BACKGROUND

- Overexpression of somatostatin receptors (SSTRs), primarily SSTR2, occurs in gastroenteropancreatic neuroendocrine tumors (GEP-NETs), and subsets of other solid tumors such as small cell lung cancer (SCLC).
- SCLC accounts for approximately 15% of lung cancers and lacks effective therapeutic options.
- Immunohistochemistry indicates that SSTR2 is overexpressed in up to 50% of SCLC, with a substantial subset showing high and homogenous expression.
- Small-molecule somatostatin analogs, such as octreotide and lanreotide, are associated with significant anti-tumor activity.
- Somatostatin receptor-2 (SSTR2) is an attractive target for future cancer therapeutics.

METHODS

- Antibodies: anti-SSTR2 monoclonal antibody.
- H-scores: Immunohistochemistry (IHC) studies to assess the cell surface expression of SSTR2 were conducted using two human lung cancer tissue microarrays (TMAs; LC2083 and LC802c).

RESULTS

- Immunohistochemistry (IHC) studies to assess the cell surface expression of SSTR2 were conducted using two human lung cancer tissue microarrays (TMAs; LC2083 and LC802c) and xenografts.
- Staining intensity was assessed using a semi-quantitative method.
- H-scores were generated for each tissue sample.

TABLE 1. Binding affinity of Rayz-1001-La to human SSTR1 to 5

<table>
<thead>
<tr>
<th>Peptide</th>
<th>SSTR1</th>
<th>SSTR2</th>
<th>SSTR3</th>
<th>SSTR4</th>
<th>SSTR5</th>
</tr>
</thead>
<tbody>
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<td>Rayz-1001-La</td>
<td>0.001</td>
<td>0.002</td>
<td>0.003</td>
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</tbody>
</table>

- Anti-tumor activity of Rayz101 (Ac-225 DOTATATE) in somatostatin receptor-expressing preclinical models of small-cell lung cancer

- BACKGROUND

- RYZ101 (Ac-225 DOTATATE) is an α-emitting radiopharmaceutical comprised of the α-emitter 225Ac and the radiolabeled somatostatin analog DOTATATE.
- It is targeted to SSTR2, which is highly expressed in SCLC.
- The goal of this study was to provide preclinical support for the use of RYZ101 in SSTR2-positive SCLC.

- MATERIALS AND METHODS

- RYZ101: A preclinical study to evaluate the safety, efficacy, and pharmacokinetics of RYZ101 in SSTR2-positive SCLC.
- Animals: BALB/c mice aged 6–8 weeks received IV RYZ101 (1 uCi, 0.037 MBq, targeted 5 Ci/mmol).
- Biodistribution analysis of RYZ101 showed:
  - RAYZ-10001-La showed efficient internalization in SSTR2+ cells (RC 50 <0.5 nM vs positive control, mean 1.8 nM).
  - RAYZ-10001-La (La-DOTATATE) had a high binding affinity (Ki 0.057 nM) to human SSTR2 with a substantial subset showing high and homogenous expression.
  - After RYZ101 administration, animals were sacrificed and selected tissues harvested at 1, 4, 15, 24, and 48 h post-injection (h3 per timepoint per sample).

- RESULTS

- Immunohistochemistry (IHC) studies to assess the cell surface expression of SSTR2 were conducted using two human lung cancer tissue microarrays (TMAs; LC2083 and LC802c) and xenografts.
- Staining intensity was assessed using a semi-quantitative method.
- H-scores were generated for each tissue sample.

- CONCLUSIONS

- RYZ101 demonstrated significant anti-tumor activity compared with SOC in the NCI-H727 model.
- RYZ101 showed superior anti-tumor efficacy compared with SOC chemotherapy, and RYZ101 in combination with SOC was superior to SOC alone in an SSTR2+ SCLC model.
- Collectively, these data strongly suggest potential for anti-tumor activity with RYZ101 in patients with SSTR2+ SCLC.

- **ACKNOWLEDGEMENTS**

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