original reports

Identification of Patients With Ovarian Cancer Experiencing the Highest Benefit From Bevacizumab in the First-Line Setting on the Basis of Their Tumor-Intrinsic Chemosensitivity (KELIM): The GOG-0218 Validation Study

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abstract

PURPOSE In patients with high-grade ovarian cancer, predictors of bevacizumab efficacy in first-line setting are needed. In the ICON-7 trial, a poor tumor intrinsic chemosensitivity (defined by unfavorable modeled cancer antigen-125 [CA-125] ELIMination rate constant K [KELIM] score) was a predictive biomarker. Only the patients with high-risk disease (suboptimally resected stage III, or stage IV) exhibiting unfavorable KELIM score < 1.0 had overall survival (OS) benefit from bevacizumab (median: 29.7 *v* 20.6 months; hazard ratio [HR], 0.78). An external validation study in the GOG-0218 trial was performed.

METHODS In GOG-0218, 1,873 patients were treated with carboplatin-paclitaxel ± concurrent-maintenance bevacizumab/placebo. Patient KELIM values were calculated with CA-125 kinetics during the first 100 chemotherapy days by the Lyon University team. The association between KELIM score (favorable ≥ 1.0, or unfavorable < 1.0) and bevacizumab benefit for progression-free survival (PFS)/OS was independently assessed by NGR-GOG using univariate/multivariate analyses.

RESULTS KELIM was assessable in 1,662 patients with ≥ 3 CA-125 available values. An unfavorable KELIM score was associated with bevacizumab benefit compared with placebo (PFS: HR, 0.70; 95% CI, 0.59 to 0.82; OS: HR, 0.87; 95% CI, 0.73 to 1.03), whereas a favorable KELIM was not (PFS: HR, 0.96; 95% CI, 0.79 to 1.17; OS: HR, 1.11; 95% CI, 0.89 to 1.39). The highest benefit was observed in patients with a high-risk disease exhibiting unfavorable KELIM, for PFS (median: 9.1 *v* 5.6 months; HR, 0.64; 95% CI, 0.53 to 0.78), and for OS (median: 35.1 *v* 29.1 months; HR, 0.79; 95% CI, 0.65 to 0.97).

CONCLUSION This GOG-0218 trial investigation validates ICON-7 findings about the association between poor tumor chemosensitivity and benefit from concurrent-maintenance bevacizumab, suggesting that bevacizumab may mainly be effective in patients with poorly chemosensitive disease. Bevacizumab may be prioritized in patients with a high-risk and poorly chemosensitive disease to improve their PFS/OS (patient KELIM score calculator available on the Biomarker Kinetics website).

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ASSOCIATED CONTENT

Data Sharing Statement
Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

In June 2018, the US Food and Drug Administration approved bevacizumab for patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel, followed by single-agent bevacizumab, after initial surgical resection.[1] This approval followed the outcomes of two parallel phase III trials, GOG-0218 and ICON-7, that demonstrated a benefit in progression-free survival (PFS) with the addition of bevacizumab to standard first-line chemotherapy in patients with an advanced stage III-IV ovarian cancer.[2,3]

Nevertheless, identifying the patients who should be prescribed adjuvant bevacizumab treatment is still a matter of controversy.[4,5] Indeed, the final survival analysis report of GOG-0218 did not find any benefit in overall survival (OS) with bevacizumab in the whole population, but suggested a potential OS gain in patients with a stage IV disease (median OS: 42.8 *v* 32.6 months; hazard ratio [HR], 0.75; 95% CI, 0.59

CONTEXT

Key Objective

To confirm the predictive value of the tumor primary chemosensitivity (assessed by modeled cancer antigen-125 [CA-125] ELIMination rate constant K [KELIM]) regarding the efficacy of bevacizumab previously reported in the ICON-7 trial in patients with advanced ovarian carcinoma.

Knowledge Generated

This external validation analysis with GOG-0218 trial data confirmed that only the patients with poorly chemosensitive disease (unfavorable KELIM score < 1.0) experienced overall survival benefit among those with a high-risk disease. The effect of bevacizumab in patients with a low-risk disease characterized by high chemosensitivity (favorable KELIM score ≥ 1.0) is uncertain.

Relevance *(K.D. Miller)*

The results from the ICON-7 and GOG-0218 trials show that primary tumor chemosensitivity predicts the overall survival benefit of adding bevacizumab; these results informed the design of ongoing validation trials. If confirmed in those ongoing studies, bevacizumab should be prioritized in patients with a high-risk disease characterized by poor chemosensitivity (unfavorable KELIM score) during the first three cycles of neoadjuvant or adjuvant chemotherapy (patient KELIM score easily calculable on CA-125 Biomarker Kinetics in routine).*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

to 0.95).[6] In the ICON-7 trial, an OS benefit was found in the predefined high-risk population (including patients with stage IV, and patients with stage III disease not suitable for surgery or having suboptimal debulking surgery with postoperative residual lesions > 1 cm; median OS: 39.3 *v* 34.5 months; HR, 0.78; 95% CI, 0.63 to 0.97).[7] This discrepancy suggests that, beyond disease stage and completeness of surgery, other covariates should be identified to select the patients likely to benefit from bevacizumab.

