

# A model to predict progression-free survival in patients with renal cell carcinoma based on week 8 change in tumor size

Laurent Claret (1), Jenny Zheng (2), Francois Mercier (1), Pascal Chanu (1), Ying Chen (3), Brad Rosbrook (4), Pithavala, Yazdi (3), Peter A. Milligan (2), Rene Bruno (1)

(1) Pharsight Consulting Services, Pharsight, a Certara™ Company, France, (2) Pfizer Pharmacometrics, Global Clinical Pharmacology, USA and UK, (3) Pfizer Clinical Pharmacology, La Jolla, CA, USA, (4) Pfizer Statistics, La Jolla, CA, USA

## OBJECTIVE

To assess the link between early tumor shrinkage (ETS) and progression-free survival (PFS) based on historical first-line metastatic renal cell carcinoma (mRCC) data.

## METHODS

### Trials and data

Data from two Phase III studies in treatment naïve mRCC patients:

Model development

- Sunitinib versus interferon, 750 patients [1]
- AGILE: axitinib or sorafenib, 288 patients [2]

Model evaluation

- Axitinib lead in period followed by titration with axitinib or placebo in patients eligible for titration, 213 patients [3]

### Baseline patient characteristics evaluated in model

Age, ECOG PS, tumor burden, prior treatments (nephrectomy, radiations), hemoglobin, albumin, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase and corrected calcium levels, neutrophil counts, platelet counts, Asian patients vs. others.

### Tumor growth inhibition (TGI) metrics

Sum of longest diameter data were modeled with simplified TGI model [4]

$$t < 0 \quad TS(t) = TS_0 \cdot \exp(KL \cdot t)$$

$$t \geq 0 \quad TS(t) = TS_0 \cdot \exp\left[KL \cdot t \cdot \frac{KDE_{t_0}}{\lambda} \cdot (1 - e^{-\lambda t})\right]$$

t=0 : time of the first dose

Early tumor shrinkage:  $ETS = TS(t)/TS(0)$ , can be predicted at any time [5]. Model parameter were estimated in NONMEM 7.3.0 [6].

### PFS model development

The loglogistic distribution is similar to the lognormal distribution but can be solved analytically and was used for implementation in NONMEM. The log-logistic hazard function  $h(t)$  is defined by:

$$h(t) = \frac{\lambda \cdot \tau \cdot (\lambda \cdot t)^{\tau-1}}{1 + (\lambda \cdot t)^\tau}$$

Where  $\tau$  is the scale parameter,  $t$  is the time and  $\lambda$  is the shape parameter with  $1/\lambda$  corresponding to the median defined by the covariates. Covariates with a significant impact on PFS were selected using a stepwise approach with forward inclusion of covariates at  $p < 0.05$  (log-likelihood ratio test), followed by backward deletion at  $p < 0.01$  using Perl speaks NONMEM.

### Model qualification and external validation

PFS distributions in quartiles of ETS and/or study hazard ratio (HR) were qualified by posterior predictive check (1000 replicates).

### Simulations

1000 replicates with 300 patients per arms were performed to explore the distribution of the expected HR, of a new investigational treatment vs. sunitinib as the function of various effect sizes of the investigational treatment on week 8 ETS.

