Nuclear export inhibitor selinexor (KPT-330) demonstrates anti-tumor efficacy alone and in combination with chemotherapy in multiple breast cancer models

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Abstract # 3075

Background

The nuclear exporter XPO1 (Exportin1 or CRM1), mediates the transport of multiple cancer-related proteins, including several tumor suppressors[1]. For this reason, XPO1 is being pursued as a promising target for cancer therapy options. Selinexor (KPT-330), a selective inhibitor of nuclear export, is an oral agent that has been shown to inhibit XPO1[2] and is currently in phase 2 trials for hematologic and solid tumors. We sought to determine the antitumor effect of selinexor in breast cancer cells *in vitro* and *in vivo*

Methods

We studied the effects of selinexor in vitro using cell proliferation assays; the half maximal inhibitory concentration (IC50) was calculated using isobologram curves after 3 days of treatment. We also tested the effects in combination with chemotherapy and calculated the combination index by the method of Chou and Talalay[3]. In vivo efficacy was tested in triple negative breast cancer (TNBC) patient derived xenografts (PDXs) with varying levels of paclitaxel sensitivity, as single agent and in combination therapy. T/C ratio was calculated using the formula: [(median tumor volume of treated group)/(median tumor volume of control group) x 100][4]

Results

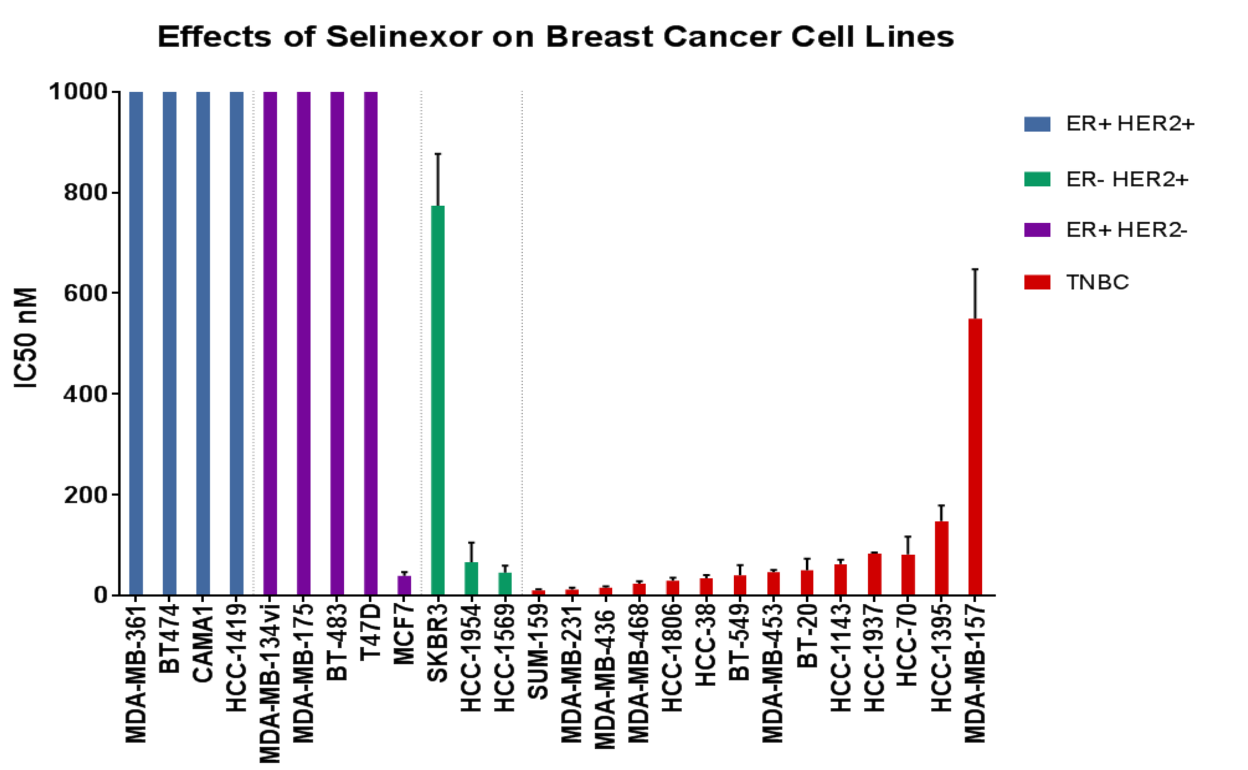

Fig 1. Selinexor alone has a significant efficacy *in vitro* Effects of selinexor on breast cancer cell lines. 26 breast cancer cell lines of various hormone receptor statuses were treated with selinexor with 10 concentrations based on a 5-fold dilution series (Range 0-100000nM). Cell growth was measured after 72 hours of treatment using SRB assay and IC50 was then calculated using isobologram curves with a median IC50 of 50nM (range 11- >1000nM).

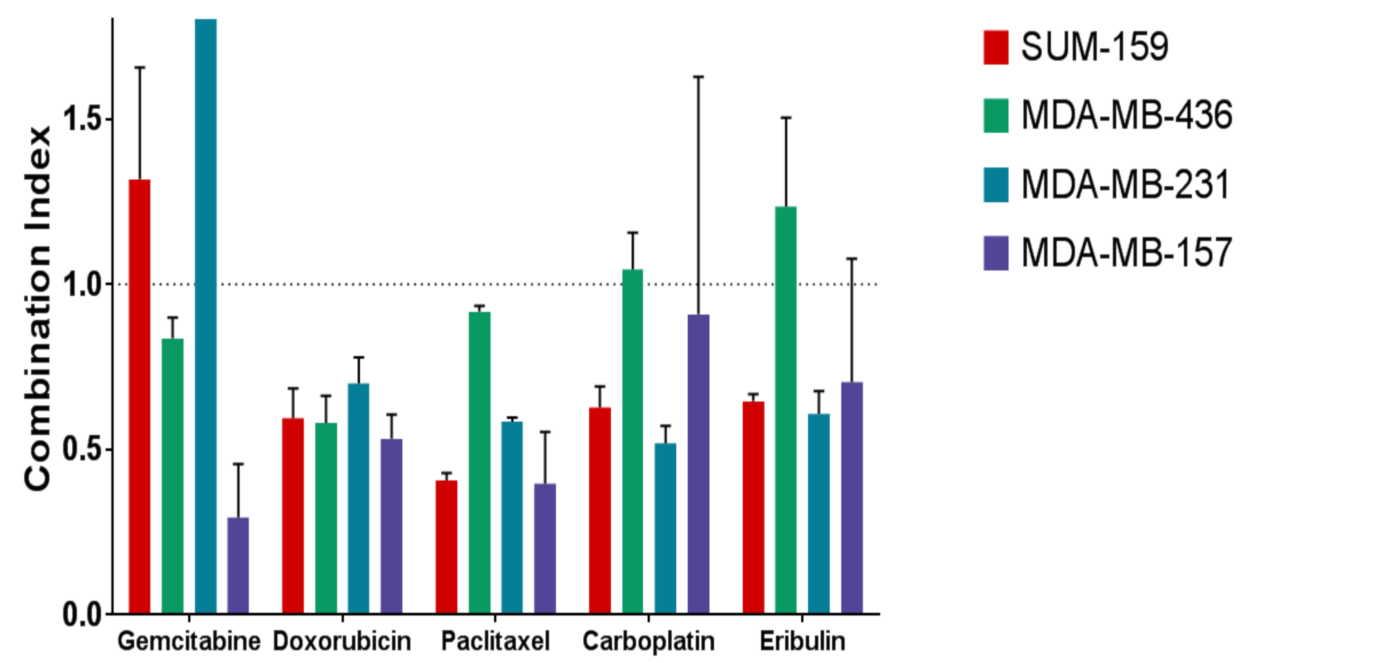

Fig 2. Effects of selinexor in combination with standard chemotherapy *in vitro*. 4 different TNBC cell lines were treated with selinexor in combination with paclitaxel, doxorubicin, gemcitabine, carboplatin and eribulin. Cell growth was measured after 72 hours of treatment using SRB assay and the combination index (CI) was then calculated using the method of Chou and Talalay, a CI value <1 indicates synergism, equal to 1 indicates addition and a CI significantly greater than 1 indicates antagonism.