Bevacizumab was shown to be active in patients with platinum-resistant recurrent ovarian cancer.[8] Therefore, the impact of the tumor chemosensitivity on the efficacy of bevacizumab has been investigated. Several indicators of the tumor intrinsic chemosensitivity have been reported in the literature.[9] Among them, the modeled cancer antigen-125 (CA-125) ELIMination rate constant K (KELIM; on the basis of the CA-125 longitudinal kinetics observed during the first 100 treatment days and calculated using mathematical modeling) was shown to be a reproducible indicator of the tumor intrinsic chemosensitivity using data from more than 12,000 patients enrolled in 12 randomized trials, the Netherlands Cancer Registry, and the Gynecologic Cancer InterGroup (GCIG) meta-analysis database.[9]

The relationship between KELIM and benefit from bevacizumab in the first-line setting was assessed in a post hoc analysis of the ICON-7 trial. Patients with a highly chemosensitive tumor, defined by a favorable KELIM score (≥ 1.0), had no benefit from bevacizumab, whether they had a low-risk or high-risk disease. However, a benefit in OS was found in patients with a high-risk disease exhibiting an unfavorable KELIM score < 1.0 (median OS: 29.7 *v* 20.6 months; absolute difference, 9.1 months; HR, 0.78; 95% CI, 0.58 to 1.04). An external validation of these data was needed.

The objective of the present project was to perform an external validation study to assess the prognostic and predictive value of KELIM regarding the benefit from bevacizumab in terms of PFS and OS in GOG-0218.

METHODS

Patients and Methods

This study was a retrospective investigation of the GOG-0218 trial (ClinicalTrials.gov identifier: NCT00262847). It was an international, multicenter, double-blind, placebo-controlled, phase III trial, in which 1,873 women with incompletely resected (optimal or suboptimal debulking surgery) stage III to IV disease were randomly assigned 1:1:1—to arm 1: intravenous carboplatin (area under the curve 6) and paclitaxel (175 mg/m^2) once every 3 weeks (1 cycle = 3 weeks) for 6 cycles; arm 2: same chemotherapy regimen plus concurrent bevacizumab (15 mg/kg once every 3 weeks on cycles 2-6); or arm 3: chemotherapy plus concurrent and maintenance bevacizumab (15 mg/kg once every 3 weeks on cycles 2-22). The initial reports, where the other inclusion and exclusion criteria were described, demonstrated a benefit in PFS of about 4 months, but the second analysis did not find any benefit in disease-specific survival or OS.[2,6]

Mathematical Modeling of Longitudinal CA-125 Kinetics and Estimation of Patient Standardized KELIM by the Lyon University Team (France)

The trial design planned that CA-125 values would be locally measured at every cycle. At least three available CA-125 values during the first 100 days of treatment are

required to ensure an accurate assessment of KELIM by the model. The mathematical modeling of the early CA-125 kinetics with a nonlinear mixed-effect model was described previously.[10-12] To normalize the distribution of CA-125 concentrations, and to eliminate right-skewness in this distribution, CA-125 levels were log-transformed. Basic details about the semimechanistic kinetic-pharmacodynamic model adjustment, and qualification, are presented in the Data Supplement (online only).[13]

In this study, individual KELIM values were estimated with the model implemented in the online calculator.[14] Individual KELIM values were computed using empirical Bayes estimates. As assessed in previous studies,[15,16] KELIM was standardized by the prespecified optimized cutoff in an adjuvant setting (cutoff, 0.07/days; prespecified in all studies, including the initial ICON-7 trial), as a way of providing an easy reading of patient KELIM outcome, with the following equation: *Standardized (std) KELIM = KELIM estimated by the model/cutoff*. As a consequence, std KELIM was a continuous covariate centered on 1.0. To help the interpretation of KELIM for prognostic analyses, KELIM was dichotomized into a KELIM score: std KELIM < 1.0 was considered as unfavorable, whereas std KELIM ≥ 1.0 was considered as favorable.

The data set with patient KELIM scores (favorable or unfavorable) was sent to the NRG-GOG team to ensure an independent assessment of KELIM score prognostic and predictive value.

