

# BRAF/MEK inhibitor hypersensitivity reactions can mimic severe cutaneous adverse reactions: a single center study

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## 1. Introduction

- BRAF inhibitors (BRAFI) – vemurafenib, dabrafenib, and encorafenib - are targeted therapy for BRAF-positive tumors that target the MEK/ERK signaling pathway
  - Indications include melanoma, papillary thyroid cancer, colorectal cancer, etc.
- MEK inhibitors (MEKI) are often concurrently administered with BRAFI to improve therapeutic efficacy and reduce incidence of cutaneous adverse events
- Cutaneous toxicities due to BRAFI therapy are common and can disrupt treatment
- These eruptions can be associated with skin pain, liver enzyme elevation, and fever and may mimic severe cutaneous adverse reactions (SCARs)
- The discussion of managing patients with severe cutaneous reactions is currently limited and suggests referral to dermatology as a primary strategy<sup>1</sup>
- We aimed to characterize and describe the management of BRAFI-induced skin toxicities, focusing on hypersensitivity reactions*

## 2. Methods

- Single center, IRB-approved retrospective cohort study
- Patients were identified through EPIC SlicerDicer based on BRAFI exposure from January 2012 – August 2023 and chart review was conducted
- The Common Terminology Criteria for Adverse Events (CTCAE) was used to retrospectively grade adverse events based on clinical features if a grade was not already recorded in the patient chart
- RegiSCAR was used to score severe reactions to determine if they met criteria for a SCAR
- Fisher's Exact Test was used to statistically analyze data

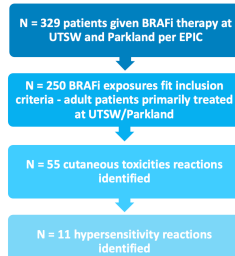


Figure 1: Cohort Selection for Chart Review

## 3. Results

### 3.1 Incidence and Distribution of Cutaneous Toxicities

- 55 cutaneous toxicities/250 BRAFI exposures (22%) were recorded
  - Most common reactions include warts (13), hypersensitivity reactions (11), actinic keratoses (11), basal cell carcinoma (8), melanoma (6), and keratoacanthoma (6)
- Vemurafenib had the highest rate of hypersensitivity rashes (6 hypersensitivity/39 vemurafenib patients, 15%), while encorafenib had the lowest (0 hypersensitivity/51 encorafenib patients)
  - Statistically significant relationship between BRAFI agent and development of hypersensitivity,  $p = 0.0035$*
- Encorafenib had the highest rate of non-hypersensitivity cutaneous reactions (16 non-hypersensitivity reactions/51 encorafenib patients, 31%)
  - Statistically significant relationship between BRAFI agent and development of non-hypersensitivity cutaneous reactions,  $p = 0.019$*
- These results indicate that cutaneous toxicities may be drug and dose specific

### Distribution of Cutaneous Toxicities

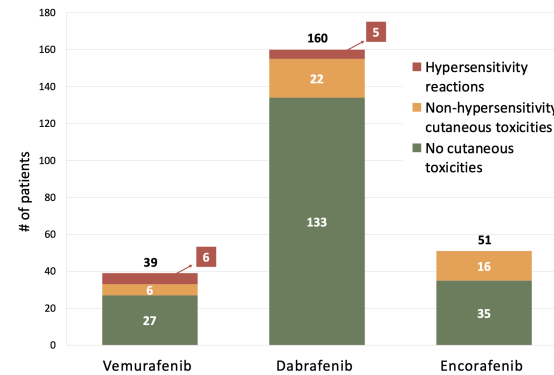


Figure 2: Incidence of cutaneous toxicities and hypersensitivity reactions across all BRAFI

### 3.2 Hypersensitivity Reactions

- 11 hypersensitivity reactions/55 cutaneous toxicities (20%) were identified
  - No patients met RegiSCAR criteria. 1 met clinical criteria for AGEP
- Hypersensitivity reactions did not predict future cutaneous toxicities, as no patient developed subsequent cutaneous reactions*

Table 1: Description of Cutaneous Hypersensitivity Reactions

ID	Severity	BRAFI/MEKI	Time of onset (days)	RegiSCAR Score
1	Grade 2 rash with eosinophilia	Dabrafenib and trametinib	10	-1
2	Grade 3 morbilliform drug eruption with fever and LFT elevation	Dabrafenib and trametinib	36	-1
3	Grade 1 rash with nausea	Dabrafenib and trametinib	41	-3
4	Grade 1 rash with fever	Dabrafenib and trametinib	28	-1
5	Grade 3 morbilliform drug eruption with fever	Dabrafenib and trametinib	54	0
6	Grade 3 rash	Vemurafenib and cobimetinib	10	0
7	Grade 3 rash	Vemurafenib monotherapy	5	-2
8	Grade 3 rash with fever	Vemurafenib monotherapy	6	0
9	Grade 3 hypersensitivity reaction with diarrhea, nausea, fever, head to toe rash, swelling in face and hands	Vemurafenib monotherapy	8	0
10	Grade 3 rash	Vemurafenib and cobimetinib	26	-1
11	Grade 3 acute generalized exanthematous pustulosis (AGEP) with fever	Vemurafenib monotherapy	7	0

