Society for Immunotherapy of Cancer (SITC) consensus definitions for resistance to combinations of immune checkpoint inhibitors with targeted therapies

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ABSTRACT
Immunotherapy offers deep and durable disease control to some patients, but many tumors do not respond to treatment with single-agent immune checkpoint inhibitors (ICIs). One strategy to enhance responses to immunotherapy is via combinations with signal transduction inhibitors, such as antiangiogenic therapies, which not only directly target cancer cells but also could potentially favorably modulate the tumor immune microenvironment. Combination strategies with ICIs have demonstrated enhanced antitumor activity compared with tumor-targeted or antiangiogenic therapy alone in randomized trials in a variety of solid tumor settings, leading to regulatory approval from the US Food and Drug Administration and agencies in other countries for the treatment of endometrial cancer, kidney cancer, melanoma, and hepatocellular carcinoma. Despite improved survival and response rates for some patients when antiangiogenic or targeted therapies are administered with ICIs, many patients continue to progress after combination treatment and urgently need new strategies to address this manifestation of resistance to immunotherapy. Previously, the Society for Immunotherapy of Cancer (SITC) published consensus definitions for resistance to single-agent anti-PD-(L)1. To provide guidance for clinical trial design and to support analyses of emerging molecular and immune profiling data surrounding mechanisms of resistance to ICI-based combinations, SITC convened a follow-up workshop in 2021 to develop consensus definitions for resistance to multigent ICI combinations. This manuscript reports the consensus clinical definitions for combinations of anti-PD-(L)1 ICIs and targeted therapies. Definitions for resistance to ICIs in combination with chemotherapy and with other ICIs will be published in companion volumes to this paper.

INTRODUCTION
Resistance to immunotherapy remains a major barrier that prevents patients from obtaining maximal clinical benefit from immune checkpoint inhibitor (ICI) therapy. Many tumors do not initially respond to ICI monotherapy (ie, primary resistance) and progression or recurrence may occur even after periods of extended disease control (ie, secondary resistance).1,2 Previously, the Society for Immunotherapy of Cancer (SITC) developed consensus definitions for clinical phenotypes of resistance to single-agent checkpoint blockade for therapies targeting programmed cell death protein 1 and its ligand (PD-1 and PD-L1).3 The definitions identified minimum drug exposure requirements, best response, and requirements for confirmatory scans to define primary resistance, secondary resistance, and disease progression after discontinuation of therapy to support standardized study enrolment criteria and facilitate appropriate comparisons in post-anti-PD-(L)1 clinical trials. The SITC-defined resistance phenotypes for monotherapy have been shown to be associated with distinct clinical factors including tumor burden, tumor growth, likelihood to receive further systemic therapy, and post-progression survival.4

Combination strategies to overcome primary and secondary resistance to anti-PD-(L)1 ICIs are an active area of investigation. Based on improved overall response rates (ORRs) as well as progression-free survival and overall survival (OS) in randomized trials, combination regimens including ICIs targeting checkpoints beyond PD-(L)1 as well as chemotherapies and targeted therapies (TTs) have gained US Food and Drug Administration (FDA) approval in a variety of solid tumor settings.5-8 Combination approaches have been approved in other countries as well. The focus of this manuscript is definitions of resistance to anti-PD-(L)1 ICI combinations with TTs, which at the time of publication included FDA-approved indications for BRAF/MEK inhibitors with ICIs.
for the treatment of melanoma, VEGF receptor tyrosine kinase inhibitors (TKIs) with ICIs for the treatment of renal cell carcinoma (RCC) and endometrial carcinoma, and the antiangiogenic anti-VEGF antibody bevacizumab for the treatment of hepatocellular carcinoma (HCC).

Mechanisms of synergy between the approved tumor-targeted and antiangiogenic therapies and ICIs have been established in preclinical models. In these models, targeted and antiangiogenic therapies have been demonstrated to require an intact immune system for maximal response. These agents also, in some animal models, induce favorable changes in the tumor microenvironment (TME) away from a suppressive cytokine and gene expression profile, reduce hypoxia, and perturb the populations of infiltrating lymphocytes and monocytic cells.8-12 Evidence for these positive impacts on the tumor immune microenvironment in the clinical setting has been less well established.

