ORIGINAL ARTICLE

Prognostic value of morphological characteristics assessed by CT scan in patients with non-small cell lung cancer treated with nivolumab

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Abstract

Background: Nivolumab is known to demonstrate superior overall survival compared with docetaxel in pretreated non-small cell lung cancer (NSCLC) patients. Programmed death-ligand 1 (PD-L1) expression is reported to predict the outcome of treatment by nivolumab in lung cancer patients. However, the significance of the morphological characteristics of chest computed tomography (CT) as predictors of nivolumab efficacy for advanced NSCLC patients remains unknown.

Methods: We performed a multicenter retrospective trial from April 2013 to March 2017, to assess the significance of CT morphological characteristics as predictors of nivolumab efficacy for advanced NSCLC patients. A total of 78 NSCLC patients pretreated with nivolumab were enrolled. A chest radiologist used chest CT to assess the following morphological characteristics of each patient's main tumor and intrathoracic status prior to nivolumab treatment; interstitial septal thickening, peritumoral ground-glass opacity, spiculated margin, air bronchogram, cavity or necrosis, adjacent organ invasion, bulky lymph node, and accumulation of small lymph nodes. Logistic regression and Cox proportional hazards regression models were used to analyze outcomes.

Results: A total of 60 (77%) patients were male and 72 (92%) had a performance status (PS) of 0 or 1. The objective response rates of male patients and heavy smokers were significantly higher than those of female patients and light or never smokers, respectively. Multivariate analysis identified light or never smoking, poor PS, histological type of squamous cell carcinoma, and interstitial septal thickening as independent negative predictors of progression free survival (PFS).

Conclusions: Interstitial septal thickening was a significant and independent predictor of PFS in NSCLC patients treated with nivolumab.

Key points

Significant findings of the study: Interstitial septal thickening is an independent predictor of progression free survival in non-small lung cancer patients treated with nivolumab.

What this study adds: The current study reveals the significance of morphological characteristics obtained via chest computed tomography as a predictor of nivolumab efficacy for advanced non-small cell lung cancer patients.

Introduction

Programmed cell death (PD)-1 immune checkpoint inhibitors have emerged as a promising treatment option for multiple cancer types. PD-1 is a receptor expressed on the surface of activated T cells.[1] Programmed death-ligand 1 (PD-L1) is a ligand of PD-1 that inhibits T cell activation and promotes tumor immune escape.[2,3] Nivolumab, a fully humanized immunoglobulin G4 PD-1 antibody, binds with high affinity to PD-1, and activates T cell effector function.[4]

Treatment using nivolumab has been shown to lead to superior overall survival in comparison to docetaxel in pretreated patients with non-small cell lung cancer (NSCLC),[5,6] and is administered in patients with previously treated NSCLC. However, less than 20% of these patients achieve a durable response with nivolumab treatment. Therefore, patient selection is crucial in order to optimize the survival benefit of nivolumab. An association between PD-L1 expression and nivolumab efficacy has been reported; however, some patients with negative PD-L1 expression tumors have been reported to have achieved treatment efficacy.[5,7] The ability of PD-L1 expression to predict the outcome of nivolumab treatment in lung cancer patients is still controversial. Tumor mutation burden has been reported to be a prognostic biomarker of nivolumab in advanced NSCLC.[8] In addition, some clinical biomarkers, such as neutrophil-to-lymphocyte ratio[9] or immune related adverse events,[10] are reported to be predictive biomarkers for nivolumab response.

Chest computed tomography (CT) is an essential investigation method for the diagnosis of lung cancer, and for assessing lung cancer response to chemotherapy.[11] However, the predictive value of CT morphological characteristics prior to treatment with nivolumab is unclear. Here, we performed a retrospective analysis to investigate whether the therapeutic response to nivolumab could be predicted by the morphological characteristics on CT images.

