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REVIEW

Precision oncology for *BRAF*-mutant cancers with *BRAF* and *MEK* inhibitors: from melanoma to tissue-agnostic therapy

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Available online xxx

BRAF activation occurs as part of the mitogen-activated protein kinase (MAPK) cellular signaling pathway which leads to increased cellular proliferation and survival. Mutations in *BRAF* can result in unbridled activation of downstream kinases with subsequent uncontrolled cellular growth that formulate the basis for oncogenesis in multiple tumor types. Targeting *BRAF* by selective inhibitors has been one of the early successes in precision oncology. Agents have been explored either as monotherapy or in combination with *MEK* inhibition in *BRAF* V600-mutant pan-cancers and with *EGFR* inhibition in colorectal cancer. Spectrum of *BRAF* inhibition has evolved from being melanoma-specific to being a pan-cancer target. In this article, we review *BRAF* and *MEK* inhibitor drug development journey from tissue-specific melanoma, non-small-cell lung cancer, and anaplastic thyroid cancer to tissue-agnostic approvals.

Key words: BRAF, MEK, cancer, precision oncology, targeted therapy

INTRODUCTION

The RAF family proteins are serine/threonine protein kinases that constitute a cornerstone of the mitogen-activated protein kinase (MAPK) pathway which is frequently dysfunctional in many human cancers. Three RAF isoforms (A-RAF, B-RAF, and C-RAF) have been described as important regulators of cell growth, differentiation, and survival. RAF isoforms are activated through binding of small G proteins to the N-terminal of RAF proteins. Activation of RAF leads to downstream phosphorylation of MEK1 and MEK2 and their downstream ERK1 and ERK2 (Figure 1).[1-3]

BRAF ALTERATIONS

BRAF mutations are the second most common alterations that occur in the MAPK pathway. Their role in cancer development was described in 2002 by Davies et al.;[4] and since then, multiple efforts have led to substantial advances in characterizing their impact and improving their targetability.

In attempt to explore tissue distribution of *BRAF* alterations, we reviewed sequencing data of 153 554 samples from different tumor types in the AACR GENIE database v12.1.[5] *BRAF* alterations were found in 9173 samples, accounting for 6% of all profiled samples. Prevalence varied significantly across different tumor types and histologies with the highest frequency of distribution observed in thyroid cancer (41%) (Figure 1).

BRAF mutations have been functionally categorized into three different classes that have variable levels of *RAS* dependency. Class I mutations, which include V600 E/K/D, are *RAS* independent and hence maintain high level of activity regardless of *RAS* signaling even in their monomeric status. Class II mutations include non-V600 mutations e.g. *G469A*, *K601E*, and *L597Q* as well as fusions and deletions. While also being *RAS*-independent, class II have intermediate monomeric kinase activity and usually require dimerization to function. Class III mutations, including *D594* and *G466*, are *RAS* dependent and need to form dimers for activation. This class is strongly dependent on upstream activation and often occurs with upstream mutations including *RAS*, unlike class I and II which usually show mutual exclusivity due to the downstream inhibition of *RAS* via *ERK*.[6-9] In our AACR GENIE analysis, class I alterations were the most prevalent being present in 4869 of *BRAF*-altered samples (53%).

DETECTION OF *BRAF* MUTATIONS

There is a wide variety of technologies that can be used for detection of *BRAF* alterations. For example, immunohistochemistry, PCR-based and sequencing-based technologies have all been validated for identification of *BRAF*

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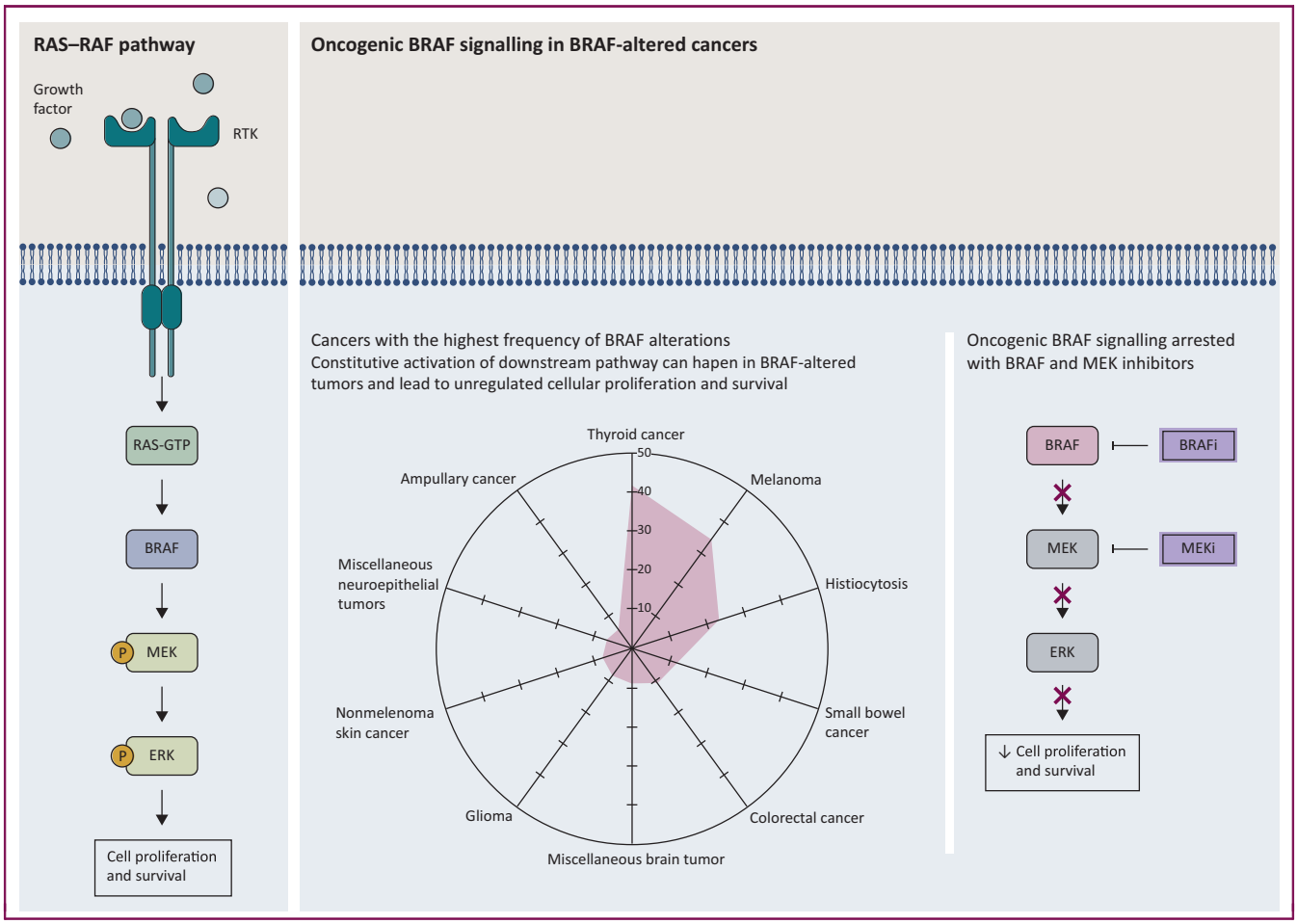

