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COMMENTS AND CONTROVERSIES

Pseudoprogression and Immune-Related Response in Solid Tumors

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Emerging cancer therapeutics target the immune system, stimulating host antitumor response. Tumor cells generate an immunosuppressive milieu with multiple mechanisms to evade immune destruction, including disruption of effective antigen presentation, reduction of effector T-cell function, and upregulation of pathways that promote tolerance and T-cell anergy.[1] The programmed death (PD) -1/PD ligand-1 (PD-L1) pathway is a critical component of tumor-mediated immunosuppression. Antibodies to PD-1 and PD-L1 have shown potential clinical benefit in advanced solid tumors.[2] The US Food and Drug Administration approved the PD-1 inhibitors pembrolizumab and nivolumab for metastatic melanoma and also recently approved nivolumab for the treatment of metastatic squamous non–small-cell lung cancer. The US Food and Drug Administration has also designated the PD-L1 inhibitor MPDL3280A as a breakthrough therapy for bladder cancer and non–small-cell lung cancer. These drugs and additional immune checkpoint inhibitors are currently under investigation in multiple clinical trials as single-agent therapy and also in combination with other agents.

As immunotherapeutics become increasingly available to patients, clinicians face a major challenge in the evaluation of these novel drugs—the accurate determination of clinical efficacy. Historically, the WHO and the RECIST Group have provided standard guidelines to define tumor response to therapy.[3,4] Although imperfect, the RECIST criteria are an accepted platform for defining the moment of disease progression and have guided clinician determination of tumor response and driven subsequent drug approval for years.[5] By RECIST criteria, a significant increase in the size of tumor lesions and the development of new lesions are considered unequivocal disease progression. Oncologists in the community routinely use RECIST criteria as operational thresholds in clinical decision making. Patients undergo scheduled restaging scans and radiographic measurements of tumor lesions to determine the extent of change in tumor size. Current therapy is discontinued and alternative treatments are initiated when patients meet parameters for disease progression. Significant tumor growth on therapy has traditionally been considered equivalent to treatment failure.

Some patients have responded to immune-targeted treatment with tumor shrinkage or stable disease that would be consistent with existing RECIST criteria; however, distinct immune-related patterns of response have also been observed. Some patients with melanoma treated with ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte–associated antigen-4, experienced initial increased size of tumor lesions, confirmed by biopsy as inflammatory cell infiltrates or necrosis, with subsequent decreased tumor burden.[6] Immune-related response patterns have been observed in clinical trials of ipilimumab, including development of new lesions associated with edema and infiltrates of immune cells and transient increases in baseline tumor lesions. Delayed clinical responses were also observed in studies of immunotherapeutic agents, such that an increase in total tumor burden was later followed by tumor regression. These findings of pseudoprogression would have been classified prematurely as progressive disease by historic WHO or RECIST criteria and have prompted the development of the immune-related response criteria.[7]

The initial report of immune-related response criteria in patients who received ipilimumab for treatment of melanoma found that 9.7% of patients (22 of 227 patients) had clinical responses (partial response and stable disease) that would have been misclassified as disease progression by WHO criteria.[7] Patients who had responses consistent with both WHO and immune criteria had a reported median survival of 31.2 months (95% CI, 27.8 to 31.2 months), whereas the median overall survival in patients with responses consistent with immune criteria only have not been reached (95% CI, 13.5 months to not reached), and these patients had improved survival profiles compared with nonresponders.[7]

