resistance, and that these studies generally allow enrollment of patients with progressive disease who have received prior PD-(L)1 inhibitors.[7] Taskforce members generally agreed, however, that enrolling patients with different clinical PD-(L)1 resistance scenarios onto the same study assessing a novel therapy may confound activity analyses and adversely affect the clinical development of otherwise active agents. As such, the taskforce agreed that the clinical scenario of PD-(L)1 inhibitor resistance is relevant and should be taken into consideration while developing consensus definitions.

Building on this premise, the taskforce specifically discussed how a patient whose cancer progressed within the first few weeks of anti-PD-(L)1 therapy may or may not have a biologically distinct mechanism of resistance compared with a patient who experienced an initial response, but then had disease progression later during treatment. The taskforce ultimately concluded that these two clinical scenarios were similar to the biological concepts of primary (or de novo/innate) and secondary (or acquired) resistance definitions that have been well

established in oncology for other systemic treatment modalities. Therefore, discussing both scenarios in relation to PD-(L)1 inhibitor therapy would be warranted.

The taskforce noted, however, that these two clinical scenarios may differ from a patient whose disease progresses or relapses after cessation of treatment following an initial response, including patients whose disease progresses following a finite course of adjuvant or neoadjuvant therapy.[8] Therefore, the taskforce also agreed to discuss clinical definitions of PD-(L)1 inhibitor resistance in the context of disease progression after treatment discontinuation, and more specifically for four settings: adjuvant treatment, neoadjuvant treatment, and after halting therapy due to aspects unrelated or related to toxicity.

Taskforce members noted other challenges in defining clinical resistance to PD-(L)1 inhibitor therapy, primarily in those patients demonstrating initial progression on imaging followed by response with continued therapy.[2 9] For example, it was apparent in the early clinical experience with the anti-CTLA-4 antibody ipilimumab in metastatic melanoma that patients could experience long-term clinical benefit despite apparent progression of disease on the first set or sets of imaging. While the majority of patients in these studies who derived clinical benefit after ipilimumab treatment had unequivocal tumor shrinkage on imaging (as defined formally by the conventional RECIST response criteria and/or as judged by the treating physician), tumor shrinkage in some patients occurred months after the original treatment had been stopped in the setting of initial radiographic progression.[10] Recognition that this phenomenon, now commonly referred to as "pseudoprogression," occurs in approximately 5%–10% of patients receiving anti-CTLA-4 or anti-PD-(L)1 therapy has resulted in the development of new imaging criteria to measure response/progression while simultaneously accounting for this scenario,[11 12] and has altered patient management by promoting treatment beyond traditional definitions of progression to confirm ICI resistance.[13] Based on these discussions, the taskforce decided to consider the appropriate timeframes and response criteria for confirming PD-(L)1 inhibitor resistance in the three agreed on clinical scenarios.

Finally, the taskforce made a few general assumptions about the patient population to which these consensus definitions could be applied.

1. The discussed definitions were developed primarily for solid tumor settings, as it was recognized that hematologic malignancies have different manifestations of disease and response criteria. Uniform definitions should be used for all solid tumors, with the exception of tumors in which standard radiographic response criteria are not commonly used, such as glioblastomas, prostate cancer, hepatocellular carcinoma and ovarian cancer, among others.
2. All definitions are to be based on patients being treated with systemic anti-PD-(L)1 monotherapy, and combinations with other ICIs and other types of systemic or local therapies are not currently being addressed.
3. The type of study (registrational, etc) should not affect the generated recommendations and definitions.

It was agreed that the goal of providing uniform definitions of resistance to PD-(L)1 inhibitor therapy was to minimize the chance that late responses would be attributable to subsequent therapies, but the taskforce recognized that available data to confirm such a cut-off were both inconsistent and limited. As such, there was general consensus that definitions should aim to identify a population of patients with a≤5% chance of having subsequent response if treatment was continued past progression with single-agent PD-(L)1 inhibitor or if therapy with single-agent PD-(L)1 inhibitor was restarted irrespective of intervening therapy, a cut-off which they agreed should be validated against existing clinical data sets from stakeholders within the field, as well as future data generated using the taskforce's current resistance definitions.

