

Preclinical PK/PD/Efficacy modelling to guide early clinical dose selection for AZD9750, a novel oral Androgen Receptor Proteolysis-targeting chimera (AR-PROTAC)



AstraZeneca

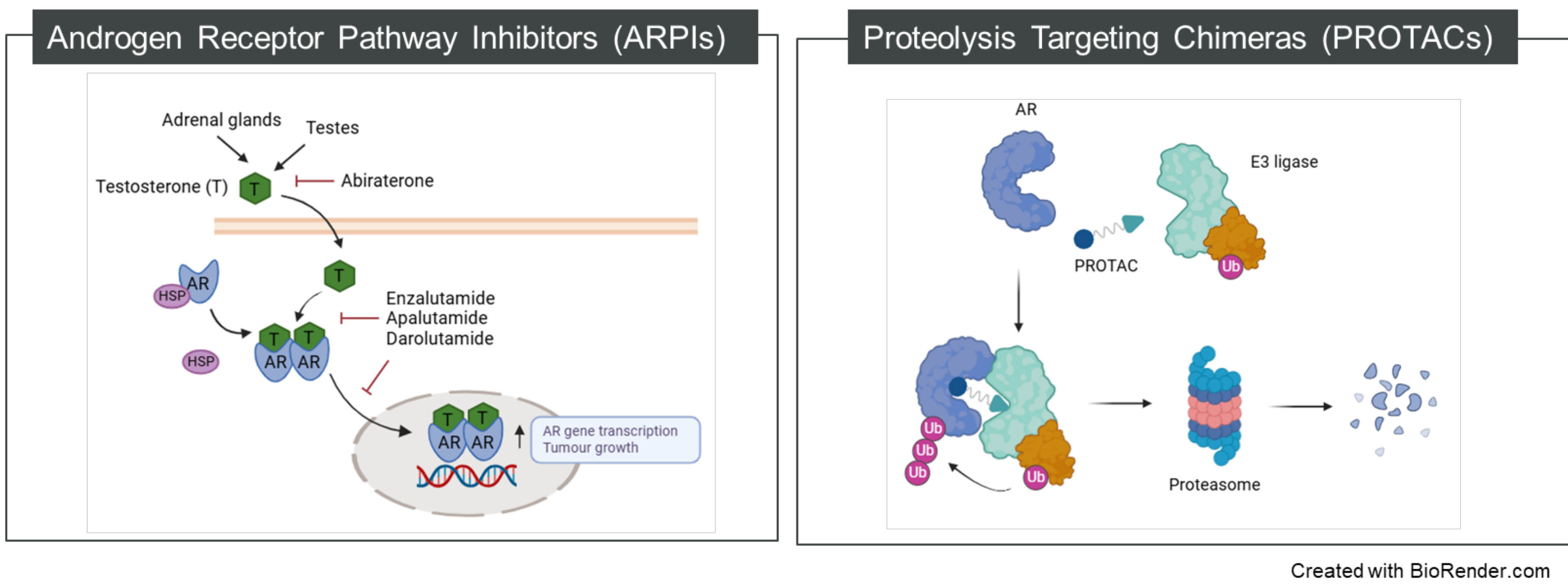
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Introduction

AR plays a pivotal role in prostate cancer pathogenesis, where it is highly expressed, making it a well-established target for therapeutic intervention in oncology. AZD9750 represents a novel, potent oral PROTAC targeting AR, due to enter phase I clinical trials in 2025. This study was designed to guide the dose selection during clinical development of AZD9750.

