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Concordance between CA-125 and RECIST progression in patients with germline *BRCA*-mutated platinum-sensitive relapsed ovarian cancer treated in the SOLO2 trial with olaparib as maintenance therapy after response to chemotherapy

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ABSTRACT

Background: Limited evidence exists to support CA-125 as a valid surrogate biomarker for progression in patients with ovarian cancer on maintenance PARP inhibitor (PARPi) therapy. We aimed to assess the concordance between CA-125 and RECIST criteria for progression in patients with *BRCA* mutations on maintenance PARPi or placebo.

Methods: We extracted data on progression as defined by GCIG CA-125, investigator- and independent central-assessed RECIST from the SOLO2/ENGOT-ov21(NCT01874353) trial. We excluded those with progression other than by RECIST, progression on date of randomisation, and no repeat CA-125 beyond baseline. We evaluated the concordance between CA-125 progression and RECIST progression, and assessed the negative (NPV) and positive predictive value (PPV).

Results: Of 295 randomised patients, 275 (184 olaparib, 91 placebo) were included. 171 patients had investigator-assessed RECIST progression. Of 80 patients with CA-125 progression, 77 had concordant RECIST progression (PPV 96%, 95%CI 90-99%). Of 195 patients without CA-125 progression, 94 had RECIST progression (NPV 52%, 45-59%). Within treatment arms, PPV was similar (olaparib: 95% (84-99%), placebo: 97% (87-100%)) but NPV was lower in patients on placebo (olaparib: 60% (52-68%), placebo: 30% (20-44%)). Of 94 patients with RECIST but without CA-125 progression, 64 (68%) had CA-125 that remained within normal range. We observed similar findings using independent-assessed RECIST.

Conclusions: Almost half the patients without CA-125 progression had RECIST progression, and most of these had CA-125 within the normal range. Regular CT imaging should be considered as part of surveillance in patients treated with or without maintenance olaparib rather than relying on CA-125 alone.

Keywords: CA-125, Ovarian cancer, BRCA mutation, olaparib, Poly(ADP-ribose) Polymerase Inhibitors, Response Evaluation Criteria in Solid Tumors , CT

Introduction

CA-125 is a validated surrogate biomarker for both response and disease progression (PD) in clinical trials in women with ovarian cancer treated with chemotherapy.(1, 2) A rising CA-125 commonly precedes radiological progression with a lead time of 3 to 4 months and is useful in diagnosing PD, particularly in patients with small volume peritoneal carcinomatosis not evident on CT imaging.(1, 2) In routine practice, the majority of patients with ovarian cancer have regular follow-up with CA-125 after completing chemotherapy with CT scans reserved for patients with CA-125 progression and/or symptoms suggestive of progression.(3, 4) In contrast, the majority of clinical trial protocols mandate routine CT scans in addition to CA-125 monitoring for assessment of progression by RECIST as progression-free survival (PFS) is usually the primary endpoint.

The Gynecologic Cancer InterGroup (GCIG) developed standardised criteria to define CA-125 progression for use in clinical trials as a study endpoint.(5, 6) Progression based on CA-125 is defined as at least a doubling of the upper limit of normal if pre-treatment CA-125 is in the normal range or elevated but subsequently normalises, or doubling of the nadir CA-125 value in those with an elevated pre-treatment level. These criteria were developed over 20 years ago in patients on surveillance following first-line chemotherapy.(6)

Over the last decade, multiple studies have demonstrated significantly improved outcomes with maintenance PARP inhibitor therapy in platinum-sensitive recurrent ovarian cancer (PSROC) (7-10) as well as in the 1st line setting (11-13). All these trials used RECIST and not CA-125 criteria to diagnose progression. Maintenance PARP inhibitors are now widely used in clinical practice but there is currently limited evidence to support the use of CA-125 alone to detect progression in patients with *BRCA1/2* mutations undergoing maintenance PARP inhibitor therapy. It is therefore imperative to assess whether CA-125

alone is sufficient for detection of progression or whether these patients should also have regular CT imaging. Rigorous and frequent CT scanning as mandated in clinical trials are rarely implemented in routine practice due to cost and inconvenience. Although a prospective trial has shown no benefit from early initiation of chemotherapy based on CA-125 doubling in asymptomatic women (14), this was in the first-line and not maintenance setting. Regular CT imaging would be useful in detecting progression and facilitating decision-making for future treatment options. To address the question whether CA-125 alone is sufficient for detection of progression or whether patients should also have regular CT imaging, we performed an exploratory study to assess the validity of CA-125 as a surrogate for progression in patients with *BRCA*-mutated PSROC on maintenance therapy with olaparib or placebo following response to chemotherapy. We specifically aimed to determine the concordance between progression as defined by the GCIG CA-125 criteria with Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 using data from the SOLO2/ENGOT-ov21 (NCT01874353) trial (8), and also assessed the interval (lead time) between CA-125 progression and subsequent RECIST PD.

