Combination of HSP90 inhibitor onalespib (AT13387) with crizotinib to treat or delay resistance in NSCLC: Preclinical and Clinical Investigations.

Disclosures

• All authors are employees of Astex Pharmaceuticals, Inc. (Cambridge, UK, Pleasanton, CA, USA)

• Discussion of non-approved agents (onalespib)
Introduction/Rationale: Why target HSP90? Why haven’t previous approaches led to an approved drug yet?

- **HSP90 as a cancer target:**
  - Senses environmental stress and coordinates cellular responses to promote survival
  - Maintains protein homeostasis in normal cells
  - Maintains functionality/stability of mutated and/or over expressed oncogenes in cancer cells
    - ALK, MET, EGFR, HER-2, etc.
  - Inhibition of HSP90 simultaneously disrupts multiple signaling pathways

- **Clinical Approaches:**
  - Single agent relapsed/refractory
    - (RR in late setting ~15%)
  - Combinations at relapse (resensitize)
    - Chemotherapy
    - Targeted therapy
Resistance to Targeted Therapies (TKIs)

- Tyrosine kinase inhibitors used successfully to treat subsets of NSCLC
- BUT responses are of limited duration with the development of resistance mediated by multiple mechanisms

Hypothesis:

- Inhibiting HSP90 compromises cancer cell robustness and may impact resistance to other therapies

HSP90 in combination with TKI may:

- Delay the development of resistance to a TKI
- Overcome acquired resistance to TKIs regardless of mechanism
Discovery of Onalespib: A Potent HSP90 Inhibitor

Fragment

\[ K_d \text{ (ITC)} = 790 \mu M \]
\[ LE = 0.26 \]

Candidate (AT13387)

\[ K_d \text{ (ITC)} = 0.00071 \mu M \]
\[ LE = 0.42 \]

- Potency increase
- Modification of physical properties to improve efficacy
- Rational SAR to modify hERG activity

Murray et al J Med Chem 2010
Woodhead et al J Med Chem 2010
Onalespib Phase 1 Experience

- **Onalespib is well tolerated. MTD defined with:**
  - Twice weekly regimen: 120 mg/m\(^2\)/ Dose Days 1, 4 for 3 weeks
  - Once weekly regimen: 260 mg/m\(^2\)/dose for 3 weeks

- **Few patients had Gr 3 toxicities and no Gr 4 AEs reported.**
  - DLTs were mainly Gr 2 GI AEs (diarrhea, vomiting) and fatigue.
  - Visual disturbances were almost all Gr 1
    - All were transient and reversible, and not dose-limiting
    - On-target class effects of potent HSP90 inhibition with good tissue distribution

- **PK exposures were dose-dependent and linear**

- **HSP70 induction of 2-11 fold magnitude confirming PD evidence of target engagement**

- **Early evidence of activity with objective PR at 220 mg/m\(^2\) dose level**

(Shapiro, et al., Clinical Cancer Research 2015)
**AT13387 Overcomes Acquired Resistance in an ALK-Positive Crizotinib-Resistant Xenograft**

H2228 tumor xenografts treated with crizotinib

EML4-ALK NSCLC xenografts acquired resistance to crizotinib through different mechanisms

- AT13387 treatment inhibits the growth of an ALK-dependent tumour xenograft with acquired resistance to crizotinib (Wallis, et al, AACR 2014)
- Exome sequencing of resistant tumors revealed clinically relevant gene changes (Courtin, et al, ESMO 2014)
“Front-Line” combination of onalspib with crizotinib delays the development of resistance in an ALK-dependent xenograft

- Combination of AT13387 and crizotinib shows improved inhibition of tumor growth over monotherapies

- Combining crizotinib upfront with AT13387 delays the emergence of resistance in vivo (Wallis, et al, WLC 2013)
Safety lead in dose escalation for the combination:

- **AT13387**: 150, 180, and 220 mg/m²;  
- **Crizotinib**: 250 mg PO twice daily 

Dose of 220 mg/m² AT13387 selected for Phase 2 combination with crizotinib.

**Part A**  
ALK+ NSCLC under treatment for 8 weeks

**Objectives:**  
- Safety 
- PK/PD 
- Activity

**Part B**
Any response

- Continue crizotinib
- Crizotinib + AT13387

N = 128 subjects

**Part C**
PD

- AT13387
- AT13387 + crizotinib

N = 35-70 subjects
## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dosing Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150 mg/m² (n=8)</td>
</tr>
<tr>
<td>Age (yrs) mean (range)</td>
<td>52 (32-64)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>4/4 (50/50%)</td>
</tr>
<tr>
<td>Histology (Adenocarcinoma/Other)</td>
<td>7/1</td>
</tr>
<tr>
<td>Prior ALK inhibitor</td>
<td>Crizotinib</td>
</tr>
<tr>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Ceritinib</td>
</tr>
<tr>
<td></td>
<td>Alectinib</td>
</tr>
</tbody>
</table>

(Besse, et al, ESMO 2014)
### Adverse Events Grade 3 or higher related to onalespib + CZT treatment

