Treating and Managing BRAF-Mutated Melanoma

BRAF Inhibitors:			
	Vemurafenib (Zelboraf®)	**Dabrafenib (Taflinar®)**	**Encorafenib (Braftovi®)**
Mechanism of Action	BRAF inhibitor	BRAF inhibitor	BRAF inhibitor
Dosing	960 mg PO twice daily	150 mg PO twice daily	450 mg PO once daily
Administration	With or without food	Empty stomach 1 hour before or 2 hours after food	With or without food
Place in Therapy	• Unresectable or metastatic melanoma with BRAF V600E mutation	• Single agent for unresectable or metastatic melanoma with BRAF V600E mutations • Combination with trametinib for: • Unresectable or metastatic melanoma with BRAF V600E/K mutations • Adjuvant treatment of melanoma with BRAF V600E/K mutations and lymph node involvement	• Unresectable or metastatic melanoma with BRAF V600E/K mutation in combination with binimetinib
Select Adverse Effects	Arthralgia, rash, alopecia, pruritus, fatigue, nausea, photosensitivity, skin papilloma, new primary malignancies, hypersensitivity reactions, skin reactions, QT prolongation, hepatotoxicity, ophthalmologic reactions, radiation sensitization and recall, renal failure	Hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, palmar-plantar erythrodysesthesia snydrome, rash (when used with trametinib), diarrhea (when used with trametinib), new primary malignancies, hemorrhage, cardiomyopathy, uveitis, hyperglycemia	Fatigue, nausea, vomiting, abdominal pain, arthralgia, hemorrhage, uveitis, QT prolongation, new primary malignancies
Monitoring	• Dermatologic evaluations at baseline, every 2 months during therapy, and up to 6 months after completion • Monitor and correct for hypocalcemia, hypomagnesemia, and hypokalemia to reduce risk of QTc prolongation • Monitor ECG and electrolytes at baseline, 15 days after initiation, monthly during first 3 months, and then at least every 3 months thereafter • Monitor LFTs at baseline and monthly during treatment • Monitor SCr at baseline and periodically	• LVEF at baseline, 1 month after initiation, and then every 2-3 months while on treatment • Dermatologic evaluations prior to initiation, every 2 months while on therapy, and up to 6 months after completion • Glucose levels in patients with preexisting diabetes or hyperglycemia	• Dermatologic evaluations at baseline, every 2 months while on therapy, and for up to 6 months after completion • Ophthalmologic evaluation at regular intervals • Monitor electrolytes before and during treatment • Monitor ECG for patients who already have or who are at significant risk for developing QTc prolongation
Drug Interactions	Strong CYP3A4 inhibitors, strong CYP3A4 inducers, CYP1A2 substrates, and P-gp substrates	Strong CYP3A/CYP2C8 inhibitors, substrates of CYP3A4, CYP2C8, CYP2C9 (warfarin), CYP2C19, and CYP2B6. Hormonal contraceptives may be ineffective. Monitor INR more frequently in patients receiving warfarin.	Strong/moderate CYP3A inhibitors and inducers, CYP3A4 substrates. Avoid coadministration with hormonal contraceptives.
Other Patient Counseling Points	• Do not crush or chew tablets • If dose is missed, it can be taken up to 4 hours prior to next dose • If dose vomited, do not take an additional dose • Avoid sun exposure, wear protective clothing, and use broad-spectrum sunscreen and lip balm when outdoors • Avoid pregnancy during therapy and for at least 2 weeks after discontinuation	• Do not open, crush, or break the capsules • If dose missed, do not take within 6 hours of the next dose • Use effective nonhormonal contraception during and for at least 2 weeks after the last dose	• If dose missed, do not take if within 12 hours of next dose • If dose vomited, do not take an additional dose • Use effective nonhormonal contraception during and for at least 2 weeks after the last dose
MEK Inhibitors:			
	Cobimetinib (Cotellic®)	**Trametinib (Mekinist®)**	**Binimetinib (Mektovi®)**
Mechanism of Action	MEK inhibitor	MEK inhibitor	MEK inhibitor
Dosing	60 mg PO once daily on days 1-21 of a 28-day cycle	2 mg PO once daily	45 mg twice daily
