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Prognostic nomogram for progression-free survival in patients with BRCA mutations and platinum-sensitive recurrent ovarian cancer on maintenance olaparib therapy following response to chemotherapy

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ABSTRACT

Background: The impact of maintenance therapy with PARP inhibitors (PARPi) on progression-free survival (PFS) in patients with *BRCA* mutations and platinum-sensitive recurrent ovarian cancer (PSROC) varies widely. Individual prognostic factors do not reliably distinguish patients who progress early from those who have durable benefit. We developed and validated a prognostic nomogram to predict PFS in these patients.

Methods: The nomogram was developed using data from a training patient cohort with *BRCA* mutations and high grade serous PSROC on the placebo arm of two maintenance therapy trials, Study 19 and SOLO2/ENGOT-ov21. We performed multivariable Cox regression analysis based on pre-treatment characteristics to develop a nomogram that predicts PFS. We assessed the discrimination and validation of the nomogram in independent validation patient cohorts treated with maintenance olaparib.

Results: The nomogram includes four PFS predictors: CA-125 at randomisation, platinum-free interval, presence of measurable disease and number of prior lines of platinum therapy. In the training cohort (internal validation C-index 0.64), median PFS in the model-predicted good, intermediate and poor risk groups was: 7.7 (95% CI 5.3-11.3), 5.4 (4.8-5.8) and 2.9 (2.8-4.4) months, respectively. In the validation cohort (C-index 0.71), median PFS in the model-predicted good, intermediate and poor risk groups was: not reached, 16.6 (13.1-22.4) and 8.3 (7.1-10.8) months, respectively. The nomogram showed good calibration in the validation cohort (calibration plot).

Conclusions: This nomogram can be used to predict PFS and counsel patients with *BRCA* mutations and PSROC prior to maintenance olaparib and for stratification of patients in trials of maintenance therapies.

Keywords: Ovarian cancer, BRCA mutation, olaparib, Poly(ADP-ribose) Polymerase Inhibitors, prognosis, nomogram

Introduction

Multiple clinical trials have demonstrated a progression-free survival (PFS) advantage when poly(ADP-ribose) polymerase inhibitor (PARPi) maintenance therapy is compared to placebo following response to chemotherapy in patients with *BRCA* mutations and platinum-sensitive recurrent ovarian cancer (PSROC) (1-6). As such, this is now an accepted standard of care (7, 8). The hazard ratios (HR) for freedom from progression or death ranges from 0.23 to 0.35 for patients with *BRCA* mutations in these trials.(1-4) Despite this, clinicians and patients may not always appreciate the significant variability in PFS. For example, in patients with *BRCA*-mutated PSROC, approximately 1 in 3 will progress within 1 year following commencement of maintenance PARPi therapy, while 1 in 5 will continue PARPi beyond 5 years.(2-4, 6) There is an unmet need for predicting durability of benefit for these patients. By individualising prognostication, nomograms can assist clinicians to counsel patients and manage expectations while also predicting outcome for future trial design.

Most patients with advanced poor prognosis cancers including ovarian cancer, desire information on prognosis, which can be challenging given significant uncertainty arising from the heterogeneity of patient outcomes.(9, 10) Frank discussions surrounding prognosis can improve patients' psychological well-being.(11) We previously developed nomograms combining pre-treatment clinical and laboratory variables to enhance prediction of PFS and overall survival (OS) in patients with PSROC receiving platinum-based chemotherapy.(12, 13) However, these nomograms may not apply to women with *BRCA*-mutated PSROC commencing maintenance PARPi therapy with better prognosis but without widely used prognostic tools available.

To address these gaps, we aimed to develop and validate a prognostic nomogram that uses readily available pre-treatment clinical and laboratory data to individualise treatment outcomes for women with *BRCA*-mutated PSROC commencing maintenance PARPi therapy.

Our goal was to develop a simple and accurate prognostic tool to assist clinicians when counselling patients as well as to stratify patients according to risk of progression for clinical trials.
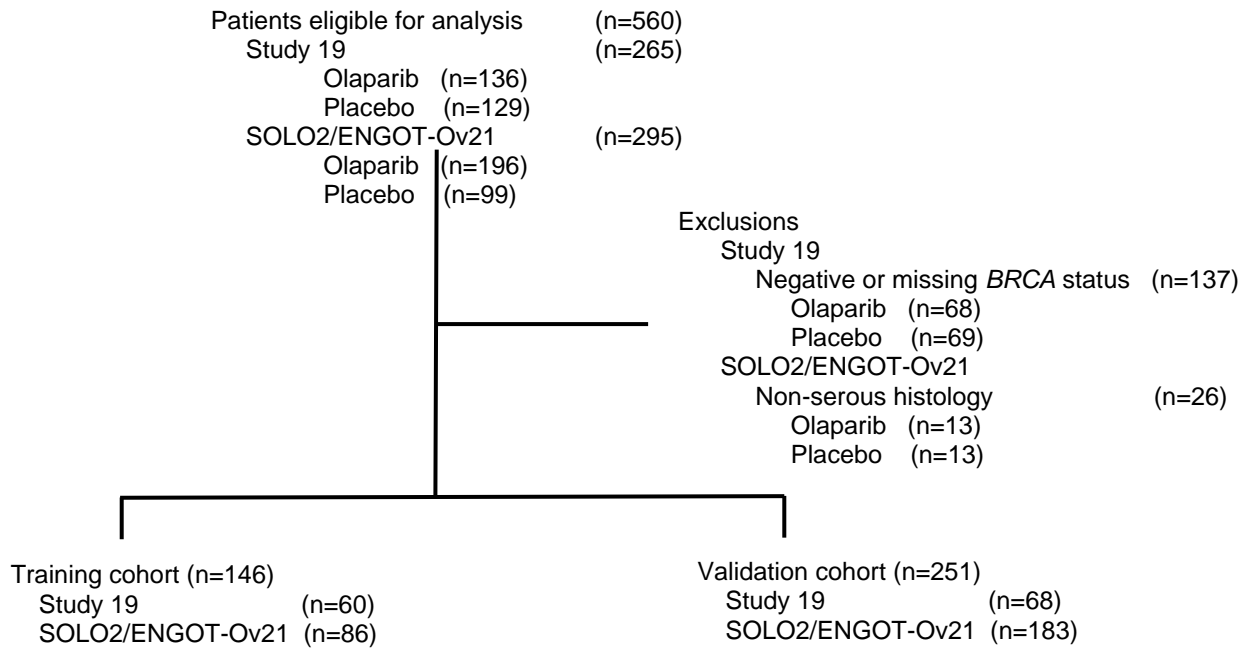
Methods

Study population

Study 19 (NCT00753545) (1) is a randomised, phase 2 study of maintenance olaparib *vs* placebo in women with high grade serous PSROC, with or without *BRCA1/2* mutation. SOLO2/ENGOT-ov21 (NCT01874353) (2) is a randomised, phase 3 study of maintenance olaparib *vs* placebo in women with *BRCA1/2* mutation-positive PSROC following response to chemotherapy. Patients were assigned to olaparib (400 mg in capsules for Study 19 and 300 mg in tablets for SOLO2/ENGOT-ov21 twice daily) or placebo until RECIST-defined progressive disease or unacceptable toxicity. Patients could remain on treatment beyond progression until the investigator deemed a patient no longer derived benefit. Both Study 19 and SOLO2/ENGOT-ov21 showed a significant PFS improvement (HR 0.35, 95% CI 0.25-0.49, P<0.001; HR 0.30, 95% CI 0.22-41; *P*<0.0001, respectively). Full details have been previously reported.(1, 2)

