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CA-125 ELIMination Rate Constant K (KELIM) Is a Marker of Chemosensitivity in Patients with Ovarian Cancer: Results from the Phase II CHIVA Trial

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ABSTRACT

Purpose: In patients with ovarian cancer receiving neoadjuvant chemotherapy, the first-line treatment success will depend on both the tumor-primary chemosensitivity and the completeness of interval debulking surgery (IDS). The modeled CA-125 ELIMination rate constant K (KELIM), calculated with the CA-125 longitudinal kinetics during the first 100 chemotherapy days, is a validated early marker of tumor chemosensitivity. The objective was to investigate the role of the chemosensitivity relative to the success of first-line medical–surgical treatment.

Experimental Design: The CA-125 concentrations were prospectively measured in the randomized phase II trial CHIVA (NCT01583322, carboplatin–paclitaxel regimen ± nintedanib, and IDS, $n = 188$ patients). The KELIM predictive value regarding the tumor response rate, likelihood of complete IDS, risk of subsequent platinum-resistant relapse (PtRR), progression-free survival (PFS), and overall survival (OS) was assessed using univariate and multivariate tests.

Results: The data from 134 patients were analyzed. KELIM was an independent and major predictor of subsequent PtRR risk, and of survivals. The final logistic regression model, including KELIM [OR = 0.13; 95% confidence interval (CI), 0.03–0.49] and complete IDS (no vs. yes, OR = 0.30; 95% CI, 0.11–0.76) highlights the preponderant role of chemosensitivity on the success of the first-line treatment. In patients with highly chemosensitive diseases, the patient prognosis was driven more by the chemotherapy-induced antitumor effects than by the surgery.

Conclusions: The tumor-primary chemosensitivity, assessed by the modeled CA-125 KELIM calculated during neoadjuvant chemotherapy (http://www.biomarker-kinetics.org/CA-125-neo), may be a major parameter to consider for decision-making regarding IDS attempt, and selecting patients for treatments meant to reverse the primary chemoresistance.

See related commentary by May and Oza, p. 4432

Introduction

The patients with stage III or IV high-grade ovarian carcinomas not amenable to primary debulking surgery procedures are usually treated with neoadjuvant platinum-based chemotherapy for 3 or 4 cycles before interval debulking surgery (IDS), in the intent of a complete cytoreduction with no macroscopic residues (CC0 surgery; refs. 1, 2). In such patients, the success of the first-line treatment will logically depend on at least the following two parameters: (i) the tumor-primary sensitivity to chemotherapy, and (ii) the likelihood of complete IDS after neoadjuvant chemotherapy. As acknowledged by a recent

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Translational Relevance

In patients treated with neoadjuvant chemotherapy and interval debulking surgery in the randomized phase II trial CHIVA, the predictive value of the modeled CA-125 kinetic parameter KELIM regarding the tumor response rate, the likelihood of complete interval debulking surgery, the risk of subsequent platinum-resistant relapse, the progression-free survival, and the overall survival was major compared with the other prognostic factors, including the radiological response rate, the completeness of surgery, or the disease-risk groups. In the case of highly chemosensitive disease, the patient prognosis was driven more by the chemotherapy-induced antitumor effects than by the completeness of surgery. The tumor-primary chemosensitivity may be a preponderant parameter to integrate for predicting the success of the first-line medical–surgical treatment, for decision-making regarding interval debulking surgery attempt, and selecting the patients to therapeutic strategies meant to reverse the chemoresistance.

consensus conference, there is a need for predictors of the tumor-primary chemosensitivity and the risk of subsequent platinum-resistant relapse (1).

The predictive values of CA-125 decline percentages during treatments were extensively investigated, with inconsistent outcomes (3–6). The Gynecologic Cancer Intergroup (GCIG) defined the CA-125 response as a 50% reduction in CA-125 levels maintained for at least 28 days, in patients treated for recurrent diseases (7).

