Background and Objectives

- Evaluation of tumor glucose metabolism has been suggested as an alternative to tumor size to assess early tumor response to therapy in cases where clinical benefit is observed but a change in tumor size is limited or delayed (e.g. cystic drugs) [1].
- Sunitinib (Sutent®) is a multi-targeted tyrosine kinase inhibitor with anti-angiogenic properties, approved for the treatment of imatinib-resistant- or -tolerant gastrointestinal stromal tumors (GIST).

The objectives of the present study are:
- To investigate potential relationships between sunitinib exposure and the time-course of the maximum and mean SUV (SUV_{max} and SUV_{mean}[2]) of individual lesions in GIST patients treated with sunitinib.
- To characterize both inter-individual (IV) and inter-lesion variability (IV) in SUV responses.
- To investigate potential relationships between SUV_{max} and overall survival (OS).

Methods

Patients and Data

Sixty-six imatinib-resistant GIST patients treated with sunitinib were included in the analysis [3].

Table 1: Summary of the data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing schedule (on/week)</td>
<td>6-week cycles (4/3); 50 mg q.d.</td>
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<td></td>
<td>4-week cycles (2/2); 50, 75 mg q.d.</td>
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<td></td>
<td>3-week cycles (2/1); 50 mg q.d.</td>
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<tr>
<td>Pharmacokinetics</td>
<td>Individual PK parameters for 44 patients [4]</td>
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<tr>
<td></td>
<td>Typical values for 22 patients [4]</td>
<td></td>
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<tr>
<td>SUV for individual lesions</td>
<td>607 baseline and post-baseline SUV\textsubscript{max} and SUV\textsubscript{mean} data from 172 lesions</td>
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<tr>
<td></td>
<td>Up to 5 lesions per patient</td>
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<td></td>
<td>Median duration of follow-up: 10 weeks</td>
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<td></td>
<td>Maximum duration of follow-up: 102 weeks</td>
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</table>

Individual lesion SUV model

- **Structured model**: Indirect response (IDR) models with inhibition of the production (\( R_\theta \)) or stimulation of the loss (\( R_\xi \)) of response were investigated to describe the time-course of SUV of individual lesions. Linear, power and exponential drug-effect relationships driven by the daily dose or the daily AUC were considered during model building. Linear and non-linear disease progression models were tested.
- **IV model**: The ILV model for a parameter \( \theta_j \) for the \( i \)th individual and the \( j \)th lesion can be written as:
  \[
  \theta_j = \theta_0 + \exp(\mu_0 + \mu_j) \]
  where \( \theta \) is the typical value in the population, \( \mu_0 \) and \( \mu_j \) model between individual differences and \( x \) model between lesion differences, with \( \mu_0 \equiv N(0,\sigma^2) \) and \( \mu_j \equiv N(0,\pi_j^2) \). A common variance is assumed between lesions, i.e., \( \pi_j^2 = \pi_j^2 = \cdots = \pi_j^2 \) for both ILV and IVL were evaluated in all model parameters.

- **Residual error model**: Individual lesion's SUV assessed from the same FDG-PET scan were allowed to have different residual error values, \( e \), which arose from a multivariate normal distribution parameterized with a zero mean vector and a covariance matrix \( \Sigma \).

- The diagonal elements of \( \Sigma \) containing the variances for each \( i \) were assumed to be the same.

- The off-diagonal elements of \( \Sigma \) containing the covariances between each \( i \) were assumed to be the same.

Overall survival model

- A parametric time-to-event model was developed to describe the OS data.

- Weibull and exponential distributions were evaluated to describe the baseline hazard for OS.

- The following predictors were evaluated on OS:
  - Maximum individual lesion SUV\textsubscript{max} at baseline (observed and predicted).
  - Summed SUV\textsubscript{max} at baseline (observed and predicted).
  - Summed SUV\textsubscript{max} time-course.
  - Relative change from baseline in summed SUV\textsubscript{max} over time.
  - Maximum relative change in individual lesion SUV\textsubscript{max} from baseline at week 1 and week 2.
  - Baseline observed tumor size (sum of longest diameters, SLD).

Discussion and Conclusions

- The developed model appropriately described the time-course of individual lesion SUV\textsubscript{max} and SUV\textsubscript{mean} in GIST patients treated with sunitinib. Significant IVL and ILV in SUV responses could be identified.
- Preliminary results showed that SUV-based metrics are related to OS, supporting that FDG-PET can be of interest to early predict clinical outcome during treatment.
- This methodology can be used to leverage data collected on individual lesions (e.g. tumor size, volume, metabolic activity) during oncologic clinical trials.

References