Pulmonary Complications of Lung Cancer Treatment

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Outline

- Approach to the patient with suspected treatment-related pulmonary toxicity
- Pulmonary toxicity related to tyrosine kinase inhibitors
- Pulmonary toxicity related to immunotherapy

Pulmonary Toxicities related to Cancer Treatment

- 10% of all cancer patients develop pulmonary toxicity related to treatment
- Patients with lung cancer appear to be at increased risk for pulmonary complications of treatment
  - High prevalence of underlying lung disease (COPD, ILD, etc.)
    - Decreased baseline pulmonary reserve
  - Diagnosis of toxicity may be difficult or delayed
    - Symptoms of toxicity may mimic symptoms of known disease
    - Radiographic findings not specific
    - Risk of pulmonary infection in immunosuppressed patients is high
  - Threshold for diagnostic evaluation, including invasive procedures, should be low

Approach to the patient with suspected treatment-related pulmonary toxicity

Typical symptoms are nonspecific

- Progressive dyspnea, nonproductive cough, chest discomfort, weight loss

In most cases, the diagnosis of drug toxicity is one of exclusion

- Exclude progression of underlying cancer
- Exclude other competing causes of pulmonary decompensation
  - Infection, congestive heart failure, noncardiogenic pulmonary edema
- Consequences of concluding drug toxicity are clinically important
  - Will influence decision regarding continuation of therapy

Approach to the patient with suspected pulmonary toxicity

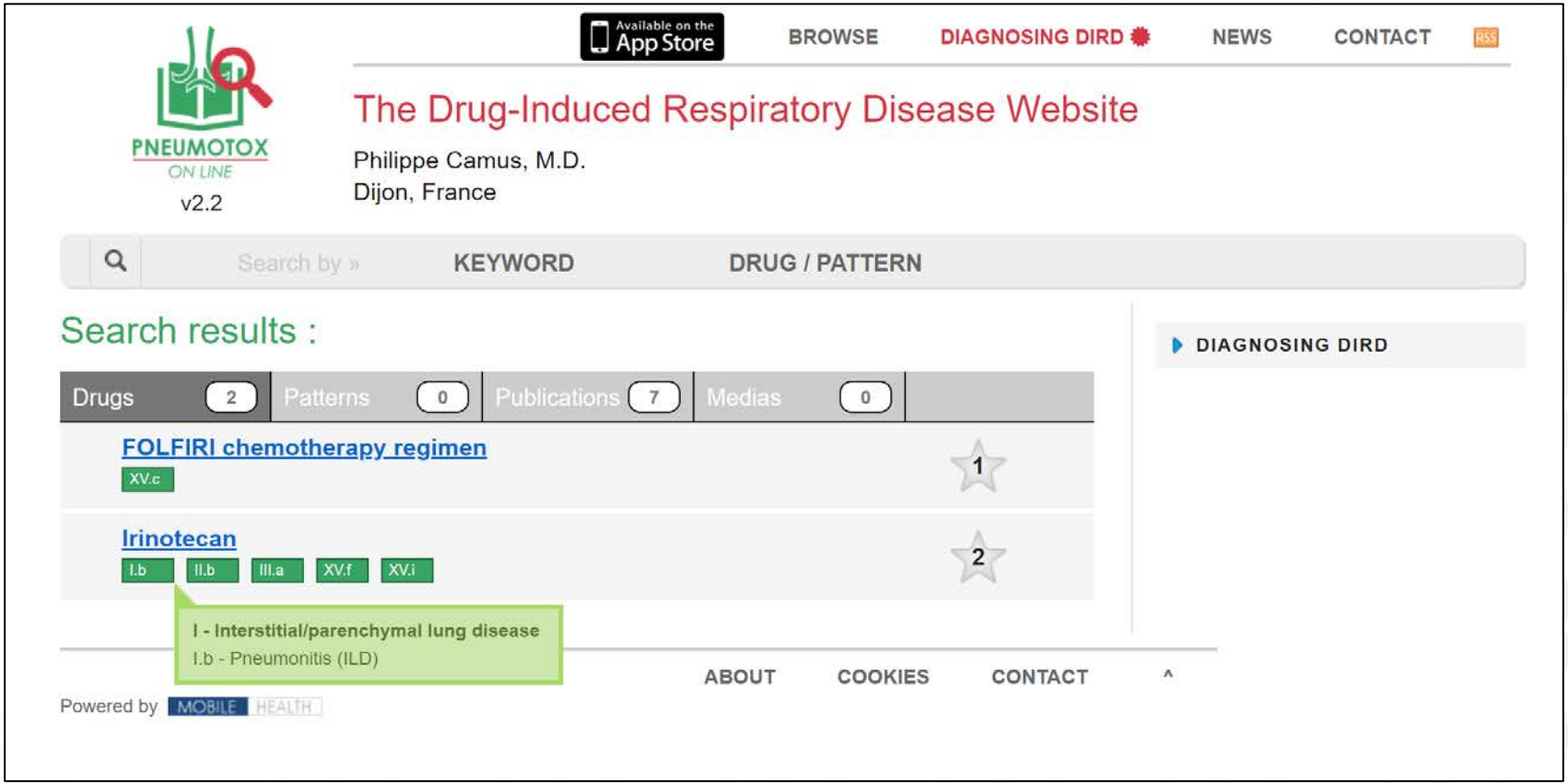
Evaluation

- Assess risk for infection
  - Neutropenia, immunosuppression
  - Lungs are the most common site of infection in cancer patients
- Pulmonary function testing with diffusion capacity (compare to baseline)
- Imaging studies: CXR, Chest CT (inspiration/expiration high resolution), echocardiogram, etc.
  - Is there evidence for a competing diagnosis (pleural/pericardial effusion, pulmonary edema, adenopathy, evidence of disease progression, etc.)
- Bronchoscopy with BAL and TBBx (role for cryobiopsy?)
- Transthoracic, CT-guided biopsy
- Surgical lung biopsy

Pulmonary Toxicities related to Cancer Treatment

Class of Drug		Pulmonary toxicities	Approach
Chemotherapy	Platinum drugs	Pneumonitis (rare), Hypersensitivity reactions (rare)	Withdraw drug. For severe toxicity (symptomatic, radiographic, physiologic findings), consider corticosteroids
	Pemetrexed	Pneumonitis (rare)	
	Etoposide	Pneumonitis (rare), Hypersensitivity reactions (rare)	
	Gemcitabine	Nonspecific dyspnea (25%), pneumonitis (rare), diffuse alveolar damage (rare), risk factors: age, prior radiation	
	Taxanes	Higher risk associated with ILD. Type 1 hypersensitivity reactions, pneumonitis. Increase risk of radiation injury (radiation recall)	
	Camptothecins	Pneumonitis, higher risk with ILD or prior radiation.	
Anti-angiogenic agents	Bevacizumab	Hemoptysis (higher in patients with squamous cell carcinoma or cavitary tumors), diffuse alveolar hemorrhage, T-E fistula with concurrent chemoradiation (? Increased VTE)	Withdraw drug. Symptomatic support.

