Oncology Oral, Skin Cancer
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
binimetinib (Mektovi®)[1]	Array BioPharma	▪ In combination with encorafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test*,†
cobimetinib (Cotellic®)[2]	Genentech	▪ Treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib (Zelboraf)
dabrafenib (Tafinlar®)[3]	Novartis	▪ As a single agent for patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test ▪ In combination with trametinib (Mekinist) for patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test* ▪ In combination with trametinib (Mekinist) for the treatment of metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test*,‡ ▪ In combination with trametinib for the adjuvant treatment of melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test and involvement of lymph node(s), following complete resection* ▪ In combination with trametinib for the treatment of locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options
encorafenib (Braftovi®)[4]	Array BioPharma	▪ In combination with binimetinib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test*,† ▪ In combination with cetuximab (Erbitux) for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy*,§
sonidegib (Odomzo®)[5]	Sun Pharma	▪ Treatment of locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or for those who are not candidates for surgery or radiation therapy

* A list of FDA approved companion diagnostics can be found at: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools

† Binimetinib (Mektovi) and encorafenib (Braftovi) are not indicated for treatment of patients with wild-type BRAF melanoma

‡ Limitation of use: dabrafenib is not indicated for the treatment of patients with wild-type BRAF melanoma or wild-type BRAF NSCLC

§ Limitation of use: encorafenib is not indicated for treatment of patients with wild-type BRAF CRC

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
trametinib (Mekinist®)[6]	Novartis	▪ As a single agent in BRAF-inhibitor treatment-naïve patients or in combination with dabrafenib (Tafinlar) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test* ▪ In combination with dabrafenib for the treatment of metastatic NSCLC with BRAF V600E mutation as detected by an FDA-approved test* ▪ In combination with dabrafenib for the adjuvant treatment of melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test and involvement of lymph node(s), following complete resection* ▪ In combination with dabrafenib for the treatment of locally advanced or metastatic ATC with BRAF V600E mutation and with no satisfactory locoregional treatment options
vemurafenib (Zelboraf®)[7]	Genentech	▪ Treatment of unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test*,‖ ▪ Treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation
vismodegib (Erivedge®)[8]	Genentech	▪ Treatment of adults with metastatic basal cell carcinoma (BCC), or with locally advanced BCC that has recurred following surgery or who are not candidates for surgery and who are not candidates for radiation

* A list of FDA approved companion diagnostics can be found at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.

‖ Limitation of use: vemurafenib (Zelboraf) is not indicated for the treatment of patients with wild-type BRAF melanoma

OVERVIEW

Skin cancers are largely divided into 2 groups, melanoma skin cancers and non-melanoma skin cancers (NMSCs). NMSC are also called keratinocyte carcinomas.[9] The most common NMSCs include basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC). The distinction between melanoma and non-melanoma skin cancers is generally based on the lack of propensity for NMSC to metastasize as compared to melanoma, which has a high risk of metastasis and is often fatal in advanced stages. Aside from melanoma, cutaneous SCC and BCC, there are other types of cancers involving the skin. These include primary cutaneous B-cell lymphomas, peripheral T-cell lymphomas, and certain sarcomas, such as dermatofibrosarcoma protuberans (a sarcoma of fibroblast origin) and AIDS-related Kaposi sarcoma[10,11,12] In addition, Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous tumor that has both a high local recurrence rate and a high risk for distant metastatic disease. The mortality associated with MCC exceeds even that of melanoma.[13] This review will focus only on melanoma and NMSC.

NMSCs are the most commonly occurring type of cancer, and their prevalence is more than that of all other types of cancers combined.[14] The number of NMSCs treated in the US in 2012 was estimated to exceed 5 million cases.[15,16] BCC is the most prevalent NMSC; it is at least twice as common as SCC. NMSC rarely metastasizes but can cause extensive local tissue destruction which can lead to

disfigurement and may affect surrounding areas including bone. BCC risk is increased by both UV-A and UV-B radiation, although the relationship between sun exposure and BCC is complex and depends on the timing, pattern, and amount of UV radiation.[17] Known risk factors for increasing susceptibility to UV damage include fair skin, red or blonde hair, and light eye color. BCC tends to occur on areas of the skin that are exposed to radiation, either from the sun or from therapeutic radiation therapy.[18] Surgery is the primary modality utilized for local BCC with Moh's micrographic surgery being the preferred surgical technique.[19] Other local modalities that have been utilized include radiation therapy, cryosurgery, photodynamic therapy, or topical therapy with 5-fluorouracil or imiquimod. While vismodegib is FDA-approved for the treatment of adults with metastatic BCC, sonidegib is not. The National Comprehensive Cancer Network (NCCN) guidelines for the treatment of BCC mirror their respective FDA-approved indications. Specifically, the role for these agents is in patients with advanced high-risk basal cell skin cancer who have residual disease after surgery and who are not able to receive further surgery and in whom curative radiation therapy is not feasible (both vismodegib and sonidegib category 2A). In the setting of nodal or distant metastases due to BCC, the NCCN guidelines note that sonidegib is not FDA approved for metastatic BCC and is, therefore, a 2B recommendation in the setting, while vismodegib or a clinical trial are 2A recommendations. Both vismodegib and sonidegib are classified as hedgehog pathway inhibitors, and the NCCN guidelines note a key limitation to hedgehog pathway inhibitors is the ability of advanced BCC to develop resistance, thus limiting the duration of response seen with these therapies.[20]

The incidence of melanoma skin cancer in the US is increasing, but the death rate due to melanoma is declining. From 2002 to 2006, the incidence of melanoma increased at a rate of 33% for men and 23% for women. Melanoma is increasing more rapidly than any other malignancy except lung cancer in women.[21] Conversely, there was a 7% annual decline in mortality due to cutaneous melanoma from 2013 to 2017. This is an improvement from a 1% mortality decline during the period of 2006 to 2010 for patients aged 50 to 64 years and a 2% to 3% annual decline over the same period for patients aged 20 to 49 years of age. For patients aged 65 years and older, there was an annual mortality decline of 5% to 6% from 2013 to 2017, where prior to 2013, the annual mortality rate had been increasing.[22] In the US, it is estimated that there will be 100,350 new cases of melanoma diagnosed in 2020, and there will be an estimated 6,850 deaths due to melanoma, which is slightly less than the 7,230 deaths reported in 2019.[23,24] The median age at diagnosis is 59 years, and, therefore, melanoma mortality results in a larger number of years of potential life lost (20.4 years) compared to 16.6 years for all other cancers.[25] Risk factors for the development of melanoma include both genetic factors (skin type, inherited germline mutations) and environmental factors (excess sun exposure, ultra violet [UV]-based artificial tanning).[26] Despite the relationship to UV exposure, melanoma can also occur in areas of the body without substantial sun exposure and can occur in any ethnic group. There are also noncutaneous forms of melanoma, arising from melanocytes present in mucosal membranes or the uveal tract of the eye. The treatment of noncutaneous melanoma may differ from that of cutaneous melanoma and treatment should be individualized for these patients.[27]

The prognosis for patients with cutaneous melanoma depends on the stage of disease at diagnosis. Fortunately, most patients (84%) present with localized disease. For patients with localized melanoma and primary tumors that are 1 mm or less in thickness, 5-year survival is more than 90%. For patients with regional lymph node involvement, 5-year survival rates drop by approximately 50%, and, historically, long-term survival for patients with distant metastatic disease has been less than 10%.[28]

However, emerging systemic therapies, including immunotherapies, are having an impact on patients with advanced melanoma and have made long-term remission a possibility for some patients.[29]

Approximately half of all patients with metastatic cutaneous melanoma are positive for a BRAF mutation. Most BRAF mutations occur at V600E but less frequently may occur at V600K.[30] Vemurafenib (Zelboraf) and dabrafenib (Tafinlar) are both BRAF inhibitors that are FDA-approved as monotherapy for patients with BRAF-mutated metastatic melanoma; encorafenib (Braftovi) is also a BRAF inhibitor, but indicated only in combination with binimetinib (Mektovi) for the treatment of advanced or metastatic melanoma. Response to BRAF inhibitor therapy in metastatic melanoma occurs relatively quickly (compared to responses seen with either chemotherapy or immunotherapy), at a median of approximately 1.5 months. Monotherapy with the BRAF inhibitors vemurafenib or dabrafenib has been shown in phase 3 trials of metastatic melanoma to improve response rates, progression-free survival (PFS), and overall survival (OS) compared with single agent cytotoxic chemotherapy (dacarbazine) for patients with BRAF-mutated melanoma.[31] However, resistance to BRAF-directed monotherapy develops quickly with a median duration of response lasting approximately 5 to 10 months, with half of the patients relapsing within 6 months.[32] Subsequently, mitogen-activated extracellular kinases (MEK) inhibitors (trametinib [Mekinist], cobimetinib [Cotellic], and binimetinib [Mektovi]) were shown to improve response rate, duration of response, PFS, and OS of metastatic melanoma when given in combination with BRAF inhibitors compared to BRAF monotherapy.[33] MEK is a signaling molecule in the RAS/RAF/MED/ERK pathway downstream of BRAF. In general, toxicities with combination therapy are similar to toxicities with monotherapy with BRAF inhibitors. Notably, combination therapy results in a lower incidence of alopecia and hyperproliferative cutaneous adverse effects, including cutaneous squamous cell carcinomas and keratoacanthomas, compared to monotherapy. Combination BRAF/MEK inhibitor therapies are associated with high rates of flu-like symptoms and musculoskeletal complaints.[34]

In 2018, the combination of dabrafenib plus trametinib received FDA approval for use in the adjuvant setting of stage 3 melanoma patients with BRAF V600E or V600K mutations who have involvement of lymph nodes and who have undergone complete resection.[35] This regimen is also now a NCCN category 1 recommendation in patients with stage 3 melanoma with a BRAF V600 activating mutation. The NCCN guidelines recommend BRAF mutation testing for patients with stage 3 melanoma at high risk for recurrence for whom future BRAF-directed therapy may be an option (category 2A). Additionally, the NCCN guidelines provide several caveats regarding further delineation of risk in stage 3 patients (e.g., sentinel lymph node metastasis greater or less than 1 mm, ulcerated versus non-ulcerated) and state that the choice of adjuvant systemic therapy or observation alone should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.[36]

