Immune Checkpoint Inhibitor Cancer Therapy: Spectrum of Imaging Findings[1]

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Abbreviations: CTLA-4 = cytotoxic T-lymphocyte antigen-4, FDA = Food and Drug Administration, irAE = immune-related adverse event, irRC = Immune-related Response Criteria, NSCLC = non–small cell lung cancer, PD-1 = programmed cell death protein 1, PD-L1 = programmed cell death 1 ligand 1, RECIST = Response Evaluation Criteria in Solid Tumors

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Discuss the mechanisms of action of clinically used immune checkpoint inhibitors.
- Distinguish tumor pseudoprogression from true progression in patients undergoing immune checkpoint inhibitor therapy.
- Describe the characteristic imaging findings of immune checkpoint inhibitor–induced colitis, hypophysitis, and pneumonitis.

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Immune checkpoint inhibitors are a new class of cancer therapeutics that have demonstrated striking successes in a rapid series of clinical trials. Consequently, these drugs have dramatically increased in clinical use since being first approved for advanced melanoma in 2011. Current indications in addition to melanoma are non–small cell lung cancer, head and neck squamous cell carcinoma, renal cell carcinoma, urothelial carcinoma, and classical Hodgkin lymphoma. A small subset of patients treated with immune checkpoint inhibitors undergoes an atypical treatment response pattern termed *pseudoprogression*: New or enlarging lesions appear after initiation of therapy, thereby mimicking tumor progression, followed by an eventual decrease in total tumor burden. Traditional response standards applied at the time of initial increase in tumor burden can falsely designate this as treatment failure and could lead to inappropriate termination of therapy. Currently, when new or enlarging lesions are observed with immune checkpoint inhibitors, only follow-up imaging can help distinguish patients with pseudoprogression from the large majority in whom this observation represents true treatment failure. Furthermore, the unique mechanism of immune checkpoint inhibitors can cause a distinct set of adverse events related to autoimmunity, which can be severe or life threatening. Given the central role of imaging in cancer care, radiologists must be knowledgeable about immune checkpoint inhibitors to correctly assess treatment response and expeditiously diagnose treatment-related complications. The authors review the molecular mechanisms and clinical applications of immune checkpoint inhibitors, the current strategy to distinguish pseudoprogression from progression, and the imaging appearances of common immune-related adverse events.

Introduction

Cancer immunotherapy using immune checkpoint inhibitors is a promising new strategy that has demonstrated unprecedented success against advanced cancers. Starting with the U.S. Food and Drug Administration (FDA) approval of ipilimumab for previously treated metastatic melanoma in early 2011, these agents have rapidly expanded in clinical use and are now standard therapies for a variety of malignancies in addition to melanoma, including non–small cell lung cancer (NSCLC), renal cell carcinoma, head and neck squamous cell carcinoma, urothelial cancer, and classical Hodgkin lymphoma (1). Numerous clinical trials are underway for a wide range of cancers, including breast, prostate, ovarian, colorectal, and pancreatic (2,3).

The immune checkpoint inhibitors in current clinical use are monoclonal antibodies that promote immune system–mediated tumor destruction by inhibiting the signaling pathways that suppress antitu-

TEACHING POINTS

- Efforts at cancer immunotherapy continued throughout the century that followed Coley's initial work. However, cancer immunotherapy has only recently been propelled into widespread clinical use by the arrival of immune checkpoint inhibitors. To date, immune checkpoint inhibitors are monoclonal antibodies that block immune checkpoints to augment T-cell–mediated tumor destruction.
- Both RECIST 1.1 and the WHO criteria have proven to be inadequate for the assessment of response to immunotherapy agents such as immune checkpoint inhibitors, partly because of the time needed to mount an antitumor immune response. Furthermore, according to recent clinical trials, an estimated 2%–14% of patients treated with immune checkpoint inhibitors develop new or enlarged lesions after treatment initiation before experiencing an eventual decrease in total tumor burden, in the atypical response known as pseudoprogression.
- In 2009, the Immune-related Response Criteria (irRC) were proposed as a way to assess tumor response to immune checkpoint inhibitors, and immunotherapeutic agents in general, by accounting for the possibility of pseudoprogression. There are two main innovations of irRC: *(a)* new or enlarged lesions are incorporated into total tumor volume rather than immediately taken to indicate disease progression, and *(b)* designation of disease progression requires an increase in tumor volume to be confirmed at two consecutive imaging studies at least 4 weeks apart. The latter stipulation was put in place because currently, when new or enlarging lesions are observed at immune checkpoint inhibitor treatment, only follow-up imaging can help distinguish pseudoprogression from true treatment failure.
- Although pseudoprogression is a clinically meaningful event, only a small group of patients will experience it, and in most instances new or enlarged lesions will prove to represent true disease progression. Furthermore, patients with increased tumor burden who continue therapy in the hope that this represents pseudoprogression risk decompensation to the point of being unable to receive salvage chemotherapy when disease progression is confirmed.
- Immune checkpoint inhibitors are associated with a unique spectrum of adverse reactions compared with cytotoxic chemotherapy. These irAEs are attributed to autoimmunity caused by hyperactivated T cells, are common, and can involve almost every organ system.

mor T-cell activity (1). Owing to this novel mechanism, immune checkpoint inhibitors can generate a tumor response pattern not found in conventional chemotherapy termed *pseudoprogression*, where an initial appearance of new or enlarged lesions is followed by tumor regression (4). For patients with pseudoprogression, evaluation of tumor response according to conventional criteria may lead to the false conclusion of therapeutic failure and lead to premature treatment termination. By stimulating the immune system, these agents can also cause a unique spectrum of immune-related adverse events (irAEs) related to autoimmunity.

Given the expanding clinical use of immune checkpoint inhibitors and the central role of radiology in the care of patients with cancer, radiologists should be familiar with these drugs and their associated imaging findings. We review the mechanisms and clinical use of immune checkpoint inhibitors, the current strategy to distinguish pseudoprogression from progression, and the imaging appearances of common adverse events.

Immune Checkpoint Inhibitors: A New Frontier in Cancer Therapy

Toward the end of the 19th century, a New York surgeon named William Coley observed rare cases of tumor regression after bacterial infections (5). Although mechanistic insights into this phenomenon were lacking, he was able to sporadically reproduce this effect through inoculation of tumors with mixtures of inactivated bacteria that were later called "Coley's toxins." Coley's efforts are now recognized as the earliest attempt to harness immune system–mediated tumor destruction for cancer therapy.

The immune system protects against malignancies by eliminating precancerous and cancerous cells (6,7). Cancer cells harbor tumor-specific genetic mutations that can create neoantigens, which are not present in normal cells. These allow the immune system to identify cancers as nonself. Antigen-presenting cells (APCs) capture and present these tumor neoantigens within the context of the major histocompatibility complex (MHC), which can then be recognized by T cells via the T-cell receptor (TCR). In the presence of an appropriate costimulatory signal, prototypically through the CD28 costimulatory receptor, TCR ligation with the MHC-antigen complex leads to T-cell activation and ultimately to immune system–mediated tumor elimination. To decrease the risk of autoimmunity and to control the immune system response, T-cell activation is balanced by inhibitory pathways known as immune checkpoints (8). Cancer cells can co-opt these pathways to escape immune system–mediated tumor destruction (7,8).

