LXS196, a novel PKC inhibitor for the treatment of uveal melanoma

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Babraham Research Campus, Cambridge, UK
May 14th 2018
Most common intraocular malignant tumor
- Estimated 2000 newly diagnosed patients in the USA per year
- Primary tumor treated by radio plaque therapy or surgical removal of the eye

Metastatic Uveal Melanoma (~50% patients)
- >90% metastases found in the liver
- No approved therapy, median survival <12 months

Characterized by GNAQ/11 activating mutations leading to constitutive signaling through Protein Kinase C (PKC)
The PKC Family

- 12 isoforms, not including splice variants
- 3 sub families: Classical, Novel, and Atypical differentiated by regulatory domains
Protein Kinase C Project

From Autoimmunity to Oncology

Autoimmunity and Transplantation

- AEB071 is a pan-PKC inhibitor designed to modulate T-cell activation
- Targeted indications
  - Graft v. host disease
  - Psoriasis
- Demonstrated efficacy in phase 2 clinical trials

Oncology

- Targeted Indications
  - Metastatic Uveal Melanoma harboring an activating mutation in GNAQ/11

Boris Bastian, AACR 2011
AEB071 is clinically active in uveal melanoma

Clinical potential may be limited:

- Responses generally limited to stable disease
- Dose escalation did not lead to a proportional increase in exposure
- Higher doses associated with increased frequency of dose limiting GI toxicities

Goal:

- Design a compound optimized for a uveal melanoma indication with improved selectivity and pharmaceutical properties
Aminopyrazines as an alternative lead scaffold

\[
\begin{align*}
\text{hinge} & = \begin{array}{c}
\text{H} & \text{N} & \text{H} & \text{O} & \text{N} & \text{H} & \text{N} & \text{OCF}_3 & \text{NH}_2 \\
\text{N} & \text{N} & \text{N} & \text{H} & \text{N} & \text{N} & \text{O} & \text{Me} & \text{N}
\end{array} \\
\alpha \text{ IC}_{50} & = 0.2 \text{ nM} \\
\theta \text{ IC}_{50} & = 2 \text{ nM} \\
92.1 \text{ AC}_{50} & = 140 \text{ nM}
\end{align*}
\]

Cmpd 1 crystal structure with PKC\(\alpha\) (2.48 Å)
Cmpd 1 affords equivalent efficacy to AEB071 at a lower dose.

\[ \alpha IC_{50} = 0.2 \text{ nM} \]
\[ \theta IC_{50} = 2 \text{ nM} \]
\[ 92.1 AC_{50} = 140 \text{ nM} \]
Is GI irritation mediated by PKC inhibition?

<table>
<thead>
<tr>
<th>Compound</th>
<th>DOSE (8d QD)</th>
<th>Route</th>
<th>Exposure (µM.h)</th>
<th>Observed GI irritation</th>
<th>Histopathology results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>50 mg/kg</td>
<td>PO</td>
<td>8</td>
<td>++</td>
<td>Stomach ulceration</td>
</tr>
<tr>
<td>2</td>
<td>10 mg/kg</td>
<td>SC</td>
<td>20</td>
<td>negative</td>
<td>negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>DOSE (8d QD)</th>
<th>Route</th>
<th>92.1 IC_{50} (µM)</th>
<th>Observed GI irritation</th>
<th>Histopathology results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120mg/kg</td>
<td>PO</td>
<td>0.14</td>
<td>++++</td>
<td>Stomach ulceration</td>
</tr>
<tr>
<td>AEB071</td>
<td>240 mg/kg</td>
<td>PO</td>
<td>0.25</td>
<td>mild</td>
<td>negative</td>
</tr>
</tbody>
</table>

GI irritation is locally mediated

GI irritation is not linked to PKC inhibition
Can selectivity be improved while retaining anti-proliferative activity?

\[
\text{Cmpd 1 crystal structure with PKC}\alpha (2.48 \text{ Å})
\]

\[
\begin{align*}
\alpha \text{ IC}_{50} &= 0.2 \text{ nM} \\
\theta \text{ IC}_{50} &= 2 \text{ nM} \\
92.1 \text{ AC}_{50} &= 140 \text{ nM}
\end{align*}
\]
Moving away from the 4-amino pyridine improves selectivity

<table>
<thead>
<tr>
<th>Compound</th>
<th>PKC IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>92.1 (nM)</th>
<th>FLT3 (nM)</th>
<th>GSK3β (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>α</td>
<td>θ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&lt;0.1</td>
<td>0.6</td>
<td>34</td>
<td>230</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
<td>1.3</td>
<td>230</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>69</td>
<td>3680</td>
<td>3000</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
<td>2</td>
<td>180</td>
<td>8460</td>
</tr>
</tbody>
</table>
Improved kinase selectivity of Cmpd 6

Percent Control
- 0%
- 0.1%
- 0.1-1%
- 1-5%
- 5-10%
- 10-35%
- > 35%

Cmpd 6 @ 1 μM

PKC

Cmpd 1 @ 1 μM
Moving away from the 4-amino pyridine improves tolerability

\[
\begin{align*}
\alpha \text{IC}_{50} &= 0.2 \text{ nM} \\
\theta \text{IC}_{50} &= 2 \text{ nM} \\
92.1 \text{AC}_{50} &= 140 \text{ nM}
\end{align*}
\]

3-Pyridyl series

\[
\begin{align*}
\alpha \text{IC}_{50} &= 0.3 \text{ nM} \\
\theta \text{IC}_{50} &= 2 \text{ nM} \\
92.1 \text{AC}_{50} &= 180 \text{ nM}
\end{align*}
\]
Is there a potential for off-target toxicity?

