Review

Molecular Cancer Therapeutics

Genomically Driven Tumors and Actionability across Histologies: *BRAF*-Mutant Cancers as a Paradigm

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Abstract

The diagnosis, classification, and management of cancer are traditionally dictated by the site of tumor origin, for example, breast or lung, and by specific histologic subtypes of site-of-origin cancers (e.g., non–small cell versus small cell lung cancer). However, with the advent of sequencing technologies allowing for rapid, low cost, and accurate sequencing of clinical samples, new observations suggest an expanded or different approach to the diagnosis and treatment of cancer—one driven by the unique molecular features of the tumor. We discuss a genomically driven strategy for cancer treatment using *BRAF* as an example. Several key points are highlighted: (i) molecular aberrations can be shared across cancers; (ii) approximately 15% of all cancers harbor *BRAF* mutations; and (iii) BRAF inhibitors, while approved only for melanoma, have reported activity across numerous cancers and related disease types bearing *BRAF* aberrations. However, *BRAF*-mutated colorectal cancer has shown poor response rate to BRAF inhibitor monotherapy, striking a cautionary note. Yet, even in this case, emerging data suggest *BRAF*-mutated colorectal cancers can respond well to BRAF inhibitors, albeit when administered in combination with other agents that impact resistance pathways. Taken together, these data suggest that molecular aberrations may be the basis for a new nosology for cancer. *Mol Cancer Ther; 15(4); 533–47. ©2016 AACR.*

Introduction

A wealth of data now suggests that molecular aberrations may be shared across multiple histologies (1). As an example, *BRAF* mutations can be detected in melanoma, colorectal tumors, lung and ovarian cancers, hairy cell leukemia, histiocytosis and many other related disease types (2; Fig. 1; Table 1). Indeed, a small subset of almost all types of malignancies may harbor a *BRAF* mutation (3, 4). Of special importance in this regard is the fact that several drugs that effectively target the *BRAF*-mutant protein product have been developed (Table 2). For instance, the BRAF inhibitors, vemurafenib and dabrafenib, have both been approved for *BRAF*-mutant melanoma based on results from the phase III BRIM-3 study (5) and the phase III BREAK-3 study (6), respectively.

A key conundrum now debated in the cancer community is whether or not targeted drugs approved for one type of histology should be administered to other histologies harboring the cognate aberration. For instance, should a BRAF inhibitor approved for *BRAF*-mutant melanoma be given to a patient with a *BRAF*-mutant tumor other than melanoma? A corollary to this question is the precise criteria needed in order to extrapolate predictive data on a biomarker for a given targeted therapy in one cancer to another cancer. These questions are of tremendous importance for the following reasons: (i) molecular aberrations, in particular amplifications, loss, and mutations, do not appear to segregate well by histology (1, 2, 4); (ii) numerous targeted drugs are becoming clinically available and they have been developed to inhibit a specific cancer signal that may be found in multiple tumor types, hence their rational application would be in tumors bearing the cognate target (3); and (iii) molecular anomalies are found in a very small percentage of diverse cancers (7), and the rarity in each histologic type presents a near-impossible challenge for classic randomized or even nonrandomized trials to determine efficacy histology by histology.

Newer study designs are beginning to accommodate these challenges. For instance, histology-agnostic trials (so-called bucket or basket trials) might include patients with a wide variety of histologies as long as they all harbor the cognate aberration. As an example, a histology-agnostic trial of the BRAF inhibitor vemurafenib can include diverse types of cancers, providing that they carry *BRAF* mutation (e.g., VE BASKET study; 8). However, these types of trials are still often perceived as signal finding. If a variety of histologies respond, what should be the next steps to approval and/or pay or coverage? To what extent can we be certain or do we need to be certain that each histology bearing the mutation will respond before it is acceptable to administer drugs across cancers based on their molecular, rather than histologic, classification? Does molecular classification actually represent a biology-based nosology?

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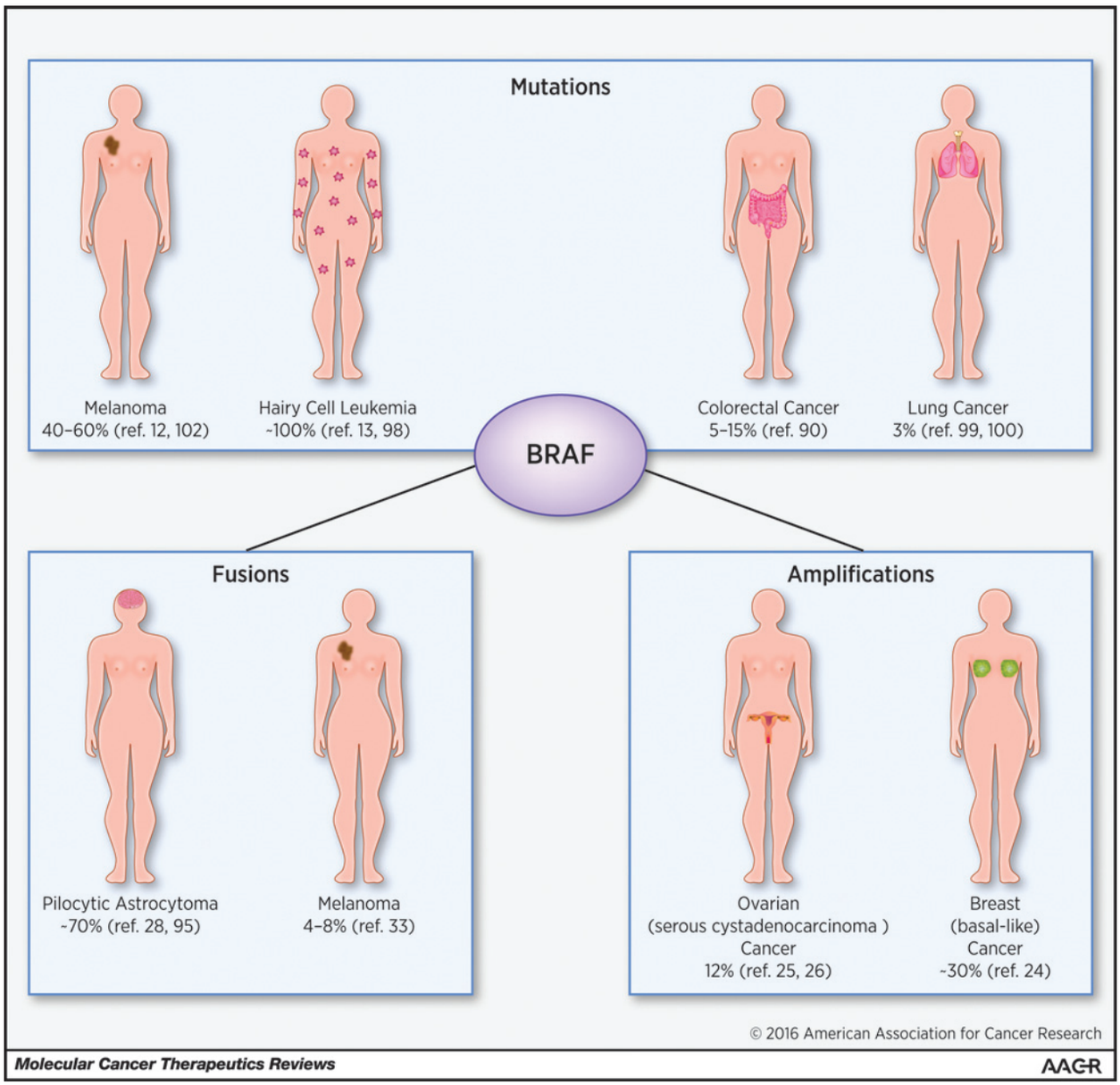

Figure 1.
Examples of organ of origin tumors that have different types of *BRAF* aberrations. For a comprehensive list of tumor types having *BRAF* aberrations, please refer to Table 1.

Herein we review this topic, using *BRAF*-mutant malignancies as a paradigm. The choice of BRAF was considered apt for the following reasons: (i) *BRAF* mutations as well as other *BRAF* anomalies (amplifications, fusions) have been described in a wide variety of tumors; (ii) two BRAF inhibitors and a MEK inhibitor have already been approved for *BRAF*-mutant melanoma; and (iii) there is a rich literature demonstrating responses, albeit at times in small numbers of patients, with the use of BRAF inhibitors in a variety of *BRAF*-mutation bearing cancers (9, 10). On the other hand, B*RAF*-mutant colorectal cancers have proved more resistant to BRAF inhibitor monotherapy, hence striking a cautionary note. The observations in *BRAF*-mutant tumors may therefore inform future conceptualization of genomically driven treatment.

BRAF Mutations in Diverse Cancers

BRAF is mutated in about 15% of all cancers (3, 11) and B*RAF* mutations can be found in solid tumors, hematologic malignancies, and related disease types (Table 1). For some cancers, *BRAF* mutations are very frequently detected: melanoma [40%–60% of patients (12)] and hairy cell leukemia [~100% (13)].

