Cancer Day For Primary Care
Immune checkpoint inhibitors
Pulmonary Panel

Medical Oncology: Dr. David Dawe

Respirology: Dr. Jacquelyn Dirks

Radiology: Dr. China-Li Hillman

10 May 2019

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Presenter Disclosure

- **Faculty / Speaker's name: David Dawe**

- **Relationships with commercial interests:**
  - **Grants/Research Support: CCMF, MMSF, CIHR**
  - **Speakers Bureau/Honoraria: Merck, AstraZeneca, Boehringer-Ingelheim**
  - **Consulting Fees: N/A**
  - **Other: Employed by CCMB, U of M, WRHA**

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Mitigating Potential Bias

- Used accepted international guidelines to guide recommendations. Evidence exists for all assertions made.
- Used generic drug names
- Indicated whenever a treatment indication is non-formulary

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Presenter Disclosure

- **Faculty / Speaker's name:** Dr. China-Li Hillman

- **Relationships with commercial interests:**
  - **Grants/Research Support: N/A**
  - **Speakers Bureau/Honoraria: N/A**
  - **Consulting Fees: N/A**
  - **Other: N/A**

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Presenter Disclosure

- **Faculty / Speaker's name:** Dr. Jacquelyn Dirks

- **Relationships with commercial interests:**
  - **Grants/Research Support:** N/A
  - **Speakers Bureau/Honoraria: GSK speaker fee for un-related product**
  - **Consulting Fees:** N/A
  - **Other:** N/A

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Mitigating Potential Bias

- Speaker fee is for unrelated product.
- Will not be making any treatment recommendations.

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Toxicity of Immunotherapy – Pulmonary immune-related adverse events

David Dawe, MD MSc FRCPC

May 10, 2019

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Learning Objectives

1. Provide the framework for identifying immunotherapy-induced pneumonitis
2. Describe the typical management of immunotherapy-induced pneumonitis

Our Case

- 57 yo female initially diagnosed with stage III non-small cell lung cancer (NSCLC) – adenocarcinoma – treated with chemoradiotherapy.
- Chemo included cisplatin-etoposide and RT was 66 Gy to the right upper lobe and mediastinum.
- On completion of chemoRT, CT showed new bilateral adrenal mets
- Started on 2nd line nivolumab

Our Case

- Completed 12 cycles of treatment with partial response of the adrenal metastases and ongoing control of the lung primary.
- Today, complains of increasing dry cough and shortness of breath on exertion.
- Starting to have more trouble walking up 1 flight of stairs
- Denies fever/chills, leg edema/pain, sick contacts, or travel.
- On exam, a couple of crackles on the right side - upper

Question 1

What is the most likely diagnosis at this point?

A. Radiation pneumonitis
B. Community acquired pneumonia
C. Cancer progression
D. Drug-induced pneumonitis
E. Pulmonary embolus

Sli.do

Question 2

What investigation has the best chance of clarifying your differential?

