ID: UMCC 2018.132	Trabectedin in Combination With Olaparib in Advanced Unresectable or Metastatic Sarcoma	NCT04076579

UMCC 2018.132

Phase II Multi-Center Trial of Trabectedin in Combination with Olaparib in Advanced Unresectable or Metastatic Sarcoma

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Coordinating Center	University of Michigan
Study Drug:	Trabectedin (Yondelis®) Olaparib (Lynparza®)
IND #	IND Exempt
Initial version:	v 1.0 24Mar2019
Amended:	v 1.1 12Apr2019 v 1.2 01Jun2019 v 1.3 27Jun2019 v.2.0 10Nov2020 v 3.0 12Jan2022

The study drug Trabectedin is provided by Janssen Scientific Affairs, LLC. The study drug Olaparib is provided by AstraZeneca.

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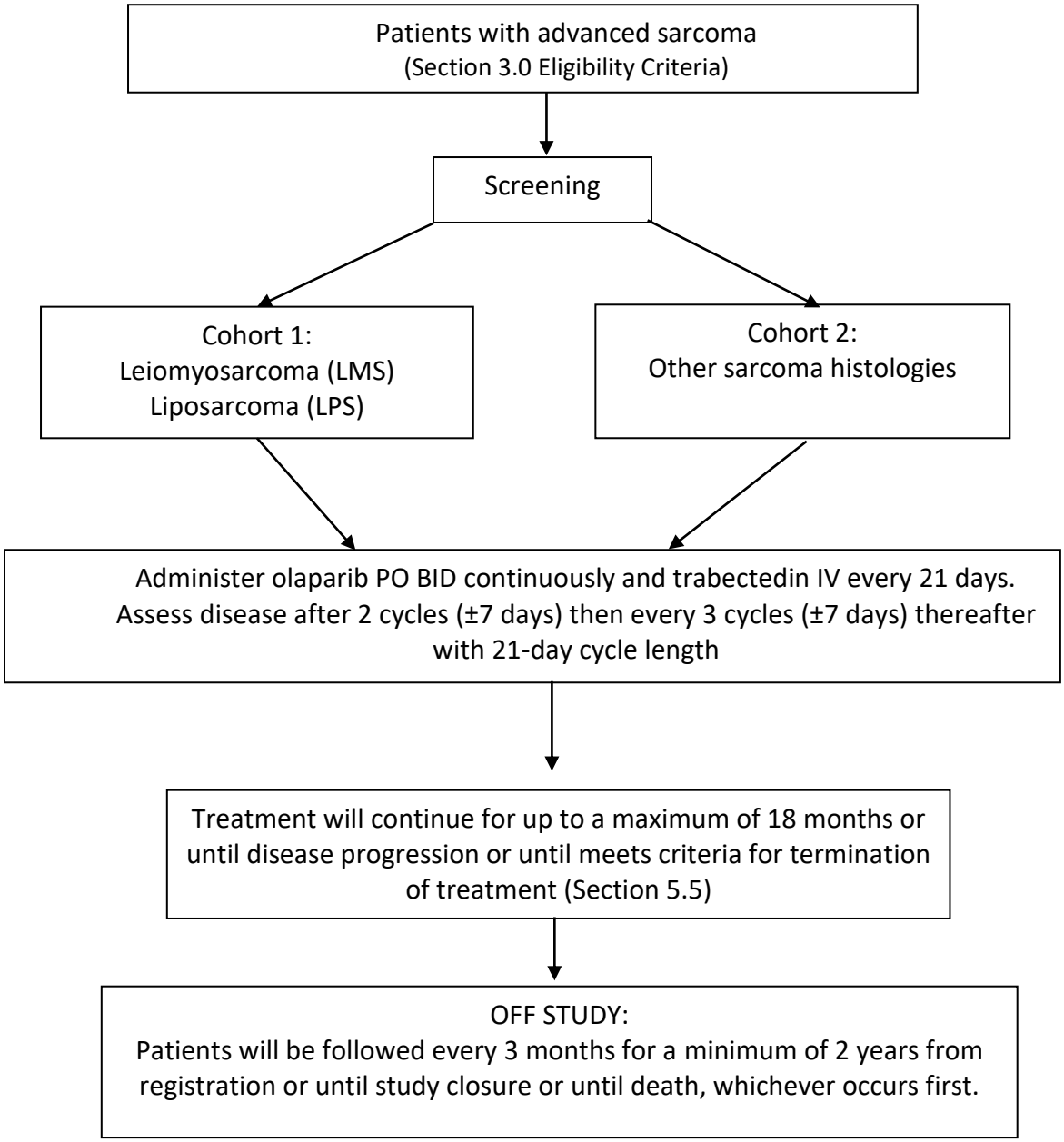
ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BER	Base Excision Repair
BID	Twice Daily
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CK	Creatine Phosphokinase
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSU	Clinical Trials Support Unit
DDLPS	Dedifferentiated Liposarcoma
DLT	Dose Limiting Toxicity
DRD	DNA Repair Defects
DSBs	Double-strand Breaks
DSMC	Data and Safety Monitoring Committee
DSMR	Data and Safety Monitoring Report
EDC	Electronic Data Capture
EF	Ejection Fraction
ES	Ewing's Sarcoma
exOS	Extraskeletal Osteosarcoma
FSA	Fibrosarcoma
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
H&P	History & Physical Exam
HIV	Human Immunodeficiency Virus
HR	Homologous Recombination
HRCT	High Resolution Computed Tomography
HRD	Homologous Recombination Deficiencies

