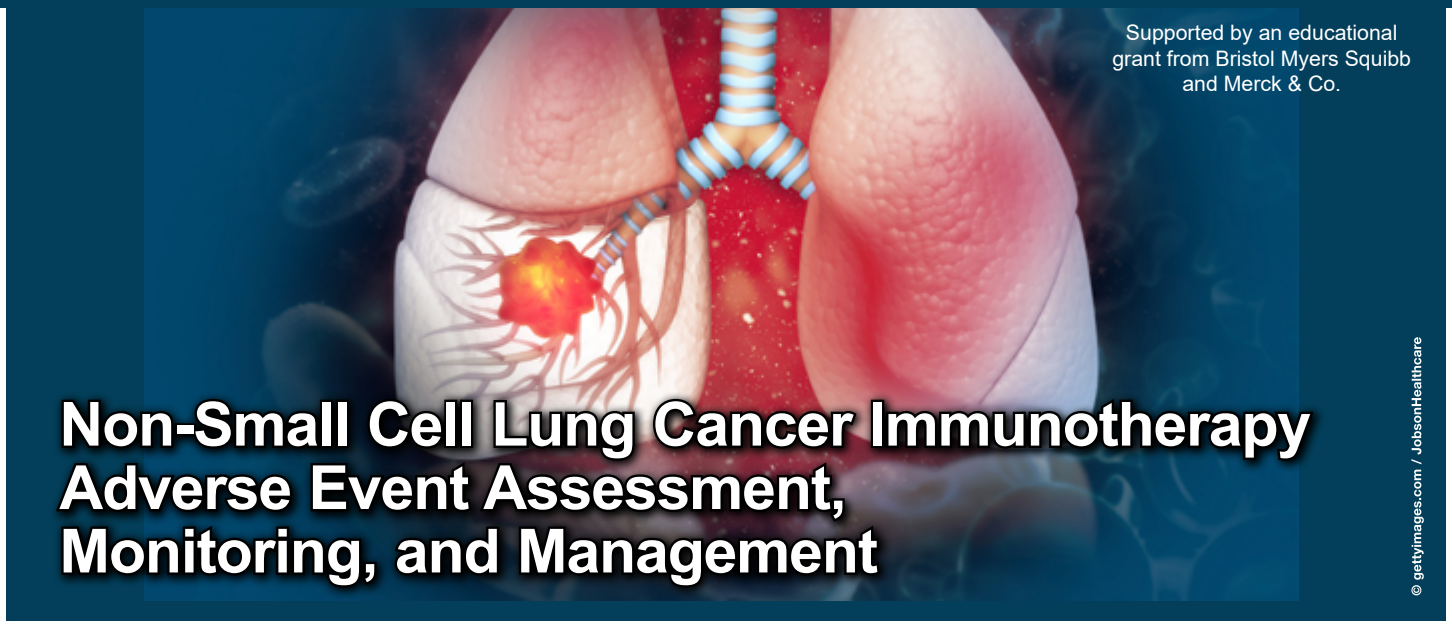

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Non-Small Cell Lung Cancer Immunotherapy Adverse Event Assessment, Monitoring, and Management

The most common organs/tissues/systems adversely affected by immunotherapy treatment for non-small cell lung cancer (NSCLC) include: skin, gut, musculoskeletal, lungs, and endocrine. However, immunotherapy indiscriminately activates the immune system, so providers could and should strongly consider any new or unexplained toxicity finding an immune-related adverse effect (irAE). The best way to assess any new toxicity is to have good patient baseline data.

Pretreatment Assessment and Documentation

Screening	Details/Focus
History	Autoimmune, infectious disease, organ-specific disease (e.g., liver, heart, lung, endocrine), bowel habit/pattern, and performance status (i.e., asthenia and fatigue)
Physical	Full skin and mucosal exam, musculoskeletal (i.e., joint) exam, and other positive findings
Blood Tests	CBC, CMP, HbA1C, lipid profile, TSH, free T4, CK, hepatitis B and C, CMV, and HIV
Pulmonary	Oxygen saturation at rest and with ambulation
Cardiac	ECG, troponin

General Recommendations for irAE Treatment

Grade	Corticosteroid Management	Treatment Impact
1	Usually not indicated	Immunotherapy continued
2	If indicated, low dose prednisone (0.5-1 mg/kg/day); once improved to ≤ grade 1, start 4-6-week taper	Hold until resolved to < grade 2, start PPI for GI prophylaxis
3 and 4	Start prednisone 1-2 mg/kg/day or equivalent (IV therapy generally considered for grade 4 patient and those in the hospital); once improved to ≤ grade 1, start 4-6-week taper	Grade 3: Hold until resolved to < grade 2 Grade 4: Discontinue therapy Both: Start PPI for GI prophylaxis; add PCP prophylaxis if on prednisone ≥ 30 mg daily (or equivalent) for more than 3 weeks

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Symptoms, Testing, Grading, and Management for Common irAEs

