A comparison of two stage and joint TGI-PFS modeling approach to simulate PFS outcome

Laurent Claret[1], Rene Bruno[1], Bei Wang[2], Mathilde Marchand[1], Chunze Li[2], Sandhya Girish[2], Jin Jin[2], Angelica Quartino[2]

1 Pharsight Consulting Services, Pharsight, a Certara™ Company, Marseille, France
2 Genentech Research and Early Development (gRED), Roche, South San Francisco, CA

Background and objective

- In anticancer drug development, tumor growth inhibition (TGI) metrics have been increasingly used to predict time to event clinical outcomes: overall survival (OS) or progression free survival (PFS) [1]
- The commonly used approach involves two step modeling (TSM): 1) a longitudinal TGI model to estimate TGI metrics and 2) a time to event model to link TGI to clinical outcome
  - The goal is to develop a model to predict PFS (or OS) based on TGI (metrics) [1]
    - *i.e.* it is not investigating exposure/dose TGI relationships
- This TSM approach has been criticized [2] because the uncertainty of the individual TGI metrics estimations is not carried forward in the time to event model likelihood, and it is proposed to use a joint model (JM) fitting simultaneously both dependent variables
- Using typical clinical trial data, JM cannot be easily applied for OS as longitudinal tumor size and time to event data are not recorded simultaneously
  - Longitudinal tumor size data are typically collected up to progressive disease when the investigational treatment is stopped
  - Death could occur months later and TGI models cannot be extrapolated after treatment stops
- The goal of this work was to evaluate JM to model and predict PFS in comparison to the TSM approach

Data

- EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine plus lapatinib (C+L) in HER2-positive locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab and a taxane [3]
  - PFS hazard ratio (T-DM1 vs. Capecitabine + Lapatinib), 0.65 (95% CI, 0.55-0.77), p<0.001

Treatment	N	N with measurable disease	N with at least one measure after baseline
Capecitabine + Lapatinib	496	386	360
T-DM1	495	392	382
Total	991	778	742

- TGI modeling approaches were limited to:
  - JM: Patients with measurable disease
  - TSM: Patients with measurable disease and at least one measurement after baseline

Methods

- A TSM approach was developed (not shown)
  - TGI model
    - Stein bi-exponential structural model [4] identified per arm (NONMEM 7.2):

$$TS(t_{ij}) = TS_{i,0} \cdot \left[\exp(-KS_i \cdot t_{ij}) + \exp(KG_i \cdot t_{ij}) - 1\right] + \varepsilon_{ij}$$
$$\theta_i = \theta \cdot e^{\eta_i},\ \eta_i \to N(0,\omega^2),\ \varepsilon_{ij} \to N(0,\sigma^2), \theta = [TS_0, KS, KG]$$
$$i = 1,\ldots,n \text{ individuals}, j = 1,\ldots,m \text{ observations}$$

    - KG is the growth rate i.e. the tumor growth inhibition metric that has been reported as being predictive of OS in a number of studies [1, 4]
    - TS is the tumor size and KS is the shrinkage rate
    - This model is dose independent and only aims to capture TGI dynamic
  - PFS model
    - Parametric model (R, survreg)
      - A Weibull distribution was selected among Weibull, log-logistic, lognormal, exponential
        - Hazard (h) and survivor (S) functions are defined as:

$$h(t) = \lambda\alpha(\lambda t)^{\alpha-1} \qquad S(t) = \exp(-\lambda t)^{\alpha}$$

