



# Antitumor Activity of Datopotamab Deruxtecan in a Co-clinical Trial with Patient Derived Xenografts

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<sup>1</sup>The University of Texas MD Anderson Cancer Center, <sup>2</sup>Daiichi Sankyo

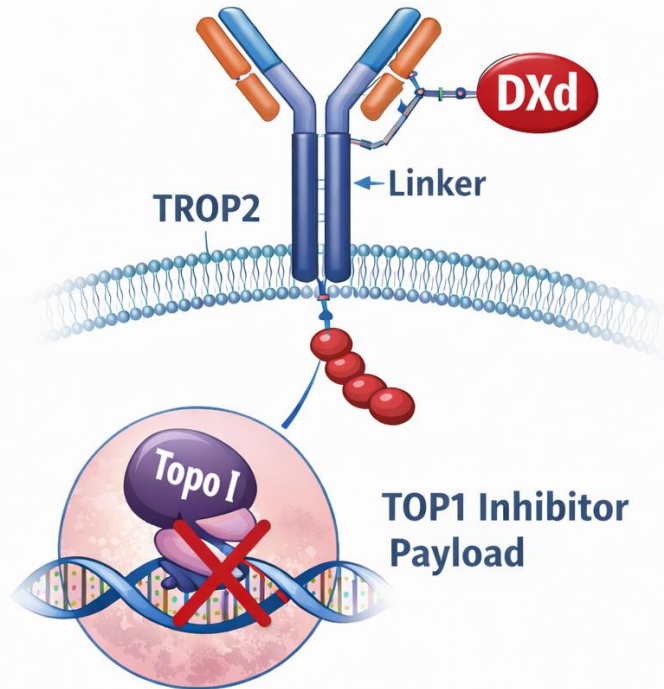
# Disclosure Information

Dhruv Chachad, Ph.D.

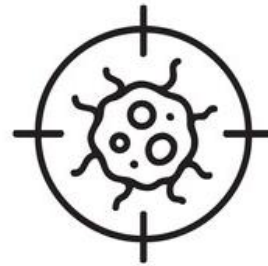
This project was partially supported by funding from Daiichi Sankyo to the Institution

# Background

TROP2-directed ADC with a potent Topo-1 inhibitor payload



Safety and efficacy first assessed in the Phase I TROPION-PanTumor01 basket trial (NCT03401385)



TARGETED THERAPY

Preliminary antitumor activity was shown in multiple tumor types, especially in breast, lung, and urothelial cancers



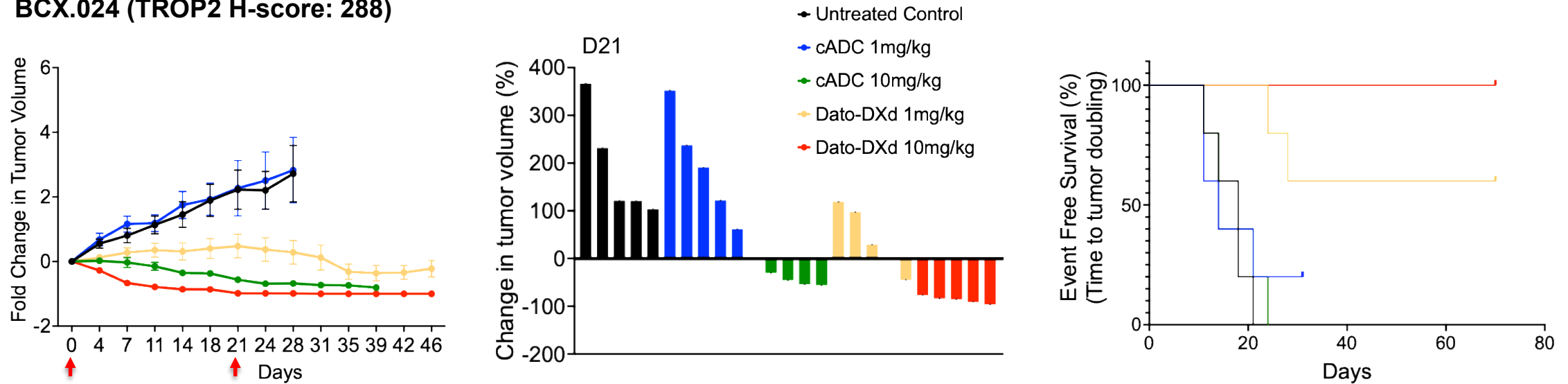
2L+ HR+/HER2- Breast Cancer  
2L+ EGFRm NSCLC

Okajima *et al.*, MCT 2021  
Shimizu *et al.*, JCO 2023  
Bardia *et al.*, JCO 2024  
Bardia *et al.*, JCO 2025

Meric-Bernstam *et al.*, ASCO GU 2025

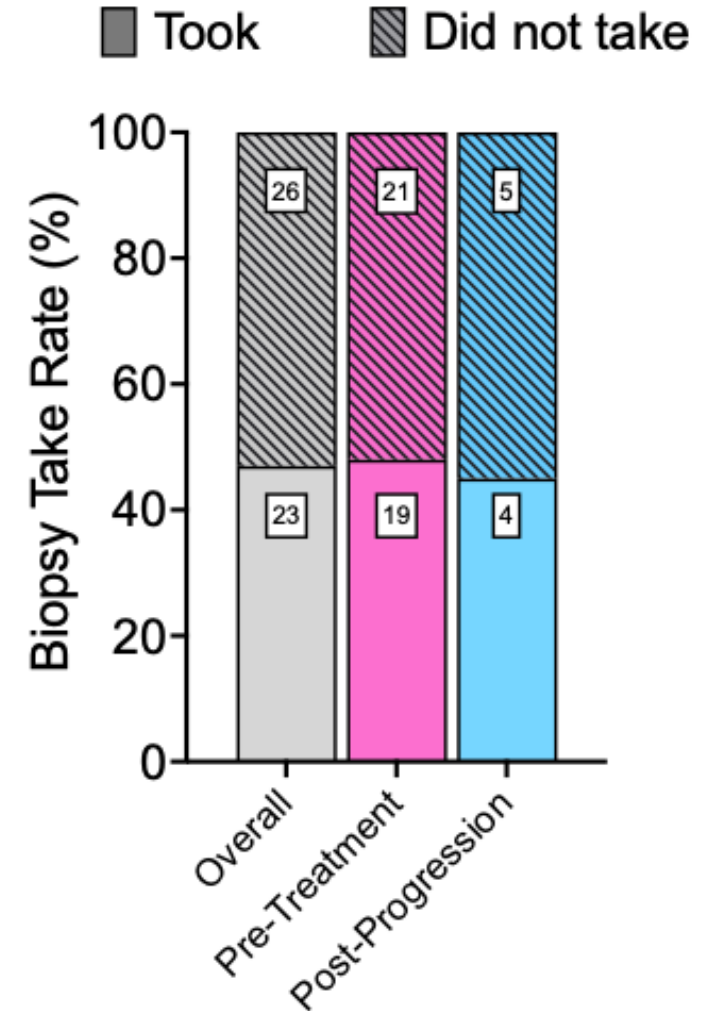
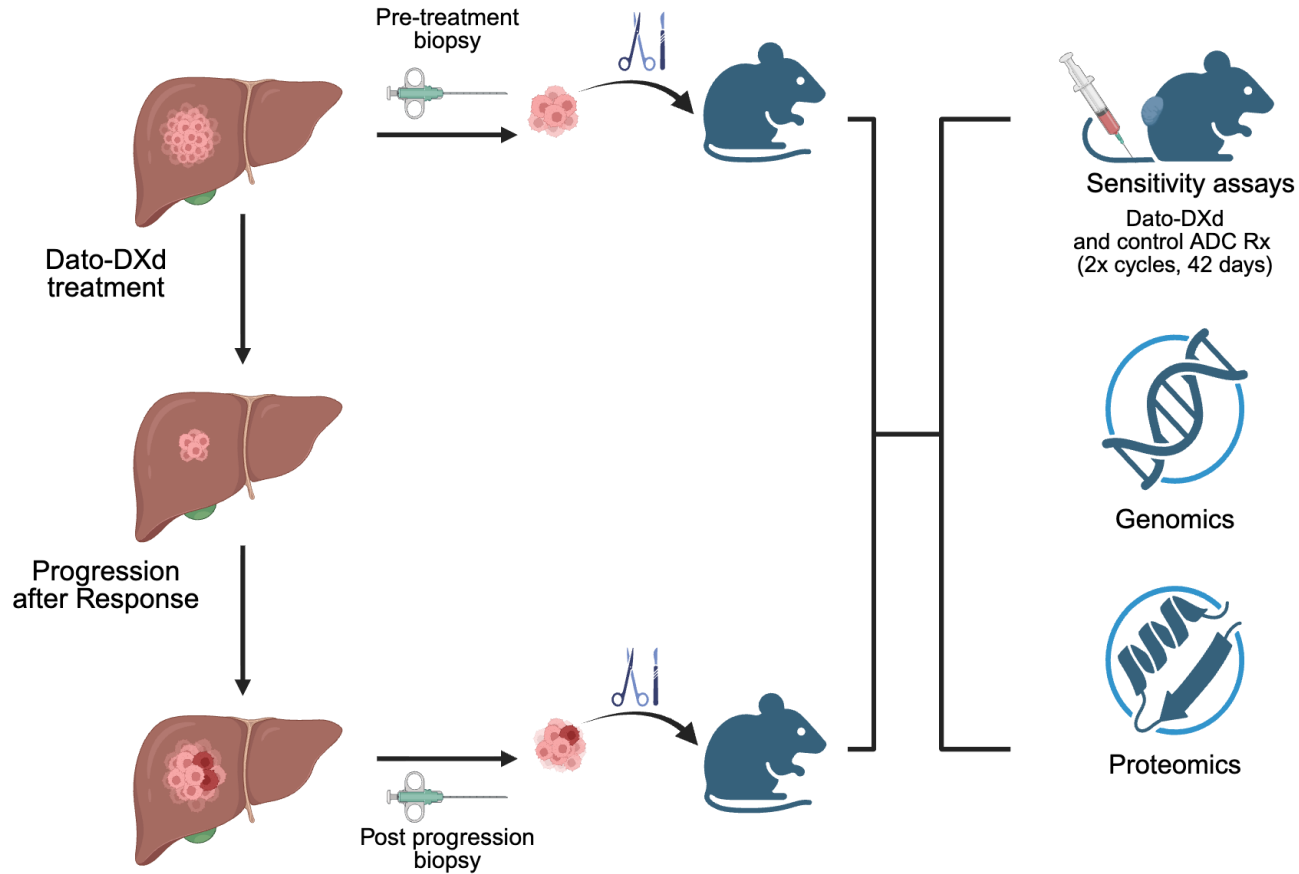
# Background

