Evaluation of dosing of E7820 in humans from preclinical and clinical data using a biomarker

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Introduction

E7820:
• novel, oral anti-cancer agent
• inhibits angiogenesis by inhibition of mRNA expression of α2-integrin[3]
• has shown to inhibit tumor growth in preclinical experiments[2] and is now being tested in phase I and II.

Aims:
• Develop a PK-PD model from preclinical experiments, describing changes in α2-integrin expression levels and tumor growth inhibition in response to treatment with E7820.
• Investigate what integrin inhibition levels are correlated with tumor stasis
• Investigate whether these target levels are achieved in patients using tolerable doses

Preclinical data

Tumor growth experiments:
• xenografted mice, 5 dose levels
• pancreatic KP-1 tumor
• doses 0–200 mg/kg, during 21 days
• α2-integrin levels were measured on platelets by FACS, tumor size using a caliper.

PK-PD modeling:
NONMEM VI, visual predictive checks constructed to judge model fit. Base model shown below. Several models for tumor growth inhibition were investigated.

Pharmacokinetics

Pharmacodynamics

Dose
E7820

α2-integrin expression

Tumor size

PK-PD model

Key findings

• Preclinical simulations:
  Moderate inhibition of integrin expression on platelets already correlated in tumor growth inhibition
  Target levels: Iα2,50 = 14.7%  Iα2,SO = 17.9%  
• Clinical simulations:
  At the MTD (100 mg qd):
  >95% of patients reached Iα2,50
  >50% of patients reached Iα2,SO

Further research

• Currently, investigations are in progress if these targets are achieved in the clinic, (at the maximum tolerable dose, or lower)
• More research is needed to investigate the validity of α2-integrin expression as a biomarker for tumor growth inhibition
• The model may aid further clinical development of E7820

References


Table 1. Expected relative integrin expression inhibition at steady state, obtained from simulations of clinical dosing regimens.

<table>
<thead>
<tr>
<th>Dosing regimen</th>
<th>Expected Iα2 at t = 21 (CI 95%)</th>
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<tbody>
<tr>
<td>50 mg qd</td>
<td>12.8% (9.1% – 17.7%)</td>
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<tr>
<td>70 mg qd</td>
<td>17.2% (11.9% – 23.3%)</td>
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<tr>
<td>100 mg qd</td>
<td>20.2% (16.5% – 30.2%)</td>
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<tr>
<td>200 mg qd</td>
<td>37.8% (29.1% – 48.0%)</td>
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