

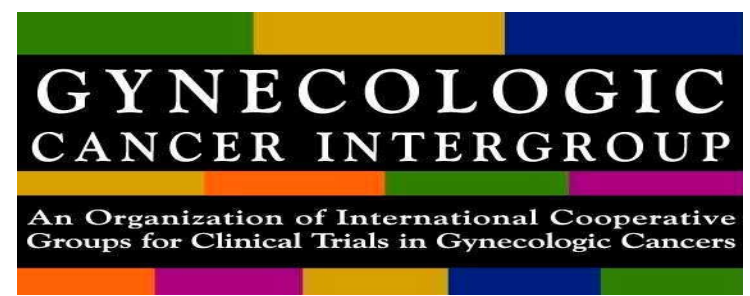


Assessment of The Prognostic Value Of The CA-125 Modeled Kinetic Parameter KELIM in GOG-0262 and MITO-7 trials.

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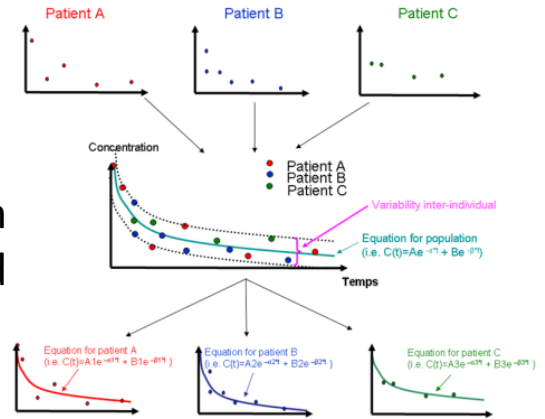
For the GINECO-GINEGEPS.

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Background

- **Need for early predictors of treatment efficacy** in ovarian cancer patients treated by chemotherapy +/- targeted agents



- **CA-125 based Rustin criteria** is commonly used to predict treatment efficacy during phase II trials

J Clin Oncol 1996; 14:1545–1551

↳ the actual value was **recently questioned!**

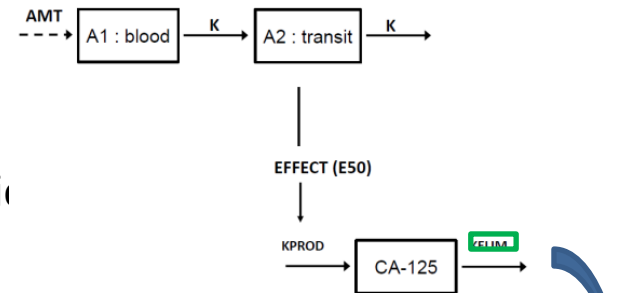
JNCI 2011; 103: 1338–1342

- **Mathematical modeling** of longitudinal CA-125 kinetic may help analyze individual CA-125 decline profiles

- The CA-125 elimination modeled parameter **KELIM** was a **significant independent prognostic factor of treatment efficacy in CALYPSO trial** (recurrent ovarian cancer patients)

Gynecol Oncol. 2013 Aug;130(2):289-94

=> Validation of KELIM prognostic factor regarding PFS in independent phase III trial cohorts of patients treated with different first line regimens was warranted



$$\begin{cases}
 (1) \frac{dA1}{dt} = -K \times A1 \\
 (2) \frac{dA2}{dt} = K \times A1 - K \times A2 \\
 (3) \frac{dA3}{dt} = KPROD \times EFFECT(E50) - \text{KELIM} \times A3 \\
 (4) EFFECT(E50) = 1 - \frac{A2}{E50 + A2} \in [0,1]
 \end{cases}$$

Recent data from phase III trials ...

