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Original Research

Survival and modelled cancer antigen-125 ELIMination rate constant K score in ovarian cancer patients in first-line before poly(ADP-ribose) polymerase inhibitor era: A Gynaecologic Cancer Intergroup meta-analysis

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Surrogate end-point

Abstract ***Background:*** In patients with advanced ovarian cancer, the modelled CA-125 ELIMination rate constant K (KELIM) is an early indicator of the tumour intrinsic chemosensitivity. We assessed the prognostic and surrogate values of KELIM with respect to those of surgery outcome (based on post-operative residual lesions) in the Gynaecologic Cancer Intergroup (GCIG) individual patient data meta-analysis MAOV (Meta-Analysis in OVarian cancer) built before the emergence of poly(ADP-ribose) polymerase (PARP) inhibitors.
Methods: The dataset was split into learning and validation cohorts (ratio 1:2). The individual modelled KELIM values were estimated, standardised by the median value, then scored as unfavourable (< 1.0) or favourable (≥1.0). Overall survival (OS) and progression-free survival (PFS) analyses were performed with a two-step meta-analytic approach and surrogacy through a two-level meta-analytic model.
Results: KELIM was assessed in 5884 patients from eight first-line trials (learning, 1962; validation, 3922). A favourable KELIM score was significantly associated with longer OS (validation set, median, 78.8 versus 28.4 months, hazard-ratios [HR] 0.46, 95% confidence interval [CI], 0.41–0.50, C-index 0.68), and longer PFS (validation set, median 30.5 versus 9.8 months, HR 0.49, 95% CI, 0.45–0.54, C-index 0.68), as were International Federation of Gynaecology and Obstetrics (FIGO) stage and debulking surgery outcome. Three prognostic groups were identified based on the surgery outcome and KELIM score, with large differences in OS (105.1, ~45.0, and 22.1 months) and PFS (58.1, ~15.0, and 8.0 months). Surrogacy for OS and for PFS was not established.
Conclusion: KELIM is an independent prognostic biomarker for survival, complementary to surgery outcome, representing a new determinant of first-line treatment success.
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1. Introduction

The standard management of high-grade ovarian carcinoma (HGOC) relies on a medical-and-surgical approach, combining platinum-based chemotherapy with or without debulking surgery, and maintenance treatment with targeted drugs [1–3]. The prognostic values of the International Federation of Gynaecology and Obstetrics (FIGO) disease stage and the surgery completeness are well established. However, there is a need for indicators of the tumour chemosensitivity for understanding the prognostic impact of this parameter relative to the success of the first-line treatment, as acknowledged by the European Society of Medical Oncology-European Society of Gynaecological Oncology (ESMO-ESGO) conference consensus [1,2].

In 2004, the Gynaecologic Cancer Intergroup (GCIG) adopted a response criterion based on the cancer antigen-125 (CA-125) percentage decline. However, it has been validated in the recurrent setting only [4]. The early modelled CA-125 ELIMination rate constant K (KELIM), calculated with the CA-125 longitudinal kinetics during the first 100 days of neo-adjuvant or adjuvant chemotherapy, was developed to be a reflection of the early serum tumour marker elimination rate during systemic treatment [1,5]. In many studies, KELIM was identified as a reliable indicator of the tumour intrinsic chemosensitivity [1]. Indeed it was found to be associated with: (1) the radiological response during neo-adjuvant chemotherapy; (2) the likelihood of complete resection at interval surgery; (3) the probability of subsequent platinum-resistant relapse; (4) the patient progression-free survival (PFS) and overall survival (OS); along with (5) the probability of long disease-free > 5 years after first-line treatment, in seven independent trial datasets and one national registry, involving altogether more than 7000 patients [6–11]. KELIM represents the rate of CA-125 decline during systemic treatment, like a kind of CA-125 'clearance', related to the tumour chemosensitivity. The higher KELIM, the faster the CA-125 elimination, the higher the chemosensitivity.

A meta-analysis study was warranted to assess the magnitude of the prognostic value of KELIM regarding survival and the potential surrogate value of KELIM [12]. When validated as a surrogate of OS, an intermediate end-

point enables an early assessment of the therapeutic anti-tumour activity, while avoiding confounding effects related to post-progression therapies [13]. The GCIG meta-analysis group built a set of individual-patient data from randomised clinical trials (RCT) conducted before the PARP (poly(ADP-ribose) polymerase)-inhibitor era (MAOV, Meta-Analysis in OVarian cancer, CRD42017068135) [14].

The aims of the present study performed with MAOV were to assess: (1) the magnitude of the prognostic value of KELIM for OS and PFS; (2) the impact of tumour chemosensitivity with respect to debulking surgery optimality relative to the success of the medical-and-surgical treatment; (3) the potential surrogate value of KELIM regarding survival.

2. Materials and methods

This meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix). The selection of trials included in MAOV was previously reported [14]. Eligible studies included RCT testing systemic treatments in first-line setting HGOC. Those that collected individual serum CA-125 measurements (minimum three available during the first 100 days of treatment) were included. A data-splitting strategy stratified on trials, randomly assigned patients into learning and validating datasets with a 1:2 ratio considering the large dataset size [15]. Disease stage according to FIGO criteria (stages I-II, III or IV); debulking surgery outcome (optimal surgery when post-operative residual lesions < 1 cm, sub-optimal when ≥1 cm).