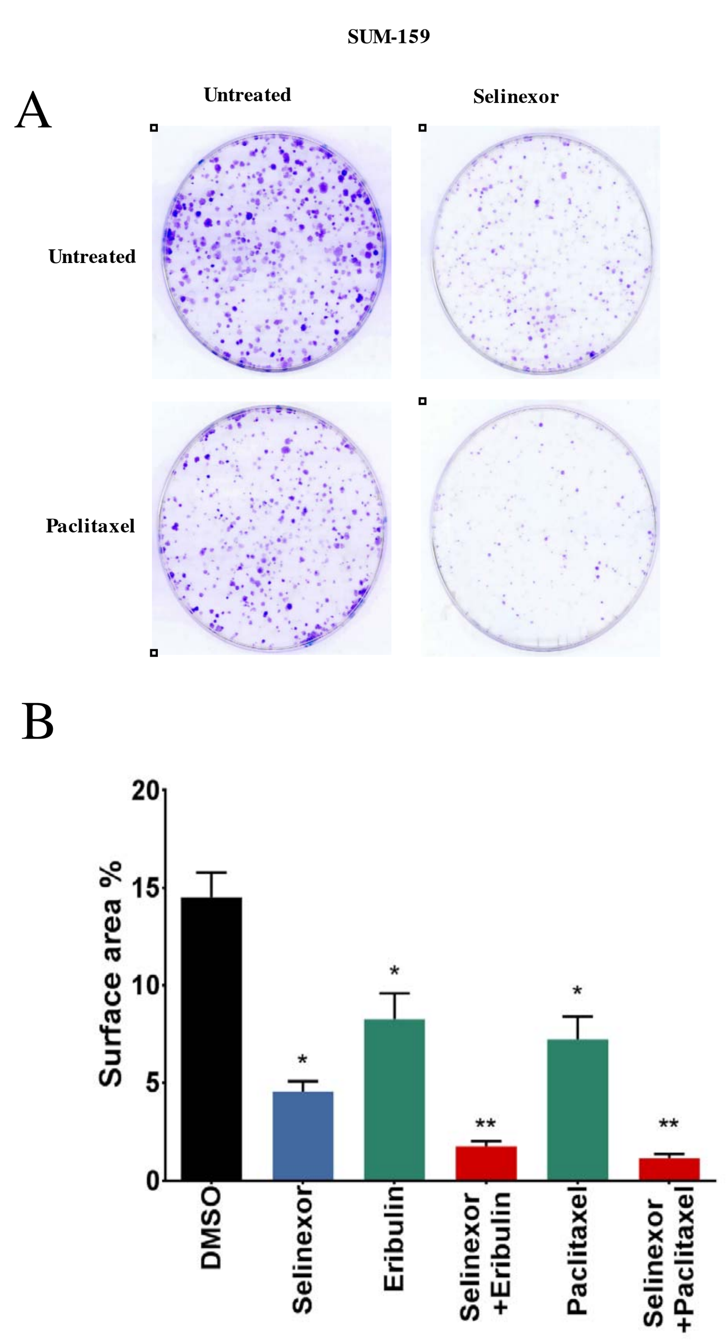

Fig 3. Selinexor in combination with paclitaxel has greater efficacy than compared to either agent alone. A. SUM-159 cells were trypsinized, counted and plated at a density of 2 × 10^3 cells/60 mm plates in triplicate for each treatment group. Cells were treated for 2 weeks with vehicle, selinexor(50nM), paclitaxel(0.5nM) or eribulin (1nM) or in combination of selinexor with paclitaxel and selinexor with eribulin colonies were then fixed and stained with crystal violet. **B.** Percent Surface area was calculated using NIH Image J v.1.48 software. Data are presented as mean ± SEM (*P<0.005 vs. control **P=0.0002 combination paclitaxel vs selinexor alone, P=0.001 combination eribulin vs selinexor alone).

