FIRST-IN-HUMAN PHASE I/II STUDY OF CYT-0851, A FIRST-IN-CLASS INHIBITOR OF RAD51-MEDIATED HOMOLOGOUS RECOMBINATION IN PATIENTS WITH ADVANCED SOLID AND HEMATOLOGIC CANCERS

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June 4, 2021
High levels of DNA damage in cancer cells enables **Synthetic Lethality** with selective inhibition of DNA repair.

**Cytidine Deaminase (CD) Overexpression Creates Dependence on DNA Repair by Homologous Recombination (HR)**

- **HIGH DNA Damage**
  - Dependence on DNA Repair
  - Cancer Cell Survival

- **LOW CD Expression**
  - LOW DNA Damage
  - LOW NEED for HR
  - VIABLE

- **HIGH CD Expression**
  - HIGH DNA Damage
  - HIGH NEED for HR
  - LETHAL

**Phenotypic Synthetic Lethality Screen**

- **Compound Library**
- **Normal Cells**
  - CD
  - LOW CD Expression
  - LOW DNA Damage
  - LOW NEED for HR
  - VIABLE

- **Cancer Cells**
  - CD
  - HIGH CD Expression
  - HIGH DNA Damage
  - HIGH NEED for HR
  - LETHAL

**CYT-0851**

Presented By: Ryan Lynch

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CYT-0851 Treatment Reduces RAD51 Foci and Increases DNA Damage Measured by γH2AX

AID+ U698 B-cell Lymphoma Cell Line
1.25 µM CYT-0851, 4-day treatment
**CYT-0851 Preclinical Characterization**

### IN VITRO BIOCHEMICAL AND CELLULAR ACTIVITY

<table>
<thead>
<tr>
<th>CYT-0851 Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellular Potency</strong></td>
<td></td>
</tr>
<tr>
<td>Daudi (Burkitt's B Cell Lymphoma) screening cell line EC$_{50}$</td>
<td>200nM</td>
</tr>
<tr>
<td><strong>Cellular Selectivity</strong></td>
<td></td>
</tr>
<tr>
<td>MEC1 CLL cell line (EC$_{50}$ AID$^+$ vs AID knockout)</td>
<td>&gt;30-fold</td>
</tr>
<tr>
<td><strong>Kinase Selectivity</strong></td>
<td></td>
</tr>
<tr>
<td>Hits with &gt;50% inhibition at 10µM (371 kinase panel)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Secondary Pharmacodynamic Selectivity</strong></td>
<td></td>
</tr>
<tr>
<td>Hits with &gt;50% inhibition at 10µM (38 human Panlabs panel)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Bone Marrow Progenitors Selectivity</strong></td>
<td></td>
</tr>
<tr>
<td>IC$_{50}$ for human erythroid, myeloid &amp; megakaryocyte progenitor inhibition</td>
<td>&gt;10µM (erythroid) 8.3µM (myeloid) 4.0µM (megakaryocyte)</td>
</tr>
<tr>
<td><strong>hERG Ion Channel Selectivity</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;3µM</td>
</tr>
</tbody>
</table>

**CYT-0851: Highly selective small-molecule inhibitor of HR with single agent activity in hematologic and solid tumor models in vivo**

### IN VIVO ANTI-TUMOR ACTIVITY

**BURKITT’S LYMPHOMA CDX MODEL**

**PANCREATIC CANCER PDX MODEL**

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CYT-0851 Phase 1 Trial Design
(Data cut-off Apr 6, 2021)

Dosing:
• Oral, 28-day continuous dosing per cycle

Design:
• 3+3 Dose Escalation
• Pharmacodynamic backfill up to 12 total patients per dose to obtain paired biopsies

Objectives/Endpoints:
• Primary
  • MTD/RP2D
• Secondary
  • Safety
  • Pharmacokinetics
  • Anti-tumor Activity
• Exploratory
  • Pharmacodynamics
  • PK/PD relationship
  • Predictive biomarkers

Key Inclusion Criteria:
• ECOG 0-1
• Measurable disease
• Relapsed/refractory B-cell malignancies
  • NHL, CLL, Multiple myeloma
• Advanced solid tumors
  • Breast, HNSCC, ovarian, soft-tissue sarcoma, SCLC and pancreatic cancer

Key Exclusion Criteria:
• Prior allogeneic SCT
• ANC < 1.0 × 10^9/L
• Plt < 75 × 10^9/L
• Hgb < 9.0 g/dL
• CrCl < 40 mL/min
• AST/ALT > 2.0 x ULN

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### Patient Characteristics, Enrollment and Disposition

#### Characteristics Total (n=35)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (54)</td>
</tr>
<tr>
<td>Male</td>
<td>16 (46)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>59 (41-82)</td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (17)</td>
</tr>
<tr>
<td>1</td>
<td>27 (77)</td>
</tr>
<tr>
<td>Prior Lines of Therapy</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>4 (1-12)</td>
</tr>
<tr>
<td>1</td>
<td>2 (6)</td>
</tr>
<tr>
<td>2</td>
<td>5 (14)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>28 (80)</td>
</tr>
<tr>
<td>Tumor Type</td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Head and Neck Cancer</td>
<td>1 (3)</td>
</tr>
<tr>
<td>SCLC</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Mucoepidermoid Cancer</td>
<td>1 (3)</td>
</tr>
<tr>
<td>NHL</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Soft-Tissue Sarcoma</td>
<td>12 (34)</td>
</tr>
</tbody>
</table>

**Enrolled (n=39)**

**Treated (n=35)**

**Safety Population (n=35)**

**Response Evaluable (n=21)**

**Ongoing (n=12)**

**Treatment Discontinued (n=23)**

- Progressive Disease n = 19
- Patient Decision n = 2
- Physician Decision n = 1
- Adverse Event n = 1*

*AST/ALT increase secondary to disease
Safety Overview

<table>
<thead>
<tr>
<th>Treatment-Related AEs (Occurring in &gt; 1 pt)</th>
<th>Any Grade n (%)</th>
<th>≥ Grade 3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Related Adverse Event</td>
<td>13 (37.1)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Blood alk phos increased</td>
<td>3 (8.6)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (8.6)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (8.6)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

- No DLTs
- No treatment-related SAEs
- No clinically significant myelosuppression
- No treatment-related discontinuation
- No grade 4/5 TRAEs

[Presented By: Ryan Lynch]
## CYT-0851 Pharmacokinetic Profile

CYT-0851 PK exhibits a long effective half-life (~3 days) with dose proportional exposure.

