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Implementing Translational Science

Disease Models in Oncology: Optimizing Trial Design to Maximize POS

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Tripos SIMCYP Pharsight

Outline

- Oncology drug development challenges
- A drug-disease modeling framework
  - Longitudinal tumor size models
  - Tumor growth inhibition metrics
  - Survival models
- Rena cell carcinoma case study
- Discussion

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Oncology drug development

- Expedited programs
  - Little learning from early clinical trials to inform late studies
  - High failure rate in late Phases
  - Large number of new agents and even larger number of combinations…
- Empirical selection of dose and dosing schedules in Phase I
  - Maximum tolerated dose (MTD)
  - Pharmacologically active dose based on biomarker responses specific to the mechanism of action
    - OK to establish proof of mechanism but not mature for dose selection
  - Cohort expansions…
- Phase II program not informative
  - Design
    - Limited to establish proof of concept; Very few randomized Phase IIb dose-ranging studies
  - Primary clinical endpoints (ORR, PFS) poorly informative
- Phase III: High failure rate
  - > 50%
- Filing: Dose justification…
- Post-marketing requests…
  - To confirm dose, optimize dosing…

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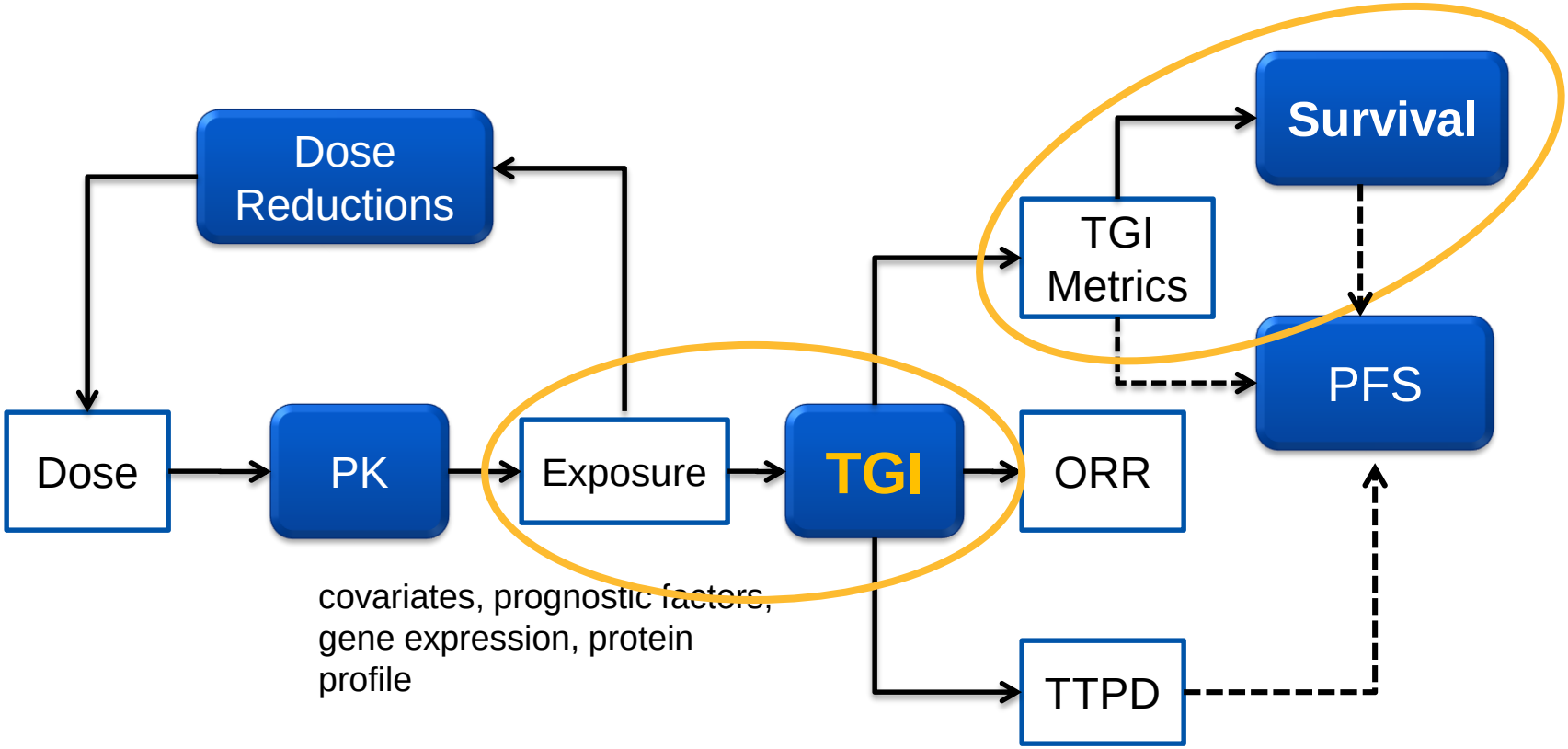
A drug-disease modeling framework to optimize trial design to maximize POS



