Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00004 (KU36-96)
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A Phase I, Open-Label Study to Assess the Safety and Tolerability of KU-0059436 in Combination with Carboplatin, KU-0059436 in Combination with a Paclitaxel / Carboplatin (TC) doublet and KU-0059436 in Combination with Paclitaxel in the Treatment of Patients with Advanced Solid Tumours

Study dates: First subject enrolled: 05 July 2007
Last subject last visit: 04 January 2013

Phase of development: Clinical pharmacology (I)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This study was a multi-centre study conducted in the UK (1 study centre), the Netherlands (2 study centres) and Belgium (1 study centre).

Publications

R van der Noll et al 2013
R van der Noll et al. Phase I study of olaparib in combination with carboplatin and/or paclitaxel in patients with advanced solid tumors. Poster presentation at the American Society of Clinical Oncology. Chicago, 2013

R van der Noll et al 2013
R van der Noll et al. Safety results from a Phase I study with a new tablet formulation of olaparib in combination with carboplatin and paclitaxel. Poster presentation at the European CanCer organisation. Amsterdam, 2013

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of the drug-combination.	AEs, laboratory tests, physical examination and vital signs. Incidence of DLTs during cycle 1 of treatment with olaparib
	Safety	To establish either the dose of olaparib which can be safely administered and which causes inhibition of PARP in combination with an active dose of a paclitaxel / carboplatin (TC) doublet, or the MTD of olaparib in combination with a paclitaxel / carboplatin (TC) doublet.	AEs, laboratory tests, physical examination and vital signs. Incidence of DLTs during cycle 1 of treatment with olaparib
Secondary	Safety	To identify the DLT of the combination of olaparib and a paclitaxel / carboplatin (TC) doublet.	AEs, laboratory tests, physical examination and vital signs. Incidence of DLTs during cycle 1 of treatment with olaparib

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Pharmacokinetic	• To determine the plasma PK profile of: • olaparib alone • olaparib in combination with carboplatin • olaparib in combination with a paclitaxel / carboplatin (TC) doublet • olaparib in combination with paclitaxel	Blood sampling for PK analysis
	Efficacy	To enable a preliminary assessment of the anti-tumour activity of olaparib when given in combination with a paclitaxel / carboplatin (TC) doublet in specific patient populations.	Best overall response (RECIST), objective response rate, duration of response, relative tumour size
	Pharmacodynamic	To investigate the PD profile over time in surrogate tissue of olaparib when given in combination with a paclitaxel / carboplatin (TC) doublet.	Blood sampling for PD analysis
	Safety	To determine the safety profile of olaparib in combination with paclitaxel given at two dose levels.	AEs, laboratory tests, physical examination and vital signs. Incidence of DLTs during cycle 1 of treatment with olaparib
	Safety	To determine the safety and tolerability profile of the olaparib Melt-Extrusion [tablet] formulation in combination with a paclitaxel/carboplatin (TC) doublet.	AEs, laboratory tests, physical examination and vital signs. Incidence of DLTs during cycle 1 of treatment with olaparib
Exploratory	Biomarker	To investigate exploratory biomarkers in whole blood, serum, urine and tumour biopsies (on-treatment and historical) to ascertain if there are any which differentiate treatment effects, and to investigate their correlation with disease progression/response to therapy or an improved understanding of disease.	Whole blood, serum, urine samples and historical tumour biopsies

