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# Influence analysis explores heterogeneity in database before data processing by a parametric population method

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### Presentation

Retrospective analysis of data from clinical studies in metastatic breast cancer

Dependent variable : sum of the longest diameter of metastatic sites measured

No pharmacokinetics (only administration protocols)

Data available [1, 2, 3] :

Phase II : Capecitabine C (n=168)

Phase III : Docetaxel D (n=223) vs. D+C (n=222)

Already treated [4, 5, 6]

### Objectives

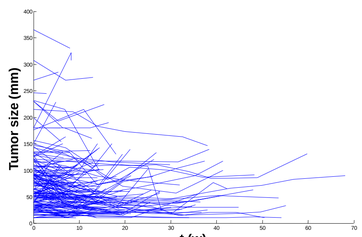
Control homogeneity in PK-PD population data by using influence analysis (leave-one-out procedure)

Assess interaction for drugs used in combination

### Tools

NONMEM V6, Matlab

## THE DATA



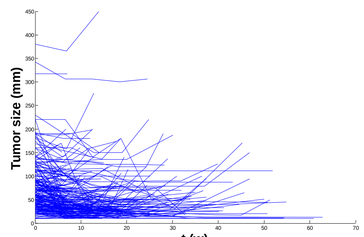

**C**

**Single agent**

**Phase II**

**n=168**

Fig1. Tumor-size profile with C in Phase II study (n=168)



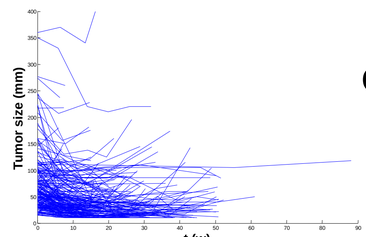

**D**

**Single agent**

**Phase III**

**n=223**

Fig2. Tumor-size profile with D in Phase III study (n=223)




**C+D**

**Combination**

**Phase III**

**n=222**

Fig3. Tumor-size profile with D+C in phase III study (n=222)

## MODELING

## Global modeling

$$\frac{dy(1)}{dt} = -KPC.y(1) + u_1(t)$$
$$\frac{dy(2)}{dt} = -KPD.y(2) + u_2(t)$$
$$\frac{dn(t)}{dt} = KL.\ln\left(\frac{\theta}{n(t)}\right).n(t) - \{KDC.\exp(-DMC.t).y(1) + KDD.\exp(-DMD.t).y(2)\}.n(t)$$

**Model explanations :**

- $y_1(t), y_2(t)$ $[g]$ : "Effective dose" for C and D respectively
- $u_1(t), u_2(t)$ $[g^{-1}.w^{-1}]$ : Administration protocols for C and D respectively
- $KP\_$ $[w^{-1}]$ : Fixed biologics constants
- $n(t)$ $[mm]$ : Tumor size
- Estimated parameters :
  - $KL$ $[w^{-1}]$ : Proliferation parameter (max tumor size : $\theta$ $[mm]$ , fixed)
  - $DM\_$ $[w^{-1}]$ : Resistance parameter distinct for each drug
  - $KD\_$ $[g^{-1}.w^{-1}]$ : Constant cell kill rate distinct for each drug
  - $n_0$ $[mm]$ : Initial tumor size

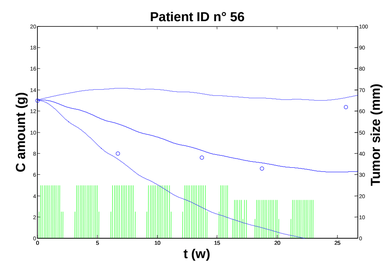
## Single agent

Models tested for single agents : with and without resistance parameter.

For the models with resistance, the leave-one-out procedure was used to detect atypical patients.

To avoid correlations, use common variability for and $KL$ . $DM$

Biologic constants were estimated and fixed for combination C+D : $KPC = 0.6\ w^{-1}$ $KPD = 0.2\ w^{-1}$



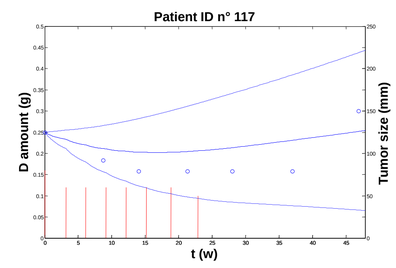




Fig4 and 5. Administered amounts (green and red for C and D, respectively) and tumor-size profile (blue circle : observations; blue solid line : simulation with population parameters; blue dashed line : confidence intervals)

### Conclusion for single agent

Best models when resistance is reported to the cell kill rate parameter; use common variability to avoid correlations

The leave-one-out procedure reveals homogeneity in C and D populations and detects some atypical patients

## Combination : the model

Families of models tested for combination

- F1 : all parameters (fixed parameters and random effects)
- F2 : without random effect on $KL$
- F3 : # # # $DMC$ and/or $DMD$
- F4 : # # # $KDC$ and/or $KDD$
- F5 : $DMC$ removed
- F6 : F5 and without random effect on $DMD$
- F7 : $DMD$ removed
- F8 : $DMC$ and $DMD$ removed

