

# A joint K-PD model with the tumor size changes and CA-125 kinetics in patients with advanced ovarian cancer (AOC): analysis of the phase II BOLD study

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#Abstract 10120

## Background & Objectives

- CA-125 serum tumor marker Kinetics modelling during chemotherapy using a Kinetic-Pharmacodynamics (K-PD) model was shown to be relevant.
  - Modeled ELIMination rate constant K (KELIM) : reproducible indicator of the tumor chemosensitivity [2].
- Objective: describing tumor size changes and the kinetics of CA-125 in a joint K-PD model with data of AOC patients enrolled in BOLD trial.
  - Determining if adding tumor size to CA-125 kinetics increase model accuracy with platinum resistant (PRR) or sensitive relapse (PSR) patients data.

## Methods

- Data: Phase II clinical trial BOLD (NCT04015739) [1]
- Selected patients: at least 3 CA-125 titers and 2 tumor size measurements.

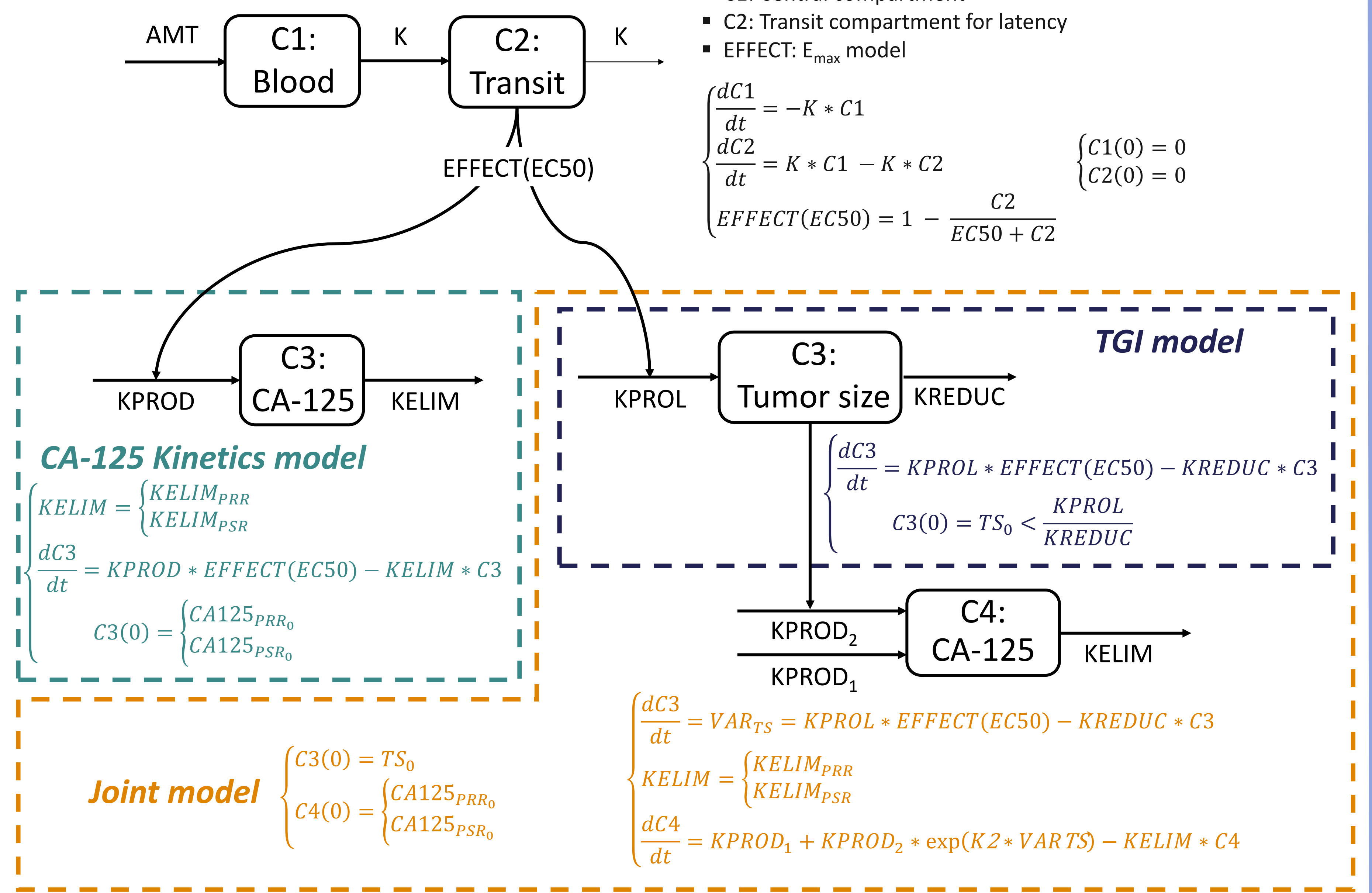
- Models: Three K-PD models were built to fit during the first 100 days of treatment (indirect effect model) :
  - CA-125 kinetics
  - Tumor growth inhibition (TGI) [3]
  - A joint model assessing relationships between TGI and CA-125 kinetics [3]

Models validation criteria: Relative Standard Errors (RSE), shrinkage values, Goodness-Of-Fits (GOF), Visual Predictive Checks (VPC) (NONMEM 7.5.0).