PRIMARY RESISTANCE

Background

The general biological definition of primary resistance to PD-(L)1 inhibitors can be defined as the inability of immune cells to mount an antitumor response on initial drug exposure.[9] Multiple potential biological mechanisms of primary resistance have been proposed, including but not limited to, ineffective priming of a T cell response, lack of tumor recognition due to defective antigen presentation, inability of T cells to traffic to or penetrate effectively into viable areas of the tumor, inability of T cells to eliminate tumor cells due to suppression via other checkpoints such as T cell immunoreceptor with Ig and ITIM domains (TIGIT) and lymphocyte-activation gene 3 (LAG-3), an abundance of immune inhibitory cells such as M2-macrophages in the tumor, and others.[14] Clinical definitions of primary resistance to PD-(L)1 inhibitor therapy, however, lack consistency across the field. For the purposes of drug development in the anti-PD-(L)1 setting, the taskforce felt it would be critical to define primary resistance with the intent of identifying patients who would not benefit from initial and more prolonged exposure to PD-(L)1 inhibitor monotherapy.

Duration of drug exposure required for primary resistance classification

It was agreed by the taskforce that an important feature of any clinical definition of primary resistance is that it must reflect patients who truly have not received "clinical benefit" from initial therapy. While the term clinical benefit can vary across the field, in this context it means either tumor response or prolonged SD, as per RECIST version 1.1, lasting 6 months or greater, although the timeframe may need to be rethought in indolent tumor types.[3] True resistance, or lack of clinical benefit, implies that drug exposure has been adequate to induce the desired biological effect required for antitumor activity,

Table 1 Definitions of primary and secondary resistance in advanced disease setting

Resistance phenotype	Drug exposure requirement	Best response	Confirmatory scan for PD requirement	Confirmatory scan timeframe
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 Response Evaluation Criteria in Solid Tumors 1.1.
CR, complete response; PD, programmed death; PR, partial response; SD, stable disease.

and additional drug exposure will not be effective; thus, it was critical to define a minimal exposure for sufficient PD-(L)1 inhibition to derive any possible clinical benefit. The taskforce noted that studies of PD-(L)1 inhibitors, which have a long circulating half-life, have involved repeat dosing every 2–4 weeks, and have failed to identify a major difference in efficacy or toxicity at doses greater than 1 mg/kg, although certain diseases may behave differently (eg, non-small cell lung cancer in the preliminary nivolumab experience), and higher doses may be necessary for certain PD-(L)1 inhibitors to induce antitumor activity.[15–20] Based on these data, workshop attendees generally agreed that two cycles of therapy would be sufficient for assessing primary resistance. As such, the taskforce reached general consensus that a patient who has disease progression after receiving at least 6 weeks of exposure to PD-(L)1 checkpoint inhibitors, generally correlating with two complete cycles of U.S. Food and Drug Administration (FDA) approved PD-(L)1 inhibitor therapy, but no more than 6 months can be considered to have primary resistant disease (table 1).

Confirmatory scan requirement for validating primary resistance

Given the possibility of delayed responses to PD-(L)1 inhibitors, the taskforce agreed that a confirmatory set of radiographic scans (or in the case of clinically measurable lesions, physical examination) should be conducted to confirm resistance in patients who have documented progression after at least 6 weeks of starting therapy. The working groups varied in opinion regarding the timeframe in which this confirmatory scan should occur, but generally agreed on a 4–12 week range after initial evidence of disease progression. In general, the taskforce felt that patients should continue on therapy, if deemed clinically safe, until this second evaluation is performed. Furthermore, there was general consensus that late responses after rapid and confirmed radiographic progression (eg, lack of shrinkage), even at short time intervals such as 4 weeks, likely occur in no more than 5% of patients, and are unlikely to significantly affect results of subsequent clinical trials in which a patient may enroll (table 1). The taskforce recognizes that this aspect will need to be further validated with emerging data.

Patients who experience early toxicity requiring steroids and cessation of PD-(L)1 inhibitors are difficult to assess for primary resistance. For the purposes of future trial eligibility, randomization stratification or a fuller description of baseline characteristics on subsequent studies, primary resistance should be documented while still on active therapy or within 12 weeks of the last dose (see section on secondary resistance). The scenario of patients discontinuing therapy for low-grade toxicities and ultimately progressing off therapy greater than or equal to 12 weeks after last dose is addressed next (see section on progression after discontinuation of ICIs).

