SM08502, a novel, small-molecule CDC-like kinase (CLK) inhibitor, demonstrates strong antitumor effects and Wnt pathway inhibition in castration-resistant prostate cancer (CRPC) models

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Disclosure information

- Conference: 2020 American Association for Cancer Research
- Speaker: Carine Bossard, PhD
- I have the following financial relationships to disclose:
  - Employee of Samumed, LLC
- I will not discuss off-label use and/or investigational use in my presentation

Disclaimers

- This presentation is not intended to provide a comprehensive overview of all studies using SM08502
- SM08502 is an investigational compound currently in clinical trials; SM08502 has not been approved by the U.S. Food and Drug Administration (FDA) or any other pharmaceutical regulatory authority, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidate
- While the complete mechanism of action (MOA) of SM08502 is unknown, further investigation is being conducted. All of the MOA information is based on nonclinical data and the relationship to clinical benefit is unknown
- This presentation is intended as a scientific exchange of medical information, is provided for educational purposes only, and is not intended for any promotional purpose or to offer medical advice

Development of therapies that overcome ARSi resistance in CRPC is an unmet medical need

ARSi resistance*

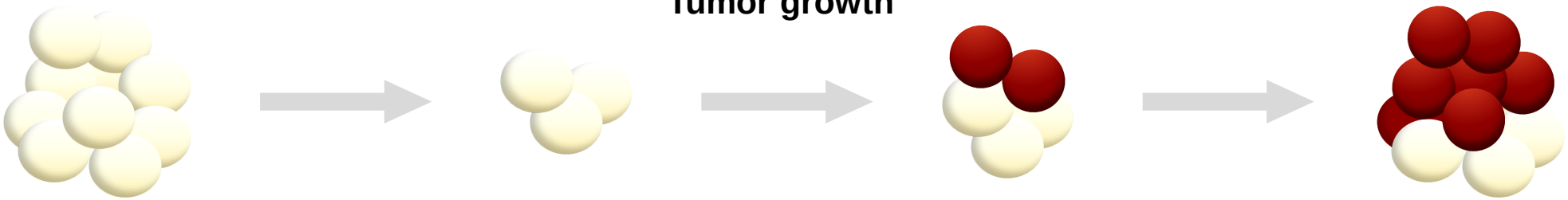
AR-dependent mechanism
- AR amplification
- AR splice variants (ARV7)

AR-independent mechanism
- Wnt activation
- PTEN, p53, Rb loss/mutation

Cancer cell
Resistant cell

Treatment with ARSi

Tumor growth



CRPC

Response

75%–85% patients

Development of resistance

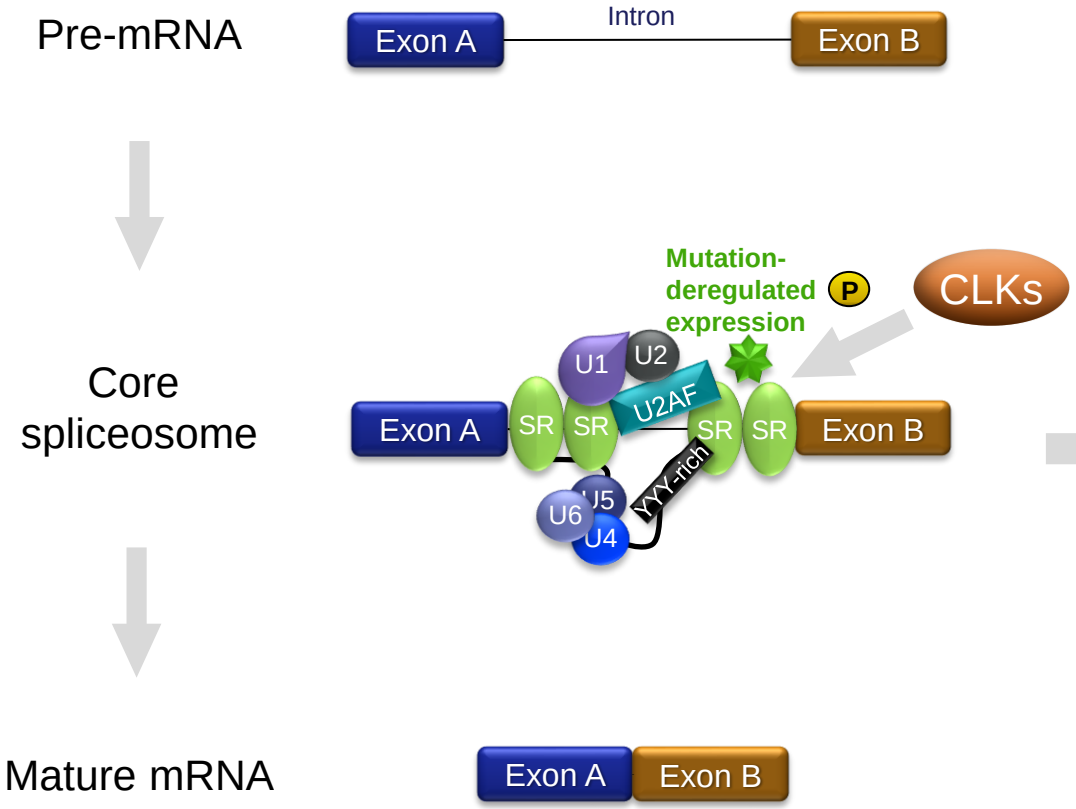
9–15 months

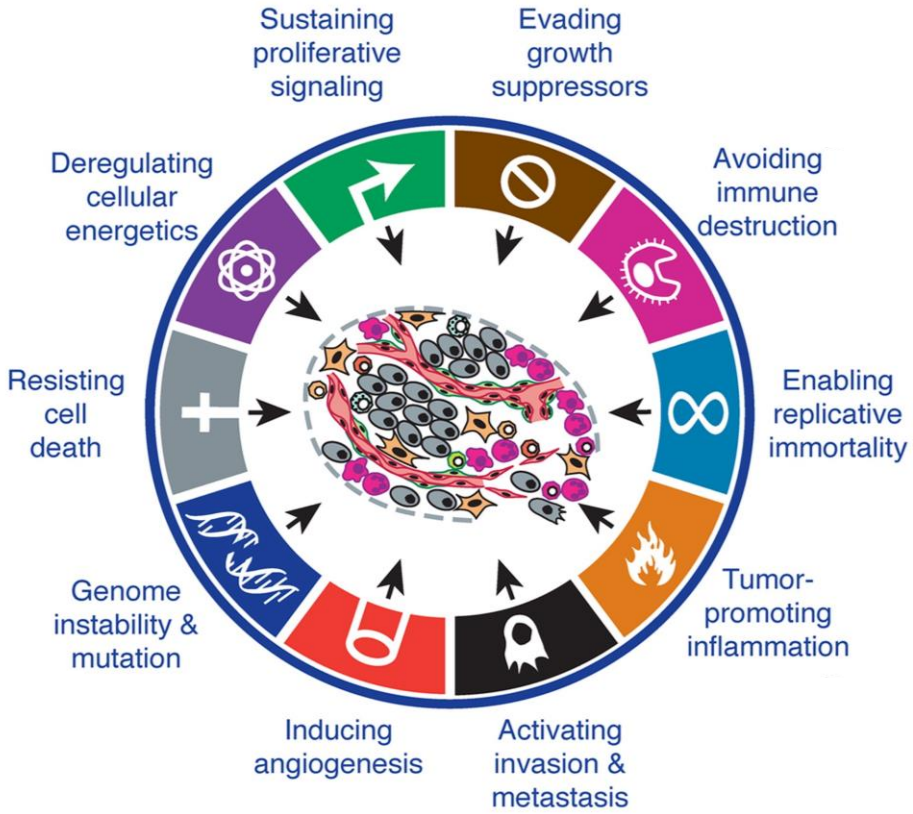
Relapse

Silberstein JL, et al. *Curr Urol Rep*. 2016.
Yeh Y, et al. *Adv Exp Med Biol*. 2019.
Isaacsson Velho P, et al. *Eur Urol*. 2020.

