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Background

- Docetaxel+ADT (Androgen Deprivation Treatment) correlated with a survival benefit in patients with hormone-naïve metastatic prostate cancer [1]
- No effective for improving the PSA-based progression-free survival (PFS) in patients presenting with rising Prostate-Specific Antigen (PSA) levels after primary local therapy and high-risk factors but no evidence of metastatic disease [2]

Objectives

- Assessing the kinetics of PSA using a Kinetic-Pharmacodynamic (K-PD) model
- Identifying a kinetic parameter of interest to assess the prognostic/predictive value of PSA early kinetics

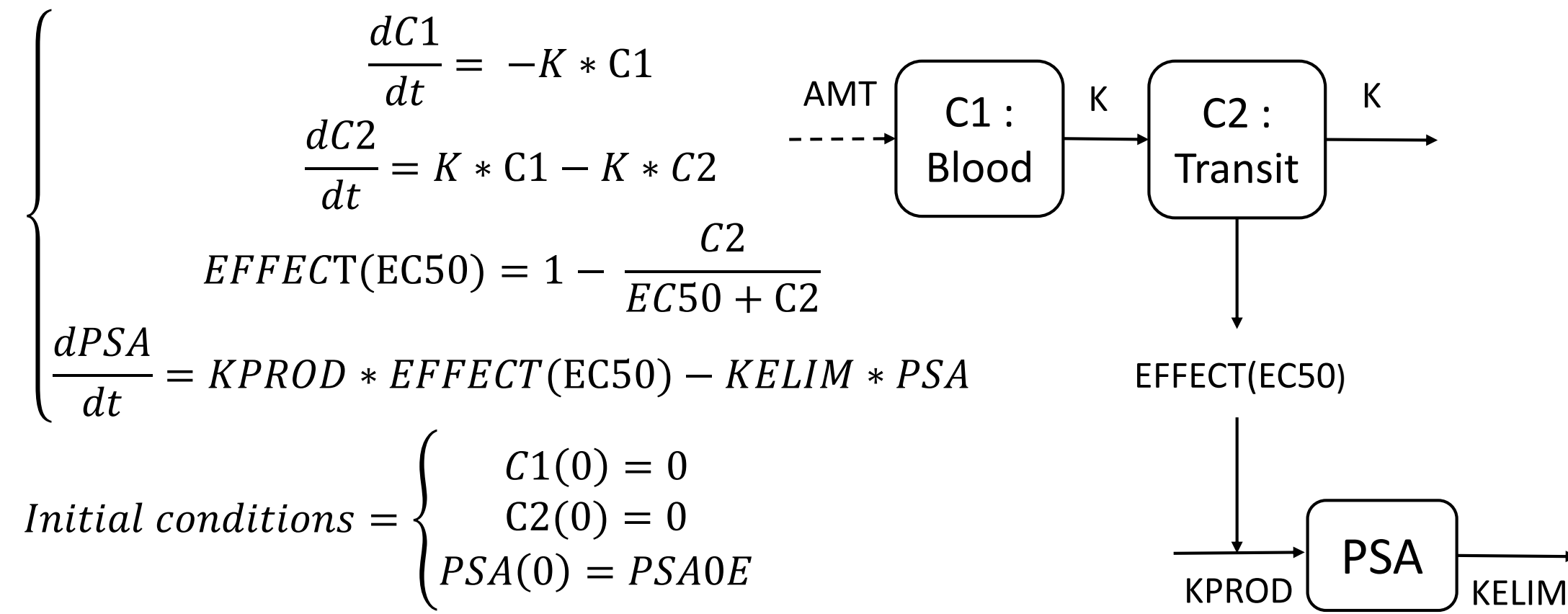
Materials & Methods

Data:

- 250 patients from phase III clinical trial, assessing benefits of Docetaxel in addition to ADT (Available clinical data).
- Patients who undergone a primary local therapy, with rising PSA levels and, with high risk of metastatic disease in terms of PSA-progression free survival (PFS) :
 - Gleason ≥ 8
 - PSA velocity 0.75 ng/mL per year
 - PSA-DT ≤ 6 months
 - time to PSA recurrence <12
- PSA levels measured after the end of the treatment until progression was noted, every 3 weeks.

Model:

- K-PD model during the first 100 days of treatment (absence of available PK data) [3]
- PSA production was inhibited by the treatment through an indirect effect model.
- Estimation method:** First Order Conditional Estimates Interaction + Laplace
- Model validation criteria : NPDE (Normalized Prediction Distribution Errors), Relative Standard Errors (RSE), shrinkage, Goodness Of Fits plots and Visual Predictive Checks using NONMEM 7.5.0.