2.1. Estimation of individual KELIM

Individual CA-125 longitudinal kinetics were characterised using a population-based approach, with the non-linear mixed effect model previously reported (Supplementary Material) [6,10].

The learning dataset was used to estimate the model parameters, with trial stratification for KELIM and baseline CA-125 level estimations, to account for multiple studies. The population parameters found in the learning dataset were used to calculate individual KELIM values in the validation set as empirical Bayesian estimates [16].

2.2. KELIM prognostic value

To assess the respective prognostic values of KELIM and of surgery outcome regarding OS and PFS, univariate survival analyses were performed using Kaplan–Meier curves and Log-rank tests. Cox proportional hazard models enabled adjustments for covariates, with a two-stage meta-analytic approach [17]. The I^2 statistic was used to assess the between-trial heterogeneity [18]. The discriminatory ability of KELIM regarding OS and PFS was evaluated using Harrell's C-index (Supplementary Material) [19].

To facilitate the clinical interpretation of survival analyses, KELIM was standardised by the median value of the dataset, this cutoff being previously found to be the optimal one [6,8,11], then dichotomised into a KELIM score: std KELIM < 1.0 was considered as unfavourable, whilst std KELIM ≥ 1.0 was considered as favourable. Analyses were implemented with a landmark time point set-up at 100 days after randomisation, excluding patients who died or progressed within this period, in order to avoid potential biases related to early events and CA-125 kinetics [20].

2.3. KELIM surrogate value

A two-stage meta-analytic approach was applied for the assessment of KELIM surrogacy (Supplementary Material) [21]. At the individual-level, the association between KELIM and survival outcomes was measured by Spearman's rank-correlation coefficient, obtained from a bivariate model based on copulas [22]. Trial-level surrogacy was performed through a linear regression between treatment effects on KELIM and on survival outcomes, and quantified by the R^2 coefficient of determination [23]. Treatment effect on KELIM was measured as the mean difference of KELIM natural logarithm between investigational and standard treatment groups, and treatment effect on survival outcomes through hazard-ratios (HR). A prespecified $R^2 \geq 0.80$, with a 95% confidence interval (CI) excluding 0.60, was required to consider the candidate end-point as a reliable surrogate [24].

2.4. Statistical analyses and computing process

NONMEM (NONlinear Mixed Effects Modelling) 7.5 software (ICON Development Solutions, USA) was used to fit CA-125 kinetics to the semi-mechanistic model [25]. Parameters were estimated using a maximum likelihood approach and the Stochastic Approximation of Expectation-Maximisation (SAEM) algorithm [16].

Survival and logistic analyses, concordance probability, meta-analytic and quantile regression analyses were performed in R software version 4.0.5. The Statistical Analysis System (SAS) macro %NORMSURV was implemented to assess KELIM surrogacy (SAS 9.4 University Edition, SAS Institute Inc., USA).

Statistical tests were performed using a two-sided 0.05 alpha-risk, except for Cochran heterogeneity tests, for which a P value < 0.10 was considered statistically significant.

2.5. Ethics approval and consent to participate

The Ethics Committee of Gustave Roussy Cancer Centre, Villejuif, France, approved this study, and the French data protection authority waived the need for informed consent for the use of deidentified data.

3. Results

3.1. Trial and patient selection

Of 11,029 patients from 17 trials included in the MAOV database, 5884 patients enrolled in eight RCT were eligible for KELIM estimation (Supplementary Table S1) [26–33]. Among them, 1962 and 3922 patients were randomly assigned to the training and validation cohorts, respectively (Fig. 1). The surgery outcome based on the post-operative residual disease was available for 1912 (97.5%) and 3802 (97.0%) patients, respectively. In both cohorts, the median KELIM was 0.06 per day (interquartile range 0.04–0.08), ranging from 0.05 to 0.08 per day across trials. As a consequence, std KELIM was calculated as individual KELIM/0.06.

3.2. Model qualification

The typical parameter estimates and qualification analyses from the final semi-mechanistic model are presented in Supplementary Table S2 and Fig. S1. Relative standard errors of KELIM typical values, representing the estimation precision, were low (4.1–11.6%), suggesting limited risks of biased individual estimates of KELIM.