Modern approaches based on artificial intelligence and mathematical modeling are promising strategies to define the equations describing the longitudinal serum tumor marker kinetics during treatment, and to subsequently extract modeled kinetic parameters expected to exhibit predictive values regarding treatment efficacy (6, 8–12). The CA-125 KELIM (meaning CA-125 ELIMination rate constant K), is an early modeled kinetic parameter that can be assimilated to a CA-125 clearance. It is calculated with minimum three observed CA-125 values during the first 100 days of chemotherapy. According to the model, a higher KELIM value can be understood as a faster CA-125 elimination rate and a higher chemotherapy sensitivity (acknowledging the unknown impact of other inflammatory conditions prone to alter CA-125 concentrations). A first retrospective study of the CALYPSO trial on 895 patients with platinum-sensitive recurrent ovarian cancers (6), and a subsequent European validation study involving 2,868 patients treated in first-line setting, in three large phase III trials, confirmed the independent prognostic and predictive values of KELIM regarding progression-free survival (PFS) and overall survival (OS) with multivariate analyses (13). In these patients treated with primary debulking surgery and adjuvant chemotherapy, the impact of the disease stage on the probability of success of the first-line treatment differed according to KELIM. Indeed, the risk of subsequent platinum-resistant relapse was similarly low (overall <20%) regardless of the disease stages I to IV in patients with favorable KELIM, whereas it was largely dependent on the disease stages in those with unfavorable KELIM (14). These outcomes suggested that the tumor chemosensitivity is a major determinant of the first-line treatment success.

On the basis of these data, we hypothesized that the modeled CA-125 kinetic parameter KELIM calculated during neoadjuvant chemotherapy and before IDS would be a major predictor of the first-line medical–surgical treatment success. The aims of this study performed on the data of patients enrolled in the randomized phase II trial CHIVA (NCT01583322) were as follows: (i) to determine the independent predictive value of KELIM regarding the tumor response to chemotherapy, the likelihood of complete IDS, the PFS and OS; and (ii) to understand the respective relationships of KELIM, completeness of IDS, and other potential predictors relative to the success of the first-line treatment.

Materials and Methods

In this French multicenter trial, patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC or IV ovarian carcinomas planned to be treated with perioperative chemotherapy and IDS were randomly allocated to (i) carboplatin AUC 5-6 and paclitaxel 175 mg/m^2 every 3 weeks combined to nintedanib at 200 mg twice daily, or (ii) the same regimen combined to placebo. The enrolled patients received 3-4 cycles before cytoreductive surgery, and then adjuvant 3-4 cycles, followed by a maintenance treatment with nintedanib/placebo for up to 2 years (15).

Nintedanib (VARGATEF) is a receptor tyrosine kinase (RTK) inhibitor with potential antiangiogenic and antineoplastic activities (16). The preliminary outcomes regarding treatment efficacy in CHIVA trial were recently presented (15).

The CA-125 concentrations were assayed in the patient local blood testing laboratories at the following times: at screening, at cycles 2 and 3, just before IDS, at each of the three adjuvant cycles, every 3 months during follow-up, and at progression, if any. The protocol was approved by the ethic committee Comité de Protection des Personnes and the French health authorities Agence Nationale de Sécurité du Médicament (ANSM) in 2012. The study was conducted in accordance with the Declaration of Helsinki ethical guidelines. All patients recruited in the study signed an informed written consent.

The following parameters were collected: pathology subtype; grade; FIGO stage, treatment arm; completeness of cytoreduction score based on postoperative disease residues as judged by the surgeon [complete with no visible disease (CCO score); incomplete with residues less than 2.5 mm (CC1); or with residues from 2.5 mm to 2.5 cm (CC2); or residues more than 2.5 cm (CC3); refs. 17, 18)]; tumor objective response to treatment according to RECIST 1.1 criteria; time interval in between the last platinum-cycle and the subsequent progression date; PFS; and OS. To ensure the accuracy and the reproducibility of the peritoneal carcinomatosis index (PCI) assessment and the completeness of cytoreduction by the surgeons, it was requested that (i) only ovarian cancer expert centers with experienced surgeons respecting good clinical practice would be activated, (ii) laparoscopy procedures would be performed in similar conditions at baseline and after neoadjuvant chemotherapy, (iii) the same surgeon would perform the initial assessment and the IDS, and (iv) PCI and completeness of cytoreduction would be documented by the surgeon in the case report form.

Mathematical modeling of longitudinal CA-125 kinetics and estimation of patient KELIM

At least three available CA-125 values during the first 100 days of neoadjuvant chemotherapy were required, to ensure an accurate assessment of KELIM by the model.

