Current Problems in Diagnostic Radiology 48 (2019) 142–147

Current Problems in Diagnostic Radiology

journal homepage: www.cpdrjournal.com

Thoracic Imaging of Non-Small Cell Lung Cancer Treated With Anti-programmed Death Receptor-1 Therapy

Mark Hammer, MD[a,b], Stephen Bagley, MD[c], Charu Aggarwal, MD, MPH[c], Joshua Bauml, MD[c], Arun C. Nachiappan, MD[b], Charles B. Simone II, MD[d], Corey Langer, MD[c], Sharyn I. Katz, MD, MTR[b,*]

[a] Department of Radiology, Brigham and Women's Hospital, Boston, MA
[b] Department of Radiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
[c] Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
[d] Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD

Purpose: Treatment with anti-programmed death receptor-1 (PD-1) therapeutics can lead to unconventional responses and side effect profiles due to their potentiating effects on the immune system. Here we evaluate the radiologic manifestations of anti-PD-1 therapy in the chest in patients with non-small cell lung cancer (NSCLC) receiving anti-PD-1 therapy.
Materials and Methods: A retrospective review of real-world clinical practice was conducted of all the patients with NSCLC receiving anti-PD-1 therapy at our institution between 2013 and 2016. All patients without adequate clinical or radiologic follow-up data in the electronic medical records were excluded. Imaging examinations for all patients deemed by their thoracic oncologists to have radiologic pseudoprogression or therapy-associated pneumonitis were reviewed by experienced thoracic radiologists.
Results: A total of 166 patients with NSCLC had available clinical and imaging data for retrospective review. Of these patients, 4 (2%) were considered to have radiologic pseudoprogression, 3 of which manifested as increased tumor size and 1 of which manifested with new lesions. A total of 5 patients (3%) were clinically deemed to have pneumonitis attributable to anti-PD-1 therapy, 4 of which had radiologic manifestations on computed tomography.
Conclusion: Radiologic pseudoprogression and drug-induced pneumonitis are uncommon but important manifestations of anti-PD-1 therapy on thoracic imaging.

Introduction

Anti-programmed-death-receptor-1 (PD-1) therapeutics are immune checkpoint inhibitors, a recently developed class of anticancer therapeutics that have been designed to disrupt certain immune regulatory interactions with an aim to boost immune antitumor activity. These therapies have generated great interest in the oncologic community since a proportion of patients with advanced malignancies have shown remarkably durable responses in a range of malignancies including non-small cell lung cancer (NSCLC).[1-12] However, immune checkpoint inhibitors can present a significant challenge to the radiologist owing to their mode of action. When successful, these drugs incite inflammation directed toward the tumor, resulting in tumor cell death. This differs from conventional chemotherapeutic drugs, which act directly on tumor cells to impede growth.

When PD-1, expressed on the host immune cell, is allowed to bind to programmed-death ligand 1 (PD-L1), often overexpressed on tumors, the host immune functionality toward the antigenicity of the tumor is dampened.[13] Thus the PD-1 or PD-L1 checkpoint protects the tumor from the host immune surveillance. Under normal conditions, this immune checkpoint interaction serves to maintain homeostasis and prevent autoimmunity by down-modulating immune cell activation in response to antigen presentation.[14] The anti-PD-1 or anti-PD-L1 therapeutics represent humanized antibodies tailored to disrupt the PD-1 or PD-L1 checkpoint will the goal of enabling the host immune system to successfully destroy tumor. Currently, Food and Drug Administration (FDA)-approved anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors include nivolumab (anti-PD-1), pembrolizumab (anti-PD-1), and atezolizumab (anti-PD-L1).

