Assessment of a model to correlate early tumor size measurements to overall survival in relapsed or refractory diffuse large B-cell lymphoma patients

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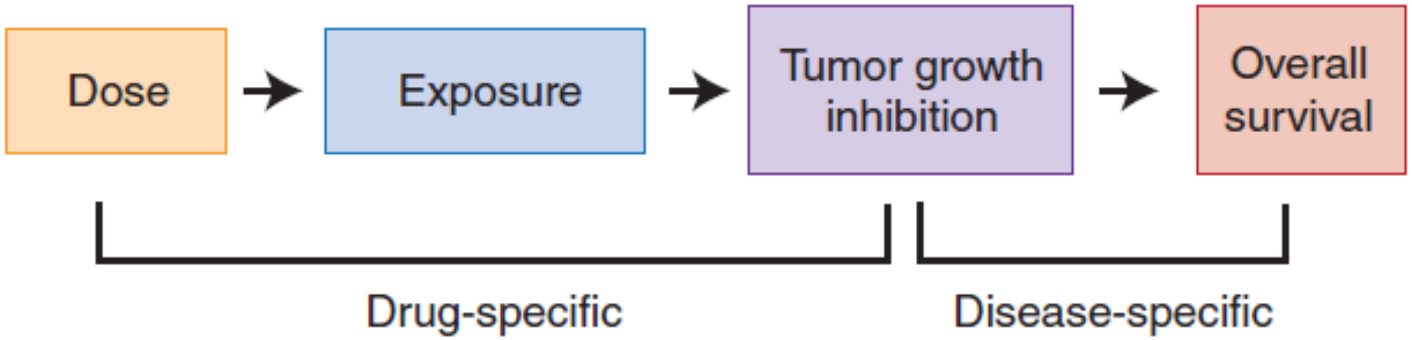
Modeling Framework



- Clinical efficacy of new molecular entities for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) is typically determined using objective response rate (ORR) and overall survival (OS)
- Model-based parameters such as tumor growth inhibition (TGI) metrics can provide quantitative insights to predict clinical response (e.g. OS) and support earlier decisions to initiate late-stage drug development[1]
- Limited TGI-OS modeling framework in literature for hematological cancers

1. Bruno et al. Clin Pharmacol Ther (2013) 93:303-5.

Objectives of the Analysis

- Describe longitudinal, continuous tumor size* measurements using TGI models
- Determine the correlation between TGI metrics, baseline covariates, and OS
- Assess whether covariate-adjusted TGI metrics can be used to rank order treatment efficacy across studies/treatment combinations for patients with R/R DLBCL

*Square root of sum of product of diameters (SPD) of the target tumors
DLBCL, diffuse large B-cell lymphoma; TGI, tumor growth inhibition; OS, overall survival; R/R, relapsed or refractory; TGI, tumor growth inhibition

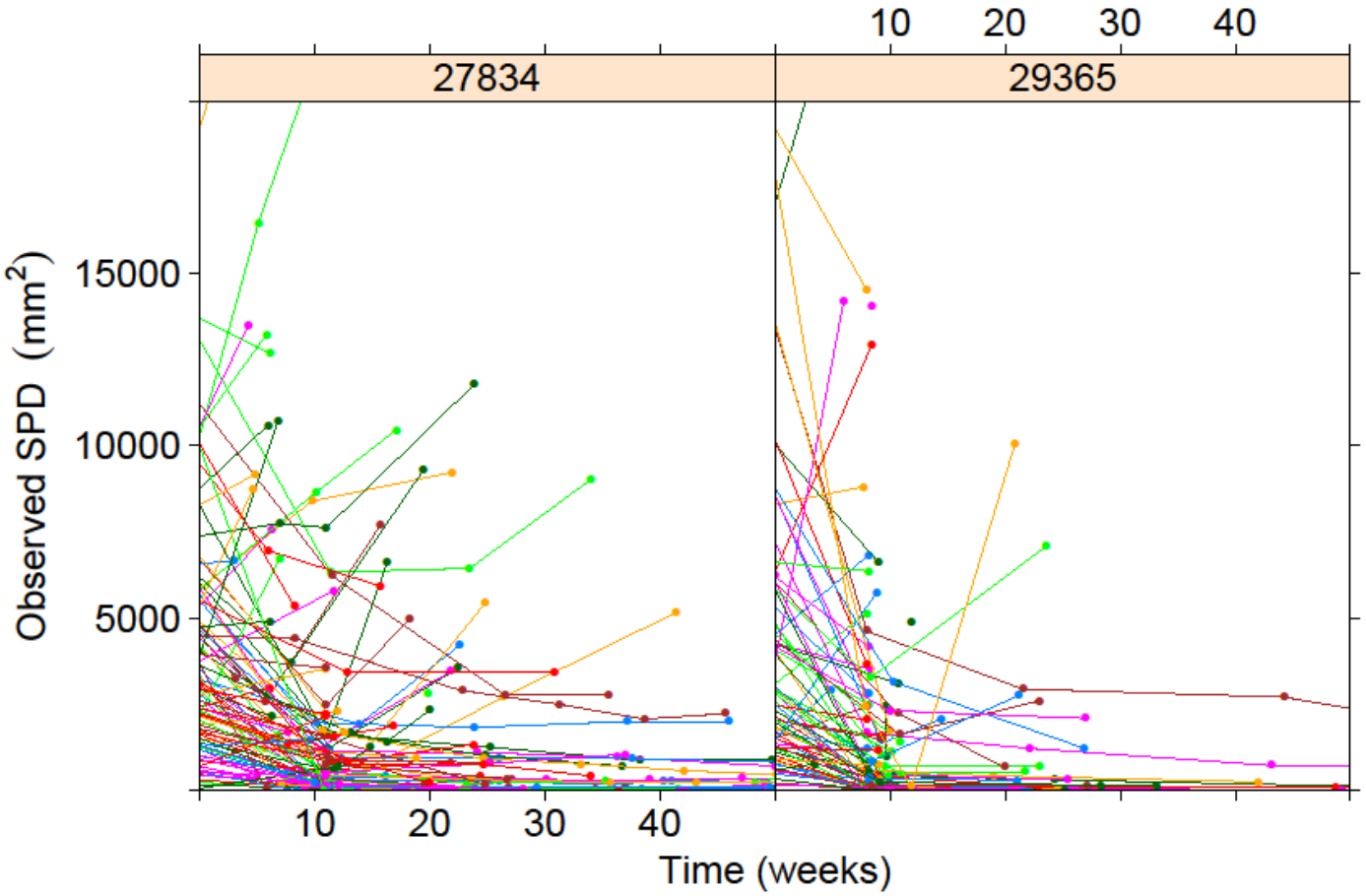
Study Inclusion and Treatment Categorization

