

# Discovery and Development of IMP1734 (EIK1003), a Potent and Selective PARP1 Inhibitor

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ABSTRACT  
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## Introduction

- Nonselective PARP1/2 inhibitors (PARPi) kill cancer cells harboring genetic mutations in critical DNA repair genes, in part by inhibiting enzyme activity and/or “trapping” PARP1/2 on DNA strands<sup>a,b</sup> (Figure 1A).
- While approved nonselective PARPi have demonstrated anti-tumor activity, associated hematologic toxicities (possibly due to PARP2 inhibition) have limited combination regimen development and expansion treatment scope<sup>c</sup>.

Figure 1A: Nonselective PARP Inhibitors Can Cause Accumulation of DSBs and Exert Synthetic Lethality in HRR-Deficient Cancer Cells

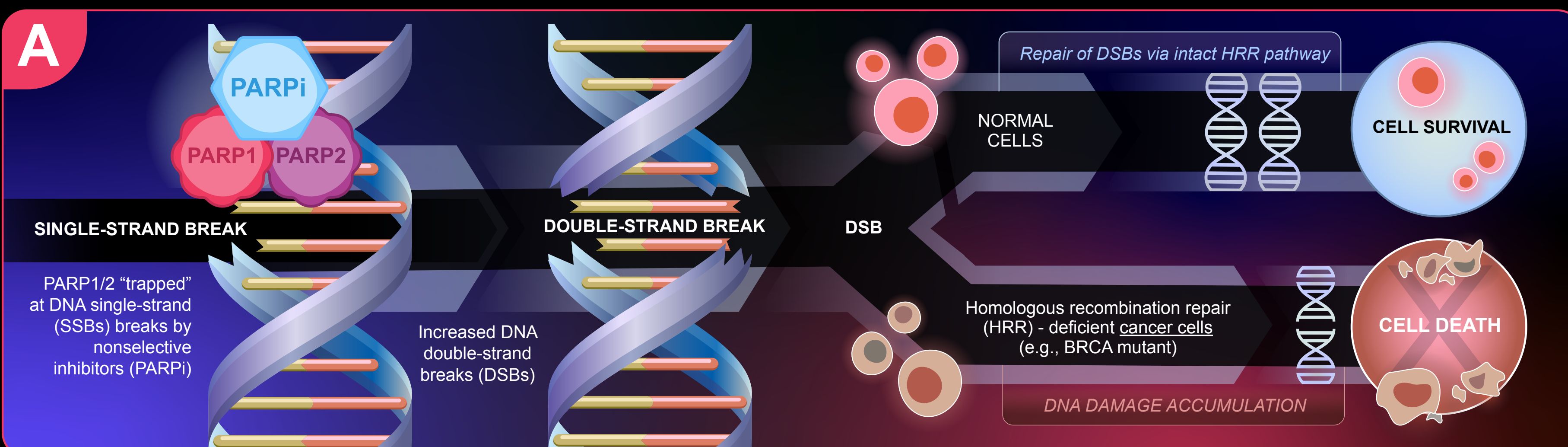
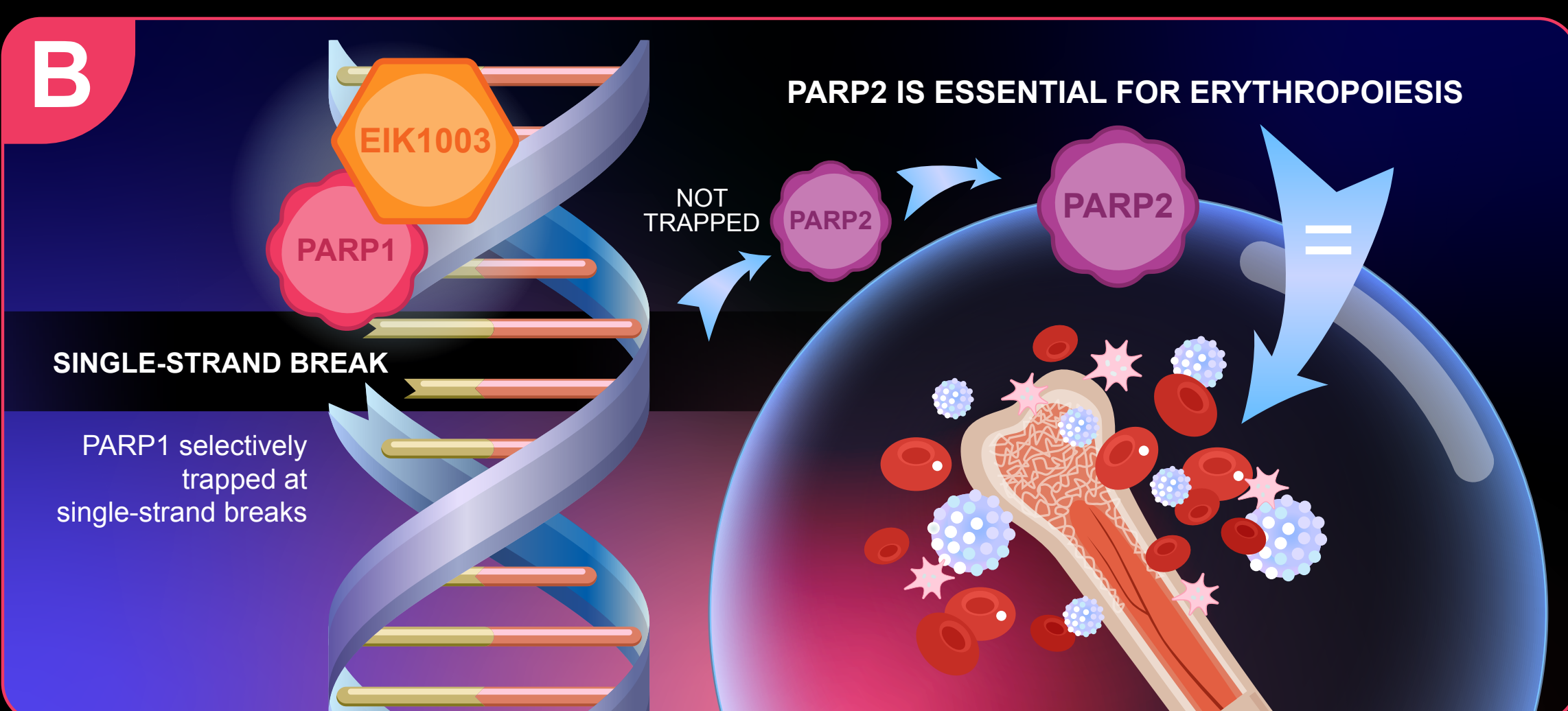