          - where $1/\alpha$ and λ are the scale and shape parameters (as parameterized in R)
    - Covariate model built from a stepwise approach.
      - Full model based on significant covariates in a univariate analysis (cox) p=0.05
      - Backward elimination: from full model with exclusion p=0.01
      - **Final covariate model: KG, KS, Albumin, ECD (HER2 extracellular domain)**
- A JM is developed
  - TGI model
    - Same structure as in TSM approach
  - PFS model
    - The hazard h(t) is defined at t and as a function of baseline covariates, x, and time dependent covariates, TS(t), or TGI model parameters (KG, KS) simultaneously estimated,

$$h(t) = f(t, x, TS(t))$$
$$S(t) = e^{-\int h(u)\cdot du}$$

      - Hazard driven as a function of TS(t), TGI metrics
      - Final covariates of TSM model are tested
      - Weibull distribution was tested
  - JM was implemented in NONMEM 7.2
- Both JM and TSM PFS models were evaluated in their abilities to simulate PFS distributions in treatment arms and treatment hazard ratio (HR)

Predictive Check

- As the goal is to predict PFS based on TGI data and covariates, the PFS models were evaluated by posterior predictive check
- PFS of the original TGI data and covariates (TSM evaluable patients) are simulated a large number of times then the 95% PI of simulated statistics are compared to observed statistics:
  - Kaplan-Meir distributions and median PFS in treatment arms
  - Hazard ratio comparing T-DM1 to capecitabine + lapatinib

References

1. Bruno R et al. *Clin Pharmacol Ther*; 95, 386-93, 2014
2. Mansmann UR et al. *J Clin Oncol*; 31, 4373, 2013
3. Verma S et al. *N Engl J Med* 367; 19, 2012
4. Stein WD et al. *Oncologist;* 13, 1046–1054, 2008

Results - Joint Model Development Sequence

	Hazard Model	N of parameters	- 2LL
M1	Int	10	32982
M2	Int + TS(t)/BSL	11	32839
M3	Int + KG	11	32837
M4	Int + KG+Albumin+ECD	13	32825
M5	Int + KG+KS+Albumin+ECD	14	32805
M6	Int + TS(t)/BSL+Albumin+ECD	13	32827
M7	Weibull (Int + KG+KS+Albumin+ECD)	15	32517

N observations = 778 and missing covariates were imputed to the median

- Hazard as a function of TS(t) did not converge, TS(t) must be normalized by baseline: TS(t)/BSL
- The best model described PFS as a function of TGI model parameters (KG and KS) and covariates: same structure as the final TSM

Results

Model parameter estimates (PFS in weeks)

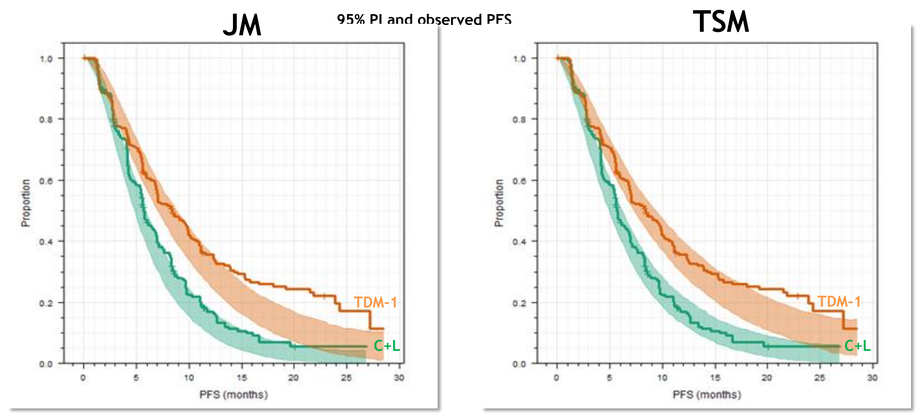
Joint Model (M7) - N=778

Parameter (unit)	Estimate	RSE (%)	Shrinkage (%)
KG_{TDM1} ($week^{-1}$)	0.0081	5.59	-
KS_{TDM1} ($week^{-1}$)	0.0349	6.25	-
KG_{C+L} ($week^{-1}$)	0.0127	5.11	-
KS_{C+L} ($week^{-1}$)	0.0417	6.82	-
TS0 (mm)	55.4	2.97	-
σ^2	46.0	8.97	-
ω_{KG}	0.495	7.10	14.4
ω_{KS}	0.566	8.41	25.3
ω_{TS0}	0.643	4.54	4.69
Intercept	-0.841	32.7	
logKG	-0.973	3.69	
Albumin (unit)	0.0203	26.3	
ECD (unit)	-0.000597	16.6	
logKS	0.241	15.7	
Log(scale)	-0.832	5.42	

