THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Evaluation and Management of Suspected Immune-Mediated Pneumonitis

Disclaimer: *This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.*

GENERAL EVALUATION

PRESENTATION

Patient presents with new onset symptoms or new infiltrates 1 week after immune checkpoint inhibitor (ICI)[1] initiation and up to 6 months after discontinuation[2]

Is there shortness of breath, cough, chest pain, fever, or increased oxygen requirements[3]?

- Yes: Moderate/severe pneumonitis (Grade 2 and above[3])
- No: Imaging[5,6] findings only → For assessment and treatment of Grade 1 pneumonitis, see Page 2, Box A

ASSESSMENT

Hold ICI and order the following:

- CT chest without contrast (if not already performed)
- Consider non-invasive infectious workup
  - Nasal swab for potential viral pathogens
  - Sputum cultures, blood cultures, urine antigen (pneumococcus and legionella)
- Urgent Pulmonary consult and evaluation for bronchoscopy with BAL
  - Absolute cell count
  - CD4 and CD8 cell counts
  - Aerobic and anaerobic cultures
  - Respiratory viral panel PCR
  - *Pneumocystis jiroveci* PCR
  - CMV PCR
  - Fungal cultures
- Screening tests[4]

TREATMENT

Alternate cause(s) of pulmonary process found?

- Yes:
  - For pneumonia, consult Infectious Diseases
  - For disease progression, defer to oncology service
- No: For further assessment/ management, see Page 2

BAL = bronchioalveolar lavage
CMV = cytomegalovirus

[1] PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab, dostarlimab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), CTLA-4 inhibitor (ipilimumab, tremelimumab)
[2] On rare occasions, pulmonary toxicities may develop beyond the 6-month window
[3] Refer to Appendix A for Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0
[4] Includes HIV, T-spot tuberculosis, and hepatitis B and C. Consider screening for fungal infections, if indicated. Preemptive in case of refractory pneumonitis necessitating infliximab therapy.
[5] CT chest (preferred) or chest x-ray
[6] Infiltrates are confined to one lobe or < 25% of the entire lung. Radiological criteria for pneumonitis grading are based on National Comprehensive Cancer Network (NCCN) expert guidelines and require validation in independent cohorts.

Department of Clinical Effectiveness V1
Approved by the Executive Committee of the Medical Staff on 10/17/2023

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

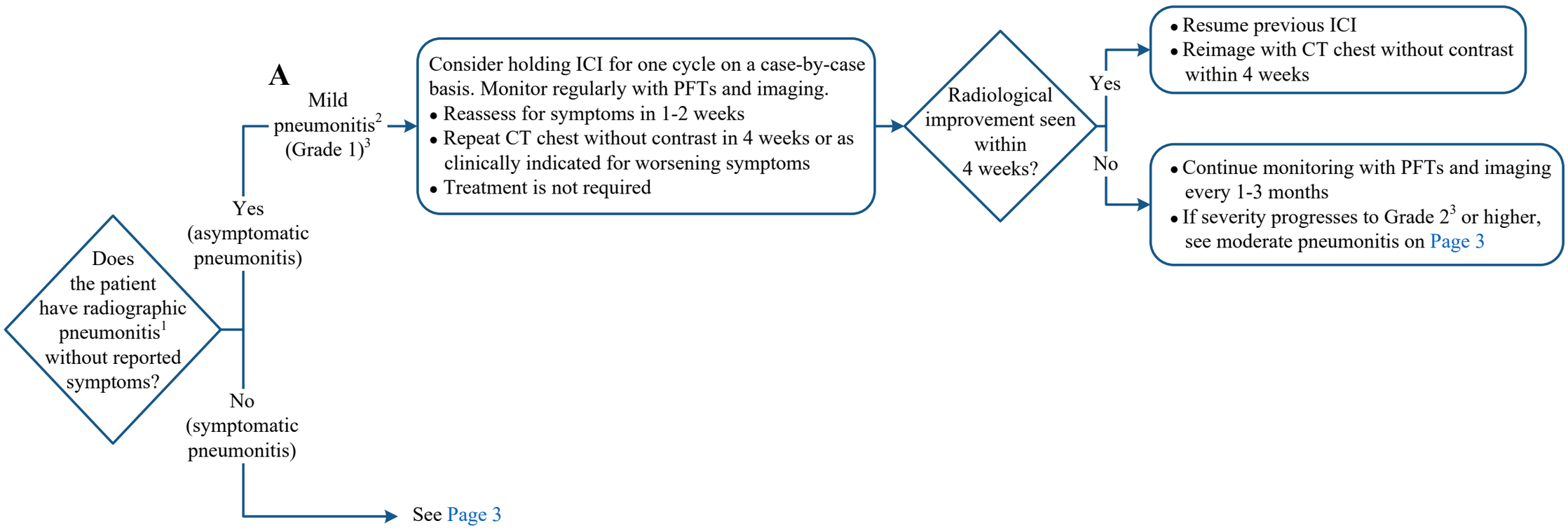
Evaluation and Management of Suspected Immune-Mediated Pneumonitis

