Mathematical modeling of the early modeled CA-125 longitudinal kinetics (KELIM-PARP) as a pragmatic indicator of rucaparib efficacy in patients with recurrent ovarian carcinoma in ARIEL2 & STUDY 10

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Summary

Background PARP inhibitors (PARPi) have revolutionized the management of advanced ovarian carcinoma, and were investigated as forefront treatment in recurrent disease. The objective was to explore if mathematical modeling of the early longitudinal CA-125 kinetics could be used as a pragmatic indicator of the subsequent rucaparib efficacy, like it is for platinum-based chemotherapy.

Methods The datasets of ARIEL2 and Study 10 involving recurrent HGOC patients treated with rucaparib were retrospectively investigated. The same strategy as those successfully developed for platinum chemotherapy, based on CA-125 ELIMination rate constant K (KELIM™), was implemented. Individual values of rucaparib-adjusted KELIM (KELIM-PARP) were estimated based on the longitudinal CA-125 kinetics during the first 100 treatment days, and then scored as favorable (KELIM-PARP $\geq$1.0) or unfavorable (KELIM-PARP <1.0). The prognostic value of KELIM-PARP regarding treatment efficacy (radiological response, and progression-free survival (PFS)) was assessed using univariable/multivariable analyses, with respect to platinum-sensitivity and homologous recombination deficiency (HRD) status.

Findings The data from 476 patients were assessed. The CA-125 longitudinal kinetics during the first 100-treatment days could be accurately assessed using the KELIM-PARP model. In patients with platinum-sensitive diseases, BRCA mutational status KELIM-PARP score and were associated with subsequent complete/partial radiological responses (KELIM-PARP: odds-ratio = 2.81, 95% CI 1.86–4.52), and PFS (KELIM-PARP: hazard-ratio = 0.67, 95% CI 0.50–0.91). The patients with *BRCA*-wild type cancer and favorable KELIM-PARP experienced long PFS with rucaparib regardless of HRD. In platinum-resistant disease patients, KELIM-PARP was associated with subsequent radiological response (odds-ratio = 2.80, 95% CI 1.82–4.72).

Interpretation This proof-of-concept study confirms the early CA-125 longitudinal kinetics during rucaparib in recurrent HGOC patients are assessable by mathematical modeling, to generate individual a KELIM-PARP score associated with the subsequent efficacy. This pragmatic strategy might be useful for selecting the patients for PARPi-based combination regimens, when identifying efficacy biomarker is challenging. Further assessment of this hypothesis is warranted.

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Research in context

Evidence before this study

In patients with recurrent high-grade ovarian carcinoma (HGOC), the standard systemic treatment includes chemotherapy with or without carboplatin, depending on the eligibility of the patients to platinum-based chemotherapy. The development of poly (ADP-ribose)-polymerase (PARP) inhibitors urged the investigation of chemotherapy-free regimens in these patients. Forefront treatment with PARP inhibitor in patients with recurrent platinum-sensitive or -resistant disease was found to be effective in several clinical trials, especially in patients with *BRCA* somatic or germline mutation, leading to the approvals of rucaparib and olaparib in patients previously treated with 2 or 3 more chemotherapy lines.

The combination of PARP inhibitors with other targeted agents, especially immune checkpoint inhibitors and anti-angiogenic drugs, is considered as a promising strategy to increase the number of recurrent HGOC patients who may benefit from PARP inhibitor-based forefront chemotherapy-free treatment beyond those with *BRCA* mutation, as recently reported in MEDIOLA (NCT02734004) and BOLD (NCT04015739) trials. However, identifying biomarkers of efficacy with these triplet regimens is challenging due to the concurrent blockade of three signaling pathways (DNA repair, immune tolerance, and angiogenesis).

In that context, investigating the potential prognostic and predictive value of the early longitudinal CA-125 kinetics during forefront treatment with a PARP inhibitor in patients with recurrent HGOC, as a potential pragmatic indicator of the treatment efficacy, is rationale since this strategy was found to be relevant for platinum-based chemotherapy.

We searched PubMed for articles published between January 1, 1990, and August 31, 2022, using the terms "ovarian cancer" AND "recurrent" AND « PARP inhibitor » (OR « rucaparib » OR « olaparib ») AND « CA-125 » to identify studies, which assessed CA-125 kinetic parameters associated with treatment efficacy with forefront PARP inhibitor. The main kinetic parameter retrieved in the litterature was based on the CA-125 percentage decline adopted by Gynecology Cancer Inter-group (GCIG) in 2004. The other most studied kinetic parameter is the modeled CA-125 ELIMination rate constant K (KELIM™), based on longitudinal CA-125 kinetics during the first 100 chemotherapy days, which was shown to be a reproducible prgamatic indicator of the tumor chemosensivity on the data of more than 13,000 patients treated with platinum-based chemotherapy in first-line or in platinum-sensitive recurrent setting.