Figure 1. Targeting BRAF pathway: figure shows the BRAF signaling pathway and cancers with the highest frequency of BRAF alterations according to AACR GENIE. Included are only cancers where BRAF was profiled in at least 100 samples.
BRAFi, BRAF inhibitor; MEKi, MEK inhibitor.

mutations.[10,11] In clinical trials of *BRAF* inhibitors, the cobas® 4800 BRAF V600 Mutation Test (Roche, Basel, Switzerland), Therascreen BRAF V600E RGQ polymerase chain reaction (PCR) Kit (QIAGEN, Hilden, Germany), Oncomine Dx Target Test (Thermo Fisher, Waltham, MA), BRAF PCR Assay (Response Genetics, Los Angeles, CA), and THxID™ BRAF assay (bioMérieux Clinical Diagnostics, Marcy l'Etoile, France) were used for confirmation of *BRAF* mutation presence in patients receiving targeted treatment options. More recently, interest has grown in detecting *BRAF* alterations in plasma or other body fluids via liquid biopsy technologies. This offers a minimally invasive tool for genetic assessment that can expand beyond baseline testing of targetability to evaluation of clonal evolution and emerging resistance mechanisms over time.[12-16]

CURRENT ACTIONABLE ALTERATIONS

Different *BRAF* alterations have been evaluated for targetability in different tumor types[17-56] (Table 1). Current Food and Drug Administration (FDA) approvals include monotherapy with vemurafenib, dabrafenib, or trametinib. Moreover, the FDA approves combinations of (dabrafenib + trametinib), (encorafenib + cetuximab), (encorafenib + binimetinib), and (vemurafenib + cobimetinib) for treatment of patients with *BRAF* mutations (Figure 2). In this review, we will focus on *BRAF* V600-targeted therapeutic options that are currently FDA approved (level 1) either as monotherapy or in combinations for treatment of *BRAF*-altered cancers.

BRAF-TARGETED MONOTHERAPY

Vemurafenib

The first FDA approval for a kinase inhibitor targeting *BRAF* was for vemurafenib in 2011. The drug is currently approved as monotherapy for treatment of patients with unresectable or metastatic melanoma who harbor *BRAF* V600E mutation and also for treatment of patients with Erdheim–Chester disease (ECD) who have a *BRAF* V600 mutation.[57]

Vemurafenib is a multikinase inhibitor that is available in oral form and possesses strong antitumor activity in cases with mutated *BRAF*. Some mutations, including V600 mutations, lead to continuous activation of the *BRAF* downstream pathway that becomes independent on upstream growth factor stimulation. In that setting, the inhibitory effect of vemurafenib can lead to cessation of cellular proliferation and tumor cell apoptosis. Preclinical data suggested paradoxical

Table 1. Level of evidence for *BRAF* alterations' targetability according to OncoKB[17]

Level	Gene	Alterations	Cancer types	Drugs
1	*BRAF*	V600	Erdheim—Chester disease	Vemurafenib
1	*BRAF*	V600	Melanoma	Vemurafenib + atezolizumab + cobimetinib
1	*BRAF*	V600E	All solid tumors (excluding colorectal cancer)	Dabrafenib + trametinib
1	*BRAF*	V600E	Anaplastic thyroid cancer	Dabrafenib + trametinib
1	*BRAF*	V600E	Biliary tract cancer, NOS	Dabrafenib + trametinib
1	*BRAF*	V600E	Colorectal cancer	Encorafenib + cetuximab
1	*BRAF*	V600E	Melanoma	Dabrafenib
1	*BRAF*	V600E	Melanoma	Vemurafenib
1	*BRAF*	V600E	Non-small-cell lung cancer	Dabrafenib + trametinib
1	*BRAF*	V600E, V600K	Melanoma	Dabrafenib + trametinib
1	*BRAF*	V600E, V600K	Melanoma	Encorafenib + binimetinib
1	*BRAF*	V600E, V600K	Melanoma	Trametinib
1	*BRAF*	V600E, V600K	Melanoma	Vemurafenib + cobimetinib
2	*BRAF*	Fusions	Pilocytic astrocytoma	Selumetinib
2	*BRAF*	Oncogenic Mutations (excluding V600)	Erdheim—Chester disease	Cobimetinib, trametinib
2	*BRAF*	Oncogenic Mutations (excluding V600)	Langerhans cell histiocytosis	Cobimetinib, trametinib
2	*BRAF*	Oncogenic Mutations (excluding V600)	Rosai—Dorfman disease	Cobimetinib, trametinib
2	*BRAF*	V600	Langerhans cell histiocytosis	Vemurafenib, dabrafenib
2	*BRAF*	V600 (excluding V600E and V600K)	Melanoma	Dabrafenib + trametinib
2	*BRAF*	V600 (excluding V600E and V600K)	Melanoma	Encorafenib + binimetinib
2	*BRAF*	V600 (excluding V600E and V600K)	Melanoma	Vemurafenib + cobimetinib
2	*BRAF*	V600E	Colorectal cancer	Encorafenib + panitumumab
2	*BRAF*	V600E	Diffuse glioma	Vemurafenib + cobimetinib
2	*BRAF*	V600E	Encapsulated glioma	Vemurafenib + cobimetinib
2	*BRAF*	V600E	Hairy cell leukemia	Vemurafenib
2	*BRAF*	V600E	Pilocytic astrocytoma	Selumetinib
2	*BRAF*	V600E	Pleomorphic xanthoastrocytoma, Pilocytic astrocytoma, Ganglioglioma	Vemurafenib + cobimetinib
3	*BRAF*	Fusions	Melanoma	Trametinib, cobimetinib
3	*BRAF*	Fusions	Ovarian cancer	Trametinib, cobimetinib
3	*BRAF*	K601	Melanoma	Trametinib
3	*BRAF*	L597	Melanoma	Trametinib
3	*BRAF*	Oncogenic Mutations (excluding V600)	Histiocytosis	Cobimetinib, trametinib
3	*BRAF*	V600	Histiocytosis	Vemurafenib, dabrafenib
4	*BRAF*	G464, G469A, G469R, G469V	All solid tumors	PLX8394
4	*BRAF*	K601	All solid tumors	PLX8394
4	*BRAF*	L597	All solid tumors	PLX8394

activation of the MAPK pathway by vemurafenib in *BRAF* wild-type tumors leading to increased cell proliferation which has been the basis of design of next generation inhibitors as well as combination with *MEK* and *EGFR* inhibitors.[58,59]

