Online resource 1

An adaptive study to determine the optimal dose of the tablet formulation of the PARP inhibitor olaparib

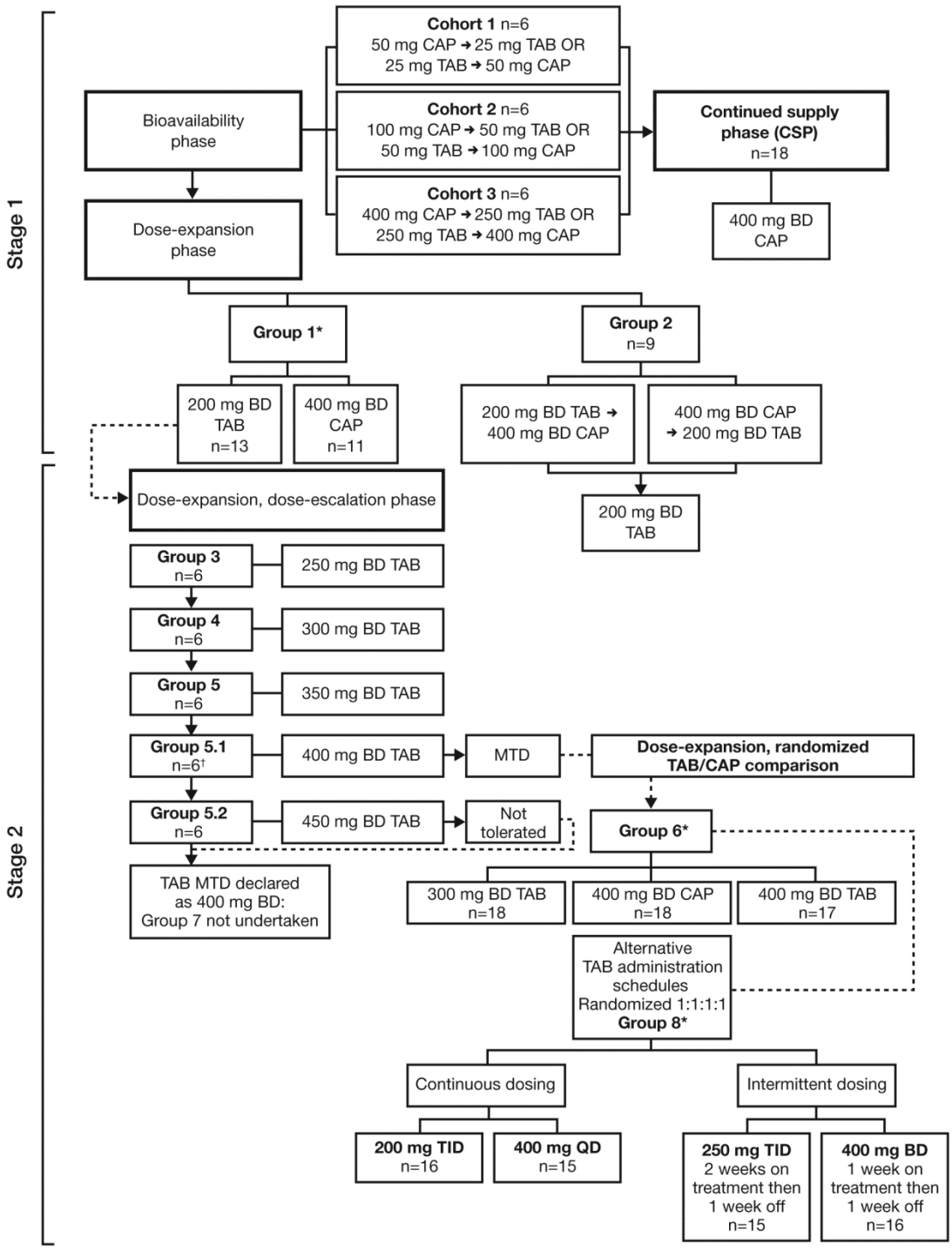
J Mateo, V Moreno, A Gupta, SB Kaye, E Dean, MR Middleton, M Friedlander, C Gourley, R Plummer, G Rustin, C Sessa, K Leunen, J Ledermann, H Swaisland, A Fielding, W Bannister, S Nicum, L Rhoda Molife

