

Population K-PD joint modeling of tumor size and CA 125 kinetics after chemotherapy in relapsed ovarian cancer (ROC) patients

Mélanie Wilboux, B. You, E. Héning, O. Colombar, G. Freyer, M. Tod

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University Claude Bernard Lyon 1

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Ovarian cancer (OC):

- Highest mortality rate among all gynecological cancers
- Majority of patients diagnosed at an advanced stage
- Primary debulking surgery followed by chemotherapy
- Majority of patients relapses



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→ Reliable clinical strategy for **early prediction** of treatment efficacy, tumor dynamics, and tumor resectability

CA 125 (*Cancer Antigen*):

- Serum marker of epithelial ovarian cancers
- Described by Bast *et al.* in 1981 ¹
- Topic of many studies to optimize the management of OC

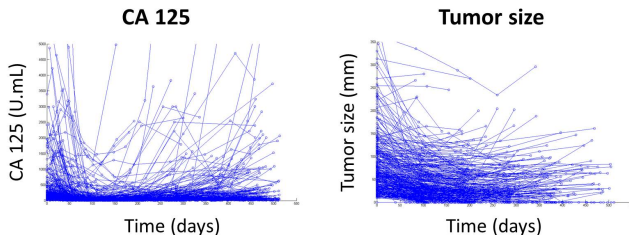
[1] Bast et al. Reactivity of a monoclonal antibody with human ovarian carcinoma. *J Clin Invest*, 1981.

Background

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Variability in CA 125 and tumor size kinetics:

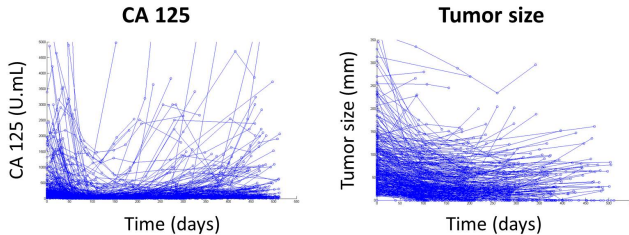


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Variability in CA 125 and tumor size kinetics:



→ **CA 125 kinetics modeling** to consider inter- and intra-individual variability

1

Build a **population K-PD semi-mechanistic** model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy

Objectives

1

Build a **population K-PD semi-mechanistic** model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy

2

Validate "externally" this model

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Assess the **prognosis** value of CA 125 on tumor dynamics

- **CALYPSO trial** ²:
 - Randomized, multicenter, phase III non-inferiority study
 - Platinum-sensitive ROC patients
 - Carboplatin - Pegylated Liposomal Doxorubicin (CD) VS Carboplatin - Paclitaxel (CP)

[2] Pujade-Lauraine et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum sensitive ovarian cancer in late relapse. *J Clin Oncol*.2010.



- **CALYPSO trial ²:**
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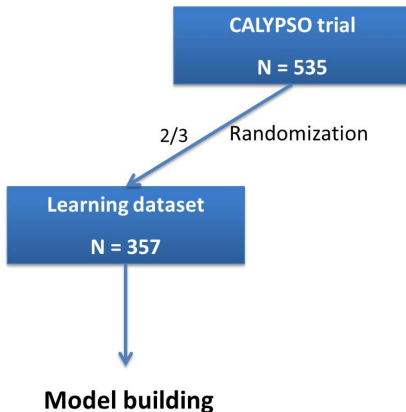
- **Data:**
 - **535** ROC patients
 - Baseline covariates: age, weight, lesion size...
 - **10 CA 125** concentrations and **4 tumor size** values per patient
 - Modeling during **500 days**

