Trends in Cancer

CellPress
REVIEWS

Special Issue: Celebrating 5 Years
Review

Clinical Development of BRAF plus MEK Inhibitor Combinations

Vivek Subbiah,[1,*] Christina Baik,[2] and John M. Kirkwood[3]

Genomic profiling shows that many solid tumors are characterized by specific driver aberrations, and this has expanded the therapeutic options for many patients. The mitogen-activated protein kinase (MAPK) pathway is a key cell signaling pathway involved in regulating cellular growth, proliferation, and survival. Driver mutations in the *BRAF* gene, a key player in the MAPK pathway, are described in multiple tumor types, including subsets of melanoma, non-small cell lung cancer (NSCLC), and anaplastic thyroid cancer (ATC), making BRAF a desirable target for inhibition. BRAF inhibitors have shown efficacy in several cancers; however, most patients eventually develop resistance. To delay or prevent resistance, combination therapy targeting BRAF and MEK, a downstream signaling target of BRAF in the MAPK pathway, was evaluated and demonstrated synergistic benefit. BRAF and MEK inhibitor combinations have been approved for use in various cancers by the US FDA. We review the clinical data for various BRAF plus MEK combination regimens in three cancer types with underlying *BRAF* driver mutations: melanoma, NSCLC, and ATC. We also discuss practical treatment considerations and management of selected combination therapy toxicities.

Highlights

Mutations in *BRAF* occur in many tumor types and contribute to the dysregulation of processes such as cell proliferation and differentiation.

Acquired resistance is common among patients receiving BRAF inhibitor monotherapies. Efforts to overcome this in *BRAF* V600 mutation-positive melanoma, NSCLC, and ATC have tested combined MEK and BRAF inhibition.

In most cases, combination therapy is more effective than monotherapy, creating new treatment options for patients with *BRAF* mutations. However, the adverse events associated with these regimens can be more frequent during the early stages of treatment, and thus necessitate proactive management.

Despite the promise of dual MEK/BRAF inhibition, acquired resistance remains a concern. Ongoing studies are assessing whether inhibition of additional host factors in tandem with MEK and BRAF will increase patient survival while curbing resistance.

BRAF as an Oncogenic Driver

The identification of oncogenic driver alterations in many human solid tumors has expanded therapeutic opportunities and made genomic profiling an important part of the treatment process. Mutations in the *BRAF* gene, a member of the **RAF family** (see Glossary) of **serine/threonine kinases** (ARAF, BRAF, CRAF), have been described in a variety of tumor types [1–3]. Part of the **mitogen-activated protein kinase** (MAPK) pathway, BRAF is essential to the regulation of cellular growth, proliferation, and survival [4]. Upstream of BRAF, growth factor binding to receptor tyrosine kinases (RTKs) at the cell surface leads to phosphorylation of **RAS** proteins, which then activate BRAF. Signal transduction continues downstream from BRAF to **MAPK kinase** (MEK) 1 and MEK2, and finally to ERK, which phosphorylates multiple targets. The best-studied activating *BRAF* mutations occur at position V600 (V600E, V600K), resulting in constitutive activation of BRAF and downstream activation of MEK and ERK. The frequency of *BRAF* mutations varies by tumor type, and mutations are observed in ~50% of patients with melanoma, ~25% of patients with **anaplastic thyroid cancer** (ATC), and 2–8% of patients with NSCLC [5,6].

Successes and Challenges in Targeting Oncogenic BRAF

Initial attempts to directly target aberrant MAPK pathway signaling in patients with oncogenic BRAF mutations were undertaken in patients with melanoma who received the multikinase inhibitor sorafenib, which inhibits CRAF, both wild-type and mutant BRAF, as well as multiple RTKs implicated in tumor angiogenesis and progression. Unfortunately, sorafenib demonstrated limited clinical activity in patients with melanoma, either as a single agent or in combination with

[1]Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[2]Department of Thoracic, Head and Neck Medical Oncology, University of Washington School of Medicine, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA
[3]Department of Medicine, Division of Medical Oncology University of Pittsburgh, and Melanoma Program, University of Pittsburgh Cancer Institute, University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center, Pittsburgh, PA 15232, USA

*Correspondence:
vsubbiah@mdanderson.org (V. Subbiah).

chemotherapy, and this is likely due, at least in part, to its weak affinity for mutant BRAF at clinically achievable concentrations [7–9].

To overcome this limitation, selective BRAF inhibitors (BRAFi) have been developed, including vemurafenib, dabrafenib, and encorafenib. Unlike sorafenib, these novel kinase inhibitors were designed to bind specifically to the ATP-binding pocket of the active conformation of BRAF, with a preference for BRAF V600E, leading to increased potency and specificity [10–12]. In mouse xenograft models of human *BRAF* V600E-mutant melanoma, vemurafenib, dabrafenib, and encorafenib each demonstrated dose-dependent tumor growth inhibition [11,13,14]. Subsequent clinical trials with BRAFi monotherapy in metastatic melanoma showed a high rate of objective response and improved overall survival (OS) vs chemotherapy [15–17].

Despite the survival advantages observed versus chemotherapy, approximately half of all patients treated with BRAFi exhibited disease progression within 6–7 months of initiating treatment [17,18]. Resistance is typically mediated through reactivation of the MAPK pathway and can occur through several mechanisms: these include upstream activating mutations (e.g., *NRAS* or *KRAS* mutations) or downstream MAPK pathway alterations (*MEK1/2* mutations, *ERK* mutations, or *CDKN2A* loss) [19–23], activation of parallel signaling pathways (e.g., PI3K) [22,24,25], increased expression of receptor tyrosine kinases (e.g., EGFR, PDGFRβ, MET, ERBB3, IGFR1) [21,22,26–28], and BRAF amplification and alternative splicing [22,25].

Another challenge with BRAFi monotherapy is the emergence of hyperproliferative cutaneous events, including squamous cell carcinoma and keratoacanthoma. Further investigation into the nature and pathogenesis of these events led to the discovery of BRAFi-induced paradoxical activation of MAPK pathway signaling in BRAF wild-type cells. In these cells, treatment with BRAFi leads to RAF dimerization (CRAF homodimers or CRAF-BRAF heterodimers) and transactivation of the drug-free member of the dimer [29,30]. This, in turn, leads to hyperactive MAPK signaling, which can induce hyperproliferative cutaneous events.

Preclinical models showed that acquired resistance to BRAFi treatment is associated with rapid recovery of MAPK pathway signaling and that complete blockade of the pathway may be necessary to induce apoptosis in *BRAF* V600-mutant melanoma [31]. To that end, the combination of BRAFi with downstream inhibition of MEK1/2 was postulated to maximize MAPK pathway inhibition and prevent resistance (Figure 1). The MEK1/2 inhibitor trametinib had been shown separately to enhance survival vs chemotherapy in patients with metastatic melanoma [32]. In organotypic cell culture models, the combination of BRAF and MEK inhibition was shown to enhance apoptosis and delay the emergence of resistance [31]. In addition, in an experimental squamous cell carcinoma mouse model, the addition of a MEK inhibitor (MEKi) blocked BRAFi-induced hyperproliferative cutaneous events, suggesting that downstream MEK inhibition may not only prevent BRAFi resistance in *BRAF*-mutant cells but also block paradoxical MAPK activation in *BRAF* wild-type cells [33].

These observations have been translated to the clinic and have led to US FDA approval of three BRAFi/MEKi combinations, including dabrafenib plus trametinib (approved in metastatic and resected stage III melanoma, NSCLC, and ATC), vemurafenib plus cobimetinib (approved in metastatic melanoma), and encorafenib plus binimetinib (approved in metastatic melanoma) (Table 1). In addition, it has been shown that *BRAF* V600 mutations are clinically actionable in a broad range of non-melanoma cancers, including tumor types in which RAF inhibition is not currently considered to be standard of care [34,35].

