**Background:**
- **LY53023414 (LY):** a dual PI3K/mTOR inhibitor. Dose-dependent tumor growth inhibition (TGI) by LY was observed in mouse xenograft models. 
- **Dose-dependent biomarker (p4EBP1) target inhibition (Ti) by LY was observed in mouse xenograft models.**

We hypothesized LY could lead in human to anti-tumor activity as observed in non-clinical models.

**Objectives:**
- To support design of the first human dose (FHD) study, aimed at defining the -biological-active-safe- dose range. 
- **-biological-active-safe- dose range - dose range leading to significant Ti, some level of reduction in tumor size (TGI) and adequate tolerability.**

**Data available:**
- PK data collected in mice, rat and dog as shown in Table 1 and 2. Ti and TGI data collected in mouse non-clinical models.

**Methods:**
- Allometric scaling was used to predict human PK based on non-clinical-PK data.
- Mouse PK, Ti and TGI data were modelled to determine the PK/PD relationship. From this information, the biological effective dose range in human was predicted.
- Assumption: Similar LY exposure (hence similar EmaxAUCmax) would be needed in human and non-clinical species to trigger Ti or TGI.

**Table 1: Data available in Rat and Dog**

<table>
<thead>
<tr>
<th>Species</th>
<th>No. animals</th>
<th>IV PK</th>
<th>PO PK</th>
<th>Dose, sample time</th>
<th>PO PK, Dose, sample time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat SD</td>
<td>0.18</td>
<td>5, 10, 20, 30 mg/kg</td>
<td>0.5, 1, 2, 4, 8, 24 h</td>
<td>0.5, 1, 2, 4, 8, 24 h</td>
<td></td>
</tr>
<tr>
<td>Rat MD</td>
<td>0.18</td>
<td>5, 15, 30 mg/kg</td>
<td>0.5, 1, 2, 4, 8, 24 h</td>
<td>0.5, 1, 2, 4, 8, 24 h</td>
<td></td>
</tr>
<tr>
<td>Dog SD</td>
<td>3.36</td>
<td>3 mg/kg</td>
<td>11.8, 12, 15, 30 mg/kg</td>
<td>0.25, 0.5, 1, 2, 4, 8, 12 h</td>
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</tr>
<tr>
<td>Dog MD</td>
<td>0.36</td>
<td>1, 3, 6, 9 mg/kg</td>
<td>0.5, 1, 2, 4, 8, 12 h</td>
<td>0.5, 1, 2, 4, 8, 12 h</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Data available in Mice**

<table>
<thead>
<tr>
<th>Model</th>
<th>PK Target inhibition (Ti)</th>
<th>Tumor growth inhibition (TGI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U187 MG</td>
<td>v</td>
<td>v</td>
</tr>
<tr>
<td>NCI-H1575</td>
<td>v</td>
<td>v</td>
</tr>
<tr>
<td>786-O</td>
<td>v</td>
<td>v</td>
</tr>
<tr>
<td>PIK3CA E545K (Ep-myc)</td>
<td>v</td>
<td>v</td>
</tr>
</tbody>
</table>

**Methods:**
- Allometric scaling was used to predict human PK based on non-clinical-PK data.
- Mouse PK, Ti and TGI data were modelled to determine the PK/PD relationship.
- From this information, the biological effective dose range in human was predicted.
- Assumption: Similar LY exposure (hence similar EmaxAUCmax) would be needed in human and non-clinical species to trigger Ti or TGI.
- NONMEM (version VII) was used for the analysis.

**Results:**
- Allometric scaling predicted an IV and PO LY clearance (CL, CLF) of 41.9 (34.0-51.7) and 55.9 (45.3-63.9) L/h in human (mean (90% CI), assuming bioavailability (F) 0.75 and body weight 70 kg. The slope of that relationship was 0.88 (see Figure 2) dose range.
- The non-clinical TGI versus exposure relationship was modelled using an Emax model. (see Figure 3)
- Estimated LY IC50 of 95.1 ng/mL (CV 40 %), corresponding to daily exposure of 2280 ng/mL following a 3 mg/kg BID dose (minimal efficacious dose in mice) (see Table 3).
- Optimal efficacious doses in mice were determined to be 6 to 10 mg/kg BID leading to daily exposure of 5380 to 9110 ng/mL (Figure 3).

**Design First in human dose (FHD):**
- Human PK prediction: LY dose range of 100-150 and 250-600 mg daily were predicted to produce in human daily exposure equivalent to exposure in mice leading to minimal- and optimal anti-tumor activity, respectively (Figure 3).
- The proposed dose range for FHD was 20 mg (starting dose) to 600 mg maximum daily dose.
- FHD primary objective: determine a recommended phase II dose.
- FHD secondary objective: Assess safely, PK/PD properties and to document antitumor activity.

**Dose Escalation Scheme:**
- 20, 40, 80, 150, 225, 325, 450 mg QD, and 150, 200, 250 mg BID.
- Observed human CLF was 64 L/h (CV 45.6%, 90%CI 60-70, n=8) after repeated doses in the 20 to 325 mg dose range.
- This is comparable to the predicted CL/F of 55.9 L/h (90%CI 45.3-68.9) (Figure 4).

**Conclusion:**
- The integration of the non-clinical data using modelling approach, enabled the prediction with good accuracy of the biological active dose range of LY in human FHD study.
- - Range for predicted optimal active daily dose = 250 – 600 mg QD. 
- - Range for observed «biological-active-safe» dose in human = 300 to 400 mg QD 
- - «biological-active-safe» dose range showing significant target inhibition and tolerated 
- - Preliminary anti-tumor activity was observed in patients treated a «biological active-safe» dose range.