Immune Checkpoint Inhibitor Therapy in NSCLC:
Current Approved Indications and Toxicity Management

Table 1: FDA-Approved ICIs for Advanced and Metastatic NSCLC (August 2022)

Agent	Approval Date	NSCLC Indication	Dosing*
Atezolizumab (PD-L1–blocking antibody)[1]	May 2020	• First-line single-agent therapy in adult patients with metastatic NSCLC and tumors with high PD-L1 tumor expression (PD-L1 stained ≥50% of tumor cells or PD-L1 stained tumor-infiltrating immune cells covering ≥10% of the tumor area) and no *EGFR* or *ALK* aberrations	840 mg IV every 2 weeks or 1200 mg IV every 3 weeks or 1680 mg IV every 4 weeks Give initial infusion over 60 minutes; when tolerance is established, follow-up infusions can be given over 30 minutes
	December 2019	• First-line therapy in combination with protein-bound paclitaxel and carboplatin for adult patients with metastatic nonsquamous NSCLC and no *EGFR* or *ALK* aberrations	
	December 2018	• First-line therapy in combination with bevacizumab, paclitaxel, and carboplatin for adult patients with metastatic nonsquamous NSCLC and no *EGFR* or *ALK* aberrations	
	April 2017	• Progressive disease in adult patients with metastatic NSCLC: o On or after platinum-based CT o Patients with an *EGFR* mutation or *ALK* rearrangement should have progression on an FDA-approved therapy for those genetic aberrations	
Cemiplimab-rwlc (PD-1–blocking antibody)[2]	February 2021	• Metastatic or locally advanced NSCLC in patients who are not candidates for chemoradiation or resection: First-line single-agent therapy in patients whose tumors have high PD-L1 tumor expression (tumor proportion score ≥50%) and no *EGFR*, *ALK*, or *ROS1* aberrations	350 mg IV over 30 minutes every 3 weeks
Durvalumab (PD-L1–blocking antibody)[3]	February 2018	• Treatment of adult patients with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based CT and radiation	Weight <30 kg: 10 mg/kg IV over 60 minutes every 2 weeks Weight ≥30 kg: 10 mg/kg IV over 60 minutes every 2 weeks or 1.5 g IV every 4 weeks Maximum duration: 1 year
Nivolumab (PD-1–blocking antibody)[4]	May 2020	• Adult patients with metastatic NSCLC expressing PD-L1 ≥1% with no *EGFR* or *ALK* aberrations as first-line therapy in combination with ipilimumab	360 mg IV over 30 minutes every 3 weeks Maximum duration: 2 years
	May 2020	• Adult patients with metastatic or recurrent NSCLC with no *EGFR* or *ALK* aberrations as first-line therapy in combination with ipilimumab and 2 cycles of platinum-based CT	
	October 2015	• Progressive disease in adult patients: o On or after platinum-based CT, or o Patients with an *EGFR* mutation or *ALK* rearrangement should have progression on an FDA-approved therapy for those genetic aberrations	240 mg IV over 30 minutes every 2 weeks or 480 mg IV over 30 minutes every 4 weeks
Pembrolizumab (PD-1–blocking antibody)[5]	April 2019 (Prior approval in October 2016 for PD-L1 ≥50%)	• First-line single-agent therapy for patients with NSCLC expressing PD-L1 TPS ≥1% and no *EGFR* or ALK aberrations	200 mg IV over 30 minutes every 3 weeks or 400 mg IV over 30 minutes every 6 weeks Maximum duration: 2 years
	May 2017	• First-line treatment of patients with metastatic nonsquamous NSCLC with no *EGFR* or *ALK* aberrations in combination with pemetrexed and platinum-based CT	
	October 2018	• First-line treatment of patients with metastatic squamous NSCLC with no *EGFR* or *ALK* aberrations in combination with carboplatin plus paclitaxel or *nab*-paclitaxel	
	October 2016 (Accelerated approval October 2015)	• Progressive disease in adult patients with metastatic NSCLC whose tumors express PD-L1 TPS ≥1% o On or after platinum-based CT, or o Patients with an *EGFR* mutation or *ALK* rearrangement should have progression on an FDA-approved therapy for those genetic aberrations	

**Until disease progression, toxicity, or maximum duration noted.*
CT = chemotherapy; ICI = immune checkpoint inhibitor; IV = intravenous; TPS = tumor proportion score.

Table 2. FDA-Approved ICIs for NSCLC Adjuvant or Neoadjuvant Treatment (August 2022)

Agent	Approval Date	Indication	Dosing Guidelines
Atezolizumab (PD-L1–blocking antibody)[1]	October 2021	• Adjuvant therapy following resection and platinum-based CT in adult patients with stage II-IIIA disease and PD-L1 tumor expression ≥1% of tumor cells	840 mg IV every 2 weeks or 1200 mg IV every 3 weeks or 1680 mg IV every 4 weeks Duration: Up to 1 year Give initial infusion over 60 minutes; when tolerance is established, follow-up infusions can be given over 30 minutes
Nivolumab (PD-1–blocking antibody)[4]	March 2022	• Adults with resectable (tumors ≥4 cm or node positive) NSCLC in the neoadjuvant setting in combination with platinum-based CT	360 mg IV over 30 minutes on same day as platinum-based CT every 3 weeks for 3 cycles

CT = chemotherapy; ICI = immune checkpoint inhibitor; IV = intravenous.