TC Taxol/Carboplatin; PD Pharmacodynamic; PK Pharmacokinetic

Study design

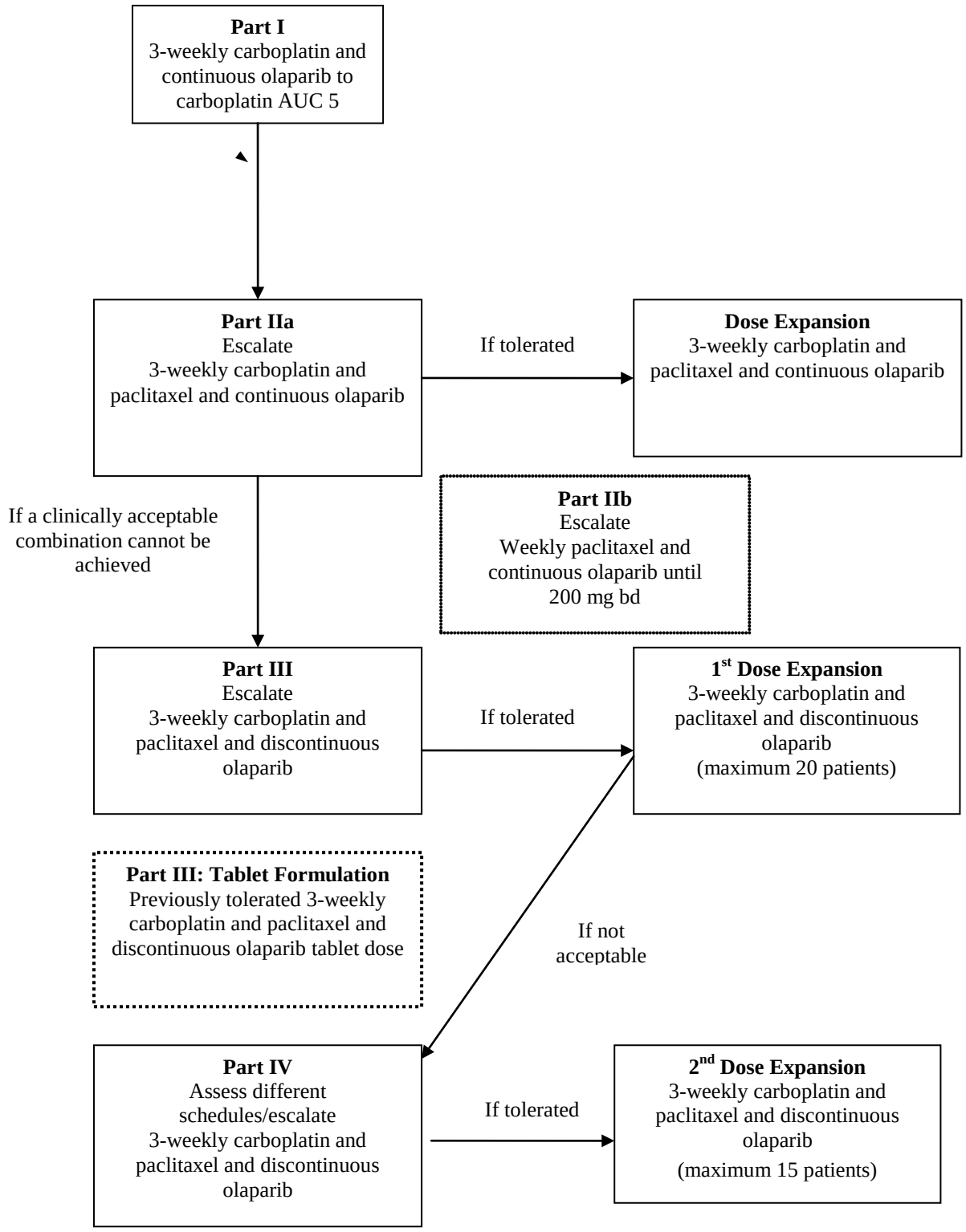
This was an open-label multi-centre, multi-national, phase I study of olaparib administered orally in combination with carboplatin alone and in combination with a paclitaxel / carboplatin (TC) doublet and in combination with paclitaxel alone. The study consisted of multiple dose escalation phases and planned expansion phases:

(i) There were 4 planned dose escalation phases (known as Part I, Part IIa, Part IIb and Part III) to firstly, establish the appropriate dose of olaparib and carboplatin given in combination (Part I) and thereafter, the appropriate dose of the olaparib and paclitaxel / carboplatin (TC) doublet (Part IIa). Part III of the study, with olaparib planned to be administered discontinuously, was only to be initiated if a clinically acceptable combination could not be achieved in Part IIa. Part IIb was to be run in parallel (as a comparison) with Part IIa (there was no planned expansion phase following Part IIb) and was designed to determine the safety profile of olaparib in combination with paclitaxel.

(ii) If, upon assessment of the first expansion cohort, it was determined by the investigators and sponsor that from a tolerability point of view the chosen dose / schedule was not appropriate for phase II / III studies, then another escalation phase, part IV of the study, could be opened to enable selection of an alternate dose / schedule. In Part IV, other discontinuous olaparib schedules consisting of olaparib (capsule or tablet) administered for any pre-determined numbers of days, up to 20 days within each treatment cycle could also be explored.

(iii) Dose expansion phase(s) of one or two chosen dose(s) and schedule(s) of the olaparib and paclitaxel / carboplatin (TC) doublet that could be safely administered in the escalation phase to further establish the safety and tolerability of the olaparib / paclitaxel / carboplatin (TC) doublet dose.