Efforts at cancer immunotherapy continued throughout the century that followed Coley's initial work. However, cancer immunotherapy has only recently been propelled into widespread clinical use by the arrival of immune checkpoint inhibitors. To date, immune checkpoint inhibitors are monoclonal antibodies that block immune checkpoints to augment T-cell–mediated tumor destruction (1). Immune checkpoint inhibitors in current clinical use target either cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed cell death protein 1 (PD-1), both of which are cell surface receptors, or the PD-1 ligand programmed cell death 1 ligand 1 (PD-L1) (9). CTLA-4 and PD-1 are expressed by T cells and inhibit their activity through different mechanisms. CTLA-4 limits T-cell activation

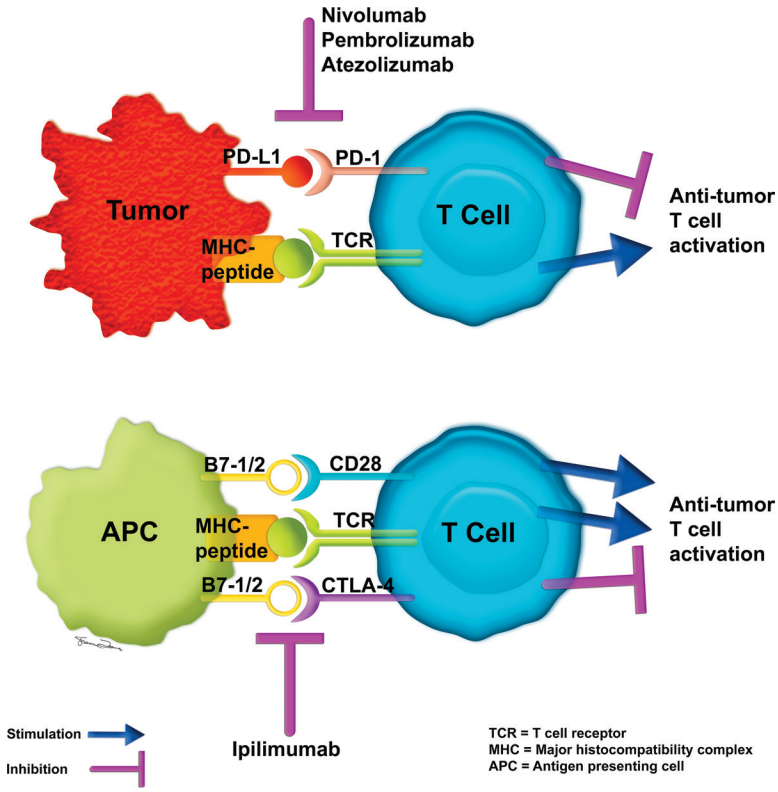


Figure 1. Illustration shows mechanisms of action of immune checkpoint inhibitors, including anti–CTLA-4 (ipilimumab), anti–PD-1 (nivolumab, pembrolizumab), and anti–PD-L1 (atezolizumab) monoclonal antibodies. The anti–CTLA-4 agent prevents binding of CTLA-4 to its ligands B7-1 and B7-2 *(B7-1/2)*, and the anti–PD-1 and anti–PD-L1 agents prevent binding of PD-1 to its ligand PD-L1. CD28 is a costimulatory receptor.

by APCs by raising the activation threshold and attenuating clonal expansion of tumor-specific T cells (Fig 1) (7,9,10). The PD-1 ligands PD-L1 and programmed cell death 1 ligand 2 (PD-L2) are expressed by APCs. PD-L1 is also present on normal nonhematopoietic cell membranes as well as on tumor cell membranes. These act as a brake on effector T-cell function, including in the tumor microenvironment (Fig 1) (7).

In 2011, the first of these agents, the anti–CTLA-4 monoclonal antibody ipilimumab, gained FDA approval for use in cases of advanced melanoma following the publication of a landmark phase 3 clinical trial in 2010 (11). In that study, ipilimumab monotherapy demonstrated improved overall survival of patients with previously treated metastatic melanoma, an unprecedented achievement (12). In 2014, the anti–PD-1 monoclonal antibodies pembrolizumab and nivolumab were also approved for advanced melanoma. In 2015, two pivotal phase 3 studies showed that nivolumab improved overall survival over that found with cytotoxic chemotherapy in patients with advanced, previously treated squamous cell and nonsquamous NSCLC (13,14). Soon afterward, a phase 3 study published in late 2016 reported that pembrolizumab improved progression-free and overall survival over that found with platinum-based chemotherapy in treatment-naive NSCLC with PD-L1 expression on 50% or higher of tumor cells (15). As a result, pembrolizumab has become the standard of care for first-line treatment of NSCLC with high PD-L1 expression. In that same year, nivolumab was also reported in a phase 3 trial to improve overall survival of patients with advanced renal cell carcinoma over that found with everolimus (16). On the basis of these and other similar successes in treatment of solid tumors, immune checkpoint inhibitors are now FDA approved for melanoma, NSCLC, renal cell carcinoma, urothelial carcinoma, and head and neck squamous cell carcinoma (Table 1).

Although immune checkpoint inhibitors have been more extensively studied in solid tumors, there has also been intense investigation of their use in hematologic malignancies (17). On the basis of dramatic successes in early-stage clinical trials, nivolumab gained accelerated FDA approval in 2016 for the treatment of classical Hodgkin lymphoma following relapse or progression after treatment with autologous stem-cell transplantation and brentuximab vedotin (17–19). In early 2017, pembrolizumab likewise gained FDA approval for treatment of refractory or relapsed classical Hodgkin lymphoma.

Challenges in Imaging Assessment of Treatment Response

Owing to its unique mechanism of action, immune checkpoint inhibitor therapy can generate a tumor response pattern different from those found with cytotoxic chemotherapy or radiation therapy. The paradigm for evaluating treatment response to cytotoxic therapy stipulates that new

Table 1: FDA-approved Immune Checkpoint Inhibitors to Date

Drug	Target	Approved Use
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, NSCLC, renal cell carcinoma, urothelial carcinoma, classical Hodgkin lymphoma
Pembrolizumab	PD-1	Melanoma, NSCLC, head and neck squamous cell carcinoma, urothelial carcinoma, classical Hodgkin lymphoma
Atezolizumab	PD-L1	Urothelial carcinoma, NSCLC
Durvalumab	PD-L1	Urothelial carcinoma