The predominant mutation detected in *BRAF*-mutated cancers is the V600E mutation, representing approximately 70% to 90%

Table 1. *BRAF* mutations in diverse cancers[a]

Cancer	BRAF mutation frequency	Source	Comments
Cholangiocarcinoma	3%–22%	Goeppert et al (93)	*BRAF* V600E (60%)
		Tannapfel et al (94)	*BRAF* V600D (13%)
			Other codons (27%)
Chronic lymphocytic leukemia	2.8%	Jebaraj et al (95)	
Colorectal cancer	5%–15%	Pakneshan et al (96)	*BRAF* V600E
MSI unstable	27.8%–51.8%	Domingo et al (97)	
MSI stable	5%–7.5%	Samowitz et al (98)	
		Benlloch et al (99)	
Erdheim-Chester disease	54%	Haroche et al (100)	*BRAF* V600E
Ganglioglioma	43%	Gupta et al (101)	*BRAF* V600E
GIST	2%–13%	Hostein et al (102)	*BRAF* V600E
		Miranda et al (103)	
Glioblastoma	1.7%	cBioPortal (25,26)	*BRAF V600E*
Hairy cell leukemia	∼100%	Sakata-Yanagimoto (104)	*BRAF* V600E
		Tiacci et al (13)	
Kidney cancer	3%	COSMIC (23)	*BRAF* V600E (85%)
			Other codons (5%)
Lung cancer adenocarcinoma	3%	Cooper et al (105)	*BRAF* V600E (50%)
		Paik et al (106)	*BRAF* G469A (39%)
			BRAF D594G (11%)
Langerhans cell histiocytosis	25%–38%	Go et al (107)	*BRAF* V600E
		Haroche et al (100)	
Melanoma	∼60%	Davies et al (12)	*BRAF* V600E (80%)
		Hodis et al (108)	*BRAF* V600K (8%)
			BRAF V600R (1%)
			Other codons (10%)
Multiple myeloma	∼6%	Lohr et al (109)	*BRAF* V600E (38%)
			Other codons (62%)
Ovarian cancer	35%–60%	Grisham et al (110)	*BRAF* V600E
Serous borderline	44.6%–71%	Bosmuller et al (111)	
Low-grade serous	5.3%–14%		
Pancreatic cancer	1%–16%	Schultz et al (112)	Schultz et al reported all mutations detected were non-*BRAF* V600E (112). COSMIC reported ∼55% of BRAF mutations were *BRAF* V600E.
		COSMIC (23)	
Pilocystic astrocytoma	70%–80%	Korshunov et al (28)	*BRAF-KIAA1549* fusion
		Gupta et al (101)	
Pleomorphic xanthoastrocytoma	66%	Schindler et al (113)	*BRAF* V600E
Prostate cancer	1.6%	COSMIC (23)	*BRAF* V600E (<1%)
			BRAF V600X (84%)
Papillary thyroid cancer	30%–80%	Xing (114)	*BRAF* V600E

[a]Multiple other tumors may have a small incidence of *BRAF* mutations not described here. Additionally some tumors may have *BRAF* amplification or fusions as noted in the comments column or as discussed in the section entitled "Abnormalities in the *BRAF* gene other than Mutations".

of all mutations in *BRAF* (12, 14–16). Substitution of glutamic acid (E) for valine (V) at codon 600 of the BRAF protein affects the activation segment of the protein by mimicking the phosphorylation of the kinase domain, causing a change in structure that favors the active conformation (14, 17). Experimental studies have confirmed that the *BRAF* V600E mutations are activating, resulting in increased BRAF kinase activity in *in vitro* studies, as well as activation of downstream effectors and oncogenic transformation in cell-based studies (12, 18, 19).

Other activating mutations in *BRAF* include additional mutations affecting codon 600 that result in substitutions other than glutamic acid. In *BRAF*-mutated melanoma, the *BRAF* V600K mutation is found at a frequency of approximately 7% to 19% (16, 20). Other rare mutations affecting codon 600 include *BRAF* V600D (0.1%), *BRAF* V600R (1%), and *BRAF* V600M (0.3%; 20). Furthermore, activating mutations in *BRAF* that affect codons other than 600 include L597 substitutions (0.5%), and K601E (0.7%; 20). Table 1 lists several other non-V600 mutations in *BRAF* and their frequencies in detected cancers (for responsiveness of non-V600E mutations to BRAF inhibitors, see section entitled "*BRAF* mutations other than V600E").

In addition, inactivating or "low-activity" mutations in *BRAF* have been identified and characterized; they typically involve substitutions at codon 594 (19, 21), although missense mutations at other codons (including codon 466) have also been shown to result in BRAF kinase inactivation or reduced activation (18).

Abnormalities in the *BRAF* Gene Other Than Mutations

In addition to mutations, other types of *BRAF* aberrations are found in cancer, including amplification and *BRAF* fusions. *BRAF* amplification involving either the wild-type gene or mutant versions of the gene is predicted to result in increased BRAF activity in tumor cells (22). In some cases where *BRAF* mutations are rare, *BRAF* amplifications dominate. For example, while mutations in *BRAF* are found in only 1% of breast cancers (23), *BRAF* amplification has been reported in 30% of basal-like

Table 2. Examples of clinically available BRAF inhibitors and their applications

Drug name	Target(s)	Approximate IC_{50} for BRAF	Development status	Indications/Stage of development[a]	Comments	Refs
Vemurafenib	*BRAF* V600E, BRAF, RAF1, ARAF, SRMS, TNK2, FGR, MAP3K5	31 nmol/L (*BRAF* V600E) 100 nm (BRAF)	Approved for *BRAF* V600E	Unresectable or metastatic melanoma with *BRAF* V600E mutation		FDA label (115) Bollag et al (116)
Dabrafenib	*BRAF* V600E, *BRAF* V600D, *BRAF* V600K, BRAF, RAF1	1.84 nm (*BRAF* V600E) 3.2 nmol/L (BRAF)	Approved for *BRAF* V600E	-Single agent for unresectable or metastatic melanoma with *BRAF* V600E mutation -In combination with trametinib for unresectable or metastatic melanoma with BRAF V600E/K mutation		FDA label (117)
Trametinib	MAP2K1, MAP2K2	N/A	Approved for *BRAF* V600E/K	Single agent or in combination with dabrafenib for unresectable or metastatic melanoma with BRAF V600E/K mutation		FDA label (62,118)
Sorafenib	BRAF, KDR, PDGFRA, PDGFRB, KIT, FLT4, FLT3, RET, RAF1, FLT1	38 nmol/L (*BRAF* V600E) 25 nmol/L (BRAF)	Approved but not related to *BRAF* aberrations	-Unresectable hepatocellular carcinoma -Advanced renal cell carcinoma - Locally recurrent, or metastatic, progressive, differentiated thyroid carcinoma	-Also in phase II trial for *BRAF*-mutant (excluding *BRAF* V600 mutations) solid tumors (NCT02029001) -Not validated clinically as an effective BRAF inhibitor	Wilhelm et al (119)
Regorafenib	BRAF, FLT1, KDR, FLT4, KIT, TEK, PDGFRA, PDGFRB, FGFR1, FGFR2, NTRK1, MAPK11, ABL1	19 nmol/L (*BRAF* V600E) 28 nmol/L (BRAF)	Approved but not related to *BRAF* aberrations	-Metastatic colorectal cancer -Locally advanced, unresectable, or metastatic GIST	-Also in phase II trial for *BRAF*- or *RAS*-mutant colorectal cancer (NCT02175654) -Not validated clinically as an effective BRAF inhibitor	Wilhelm et al (120)
Pazopanib	BRAF, FLT1, KDR, FLT4, PDGFRA, PDGFRB, KIT, FGFR1, FGFR3, CSF1R, LCK, ITK	410 nmol/L (BRAF)	Approved but not related to *BRAF* aberrations	-Advanced renal cell carcinoma -Advanced soft tissue sarcoma	-Also in phase I trial in combination with dabrafenib for *BRAF*-mutant advanced malignant tumors (NCT01713972) -Less effective at inhibition of *BRAF* V600E; at 1 μmol/L can achieve ∼80% inhibition of wild-type *BRAF* versus only ∼40% inhibition of *BRAF* V600E -Not validated clinically as an effective BRAF inhibitor	Kitagawa et al (121)
ARQ 736	BRAF, RAF1	2.7 nmol/L (*BRAF* V600E) 2.6 nmol/L (BRAF)[b]	Investigational	Phase I	In a phase I trial (now completed) for solid tumors with *BRAF* and/or *NRAS* mutations (NCT01225536)	Chen et al (122)
CEP-32496	*BRAF* V600E, BRAF, ABL1, BCR-ABL1, RET, EPHA2	60 nmol/L (*BRAF* V600E) >2,000 nmol/L (BRAF)[c]	Investigational	Phase I/II	Phase II portion of trial selecting for melanoma or colorectal cancer with either *BRAF* V600E or *BRAF* V600K mutation (NCT01877811)	James et al (123)

(Continued on the following page)

Table 2. Examples of clinically available BRAF inhibitors and their applications (Cont'd)

Drug name	Target(s)	Approximate IC_{50} for BRAF	Development status	Indications/Stage of development[a]	Comments	Refs
LGX818	*BRAF* V600E, BRAF	4 nmol/L (*BRAF* V600E)[c]	Investigational	Phase III	-In phase III trial for *BRAF* V600E-mutated melanoma (NCT01909453) -In a phase II trial for solid tumors (excluding melanoma and colorectal cancer) and hematologic malignancies with *BRAF* V600 mutation (NCT01981187)	Stuart et al (124)
MLN2480	BRAF, ARAF, RAF1	Information not available	Investigational	Phase I	-Clinical testing in solid tumors and melanoma (NCT01425008) -Not yet featured in trials with *BRAF* mutation requirements	
PLX8394	*BRAF* V600E, BRAF, RAF1	Information not available	Investigational	Phase I/II	Phase II portion of trial selecting for *BRAF*-mutated solid tumors and hairy cell leukemia (NCT02012231)	
PLX3603	*BRAF* V600E, BRAF	Information not available	Investigational	Phase I	In phase I trial for solid tumors with *BRAF* V600E mutation (NCT01143753)	
RAF265	BRAF, RAF1, KDR	<100 nmol/L (*BRAF* V600E, BRAF) 140 nmol/L (*BRAF* V600E)[c]	Investigational	Phase II	In a phase I trial (now completed) in combination with MEK162 for patients with solid tumors containing *BRAF* V600E or *NRAS* or *KRAS* mutations (NCT01352273)	Stuart et al (125)
RO5126766	BRAF, RAF1, MAP2K1, MAP2K2	8.2 nmol/L (*BRAF* V600E) 160 nmol/L (BRAF)	Investigational	Phase I	-In phase I trial (now completed) for patients with solid tumors (NCT00773526) -Not yet featured in trials with *BRAF* mutation requirements	Martinez-Garcia (126)
XL281	BRAF, RAF1	Information not available	Investigational	Phase I/II	In phase I/II trial as monotherapy or in combination with cetuximab for colorectal cancer with *BRAF* V600E mutation or with *KRAS* codon 12 or 13 mutations (NCT01086267)	

[a]Relevant examples of development are given.
[b]IC_{50} values presented are for ARQ 680, which is the active moiety of the prodrug ARQ 736.
[c]Cellular IC_{50} value.

breast tumors (24). Other cancers where *BRAF* amplification is more frequent than *BRAF* mutations include ovarian serous cystadenocarcinoma (12% vs. 0.6%, respectively; 25, 26) as well as prostate adenocarcinoma (~5% vs. 1.6%, respectively; 25, 26).