pneumotox.com



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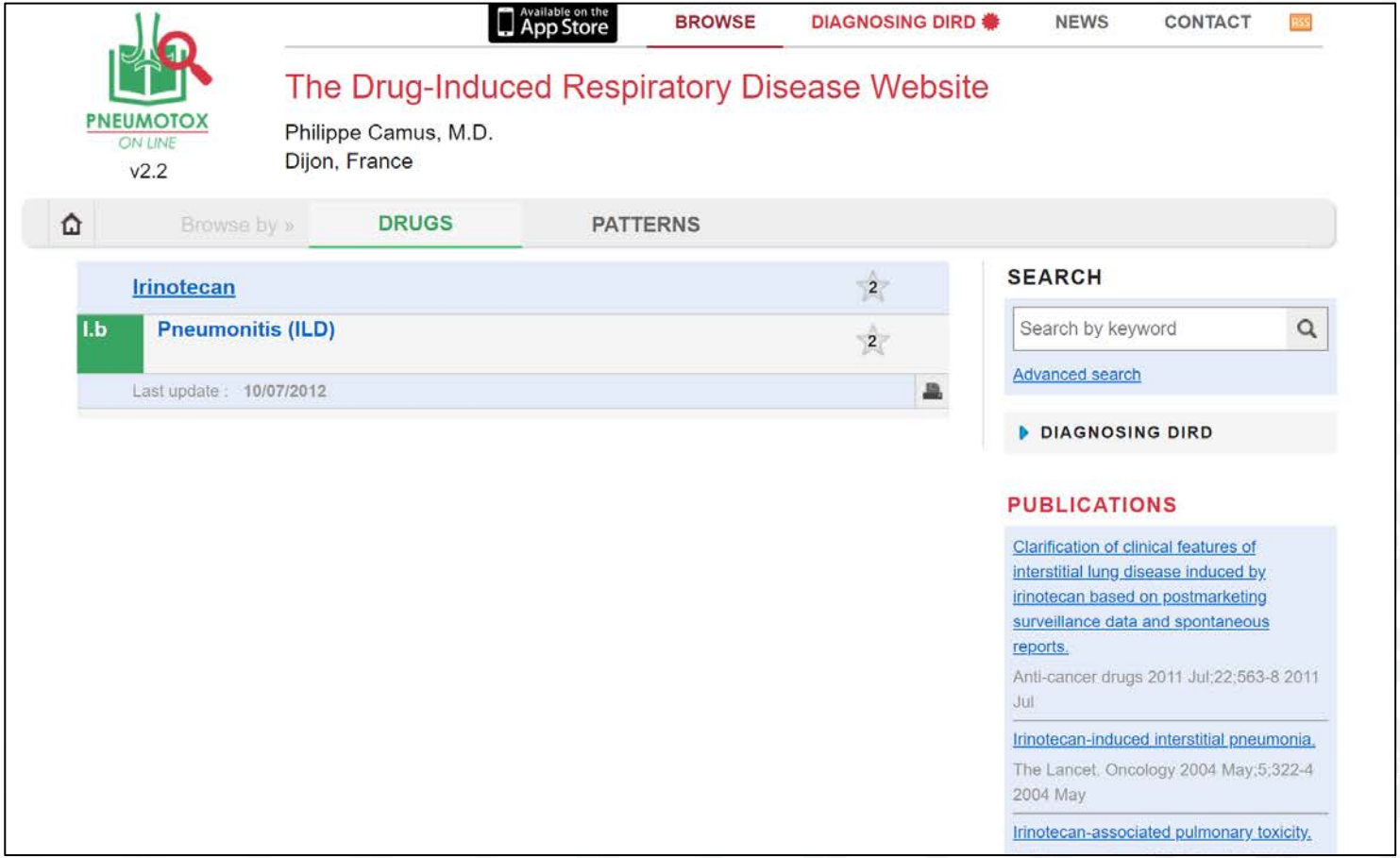


Genotype-directed targeted therapies

- Potentially targetable mutations are identified for the majority of adenocarcinomas
- Targeted tyrosine kinase inhibitors are first line therapies for patients with advanced (Stage IV) *EGFR*-mutated, *ROS1* and *ALK* rearranged NSCLC
  - Epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKI)
    - gefitinib, erlotinib, afatinib (*EGFR/HER2*), osimertinib
  - *ROS1* TKI
    - crizotinib
  - Anaplastic lymphoma kinase (*ALK*) rearrangement TKI
    - crizotinib, ceritinib, alectinib

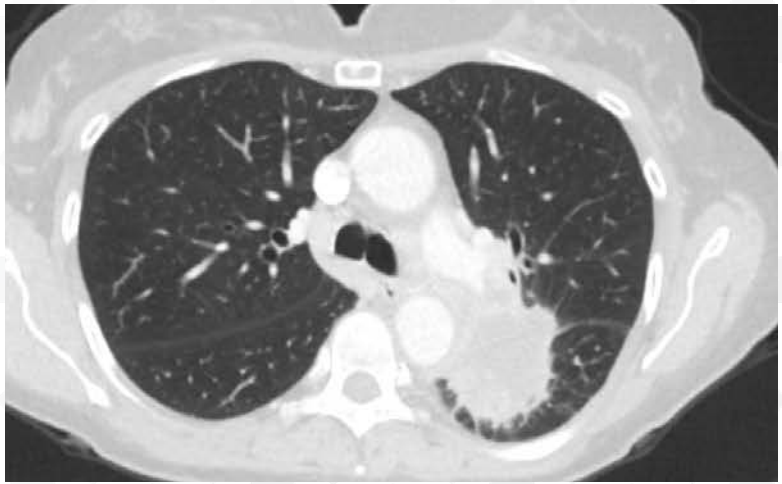
Pulmonary toxicity related to tyrosine kinase inhibitors

- All tyrosine kinase inhibitors can cause pulmonary toxicity
- EGFR inhibitors (gefitinib, erlotinib, afatinib, osimertinib)
  - 7-8% of patients develop treatment-limiting toxicities (skin, GI, lungs)
  - Most common toxicity is pulmonary: interstitial pneumonitis
    - Risk factors: Asian descent (6%), pre-existing ILD, older age, male gender, smoking, prior thoracic irradiation
    - Typically occurs quickly, within first 2 months of treatment, but may appear after many months
    - Symptoms: dry cough, exertional dyspnea
    - Treatment: discontinue drug, initiate corticosteroids for radiographic findings in combination with symptoms
    - Fatal pneumonitis observed in 2% of Japanese patients, but rare in other populations
- NB: TKIs are not immunosuppressing, and do not increase risk of infection

Case 1

RD is a 71 year old female, who presented in December 2017 with complaints of persistent dry cough and back pain for 4 months and recent 10 pound weight loss. She is a lifelong nonsmoker and had previously been in good health. A chest radiograph suggested a left lung mass; chest CT scan confirmed a 4 cm spiculated mass in the left lower lobe with mediastinal adenopathy. PET-CT imaging showed intense FDG uptake in the mass, mediastinal nodes, supraclavicular nodes, and several liver lesions. Brain MRI was negative.

Aspiration of a one of the liver lesions demonstrated TTF+ adenocarcinoma, + EGFR Exon 19-deletion mutation. Tumor PD-L1 expression was < 1%. The clinical stage was T2aN3M1c, Stage IVc.

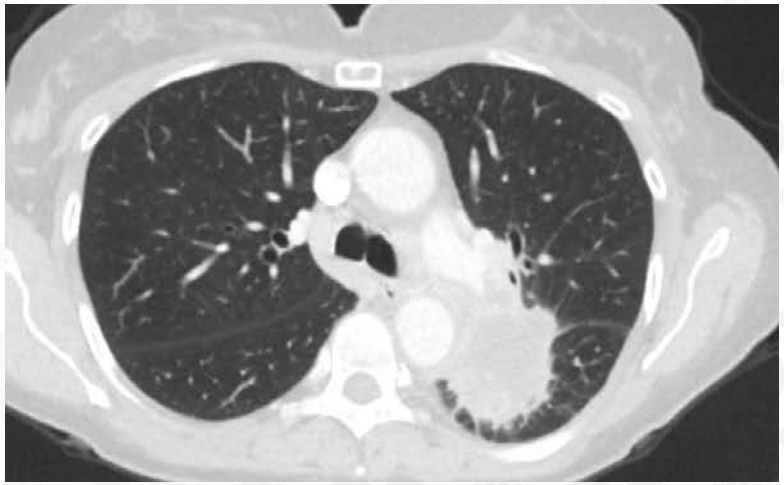


Question 1

Case 1: 71 year old women with *EGFR*-mutated adenocarcinoma (Exon 19-deletion mutation). Clinical stage: T2aN3M1c, Stage IVc.

Which of the following would NOT be an appropriate recommendation?

