CA-125 KELIM as a Potential Complementary Tool for Predicting Veliparib Benefit: An Exploratory Analysis From the VELIA/GOG-3005 Study

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PURPOSE In VELIA trial, veliparib combined with carboplatin-paclitaxel, followed by maintenance (veliparib-throughout) was associated with improved progression-free survival (PFS) compared with carboplatin-paclitaxel alone in patients with high-grade ovarian carcinomas. We explored the prognostic value of the modeled cancer antigen (CA)-125 elimination rate constant K (KELIM), which is known to be an indicator of the intrinsic tumor chemosensitivity (the faster the rate of CA-125 decline, the higher the KELIM and the higher the chemosensitivity), and its association with benefit from veliparib.

PATIENTS AND METHODS Individual KELIM values were estimated from longitudinal CA-125 kinetics. Patients were categorized as having favorable (= median) or unfavorable (< median) KELIM. The prognostic value of KELIM for veliparib-related PFS benefit was explored in cohorts treated with primary or interval debulking surgery, according to the surgery completeness, the disease progression risk group, and the homologous recombination (HR) status (BRCA mutation, HR deficiency [HRD], or HR proficiency [HRP]).

RESULTS The data from 854 of 1,140 enrolled patients were analyzed (primary debulking surgery, n = 700; interval debulking surgery, n = 154). Increasing KELIM values were associated with higher benefit from veliparib in HRD cancer, as were decreasing KELIM values in HRP cancer. The highest PFS benefit from veliparib was observed in patients with both favorable KELIM and BRCA mutation (hazard ratio, 0.28; 95% CI, 0.13 to 0.61) or BRCA wild-type HRD cancer (hazard ratio, 0.43; 95% CI, 0.26 to 0.70), consistent with the association between poly (adenosine diphosphate-ribose) polymerase inhibitor efficacy and platinum sensitivity. In contrast, seventy-four percent of patients with a BRCA mutation and unfavorable KELIM progressed within 18 months while on veliparib. The patients with HRP cancer and unfavorable KELIM might have benefited from the veliparib chemosensitizing effect.

CONCLUSION In addition to HRD/BRCA status, the tumor primary chemosensitivity observed during the first-line chemotherapy might be another complementary determinant of poly (adenosine diphosphate-ribose) polymerase inhibitor efficacy.

INTRODUCTION Platinum-based chemotherapy followed by maintenance treatment with bevacizumab and/or poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPis) is the standard first-line systemic treatment for patients with high-grade carcinomas of the ovary, fallopian tube, or peritoneum (high-grade ovarian carcinomas [HGOC]).1-4 Which patients truly benefit from PARPi maintenance remains controversial. Although BRCA mutation and, to a lesser extent, other measures of homologous recombination deficiency (HRD) are undoubtedly associated with PARPi activity,7-10 data suggest that the efficacy of these drugs cannot be unequivocally explained by these biomarkers, and there are still knowledge gaps in the understanding of determinants of PARPi efficacy. Among potential predictive biomarkers, sensitivity to platinum-based chemotherapy is very relevant. Strong relationships between platinum sensitivity and PARPi efficacy have been reported in several studies in patients treated in first-line or recurrent settings.10-12 Recent publications on more than 12,000 patients enrolled in five randomized trials, along with The Netherlands Cancer Registry and the Gynecology...
To understand the role of the tumor primary chemosensitivity (assessed by the modeled cancer antigen-125 kinetic parameter elimination rate constant K, KELIM) regarding the efficacy of the maintenance with the poly (adenosine diphosphate-ribose) polymerase inhibitor veliparib, with respect to the homologous recombination (HR) status, in patients with advanced ovarian carcinoma.

The analysis of VELIA trial revealed that higher tumor chemosensitivity was associated with higher efficacy of veliparib in terms of progression-free survival in patients with HR-deficient cancer (with/without BRCA mutation). Conversely, poor chemosensitivity was associated with limited efficacy of veliparib in patients with BRCA mutation or BRCA wild-type HR deficiency disease. In patients with HR-proficient cancer characterized by poor chemosensitivity, veliparib might have induced the chemosensitizing effect.

