

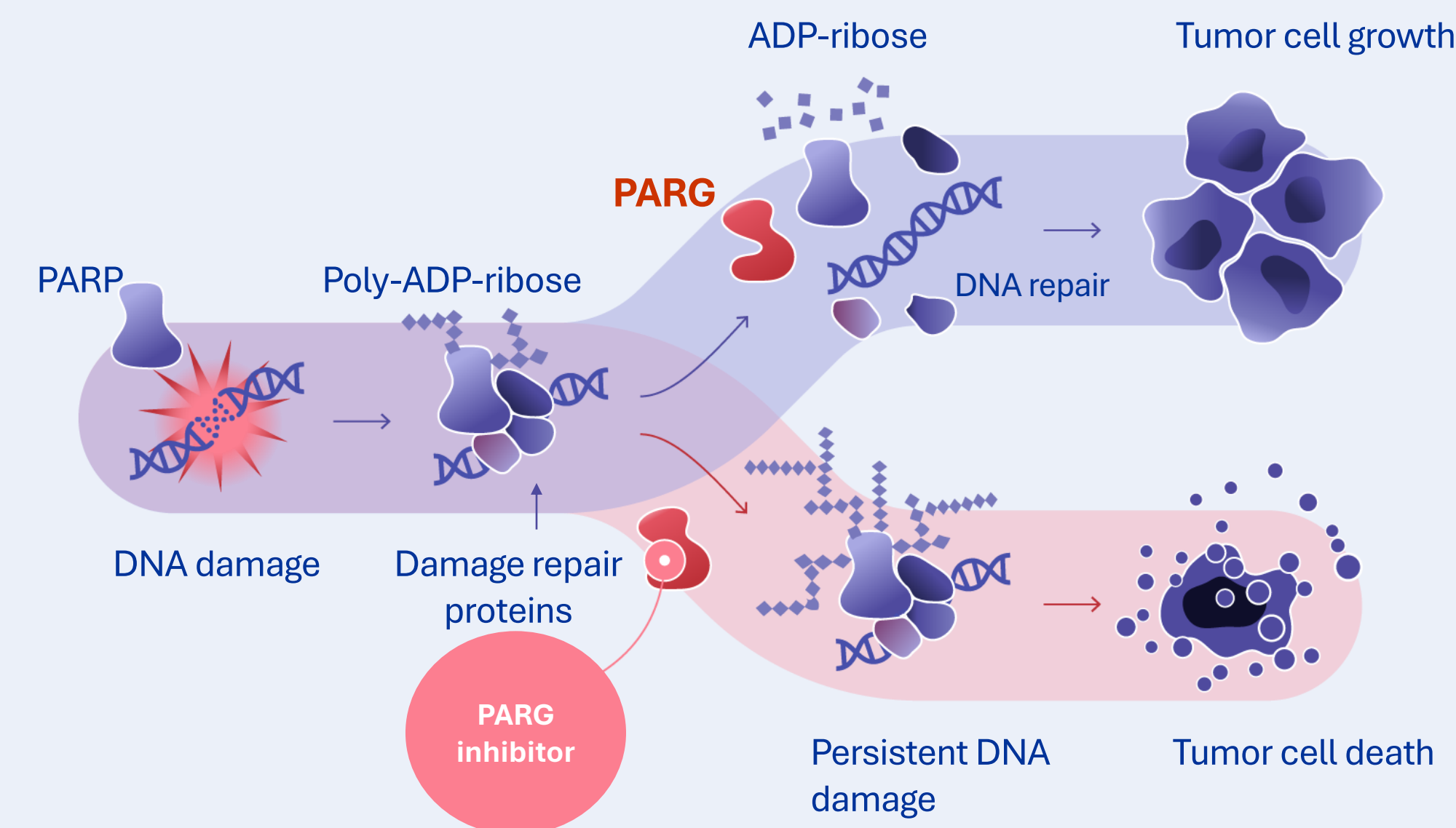
FORX-428: Best-in-Class PARP Inhibitor with Promising Anti-Tumor Activity in Preclinical Cancer Models

