San Antonio Breast Cancer Symposium - December 9-12, 2025 – Abstract 469

Intracranial Activity of Datopotamab Deruxtecan (Dato-DXd) for Patients with HER2-negative Breast Cancer and Leptomeningeal Disease (LMD): Results from Cohort C of the DATO-Base Phase 2 Trial

PS1-09-20

Paolo Tarantino, Ningxuan Zhou, Tianyu Li, Emma Kelly, Clare Strickland, Nay Nwe Nyein Chan, Michelle DeMeo, Leilani Anderson, Esther Pasternak, Carey Anders, Manmeet Ahluwalia, Reshma Mahtani, Liangge Hsu, Sarah Ossing, Adrienne G. Waks, Caroline Block, Ana C. Garrido-Castro, Susan Schumer, Ilana Schlam, David L. Rimm, Nabihah Tayob, Sara M. Tolaney, Nancy U. Lin and Sarah L. Sammons

AFFILIATIONS: Dana-Farber Cancer Institute, Boston, MA, USA; Harvard Medical School, Boston, MA, USA; Yale School of Medicine, New Haven, CT, USA; Duke Cancer Center, Durham, NC, USA; Miami Cancer Institute, Miami, FL, USA; Brigham and Women's Hospital, Boston, MA, USA

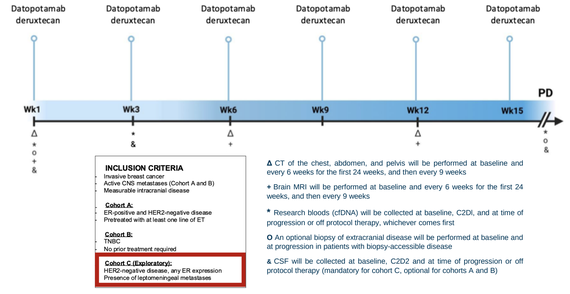
BACKGROUND

LMD represents a rare but devastating manifestation of metastatic breast cancer (MBC), historically associated with a survival of 3-4 months and representing a significant unmet need. Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed antibody-drug conjugate (ADC) that has demonstrated promising activity for HER2-negative MBC and clinical evidence of central nervous system (CNS) activity in patients with lung cancer.

METHODS

- DATO-Base (NCT06176261) is a multicenter, multicohort phase II trial enrolling patients with HER2-negative MBC and active CNS disease. Cohort C was an exploratory cohort enrolling patients with HER2-negative MBC and LMD, either newly diagnosed or progressive. Prior systemic therapy for LMD and prior ADCs were permitted.
- Patients received Dato-DXd 6 mg/kg IV Q3W until progression, unacceptable toxicity, or withdrawal. Exploratory endpoints include overall survival, radiographic and clinical response according to LANO criteria, intracranial progression-free survival (PFS), safety, neurological function according to the NANO scale and biomarker analyses.
- Recommended prophylaxis: three-drug antiemetic regimen (including dexamethasone, 5-HT3 receptor antagonist, NK1 receptor antagonist); daily steroid-containing mouthwash x4; artificial tears daily x4. Ophthalmologic assessments were done at screening, then as needed.
- Sections from archival tissue samples were stained for HER2 and TROP2 using the TROPLEX quantitative immunofluorescence assay, to obtain high-sensitivity (HS)-Trop2 and HS-HER2 expressions (attomoles/mm²).

TRIAL SCHEMA



RESULTS

A total of 10 patients were enrolled in Cohort C (**Table 1**). Median age was 49, 8 had hormone receptor–positive and 2 had triple-negative disease. Patients had a median of 2.5 (range 0-6) prior lines of cytotoxic treatment, with 7 patients who had received prior ADCs (3 with prior T-DXd, 2 with prior SG, 2 with both ADCs).

	Overall (N=10)
Age at enrollment	
Median [Min, Max]	48.9 [39.8, 76.3]
Sex	
Female	10 (100%)
Neuro symptoms at baseline	
Yes	7 (70.0%)
No	2 (20.0%)
Missing	1 (10.0%)
ER status	
Positive (>=10%)	7 (70.0%)
Low	1 (10.0%)
Negative	2 (20.0%)
HER2 status	
Negative	9 (90.0%)
Unknown	1 (10.0%)
Extracranial disease at the time of LMD diagnosis	
Yes	9 (90.0%)
No	1 (10.0%)
MRI evidence of LM	
Brain and Spine	3 (30.0%)
Brain only	4 (40.0%)
Spine only	3 (30.0%)
Prior local therapy for CNS disease	
No prior treatment	2 (20.0%)
SRS/SRT + Surgery	2 (20.0%)
Surgery	3 (30.0%)
WBRT	3 (30.0%)
Prior lines of cytotoxic treatment	
Median [Min, Max]	2.50 [0, 6.00]
Prior lines of ADC	
Median [Min, Max]	1.00 [0, 2.00]

