

Evaluation of Tumor-Size Response Metrics to Predict Survival and Progression Free Survival in First-Line Metastatic Colorectal Cancer

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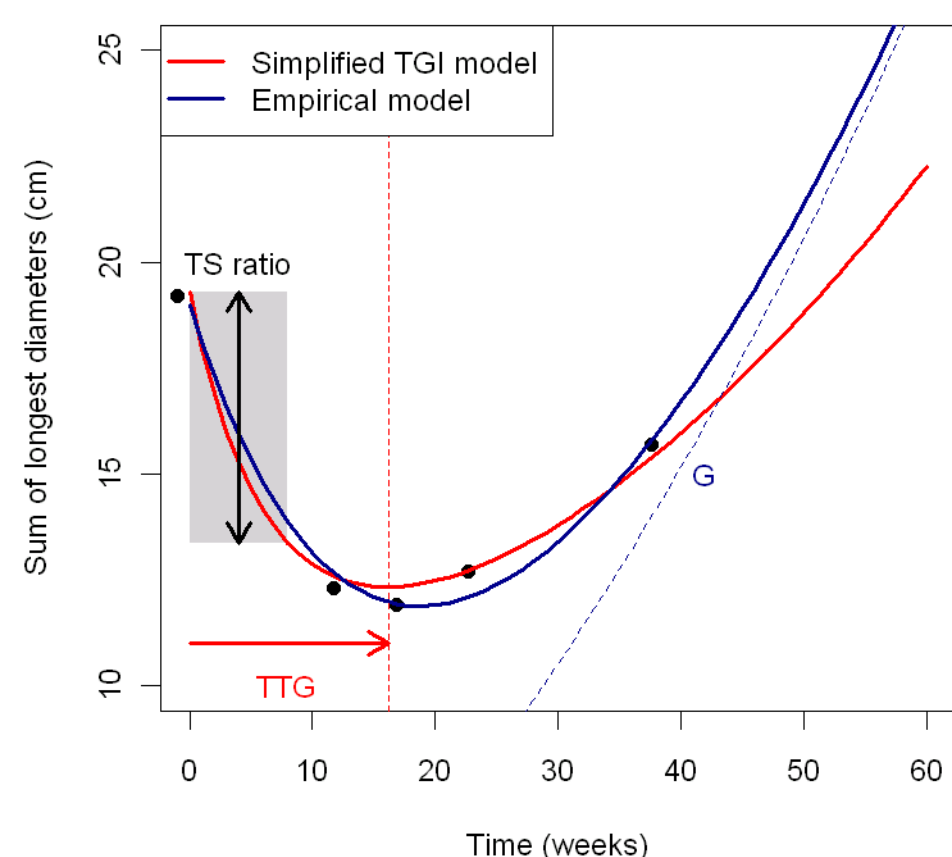
BACKGROUND

Change in tumor size from baseline at the end-of-cycle 2 (TS ratio) has been proposed as a predictor of overall survival (OS) in metastatic colorectal cancer (CRC) (1, 2) and other tumor types (1, 3, 4). The goal of this project was to assess new metrics of tumor size response to predict clinical endpoints, i.e. OS and progression free survival (PFS), and to test for any ethnic differences in the link between tumor size response and clinical endpoints in metastatic Colorectal cancer (mCRC).

METHODS

Tumor size metrics

Various metrics of tumor size response (see Figure) were estimated using longitudinal tumor size models developed from two Phase III studies comparing bevacizumab plus chemotherapy vs. chemotherapy as first-line therapy in Western (923 patients) (5) and Chinese patients (203) (6) with CRC.



The simplified TGI model

If we assume a constant exposure for patients, a simplified version of the previously published exposure-driven tumor growth inhibition (TGI) model (2) can be used to describe tumor size data:

$$KDE_0 = KD_0 \cdot \text{Exposure}$$

$$TS(t) = TS(0) \cdot \exp\left[KL \cdot t - \frac{KDE_0}{\lambda} \cdot (1 - e^{-\lambda t})\right]$$

TS ratio is defined by:

$$TS.RATIO = \frac{TS(\text{week8})}{TS(0)}$$

And time to growth by:

$$TTG = \frac{\log(KDE) - \log(KL)}{\lambda}$$

The empirical model

Recently Stein et al (7) published a simple model to describe tumor dynamics. It describes TS(t)/Baseline with a bi-exponential function (shrinkage rate and growth rate).

$$f(t) = \exp(-D \cdot t) + \exp(G \cdot t) - 1$$

They showed that log(G) is correlated with OS.

Model parameters of models are estimated with NONMEM 7.

The simplified TGI model better fit the TS data (based on log-likelihood, 14257 vs. 15105).