Figure S1 Flow chart of implemented study steps (ITT population)


Part I
3-weekly carboplatin and continuous olaparib to carboplatin AUC 5
Part IIa
Escalate
3-weekly carboplatin and paclitaxel and continuous olaparib
If tolerated
Dose Expansion
3-weekly carboplatin and paclitaxel and continuous olaparib
If a clinically acceptable combination cannot be achieved
Part IIb
Escalate
Weekly paclitaxel and continuous olaparib until 200 mg bd
Part III
Escalate
3-weekly carboplatin and paclitaxel and discontinuous olaparib
If tolerated
1st Dose Expansion
3-weekly carboplatin and paclitaxel and discontinuous olaparib
(maximum 20 patients)
Part III: Tablet Formulation
Previously tolerated 3-weekly carboplatin and paclitaxel and discontinuous olaparib tablet dose
If not acceptable
Part IV
Assess different schedules/escalate
3-weekly carboplatin and paclitaxel and discontinuous olaparib
If tolerated
2nd Dose Expansion
3-weekly carboplatin and paclitaxel and discontinuous olaparib
(maximum 15 patients)

Target subject population and sample size

The dose escalation phases of the study allowed recruitment of male and female patients with any advanced malignant solid tumour, these patients must have had no more than 2 previous platinum based chemotherapy regimens.

The planned expansion phase only allowed recruitment of patients with platinum naïve metastatic triple negative breast cancer and patients with advanced ovarian cancer where further treatment with carboplatin is indicated. It was expected that a maximum of approximately 190 patients would be enrolled in total, including up to a maximum of 30 patients enrolled in the dose expansion phase.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

The olaparib capsule formulation was supplied by Quay Pharmaceutical as hydroxypropyl methycellulose (HPMC) white (50 mg) capsules to be taken orally. The olaparib Melt-Extrusion [tablet] formulation was supplied by AstraZeneca as green, film-coated tablets containing either 25 mg or 100 mg olaparib to be taken orally.

Thirty six batches of olaparib were used in this study. Individual batch numbers and further information are included in the CSR.

Carboplatin and paclitaxel were supplied by the study sites' pharmacy.

Duration of treatment

Part I: olaparib was to be administered orally twice-daily, on days 1 through 28 in cycle 1 and on days 1 through 21 in all subsequent cycles at an escalating dose for each new cohort. Carboplatin was to be administered on day 8 of cycle 1 (28-day cycle) and on day 1 of all other cycles. It was to be administered at least 1 hour after olaparib administration.

Part IIa: olaparib was to be administered orally twice-daily, on days 1 through 28 in cycle 1 and on days 1 through 21 in all subsequent cycles. Paclitaxel followed by carboplatin were to be administered on day 8 of cycle 1 (28 day cycle) and on day 1 of a 21-day cycle for all other cycles. Initially the paclitaxel dose would be increased at each new cohort to the standard 3-weekly dose of 175 mg/m^2. Once this dose was reached, the olaparib dose would be increased.

Part IIb: in all cycles, olaparib was to be administered orally twice daily continuously, in combination with a fixed dose of paclitaxel. Olaparib was to be administered orally twice-daily, on days 1 through 35 in cycle 1 and on days 1 through 28 in all subsequent cycles at an escalating dose for each new cohort. Paclitaxel was to be administered on days 8, 15 and 22 of cycle 1 (35-day cycle) and on days 1, 8 and 15 of all other cycles (28-day cycle).

Part III: this part of the study was only to be initiated if a clinically acceptable dose could not be achieved in Part IIa. Each cycle was 21 days' duration. Initially, a discontinuous dose of olaparib was to be administered from day 1 to day 10 inclusive, but not from day 11 to day 21. Paclitaxel followed by carboplatin were to be administered on day 1 of each cycle. Within

Part III escalations or de-escalations of carboplatin or olaparib could occur to determine the most effective combination dose.

Part IV: other discontinuous olaparib schedules consisting of olaparib (capsule or tablet) administered for any pre-determined numbers of days, up to 20 days within each treatment cycle of 21 days could also be explored. Paclitaxel followed by carboplatin were to be administered on day 1 of each cycle. Within Part IV escalations or de-escalations of carboplatin or olaparib could occur to determine the most effective combination dose.

Patients could be dosed for up to 6 cycles. At the discretion of the investigator, patients could receive more than 6 cycles if they were tolerating the treatment and had at least stable disease.