Methods

SOLO2/ENGOT-ov21 (NCT01874353) (8) is a randomised phase 3 study of maintenance therapy with olaparib *vs* placebo in women with *BRCA1/2* mutation-positive PSROC following response to chemotherapy, and showed a significant PFS improvement (hazard ratio (HR) 0.30, 95% CI 0.22-41; $P<0.0001$). Patients were randomly assigned to olaparib (300 mg in tablets twice daily) or placebo until RECIST-defined PD, unacceptable toxicity or the investigator deemed a patient no longer derived benefit from treatment. The

primary end point was investigator-assessed PD by RECIST. Full details have been previously reported.(8)

We extracted and compared data on investigator-assessed tumour PD by RECIST and CA-125 PD by GCIG criteria for the primary analysis, and RECIST data by blinded independent central review (BICR) assessment as a sensitivity analysis. Patients had CT imaging at baseline, every 12 weeks up to 72 weeks, and then every 24 weeks until RECIST PD. Serum CA-125 was measured at baseline and repeated every 4 weeks up to 72 weeks, then every 12 weeks up until RECIST PD. The SOLO-2/ENGOT-ov21 sub-study steering committee approved this study.

To determine the concordance between CA-125 PD and RECIST PD, we categorised patients as: (i) CA-125 and RECIST PD concordant (both GCIG CA-125 and RECIST PD); (ii) CA-125 and RECIST non-PD concordant (both GCIG CA-125 and RECIST non-PD); (iii) CA-125 PD and RECIST non-PD discordant (GCIG CA-125 PD but not RECIST PD); and (iv) CA-125 non-PD and RECIST PD discordant (RECIST PD but without GCIG CA-125 PD). Patients were considered CA-125 and RECIST PD concordant if the initial CA-125 doubling occurred prior to or up to 7 days after RECIST PD, and was confirmed by a subsequent CA-125 measurement at least one week apart. Patients were excluded if they had clinical progression without evidence of RECIST PD, PD on date of randomisation or no repeat CA-125 beyond baseline. Patients were also excluded if they had RECIST PD but normal CA-125 measurements and did not have a CA-125 measurement within five weeks before or four weeks following RECIST PD. Patients without a repeat CA-125 measurement to confirm PD were excluded from the primary analyses but included in the sensitivity analyses. (Figure 1)

We summarised baseline categorical variables as frequency (percentage) and continuous variables as median (IQR); assessing differences between groups using the $\chi 2$ test and appropriate non-parametric methods, respectively. We assessed the interval (lead time) between CA-125 progression and subsequent RECIST PD. For patients with RECIST-only PD versus patients with both CA-125 and RECIST PD, we compared the differences in PFS (the interval between randomisation date and date of first PD), and PFS2 (the interval between initial RECIST PD to subsequent RECIST PD). To assess the concordance of CA-125 PD with RECIST PD, we computed the positive predictive value (PPV), which is defined as the probability that patients with CA-125 PD also had RECIST PD; and the negative predictive value (NPV), defined as the probability that patients without CA-125 PD also did not have RECIST PD.

Amongst those with RECIST PD but normal CA-125 measurements, we further subdivided into (i) 'rising CA-125' (CA-125 at time of RECIST PD >50% baseline); (ii) 'stable CA-125' (CA-125 within the range of up to 15% below and ≤50% above baseline); or (iii) 'falling CA-125' (CA-125 <15% below baseline). We displayed the CA-125 values of these three groups as spider plots and summarised the median (IQR). We also sub-classified RECIST PD as 'early PD' (≤12 weeks after randomisation) or 'late PD' (>12 weeks), and compared the concordance separately in these two groups. We assessed for differences between the pattern of CA-125 PD and site (presence of peritoneal disease or ascites *vs* solid organ without peritoneal disease *vs* nodal-only *vs* other) as well as type of RECIST PD (new lesion *vs* target lesion *vs* non-target lesion *vs* combination).