Modified from Bruno and Claret, Clin Pharmacol Ther, 86, 136-138, 2009

TGI = Tumor growth inhibition

ORR: Objective response rate
TTPD: Time to progressive disease
PFS: Progression free survival

Drug-specific TGI models

- Semi-mechanistic exposure-driven TGI models (simulation)
  - Tumor growth, exposure driven drug effect, resistance appearance[1-5]

- Empirical models (analysis)
  - Simplified TGI model (assumes constant exposure)[6-7]
  - Linear growth plus exponential shrinkage[8-9]
  - Exponential growth and shrinkage[10]

[1]Claret *et al*. *ASCO* 2006 and *PAGE* 2008
[2]Claret *et al. J. Clin. Oncol*. **27**:4103-8, 2009
[3]Tham *et al*. *Clin. Cancer Res*. **14**:4213-8, 2008
[4]Stein *et al*. *BMC Cancer* **12**:311, 2012
[5]Ribba *et al*. *Clin Cancer Res* **18**:5071-80, 2012

[6]Claret *et al*. *PAGE* 2012
[7]Claret *et al. J Clin Oncol* **31**:2110-14, 2013
[8]Wang *et al*. *Clin Pharmacol. Ther*. **86**:167-74, 2009
[9]Maitland *et al*. *Clin Pharmacol Ther*, **93**:345-51, 2013
[10]Stein *et al*. *Clin Cancer Res*, **17**:907-17, 2011

Recently reviewed in Ribba et al. *CPT:PSP* (2014) 3, e113; doi:10.1038/psp.2014.12.

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Models for clinical endpoints (overall survival)

- Survival time distribution is estimated (parametric model) as a function of prognostic factors and predictors
- Drug independent, disease specific model
  - TGI metric is used as a biomarker to capture drug effect
  - Historical Phase III studies can be used to develop the models
  - Overall survival models have been developed for MBC[1], CRC[2,3], pancreatic cancer, ovarian cancer[4], H&N carcinoma, multiple myeloma[5], non-hodgkin lymphoma, gastric cancer[6], renal cell carcinoma[7], NSCLC[8-10] and GIST[11]
- A few cases of external evaluations are available[2,5,12]
  - More are needed

[1]Claret *et al*. *ASCO* 2006 (abstract 2530)
[2]Claret *et al. J Clin Oncol* **27**:4103-8, 2009
[3]Claret *et al. J Clin Oncol* **31**:2110-14, 2013
[4]Lindborn *et al*. *ACoP*, 2009
[5]Jonsson *et al*. *CPT:PSP* **4***:711-19, 2015*
[6]Quartino *et al*. *PAGE* 2013
[7]Claret *et al*. *Cancer Chemother Pharmacol* **76**:917-24, 2015
[8]Wang et al *Clin.Pharmacol. Ther*. **86**:167-74, 2009
[9]Claret *et al*. *Clin. Pharmacol. Ther*. 95, 446-451, 2014
[10]Bruno *et al*. Proc ASCO 2013, abstract e19103
[11]Hansson *et al*. *CPT:PSP*, **2**:e8, 2013
[12]Claret *et al*. Clin. Pharmacol. Ther. **92**:631-4, 2012

Recently reviewed in Bruno et al. *Clin. Pharmacol. Ther.* 95, 386-393, 2014.