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INTRODUCTION

PARP - Next-Generation Target in the DNA Damage Response Field



- Poly(ADP-ribose) (PAR) chains catalyzed by PARP enzymes serve as docking platforms for DNA repair proteins that are recruited to sites of replication stress-induced DNA damage and initiate DNA repair³
- Degradation of poly(ADP-ribose) by the glycohydrolase PARG is essential to conclude DNA repair
- Pharmacological inhibition of PARG blocks PAR chain resolution thereby inhibiting DNA repair and killing tumor cells
- The mechanism of action of PARG inhibition is clearly different from PARP inhibition, opening a path to novel therapeutic opportunities

CLINICAL POTENTIAL IN CANCER:

- Cancers with HRD+ genotype - PARPi-resistant and -refractory cancer subsets
- Cancers with high DNA replication stress (biomarker-based)

SUMMARY & CONCLUSIONS

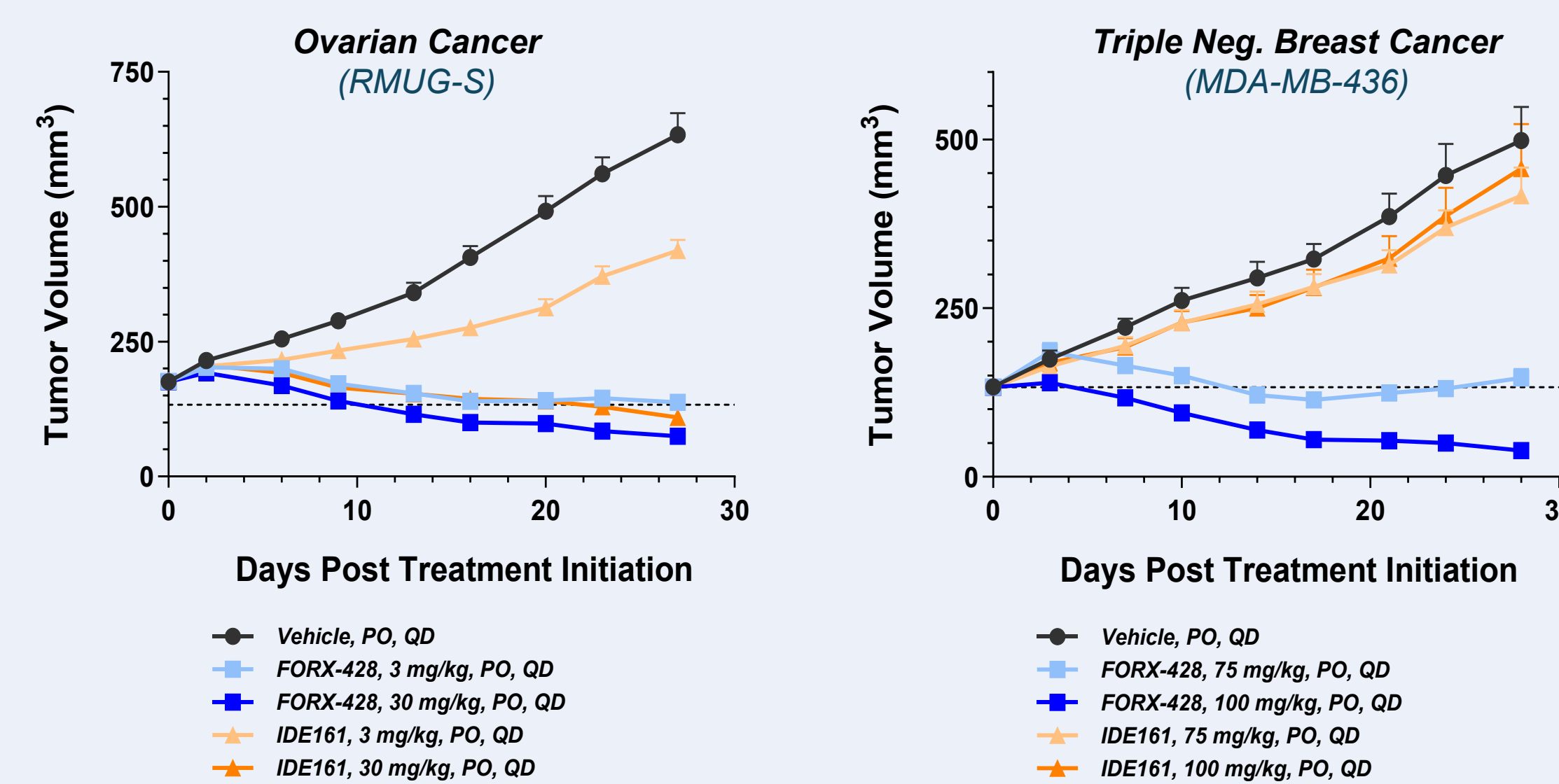
- FORX-428 demonstrated superior *in vitro* potency and best-in-class efficacy versus other clinical phase competitors
- High response rate in HRD, PARP inhibitor-resistant or replication stress high solid tumor models of various origin
- Robust and durable tumor regression in ovarian cancer PDX carrying a BRCA1 reversion mutation rendering model resistant to PARP inhibitor
- Clinical development of FORX-428 ongoing to evaluate pharmacokinetics, safety, and efficacy in HRD and RS^{high} tumors