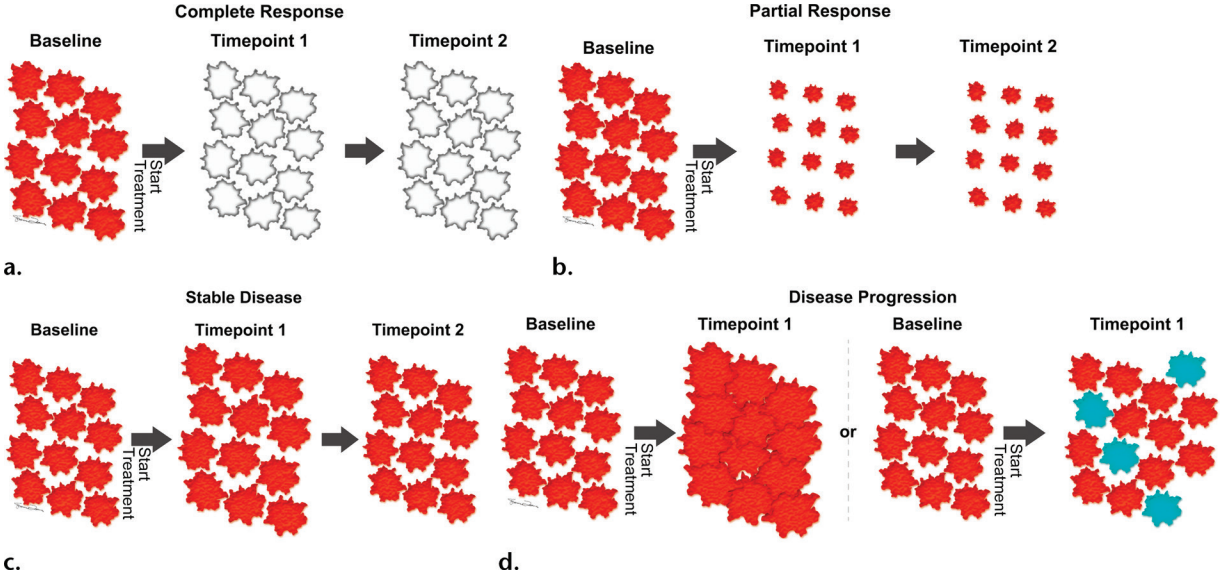


Figure 2. Illustration of conventional criteria (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 [RECIST 1.1]) for evaluation of solid tumor response to therapy (20). Time point intervals vary but are typically 4–12 weeks. Blue = new lesion, red = index lesion, white = lesion disappears. **(a)** Complete response is defined as disappearance of all target lesions. **(b)** Partial response requires at least a 30% decrease in the sum of the diameters of the target lesions compared with the baseline. **(c)** Stable disease applies when target lesions do not enlarge sufficiently to qualify for progressive disease and do not shrink sufficiently to qualify for partial response. **(d)** Progressive disease occurs when there is a 20% or more increase in the sum of the diameters of the target lesions compared with the nadir or when one or more new lesions appear.

or enlarging lesions following treatment initiation indicate disease progression and therapeutic failure (Fig 2). This underlies the RECIST 1.1 and the World Health Organization (WHO) criteria, two widely used metrics for evaluation of therapeutic response (20,21). These scoring systems are reliable for assessment of response to chemotherapy, as cytotoxicity is expected to occur soon after exposure to the drug, with continued response reflected by a continued decrease in tumor burden. However, both RECIST 1.1 and the WHO criteria have proven to be inadequate for the assessment of response to immunotherapy agents such as immune checkpoint inhibitors, partly because of the time needed to mount an antitumor immune response (3,22). Furthermore, according to recent clinical trials, an estimated 2%–14% of patients treated with immune checkpoint inhibitors develop new or enlarged lesions after treatment initiation before experiencing an eventual decrease in total tumor burden, in the atypical response known as pseudoprogression (Fig 3) (4,13,23,24). Proposed causes for this response pattern are continued tumor growth during the time needed to mount an immune response and/or immune-cell infiltration and inflammation of known lesions and those that were initially radiologically occult (4).

Pseudoprogression has been reported for anti–CTLA-4, anti–PD-1, and anti–PD-L1 agents across multiple cancers, including melanoma, lung cancer, renal cell carcinoma, and bladder cancer (1,3). An analysis of patients with melanoma found that this response pattern can occur in the lymph nodes but more commonly involves non-nodal sites such as the lungs, liver, kidneys, adrenal glands, peritoneum, and chest and abdominal walls (23). Examples

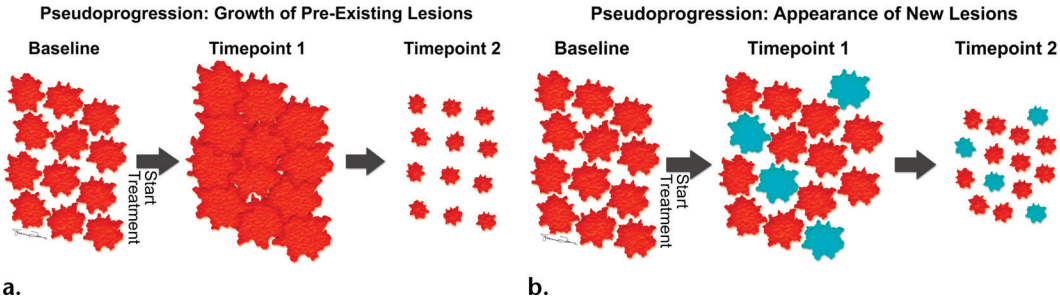


Figure 3. Pseudoprogression with immune checkpoint inhibitor therapy, which manifests as either growth of pre-existing lesions **(a)** or appearance of new lesions **(b)** after initiation of therapy, followed by an eventual decrease in total tumor burden. Time point intervals vary depending on the drug, cancer type, and treatment regimen. In the majority of cases, baseline to time point 1 is 6–12 weeks, and time point 1 to time point 2 is 4–12 weeks. Blue = new lesion, red = index lesion.

of pseudoprogression with anti–CTLA-4, anti–PD-1, and anti–PD-L1 agents are shown in Figures 4–9.

In 2009, the Immune-related Response Criteria (irRC) were proposed as a way to assess tumor response to immune checkpoint inhibitors, and immunotherapeutic agents in general, by accounting for the possibility of pseudoprogression (4). There are two main innovations of the irRC: *(a)* new or enlarged lesions are incorporated into total tumor volume rather than immediately taken to indicate disease progression, and *(b)* designation of disease progression requires an increase in tumor volume to be confirmed at two consecutive imaging studies at least 4 weeks apart (Table 2; Figs 10, 11) (4). The latter stipulation was put in place because currently, when new or enlarging lesions are observed at immune checkpoint inhibitor treatment, only follow-up imaging can help distinguish pseudoprogression from true treatment failure. In early 2017, a consensus modification of RECIST 1.1 for immune-based therapeutics (iRECIST) was issued to guide the use of RECIST 1.1 in immunotherapy trials for purposes of standardizing study design and data collection (26). This guideline also incorporates the use of follow-up imaging to differentiate true progression from pseudoprogression, where the latter is referred to in the guideline as "unconfirmed progressive disease."