All analyses were exploratory and not adjusted for multiple testing. All *p*-values were two-sided with $P < 0.05$ considered statistically significant.

Results

Of 295 patients randomised in the SOLO-2/ENGOT-ov21 trial (Figure 1), 20 were excluded, leaving 275 eligible patients (184 olaparib, 91 placebo) in the primary analysis.

Of those with RECIST PD (n=171), 77 also had GCIG CA-125 PD but 94 did not. 104 of 171 with RECIST PD had second RECIST PD, of whom 54 had GCIG CA-125 and 48 did not.

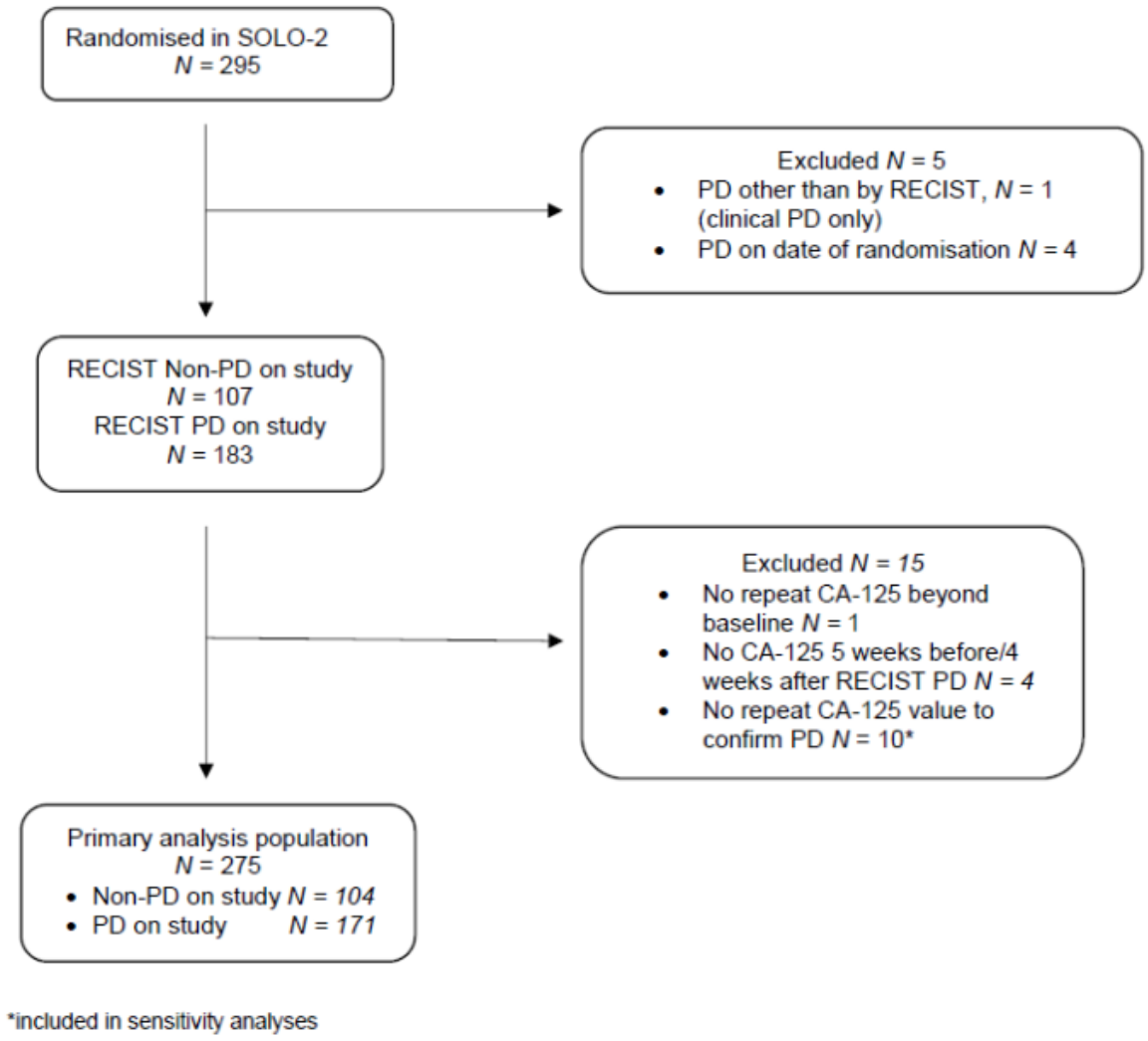

Fig 1. Study population

A greater proportion of patients with RECIST-only PD had a baseline CA-125 within normal range than those with PD defined by both RECIST and CA-125 (94% vs 69%;