Assessment of the Prognostic and Predictive Values of KELIM Regarding PFS and OS

The main objective was to confirm a benefit in OS with bevacizumab addition in patients with a high-risk disease characterized by an unfavorable KELIM, as suggested in the ICON-7 trial.

The prognostic value of KELIM score for PFS and OS was assessed using univariate and multivariate tests (C-index, Kaplan-Meier method, log-rank, and Cox model). In addition to KELIM score, the other prognostic factors assessed in univariate and multivariate analyses were disease stage and quality of debulking surgery (stage III operated with optimal surgery with postoperative residual lesions ≤ 1 cm; stage III operated with suboptimal surgery with postoperative residual lesions > 1 cm, or stage IV); pathologic subtype (serous + endometrioid, *v* others); histologic grade (grade 1, 2, or 3); ascites (yes or no); and treatment arm (arm 1, arm 2, or arm 3). The final C-index and Cox survival models were obtained using backward selections.

Moreover, the predictive value of KELIM regarding the benefit from arm 3 (bevacizumab-concurrent-maintenance group) compared with arm 1 (placebo group) was assessed in the whole population, and then in the population of patients with a high-risk disease (stage IV, and stage III disease operated with suboptimal debulking surgery) using Kaplan-Meier method and log-rank tests.

Cox hazard-ratio regression analyses and chi-square tests were performed to assess the interactions between KELIM and treatment arms regarding PFS and OS benefit from bevacizumab in the whole population, and in patients with a high-risk disease.

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 first. As CA-125 was modeled from day 0 to 100, the patients who progressed during the first 100 days were excluded to avoid bias related to the links between early progression and CA-125 kinetics, or radiologic tumor responses.[17] The median follow-up was computed using reverse Kaplan-Meier method.

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) software program was used to fit the semimechanistic model to CA-125 kinetic data.[18] XPOSE4 program was used for graphical evaluation of model fits.[19] The Kaplan-Meier analyses (LIFETEST) and Cox regression analyses (PHREG) were performed using SAS 9.4 (Cary, NC).[20]

RESULTS

Patient Characteristics

Out of 1,873 enrolled patients, 1,662 patients with ≥ 3 CA-125 available values during the first 100 days of treatment were assessable for KELIM. Among them, 1,644 and 1,657 patients were assessable for KELIM prognostic/predictive value regarding PFS and OS, respectively (87.8% and 88.4%, respectively; Data Supplement). The characteristics of the 1,657 patients assessable for OS are presented in Table 1. Among them, 575 (34.7%) had stage III disease operated with optimal debulking surgery (postoperative residual lesions ≤ 1 cm); 660 (39.8%) had stage III disease operated with suboptimal debulking surgery (postoperative residual lesions > 1 cm); and 422 patients (25.5%) had stage IV disease.

Model Qualification

Typical parameter estimates, along with the qualification analyses from the final semimechanistic models, are presented in the Data Supplement.

The median value of KELIM was 0.063 days^{-1} (95% CI, 0.061 to 0.065). Std KELIM was not different across treatment arms, similar to what has been observed in previous studies (Data Supplement).

Prognostic Value of the KELIM Score Regarding PFS and OS

The median follow-up was 98.1 months for PFS (95% CI, 94.9 to 102.9), and 100.0 months for OS (95% CI, 97.5 to 103.1). The results of the univariate C-index and log-rank tests for PFS and OS are presented in the Data Supplement.

TABLE 1. Characteristics of the Patients Assessable for Overall Survival (N = 1,657 patients)

Variable	Level	All (N = 1,657), No. (%)[a,b,c]	Placebo-Arm 1 (n = 548), No. (%)	Bevacizumab-Arm 2 (n = 560), No. (%)	Bevacizumab-Arm 3 (n = 549), No. (%)
Treatment arm	Arm 1: control (CT + P → P)	548 (33.1)			
	Arm 2: bevacizumab—concurrent (CT + B → P)	560 (33.8)			
	Arm 3: bevacizumab—concurrent and maintenance (CT + B → B)	549 (33.1)			
Disease stage and debulking status	III (optimal, ≤ 1 cm)	575 (34.7)	194 (35.4)	189 (33.7)	192 (34.9)
	III (suboptimal, > 1 cm)	660 (39.8)	221 (40.3)	227 (40.5)	212 (38.6)
	IV	422 (25.5)	133 (24.3)	144 (25.7)	145 (26.4)
Ascites	No ascites	411 (24.8)	134 (24.5)	135 (24.1)	142 (25.9)
	Ascites	1,203 (72.6)	403 (73.5)	406 (72.5)	394 (71.8)
	Missing	43 (2.6)	11 (2.1)	19 (3.4)	13 (2.4)
Tumor histology	Serous or endometrioid	1,470 (88.7)	499 (91.1)	482 (86.1)	489 (89.1)
	Other histology	187 (11.3)	49 (8.9)	78 (13.9)	60 (10.9)
Histologic grade	Well differentiated (grade 1)	70 (4.2)	31 (5.7)	24 (4.3)	15 (2.7)
	Moderately differentiated (grade 2)	264 (15.9)	93 (16.9)	80 (14.3)	91 (16.6)
	Poorly differentiated (grade 3)	1,201 (72.5)	395 (72.1)	406 (72.5)	400 (72.9)
	Missing	122 (7.4)	29 (5.3)	50 (8.9)	43 (7.8)
KELIM score	KELIM score unfavorable < 1.0	962 (58.1)	330 (60.2)	324 (57.9)	308 (56.1)
	KELIM score favorable ≥ 1.0	695 (41.9)	218 (39.8)	236 (42.1)	241 (43.9)

