A first-in-class p300/CBP bromodomain inhibitor for the treatment of prostate cancer and hematologic malignancies

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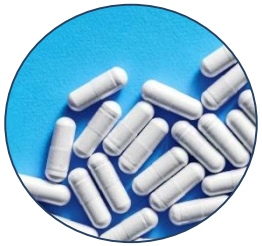
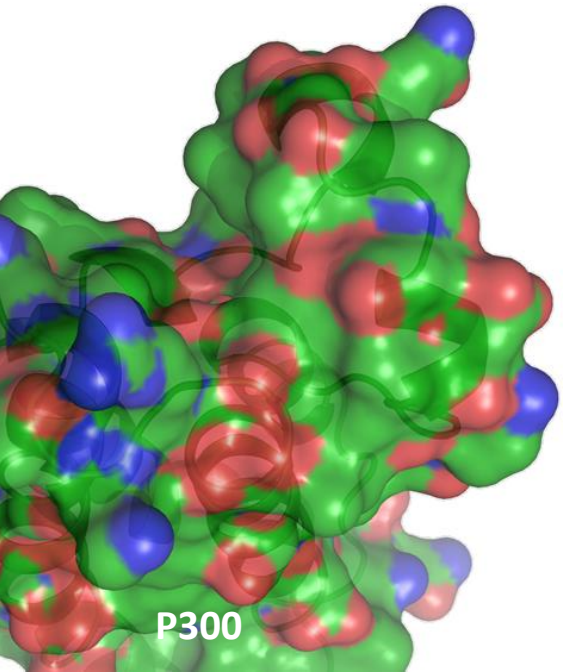
CCS1477 structure removed

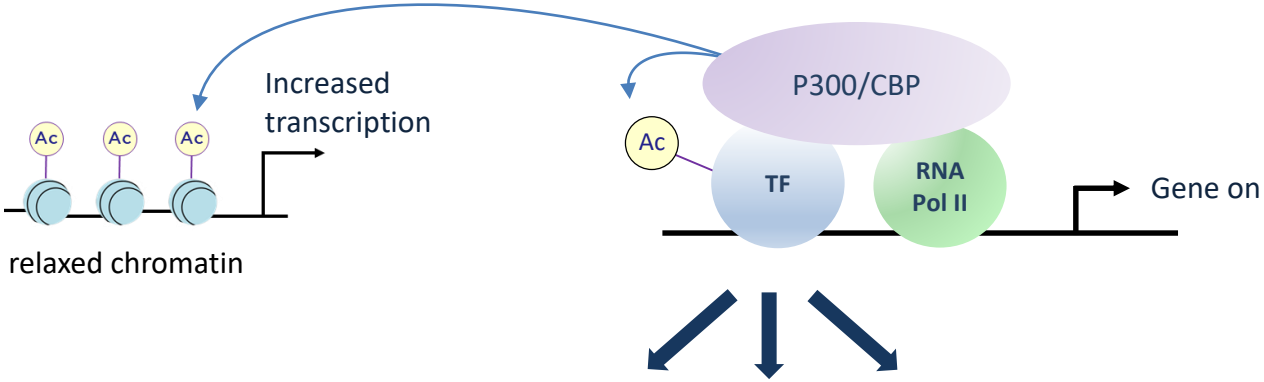


CCS1477: first-in-class p300/CBP inhibitor



- Small molecule inhibitor of twin HAT proteins p300 and CBP, key cancer gene co-regulators
- CCS1477 is a potent, selective and orally bioavailable inhibitor of the common bromodomains of p300/CBP
- Inhibiting p300/CBP address the inherent or acquired resistance to existing prostate cancer drugs
- Haem cancers also exquisitely sensitive to p300/CBP inhibition
- In Phase 1 clinical trials

P300/CBP: Critical co-regulators of transcriptional networks, relevant to prostate and haematological tumours

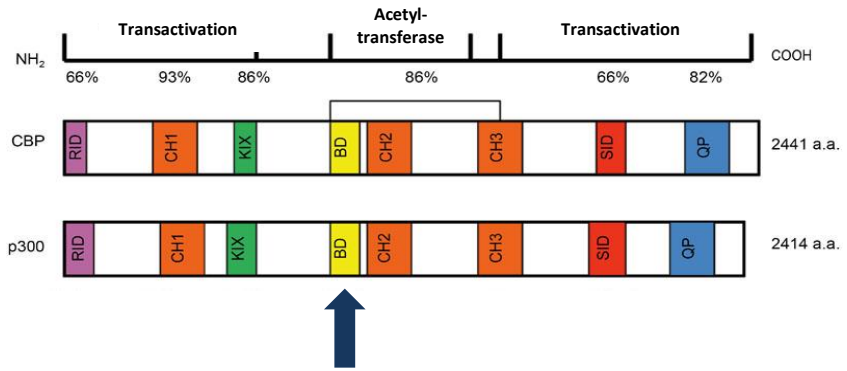


AR	c-Myc	IRF4
Prostate Cancer (CRPC)		
	Multiple Myeloma	
	AML/NHL	

Castrate resistant prostate cancer, and resistance to current 2nd generation anti-hormonal drugs, driven by AR, AR-SV, AR-mutations and c-Myc

Multiple blood cancers exquisitely sensitive to p300/CBP inhibition

CCS1477 is a potent and selective inhibitor of p300/CBP via binding to their conserved bromodomains

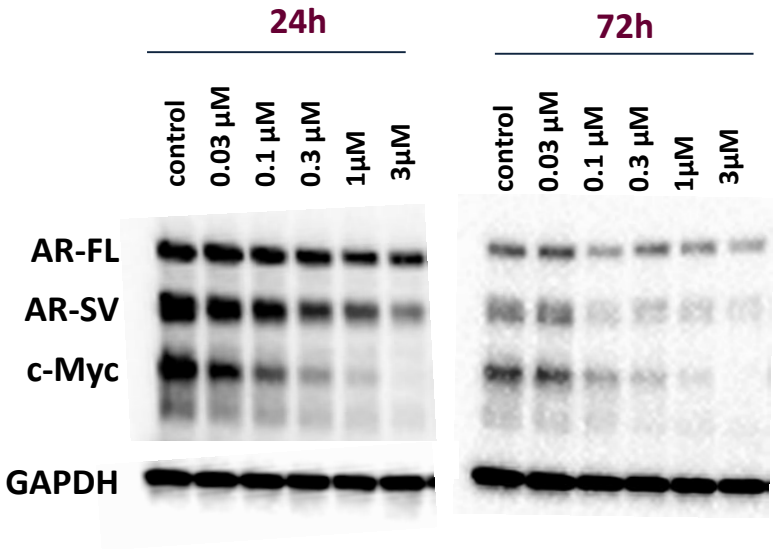


CCS1477

	CCS1477	**(R)enantiomer**
p300/CBP Kd (nM)	1.3 / 1.7	263 / -
BRD4 Kd (nM)	222	921
BRD4 Selectivity / Others	170 / >1,000	3
Kinome scan @10uM; 97 kinases	No significant activity	-
Cerep Safety Screen 44 @10uM	No significant activity	-
22Rv1 cell prol. GI50 (nM)	96	1892