A. Gefitinib
B. Erlotinib
C. Crizotinib
D. Osimertinib



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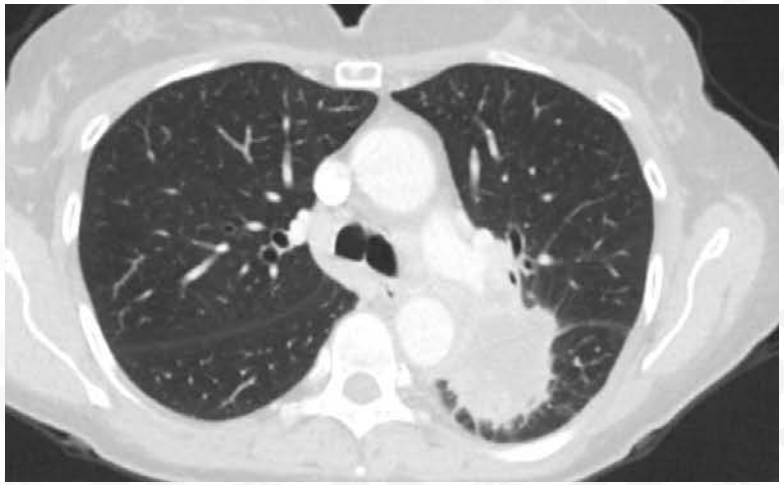
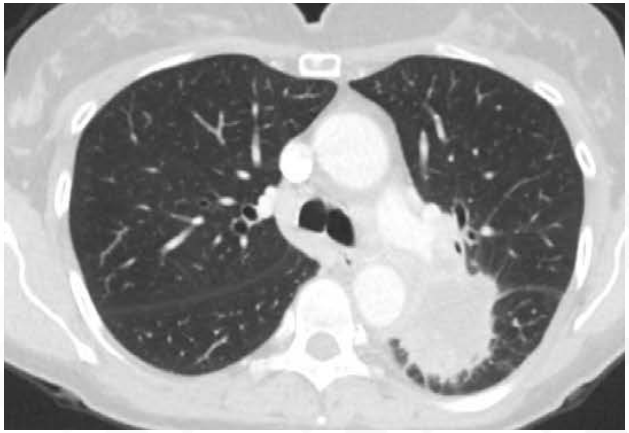


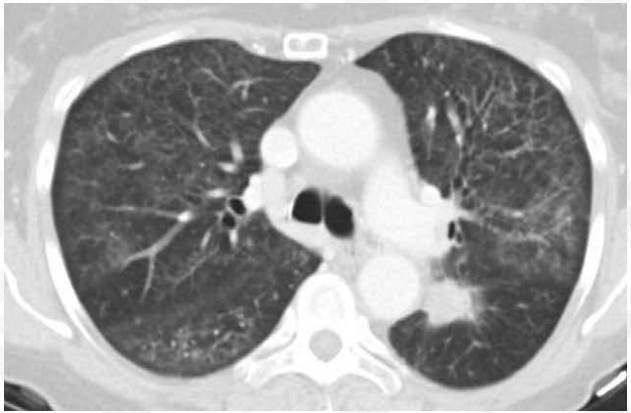
Case 1

- RD was treated with erlotinib. Over the first 3 months, the cough and back pain resolved, and there was marked improvement in her radiographs. In July of 2018, she developed persistent dry cough without other symptoms. Chest CT scan demonstrated that the original primary mass had decreased in size to 1.7 cm and mediastinal adenopathy had resolved, but the lung parenchyma demonstrated diffuse interstitial and ground glass infiltrates in all lung zones. Pulmonary function testing showed a mild restrictive defect with a decrease in diffusion capacity, both new compared to pre-treatment testing.

December 2017



July 2018

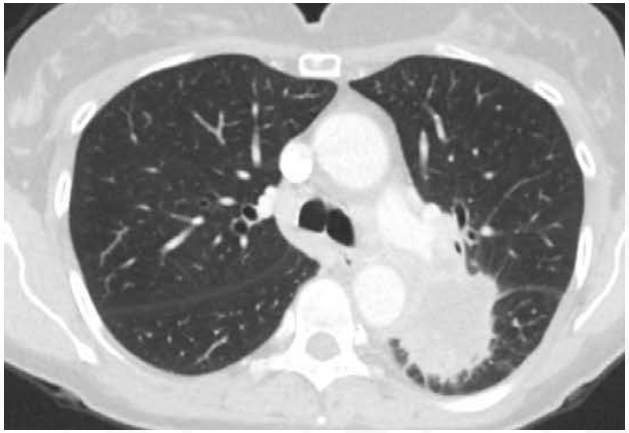


Question 2

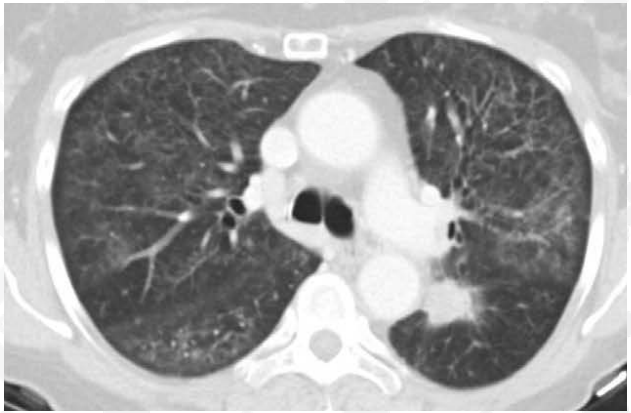
Case 1: Which of the following is the most likely explanation for the radiographic findings in June 2018?

A. Pneumocystis jiroveci pneumonia
B. Diffuse alveolar hemorrhage
C. Interstitial pneumonitis due to erlotinib
D. Lymphangitic spread of adenocarcinoma

December 2017



June 2018



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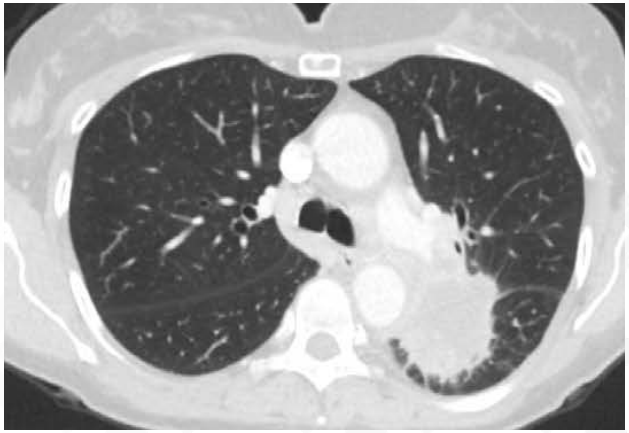

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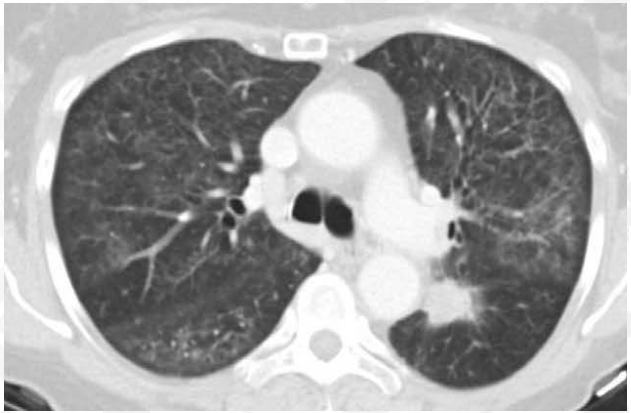
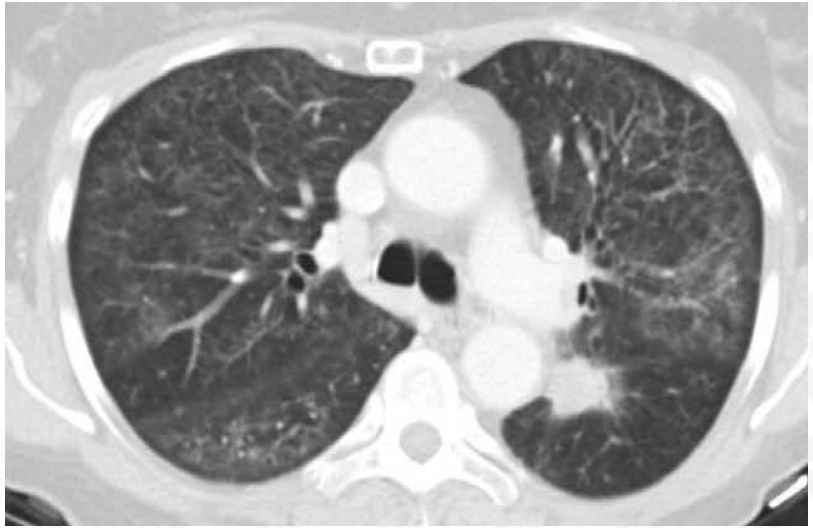


Case 1

- Bronchoscopy with BAL and biopsies of the right lung showed no evidence of infection or cancer
- RD was felt to have erlotinib-related pulmonary toxicity with acute interstitial pneumonitis. Erlotinib was discontinued and she was treated with oral corticosteroids for 3 months, with improved symptoms and PFT.