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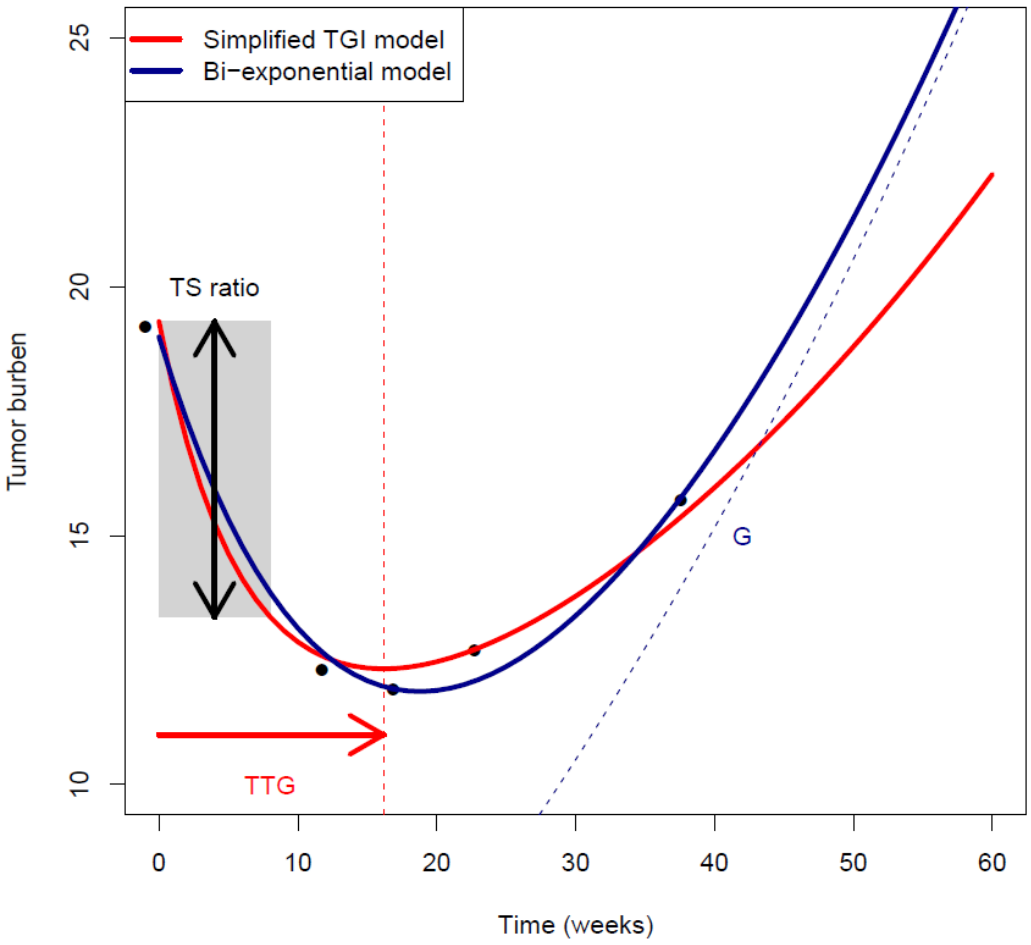
