Preliminary Evidence of Clinical Activity from Phase 1 and 1b Trials of the CLK/DYRK Inhibitor Cirtuvivint (CIRT) in Subjects with Advanced Solid Tumors

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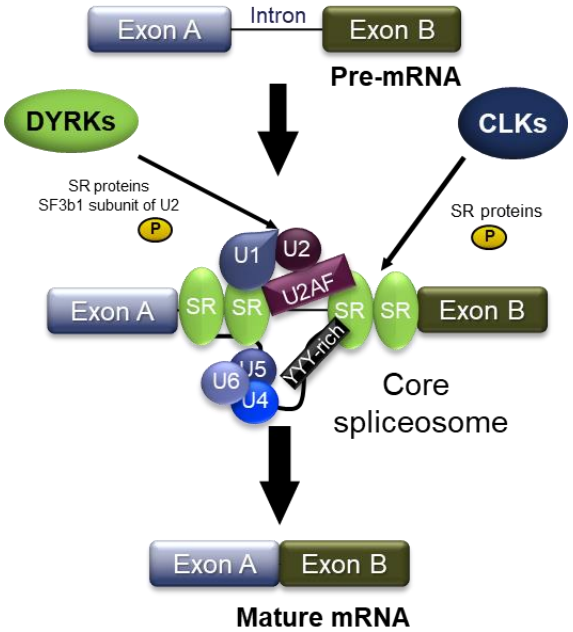
Declaration of Interests

Speaker(s): Aaron Scott, MD

- Stock and Other Ownership Interests
  - Johnson & Johnson/Janssen
- Consulting or Advisory Role
  - Exelixis, QED and Pfizer
- Research Funding
  - Exelixis, Genetech, Incyte, FivePrime, Merck
- Travel, Accommodations, Expenses
  - Exelixis, QED, Biosplice Therapeutics

Novel Mechanism of Action by Targeting Alternative Splicing

Alternative Splicing (AS)



Adapted from Biamonti, et al. 2019.
SR: SRSF (serine/arginine-rich splicing factor)

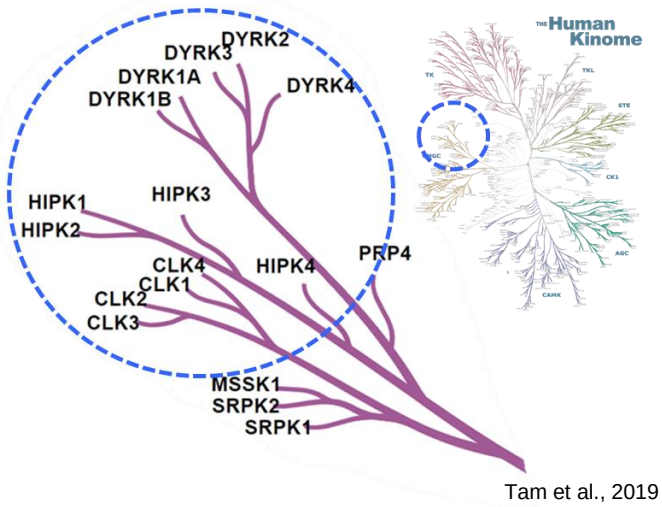
CLKs and DYRKs regulate splice site selection by phosphorylating splicing factor proteins

Tumors utilize AS to drive many of the Hallmarks of Cancer

The spliceosome has been found to be a therapeutic vulnerability

Target Class: CLK/DYRK Kinases

Cirtuvivint (SM08502) is an orally available, potent (low nM IC50s), selective, *first-in-class* pan CLK/DYRK inhibitor

