Osimertinib treatment increases expression of HER2 and combination treatment with trastuzumab deruxtecan, a HER2-directed antibody-drug conjugate, enhances its efficacy in PDX models of EGFR mutant non-small cell lung cancer

P2.02.27

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Introduction

- Osimertinib is a 3rd generation EGFR tyrosine kinase inhibitor that has demonstrated efficacy in the first-line treatment of advanced or metastatic EGFR-mutant NSCLC[1].
- Despite clinical benefit, most patients become refractory to osimertinib[2], highlighting the need for combination strategies to maximize the duration of response or address osimertinib resistance.
- Trastuzumab deruxtecan (T-DXd) is a human epithelial growth factor receptor 2 (HER2)-directed antibody drug conjugate (ADC) approved across multiple indications[3] thus, we wished to understand how T-DXd in combination with osimertinib will perform in EGFRm preclinical models

Results

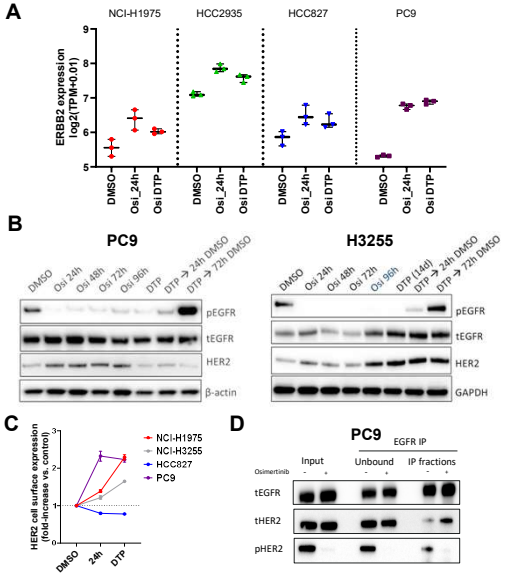


Fig. 1 Osimertinib treatment promotes upregulation of HER2 in vitro A Expression of the mRNA for HER2 in EGFRm cell lines treated with osimertinib for 24h or 21 days (DTP) plotted as log2 of transcripts per million (TPM). Expression of HER2 protein, in whole cell lysates (**B**; western blot) or cell surface (**C**; flow cytometry) in EGFRm cell lines treated with osimertinib (DTP = 14 days treatment). Where indicated DTPs were released from drug for 24 or 72h (DMSO). **D** EGFR IP in PC9 treated with osimertinib for 24h

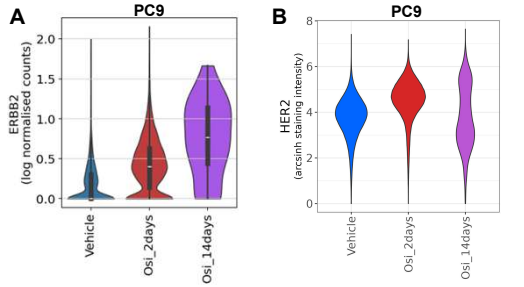


Figure 2: HER2 transcriptional and proteomic levels are heterogenous in PC9 *in vivo* cell population following osimertinib treatment. Transcriptomic (**A**) and proteomic (**B**) levels of HER2 were measured at single-cell resolution using scRNA-Seq and CyTOF, respectively. Logarithmic normalized counts are shown in A. Arcsinh transformation of staining intensity is shown in B.

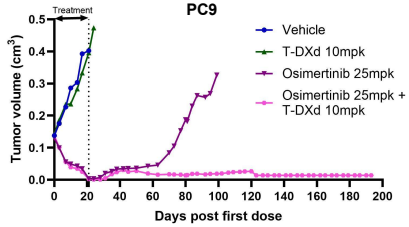
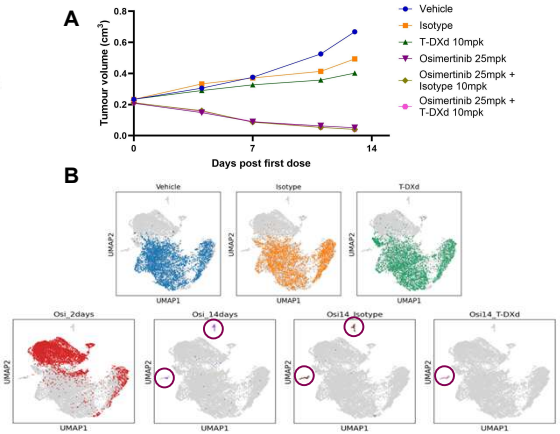


Figure 3: Combination of osimertinib and T-DXd results in delayed regrowth over osimertinib monotherapy *in vivo*. Geometric mean of tumour volume is shown. Treatment took place for 21 days and regrowth of tumours was monitored over time.