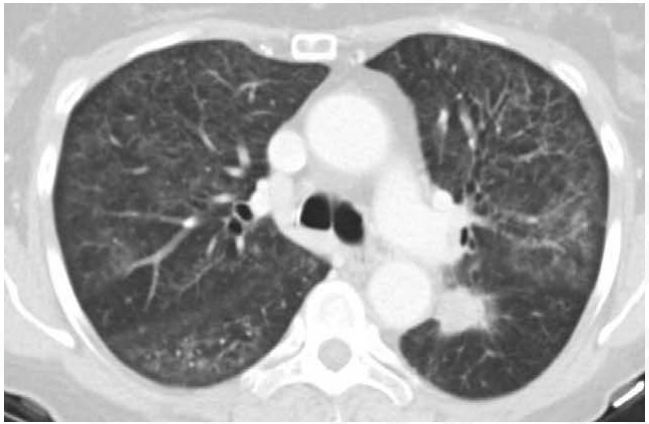
June 2018



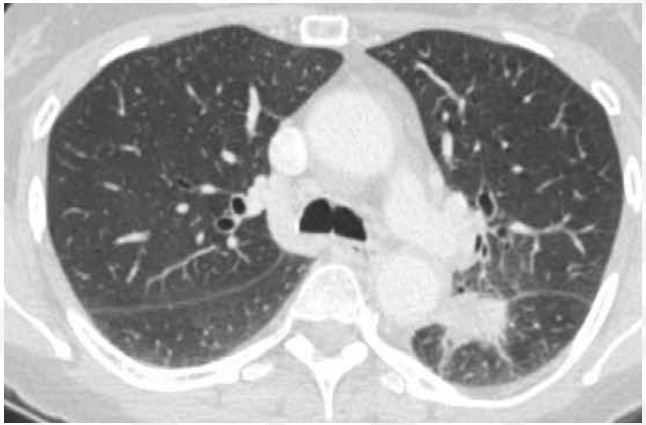
Case 1

- In October 2018, a surveillance CT showed the diffuse interstitial infiltrates had improved. However, the primary site had increased to 2.1 cm.
- Carboplatin and pemetrexed were begun x 4 cycles. RD tolerated the chemotherapy well, but in January 2019, brain MRI showed two new 6 mm enhancing nodules in the right parietal lobe, consistent with metastasis. She received gamma knife treatment to the brain metastasis.

June 2018



October 2018



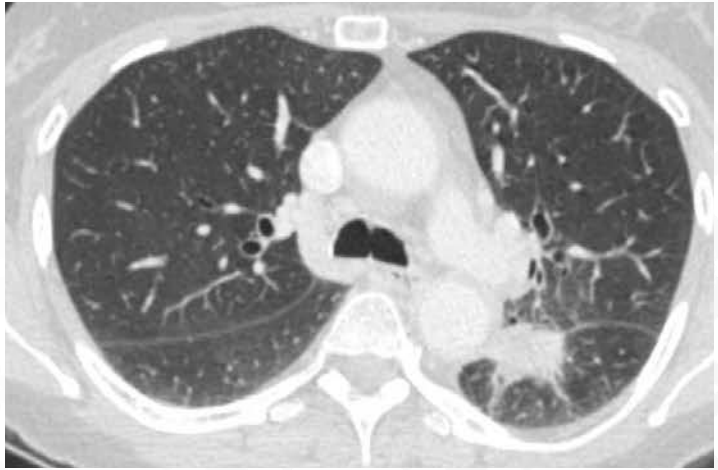
Case 1

- With evidence of recurrent disease despite chemotherapy, a tumor board multidisciplinary discussion was held.
- Because RD had *EGFR*-mutant adenocarcinoma, it was felt that immunotherapy was unlikely to be of benefit.
- It was noted that RD had never had treatment failure with erlotinib – the drug had been discontinued because of toxicity, not because of development of resistance.
- The recommendation of the tumor board was to consider osimertinib, but with careful monitoring given the prior pulmonary toxicity with erlotinib.

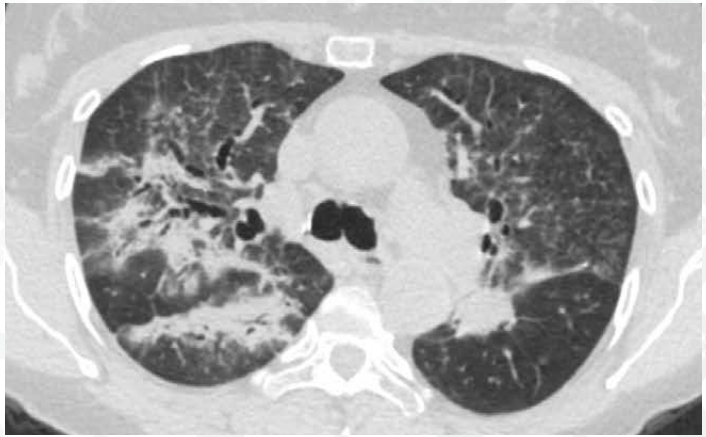
Case 1

- An informed discussion was held with RD to explain the tumor board recommendations. Osimertinib was started in late January 2019
- Within 6 weeks, RD began experiencing dry cough without fevers.
- Chest CT demonstrated diffuse interstitial infiltrates with areas of atelectasis and consolidation, felt most likely consistent with drug toxicity from osimertinib.
- Osimertinib was discontinued. RD is currently being treated with oral corticosteroids, with improvement in dyspnea.

October 2018



March 2019



Take home points: Pulmonary toxicity related to tyrosine kinase inhibitors

- All tyrosine kinase inhibitors can cause pulmonary toxicity
- Symptoms of pulmonary toxicity are nonspecific (dry cough, dyspnea) and may mimic the patient's underlying cancer or other lung disease, so suspicion always needs to be high
- Drug toxicity usually manifests radiographically as interstitial pneumonitis
- Drug toxicity usually occurs within the first few months of treatment, but can appear late, after many months
- TKIs are not immunosuppressing. Concern for pulmonary infection in a patient with lung cancer must be present, but the risk is not as high as with chemotherapy
- Treatment: discontinue drug, initiate corticosteroids for radiographic findings in combination with symptoms

Immunotherapy for treatment of lung cancer

- Checkpoint inhibitors approved for treatment of Stage IV NSCLC
  - Anti PD-1
    - Pembrolizumab (for high PD-L1 expressing tumors)
    - Nivolumab
  - Anti PD-L1
    - Durvalumab
    - Atezolizumab
    - Avelumab
- Anti-CTLA4
    - Ipilimumab
    - Tremelimumab

Immune-related adverse events (IRAEs) - NSCLC

Pillai RN et al. Comparison of Toxicity Profile of PD-1 versus PD-L1 Inhibitors in Non-small cell lung cancer: A systematic analysis of literature. Cancer 2018; 124:271-277.

23 studies of immunotherapy for NSCLC, including 5744 patients with complete data on IRAEs

Table 3

Adverse Events (AEs), Immune Related Adverse Events (IRAEs), and Overall Response Rates with PD-1 versus PD-L1 Inhibitors

	PD-1 Inhibitors (n=3284)	PD-L1 Inhibitors (n=2460)	p-value
Overall AEs (%)	64	66	0.8
Grade 3-5 AEs (%)	13	21	0.15
Fatigue, any grade (%)	19	21	0.4
Diarrhea, any grade (%)	9	12	0.4
Rash, any grade (%)	9	7	0.8
IRAEs (%)	16	11	0.07
Grade 3-5 IRAEs (%)	3	5	0.4
Hypothyroidism, any grade (%)	6.7	4.2	0.07
Pneumonitis, any grade (%)	4	2	0.01
Colitis, any grade (%)	1.7	1	0.4
Overall Response Rate (ORR) (%)	19	18.6	0.17

Immune-related adverse events (IRAEs) related to checkpoint inhibitors - NSCLC

Risk factors:

- Underlying interstitial lung disease
- Underlying auto-immune disease (typically a disqualification to eligibility for clinical trials with checkpoint inhibitors)
- Prior thoracic irradiation

Immune-related adverse events (IRAEs) – time frame

Remon J et al. Immune-related adverse events with immune checkpoint inhibitors in thoracic malignancies: focusing on non-small cell lung cancer patients. J Thorac Dis 2018; S1516-S1533.