Study/ tumor	Treatment	Study arm n	Analysis n* (% of study arm n)	Treatment duration
GO27834/ NHL Phase 1b/2	Rituximab + pinatuzumab vedotin (pina) Rituximab + polatuzumab vedotin (pola) Obinutuzumab + pola	42 39 45	34 (81) 36 (92) 34 (76)	Until progression Until progression Up to 8 cycles
GO29365/ DLBCL and FL Phase 1b/2	Bendamustine + obinutuzumab + pola Bendamustine + rituximab + pola Bendamustine + rituximab (control)	26 45 39	21 (81) 38 (84) 27 (69)	Up to 8 cycles Up to 8 cycles Up to 8 cycles
Total		236	190 (81)	

- Treatments:
  - Rituximab is a monoclonal antibody (anti-CD20)
  - Pina and pola are investigational antibody-drug conjugates (anti-CD22 and anti-CD79b, respectively), consisting of a monoclonal antibody conjugated to the cytotoxic agent, monomethyl auristatin E
  - Obinutuzumab is a humanized monoclonal antibody (anti-CD20)
  - Bendamustine is a chemotherapy drug
- All drugs were given by IV infusion

*Only subjects with tumor data after the start of treatment were included in the analysis; ClinicalTrials.gov Identifiers: NCT01691898 (GO27834) and NCT02257567 (GO29365)
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma

Square Root of Longitudinal SPD Data from Two Studies were Used for TGI Model Development



Different types of tumor size profiles were observed (e.g., progression, relapse, remission)

SPD, sum of product of diameters; TGI, tumor growth inhibition

TGI Model Development

- Base model comparisons
  - Simplified TGI model[1]
  - Stein model[2]
  - Modified Stein model with normal distribution on KSEOT

$$f(x) = \begin{cases} Baseline * e^{KG*time}, time \leq 0 \\ Baseline * \left(e^{KG*time} + e^{-KS*time} - 1\right), 0 < time \leq EOT \\ Baseline * TR_{EOT} * \left(e^{KG*time} + e^{-KSEOT*time} - 1\right), time > EOT \end{cases}$$

  - Chatterjee model[3]
- Covariate model building
  - Treatment group, age, gender, ECOG performance status, bulky disease, refractory to prior rituximab treatment, first *vs* any later relapse, baseline LDH, albumin, and hemoglobin levels were tested as covariates on each of the TGI parameters
  - Univariate screening (p-value < 0.05) to construct the full model
  - Backward elimination (p-value < 0.001) to determine the final model

ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; KG, tumor growth rate constant; KS, tumor shrinkage rate constant; KSEOT, tumor shrinkage after end of treatment
LDH, lactate dehydrogenase; TGI, tumor growth inhibition; TR, tumor ratio from baseline

1. Claret et al. J Clin Oncol (2013) 31:2110-2114. 2. Stein et al. Clin Cancer Res (2011) 17:907-917. 3. Chatterjee et al. Annals Oncol (2016) 27:1291-1298.

