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Utility of serum CA-125 monitoring in patients with ovarian cancer undergoing immune checkpoint inhibitor therapy

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HIGHLIGHTS

- In ovarian cancer patients treated with ICI, an early increase in CA-125 may not necessarily represent disease progression
- The majority of patients who achieved clinical benefit had an increase in CA-125 levels.
- Patients who achieved clinical benefit had a smaller % increase in CA-125 within 12 weeks.
- Physicians should proceed with caution when using CA-125 levels to guide ICI treatment decisions.

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ABSTRACT

Objective. This study aimed to evaluate the utility of serum cancer antigen-125 (CA-125) levels to monitor patients with epithelial ovarian cancer (EOC) undergoing immune checkpoint inhibitor (ICI) therapy.

Method. This was a single-center retrospective review of all patients with EOC who were treated with ICI therapy from January 2013 to May 2017. This study compared the percentage change in baseline CA-125 in patients who had clinical benefit, defined as complete response, partial response, or stable disease by RECIST 1.1, with duration ≥24 weeks, versus those who did not. The groups were compared by Wilcoxon rank-sum test.

Results. Fifty-nine (66%) of 89 patients who underwent ICI therapy had CA-125 data at baseline and during treatment. Of those who derived clinical benefit, 11/15 (73%) experienced an increase in CA-125 from baseline to end of treatment. Of those who did not derive clinical benefit, 36/44 (82%) experienced a CA-125 increase ($p = 0.48$). The average % increase from baseline to within 12 weeks of treatment initiation for patients with and without clinical benefit was 34% and 195%, respectively ($p = 0.008$).

Conclusion. Our analysis demonstrates a statistically significant difference in the magnitude of increase in CA-125 levels within the first 12 weeks of treatment between patients who achieved clinical benefit and those who did not. However, both groups of patients were equally likely to experience an increase in CA-125 within 12 weeks. These findings suggest that physicians should apply caution when using early CA-125 data to guide treatment decisions for patients with EOC undergoing ICI therapy.

1. Introduction

Epithelial ovarian cancer (EOC) is the fifth most common cause of cancer-related death, as well as the leading cause of death due to gynecologic malignancy, among women in the United States [1]. Due to the lack of effective screening options for the early detection of EOC and the asymptomatic nature of early-stage disease, the majority of patients are diagnosed with advanced disease and almost inevitably experience disease recurrence after treatment, representing a significant unmet need in the care of these patients [2]. Immune checkpoint inhibitors (ICIs), such as agents targeting the programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) pathway, have been explored in EOC, but with limited efficacy [3,4]. Furthermore, early, and often symptomatic, progression of EOC during ICI therapy necessitates the identification of early markers of progression or response that could inform whether therapy should be continued [5].

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In recurrent/advanced EOC, assessment of response to standard cytotoxic therapy is driven by a composite of the patient's clinical status, cancer antigen-125 (CA-125) tumor marker levels, and radiographic imaging, usually with a computed tomography (CT) scan [6]. In the arena of ICIs, with the potential for slow time to response and/or pseudo-progression, the accurate and timely determination of response to therapy is even more complex and is driven primarily by radiologic response. Data pertaining to the role of CA-125 in the setting of ICIs are limited. It is possible that during progression of disease on ICI therapy CA-125 rises, as it sometimes does with standard chemotherapeutic agents. However, the concordance of the change in CA-125 with response to chemotherapy has shown mixed results in research studies, despite its widespread use in clinical practice [7,8].

It is also possible that an inflammatory response to ICIs may lead to a rise in CA-125 in the absence of true progression of disease. This leads to the question of whether CA-125 can or should be used as a predictive marker for patients with EOC undergoing ICI therapy. This study aims to assess the predictive role of changes in CA-125 levels for patients on ICIs.

2. Methods

Patients who underwent ICI therapy for non-mucinous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (EOC) from January 2013 to May 2017 were identified (Fig. 1). Rare ovarian cancer histologic subtypes (small cell, neuroendocrine, and germ cell) were excluded from the analysis. Patients who received an ICI in combination with cytotoxic chemotherapy were excluded due to potentially confounding changes in CA-125. Patients who discontinued therapy prior to 12 weeks due to toxicity were excluded from the analysis. Approval to conduct this study was received from the Memorial Sloan Kettering Cancer Center (MSK) Institutional Review Board.

