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

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ABSTRACT

Although immunotherapy can offer profound clinical benefit for patients with a variety of difficult-to-treat cancers, many tumors either do not respond to upfront treatment with immune checkpoint inhibitors (ICIs) or progressive/recurrent disease occurs after an interval of initial control. Improved response rates have been demonstrated with the addition of ICIs to cytotoxic therapies, leading to approvals from the US Food and Drug Administration and regulatory agencies in other countries for ICI–chemotherapy combinations in a number of solid tumor indications, including breast, head and neck, gastric, and lung cancer. Designing trials for patients with tumors that do not respond or stop responding to treatment with immunotherapy combinations, however, is challenging without uniform definitions of resistance. Previously, the Society for Immunotherapy of Cancer (SITC) published consensus definitions for resistance to single-agent anti-programmed cell death protein 1 (PD-1). To provide guidance for clinical trial design and to support analyses of emerging molecular and cellular data surrounding mechanisms of resistance to ICI-based combinations, SITC convened a follow-up workshop in 2021 to develop consensus definitions for resistance to multiagent ICI combinations. This manuscript reports the consensus clinical definitions for combinations of ICIs and chemotherapies. Definitions for resistance to ICIs in combination with targeted therapies and with other ICIs will be published in companion volumes to this paper.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) as single agents or in combinations with chemotherapies and targeted therapies are now the standard of care for patients with a wide range of solid tumors. Despite offering long-lasting disease control for a subset of patients, the majority of patients treated with ICI monotherapy either do not respond (ie, de novo or primary resistance) or they progress/recur after an initial response (ie, acquired or secondary resistance). Resistance to ICIs is still incompletely understood and the mechanisms of primary and acquired resistance may involve any or all of the steps in the cancer-immunity cycle,[1] including loss of neoantigen expression, alternate immune checkpoints, effector cell exclusion, or altered interferon signaling.[2–8] Several strategies to enhance therapeutic outcomes are currently under investigation, and combination regimens involving the addition of immunotherapy, targeted therapy, or chemotherapy have advanced through late-stage clinical development.

Concepts of primary and acquired resistance were originally developed based on the study of cytotoxic chemotherapies. Resistance to chemotherapy has been attributed to causing as many as 80%–90% of the treatment failures[9] and may arise via drug efflux, altered metabolism, stromal cell contributions, as well as microRNA-dependent and autophagy-dependent mechanisms.[9–11] Some of the mechanisms by which tumors evade chemotherapy are orthogonal to determinants of immune response, yet overlapping biology may include influence on neoantigen expression, suppressor cells in the microenvironment, and lymphocytic infiltration.[12–14]

Despite potential immunosuppressive effects of cytotoxic agents,[12 15 16] some chemotherapies may enhance immunotherapy.[13 17 18] ICIs in combination with chemotherapy have demonstrated improved overall response rates as well as progression-free survival (PFS) and overall survival (OS) compared with chemotherapy alone in phase III trials.[19–23] Combinations of ICIs and chemotherapies have gained US Food and Drug Administration (FDA) approvals for the treatment of non-small cell lung cancer (NSCLC), head

and neck squamous cell carcinoma (HNSCC), cervical cancer, small cell lung cancer (SCLC), gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma, and triple-negative breast cancer (TNBC). These combinations have been approved in other countries as well.

Currently, more FDA approvals exist for ICIs + chemotherapy in the first-line metastatic setting compared with ICI monotherapy or non-chemotherapy combinations. Yet disease progression invariably still occurs in the majority of patients treated with ICIs + chemotherapy combinations. This underscores the need for uniform categorization of the clinical phenotypes of resistance in this setting to support drug development and facilitate translational research. The Society for Immunotherapy of Cancer (SITC) previously developed consensus definitions for clinical phenotypes of resistance to single-agent anti-programmed cell death protein-1 (PD-1).[24] Resistance was defined based on minimum drug exposure requirement, best response, and confirmatory scans for primary resistance, secondary resistance, and disease progression after discontinuation of therapy. These definitions have been shown to be associated with distinct clinical outcomes[25] and incorporated into a number of clinical trials' eligibility criteria, supporting their utility for drug development. An ever-increasing number of patients, however, are being treated with ICIs in the context of combination regimens, warranting the revisiting of resistance definitions for ICIs administered in combination with chemotherapy.

