A drug-independent model predicting Progression-Free Survival to support early drug development in recurrent ovarian cancer patients

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Background

➢ ***Drug development in oncology:***

- high failure rate in phase III (approx 60% [1])

→ Need for early predictor of clinical benefits to select promising drug candidates

- Early change in tumor size: predictor of survival in a number of solid tumors [2,3,4]

➢ ***Ovarian cancer :***

- Highest mortality rate among all invasive gynecologic cancers
- CA-125: serum tumor marker of epithelial ovarian cancer
- Treatment efficacy: RECIST criteria + GCIG criteria (CA-125 response: at least 50% reduction)

Objectives

- To establish the **quantitative relationships** between **CA-125 kinetics, tumor dynamics and progression-free survival** (PFS) in patients with recurrent ovarian (ROC) cancer treated with chemotherapy
- To **compare** the **predictive capacities** of tumor size changes versus CA-125 kinetics regarding PFS

Patients & Methods

➢ ***Patients:***

- **534 ROC patients** from **CALYPSO** trial: phase III comparing 2 platinum-based regimens
- 2/3 of database (N=356): **Learning dataset** → Model building
- 1/3 of database (N=178): **Validation dataset** → External validation

➢ ***Methods (approach similar to Claret et al. [4]):***

1) **Screening for significant covariates**: Kaplan-Meier & univariate Cox analysis
2) Development of a **full parametric survival model:**
   - Structure of PFS distribution
   - Quantitative link between tumor size changes, CA-125 kinetics, covariates and PFS
3) **Reduction** of the full model in 2 separate models:
   - Tumor size-based model vs CA-125-based model
   - Comparison of their predictive capacities regarding PFS (AIC)
4) Internal & external **evaluation** of the best reduced model (VPC)

Results

Relative change in tumor size and CA-125 assessment

$$\Delta TS = \frac{TS_{BL} - TS_{Week6}}{TS_{BL}} \qquad \Delta CA125 = \frac{CA125_{BL} - CA125_{Week6}}{CA125_{BL}}$$

TS_{BL} and $CA125_{BL}$: tumor size and CA-125 at baseline

TS_{Week6} and $CA125_{Week6}$: tumor size and CA-125 at week 6

Values estimated using a previously reported K-PD semi-mechanistic model [5]. TS: log transformed. CA-125: Box-Cox transformed.

Full parametric survival model

PFS best described by a log-logistic distribution:

$$\log(T) = \alpha_0 + \sigma \times \log\left(\frac{1 - S(T)}{S(T)}\right) + \alpha_{\Delta TS} \times \Delta TS + \alpha_{\Delta CA125} \times \Delta\text{CA125} + \alpha_{CA125_{BL}} \times CA125_{BL} + \alpha_{PTFI} \times \text{PTFI}$$

T: time to progression; α_0: intercept; $\frac{1-S(T)}{S(T)}$: log-logistic survival odds; α_X: slope for covariate X; $PTFI$: patient therapy-free interval (≤12 months vs >12 months)

Comparison of the predictive values of tumor size versus CA-125 changes regarding PFS

Model	AIC	Time Ratio ΔTS (1-unit change)	Time Ratio ΔCA125 (1-unit change)	Time Ratio $CA125_{BL}$ (1-unit change)
Tumor size-based model	4213	1.79	/	/
CA-125-based model	4206	/	2.08	0.88

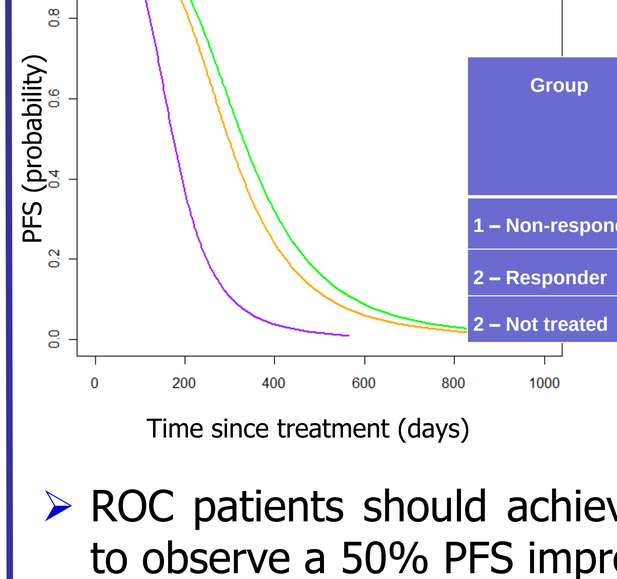
CA-125-based model is the most suitable reduced model describing PFS.

Parameter estimates of the **CA-125-based model**

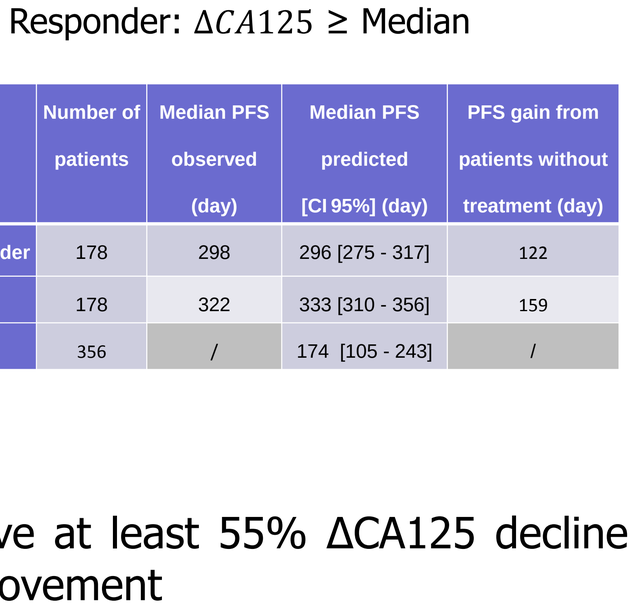
Parameter	Estimate	RSE (%)	Time Ratio	Wald p-value
Intercept	6.093	2.8	/	< 0.001
$\alpha_{CA125_{BL}}$	- 0.128	37.0	0.88	0.006
$\alpha_{\Delta CA125}$	0.735	33.4	2.08	0.002
Scale	0.256	1.2	/	/

Validation of the CA-125-based model

Internal validation from 500 simulations of the Learning dataset



External validation from 500 simulations of the Validation dataset



Model practical applications

➢ Prediction of the expected PFS based on patient $\Delta CA125$

- Non-responder: $\Delta CA125$ < Median
- Responder: $\Delta CA125$ ≥ Median

Group	Number of patients	Median PFS observed (day)	Median PFS predicted [CI 95%] (day)	PFS gain from patients without treatment (day)
1 – Non-responder	178	298	296 [275 - 317]	122
2 – Responder	178	322	333 [310 - 356]	159
2 – Not treated	356	/	174 [105 - 243]	/

➢ ROC patients should achieve at least 55% ΔCA125 decline to observe a 50% PFS improvement

Conclusions

➢ First drug-independent parametric survival model quantifying links between PFS and CA-125 kinetics in ROC patients

➢ Modeled relative change in CA-125 at week 6: a promising predictive marker of the expected gain in PFS

➢ Early predictive tool for go/no go drug development decisions

References

[1] Kola et al, *Nat Rev Drug Discov*, 2004. [2] Claret et al, *J Clin Oncol,* 2006. [3] Wang et al, *Clin Pharmacol Ther*, 2009. [4] Claret et al, *J Clin Oncol*, 2009. [5] Wilbaux et al, *PAGE,* 2012.