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Chemotherapy Response Score as a surrogate endpoint for clinical efficacy of neoadjuvant durvalumab and tremelimumab in combination with chemotherapy in newly diagnosed advanced high grade serous ovarian cancer (iPRIME): A randomized, non-comparative phase 2 clinical trial

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Abstract

Objective

To determine the efficacy of neoadjuvant dual immune checkpoint blockade with durvalumab and tremelimumab in combination with carboplatin and paclitaxel (Du-T-NACT), defined by the chemotherapy response score (CRS) 3 rate after three cycles of treatment, in newly diagnosed advanced stage high-grade serous ovarian, fallopian tube or peritoneal carcinoma.

Methods

iPRIME is an open label, non-comparative multicentre phase 2 study. Patients with FIGO stage IIIC and IV high grade serous carcinomawere randomized 2:1 to receive durvalumab and tremelimumab in combination with carboplatin and paclitaxel (Du-T-NACT) or standard neoadjuvant carboplatin and paclitaxel alone (NACT). The primary endpoint was CRS 3 rate in Du-T-NACT, with a rate exceeding 50% considered positive. Secondary endpoints included the CRS 3 rate in each arm, progression-free survival, and radiological response.

Results

40/49 (81.6%) of patients in Du-T-NACT were evaluable for chemotherapy response score. The rate of CRS 3 in Du-T-NACT was 13/40 (32%, 90% CI 20–47%). The CRS 3 rate by central review was higher in Du-T-NACT than in NACT (27% [13/49] versus 3.8% [1/26], p = 0.03), but this was not reflected in other measures of clinical benefit. Radiological response after treatment by RECIST 1.1 was similar between arms (45% versus 50%, p = 0.82), as was CA-125 response by GCIG criteria (80% versus 81%). Median progression-free survival was 14.7 months in both arms, with no difference in PFS at 12 or 24 months (p = 0.64).

Conclusion

Combining durvalumab and tremelimumab to neoadjuvant carboplatin–paclitaxel did not achieve the primary efficacy endpoint. This was the first study to utilise CRS 3 as a primary endpoint in the frontline treatment of ovarian cancer. Further research is required to assess the role of neoadjuvant dual blockade immunotherapy with chemotherapy in advanced ovarian cancer and identify biomarkers of response.

Highlights

• PD1 and PDL1 immune checkpoint inhibitors have not demonstrated a survival benefit in 1st line ovarian cancer trials, although phase II studies of dual checkpoint blockade in combination with chemotherapy suggest greateractivity. The chemotherapy response score following neoadjuvant

chemotherapy is a validated prognostic marker, but has not been used as a primary endpoint to assess efficacy in Phase II neoadjuvant trials of immune checkpoint inhibitors in combination with chemotherapy.

• Adding durvalumab/tremelimumab to neoadjuvant carboplatin–paclitaxel did not meet the pre-specified primary endpoint of CRS 3 of > 50%, although it was associated with a numerically higher chemotherapy response score 3 rate compared to the chemotherapy alone arm.

• The results support neoadjuvant chemo-immunotherapy trials and investigation of the utility of chemotherapy response score as a surrogate endpoint in Phase 2 neoadjuvant trials that include immune checkpoint inhibitors.

INTRODUCTION

Ovarian cancer is the leading cause of gynaecological cancer mortality worldwide (1, 2). Despite receiving optimal treatment, 5-year survival is 48% for patients with advanced (stage III/IV) disease, and 20% for patients with stage IV disease (1–3).

Recent advances in ovarian cancer treatment include the introduction of poly(ADP-ribose) polymerase (PARP) inhibitors and antiangiogenic therapies. The addition of bevacizumab to chemotherapy, followed by maintenance treatment, has improved progression-free survival (PFS), with overall survival (OS) benefit reported in women with high-risk disease (4, 5). Maintenance PARP inhibitors after frontline chemotherapy have also improved PFS, particularly in patients with germline BRCA mutations or homologous recombination-deficient tumours (6–9). However, there remains a substantial unmet need for patients whose disease is less responsive to chemotherapy alone, which includes those with homologous recombination-proficient ovarian cancer.

Immunotherapy has changed the treatment landscape in several gynaecological cancers, with significant OS benefits demonstrated in cervical and endometrial malignancies (10–12). In ovarian cancer, however, results have been more modest. Early-phase studies of single-agent immune checkpoint inhibitors targeting programmed death receptor-1 (PD-1) or its ligand PD-L1 reported response rates of only 6–9% in patients with recurrent ovarian cancer, while combined PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibition achieved response rates of up to 33%, although median PFS remained short (13, 14) Similarly, in the MoST-CIRCUIT trial, combined nivolumab and ipilimumab produced an objective response rate of 54% in patients with advanced ovarian and endometrial clear cell carcinoma, a histological subtype historically resistant to chemotherapy, lending further support to dual checkpoint blockade as a strategy in ovarian cancer (15). More recently, KEYNOTE-B96 reported improved PFS and OS in patients with platinum-resistant recurrent tubo-ovarian carcinoma treated with pembrolizumab combined with weekly paclitaxel, with or without bevacizumab (16).