<table>
<thead>
<tr>
<th>Cohort (AT13387 dose level, CZT at 250 mg BID)</th>
<th>150 MG (N=8)</th>
<th>180 MG (N=9)</th>
<th>220 MG (N=15)</th>
<th>Total (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>1 (11%)</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>3 (33%)</td>
<td>3 (20%)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>1 (7%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (13%)</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>0</td>
<td>0</td>
<td>1 (7%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>0</td>
<td>0</td>
<td>1 (7%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>1 (11%)</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>0</td>
<td>0</td>
<td>1 (7%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>0</td>
<td>1 (11%)</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>1 (11%)</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1 (13%)</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>0</td>
<td>1 (7%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Note: one event at the 180 mg/m2 dose level was uncoded and is omitted from this table (Besse, et al, ESMO 2014)
**Pharmacokinetics of Crizotinib with and without onalespib**

<table>
<thead>
<tr>
<th>Day</th>
<th>AUC$_{0-8}$ (ng·hr/mL)</th>
<th>C$_{max}$ (ng/mL)</th>
<th>T$_{max}$ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening (n=31)</td>
<td>2905 (1056)</td>
<td>421 (143)</td>
<td>3.8 (2.1)</td>
</tr>
<tr>
<td>Day 1 (n=30)</td>
<td>2966 (1188)</td>
<td>427 (164)</td>
<td>4.0 (1.9)</td>
</tr>
</tbody>
</table>

**Pharmacokinetics of onalespib combined with Crizotinib**

<table>
<thead>
<tr>
<th>Dose (mg/m$^2$)</th>
<th>AUC$_{0-last}$ (ng·hr/mL)</th>
<th>C$_{max}$ (ng/mL)</th>
<th>T$_{max}$ (hr)</th>
<th>T$_{1/2}$ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 (N=8)</td>
<td>2297 (368)</td>
<td>930.5 (335.8)</td>
<td>0.6 (0.2)</td>
<td>8.6 (1.3)</td>
</tr>
<tr>
<td>180 (N=8)</td>
<td>2923 (846)</td>
<td>1053 (740)</td>
<td>0.8 (0.3)</td>
<td>7.9 (1.3)</td>
</tr>
<tr>
<td>220 (N=14)</td>
<td>3585 (919)</td>
<td>1164.0 (742)</td>
<td>0.8 (0.2)</td>
<td>7.9 (1.5)</td>
</tr>
</tbody>
</table>

Data are presented as mean (±SD) (Besse, et al, ESMO 2014)
Clinical Activity

Trend toward increased activity with higher onalespib dose:
- onalespib at 150 mg/m²
  - (0 PR, 2/5 with tumor reduction)
- onalespib at 180 mg/m²
  - (1 PR, 4/6 with tumor reduction)
- onalespib at 220 mg/m²
  - (3 PR, 9/11 with tumor reduction)

Cohort (Onalespib Dose level)

<table>
<thead>
<tr>
<th>Cohort (Onalespib Dose level)</th>
<th>150 mg/m² (n=8)</th>
<th>180 mg/m² (n=9)</th>
<th>220 mg/m² (n=15)</th>
<th>Total (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessable (n)</td>
<td>5</td>
<td>8</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>CR/PR (n, %)</td>
<td>0 (0%)</td>
<td>1 (12.5%)</td>
<td>3 (25%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>SD (n,%</td>
<td>5 (100%)</td>
<td>4 (50%)</td>
<td>5 (41.7%)</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>PD (n,%</td>
<td>0 (0%)</td>
<td>3 (37.5%)</td>
<td>4 (33.3%)</td>
<td>7 (28%)</td>
</tr>
</tbody>
</table>

(Besse, et al, ESMO 2014)
Waterfall Plot of Subjects with measurable disease and at least 1 follow up scan

Onalespib dose
- 150 mg/m²
- 180 mg/m²
- 220 mg/m²

* Indicates subject still receiving treatment on study

(Besse, et al, 2014)
• Preclinical data demonstrate early combination (crizotinib + onalespib) delays regrowth of ALK-driven tumors
  – Alterations seen in progressing tumors reflect those seen clinically

• Onalespib is well tolerated at a dose up to 220 mg/m2 given weekly 3 of 4 weeks in combination with full dose CZT

• Administration of the agents in combination does not appear to change the pharmacokinetics of either agent

• Encouraging activity has been seen in the dose-escalation part of the study
  – 4 Objective PR by RECIST
  – More antitumor activity at higher dose
  – Over 50% patients with decrease in tumor size

• Arms B (prior to progression on CZT) and C (following progression on CZT are open and enrolling)
• **Patients and their families**

• Multiple sites, Investigators, coordinators, and staff:
  • B. Besse
  • E. Bertino
  • N.A. Pennell,
  • A. Wozniak
  • D. Mahadevan,
  • A. Spira,
  • J.-C. Soria
  • D.R. Camidge

• Astex personnel in Cambridge, UK, and Pleasanton, CA