Abbreviations: →, followed by; B, bevacizumab; CT, chemotherapy; KELIM, ELIMination rate constant K; P, placebo; PFS, progression-free survival.

[a]Patients in at least one of the data sets (PFS_Landmark or OS_Landmark).

[b]Landmark PFS data set: n = 1,644.

[c]Landmark OS data set: N = 1,657.

TABLE 2. Results of the Multivariate Analysis Regarding Overall Survival (N = 1,657 patients)

Covariates	Level	No.	HR	95% CI	*P*	Type III Tests	C-Index (95% CI)
KELIM score	KELIM score unfavorable < 1.0	868	Ref	Ref	Ref	< .001	0.65 (0.61 to 0.70)
	KELIM score favorable ≥ 1.0	629	0.55	0.48 to 0.62	< .001		
Histologic grade	Well differentiated (grade 1)	68	Ref	Ref	Ref	0.023	
	Moderately differentiated (grade 2)	261	1.53	1.10 to 2.12	.012		
	Poorly differentiated (grade 3)	1,168	1.54	1.13 to 2.09	.006		
FIGO stage/debulking status	III (optimal, ≤ 1 cm)	526	Ref	Ref	Ref	0.002	
	III (suboptimal, > 1 cm)	591	1.23	1.08 to 1.41	.003		
	IV	380	1.28	1.10 to 1.49	.002		
Ascites	No ascites	376	Ref	Ref	Ref	< .001	
	Ascites	1,121	1.30	1.14 to 1.49	< .001		

NOTE. Subjects with missing values for any of the independent variables were not used in the estimation of parameters.

Abbreviations: C-Index, concordance index; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; ref, reference; KELIM, ELIMination rate constant K.

In the univariate analyses for both PFS and OS, KELIM score (favorable ≥ 1.0, *v* unfavorable < 1.0) was a significant factor (Data Supplement), as were the disease stage and quality of debulking surgery (stage III operated with optimal surgery, *v* stage III operated with suboptimal surgery), ascites (yes *v* no), and histologic grade (grade 1, 2, or 3), in addition to treatment arm for PFS only (arm 1, arm 2, or arm 3).

In the final multivariate models of both PFS and OS, the following covariates were significant and independent: KELIM score (favorable ≥ 1.0, *v* unfavorable < 1.0; PFS: HR, 0.51; 95% CI, 0.46 to 0.57; OS: HR, 0.55; 95% CI, 0.48 to 0.62), disease stage and quality of debulking surgery, histologic grade, and ascites (Table 2; Data Supplement).

Benefit From Bevacizumab According to KELIM Score and Disease Risk Groups

In the whole assessable population, there was a PFS and OS improvement with bevacizumab-concurrent-maintenance arm 3 compared with the placebo arm 1 for patients with an unfavorable KELIM score (median PFS: 9.8 *v* 6.1 months;

