STOMP: Small cell lung cancer **T**rial of **O**laparib (AZD2281) as **M**aintenance **P**rogramme: a randomised, double blind, multicentre phase II trial

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NCRN National Cancer Research Network

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

UNIVERSITY OF BIRMINGHAM

CANCER RESEARCH UK

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AMENDMENTS:

The following amendments and/or administrative changes have been made to this protocol since the date of preparation

Protocol Amendment No.	Date of Amendment	Protocol Version No.	Type of amendment? (e.g. substantial/non-substantial/administrative change)
1	**13-Mar-2013**	**2.0**	Substantial. Included: • A change in the design of the trial to placebo controlled 3 arm study • Change from capsules to tablets • Increase in recruitment target • Change in primary outcome measure
2	**02-Oct-2013**	**3.0**	Substantial. Included: • Change to eligibility criteria • Clarification of types of tumour sample
3	**25-Aug-2015**	**4.0**	Substantial. Including: • Change to definition of end of study • Clarification of indemnity arrangements • Clarification of treatment schedule assessments • Clarification of data reporting requirements • Change to SAE reporting period Numerous non-substantial amendments to correct for typographical errors, bring terminology in line with current protocols, ensure consistency and to amend contact details.
4		**5.0**	Substantial. Including: • Addition of AML as an SAE reporting requirement.

GENERAL INFORMATION

CLINICAL TRIAL PROTOCOL

This clinical trial protocol is intended to provide guidance and information for the conduct of the STOMP trial, in participating sites. It is not for use as a guide for the management of other patients outside the trial. Every care has been taken in writing this document, but corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial, but sites entering patients for the first time are advised to contact the Trial Office to confirm they have the most recent version of the protocol.

Sponsor: Sheffield Teaching Hospitals NHS Foundation Trust

Independent scientific peer review

This protocol has been developed by the STOMP Trial Management Group and submitted to independent peer review through the Cancer Research UK: Clinical Trials Advisory and Awards Committee funding and evaluation process.

Trial Management Group : This trial has been developed by the Trial Management Group

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ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
AML	Acute Myeloid Leukaemia
ANC	Absolute neutrophil count
AR	Adverse Reaction
BER	Base Excision Repair
CR	Complete Response
CRF	Case Report Form
CRCTU	Cancer Research UK Clinical Trials Unit
CT	Computerised Tomography
CTC	Circulating Tumour Cells
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSB	Double Strand Break
ECOG	Eastern Co-operative Oncology Group
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IWRS	Interactive Web Response System
MDS	Myelodysplastic Syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
PARP	Polyadenosine 5'-diphosphoribose polymerisation
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
U&E	Urine and Electrolytes
ULN	Upper Limit of Normal

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1.0 BACKGROUND

1.1 Small cell lung cancer

Small cell lung cancer (SCLC) comprises 15-20% of lung cancers, representing about 3,500 new cases per annum in the UK. SCLC is initially very chemosensitive, with an objective response rate of about 80% but the majority of patients relapse and die from it. In a recent London Lung Cancer Group study involving 724 patients, the median survival was 10.3 months (Lee *et al*., 2007). The standard first line chemotherapy treatment with a platinum-based compound (cis- or carbo-platin) and etoposide has been unchanged for 20 years, and the only improvements in survival over this period are attributable to the addition of radiotherapy. Novel active treatment approaches are urgently needed.

Chemoresistant SCLC commonly has multiple abnormalities in oncogenic and tumour suppressor pathways. Abnormalities in p53 (80%), Rb (>90%), FHIT (80%) and inactivation of RASSF1 (90%) are very common in SCLC (Salgia & Skarin, 1998). These result in increased cell proliferation and deoxyribonucleic acid (DNA) damage requiring repair. Recent data have shown that the association of these with defects in DNA repair pathways, including NBS1, ATM, RAD51, Chk1/2, MDC1 and PTEN can make SCLC cells susceptible to DNA damage (Bartek *et al*., 2009; Bartkova *et al*., 2007; Hansen *et al*., 2003; Jackman & Johnson, 2005; Jiang *et al*., 2009; Medina *et al*., 2003).

1.2 Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] polymerisation (PARP)

Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] or PAR polymerisation is a unique post-translational modification of histones and other nuclear proteins that contributes to the survival of proliferating and non-proliferating cells following DNA damage. This event represents an immediate cellular response to DNA damage and involves the modification of glutamate, aspartate and lysine residues with the addition of long chains of Adenosine diphosphate (ADP)-ribose units, derived from Nicotine Adenine Dinucleotide (NAD)+, onto the DNA-binding proteins. The enzymes that catalyse this process, poly-(ADP)-ribose polymerases (PARPs), are critical regulatory components in DNA damage repair and other cellular processes. They now comprise a large and expanding family of 18 proteins, encoded by different genes, and display a conserved catalytic domain in which PARP 1 (113 kDa), the initial member, and PARP 2 (62 kDa) are so far the sole enzymes whose catalytic activity has been shown to be immediately stimulated by DNA strand breaks. Moreover, many of the identified family members interact with each other, share common partners and common sub-cellular localisations, suggesting functional redundancy and possibly fine-tuning in the regulation of post-translational modification of proteins.

The range of biological roles involving PARP proteins is wide. They include: DNA repair and maintenance of genomic integrity, regulation of protein expression at the transcriptional level, regulation of cellular replication and differentiation, regulation of telomerase activity, involvement in cell elimination pathway by necrosis and serving as a signal for protein degradation in oxidatively injured cells (Virág & Szabó, 2002).

Of the various members of the PARP enzyme family, only PARP 1 and PARP 2 have been shown to work as DNA damage sensor and signalling molecules. PARP 1 is a nuclear enzyme consisting of 3 domains; the N-terminal DNA binding domain containing 2 zinc fingers, the auto-modification domain and the C-terminal catalytic domain. It binds to both single and double stranded DNA breaks through the zinc-finger domain. PARP 1 catalyses the cleavage of NAD+ into nicotinamide and ADP-ribose, the latter is then utilised to synthesise branched nucleic acid-like polymers covalently attached to nuclear acceptor proteins. This branched ADP-ribose polymer is highly negatively charged, thereby affecting the function of the target proteins. Histones have been found to be acceptors of poly ADP-

ribose; the negative charge leads to electrostatic repulsion between DNA and histones. This has been implicated in chromatin remodelling, DNA repair and transcriptional regulation. Other transcriptional factors and signalling molecules shown to be poly-ADP-ribosylated by PARP 1 are nuclear factor-KB, DNA-dependent protein kinase, p53, topoisomerase I, lamin B and PARP 1 protein itself.

PARP 1 activation leads to DNA repair through the base excision repair (BER) pathway, and cells deficient in PARP 1 have been shown to have delayed DNA repair. Like PARP 1, PARP 2 also responds to DNA damage and is similarly involved in single strand DNA repair. For both proteins, inactivation and cleavage promotes apoptosis and is part of the apoptotic cascade. Loss of PARP 1 activity in cells or in knockout mice leads to both radio and chemo-sensitisation. Moreover, increased PARP 1 activity has been found in many tumour types. The use of PARP inhibitors has confirmed that in combination an enhancement of the anti-tumour activity of radiation and DNA damaging cytotoxic agents occurs (Virág & Szabó 2002; Nguewa *et al*., 2005).

1.3 PARP as a target for cancer treatment

There is increasing interest in synthetic lethality as a means of selectively killing cancer cells. Two genes are synthetically lethal where mutation of either gene alone is compatible with viability but simultaneous mutation of both genes leads to death. Synthetic lethal interactions between mutated oncogenes or tumour suppressor genes and molecules involved in DNA damage signalling and repair can be therapeutically exploited to preferentially kill tumour cells. The best example of this is in patients with inherited mutations of BRCA1 and BRCA2 who have defects in homologous recombination, which is a critical DNA double-strand break (DSB) repair pathway. Such cells rely on lower fidelity DSB repair pathways which confer cancer susceptibility through genomic instability. BRCA deficient cells are unable to repair the DSB damage resulting from PARP inhibition, leading to cell death (Sandhu *et al.*, 2009).

Recent evidence suggests that other cancer cells (with normal BRCA) can be susceptible to PARP inhibition if they have “Hallmarks of BRCAness” (Turner *et al.*, 2004). This can be due to epigenetic silencing of BRCA, or disruption of other non-redundant genes in the homologous recombination repair pathway (McCabe *et al*., 2006), such as those described (above) in SCLC. For example, PARP inhibitors have been shown to inhibit the growth of cancer cell lines and xenografts with wild-type BRCA but mutated PTEN (Mendes-Pereira *et al*., 2009). In vitro studies in SCLC cell lines have shown relative sensitivity (3 out of 4) to a PARP inhibitor (olaparib) as a single agent in comparison to NSCLC cell lines (AstraZeneca, personal communication).

1.4 Olaparib

Olaparib (AZD2281, KU-0059436, KuDOS/AstraZeneca) is a PARP inhibitor in development for the treatment of patients who have cancers associated with genetic BRCA mutations and in patients with deficiency in DNA repair, specifically homologous recombination repair deficiency. Clinical study data to date in patients with advanced cancer have shown olaparib to have significant anti-tumour activity as a single agent in ovarian and breast cancer patients with known homologous recombination deficiency: $BRCA1^{-/-}$ or $BRCA2^{-/-}$ (Audeh *et al.,* 2010; Fong *et al*., 2009; Tutt *et al.,* 2010). Due to the molecular targeting of olaparib to specific subsets of tumours and sparing of normal cells, this has raised the opportunity for relatively less toxic cancer monotherapy using such a PARP 1 inhibitor compared with conventional treatments, such as chemotherapy.

Olaparib has been tested in a standard range of safety pharmacology studies e.g. dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised dog

or any behavioural, autonomic or motor effects in the rat at the doses studied. The toxicology studies indicate that the target organ of toxicity is the bone marrow. Further information can be found in the current version of the olaparib Investigator's Brochure.