p<0.001). The other baseline characteristics did not differ significantly between the patient groups. (Table 1, Supplementary Table 1) Median PFS was similar for patients with RECIST-only PD (8.1 months, 95% CI 5.5-8.6) and with both CA-125 and RECIST PD (6.9 months, 95% CI 5.5-8.1; *p*=0.32). Median PFS2 was also similar for patients with RECIST-only PD (6.7 months, 95% CI 4.8-9.1) and with both CA-125 and RECIST PD (6.9 months, 95% CI 5.7-7.9).

Table 1. Baseline characteristics

Characteristic, *n* (%)	RECIST-only progression[c] (*n* = 94)	CA-125 and RECIST progression[d] (*n* = 77)	*P*-value*	No RECIST progression (n=104)	All patients (*n* = 275)
Median age, years (IQR)	57 (51-63)	55 (49-63)	0.31	56 (52-63)	56 (51-63)
ECOG performance status					
0	82 (87)	61 (79)	0.16	83 (80)	226 (82)
1	12 (13)	16 (21)		21 (20)	49 (18)
Primary tumour location					
Ovary	82 (87)	64 (83)	0.45	88 (85)	234 (85)
Fallopian tube or primary peritoneal	12 (13)	13 (17)		16 (15)	41 (15)
Histology type					
Serous	87 (93)	70 (91)	0.93	93 (89)	250 (91)
Endometrioid	6 (6)	6 (8)		5 (5)	17 (6)
Mixed	1 (1)	1 (1)		6 (6)	8 (3)
Patients with >2cm target lesions at baseline	27 (29)	15 (19)	0.33	0 (0)	42 (25)
Presence of ascites or peritoneal disease at baseline	23 (24)	22 (29)	0.54	9 (9)	54 (20)
Response to previous platinum therapy[a]					
Complete response	35 (38)	29 (38)	0.96	67 (64)	131 (48)
Partial response	57 (62)	48 (62)		37 (36)	142 (52)
Number of previous platinum-based regimens					
2	46 (49)	48 (62)	0.14	68 (65)	162 (59)
3	28 (30)	20 (26)		27 (26)	75 (27)
4	20 (21)	9 (12)		9 (9)	38 (14)
Platinum-free interval					
6-12months	41 (44)	42 (55)	0.16	23 (22)	106 (39)
>12 months	53 (56)	35 (45)		81 (78)	169 (61)
Baseline CA125					
≤35 IU/ml	88 (94)	53 (69)	**<0.001**	96 (92)	237 (86)
>35 IU/ml	6 (6)	24 (31)		8 (8)	38 (14)
Median baseline CA125, (IQR)	9 (7-18)	22 (12-38)	**<0.0001**	10 (7-17)	12 (7-23)
Median LDH, U/L (IQR)[b]	209 (184-242)	222 (193-273)	0.06	217 (180-260)	215 (187-260)

[a] n=2 missing; [b] n=5 missing; [c] Patients with RECIST progression but without CA-125 progression; [d] Patients with both CA-125 and RECIST progression;
* *P*-value for differences between RECIST-only PD *vs* CA-125 and RECIST PD

The median interval between CA-125 PD and RECIST PD was 51 days (range 6 to 218). The median interval was shorter for those on placebo (median 32 days, range 6 to 218) than on maintenance olaparib (median 59 days, range 19 to 190).

Of 275 eligible patients, 80 (29%) had CA-125 PD and 195 (71%) did not have CA-125 PD. Of the 80 patients with CA-125 PD, 77 had concordant RECIST PD, resulting in a PPV of 96% (95% CI 90-99%). Of the 195 patients without CA-125 PD, 94 had RECIST PD and 101 did not have RECIST PD, resulting in a NPV of 52% (95% CI 45-59%; Table 2a). When we examined the data within each treatment arm, we observed similar findings for PPV (olaparib: 95% (95% CI 84-99%), placebo: 97% (95% CI 87-100%)), but NPV was lower in patients on placebo (30%, 95% CI 20-44%) than olaparib (60%, 95% CI 52-68%; Table 2b & 2c).