PNEUMONITIS MANAGMENT

PRESENTATION

ASSESSMENT/TREATMENT

TREATMENT



PFT = pulmonary function tests

[1] Radiographic patterns include organizing pneumonia, interstitial pneumonitis, or other non-specific patterns of lung injury
[2] Confined to one lobe of the lung or < 25% of lung parenchyma. Radiological criteria for pneumonitis grading are based on NCCN expert guidelines and require validation in independent cohorts.
[3] Refer to Appendix A for Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

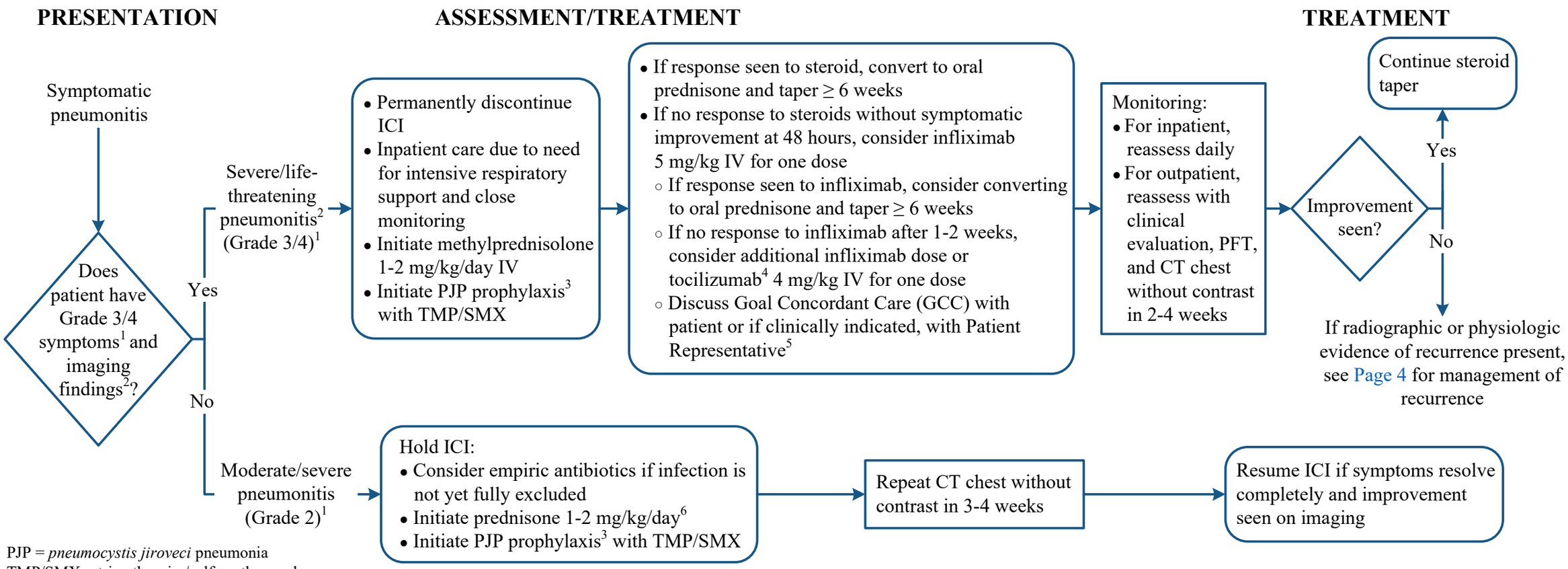
Department of Clinical Effectiveness V1
Approved by the Executive Committee of the Medical Staff on 10/17/2023

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Evaluation and Management of Suspected Immune-Mediated Pneumonitis