Activity Profile of FORX-428 and Other PARP Inhibitors

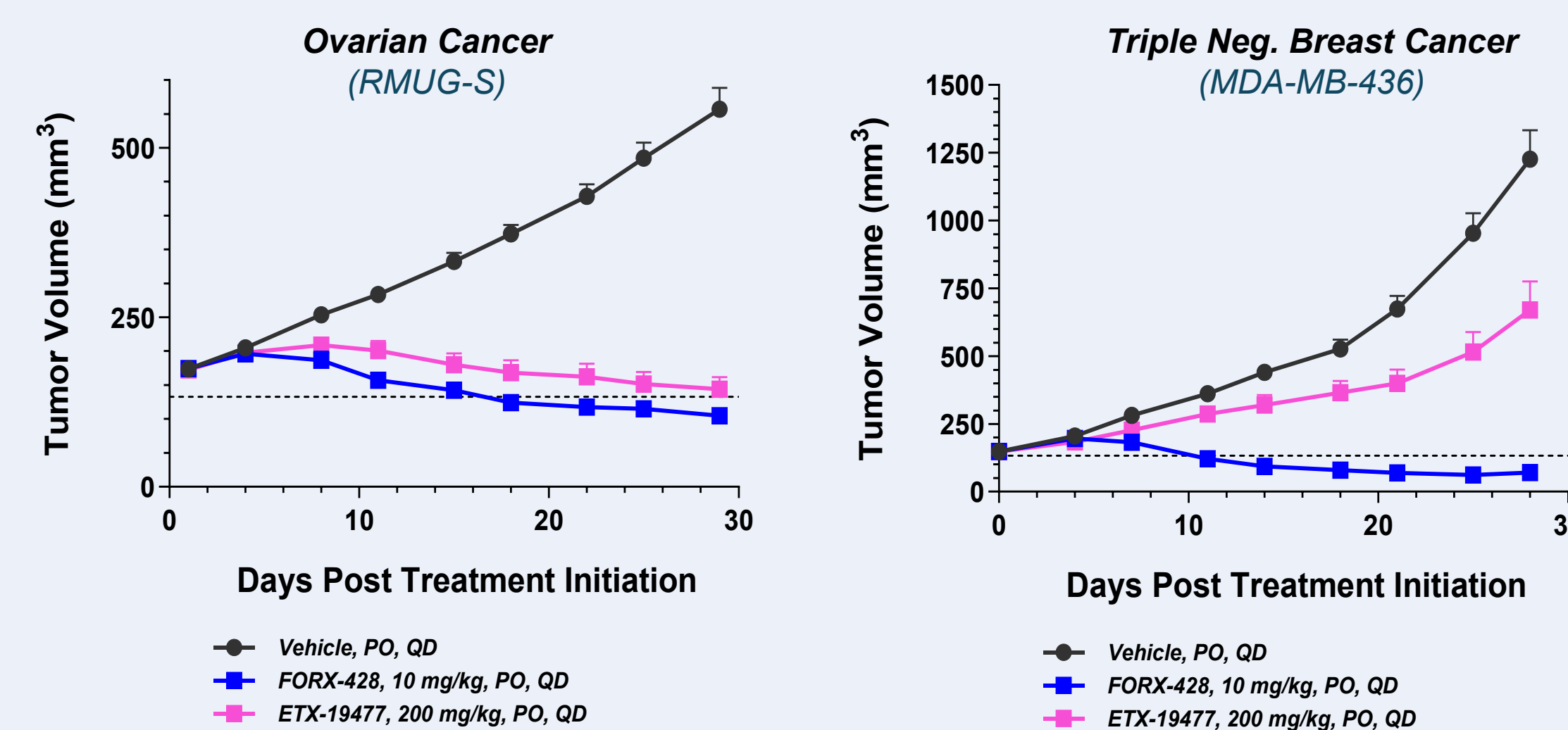
ID*	FORX-428	IDE161 ⁴	ETX-19477 ⁵
human PARG	0.3	0.7	20
GCI [†] - Kd [nM] / TRT [min]	0.06 / 104	0.13 / 47	nd
MDA-MB-436 (breast)	19	223	2,800
HCC1937 (breast)	17	188	nd
HCC1428 (breast)	1.7	11.1	nd
RMUG-S (ovarian)	<0.5	2	87
Kuramochi (ovarian)	0.6	3.9	nd
U2OS (osteosarcoma)	>5,000	>5,000	>5,000

