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

Speaker: Aaron Scott, MD, University of Arizona College of Medicine – Tucson

Authors: A. Scott, J. Call, S. Chandana, E. Borazanci, G. Falchook, R. Bordoni, S. Richey, A. Starodub, V. Chung, N. Lakhani, E. Lam, K. Schaffer, J. Wang, G. Shapiro, J. Sachdev, D. Beaupre and A. Tolcher
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)**

- **SR proteins** (SRF splicing factor)
- **U1, U2, U5, U4 snRNPs**
- **Exon A** → **Intron** → **Exon B** → **Pre-mRNA**
- **Core spliceosome**
- **Exon A** → **Exon B** → **Mature mRNA**

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

**Target Class: CLK/DYRK Kinases**

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

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

**Tumors utilize AS to drive many of the Hallmarks of Cancer**

**The spliceosome has been found to be a therapeutic vulnerability**

Tam et al., 2019
First in Human (FIH) Study

Study Design – ONC-01

<table>
<thead>
<tr>
<th>Part 1A</th>
<th>Part 1B</th>
<th>Part 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed</td>
<td>Completed</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

- **Dose Escalation:** 10-80 mg N=19
- **Dose Finding:** 30-160 mg N=46
- **NSCLC Adenocarcinoma:** N=20
- **Prostate Cancer CRPC/ARV7+:** N=20

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

Patient Characteristics

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

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

Aaron Scott, MD
Cirtuvivint has Favorable PK and Demonstrated On Target PD

**Pharmacokinetics**

- Dose proportional increase in exposure
- Low variability
- 2-fold drug accumulation (5/2 schedule)
- $t_{1/2} > 24h$

**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

---

Aaron Scott, MD

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.
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

### AEs occurring in at least 10% of subjects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>10 mg (n=1)</th>
<th>20 mg (n=1)</th>
<th>30 mg (n=10)</th>
<th>40 mg (n=4)</th>
<th>60 mg (n=7)</th>
<th>80 mg (n=7)</th>
<th>All (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreasd appetite</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (100.0)</td>
<td>3 (30.0)</td>
<td>1 (14.3)</td>
<td>0</td>
<td>1 (14.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>2 (20.0)</td>
<td>1 (14.3)</td>
<td>0</td>
<td>1 (14.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>0</td>
<td>1 (10.0)</td>
<td>1 (14.3)</td>
<td>0</td>
<td>1 (14.3)</td>
<td>2 (28.6)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1 (10.0)</td>
<td>2 (28.6)</td>
<td>0</td>
<td>0</td>
<td>1 (14.3)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>0</td>
<td>2 (20.0)</td>
<td>2 (50.0)</td>
<td>0</td>
<td>1 (14.3)</td>
<td>2 (28.6)</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (14.3)</td>
<td>2 (28.6)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>4 (40.0)</td>
<td>1 (14.3)</td>
<td>0</td>
<td>1 (14.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>0</td>
<td>0</td>
<td>1 (14.3)</td>
<td>0</td>
<td>1 (14.3)</td>
<td>3 (42.9)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>1 (10.0)</td>
<td>1 (14.3)</td>
<td>2 (50.0)</td>
<td>0</td>
<td>1 (14.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Grade 3 AEs occurring in at least 10% of subjects

<table>
<thead>
<tr>
<th>AEs</th>
<th>Number (%) of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

### DLTs

- **Diarrhoea**: 0 (0.0)
- **Increased Transaminase**: 0 (0.0)
- **Rash**: 0 (0.0)

---

**Open database**

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

---

Aaron Scott, MD

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.
Durable Stable Disease Seen in Subjects Treated with Cirtuvivint

19/65 subjects in Dose Escalation Cycle 4 treatment and beyond

Aaron Scott, MD

Open database
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).

- PSA levels Data as of 07-22-2022
  - 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).

Subject 1111001

ARV7+

CRPC subject with TP53 mutation

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

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Aaron Scott, MD

Data as of 07-22-2022
Cirtuvivint Phase 1b Combination Study

Study Design – ONC-03

<table>
<thead>
<tr>
<th>Part 1: Dose Finding</th>
<th>Part 2: Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIRT + Hormonal Tx</td>
<td>Prostate Cancer</td>
</tr>
<tr>
<td>mCRPC post-hormonal Tx</td>
<td>mCRPC</td>
</tr>
<tr>
<td>N=9-18</td>
<td>CIRT + Abiraterone</td>
</tr>
<tr>
<td>CIRT + Chemotherapy</td>
<td>CRC</td>
</tr>
<tr>
<td>NSCLC/CRC</td>
<td>CIRT + FolFIRI +/- Pan</td>
</tr>
<tr>
<td>2nd line</td>
<td>N=30</td>
</tr>
<tr>
<td>N=18-36</td>
<td>NSCLC adenoCA</td>
</tr>
<tr>
<td></td>
<td>CIRT + Taxotere</td>
</tr>
<tr>
<td></td>
<td>N=20</td>
</tr>
</tbody>
</table>

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

NCT05084859; Sponsor: Biosplice Therapeutics
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

Mutant TP53

Starting dose 80mg 5on/2off

Mutant TP53

Starting dose 120mg 5on/2off

Bone only disease

42% decline in PSA

53% decline in PSA

34% decline in PSA

C1D1

C2D1

C3D1

Study Day

-90 -60 -30 0 30 60 90

Subject 030213004

PSA level

60 40 20 10 0

CT: SD

Subject 030321001

PSA level

7 6 5 4 3 2 1 0

Bone only disease

Subject 030302001

PSA level

70 60 50 40 30 20 10 0

C1D1

C2D1

C3D1

Study Day

-175 -125 -75 -25 25 75

Subject 030309002

PSA level

70 60 50 40 30 20 10 0

C1D1

C2D1

C3D1

Study Day

-350 -300 -250 -200 -150 -100 0 50 100

Aaron Scott, MD
Early Evidence of Anti-tumor Activity in the Combination Study

Aaron Scott, MD

Tumor shrinkage

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

Open database

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.
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

Aaron Scott, MD
Thank you