Glossary

Aminotransferase: two types of this protein – alanine and aspartate aminotransferases – that are primarily found in the liver. Increased levels of these proteins in the blood are often a sign of liver damage.
Anaplastic thyroid cancer (ATC): a rapidly growing cancer of the thyroid that is relatively rare and is characterized by anaplastic, or dedifferentiated, cells.
Asthenia: medical term for physical weakness.
Creatine phosphokinase: a protein predominantly found in the brain, heart, and skeletal muscles. Increased levels of this protein in the blood can indicate damage to these organs, as might be caused by a heart attack or stroke.
G-tube: a gastrostomy tube, more commonly known as a feeding tube, that is inserted into the abdomen such that food or orally administered medications in liquid form can be delivered directly to the stomach.
Left ventricular ejection fraction (LVEF): a common measurement of how much blood the heart's left ventricle is pumping out with every heartbeat. A decrease in LVEF is indicative of heart failure.
MAPK kinase (MEK): serine/threonine kinases that phosphorylate downstream MAPKs. As with MAPKs, there are several different MEKs (i.e., MEK1 and MEK2), each with varying MAPKs that they act upon.
Mitogen-activated protein kinase (MAPK): a family of serine/threonine kinases that are activated by MAPK kinases. Activated MAPKs in turn phosphorylate additional proteins, including transcription factors that can alter gene expression, and thus regulate numerous processes including cellular proliferation and differentiation.
Pyrexia: the medical term for fever.
RAF family: a protein family that includes the serine/threonine kinases ARAF, BRAF, and CRAF, which, once activated, phosphorylate MEKs.
RAS: the multiple members of the RAS family are activated by GTP binding. These proteins in turn activate RAF family members, ultimately triggering the MAPK signaling cascade.
Serine/threonine kinases: enzymes that phosphorylate serine or threonine residues on target proteins, which can include the kinase itself. This phosphorylation can activate or deactivate the target protein.

Dabrafenib plus Trametinib

Metastatic Melanoma

The combination of the BRAFi dabrafenib with the MEKi trametinib was first evaluated in patients with metastatic melanoma. Initial observations from a Phase I/II study corroborated preclinical findings, finding a significant increase in progression-free survival (PFS; $P < 0.001$) and a significant decrease in the proportion of patients with squamous cell carcinoma ($P = 0.09$) in the group receiving dabrafenib plus trametinib compared with those receiving dabrafenib monotherapy [36].

Serous retinopathy: accumulation of fluid behind the retina of the eye, causing retinal detachment and impaired vision.

The combination was further evaluated in two large Phase III trials. COMBI-v ($n = 704$) and COMBI-d ($n = 423$) were randomized controlled trials comparing dabrafenib plus trametinib to BRAFi monotherapy – either vemurafenib (in the open-label COMBI-v trial) or dabrafenib plus placebo (in the double-blind COMBI-d trial) in patients naive to BRAFi (Table 2) [37–39].

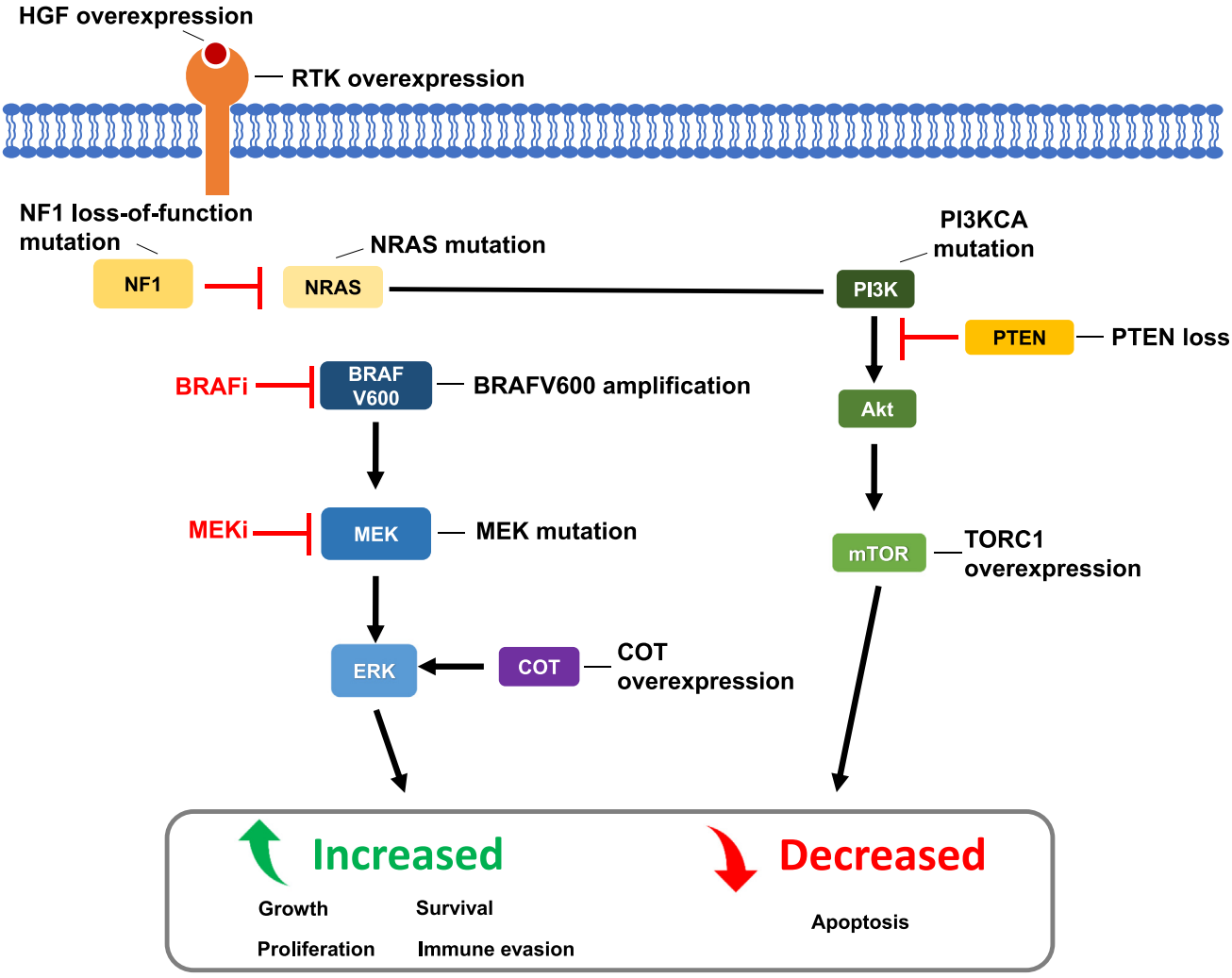

Figure 1. Oncogenic BRAF Signaling Pathway Showing BRAF, MAPK, and Alternative Pathways with Downstream Activity. Abbreviations: BRAFi, BRAF inhibitors; ERK, extracellular signal-regulated kinase; HGF, hepatocyte growth factor; MEKi, MEK inhibitors; NF1, neurofibromin 1; RTK, receptor tyrosine kinase; TORC1, target of rapamycin kinase complex 1.

Table 1. BRAF/MEK Inhibitor Combinations with Approved Indications by Tumor Type

Tumor type	Drug combination	Indication (year of FDA approval)
Malignant melanoma	Dabrafenib + trametinib	Metastatic/unresectable *BRAF* V600E/K+ (2014) Adjuvant: *BRAF* V600E/K^{+} stage III (2018)
	Vemurafenib + cobimetinib	Metastatic/unresectable *BRAF* V600+ (2015)
	Encorafenib + binimetinib	Metastatic/unresectable *BRAF* V600+ (2018)
NSCLC	Dabrafenib + trametinib	Advanced or metastatic *BRAF* V600E^{+} (2017)
ATC	Dabrafenib + trametinib	Metastatic/unresectable *BRAF* V600E^{+} (2018)

In both studies, dabrafenib plus trametinib was superior to monotherapy with respect to PFS and OS [37–39]. In COMBI-v, the risk of death was reduced by 31% ($P = 0.005$) in the dabrafenib plus trametinib group versus the vemurafenib-alone group at the preplanned interim analysis. In COMBI-d [38], PFS was significantly longer with combination therapy than with dabrafenib plus placebo (hazard ratio [HR], 0.6, 95% CI 0.53–0.84, $P = 0.0004$), and the risk of death was reduced by 29% ($P = 0.0107$). A recent pooled analysis of patients treated with dabrafenib plus trametinib in COMBI-d/v ($n = 563$) suggested potential stabilization of survival curves, where 4 and 5 year PFS rates were 21% and 19%, and 4 and 5 year OS rates were 37% and 34%, respectively [40].

