1. Astex Pharmaceuticals

2. Background & Profile
   1. Differentiation of ASTX660 from other IAP inhibitors
   2. Inhibition of XIAP, in addition to cIAP1/2
   3. Optimized dual inhibition, potency, and oral administration

3. ASTX660-01 Phase 1/2 Study
   1. Phase 1 experience
   2. Phase 2 cohorts

4. Opportunities for combination
   1. Chemotherapy
   2. Immunotherapy
   3. Radiotherapy
   4. Molecularly Targeted Agents
Astex Pharmaceuticals

Astex Pharmaceuticals, Inc.

Clinical Development based in Pleasanton, California, USA (Bay Area)
~ 120 employees and consultants:
• Clinical Development
• Clinical Operations
• Regulatory Affairs
• Quality Assurance
• Manufacturing / CMC

Astex Therapeutics, Ltd.

Drug Discovery based in Cambridge, UK
~ 120 employees and consultants
• Structural Biology & Biophysics
• Computational Chemistry & Informatics
• Medicinal Chemistry
• Biology & DMPK
• Translational Research and Development

• Dedicated to small molecule drug discovery and development in oncology, hematology & CNS
• Formed in 2011 by the merger of:
  • Astex Therapeutics Ltd: leader in fragment-based drug discovery: Cambridge, UK: multiple targeted cancer drugs in development
  • SuperGen, Inc.: California, US-based public company since 1996: developed Dacogen® approved for treatment of MDS in the US and AML in EU
  • Otsuka Acquired Astex Pharmaceuticals in 2013
Astex Pharmaceuticals

ASTX660

Background
ASTX660 is a potent, next generation small-molecule IAP antagonist

- Inhibitor of apoptosis proteins (IAPs) function to limit cell death by preventing apoptosis

- ASTX660 is a potent, next generation, small-molecule antagonist of IAPs, discovered by fragment-based drug discovery (FBDD)

- Chemically distinct from 1st generation peptidomimetic SMAC mimetics
  - Monomer, fragment derived, non-Alanine

- ASTX660 has a balanced inhibition across the family (cIAP1, cIAP2 and XIAP)

Presented at EORTC 2014. Abstract #380
IAP antagonism leads to a switch from pro-survival signaling to apoptosis

After Flygare & Fairbrother, 2010
ASTX660 is a balanced dual cIAP/XIAP antagonist

- ASTX660 demonstrates low nM XIAP inhibition and more balanced selectivity of cIAP1 over XIAP compared to 1st generation peptidomimetics

<table>
<thead>
<tr>
<th>in vitro Cell Assays</th>
<th>IC_{50} values in nM*</th>
<th>ASTX660</th>
<th>CU DC-427 (Curis)</th>
<th>LCL-161 (Novartis)</th>
<th>Debio-1143 (Debiopharm)</th>
<th>Birinapant (Tetralogic)</th>
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</thead>
<tbody>
<tr>
<td>cIAP1 (cellular activity)</td>
<td>MDA-MB-231 (cIAP1 degradation)</td>
<td>0.22</td>
<td>0.044</td>
<td>0.40</td>
<td>0.92</td>
<td>0.23</td>
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<tr>
<td>XIAP (cellular activity)</td>
<td>HEK293-XIAP-Caspase9 (binding assay)</td>
<td>2.8</td>
<td>10</td>
<td>35</td>
<td>34</td>
<td>23</td>
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<tr>
<td>Selectivity</td>
<td>cIAP1/XIAP</td>
<td>13</td>
<td>230</td>
<td>88</td>
<td>37</td>
<td>100</td>
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<tr>
<td>Proliferation</td>
<td>MDA-MB-231 (cIAP1 driven model)</td>
<td>1.8</td>
<td>3.0</td>
<td>7.8</td>
<td>18.0</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Administration Route

| Oral | Oral | Oral | Oral | Intravenous |

Presented at EORTC 2014. Abstract #380
ASTX660-01 Phase 1: Summary

1. **Enrollment in the Phase 1 is completed**
   - Dosed from 15 mg to 270 mg (fixed daily dose)
   - Maximum tolerated dose (MTD): 210 mg
   - Recommended Phase 2 dose (RP2D): 180 mg
   - Dose limiting toxicities (DLT): Asymptomatic grade 3 lipase with or without Grade 3 increased amylase elevation
   - Common adverse events included anemia, nausea, vomiting, rash, lipase and amylase elevation, ALT elevation, lymphopenia