Data from 3 independent phase III trials

AGO-OVAR 9 ⁶

Carboplatin - Paclitaxel
+/- Gemcitabine

N = 1742

AGO-OVAR 7 ⁵

Carboplatin - Paclitaxel
+/- Topotecan maintenance

N = 1308

ICON-7 ⁷

Carboplatin - paclitaxel
+/- bevacizumab

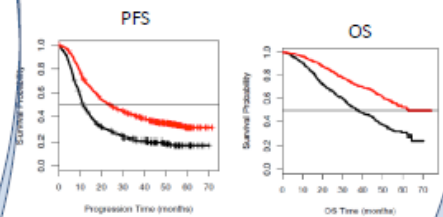
N = 1528

1) Training Step to Adjust Model Parameters And Define Prognostic KELIM Cut-off

AGO-OVAR 9

- Model parameters were adjusted to 1st line treatment patients => estimation of parameters
- CA125 kinetics were properly described during the first 100 days by the model
- Median KELIM = 0.059
- PFS = 24.0 months (if KELIM > median) vs 11.3 months (if KELIM < median), P < 0.001
- OS = 62.5 vs 37.0 months, P < 0.001
- Multivariate analysis against FIGO stage and baseline CA125 & treatment arm: HR = 0.55 (95% CI: 0.47-0.64) for KELIM

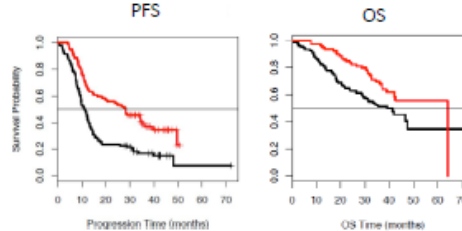
Paramètres de population	RSE*(%)	BSV*(%)	RSE***(%)	shrink(%)	SIGMA	SE	RSE†(%)
K	1.56E-01	13.5	28.6	40.0	8.14E+01	1 FIX	0
NPROD	1.19E+00	8.2	25.9	15.4	6.81E+01		
ES0	3.94E-01	19.7	34.2	59.8	6.42E+01		
KELIM	5.57E-02	2.5	56.3	2.6	1.05E+01		
CA125	1.41E+02	6.0	167.6	2.5	7.61E+00		



2) Validation Step to Assess KELIM, Prognostic Value Regarding PFS & OS

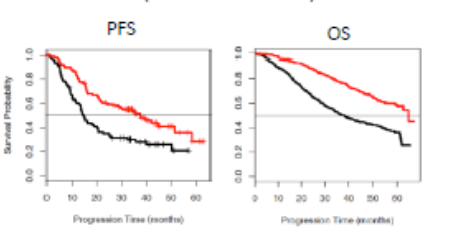
AGO-OVAR 7

- PFS = 28.3 months (if KELIM > median 0.059) vs 11.1 months (if KELIM < median 0.059), P < 0.001
- OS = 64.2 months vs 39.2 months, P < 0.001
- Multivariate analysis against FIGO stage and baseline CA125 & treatment arm: HR = 0.55(95% CI: 0.35-0.86) for KELIM



ICON-7

- PFS = 37.5 months (if KELIM > median 0.059) vs 14.7 months (if KELIM < median 0.059), P < 0.001
- OS = 65.0 months vs 38.2 months, P < 0.001
- Multivariate analysis against FIGO stage, baseline CA125, histology, grade, surgery residuals & treatment arm: HR = 0.49 (95% CI: 0.41-0.57) for KELIM