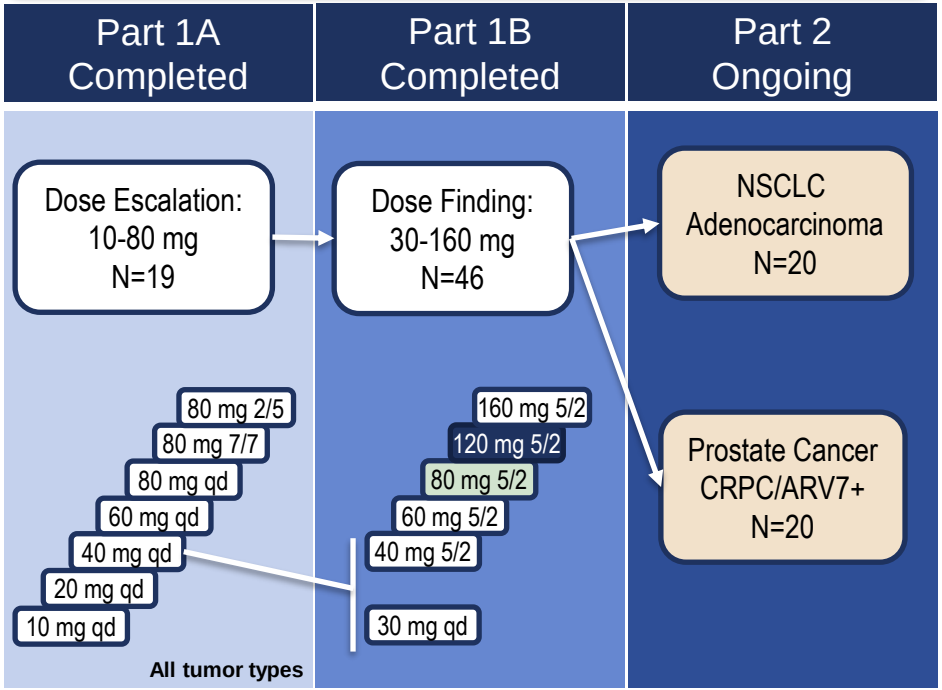


Tam et al., 2019

CLK: cdc2-like kinase
DYRK: dual-specificity tyrosine-regulated kinases

First in Human (FIH) Study

Study Design – ONC-01



NCT03355066; Sponsor: Biosplice Therapeutics

Objectives: safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy

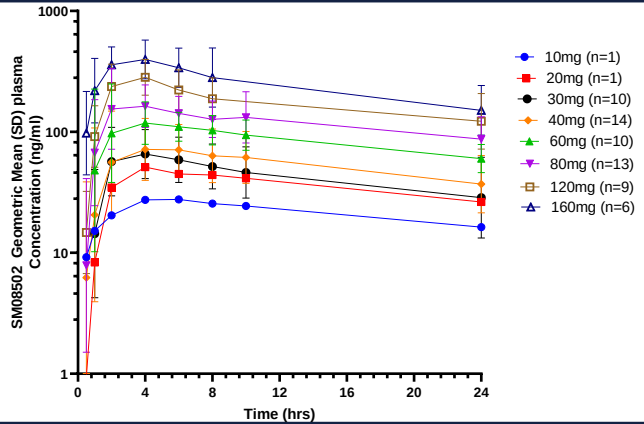
Patient Characteristics

Parameter	Category	N = 71 n (%)
Sex	Male	42 (59.2)
	Female	29 (40.8)
Median age		64.0
ECOG performance status	0	22 (31.0)
	1	49 (69.0)
Prior lines of therapy	0	1 (1.4)
	1	5 (7.0)
	2	6 (8.5)
	3	10 (14.1)
	≥ 4	49 (69.0)
Median (range) lines of therapy		5 (0 - 15)
Tumor type	Prostate	22 (31.0)
	Colorectal	19 (26.8)
	Lung	8 (11.3)
	Ovarian	6 (8.5)
	Endometrial	4 (5.6)
	Bile Duct	3 (4.2)
	Pancreatic	3 (4.2)
	Lip	2 (2.8)
	Other	4 (5.6)

Other: anal, synovial sarcoma, testicular, uterine. Cut off Date: 7/22/22

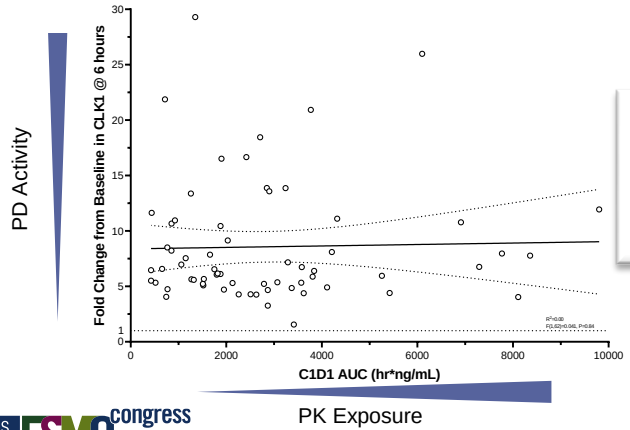
Cirtuvivint has Favorable PK and Demonstrated On Target PD

Pharmacokinetics



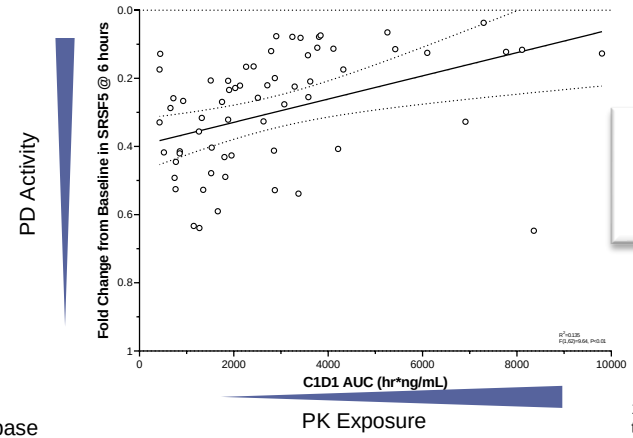
- Dose proportional increase in exposure
- Low variability
- 2-fold drug accumulation (5/2 schedule)
- t1/2 >24h