Table 2. Registration Trials for BRAFi Plus MEKi Combinations in Melanoma, NSCLC, and ATC[a]

	Dabrafenib + trametinib					Vemurafenib + cobimetinib	Encorafenib + binimetinib
Indication	Metastatic melanoma	Adjuvant melanoma	NSCLC		ATC	Metastatic melanoma	Metastatic melanoma
Trial	COMBI-d/v[b] [40]	COMBI-AD [46,47]	BRF113928		ROAR [62]	coBRIM [63,103]	COLUMBUS (part 1) [69]
			Cohort B [51]	Cohort C [53]			
n (BRAFi + MEKi arm)	563	438	57	36	28	247	192
Median follow-up, months	22	44	19 (minimum)	15.9	–	21.2	48.8
ORR, *n* (%)	383 (68)	–	38 (67)	23 (64)	18 (67)[c]	172 (70)	(64)
CR	109 (19)	–	3 (5)	2 (6)	2 (7)	52 (21)	(13)
PR	274 (49)	–	35 (61)	21 (58)	16 (59)	120 (49)	(51)
SD	130 (23)	–	8 (14)	4 (11)	6 (22)	45 (18)	(29)
Median DOR, months (95% CI)	–	–	9.8 (6.9–16.0)	10.4 (8.3–17.9)	–	13.0 (11.1–16.6)	18.6 (12.7–24.1)
Median PFS, months (95% CI)	11.1 (9.5–12.8)	–	10.2 (6.9–16.7)	10.9 (7.0–16.6)	13.8 (4.6–NE)	12.6 (9.5–14.8)	14.9 (11.0–20.2)
Median RFS, months (95% CI)	–	NE (46.9–NE)	–	–	–	–	–
Median OS, months (95% CI)	25.9 (22.6–31.5)	–	18.2 (14.3–NE)	24.6 (12.3–NE)	19.8 (8.1–NE)	22.5 (20.3–28.8)	33.6 (24.4–39.2)
Grade ≥3 AEs, %	59	41	49	69	64	78	68

[a]Abbreviations: –, not applicable/not available; AE, adverse event; ATC, anaplastic thyroid cancer; BRAFi, BRAF inhibitor; CR, complete response; DOR, duration of response; MEKi, MEK inhibitor; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RFS, relapse-free survival; SD, stable disease.
[b]Results are from a pooled analysis of the dabrafenib plus trametinib arms of the COMBI-d and COMBI-v trials.
[c]One patient was excluded from the response analysis owing to insufficient observation time at the time of cutoff.

In COMBI-v [39], the occurrence of rash was almost halved with combination treatment compared to vemurafenib monotherapy (22% vs 43%). Photosensitivity reactions, which are more common with vemurafenib than other BRAFi, occurred in 4% of patients receiving dabrafenib plus trametinib versus 22% receiving vemurafenib alone. Other cutaneous adverse events (AEs) were less frequent with combination therapy than with monotherapy, notably squamous cell carcinomas and keratoacanthomas (1% vs 18%). However, **pyrexia** was more common in the dabrafenib plus trametinib group than in the vemurafenib group (53% vs 21%).

Overall, the incidence of AEs in the combination and monotherapy groups of COMBI-d [37] followed a pattern similar to that observed in COMBI-v [39]. Patients treated with dabrafenib plus trametinib had an increased incidence of pyrexia (51% vs 28%) [37] and of the trametinib-associated AEs hypertension (22% vs 14%) and peripheral edema (14% vs 5%) versus those treated with dabrafenib plus placebo [37].

Historically, patients with melanoma brain metastases (MBM) have had a particularly poor prognosis, with a median survival of 4–5 months [41]. Evidence suggests that patients with *BRAF*-mutant melanoma may be at a higher risk for development of MBM than patients with *BRAF* wild-type melanoma [42,43].

Dabrafenib plus trametinib was evaluated in patients with *BRAF* V600-mutant MBM in the open-label, Phase II COMBI-MB trial (NCT02039947) [44]. Patients were assigned to one of four cohorts on the basis of their specific *BRAF* mutation and prior local therapy. Patients in cohort A (n = 76) had *BRAF* V600E-positive asymptomatic MBM and had not received prior local brain therapy. Patients in cohort B (n = 16) had received prior local brain therapy for *BRAF* V600E-positive asymptomatic MBM. In cohort C (n = 16), patients had *BRAF* V600D/K/R-positive asymptomatic MBM, with or without prior local brain therapy, and patients in cohort D (n = 17) had *BRAF* V600D/E/K/R-positive symptomatic MBM with or without prior local brain therapy. The investigator-assessed intracranial response rate in cohort A (primary endpoint) was 58%, and the median duration of response was 6.5 months (95% CI 4.9–10.3 months). Intracranial response rates were similar among the various cohorts at 56% in cohort B, 44% in cohort C, and 59% in cohort D. Dabrafenib plus trametinib had a manageable safety profile in patients with MBM, and there were no new safety signals.

Adjuvant Therapy of Melanoma

Surgical resection is the standard of care for most patients with early-stage melanoma and offers a very good long-term prognosis, with 5 year melanoma-specific survival rates of 98% and 90% in patients with stage I and II disease, respectively [45]. However, in patients with stage III disease who have regional nodal involvement, the risk of relapse is greater, and many more patients may ultimately die from melanoma [45]. The intent of adjuvant systemic therapy is to increase relapse-free survival (RFS) and OS by targeting and eliminating any residual disease following surgical resection. Given the heightened risk of relapse in patients with stage III melanoma and the high proportion of patients with BRAF mutations, adjuvant systemic therapy with dabrafenib plus trametinib was evaluated in the Phase III COMBI-AD trial.

COMBI-AD is the first trial to evaluate BRAFi plus MEKi combination therapy in the adjuvant setting. Patients with completely resected *BRAF* V600E/K mutation-positive, stage III (node-positive) cutaneous melanoma received ≤12 months of adjuvant dabrafenib plus trametinib versus two matched placebos [46,47]. With a minimum of 40 months of follow-up, dabrafenib plus trametinib significantly reduced the risk of relapse by 51% versus placebo [46]. The 3 and 4 year RFS rates were 59% (95% CI 55–64%) and 54% (95% CI 49–59%) in the dabrafenib plus trametinib arm

and 40% (95% CI 35–45%) and 38% (95% CI 34–44%) in the placebo arm, respectively. The rate of relapse events in the trial decreased after 3 years, when a plateau appears in the RFS plots, although further follow-up is warranted and underway. The observed RFS benefit was consistent regardless of baseline disease stage, nodal metastatic burden, or tumor ulceration [46]. Estimation of the proportion of patients who may never experience relapse using a Weibull mixture cure-rate model showed cure rates of 54% (95% CI 49–59%) in the dabrafenib plus trametinib group versus 37% (95% CI 32–42%) in the placebo group, an absolute difference of 17% [46]. Interim analysis of OS showed that treatment with dabrafenib plus trametinib led to a clinically meaningful 43% reduction in the risk of death versus placebo ($P = 0.0006$), but this P value did not cross the prespecified interim significance boundary [47].