.Cytotoxic chemotherapy can exert immunomodulatory effects, including disruption of immunosuppressive pathways and enhancement of cytotoxic T-cell responses (17) providing a biological

rationale for chemo-immunotherapy combinations, with survival benefit across multiple tumour types (18–26).

In advanced ovarian cancer, two large randomised trials evaluating the addition of a single-agent PD-1 or PD-L1 inhibitor to standard frontline chemotherapy did not improve PFS compared with chemotherapy alone (27, 28). One possible explanation is that single-agent checkpoint blockade is not sufficient to overcome the highly immunosuppressive ovarian cancer tumour microenvironment; in this context, anti-tumour immunity is likely suppressed by several overlapping inhibitory pathways rather than a single checkpoint alone. Dual checkpoint blockade targeting complementary pathways, such as PD-1/PD-L1 and CTLA-4, may therefore provide a robust and more sustained restoration of T-cell activity than either approach alone. Ovarian cancer is characterised by adaptive immune resistance due to T-cell exhaustion, regulatory T-cell infiltration, myeloid derived suppressor cells and impaired antigen presentation which may be overcome by dual checkpoint blockade, particularly when combined with combination chemotherapy which leads to antigen release and immune stimulation.

Building on this rationale, two recent non-comparative phase studies, the phase 2 KGOG 3046/TRU-D and the phase 1b INEOV study, assessed dual immune checkpoint inhibitors in combination with frontline neoadjuvant chemotherapy and demonstrated promising durable response rates (29, 30). In the KGOG 3046/TRU-D study, the ORR was 86% and CRS 3 rate 31% with a 12-month progression-free survival rate of 63.3%, exceeding the expected historical control rate of 50%, suggesting that dual checkpoint blockade with chemotherapy may provide meaningful clinical activity in this setting (30).A CRS 3 score was associated with a significantly improve PFS of 32.7 months vs 12 months for CRS 1/2 with a HR 0.36(0.18–0.74).In the phase 1b INEOV randomised trial of carboplatin and paclitaxel in combination with either durvalumab alone or with tremelimimab, the ORR ranged from 74–87% with a CRS 3 rate of 38% .

A randomised phase II study with a limited number of patients is unlikely to have adequate power to detect realistic improvements in PFS, making PFS comparisons unreliable and hence we selected chemotherapy response score(CRS) as the primary endpoint for efficacy.

CRS in the omentum is a validated 3-tier histopathologic scoring system that is prognostic for progression-free survival, based on the degree of pathological response to neoadjuvant chemotherapy in ovarian cancer (31).A CRS − 3 indicates a complete or near complete response with either no residual tumor in the omentum or scattered microscopic foci < 2mm with extensive treatment related fibrosis and inflammation. A consistent finding in CRS 3 is a median PFS of 18–24 months compared with 8–12 months with CRS1 which is defined as no or minimal response to chemotherapy with predominantly viable cancer and minimal to no fibrosis. In a systematic review and meta-analysis of 877 patients from 11 countries, CRS 3 was reported in 28% of patients following neoadjuvant chemotherapy and was associated with improved progression-free survival and overall survival compared to CRS 1/2 (32). The absence of significant heterogeneity in this analysis supports CRS as a robust prognostic marker.There have been at least 3 systematic reviews/ meta-analyses demonstrating that CRS3 is reproducible and

prognostic and CRS has been incorporated into ESGO/ESMO pathology recommendations. We hypothesized that CRS 3 could be used as a surrogate for progression-free survival and the primary endpoint in neoadjuvant trials of investigational agents such as combination immune checkpoint inhibitors in combination with chemotherapy in patients with advanced ovarian cancer, similar to the use of pathological complete response as a surrogate endpoint in ISPY trials in breast cancer (33).

The iPRIME study (immune-chemotherapy as PRIMary treatment for Epithelial ovarian cancer) aimed to evaluate the activity of the dual immune checkpoint inhibitors durvalumab (Anti-PDL-1) and tremelimumab (Anti-CTLA 4), combined with standard chemotherapy in patients with advanced high-grade serous ovarian, fallopian tube, and peritoneal carcinoma. The primary endpoint was the rate of CRS 3 in the chemo-immunotherapy arm.

PATIENTS AND METHODS

Study design

This phase II, multicentre, randomized, non-comparative study evaluated the addition of dual immune checkpoint inhibitors to neoadjuvant chemotherapy. The study consisted of a safety run-in, and patients were randomly assigned to one of two arms in a ratio of 2:1. Arm 1 received a combination of durvalumab and tremelimumab with carboplatin and paclitaxel (Du-T-NACT), while Arm 2 only received carboplatin and paclitaxel (NACT).

Key eligibility criteria were newly diagnosed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, stage III or IV according to the International Federation of Gynecology and Obstetrics (FIGO) classification, the presence of omental disease confirmed through radiological or laparoscopic assessment, medically fit to receive neoadjuvant chemotherapy and suitable candidates for interval debulking surgery. Additional eligibility criteria included being at least 18 years old, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, having adequate hematologic, renal, and hepatic function, and being willing to undergo a pre-treatment biopsy. Patients who had histology other than high-grade serous, a history of omentectomy, were inoperable or unlikely to be operable after neoadjuvant chemotherapy, had previous PD-1 or PD-L1 immunotherapies, or had contraindications for immunotherapy were excluded from the study. Randomization was conducted using the iPRIME online electronic data capture system.