ARSi: Androgen receptor signaling inhibitor
*non-exhaustive list

Abnormal RNA splicing in cancer





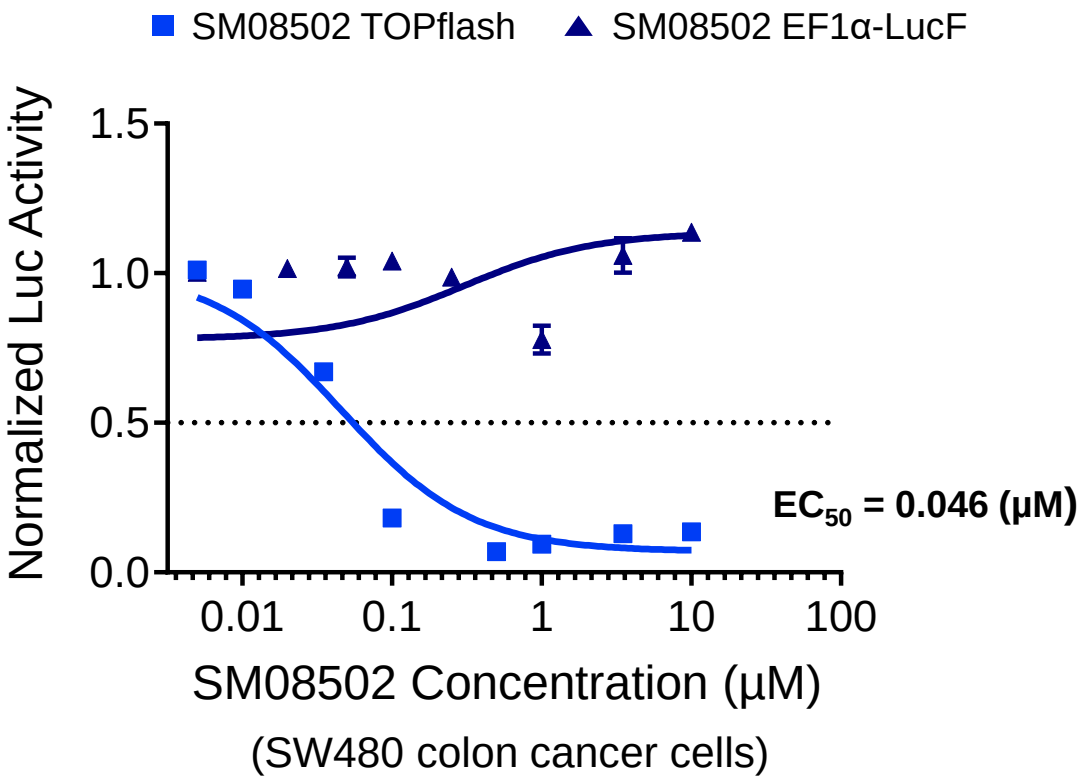
Tumor progression

Hanahan & Weinberg. *Cell*. 2011.
Bonnal S, et al. *Nat Rev Clin Onc*. 2020.
Paschalis A, et al. *Nat Rev Clin Onc.* 2018.

Illustration (left) adapted from Biamonti, et al. 2019.
SR: SRSF (serine/arginine-rich splicing factor)
CLK: CDC-like kinase

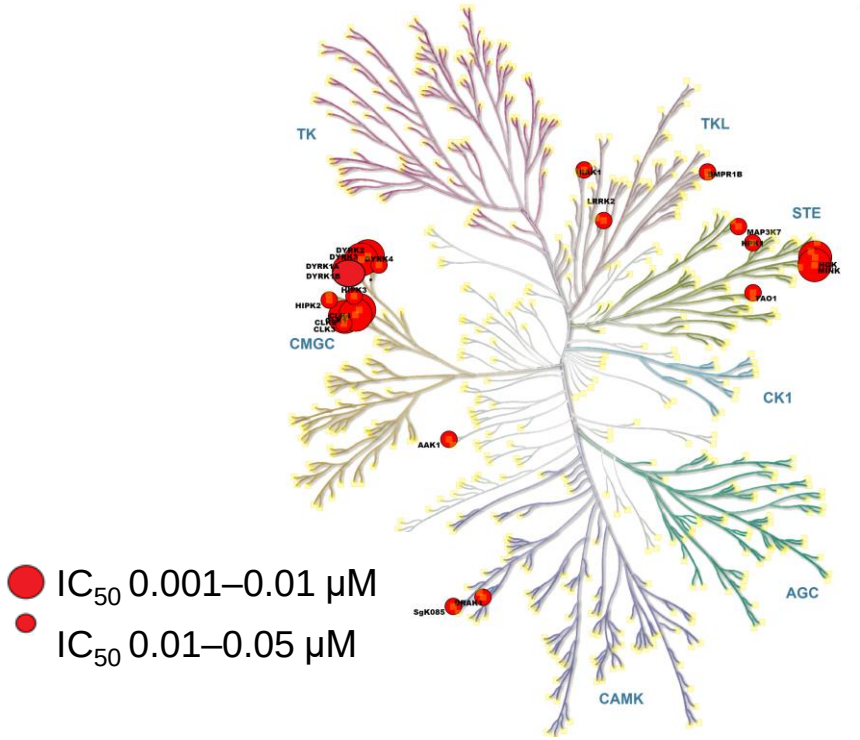
SM08502 is a potent CLK inhibitor that inhibits Wnt signaling *in vitro*

TOPflash Wnt Reporter Assay



(SW480 colon cancer cells)