SITC's Immunotherapy Resistance Committee convened a workshop in 2021 dedicated to immunotherapy combinations. At the workshop, participants were charged to define resistance phenotypes in one of three broad categories: anti-PD-1 or anti-programmed death ligand-1 (PD-L1) in combination with other ICIs, anti-PD-(L)1 in combination with chemotherapy, and anti-PD-(L)1 in combination with anti-vascular endothelial growth factor tyrosine kinase inhibitors or antiangiogenic antibodies. This paper focuses on ICI–chemotherapy combinations and definitions for resistance to ICIs in combination with other ICIs or with targeted therapies can be found in companion volumes to this manuscript.

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 pre-meeting survey results in one of three breakout rooms (focused on immunotherapy/immunotherapy combinations, immunotherapy/targeted therapy 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–chemotherapy combinations

The consensus definitions for anti-PD-(L)1 checkpoint inhibitor combinations with chemotherapy described in this paper are intended to be used in clinical trial design and drug development for solid tumors with the goal of advancing new treatment options for patients with resistant disease, which is a population that has not been well-defined and represents a substantial unmet medical need. If validated in large, randomized trials, these definitions may inform future indications for interventions in these patient populations. Importantly, these definitions are not intended to be used as recommendations for clinical management, which should be at the discretion of the treating clinician in conversation with their individual patients.

In designing immunotherapy trials for the anti-PD-(L)1-monotherapy resistant setting, the likelihood of response to re-treatment with ICIs was expected to be <5%. This threshold was originally identified based on estimated rates of pseudoprogression in melanoma[26 27] and adopted for the 2020 SITC consensus definitions of resistance to single-agent anti-PD-(L)1 ICIs.[24] There was consensus that the 5% likelihood estimate is also appropriate for definitions of resistance to ICI–chemotherapy combinations, acknowledging that the incidence of pseudoprogression may be lower when immunotherapy is given in combination with cytotoxic chemotherapy.

At the time of manuscript publication, ICIs in combination with chemotherapy were FDA-approved for the treatment of HNSCC, gastric and esophageal cancers, billiary tract cancer, cervical cancer, lung cancer, and TNBC. For some FDA-approved indications for the treatment of advanced solid tumors, both the ICI and the chemotherapy agent are continued until disease progression or unacceptable toxicity occurs. For many indications, however, one or all of the chemotherapy agents may be discontinued by design after a set number of cycles during an induction phase. The chemotherapy component of the combination regimen is also discontinued during the adjuvant phase for the indication for pembrolizumab for early-stage TNBC—considerations for the curative-intent setting are described in the **Resistance to immunotherapy–chemotherapy combinations in**

Table 1 Illustrative FDA-approved indications for ICIs in combination with chemotherapy as of 2022

Indication	FDA-approved combination	Dosing scheme
Billiary tract cancer	Durvalumab + gemcitabine and cisplatin	ICI + chemotherapy (8 cycles) → ICI maintenance until disease progression or unacceptable toxicity
HNSCC	Pembrolizumab + platinum-containing chemotherapy and FU	ICI + chemotherapy (6 cycles) → ICI maintenance for up to 2 years
Cervical cancer	Pembrolizumab + platinum-based chemotherapy (with or without bevacizumab)	Continuous for up to 2 years of the ICI
GEJ and esophageal cancer	Pembrolizumab + fluoropyrimidine and platinum-containing chemotherapy	ICI + chemotherapy (6 cycles) → ICI + fluoropyrimidine maintenance
Gastric, GEJ, and esophageal cancer	Nivolumab + fluoropyrimidine and platinum-containing chemotherapy	Continuous for up to 2 years of the ICI
NSCLC (non-squamous)	Pembrolizumab + pemetrexed and platinum-containing chemotherapy	ICI + chemotherapy (4 cycles) → ICI + pemetrexed maintenance
NSCLC (squamous)	Pembrolizumab + carboplatin and (nab)-paclitaxel	ICI + chemotherapy (4 cycles) → ICI maintenance for up to 2 years
NSCLC (any histology)	Cemiplimab + histology-appropriate chemotherapy	ICI + chemotherapy (4 cycles) → chemotherapy maintenance
NSCLC (resectable)	Nivolumab + platinum doublet chemotherapy	ICI + chemotherapy (3 cycles) → optional adjuvant chemotherapy or radiotherapy
SCLC	Atezolizumab + carboplatin and etoposide	ICI + chemotherapy (4 cycles) → ICI maintenance until disease progression or unacceptable toxicity
	Durvalumab + cisplatin or carboplatin and etoposide	ICI + chemotherapy (4 cycles) → ICI maintenance until disease progression or unacceptable toxicity
TNBC (advanced, PD-L1+CPS >10)	Pembrolizumab + chemotherapy*	Continuous for up to 2 years of the ICI
TNBC (perioperative)	Pembrolizumab + chemotherapy*	Neoadjuvant ICI + chemotherapy (24 weeks) → surgery → adjuvant ICI (up to 27 weeks, disease recurrence, or unacceptable toxicity)