Administration	With or without food	Empty stomach 1 hour before or 2 hours after food	With or without food
PLACE IN THERAPY	• Unresectable or metastatic melanoma with BRAF V600E/K mutation in combination with vemurafenib	• Unresectable or metastatic melanoma with BRAF V600E/K mutations in combination with dabrafenib • Adjuvant treatment of melanoma (with lymph node involvement) patients with BRAF V600E/K mutations in combination with dabrafenib • Single agent for unresectable or metastatic melanoma with BRAF V600E/K mutation	• Unresectable or metastatic melanoma with BRAF V600E/K mutation in combination with encorafenib
Select Adverse Effects	Diarrhea, photosensitivity, skin rash, nausea, vomiting, pyrexia, increased LFTs, increased CPK, hypophosphatemia, new primary malignancies, cardiomyopathy, retinopathy	Rash, diarrhea, lymphedema, pyrexia, nausea, chills, vomiting, hypertension, peripheral edema, fatigue, dry skin, anorexia, cough, dyspnea, new primary malignancies, hemorrhage, colitis, cardiomyopathy, ocular toxicities, hyperglycemia	Fatigue, nausea, vomiting, diarrhea, abdominal pain, visual disturbances, increased creatine, increased CPK, increased LFTs, cardiomyopathy, ocular toxicities, interstitial lung disease, hepatotoxicity
Monitoring	• LVEF at baseline, 1 month after initiation, and every 3 months during treatment • Monitor for new malignancies at baseline, while on therapy, and up to 6 months after last dose • Ophthalmological evaluation at regular intervals • LFTs baseline and at least monthly during treatment • CPK at baseline and periodically during treatment	• LVEF at baseline, after 1 month of treatment, and every 2-3 months thereafter • Ophthalmologic evaluation for any visual disturbances • Serum glucose at baseline and during treatment in patients with preexisting diabetes or hyperglycemia	• LVEF baseline, 1 month after initiation, and every 2-3 months during treatment • Ophthalmologic evaluation at regular intervals • LFTs at baseline and at least monthly during treatment • CPK and creatinine periodically and as clinically indicated
Drug Interactions	Moderate and strong CYP3A4 inhibitors and inducers	Prescribing information refers to dabrafenib drug interactions	None
Other Patient Counseling Points	• If dose missed or vomited, skip dose and take usual dose the following day • Avoid sun exposure, wear protective clothing, and use broad-spectrum sunscreen and lip balm when outdoors • Avoid pregnancy during treatment and for 4 months after last dose	• If dose missed, do not take if within 12 hours of next scheduled dose • Use effective contraception during and for at least 4 months after the last dose	• If dose missed, skip if within 6 hours of the next scheduled dose • If dose vomited, additional dose should not be taken • If encorafenib is permanently discontinued, then discontinue binimetinib • Use effective nonhormonal contraception during and for at least 30 days after the last dose

CPK = creatine phosphokinase; CYP = cytochrome P450; ECG = electrocardiogram; INR = international normalized ratio; LFTs = liver function tests; LVEF = left ventricular ejection fraction; PO = by mouth; SCr = serum creatinine

For all agents above:
• Consider holding at least 3 days before and after fractionated radiation and at least 1 day before and after stereotactic radiosurgery

References:
1. Zelboraf (vemurafenib) [Package insert]. South San Francisco, CA: Genentech, Inc.;2020.
2. Tafinlar (dabrafenib) [Package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp.;2021.
3. Braftovi (encorafenib) [Package insert]. Boulder, CO: Array BioPharma, Inc.;2020.
4. National Comprehensive Cancer Network Clinical Practice Guidelines. Cutaneous Melanoma. Version 2.2021. Accessed September 29, 2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf
5. Cotellic (cobimetinib) [Package insert]. South San Francisco, CA: Genentech, Inc.;2018.
6. Mekinist (trametinib) [Package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp.;2021.
7. Mektovi (binimetinib) [Package insert]. Boulder, CO: Array BioPharma, Inc.;2020.