More than 950 patients have now received olaparib either as monotherapy (11 studies) or in combination with other chemotherapy agents. Data from these studies indicate that olaparib is generally well tolerated as monotherapy at doses up to 400 mg bd capsules in patients with solid tumours. Administration of olaparib has been associated with:

- Anaemia, generally mild to moderate (National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] grade 1-2)
- Neutropenia, predominantly mild to moderate (CTCAE grade 1-2)
- Thrombocytopenia, generally mild to moderate (CTCAE grade 1-2), sometimes severe (CTCAE grade 3-4)
- Pneumonitis events with no consistent clinical pattern have been reported in a small number of patients
- Nausea and vomiting, generally mild to moderate (CTCAE grade 1-2), intermittent and manageable on continued treatment
- Fatigue, generally intermittent and of mild to moderate intensity (CTCAE grade 1-2)

For further information please refer to the current version of the olaparib Investigator's Brochure.

Pharmacokinetic modelling and simulation from the single dose data suggested that a tablet dose of 200mg bd would be expected to reliably deliver steady state Cmax and AUC0-12 values that would be within the range of values previously achieved in patients dosed at the 400mg bd capsule dose. Actual data obtained following dosing of cohorts of genetic breast cancer patients with the 200mg bd tablet or 400mg bd capsule dose showed that the tablet dose did deliver exposures which fell within the range of the capsule values. The average Cmax was higher (6.88µg/mL vs 5.71µg/mL) and both the average AUC0-12 and Cmin were lower (36.1µg.h/mL vs 43.1µg.h/mL and 1.00µg/mL vs 1.86µg/mL, respectively) than achieved in a separate cohort of patients following the 400mg bd capsule dose. In addition, steady state data generated from a further cohort of patients randomised to bd dosing with both the 200mg tablet and the 400mg capsule dose (n=6), demonstrated that the two formulations could not be concluded to be bioequivalent (treatment ratio for Cmax was 0.99 (90% CI: 0.85 to 1.15) but for AUC0-12 was 0.79 (90% CI: 0.65 to 0.94).

Additional work has been performed to determine the tolerability of tablet doses greater than 200mg bd and to evaluate the clinical activity of two of those dose levels. Across the dose escalation cohorts, exposure to olaparib increased as administered dose increased and in the 300 and 400mg bd efficacy expansion cohorts, the average steady state Cmax, AUC0-12 and Cmin either matched or exceeded the mean values previously achieved following a 400mg bd dose of the capsule formulation (presented in the current Investigator's Brochure).

A phase II study (D0810C000019) in platinum sensitive relapsed ovarian cancer has demonstrated the efficacy of olaparib maintenance monotherapy when using the capsule formulation (8 capsules twice daily). A more patient friendly tablet formulation (2 tablets twice daily) has been developed. Since it has been shown that the capsule and tablet formulations are not bioequivalent, a formulation switch based on bioequivalence has not been possible. The tablet doses under investigation in this study have been chosen based on data from an ongoing study, D0810C00024, where tablet doses of 300 mg bd and 200mg tds were considered to have similar efficacy in terms of tumour shrinkage in BRCA mutated ovarian cancer patients to the 400 mg bd capsule together with an acceptable tolerability profile.

The tolerability profile of the 300 mg bd and 200mg tds tablet doses in study D0810C00024 was considered similar to the 400mg bd capsule formulation. The most common Adverse Events (AEs) were consistent with the known safety profile of olaparib, namely low grade nausea, vomiting, fatigue and anaemia. Further information is provided in the Investigator Brochure.

A preliminary analysis of the effect of food (a light snack) on the pharmacokinetics of olaparib tablets was also investigated in study D0810C00024 and preliminary analysis of this data suggest that the intake of a light snack does not impact the pharmacokinetics of olaparib. Patients will be allowed to take olaparib tablets with a light snack during the proposed study.

2.0 TRIAL RATIONALE

2.1 Relapsed small cell lung cancer

Whilst SCLC is initially very chemosensitive (RR 80%), responses are often short-lived and relapse is common. SCLC cells typically exhibit a variety of genetic changes and genomic instability. We hypothesise that this results in “BRCAness” and that such cells will be susceptible to killing by a PARP inhibitor. Olaparib is given by mouth and has an excellent safety and tolerability profile.

2.2 Justification for design

In the past, new drugs were tested in first line in SCLC patients of poor prognosis, but this approach can no longer be justified, as it is unethical to deny patients established first line combinations with high response rates and significant survival benefits. However, patients with relapsed disease have chemoresistant tumours and response rates to new agents in this setting are low. We therefore propose testing olaparib as maintenance treatment in patients with responding disease, in a double-blind, placebo-controlled, randomised phase II trial.

3.0 AIMS, HYPOTHESES AND OUTCOME MEASURES

3.1 Aims

This trial will assess the activity and safety of the PARP inhibitor olaparib as maintenance treatment for patients with chemoresponsive SCLC. Stored tumour specimens and, in selected sites, blood samples, will be studied to look for variables that predict response to this treatment.

3.2 Hypotheses

Primary:

- The use of olaparib as a maintenance therapy in patients with chemoresponsive small cell lung cancer prolongs the period of progression free survival beyond that of using a placebo

Secondary:

- Olaparib is safe, tolerable and effective as maintenance therapy in patients with chemoresponsive SCLC

3.3 Outcome measures

Primary:

- Progression free survival time

Secondary:

- Progression-free rate at 4 months from randomisation
- Overall survival time
- Overall survival rate at 6 months
- Changes in performance status
- Quality of life (EQ-5D)
- Adverse events (as defined by Section 10.0)

Translational:

- Biomarkers: blood and biopsy samples will be collected for analysis of PARP and DNA repair pathways.

4.0 STUDY PLAN AND PROCEDURES

4.1 Overall trial design

This is a multicentre, prospective, double-blind, randomised, phase II trial of olaparib vs placebo, 300mg po bd or 200mg po tds, taken continuously starting no more than 42 days after day 1 of the most recent chemotherapy cycle, or 21 days after the end of the most recent dose of radiotherapy. For patients who receive chemotherapy followed by radiotherapy, the radiotherapy must begin within 35 days from the start of the last chemotherapy cycle. Those patients that fulfil the eligibility criteria will be stratified by disease extent (M0 vs M1a/b with any T or N stage, please see Appendix 1 for the American Joint Committee on Cancer (AJCC) TNM staging for lung cancer) and prior radiotherapy (concurrent vs sequential vs none). Responding patients, nearing completion of primary therapy (chemotherapy +/- radiotherapy) for SCLC, will be offered information with a view to participating in the STOMP trial. Written informed consent for entry into the trial will be sought at least 24h later (see Section 5). No trial-specific procedures will be arranged until the patient has been consented. Patients on trial will be monitored at 4-weekly intervals when safety data will be collected. Computed tomography (CT) scans will be carried out every 8 weeks with chest x-rays being performed on alternate visits.

Subject to patient consent, blood will be collected for measurement of biomarkers at baseline, after 28 days of treatment and at the end of treatment. Archived diagnostic tissue biopsies will be collected retrospectively and used for histopathological assessment and translational endpoints.

Patients will continue on trial medication for 2 years or until disease progression, death, unacceptable toxicity, or withdrawal of patient consent for data transfer.

4.2 Trial duration

It is anticipated that recruitment will take approximately two years and the trial will continue until all patients have either died or have a minimum of 6 months follow-up post treatment discontinuation.

Each patient will be followed up, as per local practice, for overall and cause-specific survival, and for distant or local progression. It is anticipated that recruitment will start in the third quarter of 2013 and be complete by the third quarter of 2015.

5.0 ELIGIBILITY

5.1 Site eligibility

Participating sites must be able to comply with the protocol and data collection requirements. All patients must be reviewed by a lung cancer Multi-Disciplinary Team. Treatment must be managed in a dedicated oncology facility under the supervision of an oncology consultant supported by an oncology research team familiar with Good Clinical Practice (GCP) requirements and the safety profile and characteristics of olaparib.

5.2 Patient eligibility

5.2.1 Inclusion Criteria

1. Pathologically confirmed SCLC (M0 or M1a/b with any T or N stage), please see Appendix 1 for the AJCC TNM staging for lung cancer
2. Completed ≥ 3 cycles of first line chemotherapy or chemo-radiotherapy with cisplatin + etoposide or carboplatin + etoposide
3. Complete Response (CR) or Partial Response (PR) to first line chemotherapy (Response Evaluation Criteria in Solid Tumours [RECIST] 1.1 – see Appendix 3)
4. Eastern Co-operative Oncology Group (ECOG) (see Appendix 2) performance status 0-2, and a life expectancy of greater than 12 weeks
5. Resolution of all previous chemotherapy toxicity (except alopecia) to grade 1 or better
6. Adequate physiological function:

   Calculated or measured creatinine clearance ≥ 50 ml/min (Cockcroft-Gault) and serum creatinine ≤ 1.5 x institutional upper limit of normal (ULN), Haemoglobin (Hb) ≥ 100 g/L, white blood cells (WBC) ≥ $3x10^9$/L, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, aspartate aminotransferase (AST) or alanine transaminase (ALT) ≤ 2.5 x institutional ULN unless liver metastases are present in which case it must be ≤ 5x ULN, total bilirubin ≤ 1.5 x institutional ULN
7. Negative pregnancy test (for female patients of child-bearing potential)
8. Agrees to comply with contraceptive measures as per Section 6.4.1
9. Provision of written informed consent
10. Able to swallow oral medication
11. Patient is willing and able to comply with the protocol for the duration of the trial including undergoing treatment and scheduled visits and examinations

5.2.2 Exclusion Criteria

1. Age ≤18 years
2. Interval from last anticancer treatment to start of trial treatment:
   - last radiotherapy fraction > 21 days*
   - start of final cycle of chemotherapy > 42 days*
   - radiotherapy must begin within 35 days of the start of the last chemotherapy cycle

- * If sequential chemotherapy then radiotherapy then apply the interval for the last radiotherapy fraction. If concurrent chemotherapy and radiotherapy then ensure the trial treatment start date is within whichever is the later interval.

3. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the trial as long as these were started at least 28 days prior to trial treatment
4. Interstitial lung disease
5. Previous malignancies (except curatively treated non-melanoma skin cancer or carcinoma *in situ* of the cervix or breast) within the past 3 years
6. History of malabsorption or major gastrointestinal tract resection likely to affect trial drug absorption
7. Treatment with any investigational product during the last 14 days (or a longer period depending on the defined characteristics of the agents used)
8. Any previous treatment with a PARP inhibitor, including olaparib
9. Patients receiving the following classes of inhibitors of CYP3A4 (see Section 6.4.2 for guidelines and wash out periods): azole antifungals, macrolide antibiotics, protease inhibitors
10. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent
11. Breast feeding women
12. Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV)
13. Patients with known active hepatic disease (i.e., Hepatitis B or C)
14. Patients with a known hypersensitivity to olaparib or any of the excipients of the product
15. Patients with uncontrolled seizures
16. Patients with myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML)
17. Major surgery within 14 days of starting trial treatment and patients must have recovered from any effects of any major surgery

5.3 Screening and consent

5.3.1 Screening

Potential patients will be identified via clinic referrals or Multi-Disciplinary Team meetings. Investigators will be expected to maintain a screening log of all potential trial candidates. This log will include limited information about the potential candidate (e.g. date of birth, initials and gender), and the date and outcome of the screening process (e.g. enrolled into trial, reason for ineligibility, or refused to participate).

The patient will be provided with the Patient Information Sheet, to allow the patient to make an informed decision regarding their participation, in accordance with relevant regulatory guidelines. If informed consent is given, the Investigator will conduct a full screening evaluation to ensure that the patient satisfies all inclusion and exclusion criteria. Note that assessments conducted as standard of care do not require informed consent and may be provided as screening data.

5.3.2 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from each patient prior to performing any trial-related procedure on them. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial, to the patient. The Investigator must also stress that the patient is completely free to refuse to take part in, or withdraw from, the trial at any time. The patient must be given ample time (at least 24h) to read the Patient Information Sheet and to discuss their participation in the trial with others outside of the site research team. The patient must be given an opportunity to ask questions, which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

If the patient decides to participate in the trial they must sign and date the latest version of the Informed Consent Form. The Investigator must then sign and date the form. A copy of the Informed Consent Form must be given to the patient, a copy filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the patient has been entered into the trial, the patient's trial number must be entered on the Informed Consent Form maintained in the ISF. . In addition, if the patient has given explicit consent a copy of the signed Informed Consent Form must be sent in the post to the STOMP Trial Office for review.

Details of the informed consent discussions must be recorded in the patient's medical notes. Throughout the trial, the patient must have the opportunity to ask questions about the trial. Any new information which may be relevant to the patient's continued participation in the trial must be shared with them, in a timely manner. On occasion it may be necessary to re-consent the patient, in which case the process described above must be followed, and the patient's right to withdraw from the trial must continue to be respected.

Electronic copies of the Patient Information Sheet, Supplementary Information Sheets and Informed Consent Form are available from the STOMP Trial Office and must be printed or photocopied onto the headed paper of the local institution.

With the patient's prior consent, their General Practitioner (GP) must also be informed that they are taking part in the trial. A template GP Letter is provided electronically for this purpose.

5.4 Trial entry and randomisation procedure

Prior to recruitment of patients into the trial, the Principal Investigator for each site, or their designee, should have returned all required documentation to the STOMP Trial Office, and the site personnel involved with the STOMP trial must have received appropriate training.

Patient eligibility will be established before treatment randomisation and randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation, with eligible patients being randomised in a 2:1:2:1 ratio according to the following pattern:

	300 mg BD	200 mg TDS	Total
Olaparib	33.3 % (2)	33.3 % (2)	66.6 %
Placebo	16.6 % (1)	16.6 % (1)	33.3 %

Randomisation will be stratified by disease extent (M0 vs M1a/b with any T or N stage, please see Appendix 1 for the AJCC TNM staging for lung cancer) and prior radiotherapy (concurrent vs sequential vs none). The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the Cenduit Interactive Web Recognition System (IWRS) database which is, for the purposes of randomisation, accessed by Cancer Research UK Clinical Trials Unit (CRCTU) on behalf of randomising sites.

Randomisation Office: 0800 371 969 (9 am till 5 pm Monday to Friday excluding University of Birmingham closed days)

A blockrandomisation will be generated and all sites will use the same list in order to minimise any imbalance in the number of patients assigned to each treatment group.

For all subsequent visits the web IWRS system should be used by the site research team to record visits and dispense the required medication.

The following information will be required at randomisation;

- Name of hospital, Investigator and person randomising the patient
- Confirmation that the patient is eligible for the trial
- Confirmation that the patient has given written informed consent
- An anonymised copy of the screening CT scan report (fax to 0121 414 2230 immediately prior to randomisation) to demonstrate response to prior treatment. The following should be clearly stated on the report: FAO: STOMP trial office, site name, patient's initials and date of birth.
- Confirmation of extent of disease and whether or not the patient has had any prior radiotherapy

Patients will be identified to Cenduit using the site number, trial number and date of birth. Once a patient has been randomised, e-mail confirmation will be sent to the sites nominated contact(s) and the STOMP Trial Office. The original patient's Informed Consent Form must be retained in the ISF for inspection, and a copy sent to the STOMP Trial Office in the post. A copy of the Randomisation Form must also be filed in the ISF and the patients details (trial number, initials, and date of birth) entered onto the screening and enrolment log.

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Cenduit will inform the sites nominated contact(s)of the MedID number to be allocated to the patient at the randomisation visit. A member of the research team (to be decided by the hospital) will log in to the Cenduit IWRS for each subsequent dispensing visit for assignment of a new MedID number. The MedID number dispensed at each visit will correspond to the treatment to which the patient was originally randomised or will assign a dose-reduced treatment where relevant.

It is recommended that patients commence trial treatment as soon as possible after randomisation, and ideally within 3 calendar days. Delays in initiation of treatment longer than this will need to be documented and approved by the STOMP Trial Office.

If a patient discontinues participation in the trial, then their trial number cannot be re-used.

6.0 TREATMENT DETAILS

6.1 Treatment schedule

All STOMP treatments will be given in an outpatient setting and according to the schedule stated below. Treatment must start within the time limits defined in the eligibility criteria – no more than 42 days after day 1 of the last chemotherapy cycle, or 21 days after the last radiotherapy fraction (whether thoracic or cranial). For patients who receive chemotherapy followed by radiotherapy, the radiotherapy must begin within 35 days from the start of the last chemotherapy cycle. Where concurrent treatment is given, and radiotherapy and chemotherapy finish on the same day, the chemotherapy timeline should be followed.

Treatment with olaparib/placebo 300mg po bd or 200mg tds, continuously will be given until death, disease progression, unacceptable toxicities or withdrawal of patient consent up to a maximum of 2 years.

The tablets should be taken at the same times each day, with a glass of water. Tablets can be taken with a light snack but should not be taken with a heavy meal because of the potential effect of food on absorption. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

If vomiting occurs shortly after the tablets are swallowed, the dose should only be replaced if all of the tablets can be seen intact and counted. Should any patient enrolled on the trial miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Patients will continue with trial drug until objective disease progression occurs (determined by RECIST 1.1 – see Appendix 3), as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

Patients will remain blinded to the trial team until after the final analysis. No crossover to olaparib is permitted.

6.2 Dose modification

Any toxicity observed during the course of the trial can be managed by dose interruption or dose reduction if deemed appropriate by the Investigator. Once the dose of trial drug has been reduced, under no account should it be re-escalated. All dose reductions and interruptions (including any missed doses), and the reasons for these will be recorded on the Case Report Form (CRF) and in the Patient Diary.

For CTCAE (version 4) grade 1 or 2 AE which the Investigator considers to be related to administration of trial drug, interruptions are discretionary.

For CTCAE **grade 3 or 4 AEs** which the Investigator considers to be related to administration of trial drug, treatment must be interrupted. Such interruptions should continue until the patient recovers completely or the toxicity reverts to CTCAE grade 1 or less. If this is not achieved within a maximum of 4 weeks (28 days) and/or the patient has already undergone a maximum of 2 dose reductions (to the minimum dose), then the patient must permanently discontinue treatment with trial drug. If all toxicity is appropriately resolved within 4 weeks, then the patient should restart treatment with trial drug, but at the 1st dose reduction level according to Table 6.2. If an AE recurs at grade 3 or 4, treatment should be interrupted again (for a maximum of 28 days as detailed above) and, if it resolves within 4 weeks, a second dose reduction should be made. If, on re-starting treatment, the event

continues to occur, the patient must permanently discontinue trial drug. Patients are only allowed two dose reductions.

Full haematology assessments for safety (including Hb, platelets, WBC, and ANC) should be performed at each visit and when clinically indicated. If the absolute value is not available please record percentage. Coagulation (activated partial thromboblastin time [APTT] and international normalised ratio [INR]) will be performed at baseline if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this trial; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Management of leukopenia and/or anaemia:

An exception to the management of olaparib-related toxicity is the occurrence of leukopenia and/or anaemia. In this case, the AE should be managed as deemed appropriate by the Investigator (with growth factor e.g. G-CSF or blood transfusions). However, growth factors must be discontinued once the AE has recovered to CTCAE grade 1 or better. They may be resumed, if necessary, if leukopenia/anaemia develops again and discontinued once it recovers.