### Common part of the three models:

- C1: Central compartment
- C2: Transit compartment for latency
- EFFECT: E<sub>max</sub> model

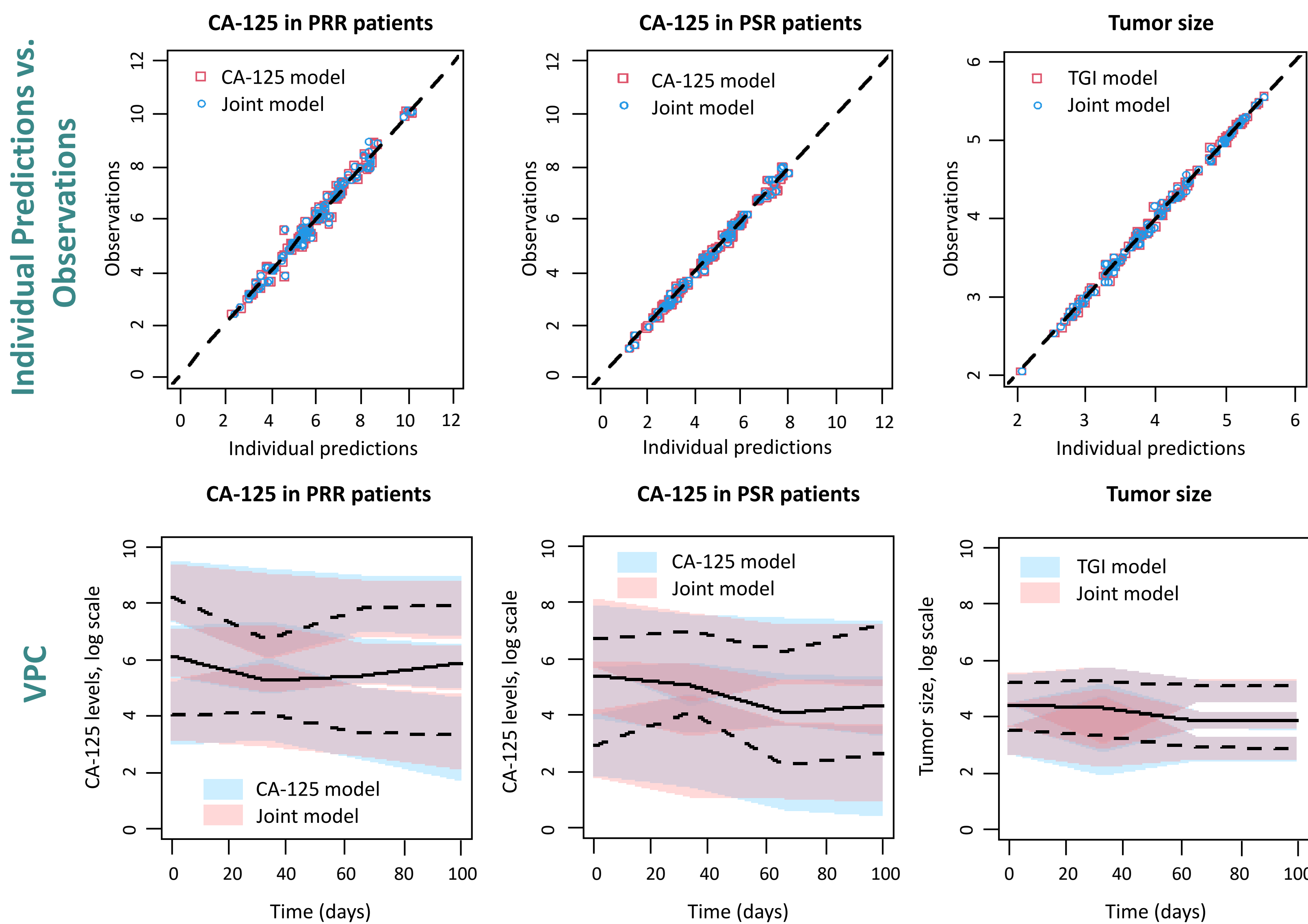
$$\begin{cases} \frac{dC1}{dt} = -K * C1 \\ \frac{dC2}{dt} = K * C1 - K * C2 \\ EFFECT(EC50) = 1 - \frac{C2}{EC50 + C2} \end{cases} \quad \begin{cases} C1(0) = 0 \\ C2(0) = 0 \end{cases}$$



## Results

- 50/74 patients selected for analyses
- Platinum-sensitivity status (PSR vs. PRR) : covariate on CA-125<sub>0</sub> and KELIM (CA-125 and joint models). Covariate non significant in TGI model.
- RSE < 50% (except K, EC50 & KPROD<sub>1</sub>)
  - lack of treatment concentrations
  - low number of patients
  - high inter-individual variability.