Best models in F5, F6 → Retained model in F6 →

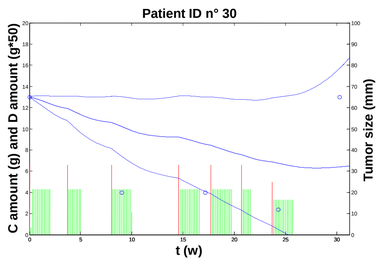



Fig6. Administered amounts (green and red for C and D, respectively) and tumor-size profile (blue circle : observations ; blue solid line : simulation with population parameters; blue dashed line : confidence intervals)

| | KL | KDC | DMC | KDD | DMD | n0 |
|---|---|---|---|---|---|---|
| C | 0.00513 | 0.000808 | | | | 61.9 |
| D | 0.00418 | | | 0.301 | 0.107 | 55.1 |
| C+D | 0.00458 | 0.000631 | | 0.516 | 0.114 | 56.6 |

Tab1. Population parameter estimated by NONMEM
Estimates for single agent (C, D) and combination (C+D)

## Combination : influence analysis and mixture model

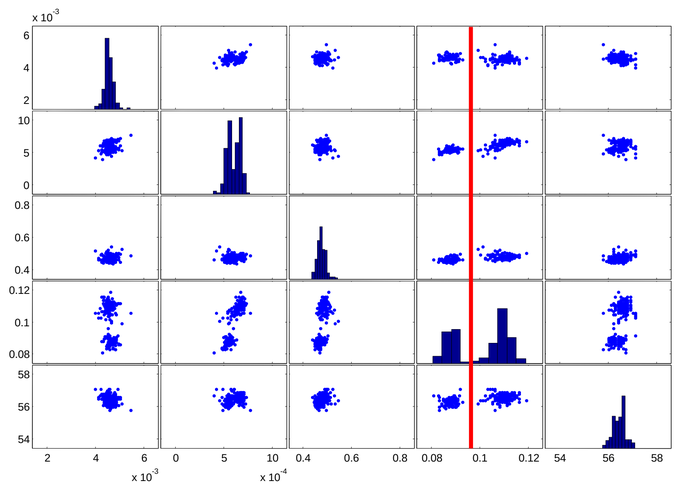



Fig7. Fixed effect parameters estimated using the leave-one-out (KL, KDC, KDD, DMD, n0)

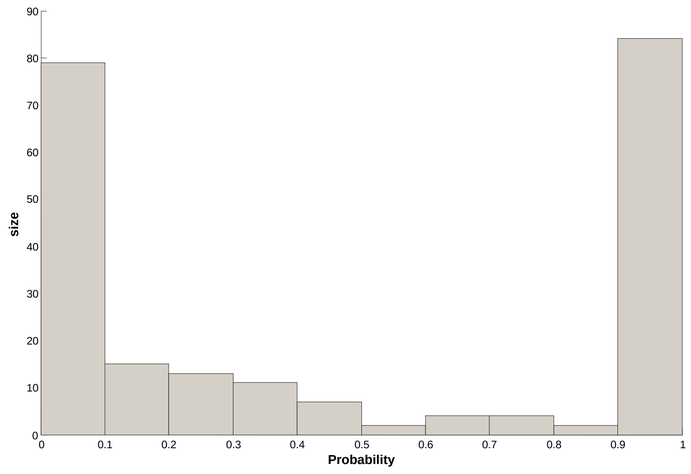



Fig8. Histogram of individual probability to belong to one of the two subpopulations computed with mixture model

### Leave-one-out

$DMD$ and $KDC$ scatter plots reveal two subpopulations (fig7).

### Mixture

Best mixture models when subpopulations are defined with $KL$ and $DMD$ ; $\Pr \neq 0$ and $\Pr \neq 1$ are verified [7].

Significant decrease in OFV as compared to the model without mixture (confirmed by AIC).

Individual OFV are obtained (PsN software [8]). They result in a high probability [9] for most of the patients to belong to the subpopulation that mixture procedure propose (fig8).

### Leave-one-out vs. Mixture

Mixture partitions the population in different sets than leave-one-out do.

In both cases, $DMD$ parameter is different in the two subpopulations.

## CONCLUSION

1. In a previous work [6], the resistance was reported to the proliferation term. Presently, resistance is reported to the cell kill rate term and models fit better to data.
2. Combination and single-agent models involve different mechanisms. In the combination model :
   - no resistance for C,
   - no random effect for D resistance.
3. Leave-one-out reveals two subpopulations. This heterogeneity was confirmed with the mixture model.
4. D resistance is the parameter responsible of the obtained partitions.
5. Partitions of individuals by the two methods are different and more investigations are in process.
6. Experimental protocols don't influence the partitions obtained.
7. As compared to single agents, combination reveals enhanced efficacy for D (interaction not characterized at the moment).

### References

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