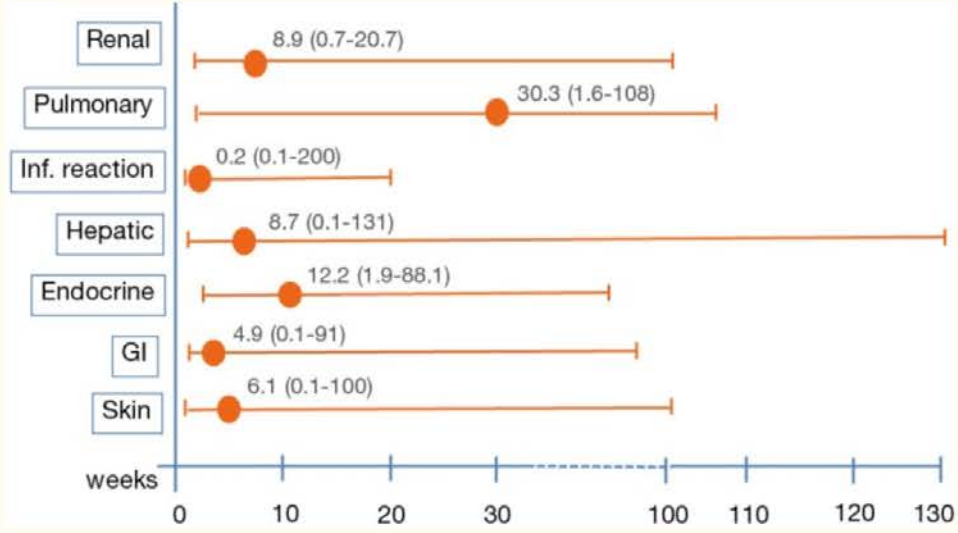
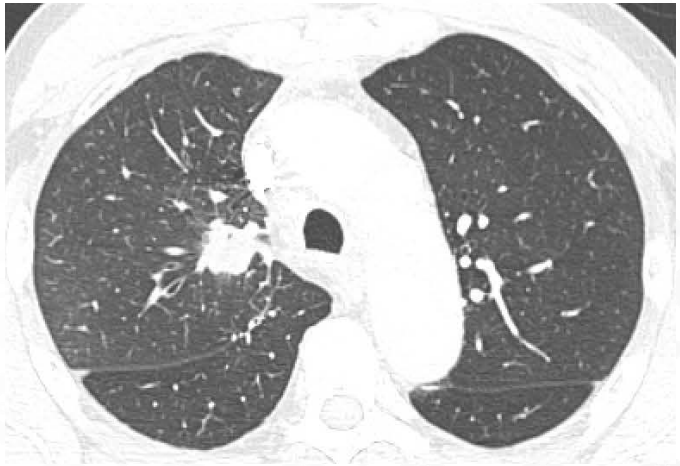


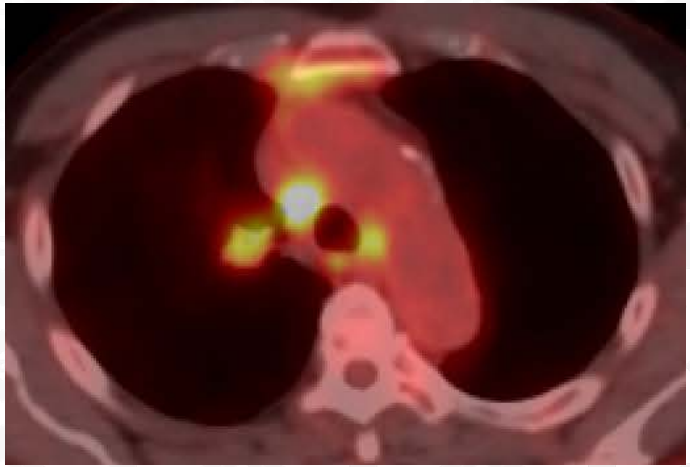
Figure 2

Median time to onset immune-related adverse events for different toxicities with anti-PD-1 (nivolumab) in NSCLC patients. Circles represent medians; bars signify ranges. Inf. reaction, infusion reaction or hypersensitivity; NSCLC, non-small cell lung cancer.

Case 2

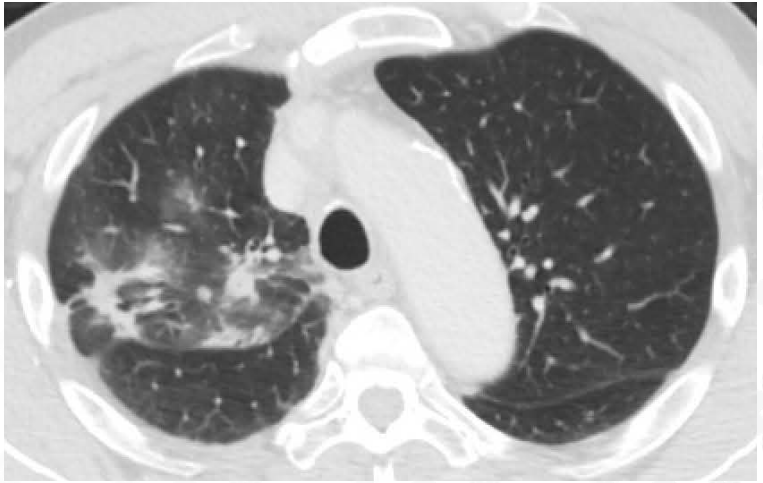
FD is a 52 year old man, diagnosed with Stage IV NSCLC in 2014 (primary site in right upper lobe, extensive mediastinal adenopathy, single metastatic focus in the right adrenal gland). The tumor was an adenocarcinoma, *EGFR* mutation-negative, ALK-rearrangement-negative, tumor PD-L1 expression > 50%. He was entered into a clinical trial comparing chemotherapy to pembrolizumab in late 2014.

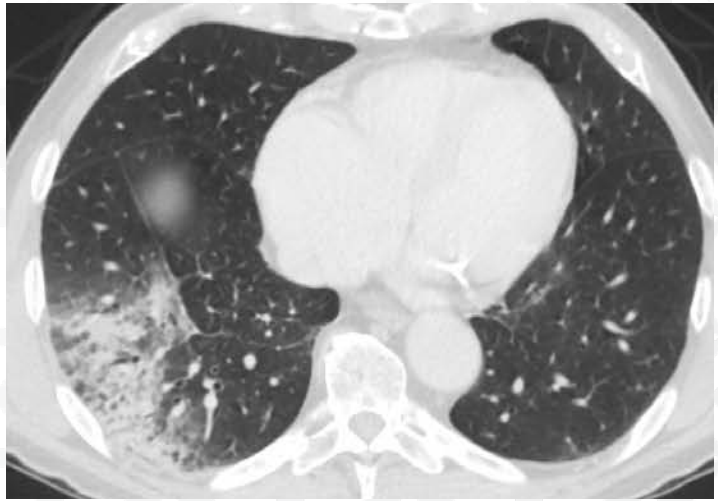




Case 2

- 6 cycles into treatment, he had resolution of the adrenal metastasis and mediastinal adenopathy, and a decrease in size of the primary tumor. However, after the 8th cycle, he presented with new onset cough and exertional dyspnea, and oxygen desaturation with ambulation. He had no fever, chest discomfort or other symptoms.
- CT demonstrated that the RUL lesion had not changed, but he had new infiltrates in the right upper and lower lobes.
- Concern was raised about the possibility of pembrolizumab-associated pulmonary toxicity





Approach to the evaluation and management of suspected immunotherapy-related pulmonary toxicity

1. Assess severity of initial clinical/radiographic presentation
    - Grade 1: Asymptomatic with radiographic changes
    - Grade 2: Symptomatic but no limitation of usual activity
    - Grade 3: Symptomatic, with oxygen requirement or limitation of activity
    - Grade 4: Severe or life-threatening
2. Exclude alternative diagnoses
    - Exclude pulmonary infection
    - Exclude other pulmonary complications (PE, hemorrhage, etc.)