In the setting of metastatic melanoma, NCCN recommendations for first-line treatment of metastatic or unresectable melanoma list single or combination immunotherapy agents) as preferred, category 1 options. Combination therapy with dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib for BRAF-mutated disease are category 1 preferred options for first-line therapy as well. All 3 of these BRAF/MEK combination therapies are preferred, category 2A recommendations in the second-line setting for patients with BRAF-mutated disease who did not receive a BRAF-targeted agent in the first line setting. The NCCN guidelines do note that BRAF-targeted therapy is preferred over immunotherapy for patients with a BRAF V600 activating mutation if an early response is needed based on the patient's clinical presentation. Randomized clinical trials are ongoing

to compare BRAF/MEK targeted therapy to immunotherapy in the front-line setting for patients with BRAF V600-mutated disease to determine the optimal sequencing of therapy.[37] Monotherapy with either trametinib or a BRAF inhibitor (dabrafenib or vemurafenib) are no longer NCCN recommended treatment options. However, if BRAF/MEK inhibitor combination therapy is contraindicated, monotherapy with dabrafenib or vemurafenib is an option, particularly in patients who are not candidates for immunotherapy.[38]

Activating BRAF (V600E) mutations are found in about 1% to 2% of lung adenocarcinomas.[39] Patients with BRAF V600E mutations are usually current or former smokers, in contrast to patients with EGFR rearrangements or ALK mutations who are more commonly nonsmokers. Mutations in BRAF typically do not occur simultaneously in patients who are either EGFR-positive or ALK-positive.[40] Upfront BRAF testing at the time of diagnosis is a NCCN category 2A recommendation for patients diagnosed with metastatic nonsquamous NSCLC, and the American Society of Clinical Oncology (ASCO) molecular testing guideline also recommends stand-alone BRAF testing in patients with advanced lung adenocarcinoma.[41] If the patient is BRAF V600E positive, the preferred first-line therapy option is dabrafenib plus trametinib. Single agent dabrafenib or vemurafenib are options if the combination of dabrafenib plus trametinib is not tolerated. Finally, a standard initial therapy option, which may include an immunotherapy agent (both category 2A), is listed by the NCCN as useful in certain circumstances. Subsequent lines of therapy may be either option that was not received in the first-line setting.

Anaplastic thyroid carcinoma (ATC) is 1 of 3 histologic subtypes of thyroid carcinoma. It is the rarest, but also the most aggressive, of the 3 subtypes representing < 1% of all thyroid carcinomas.[42] The average age at diagnosis is 71 years, and it occurs more commonly in women compared to men. ATC has a very poor prognosis, and treatment with traditional systemic chemotherapy has demonstrated only minimal effectiveness. BRAF mutations have been noted in certain patients with ATC.[43] In 2018, the combination of dabrafenib plus trametinib was approved for the treatment of patients with locally advanced or metastatic ATC who are V600E mutation-positive.[44] The FDA approval was based on a multi-cohort, non-randomized, open-label trial for patients with rare cancers exhibiting a BRAF V600 E mutation. The 23 evaluable patients with ATC had an overall response rate (ORR) of 61% as assessed by an independent review committee.[45] A phase 2, open-label trial of 16 patients with BRAF V600E-mutated ATC demonstrated an ORR of 69% (95% confidence interval [CI], 41% to 89%).[46] The NCCN guidelines recommend BRAF molecular testing be conducted in patients diagnosed with anaplastic thyroid carcinoma and note that BRAF small molecule inhibitors may be considered if clinical trials are not available or appropriate for these patients.[47]

Erdheim-Chester disease (ECD) is a rare disease that is classified as a histiocytic disorder. The excess proliferation of histiocytes results in accumulation of these cells in bones as well as various organs and tissues. The most commonly affected sites are the long bones of the arms and legs. ECD is not categorized as a cancer, immune disorder, or infection, and very little epidemiologic data exists for ECD due to the rarity of the condition. ECD can lead to organ failure including heart failure, kidney failure, or severe lung damage.[48] Vemurafenib was approved for the treatment of ECD based on results of an open-label trial that enrolled patients with various non-melanoma BRAF V600 mutation positive diseases, including 22 patients with ECD.[49]

Approximately 5% to 9% of colorectal cancers have a BRAF V600E mutation.[50] Testing for BRAF status is recommended in the setting of metastatic colorectal cancer by both the NCCN and ASCO.[51] According

to the NCCN guidelines, encorafenib plus cetuximab (Erbitux) or panitumumab (Vectibix) is a category 2A recommendation for advanced colorectal cancer patients with unresectable metastases who are BRAF V600E mutation-positive and who have received previous adjuvant FOLFOX (folinic acid, fluorouracil, and oxaliplatin)/CAPEOX (Capecitabine and oxaliplatin) within the past 12 months. Furthermore, the regimen of encorafenib plus cetuximab or panitumumab is recommended as subsequent therapy in patients with advanced or metastatic disease who have received previous chemotherapy and are BRAF V600E mutation-positive (category 2A).[52]

PHARMACOLOGY[53,54,55,56,57,58,59,60]

BRAF is an intracellular signaling kinase in the mitogen activated protein kinase (MAPK) pathway. Some mutations in the BRAF gene, including V600E, result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would typically be required for proliferation. Vemurafenib (Zelboraf), dabrafenib (Tafinlar), and encorafenib (Braftovi) are tyrosine kinase inhibitors that inhibit BRAF V600 mutations.

Trametinib (Mekinist), cobimetinib (Cotellic), and binimetinib (Mektovi) are reversible inhibitors of mitogen-activated extracellular signal regulated kinase (MEK) 1 and MEK2. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation.

Vismodegib (Erivedge) and sonidegib (Odomzo) are hedgehog pathway inhibitors. The hedgehog signaling pathway plays a role in embryonic development, and, in adults, it plays a role in regulating adult stem cells involved in tissue maintenance and regeneration. When the pathway is disrupted, it can result in abnormalities in developing fetuses. Activation of the hedgehog pathway can lead to the development of cancers, such as BCC. Vismodegib and sonidegib selectively inhibit transmembrane protein smoothened (SMO), a key transmembrane protein involved in hedgehog signal transduction of cancerous epithelial cells.

PHARMACOKINETICS[61,62,63,64,65,66,67,68]

Drug	Half-Life (hr)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Effect of High Fat Meal (%)
binimetinib (Mektovi)	3.5	97	UGT1A1 glucuronidation (primary)	Yes	Feces: 62 Urine: 31	none
cobimetinib (Cotellic)	44 (23-70)	95	CYP3A oxidation UGT2B7 glucuronidation	None	Feces: 76 Urine: 17.8	none
dabrafenib (Tafinlar)	8	99.7	CYP3A4 and CYP2C8	Hydroxy-dabrafenib; des methyl-dabrafenib	Feces: 71 Urine: 23	AUC: ▼ 31 Cmax: ▼ 51
Encorafenib (Braftovi)	3.5	86	CYP3A4, CYP2C19, and CYP2D6	No	Feces: 47 Urine: 47	AUC: none Cmax: ▼ 36
sonidegib (Odomzo)	28 days	> 97	CYP3A	None	Feces: 70 Urine: 30	AUC: ▲ 740-780 Cmax: ▲740-780
trametinib (Mekinist)	3.9-4.8 days	97.4	Deacetylation	None	Feces: > 80 Urine: < 20	AUC: ▼24 Cmax: ▼70
vemurafenib (Zelboraf)	57	> 99	Inhibitor of CYP1A2, 2A6, 2C9, 2C19, 2D6, and 3A4/5; substrate and inhibitor of P-glycoprotein (P-gP) and CYP3A4 substrate	Yes	Feces: 94 Urine: 1	AUC: ▲ 500 Cmax: ▲250
vismodegib (Erivedge)	12 (single dose) 4 days (continued use)	> 99	Oxidation, glucuronidation, pyridine ring cleavage	2 oxidative metabolites	Feces: 82 Urine: 4.4	none

CONTRAINDICATIONS/WARNINGS[69,70,71,72,73,74,75,76]

Contraindications

There are no contraindications associated with any of the drugs contained in this review.

Warnings

Vismodegib (Erivedge) and sonidegib (Odomzo) carry boxed warnings regarding fetal death or severe birth defects. Pregnancy status should be verified prior to initiating therapy. Advise females of reproductive potential of the need for contraception and advise males of the potential risk of exposure through semen.

Selected Warnings and Recommended Monitoring

Drug	Selected Warnings	Recommended Monitoring
binimetinib (Mektovi)	Cardiomyopathy; venous thromboembolism; ocular toxicities; interstitial lung disease (ILD); hepatotoxicity; rhabdomyolysis; hemorrhage; embryo-fetal toxicity	Assess ejection fraction prior to initiating treatment, 1 month after initiating treatment, and then every 2 to 3 months during treatment; signs and symptoms of venous thromboembolism; assess for visual symptoms at each visit and when patient reports vision loss or other disturbance; assess new or unexplained pulmonary symptoms; monitor liver enzymes prior to initiation, monthly during treatment, and when indicated; monitor creatine phosphokinase/creatinine prior to initiation, periodically during treatment, and when indicated; signs and symptoms of hemorrhage; pregnancy test prior to initiation and effective contraception during treatment and for ≥ 30 days following the final dose
cobimetinib (Cotellic)	The combination of cobimetinib with vemurafenib (Zelboraf) may promote the development of new cutaneous or non-cutaneous malignancies, although the incidence of these malignancies was less in the combination therapy arm compared to the vemurafenib alone arm; hemorrhage, including cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive system hemorrhage, and hematuria; cardiomyopathy; severe rash and other skin reactions including severe photosensitivity; ocular toxicities including serous retinopathy and retinal vein occlusion; hepatotoxicity; rhabdomyolysis; embryo-fetal toxicity	Perform dermatologic evaluations prior to initiation and every 2 months while on therapy; monitor patients for signs and symptoms of non-cutaneous malignancies and signs and symptoms of hemorrhage; evaluate left ventricular ejection fraction (LVEF) prior to initiation; 1 month after initiation and every 3 months thereafter, perform an ophthalmological evaluation at regular intervals; monitor liver function prior to initiation and monthly during treatment; obtain baseline creatine phosphokinase (CPK) and creatinine levels prior to initiating and periodically during treatment