TGI Final Model

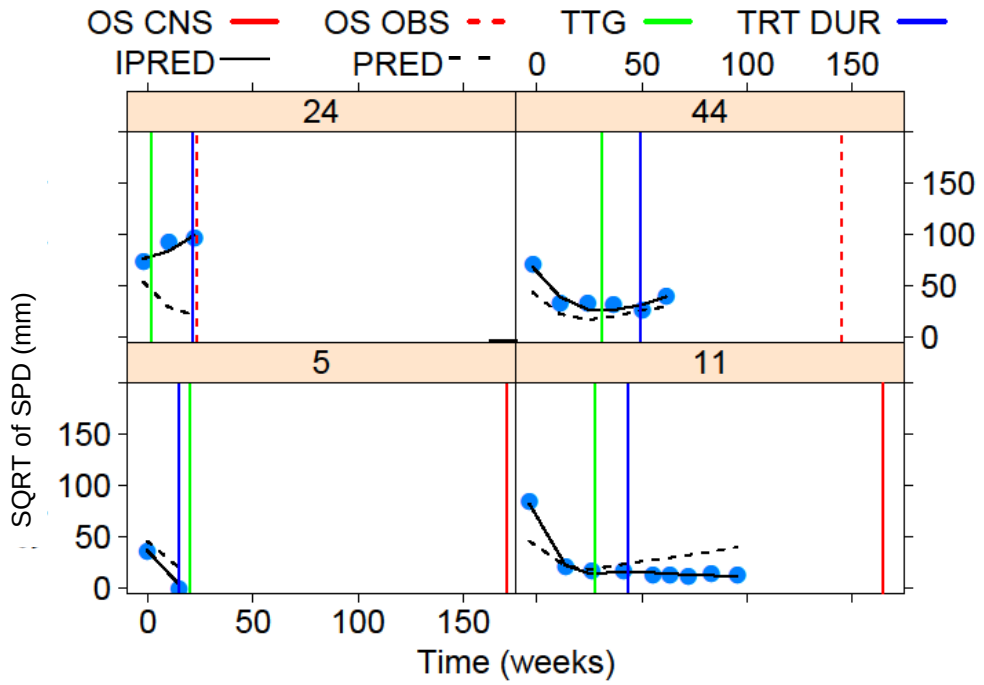
	Base model OFV = 4042.230			Final model OFV = 3932.71		
Parameter (Unit)	Estimate	RSE (%)	Shrinkage (%)	Estimate	RSE (%)	Shrinkage (%)
KG (1/week)	0.0093	16		0.0092	18	
KS (1/week)	0.0847	9		0.0832	9	
Baseline size (mm)	55.3	4		45.2	5	
KSEOT (1/week)	0.0766	9		0.0308	50	
LDH on Baseline				0.864	26	
ECOG PS = 1 on Baseline				1.05	6	
ECOG PS = 2 on Baseline				1.22	10	
Bulky Disease on Baseline				1.88	5	
Additive Residual	27.4	39		28.3	35	
IIV KG (CV%)	113	25	18	112	26	18
IIV KS (CV%)	80.0	22	24	81.4	25	24
IIV Baseline (CV%)	50.4	12	4	35.5	15	6
IIV KSEOT (CV%)	79.1	91	42	204	120	51
Corr KS-KG (r^2)	0.255			0.266		
Corr Baseline-KSEOT (r^2)	0.191			0.0554		

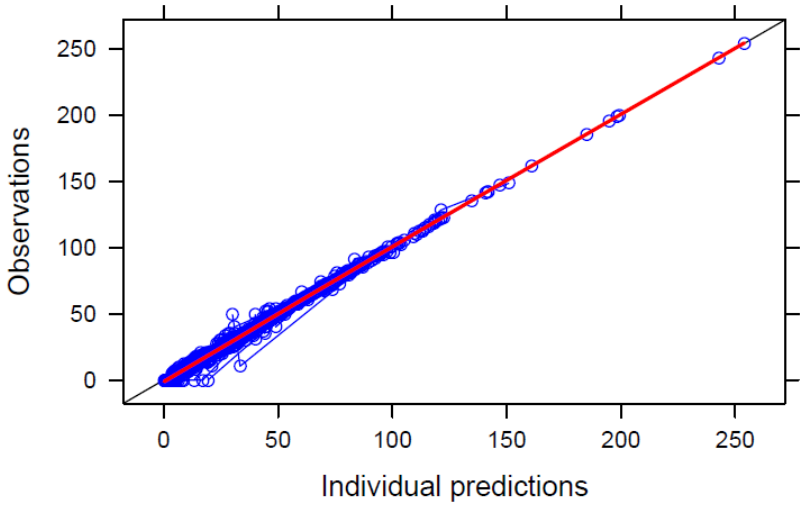
- Treatment group was not a statistically significant covariate
- Effects on baseline SPD (inside black box) are the only statistically significant baseline covariates in the final model

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; KG, tumor growth rate constant; KS, tumor shrinkage rate constant; KSEOT, tumor shrinkage after end of treatment; LDH, lactate dehydrogenase; OFV, objective function value; RSE, relative standard error; TGI, tumor growth inhibition; TR, tumor ratio from baseline