Added value of this study

The outcomes of this exploratory analysis of the ARIEL2 and Study 10 trials confirm that the early CA-125 longitudinal kinetics during the first 100 treatment days with rucaparib given as a forefront therapy in recurrent HGOC can be accurately characterized using an adjusted version of the mathematical model of KELIM™ (rucaparib-adjusted KELIM, called KELIM-PARP). Moreover, the early CA-125 longitudinal kinetics exhibit independent prognostic value regarding the benefit from rucaparib in terms of subsequent radiological response and progression-free survival in univariable and multivariable analyses. Beyond patients with *BRCA* mutation, a favorable KELIM-PARP was associated with higher efficacy of rucaparib regardless of homologous recombination deficiency status.

Implications of all the available evidence

This proof-of-concept study suggests that the assessement of the early CA-125 longitudinal kinetics during the first 100 treatment days using mathematic modeling, known to be relevant for platinum-based chemotherapy, also provides an early indicator of the subsequent treatment efficacy in patients receiving a forefront PARP inhibitor-based chemotherapy-free regimen. This pramatic strategy may help identify the patients who will experience maximum benefit from combination treatments on development, and overcome the challenge of finding biomarkers of efficacy when several signaling pathways are targeted simultaneously (such as DNA repair, immune tolerance, and angiogenesis). Assessment of KELIM-PARP prognostic value in BOLD trial (NCT04015739) and KELIM-PARP predictive value in ARIEL4 trial (NCT02855944) is warranted.

Introduction

In patients with recurrent high-grade ovarian carcinoma (HGOC), the standard treatment relies on chemotherapy, without/with carboplatin, depending on the expected platinum-sensitivity of the relapse, and/or the eligibility of the patients to platinum-based chemotherapy.[1–3] The development of poly (ADP-ribose)-polymerase (PARP) inhibitors gave the opportunity to consider chemotherapy-free regimens in patients with platinum-sensitive or -resistant disease relapse. The favorable outcomes of trials investigating PARP inhibitors as forefront single agent therapeutics in patients with recurrent HGOC (ARIEL2 & Study 10 for rucaparib[4–6]; NCT00753545 trial for olaparib)[7] led to the approvals of these drugs in adult patients with HGOC who were previouly treated with ≥2 chemotherapies for rucaparib,[8] and ≥3 chemotherapies for olaparib.[9] Subsequent studies showed that the main biomarkers of efficacy of rucaparib were the platinum-sensitivity of the

relapse (platinum-sensitive recurrence if platinum-free interval (PFI) >6 months, versus platinum-resistant recurrence if PFI <6 months) and the homologous recombination status (BRCA mutation; homologous recombination deficiency (HRD) status, characterized by the level of loss-of-heterozygosity (LOH-high, or LOH-low)).[4,10] On a practical point of view, these HRD assays are technologically complicated and costly to implement.[11–13]

PARP inhibitors are now being investigated as forefront treatment in combination with immunotherapy without/with anti-angiogenic drugs, as a way of enlarging the population of patients, who may benefit from them beyond *BRCA* mutation, as reported in MEDIOLA, or BOLD trials.[14,15] Several assumptions support this strategy: higher neo-antigen load in HRD cancer leading to more effective immune response; STING-dependent innate immune response, by inducing type I interferon and pro-inflammatory cytokine production; glycogen synthase kinase-3 (GSK-3) inactivation and upregulation of PDL1 leading to increased cancer cell apoptosis.[16] The promising preliminary outcomes of these trials imply the development of companion tests able to select the patients deriving the maximum benefit of these regimens. However, the high number of signaling pathways involved by these combinations (DNA repair, immune tolerance, and angiogenesis) will make the identification of several biomarkers of efficacy complicated and expensive. In the future, technologies of proteomics might help monitor cancer cell response, and uncover drug resistance emergence.[17]

Another option is to assess the early CA-125 longitudinal kinetics, as a pragmatic indicator of the treatment efficacy, as it was developed with success for platinum-based chemotherapy.[18] The modeled CA-125 ELIMination rate constant K (KELIM™) is calculated with the mathematical equation driving the CA-125 longitudinal kinetics (≥3 values) during the first 100 days of treatment.[19] KELIM™ can be understood as the rate of CA-125 decline during systemic treatment. The higher KELIM™, the faster the CA-125 elimination with systemic treatment, and the higher the treatment efficacy. The reliability of KELIM™ as a pragmatic independent indicator of tumor platinum-based chemosensitivity has been reproducibly shown on the data of more than 13,000 patients enrolled in 13 randomized trials, the Netherlands Cancer Registry, and the Gynecology Cancer InterGroup (GCIG) meta-analysis database.[20–25] In all studies performed so far, KELIM™ was found to exhibit better prognostic value than the official CA-125 response defined by the GCIG as a 50% reduction in CA-125 levels maintained for at least 28 days, in patients treated for recurrent disease.[20,26–30] More recently, KELIM™ was reported to be a predictor of the benefit from maintenance treatments with PARP inhibitor in VELIA trial, and with bevacizumab in ICON-7 and GOG-0218 trials.[25,31] These favorable outcomes will lead to the adoption of the modeled CA-125 KELIM™ (easily assessable online by any clinician for their patients on https://www.biomarker-kinetics.org/presentation) as a useful numeric medical tool in the future European disease management algorithms.

