Managing *BRAF* V600E–Mutant mCRC and mNSCLC

Testing and Treatment Considerations for Community Practitioners

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Metastatic Colorectal Cancer

Prevalence and Clinical Significance of *BRAF* V600E Mutations

In metastatic colorectal cancer (mCRC), *BRAF* mutations occur in approximately 8% to 12% of cases, and up to 80% of these are the V600E variant.[1] *BRAF* V600E–mutated CRC is a distinct, aggressive biologic subtype of mCRC with a poorer prognosis than *BRAF* wild-type disease.[2]

Biomarker Testing in mCRC

National guidelines recommend biomarker testing for all patients with mCRC, including assessment of *BRAF* V600E mutations, along with *RAS* mutations (*KRAS, NRAS*), microsatellite instability (MSI) or mismatch repair deficiency (dMMR), HER2 overexpression/amplification, and rare alterations such as *NTRK* and *RET* fusions.[3]

Testing for *BRAF* V600E mutation is essential to:

- Identify a high-risk disease subtype
- Inform prognosis
- Guide appropriate use of targeted therapies
- Enable timely access to optimal treatment and clinical trials

At diagnosis of metastatic disease, tumor-based molecular testing for *BRAF* V600E mutation is recommended using primary or metastatic tissue and next-generation sequencing (NGS) or polymerase chain reaction–based assays. Although no preferred testing methodology is specified, sequential single-gene testing may increase challenges related to tissue sufficiency, turnaround time, and cost. Plasma-based NGS assays analyzing circulating tumor DNA have demonstrated high concordance with tissue genotyping and can similarly inform response to targeted therapies.

Treatment Options for *BRAF* V600E–Mutant mCRC

National guidelines currently list encorafenib (a BRAF inhibitor), in combination with cetuximab (an EGFR inhibitor), and mFOLFOX6 chemotherapy as a preferred first-line therapy option for patients with *BRAF* V600E–mutant mCRC.[3]

This recommendation is based on results from the BREAKWATER trial. BREAKWATER was a phase III study of first-line encorafenib plus cetuximab (EC) with or without mFOLFOX6 chemotherapy vs physician's choice standard-of-care chemotherapy for *BRAF* V600E–mutated mCRC. This study demonstrated improved efficacy with EC plus mFOLFOX6 in terms objective response rate (ORR) and progression-free survival (PFS), and overall survival (OS) vs standard chemotherapy.[4]

BREAKWATER: Key Efficacy Outcomes

Outcome	EC (n = 158)	EC + mFOLFOX6 (n = 236)	Standard of Care (n = 243)
Median PFS, mo (95% CI)	6.8 (5.7-8.3)	12.8 (11.2-15.9)	7.1 (6.8-8.5)
• HR vs SoC (95% CI)	1.09	0.53 (0.407-0.677; *P* <.001)	
Median OS, mo (95% CI)	19.5 (17.6-22.5)	30.3 (21.7-NE)	15.1 (13.7-17.7)
• HR vs SoC (95% CI)	0.69 (0.53-0.90)	0.49 (0.38-0.63; P <.001)	
Confirmed ORR, %	45.6	65.7	37.4

Of note, patients with mCRC and a *BRAF* V600E mutation AND dMMR/MSI-high disease should start with immunotherapy; in eligible patients, doublet immunotherapy is preferred.

Metastatic Non-Small-Cell Lung Cancer

Prevalence and Clinical Significance of *BRAF* V600E Mutations

In metastatic non-small-cell lung cancer (mNSCLC), *BRAF* mutations occur in approximately 1% to 3% of cases, and approximately 50% of these are the V600E variant.[5,6]

Biomarker Testing in mNSCLC

BRAF V600E–mutant mNSCLC is a rare but actionable subtype. National guidelines recommend comprehensive molecular profiling for all patients with mNSCLC, including assessment of *BRAF* V600E mutations, at the time of diagnosis using tumor tissue or plasma-based NGS.[7]

Early identification of *BRAF* V600E–mutant disease is critical to:

- Guide appropriate use of targeted therapies
- Ensure timely access to optimal FDA-approved options

Treatment Options for *BRAF* V600E–Mutant mNSCLC

Early studies of vemurafenib (a BRAF inhibitor) in the AcSé and EURAF cohorts, as well as dabrafenib (a BRAF inhibitor) in the BRF113928 trial, demonstrated clinically meaningful activity in *BRAF* V600E–mutant mNSCLC.[8,9] These studies established BRAF V600E as an actionable oncogenic target and laid the foundation for today's combination BRAF/MEK inhibition strategies.

National guidelines list BRAF/MEK inhibitor combinations as preferred first-line therapy for *BRAF* V600E–mutant mNSCLC, including dabrafenib plus trametinib and encorafenib plus binimetinib.[7]

Key Data for BRAF/MEK Inhibitors in Patients With BRAF V600E–Mutant mNSCLC[10-13]

Agent	Key Efficacy Outcomes	Trial (N)	FDA Indication
Encorafenib + binimetinib	Treatment naive: • ORR: 75% • Median PFS: 15.0 mo Previously treated: • ORR: 46% • Median PFS: 9.3 mo	PHAROS (98)	Unresectable or mNSCLC with a *BRAF* V600E mutation, as detected by an FDA-approved test
Dabrafenib + trametinib	Treatment naive: • ORR: 63% • Median PFS: 9.7 mo Previously treated: • ORR: 64% • Median PFS: 10.9 mo	BRF113928 (93)	Unresectable or mNSCLC with a *BRAF* V600E mutation, as detected by an FDA-approved test

Note that the above data come from nonrandomized studies; there are no randomized data comparing BRAF/MEK inhibitor therapy with chemotherapy or chemotherapy/immunotherapy in patients with *BRAF* V600E–mutant mNSCLC.

References

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