Continuous dosing refers to combinations that are administered as both agents until disease progression, unacceptable toxicity, or a predefined time interval.
*Label indication does not specify the chemotherapy backbone. In the registration trials for pembrolizumab, patients received nab-paclitaxel, paclitaxel, or gemcitabine and carboplatin with pembrolizumab.
CPS, combined positive score; FDA, Food and Drug Administration; FU, fluorouracil; GEJ, gastroesophageal junction; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; nab, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1 ; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.

the perioperative setting. A summary of the FDA-approved indications for ICI–chemotherapy combinations as well as the associated administration schedules (ie, continuous vs induction followed by maintenance) is provided in table 1. The indications listed are limited to anti-PD-(L)1 in combination with chemotherapies, complex combinations involving multiple ICIs and/or targeted therapies (eg, bevacizumab, trastuzumab) were beyond the scope of this manuscript.

Finally, these definitions assume that if progression occurs during the maintenance phase, the tumor is resistant to the maintenance therapy, which may consist of ICI monotherapy (eg, SCLC indication for durvalumab + cisplatin or carboplatin and etoposide) or a combination (eg, NSCLC indication for pembrolizumab + pemetrexed and platinum-containing chemotherapy). Additional assumptions and caveats for specific clinical scenarios are described in the corresponding sections of this manuscript.

Comments on confounding factors for definitions of resistance to immunotherapy–chemotherapy combinations

One major hurdle in understanding resistance to combinations of ICIs and chemotherapy is the potential for cytotoxic agents to have opposing immunostimulatory and immunosuppressive effects. With immunotherapy-only combinations or regimens including antiangiogenic agents, the contribution of individual components can be presumed to be at least additive if not synergistic.[28 29] In contrast, chemotherapy may have dual effects on both tumor cells and immune cells. Even in maintenance scenarios after chemotherapy is discontinued, lasting impairment of mature leukocyte proliferation[30 31] as well as delayed recovery of $CD4^+$ and some memory $CD8^+$ T cell populations[15 16] may lead to protracted immune impairment.

Conversely, chemotherapy has the potential to augment immune responses. Multiple immune-stimulatory mechanisms for chemotherapy have been described including augmented neoantigen presentation and induction of immunogenic cell death, enhanced cross-priming, toll-like receptor 4 (TLR4)-dependent inflammation, T helper type 1 immunity, and depletion of suppressor cells in the tumor microenvironment.[18 32 33]

Another hypothesis is that there is no interaction at all between chemotherapy and immunotherapy and the responses with the combinations are as beneficial as expected under the null hypothesis of independent

drug action. Under this model, administering two drugs improves the likelihood of response not via additivity or synergy, but rather by bet-hedging,[34] meaning that an improvement in the aggregate population seen with the combination arises due to non-overlapping groups of individuals with a response to only one agent. Here, the challenge is not necessarily related to biological interaction, but rather a more fundamental inability to know which component of a combination is active in any given patient. Uncertainty will necessarily arise when acquired resistance occurs in how to adjudicate which of the components of the therapeutic regimen were responsible for the initial response and therefore the subsequent resistance. The problem is further compounded by the complex induction/maintenance schemes that are increasingly becoming standard of care. For example, in a patient with NSCLC who has an initial tumor response to pembrolizumab + pemetrexed and carboplatin with pembrolizumab maintenance for 9 months who then has progressive disease, it is difficult to ascribe the resistance to the chemotherapy, PD-1 blockade, or the combination.