Treatments and assessments

Neoadjuvant treatment phase

In Du-T-NACT, patients received three cycles of carboplatin (AUC 5), paclitaxel (175 mg/m2), durvalumab (1500 mg), and tremelimumab (75 mg) every 21 days, followed by interval debulking surgery. After surgery, they received three cycles of the same regimen, followed by maintenance durvalumab every 4

weeks and tremelimumab every 12 weeks for a total of 36 weeks or until disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met. In NACT, patients received three cycles of carboplatin (AUC 5) and paclitaxel (175 mg/m2) every 21 days preoperatively and three cycles postoperatively.

Interval debulking surgery

Following three cycles of neoadjuvant treatment, patients suitable for surgery underwent interval debulking surgery by a certified gynaecological oncologist, with the objective to achieve optimal cytoreduction. In cases where surgery was not performed due to disease progression or other factors, patients were removed from protocol treatment but followed for evaluable secondary endpoints.

CRS assessment

The primary endpoint of the study was the rate of CRS 3 in the combined durvalumab and tremelimumab with carboplatin and paclitaxel arm. The histopathology report from the resection specimen was required to document the pathological response in accordance with chemotherapy response score, which was assessed both locally and with central review.

Adjuvant treatment phase

Postoperative adjuvant treatment was contingent on the chemotherapy response score. Patients with CRS 3 or 2 without radiological or clinical progression received adjuvant treatment based on the allocation from the neoadjuvant treatment arm. Per protocol, patients with CRS 2 could be removed from the study at the investigator's discretion if considered clinically necessary to change their treatment regimen. Patients with CRS 1 were discontinued from the experimental treatment and received standard of care therapy as per investigator discretion and entered the follow-up period of the trial.

Study endpoints

The primary study endpoint was the rate of CRS 3 (complete or near complete pathologic response) after three cycles of combined durvalumab and tremelimumab with carboplatin and paclitaxel in patients who underwent interval debulking surgery and were evaluable for CRS. Secondary endpoints were assessed in the randomised population and included the rate of CRS 3 following neoadjuvant chemotherapy alone, radiological response to pre-operative treatment according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), progression-free survival, 12 month PFS, adverse events according to Common Terminology Criteria for Adverse Events version 4.03, residual disease at surgery, CA-125 response per Gynecologic Cancer InterGroup (GCIG) criteria, and Health-Related Quality of Life (QoL).

STATISTICAL CONSIDERATIONS

Sample size

The expected rate of CRS 3 from the primary and validation cohorts of chemotherapy response scoring is estimated to be between 27–33%. The null hypothesis for patients treated with combined durvalumab and tremelimumab with carboplatin and paclitaxel was that the true rate of CRS 3 is 30%, while a rate of ≥ 50% is considered of interest for further development. To conduct a one-sided exact test with 80% power and 5% type one error, a sample size of 43 patients in the Du-T-NACT arm was required. To account for losses to follow-up, a total of 50 patients were to be recruited. Additionally, patients were recruited for a control group treated with neoadjuvant chemotherapy alone and were randomized at a 2:1 ratio between Du-T-NACT and NACT.

Analysis populations

The ‘CRS evaluable population’ was the primary population for analysis of the primary endpoint and included all evaluable patients that proceeded to interval debulking surgery and had CRS assessed. The safety analyses included all randomized patients who commenced protocol treatment. The ‘randomized population’ was the intention-to-treat population that included all randomized patients, irrespective of eligibility or protocol adherence, and was the population for efficacy analyses other than the primary endpoint.

Statistical methods

The rate of CRS 3 was estimated in the CRS evaluable population with a two-sided 90% Clopper-Pearson confidence interval (CI). Thus, patients who did not proceed to interval debulking surgery were excluded from this analysis. Best- and worst-case sensitivity analyses were done to show how the proportion of CRS3 would vary in the Du-T-NACT arm depending on what assumption is made about the patients who did not have CRS assessed. Based on the study design, we can conclude that there was evidence of a proportion of patients with CRS 3 greater than 30% if the lower limit of the 90% confidence interval exceeded 30%.

Progression-free survival was measured from randomization to first documented disease progression or death and summarised using the Kaplan-Meier method. Pre-operative response rate, CA-125 response rate, CRS response rate and surgery completion rate were estimated for each Arm with corresponding exact 95% confidence intervals and compared between Arms using Fisher’s exact test. The reverse Kaplan-Meier method was used to estimate median follow-up time. No adjustment for multiplicity was made. All analyses of secondary objectives were hypothesis-generating and were pre-specified in the trial protocol. No other comparisons were tested.