To normalize the distribution of CA-125 concentrations, and to eliminate right-skewness in this distribution, CA-125 levels were log-transformed. The mathematical modeling of early CA-125 kinetics with a nonlinear mixed effect model was described previously (6, 13). Basic details about the semimechanistic kinetic–pharmacodynamic

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(K-PD) model adjustment and qualification are presented in the Supplementary Data (19).

Assessment of KELIM predictive value regarding the likelihood of complete IDS

The predictive value of KELIM regarding the likelihood of complete IDS (no vs. yes) was first assessed using ROC curve analysis. The Youden index was implemented to define the KELIM cutoff able to maximize the prediction of complete IDS likelihood (20). In all subsequent analyses, KELIM was standardized by this cutoff with the following equation: Standardized (std) KELIM = KELIM estimated by the model/cutoff defined by Youden index, as a way of (i) normalizing the patient KELIM outcome by this cutoff, and (ii) providing an easy reading of patient KELIM outcome [e.g., standardized patient KELIM (std KELIM) <1.0 is unfavorable].

The distributions of std KELIM among patients with or without complete surgery were assessed using box plots. The predictive value of std KELIM regarding the likelihood of complete IDS (no vs. yes) was assessed using a multivariate logistic regression model, which also integrated other already known prognostic factors: disease stage (III vs. IV), tumor histology (serous vs. others), tumor grade (well, moderately, or poorly differentiated cells), treatment arm (experimental vs. standard), GCIG CA-125 response criterion (favorable vs. unfavorable), and radiological tumor response according to RECIST criteria at the end of neoadjuvant chemotherapy. The statistical association between std KELIM and tumor response rate was assessed using box plot.

Predictive value of std KELIM, regarding the subsequent platinum-free interval and the risk of further platinum-resistant relapse

The statistical associations between std KELIM and the subsequent platinum-free intervals (PFI) categorized by the traditional cutoffs (≤6 months, 6–12 months, >12 months) were assessed using box plots. Univariate and multivariate logistic regression models were used to investigate the predictive values of std KELIM and the other potential predictors regarding the risk of subsequent platinum-resistant relapse (<6 months vs. ≥6 months). These potential predictive factors included those tested for the likelihood of complete IDS, in addition to the disease-risk groups adjusted from Oza and colleagues (high-risk group: stage IV and incompletely resected stage III diseases vs. low-risk group: all others; ref. 21). A platinum-resistant recurrence score, meant to predict the probability of platinum-resistant relapse, was developed with the covariates found significant in univariate analysis, including the std KELIM and completeness of IDS.

Assessment of std KELIM prognostic and predictive values regarding PFS and OS

The discriminatory predictive ability, along with the prognostic value of std KELIM, regarding PFS and OS was assessed using univariate and multivariate C-index, Kaplan–Meier method, log-rank, and Cox tests. The same prognostic factors as tested above were implemented in the multivariate analyses. The final C-index and Cox survival models were obtained using backward selections.

All survival analyses were implemented with a landmark time point set at 100 days after the start of neoadjuvant chemotherapy or at the surgery date, whichever occurred last. Indeed, CA-125 was modeled from day 0 to 100 and exclusion of the early progressions observed during the first 100 days avoided the biases related to the links between early progressions and CA-125 kinetics or radiological tumor responses (22).

Statistical analysis and computing process

All tests were implemented using a two-sided 0.05 alpha risk. NONMEM 7.4 (ICON Development Solutions) software was used to fit the semimechanistic model to CA-125 kinetic data (23). The XPOSE4 program was used for graphical evaluation of model fits (24). Logistic analyses, survival analyses, and concordance probability (C-index) were obtained in R software version 3.5.2.

Results

Patient selection

Out of 188 patients enrolled in the CHIVA trial, 134 (71%) had at least 3 CA-125 timepoints during the first 100 days and were included in this study (Supplementary Fig. S1). The characteristics of studied patients were not different from those enrolled in the trial (Supplementary Table S1). The median number of CA-125 values per patient was four measurements.

Model qualification

Typical parameter estimates, along with the qualification analyses from the final semimechanistic model, are presented in the Supplementary Materials (Supplementary Text; Supplementary Table S2; Supplementary Figs. S2 and S3).