Results

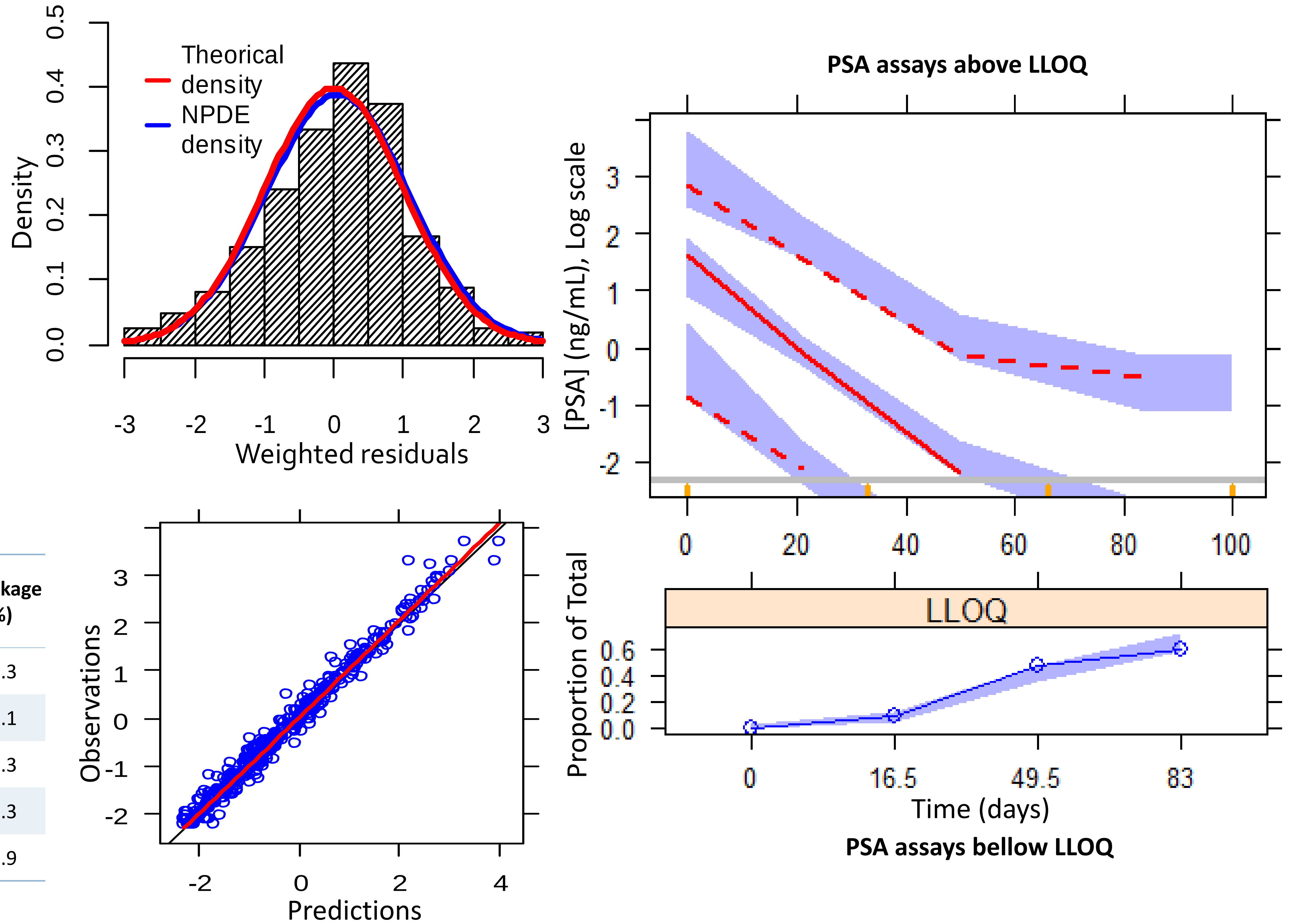
- Of the 250 patients, 177 patients were selected for PSA kinetic modelling:
 - At least 3 PSA assays during the first 100 days of treatment
 - Experienced PSA decline during the first 100 days of treatment
- Standard deviation scale: variance
- Additional error model with Lower Limit Of Quantification (LLOQ) (=0.1 ng/mL)
- 36.44% of PSA measurements were lower than LLOQ
- Five parameters were estimated:
 - K**: treatment kinetic rate constant (day^{-1})
 - KPROD**: PSA production rate (day^{-1})
 - KELIM**: PSA elimination rate constant (day^{-1})
 - PSAOE**: initial PSA value ($ng.mL^{-1}$)
 - EC50**: treatment concentration to obtain 50% of maximal effect (AU)

- Low RSE (<25%) except for K and EC50 (<80%)
- No clinical covariate improved the OF (= 497.467) when added to the model
- Shrinkage <30% except for K and EC50 (>95%)
- Weighted residuals approximately follow a Normal distribution
- Observations vs. Predictions plots does not show aberrant results
- VPC suggests good predictions of PSA kinetics.

Parameters	Population estimates			Inter-individual estimates			Shrinkage (%)
	Median	SE	RSE (%)	Median	SE	RSE (%)	
<i>K</i> (day^{-1})	2.13	0.17	33.2	0.064	0.044	69.4	97.3
<i>KPROD</i> (day^{-1})	0.0021	0.0004	19.2	4.26	0.66	15.6	18.1
<i>EC50</i> (AU)	0.38	0.15	42.3	0.14	0.11	75.9	97.3
<i>PSAOE</i> ($ng.mL^{-1}$)	4.22	0.55	13.03	1.68	0.27	16.3	13.3
<i>KELIM</i> (day^{-1})	0.081	0.0035	4.3	0.12	0.022	17.9	26.9

Conclusion

- Characterization of PSA decline in relapsed prostate cancer under ADT in addition or not to Docetaxel.
- Good PSA predictions with a simple model
- Possible modelling even with below quantification limit data
- Prognostic and predictive value of PSA kinetics on PSA Progression-free survival (PFS) and Overall survival (OS) will be investigated



References

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