## RESULTS

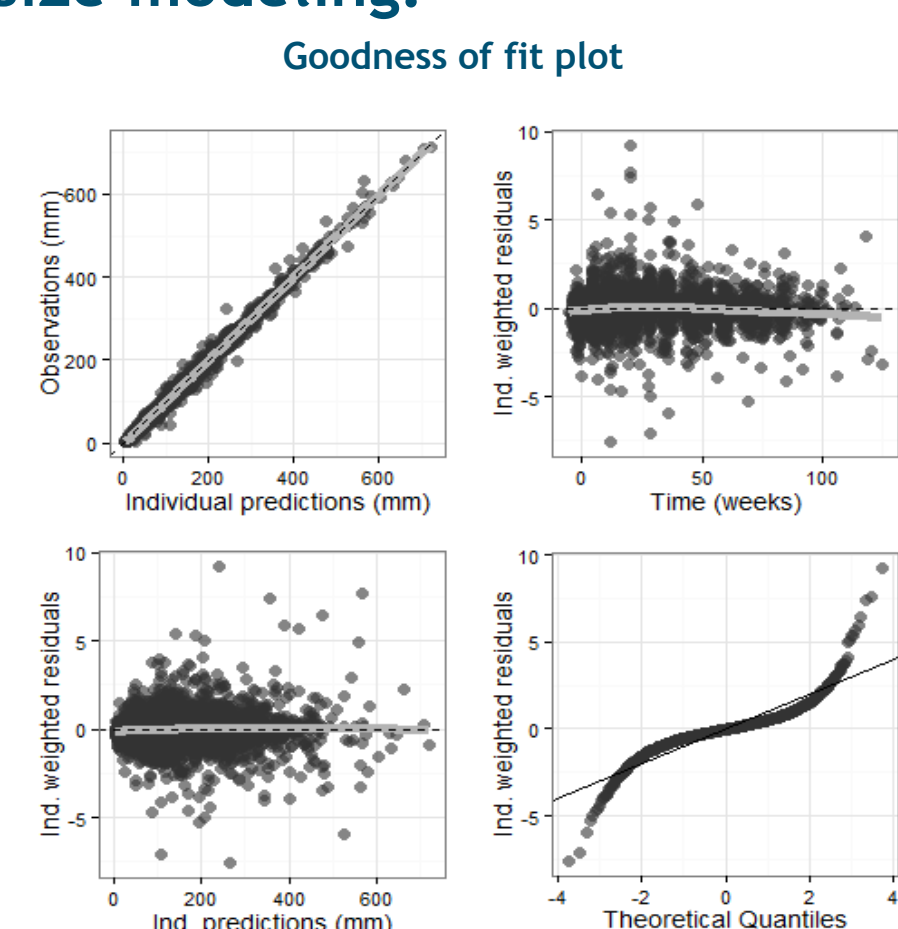
### TGI model

Out of the 1038 patients treated in the two Phase III clinical studies used to build the model, 921 (88.7%) were evaluable for tumor size modeling.

sTGI model parameter estimates

Parameter	Estimate (RSE)	$\omega^2$ (Sh%)
$TS_0$ (mm)	109.0 (2.67)	0.639 (3.35)
KL (week <sup>-1</sup> )	0.00366 (11.3)	1.46 (30.8)
KDE (week <sup>-1</sup> )	0.0239 (6.95)	0.732 (29.1)
$\lambda$ (week <sup>-1</sup> )	0.0886 (9.24)	0.798 (41.8)
$\sigma^2$ (cm <sup>2</sup> )	80.7 (9.98)	-

$\sigma$  is the standard deviation of residual error  
 $\omega$  is the standard deviation of inter-individual variability  
Sh is the shrinkage of posthoc parameter estimates



### PFS model

Final model is defined by a non linear relationship with ETS at week 8 and bone metastases and albumin as baseline covariates:

$$\text{Log}\left(\frac{1}{\lambda}\right) = \theta_{\text{int}} \cdot (1 + \theta_{\text{bone}} \cdot \text{Bonemet}) \cdot (1 + \theta_{\text{alb}} \cdot (\text{Alb} - 43)) + \theta_{\text{ETS}} \cdot \left(1 - \frac{\text{ETS}^\gamma}{\theta_{\text{ETS}50}^\gamma + \text{ETS}^\gamma}\right)$$