Disclaimer: *This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.*

PNEUMONITIS MANAGMENT



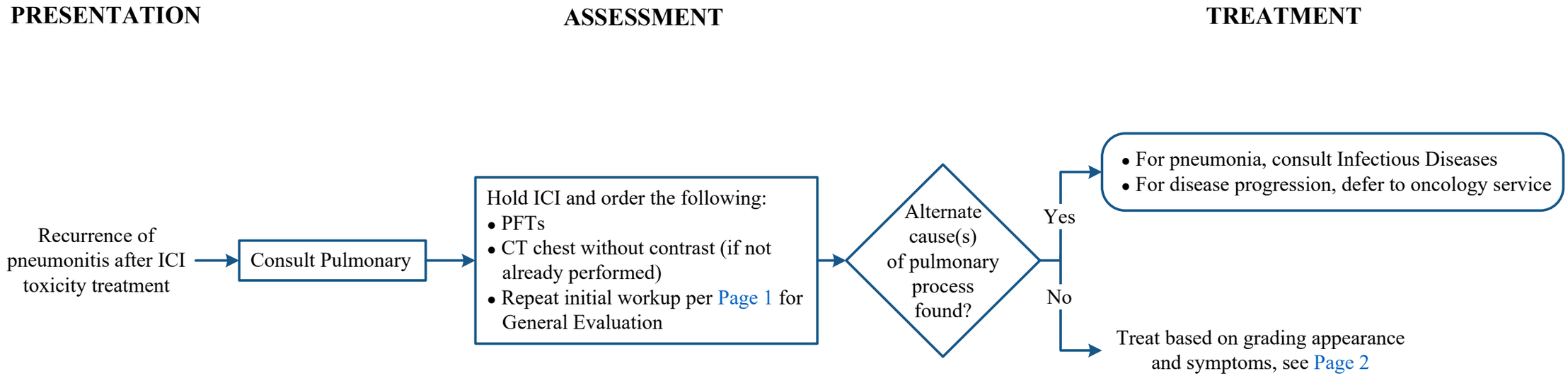
PJP = *pneumocystis jiroveci* pneumonia
TMP/SMX = trimethoprim/sulfamethoxazole

[1] Refer to Appendix A for Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0
[2] Involvement of all lung lobes or > 50% of lung parenchyma
[3] Continue PJP prophylaxis for 2 weeks after completion of steroids
[4] Use falls outside MDACC formulary restriction criteria for tocilizumab; formulary management review required prior to use
[5] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).
[6] Treat until symptom improvement to Grade ≤ 1 then taper over 4-6 weeks

Department of Clinical Effectiveness V1
Approved by the Executive Committee of the Medical Staff on 10/17/2023

Evaluation and Management of Suspected Immune-Mediated Pneumonitis

RECURRENCE MANAGMENT



THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Evaluation and Management of Suspected Immune-Mediated Pneumonitis

APPENDIX A: Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

Respiratory, Thoracic and Mediastinal Disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (*e.g.,* tracheostomy or intubation)	Death

ADL = activities of daily living

Evaluation and Management of Suspected Immune-Mediated Pneumonitis

SUGGESTED READINGS

Abdel-Wahab, N., Diab, A., Yu, R. K., Futreal, A., Criswell, L. A., Tayar, J. H., . . . Suarez-Almazor, M. E. (2021). Genetic determinants of immune-related adverse events in patients with melanoma receiving immune checkpoint inhibitors. *Cancer Immunology, Immunotherapy, 70*(7), 1939-1949. https://doi.org/10.1007/s00262-020-02797-0

Altan, M., Zhong, L., Shannon, V. R., & Sheshadri, A. (2021). Pulmonary toxicities of immunotherapy. In A. Naing, & J. Hajjar (Eds.), *Immunotherapy. Advances in Experimental Medicine and Biology* (vol. 1342, pp. 357-375). Springer International Publishing AG. https://doi.org/10.1007/978-3-030-79308-1_14

Choy, M. C., Seah, D., Faleck, D. M., Shah, S. C., Chao, C.-Y., An, Y.-K., . . . De Cruz, P. P. (2019). Systematic review and meta-analysis: Optimal salvage therapy in acute severe ulcerative colitis. *Inflammatory Bowel Diseases, 25*(7), 1169-1186. https://doi.org/10.1093/ibd/izy383

Colen, R. R., Fujii, T., Bilen, M. A., Kotrotsou, A., Abrol, S., Hess, K. R., . . . Naing, A. (2018). Radiomics to predict immunotherapy-induced pneumonitis: Proof of concept. *Investigational New Drugs, 36*(4), 601-607. https://doi.org/10.1007/s10637-017-0524-2

Fujii, T., Colen, R. R., Bilen, M. A., Hess, K. R., Hajjar, J., Suarez-Almazor, M. E., . . . Naing, A. (2018). Incidence of immune-related adverse events and its association with treatment outcomes: The MD Anderson Cancer Center experience. *Investigational New Drugs, 36*(4), 638-646. https://doi.org/10.1007/s10637-017-0534-0

Harris, J. P., Postow, M. A., & Faleck, D. M. (2022). Efficacy of infliximab dose escalation in patients with refractory immunotherapy-related colitis: A case series. *The Oncologist, 27*(4), e350-e352. https://doi.org/10.1093/oncolo/oyac019

