Operating characteristics of TGI metrics to support early Phase Ib decisions in unresectable hepatocellular carcinoma patients based on an historical Phase III study (IMbrave150)

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Antonio Gonçalves (1), Mathilde Marchand (1), Victor Poon (2), Phyllis Chan (2), René Bruno (3)

(1) Certara Strategic Consulting, Paris, France; (2) Clinical Pharmacology, Genentech, South San Francisco, California, USA; (3) Clinical Pharmacology, Genentech-Roche, Marseille, France

Background & Objective

- A modeling framework has been developed to assess the operating characteristics of tumor growth inhibition (TGI) metrics to support early decision-making in non-small cell lung cancer [1].
- Tumor growth rate constant geometric mean ratio (KG GMR) showed good operating characteristics with satisfactory power (>80%) and reasonable type 1 error (<20%) suggesting that it could be used to support early decisions.

Aims

- Explore the operating characteristics of TGI metrics in a Phase 1b trials in another indication, namely hepatocellular carcinoma (HCC)
- Compare the results to those obtained when modeling the full phase 3 data

Methods

Data

- IMbrave150 study in patients with unresectable hepatocellular carcinoma assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab (Experimental arm, n=336) or sorafenib (Control arm, n=165).
- Experimental arm showed a benefit versus control with a median overall survival (OS) at 6 months of 84.8 vs 72.2% [2].