HRPP	Human Research Protections Program
HRT	Hormone Replacement Therapy
IB	Investigators Brochure
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
IV (or iv)	Intravenously
LLN	Lower Limit of Normal
LMS	Leiomyosarcoma
LPS	Liposarcoma
LVEF	Left Ventricular Ejection Fraction
MDS	Myelodysplastic syndrome
NCI	National Cancer Institute
NER	Nucleoside Excision Repair
NGS	Next Generation Sequencing
ORR	Overall Response Rate
OS	Overall Survival
p.o.	per os/by mouth/orally
PARP	Poly-(adenosine diphosphate ribose)-polymerase
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PQC	Product Quality Complaint
PR	Partial Response
QARC	Quality Assurance Review Committee
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
SS	Synovial Sarcoma
SSBs	Single-Strand Breaks
STS	Soft Tissue Sarcoma
suPAR	Soluble urokinase Plasminogen Activator Receptor
TTE	Transthoracic Echocardiogram
ULN	Upper Limit of Normal
UP	Unanticipated Problem
UPS	Undifferentiated Pleomorphic Sarcoma
WBC	White Blood Cells
WDLPS	Well-differentiated Liposarcoma

STUDY SCHEMA



STUDY SYNOPSIS

Title	Phase II Multi-Center Trial of Trabectedin in Combination with Olaparib in Advanced Unresectable or Metastatic Sarcoma
Phase	Phase II
Methodology	Uncontrolled, Open label, Single-arm
Study Duration	3 years
Study Center(s)	Multi-center: 2 centers
Objectives	**Primary Objective:** a. To estimate the overall response rate (ORR) of combined trabectedin and olaparib in patients with advanced unresectable or metastatic sarcoma using a primary endpoint of complete + partial response as defined by RECIST 1.1. **Secondary Objectives:** a. To estimate the median progression-free survival (PFS) and 6-month PFS as defined by RECIST 1.1 b. To estimate the median, 1- and 2-year overall survival (OS) c. To describe the safety and tolerability of combined trabectedin and olaparib **Exploratory Objectives:** a. To characterize next generation sequencing (NGS) findings on available reports from archival tumor samples to identify predictors of clinical response to therapy. b. To evaluate expression of DNA damage repair pathways by IHC in available archival tumor samples and correlate with response to therapy c. To assess the impact of treatment on levels of novel cardiovascular biomarkers, and determine whether levels predict cardiotoxicity
Number of Subjects	This study will be conducted using a Simon Minimax two-stage design, with an interim analysis for efficacy to be performed after first stage. Cohort 1 (LMS/LPS): First stage – 16 patients, Second stage – additional 10 patients Cohort 2 (other sarcoma histologies): First stage – 13 patients, Second stage – additional 14 patients
Key Inclusion Criteria	• Age ≥ 16 years • Advanced unresectable or metastatic sarcoma • Received at least 1 prior standard chemotherapy. For cohort 1 patients, this must have included a prior anthracycline. • Measurable disease by RECIST 1.1 • Adequate hematologic, renal, hepatic function • Adequate creatine phosphokinase • ECOG performance status ≤ 1 • LVEF ≥ institutional LLN • Women of childbearing age and men must agree to use adequate contraception from signing informed consent to at least 6 months (females) and 5 months (men) after study drug treatment