By definition a prognostic factor identifies a better outcome regardless of the treatment and are best determined in untreated patients.(14) As Study 19 and SOLO2/ENGOT-Ov21 are both randomised studies, the prognostic factors are distributed equally between treatment arms. Therefore, the nomogram was derived in a training cohort of 146 patients with *BRCA* mutation-positive PSROC treated with placebo (60 enrolled in Study 19 and 86 in SOLO2/ENGOT-Ov21). We validated our model in an independent cohort of 251 patients (68 in Study 19 and 183 in SOLO2/ENGOT-Ov21), with similar characteristics as those in the training cohort but treated with olaparib. (Supplementary Figure 1) Examining

patients treated with placebo and olaparib separately allows us to observe the natural history (training cohort) and assess the change in the disease trajectory with the use of olaparib (validation cohort).(15)

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Patients eligible for analysis        (n=560)
    Study 19                          (n=265)
            Olaparib   (n=136)
            Placebo    (n=129)
    SOLO2/ENGOT-Ov21                  (n=295)
            Olaparib   (n=196)
            Placebo    (n=99)
                                    Exclusions
                                        Study 19
                                            Negative or missing BRCA status  (n=137)
                                                Olaparib   (n=68)
                                                Placebo    (n=69)
                                        SOLO2/ENGOT-Ov21
                                            Non-serous histology              (n=26)
                                                Olaparib   (n=13)
                                                Placebo    (n=13)


Training cohort (n=146)                 Validation cohort (n=251)
    Study 19            (n=60)              Study 19            (n=68)
    SOLO2/ENGOT-Ov21  (n=86)              SOLO2/ENGOT-Ov21  (n=183)
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Supplementary Figure 1. CONSORT diagram

Statistical method
The primary endpoint was PFS by RECIST criteria version 1.0 for Study 19 and modified RECIST criteria version 1.1 for SOLO2/ENGOT-ov21. Thirteen variables related to baseline patient and disease characteristics, past treatment, haematological, biochemical and tumour marker parameters were selected as clinically relevant prognostic factors and examined by univariate analysis in the training cohort. Multivariable Cox proportional-hazards analysis (16) was performed with backward stepwise selection including variables identified from the univariate analyses with p-value$\leq$0.20. Only variables with $p<0.05$ were retained in the final multivariable model. For clinical applicability, we categorised continuous variables.

Using the coefficients from the model, a nomogram was developed by assigning points to each predictor to allow a visualised estimation of individual prediction. These points reflect the relative contribution of each predictor in the final prediction model. Summing these points for each patient, the total score (scaled range from 0 to 100) represents a weighted sum. Using the nomogram, estimated median PFS and probability of PFS at 12 months are obtained by drawing a vertical line from the total point's axis to the outcome axes. Patients were grouped by quartiles based on the predicted probability of PFS. The first quartile formed the good-prognosis group (0-25%), the middle two quartiles formed the intermediate-prognosis group (26-75%), and the final quartile formed the poor-prognosis group (76-100%).

We validated the nomogram using two procedures. First, to determine discriminative ability, we used Harrell's discrimination concordance index statistic (C-index) for the training cohort, including developing 1000 boot-strap replications as internal validation subsets to estimate the bias-corrected C-index, and compared it with that of the validation cohort. The C-index estimates the proportion of all pairwise combinations of patients whose PFS times are ordered, such that the patient with the longest predicted PFS was the one who actually lived longer. The C-index takes on the value ranging from 0.5 to 1.0, with 0.5 indicating random prediction and 1.0 for a perfectly discriminating model. We also plotted Kaplan-Meier survival curves and used the log-rank test to illustrate the discriminatory ability of the nomogram-derived categorisation of patients in the training and validation cohorts. Second, calibration was assessed by visually comparing the nomogram-predicted probabilities for PFS at 6, 12 and 18 months with the corresponding observed PFS probability for each prognosis group. Plots resembling a 45-degree line indicate that the nomogram predictions are well-calibrated. We evaluated the treatment benefit by risk group for patients in each study and

presented the HRs and associated 95% CIs for PFS. The Study 19 and SOLO-2/ENGOT-

ov21 sub-study steering committee approved this study.

Results

The baseline characteristics of the training and validation cohorts did not differ

significantly. (Table 1) As expected, the median PFS was significantly longer in the

validation cohort than the training cohort (16.6 *vs* 5.4 months; log-rank *P*<0.0001) (Figure 1).

Characteristics	Training (n=146)		Validation (n=251)		P-value
	N	%	N	%	
Age					
25<x≤50	41	28	61	24	0.41
50<x≤100	105	72	190	76	
Tumour grade[a]					
Grade 3	118	84	208	85	0.80
Grade 2/Undifferentiated	22	16	36	15	
FIGO Stage[b]					
I/II	14	10	25	10	0.89
III/IV	132	90	224	90	
Platinum-free interval					
6-12 months	62	42	102	41	0.72
>12 months	84	58	149	59	
Response to last platinum therapy					
Complete	70	48	117	47	0.80
Partial	76	52	134	53	
Baseline ECOG performance status[c]					
0	110	76	208	84	0.06
1	35	24	41	16	
Number of previous platinum lines					
2	69	47	127	51	0.52
>2	77	53	124	49	
Presence of disease ≥1cm	54	37	88	35	0.76
Baseline CA-125[d]					
≤25	117	80	183	73	0.11
>25	29	20	68	27	
Median baseline CA-125 (IQR)	12 (7-22)		13 (8-26)		0.33
Median baseline albumin[d] (IQR)	42 (40-45)		43 (40-45)		0.35
Median baseline lymphocytes[e] (IQR)	1.5 (1.2-2.0)		1.4 (1.2-1.8)		0.49
Median baseline neutrophils[d] (IQR)	2.7 (2-3.76)		2.7 (2.1-3.4)		0.74
Median baseline NLR[e] (IQR)	1.8 (1.4-2.4)		1.8 (1.4-2.5)		0.65

[a] n=13 non-assessable [b] n=2 non-assessable [c] n=3 missing [d] n=5 missing [e] n=26 missing
FIGO = International Federation of Gynecology and Obstetrics, ECOG = European Cooperative Oncology Group,
CA-125 = cancer antigen 125, IQR = interquartile range, NLR = neutrophil-to-lymphocyte ratio
Table 1 Baseline characteristics of patients in the training and validation cohorts

