Introduction

- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor. T-DXd is currently approved for HER2+ metastatic breast cancer and gastric cancer.

- Clinically, T-DXd has demonstrated antitumor activity in both HER2+ and HER2-low patient populations.

- PARP performs a key role as a mediator in the resolution of topoisomerase I cleavage complexes (TOP1cc) through recruitment of TOP11.

- We hypothesized that combination of T-DXd with the PARP1/2 inhibitor olaparib would be able to halt the resolution of TOP1cc and enhance the activity of T-DXd (Fig. 1).

Results and interpretation

In vitro, we found that the combination had enhanced cell killing activity over single agents in 8201a) with the PARP 1/2 inhibitor olaparib has enhanced activity in a panel of breast cancer cell lines with known HER2 status. To enable options for dose-scheduling in the clinic (due to predicted overlapping bone marrow toxicities), we evaluated a gap schedule in vitro.

Conclusions

- T-DXd combined with olaparib is a potentially active combination in breast cancer, with preclinical activity demonstrated in homologous recombination deficient (HRD) and non-HRD models.

- Dose-delay of olaparib may enable an optimized therapeutic index by providing a dose holiday which can maintain anti-tumor activity and minimize toxicity.

Plain language summary

Why did we perform this research?

T-DXd is a HER2 targeting antibody-drug conjugate (ADC) that targets HER2 expressing cells with a Topoisomerase1 (Top1) inhibitor that causes DNA damage. T-DXd has demonstrated significant benefit in breast cancer patients (n=4-5). To further enhance efficacy and expand the duration of response for these patients, we explored whether a combination of T-DXd with a DNA-damage repair inhibitor, olaparib, would have greater benefit than each agent alone, in preclinical models of breast cancer.

How did we perform this research?

We tested whether the combination of T-DXd with olaparib has greater benefit than each agent alone, in breast cancer models with different levels of HER2 expression. We tested the combination in cultured tumor cells and in tumor bearing mice. We also evaluated the combination in cultured normal bone marrow cells to predict potential patient toxicities.

What were the findings of this research and what are the implications?

We identified some breast cancer models that responded better to the combination, both in tumor cell lines grown in culture and in mouse tumor models. We observed modest additional toxicity in the normal bone marrow cell cultures. Collectively, these findings suggest that there is a potential to test whether this combination will bring enhanced benefit to breast cancer patients.

References

4. Modi et al, NEJM 2020; 382:610-621
6. Shihata et al NEJM 2020; 382:25
8. CCLC (Cancer Cell Line Encyclopaedia) - https://sites.broadinstitute.org/ccle