Correspondence: Dr L Rhoda Molife MD, Drug Development Unit, The Royal Marsden/The Institute of Cancer Research, Downs Road, Sutton SM2 5PT, UK

Email: maria.bynoe@icr.ac.uk

Submission to: *Targeted Oncology*

Supplementary Figure 1. Study design



*Indicates groups where patients were required to have a confirmed *BRCA*m; †Seven patients were enrolled into group 5.1, six patients received treatment

Supplementary Table 1. Patient inclusion and exclusion criteria

Patients had to fulfil the following criteria for inclusion into the study:	**The following were regarded as criteria for exclusion from the study:**
≥18 years of age and a life expectancy of ≥16 weeks	Major surgery within 2 weeks of starting the study, and patients must have recovered from any effects of any major surgery
Histologically confirmed malignant advanced solid tumour which was refractory to standard therapies (except group 8 patients who were not platinum refractory) or for which no suitable effective standard therapy existed. If a diagnosis based on a histological sample was not available, a diagnosis based on cytology was allowed for those tumour entities in which this method was a generally accepted alternative	Patients who received any chemotherapy, radiotherapy (except for palliative reasons), or any other anticancer therapy within 4 weeks from the last dose prior to study randomization (or a longer period depending on the defined characteristics of the agents used). Patients were allowed to continue the use of bisphosphonates for bone metastases and corticosteroids, provided the dose was stable before and during the study and these were started at least 4 weeks prior to the beginning of study treatment. Patients were allowed to continue on hormone replacement therapy and on luteinizing-hormone-releasing hormone (LHRH)
ECOG performance status 0–1 (group 8 only) ECOG performance status 0–2 (all other groups)	Patients with symptomatic uncontrolled brain metastases

<table>
<tr><th>Patients had to fulfil the following criteria for inclusion into the study:</th><th>The following were regarded as criteria for exclusion from the study:</th></tr>
<tr><td rowspan="8">Patients must have had adequate organ and bone marrow function measured within 7 days prior to administration of study treatment as defined below:
▪ Haemoglobin ≥10.0 g/dL and no blood transfusions in the 4 weeks prior to randomization (group 8 only); ≥9.0 g/dL (all other groups)
▪ Absolute neutrophil count (ANC) ≥1.5x10^9/L
▪ No dysplastic features on peripheral blood smear (group 8 only)
▪ White blood cells (WBC) >3x10^9/L
▪ Platelet count ≥100x10^9/L
▪ Total bilirubin ≤1.5x institutional upper limit of normal (ULN)
▪ Aspartate transaminase (AST [SGOT])/alanine transaminase (ALT [SGPT]) ≤2.5xULN unless liver metastases were present, in which case it must have been ≤5xULN
▪ Serum creatinine ≤1.5xULN</td><td>Patients considered a poor medical risk owing to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection</td></tr>
<tr><td>Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication</td></tr>
<tr><td>Pregnant or breastfeeding women</td></tr>
<tr><td>Immunocompromised patients, eg, patients who were known to be serologically positive for human immunodeficiency virus (HIV) and were receiving antiviral therapy</td></tr>
<tr><td>Patients with known hepatic disease</td></tr>
<tr><td>Persistent toxicities (CTCAE grade 2 or greater) caused by previous cancer therapy (excluding alopecia)</td></tr>
<tr><td>Female patients must have had evidence of non-childbearing status: negative urine or serum pregnancy test within 7 days of study treatment for women of childbearing potential, or postmenopausal status</td><td>Treatment with any investigational product during the previous 14 days (or a longer period depending on the defined characteristics of the agents used)</td></tr>
</table>