Kinase Dendrogram for SM08502

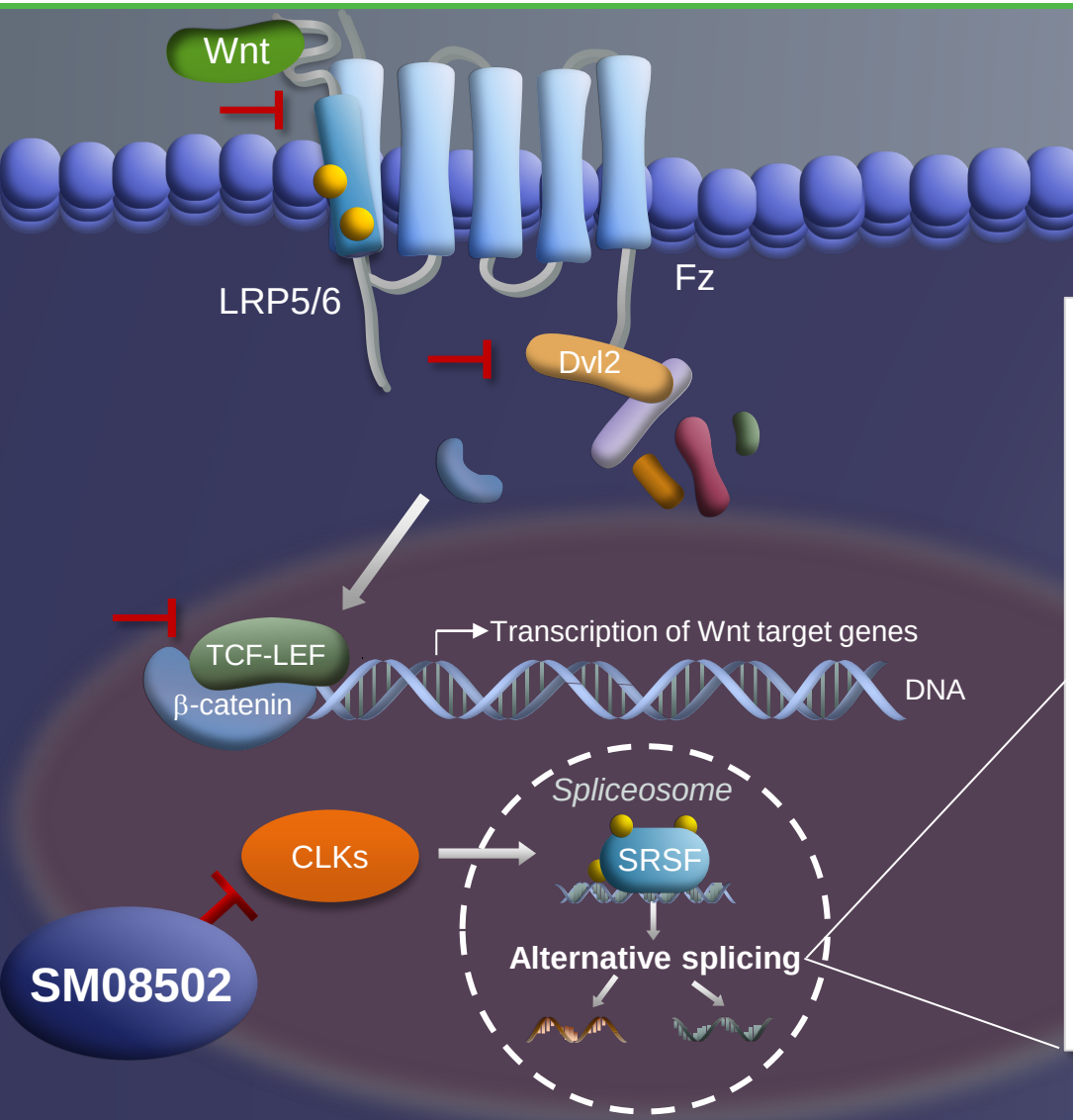


	CLK2	CLK3	CLK1	CLK4	CDK1
IC_{50} (μM)	0.002	0.022	0.008	0.001	1.1

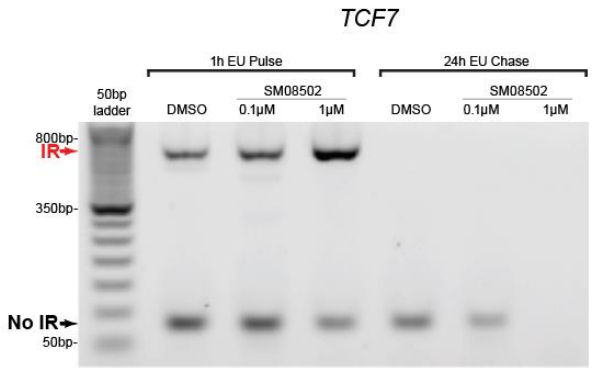
CLK: CDC-like kinase, CDK: Cyclin-dependent kinase

Tam BY, et al. *Cancer Lett*. 2019.

MOA of SM08502 for Wnt pathway inhibition

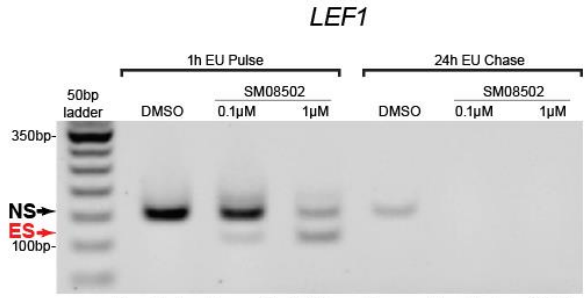


Intron retention in *TCF7*



Predicted length: 76bp without intron retention (No IR)
567bp with intron retention (IR)

Exon skipping in *LEF1*



Predicted length: 152bp - Normal splicing (NS)
111bp - Skipped exon (ES)

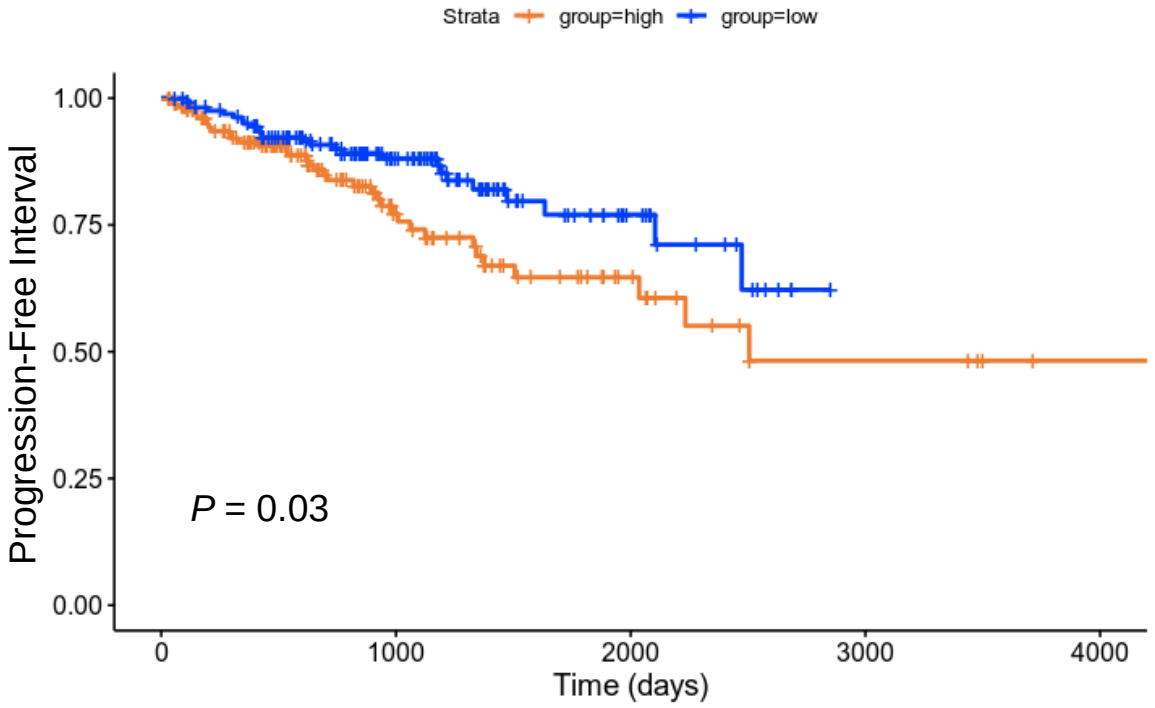
SW480 colon cancer cells
Pulse-chase RNA labeling, 6-hr SM08502 treatment; EU: 5-ethynyluridine