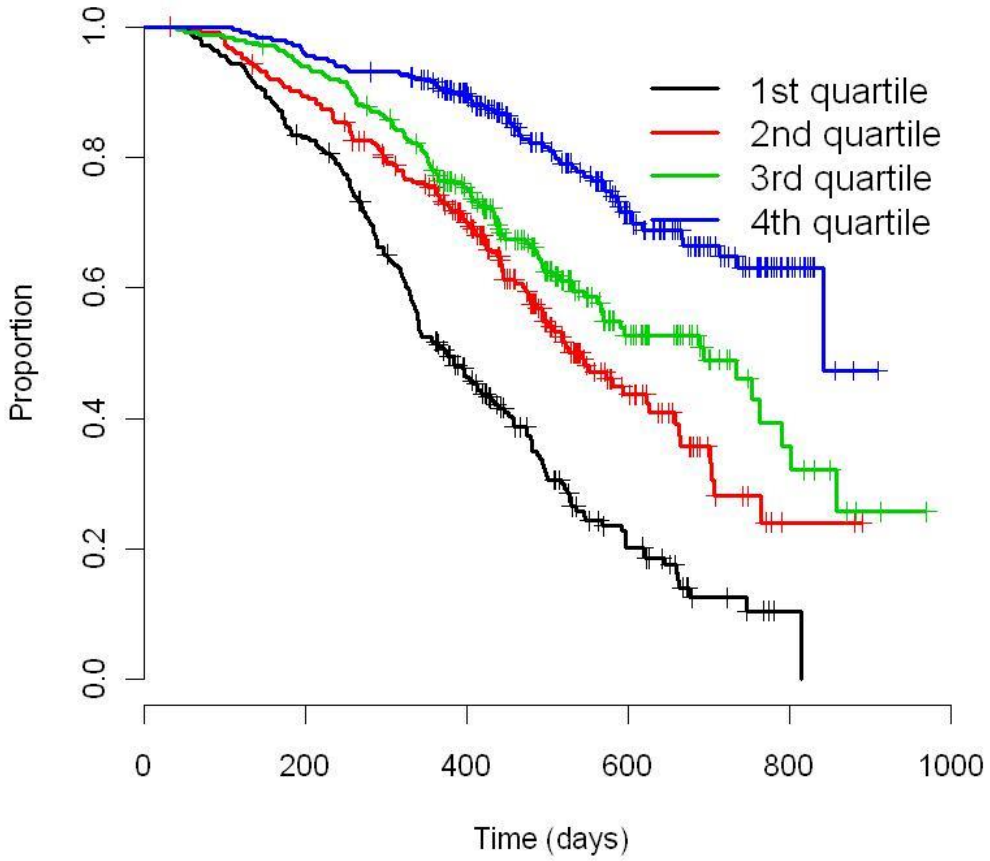
Tumor growth inhibition metrics