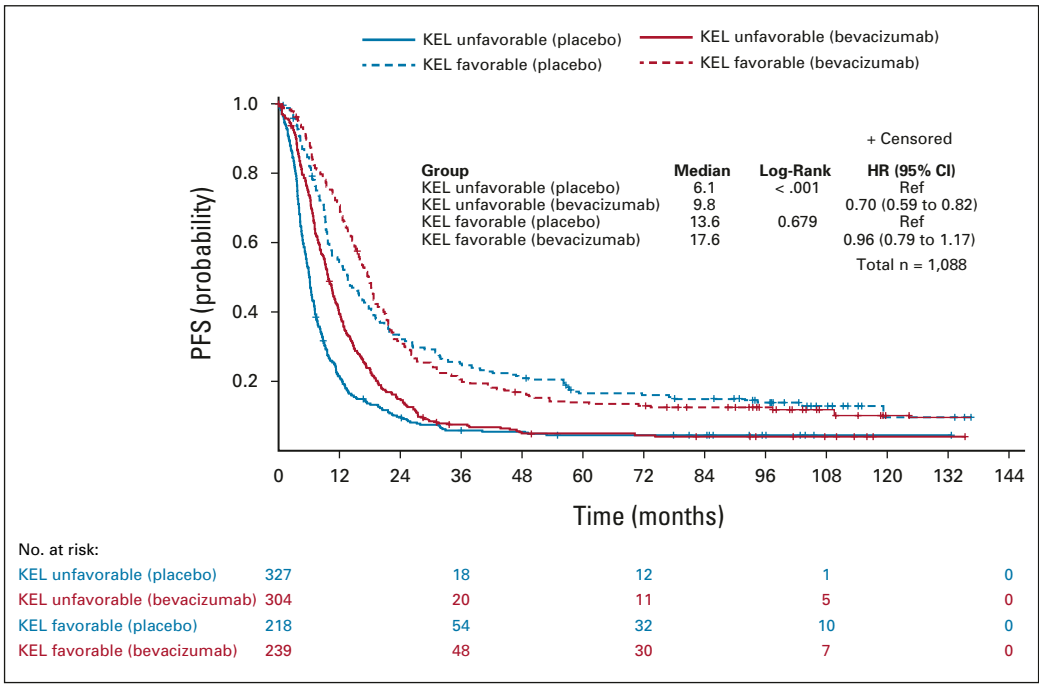

FIG 1. Kaplan-Meier curves of the PFS of patients according to treatment arm (arm 3 with bevacizumab concurrent-maintenance, *v* arm 1 with placebo) in patients with unfavorable or favorable KELIM (KEL) score, in the whole population. HR, hazard ratio; KELIM, ELIMination rate constant K; mPFS, median PFS (months); PFS, progression-free survival; Ref, reference.

HR, 0.70; 95% CI, 0.59 to 0.82; median OS: 36.3 *v* 31.8 months; HR, 0.87; 95% CI, 0.73 to 1.03), which was not observed in patients with a favorable KELIM (median PFS: 17.6 *v* 13.6 months; HR, 0.96; 95% CI, 0.79 to 1.17; median OS; 55.7 *v* 56.7 months; HR, 1.11; 95% CI, 0.89 to 1.39; Figs 1 and 2).

The maximum benefit from bevacizumab-concurrent-maintenance arm 3 compared with the placebo arm 1 was observed in patients with a high-risk disease (stage IV, or stage III operated with suboptimal surgery) exhibiting an unfavorable KELIM score (median PFS: 9.1 *v* 5.6 months; HR, 0.64; 95% CI, 0.53 to 0.78; median OS: 35.1 *v* 29.1 months; HR, 0.79; 95% CI, 0.65 to 0.97). However, as observed on Kaplan-Meier curves (Figs 3 and 4), the patients with a high-risk and highly chemosensitive disease (favorable KELIM score) did not experience benefit from bevacizumab (median PFS: 16.3 *v* 11.7 months; HR, 0.88; 95% CI, 0.68 to 1.13; median OS: 59.6 *v* 49.4 months; HR, 1.05; 95% CI, 0.79 to 1.39).

By contrast, bevacizumab was associated with a potential nonsignificant deleterious effect in terms of OS in patients with a low-risk exhibiting favorable KELIM score (median OS: 51.3 *v* 68.6 months; HR, 1.18; 95% CI, 0.83 to 1.69; Data Supplement).

The interaction tests between KELIM and treatment arms were significant for PFS (in the whole population, $P = .01$; high-risk disease group, $P = .03$) and OS in the whole population ($P = .08$; $P = .04$ by KELIM strates). However, it was not significant for OS in the high-risk disease group ($P = .1$), potentially as the consequence of the limited statistical power related to the smaller number of patients, and the more modest effects of bevacizumab on OS compared with PFS.

DISCUSSION

Many studies meant to find reproducible predictors of bevacizumab activity in patients with ovarian carcinoma treated in first-line setting have been reported in the literature.[4,5] These attempts highlight the need for biomarkers to identify which patients will benefit from this drug.[4,5]

After the publication by Oza et al[7] showing an OS gain in patients with a high-risk cancer (suboptimally resected stage III, and stage IV disease) in the ICON-7 trial, and those by Tewari et al[6] suggesting an OS benefit in patients with a stage IV disease in GOG-0218, the most widely adopted parameter for bevacizumab prescription in routine has been high disease bulk. However, the inconsistency between the two studies suggested additional biomarkers of bevacizumab efficacy were needed for improving the selection of patients.