BRAF fusions such as *KIAA1549-BRAF* and *FAM131B-BRAF* are frequently found in gliomas with the *KIAA1549-BRAF* fusion detected in up to 70% of pilocytic astrocytomas (27, 28). The *KIAA1549-BRAF* is an arrangement created by a tandem duplication event, while *FAM131B-BRAF* is generated by a large deletion event; however, both result in constitutive activation of BRAF through duplication of the BRAF activation domain, but with deletion of the N-terminal inhibitory domain (29, 30). The *KIAA1549-BRAF* fusion has been reported in preclinical studies to be resistant to PLX4720, the research analog of vemurafenib, due to RAF dimerization, but remains sensitive to a second-generation BRAF inhibitor (31). In addition, one case study described a patient with a spindle cell neoplasm harboring the *KIAA1549-BRAF* fusion as well as a homozygous deletion of *PTEN*, and frameshift mutations in *CDKN2A*, *SUFU*, and *MAP3K1* who had a 25% reduction in tumor volume following a combination therapy consisting of sorafenib (a weak BRAF inhibitor), temsirolimus, and bevacizumab, suggesting that the *KIAA1549-BRAF* fusion may be responsive to certain BRAF inhibitors in the clinic, though the precise reason for response is confounded by the other drugs in the regimen (32). The responsiveness of *FAM131B-BRAF* is currently not reported in the literature. While infrequent as compared with mutations, *BRAF* fusions have also been observed in melanoma in anywhere from 4% to 8% of "pan-negative" cases (defined as tumors negative for mutations in *BRAF*, *NRAS*, *KIT*, *GNAQ*, and *GNA11*). Two *BRAF* fusions, *PAPSS1-BRAF* and *TRIM24-BRAF*, were both shown to result in activation of the MAPK pathway, and were both reported to be sensitive to the MEK inhibitor trametinib but not the BRAF inhibitor vemurafenib as assessed by inhibition of MEK1/2 phosphorylation (33).

In summary, multiple alterations in the BRAF gene can occur. The sensitivity or lack thereof to BRAF or MEK inhibitors may vary depending on the alteration.

Clinically Available BRAF Inhibitors and Their Applications

The connection between *BRAF*-mutant, specifically *BRAF* V600E-mutant, cancers and response to BRAF inhibitors was first established in melanoma patients, where it was observed that anywhere from 50% to 60% of melanomas harbor the activating *BRAF* V600E mutation (12, 34). A phase I study reported that, in comparison with the 10% to 20% response rates for nontargeted therapies approved for the treatment of melanoma, a response rate of up to 81% was observed for *BRAF* V600E-mutated melanoma patients given the BRAF inhibitor vemurafenib (35). Furthermore, matched targeted therapy in heavily pretreated melanoma patients in the phase I setting (using mainly BRAF and MEK inhibitors), showed longer PFS as compared with each patient's first-line standard therapy (36). The phase II BRIM-2 study reported a best overall response rate of 53% and median duration of response of 6.8 months from treatment with dabrafenib for previously treated melanoma patients whose tumor harbored the *BRAF* V600E mutation (37, 38). Finally, on the basis of a phase III trial comparing vemurafenib to dacarbazine, in which it was reported that the response rate for vemurafenib was 48% as compared with the 5% response rate for decarbazine (5), vemurafenib received FDA approval for treatment of patients with melanoma whose tumors harbor the *BRAF* V600E mutation (39).

On the heels of vemurafenib, another BRAF inhibitor that proved to be efficacious in treating *BRAF* V600E-mutated melanoma patients was dabrafenib (6, 40), which received FDA approval for the treatment of patients with melanoma having the *BRAF* V600E mutation (41). Vemurafenib and dabrafenib are perfect examples of the superior efficacy that can be achieved by employing drugs that target a biomarker that drives oncogenesis; in patients with *BRAF* V600E-mutated melanoma, BRAF-directed therapy results in substantially better outcomes as compared with nontargeted therapy approaches.

Other approved drugs that act as BRAF inhibitors but are not specifically approved for *BRAF*-mutant cancers include regorafenib, which is approved for colorectal cancer and gastrointestinal stromal tumors (GIST); it is also currently in a phase II trial recruiting for colorectal cancer patients with any *BRAF* or *RAS* mutation (42).

Additional BRAF inhibitors that are either approved or currently in clinical development are summarized in Table 2. Some of these drugs are in trials selecting for *BRAF*-mutant cancers. For example, LGX818 is in a phase III trial for *BRAF* V600E- or *BRAF* V600K-positive melanoma (43) and in a phase II trial for *BRAF* V600-positive cancers (44).

Clinically Available MEK1/2 Inhibitors and Their Applications

Trametinib is currently the only approved MEK1/2 inhibitor. However, there are several other investigational MEK1/2 inhibitors being evaluated in clinical trials, including binimetinib (MEK162), cobimetinib (GDC-0973, XL518), pimasertib, refametinib, selumetinib (AZD6244), and PD-0325901.

Melanoma

Another drug approved for melanoma with *BRAF* V600E or *BRAF* V600K mutations is the MEK1/2 inhibitor trametinib (GSK1120212). Trametinib was approved on the basis of results from a phase III trial (NCT01245062) of 322 melanoma patients who harbored either *BRAF* V600E, *BRAF* V600K, or both mutations that were randomized to receive either a chemotherapy regimen (paclitaxel or dacarbazine) or trametinib. Patients receiving trametinib had a superior PFS as compared with patients receiving chemotherapy, with a median PFS of 4.8 months versus 1.5 months, respectively (45). Trametinib in combination with dabrafenib for melanoma with *BRAF* V600E or *BRAF* V600K mutations was subsequently approved on the basis of a trial of 162 melanoma patients who harbored either the *BRAF* V600E or *BRAF* V600K mutations, who were randomized to either trametinib 2 mg daily in combination with dabrafenib, trametinib 1 mg daily in combination with dabrafenib, or single-agent dabrafenib. The trametinib 2 mg daily in combination with dabrafenib yielded superior objective response rates and response duration (76% and 10.5 months, respectively, as compared with 54% and 5.6 months, respectively, in the single-agent dabrafenib arm; $P < 0.05$; 46).

Colorectal cancer

In colorectal cancer, dabrafenib and trametanib combinations have also shown activity in *BRAF*-mutated disease (47). Of 43

Table 3. Predictive value of *BRAF* mutations for BRAF and/or MEK inhibitor therapy in diverse cancers

Cancer	% BRAF mutated	Treatment regimen	Reported outcomes	Comments	Reference
Cholangiosarcoma	3%–22%	Vemurafenib	12.5% with PR (1 of 8) or SD $\geq$ 6 months. All patients with either PR or SD had tumors with *BRAF* V600E mutations.	Phase II	Hyman et al (8)
Erdheim-Chester disease (ECD)	54%	Vemurafenib	Rapid clinical and biological improvement with tumor response ($N = 4$). All 4 patients had *BRAF* V600E mutations.	Case reports	Haroche et al (10) Tzoulis et al (127)
Langerhans histiocytosis (LCH)	25%–38%	Vemurafenib	One patient with SD and almost complete metabolic remission. Disease positive for *BRAF* V600E mutation.	Case report	Bubolz et al (128)
ECD/LCH	N/A	Vemurafenib	7% CR (1 of 14); 36% PR (5 of 14); 29% with SD $\geq$ 6 months (4 of 14). All patients with V600E.	Phase II	Hyman et al (8)
Ganglioglioma	43%	Vemurafenib	2 patients with PR (2 months PFS in one patient; 20+ months PFS in another; $N = 2$). 1 patient had radiological and clinical response sustained after 6 months from vemurafenib ($N = 1$). All patients had *BRAF* V600E mutant tumors.	Case reports	Bautista et al (55) del Bufalo et al (129)
Glioma	Varies depending on type of glioma	Vemurafenib	1 of 8 patients had SD $\geq$ 6 months. Patient had V600E.	Phase II	Hyman et al (8)
GIST	2%–13%	Dabrafenib	One patient with tumor regression (PFS = 8 months). One SD with 17% decrease in tumor volume ($N = 1$). Both tumors positive for *BRAF* V600E.	Case report and phase I study	Falchook et al (53) Falchook et al (40)
Glioblastoma	1.7%	Vemurafenib	CR (PFS = 6+ months). Tumor positive for *BRAF* V600E.	Case report	Robinson et al (54)
Hairy cell leukemia	~100%	Dabrafenib; Vemurafenib	CR ($N = 3$) and PR ($N = 2$) in dabrafenib studies. 38% CR (19 of 50) and 60% with PR (30 of 50). All patients in clinical reports had *BRAF* V600E mutation.	Case reports for dabrafenib; phase II study for vemurafenib	Vergote et al (130) Samuel et al (56) Munoz et al (9) Follows et al (131) Dietrich et al (57) Tiacci et al (132)
Multiple myeloma	~6%	Vemurafenib	Case: 1 PR in patient with *BRAF* V600E mutation.		Andrulis et al (133)
NSCLC	3%	Vemurafenib; dabrafenib	Phase II study: 42% with PR (8 of 19) and (3 of 19) with SD $\geq$ 6 months; all patients except one who was *BRAF* V600 unknown had the V600E mutation. Phase I study:1 PR ($N = 1$) with 83% decrease in tumor volume from dabrafenib.	Phase II for vemurafenib; phase I study for dabrafenib	Hyman et al (8) Falchook et al (40)
Ovarian cancer	35%–60%	Selumetinib; dabrafenib; vemurafenib	No patients demonstrated a tumor response to selumetinib ($N = 2$). 1 SD ($N = 1$) with 28% decrease in tumor volume from treatment with dabrafenib in phase I study. 1 PR in a serous ovarian cancer patient ($N = 1$) in phase II vemurafenib study. All patients in these studies had *BRAF* V600E disease.	Phase II for selumetinib study; phase II for vemurafenib; phase I for dabrafenib	Farley et al (134) Falchook et al (40) Hyman et al (8)
Pilomyxoid astrocytoma	Rare	Vemurafenib	Tumor regression. Tumor was *BRAF* V600E mutation positive.	Case report	Skrypek et al (135)
Anaplastic pleomorphic xanthoastrocytoma	66%	Vemurafenib	Phase II: 75% PR (3 of 4). Case report: near clinical response ($N = 1$). Case report: 1 PR and 1 SD $\geq$ 6 months ($N = 4$). Patients in all studies had *BRAF* V600E	Phase II and case reports	Hyman et al (8) Lee et al (136) Chamberlain (137)

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Table 3. Predictive value of *BRAF* mutations for BRAF and/or MEK inhibitor therapy in diverse cancers (Cont'd)

