Miransertib and ARQ 751 exhibit superior cell-death-inducing properties compared to other AKT inhibitors and can overcome resistance to other allosteric AKT inhibitors.

**Figure 1: ARQ 751 and ARQ 092 are more biologically active compared to other allosteric and ATP-competitive inhibitors of AKT.**

- **A:** ARQ 092 and ARQ 751 exhibit equal or superior biological activity against a panel of clinical AKT inhibitors at lower drug concentrations.
- **B:** ARQ 092 and ARQ 751 can elicit significant cell death at shorter drug exposure times compared to MK-2206.

**Figure 2: Disruption of the PH-domain/kinase-domain interaction by the D323H mutation confers biochemical resistance to ARQ 751 and ARQ 092.**

- **A:** Ectopic expression of either AKT1-W80A or AKT1-W80A confers resistance to MK-2206. However, AKT1-W80A expressing cells are partially sensitive to ARQ 751.
- **B:** Western blots from cells treated as in A. Consistent with the cytotoxic effects of ARQ 751, the PH-domain of wild-type AKT1 is more resistant to ARQ 751 and ARQ 092 but not MK-2206.

**Figure 3: An ATM phosphorylation signature is inhibited by allosteric AKT inhibitors but activated by ATP-competitive compounds.**

- **A:** MDA-MB-361 and ZRC-1 cells were treated with allosteric and ATP-competitive AKT inhibitors as indicated. Treated cells were subjected to western blotting for the indicated proteins.
- **B:** Treatment of AKT-dependent cells with allosteric AKT inhibitors induces a decrease in an ATM-dependent phospho-peptide signature, while treatment with ATP-competitive inhibitors causes the opposite effect. However, both types of compounds synergize with ATM inhibitors to induce cell death suggesting that ATP-dependent cell survival may be in part regulated by ATM, and that allosteric inhibitors could be sub-optimal inhibitors of AKT-dependent ATM activity.

**References**