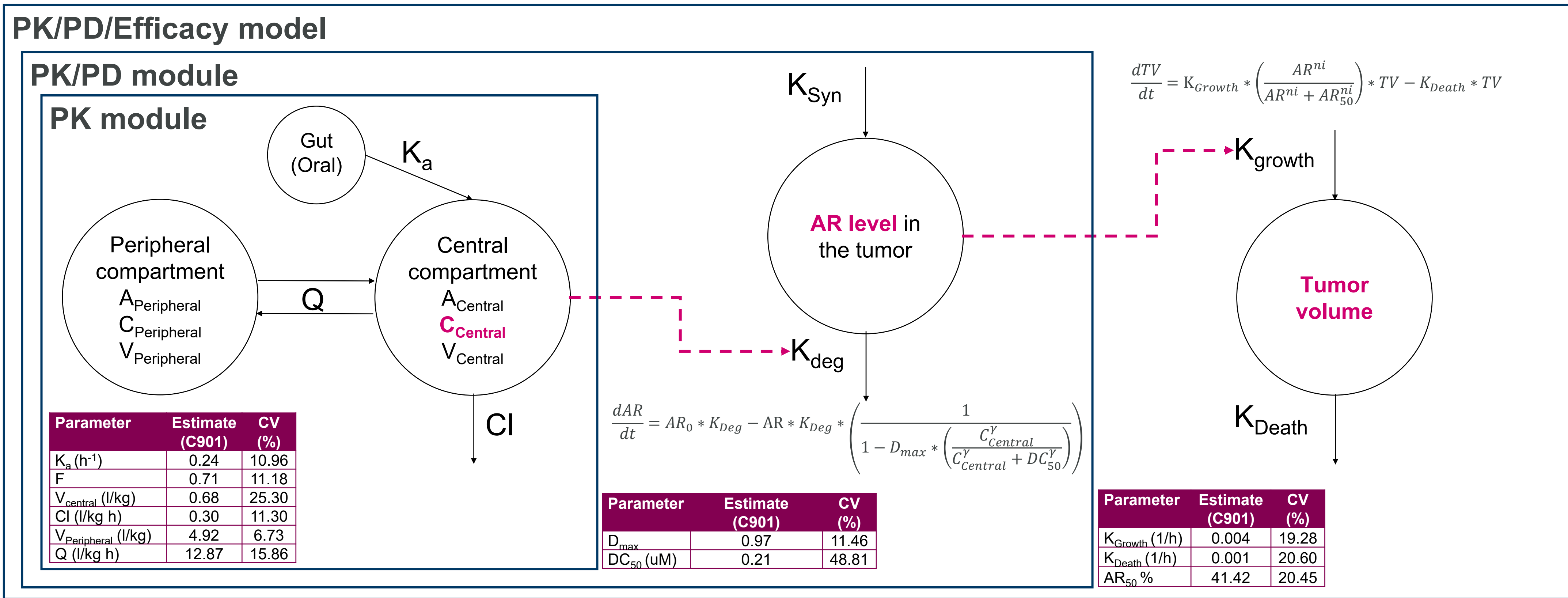
The AZD9750 mechanism of action involves simultaneous binding to AR and cereblon (CRBN), a component of the E3 ubiquitin ligase complex. This concurrent binding facilitates the recruitment of the ubiquitin-proteasome system, resulting in the ubiquitination and degradation of AR.



