

## Targeted Molecular Therapies in Cutaneous Oncology: Ammunition Not Without Some Backfire

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There have been notable advances in the management of advanced cutaneous malignancies over the last 18 months. With the advent of targeted molecular therapies, clinicians are able to target inoperable tumors by manipulating specific biomolecular machinery, rendering the current treatment options for metastatic as well as advanced melanomas and nonmelanoma skin cancers (NMSCs) obsolete. As the incidence and prevalence of melanoma and NMSCs continue to rise,<sup>1</sup> the number of advanced or unresectable cases has also increased. Furthermore, as solid organ transplantation and long-term immunosuppressive medications become more common, increasing numbers of aggressive cutaneous malignancies have been reported.<sup>2</sup>

According to the National Cancer Institute, 76,250 individuals were diagnosed with cutaneous melanoma in 2012, with 9180 patients dying from their disease.<sup>3</sup> Until recently, therapeutic options for patients with stage III or IV melanoma were limited to treatment with dacarbazine and interferon, which have been associated with low cure rates.<sup>4,5</sup> Not surprisingly, the median survival rate for patients with metastatic melanoma is 6 to 10 months.<sup>6</sup>

In March 2011, the US Food and Drug Administration (FDA) approved ipilimumab (Yervoy, Bristol-Myers Squibb Company), a human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen 4, to treat unresectable or metastatic melanoma. In one study, administration of ipilimumab resulted in a median overall survival of 10.1 months and a 12-month overall survival rate of 45.6%.<sup>7</sup> In August 2011, the FDA approved vemurafenib (Zelboraf, Genentech USA, Inc) for treatment of unresectable or metastatic melanoma containing a V600E-mutated BRAF protein.<sup>8</sup> The response rate was 53% with a median overall survival of 16 months.<sup>9</sup>

Both drugs have shown promise in treating patients whose prognosis was otherwise bleak; however, both have toxicities that limit their widespread application.

Because of its unregulated activation of T cells and the immune system, ipilimumab has been associated with grade 3 or higher immune-related adverse events in 10% to 26% of patients, some of which were fatal.<sup>10,11</sup> The most common serious events included immune-related enterocolitis; hepatitis; dermatitis, including toxic epidermal necrolysis; and endocrinopathy.<sup>12</sup> More concerning is that such events have occurred weeks to months after treatment cessation,<sup>12</sup> making it possible for patients to present to their dermatologists with these concerns at a later date.

Vemurafenib has been associated with similar side effects, some considerable enough to require dose modifications or even treatment cessation.<sup>4</sup> One of the most concerning side effects has been the development of cutaneous squamous cell carcinomas (SCCs) and keratoacanthomas (KAs) in 15% to 30% of treated patients. Lesions typically arose after 8 to 12 weeks of therapy but sometimes appeared later.<sup>8</sup> Preclinical models have shown that BRAF inhibitors paradoxically may enhance mitogen-activated protein kinase (MAPK) pathway activation in cancer cells with *ras* mutations; further inhibition of the MAPK pathway is required to block this effect.<sup>13</sup> Trials currently are underway to evaluate the coadministration of BRAF and MEK inhibitors, which show promise in preventing SCC and KA formation.<sup>14</sup> Although most SCCs and KAs in patients treated with vemurafenib are successfully treated with local excision, the rapid development of the tumors as well as substantial tumor burden or development of squamous proliferations at noncutaneous sites from prolonged therapy are valid concerns. Changing nevi also have been noted in patients taking vemurafenib.<sup>15</sup> These patients therefore require frequent and close examination of the skin by medical oncologists and dermatologists.

There also has been an increase in available treatment options for advanced and unresectable NMSCs. In January 2012, vismodegib (Erivedge, Genentech USA, Inc) was approved by the FDA for treatment of advanced and unresectable basal cell carcinoma.<sup>16</sup> In initial trials of vismodegib, the response rate was 30% for metastatic disease and 43% for locally advanced disease.<sup>14</sup> Although these results are impressive, the frequent and life-altering side effects associated with

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this drug also are notable. Fifty-one percent to 68% of patients experienced alopecia, dysgeusia, and muscle spasms, which can limit a patient's ability to tolerate treatment. Furthermore, 25% of patients experienced serious or life-threatening side effects, with 7 unaccountable deaths reported.<sup>14</sup> These side effects must be discussed at length with the patient, especially because cessation of therapy can lead to more rapid tumor recurrence, as vemurafenib appears to produce tumor quiescence rather than apoptosis.<sup>17</sup> Thus the patient and the clinician must be vigilant after treatment.

Advanced, unresectable, and metastatic cutaneous SCCs recently have been treated with cetuximab (Erbix, Bristol-Myers Squibb Company) with promising results. When treated with cetuximab, 69% of patients with unresectable SCCs demonstrated disease control after 6 weeks of therapy.<sup>18</sup> Acneiform eruptions were well documented in up to 80% of patients, with greater responses correlating with worsening rash.<sup>16</sup> Cetuximab also may cause severe side effects and comes with a black-box warning that cites a 3% incidence of serious infusion reactions and a 2% incidence of cardiopulmonary arrest and/or sudden death.<sup>19</sup> In the phase 2 trial (N=36), 2 participants developed grade 4 infusion reactions and 1 had grade 3 interstitial pneumopathy.<sup>18</sup> Thus clinicians must be cognizant of the rare but serious risks associated with cetuximab treatment as well as patient comorbidities.

Although the need for new therapies for advanced cutaneous malignancies has never been greater, clinicians should not rush to implement new treatments without being aware of the potential for adverse events. In our desire to use our new tools to help our patients, we must not forget that our role as physicians is first to do no harm.

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