

Identification of EIK1004 (IMP17307): A CNS Penetrant, Potent and Selective PARP 1 Inhibitor Poised for Testing in Patients with HRD Mutant Tumors

Melissa Dumble¹, Ye Edward Tian², Ali Tabatabaei¹, Brenda Smith¹, Viola Chen¹, Ning Ma², Xiaozhu Wang², Yuxiao Zhao², Ruiyu Zhou², Yangzhen Jiang², Mu Chen² and Sui Xiong Cai²

¹Eikon Therapeutics, Inc., 230 Harriet Tubman Way, Millbrae, CA 94030, USA, ²IMPACT Therapeutics (Shanghai), Inc., 27F, 399 Haiyang West Road, Shanghai 200126, China

ABSTRACT
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Introduction

- Non-selective PARP inhibitors have proven to be effective in patients with breast, ovarian, prostate and pancreatic tumors that harbor deficits in proteins involved in homologous recombination (HRD).
- Efficacy of non-selective PARP inhibitors is hampered by dose reductions and suspensions due to on-target toxicity resulting from PARP2 inhibition manifesting hematological suppression.
- Given this experience and knowledge that approximately 80-95% of cellular PARylation is performed by PARP1, selective PARP1 inhibitors are being developed to overcome the limitations of the pan-PARP inhibitors.
- We have identified a highly potent and selective PARP1 inhibitor EIK1004 (also known as IMP17307) that can penetrate the brain. This poster describes the pre-clinical characterization of the molecule's potency, selectivity, pharmaceutical properties and anti-tumor activity. EIK1004 is currently in a Phase I clinical study to evaluate its safety, PK and preliminary efficacy in patients with specific homologous recombination repair gene mutations with and without metastasis to the brain (NCT# 06907043).

Methods

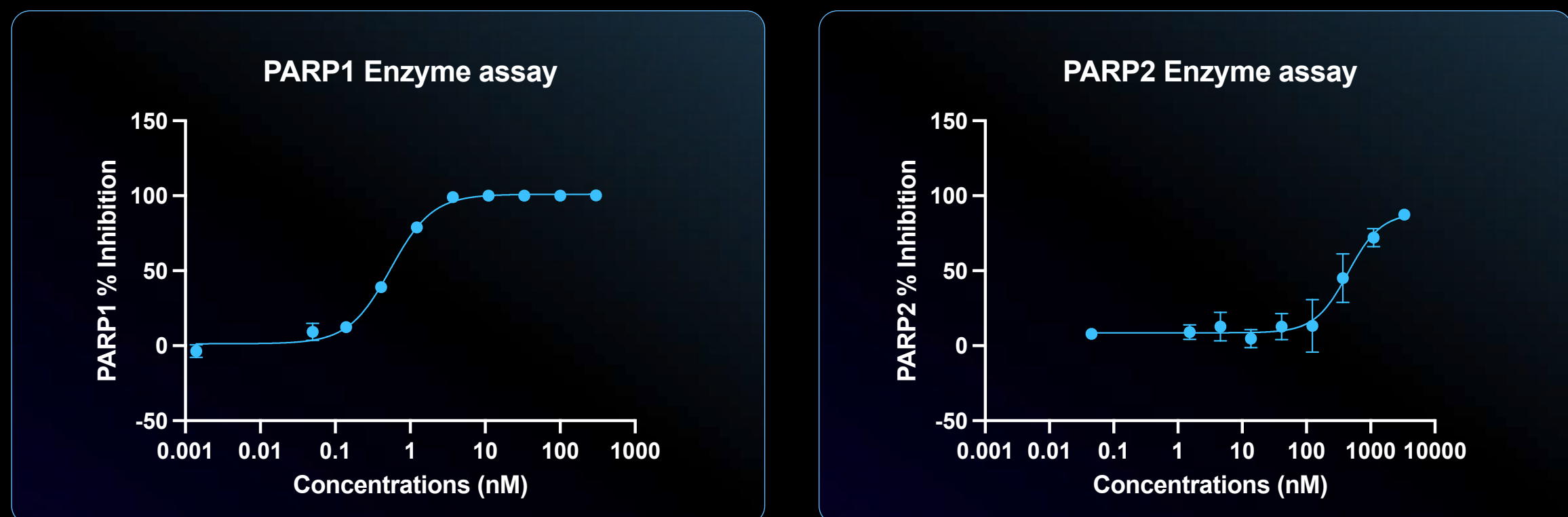
- Early lead PARP1 inhibitors with novel structures were optimized for selectivity and CNS penetration leading to the discovery of EIK1004
- In vitro biological studies:
 - The PARP family enzymatic activity was assessed using chemiluminescent PARylation assays.
 - The trapping assay of PARP1 was carried out tested using a DNA-Trap HTRF binding assay.
 - The cytotoxicity assays (CTG and CCK8) were conducted using BRCA-deficient cancer cells, including MDA-MB-436 and the isogenic pair of DLD-1 (wild type and BRCA2 knock out) cell lines.
- In vivo PD and efficacy studies:
 - EIK1004 was tested for efficacy in two subcutaneous cell line xenograft models, MDA-MB-436 and DLD1 KO grown in NOD/SCID mice.
 - To demonstrate brain penetrance, the MDA-MB-436 cell line expressing luciferase was delivered by stereotactic injection to the frontal cortex of mice to generate a model of breast cancer brain metastasis and imaged weekly.
- Pharmacokinetics (PK) profile:
 - EIK1004 was administered via intravenous and oral routes to mice, rats, dogs and monkeys. Plasma and brain samples were collected at various time points and analyzed by LC-MS/MS.