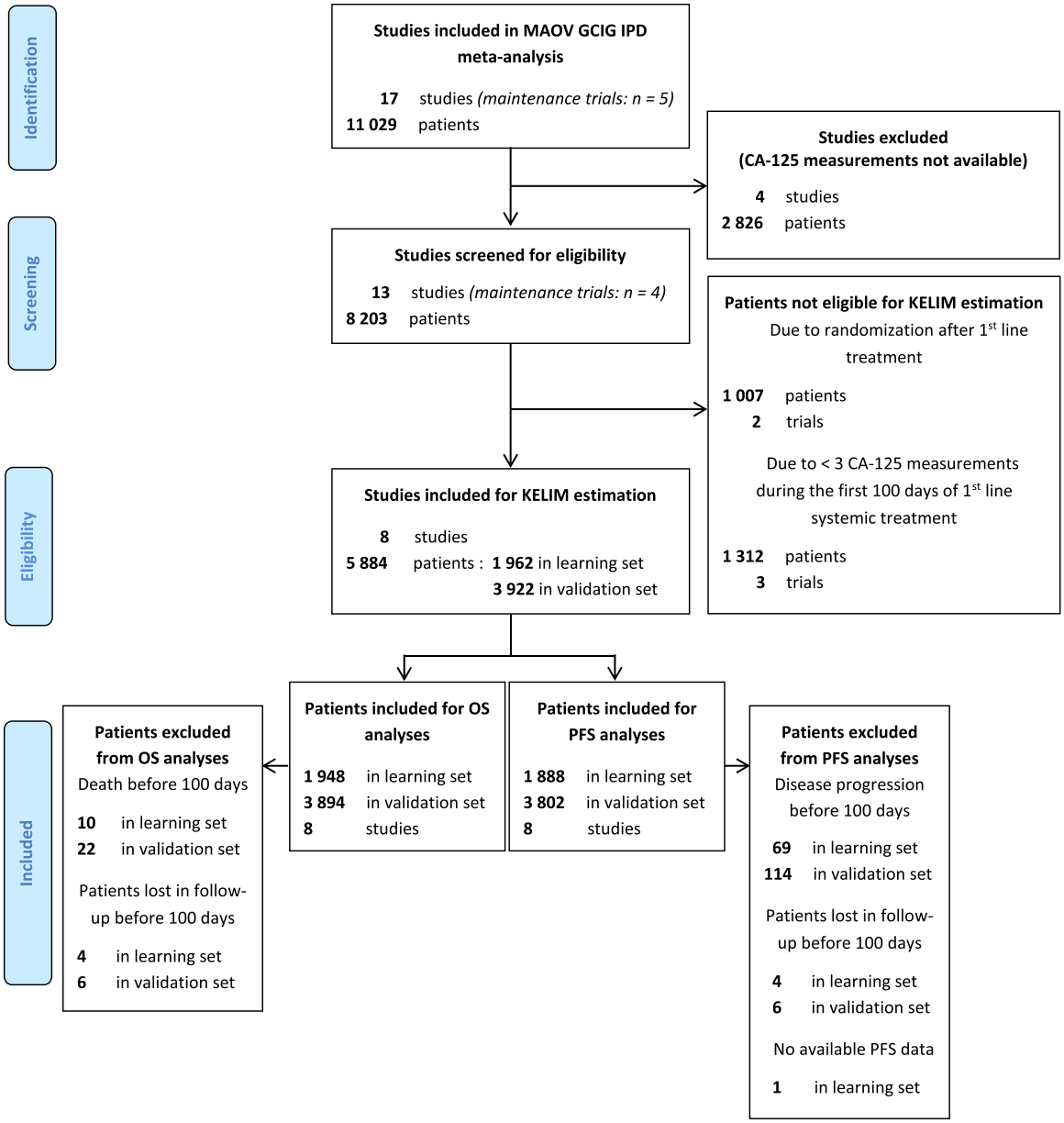

Fig. 1. PRISMA-IPD flow diagram for trial and patient selection (learning and validation sets). GCIG, Gynaecologic Cancer Intergroup; IPD, individual patient data; OS, overall survival; PFS, progression-free survival; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

3.3. Prognostic value

3.3.1. Overall survival

The data from 1948 and 3894 patients were assessable in the learning and validation sets, respectively. The patients with a favourable KELIM score (≥1.0) experienced significantly longer OS than those with an unfavourable score (< 1.0): learning set, median OS, 81.8 months (95% CI, 68.7– non-reached (NR)) versus 31.1 months (95% CI, 29.2–35.7); validation set, median OS, 78.8 months (95% CI, 72.9–89.1) versus 28.4 months (95% CI, 26.7–30.8); log-rank $P < 0.0001$ (Fig. 2A). In univariate OS analyses, the C-index associated with KELIM were 0.60 (95% CI, 0.58–0.62), and 0.62 (95% CI, 0.60–0.64) in the two sets, respectively. In the multivariate models, a favourable KELIM score was independently associated with a better OS (learning set, HR, 0.51, [95% CI, 0.44–0.59]; validation set, HR, 0.46, [95% CI, 0.41–0.52]), as were the FIGO stage and the surgery outcome (Fig. 2B and Supplementary Table S3).