Data splitting

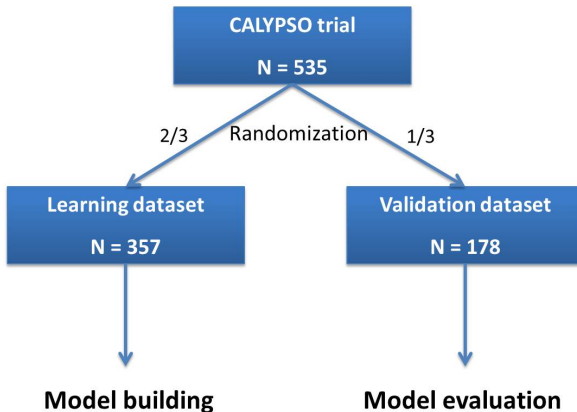
CALYPSO trial

N = 535

Data splitting



Data splitting



Model building

Learning dataset

- K-PD model
- Population analysis: Monolix 4.1.2
- Model internal evaluation:
 - goodness-of-fits plots
 - simulation-based diagnostics

- **Model structure**
- **Parameters distributions**

Model building

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Model evaluation

- Tumor size and CA 125 predictions
- Evaluation metric: **Normalised Prediction Distribution Errors (NPDE)**

Validation dataset

Patients and Methods

K-PD semi-mechanistic model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy

Drug kinetics

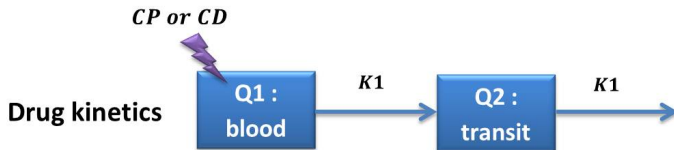
Tumor dynamics

CA 125 kinetics



Patients and Methods

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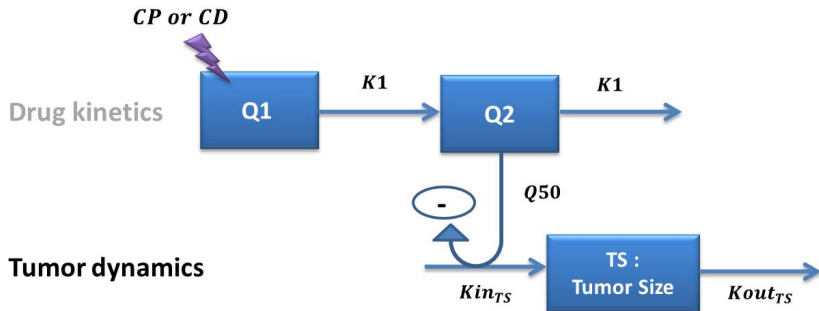


Tumor dynamics

CA 125 kinetics

Patients and Methods

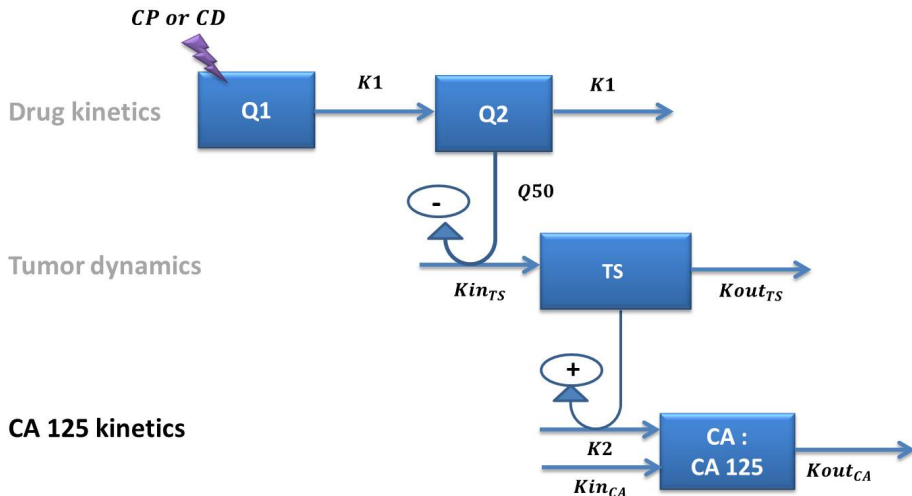
K-PD semi-mechanistic model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy



CA 125 kinetics

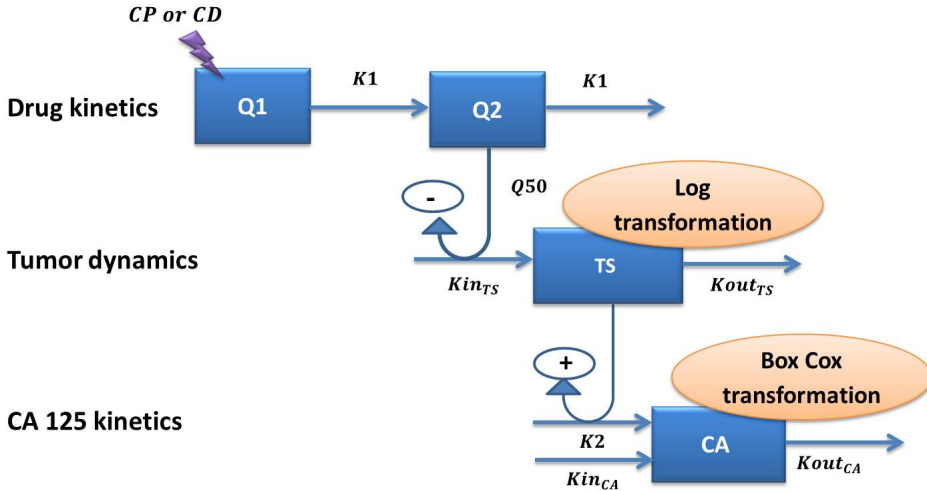
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Patients and Methods

K-PD semi-mechanistic model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy



Results

Typical parameters and inter-individual variability estimated

Parameter	Unit	Estimate	RSE estimate (%)	IIV (CV)	RSE IIV (%)	Shrinkage (%)
$K1$	day^{-1}	0.054	4	0.63	5	26
Kin_{TS}	$mm \cdot day^{-1}$	0.0894	9	15.00	5	38
$Q50$	IU	0.000306	16	1339.86	21	33
$Kout_{TS}$	day^{-1}	0.00228	8	535.09	5	29
Kin_{CA}	$U \cdot mL \cdot day$	5.32	9	0.31	4	16
$K2$	$mm^{-1} \cdot day$	33.4	7	0.04	5	30
$Kout_{CA}$	day^{-1}	0.0307	4	23.19	5	36

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Covariates at baseline:

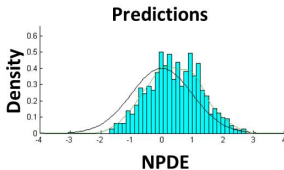
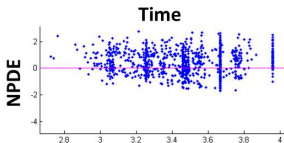
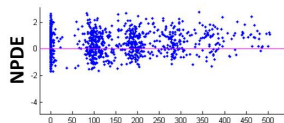
- **Basal lesion size on Kin_{TS} :** larger tumor growth for patients with a lesion size $> 5cm$
- **Basal number of lesions on $Q50$:** treatment more potent in patients with only 1 lesion site



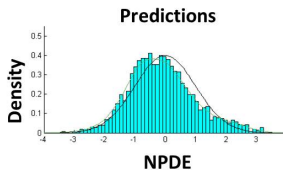
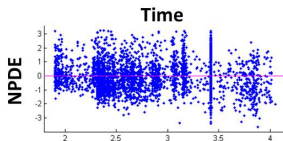
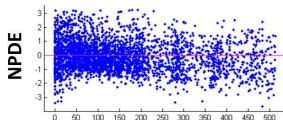
Results