Development of the nomogram

In the training cohort, the median follow-up duration was 21.9 months (range 0-27.5). The proportion of women with PFS at 6 months was 35% (95% CI 27-43%) and 12 months was 14% (95% CI 8-21%; Figure 1).
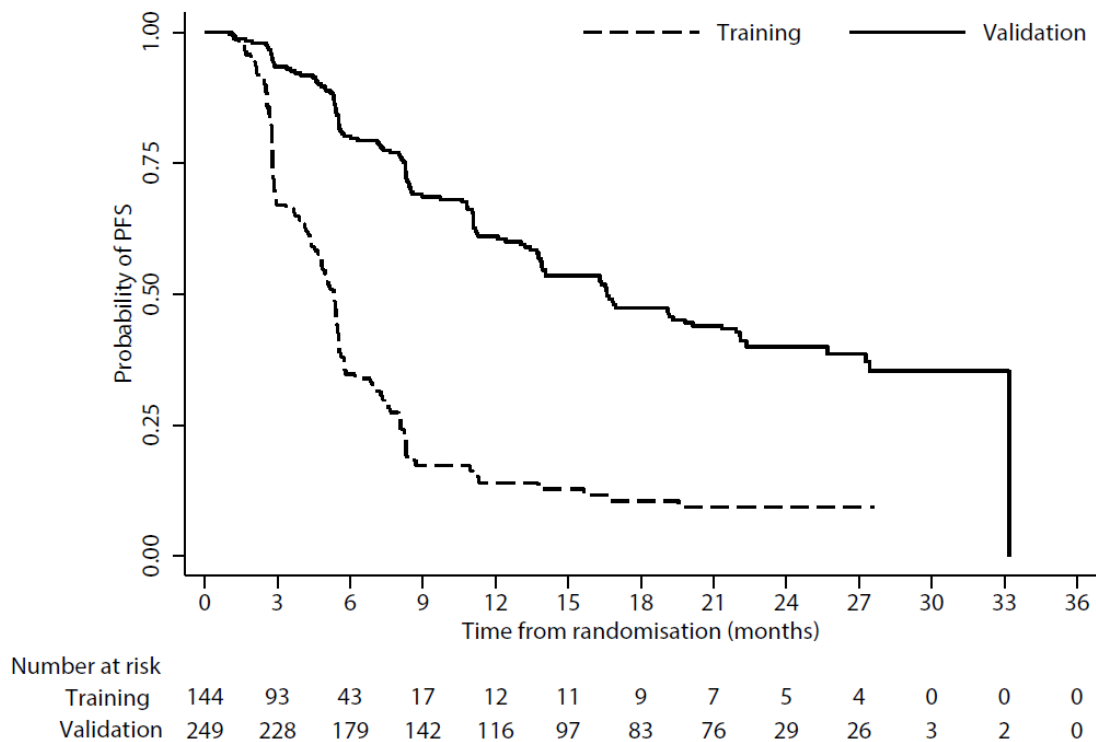

Figure 1 PFS in the training and validation cohorts

From the univariate analysis, the following variables were identified to be candidate variables for the multivariate model: platinum-free interval (PFI), response to last platinum therapy, number of prior lines of platinum therapy, presence of measurable disease and CA-125 at randomisation. (Table 2) The Kaplan-Meier curve of PFS stratified by CA-125 and *BRCA* mutation are shown in Supplementary Figures 2 & 3, respectively.

	Patients with an outcome (n=117)	Patients without an outcome (n=27)	Hazard ratio	95% CI	*P*-value
BRCA mutation					
*BRCA*1	78	18	1.00	-	0.18
*BRCA*2	37	8	0.77	0.52-1.14	
Tumour grade[a]					
Grade 3	96	21	1.00	-	0.26
Grade 2/Undifferentiated	16	5	0.75	0.44-1.27	
FIGO Stage[b]					
I/II	9	4	1.00	-	0.38
III/IV	23	107	1.35	0.68-2.67	
Platinum-free interval					
6-12 months	59	3	1.00	-	0.0019
>12 months	58	24	0.56	0.39-0.80	
Response to last platinum therapy					
Complete	51	19	1.00	-	0.018
Partial	66	8	1.55	1.08-2.24	
Baseline ECOG performance status[c]					
0	90	18	1.00	-	0.35
1	27	8	0.82	0.53-1.26	
Number of prior platinum lines					
2	47	21	1.00	-	0.001
>2	70	6	1.88	1.28-2.75	
Presence of disease ≥1cm					
No	70	21	1.00	-	0.02
Yes	47	6	1.60	1.10-2.33	
Baseline CA-125 (continuous)	117	27	1.01	1.008-1.02	0.0003
Baseline CA-125					
≤25 IU/L	89	26	1.00	-	0.002
>25 IU/L	28	1	2.07	1.34-3.20	
Baseline albumin[d]	114	26	0.98	0.93-1.03	0.45
Baseline lymphocytes[e]	109	26	1.10	0.81-1.50	0.55
Baseline neutrophils[c]	116	27	1.06	0.97-1.16	0.21
Baseline NLR[e]	109	26	1.04	0.92-1.18	0.56

[a] n=6 non-assessable [b] n=1 non-assessable [c] n=1 missing [d] n=4 missing [e] n=9 missing

n=2 not included in univariate analysis as PFS time is 0

The continuous variable of age was not available due to patient privacy and therefore age was not evaluated

BRCA = breast cancer gene, FIGO = International Federation of Gynecology and Obstetrics, ECOG = European Cooperative Oncology Group, CA-125 = cancer antigen 125, NLR = neutrophil-to-lymphocyte ratio

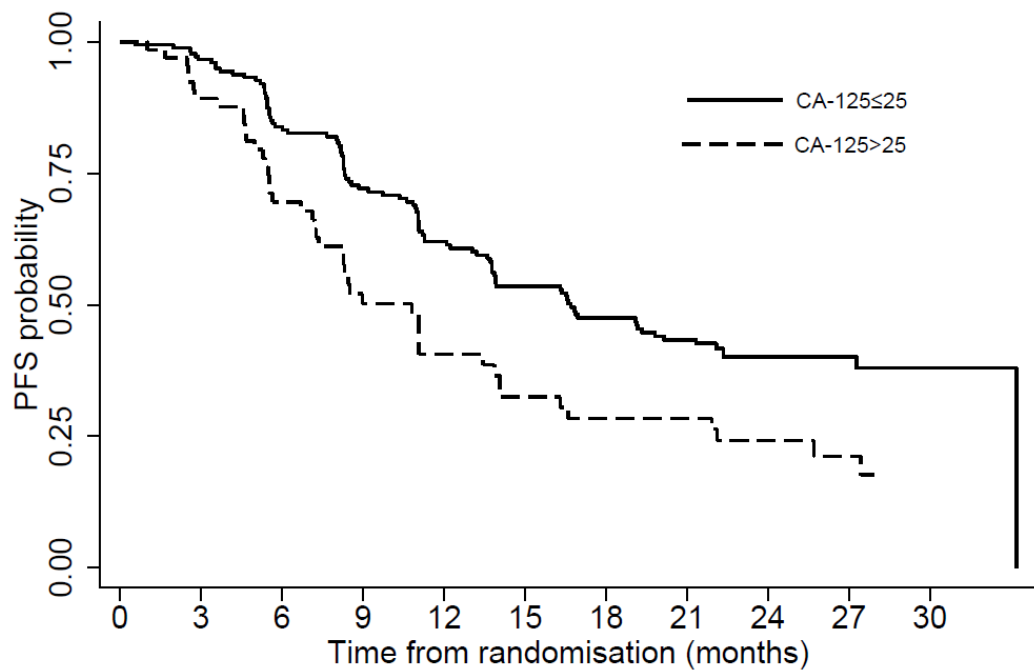**Table 2 Univariate analysis for the training cohort**