Application of the irRC paradigm to two phase 2 studies of ipilimumab in treatment of melanoma showed that, of 227 patients treated with the immune checkpoint inhibitor, 22 (9.7%) were initially designated as having disease progression by WHO criteria demonstrated treatment response by irRC (4). An analysis of phase 1 and 2 immune checkpoint inhibitor trials at our institution found that, of 356 enrolled patients, 2%–6% demonstrated pseudoprogression, which was more commonly seen with anti–CTLA-4 therapy than with anti–PD-1 monoclonal antibody therapy (24). Cancer types in the cohort included melanoma, NSCLC, small cell lung cancer, and breast cancer. Immune checkpoint inhibitors included anti–CTLA-4, anti–PD-1, and anti–PD-L1 agents. In a recent phase 3 trial, 28 (21%) of 135 patients with squamous cell NSCLC continued treatment with nivolumab beyond RECIST 1.1 disease progression. Nine of these patients displayed a "nonconventional pattern of benefit," defined as a reduction in the size or number or both of target lesions with the simultaneous appearance of new lesions, initial disease progression followed by tumor reduction, or no further progression for at least two tumor assessments (13).

Although pseudoprogression is uncommon, its potential clinical consequences were demonstrated by a recent analysis of a phase 1b trial of pembrolizumab in patients with advanced melanoma (23). Of 592 patients who survived past 12 weeks, 84 (14%) showed disease progression by RECIST 1.1 but not by irRC. This patient cohort showed a better overall survival rate (37.5%) at 2 years than did the group with progressive disease by both RECIST 1.1 and irRC (17.3%). Notably, this was still inferior to the survival rate of the group with nonprogressive disease by both criteria (77.6%). A failure to account for pseudoprogression may result in the premature termination of a beneficial drug. However, it should be emphasized that although pseudoprogression is a clinically meaningful event, only a small group of patients will experience it, and in most instances new or enlarged lesions will prove to represent true disease progression. Furthermore, patients with increased tumor burden who continue therapy in the hope that this represents pseudoprogression risk decompensation to the point of being unable to receive salvage chemotherapy when disease progression is confirmed. Ultimately, decisions regarding therapy must also take into account other factors such as changes in performance status, symptoms, therapeutic alternatives, and pace of tumor growth.

There is no consensus guideline on the timing of radiologic assessment of immune checkpoint inhibitor response. However, guidance for clinical

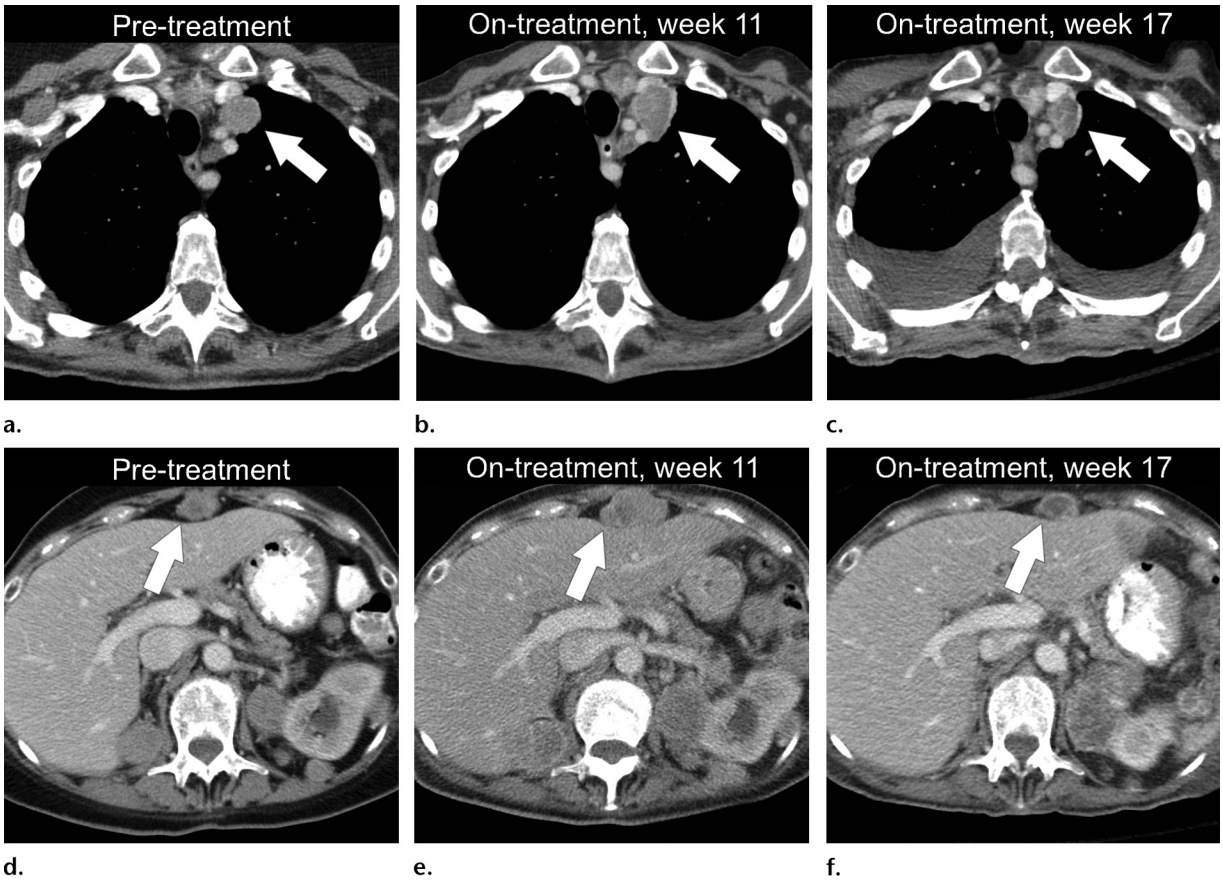


Figure 4. Pseudoprogression of melanoma in a 75-year-old woman after initiation of ipilimumab therapy. Axial contrast-enhanced computed tomographic (CT) images show a preexisting mediastinal lymph node (arrow in **a**–**c**) and peritoneal nodule (arrow in **d**–**f**) that demonstrated initial growth (**b, e**) followed by a decrease in size (**c, f**).

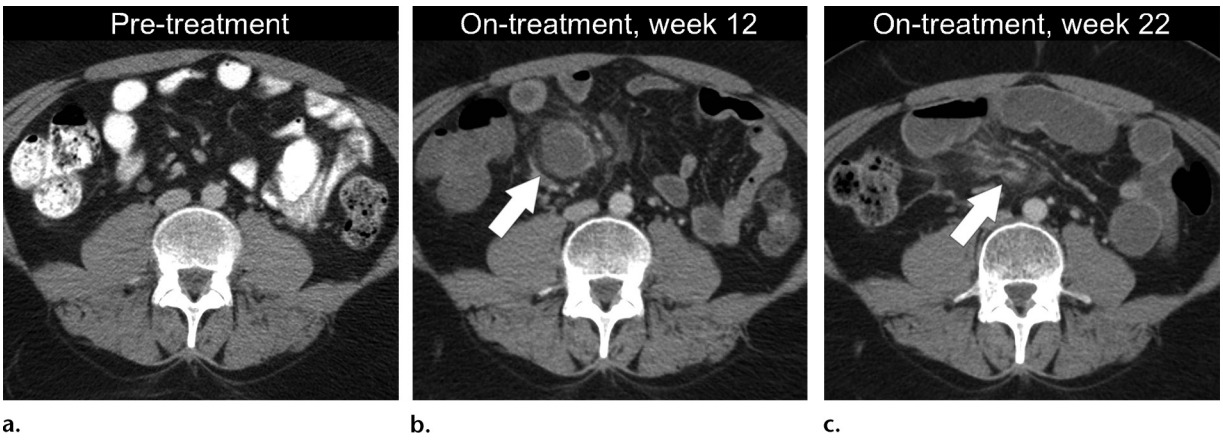


Figure 5. Pseudoprogression of melanoma in a 31-year-old man after initiation of ipilimumab therapy. **(a)** Axial contrast-enhanced baseline CT image was obtained before treatment. **(b, c)** Axial contrast-enhanced CT images show a new mesenteric nodule (arrow) that appeared after the start of therapy **(b)** and decreased in size at follow-up CT **(c)**.

