RS-2024-00333115

Development of the candidate for Standard Treatment-Resistant/Refractory Prostate Cancer through direct inhibition of XBP1s, a Mediator of ER stress

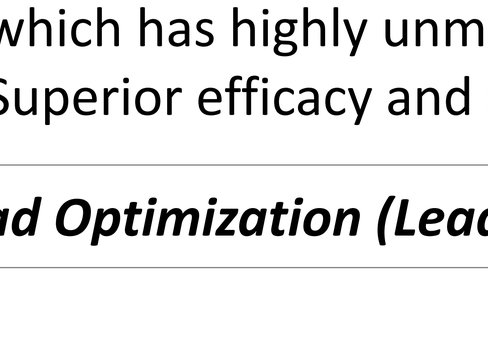
JW C&C Research Laboratories

Disease Area	***Solid cancer***
Product Type	Chemical- Small Molecule
Indication	Metastatic Castration-resistant prostate cancer (mCRPC) XBP1s-dependent SoC resistant Solid cancer
Target	X-Box-binding Protein 1 splicing form (XBP1s)
Mechanism of Action	Directly binds to XBP1s and induces its protein degradation → Downregulates target gene expression, Leading to inhibition of cell growth
Competitiveness	▪ Novel first-in-class inhibitor by directly binding to XBP1s protein ▪ Strong anti-tumor effects against resistant/refractory patients to mCRPC SoC (ARi) which has highly unmet medical needs ▪ Superior efficacy and safety over MKC-8866 (IRE1α RNase inhibitor, Phase 2)
Development Stage	***Lead Optimization (Lead to Candidate)***
Route of Administration	Oral Administration

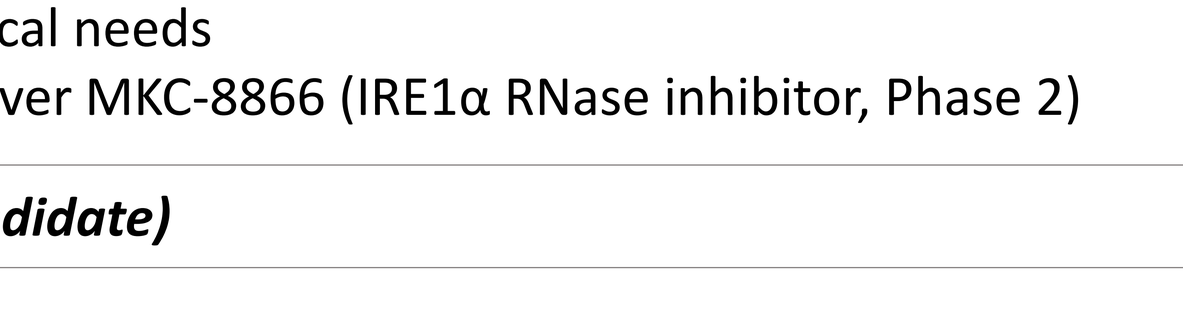
Key Data

- XP-1245 was confirmed to bind to XBP1s protein in a concentration-dependent 1:1 manner, regulating the stability of XBP1s and decreasing its expression
- XP-1245 decreases the expression of target genes, notably reducing the expression and secretion of PSA, a biomarker of prostate cancer
- In a xenograft model, XP-1245 exhibited significant anti-tumor efficacy compared to the MKC-8866

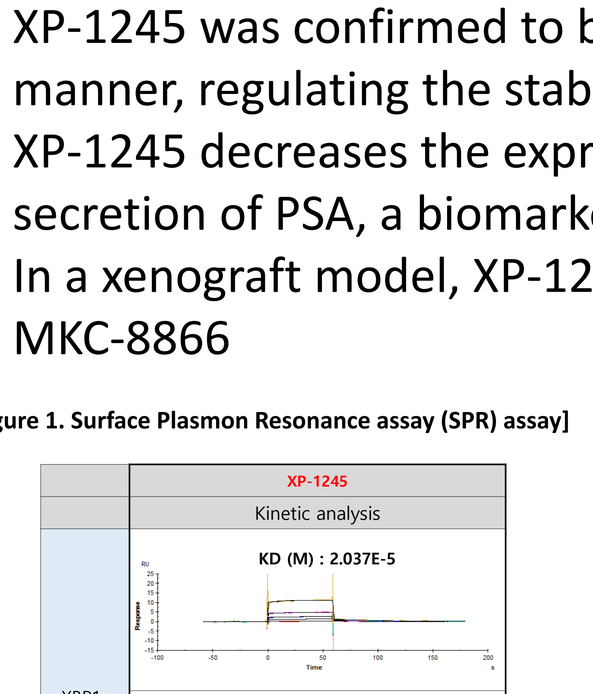
[Figure 1. Surface Plasmon Resonance assay (SPR) assay]



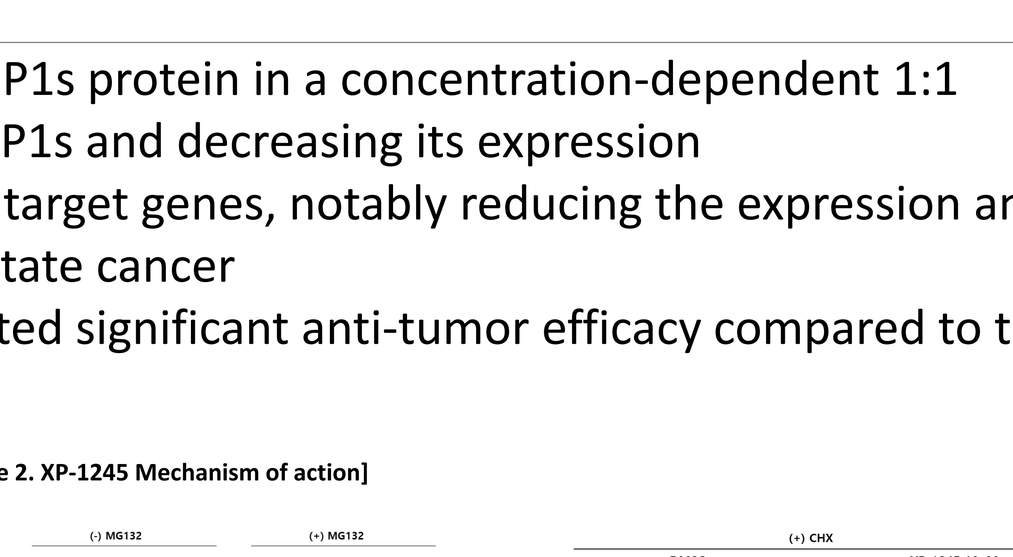
[Figure 2. XP-1245 Mechanism of action]



[Figure 3. Protein expression of XBP1s and PSA in AR-activated LNCaP]



[Figure 4. *In vivo* efficacy test – LNCaP xenograft model]



Group	Dose (mg/kg)	Route	TGI(%)	T/C(%)	B.W change(%)
1. Vehicle	0	p.o	-	-	92.74
2. MKC-8866	300	p.o	60.96	69.10	85.84
3. XP-1245	75	p.o	94.00	53.79	93.87

	Vehicle	MKC-8866 300 mg/kg	XP-1245 75 mg/kg
average PSA (pg/mL)	20311	35055	14527

IP

After generation of candidate in 2025, domestic priority and PCT applications are planned as