Potent and selective AXL tyrosine kinase inhibition demonstrates significant anti-tumor efficacy in combination with standard of care therapeutics in preclinical models


Arcus Biosciences, Hayward, CA
Susan L. Paprcka

I have the following financial relationships to disclose:

Stockholder in: Arcus Biosciences (RCUS)

Employee of: Arcus Biosciences

I will not discuss off label use and/or investigational use in my presentation.
High AXL Expression Is Associated With Resistance to TKI Therapy

- Increased pro-tumorigenic signaling
- Decreased immune cell engagement & activation

• High AXL expression is correlated with lack of clinical response to Sorafenib
• High AXL expression is correlated with resistance to EGFR TKI’s in vitro

Dataset: GSE33072 BATTLE trial
Dataset: GSE38310
Dataset: GSE106765
Novel Arcus AXL Inhibitors Are Potent & Highly Selective

Characterization & Comparison of Novel Arcus & Benchmark AXL Inhibitors

<table>
<thead>
<tr>
<th>Assay</th>
<th>Compound A</th>
<th>Compound D</th>
<th>Bemcentinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>hAXL HTRF IC₅₀ (biochemical, nM)</td>
<td>2.8</td>
<td>3.0</td>
<td>5.2</td>
</tr>
<tr>
<td>mAXL HTRF IC₅₀ (biochemical, nM)</td>
<td>0.95</td>
<td>1.4</td>
<td>2.7</td>
</tr>
<tr>
<td>hMERTK / hTYRO3 HTRF selectivity</td>
<td>130x / 39x</td>
<td>64x / 22x</td>
<td>42x / 33x</td>
</tr>
<tr>
<td>(biochemical, enzyme IC₅₀ over AXL IC₅₀)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hAXL NanoBRETT™ Kᵦ (cellular, nM)</td>
<td>13</td>
<td>6.8</td>
<td>135</td>
</tr>
<tr>
<td>hERG (% inhibition at 10uM)</td>
<td>85</td>
<td>35</td>
<td>96</td>
</tr>
</tbody>
</table>

1 Kinase activity of AXL, MERTK and TYRO3 were tested using HTRF KinEASE – TK kit (CisBio) in the presence of 700 µM ATP. Inhibitor engagement to intracellularly expressed AXL kinase domain was detected using AXL NanoBRETT™ TK intracellular kinase assay (Promega) with transiently transfected HEK293 cells.

2 Data generated by Arcus. Compound purchased from Synnovator.
Compounds A & D Inhibit pAXL Under Physiological (High Serum) Conditions

Concentration-Dependent Inhibition of AXL Phosphorylation Is Observed In Both Media & Human Serum

H1299 cells were incubated with AXL inhibitors for 1hr followed by stimulation with Gas6 for 15min

Panc1 cells were treated with AXL inhibitors for 1hr followed by addition of Gas6. AXL MFI and percentage was evaluated by flow cytometry and supernatant was used to determine soluble AXL levels by ELISA after 72hrs
Combined AXL & TKI Inhibition Results in Significant Tumor Control

Compound A Increases Circulating Soluble AXL Levels Indicative of Target Engagement

Mouse Plasma Soluble AXL

Compound A Significantly Reduces Tumor Growth In Combination With TKI Inhibitors

786-O

Vehicle
Sunitinib
Axitinib
Compound A
Compound A + Sunitinib
Compound A + Axitinib
Dose Start

Vehicle
Osimertinib
Compound A
Compound A + Osi

Compound A: 100mg/kg BID
Sunitinib: 40mg/kg QD
Axitinib: 40mg/kg BID

PC-9

Vehicle
Osimertinib
Compound A
Compound A + Osi

Compound A: 100mg/kg BID
Osimertinib ("Osi"): 5mg/kg QD

All compounds given orally (PO) either twice-daily (BID) or once daily (QD)

AXL Is Highly Expressed In Tumor Cell Lines Used in Xenograft Studies

AXL

786-O

PC-9

AXL

AXL

AXL

AXL

AXL

AXL

AXL

AXL
**Significant Efficacy Is Observed With AXL Inhibition In Combination with Osimertinib Initially & Post Relapse**

- **PC-9**

![Graph showing tumor volume over time for different treatments](image)

- **Osimertinib (5mg/kg)**
- **Compound A + Osi (5mg/kg)**
- **Osi (2.5mg/kg)**
- **Compound A + Osi (2.5mg/kg)**
- **Compound A + Osi (2.5mg/kg)**
- **Post Osi Relapse**

- **Tumors collected at end of study (day 56)**
- **Significant reduction in viable tumor content with Compound A + 5mg/kg Osi vs. 5mg/kg Osi alone**

- **No significant differences in tumor size with Compound A treated with 2.5mg/kg Osi initially vs. post-relapse**

**Compound A: 100mg/kg BID**

**Osimertinib ("Osi"): 5 or 2.5mg/kg QD**
Summary & Conclusions

- Novel potent (single-digit nanomolar potency) and selective inhibitors of AXL tyrosine kinase activity have been identified.
- Arcus AXL inhibitors reduce both ligand-dependent and ligand-independent AXL activation/phosphorylation.
- Significant anti-tumor activity is observed with specific AXL inhibitors in combination with targeted therapy and upon acquired resistance to TKI in xenograft models.
- Selective AXL inhibition is a promising approach to overcome therapeutic resistance of tumors.