## BCX.024 (TROP2 H-score: 288)



- **Hypothesis:** It is feasible to create PDXs from pre-treatment biopsies on Phase I trial, and that PDX response will be concordant with matching patient response. Further, the PDXs will serve as a tool to test whether Dato-DXd activity can be further enhanced with rational combinations.

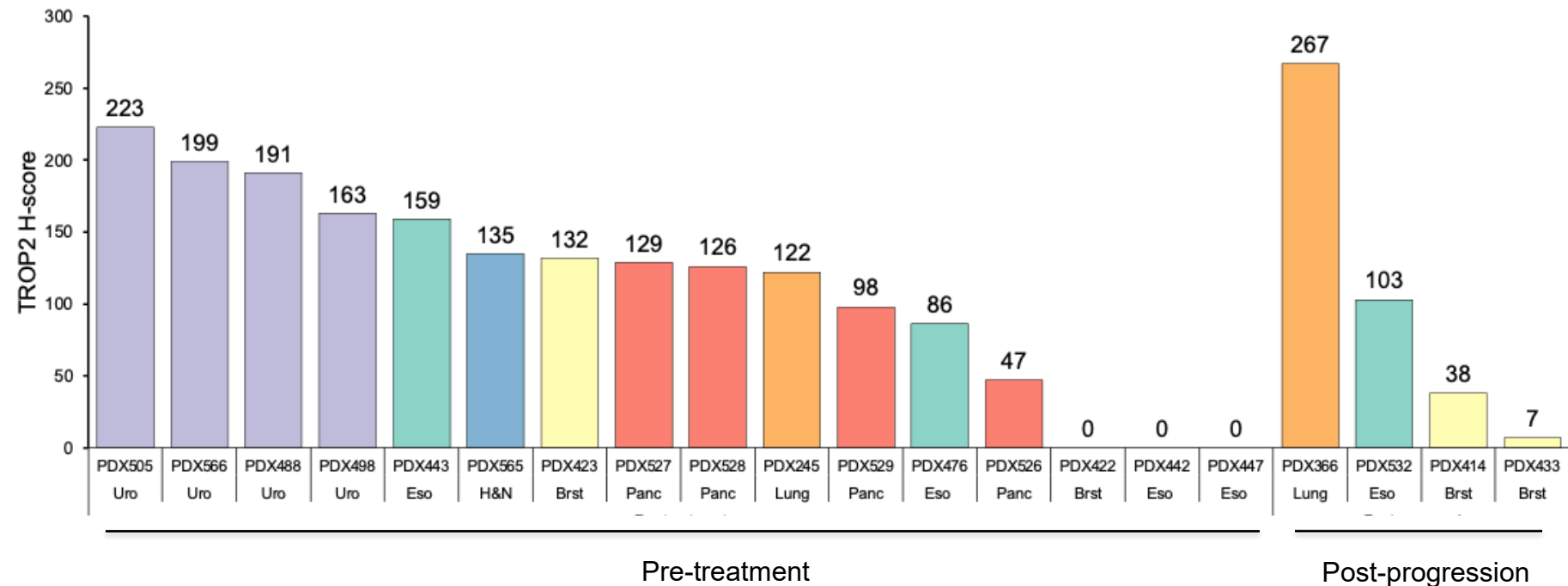
# Study Design and Overview



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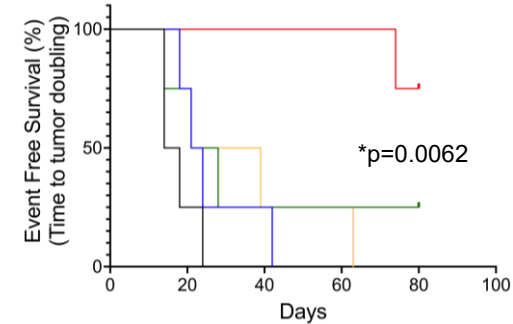
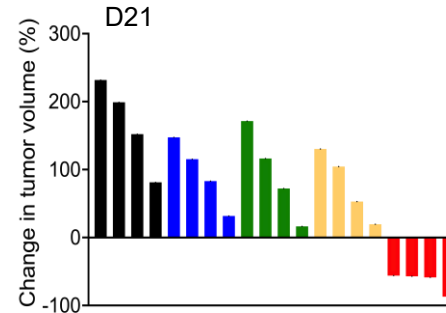
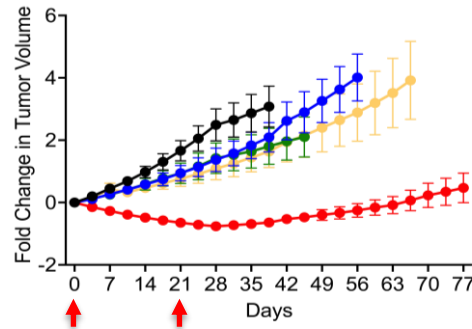
- Breast Invasive Ductal Carcinoma
- Bladder/Urothelial Carcinoma
- Pancreatic Adenocarcinoma
- Lung Adenocarcinoma
- Esophageal Adenocarcinoma
- Head and Neck Carcinoma

**Total = 20 PDX models**



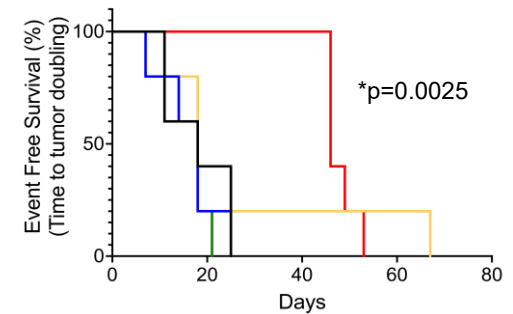
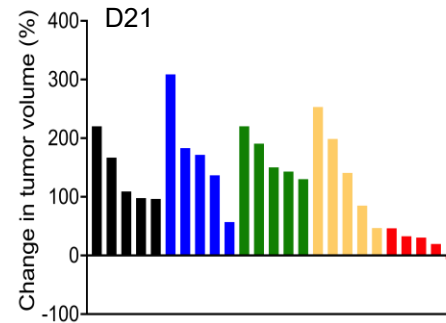
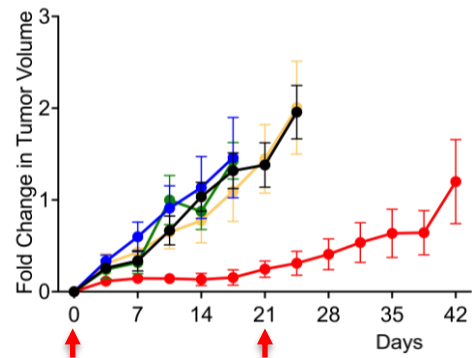
# Dato-DXd shows Antitumor Activity in Different Tumor Types

PDX565
Head and Neck squamous cell carcinoma
TROP2 H-Score: 135
EFS-2 p-value: 0.0062



- Untreated Control
- cADC 1mg/kg
- cADC 10mg/kg
- Dato-DXd 1mg/kg
- Dato-DXd 10mg/kg

PDX527
Pancreatic adenocarcinoma
TROP2 H-Score: 129
EFS-2 p-value: 0.0025

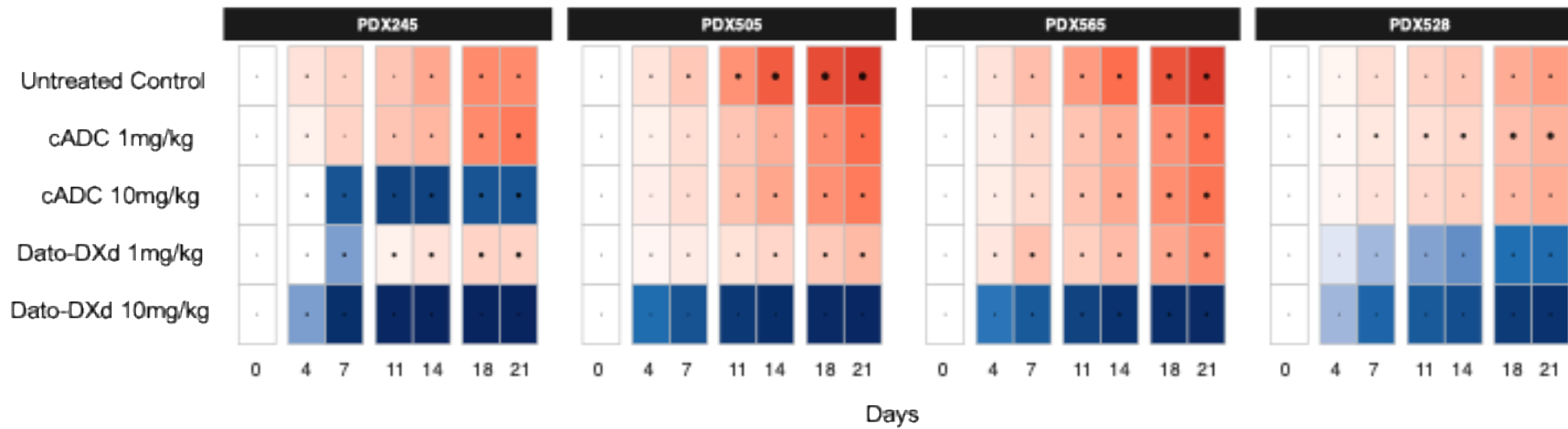


# Dato-DXd Significantly Extends Time to Tumor Doubling

PR: 30% or greater decrease in tumor volume

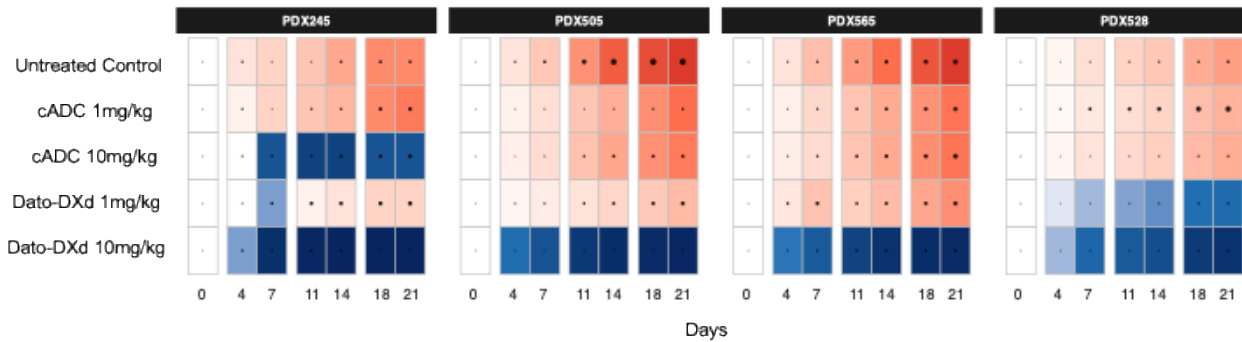


Model	Tumor Type	TROP2 H-score	EFS-2 p-value (Unt. ctrl vs. Dato-DXd 10mg/kg)
PDX245	Lung	122	*0.0067
PDX505	Uro	223	*0.0246
PDX565	H&N	135	*0.0062
PDX528	Panc	126	*0.0246



4 of 14 pre-treatment models showed PR

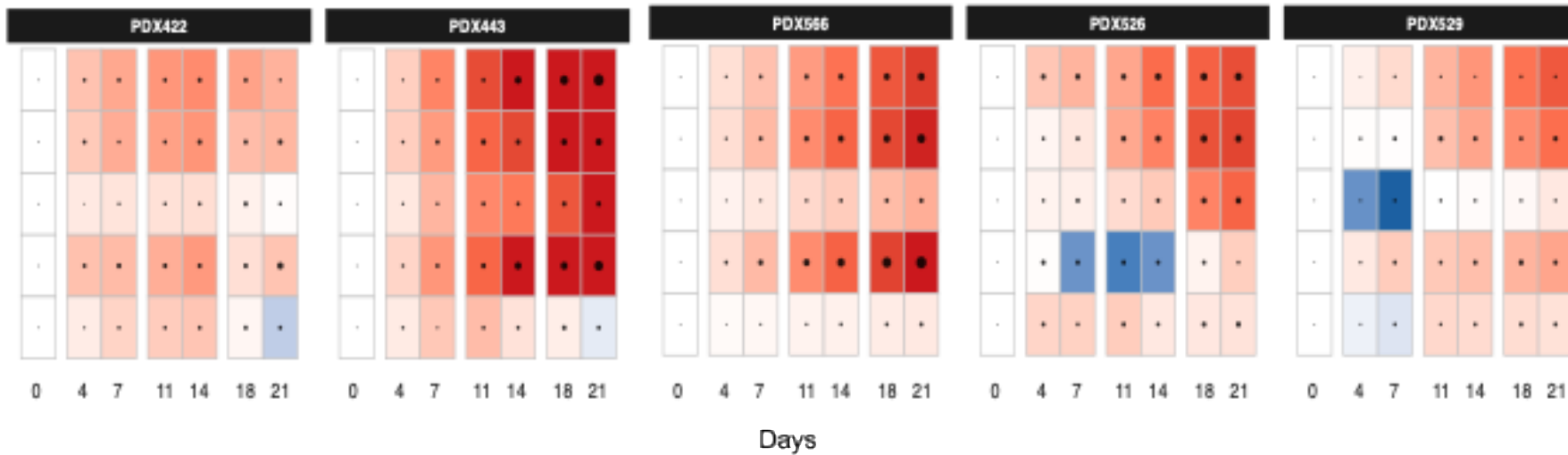
# Dato-DXd Significantly Extends Time to Tumor Doubling



