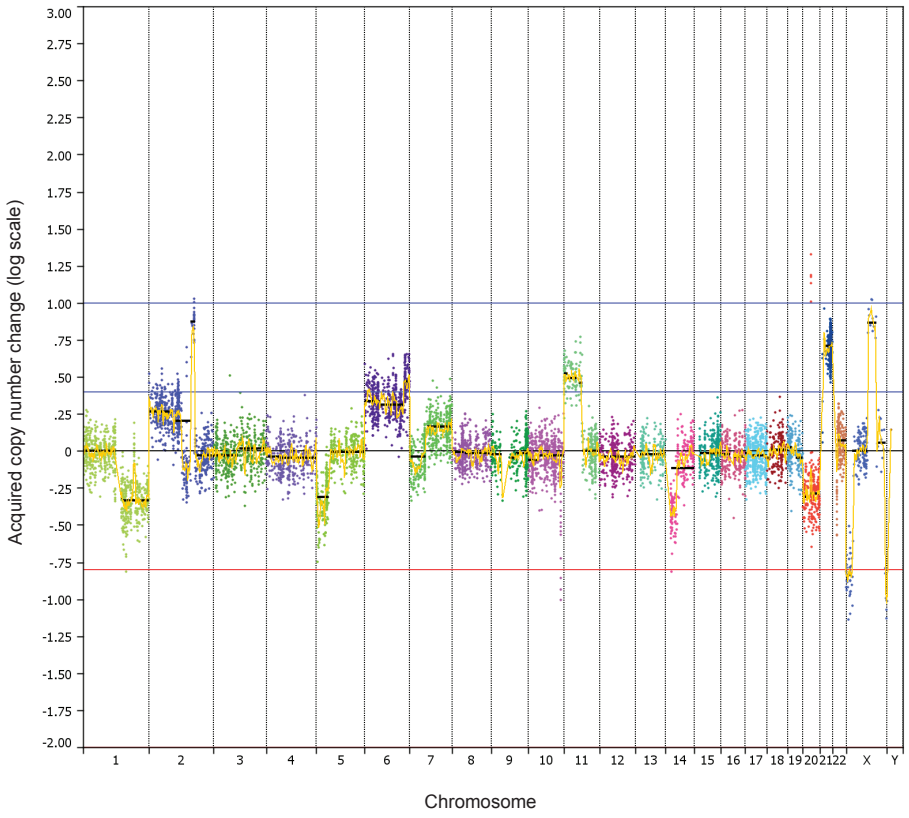
A

Gene	Protein Change	Chromo-some	DNA Change (hg19)	Allelic Fraction (%)	Coverage
MUC2	L58P	11	g.1075747T>C	22.6	75x
MUC2	E470Q	11	g.1081112G>C	20	30x
MUC2	S562T	11	g.1081757G>C	40.5	42x
MUC2	T1207I	11	g.1088835C>T	25.4	71x
NRAS	Q61R	1	g.115256529A>C	29.1	148x

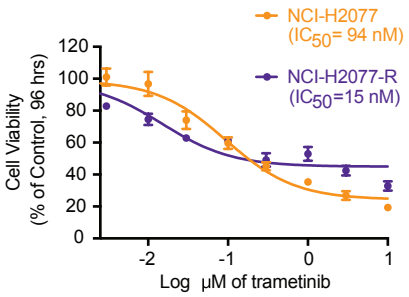
B

Chromosome region	Length	Cytoband	Event	# Genes in region
Chr20:29,622,585-30,583,282	960698	q11.21	High Copy Gain	26
Chr6:149,909,750-171,115,067	21205318	q25.1-q27	CN Gain	131
Chr11:0-12,369,297	12369298	p15.5-p15.3	CN Gain	281
Chr11:13,918,510-48,888,840	34970331	p15.2-p11.12	CN Gain	212
Chr11:55,207,363-67,694,795	12487433	q11-q13.2	CN Gain	401
Chr21:15,374,230-48,129,895	32755666	q11.2-q22.3	CN Gain	288
Chr2:157,266,024-170,987,694	13721671	q24.1-q31.1	CN Gain	70

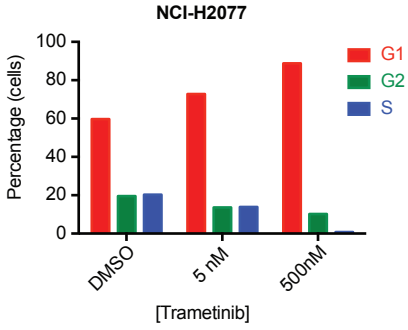
C



D



E



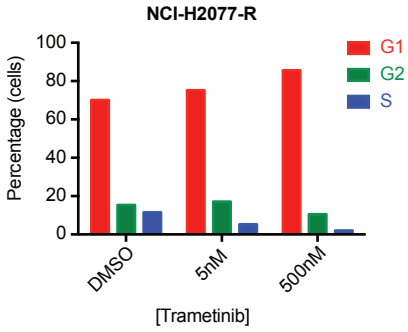


Figure S6

Figure S6, related to Figure 4. Genomic analysis of resistant NCI-H2077 cells

A) Illumina sequencing of a panel of 504 cancer and cancer-related genes reveals five acquired mutations in NCI-H2077 BGJ398-resistant cells (NCI-H2077-R). Four mutations were identified in *MUC2* gene, and are likely sequencing artifacts. H2077-R cells acquired an *NRAS* Q61R mutation at an approximate 30% allelic fraction with 148x coverage.

B) Copy number gains and losses in NCI-H2077-R cells compared to parental cells, identified by analysis of paired-end Illumina sequencing reads.

C) Copy number analysis by Illumina sequencing identifies chromosomal gains and losses compared to parental cells in NCI-H2077-R.

D) Cell viability at 96 hours following treatment with trametinib (MEK inhibitor) in NCI-H2077-R cells and parental NCI-H2077 cells.

E) Trametinib arrests NCI-H2077 and NCI-H2077-R cells in G1. Percentage of cells in each stage of the cell cycle after treatment with trametinib is shown, as measured by flow cytometry.

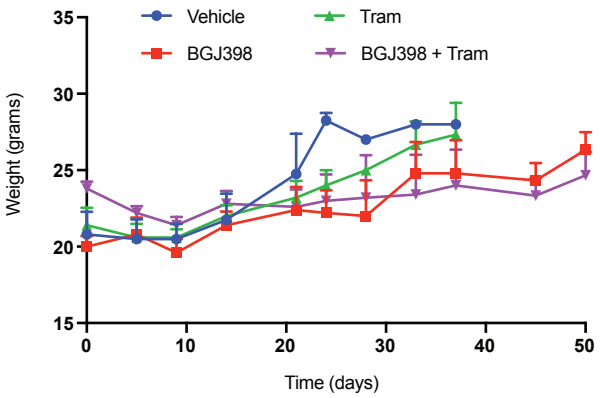

Vehicle
Tram
BGJ398
BGJ398 + Tram
Weight (grams)
35
30
25
20
15
0
10
20
30
40
50
Time (days)

Figure S7

Figure S7, related to Figure 6. BGJ398 in combination with MEK inhibitor is well tolerated in NCI-H2077 xenograft models

Mouse weight was monitored at the beginning of the treatment, then twice weekly until the end of the treatment. The combination of BGJ398 with trametinib appeared to be well tolerated with no weight loss.