Results

In Vitro Activity

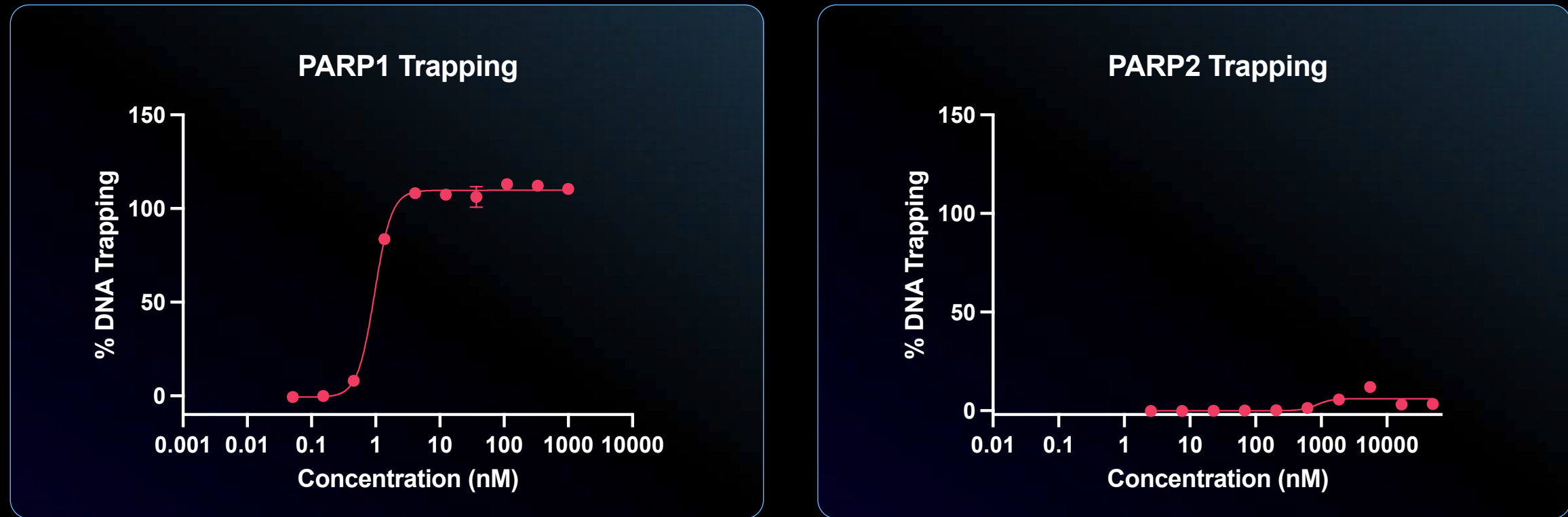
Excellent selectivity among PARP family

IC ₅₀ (nM)	EIK1004	AZD9574
PARP1	< 1	2.05
PARP2	500	4139