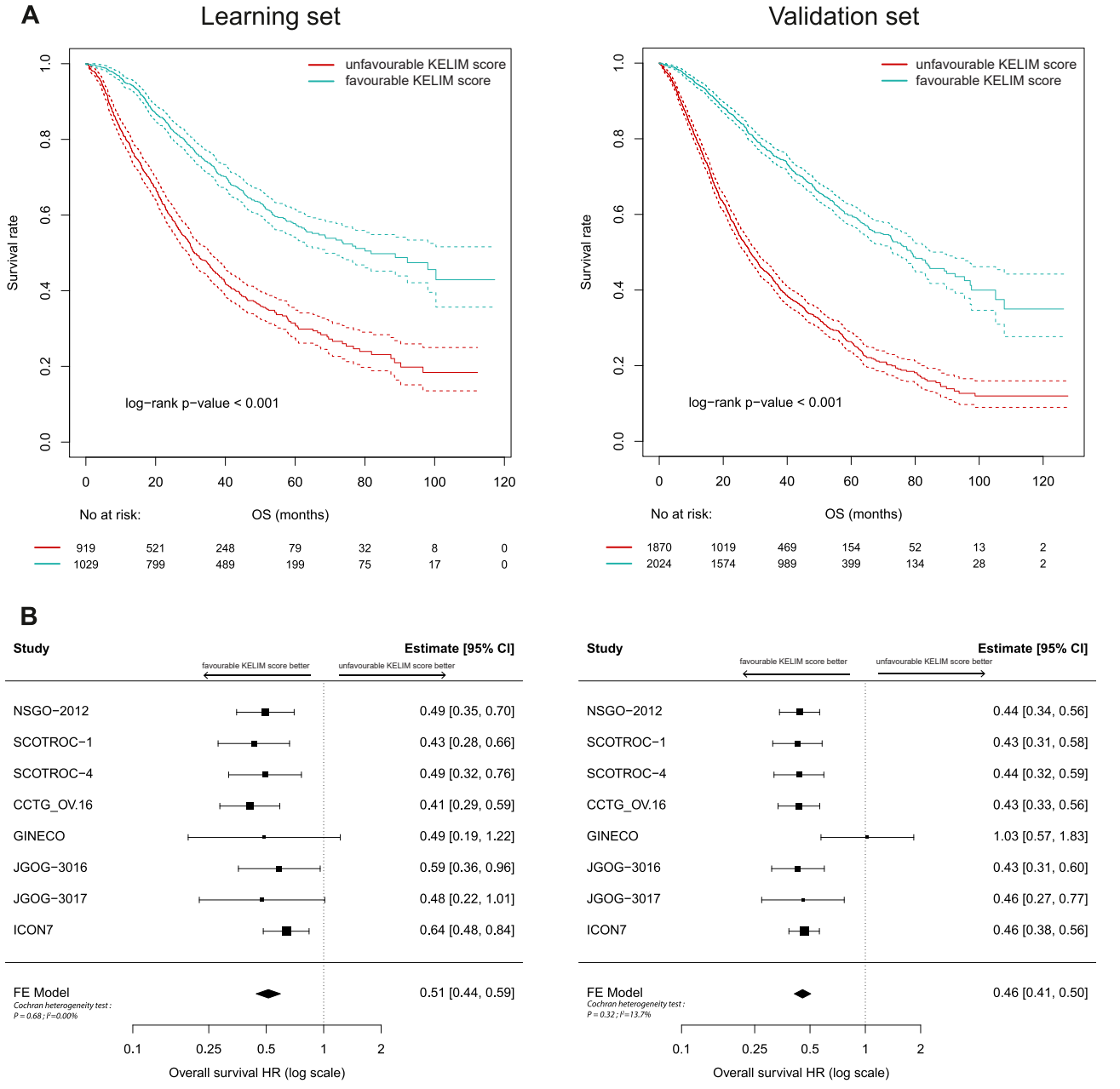

Fig. 2. Analyses of the prognostic value of KELIM score regarding overall survival. (A) Kaplan-Meier overall survival curves according to KELIM score (unfavourable, standardised KELIM < 1.0; favourable, standardised KELIM ≥ 1.0) in learning set (left panel) and in validation set (right panel). Dashed lines indicate the 95% confidence intervals of the Kaplan-Meier estimates; (B) Forest plots of standardised KELIM (binary covariate) prognostic value on overall survival in the learning set (left panel) and in the validation set (right panel). The impact of KELIM was estimated in each trial with a multivariate Cox regression model, then combined to estimate an overall hazard ratio. CI, confidence interval; FE, fixed effect; KELIM, CA-125 ELIMination rate constant K; HR, hazard ratio; OS, overall