Immune-Related Adverse Events (irAEs) With ICIs

- Unique to immunotherapy and driven by the immune response
- Most occur with 3 months of treatment initiation though can occur at any time during or after treatment

Patient Monitoring During Treatment

- With each new treatment cycle:
  - o Clinic visit with oncology care team
  - o Labs: comprehensive metabolic panel, complete blood count, thyroid-stimulating hormone, other tests based on patient symptoms
  - o Disease-directed imaging of chest with or without abdomen/pelvis

irAE Management[6]

- It is important to educate patients and caregivers about potential irAEs associated with ICI therapy, as a key factor in their successful management is early recognition and treatment
  - o Provide education and detailed information on potential side effects of immune checkpoint inhibition prior to therapy initiation, throughout treatment, and beyond
    - ■ Most are manageable when recognized and treated promptly
    - ■ Potentially life-threatening toxicities may occur but are rare
- It is important to consider any side effect as possibly related to immunotherapy; educate patients and caregivers to notify the healthcare team immediately
  - o Provide detailed instructions for when and how to contact the healthcare team
  - o Patient checklist below
  - o Immunotherapy wallet card is available from Oncology Nursing Society

Table 3. Potential Signs and Symptoms of Selected irAEs[1-6]

irAE	Potential Presentation
Dermatologic or Skin	Pruritus with or without maculopapular rash on trunk or upper limbs, spreading to the extremities; ulcers or sores on head and neck or genital area; macules, papules, or plaques; vitiligo
Colitis	Diarrhea; severe abdominal pain; stool with blood or mucus; fever; vomiting
Hepatitis	Dark urine; abdominal pain; jaundice; asymptomatic and diagnosed upon LFT evaluation
Pneumonitis	New or worsening cough; chest pain; dyspnea; increased oxygen requirements
Endocrine	Headache; mood changes; weight changes; visual field changes; excessive fatigue; cold intolerance; constipation; polyuria; polydipsia
Renal	Urine output change; hematuria; cloudy urine; edema; weight gain; ankle swelling; hypertension; elevated creatinine
Ocular	Vision changes; blurry vision; eye redness; sensitivity to light; photophobia; pain with eye movement
Neurologic	Confusion; memory problems; balance problems; sensory-motor deficits; fluctuating muscle weakness; seizures; neck stiffness; neuropathies
Cardiovascular	Fatigue; dyspnea; edema; chest pain; reduced ejection fraction
Musculoskeletal	Myalgias; myositis; joint pain and swelling; stiffness after inactivity

LFT = liver function tests.

Table 4. General Principles of irAE Management[1-6]

Toxicity Grade	Management*
1 (Mild)	• Symptomatic management • Continue therapy • Immunosuppression not needed
2 (Mild to Moderate)	• Symptomatic management • Consider discontinuing until resolution to grade 1 • Consider immunosuppression if intolerable or persistent • Involve consultants as needed
3 or Higher (Severe)	• Hold or discontinue therapy • Start immunosuppression • Refer/involve consultants • At resolution, gradually taper off immunosuppression

**See references for more specific and detailed management strategies.*

References
1. Atezolizumab PI.; 2. Cemiplimab-rwlc PI.; 3. Durvalumab PI.; 4. Nivolumab PI.; 5. Pembrolizumab PI.; 6. Schneider. JCO. 2021; 39:4073.

Patient Checklist: When to Call Your Doctor

Call your healthcare provider if you are experiencing any of the following symptoms[1-5]

Lung inflammation (pneumonitis)

___ New or worsening cough
___ Chest pain
___ Shortness of breath

Intestinal inflammation (colitis)

___ Diarrhea or excessive number of bowel movements
___ Blood or mucus in your stools or dark, tarry, sticky stools
___ Abdominal pain or tenderness

Liver problems (hepatitis)

___ Yellowing of skin or whites of your eyes
___ Dark urine (tea colored)
___ Nausea or vomiting
___ Pain on the right side of your abdomen
___ Bleeding or bruising more easily than normal

Skin reactions

___ Skin rash, with or without itching
___ Sores in your mouth
___ Blistered or peeling skin
___ Itching

Nerve problems

___ Unusual weakness of legs, arms, or face
___ Numbness or tingling in hands or feet

Eye inflammation

___ Blurry vision, double vision, or other vision problem
___ Eye pain or redness

Kidney inflammation or failure

___ Decrease in volume of urine
___ Blood in urine
___ Swollen ankles
___ Loss of appetite

Pituitary gland inflammation (hypophysitis)

___ Persistent or unusual headache
___ Extreme weakness
___ Dizziness
___ Fainting
___ Vision changes
___ Nausea
___ Vomiting
___ Severe fatigue

Thyroid problems

___ Hyperthyroidism (fatigue, hand tremors, mood swings, rapid heartbeat)
___ Hypothyroidism (changes in menstrual cycle, constipation, depression, dry hair/hair loss, fatigue)

Other problems

___ Severe or persistent muscle or joint pains
___ Severe muscle weakness

REFERENCES

1. Atezolizumab PI.
2. Cemiplimab-rwlc PI.
3. Durvalumab PI.
4. Nivolumab PI.
5. Pembrolizumab PI.

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