The same pragmatic approach could be relevant for PARP inhibitor-based chemotherapy-free regimens. We hypothesized that the early longitudinal kinetics of CA-125 observed during treatment with rucaparib, and assessed using KELIM™ adjusted to rucaparib (called KELIM-PARP), may be helpful for identifying the patients who will benefit from rucaparib. The objective of the present post-hoc study of ARIEL2 and Study 10 was to assess the prognostic value of KELIM-PARP regarding the benefit from rucaparib, with respect to the other reported prognostic factors, especially platinum-sensitivity and HRD biomarkers.

Methods

Patients and data retrieved

ARIEL2 (NCT01891344) and Study 10 (NCT01482715) were international multicenter, two-part, phase 2 open-label studies assessing oral rucaparib given at 600 mg twice daily until disease progression, unacceptable toxicity, or death in adult women with platinum-sensitive or platinum-resistant recurrent HGOC. The methodology of these trials was previously reported.[6] Eligibility criteria are detailed in Supplementary Material.

ARIEL2 study was done in Australia, Canada, France, Spain, the UK, and the USA; whilst Study 10 was conducted in the USA, the UK and Canada. ARIEL2 and Study 10 were approved by the institutional review board at each study site and was done in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation (Supplementary Material). Patients provided written informed consent before participation.

CA-125 was measured every 3 (Study 10) or 4 weeks (ARIEL2). The patients analyzed in the present retrospective study should have ≥3 available CA-125 values during the first 100 days of treatment. HRD status was based on the presence of a deleterious *BRCA*1/2 mutation, or loss-of-heterozygosity (LOH)-high (≥16%) in tumor tissues using Foundation Medicine's next-generation sequencing assay.[10] In the current study, platinum-sensitivity was defined as: platinum-refractory disease with PFI <1 month; platinum-resistant disease with PFI 1–6 months; and platinum-sensitive disease with PFI >6 months.

Modeling of CA-125 kinetics

To normalize the distribution of CA-125 concentrations and to eliminate right-skewness in the distribution, CA-125 levels were log-transformed. The mathematical modeling of early CA-125 kinetics with a non-linear mixed-effect model was previously described.[20,21] Basic

details about the semi-mechanistic kinetic-pharmacodynamic (K-PD) model adjustment and qualification are presented in the Supplementary Material.[32]

Consistently with previous analyses of ARIEL2 and Study 10 reporting the platinum-sensitivity of the relapse as a major prognostic factor of efficacy, the different kinetics of CA-125 among patients with platinum-sensitive or –resistant relapse led us to use the same model for both cohorts, and to estimate different population parameters for the baseline CA-125 and for KELIM-PARP. KELIM-PARP was standardized by a cutoff, as a way of providing an easy reading of patient KELIM-PARP outcome, with the following equation: *Standardized (std) KELIM-PARP = KELIM-PARP estimated by the model/cutoff*. Based on our experience for identifying the optimal cutoff for KELIM™ in patients treated with chemotherapy concluding that the best KELIM™ thresholds were similar to the median values,[21–23,33] the cutoffs in each platinum-sensitive and –resistant cohort were selected as the respective median values of KELIM-PARP. As a consequence, std KELIM-PARP was a continuous covariate centered by 1.0. To help the interpretation of KELIM-PARP for prognostic analyses, std KELIM-PARP was dichotomized with a KELIM-PARP score: std KELIM <1.0 was considered as unfavorable, whilst std KELIM ≥1.0 was considered as favorable.

Moreover, the CA-125 response according to the GCIG was assessed in the same patients who had baseline CA-125 > 70 IU/mL, as per Rustin et al. rules.[27,34] A GCIG CA-125 response was confirmed when a decline of CA-125 by minimum 50% was observed and maintained on a 28 day period.

Relationships between std KELIM-PARP and homologous recombination deficiency (HRD) status

The distributions of std KELIM-PARP in patients carrying a *BRCA* mutation, *BRCA* wild-type (WT) LOH-high, *BRCA*-WT LOH-low were assessed using box plots. The statistical significances of differences were assessed using Kruskal–Wallis test.

Relationships between std KELIM-PARP and radiological response to rucaparib

The distributions of std KELIM-PARP among patients experiencing complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) as the best responses according to RECIST 1.1 criteria, observed after the 100th day of treatment, were assessed using box plots and waterfall plots. The ORR was defined as the percentage of patients who experienced CR or PR, as the best responses, while disease control rate (DCR) was defined as the percentage of patients who experienced best response of CR, PR, or SD. The statistical significances of differences were assessed using Wilcoxon rank sum test with continuity correction.

Univariable logistic regressions were used to assess the covariates significantly associated with the probability of CR/PR (compared to SD/PD) among KELIM-PARP (considered as a continuous covariate; or a categorical covariate (favorable, vs. unfavorable)); histology (clear cell, vs. others); HRD status (*BRCA* mutation, vs. *BRCA*-WT LOH-high, vs. *BRCA*-WT LOH-low); and GCIG CA-125 response.[10] Those found significant in univariable analyses were then tested with a multivariable logistic regression model with backward selection procedure. The diagnostic accuracy was assessed using Area Under the ROC curve (ROC AUC). Moreover, C-index analyses were used to assess the prediction improvement related to the incorporation of KELIM-PARP and the other covariates in the logistic regression models. Accuracy of the final logistic model was evaluated using a repeated 10-fold cross-validation method.