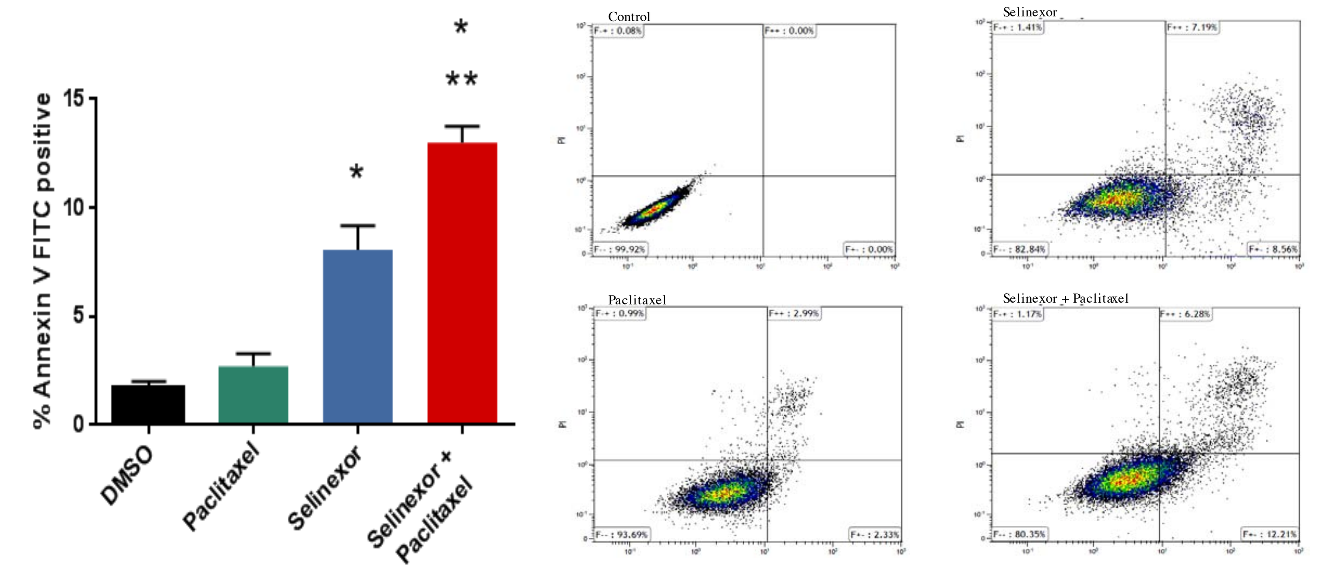

Fig 4. Selinexor induces apoptosis and PARP cleavage. A. SUM-159 cells were treated with 0.5nM paclitaxel alone , 400nM selinexor alone , and combination of both. After 72 hours, Annexin V–positive cells were determined by FACS analysis. (*P<0.0006 vs. control **P=0.004 vs selinexor alone)