Cancer	% BRAF mutated	Treatment regimen	Reported outcomes	Comments	Reference
Papillary thyroid cancer	30%–80%	Selumetinib; dabrafenib; vemurafenib	Phase II: Longer PFS on selumetinib observed in *BRAF* V600E-mutated patients versus *BRAF* wild-type patients (33 *vs.* 11 weeks, respectively, $P = 0.3$). Phase I: 1 PR and 2 SD reported in one dabrafenib study ($N = 3$). 33% (3 of 10) with PR and 10% (1 of 10) with PD in another dabrafenib study. Phase I: 3 of 5 evaluable with CR or PR from vemurafenib; remaining 2 had SD. All patients in these studies had *BRAF* V600E-positive disease.	Phase II for selumetinib study; Phase I for dabrafenib studies; Phase I for vemurafenib study	Hayes et al (138) Kim et al (52) Falchook et al (40) Flaherty et al (35)
Anaplastic tyhyroid cancer	23% (139)	Vemurafenib	14% CR (1 of 7) and 14% PR (1 of 7); both patients with V600E	Phase II	Hyman et al (8)
Pancreatic cancer	1%–16%	Vemurafenib	One V600E-positive patient with SD lasting ∼7 months (1 of 1)	Phase II	Hyman et al (8)
Thoracic clear cell sarcoma	4.5% (140)	Vemurafenib	One V600E-positive patient with CR (1 of 1)	Phase II	Hyman et al (8)
Salivary gland cancer	7% (141)	Vemurafenib	One V600E-positive patient with CR (1 of 1)	Phase II	Hyman et al (8)

NOTE: Key to drug actions: Dabrafenib = BRAF inhibitor; Selumetinib = MEK inhibitor; Vemurafenib = BRAF inhibitor.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

patients, five (12%) achieved a partial response or better, including one (2%) complete response, with duration of response > 36 months; 24 patients (56%) achieved stable disease as best confirmed response. Ten patients (23%) remained in the study > 6 months.

Companion Diagnostics for *BRAF* Detection

There exist FDA-approved companion diagnostics for vemurafenib (COBAS 4800 BRAF V600 Mutation Test) to identify those melanoma patients harboring the *BRAF* V600E mutation (39, 48) and for the approved combination regimen of dabrafenib and trametinib (THxID BRAF kit) for those melanoma patients harboring the *BRAF* V600E or *BRAF* V600K mutation (41). However, these diagnostics, while well validated, are limited by their inability to detect other mutations, as well as amplifications and rearrangements in *BRAF*. They also cannot detect additional genomic abnormalities that coexist in most patient tumors. Other technologies such as next-generation sequencing are better suited to the more comprehensive analysis that is often needed (49).

Predictive Value of *BRAF* Mutations for BRAF and/or MEK Inhibitor Therapy in Diverse Cancers and Related Conditions

BRAF V600E mutation

Since the approval of vemurafenib for *BRAF* V600E-mutated melanoma, accumulating evidence presented in published reports supports the idea that what works for *BRAF* V600E-mutated melanoma is often also effective for other cancers characterized by the *BRAF* V600E aberration (Table 3). Dabrafenib was granted the Breakthrough Therapy designation for treatment of patients with metastatic *BRAF* V600E mutation-positive non–small cell lung cancer (NSCLC; 50) based on a phase II study that reported a response rate of 54% *for BRAF* V600E mutation—positive, pre-treated NSCLC patients receiving treatment with dabrafenib (51). A phase I study reported three papillary thyroid cancer patients whose disease was characterized by *BRAF* V600E, had either a partial response or stable disease in response to treatment with dabrafenib (52), a gastrointestinal stromal patient whose tumor harbored the *BRAF* V600E mutation experienced continuing tumor regression while being treated with dabrafenib (53), a child with glioblastoma multiforme harboring the *BRAF* V600E aberration had complete clinical regression from treatment with vemurafenib (54), glioma patients whose tumors carried the *BRAF* V600E mutation were reported to respond to treatment with vemurafenib (55), and several case studies have reported clinical benefit from treatment with vemurafenib for *BRAF* V600E-mutated hairy cell leukemia patients (9, 56–58). One study consisting of three *BRAF* V600E-mutated multisystemic and refractory Erdheim-Chester disease patients reported substantial and rapid clinical and biologic improvement from treatment with vemurafenib lasting 4 months (10, 59). In addition, a phase II trial of vemurafenib in *BRAF* V600-mutated Erdheim-Chester disease (a non-Langerhans histiocytosis) and Langerhans cell histiocytosis reported an overall response rate (defined as percentage of patients with either complete or partial response) of 36.4%, with one patient achieving a complete response (9.1%) and three patients with partial response (27.3%); none of the 11 evaluable patients had progressive disease (60).

Of interest, a basket study of vemurafenib reported clinical activity of vemurafenib in predominantly *BRAF* V600E-mutated nonmelanoma cancers. Complete or partial responses, tumor regression and prolonged disease stabilization were observed in several tumor types including NSCLC, Erdheim-Chester disease or Langerhans' histiocytosis, anaplastic thyroid cancer, pleomorphic xanthoastrocytoma, cholangiocarcinoma, salivary-duct cancer, ovarian cancer, clear-cell sarcoma, glioblastoma, anaplastic ependymoma, pancreatic cancer, and carcinoma of unknown primary types, and among patients with colorectal cancer who received vemurafenib and cetuximab (8). This study confirms that multiple histologic types of cancer with *BRAF* mutations respond to

BRAF inhibitors, though precise response rates may differ (and were hard to elucidate exactly in this study since numbers of patients in each group were small). In some types of tumors (e.g., colorectal cancer), BRAF inhibitors need to be given with other drugs that impact resistance pathways.

BRAF mutations other than V600E

BRAF mutations affecting codon 600 have generally been associated with sensitivity to BRAF inhibitors, with the drugs vemurafenib and dabrafenib being approved for melanoma patients with the *BRAF* V600E mutation (39, 61), and trametinib approved for melanoma patients with the *BRAF* V600E and *BRAF* V600K mutation (62). The BRIM7 and coBRIM studies have reported mutations at codon 600 to be sensitive to combination therapies of the MEK inhibitor cobimetinib with vemurafenib (63, 64).

In addition, there are a few clinical reports on the responsiveness of *BRAF* mutations other than those affecting codon 600. A melanoma patient harboring the *BRAF* K601E aberration was reported to have prolonged partial response to the MEK inhibitor trametinib (65); however, two other melanoma patients harboring this aberration were reported to not derive clinical benefit from treatment with dabrafenib (40). Resistance to treatment, though, may not necessarily be due to insensitivity of the mutation, but rather to other unrelated molecular drivers that may be present in patients and supplant the role of *BRAF*. One patient with *BRAF* L597R-harboring melanoma was reported to derive clinical benefit after treatment with vemurafenib (66); however, L597R was also associated with disease progression in a melanoma patient with brain metastases who received BRAF inhibitor treatment (67). Again, it is plausible that the brain is a sanctuary in this patient, and that resistance may not be due to insensitivity to the drug. Similarly, a melanoma patient with the *BRAF* L597Q aberration had disease progression within 2 months of treatment with a BRAF inhibitor (67), but another melanoma patient with this aberration had a partial response to treatment with trametinib (68). Finally, a *BRAF* L597S–positive melanoma patient was reported to derive clinical benefit after treatment with the MEK inhibitor, TAK-733 (69).

Other activating mutations in *BRAF* affecting codons other than 600 that have been shown to be sensitive to either MEK inhibitors or BRAF inhibitors in preclinical studies include *BRAF* L597R, *BRAF* L597Q, *BRAF* L597S, and *BRAF* K601E (69). However, some activating mutations in *BRAF* have been shown to be less sensitive or even resistant to BRAF inhibitors in preclinical studies. For example, the activating *BRAF* L505H mutation appears to be resistant to vemurafenib (70). In addition, some mutations in *BRAF*, including substitutions at codon 466, are inactivating (18); BRAF inhibitors are predicted to be ineffective for such mutations.

BRAF Inhibitors in *BRAF*-Mutant Colorectal Cancer

Despite the evidence that BRAF inhibitors are efficacious in melanoma and several other different cancers characterized by the *BRAF* V600E mutation, at least one cancer type seems more resistant to these drugs—colorectal cancer. Fewer than 10% of *BRAF* V600E-mutated colorectal cancers have responded to BRAF inhibitor monotherapy in early-phase trials (40, 71). The underwhelming response of *BRAF* V600E-mutated colorectal cancer patients to BRAF inhibitors initially may seem to provide evidence that biomarker-driven approaches to the treatment of cancers are not sufficient unless taken within histologic context. However, a deeper analysis of the literature appears to suggest otherwise.

Role of EGFR

Preclinical studies initially discovered that, in *BRAF* V600E-positive colorectal cancer cells, inhibition of *BRAF* V600E by vemurafenib results in decreased negative feedback of the EGFR pathway (72, 73), Therefore, the attenuated clinical response to vemurafenib in *BRAF* V600E-mutated colorectal cancer compared with *BRAF* V600E-mutated melanoma could be attributable to differences in the importance of the EGFR signal present in these two cancer types (74). Specifically, these studies reported that melanoma cells express low levels of EGFR and as such are not poised, as high EGFR-expressing colorectal cancer cells are, for vemurafenib-stimulated EGFR pathway activation. Both studies demonstrated that a combination of vemurafenib with an EGFR inhibitor, such as cetuximab, erlotinib, or gefitinib, in *BRAF* V600E-mutated colorectal cancer cells, inhibited vemurafenib-induced feedback activation of EGFR and increased therapeutic efficacy *in vitro* and in tumor xenografts (72, 73).

The therapeutic efficacy of a BRAF inhibitor in combination with an EGFR inhibitor observed in preclinical models has subsequently translated into clinical efficacy seen in patients. One case study described a patient with colorectal cancer whose tumor had both the *BRAF* V600E mutation and *EGFR* amplification, with a partial remission from the combination of vemurafenib and panitumumab (an EGFR antibody; 75). Another case study reported a patient with colorectal cancer whose tumor carried the *BRAF* V600E mutation and proved to be refractory to treatment with several drugs including cetuximab monotherapy, but achieved symptom stabilization from the combination of cetuximab and vemurafenib (76). Another case report described a *BRAF* V600E-mutated colorectal cancer patient who had a 7-month long PFS and mixed response to combination therapy of sorafenib, a weak BRAF inhibitor, and cetuximab, with some areas showing dramatic improvement and other areas showing stable disease (77). Recently, a vemurafenib basket study confirmed that, in colorectal cancer, salutary effects can be attained with the combination of vemurafenib and an EGFR inhibitor in *BRAF*-mutated colorectal cancer (8). Studies are now ongoing with these combinations [NCT01719380 (78), NCT01791309 (79), NCT01750918 (80)], with early promising results from NCT01719380 recently being presented at the 2014 and 2015 ASCO Annual Meeting. This phase I study of the BRAF inhibitor LGX818 in combination with cetuximab, with or without the PIK3CA inhibitor BYL719, in advanced *BRAF*-mutated and *KRAS* wild-type colorectal cancer patients reported no complete responses but 7 (∼30%) partial responses from the dual combination of LGX818 with cetuximab and 6 (∼30%) partial responses from the triple combination of LGX818, cetuximab, and BYL719 (81). Finally, preliminary results from a phase Ib trial of vemurafenib in combination with irinotecan and cetuximab in *BRAF*-mutated advanced cancers and colorectal cancer patients reported that 6 of 17 evaluable *BRAF* V600E-mutated colorectal cancer patients achieved a partial response Hong and colleagues (82).