Tumorigenesis, stemness, and proliferation

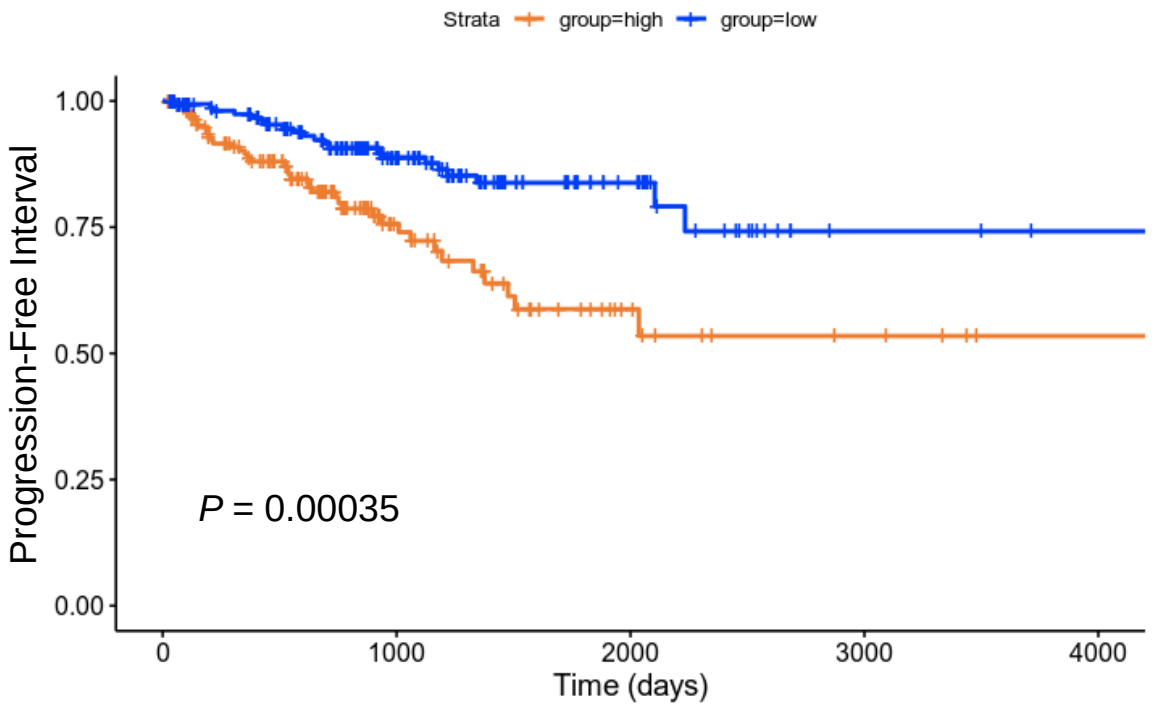
Figure adapted from Saygin C, et al. *Cell Stem Cell*. 2019.
Tam BY, et al. *Cancer Lett*. 2019.

Elevated expression of CLK1/2 was associated with poorer survival in prostate cancer

Progression-free interval of TCGA-PRAD patients expressing high and low *CLK1*



Progression-free interval of TCGA-PRAD patients expressing high and low *CLK2*



Cho, et al. AACR 2020; Session PO.EP01.05 - Prostate and Other Genitourinary Cancers
3521 / 18 - Transcriptome analysis of TCGA prostate cancer samples identifies an association of poorer survival and aggressive disease biology with CDC-like kinase (CLK) expression and spliceosome regulation

