

Series Editor: William W. Huang, MD, MPH

## Medications for Advanced Melanoma

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Dr. Strowd is from Clinical Associates at Reisterstown, Maryland. The author reports no conflict of interest.

Generic Name	Brand Name (Manufacturer)	Mechanism of Action	Method of Administration	Cutaneous Side Effects	Drug Efficacy From Phase 3 Clinical Trials	Notes
<b>BRAF Inhibitors</b>						
Dabrafenib	Tafinlar (GlaxoSmithKline)	Blocks <i>BRAF</i> mutations in the Ras/ERK pathway preventing cell proliferation	Oral pill	Eruptive SCC, keratosis pilaris, seborrheic dermatitis-like eruptions	5 mo median PFS vs 2.7 mo on dacarbazine	Indicated as monotherapy for patients with unresectable or metastatic melanoma with <i>BRAF</i> V600E mutations; used in combination with trametinib for <i>BRAF</i> V600E or V600K mutations; not indicated for wild-type <i>BRAF</i> melanoma
Vemurafenib	Zelboraf (Genentech USA, Inc)	Blocks <i>BRAF</i> mutations in the Ras/ERK pathway preventing cell proliferation	Oral pill	Eruptive SCC, keratosis pilaris, seborrheic dermatitis-like eruptions	4 mo increase in median PFS vs dacarbazine; 3 mo improvement in median OS compared to dacarbazine	Indicated for unresectable or metastatic melanoma with <i>BRAF</i> V600E mutation; not indicated for wild-type <i>BRAF</i> melanoma
<b>MEK Inhibitors</b>						
Trametinib	Mekinist (GlaxoSmithKline)	Blocks <i>BRAF</i> mutations in the Ras/ERK pathway preventing cell proliferation	Oral pill	Morbilliform eruption, acne/rosacea, dry skin	3 mo improvement in median OS compared to traditional chemotherapy	Indicated as monotherapy and in combination with dabrafenib in patients with unresectable or metastatic melanoma with <i>BRAF</i> V600E or V600K mutations

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Generic Name	Brand Name (Manufacturer)	Mechanism of Action	Method of Administration	Cutaneous Side Effects	Drug Efficacy From Phase 3 Clinical Trials	Notes
<b>MEK Inhibitors</b> (continued)						
Cobimetinib	N/A	Blocks <i>BRAF</i> mutations in the Ras/ERK pathway preventing cell proliferation	Oral pill	SCC, photosensitivity, morbilliform eruption	3 mo improvement in median OS when combined with vemurafenib vs vemurafenib alone	Not yet FDA approved; has shown improved survival when combined with vemurafenib for <i>BRAF</i> V600 mutation
<b>Antibodies</b>						
Pembrolizumab	Keytruda (Merck & Co, Inc)	Human IgG4 monoclonal antibody to PD-1, causes T-cell activation	IV infusion	Pruritus, morbilliform eruption	Overall response rate was 24%, median OS was 18 mo	Indicated for unresectable or metastatic melanoma and disease progression following ipilimumab and a BRAF inhibitor if <i>BRAF</i> V600 mutation positive
Nivolumab	Opdivo (Bristol-Myers Squibb Company)	Human IgG4 monoclonal antibody to PD-1, causes T-cell activation	IV infusion	Morbiliiform eruption	Median PFS was 11.5 mo with nivolumab + ipilimumab, 2.9 mo with ipilimumab alone, and 6.9 mo with nivolumab alone	Indicated for unresectable or malignant melanoma and disease progression following ipilimumab and a BRAF inhibitor if <i>BRAF</i> V600 mutation positive
Ipilimumab	Yervoy (Bristol-Myers Squibb Company)	Monoclonal antibody to CTLA-4, prevents T-cell inactivation	IV infusion	Morbiliiform eruption, TEN	Average OS for ipilimumab + gp100 was 10.1 mo compared to 6.4 mo with gp100 alone	Indicated for unresectable or metastatic melanoma, can result in severe and fatal immune-mediated reactions involving any organ system (most common are enterocolitis, hepatitis, dermatitis, neuropathy, and endocrinopathy)

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Generic Name	Brand Name (Manufacturer)	Mechanism of Action	Method of Administration	Cutaneous Side Effects	Drug Efficacy From Phase 3 Clinical Trials	Notes
<b>Alfa Interferons</b>						
Recombinant interferon alfa-2b	Intron A (Merck & Co, Inc)	Direct antiproliferative effect, enhancement of natural killer cell activity, upregulation of tumor antigens and HLA class I and II antigens	IV infusion followed by SQ injection	Raynaud phenomenon, acute hypersensitivity reaction, worsening of sarcoidosis and psoriasis	3 mo PFS and similar efficacy to monochemotherapy	Adjuvant to surgical treatment in patients with high risk for systemic recurrence of malignant melanoma
Peginterferon alfa-2b	Sylatron (Merck & Co, Inc)	Direct antiproliferative effect, enhancement of natural killer cell activity, upregulation of tumor antigens and HLA class I and II antigens	SQ injection	Urticaria, angioedema	Increase recurrence-free survival time by 8 mo compared to observation, no increase in OS	Indicated for adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy
<b>IL-2 Cytokine</b>						
Aldesleukin	Proleukin (Prometheus Laboratories, Inc)	IL-2 cytokine promotes T-cell activation	IV infusion	Morbilloform eruption, vitiligo	Overall objective response rate was 16%	
<b>Other</b>						
Dacarbazine	DTIC-Dome (Bayer Pharmaceuticals Corporation)	Purine analog that inhibits DNA synthesis, acts as an alkylating agent, interacts with sulfhydryl groups	IV infusion	Urticaria, angioedema	Mean PFS 2.3 mo	Not particularly efficacious for melanoma, response seen in <20% of patients

Abbreviations: ERK, extracellular signal-regulated kinase; SCC, squamous cell carcinoma; PFS, progression-free survival; OS, overall survival; MEK, mitogen-activated protein kinase; N/A, not available; FDA, US Food and Drug Administration; PD-1, programmed cell death protein 1; IV, intravenous; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; TEN, toxic epidermal necrolysis; SQ, subcutaneous.

## Practice Questions

- 1. Which of the following medications is considered an MEK inhibitor?**
  - a. aldesleukin
  - b. dacarbazine
  - c. ipilimumab
  - d. recombinant interferon alfa-2b
  - e. trametinib
  
- 2. Which of the following medications has been shown to be associated with toxic epidermal necrolysis?**
  - a. aldesleukin
  - b. dacarbazine
  - c. ipilimumab
  - d. recombinant interferon alfa-2b
  - e. trametinib
  
- 3. What medication can be administered as a subcutaneous injection?**
  - a. aldesleukin
  - b. dacarbazine
  - c. ipilimumab
  - d. recombinant interferon alfa-2b
  - e. trametinib
  
- 4. Which of the following medications is a monoclonal antibody to cytotoxic T-lymphocyte-associated antigen 4?**
  - a. aldesleukin
  - b. dacarbazine
  - c. ipilimumab
  - d. recombinant interferon alfa-2b
  - e. trametinib
  
- 5. Which of the following medications is an IL-2 cytokine?**
  - a. aldesleukin
  - b. dacarbazine
  - c. ipilimumab
  - d. recombinant interferon alfa-2b
  - e. trametinib

*Fact sheets and practice questions will be posted monthly. Answers are posted separately on [www.cutis.com](http://www.cutis.com).*