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Hidden in plain sight – Survival consequences of baseline symptom burden in women with recurrent ovarian cancer

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HIGHLIGHTS

- Patients with recurrent ovarian cancer report a high symptom burden at baseline prior to commencing chemotherapy.
- The high symptom burden is not reflected by performance status alone.
- High symptom burden is strongly associated with early progression and death.
- Symptom burden should be documented, actively managed and used to stratify patients in clinical trials.

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ABSTRACT

Objective. To describe the baseline symptom burden(SB) experienced by patients(pts) with recurrent ovarian cancer(ROC) prior and associations with progression free survival (PFS) and overall survival (OS).

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Methods. We analysed baseline SB reported by pts. with platinum resistant/refractory ROC (PRR-ROC) or potentially-platinum sensitive ROC receiving their third or greater line of chemotherapy (PPS-ROC≥3) enrolled in the Gynecologic Cancer InterGroup - Symptom Benefit Study (GCIG-SBS) using the Measure of Ovarian Symptoms and Treatment concerns (MOST). The severity of baseline symptoms was correlated with PFS and OS.

Results. The 948 pts. reported substantial baseline SB. Almost 80% reported mild to severe pain, and 75% abdominal symptoms. Shortness of breath was reported by 60% and 90% reported fatigue. About 50% reported moderate to severe anxiety, and 35% moderate to severe depression. Most (89%) reported 1 or more symptoms as moderate or severe, 59% scored 6 or more symptoms moderate or severe, and 46% scored 9 or more symptoms as moderate or severe. Higher SB was associated with significantly shortened PFS and OS; five symptoms had OS hazard ratios larger than 2 for both moderate and severe symptom cut-offs (trouble eating, vomiting, indigestion, loss of appetite, and nausea; $p < 0.001$).

Conclusion. Pts with ROC reported high SB prior to starting palliative chemotherapy, similar among PRR-ROC and PPS-ROC≥3. High SB was strongly associated with early progression and death. SB should be actively managed and used to stratify patients in clinical trials. Clinical trials should measure and report symptom burden and the impact of treatment on symptom control.

1. Background

Patients with recurrent ovarian cancer (ROC) commonly experience a broad range of symptoms that are not commonly analysed or reported in ovarian cancer trials [1] although are available as they are captured in quality of life assessments completed by patients in the majority of randomised clinical trials. An important aim of systemic treatment is palliation of symptoms which is not reflected in progression free survival(PFS), the most common primary endpoint in clinical trials in this population which is an important shortcoming and limits the interpretation of the results of clinical trials. This is discussed in detail in a recent position paper highlighting the limitations of PFS as the primary endpoint in clinical trials [2]. Although health-related quality of life (HRQL) is now almost always collected in phase 3 clinical trials and included as a secondary endpoint; there is little evidence or effort taken to demonstrate that palliative systemic therapy impacts on symptom control or improves HRQL [3]. Furthermore, there is discordance between clinician and patient reporting, rating/grading of cancer related symptoms and adverse effects of treatment which argues for prioritising analysing and reporting patient reported outcomes in clinical trials [4,5]. There is growing evidence to support the importance of recognising and treating troublesome symptoms experienced by patients receiving palliative treatment as prompt and effective interventions can lead to improved HRQL, reduced hospitalisations and allow patients to continue systemic therapy for longer [6,7]. For example, in patients with advanced lung cancer, early involvement of the palliative care team, and prompt management of symptoms not only resulted in improved HRQL, but also was associated with an increase in survival [8]. Basch et al found similar results in randomised trial of patients receiving routine outpatient chemotherapy for advanced solid tumours [6]. A similar study has not been carried out yet in patients with ROC, although comprised a subset of patients recruited to a randomised clinical trial reported by Zimmermann et al a decade ago [9]. It is likely that patients with a high symptom burden at baseline are more likely to progress rapidly and a high symptom burden could possibly be used to identify the 30–40% of patients with platinum resistant/refractory ROC (PRR-ROC) who progress rapidly and often within 8 weeks of commencing chemotherapy and who are therefore less likely to benefit from treatment. They may be better off not enrolling in a trial or at least having symptoms controlled before they do.

The primary aim of the Gynaecologic Cancer InterGroup - Symptom Benefit Study (GCIG-SBS) was to develop and validate a fit for purpose instrument to document symptoms (both frequency and severity) reported by patients with PRR-ROC or potentially-platinum sensitive ROC receiving their third or greater line of chemotherapy (PPS-ROC≥3). We included these 2 subgroups as they comprise a large proportion of patients with ROC who are included in clinical trials and generally have a poor prognosis with a median overall survival ranging from 6 to 18 months [10–15]. The resultant patient-reported outcome instrument is the Measure of Ovarian Symptoms and Treatment concerns (MOST) [16,17]. The ultimate objective was that MOST would be incorporated into clinical trials and used to measure the impact of palliative chemotherapy on both ovarian cancer related symptoms and the trade-off with symptoms related to adverse effects of treatment. In an earlier publication that included 126 Australian patients with PRR-ROC recruited in Stage 1 of GCIG-SBS we reported a high symptom burden [18]. At baseline, prior to commencing palliative chemotherapy, the majority of patients reported high SB (almost 70% had 9 or more symptoms) [19]. The aim of this paper is to extend the initial Stage 1 analyses to 948 real world patients with PRR-ROC/PPS-ROC≥3 recruited to Stage 2 of GCIG-SBS. Specific aims were to document patient reported SB at baseline prior to commencement of systemic therapy, the proportion of patients experiencing multiple symptoms at moderate-severe levels and whether a higher SB measured using MOST questionnaire correlated with shorter progression-free and overall survival.

2. Methods

The GCIG-SBS (Australian New Zealand Clinical Trials Registry ANZCTRN12607000603415) was a prospective, observational, cohort study which enrolled patients with ROC from collaborating GCIG clinical trials groups in 11 countries. It was led by ANZGOG on behalf of the GCIG Symptom Benefit Committee, and was coordinated by the NHMRC Clinical Trials Centre in Sydney, Australia. Patients with epithelial ovarian, primary peritoneal or fallopian tube cancers were eligible if they had recurrent cancer based on CA125, radiological, or clinical criteria, and were considered to have PPS-ROC≥3, or if they had PRR-ROC and were considered suitable for palliative chemotherapy. Additional eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 3, ability to complete HRQL questionnaires independently, and a life expectancy of at least 3 months. The study was performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans and the Declaration of Helsinki. Ethical approval was obtained at all participating sites and all participants provided signed, written, informed consent. Consenting patients were recruited from participating sites prior to starting palliative chemotherapy.

2.1. Patient-reported outcomes

2.1.1. Symptom burden

The Measure of Ovarian Symptoms and Treatment concerns (MOST-T35) was developed and validated in the GCIG-SBS as a measure of symptom burden and impact of treatment on symptom improvement

in patients with ROC. The MOST-T35 contains 35 items: 2 assess abdominal symptoms most likely caused by ovarian cancer, 18 assess symptoms that may be caused by ovarian cancer and chemotherapy, 6 assess chemotherapy-related side-effects, 6 assess treatment-related concerns, and 3 assess well-being (physical, emotional, and overall) [16]. Symptoms and treatment-related concerns are rated on a numeric rating scale with integers from zero to 10, with five verbal anchors: 'No trouble at all' (0), 'Mild' [1–3], 'Moderate' [4–6], 'Severe' [7–10], and 'Worst I can imagine' [10]. The 3 well-being items range from 0 ('worst possible') to 10 ('best possible'). In this paper, we focused on the 20 symptoms that may be caused by ovarian cancer, which include both physical and psychological symptoms. The MOST items can also be scored into five indexes [17]; in this paper, we utilised three of these indexes for analyses. One was the average of the two MOST abdominal symptom items, hence named the MOST-Abdo. The second was the average of the two psychological symptoms, hence named the MOST-Psych. The third was the average of 16 physical symptoms that may be caused by disease or treatment, hence named the MOST-DorT; these symptoms were fatigue, trouble eating, indigestion, nausea, vomiting, diarrhea, constipation, shortness of breath, difficulty swallowing, trouble sleeping and bladder problems, and as we were reporting baseline data, we assumed these symptoms were caused by disease rather than treatment.

2.2. Statistical analysis

Baseline characteristics were summarised with descriptive statistics and comparer between PRR-ROC versus PPS-ROC≥3 groups using chi-square tests; the ordinal (linear) test was applied when categories were ordered. Symptom burden at baseline was analysed in several ways. First, we summarised the distribution of scores for each symptom in the MOST questionnaire in terms of the mean, standard deviation, median, and interquartile ranges. We tested for the difference in score distributions between PRR-ROC versus PPS-ROC≥3 groups with the Wilcoxon-rank sum tests. Second, we calculated the proportion of patients who rated their experience as 'none at all' (0), mild [1–3], moderate [4–6], and severe [7–10], testing differences between the groups with ordinal Chi-squared tests. Third, we summarised cumulative symptom burden by calculating the number of symptoms each patient reported as moderate or severe (i.e. scored 4 or more), and reported the proportion of patients who experienced this intensity for only one symptom, for two symptoms, three symptoms and so on, up to the 20 symptoms assessed by MOST. Univariable associations between baseline symptom burden (no/mild versus moderate/severe) and disease progression and death during the follow-up period were analysed with survival analysis, and unadjusted hazard ratios were estimated. Hazard ratios, median PFS and OS were calculated for each symptom separately, for three MOST symptom indices (MOST-Abdo, MOST-DorT, MOST-Psych), and for all 20 symptoms collectively. Median PFS and OS of patients with no/mild symptoms versus moderate/severe symptoms were compared with a log rank test. Cumulative incidence rates of progression/death were calculated at 8 and 12 weeks by symptom burden and compared between PRR-ROC versus PPS-ROC≥3 groups with a z test.

3. Results

3.1. Demographics and reasons for treatment

The GCIG-SBS recruited 948 patients at 120 sites in 11 countries; Table 1 reports their baseline characteristics. Their mean age was 63 years, and the majority (89%) were reported to have a good performance status (ECOG 0–1), 570 had PRR-ROC and 378 had PPS-ROC≥3; 68% of patients with PRR-ROC had received at least 2 lines of chemotherapy; 40% of the patients with PPS-ROC≥3 had received 2 prior lines of chemotherapy and 60% had received 3 or more prior lines of chemotherapy. Documented reasons for chemotherapy included radiological progression (77%), CA125 progression (63%) and symptom control 71%, and was similar between groups.

3.2. Baseline symptoms

Baseline questionnaire completion rates were excellent (95%); 903 subjects completed some or all of the MOST questionnaire Symptom burden was substantial (Fig. 1, Supplementary Table 1), with little difference observed between patients with PRR-ROC versus PPS-ROC≥3 (Supplementary Tables 2 and 3, $p > 0.05$ for all items). The most prevalent symptoms were fatigue, pain, poor appetite, abdominal symptoms (including pain/discomfort and bloating/fullness), anxiety, depression, and trouble sleeping. Almost 80% of patients reported pain, 90% reported fatigue, and 60% reported shortness of breath. Abdominal symptoms were common and often co-occurred: the two MOST questionnaire items 'abdominal swelling, bloating and/or fullness' and for 'abdominal pain, discomfort, and/or cramps' were each endorsed by about 75% of patients as mild to severe, and either or both were reported as severe by 28% of patients, moderate by 35%, mild by 46%, and no trouble at all by 35%. Additionally, about half the patients reported anxiety as moderate or severe and 35% reported depression as moderate or severe. There was no statistical difference between the two ROC groups in baseline physical, emotional, and overall wellbeing (Supplementary Table 3).

The majority of participants (88%) reported one or more symptoms as moderate or severe (MOST item score of 4–10), 50% reported 6 or more symptoms moderate or severe, and 30% reported 9 or more symptoms as moderate or severe (Supplementary table 4). Supplementary Fig. 1 shows the number of patients in each group who experienced only one symptom as moderate or severe, two symptoms, and so on up to the maximum number of symptoms assessed by the MOST questionnaire.

The associations between PFS and moderate to severe baseline symptom scores are shown in Fig. 2 and Supplementary Table 5; here, hazard ratios >1 indicate higher symptom burden was associated with earlier disease progression. Using the moderate intensity score cut-off (≥ 4, Fig. 2A), 12 of these 20 symptoms were associated with disease progression, with hazard ratios statistically significantly larger than 1 ($p < 0.05$), indicating higher symptom burden was associated with greater risk of disease progression. Eight of these had PFS hazard ratios larger than 1.25 (most $p < 0.001$): trouble eating had the largest hazard ratio (1.43), followed in order by indigestion, vomiting, nausea, pain, fatigue, abdominal pain/discomfort/cramps, and abdominal swelling/bloating/fullness. Using the severe intensity score cut-off (≥7, Fig. 2B), 10 of the 20 items had PFS hazard ratios statistically significantly larger than 1 ($p < 0.05$), and 5 had hazard ratios larger than 1.25 (trouble eating, indigestion, vomiting, nausea and poor appetite).

Fig. 3 and Supplementary Table 6 shows corresponding associations for OS; here, hazard ratios >1 indicate higher symptom burden was associated with earlier death. In addition to the twelve baseline symptoms that were statistically significant for PFS noted in Supplementary Table 5, a further five were statistically significant ($p < 0.05$) for OS using the moderate intensity score cut-off (≥4, Fig. 3B; shortness of breath, difficulty swallowing, diarrhea, bladder problems, trouble concentrating) but only two of these (shortness of breath and bladder problems) achieved statistical significance for the higher cut-off (≥7, Fig. 3B) due to smaller numbers of patients experiencing severe levels of the other symptoms. The hazard ratios for OS were notably larger than those for PFS, with many larger than 2.0 representing a doubling of the risk of death. Five symptoms had OS hazard ratios larger than 2 for both moderate and severe cut-offs (trouble eating, vomiting, indigestion, loss of appetite, and nausea), with poor appetite also for the severe cut-off.

Considering the MOST indexes, patients who reported a higher burden of abdominal symptoms (MOST-Abdo) and other symptoms

Table 1
Patient characteristics at baseline, treatment duration and reasons for having treatment and ceasing treatment ($n = 948$).

Variable	Category	Resistant/Refractory (PRR-ROC) ($n = 570$) n (%)	Sensitive (PPS-ROC ≥ 3) ($n = 378$) n (%)	*P*-value	Total ($n = 948$) n (%)
Age (years)	<40	11 (2)	5 (1)	0.071	16 (2)
	40–49	65 (11)	29 (8)		94 (10)
	50–59	150 (26)	107 (28)		257 (27)
	60–69	191 (34)	121 (32)		312 (33)
	70–79	135 (24)	97 (26)		232 (25)
	80+	18 (3)	19 (5)		37 (4)
ECOG performance status:	0	203 (36)	126 (33)	0.738	329 (35)
	1	296 (52)	221 (59)		517 (55)
	2	68 (12)	27 (7)		95 (10)
	3	3 (1)	4 (1)		7 (1)
No. previous lines of chemotherapy:	1	183 (32)	2 (0.5)*	<0.001	185 (20)
	2	207 (36)	150 (40)		357 (38)
	3	103 (18)	108 (29)		211 (22)
	4	36 (6)	71 (19)		107 (11)
	5+	40 (7)	45 (12)		85 (9)
	Missing	1	2		3
Cancer related symptoms:	Yes	413 (73)	263 (70)	0.325	676 (71)
Symptomatic Ascites:	Yes	148 (26)	62 (16)	<0.001	210 (22)
Symptoms of cramping abdominal pain or intermittent/incomplete bowel obstruction	Yes	234 (41)	148 (39)	0.567	382 (40)
Response to MOST recent line:	CR	52 (9)	67 (18)	<0.001	119 (13)
	PR	137 (24)	118 (31)		255 (27)
	SD	94 (17)	63 (17)		157 (17)
	PD	266 (47)	116 (31)		382 (41)
	UK (not being assessed)	18 (3)	11 (3)		29 (3)
	Missing	3	3		6
Pathology:	Clear Cell	32 (6)	12 (3)	0.386	44 (5)
	Endometrioid	25 (4)	19 (5)		44 (5)
	Mixed	17 (3)	17 (5)		34 (4)
	Mucinous	10 (2)	4 (1)		14 (2)
	Serous	418 (74)	280 (74)		698 (74)
	Transitional	2 (0.4)	2 (0.5)		4 (0.4)
	Undifferentiated	19 (3)	8 (2)		27 (3)
	Other	42 (7)	34 (9)		76 (8)
	Missing	5	2		7
Initial diagnosis - Grade:	High Grade (includes 2 and 3)	508 (94)	324 (89)	0.011	832 (92)
	Low Grade	35 (6)	41 (11)		76 (8)
	Missing	27	13		40
Extent of Disease at initial diagnosis – elevated CA125	Yes	515 (93)	321 (90)	0.109	836 (92)
	No	38 (7)	35 (10)		73 (8)
	Missing	17	22		39
Reasons for chemotherapy:					
Symptom control/palliation:	Yes	406 (72)	260 (70)	0.491	666 (71)
	No	161 (28)	114 (30)		275 (29)
	Missing	3	4		7
If asymptomatic to delay the development of symptoms	Yes	162 (33)	126 (40)	0.031	288 (36)
	No	334 (67)	188 (60)		522 (64)
	Missing	74	64		138
Rising CA125:	Yes	334 (62)	226 (64)	0.592	560 (63)
	No	201 (38)	126 (36)		327 (37)
	Missing	35	26		61
Radiological evidence of progression:	Yes	386 (77)	248 (76)	0.670	634 (77)
	No	113 (23)	78 (24)		191 (23)
	Missing	71	52		123
Treatment duration (weeks)	None	9 (2)	3 (1)	<0.001	12 (1)
	≤4	36 (6)	16 (4)		52 (6)
	>4–8	83 (15)	29 (8)		112 (12)
	>8–12	126 (22)	63 (17)		189 (20)
	>12–16	80 (14)	63 (17)		143 (15)
	>16–20	47 (8)	55 (15)		102 (11)
	>20–24	47 (8)	54 (14)		101 (11)
	>24	137 (24)	90 (24)		227 (24)
	Not applicable	5	5		10
Reason for ceasing treatment	Adverse Event	28 (5)	32 (9)	<0.001	60 (7)
	Clinician preference	21 (4)	28 (8)		49 (5)
	Completed protocol treatment	63 (11)	78 (21)		141 (15)
	Death	47 (8)	29 (8)		76 (8)
	Disease Progression	342 (61)	165 (44)		507 (54)
	Patient preference	36 (6)	17 (5)		53 (6)
	Other	26 (5)	23 (6)		49 (5)
	Missing	7	6		13

PRR-ROC, platinum resistant/refractory recurrent ovarian cancer; PPS-ROC≥3, potentially-platinum sensitive ROC receiving their third or greater line of chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

* 1 patient was included who had 1 previous line of therapy.

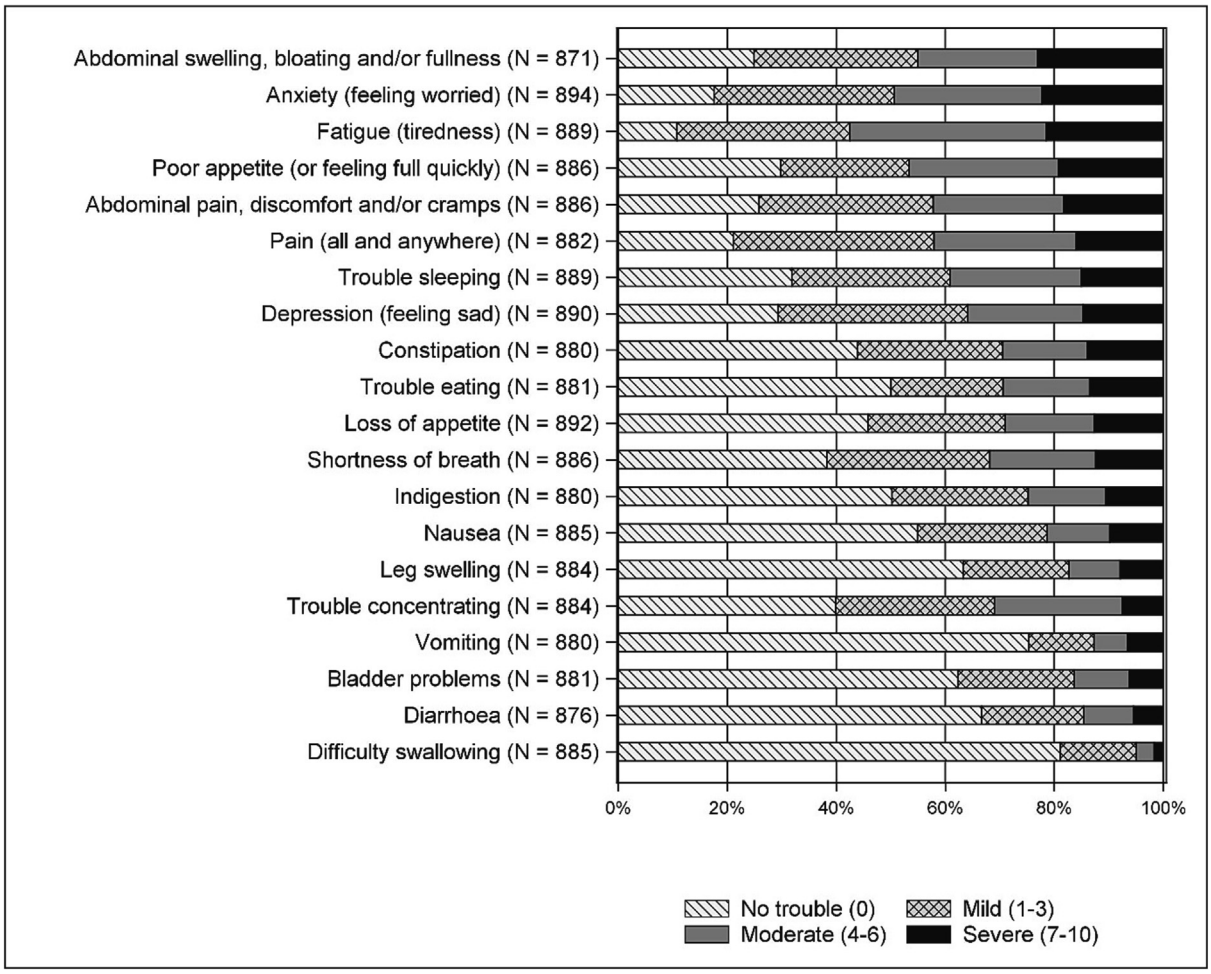


Fig. 1. Baseline prevalence of symptoms assessed by the MOST questionnaire ($n = 903$).

(MOST-DorT) had statistically significant hazard ratios for both moderate and severe cut-offs ($p < 0.001$) for PFS (Fig. 2) and OS (Fig. 3). Patients who reported at least 5 of the 20 MOST symptoms at moderate or severe levels had a PFS hazard ratio of 1.28 ($p < 0.001$) and at severe levels the PFS hazard ratio was 1.23 ($p = 0.015$). Corresponding values of OS hazard ratios were 1.86 ($p < 0.001$) and 1.80 ($p < 0.001$).

Patients with no or mild baseline symptoms had longer PFS than those with moderate/severe cancer symptoms for 12 of the 20 symptoms (Table 2, $p < 0.05$). Results for OS were even more striking: patients with no or mild baseline symptoms survived longer than those with moderate/severe symptoms for 17 of the 20 symptoms (Table 3, $p < 0.05$); the three symptoms for which this did not hold were baseline anxiety, depression and leg swelling.

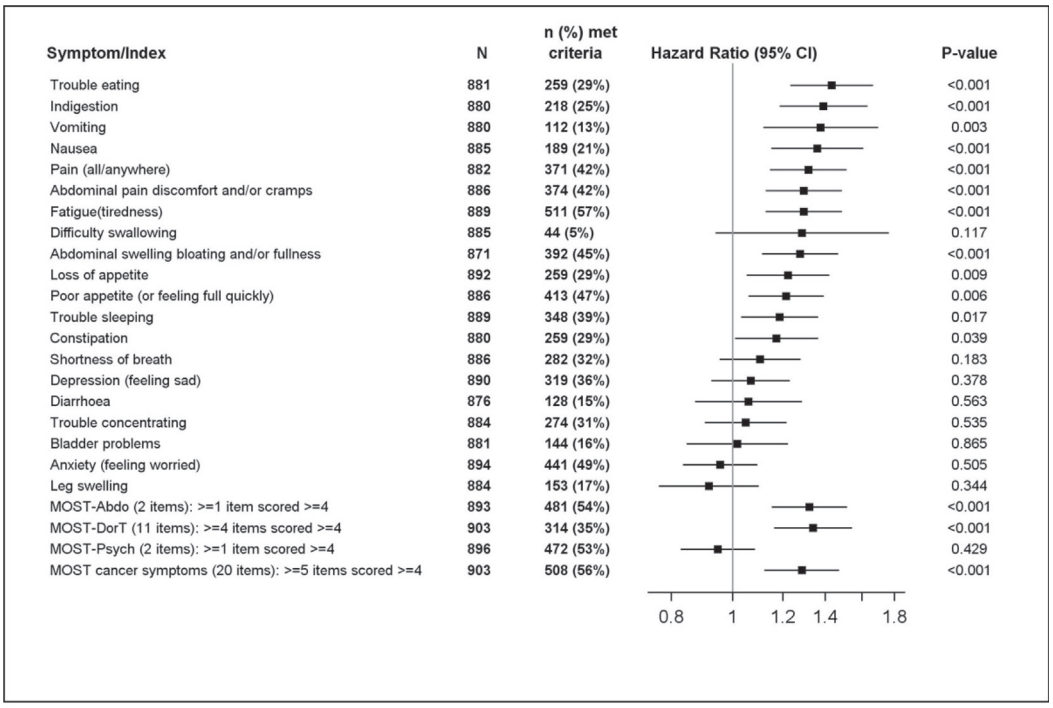
The cumulative incidence of progression or death at 8 weeks of patients is reported by baseline symptom burden status in Supplementary Table 7. Participants who experienced moderate to severe symptoms of trouble eating, poor or loss of appetite, indigestion, nausea, vomiting, were more likely to experience early progression or death at 8 weeks, compared to those with no or mild symptoms (all $p < 0.001$), with a further 8 symptoms significant at the $p < 0.05$ level. Similar results were observed at 12 weeks (Supplementary Table 8).

4. Discussion

The findings of this study clearly demonstrate the high symptom burden reported by patients with ROC as assessed by the MOST questionnaire at baseline prior to commencing palliative chemotherapy which are hidden in plain sight. There was little difference in the symptoms experienced and reported by patients with either PRR-ROC or PPS-ROC≥3. For example, 75% of patients in both groups reported abdominal pain, cramping, swelling or bloating. Approximately 50% of the patients in both groups reported anxiety and 30% of the patients in both groups reported depression. Almost 90% of patients reported one or more symptoms as being moderate or severe, and 50% reported 6 or more symptoms as moderate or severe. Our various analyses of the association between degree of symptom burden and PFS and OS demonstrate conclusively that patients with higher symptom burden at baseline are at greater risk of disease progression and death, and experience shorter survival. This may seemingly be self-evident but is not captured by ECOG performance status and not considered among the long list of eligibility criteria or as a stratification factor in clinical trials. The results of this study are in accordance with those reported by the North-Eastern German Society of Gynecological Oncology and Working Group Gynecological Oncology that HRQL measures such as global QoL or the EORTC QLQ-C30 summary score improved prediction of survival in patients with recurrent ovarian cancer [20].

The symptoms most reported by patients in MOST at a moderate to severe level included fatigue, poor appetite, abdominal swelling/ bloating/ fullness, abdominal pain/discomfort/ cramps, general pain, anxiety, depression and trouble sleeping. These were similar among patients with either PRR-ROC or PPS-ROC≥3. We previously reported that the median overall survival in patients with PRR-ROC was 11.1 months, and median PFS was 3.6 months [21] while in patients with PPSROC≥3 the median OS was 16.6 months and median PFS was 5.3 months [22].

Panel A, using the moderate intensity score cut-off (scored ≥4/10)



Panel B, using the severe intensity score cut-off (scored ≥7/10)

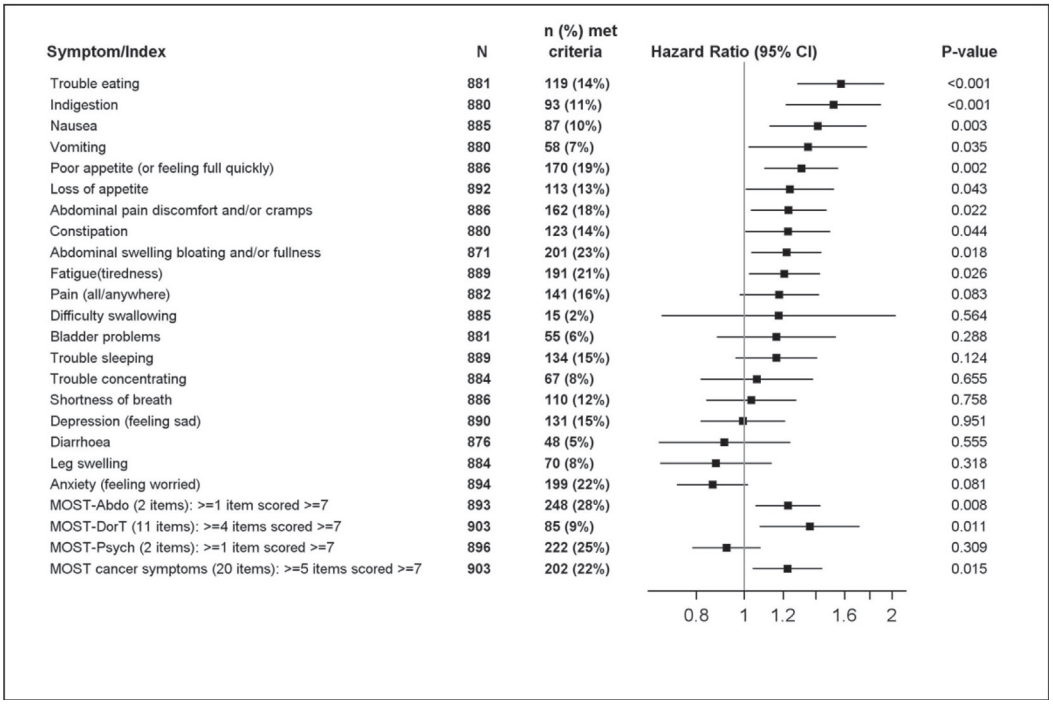
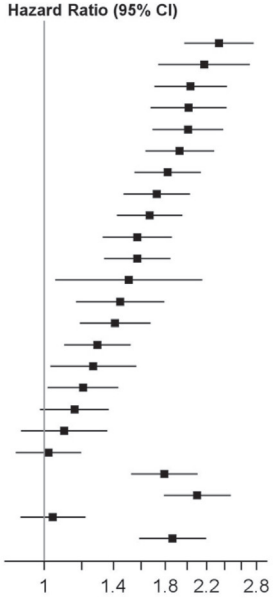


Fig. 2. Associations between disease progression and moderate to severe baseline scores for items of the 20 MOST cancer symptoms and the MOST-Abdo, MOST-DorT and MOST-Psych.
Panel A, using the moderate intensity score cut-off (scored ≥4/10).
Panel B, using the severe intensity score cut-off (scored ≥7/10).
Abbreviations: Measure of Ovarian Symptoms and Treatment (MOST), MOST abdominal symptom items (MOST-Abdo), MOST psychological symptoms (MOST-Psych), MOST physical symptoms that may be caused by disease or treatment (MOST-DorT).

The present study reveals that patients who experience moderate to severe symptoms related to ovarian cancer at baseline are more likely to experience disease progression and death significantly earlier than patients who have no symptoms or mild symptoms at baseline. As a corollary, a higher proportion of patients with moderate to severe symptom burden will experience progression or death at 8 weeks compared to those patients with no or mild symptoms at baseline. The baseline symptoms that flag a poorer prognosis include trouble eating,

Panel A, using the moderate intensity score cut-off (scored ≥4/10)

Symptom/Index	N	n (%) met criteria	P-value
Trouble eating	881	259 (29%)	<0.001
Vomiting	880	112 (13%)	<0.001
Indigestion	880	218 (25%)	<0.001
Nausea	885	189 (21%)	<0.001
Loss of appetite	892	259 (29%)	<0.001
Fatigue(tiredness)	889	511 (57%)	<0.001
Poor appetite (or feeling full quickly)	886	413 (47%)	<0.001
Abdominal swelling bloating and/or fullness	871	392 (45%)	<0.001
Abdominal pain discomfort and/or cramps	886	374 (42%)	<0.001
Shortness of breath	886	282 (32%)	<0.001
Pain (all/anywhere)	882	371 (42%)	<0.001
Difficulty swallowing	885	44 (5%)	0.024
Diarrhoea	876	128 (15%)	<0.001
Constipation	880	259 (29%)	<0.001
Trouble sleeping	889	348 (39%)	0.002
Bladder problems	881	144 (16%)	0.025
Trouble concentrating	884	274 (31%)	0.031
Depression (feeling sad)	890	319 (36%)	0.085
Leg swelling	884	153 (17%)	0.364
Anxiety (feeling worried)	894	441 (49%)	0.797
MOST-Abdo (2 items): >=1 item scored >=4	893	481 (54%)	<0.001
MOST-DorT (11 items): >=4 items scored >=4	903	314 (35%)	<0.001
MOST-Psych (2 items): >=1 item scored >=4	896	472 (53%)	0.596
MOST cancer symptoms (20 items): >=5 items scored >=4	903	508 (56%)	<0.001



Panel B, using the severe intensity score cut-off (scored ≥7/10)

Symptom/Index	N	n (%) met criteria	P-value
Trouble eating	881	119 (14%)	<0.001
Poor appetite (or feeling full quickly)	886	170 (19%)	<0.001
Loss of appetite	892	113 (13%)	<0.001
Vomiting	880	58 (7%)	<0.001
Nausea	885	87 (10%)	<0.001
Indigestion	880	93 (11%)	<0.001
Fatigue(tiredness)	889	191 (21%)	<0.001
Abdominal swelling bloating and/or fullness	871	201 (23%)	<0.001
Constipation	880	123 (14%)	<0.001
Difficulty swallowing	885	15 (2%)	0.157
Pain (all/anywhere)	882	141 (16%)	<0.001
Bladder problems	881	55 (6%)	0.008
Abdominal pain discomfort and/or cramps	886	162 (18%)	<0.001
Shortness of breath	886	110 (12%)	0.003
Trouble concentrating	884	67 (8%)	0.126
Diarrhoea	876	48 (5%)	0.323
Trouble sleeping	889	134 (15%)	0.151
Leg swelling	884	70 (8%)	0.757
Depression (feeling sad)	890	131 (15%)	0.911
Anxiety (feeling worried)	894	199 (22%)	0.403
MOST-Abdo (2 items): >=1 item scored >=7	893	248 (28%)	<0.001
MOST-DorT (11 items): >=4 items scored >=7	903	85 (9%)	<0.001
MOST-Psych (2 items): >=1 item scored >=7	896	222 (25%)	0.687
MOST cancer symptoms (20 items): >=5 items scored >=7	903	202 (22%)	<0.001

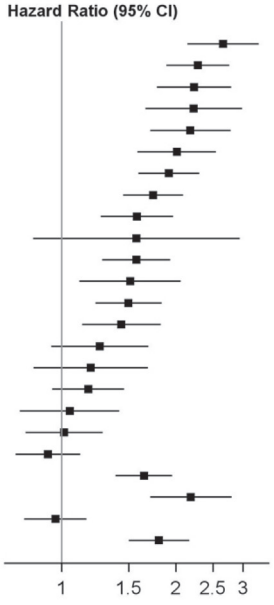


Fig. 3. Associations between overall survival and moderate to severe baseline scores for items of the 20 MOST cancer symptoms and the MOST-Abdo, MOST-DorT and MOST-Psych.
Panel A, using the moderate intensity score cut-off (scored ≥4/10).
Panel B, using the severe intensity score cut-off (scored ≥7/10).
Abbreviations: Measure of Ovarian Symptoms and Treatment (MOST), MOST abdominal symptom items (MOST-Abdo), MOST psychological symptoms (MOST-Psych), MOST physical symptoms that may be caused by disease or treatment (MOST-DorT).

indigestion, nausea, vomiting, and poor or loss of appetite. Additional symptoms including fatigue, constipation, diarrhea, shortness of breath, trouble sleeping, abdominal pain discomfort and/or cramps, swelling, bloating and/or fullness were also correlated with higher likelihood of progression or death at 8 weeks, and a shorter PFS and OS. Previous analysis of the GCIG-SBS Stage 2 MOST data by our group revealed constellations of co-occurring symptoms; specifically, abdominal symptoms, symptoms caused by chemotherapy, other symptoms that may

Table 2
Median Progression-Free Survival per symptom by baseline symptom burden status (none/mild vs moderate/severe).

		None or mild (<4)		Moderate or Severe (≥ 4)		
Item variable	*Baseline symptoms*	*n*	*Median (mths, 95% CI)*	*N*	*Median (mths, 95% CI)*	*P-value (Log-rank)*
MOST4_r2	Fatigue (tiredness)	378	5.3 (4.4–5.8)	511	3.7 (3.5–4.2)	<0.001
MOST4_r6	Trouble eating	622	5.2 (4.6–5.6)	259	2.9 (2.6–3.6)	<0.001
MOST4_r5	Abdominal swelling, bloating and/or fullness	479	5.2 (4.4–5.5)	392	3.7 (3.1–4.0)	<0.001
MOST4_r4	Abdominal pain, discomfort and/or cramps	512	5.1 (4.3–5.5)	374	3.5 (2.9–3.9)	<0.001
MOST4_r3	Poor appetite (or feeling full quickly)	473	5.1 (4.3–5.5)	413	3.7 (3.3–4.1)	0.005
MOST4_r1	Pain (all/anywhere)	511	5.1 (4.3–5.4)	371	3.6 (3.0–3.9)	<0.001
MOST4_r7	Indigestion	662	5.0 (4.3–5.4)	218	2.9 (2.5–3.5)	<0.001
MOST4_r22	Loss of appetite	633	4.9 (4.4–5.4)	259	3.1 (2.7–3.8)	0.009
MOST4_r8	Nausea	696	4.9 (4.3–5.3)	189	2.8 (2.3–3.6)	<0.001
MOST4_r15	Trouble sleeping	541	4.9 (4.2–5.4)	348	3.7 (3.4–4.2)	0.017
MOST4_r9	Vomiting	768	4.7 (4.2–5.2)	112	2.5 (2.0–3.4)	0.003
MOST4_r13	Shortness of breath	604	4.7 (4.1–5.3)	282	3.7 (3.3–4.2)	0.181
MOST4_r31	Trouble concentrating	610	4.7 (4.0–5.3)	274	3.7 (3.4–4.3)	0.537
MOST4_r11	Constipation	621	4.6 (3.9–5.2)	259	3.7 (3.4–4.4)	0.038
MOST4_r33	Depression (feeling sad)	571	4.5 (3.9–5.1)	319	3.9 (3.4–5.1)	0.376
MOST4_r21	Difficulty swallowing	841	4.4 (3.9–5.0)	44	3.8 (2.6–5.0)	0.115
MOST4_r32	Anxiety (feeling worried)	453	4.4 (3.7–5.1)	441	4.3 (3.7–5.0)	0.503
MOST4_r10	Diarrhea	748	4.3 (3.8–4.9)	128	3.5 (2.8–4.9)	0.561
MOST4_r14	Leg swelling	731	4.3 (3.7–4.9)	153	4.0 (3.5–5.3)	0.342
MOST4_r12	Bladder problems	737	4.2 (3.8–4.9)	144	4.9 (3.5–5.6)	0.865

Abbreviation: Measure of Ovarian Symptoms and Treatment (MOST).

be caused by ovarian cancer and chemotherapy, and psychological symptoms [23]. In this paper, we demonstrate that moderate to high symptom burden within clusters of physical symptoms of ovarian cancer at baseline are associated with poorer prognosis.

The high symptom burden experienced by patients with ROC underscores the importance of collecting, documenting and addressing patient reported symptoms not only in clinical trials but in routine clinical practice as well [7]. Many of these symptoms may be controlled or reduced if recognised and effort taken to manage them rather than rely on chemotherapy alone to palliate symptoms given the relatively low response rates. There is a growing body of evidence that prompt attention to symptom management not only reduces symptoms but can also improve HRQL and survival in patients with advanced cancer [6,8,24–26]. To date, no published studies have focussed specifically on managing symptoms in patients with recurrent ovarian cancer who are receiving palliative chemotherapy. It is possible that similar benefits will be observed in patients with ROC as has been observed in lung cancer and other advanced cancers, but this does need to be confirmed in prospective trials which could be embedded within the numerous phase 3 trials and enrich the findings [7]. Current systematic reviews point to the many benefits of routine collection of patient reported outcomes as standard of care, recognising that further adequately powered studies are needed [27,28]. Measuring HRQL at baseline when considering palliative chemotherapy could also potentially help identify a subset of patients with a particularly poor prognosis who are unlikely to benefit from chemotherapy and could therefore be spared unnecessary treatment and toxicity in their last months of life [21]. The majority of patients in this study were reported to have an ECOG performance status (PS) of 0–1 which does not concord with the high symptom burden reported by patients. The ECOG PS is widely used to assess the functional status of cancer patients and underscores the significant discordance between clinician and patient reporting of ECOG PS. This

Table 3
Median Overall Survival per symptom by baseline symptom burden status (none/mild vs moderate/severe).

		None or mild (<4)		Moderate or Severe (≥ 4)		
Item variable	*Baseline symptoms*	*n*	*Median (mths, 95% CI)*	*n*	*Median (mths, 95% CI)*	*P-value (Log-rank)*
MOST4_r2	Fatigue (tiredness)	378	18.9 (16.2–22.2)	511	9.1 (8.4–10.7)	<0.001
MOST4_r3	Poor appetite (or feeling full quickly)	473	16.9 (14.7–19.2)	413	8.8 (7.8–10.2)	<0.001
MOST4_r5	Abdominal swelling, bloating and/or fullness	479	16.9 (14.7–18.9)	392	8.8 (7.7–10.4)	<0.001
MOST4_r6	Trouble eating	622	16.2 (14.3–18.4)	259	6.6 (5.6–8.3)	<0.001
MOST4_r1	Pain (all/anywhere)	511	16.2 (14.3–17.8)	371	9.1 (8.1–10.5)	<0.001
MOST4_r4	Abdominal pain, discomfort and/or cramps	512	15.9 (14.3–18.2)	374	8.8 (7.8–10.3)	<0.001
MOST4_r22	Loss of appetite	633	15.1 (14.0–17.5)	259	7.6 (6.2–9.0)	<0.001
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MOST4_r13	Shortness of breath	604	14.7 (13.3–16.5)	282	9.6 (7.4–11.3)	<0.001
MOST4_r8	Nausea	696	14.5 (13.3–16.5)	189	7.2 (6.0–8.8)	<0.001
MOST4_r15	Trouble sleeping	541	14.2 (12.7–16.5)	348	10.6 (8.9–12.5)	0.002
MOST4_r9	Vomiting	768	14.0 (12.9–15.3)	112	5.4 (3.7–7.5)	<0.001
MOST4_r11	Constipation	621	13.9 (12.5–15.1)	259	11.2 (8.7–12.8)	<0.001
MOST4_r33	Depression (feeling sad)	571	13.7 (12.5–14.8)	319	11.3 (9.6–13.7)	0.084
MOST4_r31	Trouble concentrating	610	13.7 (12.5–14.8)	274	10.5 (8.8–12.6)	0.031
MOST4_r10	Diarrhea	748	13.5 (12.2–14.7)	128	9.6 (7.2–12.3)	<0.001
MOST4_r32	Anxiety (feeling worried)	453	13.5 (12.2–14.7)	441	12.2 (10.7–14.0)	0.797
MOST4_r12	Bladder problems	737	13.4 (12.3–14.5)	144	10.3 (8.2–12.9)	0.025
MOST4_r21	Difficulty swallowing	841	13.3 (12.1–14.2)	44	8.9 (6.2–11.2)	0.023
MOST4_r14	Leg swelling	731	13.1 (11.9–14.3)	153	12.0 (8.0–14.2)	0.363

Abbreviation: Measure of Ovarian Symptoms and Treatment (MOST).

argues for using patient reported PS rather than clinician reporting of PS alone particularly in trials that enrol patients with a moderate to high symptom burden [29]. We demonstrated that those with a higher symptom burden compared with those with a lower symptom burden experienced significantly shortened survival, which highlights the importance of discussing the potential benefit of palliative chemotherapy in patients with a high symptom burden which could temper expectations of benefit of systemic therapy and aid decision making. The potential importance of this is well illustrated in the Kaplan Meier curves of PFS in all contemporary clinical trials in patients with PRR-ROC with at least 30–40% of patients progressing and ceasing treatment within 8 weeks of starting treatment [30,31]. These patients don't benefit from inclusion in the trial and the relatively high proportion who come off treatment dilutes and distorts the potential benefits of the investigational therapy.

Palliating symptoms is an important goal of treatment in this population. Although many patients with PRR-ROC and PPSROC≥3 report a substantial symptom burden, there is unfortunately a paucity of evidence in clinical trials as to whether the goal of palliating symptoms is achieved by chemotherapy, which can be associated with the added burden of toxicity. We have previously reported that in the GCIG-SBS Stage 2, improvement in symptoms was reported by approximately 40% of patients with moderate or severe symptoms at baseline, with a median time to improvement of <2 months. However, the majority did not experience a meaningful improvement in symptoms during chemotherapy [32]. There have been many missed opportunities in the large number of clinical trials in patients with ROC and there has been little effort to document the proportion of patients who are symptomatic and whether palliative chemotherapy reduces symptoms and improves wellbeing. The primary endpoint in most trials is progression free survival which does not reflect impact of treatment on symptoms or indeed whether an increase in PFS is associated with improved wellbeing and reduction of symptoms. We suggest that symptom improvement should be considered as an additional endpoint in future clinical trials and reported. This aligns well with the recent recommendations for a recalibrated approach to endpoints in clinical trials to include endpoints that prioritises patients' needs which the proponents have termed “common sense oncology” which fits with what we are proposing [33].

We have focused on symptoms at baseline prior to commencing chemotherapy but recognise that symptoms may be dynamic and change over time depending on the disease trajectory as well as adverse effects associated with treatment. Careful attention to patient reported symptoms at baseline and during treatment is essential to identify and treat troublesome symptoms that may be disease /treatment related.

The strengths of this study include its prospective design, international participation, and large sample size including a real world population of patients with PRR-ROC and women with PPS-ROC≥3 from across 11 countries. Completion of patient-reported questionnaires and data collection at baseline was high. The broad and inclusive eligibility criteria support the applicability of the results to routine clinical practice. An important limitation of this study was that patient-reported symptoms were collected for research purposes and not relayed to the treating clinicians in real time which could have resulted in referral to palliative care and improved management of symptoms.

5. Conclusions

The symptom burden experienced by patients with ROC is high and similar among patients with PRR-ROC and PPS-ROC≥3. Future clinical trials investigating the clinical utility of using patient-reported measures in routine clinical care of women with ROC during treatment and their effect on improving symptoms and HRQL as well as potential impacts on delaying disease progression and survival are needed [7]. Incorporating patient-reported outcomes in clinical trial design investigating new therapeutics and combinations in ROC over time is fundamental to evaluating clinical benefit and may be more meaningful to patients than progression free survival, which is typically the primary endpoint in clinical trials in this population of patients [1,34].

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CRediT authorship contribution statement

Felicia Roncolato: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Writing – original draft, Writing – review & editing. **Madeleine T. King:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Rachel L. O'Connell:** Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. **Yeh Chen Lee:** Methodology, Writing – review & editing. **Florence Joly:** Data curation, Writing – review & editing. **Felix Hilpert:** Data curation, Writing – review & editing. **Anne Lanceley:** Data curation, Writing – review & editing. **Yoshio Yoshida:** Data curation, Writing – review & editing. **Jane Bryce:** Data curation, Writing – review & editing. **Paul Donnellan:** Data curation, Writing – review & editing. **Amit Oza:** Data curation, Writing – review & editing. **Elisabeth Avall-Lundqvist:** Data curation, Writing – review & editing. **Jonathan A. Ledermann:** Data curation, Writing – review & editing. **Dominique Berton:** Data curation, Writing – review & editing. **Jalid Sehouli:** Data curation, Writing – review & editing. **Marie-Christine Kaminsky:** Data curation, Writing – review & editing. **Martin R. Stockler:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing. **Michael Friedlander:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Conflict of interest statement

FR acknowledges travel grant from Pfizer. Y-CL acknowledges institutional research grant from Beigene, honoraria from Astra Zeneca for educational event and received honoraria from GSK for participation in advisory board. MF acknowledges institutional grants from Astra Zeneca, Beigene, Novartis; received honoraria from Astra Zeneca, GSK, MSD; consulting fees from Astra Zeneca, Novartis, GSK, Incyclix. JL acknowledges grants from Astra Zeneca, MSD/Merck; advisory board for Astra Zeneca, Clovis Oncology, GSK, Artios Pharma, MSD/Merck, VBL Therapeutics, BMS, Nuvation, Ellipses, Immagene, Incyte, Immunogen; educational events for Astra Zeneca, MSD/Merck, GSK, Eisai, Neopharm, and data safety monitoring board for Mersana. AO acknowledges data safety monitoring board for Morphosys, Astra Zeneca, BMS, and uncompensated leadership role for Ozmosis Research where he is CEO and Board member. FH acknowledges grants from GSK, Astra Zeneca, MSD, PharmaMar, Immunogen, consulting fees from Immunogen, MSD, Astra Zeneca; honoraria from GSK, Astra Zeneca, MSD, Pharma Mar; and has been on data safety monitoring boards for MSD, GSK and Astra Zeneca. JB acknowledges grants from Tesaro, Eisai, Immunogen, Karyopharm. MS acknowledges institutional grants from Astellas, Amgen, Astra Zeneca, Bionomics, BMS, Celgene, Medivation, Merck, Sharp and Dohme, Pfizer, Roche and Sanofi. MK, RO, EA-L, FJ, M-CK, YY, DB and AL declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2024.02.025.

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