PK/PD/Efficacy modelling and parameter estimation strategy

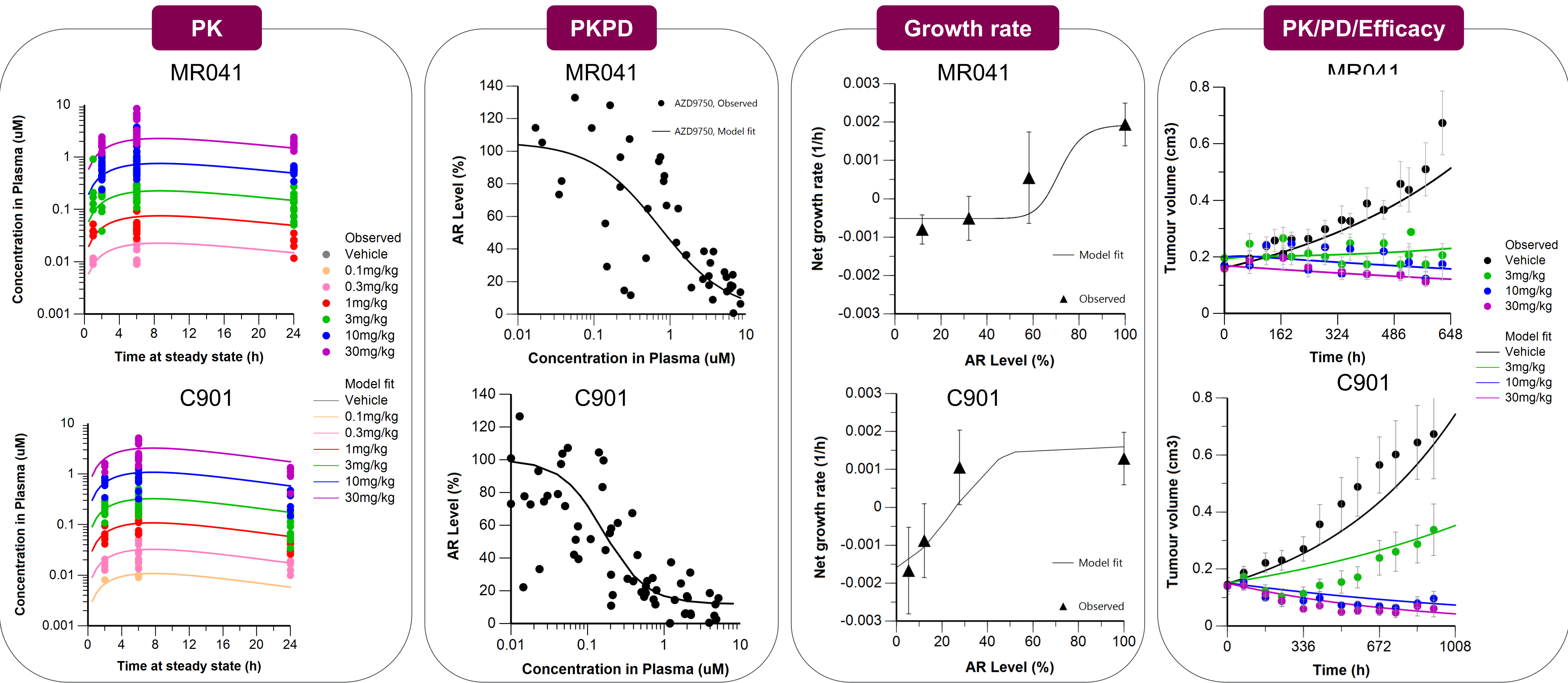
A mechanistic model was developed based on internal preclinical studies using MR041 and C901 PDX models. Data included individual longitudinal PK, AR levels, and tumour size metrics.

The PK module consists of a two-compartment model with first-order absorption. The indirect PKPD module accounts for endogenous AR turnover rate and compound-induced AR degradation. Finally, the complete PK/PD/Efficacy model assumes tumor homogeneity and AR-dependent tumor growth rate.



Modelling and observed data results for MR041 and C901 PDX models

The model parameters were independently and sequentially determined by module (PK, PK/PD & PK/PD/Efficacy), taking into account interindividual variability at each step (bioavailability, clearance, initial AR levels, and tumour size). All parameters within the model were estimated through Non-Linear Mixed Effect modelling (Phoenix®, Certara).



Conclusions

This study provides mechanistic, integrated and quantitative insights into the interplay between AZD9750 exposure, AR modulation, and anti-tumour effect, thereby enhancing our understanding of the required target modulation levels needed to maximize the antitumor effect in hormone-sensitive PDX tumour models. This understanding is valuable for contextualizing AZD9750-induced AR level modulation, for given doses and schedules in patients, facilitating informed dose selection decisions during initial clinical evaluation.

References

Acknowledgements.

1. Guzzetti, S. and Morentin, P. J. Pharmacokinet. Pharmacodyn. 50(5): 327-349, 2023

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