Patients had to fulfil the following criteria for inclusion into the study:	**The following were regarded as criteria for exclusion from the study:**
Patients must have had solid tumours originating from the ovary or breast with a confirmed genetic *BRCA1/2* mutation (group 8 g*BRCA* ovarian [including primary peritoneal and fallopian tube] cancer patients only). The mutation must have been confirmed as a loss-of-function mutation, ie, a known deleterious or suspected deleterious mutation (groups 1, 6, 7 and 8)	Patients who were at the time of the study experiencing seizures or who were at the time of the study being treated with only anti-epileptics for seizures (use of anti-epileptic drugs to control pain was allowed in patients not suffering from seizures), unless drug was excluded because of CYP3A4 induction
Patients must have had at least one lesion, not previously irradiated, that could be accurately measured as ≥10 mm in the longest diameter with spiral computed tomography (CT) or as ≥20 mm with conventional techniques (conventional CT or magnetic resonance imaging [MRI]) and which was suitable for accurate repeated measurements (groups 1, 6, 7 and 8)	Patients who received the following classes of inhibitors of CYP3A4 (azole antifungals, macrolide antibiotics, protease inhibitors) Group 8 only: ▪ Patients with myelodysplastic syndromes/acute myeloid leukemia ▪ Patients who were platinum refractory ▪ Patients who had previously received a PARP inhibitor

Pharmacodynamics

Methods

Samples for assessment of PARP inhibition in peripheral blood mononuclear cells (PBMC) were collected from patients participating in stage 1 of the study, in each of the single-dose treatment periods at pre-dose and 3, 10 and 24 hours post-dose.

Supplementary Table 2. Mean percentage inhibition of PARP-1 from baseline (± standard error) in peripheral blood mononuclear cell (PBMC) samples following administration of single oral doses of the tablet or capsule formulation (n=6 per cohort; stage 1)

Time after dose (h)	Tablet formulation			Capsule formulation		
	25 mg dose	50 mg dose	250 mg dose	50 mg dose	100 mg dose	400 mg dose
3	49.4 ± 43.5	58.2 ± 22.0	22.4 ± 43.0	42.8 ± 282	66.9 ± 167	50.5 ± 274
10	69.9 ± 31.0	74.9 ± 55.0	89.4 ± 63.0	66.9 ± 331	55.7 ± 47.0	83.7 ± 28.0
24	39.0 ± 45.0	41.5 ± 174	46.2 ± 215	16.7 ± 402	83.6 ± 100	54.4 ± 256

Median PARP inhibition relative to baseline ranged over 22–67% 3 hours after dosing, with maximum levels 10 hours post-dose

Supplementary Table 3. Germline *BRCA* mutation status of patients in dose-expansion groups 1, 6 and 8

Treatment group	Primary tumour location	*BRCA* mutation type		
		BRCA1	***BRCA2***	***BRCA1* and *BRCA2***
Group 1				
200 mg TAB (n=13)	Ovary (n=8)[a]	5	2	1
	Breast (n=5)	1	1	3
400 mg CAP (n=11)	Ovary (n=7)	3	1	3
	Breast (n=4)[b]	0	3	0
Group 6				
300 mg TAB (n=18)	Ovary (n=13)	10	3	0
	Breast (n=5)	2	3	0
400 mg TAB (n=17)	Ovary (n=12)	9	3	0
	Breast (n=5)	3	2	0
400 mg CAP (n=18)	Ovary (n=13)	9	4	0
	Breast (n=5)	4	1	0
Group 8				
200 mg TID TAB cont (n=16)	Ovary (n=16)	11	3	2
250 mg TID TAB inter (n=15)	Ovary (n=15)	12	3	0
400 mg BD TAB inter (n=16)	Ovary (n=16)	13	3	0
400 mg OD TAB cont (n=15)	Ovary (n=15)	9	6	0

[a]One patient was incorrectly stratified as having primary breast cancer, when this should have been stratified as ovarian cancer. This patient was excluded from the ovarian cancer subset as this was based on randomization stratification data but included as ovarian cancer in summaries of primary

tumour location; [b]*BRCA*m data missing for one patient with breast cancer receiving 400 mg CAP. CAP, capsule formulation; cont, continuous dosing schedule; inter, intermittent dosing schedule; TAB, tablet formulation.