### 3.3 Dose Limiting Reactions

- Hypersensitivity reactions were more dose limiting than other cutaneous toxicities* (9 dose limiting reactions/11 hypersensitivity patients vs. 7 dose limiting reactions/44 non-hypersensitivity reactions),  $p=0.00007$
- One patient successfully switched BRAFI agents without recurrence of reaction

Table 2: Dose Limiting Reactions among Non-Hypersensitivity Cutaneous Reactions

	Non-dose limiting reactions	Dose interruption	Dose modification	BRAFI stopped	Switched BRAFI agents
Vemurafenib	5	1	0	0	0
Dabrafenib	19	1	1	1	0
Encorafenib	13	1	2	0	0

Table 3: Dose Limiting Reactions among Hypersensitivity Reactions

	Non-dose limiting reactions	Dose interruption	Dose modification	BRAFI stopped	Switched BRAFI agents
Vemurafenib	0	2	2	1	1
Dabrafenib	2	0	2	1	0
Encorafenib	0	0	0	0	0

## 4. Discussion

- BRAFI hypersensitivity eruptions were a greater source of dose-limiting toxicity than squamoproliferative lesions in our cohort
- Hypersensitivity-like eruptions may sometimes mimic SCARs, but do not always necessitate stopping BRAFI therapy
- 8/11 hypersensitivity reactions in this cohort were Grade 3 based on CTCAE criteria, but none met RegiSCAR criteria
- Our findings show that the RegiSCAR scoring system is a useful tool for clinicians to use to differentiate hypersensitivity reactions from SCARs*
- Patients in our cohort tolerated dose modification or switching BRAFI agents to manage severe cutaneous toxicities*
  - This finding concurs with prior reports suggesting these same strategies<sup>2-3</sup>

## 5. Conclusion

- Given that BRAFI tend to be a late-line therapy option, it is critical that clinicians are familiar with BRAFI induced rashes, especially hypersensitivity reactions that may mimic SCARs
- Trialing a different BRAFI in these patients may allow patients to remain on critical cancer therapy

## References

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**Introduction:** BRAF inhibitors (BRAFi) - vemurafenib, dabrafenib, and encorafenib - are targeted therapy for BRAF-positive tumors like melanoma, thyroid cancer, and colon cancer among others. Cutaneous toxicities such as warts, squamous cell carcinoma, and rash are common and may disrupt treatment. We aimed to characterize BRAFi-induced skin toxicities, focusing on hypersensitivity reactions. These eruptions can be associated with skin pain, liver enzyme elevation, and fever and may mimic severe cutaneous adverse reactions (SCARs).

**Methods:** This study was approved by the UTSW Institutional Review Board. Epic SlicerDicer was used to identify all patients exposed to BRAFi therapy from Jan 2012 - Aug 2023 at UTSW and Parkland Hospital. Charts were individually reviewed to categorize skin toxicities and analyzed with Fisher's exact test.

**Results:** 236 patients were identified for this study. 53/236 (23%) developed any cutaneous reaction, with varying rates across BRAFi. 16/53 reactions were dose limiting, resulting in a therapy break (5/16), dose reduction (7/16), or drug cessation (4/16). Of all BRAFi, vemurafenib had the greatest rate of patients who developed dose-limiting reactions out of all patients exposed to the drug (7/39, 18%,  $p = 0.0078$ ).

12/236 patients specifically developed a BRAFi hypersensitivity rash. Morphologies varied from tender pink patches to fulminant, whole-body eruptions. Hypersensitivity reactions were more dose limiting than other skin toxicities (9/12, 75%,  $p = 0.00069$ ). Vemurafenib had the highest rate of hypersensitivity rashes (6/39, 15%,  $p = 0.0035$ ), while encorafenib had the lowest (0/51). Encorafenib, however, had the highest rate of non-hypersensitivity cutaneous reactions (16/51, 31%,  $p = 0.015$ ). We found that while 8/12 hypersensitivity cases resembled SCARs, the RegiSCAR scoring system could effectively differentiate these reactions. 4/12 patients had dose reduction and continued on therapy. One patient with a Grade 3 reaction switched to an alternative BRAFi which was tolerated.

**Conclusion:** Recognizing the distinct morphology and presentation of BRAFi hypersensitivity reactions is important. Reactions may be drug and dose specific. Unfamiliarity with these eruptions could lead to preemptive termination of critical cancer therapy.