Prognostic value of KELIM-PARP score regarding progression-free survival (PFS)

The prognostic value of KELIM-PARP score regarding PFS, categorized as unfavorable or favorable, was assessed using Log-rank test, Kaplan–Meier method, and multivariable hazard-ratio Cox models. The other prognostic factors tested in univariable analyses were the same as those described above. Those found significant in univariable analyses ($P < 0.10$), were included in the multivariable Cox model, and assessed using backward selections.

All survival analyses were implemented with a landmark time point set at 100 days after the start of rucaparib. As already done in other KELIM studies, CA-125 was modeled from day 0–100, 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.[35] Progression-free survival was calculated as the time elapsed between inclusion and disease progression or death, whichever occurred first. Missing data were automatically excluded from analyses.

Statistics and computing process

All tests were implemented using a two-sided 0.05 alpha risk. NONMEM 7.5 (ICON Development Solutions, Ellicott City, MD, USA) software was used to fit the semi-mechanistic model to CA-125 kinetic data.[36] The XPOSE4 program was used for graphical evaluation of model fits.[37] Logistic analyses, cross-validation, survival analyses and concordance probability (C-index) were obtained in R software version 4·1·0. The cross validation was performed under R (4.1.0) software using the function *cv.glm*: Cross-validation for Generalized Linear Models (boot package). Additonal details are presented in Supplementary Material.

Role of funders

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Oncology provided the data of ARIEL2 and Study 10 trials. The statistical analyses, and the manuscript writing, were independently performed by Lyon University team.

Results

Patients

Out of 545 enrolled patients (ARIEL2 n = 491; Study 10, n = 54), the data from 476 patients (87.3%) could be assessed for KELIM-PARP (Table 1; Supplementary Fig. S1). 63% of them had platinum-sensitive disease, whilst 29% had platinum-resistant disease, and 8% had refractory disease. 37% of patients carried a *BRCA* mutation (*BRCA*1, 25%; *BRCA*2, 12%), and 63% of them had *BRCA*-WT tumors. The patients with *BRCA*-WT tumor were classified as LOH-high (126 patients; 26%), LOH-low (152 patients; 32%), and LOH-unknown (24 patients; 5%).

The median follow-up was 6 months (95% CI 5.5–7.1). Taking into account the 100 days landmark analyses, the data from 352 to 353 patients could be assessed for the radiological response and PFS, respectively (Supplementary Fig. S1). In patients with platinum-sensitive recurrent disease, the ORR and DCR were 50% and 96%, respectively. In the platinum-resistant cohort, these numbers were 30% and 90%, respectively. The median PFS was 4.5 months (95% CI 4.1–5.8) for the whole population, including 5.3 months (95% CI 4.1–6.0) in the platinum-sensitive cohort, and 4.1 months (95% CI 4.1–5.5) in the platinum-resistant/refractory cohort.

Modeling of early longitudinal CA-125 kinetics

Median of 4 CA-125 values (range: 3–9) were available in each patient. Strong differences in CA-125 kinetics were observed between patients with platinum-sensitive disease and those with platinum-resistant/refractory disease (Supplementary Fig. S2). The qualification analyses from the final semi-mechanistic models, are presented in Supplementary Fig. S3. The median values of KELIM-PARP in patients with platinum-sensitive disease and platinum-resistant/refractory populations were 0.020 $days^{-1}$ and 0.010 $days^{-1}$, respectively (Wilcoxon rank sum test, $P < 0.001$). These values were used for standardizing (std) KELIM-PARP, and scoring them as unfavorable (<1.0) or favorable (≥1.0) for the rest of the study.

Relationships between std KELIM-PARP and homologous recombination biomarkers

As expected, KELIM-PARP tended to be higher in patients carrying HRD diseases. In the platinum-sensitive cohort, std KELIM-PARP was gradually higher among patients carrying *BRCA* mutations, followed by those