practice can be obtained from drug trials. Initial ipilimumab trials for melanoma showed that new or enlarged lesions were usually evident by week 12 after treatment initiation, with a trend toward treatment response after 4 more weeks (4,23). In a retrospective review of phase 1 and 2 clinical trials at our institution, the mean time from tumor baseline to progression was 10.6 weeks and from progression to response was 13.4 weeks by RECIST 1.1 tumor measurement metrics (24). Using irRC tumor measurement parameters, these times were 12.6 and 14.1 weeks, respectively. Examples of time points used for assessment of treatment response in clinical trials and at our own institution are summarized in Table 3. The 2010 phase 3 trial of ipilimumab in treatment of advanced melanoma

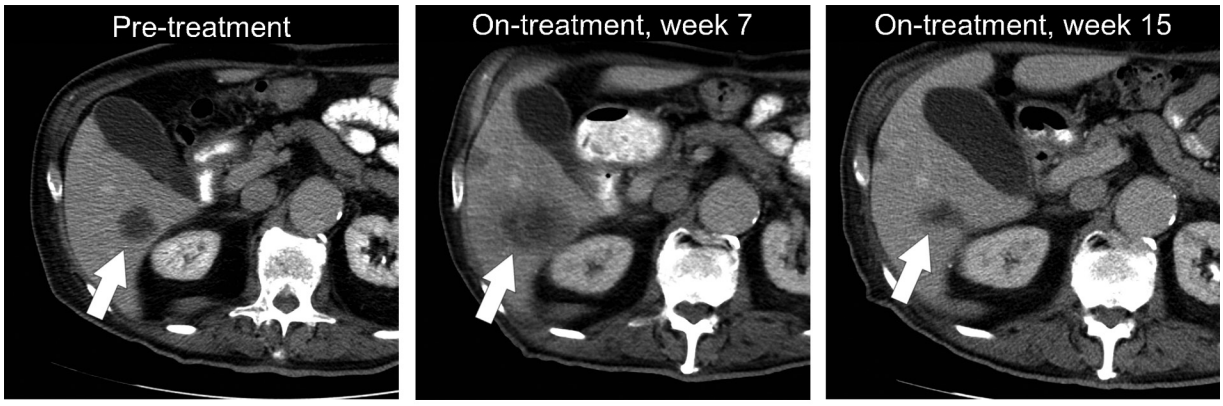


Figure 6. Pseudoprogression of metastatic squamous cell lung cancer in a 74-year-old man after initiation of nivolumab (anti–PD-1 monoclonal antibody) therapy. Axial contrast-enhanced abdominal CT images show a hepatic metastasis (arrow) that was apparent before treatment **(a)** and demonstrated initial growth **(b)** followed by a decrease in size **(c)**.

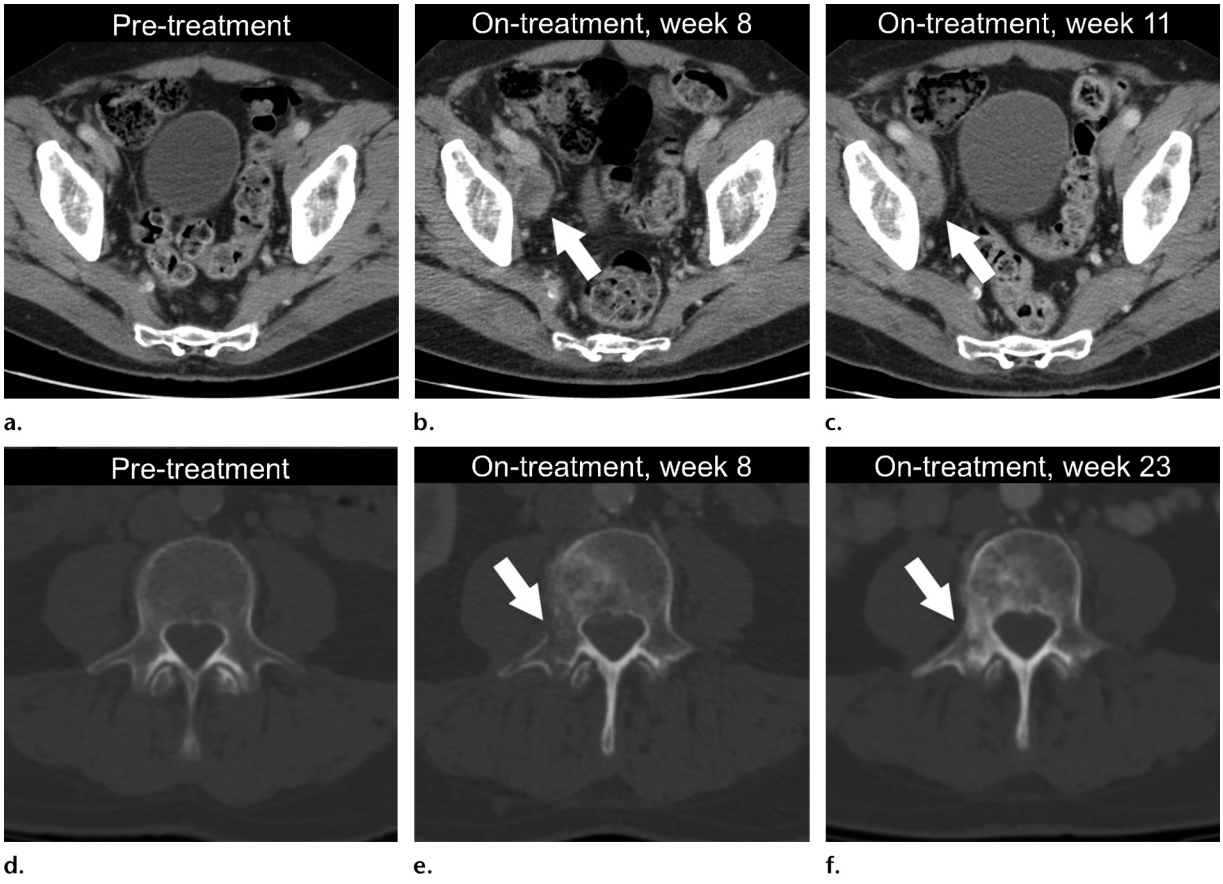


Figure 7. Pseudoprogression of metastatic melanoma in a 74-year-old man after initiation of pembrolizumab (anti–PD-1 monoclonal antibody) therapy. Axial contrast-enhanced CT images show a new right external iliac lymph node (arrow in **b** and **c**) and a new lytic lesion (arrow in **e** and **f**) with pathologic fracture in the right L4 vertebral pedicle and transverse process, findings that appeared after the start of therapy. The lymph node decreased in size **(c)** and the lytic lesion became sclerotic **(f)** at follow-up CT.