*Unless otherwise specified, all IC₅₀ values are reported in nM; [†]GCI measurements was performed at 25°C

Head-to-head comparison FORX-428 vs. IDE161

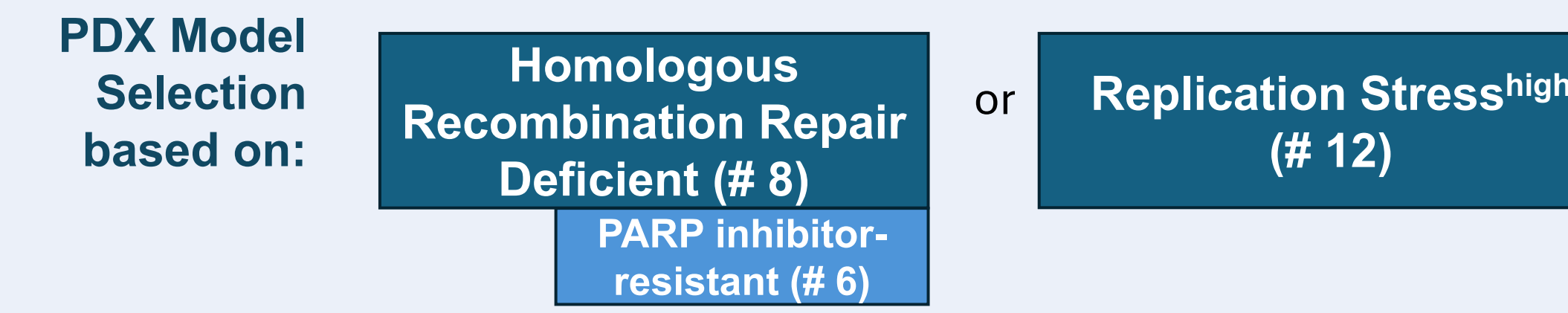


Head-to-head comparison