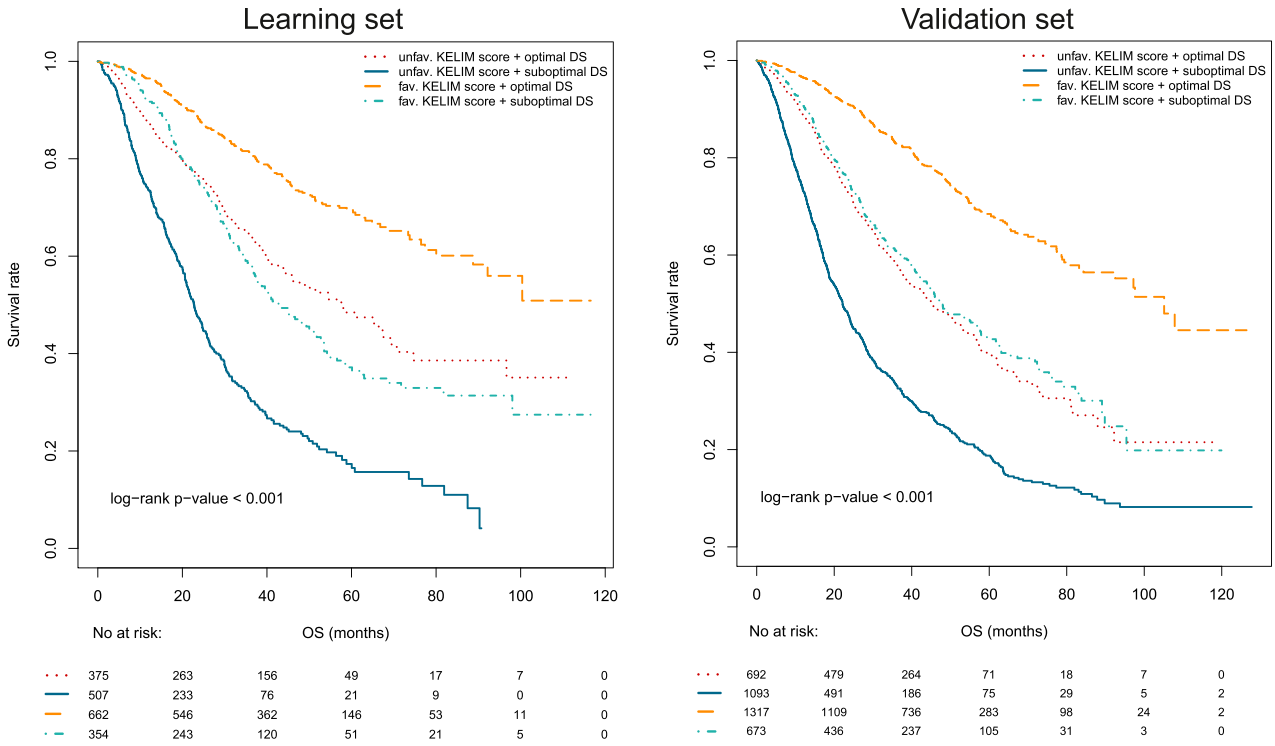

Fig. 3. Kaplan-Meier overall survival curves according to KELIM score and to residual disease after debulking surgery. KELIM score was determined as unfavourable (standardised KELIM < 1.0) or favourable (standardised KELIM ≥ 1.0). The optimality of debulking surgery was assessed with post-operative lesions < or ≥1 cm. Data from the learning set are shown on the left panel, and data from the validation set are shown on the right panel. DS, debulking surgery; fav, favourable; KELIM, CA-125 ELIMination rate constant K; unfav, unfavourable.

The inclusion of the three covariates improved the C-index to 0.67 (95% CI, 0.64–0.70) and to 0.68 (95% CI, 0.65–0.71) in learning and validation sets, respectively (Supplementary Fig. S2). The prognostic value of KELIM was found to be stable through analyses performed at different horizon times, on up to a 5-year follow-up (Supplementary Fig. S3).

When OS curves were adjusted for surgery outcome, three different prognostic populations were delineated (Fig. 3): (1) a good prognosis population, with favourable KELIM score *and* optimal surgery (validation cohort, median OS, 105.1 months; 95% CI, 92.5–NR; (2) an intermediate prognosis population, with *either* favourable KELIM score and sub-optimal surgery (median OS, 48.0 months; 95%, CI 44.0–57.1), or unfavourable KELIM score and optimal surgery (median OS, 45.0 months; 95% CI, 39.7–52.6); and (3) a poor prognosis population, with unfavourable KELIM score *and* sub-optimal surgery (median OS, 22.1 months; 95% CI, 20.7–24.0).

3.3.2. *Progression-free survival*

The data from 1888 and 3802 patients were assessable for PFS analyses in the learning and validation sets, respectively. The outcomes were consistent with those found for OS. Patients with a favourable KELIM score experienced longer PFS: learning set, median PFS, 26.8 months (95% CI, 23.6–32.1) versus 10.3 months (95% CI, 9.6–11.7); validation set, 30.5 months (95% CI 28.0–34.3) versus 9.8 months (95% CI 9.4–10.3); log-rank $P < 0.0001$ (Fig. 4A). In the multivariate Cox analyses, a favourable KELIM score was associated with better PFS (learning set, HR 0.59; 95% CI, 0.52–0.66; validation set, 0.49; 95% CI, 0.45–0.54, Fig. 4B), as were FIGO stage and surgery outcome (Supplementary Table S3). The association of KELIM with FIGO stage and surgery outcome in the multivariate model led to a C-index improvement to 0.66 (95% CI 0.64–0.69), compared to KELIM, FIGO or surgery outcome considered alone (0.59 [95% CI 0.57–0.60], 0.58 [95% CI 0.54–0.61], and 0.60 [95% CI 0.57–0.62] respectively). KELIM prognostic value was stable for up to a 5-year follow-up (Supplementary Fig. S4).

The same three prognostic groups based on the combination of both KELIM score and surgery outcome were found, with large median PFS differences: (1) 58.1 months for the good prognosis population, (2) 15.1 months in the case of favourable KELIM score and suboptimal surgery, 14.9 months with unfavourable KELIM score and optimal surgery and (3) 8.0 months in the poor prognosis population (Fig. 5).