To develop clinical definitions of primary resistance, secondary resistance, and resistance that develops after discontinuation of therapy for multidrug approaches, SITC’s Immunotherapy Resistance Committee convened a workshop dedicated to immunotherapy combinations. At the workshop, participants were charged to define resistance phenotypes in one of three broad categories: anti-PD-(L)1 in combination with other ICIs, anti-PD-(L)1 in combination with chemotherapy, and anti-PD-(L)1 in combination with TTs. This manuscript reports on the definitions developed for anti-PD-(L)1 in combination with TT and anti-VEGFR TKIs or antiangiogenic antibodies. Definitions for the other classes of combinations (ie, anti-PD-(L)1 plus other ICIs or chemotherapy) may be found in companion manuscripts. The definitions reported in this paper are based on the consensus of the SITC Immunotherapy Resistance Committee Immunotherapy Combinations Working Group.

METHODS

To generate expert consensus definitions on clinical phenotypes of resistance to immunotherapy combinations, SITC convened representatives from academia, industry, and government for a daylong workshop, held virtually in May 2021. Prior to the workshop, attendees completed a survey describing clinical scenarios for resistance to immunotherapy combinations. Discussion of the premeeting survey results in one of three breakout rooms (focused on immunotherapy/immunotherapy combinations, immunotherapy/TT combinations, and immunotherapy/chemotherapy combinations) led to the definitions reported in this manuscript and its companion volumes. Workshop attendees are listed in online supplemental file 1.

Disclosures of potential conflicts of interest were made prior to the onset of manuscript development and updated on an annual basis. Recognizing that workshop attendees are among the leading experts on the subject matter under consideration, any identified potential conflicts of interests were managed as outlined in SITC’s disclosure and conflict of interest resolution policies. As noted in these policies, attendees disclosing a real or perceived potential conflict of interest may be permitted to participate in consideration and decision making of a matter related to that conflict, but only if deemed appropriate after discussion and agreement by the participants.

General assumptions on resistance to immunotherapy–TT combinations

In a continuation of the 2020 SITC definitions for resistance to anti-PD-(L)1 monotherapy, the consensus definitions for checkpoint inhibitor combinations provided in this paper are intended for clinical trial design and drug development for solid tumors. The 2020 definitions were intended to be broadly applicable to identify patients that would have a ≤5% chance of subsequent clinical benefit if anti-PD-1 monotherapy was continued past progression.8 The participants felt that occurrence of pseudoprogression with regimens including TT and antiangiogenic therapies is rather rare and for the purposes of this combination-focused effort, this particular guiding principle (<5% pseudoprogression) was not necessary (discussed later in this section). These definitions are not intended to be used as recommendations for clinical management, which should be based on the best judgment of the treating physicians for their individual patients.

TT and antiangiogenic therapies may enhance responses to ICIs via modulation of multiple aspects of the tumor–immunity cycle,13 including by increasing neoantigen presentation, promoting lymphocyte trafficking to the tumor, alleviating immunosuppression within the TME, and augmenting cytotoxic effector functions.8 14 15 At the time of manuscript development, the combinations approved by the US FDA all included an anti-PD-(L)1 ICI as the immunotherapy backbone. Available TTs for combination with ICIs in 2021 fell into two broad categories: inhibitors of BRAF and MEK and inhibitors of VEGF, which include TKIs and antibodies against VEGF pathway components. Ongoing studies are evaluating ICIs in combination with other TT such as PARP inhibitors,16 CDK4/6 inhibitors,17 or agents targeting altered tumor metabolism such as glutaminase inhibitors,18 all of which may also possess some immunostimulatory properties.