(A)
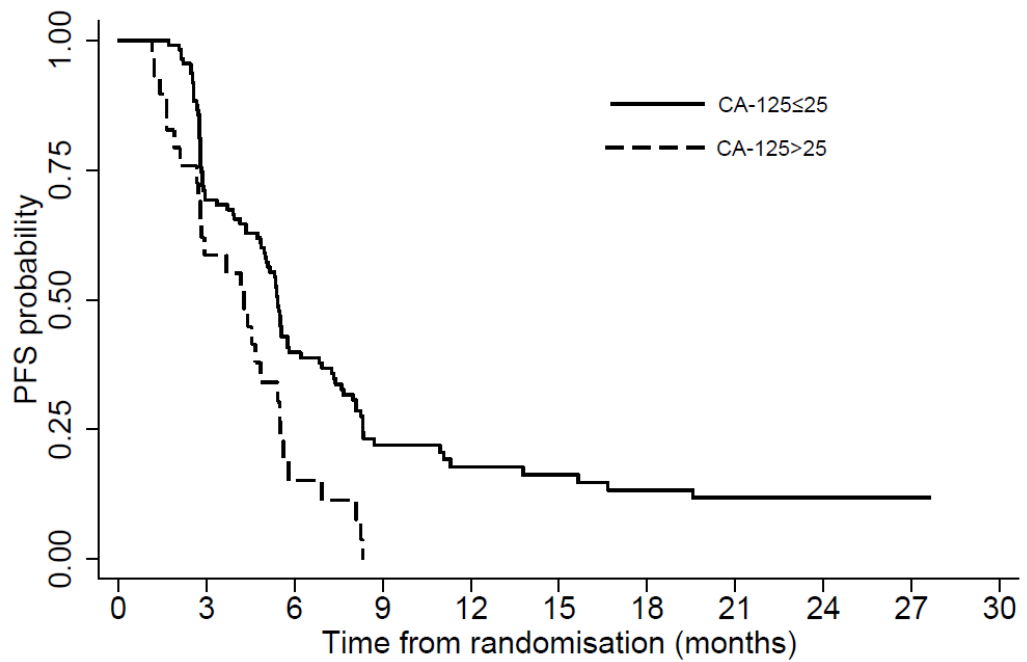
Number at risk										
CA-125 ≤25	115	76	39	17	12	11	9	7	5	4	0
CA-125 >25	29	17	4	0	0	0	0	0	0	0	0

(B)

Number at risk										
CA-125 ≤25	182	170	138	115	95	81	69	62	20	19	3
CA-125 >25	67	58	41	27	21	16	14	14	9	7	0

Supplementary Figure 2 PFS by CA-125 status in the (A) training and (B) validation cohort

(A)

Number at risk										
BRCA1	96	57	25	9	6	5	4	3	2	2	0
BRCA2	45	33	16	8	6	6	5	4	3	2	0

(B)

Number at risk										
BRCA1	165	152	118	93	75	63	54	50	18	15	1
BRCA2	79	71	59	47	39	34	29	26	11	11	2
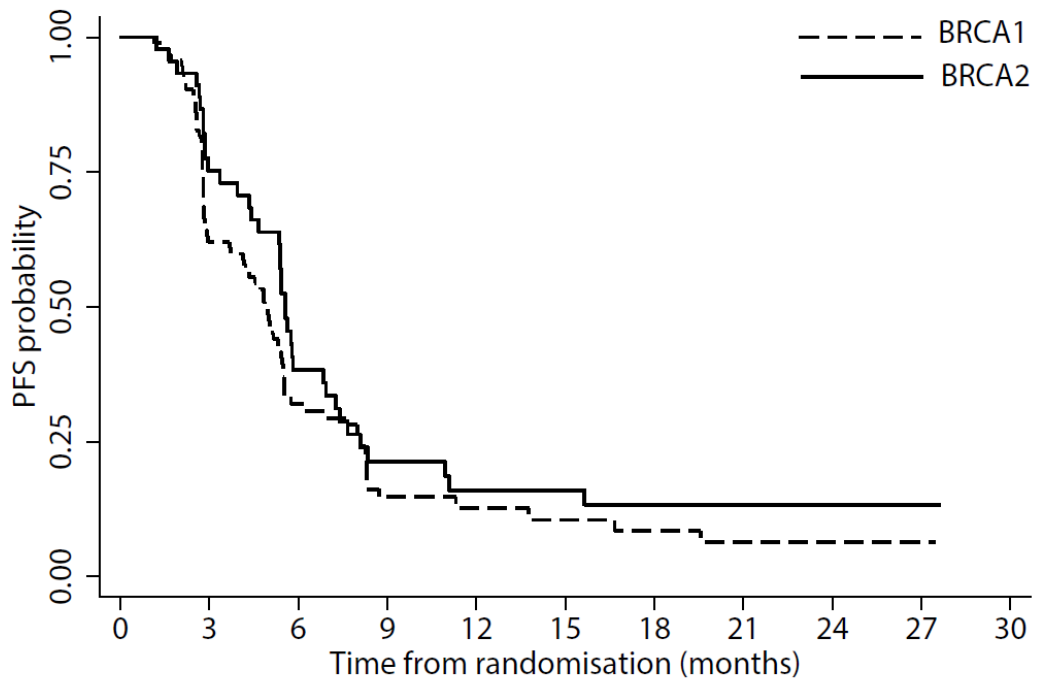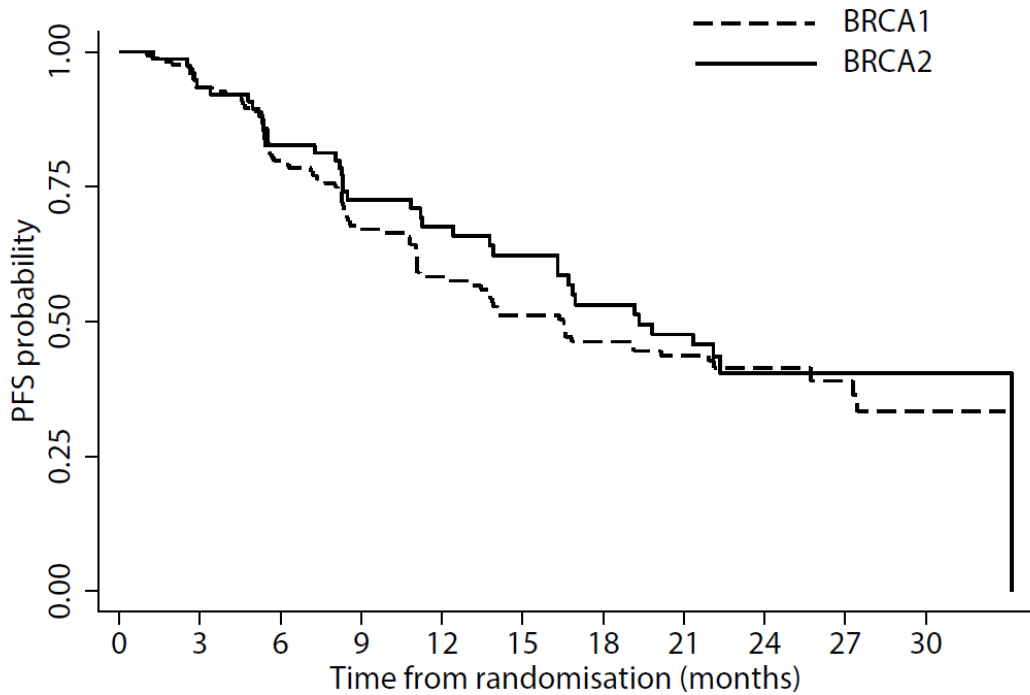
Supplementary Figure 3 PFS by BRCA status in the (A) training and (B) validation cohort

The final multivariable model includes four predictors: number of prior lines of platinum therapy (HR 1.50 (95% CI 1.002-2.24), PFI (HR 1.65, 95% CI 1.12-2.42), presence of measurable disease (HR 1.55, 95% CI 1.05-2.27), and CA-125 at randomisation (HR 1.69, 95% CI 1.09-2.64). (Table 3) The point scale assigned to each of the four variables were: CA-125>25 assigned 28 points, PFI (6-12 months) 27 points, presence of measurable disease 24 points and >2 previous platinum lines 21 points. (Figure 2)

In the training cohort, the model showed good discrimination (C-index 0.63, boot-strapped C-index 0.64). The model-predicted good prognosis group comprised of 43 patients (30%) with a median PFS 7.7 months (95% CI, 5.3-11.3) and 1-year PFS of 32% (95% CI, 16-48%). The intermediate-prognosis group comprised of 73 patients (51%) with a median PFS of 5.1 months (95% CI, 3.7-5.5) and 1-year PFS of 10% (95% CI, 4-19%). The poor-prognosis group comprised of 28 patients (19%) with a median PFS of 3.6 months (95% CI, 2.8-4.7) and 1-year PFS of 0%. The Kaplan-Meier curve of the PFS stratified according to prognosis groups showed good discrimination (log-rank $P < 0.0001$; Figure 3A).