Variable	N = 476
Cancer type	
Epithelial ovarian cancer	386 (81%)
Fallopian tube cancer	43 (9%)
Primary peritoneal cancer	47 (10%)
Histological classification	
Serous	449 (94%)
Others	27 (6%)
Platinum-sensitivity of the recurrent disease	
Sensitive	299 (63%)
Resistant	138 (29%)
Refractory	39 (8%)
BRCA mutational status	
*BRCA*1	117 (25%)
*BRCA*2	57 (12%)
BRCA wild-type	302 (63%)
Homologous recombination deficiency (HRD) status	
*BRCA*1 mutation	117 (25%)
*BRCA*2 mutation	57 (12%)
BRCA, wild type LOH-high	126 (26%)
BRCA, wild type LOH-low	152 (32%)
BRCA, wild type LOH(unknown)	24 (5%)
Best radiological response after 100 days according to RECIST criteria	
Complete response	23 (5%)
Partial response	125 (26%)
Stable disease	141 (30%)
Progressive disease	63 (13%)
Not evaluable	124 (26%)
CA-125 response according to the GCIG	
Unfavorable	175 (37%)
Favorable	107 (22%)
Not evaluable[a]	194 (41%)
Key outcome measures	
Platinum-sensitive cohort (n = 299)	
Best subsequent radiological response	
Complete response	21 (7%)
Partial response	96 (32%)
Stable disease	92 (31%)
Progressive disease	37 (12%)
Not evaluable	53 (18%)
Progression-free survival (PFS) with a 100 day landmark	5.3 [4.1–6.00]
Platinum-resistant cohort (n = 177)	
Best subsequent radiological response	
Complete response	2 (1%)
Partial response	29 (16%)
Stable disease	49 (28%)
Progressive disease	26 (15%)
Not evaluable	71 (40%)
Progression-free survival (PFS) with a 100 day landmark	4.1 [4.0–5.5]

LOH: loss-of-heterozygosity. [a]CA-125 response according to the GCIG: baseline CA-125 not available or baseline <2 N (70 kU/L).

Table 1: **Characteristics of assessed patients.**

with *BRCA*-WT LOH-high tumors, and then by those with *BRCA*-WT LOH-low tumors (median std KELIM-PARP, 1.53, vs. 1.05, vs. 0.68, respectively (Wilcoxon rank sum test, P < 0.001 for all pairwise comparisons) (Supplementary Fig. S4).

In the platinum-resistant/refractory cohort, std KELIM-PARP was higher among patients carrying *BRCA* mutation compared to those with *BRCA*-WT LOH-high tumors (median, 1.08 vs. 0.48, Wilcoxon rank sum test, P < 0.001). However, unlike the above platinum-sensitive population, std KELIM-PARP was not different between patients with *BRCA*-WT diseases associated with LOH-high or LOH-low (median, 0.48 vs. 0.52, P = 0.29, Wilcoxon rank sum test, P = 0.29) (Supplementary Fig. S4).

Prognostic value of std KELIM-PARP regarding subsequent radiological response and PFS

Platinum-sensitive recurrent cohort

A strong correlation was found between std KELIM-PARP and subsequent radiological response assessed using RECIST criteria. Indeed, patients experiencing CR, or PR, had higher std KELIM-PARP than those experiencing SD, or PD (Fig. 1; Supplementary Table S1). The association between std KELIM-PARP and ORR was observed among patients regardless of the HRD status (Supplementary Fig. S5).

The univariable logistic regression models identified three significant prognostic factors associated with the probability of subsequent complete/partial response to rucaparib: HRD status; GCIG CA-125 response; and KELIM-PARP (Supplementary Table S2). The GCIG CA-125 response that was assessable in only 53% of patients was not kept for the multivariable analysis. In the final multivariable logistic analysis, std KELIM-PARP and HRD status were significantly associated with the likelihood of complete/partial response to rucaparib: std KELIM-PARP (odds-ratio (OR), 2.81, 95% CI 1.86–4.52); HRD status (*BRCA* mutation, reference, *BRCA*-WT LOH-high, OR 0.38, 95% CI 0.18–0.77, *BRCA*-WT LOH-low, OR 0.12, 95% CI 0.05–0.27) (Table 2; Supplementary Fig. S8).

The following covariates were associated with PFS in univariable analyses: HRD status; GCIG CA-125 response; and KELIM-PARP score (Supplementary Table S3). The GCIG CA-125 response that was assessable in 54.5% of patients only, was not kept in the multivariable analysis. In the final multivariable Cox hazard-ratio model, both KELIM-PARP score and HRD status were significant and independent prognostic factors of PFS: KELIM-PARP score (favorable vs. unfavorable, HR, 0.67, 95% CI 0.50–0.91); HRD status (*BRCA* mutation (reference) vs. *BRCA*-WT LOH-high,