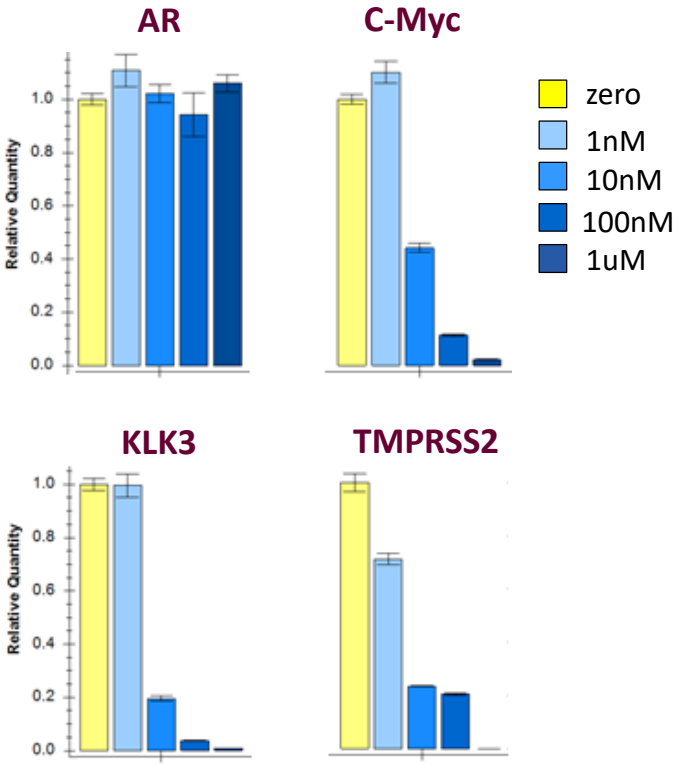
CCS1477 degrades AR-FL, AR-SV and c-Myc proteins, key drivers of CRPC, and reduces expression of AR-target genes in 22Rv1 cells

Protein



Effects on AR protein are mediated by the proteasomal pathway (MG132 reversed)