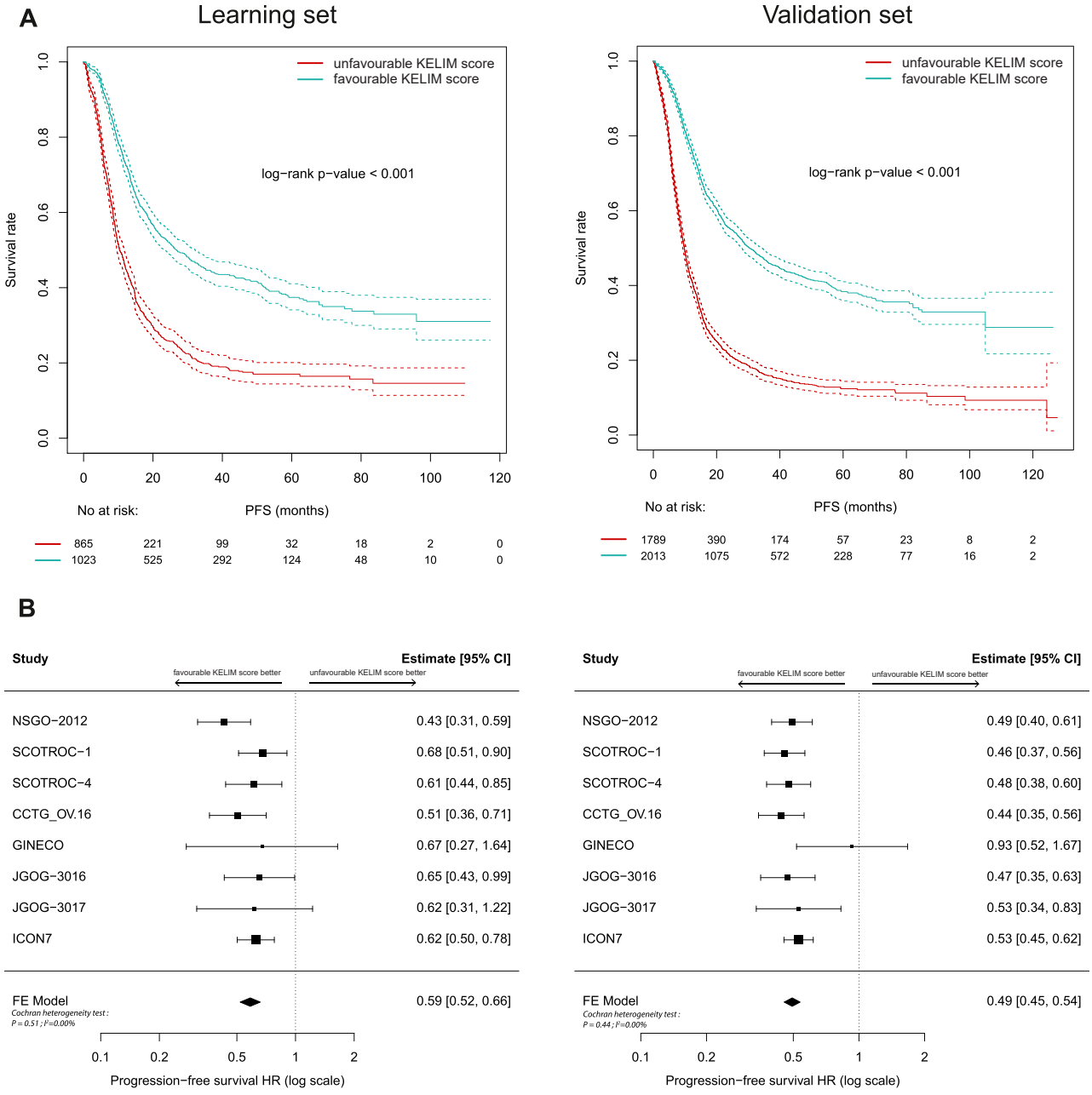

Fig. 4. Analyses of the prognostic value of KELIM score regarding progression-free survival. (A) Kaplan-Meier progression-free survival curves according to KELIM score (unfavourable, standardised KELIM < 1.0; favourable, standardised KELIM ≥ 1.0) in learning set (left panel) and in validation set (right panel). Dashed lines indicate the 95% confidence intervals of the Kaplan-Meier estimates; (B) Forest plots of standardised KELIM (binary covariate) prognostic value on progression-free survival in learning set (left panel) and in validation set (right panel). The impact of KELIM was estimated in each trial with a multivariate Cox regression model, then combined to estimate an overall hazard ratio. CI, confidence interval; FE, fixed effect; KELIM, CA-125 ELIMination rate constant K; HR, hazard ratio; PFS, progression-free survival.

Continuous std KELIM was also independently associated with a higher probability of long disease-free > 5 years (Supplementary Fig. S5).

3.4. Surrogate value

Experimental treatments had no effect on OS and on PFS at the overall population level, or at the trial level (Supplementary Fig. S6). The individual-level association between continuous std KELIM and OS, measured by the Spearman's correlation coefficient, reached 0.37 (95% CI, 0.32–0.42) and 0.43 (95% CI, 0.40–0.47) in the learning and validation sets, respectively, indicating a low correlation. R^2 for trial-level association of treatment effects was 0.59 (95% CI, 0.12–1.00) and 0.19 (95% CI, 0.00–0.72), respectively, failing to demonstrate a strong trial association (Supplementary Fig. S7A).