Key Exclusion Criteria	• Prior therapy with PARP inhibitor • Prior therapy with trabectedin • Additional active malignancy or treatment for alternative cancer (excluding non-melanoma skin cancer) requiring treatment within the past two years • Pregnant or breastfeeding women • Known hypersensitivity to trabectedin
Study Product(s), Dose, Route, Regimen	Olaparib 150 mg PO BID continuously Trabectedin 1.1 mg/m^2 IV every 21 days
Duration of Administration	Treatment consists of 21-day cycles. Therapy will continue until disease progression or patient meets one of the off-study criteria for a maximum of 18 months.
Reference Therapy	No comparator. Historical controls of single agent trabectedin in soft tissue sarcoma.
Statistical Methodology	A Simon Minimax two-stage design is utilized for this study. Based on currently available phase III data, the ORR for LMS/LPS subgroup to trabectedin monotherapy is 9%. We will target a response rate (RR) of 25% with combination trabectedin and olaparib. In cohort 2, the ORR is approximately 5% with trabectedin monotherapy. We will target a RR of 20% for this combination. This trial is designed with a type 1 error of 10% in cohort 1 and 5% in cohort 2 with a power of 80%. Cohort 1: 16 patients will be enrolled in stage 1. If ≤ 1 patient has an objective response, we will terminate the study. If > 1 objective response, an additional 10 patients will be enrolled. If ≥ 5 of 26 patients have an objective response, we will declare the combination as promising and worthy of further study. Cohort 2: 13 patients will be enrolled in stage 1. If 0 patients have an objective response, we will terminate the study. If ≥ 1 objective response, an additional 14 patients will be enrolled. If ≥ 4 of 27 patients have an objective response, we will declare the combination as promising and worthy of further study.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Sarcomas are a group of rare, aggressive malignancies that are often fatal despite aggressive therapies. The American Cancer Society predicts approximately 12,300 new sarcoma diagnoses in 2017, with 5000 sarcoma-related deaths. Surgery remains the mainstay of treatment in localized disease, however even optimal local treatment does not prevent the occurrence of distant metastases in some patients, particularly those with high-grade tumors. Approximately 50% of patients present with or develop advanced, unresectable or metastatic disease. Unfortunately, available systemic treatment options in this setting have limited efficacy, and thus prognosis remains poor, underscoring the need for development of novel treatment strategies.

1.2 Study Agent(s) Background

Trabectedin

Trabectedin is a synthetic marine-derived drug that is known to have activity in advanced soft-tissue sarcoma (STS) and is currently approved for treatment in unresectable or metastatic leiomyosarcoma (LMS) and liposarcoma (LPS) previously treated with an anthracycline. A phase II study of trabectedin after standard chemotherapy as compared to best supportive care in various subtypes of STS showed a median progression free survival (PFS) of 5.6 months versus 0.9 months with a hazard ratio (HR) of 0.70 [1]. The most common adverse events were nausea, anorexia, neutropenia, and increased alanine aminotransferase. A subsequent phase III trial was conducted to evaluate the safety and efficacy of trabectedin versus dacarbazine in metastatic LMS and LPS. A total of 518 patients were enrolled and trabectedin-treated patients had a significantly improved PFS as compared to dacarbazine, 4.2 vs 1.5 months respectively with a HR of 0.55 [2]. Trabectedin has also been evaluated in the front-line setting in a phase IIb study comparing trabectedin to doxorubicin in patients with advanced or metastatic untreated STS. There was no significant improvement in PFS in the trabectedin arm as compared to doxorubicin, therefore doxorubicin remains standard of care as first-line therapy [3].

Olaparib

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB).

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerization (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents. It is currently approved for treatment of both ovarian and breast cancer (patients selected for therapy based on an FDA-approved companion diagnostic for Lynparza [olaparib] and for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer).