The tumor primary chemosensitivity, assessable by elimination rate constant K score (KELIM calculable online), may be a complementary parameter to integrate with BRCA mutation and HR status for understanding the prognosis and the benefit to expect from maintenance with the poly (adenosine diphosphate-ribose) polymerase inhibitor veliparib.
To be included in the present analysis, patients had to have at least three available values of CA-125 during the first 100 days of adjuvant chemotherapy after primary debulking surgery (PDS) or before the date of IDS. The following data were collected: age, somatic or germline BRCA mutation status (BRCA mutation or BRCA wild-type), HR status as determined by the Myriad BRACAnalysis CDx or myChoice HRD CDx assay (HRD: BRCA-mutated or GIS = 33; or HR-proficient (HRP): BRCA wild-type and GIS < 33), disease stage (III or IV), completeness of surgery on the basis of postoperative lesions assessed by the surgeon (complete surgery with no residual lesions or incomplete surgery with microscopic residual lesions between 0 and 1 cm or with macroscopic residual lesions > 1 cm).

**Estimation of KELIM for Patients Enrolled in the VELIA Trial**

In a collaboration with the Lyon University team (EA 3738, CICLY, France), the development of the KELIM model was conducted by the AbbVie team based on previous publications, with the following modifications: patients in the VELIA study were initially pooled together to model individual KELIM values, on the basis of the CA-125 kinetics during the first 100 days of chemotherapy (starting on cycle 1 day 1). The patients were then separated into two subgroups according to timing of surgery (PDS or IDS). The median values of KELIM for each subgroup were then calculated to categorize the patient as having a high tumor primary chemosensitivity (favorable KELIM value ≥ median) or an poor tumor primary chemosensitivity (unfavorable KELIM value < median).

**Statistical Analysis**

The prognostic value of KELIM for PFS, along with the association between KELIM and veliparib efficacy, was assessed in patients treated in the veliparib-throughout arm (arm 3) and in the placebo arm (arm 1), using the Kaplan-Meier method and univariate and multivariate Cox proportional hazards models.

Patients were analyzed all together (whole population) and then separately in the PDS and IDS cohorts as a way of accounting for their different prognosis. In addition to KELIM, the other prognostic factors assessed in univariate and multivariate analyses were as follows: treatment arm (3 v 1), disease stage (III v IV), surgery outcome on the basis of postoperative lesions (no residual lesion, v microscopic residual lesion, v any other residual lesion), and HR status (BRCA mutation, BRCA wild-type HRD, and HRP). The final Cox survival models were obtained using backward selection.

Additional analyses were performed to further assess the interactions between KELIM and treatment arms regarding veliparib-related PFS benefit, along with the association between KELIM and veliparib activity across important prognostic subgroups: disease stage (stage III or stage IV), completeness of surgery on the basis of postoperative residual lesions; disease progression risk groups (low-risk disease: stage III disease with no or microscopic residual lesions after surgery; high-risk diseases: stage III disease with postoperative macroscopic residual lesions or stage IV diseases), and HRD/HRP/BRCA mutation status.

All survival analyses were implemented with a landmark time point set at 100 days after the start of neoadjuvant chemotherapy. As CA-125 was modeled from days 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 radiological tumor responses.

The hazard ratios were computed using the Cox proportional hazard model and with the 95% CI.

All analyses were performed using R program (Lucent technology, Murray Hill, NJ).

**RESULTS**

**Patient Characteristics**

One thousand one hundred forty patients were enrolled in the VELIA study. Among 854 patients with ≥ 3 available measurements of CA-125 during the first three cycles of neoadjuvant or adjuvant chemotherapy, 700 patients (81.9%) received PDS and 154 patients (18.1%) received IDS (Data Supplement, online only and Table 1). The distribution of patients treated with the 3-weekly or the weekly carboplatin-paclitaxel regimens was well balanced between patients with favorable or unfavorable KELIM. The median number of CA-125 measurements per patient was four in the PDS cohort and three in the IDS cohort. Key demographic and clinical characteristics of the 854 patients are given in Table 1.

**Model Adjustment and Qualification**

Typical parameter estimates, along with the qualification analyses from the final semimechanistic model, are presented in Appendix 1 (online only; Appendix Table A1, online only; and Data Supplement).

**Characterization of KELIM in VELIA Trial**

The median KELIM was 0.023 for all 854 patients, 0.017 for the IDS cohort, and 0.024 for the PDS cohort. Patients in the IDS cohort tended to have a less favorable KELIM than those in the PDS cohort, which was expected since these patients still had tumor in place. The distributions of KELIM values across treatment arms in the PDS and IDS are shown in the Data Supplement. Consistent with previous publications, KELIM did not differ significantly across treatment arms, confirming that KELIM could be assessed as an indicator of the primary tumor chemosensitivity. As expected, the percentages of BRCA mutations and HRD tumors tended to be higher in favorable KELIM groups, compared with those in unfavorable KELIM groups, regardless of the treatment arms and surgery types (Table 1 and Data Supplement).
Associations Between KELIM and PFS

**Prognostic value of KELIM.** The median follow-up times were 28.6 and 28.2 months for the veliparib-throughout arm and the control arm, respectively.