Pharmacodynamics: CLK1 (exon 4 inclusion)



Approximately 8-fold increase in CLK1 splicing at all doses

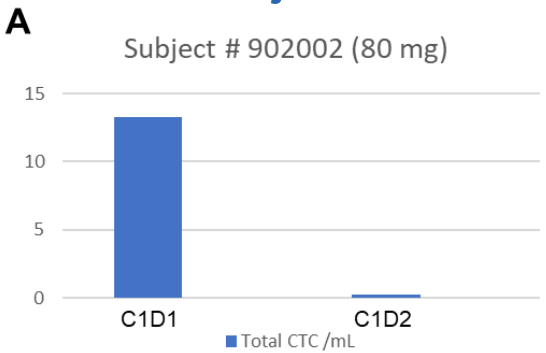
Pharmacodynamics: SRSF5 (intron 5-6 retention)

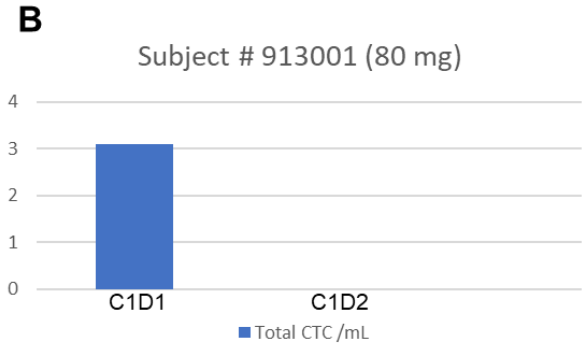


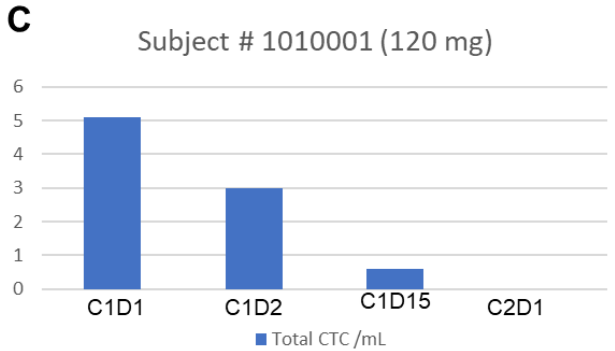
Dose dependent increase in SRSF5 splicing

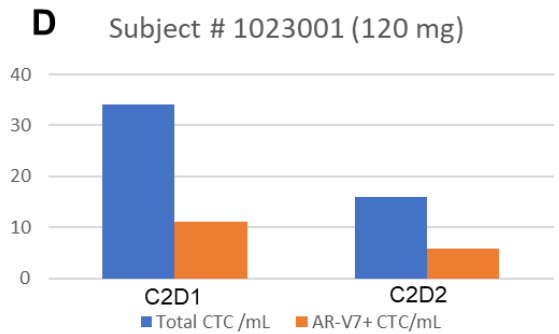
1 data point in the analysis is outside the axis limits

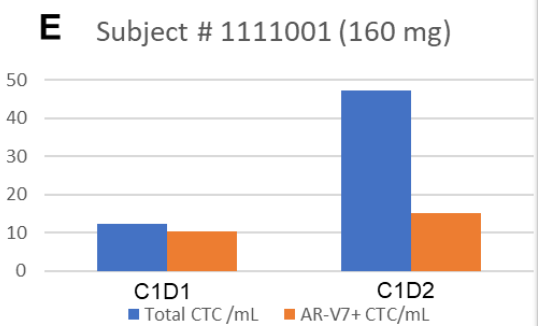
Cirtuvivint Demonstrated a Pharmacodynamic Effect on Total and AR-V7+ CTCs in CRPC subjects











- 5 out of 11 subjects tested had measurable CTCs
- 4 out of 5 subjects treated with cirtuvivint monotherapy demonstrated a drop in total CTCs (**Panels A-D**)
- In one subject (**Panel D**), both total CTCs and AR-V7+ CTCs were decreased (for this subject, C2D1 and C2D2 data are shown since the C1D1 baseline samples were not available).
- In one subject (**Panel E**), despite an increase in CTCs a drop in the percentage of ARV7+ CTCs (84% to 32%) was observed.
- Data represents the maximum PD effect for each subject.