PARP1/2 (Fold)	>800	2019
PARP3	>30000	NT
PARP5a	>30000	NT
PARP5b	>1000	NT
PARP6	>30000	NT



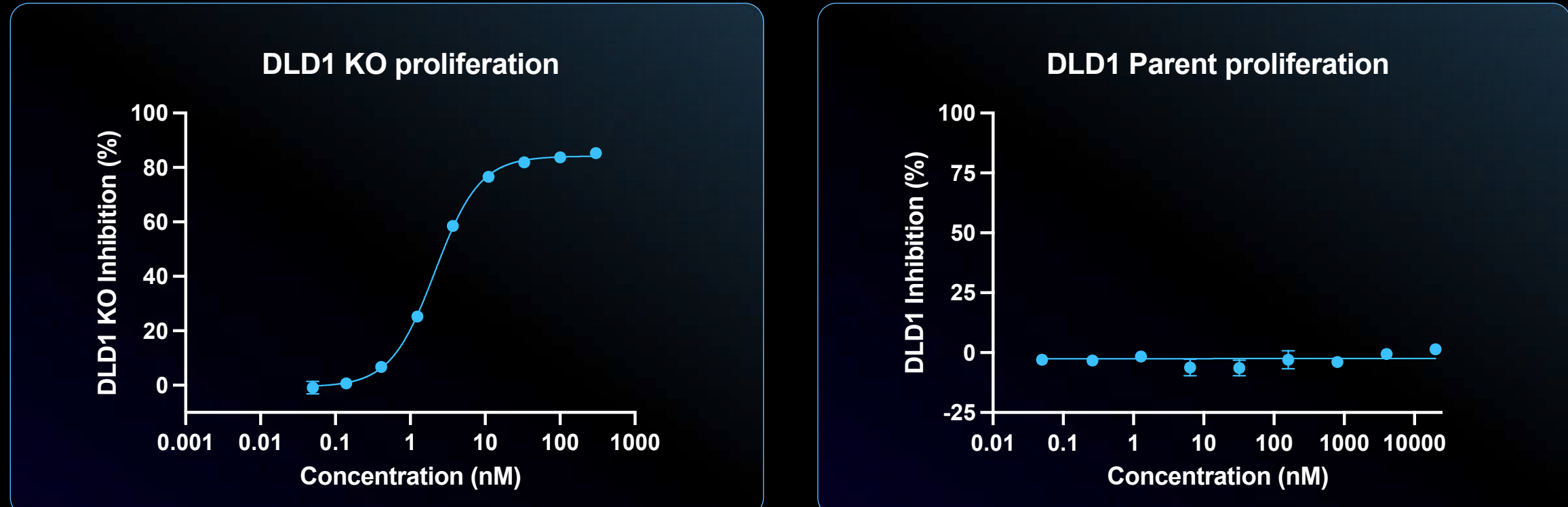
Potent trapping activity on PARP1 but not PARP2