Immunotherapy targets of interest included PD-1, PD-L1, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and lymphocyte-activation gene 3 (LAG-3) alone or in combination therapy. This study looked at clinical benefit rate (CBR), defined as best overall response of complete response (CR), partial response (PR), or stable disease (SD) that persisted for ≥24 weeks. Patients were included in the study if they had the following data in their electronic medical records:

- A baseline serum CA-125 measurement within 6 weeks prior to the first day of therapy
- Two or more available CA-125 measurements from between 6 weeks pre-treatment until 1 week after end of treatment

The majority of patients were treated on clinical trial protocols, of which some did not require CA-125 measurement; therefore, the timing of the CA-125 data was not uniform and was at the discretion of the treating physician. The change of CA-125 from pre-treatment to end of treatment was calculated as a percentage. A descriptive plot was created to demonstrate the change in CA-125 levels, as shown in Fig. 2a and b.

We analyzed % change in CA-125 levels from baseline to end of treatment and from baseline to 12 weeks of ICI therapy in those who achieved clinical benefit and those who did not. The CA-125 value used for the end-of-treatment calculation was the value obtained closest to end of treatment. The CA-125 value used for the 12-week calculation was the value obtained closest to 12 weeks but not after 12 weeks.

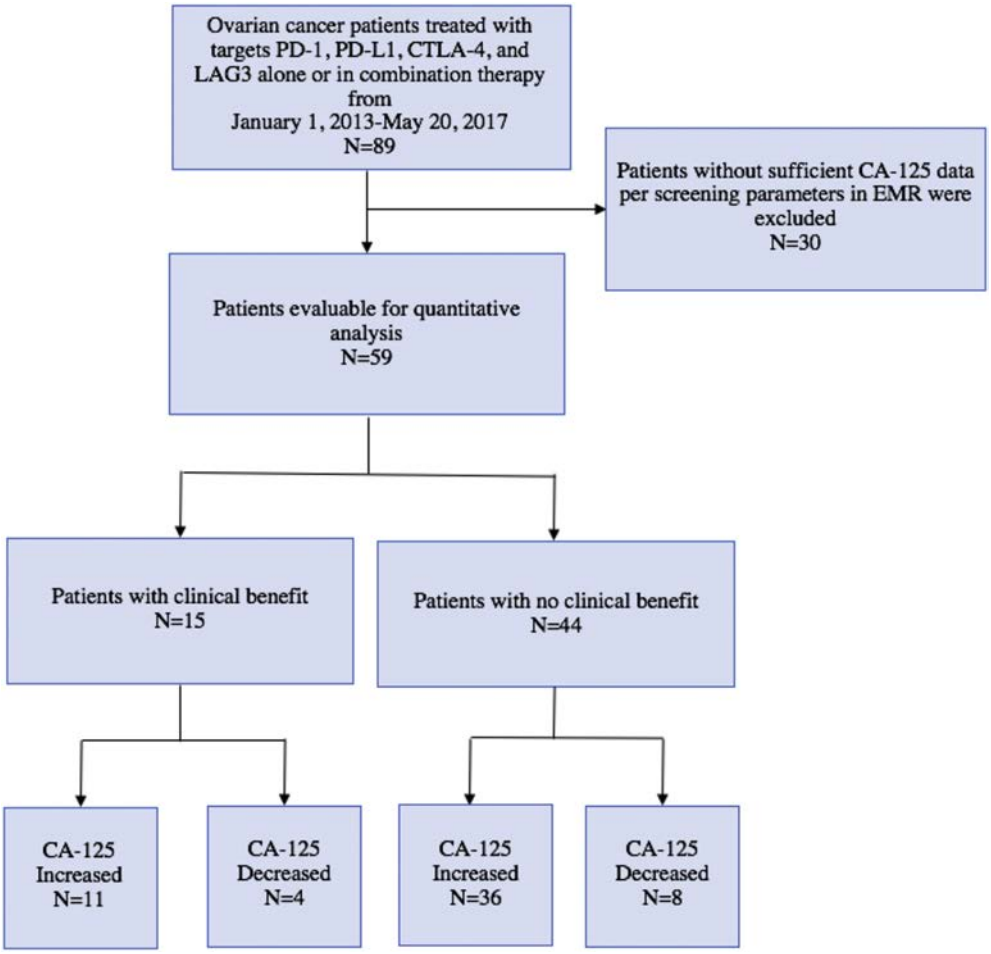

Fig. 1. CONSORT diagram.