SD: -30% < tumor volume change < 20%

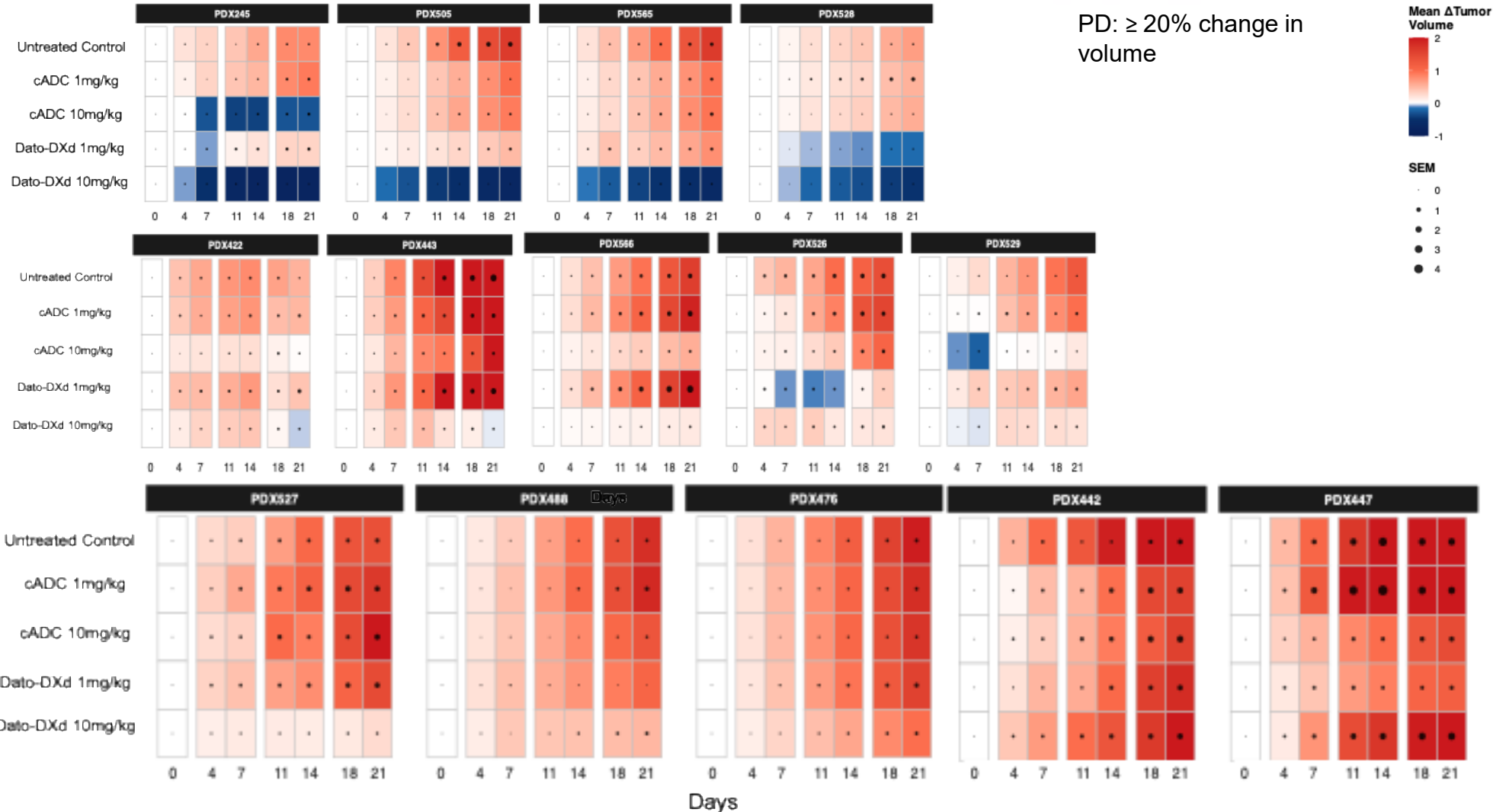


Model	Tumor Type	TROP2 H-score	EFS-2 p-value (Unt. ctrl vs. Dato-DXd 10mg/kg)
PDX245	Lung	122	*0.0067
PDX505	Uro	223	*0.0246
PDX565	H&N	135	*0.0062
PDX528	Panc	126	*0.0246
PDX422	Breast	0	*0.0067
PDX443	Eso	159	*0.002
PDX566	Uro	199	*0.0246
PDX526	Panc	47	*0.0082
PDX529	Panc	98	*0.0295



5 of 14 pre-treatment models showed SD

# Dato-DXd Significantly Extends Time to Tumor Doubling

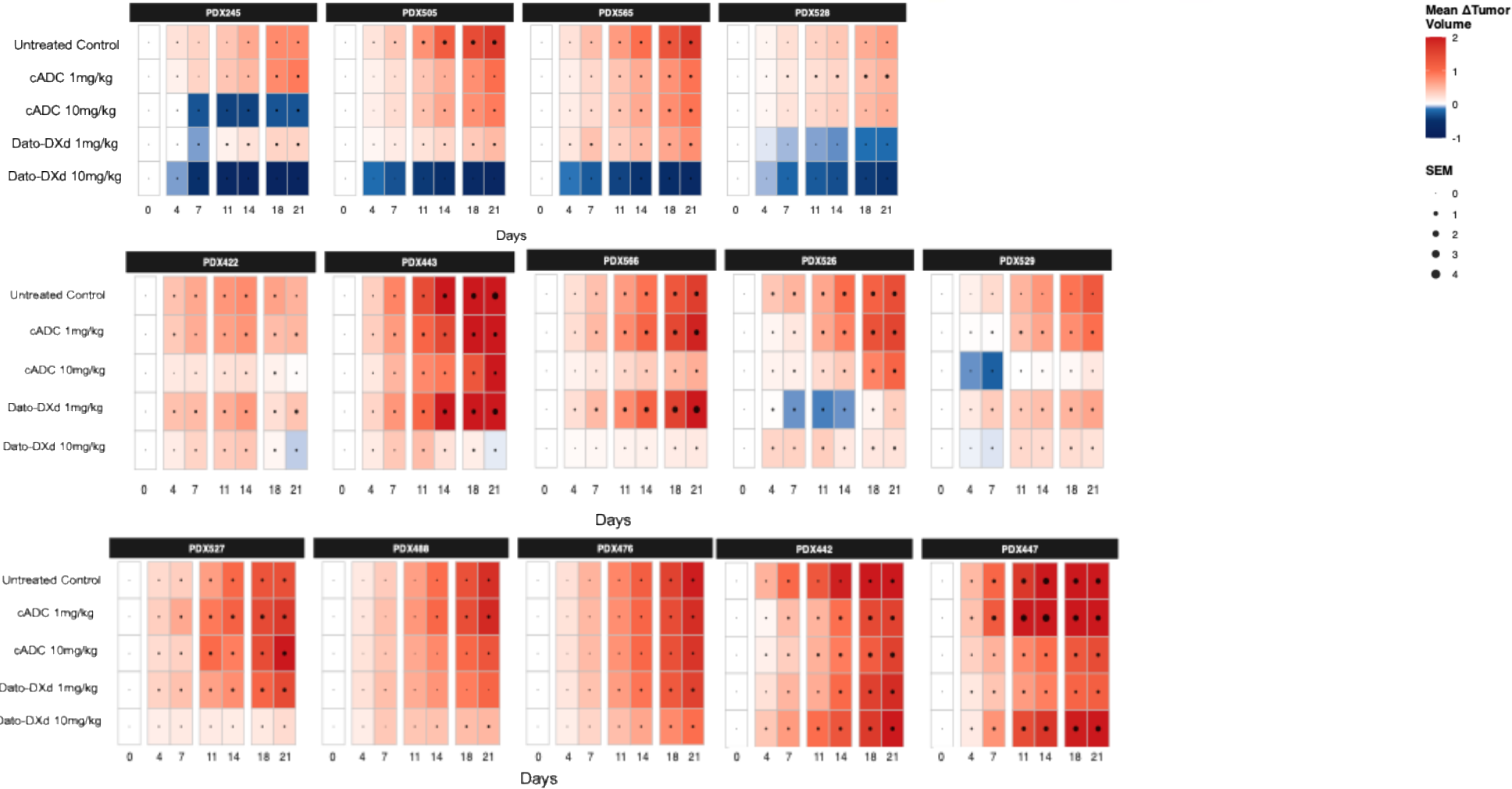


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PDX566	Uro	199	*0.0246
PDX526	Panc	47	*0.0082
PDX529	Panc	98	*0.0295
PDX527	Panc	129	*0.0025
PDX488	Uro	191	*0.0246
PDX476	Eso	86	*0.0295
PDX442	Eso	0	*0.0326
PDX447	Eso	0	0.3765