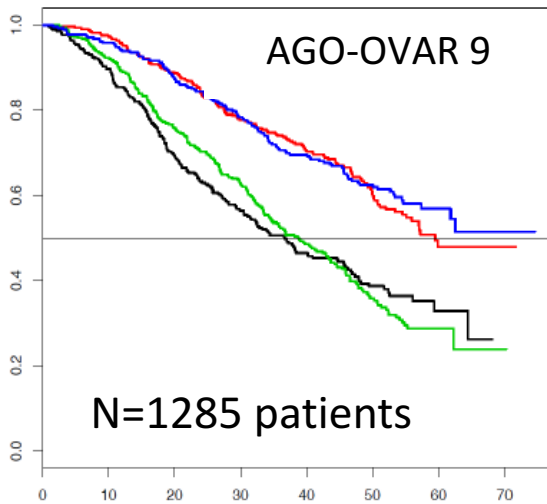


KELIM prognostic value is independent on chemotherapy regimens



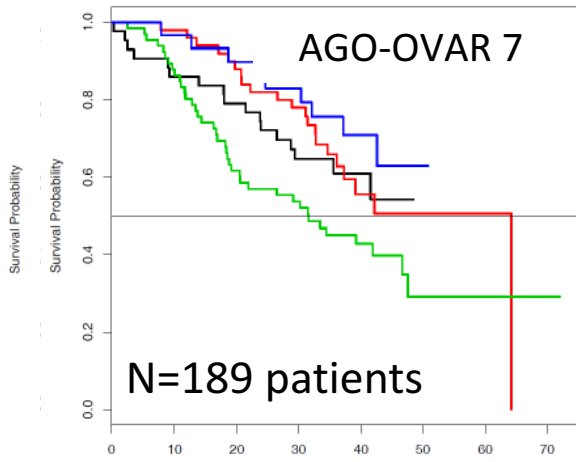
	Treatment	PFS (months)		OS (months)	
		Favorable KELIM > 0.059	Unfavorable KELIM ≤ 0.059	Favorable KELIM > 0.059	Unfavorable KELIM ≤ 0.059
AGO/OVAR9	CP	25.6	11.4	59.5	36.6
	CP + Gemcitabine	21.9	11.2	NR, >70	38.7
AGO/OVAR7	CP	28.3	12.8	NR, > 60	45.5
	CP + topotecan	19.5	10.2	NR, > 60	31.6
ICON7	CP	25.2	8.8	NR, > 60	36.2
	CP + bevacizumab	20.7	13.9	65.0	38.7

NR: not reached



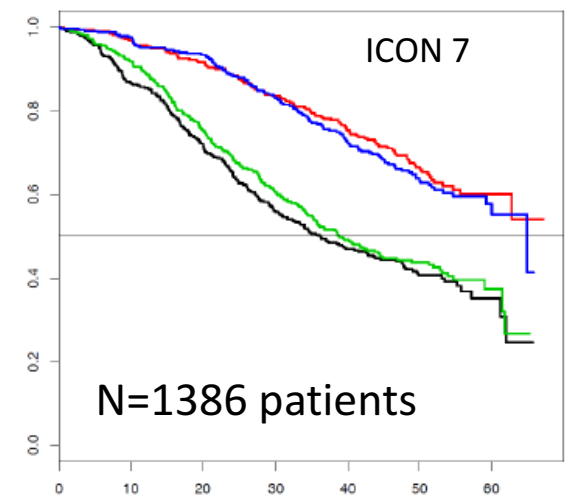
N=1285 patients

Kaplan Meier	Survival median (months)
TC, KELIM < Cut-off.	36.6
TC, KELIM ≥ Cut-off.	59.5
TCG, KELIM < Cut-off.	38.7
TCG, KELIM ≥ Cut-off.	NA



N=189 patients

Kaplan Meier	Survival median (months)
TC, KELIM < Cut-off.	NA
TC, KELIM ≥ Cut-off.	64.2
TCTop, KELIM < Cut-off.	31.6
TCTop, KELIM ≥ Cut-off.	NA



N=1386 patients

Kaplan Meier (P = 0)	Survival median (months)
CARBOPLATIN PLUS PACLITAXEL CHEMOTHERAPY, KELIM < Cut-off.	36.2
CARBOPLATIN PLUS PACLITAXEL CHEMOTHERAPY, KELIM ≥ Cut-off.	NA
CARBOPLATIN PLUS PACLITAXEL CHEMOTHERAPY PLUS BEVACIZUMAB, KELIM < Cut-off.	38.7
CARBOPLATIN PLUS PACLITAXEL CHEMOTHERAPY PLUS BEVACIZUMAB, KELIM ≥ Cut-off.	65.0

Hypotheses

- KELIM, estimated in the first 100 days during first line chemotherapy
 - ↳ Discriminates 2 prognostic populations of ovarian cancer patients whatever received treatments
Median survival of 35 months vs > 60 months
- Marker of chemo-resistance ?
- What would be the impact of administration schedules on KELIM ?
- Role for dose-dense chemo in unfavorable KELIM patients ?

Proposal

- **MITO-7 trial:**

Carboplatin AUC6 + paclitaxel 175 mg/m² Q3W vs
carboplatin AUC2 + paclitaxel 60 mg/m² Q1W

- **GOG-0262:**

Carboplatin AUC6 + paclitaxel 175 mg/m² Q3W vs
carboplatin AUC6 Q3W +
paclitaxel 80 mg/m² Q1W

Impact of
chemotherapy
administration
schedules and doses
on KELIM ?

Would dose-dense
paclitaxel
counterbalance
unfavorable KELIM ?