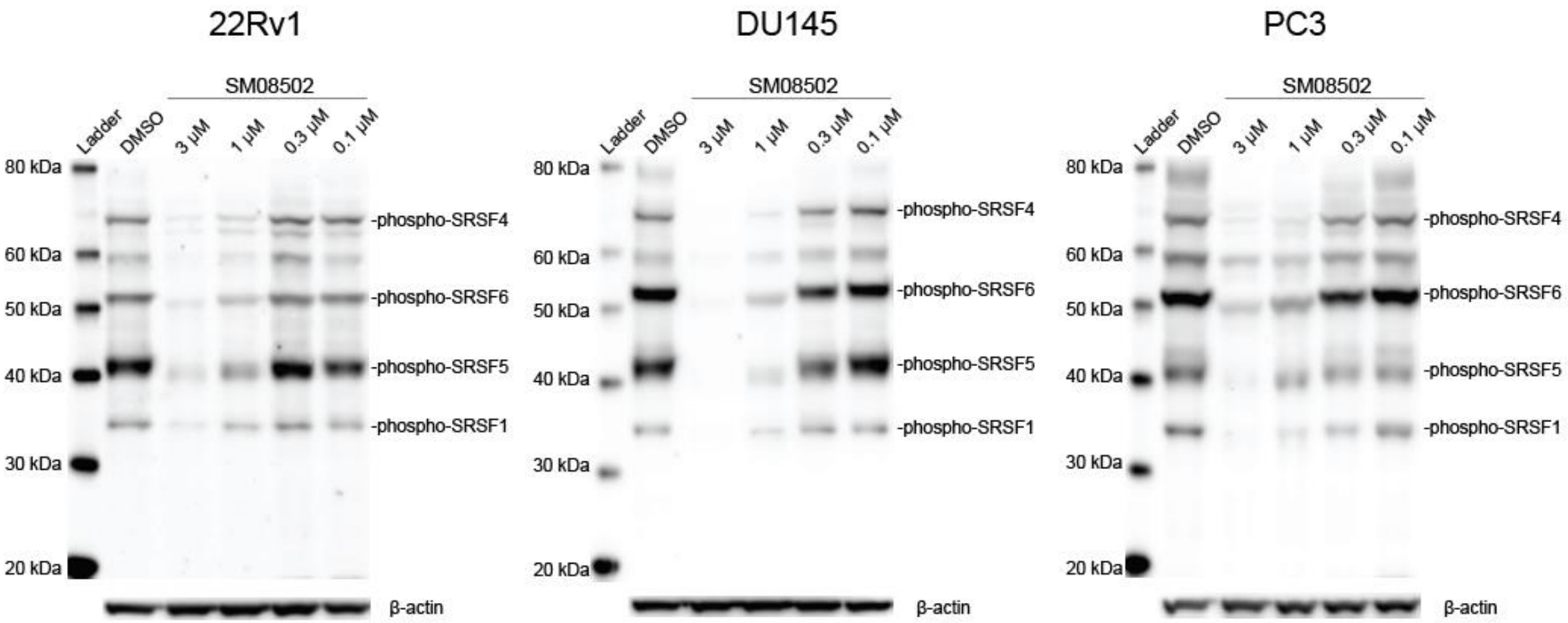
n=165 per high and low group

SM08502 inhibited viability of prostate cancer cell lines regardless of subtype

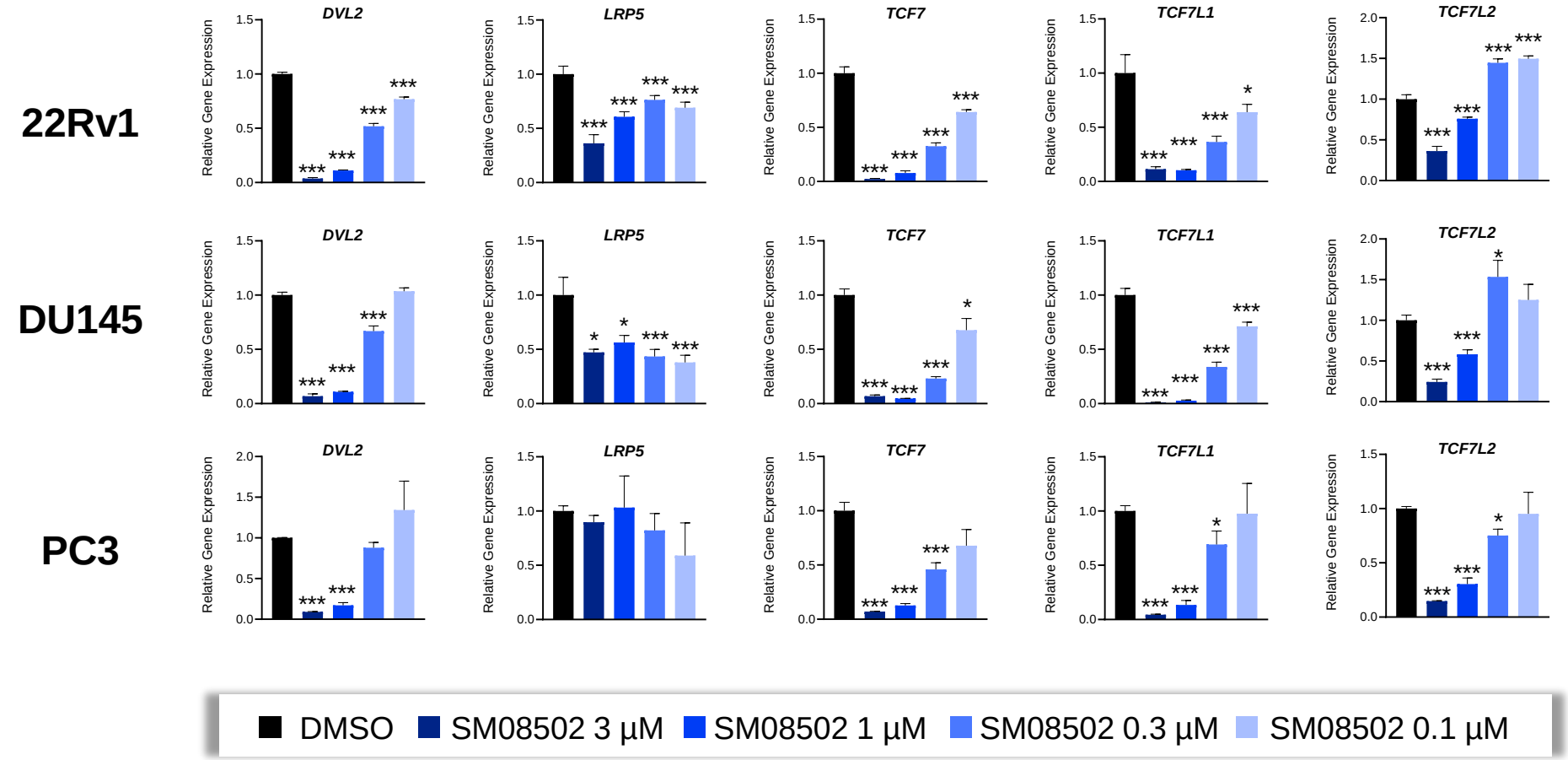
Subtype	Cell lines	Mutations	EC_{50} (μM)
CRPC	PC3	*AR-, TP53-/-, PTEN-/-*	0.237
CRPC	DU145	*AR-, PTEN+/-, TP53*	0.377
CRPC	22Rv1	*ARV7*	0.191
Hormone-sensitive	LNCAP	*PTEN -/-*	0.329
Hormone-sensitive (partial)	VCaP	*TP53*	0.462

CRPC: Castration-resistant prostate cancer, AR: Androgen receptor, ARV7: Splice variant 7

SM08502 inhibited SRSF phosphorylation in CRPC cell lines

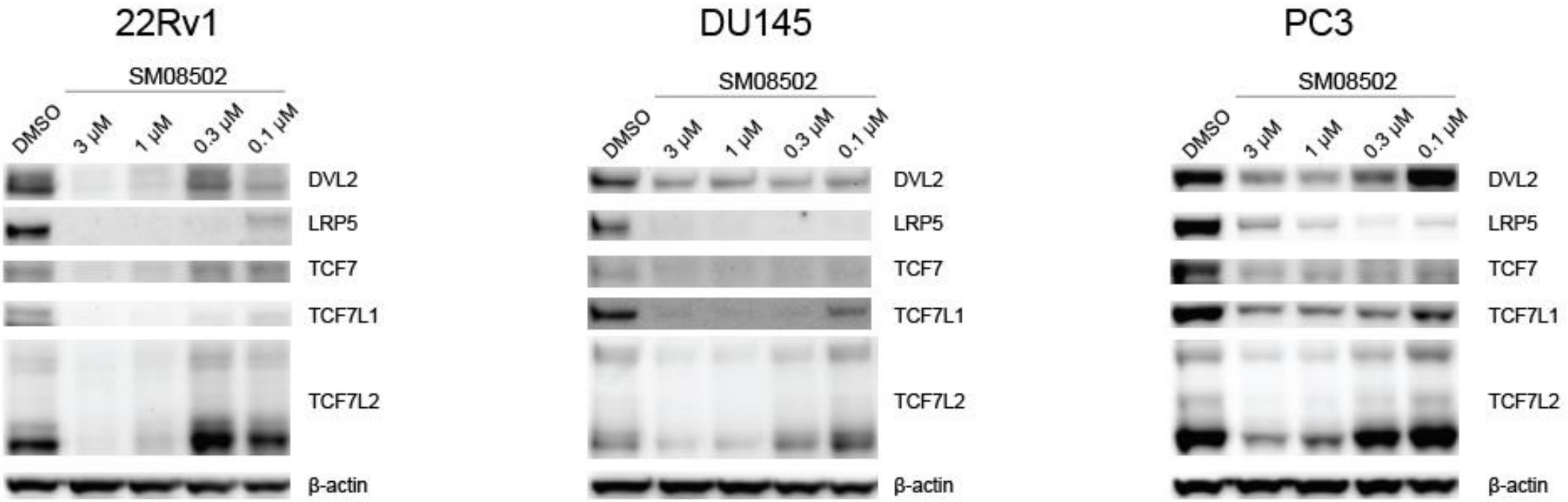


SM08502 inhibited Wnt pathway-related gene expression in CRPC cell lines

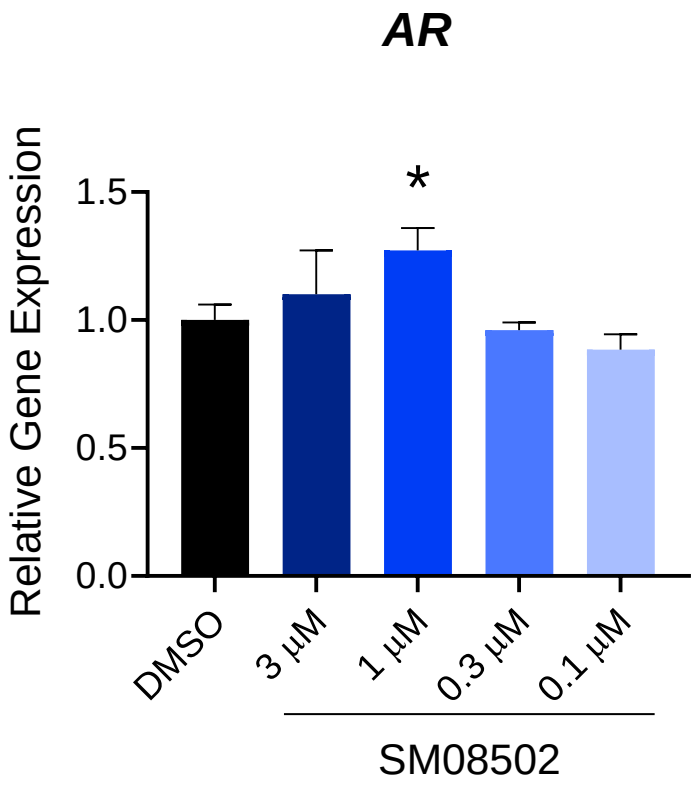


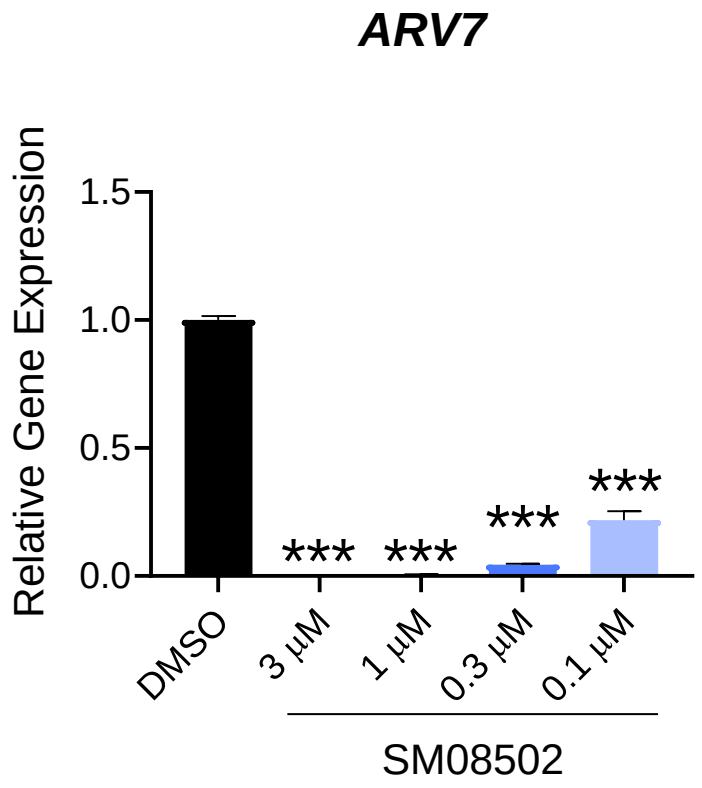
Gene expression: n=3; Mean ± SD; *P<0.05, ***P<0.001 vs. vehicle

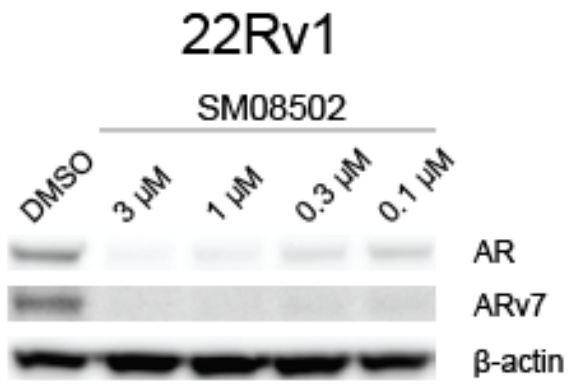
SM08502 inhibited Wnt pathway-related protein expression in CRPC cell lines



SM08502 decreased *AR* and *ARV7* expression in the 22Rv1 prostate cancer cell line

