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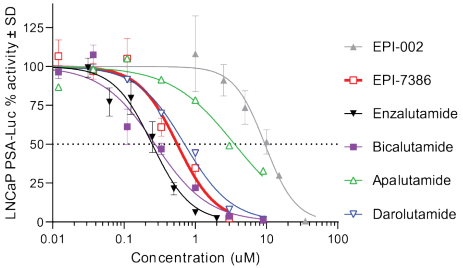
MP79-04

The preclinical characterization and development of EPI-7386, an N-terminal domain androgen receptor inhibitor for the treatment of prostate cancer

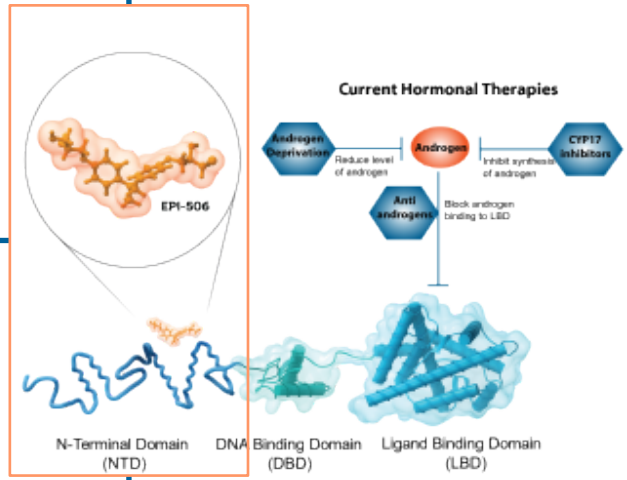
Ronan Le Moigne, Nan Hyung Hong, C. Adriana Banuelos, Nasrin R Mawji, Teresa Tam, Jun Wang, Kunzhong Jian, Raymond J. Andersen, Alessandra Cesano, Marianne D. Sadar, Han-Jie Zhou, Peter Virsik

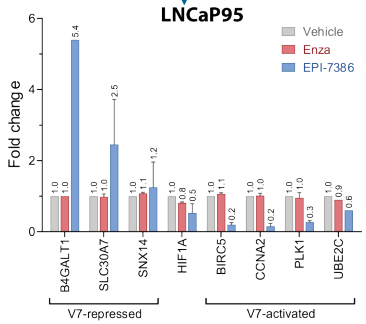
Androgen receptor (AR) NTD inhibitor EPI-7386 is active against full length and splice variant AR and can be combined with enzalutamide for broader and deeper pathway inhibition

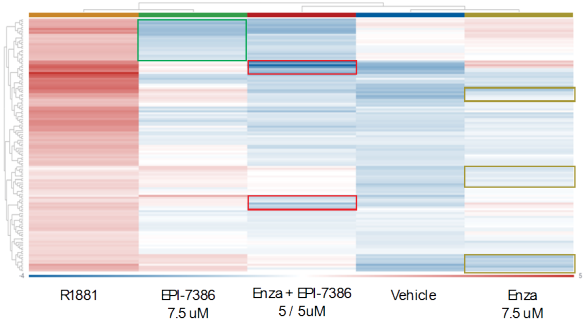
Inhibition of AR full length activity



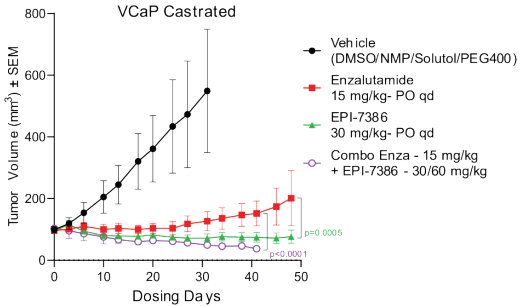
Inhibition of AR splice variant activity







Broader and deeper anti-AR effect in combination with enzalutamide



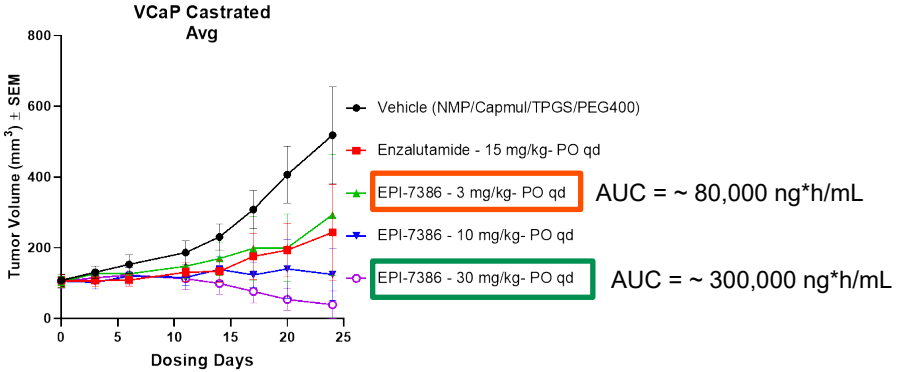
EPI-7386 was well tolerated in tox studies and showed efficacy in xenograft models at exposures well below HNSTD exposures

28-day GLP tox studies in rats and dogs

Species	Dose (mg/kg/day)	AUC0–24h steady state (ng·h/mL)	Major Findings	Conclusion
Rat	60	1,119,000	Well tolerated and non-adverse	Below NOAEL
	120	1,640,000	Well tolerated and non-adverse	NOAEL
	240	2,350,000	Adverse body weight and food consumption loss. No other significant clinical or anatomical pathology findings	HNSTD
Dog	20	529,000	Well tolerated and non-adverse	NOAEL
	50	1,350,000	Well tolerated and non-adverse	Below HNSTD
	90/70	1,850,000	Adverse body weight and food consumption loss. No other significant clinical or anatomical pathology findings	HNSTD

NOAEL: No-observed -adverse-event level; HNSTD: Highest non-severe toxic dose.

Antitumor activity in mouse xenografts



AUC = ~ 80,000 ng*h/mL

AUC = ~ 300,000 ng*h/mL

Projected exposure in human based on in vitro in vivo correlation

Dose (mg)	Cmax (ng/mL)	AUC0-24 (ng*hr/mL)
50	1,729	34,320
100	3,458	68,639
200	6,915	137,278
400	13,830	274,556
800	27,659	549,113

AUC and Cmax calculated at steady state

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