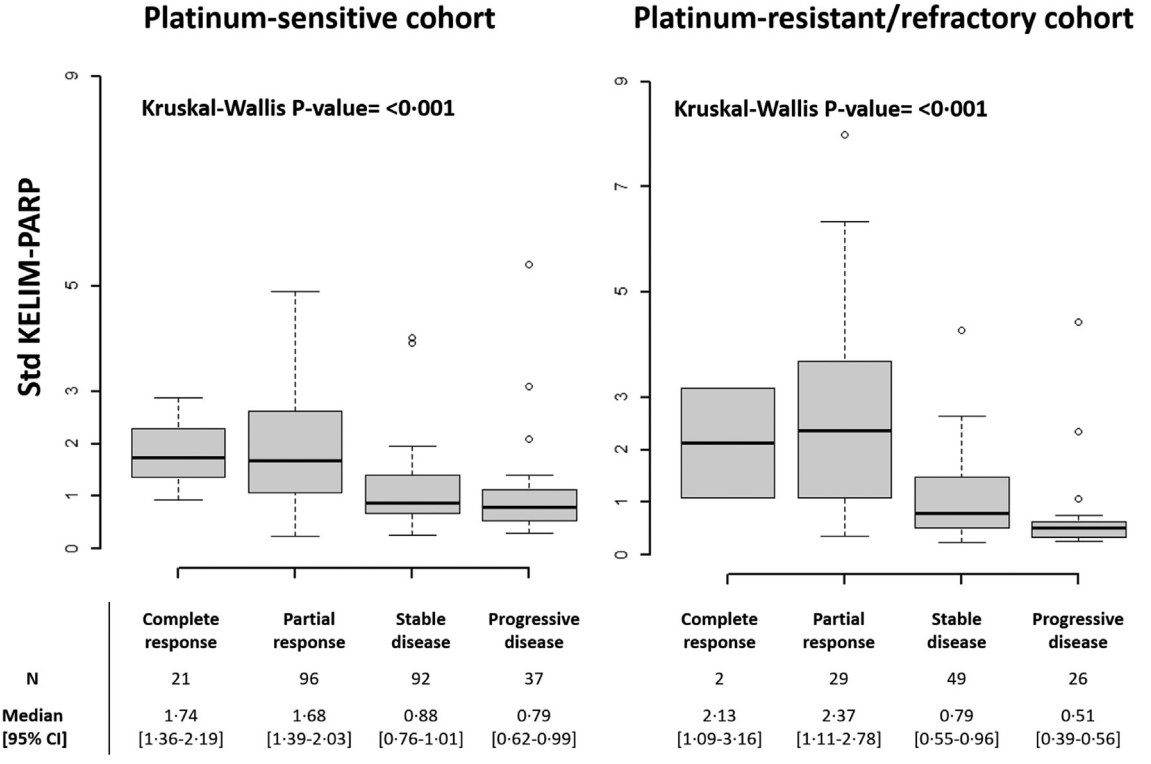

Fig. 1: Best radiological responses as per RECIST criteria according to std KELIM-PARP in the platinum-sensitive and platinum-resistant/refractory cohort (Kruskal–Wallis test).

N = 237 (progressive or stable disease = 124, partial or complete response = 113)							
	n	Estimate	OR	95% CI	P	C-index [95% CI]	Accuracy
Intercept		−0.73	0.48	0.22–1.03	0.063	0.84 [0.78–0.89]	77%
Std KELIM-PARP	237	1.03	2.81	1.86–4.52	<0.001		
Homologous recombination deficiency (HRD) status							
BRCA mutation	105			REF			
BRCA, wild type LOH-high	64	−0.96	0.38	0.18–0.77	0.007		
BRCA, wild type LOH-low	68	−2.11	0.12	0.05–0.27	<0.001		

OR: odds ratio; 95% CI: 95% confidence interval; REF: reference class; Accuracy: repeated 10-fold cross-validation accuracy; LOH: loss-of-heterozygosity.

Table 2: **Final multivariable logistic regression model regarding the probability of complete/partial response in the platinum-sensitive cohort.**

HR, 1.35 (95% 0.97–1.87); *BRCA* mutation (reference) vs. *BRCA*-WT LOH-low, HR, 1.98 (95% 1.39–2.81)) (Table 3).

In line with these data, the Kaplan–Meier PFS curves according to KELIM-PARP score and HRD status suggest that patients with *BRCA*-mutated disease had long PFS regardless of KELIM-PARP score (median PFS 6.7–7.6 months) (Fig. 2). However, among patients with *BRCA*-WT tumor, only those with favorable KELIM-PARP score had long PFS regardless of LOH status (favorable KELIM-PARP score, median PFS 5.5–7.9 months; unfavorable KELIM-PARP score, median PFS 2.2–2.3 months). Of note, the PFS difference between patients with *BRCA*-WT LOH-high or *BRCA*-WT LOH-low tumors was not significant.

Platinum-resistant recurrent cohort

In patients with platinum-resistant/refractory recurrent disease, equivalent relationships between std KELIM-PARP and radiological response was found (Fig. 1, and Supplementary Table S4). The ORR was consistently higher among patients with favorable KELIM-PARP score, regardless of the HRD status (Supplementary Fig. S6).

In univariable logistic regression analysis, three significant prognostic factors were significantly associated with the probability of CR/PR to rucaparib: *BRCA* mutational status (mutated vs. not); GCIG CA-125 response (yes vs. no); and std KELIM-PARP (Supplementary Table S5). In the multivariable logistic analysis, only std KELIM-PARP was significant (OR, 2.80, 95% CI 1.82–4.72) (Supplementary Table S6; Supplementary Fig. S7).

No covariate was significantly associated with PFS in this cohort (Supplementary Fig. S9, Supplementary Table S7).