In the whole population, KELIM status was a significant prognostic covariate in univariate (hazard ratio, 0.63; 95% CI, 0.51 to 0.79) and multivariate survival analyses (hazard ratio, 0.68; 95% CI, 0.56 to 0.85), together with the treatment arm and HR status (Data Supplement).

In the PDS cohort, the median PFS was longer in patients with favorable KELIM compared with those with unfavorable KELIM in both treatment arms, consistent with the previously reported prognostic value of KELIM (Fig 1). For example, the median PFS of patients treated in the

### TABLE 1. Characteristics of Assessed Patients

| Characteristic | Veliparib-Throughout Arm | Control Arm | Veliparib-Throughout Arm | Control Arm |
|---------------|--------------------------|-------------|--------------------------|-------------|
|               | Favorable KELIM (n = 120) | Unfavorable KELIM (n = 116) | Favorable KELIM (n = 117) | Unfavorable KELIM (n = 121) |
| Age, years    |                          |                          |                          |                          |
| Median, years (range) | 57 (33-82) | 63 (30-84) | 55 (33-79) | 64 (39-79) |
| BRCA mutational status, No. (%) |                          |                          |                          |                          |
| BRCA wild-type | 76 (60.0) | 76 (65.5) | 78 (66.7) | 87 (71.9) |
| BRCA 1/2 mutations | 41 (34.2) | 36 (31.00) | 34 (29.1) | 28 (23.1) |
| Missing       | 7 (5.8) | 4 (3.4) | 5 (4.3) | 6 (5.0) |
| HR status, No. (%) |                          |                          |                          |                          |
| HRP           | 34 (28.3) | 36 (31.0) | 32 (27.4) | 44 (36.4) |
| HRD           | 78 (65.0) | 74 (63.8) | 75 (64.1) | 66 (54.5) |
| Missing       | 8 (6.7) | 6 (5.2) | 10 (8.5) | 11 (9.1) |
| Disease stage, No. (%) |                          |                          |                          |                          |
| Stage III     | 102 (85.0) | 90 (77.6) | 102 (87.2) | 99 (81.8) |
| Stage IV      | 18 (5.0) | 26 (22.4) | 15 (12.8) | 22 (18.2) |
| ECOG PS, No. (%) |                          |                          |                          |                          |
| ≥ 1           | 42 (35.0) | 51 (44.0) | 43 (36.8) | 42 (34.7) |
| 0             | 78 (65.0) | 65 (56.0) | 74 (63.2) | 79 (65.3) |
| Chemotherapy dosing schedule with carboplatin-paclitaxel, No. (%) |                          |                          |                          |                          |
| Three-weekly dosing regimen | 68 (56.7) | 45 (38.8) | 61 (52.1) | 49 (40.5) |
| Weekly dosing regimen | 52 (43.3) | 71 (61.2) | 56 (47.9) | 72 (59.5) |
| Postoperative lesions, No. (%) |                          |                          |                          |                          |
| Any macroscopic residual disease | 43 (35.8) | 30 (25.9) | 37 (31.6) | 36 (29.8) |
| Microscopic residual disease | 21 (17.5) | 25 (21.6) | 24 (20.5) | 30 (24.8) |
| No residual disease | 56 (46.7) | 61 (52.6) | 56 (47.9) | 55 (45.5) |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HR, homologous recombination; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; IDS, interval debulking surgery; KELIM, elimination rate constant K; PDS, primary debulking surgery.
veliparib-throughout arm was 29.6 months for those who had favorable KELIM and 18.2 months for those who had unfavorable KELIM (hazard ratio, 0.61; 95% CI, 0.42 to 0.87). In the control arm, the median PFS was 20.9 months for patients with favorable KELIM and 15.4 months for those who had unfavorable KELIM (hazard ratio, 0.61; 95% CI, 0.42 to 0.87), along with the treatment arm, surgery outcomes on the basis of postoperative lesions, and HR status (Data Supplement).

Similar data of the prognostic value of KELIM were observed in the IDS cohort, with larger CIs because of the lower number of patients (Fig 1 and Data Supplement).