Symptom	Testing	Grading	Management
Rash/skin changes	History/physical exam (findings of maculopapular rash/dermatitis) CBC w/ differential and CMP for patients with grade 3	G1: Macules/papules covering < 10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	G1: Continue immunotherapy Oral antihistamines Cetirizine/loratadine 10 mg daily; hydroxyzine 10-25 mg QID, or at bedtime Topical corticosteroids Class I topical corticosteroid (e.g., clobetasol propionate, halobetasol propionate, betamethasone dipropionate cream or ointment) for body; Class V/VI topical corticosteroid (e.g., aclometasone, desonide, hydrocortisone 2.5% cream) for face
		G2: Macules/papules covering 10% to 30% BSA with or without symptoms; limiting instrumental ADL	G2: Continue immunotherapy Non-urgent dermatology referral Oral antihistamines and topical corticosteroids as listed for grade 1
		G3: Macules/papules covering > 30% BSA with or without associated symptoms; limiting self-care ADL	G3: Hold immunotherapy Same day dermatology consult Rule out systemic hypersensitivity (CBC with differential, CMP) Oral antihistamines as for grade 1 Start prednisone 0.5-1 mg/kg/day (or equivalent)
Diarrhea	History/physical exam Blood and stool infection work-up, inflammatory markers, imaging, endoscopy and GI consult (generally for G3 or G4)	G1: Asymptomatic; clinical or diagnostic observations only [diarrhea frequency ≤ 4/day]	G1: Continue immunotherapy Close follow-up within 24-48 hours for changes
		G2: Abdominal pain; mucus or blood in stool [diarrhea frequency 4-6/day]	G2: Hold immunotherapy Diarrhea only: observe changes for 2-3 days; if no improvement, start prednisone 1 mg/kg/day Colitis symptoms (abdominal pain +/- blood in stool): prednisone 1 mg/kg/day
		G3: Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs [diarrhea frequency ≥ 7/day]	G3: Withhold immunotherapy; consider resuming later Start IV prednisone (or equivalent) 1-2 mg/kg/day
		G4: Life-threatening consequences; urgent intervention indicated	G4: Permanently discontinue immunotherapy and hospitalize Start IV prednisone (or equivalent) 1-2 mg/kg/day

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Symptoms, Testing, Grading, and Management for Common irAEs

Symptom	Testing	Grading	Management
Joint pain	History/physical exam	G1: Mild pain with inflammatory symptoms, erythema, or joint swelling	G1: Continue immunotherapy Analgesics: NSAIDs for 4-6 weeks
		G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	G2: Consider holding immunotherapy Start prednisone 20 mg/day for 2-4 weeks, increase to 1 mg/kg/day Rheumatology referral to confirm inflammatory arthritis; assess need for intra-articular injection and examine for signs of early bone damage
		G3: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage (e.g., erosion); disabling; limiting self-care ADL	G3: Consider holding immunotherapy Rheumatology referral Start prednisone 1 mg/kg/day for 2-4 weeks or until symptoms ≤ grade 1
Dyspnea (pneumonitis)	History/physical exam Chest imaging (commonly CT scan)	G1: Asymptomatic; clinical or diagnostic observations only	G1: Consider holding immunotherapy Consider pulmonary and infectious disease consult Reimage at least prior to every immunotherapy cycle Self-monitor symptoms and oxygen saturation every 2-3 days; weekly clinic visits
		G2: Symptomatic; limiting instrumental ADL; medical intervention indicated	G2: Hold immunotherapy Consider hospitalization Pulmonary consultation for bronchoscopy with bronchoalveolar lavage; consider biopsies for atypical lesions Start methylprednisolone 1 mg/kg/day (IV or oral equivalent)
		G3: Severe symptoms; limiting self-care ADL; oxygen indicated	G3: Permanently discontinue immunotherapy Hospitalize; consider ICU care Pulmonary consultation for bronchoscopy with bronchoalveolar lavage; consider biopsies for atypical lesions Start methylprednisolone IV 2 mg/kg/day
		G4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., intubation)	G4: Permanently discontinue immunotherapy Pulmonary consultation for bronchoscopy with bronchoalveolar lavage; consider biopsies for atypical lesions Start methylprednisolone IV 2 mg/kg/day

Symptoms, Testing, Grading, and Management for Common irAEs

Symptom	Testing	Grading	Management
Fatigue and headache (possible anorexia, nausea)	Two most common endocrine diagnoses are hypophysitis and thyroid disease; test TSH and free T4	*Primary Hypothyroidism:* G1: Asymptomatic; clinical or diagnostic observations only	G1: Continue immunotherapy Intervention not indicated
		G2: Symptomatic; limiting instrumental ADL	G2: Continue immunotherapy Thyroid replacement (full dose 1.6 mcg/kg in young healthy patients; 25-50 mcg/day in elderly and those with cardiovascular disease)
	TSH high and free T4 low – primary hypothyroidism	G3: Severe symptoms; limiting self-care ADL; hospitalization indicated	G3/4: Hold immunotherapy, may continue when symptoms resolve to grade 2 Thyroid replacement (see above)
	TSH and free T4 both low – likely central hypothyroidism, which warrants additional testing and MRI of the sella w/ pituitary cuts to diagnose hypophysitis	G4: Life-threatening consequences; urgent intervention indicated	

Abbreviations: ADL = activities of daily living; BSA = body surface area; CBC = complete blood count; CK = creatinine kinase; CMP = comprehensive metabolic panel; CMV = cytomegalovirus; CT = computed tomography; ECG = electrocardiogram; G1 = grade 1; G2 = grade 2; G3 = grade 3; G4 = grade 4; GI = gastrointestinal; HbA1C = hemoglobin A1C; HIV = human immunodeficiency virus; ICU = intensive care unit; IV = intravenous; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; PCP = pneumocystis pneumonia; PPI = proton pump inhibitor; QID = four times daily; TSH = thyroid-stimulating hormone

Reference: Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):95. doi:10.1186/s40425-017-0300-z.

This information is not meant to serve as a guideline for patient management. Treatment should not be used by clinicians without evaluation of their patients' conditions, and possible contraindications on dangers in use, (review of any applicable manufacturer's product information) and comparison with recommendations of other authorities. The author, sponsor, and publisher of this tool, developed to accompany a continuing education activity, have made all reasonable efforts to ensure that all information contained herein is accurate in accordance with the latest available scientific knowledge at the time of acceptance for publication