One exception to the requirement for confirmatory scans concerns patients who experience clear clinical progression, defined as a decline in the pretreatment performance status directly attributable to disease or increased disease-related symptoms and radiographic progression. The taskforce recognized that continued PD-(L)1 inhibitor therapy in patients with rapidly progressive disease would be unsafe, and the group subsequently indicated that the clinical judgment of the physician/clinical investigator might dictate an immediate change in the course of treatment, including enrollment onto clinical trials without fulfilling confirmatory imaging.

Response evaluation criteria for determining primary resistance

The working groups differed on which radiographic response evaluation criteria should be utilized to measure disease progression on PD-(L)1 inhibitors. The FDA typically uses RECIST1.1 as a primary trial endpoint, although alternative response criteria are used for solid tumors with disease sites/patterns of progression that are not well characterized by RECIST1.1. Additionally, immune RECIST (iRECIST) was specifically developed to address issues of mixed responses and pseudoprogression, but has yet to be the sole response criterion used to validate efficacy of anti-PD-(L)1 therapy in registration trials.[12] One working group showed no preference between RECIST1.1 and iRECIST, while one working group each preferred the use of RECIST1.1 or iRECIST, respectively. The general consensus of the taskforce was that iRECIST was not yet standard and required additional validation. Efforts are ongoing to develop response criteria using positron emission

tomography (PET) scans to measure changes in flurodeoxyglucose (FDG) uptake,[21] yet the taskforce consensus was that this modality has not yet been sufficiently developed or validated. All three working groups agreed that FDG/PET may be an indicator of response to PD-(L)1 inhibitors and that interpretation may be confounded by metabolically active immune infiltrates that can accompany regressing tumor lesions. All three groups also stated that they were primarily concerned with ensuring that no more than 5% of patients enrolled on clinical trials are incorrectly determined to have primary resistant disease and felt that either RECIST1.1 with required confirmatory scans described above or iRECIST would accomplish this.

Patients who have initial SD by RECIST1.1 or iRECIST pose a challenge. There was considerable discussion regarding a duration of SD that would denote responsiveness rather than primary resistance. The general taskforce consensus was that patients who initially have SD on imaging but meet criteria for disease progression within less than 6 months of initiation of PD-(L)1 inhibitors are considered to have primary resistance.

Key caveats on primary resistance

All working groups identified important caveats and exceptions to the general definitions for primary resistance:

1. It was agreed that recommendations should not be applied to patients who discontinued treatment early due to adverse events and have subsequent disease progression. These specific scenarios are described more fully in the "progression after treatment discontinuation" section.
2. It was recognized that the timeframes for confirmatory scans may be dependent on tumor histology, with one example being small cell lung cancer where a shorter interval may be more clinically appropriate due to rapid progression.[22]
3. The extent and location of tumor growth on PD-(L)1 inhibitors might define variable biological entities. For example, rapid tumor growth in all sites is likely different from isolated progression or emergence of new lymph node disease. However, for the purpose of clinical trial design, the taskforce felt that the aforementioned definitions should be applied generally. Documentation by biopsy should be considered for progression only in lymph node sites. For patients with oligometastatic progression, local therapy to address the progressing lesion could be appropriate.
4. Multiple studies have investigated treatment beyond progression and/or retreatment after relapse using alternative definitions of primary resistance, including in the context of PD-(L)1 blockade.[4 23 24] As such, the taskforce chose to implement the above-described 5% error rule to help form the primary resistance definition described in this manuscript. 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. The expectation is that the 5% error rule used to inform the definition of primary resistance will be validated using existing databases, and ideally, prospective data sets.