Figure 1: Overall survival Kaplan – Meier plot from [2]
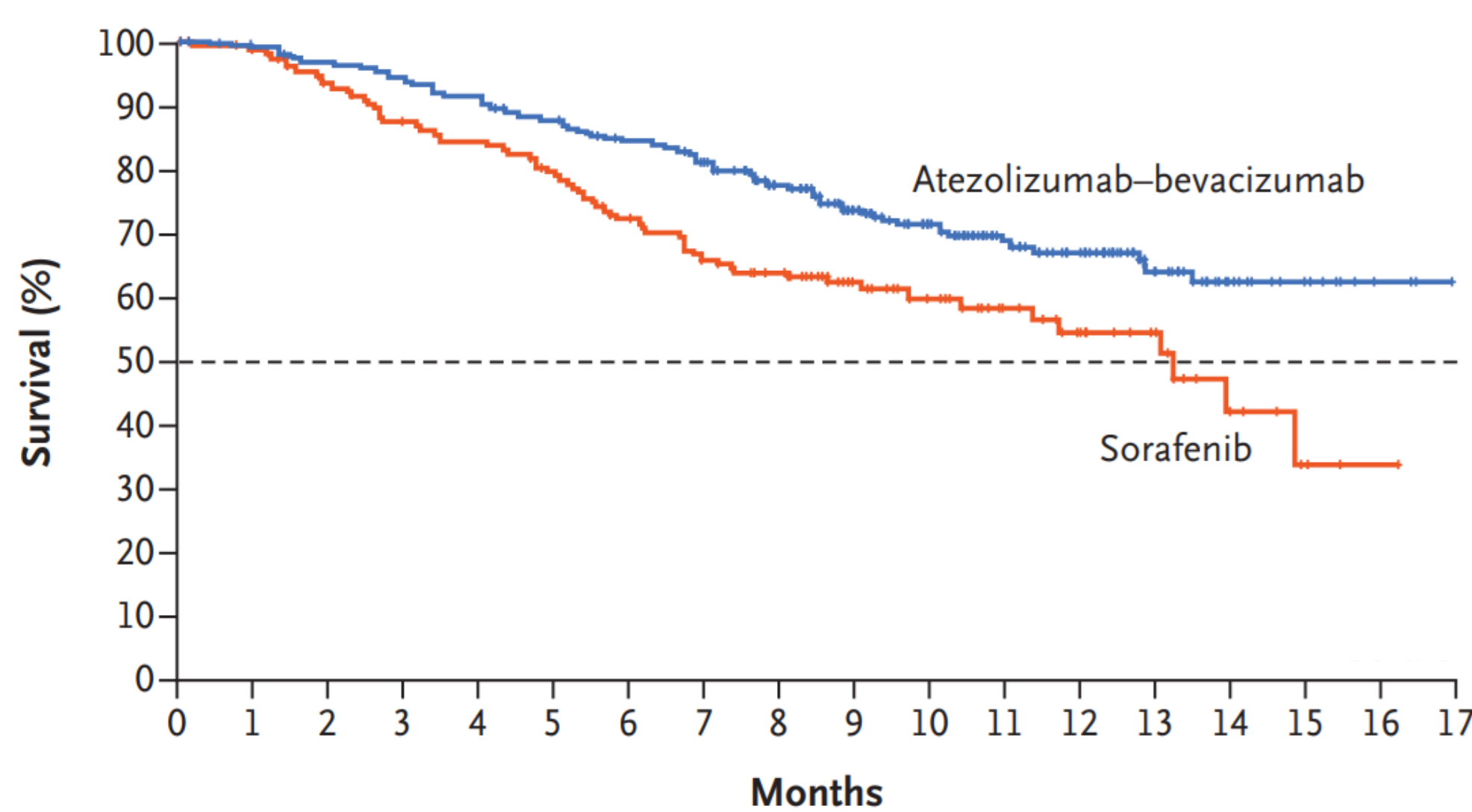
Experimental design
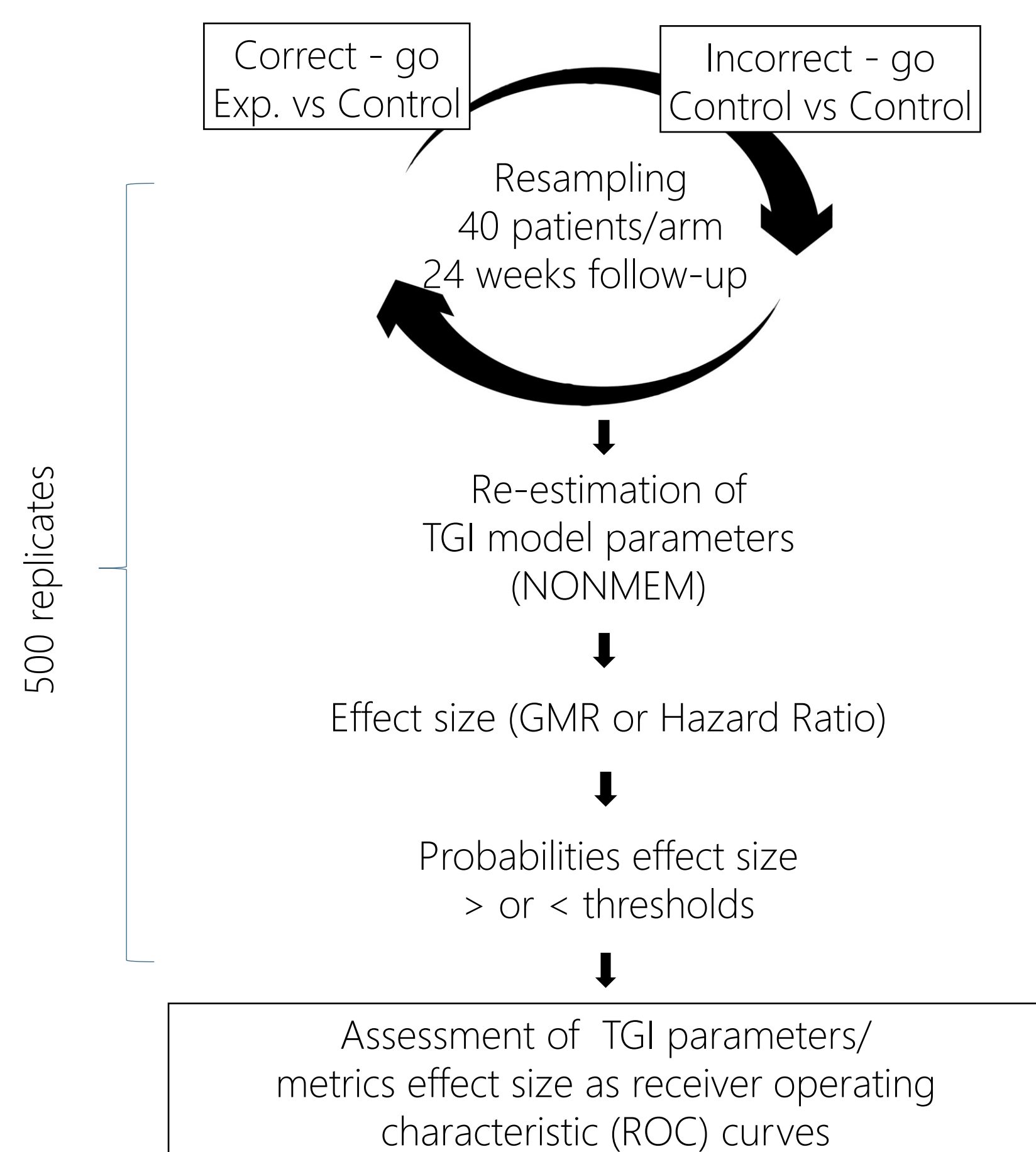
Model [3,4]

$$TS(t) = \begin{cases} TS_0 \cdot e^{KG \cdot t} & , if\ t < 0 \\ TS_0 \cdot (e^{-KS \cdot t} + e^{KG \cdot t} - 1) & , if\ t \geq 0 \end{cases}$$

t is the time (week) with time 0 at the start of treatment; TS is the tumor size (mm), TS_0 is the tumor size at the start of treatment (mm); KS is the tumor shrinkage rate constant (week^{-1}) and KG is tumor growth rate constant (week^{-1})