Model internal evaluation: NPDE distribution

Tumor size



CA 125

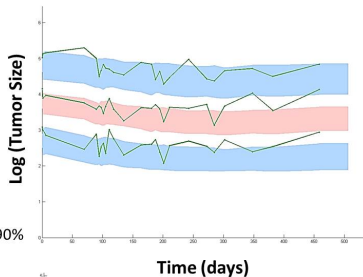


Results

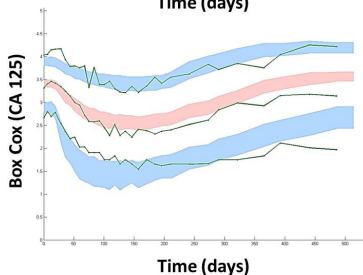
Model internal evaluation: Visual Predictive Check

Tumor size

- Observations percentiles
- Simulated confidence interval 90%
- Simulated c.i 50%
- Simulated c.i 10%



CA 125



Results

Model internal evaluation

K-PD combined model of drug kinetics, tumor dynamics and CA 125 kinetics:

- Data satisfactorily described (GOFs, not shown)
- Adequate predictive performance (NPDEs, VPCs)

→ Model internal validation **achieved**



Results

Model "External" evaluation

- **Method:**
 - Model structure
 - Parameters distributions
 - Validation dataset
- Tumor size and CA 125 predictions

Results

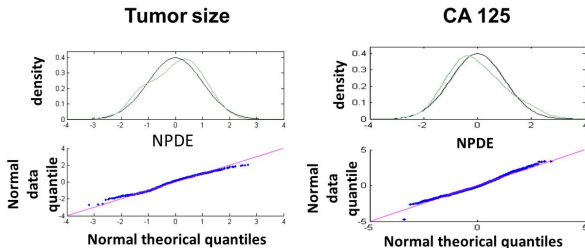
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→ Tumor size and CA 125 predictions

- **NPDE:**

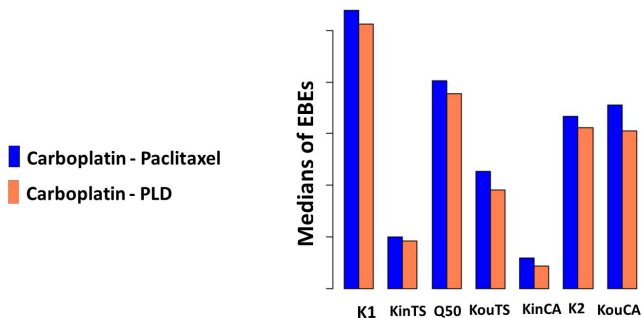


→ Model "external" validation **achieved**

Results

Clinical applications: Treatment comparison

Carboplatin - Pegylated Liposomal Doxorubicin (CD) **VS** Carboplatin - Paclitaxel (CP):

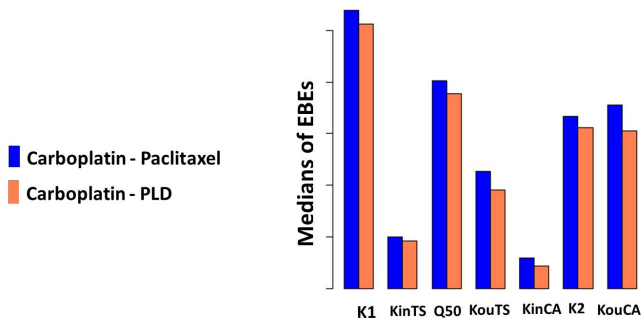


EBEs not significantly different in both groups

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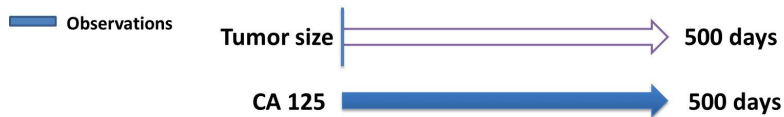
EBEs not significantly different in both groups

-> In agreement with CALYPSO trial conclusions



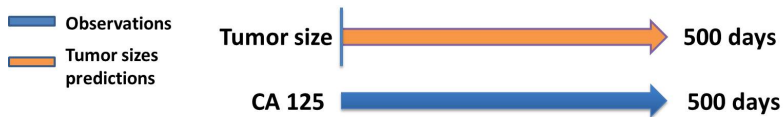
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Clinical applications: Tumor size monitoring