Cirtuvivint has a Manageable Safety Profile

	Number (%) of subjects												
	10 mg (n=1)	20 mg (n=1)	30 mg (n=10)	40 mg (n=7)	60 mg (n=4)	40 mg 5 on/2 off (n=7)	60 mg 5 on/2 off (n=7)	80 mg 5 on/2 off (n=7)	80 mg 2 on/5 off (n=4)	80 mg 7 on/7 off (n=2)	120 mg 5 on/2 off (n=15)	160 mg 5 on/2 off (n=6)	All Subjects N=71
AEs occurring in at least 10% of subjects													
Nausea	0	1 (100.0)	5 (50.0)	6 (85.7)	2 (50.0)	3 (42.9)	4 (57.1)	3 (42.9)	2 (50.0)	1 (50.0)	13 (86.7)	5 (83.3)	45 (63.4)
Diarrhoea	0	1 (100.0)	3 (30.0)	3 (42.9)	3 (75.0)	5 (71.4)	3 (42.9)	5 (71.4)	1 (25.0)	2 (100.0)	11 (73.3)	5 (83.3)	42 (59.2)
Fatigue	0	0	5 (50.0)	2 (28.6)	2 (50.0)	0	3 (42.9)	0	2 (50.0)	2 (100.0)	7 (46.7)	4 (66.7)	27 (38.0)
Vomiting	0	1 (100.0)	4 (40.0)	3 (42.9)	2 (50.0)	2 (28.6)	1 (14.3)	2 (28.6)	0	1 (50.0)	8 (53.3)	3 (50.0)	27 (38.0)
Decreased appetite	0	0	2 (20.0)	3 (42.9)	2 (50.0)	1 (14.3)	1 (14.3)	0	0	1 (50.0)	7 (46.7)	2 (33.3)	19 (26.8)
Anaemia	0	0	0	2 (28.6)	1 (25.0)	1 (14.3)	1 (14.3)	3 (42.9)	0	0	6 (40.0)	1 (16.7)	15 (21.1)
Dehydration	0	0	2 (20.0)	1 (14.3)	0	1 (14.3)	1 (14.3)	2 (28.6)	0	0	5 (33.3)	2 (33.3)	14 (19.7)
Abdominal pain	0	0	2 (20.0)	2 (28.6)	0	2 (28.6)	0	1 (14.3)	0	1 (50.0)	2 (13.3)	2 (33.3)	12 (16.9)
Dizziness	0	1 (100.0)	3 (30.0)	1 (14.3)	0	0	1 (14.3)	0	0	0	3 (20.0)	2 (33.3)	11 (15.5)
Hypokalaemia	0	0	0	0	0	0	0	3 (42.9)	1 (25.0)	1 (50.0)	5 (33.3)	1 (16.7)	11 (15.5)
Constipation	0	0	2 (20.0)	0	1 (25.0)	0	1 (14.3)	0	0	0	4 (26.7)	2 (33.3)	10 (14.1)
Dyspnoea	0	0	1 (10.0)	1 (14.3)	0	1 (14.3)	2 (28.6)	1 (14.3)	1 (25.0)	0	2 (13.3)	1 (16.7)	10 (14.1)
Headache	0	0	1 (10.0)	2 (28.6)	0	0	0	1 (14.3)	1 (25.0)	0	3 (20.0)	1 (16.7)	9 (12.7)
Oedema peripheral	0	0	2 (20.0)	0	2 (50.0)	0	1 (14.3)	2 (28.6)	0	0	0	1 (16.7)	8 (11.3)
Weight decreased	0	0	0	0	1 (25.0)	0	1 (14.3)	2 (28.6)	0	0	4 (26.7)	0	8 (11.3)
Arthralgia	0	0	4 (40.0)	1 (14.3)	0	0	1 (14.3)	0	0	0	0	1 (16.7)	7 (9.9)
Fall	0	0	0	1 (14.3)	0	0	1 (14.3)	3 (42.9)	0	0	1 (6.7)	1 (16.7)	7 (9.9)
Hypotension	0	0	1 (10.0)	1 (14.3)	2 (50.0)	0	0	1 (14.3)	0	0	1 (6.7)	1 (16.7)	7 (9.9)
Grade 3 AEs occurring in at least 10% of subjects													
Anaemia	0	0	0	1 (14.3)	1 (25.0)	1 (14.3)	1 (14.3)	2 (28.6)	0	0	4 (26.7)	0	10 (14.1)
Diarrhoea	0	1 (100.0)	0	0	0	1 (14.3)	0	1 (14.3)	0	2 (100.0)	2 (13.3)	0	7 (9.9)
DLTs													
Diarrhoea	0	0	0	0	0	0	0	0	0	1 (50.0)	1 (6.7)	0	2 (2.8)
Increased Transaminase	0	0	0	1 (14.3)	0	0	0	0	0	0	0	0	1 (1.4)
Rash	0	0	0	0	0	0	0	0	0	0	0	1 (16.7)	1 (1.4)