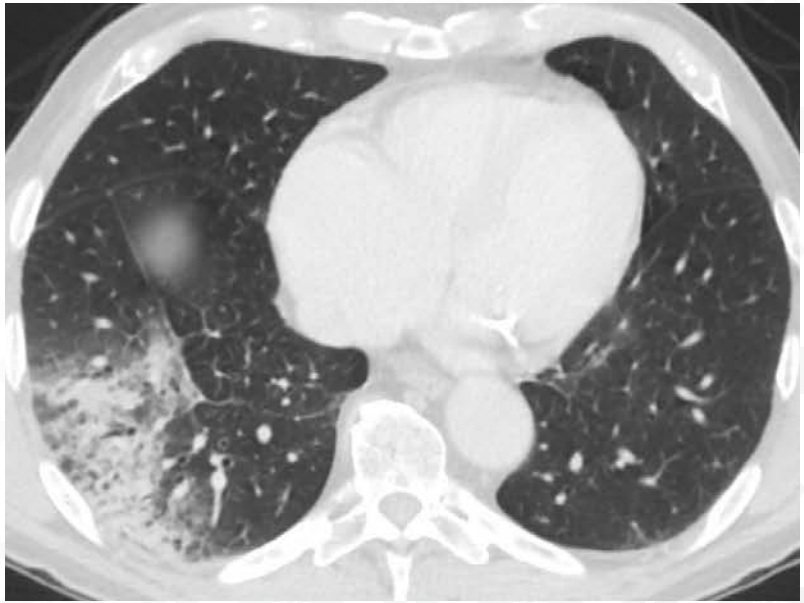
Approach to the evaluation and management of suspected immunotherapy-related pulmonary toxicity

3. Approach initial management based on grade of toxicity
    - Grade 1: Continue therapy with close observation, escalate to treatment for symptoms or radiographic worsening
    - Grade 2: Hold therapy, consider bronchoscopy, institute oral prednisone 1 mg/kg/day if no improvement
    - Grade 3-4: Discontinue therapy, bronchoscopy, institute oral prednisone 1-2 mg/kg/day or IV corticosteroids at equivalent dose
4. Assess response to management
    - Taper steroids over 4-6 weeks as directed by response
    - For mild cases, can consider rechallenge with immunotherapy
    - If no response, consider surgical lung biopsy to clarify process

Case 2

- FD declined bronchoscopy. CT-guided core needle biopsy revealed organizing pneumonia. Cultures from the biopsy were negative.
- Contrast CT – negative for pulmonary embolism, no evidence for mediastinal adenopathy
- Assessment: Pembrolizumab-associated organizing pneumonia, Grade 3 IRAE

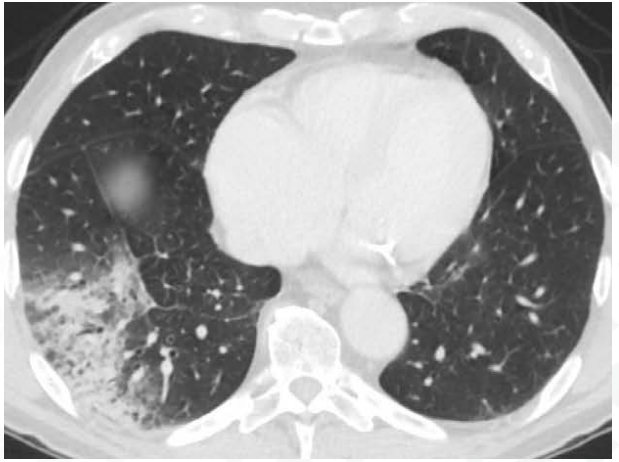
November 2016



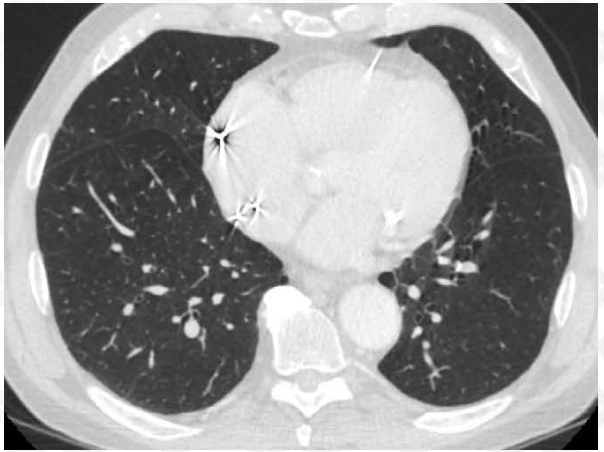
Case 2

- FD was started on prednisone at 1 mg/kg/day in late 2016
- By February 2017, the right upper lobe infiltrate had substantially improved and the right lower lobe infiltrate had resolved. Prednisone was tapered off.
- FD has not received any further cancer therapy. He remains clinically without evidence of recurrence of cancer.

November 2016



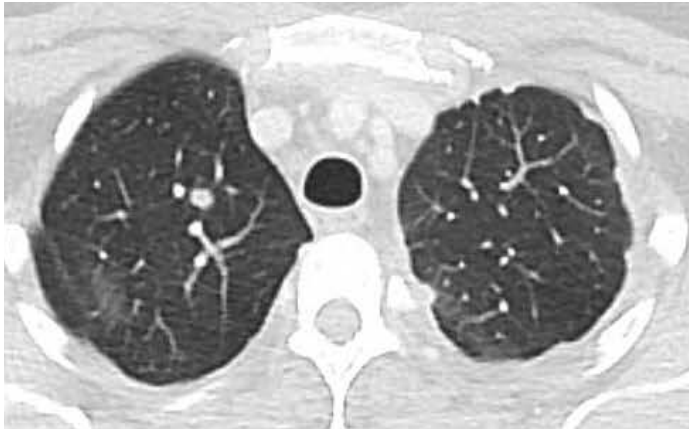
February 2017

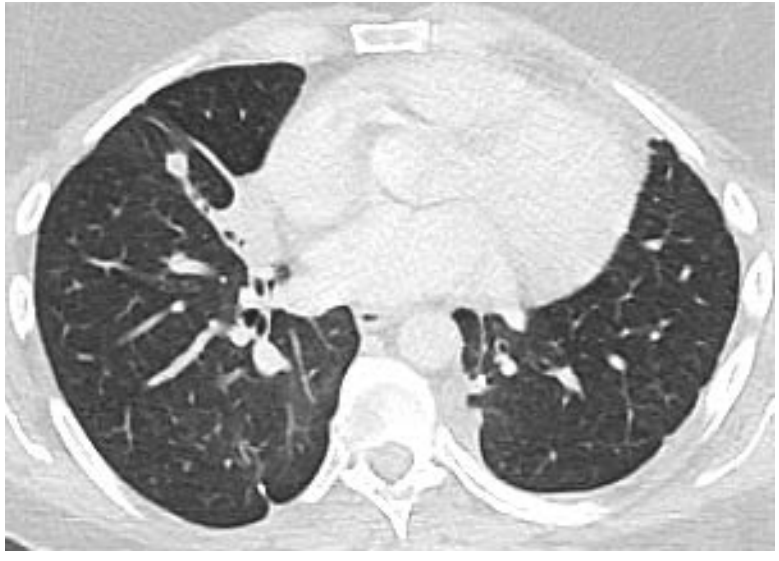


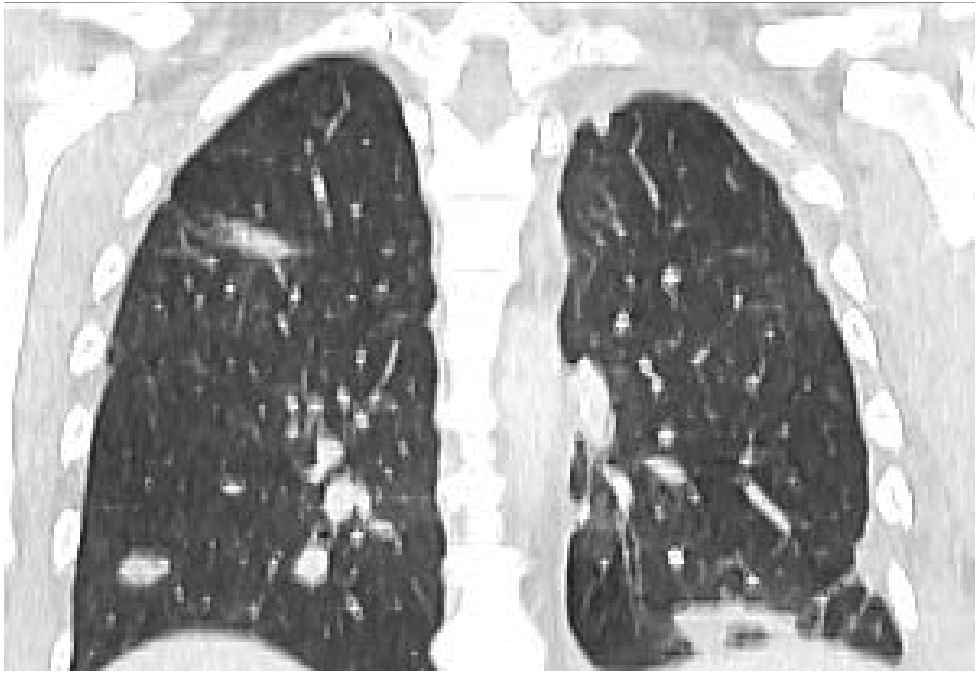
Case 3

(courtesy Scott Gettinger MD and Jennifer Possick MD, Yale Thoracic Oncology Program)

- A 60 year old woman, 30 pack-year former smoker, has a history of LLLobectomy and adjuvant vinorelbine and docetaxel in 2010 for T2aN1M0 adenocarcinoma.
- She was disease-free until 2014, when she was noted to have a growing 8 mm RLL nodule. This was felt clinically to be a second primary; the patient underwent RLL wedge resection that confirmed adenocarcinoma.
- In 2015 she developed several more small, bilateral pulmonary nodules. CT-guided needle biopsy of a right middle lobe 6 mm nodule again demonstrated adenocarcinoma. At this time it was felt she had Stage IV disease with multiple pulmonary metastases. She was treated with a platinum based chemotherapy doublet, which she tolerated poorly. Follow up chest CT demonstrated that the nodules were again increasing in size and were more numerous.