Contraindications/Warnings (continued)

Drug	Selected Warnings	Recommended Monitoring
dabrafenib (Tafinlar)	New primary cutaneous (SCC, BCC, keratoacanthomas, melanoma) and non-cutaneous malignancies; tumor promotion in wild-type BRAF tumors (melanoma and non-melanoma tumors); hemorrhage, including fatal hemorrhage; venous thromboembolism; cardiomyopathy, serious febrile reactions; ILD; ocular toxicities including retinal pigment epithelial detachment, retinal vein occlusion, uveitis, and iritis; severe cutaneous adverse drug reactions (SCARs), including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS); hyperglycemia; glucose-6-phosphate dehydrogenase deficiency (G6PD); embryo-fetal toxicity	Dermatologic evaluations every 2 months while on therapy and for up to 6 months following discontinuation; monitor for signs and symptoms of non-cutaneous malignancies; baseline assessment of left ventricular ejection fraction (LVEF) and at, 1 month after initiation and then at 2 to 3 month intervals while on treatment; monitor for signs and symptoms of uveitis including change in vision, photophobia or eye pain; serum creatinine during and following severe pyrexia; serum glucose upon initiation and as clinically appropriate in patients with preexisting diabetes or hyperglycemia; signs and symptoms of venous thromboembolism; temperature; visual symptoms; complete blood count (CBC); advise females of reproductive age of potential risk to fetus and use of effective non-hormonal contraceptive; advise males with female partners of reproductive age to use condoms during treatment and for ≥ 2 weeks after the last dose
encorafenib (Braftovi)	New primary malignancies; tumor promotion in BRAF wild-type tumors; hemorrhage; uveitis; QT prolongation; embryo-fetal toxicity; use in monotherapy (e.g. dermatologic adverse effects)	Dermatologic evaluations before, during and after treatment; assess for visual symptoms at each visit and ophthalmologic evaluation at regular intervals for new of worsening disturbances; monitor electrolytes and control other cardiac risk factors, withhold if QTc > 500 ms; avoid use with other QT-prolongation agents; pregnancy test and non-hormonal contraception
sonidegib (Odomzo)	Embryo-fetal toxicity, musculoskeletal adverse reactions, premature fusion of the epiphyses in pediatric patients exposed to sonidegib	Verify pregnancy status of females of reproductive potential; advise contraception for at least 20 months after the last dose in females and for at least 8 months after the last dose in males; advise patients against blood donations for at least 20 months after last dose; baseline renal function and serum creatine kinase (CK) levels and periodically during treatment and as clinically indicated (at least weekly in patients with musculoskeletal adverse reactions with concurrent CK elevation > 2.5 times upper limit of normal [ULN])

Contraindications/Warnings (continued)

Drug	Selected Warnings	Recommended Monitoring
trametinib (Mekinist)	Cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, uveitis, iritis, ILD, hemorrhage, venous thromboembolism, cardiomyopathy, SCARs including SJS and DRESS, serious febrile reactions, hyperglycemia, new primary malignancies (both cutaneous and non-cutaneous), embryo-fetal toxicity, colitis and gastrointestinal (GI) perforation	Monitor LVEF at baseline, after 1 month of treatment and approximately every 2 to 3 months thereafter; monitor for visual disturbances and perform ophthalmological evaluation periodically and with any report of visual disturbances; pulmonary symptoms, fever, and signs and symptoms of venous thromboembolism, serum creatinine during and following severe pyrexia; serum glucose at initiation and as clinically appropriate; monitor for new or worsening serious skin reactions; signs and symptoms of colitis and GI perforations; advise females of reproductive age of potential risk to fetus and use of effective contraceptive during treatment and for ≥ 4 months following therapy; advise males with female partners of reproductive age to use condoms during treatment and for ≥ 4 months after the last dose
vemurafenib (Zelboraf)	New primary malignancies including cutaneous and non-cutaneous (SCC, keratoacanthoma, melanoma) tumor promotion in BRAF wild-type melanoma; serious hypersensitivity reactions/anaphylaxis; severe dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); QT prolongation and torsade de pointes; hepatotoxicity; mild/severe photosensitivity; ophthalmologic reactions (uveitis, blurry vision, photophobia); radiation sensitization and recall involving cutaneous and visceral organs in patients treated with radiation prior to, during or subsequent to vemurafenib treatment; renal failure, including acute interstitial nephritis and acute tubular necrosis; Dupuytren's contracture and plantar fascial fibromatosis; myeloid neoplasms in ECD patients	Dermatologic evaluations prior to initiation and every 2 months while on therapy, consider dermatologic monitoring for 6 months following discontinuation; ECG and electrolytes prior to initiation, after 15 days, monthly during the first 3 months and then every 3 months thereafter or more often as clinically indicated as well as after any dose modification; monitor transaminases, alkaline phosphatase, and bilirubin before initiation of treatment and monthly during treatment or as clinically indicated; signs and symptoms of uveitis; monitor closely if receiving concomitant or sequential radiation treatment; measure serum creatinine before initiation of treatment and periodically during treatment; monitor CBC in patients with ECD with co-existing myeloid malignancies
vismodegib (Erivedge)	Embryo-fetal toxicity, blood donation while on drug and up to 24 months after last dose is not recommended, male patients should not donate semen during and for 3 months after the final dose of vismodegib; premature fusion of the epiphyses has been reported in pediatric patients exposed to vismodegib and in such cases fusion progressed after drug discontinuation	Verify pregnancy status of females of reproductive potential within 7 days prior to initiating vismodegib therapy; advise females of reproductive potential to use effective contraception during therapy with vismodegib and for 24 months after the final dose; advise male patients to use condoms, even after a vasectomy, to avoid potential drug exposure in pregnant partners and female partners of reproductive potential during therapy and for 3 months after final dose

Dabrafenib and/or trametinib should be permanently discontinued for all grade 4 hemorrhagic events and for any persistent grade 3 hemorrhagic events.

Permanently discontinue dabrafenib for persistent grade 2 or greater uveitis of > 6 weeks duration.

Permanently discontinue trametinib for cases of life threatening pulmonary embolism (PE), for symptomatic cardiomyopathy or persistent, asymptomatic LV dysfunction of > 20% from baseline that is below the lower limit of normal (LLN) that does not resolve within 4 weeks or for patients diagnosed with treatment-related ILD or pneumonitis.

Permanently discontinue vemurafenib in patients who experience a severe hypersensitivity reaction or a severe dermatologic reaction.

Do not initiate vemurafenib treatment in patients with uncorrectable electrolyte abnormalities (including potassium, magnesium, and calcium), QTc > 500 ms or long QT syndrome or in patients who are taking other medications known to prolong the QT interval. Permanently discontinue vemurafenib if QTc interval remains > 500 ms and increased > 60 ms from pre-treatment values after controlling cardiac risk factors for QT prolongation (e.g., electrolyte abnormalities, congestive heart failure, bradyarrhythmias).

DRUG INTERACTIONS[77,78,79,80,81,82,83,84]

Cytochrome p450 3A (CYP3A)

CYP3A Inhibitors

Avoid concurrent use of cobimetinib (Cotellic) and strong or moderate CYP3A inhibitors. If concurrent short-term use (≤ 14 days) of a moderate CYP3A inhibitor, including certain antibiotics (erythromycin, ciprofloxacin), is unavoidable in patients receiving cobimetinib 60 mg, reduce the dose to 20 mg and resume previous dose after discontinuation of the moderate CYP3A inhibitor. Use an alternative medication to a strong or moderate CYP3A inhibitor in patients who are taking a reduced dose of cobimetinib (20 mg or 40 mg daily).

Avoid concomitant administration of sonidegib (Odomzo) with moderate CYP3A inhibitors (e.g., atazanavir, diltiazem, fluconazole). If a moderate CYP3A inhibitor must be used, administer the moderate CYP3A inhibitor for less than 14 days and monitor closely for adverse reactions, particularly musculoskeletal adverse reactions

Avoid coadministration of strong CYP3A4 inhibitors with vemurafenib, which may lead to increased toxicity of vemurafenib. If coadministration is unavoidable, consider dose reduction of vemurafenib if clinically indicated.

Avoid concurrent use of strong or moderate CYP3A4 inhibitors during treatment with encorafenib (Braftovi). If concomitant use of a strong or moderate CYP3A4 inhibitor is unavoidable, reduce the encorafenib dose to one-third of the encorafenib dose prior to concurrent use of strong CYP3A4 inhibitors or one-half of the encorafenib dose prior to concurrent use of moderate CYP3A4 inhibitors. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the encorafenib dose that was taken prior to initiating the CYP3A4 inhibitor.

CYP3A Inducers

Avoid concurrent use of cobimetinib and strong or moderate CYP3A inducers (e.g., carbamazepine, efavirenz, phenytoin, rifampin, St. John's wort) as these may decrease the systemic exposure of cobimetinib and reduce its efficacy.

Avoid concomitant use of strong CYP3A4 inducers with vemurafenib (Zelboraf). If concomitant use is unavoidable, increase the dose of vemurafenib by 240 mg (1 tablet) as tolerated.

Concomitant administration of encorafenib (Braftovi) with a strong or moderate CYP3A4 inducer may decrease encorafenib plasma concentrations and may decrease encorafenib efficacy. Avoid concomitant administration of strong or moderate CYP3A4 inducers with encorafenib.

Substrates of CYP3A4

Vemurafenib is an inhibitor of CYP3A4, and, when co-administered with drugs eliminated by this enzyme, has the potential to increase the plasma concentrations of the CYP3A4 substrates. Caution is advised when using vemurafenib with CYP3A4 substrates that have a narrow therapeutic index (e.g., alfentanil, cyclosporine, ergot alkaloids, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).