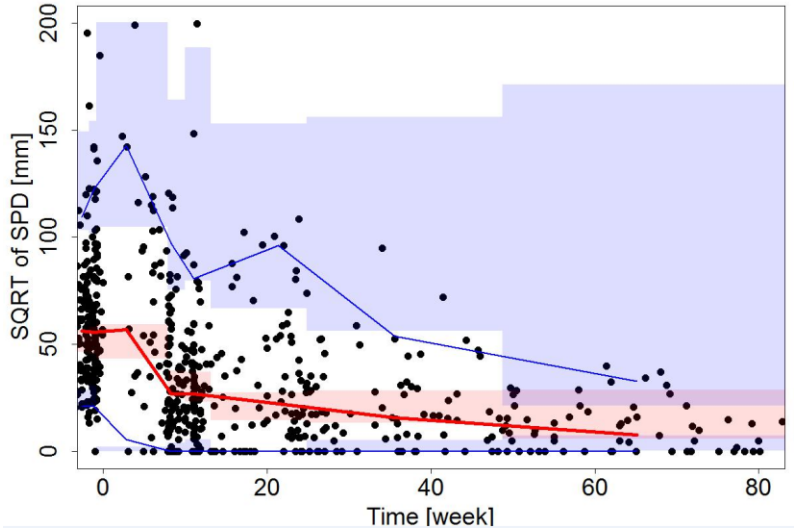
Model Estimation of Tumor Size Profiles and Model Diagnostics

- Modified Stein model adequately describes individual tumor size profiles





DV vs. IPRED



VPC

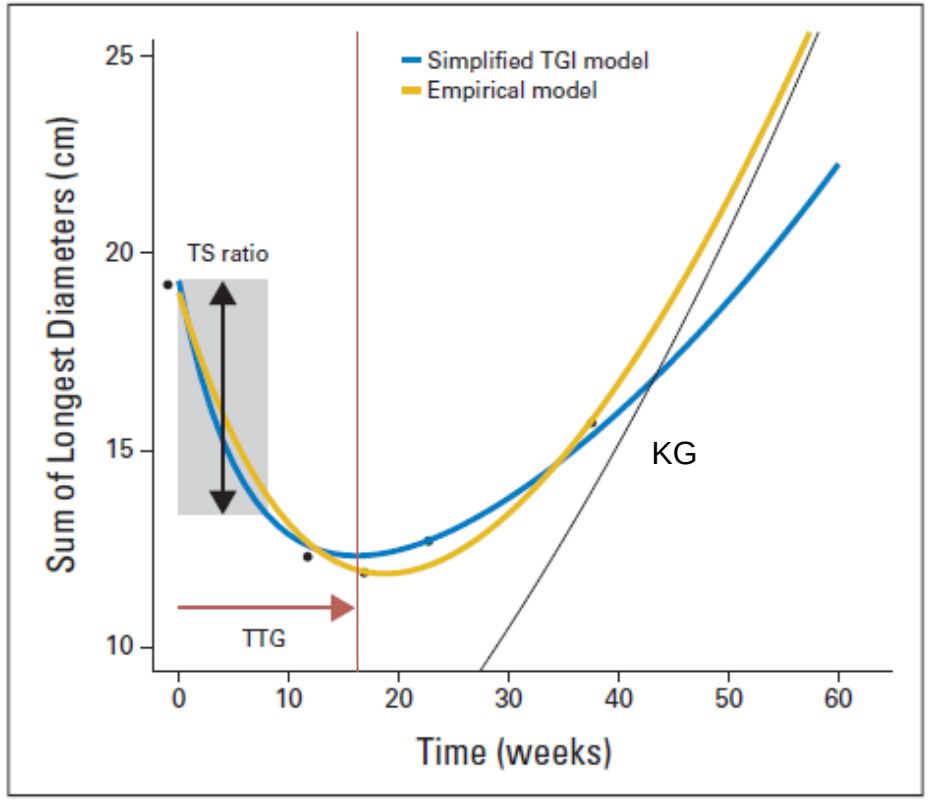
*Simulated data subsequent to 20% increase from nadir per subject were excluded

CNS, censored; DV, observations; IPRED, individual predictions; OS overall survival; OBS, observed; PRED, population predictions; SPD, sum of product of diameters; SQRT, square rootTRT DUR, treatment duration;
TTG, time to tumor growth; VPC, visual predictive check

Key TGI Metrics of Interest

- KG: tumor growth rate (1/week)
- TTG: time to tumor growth (week)
- TR8: tumor size ratio of week 8/baseline
- TR12: tumor size ratio of week 12/baseline

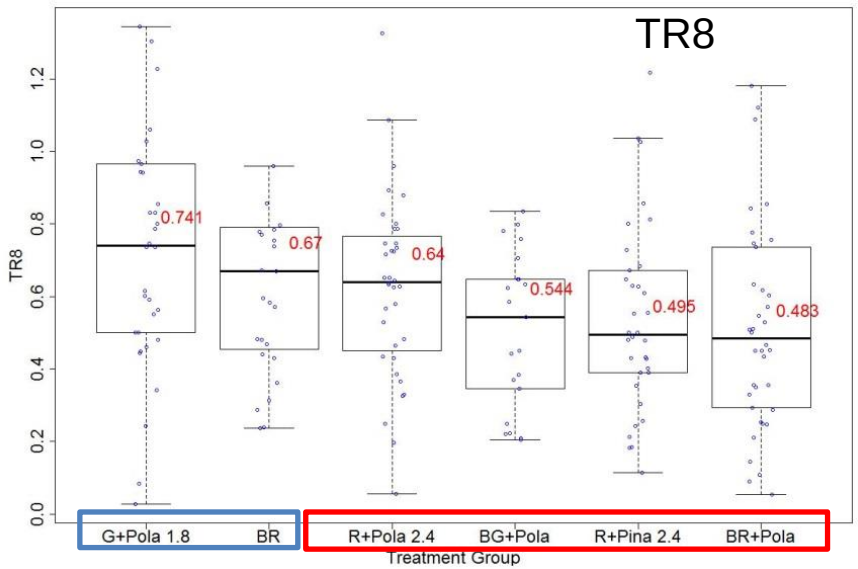
$$TTG = \begin{cases} \frac{lnKS - lnKG}{KS + KG}, 0 \le time \le EOT \\ \frac{lnKSEOT - lnKG}{KS + KG}, time > EOT \end{cases}$$