5 of 14 pre-treatment models showed PD; Dato-DXd significantly extended time to tumor doubling in 4 out of 5 models that showed PD

DO NOT POST

# Dato-DXd Significantly Extends Time to Tumor Doubling



Model	Tumor Type	TROP2 H-score	EFS-2 p-value (Unt. ctrl vs. Dato-DXd 10mg/kg)
PDX245	Lung	122	*0.0067
PDX505	Uro	223	*0.0246
PDX565	H&N	135	*0.0062
PDX528	Panc	126	*0.0246
PDX422	Breast	0	*0.0067
PDX443	Eso	159	*0.002
PDX566	Uro	199	*0.0246
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PDX488	Uro	191	*0.0246
PDX476	Eso	86	*0.0295
PDX442	Eso	0	*0.0326
PDX447	Eso	0	0.3765

Dato-DXd significantly extended time to tumor doubling in 13 of 14 pre-treatment models

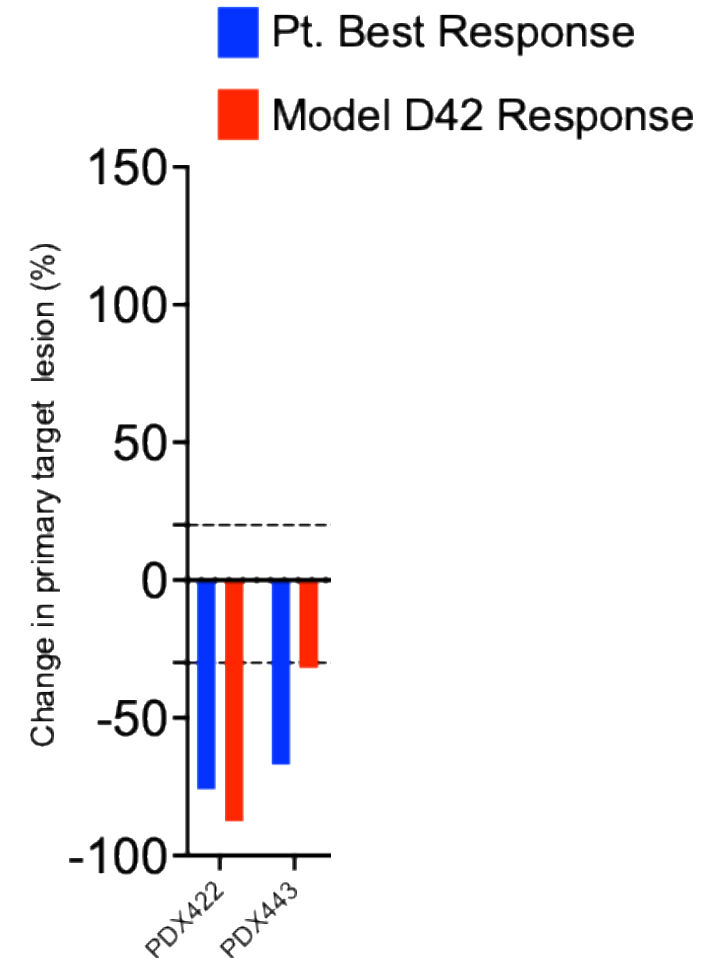
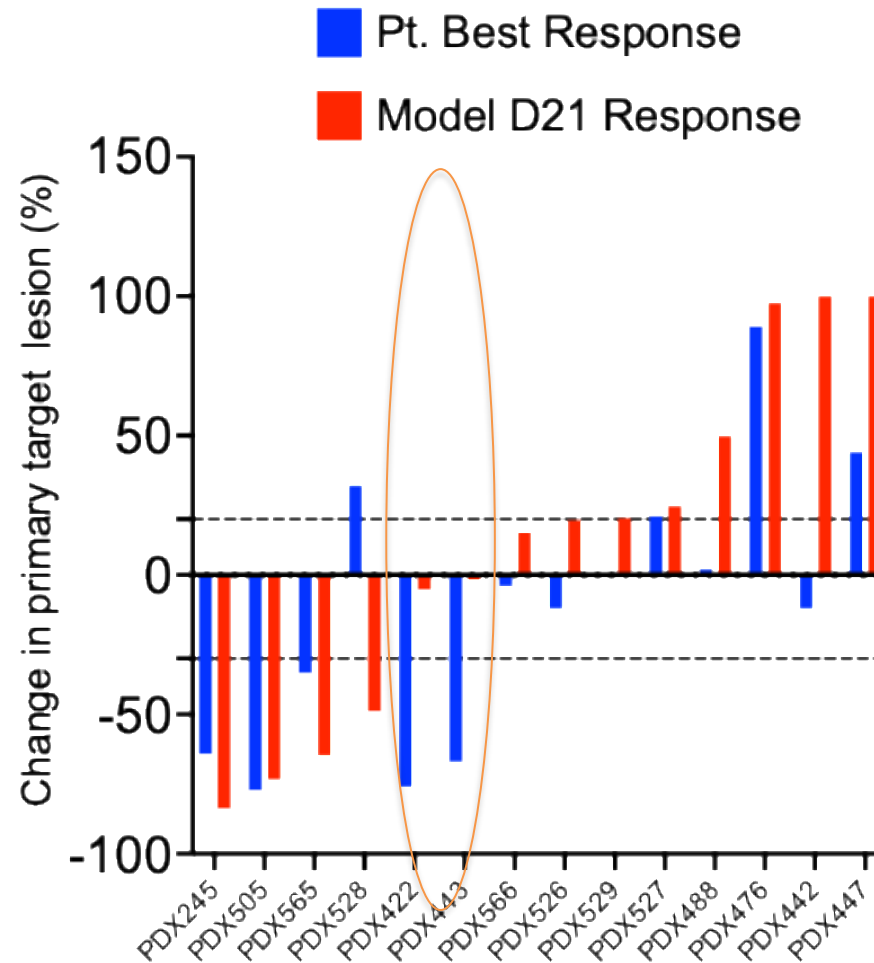
# Model Response is Concordant with Patient Response

Patient responses classified by RECIST1.1 by a central quantitative imaging service at UT MD Anderson