- Patients who develop a requirement for repeated blood transfusions within 4-6 weeks should be dose reduced
- Patients who develop grade 3 anaemia should be dose reduced

Management of prolonged haematological toxicities including anaemia, neutropenia or thrombocytopenia whilst on trial treatment:

If trial treatment is interrupted/delayed because of one or more of the following:

- ≥2 week interruption/delay in trial treatment due to CTCAE grade >2 neutropenia
- ≥2 week interruption/delay in trial treatment due to CTCAE grade >2 thrombocytopenia
- ≥2 week interruption/delay in trial treatment due to CTCAE grade >2 anaemia and or development of blood transfusion dependence

Weekly blood counts should be performed during the trial treatment interruption/delay. If the levels have still not recovered to CTCAE grade ≤1 after 4 weeks of dose interruption, the patient should be referred to a haematologist for further investigations. Bone marrow analysis or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Development of MDS/AML should be reported as a Serious Adverse Event (SAE) and full reports must be provided by the Investigator for documentation on the pharmacovigilance database.

Pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in trial drug dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then trial treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Chief Investigator.

Table 6.2 Dose reductions for olaparib / placebo

Reduction	Dose Level	
Initial Dose Level	300mg bd	200mg tds
1st dose reduction	250mg bd	150mg tds
2nd dose reduction	200mg bd	100mg tds
3rd dose reduction	No further reduction allowed withdraw patient	No further reduction allowed - withdraw patient

Surgery and radiotherapy

Trial drug should be stopped before surgery and re-started following recovery. No stoppage of trial drug is required for any biopsy procedures.

Trial drug should be discontinued for a minimum of 7 days before a patient undergoes therapeutic radiation treatment. Dose interruption is not required for single palliative fractions.

6.3 Trial treatment period

- The trial treatment period begins on the day of starting the trial drug. Treatment should start within 3 calendar days of randomisation and will continue for 2 years or until disease progression, death, unacceptable toxicity, or withdrawal of patient consent for data transfer
- For the purposes of pharmacovigilance reporting the end of the trial treatment period is 28 days after the final dose of trial drug has been taken

6.4 Restrictions during the trial

6.4.1 Contraception

Patients of child bearing potential (female patients who have experienced menarche, are not post-menopausal and have not been permanently sterilised) and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the trial and for 3 months after last dose of trial drug:

- Condom with spermicide

and one of the following:

- Oral contraceptive or
- Hormonal therapy (e.g. hormone implants) or
- Placement of an intra-uterine device

6.4.2 Concomitant Therapy

Please refer to the Investigator Brochure for all known contraindications for olaparib.

The use of any natural/herbal products or other “folk remedies” should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded on the Concomitant Medication Log.

6.4.3 Olaparib and CYP3A4

Olaparib is an investigational drug for which no data on *in vivo* interactions are currently available. Based on *in vitro* data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. *In vitro* data have, however, also shown that the principal enzyme responsible for the formation of the three main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this trial for any patient receiving olaparib.

While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfanvir

For patients taking any of the above, the required wash-out periods prior to starting olaparib/placebo is one week.

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 inducers should be avoided:

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John’s Wort (Hypericum perforatum)

For patients taking any of the above, the required wash-out periods prior to starting olaparib/placebo are:

- phenobarbitone 5 weeks, and
- for any of the others, 3 weeks

After randomisation if the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient’s safety and welfare, the Investigator must contact the STOMP Trial Office for referral to the Chief Investigator. A decision to allow the patient to continue in the trial will be made on a case-by-case basis.

6.4.4 Other Concomitant Medications

Medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the trial or until 28 days from the end of the last protocol treatment and different from the trial medication must be documented. This includes any medications, with the exceptions noted in Section 6.4.2, which are considered necessary for the patient's welfare, and which it is believed will not interfere with the trial medication. These may be given at the discretion of the Investigator, providing the medications, the doses, dates and reasons for administration are recorded on the relevant CRF.

Live Vaccines: Live virus and bacterial vaccines should not be administered whilst the patient is receiving trial medication and during the 28 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown. Other routine vaccinations, e.g. for seasonal influenza are permitted.

Anticoagulant Therapy: Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

Anti-emetics/Anti-diarrhoeals: Prophylactic anti-emetics and/or anti-diarrhoeals will not routinely be given. Should a patient develop nausea, vomiting and/or diarrhoea, which, in the Investigator's opinion, is considered related to the trial medication, then appropriate prophylactic treatment may be given.

The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the relevant CRF.

6.4.5 Palliative Radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the trial period. Trial drug interruption is not required (Section 6.2).

6.4.6 Administration of Other Anti-cancer Agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on trial treatment. Patients may continue the use of bisphosphonates for bone disease and corticosteroids provided the dose is stable before and during the trial and they were started at least 4 weeks prior to beginning trial treatment. Short courses of corticosteroids can be given if clinically indicated for acute exacerbations of chronic obstructive pulmonary disease.

6.5 Follow up period

Patient follow-up will continue until 2 ½ years after the last patient has been recruited.

Patients who discontinue treatment for reasons other than progression should continue to have CT scans every 8 weeks until progression or alternatively until the follow-up period is complete.

The frequency of follow-up for patients, after the treatment phase has ended, will be at the discretion of the Investigator at the recruiting sites. It is anticipated that patients will be seen as a minimum every three months.

A Follow-up Form should be completed by the Investigator or a delegated member of the site research team and returned to the STOMP Trial Office every three months until the patient dies or the end of the follow-up period as defined above. This form will capture the date the patient was last seen in that 3 month follow-up period.

Every endeavour should be made to follow patients up in accordance with the protocol. Where patients fail to attend clinic the patient's GP should be contacted for follow-up information, patient consent permitting.

6.6 Definition and recording of recurrence and disease progression

Disease progression is defined by RECIST (v1.1) as an increase by 20% in the sum of tumour diameters for target lesions, or the appearance of new lesions, taking as reference the smallest sum of tumour diameters since randomisation (including the baseline sum) or the unequivocal progression of non-target lesions.

Recurrence is defined as clinical or radiological progression of disease from remission status at trial entry (CR or PR).

Details of all recurrences must be included on the CRF along with their subsequent clinical response.

6.7 Translational studies

The translational studies are an intrinsic part of the STOMP trial and include blood and tumour sample collection. Consent for these optional studies will be obtained. Refusal of patients to consent to tissue sample collection will not exclude them from participating in the rest of the trial.

See Section 9 for more details.

7.0 TRIAL ASSESSMENTS

7.1 Assessment schedule

See Scheme of Trial Assessments (see Table 7.1).

Assessment will be timed in weeks or months from randomisation unless specified.

7.1.1 Screening (day -28 to 0, i.e. Randomisation Date)

The following assessments should be performed to assess eligibility during the screening period:

- Medical history including AE review (from time of consent) and concomitant medication review
- Physical examination (including height and weight) to assess fitness and ECOG performance status
- Blood pressure (supine), pulse and temperature
- The following tests should be conducted to confirm patient eligibility:
    - Hb
    - WBC
    - ANC
    - Platelet count
    - Calculated or measured creatinine clearance
    - AST/ALT
    - Total bilirubin
- Coagulation tests (APTT and INR) if clinically indicated (unless the patient is receiving warfarin)
- Peripheral blood smear to test for MDS and AML (if clinically indicated)
- Pregnancy test for female patients of child-bearing potential (see Section 6.4.1)

- CT chest and upper abdomen (to include liver and adrenals) performed in accordance with RECIST 1.1 (see Appendix 3)
- Final confirmation of eligibility (at point of randomisation)

7.1.2 Pre Cycle 1 (-7 Days to Treatment Commencement)

The following assessments should be performed within 7 days prior of commencing the first cycle of trial medication:

- Chest X-Ray **(within 7 days of randomisation)**
- Physical examination to include ECOG performance status
- Blood pressure (supine), pulse and temperature
- Haematology (to include Hb, WBC, ANC and platelets) and clinical chemistry to include (sodium, potassium, adjusted calcium, urea, creatinine, albumin, total serum protein, total bilirubin, alkaline phosphatase, AST/ALT)

Once the patient has consented to the trial the following should be performed:

- Patients agreeing to participate in the Quality of Life study should be asked to complete a Quality of Life questionnaire. Prior to completing the baseline questionnaire a member of the site research team should discuss the questionnaires with the patient and answer any questions they may have. Once the questionnaire has been completed by the patient the site research team should check to make sure that all of the questions have been completed. The site research team should complete the Quality of Life Compliance Form ensuring that the time point (i.e. in this instance Baseline) and date the questionnaire was completed are accurately recorded. Please note if a quality of life assessment is missed for any reason the Quality of Life Compliance Form should still be returned to document the fact that the assessment was not performed.
- Collection of blood sample for biomarker and if applicable Circulating Tumour Cell (CTC) analysis if the patient has consented to this optional sub-study (see Section 9 and the separate Translational Study Guidelines)
- Give the patient the relevant Patient Diary and request that they complete it each day while on treatment

Please note: If the patient is receiving warfarin it is recommended that prothrombin time (APTT and INR) is monitored at least once per week for the first month (see Section 6.2).

7.1.3 Cycle 2 and all Subsequent Cycles (Day 1 of 4 Weekly Visit)

All patients will be assessed by the following methods every 4 weeks whilst receiving STOMP trial medication. All assessments should ideally be carried out on the visit date but can be carried out up to 3 days prior to the visit. Unless otherwise specified data will be collected on a cycle specific Treatment Form which will be completed at the end of the cycle of treatment to capture all data relevant to that cycle.