Multiple clinical trials have shown data favoring the use of vemurafenib as a single agent in different tumor types and led to current approvals (Table 2). Four trials are considered the basis for FDA approval of vemurafenib in treatment of *BRAF* V600E melanoma and non-melanoma cancers.[57] The first randomized, controlled trial (BRIM-3; NCT01006980) explored the use of vemurafenib in treatment-naive patients with *BRAF* V600-mutated unresectable or metastatic melanoma. Patients in the vemurafenib arm showed improved overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) compared with patients in the dacarbazine control arm.[18-20] Further testing was done in previously treated patients in the phase II NCT00949702 trial where vemurafenib induced clinical response in more than half of included patients.[21] Another phase II trial (NCT01378975) investigated the use of vemurafenib in patients with pretreated and treatment-naive brain metastasis from *BRAF* V600 melanoma and reported intracranial responses in 18% of patients.[22]

Since *BRAF* V600 mutations are seen in multiple non-melanoma cancers, activity of monotherapy vemurafenib was explored in one of the first histology-independent trials ever designed—the VE-BASKET study.[25] The trial showed activity of vemurafenib in non-small-cell lung cancer (NSCLC; 42%), ECD (43%), and multiple other rare tumors (including pleomorphic xanthoastrocytoma, anaplastic thyroid cancer (ATC), cholangiocarcinoma, salivary duct cancer, ovarian cancer, and clear-cell sarcoma). Such initial results were unprecedented and established *BRAF* as a potential pan-cancer target. In colorectal cancer (CRC), however, there was limited activity of vemurafenib monotherapy in patients harboring *BRAF* V600 mutation. A preclinical study suggested that unresponsiveness of CRC to *BRAF* inhibition was mediated through feedback activation of *EGFR* and might benefit from combination therapy of *BRAF* and *EGFR* inhibitors.[60] So, the protocol was amended to add an arm of vemurafenib and cetuximab which successfully demonstrated response in CRC patients. Follow-up data of all the 172 included patients with 26 nonmelanoma cancer types showed responses in 13 different cancers.[23] Striking responses were observed in patients with ECD/Langerhans cell histiocytosis who harbor *BRAF* V600 mutation which formed the basis for FDA approval of vemurafenib in ECD.[23,24]

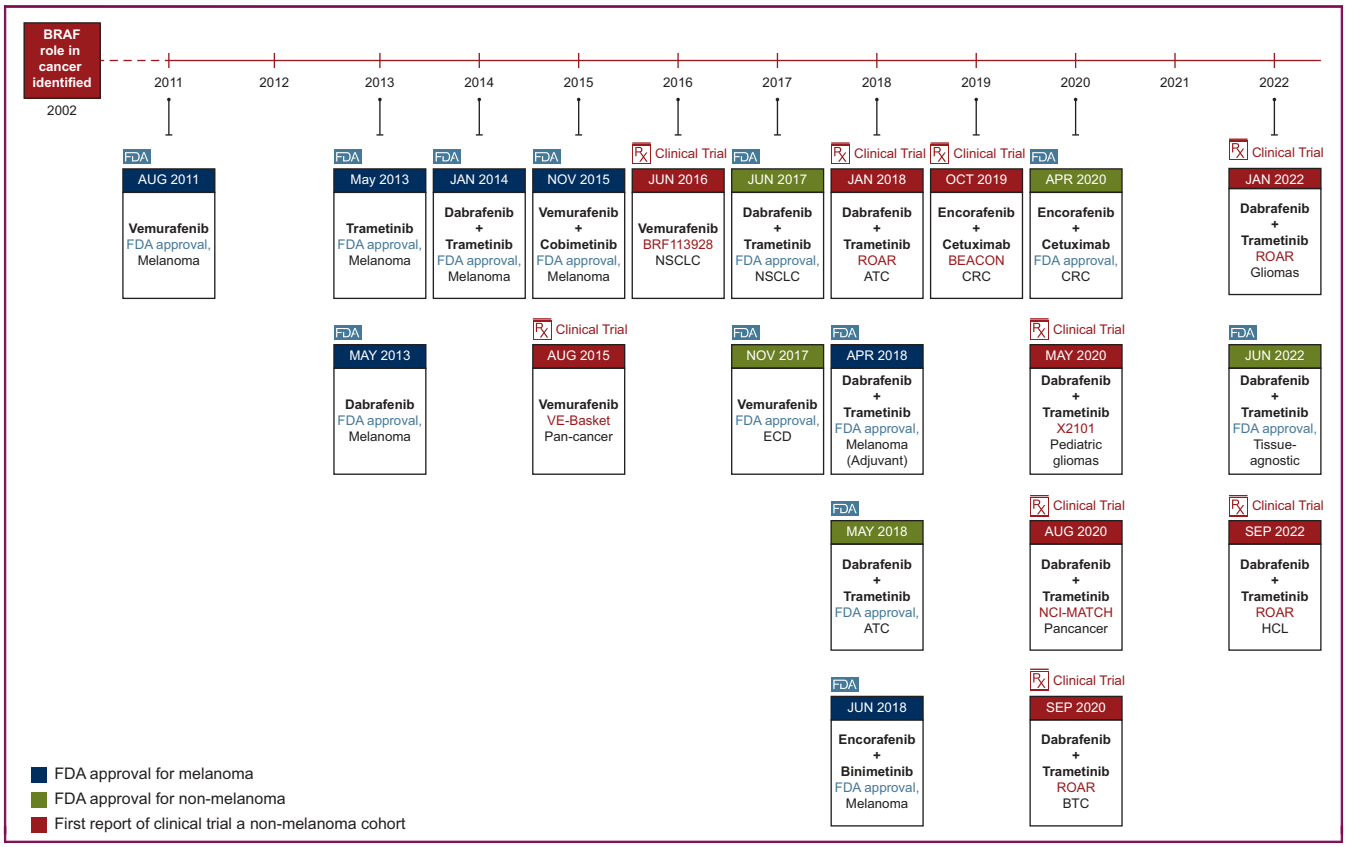

Figure 2. Timeline of BRAF inhibitor drug development from melanoma to tissue-agnostic approval.
ATC, anaplastic thyroid carcinoma; BTC, biliary tract cancer; CRC, colorectal cancer; ECD, Erdheim—Chester disease; FDA, Food and Drug Administration; HCL, hairy cell leukemia; NSCLC, non-small-cell lung cancer.