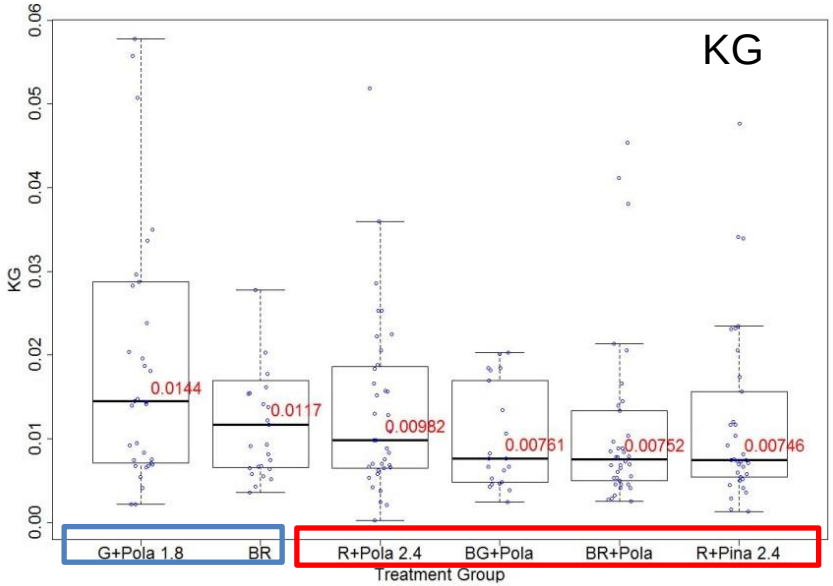


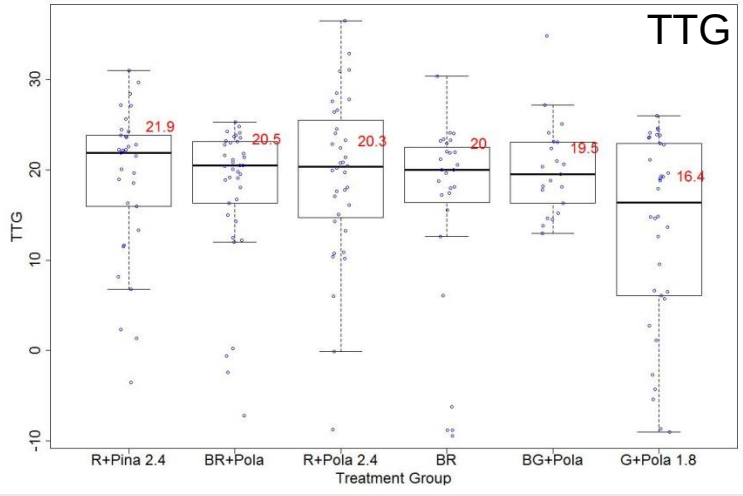
From Claret et al. J Clin Oncol (2013) 31:2110-2114.

KS, tumor shrinkage rate constant; KSEOT, tumor shrinkage after end of treatment; TGI, tumor growth inhibition