Concomitant administration of sensitive CYP3A4 substrates with encorafenib (Braftovi) may result in decreased efficacy or increased toxicity or of these agents. Coadministration of encorafenib with hormonal contraceptives that are CYP3A4 substrates can result in decreased concentrations, leading to loss of hormonal contraceptive efficacy; use of hormonal contraceptives should be avoided.

CYP2B6 and CYP2C8 Enzyme Inhibitors or Substrates

CYP2B6 and CYP2C8 Inhibitors

Avoid concomitant use of dabrafenib (Tafinlar) with strong CYP2C8 inhibitors (e.g., gemfibrozil).

CYP2C9 Enzyme Inhibitors or Substrates

Dabrafenib induces CYP2C9 and may result in loss of efficacy with dexamethasone or hormonal contraceptives.

CYP1A2 Substrates

Coadministration of vemurafenib with tizanidine, a sensitive CYP1A2 substrate, increased tizanidine systemic exposure by 4.7-fold. Avoid concomitant use of vemurafenib with drugs having a narrow therapeutic window that are predominantly metabolized by CYP1A2. If coadministration cannot be avoided, monitor closely for toxicities, and consider a dose reduction of concomitant CYP1A2 substrates.

Warfarin

Warfarin is metabolized by CYP2C9 and CYP3A4.

Dabrafenib induces CYP2C9 and CYP3A4 and decreases the exposure to R-warfarin. International normalized ratio (INR) levels should be monitored frequently in patients receiving warfarin during initiation or discontinuation of dabrafenib.

Patients receiving warfarin and vemurafenib should have their INRs monitored closely.

P-glycoprotein (P-gP) Inhibitors and Substrates

P-gP Inhibitors

Vemurafenib is an inhibitor of P-gP and has the potential to increase levels of P-gP substrates (e.g., digoxin, quinidine, loperamide).

P-gP Substrates

Vemurafenib is both a substrate and inhibitor of P-gP. Coadministration of vemurafenib and digoxin increased digoxin systemic exposure by 1.8-fold. Avoid concurrent use of vemurafenib and P-gp substrates known to have narrow therapeutic indices. If use of these medications is unavoidable, consider dose reduction of the P-gp substrates with narrow therapeutic indices.

Vismodegib (Erivedge) is a substrate of P-gP. When it is co-administered with P-gP inhibitors (e.g., tacrolimus, verapamil, ritonavir), systemic exposure of vismodegib may be increased.

Antacids

Solubility of vismodegib may be altered with drugs that affect pH of the upper GI tract.

Histamine$_2$- Receptor Blockers/Proton Pump Inhibitors

Drugs that alter the pH of the upper GI tract may alter the solubility of dabrafenib and reduce its bioavailability. However, no formal clinical trial has been conducted to evaluate the effect of gastric pH-altering agents on the systemic exposure of dabrafenib.

Ipilimumab (Yervoy®)

Concurrent administration of vemurafenib and ipilimumab caused an increase in transaminases and bilirubin in the majority of patients who received the combination

ADVERSE EFFECTS[85,86,87,88,89,90,91,92]

Drug	Rash	Hemorrhage	Pyrexia	Increased AST/ALT	Cutaneous	Ocular Toxicities	Cardiomyopathy
binimetinib (Mektovi) + encorafenib (Braftovi) n=192 vemurafenib (Zelboraf) n=186 metastatic melanoma	22 (53)	19 (9)	18 (30)	27-29 (24-27)	panniculitis = < 10 cutaneous malignancies = 1.6-2.6	20 (2-4)	7
cobimetinib (Cotellic) + vemurafenib (Zelboraf) n=247 vemurafenib (Zelboraf) + placebo n=246 metastatic melanoma	11 (16)	13 (7)	28 (23)	73 (44)	SCC = 6 (20) BCC = 4.5 (2.4) Second primary melanoma = 0.8 (2.4)	15 (< 1)	26 (19)
dabrafenib (Tafinlar) n=187 dacarbazine n=59	17 (0)	nr	18 (10)	nr	Hyperkeratosis = 37 (0) SCC = 7 (0)	nr	nr
dabrafenib (Tafinlar) + trametinib (Mekinist) n=559 dabrafenib (Tafinlar) n=211 metastatic melanoma	32 (27)	19 (15)	54 (33)	nr	BCC = 3.3 (6) SCC/keratoacanthoma = 3 (10) Second primary melanoma = 0.5 (1.9)	1 (2)	6 (2.9)
dabrafenib (Tafinlar) + trametinib (Mekinist) n=435 adjuvant melanoma	37 (17)	nr	63 (11)	57 (11)	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group or comparator drug are indicated in parentheses unless otherwise specified.
nr = not reported, SCC = squamous cell carcinoma, BCC = basal cell carcinoma

Adverse Effects (continued)

Drug	Rash	Hemorrhage	Pyrexia	Increased AST/ALT	Cutaneous	Ocular Toxicities	Cardiomyopathy
dabrafenib (Tafinlar) + trametinib (Mekinist) n=93 NSCLC	28	23	55	61/32	dry skin = 31 rash = 28	nr	nr
encorafenib (Braftovi) + cetuximab (Erbitux) n=216 irinotecan with cetuximab or FOLFIRI with cetuximab n=193 metastatic colorectal cancer	26 (26)	19 (9)	17 (15)	17/29 (15/22)	Dermatitis acneiform: 32 (43) Melanocytic nevus: 14 (0) Pruritus: 14 (6)	nr	nr
sonidegib (Odomzo)	nr	nr	nr	19	nr	nr	nr
trametinib (Mekinist) n=211 chemotherapy n=99	57 (10)	13 (0)	nr	60 (16)	Acneiform dermatitis = 19 (1)	reported	reported
vemurafenib (Zelboraf) n=336 (dacarbazine) n=287	37 (2)	nr	19 (9)	2.8 (1.9)	SCC = 24 (< 1)	2.1 (0)	nr
vemurafenib (Zelboraf) n=22 ECD	59	nr	nr	9.1	SCC of skin=36	nr	nr
vismodegib (Erivedge) n=138	nr	nr	nr	nr	Alopecia = 63.8	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group or comparator drug are indicated in parentheses unless otherwise specified.
nr = not reported, SCC = squamous cell carcinoma, BCC = basal cell carcinoma

The most common adverse events (> 10%) with sonidegib (Odomzo) were muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus. Adverse reactions that led to discontinuation of sonidegib in at least 2 patients were muscle spasms and dysgeusia, asthenia, increased lipase, nausea, fatigue, decreased appetite, alopecia, and decreased weight.

The most common adverse reactions (> 10%) reported with vismodegib (Erivedge) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia. In postmarketing experience, the increase of blood creatine phosphokinase (CPK) and drug-induced liver injury with vismodegib have been reported. In a pooled analysis of clinical trials, 30% of premenopausal women developed amenorrhea while receiving vismodegib.

The adverse effects experienced with dabrafenib (Tafinlar), used in combination with trametinib, in patients with BRAF V600E-mutation positive ATC in clinical trials were similar to those observed in other approved indications.

The most common (≥ 25%) adverse reactions in patients receiving binimetinib (Mektovi) in combination with encorafenib (Braftovi) were fatigue (43%), nausea (41%), diarrhea (36%), vomiting (30%), and abdominal pain (28%).

SPECIAL POPULATIONS[93,94,95,96,97,98,99,100]

Pediatrics

None of the agents included in this review have been established to be safe and effective for use in patients < 18 years of age.

Premature fusion of the epiphyses has been reported in pediatric patients exposed to vismodegib (Erivedge). In some cases, fusion progressed after drug discontinuation.

Geriatrics

Clinical studies of vismodegib and cobimetinib (Cotellic) did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger patients.

No difference in efficacy or safety between older and younger patients was observed with dabrafenib (Tafinlar) monotherapy. There were an insufficient number of patients aged ≥ 65 years who received trametinib (Mekinist) monotherapy to determine if they respond differently from younger patients. Clinical studies of dabrafenib (Tafinlar) in combination with trametinib (Mekinist) for the treatment of melanoma found no difference in efficacy between older and younger patients; however, peripheral edema and anorexia occurred at a higher rate in older patients.

There were no overall differences in effectiveness of sonidegib (Odomzo) between patients who were ≥ 65 years of age and those who were younger. There was a higher incidence of grade 3 and 4 adverse events and adverse events requiring dose interruption or discontinuation in patients ≥ 65 years compared to younger patients.

Elderly patients (≥ 65 years old) on vemurafenib (Zelboraf) may be more likely to experience some adverse reactions, including cutaneous squamous cell carcinoma (cuSCC), nausea, decreased appetite,

peripheral edema, keratoacanthoma, and atrial fibrillation. The effects of vemurafenib on overall survival (OS), progression-free survival (PFS), and best overall response rate (ORR) were similar in the elderly compared with younger patients.

No overall differences in the safety or effectiveness of binimetinib (Mektovi) in combination with encorafenib (Braftovi) were observed in elderly patients as compared to younger patients.

Pregnancy

Based on findings from animal reproduction studies and its mechanism of action, cobimetinib can cause fetal harm when administered to a pregnant woman. In animal studies, cobimetinib was teratogenic and embryotoxic at exposures that were 0.9 to 1.4 times those observed in humans at the recommended dose. Pregnant women should be advised of the potential risk to the fetus. Females of reproductive potential should use effective contraception during treatment with cobimetinib and for 2 weeks after the final dose.

Females of reproductive potential taking dabrafenib should use highly effective, non-hormonal contraception during treatment and for at least 2 weeks after treatment. Dabrafenib can render hormonal contraceptives ineffective. Male patients with female partners of reproductive potential should use condoms during treatment with trametinib and for > 2 weeks after the last dose.

There are no available data on the use of sonidegib in pregnant women but, based on its mechanism of action and data from animal reproduction studies, sonidegib can cause fetal harm when administered to pregnant women. Females of reproductive potential should use effective contraception during treatment with sonidegib and for at least 20 months after the last dose.

Female patients of reproductive potential should use highly effective contraception during treatment with trametinib and for > 4 months after the last dose of trametinib. Male patients with female partners of reproductive potential should use condoms during treatment with trametinib and for > 4 months after the last dose.

