Poster #1840: Potent antitumor efficacy of Dato-DXd compared with sacituzumab govitecan in a brain metastasis mouse model of triple-negative breast cancer

Presenter: Chikako Funasaka[1,2,3,4]

Co-authors: Hiroki Takashima[3], Daisuke Okajima[5], Takanori Maejima[5], Satoru Yasuda[5], Tsuyoshi Karibe[5], Shuichi Mitsunaga[4,6], Toru Mukohara[1,4], Toshihiko Doi[2], Masahiro Yasunaga[3]

Departments of [1]Medical Oncology, [2]Experimental Therapeutics, and [6]Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa city, Chiba, Japan.

[3]Division of Developmental Therapeutics, National Cancer Center Exploratory Oncology Research and Clinical Trial Center, Kashiwa city, Chiba, Japan

[4]Courses of Advanced Clinical Research of Cancer, Juntendo University Graduate School of Medicine, Hongo, Tokyo, Japan.

[5]Daiichi Sankyo Company, Limited, Shinagawa, Tokyo, Japan.

BACKGROUND:

The prognosis for patients with brain metastases is poor. The brain tissue and intrathecal space are difficult environments for drugs to reach because of the blood–brain barrier.

In recent years, the use of anti-HER2 drugs has been shown to improve prognosis in HER2-positive breast cancer (BC) (1). Among antibody–drug conjugates (ADCs), trastuzumab deruxtecan (T-DXd) has a higher intracranial objective response rate (iORR) than trastuzumab emtansine (T-DM1). In metastatic brain tumors of triple-negative breast cancer (TNBC), cytotoxic anticancer agents are the mainstay of treatment. Sacituzumab govitecan (SG), an anti-TROP2-ADC, is approved in the USA for advanced TNBC, but the iORR was only 3% (2). Datopotamab deruxtecan (Dato-DXd), another anti-TROP2-ADC, delivers its payloads to the tumor via a cleavable tetrapeptide-based linker (3). Dato-Dxd is approved in the USA and Japan for HR+ HER2- BC and is being investigated in TNBC as a monotherapy and in combination with durvalumab (TROPION-Breast02 and TROPION-Breast05, respectively). Dato-DXd showed a favorable antitumor effect in TNBC brain metastases (4), but the pharmacodynamics of Dato-DXd in brain metastases have not been determined. Here, we evaluated the efficacy and payload distribution of Dato-DXd and SG in a mouse brain metastasis model of TNBC.

OBJECTIVES:

1: To generate mouse models of metastatic brain tumors from TNBC cell lines
2: To evaluate changes in expression of drug target molecules in brain metastatic foci
3: To evaluate the efficacy of anti-TROP2-ADC in metastatic brain tumor models
4: To visualize and quantify the distribution of antibody and payload components of these ADCs in metastatic brain tumor models

METHODS (schema):

Experiment 1: Creation of a brain tumor model

A brain metastasis model was created by intracranial injection of cancer cells.

Experiment 2: Biological characterization of the tumor

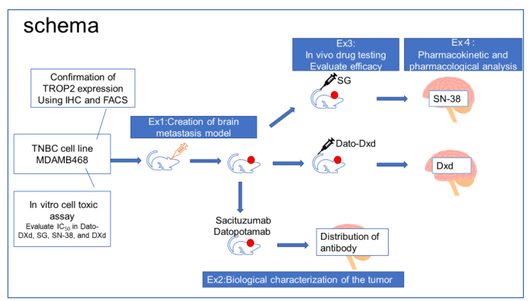
The expression status of the drug target molecule, TROP2, was evaluated histopathologically in tumor tissues collected after tumor formation.

Experiment 3: In vivo drug testing

Once the tumors reached the standard size (set value based on IVIS analysis), the animals were randomly divided into groups treated with Dato-DXd or SG. The drugs were administered intravenously to each group. Tumor chemiluminescence (measured by IVIS Lumina S5) and body weight were measured to observe the treatment effect and toxicity, respectively.

Experiment 4: Pharmacokinetic and pharmacological analysis

The animals were randomly grouped into mice treated with Dato-DXd or SG. The drugs were administered intravenously to each group. At 0 (immediately after administration), 6, 24, 48, and 72 hours after administration, tumor and blood samples were collected under anesthesia from each group for pharmacokinetic analysis.



RESULTS

MDA-MB-468 cells had moderately high TROP2 expression and uniformly expressed TROP2 in immunohistochemical staining (Figure 1). Datopotamab (antibody of Dato-DXd) and sacituzumab (antibody of SG) showed the same binding ability to each cell line (Figure 2).