The inflammatory action characteristic of immune checkpoint inhibitors can result in unconventional imaging responses to therapy. For example, initial tumor enlargement with subsequent tumor regression, termed pseudoprogression, can be misinterpreted as actual progression on reimaging.[15-17] Immune checkpoint inhibitors can also incite autoimmune-mediated inflammation in normal tissues that can complicate image

* Reprint requests: Sharyn Katz, MD, MTR, Department of Radiology, Hospital of the University of Pennsylvania, 1 Silverstein Building, 3400 Spruce St, Philadelphia, PA 19104.
E-mail address: sharyn.katz@uphs.upenn.edu (S.I. Katz).

https://doi.org/10.1067/j.cpradiol.2018.01.005
0363-0188/

TABLE
Patient characteristics of patients treated with anti-PD1 agents for non–small cell lung cancer (NSCLC)

	n = 166
Age, y (median, range)	66.5 (34-88)
Histology	
Adenocarcinoma	122 (73%)
Squamous cell carcinoma	36 (22%)
Other NSCLC	8 (5%)
Immunotherapy agent	
Nivolumab	132 (80%)
Pembrolizumab	34[a] (20%)

[a] One patient treated with pembrolizumab and ipilimumab concurrently.

interpretation, including pneumonitis,[18] colitis, and sarcoid-like reactions. Immune-related adverse events that are radiologically evident have been reported to manifest in up to approximately one-third of patients on immune checkpoint inhibitor therapy.[19]

The purpose of this study was to estimate incidence and appearance of radiologic pseudoprogression and anti-PD-1 therapy-associated pneumonitis which can complicate interpretation of thoracic imaging in patients with NSCLC receiving anti-PD-1 therapy for routine clinical management and to characterize the nature of these changes.

Materials and Methods

Patient Chart Review

After obtaining institutional review board approval for this study, all adult patients with a diagnosis of NSCLC that received anti-PD-1 therapy at our institution between June 2013 and April 2016 were identified. The electronic medical records of these patients were then reviewed to identify those patients diagnosed with pneumonitis attributed to anti-PD-1 therapy. The computed tomography (CT) imaging of patients with clinical evidence of pneumonitis attributed to anti-PD-1 therapy were reviewed. Clinical symptoms of pneumonitis, including the development of shortness of breath, hypoxia, or cough, were considered to be attributable to anti-PD-1 therapy when symptoms occurred following the start of anti-PD-1 therapy, there was no clinical evidence of infection and symptoms improved on steroids or termination of anti-PD-1 therapy. The real-world, clinical assessment of disease response at first reimaging, as determined by their thoracic oncologist, was also recorded for all patients. Patients were considered to have radiologic pseudoprogression when tumors were increased in size, or new lesions were detected, at first reimaging with subsequent decreased tumor burden at second reimaging on sustained anti-PD-1 therapy. No clinical trial tumor response criteria were used to quantify these changes since this study sought to assess real-world clinical management of NSCLC in the setting of immune checkpoint inhibition. Any patients that did not have adequate clinical or imaging data were excluded from the study.

Imaging Review

The CT examinations of patients identified as having anti-PD-1 therapy induced pneumonitis were reviewed by experienced thoracic radiologists with a combined total of over 15 years of experience. The timing, with respect to the start of therapy, and appearance of changes on CT attributed to anti-PD-1 therapy induced pneumonitis was recorded. The CT examinations of patients with radiologic pseudoprogression were also reviewed and the pattern of pseudoprogression noted (development of new lesions or tumor enlargement).

Statistical Analysis

Excel Toolpak (ver 14.6.7) was used for statistical analysis of data, including calculating means and Student's t-tests.

Results

Patient Population

A total of 226 consecutive adult patients with NSCLC were treated with an anti-PD-1 therapy agent, either nivolumab or pembrolizumab, during the study period. Of these patients, 166 (Table) had adequate clinical and imaging data for review. Most patients had adenocarcinoma of the lung (73%) and received nivolumab (80%) for anti-PD-1 therapy.

Unconventional Patterns of Therapy Response in Patients With NSCLC on Anti-PD1 Therapy

Tumor responses were considered an unconventional pattern of response, or radiologic pseudoprogression, when tumor size