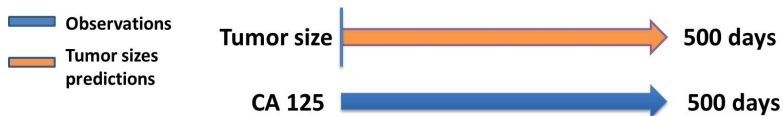
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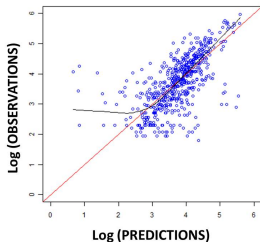


Results

Clinical applications: Tumor size monitoring



Tumor size Predictions versus Observations

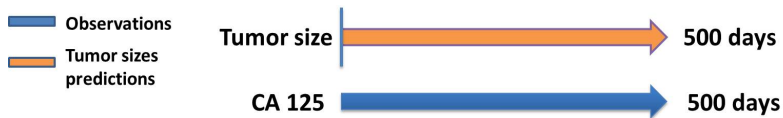


Unbiased (MPE = 2 %)

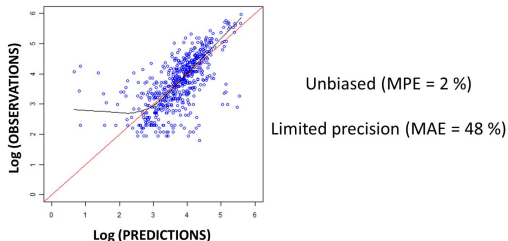
Limited precision (MAE = 48 %)

Results

Clinical applications: Tumor size monitoring



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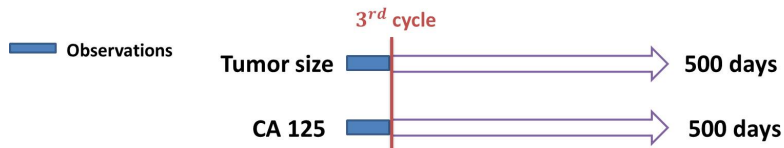


→ Tumor size **prediction** from CA 125 at the population level (high values)



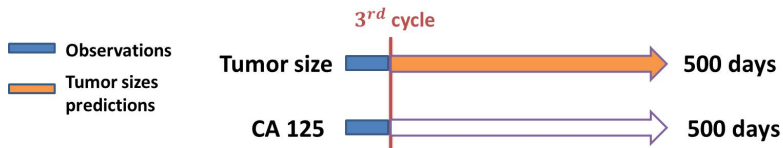
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Clinical applications: Tumor size forecast



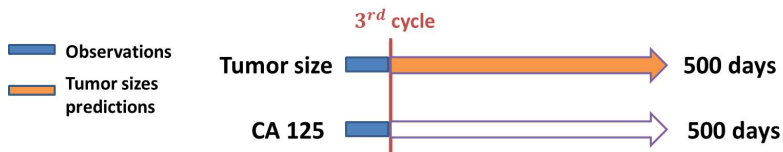
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Clinical applications: Tumor size forecast

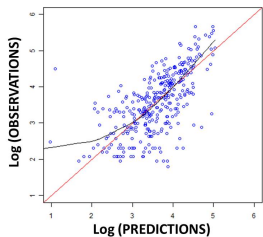


Results

Clinical applications: Tumor size forecast



Tumor size Predictions versus Observations

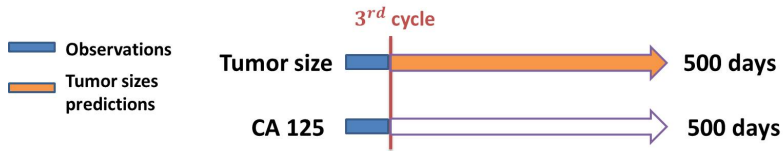


Unbiased (MPE = 0.5 %)

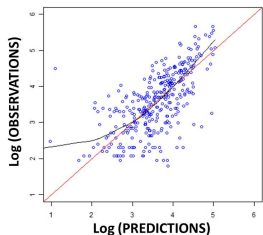
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Results

Clinical applications: Tumor size forecast



Tumor size Predictions versus Observations



Unbiased (MPE = 0.5 %)

Limited precision (MAE = 48 %)

→ Prognosis value of modeled CA 125 to **early forecast** tumor size at the population level



First combined model, internally and externally validated, characterizing tumor size and CA 125 kinetics in ROC patients, after chemotherapy.