The AURELIA trial demonstrated that bevacizumab was active in women with platinum-resistant recurrent ovarian cancer,[8] and supported the concept of an association between bevacizumab efficacy and tumor chemosensitivity. The investigation of the predictive value of KELIM in the ICON-7 trial suggested that only the patients with poorly chemosensitive disease, characterized by an unfavorable KELIM score, experienced a survival benefit (9 months) from

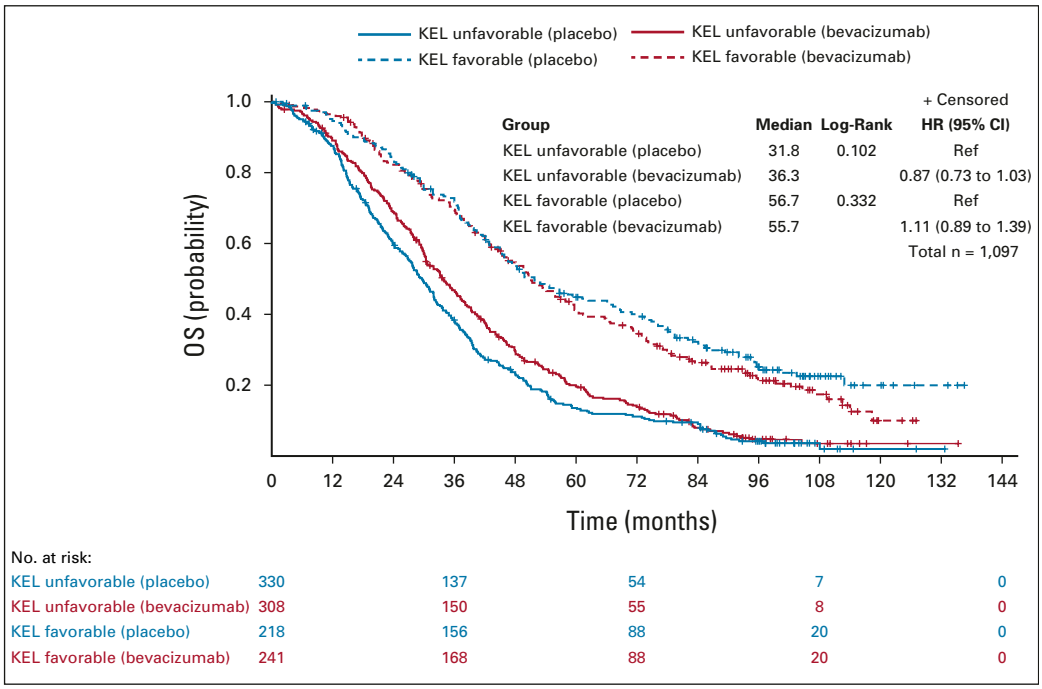

FIG 2. Kaplan-Meier curves of the OS of patients according to treatment arm (arm 3 with bevacizumab concurrent-maintenance, *v* arm 1 with placebo) in patients with unfavorable or favorable KELIM (KEL) score, in the whole population. HR, hazard ratio; KELIM, ELIMination rate constant K; mPFS, median PFS (months); PFS, progression-free survival; Ref, reference.

