EXPERT OPINION

Long-term effects of BRAF inhibitors in melanoma treatment: friend or foe?

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The clinical development of selective BRAF inhibitors for metastatic *BRAF* V600 mutant melanoma patients has been a major breakthrough in targeted therapeutics. Objective response rates of approximately 50% have been observed in the Phase III studies of the BRAF inhibitors vemurafenib and dabrafenib. The side effects can be relatively common, including proliferative skin toxicities. The latter range from hyperkeratosis and keratoacanthomas (KAs) to squamous cell carcinomas (SCCs) and new primary melanomas. In addition, case reports on the emergence of gastric/colonic polyps and *RAS* mutant malignancies have been described during BRAF inhibitor therapy. These events have been attributed to paradoxical activation of the MAPK pathway in *BRAF* wild-type cells exposed to selective BRAF inhibitors in addition to increased RAS activity. Combined BRAF and MEK inhibition appears to improve clinical outcomes and reduce cutaneous proliferation events as fewer KAs and SCCs have been observed with combination therapy. Next-generation pan-RAF inhibitors ('paradox breakers') and ERK inhibitors may further enhance clinical activity in metastatic *BRAF*-mutant melanoma patients and mitigate this paradoxical oncogenesis. Further investigation into the potential long-term effects of selective BRAF inhibitors is warranted as expanded use of these agents is expected in patients with BRAF-mutant melanoma and other malignancies.

Keywords: BRAF, dabrafenib, MAPK, melanoma, paradoxical oncogenesis, vemurafenib

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1. BRAF in melanoma

Although *NRAS* mutations were first described in melanoma in 1984, the development of targeted therapy for metastatic melanoma truly gained its footing with the identification of activating mutations in *BRAF* in 2002 [1]. Mutations in exon 15 of the *BRAF* gene occur in 40 – 60% of cutaneous melanomas, with the most common being the V600E mutation [2]. This gain-of-function change leads to constitutive activation of the MAPK pathway (**Figure 1A**), resulting in increased cell growth, proliferation and invasiveness. Metastatic melanoma harboring *BRAF* mutations have been associated with worse overall survival prior to the development of targeted agents [2]. We have now seen the rapid development of selective BRAF and MEK inhibitors (BRAFi and MEKi, respectively) as targeted therapy for *BRAF* V600 mutant melanoma.

In the last 3 years, the US FDA has approved three targeted agents for metastatic *BRAF*-mutant melanoma patients (**Figure 1B**). Vemurafenib, a selective BRAF V600 mutant kinase inhibitor, was FDA approved in August 2011 based on the BRIM3 Phase III study showing improved clinical outcomes compared to dacarbazine [3]. The objective response rate for vemurafenib was 48%, with a median progression-free survival (mPFS) of 5.3 months and an overall survival of 84% after 6 months. A second BRAFi dabrafenib was FDA approved in May 2013 after the randomized Phase III trial (BREAK3) also confirmed superiority over dacarbazine.

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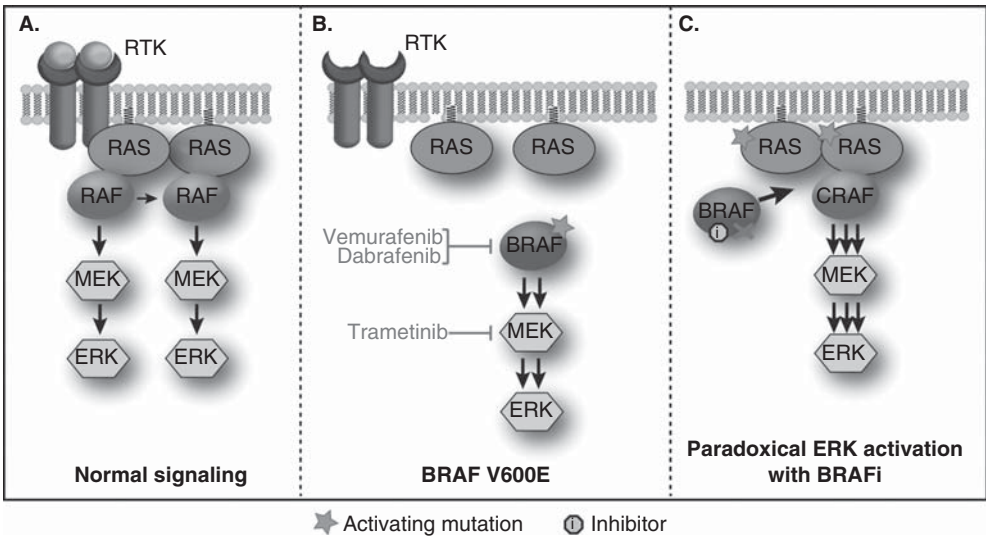