First combined model, internally and externally validated, characterizing tumor size and CA 125 kinetics in ROC patients, after chemotherapy.

- Treatment or dosing regimen comparison
- Tumor size monitoring using CA 125 at the population level
- CA 125 is not a surrogate marker of measured lesion size at the individual level

Discussion

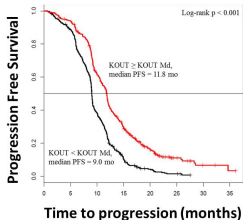
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- Predictive value of CA 125 kinetics on Progression Free Survival in a similar ROC patients population ³:

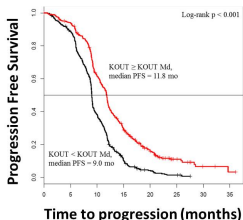


[3] You et al. Mathematical modeling of CA125 kinetics in recurrent ovarian cancer (ROC) patients treated with chemotherapy and predictive value of early modeled kinetic parameters in CALYPSO trial: A GCIG study. *J Clin Oncol*. 2011(suppl; abstr 5065).



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→ Interest of CA 125 kinetics analysis to predict treatment success or failure

- 1 To confirm our results on other data in ROC

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- 2 To apply population modeling approach on other biomarkers:
 - PSA in prostate cancer ⁴
 - hCG in gestational trophoblastic disease ⁵
 - ...

[4] You et al. Prognostic value of modeled PSA clearance on biochemical relapse free survival after radical prostatectomy. *Prostate*, 2009.

[5] You et al. Predictive values of hCG clearance for risk of methotrexate resistance in low-risk gestational trophoblastic neoplasias. *Ann Oncol*, 2010.

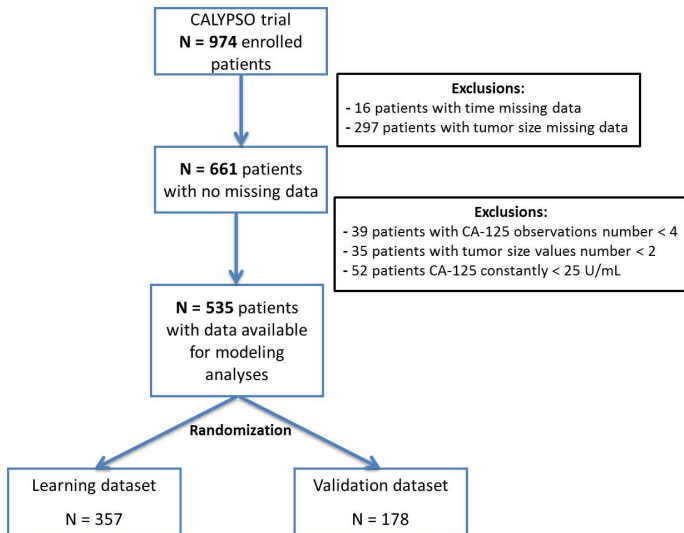


Thank you !



