An R-Shiny Web Application to Support Early Assessment and Decision Making of Oncology Studies Using Multivariate Tumor Growth Inhibition and Overall Survival Disease Models

Mathilde Marchand[1], Laurent Claret[2], Wan-Ting Lin[2], Shang-Chiung Chen[2], Helen Winter[2], Sandhya Girish[2], Jin Y. Jin[2], René Bruno[2]

[1] Certara Strategic Consulting, Marseille, France ; [2] Genentech/Roche, Marseille, France and South San Francisco, CA, USA

Objective

To develop a disease modelling and simulation (M&S) R-Shiny application (Apps) to help assess novel treatments or combinations in comparison to historical control (standard of care (SOC)) during early oncology clinical development.

Methods

The Apps requires a tumor growth inhibition (TGI) population model with covariates effects for SOC and a TGI-Overall survival (OS) model in the tumor type of interest [1]. A bi-exponential TGI model [2] with baseline covariates (*e.g.,* demographics, prognostic factors, inflammatory markers) effects on growth rate (KG) was available. Multiple case examples suggest KG is a good predictor of OS [1, 2]. A multivariate lognormal model of OS was also available with baseline covariates and KG estimates. An interactive application was developed using the RStudio "Shiny" package [3] to explore and compare KG and OS for the combination relative to SOC.

References

- [1] Bruno et al. Clin Pharmacol Ther 95, 386, 2014
- [2] Stein et al. Clin Cancer Res 17, 907, 2011
- [3] <http://CRAN.R-project.org/package=shiny>

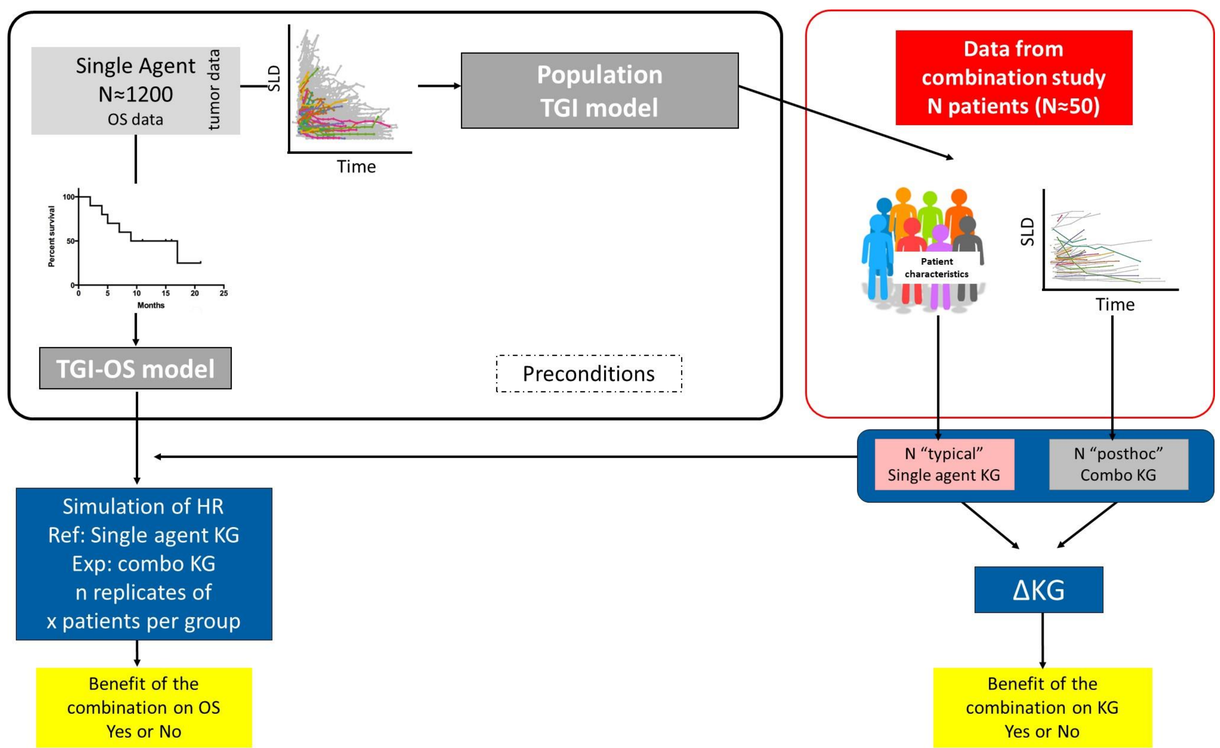
Conclusions

- The R-Shiny Application is proposed to support early assessment and decision making in oncology studies (*e.g.,* Phase 1b with new combinations)
  - Tumor data from an ongoing study of an investigational treatment (*e.g.,* a new combination) are used to estimate a TGI metrics: *e.g.,* KG
  - The application compares TGI metric estimates to typical covariate-adjusted estimates for SOC (*e.g.,* single agent)
  - The application simulates expected OS benefit for the investigational treatment vs. SOC
- The application uses models that need to be available
  - TGI model with covariate effects for SOC
  - TGI-OS model for the TGI metrics of interest in the tumor type of interest
- This approach can be used to assess other new therapies in combinations or extended to other investigational treatments in other diseases
  - Dedicated to internal use
- Accelerated development of anti-cancer therapies, particularly in combination setting, is often challenging and highly competitive with small size Phase Ib studies
  - High quality M&S with rapid turnaround is critical to inform and impact early development decision making (*e.g.,* go-no go, treatment prioritization, etc.).

Results

In the current example SOC is single agent (SA) therapy. The models were used to assess the benefit of combination treatment on KG adjusted to baseline patients characteristics and project expected OS and benefit (hazard ratio (HR)) relative to SA (Figure 1).