Rank Order of Median TGI Final Model Tumor Metrics by Treatment



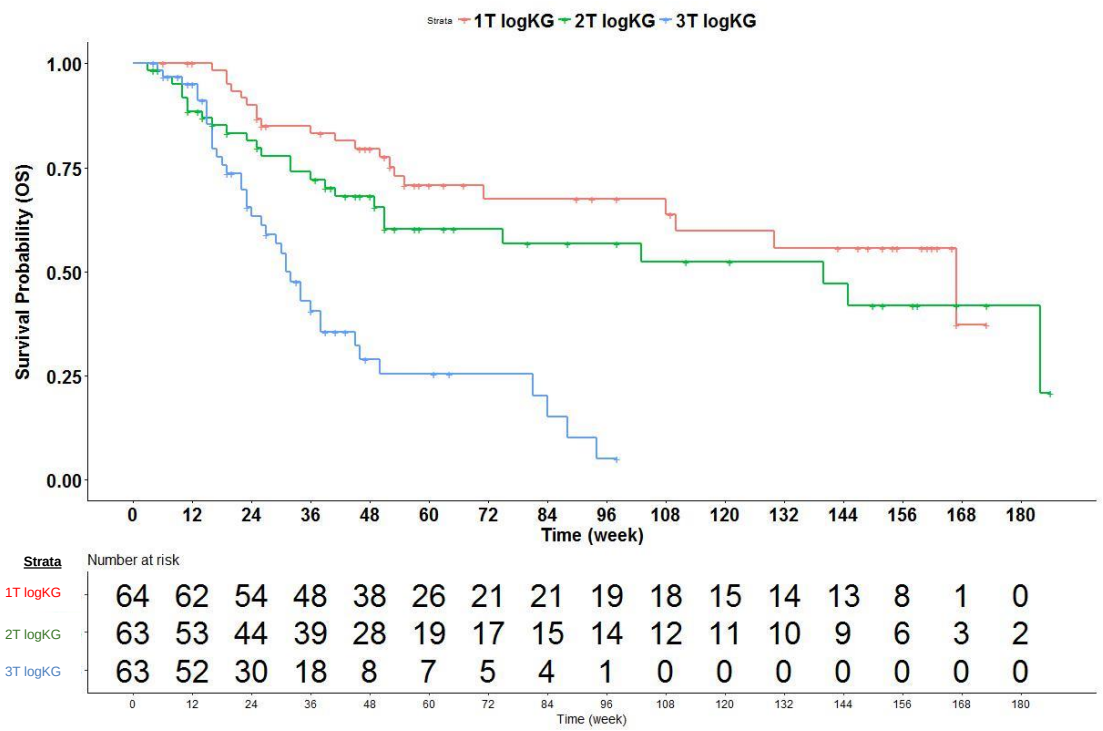


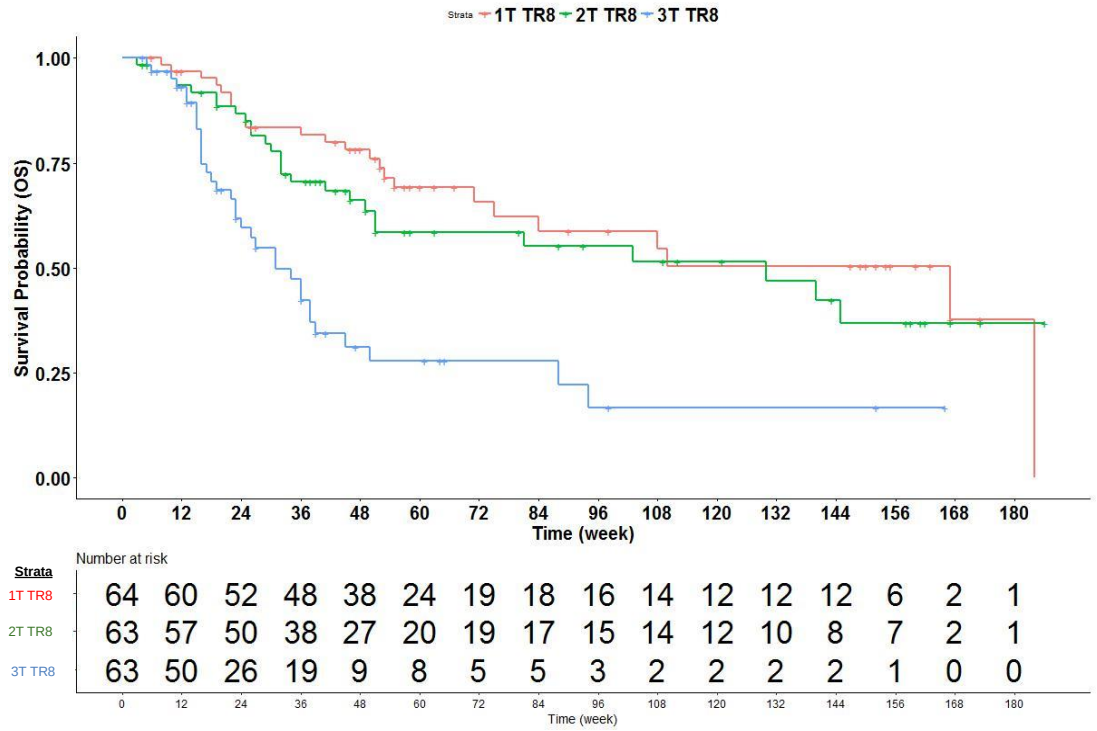


- Lower TR8 and KG are expected to have better efficacy
- Consistent rank ordering between TR8 and KG
- Rank order by TR8 and KG differentiates treatments based on TGI into two groups
- Lack of differentiation by treatment group in TTG

G, obinutuzumab; B, bendamustine; KG, tumor growth rate constant; pina, pinatuzumab vedotin; pola, polatuzumab vedotin; R, rituximab; TGI, tumor growth inhibition; TR8, tumor size ratio of week 8/baseline; TR12, tumor size ratio of week 12/baseline; TTG, time to tumor growth

Kaplan Meier Plot – LogKG and TR8 from Final TGI Model





- Similar trends observed between logKG and TR8
- Lowest tertile has shorter OS compared to the rest
- Overall ranking of OS curves is consistent with the ordering of model-estimated logKG tertile (i.e. higher logKG is associated with shorter OS)

KG, tumor growth rate constant; OS, overall survival; TGI, tumor growth inhibition; TR8, tumor size ratio of week 8/baseline; TR12, tumor size ratio of week 12/baseline; TTG, time to tumor growth