Predictive value of std KELIM regarding the tumor response rate and the likelihood of complete IDS

A complete IDS was obtained in 48% of studied patients. The discriminative ability of KELIM regarding the likelihood of complete surgery estimated with the ROC curve analysis was as follows: AUC = 0.76 (95% confidence interval (CI), 0.68–0.84). The best cutoff defined with Youden index was 0.07 $days^{-1}$ (Sensitivity = 59%; Specificity = 89%; Supplementary Fig. S4). In all further analyses, std KELIM was calculated as patient KELIM/0.07.

The median std KELIM was significantly higher in patients with complete surgery (1.04 with complete surgery vs. 0.54 with incomplete surgery; $P < 0.01$; Supplementary Fig. S5A). The outcomes of the univariate logistic analyses regarding the likelihood of complete IDS are presented in Supplementary Table S3. The only significant parameter was std KELIM, whether it was considered as a continuous covariate (OR = 16.13; 95% CI, 5.51–53.38) or as a discrete covariate categorized by the threshold at 1.0 (OR = 13.07; 95% CI, 5.25–37.78). In the final multivariate logistic regression model integrating std KELIM as a continuous covariate and the best two other covariates [FIGO stage at diagnosis (stage III vs. IV) and radiological response rate at the end of neoadjuvant chemotherapy], only std KELIM was significant regarding the complete surgery likelihood (Supplementary Tables S3 and S4; Supplementary Fig. S5B). A gradual association was found between increasing std KELIM values and higher radiological tumor response (**Fig. 1A**).

Predictive value of std KELIM regarding the risk of further platinum-resistant relapse

A total of 134 patients were assessable for the subsequent PFI. Box plot and Kruskal–Wallis tests suggested gradual associations between increasing std KELIM and better PFI categorized by the traditional cutoffs (**Fig. 1B**). The results of the univariate logistic regression tests for the probability of subsequent platinum-resistant relapse <6 months are presented in Supplementary Table S5. Std KELIM was a significant factor, whether it was considered as a continuous covariate or a discrete covariate. Both the completeness of IDS and disease-risk group were also significant covariates in univariate analyses. However, only the

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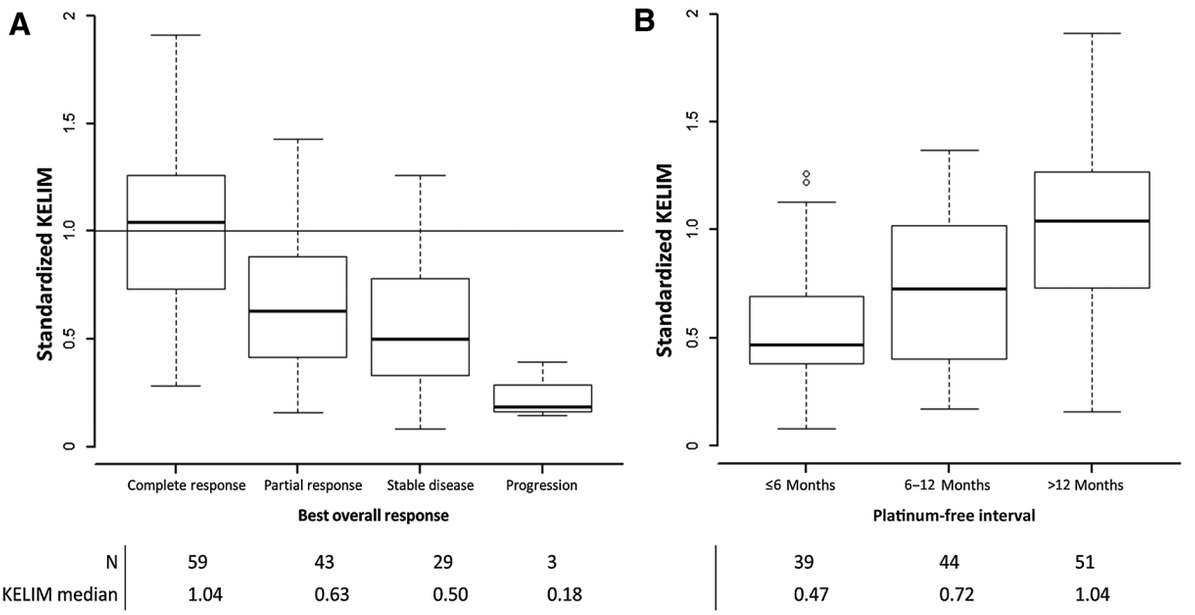

Figure 1.