A. Blood work – CBC, biochemistry, CRP
B. CXR
C. Pulmonary function tests
D. CT Chest

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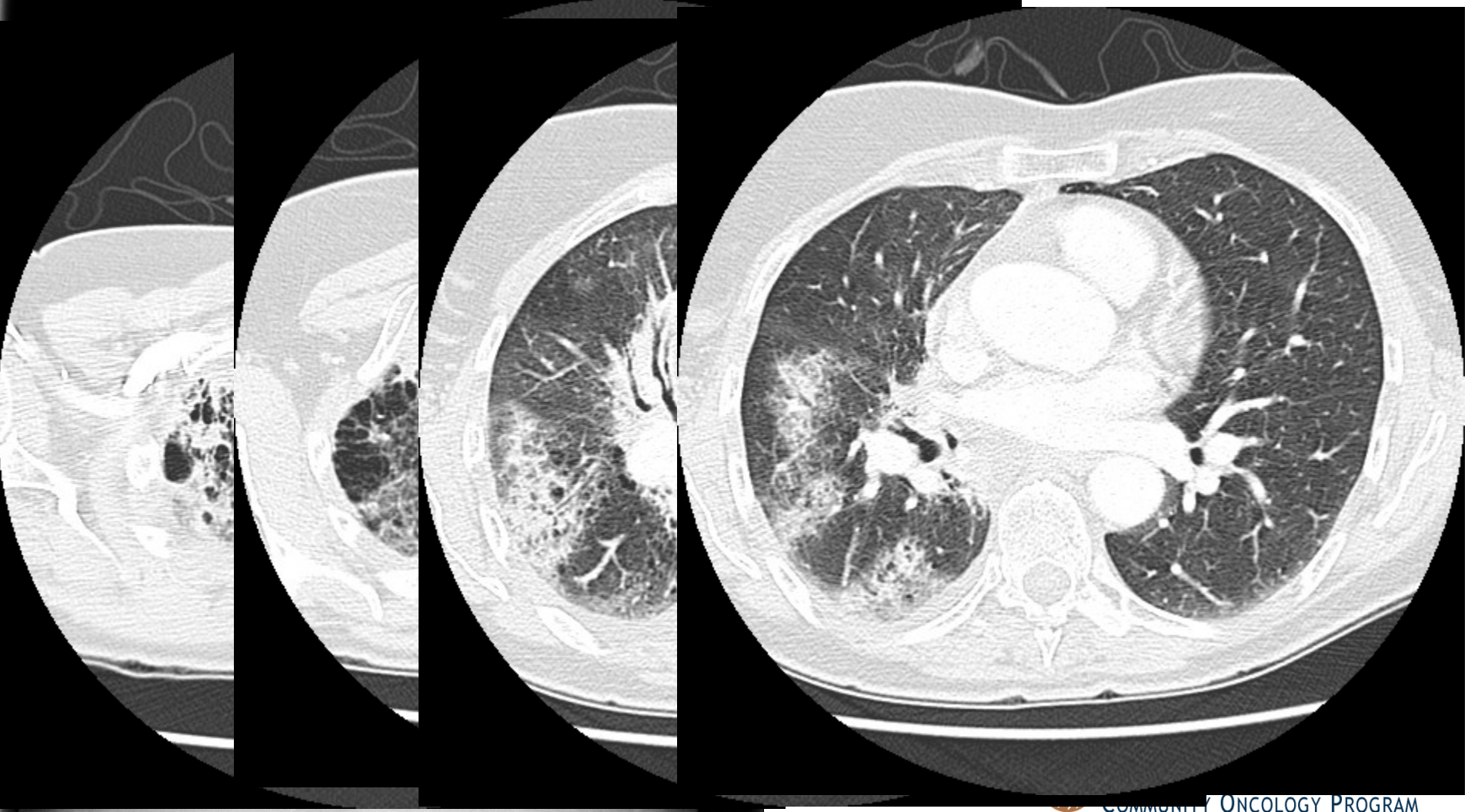

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Question 3

Whom should you call next?