There was consensus that resistance may vary depending on the mechanism of action of the cytotoxic partner for the ICI in combination regimens, as different mechanisms underlie resistance to these chemotherapies as single agents.[35 36] A detailed accounting of the mechanisms of synergy and antagonism between chemotherapies and immunotherapies is beyond the scope of this clinically-focused consensus statement. However, an overview of select immune-modulating effects of the four broad classes of chemotherapies for which FDA-approved combinations with ICIs were available at the time of manuscript writing is provided in table 2.

Finally, corticosteroids—often a component of chemotherapy regimens as supportive care and used for palliation of symptoms—can suppress proliferation and differentiation of naïve T cells,[37] potentially further confounding the establishment of bona fide resistance to immunotherapy in combination settings. It is currently not known whether steroids negatively affect the efficacy of checkpoint inhibition in combination with chemotherapy, and additional data are needed. Steroids are an essential component of premedication for some chemotherapy regimens as well as for the management of immune-related adverse events (irAEs) and these standards of care should be followed. Although the use of steroids for the management of irAEs does not appear to negatively influence survival, at least one study has shown an association between palliative steroid use and poor PFS outcomes for patients with lung cancer being treated with ICIs.[38]

Given the multiple potential variables described above, the consensus was that additional research is needed to understand the interplay between host and external factors contributing to sensitivity and resistance to immunotherapy–chemotherapy combinations. The SITC Immunotherapy Resistance Committee advocates for future research and data sharing to elucidate the resistance phenomena that are not currently definable based on the available data and evaluation methods.

Primary resistance to immunotherapy–chemotherapy combinations

Tumors are considered to have primary resistance to a regimen if patients receive no initial benefit with treatment. In order to define a tumor as primary resistant to a regimen, adequate drug exposure must be achieved (ie, the minimum dose that would be expected to lead to response in a susceptible tumor). In the definitions for single-agent anti-PD-(L)1 ICIs, that minimum drug exposure was defined as 2 cycles based on the expected response kinetics of immune-based agents.

The approved indications for ICI–chemotherapy combinations at the time of manuscript preparation include substantial variability in what is defined as a cycle, depending on the cytotoxic agent used as backbone. Additionally, since the initial publication of the 2020 SITC consensus definitions,[24] alternate administration schedules for ICIs have also been approved with less frequent infusions and higher doses of the anti-PD-(L)1 agent. There was agreement that a lack of response with any exposure may be sufficient to suspect the tumor as resistant—especially given the expected activity of cytotoxic

Table 2 Potential immune-enchancing and immune-inhibitory effects of FDA-approved chemotherapy partners for ICIs, as reviewed in[12–14 18 54 55]

Chemotherapy class	Agents approved for use with ICIs	Mechanisms of potential immune synergy
Alkylating agents	Platinum-containing agents (eg, carboplatin, cisplatin).	► Immunogenic cell death. ► Neoantigen presentation in the TME. ► Inhibition of suppressive cells.
Antimetabolites	Nucleoside analogs (eg, fluoropyrimidines, gemcitabine).	► Inhibition of suppressive cells. ► Enhanced DC function.
Microtubule-disrupting agents	Taxanes (eg, paclitaxel).	► Enhanced DC function. ► Promotion of Th1 immunity.
Topoisomerase inhibitors	Podophyllotoxins (eg, etoposide), anthracyclines.	► Immunogenic cell death. ► Neoantigen presentation in the TME. ► Enhanced DC function.

DC, dendritic cell; Th1, T helper type 1; TME, tumor microenvironment.

chemotherapy. Practically, however, 6–8 weeks (or 2 cycles of the immunotherapy component) on therapy is likely necessary to rule out a potential for response with treatment and therefore should be considered the minimum drug exposure requirement in the majority of cases to define resistance. In cases where slight radiographic progression occurs without any deterioration in symptoms (as compared with clear clinical worsening), it was acknowledged that there may be hesitation to change therapies given that very few options with high likelihood of response are available for next-line treatment after ICI–chemotherapy combinations. As such, for patients with isolated foci of progression who are otherwise clinically stable, local therapy may be considered. There was unanimous agreement that in the setting of rapidly progressing disease, a full 6–8 weeks of exposure may not be necessary to classify a tumor as resistant.