These definitions focus on anti-PD-(L)1 combined with BRAF/MEK inhibitors (approved for the treatment of melanoma), anti-PD-(L)1 combined with anti-VEGF TKIs (approved for the treatment of RCC and endometrial carcinoma), and anti-PD-(L)1 combined with the antiangiogenic antibody bevacizumab (approved for the treatment of HCC). Investigational approaches such as combination regimens involving TT and antiangiogenic therapy plus ICIs targeting checkpoints other than PD-1 were not included in these definitions due to a scarcity of data at the time of manuscript publication.
Importantly, preclinical models support that the contribution to anti-tumor activity of the approved TT and antiangiogenic therapies is at least not antagonistic to that of anti-PD-1 and may possibly be additive or synergistic for some agents. ICI-based regimens that include chemotherapy in addition to TT and antiangiogenic therapies were not considered for the purposes of these definitions. Because chemotherapy may antagonize the activity of immunotherapy, parsing bona-fide resistance versus interactions between the components is likely not feasible based on current data and therefore is beyond the scope of this effort. As additional combination regimens including ICIs administered with agents with mechanisms of action beyond inhibiting angiogenesis and MAPK signaling advance through clinical development, however, it will be important to validate if the general principles described in these definitions apply across TT agents.

This manuscript defines resistance based on clinical response (or lack thereof), drug exposure, and duration of clinical benefit (if any). The definitions fall into four main categories: (1) primary resistance, where no benefit is obtained with treatment; (2) secondary resistance, where initial clinical benefit occurs but then progression subsequently ensues; (3) resistance in the adjuvant and neoadjuvant settings for early-stage disease; and (4) resistance after discontinuation of therapy for metastatic disease. For resistance in the perioperative setting, the definitions assume that surgery occurs within 6 weeks after the last dose of neoadjuvant therapy and that adequate drug exposure was received during adjuvant therapy.

The majority of approved indications for anti-PD-(L)1 ICIs in combination with TT prescribe continuous administration of both agents. Therefore, primary and secondary resistance as defined in the subsequent sections of this manuscript can be assumed to be to the full combination. In scenarios where one drug is discontinued, as described in later sections of this manuscript, it may not be possible to parse resistance to monotherapy versus the full combination. In these scenarios, monoclonal antibodies (such as ICIs) were assumed to have half-lives on the order of 2–3 weeks and small molecule TKIs were assumed to have half-lives on the orders of hours to days. Additionally, although spatially and temporally distinct lineages of variant cancer cells may arise throughout the course of treatment and these subpopulations likely play an important role in the genesis of resistance, intratumoral heterogeneity is beyond the scope of these definitions.

Finally, for the purposes of this manuscript, progressive disease (PD), stable disease (SD), partial response and complete response are assessed as described in the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1). For the tumors in which standard RECIST v1.1 are not commonly used (eg, glioblastoma, prostate cancer, HCC, and ovarian cancer), however, the disease-specific radiographic response criteria should be applied. Paradoxical increases in tumor size due to necrosis are a possibility with TTs. These morphological changes can be ruled out as true progression, however, using metabolic imaging or MRI, as recommended in RECIST v1.1. Atypical radiologic responses are a possibility after anti-PD-(L)1 monotherapy, including apparent tumor growth followed by regression. However, pseudoprogression is rarely, if ever, observed in patients treated with ICIs in combination with TT and antiangiogenic therapies. As such, the consensus was that confirmatory scans are not required in any setting for these definitions.

The key foundational assumptions that apply across resistance categories for ICI combinations with TTs are summarized in Box 1. Additional caveats to the resistance definitions for each scenario are described in the corresponding sections of this manuscript.

**Primary resistance to immunotherapy–TT combinations**

TTs may synergize with immunotherapy via multiple mechanisms to alleviate immunosuppression in the TME and thus overcome primary resistance to ICIs. Despite well-established preclinical rationale and high ORRs reported in several studies, a relevant proportion of patients have tumors that do not respond to ICI–TT combinations. For example, in the registrational trials leading to approval of ICI–TKI combinations for RCC, roughly 10% of treated patients had PD as best response after initial therapy and another substantial proportion of patients has SD lasting less than 6 months.

