A MODEL RELATING OVERALL SURVIVAL RELATED TO TUMOR GROWTH INHIBITION IN RENAL CELL CARCINOMA PATIENTS TREATED WITH SUNITINIB, AXITINIB OR TEMSIROLIMUS

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OBJECTIVE

Tumor growth inhibition (TGI) metrics estimated with TGI models have been shown to be predictive of overall survival (OS) in a variety of tumor types[1] . The objectives of this work were

1) to leverage historical data and assess the link between TGI and OS
2) to identify TGI thresholds that are predictive of expected OS benefit and could be used as targets to support early decisions at end of Phase II, or at an interim point of a Phase III clinical trial.

METHODS

Table 1: Characteristics of the studies

Study	Phase	Line	N*	N_{eval}**	Treatment groups
Temsirolimus 1098	III	1st, poor prognosis	501	496	Temsirolimus, interferon, temsirolimus+interferon
Sunitinib 1006	III	2nd, refract[2]	106	105	Sunitinib 50 mg qd 4/2
Sunitinib 1034	III	1st	725	709	Interferon, Sunitinib 50 mg qd 4/2
Sunitinib 1065	II	1st	289	267	Sunitinib 50 mg qd 4/2, and 37.5 mg qd cont
Sunitinib 1072	II	1st and 2nd	51	51	Sunitinib 50 mg qd
Sunitinib 1110	NA	Long term extension	118	113	Sunitinib long term safety and tolerability
Axitinib 1012	II	2nd refract[2]	52	48	Axitinib 5 mg bid
Axitinib 1023	II	2nd, refract[1]	62	50	Axitinib 5 mg bid
Axitinib 1032 (AXIS)	III	2nd	714	651	Axitinib 5 mg bid, Sorafenib 400 mg bid
Axitinib 1035	II	2nd, refract[2]	64	62	Axitinib 5 mg bid
TOTAL			2628	2552 (97.1%)	

*N: patients with tumor size data
**Neval: Patients "evaluable" with at least one post-baseline tumor size measurement in addition to baseline
[1] sorafenib refractory
[2] cytokine refractory

REFERENCES

1 Bruno R. et al. Clin Pharmacol Ther. 2014 Apr;95(4):386-93.

2 Claret L. et al. JCO, 2013 Dec 1;31(34):4374-5.

METHODS

- TGI data (sum of longest diameters) was adequately described using the model[2] :

$$Y_{ij} = \begin{cases} Y_{0i} \cdot e^{KL_i \cdot t_{ij}} & before\ treatment \\ Y_{0i} \cdot e^{\left(KL_i \cdot t_{ij} - \frac{KD_i}{\lambda_i}\left(1 - e^{-\lambda_i \cdot t_{ij}}\right)\right)} & afterward \end{cases}$$

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

$$\theta_i = \theta \cdot e^{\eta_i},\ \eta_i \sim N(0, \omega^2),\ \varepsilon_{ij} \sim N(0, \sigma^2),$$

- The purpose of this model is to derive patient-level TGI metrics[1] (Early tumor shrinkage (ETS) at week 8, 10, 12, or time to growth (TTG))

$$week\ x\ ETS_i = \frac{Y_{Weekx,i}}{Y_{0i}}$$

$$TTG_i = \frac{log(KD_i) - log(KL_i)}{\lambda_i}$$

- OS parametric model was built by backward stepwise elimination
  - select the best distribution describing OS data by Akaike Information Criteria (AIC)
  - "full" model including significant covariates from univariate analysis (p<0.05 per the log-likelihood ratio test).
  - stepwise elimination: p<0.01.
- The model simulation performances were evaluated using posterior predictive checks (PPC). OS distribution and hazard ratios (HR) were simulated 1000 times for the patients, as in the original studies.
- Simulations of the OS model were performed to assess the relationship between the expected effect size in OS (HR) of an investigational treatment and the difference (δ) i.e. the effect size in TGI metric (e.g. week 8 ETS). Multiple replications (n=1000) of virtual Phase III studies comparing an investigational treatment to standard of care were simulated. The power of the Phase III studies was also calculated conditional on the difference in TGI, δ.
- This setting would mimic the calculation of expected HR that could be done as soon as tumor size data are available to estimate TGI, and support interim or end of phase II decisions or interim analysis of phase III.

RESULTS

Table 2: Parameter estimates of lognormal distribution OS model in days

Parameter	Estimate (SE)	p-value
(Intercept)	8.07 (0.270)	<0.001
Week 8 ETS	-1.99 (0.135)	<0.001
Hemoglobin (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
Corrected calcium (mg/dL)	-0.104 (0.019)	<0.001
Log(# metastases)	-0.209 (0.032)	<0.001
Time from diagnosis (days)	8.0E-5 (1.7E-5)	<0.001
Baseline LDH (U/L)	-3.7E-4 (9.2E-5)	<0.001
Lung metastases (yes)	-0.138 (0.046)	0.002
Log(scale)	-0.107 (0.020)	<0.001

SE: standard error, p: wald test (χ^2)
+ sign favorable; - sign not favorable

Figure 1: Predictive check of week 8 ETS OS model by tertiles of week 8 ETS (large light grey, medium grey and low dark grey)

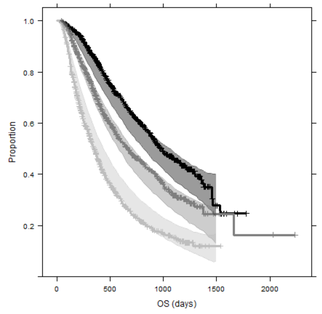


Figure 2: Predictive check of the sunitinib to INF-α HR in first-line sunitinib study (1034)

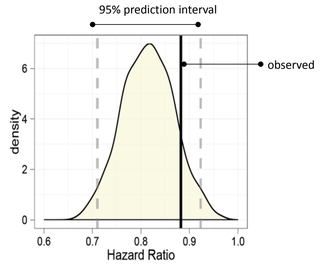
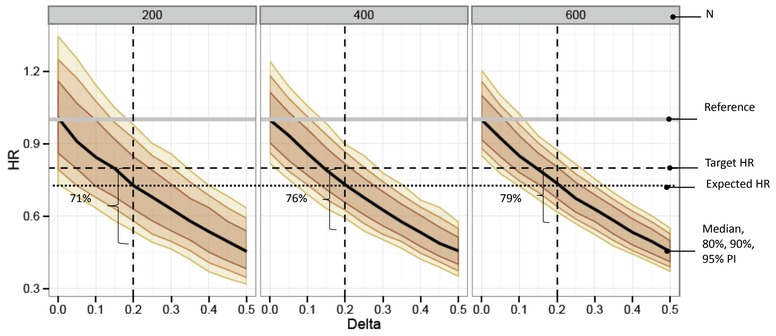


Figure 3: Predictive distribution of HR comparing an investigational treatment to sunitinib in a 200, 400 and 600 patient study (N/2 per arm) as a function of difference in tumor growth inhibition (delta in week 8 ETS)



- According to the simulations, an investigational treatment that would induce a 20% week 8 ETS difference from reference may result in an improved OS with a expected HR ~ 0.75
- A 300 patient per arm Phase III study would have a 79% probability to show HR < 0.8

CONCLUSION

- Week 8 ETS, an early measure of tumor growth inhibition, had satisfactory performance to predict OS in a variety of clinical studies in mRCC
- The OS model was used to simulate clinically relevant ETS targets for future Phase 2 studies with investigational treatments.

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