	Patients with an outcome (n=117)	Patients without an outcome (n=27)	β-coefficient	Hazard ratio	95% CI	p-value
Platinum-free interval						
>12 months	58	24	0.50	1.00	-	0.01
6-12 months	59	3		1.65	1.12-2.42	
Presence of disease ≥1cm						
No	70	21	0.44	1.00	-	0.03
Yes	47	6		1.55	1.05-2.27	
Number of previous platinum lines						
2	47	21	0.40	1.00	-	0.049
>2	70	6		1.50	1.002-2.24	
Baseline CA-125						
≤25	89	26	0.53	1.00	-	0.02
>25	28	1		1.69	1.09-2.64	

C-statistic 0.63, bootstrapped C-index 0.64

Table 3 Multivariate proportional hazard regression model for predicting progression-free survival using data from the training cohort
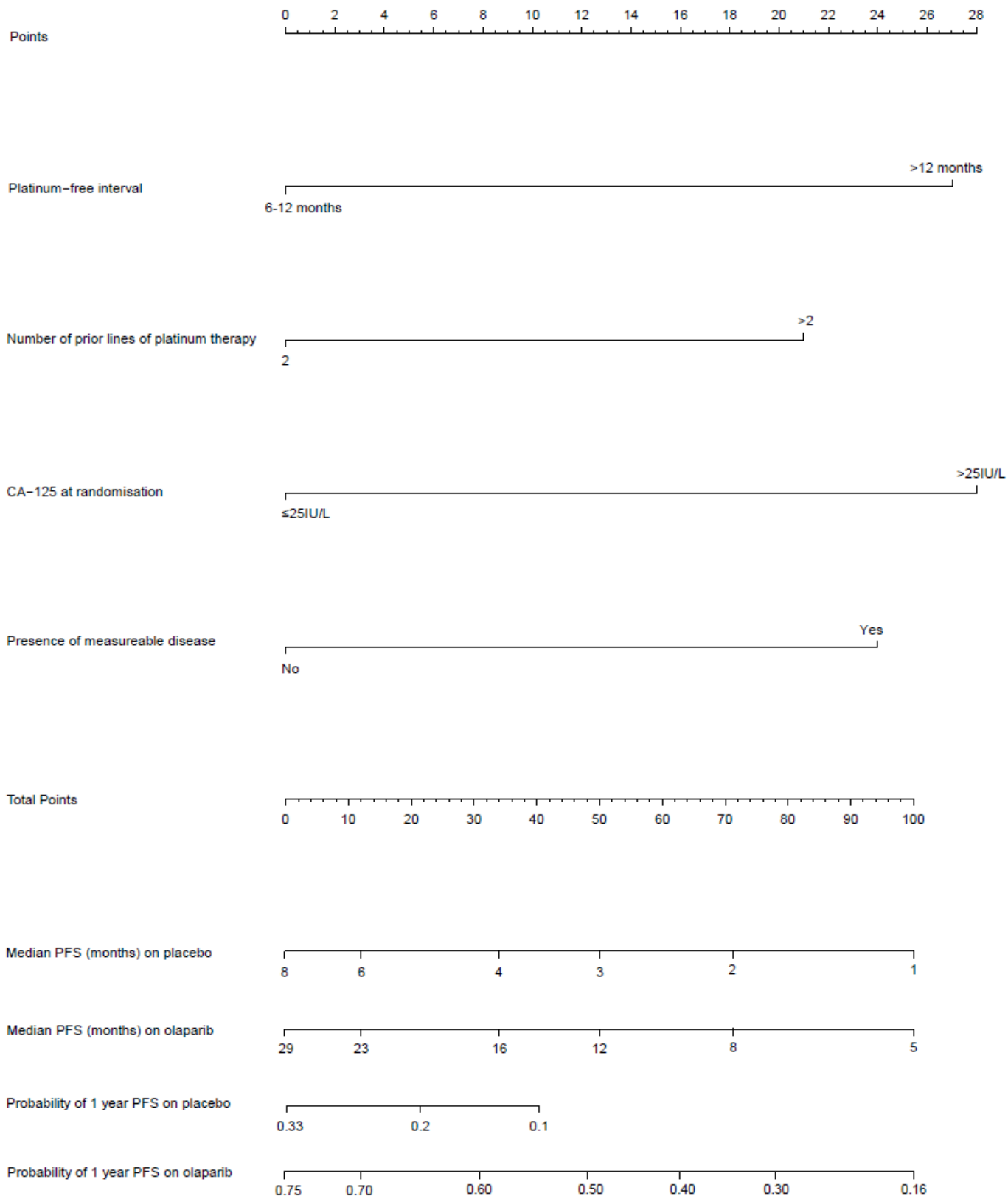
Figure 2 Nomogram for predicting PFS in high grade serous relapsed platinum-sensitive recurrent ovarian cancer with *BRCA1/2* germline mutation

(A)
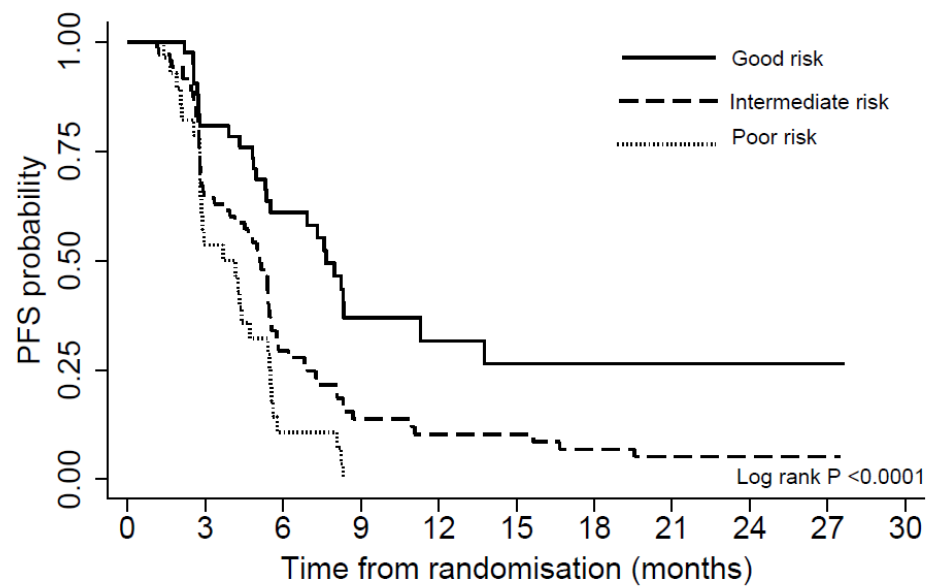
Number at risk										
Good risk	43	33	21	9	6	5	5	4	3	3	0
Intermediate risk	73	45	19	8	6	6	4	3	2	1	0
Poor risk	28	15	3	0	0	0	0	0	0	0	0