Some tumor-intrinsic mechanisms of resistance to TTs overlap with determinants of non-response to ICIs such as hypoxia in the TME and mesenchymal phenotype. Other mechanisms of resistance to TTs are immune-orthogonal, such as efflux transporters and angiogenic escape. Because of the partially overlapping—yet non-identical—pathways by which tumors escape response to initial therapy, it can be challenging to determine if PD represents resistance to the full combination or to individual constituent monotherapies. However, primary resistance likely represents resistance to both components or subadditive effects of the combination. Resistance to individual therapies may be defined in scenarios where combination is halted, as described in more detail in the Resistance after halting therapy for patients with metastatic disease section. Future trials may
identify biomarkers associated with resistance to immunotherapy and/or TTs, but no readily applicable validated assays are currently available.

Similar to the definition for primary resistance to anti-PD-(L)1 monotherapy, a minimum drug exposure requirement of 8–12 weeks or roughly two doses of the immunotherapy component was determined to be required to define resistance. Lack of benefit was defined as PD at the time of the first planned assessment or SD lasting less than 6 months. As described in the General assumptions on resistance to immunotherapy–TT combinations sections, pseudoprogression does not frequently occur for tumors treated with targeted or antiangiogenic therapies and therefore confirmatory scans are not required at PD. The clinical presentation that defines primary resistance is summarized in table 1.

Importantly, this definition for primary resistance assumes that the tumor received adequate drug exposure while on treatment. As such, toxicity leading to discontinuation of therapy occurring during the 8–12 weeks of initial drug exposure may confound attribution of primary resistance. Dose reduction or interruption for toxicity management with TKIs are common in real-world practice. Resistance to a combination may not necessarily correspond to resistance to individual components, especially if one agent was not given at the full dose or if the contribution of each constituent is subadditive.

In addition, there was a consensus that the natural history of the disease should be taken into account for the definition of primary resistance and the drug exposure requirement may be shorter for rapidly growing tumors.

**Secondary resistance to immunotherapy–TT combinations**

Secondary resistance describes scenarios where a patient initially derived clinical benefit from the immunotherapy–antiangiogenic or immunotherapy–TT combination, yet developed PD while on treatment. As with primary resistance, the mechanisms by which a tumor acquires resistance to ICIs and antiangiogenic and TTs may be partially overlapping. In preclinical models, acquired resistance to VEGF-targeting therapies has been demonstrated to involve the influx of M2 macrophages and myeloid-derived suppressor cells (MDSCs), and BRAF/MEK inhibition has been shown to induce cross-resistance to ICIs. Although the contributions of components of a regimen to disease control may be important, the consensus was that it may not be feasible to parse response to individual agents in the setting of secondary resistance and, therefore, scenarios where one drug is stopped were not defined. Definitions of secondary resistance are summarized in table 2.

The definitions of secondary resistance were developed at a time when the approved immunotherapy–TT combinations included indications for melanoma, endometrial carcinoma, HCC, and RCC. As with the definition for primary resistance, the natural history of the tumor being treated must be taken into account. For diseases with a more indolent course, time without disease progression may not directly correlate with magnitude of clinical benefit from therapy. Ongoing research into more dynamic and sensitive biomarkers of tumor burden such as ctDNA may provide more nuanced insights into innate and acquired resistance than radiographic assessment, and these definitions are intended to support future translational research.

**Resistance to immunotherapy–TT combinations in the perioperative setting**

Immunotherapy in the perioperative setting is an emerging frontier. At the time of publication, several indications were approved by the US FDA for ICIs in this setting, including for the treatment of high-risk early-stage melanoma, bladder cancer (non-muscle invasive and muscle invasive), and breast and non-small cell lung cancer (in combination with chemotherapy). The optimal timing and combination approach for neoadjuvant and adjuvant immunotherapy are active and ongoing areas of research, with encouraging results reported in a variety of solid tumors. Currently, no combinations of immunotherapy and TT are approved by the US FDA in the adjuvant setting nor are results available for large-scale trials. Acknowledging a lack of available evidence on outcomes of immunotherapy–TT combinations before or after curative-intent surgery, consensus definitions for resistance in the neoadjuvant and adjuvant settings for the purposes of clinical trial design were developed, which are summarized in table 3.

