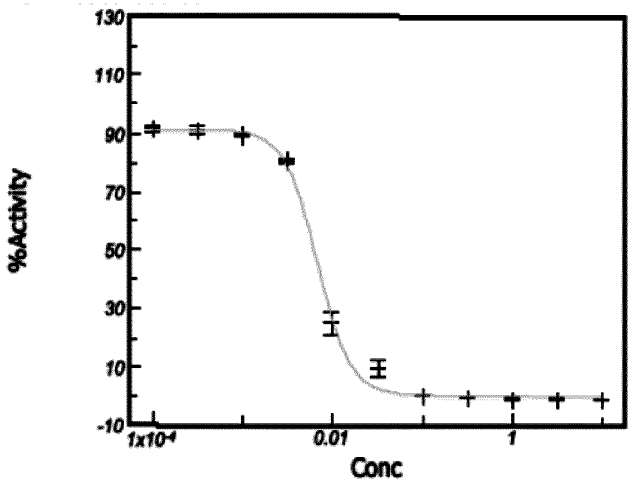
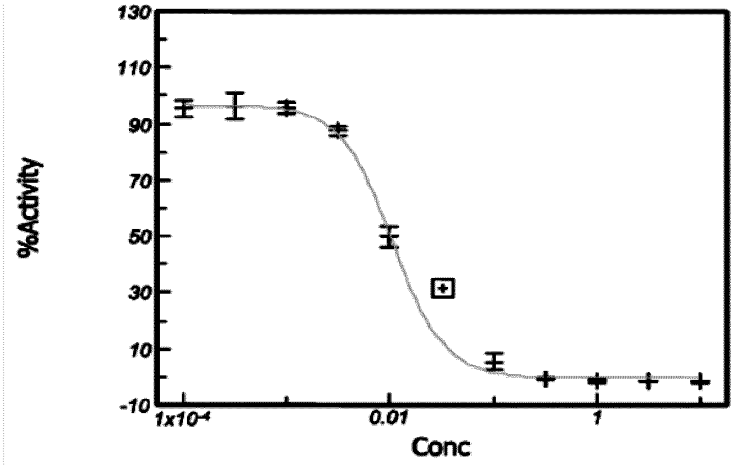
Figure 1