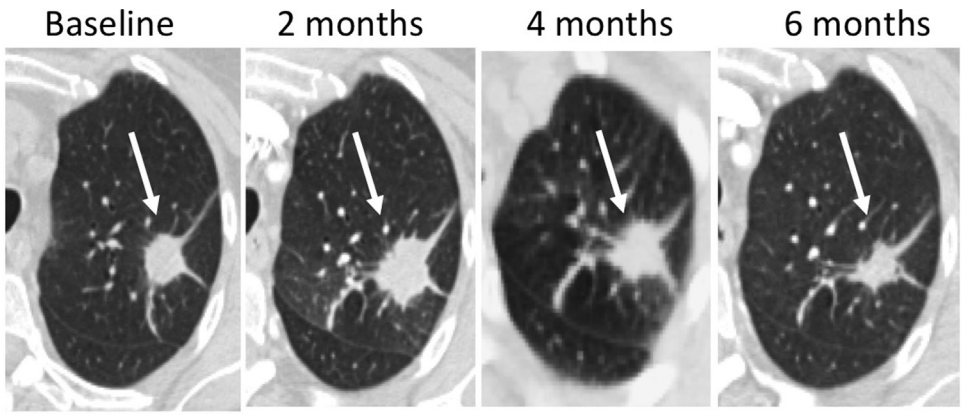

FIG. 1. Radiologic pseudoprogression on CT manifesting as enlargement of the primary tumor while on nivolumab therapy. A 73-year-old female patient with adenocarcinoma of the lung with the primary tumor in the left lung apex started nivolumab as second-line therapy (arrows). Axial CT of the chest was obtained at baseline and 2, 4, and 6 months following the start of nivolumab. At 2 months of therapy, the left apical tumor increased by 26% in largest axial diameter. Reimaging revealed subsequent tumor size decrease to 10% and 16% below baseline at 4 months and 6 months of therapy, respectively.

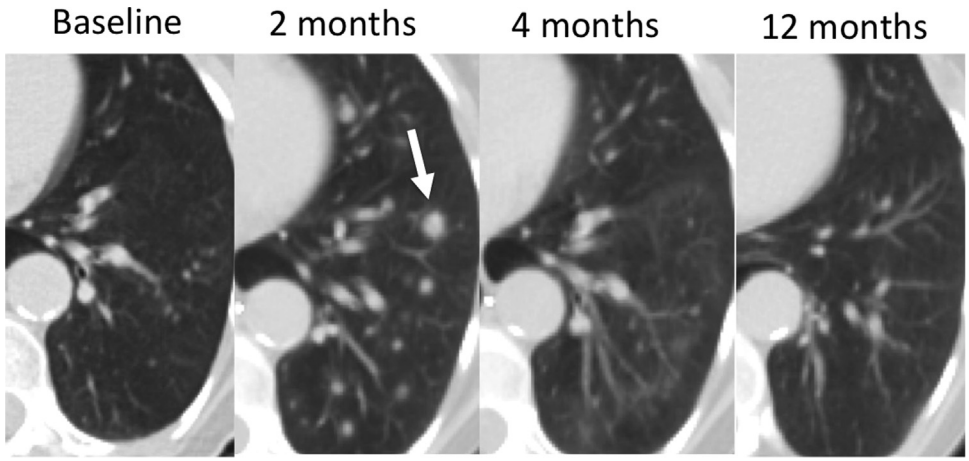

FIG. 2. Radiologic pseudoprogression on CT manifesting as new lesions while on nivolumab therapy. A 68-year-old female with a history of prior right upper lobectomy and radiation therapy for adenocarcinoma of the lung began second-line therapy with nivolumab for metastatic disease, which included pulmonary parenchymal metastasis. Unenhanced CT of the chest was performed at baseline and 2, 4 and 12 months following the start of therapy with nivolumab. CT at 2 months after the initiation of nivolumab revealed new and larger pulmonary nodules (arrows) and was interpreted radiologically as progression. Subsequent CT performed at 4 and 6 months (data not shown) of therapy revealed near resolution of the pulmonary metastases. These findings remained stable at 12 months of therapy. Of note, CT at 4 months reveals faint ground glass opacities favored to represent pneumonitis related to nivolumab therapy.

was initially increased in size or developed new lesions followed by decreased tumor burden on subsequent imaging.[17] Of the 166 patients with NSCLC, the majority demonstrated a conventional pattern of response to therapy with a total 39 patients (23%) considered partial or complete responders at first reimaging, with the remainder (75%) deemed stable or progressive disease. By comparison, a total of 4 patients (2%) demonstrated radiologic pseudoprogression at first reimaging (median = 2 months of therapy, range: 1-3 months), which was followed by improvement in tumor burden on subsequent reimaging at 4-6 months of therapy (mean = 4 months). For 3 of the 4 patients, this unconventional pattern of tumor response to anti-PD-1 therapy manifested as enlargement of the primary tumor (Fig 1). One of the 4 patients initially manifested numerous new and increased in size subcentimeter solid appearing metastatic pulmonary nodules at reimaging at 2 months of anti-PD-1 therapy followed by regression of these nodules at 4 months of therapy (Fig 2).

