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Randomized Phase II Trial of Tremelimumab and Durvalumab in Combination versus Sequentially in Recurrent Platinum-Resistant Ovarian Cancer

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Abstract

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Declarations

Ethics approval and consent to participate: This study was approved by the United States Food and Drug Administration and Institutional Review Board of the University of Texas MD Anderson Cancer Center (protocol #2016–0093, NCT03026062). All patients provided written informed consent prior to the initiation of treatment.

Consent for publication: All authors have approved the manuscript and agreed with its submission.

Conflict of interest:

AKS reports consulting for KIYATEC, Merck & Co., GSK, Onxeo, ImmunoGen, Iylon, and AstraZeneca; being a stockholder in Bio-Path Holdings; and licensed patent (EGFL6 antibody). SNW reports consulting for AstraZeneca, Caris, Clovis Oncology, Eisai, EQRX, Gilead, GSK, Immunocore, ImmunoGen, Lilly, Merck, Mereo, Mersana, NGM Bio, Nuvectis, Roche/Genentech, SeaGen, Verastem, Vincerx, Zentalis, ZielBio and research funds to institution from Astra Zeneca, AvengeBio, Bayer, Bio-Path, Clovis Oncology, GSK, Jazz Pharmaceuticals, Mereo, Novartis, Nuvectis, Roche/Genentech, Zentalis. PTS reports consulting for GSK, Aadi, ImmunoGen. LAM reports being a stockholder in Johnson&Johnson, Bristol Myer Squibb, Denali. AAJ reports consulting for Guidepoint, Gerson Lehrman Group, Macrogenics, Xencor, Theolytics, Avenge Bio, and Green Fire Bio, and clinical trial funding to the Institution from Merck, AstraZeneca, Bristol Myers Squibb, Iovance, Macrogenics, Eli Lilly, Alaunos, Immatics, Xencor, Break Through Cancer, and Imunon. Y.Y. reports consulting for AbbVie, Amgen, Bexion, Boehringer Ingelheim Pharmaceuticals, Bristol Myers Squibb, Century, Enliven, GT Medical, NeoImmueTech, Merck, NGM, Repare, Servier, Transthera, Xinthera, and Vertex.

Background: Single agent immune checkpoint inhibitors (ICI) have demonstrated limited responses in recurrent ovarian cancer, however 30–40% of patients achieve stable disease. The primary objective was to estimate progression free survival (PFS) after sequential versus combination CTLA-4 and PD-L1 ICI in patients with platinum resistant high-grade serous ovarian cancer (HGSOC).

Methods: Patients were randomized to sequential arm (tremelimumab followed by durvalumab upon progression) or combination arm (tremelimumab plus durvalumab, followed by durvalumab) using a Bayesian adaptive design that made it more likely for patients to be randomized to the more effective arm. The primary endpoint was immune-related PFS (irPFS).

Results: 61 subjects were randomized to sequential (N=38) or combination therapy (n=23). Thirteen (34.2%) patients in the sequential arm received durvalumab. There was no difference in PFS in the sequential (1.84 months; 95%CI:1.77–2.17) compared with the combination arm (1.87 months; 95%CI:1.77–2.43) (p=0.402). In the sequential arm, no responses were observed, although 12 patients (31.6%) demonstrated stable disease (SD). In the combination arm, 2 patients had partial response (8.7%) while one patient (4.4%) had SD. Adverse events were consistent with that previously reported for ICI. Patient-reported outcomes were similar in both arms.

Conclusions: There was no difference in irPFS for combination tremelimumab plus durvalumab compared to tremelimumab alone (administered as part of a sequential treatment strategy) in a heavily pretreated population of patients with platinum resistant HGSOC. Response rates were comparable to prior reports, though the combination regimen did not add significant benefit as has been previously described.

Precis

There was no difference in the median progression-free survival for combination tremelimumab plus durvalumab compared to tremelimumab alone (administered as part of a sequential treatment strategy) in a heavily pretreated population of patients with platinum resistant high-grade serous ovarian cancer. The adverse event profile was consistent with that previously reported for immune checkpoint blockade, and patient-reported outcomes were similar in both arms.

Keywords

ovarian neoplasms; immune checkpoint inhibitors; randomized controlled trial; patient reported outcome measures; immunotherapy

Introduction

Ovarian cancer remains the most lethal gynecologic malignancy, despite recent advances in treatment such as the introduction of bevacizumab and Poly (ADP-ribose) polymerase (PARP) inhibitors[1]. Therefore, other therapeutic options are being explored, such as immune checkpoint inhibitors (ICI), which have proven effective in many solid tumor types. The biologic plausibility of efficacy is based on the fact that presence of tumor-infiltrating lymphocytes (TILs) in ovarian cancer is correlated with improved survival[2], however epithelial ovarian cancer (EOC) has classically been considered scarcely immunogenic.

Thus, the use of ICI may enhance tumor T-lymphocyte infiltration and limit the immunosuppressive pathways present in the ovarian cancer tumor microenvironment.

Unfortunately, the activity of programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) immune checkpoint inhibitors as monotherapy in recurrent ovarian cancer has been disappointingly low, with reported response rates of 5–15%[3]. For example, recent publications including the phase II KEYNOTE-100 study, NINJA study, and the JAVELIN study describe response rates of 8%, 7.6%, and 9.6% and median PFS of 2.1, 2.0, and 2.6 months for pembrolizumab, nivolumab, and avelumab, respectively, in a pretreated advanced recurrent EOC population[4–6]. There is emerging data that the use of ICI in combination with other agents (e.g. cyclophosphamide and bevacizumab) in recurrent EOC may have improved efficacy[7]. Also, notably, in most trials of ICI for recurrent ovarian cancer, a sizeable portion of subjects exhibit stable disease (SD) of variable duration as their best overall response (29–42%).[4–6] This led us to hypothesize that sequential use of anti-CTLA-4 and anti-PD-1/PD-L1 may serve as an alternative strategy to combination use for extending PFS in patients with platinum-resistant ovarian cancer. There is little published data on efficacy of sequential ICI strategies. However, one phase 2 trial that examined sequential administration of nivolumab and ipilimumab in advanced melanoma (CheckMate 064) found similar response rates with sequential treatment, compared to historical rates with concurrent ICI therapy, but slightly lower frequency of adverse events[8].

A randomized trial of combination checkpoint inhibition, GY003, provided a signal that potentially combination therapy may have increased response. Zamarin *et al.* evaluated ipilimumab plus nivolumab compared to nivolumab alone in women with persistent or recurrent EOC[9]. They reported a 12.2% response rate with nivolumab monotherapy which was significantly lower than the 31.4% response rate seen with the nivolumab plus ipilimumab combination. The median PFS was limited, though also slightly improved in the combination arm (2.0 vs 3.9 months, HR 0.53). Notably, this trial allowed up to only three prior lines of therapy and only 62% of patients had a platinum-free interval of less than 6 months. Additionally, all EOC histologic subtypes were included, including ovarian clear cell carcinoma which demonstrated a greater likelihood of response. Therefore, the patients within this trial represent a heterogeneous population, making it difficult to determine the exact relevant benefit of combination ICI.

We conducted a phase II adaptively randomized open label trial to investigate the efficacy and tolerability of tremelimumab and durvalumab, administered in combination or sequentially, and the ability of these respective administration strategies to extend PFS in patients with platinum-resistant ovarian cancer. We herein report the results for the subset of patients with high grade serous ovarian carcinoma (HGSOC) histology. We additionally included patient-reported outcome (PRO) assessments, which have been poorly explored in immunotherapy clinical trials[10–12], to better understand patient experience and quality of life (QOL) throughout this trial.

Methods

Study Approval

This study was approved by the United States Food and Drug Administration and the Institutional Review Board of the University of Texas MD Anderson Cancer Center (#2016–0093, NCT03026062). The study monitoring was performed by the MD Anderson Investigational New Drug Office. This study was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent prior to the initiation of treatment.

Patient Selection

Patients with high grade serous ovarian carcinoma were required to meet eligibility criteria including platinum resistant or refractory disease, defined as a platinum-free interval of less than 6 months or progression on platinum-based therapy. There were no limitations with regards to number of prior treatment regimens. All patients were required to have measurable disease based on modified Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)[13] and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 with adequate organ and bone marrow function. Any previous treatment with adoptive T cells therapy, a PD-1 or PD-L1 inhibitor or any anti-CTLA4 therapy was not allowed.

Trial Design and Interventions

NCT03026062 is an open-label adaptively randomized phase II trial of tremelimumab (treme) and durvalumab (durva) administered in combination or sequentially. Sequential therapy included tremelimumab 3 mg/kg every 4 weeks (q4w) for up to 4 doses, followed (at the time of confirmed progression) by durvalumab 1.5g every 4 weeks for up to 9 doses or continued progression, unless patients rapidly progressed, changed treatment (per treating physician recommendation), or withdrew consent. Any patients who did not progress after 4 doses of tremelimumab were surveilled until progression and then started at that time on durvalumab, if deemed appropriate. Combination therapy consisted of tremelimumab 1 mg/kg plus durvalumab 1.5g q4w for up to 4 doses followed by durvalumab monotherapy 1.5g for up to 9 doses. Tremelimumab dosing of 1 mg/kg for the combination regimen was selected based on pooled safety data at the time of protocol development from five combination trials of patients who received durva (20 mg/kg, which is 1.5g for average body weight of 75kg) and treme (1 mg/kg) q4w and had <20% rate of adverse events of special interest (NCT02262741)[14–17]. Treatment beyond progression was allowed based on investigator determination of ongoing potential clinical benefit and patient tolerance of therapy.

The first 20 patients were 1:1 randomized to the sequential arm or combination arm. After that, a Bayesian adaptive randomization[18] was used to adaptively assign patients in favor of the arm that had better immune-related progression free survival (irPFS), such that patients were more likely to be randomized to the more effective arm. The design also included Bayesian futility and efficacy monitoring rules to allow for early termination of the futile arm and early selection of the superior arm. Accrual to an arm would be suspended for

futility if the posterior probability of that arm being greater than the other arm was less than 0.10, or the posterior probability that the median irPFS < 3.25 months in that arm was less than 0.10. Conversely, an arm would be selected early for superiority if at any given time the posterior probability of that arm having better irPFS was greater than 0.90. For the posterior calculation, we assumed the median irPFS of each arm followed an inverse gamma distribution with mean of 3 months and standard deviation of 0.5 months. The assumption of 3 month irPFS is based on the average PFS reported in a number of clinical investigations using cytotoxic and biological drugs in this population[19]. The design also included methods of Thall and Simon to guard against an excessive toxicity rate of 60% or higher[20].

RECIST v1.1 modified for immunotherapy[21] was used to assess response. Disease was assessed with imaging every 8 weeks of therapy; any subject who developed progression of disease during investigational agent treatment cycles was required to undergo confirmatory imaging in order to verify the reliability of the radiologic finding per immune-related response guidelines. Progression-free survival was calculated using the time of first documented progression (not the confirmatory scan). Overall survival was calculated from the time of study registration to earliest date of death or last follow up (Data cutoff March 6, 2021). Adverse events (AEs) and serious adverse events (SAEs) were recorded from time of first protocol-specific intervention, throughout the treatment period and including the follow-up period (30 days after the last dose of study drug). All toxicities were graded according to NCI CTCAE v4.03.

Patient-reported outcomes (PROs)

English-speaking patients completed a series of validated PRO instruments to explore symptom burden and severity and their impact on patients' QOL. All PROs were administered electronically via REDCap[22]. The MD Anderson Symptom Inventory for Ovarian Cancer (MDASI-OC) with additional symptom questions to capture immunotherapy toxicity were administered at baseline, with every cycle, at the end of treatment and 30 days after treatment completion[23]. The following PRO instruments were administered at baseline, after every alternating cycle, at the end of treatment, and 30 days after treatment completion. The Functional Assessment of Cancer Therapy – Epidermal Growth Factor Receptor-18 (FACT-EGFRI-18) assessed dermatologic adverse events[24]. The Functional Assessment of Cancer-Therapy-Ovarian (FACT-O) evaluated cancer-related QOL[25]. The EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) Visual Analog Scale (VAS) assessed patients' impressions of their current health status[26]. Lastly, the Center for Epidemiologic Studies Depression Scale (CESD-20) and Generalized Anxiety Disrder-7 (GAD-7) were used to screen for depression and anxiety, respectively, at baseline and after every fourth cycle[27]. Descriptive statistics, the Mann Whitney test, and generalized linear mixed effects models were used to analyze the PROs and describe changes in the patterns of symptoms and QOL during the study period. PRO analyses were limited to baseline, cycle 1 and cycle 2 because of the treatment drop-off rate.

Endpoints and Statistical Analysis

The primary objective was to assess irPFS, which was defined as the time from the date of randomization to the earliest date of progression or death; subjects alive and progression-

free were censored at their last clinic visit assessed for progression. Each treatment strategy was compared to the historical median PFS for platinum resistant ovarian cancer of 3 months[19]. Secondary objectives were to determine the rate of treatment-related toxicity in each experimental arm and to determine overall survival (OS), objective response rate (ORR), and clinical benefit rate (CBR; proportion of subjects with complete/partial response or stable disease). OS was estimated using the Kaplan Meier method and compared using the log-rank test. Demographic and clinical characteristics were compared by trial arm using t-test, ANOVAs (or non-parametric test) for continuous variables and Fisher's exact test for categorical variables. All statistical analyses were performed using Stata/MP v16.0 (College Station, TX).

Results

Patient Characteristics

Between May 2017 and January 2020, 61 patients with platinum resistant HGSOC were enrolled, 38 in the sequential arm and 23 in the combination arm. Of those in the sequential arm, 25 patients (65.8%) did not receive durvalumab due to rapid progression, change in therapy (per discretion of the treating physician), or withdrawal of consent. Accrual was completed over 33 months with a median follow up of 7.33 months (range 0.62–23.95); notably, in December of 2019, based on emerging data of increased response rates in the ovarian clear cell carcinoma (OCCC) histological subtype, the protocol was amended to limit further enrollment to only clear cell carcinoma. The amendment did not change the original primary, secondary, and exploratory objectives of the trial, and results for the OCCC cohort will be reported separately. Baseline characteristics were similar between arms (Table 1), with a median age of 60 years. The majority of patients were White (78.7%), had an ECOG score of 0 (77.0%), and received a median of 4 prior lines of cytotoxic chemotherapy (range 1–10).

Efficacy

Patient disposition is detailed in Figure 1. In both arms, all patients experienced either disease progression or death; 31 of those in the sequential arm (81.6%) and 15 (65.2%) in the combination arm died within the follow up period. The median progression free survival in the sequential arm was 1.84 months (95% CI 1.77–2.17) and in the combination arm was 1.87 months (95% CI 1.77–2.43) (Figure 2a) with no observed difference between arms (p=0.402), with a hazard ratio of 0.80 (95% CI 0.47–1.38, p=0.415) for the combination compared to sequential arm. There was no difference in median OS in the sequential and combination arms at 10.61 months (95% CI 5.95–15.34) and 7.26 months (95% CI 4.24–15.57), respectively (p = 0.810), with a hazard ratio of 0.93 (95% CI 0.49–1.75, p=0.811) (Figure 2b). Fourteen patients met criteria for treatment beyond progression, the majority of whom were in the sequential arm (n=13, 34.2%) and received durvalumab beyond progression, as compared to 1 in the combination arm (4.4%). Almost half of these 14 patients (n=6, 42.8%) achieved stable disease during treatment beyond progression.

In terms of response evaluation (Table 2, supplementary Figure 1), only 2 patients (8.7%) had a partial response (PR), both of whom were in the combination arm. While there

were therefore more responses in the combination arm, the clinical benefit rate that included stable disease (SD) was higher in the sequential arm, with 12 women (31.6%) in the sequential arm demonstrating stable disease with median duration of response of 3.65 months (95% CI 1.77–4.67). The distribution of responses [progressive disease (PD), PR, and SD] was significantly different between the two arms (p=0.005). Notably, in the sequential arm patients experienced stable disease in both the tremelimumab and durvalumab portions of that arm, and one patient experienced stable disease during both therapies. Best percentage change in target lesion size from baseline by cohort are illustrated in a waterfall plot (Supplementary Figure 2) and spider plots (Supplementary Figure 3) by treatment arm.

Safety

Grade 3 or greater immune related adverse events occurred in 9 patients (23.7%%) in the sequential arm, and 7 patients (30.4%) in the combination arm (Table 3). The most common adverse event was hepatic/pancreatic enzyme elevations, seen in 14.5% of the total cohort, followed by colitis (8.2%). Adrenal insufficiency occurred in one patient and was managed with steroids until time of demise. Cerebellitis also occurred in one patient, with symptom onset 9 weeks after starting dual ICI; she improved with steroids and discontinuation of immunotherapy. The difference in the frequency of grade 3 immune related adverse events and for each system between the treatment groups was not significant. There were no treatment related deaths, as all the deaths that occurred within the study follow up period were related to cancer progression.

Patient-reported Outcomes

A total of 53 patients (86.9%) completed PRO assessments, 35 patients (92.1%) in the sequential arm and 18 patients (78.3%) in the combination arm. Table 4 shows PROs at two timepoints within each treatment arm. Consistent with the reported AEs, dermatologic-associated QOL significantly decreased in the sequential arm between the two timepoints (p=0.03). Social well-being significantly diminished in the combination arm between the two timepoints (p=0.02). Supplementary Figure 4 shows changes in mean scores of the top five most severe symptoms and symptom interference of psychosocial and physical functioning over time between the treatment arms. The mean and standard deviations of the top five severe symptoms reported by patients were fatigue (M=3.01, SD=2.42), pain (M=2.47, SD=2.62), abdominal pain (M=2.32, SD=2.55), sleep disturbance (M=2.28, SD=2.52), and bloating (M=2.14, SD=2.66). Although patients in the combination therapy arm reported worse symptom burden and interference, as well as QOL and health status, compared to those in the sequential arm, these differences were not statistically significant. Supplementary Figure 5 shows changes in FACT-O and the individual domains.

The MDASI-OC completed by patients who had grade 3 or higher adverse events before, during and after their reported toxicities were assessed for potential signals. Although we found no statistically significant differences in the aggregate data, at the patient level, there were early signs noticed in the PROs prior to the reported toxicities. Four of the five patients with colitis/diarrhea rated their diarrheal symptom 5 or higher (MDASI-OC scale 0 −10)

prior to the documentation of grade 3 AE. Similarly, the patient with grade 3 maculopapular rash rated her rash as 7/10 on the MDASI prior to documentation of her AE.

Discussion

In this adaptively randomized trial investigating combination versus sequential administration of ICI, there was no difference in PFS compared to historic estimates in a cohort of heavily pretreated platinum resistant high grade serous ovarian cancer patients, with an overall low response rate. Additionally, there was no difference in overall survival between sequential and combination administration, although this study was not powered to detect this difference. It should be noted that there was a difference in distribution of responses/stable disease, with significantly more patients in the sequential arm having some clinical benefit (32% with stable disease). This is consistent with our initial hypothesis that sequential (vs combination) use of anti-CTLA-4 and anti-PD-1/PD-L1 may serve as an alternative strategy to improve disease control in this cohort. The AE profile noted within this study was manageable and similar to what has been previously reported for ICI. The greatest proportion of adverse events were elevations in pancreatic and hepatic enzymes, without evidence of pancreatitis. Importantly, the current trial did not show significant worsening of toxicity in the combination arm, though this has been reported in multiple other studies and tumor types.[28–30]

Similar to the AE profile, there were no statistically significant differences in the mean scores of the PROs assessed. The worsening fatigue over the course of the study period indicates that fatigue was likely driven by treatment and not just disease burden alone. Skin rash and diarrhea were notable symptoms with PRO signals preceding grade 3 AEs. This study can inform optimal integration of PROs into future immunotherapy clinical trials, so that clinicians may be alerted and intervene earlier. The lack of statistically significant differences could be attributed to the sample size included in each treatment arm, the inclusion of only three timepoints in the PRO analysis, and the timing of PRO assessment. Assessing PROs more frequently will allow for more patient input and limit recall bias, although this can be resource intensive and difficult to accomplish in smaller practices. These data are hypothesis generating and support the need for PRO assessments to better understand patients' experiences with treatment for high grade ovarian carcinoma and the impact of both disease and treatment on their overall well-being and QOL.

From a clinical standpoint, we did not find benefit with combination ICI, as seen in the previously reported trial (GY003) utilizing combination ipilimumab and nivolumab, where the combination strategy reported a 31.4% response rate. Key differences in the two study designs provide insight into possible explanations for the difference in results. First, the patients included in the current trial were more heavily pretreated, with a median of 4 prior lines of therapy. In GY003, all patients had 3 or fewer prior lines of therapy, as this was an inclusion criterion, and 24% had received only one prior cytotoxic regimen. Additionally, the trial requirements regarding platinum free interval differed; 38% of patients who received ipilimumab/nivolumab on GY003 had a platinum free interval of over 6 months, while the current trial only included platinum-resistant patients. GY003 also included patients with multiple histologies, while the current study reports on a cohort with high

grade serous histology only. Therefore, the current trial represents a more homogeneous cohort of patients further along in their treatment course and all with platinum-resistant high-grade serous carcinoma. It should be noted that despite the better prognostic patient population of GY003 and the response rate of 31.4%, the overall duration of benefit even for responders was short, with a median of 3.9 months in the combination ipilimumab/nivolumab arm. Finally, given that the current trial largely compares combination therapy to single agent CTLA-4 blockade (as only 34% of the sequential treatment arm actually received durvalumab), as opposed to GY003 which compared combination to single agent PD-1 blockade, the difference in results may be partially attributed to the different monotherapy arms.

The results herein highlight the limited clinical benefit of ICI for this patient group, even with combination ICI strategies. However, there may still be benefit to ICI in this cohort of patients when combined with other treatment modalities, including anti-angiogenic and targeted agents. A recently published trial demonstrates a 47.5% response rate and 95.0% clinical benefit rate for patients with recurrent ovarian cancer who received pembrolizumab, bevacizumab, and oral metronomic cyclophosphamide[7]; patients in this trial who had platinum-sensitive disease and those who had received 3 or fewer prior lines of therapy did particularly well, indicating that these may be subgroups to consider for ICI combination therapy both in clinical practice and in future trials.

There is emerging literature further investigating subpopulations of ovarian malignancy who may have increased benefit from ICI, such as those with clear cell histology. In GY003, this cohort had a five-fold increased likelihood of response, consistent with other ovarian cancer trials evaluating ICI monotherapy.[5,9] The current trial was amended to increase enrollment for this more rare subtype, and the results of that cohort will be reported separately.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of data and materials:

The data generated in this study are available upon request from the corresponding authors.

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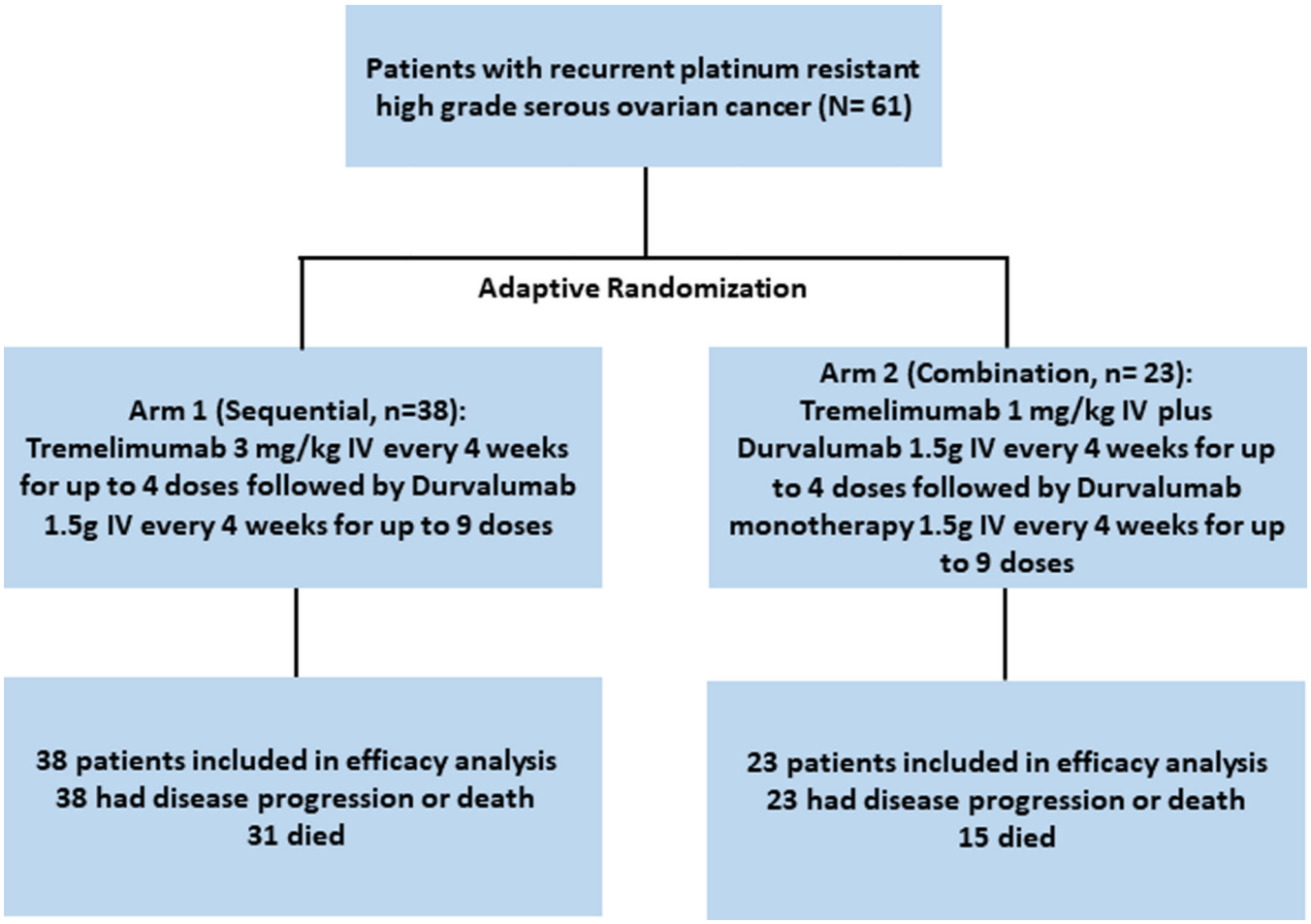
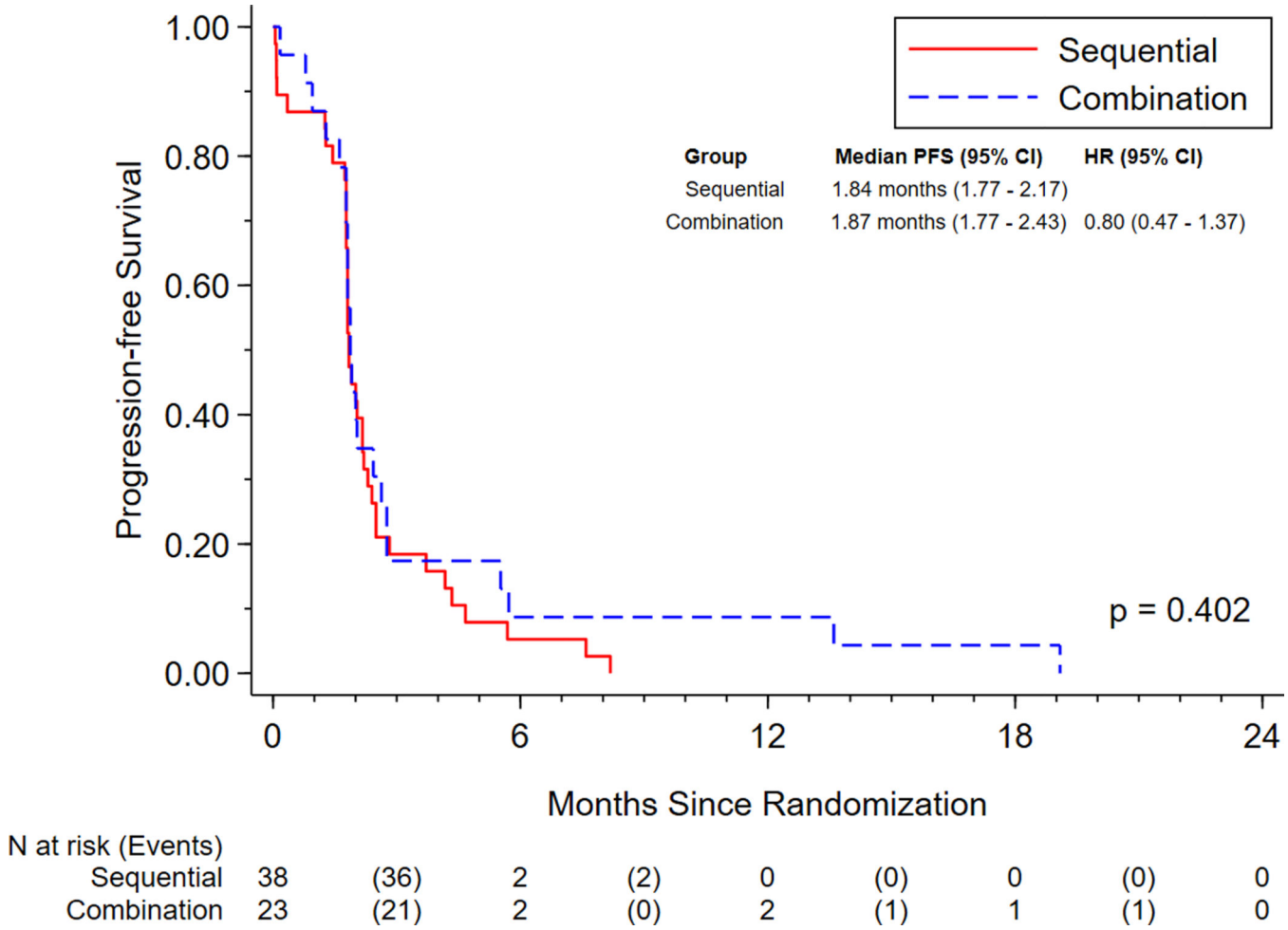


Figure 1. Study schema.

Study design and adaptive randomization to Arm 1 (left) and Arm 2 (right) with details on number of subjects included in efficacy analysis and follow-up with respect to progression and death.



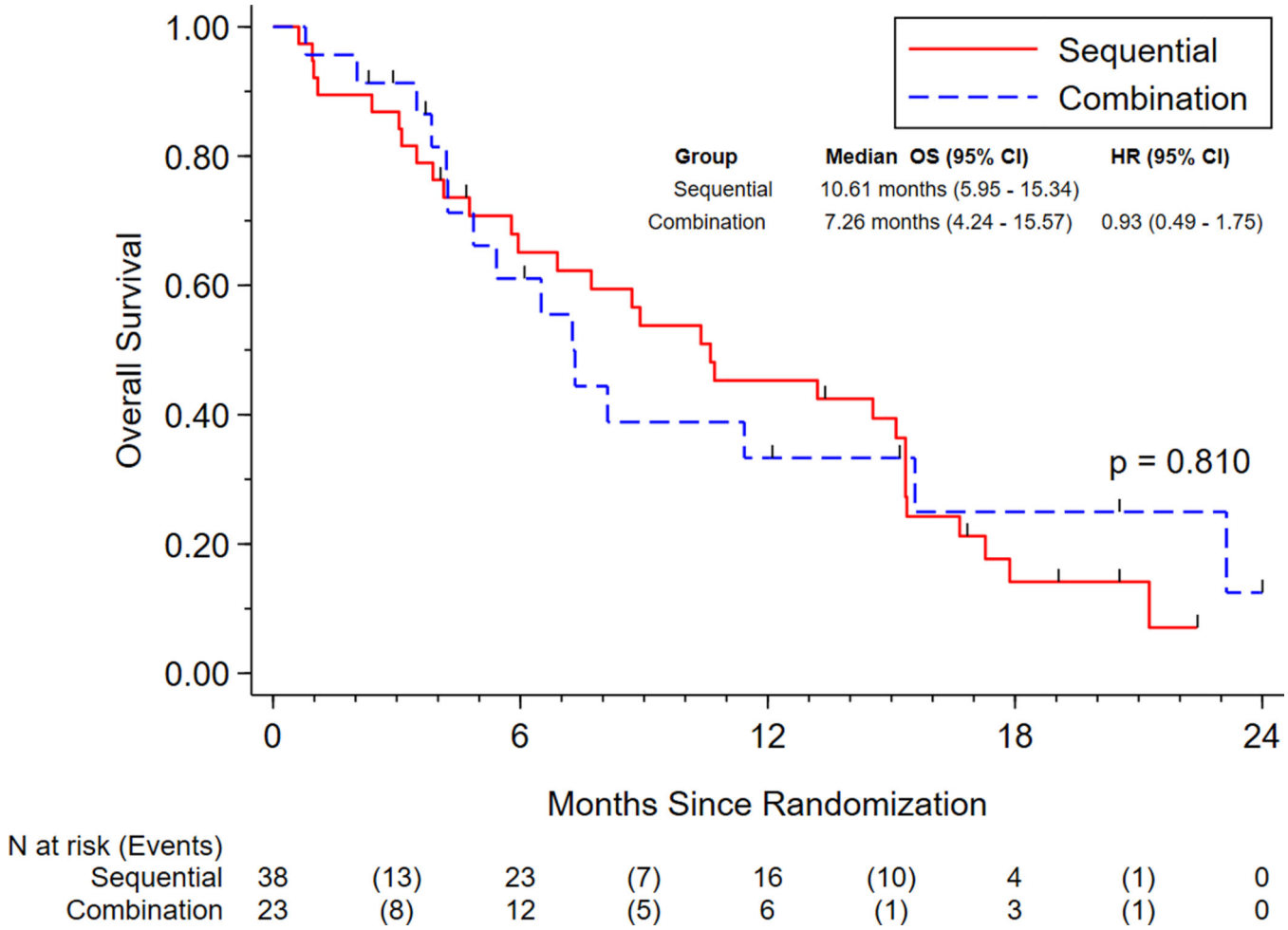


Figure 2. Kaplan-Meier Plots.

(A) Progression-free survival (PFS) per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) according to treatment group (n=38 for sequential arm, n=23 for combination arm). (B) Overall survival (OS) according to treatment group.

Table 1.

Demographic and clinical characteristics of the study population by arm

Characteristic	Sequential (n = 38)	Combination (n = 23)	*P-value*
Age (at first treatment)			0.929
Median (min-max)	60 (28–73)	61 (29–74)	
Race (N,%)			0.210
White/Caucasian	31 (81.58)	17 (73.91)	
Black	3 (7.89)	1 (4.35)	
Asian	1 (2.63)	4 (17.39)	
Other	3 (7.89)	1 (4.35)	
Baseline ECOG score (N,%)			0.861
0	29 (76.32)	18 (78.26)	
1	9 (23.68)	5 (21.74)	
BRCA status (N,%)			0.823
BRCA 1/2 – VUS	1 (2.63)	0 (0)	
No	29 (76.32)	17 (85)	
Yes	8 (21.05)	3 (15)	
Prior therapy (N,%)			
Bevacizumab	26 (68.42)	14 (60.87)	0.547
PARP inhibitor	16 (42.11)	8 (34.78)	0.570
IP chemotherapy	8 (21.05)	4 (17.39)	>0.999
No. of prior cytotoxic regimens			0.427
Median (min-max)	4 (1–10)	4 (1–7)	
Treatment beyond first progression (N,%)			0.010
No	25 (65.79)	22 (95.65)	
Yes	13 (34.21)	1 (4.35)	

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Table 2.

Best overall responses

Table 2a. Best overall response (BOR) throughout treatment

BOR	Sequential N (%)	Combination N (%)	*P-value*
Progression of disease (PD) *	26 (68.4)	20 (87.0)	0.005
Stable disease (SD)	12 (31.6)	1 (4.4)	
Partial response (PR)	0 (0)	2 (8.7)	

* includes 7 deaths with no imaging response

Table 2b.

Best overall response (BOR) in sequential arm

BOR	Treme N (%)	Durva N (%)
Progression of disease (PD) *	29 (76.3)	9 (69.2)
Stable disease (SD)	9 (23.7)	4 (30.8)
Partial response (PR)	0 (0)	0 (0)

* includes deaths with no imaging response

Table 3.

Grade 3 or higher immune related adverse events

Organ System	Sequential (n = 38) (N,%)	Combination (n = 23) (N,%)	*P-value*
Gastrointestinal			
Liver/pancreatic enzyme elevation	5 (13.2)	4 (17.4)	0.72
Colitis/diarrhea	3 (7.9)	2 (8.7)	1.0
Endocrine			
Adrenal insufficiency	1 (2.6)	0 (0)	1.0
Dermatologic			
Rash	1 (2.6)	0 (0)	1.0
Neurologic			
Cerebellitis	0 (0)	1 (4.3)	0.38

Table 4.

Changes in patient-reported outcomes from baseline to completion of treatment cycle 2 reported as mean survey score (standard deviation) per treatment arm.

PRO Instrument	Sequential Arm			Combination Arm		
	Baseline	Within 30-days of Cycle 2	p-value	Baseline	Within 30-days of Cycle 2	p-value
MDASI-OC [a]						
Fatigue	2.7 (2.7)	3.2 (2.3)	0.05	2.7 (2.5)	4.3 (2.1)	0.06
Pain	2.4 (3.0)	2.2 (2.5)	0.65	2.8 (2.8)	3.1 (2.6)	0.34
Abdominal Pain	2.1 (2.6)	2.4 (2.6)	0.17	2.1 (2.3)	3.1 (2.6)	0.22
Sleep	2.3 (2.6)	2.2 (2.2)	1.00	3.4 (3.1)	2.6 (2.7)	0.78
Bloating	2.0 (2.4)	2.5 (3.0)	0.11	1.5 (2.3)	2.7 (2.9)	0.06
WAW	1.6 (2.3)	2.1 (2.0)	0.30	1.7 (2.3)	2.4 (2.0)	0.55
REM	1.5 (2.1)	1.4 (1.8)	0.75	1.4 (1.6)	1.8 (1.7)	0.73
Interference	1.5 (2.1)	1.7 (1.8)	0.67	1.5 (1.8)	2.1 (1.7)	0.56
FACT-EGFRI-18 [b]	68.5 (3.8)	66.8 (6.4)	0.03	68.6 (3.3)	67.1 (5.9)	0.19
CESD-20 [c]	10.2 (7.7)	-	-	11.4 (7.3)	-	-
GAD-7 [d]	3.4 (3.6)	-	-	3.7 (3.6)	-	-
EQ-5D-5L, VAS [e]	72.9 (17.2)	74.8 (16.8)	0.64	70.3 (19.4)	70 (21.7)	0.49
FACT-O [f]	120.3 (16.5)	116.9 (18.9)	0.51	116.9 (19.8)	109.3 (20.6)	0.11
FACT-G[g]	87 (13.6)	84.1 (15.3)	0.45	84.1 (15.1)	78.9 (14.2)	0.12
PWB	23.9 (3.7)	22.9 (4.4)	0.35	22.1 (6.2)	21.5 (4.2)	0.57
SWB	24.7 (4.0)	24 (4.2)	0.20	24.4 (3.6)	23.1 (4.0)	0.02
EWB	17.5 (5.0)	18.0 (4.7)	0.27	17.8 (3.8)	16.7 (5.3)	0.07
FWB	20.9 (4.9)	19.2 (6.6)	0.43	19.8 (6.0)	17.7 (6.6)	0.86
OCS	33.3 (5.0)	32.7 (5.2)	0.79	32.8 (5.9)	30.4 (7.3)	0.22
FACT-O TOI [h]	78.1 (11.4)	74.8 (13.7)	0.52	74.7 (15.9)	69.5 (16.4)	0.51

Recall period for PROs: MDASI = within last 24 hours; FACT-G = the past 7 days; EQ-5D-5L 9 (VAS) = within last 24 hours; CESD-20 = past 7 days; GAD-7 = past 14 days.

[a]MD Anderson Symptom Inventory-Ovarian Cancer (**MDASI-OC**) assessed common cancer symptoms and ovarian cancer specific symptoms on a scale of 0 – 10 (least severe to most severe). The top 5 most severe symptoms (i.e. fatigue, pain, abdominal pain, sleep, and bloating), as well as their interference with psychosocial and physical functioning (i.e. **WAW**=Walking, Activity, Work; **REM**=Relation with others, Enjoyment of Life, Mood; and overall interference) are reported.

[b]The Functional Assessment of Cancer Therapy – Epidermal Growth Factor Receptor-18 (**FACT-EGFRI-18**) assessed dermatologic adverse events. Score range 0–72 where 0=severely symptomatic patient.

[c]The Center for Epidemiologic Studies Depression Scale (**CESD-20**) screened for symptoms of depression over the past week. Cut-off score of 16 or greater identifies patients at risk for clinical depression.

[d]The Generalized Anxiety Disrder-7 (**GAD-7**) screened for symptoms of anxiety over the past 2 weeks. Score range 0–21 (0–4 minimal, 5–9 mild, 10–14 moderate, 15–21 severe anxiety).

[e]The EuroQol-5 Dimensions-5 Levels(**EQ-5D-5L**), Visual Analog Scale (**VAS**) assessed patients' impression of their current health status in the last 24 hours. Score range 0–100, where 100 = best health status.

[f]The Functional Assessment of Cancer-Therapy-Ovarian (**FACT-O**) evaluated cancer-related QOL and comprises of the FACT-G subscales plus the Ovarian Cancer-Specific Subscale (**OCS**). 38 items. Total score range 0–152, higher score = better QOL.

[g]Functional Assessment of Cancer Therapy – General (**FACT-G**) domains:

- Physical Well-being (**PWB**), score range 0–28, higher score = better PWB.
- Social Well-being (**SWB**), score range 0–28, higher score = better SWB.
- Emotional Well-being (**EWB**), score range 0–24, higher score = better EWB.
- Functional Well-being (**FWB**), score range 0–28, higher score = better FWB.

[h]FACT-O Trial Outcome Index (**FACT-O TOI**) = PWB + FWB + OCS; 25 items; Score range 0–100; higher score = better QOL