2. **Target exposures achieved at the 180 mg RP2D**
   - PK becomes non-proportional at and above 210 mg

3. **Biological and preliminary clinical activity observed at 180 mg**
   - cIAP1 suppression in PBMC - deep and sustained
   - Clinical response seen in cutaneous T cell lymphoma

4. **Phase 2 is currently ongoing (USA, Europe)**

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2017, Abstract #A091
ASTX660-01 Phase 1: Dose Escalation Summary

- 45 patients received at least one dose of ASTX660
- DLTs were reported in 4 subjects (asymptomatic G3 lipase elevation with or without amylase elevation)
- Most DLTs resolved on dose interruption and rechallenge was successful at a lower dose
- One subject discontinued study treatment due to a study drug related AE (Grade 3 lipase elevation)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose (mg QD)</th>
<th>Form</th>
<th>N pts</th>
<th>DLTs</th>
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<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>Powder</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>In Bottle</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td></td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td></td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>180</td>
<td></td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>180</td>
<td>Capsule</td>
<td>6</td>
<td>3 (G3 lipase elevation)</td>
</tr>
<tr>
<td>7</td>
<td>270</td>
<td></td>
<td>6</td>
<td>1 (G3 lipase elevation)</td>
</tr>
<tr>
<td>8</td>
<td>210 MTD</td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Dose Expansion</td>
<td>180 RP2D</td>
<td></td>
<td>8</td>
<td></td>
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Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2017, Abstract #A091
# ASTX660-01 Phase 1: Adverse Events Regardless of Relationship in ≥10% Subjects

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>15 (33%)</td>
<td>0</td>
<td>15 (33%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (18%)</td>
<td>6 (13%)</td>
<td>14 (31%)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>8 (18%)</td>
<td>6 (13%)</td>
<td>14 (31%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (31%)</td>
<td>0</td>
<td>14 (31%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (29%)</td>
<td>0</td>
<td>13 (29%)</td>
</tr>
<tr>
<td>Lymphocyte count decreased/lymphopenia</td>
<td>5 (11%)</td>
<td>7 (16%)</td>
<td>12 (27%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10 (22%)</td>
<td>0</td>
<td>10 (22%)</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>9 (20%)</td>
<td>0</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>8 (18%)</td>
<td>0</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (16%)</td>
<td>1 (2%)</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>AST increased</td>
<td>7 (16%)</td>
<td>0</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>7 (16%)</td>
<td>0</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>7 (16%)</td>
<td>0</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>5 (11%)</td>
<td>1 (2%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (13%)</td>
<td>0</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5 (11%)</td>
<td>1 (2%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>3 (6.7%)</td>
<td>3 (6.7%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (11.1%)</td>
<td>0</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (8.9%)</td>
<td>1 (2.2%)</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>5 (11.1%)</td>
<td>0</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5 (11.1%)</td>
<td>0</td>
<td>5 (11.1%)</td>
</tr>
</tbody>
</table>

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2017, Abstract #A091
1. **180 mg** achieves **targeted therapeutic range exposures** (based on xenografts)

2. PK becomes non-proportional above 180 mg
   - Supraproportionally at higher exposures at 210 and 270 mg

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2017, Abstract #A091
➢ Rapid, sustained, dose-dependent decreases in PBMC cIAP-1 with 180mg

➢ Prolonged cIAP-1 degradation in cycle 2 with ≥180mg ASTX660

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2017, Abstract #A091
• One clinical response was observed at the 180 mg dose in a subject with folliculotropic mycosis fungoides
Phase 2 part of the study will explore the single-agent antitumor activity of ASTX660 in selected tumor types with molecular features that potentially may confer sensitivity to ASTX660