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HR deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor

types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo[4, 5] and in the clinic [6]. The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair[7, 8]. Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

1.3 Rationale

Trabectedin has a unique mechanism of action, which includes binding to the minor groove of DNA and bending the helix to the major groove, thus impairing the cell cycle [9]. Studies have demonstrated a complex mechanism of action that includes direct killing of cancer cells by interfering with the cell cycle and by inhibiting activated transcription. Specifically, trabectedin is thought to trap members of the nucleoside-excision repair (NER) mechanism forming large complexes that inhibit NER activity resulting in single-strand DNA breaks (SSBs) [10]. These SSBs subsequently stall replication forks leading to double-strand DNA breaks (DSBs), thus resulting in cell death. Interestingly, cell lines deficient in NER proteins have been shown to be less sensitive to trabectedin [10-12]. Furthermore, defects in homologous recombination (HR), a mechanism used to repair DSBs, have been associated with higher sensitivity to trabectedin, suggesting induction of synthetic lethality [12, 13].

PARP enzymes are essential for repair of SSBs. Upon binding to the area of DNA damage, PARP is activated and catalyzes addition of long polymers of ADP-ribose on several proteins including histones and DNA repair proteins[14]. Intracellular signaling is activated resulting in activation of BER and SSB repair pathways. Inhibition of PARP thus allows propagation of SSBs, ultimately resulting in DSBs and cell apoptosis.

Based on the mechanisms of action of PARP inhibitors and trabectedin, potential for synthetic lethality was hypothesized. Synthetic lethality is a concept in which a single gene defect is compatible with cell viability, but the combination of gene defects results in cell death [15, 16]. Synthetic lethality provides a potential mechanism for therapeutic targeting of genetic abnormalities in cancers. One example includes inhibition of PARP leading to enhanced platinum sensitivity in breast and ovarian cancer models harboring mutations in BRCA1/2 genes. The accumulation of lethal DSBs in a setting of HR deficiency, such as in BRCA 1/2 mutants, suggests increased sensitivity to PARP inhibition in the presence of DNA repair defects [17, 18].

Avila-Arroyo *et al*. combined trabectedin with the PARP inhibitors olaparib, veliparib and iniparib in BRCA1 proficient and deficient breast tumor cells. Synergistic anti-proliferative effects were observed in all breast cancer cell lines with the combination of trabectedin and olaparib [19]. Importantly, this synergy was noted regardless of BRCA1 status, suggesting rationale for this combination in BRCA proficient tumors.

Role for combination in Sarcoma

Pignochino *et al.* explored the role of trabectedin in combination with olaparib in various bone and soft tissue sarcoma cell lines including LMS, undifferentiated pleomorphic sarcoma (UPS), dedifferentiated liposarcoma (DDLPS), fibrosarcoma (FSA), synovial sarcoma (SS), osteosarcoma and Ewing's sarcoma (ES) [20]. They noted a significant

increase in gamma H2AX (P-H2AX), a marker of DNA DSBs, in cell lines treated with trabectedin. The combination of trabectedin with olaparib resulted in further increase in γH2AX compared to monotherapy, and irreparable DNA fragmentation was significantly increased after 48 hours of therapy. They subsequently found that olaparib inhibited both basal and trabectedin-induced PARP1 activation in 50% of treated cell lines. Strong synergistic antitumor activity was found with combination of trabectedin plus olaparib in 18/20 tested cells lines. Synergy was also noted in 15/19 cell lines treated with trabectedin plus veliparib, a PARP inhibitor. Interestingly, a doxorubicin-resistant LMS cell line showed cross-resistance to single-agent trabectedin. Addition of olaparib to trabectedin significantly restored sensitivity, suggesting a role for trabectedin-PARP inhibitor combination in previously treated, trabectedin-resistant patients. In mouse xenograft models, Pignochino *et al*. also noted a significant reduction in tumor volume with combination therapy compared to control or monotherapy.