- GOF plots & VPC suggested good predictions in all models.



| Parameters                                                   | Typical value | RSE (%) | BSV (%) | RSE (%) | Shrinkage (%) |
|--------------------------------------------------------------|---------------|---------|---------|---------|---------------|
| CA-125 Kinetics model                                        |               |         |         |         |               |
| K (day <sup>-1</sup> )                                       | 1.16          | 48.19   | 112.25  | 33.77   | 91.02         |
| KPROD (kU.mL <sup>-1</sup> .day <sup>-1</sup> )              | 1.06          | 60.75   | 170.88  | 20.55   | 39.11         |
| EC50 (AU)                                                    | 0.29          | 73.33   | 55.68   | 52.26   | 93.34         |
| CA-125 <sub>PRR,0</sub> (kU.mL <sup>-1</sup> )               | 559.0         | 30.95   | 165.83  | 19.09   | 1.20          |
| CA-125 <sub>PSR,0</sub> (kU.mL <sup>-1</sup> )               | 141.0         | 35.67   |         |         |               |
| KELIM <sub>PRR</sub> (day <sup>-1</sup> )                    | 0.01          | 45.92   | 129.23  | 27.37   | 22.53         |
| KELIM <sub>PSR</sub> (day <sup>-1</sup> )                    | 0.02          | 50.05   |         |         |               |
| TGI model                                                    |               |         |         |         |               |
| K (day <sup>-1</sup> )                                       | 0.33          | 31.83   | 91.05   | 89.87   | 43.10         |
| EC50 (AU)                                                    | 0.29          | 81.12   | 73.96   | 65.90   | 64.69         |
| TS <sub>0</sub> (mm)                                         | 58.10         | 11.24   | 77.91   | 8.48    | 1.25          |
| KREDUC (day <sup>-1</sup> )                                  | 0.02          | 102.25  | 90.55   | 19.33   | 69.16         |
| KPROL (mm.day <sup>-1</sup> )                                | 3.67          | 27.25   | 131.53  | 25.49   | 81.27         |
| Joint model                                                  |               |         |         |         |               |
| K (day <sup>-1</sup> )                                       | 0.30          | 41.69   | 29.65   | 55.80   | 72.70         |
| EC50 (AU)                                                    | 0.40          | 80.15   | 167.03  | 25.09   | 34.49         |
| TS <sub>0</sub> (mm)                                         | 57.80         | 11.26   | 78.10   | 13.11   | 0.90          |
| KREDUC (day <sup>-1</sup> )                                  | 0.02          | 51.23   | 70.29   | 97.98   | 73.02         |
| KPROL (mm.day <sup>-1</sup> )                                | 3.35          | 23.85   | 90.22   | 74.94   | 83.04         |
| KPROD <sub>1</sub> (kU.mL <sup>-1</sup> .day <sup>-1</sup> ) | 0.19          | 128.65  | 122.88  | 26.82   | 82.84         |
| KPROD <sub>2</sub> (kU.mL <sup>-1</sup> .day <sup>-1</sup> ) | 1.43          | 61.61   | 130.77  | 22.87   | 38.09         |
| CA-125 <sub>0,PRR</sub> (kU.mL <sup>-1</sup> )               | 567.0         | 31.04   | 164.92  | 15.92   | 0.85          |
| CA-125 <sub>0,PSR</sub> (kU.mL <sup>-1</sup> )               | 144.0         | 36.18   |         |         |               |
| KELIM <sub>PRR</sub> (day <sup>-1</sup> )                    | 0.01          | 46.95   | 138.92  | 15.91   | 18.33         |
| KELIM <sub>PSR</sub> (day <sup>-1</sup> )                    | 0.03          | 46.13   |         |         |               |
| K2 (day.mm <sup>-1</sup> )                                   | 0.18          | 51.64   | 35.92   | 99.61   | 90.57         |

## Conclusion

- Three models were able to characterize individually CA-125 kinetics and TGI in AOC patients during the first hundred days of treatment administration.
- Joint model : more complex and precise modelling.
- The prognostic value regarding PFS and OS of parameters extracted from these models will be investigated.

## References

- Freyer, G., et al., 733P Bevacizumab (Bev), olaparib (Ola) and durvalumab (Durva) in patients with recurrent advanced ovarian cancer (AOC): The GINECO BOLD study. Annals of Oncology, 2021.
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