Role of the PI3K/AKT/mTOR axis

Another perspective for this issue derives from studies showing that, in colorectal cancer patients, aberrations in the KRAS/BRAF

Table 4. Predictive value of *BRAF* mutations for BRAF and/or MEK inhibitor therapy in colorectal cancer

Type of study	Treatment regimen	Reported outcomes[a]	Reference
Phase II	Vemurafenib + cetuximab	0 CR. 0 PR, although one nonconfirmed patient had ~70% reduction target lesion size. 11 SD (65%). 6 PD (35%; *N* = 17).	Tabernero et al (142)
Phase II	Dabrafenib + trametinib	1 (3%) CR, 3 (9%) PR, 18 (53%) SD. Median PFS = 3.5 months (*N* = 34).	Corcoran et al (51)
Phase II	Vemurafenib + cetuximab	4% PR (1 of 26) and 19% with SD disease ≥ 6 months (5 of 26). 90% of patients had *BRAF* V600E and the other 10% were *BRAF* V600 unknown.	Hyman et al (8)
Phase	Vemurafenib + panitumumab + trametinib	26% (9 of 35) with CR or PR.	Atreya et al (88)
?	Dabrafenib + trametinib	2% CR (1 of 43), 10% PR (4 of 43), 56% SD (24 of 43). 23% (10 patients) remained on study greater than 6 months. All patients with *BRAF* V600X.	Corcoran et al (47)
Phase I/II	Dabrafenib + trametinib	1 (5%) PR, 10 (50%) SD. Minor responses (>10% to <30% tumor shrinkage) were observed in 4/10 patients (40%) with stable disease (*N* = 20).	Corcoran et al (143)
Phase I/II	Dabrafenib + trametinib	1 (2%) CR, 4 (9%) PR, 22 (51%) SD of which 11 (26%) patients had a minor response (10% to 30% tumor reduction; *N* = 43).	Corcoran et al (144)
Phase I/II	Vemurafenib + cetuximab; vemurafenib + cetuximab + trametinib	2 PR and 11 SD for vemurafenib + cetuximab combinations (*N* = 15). 1 CR, 5 PR, and 6 SD for vemurafenib + cetuximab + trametinib (*N* = 15).	Bendell et al (145)
Phase I	LGX818 + cetuximab +/− BYL719	7 PR (~30%) and 6 PR (30%) in dual and triple combinations, respectively.	Van Geel et al (81)
Phase I	Vemurafenib	1 PR and 4 SD (≥10% shrinkage). 5 patients showed a mixed response pattern (i.e., with both regressing and progressing lesions). Median PFS = 3.7 months (*N* = 19).	Kopetz et al (71)
Phase I	PLX3603	No PR, no SD > 16weeks (*N* = 3).	Dienstmann et al (146)
Phase I	Dabrafenib	1 PR with 72% decrease in tumor volume. 7 SD. (*N* = 9)	Falchook et al (40)
Phase Ib	Vemurafenib + cetuximab + irinotecan	35% PR (6 of 17).	Hong et al (82)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
[a]Key to drug actions: Dabrafenib = BRAF inhibitor; Vemurafenib= BRAF inhibitor; PLX3603 = BRAF inhibitor; trametinib = MEK inhibitor; cetuximab = EGFR inhibitor; panitumumab = EGFR inhibitor.

axis often coexist with aberrations in the PI3K/AKT/mTOR axis (83–85), with each being a resistance pathway for the other (86, 87). These co-mutations occur in other cancers as well, but not as frequently.

Role of combinations of BRAF and MEK inhibitors

Finally, CRAF activation may occur as a resistance mechanism. Recently, *BRAF*-mutated colorectal cancer has been shown to respond to combinations of a BRAF inhibitor dabrafenib together with the MEK inhibitor trametinib. Of 43 patients, five (12%) achieved a partial response or better, including one (2%) complete response, with duration of response > 36 months; 24 patients (56%) achieved stable disease as best confirmed response. Ten patients (23%) remained in the study > 6 months (47).

Targeting multiple resistance pathways

Targeting multiple pathways of resistance in *BRAF*-mutated colorectal cancer may be the most efficacious route as suggested by recent preliminary results from a phase II study of the triple combination of vemurafenib, anti-EGFR antibody panitumumab, and trametinib versus dual combination therapy of vemurafenib with trametinib. The triple combination had acceptable tolerability and improved response rate as compared with doublet therapy in *BRAF* V600E-mutated colorectal cancer patients, with 9 (26%) of patients treated with the triple combination achieving either a partial or complete response as compared with 2 (10%) treated with the doublet combination (88). Table 4 summarizes clinical studies using BRAF and/or MEK inhibitors in the treatment of *BRAF*-mutated colorectal cancer.

BRAF in colorectal cancer summary and implications for resistance in other tumors

Taken together, it appears likely that *BRAF* mutations may indeed be actionable in colorectal cancers, but that a more complete picture of the molecular portfolio of the patient needs to be taken into account, and customized combinations created, a situation that is almost certainly relevant to other tumor types in which resistance pathways in addition to BRAF are also activated. These observations may also be relevant to *BRAF*-mutated melanoma, in that, patients who relapse or are resistant upfront to BRAF inhibitors may still need such a drug in their treatment regimen, albeit in combination with other drugs that target molecular aberrations that coexist and mediate resistance. Indeed, even melanoma patients whose tumors are sensitive to BRAF inhibitors probably need customized combinations, since most do not achieve complete remissions, and relapse after a few months is routinely observed. Several preclinical reports have identified mechanisms of resistance to BRAF inhibitors in *BRAF*-mutated melanoma that would suggest the use of specific BRAF inhibitor-containing combinations. These include but are not limited to generation of drug-tolerant microenvironments characterized by high integrin β1/FAK/Src signaling via paradoxical BRAF inhibitor-mediated activation of melanoma-associated fibroblasts (89; suggestive of use of BRAF inhibitor in combination with FAK or Src inhibitor), upregulation of many ERBB pathway genes in response to BRAF inhibition (90; suggestive of use of BRAF inhibitor in combination with ERBB inhibitors), and BRAF inhibitor-induced activation of cryoprotective autophagy (91;

suggestive of use of BRAF inhibitor in combination with autophagy inhibitor).

Final Perspectives

A key question for the treatment of cancer in the emerging genomics era is whether or not we can extrapolate predictive data on a biomarker for a given targeted therapy in one cancer to another cancer. In this scenario, clinical research-informed treatment options from one histology with that biomarker are applied to another cancer type with that same biomarker where such research is not available or limited in scope. The corollary to this question is whether or not the biomarker defines the tumor and represents a nosology in and of itself. Herein, we have used *BRAF*-mutant cancers as one example in support of such a restructuring of cancer classification, but others have proposed a similar genetic-centric nosology such as ALKomas for tumors encompassing multiple organs but harboring aberrations in ALK that have either been shown to or are likely to respond to ALK inhibitors (92). While not clear-cut, increasingly the data show that the presence of certain genomic drivers, such as *BRAF* aberrations, predicts response to cognate inhibitors across multiple (though not all) tumor types. Even in tumors such as colorectal cancer that are considered an important exception, emerging data suggest that BRAF is a relevant target, but must be prosecuted in the context of combination therapy (e.g., a BRAF inhibitor together with a EGFR or MEK inhibitor) that impacts pertinent coactivated pathways. Indeed, an important lesson from the "resistance" of *BRAF*-mutant colon cancer may be extrapolated to "sensitive" tumors such as melanoma, in that most patients with *BRAF*-mutant melanoma do not achieve complete remissions on BRAF inhibitors and they often relapse within months; these "sensitive" tumors, like "resistant" BRAF-mutant colorectal cancer, may require combination regimens to overcome the therapeutic plateau.

It seems that the current research points to a fork in the road. On the one hand, the approach might be to continue to explore and approve genomic marker-driven treatments histology by histology. The advantage to this strategy is more definitive data in each defined histology. The disadvantages, however, are substantial. Most importantly, it will be nearly impossible from the point of view of resources to perform studies for each biomarker within each histology or each organ of origin for a tumor. Therefore, one of the key points that should be established is the overall response rates in bucket, histology-agnostic biomarker driven trials, and whether these response and benefit rates suggest that patients are better off being treated on the basis of the biomarker, regardless of histology, or by classic treatments. A related alternative is to approve the targeted therapy across tumor types, but require post-approval outcome collection, perhaps within a phase IV setting such that indications can be refined if needed. The basic principle of clinical research should be maintained, that is, showing that, overall, patients have improved outcomes with a certain approach. Importantly, nonresponding patients regardless of histology may have additional genetic drivers, be it co-mutations in a given biomarker, or alterations in other biomarkers, that may provide a biologic rationale for their lack of response and suggest new drug development opportunities or combinations therapies that may be more effective for these patients, with *BRAF*-mutated colorectal cancer being an emerging example of the latter.

In conclusion, it is increasingly clear that many oncogenic drivers do not segregate by organ of tumor origin. In these cases, a new method of classifying cancers on the basis of the genomic aberration itself may be useful. New trial designs, such as histology-agnostic, genomically defined bucket trials are being used more frequently. Using the example of *BRAF* aberrations, the literature shows that this powerful driver is present in multiple tumor types and that the use of cognate inhibitors can be effective across many, even if not all, tumor types. Touted exceptions such as colorectal cancer, however, may still be responsive to BRAF inhibitors, albeit at lower rates. Furthermore, when important coexisting pathways such as EGFR or CRAF that drive innate resistance are taken into consideration, and combination therapy given (e.g., combine BRAF and EGFR inhibitor regimens or BRAF and MEK inhibitors in colorectal cancer), impressive responses can be seen. By the same token, even in histologic types with high response rates, there are nonresponders as well as a large numbers of patients that relapse after BRAF inhibitor monotherapy. In order to abrogate resistance, these tumors may require combination strategies that include a BRAF inhibitor and a drug that impacts other concomitantly activated driver pathways. Indeed, in melanoma, the combination of a BRAF and MEK inhibitor is associated with outcomes superior to BRAF inhibitor therapy alone (46). Taken together, these observations suggest that consideration for genomically based approval strategies are rational and merit consideration.