Supplementary Table 4. Pharmacokinetic parameters and relative bioavailability for olaparib following single dosing of CAP and TAB formulations in cohorts 1–3 and following multiple doses of CAP 200 mg and TAB 200 mg in the PK comparison phase of group 2

	Olaparib dose and formulation groups					
	Cohort 1		Cohort 2		Cohort 3	
	25 mg	50 mg	50 mg	100 mg	250 mg	400 mg
PK parameter	TAB	CAP	TAB	CAP	TAB	CAP
C_{max} (µg/mL), geometric mean (CV%)	1.17 (48)	1.82 (26)	2.22 (36)	2.90 (23)	8.81 (23)	5.67 (47)
t_{max} (h), median	1.0	1.5	0.5	1.25	1.25	1.25
(range)	(0.5–3.0)	(1.0–3.0)	(0.5–2.0)	(1.0–2.0)	(1.0–4.0)	(1.0–8.0)
AUC (µg·h/mL), geometric mean (CV%)	5.15 (69)	10.0 (45)	8.34 (42)	16.9 (32)	63.0 (37)	57.9 (78)
Half-life (h), arithmetic mean (SD)	7.27 (0.79)	7.87 (1.72)	7.47 (1.02)	8.44 (2.94)	6.17 (0.88)	11.9 (4.82)
CL/F (L/h), arithmetic mean (SD)	5.65 (3.29)	5.38 (2.37)	6.42 (2.60)	6.18 (2.08)	4.19 (1.64)	8.64 (7.11)
V_{area}/F (L), mean (SD)	59.3 (36.3)	60.6 (31.3)	69.2 (31.2)	81.1 (49.8)	36.2 (10.7)	167 (196)

	Olaparib dose and formulation groups		
	Cohort 1	**Cohort 2**	**Cohort 3**
Relative bioavailability	**25 mg TAB vs 50 mg CAP**	**50 mg TAB vs 100 mg CAP**	**250 mg TAB vs 400 mg CAP**
C_{max} ratio[a] (90% CI)	1.29 (1.10–1.52)	1.53 (1.11–2.11)	2.49 (1.87–3.31)
AUC ratio[a] (90% CI)	1.03 (0.85–1.24)	0.99 (0.69–1.42)	1.74 (1.36–2.23)
	PK comparison phase of group 2, 200 mg TAB and 400 mg CAP – crossover		
PK parameter	**200 mg TAB**	**400 mg CAP**	**TAB:CAP ratio**
$C_{max,ss}$ (µg/mL), geometric mean (CV%)	8.02 (38)	8.10 (35)	0.991
AUC_{ss} (µg·h/mL), geometric mean (CV%)	38.36 (46)	48.48 (52)	0.791
$C_{min,ss}$ (µg/mL), geometric mean (CV%)	0.68 (86)	1.38 (101)	0.540

[a]C_{max} and AUC values were normalized for administered dose. CV, coefficient of variation

Supplementary Table 5. Number (%) of patients who had at least one AE of any grade (≥20% incidence in any treatment group) in the dose-expansion phase for groups 1 (200 mg TAB and 400 mg CAP) and 6 and dose-escalation groups 3, 4, 5, 5.1 and 5.2