RESULTS

A total of 75 patients were enrolled across 10 Australian sites between June 2018 and July 2021. There were 49 patients in the Du-T-NACT arm. and 26 patients in the NACT arm. In Du-T-NACT, 41 out of 49 patients (83.6%) received neoadjuvant treatment and underwent interval debulking surgery, while one patient did not receive neoadjuvant treatment, and seven patients did not undergo surgery (1 due to progressive disease, 1 due to significant adverse effects, 1 extensive disease, 4 otherwise unsuitable for surgery). In NACT, 21 out of 26 patients (80.7%) underwent interval debulking surgery. For the analysis of the study primary endpoint of chemotherapy response score, 40 patients (84.7%) in Du-T-NACT and 19 patients (73.1%) in NACT were considered eligible. Three patients, one in Du-T-NACT and two in NACT, were not eligible for chemotherapy pathological response score assessment after undergoing interval debulking surgery due to a change in histological diagnosis (Fig. 1).

Baseline characteristics are outlined in Table 1. The median age was 63 years (range 35–77), and 64% of patients had FIGO stage IIIC disease. 67 (89%) patients had no pathogenic germline BRCA1/2 mutations, while six (8%) had pathogenic germline BRCA1/2 mutations, and 2 patients did not have germline testing. All BRCA1/2 mutation carriers were randomized to the Du-T-NACT arm. The study concluded its follow-up on July 29th, 2023, which was 2 years after the last patient began treatment, with a median duration of follow-up of 4.1 years. At study closure, there were 57 patients who either experienced disease progression or died (36 in Du-T-NACT and 21 in NACT). Ten patients in follow-up were still alive (8 in Du-T-NACT and 2 in NACT at the study close-out date, and 8 patients were censored earlier .

Table 1: Baseline Characteristics

	Treatment		
Characteristic	**Du-T-NACT (n = 49)**	**NACT (n = 26)**	**Total (n = 75)**
Age, years, n (%)			
Mean (SD)	61 (9)	63 (11)	62 (10)
Median [range]	61 [36 - 74]	66 [35 - 77]	63 [35 - 77]
IQR	55 - 69	58 - 71	56 - 70
ECOG performance status, n (%)			
0	24 (49%)	11 (42%)	35 (47%)
1	25 (51%)	15 (58%)	40 (53%)
FIGO Stage at Initial Diagnosis, n (%)			
Stage IIIC	31 (63%)	17 (65%)	48 (64%)
Stage IV (including IVA and IVB)	18 (37%)	9 (35%)	27 (36%)
BRCA mutation test, n (%)			
BRCA 1	4 (8%)	0	4 (5%)
BRCA 2	2 (4%)	0	2 (3%)
No BRCA 1/2 Mutation	42 (86%)	25 (96%)	67 (89%)
Not done	1 (2%)	1 (4%)	2 (3%)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FIGO:International Federation of Gynecology and Obstetrics; BRCA:Breast Cancer gene

Efficacy analyses

Primary Endpoint: rate of CRS 3 following combined durvalumab and tremelimumab with carboplatin and paclitaxel in the CRS evaluable population. Of the 49 patients randomized to Du-T-NACT, 40 were

evaluable for CRS. Nine patients were not evaluable due to: being deemed unsuitable for surgery (5 patients), disease progression (1 patient), discontinuation due to adverse events (1 patient), change of diagnosis to carcinosarcoma (1 patient), and withdrawal of consent prior to any protocol treatment (1 patient). The rate of CRS 3 by central review was 32% (13/40) (90% CI, 20–47), which did not meet the primary endpoint. To assess the potential impact of non-evaluable patients, a best–worst case sensitivity analysis was performed in the randomised Du-T-NACT population. Under the most conservative assumption that all non-evaluable patients did not achieve CRS 3, the CRS 3 rate was 13/49 (27%). Under the most favourable assumption that all non-evaluable patients achieved CRS 3, the CRS 3 rate was 22/49 (44%).

Secondary endpoints

All 75 randomized patients were included in the analysis of secondary endpoints. Comparing the rate of CRS 3 between the Du-T-NACT arm and NACT arm in the randomised population was a secondary study objective. The rates of CRS 3 by central review were 13/49 (27%) in Du-T-NACT and 1/26 (3.8%) in NACT, respectively (p = 0.03).Objective response to pre-operative treatment (complete or partial response by RECIST 1.1) was 45% in Du-T-NACT and 50% in NACT (p = 0.82). CA-125 response rate by GCIG criteria was 80% in Du-T-NACT and 81% in NACT.

There were 57 progression-free survival events, and the median progression-free survival for both Arms 1 and 2 was 14.7 months (Fig. 2). The rate of progression-free survival at 12 and 24 months for all patients was 63% (95% CI 52–75) and 28% (95% CI 19–41), respectively, with no differences between the arms (p = 0.64).

Six patients had pathogenic germline BRCA mutations, and all were randomized to the combined durvalumab and tremelimumab with carboplatin and paclitaxel arm, including 3 patients (50%) who had a chemotherapy pathological response score 3, and 3 (50%) were CRS 1 or 2.

At the conclusion of the study follow-up period, 10 patients were alive without progressive disease, including 8 (16%) in Du-T-NACT and 2 (8%) in NACT. A further 8 patients were lost to follow-up, 5 (10%) in Du-T-NACT and 3 (12%) in NACT (3 withdrew consent, 3 discontinued treatment (two without a disease assessment, one before surgery), 1 was taken off study at the investigator’s discretion, 1 was otherwise lost to follow-up).