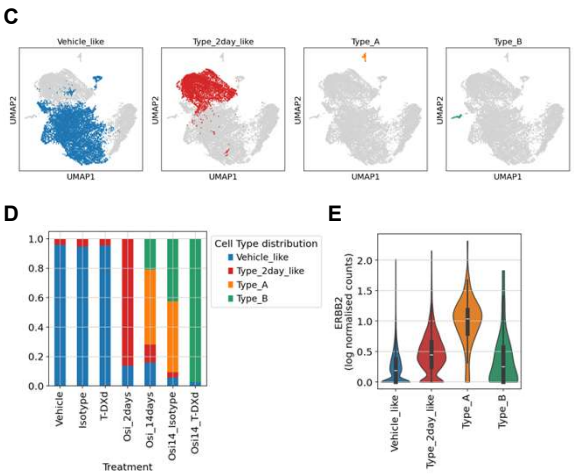
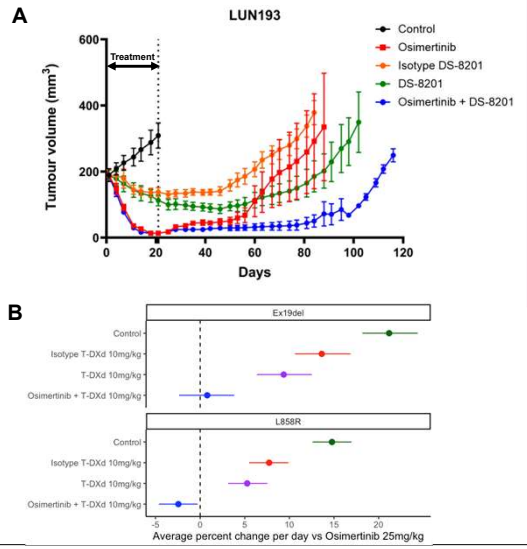


Figure 4.- Combination of osimertinib and T-DXd selectively eliminates a population of osimertinib persister cells with higher levels of HER2 *in vivo*. **A.** *In vivo* efficacy with indicated treatments in the PC9 model. **B, C.** UMAP visualisation of cells coloured according to treatment (**B**) and cell type (**C**). Osimertinib persister population is transcriptionally heterogenous and different to acute treatment. **D.** Type A cells are specifically ablated by the combination treatment. **E.** Type A depleted cells show higher transcriptional levels of ERBB2.



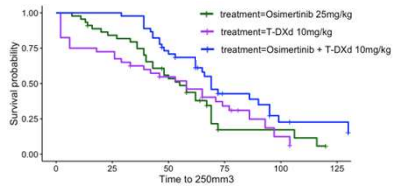


Fig. 5 Combining Osimertinib and T-DXd gives improved efficacy over Osimertinib monotherapy in a subset of 9 (3Ex19 del/6 L858R) EGFRm PDX models *in vivo*. A *In vivo* efficacy with the indicated treatments in the LUN193 PDX model. Antibody therapy was administered on Day 1, while osimertinib treatment continued daily for 21 days, after which there was a drug-free regrowth phase. **B** Comparison of average percent change per day over day 21 versus osimertinib monotherapy. **C** Survival probability, as determined by time to tumours reaching 250 mm², across 9 EGFRm PDX models for the indicated treatment groups.

Conclusions

- Osimertinib treatment leads to increased expression of HER2 at the mRNA and protein level, translating to enhanced levels at the cell surface.
- scRNAseq of PC9 xenografts shows a subset of osimertinib residual cells have high HER2 expression, and this cell population is eliminated by co-treatment with T-DXd.
- The T-DXd/osimertinib combination leads to improved efficacy over osimertinib monotherapy in 4/9 first-line EGFRm PDX models tested.
- Our preclinical data show the potential of a new combination treatment strategy with T-DXd to be used in the first line setting to enhance osimertinib efficacy.

References

1 - Planchard et al., *N Engl J Med 389*(21): 1935-1948, 2023.
2- Leonetti et al., *Br J Cancer.* 121(9):725-737., 2019.
3- Martin et al., Crit Rev Oncol Hematol., 198:104355. 2024

Acknowledgements

We thank PILs, formulation and cell provision teams for their contributions to this study.
This study is sponsored by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).