Statistical methods

No formal statistical analyses were carried out; descriptive statistical analyses were performed by Theradex®, Princeton, NJ, USA using SAS™ version 8.01, and were performed in accordance with the Statistical Analysis Plan which was finalised before database soft lock. The safety and tolerability profile of olaparib in combination with carboplatin and/or paclitaxel was assessed by adverse events, laboratory tests, physical examination and vital signs. Adverse events were summarised by system organ class and preferred term assigned to the event using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary.

Subject population

Throughout the results section, patients have been grouped according to their initial treatment regimen. Please refer to Figure S1 for an overview of the study design. The results are further organized into high-level groups, as follows:

- Group A: olaparib capsules plus carboplatin (Group 1)
- Group B: olaparib capsules plus paclitaxel (Group 2)
- Group C: olaparib capsules (continuous and discontinuous dosing) plus paclitaxel / carboplatin (Groups 3 and 4)
- Group D: olaparib tablets (discontinuous dosing) plus paclitaxel/carboplatin (Groups 5, 6 and 7)

Group A: twenty six patients with advanced solid tumours were enrolled and of these, 25 received study medication. The population 16 (64.0%) male and 9 (36.0%) female patients, aged between 24 years and 70 years; the median age was 59.0 years. Twenty-four (96.0%) patients were white (Caucasian) and one (4.0%) patient was Asian. The majority of patients had an ECOG performance status of 0 or 1 at baseline; only one (4.0%) patient had a baseline status of 2.

Group B: twelve patients with advanced solid tumours were enrolled and all patients received study medication. The population comprised 6 (50.0%) male and 6 (50.0%) female patients,

aged between 30 years and 63 years; the median age was 52.0 years. All patients were white and all had a baseline ECOG performance status of 0 or 1.

Group C: Fifty two patients were enrolled and of these, 50 received study medication. The population comprised 20 (40.0%) male and 30 (60.0%) female patients, aged between 25 years and 74 years; the median age in Group 3 (continuous olaparib capsules) was 51.0 years and in Group 4 (discontinuous olaparib capsules) was 52.5 years. The majority, (47; 94.0%) of patients were white, and all but one patient had a baseline ECOG performance status of 0 or 1.

Group D: Hundred and two patients were enrolled and all patients received study medication. As expected, the majority of the population was female (97 patients; 95.1%). The population was aged between 25 years and 74 years; the median ages in Groups 5, 6 and 7 were 50.0 years, 54.0 years and 55.5 years, respectively. The majority (101; 99.0%) of patients were white and most (98 patients; 96.1%) had a baseline ECOG performance status of 0 or 1.

Summary of efficacy results

In Group A the objective response rate (CR + PR) in Group A was 5.9% (1 of 17 patients with measurable disease) and in Group B this was 20.0% (2 of 10 patients with measurable disease). In group C the objective response rate (CR + PR) was 22.7% (10 of 44 patients with measurable disease) and in Group D this was 51.2% (42 of 82 patients with measurable disease). These responses are in keeping with the previously noted overall objective response rates seen in ovarian patients receiving treatment with the doublet chemotherapy of paclitaxel and carboplatin alone.

Duration of response could not be calculated for the majority of patients with a confirmed PR or CR because only 6 cycles of study data was collected, following the introduction of protocol amendment 6.

Summary of pharmacokinetic results

When co-administered with the capsule formulation of olaparib carboplatin had little/no effect on olaparib steady state exposure. Also, when co-administered with the capsule formulation of olaparib, paclitaxel (either alone or in combination with carboplatin) reduced steady state exposure to olaparib at all olaparib doses studied.

Following a single 200 mg dose of the tablet formulation in combination with carboplatin/paclitaxel AUC4/175, olaparib exposure (C_{max} and AUC_{0-8}) was higher than achieved following a 200 mg dose of the capsule formulation in combination with the same chemotherapy regimen.

Based on the sampling in this study it was not possible to draw conclusions regarding the effect of olaparib on carboplatin or paclitaxel pharmacokinetics.

Summary of pharmacodynamic results

Not applicable

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable

Summary of pharmacogenetic results

A blood sample (9 mL) was collected from each patient who gave consent to undergo blood sampling for genetic research. Samples were frozen and stored for later analysis. The results of the genetic study are not part of this CSR. The results of the genetic study may be pooled with genetic results from other studies and reported at a later date.

Summary of safety results

Three patients experienced a DLT in cycle 1; two patients in cohort 2 and one patient in cohort 20.