**Comments on resistance to immunotherapy–TT combinations in the neoadjuvant setting**

Limited data are available on long-term survival outcomes for neoadjuvant immunotherapy–targeted therapy combinations, although encouraging rates of margin-negative
resection and major pathological responses have been reported in early-phase studies in HCC, melanoma, and RCC. The neoadjuvant setting also offers a unique opportunity for translational research on resistance mechanisms. Examination of resection specimens provides direct confirmation of response to therapy and correlative studies on degree of lymphocytic infiltration or inflammatory gene expression signatures in the surgical sample may provide evidence for immune-mediated tumor killing or lack thereof.

Because neoadjuvant therapy is typically administered for only a few cycles prior to surgery, a lack of response in the resection specimen defines primary resistance. Acknowledging that the duration of neoadjuvant therapy may affect the depth of response, a minimum of 6 weeks of drug exposure was deemed to be required to evaluate resistance. Individual cancers may have their own cutoffs for degree of pathological response that defines clinical benefit with neoadjuvant therapy; however, the consensus was that <50% of tumor death in the surgical sample should be considered as a lack of response to immunotherapy–TT combinations. Further research is needed to determine if major pathological responses at the time of surgery correlate with long-term disease control for neoadjuvant immunotherapy combinations. Finally, resistance cannot be evaluated in the neoadjuvant setting if there is a substantial delay between cessation of systemic therapy and surgery, and the maximum interval was set at 6 weeks.

Comments on resistance to immunotherapy–TT combinations in the adjuvant setting

Assuming disease progression in the setting of adjuvant therapy, the consensus was that PD during or <12 weeks after the last administered dose defines primary resistance. This definition is inclusive of cancers where other markers beyond radiographic progression (eg, biochemical progression for prostate cancer) are used to monitor recurrent disease. In the future, more sensitive measures of disease burden (eg, ctDNA, as used in IMvigor010) may offer more nuanced criteria for defining resistance in the adjuvant setting.

Importantly, in the adjuvant setting, resistance to the combination does not necessarily define resistance to the targeted or antiangiogenic therapy (for TKIs), which may be cleared quickly after discontinuation.

In most trials to date, prior adjuvant ICI therapy has been allowed and patients were not considered resistant to the therapy if a disease-free interval of ≥6 months elapsed after the last dose. However, durable changes in the immune system likely persist long-term after cessation of treatment with ICIs—evidenced, in part, by the occurrence of delayed-onset immune-related adverse events as well as durable benefit in some patients. Although some antitumor activity may be reasonably anticipated with retreatment with TT and antiangiogenics for recurrent disease more than 6 months after the final dose, curative responses with immunotherapy would not be expected in the group of patients that had previously been treated with ICIs in the perioperative setting. There was consensus that although recurrent disease ≥6 months after the final dose of a complete course of adjuvant ICI–TT combination therapy should not be cause for exclusion from future trials including one or both agents in the combination, stratification criteria are needed for these patients. A need for new nomenclature was additionally identified for recurrence that occurs after longer than 3 months but prior to 6 months post-discontinuation of therapy, a resistance phenomenon that remains to be defined.