Figure 1. Activation of the MAPK pathway. A. During normal signaling conditions, the MAPK cascade is initiated through ligand-mediated activation of receptor tyrosine kinases. In this model, the binding of ligand to its cognate receptor leads to recruitment of RAS to the plasma membrane, the formation of RAF dimers, and ultimately downstream activation of MEK and ERK. **B.** Acquisition of mutations in BRAF at codon position 600 (V600E) leads to constitutive activation of the MAPK pathway that is not dependent on upstream RTK or RAS activity. The kinase inhibitors vemurafenib and dabrafenib target the mutant form of BRAF, and trametinib targets MEK. **C.** In cells with a wild-type BRAF and either upstream growth-factor–activated or mutated RAS, the inhibitor binds BRAF and promotes BRAF-CRAF dimer formation leading to paradoxical activation of MAPK through transactivation of the uninhibited CRAF protomer.

Dabrafenib yielded a response rate of 50%, with an mPFS of 5.1 months and an overall survival of 74% at 6 months [4]. Long-term follow-up for both studies have demonstrated mPFS over 6 months. More importantly, 26% of the patients are still alive 3 years after initiating treatment with BRAFi (vemurafenib), indicating that durable benefit is achieved in a subset of patients [5]. The third FDA-approved targeted agent is trametinib, an MEKi. However, a lower objective response rate (22%) and shorter mPFS were demonstrated with trametinib in the Phase III METRIC trial as compared to data for vemurafenib and dabrafenib, making a BRAFi the preferred single-agent *BRAF* V600 mutant melanoma targeted therapy [6].

While vemurafenib and dabrafenib both have demonstrated clinical benefit, treatment-related adverse events are relatively common. In patients treated with vemurafenib on BRIM3, 38% required a dose reduction because of short-term side effects; 28% of patients treated with dabrafenib on BREAK3 required a dose reduction [3,4]. Most of these toxicities are tolerable and reversible. However, concern has arisen over an increase in proliferation events, most notably squamous cell carcinomas (SCCs), keratoacanthomas (KAs) and melanomas *de novo* [7].

2. Paradoxical toxicities of selective BRAF inhibitors

Most targeted agents would be expected to have a suppressive effect (or null effect) on pathway signaling in cellular processes regardless of the genetic composition. A paradoxical effect has been observed with selective BRAF V600E mutant kinase inhibitors, where exposure to these drugs can lead to MAPK pathway activation in *BRAF* wild-type and low-activity *BRAF*-mutant cells [7]. The underlying mechanisms of paradoxical MAPK activation have been attributed to promotion of wild-type BRAF and CRAF dimerization and transactivation of the noninhibited RAF protein leading to subsequent MAPK pathway activation (**Figure 1C**). This process also appears to be dependent on upstream RAS signaling, such as through receptor tyrosine kinase activation and oncogenic *RAS* mutations. The paradoxical MAPK activation with selective BRAFi is believed to be involved in the proliferative events (paradoxical oncogenesis) seen during vemurafenib and dabrafenib treatment.

2.1 Cutaneous

In the BRIM3 study of vemurafenib, 199 grade 2 – 3 cutaneous adverse events were reported in 336 patients [3]. Similarly, a high number of cutaneous side effects were reported in the BREAK3 study of dabrafenib (52 grade 2 – 3 cutaneous events in 187 patients) [4]. While many of these toxicities included rash, alopecia, pruritus and hyperkeratosis, other more concerning proliferative toxicities were seen. With vemurafenib, SCCs and KAs occurred in 12 and 8% of patients, respectively [3,8]. With dabrafenib, SCCs or KAs occurred in 6% of patients [4]. Moreover, verrucal keratoses have been reported in up to 49% of patients on dabrafenib in an Australian series [9]. The vast majority of SCCs occur

in chronically sun-damaged skin. Histologically, the SCCs tend to be well-differentiated lesions [9].

The mean time to diagnosis of the first cutaneous SCC/KA is 8 – 10 weeks, although lesions appear as early as 3 weeks [9]. This short time lapse suggests that selective BRAFi may not have direct carcinogenic effects, but instead may potentiate preexisting initiating oncogenic events. In approximately 60% of cases, *RAS* mutations have been identified (predominately *HRAS*) [8]. Both SCCs and KAs can be treated by simple excision or cryotherapy. Occasionally, the distribution of these lesions can be quite extensive, but so far, no cases of metastases have been reported. Although less common, another proliferative skin disorder reported in patients on BRAFi is the occurrence of new melanocytic nevi and melanoma, commonly having a wild-type *BRAF* status [9]. The long-term consequences of these proliferative events remain unclear. The time to development of cutaneous lesions can be delayed as late as 25 weeks and tends to continue during the course of therapy [10].

