



**Fig.S6. Development of trametinib resistance is consistent in independent studies with BT-40 xenografts.**

*Upper panel:* Schematic of the protocol used to select resistance to trametinib. Mice were transplanted with BT-40 tumor and treated with trametinib (1 mg/kg daily x 42). The first tumor to regrow after stopping treatment was transplanted and the treatment repeated until tumors progressed (>25% increase in volume) during the treatment cycle. A similar protocol was used to select trametinib resistance in NCH-MN-1 and IC3635 PDX models.

*Lower panel:* Development of resistance to trametinib. Resistance to trametinib was developed in four independent BT-40 experiments (see Fig. 3). Curves show the mean tumor response (n=10) for the first (1) through fourth (4) cycle of trametinib treatment (1 mg/kg daily x 42 days). Growth of control (untreated tumors) is shown by the black solid line in each panel.