Disclosure of Potential Conflicts of Interest

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References

1. Hoadley KA, Yau C, Wolf DM, Cherniack AD, Tamborero D, Ng S, et al. Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. Cell 2014;158:929–44.
2. Munoz J, Swanton C, Kurzrock R. Molecular profiling and the reclassification of cancer: divide and conquer. Am Soc Clin Oncol Educ Book 2013;33:127–34.
3. Tsimberidou A-M, Iskander NG, Hong DS, Wheler JJ, Falchook GS, Fu S, et al.Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. Clin Cancer Res 2012;18:6373–83.
4. Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, et al.Mutational landscape and significance across 12 major cancer types. Nature 2013; 502:333–9.

5. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507–16.
6. Hauschild A, Grob J-J, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358–65.
7. Wheler JJ, Parker BA, Lee JJ, Atkins JT, Janku F, Tsimberidou AM, et al. Unique molecular signatures as a hallmark of patients with metastatic breast cancer: implications for current treatment paradigms. Oncotarget 2014;5:2349–54.
8. Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay J-Y, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med 2015;373:726–36.
9. Munoz J, Schlette E, Kurzrock R. Rapid response to vemurafenib in a heavily pretreated patient with hairy cell leukemia and a BRAF mutation. J Clin Oncol 2013;31:e351–2.
10. Haroche J, Cohen-Aubart F, Emile J-F, Arnaud L, Maksud P, Charlotte F, et al.Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. Blood 2013;121: 1495–500.
11. El-Osta H, Falchook G, Tsimberidou A, Hong D, Naing A, Kim K, et al. BRAF mutations in advanced cancers: clinical characteristics and outcomes. PLoS ONE 2011;6:e25806.
12. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417: 949–54.
13. Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, et al. BRAF mutations in hairy-cell leukemia. N Engl J Med 2011;364: 2305–15.
14. Roskoski R. RAF protein-serine/threonine kinases: structure and regulation. Biochem Biophys Res Commun 2010;399:313–7.
15. Wellbrock C, Karasarides M, Marais R. The RAF proteins take centre stage. Nat Rev Mol Cell Biol 2004;5:875–85.
16. Menzies AM, Haydu LE, Visintin L, Carlino MS, Howle JR, Thompson JF, et al.Distinguishing clinicopathologic features of patients with V600E and V600K BRAF-mutant metastatic melanoma. Clin Cancer Res 2012;18: 3242–9.
17. Brummer T, Martin P, Herzog S, Misawa Y, Daly RJ, Reth M. Functional analysis of the regulatory requirements of B-Raf and the B-Raf(V600E) oncoprotein. Oncogene 2006;25:6262–76.
18. Wan PTC, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, Good VM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell 2004;116:855–67.
19. Ikenoue T, Hikiba Y, Kanai F, Tanaka Y, Imamura J, Imamura T, et al. Functional analysis of mutations within the kinase activation segment of B-Raf in human colorectal tumors. Cancer Res 2003;63:8132–7.
20. Ihle MA, Fassunke J, König K, Grünewald I, Schlaak M, Kreuzberg N, et al. Comparison of high resolution melting analysis, pyrosequencing, next generation sequencing and immunohistochemistry to conventional Sanger sequencing for the detection of p.V600E and non-p.V600E BRAF mutations. BMC Cancer 2014;14:13.
21. Smalley KSM, Xiao M, Villanueva J, Nguyen TK, Flaherty KT, Letrero R, et al.CRAF inhibition induces apoptosis in melanoma cells with non-V600E BRAF mutations. Oncogene 2009;28:85–94.
22. Tanami H, Imoto I, Hirasawa A, Yuki Y, Sonoda I, Inoue J, et al.Involvement of overexpressed wild-type BRAF in the growth of malignant melanoma cell lines. Oncogene 2004;23:8796–804.
23. COSMIC: Catalogue of somatic mutations in cancer [Internet]. Wellcome Trust Sanger Institute; [cited 2014 Jan 2]. Available from: http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/
24. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70.
25. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013;6:pl1–pl1.
26. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al.The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov 2012;2:401–4.
27. Kieran MW.Targeting BRAF in pediatric brain tumors. Am Soc Clin Oncol Educ Book 2014;34:e436–40.
28. Korshunov A, Meyer J, Capper D, Christians A, Remke M, Witt H, et al. Combined molecular analysis of BRAF and IDH1 distinguishes pilocytic astrocytoma from diffuse astrocytoma. Acta Neuropathol 2009; 118:401–5.
29. Jones DTW, Kocialkowski S, Liu L, Pearson DM, Bäcklund LM, Ichimura K, et al.Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res 2008;68:8673–7.
30. Cin H, Meyer C, Herr R, Janzarik WG, Lambert S, Jones DTW, et al. Oncogenic FAM131B-BRAF fusion resulting from 7q34 deletion comprises an alternative mechanism of MAPK pathway activation in pilocytic astrocytoma. Acta Neuropathol 2011;121:763–74.
31. Sievert AJ, Lang S-S, Boucher KL, Madsen PJ, Slaunwhite E, Choudhari N, et al.Paradoxical activation and RAF inhibitor resistance of BRAF protein kinase fusions characterizing pediatric astrocytomas. Proc Natl Acad Sci U S A 2013;110:5957–62.
32. Subbiah V, Westin SN, Wang K, Araujo D, Wang W-L, Miller VA, et al. Targeted therapy by combined inhibition of the RAF and mTOR kinases in malignant spindle cell neoplasm harboring the KIAA1549-BRAF fusion protein. J Hematol Oncol 2014;7:8.
33. Hutchinson KE, Lipson D, Stephens PJ, Otto G, Lehmann BD, Lyle PL, et al.BRAF fusions define a distinct molecular subset of melanomas with potential sensitivity to MEK inhibition. Clin Cancer Res 2013;19: 6696–702.
34. Kainthla R, Kim KB, Falchook GS. Dabrafenib for treatment of BRAF-mutant melanoma. Pharmgenomics Pers Med 2014;7:21–9.
35. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 2010;363:809–19.
36. Henary H, Hong DS, Falchook GS, Tsimberidou A, George GC, Wen S, et al.Melanoma patients in a phase I clinic: molecular aberrations, targeted therapy and outcomes. Ann Oncol 2013;24:2158–65.
37. Ribas A, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Weber JS, et al. BRIM-2: An open-label, multicenter phase II study of vemurafenib in previously treated patients with *BRAF* V600E mutation-positive metastatic melanoma. J Clin Oncol 29: 2011 (suppl; abstr 8509)
38. Ravnan MC, Matalka MS. Vemurafenib in patients with BRAF V600E mutation-positive advanced melanoma. Clin Ther 2012;34: 1474–86.
39. Press Announcements - FDA approves Zelboraf and companion diagnostic test for late-stage skin cancer [Internet]. FDA. 2011. Available from: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm268241.htm
40. Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet 2012;379: 1893–901.
41. Press Announcements - FDA approves two drugs, companion diagnostic test for advanced skin cancer [Internet]. FDA. 2013. Available from: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm354199.htm
42. NCT02175654 [Internet]. ClinicalTrials.gov; [cited 2014 Oct 20]. Available from: http://clinicaltrials.gov/show/NCT02175654
43. NCT01909453 [Internet]. ClinicalTrials.gov; [cited 2014 Oct 20]. Available from: http://www.clinicaltrials.gov/show/NCT01909453
44. NCT01981187 [Internet]. ClinicalTrials.gov; [cited 2014 Oct 20]. Available from: http://www.clinicaltrials.gov/show/NCT01981187
45. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012;367:107–14.
46. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012;367:1694–703.
47. Corcoran RB, Atreya CE, Falchook GS, Kwak EL, Ryan DP, Bendell JC, et al.Combined BRAF and MEK inhibition with dabrafenib and trametinib in BRAF V600-mutant colorectal cancer. J Clin Oncol 2015;: JCO.2015.63.2471.
48. FDA approves Zelboraf (vemurafenib) and companion diagnostic for BRAF mutation-positive metastatic melanoma, a deadly form of skin cancer [Internet]. Roche; 2011. Available from: http://www.roche.com/media/media_releases/med-cor-2011-08-17.htm

