A model relating overall survival to tumor growth inhibition in renal cell carcinoma patients treated with sunitinib, axitinib or temsirolimus

Francois Mercier[1], Brett Houk[2], Laurent Claret[1], Peter Milligan[3], Rene Bruno[1]

[1]Pharsight, a CertaraTM company, St. Louis, MI, USA; [2]Pfizer Clinical Pharmacology, La Jolla, CA, USA, [3]Pfizer Pharmacometry, Sandwich, UK

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Background and objectives

- Tumor growth inhibition (TGI) metrics estimated with longitudinal tumor size (TS) models have been shown to be predictive of overall survival (OS) in a variety of tumor types[1] including metastatic renal cell carcinoma (mRCC).
- **The objective of this work** is to assess the predict the overall survival time (OS) in a population of mRCC patients treated with either one of the following product: sutinib, axitinib, temsirolimus.

Data and Methods

- Data originated from 10 different studies, corresponding to a total of 2628 patients.

Study	Phase	Line	N_{tot}	N_{eval}*	Treatment groups
A4061012 (1012)	II	2nd	48	48	Axitinib 5 mg bid
A4061023 (1023)	II	2nd, refract[1]	50	50	Axitinib 5 mg bid
A4061032 (1032)	III	2nd	699	651	Axitinib 5 mg bid, Sorafenib 400 mg bid
A4061035 (1035)	II	2nd	62	62	Axitinib 5 mg bid
A6181006 (1006)	III	2nd, refract[2]	105	105	Sunitinib 50 mg qd
A6181034 (1034)	III	1st	725	709	IFNa 3m qd, Sunitinib 50 mg qd
A6181065 (1065)	II	1st	269	267	Sunitinib 50 mg qd, and 37.5 mg qd
A6181072 (1072)	II	1st and 2nd	51	51	Sunitinib 50 mg qd
A6181110 (1110)	II	1st	118	113	Sunitinib 37.5 mg qd
B1771098 (1098)	III	1st, poor prognosis	501	496	Temsi 15 mg+IFNa 6m, IFNa 18m, Temsi 25 mg
TOTAL			2628	2552 (97.1%)	

[1] sorafenib refractory; [2] cytokine refractory; *N_{eval}: "Evaluable" patients have at least one value post-baseline in addition to baseline.

- Available data included baseline characteristics, survival and censoring times, and the sum of longest diameter (SLD) measured repeatedly over time in each patient.

- The main trend and inter-individual variability in SLD biphasic time dynamics was adequately described using the below model[2] (which outperformed simpler alternatives like the model proposed by Stein[3]):

Exponential tumor 'growth' or 'proliferation

Decay as function of time

$$Y_{ij} = \begin{cases} Y_{0i} \cdot e^{KL_i \cdot t_{ij}} & \text{..... when time} \le 0 \\ Y_{0i} \cdot e^{\left(KL_i \cdot t_{ij} - \frac{KD_i}{\lambda_i}\left(1 - e^{-\lambda_i \cdot t_{ij}}\right)\right)} & \text{..... otherwise} \end{cases}$$

$$Y_{ij} = \tilde{Y}_{ij} + \varepsilon_{ij}$$

$$\theta_i = \theta \cdot e^{\eta_i},\ \eta_i \sim N(0, \omega^2),\ \varepsilon_{ij} \sim N(0, \sigma^2),$$
$$\theta = [Y_0, KL, KD, \lambda]$$

Table 1: SLD longitudinal model parameters estimates

Parameter	Estimate (CV%)	ω^2 (Sh%)	$\omega_{(KL, KD)}$ (cor)
Y_0 (cm)	10.1 (0.164)	0.662 (4.33)	
KL (week^{-1})	3.74x10^{-3} (6.64)	1.42 (34.6)	0.108 (0.103)
KD (week^{-1})	2.42x10^{-2} (4.30)	0.766 (31.6)	
λ	9.22x10^{-2} (8.35)	1.15 (45.6)	
σ^2	0.996 (0.830)	-	

- The purpose of this model exercise is to derive patient-level tumor growth inhibition metrics (Early tumor shrinkage (ETS) at week 8, 10, 12, or time to growth (TTG)) that would be good predictors of the overall survival at the group-level.
- ETS8 (ratio of SLD at week 8 vs. SLD at baseline) was found to be a good metric to summarize the SLD time dynamics with our data.