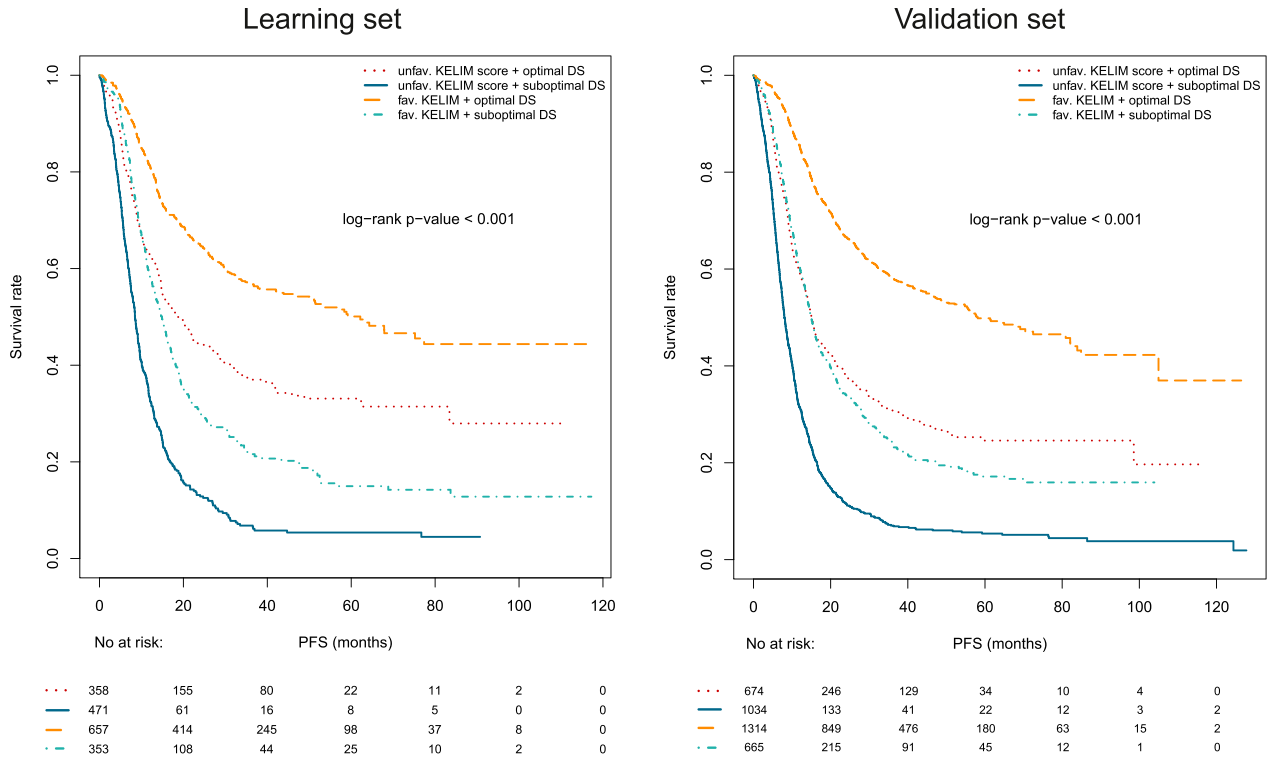

Fig. 5. Kaplan-Meier progression-free survival curves according to KELIM score and to residual disease after debulking surgery. KELIM score was determined as unfavourable (standardised KELIM < 1.0) or favourable (standardised KELIM ≥ 1.0). The optimality of debulking surgery was assessed with post-operative lesions < or ≥1 cm. Data from the learning set are shown on the left panel, and data from the validation set are shown on the right panel. DS, debulking surgery; fav, favourable; KELIM, CA-125 ELIMination rate constant K; unfav, unfavourable.

At patient-level, Spearman's coefficient for PFS was 0.25 (95% CI, 0.20–0.29) and 0.35 (95% CI, 0.32–0.38), respectively, and R^2-trial was 0.18 (95% CI, 0.00–0.70) and 0.46 (95% CI, 0.00–1.00), indicating no significant trial-level association (Supplementary Fig. S7B).

4. Discussion

This confirmatory study, based on an individual-patient-data meta-analysis database, validates the role of KELIM as a reproducible and independent prognostic biomarker of OS and PFS, through a highly robust two-step meta-analytic approach and cross-validation. Patients with a favourable KELIM score consistently experienced higher OS than those with an unfavourable KELIM score, with a hazard-ratio close to 0.5, and highly clinically significant median OS differences (~80 against ~30 months), in line with previous reports [6–11,34].

The official GCIG CA-125 response criterion, defined as a reduction of at least 50% in CA-125 levels on a 28-day period, [4] is considered applicable to patients with recurrent ovarian cancers only. Therefore, it was not directly compared to KELIM in the present study. Nevertheless, we could calculate it for 60% of women only, and the univariate C-index was 0.56 for OS (95% CI, 0.54–0.58), and 0.55 for PFS (95% CI, 0.53–0.57) (validation sets).

A clinically relevant outcome relates to the combination of KELIM (representing the biological debulking) and surgery outcome, delineating three distinct prognostic groups: (1) a good prognosis population with favourable KELIM and optimal surgery (median OS ~105 months); (2) an intermediate prognosis in patients with either unfavourable KELIM or sub-optimal surgery (median OS ~45 months); (3) a poor prognosis in patients with unfavourable KELIM and sub-optimal surgery (median OS ~22 months). Equivalent outcomes with the same prognostic groups were found in an exploratory analysis of ICON-8 trial [9], thereby highlighting the major independent prognostic values of both components of the medical-and-surgical treatment backbone. The poorest prognosis group should be prioritised for therapeutic adjustments and innovative drug development, meant to improve the tumour chemosensitivity.

A recent study from ICON-8 trial showed that the weekly dose-dense regimen was associated with improved PFS and OS compared to the standard three-weekly regimen in patients belonging to this poor prognostic group [9]. The addition of bevacizumab may also be of interest in this situation. Indeed, an external validation study on Gynecologic Oncology Group (GOG)-0218 trial data [35] confirmed the hypotheses raised in ICON-7 trial [7] that bevacizumab combination to the standard first-line chemotherapy was

associated with PFS and OS gains in this high-risk population. The trials assessing rare subtypes of high-grade ovarian cancers (e.g. ovarian cancer clear cell carcinoma) were not excluded from the present analyses, because we had data from previous studies and the present meta-analysis dataset suggesting that the KELIM prognostic value would not be impacted by these histology types (data not shown) [6,8,9].