The safety profile of dabrafenib plus trametinib in the adjuvant setting was consistent with that observed in patients with metastatic melanoma [47]. Notably, the rate of discontinuation due to AEs was higher in the COMBI-AD trial (26%) than that reported in Phase III trials in the metastatic setting (14–16%). This could potentially be attributable to the nature of adjuvant therapy and the lower threshold for AE tolerance in this setting [47].

Non-Small Cell Lung Cancer

NSCLC is the second most common cancer in the USA [48] and makes up 85% of all lung cancers [49]. The 5 year survival rate across all disease stages remains approximately 16–18% despite improved therapies, in part because the early stages of NSCLC are asymptomatic, delaying diagnosis. Although the proportion of patients with NSCLC who carry *BRAF* mutations (2–8%) is relatively small [5,6], it represents a sizeable population given the overall incidence of NSCLC.

Dabrafenib monotherapy and dabrafenib plus trametinib were evaluated in patients with *BRAF* V600E-positive metastatic NSCLC in a three-cohort, single-arm, open-label, Phase II trial [50–53]. Patients in cohorts A and B had progressed on ≥1 platinum-based chemotherapy. Patients in cohort A received dabrafenib monotherapy [52], and those in cohort B received dabrafenib plus trametinib [50,51]. Patients in cohort C received dabrafenib plus trametinib as first-line therapy [53].

In cohort A, the overall response rate (ORR) and median PFS in patients receiving dabrafenib monotherapy were modest at 33% and 5.5 months, respectively, and the safety profile was consistent with other studies of dabrafenib monotherapy [52]. The confirmed ORRs with combination therapy in cohorts B and C were 67% and 64%, respectively, approximately double the percentage seen with monotherapy [51,53]. In previously treated patients (cohort B), the median investigator-assessed PFS was 10.2 months (95% CI 6.9–16.7 months); 1 and 2 year PFS rates were 43% and 22%, respectively, with a median OS of 18.2 months (95% CI 14.3 months to not estimable) [50,51].

In patients receiving dabrafenib plus trametinib as first-line therapy (cohort C), the median PFS was 10.9 months (95% CI 7.0–16.6 months), with a median OS of 24.6 months (95% CI 12.3 months to not estimable) and a 2-year OS rate of 51% (95% CI 33–67%) [53]. The median PFS and OS with combination therapy were numerically higher compared with monotherapy; however, this was not a randomized trial.

In previously treated patients [50], common AEs of any grade (with a frequency of ≥30%) included pyrexia (46%), nausea (40%), vomiting (35%), diarrhea (33%), **asthenia** (32%), and decreased appetite (30%). The most common serious AEs were pyrexia (16%) and anemia (5%). The pattern of AEs was similar in treatment-naive patients [53].

The results of this Phase II study are the first to demonstrate the efficacy of combination targeted therapy in *BRAF* V600-positive metastatic NSCLC in both the first- and second-line settings.

Anaplastic Thyroid Cancer

ATC is a rare and aggressive malignancy, and all cases are considered to be stage IV at diagnosis [54]. Of the 2–5% of Americans who develop thyroid nodules during their lifetime, which translates to approximately 60 000 new diagnoses annually, <1% develop ATC. ATC disproportionately affects women and has a median age of diagnosis of 70 years [55,56]. Approximately 20–50% of anaplastic thyroid tumors harbor *BRAF* V600E/K mutations [57–60]. Before the availability of targeted therapy, the response rate with systemic therapy was <15%, with a median survival of 5–12 months [61].

To assess the efficacy and safety of BRAF plus MEK inhibition, an open-label Phase II trial evaluated dabrafenib plus trametinib in patients with nine rare tumor types, including patients with ATC (n = 28) [61,62]. The ORR was 67%, including two complete responses. In the subset of patients with centrally confirmed *BRAF* V600E mutation-positive tumors (n = 24), the ORR was 75%. Two-thirds of patients with a response (12 of 18 patients) had a duration of response of ≥6 months. Median PFS was 13.8 months (95% CI 4.6 months to not estimable). The median OS was 19.8 months (95% CI 8.1 months to not estimable) and showed a plateau beginning at ~20.7 months.

Overall, the safety profile was similar to that of the combination in other indications; the most frequent AEs were pyrexia (50%), fatigue (39%), and nausea (36%) [62]. Four of 28 patients (14%) discontinued treatment owing to AEs.

Vemurafenib plus Cobimetinib

Metastatic Melanoma

Clinical development of vemurafenib plus cobimetinib paralleled that of dabrafenib plus trametinib in metastatic melanoma. The coBRIM trial (N = 495) was a large randomized controlled trial evaluating vemurafenib plus cobimetinib versus vemurafenib plus placebo in patients with treatment-naive, *BRAF* V600 mutation-positive, unresectable, locally advanced or metastatic melanoma [63]. Combination treatment was superior to monotherapy in median PFS (12.3 months, 95% CI 9.5–13.4 months; vs 7.2 months, 95% CI 5.6–7.5 months) and significantly reduced the risk of death by 30% (P = 0.005).

There was a lower incidence of squamous cell carcinoma, keratoacanthoma, and Bowen disease with the combination regimen than with monotherapy (6% vs 20%) [63]. However, photosensitivity was increased with vemurafenib plus cobimetinib versus vemurafenib (34% vs 20%). As expected, AEs associated with MEK inhibition were more frequent with the addition of cobimetinib, including **serous retinopathy,** decreased **left ventricular ejection fraction** (LVEF), and increased **creatine phosphokinase** levels. Discontinuations due to treatment-related AEs were somewhat more frequent with vemurafenib plus cobimetinib than with vemurafenib (14% vs 7%).

Non-Small Cell Lung Cancer

Vemurafenib demonstrated clinical activity as monotherapy (n = 62, ORR 37%) in *BRAF* V600-positive unresectable or metastatic NSCLC in a Phase II study [64]. Safety and tolerability profiles were similar to those seen with monotherapy in metastatic melanoma. No prospective evaluation of vemurafenib in combination with cobimetinib has been reported in patients with metastatic NSCLC.

Anaplastic Thyroid Cancer

BRAFi monotherapy was evaluated with vemurafenib in a Phase II basket trial of nonmelanoma cancers, including seven patients with ATC [34]. Two of seven patients had an objective

response, with one complete response and one partial response. Although we know of no prospective clinical trial data on the efficacy of vemurafenib plus cobimetinib in patients with ATC, a recent case report showed impressive tumor reduction and disappearance of distant metastases in a patient with ATC treated with the combination of vemurafenib plus cobimetinib, thus also demonstrating clinical activity in ATC [65].

Encorafenib plus Binimetinib

Metastatic Melanoma

Encorafenib plus binimetinib was the latest BRAFi/MEKi combination to be approved by regulatory authorities. Although encorafenib has a similar potency to dabrafenib against BRAF V600E, it has a higher potency for wild-type BRAF and CRAF [10]. This has been hypothesized to potentially mitigate some resistance mechanisms and/or reduce paradoxical MAPK pathway activation versus its predecessors. In addition, encorafenib has shown a longer dissociation half-life *in vitro*, which could potentially lead to prolonged effect [13].

The COLUMBUS trial was a two-part, randomized, open-label, Phase III study comparing encorafenib plus binimetinib versus encorafenib or vemurafenib monotherapy. Because earlier studies found that encorafenib was better tolerated when combined with binimetinib, part 1 [66,67] evaluated encorafenib 450 mg once daily (QD) plus binimetinib 45 mg twice daily (BID), versus encorafenib 300 mg QD, versus vemurafenib 960 mg BID. Part 2 assessed encorafenib 300 mg QD plus binimetinib 45 mg BID versus encorafenib 300 mg QD [68]. Patients were either treatment-naive or had progressed on or after first-line immunotherapy.