mRNA

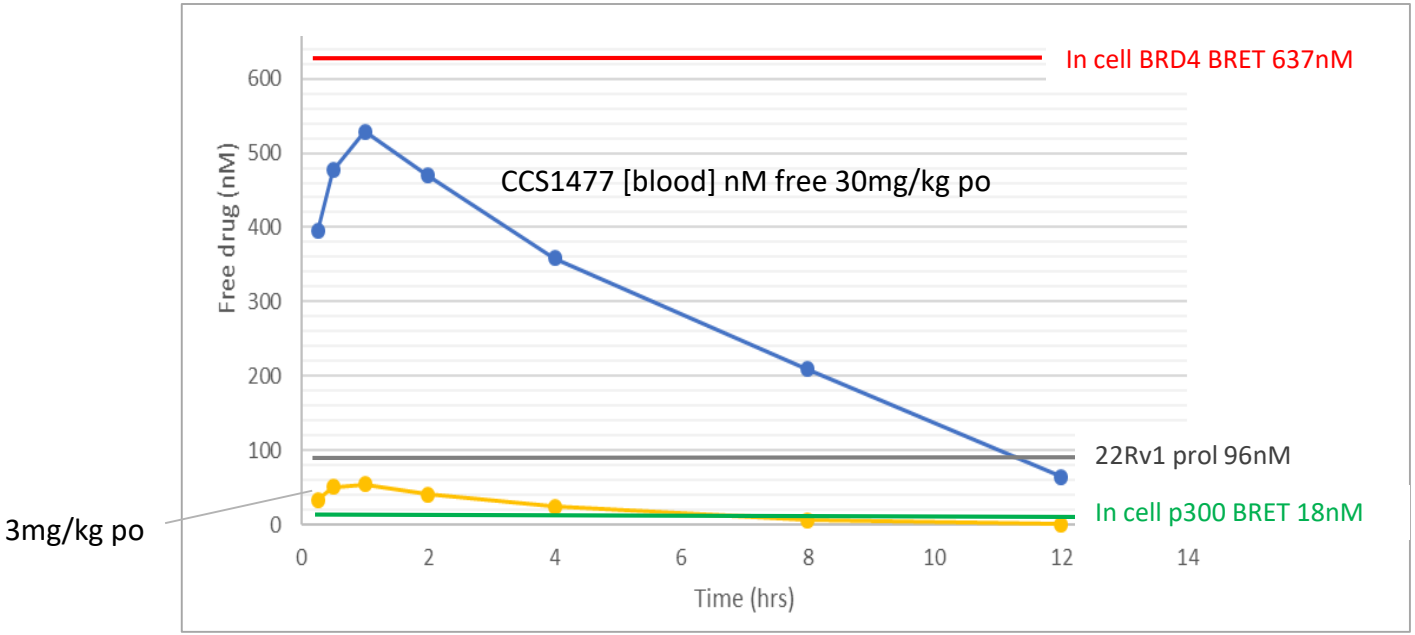


CCS1477 preferentially inhibits AR-driven prostate cancer cells

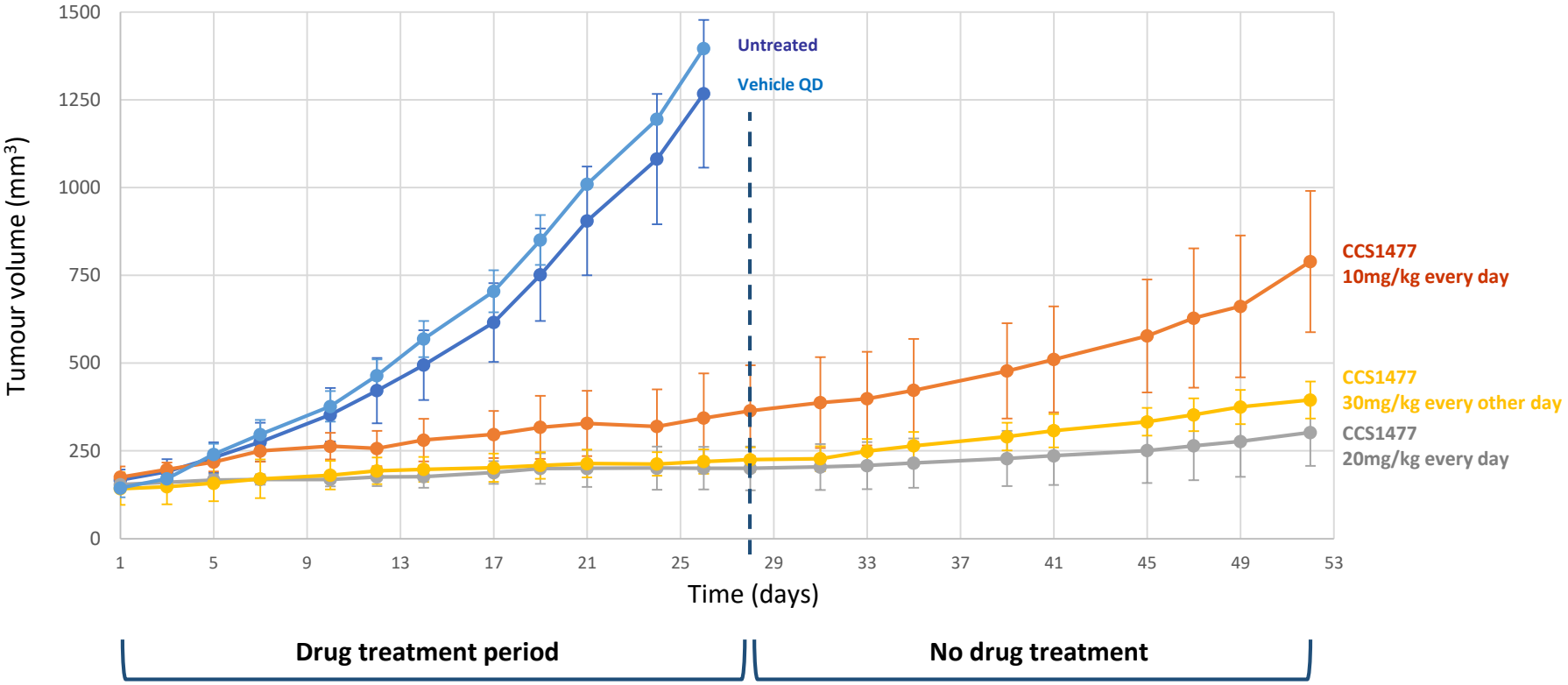
AR status	Cell Line	Model	CCS1477 Proliferation GI50 mM
AR-FL	LNCaP	Hormone responsive	0.230
AR-FL over-expressed	LNCaP-AR	CRPC	0.150
AR-FL, AR-SV	VCaP	CRPC	0.049
AR-FL, AR-SV	22Rv1	CRPC	0.096
AR negative	DU145	Hormone independent	1.280
AR negative	PC3	Hormone independent	1.490

Cell cycle analysis indicates G1 arrest for CCS1477 treated cells

CCS1477 free drug level (mouse) covers proliferation IC50 for 12hrs; and below BRD4 in-cell binding

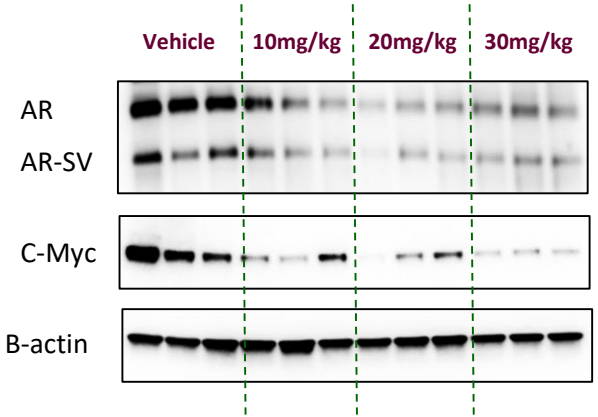


CCS1477 blocks tumour growth in 22Rv1 mouse model of CRPC: including continued tumour growth block following drug withdrawal

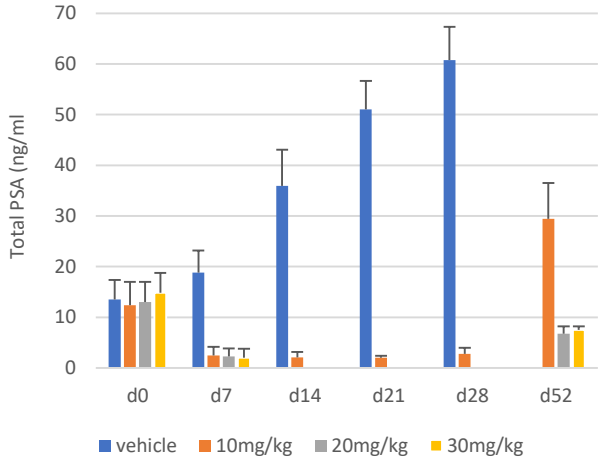


CCS1477 reduces biomarker expression in 22Rv1 xenograft

Reduction in biomarkers *in vivo* (day 7)