Additional *in vivo* and *in vitro* studies have been conducted utilizing sarcoma cell lines derived from patients with UPS, DDLPS, LMS, well-differentiated liposarcoma (WDLPS) and extraskeletal osteosarcoma (exOS) by Laroche *et al*. They noted 9/9 cell lines to be sensitive to trabectedin and 3/9 sensitive to rucaparib, a PARP inhibitor monotherapy [21]. The combination of rucaparib with trabectedin increased DNA damage, induced apoptosis and cell cycle arrest in all treated cell lines. UPS mice xenografts treated with the combination had a longer tumor volume doubling time as compared to monotherapy (17.1 days with combination, 14.8 days with trabectedin ($p=0.045$), 6.6 days with rucaparib ($p<0.0001$)). Twenty-five percent of tumors in the combination group had at least 60% necrosis, and the authors noted no observed signs of toxicity with the combination.

A phase 1b study combining trabectedin and olaparib in advanced sarcoma reported the combination was safe and tolerable [22]. Dose-limiting toxicities were thrombocytopenia and prolonged neutropenia and the recommended phase 2 dose was trabectedin 1.1 mg/m2 on day 1 and olaparib 150 mg twice daily[23]. Other treatment-related adverse events included anemia, leukopenia, febrile neutropenia, fatigue, nausea, elevated liver enzymes, mucositis and elevated amylase/lipase. There was no significant drug-drug interaction noted on pharmacokinetic evaluation and pharmacodynamics evaluation confirmed PARP1 inhibition.

Based on these data, we propose to combine trabectedin with olaparib in patients with previously treated advanced sarcoma. The use of this combination in sarcoma is investigational, and we hypothesize that the combination of olaparib and trabectedin will be safe and effective in patients with advanced sarcoma.

1.4 Exploratory Studies

1.4.1 Next Generation Sequencing

The presence of DNA repair defects (DRD) was correlated to PARP inhibitor response in men with metastatic castration resistant prostate cancer receiving abiraterone with or without the PARP inhibitor veliparib stratified by presence or absence of ETS fusion [24]. Molecular analysis included evaluation for BRCA1/2, ATM, FANCA, PALB2, RAD51B/RAD51C, PTEN, TP53, PIK3CA. Eighty patients underwent tissue sequencing with 42 (53%) being ETS-positive and 19 (25%) had DRD. Irrespective of treatment arm, patients with DRD had a higher ORR (58% vs 39%, $p=0.002$) and longer median PFS (16.6 vs 8 mo, $p=0.02$) compared to placebo. PFS was also longer in patients with normal PTEN, TP53 and PIK3CA. Controlling for clinical factors, the authors concluded that DRD, PTEN, TP53 and PIK3CA were associated with PFS, with DRD having the most

impact. These data suggest a role for correlating disease response to PARP inhibition in the setting of DRD in other tumor types.

Results of comprehensive next generation sequencing performed on existing or available archival tumor samples will be evaluated for genomic alterations in order to identify predictors of clinical response to therapy.

1.4.2 DNA Damage Repair Defects

Presence of DNA repair defects has been correlated with improved response to trabectedin[25]. A retrospective analysis of BRCA mRNA in tumor samples from patients with advanced sarcoma noted improved response to trabectedin and better disease control rate in patients with low tumor BRCA mRNA expression [26].

We will evaluate existing samples for defects in DNA repair pathways by immunohistochemistry (IHC) which may include γH2AX, RAD51, RAD52, XRCC1, PARP1, Schlafen-11, BRCA1/2, amongst others. The decrease or increase in expression level of DNA repair pathways genes will be correlated with disease response to therapy.

1.4.3 Cardiotoxicity

Whether trabectedin use in the treatment of sarcoma is associated with increased risk of cardiotoxicity is unclear. Earlier studies have suggested that the risk of drug-related cardiac adverse events was low, ranging from 0.2% to 7%.[27, 28] More recent studies have suggested that ventricular dysfunction occurs in up to 14% of patients with 3% in overt heart failure compared to 11% and 1% with dacarbazine.[29]

Soluble urokinase plasminogen activator receptor (suPAR) is a marker of immune activation and pathogenic factor in kidney disease. Levels of suPAR have been strongly associated with heart failure and incident cardiovascular disease.[30-32] We will measure suPAR along with traditional cardiovascular markers (BNP, high sensitivity troponin-I and high-sensitivity CRP) levels at baseline and after 2 doses of trabectedin, and determine whether levels are significantly altered by therapy, and whether baseline or early changes in levels are predictive of a later decline in left ventricular function.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To estimate the overall response rate (ORR) of combined trabectedin and olaparib in patients with advanced unresectable or metastatic sarcoma as measured by complete response + partial response using RECIST 1.1.