Based on its mechanism of action, vemurafenib can cause fetal harm when administered to a pregnant woman. There are no available data to determine the drug-associated risk; however, placental transfer of vemurafenib to a fetus has been reported. Women of child-bearing potential should be advised of the potential harm to a fetus. Female patients of reproductive potential should use highly effective contraception during treatment with vemurafenib and for 2 weeks after the last dose of vemurafenib.

There are no human data on the use of vismodegib in pregnant women. In animal reproduction studies, administration of vismodegib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats. Females of reproductive potential should be advised to use effective contraception during therapy and for 24 months after the final dose.

Male patients receiving vismodegib or sonidegib should use condoms with spermicide, even after a vasectomy, during sexual intercourse with female partners while being treated and for ≥ 2 months after the last dose of vismodegib and for ≥ 8 months after the last dose of sonidegib to avoid exposing an embryo or fetus to these agents.

Based on findings from animal reproduction studies and its mechanism of action, binimetinib (Mektovi) and encorafenib (Braftovi) can cause fetal harm when administered to a pregnant woman. Females of

reproductive potential should use non-hormonal contraception because encorafenib has the potential to render hormonal contraceptives ineffective. Effective contraceptive methods are recommended during treatment with binimetinib and encorafenib and for at least 30 days after the final dose.

Renal Impairment

No clinical studies were conducted with binimetinib, sonidegib, or vismodegib in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of these agents is recommended in patients with renal impairment.

Dose adjustment of cobimetinib is not recommended for mild to moderate renal impairment (creatinine clearance [CrCl], 30 to 89 mL/min) based on population pharmacokinetic analysis; however, a recommended dose has not been established for patients with severe renal impairment.

No dose adjustment of dabrafenib or trametinib is recommended in patients with mild or moderate renal impairment; the appropriate doses of dabrafenib and trametinib have not been established in patients with severe renal impairment.

No adjustment to the starting dose of vemurafenib is needed for patients with pre-existing mild and moderate renal impairment. Vemurafenib should be used with caution in patients with pre-existing severe renal impairment.

No dose adjustment is recommended for encorafenib patients with mild to moderate renal impairment (CrCl, 30 to 89 mL/min). A recommended dose has not been established for patients with severe renal impairment (CrCl < 30 mL/min).

Hepatic Impairment

No starting dose adjustment is required for cobimetinib for patients with any degree of hepatic impairment (Child-Pugh A, B, or C).

No dose adjustment is recommended for dabrafenib, trametinib or sonidegib with mild hepatic impairment, but these agents have not been studied in patients with moderate to severe hepatic impairment. Patients with moderate to severe hepatic impairment may have increased exposure to dabrafenib as hepatic metabolism and biliary secretion are the primary elimination routes.

No adjustment to the starting dose of vemurafenib is needed for patients with pre-existing mild and moderate hepatic impairment. It should be used with caution in patients with pre-existing severe hepatic impairment.

No dose adjustment is required for patients with hepatic impairment who are receiving vismodegib.

No dose adjustment is recommended for binimetinib patients with mild hepatic impairment. Reduce the starting dose of binimetinib to 30 mg twice daily for patients with moderate or severe hepatic impairment. Likewise, no dose adjustment is recommended for encorafenib patients with mild hepatic impairment; however, a recommended dose has not been established for patients with moderate to severe hepatic impairment.

DOSAGES[101,102,103,104,105,106,107,108]

Drug	Melanoma	Basal Cell Carcinoma	Non-Small Cell Lung Cancer	Other Indications	Administration Comments	Available Strengths
binimetinib (Mektovi)	In combination with encorafenib (Braftovi): 45 mg twice daily	--	--	--	--	15 mg tablets
cobimetinib (Cotellic)	In combination with vemurafenib (Zelboraf): 60 mg (three 20 mg tablets) orally once daily for the first 21 days of each 28-day cycle	--	--	--	--	20 mg tablets
dabrafenib (Tafinlar)	As a single agent: 150 mg every 12 hours In combination with trametinib (Mekinist): 150 mg every 12 hours	--	In combination with trametinib: 150 mg twice daily	**Anaplastic Thyroid Carcinoma:** 150 mg twice daily in combination with trametinib	Do not open, crush or break capsules; take at least 1 hour before or 2 hours after a meal	50 mg, 75 mg capsules
encorafenib (Braftovi)	In combination with binimetinib (Mektovi): 450 mg twice daily	--	--	**Metastatic colorectal cancer:** In combination with cetuximab (Erbitux): 300 mg once daily	May be taken with or without food.	75 mg capsules
sonidegib (Odomzo)	--	200 mg orally once daily	--	--	Take on an empty stomach, at least 1 hour before or 2 hours after a meal	200 mg capsule
trametinib (Mekinist)	As a single agent: 2 mg once daily In combination with dabrafenib (Tafinlar): 2 mg once daily	--	In combination with dabrafenib: 2 mg once daily	**Anaplastic Thyroid Carcinoma:** 2 mg once daily in combination with dabrafenib	Take 1 hour before or 2 hours after a meal	0. 5 mg, 2 mg tablets

Consult package insert for each individual medication for additional detailed information related to dosing and dose modifications.

Dosages (continued)

Drug	Melanoma	Basal Cell Carcinoma	Non-Small Cell Lung Cancer	Other Indications	Administration Comments	Available Strengths
vemurafenib (Zelboraf)	960 mg (four 240 mg tablets) twice daily (12 hours apart)	--	--	**Erdheim-Chester Disease:** 960 mg (four 240 mg tablets) every 12 hours	May be taken with or without food; swallow capsules whole with water; do not crush or chew tablets	240 mg tablets
vismodegib (Erivedge)	--	150 mg once daily	--	--	May be taken with or without food; swallow capsules whole	150 mg capsule

Consult package insert for each individual medication for additional detailed information related to dosing and dose modifications.

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled, phase 3 trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to a paucity of data in the literature, clinical trials that are open-label, placebo-controlled, and have dropout rates in excess of 20% have been included in this therapeutic class review. In addition, where published phase 3 data for the FDA-approved indications is lacking, phase 1/2 studies cited in the package insert are included in this therapeutic class review.

Anaplastic Thyroid Carcinoma

dabrafenib (Tafinlar) plus trametinib (Mekinist)

A phase 2, open-label trial enrolled patients with BRAF V600E-mutated rare malignancies. One cohort of the study included 16 evaluable patients with BRAF V600E-mutated anaplastic thyroid carcinoma (ATC).[109] Enrolled patients received dabrafenib 150 mg twice daily and trametinib 2 mg once daily until unacceptable toxicity, disease progression, or death. The primary endpoint was objective response rate (ORR) as assessed by the investigator. Secondary endpoints included duration of response, PFS, OS, and safety. Of the 16 ATC patients, all had received prior radiation therapy and/or surgery and 6 had received prior systemic therapy. At a median follow up of 47 weeks, the investigator-assessed ORR was

69%. Although median PFS and OS had not been reached, 12-month estimates were 79% and 80%, respectively. In the overall study population of 100 patients, the most common adverse events noted were fatigue (38%), pyrexia (37%), and nausea (35%).

Basal Cell Carcinoma

sonidegib (Odomzo)

BOLT was a multicenter, randomized, double-blind phase 2 trial in patients with locally advanced BCC (not amendable to curative surgery or radiation therapy) or metastatic BCC.[110] Patients (n=230) were randomized 1:2 to receive 200 mg (n=79) or 800 mg (n=151) of oral sonidegib daily. The primary endpoint was ORR. Secondary endpoints included time to tumor response and duration of response. Response evaluation was conducted by a central review committee as well as investigators at baseline, weeks 5 and 9, and then every 8 weeks during year 1 and every 12 weeks thereafter. Response for patients with locally advanced BCC (laBCC) was conducted utilizing the modified Response Criteria in Solid Tumors (RECIST) (modification included the use of digital photographs), and RECIST version 1.1 was used to assess patients with metastatic BCC (mBCC). At a median follow-up of 13.9 months, 63% of patients had discontinued treatment, and at 12-months after the last patient was randomized, 78% of patients had discontinued treatment due to adverse events, patient choice, or disease progression. At a median follow-up of 13.9 months, the ORR was 36% (95% CI, 24 to 50) for the sonidegib 200 mg group and 34% (95% CI, 25 to 43) for the sonidegib 800 mg group. For both dosages, the ORR was higher in patients with locally advanced BCC, (43% response in the 200 mg group and 38% in the 800 mg group) compared to the patients with metastatic BCC (15% in the 200 mg group and 17% in the 800 mg group). Fewer adverse events leading to dose interruptions or dose reductions occurred in the sonidegib 200 mg group compared to the sonidegib 800 mg group. The most common grade 3 to 4 adverse events were raised creatine kinase (5 in the 200 mg group versus 19 in the 800 mg group) and lipase concentration (4 versus 8, respectively). Serious adverse events occurred in 11 of 79 patients in the 200 mg group and 45 of 150 patients in the 800 mg group. With a follow up of 12-months after the last patient was randomized, the ORR was 57.6% in the 200 mg group and 43.8% in the 800 mg group.[111] Response rates over this longer period of time had improved in the patients with locally advanced BCC while they remained similar in patients with metastatic BCC. Median time to tumor response was 4 and 3.8 months in the 200 mg and 800 mg groups, respectively, by central review. Retrospective median durations of response by investigator review were 20.2 months and 19.8 months for the 2 groups. Adverse events reported at the longer follow up time were similar to those reported in the initial analysis and included muscle spasms, alopecia, dysgeusia, nausea, increased creatine kinase, weight loss, decreased appetite, myalgia, and vomiting. Increased creatine kinase was the most common grade 3/4 event. Published 30 month follow up data of the BOLT study indicated the median duration of response was 26.1 months according to centralized review for patients with laBCC and 24 months assessed by central review for patients with mBCC. Median OS was not reached in either population, but 2 year OS was 93.2% for laBCC and 69.3% for mBCC.[112] A 42 month follow up of the BOLT trial revealed similar analyses as those reported at 12, 18, and 30 months with a median duration of response exceeding 2 years.[113]

vismodegib (Erivedge)

ERIVANCE was a phase 2, single-arm, open-label, multicenter, 2-cohort trial conducted in 104 patients with either metastatic basal cell carcinoma (mBCC) (n=33) or locally advanced basal cell carcinoma

(laBCC) (n= 71).[114] About 95% of patients were previously treated with surgery, radiation, and/or systemic therapies. All patients received 150 mg vismodegib per day until disease progression or unacceptable toxicity occurred. The median duration of treatment was 10.2 months (range, 0.7 to 18.7 months). The major efficacy outcome measure of the trial was ORR as assessed by an independent review facility. Of the 104 patients enrolled, 96 patients were evaluable for ORR. Complete response (CR) was reported in 0% of subjects in the mBCC group and 20.6% in the laBCC group. Partial response was reported in 30.3% of subjects in the mBCC group and 22.2% in the laBCC group. Median response duration was 7.6 months in both cohorts. Serious adverse events were reported in 25% of patients; 7 deaths due to adverse events were noted. At a 12-month follow up after the primary analysis, the ORR had increased from 30.3% to 33.3% in the mBCC group and from 42.9% to 47.6% in the laBCC.[115] Median duration of response increased for patients with laBCC from 7.6 months to 9.5 months. No new safety signals were discovered.