Claret *et al*. *J. Clin. Oncol.*, **31**:2110-2114, 2013

TGI metrics are well correlated with OS e.g. TTG in CRC

Claret *et al*. *J. Clin. Oncol.*, **31**:2110-2114, 2013



OS by quartiles of TTG

Data from two randomized phase III studies of bevacizumab plus chemotherapy in the 1st-line treatment of CRC in 813 Western patients (Hurwitz, 2004) and in 203 Chinese patients (Guan, 2011)

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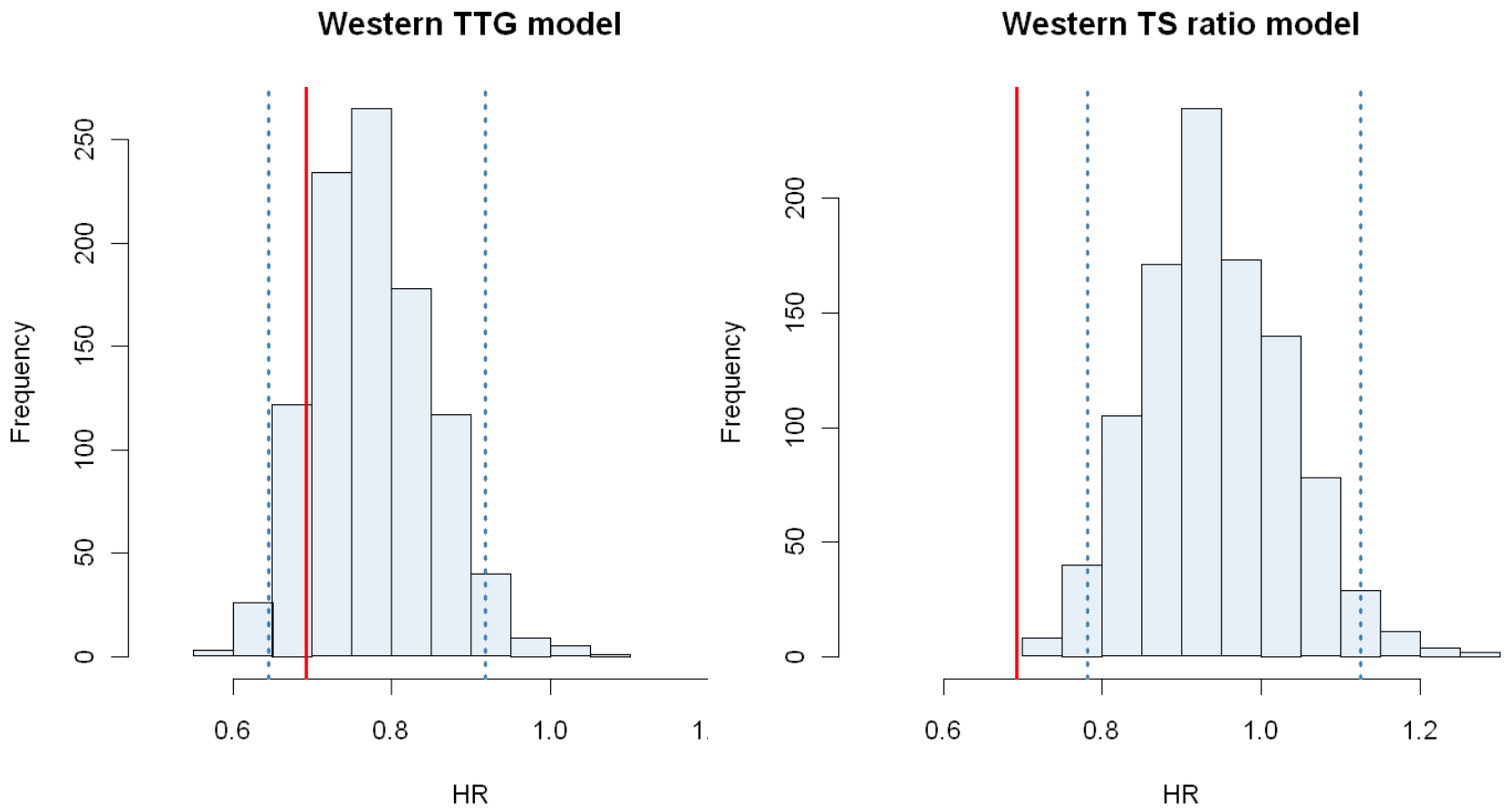
Correlation with OS is nice but not enough: The TGI metric should capture treatment effect (HR) too…



Colorectal cancer OS model assessment (bevacizumab hazard ratio):

The model with TTG does the job when TS ratio (week 8 to baseline ratio) does not

Claret *et al*. *J. Clin. Oncol.*, **31**:2110-2114, 2013

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Modeling and simulations relating overall survival to tumor growth inhibition in renal cell carcinoma patients

Laurent Claret[1] · Francois Mercier[2,3] · Brett E. Houk[4] · Peter A. Milligan[5] · Rene Bruno[1]

Cancer Chemother Pharmacol
DOI 10.1007/s00280-015-2820-x

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Metastatic renal cell carcinoma (mRCC) OS model