Primary resistance is considered a lack of benefit with initial treatment and the consensus was that any progression within 6 months of initiating therapy should be included, irrespective of the initial response. It was acknowledged that a complete response (CR) followed by recurrence within the first 6 months of therapy likely would not represent primary resistance, however this scenario is expected to be very rare. The definitions of resistance to anti-PD-(L)1 monotherapy required documented progressive disease, stable disease, partial response and CR assessed as described in the Response Evaluation Criteria In Solid Tumors v1.1 (RECIST v1.1).[39] There was hesitation in anchoring the definitions to formal evaluation by RECIST for the definitions of resistance, especially for patients who were initially treated with ICI–chemotherapy combinations in the standard-of-care setting where RECIST is not expected to be a component of routine clinical documentation. Acknowledging the tension between evaluating homogenous patient populations in clinical trials and establishing insurmountably stringent enrollment criteria, there was consensus that documented progression by RECIST is preferred for the definitions of resistance. There was also consensus that the definitions should include patients who experience clinical deterioration without evidence of radiographic progression. Given the relative rarity of pseudoprogression with cytotoxic therapy and a desire to avoid unnecessarily burdensome enrollment criteria in future clinical trials, confirmatory scans were deemed to be not required to define primary resistance.

Currently, there was consensus that it is not possible to identify the contribution of components to primary resistance based on this clinical definition alone. Even in cases where one of the drugs is exchanged for an agent of a different class and response occurs, it is not possible to rule out lingering effects of cytotoxic chemotherapy nor delayed effects of ICIs[40] nor antagonism between the agents when administered concurrently. There was also acknowledgment that the 6-month cut-off may not be appropriate for slow-growing malignancies. Finally, given that these definitions are not intended to be used as guidelines for clinical management, there was acknowledgment that there may be patients that obtain clinical benefit when treatment is continued beyond progression in cases that would be captured under this definition of primary resistance.

Secondary or late resistance to immunotherapy–chemotherapy combinations

Acquired resistance to chemotherapy is understood as an adaptive process based on selection for variant clones that enable tumor escape after a preliminary interval of disease control.[9 11 36] Secondary resistance to ICIs, though not well understood, is similarly considered to arise due to changes in the tumor or in the host immune response occurring de novo during treatment that cause initial clinical benefit to wane.[4 5 7 41–43] Establishment of initial clinical benefit is central to the definition of secondary or late resistance to an agent, regardless of whether the mechanisms of action responsible for disease control is immune-mediated or direct cytotoxicity. However, as discussed previously, when ICIs are administered with chemotherapy it is not possible to definitively establish whether initial response was due to the combination or one of the monotherapies alone.

Because of the impossibility of establishing the individual contributions of components of an ICI–chemotherapy combination to tumor response, the consensus was that disease progression after initial clinical benefit should be defined as 'secondary or late resistance'. Further methods to validate response to immunotherapy such as advanced radiomic approaches to visualize effector T cell function or gene expression profiling is needed in order to clinically define secondary or late resistance to ICI–chemotherapy combinations.

Resistance to immunotherapy–chemotherapy combinations in the perioperative setting

Two ICI–chemotherapy combinations were FDA-approved in the curative intent setting at the time of manuscript publication. The first approval was based on KEYNOTE-522, in which the addition of pembrolizumab to standard neoadjuvant chemotherapy and continued into the adjuvant setting for the treatment of high-risk early-stage TNBC was associated with improved pathologic complete response (pCR) rates as well as event-free survival (EFS) compared with chemotherapy alone.[22] Approval for neoadjuvant nivolumab in combination with platinum doublet chemotherapy for the treatment of resectable NSCLC was based on improved EFS and pCR in CheckMate 816.[44] Ongoing trials are evaluating neoadjuvant ICI–chemotherapy combinations based on the rationale that establishment of an immune response while the tumor is in situ (and inflamed due to the activity of the cytotoxic agent) may lead to more robust control after curative intent surgery.[45–47]

No definitions were developed for resistance in the perioperative setting. Despite emerging evidence for benefit with neoadjuvant and adjuvant ICI–chemotherapy

combinations, it is not known whether improvement in short-term endpoints such as pCR and EFS truly correspond to OS benefit nor the optimal duration and dosing schedule for adjuvant therapy. In the future, sensitive and dynamic methods for measuring minimal residual disease such as quantification of circulating tumor DNA (ctDNA)[48 49] may be used as the basis for evaluation of resistance to ICI–chemotherapy combinations.

