Poster 1911

Dato-DXd mediates anti-tumor activity in preclinical TROP2-expressing intracranial tumor model

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Objective

- To validate Dato-DXd infiltration across the Blood Brain Barrier (BBB) and mediate anti-tumor activity in a TROP2-expressing intracranial tumor model.

Summary

- We successfully generated data supporting Dato-DXd infiltration across the BBB to mediate anti-tumor activity in H1373-Luc intracranial tumors.
- Treatment with Dato-DXd provided a significant survival benefit over treatment with the non-targeting Control ADC.
- We detected increased presence of Dato-DXd within the brain tumor as compared to Control ADC, providing key insights into the ADC biodistribution in brain tumors

Why did we perform this research?

- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate (ADC) consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase I (TOP1) inhibitor payload via a stable, tumor-selective, tetrapeptide-based cleavable linker[1].
- Pharmacotherapy of brain tumors can be limiting due to restricted drug delivery across blood brain and blood tumor barrier. Trastuzumab deruxtecan, an ADC that uses the same DXd ADC technology, has reported clinical activity in patients with brain metastases from HER2+ breast cancer[2], but very little information is available on what drives ADC biodistribution and activity in CNS-involved cancers.
- Here we certify that systemically administered ADCs can penetrate the brain microenvironment and mediate anti-tumor activity in a preclinical model.

How did we perform this research?

- We implanted Luciferase-tagged H1373 (TROP2-expressing NSCLC, H1373-Luc) tumor cells intracranially into NSG mice to evaluate Dato-DXd biodistribution and anti-tumor activity.
- Tumor-bearing mice were dosed with Dato-DXd or matched isotype Control IgG-ADC (DAR4) at 10mpk 7 days or 14 days post intracranial tumor implant and tumor growth was evaluated using IVIS.
- We utilized Immunohistochemistry (IHC) to evaluate ADC localization to the brain tumor.

What were the findings of this research?

- Our study revealed that Dato-DXd inhibited intracranial tumor growth better than Control ADC (Day 7: 105% TGI vs 38% TGI; Day 14: 65% TGI vs <10% TGI, respectively, compared to Vehicle)
- Immunohistochemistry analysis of brain tissue validated localization of Dato-DXd in the tumor, suggesting Dato-DXd can distribute into the local tumor microenvironment in this preclinical tumor model.
- Additionally, treatment with Dato-DXd provided a significant survival benefit over Control ADC (Median survival of 63 days vs 43 days, P=0.0002).

What are the implications of this research?

- This preclinical study supports the inclusion of Dato-DXd in treatment of patients with CNS-involved tumors.
- Understanding the pharmacological determinants of Dato-DXd activity in the CNS will help outline strategies to implement Dato-DXd-based treatment of patients with CNS-involved tumors.

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Introduction

- Dato-DXd is an ADC consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent TOP1 inhibitor payload via a stable, tumor-selective, tetrapeptide-based cleavable linker.
- TROP2 is a cell surface glycoprotein widely expressed across a number of solid tumors with limited expression in normal tissue.

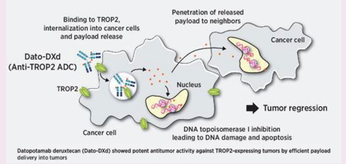
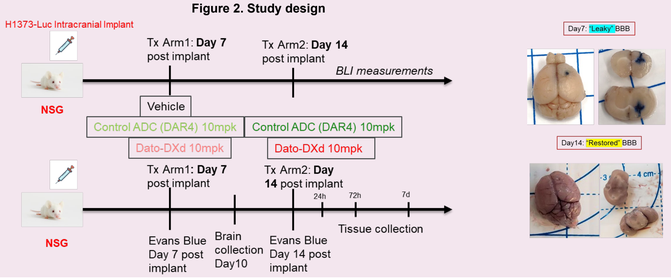


Figure 1. Mechanism of Dato-DXd payload delivery[1].

Methods

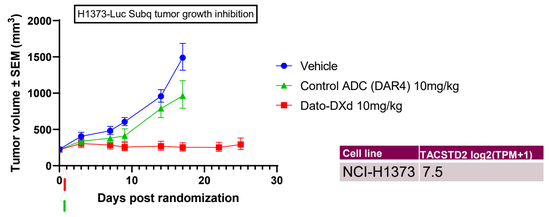
- Animal Procedures: H1373-Luc tagged cells were implanted subcutaneously into Athymic Nude mice (Envigo) or intracranially into NSG mice (Jackson Labs). Evans Blue was injected intravenously at 7 days or 14 days post intracranial tumor implant; brain tissue were imaged to evaluate Evans Blue extravasation into the brain to assess BBB integrity. Vehicle, Control ADC or Dato-DXd was administered intravenously as a single dose at 7 days or 14 days post intracranial implant. Bioluminiscent imaging was performed weekly using an IVIS Spectrum (PerkinElmer) and analysis was performed using LivingImage (Caliper Life Sciences).
- Immunohistochemistry: Formalin fixed brain tissues were analyzed for TROP2 and hulgG expression using TROP2 (Abcam) and hulgG (Human IgG, Jackson ImmunoResearch Labs) Abs respectively. IHC images of γH2A.X foci quantified using digital scoring.