References

1 Bruno R. et al. *Clin. Pharmacol. Ther.*, 2014; doi: 10.1038/clpt.2014.4

2 Claret B. et al. JCO, 2013; doi: 10.1200/JCO.2013.49.3635

3 Stein W. et al. *The Oncologist* 2008; doi: 10.1634/theoncologist.2008-0075.

Conclusions

- **A parametric time-to-event model informed by individual estimates of tumor growth inhibition was used to study OS in ~2500 RCC patients treated with sutinib, axitinib, temsirolimus.**
- **The model was then used to simulate various clinical trials scenarios showing how early tumor shrinkage data could be used to optimize sample size in Phase III (*i.e.* reduce drug development time and cost).**

Survival model

- Survival times were best described using a parametric model with a lognormal distribution:

$$S(t) = 1 - \Phi\left\{\frac{ln(t) - \mu}{\sigma}\right\}$$

where Φ is the Normal cumulative distribution function and $\mu = X\beta$ (with X, vector of covariates)

- In parallel, the assessment of baseline covariates effects using sequentially univariate and multivariate (backward elimination) Cox (PH) models revealed that hemoglobin (Hb), LDH, corrected calcium (cCa), as well as time from diagnosis (Tdiag), number of metastases (Met), presence of metastases in lung (Lung) and ECOG (two categories: 1, >1) were sufficiently influential to be needed in the survival model (Table 2).

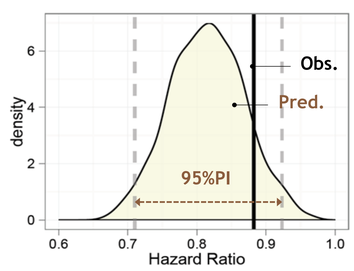
Table 2: Parameter estimates of the lognormal overall survival model (in days)

Parameter	Estimate (SE)	*p*-value
(Intercept)	8.07 (0.270)	<0.001
ETS8	-1.99 (0.135)	<0.001
Hb (g/L)	0.133 (0.111)	<0.001
ECOG=1	-0.400 (0. 048)	<0.001
ECOG=(2, 3)	-0.163 (0.077)	0.033
Log(Met)	-0.209 (0.032)	<0.001
cCa (mg/dL)	-0.104 (0.019)	<0.001
TDiag (Days)	8.0E-5 (1.7E-5)	<0.001
LDH (U/L)	-3.7E-4 (9.2E-5)	<0.001
Lung (yes)	-0.138 (0.046)	0.002
Log(σ)	-0.107 (0.020)	<0.001

SE: Standard error.

Using the model "in simulation mode"

Figure 1: Observed vs. predicted HR in study 1034



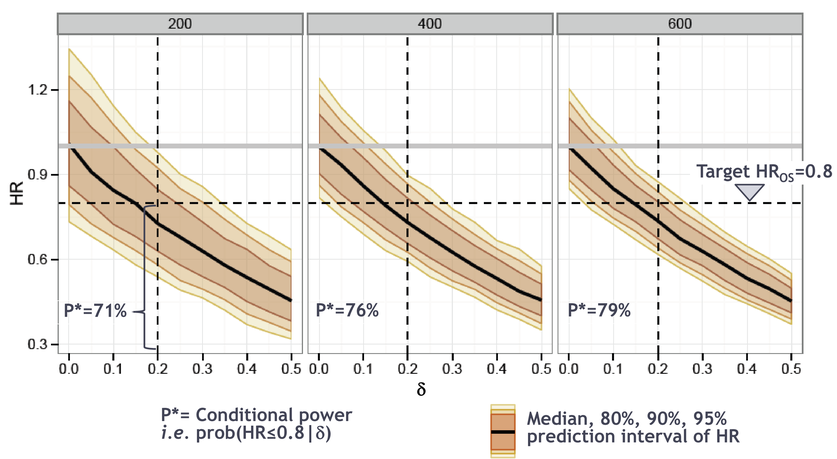
Internal validation (PPC)

- N_{sim}=1000 replicates of simulated survival time **illustrating the uncertainty of the model parameters** were generated using the same baseline covariate and ETS8 data as the ones observed in the source clinical trials.
- The hazard ratio (HR) observed in study 1034 (dark line) between IFNα 3μ and Sun 50 mg was overlaid to the ones obtained from the simulated data (distribution), showing **no major biais in the model** parameter estimates (Figure 1).

Optimizing sample size in Phase III

- Consider a new hypothetical phase III trial with similar population characteristics to the one observed in study 1034. We compare the increase in OS in RCC patients treated with a reference treatment (REF, e.g. sunitinib) vs. a new treatment (EXP, new compound or combination).
- Assuming a total sample size N (with allocation ratio 1:1), and a shift to the δ in ETS8 between REF and EXP corresponds to a decrease in tumor size .
- Conditional on the observed δ=0.2 at end of phase II (or at an interim analysis of phase III), the phase III study power (i.e. probability of HR≤target) increases with N (total sample size) (Figure 2).

Figure 2: Anticipated HR in RCC patients as a function of the difference between groups (EXP vs. REF) in tumor growth inhibition (δ), when the sample size (per group) is 200, 400 or 600



P*= Conditional power
i.e. prob(HR≤0.8|δ)

Median, 80%, 90%, 95% prediction interval of HR