Dabrafenib

Dabrafenib is an ATP-competitive inhibitor of *RAF* kinases that has potent activity against *BRAF* V600 mutations.[61] It received its first FDA approval as a single agent in 2013 and is currently approved as monotherapy for treatment of patients with *BRAF* V600E-mutated unresectable or metastatic melanoma.[62]

Dabrafenib was investigated in multiple clinical trials for treatment of melanoma with *BRAF* V600E alteration. Two clinical trials represent the basis for FDA current approvals (Table 2). In the phase III randomized, controlled trial (BREAK-3; NCT01227889), dabrafenib-treated patients showed a significantly improved PFS and ORR compared with dacarbazine-treated patients.[26,27] Another phase II trial (BREAK-MB study; NCT01266967) evaluated the intracranial efficacy of dabrafenib monotherapy in patients with *BRAF* V600E metastatic melanoma to the brain and reported intracranial responses and an acceptable safety profile in both untreated and previously treated cohorts.[28]

Most of the subsequent advances, however, in use of dabrafenib were related to its use in combination with the *MEK* inhibitor, trametinib, which is discussed later in this review. Combination therapy offered better clinical outcomes compared with monotherapy using either drug; and is, therefore, considered the current standard of care.

Trametinib

Trametinib is currently approved as monotherapy for treatment of patients with *BRAF* V600E or *BRAF* V600K metastatic or unresectable melanoma who have not received prior treatment with a *BRAF* inhibitor.[63] It acts by reversible inhibition of *MEK1* and *MEK2* which are upstream regulators of ERK. Although trametinib does not exert a direct inhibitory effect on *BRAF*, its action would stop the constitutive activation of the BRAF pathway that occurs with different *BRAF* alterations including *BRAF* V600 mutations.[64]

The METRIC study (NCT01245062) is a randomized, controlled phase III trial that was the basis for the drug FDA approval. In this study, patients were randomized to receive either trametinib monotherapy or chemotherapy (dacarbazine or paclitaxel). Patients who received trametinib had a significantly longer PFS compared with patients who received chemotherapy (Table 2).[29,30] Further success has been achieved by combining trametinib with the *BRAF* inhibitor, dabrafenib, which is discussed later in this review.

BRAF-TARGETED COMBINATION THERAPIES

Rationale behind combination therapies

Drug combinations targeting different steps in a signaling pathway have been long used in cancer therapy for

Table 2. Summary of trials leading to current FDA approvals for BRAF inhibitors. Independent review data are used whenever reported in the most updated analysis

Vemurafenib

Study	Phase	Population	Design	PFS, months (median)		OS, months (median)		ORR (%)		Cohort
				Drug	Control	Drug	Control	Drug	Control	
BRIM-3 study (NCT01006980)[18-20]	Phase III	Patients with treatment-naive *BRAF* V600-mutated unresectable or metastatic melanoma	Patients were randomized to receive vemurafenib 960 mg orally twice daily (n = 337) or dacarbazine 1000 mg/m^2 i.v. every 3 weeks (n = 338)	6.9 For V600E (5.9 for V600K)	1.6 For V600E (1.7 for V600K)	13.6 For V600E (14.5 for V600K)	9.7 For V600E (7.6 for V600K)	57	9	
NCT00949702[21a]	Phase II	Patients with previously treated *BRAF* V600-mutated metastatic melanoma	Patients received vemurafenib 960 mg orally twice daily (n = 132)	6.8		15.9		53		
NCT01378975[22b]	Phase II	Patients with *BRAF* V600-mutated melanoma who have metastatic disease in the brain	Patients received vemurafenib 960 mg orally twice daily (n = 146) and were categorized into two cohorts. Cohort 1 included patients with no prior local therapy for brain metastasis (n = 90) whereas cohort 2 included patients who progressed after prior local therapy (n = 56)	3.7		8.9		33 For EC RR (18 for IC RR)		Cohort 1
				4		9.6		23 For EC RR (18 for IC RR)		Cohort 2
VE-BASKET (NCT01524978)[23-25]	Phase II	Patients with *BRAF* V600-mutated nonmelanoma solid tumors	Patients received vemurafenib 960 mg orally twice daily (n = 172). A separate analysis included 22 patients with ECD and was the basis for FDA approved indication[24]	5.8		17.6		33		Overall cohort (Responses seen in 13 cancers)
				7.3		NR		42		NSCLC
				NR		NR		62		ECD/LCH
								12		CGC
								29		ATC
				4.5 (3.7 for combo)		9.3 (7.1 for combo)		0 (4 with combo)		CRC
Dabrafenib										
BREAK-3 Study (NCT01227889)[26,27c]	Phase III	Patients with *BRAF* V600E-mutated unresectable or metastatic melanoma	Patients were randomized to receive dabrafenib 150 mg orally twice daily (n = 187) or dacarbazine 1000 mg/m^2 i.v. every 3 weeks (n = 63)	6.9	2.7	18.2	15.6	50	6	
BREAK-MB Study (NCT01266967)[28d]	Phase II	Patients with *BRAF* V600E- or V600K-mutated melanoma who	Patients received dabrafenib 150 mg orally twice daily (n = 172) and were	16.1 For V600E (8.1 for V600K)		33.1 For V600E (16.3 for V600K)		28 For V600E (0 for V600K)		Cohort A
				16.6 For V600E (15.9 for V600K)		31.4 For V600E (21.9 for V600K)		23 For V600E (11 for V600K)		Cohort B