A, Best overall response according to RECIST V 1.1 versus standardized (std) KELIM. Kruskal–Wallis $P < 0.01$. **B,** Subsequent PFI versus standardized KELIM. Kruskal–Wallis $P < 0.01$.

first one was kept in the multivariate survival model because both parameters were deeply related, and the surgery completeness was more significant. Both std KELIM (continuous covariate, OR = 0.13; 95%, 0.03–0.49) and complete IDS (no vs. yes, OR = 0.30; 95% CI, 0.11–0.76) were significant in the multivariate logistic regression model (**Table 1**). This model was used to develop a platinum-resistant recurrence score meant to provide the probability of subsequent platinum-resistant relapse based on std KELIM value and IDS completeness (**Fig. 2**).

Prognostic and predictive values of std KELIM regarding PFS and OS

The median follow-up for OS was 31.0 months. A total of 130 and 134 patients were assessable for PFS and OS analyses, respectively. The results of the univariate C-index and log-rank tests for PFS and OS are presented in **Table 2**. Std KELIM was a significant factor, whether it was considered as a continuous covariate or a discrete covariate. The survival curves illustrate the gradual associations between survivals and std KELIM terciles regarding PFS and OS (**Fig. 3**). Both the completeness of IDS and disease-risk group were also significant covariates in univariate analyses. The outcomes of the final multivariate analyses are presented in **Table 3** and demonstrate the predominant prognostic and predictive values of std KELIM.

Explorative analyses were performed to assess the PFS and OS of patients, with or without complete IDS or high or low-risk diseases according to std KELIM terciles. The median PFS and OS of patients with favorable std KELIM terciles were high regardless of IDS completeness or of disease-risk groups contrarily to those patients with less favorable KELIM (Supplementary Figs. S6–S9).

Table 1. Parameters of the final logistic model regarding the risk of platinum-resistant relapse.

	Final logistic model			
***N* = 134**	**Estimate**	**OR**	**95% CI**	***P***
Std KELIM (continuous)	−2.00	0.13	(0.03–0.49)	<0.01
Complete IDS				
Incomplete	REF	REF	REF	REF
Complete	−1.20	0.30	(0.11–0.76)	0.01

Note: Std KELIM = KELIM/0.07.
Abbreviation: REF, reference.

Discussion

In the recent GOG-0213 trial publication, the secondary debulking surgery did not provide any OS advantage when added to chemotherapy in patients with platinum-sensitive relapses, especially in those with PFIs >12 months (25).

This unexpected outcome would suggest that the prognosis of patients with very chemosensitive diseases may be driven more by the chemosensitivity than by surgery. Our previous study in adjuvant setting also established the chemosensitivity, assessed by the modeled CA-125 kinetic parameter KELIM, as a major predictor of the first-line treatment success with respect to disease stages (14).

In this study, based on a prospective phase II trial, the role of KELIM as a reproducible indicator of the tumor-primary chemosensitivity was confirmed through the independent predictive value regarding the tumor response rate, likelihood of complete IDS, PFS, subsequent PFI, and OS. Moreover, the data are consistent with the concept of preponderant prognostic role of the chemosensitivity regarding the success of the first-line treatment. Indeed, the recurrence score suggests that the impact of the completeness of IDS (complete vs. incomplete) on the patient prognosis is major in patients with unfavorable KELIM <1.0, but would be less important in patients with

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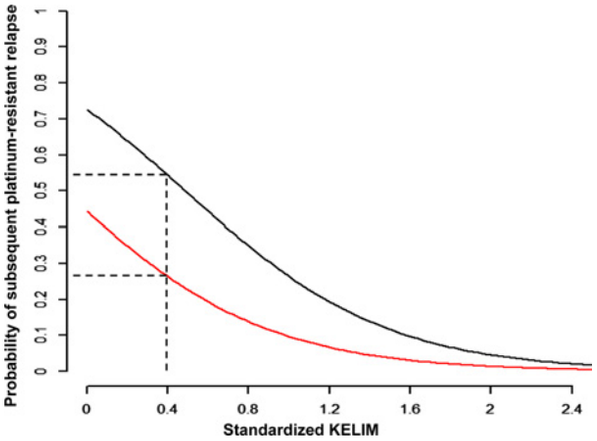

