Poster Number: CT071
AACR 2025

Phase I trial of trastuzumab deruxtecan in combination with neratinib in solid tumors with HER2 alterations (NCI 10495)

Andrew A. Davis[1], Haeseong Park[2], Ecaterina E. Dumbrava[3], Nataliya V. Uboha[4], Aparna Kalyan[5], Farshid Dayyani[6], Mili Arora[7], Miguel A. Villalona-Calero[8], Haider S. Mahdi[9], Reema A. Patel[10], Floor Backes[11], Jessica Porzel[1], Whitney L. Hensing[12], Cheryl Pickett[13], Cynthia X. Ma[1], Ron Bose[1]

[1]Washington University in St. Louis, [2]Dana-Farber Cancer Institute, [3]MD Anderson Cancer Center, [4]University of Wisconsin Madison, [5]Northwestern University, [6]University of California, Irvine, [7]Univeristy of California, Davis, [8]City of Hope, [9]University of Pittsburgh Medical Center, [10]University of Kentucky, [11]The Ohio State University, [12]Saint Luke's Cancer Institute, [13]National Cancer Institute

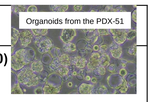
NCT05372614

aadavis@wustl.edu

BACKGROUND

Patient-derived xenograft (PDX) models of *HER2* mutated advanced breast cancer demonstrate synergy of trastuzumab deruxtecan (T-DXd) and neratinib.

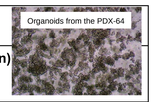
PDX-51



***ERBB2* G776insYVMA (HER2 exon20)**
PIK3CA H1047R
HER2 IHC 2+, ER/PR+

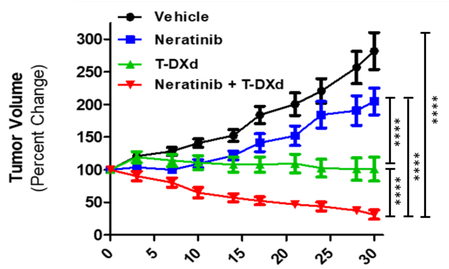
Prior Hormonal Therapy	Prior Chemotherapy
Tamoxifen, Letrozole, Exemestane, Fulvestrant Exemestane + Everolimus	CMF, Paclitaxel, Capecitabine, Carboplatin, Gemcitabine

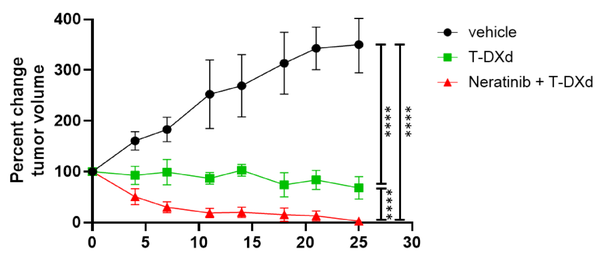
PDX-64



ERBB2 L869R (HER2 Kinase Domain)
PIK3CA WT
HER2 IHC 1+, ER+, PR neg.

Prior Hormonal Therapy	Prior Chemotherapy
Tamoxifen Anastrozole Exemestane + Everolimus	Docetaxel, Doxorubicin, Cyclophosphamide, Capecitabine





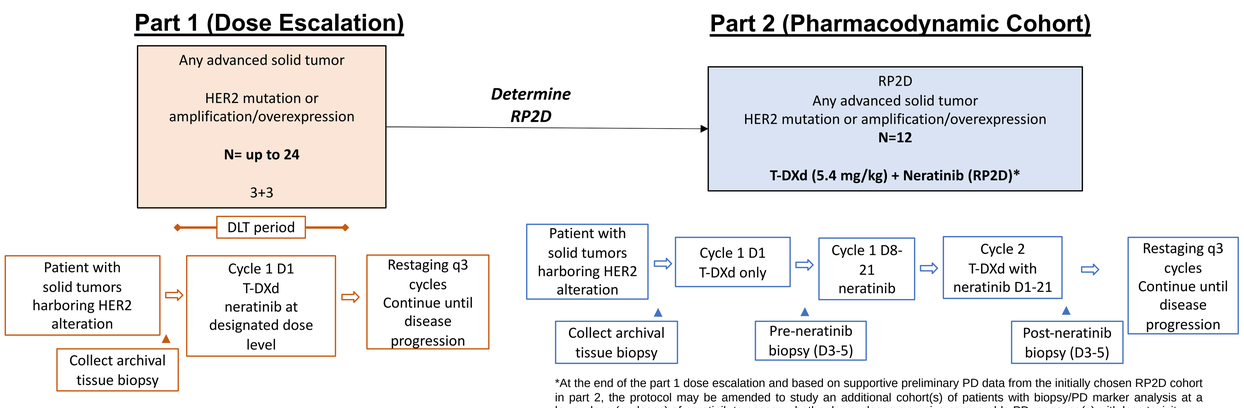
****** p<0.0001**

Bose et al. SABCS 2020

- Neratinib is an oral, irreversible pan-HER tyrosine kinase inhibitor.
- T-DXd is an antibody-drug conjugate targeting HER2 with a topoisomerase I inhibitor payload.
- The mechanism of synergy is proposed to occur via enhanced endocytosis via HSP90 binding to the HER2 receptor, thereby inducing receptor ubiquitination and internalization.