EC ₅₀ (nM)	EIK1004	AZD9574
PARP1	< 1.0	3.0
PARP2	>50000	>50000
PARP1/2 (Fold)	>52000	>16667



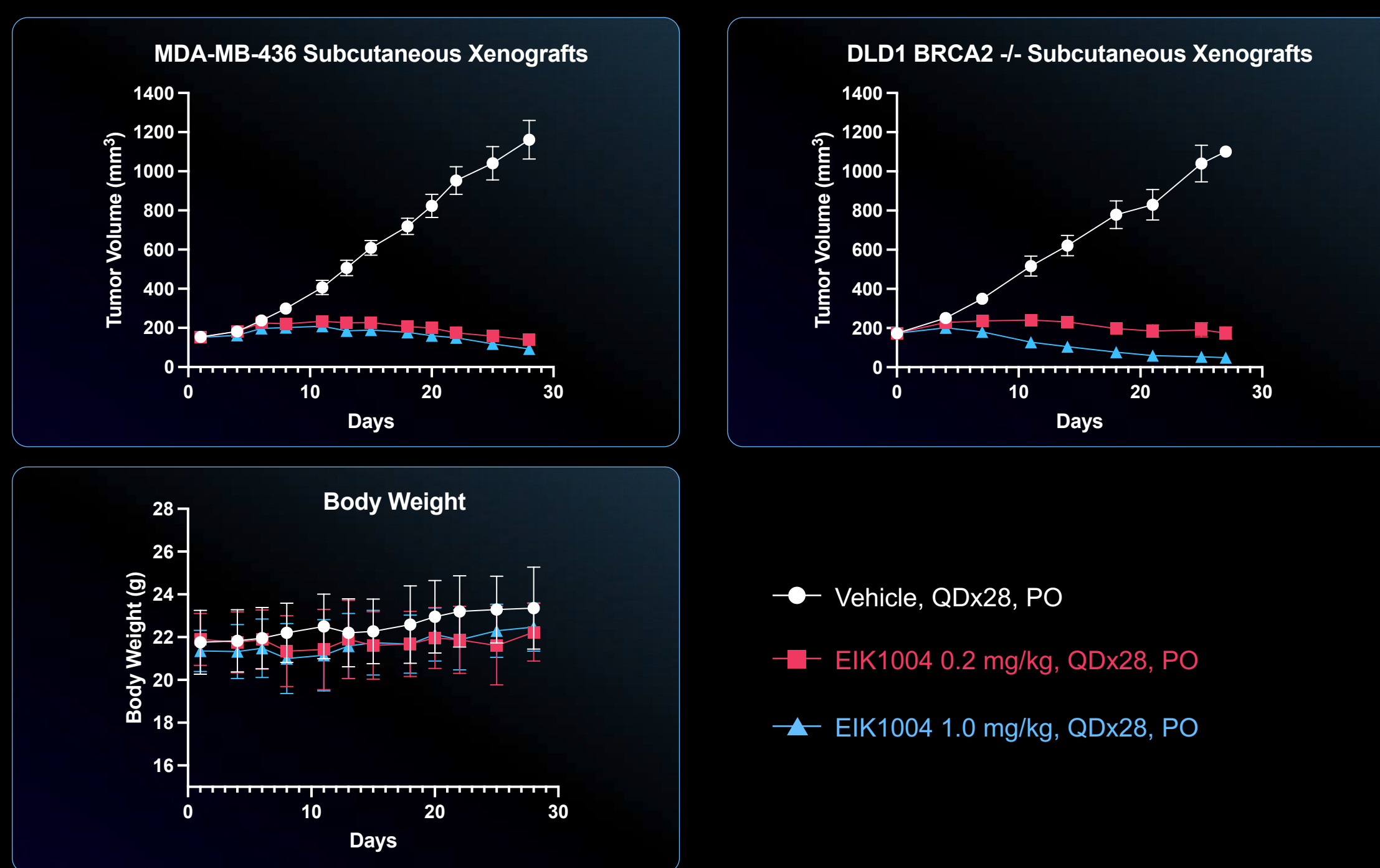
Excellent antiproliferative effect on cell lines with BRCA mutation or deletion