### CYT-0851 Human Pharmacokinetics Summary for C1D15/22

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Dose (mg)</th>
<th>15 BID (n=1)</th>
<th>20 BID (n=1)</th>
<th>30 BID (n=3)</th>
<th>45 BID (n=6)</th>
<th>90 QD (n=3)</th>
<th>130 QD (n=6)</th>
<th>200 QD (n=4)</th>
<th>300 QD (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (h)</td>
<td></td>
<td>2.0</td>
<td>2.0</td>
<td>4 (2, 4)</td>
<td>2.25 (1.5, 6)a</td>
<td>2.5 (1.5, 3)a</td>
<td>4.0 (1.5, 6)a</td>
<td>6.0 (6, 8)a</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td></td>
<td>338</td>
<td>670</td>
<td>770 ± 390</td>
<td>1170 ± 375b</td>
<td>1740 ± 930b</td>
<td>1700 ± 298b</td>
<td>2980 ± 1690b</td>
<td>6490 ± 2560b</td>
</tr>
<tr>
<td>AUC_{0-8} (ng.h/mL)</td>
<td></td>
<td>1890</td>
<td>4410</td>
<td>4710 ± 2140</td>
<td>7450 ± 3030b,c</td>
<td>11500 ± 5570b</td>
<td>10800 ± 2510b</td>
<td>18900 ± 9490b</td>
<td>41800 ± 16200b</td>
</tr>
</tbody>
</table>

a: median (min, max)  b: mean ± standard deviation (SD)  c: n=5
PD Effects: Selective Increase in DNA damage (γH2AX) observed in CTCs (Patient 015) at 45 mg BID

Increased γH2AX observed in CTCs from 3 of 6 biomarker-evaluable patients with epithelial cancers consistent with proposed mechanism of action
CYT-0851 Efficacy: Change in Tumor Burden

21 patients were response-evaluable

3 partial responses
1) DLBCL (Pt 013)
2) Follicular lymphoma (Pt 021)
3) Soft-tissue sarcoma (Pt 006) (unconfirmed)

- 10 patients had stable disease
**CYT-0851 Duration of Treatment**

- **Durable benefit** has been observed in patients with clinical response.
- Four patients received CYT-0851 for 6+ months with no evidence of cumulative toxicity.

*Patient died due to CNS progression after the data cut-off*
Response #1: DLBCL (Patient 013)

- 81 yo male with DLBCL previously treated with 2 lines of therapy (R-CHOP, R-Benda/XRT)
- Treated with 45 mg PO BID for 5 cycles and then increased to 130 mg PO QD for 2 cycles
- No treatment related adverse events reported in 6+ months on therapy
- He experienced disease progression in the CNS and died after the data cutoff
Response #2: Follicular Lymphoma (Patient 021)

- 59 yo male with follicular lymphoma previously treated with 3 lines of therapy (Rituximab, R-CVP, PI3K inhibitor)

- Treated with 45 mg PO BID for 4 cycles, 130 mg PO QD for 2 cycles, then 200 mg PO QD

- No treatment related adverse events reported in 6+ months on therapy

- Patient’s treatment and response is ongoing
Response #2: Follicular Lymphoma (Patient 021)

- 59 yo male with follicular lymphoma previously treated with 3 lines of therapy (Rituximab, R-CVP, PI3K inhibitor)
- Treated with 45 mg PO BID for 4 cycles, 130 mg PO QD for 2 cycles, then 200 mg PO QD
- No treatment related adverse events reported in 6+ months on therapy
- Patient’s treatment and response is ongoing
Response #3: Myxofibrosarcoma (Patient 006)

- 73 yo male with myxofibrosarcoma previously treated with 4 lines of therapy
- Treated with 45 mg PO BID for 8 cycles, 90 mg PO QD for 1 cycle, then 130 mg PO QD for 1 cycle
- No treatment related adverse events reported in 10+ months on therapy
- He experienced disease progression and has subsequently discontinued treatment after the data cutoff

<table>
<thead>
<tr>
<th>Site</th>
<th>Baseline</th>
<th>Cycle 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Wall Posterior R Shoulder</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>Pleura Right Costophrenic</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
</tbody>
</table>
Conclusions: CYT-0851 Phase 1 Interim Analysis

- CYT-0851 has been evaluated in 8 dose-escalation cohorts with no DLTs. Escalation is ongoing to define the MTD.
- Treatment-related adverse events occurred infrequently and were low-grade and manageable.
- The pharmacokinetic profile exhibits dose proportional exposure and a long half-life supporting once-daily oral administration with predicted PD effects.
- Responses were observed in DLBCL, FL, and soft tissue sarcoma with tumor shrinkage in pancreatic cancer and ovarian cancer at biologically-active doses.

CYT-0851 is the first DDR-targeted agent with monotherapy activity in solid tumors and NHL and a non-myelosuppressive safety profile
Acknowledgments

On behalf of the study team, the authors and Sponsor want to thank the patients, their families and caregivers for their participation in this study.