TSM - N=742

Parameter (unit)	Estimate	RSE (%)	Shrinkage (%)
KG_{TDM1} ($week^{-1}$)	0.0078	5.98	-
KS_{TDM1} ($week^{-1}$)	0.0341	6.16	-
KG_{C+L} ($week^{-1}$)	0.0126	5.28	-
KS_{C+L} ($week^{-1}$)	0.0416	6.58	-
TS0 (mm)	55.6	2.98	-
σ^2	46.3	8.93	-
ω_{KG}	0.455	7.82	21.3
ω_{KS}	0.580	8.28	25.9
ω_{TS0}	0.641	4.57	4.78
Intercept	-0.860	36.4	
logKG	-1.02	4.28	
Albumin (unit)	0.0157	37.5	
ECD (unit)	-0.000511	26.4	
logKS	0.222	19.4	
Log(scale)	-0.623	5.57	

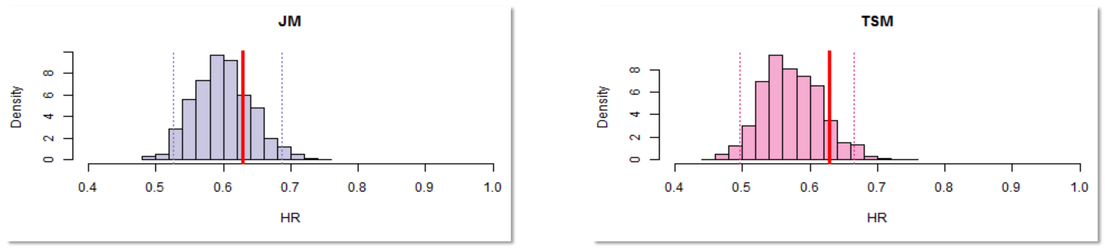
PPC of PFS distributions by arm



	Observed	JM		TSM	
	Median * (months)	Predicted (months)	95% PI (months)	Predicted (months)	95%PI (months)
C+L	5.72	5.35	(4.84,5.9)	5.54	(4.99,6.18)
TDM-1	8.39	7.89	(7.08,8.89)	8.33	(7.36,9.37)

* TSM evaluable patients N=742

PPC of hazard ratio



	Observed*	Predicted	95% PI
TSM	0.629	0.568	(0.496,0.665)
JM	0.629	0.597	(0.525,0.687)

* TSM evaluable patients N=742

The JM approach improved PFS parameter estimates precision and KG shrinkage

Discussion

- KG was as good a predictor of PFS as time dependent baseline normalized tumor size: TS(t)/baseline
  - One would expect that the use of time dependent metric TS(t) may be more efficient than static TGI parameters or metrics estimates
  - The Weibull assumption of hazard provided a better fit than hazard dependent on time dependent metric TS(t)
- The final structure of the joint model was identical to that of the TSM one
  - JM improved KG shrinkage and precision of PFS model parameter estimates
  - Overall, model parameter estimates and model performances were similar
  - JM model development included all patients with measurable disease

Conclusions

- This comparison, based on an analysis of a single study, shows that despite a slightly better precision of JM model parameter estimates, structural models and prediction performances are similar for both approaches
- TGI metrics are similar than time-varying baseline-normalized tumor size to drive PFS hazard function
- Ultimately, the goal of the model will have to be accounted for to select the preferred approach:
  1. Assess an early marker of effect to support clinical trial decisions
  2. Develop the best model to simulate alternative dosing regimen or clinical trial designs
  3. Predict individual patient outcome to support therapeutic decisions
- For some of those applications and especially 2. and 3., a more mechanistic TGI model linking dose-PK-TGI-PFS might be required when inferences need be made for alternative dose regimen (dose and schedules)