- Physical examination (including weight)
- ECOG performance status
- Blood pressure (supine), pulse and temperature
- Haematology (to include Hb, WBC, ANC and platelets) and clinical chemistry to include (sodium, potassium, adjusted calcium, urea, creatinine, albumin, total serum protein, total bilirubin, alkaline phosphatase, AST/ALT)

- APTT and INR recommended for patients on warfarin (see Section 6.2)
- AE review. Complete an Adverse Event Monitoring Form capturing all AEs suffered during the previous cycle (i.e. Cycle 1 Adverse Event Monitoring Form is completed on day 1 of Cycle 2 and so on)
- Concomitant medication review. Complete a Concomitant Medication Log capturing the concomitant mediation taken during the previous cycle (i.e. Cycle 1 Concomitant Medication Log is completed on day 1 of Cycle 2 and so on)

In addition:

- The patient should be given the relevant Patient Diary and the previous cycle's diary should be collected and returned to STOMP Trial Office
- The patient should be asked to complete a Quality of Life questionnaire. The site research team should ensure that the date the questionnaire was completed and the time point (the cycle 1 questionnaire is completed at the cycle 2 day 1 visit and so on) are appropriately recorded on the Quality of Life Compliance Form before returning to the STOMP Trial Office. Please note if a quality of life assessment is missed for any reason the Quality of Life Compliance Form should still be returned to document the fact that the assessment was not performed
- Blood samples for biomarker, and if applicable CTC analysis, should be taken 28 days after commencing treatment (or day 1 of cycle 2) only. See Section 9 and the separate Translational Study Guidelines

7.1.4 End of Odd Cycles

A chest x-ray should be performed at the end of every odd cycle; this will be four weeks from randomisation in the first instance. The results should be recorded on the odd numbered Treatment Forms commencing with cycle 1 (see Section 11.1).

7.1.5 End of Even Cycles

A CT scan should be performed at the end of every even cycle; this will be 8 weeks from randomisation in the first instance. The results should be recorded on the even numbered Treatment Forms commencing with cycle 2 (see Section 11.1). CT scans can be performed up to 7 days prior to the assessment date to allow for reporting ahead of the next cycle. The results of the CT scan should be documented on a Tumour Response Form in accordance with RECIST (Version 1.1) (see Appendix 3).

Every effort should be made to follow the protocol specified schedule of assessments in particular the CT scan (see Table 7.1).

7.1.6 Treatment Discontinuation (28 Days Post-completion of Treatment)

For patients who discontinue treatment the following assessments should be carried out approximately 28 days after taking their last dose of trial medication:

- Haematology (to include Hb, WBC, ANC and platelets) and clinical chemistry to include (sodium, potassium, adjusted calcium, urea, creatinine, albumin, total serum protein, total bilirubin, alkaline phosphatase, AST/ALT)
- AE review. Complete an Adverse Event Monitoring Form
- Concomitant medication review. Complete a Concomitant Medication Log≠

In addition:

- The patient should be asked to complete a Quality of Life questionnaire. The site research team should ensure that the date the questionnaire was completed and the time point (in this instance this will be the End of Treatment Assessment) are appropriately recorded on the Quality of Life Compliance Form before returning to the STOMP Trial Office. Please note if a quality of life assessment is missed for any reason the Quality of Life Compliance Form should still be returned to document the fact that the assessment was not performed.
- Blood samples for biomarker, and if applicable CTC analysis should be taken. See Section 9 and the separate Translational Study Guidelines[†]

[≠] If the patient commences second line therapy before the treatment discontinuation assessment is due please provide data up until the commencement of second line therapy

[†] If the patient has progressed and is to commence second line therapy please ensure samples are taken prior to commencing second line treatment

Patients who discontinue treatment for reasons other than progression should continue to have CT scans every 8 weeks until progression, or alternatively until the follow-up period of the trial is complete. Patients who discontinue for progression should be managed in accordance with Section 7.2.

7.1.7 Follow-up Assessments

Patient should be followed up as detailed in Section 6.5. A Follow-up Form should be completed every 3 months for all patients following discontinuation of treatment (unless patient has withdrawn consent for future data transfer). Patients who discontinue treatment for reasons other than progression should continue to have CT scans every 8 weeks until progression, or alternatively until the follow-up period of the trial is complete. A Response Form should therefore be completed every 8 weeks for these patients.

Archival tumour tissue samples will be requested retrospectively during the follow-up period (see Section 9).

Table 7.1 Schema of trial assessments

	Screening (Day -28 to 0)	**Pre-cycle 1** (Day -7 to treatment commence-ment)	**Cycle 2 and all subsequent cycles** (Day 1 of 4 weekly visit)	**End of odd cycles**[i]	**End of even cycles**[j]	**Treatment discont-inuation** (28 days post completion of treatment)	**Follow-up**[l]
Informed consent	X						
Medical history	X						
Review of Inclusion/exclusion criteria	X						
Peripheral blood smear to test for MDS & AML (if clinically indicated)	X						
Physical examination	X	X	X				
Vital signs, body weight (includes BP, pulse and temperature) Height only at screening	X	X	X				
ECOG performance status	X	X	X				
Haematology[a] / clinical chemistry[b]	X	X	X			X	
Pregnancy test[c]	X						
Coagulation tests (if clinically indicated)[d+e]	X		X				
Blood sample for biomarker analysis & CTC		X	X[h]			X	
Tumour Assessment (CT according to RECIST)	X				X[k]		X[m]
Chest X-ray[f]		X		X			
Patient Diary		X	X				
Quality of Life Questionnaire (EQ-5D-3L)		X	X			X	
Adverse Events	X		X			X	
Concomitant medications	X		X			X	
Randomisation (day 0 only)	X						
Olaparib/placebo dispensed/returned		X[g]	X				
Archival tumour sample (when available)							X
Survival							X

a Haematology to include Hb, WBC, ANC, platelets.
b Clinical chemistry to include calculated or measured creatinine clearance, AST/ALT and total bilirubin at screening and sodium, potassium, adjusted calcium, urea, creatinine, albumin, total serum protein, total bilirubin, alkaline phosphatase, AST/ALT at all other time points.
c For female patients of child-bearing potential as defined in Section 6.4.1.
d Coagulation test to include INR and APTT.

[e] Recommended during treatment if patient is receiving warfarin, measured weekly for first month and monthly thereafter.
[f] Baseline chest x-ray to be performed within 7 days of randomisation.
[g] Treatment should commence within three days of randomisation.
[h] 28 days after commencing treatment (or day 1 of cycle 2) only.
[i] Four weeks from treatment commencement in first instance.
[j] Eight weeks from treatment commencement in first instance.
[k] CT scans can be performed up to 7 days prior to the assessment date to allow for reporting ahead of the next cycle.
[l] Follow up data should be obtained at three monthly intervals from treatment discontinuation.
[m] Patients who discontinue treatment for reasons other than progression should continue to have CT scans every 8 weeks until progression.

7.2 Management of progression

If progression is suspected from clinical examination or a chest X-ray then this should be confirmed by a CT scan.

At disease progression, patients will stop trial treatment and further treatment will be at the discretion of the Investigator, according to local clinical practice.

Refer to Section 7.1.5 regarding assessments to be performed on discontinuation of treatment.

All patients must continue to be followed-up for survival unless they explicitly withdraw consent for this (see Section 7.4).

7. 3 Tumour evaluation

RECIST 1.1 will be used to assess patient response to treatment to determine progression free survival (PFS) times (Section 6.7). The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are defined in Appendix 3.

CT scans of thorax and upper abdomen will be used to assess tumour burden at baseline and at each subsequent follow-up assessment.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 8 weeks until objective disease progression as defined by RECIST 1.1.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 of response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on trial). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

For patients with non-measurable disease only at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 of response: CR PD and Non CR/Non PD.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesion or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

7.4 Patient withdrawal

7.4.1 Withdrawal from Trial

In the event of a patient's decision to withdraw from the trial, the Investigator must ascertain from which aspects of the trial the patient wishes to withdraw, and record the details on the Withdrawal Form. All patients will continue to be followed-up, and all information and tissue samples collected up until the point of withdrawal will be retained and analysed.

7.4.2 Withdrawal from Treatment

If a patient chooses to withdraw from treatment only, the patient should discontinue treatment but continue to be assessed in accordance with the protocol (including continuation of CT scans).

If a patient wishes to withdraw from the trial (i.e. including trial specific assessments), but is willing for further data to be supplied to the STOMP Trial Office, then further routine "follow-up" data (e.g. progression status, survival, further treatment) will continue to be supplied by the Investigator to the STOMP Trial Office.

Patients may be discontinued from Investigational Medicinal Product (IMP) in the following situations:

- Patient decision. The patient is at any time free to discontinue trial drug, without prejudice to further treatment
- After suffering an AE
- Severe non-compliance to trial protocol
- Any CTCAE grade 3 or 4 events that have not reverted to CTCAE grade 1 or less within 4 weeks (28 days). At the Investigator's discretion, following dose interruption, patients may be considered for dose reductions providing they have not already undergone the maximum number of dose reductions allowed - for guidelines see Section 6.2. However, if upon re-challenging with olaparib/placebo at the lowest reduced dose any CTCAE grade 3 or 4 AE recur, the patient must be discontinued
- Objective progression according to RECIST 1.1

If the patient decides to withdraw from the trial and is not willing to supply any further data then this wish should be explicitly stated in the source data.

8.0 TRIAL DRUG

8.1 Investigational Medicinal Products

For the purposes of this trial olaparib and the matched placebo are regarded as IMPs.

Full details of the IMPs are contained in the Pharmacy Manual, which also lists the Pharmacists' responsibilities, details of labelling, record keeping for prescribing, dispensing,

and accountability of the IMP. The STOMP Pharmacy Manual will be sent to the responsible Pharmacist.

Olaparib is a PARP inhibitor licensed by the European Medicines Agency (EMA) in 2014 for use as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed BRCA mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy. The IMP is therefore being used outside of its licensed indication.

8.2 Supply, storage, labelling and accountability.

8.2.1 Supply

Olaparib/placebo will be supplied by Astra Zeneca free of charge for all STOMP trial patients and will be packaged and distributed by Fisher Clinical Services. An initial supply will be sent automatically once the site has been activated. Re-supply levels will be managed by the IWRS and will not require action by the Pharmacy Department.