Table 1 – Clinicopathologic characteristics of patients in Cohort C

Response rate by LANO criteria was 30% (n=3/10), with two partial responses in ADC-naive patients and one complete response in an ADC-pretreated patient (prior SG). (**Figure 1**)

With a median follow up of 8.1 months, the **median intracranial PFS was 4.1 months** (95% CI: 0.7 to NR), and **median OS was 4.7 months** (95% CI: 0.7 to NR). **ADC-naïve patients (n=3) experienced numerically longer intracranial PFS** (5.9 vs 1.4 months)**, and longer OS** (13.3 vs 3.7 months) compared with ADC-pretreated patients. (**Figure 2**)

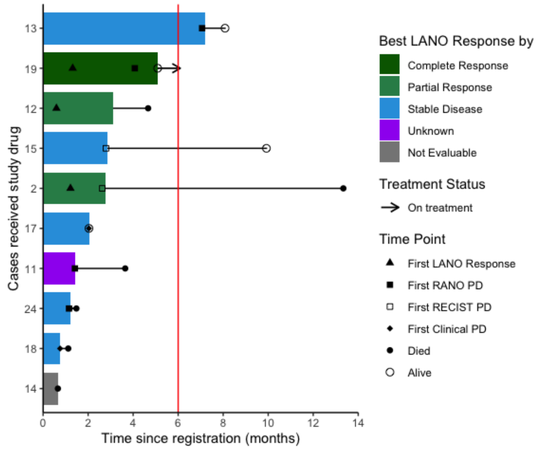


Figure 1 – Response to Dato-DXd according to LANO criteria

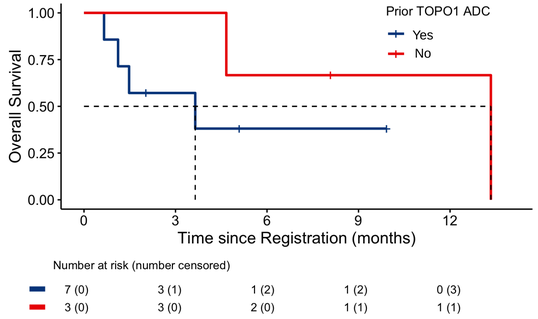


Figure 2 – Overall Survival according to prior receipt of TOPO1 ADCs

Among 8 patients with Troplex data available, **all had HS-Trop2-high disease (above Level of Quantification), whereas only 50% had HS-HER2-high disease**. Descriptive OS curves according to HS-Trop2 and HS-HER2 are reported in **Figure 3**.

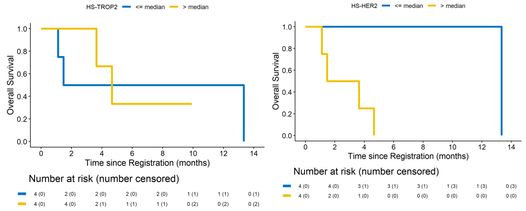


Figure 3 – Overall Survival according to HS-Trop2 and HS-HER2

The most common treatment emergent adverse events (TRAEs) were fatigue, mucositis, and nausea (**Table 2**). Serious adverse events were reported in 4 patients (40%), with 2 (20%) considered treatment-related by the investigator. No interstitial lung disease nor grade 5 TRAEs were observed.

Out of 7 patients who had neurological symptoms at baseline, improvement in at least one was observed in 5 patients, with 1 patient showing stable symptoms and 1 missing follow up NANO assessment.

TEAE (>=20%)	Total (N = 10)	
	All Grade	Grade >=3
	N (%)	N (%)
Fatigue	5 (50%)	2 (20%)
Mucositis oral	4 (40%)	2 (20%)
Nausea	4 (40%)	2 (20%)
Vomiting	3 (30%)	2 (20%)
Headache	3 (30%)	2 (20%)
Anemia	3 (30%)	0 (0%)
Thrush	3 (30%)	0 (0%)
Dyspnea	2 (20%)	1 (10%)
Hydrocephalus	2 (20%)	2 (20%)
Seizure	2 (20%)	1 (10%)
Cough	2 (20%)	1 (10%)
Thromboembolic event	2 (20%)	1 (10%)
Neutrophil count decreased	2 (20%)	0 (0%)

Table 2 – Treatment Emergent Adverse Events

CONCLUSIONS

In this exploratory cohort, **Dato-DXd** demonstrated promising intracranial activity in patients with HER2-negative MBC and LMD, including **radiographic responses** and **improvement in neurological symptoms in most patients with baseline deficits**. Outcomes appeared **more favorable in ADC-naïve patients**, although numbers were limited.

CORRESPONDING AUTHOR:
Paolo Tarantino, MD, PhD
Paolo_Tarantino@DFCI.HARVARD.EDU
@PTarantinoMD

Funding: Daiichi Sankyo, AstraZeneca, Kiki Fund for Leptomeningeal Research, Terri Brodeur Foundation, METAvivor.

This presentation is the intellectual property of the author/presenter. Contact them at for permission to reprint and/or distribute.