In addition to radiologic pseudoprogression, one patient manifested a sarcoid-like like drug reaction to anti-PD-1 therapy with development of new mediastinal and hilar lymphadenopathy and perilymphatic nodularity (Fig 3), which manifested at reimaging at 2 months of therapy and resolved by 12 months of therapy.

Patterns of Anti-PD-1 Therapy-Induced Pneumonitis in Patients With NSCLC

Of the 166 patients with NSCLC reviewed in this study, 5 patients (3%) developed clinically significant pneumonitis that

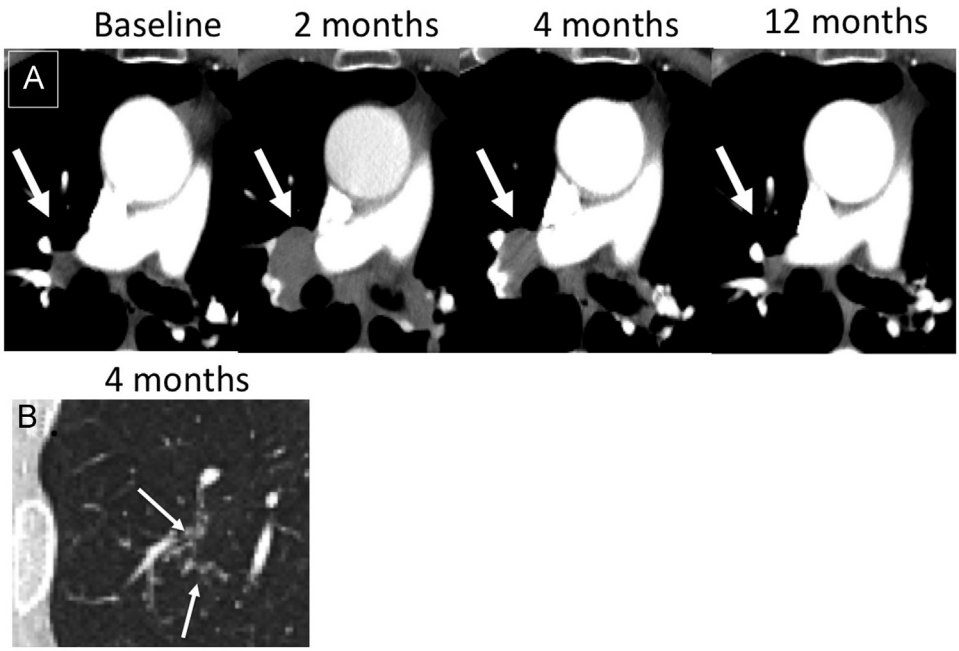

FIG. 3. Sarcoid-like drug reaction in a NSCLC patient on pembrolizumab. A 73-year-old male with squamous cell carcinoma status post lobectomy followed by resected oligometastatic disease developed new bilateral hilar lymphadenopathy (thick arrows) at reimaging at 2 months of pembrolizumab therapy. At 4 months of therapy, this adenopathy increased in size and was accompanied by new perilymphatic nodularity (thin arrows), which was suspicious for lymphangitic carcinomatosis. Therapy was continued since the patient was doing well clinically and by 7 months of therapy (data not shown), both the adenopathy and perilymphatic nodules had begun to decrease and were completely resolved by 1 year of therapy with pembrolizumab.

