Population PD modelling of circulating biomarkers in patients with melanoma treated with interferon α2b

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OBJECTIVES

To stablish a semi-mechanistic model describing the time course of several circulating biomarkers (LDH, S100B, and MIA) in advanced melanoma patients treated with adjuvant high-dose interferon-α2b (IFN-α2b) to study if increased LDH, MIA and S100B levels correlate with decreased overall survival (OS) in patients with advanced disease.

METHODS

Available data:

- Data analysis included different biomarker levels from 48 melanoma patients treated with adjuvant IFN-α2b.
- The high-dose regimen followed the Kirkwood scheme: $20x10^6$ U/m^2/day intravenous in the induction phase (20 doses: 5 days/week during 4 weeks) and $10x10^6$ U/m^2/day subcutaneous administration in the maintenance phase (3 days/week during 48 weeks).

Table 1. Data summary

Data:	Overall population (N=48)
Dose modifications and delays:	
Patients with dose reduction	17 (35%)
Patients with dose delays	25 (52%)
Patients that complete induction phase	30 (62%)
Patients that complete maintenance phase	21 (43%)
Biomarker data:	
Patients with **LDH** data	**48 (100%)**
Patients with **MIA** data	**39 (81%)**
Patients with **S100B** data	**38 (79%)**

An exploratory survival analysis was performed stratified by high and low biomarker values at the end of the study, to see the strength of those biomarkers as adverse prognostic factors in malignant melanoma.

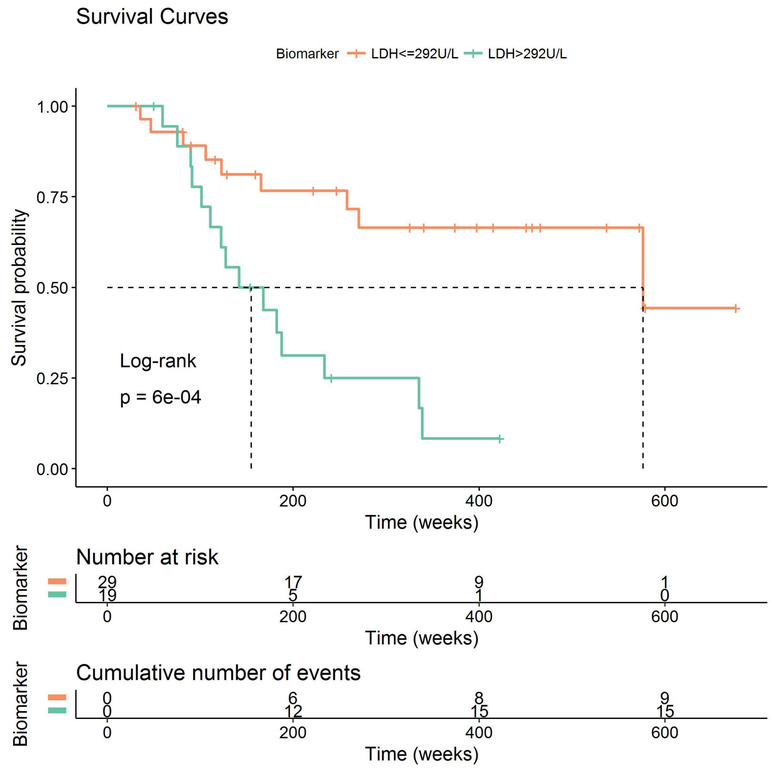
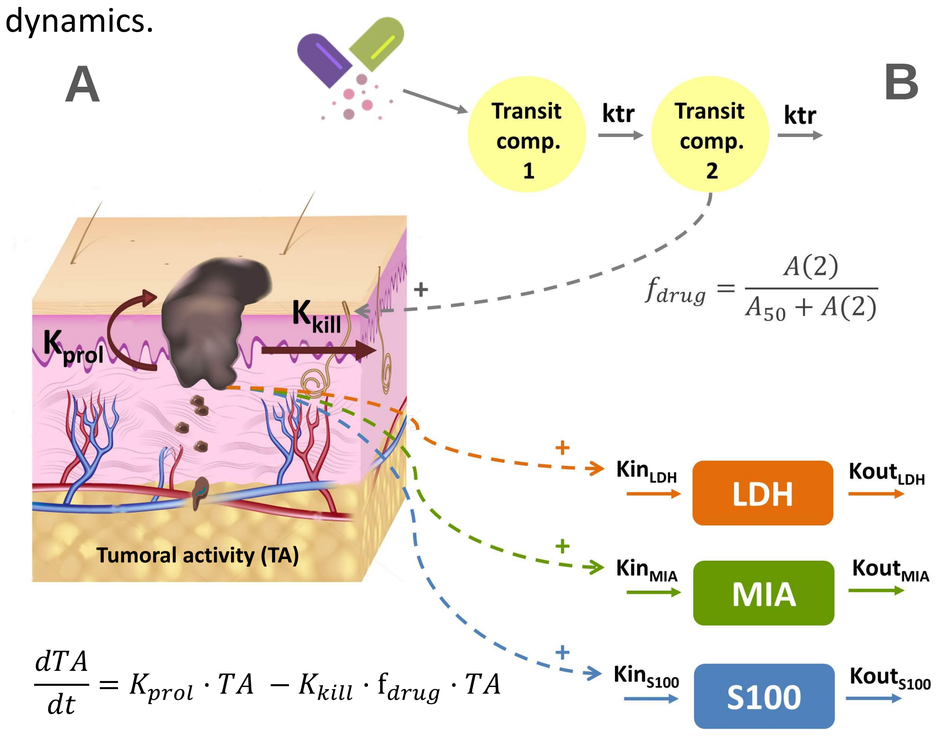