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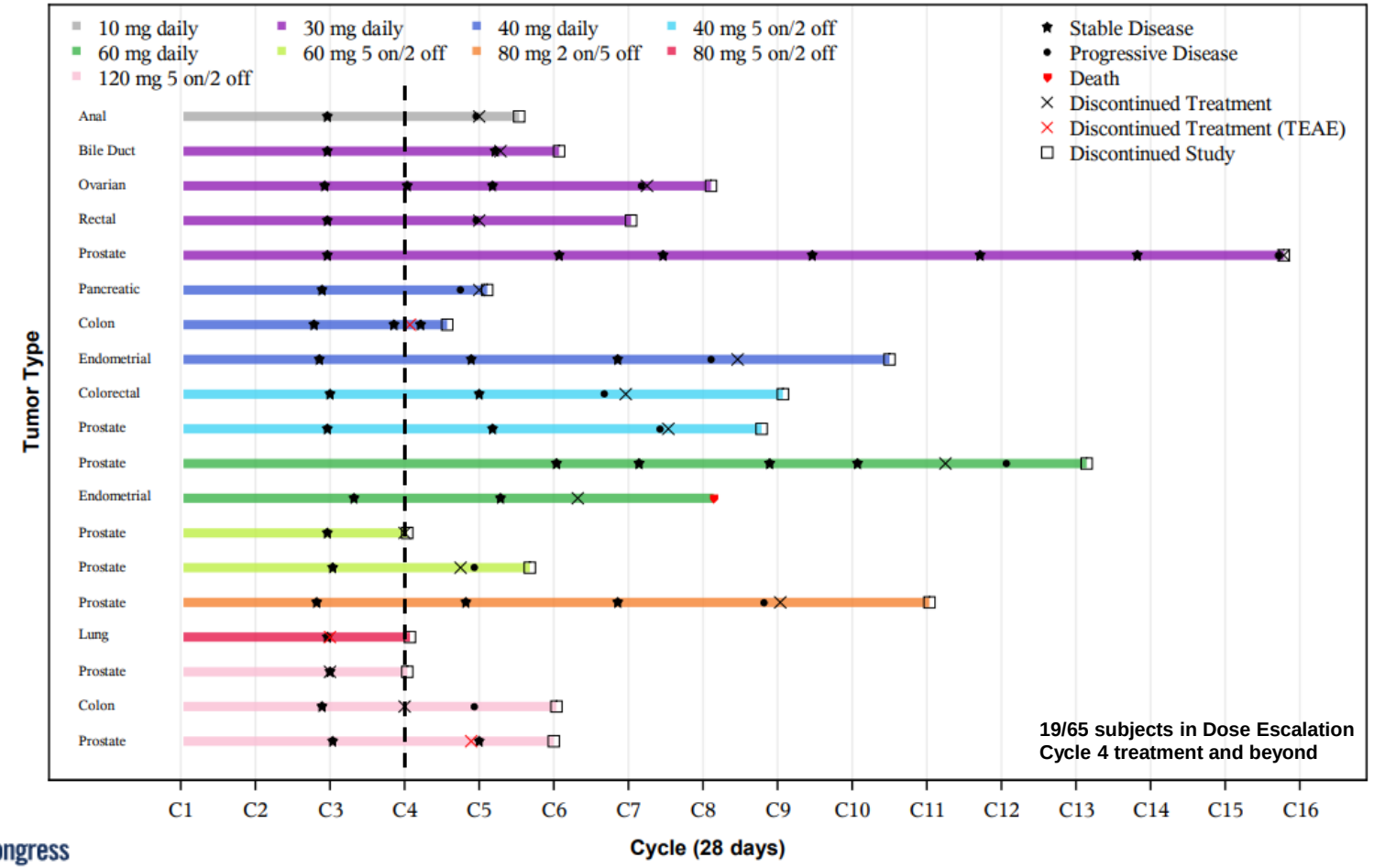
Open database