The Safety Events in Vismodegib Study (STEVIE) was a multicenter, open-label trial involving 1,232 patients with either locally advanced BCC (n=1,119) or metastatic BCC (n=96) who were ineligible for surgery.[116] All patients were treated with vismodegib 150 mg daily until disease progression, unacceptable toxicity, or withdrawal of consent, death, or other reasons for discontinuation. The primary objective of the study was safety and efficacy (overall response) was a secondary endpoint. At a follow up of 12 months or longer, 80% of patients had discontinued drug, 36% had adverse events, 14% had progressive disease, and 10% requested to stop treatment. Median duration of treatment was 36.4 weeks. Adverse events occurred in 98% of patients with the most common events being muscle spasms (66%), dysgeusia (55%), alopecia (62%), decreased weight (41%), decreased appetite (25%), and asthenia (24%). Most adverse events were grade 1 or 2, while 24% of patients experienced serious adverse events, and there were 46 deaths with 7 considered to be related to vismodegib. Patients with locally advanced BCC had an investigator-assessed response rate of 68.5% compared to 36.9% of patients with metastatic BCC.

Colorectal Cancer (CRC)

encorafenib (Braftovi) plus cetuximab ((Erbitux) versus irinotecan plus cetuximab or FOLFIRI plus cetuximab

BEACON CRC was a global, multicenter, randomized, open-label, phase 3 study, evaluating the efficacy and safety of cetuximab combined with encorafenib versus irinotecan plus cetuximab or FOLFIRI (leucovorin, fluorouracil, irinotecan) plus cetuximab in patients with BRAF V600E mutation-positive metastatic colorectal cancer (mCRC) whose disease had progressed after 1 or 2 prior regimens in the metastatic setting.[117,118] A total of 665 patients were randomized in a 1:1:1 ratio into 3 groups (triplet-therapy, doublet-therapy, control arm). Patients in the triplet-therapy group received oral encorafenib (300 mg daily), oral binimetinib (45 mg twice daily), and cetuximab (400 mg/m^2 intravenously (IV) for the first dose followed by 250 mg/m^2 weekly). Similarly, patients in the doublet-therapy group received oral encorafenib and IV cetuximab, administered in the same doses and on the same schedule as the triplet-therapy group. Patients in the control group received the investigators' choice of either cetuximab with irinotecan 180 mg/m^2 IV on days 1 and 15 of each 28-day cycle or with FOLFIRI IV (irinotecan 180 mg/m^2 on days 1 and 15; folinic acid 400 mg/m^2 on days 1 and 15; then fluorouracil 400 mg/m^2 bolus on days 1 and 15 followed by fluorouracil 2,400 mg/m^2/day via continuous infusion over 2 days). The primary endpoints were analyzed for the triplet-therapy group and included overall survival (OS) and ORR, as assessed by blinded central reviewers using RECIST criteria, version 1.1. The

secondary endpoints included OS and ORR in doublet-therapy group versus control group, and progression free survival (PFS) in all groups. The median OS was 9 months in the triplet-therapy group compared to 5.4 months in the control group (hazard ratio [HR], 0.52; 95% CI, 0.39 to 0.7; p<0.0001), while the median OS in the doublet-therapy group was 8.4 months (95% CI, 7.5 to 11) compared to 5.4 months in the control group (HR, 0.6; 95% CI 0.45 to 0.79; p<0.0001). The ORR was 26% (95% CI, 18 to 35) in the triplet-therapy group compared to 2% (95% CI, 0 to 7) in the control group, while the ORR was 20% (95% CI, 13 to 29) in doublet-therapy group. Additionally, PFS was reported in the doublet-therapy group (4.2 months) and control group (1.5 months) (HR, 0.4; 95% CI, 0.31 to 0.52; p<0.0001). The most common adverse reactions (>25%) for the combined cetuximab plus encorafenib were fatigue, nausea, diarrhea, dermatitis acneiform, abdominal pain, decreased appetite, arthralgia, and rash.[119] Discontinuation of therapy due to an adverse event was reported in 7% (triplet-therapy), in 8% (doublet-therapy), and in 11% (control group). Fatal adverse events occurred in 4%, 3%, and 4% of the patients, respectively, including treatment-related deaths due to colonic perforation (n=1), anaphylaxis (n=1), and respiratory failure in the triplet-therapy and control groups.[120]

Erdheim-Chester Disease (ECD)

vemurafenib

The VE-BASKET trial was an open-label, nonrandomized, multicohort study for patients with nonmelanoma cancers harboring the BRAF V600 mutation. One cohort of this study enrolled patients with either ECD (n=22) or Langerhans cell histiocytosis (n=4) with BRAF V600E-mutant disease.[121] Patients were treated with vemurafenib 960 mg twice daily until disease progression, study withdrawal, or occurrence of intolerable adverse effects. The primary endpoint was ORR by RECIST v1.1. The confirmed ORR was 54.5% in patients with ECD. At a median follow up of 28.8 months, 2-year PFS was 86% and 2-year OS was 96% in the overall cohort. The most common adverse events were arthralgia, maculopapular rash, fatigue, alopecia, prolonged QT interval, skin papilloma, and hyperkeratosis.

Melanoma – Adjuvant Therapy -Stage 3/BRAF V600 Mutation Positive

dabrafenib plus trametinib versus placebo

COMBI-AD was a randomized, double-blind, placebo-controlled trial (n=870) that enrolled patients with completely resected stage 3 melanoma with BRAF V600E or V600K mutations. [122]Enrolled patients had received no prior systemic anticancer therapy or radiation therapy for melanoma and were randomized (1:1) to receive trametinib 2 mg once daily in combination with dabrafenib 150 mg twice daily or 2 placebos for up to 1 year. The primary endpoint was relapse-free survival. Secondary endpoints included OS, distant metastasis-free survival, freedom from relapse and safety. Relapse-free survival (RFS) was defined as the time from randomization to disease recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurred first as assessed by the investigator. At a median follow up of 2.8 years, the estimated 3-year rate of relapse-free survival was 58% in the combination therapy group and 77% in the placebo group (HR, 0.57; 95% CI, 0.42 to 0.79; p=0.0006). Despite the significant p-value, the between-group difference was not significant because it did not cross the prespecified interim boundary of p=0.000019. The estimated rates of RFS in the combination therapy group were 88%, 67%, and 58% in years 1 to 3, respectively, compared to 56%, 44%, and 39%, respectively, in the placebo group. OS at 2.8 years was 86% in the

combination therapy arm and 78% in the placebo arm. Median OS had not been reached in either group. The most common adverse events in the combination therapy arm (occurring in > 10% of patients) were pyrexia (any grade, 63 %,), fatigue (any grade, 47%), and nausea (any grade, 40%). One fatal case of pneumonia occurred in the combination therapy group, and new primary melanoma was reported in 11 patients (3%) of the combination therapy group and in 10 patients (2%) of the placebo group.

Melanoma – Unresectable or Metastatic/*BRAF* V600 Mutation-Positive

combined binimetinib (Mektovi) plus encorafenib (Braftovi) versus vemurafenib (Zelboraf)

COLUMBUS, a 2-part international, multicenter, randomized, phase 3 study, evaluated the efficacy and safety of binimetinib combined with encorafenib versus vemurafenib in patients with unresectable, locally advanced or metastatic *BRAF* V600 mutation-positive melanoma who were previously untreated or had progressed on or after previous first-line immunotherapy.[123,124] A total of 577 patients were randomized in a 1:1:1 ratio to receive oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily (encorafenib plus binimetinib group), oral encorafenib 300 mg once daily (encorafenib group), or oral vemurafenib 960 mg twice daily (vemurafenib group). The primary endpoint was PFS as assessed by blinded central reviewers using RECIST criteria, version 1.1. The secondary endpoints included overall survival (OS), ORR, duration of response, and safety. Part 1 of COLOMBUS reported a median follow up for PFS at 16.6 months (range, 14.8 to 16.9 months). The PFS was 14.9 months in the encorafenib plus binimetinib group compared to 7.3 months in the vemurafenib group (HR, 0.54; 95% CI, 0.41 to 0.71; p<0.0001). The centrally-assessed ORR was 63% in the encorafenib plus binimetinib arm compared with 40% in the vemurafenib arm. Part 2 of the trial reported that median OS was 33.6 months with encorafenib plus binimetinib and 16.9 months with vemurafenib (HR, 0.61; 95% CI, 0.47 to 0.79]; p<0.0001).[125]

dabrafenib (Tafinlar) versus dacarbazine

BREAK-3 was a randomized (3:1), open-label, active-controlled, international, multicenter trial conducted in 250 patients using dabrafenib for untreated *BRAF* V600E mutation-positive, unresectable or metastatic melanoma which assessed progression-free survival (PFS) as the primary efficacy outcome.[126] Patients were randomized to receive dabrafenib 150 mg orally twice daily (n=187) or dacarbazine 1,000 mg/m^2 IV every 3 weeks (n=63). The trial indicated there was a statistically significant increase in PFS in patients treated with dabrafenib. Median PFS was 5.1 months for dabrafenib and 2.7 months for dacarbazine, with a hazard ratio of 0.3 (95% CI, 0.18 to 0.51; p<0.0001). Forty-four percent of the dacarbazine patients crossed over at disease progression into the dabrafenib treatment group. When examining the ORR, 3% and 0% of patients had a CR in the dabrafenib and dacarbazine groups, respectively. Additionally, 48% and 17% of the dabrafenib and dacarbazine groups, respectively, had a partial response. Treatment-related adverse events occurred in 53% of the dabrafenib-treated patients and 44% of the dacarbazine-treated patients. The most frequent adverse events that occurring with dabrafenib treatment included skin-related toxic effects, fever, arthralgia, and headache, while dacarbazine-treated patients experienced more nausea, vomiting, neutropenia, and asthenia. Both groups commonly experienced fatigue; grade 3 to 4 adverse events were uncommon in both groups.