Investigational product[a]	Dosage form and strength	Manufacturer
Olaparib	100mg tablet 150mg tablet	AstraZeneca
Placebo to match olaparib	100mg tablet 150mg tablet	AstraZeneca

[a] Descriptive information for olaparib can be found in the Investigator's Brochure

For all sites, olaparib or matching placebo tablets will be packed in bottles of 32 tablets, induction sealed with desiccant. Each patient will receive sufficient medication at each visit to complete 28 days of treatment. Trial drug will be dispensed to patients on day 1 and every 28 days thereafter until the patient completes the trial, withdraws from the trial or closure of the trial, up to a maximum of 2 years.

8.2.2 Storage

All trial drugs must be kept in a secure place under appropriate storage conditions and may only be dispensed by a pharmacist or a qualified designee. The IMP label on the bottle and the Investigator Brochure and the Pharmacy Manual specifies the appropriate storage and shipment.

Trial drug must be stored at room temperature, below 30^{o}C. It must not be refrigerated.

Any temperature excursions must be reported to the STOMP Trial Office detailing the circumstances, period of excursion and supplies which may be affected on a Temperature Deviation Form.

8.2.3 Labelling

Fisher Clinical Services have been contracted on behalf of AstraZeneca to perform labelling of olaparib (AZD2281) and/or matching placebo in accordance with the EU directive (Directive 2001/20/EC). Each bottle will have a label permanently affixed to the outside

stating that the material is for clinical trial/investigational use only and should be kept out of reach of children.

8.2.4 Drug Accountability

The Investigator must maintain adequate records documenting the use, loss, or other disposition, of the IMP. The STOMP Trial Office will supply a drug accountability log which must be used for the IMPs, or you may request to use your standard dispensing forms by contacting the STOMP Trial Office. In either case, the forms must identify the IMP, including batch or code numbers and expiry dates, and account for its allocation on a patient-by-patient basis, including specific dates and quantities. The forms must be signed by the individual who dispenses the drug, and copies must be provided to the STOMP Trial Office as requested or at the end of the trial. The prescribed dose must also be recorded in the patient's medical records.

8.3 Treatment compliance

Patients should be given clear instructions on how and when to take their trial medication. Patients will be given a Patient Diary to complete to document when they took their medication. All patients must return their bottle(s) of trial medication at the appropriate scheduled visit, when new bottles will be dispensed. Patients will be instructed to notify trial site personnel of missed doses.

Treatment compliance will be measured at each clinic visit and recorded on the Treatment Form. All dose modifications, delays and omissions must be recorded. If treatment is permanently discontinued due to toxicity, the Withdrawal and Treatment Discontinuation Forms must be completed.

A tablet count will also be recorded in the appropriate section of the Patient Drug Accountability Log. After the tablet count has been performed, the remaining tablets will be retained by the Investigative site for destruction as per local policy (see the Pharmacy Manual for additional information).

Patients must return all containers and any remaining tablets at the end of their trial treatment.

8.4 Protocol compliance

The olaparib provided for this trial is for use only within the context of the trial and as directed in the trial protocol. It is the Investigator/institution's responsibility to establish a system for handling trial medication, including IMPs, so as to ensure that:

- Deliveries of such products from Fisher Clinical Services are correctly received by a responsible person
- Such deliveries are recorded
- Trial treatments are handled and stored safely and properly as stated on the label
- Trial treatments are only dispensed to trial patients in accordance with the protocol
- The trial personnel will account for all trial medications dispensed and returned
- Certificates of delivery and destruction should be signed

At the end of the trial, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the

person to whom the trial treatment was dispensed, the quantity and date of dispensing and unused trial treatment destroyed. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by a pharmacist/pharmacy technician/pharmacy assistant, and copies retained in the Pharmacy Site File.

8.5 Blinding and procedures for unblinding the trial

8.5.1 Methods for Ensuring Blinding

Olaparib and placebo matching olaparib treatment will be blinded.

The active and placebo tablets will be matching in terms of size and colour and presented in the same packaging to ensure blinding of the trial medication.

8.5.2 Methods for Unblinding the Trial Patients

The process of unblinding will be integrated within IWRS and via a telephone service operated by the Cenduit helpdesk. Both processes will be available 24/7, 365 days, and permission for access to these systems will be governed by the STOMP Trial Office.

Instructions for this will be included in the ISF and Pharmacy Site File that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. Unblinding by Investigators can be performed using IWRS. The Investigator should document the unblind and report the action to STOMP Trial Office, without revealing the outcome of the unblinding. Please note patients unblinded by this mechanism will automatically be discontinued from trial medication.

The Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

9.0 TRANSLATIONAL STUDIES

9.1 Archival tumour tissue

Patients will be invited to give consent for their paraffin-embedded tumour tissue blocks (where available) to be used in future research. Tumour tissue block samples can be in the following formats: whole paraffin embedded tumour block, whole paraffin embedded cytology sample, 10 glass slides containing tumour samples.

The STOMP Translational Sub-study is optional. If a patient decides not to participate in the Translational Sub-study it will not affect their participation in the main STOMP trial.

Archival tumour tissue paraffin block from resection or a core biopsy from the primary tumour or metastases will be collected by the STOMP Trial Office, at the end of trial, by request from the relevant pathology department(s). Alternatively, sections mounted on glass slides prepared from the block can be provided. This material may be used for, but not restricted to, the elucidation of mechanism of response, understanding the mode of action of olaparib and improving the understanding of disease progression.

Refer to the STOMP Translational Study Guidelines for more information.

9.2 Circulating biomarker sub-study

Not all sites will be willing and able to comply with all procedures for handling and storage of samples. Sites are invited to take part in translational aspects to the best of their ability and participation in the main trial is not predicated on full translational participation. Sites participating in the biomarker sub-study will be identified at the site initiation visit. All patients enrolled at these sites will be invited to participate in the sub-study. Participation in the CTC sub-study will be by invitation and is expected to be limited to 3 sites.

At those sites willing and able to participate in the collection, preparation and storage of trial patient blood samples, consenting patients will supply serum, whole blood and plasma samples for biomarker research. Blood samples for biomarker and CTC analysis will be taken at baseline, after 4 weeks of trial treatment and at the end of treatment.

Full details for sample processing, handling and shipment are contained within the STOMP Translational Study Guidelines. In brief the following samples are required:

- Approximately 10ml serum
- Approximately 12ml plasma
- Approximately 6ml whole blood
- Approximately 20 ml blood for CTC samples

Sample analysis will be performed in collaboration with external facilities in the Universities of Manchester and Sheffield holding Human Tissue Act licenses.

9.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

Sample Logs are provided to the site to document collection, storage and shipment of samples to the collaborating laboratories.

The sample receiver will keep full traceability of the samples from the point of receipt.

The STOMP Trial Office keeps oversight of the entire life cycle through internal procedures, monitoring of trial sites and auditing of external laboratory providers.

10.0 ADVERSE EVENT REPORTING

The collection and reporting of AEs will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 4. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the Investigator Brochure provided by the STOMP Trial Office.

10.1 Reporting requirements

10.1.1 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 4 for definition) should be reported with the exception of abnormal laboratory findings for which only abnormal laboratory findings of ≥ grade 3 will be reported.

10.1.2 Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE (see Appendix 4 for definition).

10.1.2.1 Myelodysplastic Syndrome and Acute Myeloid Leukaemia

Development of MDS/AML during the SAE reporting period must be reported as an SAE and full reports must be provided by the Investigator for documentation in the pharmacovigilance database.

10.1.2.2 Overdose

An overdose of trial medication should also be reported as an SAE. There is currently no specific treatment in the event of an overdose with olaparib and possible symptoms of overdose are not established.

10.1.3 Monitoring Pregnancies for Potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the STOMP Trial Office as soon as possible. If it is the patient who is pregnant provide outcome data on a follow-up Pregnancy Notification Form. Where the patient's partner is pregnant consent must first be obtained and the patient should be given a Release of Medical Information Form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the Release of Medical Information Form. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form. If appropriate also complete an SAE Form as detailed below.

10.2 Reporting Period

Details of all AEs (except those listed above) will be documented and reported from the date that the patient is consented into the trial until 28 days after the administration of the last dose of trial medication.

SAEs that are judged to be at least possibly related to trial treatment must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

10.3 Reporting procedure

10.3.1 Site

10.3.1.1 Adverse Events

AEs should be reported on an AE Form (and where applicable on an SAE Form). An AE Form should be completed at each visit and returned to the STOMP Trial Office.

AEs will be reviewed using the CTCAE, version 4.0 (see Appendix 5). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

10.3.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in section 5.0 of the ISF.

AEs defined as serious and which require reporting as an SAE should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the Trial Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

0121 414 2230 or 0121 414 7989

On receipt the STOMP Trial Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Trial Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Trial Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Trial Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

10.3.1.3 Provision of Follow-up Information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

10.3.2 Trial Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Investigator Brochure) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

10.3.2.1 Reporting to the Competent Authority and Research Ethics Committee

Suspected Unexpected Serious Adverse Reactions

The Trials Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA and Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

Serious Adverse Reactions

The Trial Office will report details of all SARs (including SUSARs) to the MHRA and REC annually from the date of the Clinical Trial Authorisation, in the form of an Annual Safety Report.

Adverse Events

Details of all AEs will be reported to the MHRA on request.

Other Safety Issues Identified During the Course of the Trial

The MHRA and REC will be notified immediately if a significant safety issue is identified during the course of the trial.

10.3.2.2 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

10.3.2.3 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

10.3.2.4 Manufacturer of Investigational Medicinal Product

All SAEs will be reported to the manufacturer of the IMP within 24 hours by fax.

10.4 Deaths

All deaths that occur during the trial, or within 28 days after the administration of the last dose of trial medication, must be reported as follows:

Death clearly the result of disease progression should be documented on a Death Form but should not be reported as a SAE.

Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as a SAE within **24h.** The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured on the Death Form.

Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death and, if performed, a copy of the post-mortem results should be forwarded to the STOMP Trial Office within the usual timeframes.