49. Dienstmann R, Rodon J, Barretina J, Tabernero J. Genomic medicine frontier in human solid tumors: prospects and challenges. J Clin Oncol 2013;31:1874–84.
50. Tafinlar® receives FDA Breakthrough Therapy designation for non-small cell lung cancer with BRAF mutation | GSK US. GlaxoSmithKline; 2013. Available from: http://us.gsk.com/en-us/media/press-releases/2014/tafinlar-receives-fda-breakthrough-therapy-designation-for-non-small-cell-lung-cancer-with-braf-mutation/
51. Corcoran RB, Falchook GS, Infante JR, Hamid O, Messersmith WA, Daud A, et al.Pharmacodynamic and efficacy analysis of the BRAF inhibitor dabrafenib (GSK436) in combination with the MEK inhibitor trametinib (GSK212) in patients with BRAFV600 mutant colorectal cancer (CRC). J Clin Oncol 31, 2013 (suppl; abstr 3507)
52. Kim KB, Cabanillas ME, Lazar AJ, Williams MD, Sanders DL, Ilagan JL, et al.Clinical responses to vemurafenib in patients with metastatic papillary thyroid cancer harboring BRAF(V600E) mutation. Thyroid 2013;23:1277–83.
53. Falchook GS, Trent JC, Heinrich MC, Beadling C, Patterson J, Bastida CC, et al.BRAF mutant gastrointestinal stromal tumor: first report of regression with BRAF inhibitor dabrafenib (GSK2118436) and whole exomic sequencing for analysis of acquired resistance. Oncotarget 2013;4:310–5.
54. Robinson GW, Orr BA, Gajjar A. Complete clinical regression of a BRAF V600E-mutant pediatric glioblastoma multiforme after BRAF inhibitor therapy. BMC Cancer 2014;14:258.
55. Bautista F, Paci A, Minard-Colin V, Dufour C, Grill J, Lacroix L, et al. Vemurafenib in pediatric patients with BRAFV600E mutated high-grade gliomas. Pediatr Blood Cancer 2014;61:1101–3.
56. Samuel J, Macip S, Dyer MJS. Efficacy of vemurafenib in hairy-cell leukemia. N Engl J Med 2014;370:286–8.
57. Dietrich S, Glimm H, Andrulis M, Kalle von C, Ho AD, Zenz T. BRAF inhibition in refractory hairy-cell leukemia. N Engl J Med 2012;366:2038–40.
58. Dietrich S, Hüllein J, Hundemer M, Lehners N, Jethwa A, Capper D, et al. Continued response off treatment after BRAF inhibition in refractory hairy cell leukemia. J Clin Oncol 2013;31:e300–3.
59. Munoz J, Janku F, Cohen PR, Kurzrock R. Erdheim-Chester disease: characteristics and management. Mayo Clin Proc 2014;89:985–96.
60. Hyman DM, Diamond E, Subbiah V, Blay J-Y, Lockhart AC, Abdel-Wahab O, et al.The Efficacy of Vemurafenib in Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Preliminary Results from VE-Basket Study. Blood 124, 2014 (suppl; abstr 635).
61. Dabrafenib [Internet]. FDA; 2013. Available from: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm354477.htm
62. Trametinib [Internet]. FDA; 2013. Available from: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm354478.htm
63. Roche presents final Phase 1b data on its investigational MEK-BRAF inhibitor combination therapy for metastatic melanoma at EADO 2014 [Internet]. Roche; 2014. Available from: http://www.roche.com/investors/updates/inv-update-2014-05-07.htm
64. Roche's investigational medicine cobimetinib, used in combination with Zelboraf (vemurafenib), helped people with advanced melanoma live significantly longer without their disease worsening [Internet]. Roche; 2014. Available from: http://www.roche.com/media/media_releases/med-cor-2014-07-14.htm
65. Kim KB, Kefford R, Pavlick AC, Infante JR, Ribas A, Sosman JA, et al.Phase II study of the MEK1/MEK2 inhibitor Trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. J Clin Oncol 2013;31:482–9.
66. Bahadoran P, Allegra M, Le Duff F, Long-Mira E, Hofman P, Giacchero D, et al.Major clinical response to a BRAF inhibitor in a patient with a BRAF L597R-mutated melanoma. J Clin Oncol 2013;31:e324–6.
67. Kim DW, Nowroozi S, Kim K, Davies MA, Routbort M, Lazar AJ, et al. Clinical characteristics of patients with non-*V600 BRAF* mutant melanomas. J Clin Oncol 32:5s, 2014 (suppl; abstr 9100)
68. Bowyer SE, Rao AD, Lyle M, Sandhu S, Long GV, McArthur GA, et al. Activity of trametinib in K601E and L597Q BRAF mutation-positive metastatic melanoma. Melanoma Res 2014;24:504–8.
69. Dahlman KB, Xia J, Hutchinson K, Ng C, Hucks D, Jia P, et al.BRAF(L597) mutations in melanoma are associated with sensitivity to MEK inhibitors. Cancer Discov 2012;2:791–7.
70. Choi J, Landrette SF, Wang T, Evans P, Bacchiocchi A, Bjornson R, et al.Identification of PLX4032-resistance mechanisms and implications for novel RAF inhibitors. Pigment Cell Melanoma Res 2014;27:253–62.
71. Kopetz S, Desai J, Chan E, Hecht JR, O'Dwyer PJ, Lee RJ, et al.PLX4032 in metastatic colorectal cancer patients with mutant BRAF tumors. J Clin Oncol 28:15s, 2010 (suppl; abstr 3534)
72. Prahallad A, Sun C, Huang S, Di Nicolantonio F, Salazar R, Zecchin D, et al.Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. Nature 2012;483:100–3.
73. Corcoran RB, Ebi H, Turke AB, Coffee EM, Nishino M, Cogdill AP, et al. EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. Cancer Discov 2012;2:227–35.
74. Stites EC. The response of cancers to BRAF inhibition underscores the importance of cancer systems biology. Sci Signal 2012;5:pe46–6.
75. Capalbo C, Marchetti P, Coppa A, Calogero A, Anastasi E, Buffone A, et al. Vemurafenib and panitumumab combination tailored therapy in BRAF-mutated metastatic colorectal cancer: a case report. Cancer Biol Ther 2014;15:826–31.
76. Connolly K, Brungs D, Szeto E, Epstein RJ. Anticancer activity of combination targeted therapy using cetuximab plus vemurafenib for refractory BRAF (V600E)-mutant metastatic colorectal carcinoma. Curr Oncol 2014;21:e151–4.
77. Al-Marrawi MY, Saroya BS, Brennan MC, Yang Z, Dykes TM, El-Deiry WS. Off-label use of cetuximab plus sorafenib and panitumumab plus regorafenib to personalize therapy for a patient with V600E BRAF-mutant metastatic colon cancer. Cancer Biol Ther 2013;14:703–10.
78. NCT01719380 [Internet]. ClinicalTrials.gov; [cited 2014 Oct 21]. Available from: http://clinicaltrials.gov/show/NCT01719380
79. NCT01791309 [Internet]. ClinicalTrials.gov; [cited 2014 Oct 21]. Available from: http://clinicaltrials.gov/show/NCT01791309
80. NCT01750918 [Internet]. ClinicalTrials.gov; [cited 2014 Oct 21]. Available from: http://clinicaltrials.gov/show/NCT01750918
81. Van Geel R, Elez E, Bendell JC, Faris JE, Lolkema MP, Eskens F, et al.Phase I study of the selective $BRAF^{V600}$ inhibitor encorafenib (LGX818) combined with cetuximab and with or without the α-specific PI3K inhibitor BYL719 in patients with advanced *BRAF*-mutant colorectal cancer. J Clin Oncol 32:5s, 2014 (suppl; abstr 3514).
82. Hong DS, Morris VK, Osta El BE, Fu S, Overman MJ, Piha-Paul SA, et al. Phase Ib study of vemurafenib in combination with irinotecan and cetuximab in patients with *BRAF*-mutated metastatic colorectal cancer and advanced cancers. J Clin Oncol 33, 2015 (suppl; abstr 3511)
83. Velho S, Oliveira C, Ferreira A, Ferreira AC, Suriano G, Schwartz S, et al.The prevalence of PIK3CA mutations in gastric and colon cancer. Eur J Cancer 2005;41:1649–54.
84. Ollikainen M, Gylling A, Puputti M, Nupponen NN, Abdel-Rahman WM, Butzow R, et al.Patterns of PIK3CA alterations in familial colorectal and endometrial carcinoma. Int J Cancer 2007;121:915–20.
85. Janku F, Lee JJ, Tsimberidou AM, Hong DS, Naing A, Falchook GS, et al. PIK3CA mutations frequently coexist with RAS and BRAF mutations in patients with advanced cancers. PLoS ONE 2011;6:e22769.
86. Janku F, Hong DS, Fu S, Piha-Paul SA, Naing A, Falchook GS, et al. Assessing PIK3CA and PTEN in early-phase trials with PI3K/AKT/mTOR inhibitors. Cell Rep 2014;6:377–87.
87. Garrido-Laguna I, Hong DS, Janku F, Nguyen LM, Falchook GS, Fu S, et al. KRASness and PIK3CAness in patients with advanced colorectal cancer: outcome after treatment with early-phase trials with targeted pathway inhibitors. PLoS ONE 2012;7:e38033.
88. Atreya CE, Van Cutsem E, Bendell JC, Andre T, Schellens JH, Gordon MS, et al.Updated efficacy of the MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in patients (pts) with *BRAF* V600E mutated (BRAFm) metastatic colorectal cancer (mCRC). J Clin Oncol 33, 2015 (suppl; abstr 103).
89. Hirata E, Girotti MR, Viros A, Hooper S, Spencer-Dene B, Matsuda M, et al. Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin β1/FAK signaling. Cancer Cell 2015;27:574–88.
90. Capaldo BJ, Roller D, Axelrod MJ, Koeppel AF, Petricoin EF, Slingluff CL, et al.Systems analysis of adaptive responses to MAP kinase