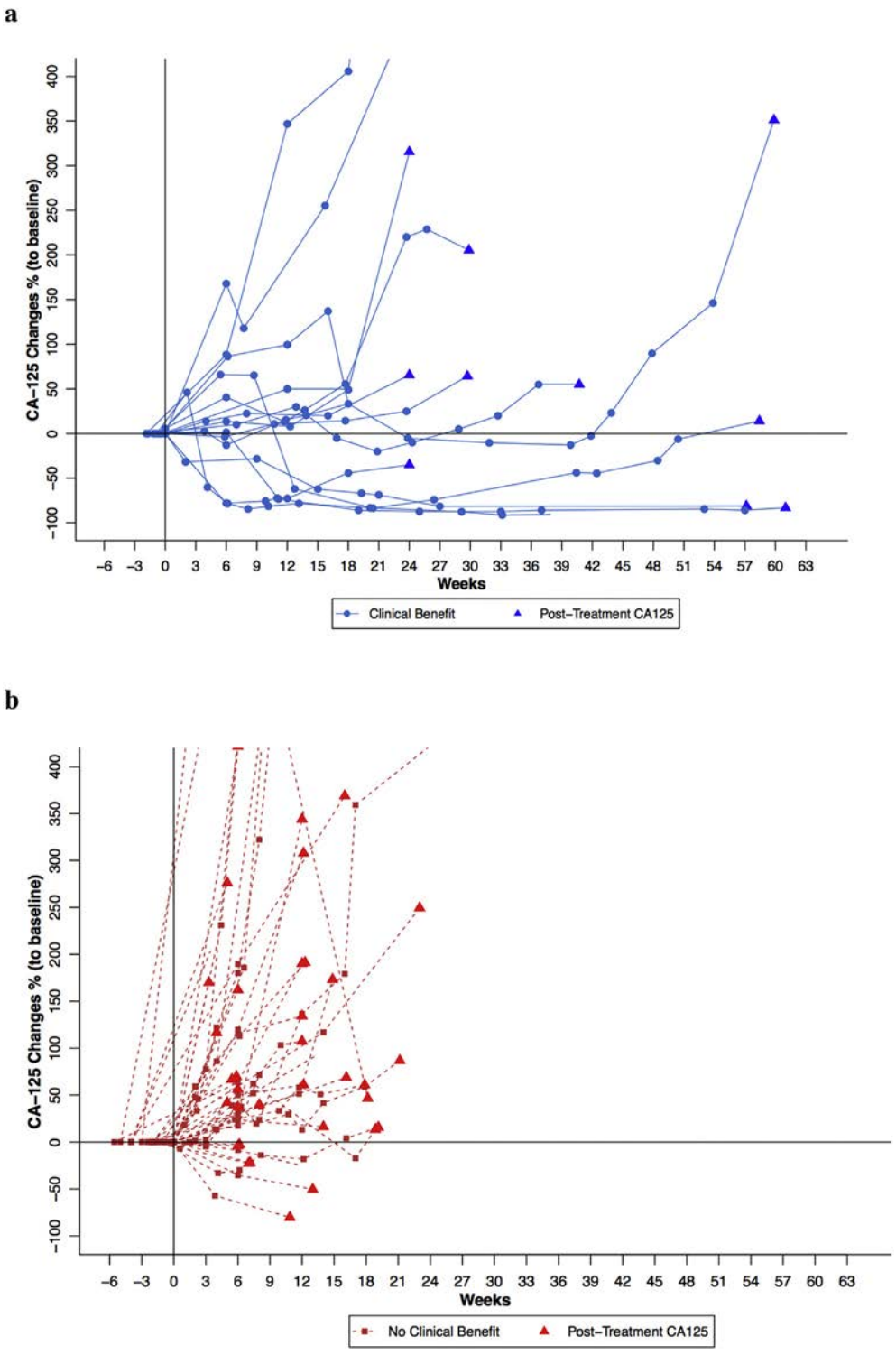

Fig. 2. a. CA-125 trend for patients who achieved clinical benefit, $n = 15$. All available CA-125 data were plotted to represent the change in CA-125 in patients who achieved clinical benefit. Post-treatment values are noted by a triangle. b. CA-125 trend for patients who did not achieve clinical benefit, $n = 44$. All available CA-125 data were plotted to represent the change in CA-125 in patients who did not achieve clinical benefit. Post-treatment values are noted by a triangle.

Wilcoxon rank-sum tests were performed for comparisons between the two subgroups. R3.2 was utilized for all analyses. $p < 0.05$ was considered statistically significant.