CONCLUSIONS

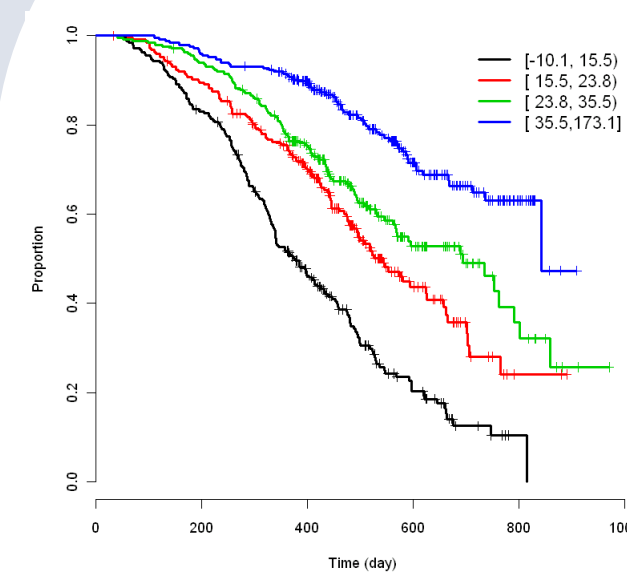
TTG and G are a better tumor size metrics than TS ratio to capture bevacizumab effect and predict OS and PFS in first-line CRC patients. As opposed to TS ratio, they capture the duration of drug action that may explain the better performance for targeted therapy such as bevacizumab. There is no impact of Chinese ethnicity on TTG-survival or PFS relationships. Longitudinal tumor size data coupled with model-based approaches offer a powerful alternative in the design and analysis of early clinical studies in both Western and Chinese patients (8).

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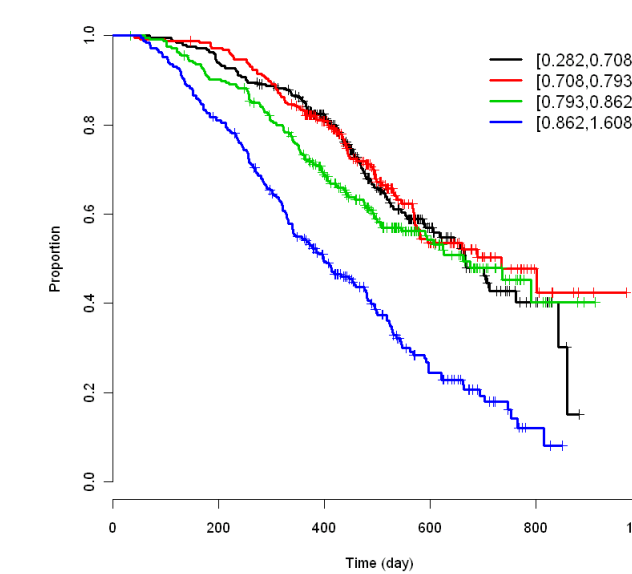
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RESULTS

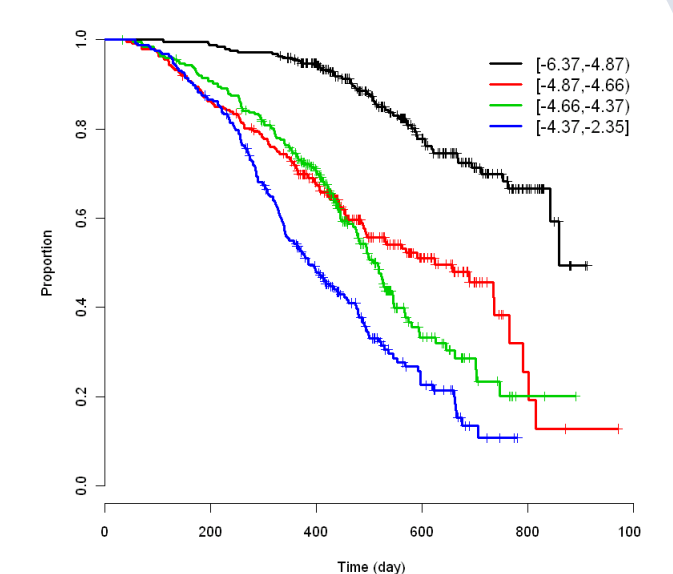
OS ~TTG



OS ~TS ratio



OS ~log(G)



Survival model development

Survival distribution was best described by a Weibull function Univariate Cox analysis showed that ECOG (>0), TS at baseline, number of lesions at entry, TS ratio, TTG, log(G) and bevacizumab treatment were significant predictors of survival Multivariate analysis (backward stepwise and log likelihood ratio test) selected TTG, ECOG and number of lesions TTG and G were similar in term of likelihood (delta=-1.8 in favor of G) but TTG did a bit better in the PPC of the hazard ratio Bevacizumab effect is explained by TTG (or log(G)) but not by TS ratio