A tolerable dose of olaparib capsules 200 mg bd (10d) in combination with carboplatin AUC4 and paclitaxel 175 mg/m^2 was identified in Cohort 11, for use in future studies.

A tolerable dose of olaparib capsules 100 mg bd (28d) plus paclitaxel 80 mg/m^2 was identified in Cohort 6, for use in future studies.

Tolerable doses of olaparib tablets which could be considered for use in future studies are 50 mg or 100 mg bd for 2 days every 21 day cycle in combination with Carboplatin AUC5 + 175mg/m^2 paclitaxel.

Patients in Group A received between one and 13 cycles of combination therapy. The median duration of exposure to olaparib and carboplatin was 63.0 days (range 12 to 271 days) and 39.5 days (range 1 to 242 days) respectively. Five (20.0%) patients had olaparib dose reductions and/or interruptions. In each case this was due to an adverse event. Twelve (48.0%) patients had carboplatin dose reductions and/or delays. All carboplatin dose reductions were due to an adverse event

In Group B, patients received between one and 22 cycles of combination therapy. The median duration of exposure to olaparib and paclitaxel was 171.0 days (range 6 to 651 days) and 155.0 days (range 43 to 638 days), respectively. Five (41.7%) patients had olaparib dose reductions and/or interruptions. In each case this was due to an adverse event. There were no paclitaxel dose reductions. Nine (81.8%) patients had a dose delay, mainly due to adverse events and other (logistical) reasons.

In Group C, patients with continuous olaparib dosing received between one and 17 cycles of combination therapy the median duration of exposure to olaparib, carboplatin and paclitaxel was 67.5 days(range 60 to 204 days), 52.0 days (range 56 to 200 days) and 52.0 days (range 56 to 200 days), respectively. All carboplatin or paclitaxel dose reductions were due to an adverse event. Patients with discontinuous olaparib dosing received between one and nine cycles. Overall in the group, thirty-four (68.0%) patients experienced olaparib dose reductions, or interruptions or delays or combinations thereof. All olaparib dose reductions were due to an adverse event. Interruptions were due to adverse events and/or “other” reasons,

which were primarily patient non-compliance. Five (10.0%) patients each had carboplatin or paclitaxel dose reductions and/or delays. Delays were due to adverse events and "other" reasons which were primarily logistical reasons.

In Group D, patients in Group 5 received between one and 11 cycles of combination therapy, with a median of six cycles initiated. The median duration of exposure to olaparib, carboplatin and paclitaxel was 122.0 days, 52.0 days and 52.0 days, respectively. In Group 6, patients received between one and six cycles of combination therapy, with a median of six cycles initiated. The median duration of exposure to olaparib, carboplatin and paclitaxel was 114.5 days, 108.0 days and 106.0 days, respectively. Finally, in Group 7, patients received between three and six cycles of combination therapy, with a median of four cycles initiated. The median duration of exposure to olaparib, carboplatin and paclitaxel was 86.0 days, 74.0 days and 74.0 days, respectively. Overall in the group, eighty-one (79.4%) patients experienced olaparib dose reductions, or interruptions or delays or combinations thereof. The majority of olaparib dose reductions were due to an adverse event, although one patient had an olaparib dose reduction by Investigator decision. Olaparib dose interruptions were due to adverse events and/or "other" reasons, which were primarily logistical reasons or patient non-compliance. Seventy-seven (75.5%) patients had carboplatin dose delays and/or reductions and 79 (77.5%) patients had paclitaxel dose delays and/or reductions. Dose reductions were due to adverse events. The majority of dose delays were due to adverse events or were for "other" reasons which were primarily logistical reasons.

As expected in patients with advanced cancer, the majority of the patients in this study (98.9%) experienced at least one TEAE.

TEAEs that were attributed to olaparib administration by the Investigator were experienced by 163 (86.2%) patients. Carboplatin and paclitaxel-related TEAEs were experienced by 169 (89.4) and 159 (84.1%) patients, respectively. TEAEs of severity CTCAE grade ≥3 were experienced by 131 (69.3%) patients.

No patient had a TEAE with an outcome of death in this study (events that were unequivocally due to progressive disease were not reported as adverse events, per protocol). Forty-six (24.3%) patients had at least one SAE.

Thirty-four (18.0%) patients had a TEAE that led to discontinuation of study medication.