Results

TGI-OS analysis – all data

Table 1: OS models parameter estimates

Model with log(KG) from [5]

Parameter	Estimate	SE	z	P
(Intercept)	3.15	0.559	5.63	1.8x10^{-8}
Log(KG)	-0.662	0.0621	-10.65	<2x10^{-16}
BSLD	-0.00305	0.000788	-3.87	1.1x10^{-4}
CHLDPGH	-0.437	0.105	-4.16	3.2x10^{-5}
MVIEHS	-0.407	0.108	-3.77	1.6x10^{-4}
ALBU	0.0282	0.0102	2.77	5.5x10^{-3}
ECOG	-0.225	0.0904	-2.49	1.3x10^{-2}
Log(scale)	-0.205	0.0464	-4.41	1.0x10^{-5}

Model with log(TR24)

Parameter	Estimate	SE	z	P
(Intercept)	9.55	0.590	16.2	<2x10^{-16}
Log(TR24)	-0.989	0.107	-9.25	<2x10^{-16}
BSLD	-0.00326	0.00078	-4.18	2.9x10^{-05}
CHLDPGH	-0.482	0.982	-4.91	9.1x10^{-07}
LogAFP	-0.0416	0.0135	-3.08	2.1x10^{-03}
logLDH	-0.420	0.110	-3.81	1.4x10^{-04}
Log(scale)	-0.205	0.0473	-4.14	3.5x10^{-05}

KG: tumor growth rate constant; TR24: tumor ratio at week 24; BSLD: baseline tumor size; CHLDPGH: Child-Pugh score (A6/B1 vs A5); MVIEHS: macrovascular invasion / extrahepatic spread (yes vs no); ALBU: albumin; ECOG: Eastern Cooperative Oncology Group performance status (+1 vs 0) ; AFP: alpha-fetoprotein; LDH: lactate dehydrogenase

Figure 2: Qualification of TGI-OS models
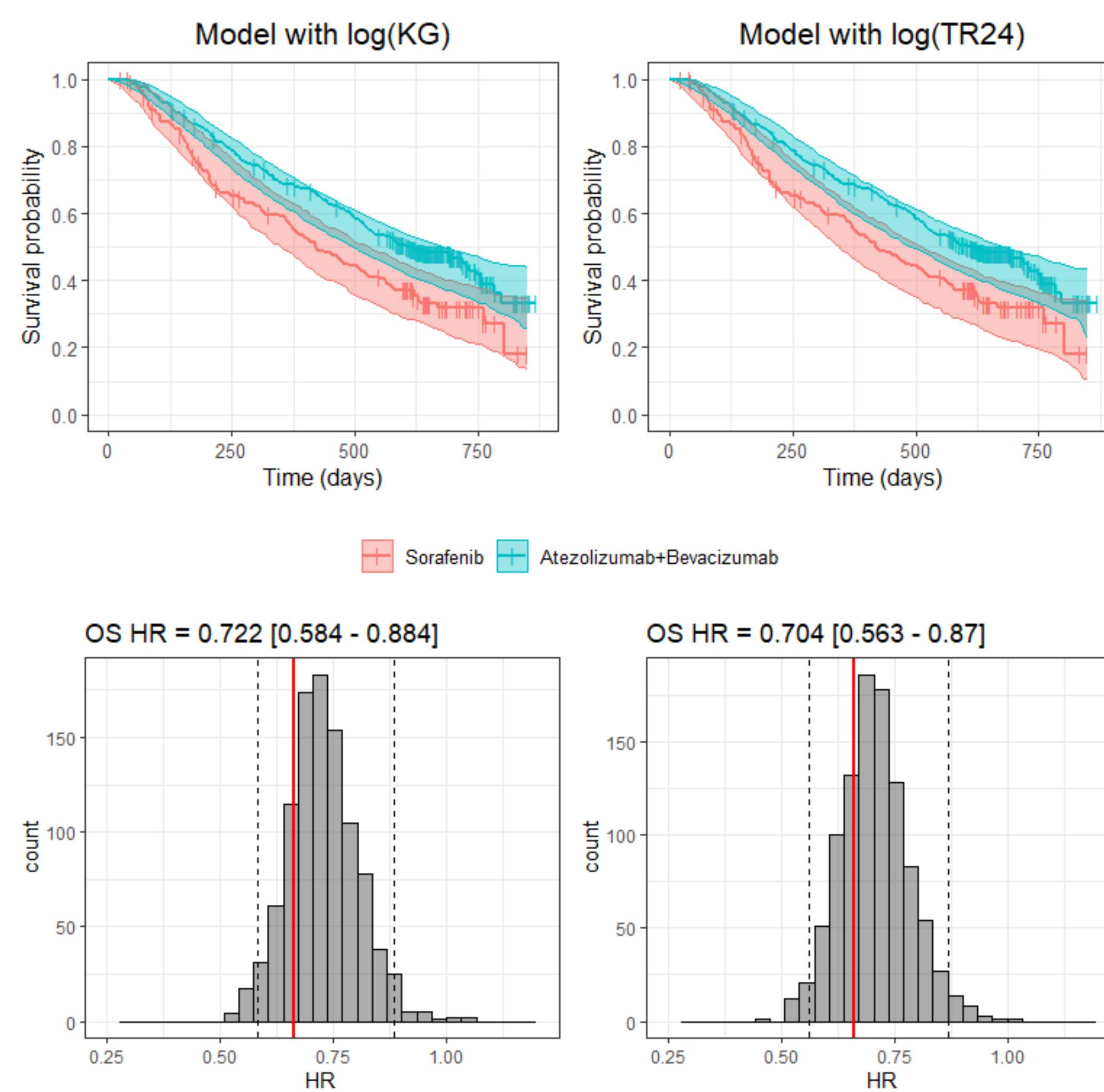
- Two parametric TGI-OS models were previously developed, using log(KG) [5] or log(TR24) as the TGI metric in the model.
- Both models assumed a lognormal distribution for the baseline hazard.
- Although the model with log(TR24) provided the best fit to the data (AIC = 3663.5 vs 3734.1) both models well predict the OS distribution of the full Phase III data.
- Median OS HR [95%PI] = 0.722 [0.584 – 0.884] and 0.704 [0.563 – 0.870]; vs. observed HR = 0.67).