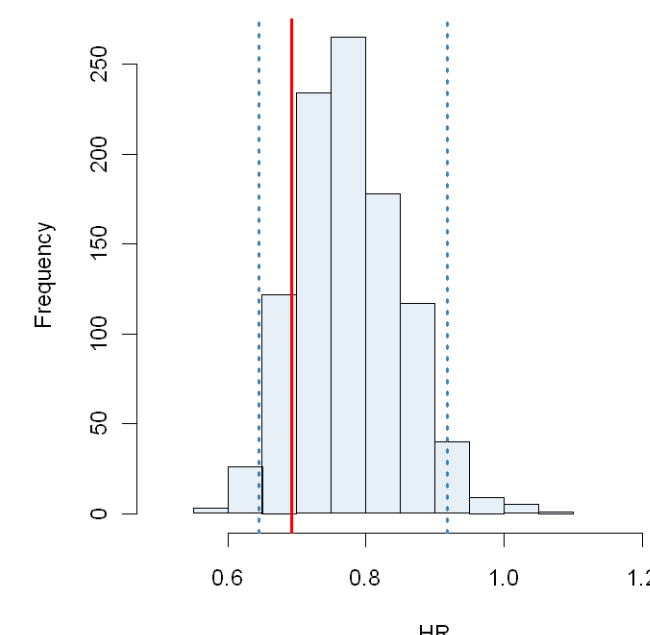
No interaction between TTG effect and Western/Chinese study

OS model parameter estimates

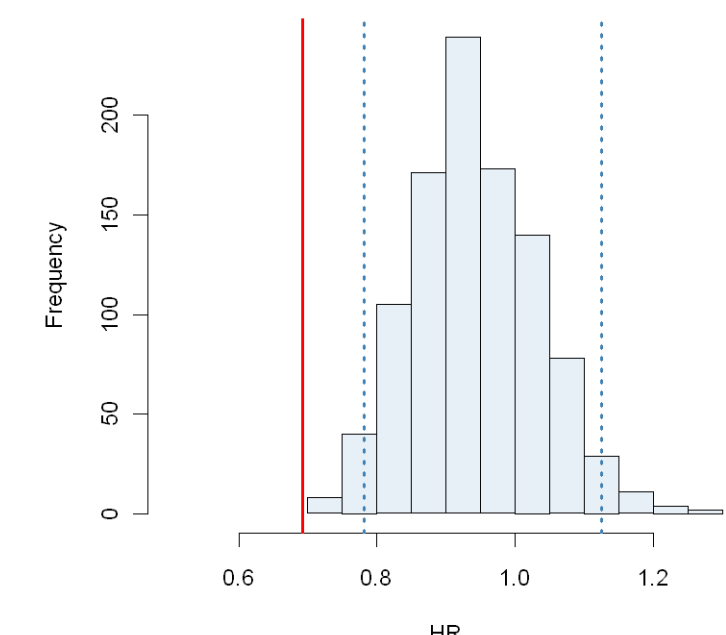
	Value	Std. Error	z	p
(Intercept)	6.2194	0.05488	113.3	0.00E+00
TTG	0.0205	0.00188	10.9	9.52E-28
ECOG>0	-0.3244	0.04699	-6.9	5.07E-12
Number of lesion > 2	-0.1841	0.04979	-3.7	2.18E-04
Log(scale)	-0.7116	0.03856	-18.5	4.90E-76

Posterior predictive check of the bevacizumab hazard ratio (in Western patients)

TTG Model



TS ratio Model



PFS model development

Survival distribution was best described by a Weibull function Univariate Cox analysis showed that ECOG, TS at baseline, number of lesions at entry, TS ratio, TTG, log(G) and bevacizumab were significant predictor of PFS (same as for survival)

Multivariate analysis selected TTG, ECOG and bevacizumab treatment

Bevacizumab treatment effect was not fully explained by TTG (it was not by log(G) or TS ratio either)

No interaction between TTG effect and western/chinese study

No interaction between bevacizumab effect and western/chinese study

The TTG model is superior to both TS and log(G) ones in term of likelihood

PFS Model parameter estimates

	Value	Std. Error	z	p
(Intercept)	5.0221	0.05001	100.42	0.00E+00
TTG	0.0244	0.00158	15.4	1.54E-53
ECOG>0	-0.1553	0.03947	-3.93	8.34E-05
bevacizumab	0.1901	0.03995	4.76	1.96E-06
Log(scale)	-0.6744	0.02939	-22.94	1.71E-116