Five years after the introduction of the immune response criteria, it is necessary to fully characterize the patterns of immune-related phenomena, to understand these patterns across multiple solid tumor types, and to evaluate how these guidelines are used in current clinical practice. Recent studies have evaluated the role of immune-related response criteria in patients with melanoma. One study of patients with metastatic melanoma treated with nivolumab reported that 10% (11 of 107 patients) experienced distinct immune-related responses.[8] Data from another clinical trial of the anti–PD-1 monoclonal antibody pembrolizumab in patients with advanced melanoma found that 3.6% (seven of 192 patients) experienced RECIST progressive disease at first assessment, followed by clinical response at second assessment. An additional 3.1% of patients (six of 192 patients) on this study had RECIST progressive disease followed by delayed clinical response at later clinical assessment, for a total of 6.7% of patients (13 of 192 patients) with pseudoprogression. Furthermore, Hodi et al[9] conducted a study-wide analysis and found that 12% of patients (51 of 411 patients) with melanoma treated with pembrolizumab were classified as responders or as having stable disease by immune response criteria but would have been classified as having progressive disease by RECIST. This patient cohort had improved overall survival compared

with the patients who met criteria of progressive disease by both immune response criteria and RECIST criteria.[9]

Multiple recent clinical trials using antibodies to PD-1 and PD-L1 in the treatment of advanced solid tumors have been completed and published,[10-22] enabling broader evaluation of pseudoprogression across solid tumors. The majority of these clinical trials evaluated the safety and efficacy of immune checkpoint blockade in the treatment of patients with melanoma. However, additional studies were conducted in patients with bladder cancer, breast cancer, colorectal cancer, esophageal cancer, gastric cancer, head and neck cancer, lung cancer, pancreatoduodenal cancer, ovarian cancer, renal cell cancer, sarcoma, and uterine cancer. The observed incidence of distinct immune responses across different solid tumor types is provided in Table 1.

In these studies, tumor assessments included physical examination and radiologic assessment with computed tomography and/or magnetic resonance imaging. Tumor assessments were confirmed with repeat imaging studies or by an independent radiology review. Primary response criteria for the studies included RECIST 1.0, RECIST 1.1, and modified WHO criteria. The majority of existing trials used immune response criteria determined by investigator as a corollary to the RECIST criteria. For example, these criteria were referenced for clinical decision making in the event of mixed response, such as decrease in target lesions and development of new nontarget lesions. In other trials, the immune-related response criteria were used as an exploratory end point. Immune-related response criteria were not used in the reporting of objective response rates in 71% of the studies (10 of 14 studies).

Immune-related responses distinct from RECIST responses have been reported in recently published studies of immune checkpoint blockade. Half of the clinical trials reported the presence of a few additional patients with distinct immune-related patterns of response that did not meet RECIST criteria (44 of 1,126 total patients; an approximate overall incidence of 4%). This incidence calculation may be an underestimation because immune-related response criteria were not evaluated across all patients in these studies. In some studies, there was limited anecdotal reporting of patients meeting immune-related response criteria. The most common pattern reported was a decrease in target tumor lesions in the presence of new lesions. Cases of initial tumor enlargement with delayed shrinkage were also reported.

Table 1. Clinical Response Rates for Programmed Death-1 and Programmed Death Ligand-1 Inhibitors Across Solid Tumors