Figure 1B: Selective Inhibition of PARP1 May Retain Antitumor Activity While Avoiding PARP2-Mediated Toxicity



- Drugs that selectively inhibit PARP1 but spare PARP2 may improve the risk-benefit profile for patients by preserving anti-tumor activity while reducing PARP2-related toxicities (Figure 1B).
- IMP1734 is a potent, PARP1-selective inhibitor that inhibits tumor growth in nonclinical models and may widen the therapeutic index in tumors where non-selective PARPi have demonstrated efficacy.

## Methods

- IMP1734 is a highly selective PARP1 inhibitor that has been characterized in a series of nonclinical studies, described here. IMP1734 is currently in a phase I clinical study to evaluate its PK, safety profile and preliminary efficacy in patients with specific homologous recombination repair (HRR) genes mutations (NCT06253130).

- IMP1734 was evaluated in biological *in vitro* assays:

- \* PARP family enzymatic activity was assessed using PARylation chemiluminescent assays.
- \* PARP1 trapping was tested using a DNA-Trap HTRF binding assay.
- \* Cytotoxicity assays (CTG and CCK8) were conducted using BRCA-deficient cancer cells, including MDA-MB-436, isogenic pairs of DLD-1 (wild type and BRCA2 knock out) and UWB1.289 (BRCA1 mutation and BRCA1 knock in) cell lines.

- In vivo* efficacy and PK/PD studies were conducted using BRCA-deficient TNBC CDX models. The studies evaluated dose-dependent tumor growth inhibition (TGI) and the correlation between the pharmacodynamic marker (PARylation) and PK plasma concentration.

- Pharmacokinetics (PK) parameters for IMP1734 were assessed following administration via intravenous and oral routes to mice, rats and dogs. Plasma samples were collected at various time points, and the drug concentrations were analyzed using LC-MS/MS.