2.2 Secondary Objectives

2.2.1 To estimate the median progression-free survival (PFS) and 6-month PFS as defined by RECIST 1.1

2.2.2 To estimate the median, 1- and 2-year overall survival (OS)

2.2.3 To describe the safety and tolerability of combined trabectedin and olaparib

2.3 Exploratory Objectives

2.3.1 To characterize next generation sequencing (NGS) findings on available reports from archival tumor samples to identify predictors of clinical response to therapy.

2.3.2 To evaluate expression of DNA damage repair genes by IHC in available archival tumor samples and correlate with response to therapy.

2.3.3 To assess the impact of treatment on levels of novel cardiovascular biomarkers and determine whether levels predict cardiotoxicity.

2.4 Endpoints

The primary endpoint is objective response (CR + PR) as based on RECIST 1.1 criteria anytime within a minimum of 18 months after start of treatment but no more than 2 years from registration. Disease response will be assessed after 2 cycles (± 7 days), then every 3 cycles thereafter.

Secondary endpoints include progression-free survival as time from start of treatment to progression or death, or censored at the date of last tumor assessment if no progression and alive; overall survival, as time from start of treatment to death, or censored at the date of last follow-up if alive and occurrence of adverse events as graded by CTCAE v5.0.

Exploratory endpoints include the presence of mutations in DNA repair genes identified by next generation sequencing, presence of DNA repair defects identified by IHC changes in novel cardiovascular biomarkers.

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

3.1 Inclusion Criteria

3.1.1 Advanced unresectable or metastatic sarcoma
- Cohort 1: LMS/LPS
- Cohort 2: Other histologies (excluding Gastrointestinal Stromal Tumors)

3.1.2 Must have received at least 1 prior standard systemic therapy regimen. For cohort 1 patients, this must have included a prior anthracycline.

3.1.3 Measurable disease by RECIST 1.1 criteria

3.1.4 Age ≥ 16 years

3.1.5 ECOG ≤ 1

3.1.6 Adequate hematologic, renal and hepatic function within 14 days prior to administration of study treatment as defined below:

Hemoglobin	≥ 10 g/dL with no blood transfusion within 28 days
Absolute neutrophil count	≥ 1.5 x 10^9/L
Platelets	≥ 100 x 10^9/L

Total Bilirubin	≤ 1.5 x institutional upper limit of normal (ULN). **NOTE**: patients with elevated bilirubin secondary to Gilbert's disease are eligible to participate (<2.0x ULN should be used)
Aspartate aminotransferase (AST) & alanine aminotransferase (ALT)	≤ 2.5 x institutional ULN unless liver metastases are present in which case AST and ALT must be ≤ 5 x ULN
Serum creatinine	Estimated or calculated creatinine clearance (Cockcroft-Gault formula) ≥51 mL/min using the Cockcroft-Gault equation or based on a 24-hour urine test: Estimated creatinine clearance = (140-age [years]) x weight (kg) (x F)[a] serum creatinine (mg/dL) x 72 [a] where F=0.85 for females and F=1 for males.

3.1.7 Creatine phosphokinase ≤ 2.5 x institutional ULN

3.1.8 Women must be postmenopausal or have a negative urine or serum pregnancy test within 28 days of study treatment.

Postmenopausal is defined as any of the following:

- Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
- Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50
- radiation-induced oophorectomy with last menses >1 year ago
- chemotherapy-induced menopause with >1-year interval since last menses
- surgical sterilization (bilateral oophorectomy or hysterectomy)

3.1.9 Women of childbearing potential must agree to use adequate contraception from signing informed consent to at least 6 months after the last dose of study treatment. ([see Appendix B for acceptable methods])

3.1.10 Men must agree to use barrier contraception or abstinence and not donate sperm during treatment and for 5 months after the last dose of study treatment. Female partners of male patients should also use a highly effective form of contraception ([see Appendix B for acceptable methods]) if they are of childbearing potential.