Collection of biopsy samples and banking of resection specimens was recommended as a tissue source for future reverse translational studies to understand mechanisms of resistance. In the adjuvant setting, confirmatory biopsies may sometimes provide information that alters the management of distal recurrences.[50] However, the need for pathologic confirmation varies depending on the original tumor and the site of the recurrent lesion. In the neoadjuvant setting, a lack of pathologic response in the resection specimen may indicate a lack of activity of the regimen. However, the threshold values for degree of tumor death in the surgical sample that correspond to survival benefit have not been determined for ICI–chemotherapy combinations and likely vary depending on the tissue of origin and disease histology.

Resistance after halting immunotherapy–chemotherapy combinations for patients with metastatic disease

Multiple factors may cause a patient to discontinue therapy during treatment for stage IV disease including financial or social obstacles to treatment, toxicity, protocol-specified cessation, or achievement of perceived maximal clinical benefit.[51 52] There was consensus that discontinuation due to toxicity should not be included in the definitions of resistance. 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.

Even after discontinuation of therapy, ICIs may persistently occupy the PD-1 receptor beyond the expected serum half-life and treatment may also induce durable immunological memory.[51 52] Responses to ICIs may even deepen over time via epitope spreading,[53] circumventing immune selection for escape variants and leading to long-term clinical benefit in some patients. Chemotherapy may also cause lingering effects, including impaired T cell proliferation, after discontinuation of therapy.[30 31]

The consensus was that resistance after halting therapy for patients with stage IV disease should be dictated by the duration of the ICI-chemotherapy regimen. As stated in the **General assumptions on resistance to immunotherapy–chemotherapy combinations**, disease progression while on maintenance therapy (or following maintenance therapy) can be assumed to be resistance to that agent whether ICI monotherapy (eg, lung cancer indications) or the full combination (eg, HSNCC, gastric cancer, TNBC). Although no consensus could be reached on the duration between discontinuation of therapy and recurrence that defines resistance to ICI–chemotherapy combinations, there is some period of time after which a patient could be considered naïve and rechallenge could be considered. This time interval should be defined by the level of comfort of the sponsor and investigators in concert with regulatory authorities if using these definitions to help clarify enrollment for a clinical trial.

CONCLUSION

This paper describes clinical scenarios that define resistance to ICIs in combination with chemotherapy. Due to the relative paucity of available data and complexity in attributing response to one component of regimens that may act synergistically as well as antagonistically, these definitions of resistance to ICI–chemotherapy combinations were developed based on expert consensus of the workshop attendees. The definitions described are summarized in table 3. Future research is needed to validate the clinical relevance of these definitions and correlate the resistance scenarios described in this paper with biological mechanisms.

A number of important areas for future data collection were identified in the consensus discussions for the development of this manuscript. In particular, it will be important to identify what are the key differences between progression after stopping therapy and progression while on therapy and what is an acceptable false-positive rate of classifying disease progression. To address these questions, long-term follow-up data should be collected on patients classified by individual resistance scenarios. Additionally, data is needed on outcomes after rechallenge stratified by time interval. Continued

Table 3 Minimum exposure and best response definition for primary resistance to immune checkpoint inhibitor–chemotherapy combinations in advanced tumor settings

Resistance phenotype	Exposure requirement	Timing of RECIST progression*	Confirmatory scan
Primary resistance†	6–8 weeks‡	≤6 months	Not required
Secondary or late resistance†	>6 months	>6 months	Not required

*Regardless of best response.
†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.
RECIST, Response Evaluation Criteria In Solid Tumors.

validation of ctDNA as a measure of disease burden and response is also needed, and samples should be collected at baseline and on-treatment in future trials to enable these studies. Multi-biomarker-based approaches may also be helpful in defining resistance in the future by identifying patients with tumors that would be expected to respond to ICI-based combinations (eg, the threshold for classifying resistance would be lower for tumors with high PD-L1 expression, high tumor mutation burden (TMB), and evidence of interferon gene signature expression). Open data sharing between industry sponsors and academic investigators will be essential to answer these critical questions. Finally, although the resistance definitions described in this paper were strictly based on clinical parameters, the SITC Immunotherapy Resistance Committee advocates for future reverse translational research to understand the mechanisms of resistance to immunotherapy combinations so that one day even more patients may benefit.

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