SECONDARY RESISTANCE

Background

In general terms, the taskforce considered secondary resistance as that which arises when a patient is treated with antineoplastic therapy, has a documented, confirmed objective response or prolonged SD (>6 months), and then has disease progression in the setting of ongoing treatment. Biologically, this type of resistance may occur through adaptation of tumor cells, and may involve one or more epigenetic, transcriptomic and/or proteomic changes. Secondary resistance may also arise through the clonal selection or clonal evolution of tumor cells with outgrowth of clones containing genetic changes imparting resistance to therapy.[2 9 14 25] Otherwise known as "acquired resistance," secondary resistance mechanisms have been described with every type of antineoplastic therapy and, with respect to PD-(L)1 inhibitors, investigation into these mechanisms has only recently begun. To date, resistance-defining mechanisms include mutations in the interferon gamma response genes JAK1 and JAK2,[25–27] and alterations in antigen presentation pathways, including downregulation and/or loss of beta-2-microglobulin.[26] Additional potential mechanisms of secondary resistance include upregulation of proteins involved in alternative immune checkpoints, such as LAG-3 and T cell immunoglobulin and mucin domain 3 (TIM-3).[25 28 29] Another general mechanism of secondary resistance is an increase in immunosuppressive cellular subsets in the tumor microenvironment such as T-regulatory cells (T-regs), myeloid-derived suppressor cells (MDSCs), and M2 macrophages (M2).[30 31]

As described above, the taskforce discussed whether distinguishing patients with primary from secondary resistance was necessary and, ultimately, came to the consensus that since the kinetics and/or biological mechanisms may be potentially distinct, it would be useful to do so. It was also agreed that the generated definitions herein would not aim to address these biological aspects at this time, but would rather be used to ensure that patients are being appropriately triaged for clinical trials testing new drugs or drug regimens, and are not being excluded from potential treatments and/or clinical trials. Studies addressing the treatment of anti-PD-1/PD-L1 resistant tumors can potentially use the generated definitions for:

1. Patient eligibility (defining who qualifies as having primary vs secondary resistance).
2. Stratification in randomized trials (by primary vs secondary resistance).
3. Development of analysis plans for clinical trials and in the research community

Duration of time required for secondary resistance classification

For patients who derived clear clinical benefit (complete response (CR) or partial response (PR)) from PD-(L)1 inhibitors, the taskforce generally defined secondary resistance as the development of disease progression ≥6 months from initiation of PD-(L)1 inhibitors while still on active therapy. Scenarios involving patients with SD (defined by either RECIST1.1 or iRECIST), however, were not as easily classified within the secondary resistance definition and were further discussed in each of the three working groups, and among the taskforce at large. Some members of the taskforce expressed the opinion that patients with slow, steady disease growth that took 6 months to qualify as disease progression represented a different group of patients than those with any degree of disease regression, although not enough to meet objective criteria for a PR. Ultimately, the taskforce consensus was that patients with SD for ≥6 months who then had overall disease progression, independent of the target lesion measurements (ie, overall tumor regression of <30% or tumor growth <20%), would be considered as having secondary resistance (table 1). The taskforce noted that this definition might not be applicable to indolent tumors (see caveats below).

Validating secondary resistance with confirmatory imaging

Two of three working groups recommended a confirmatory scan for validation of secondary resistance. Similar to the recommendations for primary resistance, the timeframe recommended by both working groups in favor of confirmation for such a scan was within 4–12 weeks after evidence of initial disease progression. In addition, these two working groups agreed that disease progression should be verified at ≥two metastatic sites/lesions in patients with multiple metastases, and that asymptomatic nodal-only disease progression was insufficient for classifying a patient as having secondary resistance without pathological confirmation. The third working group indicated no preference for a requirement of a confirmatory scan. The rationale given by this group was that the false-positive rate for defining progressive disease on therapy following clinical benefit, particularly in the setting of a CR or PR, is less than the agreed 5% threshold based on a single scan alone.

As in the setting of primary resistance, the taskforce was in agreement that patients who have clear clinical progression should not require a confirmatory scan to move onto subsequent treatment.

Response evaluation criteria for determining secondary resistance

Similar to discussions concerning primary resistance, the working groups differed on which response criteria should be utilized for secondary resistance (RECIST1.1 vs iRECIST). While one group had indicated no preference, one preferred RECIST1.1 and the other iRECIST. Overall, the consensus of the taskforce was to ensure that the selected criteria would limit the false-positive rate of secondary resistance classification. In the absence of specific validation of either or both response evaluation criteria, it was felt to be reasonable to use either RECIST1.1 or iRECIST or both for clinical trial enrollment criteria.

