

P3.144 Therapeutic effects of inhibitors to putative DTP-associated pathways in *EGFR*-mutant lung cancer PDX models

INTRODUCTION

Resistance to EGFR tyrosine kinase inhibitors in *EGFR*-mutant lung cancer almost universally occur during patient treatment. Drug-tolerant persisters (DTPs) are a subpopulation of low proliferative tumor cells that can survive targeted therapy and serve as reservoir for the development of drug resistant cells. Although kinase signaling pathways and epigenetic mechanisms have been implicated in DTP formation, *in vivo* functional validation of their roles in patient-derived xenograft (PDX) models has been limited (Mikubo et al.). Our goal is to assess the efficacy of inhibitors targeting these DTP markers in osimertinib (osi)-induced DTPs of *EGFR*-mutant PDX models.

METHODS

Table 1. *EGFR* mutant models derived from patient tumor collections.

Model ID	<i>EGFR</i> mutation	Patient treatment prior to collection for PDX	Patient tumor collection site for PDX
PHLC137	Del 19	none	Lung primary, chemo-naïve
PHLC164	Del 19 T790M	none	Lung primary, chemo-naïve

Figure 1. PDX experiment design using molecularly targeted drugs.

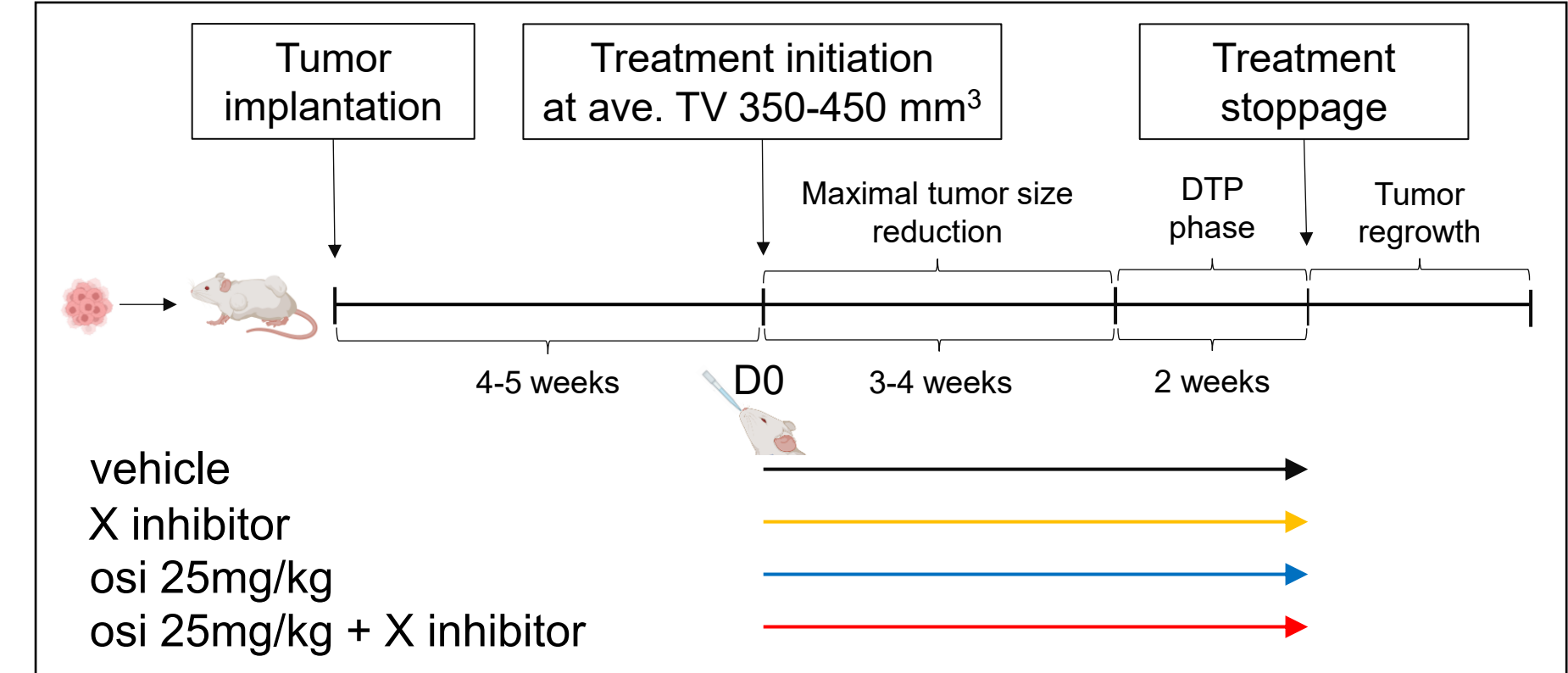
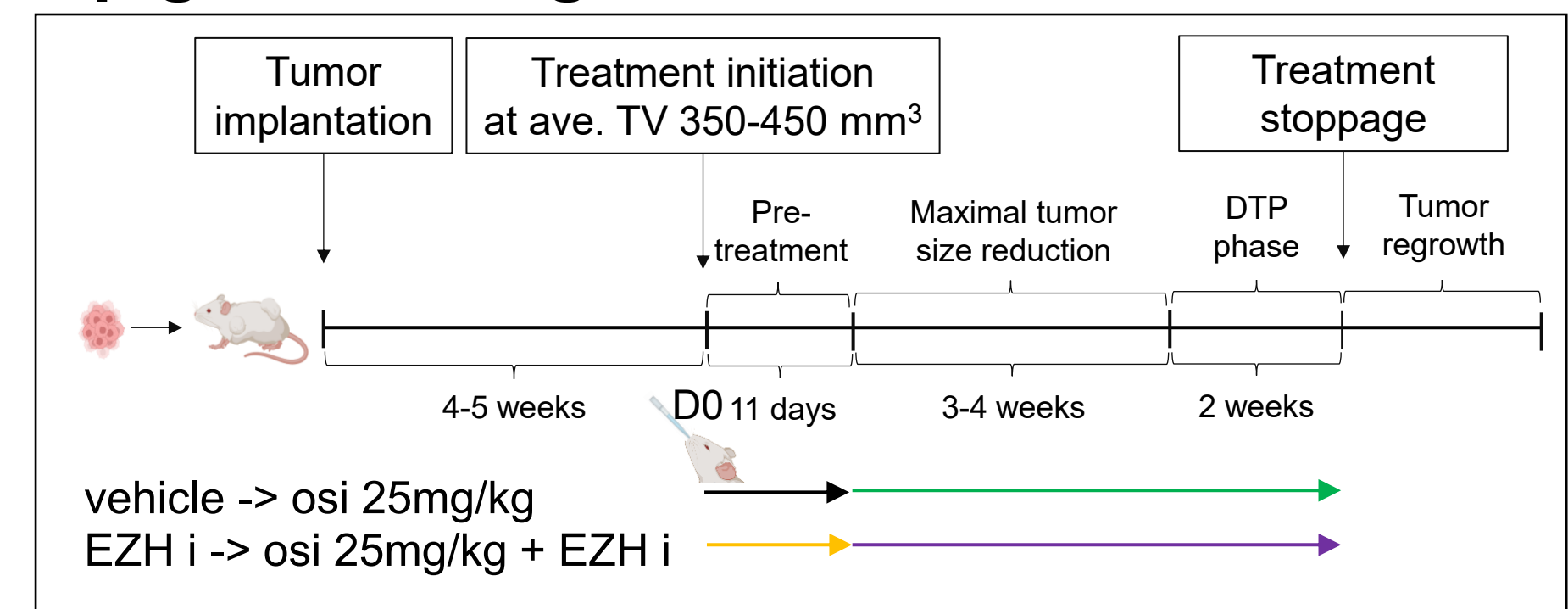


Figure 2. PDX experiment design using epigenetic drugs.