In part 1 (n = 577) [66], combining encorafenib with binimetinib significantly reduced the risk of death by 39% versus vemurafenib (two-sided $P < 0.0001$). OS in the encorafenib plus binimetinib and encorafenib arms was not significantly different (HR 0.81, 95% CI 0.61–1.06, two-sided $P = 0.12$). PFS was prolonged in the encorafenib plus binimetinib arm, with a median of 14.9 months (95% CI 11.0–20.2 months) compared with that of monotherapy (encorafenib, 9.6 months, 95% CI 7.4–14.8 months; vemurafenib, 7.3 months, 95% CI 5.6–7.9 months, HR 0.51, 95% CI 0.39–0.67, two-sided $P < 0.0001$ for the combination vs vemurafenib). In a recent updated analysis, 4 year PFS and OS rates in patients treated with encorafenib plus binimetinib were 25% and 39%, respectively [69]. These rates were similar to the 4 year PFS and OS rates observed with dabrafenib (21% and 37%) [40], and it remains unclear if the favorable pharmacologic and preclinical properties of encorafenib translate to greater clinical efficacy.

AEs of special interest included increased **aminotransferase** levels, serous retinopathy, and left ventricular dysfunction, which were more frequent with encorafenib plus binimetinib [66].

Dose adjustment or interruption of treatment because of AEs occurred in 53% of patients in the encorafenib plus binimetinib group, 71% in the encorafenib group, and 62% in the vemurafenib group. Fifteen percent of patients in the encorafenib plus binimetinib group discontinued treatment due to AEs.

In part 2 (n = 344), median PFS was longer with encorafenib 300 mg QD plus binimetinib 45 mg BID than with encorafenib 300 mg QD (12.9 vs 9.2 months, HR 0.77, 95% CI 0.61–0.97, nominal $P = 0.029$) [68]. The AE profile was similar between parts 1 and 2, suggesting that the higher encorafenib dose used in part 1 did not introduce new safety or tolerability concerns.

Practical Treatment Considerations

Many practical issues need to be considered in the clinical management of BRAFi/MEKi combination therapy, such as the feasibility of treatment administration and management of toxicities.

The combination BRAFi and MEKi therapies discussed in this review were all administered as oral tablets; however, patients with ATC often have difficulty swallowing as a result of an increasing burden of locoregional disease in the neck. Thus, administration is an important challenge in the clinic. Liquid formulations or suspensions suitable for delivery via a **G-tube** would enhance the quality of care in this patient population. Indeed, oral formulations of some BRAFi and MEKi are currently being evaluated (NCT01677741) [70]. Pill burden also differs between approved agents, and as few as five pills per day are required with dabrafenib plus trametinib, 11 pills per day with vemurafenib plus cobimetinib, and 12 pills per day with encorafenib plus binimetinib. Dabrafenib and trametinib should be taken ≥1 h before or 2 h after a meal. All other regimens can be taken with or without food. Coadministration with CYP3A4 inhibitors should be avoided with all three BRAFi. Each regimen has additional guidance for concomitant medication: refer to the package insert before administering a BRAFi/MEKi regimen.

AEs associated with BRAFi and MEKi monotherapy are best characterized in patients with metastatic melanoma (Table 3) [71]. With the exception of higher rates of pyrexia with dabrafenib and higher rates of photosensitivity with vemurafenib, the occurrence of treatment-associated AEs is similar among BRAFi (Table 3). Treatment-emergent AEs reported in clinical trials of BRAFi/MEKi

Table 3. Class-Effect Toxicities Associated with BRAF and MEK Inhibition[a]

BRAFi	MEKi
Constitutional	Constitutional
Pyrexia[b] fatigue	Fatigue, anemia
Cutaneous	Cutaneous
Rash	Rash
Photosensitivity[c]	Pruritus
Pruritus	Acneiform dermatitis
Dry skin	
Papilloma, alopecia, secondary cutaneous carcinoma, keratoacanthoma	
Hepatic	Cardiovascular
Elevated hepatic transaminases	Decreased ejection fraction, left ventricular dysfunction
	Gastrointestinal
	Nausea, diarrhea, vomiting
	Hepatic
	Ocular
	Blurred vision, serous retinal detachment, retinal vein occlusion, chorioretinopathy
	Respiratory
	Interstitial lung disease
	Pneumonitis

[a]Details in [71,96,104].
[b]More frequent with dabrafenib.
[c]More frequent with vemurafenib.

therapy are similar regardless of the primary tumor being treated [71]. Most are grade 1 or 2 and are consistent with those associated with the BRAFi or MEKi alone, with some variations in frequency. The evidence suggests that the incidence of AEs with BRAFi plus MEKi may decline over time on treatment. In patients receiving dabrafenib and trametinib, the incidence of each of the most common AEs was highest during the initial 6 months of treatment and declined thereafter, as did the frequency of dose reductions or interruptions due to AEs [72]. These findings highlight the need to effectively manage AEs early during treatment (Box 1).

Next-Generation Combination Therapy

In metastatic melanoma, the introduction of BRAFi/MEKi targeted therapies, as well as immune checkpoint inhibitors, has revolutionized treatment, and 1 year OS is now >70% [73]. However, it has been hypothesized that combining the two modalities concurrently may lead to durable responses in a higher proportion of patients.

Aside from the additive effects of combining their mechanisms of action, there is evidence to suggest that BRAFi/MEKi treatment may lead to a favorable immune microenvironment and enhance the efficacy of immune checkpoint inhibition with anti-PD-1 agents. In BRAF-mutant cell lines,

Box 1. Management of Selected BRAFi- or MEKi-Associated Toxicities

Constitutional Pyrexia [90,91].

The initial episode of pyrexia typically occurs within the first month, and has a median duration of 9 days. With prompt interruption of both BRAFi and MEKi at the first sign of pyrexia or its prodrome, symptoms resolve within 24 h in most cases. Acetaminophen or nonsteroidal anti-inflammatory drugs can be used to manage symptoms. Treatment can then be resumed at full dose 24 h after symptom resolution.

Pyrexia can be episodic, and recurrences are generally shorter than the initial episode. Intermittent dosing at full dose should be considered for patients with recurrent or severe pyrexia. Corticosteroids may be helpful as secondary prophylaxis. Patients should be evaluated if fever does not resolve within 24 h despite dose hold and if the patient experiences localizing symptoms, as well as confusion and signs of volume depletion.

Cutaneous Rash

Rash is typically managed through mitigation of symptoms. Treatment may include emollients, antihistamines, and analgesics to relieve symptoms and improve quality of life [92–94]. A short course of steroids may be necessary. Dose reductions or interruptions and consultation with a dermatologist should be considered if the rash is severe.

Photosensitivity [93–95]

Patient education is important to prevent or minimize photosensitivity reactions. Use of sunblock with a high sun protection factor is needed, and UV-protective clothing should be worn. Patients also should be warned to cover themselves if sitting near windows, such as in a car, because UV-A rays can pass through glass.

Cardiac [96] LVEF decrease

Several cardiac toxicities have been described in patients receiving BRAFi/MEKi therapy. These include decreased LVEF, peripheral edema, and hypertension. Before initiating BRAF/MEK inhibition, LVEF should be assessed and changes monitored after 1 month and every 2–3 months thereafter. Treatment interruption, reduction, or discontinuation can be used to manage decreased LVEF if it occurs.

Hepatic [97,98]

Liver enzymes should be measured before initiating a BRAFi/MEKi regimen and monitored monthly throughout the course of treatment. Persistent or recurrent grade 2 liver enzyme elevations and grade ≥3 events should be managed through dose reductions or interruptions as indicated, or, if necessary, permanent discontinuation of treatment.