The present study has some limitations. The optimality of debulking surgery was based on post-operative residual lesions < or ≥1 cm, as the standard surgery criterion when the trials were conducted, although the completeness of surgery with non-visible microscopic residual is now the recommended quality criterion [2]. More recent studies demonstrated that KELIM independent prognostic value was similar when the completeness of surgery was assessed [8,9]. Furthermore, individual data about tumour histology and grade were not assessable, due to the absence of central pathological review and changes of pathological definitions over time. *BRCA* mutational status or homologous recombination deficiencies were not available, since they were not determined in standard practice at that time. However, the prognostic value of KELIM was found to be independent of these covariates in other studies [8,9,11].

Two hypotheses can be considered for the lack of surrogate value of KELIM despite a strong prognostic value. Either KELIM is actually a surrogate marker, but it could not be revealed here due to the lack of treatment effect in the available trials, as already reported with the same database [14], or KELIM would mainly exhibit a prognostic value regarding patient survival. Of note, such a prognostic value does not exclude a predictive value regarding the efficacy of specific drugs whose mechanisms of efficacy are related to chemosensitivity, as it is the case for bevacizumab or PARP inhibitors [34,35]. Analyses are currently being conducted to assess KELIM prognostic and predictive values in PARP-inhibitor trials. A promising post-hoc analysis of the VELIA trial suggested that KELIM could be a predictive marker of the benefit from subsequent maintenance treatment with veliparib [34]. Moreover, KELIM is being prospectively assessed in the on-going NIRVANA-1 trial (NCT05183984) and Arbeitsgemeinschaft Gynäkologische Onkologie Ovarian Cancer Study Group (AGO-OVAR) 28/ENGOT (European Network for Gynaecological Oncological Trial groups)-ov57 trial (NCT05009082), comparing niraparib with or without bevacizumab in patients operated with complete primary surgery.

5. Conclusions

The outcomes of the present meta-analysis study confirm those of previous publications, about the strong association of KELIM score with patient prognosis and survival, independently on surgery completeness (all together on the data from more than 12,000 patients enrolled in 14 trials and a national cancer registry, Supplementary Fig. S8) [6–9,11,34]. In particular, a poor prognostic population of ovarian cancer patients characterised with a low chemosensitive disease that could not be operated with complete debulking experiencing short 20-month median OS was identified. Based on these results, the European phase III trial SALVOVAR will evaluate in this poor prognosis population the efficacy of a weekly dose-dense regimen in order to reverse the chemoresistance.

In the meantime, KELIM individual calculation might be integrated in the management algorithms of newly diagnosed advanced ovarian cancer, as a help for interpreting chemotherapy efficacy [1]. Easily calculable with the online calculator and smartphone application (https://www.biomarker-kinetics.org/) with blood CA-125 concentrations measured at each cycle during the first three cycles [36], KELIM is a pragmatic and reproducible tool available for both routine patient management, and drug development.

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Data sharing statement

Researchers with appropriate proposals can request deidentified individual participant data. Data with identifiers are not available. The statistical analysis plan and scripts are available, and can be requested by qualified researchers. Requests should be sent to the corresponding author. The data will be shared after approval of a proposal, with a signed data access agreement.

CRediT authorship contribution statement

Pauline Corbaux: Methodology, Funding acquisition, Formal analysis, Writing – original draft, Visualization, Writing – review and editing. Benoit You: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization, Supervision, Writing – review and editing. Rosalind M. Glasspool: Conceptualization, Funding acquisition, Investigation, Formal analysis, Writing – review and editing. Nozomu Yanaihara: Investigation, Writing – review and editing. Anna V. Tinker: Investigation, Writing – review and editing. Kristina Lindemann: Investigation, Writing –

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Benoit You has received compensation for his advisory role for MSD, AstraZeneca, GSK-TESARO, BAYER, Roche-Genentech, ECS Progastrine, Novartis, LEK, Amgen, Clovis Oncology and Merck Serono. Rosalind Glasspool declares personal financial interests for her advisory role for AstraZeneca, MSD, Clovis Oncology, GSK/Tesaro and Immunogen. She also has received compensation for speaker fees and funding to attend medical conferences from TSK/Tesaro, and consultancy fees from Sotio. Anna Tinker has received honoraria from AstraZeneca and Eisai, a research grant from AstraZeneca and declares her role within the advisory committee and speaker's bureau of GSK. Kristina Lindemann has received compensation for her advisory role for GSK, AstraZeneca and Eisai, and a research grant from GSK. Isabelle Ray-Coquard declares personal fees from AstraZeneca, GSK, Clovis Oncology, Mersana, Deciphera, Eisai, Amgen, BMS, Onxena, Aravive and Roche. Mansoor Raza Mirza has received compensation for his advisory role for AstraZeneca, Biocad, GSK, Karyopharm, Merck, Roche and Zailab. He also received financial interest from Karyopharm as a member of the board of directors and related to stocks and shares. Julien Péron declares compensation from Fab'entech for advisory role; from Eisai as invited speaker, consultant and member of board of directors and from Lilly as invited speaker. He also has received research funding from Roche. Iain McNeish has received compensation for his advisory role for AstraZeneca, Clovis Oncology, GSK, Roche and ScannCell. All remaining authors have declared no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.112966.

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