Methods

Patients

We reviewed the medical records of patients with recurrent or advanced NSCLC who were treated with nivolumab and were followed-up for at least three months at Gunma Prefectural Cancer institute, Ibaraki Central Hospital, Fukushima Medical University Hospital, Tochigi Cancer Center Hospital or Aizu Medical Center Hospital between April 2013 and March 2017. We identified a total of 115 pretreated advanced NSCLC patients who had been treated with nivolumab. Of these patients, 78 had undergone chest CT imaging before initiation of nivolumab treatment. CT data was delivered using the raw Digital Imaging and Communications in Medicine (DICOM) format. Tumor response was assessed by CT according to the Response Evaluation Criteria in Solid Tumor, version 1.1.[12] Objective response rate (ORR) was defined as the proportion of patients whose best response was either complete response (CR) or partial response (PR). Disease control rate (DCR) was defined as the proportion of patients whose best responses were CR, PR or stable disease (SD) against the total number of subjects. Progression-free-survival (PFS) was defined as the duration between initiation of treatment and clinical or radiographic progression, or death from any cause. Overall survival (OS) was defined as the duration between first-line treatment initiation and death. Nivolumab was administered intravenously at a dose of 3 mg/kg every two weeks. The present study was performed according to the protocols approved by the institutional review boards of each hospital; informed consent was waived for retrospective review of patient records and images. The study is registered with the University Hospital Medical Information Network Clinical Trial Registry in Japan (UMIN000026294).

CT scan

CT was performed as a part of a routine examination for the evaluation of lung cancer and was performed using 5 mm and 2 mm collimations. Most CT images were photographed using both mediastinal (level, 40 HU; width, 400 HU) and lung (level, −600 HU; width, 1600 HU) window settings; however, some patients' data could only be analyzed at the mediastinal setting.

Morphological characteristics

Morphological characteristics were selected from General Rule for Clinical and Pathological Record of Lung Cancer, eighth edition.[13] Most patients had advanced disease, and measurement of solitary lesions therefore was difficult. The CT scan had a 5 mm slice thickness, and some CT images were photographed in the mediastinal setting; we considered measurability, and selected the following target morphological characteristics: peritumoral interstitial septal thickening, peritumoral ground-glass opacity, spiculated margin, air bronchogram, cavity or necrosis, adjacent organ invasion (Fig 1), bulky lymph node (≥ 2.5 cm), and accumulation of small lymph nodes. A chest radiologist reviewed the aforesaid characteristics on all patients' CT images, and was blinded to the patients' clinical histories and data.

Statistical analysis

Statistical analysis with a Chi-squared test was used to evaluate the clinical parameters associated with nivolumab efficacy. Kaplan-Meier analysis of PFS was performed on these clinical characteristics, with differences between each pair of groups being assessed using the log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) were calculated using the univariate Cox proportional hazard model. Two-sided *P*-values of <0.05 were considered statistically significant. A multivariate Cox proportional hazards model was developed for clinically relevant factors and covariates that were determined to be statistically significant in the univariate analysis. The database was locked on 12 January 2018. All statistical analyses were performed using the STATA/SE version 14 statistical software package (StatCorp., College Station, TX, USA).
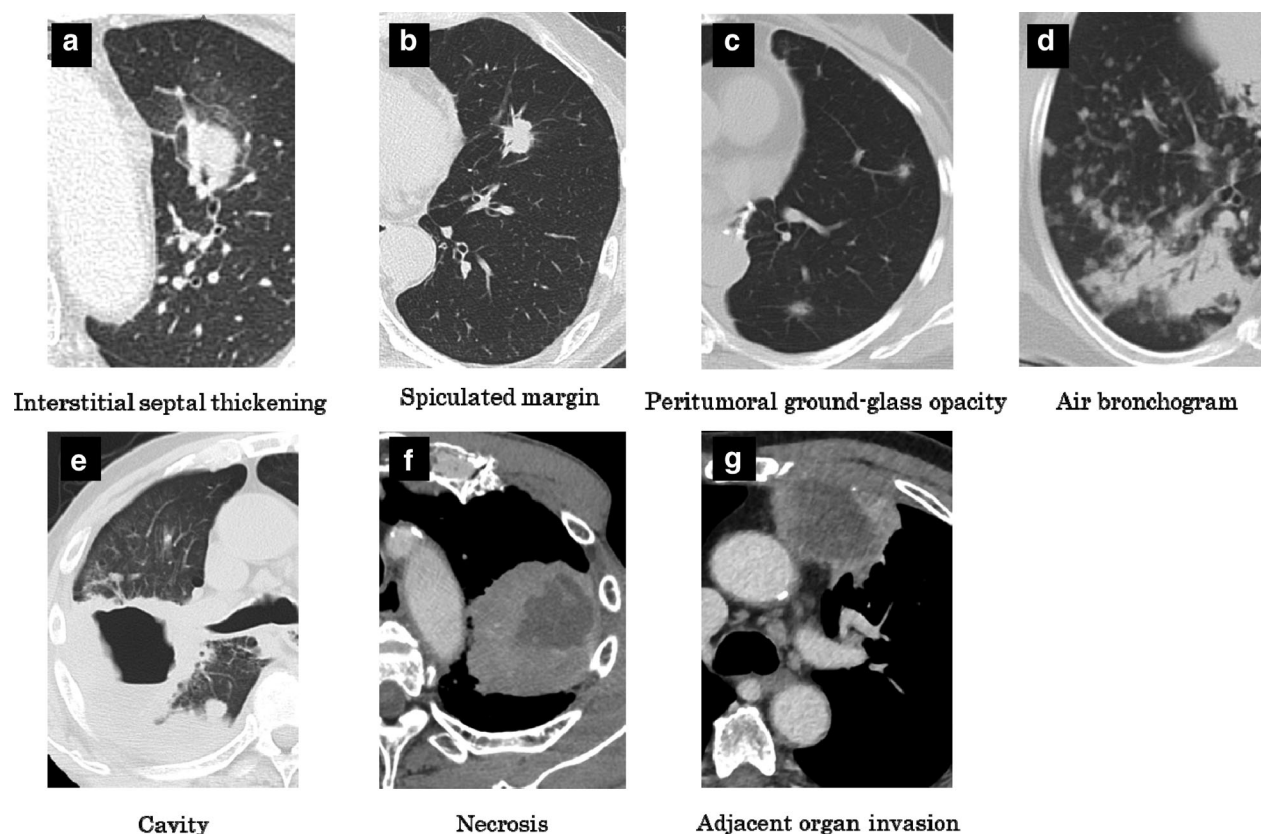