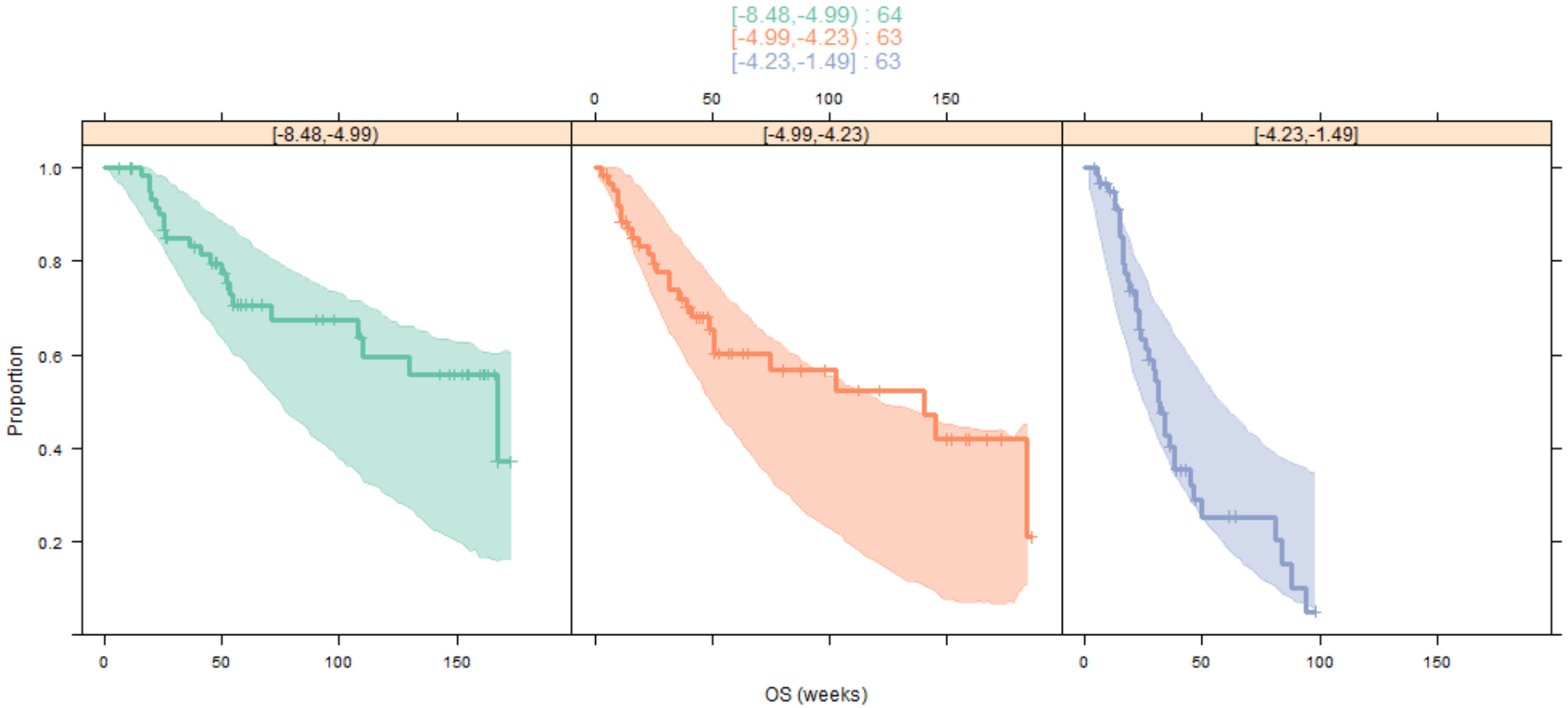
TGI-OS Survival Model

- A TGI-OS model describing the correlation between TGI model-derived parameters and OS was developed using Cox-proportional hazard models
- Covariates for the full model
  - Selected using univariate screening, based on the criterion of p-value < 0.005
  - Among the TGI metrics, logKG was the most statistically significant tumor metric predicting OS; TR8 was the second (p-values $2.2x10^{-08}$ and $2.4x10^{-05}$ by LRT test, respectively)
  - logKG + baseline size + bulky disease + ECOG PS + hemoglobin + LDH
  - Directions of covariate correlations are consistent with trends from prior knowledge
  - Treatment is not a statistically significant covariate
- Final model developed with parametric survival analysis (using backward elimination from full model based on p-value < 0.001) of lognormal distribution: logKG + baseline size

ECOG PS, Eastern Cooperative Oncology Group Performance Status; KG, tumor growth rate constant; LDH, lactate dehydrogenase; OS, overall survival; TGI, tumor growth inhibition; TR8, tumor size ratio of week 8/baseline;

PPC Plots Stratified by LogKG Tertiles (TGI-OS Final Model)