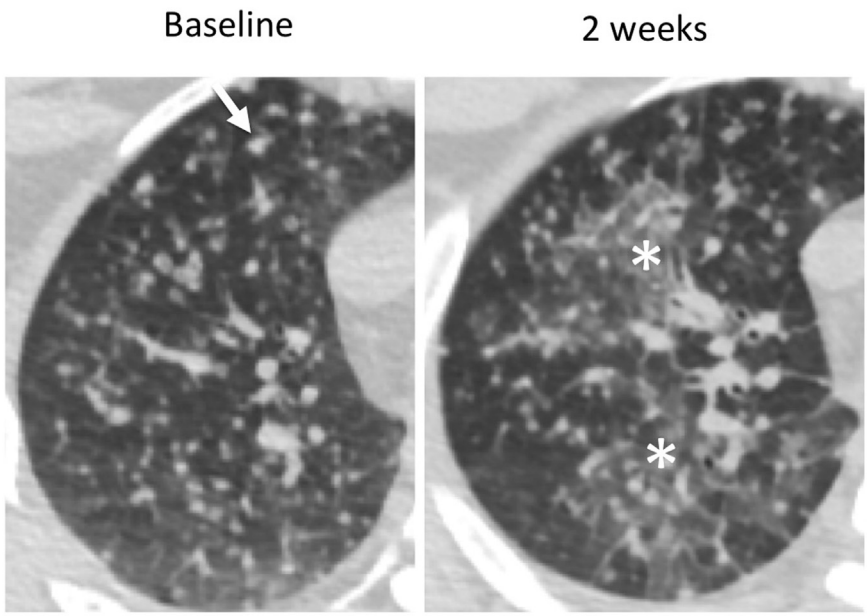

FIG. 4. Pneumonitis manifesting as ground glass opacities at 2 weeks of therapy with nivolumab. 40 year-old male patient with poorly differentiated metastatic lung cancer was started on second-line therapy with nivolumab with multiple metastatic pulmonary nodules (arrow) at baseline. At 2 weeks of therapy, the patient developed dyspnea and CT of the chest revealed bilateral patchy peribronchial ground glass opacities. Symptoms were rapidly improved on high-dose steroids, and nivolumab therapy was discontinued.

was attributed to anti-PD-1 therapy. A total of 4 of the 5 patients had changes seen on CT obtained at the time that patients were symptomatic, occurring at 2-11 weeks of therapy (mean = 8 weeks). In 2 patients, pneumonitis manifested as patchy ground glass opacities which occurred in either a peribronchial distribution (Fig 4) or in a peripheral, subpleural distribution (Fig 5). In 2 patients, anti-PD-1 associated pneumonitis manifested as overly robust consolidation in the region of radiation therapy in patients receiving concurrent or recent prior radiation (Fig 6) therapy.

Discussion

Immune checkpoint inhibitors present unique challenges to imaging since they act on the tumor by potentiating the immune system rather than by directly inhibiting tumor growth through cytotoxic effects, typical of conventional chemotherapeutics. As a result, therapy with these agents may result in unconventional patterns of tumor response and induce inflammation in normal tissues, which may affect imaging. Here, we sought to determine