performed initial assessments at weeks 12, 16, and 24, then every 3 months thereafter (12). A more recent study of pembrolizumab versus ipilimumab in advanced melanoma performed initial imaging at 12 weeks and follow-up imaging every 6 weeks (27). In a trial of nivolumab for renal cell carcinoma, imaging was performed every 8 weeks for the 1st year and every 12 weeks thereafter (16). In trials of nivolumab in previously treated NSCLC, initial imaging was at week 9, then every 6 weeks thereafter (13,14); for pembrolizumab in untreated NSCLC, patients were assessed every 9 weeks (15). In our practice we perform initial imaging for NSCLC at week 6 and then every 6–12

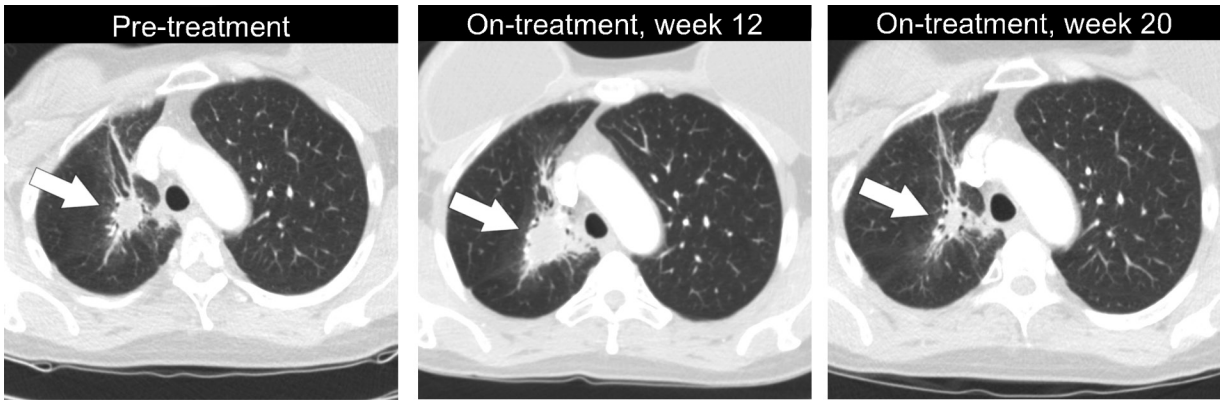


Figure 8. Pseudoprogression of metastatic invasive ductal carcinoma of the breast in a 45-year-old woman after initiation of MPDL2380A (an anti–PD-L1 monoclonal antibody) therapy. Axial contrast-enhanced chest CT images show a lung metastasis (arrow) that was present at baseline **(a)** and demonstrated initial growth **(b)** followed by a decrease in size **(c)**.

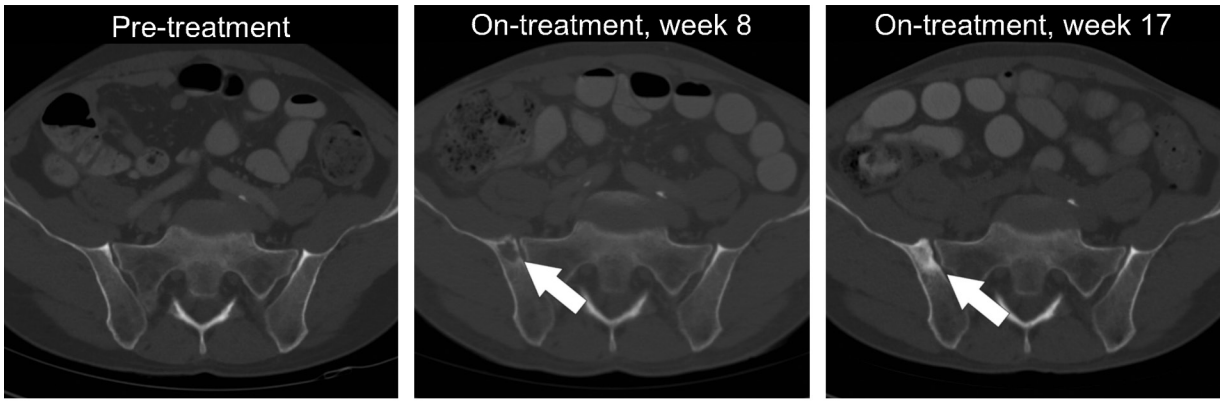


Figure 9. Pseudoprogression of metastatic lung adenocarcinoma in a 56-year-old man after initiation of MPDL2380A therapy. Axial contrast-enhanced CT images show a new lytic bone lesion (arrow) that appeared after the start of therapy **(b)** and then became sclerotic at subsequent CT **(c)**.

weeks thereafter. For patients with melanoma, initial imaging is typically performed 8–12 weeks following initiation of therapy, then every 12 weeks in patients with initially stable or responding disease. These time points are designed to enable early assessment of treatment response and differentiation of progression from pseudoprogression and to minimize the frequency of imaging sessions.

Immune-related Adverse Events

Immune checkpoint inhibitors are associated with a unique spectrum of adverse reactions compared with cytotoxic chemotherapy. These irAEs are attributed to autoimmunity caused by hyperactivated T cells, are common, and can involve almost every organ system (28). The most common irAEs overall are dermatologic, including vitiligo in patients with melanoma, rash, and erythema. Numerous other adverse events have been reported, including uveitis, thyroid dysfunction, adrenal insufficiency, and hepatitis (28). Although the irAEs caused by anti–CTLA-4 and anti–PD-1/PD-L1 drugs are similar, the incidence of adverse events differs between the two classes. A meta-analysis of 23 clinical trials, predominantly phase 1 and 2, between 2005 and 2015 found a higher incidence of irAEs with anti–CTLA-4 (54%) than with anti–PD-1 (26%) and anti–PD-L1 (13.7%) agents (29). A phase 3 trial of ipilimumab versus pembrolizumab in advanced melanoma also showed a lower rate of severe-to–life-threatening adverse events with pembrolizumab, the PD-1 inhibitor (27). A number of irAEs such as autoimmune pancreatitis and thyroiditis have associated imaging findings, described in a recent review (30). The following discussion is limited to the most common irAEs for which imaging has an important role for evaluation and management. These are colitis (7%–17% incidence) (29,31) and hypophysitis (4%–11%) (32,33) with the anti–CTLA-4 monoclonal antibody ipilimumab, and pneumonitis (3%–6%) with anti–PD-1 agents (13–15,34).