Operating characteristics

Figure 3: ROC curves for model parameters - 40 patients 24 weeks
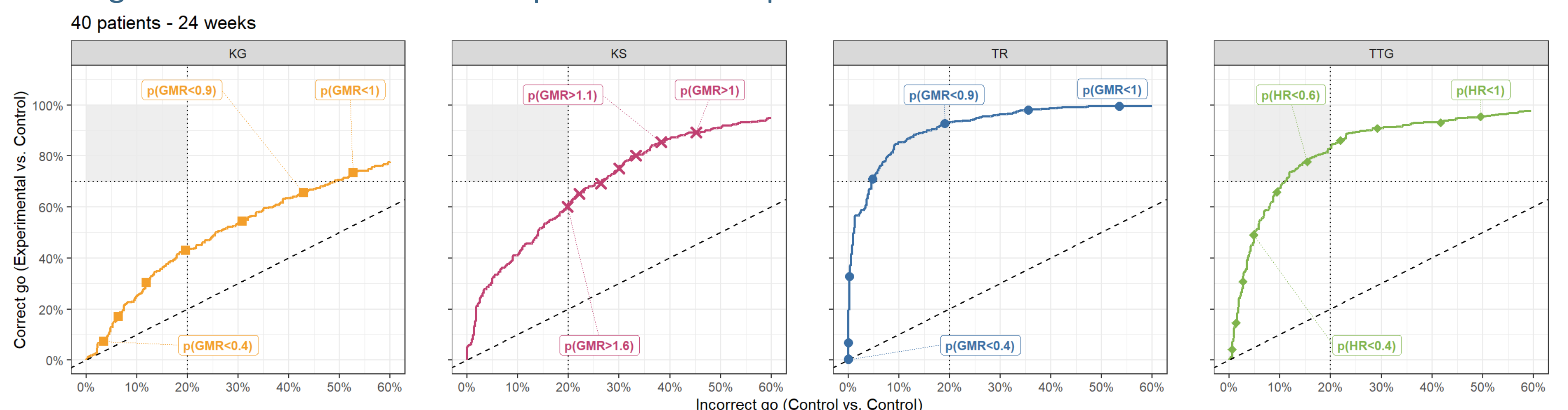
- p(KG GMR<0.9) provided insufficient power (66%) and high type 1 error (43%)
- Alternatives to KG GMR:
  - p(TTG HR<0.6) had good power (79%) and low type 1 error (<20%)
  - p(TR24 GMR<0.9) had good power (91%) and low type 1 error (<20%)

Conclusions

- KG may provide a good prediction of Phase 3 outcome (OS HR) but does not necessarily have good operating characteristics
- TR24 or TTG could be used as relevant alternatives to support early decisions

Perspectives

- Investigation of other models (see Marchand et al. poster) to estimate alternative TGI metrics
- Use of machine learning approaches to establish the relationship between TGI metrics, baseline prognostic factors and OS

References

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