Preclinical pharmacokinetic (PK) and tumour growth inhibition (TGI) modelling for mANK-101, an anchored murine interleukin-12 (IL-12) complex for intratumoural administration for solid cancer.

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Introduction

IL-12 is a pro-inflammatory cytokine capable of inducing a robust anti-tumour immune response. However, issues with systemic toxicity have limited its potential for use within a clinical setting.

Ankyra Therapeutics has developed a novel anchored drug delivery platform that locally retains immune agonists such as IL-12 following intratumoral (IT) delivery. ANK-101 and its murine surrogate mANK-101 consist of Alhydrogel® scaffolds anchored to genetic fusions of IL-12 and Alum-binding peptide (ABP). This work describes a model-based assessment of the mechanism of action in CT26 models, as well as the development of a PK-Tumour Growth Inhibition (TGI) model that describes all studies in the CT26 syngeneic mouse model.

Material and methods

Model-based assessment of TGI:

Tumour growth inhibition was assessed in CT26 syngeneic tumour models. In order to assess if a treatment effect exists, the model is first fit to the data assuming there is no treatment effect,

\[ M_1: R_t = R_0 + g_t \cdot t + \epsilon_t \]

Where \( R_t \) is the radius at time \( t \) (for mouse \( i \)) and is equal to the initial \( R_0 \), assumed to be the same for all mice, \( g_t \) assumed to be normally distributed with unknown mean and variance represents the tumour growth rate for mouse \( i \). Residual error, \( \epsilon_t \), is the unexplained variance in the data and is assumed to be normally distributed with mean 0 and unknown variance.

To assess if there is a treatment effect, the likelihood ratio-test (LRT) is used to compare the above model to \( M_2 \):

\[ M_2: R_t = R_0 + (g_t + d) \cdot t + \epsilon_t \]

Where \( d \) and \( d \) are treatment effect parameters representing the injection of free murine IL-12 and mANK-101 respectively.

Model-based biomarker validation:

The relationship between observed biomarker estimates and tumour growth rate after administration of mANK-101 was performed by comparing the %CV (coefficient of variation of the growth rate distribution) with/without any covariates between model M1 and M3.

\[ M_1: R_t = R_0 + g_t \cdot t + \epsilon_t \]

\[ M_3: R_t = R_0 + (g_t + a_0 + \text{Covariate}) \cdot t + \epsilon_t \]

Where Covariate is the biomarker value of mouse \( i \). Models were compared for statistical significance using the LRT, and assessing how the covariate impacted the coefficient of variation (%CV) of the baseline tumour growth rate.

PK-TGI Model:

The following model was fitted to efficacy study data assessing the role of mANK-101 on CT26 syngeneic tumour models.

\[ \frac{dD_{\text{IL-12}}}{dt} = -k_{\text{act}} D_{\text{IL-12}} \]

\[ \frac{dC}{dt} = k_{\text{act}} D_{\text{IL-12}} + k_{P} P - (k_{P} + k_{C}) C \]

\[ \frac{dP}{dt} = -k_{P} P + k_{C} C \]

\[ \frac{d}{dt} = g - \frac{d}{EC50 + R} \]

Plasma Concentration(\( C \)) = \( C/V(F,V) \)

The PK model was derived from Momir et al. [1], where \( D_{\text{IL-12}} \) represents IL-12 injected into the tumour (either using mANK-101 or murine IL-12), \( C \) represents the central compartment, and \( P \) represents the peripheral compartment. The TGI model assumes that there is a finite immune response which is recruited that is proportional to the concentration of IL-12 within the plasma \( (\alpha) \). The activated response \( \alpha \) is capable of inhibiting the growth rate of the tumour \( (\beta) \) at rate \( d \) and given affinity \( EC50 \). PK parameters were fitted initially, and fixed when fitting TGI parameters \( k_{\text{act}}, g, d \) and \( EC50 \).

Model-based assessment of TGI confirms a significant reduction in tumour growth rate of CT26 tumours after administration of mANK-101.

The PK model was able to successfully capture the growth delay induced by mANK-101 in CT26 syngeneic tumours. The model (solid black line) was found to describe all the data (coloured dots) equally well (Figure 3). The parameter values were estimated with good precision (Table 2).

Conclusions

A PK-TGI model that describes all the PK and TGI data available for mANK-101 across numerous different studies was developed. The final model was able to describe all the efficacy studies done with different schedules, detections, injection sites and starting volumes well. The PK modelling highlighted the lower systemic bioavailability of alanmanchored mIL12/ABP versus free mIL12/ABP and also highlighted that for alanmanchored mIL12/ABP the absorption rate into plasma is significantly lower than elimination from plasma. Furthermore, the biomarker analysis conducted is consistent with a mechanism of drug action of tumour cell death mediated by IL-12 mediated T-cell activation.

References


Table 1. Results of assessing the correlation of biomarkers to treatment effect in the CT26 model.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>LRT p-value</th>
<th>%CV Base</th>
<th>%CV with Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>%CD8 per CD3</td>
<td>0.027</td>
<td>28.5</td>
<td>13</td>
</tr>
<tr>
<td>%CD8 per CD45</td>
<td>0.002</td>
<td>28.5</td>
<td>13.4</td>
</tr>
<tr>
<td>CD11b/PDL1</td>
<td>0.004</td>
<td>28.5</td>
<td>14.2</td>
</tr>
<tr>
<td>CD45 CD86</td>
<td>0.237</td>
<td>28.5</td>
<td>19</td>
</tr>
<tr>
<td>CD45 % of live</td>
<td>0.141</td>
<td>28.5</td>
<td>21.6</td>
</tr>
<tr>
<td>%Ly6G per CD45</td>
<td>0.471</td>
<td>28.5</td>
<td>24.9</td>
</tr>
<tr>
<td>CD19</td>
<td>0.854</td>
<td>28.5</td>
<td>28.2</td>
</tr>
</tbody>
</table>

Table 2. Final parameter values for the TGI model. CI – confidence interval

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_{\text{act}} )</td>
<td>L/μg</td>
<td>0.10 (0.06, 1.63)</td>
</tr>
<tr>
<td>( g )</td>
<td>mm/day</td>
<td>0.47 (0.44, 0.50)</td>
</tr>
<tr>
<td>( d )</td>
<td>1/day</td>
<td>0.12 (0.11, 0.13)</td>
</tr>
<tr>
<td>EC50</td>
<td>%</td>
<td>5.4 (3.2, 9.1)</td>
</tr>
</tbody>
</table>

Figure 1. Left-panel Plot of the tumour growth data from the CT-26 biomarker study – volumes converted to radius by mapping volumes onto a sphere. Right-panel Plot showing the individual fits (solid red line) to the raw tumour size data (blue-dots) for the CT26 biomarker study.

Figure 2. Plots comparing tumour-infiltrating biomarkers as measured by flow cytometry for the 3 treatment groups in the CT26 model.

Figure 3. Plots showing the model fits (black lines) to all the TGI data (encoded dots/lines) across all CT26 data provided.