Jain, A., Shannon, V. R., & Sheshadri, A. (2018). Immune-related adverse events: Pneumonitis. In A. Naing, & J. Hajjar (Eds.), *Immunotherapy. Advances in Experimental Medicine and Biology, 995*, 131-149. Springer International Publishing AG. https://doi.org/10.1007/978-3-030-02505-2_6

Kim, S. T., Sheshadri, A., Shannon, V., Kontoyiannis, D. P., Kantarjian, H., Garcia-Manero, G., . . . Daver, N. (2021). Distinct immunophenotypes of T cells in bronchoalveolar lavage fluid from leukemia patients with immune checkpoint inhibitors-related pulmonary complications. *Frontiers in Immunology, 11*, 590494. https://doi.org/10.3389/fimmu.2020.590494

Lai, K. A., Sheshadri, A., Adrianza, A. M., Etchegaray, M., Balachandran, D. D., Bashoura, L., . . . Faiz, S. A. (2020). Role of infliximab in immune checkpoint inhibitor-induced pneumonitis. *Journal of Immunotherapy and Precision Oncology, 3*(4), 172-174. https://doi.org/10.36401/JIPO-20-22

MD Anderson Institutional Policy #CLN1202 - Advance Care Planning Policy
Advance Care Planning (ACP) Conversation Workflow (ATT1925)

Mendoza, T., Sheshadri, A., Altan, M., Hess, K., George, G., Stephen, B., . . . Naing, A. (2020). Evaluating the psychometric properties of the immunotherapy module of the MD Anderson Symptom Inventory. *Journal for Immunotherapy of Cancer, 8*(2), e000931. https://doi.org/10.1136/jitc-2020-000931

National Comprehensive Cancer Network. (2023). *Management of immunotherapy-related toxicities* (NCCN Guideline Version 2.2023) Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Continued on next page

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Evaluation and Management of Suspected Immune-Mediated Pneumonitis

SUGGESTED READINGS - continued

Schneider, B. J., Naidoo, J., Santomasso, B. D., Lacchetti, C., Adkins, S., Anadkat, M., . . . Bollin, K. (2021). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO Guideline update. *Journal of Clinical Oncology, 39*(36), 4073-4126. https://doi.org/10.1200/JCO.21.01440

Sheshadri, A., Goizueta, A. A., Shannon, V. R., London, D., Garcia-Manero, G., Kantarjian, H. M., . . . Daver, N. G. (2022). Pneumonitis after immune checkpoint inhibitor therapies in patients with acute myeloid leukemia: A retrospective cohort study. *Cancer, 128*(14), 2736-2745. https://doi.org/10.1002/cncr.34229

Shroff, G. S., Strange, C. D., Ahuja, J., Altan, M., Sheshadri, A., Unlu, E., . . . Vlahos, I. (2022). Imaging of immune checkpoint inhibitor immunotherapy for non-small cell lung cancer. *Radiographics, 42*(7), 1956-1974. https://doi.org/10.1148/rg.220108

Xu, T., Wu, L., Gandhi, S., Jing, W., Nguyen, Q.-N., Chen, A., . . . Liao, Z. (2022). Treatment-related pulmonary adverse events induced by chemoradiation and durvalumab affect survival in locally advanced non-small cell lung cancer. *Radiotherapy and Oncology, 176*, 149-156. https://doi.org/10.1016/j.radonc.2022.10.002

Zhong, L., Altan, M., Shannon, V. R. & Sheshadri, A. (2020). Immune-related adverse events: Pneumonitis. In A. Naing, & J. Hajjar (Eds.), *Immunotherapy. Advances in Experimental Medicine and Biology 1244*, 255-269. Springer International Publishing AG. https://doi.org/10.1007/978-3-030-41008-7_13

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Evaluation and Management of Suspected Immune-Mediated Pneumonitis

DEVELOPMENT CREDITS

This practice consensus statement is based on majority opinion of the Immune-mediated Pneumonitis experts at the University of Texas MD Anderson Cancer Center for the patient population. These experts included:

Core Development Team Leads

Ajay Sheshadri, MD (Pulmonary Medicine)

Workgroup Members

Mehmet Altan, MD (Thoracic/Head & Neck Medical Oncology)
Jianjun Gao, MD, PhD (Genitourinary Medical Oncology)
Wendy Garcia, BS♦
Aung Naing, MD (Investigational Cancer Therapeutics)
Amy Pai, PharmD♦
Vickie Shannon, MD (Pulmonary Medicine)

♦ Clinical Effectiveness Development Team