3. Results

Of 89 patients treated with an ICI at a single institution, 59 (66%) met the inclusion criteria and were evaluable for analysis (Fig. 1). The baseline characteristics of these patients are summarized in Table 1. The majority of patients ($n = 51$; 86%) had high-grade serous carcinoma; 5 patients (8.5%) had clear cell carcinoma. Almost all patients (93%) had been treated on prospective clinical trials, none of which mandated the timing of CA-125 measurement. Of the 59 patients on study, 15 (25%) achieved clinical benefit and 44 (75%) did not achieve clinical benefit while on ICI therapy. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.

Table 1
Baseline patient characteristics.

Clinical characteristic	Whole cohort N = 59	ICI clinical benefit ≥24 weeks n = 15 (25%)	No ICI clinical benefit <24 weeks n = 44 (75%)
Median age at start of therapy, years (range)	60 (36–74)	58 (36–69)	60 (42–74)
Histology			
High-grade serous	51 (86%)	10 (67%)	41 (93%)
Clear cell carcinoma	5 (8.5%)	3 (20%)	2 (4.5%)
Endometrioid carcinoma	1 (1.7%)	1 (6.7%)	
Low-grade serous	1 (1.7%)	1 (6.7%)	
Mixed serous and endometrioid	1 (1.7%)		1 (2.3%)
ECOG screening			
0	38 (64%)	7 (47%)	31 (71%)
1	21 (39%)	8 (53%)	13 (30%)
Median number of prior lines of therapy (range)	4 (2−12)	4 (2–7)	4 (2–12)
CA-125 at screening, U/mL			
Median	276	313	270
Minimum	4	4	10
Maximum	8547	1841	8547

ICI, immune checkpoint inhibition; ECOG, Eastern Cooperative Oncology Group.

The median number of prior lines of therapy for both cohorts was 4 (range, 2–12).

The cohort of patients who achieved clinical benefit included 3 of the 5 patients with clear cell carcinoma, representing 20% of the benefitting patients. Of the 5 patients with clear cell carcinoma, all had abnormally elevated baseline CA-125 levels. Sixty-seven percent of the patients who achieved clinical benefit had disease of high-grade serous histology. Of the patients who did not achieve clinical benefit, 93% had disease of high-grade serous histology.

Baseline serum CA-125 measurement recorded within 6 weeks of the first day of therapy had a median measurement time of 1 day (range, 0–39). Sixty-seven percent of patients had a baseline serum CA-125 level obtained within 7 days of initiating therapy. Baseline CA-125 levels are shown in Fig. 3. The median pre-treatment CA-125 level was 276 U/mL (range, 4–8785 U/mL). The median CA-125 level at baseline was 313 U/mL in the clinical benefit group compared to 270 U/mL in the non-clinical benefit group. Only 9 patients (15%) had pre-treatment values in the normal range (<35 U/mL)—3 (20%) in the clinical benefit group and 6 (14%) in the non-clinical benefit group. All patients had measurable disease on CT scan per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [9].

Eleven (73%) of the 15 patients who achieved a clinical benefit experienced an increase in CA-125, compared with 36 (82%) of the 44 patients who did not achieve a clinical benefit ($p = 0.48$) (Table 2). The average change in CA-125 level from baseline to end of treatment was +130% in the patients who achieved a clinical benefit and 424% in those who did not achieve a clinical benefit. The median day of obtaining end-of-treatment measurement of CA-125 was on the last day of treatment, and 64% of the patients had end-of-treatment values obtained within 7 days of their last treatment. One patient did not have a CA-125 measurement obtained within 12 weeks of initiating therapy and is not included in the calculation.

The average % change from baseline to within 12 weeks of initiating ICI treatment was +34% (range, −81% to 347%) for the clinical benefit group versus +195% (range, −80% to 1233%) for the non-clinical benefit group. The % change in CA-125 levels within 12 weeks was statistically significant, with a Wilcoxon rank-sum test yielding $p = 0.008$. The average change from baseline to end of treatment was not statistically significant ($p = 0.185$). The qualitative difference in trends of CA-125 in patients who achieved clinical benefit versus those who did not is depicted in Fig. 2a and b, respectively.