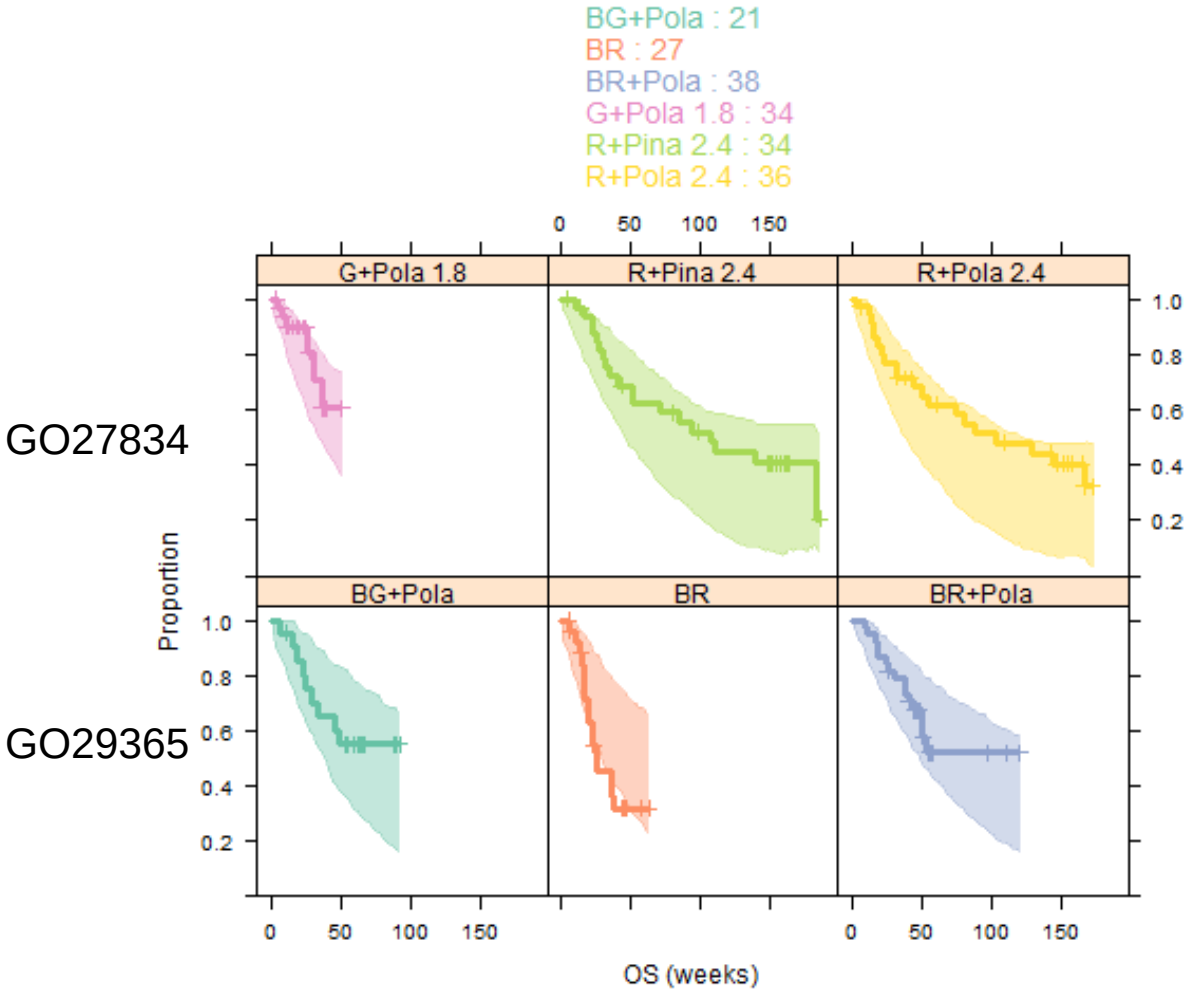
- Model qualification conducted using posterior predictive check (PPC) plots
  - Simulation for PPC created using 1000 replicates
  - Model parameters were sampled from the estimated mean values and uncertainty in parameter estimates
  - Study duration was sampled in a uniform distribution for up to 186 weeks, consistent with the maximum time period in the study



- Observed KM curves stratified by logKG were largely captured by model prediction intervals

KM, Kaplan-Meier; KG, tumor growth rate constant; TGI, tumor growth inhibition

PPC Plots Stratified by Treatment (TGI-OS Final Model)



- PPC plots stratified by treatment, model-estimated baseline tumor size, and statistically significant covariates in the full model, also show that final TGI-OS model adequately describes observed data
- Wide prediction intervals could be attributed to small sample size
- Rank order by model-predicted OS largely consistent with observed ORR
- BR + pola has longer OS than BR

ClinicalTrials.gov Identifiers: NCT01691898 (GO27834) and NCT02257567 (GO29365)

B, bendamustine; G, obinutuzumab; ORR, objective response rate; OS, overall survival; pina, pinatuzumab vedotin; pola, polatuzumab vedotin; PPC, posterior predictive check; R, rituximab; TGI, tumor growth inhibition

Summary and Future Work

- TGI model provides rank-order of key TGI parameters (logKG and TR8) that might inform treatment efficacy
  - Longitudinal tumor size (square root of SPD) was adequately described using a modified Stein model with low shrinkage values and acceptable goodness-of-fit plots and visual predictive check
- TGI-OS model may provide rank order of clinical efficacy endpoints
  - Multivariate parametric survival models with lognormal distribution were developed to describe OS based on TGI metrics and baseline characteristics
  - The results demonstrate that model-estimated tumor-size metrics from as early as 8 weeks could be of value to predict OS to enable early decision making
- Data were from small studies with multiple treatments, and for predicting HR, more data might be needed for better prediction

HR, hazard ratio; KG, tumor growth rate constant; OS, overall survival; SPD, sum of product of diameters; TGI, tumor growth inhibition; TR8, tumor size ratio of week 8/baseline;

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