STUDY SCHEMA

Primary endpoint: Dose-limiting toxicities during the first 2 cycles of T-DXd and neratinib in advanced solid tumors with HER2 alterations and incidence of treatment-emergent adverse events



*At the end of the part 1 dose escalation and based on supportive preliminary PD data from the initially chosen RP2D cohort in part 2, the protocol may be amended to study an additional cohort(s) of patients with biopsy/PD marker analysis at a lower dose (or doses) of neratinib to assess whether lower doses may give comparable PD response(s) with less toxicity

- Part 2 of the study opened to enrollment in March 2025

RESULTS

Dose Level 3 was selected as the Recommended Phase 2 Dose (RP2D)

Dose Level	Neratinib	T-DXd	Cycle Length
Level -1	120 mg PO, QD	5.4 mg/Kg, IV, Q3W	21 days All patients received mandatory loperamide prophylaxis for diarrhea
Level 1*	120 mg PO, QD C1D1-7 160 mg, PO, QD C1D8 onward	5.4 mg/Kg, IV, Q3W	
Level 2	120 mg PO, QD C1D1-7 160 mg, PO, QD C1D8-14 200 mg, PO, QD C1D15 onward	5.4 mg/Kg, IV, Q3W	
Level 3	120 mg PO, QD C1D1-7 160 mg, PO, QD C1D8-14 240 mg, PO, QD C1D15 onward	5.4 mg/Kg, IV, Q3W	

*Starting Dose Level. PO = Orally, QD = Once daily, IV = Intravenous, Q3W = Once every 3 weeks

Dose limiting toxicities (DLT)
DL1: 1 (acute kidney injury)

DL2: 0

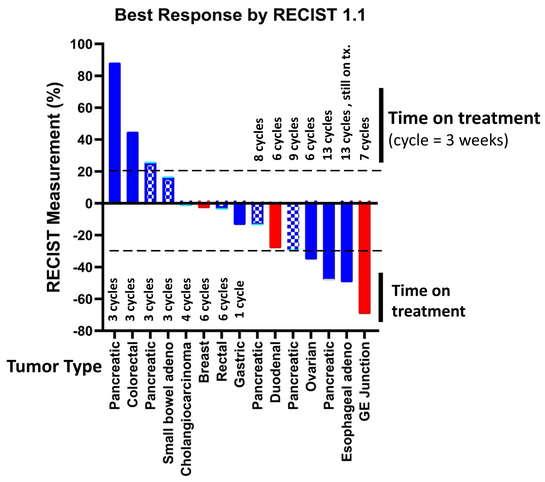
DL3: 1 (fatigue leading to early drug discontinuation)

Common treatment-emergent adverse events (all grade)

AE	Dose Level 1 (n=7)		Dose Level 2 (n=4)			Dose Level 3 (n=9)		Overall (n=20)
	Any Grade	Grade 3	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	
Diarrhea	6 (86%)	1 (14%)	3 (75%)	2 (50%)		6 (67%)	1 (11%)	15 (75%)
Nausea	6 (86%)	1 (14%)	3 (75%)			6 (67%)	1 (11%)	15 (75%)
Fatigue	5 (71%)	1 (14%)	2 (50%)			6 (67%)	1 (11%)	13 (65%)
Hypokalemia	4 (57%)	1 (14%)	4 (100%)	2 (50%)		3 (33%)		11 (55%)
Anemia	5 (71%)	4 (57%)	3 (75%)	1 (25%)		2 (22%)	1 (11%)	10 (50%)
Neutrophil count decreased	5 (71%)		3 (75%)		1 (25%)	2 (22%)		10 (50%)
Vomiting	3 (43%)		2 (50%)			5 (56%)	1 (11%)	10 (50%)
Hypoalbuminemia	4 (57%)		3 (75%)			2 (22%)		9 (45%)
Constipation	3 (43%)		1 (25%)			4 (44%)		8 (40%)
Lymphocyte count decreased	2 (29%)		2 (50%)			4 (44%)	1 (11%)	8 (40%)
Weight loss	3 (43%)		2 (50%)			3 (33%)		8 (40%)
ALT increased	3 (43%)		2 (50%)			2 (22%)		7 (35%)
Hyponatremia	3 (43%)		1 (25%)			3 (33%)		7 (35%)
White blood cell decreased	3 (43%)		2 (50%)			2 (22%)		7 (35%)
Anorexia	5 (71%)	1 (14%)	1 (25%)					6 (30%)
Cough	3 (43%)		2 (50%)			1 (11%)		6 (30%)
Hypertension	3 (43%)		1 (25%)			2 (22%)		6 (30%)
Hypomagnesemia	3 (43%)		2 (50%)			1 (11%)		6 (30%)

- The most common all grade toxicities were diarrhea, nausea, and fatigue.
- Grade 3-4 toxicities were less common.
- No treatment-related deaths occurred.
- 3 patients experienced Grade 1 pneumonitis/ILD: 2 at DL1 and 1 at DL3.

Response data



- 5 patients were not included in the waterfall plot: (3) patients did not have any follow up scans post baseline and (2) patients came off therapy due to disease-related factors

Red = HER2 mutation

Solid Blue = HER2 3+ IHC

Hatched Blue = HER2 amplified by NGS or FISH

- Data cutoff 2/17/25
- There were 3 confirmed partial responses (PR) and 1 unconfirmed PR (ovarian cancer patient)

The combination of T-DXd and neratinib had a manageable safety profile with DL3 selected as the RP2D. Promising signals of activity were observed, and Phase II studies are planned.

We are thankful for the support from NCI CTEP, UM1CA18668907, Puma Biotechnology, Daiichi Sankyo/AstraZeneca, the Foundation for Barnes-Jewish Hospital, and the Siteman Cancer Center. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).