**Association between KELIM and benefit from veliparib.** The magnitude of the PFS difference between patients treated in the veliparib-throughout arm or in the placebo arm was

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**FIG 1.** PFS according to treatment arms (VEL-throughout vs placebo [control]) and KELIM (favorable or unfavorable) in cohort of patients operated with (A) PDS and (B) neoadjuvant chemotherapy and IDS. IDS, interval debulking surgery; KELIM, elimination rate constant K; NA, not available; PDS, primary debulking surgery; PFS, progression-free survival; VEL, veliparib.

**FIG 2.** Generalized additive model with Cox proportional hazard ratios of PFS benefit in veliparib-throughout arm 3 versus placebo arm 1 according to KELIM in (A) patients with BRCA mutation, (B) BRCA wild-type HRD cancer, and (C) HRP cancer. The cutoff at 0.024 was the KELIM median value. HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; KELIM, elimination rate constant K; PFS, progression-free survival.
higher in patients who had favorable KELIM compared with those who had unfavorable KELIM, thereby suggesting a potential predictive value of KELIM regarding the benefit from veliparib. In the PDS cohort, the PFS hazard ratio was 0.67 (95% CI, 0.47 to 0.97) for patients with favorable KELIM and 0.77 (95% CI, 0.56 to 1.06) for patients with...
unfavorable KELIM (Fig 1). Moreover, in the IDS cohort, the veliparib-throughout arm was associated with longer median PFS for patients with favorable KELIM only (29.3 v 20.8 months; hazard ratio, 0.54; 95% CI, 0.27 to 1.07; Fig 1). These data suggest a potential association between veliparib benefit and KELIM value.

**Association between veliparib activity and KELIM, according to the completeness of surgery and disease progression risk group.** The outcomes of the analyses are presented in Appendix 1. A strong association was found between KELIM estimated during neoadjuvant chemotherapy before surgery and the completeness of subsequent IDS (Data Supplement and Table 1). Higher benefit from veliparib in patients with favorable KELIM compared with those with unfavorable KELIM was observed, regardless of the completeness of surgery or disease risk group (Data Supplement).

**Association between veliparib activity and KELIM according to HR status.** The BRCA mutation and tumor HR status were available in 794 (93%) and 763 (89%) patients.

The generalized additive model with Cox proportional hazard ratios suggested different interactions between KELIM value and benefit from veliparib, depending on the HR status. In patients with BRCA mutation and BRCA wild-type HRD cancers, increasing KELIM value was associated with higher benefit from veliparib. However, in patients with HRP cancers, decreasing KELIM value seemed to be associated with higher benefit from veliparib (Fig 2).

In patients treated with PDS, the subgroup of patients who derived the highest benefit from veliparib, in comparison with the placebo arm, were those with both favorable KELIM and either BRCA mutation (hazard ratio, 0.28; 95% CI, 0.13 to 0.61) or BRCA wild-type HRD cancers (hazard ratio, 0.43; 95% CI, 0.26 to 0.71), whereas those with HRP tumors had no PFS improvement (Figs 3A and 4). The interaction tests between the treatment arm and KELIM status were consistent with higher benefit from veliparib in patients with HRD cancer exhibiting favorable KELIM: BRCA mutation (n = 139 patients), hazard ratio, 0.45; 95% CI, 0.16 to 1.26; BRCA wild-type HRD cancer (n = 147 patients), hazard ratio, 0.54; 95% CI, 0.23 to 1.30; and HRD cancer (n = 286 patients), hazard ratio, 0.50; 95% CI, 0.26 to 0.96. By contrast, the patients with unfavorable KELIM derived no benefit from veliparib whether they were carrying BRCA mutation or had HRD cancer (Fig 3B). For example, 74% of patients with BRCA mutation and unfavorable KELIM treated with veliparib had short PFS < 18 months. The discriminative accuracy (receiver operating characteristic curve area under the curve) of KELIM (unfavorable v favorable) for identifying the patients likely to experience early progression < 18 months was 0.75 (95% CI, 0.63 to 0.86; sensitivity, 0.62 and specificity, 0.74 for a KELIM cutoff at 0.024; Data Supplement).

Consistent with the generalized additive model curve analysis (Fig 2), a nonsignificant PFS benefit with veliparib was observed in patients with HRP cancer characterized by unfavorable KELIM. Compared with patients treated with placebo arm 1, this PFS gain was temporary in patients treated with the concomitant-veliparib arm 2 (median PFS, 10.2 v 6.7 months; hazard ratio, 0.79; 95% CI, 0.49 to 1.30; Fig 5A) and maintained in patients treated with the veliparib-throughout arm (arm 3; median PFS, 14.7 v 6.7 months; hazard ratio, 0.62; 95% CI, 0.37 to 1.05; Figs 3B and 5B).