A. Medical Oncologist
B. Respirologist
C. Internal Medicine
D. Radiologist

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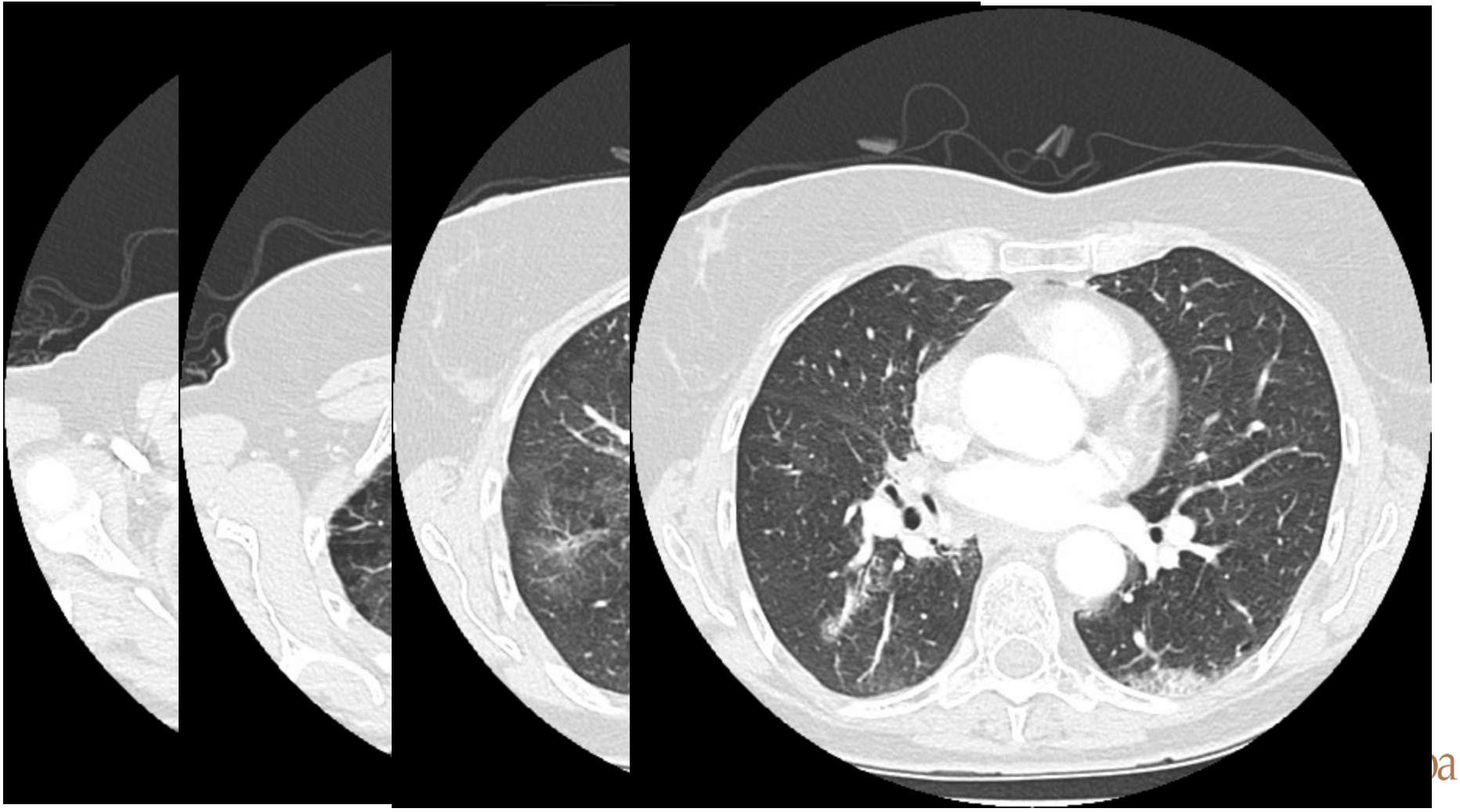
Question 4

What is the initial management?

A. Azithromycin
B. Prednisone 50 mg x 5 d + Azithromycin
C. Dalteparin 200 iu/kg x 1 month then 150 iu/kg
D. Prednisone 0.5-1 mg/kg and taper over 4-6 weeks
E. Infliximab



Why does this matter?

- As you heard earlier today:
  - IO therapies are becoming increasingly important in cancer treatment
  - Pulmonary complications are among the most common serious irAEs
  - Lung cancer is the most common malignancy currently treated with IO and carries a higher risk of pneumonitis

Who's eligible for IO?

- Patients with melanoma, lung, H&N, MSI high cancers, kidney, bladder, and Merkel cell (at least)
- Recent study estimates that 43.63% of cancer patients are eligible for immune checkpoint inhibitors based on FDA indications
- In Manitoba, that would equate to about 2800 patients per year if correct

Haslam A. JAMA Netw Open. 2019; 2(5):e192535
CCMB Epidemiology Report 2015

What puts you at risk of pneumonitis?

- PD-1/PD-L1 vs CTLA-4 inhibitors
- Combination of PD-1/PD-L1 with CTLA-4 inhibitor
- Lung Cancer (vs Melanoma)
- Pre-existing interstitial lung disease
- Pembrolizumab? – network meta-analysis
- No obvious impact of smoking, thoracic RT, dose

Haanen JBAG. Ann Oncol 2017 – ESMO Guideline
Brahmer JR. J Clin Oncol. 2018 – ASCO Guideline
Xu C. BMJ 2018
Cho JY. Lung Cancer. 2018