Continued

https://doi.org/10.1016/j.esmoop.2023.100788

Table 2. Continued

Study	Phase	Population	Design	PFS, months (median)		OS, months (median)		ORR (%)		Cohort
				Drug	Control	Drug	Control	Drug	Control	
Vemurafenib										
		have metastatic disease in the brain	categorized into two cohorts. Cohort A included patients with no prior local therapy for brain metastasis ($n = 89$) whereas cohort B included patients who progressed after prior local therapy ($n = 83$)							
Trametinib										
METRIC study (NCT01245062)[29,30]	Phase III	Patients with *BRAF* V600E- or V600K-mutated unresectable or metastatic melanoma	Patients were randomized to receive trametinib 2 mg orally once daily ($n = 214$) or chemotherapy [dacarbazine 1000 mg/m^2 i.v. every 3 weeks or paclitaxel 175 mg/m^2 i.v. every 3 weeks] ($n = 108$)	4.9	1.5	15.6	11.3	29	9	
Dabrafenib + trametinib										
COMBI-d Study (NCT01584648)[31,32]	Phase III	Patients with *BRAF* V600E- or V600K-mutated unresectable or metastatic melanoma	Patients were randomized to receive either a combination of dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily) ($n = 211$) or dabrafenib and placebo ($n = 212$)	9.3	8.8	NR	NR	68	55	
COMBI-v Study (NCT01597908)[33]	Phase III	Patients with *BRAF* V600E- or V600K-mutated unresectable or metastatic melanoma	Patients were randomized to receive either combination of dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily) ($n = 352$) or vemurafenib 960 mg orally twice daily ($n = 352$)	11.4	7.3	NR	17.2	64	51	
COMBI-MB Study (NCT02039947)[34]	Phase II	Patients with *BRAF* V600E- or V600K-mutated melanoma with brain metastasis	Patients ($n = 125$) received dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily in four cohorts. Cohort A ($n = 76$) included	5.6 7.2 4.2 5.5		10.8 24.3 10.1 11.5		58 56 44 65		Cohort A Cohort B Cohort C Cohort D

Continued

Table 2. Continued

Vemurafenib

Study	Phase	Population	Design	PFS, months (median)		OS, months (median)		ORR (%)		Cohort
				Drug	Control	Drug	Control	Drug	Control	
			asymptomatic patients with *BRAF* V600E mutation who had no prior local brain therapy. Cohort B (n = 16) included asymptomatic patients with *BRAF* V600E mutation who had prior local therapy. Cohort C (n = 16) included asymptomatic patients with *BRAF* V600D/K/R mutations who had no prior local brain therapy. Cohort D (n = 17) included patients with symptomatic disease regardless of local therapy or mutation subtype							
COMBI-AD (NCT01682083)[35]	Phase II	Patients with completely resected *BRAF* V600E- or V600K-mutated stage III melanoma	Patients were randomized to receive either combination of dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily) (n = 438) or placebo (n = 432) for 12 months	NR (RFS)	16.6 (RFS)	NR	NR	37 (Recurrence)	57 (Recurrence)	
Study BRF113928 (NCT01336634)[36-39]	Phase II	Patients with *BRAF* V600E-mutated metastatic NSCLC	Patients (n = 171) received dabrafenib 150 mg orally twice daily in cohort A (n = 78) or dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily in cohort B (n = 57) and cohort C (n = 36). Cohorts A and B included patients with at least one prior therapy. Cohort C included patients with treatment-naive disease	5.5 10.2 10.8		12.6 18.2 17.3		33 68 64		Cohort A Cohort B Cohort C

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https://doi.org/10.1016/j.esmoop.2023.100788

Table 2. Continued

Vemurafenib

Study	Phase	Population	Design	PFS, months (median)		OS, months (median)		ORR (%)		Cohort
				Drug	Control	Drug	Control	Drug	Control	
ROAR Trial; BRF117019 (NCT02034110)[40-43,56e]	Phase II	Patients with *BRAF* V600E-mutated rare cancers, including anaplastic thyroid cancer (ATC) ($n = 36$), high-grade glioma (HGG) ($n = 45$), low-grade glioma (LGG) ($n = 13$), and biliary tract cancer (BTC) ($n = 43$)	Patients received dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily	5.5 9 14 4.5 NR		14.5 14 NR 17.6 NR		53 47 69 31 89		ATC BTC LGG HGG HCL
NCI-MATCH Study (arm H); EAY131-H (NCT02465060)[44]	Phase II	Patients with *BRAF* V600E-mutated cancers other than thyroid, melanoma, and CRC	Patients received dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily ($n = 35$)	11.4		28.6		38		Overall cohort (Responses seen in 7 cancers)
CTMT212X2101; Study X2101 (NCT02124772)[45,55f]	Phase I/II	Pediatric patients with *BRAF* V600-mutated solid tumors	Patients received dabrafenib 5.25 mg/kg/day and trametinib 0.032 mg/kg/day ($n = 48$)	36.9				25		LGG Cohort
Encorafenib + binimetinib										
COLUMBUS (NCT01909453)[46-48g]	Phase III	Patients with *BRAF* V600E- or V600K-mutated unresectable or metastatic melanoma	Patients were randomized to receive encorafenib 450 mg orally once daily in combination with binimetinib 45 mg twice daily ($n = 192$), encorafenib 300 mg orally once daily ($n = 194$), or vemurafenib 960 mg twice daily ($n = 191$)	14.9 For combo	7.3 For vemurafenib (9.6 for encorafenib)	33.6 For combo	16.9 For vemurafenib (23.5 for encorafenib)	64 For combo	41 For vemurafenib (52 for encorafenib)	
Encorafenib + cetuximab										
BEACON CRC (NCT02928224)[49-51]	Phase III	Patients with previously untreated *BRAF* V600E-mutated metastatic	Patients were randomized to receive either a doublet combination of encorafenib (300 mg	4.3 For doublet	1.5 For control (4.5 for triplet)	9.3 For doublet	5.9 For control (9.3 for triplet)	20 For doublet	2 For control (27 for triplet)	

Continued

Table 2. Continued

Study	Phase	Population	Design	PFS, months (median)		OS, months (median)		ORR (%)		Cohort
				Drug	Control	Drug	Control	Drug	Control	
Vemurafenib										
		colorectal cancer	orally once daily) and cetuximab (400 mg/m^2 initial dose then 250 mg/m^2 once a week) ($n = 220$), triplet combination of encorafenib, cetuximab, and binimetinib (45 mg twice daily) ($n = 224$), or control of investigator's choice [cetuximab + irinotecan or cetuximab + FOLFIRI] ($n = 221$)							
Vemurafenib + cobimetinib										
coBRIM Trial (NCT01689519)[52-54]	Phase III	Patients with previously untreated *BRAF* V600-mutated unresectable or metastatic melanoma	Patients ($n = 495$) received vemurafenib 960 mg orally twice daily and were randomized to receive cobimetinib 60 mg orally once daily D1-21 of an every 28-day cycle ($n = 247$) or matching placebo ($n = 248$)	12.6	7.2	22.5	17.4	70	50	

ATC, anaplastic thyroid carcinoma; BTC, biliary tract cancer; CGC, cholangiocarcinoma; CRC, colorectal cancer; EC, extracranial; ECD, Erdheim—Chester disease; FDA, Food and Drug Administration; HCL, hairy cell leukemia; HGG, high-grade glioma; IC, intracranial; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

[a]Investigator-assessed ORR was 57% with a concordance of 83% between investigators' assessment and assessment by independent review committee (IRC).