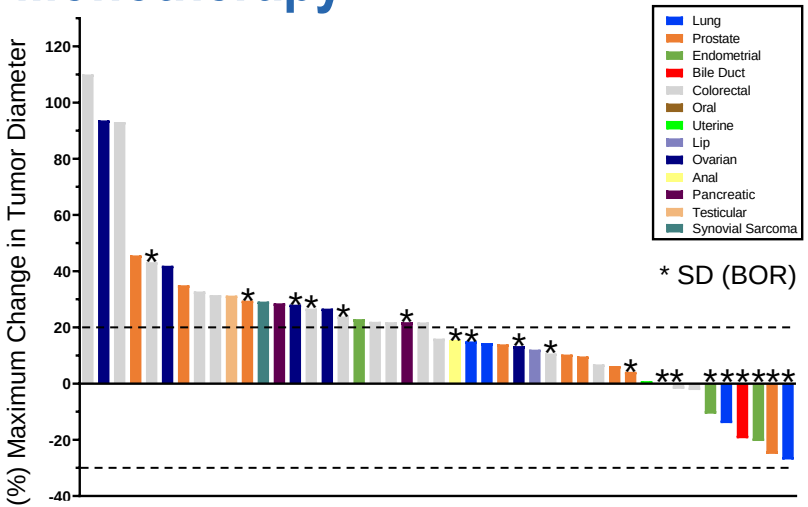
4 DLTs observed , Maximum Tolerated Dose: 120mg 5 on/2 off

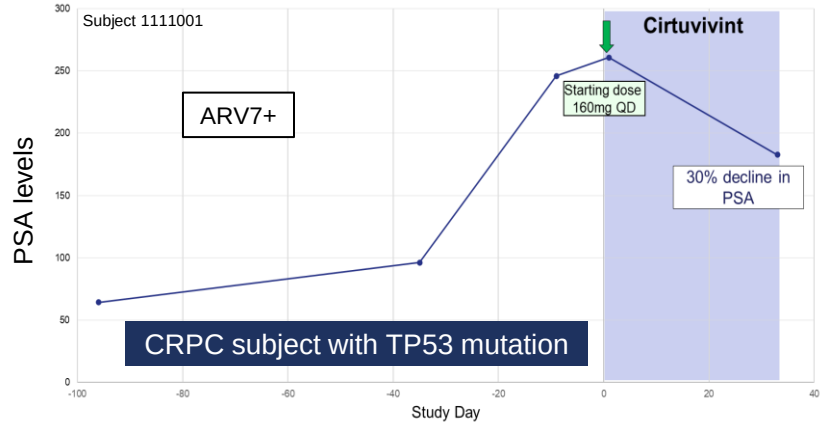
Durable Stable Disease Seen in Subjects Treated with Cirtuvivint



Early Evidence of Anti-tumor Activity as Monotherapy

- Tumor shrinkage (>10%) seen in 6 subjects:
  - NSCLC (27% and 14%)
  - CRPC (25%)
  - Endometrial cancer (20% and 11%)
  - Bile duct cancer (19%)
- PSA30 response observed in 3 CRPC subjects
- A favorable change in PSA kinetics was observed in several CRPC subjects
- CTC reductions observed post dosing with cirtuvivint in 4/5 CRPC subjects
- Stable disease reaching cycle 6 and beyond was observed in 12 subjects which exceeds the median TTF and median PFS for phase 1 trials (2-3 months)

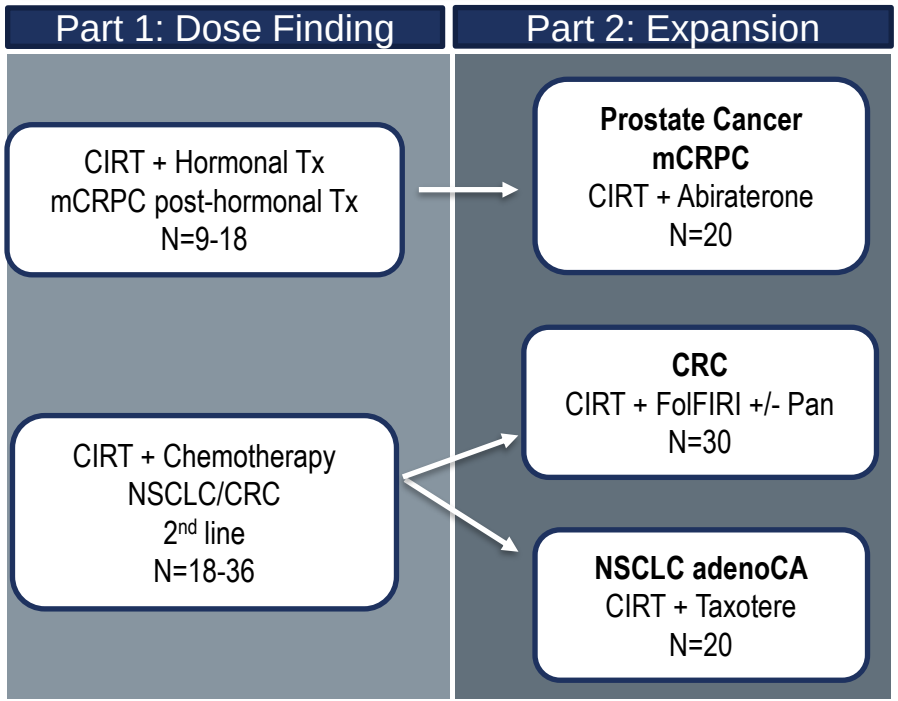




Prior treatments: leuprolide, abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223.