Important caveats on secondary resistance

The taskforce identified important caveats and exceptions to the general recommendations for defining secondary resistance.

1. It was agreed that this definition should not be applied to patients who have disease progression after discontinuation due to adverse events and did not receive at least 6 months of PD-(L)1 inhibitor therapy.
2. Combination regimens, such as those including anti-PD-1 and anti-CTLA-4 antibodies, or chemotherapy/targeted therapy and PD-(L)1 inhibitors, require alternative criteria for determining secondary resistance. Therefore, these definitions only apply to anti-PD-(L)1 monotherapy and not to dual therapy regimens.
3. The taskforce is aware that a "gray zone" exists between the above definitions of primary and secondary resistance. Specifically, patients with a PR or CR on first imaging who then develop disease progression within 6 months of initiating PD-(L)1 inhibitor therapy share characteristics of both definitions. For simplification and clinical trial eligibility, the taskforce defines these patients as having primary resistance seeing that resistance developed within 6 months. The taskforce felt that this likely occurs <5% of the time, but this will require prospective validation through clinical data analyses.
4. One of the working groups questioned whether specific secondary resistance definitions would be required for different types of disease. While it was noted that there are disease-specific qualities to response and progression in the setting of immune checkpoint inhibition, the consensus was that the above definition would be generally applicable to solid tumors in the context of PD-(L)1 inhibitor therapy.
5. The specifics of how the patient is progressing may matter. For example, there was full consensus that a patient on PD-(L)1 inhibitor therapy who had responded in some lesions and then had multifocal disease progression should be a candidate for a clinical trial and would be classified as having secondary resistance. However, there was less than full consensus that single-site progression in patients with multiple sites of disease, particularly if radiographic progression is occurring only in lymph nodes or lung lesions, as lesion growth might predominantly be due to inflammation. There was consensus that biopsies should be obtained when possible to confirm tumor growth, but these are not always conclusive or feasible. For the purposes of defining secondary resistance, the taskforce would include a patient when biopsies are not possible or in-

conclusive in the definition of secondary resistance, but acknowledges that this scenario may be distinct.
6. Six months of SD is sufficient to determine clinical benefit for most tumor types. However, exceptions might be necessary for tumors that tend to be more indolent.
7. As with the definition of primary resistance, these recommendations are not based on empirical data from clinical trials, patient registries, or previous studies investigating treatment beyond progression and/or treatment after relapse.[4 23 24] Comparison of these definitions against databases from large clinical trials and/or patient registries would be helpful to determine the true frequency of a second response with further use of PD-(L)1 inhibitors after initial response and progression, as this might vary between drugs and tumor types, which again would expectedly validate the proposed 5% error rule.

DISEASE PROGRESSION AFTER DISCONTINUATION OR HALTING OF CHECKPOINT INHIBITORS

Background

Single agent PD-(L)1 inhibitors are effective for advanced disease in multiple tumor types, translating into overall survival benefit, and in some cases, leading to long-term responses off-treatment.[2] Additionally, these agents are being increasingly utilized in the adjuvant and neoadjuvant settings, where a fixed treatment duration is employed. Anti-PD-1 therapies have been approved by the FDA as adjuvant treatment for patients with melanoma,[32 33] and additional adjuvant/neoadjuvant indications are currently being tested in clinical trials.[7] Based on the increased use of PD-(L)1 inhibitors in these settings, the taskforce decided to discuss adjuvant and neoadjuvant therapy in the context of progression after discontinuation of ICIs. In parallel, considering the fact that therapy could be discontinued in the metastatic setting either secondary to toxicity or after achieving maximal benefit, the taskforce also addressed this setting in its deliberations.