IC ₅₀ (nM)	EIK1004	AZD9574
MDA-MB-436		
BRCA1 m	< 1.0	3.93
BRCA2 KO	~ 2.0	11.3
DLD-1 isogenic pair		
BRCA2 wt	>20000	>20000
Fold	>9000	>1770

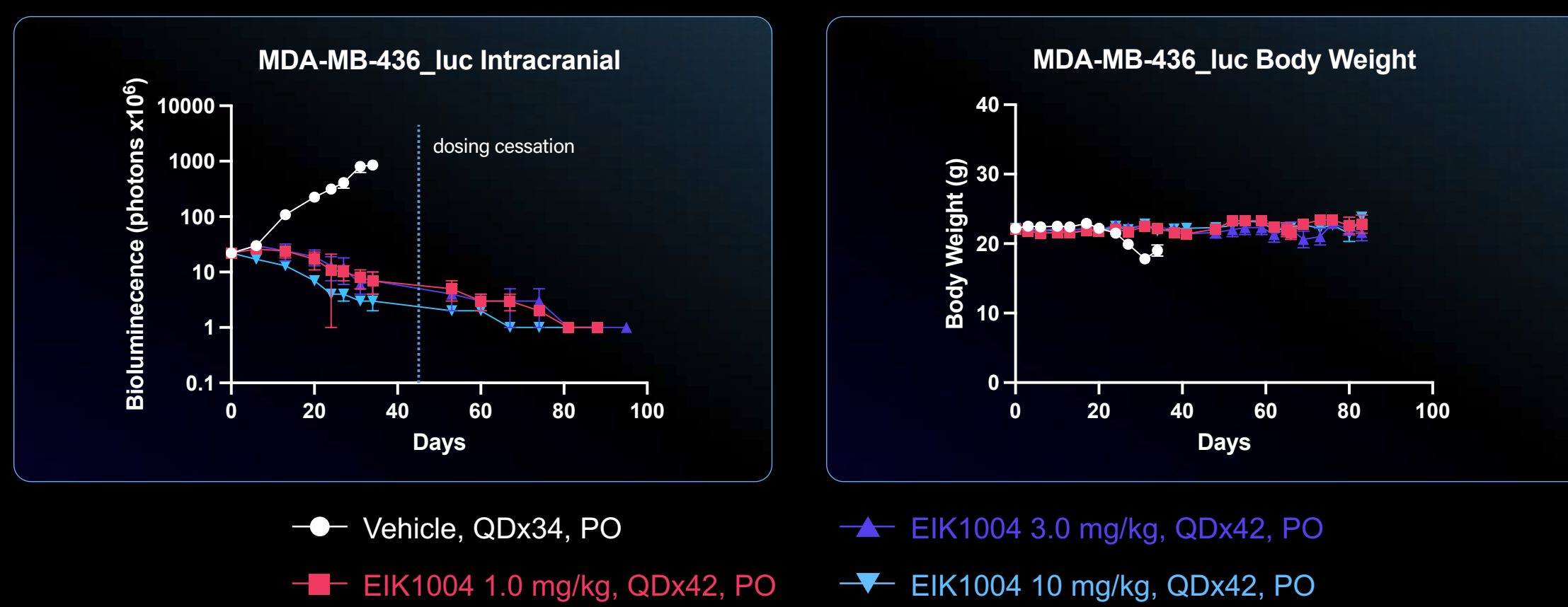
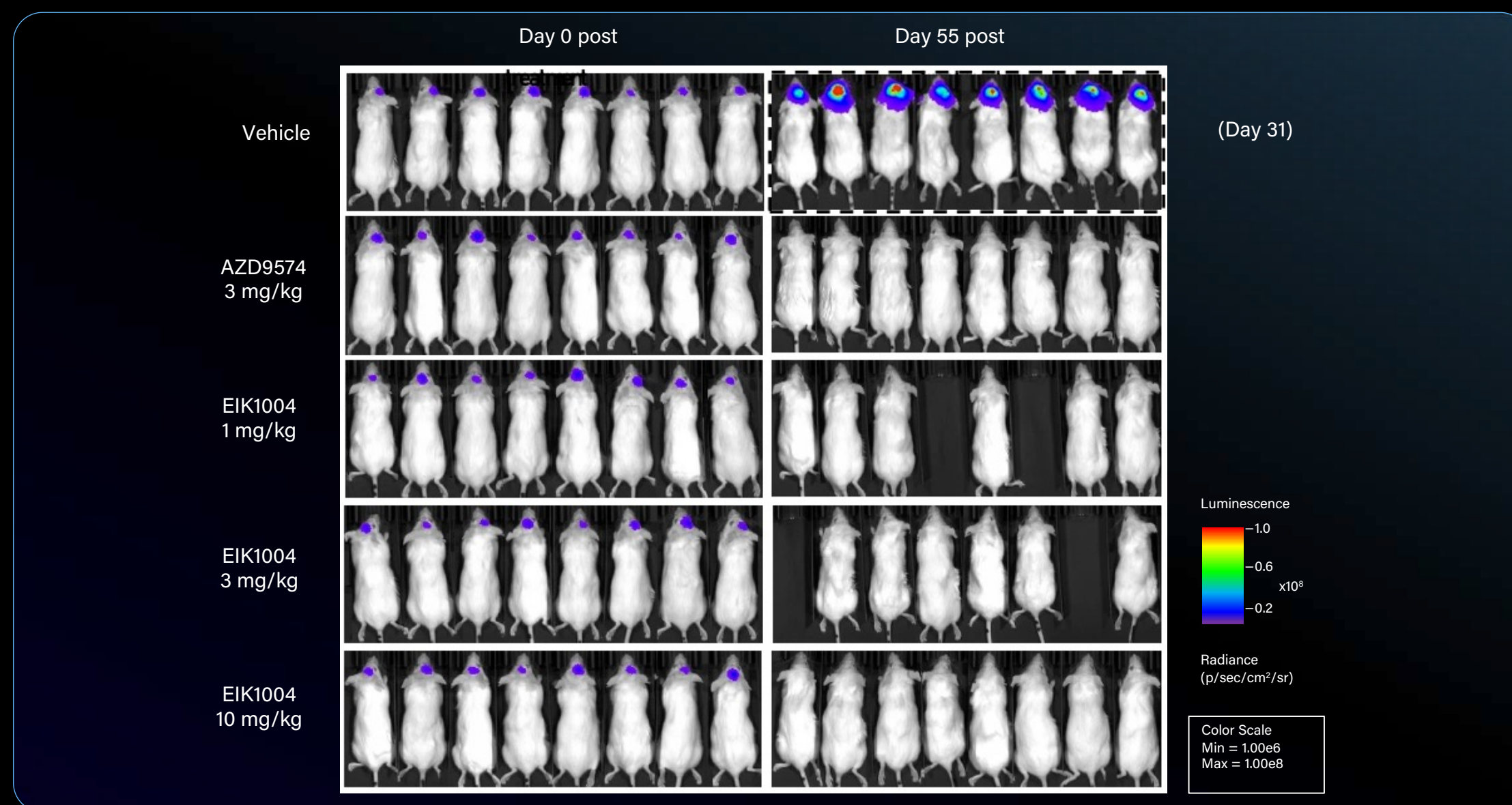