(B)
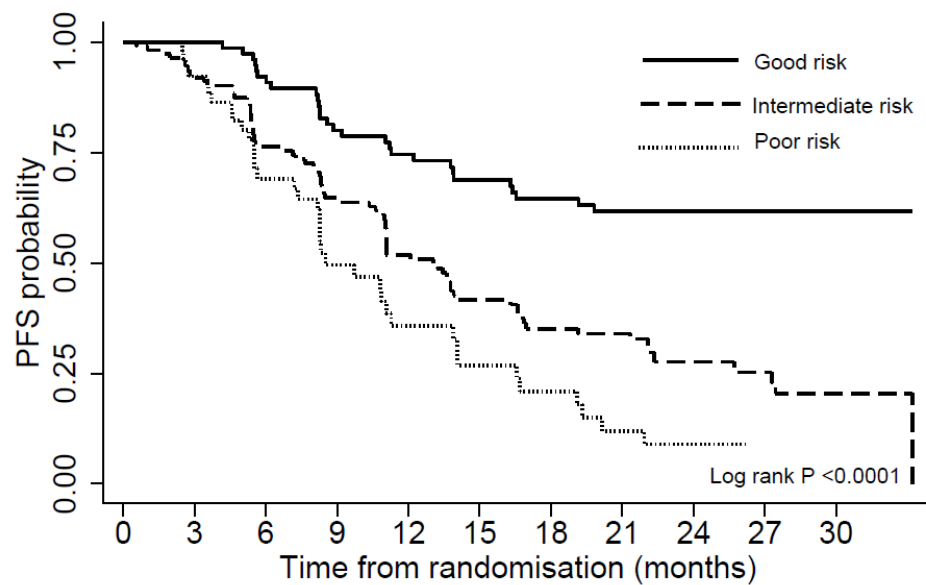
Number at risk										
Good risk	82	79	70	59	52	48	45	42	15	15	1
Intermediate risk	114	101	79	65	51	40	31	30	12	11	2
Poor risk	53	48	30	18	13	9	7	4	2	0	0

Figure 3 PFS stratified according to prognosis groups in (A) training and (B) validation cohort

Validation of the nomogram

In the validation cohort, the median follow-up was 22.1 months (range 0-33.2). The proportion of women with PFS at 6 months was 80% (95% CI 75-85%) and 12 months was 61% (95% CI 54-67%; Figure 1). The C-index was 0.71.

The model-predicted good prognosis group comprised of 82 patients (33%) with median PFS not reached and 1-year PFS of 75% (95% CI, 63-83%). The intermediate-prognosis group comprised of 114 patients (46%) with a median PFS of 13.1 months (95% CI, 11.0-16.3) and 1-year PFS of 52% (95% CI, 42-61%). The poor-prognosis group comprised of 53 patients (21%) with a median PFS of 8.5 months (95% CI, 7.4-13.9) and 1-year PFS of 36% (95% CI, 21-50%). The Kaplan-Meier curve of the PFS stratified according to prognosis groups showed good discrimination between the three prognosis groups (log-rank *P* <0.0001; Figure 3B). The calibration plot of the actual *vs* predicted 6, 12 and 18-month PFS for each of the three prognosis groups appears to be well-calibrated. (Figure 4) Regardless of risk group, all patients benefited from olaparib treatment. (Supplementary Figure 4)
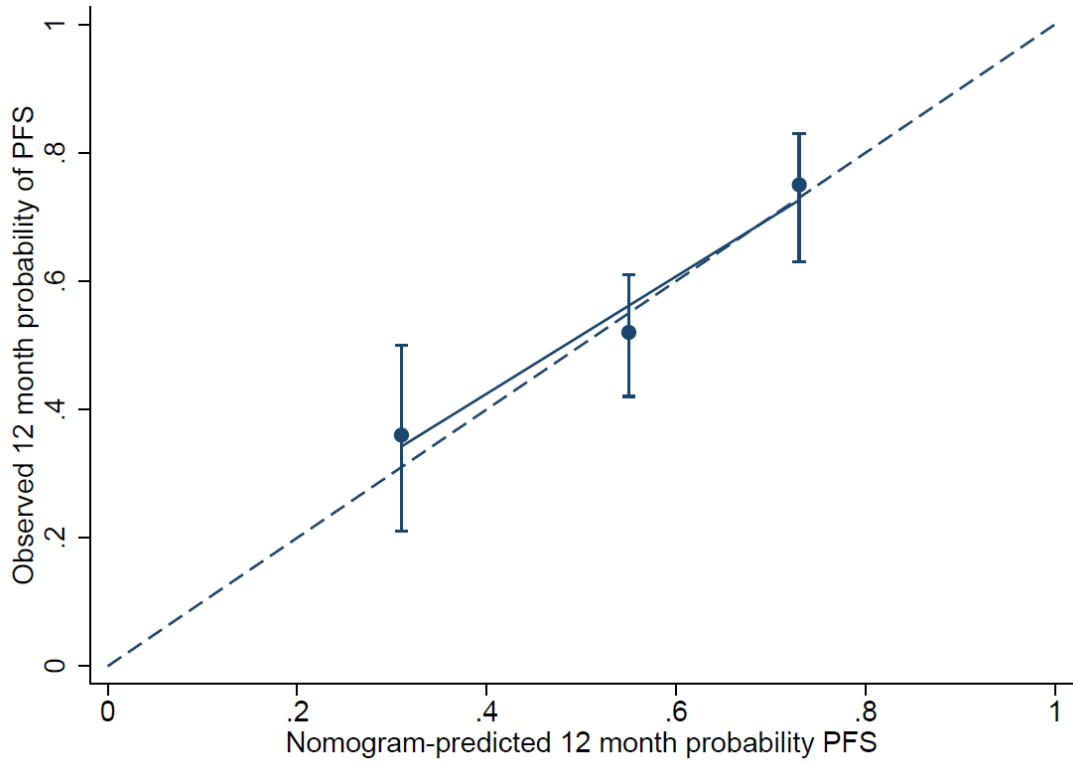
Web-based interface