Figure 2. Study design



Dato-DXd exhibits anti-tumor activity in H1373-Luc subcutaneous tumor model

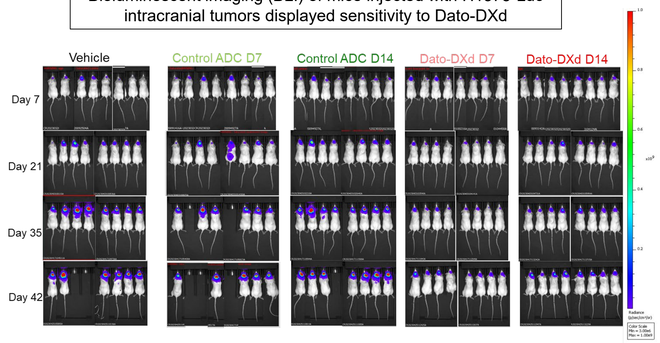
H1373-Luc (subcutaneous xenograft) tumor model is sensitive to Dato-DXd



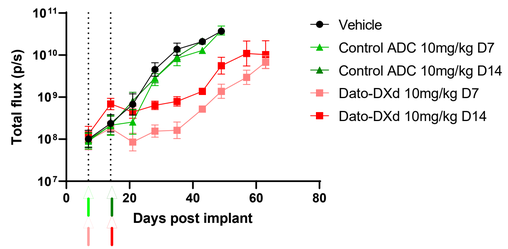
Cell line	TACSTD2 log2(TPM+1)
NCI-H1373	7.5

Dato-DXd is efficacious in H1373-Luc intracranial tumor model, irrespective of the leakiness of BBB

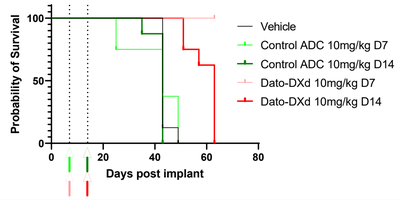
Bioluminescent imaging (BLI) of mice injected with H1373-Luc intracranial tumors displayed sensitivity to Dato-DXd



Quantification of BLI data

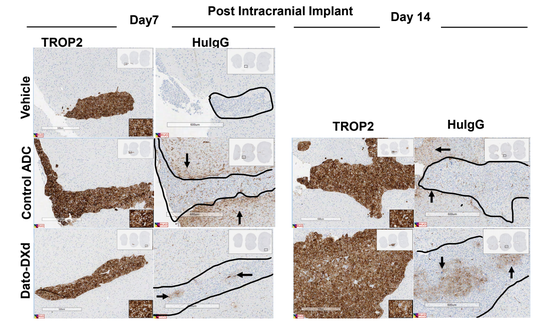


Treatment with Dato-DXd provided a significant survival benefit over treatment with the non-targeting Control ADC

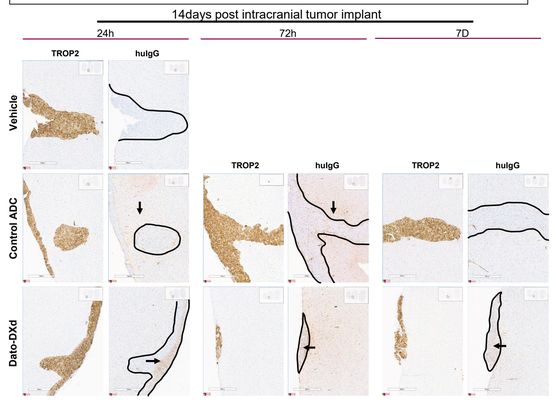


Dato-DXd localizes to brain tumor and potentiates DNA damage induction

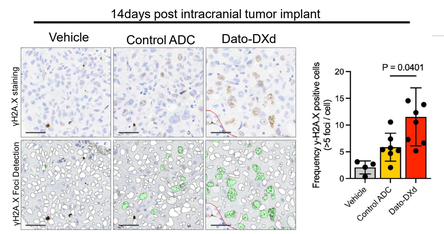
Dato-DXd detected within H1373-Luc brain tumor, while Control ADC detected at the periphery (black arrows), 72h post ADC dose, suggesting TROP2 mediated Dato-DXd activity



Dato-DXd can be detected in the H1373-Luc brain tumor up to 7 days post ADC dosing



Dato-DXd treatment results in significant increase of γH2A.X foci, 72h post ADC dose, suggesting DNA damage induction.



Conclusions

- **The H1373-Luc NSCLC tumor model was utilized to evaluate Dato-DXd biodistribution across blood brain barrier; Dato-DXd can penetrate across the BBB, irrespective of its leakiness and localize into the intracranially implanted tumor.**
- **Dato-DXd efficacy in H1373-Luc intracranial tumor is target-dependent, as evidenced by lack of non-targeted Control ADC activity.**
- **Dato-DXd treatment provides a significant survival benefit over Control ADC.**
- **Collectively, this study provides preclinical proof of concept for Dato-DXd biodistribution and activity in NSCLC intracranial tumor; efforts ongoing to investigate additional models of brain metastasis.**

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Disclosures

All authors are employees of AstraZeneca Pharmaceuticals..

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