	Group 1		Group 3	Group 4	Group 5	Group 5.1	Group 5.2	Group 6		
	200 mg BD TAB n=13	400 mg BD CAP n=11	250 mg BD TAB n=6	300 mg BD TAB n=6	350 mg BD TAB n=6	400 mg BD TAB n=6	450 mg BD TAB n=6	300 mg BD TAB n=18	400 mg BD TAB n=17	400 mg BD CAP n=18
Any AE, n (%)	13 (100)	10 (91)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	18 (100)	17 (100)	18 (100)
Blood and lymphatic system disorders										
Anaemia	1 (8)	0	1 (17)	2 (33)	1 (17)	2 (33)	3 (50)	7 (39)	9 (53)	6 (33)
Neutropenia	0	0	0	1 (17)	0	1 (17)	1 (17)	3 (17)	1 (6)	2 (11)
Thrombocytopenia	0	0	0	0	0	0	1 (17)	1 (6)	3 (18)	0
Gastrointestinal disorders										
Abdominal pain	1 (8)	1 (9)	0	1 (17)	2 (33)	1 (17)	1 (17)	2 (11)	2 (12)	0
Constipation	7 (54)	1 (9)	3 (50)	1 (17)	1 (17)	3 (50)	2 (33)	4 (22)	1 (6)	2 (11)
Diarrhoea	4 (31)	3 (27)	4 (67)	4 (67)	2 (33)	1 (17)	3 (50)	9 (50)	4 (24)	2 (11)
Dyspepsia	1 (8)	2 (18)	3 (50)	2 (33)	0	0	3 (50)	1 (6)	2 (12)	3 (17)
Nausea	10 (77)	7 (64)	5 (83)	5 (83)	5 (83)	6 (100)	5 (83)	13 (72)	15 (88)	15 (83)
Stomatitis	0	0	0	0	2 (33)	1 (17)	2 (33)	0	1 (6)	1 (6)
Vomiting	5 (39)	3 (27)	2 (33)	4 (67)	1 (17)	1 (17)	0	8 (44)	6 (35)	5 (28)
General disorders										
Alopecia	0	1 (9)	0	0	1 (17)	0	2 (33)	1 (6)	1 (6)	1 (6)
Oedema peripheral	1 (8)	1 (9)	1 (17)	0	2 (33)	1 (17)	2 (33)	4 (22)	1 (6)	1 (6)

	Group 1		Group 3	Group 4	Group 5	Group 5.1	Group 5.2		Group 6	
	200 mg BD TAB n=13	400 mg BD CAP n=11	250 mg BD TAB n=6	300 mg BD TAB n=6	350 mg BD TAB n=6	400 mg BD TAB n=6	450 mg BD TAB n=6	300 mg BD TAB n=18	400 mg BD TAB n=17	400 mg BD CAP n=18
Fatigue	9 (69)	5 (45)	5 (83)	6 (100)	3 (50)	5 (83)	4 (67)	13 (72)	14 (82)	9 (50)
Non-cardiac chest pain	1 (8)	0	0	2 (33)	0	0	0	1 (6)	2 (12)	0
Pyrexia	0	0	0	1 (17)	0	0	0	0	6 (35)	0
Infections										
Lower respiratory tract infection	0	1 (9)	1 (17)	2 (33)	0	1 (17)	1 (17)	2 (11)	3 (18)	2 (11)
Urinary tract infection	2 (15)	1 (9)	1 (17)	0	0	1 (17)	0	7 (39)	3 (18)	2 (11)
Metabolism and nutritional disorders										
Decreased appetite	7 (54)	3 (27)	2 (33)	2 (33)	1 (17)	3 (50)	1 (17)	9 (50)	5 (29)	8 (44)
Musculoskeletal disorders										
Arthralgia	2 (15)	2 (18)	0	3 (50)	0	1 (17)	1 (17)	2 (11)	1 (6)	2 (11)
Back pain	5 (39)	3 (27)	1 (17)	1 (17)	0	0	1 (17)	3 (17)	4 (24)	2 (11)
Musculoskeletal chest pain	3 (23)	0	0	0	1 (17)	0	1 (17)	0	1 (6)	1 (6)
Musculoskeletal pain	0	1 (9)	0	1 (17)	0	0	2 (33)	2 (11)	3 (18)	0
Pain in extremity	2 (15)	1 (9)	0	1 (17)	0	2 (33)	0	0	1 (6)	1 (6)

	Group 1		Group 3	Group 4	Group 5	Group 5.1	Group 5.2		Group 6	
	200 mg BD	400 mg BD	250 mg BD	300 mg BD	350 mg BD	400 mg BD	450 mg BD	300 mg BD	400 mg BD	400 mg BD
	TAB	CAP	TAB	TAB	TAB	TAB	TAB	TAB	TAB	CAP
	n=13	n=11	n=6	n=6	n=6	n=6	n=6	n=18	n=17	n=18
Nervous system disorders										
Dizziness	1 (8)	1 (9)	0	1 (17)	0	2 (33)	0	2 (11)	1 (6)	0
Dysgeusia	0	0	1 (17)	2 (33)	0	0	1 (17)	6 (33)	3 (18)	2 (11)
Headache	1 (8)	0	1 (17)	1 (17)	1 (17)	2 (33)	3 (50)	2 (11)	1 (6)	2 (11)
Paraesthesia	1 (8)	1 (9)	0	0	1 (17)	0	2 (33)	0	0	1 (6)
Renal and urinary disorders										
Pollakiuria	0	0	0	2 (33)	0	0	0	1(6)	0	0
Respiratory, thoracic and mediastinal disorders										
Cough	5 (39)	1 (9)	2 (33)	1 (17)	1 (17)	1 (17)	0	3 (17)	2 (12)	2 (11)
Dyspnoea	2 (15)	2 (18)	0	1 (17)	0	1 (17)	1 (17)	5 (28)	4 (24)	4 (22)
Dyspnoea exertional	1 (8)	0	0	0	0	1 (17)	2 (33)	2 (11)	1 (6)	1 (6)

Supplementary Table 6. Summary of haematological toxicity – maximum overall CTCAE grade change in haemoglobin (g/L), neutrophils (10^9/L) and platelets (10^9/L) during treatment for groups 6 and 8

Group/treatment	Baseline CTCAE grade[a] Total	Patients at baseline with one on-treatment measurement, n (%)[b]	Patients with maximum overall CTCAE grade during treatment, n (%)[c]		
			Grade ≤2	Grade 3	Grade 4
Group 6					
300 mg BD TAB	**Haemoglobin**				
	0	6 (33.3)	5 (27.7)	1 (5.6)	0
	1	10 (55.6)	8 (44.4)	1 (5.6)	1 (5.6)
	2	2 (11.1)	1 (5.6)	0	1 (5.6)
	Total	18 (100)	14 (77.7)	2 (11.1)	2 (11.1)
400 mg BD TAB	**Haemoglobin**				
	0	8 (47.1)	4 (23.5)	2 (11.8)	2 (11.8)
	1	6 (35.3)	5 (29.4)	1 (5.9)	0
	2	3 (17.6)	2 (11.8)	1 (5.9)	0
	Total	17 (100)	11 (64.7)	4 (23.5)	2 (11.8)

Group/treatment	Baseline CTCAE grade[a] Total	Patients at baseline with one on-treatment measurement, n (%)[b]	Patients with maximum overall CTCAE grade during treatment, n (%)[c]		
			Grade ≤2	Grade 3	Grade 4
400 mg BD CAP	**Haemoglobin**				
	0	12 (66.7)	11 (61.1)	1 (5.6)	0
	1	6 (33.3)	5 (27.7)	1 (5.6)	0
	Total	18 (100)	16 (88.8)	2 (11.1)	0
Group 8					
200 mg TID TAB	**Haemoglobin**				
cont	0	11 (68.8)	10 (62.5)	1 (6.3)	0
	1	5 (31.3)	5 (31.3)	0	0
	Total	16 (100)	15 (93.8)	1 (6.3)	0
250 mg TID TAB	**Haemoglobin**				
inter	0	11 (73.3)	11 (73.3)	0	0
	1	4 (26.7)	3 (20.0)	1 (6.7)	0
	Total	15 (100)	14 (93.3)	1 (6.7)	0

Group/treatment	Baseline CTCAE grade[a] Total	Patients at baseline with one on-treatment measurement, n (%)[b]	Patients with maximum overall CTCAE grade during treatment, n (%)[c]		
			Grade ≤2	Grade 3	Grade 4
400 mg BD TAB	**Haemoglobin**				
inter	0	13 (81.3)	13 (81.3)	0	0
	1	3 (18.8)	3 (18.8)	0	0
	Total	16 (100)	16 (100)	0	0
400 mg TID TAB	**Haemoglobin**				
cont	0	10 (66.7)	10 (66.7)	0	0
	1	5 (33.3)	5 (33.3)	0	0
	Total	15 (100)	15 (100)	0	0