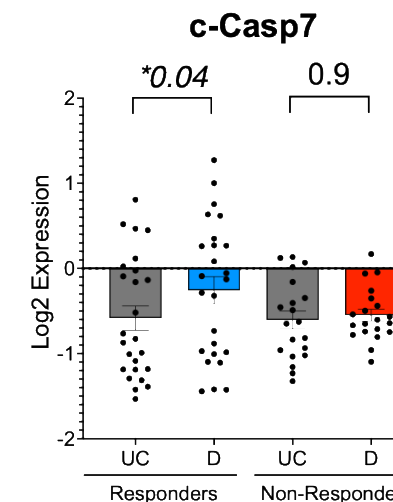
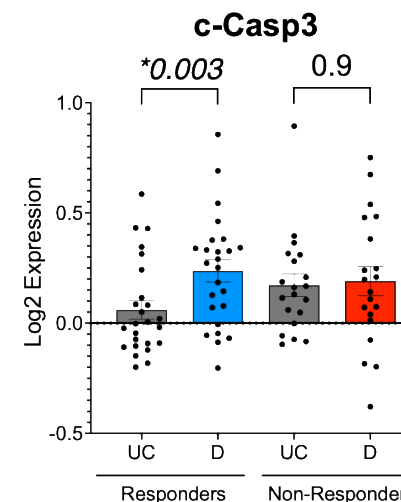
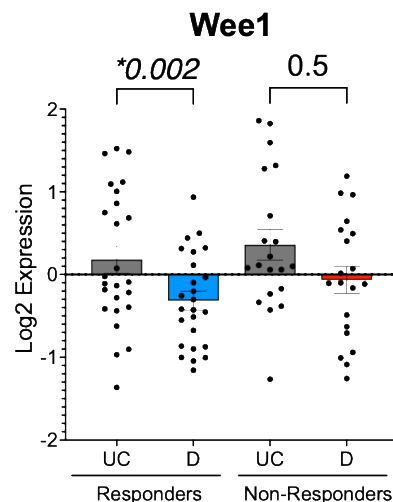
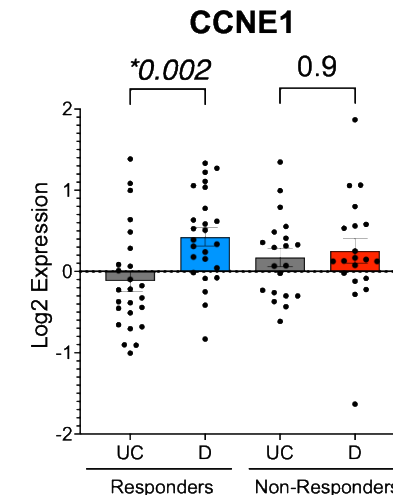
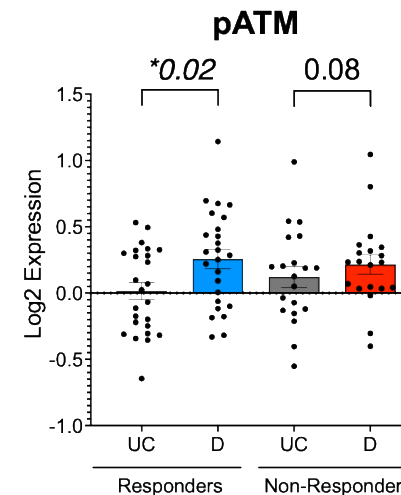
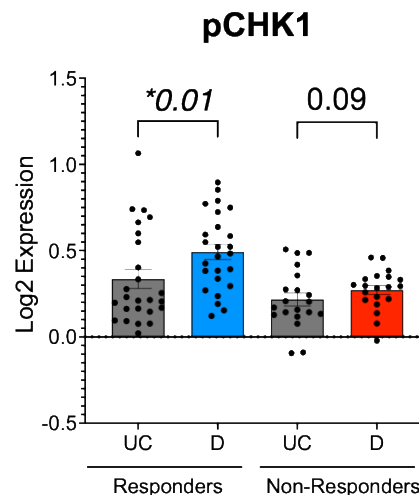
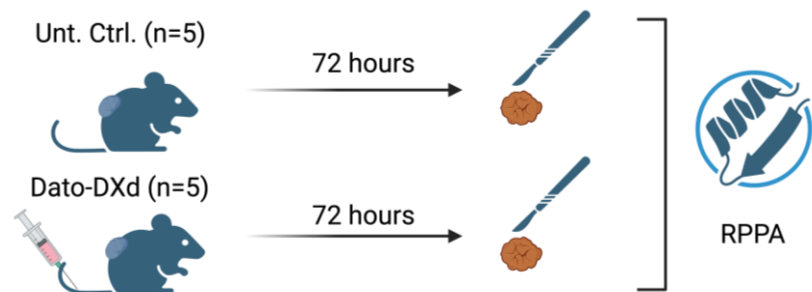
PDX responses classified as:

PR: 30% or greater decrease in tumor volume  
 SD: -30% < tumor volume change < 20%  
 PD: ≥ 20% increase in tumor volume

Objective Response at 21 days or Best Response by 42 days



# Dato-DXd Enhances DDR and Activates Apoptosis

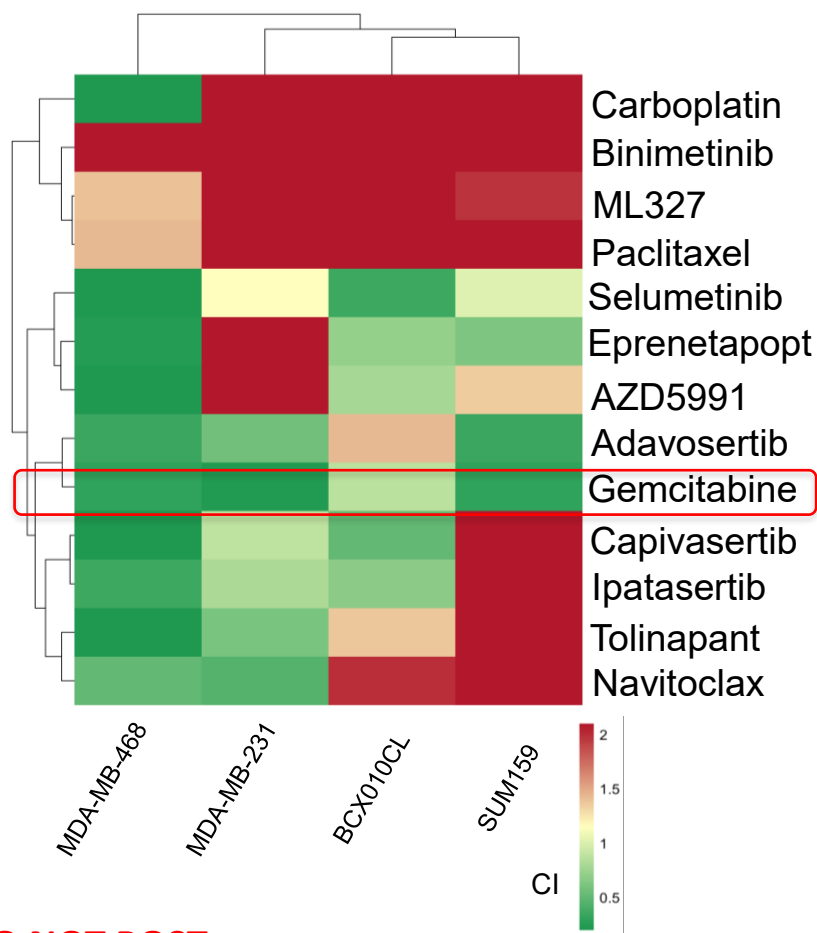


Sr. No.	Model	Disease	TROP2 H-Score	Model Response
1	PDX443	Esophageal	159	PR
2	PDX505	Bladder	223	PR
3	PDX565	H&N	135	PR
4	PDX245	Lung	122	PR
5	PDX526	Pancreatic	47	SD
6	PDX488	Bladder	191	PD
7	PDX527	Pancreatic	129	PD
8	PDX476	Esophageal	86	PD
9	PDX442	Esophageal	0	PD

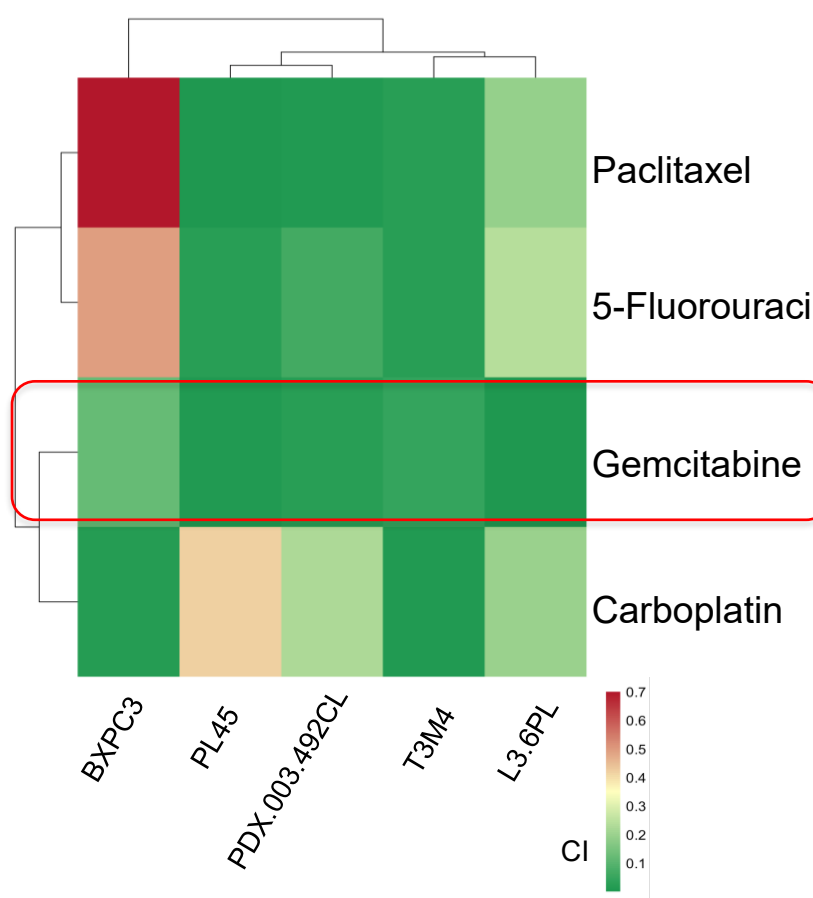
UC – Untreated Control  
 D – Dato-DXd 10mg/kg