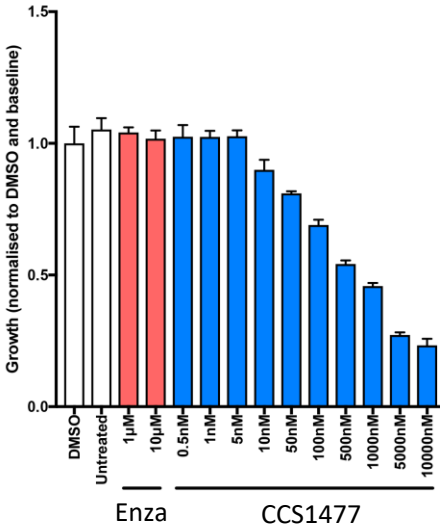


Inhibition of plasma PSA



CCS1477 active in enzalutamide-resistant prostate models

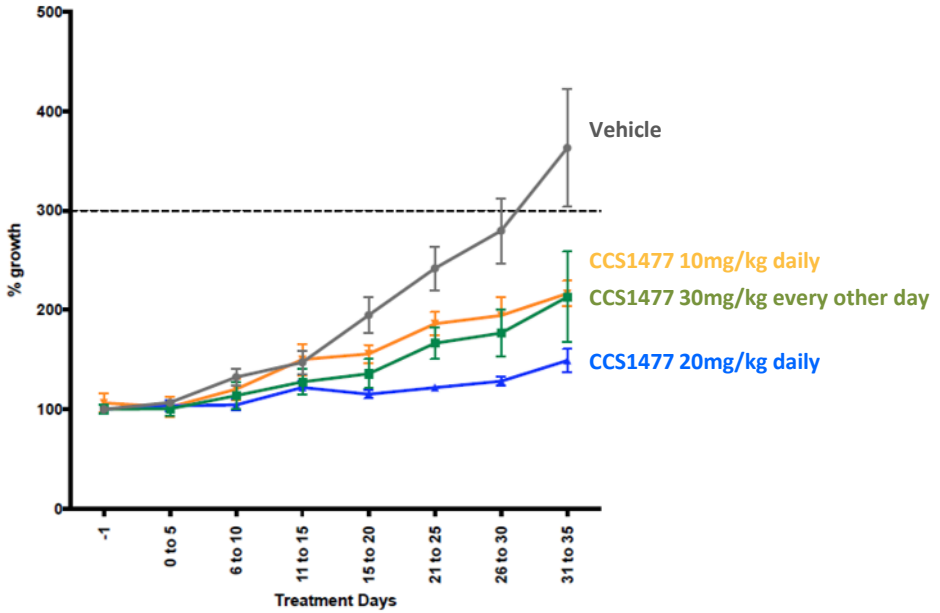
LNCaP95 cells with acquired resistance to enzalutamide



CCS1477 inhibits proliferation in enzalutamide-resistant cancer cells

Data from Jon Welti/Johann De Bono – ICR

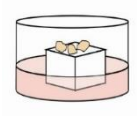
Patient derived xenograft (PDx) model with enzalutamide resistance



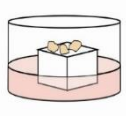
Data from Jon Welti/Johann De Bono – ICR

CCS1477 active in patient explants and in combination with enzalutamide in resistant xenograft model

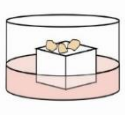
Prostate explants following radical prostatectomy



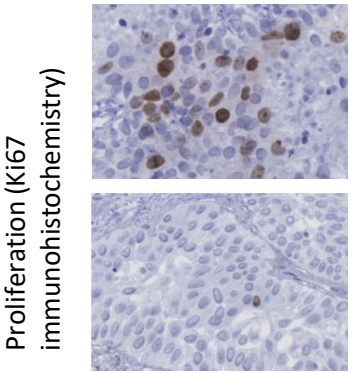
Vehicle

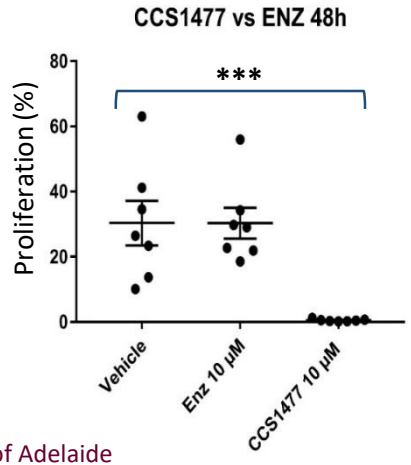


ENZ (10uM)



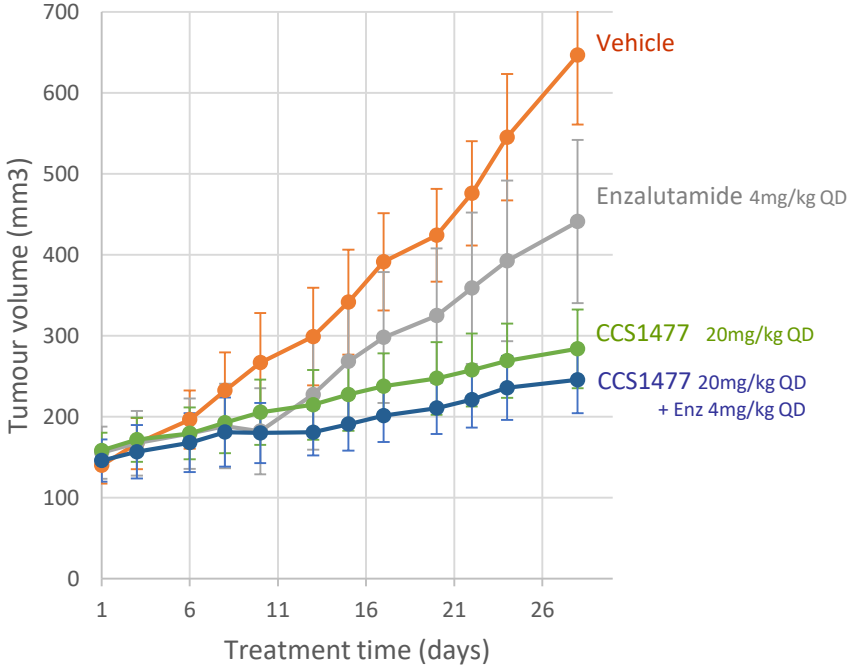
CCS1477 (10uM)





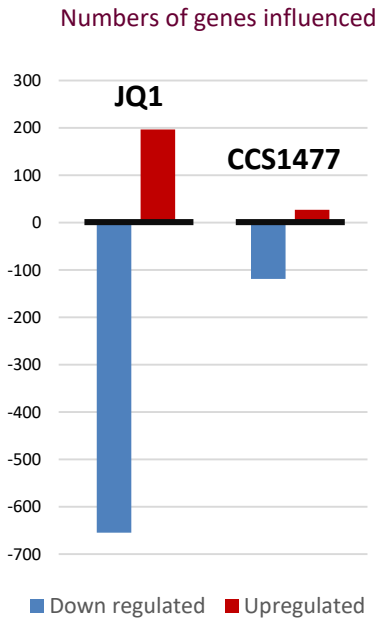
Data from Lisa Butler – University of Adelaide