The rate of complete cytoreduction (R0) after neoadjuvant treatment was higher in Du-T-NACT compared to NACT (51% vs. 32%), although the confidence intervals for these proportions were wide (*p = 0.26)*.

Safety

Safety analysis included 74 patients who received at least one cycle of treatment. Treatment-related adverse events of any grade were evaluated and are summarised in Table 2. All patients experienced treatment-related adverse events during treatment, with the most common adverse events (> 10% of patient population) being infusion-related reactions, diarrhea, constipation, peripheral neuropathy,

fatigue, anaemia, alopecia, pruritus, maculopapular rash, and arthralgia. Over 50% of patients in both arms experienced grade 3–4 treatment-related adverse events. The most prevalent grade 3–4 treatment-related adverse events included febrile neutropenia and maculopapular rash. All treatment-related adverse events, including severe adverse events, were effectively managed, and no new safety concerns were identified in this study.

Table 2
Adverse events (worst grade) experienced by more than 10% of patients in either arm regardless of relation to treatment

Adverse Event	Du-T-NACT (n = 48)		NACT (n = 26)	
	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade
Immune-Mediated Adverse Events[1]				
Diarrhea (colitis)	2 (4%)	20 (42%)	1 (4%)	5 (19%)
Alanine Aminotransferase Increased (hepatotoxicity)	1 (2%)	7 (15%)	0	0
Peripheral Sensory Neuropathy (neuromuscular toxicity)	0	28 (58%)	0	17 (65%)
Hypothyroidism (endocrinopathy)	0	7 (15%)	0	1 (4%)
Rash Maculo-Papular (dermatitis)	14 (29%)	31 (65%)	0	2 (8%)
Pruritis (dermatitis)	2 (4%)	22 (46%)	0	0
Other Adverse Events				
Thromboembolic Event	3 (6%)	3 (6%)	2 (8%)	5 (19%)
Nausea	0	17 (35%)	2 (8%)	13 (50%)
Febrile Neutropenia	8 (17%)	8 (17%)	1 (4%)	1 (4%)
Neutrophil Count Decreased	4 (8%)	7 (15%)	1 (4%)	1 (4%)
Abdominal Pain	3 (6%)	11 (23%)	1 (4%)	7 (27%)
Vomiting	1 (2%)	9 (19%)	1 (4%)	2 (8%)
Constipation	0	20 (42%)	1 (4%)	8 (31%)
Anemia	4 (8%)	11 (23%)	0	1 (4%)
Infusion Related Reaction	1 (2%)	15 (31%)	0	7 (27%)
Urinary Tract Infection	1 (2%)	6 (12%)	0	3 (12%)
Fatigue	1 (2%)	29 (60%)	0	12 (46%)
Arthralgia	1 (2%)	15 (31%)	0	4 (15%)
Pain	1 (2%)	8 (17%)	0	3 (12%)
Fever	1 (2%)	7 (15%)	0	1 (4%)
Mucositis Oral	1 (2%)	7 (15%)	0	0
Alopecia	0	28 (58%)	0	14 (54%)

Adverse Event	Du-T-NACT (n = 48)		NACT (n = 26)	
	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade
Immune-Mediated Adverse Events[1]				
Hypomagnesemia	0	9 (19%)	0	5 (19%)
Myalgia	0	13 (27%)	0	6 (23%)
Gastroesophageal Reflux Disease	0	1 (2%)	0	4 (15%)
Anorexia	0	8 (17%)	0	3 (12%)
Insomnia	0	6 (12%)	0	0
Dysgeusia	0	7 (15%)	0	3 (12%)
Headache	0	7 (15%)	0	2 (8%)
Any Adverse Event†	**25**	**47 (98%)**	**9**	**25 (96%)**

[1]Immune-mediated adverse events of special interest (AESI) classified per protocol-defined categories for durvalumab and tremelimumab, encompassing diarrhea/colitis, ALT/AST increases (hepatotoxicity), neuropathy/neuromuscular toxicity, endocrinopathies, and rash/dermatitis. Pneumonitis, nephritis, pancreatitis, and myocarditis were also protocol-defined AESI categories but are not listed above as they did not meet the > 10% reporting threshold in either arm.

Health-related Quality of Life

QoL outcomes were collected using the trial outcome index from the Functional Assessment of Cancer Therapy - Ovarian cancer (FACT-O) tool. A QoL assessment was completed by most patients during the first three cycles. At baseline, there were no disparities in FACT-O global health scores between treatment arms. Eleven patients did not complete the QoL assessment at the pre-surgical visit. Approximately half of the participants completed QoL assessment during adjuvant cycles, while few completed QoL assessment during maintenance therapy. No patients completed QoL assessment when they discontinued treatment.

Mean Trial Outcome Index tended to increase with successive study visits but did not differ by arm (Fig. 3). The mean change from baseline in the global health score indicated no impact of treatment on QoL and no difference in mean change over time between arms.

DISCUSSION

The primary aim of this study was to evaluate the efficacy of combining durvalumab and tremelimumab with chemotherapy as neoadjuvant treatment for advanced-stage ovarian cancer. This represented a novel approach at the time the study was designed, contrasting with the large, negative frontline

randomised controlled trials of single-agent PD-1 or PD-L1 inhibitors combined with carboplatin and paclitaxel (27, 28), but aligning with the more recently reported KGOG TRU-D study of neoadjuvant dual immune checkpoint blockade in combination with chemotherapy, including its final phase II analysis (34).