## RESULTS

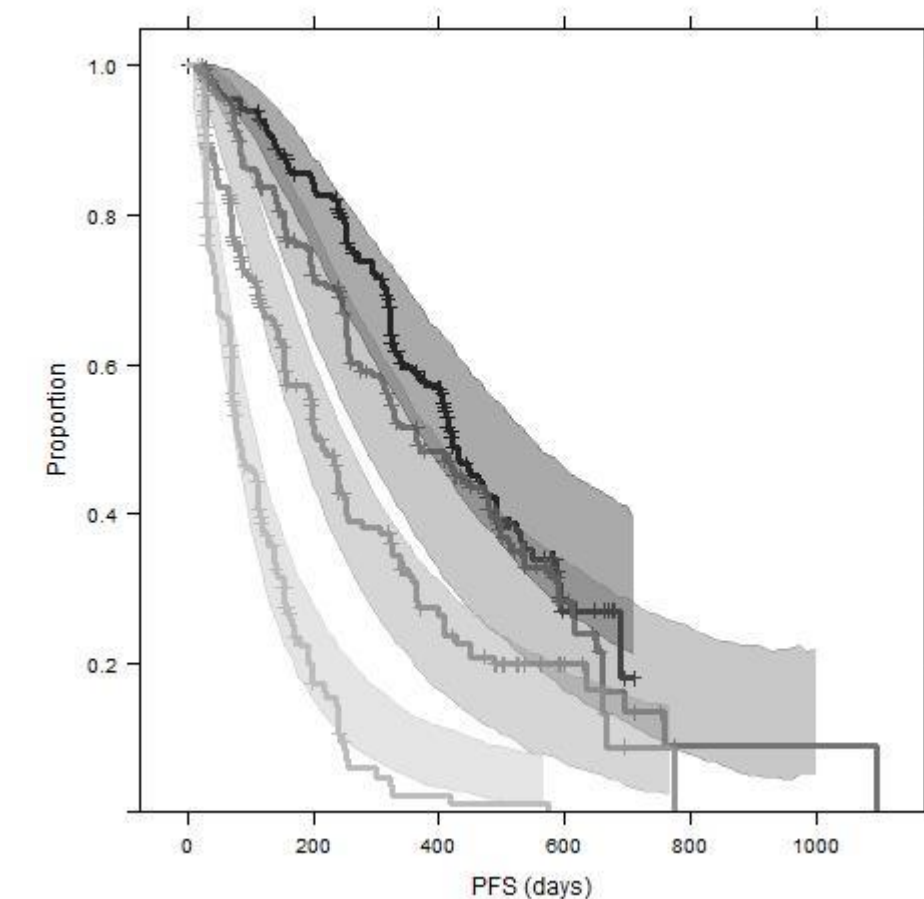
### Model parameter estimates

	Estimate	SE	p
$\theta_{\text{int}}$	3.68	0.0978	<0.0001
$\theta_{\text{ETS}}$	2.52	0.1234	<0.0001
$\theta_{\text{ETS}50}$	0.978	0.0114	<0.0001
$\gamma$	13.1	1.3684	<0.0001
$\theta_{\text{bone}}$	-0.0641	0.0205	0.0018
$\theta_{\text{alb}} \text{ (L/g)}$	0.011	0.0019	<0.0001
$-\log(\tau)$	-0.660	0.0337	<0.0001

SE: standard error, p: Wald test ( $\chi^2$ ), PFS in days;  $\theta_{\text{bone}}$ : regression coefficient in presence of bone metastases;  $\theta_{\text{alb}}$  is the regression coefficient for albumin effect centered to the median of 43 g/L;  $\theta_{\text{ETS}}$ ,  $\theta_{\text{ETS}50}$  and  $\gamma$  describe the nonlinear sigmoidal relationship between week 8 ETS and  $1/\lambda$ .