Results

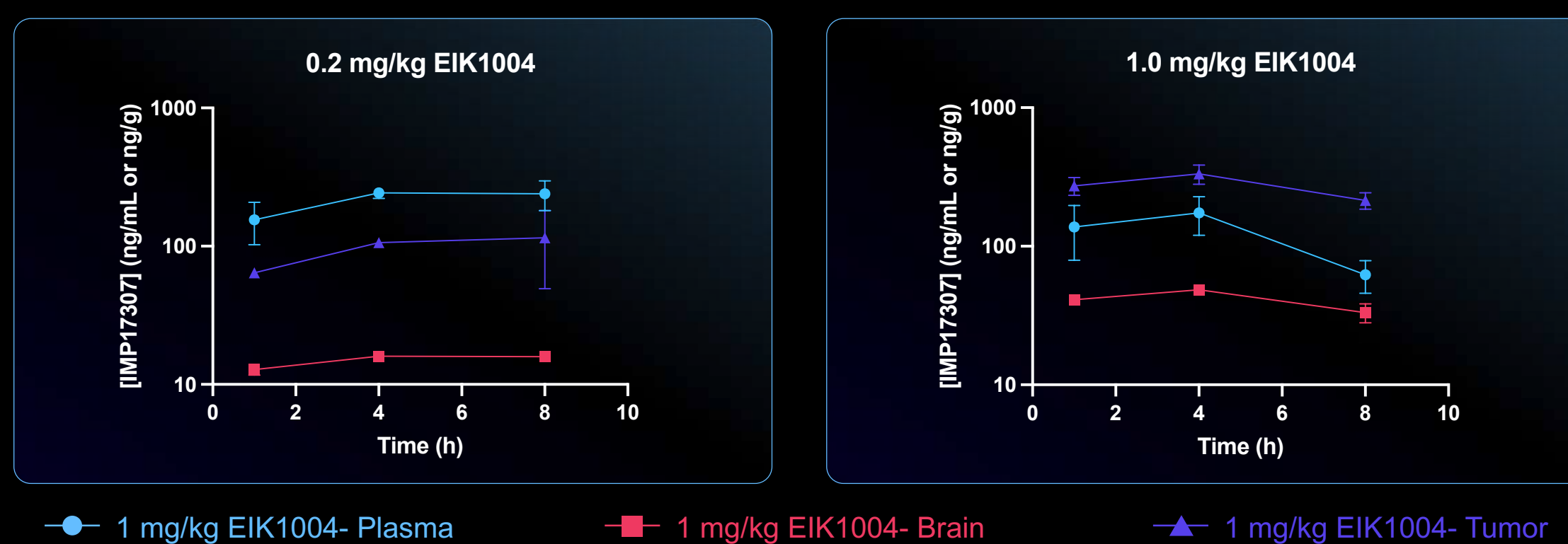
In Vivo Activity



Robust tumor regression in an MDA-MB-436 TNBC model of brain metastasis



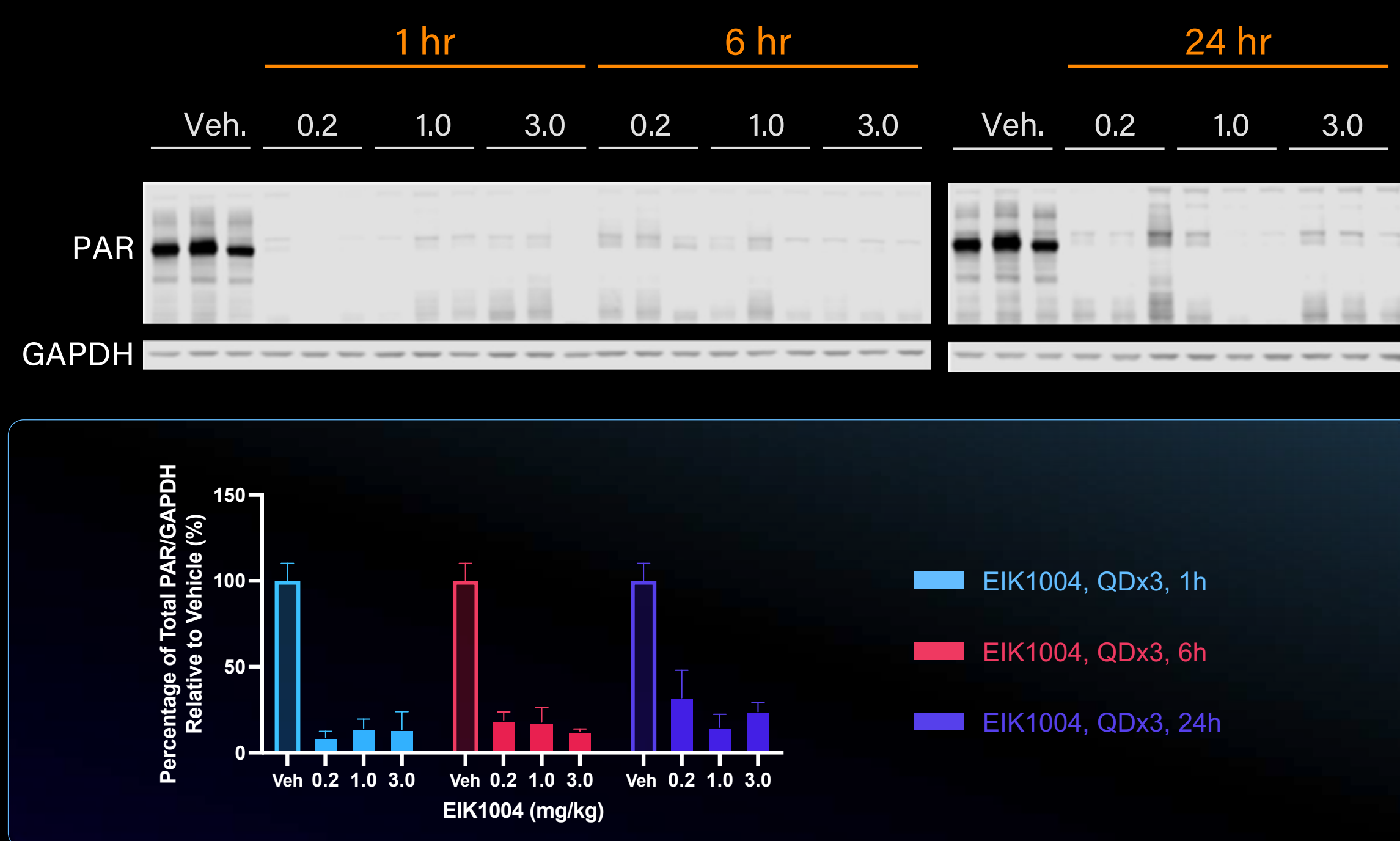
Robust tumor regression in an MDA-MB-436 TNBC model of brain metastasis



Results

In Vivo Pharmacodynamic Effect

Complete inhibition of total PAR levels in MDA-MB-436 TNBC tumors grown in the brain



PK Profile

Species	T _{1/2} (hr)	CL (mL/min/kg)	V _d (L/kg)	F%
Mouse	10	0.4	0.3	>100
Rat	6	1.4	0.8	>100
Dog	3	11	2.4	>100
Monkey	5	1.7	0.7	~60

EIK1004 has a K_{p,uu} in mouse and rat consistent with adequate brain exposure

Species	AUC _{Plasma} (ng.h/mL)	CL (ng.h/mL)	Plasma f _u	Brain f _u	K _p	K _{p,uu}
Mouse	10	0.4	1	4	0.1	0.5
Rat	6	1.4	2	4	0.2	0.5

Summary

- Highly potent PARP1 inhibitor with excellent PARP1/2 selectivity (>800-fold).
- Highly potent cytotoxic activity against cancer cells with BRCA mutations, i.e. MDA-MB-436 (BRCA1m) cells (IC₅₀ = < 1.0 nM).
- Robust tumor regression in mouse xenograft models of BRCA mutant cancers (MDA-MB-436 and DLD1) with a minimally efficacious dose of 0.2 mg/kg.
- EIK1004 penetrates the brain with a K_{p,uu} of 0.5 in both mouse and rat, and results in complete tumor regression in a brain metastasis model of TNBC.
- Long-lasting anti-tumor effect even after drug discontinuation.
- Good oral bioavailability across multiple non-clinical species.