[b]Investigator-assessed extracranial ORR was 32% and 23%, whereas intracranial ORR was 29% and 23% for cohorts 1 and 2, respectively.

[c]Investigator-assessed ORR was 53% and 19% for dabrafenib and control, respectively.

[d]In the original paper published in Lancet Oncology, investigator and IRC assessments were discordant in 72 (42%) patients. Per the investigators, the discordance between the investigator and review committee response assessment, particularly for intracranial disease, led to a blinded adjudication, in which investigator assessments were upheld in two-thirds of cases. Therefore, the reported investigator-assessed overall ORR for BREAK-MB was 38% and 31% in patients with V600E mutation in cohorts A and B, respectively (0% and 28% in patients with V600K); which is quite different from the IRC-assessed ORR which is reported in the Table 2. It is of note that the intracranial ORR was 39% and 31% for patients with V600E; and 7% and 22% for patients with V600K in cohorts A and B, respectively.

[e]Investigator-assessed ORR was the primary endpoint in the ROAR study and was reported as 56%, 51%, 69%, 33%, and 89% in ATC, BTC, LGG, HGG, and HCL, respectively. Table contains IRC-reported ORR for ATC, BTC, LGG, and HGG but not HCL since it was not reported in the original study.

[f]Investigator-assessed ORR was 53% in the combination group.

[g]By local review, ORR was observed in 76%, 58%, and 49% in combination, encorafenib monotherapy, and vemurafenib groups, respectively.

https://doi.org/10.1016/j.esmoop.2023.100788

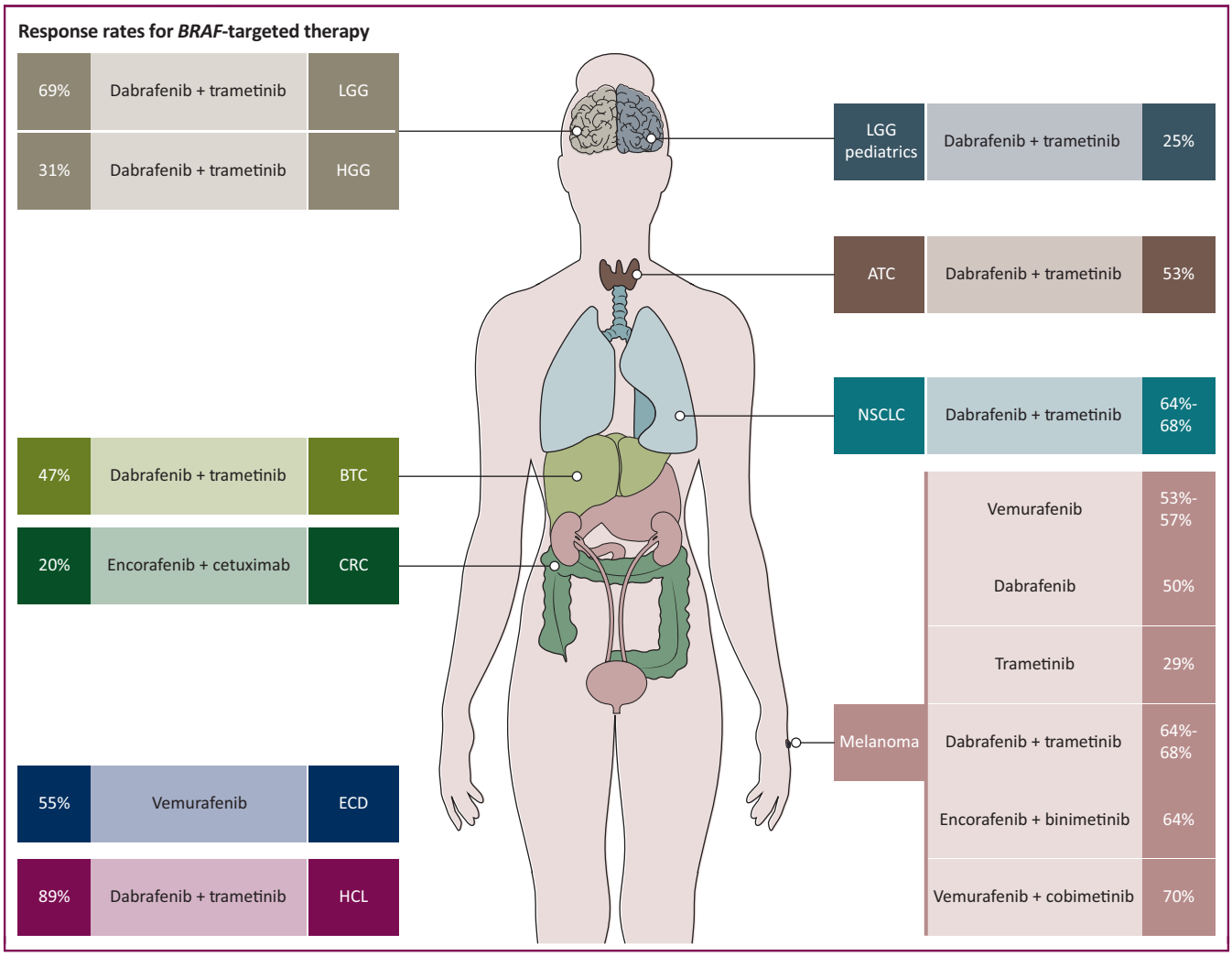

Figure 3. Response rates in different tumor types for BRAF inhibitors as monotherapy and in combination with MEK inhibitors in multiple tumors and EGFR inhibitors in colorectal cancer. Independent review data are used whenever reported in the most updated analysis.
ATC, anaplastic thyroid carcinoma; BTC, biliary tract cancer; CRC, colorectal cancer; ECD, Erdheim—Chester disease; HCL, hairy cell leukemia; HGG, high-grade glioma; LGG, low-grade glioma; NSCLC, non-small-cell lung cancer.