Figure 1

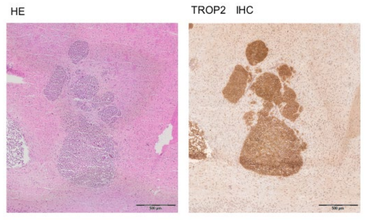
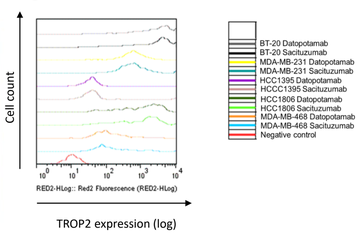


Figure 2



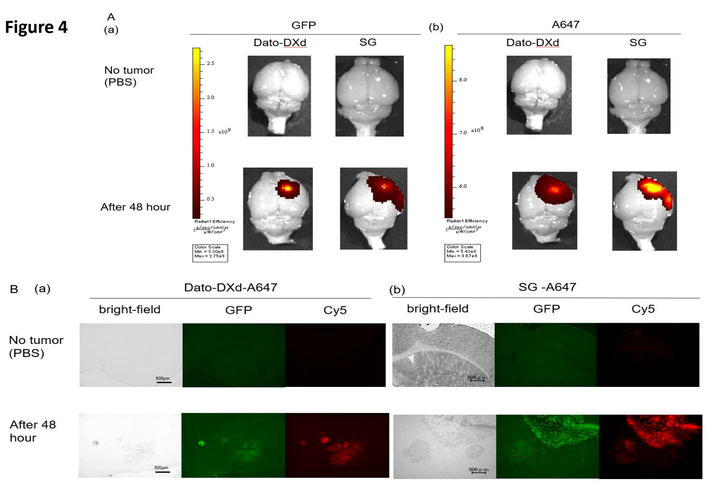
We evaluated in vitro cell cytotoxicity (IC_{50}) of SG, Dato-DXd, SN-38, and DXd. Dato-DXd showed a higher IC_{50} than other compounds (Table 1).

Table 1. IC_{50} of SG, Dato-DXd, SN-38, and Dxd

Cell line		SG (nM)	Dato-DXd (nM)	SN-38 (nM)	DXd (nM)
HCC1806	Average ± SD	114.4 ± 16.0	>200	158.0 ± 28.3	180.7 ± 88.1
MDA-MB-231	Average ± SD	173.7 ± 27.8	>200	213.9 ± 16.0	191.6 ± 11.2
MDA-MB-468	Average ± SD	136.1 ± 164.7	>200	49.7 ± 46.6	87.4 ± 48.1
HCC1395	Average ± SD	207.5 ± 15.6	>200	152.4 ± 20.3	221.0 ± 6.41
BT-20	Average ± SD	161.3 ± 35.3	>200	154.5 ± 10.8	154.0 ± 5.75

Both Dato-DXd and SG accumulated in accordance with tumor localization (GFP in Figure 4A–B). In the high-magnification image, the antibodies were mainly distributed at the edge of the tumor (Figure 4B).

Figure 4



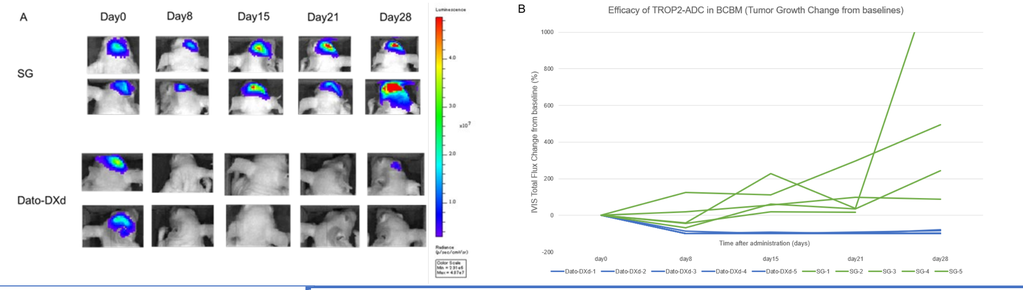
References

1. Niwinska A, et al. Intracranial Response Rate in Patients with Breast Cancer Brain Metastases after Systemic Therapy. Cancers. 2022;14(4):965. 2.Véronique Diéras, et al. Abstract PD13-07: Subgroup Analysis of Patients with Brain Metastases from the Phase 3 ASCENT Study of Sacituzumab Govitecan Versus Chemotherapy in Metastatic Triple-Negative Breast Cancer. Cancer Res 15 February 2021; 81 (4_Supplement): PD13–07.
3 Okajima D, et al. Datopotamab Deruxtecan, a Novel TROP2-directed Antibody-drug Conjugate, Demonstrates Potent Antitumor Activity by Efficient Drug Delivery to Tumor Cells. Mol Cancer Ther. 2021;20(12):2329-40. 4.Bardia A, et al. Datopotamab Deruxtecan in Advanced or Metastatic HR+/HER2– and Triple-Negative Breast Cancer: Results From the Phase I TROPION-PanTumor01 Study. Journal of Clinical Oncology. 2024;42(19):2281-94.