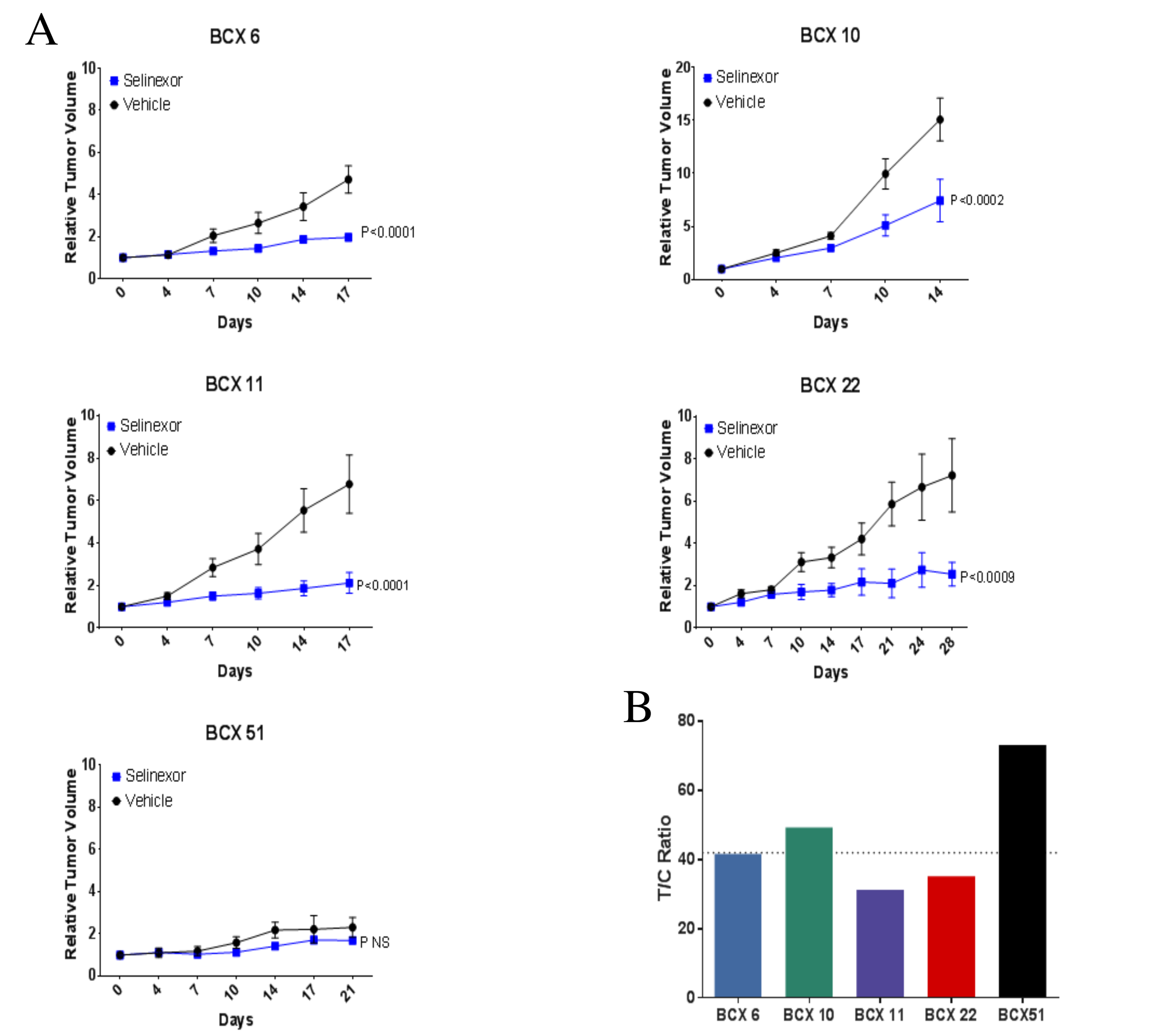

Fig 5. Selinexor has *in vivo* efficacy in TNBC PDX models. A. Mice bearing BCX 6, BCX10, BCX 11, BCX22 and BCX51 TNBC patient derived xenografts were treated with vehicle or Selinexor 12.5mg/kg twice a week . **A.** Data is presented as mean ±SEM of relative tumor volume. The tumor volumes at the conclusion of experiment were compared to vehicle and data was analyzed by two-way ANOVA to determine statistical significance. **B.** T/C ratios calculated using the formula: [(median tumor volume of treated group)/(median tumor volume of control group)] × 100. Activity defined as % T/C ratio <40%