Table 2. (a) Concordance between RECIST-defined disease progression and disease progression according to CA-125 criteria, (b) olaparib, and (c) placebo treatment arm

(a)

Disease status by CA-125 criteria	RECIST-defined disease progression (*n* = 171)	No RECIST-defined disease progression (*n* = 104)	Total (*n* = 275)
Progressive disease, *n* (%)	77 (96%)	3 (4%)	80
Non-progressive disease, *n* (%)	94 (48%)	101 (52%)	195

(b)

Disease status by CA-125 criteria	RECIST-defined disease progression (*n* = 97)	No RECIST-defined disease progression (*n* = 87)	Total (*n* = 184)
Progressive disease, *n* (%)	40 (95%)	2 (5%)	42
Non-progressive disease, *n* (%)	57 (40%)	85 (60%)	142

(c)

Disease status by CA-125 criteria	RECIST-defined disease progression (*n* = 74)	No RECIST-defined disease progression (*n* = 17)	Total (*n* = 91)
Progressive disease, *n* (%)	37 (97%)	1 (3%)	38
Non-progressive disease, *n* (%)	37 (70%)	16 (30%)	53

We performed a sensitivity analysis by including the additional 10 patients with a CA-125 rise but no repeat measurement to confirm PD by GCIG criteria. Similar PPV (97%; 95% CI 91-99%) and NPV (52%; 95% CI 45-59%) were demonstrated when compared to the

patient cohort in the primary analysis. (Supplementary Table 2) In a further sensitivity analysis of RECIST outcome by BICR, we found similar findings with NPV lower in patients on placebo (37%, 95% CI 26-50%) than olaparib (72%, 95% CI 64-79%). (Supplementary Table 3)

Of the 94 patients with RECIST PD but without CA-125 PD, 64 (68%) had CA-125 levels that always remained within the normal range, while 28 (30%) had rising and elevated CA-125 that did not meet GCIG criteria for CA-125 PD. In two patients (2%), CA-125 levels decreased. Of the 64 patients with CA-125 levels within the normal range, 28 (44%) had rising CA-125, 28 (44%) had stable CA-125 and 8 (13%) had falling CA-125. (Figure 2) Further, among these 94 patients, 39 (41%) had hepatic or splenic metastases at the time of RECIST PD, of whom half had CA-125 within the normal range. A greater proportion of patients with visceral recurrence but without peritoneal disease had CA-125 non-PD (68%) than patients with the presence of peritoneal disease (48%), nodal recurrence only (41%) or other site of recurrence (61%). (Supplementary Table 4) Similarly, a greater proportion of patients with target lesion only RECIST PD had CA-125 non-PD than patients with RECIST PD due to a new lesion, non-target lesion or a combination of new, target and non-target lesion. (Supplementary Table 5) Discordance of patients not meeting the criteria for GCIG CA-125 PD prior to or within 7 days of RECIST PD was similar in patients with early or late PD (56% *vs* 55%, respectively; $p = 0.96$).

A minority (n=3, 1%; n=8, 3%) of patients had CA-125 PD without RECIST PD as per investigator and BICR assessment, respectively.