Dato-DXd and SG, both at 10 mg/kg, were administered intravenously on day 1.

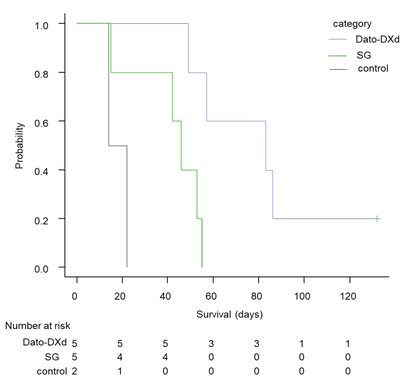
The percentage change in total flux [p/s] from baseline in the brain metastasis model was higher in the Dato-DXd group (average: –97.28%) than in the SG group (–1.8%) at day 8 after administration (Figure 3A–B) and Dato-DXd led to significantly greater tumor regression than SG. On day 15, tumor regrowth was observed in the SG group (Figure 4A), but shrinkage was maintained until day 28 in the Dato-DXd group.

Figure 3



Dato-DXd treatment led to prolonged survival. The median survival of animals with brain metastases was 18 days (range: 14 - 22 days) in the control group, 48 days (15 - 55 days) in the SG group, and 83 days (49 – not reached[NR] days) in the Dato-DXd group (p=0.0018; Figure 5).

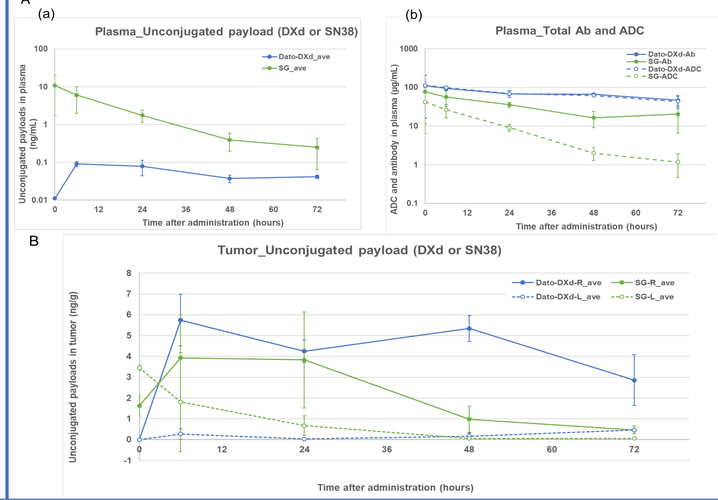
Figure 5



Unconjugated payload in the plasma was lower in Dato-DXd than in SG (Figure 6A (a) and (b)). The payload in the brain tumor remained higher over time in Dato-DXd than SG (Figure 6B). The area under the payload concentration-time curve was higher in the Dato-DXd group (320.9 ng.hr/g) than in the SG group (161.8 ng.hr/g).

The unconjugated payload of SG in plasma and tumor decreased over time. The unconjugated payload in the normal tissue (left hemisphere) of the brain was lower than in the tumor side in both Dato-DXd and SG groups. The area under the payload concentration-time curve in the normal brain was 13.7 ng.hr/g in the Dato-DXd group and 48.5 ng.hr/g in the SG group.

Figure 6



Conclusions

Dato-DXd has potent antitumor activity compared to SG in a TNBC brain tumor mouse model (Figures 3A–B and 5). Although the delivery of the antibody of both ADCs was similar, the concentration and retention time of the free payload were different between the ADCs. While the free payload of SG showed low accumulation in brain tumors and the concentration in tumors decreased within a short period, that of Dato-DXd was maintained in the brain tumors. Our study suggests that the retained concentration of DXd results in greater efficacy (Figures 3 and 6B). Thus, ADCs that can retain their payloads in tumors might be suitable therapeutics against intraparenchymal lesions. A limitation of this study is that the recommended doses for patients are 10 mg/kg SG on day 1 and day 8 every 3 weeks and 6 mg/kg Dato-DXd once every 3 weeks, and the dosing used in this model does not directly correlate with human dosages, necessitating caution in interpreting the results.