Table 2: Comparison of Progressive Disease Designation by Conventional Criteria (RECIST 1.1) with irRC

Treatment Response	RECIST 1.1	irRC
Progressive disease	≥20% increase in lesion sum* (absolute size increase ≥5 mm) or 1+ new lesions at any single observation	≥25% increase in tumor burden† versus nadir in two consecutive observations ≥4 weeks apart
New measurable‡ lesions	Always represent progressive disease	Incorporated into tumor burden
New nonmeasurable lesions	Considered equivocal; followed at future examinations to clarify whether it is truly new disease	Does not define progression but precludes complete response

Note.—Adapted, with permission, from reference 25.
*Sum of lesion diameters, which equals the sum of the longest diameter in the plane of measurement for non-nodal target lesions and short-axis diameter for target nodal lesions.
†Tumor burden is based on the sum of the products of the two largest perpendicular diameters of all index lesions.
‡Measurable lesion for RECIST 1.1 is ≥10 mm at CT and for irRC is ≥10 × 10 mm at CT. Lesions smaller than these are considered nonmeasurable.

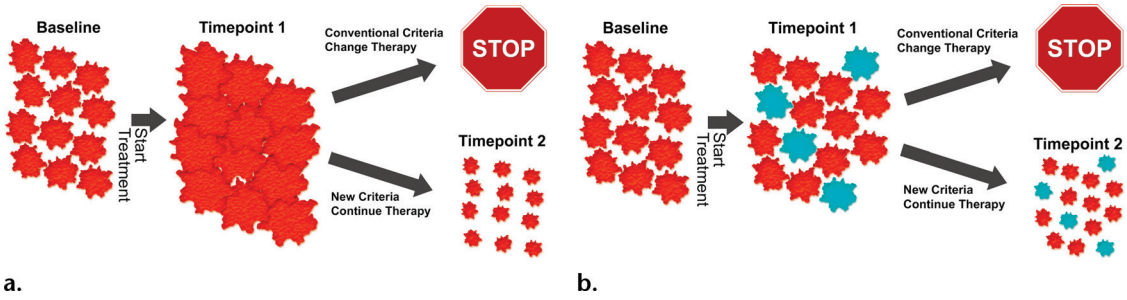


Figure 10. Schematics of tumor pseudoprogression due to enlargement of preexisting lesions **(a)** or appearance of new lesions **(b)** followed by a decrease in tumor burden while continuing treatment. In either of these scenarios, evaluation of tumor response by conventional criteria would lead to an inappropriately premature cessation of therapy. The irRC were developed to help prevent this error. Time point intervals vary depending on the drug, cancer type, and treatment regimen. In the majority of cases, baseline to time point 1 is 6–12 weeks, and time point 1 to time point 2 is 4–12 weeks. Blue = new lesion, red = index lesion.

Figure 11. Flowchart of clinical decision making on the basis of RECIST 1.1 versus irRC evaluation of tumor response to immune checkpoint inhibitor treatment.

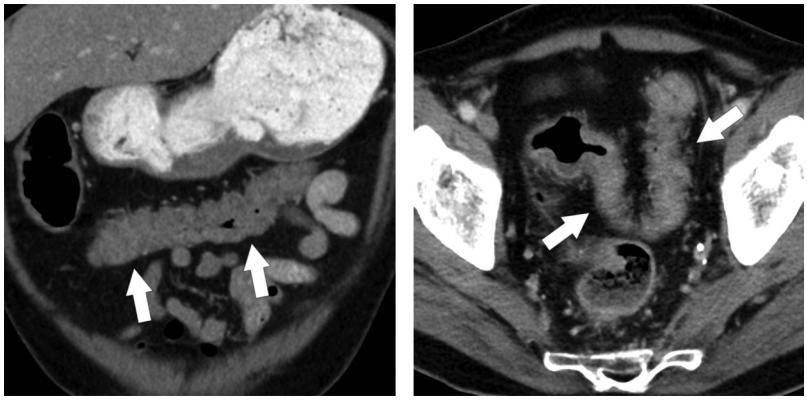
Gastrointestinal irAEs such as diarrhea and colitis typically occur 6–7 weeks after initiation of ipilimumab treatment (32). An analysis of 162 patients with melanoma treated with ipilimumab found radiographically evident colitis in 28 (19%), with a median time of onset of 1.9 months (31). Colonic involvement was diffuse in 26 of 28 cases and showed a segmental pattern in the remainder. Characteristic CT findings include mesenteric hyperemia, bowel wall thickening, increased mucosal enhancement, and a fluid-filled colon (31). Rarely, colitis can lead to perforation and death (35). A case of ipilimumab-associated colitis is show in Figure 12. At histologic analysis, there can be a neutrophilic infiltrate, a lymphocytic infiltrate, or a mix of both (32).

A longitudinal analysis of ipilimumab-induced hypophysitis in patients with metastatic

Table 3: Examples of Imaging Time Points Used for Assessment of Response to Immune Checkpoint Inhibitor Treatment

Cancer Type	Drug	Imaging Time Points	References
Melanoma	Ipilimumab	Weeks 12, 16, 24, then every 3 months	12
	Ipilimumab, pembrolizumab	Week 12, then every 6 weeks	27
	Not specified	Weeks 8–12, then every 12 weeks*	…
NSCLC	Nivolumab	Week 9, then every 6 weeks	13, 14
	Pembrolizumab	Every 9 weeks	15
	Not specified	Week 6, then every 6–12 weeks*	…
Renal cell carcinoma	Nivolumab	Every 8 weeks for 1 year, then every 12 weeks	16

*These are the typical imaging time points used at our institution.

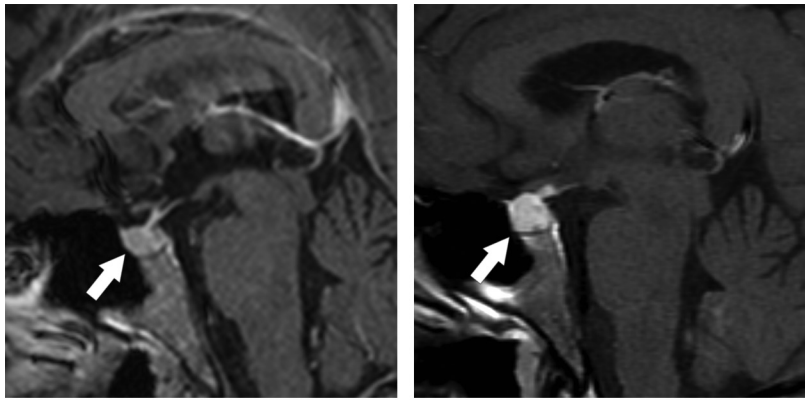


a. b.

Figure 12. Colitis secondary to immune checkpoint inhibitor therapy in a 58-year-old man who presented with diarrhea 9 weeks after initiation of ipilimumab therapy for melanoma. Coronal **(a)** and axial **(b)** contrast-enhanced abdominal and pelvic CT images demonstrate wall thickening of the transverse colon (arrows in **a**) and sigmoid colon (arrows in **b**). The colitis resolved following cessation of ipilimumab therapy and with corticosteroid treatment.

