

# Successful dabrafenib transition after vemurafenib-induced toxic epidermal necrolysis in a patient with metastatic melanoma



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## INTRODUCTION

Vemurafenib improves survival in advanced metastatic melanoma, but has rarely been associated with severe skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).<sup>1,2</sup> Dabrafenib is a BRAF inhibitor that shares a sulfonamide moiety with vemurafenib, and only one prior report documents a switch to dabrafenib after the development of SJS/TEN with vemurafenib.<sup>2,3</sup> We report a case of vemurafenib-induced TEN followed by successful transition to full-dose therapy with dabrafenib in a patient with metastatic melanoma.

## CASE REPORT

A 47-year old white woman with no known allergies being treated for metastatic melanoma with cobimetinib, 200 mg daily, plus vemurafenib, 960 mg (coBRIM) twice daily for 13 days, was admitted to the hospital with a worsening rash and multiorgan system failure. Erythematous, tender patches began on the trunk and progressed to the extremities with significant crusting and erosions on the lips and vulva. A dermatology consult confirmed TEN clinically and histologically. After discontinuing

### Abbreviations used:

coBRIM:	combined cobimetinib and vemurafenib therapy
LTT:	lymphocyte transformation test
NO:	nitric oxide
RIP3:	receptor-interacting protein kinase 3
SJS:	Stevens-Johnson syndrome
TEN:	toxic epidermal necrolysis

all medications, the diagnosis of vemurafenib-induced TEN was established. Despite immediate drug withdrawal, she continued to slowly progress with large bullae and edema in the lower extremities. Her fluid balance remained neutral and creatinine stable. Bullae were drained, and petrolatum gauze was applied to denuded skin. On day 5, her lower extremity wounds started to emit an odor, and cultures confirmed *Pseudomonas*. The infectious disease department recommended empiric antibiotics and she received dilute bleach water baths daily. Her wounds and odor improved over the next 24 hours, and she remained afebrile with a normal white count. She was discharged after 2 weeks without complications.

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Before coBRIM therapy, the patient was diagnosed with brain metastasis with a left, lower eyelid primary tumor. Her initial treatment consisted of surgical resection, radiation, and ipilimumab, which was later switched to nivolumab because of disease progression. Despite 6 months of therapy, her disease progressed, which led to coBRIM therapy and subsequent TEN. After resolution of TEN, positron emission tomography/computed tomography scan found improvement of axillary lymph nodes and mesenteric mass. The improvement was likely caused by drug response, but the dramatic improvement led to speculation about a possible antitumor response generated by the TEN. Because of this improvement, the patient elected for active surveillance over clinical trials.

Two months later, the patient exhibited increased lymph node involvement indicating progressive disease. Because of the patient's wish to avoid surgery and the lengthy washout period after prior immunotherapy required by available investigational combination therapy studies, she was started on ipilimumab. Considering the patient's response to previous BRAF inhibitor therapy and continued advancement of disease, it was mutually decided that the greater benefits of therapy outweighed the potential risk of TEN.

Allergists were consulted and recommended against lymphocyte transformation test (LTT) given the low sensitivity. Additionally, a positive LTT may not have precluded treatment, as the patient expressed a desire to attempt gradual dose escalation even with understanding that BRAF inhibitor therapy may result in potentially fatal TEN.

Given the limited options, we proceeded with gradual dose escalation of dabrafenib and close monitoring in combination with trametinib and corticosteroids to prevent recurrent TEN (Table I). Within a week, she had dramatic response of her right axillary lymphadenopathy and greatly decreased discomfort.

The patient's disease remained stable, and she had minimal side effects on therapy; however, her right axillary disease once again started to progress after 2 months of treatment. Although the development of resistant disease might have been spontaneous, gradual dose escalation may have contributed to the development of a resistant clone.

## DISCUSSION

Vemurafenib targets the oncogenic mutation *BRAF*<sup>V600E</sup>, which drives the MAPK/ERK signaling pathway stimulating cellular proliferation, differentiation, and survival.<sup>4</sup> *BRAF* mutations are found in 40% to 60% of melanomas, although vemurafenib is associated with improved survival in melanoma irrespective of mutation.<sup>1</sup>

The patient's medications at the time included omeprazole and Zyrtec daily, which she had been taking for years, in addition to Zofran and acetaminophen or ibuprofen when needed. Given the patient's previous exposure to all of these medications, no new medications having been administered besides coBRIM therapy, the reaction soon after coBRIM therapy, and the documented history of SJS/TEN with sulfonamide drugs, we suspected vemurafenib-induced TEN. Additionally, SJS/TEN-type toxicity is seen in BRAF inhibitor monotherapy, but this reaction is decreased when MEK inhibitors, such as cobimetinib in coBRIM, are used in combination therapy.<sup>5</sup>

