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Background

MEK 1/2 kinases are central proteins in the mitogen-activated protein kinase (MAPK) pathway. Abnormal activation of this pathway results in the formation and progression of tumors, fibrosis, and other diseases. MEK inhibitors block phosphorylation (activation) of extracellular signal-regulated kinases ("ERK"), which can lead to cell death and inhibition of tumor growth. MEK inhibitors have been approved to treat several BRAF-driven solid tumors as well as plexiform neurofibromas associated with neurofibromatosis (NF1) in pediatric patients.

PAS-004 is the first macrocyclic MEKi and consistent with macrocycle attributes that lead to long circulation half-life and potent inhibition of MEK 1/2 autophosphorylation (activation). PAS-004 exhibits a similar mechanism of action. PAS-004 was compared with the approved MEKis selumetinib and binimetinib (2.5, 5, 10 mg/kg) dosed twice daily (BID). Tumor volumes were measured daily until mice were euthanized when the average tumor volume reached ≥2000 mm3. Body weight loss was assessed daily and tumor-bearing mice were monitored twice daily.

Results

In Vitro Cell Growth Assays

• PAS-004 inhibits the growth of NRAS mutant cell lines.

In Vivo Xenograft Studies

• PAS-004 has more potent anti-tumor activity than selumetinib and binimetinib in NRAS mutant tumor xenografts (QD vs. BID).

Table 1. PAS-004 inhibition of NRAS mutant cancer cell lines

<table>
<thead>
<tr>
<th>Compound</th>
<th>RelC (μM)</th>
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</thead>
<tbody>
<tr>
<td>Selumetinib</td>
<td>0.044</td>
</tr>
<tr>
<td>Binimetinib</td>
<td>0.003</td>
</tr>
<tr>
<td>AZD6244</td>
<td>0.306</td>
</tr>
<tr>
<td>PAS-004</td>
<td>0.082</td>
</tr>
<tr>
<td>Trametinib</td>
<td>0.055</td>
</tr>
</tbody>
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• PAS-004 exhibit a dose-dependent anti-tumor efficacy in the liver cancer xHepG2 and the lung cancer NCI-H1299 cell-line xenograft model.

• PAS-004 inhibition of in vivo NRAS mutant cancer cell lines is greater than selumetinib and binimetinib in NSCLC cell line tested and is comparable to trametinib.

• PAS-004 activity in NRAS mutant lines does not plateau at highest levels tested.

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Conclusions & Future Directions

• PAS-004 has similar maximal tumor reduction as selumetinib and binimetinib when administered once daily vs twice daily (QD vs. BID).

• PAS-004 did not result in any body weight loss.

• PAS-004 exhibit a dose-dependent anti-tumor efficacy in the liver cancer xHepG2 and the lung cancer NCI-H1299 cell-line xenograft model.

• PAS-004 inhibition of in vivo NRAS mutant cancer cell lines is greater than selumetinib and binimetinib in NSCLC cell line tested and is comparable to trametinib.

• PAS-004 activity in NRAS mutant lines does not plateau at highest levels tested versus other MEK inhibitors tested.

• PAS-004 has superior activity versus selumetinib and binimetinib in NSCLC xenograft studies and similar to that of binimetinib and superior to that of selumetinib in hepatocellular xenograft cancer model.

• In the NSCLC xenograft study, PAS-004 exhibit a dose-dependent tumor pERK suppression, reaching up to 75% at the highest dose tested.

• PAS-004 is a potential new treatment option with a more convenient dosing regimen for patients with advanced cancer and patients with NF-1.