A MODEL RELATING OVERALL SURVIVAL RELATED TO TUMOR GROWTH INHIBITION IN RENAL CELL CARCINOMA PATIENTS TREATED WITH SUNITINIB, AXITINIB OR TEMSIROLIMUS

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OBJECTIVE

Tumor growth inhibition (TGI) metrics estimated with TGI models have been shown to be predictive of overall survival (OS) in a variety of tumor types1. The objectives of this work were:

1. To leverage historical data and assess the link between TGI and OS
2. To identify TGI thresholds that are predictive of expected OS benefit and could be used as targets to support early decisions at end of Phase II, or at an interim point of a Phase III clinical trial.

METHODS

TGI data (sum of longest diameters) was adequately described using the model 2:

\[ Y_{ij} = \frac{Y_0}{\frac{1+e^{-\lambda ETS_{ij}}} \cdot \frac{1+e^{-\lambda ETS_{ij}}}{\lambda ETS_{ij}}} \]

before treatment

\[ Y_{ij} = Y_{ij} + \epsilon_{ij} \]

afterward

\[ \theta_i = \delta \cdot e^{\tau_i}, \epsilon_{ij} = N(0, \omega^2_i), \epsilon = N(0, \alpha^2) \]

The purpose of this model is to derive patient-level TGI metrics1 (Early tumor shrinkage (ETS) at week 8, 10, 12, or time to growth (TGI))

• OS parametric model was built by backward stepwise elimination
  • select the best distribution describing OS data by Akaike Information Criteria (AIC)
  • "full" model including significant covariates from univariate analysis (p<0.05 per the log-likelihood ratio test).
  • stepwise elimination: p<0.01.

The model simulation performances were evaluated using posterior predictive checks (PPC). OS distribution and hazard ratios (HR) were simulated 1000 times for the patients, as in the original studies.

Simulations of the OS model were performed to assess the relationship between the expected effect size in OS (HRr) of an investigational treatment and the difference (Δ) i.e. the effect size in TGI metric (e.g. week 8 ETS). Multiple replications (n=1000) of virtual Phase III studies comparing an investigational treatment to standard of care were simulated. The power of the Phase III studies was also calculated conditional on the difference in TGI, Δ.

• This setting would mimic the calculation of expected HR that could be done as soon as tumor size data are available to estimate TGI, and support interim or end of phase II decisions or interim analysis of phase III.

RESULTS

Figure 1: Predictive check of week 8 ETS OS model by tertiles of week 8 ETS (large light gray, medium gray and low dark gray)

Figure 2: Predictive check of the sunitinib to IFN-a HR in first-line sunitinib study (2034)

Table 2: Parameter estimates of lognormal distribution OS model in days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (SE)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Intercept</td>
<td>6.07 (0.270)</td>
<td>&lt;0.001</td>
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<tr>
<td>Week 8 ETS</td>
<td>-1.99 (0.132)</td>
<td>&lt;0.001</td>
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<tr>
<td>Hemoglobin (g/L)</td>
<td>0.133 (0.111)</td>
<td>&lt;0.001</td>
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<tr>
<td>ECOG=1</td>
<td>-0.490 (0.048)</td>
<td>&lt;0.001</td>
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<tr>
<td>ECOG=2 (3)</td>
<td>-0.163 (0.077)</td>
<td>0.033</td>
</tr>
<tr>
<td>Corrected calcium (mg/dL)</td>
<td>-0.609 (0.039)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log(time to diagnosis)</td>
<td>0.200 (0.032)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline LDH (U/L)</td>
<td>-0.761 (0.265)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung metastases (yes)</td>
<td>-0.138 (0.046)</td>
<td>0.012</td>
</tr>
<tr>
<td>Log(Δ)</td>
<td>-0.107 (0.020)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
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Figure 3: Predictive distribution of HR comparing an investigational treatment to sunitinib in a 200, 400 and 600 patient study (10/3 per arm) as a function of difference in tumor growth inhibition (delta in week 8 ETS)

CONCLUSION

• Week 8 ETS, an early measure of tumor growth inhibition, had satisfactory performance to predict OS in a variety of clinical studies in mRCC
• The OS model was used to simulate clinically relevant ETS targets for future Phase 2 studies with investigational treatments.

REFERENCES