Preclinical characterization of ARRY-575

A potent, selective, and orally bio-available small molecule inhibitor of Chk1

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Chemotherapeutics induce DNA damage and activate the DNA damage response (DDR)

- The DDR is a key mechanism of chemotherapeutic resistance

- **Chk1 inhibitor/chemotherapy combination:**
  - Inhibit DNA repair
  - Induce checkpoint override
  - Drive mitotic catastrophe and apoptotic cell death
  - Potentiate the cell killing effect of chemotherapy
**ARRY-575: in vitro profile**

**ARRY-575 is potent**

<table>
<thead>
<tr>
<th>Chk1 Enzyme Assay</th>
<th>IC$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRY-575</td>
<td>2</td>
</tr>
</tbody>
</table>

**ARRY-575 is selective**

- **Inhibition**
  - > 80%
  - 50-80%
  - < 50%

**100 nM ARRY-575**

- Rsk3
  - IC$_{50}$ 39 nM
- Rsk4
  - IC$_{50}$ 308 nM
- MYLK
  - IC$_{50}$ 48 nM

[Each box represents an individual kinase]

**ARRAY-575 enhances apoptosis**

- **SW620 cells**
  - CPT+ 100 nM ARRY-575
  - 5X
  - CPT

**ARRAY-575 overrides checkpoints**

- **HT-29 Cells**
  - IC$_{50}$: 25 nM

[Each box represents an individual kinase]
Checkpoint activation is protracted *in vivo*

- Chemotherapeutics that target replication induce sustained checkpoint activation

HT-29 tumors
Prolonged Chk1 inhibition is required for maximal checkpoint override

**Pharmacodynamics**

- Normalized p-cdc2 (POC)

  - **Vehicle**
  - **CPT-11**
  - **ARRY-575**

**Efficacy**

- Mean Tumor Volume (mm$^3$)

  - **gem and ARRY-575**

  - **0% regression**
    - 4 / 7 CRs
  - **97% regression**

**Oral delivery provides flexibility for multi-day dosing**

- HT-29 tumors

- *gem: 120 mg/kg (IP)*
- *ARRY-575: 25 mg/kg BID (PO)*
- *3 cycles of dosing*
Checkpoint override correlates with efficacy

**Pharmacodynamics**

- **Normalized p-cdc2 (POC)**
  - Vehicle
  - CPT-11 (5 mg/kg, 3 days BID)
  - CPT-11 (10 mg/kg, 3 days BID)
  - CPT-11 (25 mg/kg, 3 days BID)
  - ARRY-575 (5 mg/kg)

**Efficacy**

- **Mean Tumor Volume (mm3)**
  - Vehicle
  - CPT-11 (100 mg/kg, IP)
  - ARRY-575 (PO, BID for 3 days)
  - CPT-11 + 5 mg/kg ARRY-575
  - CPT-11 + 10 mg/kg ARRY-575
  - CPT-11 + 25 mg/kg ARRY-575

- **HT-29 tumors**
  - 5% regression
  - 59% regression
  - 61% regression
  - 1 / 7 CR
  - 4 / 7 CRs

CPT-11: 100 mg/kg (IP)
ARRAY-575: PO, BID for 3 days
2 cycles of dosing
ARRY-575 potentiates CPT-11 in patient derived explants

<table>
<thead>
<tr>
<th>Treatment groups (N=8/group)</th>
<th>Growth delay (days)</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>N/A</td>
<td>-</td>
</tr>
<tr>
<td>CPT-11</td>
<td>16.2</td>
<td>0/7</td>
</tr>
<tr>
<td>25 mg/kg ARRY-575</td>
<td>0</td>
<td>0/7</td>
</tr>
<tr>
<td>CPT-11+ 10 mg/kg ARRY-575</td>
<td>21.7</td>
<td>7/8</td>
</tr>
<tr>
<td>CPT-11+ 25 mg/kg ARRY-575</td>
<td>34.1</td>
<td>8/8</td>
</tr>
</tbody>
</table>

PR: Partial response, ≥ 50% regression of an individual tumor

CRC human explant model (KRAS mt)

CPT-11: 100 mg/kg (IP)
ARRY-575: PO, BID for 3 days
2 cycles of dosing
ARRY-575 combination therapy is active following tumor re-growth

CRC human explant model (KRAS mt)

CPT-11 alone: 5 cycles
Combination:
CPT-11: 4 cycles
ARRY-575: QD for 3 days per cycle

Re-treatment initiated when average tumor volume ≈ 650 mm³

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initial Treatment</th>
<th>Re-growth Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Mean Tumor Regression</td>
<td>PR</td>
</tr>
<tr>
<td>CPT-11</td>
<td>5</td>
<td>1/8</td>
</tr>
<tr>
<td>CPT-11 + ARRY-575</td>
<td>79</td>
<td>8/8</td>
</tr>
</tbody>
</table>
ARRY-575 mono-therapy

ARRY-575 displays anti-tumor activity on intermittent dose schedules

Work is ongoing to understand the underlying determinant of sensitivity
ARRY-575: oral Chk1 inhibitor delivers superior efficacy

- Chk1 inhibition provides a mechanism to potentiate chemotherapy
  - Prolonged Chk1 inhibition maximizes efficacy and biomarker inhibition
  - Checkpoint override correlates with efficacy
  - Oral inhibitor allows for flexible and prolonged multi-day targeting of Chk1

- ARRAY-575 is highly potent, selective, orally bioavailable Chk1 inhibitor
  - Potentiates clinically important cytotoxics
  - Potentiates irinotecan in clinically relevant patient derived tumor models
  - Exhibits single-agent activity in select tumor models

- GLP safety studies complete

- IND slated for 3Q 2011
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