Table S1 Summary of number (%) of patients who had at least one AE in any category: Safety population

	N (%) of patients		
	Olaparib capsules	**Olaparib tablets**	**Overall**
Number of patients	**87**	**102**	**189**
Treatment-Emergent Adverse Events[a,b]			
Number of events of any TEAEs	1256	2115	3371

	N (%) of patients		
	Olaparib capsules	**Olaparib tablets**	**Overall**
Number of patients	**87**	**102**	**189**
Patients with any TEAEs	85 (97.7)	102 (100)	187 (98.9)
Olaparib-related TEAEs[c]	67 (77.0)	96 (94.1)	163 (86.2)
Carboplatin-related TEAEs[c]	68 (78.2)	101 (99.0)	169 (89.4)
Paclitaxel-related TEAEs[c]	57 (65.5)	102 (100)	159 (84.1)
TEAEs of CTCAE grade ≥3[d]	55 (63.2)	76 (74.5)	131 (69.3)
Olaparib-related TEAEs of CTCAE grade ≥3[c,d]	40 (46.0)	51 (50.0)	91 (48.1)
Carboplatin-related TEAEs of CTCAE grade ≥3[c,d]	38 (43.7)	64 (52.7)	102 (54.0)
Paclitaxel-related TEAEs of CTCAE grade ≥3[c,d]	35 (40.2)	64 (52.7)	99 (52.4)
TEAEs with outcome=death	0	0	0
SAEs (including events with outcome=death)	19 (21.8)	27 (26.5)	46 (24.3)
TEAEs leading to discontinuation of treatment	17 (19.5)	17 (16.7)	34 (18.0)

[a] Patients with multiple events in a category were counted only once in that category. Patients with events in more than one category were counted once in each category. Includes TEAEs and AEs occurring post-treatment during the 30 day f/u. Treatment-Emergent AEs (TEAEs) are defined as all AEs that occurred after the first dose of study medication or within 30 day post-treatment period.
[b] Percentages in each category were calculated using number of patients as the denominator.
[c] Relationship to treatment = yes for a given preferred term, as assessed by the investigator
[d] CTCAE Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening or disabling, 5=Death related to AE.

In Group A, twenty-four (96.0%) patients in Group A experienced a TEAE. TEAEs occurring in ≥20% of patients were: fatigue (19 patients; 76.0%); neutropenia (12 patients; 48.0%); constipation (10 patients; 40%); tachycardia, and nausea (each in 9 patients, 36.0%); anaemia, and thrombocytopenia (each in 8 patients, 32.0%); diarrhoea, and dyspnoea (each in 6 patients; 24.0%); and vomiting, and nasopharyngitis (each in 5 patients; 20.0%).

In Group B, eleven (91.7%) patients in Group B experienced a TEAE. TEAEs occurring in ≥20% of patients were: nasopharyngitis (8 patients; 66.7%); fatigue, peripheral sensory neuropathy and alopecia (each in 7 patients; 58.3%); neutropenia (6 patients; 50.0%); diarrhoea, nausea, and vomiting (each in 5 patients; 41.7%); stomatitis, and dry skin (each in 4 patients; 33.3%); and constipation, epistaxis, headache, influenza like illness, nail disorder, oedema peripheral, pyrexia, rash, and tachycardia (each in 3 patients; 25%).

In Group C, fifty (100%) patients in Group C experienced a TEAE. TEAEs occurring in ≥20% of patients were: fatigue (41 patients; 82.0%); alopecia (32 patients; 64.0%); neutropenia, and nausea (each in 29 patients; 58.0%); dyspnoea (19 patients; 38.0%); anaemia (17 patients;

34.0%); thrombocytopenia, and diarrhoea (each in 15 patients; 30.0%); constipation, myalgia, and peripheral sensory neuropathy (each in 13 patients; 26.0%); vomiting (12 patients; 24.0%); and stomatitis (11 patients; 22.0%).

In Group D, all 102 (100%) patients in Group D experienced a TEAE. TEAEs occurring in ≥20% of patients were: alopecia (95 patients; 93.1%); fatigue (84 patients; 82.4%); nausea (74 patients; 72.5%); peripheral sensory neuropathy (70 patients; 68.6%); constipation (56 patients; 54.9); myalgia (51 patients; 50.0%); diarrhoea (49 patients; 48.0%); neutropenia (44 patients; 43.1%); thrombocytopenia (42 patients; 41.2%); dysgeusia (35 patients; 34.3%); vomiting (33 patients; 32.4%); anorexia (32 patients; 31.4%); adverse drug reaction (27 patients; 26.5%); dyspnoea (26 patients; 25.5%); nasopharyngitis (23 patients; 22.5%); and pyrexia (22 patients; 21.6%).