- To leverage historical data and assess the link between TGI and OS

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

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TGI model

- TGI data (sum of longest diameters) adequately described using a previously published model (Claret L. et al. JCO, 2013)

$$Y_{ij} = \begin{cases} Y_{i0} \cdot e^{KL_i \cdot t_{ij}} & \text{before treatment} \\ Y_{i0} \cdot e^{\left(KL_i \cdot t_{ij} - \frac{KD_i}{\lambda_i} \cdot \left(1 - e^{-\lambda_i \cdot t_{ij}}\right)\right)} & \text{afterward} \end{cases}$$

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

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

$$\text{week x ETS}_i = \frac{Y_{Weekx,i}}{Y_{i0}} \qquad TTG_i = \frac{\log(KD_i) - \log(KL_i)}{\lambda_i}$$

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OS model

- OS parametric model built by backward stepwise elimination
  - Lognormal distribution
  - Drug effect captured by week 8 ETS

	Parameter	Estimate (SE)	p-value
	(Intercept)	8.07 (0.270)	<0.001
Drug effect →	Week 8 ETS	-1.99 (0.135)	<0.001
Prognostic factors	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
OS in days

Claret et al. Cancer Chemother Pharmacol, 76, 567-573, 2015

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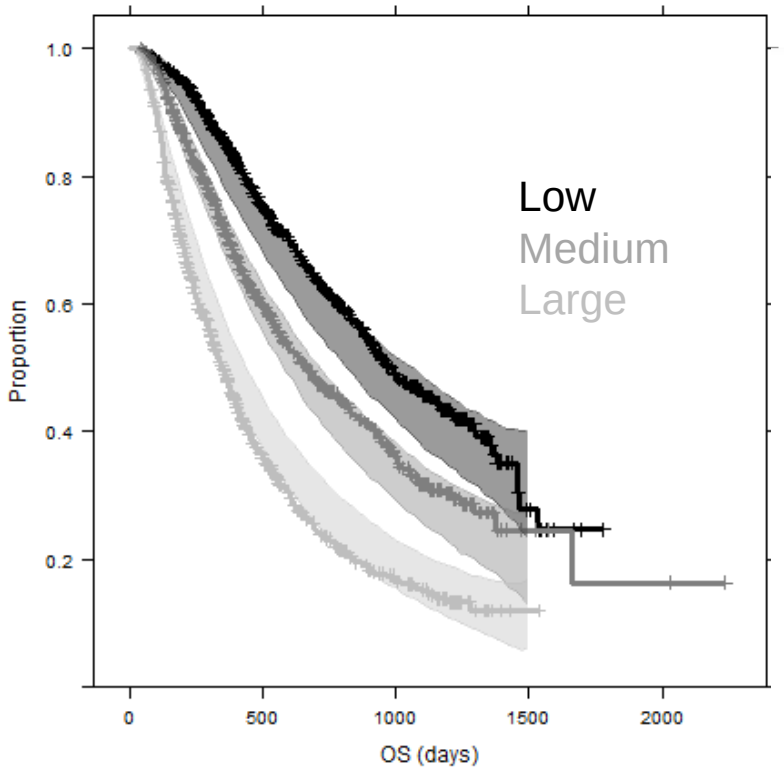
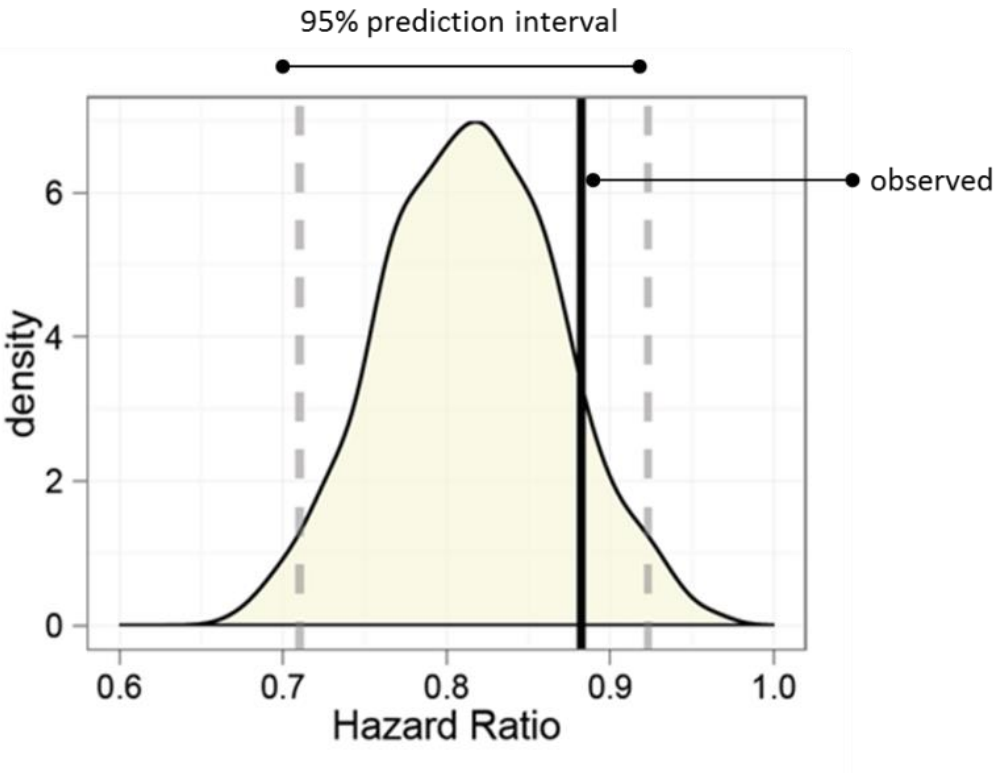
OS Model Validation