![FIG 4](https://example.com/figure4.png) PFS according to KELIM (favorable or unfavorable) and treatment arms (VEL-throughout arm three v placebo [control] arms) in patients operated with PDS carrying tumors associated with (A) BRCA mutation or (B) BRCA wild-type HRD. HRD, homologous recombination deficiency; KELIM, elimination rate constant K; NA, not available; PDS, primary debulking surgery; PFS, progression-free survival; VEL, veliparib.

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FIG 5. PFS according to KELIM (favorable or unfavorable) and treatment arms (A) VEL-concurrent arm 2 vs placebo (control) arm 1 and (B) VEL-throughout arm 3 vs placebo (control) arm 1 in patients operated with PDS carrying tumors associated with HRP. HRP, homologous recombination proficiency; KELIM, elimination rate constant K; NA, not available; PDS, primary debulking surgery; PFS, progression-free survival; VEL, veliparib.

In the IDS cohort, the low numbers of patients in the BRCA-mutated and HRD cancer subgroups did not allow us to perform meaningful analyses.

**DISCUSSION**

To our knowledge, this is the first study to explore the role of the tumor primary chemosensitivity, assessed by the modeled CA-125 kinetic parameter KELIM, in PARPi efficacy in newly diagnosed advanced HGOC.

The data confirmed our previous findings about the prognostic role of KELIM in both PDS and IDS cohorts, regardless of treatment arms. Consistent with the role of KELIM as an indicator of chemosensitivity, we found that favorable KELIM was associated with higher likelihood of complete surgery in the IDS cohort, suggesting that it could be factored into algorithms designed to optimize the timing of IDS.

We also found that favorable KELIM was associated with veliparib benefit in patients with BRCA mutation or BRCA wild-type HRD cancer. These outcomes suggest a higher benefit from veliparib in patients with platinum-sensitive diseases are consistent with the literature, as shown with other PARPi. In contrast to SOLO-1, PAOLA-1, ATHENA, and PRIMA trials, where patients were selected on the basis of their platinum sensitivity, VELIA enrolled patients without prior assessment of their sensitivity to chemotherapy. The present study suggests that the PFS benefit from veliparib might have been higher if patients with HRD cancer had been selected for their platinum sensitivity. For example, the PFS relative benefit in the veliparib-throughout arm compared with the placebo arm in patients carrying BRCA mutation and favorable KELIM (hazard ratio, 0.28; 95% CI, 0.13 to 0.61) appears to be higher than those reported in patients who were not selected on KELIM in VELIA trial (hazard ratio, 0.44; 95% CI, 0.28 to 0.68). Conversely, lower benefit from veliparib was found in patients carrying BRCA mutation or with HRD tumor characterized by unfavorable KELIM. The large majority of patients with BRCA mutation and unfavorable KELIM experienced short PFS < 18 months, confirming that HR status is not the only determinant of veliparib efficacy. It indirectly suggests the complementary predictive role of the tumor chemosensitivity in addition to HR status and justifies the selection of patients on the basis of their response to platinum-based chemotherapy in the other phase III trials.

In patients with HRP cancer, a favorable KELIM was not associated with a higher benefit from veliparib. However, some patients carrying HRP cancer characterized by poor chemosensitivity (unfavorable KELIM) might have derived a temporary nonsignificant PFS benefit from the addition of veliparib to chemotherapy (arm 2) and a more sustained PFS benefit from veliparib-throughout (arm 3), potentially as a result of a chemosensitizing effect of veliparib. This hypothesis needs to be explored.

There are several limitations in the present study that should be considered. As all analyses were performed retrospectively, these findings could conceivably be confounded by unaccounted biases. Moreover, subgroup analyses were
hindered by the low number of patients in each subgroup. For example, there were only 45 patients in the veliparib-throughout arm in the IDS cohort. Among them, a disproportionate of 31 (69%) patients were classified as having a favorable KELIM, whereas only 14 patients (31%) as unfavorable KELIM. If the BRCA mutation status of patients at the time of data collection had to be documented (mutated or wild-type), the differential BRCA1 or BRCA2 mutation status was not used for random assignment, thereby limiting the possibility of additional analyses.