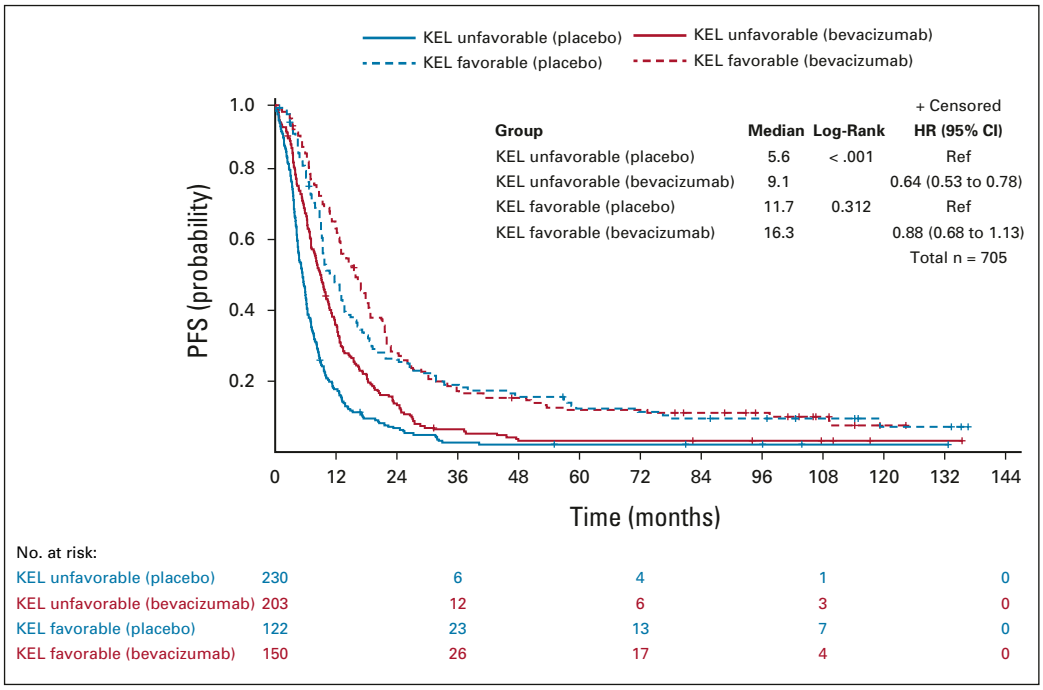

FIG 3. Kaplan-Meier curves of the PFS of patients according to treatment arm (arm 3 with bevacizumab concurrent-maintenance, *v* arm 1 with placebo) in patients with favorable or unfavorable KELIM (KEL) score, in the population of patients with a high-risk disease (stage IV + stage III operated with suboptimal surgery). HR, hazard ratio; KELIM, ELIMination rate constant K; mPFS, median PFS (months); PFS, progression-free survival; Ref, reference.

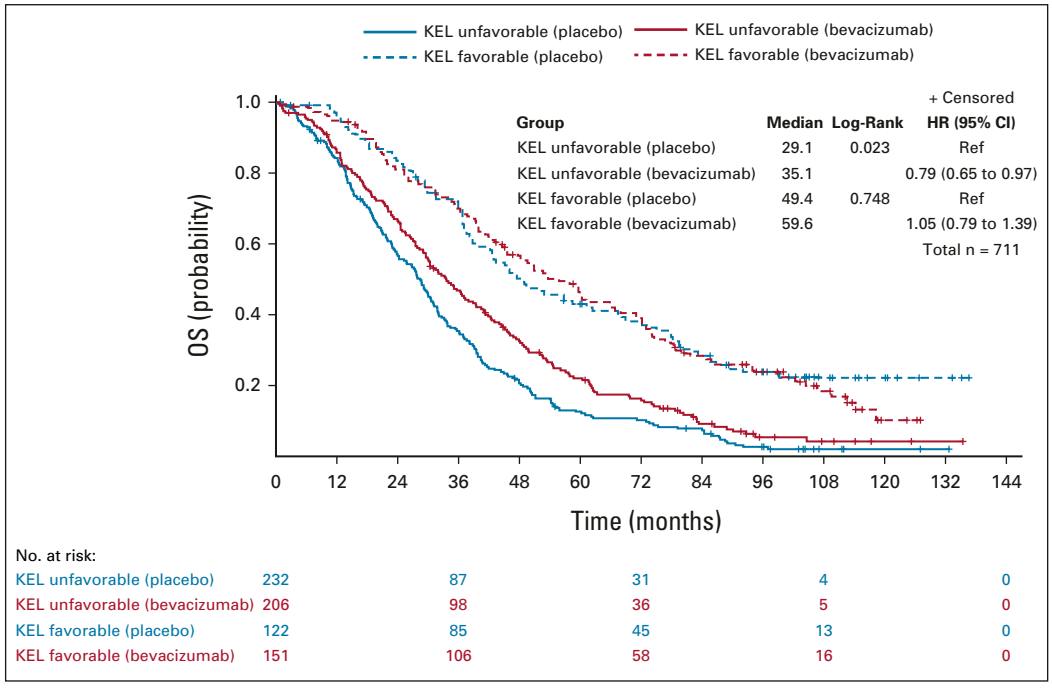

FIG 4. Kaplan-Meier curves of the OS of patients according to treatment arm (arm 3 with bevacizumab concurrent-maintenance, *v* arm 1 with placebo) in patients with favorable or unfavorable KELIM (KEL) score, in the population of patients with a high-risk disease (stage IV + stage III operated with suboptimal surgery). HR, hazard ratio; KELIM, ELIMination rate constant K; mPFS, median PFS (months); OS, overall survival; PFS, progression-free survival; Ref, reference.

bevacizumab among those with a high-risk disease.[21] This finding needs to be verified.

The current external validation study on the GOG-2018 trial data was performed in collaboration with the US NRG-GOG group. The statistical analyses, independently performed by the NGR-GOG statistician team, confirm the initial ICON-7 trial findings. The tumor-intrinsic chemosensitivity assessed by the KELIM score exhibits predictive value for benefit from the addition of bevacizumab in the first-line setting. An unfavorable KELIM score < 1.0 is associated with benefit from bevacizumab, whereas a favorable KELIM score ≥ 1.0 is related to a lack of benefit from bevacizumab.

Consistent with the ICON-7 trial results, the maximum benefit from bevacizumab was observed in patients with a high-risk disease associated with unfavorable KELIM score. The superimposability of the OS curves according to treatment arm and KELIM scores in ICON-7 and GOG-0218 reconciles the data from these two large front-line phase III trials of bevacizumab, and strongly suggests that KELIM optimizes the identification of patients benefiting from this drug (Data Supplement). Bevacizumab should be prioritized in patients with a high-risk and poorly chemosensitive disease. By contrast, it may be avoided in patients with a low-risk disease and favorable KELIM score, as the effect on OS is unclear (Data Supplement).

These data are also consistent with a recent investigation of the predictive value of KELIM score in the ICON-8 trial, suggesting that the patients belonging to a poor prognostic group (characterized by an incomplete debulking surgery and an unfavorable KELIM score) were those who had the maximum benefit from the weekly dose-dense chemotherapy compared with the standard three-weekly regimen.[22] Several preclinical studies have suggested that metronomic taxane administration is associated with improved drug delivery and antiangiogenic effects.[23,24]

The present analysis has several limitations. First, this is a post hoc analysis of the GOG-0218 trial, and the predictive value of KELIM was not prospectively assessed in this trial. The prespecified KELIM score identified 58% of patients with an unfavorable KELIM score and 42% of patients with a favorable KELIM score, which is slightly different from the distribution of the ICON-7 trial (42% and 58%, respectively). In both trials, the percentages of patients with unfavorable KELIM score were higher among those with high-risk disease (63% of patients in the GOG-0218 trial, and 53% of patients in the ICON-7 trial). As per inclusion criteria, a higher proportion of patients with a high-risk disease were enrolled in the GOG-0218 trial compared with the ICON-7 trial, which may explain this difference. The proportionality of hazard assumption was confirmed for Figure 4 (OS in patients with a high-risk disease), but failed for Figures 1-3. To address this issue, the interaction term was computed using the parameter estimates and the standard errors from the models stratified by KELIM. Since the hazard-ratio results and the *P* values for the interactions (between treatment and KELIM score) between the initial model and the stratified models were significant, the results about the initial model were considered reliable. The nonsignificativity of the interaction tests between KELIM score and treatment arms regarding OS in the patients with high-risk disease might not be related to a lack of discriminative power of KELIM score, but rather to the reduced number of patients, and the lower impact of bevacizumab on OS compared with PFS. Moreover, GOG-0218 was conducted before the emergence of poly(ADP-ribose) polymerase (PARP) inhibitors, which have changed the prognosis and the standard management of patients with ovarian cancer. As a consequence, these results may not be applicable to the current patients who are frequently treated with PARP inhibitors, especially when bevacizumab is given concurrently with olaparib as done in the PAOLA-1 trial.[4,25,26] The prognostic value of *BRCA* mutational status was not assessed in this study, but this covariate was already investigated by Tewari et al, and was not found to be associated with the benefit from bevacizumab.[6,27] Integrating this parameter in this study would have led to very small subgroups with limited statistical power. However, a post hoc analysis of the VELIA trial, where patients were treated with carboplatin-paclitaxel $\pm$ concurrent and maintenance veliparib, suggested that KELIM could help select the patients with highly chemosensitive disease (favorable KELIM score), who would have maximum benefit from this PARP inhibitor.[28]

The objective of the present validation study on the GOG-0218 trial was to externally confirm the predictive value of the KELIM score regarding the benefit from bevacizumab in the first-line setting, as initially reported in the ICON-7 trial. Bevacizumab should be prioritized in patients with a high-risk and poorly chemosensitive disease to improve their PFS and OS. Since patient KELIM score can easily be calculated on the basis of a minimum of three CA-125 values observed during the first three cycles of chemotherapy using the online calculator (Biomarker Kinetics[29] for patients treated with neoadjuvant chemotherapy, and Biomarker Kinetics[14] for patients treated with adjuvant chemotherapy), this parameter could be used routinely for adjusting the disease management.

A prospective validation of KELIM score utility is warranted. The predictive value of KELIM score is being prospectively assessed in the ongoing large international phase III trial NIRVANA-1, which compares the efficacy of niraparib with/without bevacizumab in patients who have undergone complete primary debulking surgery (ClinicalTrials.gov identifier: NCT05183984). Moreover, on the basis of the consistent outcomes from ICON-7, ICON-8, and GOG-0218 trials, a prospective trial will be conducted soon. It will assess the efficacy of a salvage weekly chemotherapy combined with bevacizumab and an innovative chemoresistance reverser in patients with unfavorable KELIM score during neoadjuvant chemotherapy and incomplete interim debulking surgery.

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Identification of Patients With Ovarian Cancer Experiencing the Highest Benefit From Bevacizumab in the First-Line Setting on the Basis of Their Tumor-Intrinsic Chemosensitivity (KELIM): The GOG-0218 Validation Study

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