Hypothesis:

1. High BAD activity means cells are “primed for death”. Therefore, chemo therapeutics drugs alone likely to work.
2. Low BAD activity means cells are not primed for death. BCL2 inhibitors will make those cell lines closer to apoptotic cleft.
3. Targeting the pathway is likely to push cells towards “the apoptotic cleft”. If BAD is low, using BCL2 are likely to make the cell lines to apoptosis. Therefore, targeted therapy+chemo/BH3 mimetics are likely effective.

* Compare single agents with single agent targeted therapy + chemo/BH3 mimetics combo.

1. Often both EGFR/MEK/RAF/ERK and BAD pathway activity positively correlated. We want to compare chemo or targeted MEK inhibitor has better response.

* Compare chemo +/- MEK/EGFR inhibitor response if BAD high
* Compare chemo alone, MEK/EGFR inhibitor alone and Obatoclax+MEK inhibitor.

1. PI3K inhibitors/akt inhibitors can inhibit autophagy. If the cells are driven by autophagy rather than mitochondrial apoptosis, autophagic inhibitors will identify the driving event. But all autophagy inhibitors are essentially pi3k/akt inhibitors (3-MA , wortmanian, LY294002).