Immune Checkpoint Inhibitors in First-line Therapy for Advanced Melanoma

SINGLE-AGENT IMMUNE CHECKPOINT INHIBITOR REGIMENS

Nivolumab

Mechanism of Action	Anti–PD-1 inhibitor
Dosing	240 mg every 2 weeks; 480 mg every 4 weeks
Administration	IV over 30 minutes
Place in Therapy	Adjuvant therapy (preferred) Unresectable and metastatic disease (preferred) → First-line therapy → Second-line or subsequent therapy

Pembrolizumab

Mechanism of Action	Anti–PD-1 inhibitor
Dosing	200 mg every 3 weeks; 400 mg every 6 weeks
Administration	IV over 30 minutes
Place in Therapy	Adjuvant therapy (preferred) Unresectable and metastatic disease (preferred) → First-line therapy → Second-line or subsequent therapy

Ipilimumab

Mechanism of Action	Anti–CTLA-4 inhibitor
Dosing	Adjuvant: 10 mg/kg every 3 weeks for 4 doses, then 10 mg/kg every 12 weeks for up to 3 years Metastatic and unresectable: 3 mg/kg every 3 weeks for a total of 4 doses
Administration	IV over 90 minutes
Place in Therapy	Adjuvant therapy, if prior exposure to anti–PD-1 therapy Unresectable and metastatic disease → Second-line or subsequent therapy

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COMBINATION IMMUNE CHECKPOINT INHIBITOR REGIMENS

Nivolumab + Ipilimumab

Mechanisms of Action	Nivolumab: Anti–PD-1 inhibitor Ipilimumab: Anti–CTLA-4 inhibitor
Dosing	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for a total of 4 doses; then, single-agent nivolumab *Alternative, off-label dosing: nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks for a total of 4 doses; then, single-agent nivolumab*
Administration	Nivolumab: IV over 30 minutes, prior to ipilimumab Ipilimumab: IV over 90 minutes, after nivolumab
Place in Therapy	Unresectable and metastatic disease (preferred) → First-line therapy → Second-line or subsequent therapy

Pembrolizumab + Ipilimumab

Mechanisms of Action	Pembrolizumab: Anti–PD-1 inhibitor Ipilimumab: Anti–CTLA-4 inhibitor
Dosing	Pembrolizumab 200 mg + ipilimumab 1 mg/kg every 3 weeks for a total of 4 doses; then, single-agent pembrolizumab
Administration	Pembrolizumab: IV over 30 minutes, prior to ipilimumab Ipilimumab: IV over 90 minutes, after pembrolizumab
Place in Therapy	Unresectable and metastatic disease (off-label) → First-line therapy → Second-line or subsequent therapy, if progressed on prior anti–PD-1 therapy

3-DRUG REGIMENS

Atezolizumab + Vemurafenib + Cobimetinib

Mechanisms of Action	Atezolizumab: Anti–PD-L1 inhibitor Vemurafenib: BRAF inhibitor Cobimetinib: MEK inhibitor
Dosing	C1D1-21: Vemurafenib 960 mg twice daily + cobimetinib 60 mg daily C1D22-28: Vemurafenib 720 mg twice daily C2D1+: Atezolizumab 840 mg every 2 weeks *OR* 1,200 mg every 3 weeks *OR* 1,680 mg every 4 weeks + vemurafenib 720 mg twice daily + cobimetinib 60 mg daily on days 1-21/28
Administration	Atezolizumab: IV over 60 minutes for the first infusion; if well-tolerated, subsequent infusions over 30 minutes Vemurafenib + cobimetinib: Oral with or without food
Place in Therapy	Unresectable and metastatic disease, if *BRAF* V600-activating mutation is present → First-line therapy

Pembrolizumab + Dabrafenib + Trametinib

Mechanisms of Action	Pembrolizumab: Anti–PD-1 inhibitor Dabrafenib: BRAF inhibitor Trametinib: MEK inhibitor
Dosing	Pembrolizumab: 200 mg every 3 weeks Dabrafenib: 150 mg twice daily Trametinib: 2 mg daily
Administration	Pembrolizumab: IV over 30 minutes Dabrafenib/trametinib: Oral on an empty stomach
Place in Therapy	Unresectable and metastatic disease, if *BRAF* V600-activating mutation is present (off-label) → First-line therapy

IMMUNE CHECKPOINT INHIBITOR TOXICITY

Pearls	→ Inflammatory in nature → Can occur in any organ of the body → Most common during first 14 weeks of treatment → Endocrinopathy can occur throughout treatment
Management Guidelines	ASCO Guidelines. *Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy* NCCN Clinical Practice Guidelines in Oncology: *Management of Immunotherapy-Related Toxicities*

ASCO, American Society for Clinical Oncology; CTLA-4, cytotoxic T-lymphocyte–associated antigen-4; IV, intravenous; MEK, mitogen-activated extracellular kinase; NCCN, National Comprehensive Cancer Network; PD-1, programmed cell death-1.

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