Discussion

This study is the first analysis of the prognostic value of the early modeled CA-125 kinetics during a forefront treatment with the PARP inhibitor rucaparib. The outcomes show that: *1)* CA-125 kinetics during rucaparib treatment can be successfully described using the same model structure as developed for platinum-based chemotherapy; *2)* the early decline of CA-125 during rucaparib monotherapy is less marked than those observed with chemotherapy, especially in patients with platinum-resistant disease; *3)* there are strong relationships between the early CA-125 kinetics and: *a)* subsequent radiological tumor response to rucaparib in patients with platinum-sensitive or resistant/refractory disease; *b)* PFS in patients with platinum-sensitive relapse. In contrast with patients with platinum-sensitive relapse disease, the strong impact of rucaparib on tumor bulk observed in those with

N = 237[a]	HR	95% CI	P	Analysis of deviance	C-index [95% CI]
KELIM-PARP score					0.63 [0.59–0.66]
Unfavorable score		REF		0.01	
Favorable score	0.67	0.50–0.91	0.009		
Homologous recombination deficiency (HRD) status					
BRCA mutation		REF		<0.01	
BRCA, wild type LOH-high	1.35	0.97–1.87	0.07		
BRCA, wild type LOH-low	1.98	1.39–2.81	<0.001		

HR: hazard-ratio; 95% CI: 95% confidence interval; REF: reference class; Analysis of Deviance Table (Type II tests): wald; LOH: loss-of-heterozygosity. [a]9 Observations deleted due to missing data.

Table 3: **Final multivariable cox model and C-index regarding PFS in the platinum-sensitive recurrent cohort.**

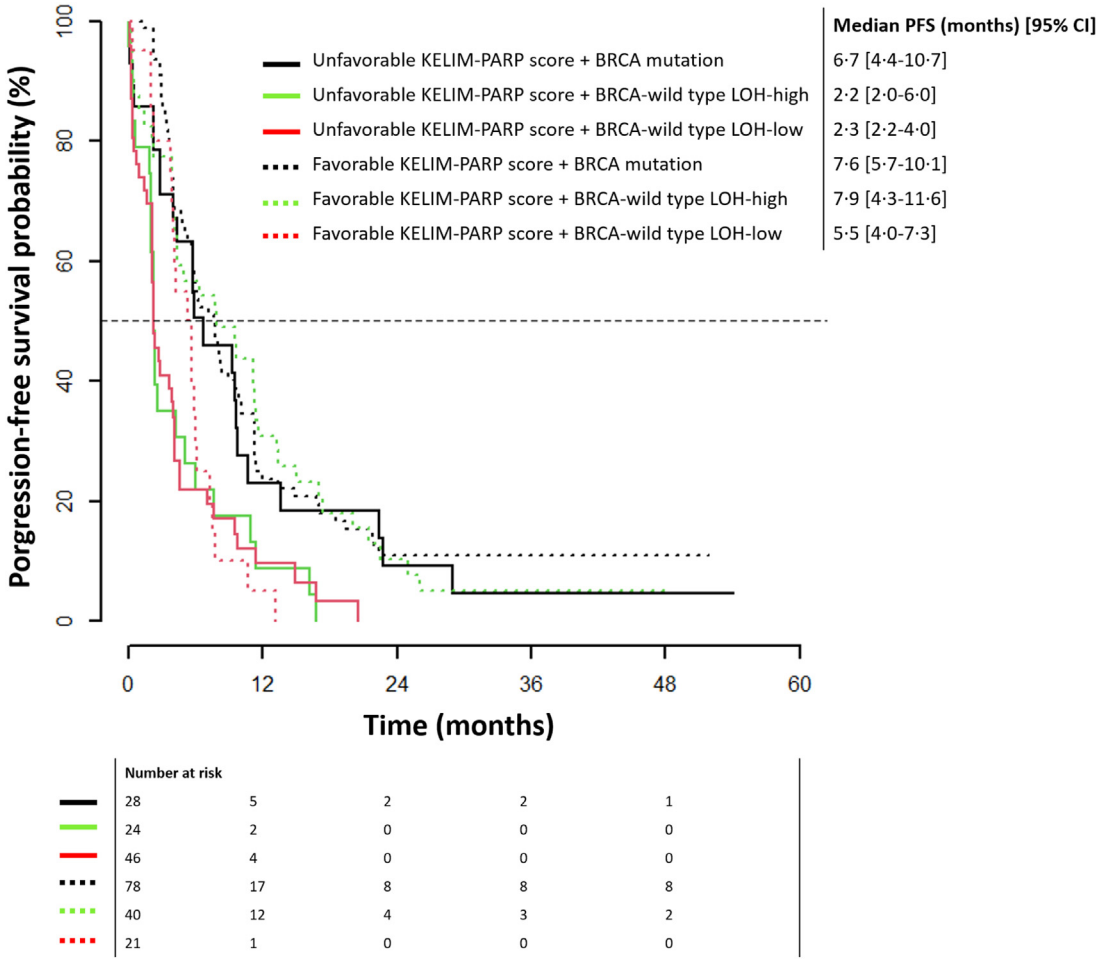

Fig. 2: Kaplan–Meier PFS curves according to KELIM-PARP score and HRD status (*BRCA* mutation; *BRCA* wild-type LOH-high; *BRCA* wild-type LOH-low) in the platinum-sensitive cohort.

platinum-resistant relapse with a favorable std KELIM-PARP (ORR, 47%–63%, Supplementary Fig. S5) did not translate into a PFS advantage, probably as a result of the poor prognosis of these patients.