FORX-428 vs. ETX-19477

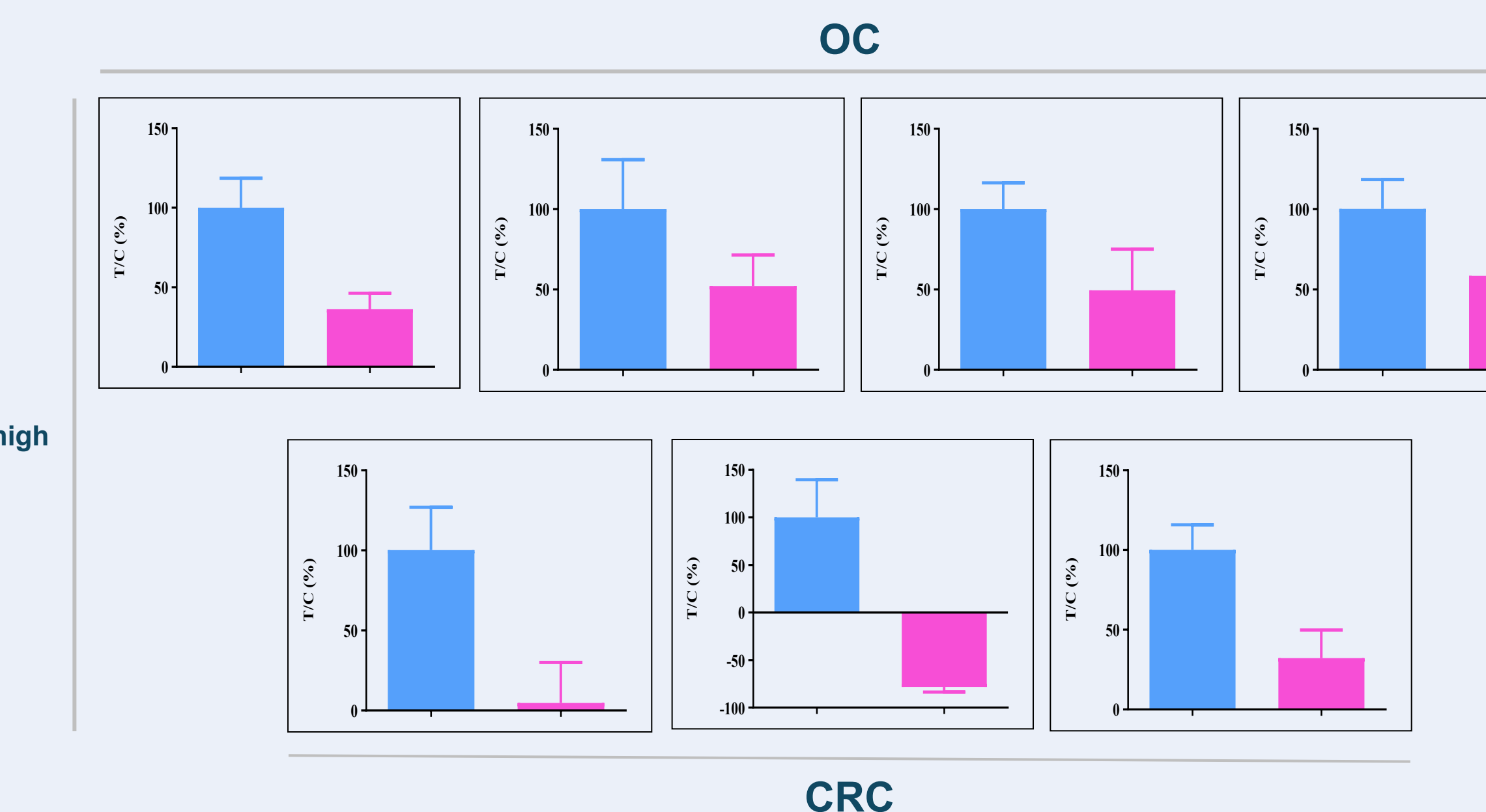
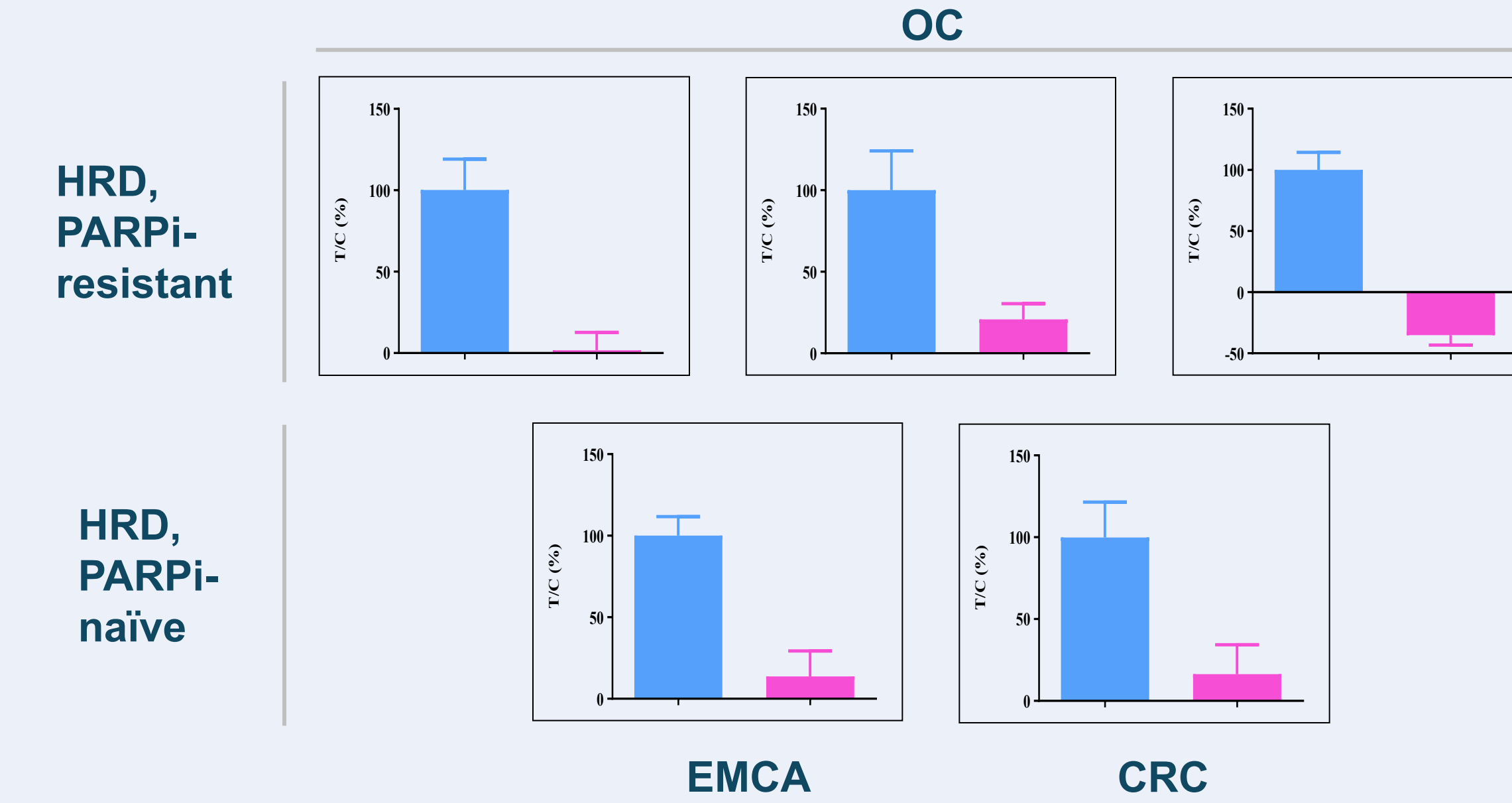


