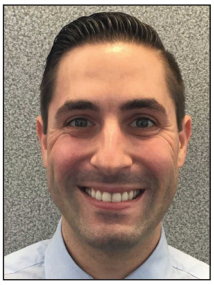
Update in Melanoma Therapies

By Matthew Clark, MD

GENERIC NAME	BRAND NAME	ROUTE	MOA	INDICATION	SIDE EFFECTS	OTHER
Chemotherapy						
Dacarbazine	DTIC-Dome	IV	Cell cycle nonspecific alkylating agent	Stage IV melanoma	GI side effects **(strong vomiting)**, thrombocytopenia, hepatic necrosis, alopecia, facial flushing, and facial paresthesias	Requires hepatic metabolism for activation; response rates 5-20% and usually only short duration Often used as palliative treatment
Immunotherapies						
Pegylated IFN-a-2b (Interferon)	Intron A, Sylatron, PEG-intron	IV, SQ	Unknown; activates immune response → tumor apoptosis	High risk stage II & III melanoma; often used after resection	Rash, pruritus, GI symptoms, myelosuppression, hepatotoxicity, GI bleeding, pancreatitis, pulmonary toxicity, myocardial infarction, arrhythmias, hypertension, psychological disturbances	Useful as an adjuvant; **black box warning** that may aggravate fatal or life-threatening autoimmune, infectious, ischemic, or neuropsychiatric disorders; no overall benefit on survival demonstrated Has fallen out of favor as TOC with advent of newer immuno/targeted therapies
Interleukin-2 (IL-2)	Proleukin/ IL-2, Aldesleukin	IV	Activates immune response **(T-cell growth factor)** → tumor apoptosis	Metastatic melanoma	**High toxicity** profile: hypotension, renal insufficiency, hypoxia, flu-like symptoms, **capillary leak syndrome**	**Black box warning** that it can only be used in patients with normal thallium stress tests and PFTs; may cause **capillary leak syndrome** or serious infections due to decreased neutrophil function 5-7% of patients show durable complete clinical responses
Anti-tumor vaccines	i.e. gp100 vaccine	ID	Monocyte-derived DCs matured and loaded with MHC class II–restricted tumor peptides	Advanced metastatic melanoma	Eosinophilia, injection site reactions, fever	2017 study showed 19% overall 10-year survival, comparable to ipilimumab May be useful as adjuvant therapy; more studies needed
Adoptive Cell Therapy (ACT)	N/A	IV	Ex vivo expansion of autologous tumor-specific cytotoxic T-cells → transferred back to patient to boost anti-tumor immunity	Refractory metastatic melanoma	Anti-melanocyte side effects **(vitiligo, uveitis)** and chemotherapy or IL-2 related side effects (myelosuppression, opportunistic infections, etc.)	Often administered with lymphodepleting chemo and/or high dose IL-2 Phase II trials showed 50% response rate Combination ACT + ipilimumab showed complete remission at 107-week follow up in 2/10 patients Cons: labor intensive and requires high laboratory expertise
Immune Checkpoint Inhibitors						
CTLA-4 Inhibitors: **Ipilimumab**	Yervoy	IV	Human monoclonal antibody (IgG1) against **CTLA-4 inhibition** of T-cells → enhanced T-cell response	Metastatic or unresectable melanoma	**Autoimmune toxicities/ immune related adverse events (irAEs)** (bolded more common for CTLA-4 inhibitors): - Skin: **rash, pruritus**, vitiligo - GI: **colitis**, hepatotoxicity - Endo: **hypopituitarism**, hyper/hypothyroidism - Lung: **pneumonitis**	Pregnancy category C; black box warning that may cause **severe or fatal immune-mediated reactions** due to T-cell activation and proliferation
PD-1 Inhibitors: **Nivolumab** **Pembrolizumab**	Opdivo Keytruda	IV	Humanized monoclonal antibody (IgG4) against **PD-1 receptor**	Metastatic or unresectable melanoma	**irAEs** (bolded more common for PD-1 inhibitors): - Skin: **vitiligo**, rash, pruritus - GI: colitis, hepatotoxicity - Endo: **type 1 diabetes hyper/hypothyroidism** - Lung: pneumonitis	Can be effective regardless of BRAF or PDL1 status; anti-PD-1 agents have higher response rates and lower incidence of grade ≥3 autoimmune toxicities compared to anti-CTLA-4 agents→anti-PD-1 agents typically preferred to anti-CTLA-4 agents Phase III trial showed PD-1-inhibitor + CTLA-4-inhibitor > either as monotherapy
Gene-Targeted Therapies						
BRAF Inhibitors (BRAFIs): **Vemurafenib**	Zelboraf	PO	Kinase inhibitor of the mutant BRAF **($BRAF^{V600E}$)**	Advanced $BRAF^{V600E}$ advanced melanoma	Rash, photosensitivity, **seborrheic keratoses, SCC, keratoacanthomas, papillomas (via paradoxical RAS-MAPK activation), new primary melanoma (via wildtype BRAF)**, alopecia, hyperkeratosis, pruritus, GI side effects, increased LFTs, QT prolongation	**BRAF is the most common gene mutated in melanomas (approx 40%)**; not effective against wild type *BRAF* BRAF mutations: acquired & dysplastic nevi, melanomas on intermittently sun damaged skin ***Helpful hint:* all BRAF inhibitors have the letters B-R-A-F somewhere in their name** Prompt and high response rates but duration is short-lived with most patients developing tumor progression within 6 months due to **development of resistance→ thus often used in combo with MEK inhibitors to delay resistance** May be useful in intracranial mets
Dabrafenib	Tafinlar	PO	Kinase inhibitor of the mutant BRAF **($BRAF^{V600E}$ & $BRAF^{V600K}$)** BRAF mutation: substitution of **glutamic acid for valine** at amino acid position 600 BRAF: encodes serine/threonine protein kinase→RAS-RAF-MEK-ERK MAPK pathway	Advanced $BRAF^{V600E}$ & $BRAF^{V600K}$ melanoma **Testing for +BRAF mutation required prior to starting**		