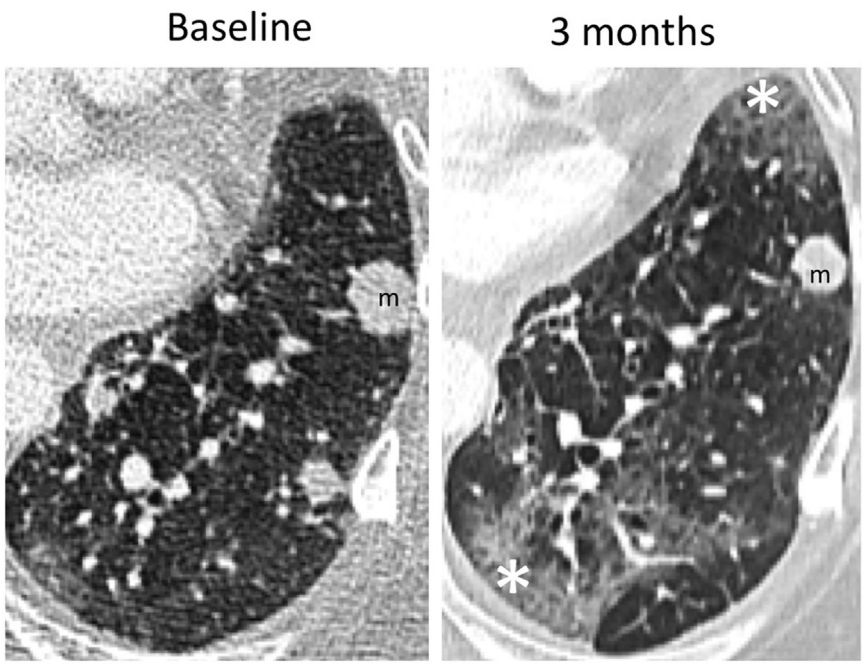

FIG. 5. Pneumonitis manifesting as ground glass opacities at 2 months following the start of nivolumab. A 60-year-old female with prior history of left upper lobectomy for adenocarcinoma of the lung started nivolumab for second-line therapy for metastatic disease to the lungs. At 2 months of therapy, the patient became short of breath and hypoxic, requiring hospitalization. The symptoms were attributed to drug toxicity and improved on high-dose steroids. CT of the chest was performed at baseline (A) and at 3 months of nivolumab therapy (B) and revealed development of bilateral pulmonary ground glass opacities (star) in a peripheral distribution with decrease in the size of the pulmonary metastasis (m). Nivolumab was subsequently discontinued due to pneumonitis, and the patient developed evidence of new metastatic disease (not shown).

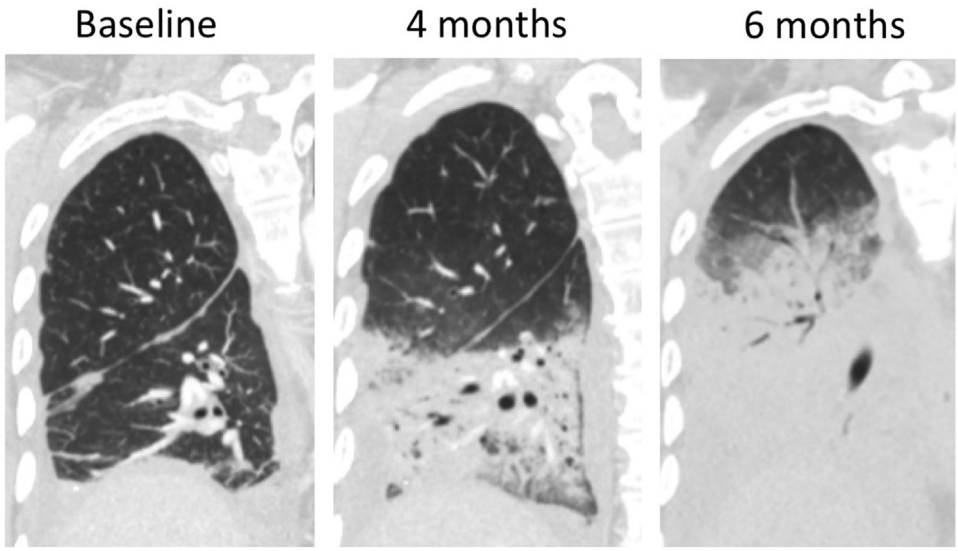

FIG. 6. Severe pneumonitis following concurrent radiation therapy while on nivolumab therapy. A 64-year-old female with adenocarcinoma of the lung metastatic to the right pleura, started on nivolumab as second-line therapy with concurrent radiation therapy to the lower right chest for palliation of chest wall pain. At 3 months of therapy with nivolumab, the patient developed a worsening cough and became increasingly short of breath which improved but was not well-controlled by high-dose steroids. CT chest was obtained at baseline (A) and at 4 months (B) and 6 months (C) of therapy with nivolumab. At 4 months, the CT demonstrated new dense consolidation in the distribution of the radiation portal in keeping with radiation pneumonitis which increased by 6 months of therapy. Nivolumab was finally discontinued at 6 months of therapy due to refractory symptoms of pneumonitis.

the appearance and incidence of these potentially confounding radiologic manifestations of anti-PD-1 therapy on thoracic imaging follow-up of patients with NSCLC.

Radiologic pseudoprogression is characterized by initial tumor enlargement or development of new lesions followed by eventual tumor regression on sustained therapy. In our study of real-world clinical practice, radiologic pseudoprogression occurred in 2% of patients with NSCLC receiving immune checkpoint inhibitors and primarily manifested as an increase in the size of the primary malignancy rather than the development of new lesions. Our observed rate of 2% radiologic pseudoprogression is in the range of the reported rate of 0%-6% for pseudoprogression in anti-PD-1 therapy for NSCLC in clinical trials.[1,12,16,20,21] Although uncommon, radiologic pseudoprogression can be a significant confounder to radiologic interpretation, typically manifesting at first reimaging at 2-3 months of therapy. In this study, all patients with radiologic pseudoprogression revealed subsequent decreased tumor burden by second reimaging at 4-6 months of therapy.