This form of resistance could have elements of either primary or secondary resistance as defined above. For instance, long-term disease-free survival following adjuvant therapy is achieved through either complete elimination of tumors or from ongoing antitumor immunological memory. Recurrence after discontinuation of therapy can be attributed to the kinetics of disease relapse with early relapse on adjuvant therapy resembling primary resistance, and late recurrence after therapy discontinuation and initial disease control resembling secondary resistance. The underlying mechanisms could thus be possibly related to the inability of immunotherapy to eradicate malignant cells because of lack of priming and activation of tumor antigen-specific immune cells, or the inability of cytolytic cells to infiltrate and/or kill tumor cells, a scenario consistent with the above described potential mechanisms of primary resistance. Alternatively, adjuvant immunotherapy might induce a new immune equilibrium that eventually results in sufficient immune editing of remaining tumor cells leading to the emergence of resistant clones, or immune cell exhaustion secondary to various mechanisms. The latter scenario would be more consistent with the definitions of secondary or acquired resistance as presented above. A noted difference between these two settings and resistance in the advanced setting, however, is that the bulk of the tumor is not present in the adjuvant setting.

In addition, there are pharmacokinetic and pharmacodynamic implications to the discontinuation of therapy. Available evidence indicates that receptor occupancy with anti-PD-1 nivolumab begins to decline 2–3 months after the single drug dose and is generally not identifiable at 6 months.[15] While acknowledging that T cell activation may continue in the absence of receptor occupancy, those timeframes serve to provide guidance on defining resistance in this setting.

Resistance during and after adjuvant therapy

The use of PD-(L)1 inhibitors in earlier stages of disease, and specifically the adjuvant setting, highlights new challenges:
1. There is no direct established method to assess the response of micrometastatic residual disease to therapy; therefore, the only reliable measure of activity is the time to relapse after therapy has been discontinued.
2. Conceptually, a lower burden of microscopic disease may stochastically decrease the emergence of resistant clones. However, it is conceivable that resistant clones arising in this setting may be biologically more aggressive. Either way, it is possible that resistance emerging after adjuvant treatment may involve mechanisms different than those observed in primary resistance, or in acquired resistance.
3. There is a lower threshold in this setting to discontinue therapy secondary to toxicity, which makes the interplay of toxicity and efficacy more difficult to assess.

Duration of time during or after adjuvant treatment required to classify resistance

There was considerable discussion within the taskforce regarding the timeframe after which a patient could be labeled as having resistant disease in the adjuvant setting. Patients could be classified into two groups: “adequate treatment exposure” and “inadequate treatment exposure.” The adequate exposure group included patients who had disease progression within 6–12 weeks after the last dose of adjuvant therapy; after discussion all working groups generally agreed that this population of patients should be considered as having primary resistance to checkpoint inhibitors and subsequently follow the definitions/protocols as described above. The “inadequate exposure” population includes patients who had disease progression >12 weeks after their last dose of checkpoint inhibitor (table 2). Two of the three working groups suggested 6 months as a cut-off for the “relapse after cessation of treatment” population, but participants ultimately

Table 2 Definitions of adjuvant therapy resistance

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.
PD, programmed death.

agreed on 12 weeks as consensus as to limit potential confusion in the event a patient has disease progression after adjuvant therapy in a timeframe between 12 weeks and 6 months (table 2).

Confirmatory scan requirement for validating resistance during adjuvant treatment

Members of the taskforce generally agreed that patients who have progressive and/or recurrent disease after adjuvant therapy should undergo a biopsy to confirm recurrence. None of the working groups indicated that a confirmatory radiographic scan would be necessary (table 2).

Important caveats on resistance during adjuvant treatment

All working groups identified exceptions to the general recommendations for resistance during adjuvant treatment.

1. One working group suggested that a patient who has disease progression >6 months after their last dose of checkpoint inhibitor and has no evidence of clinical deterioration and/or a decrease in performance status may still respond to a rechallenge with single agent PD-(L)1, and that such rechallenge may be needed to verify resistance.
2. There was significant discussion on how to classify patients with resistant disease in the adjuvant setting. While the taskforce generally agreed to separate patients by the time that had lapsed from last dose to relapse (adequate exposure vs inadequate exposure, described above), an alternative proposed classification was "early relapse" (PD 6–12 weeks after last dose of adjuvant therapy) versus "late relapse" (PD >12 weeks after last dose of adjuvant therapy), with the understanding that late relapse patients may have >5% chance of responding to rechallenge. As data mature, revisiting how to categorize patients in the adjuvant setting will be prioritized.
3. A second group suggested that as technology evolves, pharmacodynamic assessment of receptor occupancy might be utilized to ascertain whether a patient treated in the adjuvant setting is resistant to PD-(L)1 inhibitors.