potentiating the antineoplastic effect.[65] In the BRAF pathway, different agents have been tested for use as monotherapies with a mechanism of action including inhibition of either *BRAF* or *MEK* kinases. Despite promising results in monotherapy trials as discussed above, acquired resistance to *BRAF* inhibitors can develop and limit their duration of response.[66,67] Moreover, single-agent inhibitors have been associated with the development of secondary skin cancers which was linked to activation of the MAPK pathway that can happen with monotherapy.[18,68]

Most of the current approved combination options include a *BRAF* and a *MEK* inhibitor. The dual inhibition of upstream *BRAF* and downstream *MEK* kinases can lead to interruption of the BRAF signaling pathway that associates with increased cellular proliferation in *BRAF*-mutated cancers. Compared with single-agent *BRAF* and *MEK* inhibitors, a combination of *BRAF* and *MEK* inhibition showed a lower incidence of skin hyperproliferation and a delayed emergence of resistance; which led to improved PFS. Another currently approved combination uses an *EGFR* antibody along with a *BRAF* inhibitor, with the aim of overcoming *EGFR*-mediated adaptive feedback signaling that leads to reactivation of the MAPK pathway following *BRAF*-targeted monotherapy.[69]

Current drugs included as part of FDA-approved combination therapies include the *BRAF* inhibitors vemurafenib, dabrafenib, and encorafenib, the *MEK* inhibitors trametinib, binimetinib, and cobimetinib, and the *EGFR* inhibitor cetuximab. Since *BRAF* resistance mechanisms are complex,[70] other studies have explored combinations including mammalian target of rapamycin (mTOR) inhibitors, *MET* inhibitors, and chemotherapy, but showed limited successes.[71-74]

Dabrafenib + trametinib

Via a synergistic effect, dabrafenib and trametinib work by exerting a targeted inhibition of two different kinases in the BRAF pathway: *BRAF* and *MEK*. Preclinical data suggested that the combination led to greater activity against *BRAF* V600-mutated tumors compared with either drug given as monotherapy.[75,76]

Based on data from clinical trials (Table 2), the dabrafenib and trametinib combination is currently approved by FDA for treatment of patients with unresectable or metastatic melanoma and *BRAF* V600E or V600K mutation, metastatic NSCLC and *BRAF* V600E mutation, locally advanced or metastatic ATC with *BRAF* V600E mutation and no locoregional treatment options, and locally advanced melanoma with involved lymph nodes and V600E or V600K mutation following complete resection as part of adjuvant therapy.[62]

The COMBI-d (NCT01584648) and COMBI-v (NCT01597908) were phase III trials that evaluated the use of dabrafenib and trametinib combination compared with dabrafenib or vemurafenib as controls in patients with metastatic or unresectable melanoma. Both trials demonstrated a significant improvement in PFS and OS as well as a lower rate of incidence for hyperproliferative skin adverse events.[31-33] A pooled long-term analysis of both trials suggested PFS and OS rates of 19% and 34% at 5 years as well as a complete response in 19% of included patients.[77] The COMBI-MB phase II trial (NCT02039947) provided substantial evidence on intracranial activity and extracranial clinical benefit from the dabrafenib/trametinib combination in patients with melanoma and brain metastasis as well as a tolerable safety profile.[34] The first approval for use in the adjuvant setting came based on data from COMBI-AD trial (NCT01682083) that assessed the use of dabrafenib and trametinib combination versus placebo in patients with stage III melanoma who had lymph node disease and *BRAF* V600E or V600K mutations. Data suggested a lower risk of recurrence in patients receiving the combination therapy compared with placebo controls.[35]

Tissue-agnostic activity of dabrafenib + trametinib

Expanding the reach of *BRAF* targetability beyond melanoma started with the study BRF113928 (NCT01336634) which was a phase II trial that established the efficacy of dabrafenib and trametinib combination in previously treated and untreated patients with *BRAF* V600E-mutant NSCLC leading to subsequent approval.[36-39] *BRAF* inhibitor tissue-agnostic drug development, however, has been quite challenging stemming from the unresponsiveness of CRC patients to monotherapy *BRAF* inhibition, which raised a question if *BRAF* V600 can be a tissue-agnostic target. Beyond melanoma and lung, *BRAF* V600 is also seen in a variety of tumor types; and although monotherapy with vemurafenib showed responses, resistance quickly emerges and leads to refractory disease progression.[78] With *BRAF* and *MEK* combination emerging as standard of care in melanoma tumors, the ROAR (Rare Oncology Agnostic Research) trial (BRF117019; NCT02034110) was designed as a basket trial to investigate the use of combined dabrafenib and trametinib in none different tumor types harboring *BRAF* V600 alterations.[40-43,56] Given the dramatic responses in ATC, one of the most lethal forms of thyroid cancers, and in an area of huge unmet need, the combination received FDA approval as the first targeted therapy for *BRAF* V600-mutant anaplastic thyroid carcinoma.[40,41] A notable response rate (51% ORR per investigator assessment) was also seen in *BRAF* V600-mutant biliary tract cancers leading to inclusion of the combination as a potential treatment option in National Comprehensive Cancer Network (NCCN) guidelines.[43] Subsequently, promising data in brain tumors from low-grade glioma (ORR = 69%) and high-grade glioma (ORR = 33%) validated the expanded spectrum of dabrafenib/trametinib antitumor activity. In addition to solid tumors, the combination was active in hairy cell leukemia with an investigator-assessed ORR of 89%.[56] Contemporaneously, arm H of the NCI-MATCH trial (EAY131-H; NCT02465060) tested the combination of dabrafenib and trametinib in a pan-cancer cohort and showed promising results in seven distinct tumor types with ORR of 38%.[44] Another study (Study X2101; NCT02124772) evaluated the use of the combination in pediatric patients and has so far reported a response rate of 25% in patients with low-grade gliomas[45,55,79] (Figure 3).