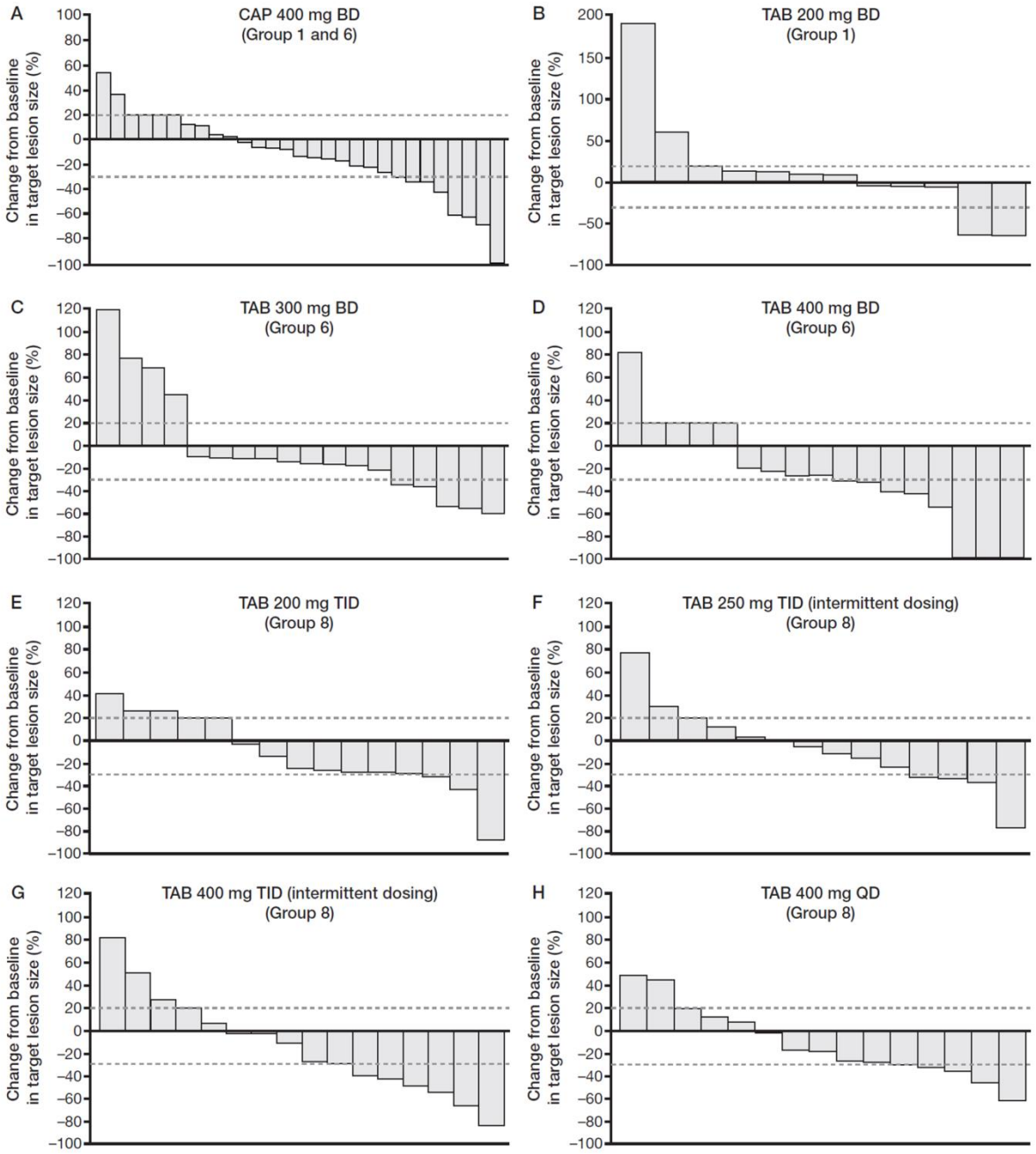
[a]Baseline was defined as the last result obtained prior to the start of olaparib; [b]Patients with a baseline value and at least one on-treatment value; percentages have been calculated using the number of patients at baseline; [c]Derived from laboratory assessments between the start of treatment and 30 days following the date of last dose of olaparib

Supplementary Table 7. Summary of number (%) of patients with interruptions and dose reductions of olaparib as a result of adverse events for groups 6 and 8