4. Discussion

Our study demonstrates that patients who achieve clinical benefit often experience an increase in CA-125 within 12 weeks of initiating ICI therapy and from baseline to end of treatment; this trend was similar in patients who did not achieve clinical benefit. Additionally, some patients who did not achieve a clinical benefit on an ICI experienced a decline in CA-125. The degree of CA-125 increase, however, was lower in the patients who eventually achieved clinical benefit, perhaps suggesting that specific cutoffs could be potentially implemented to identify the

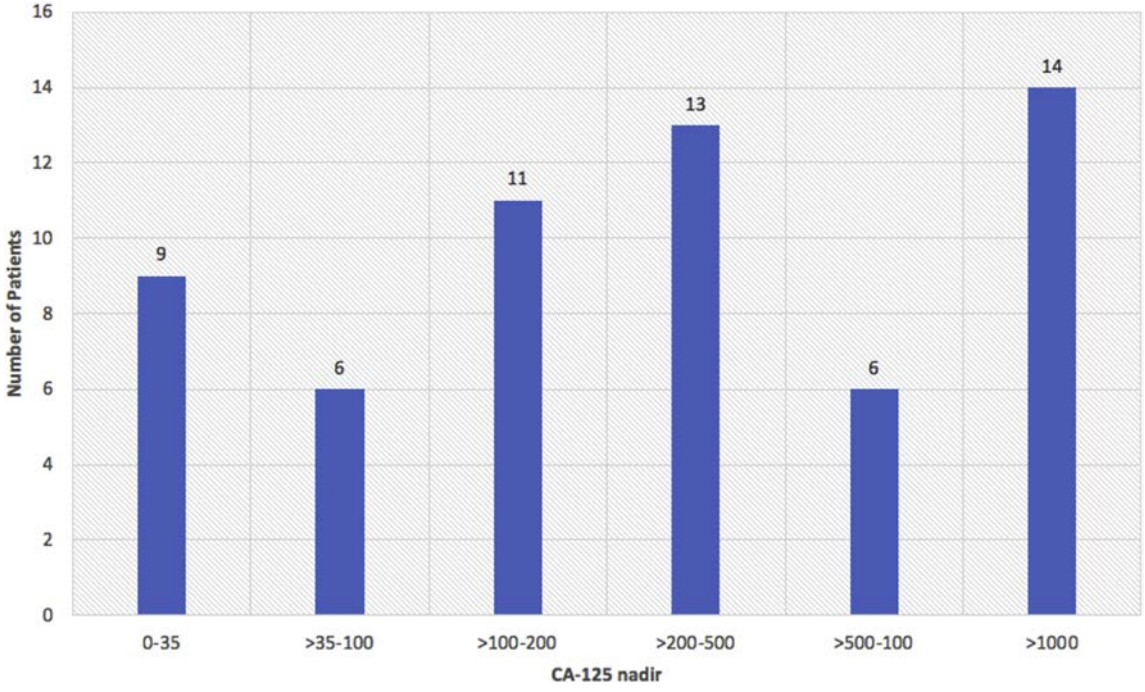

Fig. 3. Baseline CA-125 levels, $N = 59$. Distribution of baseline CA-125 levels among patients.

Table 2
Change in CA-125 levels.

	Total N = 59	ICI clinical benefit n = 15	No ICI clinical benefit n = 44	p*
Patients with % change decrease from baseline to EOT	12 (20%)	4 (27%)	8 (18%)	
Patients with % change increase from baseline to EOT	47 (80%)	11 (73%)	36 (82%)	
Average % change from baseline to EOT	+349%	+130%	+424%	
Median % change from baseline to EOT	+87%	+55%	+112%	
% change from baseline to EOT				0.185
	Total N = 58	Clinical benefit n = 15	No clinical benefit n = 43	p
Average % change from baseline to within 12 weeks	+154%	+34%	195%	
Median % change from baseline to within 12 weeks	+59%	+14%	+70%	
% change from baseline to within 12 weeks				0.008

ICI, immune checkpoint inhibition; EOT, end of treatment.
* Wilcoxon rank-sum test.

patients who are less likely to benefit. Most of the patients in this study had high-grade serous ovarian cancer (86%), and given the small numbers of other cancer subtypes, it was not possible to control for histology in this study. EOCs with clear cell histology are less likely to express CA-125, and these patients often have lower CA-125 levels compared to patients with EOC of other histologic subtypes [10,11]. There were 5 patients with clear cell carcinoma in this study, all of whom had abnormally elevated CA-125 levels.