Grade I-II dermatologic side effects are commonly seen with BRAF inhibitor use, but severe reactions to therapy such as SJS/TEN are more rarely described.<sup>6</sup> Overcoming vemurafenib-induced SJS/TEN has been reported twice before; desensitization and treatment with a lower dose of vemurafenib and switching to an alternate BRAF inhibitor have been documented.<sup>3,7</sup> Our dose escalation after switching to dabrafenib differs from the previous reported switch, as we administered prednisone concurrently.<sup>3</sup>

LTT has been used since the 1970s for identifying particular drugs in drug hypersensitivity reactions and is currently accepted as the best diagnostic assay for severe cutaneous drug reactions.<sup>8</sup> The test is performed by isolating a patient's peripheral mononuclear cells and plating them with buffer and AB-serum or autologous plasma; the pure form of a drug is added to the cell culture, and subsequent cell proliferation is measured on a dose-response curve by methods such as radio-labeled thymidine uptake and flow cytometry.<sup>9</sup> Unfortunately, although LTT has a high specificity (98%-99%), it has a considerably low sensitivity of 20% to 48% depending on the drug assayed, with sulfa drugs on the lowest end of the spectrum.<sup>8</sup> Tang et al<sup>10</sup> described markedly decreased sensitivity of LTT after the first week of recovery; however, Kano et al<sup>11</sup> found a low sensitivity regardless of when LTT is performed. Thus, LTT was not deemed beneficial in this patient's case before dabrafenib therapy.

Interestingly, LTT assay exhibits cross-reactivity between vemurafenib, dabrafenib, and sulfamethoxazole, yet no cases of dabrafenib-induced TEN have been reported to date.<sup>2,12</sup> Structurally, dabrafenib shares the same sulfonamide functional group as vemurafenib and other sulfonamides predisposing to TEN. Unlike vemurafenib, however, dabrafenib may possess a unique TEN-protective profile due to its strong inhibition of receptor-interacting protein kinase (RIP3). RIP3-dependent

**Table I.** Dose escalation of dabrafenib

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Wk 1	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)
	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Wk 2	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)
	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Wk 3	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)
	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Wk 4	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)
	Day 29	Day 30	Day 31	Day 32	Day 33	Day 34	Day 35
Wk 5	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)
	Day 36	Day 37	Day 38	Day 39	Day 40	Day 41	Day 42
Wk 6	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)
	Day 43	Day 44	Day 45	Day 46	Day 47	Day 48	Day 49
Wk 7	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)
	Day 50	Day 51	Day 52	Day 53	Day 54	Day 55	Day 56
Wk 8	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg) Dabr (75 mg)
	Day 57	Day 58	Day 59	Day 60	Day 61	Day 62	Day 63
Wk 9	Tram (2 mg) Pred (30 mg) Dabr (75 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)
	Day 64	Day 65	Day 66	Day 67	Day 68	Day 69	Day 70
Wk 10	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)
	Day 71	Day 72	Day 73	Day 74	Day 75	Day 76	Day 77
Wk 11	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg)
	Day 78	Day 79	Day 80	Day 81	Day 82	Day 83	Day 84
Wk 12	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)
	Day 85	Day 86	Day 87	Day 88	Day 89	Day 90	Day 91
Wk 13	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg) Dabr (150 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg)

Continued

**Table I.** Cont'd

	Day 92	Day 93	Day 94	Day 95	Day 96	Day 97	Day 98
Wk 14	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg)
	Day 99	Day 100	Day 101	Day 102	Day 103	Day 104	Day 105
Wk 15	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)
	Day 106	Day 107	Day 108	Day 109	Day 110	Day 111	Day 112
Wk 16	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)
	Day 113	Day 114	Day 115	Day 116	Day 117	Day 118	Day 119
Wk 17	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)	Tram (2 mg) Pred (30 mg) Dabr (300 mg)		

Dabr, Dabrafenib; Pred, prednisone; Tram, trametinib.

phosphorylation leads to a potent mechanism of inflammatory disease pathogenesis via activation of pore-forming proteins and disruption of membrane integrity.<sup>13</sup> Programmed necrosis mediated by tumor necrosis factor (TNF)- $\alpha$  and nitric oxide (NO) is potentiated by high RIP levels; TNF- $\alpha$ , NO, and RIP3 are found in abundance in TEN.<sup>14</sup> Importantly, dabrafenib directly inhibits RIP3 kinase activity, in addition to TNF- $\alpha$  and NO-induced necroptosis of keratinocytes.<sup>14,15</sup>

Dabrafenib may be an appropriate first-line agent in patients with an indication for BRAF inhibitor therapy, especially in the setting of sulfonamide hypersensitivity. Working around life-threatening mucocutaneous reactions by means other than medication withdrawal is possible in patients on otherwise life-saving BRAF inhibitor therapy. No standard protocol exists in such cases, and we thus describe successful administration of dabrafenib after vemurafenib-induced TEN.

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