Tumour growth model to improve early PFS estimation thereby enhancing phase II go/no decisions

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BACKGROUND

- Survival is considered the most reliable endpoint in cancer clinical trials, but adequate determination of overall survival is often not feasible because of:
  - small sample sizes
  - short follow-up in early phase studies
- An early but reliable estimate of progression-free survival (PFS) in phase II can serve as decision criterion to
  - carry the investigational drug to the next phase III trial
  - stop further investigations of the anti-cancer compound
- High failure rates of phase III trials (~ 60%) and high costs emphasize high importance of improving the decision process for pharmaceutical companies especially in the field of oncology
- Early PFS estimations are often used to start planning pivotal phase III trials, but estimations with less than 50% of events observed do not use all available information from tumour measurements over time

➢ Tumour-growth models can use all longitudinal information and could potentially improve early PFS estimations

METHOD

TUMOUR-GROWTH MODEL

- Mixed-effects models to quantify non-linear individual relationships between time from randomisation and tumour burden *using all available tumour measurements*
- Applied model is flexible, allowing for wide range of different shaped growth curves (u-, j-, n- or linear-shaped)
- Tumour burden is measured by Sum of Diameter (SoD) of target lesions (TL) for each patient i over (continuous) time t by the following linear mixed model:

$$SoD(t,i) = \boldsymbol{\beta_0} + \boldsymbol{\beta_1} * t + \boldsymbol{\beta_2} * \log(t+1) + \boldsymbol{bi_0} + \boldsymbol{bi_1} * t + \boldsymbol{bi_2} * \log(t+1) + \boldsymbol{\beta_3} * treatment(i) * t + \boldsymbol{\beta_4} * treatment(i) * \log(t+1) + \boldsymbol{\varepsilon}(t,i)$$

with $\boldsymbol{\beta_0}, \boldsymbol{\beta_1}, \boldsymbol{\beta_2}, \boldsymbol{\beta_3}, \boldsymbol{\beta_4}$ fixed effects
$\boldsymbol{bi}$ individual patient effects over time (random effects)
$\boldsymbol{\varepsilon} \sim \boldsymbol{N}(0, \boldsymbol{\sigma^2})$ measurement errors (depending on time and patient)
$\boldsymbol{\beta_3}, \boldsymbol{\beta_4}$ treatment effects over time (test and reference)

- Optimal parameterisation of tumour-growth in non-small cell lung cancer (NSCLC) was published implying time-dependent Hazard Ratios (HR) [1]:

Fixed effects, i.e. population mean over time:

$$\beta_0 = 88.305,\ \beta_1 = 3.592,\ \beta_2 = 2.423,\ \beta_3 = 1.335,\ \beta_4 = -12.748$$

Random effects:

$$\begin{pmatrix} bi_0 \\ bi_1 \\ bi_2 \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 5.595 & -2.155 & 0.679 \\ -2.155 & 16.842 & -3.082 \\ 0.679 & -3.082 & 3.865 \end{pmatrix} \right)$$

- For each patient i the mixed model yields a trajectory describing patient-specific tumour dynamics over time t (see Figures 1 and 2):

$$\widehat{SoD}(t,i) = \widehat{\beta_0} + \widehat{\beta_1} * t + \widehat{\beta_2} * \log(t+1) + \widehat{bi_0} + \widehat{bi_1} * t + \widehat{bi_2} * \log(t+1) + \widehat{\beta_3} * treatment(i) * t + \widehat{\beta_4} * treatment(i) * \log(t+1) + \hat{\varepsilon}(t,i)$$

- Forecast for timepoint of tumour progression for each patient calculated by applying Response Evaluation Criteria In Solid Tumours (RECIST 1.1) on patient-specific tumour trajectories:
  - At least 20% increase in SoD of TL, taking smallest sum on study (nadir) as reference and
  - Absolute increase of at least 5mm in SoD or
  - Appearance of one or more new lesions (not applicable for our simulations because we simulate neither the occurrence of new lesions nor death)
- These event times are used to calculate HR of PFS for two treatment arms by means of Cox regression with treatment as covariate

SIMULATION

- A simulation study of 1000 repetitions each assuming 6 months accrual was conducted for 7 scenarios:
  - Proof of Concept (PoCP) scenarios 1 and 2 with 1000 patients each and follow-up time of 2 or 6 months for scenario 1 and 2
  - Phase II scenarios 3-7 with 80 patients each and follow-up time of 6 months
- Each simulation run based on the published parameterisation of [1]