Figure 2.
Platinum-resistant recurrence score. Probability of subsequent platinum-resistant recurrence according to standardized (std) KELIM. Red curve: probability line for patients operated with complete IDS; Black curve: probability line for patients operated with incomplete IDS. Dashed black line: illustration for a patient with std KELIM = 0.4; the risk of platinum-resistant relapse probability of 26% if IDS was complete, or 54% if IDS was incomplete.

favorable std KELIM (e.g., those with std KELIM >1.2). Acknowledging the limitations of subgroup analyses, the median PFS and OS of patients with favorable std KELIM terciles were high regardless of IDS completeness or disease-risk groups as per Oza and colleagues, contrarily to the patients with less favorable KELIM (Supplementary Figs. S6–S9), thereby corroborating these predictions.

Such outcomes may be of high importance for patient management in routine and also for drug development. The platinum-resistant recurrence score may be a helpful tool for go/no-go decision-making regarding IDS attempt at the end of neoadjuvant chemotherapy when the surgeons hesitate to perform the surgery procedure due to the uncertain operability or high risks of sequelaes after an aggressive procedure. In patients with unfavorable std KELIM <1.0, obtaining a complete CC0 IDS is essential. However, the good prognosis of patients with std KELIM >1.2 may not be so highly impacted by the IDS, and postponing/avoiding aggressive surgical procedures could be considered, especially when the operability is still uncertain.

Moreover, we envision that KELIM might help identify a population of poor prognosis patients that would warrant innovative experimental strategies meant to reverse chemoresistance using immunotherapy or cell-cycle checkpoint inhibitors (26, 27). Indeed, strong associations were reported between the tumor response to chemotherapy, disease bulk (stage or completeness of surgery), and PARP inhibitor benefit in

Table 2. Univariate C-index and log-rank tests for PFS and OS.

	PFS (*n* = 130 - Events = 109 - Median = 12.1 (10.9–15.3))				OS (*n* = 134 - Events = 73 - Median = 36.1 (31.0–46.2))			
	n	Survival medians 95% CI (months)	*P*	C-Index	*N*	Survival medians 95% CI (months)	*P*	C-Index
Treatment arm								
Placebo	47	14.4 (10.4–21.3)	0.08	0.53 (0.48–0.58)	47	40.8 (29.2–NR)	0.20	0.52 (0.46–0.58)
Nintedanib	83	11.6 (10.4–15.3)			87	35.3 (29.8–44.6)		
FIGO stage at diagnosis								
Stage IIIc	102	12.1 (11.1–16.8)	0.60	0.51 (0.46–0.55)	105	36.1 (30.1–44.6)	0.50	0.50 (0.45–0.55)
Stage IV	28	11.4 (10.1–20.4)			29	40.8 (21.9–NR)		
Histology types								
Others	13	14.4 (10.4–NR)	0.60	0.51(0.47–0.54)	14	22.5 (16.8–NR)	0.20	0.53 (0.50–0.57)
Serous/papillary	117	12.1 (10.4–15.3)			120	36.4 (32.9–46.2)		
Histologic grade								
Grade 1	3	8.2 (7.2–NR)	0.80	0.51 (0.47–0.54)	4	22.6 (17.9–NR)	0.60	0.53 (0.50–0.57)
Grade 2	9	11.6 (7.1–NR)			9	34.4 (17.1–NR)		
Grade 3	96	12.1 (10.4–17.2)			99	36.4 (29.2–46.2)		
GCIG CA-125 Response								
Unfavorable	38	10.9 (8.5–16.0)	0.07	0.54 (0.50–0.59)	41	30.1 (24.2–NR)	0.20	0.53 (0.48–0.59)
Favorable	92	13.7 (11.1–17.2)			93	36.5 (32.9–NR)		
Complete IDS								
Incomplete	63	9.9 (8.4–12.1)	<0.001	0.61 (0.57–0.66)	67	25.7 (21.9–NR)	0.02	0.61 (0.57–0.66)
Complete	64	17.2 (13.3–21.3)			64	37.7 (35.5–NR)		
Disease risk group[a]								
Low-risk group	51	17.4 (11.9–28.3)	<0.01	0.60 (0.55–0.64)	51	43.7 (36.1–NR)	0.06	0.58 (0.53–0.64)
High-risk group	76	10.4 (8.8–13.0)			80	30.1 (22.2-NR)		
Std KELIM (tercile)								
Unfavorable < 0.50	38	8.4 (7.1–12.1)	<0.001	0.64 (0.58–0.69)	42	19.7 (17.2–29.8)	<0.001	0.66 (0.60–0.73)
Intermediate (0.50–1.00)	49	11.4 (10.4–17.2)			49	44.6 (34.9–NR)		
Favorable > 1.00	43	20.4 (15.1–31.1)			43	40.8 (36.4–NR)		
Radiological response at end of neoadjuvant therapy								
Stable or progression	69	11.9 (10.9–15.1)	0.01	0.54 (0.49–0.60)	72	34.9 (27.7–43.7)	0.03	0.55 (0.49–0.61)
Complete or partial	56	14.1 (10.1–22.3)			56	NR (30.1–NR)		