Bicalutamide resistant LNCaP xenograft model

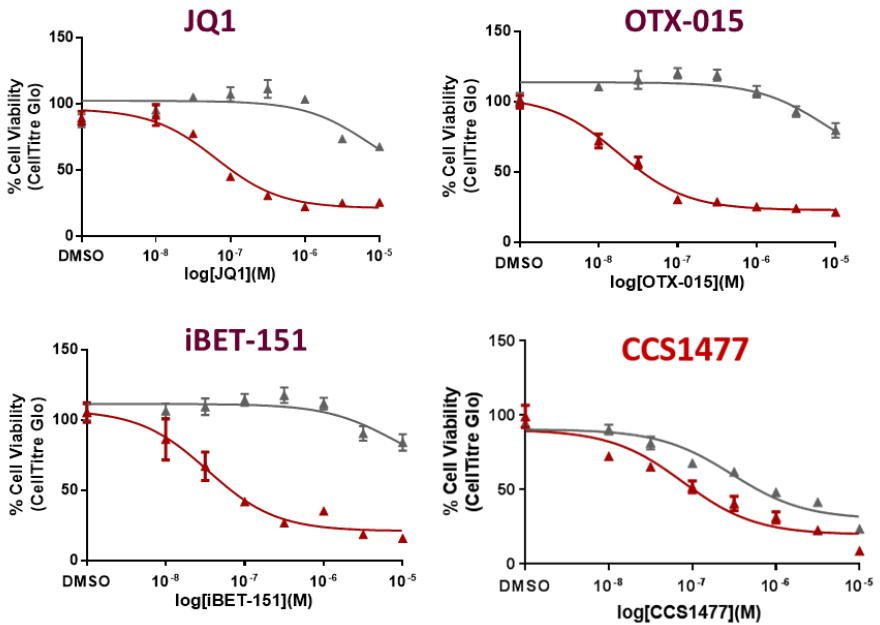


Differentiation from BET inhibitors

CCS1477 affects less/different genes than JQ1 in 22Rv1 cells

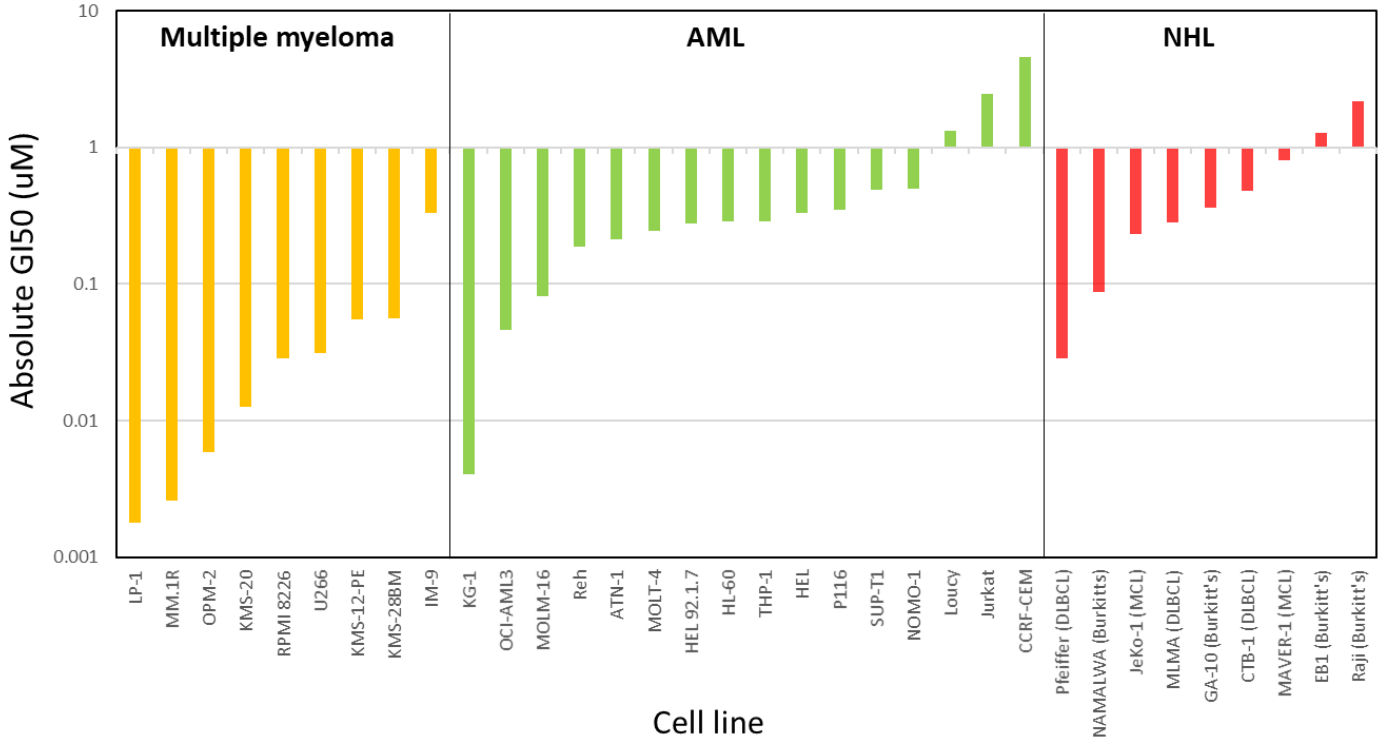


CCS1477 retains activity in a JQ1/BETi resistant 22Rv1 cell-line

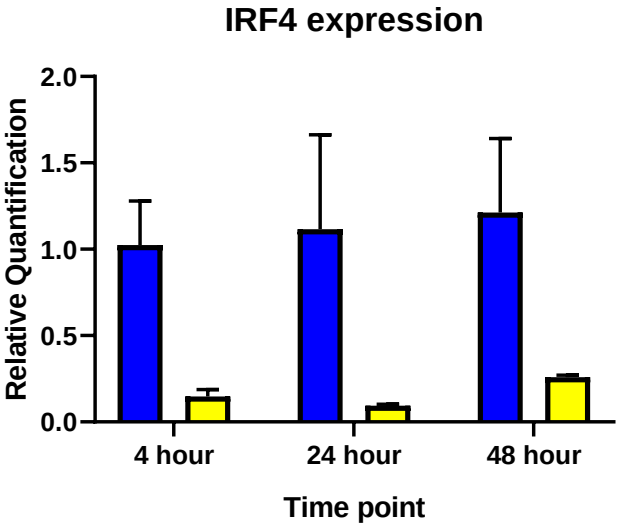


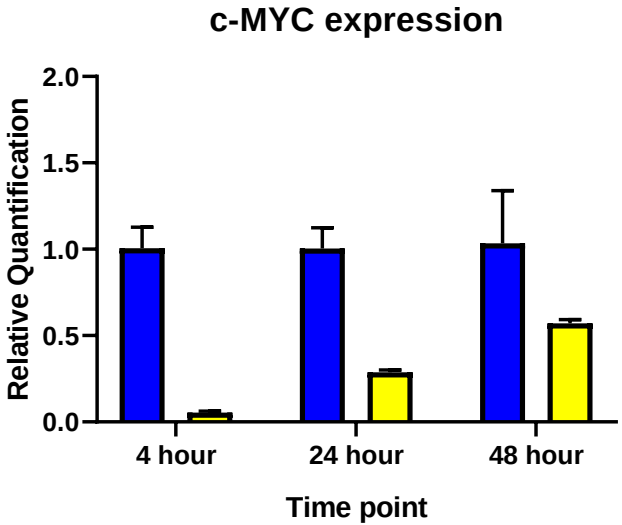
N.B. CCS1477 differentiated from BET inhibitors – Poster 3826 Tues 2nd, Apr 1-5pm

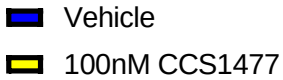
CCS1477 sensitivity: Cell panel screen in multiple myeloma, AML and NHL cell lines



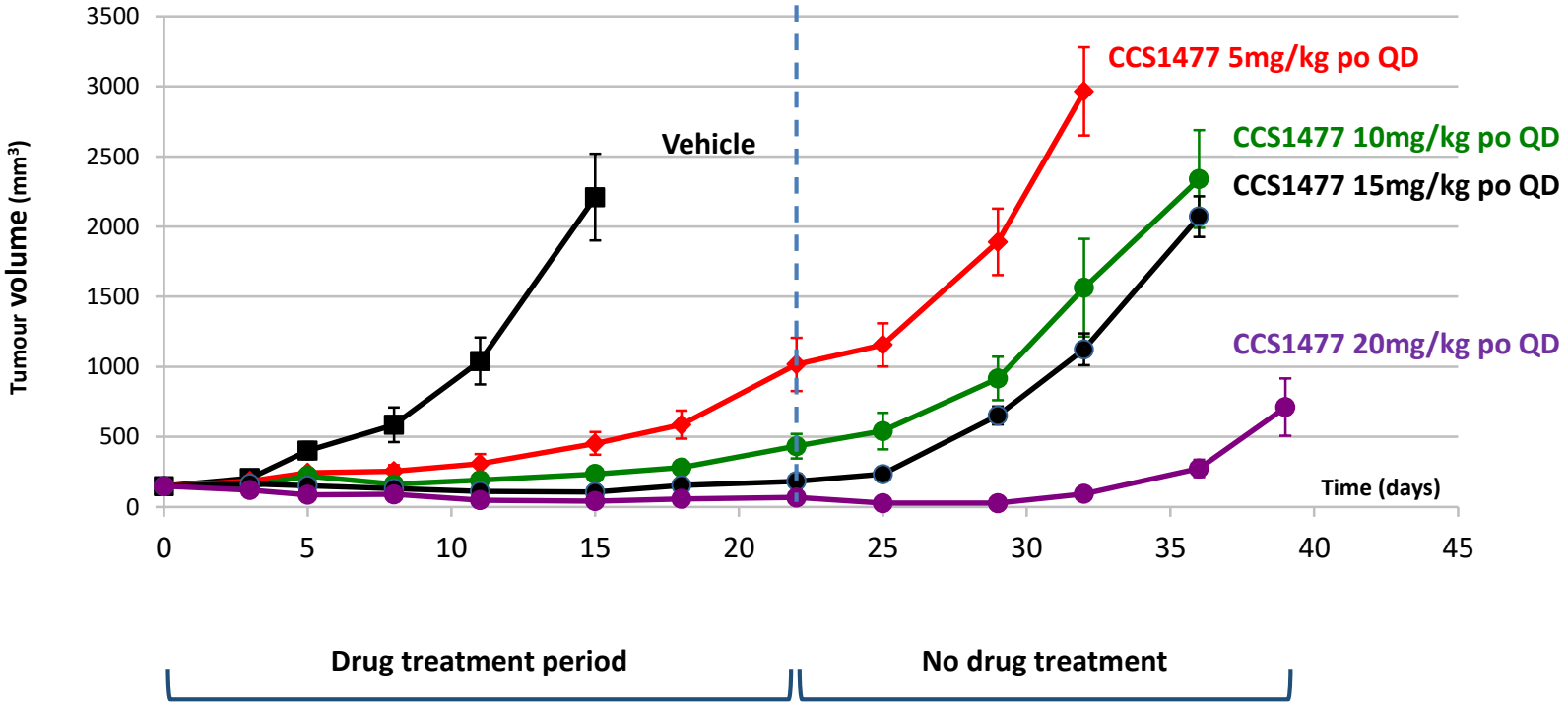
CCS1477 reduces IRF4 and c-Myc in OPM2 multiple myeloma cells



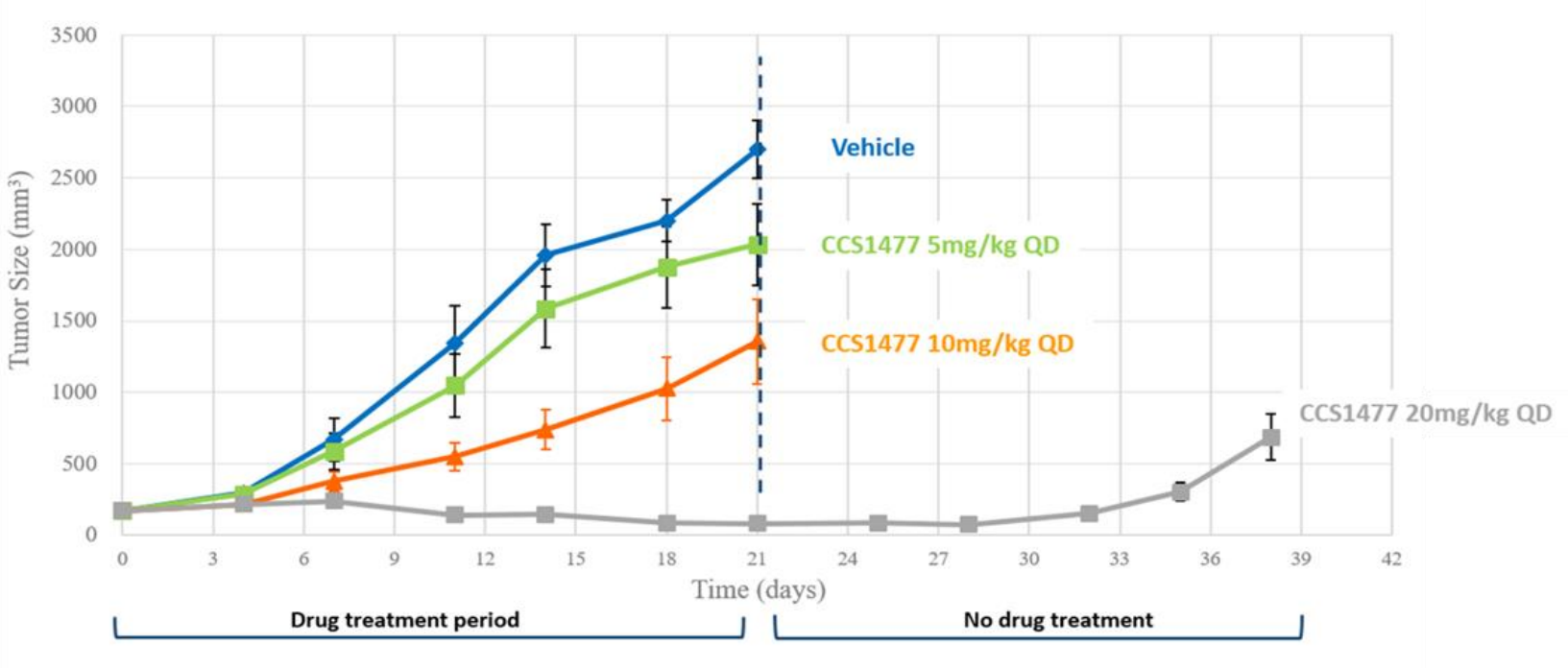




CCS1477 causes tumour regression in OPM2 xenograft model of multiple myeloma, and continued tumour growth inhibition following drug withdrawal

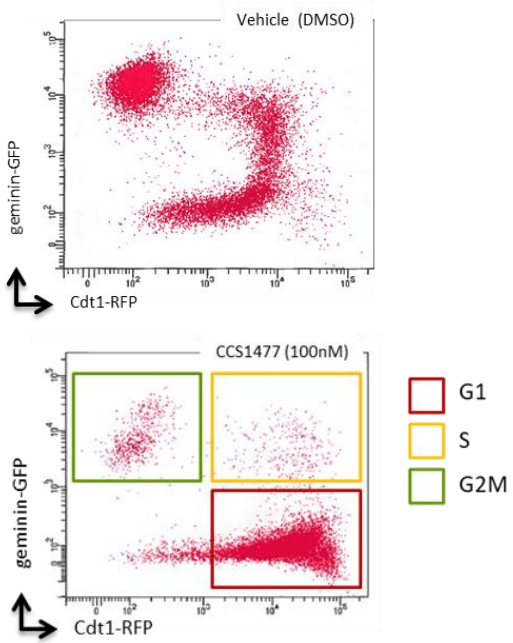


CCS1477 causes tumour regression in AML MOLM16 xenograft: extended tumour growth inhibition



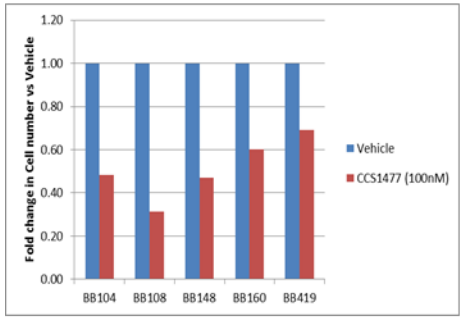
CCS1477 inhibits the proliferation of AML cells via G1 cell cycle arrest and promotes myeloid differentiation in patient derived primary AML cells

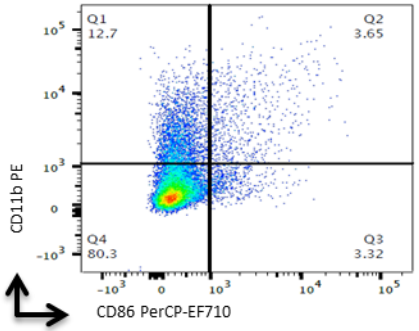
CCS1477 inhibits proliferation of THP-1 cells mediated via G1 cell cycle arrest

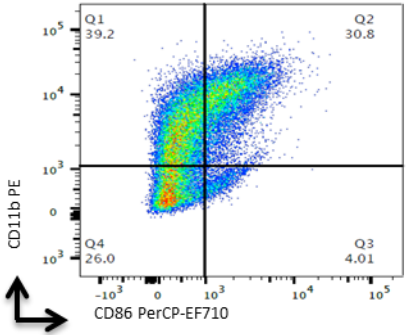


Data from Tim Somervaille (CRUK, Manchester Institute)

CCS1477 (100nM) in patient derived AML cells







CCS1477 preclinical PK

CCS1477 PK properties

0.5mg/kg iv	mouse	rat	dog 1mg/kg iv
T1/2 (hr)	0.96	1.6	1.2
Clobs (ml/min/kg)	14	13.2	35
Vss (l/kg)	1.1	1.6	2.6