Symptoms and Incidence

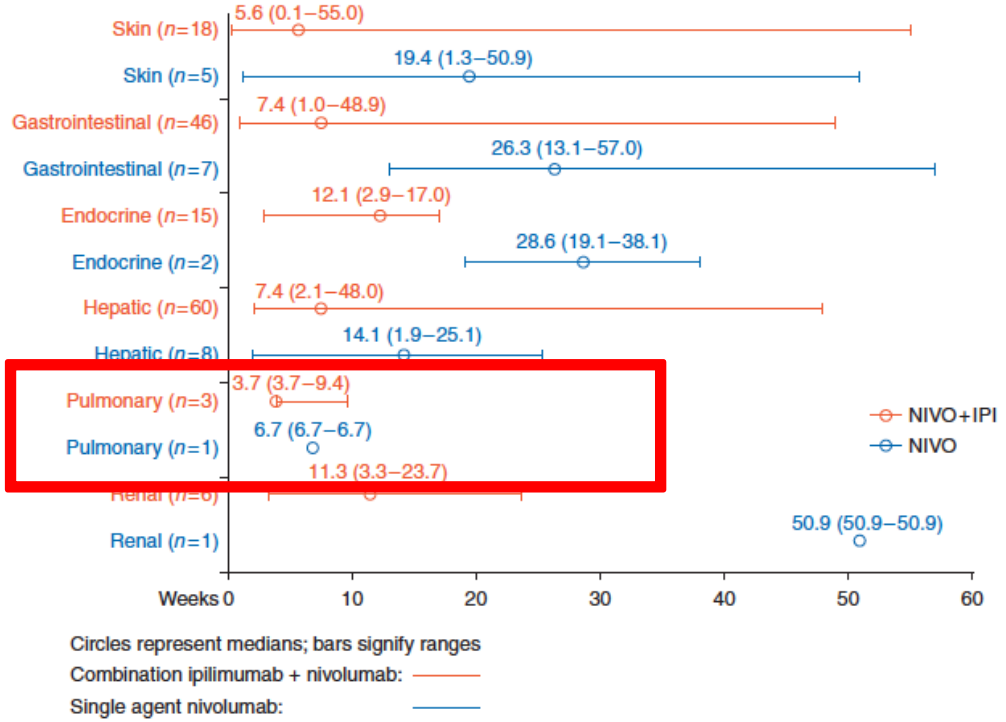
- Symptoms
  - New or worsening cough (usually dry)
  - New or worsening SOB
  - Fever, chest pain, hypoxemia
  - No symptoms are pathognomonic for pneumonitis
- Incidence
  - For PD-1/PD-L1 alone – ranges from 0-10%, recent meta-analysis estimates 2.7%
  - For lung cancer – reported frequency of 1.4-13.2%, grade 3-4 1.0-4.1%

Brahmer JR. J Clin Oncol. 2018 – ASCO Guideline
Cho JY. Lung Cancer. 2018

Onset

Onset reported as
2-24 months

Median 3 months



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Radiology

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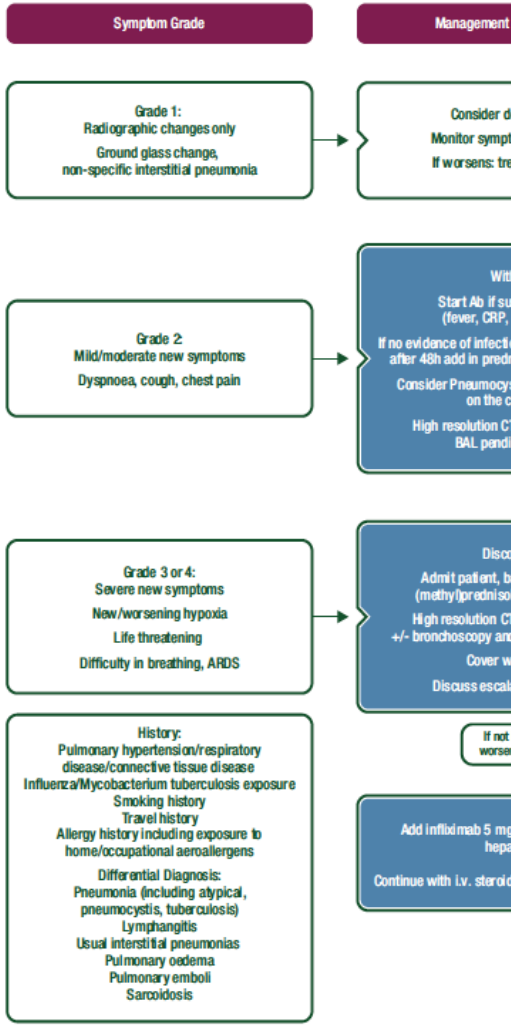

Figure 9. ICPi-related toxicity: management of pneumonitis.