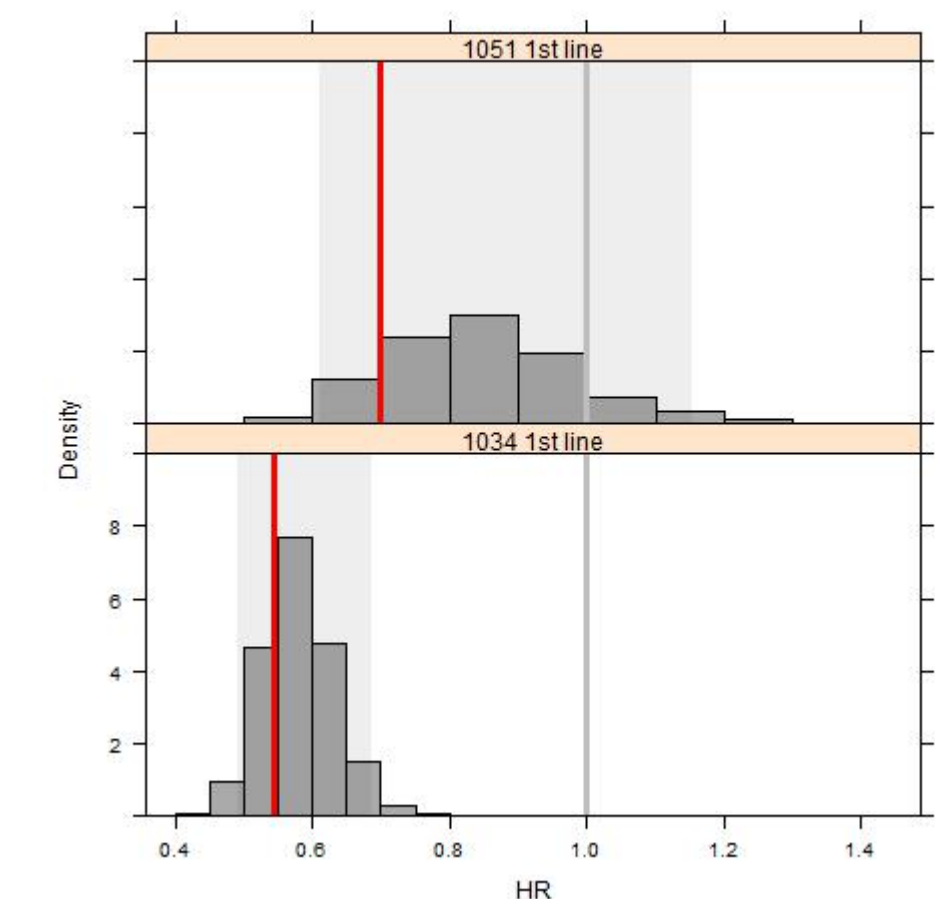
### Model qualification

Predictive check of the final PFS model by quartiles of week 8 ETS



solid lines: observed Kaplan-Meier plots by quartiles of week 8 ETS: dark grey: 1<sup>st</sup> quartile [0.39,0.80], medium grey: 2<sup>nd</sup> quartile [0.80, 0.89], medium light grey: 3<sup>rd</sup> quartile [0.89,0.95], light grey: 4<sup>th</sup> quartile [0.95, 2.62]; areas: 95% prediction intervals by the model.

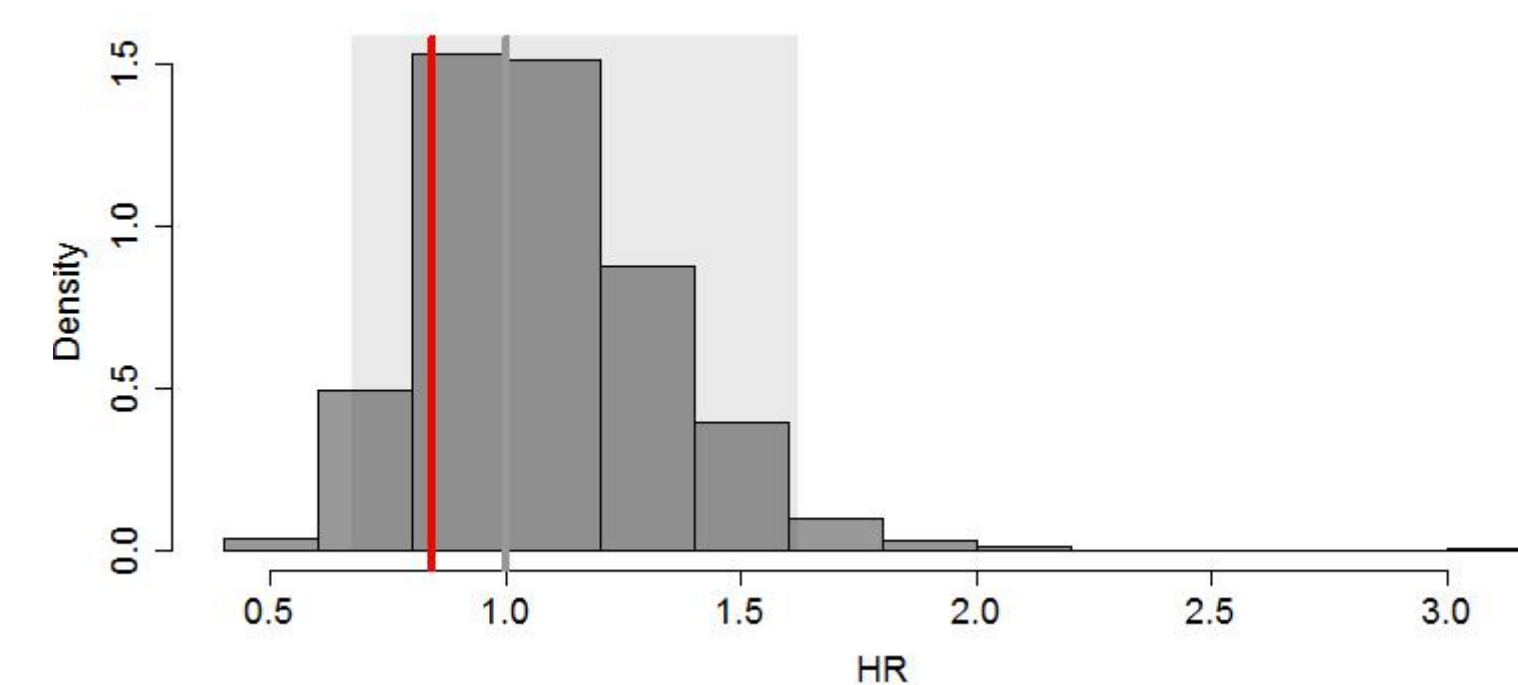
Predictive check of axitinib vs sorafenib HR (upper panel) and sunitinib vs INF- $\alpha$  HR (lower panel) using the final PFS model



Predictive distribution with 95% prediction intervals in light grey vs observed, red line; grey line represents the HR=1.