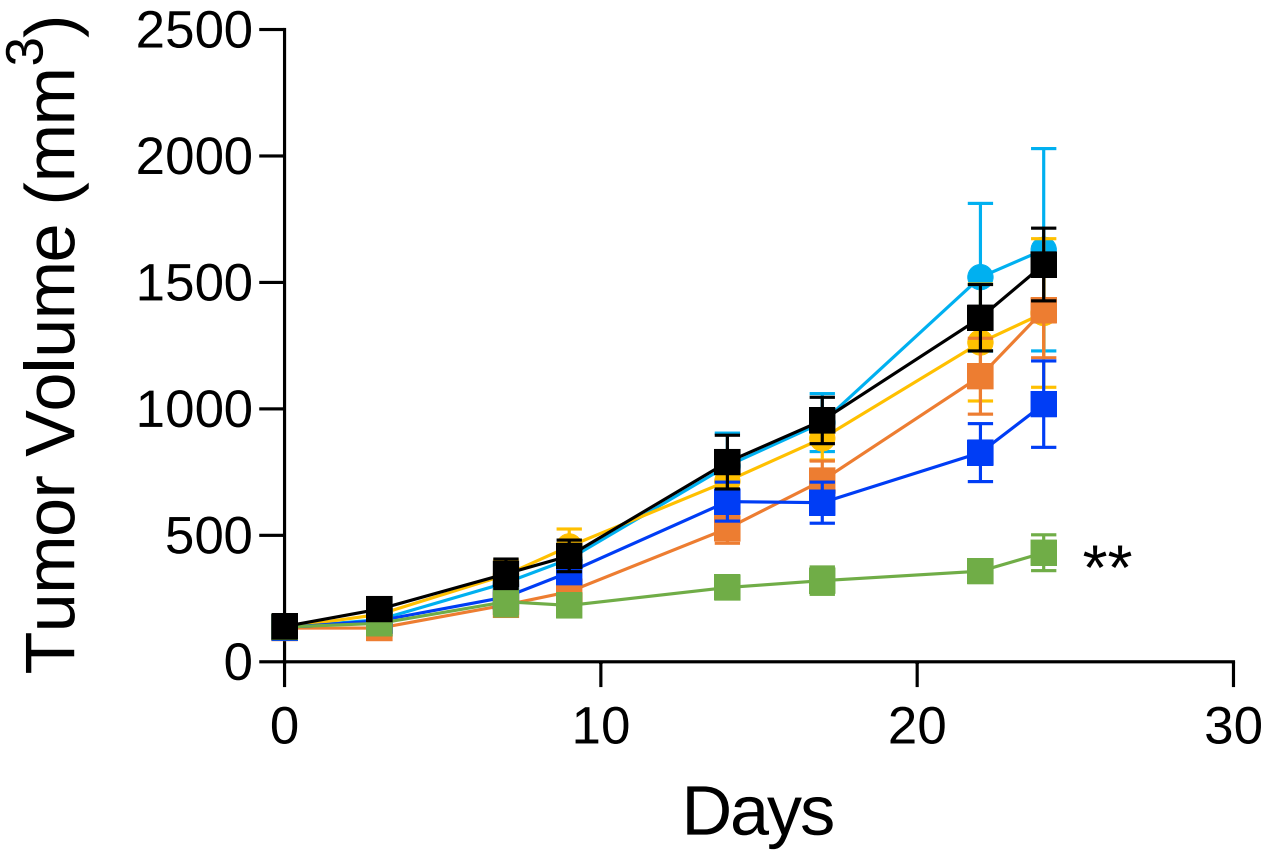






Gene expression: n=3; Mean ± SD; *P<0.05, ***P<0.001 vs. vehicle

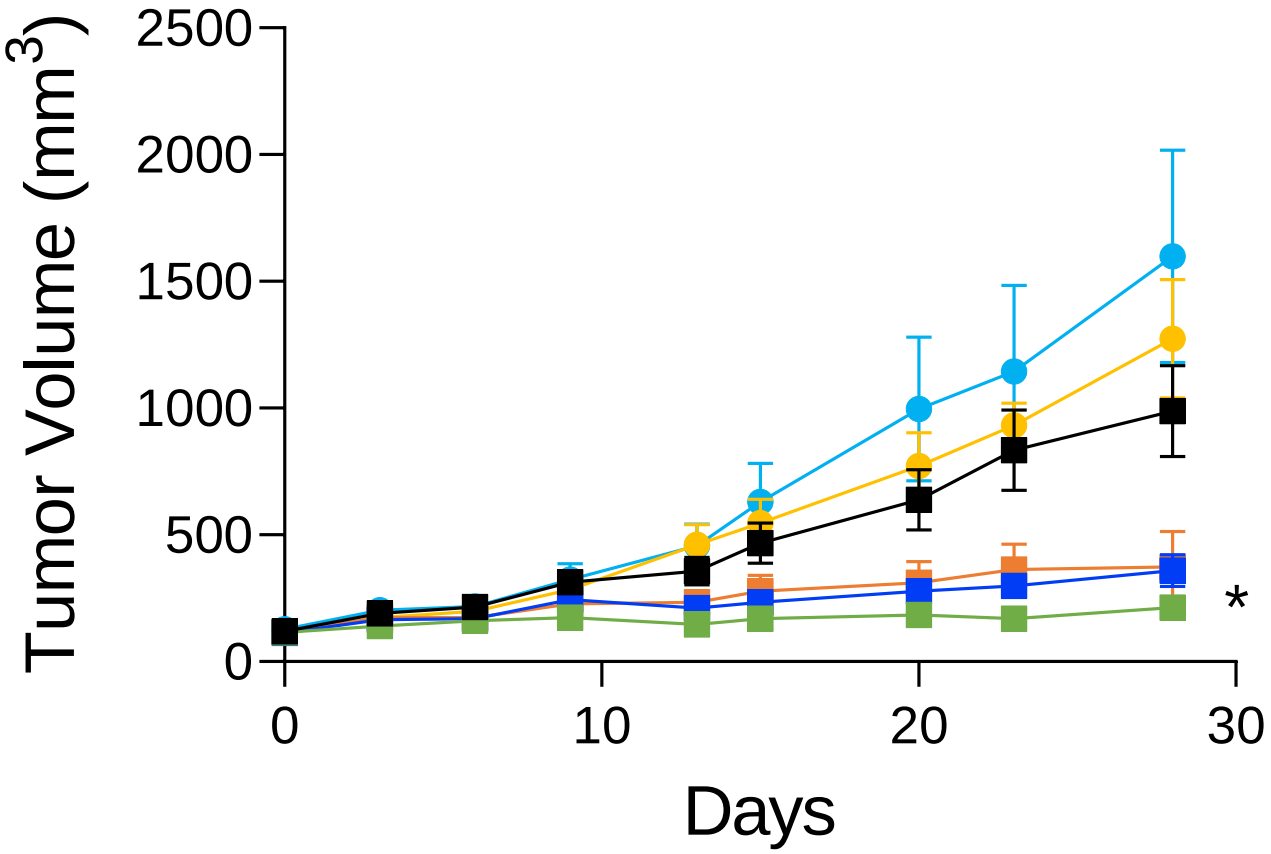
SM08502 demonstrated strong antitumor activity in a SOC-resistant 22Rv1 xenograft model



	TGI
Vehicle	
Abiraterone 75 mg/kg	none
Enzalutamide 30 mg/kg	12%
SM08502 6.25 mg/kg	12%
SM08502 12.5 mg/kg	35%
SM08502 25 mg/kg	73%

22Rv1 tumor growth
PO QD dosing; Mean tumor volume ± SEM; n=6 per group; ***P*<0.01 vs. vehicle
All treatments were tolerated (mean bodyweight loss ≤5%)
SOC: Standard of care

SM08502 demonstrated strong antitumor activity in a SOC-resistant *PTEN-/-* xenograft model of CRPC



	TGI
Vehicle	
Abiraterone 75 mg/kg	none
Enzalutamide 30 mg/kg	none
SM08502 6.25 mg/kg	62%
SM08502 12.5 mg/kg	64%
SM08502 25 mg/kg	78%