combined dabrafenib (Tafinlar) and trametinib (Mekinist) versus dabrafenib (Tafinlar) plus placebo

COMBI-d was a phase 3 trial which randomized 423 previously untreated patients with unresectable stage 3C or stage 4 melanoma and a *BRAF* V600E or V600K mutation to receive a combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) or dabrafenib plus placebo. The primary endpoint was PFS and OS was a secondary endpoint. The median PFS was 9.3 months in the combination group and 8.8 months in the dabrafenib only group (HR for disease progression or death in the combination group, 0.75; 95% CI, 0.57 to 0.99; p=0.03). Rates of adverse events were similar in the 2 groups, although more dose modifications were required in the combination arm. The rate of cutaneous SCC was lower in the combination arm than in the dabrafenib only group (2% versus 9%, respectively) while the rates of pyrexia were increased in the combination arm.[127] At the time of final data cutoff, 222 of the 423 randomized patients had died. Median OS was 25.1 months (95% CI, 19.2 to not reached) in the combination group and 18.7 months (95% CI, 15.2 to 23.7) in the dabrafenib only arm (HR, 0.71; 95% CI, 0.55 to 0.92; p=0.0107). OS at 1 year was 74% for the combination therapy group and 68% in the dabrafenib only group. Two-year survival for these same groups was 51% versus 42%, respectively, and 3-year OS was 44% versus 32%.[128,129]

combined dabrafenib (Tafinlar) and trametinib (Mekinist) versus vemurafenib (Zelboraf)

COMBI-v was an open-label, phase 3 trial which randomly assigned 704 patients with metastatic melanoma harboring a *BRAF* V600 mutation to receive either a combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) or vemurafenib (960 mg twice daily) as first-line therapy.[130] The primary endpoint was OS. At the preplanned interim analysis, the OS rate at 12 months was 72% in the combination therapy arm and 65% in the vemurafenib group (HR, 0.69; 95% CI, 0.53 to 0.89; p=0.005). The prespecified interim stopping boundary was crossed. Median PFS was 11.4 months in the combination arm and 7.3 months in the vemurafenib arm (HR, 0.56; 95% CI, 0.46 to 0.69; p<0.001). Severe adverse effects and discontinuations were similar in the 2 groups. Cutaneous squamous cell carcinoma and keratoacanthoma occurred in 1% of patients in the combination therapy group and 18% in the vemurafenib group. As part of a pre-specified exploratory analysis, health related quality of life (HRQoL) was also assessed during the COMBI-v trial using validated measurement tools at baseline, during study treatment, at time of disease progression, and after disease progression.[131] Similar HRQoL and symptom scores were reported at baseline for both groups, but scores for the patients randomized to the combination therapy arm were statistically superior to the vemurafenib monotherapy arm during the study treatment and at disease progression.

combined dabrafenib (Tafinlar) and trametinib (Mekinist) versus dabrafenib (Tafinlar; plus placebo) or vemurafenib (Zelboraf)

To assess long-term clinical outcomes associated with combined dabrafenib plus trametinib therapy in previously untreated patients with BRAF-mutated melanoma, the data from both the COMBI-d and the COMBI-v trials were pooled for analysis.[132] For patients enrolled in those trials who were treated with dabrafenib plus trametinib, the PFS was 21% at 4 years and 19% at 5 years. The OS rates were 37% at 4 years and 34% at 5 years.

trametinib (Mekinist) versus IV chemotherapy (dacarbazine or paclitaxel)

METRIC: A phase 3, open-label trial was conducted in 322 patients with metastatic melanoma harboring a V600E or V600K *BRAF* mutation to assess PFS (primary endpoint) and OS (secondary endpoint).[133] Patients were randomized 2:1 ratio to receive trametinib (2 mg orally once daily) or an IV

chemotherapy treatment, dacarbazine (1,000 mg/m^2 body-surface area [BSA]), or paclitaxel (175 mg/m^2) every 3 weeks. Patients treated with chemotherapy who had disease progression were allowed to cross-over into the trametinib group at time of disease progression. Tumor assessments were performed at weeks 6, 12, 21, and 30 and then every 12 weeks thereafter. Of the 322 patients in the intention-to-treat (ITT) population, the median duration of PFS was 4.8 months and 1.5 months in the trametinib group and chemotherapy group, respectively (HR for progression, 0.45; 95% CI, 0.33 to 0.63; p<0.001) The 6-month OS rate was 81% and 67% in the trametinib and chemotherapy group, respectively. The percentage of patients with a confirmed complete or partial response, using the RECIST version 1.1, was 22% and 8% in the trametinib and chemotherapy group, respectively (p=0.01). The study found a reduction of 55% in the risk of disease progression or death in the trametinib group. Patients in the chemotherapy group who had disease progression and crossed over (n=51) had a 46% reduction in risk of death among patients receiving trametinib. Rash, diarrhea, and peripheral edema were the most common adverse events in the trametinib group. Secondary cutaneous malignancies were not observed. A simultaneous quality of life assessment found trametinib was associated with less functional impairment, smaller declines in health status, and less exacerbation of symptoms compared with the chemotherapy.[134] The study concluded trametinib improved PFS and OS in patients who had melanoma with a V600E or V600K *BRAF* mutation compared to chemotherapy. Long-term follow up of this trial reported the OS for trametinib versus chemotherapy was 60.9% versus 49.6%, respectively, at year 1, 32% versus 29.4%, respectively, at year 2, and 13.3% versus 17%, respectively, at year 5. Most patients from the chemotherapy arm crossed over to the trametinib arm early in their treatment.[135]

vemurafenib (Zelboraf) versus dacarbazine

BRIM-3: The efficacy and safety of vemurafenib in patients with treatment-naïve, *BRAF* V600E mutation-positive unresectable or metastatic melanoma as detected by the Cobas 4800 *BRAF* V600 Mutation Test were assessed in a phase 3, randomized, open-label, international trial of 675 patients.[136] Patients were randomized to vemurafenib 960 mg orally twice daily or dacarbazine 1,000 mg/m^2 IV every 3 weeks. The co-primary efficacy endpoints were OS and PFS. At 6 months, OS was 84% (95% CI, 78 to 89) in the vemurafenib arm and 64% (95% CI, 56 to 73) in the dacarbazine arm. In the interim analysis for OS and final analysis for PFS, compared with dacarbazine, vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression (p<0.001 for both comparisons). PFS was significantly longer in those initially treated with vemurafenib (Zelboraf): median 5.3 months compared with 1.6 months (hazard ratio [HR], 0.26; 95% CI, 0.2 to 0.33) in patients treated with dacarbazine. After review of the interim analysis by an independent review committee, crossover from dacarbazine to vemurafenib was recommended. Response rates were 48% and 5% for vemurafenib and dacarbazine, respectively. The most common serious adverse events with vemurafenib were cutaneous, including squamous cell carcinomas, keratoacanthomas, and photosensitivity. A total of 38% of patients required dose modification due to toxic effects.

An extended follow-up of the BRIM-3 trial was conducted after 399 (59%) of enrolled patients had died.[137] At that time, there was a median of 12.5 months follow up for the vemurafenib group and 9.5 months for the dacarbazine group. The median OS which was censored at the point of crossover from dacarbazine to vemurafenib, was 13.6 months (95% CI, 12 to 15.2) in the vemurafenib group versus 9.7 months (95% CI, 7.9 to 12.8) in the dacarbazine group with a hazard ratio for death in the vemurafenib

group of 0.7 (95% CI, 0.57 to 0.87; p=0.0008). Median PFS censored at crossover was significantly longer in the vemurafenib group than in the dacarbazine group (6.9 months [95% CI, 6.1 to 7] versus 1.6 months, respectively; HR, 0.38; 95% CI, 0.32 to 0.46; p<0.0001). Secondary cutaneous squamous-cell carcinomas occurred in about 20% of patients in the vemurafenib group, and 8 vemurafenib-treated patients were diagnosed with new primary melanomas.

combined vemurafenib (Zelboraf) plus cobimetinib (Cotellic) versus vemurafenib (Zelboraf)

CoBRIM, an international, multicenter, randomized phase 3 study, evaluated the efficacy and safety of cobimetinib combined with vemurafenib in previously untreated patients with unresectable, locally advanced or metastatic *BRAF* V600 mutation-positive melanoma.[138] A total of 495 patients were randomized in a 1:1 ratio to receive vemurafenib 960 mg orally twice daily with either placebo or cobimetinib (60 mg once daily for 21 days of a 28-day cycle). The primary endpoint was PFS as assessed by the investigators using RECIST criteria, version 1.1. The secondary endpoints included OS, confirmed objective response, duration of response, PFS as assessed by an independent review facility, and safety. The median follow up occurred at 7.3 months (range, 0.5 to 16.5 months) when the prespecified number of progression events (206) had occurred. At the time of data cutoff, a total of 85 patients had died. The PFS was 9.9 months in the combination treatment arm compared to 6.2 months in the vemurafenib monotherapy arm (HR, 0.51; 95% CI, 0.39 to 0.68; p<0.001). The investigator-assessed ORR was 68% in the combination arm compared with 45% in the control group (p<0.001). The rate of CR was also significantly higher in the combination group compared to the control group (10% versus 4%, respectively). The median duration of response was 7.3 months in the control group and had not been reached at time of reporting for the combination group. The interim analysis of OS at 9 months was 81% for the combination arm versus 73% with vemurafenib plus placebo, which was not statistically different. The final analysis of OS will occur after 385 deaths have been recorded. The combination of vemurafenib plus cobimetinib was associated with a higher frequency of certain adverse events compared to vemurafenib alone; this included retinopathy, gastrointestinal events (diarrhea, nausea, or vomiting), photosensitivity, elevated aminotransferase levels, and an increased creatine kinase level. However, the number of secondary cutaneous cancers decreased with the combination therapy compared to vemurafenib monotherapy. The incidence of grade 3 or higher adverse events or rate of study drug discontinuation did not differ between the 2 groups. An updated analysis occurred with a median follow up of 14.2 months.[139] The updated investigator-assessed median PFS was 12.3 months for the combination arm versus 7.2 months for the vemurafenib plus placebo arm (HR, 0.58; 95% CI, 0.46 to 0.72; p<0.0001). Median OS was 22.3 months for the combination treatment arm and 17. 4 months for vemurafenib alone which was statistically significant (HR, 0.7; 95% CI, 0.55 to 0.9; p=0.005). No new safety signals were observed during the longer follow up period.