To more accurately quantify treatment response for patients receiving immune checkpoint inhibitors on clinical trials, several new immune tumor response criteria have been proposed including the immune-related response criteria,[15,17] unidimensional immune-related response criteria[22] and iRECIST.[23] For the purpose of this study, our goal was to examine the incidence of anti-PD-1 therapy-associated radiologic pseudoprogression and pneumonitis in NSCLC in a real-world clinical setting. As such we did not measure progression or response using clinical trial response criteria but rather by assessment by the thoracic oncologist. In future studies, we plan to examine the performance of the immune response criteria in the setting of suspected radiologic progression since there is evidence to suggest that these immune response criteria may have an advantage in more accurately classifying progressive disease in the setting of immune checkpoint inhibition.[21]

In our experience, radiologically evident anti-PD-1 therapy-associated pneumonitis was observed in 3% of patients with NSCLC. These rates are similar to the reported literature where the incidence of anti-PD-1 associated pneumonitis was reported to be 2%-7%,[4,12,24-26] which typically presents with dyspnea and cough often accompanied by fever and chest pain. In our experience, anti-PD-1 therapy-associated pneumonitis manifested as either patchy ground glass opacities or as an overly robust pneumonitis in response to concurrent or recent prior radiation therapy. These results are in keeping with the findings of a study of 20 patients with nivolumab-induced pneumonitis by Nishino et al[18,27] who described patterns of organizing pneumonia and non-specific interstitial pneumonia (NSIP) in these patients. In addition, there are a number of case reports and small case series similarly reporting anti-PD-1 therapy-associated pneumonitis manifesting as ground glass,[28-30] sometimes in a peripheral distribution suggestive of organizing pneumonia, consolidation-predominant[28,30-34] in keeping with organizing pneumonia, and, less commonly, as a diffuse alveolar damage pattern.[24,31] In this study, all 4 cases of radiologically evident, anti-PD-1 associated, clinically significant pneumonitis occurred within the first 3 months of therapy, which appears consistent with the timing of the appearance of anti-PD-1 therapy-induced pneumonitis reported in the literature,[27,28] although there have been some reports of delayed emergence of pneumonitis associated with these agents.[35]

In conclusion, immune checkpoint inhibitors are emerging as an important new therapy for the treatment of solid malignancies, including NSCLC. As these agents work by stimulating the immune system, rather than producing direct cytotoxic effects, tumors may respond in an unconventional pattern, and imaging interpretation can be complicated by manifestations of immune-related adverse effects. In our experience, these unconventional responses to therapy are uncommon on imaging of anti-PD-1 therapy response in NSCLC, but represent an important potential confounder to therapeutic response assessment and radiologists should be aware of these features when interpreting restaging scans in these patients.

References

1. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–39.
2. Aguiar PN Jr., Santoro IL, Tadokoro H, et al. A pooled analysis of nivolumab for the treatment of advanced non-small-cell lung cancer and the role of PD-L1 as a predictive biomarker. Immunotherapy 2016;8:1011–9.