<sup>a</sup> Lord, C. J. and A. Ashworth (2017), “PARP inhibitors: Synthetic lethality in the clinic.” *Science* 355(6330): 1152-1158.

<sup>b</sup> Petropoulos, M., et al. (2024), “Transcription-replication conflicts underlie sensitivity to PARP inhibitors.” *Nature* 628(8007): 433-441.

<sup>c</sup> LaFargue, C. J., et al. (2019), “Exploring and comparing adverse events between PARP inhibitors.” *Lancet Oncol* 20(1): e15-e28.

## Results

### In Vitro Activity

#### IMP1734 Selectively Inhibits PARP1

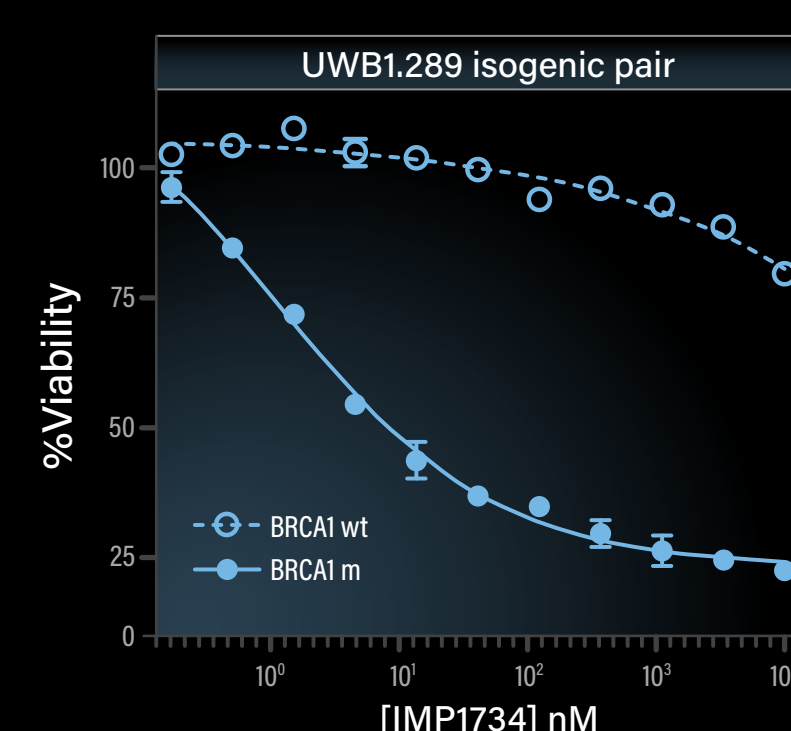
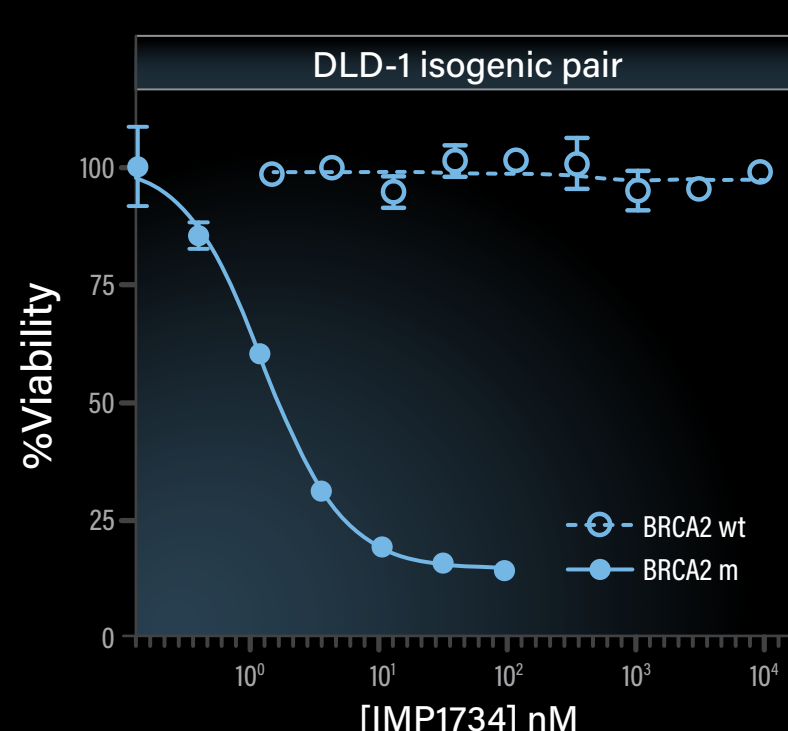
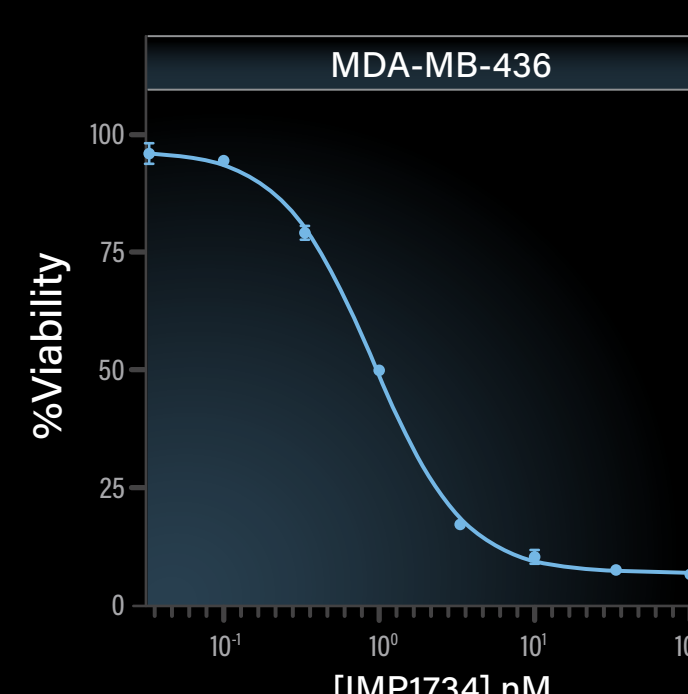
| IC <sub>50</sub> (nM) | IMP1734 | AZD5305 |
|-----------------------|---------|---------|
| PARP1                 | 1.57    | 0.99    |
| PARP2                 | 1018    | 17.96   |
| PARP1/2 (Fold)        | 648     | 18      |
| PARP3                 | >30000  | 1962    |
| PARP5a                | 1535    | 1238    |
| PARP5b                | 433     | 381     |
| PARP6                 | >30000  | 5161    |