<table>
<thead>
<tr>
<th>#</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Head and neck squamous cell cancer (HNSCC)</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse Large B Cell Lymphoma (DLBCL)</td>
</tr>
<tr>
<td>3</td>
<td>Peripheral T Cell Lymphoma (PTCL)</td>
</tr>
<tr>
<td>4</td>
<td>Cutaneous T Cell Lymphoma (CTCL)</td>
</tr>
<tr>
<td>5</td>
<td>Feature that may confer sensitivity (Molecular)</td>
</tr>
<tr>
<td>6</td>
<td>Cervical carcinoma (Cervical)</td>
</tr>
</tbody>
</table>

Combination Opportunities
ASTX660 offers dual antagonism of cIAP and XIAP anti-apoptotic effects

**Extrinsic Apoptosis Pathway**
(FasL, TNF-α, TRAIL, Immunotherapy, chemotherapy)

**Intrinsic Apoptosis Pathway**
(chemotherapy, radiotherapy)

**Caspase activation**

**cIAP1, cIAP2**

**ASTX660**

**Active caspases**

**XIAP**

**Cytochrome C**

**APOPTOSIS**
Combinations of Paclitaxel and ASTX660 enhanced tumour growth inhibition in vivo in triple negative breast cancer (TNBC) models.

Presented at the AACR Annual Meeting 2016. Abstract #1287
Dual cIAP/XIAP antagonism may exhibit positive immuno-stimulatory activities

**Dendritic cell maturation and antigen presentation**
- IAP antagonist (LCL-161) promotes dendritic cell maturation (Knights 2012)
  - Increases population expressing DC markers
  - Increases marker density
  - Protects from apoptosis

**Direct effects on T cells**
- IAP antagonists (M1, LCL-161) enhance the stimulation of multiple immune effectors in vitro (Dougan 2010, Knights 2012)
  - Increased cytokine production in CD8+ T cells treated with IAP antagonist + stimuli such as anti-CD3/CD28
  - Similar observation for CD4+, splenocytes & lymph node and NK cells
  - Increases cytokine-producing CD8+ cells (similar data on CD4+)

**Dual cIAP/XIAP antagonism may be advantageous**
- High expression of XIAP renders tumour cells resistant to ADCC through inhibition of caspase and ROS suppression (Evans et al 2016)
- Defects in mitochondrial apoptotic pathways and elevated XIAP expression confer resistance to CTL-mediated killing (Kashkar et al, Blood 2006)
ASTX660 Combination with Anti-PD-L1 Therapy

- ASTX660 in combination with anti-PD-L1 induced tumor regression and enhances survival in vivo in CT26 syngeneic colorectal cancer model

*Astex in-house data presented at Tumor Immunology and Immunotherapy, 20-23 Oct 2016, Boston, USA
ASTX660 Combination with Radiotherapy and Anti-PD1

- ASTX660 combined with cisplatin and radiation induced tumor growth inhibition and enhanced survival in HPV- and HPV+ HNSCC models

- The greatest inhibition of syngeneic MOC-1 tumors was observed when ASTX660 was combined with both radiation and anti-PD-1 therapy

Carter VanWaes Group, presented at AACR 2017, Abstract #1086
ASTX660 potentiates trametinib (MEKi) activity *in vitro* and *in vivo*

- Cells treated with a combination of ASTX660 and trametinib show an increase in caspase activation over either single-agent treatment.

- ASTX660 and trametinib have moderate single-agent activity on HCC44 (KRAS mutant NSCLC) xenograft

- The combination of ASTX660 and trametinib caused regression and this persisted 1 week after treatment withdrawal

HDAC inhibitors can sensitise cancer cells to ASTX660 treatment

- Entinostat-induced FLIP downregulation sensitises CRC cells to ASTX660
- Entinostat and ASTX660 combination reduces CRC cell viability

Presented at the 2017 NCRI Cancer Conference, Liverpool UK, November 5 - 8 – K Stott et al
Thank you