Note: Std KELIM = KELIM/0.07.
Abbreviations: C-Index, concordance index; NR, not reached.
[a]High-risk group: Stage IV and incompletely resected stage III diseases.

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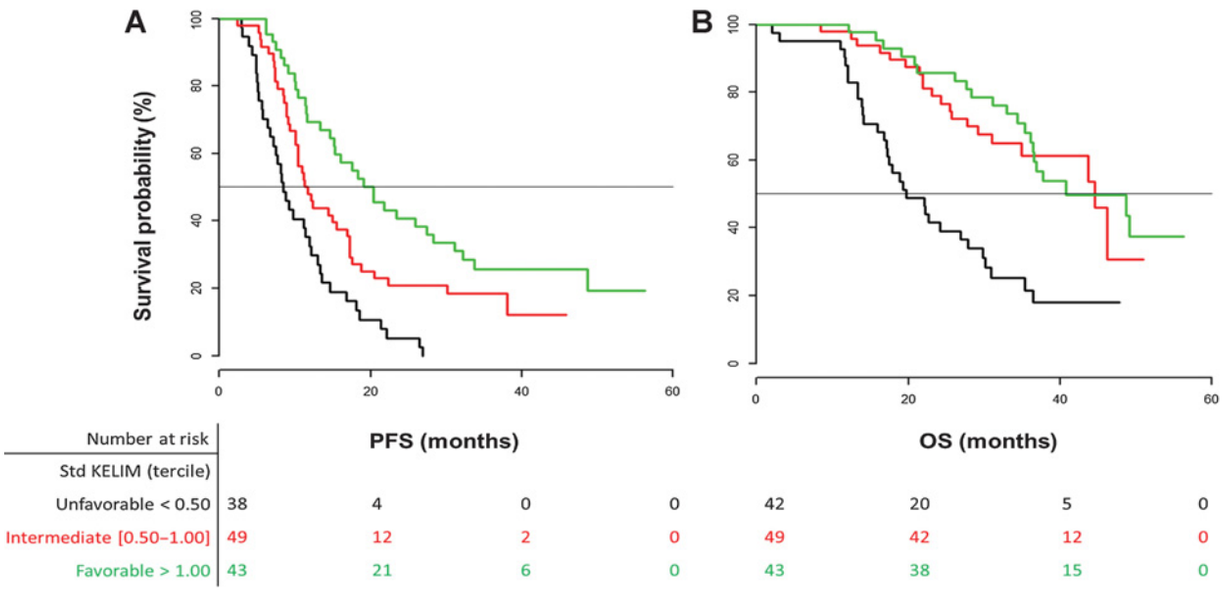

Figure 3.
Kaplan–Meier curves of **A**. PFS, and **B**. OS according to standardized (std) KELIM terciles. The median follow-up for OS was 31.0 months.

first-line setting, as well as in recurrent diseases (28–31). As a consequence, the future broader prescription of PARP inhibitors in first-line settings might increase the survival differences between patients with chemosensitive and chemoresistant diseases, thereby highlighting a new medical need.

To ensure the access of this tool to clinicians at bedside, the model enabling the calculation of std KELIM based on observed patient CA-125 dates and values during the first 100 days of neoadjuvant or adjuvant chemotherapy was implemented online (http://www.biomarker-kinetics.org/CA-125-neo).

