Joint modeling of longitudinal tumor burden and time-to-event data to predict survival: application to aflibercept in second line metastatic colorectal cancer

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Introduction

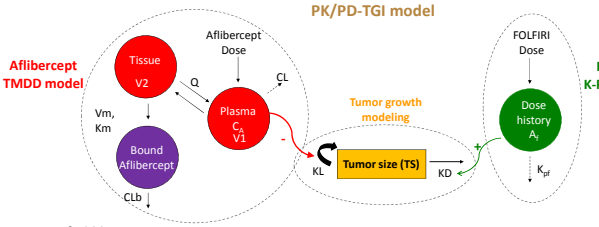
- Aflibercept (ziv-aflibercept in the US, ZALTRAP®) is a fusion protein of human vascular endothelial growth factor (VEGF) receptor domains that binds to VEGF-A, VEGF-B, and PlGF and inhibits tumor growth (1).
- In metastatic colorectal cancer, the VELOUR trial demonstrated significantly improved overall survival (OS) for aflibercept in combination with FOLFIRI (leucovorin, 5-fluorouracil, irinotecan) after failure of an oxaliplatin based regimen (2).
- Joint modeling of longitudinal data and time-to-event data at presence of dropout has gained much interest in oncology drug development to predict survival.

Objectives

- To analyze the treatment effect on tumor growth kinetics and the link to survival using a joint modeling framework accounting for informative dropouts.

Joint modeling

- 1069 evaluable patients from the VELOUR trial were used for model building.
  - Aflibercept arm (N=540): aflibercept 4 mg/kg + FOLFIRI every 2 weeks
  - Reference arm (N=529): placebo + FOLFIRI every 2 weeks
- Longitudinal data of tumor size (TS) (i.e. sum of target lesions) were first analyzed alone using a tumor growth inhibition (TGI) model which describes the effect of both aflibercept and FOLFIRI on tumor kinetics.
- Then, informative dropouts (between last TS measurement and next planned visit) and OS data were both included for joint modeling using hazard frailty models (3) with shared latent random effects.



Dropout model (interval censored data)

$$h_D(t) = h_{0,D}(t) \cdot e^{\eta_u \cdot e^{\beta_{TS,D}} \cdot TS(t)}$$

$$h_{0,D}(t) = \lambda_D \cdot e^{\beta_D} \cdot \log(t)$$ Weibull distribution

Survival model (time to event data)

$$h_S(t) = h_{0,S}(t) \cdot e^{\eta_u \cdot e^{\beta_{TS,S}} \cdot TS(t)}$$

$$h_{0,S}(t) = \frac{(\beta_S/\alpha_S) \cdot (t/\alpha_S)^{(\beta_S - 1)}}{1 + (t/\alpha_S)^{\beta_S}}$$ Log-logistic distribution

$$\frac{dTS(t)}{dt} = K_L \cdot (1 - \beta_A \cdot C_A(t)) \cdot TS(t) - K_D \cdot Kpf \cdot Af(t) \cdot e^{-\lambda t} \cdot TS(t); \; TS(0) = TS_0$$

K_L: tumor growth rate
K_D: drug constant-cell-kill rate
λ: resistance appearance rate
TS0: tumor size at baseline
β_A: effect of Aflibercept (inhibition of K_L)
Kpf: effect of FOLFIRI (stimulation of K_D)
$\beta_{TS,D}$: link between TS and the risk of dropout
$\beta_{TS,S}$: link between TS and the risk of death
η_u: share latent random effect
λ_D, β_D : Weibull parameters
α_S, β_S : log-logistic parameters

- Individual PK parameters of aflibercept was obtained as post doc estimates from the previous analysis (4).
- Parameters were estimated by maximizing the joint likelihood with the SAEM algorithm implemented in MONOLIX 4.3.2.
- Model selection was based on log-likelihood ratio tests and BIC.
- VPC and Kaplan-Meier plots were generated using simulation with 100 replications to explore the impact of dropouts and to evaluate model performance.