Immune checkpoint blockade has demonstrated modest response rates among patients with ovarian cancer; however, select patients have achieved lasting clinical benefit with this approach [4,12,13]. CA-125 remains the only tumor marker routinely used in EOC despite limitations in its use and prognostic value in cytotoxic therapy. Infiltration of immune cells into the tumor can cause a transient growth in tumor on imaging [14]; by a similar mechanism, it is conceivable that immune infiltration could lead to a rise in CA-125. An increase in CA-125 could be driven by an inflammatory state, as CA-125 can similarly increase systemic cytokines [15]. Due to the variability in patterns of responses to ICIs, specific imaging guidelines and immune-related response evaluation criteria in solid tumors (irRECIST) were developed to account for the differing responses to immune therapeutics compared to chemotherapeutics [16]. However, there are limited data pertaining to the role and dynamics of CA-125 in patients with ovarian cancer undergoing ICI treatment.

In a study of the anti–PD-L1 antibody avelumab in recurrent ovarian cancer, the majority of patients (79.5%) experienced an increase in CA-125 level [4]. Notably, of the 12 patients who achieved an objective response, 7 experienced a decrease in CA-125 levels from baseline; response was unknown in the other 5 patients [4]. In a phase II study of pembrolizumab in recurrent ovarian cancer, the median CA-125 change from baseline was −69.1% for responders and +15.3% for those with SD [12]. The change from nadir for patients with progression of disease was +60.2% [12]. A noteworthy case documents a patient with EOC who had a decrease in CA-125 from baseline after ipilimumab [17]. This patient's decrease in CA-125 mirrored an immune-related adverse effect of a maculopapular rash [17]. Additionally, the decline in CA-125 coincided with regression of metastases [17]. Furthermore, in a study of the anti–PD-1 antibody nivolumab in recurrent ovarian cancer, 2 patients who achieved a CR experienced a marked reduction in CA-125 levels, which normalized to <35 U/mL in both patients [13].

This study has a relatively small sample size of 59 patients. It is limited by its retrospective nature and heterogenous immunotherapies of anti–PD-1, PD-L1, CTLA-4, and LAG-3. We also acknowledge the lack of uniform timing in the measurements of CA-125. The use of a single pre-treatment value rather than multiple pre-treatment CA-125 values also limits the analysis. Further studies correlating CA-125 values based on specific RECIST 1.1 responses would also be of value for gynecologic oncologists. Of note, however, our findings highlight that CA-125 has limited utility in early disease monitoring in patients with EOC undergoing ICI therapy, and we caution against using the biomarker in decision making regarding treatment continuation or switching therapy.

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CRediT authorship contribution statement

Julia L. Boland: Methodology, Data curation, Writing - original draft. **Qin Zhou:** Formal analysis, Writing - original draft. **Alexia E. Iasonos:** Formal analysis, Writing - original draft. **Roisin O'Cearbhaill:** Formal analysis, Writing - original draft. **Jason Konner:** Formal analysis, Writing - original draft. **Margaret Callahan:** Formal analysis, Writing - original draft. **Claire Friedman:** Formal analysis, Writing - original draft. **Carol Aghajanian:** Formal analysis, Writing - original draft. **Paul Sabbatini:** Formal analysis, Writing - original draft. **Dmitriy Zamarin:** Methodology, Data curation, Writing - original draft. **Karen A. Cadoo:** Methodology, Data curation, Writing - original draft.

Declaration of competing interest

Outside the submitted work: Dr. Zamarin reports personal fees from Merck, Agenus, Hookipa Biotech, and Western Oncolytics, grants from Merck, sponsored trave from Genentech, and stock options from Calidi Biotherapeutics. Dr. Konner reports personal fees from Astra-Zeneca, Inc. Dr. Callahan reports grants, as well as "other" (family member is an employee) from Bristol Myers Squibb, and personal fees from Merck, InCyte, Moderna, and AstraZeneca. Dr. Cadoo reports travel/expenses and institutional support from AstraZeneca, institutional support from Syndax Pharmaceuticals, as well as personal fees and travel/expenses from Tessaro and personal fees from OncLive. Dr. Friedman reports steering committee (compensation waived, research financial support to institution) from Genentech and Merck, institutional support from Bristol Myers Squibb, and personal fees from AstraZeneca. Dr. O'Cearbhaill reports personal fees from Tesaro, GlaxoSmithKline, and Clovis, and she is a non-compensated steering committee member for the PRIMA (niraparib) study and DUO-O (olaparib) study. Dr. Aghajanian reports personal fees from Tesaro, Immunogen, Clovis, Mateon Therapeutics, Eisai/Merck, Mersana Therapeutics, and Roche, as well as grants from Clovis, grants from Genentech, AbbVie, and AstraZeneca. Dr. Sabbatini reports institutional support from Bristol Myers Squibb. Dr. Iasonos reports personal fees from Intelligencia, Mylan, and Brightpath.

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