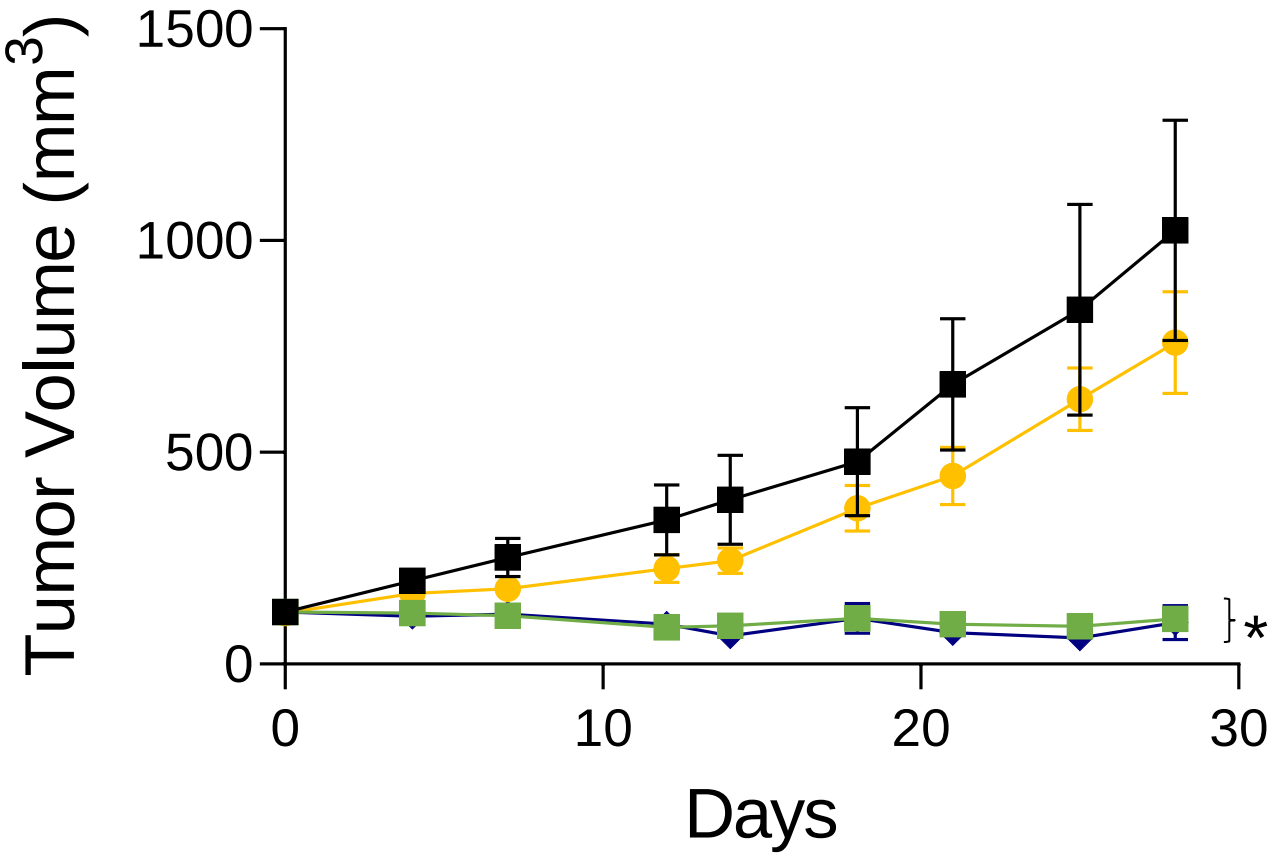
PC3 (*AR-*, *PTEN -/-*, *TP53 -/-*) tumor growth

PO QD dosing; Mean tumor volume ± SEM; n=6 per group, n=5 per vehicle and abiraterone group; *P<0.05 vs. vehicle

All treatments were tolerated (mean bodyweight loss ≤10%)

SOC: Standard of care, CRPC: Castration-resistant prostate cancer

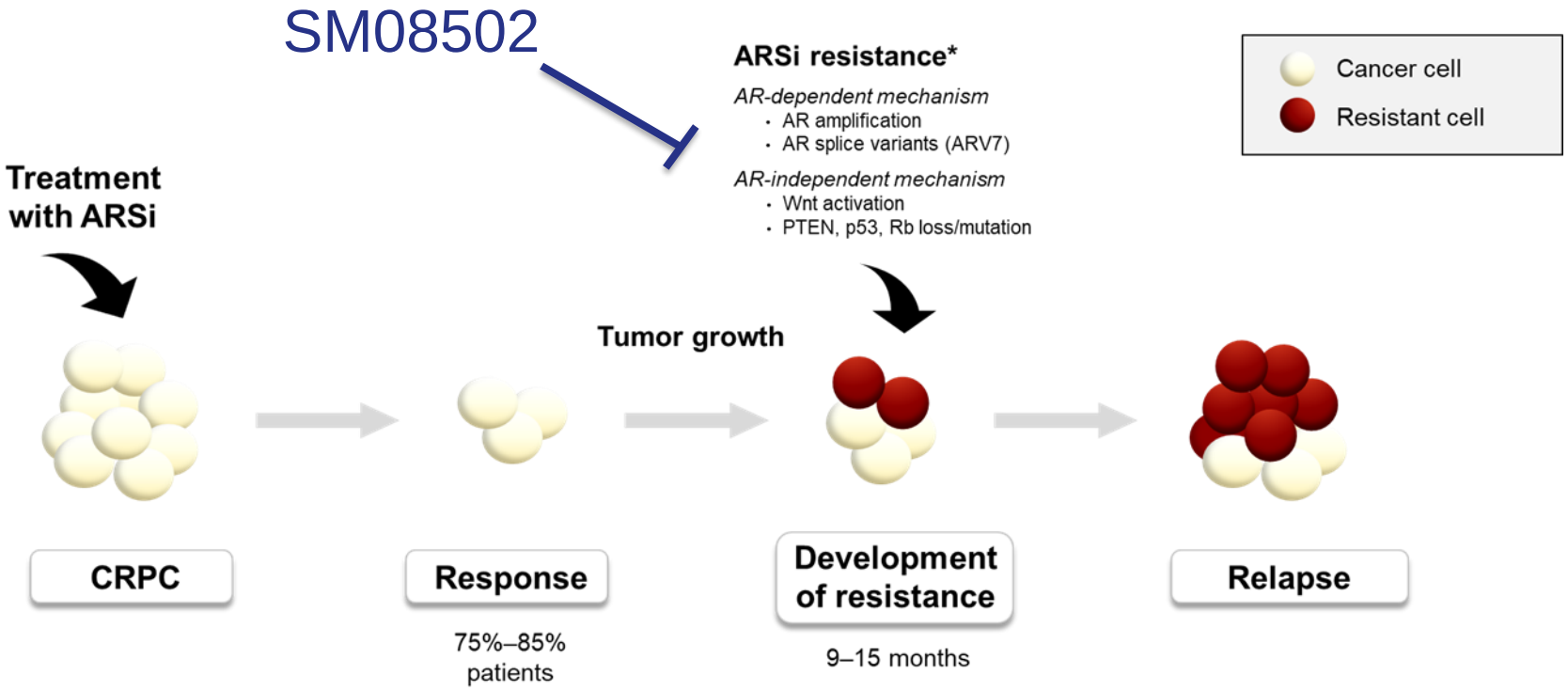
SM08502 potently inhibited tumor growth and appeared more efficacious than docetaxel in a xenograft model of CRPC



	TGI	Regression
Vehicle		
Docetaxel 10 mg/kg	26%	0/6
SM08502 25 mg/kg	90%	2/6
SM08502 + Docetaxel	90%	4/6

PC3 (*AR*-, *PTEN* -/-, *TP53* -/-) tumor growth
PO QD dosing for SM08502, IP Q7D dosing for docetaxel; Mean tumor volume ± SEM; n=6 per group, **P*<0.05 vs. vehicle
All treatments were tolerated (mean bodyweight loss ≤10%)
CRPC: Castration-resistant prostate cancer

Summary



- *In vivo*, SM08502 (25 mg/kg) demonstrated strong antitumor effects in CRPC xenografts
- SM08502 has the potential to provide clinical benefit to patients with treatment-resistant CRPC
- A Phase 1 study of SM08502 in subjects with advanced solid tumors is ongoing (NCT03355066)

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Thank You