Table 3. Management of Lung irAEs in Patients Treated With ICPis

3.0 Lung Toxicities

3.1 Pneumonitis

Definition: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging)
No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis

Diagnostic work-up
Should include the following: CXR, CT, pulse oximetry
For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity

Grading	Management
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	Hold ICPi with radiographic evidence of pneumonitis progression May offer one repeat CT in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 Monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or >50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy Patients should be hospitalized for further management

Additional considerations
GI and *Pneumocystis* prophylaxis with PPI and Bactrim may be offered to patients on prolonged corticosteroid use (> 12 weeks), according to institutional guidelines[34-37]
Consider calcium and vitamin D supplementation with prolonged corticosteroid use
The role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear, and physicians should proceed according to institutional guidelines[33]
Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy

All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.

Abbreviations: ADL, activities of daily living; BAL, bronchoalveolar lavage; CT, computed tomography; CXR, chest x-ray; DLCO, diffusing capacity of lung for carbon monoxide; G, grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; PPI, proton pump inhibitor.

Work-Up

ASCO

Recommendation 3.1a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- Chest x-ray (CXR), CT, pulse oximetry
- For grade 2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, and urine culture and sensitivity

ESMO

- All patients presenting with pulmonary symptoms, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by CT.
- In general, lung biopsy is not required for subsequent patient management.
- Bronchoscopy with bronchoalveolar lavage will support identification of infections

Haanen JBAG. Ann Oncol 2017 – ESMO Guideline
Brahmer JR. J Clin Oncol. 2018 – ASCO Guideline

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Grading

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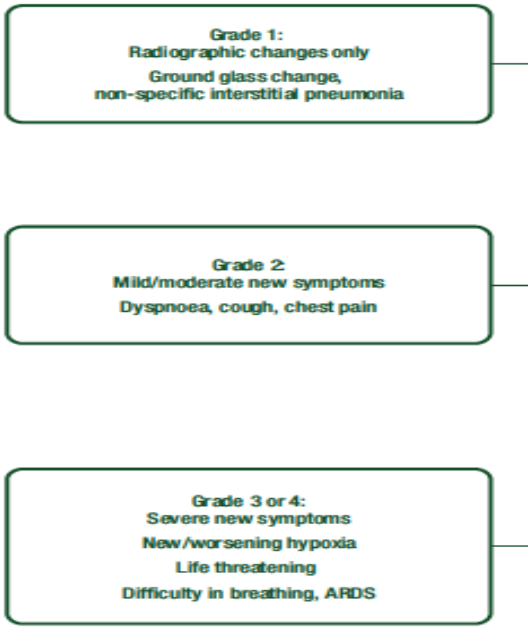
Grading
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL
G3: Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)

ESMO



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Work-Up

- Grade 2+
  - Consider bronchoscopy if diagnosis questionable
- Grade 3+
  - Consider Respirology and Infectious Diseases consults

Brahmer JR. J Clin Oncol. 2018 – ASCO Guideline

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Respirology

Dr. Jacquelyn Dirks

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Management

- Grade 1
  - Hold ICI. If no improvement in 1 week, treat as grade 2
- Grade 2
  - Hold ICI. Prednisone 1 mg/kg/day, taper over 4-6 weeks. If no improvement in 48-72 hours, treat as grade 3.
- Grade 3/4
  - Permanently stop ICI. Empirical antibiotics. Methylprednisolone 2-4 mg/kg/day.
  - If no improvement in 48 hours, add infliximab/mycophenolate/cyclophosphamide/IVIG

Brahmer JR. J Clin Oncol. 2018 – ASCO Guideline

After recovery?

Once improved to baseline:
Grade 2: wean oral steroids over at least 6 weeks, titrate to symptoms

Grade 3/4: wean steroids over at least 8 weeks

Steroid considerations:
Calcium & Vitamin D supplementation as per local guidelines

Pneumocystis prophylaxis - cotrimoxazole 480 mg bd M/W/F or inhaled pentamidine if cotrim allergy

Haanen JBAG. Ann Oncol 2017 – ESMO Guideline

References

- Included throughout the presentation.
- Main references:
  - Haanen JBAG. Ann Oncol 2017 – ESMO Guideline
  - Brahmer JR. J Clin Oncol. 2018 – ASCO Guideline

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