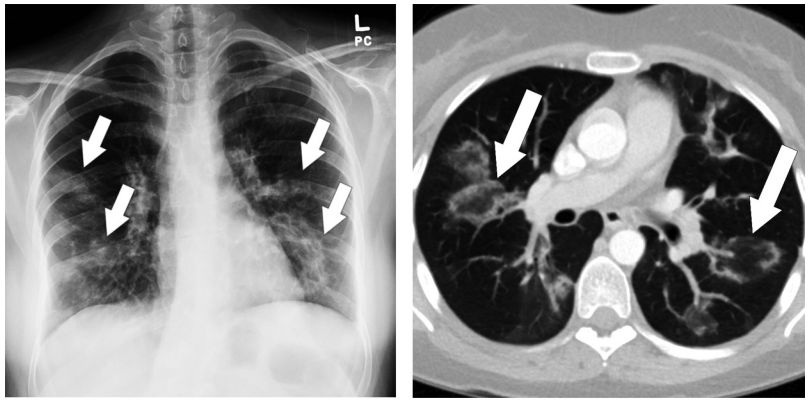
melanoma treated with ipilimumab performed at our institution showed a median time of 8.4 weeks from initiation of immunotherapy to diagnosis (33). This study cohort comprised 154 adults, with hypophysitis diagnosed in 17. These patients most commonly presented with headache and fatigue. All developed anterior hypopituitarism, with the majority demonstrating multiple hormonal deficiencies. In most, hypopituitarism was persistent at long-term follow-up. At magnetic resonance (MR) imaging, all demonstrated mild-to-moderate diffuse pituitary enlargement without compression of the optic chiasm. Thickening of the pituitary stalk was present in 10 of 17 cases. Postcontrast images demonstrated both homogeneous and heterogenous pituitary enhancement. These findings correspond to earlier case reports of ipilimumab-induced hypophysitis (36). In eight of these patients, pituitary enlargement could be retrospectively seen at MR imaging several weeks before the clinical diagnosis. All patients with follow-up MR imaging performed within 40 days of diagnosis showed reversal of pituitary enlargement following initiation of glucocorticoid treatment. An example of ipilimumab-induced hypophysitis is provided in Figure 13.

Whereas colitis and hypophysitis are more common with anti–CTLA-4 therapy, pneumonitis is predominantly seen with PD-1 inhibitors (37). This irAE is of particular clinical concern as it can become severe or life threatening, and it was a cause of treatment-related deaths in early studies (38,39). In phase 3 clinical trials, pneumonitis was reported in 2%–6% of patients treated with either nivolumab or pembrolizumab for advanced melanoma, renal cell carcinoma, or NSCLC; the incidence of severe or life-threatening pneumonitis was 1%–3% in these studies (13–16,27,40). Interim analysis from an ongoing phase 2 study of nivolumab in classical Hodgkin lymphoma reported a 3% incidence of pneumonitis (18). A meta-analysis found a higher rate of pneumonitis in NSCLC and renal cell carcinoma versus in melanoma (odds ratio, 1.43 and 1.59, respectively) (41). However, analysis of a series of 915 patients who received anti–PD-1/PD-L1 agents demonstrated a similar incidence of pneumonitis between melanoma and NSCLC (5% vs 4%) (42). In that case series, which included numerous other cancer types, including renal cell carcinoma, pancreatic carcinoma, and hematologic malignancy, median time to onset of pneumonitis was 2.8 months, with a range of 9 days to



a. b.

Figure 13. Hypophysitis secondary to immune checkpoint inhibitor therapy in a 47-year-old woman who presented with headache and eye pressure 2 weeks after initiation of ipilimumab therapy for melanoma. Sagittal postcontrast T1-weighted MR images of the pituitary gland (arrow) demonstrate a normal appearance before initiation of ipilimumab therapy **(a)** and diffuse enlargement at the time of presentation **(b)**.



a. b.

Figure 14. Pneumonitis secondary to immune checkpoint inhibitor therapy in a 29-year-old woman who presented 9 weeks after initiation of nivolumab therapy for Hodgkin lymphoma and reported several weeks of cough. **(a)** Frontal chest radiograph shows bilateral patchy opacities (arrows). **(b)** Axial contrast-enhanced chest CT image shows multifocal central ground-glass opacities (arrows) with peripheral consolidation. Note the reversed halo sign. The findings are consistent with a cryptogenic organizing pneumonia pattern. The patient's symptoms and CT findings resolved after cessation of nivolumab therapy and treatment with corticosteroids.

19.2 months. Median time from start of therapy to onset of pneumonitis in phase 3 NSCLC trials was 3.8–7.8 months, with a similarly wide range. There are case reports that patients with immune checkpoint inhibitor–induced pneumonitis can undergo a recurrent "pneumonitis flare" phenomenon months after discontinuation of immunotherapy and following steroid treatment of the irAEs (43). Interestingly, although anti–PD-1 and anti–PD-L1 agents affect the same signaling pathway and produce a similar spectrum of irAEs, early data from ongoing clinical trials in patients with NSCLC suggest that pneumonitis may be less frequently observed with the anti–PD-L1 agents atezolizumab and durvalumab (34). A recently published study of 20 patients with nivolumab-induced pneumonitis identified four CT patterns: cryptogenic organizing pneumonia (COP) in 13 (65%) patients, nonspecific interstitial pneumonia in three (15%), hypersensitivity pneumonitis in two (10%), and acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) in two (10%) (43). An example of nivolumab-induced pneumonitis in a COP pattern is shown in Figure 14. At CT, the COP pattern is associated with patchy ground-glass opacities and consolidation in a subpleural, peribronchial, or band pattern, sometimes accompanied by the reversed halo sign, as seen in Figure 14 (44,45). The nonspecific interstitial pneumonia pattern at CT consists of bilateral ground-glass opacities with reticular

opacities, traction bronchiectasis or bronchiolectasis, and minimal or absent honeycombing in a basal distribution with subpleural sparing (44,45). The typical findings of hypersensitivity pneumonitis at CT are centrilobular nodules and mosaic attenuation due to air trapping with an upper lobe–predominant distribution (45). The AIP/ARDS pattern at CT consists of patchy bilateral ground-glass opacities with consolidation in the dependent lung (45).

Most irAEs are usually mild or moderate, and most are readily reversed by stopping the agent and initiating corticosteroid treatment (28,34,46). Notable exceptions to this are endocrinopathies such as hypophysitis, thyroid dysfunction, and adrenal insufficiency, which are typically irreversible (47). More severe and life-threatening events require hospitalization and possible intensive care unit admission. In these cases, treatment may require prophylactic antibiotics, high-dose intravenous corticosteroids with a long steroid taper, and additional immunosuppression therapy (eg, cyclophosphamide, infliximab, or mycophenolate mofetil) (46). To help expedite appropriate treatment and prevent milder manifestations from becoming potentially life threatening, the radiologist should be aware of and communicate the possibility of irAEs to nononcology members of the clinical team who may not be familiar with the adverse effects of immune checkpoint inhibitors.

Conclusion

Immune checkpoint inhibitors represent a new class of agents that have demonstrated dramatic successes in the treatment of advanced cancer. They are widely used for a number of tumor types, and the indications for clinical use are rapidly expanding. To contribute to the current care of patients with cancer, radiologists must be knowledgeable about the atypical tumor response pattern and common adverse events seen at imaging of patients undergoing treatment with this novel class of drugs.

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