Cirtuvivint Phase 1b Combination Study

Study Design – ONC-03



NCT05084859; Sponsor: Biosplice Therapeutics

Objectives

- Safety
- Pharmacokinetics
- Preliminary antitumor activity

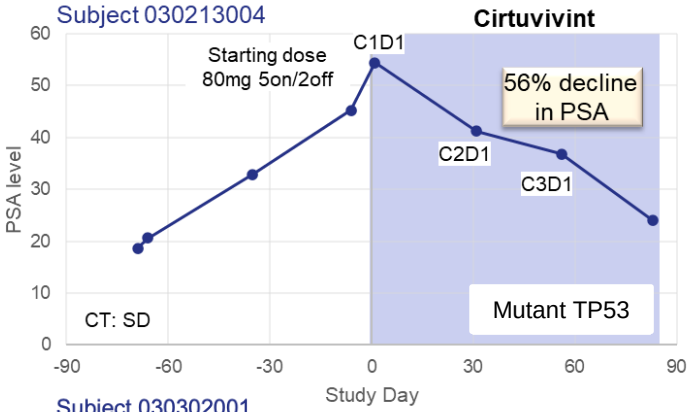
Safety

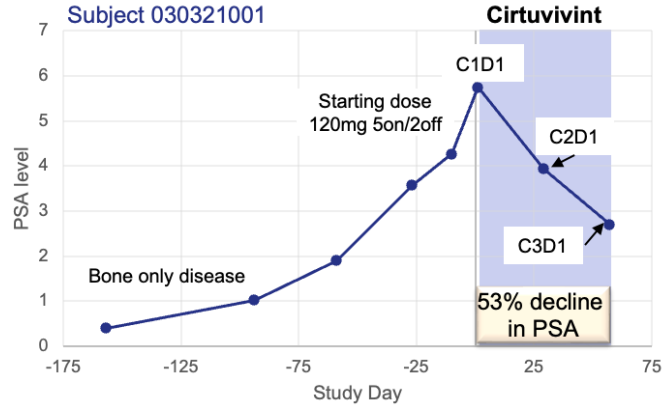
Thus far no unexpected safety signals relative to those known to occur with cirtuvivint or the combination partners were observed

Dose escalation is ongoing and MTD has not been reached as of 7-22-22

PSA Impacted in Subjects Treated with Cirtuvivint and Abiraterone

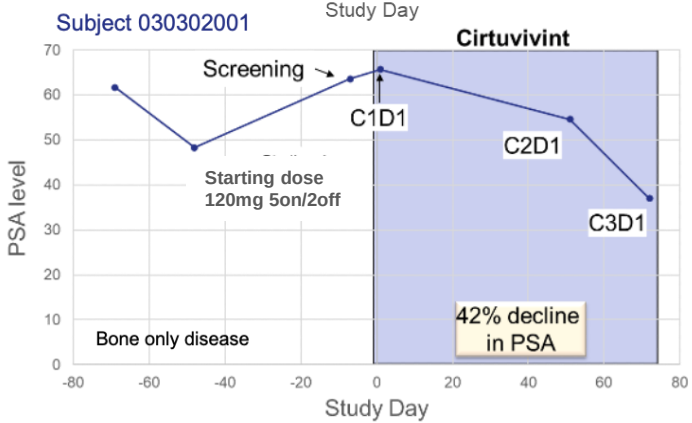
Prior therapies for advanced disease: leuprolide, enzalutamide, docetaxel, cabazitaxel, clinical trials

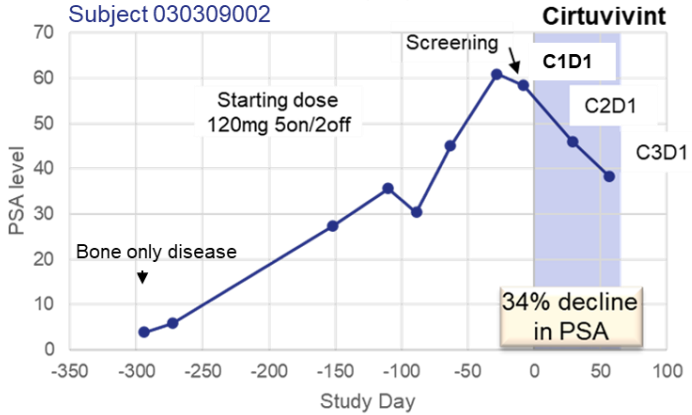




Prior therapies for advanced disease: leuprolide plus bicalutamide, **abiraterone** plus prednisone, enzalutamide, docetaxel