Figure 1. Evaluation of the overall survival of the patients with high (>292U/L) and low (<292U/L) biomarker concentrations at the end of the study. MIA and S100 biomarker Kaplan Meier curves showed equivalent results.

RESULTS

The structural model combines indirect response-based models representing synthesis and degradation processes of tumor biomarkers driven by an underlying unobserved variable (Tumoral activity) corresponding to the tumor progression dynamics.



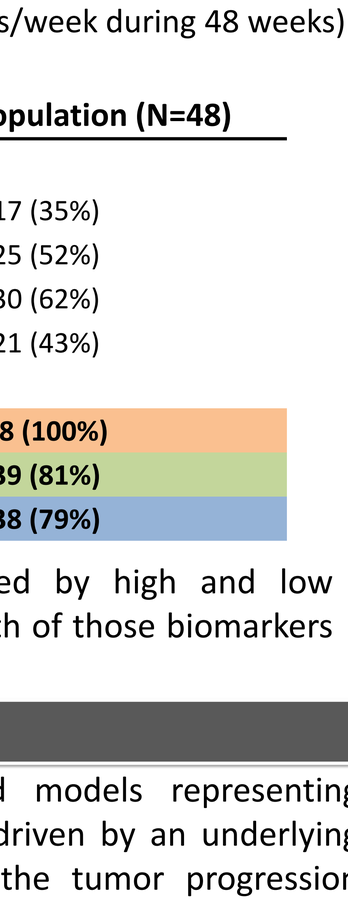


Figure 2. A) Schematic representation of the K-PD model proposed for the IFN-α2b effect on biomarker levels. B) 3 individual biomarker profiles (Observation VS Prediction).

Table 2. Estimated model parameters.

Parameters	LDH		MIA		S100B	
	Typical estimate	Variability	Typical estimate	Variability	Typical estimate	Variability
MTT (weeks)	22.3	59.8%	33.1	63.7%	31.9	32.8%
A_{50} (U· 10^6)	23.7	-	25.2	-	25.8	-
Basal (conc)	225 (U/L)	31%	7.53 (ng/ml)	45%	0.0542 (ng/ml)	42%
Kprol (weeks^{-1})	0.0029	58%	0.0028	75.6 %	0.0023	56.5%
K_{KILL} (weeks^{-1})	0.0077	34%	0.0058	34%	0.0063	-
Kout (weeks^{-1})	0.321	-	0.369	-	2.1	-
Prop. Error	0.0521	-	0.248	-	0.348	-

Overall survival and the K-PD model were simultaneously analysed in Nonmem 7.3.

The exponential model characterized the OS hazard (BASE=0.0023).