Figure 1 Representative graphics of morphological characteristics of lung cancer assessed by computer tomography scan. (**a**) Interstitial septal thickening: the surrounding bronchial vascular bundle of the left upper lobe lesion presents interstitial septal thickening. (**b**) Spiculated margin: the fluffy shadow projects from the tumor, reaching the interlobar pleura. (**c**) Peritumoral ground-glass opacity: tumors are surrounded by a region like ground-glass. (**d**) Air bronchogram: in the infiltrative shadow, radiolucent shadows of the bronchus are observed. (**e**) Cavity: the right lower lobe lesion was a cavitary lesion. (**f**) Necrosis: low-density area in the left upper lobe tumor suggests the presence of necrotic materials. (**g**) Adjacent organ invasion: left upper lobe tumor invades the chest wall.

Results

Patient demographics

The study population consisted of 78 patients (60 men and 18 women; median age, 65; range, 32–84 years), whose characteristics are summarized in Table 1. Among all patients, 92% had a PS of 0 or 1 and 62% had adenocarcinoma. The ORR and DCR were 17.9% and 48.7%, respectively. The Kaplan-Meier curves for PFS and OS are shown in Fig 2. The ORR of nine patients were not evaluated. At the time of the database lock, 61 PFS and 27 OS events had occurred.

The patients' characteristics of squamous and nonsquamous cell carcinoma were as follows. The median age of patients with squamous cell carcinoma was 70 years and that of patients with nonsquamous cell carcinoma was 65.5 years (data not shown); however, the difference did not reach statistical significance ($P = 0.097$). A total of 94% of the patients with squamous cell carcinoma were heavy smokers, compared with 60% of those with nonsquamous cell carcinoma ($P = 0.015$). However, the proportions of gender and PS were not significantly different between the patients with squamous and nonsquamous cell carcinoma.