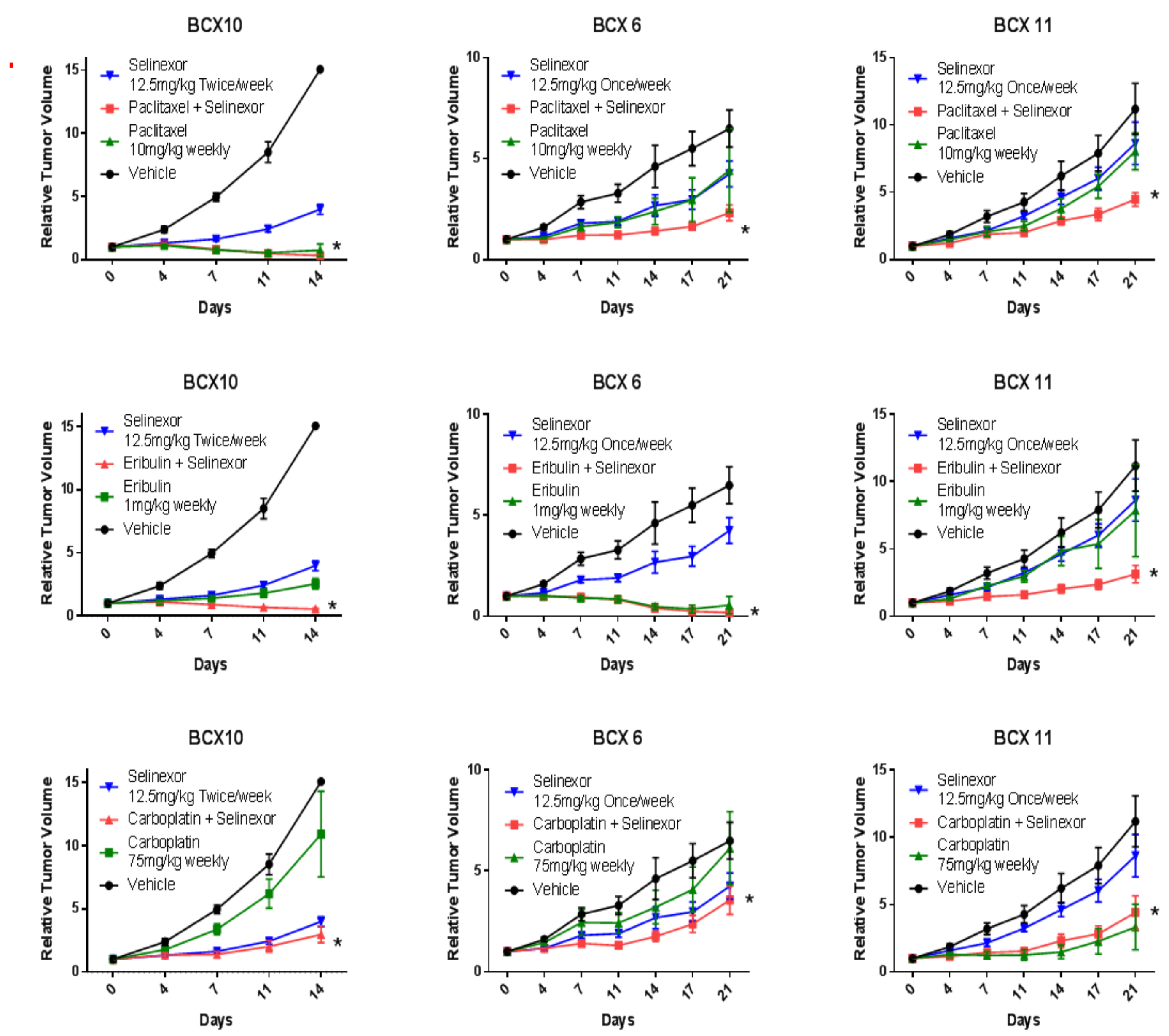

Fig 6. Selinexor has greater antitumor efficacy *in vivo* in combination with standard chemotherapy. Mice bearing three different TNBC patient derived xenografts were treated with vehicle, selinexor 12.5mg/kg twice a week for BCX10 and once weekly for BCX 6 and 11, paclitaxel 10mg/kg weekly, eribulin 1mg/kg weekly, carboplatin 75mg/kg weekly and in combination of selinexor with each chemotherapy agent. Data is presented as mean ±SEM. The tumor volumes at the conclusion of experiment were compared to vehicle and the data was analyzed by two-way ANOVA to determine statistical significance (* P<0.001 vs. control).

Conclusion

Collectively these findings strongly suggest that selinexor is a promising therapeutic option for breast cancer.

References

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