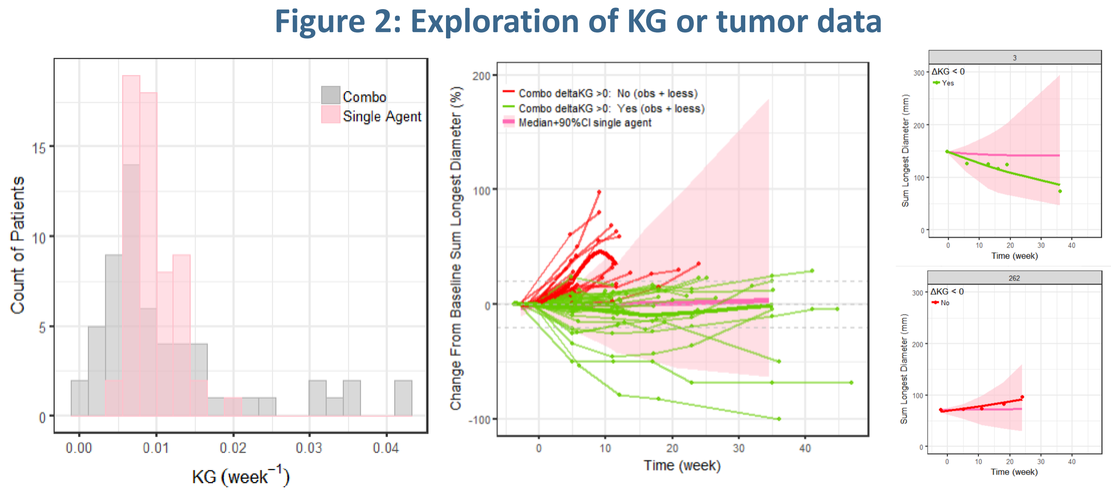
Figure 1: Schematics of operations



Patient's characteristics and KG estimates obtained with the combination are required as an input to the shiny apps. In the Apps, there is a panel for instructions and upload new data sets (csv files) with relevant covariates, sum of longest diameter (SLD) vs. time and individual predictions (IPRED) vs. time.

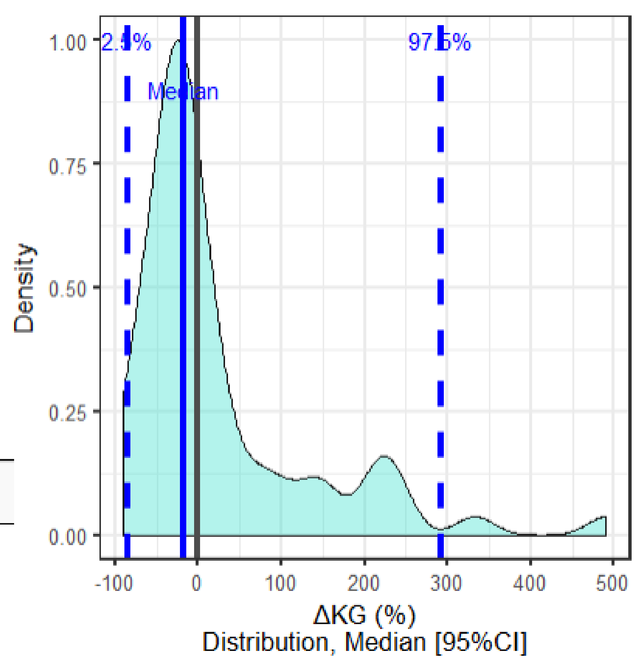
The application allows the user to explore both KG and tumor profile data of the combination compared to covariate-adjusted SA at individual and study levels (Figure 2).

Figure 2: Exploration of KG or tumor data



KG estimates for the combination are compared to covariate-adjusted typical SA KG to assess the benefit of the combination on KG (ΔKG). For the current example the benefit on KG is modest (18% slower than SA) (Figure 3).

Figure 3: Overall ΔKG

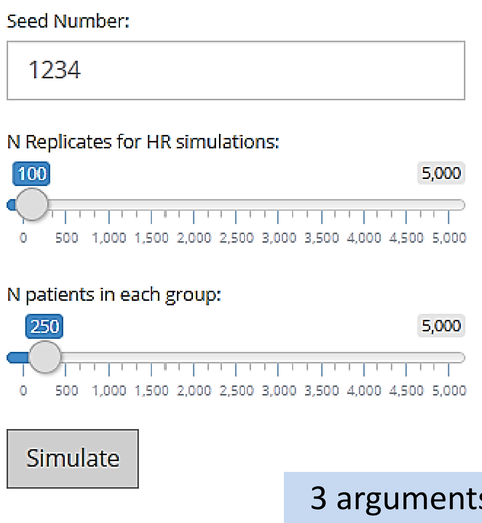


Overall ΔKG (%)	95%CI
-18	[-84.3 ; 292]

Small benefit of the combination on KG

HR of the combination vs. SA is derived using simulated expected OS. For the current example, the benefit of the combination on OS is small (Figure 4). The user can change some arguments of the simulations to explore the impact on the outcome. Simulated expected HR (N=5000 by group) would be 0.91 [0.87;0.96] for this example. A clinical trial like prediction is given in Figure 4 with 250 patients per group.

Figure 4: Hazard Ratio Simulations using TGI-OS Model



variable	Unit	50%	2.5%	97.5%
HR		0.905	0.745	1.12
Median_OS.ref	days	458	391	518
Median_OS.exp	days	479	409	551

Small benefit of the combination on OS
HR 0.91 [0.75; 1.12]

3 arguments of the simulations can vary to assess the impact on HR, OS and prediction interval