This study utilised a novel endpoint for a neoadjuvant ovarian cancer study, the chemotherapy response score (CRS), which is prognostic for progression-free and overall survival (32), although CRS 3 has not been used as a surrogate endpoint of efficacy in trials of neoadjuvant novel combinations in patients with ovarian cancer (29, 30). The aim was to evaluate CRS 3 rates following neoadjuvant dual immune checkpoint blockade in combination with chemotherapy based on a large body of evidence that CRS is prognostic and a potential surrogate for clinical outcomes in ovarian cancer..There is precedent for using complete pathological response rates as a surrogate endpoint in neoadjuvant trials in breast cancer as well as major pathological response(< 10% viable tumor) in neoadjuvant chemo-immunotherapy trials in resectable non small cell lung cancer .

The CRS 3 rate in the combined durvalumab and tremelimumab with carboplatin and paclitaxel arm was 32%, which was a similar rate to the historical controls. The purpose of the neoadjuvant chemotherapy alone arm was to compare the efficacy outcomes in this selected group of patients matched with what was expected from historical data. Despite the primary interest being to assess the efficacy of Du-T-NACT alone, the treatment arms were also compared in an exploratory context. In this secondary endpoint analysis, Du-T-NACT demonstrated a numerically higher CRS 3 rate when compared to NACT. Although this difference in CRS 3 suggests a pathological response signal favouring Du-T-NACT, the finding should be interpreted with caution, as the study was not designed as a formal comparative efficacy trial, and a progression-free survival benefit was not demonstrated. It is difficult to draw conclusions from the progression-free survival data given that only 25 patients remained at risk after 18 months of follow-up, and that 8 of 18 patients were censored for informative reasons. .

The median progression-free survival in our study was 14.7 months, with no difference between the two treatment arms. The progression-free survival rate at 12 months in Du-T-NACT was 60%, similar to the rate reported in the KGOG 3046/TRU-D study, which was 63.6%. The KGOG study also reported similar rates of progression-free survival at 24 and 30 months compared to their historical arms, suggesting the possibility of long-term responders when treated with a combination of chemotherapy and immunotherapy. Additional follow-up is necessary to confirm these findings.

Complete cytoreduction to no visible residual disease is associated with improved progression-free survival and overall survival (35). In our study, there was a higher proportion of complete cytoreduction in Du-T-NACT compared to NACT, although the 95% CIs were wide. Similar results have been observed in other phase 2 studies utilizing a combination of chemotherapy and immunotherapy, such as the KGOG-3046, INEOV (NCT03249142) and NeoPembrOV (29, 30, 35).

The addition of immunotherapy to chemotherapy was associated with increased rates of toxicity. However, the immune-related adverse events were expected and did not result in reduced rates of

interval debulking surgery or significant change in QoL. The current study had several limitations. The final number of patients eligible for assessment of the primary end point was less than anticipated in the statistical analysis, as a higher number of patients than expected did not proceed to surgery. The non-comparative design is also open to criticism, and in hindsight, a larger single-arm study may have served the trial better than pairing it with a small comparator arm. In addition, this study did not include maintenance therapy with bevacizumab or PARP inhibitors, which are now the standard of care. At the time of trial design, there was insufficient safety data to add vascular endothelial growth factor inhibitors or PARP inhibitors to dual immunotherapy combinations and thus patients who required bevacizumab were withdrawn from the study following surgery. BRCA status was not known at the time of enrolment, and by chance, all six patients with pathogenic germline BRCA1/2 mutations were randomised to Du-T-NACT; these patients were subsequently offered maintenance PARP inhibitor therapy as standard of care and came off study, which impacts on interpretation of dual immune checkpoint inhibitors on PFS and OS. .Another potential limitation is that although CRS following neoadjuvant chemotherapy is prognostic for PFS and OS, the relationship of CRS with immunotherapy, particularly with respect to long-term outcomes, is unknown. However, it is noteworthy that CRS 3 was a secondary endpoint in KGOG – 3046 associated with a median PFS of 32.7 months vs 12.4 months for CRS 1 /2. When the study was planned, we thought that a 50% CRS 3 would be indicative of increased efficacy of the combined therapy. The CRS 3 rate in our trial was very similar to KGOG – 3046 and INEOV trials. Further studies with longer follow-up are needed to assess whether combination chemoimmunotherapy can lead to durable response and improve overall survival. Ongoing studies are also evaluating combinations of immunotherapy and PARP inhibitors as an adjuvant treatment approach.

Conclusions

This was the first study to utilise pathological response as a primary endpoint in frontline neoadjuvant treatment of ovarian cancer. While the primary endpoint was not met, the observed CRS 3 rate was consistent with that reported in other neoadjuvant dual checkpoint blockade studies. CRS should be further investigated as an intermediate endpoint of efficacy in neoadjuvant window of opportunity trials in ovarian cancer.

