

Patient #	Combination	Therapy	Best response by RECIST	Duration of treatment	Resistance mechanism
1	RAF/EGFR (prior RAF/MEK)	Encorafenib + cetuximab (prior dabrafenib + trametinib)	+3% (-15%)	4.5 months (7.3 months)	<i>KRAS</i> amplification
2	RAF/EGFR	Dabrafenib + panitumumab	-24%	4.8 months	<i>BRAF</i> amplification
3	RAF/MEK	Dabrafenib + trametinib	-34%	5.5 months	MEK1 F53L (ARAF Q489L*)

Table S1: Patient characteristics and MAPK pathway reactivating resistance mechanisms of *BRAF*-mutant CRC patients with clinical acquired resistance to RAF/EGFR or RAF/MEK inhibitor combinations. Best response by RECIST indicates maximum reduction in cumulative tumor diameter achieved by RECIST criteria. (* patient #3 had an ARAF Q489L mutation identified in the post-progression biopsy, but validation studies failed to show a clear role for this mutation in promoting resistance)

Table S2: Summary of variant calls from WES analysis of matched pre-treatment and post-progression biopsies. Table provided as excel file.