Evaluation of tumor kinetics metrics as early endpoint to support decision making in early drug development

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1 – Introduction

In the process of drug development in oncology, moving from early to late phase is a critical and complex step. Usually, decisions are based on the overall response rate (ORR) derived from RECIST[1] criterion, and assessed on a limited number of patients (often 20-40). However this is often challenging because of the high variability in disease and in response to treatment and the limited amount of information available.

Objective

Explore the benefits of using metrics based on longitudinal tumor kinetic modeling to inform decision making in early drug development.

A simulation study is conducted to assess whether decision based on Tumor Kinetic Metrics (TKM) can be valuable and to compare TKM derived from observations to TKM derived from predicted values.

2 – Materials & Methods

Simulation study - Data:

Typical Phase Ib trial enrolling a limited number of subjects (=*nPat)* is considered. Individual tumor kinetic profiles are simulated according to a **bi-exponential tumor growth inhibition** model as proposed in Stein[1]

$$TS(t_{ij}) = TS_{i0}.exp[KG_i t_{ij}]1_{]-\infty;0]} + TS_{i0}[exp(-KS_i t_{ij}) + exp(KG_i t_{ij}) - 1]1_{[0;\infty[} + \varepsilon_{ij}$$

Where:

$\theta_i = [TS_{i0}, KS_i, KG_i]$, $\theta_i = \theta e^{\eta_i}$ and $\eta_i \sim N(0, \omega^2)$ $\varepsilon_i \sim N(0, \sigma^2)$

$i = 1, \dots, n$ patients and $j = 1, \dots, m$ observations

KG is the growth rate constant (≥0) and KS the shrinkage rate constant (≥0)

- **Simulated Data** consisted in the **Sum of the Longest Diameters** (SLD) of tumor lesions (Figure 1A) with tumor assessments performed at baseline and every *dTA* weeks in mean. Patients' participations to the study are based on the status of their disease: Patients will stay in the study as long as no progression of the disease is observed. (Figure 1B).
- Disease Progression is assumed only related to the change in Sum of the Longest Diameters of tumor lesions (new lesion, consent withdrawn, clinical deterioration not simulated)
- **Patients accrual** is simulated according to Poisson process with an intensity λ patients per month (Figure 1C).
- **Censoring**: cut off for decision point is the time at which all patients have at least a predefined number of tumor assessments (noted *TAcut*) or progression occurred.
- **Parameters** used for simulation are provided in Table 1 and correspond to those of an Immunotherapy agent.

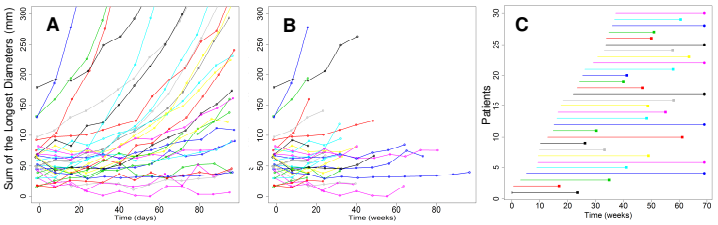

Figure 1: (A) Simulated patients SLD – (B) Change in SLD relative to NADIR – (C) Patient accrual and follow up (squares represent a tumor progression and dots a censor)- Design parameters used for simulation are the following: nPat= 30, dTA=8, λ=3pts/mo, TAcut = 4, individual TS0, KG, and KS are drawn from a normal distribution using the parameters provided in Table 1.

Table 1: Parameter values used for the simulations of SLDs

Parameter (unit)	θ	ω
KG (wk-1)	0.0110	0.0012
KS (wk-1)	0.0147	0.0024
TS_0(mm)	69.9	2.81
σ^2(mm²)	39.0	4.87
ω^2_{KG}	0.586	0.0864
ω^2_{KS}	0.808	0.199
ω^2_{TS0}	0.374	0.0362

Population data analysis

The data were modeled using the Stein[2] model embedded in a **population model**. The nonlinear mixed effects modeling approach was performed using NLME package in R (version 3.1-117 - Pinheiro, 2014 [3]) for the parameters estimation and graphical analyses. Residual variability was modeled with an additive error model.

Tumor kinetic Metric derivation

2 kinds of Tumor Kinetic Metrics (TKM) were explored:

- TKM derived **from observations** (oTKM)
- TKM derived from **individual predicted SLD values** (pTKM)

Study outcome based on Tumor kinetic Metrics

Table 2: Metrics based on SLDs values (observed or predicted), and related decision criteria to declare success or failure of the study. Last column is obtained from Table 1 to derive the right decision

Tumor Kinetic Metrics	Targeted event (endpoint)	Decision Criterion	Truth (TKM derived from scenario)
Max Tum Shrink (MTS)	MTS > 10%	P(MTS >10%)> 20%	P(MTS >10%)=37%
Time to Growth (TTG)	TTG > 10 weeks	P(TTG>10 wks)> 40%	P(TTG>10 wks)=49%
Time to Progress. (TTP)	TTP > 26 weeks	P(TTP>26 wks) >40%	P (TTP>26 wks) =65%