Question 3

Case 3

The patient's performance status is 0-1. Molecular testing of the most recently resected adenocarcinoma shows no targetable mutations. Which of the following would you recommend for treatment?

A. Pemetrexed
B. Erlotinib
C. Immune checkpoint inhibitor
D. SBRT to the largest nodules

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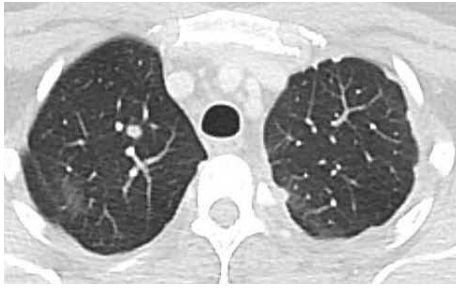
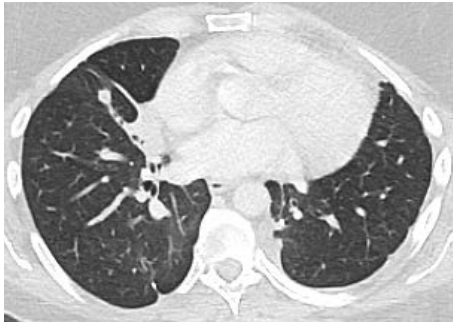
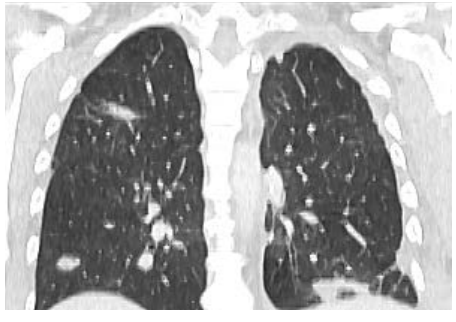
The patient was started on Nivolumab on an every 3 week schedule. 6 weeks into treatment, chest CT demonstrated that the nodules were increasing in size, and some demonstrated adjacent ground glass infiltrate.

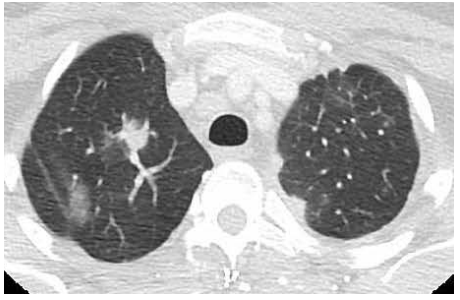
Pre Anti-PD1

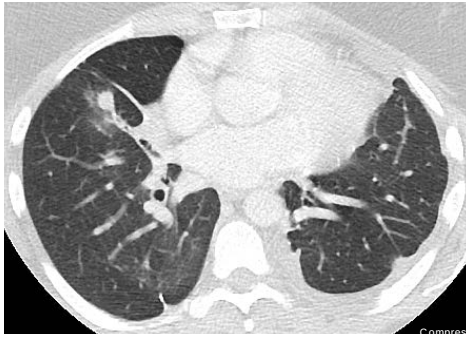


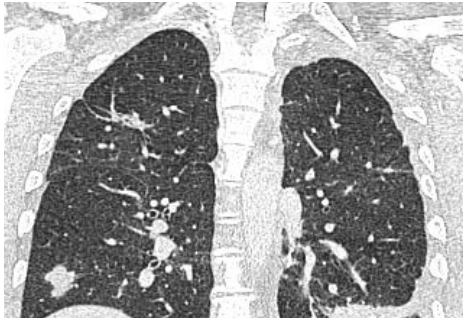




6 weeks into treatment





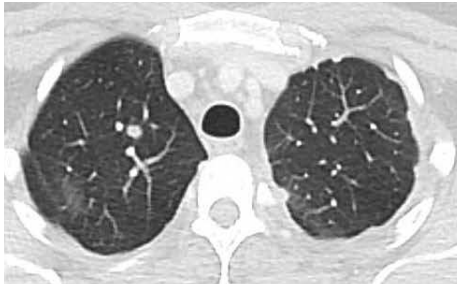
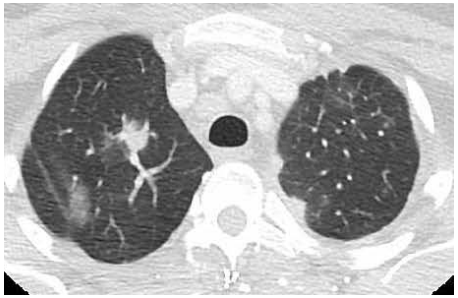
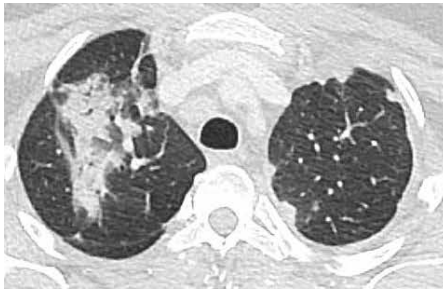
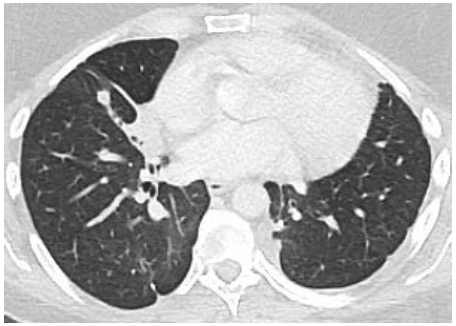
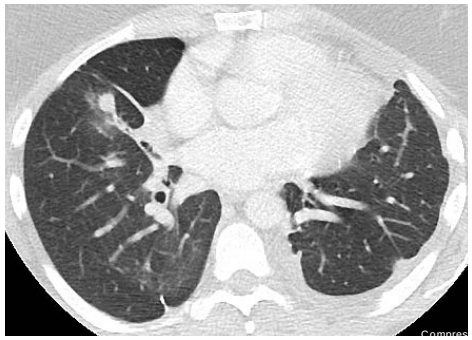
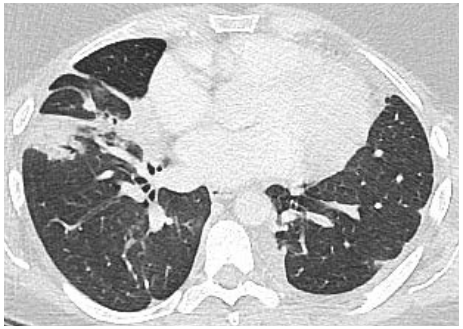
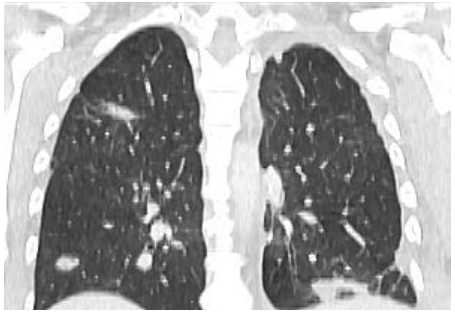
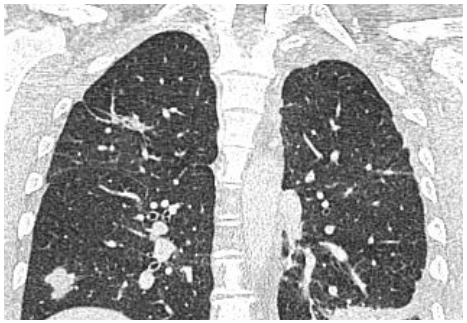
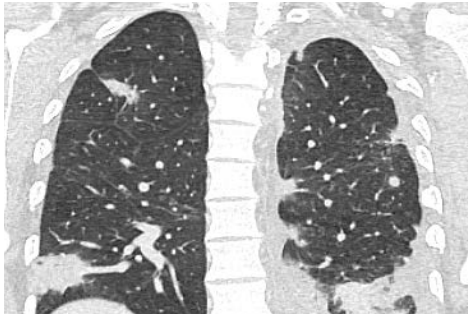


3 months into treatment, the patient was generally feeling well, with a mild non-productive cough and occasional low grade fever.