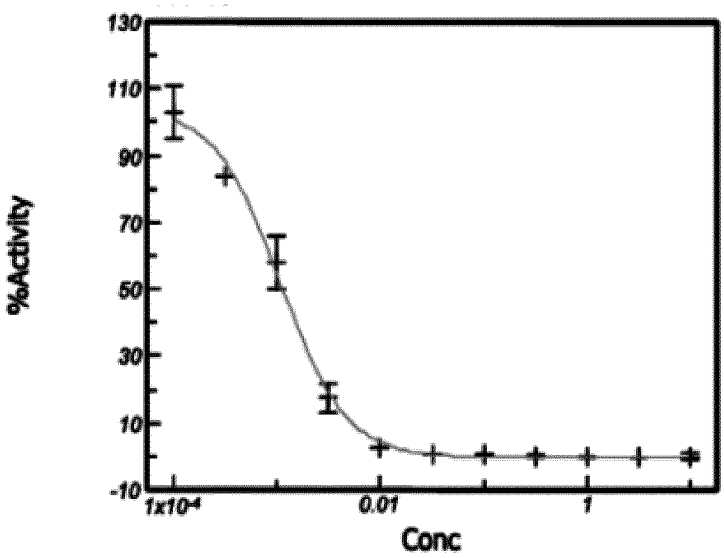
A375 inhibition - Example 1

Figure 2



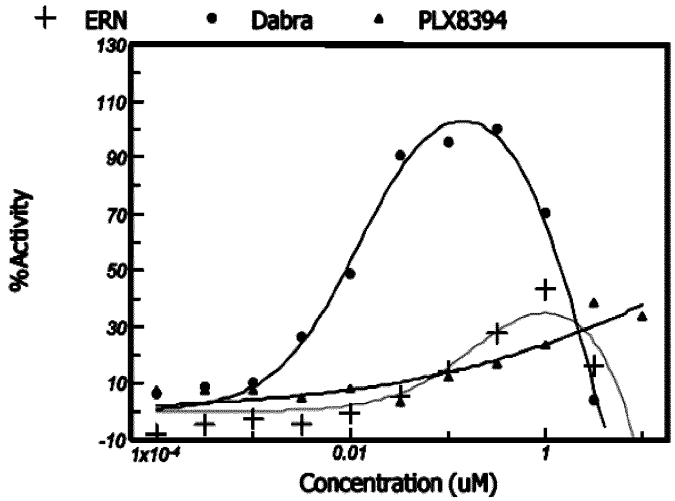
A375 inhibition - Example 2

Figure 3



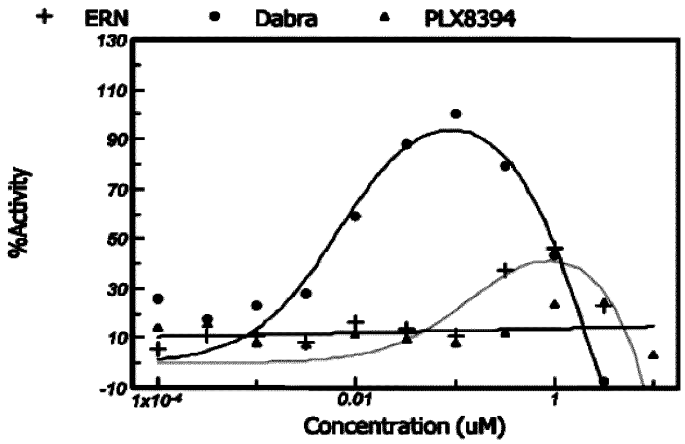
A375 inhibition - Example AR-25

Figure 4



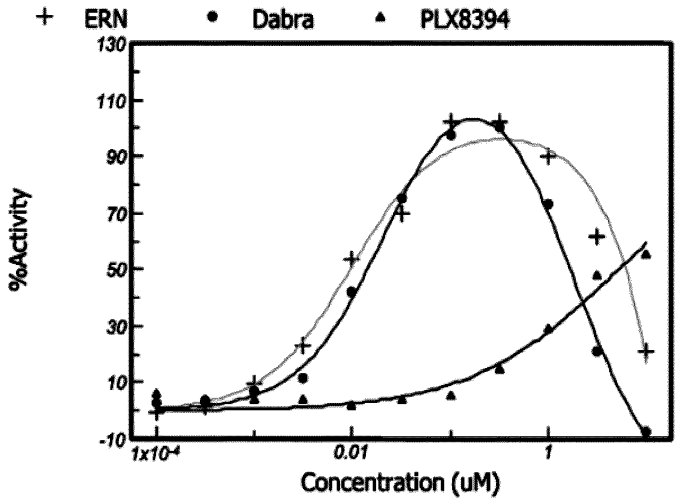
HCT-116 activation; Example 1 = ERN; max. activation of paradox inducer Dabrafenib is set to 100%; PLX8394 is a positive control for a paradox breaker