- DTPs were induced in *EGFR* mutated PDX models (PHLC137 or PHLC164) by oral gavage with osi (25 mg/kg QD) and osi combination treatment with bemcentinib (AXL inhibitor), BI-847325 (AURK inhibitor), valemestostat (EZH1/2 inhibitor), tazemetostat (EZH2 inhibitor), or selinexor (XPO1 inhibitor).
- Treatment was continued for 14 days once maximal tumor size reduction was achieved (DTP phase), then was discontinued to monitor tumor regrowth. Tumor regrowth time was determined starting from drug stoppage day.
- In vitro, the X137CL (PHLC137 xenograft-derived cell line) and XDO137 (PHLC137 xenograft-derived organoid) was treated with osi (1 μ M) with or without bemcentinib (0.5 μ M) to induce DTPs to evaluate effects on signaling pathways.

RESULTS

Figure 3. Among molecularly targeted drugs, compared to osi alone, osi combined with bemcentinib significantly delayed tumor regrowth.

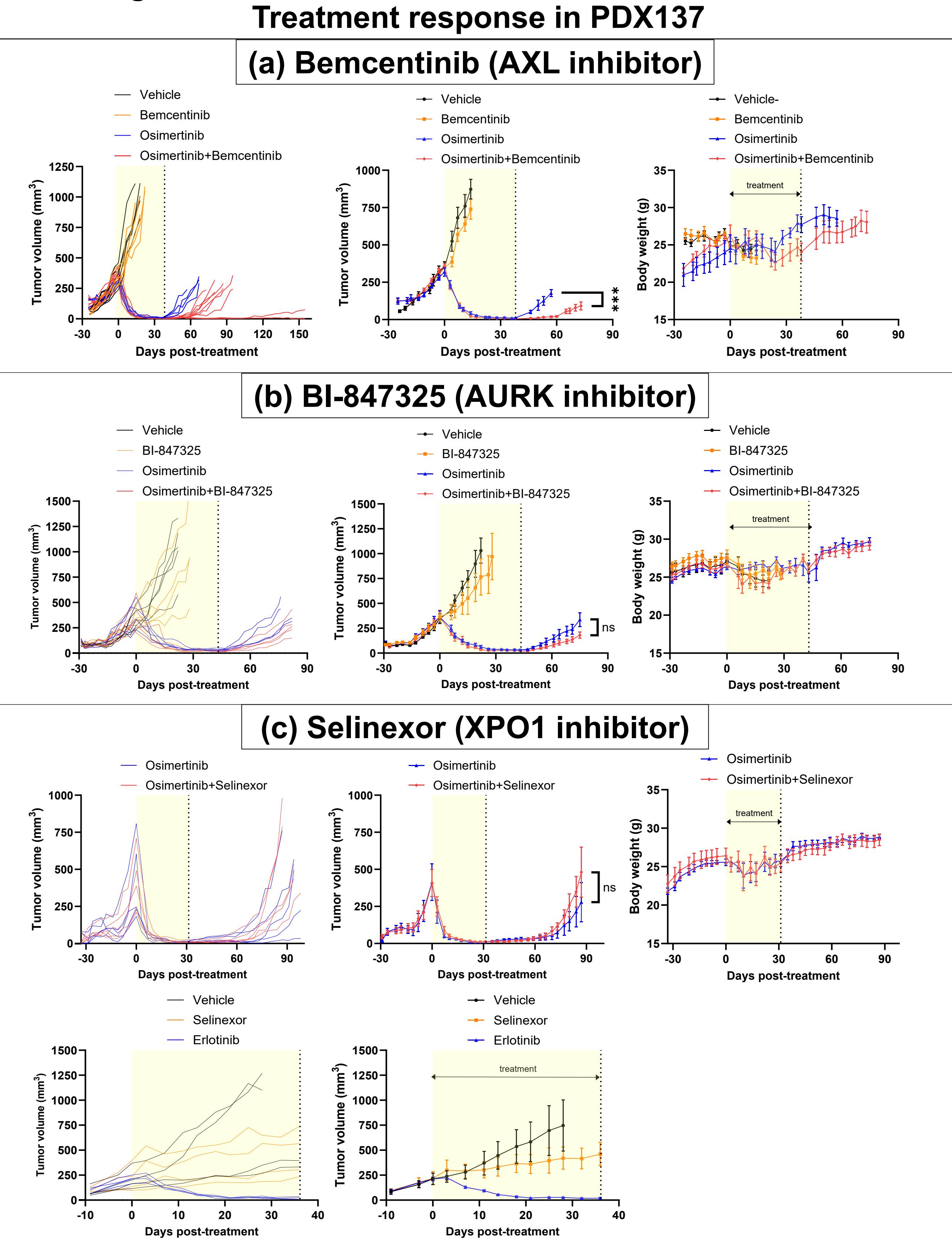


Figure 4. The efficacy of osi plus bemcentinib was confirmed in a second PDX model (PHLC164) harboring EGFR ex19del and T790M mutations.

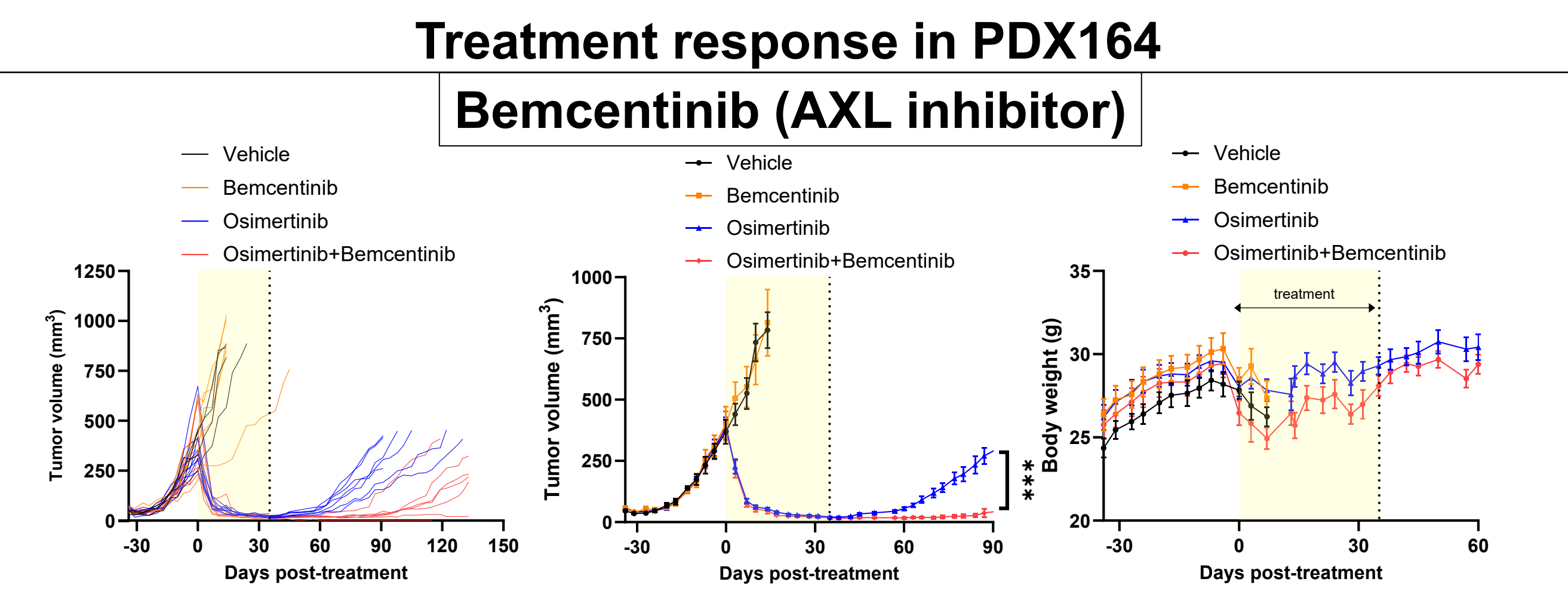


Figure 5. Compared to osi alone, osi with combination with valemestostat significantly delayed tumor regrowth. This effect was also reproduced with osi plus tazemetostat, a selective EZH2 inhibitor.