Pre Anti-PD1

6 weeks into treatment

12 weeks into treatment

Question 4

Case 3

What do you feel is the most likely explanation for this patient's radiographic progression?

A. Progression of malignancy
B. Infectious process
C. Pseudo-progression related to Nivolumab
D. Hypersensitivity reaction to Nivolumab

Question 4

Case 3

What do you feel is the most likely explanation for this patient's radiographic progression?

A. Progression of malignancy
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C. Pseudo-progression related to Nivolumab
D. Hypersensitivity reaction to Nivolumab

Question 5

Case 2

What would you recommend to this patient as the next step?

A. Bronchoscopy
B. Surgical lung biopsy
C. Prednisone 60 mg/day and continue Nivolumab
D. Discontinue Nivolumab

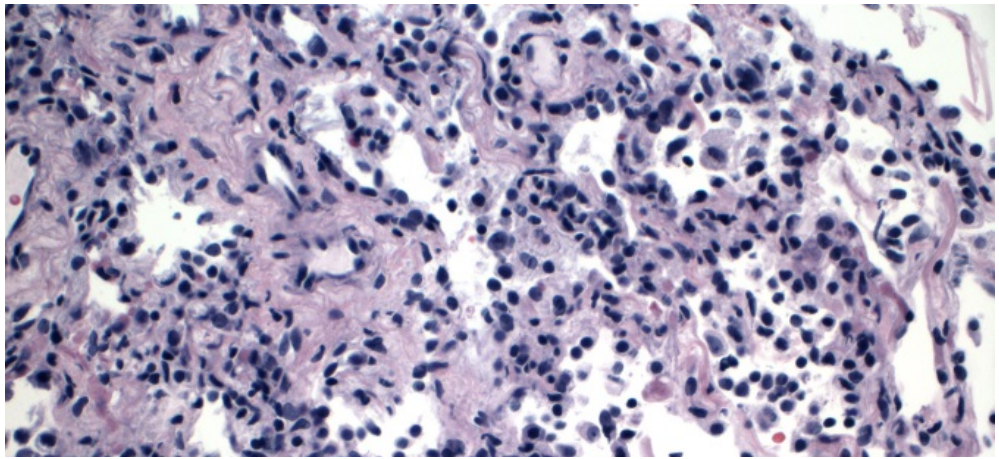
Question 5

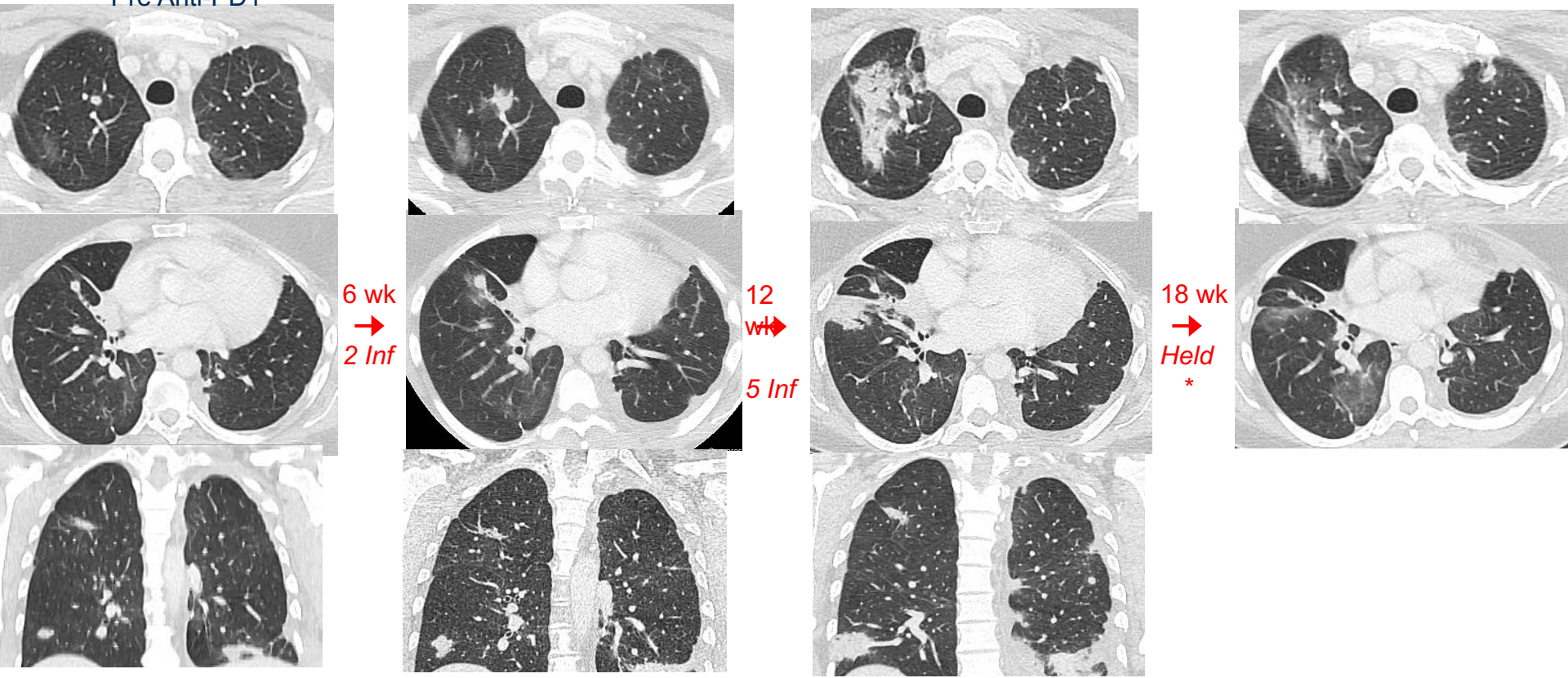
Case 2

What would you recommend to this patient as the next step?

A. Bronchoscopy
B. Surgical lung biopsy
C. Prednisone 60 mg/day and continue Nivolumab
D. Discontinue Nivolumab

- Bronchoscopy was performed, with BAL and transbronchial biopsies
- Culture of BAL was negative
- Transbronchial biopsies:
  - No malignant cells
  - Lymphocytic infiltrate with foamy macrophages
  - No granuloma, eosinophils, organizing pneumonia, or type II pneumocyte hyperplasia





The patient had no further treatment. Nivolumab was discontinued She remained without evidence of active disease 1 year after Nivolumab was discontinued.

Take home points – Pulmonary toxicity related to Immunotherapy

- Approximately 4% of patients with NSCLC treated with immunotherapy develop pulmonary toxicity in the setting of clinical trials
  - This may under-estimate the number of patients with NSCLC treated with immunotherapy who develop pulmonary toxicity in general practice
  - Anti-PD1 agents have an increased likelihood of toxicity, compared to anti-PDL1 agents
- Assessment of the grade of toxicity is important, and will guide treatment
  - Radiographic changes may reflect treatment response, not toxicity. The determination of response vs. toxicity will inform decision making
- Treatment of IRAEs with corticosteroids does not appear to affect treatment response

Pulmonary Complications of Lung Cancer Treatment

- 10% of all cancer patients develop pulmonary toxicity related to treatment
- Patients with lung cancer appear to be at increased risk for pulmonary complications of treatment
- Resource for drug toxicities: Pneumotox.com
- Targeted therapy tyrosine kinase inhibitors
  - 7-8% of patients develop treatment-limiting toxicities (skin, GI, lungs)
  - Risk factors: Asian descent (6%), pre-existing ILD, older age, male gender, smoking, prior thoracic irradiation
- Immunotherapy
  - 4% of patients develop treatment-related pulmonary toxicity
- Threshold for diagnostic evaluation, including invasive procedures, should be low