3. Gettinger S, Rizvi NA, Chow LQ, et al. Nivolumab monotherapy for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2016; 34(25):2980–7. http://dx.doi.org/10.1200/JCO.2016.66.9929. Epub 2016 Jun 27.
4. Rizvi NA, Hellmann MD, Brahmer JR, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2016;34(25):2980–7. http://dx.doi.org/10.1200/JCO.2016.66.9929. Epub 2016 Jun 27.
5. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet 2016;387:1540–50.
6. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123–35.
7. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375 (19):1823–33. Epub 2016 Oct 8.
8. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: A randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497–508.
9. Hui R, Garon EB, Goldman JW, et al. Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non–small-cell lung cancer: A phase 1 trial. Ann Oncol 2017;28:874–81.
10. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): Results of an open-label, phase 1, multicohort study. Lancet Oncol 2017;18:31–41.
11. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017;376:2415–26.
12. Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol 2015;33:2004–12.
13. Pauken KE, Wherry EJ. Overcoming T cell exhaustion in infection and cancer. Trends Immunol 2015;36:265–76.
14. Seliger B, Marincola FM, Ferrone S, et al. The complex role of B7 molecules in tumor immunology. Trends Mol Med 2008;14:550–9.
15. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412–20.
16. Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. J Clin Oncol 2015;33:3541–3.
17. Hoos A, Eggermont AM, Janetzki S, et al. Improved endpoints for cancer immunotherapy trials. J Natl Cancer Inst 2010;102:1388–97.
18. Nishino M, Sholl LM, Hodi FS, et al. Anti-PD-1-related pneumonitis during cancer immunotherapy. N Engl J Med 2015;373:288–90.
19. Tirumani SH, Ramaiya NH, Keraliya A, et al. Radiographic profiling of immune-related adverse events in advanced melanoma patients treated with ipilimumab. Cancer Immunol Res 2015;3:1185–92.
20. Nishino M, Ramaiya NH, Chambers ES, et al. Immune-related response assessment during PD-1 inhibitor therapy in advanced non-small-cell lung cancer patients. J Immunother Cancer 2016;4:84.
21. Kim HK, Heo MH, Lee HS, et al. Comparison of RECIST to immune-related response criteria in patients with non-small-cell lung cancer treated with immune-checkpoint inhibitors. Cancer Chemother Pharmacol 2017;80(3): 591–8. http://dx.doi.org/10.1007/s00280-017-3396-4. Epub 2017 Jul 21.
22. Nishino M, Giobbie-Hurder A, Gargano M, et al. Developing a common language for tumor response to immunotherapy: Immune-related response criteria using unidimensional measurements. Clin Cancer Res 2013;19:3936–43.
23. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–52.
24. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: A systematic review and meta-analysis. JAMA Oncol 2016;2(12):1607–16. http://dx.doi.org/10.1001/jamaoncol.2016.2453. Epub 2016 Jun 27.
25. Costa R, Carneiro BA, Agulnik M, et al. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: A systematic review and meta-analysis of randomized clinical trials. Oncotarget 2017;8:8910–20.
26. Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of pneumonitis with use of PD-1 and PD-L1 inhibitors in non-small-cell lung cancer: A systematic review and meta-analysis of trials. Chest 2017;152(2):271–81. http://dx.doi.org/10.1016/j.chest.2017.04.177. Epub 2017 May 10. Review.
27. Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: Radiographic patterns and clinical course. Clin Cancer Res 2016;22:6051–60.
28. Nishino M, Chambers ES, Chong CR, et al. Anti-PD-1 inhibitor-related pneumonitis in non-small-cell lung cancer. Cancer Immunol Res 2016;4:289–93.
29. Tada K, Kurihara Y, Myojo T, et al. Case report of nivolumab-related pneumonitis. Immunotherapy 2017;9:313–8.
30. Kato T, Masuda N, Nakanishi Y, et al. Nivolumab-induced interstitial lung disease analysis of two phase II studies patients with recurrent or advanced non-small-cell lung cancer. Lung Cancer 2017;104:111–8.
31. Imafuku K, Yoshino K, Yamaguchi K, et al. Two cases of nivolumab readministration after pneumonitis as immune-related adverse events. Case Rep Oncol 2017;10:296–300.
32. Li H, Ma W, Yoneda KY, et al. Severe nivolumab-induced pneumonitis preceding durable clinical remission in a patient with refractory, metastatic lung squamous cell cancer: A case report. J Hematol Oncol 2017;10:64.
33. Gounant V, Brosseau S, Naltet C, et al. Nivolumab-induced organizing pneumonitis in a patient with lung sarcomatoid carcinoma. Lung Cancer 2016;99: 162–5.
34. Leroy V, Templier C, Faivre JB, et al. Pembrolizumab-induced pneumonitis. ERJ Open Res 2017;3(2):1–4, pii: 00081-2016. http://dx.doi.org/10.1183/23120541.00081-2016. eCollection 2017 Apr. PMID: 28480216.
35. Diamantopoulos PT, Gaggadi M, Kassi E, et al. Late-onset nivolumab-mediated pneumonitis in a patient with melanoma and multiple immune-related adverse events. Melanoma Res 2017;27:391–5.