#### IMP1734 Selectively Traps PARP1 vs PARP2

| EC <sub>50</sub> (nM) | IMP1734 | AZD5305 |
|-----------------------|---------|---------|
| PARP1                 | 2.48    | 1.9     |
| PARP2                 | >50000  | 1997    |
| PARP1/2 (Fold)        | >20169  | 1041    |

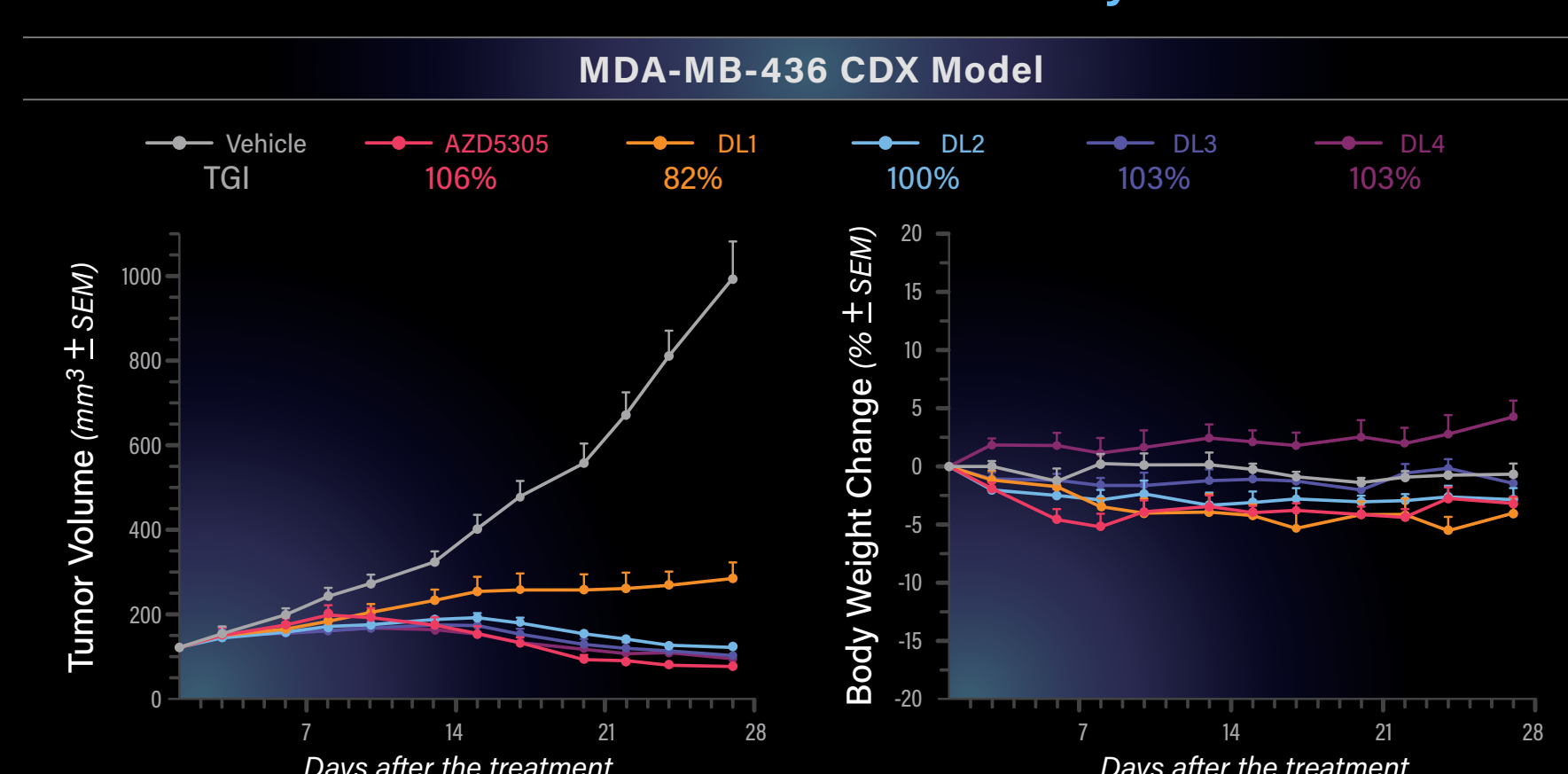
#### IMP1734 Demonstrates Antiproliferative Activity Against BRCA-Deficient Cell Lines

| IC <sub>50</sub> (nM)           | IMP1734 | AZD5305 |
|---------------------------------|---------|---------|
| MDA-MB-436 BRCA1 m              | 0.97    | 1.22    |
| DLD-1 isogenic pair BRCA2 m     | 1.3     | 1.4     |
| DLD-1 isogenic pair BRCA wt     | >10000  | >10000  |
| Fold                            | >7634   | >7633   |
| UWB1.289 isogenic pair BRCA1 m  | 8.4     | 3.4     |
| UWB1.289 isogenic pair BRCA1 wt | >10000  | >10000  |
| Fold                            | >1245   | >2941   |