### External Validation

Predictive check of the axitinib vs placebo HR using the final PFS model

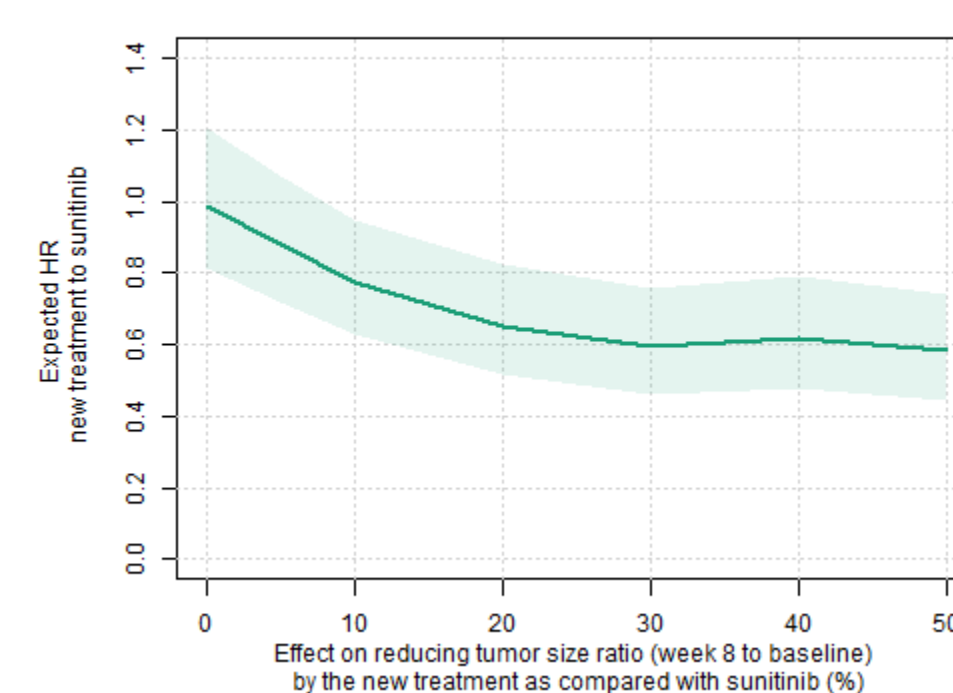


Predictive distribution with 95% prediction intervals in light grey vs observed, red line; grey line represents the HR=1

### Model Simulations

The simulations suggest that if a new investigational treatment could further reduce ETS at week 8 by 30% compared with sunitinib, an expected HR [95% PI] of the new treatment vs. sunitinib would be 0.59 [0.46,0.79].

Prediction of HR of an investigational treatment vs sunitinib as a function of difference in week 8 ETS



Envelope: 95% prediction interval. Line: expected median.

## CONCLUSIONS

A model that uses early change in tumor size to predict the HR for PFS between treatments for first-line mRCC has been developed. Such a model can be used to support early decisions for investigational agents in development for this indication.

## REFERENCES

- [1] Motzer RJ, Hutson TE, Tomczak P et al (2007) Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356:115-124.
- [2] Hutson TE, Lesovoy V, Al-Shukri S et al (2013). Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncol 14:1287-1294.
- [3] Rini BI, Melichar B, Ueda T et al (2013). Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomized double-blind phase 2 trial. Lancet Oncol 14:1233-1242
- [4] Claret L, Gupta M, Han K, et al (2013) Evaluation of tumor size response metrics to predict overall survival in western and Chinese patients with first line metastatic colorectal cancer. J Clin Oncol 31:2110-2114.
- [5] Bruno R, Mercier F, Claret L (2014) Evaluation of tumor-size response metrics to predict survival in oncology clinical trials. Clin Pharmacol Ther 95:386-393.
- [6] Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA.