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Patient self-reporting of tolerability using PRO-CTCAE in a randomized double-blind, placebo-controlled phase II trial comparing gemcitabine in combination with adavosertib or placebo in patients with platinum resistant or refractory epithelial ovarian carcinoma

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HIGHLIGHTS

- Cell cycle modulation with Wee1 inhibition has promising activity in platinum resistant and refractory ovarian cancer.
- A phase II trial showed improved PFS and OS with adavosertib and gemcitabine, compared to placebo and gemcitabine.
- PRO-CTCAEs provide objective assessment of symptomatic adverse events (syAEs) and patient reported tolerability.
- High scores of syAEs showed more frequent diarrhea in the adavosertib arm (25%) vs placebo arm (0%).
- Longitudinal syAE assessment showed higher fatigue and difficulty swallowing severity in the adavosertib arm.

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ABSTRACT

Background. A double-blind, randomized, placebo-controlled, phase 2 trial assessed gemcitabine in combination with the wee1 inhibitor adavosertib or placebo in platinum resistant or refractory high grade serous ovarian cancer (HGSOC), demonstrating improved progression free and overall survival favouring the adavosertib/gemcitabine arm. An exploratory objective of the study included the PRO-CTCAE assessment, to capture self-reporting of frequency, severity and/or interference of symptomatic adverse events (syAEs).

Methods. PRO-CTCAE items at baseline, days 1 and 15 of each cycle and off treatment, were completed in two centres, with the objective of characterizing syAEs in the first three months of therapy. The maximum post-baseline score proportion for each syAE was tabulated per patient. The 12-week area under the curve (AUC12w) as a measure of syAE over-time and incremental AUC12w (iAUC12w) for adjustment to baseline syAEs.

Results. Sixty-one patients were approached for PRO-CTCAE surveys and 55 were evaluable. Among patients with HGSOC, 28 received gemcitabine/adavosertib (arm A) and 19 gemcitabine/placebo (arm B). Survey completion rates were high. The proportion of participants with positive (≥1) PRO-CTCAE scores was higher for difficulty swallowing with gemcitabine/adavosertib (arm A 35.7% vs arm B 5.3%, $p = 0.02$). The high score (≥3) syAEs showed more frequent diarrhea with gemcitabine/adavosertib (arm A 25% vs arm B 0%, $p = 0.03$). The proportions of worsening syAEs over time were higher in patients receiving gemcitabine/adavosertib for difficulty swallowing (arm A 35.7% vs arm B 5.3%; $p = 0.03$) and fatigue severity (arm A 71.43% vs arm B 42.1%; $p = 0.04$).

Abbreviations: HGSOC, High grade serous ovarian cancer; syAEs, Symptomatic adverse events; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; F, Frequency; S, Severity; I, Interference.

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Conclusions. The longitudinal assessment of patient self-reported tolerability showed greater difficulty swallowing and fatigue severity in patients receiving gemcitabine/adavosertib, compared to gemcitabine/placebo. PRO-CTCAE provides complementary and objective assessment of drug tolerability from a patient's perspective.

1. Introduction

Epithelial Ovarian Cancer (EOC) is the seventh most commonly diagnosed cancer in women [1]. Survival in platinum resistant EOC is poor, with response rates to single-agent chemotherapy as low as 10–15% and median overall survival estimated at approximately 12 months [2]. We previously reported results of a double-blind, randomized, placebo-controlled, phase II trial assessing gemcitabine with either oral adavosertib (wee1 inhibitor) or placebo, in women with recurrent platinum-resistant or platinum-refractory high-grade serous ovarian carcinoma [3]. 124 patients were enrolled, of whom 99 had high-grade serous ovarian cancer and were randomly assigned to gemcitabine and adavosertib (65 [66%]) or gemcitabine and placebo (34 [34%]). Additionally, 25 patients with non-high-grade serous ovarian cancer were enrolled in an exploratory cohort, where the combination of gemcitabine and adavosertib was administered to all patients. Progression-free survival (PFS) was longer with adavosertib plus gemcitabine (median 4.6 months with gemcitabine/adavosertib vs 3 months with gemcitabine/placebo; hazard ratio 0.55 [95% CI 0.35–0.90], $p = 0.015$). Median overall survival was 11.4 months in those receiving gemcitabine and adavosertib versus 7.2 months in the gemcitabine and placebo arm (HR 0.56 [95% CI 0.35–0.91], $p = 0.017$). The most frequent grade ≥ 3 adverse events (AEs) were hematological and fatigue. Similarly, the AEs most commonly leading to dose interruption or reduction were hematological.

The contemporary therapeutic landscape in oncology continues to evolve and novel agents with diverse toxicities are rapidly being incorporated. Adverse event reporting has been standardized with the use of Common Terminology Criteria for Adverse Events (CTCAE), which has provided a framework to objectively measure and document toxicities [4]. An important and often unrecorded aspect of AE reporting has been the patients' perspective, with direct qualitative and quantitative self-assessment. Basch et al. have demonstrated that integrating patient reported outcome assessment with routine cancer treatment improves survival [5]. In this setting, the Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer Inter Group recommended that in platinum resistant ovarian cancer PFS should not be the only endpoint, and must be supported by additional endpoints such as patient reported outcomes (PROs) [6].

To permit patient self-reporting of symptomatic adverse events, the U.S. National Cancer Institute (NCI) has developed, tested and implemented a measurement system, the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) [7]. The PRO-CTCAE item library consists of 124 items that assess 78 symptomatic toxicities. Drawn from the CTCAE, these symptomatic toxicities of cancer treatment were identified as amenable to patient self-reporting. PRO-CTCAE items cover a wide range of symptomatic AEs [7]. For each of these symptomatic AEs, items were developed reflecting the attributes of presence or absence, frequency (F), severity (S) and/or interference (I) with usual or daily activities. Each symptomatic AE is assessed with respect to 1 to 3 of these attributes, and a recall period of 'the past 7 days'. PRO-CTCAE responses are scored from 0 to 4 (or 0/1 for absent/present). In any given trial, investigators select a subset of these items for surveillance based on knowledge of the anticipated pattern of regimen-related toxicities as well as study hypotheses and prior research. The PRO-CTCAE item library offers a systematic yet flexible approach to capture symptomatic adverse events.

2. Methods

The correlative study of PRO-CTCAE surveys were implemented in two of the 11 participating centres (Princess Margaret Cancer Centre and London Health Sciences, Canada) from a double-blind, randomized, placebo-controlled phase 2 trial assessing gemcitabine in combination with adavosertib (arm A) or placebo (arm B) in platinum resistant or refractory high grade serous ovarian carcinoma (NCT02151292). A third, non-randomized exploratory arm included patients with platinum resistant or refractory non-high-grade serous ovarian carcinoma in a single-arm cohort (arm C). Patients enrolled in the exploratory cohort received adavosertib and gemcitabine combination. Treatment with gemcitabine was administered at 1000 mg/m^2 intravenously on days 1, 8, and 15 with either oral adavosertib (175 mg once daily on days 1, 2, 8, 9, 15, and 16) or oral placebo on the same schedule, in a 28-day cycle. Clinical results with the primary PFS endpoint have been already reported [3].

Eligible patients were ≥ 18 years old, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and a life expectancy of ≥3 months. The number of previous lines of therapy was unlimited. The patients previously treated with gemcitabine or with active bowel obstruction were ineligible. All patients provided written informed consent. The trial was approved by each of the participating site's institutional research ethics board and performed in accordance with the Declaration of Helsinki and Good Clinical Practice standards.

A predetermined exploratory objective of the study was to characterize the symptomatic AEs in the first three months of therapy, collected on day one and 15 of each cycle, and off-treatment. English speaking patients from two of the Canadian centres completed the PRO-CTCAE surveys electronically in clinic at baseline, day 1 and day 15 of each cycle and off treatment. The PRO-CTCAE items included nine symptomatic AEs: abdominal pain (F/I/S), anxiety (F/I/S), bloating (F/S), diarrhea (F), difficulty swallowing (S), fatigue (S/I), mucositis (I/S), nausea (F/S), vomiting (F/S). The symptom selection was based on symptoms frequently associated with ovarian cancer [8], and those described for adavosertib or gemcitabine [9–11]. Other patient reported symptomatic AEs beyond study-specific survey items was recorded through free-text entries.

2.1. Statistical analysis

The proportion of patients who completed expected PRO-CTCAE surveys was assessed as a measure of feasibility and data quality. The survey completion rate was calculated as the sum of number of surveys, divided by the sum of expected number of surveys.

The maximum post-baseline score proportion for each symptomatic AE was tabulated per patient. The proportion of participants by group with a maximum score >0, and a score of 3 or more were assessed both at baseline and post-baseline. Between-group comparison was performed using Chi-Square or Fisher's test.

The area under the curve (AUC) was calculated using the average of the nearest symptom scores (interval between surveys) to multiply the time interval between the two scores and add them over time for each patient [12]. The AUC was calculated as a longitudinal symptomatic AE measure. The 12-week area under the curve (AUC12w) was calculated as a measure of symptomatic AEs over-time, individually in each patient and per treatment group. The correlation between AUC measures and

treatment discontinuations and dose reductions was made using *t*-test. The incremental AUC12w (iAUC12w) was used for adjustment to baseline symptomatic AEs and was calculated for each participant and per treatment group. In patients with two baseline surveys, the results of the survey closest to C1D1 was selected. The PRO-CTCAE outcomes in patients randomized to the gemcitabine/adavosertib and gemcitabine/placebo arms were compared using an independent samples *t*-test.

To address the symptomatic AEs that were recorded as high frequency, severity and/or interference, scores three or four at each survey time-point were selected. The proportion of high scores at six time-points (corresponding to days 1 and 15 of the first three cycles) were assessed. The gemcitabine/adavosertib and gemcitabine/placebo arms were compared using Fisher's Exact-Test at each survey, and overall using GEE model [13]. Write-ins were independently coded by two experts in the NCI, and disagreements were discussed. Results were analyzed descriptively and graphically.

The results of the exploratory cohort (non-high grade serous histologies) are provided for descriptive purposes.

3. Results

Between 2014 and 2018, sixty-one patients from two of the participating centres were approached for PRO-CTCAE surveys and 55 were evaluable (Fig. 1). Among the patients with high grade serous ovarian carcinoma, 28 received gemcitabine plus adavosertib and 19 gemcitabine plus placebo. Additionally, eight patients with non-high grade serous ovarian cancer received gemcitabine plus adavosertib (exploratory).

Median age was 61 (range 33–75), and ECOG status was ≤1 in 93%, 95% and 100%, in the gemcitabine/adavosertib, gemcitabine/placebo and exploratory arms, respectively (Table 1). All the patients had platinum resistant or refractory disease. Median number of cycles of therapy were five (range 1–16) in the gemcitabine/adavosertib arm, two (range 1–16) in the gemcitabine/placebo arm and two (range 1–8) in the exploratory cohort. Treatment discontinuations due to adverse events occurred in 14% (4/28) in the gemcitabine/adavosertib arm, none in the gemcitabine/placebo, and 12% (1/8) in the exploratory cohort. Reasons for discontinuation were infection ($n = 2$), hematological toxicity, fatigue, pneumonitis ($n = 1$, each). Dose reductions of gemcitabine occurred in 86% of patients (24/28) receiving gemcitabine/adavosertib, 37% (7/19) receiving gemcitabine/placebo and 62.5% (5/8) of patients in the exploratory cohort. The main cause for dose reduction of gemcitabine was hematologic toxicity, across arms.

Survey completion rates were high in the first 12 weeks (gemcitabine/adavosertib 93%, gemcitabine/placebo 95%, exploratory 91%) and through the study (gemcitabine/adavosertib 93%, gemcitabine/placebo 96%, exploratory 88%). The baseline questionnaire was missing in only one patient (gemcitabine/adavosertib arm). Symptomatic AEs at baseline were well balanced between the gemcitabine/adavosertib and the gemcitabine/placebo arms (Table S1).

3.1. Prevalence of symptomatic AEs in the first 12-weeks of treatment

Any grade abdominal pain, bloating, anxiety, fatigue and nausea were high in both treatment arms, occurring in >70% of patients (Table 2). The most frequent high score (3–4) symptomatic AEs occurring in >30% of patients were abdominal pain, anxiety, bloating and fatigue. The comparison of the proportion of participants with PRO-CTCAE scores higher than zero, revealed that difficulty swallowing was more frequent in patients in the gemcitabine/adavosertib arm, compared to gemcitabine/placebo (35.7% vs 5.3%, $p = 0.02$). There was a between-group difference in mucositis severity (gemcitabine/adavosertib 53.6% vs gemcitabine/placebo 26.3%, $p = 0.06$), but did not reach statistically significant. The high score (3 or 4) between-group differences were only detected for diarrhea, which was also more frequent in the gemcitabine/adavosertib arm (gemcitabine/adavosertib 25% vs gemcitabine/placebo 0%, $p = 0.03$).

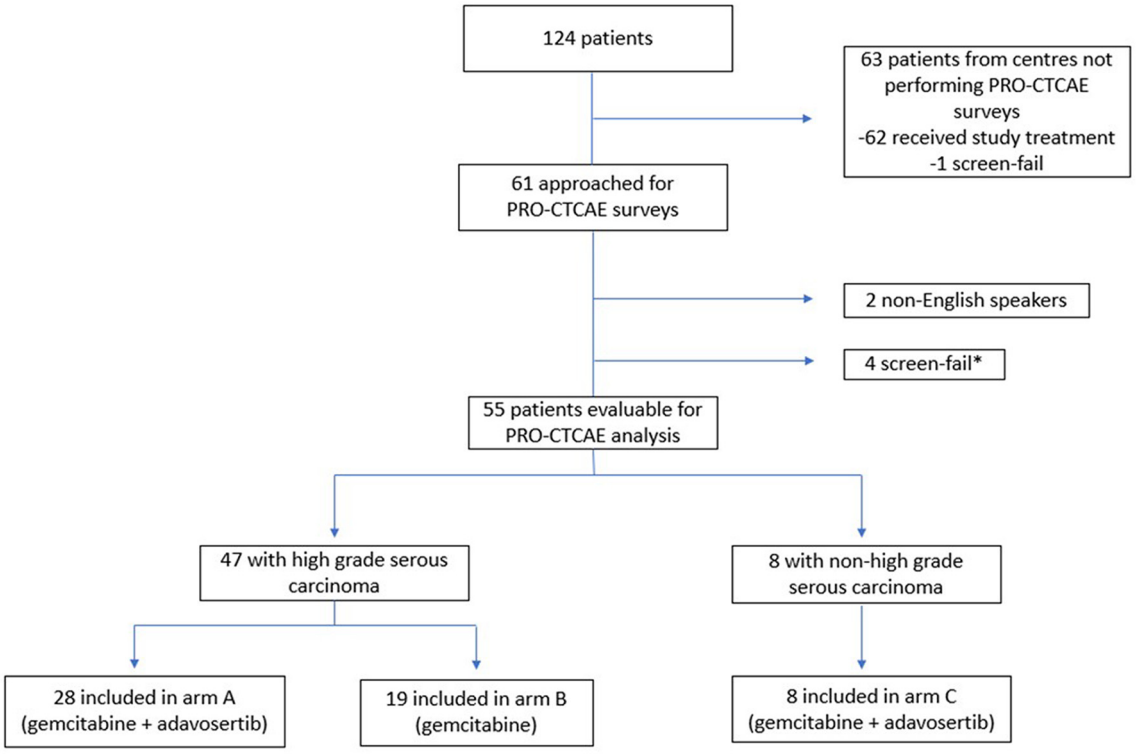

Fig. 1. CONSORT diagram of patients enrolled in the study.
* Completed baseline survey.

Table 1
Baseline characteristics of treated patients. Data are median (range) or n (%). ECOG: Eastern Cooperative Oncology Group.

	Arm A - Gemcitabine + Adavosertib ($n = 28$)	Arm B- Gemcitabine + Placebo ($n = 19$)	Arm C- Exploratory - Gemcitabine + Adavosertib ($n = 8$)
Histology			
High grade serous	28 (100)	19 (100)	0
Low grade serous	0	0	4 (50)
Endometrioid	0	0	2 (25)
Carcinosarcoma	0	0	1 (12.5)
Clear cell	0	0	1 (12.5)
Mixed clear cell and endometrioid	0	0	1 (12.5)
Primary tumour location			
Ovary	27 (96.4)	17 (89.5)	5 (62.5)
Primary Peritoneal	1 (3.6)	1 (5.3)	3 (37.5)
Fallopian tube	0	1 (5.3)	0
Prior lines of therapy, median	3 (1–7)	3 (1–7)	3 (1—10)
Primary platinum refractory			
Yes	2 (7.1)	2 (10.5)	1 (12.5)
No	25 (89.3)	17 (89.5)	6 (75)
Unknown	1 (3.6)	0	1 (12.5)
Race			
White	21 (75)	13 (68.4)	4 (50)
Asian	4 (14.3)	2 (10.5)	2 (25)
Black/African American	1 (3.6)	3 (15.8)	1 (12.5)
Native American	1 (3.6)	0	1 (12.5)
Unknown	1 (3.6)	1 (5.3)	0
Age, years	62 (48–75)	59 (43–72)	57 (33–71)
ECOG status			
0	3 (10.7)	3 (15.8)	2 (25)
1	23 (82.1)	15 (78.9)	6 (75)
2	2 (7.1)	1 (5.3)	0

3.2. Symptomatic AEs over-time in the first 12-weeks of treatment (longitudinal assessment)

There were no significant differences between-arms in any score or high score (3 or 4) symptomatic AEs overall using GEE modeling. Proportions of the symptomatic AEs with high scores (3 and 4) were only significantly higher at cycle one day 15 for fatigue severity in the gemcitabine/adavosertib arm (gemcitabine/adavosertib 55% vs gemcitabine/placebo 19%, $p = 0.04$). No significant differences were seen in other high scores per survey time. Refer to Fig. 2 and supplementary fig. 1 for an overview of the mean scores of symptomatic AEs in the first 12-weeks of treatment.

Table 3 presents the area under the curve at 12 weeks (AUC12w) of each prospectively solicited symptomatic adverse events from baseline to 12 weeks. No correlation was observed between treatment discontinuations due to AEs and the AUC12w of the solicited symptomatic AEs. A significant association between gemcitabine dose reduction and high AUC12w diarrhea frequency ($p = 0.003$), difficulty swallowing severity ($p = 0.042$) and fatigue severity ($p = 0.01$) and interference ($p = 0.025$) was detected.

Table 2
Prevalence of the highest post-baseline symptomatic AE score across the first 12 weeks.

Pro-CTCAE item	Score > 0				Score 3–4			
	Arm A- Gemcitabine + Adavosertib (n = 28)	Arm B- Gemcitabine + Placebo (n = 19)		Arm C- Exploratory - Gemcitabine + Adavosertib (n = 8)	Arm A- Gemcitabine + Adavosertib (n = 28)	Arm B- Gemcitabine + Placebo (n = 19)		Arm C- Exploratory - Gemcitabine + Adavosertib (n = 8)
	n (%)	**n (%)**	**p***	**n (%)**	**n (%)**	**n (%)**	**p***	**n (%)**
Abdominal Pain F	26 (92.9)	17 (89.5)	>0.95	8 (100)	10 (35.7)	9 (47.4)	0.42	1 (12.5)
Abdominal Pain S	26 (92.9)	17 (89.5)	>0.95	8 (100)	9 (32.1)	5 (26.3)	0.67	0 (0)
Abdominal Pain I	19 (67.9)	14 (73.7)	0.75	5 (62.5)	7 (25)	4 (21.1)	>0.95	1 (12.5)
Anxiety F	27 (96.4)	16 (84.2)	0.29	8 (100)	7 (25)	6 (31.6)	0.62	2 (25)
Anxiety S	27 (96.4)	16 (84.2)	0.29	8 (100)	4 (14.3)	2 (10.5)	>0.95	0 (0)
Anxiety I	20 (71.4)	12 (63.2)	0.55	6 (75)	5 (17.9)	2 (10.5)	0.68	0 (0)
Bloating F	24 (85.7)	14 (73.7)	0.45	5 (62.5)	10 (35.7)	5 (26.3)	0.50	1 (12.5)
Bloating S	24 (85.7)	14 (73.7)	0.45	5 (62.5)	9 (32.1)	3 (15.8)	0.31	1 (12.5)
Diarrhea F	23 (82.1)	11 (57.9)	0.1	5 (62.5)	7 (25)	0 (0)	0.03	2 (25)
Difficulty swallowing S	10 (35.7)	1 (5.3)	0.02	0 (0)	0 (0)	0 (0)		0 (0)
Fatigue S	27 (96.4)	19 (100)	>0.95	8 (100)	16 (57.1)	6 (31.6)	0.08	4 (50)
Fatigue I	27 (96.4)	18 (94.7)	>0.95	8 (100)	17 (60.7)	7 (36.8)	0.11	5 (62.5)
Mucositis oral I	8 (28.6)	3 (15.8)	0.48	1 (12.5)	0 (0)	0 (0)		0 (0)
Mucositis oral S	15 (53.6)	5 (26.3)	0.06	1 (12.5)	0 (0)	0 (0)		0 (0)
Nausea F	26 (92.9)	16 (84.2)	0.38	7 (87.5)	5 (17.9)	4 (21.1)	>0.9	2 (25)
Nausea S	26 (92.9)	16 (84.2)	0.38	7 (87.5)	5 (17.9)	2 (10.5)	0.68	1 (12.5)
Vomiting F	15 (53.6)	9 (47.4)	0.68	4 (50)	1 (3.6)	3 (15.8)	0.29	0 (0)
Vomiting S	14 (50)	9 (47.4)	0.86	4 (50)	1 (3.6)	3 (15.8)	0.29	0 (0)

* Based on Chi-Square or Fisher's test.

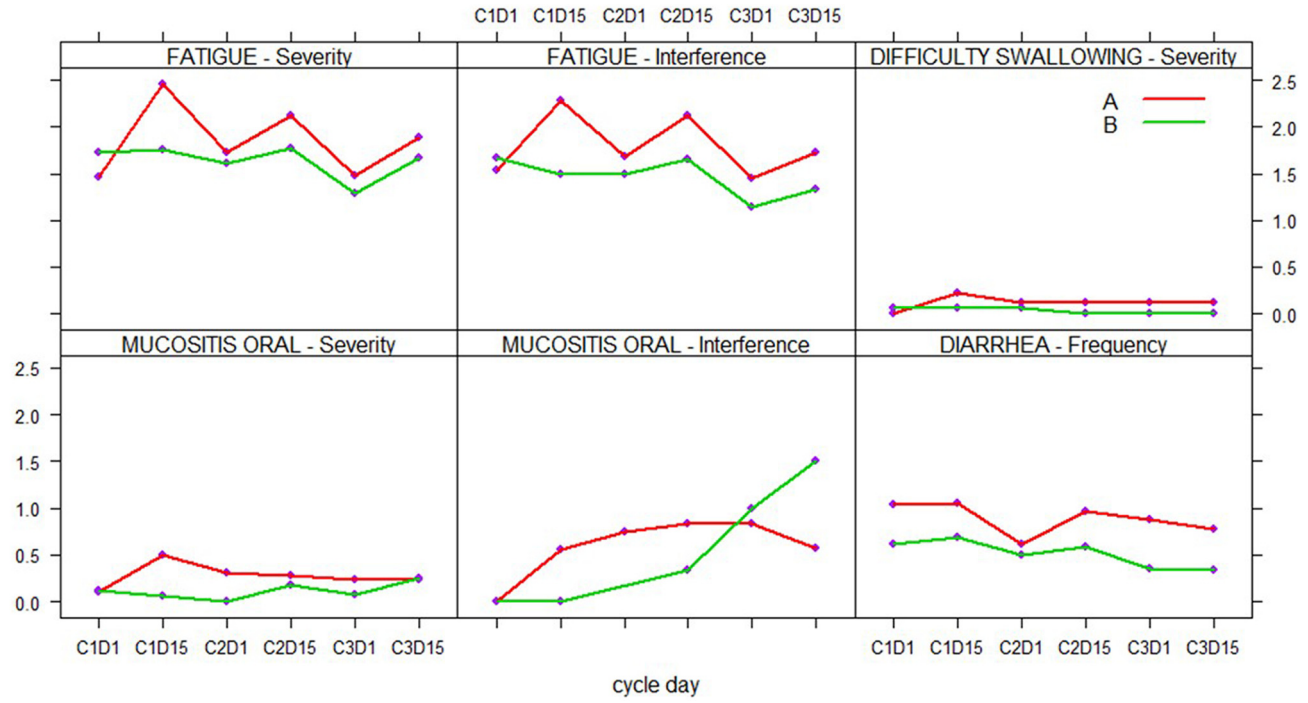

Fig. 2. Mean scores of fatigue, difficulty swallowing, mucositis and diarrhea over-time. Other symptomatic AEs are shown on supplementary 1. The gemcitabine and adavosertib arm is represented in red (A), and the gemcitabine and placebo arm in green (B).

Table 3
Area under the curve at 12 weeks (AUC12w) of prospectively solicited symptomatic adverse events. Include in table: mean (standard error).

	Arm A- Gemcitabine + Adavosertib (n = 28)	Arm B- Gemcitabine + Placebo (n = 19)	*p* value*	Arm C- Exploratory - Gemcitabine + Adavosertib (n = 8)
Abdominal pain F	96 (11)	96 (19)	0.91	54 (14)
Abdominal pain S	83 (9)	74 (15)	0.55	44 (13)
Abdominal pain I	52 (9)	56 (15)	0.81	36 (13)
Anxiety F	118 (13)	88 (16)	0.15	77 (18)
Anxiety S	96 (12)	66 (12)	0.09	63 (13)
Anxiety I	67 (13)	47 (12)	0.29	39 (14)
Bloating F	115 (16)	87 (17)	0.17	34 (12)
Bloating S	90 (13)	75 (14)	0.33	35 (13)
Diarrhea F	70 (12)	33 (9)	0.01	44 (17)
Difficulty Swallowing S	10 (3)	2 (2)	0.02	0
Fatigue S	152 (9)	112 (10)	0.005	91 (15)
Fatigue I	144 (11)	98 (15)	0.02	91 (15)
Mucositis oral S	23 (6)	6 (3)	0.01	3 (2)
Mucositis oral I	29 (9)	22 (6)	0.145	0
Nausea F	69 (10)	54 (8)	0.28	33 (10)
Nausea S	62 (8)	48 (10)	0.28	26 (5)
Vomiting F	15 (4)	26 (8)	0.20	13 (5)
Vomiting S	15 (4)	24 (8)	0.36	13 (5)

* Based on t-test.

The incremental area under the curve (iAUC) at 12 weeks was used to assess symptomatic AEs over-time, adjusted to baseline symptoms (Table S2). Positive values of iAUC at 12 weeks are considered worsening of symptomatic AEs, whereas zero or negative values were considered stable or improved symptomatic AEs, respectively. The proportions of worsening symptomatic AEs from baseline per treatment-arm were only statistically significantly higher in those patients receiving gemcitabine/adavosertib for difficulty swallowing severity (worsened in 35.7% in the gemcitabine/adavosertib arm vs 5.3% in the gemcitabine/placebo arm; $p = 0.03$) and fatigue severity (worsened in 71.43% in the gemcitabine/adavosertib arm vs 42.1% in the gemcitabine/placebo arm, $p = 0.04$; Table 4).

3.3. Additional symptomatic AEs: Write-ins

At least one write-in was provided by 30 patients (55% of participant overall; distribution per arm and over-time in Supplementary Fig. 2), and 8 patients provided a write-in at baseline. The total number of unique write-ins were 353. The most prevalent verbatim (first instance per subject) during treatment was arm or leg swelling, which was reported by seven patients, across all treatment arms. Additionally, six patients reported constipation and headache across all arms. Whereas the most prevalent write-ins reported only in adavosertib arms were rash ($n = 6$), and numbness and tingling ($n = 5$).

Table 4
Proportion of patients with worsening symptomatic AEs* across the first 12 weeks of treatment.

	Arm A- Gemcitabine + Adavosertib (n = 28)	Arm B- Gemcitabine + Placebo (n = 19)	p#	Arm C- Exploratory - Gemcitabine + Adavosertib (n = 8)
Diarrhea F	46.4%	26.3%	0.16	37.5%
Difficulty Swallowing S	35.7%	5.3%	0.03	0
Fatigue S	71.4%	42.1%	0.04	50%
Fatigue I	60.7%	36.8%	0.11	37.5%
Mucositis Oral S	50%	26.3%	0.10	12.5%
Mucositis Oral I	22.2%	14.3%	>0.9	0
Nausea F	71.4%	57.9%	0.34	75%
Nausea S	67.9%	57.9%	0.49	62.5%
Vomiting F	50%	36.8%	0.37	25%
Vomiting S	46.4%	26.3%	0.16	25%
Abdominal Pain F	35.7%	36.8%	0.94	37.5%
Abdominal Pain S	39.3%	26.3%	0.36	37.5%
Abdominal Pain I	28.6%	26.3%	0.86	12.5%
Anxiety F	17.9%	31.6%	0.31	12.5%
Anxiety S	42.9%	26.3%	0.25	12.5%
Anxiety I	32.1%	36.8%	0.74	25%
Bloating F	25%	15.8%	0.72	12.5%
Bloating S	25%	26.3%	>0.95	25%

* Based on incremental AUC (iAUC) in the first 12 weeks of therapy, adjusted for baseline symptoms (Table S2). Positive values of iAUC at 12 weeks were considered worsening of symptomatic AEs, whereas zero or negative iAUC values were considered stable or improved, respectively.
# Based on Chi-Square or Fisher's test.

Several verbatim symptoms potentially reflected oral toxicity. The PRO-CTCAE items "mouth sores" and "difficulty swallowing" were reported more frequently in patients receiving gemcitabine/adavosertib compared to those on gemcitabine/placebo. Similarly, some of the verbatim symptoms that may reflect the severity and consequences of oral AEs, including tooth pain ($n = 3$), periodontal disease ($n = 1$), thrush ($n = 1$) and cheilosis ($n = 1$), were offered by five patients receiving adavosertib. None of the patients receiving gemcitabine/placebo reported verbatim reflecting a similar pattern of oral toxicity symptoms.

4. Discussion

Capture of PRO-CTCAE data is important and desirable in early phase clinical trials. This trial demonstrated that it was feasible and acceptable for participants with advanced platinum resistant or refractory ovarian carcinoma and high symptom burden (Table S1). The solicited symptomatic AE measures could be divided in those that could be linked to metastatic ovarian cancer per se, such as abdominal pain and bloating, and those that may be enhanced by the administration of gemcitabine and/or adavosertib, such as diarrhea, fatigue, mucositis and difficulty swallowing. Interestingly, likely disease-related symptoms did not significantly differ between patients receiving gemcitabine/adavosertib compared to gemcitabine/placebo overall or longitudinally in the first 12 weeks of therapy.

The PRO-CTCAE surveys were performed every two weeks (on day 1 and 15 of each cycle), with a seven-day recall period. The treatment administration schedule provided a week off-therapy on each cycle (adavosertib/placebo was administered on days 1–2, 8–9 and 15–16 of each cycle, with gemcitabine once a week in a three weeks-on and one week-off schedule), which may have an impact in the symptomatic AE scoring over-time. In this case, higher fatigue was detected on day 15 of the cycle, and it improved by day 1 of the cycle (Fig. 2).

The write-ins provided feasible and meaningful information, and results of this study showcase that they are helpful in assessing the symptomatic AEs when a crude signal is not well refined. The write-ins related to oral toxicity were helpful in amplifying its potential consequences. Gastrointestinal toxicity was observed during early phase studies with adavosertib [14]. Mucositis and/or dysphagia were not commonly observed (<30% in the profile of clinician reported AEs) [3]. However, we found significant between group differences on PRO-CTCAE for mouth sores and difficulty swallowing. We were also intrigued by some of the verbatim symptoms offered that may reflect the severity and consequences of oral toxicity, including periodontal disease, tooth pain, and cheilosis. Similarly, rash as a write-in was reported by six patients in the adavosertib arms, and none in the gemcitabine/placebo arm. Using CTCAE reporting rash was observed in 44% of patients in the gemcitabine/adavosertib arm and 9% in the gemcitabine/placebo arm, also mirroring the between-arm difference observed in the write-ins. Our observations about these additional verbatim concerns can be applied in the selection of PRO-CTCAE items for the definitive phase III study.

The study demonstrates that CTCAE and PRO-CTCAE can be meaningfully interpreted in conjunction with each other. Our findings also show that there is overall good correspondence between the two measures, which supports the precision and accuracy of clinician reports and patient self-reporting. The use of PRO-CTCAE in this placebo-controlled trial provided a unique opportunity to isolate the symptomatic AEs that were potentially attributable to adavosertib and gemcitabine. Inspection of the incremental AUC at 12 weeks and consideration of the free text reports supports a conclusion that compared to gemcitabine/placebo, fatigue, mucositis, and difficulty swallowing appear to be AEs attributable or potentially attributable to the addition of adavosertib to gemcitabine. The use of PRO-CTCAEs allowed us to confirm the observation made in the primary analysis about the toxicity profile of this regimen [3]. The study also showed that high AUC12w of diarrhea, fatigue and difficulty swallowing correlated with gemcitabine dose reductions. The assessment of CTCAE and PRO-CTCAE data in conjunction provide further support on the use of potential prevention measures, such as oral hygiene, and support measures for diarrhea, fatigue and mucositis management. The patient reported outcome findings also provide definitive justification and motivation for PRO-CTCAE item selection for the phase III trial of adavosertib in ovarian cancer.

One of the limitations of the study is its small sample size. However, data quality was excellent with high rates of completion across all arms. The PRO-CTCAE analysis was performed in two of the participating centres and was offered to English speaking patients (two patients from the centres performing PRO-CTCAEs did not complete the surveys due to a language barrier). Although the PRO-CTAE surveys only took place in two of the centres for feasibility purposes, approximately half of the trial population was included. The pattern of clinician reported toxicity for both all grade and high grade, was comparable for those who completed PRO-CTCAE and the patients from centres where PRO-CTCAEs were not implemented (data not shown). Similarly, the progression

free survival and overall survival were comparable in the patients completing PRO-CTCAE reports and those who did not (Supplementary Fig. 3). These observations support our assertion that the findings reported here reflect a representative subset of all patients on the trial.

An important outcome of the study was that duration of therapy diverged between-arms, as a result of improved disease control, with a median of three cycles of treatment in the gemcitabine/adavosertib arm and two in the gemcitabine/placebo and exploratory arms. Given that the duration of therapy was longer for those patients in the gemcitabine/adavosertib arm, it is possible that the increased toxicity observed, as determined by proportions and AUC at 12 weeks, is not fully attributed to adavosertib, but also to the greater number of cycles of gemcitabine. To minimize the between-group differences on treatment length, the longitudinal assessment and area under the curve analysis were performed at a 12-week timeline. Moreover, the incremental AUC at 12 weeks, which adjusts for baseline symptoms, minimized the effect on the differences on treatment duration between groups. Another limitation of the study is that the questionnaires were administered every two weeks, with a seven-day recall period, thus being possible to have some silent symptoms at certain time-points in the cycle. While the proportion of worsening in all other symptoms was generally comparable between-arms, we acknowledge sampling variation and the between-group difference in the number of treatment cycles may have caused artefactual effects and influenced our estimates of AE prevalence.

This study demonstrates that collection of PRO-CTCAE data every two-weeks in early-phase trials is feasible, with high completion rates in a heavily pretreated population with high symptom burden at baseline. The between-group symptomatic AE differences were well evaluated with the PRO-CTCAE, providing valuable complementary information to the clinician reported toxicity and improving toxicity reporting accuracy. An important consideration for future studies is to incorporate and evaluate PRO-CTCAE in real time in the research protocol, and use this information, in conjunction with CTCAE, when determining treatment tolerability.

5. Conclusion

The implementation of PRO-CTCAEs and assessment of patient write-ins provided meaningful information about the patient reported tolerability of adavosertib and gemcitabine, confirming the quality of clinician reporting of adverse events. Symptomatic adverse events that should be evaluated in future studies with gemcitabine and adavosertib include fatigue, diarrhea, difficulty swallowing and oral toxicity.

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The data underlying this article will be shared on reasonable request to the corresponding author.

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Appendix A. Supplementary data

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