Non-Small Cell Lung Cancer (NSCLC)

dabrafenib or dabrafenib plus trametinib

An open-label, non-randomized phase 2 trial enrolled 171 patients with metastatic BRAF V600E mutation-positive NSCLC with no prior exposure to BRAF or MEK inhibitors.[140,141] Patients were excluded if they had identified EGFR or ALK mutations. Patients were enrolled into 1 of 3 cohorts. Patients in cohorts A (n=78) and B (n=57) had progressive disease after ≥ 1 previous platinum-based regimen. Eligible patients could have received ≤ 3 prior chemotherapy regimens. Patients in cohort C

(n=36) had received no prior systemic therapy for their metastatic NSCLC. Patients in cohort A were given dabrafenib 150 mg twice daily only, while patients in cohorts B and C were given dabrafenib 150 mg twice daily and trametinib 2 mg once daily. The ORR for cohort A (dabrafenib only) was 27% compared to cohort B plus cohort C (dabrafenib plus trametinib) with an ORR of 63% in previously treated patients and 61% in treatment-naive patients. The median duration of response was 9.9 months for dabrafenib alone arm (cohort A) and 12.6 months for cohort B and not estimable for cohort C. Published results of patients in cohort B reported serious adverse events occurred in 56% of cohort B patients. The most common grade 3 or 4 adverse events in cohort B were neutropenia (9%), hyponatremia (7%), and anemia (5%).142 In the updated study, cuSCC occurred in 3.2% (3/93) of patients and cardiomyopathy occurred in 9% (8/93) of patients receiving dabrafenib plus trametinib.[143]

META-ANALYSES

A systematic review was conducted to evaluate the clinical experience with hedgehog pathway inhibitors (HPIs).[144] The review included clinical trials, retrospective medical record reviews and prospective case series involving HPIs for the treatment of either locally advanced BCC or metastatic BCC. The review included 8 articles related to vismodegib but was unable to locate enough publications regarding sonidegib to include an analysis of that drug. The analysis of vismodegib included 704 clinically evaluable patients and revealed an average ORR for locally advanced BCC of 64.7% and a CR rate of 31.1%. Objective response to vismodegib for metastatic BCC was 33.6% with a CR average of 3.9%. Median duration of therapy across the 8 trials was 35.8 weeks. A subsequent meta-analysis of the hedgehog inhibitors in basal cell carcinoma consisting of 18 articles found similar ORRs with sonidegib and vismodegib; however, they found a difference in CR rates (3% for sonidegib versus 31% with vismodegib) and ORR specifically in metastatic disease (15% for sonidegib versus 39% with vismodegib) favoring vismodegib.[145] Adverse effects were generally similar between the agents. Notably, the trials were highly heterogeneous.

Four trials met the inclusion criteria for a comparative systematic review and meta-analysis regarding the efficacy and toxicity of doublet BRAF/MEK inhibition compared to monotherapy with a BRAF inhibitor for patients with BRAF-mutated advanced melanoma.[146] The efficacy analysis demonstrated that BRAF/MEK inhibitors combination therapy is associated with a significant improvement in ORR, PFS and OS (HR for OS, 0.7; 95% CI, 0.58 to 0.84; p=0.0001). The combination therapy was also associated with a higher risk of diarrhea, decreased ejection fraction, acneiform dermatitis and pyrexia compared to monotherapy.

SUMMARY

Malignant cutaneous cancers are largely divided into 2 groups: melanoma skin cancers and non-melanoma skin cancers. Of the 2, melanoma is associated with a much higher mortality rate as it is an aggressive tumor that may produce distant metastatic disease. Non-melanoma skin cancers, such as basal cell carcinoma (BCC), rarely metastasize to distant sites but may create local destruction by invading surrounding tissue and bone. BCC is most commonly treated with a surgical approach.

Both vismodegib (Erivedge) and sonidegib (Odomzo) are FDA-approved agents for the treatment of locally advanced BCC where other options including surgery and radiation are not appropriate. Vismodegib is also approved in the setting of metastatic BCC. The National Comprehensive Cancer Network (NCCN) guidelines for these 2 agents mirror their respective FDA-approved indications.

Vismodegib and sonidegib are both NCCN category 2A recommendations in patients with advanced high-risk BCC who have residual disease after surgery and who are not able to receive further surgery and curative radiation therapy is not feasible. In the setting of nodal or distant metastases due to BCC, the NCCN guidelines note that sonidegib is not FDA-approved for metastatic BCC; thus, NCCN has downgraded sonidegib to a 2B recommendation in this setting, while vismodegib or a clinical trial are 2A recommendations.

Approximately half of all patients with metastatic cutaneous melanoma are positive for a BRAF mutation which has been found to be an actionable target for drug therapy. There are now 6 drugs approved for patients with metastatic or unresectable melanoma who harbor a BRAF V600 mutation. These medications are not indicated in patients who display wild-type BRAF. Both dabrafenib (Tafinlar) and vemurafenib (Zelboraf) are BRAF inhibitors that are FDA-approved as monotherapy in this setting; a third BRAF inhibitor, encorafenib (Braftovi) is only approved in combination with binimetinib (Mektovi) in the setting of metastatic melanoma. While initial response rate to these drugs is high, resistance quickly develops, usually after approximately 6 months of therapy. MEK is a signaling molecule downstream of BRAF, and it has been demonstrated that combining MEK inhibitors (cobimetinib [Cotellic], trametinib [Mekinist], and binimetinib [Mektovi]) with BRAF inhibitors (vemurafenib, dabrafenib, and encorafenib, respectively) leads to improved response rates, duration of response, progression free survival, and overall survival. In addition, the combination of a BRAF inhibitor and a MEK inhibitor (vemurafenib + cobimetinib, dabrafenib + trametinib, or encorafenib + binimetinib) reduces the development of new cutaneous malignancies compared to monotherapy with a BRAF inhibitor. NCCN guidelines no longer recommend single agent therapy with dabrafenib, vemurafenib, or trametinib as recommended treatment options. Instead, NCCN recommendations for first-line and second-line therapy of metastatic or unresectable BRAF-mutated melanoma include combination therapy with dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib (all 3 options are category 1 recommendations for first-line therapy and category 2A for second-line therapy). However, the NCCN guidelines note that if BRAF/MEK combination therapy is contraindicated, monotherapy with dabrafenib or vemurafenib is an option, particularly in patients who are not candidates for immunotherapy. The combination of vemurafenib/cobimetinib seems to be associated with more diarrhea, rash and increased transaminases compared with the combination of dabrafenib/trametinib, which is associated with a higher incidence of pyrexia. Encorafenib and binimetinib may offer advantages in terms of lower rates of increased transaminases and pyrexia.

In April 2018, the FDA approved the combination of dabrafenib and trametinib for use in the adjuvant setting of patients with stage 3 melanoma with BRAF V600E or V600K mutations who have lymph node involvement of their disease and who have undergone a complete resection. The NCCN guidelines list the use of this regimen as a category 1 recommendation in patients with stage 3 melanoma with a BRAF V600 activating mutation. The NCCN guidelines state the choice of adjuvant systemic therapy or observation alone should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.

Approximately 1% to 2% of all lung adenocarcinomas are BRAF-positive. BRAF testing should be undertaken at time of diagnosis of advanced NSCLC to identify these patients. If the patient with advanced NSCLC is determined to be BRAF V600E mutation-positive, first-line therapy options include either dabrafenib plus trametinib or standard therapy, possibly including an immunotherapy agent.

Both options are listed as NCCN category 2A recommendations. Subsequent lines of therapy may be either option that was not received in the first-line setting. The NCCN guidelines also note that single-agent vemurafenib or dabrafenib are treatment options in this setting if the combination of dabrafenib plus trametinib is not tolerated.

The combination of dabrafenib and trametinib is also approved for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutations and no satisfactory locoregional treatment options. Single agent vemurafenib is FDA approved for the treatment of the rare disease, Erdheim-Chester Disease (ECD) with BRAF V600 mutation. Both the ATC indication and the ECD indication were approved based on small multi-cohort, non-randomized, open-label trials for patients with rare, non-melanoma cancers exhibiting a BRAF V600 E mutation.

In April 2020, the FDA approved the combination of encorafenib plus cetuximab (Erbitux) for the treatment of patients with metastatic colorectal cancer (mCRC) with BRAF V600E mutations after prior therapy. This regimen is a NCCN 2A recommendation for advanced colorectal cancer patients with unresectable metastases who are BRAF V600E mutation-positive and who have received previous adjuvant FOLFOX/CAPEOX within the past 12 months. Furthermore, the regimen is recommended by the NCCN as subsequent therapy in patients with advanced or metastatic disease who have received previous chemotherapy and are BRAF V600E mutation-positive (category 2A).

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