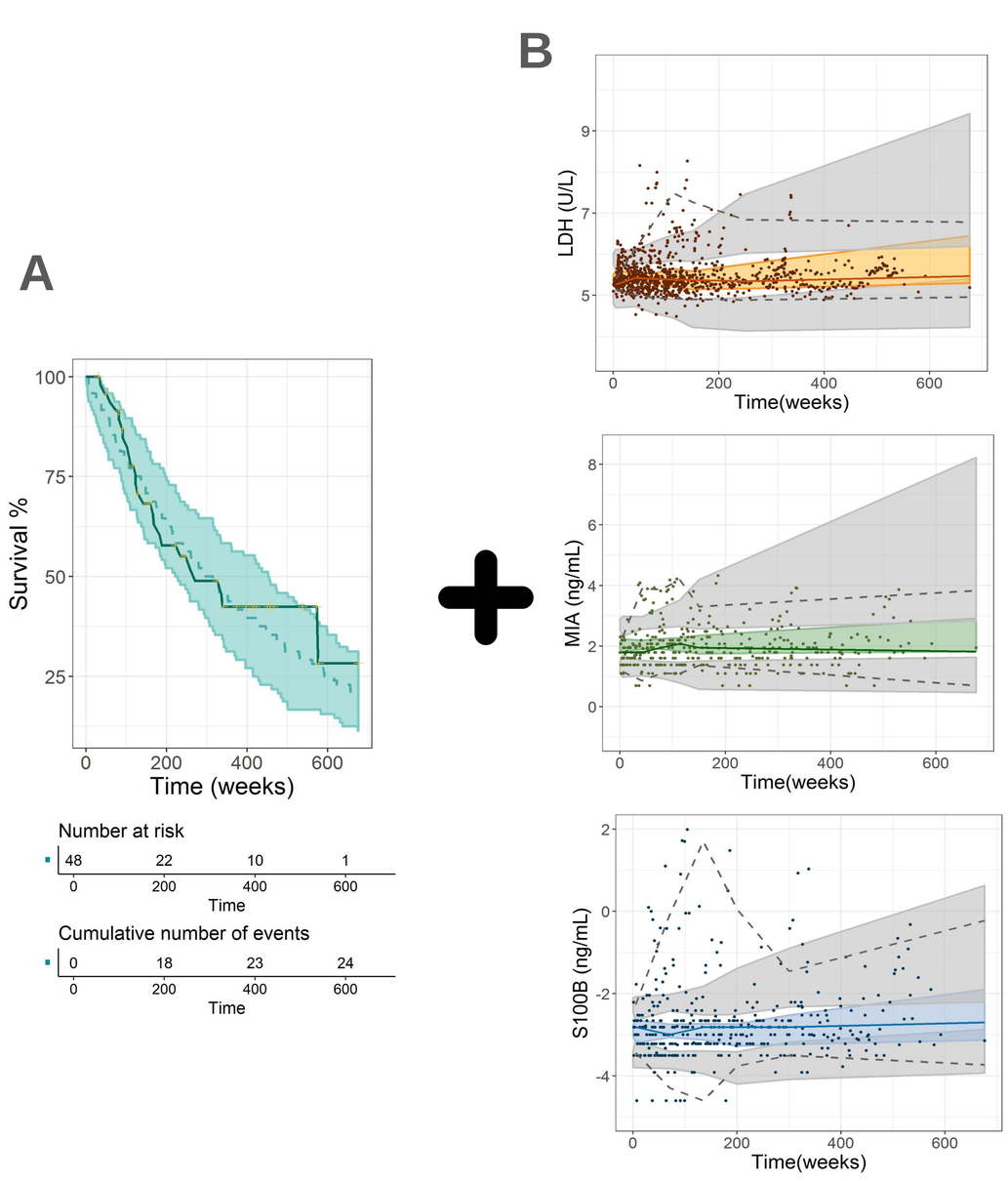


Figure 5. Model evaluation: Visual Predictive Checks. A) Kaplan Meier Overall Survival. B) LDH, MIA and S100B values (log scale); Median (solid colored line), 5th and 95th percentiles (dashed grey line) of the observed data. 90% confidence Intervals for median (shaded colored area), 5th and 95th percentiles (shaded green areas) of the simulated data.

CONCLUSIONS & FUTURE PERSPECTIVES

A model for the dynamics of circulating biomarkers has been established and evaluated in patients with melanoma during treatment with IFN-α2b, open the possibility to study the link between the biomarker levels and the prognosis capability of those biomarkers on disease progression or overall survival using parametric survival analysis.

References

1. Jacqmin P., et al. *J Pharmacokinet Pharmacodyn.* (2007).
2. Espinosa, E., et al. *Melanoma Research* (2016).

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