# Gemcitabine shows Synergy with Dato-DXd *in vitro*

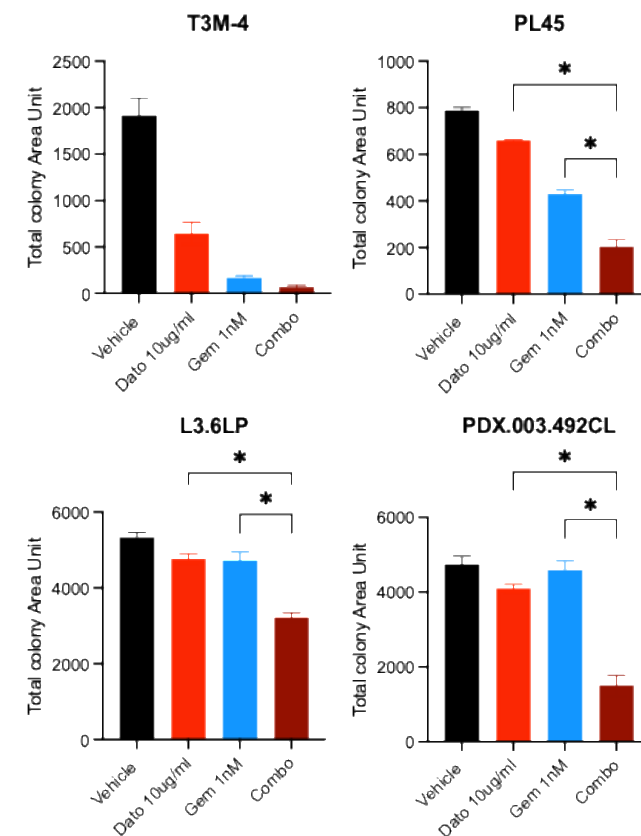
Synergy screen for DXd in breast cancer cell lines



Synergy screen for Dato-DXd in pancreatic cancer cell lines



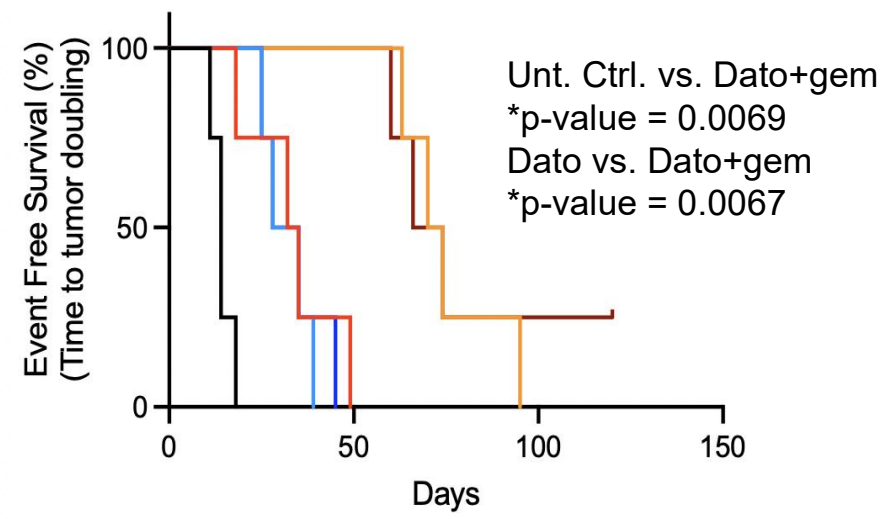
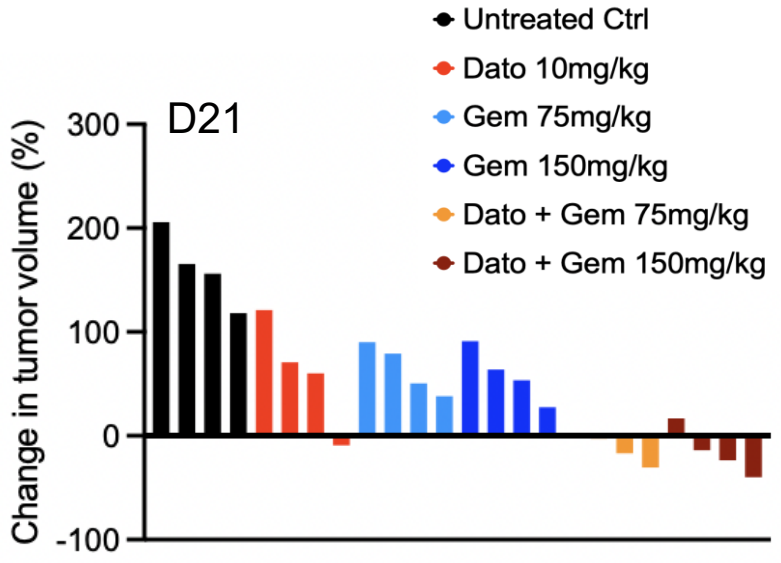
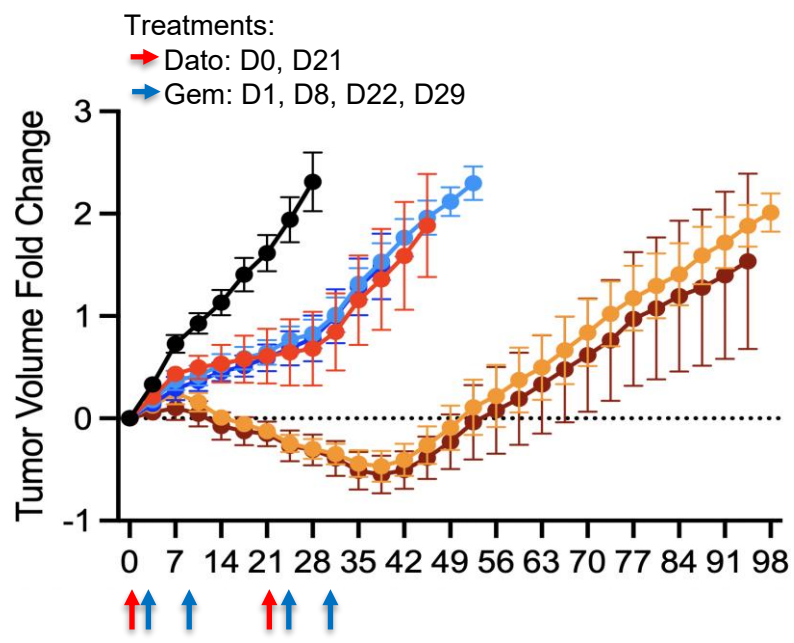
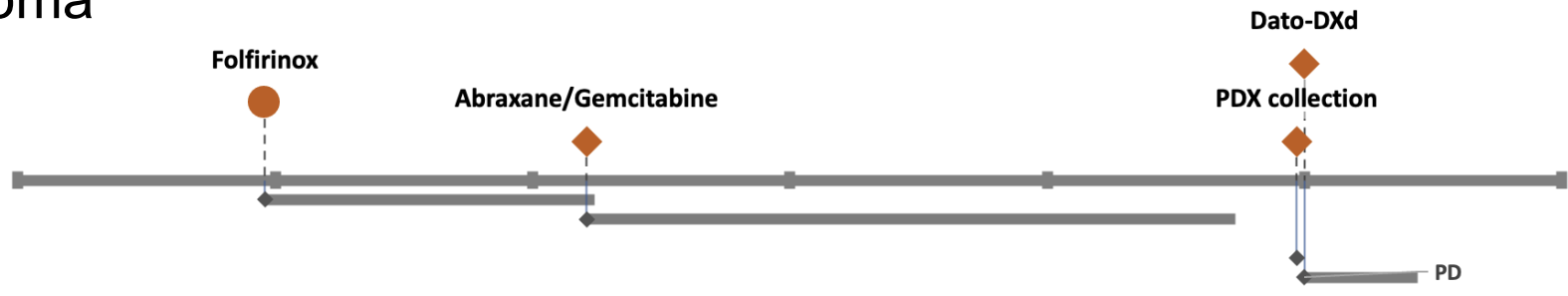
Colony Formation Assay in pancreatic cancer cell lines