Decision to declare success or failure of the trial is based **on the lower bound of the Clopper-Pearson exact interval** for proportion (low sample size), $qBe\left(\frac{\alpha}{2}; p, n-p+1\right)$, *n* being the number of evaluable patients for each endpoint and *p* the number of patients having experienced the targeted event. Confidence interval at one sided α-level 10%

4 – Results

Different likely scenario of phase Ib trials were considered (Table 3). For each of them 500 clinical trials were simulated. The mean number of tumor assessments (TA) per patients and the duration of follow are plotted in Figure 2 to illustrate a scenario of **30pts/dTA=8** which will be used as a running example

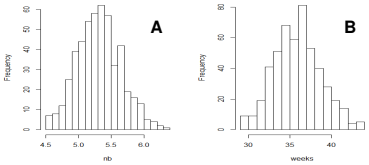

Figure 2: Mean number of TA (A) and mean follow up time (B) per patients for a scenario of 30pts/dTA=8

Table 3: Explored scenarios of Phase Ib clinical trials

Trial simulation parameters	Value
nPat, Number of patients in the trial	20, 25, 30, 35, 40
Rate, Accrual rate: number of pts per week	3pts / 4wk
dTA, TA period, i.e. time interval between 2 TAs, in week	6, 8, 9
Tacut, Min required number of TA (unless event) before decision point	4

Due to the limited amount of information, some simulations did not lead to a successful estimation of the model parameters. Table 4 provides the percentages of trials for which NLME fitting has converged, for the different scenarios.

Table 4: Percentage of converged fits for the different explored scenarios.

Npat	20	30	40
dTA=6	32%	42%	51%
dTA=8	37%	42%	48%
dTA=9	40%	40%	52%

For each scenario, decision on the **trial outcome** was assessed according to the TKM criteria (Table 2) **derived from observations and derived from predicted SLD values**. As shown in Figure 3 (with scenario **30pts/dTA=8)** the oTKM and pTKM metrics may lead to different decisions.

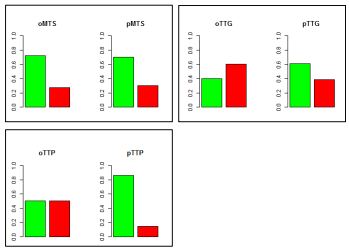

Figure 3: Decision (green is for success and red for failure) derived from the different TKMs based on observation (o - left) and based on predicted SLD (p -right). Outcomes of scenario 30pts/dTA=8

Performances : percentage of right decisions

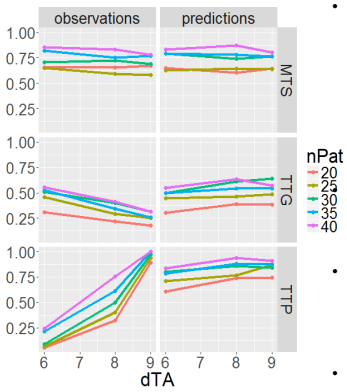

Figure 4: Percentage of right decisions when using the different TKM, for the explored scenarios.

- To assess the performances of TKM with regard to the decision, trial outcome is derived according to each of the criterion provided in Table 2. Decision is then compared to the **right decision**. The right decision is determined upfront on the basis of the known parameter values (Table 1) used to simulate patient's data and the decision criteria (Table 2).
  Both oTKM and pTKM are evaluated and compared in each of the proposed scenarios. **Percentages of right decisions** are displayed in Figure 4.
- As shown in Figure 4, the pTKM perform globally better than oTKM. The probability of wrong decision tend to be high for oTTG and oTTP contrary to the corresponding TKM derived from predicted value
- pTKM are more robust (less sensitive) than oTKM with respect to dTA.

5 – Discussion

- A minimum amount of data is required to perform TK modeling otherwise convergence issues may occur. In our simulation framework, only around 50% of trial fits converged.
- In the scenarios explored with the above predefined decision criteria, the simulations show that metrics derived from predicted values (pTKM) performed globally better than metrics derived from observations (oTKM).
- When the timing of TA are not optimal **pTKM would likely perform better than oTKM.** TK modelling is valuable when design (TA) does **not well capture the endpoint**
- Other decision criteria have been tested (not shown) and results were similar to those described here. However, performances of pTKM vs. oTKM **may depend on these criteria**. Therefore, It could be useful to perform a simulation study before running a trial whose decision criteria would be based on a TKM derived from predicted SLDs.
- **Threshold for decision criteria** would gained to be set in accordance with the late clinical endpoint, **overall survival**.
- From our view, decision to declare a trial as a success or a failure, should be **multifactorial** (as an assessment with regards to Target Product Profile). This means that it should deal with different endpoints and endpoints derived from TK modeling offer here a good option.

6 – References

[1] Eisenhauer, E., et. al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer*, *45*(2), 228-247.

[2] Stein, Wilfred D., et al. "Tumor regression and growth rates determined in five intramural NCI prostate cancer trials: the growth rate constant as an indicator of therapeutic efficacy." *Clinical Cancer Research* 17.4 (2011): 907-917.

[3] Pinheiro, J., et. al. (2014). R Core Team (2014) nlme: linear and nonlinear mixed effects models. R package version 3.1-117. *Available at h ttp://CRAN. R-project. org/package= nlme.*