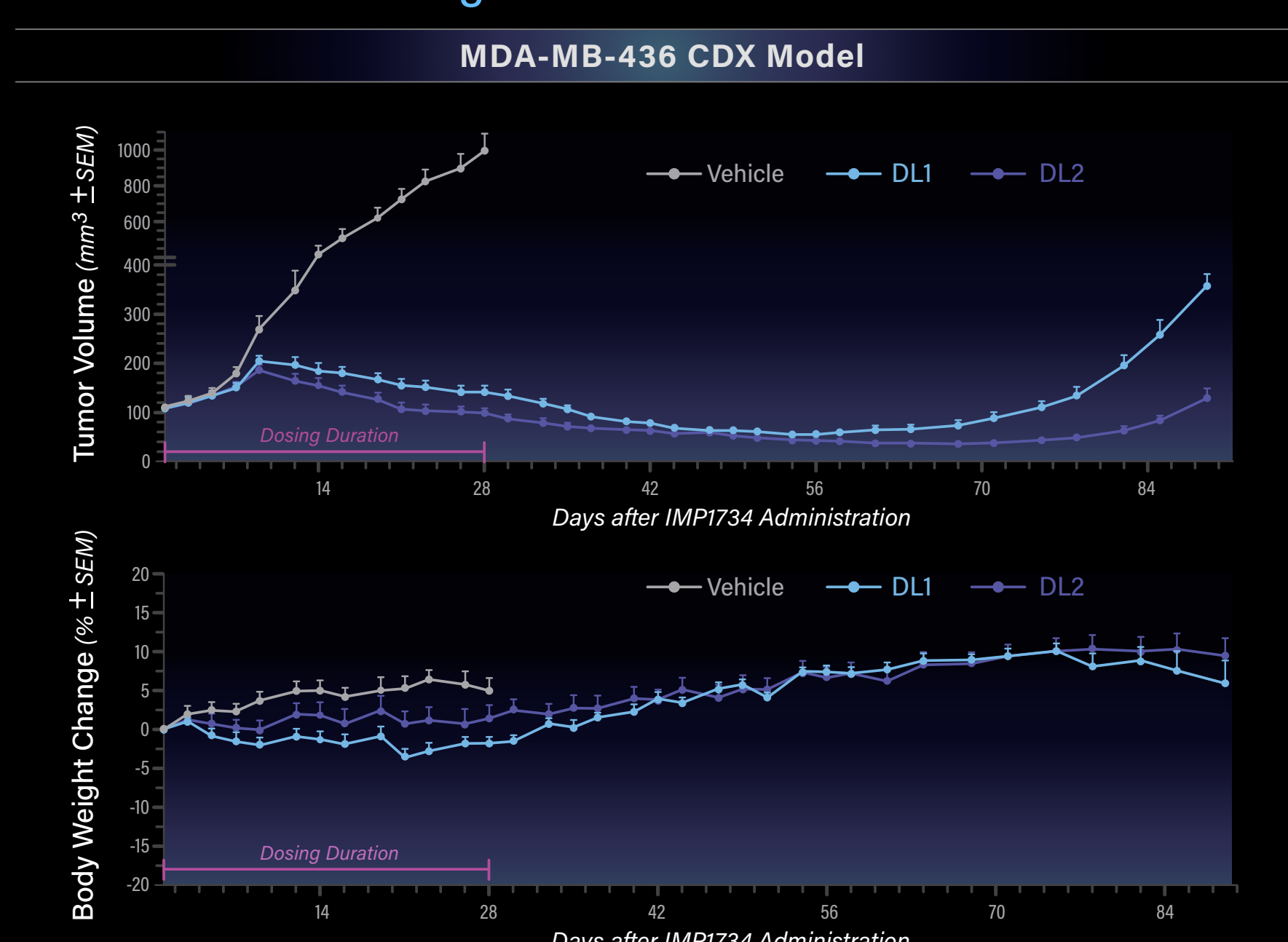


### In Vitro Efficacy

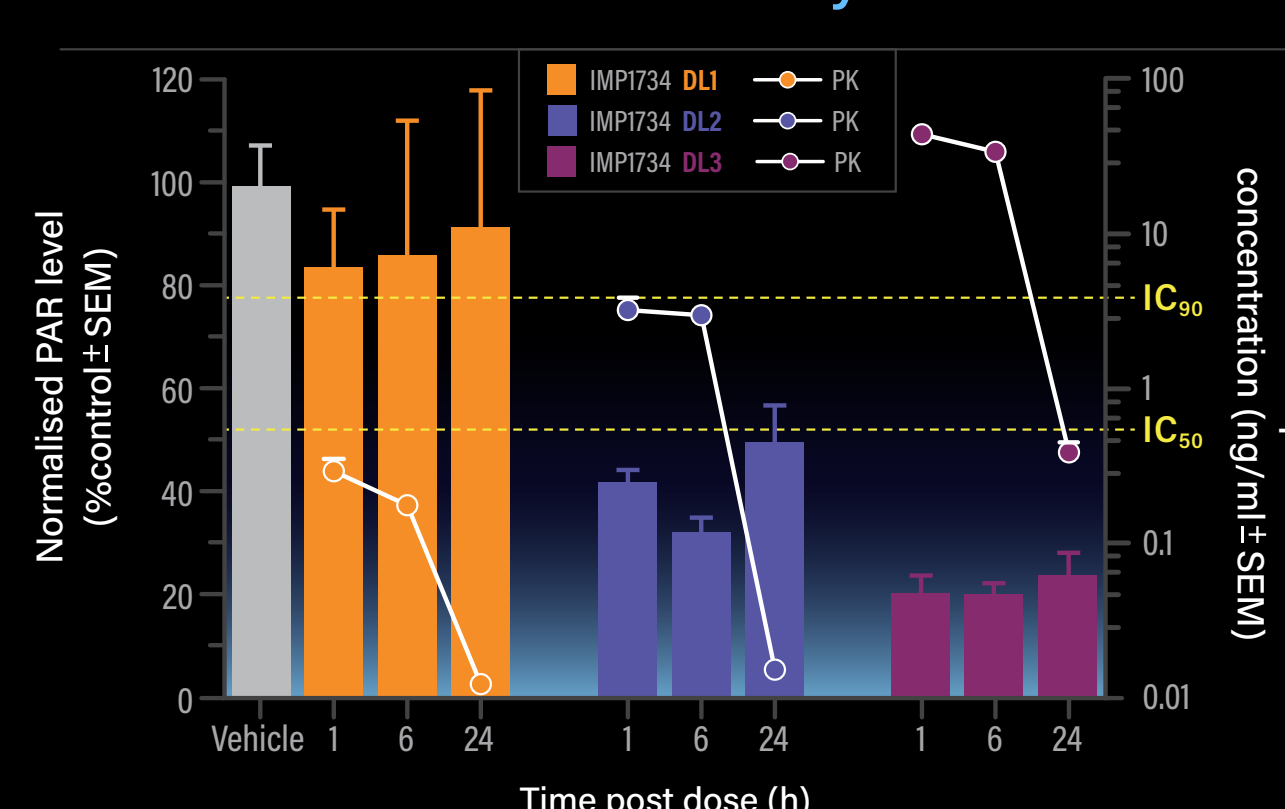
#### IMP1734 is Well-Tolerated and Exhibits Robust Antitumor Activity