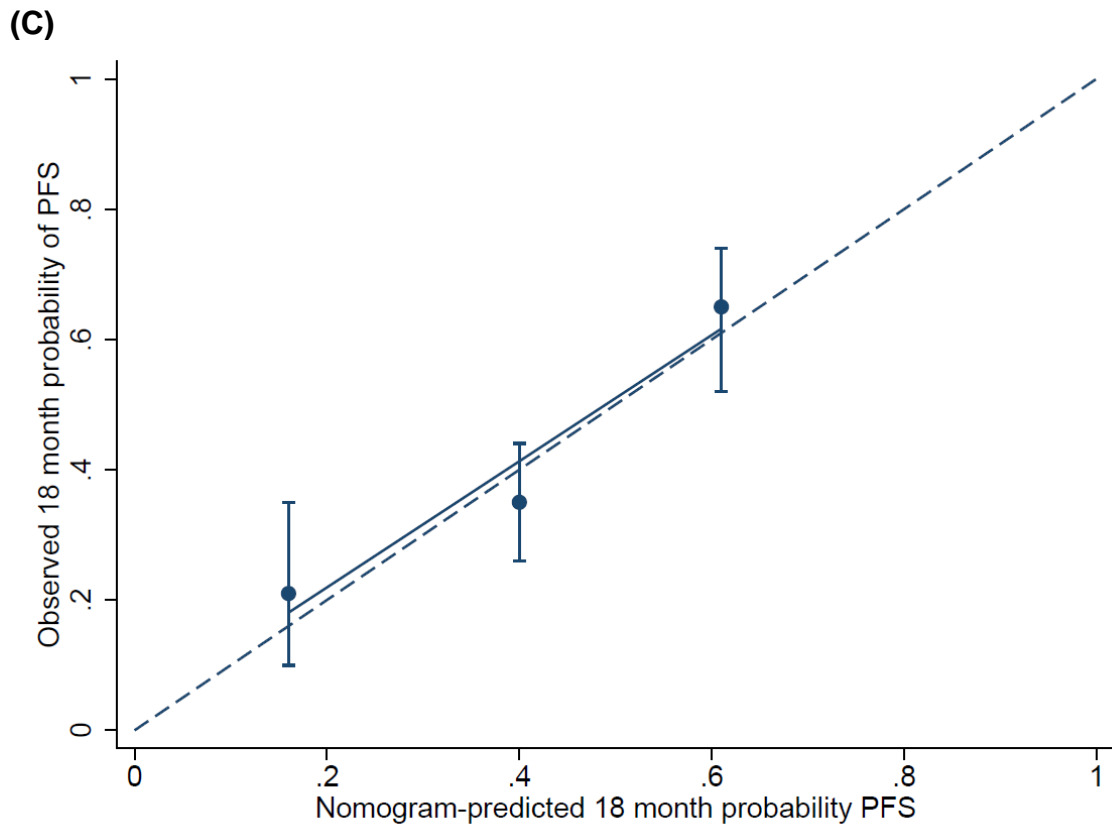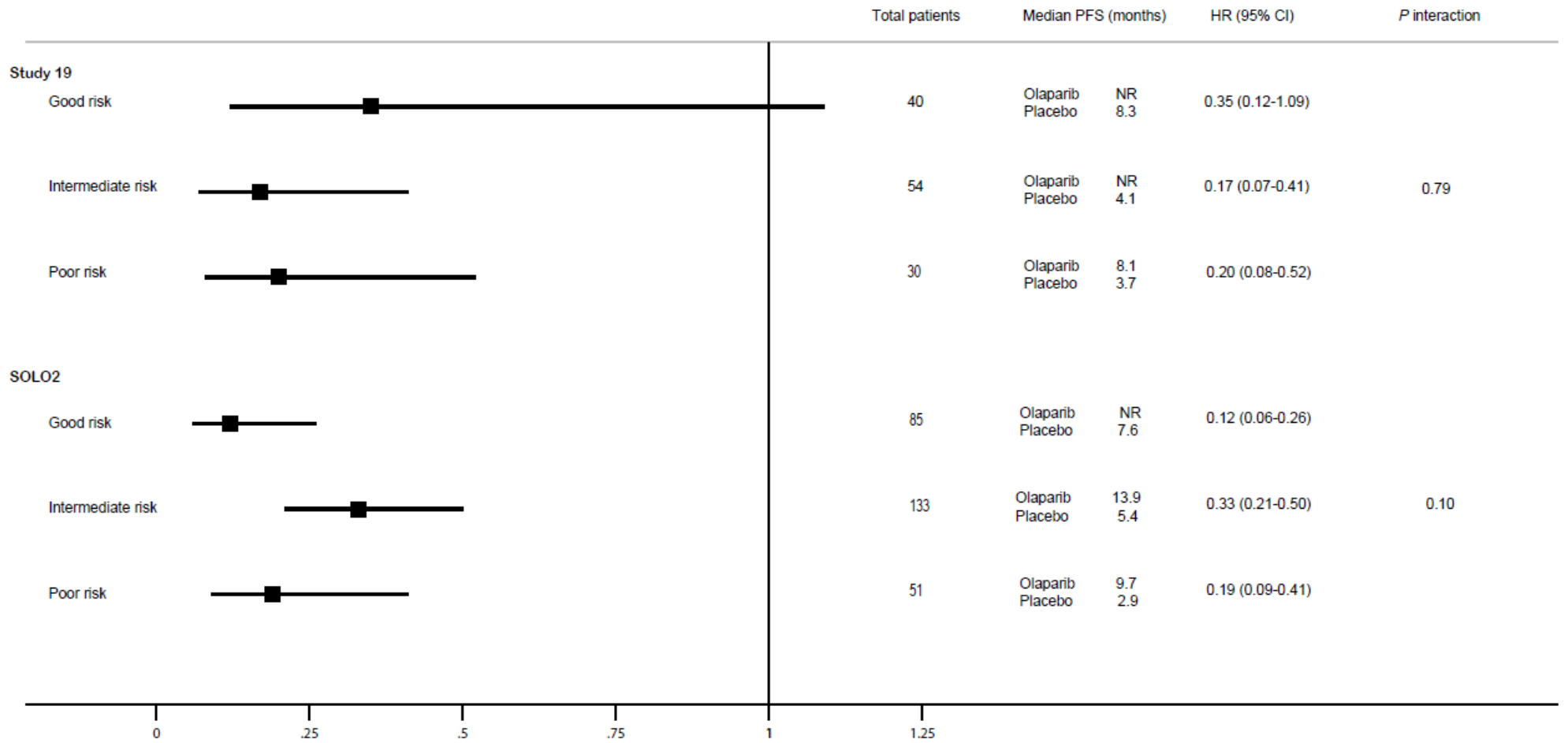A web-based version of our nomogram can be used to provide individualised estimates of PFS and is available at https://ctc.usyd.edu.au/prognostic-tools/brca-and-platinum-sensitive/.
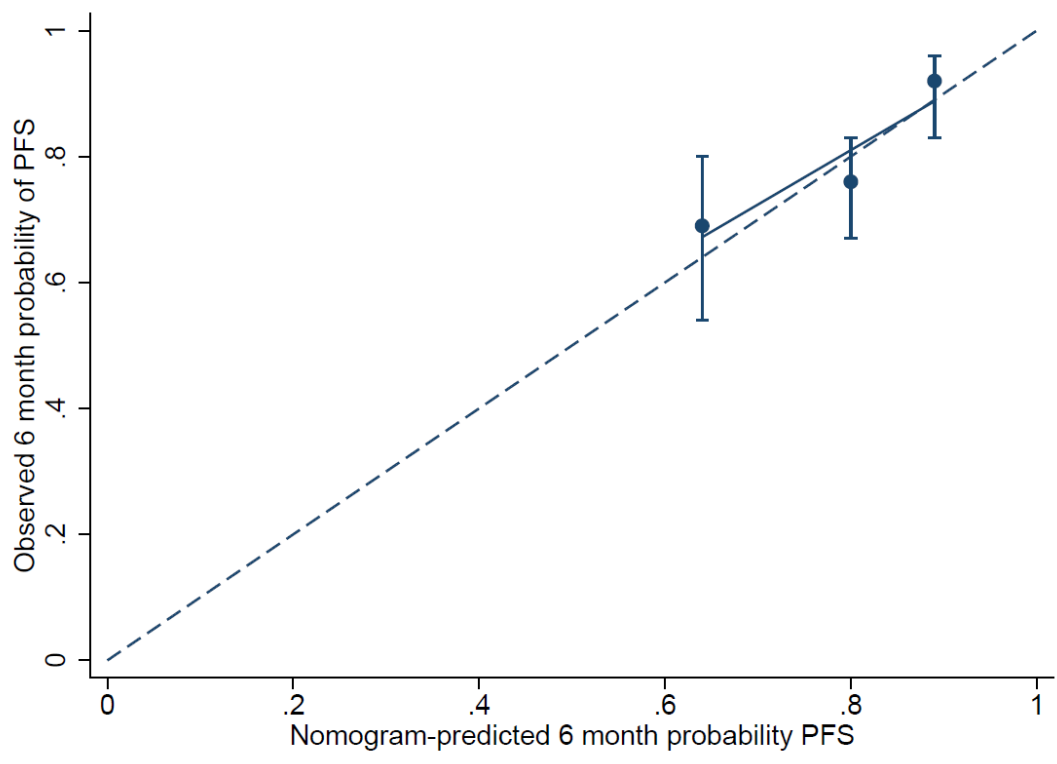
Figure 4 Calibration plots for (A) 6 month (B) 12 month and (C) 18 month PFS in the validation cohort