Cmpd 6 has potent 5-HT$_{2B}$ agonist activity

- Cmpd 6 has an improved profile to limit potential for off-target toxicity
- 5-HT$_{2B}$ agonist activity strongly implicated in valvular heart disease
Modifications to mitigate $5\text{HT}_{2B}$ agonism

Substitution of the piperidine ring should mitigate $5\text{-HT}_{2B}$ activity

5-\(\text{HT}_{2B}\) crystal structure with ergotamine

Overlay of ergotamine X-ray structure and cmpd 6 model

Docking model of cmpd 6 in 5-\(\text{HT}_{2B}\) structure

Stevens, R. C. Science, 2013, 615
Substitution of the piperidine ring does mitigate 5-HT$_{2B}$ activity.
Addition of a geminal methyl removes 5-HT_{2B} agonist activity

\[ \alpha IC_{50} = 0.2 \text{nM} \]
\[ \theta IC_{50} = 2 \text{nM} \]
\[ 92.1 AC_{50} = 140 \text{nM} \]

3-Pyridyl series

\[ \alpha IC_{50} = 0.3 \text{nM} \]
\[ \theta IC_{50} = 2 \text{nM} \]
\[ 92.1 AC_{50} = 180 \text{nM} \]
\[ 5-HT_{2B} = 0.2 \mu\text{M} \]
LXS196 maintains improved efficacy over AEB071

- Regression achieved with LXS196 at multiple doses, in contrast to AEB071 where maximum efficacy at MTD is stasis.
Can we predict human clearance?

Dose dependent exposure across species and good ivivc

<table>
<thead>
<tr>
<th>Activity</th>
<th>Mouse</th>
<th>Rat</th>
<th>Dog</th>
<th>Monkey</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatocyte clearance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CL_{int}$ (mL/min/kg)</td>
<td>33</td>
<td>22</td>
<td>8.4</td>
<td>16</td>
<td>6.9</td>
</tr>
<tr>
<td><strong>In vivo clearance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mL/min/kg)</td>
<td>26</td>
<td>17</td>
<td>5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Plasma protein binding</strong></td>
<td>92.5%</td>
<td>85.4%</td>
<td>90.4%</td>
<td>83.5%</td>
<td>70.6%</td>
</tr>
</tbody>
</table>
Human Pharmacokinetics

LXS196 total plasma concentration profiles on Cycle 1 Day 1 and Day 15 following multiple oral doses of 100 to 1000 mg QD and 200 to 400 mg BID

- Moderate PK variability for $C_{\text{max}}$ and $AUC_{\tau}$
- Rapid absorption ($T_{\text{max}} \sim 1$ hr post dose)
- Consistent terminal half-life across different doses (8 - 13 hr, median $\sim 11$ hr)
- No or minimal accumulation with repeated administration
Preliminary clinical activity and safety

- As of the data cut-off date (15-Aug-2017), 55 patients had completed at least 1 post-baseline assessment
- Of these, 5 patients achieved partial responses (PR)
- A further 38 patients have achieved stable disease (SD)
- The most common LXS196 related AEs (all grades, all doses) were nausea (57%), diarrhea (35%), vomiting (25%) and hypotension (22%)
- GI toxicities are generally low grade (Grade 1 or 2) and manageable
Preliminary Clinical Activity – QD schedule

Data cut-off date 15 Aug 2017

SD, stable disease; PD, progressive disease; PR, confirmed partial response; QD, once daily;
Preliminary Clinical Activity – BID schedule

# Prior anti-PD-1 and/or anti-CTLA-4 treated patients
* Patients ongoing as of the data cut-off date

Data cut-off date 15 Aug 2017

SD, stable disease; PR, confirmed partial response; PD, progressive disease; uPR, unconfirmed partial response;
History of primary uveal melanoma resected 2009

Developed metastatic disease involving liver, lung, adrenal and bone Apr-2016

Progressive disease after treatment with Pembrolizumab (May to Jun-2016)

Commenced 300 mg QD LXS196 (Jul-2016)

PR (-41% reduction) after 2 cycles, subsequently confirmed after 4 cycles

Confirmed PR in a 72 y/o male patient with metastatic uveal melanoma on LXS196
We have optimized the aminopyrazine series to afford a selective inhibitor of Protein Kinase C

- Improved selectivity afforded increased tolerability in preclinical species
- Full regression of tumors achieved in mouse xenograft studies
- SBDD leveraged to rapidly move away from unwanted 5-HT\textsubscript{2B} agonist activity
- Dose dependent exposure observed across multiple preclinical species

LXS196 has been advanced to the clinic for the treatment of metastatic uveal melanoma (NCT02601378)
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