Despite these limitations, the present exploratory study supports the concept that intrinsic chemosensitivity, assessed by KELIM, is a relevant complementary parameter to integrate with BRCA mutation status and HRD status for understanding the patient prognosis in the first-line setting and for identifying the patients who would receive maximum benefit from veliparib. For example, KELIM could be assessed in patients with the CA-125 values observed during the first three to four cycles of adjuvant/neoadjuvant chemotherapy, and veliparib would be associated with chemotherapy and then given as a maintenance treatment in patients with favorable KELIM and BRCA mutation or HRD cancer. Of note, KELIM of patients is easily calculable online (for both neoadjuvant chemotherapy and adjuvant chemotherapy). In addition, KELIM might be of interest for identifying the patients who are more likely to benefit from other PARPis. KELIM is being prospectively assessed in the phase III trial NIVARNA-1 comparing the efficacy of niraparib with/without bevacizumab in patients operated with complete PDS (ClinicalTrials.gov identifier: NCT05183984).

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CA-125 KELIM as a Potential Complementary Tool for Predicting Veliparib Benefit: An Exploratory Analysis From the VELIA/GOG-3005 Study

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APPENDIX 1.

Structure of the Semimechanistic Model of Elimination Rate Constant K

Treatment kinetics were described by a two-compartment model: central compartment (C1) receiving chemotherapy dosing (doses set to 1) and a transit compartment (C2) to describe the treatment lag-time effect. The cancer antigen (CA)-125 production inhibition induced by the treatment is expressed by an indirect effect model using an E_{max} (E_{50}) relationship

where K is the treatment kinetic rate constant (days^{-1}), K_{PROD} is the CA-125 tumor production rate (days^{-1}), E_{50} is the concentration producing 50% of the maximum effect (AU), and elimination rate constant K (K_{ELIM}) is the CA-125 elimination rate (days^{-1}).

Association Between Veliparib Activity and K_{ELIM}, According to the Completeness of Surgery and Disease Progression Risk Group

In the primary debulking surgery cohort, as expected, complete surgery was associated with better progression-free survival outcomes compared with incomplete surgery. The positive discriminatory impact of a favorable K_{ELIM} regarding the benefit from veliparib was especially marked in patients operated with complete primary debulking surgery (favorable K_{ELIM}: 34.7 in the veliparib-throughout arm v 32.9 months in the standard arm; hazard ratio, 0.83; 95% CI, 0.46 to 1.46; unfavorable K_{ELIM}: 19.5 months in the veliparib-throughout arm v 23.3 months in the standard arm; hazard ratio, 1.23; 95% CI, 0.76 to 2.00; Data Supplement). The same analyses were performed in the interval debulking surgery cohort, but the low number of patients reduced the power of the analyses. Nevertheless, a trend for higher benefit with veliparib was observed only among patients with favorable K_{ELIM} (Data Supplement).

Similar outcomes were found when patients were categorized according to the disease risk groups, with a trend for higher benefit from veliparib among patients with favorable K_{ELIM} compared with those with unfavorable K_{ELIM} (Data Supplement).

**TABLE A1.** Parameter Estimates From the Final Semimechanistic Model

| Parameter                        | Estimate | RSE* on Estimate, % | IIIV, % | CV | Shrinkage, % |
|----------------------------------|----------|---------------------|--------|----|--------------|
| K, d^{-1}                        | 0.9230   | 25.00               | 13.34  | 99.8 |              |
| K_{PROD}, IU·mL^{-1}·d^{-1}       | 0.0547   | 3.93                | 16.70  | 86.8 |              |
| E_{50}, AU                       | 0.5730   | 31.40               | 15.65  | 99.8 |              |
| K_{ELIM}, D^{-1} (covariate = 0) | 0.0235   | 1.61                | 29.24  | 23.6 |              |
| K_{ELIM}, D^{-1} (covariate = 1) | 0.0167   | 2.99                | 29.24  | 23.6 |              |
| CA_{0}, IU·mL^{-1}               | 4.9400   | 3.75                | 38.85  | 71.5 |              |

NOTE. RSE was computed using bootstrapping of 500 samples. Covariate: 0 = primary debulking surgery; 1 = interval debulking surgery. CA_{0} = estimated CA-125 basal concentration.

Abbreviations: CA, cancer antigen; CV, coefficient of variation; IIIV, interindividual coefficient of variation; K_{ELIM}, elimination rate constant K; K_{PROD}, modeled CA-125 production rate constant K; RSE, relative standard error.

*RSE calculated as (SE/estimated parameter) × 100.

*IIIV calculated as square root (variance of random effect) × 100.

*Percentage on the standard deviation scale.