- The model was evaluated using posterior predictive checks
  - OS distribution and hazard ratios (HR) were simulated (1000 replicates).

Week 8 ETS OS model by tertiles of week 8 ETS



Sunitinib to INF-α HR in the first-line sunitinib study (1034)



Claret et al. Cancer Chemother Pharmacol, 76, 567-573, 2015

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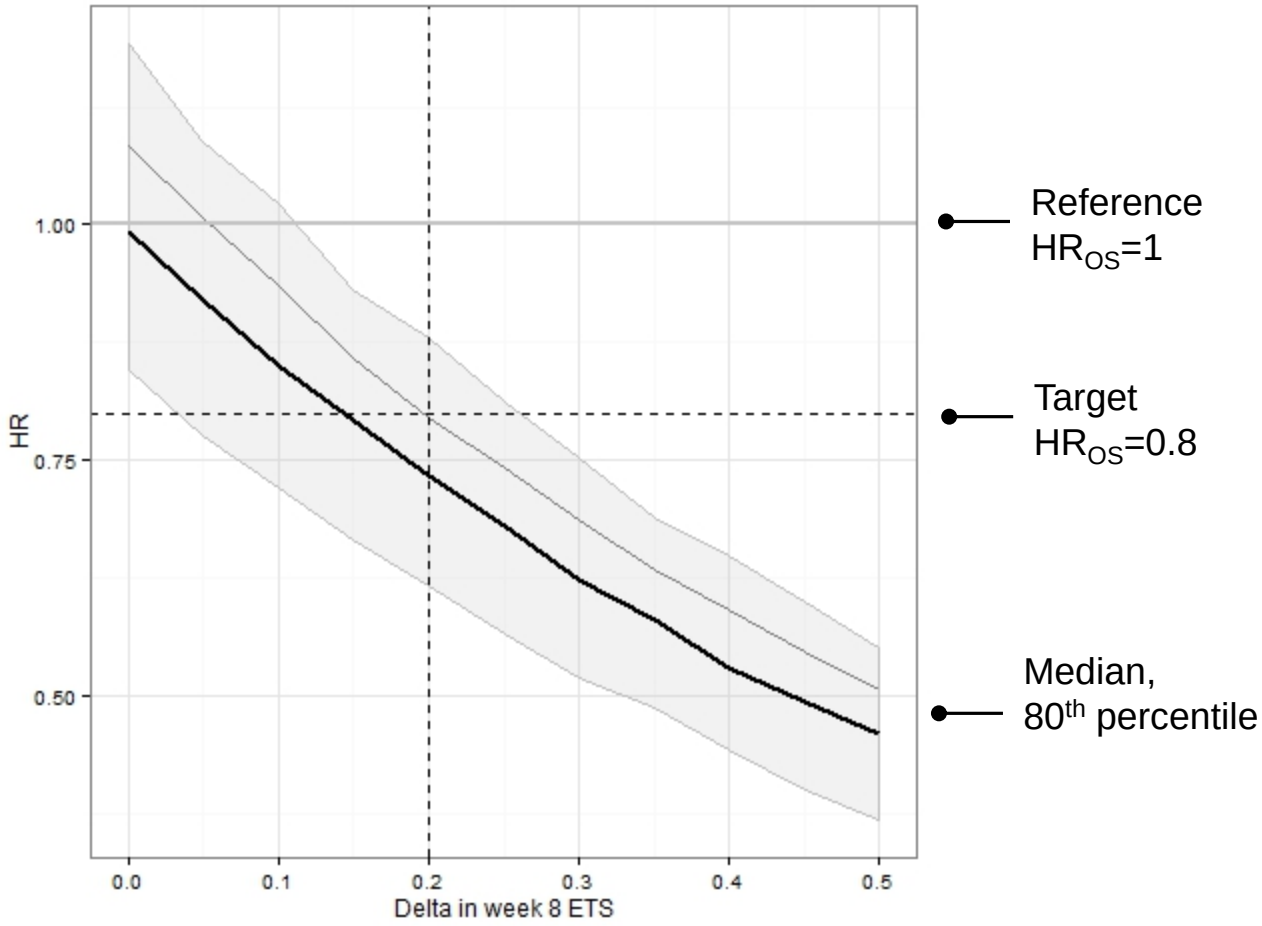
Metastatic renal cell carcinoma (mRCC) OS model

- Model simulations
  - Predictive distribution of HR comparing an investigational treatment to sunitinib in a 600 patient study (300 per arm) as a function of difference in tumor growth inhibition (delta in week 8 ETS)



A 300 patients per arm Phase III study would have a 80% probability of technical success to show a HR < 0.80 (target product profile)

Claret et al. Cancer Chemother Pharmacol, 76, 567-573, 2015

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Summary

- Week 8 ETS, an early measure of tumor growth inhibition, had satisfactory performance to predict OS in 10 clinical studies of a variety of treatments in metastatic RCC
- Clinically relevant ETS targets for future Phase 2 studies with investigational treatments were simulated
- One can play with the simulations to adapt to desired product profile, investigational treatment and number of patients in pivotal study
- This model and another one for PFS (published soon) are being used to support interim decisions in ongoing studies

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Discussion

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Clinical development questions to maximize POS

- POM-POC: Is the drug doing anything?
  - Demonstrate exposure-response with appropriate biomarkers, sensitive metrics or drug effect
- Is the dose/schedule right?
  - Take advantage of exposure variability to simulate dose response (efficacy and/or safety)
- What is the most informative Phase II study design?
  - Use an early TGI metric as endpoint
  - Assess target effect associated with desired OS improvement
- End-of-Phase II decision: Is the effect seen in Phase II worth it?
  - Simulate expected OS advantage based on TGI
- Phase III study design and conduct
  - Simulate probability of technical success
  - Support interim futility analysis based on TGI

- Use of longitudinal tumor size data and sensitive TGI metrics is much more informative than traditional endpoints
  - No regulatory issue as far as limited to support decision making
  - Has also been accepted to address PMR and avoid a clinical study

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Acknowledgements

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  - P. Chanu, F. Mercier (now with Roche), P. Girard (now with Merck-Serono)
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