Efficacy

The details of the ORR of nivolumab based upon the clinical parameters are shown in Table 2. The ORRs of the male patients and heavy smokers were significantly higher

Table 1 Patient characteristics

Items	Median (range) or number
Age	65 (32–84)
Male/female	60/18
ECOG performance status 0 or 1/2/3	72/5/1
Histology (adeno/squamous/others)	48/18/12
Clinical stage IIB/IIIA and B/IV	1/14/51
Smoking (heavy/light or never)	56/22
EGFR mutation/*ALK* translocation	9/0
Treatment line second/third or more	44/34
CT morphological characteristics	
Interstitial septal thickening	17
Peritumoral ground-glass opacity	41
Spiculated margin	16
Air bronchogram	8
Cavity or necrosis	16
Adjacent organ invasion	11
Bulky lymph node (≥2.5 cm)	11
Accumulation of small lymph nodes	4

$N = 78$. Clinical stage was classified using TNM version 7. Heavy smoker, Brinkman index ≥400; Light or never smoker, Brinkman index <400.
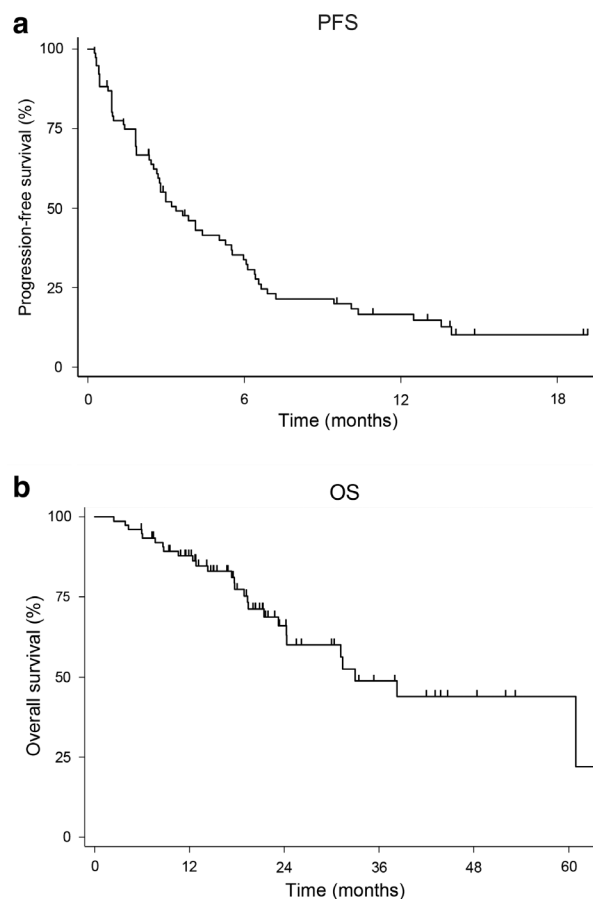
Figure 2 Progression-free survival and overall survival among the study patients. Kaplan–Meier curves for progression-free survival (**a**) and overall survival (**b**) are shown.

than those of the female patients and light or never smokers, respectively.

Survival analysis

Univariate Cox proportional hazard analysis revealed that poorer ECOG PS, squamous cell carcinoma, and interstitial septal thickening were predictors of shorter PFS in the patients treated with nivolumab (Table 3). Furthermore, multivariate Cox analysis demonstrated that interstitial septal thickening was a predictor of shorter PFS, independent of other clinical features (Table 4).

The univariate Cox proportional hazard analysis revealed that poorer ECOG PS and interstitial septal thickening were associated with shorter OS in the patients treated with nivolumab (Table 5). The multivariate Cox analysis demonstrated that smoking status, ECOG PS and interstitial septal thickening were predictors of shorter OS, independent of other clinical features (Table 6).

Table 2 Difference of the response to nivolumab according to the clinical parameters and CT morphological characteristics

Parameters		Response to nivolumab, N	*P*-value
Age	≥75 (*n* = 11)	2	0.85
	<75 (*n* = 58)	12	
Gender	Male (*n* = 52)	14	< 0.05
	Female (*n* = 17)	0	
Smoking	Heavy smoker (*n* = 49)	14	< 0.05
	Light or never smoker (*n* = 20)	0	
ECOG performance status	0,1 (*n* = 64)	13	0.987
	2 (*n* = 5)	1	
EGFR mutation	Positive (*n* = 8)	1	0.547
	Negative (*n* = 60)	13	
Histology	Squamous cell carcinoma (*n* = 16)	4	0.286
	Others (*n* = 53)	10	
Interstitial septal thickening	Positive (*n* = 16)	1	0.093
	Negative (*n* = 50)	13	
Peritumoral ground-glass opacity	Positive (*n* = 37)	5	0.099
	Negative (*n* = 30)	9	
Spiculated margin	Positive (*n* = 13)	1	0.21
	Negative (*n* = 56)	13	
Air bronchogram	Positive (*n* = 6)	1	0.817
	Negative (*n* = 63)	13	
Cavity or necrosis	Positive (*n* = 14)	3	0.906
	Negative (*n* = 55)	11	
Adjacent organ invasion	Positive (*n* = 8)	1	0.56
	Negative (*n* = 61)	13	
Bulky lymph node (≥2.5 cm)	Positive (*n* = 10)	2	0.98
	Negative (*n* = 59)	12	
Accumulation of small lymph nodes	Positive (*n* = 3)	1	0.566
	Negative (*n* = 66)	13	

Objective response rate could be evaluated in 69 of 78 subjects. Heavy smoker, Brinkman index ≥400; Light or never smoker, Brinkman index <400.

Discussion

In the present study, smoking status, PS and presence of interstitial septal thickening around the tumor were found to be related to poor PFS. To the best of our knowledge, the present study is the first to demonstrate a possible association between CT morphological characteristics and nivolumab efficacy in a real-world setting. A previous study reported an association between the morphological characteristics of stage I lung adenocarcinoma and prognosis.[14] Another study reported the relationship between CT morphological characteristics at diagnosis and EGFR tyrosine kinase inhibitor (TKI).[15] Recently deep learning of serial CT imaging was reported to predict the treatment response of patients with locally advanced NSCLC.[16] The combination of deep learning technology and CT imaging may bring another biomarker to predict the efficacy of nivolumab in NSCLC in the future. However, few studies have discussed the relationship between morphological characteristics detected using CT in advanced NSCLC and therapeutic efficacy of treatment for lung cancer.

The CT patterns of interstitial septal thickening around tumors contain pulmonary lymphangitic carcinomatosis.[17]

Table 3 Univariate Cox proportional hazard analysis predicting shorter progression-free survival in patients with non-small cell lung cancer treated with nivolumab

Variate	HR (95% CI)	*P*-value
Age ≥ 75	1.12 (0.57–2.22)	0.740
Male gender	1.20 (0.64–2.21)	0.565
Heavy smoker	0.73 (0.42–1.29)	0.268
ECOG performance status ≥2	5.44 (2.10–14.1)	0.000
EGFR-mutant	0.84 (0.36–1.96)	0.691
Squamous cell carcinoma	2.03 (1.12–3.68)	0.019
Interstitial septal thickening	2.15 (1.13–4.09)	0.019
Peritumoral ground-glass opacity	1.35 (0.80–2.26)	0.256
Spiculated margin	0.94 (0.51–1.75)	0.857
Air bronchogram	0.66 (0.26–1.66)	0.375
Cavity or necrosis	1.33 (0.67–2.65)	0.410
Adjacent organ invasion	2.38 (0.97–5.82)	0.057
Bulky lymph node (≥2.5 cm)	1.82 (0.96–3.44)	0.065
Accumulation of small lymph nodes	0.67 (0.21–2.16)	0.505

CI, confidence interval; HR, hazard ratio,

Lung cancer with pulmonary lymphangitic carcinomatosis rarely responds to chemotherapy and has a poor prognosis.[18] The presence of peritumoral interstitial thickening on

Table 4 Multivariate Cox proportional hazard analysis predicting shorter progression-free survival in patients with non-small cell lung cancer treated with nivolumab

Variate	HR (95%CI)	*P*-value
Age ≥75	0.84 (0.41–1.72)	0.631
Male gender	1.61 (0.74–3.50)	0.278
Heavy smoker	0.36 (0.18–0.75)	0.006
ECOG performance status ≥2	8.55 (3.09–23.7)	0.000
EGFR-mutant	0.76 (0.26–2.15)	0.606
Squamous cell carcinoma	2.41 (1.24–2.15)	0.011
Interstitial septal thickening	2.48 (1.24–4.94)	0.010

CI, confidence interval; HR, hazard ratio.

