Kaplan-Meier Survival Curve of BRAF V600E–Mutated mCRC Patients vs BRAF Wild-Type mCRC Patients

BEACON: Overall Survival, Triplet Regimen vs. Control

Median Overall Survival (mo (95% CI))
- Triplet: 9.0 (8.0-11.4)
- Control: 5.4 (4.8-6.6)

Hazard ratio for death:
- 0.52 (95% CI, 0.39-0.70)
- \( P < 0.001 \)

ORR = 26% (95% CI, 18-35; \( P < 0.001 \) vs. control)

BEACON: Overall Survival, Doublet Regimen vs. Control

Median Overall Survival (mo (95% CI))
- Doublet: 8.4 (7.5-11.0)
- Control: 5.4 (4.8-6.6)

Hazard ratio for death, 0.60 (95% CI, 0.45-0.79)

P < 0.001

ORR = 20% (95% CI, 13-29; P < 0.001 vs. control)

Comparison between the initial findings from BEACON and the subsequent updated, mature analysis

**BEACON TRIAL**
Table: Findings demonstrate that the triplet and doublet are equally effective with regard to median overall survival as well as hazard ratio for death.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prespecified Interim Analysis</th>
<th>Updated/Mature Analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Triplet</td>
<td>Doublet</td>
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<tr>
<td>Median Overall Survival (months)</td>
<td>9.0</td>
<td>8.4</td>
</tr>
<tr>
<td>Hazard Ratio (HR)</td>
<td>0.52</td>
<td>0.60</td>
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<tr>
<td>Objective Response Rate (%)</td>
<td>26</td>
<td>20</td>
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Shown are the best percentage changes from baseline in the sum of the diameters of the target lesions in each patient in the three groups, as determined by central review. The dashed lines at 20% and −30% indicate progressive disease and partial response, respectively, according to Response Evaluation Criteria in Solid Tumors, version 1.1. The asterisks indicate patients who had a complete response, partial response, or stable disease with respect to target lesions but who had a new lesion, a progressing nontarget lesion, or both.
Activation Pathways in BRAF V600E-Mutated Colorectal Cancer

**A,** Under normal circumstances in colorectal cancer with BRAF V600E mutation, activated monomer BRAF V600E activates MEK and ERK, downstream signals in the MAPK pathway, which leads to cell growth. Activated ERK suppresses the upstream activation of the MAPK pathway through negative feedback on a receptor tyrosine kinase such as EGFR.

**B,** Monotherapy with BRAF inhibitors blocks the monomeric activity of BRAF V600E, which relieves the negative feedback suppression of EGFR and results in paradoxical activation of the MAPK pathway through RAS and RAF dimers.

**C,** Combination of BRAF inhibitors with an anti-EGFR such as cetuximab (CET) or panitumumab (PAN) can abrogate a negative feedback loop activation of the MAPK pathway. In addition, inhibition of MEK or ERK can further reduce MAPK signaling and limit adaptive therapeutic resistance.