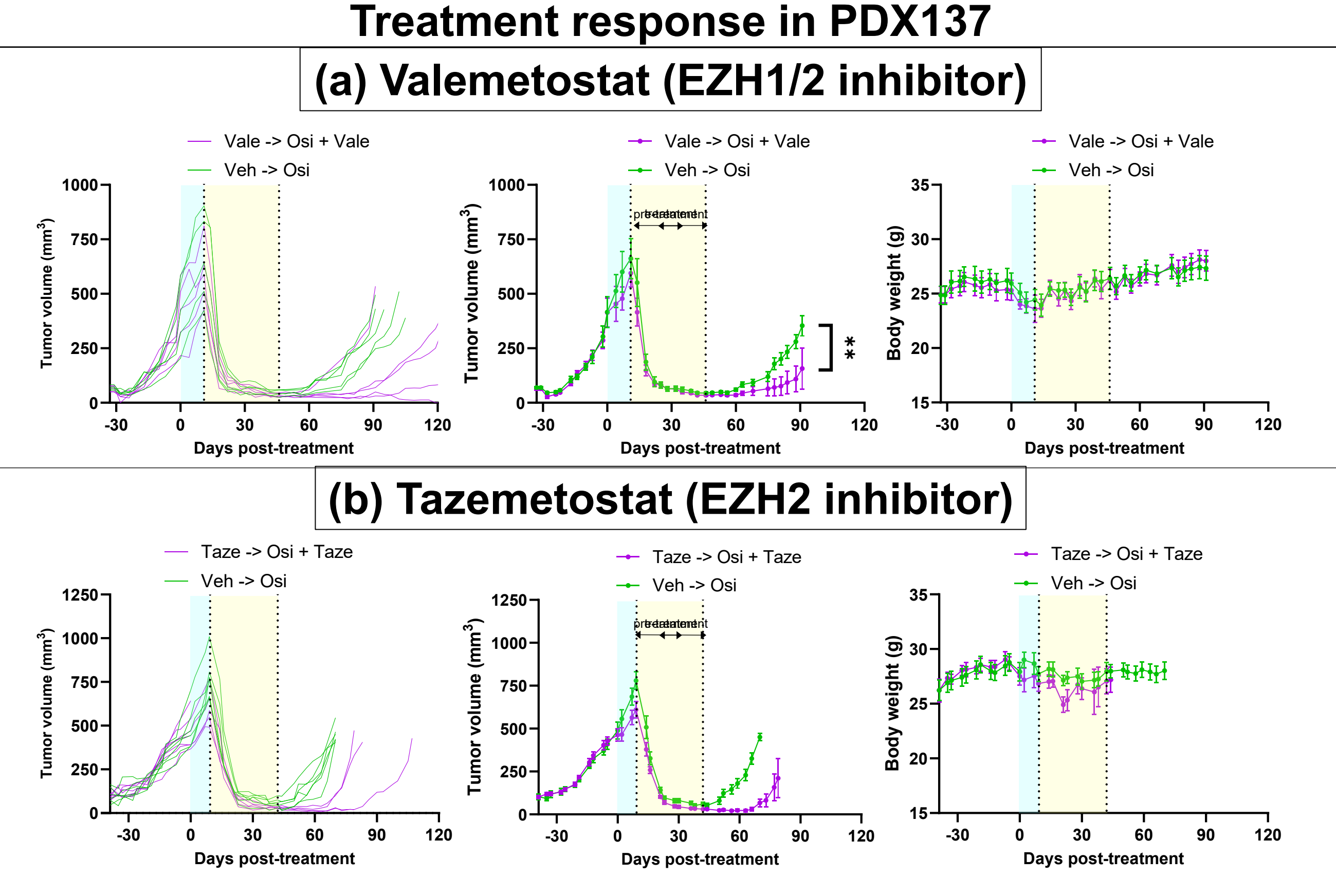
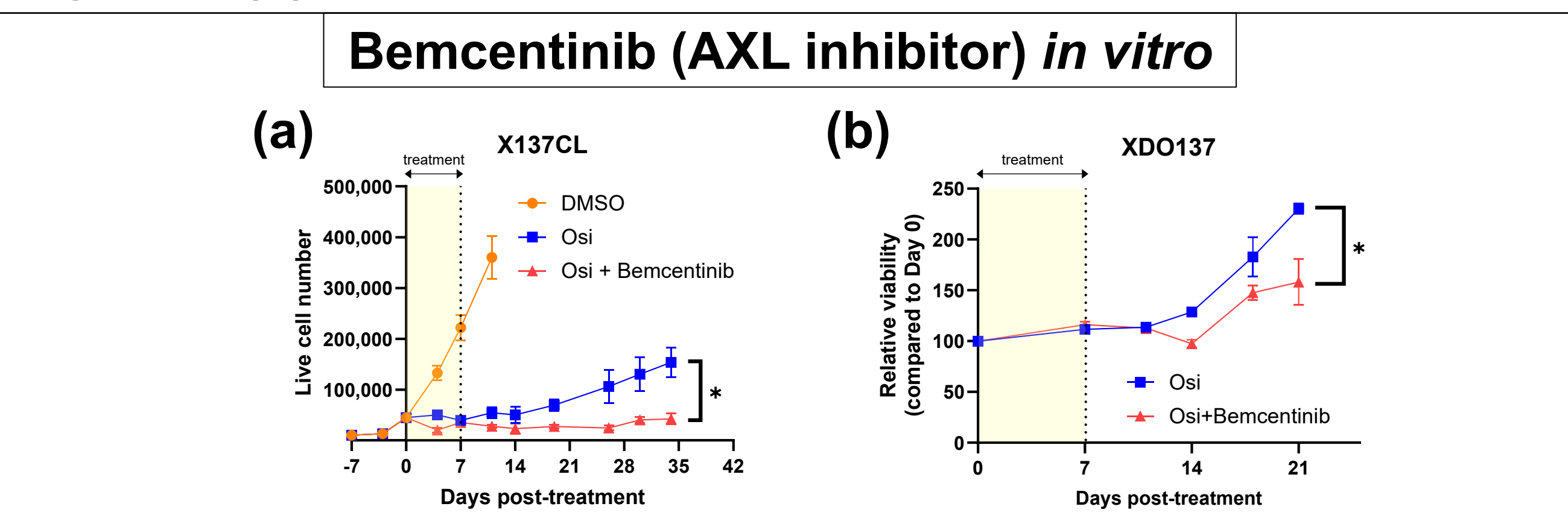


Figure 6. The DTP-suppressive activity of osi plus bemcentinib was recapitulated in the X137CL cell line (a) and the XDO137 organoid (b).



DISCUSSION AND CONCLUSION

- In patient-derived models, AXL pathway and epigenetic regulators may represent additional vulnerabilities in osi-induced DTPs.
- However, despite delay in regrowth, all single agent combination treatments with osi did not achieve complete eradication of the DTP cells.
- Our results suggest that multiple combinatorial strategies may be required to overcome DTPs.

REFERENCES

1. Mikubo M, et al. J Thorac Oncol, 2021, PMID: 34352380.

ACKNOWLEDGMENTS

Supported by the Canadian Institutes of Health Research grant PJT-195924 and the Princess Margaret Cancer Foundation