Resistance during and after neoadjuvant therapy

General definitions of resistance during neoadjuvant treatment

The use of neoadjuvant immunotherapy remains a nascent practice and is still generally performed in the setting of a clinical trial. This discussion occurred within the taskforce in anticipation of increasing utilization within this space, and may need to be revisited after a critical mass of clinical evidence becomes available. The taskforce generally agreed that definitions of resistance in primary or secondary settings could also be applied to patients who received neoadjuvant therapy. One major difference from the adjuvant setting, however, is that there is macroscopic tumor at the time of initiation of therapy and objective tumor assessment of radiographically or clinically evident disease to immunotherapy is possible in the neoadjuvant setting. It was generally agreed that patients who achieve a major pathological response to immunotherapy (CR, near CR, or major PR) before surgery and then later recur after surgery may better fit the definition of secondary resistance, while patients who do not achieve a pathological response before surgery are more consistent with primary resistance.[34 35] Therefore, therapeutic rechallenge may not be necessary if a patient had evidence of primary resistance to PD-(L)1 inhibitors during neoadjuvant treatment, as demonstrated by a lack of pathological response at the time of surgery (table 3). If adjuvant immunotherapy is administered in the treatment regimen, recurrence that occurs during or after the neoadjuvant phase should otherwise be regarded as similar to the adjuvant setting.

Disease progression after discontinuation of therapy in the setting of metastatic disease

General definitions of resistance following disease progression after discontinuation of PD-(L)1 inhibitors in the advanced setting

There was general agreement that discontinuation of therapy in this setting can be due to various reasons, including the completion of a treatment regimen,

Table 3 Definitions of neoadjuvant therapy resistance

Neoadjuvant therapy		
Major pathological response	Yes	No
Resistance definition recommendations	Follow secondary resistance definitions	Follow primary resistance definitions

Table 4 Definitions of resistance after discontinuing treatment for metastatic disease

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

CR, complete response; PD, programmed death; PR, partial response.

achievement of "maximal benefit" (CR or PR), social and/or financial factors, patient's preference, and the occurrence of toxicity. Based on these potential options, the taskforce addressed two major categories of patients: those who stopped treatment due to reasons unrelated to toxicity, and those who discontinued due to an adverse event.

In instances where a patient with metastatic disease stopped PD-(L)1 inhibitors for any reason unrelated to toxicity and had no evidence of prior clinical benefit while on therapy, the taskforce felt these patients would best be defined as having primary resistance and would not benefit from therapeutic rechallenge (table 4). Additionally, the taskforce felt that a confirmatory scan in this population would be unnecessary.

Alternatively, the taskforce generally felt that patients who had experienced clinical benefit (PR/CR) and had stopped treatment due to maximal benefit, trial design, or other social/financial rationale, could be stratified as resistant based on the duration of time from a patients last ICI dose prior to evidence of progressive disease. The taskforce generally recommended that patients with evidence of progressive disease ≤12 weeks after their last dose of checkpoint inhibitor could be defined as having secondary resistance (table 4), and recommended a confirmatory scan in these scenarios. For patients with progressive disease >12 weeks after stopping treatment, the taskforce felt that rechallenge with a PD-(L)1 inhibitor could potentially produce clinical benefit (exceeding the 5% threshold), and thus felt it would be difficult to classify disease as resistant without a therapeutic rechallenge.

For patients developing toxicity and unable to continue PD-(L)1 inhibitor therapy, the taskforce generally suggested that the appropriate resistance definition be dictated by whether the patient had derived clinical benefit prior to discontinuation. The taskforce generally agreed that a patient who discontinued PD-(L)1 inhibitor therapy due to toxicity and had no evidence of initial clinical benefit would be best classified as having primary resistance. Alternatively, if a patient had derived CR or PR prior to discontinuation due to toxicity and then had disease progression, the taskforce generally recommended, as above for patients who stopped for other reasons, that patients with evidence of progressive disease ≤12 weeks after their last dose of checkpoint inhibitor could be defined as having secondary resistance (table 4), and recommended a confirmatory scan in these scenarios. For patients with progressive disease >12 weeks after stopping treatment, the taskforce felt that rechallenge with a PD-(L)1 inhibitor could potentially produce clinical benefit (exceeding the 5% threshold), and thus felt it would be difficult to classify disease as resistant without a therapeutic rechallenge.

