**Figure 2. Intermittent BRAF inhibitor therapy to forestall the onset of drug-resistant melanoma**

Graph A reflects pERK level. Optimal tumor growth occurs when the cells have an optimal pERK level (green zone). Tumor cells with excess or insufficient pERK (red zones) will not grow optimally. The tumor volume (of both drug-sensitive and drug-resistant tumor cells) corresponding to the different pERK levels is depicted in graph B.

Prior to initiation of BRAF inhibitor therapy for BRAF-mutated melanomas, the bulk of the cells have optimal BRAF$^\text{V600E} \rightarrow$MEK$\rightarrow$ERK (pERK) activity for tumor growth (graph A: the tumor cells are in the green zone with optimal pERK levels). In this state, tumor cells that will be sensitive to BRAF inhibitor (drug-sensitive) are growing at an optimal rate (graph A: blue line is in the green zone) and the rare variant cells possessing intrinsic drug resistance are not growing optimally (Graph A: black line is in the red zone). The corresponding tumor volume (Graph B) shows a greater volume of drug-sensitive blue cells and few drug-resistant black cells. Addition of BRAF inhibitor leads to insufficient BRAF$^\text{V600E} \rightarrow$MEK$\rightarrow$ERK activity in the bulk of the drug-sensitive tumor, leading to tumor regression (blue line heads into the red zone in Graph A). However, BRAF inhibitor therapy immediately begins to select for expansion of melanoma cells with elevated BRAF$^\text{V600E}$ expression, corresponding to drug-resistant tumor cells, and these cells now get pushed into the optimal green zone in graph A; they begin to grow because of tumor fitness benefit in the presence of drug. Upon cessation of drug administration, drug-resistant melanoma cells slow their growth, and the drug-sensitive tumor cells reinitiate proliferation. In short, as the drug is alternately administered or withdrawn, the drug-sensitive tumor cells go from optimal to insufficient levels of pERK and back again, while the drug-resistant tumor cells go from optimal to excessive levels of pERK and back again. Thus, the volume of drug-sensitive and drug-resistant tumor cells keeps rising and falling in opposite directions, creating a homeostasis that keeps the cancer from growing out of control, which may translate to increased patient survival.