Table 6 Multivariate Cox proportional hazard analysis predicting shorter overall survival in patients with non-small cell lung cancer treated with nivolumab

Variate	HR (95% CI)	*P*-value
Age ≥75	0.70 (0.19–2.46)	0.579
Male gender	1.67 (0.54–5.21)	0.375
Heavy smoker	0.30 (0.10–0.86)	0.025
ECOG performance status ≥2	17.9 (5.17–62.0)	0.000
EGFR-mutant	0.26 (0.05–1.28)	0.099
Squamous cell carcinoma	0.43 (0.15–1.30)	0.135
Interstitial septal thickening	3.44 (1.19–9.33)	0.099

CI, confidence interval; HR, hazard ratio.

Table 5 Univariate Cox proportional hazard analysis predicting shorter overall survival in patients with non-small cell lung cancer treated with nivolumab

Variate	HR (95% CI)	*P*-value
Age ≥75	0.57 (0.17–1.92)	0.370
Male gender	1.27 (0.47–3.38)	0.638
Heavy smoker	0.77 (0.73–4.17)	0.207
ECOG performance status ≥2	8.11 (3.17–20.7)	0.000
EGFR-mutant	0.44 (0.57–3.67)	0.436
Squamous cell carcinoma	1.13 (0.45–2.83)	0.787
Interstitial septal thickening	2.15 (1.13–4.09)	0.019
Peritumoral ground-glass opacity	1.13 (0.51–2.50)	0.757
Spiculated margin	1.00 (0.38–2.68)	0.986
Air bronchogram	0.42 (0.10–1.79)	0.241
Cavity or necrosis	1.47 (0.59–3.66)	0.412
Adjacent organ invasion	1.47 (0.59–3.66)	0.207
Bulky lymph node (≥2.5 cm)	1.75 (0.73–4.18)	0.938
Accumulation of small lymph nodes	1.08 (0.14–8.16)	0.938

CI, confidence interval; HR, hazard ratio.

preoperative CT appears to predict pathological lymphovascular invasion and recurrence,[19] and pulmonary lymphangitic carcinomatosis suggests retrograde lymphatic spread of tumor cells from mediastinal and hilar lymph node metastases into the pulmonary lymphatics.[20] This may cause poor response to nivolumab in cases of NSCLC with pulmonary lymphangitic carcinomatosis.

Performance status, smoking status, *EGFR* status and metastatic site have been reported to be predictive clinical parameters for response to nivolumab.[21, 22, 23] Consistent with the results of a previous study, poorer PS was associated with shorter PFS and OS during nivolumab treatment in the present study. However, one of these studies[21] reported that *EGFR* status is a negative predictor of PFS, which is inconsistent with our analysis. The reason for this may be partly due to the current study's relatively small number of subjects. Since the ORR is comparable to those from other clinical trials that assessed nivolumab, the efficacy of nivolumab in the present study seemed to be identical to those trials.[5, 6] PD-L1 expression has been reported

to be related with the response to nivolumab,[7] and there might be an association between CT morphological characteristics and PD-L1 expression. However, we could not investigate this association because the measurement of PD-L1 expression was not mandatory in clinical settings during our study period.

In the current analysis, the PFS of patients with squamous cell carcinoma was significantly shorter than that of the patients with nonsquamous cell carcinoma. This is in contrast to previous studies, which reported the PFS of squamous cell carcinoma patients to be significantly longer than that of patients with adenocarcinoma.[24] Regarding heavy smokers, there were significantly more in the patients with squamous cell carcinoma than in those with nonsquamous cell carcinoma in the present study. One possible reason for this is that the squamous cell carcinoma patients in our analysis tended to be older than the nonsquamous cell carcinoma patients, although this difference did not reach statistical significance (*P* = 0.097). Another reason is that PD-L1 expression in these two groups might have been different.

There are some limitations to the present study. First, the study was retrospective in nature, so information bias cannot be excluded. Second, our multivariate analysis did not include significant potential confounding factors, such as tumor mutation burden, which is a predictive marker of efficacy of nivolumab.[25] Analysis for tumor mutation burden was not performed in the present study. Third, CT imaging settings were not unified among the institutes that participated in the study. Moreover, we did not elucidate the precise mechanisms governing the relationship between radiological characteristics, interstitial septal thickening, and the outcome of patients with NSCLC after nivolumab treatment. Finally, overall survival data were immature. Further pathological and prospective studies are needed to determine the predictive value of morphological characteristics detected using CT in NSCLC treated with nivolumab.

In conclusion, NSCLC with interstitial septal thickening may respond poorly to nivolumab.

Acknowledgments

Disclosure

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