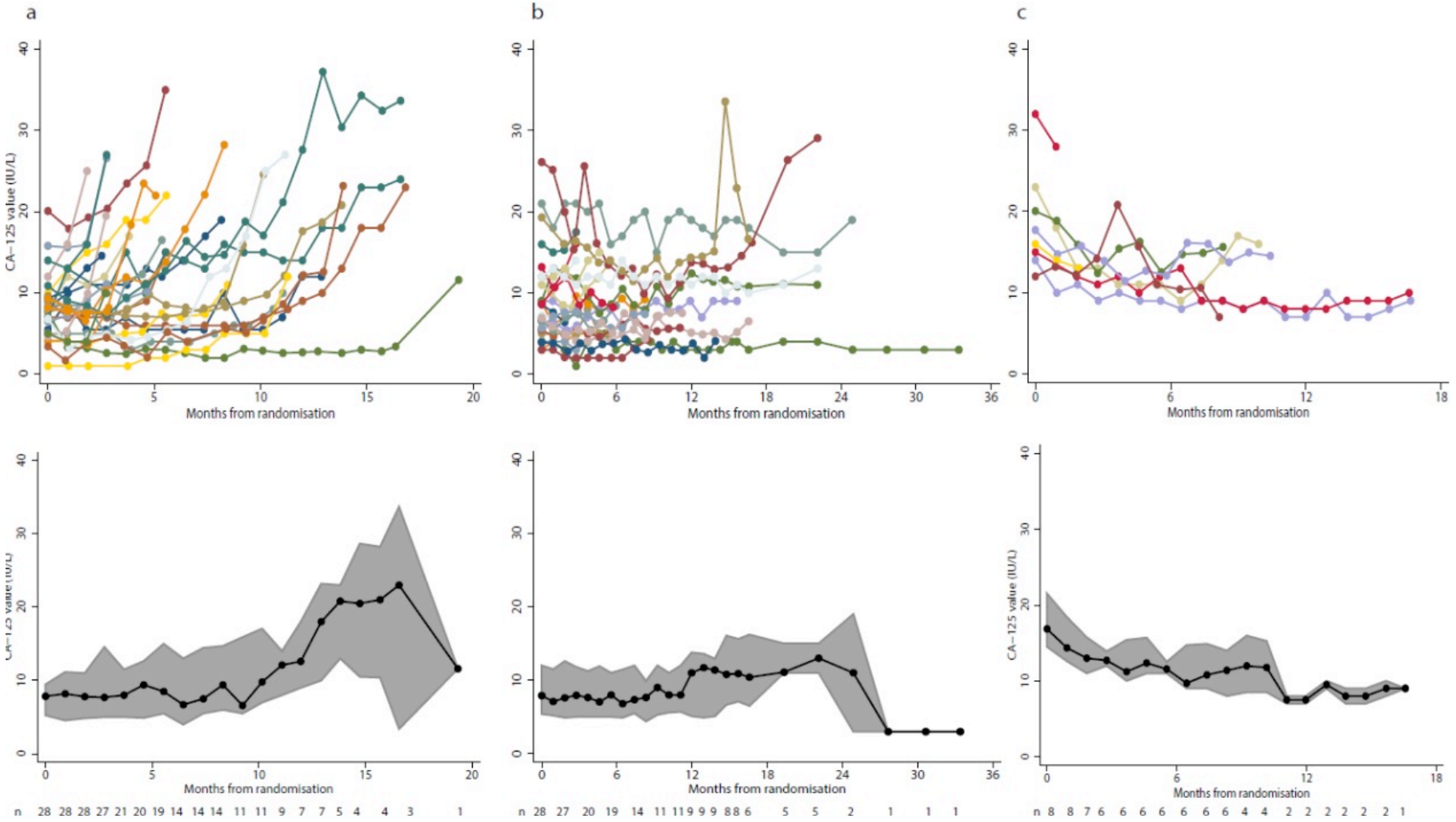

Fig 2. Spider plots and median (IQR) for patients with RECIST PD but CA-125 within the normal range and (a) rising CA-125, (b) stable CA-125, and (c) falling CA-125. Top row: Each line represents an individual patient and dots representing CA-125 values; Bottom row: Dots represent the median CA-125 value at the particular time-point with the shaded area representing the associated interquartile range

Discussion

Our analysis of the SOLO2/ENGOT-ov21 trial found a strong concordance between GCIG CA-125 PD and RECIST PD but poor concordance between CA-125 non-PD and RECIST progression. Of those without GCIG CA-125 PD, approximately 1 in 3 patients on maintenance olaparib and 2 of 3 on placebo had RECIST PD, and most of these had CA-125 readings in the normal range. Of patients without GCIG CA-125 PD but with RECIST PD, approximately 40% had hepatic or splenic progression at RECIST PD, and half of these still had normal range CA-125 readings. Most patients with RECIST-only PD (94%) had normal baseline CA-125.

CA-125 elevation precedes radiological PD in approximately 70% of ovarian cancer patients with a median lead time of 2 to 4 months.(5, 6, 15) In several validation studies of large trials in PSROC treated with chemotherapy (6, 16), CA-125 doubling was demonstrated to have a high PPV of 98-99%, accurately predicting for PD. Furthermore, the magnitude of treatment effect in PSROC studies was consistent when using either CA-125 or radiologic criteria for progression, supporting CA-125 as an appropriate surrogate endpoint.(16, 17) Based on these earlier studies, CA-125 monitoring is widely used for surveillance following chemotherapy.(3, 4) However, the low NPV of CA-125 is less widely appreciated, with NPV ranging from 46% to 75%. (6, 16) In one study (16) of 239 patients without CA-125 progression, 128 (54%) had clinical progression and 111 did not, resulting in a NPV of 46%. In other studies, the discordance between CA-125 non-PD and RECIST PD was approximately 60%.(18, 19) Detecting RECIST PD is essential to avoid futile treatment and unnecessary costs associated with maintenance therapy (20), and identify patients for alternative therapy.(21)