Ocular [99–102]

The potential for ocular toxicities related to MEK inhibition requires regular monitoring. Patients should be advised of the importance of reporting visual disturbances, blurred vision, red eyes, and eye pain. However, ocular toxicities are transient and reversible with dose reduction, interruption, or discontinuation. Some ocular AEs (e.g., iritis) may require local steroids.

blocking mutant BRAF signaling reduced the release of immunosuppressive cytokines (e.g., interleukin-6, interleukin-10), which was supported by data from patient samples that demonstrated reduced immunosuppressive cytokine levels in post-treatment tumor samples versus pretreatment samples [74,75]. Following BRAF inhibition, an increase in tumor-infiltrating lymphocytes ($CD8^+$ and $CD4^+$ T cells) that may recognize the tumor and drive tumor lysis, as well as an increase in PD-L1 expression (which is associated with improved outcomes in patients treated with anti-PD-1 agents), have been observed [74,76,77]. When melanoma cells were cocultured with MART-1-specific and gp100-specific T cells, interferon-γ release was increased following BRAF inhibition, suggesting enhanced melanoma cell recognition by the T cells [78]. Finally, in patient tumor samples, granzyme B and perforin expression is elevated following treatment with BRAFi, which suggests increased cytotoxic T-cell activity [74]. Taken together, these data provide the basis for potential synergistic antitumor activity when BRAFi/MEKi are combined with anti-PD-1 therapy. Indeed, in a preclinical melanoma mouse model (SM1), the combination of an anti-PD-1 antibody with BRAFi/MEKi therapy provided superior antitumor activity versus either treatment alone [79].

The Phase II KEYNOTE-022 trial first reported the evaluation of pembrolizumab in combination with dabrafenib and trametinib versus placebo plus dabrafenib and trametinib. The primary endpoint of improved PFS was not met in this trial, although clinically meaningful improvements in response duration were observed, and a clear separation of Kaplan–Meier survival curves was evident with extended follow-up (median PFS for pembrolizumab plus dabrafenib and trametinib vs placebo plus dabrafenib and trametinib was 16.9 months vs 10.7 months; HR 0.53, 95% CI 0.34–0.83) [80,81]. However, patients treated with pembrolizumab plus dabrafenib and trametinib had a higher incidence of grade ≥3 treatment-related AEs (58% vs 25%) and discontinuations due to AEs (43% vs 18%), and one patient died due to pneumonitis related to treatment.

The Phase III COMBI-i trial (NCT02967692) is evaluating the anti-PD-1 antibody spartalizumab in combination with dabrafenib and trametinib. Data from the nonrandomized parts 1 and 2 of COMBI-i (n = 36) have demonstrated a high rate of complete response (42%) and a median PFS of nearly 2 years (23.7 months, 95% CI 12 months to not reached) [82]. Grade ≥3 treatment-related AEs were reported in 72% of patients, and AEs led to discontinuation of all three study drugs in 17% of patients. Results from the randomized part 3 of the COMBI-i trial, as well as the Phase III TRILOGY trial (NCT01656642) combining the anti-PD-L1 antibody atezolizumab plus vemurafenib and cobimetinib, are eagerly anticipated and should provide further insight into the risk–benefit profile of combining immune checkpoint inhibitors with targeted therapy.

In addition to evaluating novel combinations to improve efficacy in existing indications, targeted therapy combinations are also being used to treat *BRAF*-driven tumor types that were less responsive to BRAFi/MEKi alone, such as colorectal cancers (CRCs). A surprising lack of efficacy was initially observed in patients with CRC treated with BRAFi [83–85]. It was later explained that, unlike *BRAF*-mutant melanomas, *BRAF*-mutant CRC exhibited robust adaptive feedback signaling upon treatment with BRAFi, leading to reactivation of the MAPK pathway [83,85]. Treatment with BRAFi is proposed to lead to a loss of ERK-dependent negative feedback, which allows greater RTK-meditated RAS activation and subsequent activation of CRAF, bypassing BRAF inhibition. Therefore, clinical strategies have sought to combine BRAFi with or without MEKi and EGFR blockade in *BRAF*-mutant CRC.

Initial evaluations in patients treated with dabrafenib plus trametinib plus panitumumab demonstrated a higher response rate in patients receiving the triple combination (21%) versus those

who received dabrafenib plus panitumumab (10%) or trametinib plus panitumumab (0%) [86]. Recently, encorafenib plus cetuximab received US FDA approval for use in patients with previously treated *BRAF* V600E-mutant metastatic CRC. This approval was based on results from the Phase III BEACON trial, which demonstrated significant OS benefit ($P < 0.001$) in patients treated with encorafenib plus cetuximab versus cetuximab plus investigator's choice of chemotherapy [87]. Median OS was similar in patients who received encorafenib plus cetuximab (8.4 months) and those who received encorafenib plus binimetinib plus cetuximab (9.0 months).

In addition, given the strong association between co-occurring PI3K–mTOR pathway aberrations and primary resistance to BRAF-targeted therapy [88], BRAF and mTOR therapies have also been explored in the clinic [89].

Concluding Remarks

Targeting oncogenic *BRAF* mutations with combination BRAFi/MEKi has revolutionized treatment for many patients. Novel combinations may further improve outcomes and open the door to targeting additional tumor types that are not amenable to BRAFi/MEKi therapy (see Outstanding Questions).

Outstanding Questions

Can baseline biomarkers help to determine patients who will have durable long-term disease control with BRAFi plus MEKi therapy?

Can noninvasive techniques such as liquid biopsy be used to monitor for resistance, and are there therapeutic interventions that could help to slow or prevent the acquired BRAFi/MEKi resistance?

Can novel combination approaches (e.g., BRAF/MEK inhibition plus anti-PD-1 therapy) provide more durable benefit for more patients?

What factors should be considered in determining the best treatment sequence or treatment combination for patients with *BRAF* mutations?

Is treatment with BRAF plus MEK inhibition or combinations efficacious in other *BRAF*-mutant tumors (e.g., colorectal cancer)?

In the absence of head-to-head data, what drives the choice of BRAFi/MEKi regimen in tumors where multiple combinations are approved for use (e.g., metastatic melanoma)?

Is rechallenge with BRAFi/MEKi in patients who were previously treated with a combination regimen a potential strategy, and when is it appropriate?

Acknowledgments

Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation. We thank Michael Demars (ArticulateScience) for medical editorial assistance with this manuscript. Authors had full control of the content and made the final decision for all aspects of this article.

Disclaimer Statement

V.S. has received clinical trial research grants from GlaxoSmithKline and Novartis, as well as grants from AbbVie, Agensys, Alfa-Sigma, Amgen, Bayer, Berghealth, Blueprint Medicines, Boston Biomedical, Celgene, D3, Exelixis, Fujifilm, Idera Pharma, Incyte, Inhibrx, Loxo Oncology, MultiVir, NanoCarrier, Northwest Biotherapeutics, Pfizer, PharmaMar, and Vegenics, and travel support from Helsin, Incyte, Novartis, PharmaMar, the American Society of Clinical Oncology, and the European Society for Medical Oncology. C.B. has received grant funding from AstraZeneca, Blueprint Medicines, Celgene, Daiichi Sankyo, F. Hoffmann-La Roche, Genentech, Loxo Oncology, Novartis, Pfizer, Spectrum, and the National Institutes of Health/National Cancer Institute, as well as consulting fees from AstraZeneca, F. Hoffmann-La Roche, and Novartis. J.M.K. has received grant funding from Amgen, Bristol Myers Squibb, Immunocore, Iovance, Merck, Novartis, and Prometheus, as well as personal fees from Amgen, Array BioPharma, Bristol Myers Squibb, Elsevier, Immunocore, Iovance, Merck, Novartis, and Roche.