Prior therapies for advanced disease: leuprolide, enzalutamide, docetaxel



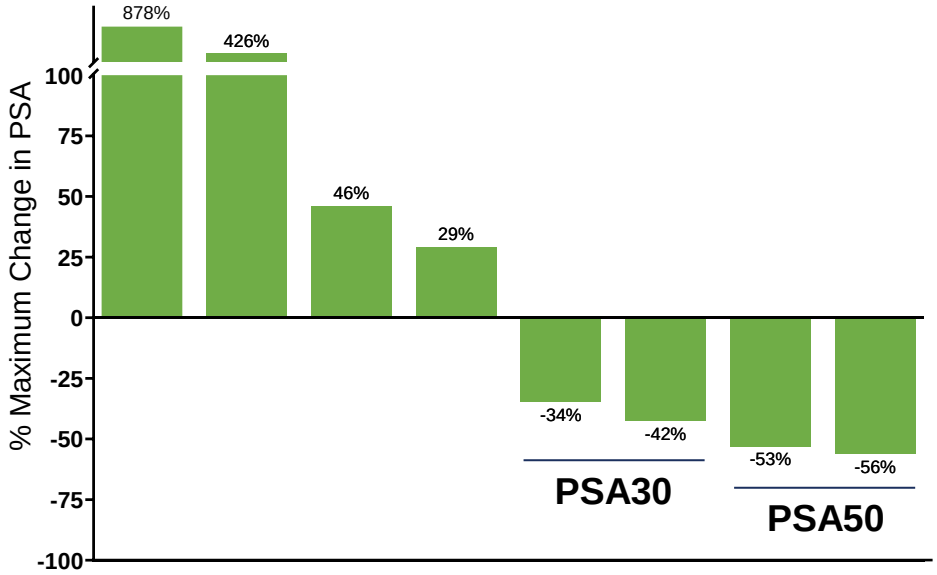


Prior therapies for advanced disease: leuprolide plus enzalutamide, docetaxel

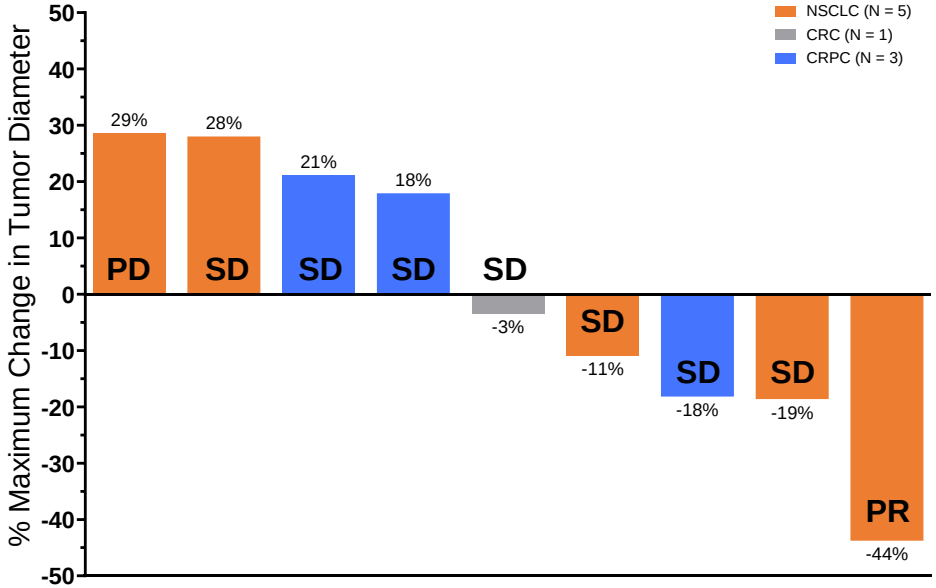
Open database

Early Evidence of Anti-tumor Activity in the Combination Study

PSA



Tumor shrinkage



Tumor data displayed is for evaluable subjects (9/26)
BOR at time of data cut off shown in the bar graphs

Conclusions

Novel Mechanism of Action

- First in class pan CLK/DYRK inhibitor that modulates alternative splicing
- Targeting alternative splicing offers the opportunity to disrupt key pathways that drive cancer

Phase 1 trial results

- Favorable PK, manageable safety profile, and PD provided evidence for Proof of Mechanism

Evidence of clinical benefit and anti-tumor activity

- FIH study: Reduction in CTCs, decline in PSA, tumor shrinkage, and prolonged stable disease in multiple subjects
- Combination study: evidence suggesting reversal of hormonal therapy resistance in CRPC and anti-tumor activity in combination with chemotherapy

Both studies are ongoing and transitioning into the Part 2 expansions

- Evaluating biomarker selection strategies

Thank you

Aaron Scott, MD