An important outcome of the present study is the independent and complementary prognostic values of both the BRCA mutational status and CA-125 KELIM-PARP in terms of PFS in patients with platinum-sensitive recurrent HGOC. This exploratory analysis confirms our assumption that the early CA-125 longitudinal kinetics could be a potential pragmatic indicator of the subsequent efficacy to expect with rucaparib, and other PARP inhibitors, when used as forefront therapeutics in patients with recurrent HGOC. Based on these outcomes, the assessment of the predictive value of KELIM-PARP regarding rucaparib activity is planned in the randomized clinical trial ARIEL4 (NCT02855944), which assessed the superiority of rucaparib over standard-of-care chemotherapy in patients with recurrent HGOC and BRCA mutation.[38,39]

The same success story as those seen with KELIM™ in patients treated with platinum-based chemotherapy can be expected. KELIM™ is being prospectively investigated as prognostic factor in on-going large phase III trials (such as NIRVANA trial, assessing niraparib ± bevacizumab in first-line setting (NCT04734665)), and will soon be recognized as a useful numeric tool by the European guidelines. Patient KELIM™ score calculation is easily available online to clinicians (https://www.biomarker-kinetics.org/presentation).

More largely, this positive exploratory study may have important consequences for the development of the future chemotherapy-free combination regimens based on PARP inhibitors being investigated in patients with recurrent HGOC. Indeed, it shows that the early CA-125 longitudinal kinetics assessed using mathematical modeling could provide relevant information about the benefit to expect in patients, and overcome the current challenge for finding efficacy biomarkers in the context of multiple signaling pathways blockade. The

assessment of the prognostic value of KELIM-PARP is planned in recurrent HGOC patients treated with olaparib + durvalumab + bevacizumab in BOLD trial (NCT04015739), as an external validation dataset.

The results presented here should be analyzed with caution due to several limitations. This is the post-hoc retrospective pooled analysis of two single-arm open-label phase II trials. Moreover, KELIM-PARP was assessable in only 87% of study patients, because there were not enough available CA-125 values for the other ones. Of note, this percentage remains higher than those of patients assessable for the GCIG CA-125 response (~59%), due to the complexity of the Rustin et al. algorithm. The reduced number of patients evaluable for the GCIG CA-125 response led us to eliminate it for multivariable tests in order to maintain the statistical power. Nevertheless, the final multivariable analysis with all the covariates found to be significant in univariable tests showed that this criterion was not significant after backward elimination procedure. Beyond HRD status, other biomarkers might have been relevant for prognostic analyses, such as the mismatch repair status.[40] However, these covariates were not available in the datasets. Another limiting point relates to the 100 day time-window required for KELIM-PARP assessment, which obliges to apply a landmark analysis at 100 days, and excludes all patients who progressed within this time window, representing 26% of patients for PFS analysis. On the other hand, the objective of KELIM-PARP calculation is to identify patients who would experience long PFS while treated with rucaparib. If KELIM-PARP predictive value was confirmed, patient KELIM-PARP could be easily calculated online. In the future, technologies of proteomics may help.

In summary, this proof-of-concept study suggests that the early longitudinal kinetics of CA-125 during the first 100 days of treatment with rucaparib, are associated with subsequent radiological response and PFS in patients with recurrent ovarian cancer. The mathematical modeling-based approach, found to be useful for characterizing the tumor primary chemosensitivity in patients treated with platinum-based chemotherapy, may also be relevant for patients treated with PARP inhibitor-based chemotherapy-free regimens in recurrent setting. The modeled CA-125 kinetic parameter KELIM-PARP might represent a pragmatic numeric tool, complementary to platinum-sensitivity and HRD status, for identifying the patients who will derive the maximum benefit from forefront combination regimens based on PARP inhibitor, when the identification of efficacy biomarker is challenging. Additional studies on clinical trials and meta-analyses are warranted to confirm this assumption.

Contributors

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Data sharing statement

Clovis Oncology (Clovis) is committed to ensuring that health care professionals (HCPs), researchers, trial participants, regulators, and other individuals or parties can access clinical trial data. Upon request, Clovis will provide access to clinical trial data from Clovis-sponsored trials in response to unsolicited requests for scientifically or clinically valid research proposals.

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- Is your nonclinical or clinical research question clearly stated?
- Does your question have a valid scientific and/or clinical rationale? Is it achievable?
- Does the researcher have the expertise to answer the research question?
- Does your proposal have a valid statistical analysis plan?
- What do you intend to do with the data? Do you have a plan to present or publish the data at a scientific meeting and/or in a peer-reviewed journal?
- Will the research or data be conducted and disclosed in good faith?

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Declaration of interests

OC: None. Employee of Lyon University Hospital.

BY: Consulting for MSD, Astra-Zeneca, GSK-TESARO, BAYER, Roche-Genentech, ECS Progastrine, Novartis, LEK, Amgen, Clovis Oncology, Merck Serono, BMS, SEAGEN, Myriad.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2023.104477.

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