References

1. Brose, M.S. *et al.* (2002) BRAF and RAS mutations in human lung cancer and melanoma. *Cancer Res.* 62, 6997–7000
2. Cohn, A.L. *et al.* (2017) BRAF(V600) mutations in solid tumors, other than metastatic melanoma and papillary thyroid cancer, or multiple myeloma: a screening study. *Onco Targets Ther.* 10, 965–971
3. Davies, H. *et al.* (2002) Mutations of the BRAF gene in human cancer. *Nature* 417, 949–954
4. Eblen, S.T. (2018) Extracellular-regulated kinases: signaling from Ras to ERK substrates to control biological outcomes. *Adv. Cancer Res.* 138, 99–142
5. Hall, R.D. and Kudchadkar, R.R. (2014) BRAF mutations: signaling, epidemiology, and clinical experience in multiple malignancies. *Cancer Control* 21, 221–230
6. Lin, L. *et al.* (2014) Mapping the molecular determinants of BRAF oncogene dependence in human lung cancer. *Proc. Natl. Acad. Sci. U. S. A.* 111, E748–E757
7. Eisen, T. *et al.* (2006) Sorafenib in advanced melanoma: a phase II randomised discontinuation trial analysis. *Br. J. Cancer* 95, 581–586
8. Hauschild, A. *et al.* (2009) Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. *J. Clin. Oncol.* 27, 2823–2830
9. Bayer HealthCare (2015) *Nexavar (Sorafenib)*. package insert, Bayer
10. Koelblinger, P. *et al.* (2018) Development of encorafenib for BRAF-mutated advanced melanoma. *Curr. Opin. Oncol.* 30, 125–133
11. Rheault, T.R. *et al.* (2013) Discovery of dabrafenib: a selective inhibitor of Raf kinases with antitumor activity against B-Raf-driven tumors. *ACS Med. Chem. Lett.* 4, 358–362
12. Tsai, J. *et al.* (2008) Discovery of a selective inhibitor of oncogenic B-Raf kinase with potent antimelanoma activity. *Proc. Natl. Acad. Sci. U. S. A.* 105, 3041–3046
13. Delord, J.P. *et al.* (2017) Phase I dose-escalation and -expansion study of the BRAF inhibitor encorafenib (LGX818) in metastatic BRAF-mutant melanoma. *Clin. Cancer Res.* 23, 5339–5348
14. Yang, H. *et al.* (2010) RG7204 (PLX4032), a selective BRAFV600E inhibitor, displays potent antitumor activity in preclinical melanoma models. *Cancer Res.* 70, 5518–5527
15. Chapman, P.B. *et al.* (2011) Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N. Engl. J. Med.* 364, 2507–2516
16. Chapman, P.B. *et al.* (2017) Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. *Ann. Oncol.* 28, 2581–2587

17. Hauschild, A. *et al.* (2012) Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 380, 358–365
18. Sosman, J.A. *et al.* (2012) Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N. Engl. J. Med.* 366, 707–714
19. Johnson, D.B. *et al.* (2015) Acquired BRAF inhibitor resistance: a multicenter meta-analysis of the spectrum and frequencies, clinical behaviour, and phenotypic associations of resistance mechanisms. *Eur. J. Cancer* 51, 2792–2799
20. Marusiak, A.A. *et al.* (2014) Mixed lineage kinases activate MEK independently of RAF to mediate resistance to RAF inhibitors. *Nat. Commun.* 5, 3901
21. Nazarian, R. *et al.* (2010) Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. *Nature* 468, 973–977
22. Welsh, S.J. *et al.* (2016) Resistance to combination BRAF and MEK inhibition in metastatic melanoma: where to next? *Eur. J. Cancer* 62, 76–85
23. Wheler, J. *et al.* (2015) Next generation sequencing of exceptional responders with BRAF-mutant melanoma: implications for sensitivity and resistance. *BMC Cancer* 15, 61
24. Penna, I. *et al.* (2016) Primary cross-resistance to BRAFV600E-, MEK1/2- and PI3K/mTOR-specific inhibitors in BRAF-mutant melanoma cells counteracted by dual pathway blockade. *Oncotarget* 7, 3947–3965
25. Shi, H. *et al.* (2014) Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. *Cancer Discov.* 4, 80–93
26. Straussman, R. *et al.* (2012) Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature* 487, 500–504
27. Villanueva, J. *et al.* (2010) Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by cotargeting MEK and IGF-1R/PI3K. *Cancer cell* 18, 683–695
28. Wilson, T.R. *et al.* (2012) Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. *Nature* 487, 505–509
29. Hatzivassiliou, G. *et al.* (2010) RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature* 464, 431–435
30. Poulikakos, P.I. *et al.* (2010) RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. *Nature* 464, 427–430
31. Paraiso, K.H. *et al.* (2010) Recovery of phospho-ERK activity allows melanoma cells to escape from BRAF inhibitor therapy. *Br. J. Cancer* 102, 1724–1730
32. Flaherty, K.T. *et al.* (2012) Improved survival with MEK inhibition in BRAF-mutated melanoma. *N. Engl. J. Med.* 367, 107–114
33. Su, F. *et al.* (2012) RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. *N. Engl. J. Med.* 366, 207–215
34. Hyman, D.M. *et al.* (2015) Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N. Engl. J. Med.* 373, 726–736
35. Subbiah, V. *et al.* (2020) Pan-cancer efficacy of vemurafenib in BRAF (V600)-mutant non-melanoma cancers. *Cancer Discov.* 10, 657–663
36. Flaherty, K.T. *et al.* (2012) Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N. Engl. J. Med.* 367, 1694–1703
37. Long, G.V. *et al.* (2014) Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N. Engl. J. Med.* 371, 1877–1888
38. Long, G.V. *et al.* (2015) Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet* 386, 444–451
39. Robert, C. *et al.* (2015) Improved overall survival in melanoma with combined dabrafenib and trametinib. *N. Engl. J. Med.* 372, 30–39
40. Robert, C. *et al.* (2019) Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N. Engl. J. Med.* 381, 626–636
41. Davies, M.A. *et al.* (2011) Prognostic factors for survival in melanoma patients with brain metastases. *Cancer* 117, 1687–1696
42. Jakob, J.A. *et al.* (2012) NRAS mutation status is an independent prognostic factor in metastatic melanoma. *Cancer* 118, 4014–4023
43. Maxwell, R. *et al.* (2017) BRAF-V600 mutational status affects recurrence patterns of melanoma brain metastasis. *Int. J. Cancer* 140, 2716–2727
44. Davies, M.A. *et al.* (2017) Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol.* 18, 863–873
45. Gershenwald, J.E. *et al.* (2017) Melanoma staging: evidence-based changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. *CA Cancer J. Clin.* 67, 472–492
46. Hauschild, A. *et al.* (2018) Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected BRAF V600-mutant stage III melanoma. *J. Clin. Oncol.* 36, 3441–3449
47. Long, G.V. *et al.* (2017) Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *N. Engl. J. Med.* 377, 1813–1823
48. American Cancer Society (2018) *Cancer Facts & Figures 2018*, ACS
49. Chatziandreou, I. *et al.* (2015) Comprehensive molecular analysis of NSCLC; clinicopathological associations. *PLoS One* 10, e0133859
50. Planchard, D. *et al.* (2016) Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol.* 17, 984–993
51. Planchard, D. *et al.* (2017) Updated survival of patients (pts) with previously treated BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC) who received dabrafenib (D) or D + trametinib (T) in the phase II BRF113928 study. *JCO* 35, 9075
52. Planchard, D. *et al.* (2016) Dabrafenib in patients with BRAF (V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol.* 17, 642–650
53. Planchard, D. *et al.* (2017) Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol.* 18, 1307–1316
54. Haddad, R.I. *et al.* (2015) Anaplastic thyroid carcinoma, version 2.2015. *J. Natl. Compr. Cancer Netw.* 13, 1140–1150
55. Gilliland, F.D. *et al.* (1997) Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the surveillance, epidemiology and end results (SEER) program 1973-1991. *Cancer* 79, 564–573
56. Kebebew, E. *et al.* (2005) Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. *Cancer* 103, 1330–1335
57. Kunstman, J.W. *et al.* (2015) Characterization of the mutational landscape of anaplastic thyroid cancer via whole-exome sequencing. *Hum. Mol. Genet.* 24, 2318–2329
58. Landa, I. *et al.* (2016) Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *J. Clin. Invest.* 126, 1052–1066
59. Sandulache, V.C. *et al.* (2017) Real-time genomic characterization utilizing circulating cell-free DNA in patients with anaplastic thyroid carcinoma. *Thyroid* 27, 81–87
60. Guerra, A. *et al.* (2013) Genetic mutations in the treatment of anaplastic thyroid cancer: a systematic review. *BMC Surg.* 13, S44
61. Subbiah, V. *et al.* (2018) Dabrafenib and trametinib treatment in Patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. *J. Clin. Oncol.* 6, 7–13
62. Keam, B. *et al.* (2018) Updated efficacy and safety data of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600E-mutated anaplastic thyroid cancer (ATC). *Ann. Oncol.* 29, 645–648
63. Ascierto, P.A. *et al.* (2016) Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma

(coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 17, 1248–1260
64. Subbiah, V. *et al.* (2017) Efficacy of vemurafenib in patients (pts) with non-small cell lung cancer (NSCLC) with BRAFV600 mutation. *J. Clin. Oncol.* 35, 9074
65. Green, P. *et al.* (2017) Exceptional response to vemurafenib and cobimetinib in anaplastic thyroid cancer 40 years after treatment for papillary thyroid cancer. *Int. J. Endocr. Oncol.* 4, 159–165
66. Dummer, R. *et al.* (2018) Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 19, 1315–1327
67. Dummer, R. *et al.* (2018) Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 19, 603–615
68. Dummer, R. *et al.* (2017) Results of COLUMBUS part 2: a phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) versus ENCO in BRAF-mutant melanoma. *Ann. Oncol.* 28, 428–448
69. Liszkay, G. *et al.* (2019) Update on overall survival in COLUMBUS: a randomized phase III trial of encorafenib (ENCO) plus binimetinib (BINI) versus vemurafenib (VEM) or ENCO in patients with BRAF V600-mutant melanoma. *J. Clin. Oncol.* 37, 9512
70. Cox, D.S. *et al.* (2015) Relative bioavailability of pediatric oral solution and tablet formulations of trametinib in adult patients with solid tumors. *Clin. Pharmacol. Drug Dev.* 4, 287–294
71. Daud, A. and Tsai, K. (2017) Management of treatment-related adverse events with agents targeting the MAPK pathway in patients with metastatic melanoma. *Oncologist* 22, 823–833
72. Grob, J.J. *et al.* (2017) Pooled analysis of safety with extended 3-year follow-up across combination dabrafenib and trametinib phase 3 trials. *J. Oncol.* 8, 1717
73. Ugurel, S. *et al.* (2017) Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. *Eur. J. Cancer* 83, 247–257
74. Frederick, D.T. *et al.* (2013) BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. *Clin. Cancer Res.* 19, 1225–1231
75. Sumimoto, H. *et al.* (2006) The BRAF-MAPK signaling pathway is essential for cancer-immune evasion in human melanoma cells. *J. Exp. Med.* 203, 1651–1656
76. Hodi, F.S. *et al.* (2018) Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol.* 19, 1480–1492
77. Wilmott, J.S. *et al.* (2012) Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. *Clin. Cancer Res.* 18, 1386–1394
78. Boni, A. *et al.* (2010) Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. *Cancer Res.* 70, 5213–5219
79. Hu-Lieskovan, S. *et al.* (2015) Improved antitumor activity of immunotherapy with BRAF and MEK inhibitors in BRAF (V600E) melanoma. *Sci. Transl. Med.* 7, 279ra241
80. Ascierto, P.A. *et al.* (2019) Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma. *Nat. Med.* 25, 941–946
81. Ferrucci, P.F.A. *et al.* (2019) Updated survival in patients with *BRAF*-mutant melanoma administered pembrolizumab, dabrafenib, and trametinib. In *Oral presentation at the 16th International Congress of the Society for Melanoma Research, Salt Lake City*
82. Dummer, R.G. *et al.* (2019) Spartalizumab + dabrafenib + trametinib in first-line treatment of *BRAF* V600-mutant melanoma: clinical outcomes and biomarker analyses from COMBI-i parts 1 and 2. In *Poster presentation at the 16th International Congress of the Society for Melanoma Research, Salt Lake City*
83. Corcoran, R.B. *et al.* (2012) EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. *Cancer Discov.* 2, 227–235
84. Kopetz, S. *et al.* (2015) Phase II pilot study of vemurafenib in patients with metastatic BRAF-mutated colorectal cancer. *J. Clin. Oncol.* 33, 4032–4038
85. Prahallad, A. *et al.* (2012) Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature* 483, 100–103
86. Corcoran, R.B. *et al.* (2018) Combined BRAF, EGFR, and MEK inhibition in patients with BRAF(V600E)-Mutant colorectal cancer. *Cancer Discov.* 8, 428–443
87. Kopetz, S. *et al.* (2019) Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. *N. Engl. J. Med.* 381, 1632–1643
88. Sen, S. *et al.* (2017) Co-occurring genomic alterations and association with progression-free survival in BRAFV600-mutated nonmelanoma tumors. *J. Natl. Cancer Inst.* 109, djx094
89. Subbiah, V. *et al.* (2018) Phase I study of the BRAF inhibitor vemurafenib in combination with the mammalian target of rapamycin inhibitor everolimus in patients with braf-mutated malignancies. *JCO Precis. Oncol.* 2, 00189
90. Atkinson, V. *et al.* (2016) Optimizing combination dabrafenib and trametinib therapy in BRAF mutation-positive advanced melanoma patients: guidelines from Australian melanoma medical oncologists. *Asia Pac. J. Clin. Oncol.* 12, 5–12
91. Menzies, A.M. *et al.* (2015) Characteristics of pyrexia in BRAFV600E/K metastatic melanoma patients treated with combined dabrafenib and trametinib in a phase I/II clinical trial. *Ann. Oncol.* 26, 415–421
92. Lacouture, M.E. *et al.* (2013) Analysis of dermatologic events in vemurafenib-treated patients with melanoma. *Oncologist* 18, 314–322
93. Livingstone, E. *et al.* (2014) BRAF, MEK and KIT inhibitors for melanoma: adverse events and their management. *Chin. Clin. Oncol.* 3, 29
94. Welsh, S.J. and Corrie, P.G. (2015) Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther. Adv. Med. Oncol.* 7, 122–136
95. Dummer, R. *et al.* (2012) Ultraviolet A and photosensitivity during vemurafenib therapy. *N. Engl. J. Med.* 366, 480–481
96. Bronte, E. *et al.* (2015) What links BRAF to the heart function? New insights from the cardiotoxicity of BRAF inhibitors in cancer treatment. *Oncotarget* 6, 35589–35601
97. Genentech Inc. (2017) Zelboraf (Vemurafenib). package insert. Genentech
98. Pfizer Inc. (2019) MEKTOVI (Binimetinib). package insert. Pfizer
99. Schoenberger, S.D. and Kim, S.J. (2013) Bilateral multifocal central serous-like chorioretinopathy due to MEK inhibition for metastatic cutaneous melanoma. *Case Rep. Ophthalmol. Med.* 2013, 673796
100. Urner-Bloch, U. *et al.* (2014) Transient MEK inhibitor-associated retinopathy in metastatic melanoma. *Ann. Oncol.* 25, 1437–1441
101. van der Noll, R. *et al.* (2013) Effect of inhibition of the FGFR–MAPK signaling pathway on the development of ocular toxicities. *Cancer Treat. Rev.* 39, 664–672
102. van Dijk, E.H. *et al.* (2016) Loss of MAPK pathway activation in post-mitotic retinal cells as mechanism in MEK inhibition-related retinopathy in cancer patients. *Medicine* 95, e3457
103. McArthur, G.A.D. *et al.* (2019) Five-year survival update of cobimetinib plus vemurafenib in *BRAF*V600 mutation-positive advanced melanoma: final analysis of the coBRIM study. In *Oral presentation at the 16th International Congress of the Society for Melanoma Research, Salt Lake City*
104. Rubin, K.M. (2017) MAPK pathway-targeted therapies: care and management of unique toxicities in patients with advanced melanoma. *Clin. J. Oncol. Nurs.* 21, 699–709