This study presents some limitations. First, the data are based on a small number of patients, and the statistical powers of subgroup analyses were reduced. The predictive value of KELIM regarding nintedanib efficacy was not investigated because CHIVA was a negative trial (15). The data on the peritoneal carcinomatosis index and on the completeness of IDS by surgeons could have been influenced by high interoperator variability. However, as explained in the methodology section the trial procedures were designed to minimize this risk and to ensure the maximum accuracy and reproducibility in surgical assessments. These conditions were largely met because 97% of enrolled patients were operated with the same surgical team (trained to CHIVA trial) as the one for the initial assessment and 87% of enrolled patients were operated by the same surgeon. The CA-125 level measurements were performed in patient local blood testing laboratories and were therefore not centralized. As a consequence, multiple assays were probably used. It may have introduced heterogeneity in CA-125 concentration results. However, it should not have impacted KELIM estimations. Indeed, study patients were requested to use the same laboratory during the trial. Furthermore, the model-based approach integrates multiple CA-125 timepoints (median four timepoints/patient in CHIVA trial) to calculate the individual mathematical equations of the longitudinal CA-125 kinetics, thereby minimizing the impact of the assay-related variability. Furthermore, the use of real-life CA-125 data for this study reinforces the extrapolability of the outcomes to clinical routine. Tumor biomarkers that may also exhibit predictive values such as BRCA mutational status or homologous

Table 3. Multivariate C-index and Cox model for PFS and OS.

	PFS				OS			
	N	**HR (95% CI)**	***P***	**C-Index**	**N**	**HR (95% CI)**	***P***	**C-Index**
Std KELIM (tercile)				0.66 (0.60-0.71)				0.66 (0.60–0.73)
Unfavorable < 0.50	37	REF	REF		42	REF	REF	
Intermediate (0.50–1.00)	48	0.50 (0.31–0.79)	<0.01		49	0.31 (0.17–0.55)	<0.001	
Favorable > 1.00	42	0.36 (0.21–0.62)	<0.001		43	0.28 (0.16–0.50)	<0.001	
Complete IDS [a]							Not significant	
Incomplete	63	REF	REF					
Complete	64	0.58 (0.38–0.89)	0.01					

Note: Std KELIM = KELIM/0.07.
Abbreviations: C-Index, concordance index; REF, reference.
[a]Complete IDS: 3 missing data.

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recombination (HR) deficiencies could not be assessed because it was not a standard practice in first-line setting when CHIVA trial was activated in 2012. The relationship between KELIM and tumor cell HR status will be explored because platinum sensitivity and HR status are known to be linked (32). Although the actual radiological tumor overall response rate assessed with RECIST 1.1 criteria after three neoadjuvant cycles of carboplatin–paclitaxel is not so clear in the literature, the tumor response rate (44%) observed here could be considered as low. However, it had no impact of KELIM estimation because the CA-125 KELIM model does not integrate tumor size data. Finally, the median follow-up for OS was limited. Beyond the negative prognostic information already provided by an unfavorable KELIM, further analyses with later data will be necessary to establish the exact relationships between KELIM and OS.

Providing new data about the respective roles of the tumor-primary chemosensitivity during neoadjuvant chemotherapy and the completeness of IDS relative to the success of the first-line treatment, this study corroborates our previous findings about the major predictive value of KELIM in first-line setting. Given the influence of the platinum sensitivity and disease bulk on PARP inhibitor efficacy, this prognostic impact may increase with the future broader use of PARP inhibitors, thereby urging the development of innovative strategy meant to reverse the chemoresistance.

Disclosure of Potential Conflicts of Interest

C. Louvet is an advisory board member/unpaid consultant for MSD, Roche, Halozyme, and Celgene. J. Kurtz is an advisory board member/unpaid consultant for AstraZeneca and Tesaro. F. Joly reports receiving other remuneration from Roche, AstraZeneca and Tesaro/GSK. A. Leary is an employee/paid consultant for AstraZeneca, Tesaro, and Clovis. E. Pujade-Lauraine is an employee/paid consultant for ARCAGY-GINECO, ARCAGY Research, Roche, AstraZeneca, Clovis, Abbvie, Incyte, and Merck. No potential conflicts of interest were disclosed by the other authors.

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