Important caveats on resistance following disease progression after treatment discontinuation

1. The taskforce recognized that patients may be treated with intercurrent therapies—including chemotherapy, radiation therapy, and/or targeted therapy—after stopping PD-(L)1 inhibitor therapy, and questioned how to define resistance in this population. The taskforce noted that these approaches can potentially modify the tumor microenvironment, which could impact the activity of subsequent PD-(L)1-based combination regimens. After much discussion, the taskforce generally felt these patients should be included in the current definitions and that resistance should still be defined using the date of the last known PD-(L)1 inhibitor dose, as systematic analyses capable of delineating the response rate to PD-(L)1 inhibitor therapy following intercurrent treatment are not currently available within the field.
2. It was suggested that patients who derived initial clinical benefit from PD-(L)1 inhibitors, stopped therapy, and then had progressive disease >12 weeks after their last dose may be appropriately randomized to single agent therapy in the setting of a randomized controlled study, similar to trials assessing first-line ICI treatments in melanoma that currently allow patients who had received adjuvant therapy >6 months before recurrence.
3. As with the other resistance definitions, the taskforce recognizes limited available data for validation and will revisit these definitions as more data sets are developed and become available

CONCLUSIONS

As immunotherapies continue to expand into oncology practice, further refinement of the current knowledge base regarding tumor response and resistance will be necessary to maximize therapeutic potential and guide development of new therapies. As a byproduct of the

Box 1 Key questions and aspects concerning immunotherapy resistance as identified by the taskforce

1. Identifying rate of pseudoprogression with described definitions using large clinical trial databases
2. Characterizing long-term clinical outcomes of patients with partial response/stable disease<6 months
3. Collecting and analyzing data concerning patients with primary/secondary resistant tumors retreated with programmed death-ligand 1 inhibitors
4. Defining resistance for individual drugs
5. Defining resistance for distinct tumor types

rapid adoption of checkpoint inhibitors, specifically PD-1 and PD-L1 inhibitors, the field needs to adapt to the specific properties of these novel therapies, including prolonged half-life, varied tumor response kinetics, inflammatory responses mimicking disease progression, and heterogeneity of response within individuals. To aid future drug development in the setting of prior PD-(L)1 exposure and ensure continued momentum in the field, SITC convened a taskforce to help assist in defining clinical aspects of PD-(L)1 inhibitor resistance. For three different clinical resistance scenarios—primary resistance, secondary resistance, and progression after treatment discontinuation—the taskforce clarified timelines, characterized the necessity of confirmatory scans, and identified important caveats that should be readily investigated in future preclinical and clinical studies.

A major goal of this task force was to identify a PD-(L)1 "resistant" population that, when enrolled in a subsequent clinical trial, would have a false-positive rate for activity of the new agent of no more than 5%. While the taskforce drew on existing clinical trial data and experience treating patients with these agents, it is important to note that these definitions were not based on an exhaustive analysis of existing data sets. The taskforce identified key questions for the field to consider in conjunction with the above definitions (box 1). As many of these questions involve subsequent data analyses with stakeholder clinical trial data, one of the key action items from this meeting was for the taskforce to facilitate future discussion with investigators, industry sponsors, the National Cancer Institute and the FDA to make available data sets that could be queried to help validate and refine these definitions. While it was hoped that these analyses could potentially be completed before the publication of the taskforce's recommendations, it was felt that the unmet need for practical definitions was too great to await that level of confirmation. Thus, the definitions published herein should be considered the first version of the taskforce's recommendations, and additional updates can be expected when new data are available or other factors emerge that influence the validity of the current iteration. The taskforce uniformly agreed that this effort was focused on solely defining the scenarios of clinical resistance to PD-(L)1 inhibitors, yet recognized the importance of further understanding the biology underlying each of these clinical scenarios. It is anticipated that the above-described definitions can help guide translational analyses to uncover key biological questions.

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