		Number of patients with an interruption					Number of patients with a dose reduction					Total number of patients with a dose interruption and/or reduction				
	n	**Total**	**1**	**2**	**≥3**	**AE**	**Total**	**1**	**2**	**≥3**	**AE**	**Total**	**1**	**2**	**≥3**	**AE**
Group 6																
300 mg BD TAB	18	8	3	2	3	7	4	3	0	1	4	9	2	3	4	8
		(44.4)	(16.7)	(11.1)	(16.7)	(38.9)	(22.2)	(16.7)		(5.6)	(22.2)	(50.0)	(11.1)	(16.7)	(22.2)	(44.4)
400 mg BD TAB	17	10	5	4	1	10	11	7	2	2	11	13	4	2	7	13
		(58.8)	(29.4)	(23.5)	(5.9)	(58.8)	(64.7)	(41.2)	(11.8)	(11.8)	(64.7)	(76.5)	(23.5)	(11.8)	(41.2)	(76.5)
400 mg BD CAP	18	6	3	2	1	3	3	3	0	0	3	8	4	3	1	6
		(33.3)	(16.7)	(11.1)	(5.6)	(16.7)	(16.7)	(16.7)			(16.7)	(44.4)	(22.2)	(16.7)	(5.6)	(33.3)
Group 8																
200 mg TID TAB	16	13	2	4	7	7	4	3	1	0	3	13	2	2	9	7
cont		(81.3)	(12.5)	(25.0)	(43.8)	(43.8)	(25.0)	(18.8)	(6.3)		(18.8)	(81.3)	(12.5)	(12.5)	(56.3)	(43.8)
250 mg TID TAB	15	11	1	2	8	7	2	2	0	0	1	11	1	2	8	7
inter		(73.3)	(6.7)	(13.3)	(53.3)	(46.7)	(13.3)	(13.3)			(6.7)	(73.3)	(6.7)	(13.3)	(53.3)	(46.7)

		Number of patients with an interruption					Number of patients with a dose reduction					Total number of patients with a dose interruption and/or reduction				
	n	**Total**	**1**	**2**	**≥3**	**AE**	**Total**	**1**	**2**	**≥3**	**AE**	**Total**	**1**	**2**	**≥3**	**AE**
400 mg BD TAB	16	16	6	3	7	8	6	5	0	1	6	16	4	5	7	8
inter		(100)	(37.5)	(18.8)	(44.0)	(50.0)	(37.5)	(31.3)		(6.3)	(37.5)	(100)	(25.0)	(31.3)	(43.8)	(50.0)
400 mg OD TAB	15	7	3	2	2	5	2	1	0	1	2	7	3	2	2	5
cont		(46.7)	(20.0)	(13.3)	(13.3)	(33.3)	(13.3)	(6.7)		(6.7)	(13.3)	(46.7)	(20.0)	(13.3)	(13.3)	(33.3)

Supplementary Figure 2. Waterfall plots of percentage change in target lesion size at 16 weeks (a) following multiple dosing of olaparib capsule 400 mg BD (groups 1 and 6), (b) following multiple dosing of the tablet 200 mg BD to patients in group 1, (c) following multiple dosing of the tablet 300 mg BD to patients in group 6, (d) following multiple dosing of the tablet 400 mg BD to patients in group 6, (e) following continuous dosing of the tablet 200 mg TID to patients in group 8, (f) following intermittent dosing of the tablet 250 mg TID to patients in group 8, (g) following intermittent dosing of the tablet 400 mg TID to patients in group 8, and (h) following continuous dosing of the tablet 400 mg OD to patients in group 8


A
CAP 400 mg BD
(Group 1 and 6)
B
TAB 200 mg BD
(Group 1)
C
TAB 300 mg BD
(Group 6)
D
TAB 400 mg BD
(Group 6)
E
TAB 200 mg TID
(Group 8)
F
TAB 250 mg TID (intermittent dosing)
(Group 8)
G
TAB 400 mg TID (intermittent dosing)
(Group 8)
H
TAB 400 mg QD
(Group 8)
Change from baseline in target lesion size (%)