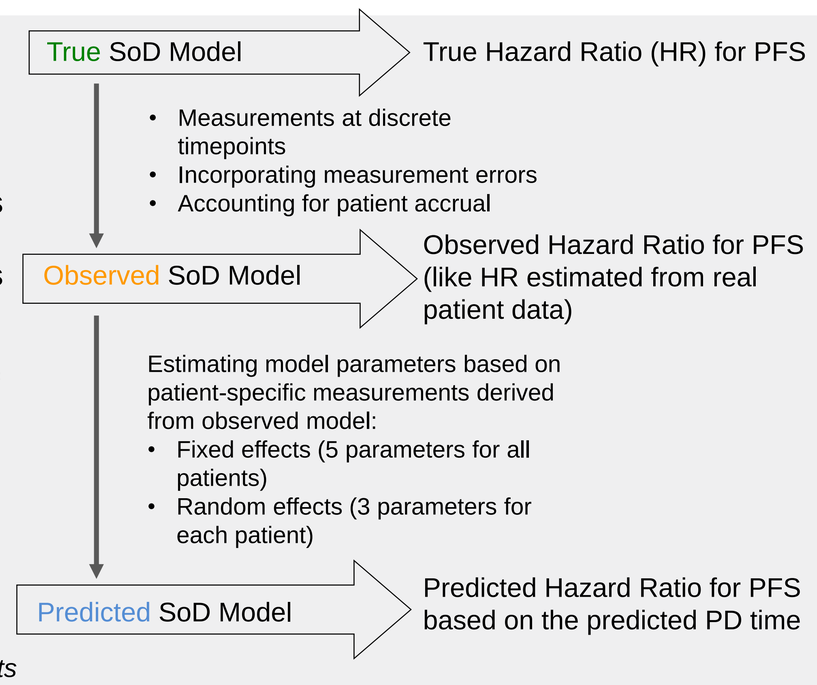

Figure 1: *Measurements until PD or censored from test or reference as input for estimating parameters (fixed and random effects) of the Linear Mixed Model for randomly selected patients*

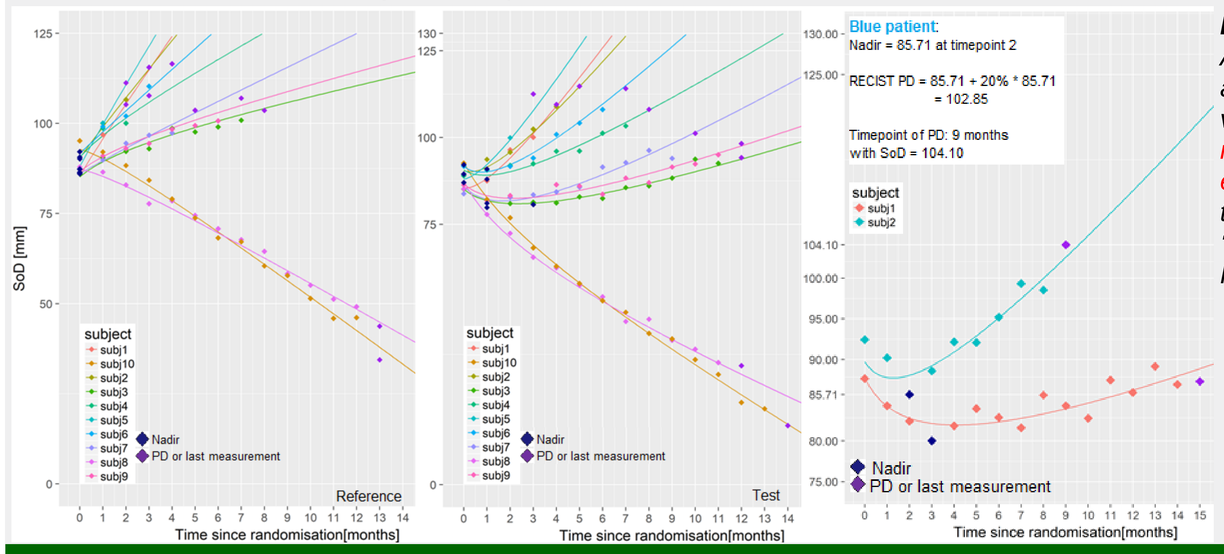

Figure 2: *Assessing SoD at scheduled visits with measurement errors in treatment group "test": Nadir and PD*

RESULTS

- Observed PFS estimation resulted in HR of 0.34 (95%-percentiles: 0.29-0.40) (see Table 1)
- Predicted HR was estimated as 0.77 to 0.71 depending on the scenario (see Table 1)
- Overall true HR was 0.78 (95% perc.: 0.69-0.85)
- For 6, 12 and 120 months the time varying HRs were 0.41 (0.36, 0.47), 0.60 (0.54, 0.66) and 0.77 (0.69, 0.85)

Table 1: *Results of different simulation scenarios*

		Observed		Predicted	
Scenario	**Measurement error σ^2**	**% events**	**HR Median (95% CI)**	**% events**	**HR Median (95% CI)**
Proof of Concept (PoCP) scenarios					
1	1	37%	0.34 (0.29, 0.40)	84%	0.77 (0.69, 0.85)
2	1	62%	0.52 (0.47, 0.58)	84%	0.77 (0.69, 0.84)
Phase II study scenarios					
3	1	62%	0.52 (0.30, 0.93)	84%	0.77 (0.46, 1.24)
4	1.5	62%	0.52 (0.28, 0.91)	84%	0.76 (0.45, 1.26)
5	2	63%	0.53 (0.29, 0.92)	85%	0.76 (0.43, 1.28)
6	9	66%	0.55 (0.31, 0.93)	85%	0.75 (0.43, 1.27)
7	25	74%	0.61 (0.36, 1.03)	84%	0.71 (0.40, 1.32)

CONCLUSIONS

- Tumour-growth models should be used to improve PFS estimations based on early readouts, especially in the presence of time dependent HRs, since they consistently provide far better estimates of the overall true HR by more than 10 points in all simulations.
- In general, tumour-growth models can support decision making in drug development, as supplement to classical PFS estimations and facilitate a better understanding of the mode of action of a drug [2,3].
- Not incorporating occurrence of new lesions or death limits tumour-growth models to indications and treatment lines where those are not the primary source for PD. However, model extensions incorporating those processes are straightforward.

ACKNOWLEDGEMENTS

Nothing to declare.

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