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Declarations

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Competing interests:

TM: Consulting for BMS, MSD, AstraZeneca, Novartis, GSK and Eisai. Honoraria from AstraZeneca. Meeting and travel expenses support from AstraZeneca and BMS. Advisory Board participation with

BMS, MSD, AstraZeneca, Novartis, GSK and Eisai. JL: Advisory Board participation with AstraZeneca, Honoraria from Gilead, Eisai and Novartis. Meeting and travel expenses support from GSK and Novartis. Chair of Uterine Tumor Working Group with ANZGOG. CS: Honoraria from Astra Zeneca, Gilead, GSK, Eli Lilly, Novartis, MSD and Eisai. Member of Safety Committee for iPRIME study and the Ovarian Cancer working group with ANZGOG LM: Research funding from AstraZeneca. JG: Grant funding from NHMRC. Consulting for GSK, Eisai and Bayer. Honoraria from MSD, Eisai, Pfizer, Bayer. Meeting and travel expenses support from Bayer and Astellas. BG: Nil KWeb: Consulting for MSD and Abbvie and honoraria from MSD. MFr: Consulting for Astra Zeneca, Novartis, GSK, Incyclix, Abbvie, Biontec and honoraria from AstraZeneca, GSK, MSD and Limbic. Participation in AGITG iDSMB and ENDO-3 and DOMENICA advisory committees. Research grants from Astra Zeneca, Beigene and Novartis.

Patient consent for publication: Not required.

Ethics approval: The protocol was approved by a central human research ethics committee 18 (HREC) and all site HRECs.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplemental information. Individual 25 deidentified subject data that underlie the results reported in this article will be shared upon 26 reasonable request. Study protocol has been shared. Additional related documents will be available (e.g. statistical analysis plan) upon reasonable request.

Author Contribution

All authors reviewed the manuscript. TM, JL, CS, LM, JG, BG, KW, NDP, JA, KWe, TM and MF contributed to the conception and design of the study and development of the study protocol. MFa contributed to the statistical methodology and analysis plan. CSte contributed pathology expertise and review of the translational components of the study. TMa and NDP drafted the initial manuscript. MB reviewed and revised the manuscript for publication. All authors critically reviewed and revised the manuscript for important intellectual content, approved the final version for publication, and agreed to be accountable for all aspects of the work.

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Collaborators: Australia New Zealand Gynaecological Oncology Group (ANZGOG).