# Dato-DXd and Gemcitabine Combination Overcomes Resistance to Monotherapy in a PDAC Model

## PDX527 – Pancreatic adenocarcinoma

TROP2 H-score: 129  
 Prior treatment: Irinotecan and Gemcitabine  
 Pt. Best Response on Dato-DXd: PD



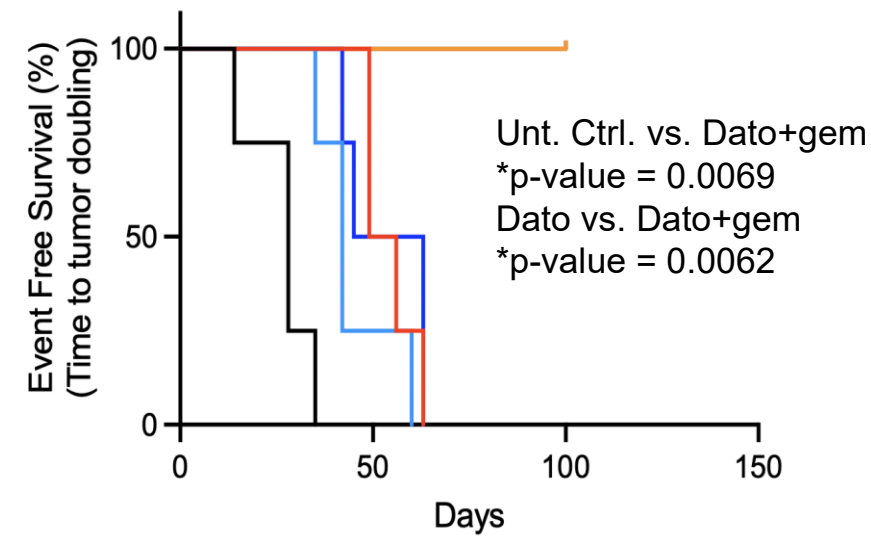
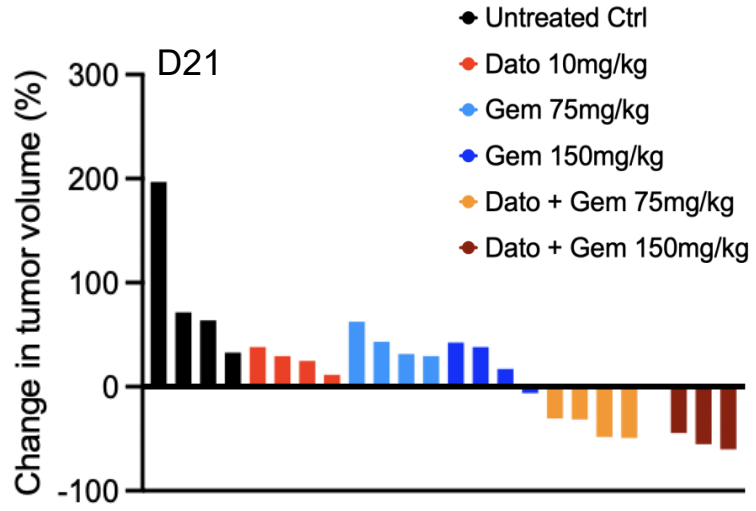
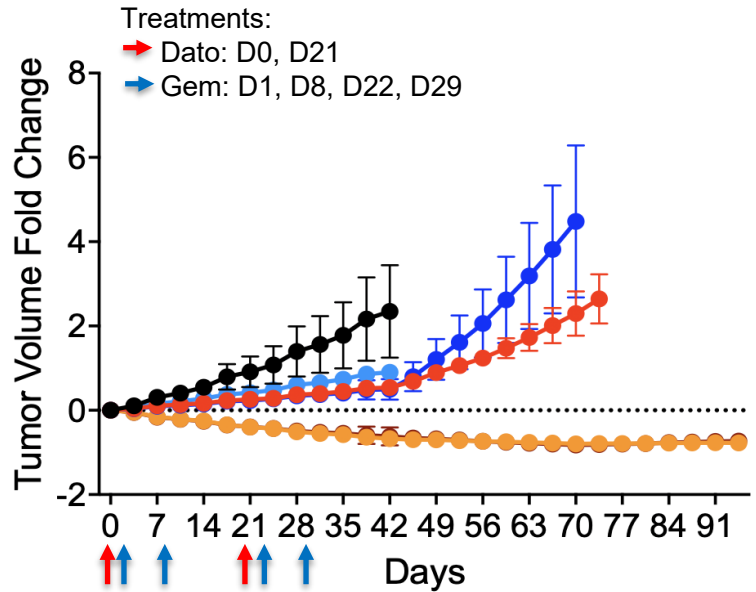
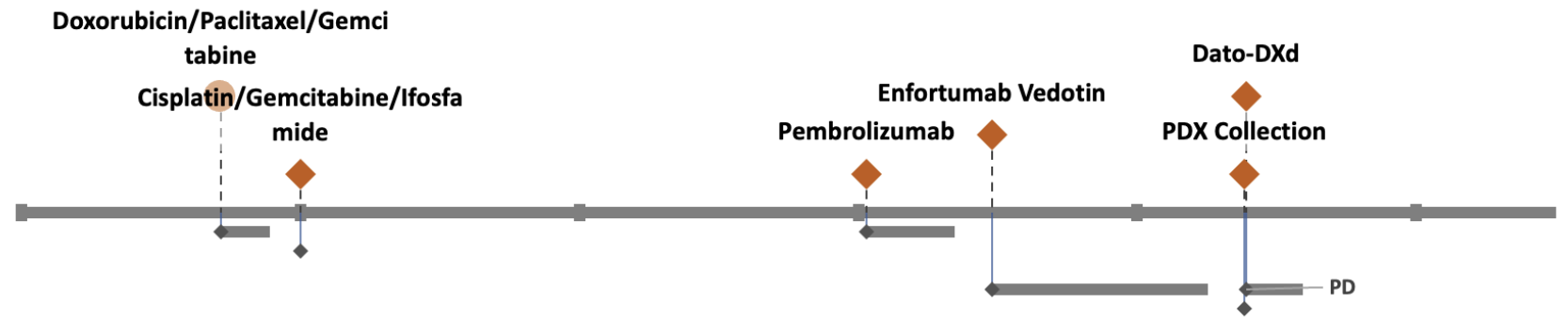
# Dato-DXd and Gemcitabine Combination Overcomes Resistance to Monotherapy in Bladder Carcinoma

## PDX488 – Bladder carcinoma

TROP2 H-score: 191

Prior Treatment: Gemcitabine

Pt. Best Response on Dato-DXd: PD



# Conclusions

- It is feasible to generate PDX models for co-clinical modeling
- Dato-DXd shows antitumor activity in several different cancer types
- PDX models show high concordance to Dato-DXd treatment compared to patients
- Activation of DDR by Dato-DXd in tumors with antitumor activity
- Combination with gemcitabine overcomes resistance to monotherapy in tumors that have been previously treated

- Multi-omics approach to determine biomarkers of sensitivity and resistance to Dato-DXd
- Drug screens to identify synergistic combinations in different tumor types
- Translation of preclinical findings to the clinic

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Thank you!

Questions?