With >20 different tumor types showing antitumor activity with dabrafenib and trametinib combination in ROAR, NCI-MATCH, and Study X2101 studies, and considering the totality of evidence, the combination received US FDA accelerated approval for the treatment of adult and pediatric patients ≥6 years of age with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.[62,79,80] The exception for tissue-agnostic indication was CRC because of known intrinsic resistance mechanism. This approval was distinct being the first tissue-agnostic approval for a treatment targeting a specific genetic mutation. Prior tissue-agnostic approvals were based on *NTRK* fusions, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) cancers, and tumors with high tumor mutational burden (TMB).[80]

Encorafenib + binimetinib. Encorafenib is a kinase inhibitor that acts on both *BRAF* V600E and wild-type *BRAF* as well as other kinases to suppress cellular signaling and lead to tumor regression. It is currently approved in combination with binimetinib, a selective *MEK* inhibitor, for treatment of patients with unresectable or metastatic melanoma who harbor a *BRAF* V600E or *BRAF* V600K mutation.[81]

Compared with either drug alone, the combination led to higher antitumor activity and more delayed emergence of resistance in *BRAF* V600E-mutant melanoma xenografts. The COLUMBUS trial (NCT01909453) represents the current basis for FDA approval of the combination (Table 2). In this phase III trial, patients with metastatic or unresectable melanoma who harbored *BRAF* V600E or V600K mutations were randomized to receive the encorafenib/binimetinib combination, encorafenib monotherapy, or vemurafenib. Results suggested greater response rate as well as PFS and OS in the combination group when compared with vemurafenib control.[46-48]

Encorafenib + cetuximab. Encorafenib has also been approved in combination with the monoclonal anti-*EGFR* antibody, cetuximab, for treatment of adult patients with

metastatic CRC who have a *BRAF* V600E mutation.[81] In *BRAF*-mutated CRC, reactivation of the MAPK pathway via *EGFR*-mediated feedback has been suggested as a potential mechanism of resistance to *BRAF* inhibitors.[69] Therefore, the use of combination was postulated to lead to blockade of the EGFR pathway and potentiate the effect of the *BRAF*-targeting encorafenib.

BEACON CRC (NCT02928224) was the phase III study that led to the FDA approval (Table 2). The study showed improved survival rates and response in patients treated with the combination of encorafenib plus cetuximab compared with control. The effect was comparable to that of a triplet regimen including encorafenib/cetuximab/binimetinib and was markedly different from that of control regimens including cetuximab and conventional chemotherapy.[49-51]

Vemurafenib + cobimetinib. The combination of vemurafenib and cobimetinib was approved in 2015 for treatment of patients with unresectable or metastatic melanoma *who* harbor a *BRAF* V600E or V600K mutation.[57] Cobimetinib is a selective inhibitor of *MEK* kinases which when combined with the *BRAF* inhibitory effect of vemurafenib led to a halt of the activated MAPK pathway in *BRAF*-mutant cancers.

Vemurafenib and cobimetinib combination was tested in the setting of the coBRIM trial (NCT01689519) where patients were randomized in a phase III randomized, controlled trial to receive vemurafenib alone or in combination with cobimetinib. Patients in the vemurafenib/cobimetinib arm had greater ORR, PFS, and OS compared with patients in the control arm (Table 2).[52-54]

LANDSCAPE OF ONGOING CLINICAL TRIALS AND FUTURE DIRECTIONS

The list of targeted therapeutic options that work by inhibiting the BRAF pathway is growing (Table 1). Even more drugs are currently explored in preclinical studies and early phase clinical trials for treatment of *BRAF*-altered cancers. As of 9 November 2022 and using clinicaltrials.gov[82] as a data source, we were able to identify 369 studies registered as either phase I, phase II, or phase III trials. Of those, only 76 trials had results available or published. This can provide a glimpse on the future potential of *BRAF* targetability expansion in different tumor types.

Future directions would primarily be focused on two main trajectories. First, researchers are trying to improve the inherent drug characteristics including pharmacokinetics and pharmacodynamics that can lead to better efficacy. For example, researchers have been trying to explore the possibility of improving brain penetration abilities of *BRAF* inhibitors. Although the current *BRAF* inhibitors have some brain penetration, brain-penetrant *BRAF* inhibitors with superior blood—brain barrier penetration, e.g. PF-07284890 (NCT04543188) have been developed, and are being explored in early phase trials.[83] Second, researchers have explored other approaches for targeting the BRAF pathway. For example, drugs with an expanded spectrum of activity against non-V600 mutations have been explored, e.g. PLX8394 (NCT02012231).[84-86] Selective degraders of mutant *BRAF* for the treatment of *BRAF*-driven cancers, e.g. CFT1946, are also being developed in *BRAF*-altered cancers.[87]

Conclusion

BRAF is an important cornerstone in the development and treatment of cancer. Several agents are currently approved for treatment of patients with *BRAF* alterations and work by inhibiting either *BRAF* or *MEK* kinases. Combination therapies can overcome limitations of *BRAF* inhibitor monotherapy and improve PFS. The spectrum of *BRAF* inhibition has expanded in the past decade from melanoma to tissue-agnostic indications. In the years to come, better options may be available for currently druggable and undruggable *BRAF* alterations.

ACKNOWLEDGEMENTS

VS is an Andrew Sabin Family Foundation fellow at the University of Texas MD Anderson Cancer Center. VS acknowledges the support of the Jacquelyn A. Brady Fund.

Figures 1 and 2 are created using tools from Biorender.com.

FUNDING

This work was supported by a United States National Institutes of Health (NIH) grant [grant numbers R01CA242845, R01CA273168 to VS]; MD Anderson Cancer Center Department of Investigational Cancer Therapeutics is supported by the Cancer Prevention and Research Institute of Texas [grant number RP1100584], the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy [grant number 1U01 CA180964], an NCATS (Center for Clinical and Translational Sciences) grant [grant number UL1 TR000371], and the MD Anderson Cancer Center Support Grant [grant number P30 CA016672].

DISCLOSURE

VS reports research funding/grant support for clinical trials from AbbVie, Agensys, Inc., Alfasigma, Altum, Amgen, Bayer, Berg Health, Blueprint Medicines Corporation, Boston Biomedical, Inc., Boston Pharmaceuticals, Celgene Corporation, D3 Bio, Inc., Dragonfly Therapeutics, Inc., Exelixis, Fujifilm, GlaxoSmithKline, Idera Pharmaceuticals, Inc., Incyte Corporation, Inhibrx, Loxo Oncology, MedImmune, MultiVir, Inc., NanoCarrier, Co., National Comprehensive Cancer Network, NCI-CTEP, Northwest Biotherapeutics, Novartis, PharmaMar, Pfizer, Relay Therapeutics, Roche/Genentech, Takeda, Turning Point Therapeutics, UT MD Anderson Cancer Center, and Vegenics Pty Ltd.; travel support from ASCO, ESMO, Helsinn Healthcare, Incyte Corporation, Novartis, and PharmaMar; consultancy/advisory board participation for Helsinn Healthcare, Jazz Pharmaceuticals, Incyte Corporation, Loxo Oncology/Eli Lilly, MedImmune, Novartis, QED Therapeutics, Relay Therapeutics, Daiichi-Sankyo, and R-Pharm US; and other relationship with Medscape. MG has declared no conflicts of interest.

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