Our study confirmed a high PPV but low NPV in patients with *BRCA*-mutation positive PSROC treated with or without maintenance olaparib therapy. In our study, 96% of patients with CA-125 PD had radiological PD and the median lead time was 51 days, in keeping with the evidence that GCIG CA-125 PD has a high PPV for RECIST PD.(6, 22) However, up to approximately half of the patients without GCIG CA-125 PD had RECIST PD (48% by investigator-review, 38% BICR); highlighting the low NPV of CA-125. Our finding of a higher NPV for those on olaparib (60% by investigator-review, 72% BICR) compared with placebo (30% by investigator-review, 37% BICR) reflects the lower proportion of RECIST PD in patients on olaparib (53%) compared to placebo (81%). Despite the higher NPV, approximately 1 in 3 patients on olaparib without GCIG CA-125 PD still had RECIST PD, questioning the value of CA-125 in assessing PD in this population.

The low NPV in our study may be due to a stringent GCIG criteria for CA-125 PD, which requires a confirmatory reading. In clinical practice, a rising CA-125 that does not necessarily meet the GCIG criteria may trigger CT imaging. However, by doing so, we found that 40% of patients with RECIST PD but without rising CA-125 would still be missed. The low NPV may also reflect heterogeneous tumour biology, particularly a subgroup of tumours or metastatic deposits that do not secrete CA-125.(23) In our study, a greater proportion of patients with peritoneal recurrence had concordant CA-125 and RECIST PD compared to those with solid organ recurrence without peritoneal disease. While we did not observe a significant difference in median PFS or PFS2 for patients with RECIST-only PD and PD by both RECIST and CA-125 to suggest different tumour biology between the two groups, the majority of patients with RECIST-only PD had CA-125 levels that always remained normal; hence CA-125 may not be evaluable in these patients. Therefore, it is important to appreciate that CA-125 not meeting GCIG criteria for PD does not preclude PD and may provide false reassurance.

Our study has several strengths. Rather than limit the concordance of CA-125 to only patients with RECIST-PD, as presented in a prior study (19), we assessed the concordance in all patients, with and without RECIST-PD. Because it is not possible to predict which patients will have RECIST PD at baseline, including patients without RECIST-PD strengthens our analysis, and allows us to estimate NPV and PPV to consider the impact on clinical decision-making. Further, by assessing patients treated with placebo and demonstrating a similar high discordance of CA-125 non-PD among those with RECIST PD, our findings are potentially generalisable to *BRCA1/2* mutant patients in other treatment settings. While we used investigator-assessed RECIST-defined PD in our primary analyses, which is reflective of routine clinical care, we also included BICR-defined RECIST PD in the sensitivity analyses. The similar concordance between CA-125 and BICR- and investigator-assessed RECIST PD lends validity to our findings.

We also acknowledge the limitations of this study. The data used for analysis were derived from the SOLO2/ENGOT-ov21 trial, which was not prospectively designed to examine the surrogate properties of CA-125. While this study only examined olaparib *vs* placebo in the *BRCA*-mutated, relapse setting, it is important to corroborate our findings in the first-line maintenance setting, with different PARP inhibitors and also in non-*BRCA* mutation carriers.(11-13) Furthermore, the primary outcome measure in this trial was investigator-assessed RECIST-defined PD, and CA-125 was not routinely measured after RECIST PD; limiting our ability to assess those with CA-125 PD following RECIST PD. The cost-effectiveness of CT surveillance remains unknown and should be an area of future research.

In conclusion, we observed poor concordance between CA-125 non-PD and RECIST progression. Approximately 1 in 3 patients on maintenance olaparib and 2 of 3 on placebo without CA-125 PD had RECIST PD and the majority of these had normal range CA-125 readings. Our study findings raise the need to consider regular imaging as part of surveillance in patients with *BRCA*-mutation positive PSROC treated with or without maintenance PARP inhibitor therapy rather than relying on CA-125 alone.

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Author's disclosures of potential conflicts of interest

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