RESULTS

MiniPDX Screening Campaign⁶

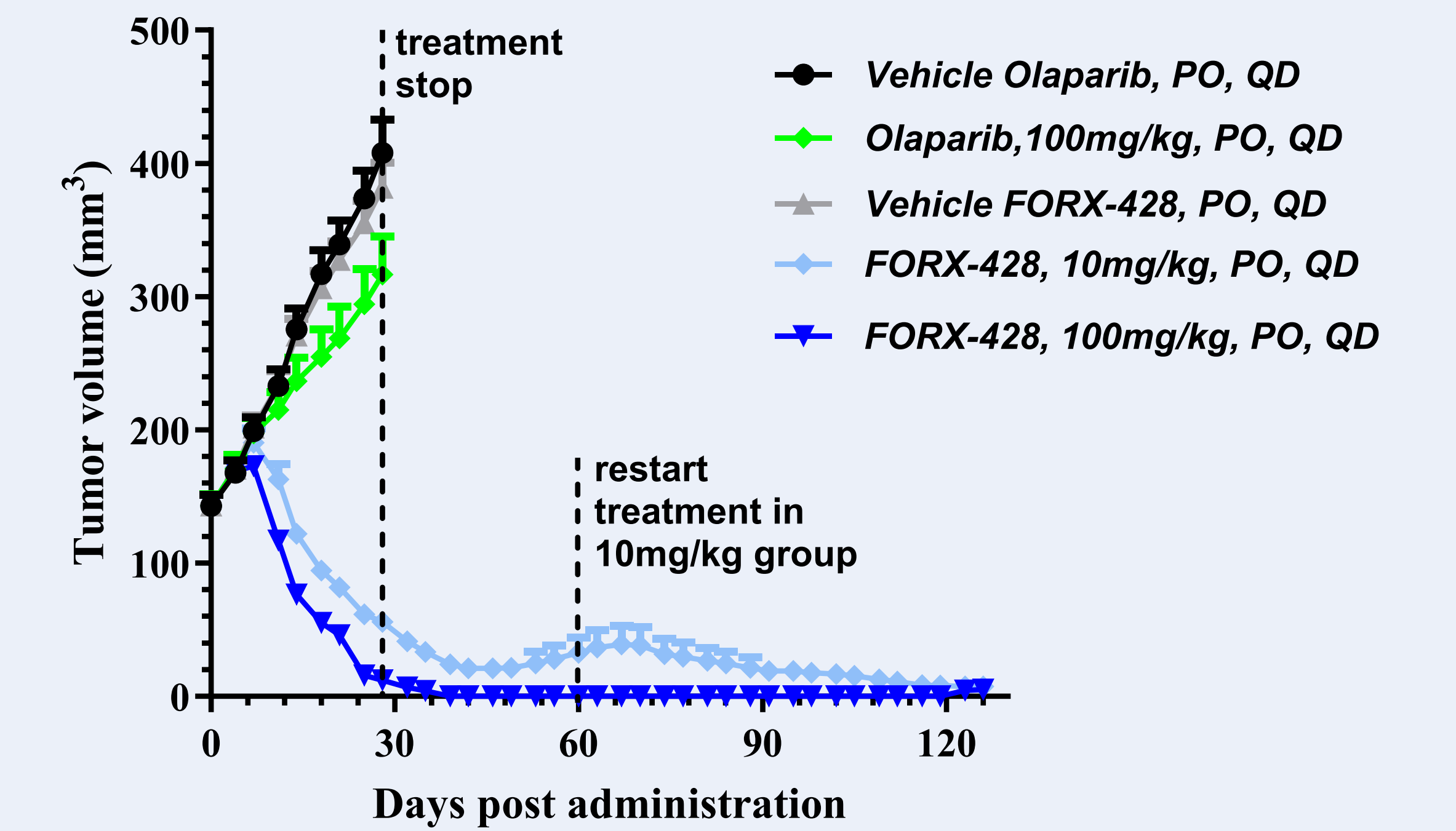


Responders: 5 out of 8 = 62.5% 7 out of 12 = 58%



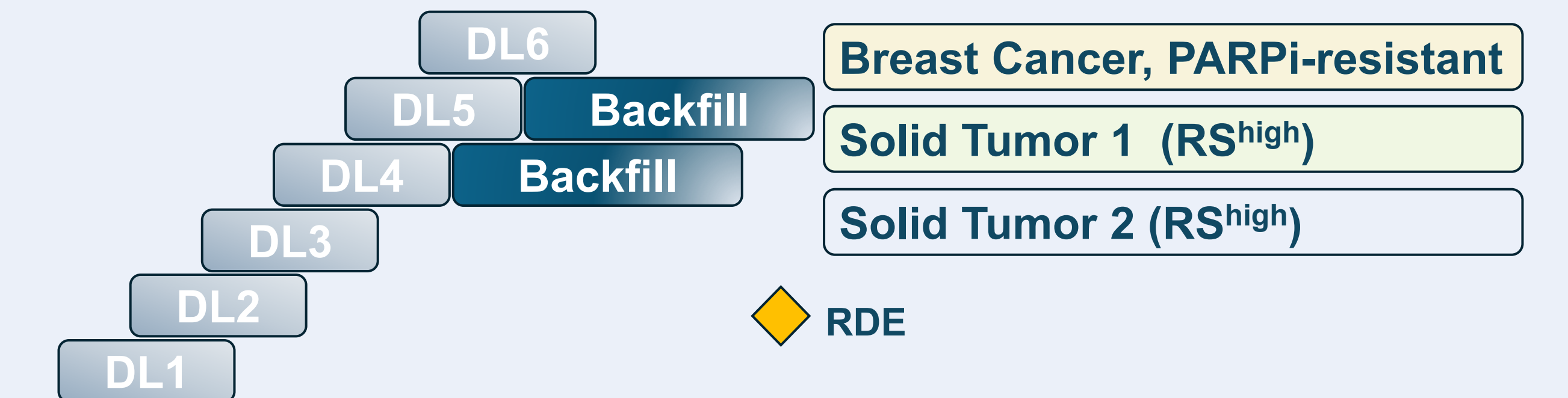
Activity in PARPi Resistant Tumor Model

Ovarian Cancer (PDX) (BRCA1 mut reversion)



Clinical Development

Phase 1 study of PARP inhibitor FORX-428 in patients with advanced solid tumors with BRCA1/2 mutations or other DDR deficiencies or high replication stress



Dose Escalation (30-40 pts)

- Bayesian Optimal Interval design (BOIN); backfilling up to total n=12 per DL
- DLT observation period: 28 days; mandatory biopsies in backfilling cohorts
- n ~30-40 patients
- 8 US sites
- Duration 12-14 m

Dose Expansion (30 pts/cohort)

- Simon 2-stage design; clear go/no-go decisions; no entry-testing for any cohorts
- n ~90 patients
- ~20 US/EU sites
- Recruitment ~1 yr

Literature: ³ Gros Lambert et al., PARPs and ADP-ribosyl hydrolases in cancer therapy: From drug targets to biomarkers. DNA Repair 2025 Aug;152:103863. ⁴ IDE161, a potential first-in-class clinical candidate PARP inhibitor, selectively targets homologous-recombination-deficient and PARP inhibitor resistant breast and ovarian tumors, AACR 2023, Abstract number: 6093; ⁵ Discovery of ETX-19477, a novel and selective PARP inhibitor with high potency against tumors with underlying replication stress, AACR 2024, Abstract Number: 2083; WO 2025/111339; ⁶ Zhang et al., Characterization of drug responses of mini patient-derived xenografts in mice for predicting cancer patient clinical therapeutic response. Cancer Commun 2018 Sep 26;38:60.

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