Figure 5



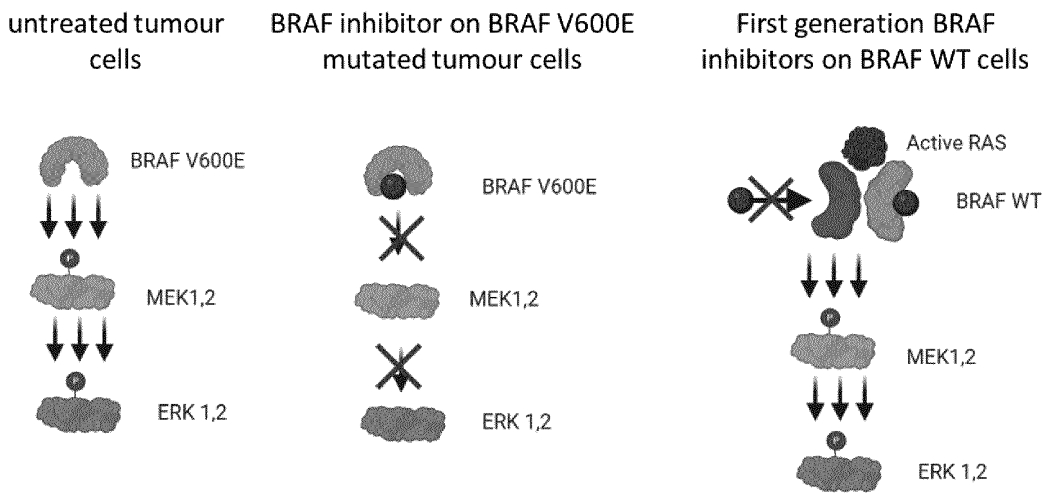
HCT-116 activation; Example 2 = ERN; max. activation of paradox inducer Dabrafenib is set to 100%; PLX8394 is a positive control for a paradox breaker

Figure 6



HCT-116 activation; AR-25 = ERN; max. activation of paradox inducer Dabrafenib is set to 100%; PLX8394 is a positive control for a paradox breaker

Figure 7



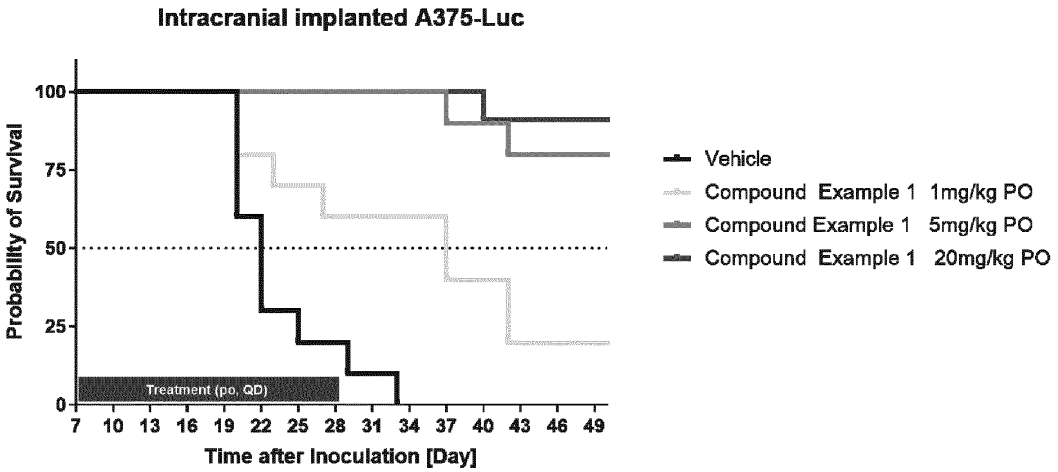
First generation BRAF inhibitors induce paradoxical activation of the MAP kinase signaling pathway in BRAF WT cells

Left: BRAF is part of the first node of the MAP kinase signalling pathway and mutant BRAF is an oncogenic driver.

Center: In BRAF V600E/K mutated tumors BRAF signals as monomer, a condition in which the protein is inhibited by first generation BRAF inhibitors.

Right: First generation BRAF inhibitors promote BRAF WT homo and/or hetero dimerization. In this context the protomer non occupied by the BRAF inhibitor acquires a conformation unfavourable for inhibitor binding. The outcome of the treatment with a first generation BRAF inhibitor, in this context, is paradoxically increased MAPK activation and consequent tumor growth in BRAF WT cells.

Figure 8



Compound Example 1 triggered dose dependent antitumor activity starting from 1 mg/kg daily evidencing potent brain-permeability mediated efficacy