pathway blockade in BRAF mutant melanoma. PLoS ONE 2015;10: e0138210.
91. Ma X-H, Piao S-F, Dey S, McAfee Q, Karakousis G, Villanueva J, et al. Targeting ER stress-induced autophagy overcomes BRAF inhibitor resistance in melanoma. J Clin Invest 2014;124:1406–17.
92. Mano H. ALKoma: a cancer subtype with a shared target. Cancer Discov 2012;2:495–502.
93. Goeppert B, Frauenschuh L, Renner M, Roessler S, Stenzinger A, Klauschen F, et al.BRAF V600E-specific immunohistochemistry reveals low mutation rates in biliary tract cancer and restriction to intrahepatic cholangiocarcinoma. Mod Pathol 2014;27:1028–34.
94. Tannapfel A, Sommerer F, Benicke M, Katalinic A, Uhlmann D, Witzigmann H, et al.Mutations of the BRAF gene in cholangiocarcinoma but not in hepatocellular carcinoma. Gut 2003;52:706–12.
95. Jebaraj BMC, Kienle D, Bühler A, Winkler D, Döhner H, Stilgenbauer S, et al.BRAF mutations in chronic lymphocytic leukemia. Leuk Lymphoma 2013;54:1177–82.
96. Pakneshan S, Salajegheh A, Smith RA, Lam AK-Y. Clinicopathological relevance of BRAF mutations in human cancer. Pathology 2013; 45:346–56.
97. Domingo E, Laiho P, Ollikainen M, Pinto M, Wang L, French AJ, et al.BRAF screening as a low-cost effective strategy for simplifying HNPCC genetic testing. J Med Genet 2004;41:664–8.
98. Samowitz WS, Sweeney C, Herrick J, Albertsen H, Levin TR, Murtaugh MA, et al.Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancers. Cancer Res 2005;65:6063–9.
99. Benlloch S, Payá A, Alenda C, Bessa X, Andreu M, Jover R, et al.Detection of BRAF V600E mutation in colorectal cancer: comparison of automatic sequencing and real-time chemistry methodology. J Mol Diagn 2006; 8:540–3.
100. Haroche J, Charlotte F, Arnaud L, Deimling von A, Hélias-Rodzewicz Z, Hervier B, et al.High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. Blood 2012;120:2700–3.
101. Gupta K, Orisme W, Harreld JH, Qaddoumi I, Dalton JD, Punchihewa C, et al.Posterior fossa and spinal gangliogliomas form two distinct clinicopathologic and molecular subgroups. Acta Neuropathol Commun 2014;2:18.
102. Hostein I, Faur N, Primois C, Boury F, Denard J, Emile J-F, et al.BRAF mutation status in gastrointestinal stromal tumors. Am J Clin Pathol 2010;133:141–8.
103. Miranda C, Nucifora M, Molinari F, Conca E, Anania MC, Bordoni A, et al.KRAS and BRAF mutations predict primary resistance to imatinib in gastrointestinal stromal tumors. Clin Cancer Res 2012;18: 1769–76.
104. Sakata-Yanagimoto M, Enami T, Yokoyama Y, Chiba S. Disease-specific mutations in mature lymphoid neoplasms: recent advances. Cancer Sci 2014;105:623–9.
105. Cooper WA, Lam DCL, O'Toole SA, Minna JD. Molecular biology of lung cancer. J Thorac Dis 2013;5Suppl 5:S479–90.
106. Paik PK, Arcila ME, Fara M, Sima CS, Miller VA, Kris MG, et al.Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. J Clin Oncol 2011;29:2046–51.
107. Go H, Jeon YK, Huh J, Choi SJ, Choi Y-D, Cha HJ, et al.Frequent detection of BRAF(V600E) mutations in histiocytic and dendritic cell neoplasms. Histopathology 2014;65:261–72.
108. Hodis E, Watson IR, Kryukov GV, Arold ST, Imielinski M, Theurillat J-P, et al.A landscape of driver mutations in melanoma. Cell 2012; 150:251–63.
109. Lohr JG, Stojanov P, Carter SL, Cruz-Gordillo P, Lawrence MS, Auclair D, et al.Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. Cancer Cell 2014;25:91–101.
110. Grisham RN, Iyer G, Garg K, DeLair D, Hyman DM, Zhou Q, et al.BRAF mutation is associated with early stage disease and improved outcome in patients with low-grade serous ovarian cancer. Cancer 2013;119: 548–54.
111. Bösmüller H, Fischer A, Pham DL, Fehm T, Capper D, Deimling von A, et al.Detection of the BRAF V600E mutation in serous ovarian tumors: a comparative analysis of immunohistochemistry with a mutation-specific monoclonal antibody and allele-specific PCR. Hum Pathol 2013;44:329–35.
112. Schultz NA, Roslind A, Christensen IJ, Horn T, Høgdall E, Pedersen LN, et al.Frequencies and prognostic role of KRAS and BRAF mutations in patients with localized pancreatic and ampullary adenocarcinomas. Pancreas 2012;41:759–66.
113. Schindler G, Capper D, Meyer J, Janzarik W, Omran H, Herold-Mende C, et al.Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. Acta Neuropathol 2011;121:397–405.
114. Xing M. BRAF mutation in thyroid cancer. Endocr Relat Cancer 2005; 12:245–62.
115. Zelboraf [package insert] [Internet]. 2011. Available from: http://www.gene.com/download/pdf/zelboraf_prescribing.pdf
116. Bollag G, Hirth P, Tsai J, Zhang J, Ibrahim PN, Cho H, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature . 2010;467:596–9.
117. Tafinlar [package insert] [Internet]. GlaxoSmithKline; 2013. Available from: https://www.gsksource.com/gskprm/htdocs/documents/TAFINLAR-PI-MG.PDF
118. Mekinist [package insert] [Internet]. 2014. Available from: https://www.gsksource.com/gskprm/htdocs/documents/MEKINIST-PI-PIL.PDF
119. Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov 2006;5:835–44.
120. Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer 2011;129:245–55.
121. Kitagawa D, Yokota K, Gouda M, Narumi Y, Ohmoto H, Nishiwaki E, et al. Activity-based kinase profiling of approved tyrosine kinase inhibitors. Genes Cells 2013;18:110–22.
122. Chen CR, Szwaya J, Lapierre JM, Ashwell MA, France DS. Abstract 3565: Abrogation of the paradoxical activation of the MAPK pathway following RAF inhibition by ARQ 680, a potent inhibitor of the RAF family of serine/threonine kinases. Cancer Res 71, 2011 (suppl; abstr 3565)
123. James J, Ruggeri B, Armstrong RC, Rowbottom MW, Jones-Bolin S, Gunawardane RN, et al.CEP-32496: a novel orally active BRAF(V600E) inhibitor with selective cellular and *in vivo* antitumor activity. Mol Cancer Ther 2012;11:930–41.
124. Stuart DD, Li N, Poon DJ, Aardalen K, Kaufman S, Merritt H, et al.Abstract 3790: preclinical profile of LGX818: a potent and selective RAF kinase inhibitor. Cancer Res 72, 2012 (suppl; abstr 3790).
125. Stuart D, Aardalen K, Venetsanakos E, Nagel T, Wallroth M, Batt D, et al.RAF265 is a potent Raf kinase inhibitor with selective antiproliferative activity *in vitro* and *in vivo*. Cancer Res 68, 2008 (suppl; abstr 4876).
126. Martinez-Garcia M, Banerji U, Albanell J, Bahleda R, Dolly S, Kraeber-Bodéré F, et al.First-in-human, phase I dose-escalation study of the safety, pharmacokinetics, and pharmacodynamics of RO5126766, a first-in-class dual MEK/RAF inhibitor in patients with solid tumors. Clin Cancer Res 2012;18:4806–19.
127. Tzoulis C, Schwarzlmüller T, Gjerde IO, Søfteland E, Neckelmann G, Biermann M, et al.Excellent response of intramedullary Erdheim-Chester disease to vemurafenib: a case report. BMC Res Notes 2015; 8:171.
128. Bubolz A-M, Weissinger SE, Stenzinger A, Arndt A, Steinestel K, Brüderlein S, et al.Potential clinical implications of BRAF mutations in histiocytic proliferations. Oncotarget 2014;5:4060–70.
129. del Bufalo F, Carai A, Figà-Talamanca L, Pettorini B, Mallucci C, Giangaspero F, et al.Response of recurrent BRAFV600E mutated ganglioglioma to Vemurafenib as single agent. J Transl Med 2014;12:356.
130. Vergote V, Dierickx D, Janssens A, Verhoef G, Tousseyn T, Vandenberghe P, et al.Rapid and complete hematological response of refractory hairy cell leukemia to the BRAF inhibitor dabrafenib. Ann Hematol 2014; 93:2087–9.
131. Follows GA, Sims H, Bloxham DM, Zenz T, Hopper MA, Liu H, et al.Rapid response of biallelic BRAF V600E mutated hairy cell leukaemia to low dose vemurafenib. Br J Haematol 2013;161:150–3.
132. Tiacci E, Park JH, De Carolis L, Chung SS, Broccoli A, Scott S, et al.Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. N Engl J Med 2015;373:1733–47.

133. Andrulis M, Lehners N, Capper D, Penzel R, Heining C, Huellein J, et al. Targeting the BRAF V600E mutation in multiple myeloma. Cancer Discov 2013;3:862–9.
134. Farley J, Brady WE, Vathipadiekal V, Lankes HA, Coleman R, Morgan MA, et al.Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. Lancet Oncol 2013;14:134–40.
135. Skrypek M, Foreman N, Guillaume D, Moertel C. Pilomyxoid astrocytoma treated successfully with vemurafenib. Pediatr Blood Cancer 2014;61:2099–100.
136. Lee EQ, Ruland S, LeBoeuf NR, Wen PY, Santagata S. Successful treatment of a progressive BRAF V600E-mutated anaplastic pleomorphic xanthoastrocytoma with vemurafenib monotherapy. J Clin Oncol 2014;: JCO.2013.51.1766.
137. Chamberlain MC. Salvage therapy with BRAF inhibitors for recurrent pleomorphic xanthoastrocytoma: a retrospective case series. J Neurooncol 2013;114:237–40.
138. Hayes DN, Lucas AS, Tanvetyanon T, Krzyzanowska MK, Chung CH, Murphy BA, et al.Phase II efficacy and pharmacogenomic study of Selumetinib (AZD6244; ARRY-142886) in iodine-131 refractory papillary thyroid carcinoma with or without follicular elements. Clin Cancer Res 2012;18:2056–65.
139. Wu H, Sun Y, Ye H, Yang S, Lee SL, las Morenas de A. Anaplastic thyroid cancer: outcome and the mutation/expression profiles of potential targets. Pathol Oncol Res 2015;21:695–701.
140. Hocar O, Le Cesne A, Berissi S, Terrier P, Bonvalot S, Vanel D, et al.Clear cell sarcoma (malignant melanoma) of soft parts: a clinicopathologic study of 52 cases. Dermatol Res Pract 2012;2012:984096–8.
141. Nardi V, Sadow PM, Juric D, Zhao D, Cosper AK, Bergethon K, et al. Detection of novel actionable genetic changes in salivary duct carcinoma helps direct patient treatment. Clin Cancer Res 2013;19:480–90.
142. Tabernero J, Chan E, Baselga J, Blay J-Y, Chau I, Hyman DM, et al.VE-BASKET, a Simon 2-stage adaptive design, phase II, histology-independent study in nonmelanoma solid tumors harboring BRAF V600 mutations (V600m): activity of vemurafenib (VEM) with or without cetuximab (CTX) in colorectal cancer (CRC). J Clin Oncol 32:5s, 2014(suppl; abstr 3518^).
143. Corcoran RB, Falchook GS, Infante JR, Hamid O, Messersmith WA, Kwak EL, et al.BRAF V600 mutant colorectal cancer (CRC) expansion cohort from the phase I/II clinical trial of BRAF inhibitor dabrafenib (GSK2118436) plus MEK inhibitor trametinib (GSK1120212). J Clin Oncol 30, 2012(suppl; abstr 3528).
144. Corcoran RB, Atreya CE, Falchook GS, Infante JR, Hamid O, Messersmith WA, et al.Phase 1-2 trial of the BRAF inhibitor dabrafenib (D) plus MEK inhibitor trametinib (T) in BRAF V600 mutant colorectal cancer (CRC): Updated efficacy and biomarker analysis. J Clin Oncol 32:5s, 2014(suppl; abstr 3517).
145. Bendell JC, Atreya CE, André T, Tabernero J, Gordon MS, Bernards R, et al. Efficacy and tolerability in an open-label phase I/II study of MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in combination in patients (pts) with BRAFV600E mutated colorectal cancer (CRC). J Clin Oncol 32:5s, 2014(suppl; abstr 3515).
146. Dienstmann R, Serpico D, Rodon J, Saura C, Macarulla T, Elez E, et al. Molecular profiling of patients with colorectal cancer and matched targeted therapy in phase I clinical trials. Mol Cancer Ther 2012;11:2062–71.