<table>
<thead>
<tr>
<th>Resistance scenario</th>
<th>Drug exposure requirement</th>
<th>Best response</th>
</tr>
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<tbody>
<tr>
<td>Neoadjuvant setting</td>
<td>Minimum of 6 weeks</td>
<td>&lt;50% tumor death in resection specimen</td>
</tr>
<tr>
<td>Adjuvant setting</td>
<td>A minimum of 6 weeks to adjuvant therapy completion</td>
<td>Recurrence &lt;12 weeks after the last administered dose</td>
</tr>
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Figure 1  Clinical scenarios defining resistance to checkpoint blockade in combination with tumor-targeted and antiangiogenic therapies after discontinuation of both agents. *This schematic assumes at least additive effects of the ICI and targeted/antiangiogenic therapy and uncompromised immunotherapy (ie, no long-term steroids and adequate dosing). ICI, immune checkpoint inhibitor; PD, progressive disease.
Resistance after halting therapy for patients with metastatic disease

Although the optimum duration of ICI therapy has not been established, multiple scenarios may lead to a patient discontinuing treatment, including toxicities, trial design, socioeconomic reasons, patient/physician choice, or other factors. Even after discontinuation of therapy, the effects of ICIs are expected to persist for some time due to extended receptor occupancies and induction of immunological memory.\textsuperscript{54,55} Responses to ICIs may even deepen over time via epitope spreading,\textsuperscript{56} circumventing immune selection for escape variants and leading to long-term clinical benefit in some patients. For future trials evaluating treatments for recurrent disease after cessation of immunotherapy–TT combinations, it is important to define resistance scenarios.

Importantly, the pharmacokinetics and pharmacodynamics of ICIs predict that the effects of these agents persist after therapy is halted. Therefore, in scenarios where immunotherapy–TT combinations are discontinued, there will be a time period (roughly 5 half-lives or 12 weeks\textsuperscript{57}) where the ICI will still be present in the body and the TKI is presumed to no longer exert antitumor activity. Therefore, PD ≤12 weeks after discontinuation of therapy for immunotherapy–TKI combinations is defined as resistance to the ICI. For combinations of ICIs and antiangiogenic antibodies such as bevacizumab that also have long serum half-lives, PD ≤12 weeks after discontinuation of therapy would be defined as resistance to the combination.

Categorization of resistance within 12 weeks after discontinuation of therapy as primary or secondary is complicated for several reasons. Clinical benefit with a combination regimen could occur for a tumor that has primary resistance to an ICI yet responds to the TT or antiangiogenic component of the regimen. With current technologies there is no way to rule out additive versus synergistic contributions of the individual ICI and TKI components to disease control. In such a case, resistance to the TT or antiangiogenic alone would present clinically as resistance to the combination. Resistance may be attributed to the ICI component within 12 weeks after discontinuation provided the immunotherapy was not compromised due to interruption of therapy or steroids \textsuperscript{58-60} and that the combination was not subadditive after discontinuation of ICI–TT and antiangiogenic therapy are summarized in figure 1.

CONCLUSION

This paper describes clinical phenotypes of primary and secondary resistance to ICIs in combination with targeted and antiangiogenic therapies, including anti-VEGFR TKIs, BRAF/MEK inhibitors, and anti-VEGF antibodies. In developing these definitions, a number of important areas for future research were identified. Reverse translational studies are also needed to understand the orthogonal and overlapping mechanisms of resistance to ICIs and TTs. Evidence for cross-resistance between ICIs and BRAF/MEK inhibitors has been described\textsuperscript{12} and M2 macrophages and MDSCs have been shown to mediate resistance to anti-VEGF therapies.\textsuperscript{38,41} Future investigations should use the definitions described in this paper to categorize mechanisms of primary and secondary resistance to monotherapies and combinations.

To validate these definitions of resistance, it will be necessary to collect long-term follow-up data on OS rates from the time of disease progression classified by primary and secondary resistance scenarios. It will also be necessary to collect outcomes after rechallenge stratified by pre- or post-12-week time interval as defined in the Resistance after halting therapy for patients with metastatic disease section. Additionally, it will be important to lay the groundwork for validation of more sensitive and dynamic markers of tumor burden, which is why collection of samples for baseline and serial monitoring of ctDNA during treatment with ICI–TT combinations is recommended. Finally, the SITC Immunotherapy Resistance Committee advocates for data-sharing and collaboration between stakeholders in industry, academia, and regulatory agencies to move the field forward and ultimately offer all patients being treated with immunotherapy the best possible outcomes.

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