Data Availability

All data supporting the findings of this study are available within the paper

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Figures



Figure 1

Study CONSORT diagram

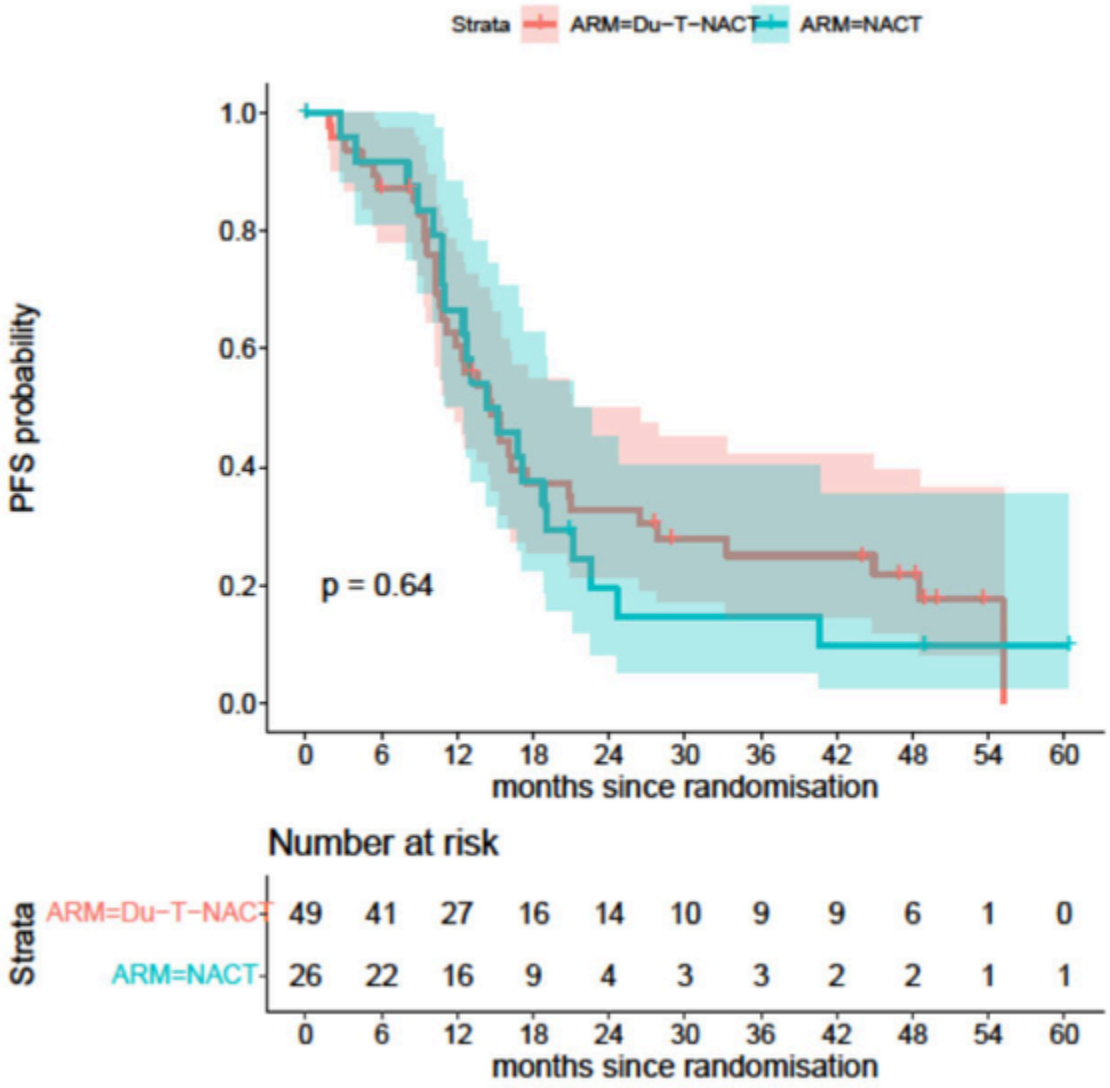


Figure 2

Kaplan-Meier curve of PFS probability

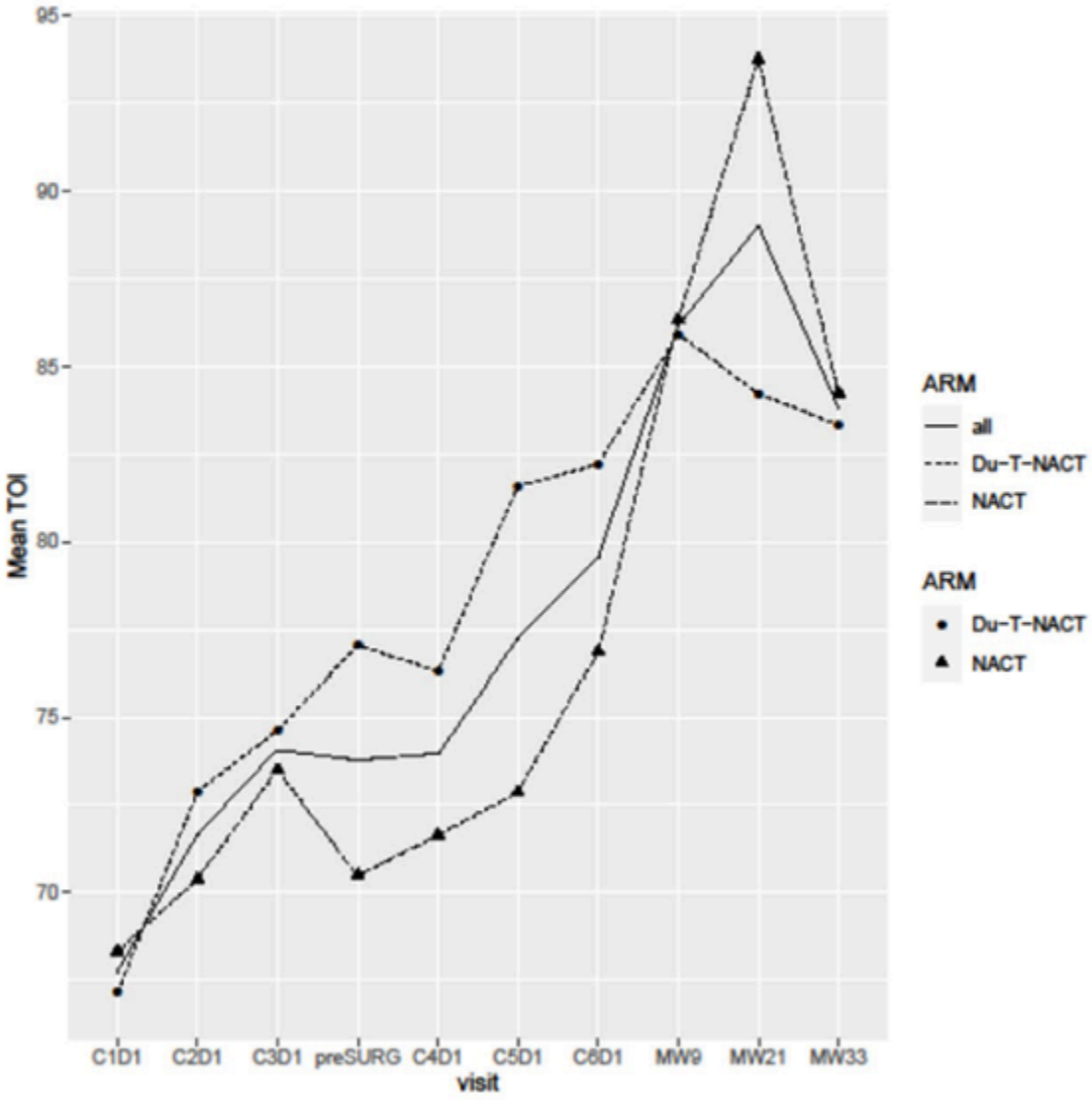


Figure 3

Mean Trial Outcome Index by visit and arm