2.2 Gastrointestinal

Apart from diarrhea, nausea and vomiting, which are the most frequently reported side effects after cutaneous toxicities, the development of colonic and gastric polyps has been reported in patients receiving vemurafenib. In the Phase I trial of vemurafenib, four out of eight long-term responders (> 2 years) underwent endoscopic analysis; three of these patients harbored multiple colonic adenomas and/or gastric polyps, an uncommonly high ratio [11]. One of these patients presented with a gastrointestinal bleed and was found to have 11 colonic and gastric polyps and a bleeding duodenal ulcer; he had an unrevealing endoscopy just 5 months before starting vemurafenib. The majority of the lesions sequenced harbored mutations in the *APC* tumor suppressor gene, which is known to be associated with sporadic and hereditary colorectal cancer. This is an unsettling finding since some evidence suggests that APC loss and MAPK signaling are required for the development of colorectal carcinoma in mouse models [7].

Furthermore, a case of recurrent *KRAS* mutant colon cancer has been reported in a patient during treatment with dabrafenib plus trametinib therapy for metastatic *BRAF*-mutant melanoma [12]. Prior to his melanoma diagnosis, he underwent resection of localized colon cancer. His melanoma responded to BRAFi/MEKi therapy; however, after 12 weeks, an isolated brain lesion developed. After resection of this brain metastasis, pathology confirmed that it was a recurrence of his prior colon cancer. Cell lines derived from this *KRAS* mutant adenocarcinoma brain metastasis showed sensitivity to trametinib, whereas dabrafenib increased cell proliferation. After a temporary hold of drugs in this patient, single agent dabrafenib was restarted. Despite showing response in his melanoma disease, he experienced a rise in CEA levels, new pleural disease and a second brain metastasis confirmed to be colon adenocarcinoma.

2.3 Other proliferative disorders

The proliferative effects of paradoxical MAPK activation are not restricted to skin and gastrointestinal tract. The emergence of other types of malignancies has been described, such as *RAS* mutant leukemia, where vemurafenib was stimulating the growth of preexisting *NRAS* mutant chronic myelomonocytic leukemia cells by causing hyperactivation of ERK, after a mere 11 days of treatment [7].

3. Expert opinion

The field of BRAF targeted therapy is rapidly evolving. While the main goal is to increase clinical efficacy and duration of response, we will hopefully also see a reduction in paradoxical MAPK activation and secondary malignancies. One such strategy is the combination of BRAF and MEK inhibitors. The rationale is based on the reactivation of the MAPK pathway that occurs at time of BRAFi resistance. Indeed, the Phase I/II study of dabrafenib plus trametinib in metastatic BRAF V600 mutant melanoma demonstrated a higher objective response rate and longer mPFS with the combination; a Phase III study of dabrafenib plus trametinib versus dabrafenib plus placebo is ongoing [13]. The addition of MEKi also appears to reduce paradoxical MAPK activation, as the incidence of SCCs was 19% in the dabrafenib only cohort and 7% in the dabrafenib plus trametinib cohorts. However, the addition of MEKi can increase the risk of other side effects. MEKis are associated with peripheral edema, hypertension, decreased cardiac ejection fraction, and ocular events. Combination therapy does not fully prevent the development of secondary malignancies, but it does dramatically lower the prevalence of SCCs from 19% for dabrafenib alone to 2 – 7% in combination with trametinib [6].

Perhaps the new generation of MAPK pathway inhibitors will overcome the paradoxical MAPK activation seen with selective BRAFi. These include RAF kinase inhibitors with more potent inhibition of all RAF isoforms, called paradox breakers. An example is the development of TAK-632, which suppresses RAF activity in BRAF wild-type cell with minimal paradoxical MAPK activation and has potent activity in BRAF-mutant melanoma cell lines [14]. ERK inhibitors are also being developed as single agents and in combination with BRAFi, which may also increase antitumor activity and eliminate paradoxical oncogenesis [15].

As of yet, no trials have been conducted to specifically investigate the consequences of long-term BRAFi therapy. With emerging data on secondary cancers and more widespread use of BRAFi in patients with *BRAF*-mutant melanoma and other malignancies, this will be an important concept to address. While no firm guidelines exist, we recommend close follow-up by a dermatologist after commencing BRAF targeted therapy. Since BRAFi treatment seems to provoke previous existing or dormant *RAS* mutant cancers, caution is warranted in the treatment of patients

with a history of such malignancies. Once more data on the emergence of colonic and gastric polyps is available, the role of endoscopic screening can be better addressed. Identification of these paradoxical effects and toxicities will be necessary for the clinician to recognize and for future research development.

Declaration of interest

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