		Primary Response Criteria				Immune-Related Response Criteria		
Regimen and Trial	Cancer Type	No. of Evaluable Patients	No. of Responses	Objective Response Rate (%)	Primary Response Criteria	No. of Evaluable Patients	No. of Responses*	Objective Response Rate (%)
Nivolumab								
Brahmer et al[20] (2010)	Colorectal, melanoma, renal cell	39	3	8	RECIST 1.0	Not reported	Not reported	Not reported
Brahmer et al[19] (2012)	Multiple	135	17	13	RECIST 1.0	Not reported	4 additional	Not reported
	Melanoma	52	9	17				
	Non–small-cell lung	49	5	10				
	Ovarian	17	1	6				
	Renal cell	17	2	12				
Motzer et al[16] (2015)	Renal cell	168	35	21	RECIST 1.1	168	38	23
Rizvi et al[21] (2015)	Non–small-cell lung (squamous)	117	17	14.5	RECIST 1.1	Not reported	Not reported	Not reported
Topalian et al[13] (2012)	Multiple	236	49	21	RECIST 1.0	Not reported	8 additional	Not reported
	Melanoma	94	26	28				
	Non–small-cell lung	76	14	18				
	Renal cell	33	9	27				
Topalian et al[12] (2014)	Melanoma	107	33	31	RECIST 1.0	Not reported	4 additional	Not reported
Weber et al[11] (2013)	Melanoma	87	22	25	RECIST 1.1	Not reported	Not reported	Not reported
Weber et al[22] (2015)	Melanoma	120	38	31.7	RECIST 1.1	Not reported	10 additional†	Not reported
Wolchok et al[10] (2013)	Melanoma	52	21	40	Modified WHO	Not reported	4 additional	Not reported
Lambrolizumab								
Hamid et al[18] (2013)	Melanoma	117	44	38	RECIST 1.1	135	50	37%
Pembrolizumab								
Hodi et al[9] (2014)	Melanoma	411	115‡/164§	40/28	RECIST 1.1	192	13 additional	Not reported
Robert et al[14] (2014)	Melanoma	157	41	26	RECIST 1.1	173	51	29%
MPDL3280A								
Herbst et al[17] (2014)	Multiple‖	175	32	18	RECIST 1.1	Not reported	Not reported	Not reported
	Melanoma	43	11	26				
	Non–small-cell lung	53	11	21				
	Renal cell	56	7	13				
Powles et al[15] (2014)	Bladder	65	17	26	RECIST 1.1	Not reported	1 additional	Not reported

*Some studies reported additional patients with immune-related patterns of response or pseudoprogression, although immune-related response criteria were not used for calculation of objective response rates.
†Weber et al[22] reported that of 37 patients maintained on therapy past RECIST progressive disease, 10 patients achieved immune-related response.
‡The number of responses in patients with melanoma previously treated with ipilimumab.
§The number of responses in ipilimumab-naïve patients with melanoma.
‖Multiple tumor types were tested in this study, including breast, colorectal, esophageal, gastric, head and neck, ovarian, pancreatoduodenal, sarcoma, and uterine.

Immune response distinct from RECIST response was reported in multiple patients with melanoma (6.6%; 31 of 471 patients). However, there were isolated occurrences of immune response not captured by RECIST response reported in patients with bladder cancer (1.5%; one of 65 patients), renal cell cancer (1.8%; three of 168 patients), and lung cancer (unquantified; reported in a study with multiple malignancies). Head-to-head comparison of RECIST criteria and immune-related response criteria was performed in less than a third of the studies (four of 14 studies), with similar response rates.

Pseudoprogression and immune-related patterns of mixed response pose a growing clinical challenge for practitioners and patients. Increasing numbers of patients with cancer will have opportunities to receive immunotherapy through experimental trials and recent drug approvals. Patients may continue treatment in the presence of tumor enlargement or new tumor lesions on imaging scans when informed of potential pseudoprogression. However, some of these patients have true disease progression and may consider transitioning to alternative treatment options. The overall reported incidence of pseudoprogression in solid tumors is low. Additional information is necessary for oncologists to use the immune response criteria in the context of treatment decisions and to counsel patients about the incidence of immune-related responses in their tumor types.

Given the current evidence published in clinical trials and supplemental data, a small percentage of patients achieve immune-related responses that are not captured by RECIST criteria. This low reported percentage may be related in part to the unique mechanism of action of immunotherapeutics. Immune agents impact host antitumor response and may require additional time to achieve measurable or sustained clinical effects compared with traditional cytotoxic chemotherapy. It remains unclear whether these response patterns reported in patients with melanoma occur within the same time frame and to the same extent in patients with other solid tumors. Increased reporting of immune-related response phenomena in ongoing trials is necessary to determine whether pseudoprogression is a surrogate for clinical benefit and increased survival and to further elucidate the complex dynamics of tumor interactions with the immune system.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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