A simulation study to assess the impact of time to growth estimation shrinkage on overall survival association

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OBJECTIVE

Model based estimate of time to growth (TTG) of sum of longest tumor diameters (SLD) has been proposed to predict overall survival (OS) in metastatic cancer patients in several diseases (1, 2). TTG is superior to earlier metrics such as tumor size ratio at landmarked time point (e.g. end of cycle 2). Recent correspondences and discussions have raised questions about this modeling approach (3-7). The tumor growth inhibition (TGI) observations are limited by the disease progression defined by an SLD increase of 20% for the minimum and/or death (RECIST). The objective of this simulation work is to evaluate the impact of model parameter shrinkage on TTG estimate with limited number of observations and on the subsequent association with OS.

METHODS

Simulations

500 replications of TTG of 500 patients were simulated based on previously published models (1).

$$TS_i\left(t_{ij}\right) = TS_{0,i} \cdot \exp\left[KL_i\ t_{ij} - \frac{KDE_{0,i}}{\lambda_i} \cdot \left(1-e^{-\lambda \cdot t_{ij}}\right)\right] + e_{ij}$$

where TS is the tumor size; KL and KD_0 are the tumor growth rate and tumor growth inhibition rate, respectively; λ is the rate constant that accounts for a decrease in tumor growth inhibition rate (KD) over time; TS0 is the observed tumor size at baseline.

Patient tumor size were simulated every 8 weeks over 120 weeks in 500 patients (using the same previously published tumor size model (1)), observations were limited by disease progression defined by an increase of 20% from the minimum or death (8).

Table I: TS model parameters

	Value	IIV
KL (week^{-1})	0.00583	1.06
KDE_0 (week^{-1})	0.0498	0.63
λ (week^{-1})	0.0866	0.63
TS_0(cm)	9.67	0.71
Residual error (cm^2)	0.98	-

Abbreviations: KL: growth rate, KDE: tumor growth inhibition rate, λ: exponential decrease in tumor growth inhibition rate,
IIV: standard deviation of inter-individual variability

Patient TTG can be computed

$$TTG_i = \frac{\log\left(KDE_{0,i}\right) - \log\left(KL_i\right)}{\lambda_i}$$

OS was simulated (500 replications of 500 patients) with a Weibull distribution (1).

Table II: OS model parameters

	Value
θ_0	5.987
θ_{TTG}	0.022
Log(1/α)	-0.683

TTG: time to growth,
survival time analyzed in days

$$S(t) = \exp\left(-\kappa \cdot t\right)^{\alpha}$$

$$h(t) = \kappa\alpha\left(\kappa \cdot t\right)^{\alpha-1}$$

$$\kappa = 1/\exp\left[\left(\theta_0 + \tau\right) + \theta_{TTG} \cdot TTG \cdot \varphi + \left(1-\varphi\right) \cdot \theta_{TTG} \cdot 25\right]$$

$$\text{median}(OS) = \log(2)^{1/\alpha}/\kappa \quad \text{and} \quad HR_{\Delta TTG} = 1/\exp\left[\theta_{TTG} \cdot \Delta TTG \cdot \alpha\right]$$

Where S(t) is the survivor function and h(t) is the hazard function.

Several assumptions on the strength of the association (none to full) and on the time difference between TTG and OS were simulated to evaluate the impact on TTG and the TTG-OS association:

- **full association φ=1, scenarios A and B**
- **no association φ=0, scenarios C, D and E**
- **median(OS) = 83 weeks τ= 0 scenarios A and C**
- **median(OS) = 41.5 weeks τ = -log(2), scenarios B and D**
- **median(OS) = 83 weeks τ = -log(4), scenario E**

Estimations

TTG and the TTG-OS association were estimated by a two stage approach:

1) **simplified TGI nonlinear mixed effect model (NONMEM, FOCE) to estimate TTG**
2) **Cox proportional hazard semi-parametric model (coxph in R) to estimate the TTG-OS association. For each of replication the bias and the shrinkage of TTG and the TTG-OS association were evaluated. Alternative tumor size observation schedules were also evaluated in order to improve TTG estimation.**

To help assess clinical relevance, HRs were computed for a 7.5 week difference in TTG i.e. roughly the difference observed between the two treatment arms in the study modeled in reference 1, that translated in clinically relevant OS difference.

$$HR_{7.5weeks} = \exp\left(7.5 \cdot \beta_{TTG}\right)$$

Where β_{TTG} is the cox regression parameter estimate.

TTG Shrinkage was computed from the "true" standard deviation

$$Shr_{TTG} = 1 - \frac{SD\left(TTG_{Estimated}\right)}{SD\left(TTG_{True}\right)}$$

RESULTS

Table III: Assumptions and results of simulation scenarios

Model Assumptions				Model Estimations			
Scenarios	$HR_{7.5weeks}$*	Median OS (week)	Median TTG (week)	% of P<0.05	$HR_{7.5weeks}$*	95% PI	Shr_{TTG} (%)
A	0.72	83	25	100	0.76	0.74 0.80	40.6
B	0.72	41.5	25	100	0.77	0.76 0.81	40.7
C	1	83	25	5.51**	0.99	0.98 1.03	43.7
D	1	41.5	25	13**	0.98	0.97 1.02	49
E	1	21	25	10**	0.98	0.96 1.03	59

*Hazard ratio computed for a clinically relevant TTG difference of 7.5 weeks (see text for explanation). HR of 1 assumes no association between TTG and OS i.e. a Cox parameter estimate close to 0
** Type 1 error of the Wald test
HR and median OS of model assumptions can be computed from OS model parameter estimate of the Weibull distribution

- **In scenarios assuming no association (C, D and E),**
  - **TTG shrinkage was high (44-59%) and increased with shorter OS;**
  - **Type 1 error (p<5%) was 5.5% for an OS of 83 weeks as in (1) (scenario C) and up to 13% when the median OS was divided by 2 (scenario D) (41.5 weeks).**
  - **The HRs were estimated at most at 0.96 (2.5th percentile) with 95% CI always including 1, indicating no clinical relevance even when p values were < 5%.**

- **In scenarios assuming association (A and B),**
  - **TTG shrinkage was about 40%,**
  - **Type 2 error was 0%**
  - **HRs were estimated above the "true" values, a bias likely due to the TTG shrinkage, suggesting that the model is conservative.**
  - **The 95% CI was always below 1 indicating significant effect i.e. clinical relevance.**

- **The shrinkage appeared to be more impacted by the lack of association (C, D and E) than by the time difference between TTG and OS (A and B).**

CONCLUSIONS

Despite a relatively large shrinkage of TTG due to a limited number of observations, the association between TTG and OS does not seem to be problematically impacted. This shrinkage depends on the time difference between TTG and OS and the observation schedule. TGI models are developed from the SLD as defined by RECIST (7), it would be worth to optimize tumor size observation schedule to extract more information on the TGI dynamic.

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