Backslide

CALYPSO patients exclusion



Data distribution of dependent variables tumor size and CA 125

Characteristics	Data					
	Min.	1 st Qu.	Median	Mean	3 rd Qu.	Max.
CA 125 values number/patient	4.0	8.0	10.0	10.2	12.0	21.0
CA 125 values (U/mL)	1.0	18.0	50.5	341.0	173.0	75410.0
Tumor size values number/patient	2.0	3.0	4.0	3.9	5.0	9.0
Tumor size values (mm)	0.0	11.0	33.0	49.1	68.0	400.0
Dropout times (days)	59.0	357.5	485.0	512.8	658.0	1342.0

Continuous and categorical covariates distributions

Continuous covariates	Data					
	Min.	1 st Qu.	Median	Mean	3 rd Qu.	Max.
Age (years)	27.11	54.34	61.25	60.63	67.71	82.49
Weight (kg)	41.00	60.00	69.00	70.08	78.00	150.00
Height (cm)	139.0	158.0	162.0	162.3	167.0	183.0
BSA (m2)	1.320	1.620	1.730	1.742	1.85	2.59
Creatinine (umol/L)	6.20	61.90	70.70	72.07	82.00	154.00
PFS 1 st chimio (months)	2.76	15.07	20.66	26.35	31.09	144.40
Patient Therapy Free Interval (months)	6.0	6.0	12.0	9.757	12.0	12.0

Categorical covariates	Data (number of patients)			
	Treatment	CP		CD
	284		251	
Any surgery within 28 days	Yes		No	
	43		492	
FIGO stage	I	II	III	IV
	24	38	395	66
Primary tumor site	Fallopian	Ovary	Peritoneal	
	19	475	41	
Elevated weight blood cells	Yes		No	
	341		192	
Ascite involvement	Yes		No	
	531		4	
Measurable lesion	Yes		No	
	494		41	
Lesion sites number	1		> 1	
	163		372	
Target lesion size	< 5		> 5	
	390		145	
Number of cycles	1 – 3	4 – 6	7 – 9	10 – 14
	33	376	107	19

$$CA\ 125'_\lambda = \frac{CA\ 125^\lambda - 1}{\lambda}$$

$$\lambda = -0.16$$

Model equations

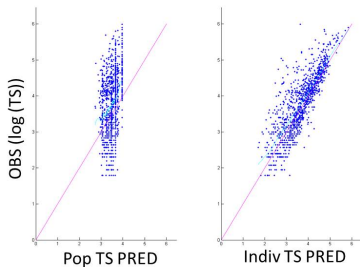
$$\left\{ \begin{array}{l} \frac{dQ1}{dt} = -K1 \times Q1 \\ \frac{dQ2}{dt} = K1 \times Q1 - K1 \times Q2 \\ \frac{dTS}{dt} = Kin_{TS} \times \left(1 - \frac{Q2}{Q50 + Q2} \right) - Kout_{TS} \times TS \\ \frac{dCA}{dt} = Kin_{CA} \times \exp(K2 \times VARTS) - Kout_{CA} \times CA \end{array} \right.$$

Results

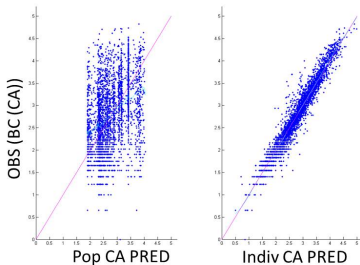
Model internal evaluation: Predictions versus Observations

Tumor size

• Observed data
— Spline

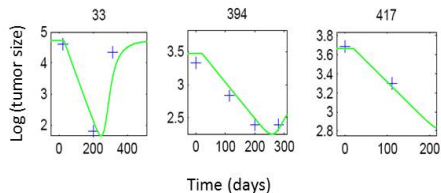


CA 125

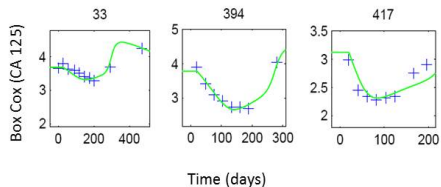


Individual Fits

- Example of tumor size individual fits for 3 ROC patients



- Example of CA 125 individual fits for 3 ROC patients



- Bias measure \rightarrow Mean Prediction Error (MPE):

$$MPE = \frac{\sum_{i=1}^N (Predicted - Observed)}{N}$$

- Precision measure \rightarrow Mean Absolute prediction Error (MAE):

$$MAE = \frac{\sum_{i=1}^N |Predicted - Observed|}{N}$$