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Update in Melanoma Therapies *(continued)*

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Gene-Targeted Therapies						
MEK Inhibitors (MEKIs): **Trametinib** **Cobimetinib**	Mekinist Cotellic	PO PO	Selectively inhibits MEK1 and MEK2 → disruption of MAPK proliferation pathway	Metastatic or unresectable melanoma	Rash, **acneiform dermatitis**, alopecia, nausea, vomiting, diarrhea, constipation, fatigue, peripheral edema, hypertension	***Helpful hint:* MEK inhibitors contain "met" in the name (think 'met'→ 'mek')** Often used in combination with BRAFIs to prevent resistance Combination therapy using MEKI + BRAFI = longer progression free survival Combination therapy decreases paradoxical SCC development seen with BRAFI monotherapy
MEK Inhibitors (in development): **Binimetinib** **Selumetinib**		PO PO	Selective, non-ATP-competitive inhibitor of MEK1 and MEK2 → inhibition of MAPK proliferation pathway	***NRAS-mutated and BRAF^{V600E}***	Rash, acneiform dermatitis, pruritus, GI side effects, edema (facial, periorbital, peripheral), **increased CPK**, dysgeusia, central serous retinopathy-like events, **small bowel perforation (NRAS patients), malaise and general health deterioration (BRAF patients)**	***NRAS mutations occur in approximately 15-20% of melanomas*** NRAS mutations associated with thicker primary tumors, older patients, and melanomas on chronically sun-damaged skin
Viral Immunotherapy						
Talimogene laherparepvec	Imlygic "T-VEC"	IL	**Tumor-specific modified HSV-1** → insertion/expression of gene encoding **(GM-CSF)**→ direct anti-tumor effect secondary to viral infection and induction of immune response	Loco-regionally stage III and IVM1a melanoma Good for in-transit disease Injected directly into cutaneous/subcutaneous tumors	Glomerulonephritis, vasculitis, psoriasis exacerbation, fever, GI side effects, fatigue, headache, disseminated herpes infection	Phase III trial showed 16.3% of patients had decrease in skin/LN tumor size lasting at least 6 months No increase in overall survival
Other Non-FDA-Approved Therapies						
KIT-Inhibitors: **Imatinib** **Dasatinib** **Nilotinib**	Gleevec Sprycel Tasigna	PO	BCR-ABL1/KIT tyrosine kinase inhibitor	***KIT-mutated*** advanced melanoma	Ascites, pleural effusion, pulmonary edema, CHF, GI bleeding, myelosuppression, hepatotoxicity, SJS, photosensitivity, **QT prolongation**, HBV reactivation	KIT mutations most common in **acral and mucosal melanomas**

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