Superior Efficacy of Novel Albumin-binding Auristatin E-based Drugs Compared to Auristatin E in a Panel of Human Xenograft Models in Mice


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Abstract # 3703

INTRODUCTION & RATIONALE:

Albumin-based Drug Delivery Concept

- Rapid binding to Cys34 residue of serum albumin
- Preferential, acid-promoted drug release in the target tissue
- Acidity-sensitive hydrazone moiety promotes the release of the active drug at the tumor site.

RESULTS:

- pH- and plasma-stability of the two albumin drug conjugates
  - AE-Keto-Sulf07
    - Free drug released
      - pH 7.4: 4 h
      - pH 4.1: 5
    - Murine Plasma (CD1)
      - < 0.1
    - Human Plasma (pooled)
      - < 0.1
  - AE-Ester-Sulf07
    - Free drug released
      - pH 7.4: 20 h
      - pH 4.1: 5
    - Murine Plasma (CD1)
      - 1.0
    - Human Plasma (pooled)
      - 1.0


- Plasma-stability: AE-Keto-Sulf07 as well as its release product, AE-Keto, are stable in both murine and human plasma. For AE-Ester-Sulf07, a higher release is observed. In murine plasma, the released AE-Ester is rapidly converted to Auristatin E, while in human plasma the conversion to AE is significantly slower.

CONCLUSIONS:

- Efficacy: Both AE-Keto-Sulf07 and AE-Ester-Sulf07 demonstrated excellent antitumor activity in all selected human tumor xenograft models.
  - The albumin-binding drugs induced long-term partial and complete tumor regressions, even in models with large starting tumor volumes (270-380 mm³).
  - The albumin-binding drugs showed statistically significant superior activity compared to the parent drug auristatin E in 8 of the 9 models tested.

- Toxicity: AE-Keto-Sulf07 induced average body weight change of ~6% at the end of the studies.
  - AE-Ester-Sulf07 induced body weight loss only in the NSCLC models (> 15%). However, nude mice related skin lesions due to scratching and biting were consistently observed.

Antitumor activity of both albumin-binding drugs in further human xenograft models in nude mice

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Starting tumor volume (mm³)</th>
<th>Dose in AE equiv. (mg/kg)</th>
<th>Efficacy (end of study)</th>
<th>No. of mics per group</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 375 melanoma</td>
<td>130</td>
<td>3.0</td>
<td>5 CR 2 PR</td>
<td>0 7</td>
</tr>
<tr>
<td>MDA-MB 435 melanoma</td>
<td>90</td>
<td>4.0</td>
<td>6 CR 1 PD</td>
<td>0 7</td>
</tr>
<tr>
<td>A 2780 ovarian</td>
<td>140</td>
<td>3.0</td>
<td>2 CR 3 PR 1 T</td>
<td>1 7</td>
</tr>
<tr>
<td>LXFA 737 NSCLC</td>
<td>140</td>
<td>4.5</td>
<td>7 CR</td>
<td>0 7</td>
</tr>
<tr>
<td>LXFE 937 NSCLC</td>
<td>270</td>
<td>4.5</td>
<td>8 CR</td>
<td>0 8</td>
</tr>
</tbody>
</table>

- AE-Keto-Sulf07
  - A 2780 ovarian: 170
  - LXFA 737 NSCLC: 130
  - LXFE 937 NSCLC: 270

- AE-Ester-Sulf07
  - A 2780 ovarian: 170
  - LXFA 737 NSCLC: 130
  - LXFE 937 NSCLC: 270

Values for % free drug released were calculated with Mann-Whitney U-test. Data for toxicity was calculated with Kruskal-Wallis test followed by Dunn’s method. SDs are given in the table.