#### IMP1734 Exhibits Durable Antitumor Activity Following Treatment Discontinuation



#### IMP1734 Demonstrates Plasma Concentration-Dependent Inhibition of PARylation

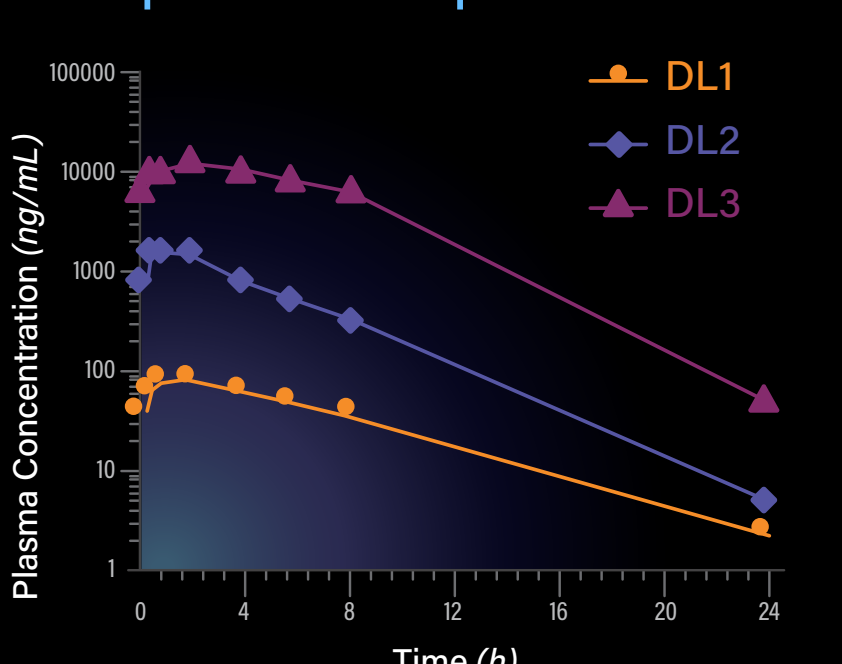


### Pharmacokinetic Profile

#### Oral IMP1734 Has Robust PK Parameters in Multiple Species

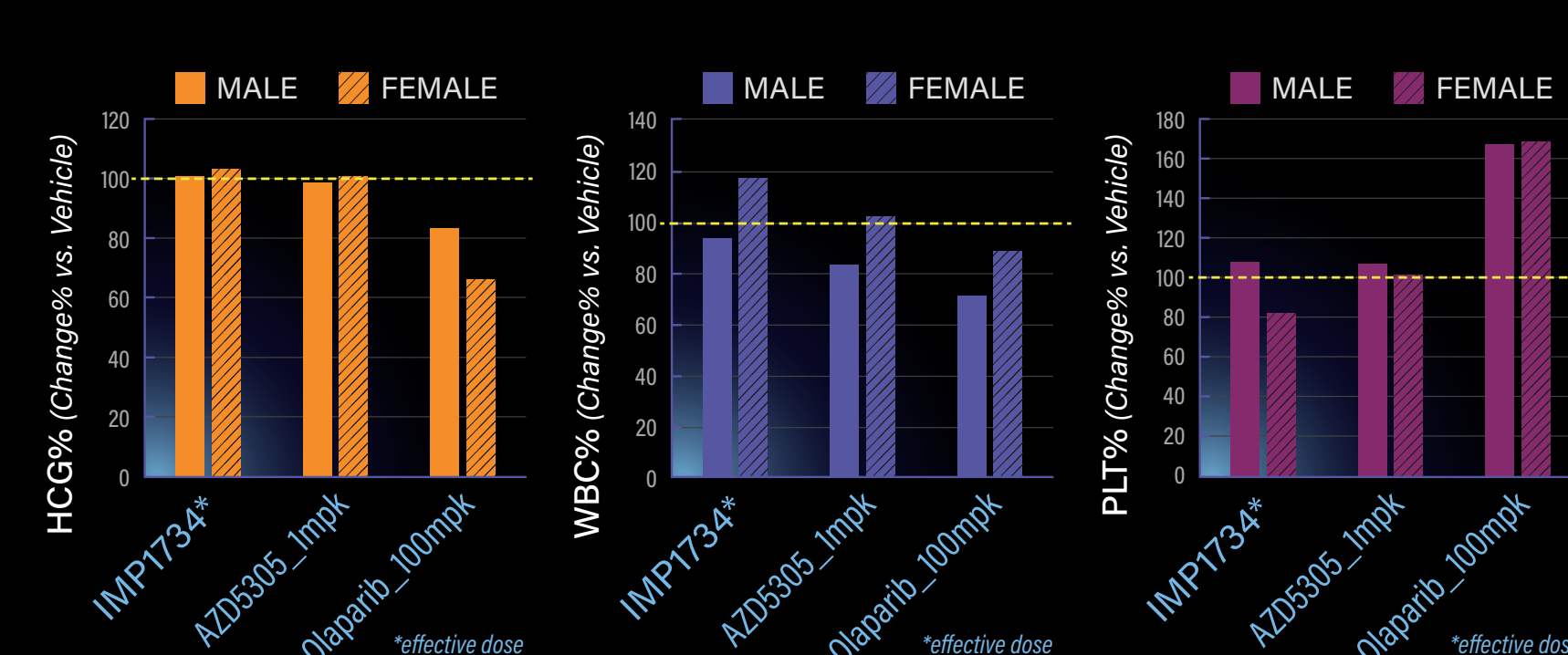
| Species                     | Mice | Rat  | Dog  |
|-----------------------------|------|------|------|
| T <sub>1/2</sub> (hr)       | 3.0  | 4.5  | 8.9  |
| CL <sub>L</sub> (mL/min/kg) | 2.5  | 1.8  | 6.2  |
| V <sub>d</sub> (L/kg)       | 0.50 | 0.50 | 3.7  |
| F%                          | 113  | 70.5 | 87.1 |

#### IMP1734 Shows Dose-Proportional Exposure in Mice



### Hematologic Toxicity

#### 14-Day Administration of IMP1734 Results in Improved Hematologic Toxicity Profile Relative to Olaparib



## Summary

- Potent PARP1 inhibitor with excellent PARP1 vs PARP2 selectivity (648-fold).
- Potent anti-proliferative activity against cancer cells with BRCA mutations, i.e. MDA-MB-436 (BRCA1m) cells (IC<sub>50</sub> = 0.97 nM).
- Robust *in vivo* efficacy and tolerability in BRCA1m MDA-MB-436 CDX mouse model.
- Long-lasting anti-tumor effect even after cessation of administration.
- Excellent oral bioavailability and PK profile across multiple non-clinical species.
- Lower hematologic toxicity when measured in rats compared to non-selective PARP inhibitor.