Results

Table 1: Parameter estimates

	Parameters	Estimate	RSE (%)
	TS0 (mm)	91.3	2
	K_L (mL.µg^{-1}.wk^{-1})	0.013	4
Aflibercept effect	β_A	0.037	5
	K_D (wk^{-1})	3.56E-05	4
	λ (wk^{-1})	0.13	4
	K_{pf} (wk^{-1})	0.16	8
Fixed effects	λ_D	0.0016	6
	β_D	0.91	0.2
Link between TS & dropouts	$\beta_{TS,Drop}$	0.0057	8
	α_S	77.7	4
Link between TS & OS	β_S	2.82	6
	$\beta_{TS,Survival}$	0.0057	6
	ωTS0	75.1	2
	ωK_L	94.0	4
Interindividual variability (%)	$\omega\beta_A$	46.8	6
	ωK_D	54.3	5
	$\omega\lambda$	66.7	4
	ωKpf	137	5
Shared random effects	ωu	78.7	6
Residual variability	additive error (mm)	5.94	1

Figure 1: Examples of individual fits for tumor size

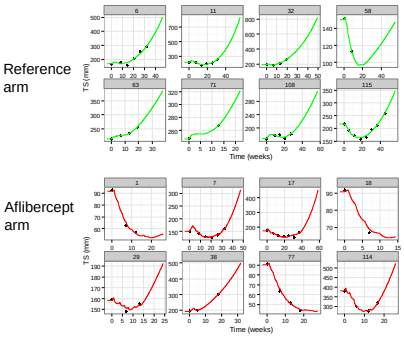
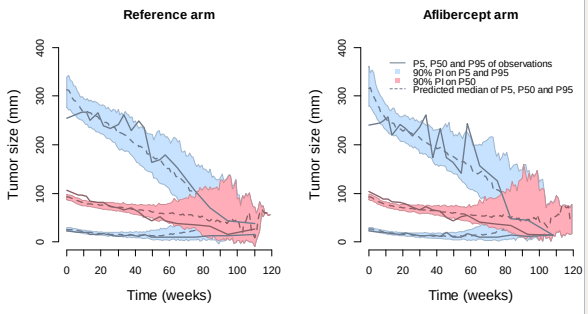


Figure 2: VPC for longitudinal tumor size



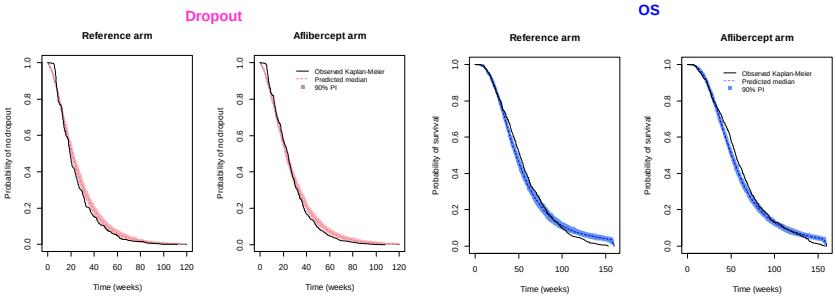
- The joint model predicted reasonably well the time-course of tumor size

- Parameters were estimated with good precision but associated with high variability
- Dropouts and OS shared similar link with tumor size

Table 2: Simulated vs observed median OS and hazard ratio (HR)

	Median OS [90% PI] (months)		HR (median [90% PI])	
	Observed	Simulated	Observed	Simulated
Reference arm	11.8	10.7 [10.3-11.3]		
Aflibercept arm	12.8	11.5 [11.1-12.1]	0.84	0.89 [0.83-0.99]

Figure 3: Kaplan-Meier plots for dropouts and OS data



- Simulated dropouts and OS data were in agreement with those observed in both reference and treatment arm

Conclusions

- The time-course of tumor size, the treatment effect and the observed OS of patients in the VELOUR trial were well characterized.
- By linking the full time-course of tumor size to survival and taking into account the informative dropouts, this present model should provide a good prediction of clinical outcomes [5] (e.g. survival in oncology) when performing model-based simulations of new clinical trials (e.g. new dose regimen, dose intensification in subpopulations of interest).
- This framework is an example of how to model jointly several outcomes in a oncology trial, based on efficacy component. A safety component should also be taken into account in this framework to ensure an adequate efficacy/safety balance.

References

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