	Total patients	Median PFS (months)		HR (95% CI)	P interaction
Study 19					
Good risk	40	Olaparib Placebo	NR 8.3	0.35 (0.12-1.09)	
Intermediate risk	54	Olaparib Placebo	NR 4.1	0.17 (0.07-0.41)	0.79
Poor risk	30	Olaparib Placebo	8.1 3.7	0.20 (0.08-0.52)	
SOLO2					
Good risk	85	Olaparib Placebo	NR 7.6	0.12 (0.06-0.26)	
Intermediate risk	133	Olaparib Placebo	13.9 5.4	0.33 (0.21-0.50)	0.10
Poor risk	51	Olaparib Placebo	9.7 2.9	0.19 (0.09-0.41)	

Supplementary Figure 4 Forest plot of risk groups by Study 19 and SOLO2 trials

Discussion

Our nomogram for *BRCA*-mutated PSROC in women undergoing maintenance olaparib therapy or placebo includes four clinicopathological variables (PFI, presence of disease, number of prior platinum lines and CA-125 at randomisation). This tool is easy to use, available in both a paper and online format to facilitate an individualised, risk-stratified approach to prognostication to improve communication, support clinical decision-making and future trial design.

By using a training cohort of *BRCA*-mutated PSROC treated with placebo and validating the nomogram among patients treated with maintenance olaparib therapy, our study provides insight to the natural history of patients with *BRCA*-mutated PSROC with and without olaparib maintenance therapy in each risk group. For patients treated with olaparib compared to untreated patients, we observed an improvement in the median PFS for each model-predicted risk group. Our model provided good discrimination and calibration for classifying risk-stratified prognosis based on quartiles among patients treated with placebo or olaparib.

The clinical significance of three of the nomogram predictors, namely PFI, presence of measurable disease and CA-125, is already well-established for women with recurrent ovarian cancer.(17-20) We hypothesise that multiple lines of prior platinum therapy as a prognostic factor may reflect the increased likelihood of *BRCA* reversion mutations with additional lines of treatment. *BRCA* reversion mutations are thought to be a key mechanism of resistance to PARPi by restoring protein function and homologous recombination repair proficiency; undermining synthetic lethality and ultimately promoting cell survival.(21, 22) While the nomogram predictors, CA-125 and PFI, are consistent with our previous nomogram for unselected patients with PSROC (12), other predictors, such as prior lines of platinum therapy in our current nomogram and white blood count in the previous nomogram,

differed. Our previous nomogram also demonstrated longer median PFS compared to our current nomogram with the difference likely relating to the different time-points in the disease trajectory; we developed our previous nomogram for patients with PSROC at the time of progression about to receive further chemotherapy and our current nomogram after response to chemotherapy and about to commence maintenance PARPi therapy.

The CA-125 cutoff of 25IU/ml used in our nomogram is lower than the standard CA-125 cutoff of 35IU/ml (23) and also reflects the time-point at which prognostication is made. The vast majority of our cohort have CA-125 reading within the normal range following response to platinum-based chemotherapy prior to the commencement of maintenance PARPi therapy. By contrast, we previously developed prognostic nomograms for women with PSROC and platinum-resistant recurrent ovarian cancer at the time of progression with CA-125 cutoff of 100U/ml as the majority of these women had an elevated CA-125.(12, 13, 24)

We did not find patients with *BRCA2*-mutated PSROC to have a more favourable PFS compared to those with *BRCA1* mutation.(25, 26) The survival advantage seen with *BRCA2* mutation is consistent with the findings of other observational studies (27, 28) and likely relates to the distinct and separate roles of *BRCA1* and *BRCA2* in DNA damage repair.(29) Although we observed a non-significant PFS advantage for *BRCA2* over *BRCA1* mutation (HR 0.77, 95% CI 0.52-1.14) in the univariate analysis, multivariable analysis did not identify *BRCA1/2* status as an independent prognostic factor; likely reflecting the small patient numbers within these groups.

Our online tool can support doctor-patient communication surrounding prognosis prior to commencing maintenance PARPi therapy. Patients and clinicians commonly overestimate PFS(30) and OS(31, 32); hindering patients from making important decisions such as advanced care planning. In addition to providing evidence-based estimates of PFS,

our online tool further provides an appropriate level of uncertainty surrounding individual estimates for the typical (half to double the median survival), best-case (≥triple the median) and worst-case (≤one quarter of the median) scenarios.(33) Empowering and enabling clinicians to communicate worst-case scenario increases the likelihood that patients' understanding are concordant with the treating doctors'.(34)

Our study has several strengths. Focusing on clinical applicability, our nomogram comprises of four easily accessible variables. Rather than develop a tool that sums the presence or absence of prognostic factors and equating more adverse factors to poorer outcomes, our nomogram ranks and assigns weights according to the importance of variables relative to each other. By developing our nomogram in the placebo arm, our model has the advantage of performing well among patients with *BRCA*-mutations and PSROC, independent of treatment received and likely would be applicable for other PARPi.

Our study also has several limitations. While this study only examined *BRCA*-mutated, high grade serous PSROC, it is important to test our nomogram in patients with non-*BRCA* mutated PSROC who are now also offered maintenance PARPi therapy. As an increasing number of patients with advanced ovarian cancer with or without *BRCA* mutations receive maintenance PARPi therapy following 1st line therapy, results of trials investigating re-treatment with PARPi therapy such as OREO (NCT03106987) are awaited. If re-treatment with olaparib results in a meaningful clinical benefit, our nomogram will need to be remodeled to take prior PARPi and PARPi-free interval into consideration. Finally, we examined PFS and not OS. PSROC is an incurable disease and it would be important to validate whether the prognostic factors in our nomogram also influence OS.

The ability to reliably risk-stratify patients with *BRCA*-mutations and PSROC using our nomogram has implications for future trial design. Currently, there are several studies exploring combination PARPi therapy with anti-angiogenesis therapy (e.g. NCT03278717) or

immune checkpoint blockade (e.g. NCT02571725 and NCT02485990) in patients with PSROC. However, combination therapy is associated with increased toxicity. For example, among patients with newly diagnosed ovarian cancer, the addition of bevacizumab to olaparib compared to olaparib alone is associated with increased grade 3 or higher adverse events (57% *vs* 39%) and treatment discontinuation (20% *vs* 11.5%).(35, 36) Future trials are needed to determine whether using combination PARPi therapy should be reserved for poor risk patients while those of good or intermediate risk can avoid additive toxicity associated with combination therapy if the impact is small.

Future studies are also needed to assess the prognostic value of molecular biomarkers in order to further individualise risk stratification including presence or absence of *BRCA* reversion mutations in circulating tumor DNA. In a study investigating the molecular and clinical characteristics of long- and short-term responders to maintenance olaparib, Lheureux *et al* observed genetic alterations in the *PTEN* gene in long-term responders but not in the short-term responders, requiring further investigation.(37) By allowing for prospective identification of a poor risk subgroup of patients with limited response to PARPi therapy, our nomogram would facilitate molecular biomarker research to better understand the mechanisms underlying therapeutic resistance. Our nomogram also provides a platform to incorporate additional prognostic molecular markers in the future.

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