3mg/kg po	mouse	rat	dog
T1/2 (hr)	1.6	2.5	2.2
Clobs/F (ml/min/kg)	20	17.4	84
Vz/F (l/kg)	2.9	3.8	18
F (AUCall) %	73	75	45

	mouse	rat	dog	human
Free fraction (%)	3.0-3.2	4.0-5.8	8.4-9.8	1.7-2.7

Predicted human PK/dose

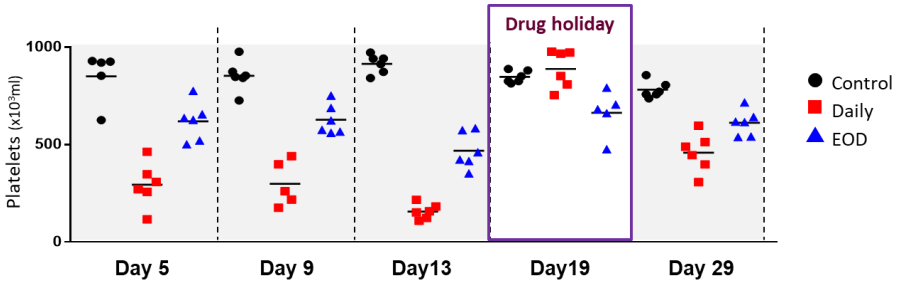
- Cl 0.99ml/min/Kg
- Vss 0.94L/Kg
- $T_{1/2}$ 11hrs
- Dose 85-175mg daily

CCS1477 Preclinical Safety

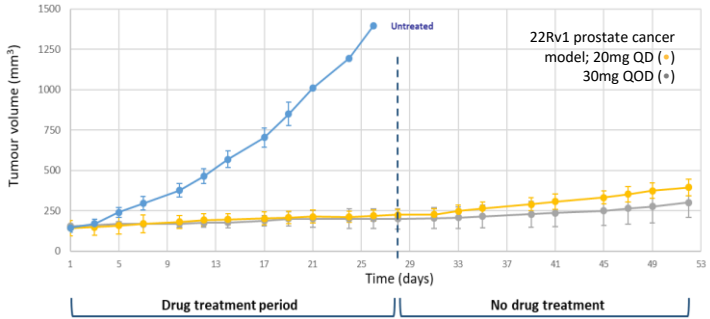
Findings consistent with primary mode of action

- 28d toxicity studies in rodent (rat) and non-rodent (dog)
- Rat 28 day study – dose proportional weight reduction in male androgen-dependent organs
- No cardiac effects in an *in vivo* dog telemetry study

- Dose-proportional reduction in platelets
  - Fully reversible
  - Impact reduced by less frequent dosing
  - No greater effect on re-dosing



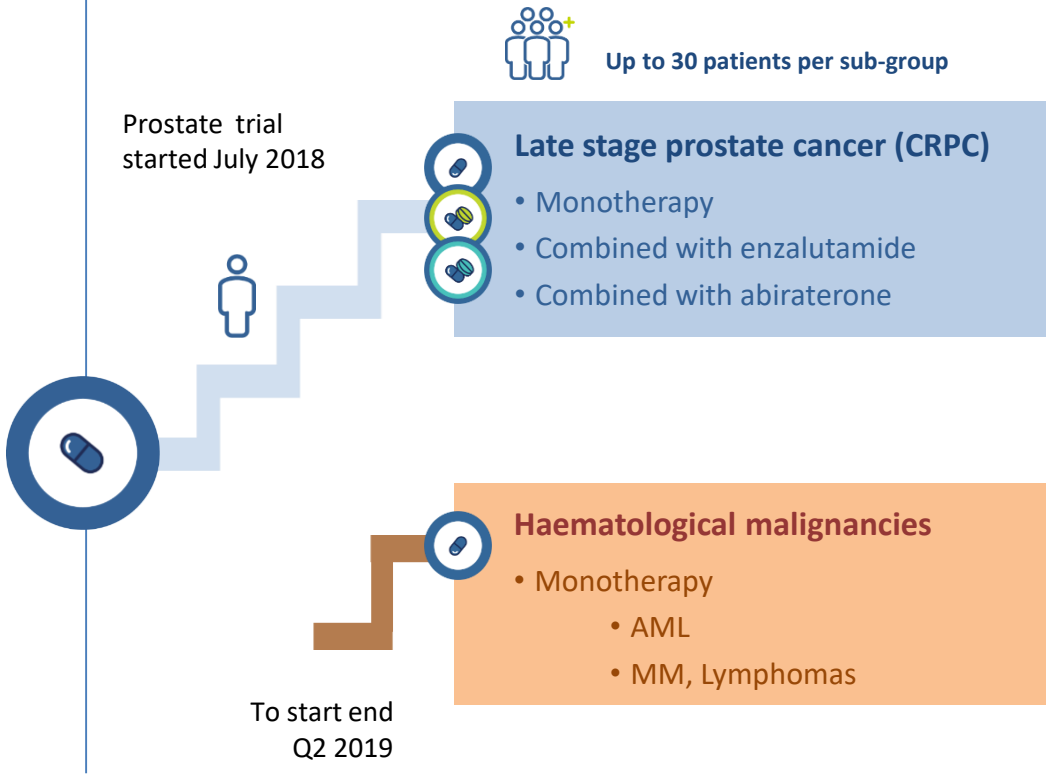
CCS1477's unusual off-drug duration of effect allows intermittent dosing to be explored if required, without potential loss of efficacy

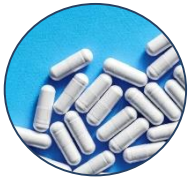


CCS1477 drug supply: into the clinic

- API - 4 stage GMP process
- No chromatography
- Multi-Kg scale

- Drug Product - Simple capsule of API in semi-solid lipid excipient
- Available in 100mg, 50mg, 25mg capsules
- Suitable for 1 or 2 capsules per dose





Summary

- CCS1477: potent, selective and orally bioavailable inhibitor of p300/CBP bromodomains
- Causes significant tumour growth inhibition in models of prostate cancer and haematological malignancies
- Accompanying changes in biomarkers are consistent with the mechanism of action
- Extended duration of tumour growth inhibition in the absence of drug
- Bromodomain inhibition of p300/CBP represents a differentiated approach
- Can be used as a monotherapy or in combination with SOC agents
- CCS1477 in Phase 1 for CRPC. Phase 1 for AML/MM/NHL shortly to follow.

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