Comparative Biodistribution and Radiotherapeutic Efficacy of the Fibroblast Activation Protein (FAP)–Targeting Agents FAP-2286 and FAPI-46

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Introduction

- Fibroblast activation protein (FAP) is a membrane-bound protease under investigation as a pan-cancer target given its limited expression in normal adult tissues but high expression on cancer-associated fibroblasts\(^1\)

- FAP-targeting agents, FAP-2286 and FAPI-46, have shown great promise as positron emission tomography (PET) imaging agents when chelated to Gallium-68

- The goals of these studies were to evaluate the biodistribution of FAP-2286 and FAPI-46, when chelated to the beta emitter Lutetium-177, and to correlate these results with the efficacy observed in the HEK-FAP mouse tumor model

\(^1\)Pure et al. *Oncogene*. 2018;37:4343-57
SPECT/CT imaging showed longer HEK-FAP tumor retention of \(^{177}\text{Lu}\)-FAP-2286 compared with \(^{177}\text{Lu}\)-FAPI-46, resulting in more than 8-fold higher absorbed dose delivered to the tumors.
Tumor Efficacy in HEK-FAP Mice

Tumor Growth

Survival

177Lu-FAP-2286 demonstrated greater HEK-FAP tumor growth inhibition compared with 177Lu-FAPI-46

<table>
<thead>
<tr>
<th>Compound</th>
<th>MTV ± SEM (mm³, day 0)</th>
<th>MTV ± SEM (mm³, P value, day 9)</th>
<th>MTV ± SEM (mm³, day 23)</th>
<th>TGI (%) (day 9)</th>
<th>MST (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>169 ± 21</td>
<td>952 ± 195 (P=0.0001)</td>
<td>NA</td>
<td>NA</td>
<td>16.5</td>
</tr>
<tr>
<td>177Lu-FAP-2286</td>
<td>169 ± 23</td>
<td>107 ± 15 (P&lt;0.0001)</td>
<td>12 ± 4</td>
<td>108</td>
<td>undefined</td>
</tr>
<tr>
<td>177Lu-FAPI-46</td>
<td>168 ± 22</td>
<td>245 ± 76 (P=0.0006)</td>
<td>1210 ± 185 (P&lt;0.0001)</td>
<td>90</td>
<td>27.5</td>
</tr>
</tbody>
</table>

MST, median survival time; MTV, mean tumor volume; TGI, tumor growth inhibition

*P value was determined for day 9 comparisons to the vehicle group (n=10 for all groups), while day 23 comparison was between 177Lu-FAP-2286 (n=10) and 177Lu-FAPI-46 (n=9).
Live cell fluorescence microscopy with AlexaFluor488-labeled compounds showed longer intracellular retention for FAP-2286 compared to FAPI-46.

- Similar extracellular binding to HEK-FAP cells
- Blocking with unlabeled competitor showed specific binding
177Lu-FAP-2286 showed longer tumor retention, resulting in greater tumor growth inhibition as compared to 177Lu-FAPI-46

The prolonged tumor retention of FAP-2286 correlated with a higher intracellular accumulation

The phase 1/2 LuMIERE clinical trial (NCT04939610) is evaluating FAP-2286 as a therapeutic (177Lu-FAP-2286) and imaging (68Ga-FAP-2286) agent in multiple FAP-expressing tumor types

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