11.0 DATA HANDLING AND RECORD KEEPING

11.1 Data collection

The CRF must be completed, signed/dated and returned to the STOMP Trial Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed below in Table 11.1. The exception is the SAE Form which must be co-signed by the Investigator. See AE reporting Section 10.2 for further details.

Table 11.1 Standard forms and time points for data collection

Form Type	Time point
Eligibility Checklist	Complete during screening and return immediately following randomisation of the patient
Randomisation	Complete at randomisation and return immediately following randomisation of the patient
Baseline Form	Complete immediately following randomisation
Treatment Form	Complete 1 form per cycle of treatment (given for up to a maximum of 2 years). Complete the form at the end of the cycle and capture all information relevant to that cycle of treatment **Please note:** Chest x-rays are recorded on the odd numbered cycle forms and CT scans are recorded on the even numbered cycle forms
Response Form	Complete every 8 weeks until progression **Please note:** During treatment response data is recorded on even numbered cycle forms unless a scan is performed a cycle early due to disease progression
Adverse Event Monitoring Form	Complete at baseline (i.e. immediately following randomisation) and on completion of each treatment cycle (as per treatment forms)
Concomitant Medication Log	Complete at baseline (i.e. immediately following randomisation) and on completion of each treatment cycle (as per treatment forms)
Treatment Discontinuation Form	Complete when the patient finishes treatment regardless of cause

Follow-up Form	Complete the first follow-up form 3 months after discontinuation of trial medication. Forms should then be retuned every 3 months until death, withdrawal of consent for data transfer or the end of the trial.
SAE Form	Complete the form within 24h of first awareness of the event and fax to the Trials Office immediately (see Section 10.2)
Withdrawal Form	Complete when a patient withdraws from the trial
Death Form	Complete immediately on being notified of patient death
Pregnancy Notification Form	Complete immediately on being notified of patient pregnancy
Deviation Form	Completed immediately in the event of a deviation from the protocol
Patient Diaries	Completed by the patient during treatment and collected at each treatment visit
Quality of Life Questionnaire and (only for patients participating in the optional quality of life study)	Should be completed by the patient at baseline, on commencement of the start of each cycle of chemotherapy and treatment discontinuation
Quality of Life Compliance Form (only for patients participating in the optional quality of life study)	Complete when a patients quality of life assessment is due at baseline, on commencement of the start of each cycle of chemotherapy and at treatment discontinuation. Return attached to the Quality of Life Questionnaire

Entries on the CRF should be made in ballpoint pen, in black or blue ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections of a form must be completed before returning to the STOMP Trial Office.

Source data consist of all the information in original records and certified copies of original records of clinical findings, observations, or other activities in the trial, which are necessary for the reconstruction and evaluation of the trial.

For the purposes of this trial the Quality of Life questionnaires and Patient Diaries will act as source data. The original documents will be sent to the STOMP Trial Office.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate. The completed original CRF must be sent promptly to the STOMP Trial Office and a copy filed in the ISF.

Trial CRF may be amended by the Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the CRF must be implemented by participating sites immediately on receipt.

12.0 ARCHIVING

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, ISF, Pharmacy Files, patients' hospital notes, copies of CRFs etc) at their site are securely retained for at least 15 years

after the end of the trial. Participating centres will be sent a letter specifying the permissible disposal date.

13.0 QUALITY MANAGEMENT

The trial is being managed under the auspices of the CRCTU according to the current guidelines for GCP and according to their local procedures. Participating sites will be monitored by CRCTU staff to confirm compliance with the protocol, and the protection of patients' rights as detailed in the Declaration of Helsinki.

13.1 Site set up

All sites will be required to sign a Clinical Study Site Agreement prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements, STOMP trial registration forms, and supply a current CV to the STOMP Trial Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Trial Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trial Office must be informed immediately of any change in the site research team.

13.2 On-site monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the STOMP Quality Management Plan. Additional on-site monitoring visits may be triggered by poor CRF return, poor data quality, excess toxicity, excessive number of patient withdrawals or deviations. If a monitoring visit is required, the Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the STOMP trial staff access to source documents as requested.

13.3 Central monitoring

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming CRF for compliance with the protocol, data consistency, missing data and timing. Where a patient has given explicit consent sites are also requested to send in copies of signed Informed Consent Forms for in-house review. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group (TMG) and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and the MHRA.

14.0 END OF TRIAL DEFINITION

For the purposes of Clinical Trial Authorisation (CTA) under the European Union Directive 2001/20/EC and REC approval, the trial is deemed to have ended 3 ½ years after the last patient has been enrolled into the trial. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The STOMP Trial Office will notify the Sponsor, the MHRA and REC that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

15.0 STATISTICAL CONSIDERATIONS

15.1 Definition of primary outcome measure

The primary outcome measure is PFS time. PFS is defined as the interval in whole days between the date of randomisation into the trial and either the earliest date of detection of progression (where progression is defined by RECIST as an increase by 20% in the sum of tumour diameters or the appearance of new lesions) or date of death without recorded progression. For those patients who neither die nor experience progression during the course of the trial, progression-free survival time will be censored at the date when they were last known to be alive and free of progression.

15.2 Definition of secondary outcome measures

Overall survival time is defined as the interval in whole days between the date of randomisation into the trial and date of death from any cause. Patients who do not die during the course of the trial will be censored at the date when they were last known to be alive. The median survival will be reported as will the six month survival rate, both of which will be calculated using the method of Kaplan-Meier estimation.

Performance status of the patient is classified by the clinician at each treatment visit according to ECOG definitions (Oken *et al*., 1982). The trial will assess the change over time in this measure.

AEs will be recorded according to the definitions given in Appendix 4 of the protocol with grade of events recorded by CTCAE version 4.0. Treatments will specifically be compared in terms of the number of patients who experience at least one grade 3 or grade 4 AE.

15.3 Trial design and sample size calculations

The power and sample size calculation is based on the primary outcome measure of PFS. A median PFS time of 4.8 months is assumed on the control arm. This has been calculated from the raw data of the relevant population from a recent large UK study in SCLC (Lee *et al* 2009). The STOMP trial population will be those patients in the Lee study that were categorised as responders after 4 cycles of chemotherapy. This trial aims to detect an improvement in median PFS to 7.8 months for either of the two experimental arms. A one-tailed significance level of 10% was selected, however, to adjust for multiplicity in comparing the two experimental arms separately to the control arm, the calculation is based on a log-rank test with a one-tailed significance level of 5% (equivalent to a two-tailed level of 10%).

The PFS analyses will be performed when approximately 105 events per comparison have occurred. With 105 events per comparison (assuming 1:1 randomisation) there is 80% power to detect a difference in treatments at a 5% 1-sided significance level, if the true (alternate) hazard ratio was hypothesised to be 0.62 (a reduction in risk of progression of 38%). If the median PFS in the control arm is expected to be 4.8 months, this equates to a 3 month increase in median PFS. Assuming 105 PFS events occur, an observed hazard ratio of 0.72 (a 28% reduction in risk of progression) will give a 1-sided p-value <0.05 within the

trial (a hazard ratio of 0.72 corresponds to 1.9 month increase in median PFS, assuming exponential distribution and proportional hazards).

With the duration of the trial set as 2.5 years (24 months accrual and 6 months follow up) it is estimated that the trial will require 75 patients per treatment arm. Therefore in total a target recruitment of 225 patients is estimated to be required for this trial.

The sample size has been calculated employing the methodology for exponential survival using median survival times reported in Machin D, Campbell MJ, Tan SB, Tan SH: Sample Size Tables for Clinical Studies, 3rd Edition, 2009.

15.4 Methods for analysis

All analyses will be carried out on an intention-to-treat basis. Median progression-free survival time and overall survival time will be reported using Kaplan-Meier estimates together with 90% confidence intervals. In addition the survival rates at 4 and 6 months will be estimated and provided with 90% confidence intervals. Progression-free survival will be compared for each treatment arm to the pooled control group using the log-rank test.

In addition to the log-rank test, analysis of PFS using a Cox proportional hazards model will be considered. This analysis of PFS will adjust for prognostic factors in addition to the trial stratification factors. These factors may include stage and performance status at diagnosis. Consideration will also be given to the use of an interval censored data approach to the analysis of PFS.

Once 105 PFS events have been observed then there will also be an interim assessment of overall survival. A further analysis of overall survival will be performed after a further 6 months of follow up.

Changes in performance status over time will be assessed using longitudinal methods of analysis and will account for informative dropout. AEs, as a whole, will be reported as the number of patients on each treatment arm experiencing each event at each grade. In particular, the difference in the number of patients experiencing at least one grade 3 or grade 4 AE will be estimated with a 95% confidence interval.

16.0 TRIAL ORGANISATIONAL STRUCTURE

16.1 Sponsor

Sheffield Teaching Hospitals NHS Foundation Trust is the Sponsor the trial. The University of Birmingham is contracted to perform trial management functions in line with this protocol.

16.2 Trial Management Group

A TMG will be established, and will include the Chief Investigator, Local Principal Investigator and other identified collaborators, the Trial Statistician, the Trial Co-ordinator, and Senior Trial Managers. Key trial personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups.

Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference or in-person as required.

16.3 Data Monitoring Committee

An independent DMC will be established to oversee the safety and interim efficacy of the trial. This committee will be assembled according to GCP.

Data analyses will be supplied in confidence by the trial statistician to the DMC, who will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The trial statistician and members of the DMC will be the only individuals who see the confidential, accumulating data to the trial; however the Chief Investigator and Trial Coordinator will receive subsets of the report as seen fit by the DMC (e.g. accrual, compliance, data completeness).

During the recruitment phase of the trial the DMC will meet one year after the trial opens and then annually thereafter until the trial closes to recruitment. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the CRCTU who will convey the findings of the DMC to the TMG and Sponsor.

The DMC may consider discontinuing the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety. The trial would also stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community. The DMC may also recommend continuation beyond the planned number of patients in the trial if it is felt that further information is required to reliably address the hypothesis in question.

If any change to the trial is suggested it will be submitted as a substantial amendment to the MHRA and REC prior to implementation unless it is an urgent safety measure.

16.4 Finance

This trial is a clinician-initiated and clinician-led trial. The trial administration at the Sponsor institution is funded and supported by Cancer Research UK. AstraZeneca will supply the olaparib and matching placebo at no cost for trial patients and fund the STOMP Trial Office in pursuance of its delegated Sponsor responsibilities.

16.5 NCRN adoption

The STOMP trial is Cancer Research UK funded and endorsed. It is therefore included in the NIHR trials portfolio.

17.0 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964, amended at the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 (see Appendix 6).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 1998 and Human Tissue Act 2008) and the EU GCP Directive (2005/28/EC). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the REC prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local Research and Development (R&D) approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the STOMP Trial Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

18.0 CONFIDENTIALITY AND DATA PROTECTION

The personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act, 1998. To preserve the patient's anonymity, their unique trial number, initials, date of birth, and hospital name and/or number will be recorded on the CRF. If the patient's name appears on any documents (e.g. pathologist report) it must be obliterated before a copy of the document is supplied to the Trial Office (with the exception of the consent form if the patient has given prior consent for its collection). With the patient's prior permission, their name and National Health Service (NHS), or in Scotland the Community Health Index (CHI), number will be used to allow flagging with the Medical Research Information Service (part of the NHS Information Centre) to assist with long-term follow-up via other health care professionals (e.g. patient's GP).

Trial findings stored on a computer will be stored in accordance with data protection laws. The patients will be informed that representatives of the Sponsor or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Trial Office will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party, other than those directly involved in the treatment of the patient's cancer. If the results are published, the patient's identity will remain confidential.

Representatives of the STOMP Trial Office may be required to have access to patient's hospital records for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

The Investigator must maintain documents not for submission to the STOMP Trial Office (e.g. patient logs) in strict confidence. In the case of special problems and/or regulatory authority queries, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

19.0 INSURANCE AND INDEMNITY

The University of Sheffield indemnifies the CRCTU and Sponsor, their employees and agents involved in the trial, against any claims or proceedings in respect of personal injury made or brought against them by trial participants which are the result of a negligent error or omission in the protocol.

No provision has been made for indemnity in the event of a claim for non-negligent harm.

In terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is only available via NHS indemnity in the event of clinical negligence being proven.

The trial is coordinated by CRCTU at the University of Birmingham and its employees are indemnified by the University insurers for negligent harm caused by the co-ordination of the clinical trials they undertake whilst in the University's employment.

20.0 PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by the TMG and authorship will be determined by mutual agreement. The Chief Investigator, Trial Statistician and Trial Co-ordinator will be co-authors.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding

issues. Authors must acknowledge that the trial was performed with the support of Sheffield Teaching Hospitals, University of Birmingham, AstraZeneca and CTAAC. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

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APPENDIX 1 – AMERICAN JOINT COMMITTEE ON CANCER TNM STAGING FOR LUNG CANCER

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Definitions

Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0 No evidence of primary tumor

Tis Carcinoma in situ

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (for example, not in the main bronchus)[1]

T1a Tumor 2 cm or less in greatest dimension

T1b Tumor more than 2 cm but 3 cm or less in greatest dimension

T2 Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a Tumor more than 3 cm but 5 cm or less in greatest dimension

T2b Tumor more than 5 cm but 7 cm or less in greatest dimension

T3 Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina[2] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

M1a Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (or pericardial) effusion[2]

M1b Distant metastasis (in extrathoracic organs)

Notes

[1] The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

[2] Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

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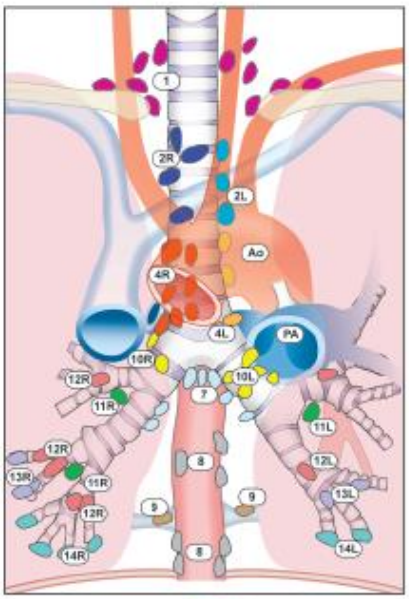
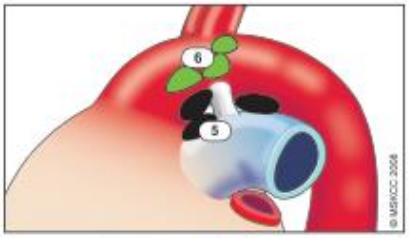
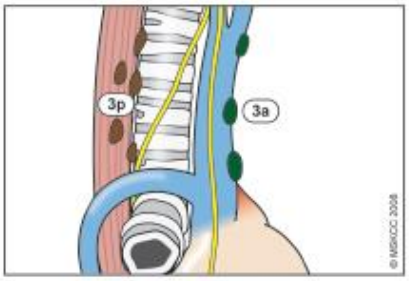
American Joint Committee on Cancer

Lung Cancer Staging

7th EDITION







Supraclavicular zone

- **1** Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes

Upper zone

- **2R** Upper Paratracheal (right)
- **2L** Upper Paratracheal (left)
- **3a** Pre-vascular
- **3p** Retrotracheal
- **4R** Lower Paratracheal (right)
- **4L** Lower Paratracheal (left)

Aortic Nodes

AP zone

- **5** Subaortic
- **6** Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

Subcarinal zone

- **7** Subcarinal

Lower zone

- **8** Paraesophageal (below carina)
- **9** Pulmonary ligament

N_1 Nodes

Hilar/Interlobar zone

- **10** Hilar
- **11** Interlobar

Peripheral zone

- **12** Lobar
- **13** Segmental
- **14** Subsegmental

Regional Lymph Nodes (N)

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastases
- **N1** Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
- **N2** Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
- **N3** Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

ILLUSTRATION

The IASLC lymph node map shown with the proposed amalgamation of lymph into zones.

(© Memorial Sloan-Kettering Cancer Center, 2009.)

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APPENDIX 2 - EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Oken, M.M et al. (1982)

APPENDIX 3 - RECIST 1.1

The following contains excerpts from the RECIST version 1.1 plus study specific instructions.

A free copy of the revised guidelines is available from http://www.eortc.be/recist/default.htm

(Eisenhauer *et al*., 2009)

Measurability of Tumour Lesions at Baseline

At baseline there may be no target lesions as the patient could have experienced a complete response prior to entry to the trial. If the patient has had a partial response prior to trial entry then they should report target and/or non-target lesions at baseline.

Measurable lesions are those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable). For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by a CT scan (at baseline and during treatment, only the short axis will be measured and followed).

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to > 15 mm short axis) and truly non-measurable lesions.

Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Lesions with prior local treatment can be considered measureable. All measurements should be recorded in metric notation using callipers (or a ruler) if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

Specifications by Methods of Measurements

The same method of assessment and the same technique (CT) should be used throughout the trial. Image-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment. CT is the best currently available and reproducible method for measuring target lesions selected for response assessment. Investigators should utilize the best available CT imaging technique available to them for determining response and PFS of patients participating in the STOMP trial.

Tumour Response Evaluation

Baseline Documentation of "Target" and "Non-target" Lesions (if applicable)

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as “target” lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate, reproducible, repeated measurements.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterise the objective tumour response.

All other lesions (or sites of disease) should be identified as “non-target” lesions and should also be recorded at baseline. Measurements of these lesions are not required but these lesions should be followed as ‘present’, ‘absent’ or in rare cases ‘unequivocal progression’ and recorded.

Response Criteria

A. Evaluation of Target Lesions

Response Category	Description
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. In addition to this, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more lesion is also considered progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

B. Evaluation of Non-target Lesions

Response Category	Description
Complete Response (CR)	Disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD)	Persistence of one or more non-target lesion(s)
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions [1]

Notes:

1. To achieve “unequivocal progression” on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.

C. Overall Responses for all Possible Combinations of Tumour Responses in Target and Non-target Lesions With or Without the Appearance of New Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
None	None	No	Non - PD
Complete response (CR)	CR	No	CR
Complete response (CR)	Non-CR/non-PD	No	PR
Complete response (CR)	Not evaluated	No	PR
Partial response (PR)	Non-PD	No	PR
Stable disease (SD)	Non-PD	No	SD
Not all evaluated	Non-PD	No	Not evaluable (NE)
Progressive disease (PD)	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Frequency of Tumour Re-evaluations

For the STOMP trial, PFS will be evaluated radiologically by a CT scan at baseline and at 8 weekly intervals until progression.

For patients who discontinue treatment prior to progression CT scans should continue to be performed in accordance with the Scheme of Trial Assessments (Table 7.1).

APPENDIX 4- DEFINITION OF ADVERSE EVENTS

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an IMP, whether or not related to the IMP.

Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an Adverse Reaction (AR). The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event

Any untoward medical occurrence or effect that at any dose:

- Results in death (unrelated to original cancer)
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator***

  For the purposes of the STOMP trial development of MDS/AML is considered significant and should be reported as an SAE

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction

An AR which also meets the definition of a SAE.

Suspected Unexpected Serious Adverse Reaction

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.

A SUSAR should meet the definition of an AR, UAR and SAR.

Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

APPENDIX 5 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the CTCAE, version 4.0. The full CTCAE document is available on the National Cancer Institute website, the following address was correct when this version of the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX 6 - WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964 and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, 35th World Medical Assembly, Venice, Italy, October 1983, 41st World Medical Assembly, Hong Kong, September 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the WMA binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the WMA has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment

is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.