COMMUNITY COLLABORATION

Identifying and Mitigating Adverse Events Associated With BRAF Inhibitor–Based Treatment

- *BRAF* V600 mutations occur in approximately 8% of metastatic colorectal cancer (mCRC)[1] and in 1% to 3% of metastatic non-small-cell lung cancer (mNSCLC) cases.[2]
- BRAF inhibitor–based regimens are established targeted therapy standards in mCRC and mNSCLC.
  - National guidelines include encorafenib (a BRAF inhibitor) plus cetuximab (an EGFR inhibitor), with chemotherapy (including mFOLFOX6), as a preferred first-line targeted therapy option for patients with *BRAF* V600E–mutant mCRC.[3]
  - Combinations of BRAF inhibitors (dabrafenib or encorafenib) with MEK inhibitors (trametinib or binimetinib) are listed in national guidelines as standard targeted therapy options for patients with *BRAF* V600E–mutant mNSCLC.[4]

Adverse Event Profile of BRAF Inhibitor–Based Regimens in mCRC and mNSCLC[5-8]

- Each BRAF inhibitor–based combination has characteristic toxicities that can guide monitoring and supportive care

Regimen	Trial	Most Common Adverse Events (Any Grade Incidence)		Most Common Grade 3/4 Adverse Events*
Encorafenib + cetuximab (mCRC)	BEACON	• Fatigue (51%) • Nausea (34%) • Diarrhea (33%) • Acneiform dermatitis (32%) • Abdominal pain (30%)	• Arthralgia (27%) • Appetite dec. (27) • Rash (26%) • Vomiting (21%) • Headache (20%)	• Fatigue (7%) • Lymphopenia (7%) • Abdominal pain (4%) • Anemia (4%) • Alk. phosph. inc. (4%)
Encorafenib + cetuximab + mFOLFOX6 (mCRC)	BREAKWATER	• Peripheral neuropathy (64%) • Nausea (54%) • Fatigue (53%) • Diarrhea (42%) • Vomiting (36%)	• Rash (36%) • Hemorrhage (34%) • Arthralgia (32%) • Abdominal pain (32%) • Pyrexia (29%)	• Neutropenia (37%) • Lipase inc. (53%) • Peripheral neuropathy (19%) • Hgb inc. (19%)
Encorafenib + binimetinib (mNSCLC)	PHAROS	• Fatigue (61%) • Nausea (58%) • Diarrhea (52%) • Myalgia (48%) • Vomiting (37%)	• Abdominal pain (32%) • Visual impairment (29%) • Rash (27%) • Dyspnea (27%) • Constipation (27%)	• Lipase inc. (14%) • Anemia (11%) • Hyponatremia (11%) • AST/ALT inc. (10%/9%) • Fatigue/dyspnea (8%)
Dabrafenib + trametinib (mNSCLC)	BRF113928	• Pyrexia/chills (55%) • Fatigue (51%) • Nausea (45%) • Vomiting (33%) • Diarrhea (32%)	• Dry skin (31%) • Appetite dec. (29%) • Edema (28%) • Rash (28%) • Hemorrhage (23%)	• Hyponatremia (17%) • Lymphopenia (14%) • Anemia (10%) • Hyperglycemia (9%) • Leukopenia/neutropenia (8%)

Refer to the prescribing information and guidelines for complete safety and management details.

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Key Adverse Events: Timing, Presentation, and Collaborative Management[5-8]

- Most adverse events are reversible and manageable in the community setting; routine monitoring and early recognition support timely intervention, including supportive care, treatment interruption, or dose adjustment when needed.
- Clear guidance on when to escalate care can support shared management between community oncologists and academic centers for complex or severe toxicities.

AE	Management Considerations

Dermatologic	• Prophylaxis: sunscreen + emollients; consider doxycycline/minocycline (first 6–8 wk)
	• Management:
	  ○ Grade 1/2: topical steroids + clindamycin
	  ▪ For grade 2, for encorafenib, if no improvement in 2 wk, withhold until grade 0/1 and then resume at same dose; for dabrafenib, if intolerable, withhold up to 3 wk, if improvement noted, resume at lower dose
	  ○ Grade 3: oral antibiotics, dermatology consult
	  ▪ For encorafenib, withhold until grade 0/1, and then resume at same dose if first occurrence or reduce dose if recurrent; for dabrafenib, as with grade 2

Gastrointestinal	• Diarrhea: loperamide, rule out infection, aggressive hydration • Nausea: scheduled 5-HT3 antagonist; consider taking with food
Ocular	• No routine exams unless symptomatic • If symptoms, urgent ophthalmology referral
Cardiac	• QTc monitoring (encorafenib) • Baseline and periodic ECG

Guidance shown is informational and not a substitute for clinical judgment or prescribing information. Consider subspecialty consultation for severe or refractory toxicities.

Dose Modification and Supportive Care Principles (BRAF Inhibitor–Based Therapy)

- A proactive, structured approach to dose modification and supportive care can help maintain treatment continuity while minimizing toxicity with BRAF inhibitor–based therapies.

- **Early recognition and intervention** reduce treatment interruptions and discontinuation
- **Temporary treatment interruption** may be effective for managing acute grade ≥2-3 toxicities
- **Dose reductions or schedule modifications** should follow prescribing information for the specific regimen
- **Rechallenge may be considered** once toxicity improves to grade ≤1, where clinically appropriate
- **Supportive care** (topical/systemic agents, hydration, antipyretics, symptom-directed therapy) should be optimized before permanent discontinuation
- **Collaboration with an academic center** is recommended for complex, severe, or recurrent toxicities or when continuation of therapy is uncertain

References

1. Davies. Nature. 2002;417:949.
2. Marchetti. J Clin Oncol. 2011;29:3574.
3. NCCN. Clinical practice guidelines in oncology: colon cancer. v.2.2026. nccn.org.
4. NCCN. Clinical practice guidelines in oncology: non-small cell lung cancer. v.3.2026. nccn.org.
5. Encorafenib PI.
6. Binimetinib PI.
7. Dabrafenib PI.
8. Trametinib PI.

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