3.1.11 Left ventricular ejection fraction ≥ institutional LLN

3.1.12 Ability to understand and the willingness to sign a written informed consent.

3.1.13 Must have a life expectancy ≥ 16 weeks

3.2 Exclusion Criteria

3.2.1 Prior therapy with PARP inhibitor, including olaparib

3.2.2 Prior therapy with trabectedin

3.2.3 Other malignancy unless curatively treated with no evidence of disease for ≥2 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma.

3.2.4 Current pregnancy or breast feeding. Pregnant women are excluded because the teratogenicity of both trabectedin and olaparib are unknown. Because there is an unknown risk to nursing infants from treatment of the mother trabectedin and/or olaparib, breastfeeding should be discontinued.

3.2.5 Known hypersensitivity to trabectedin or olaparib or any of the excipients of the products

3.2.6 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 study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.

3.2.7 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, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

3.2.8 Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (eg., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.

3.2.9 Persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE) grade 2) caused by previous cancer therapy, excluding alopecia.

3.2.10 Patients with myelodysplastic syndrome (MDS) /acute myeloid leukemia (AML) or with features suggestive of MDS/AML

3.2.11 Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

3.2.12 Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV).

3.2.13 Patients with known active hepatitis (i.e. Hepatitis B or C).

3.2.14 Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment

3.2.15 Concomitant use of known strong CYP3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or

cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment is 2 weeks.

3.2.16 Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

3.2.17 Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

3.2.18 Participation in another clinical study with an investigational product administered in the last 30 days prior to anticipated study treatment.

3.2.19 Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

3.2.20 Has received a live vaccination with 2 weeks of enrollment.

3.2.21 Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation

3.2.22 Involvement in the planning and/or conduct of the study

3.2.23 Previous enrollment in the present study

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

Patient registration for this trial will be centrally managed by the Oncology Clinical Trials Support Unit (i.e. the Coordinating Center) of The University of Michigan Rogel Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on a Screening and Enrollment Log.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient registration request to the Coordinating Center. After patient eligibility has been determined, a copy of the completed Eligibility Worksheet together with all the pertinent redacted source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

A Multi-Site Coordinator of the Coordinating Center, who acts as the registrar, will review the submitted documents and process the registration. Sites should inform the Multi-Site Coordinator of a potential registration by 5 p.m. on the day prior to registration. Same day registrations cannot be guaranteed.

The registrar will send an email to the requesting site registrar to confirm patient registration and to provide the study identification number assigned to the patient. In addition, a copy of the

completed Eligibility Worksheet signed and dated by the registrar will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them and will not receive study treatment.

Patients will be enrolled to cohort 1 if they have a leiomyosarcoma or liposarcoma. All other sarcoma histologies will be enrolled to cohort 2. All patients receive the same treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within 14 business days of registration to the study.

Trabectedin 1.1 mg/m^2 will be administered intravenously over a 24-hour continuous infusion once every 21 days. Actual body weight from screening will be used to calculate dose. If weight changes by more than 10% from baseline, recalculate the dose.

Olaparib 150 mg tablets will be taken orally twice daily with a cycle length of 21 days. Olaparib should be taken at the same time every day, 12 hours apart with one glass of water. Olaparib can be taken with or without food. Tablets should be taken whole, not crushed or mixed into food. It is prohibited to consume grapefruit juice while on olaparib therapy. If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study 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 be requested to maintain a medication diary of each dose of medication. The medication diary should be returned and/or reviewed by clinic staff at each scheduled clinic visit during the course of treatment.

REGIMEN DESCRIPTION					
Agent	**Pre-medications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Trabectedin	Pre-medicate with dexamethasone 20 mg IV approximately 30 min prior to trabectedin. Pre-medicate with palonosetron 0.25 mg IV (or similar anti-emetic per institutional guidelines) prior to trabectedin	1.1 mg/m^2	IV continuous infusion over 24 hours (+/- 2 hours)	Day 1	3 weeks (21 days)
Olaparib	It is prohibited to consume grapefruit, grapefruit juice and Seville oranges for duration of therapy. No routine prophylactic anti-emetic treatment is	150 mg	PO	BID, continuous	

	required; however, patients should receive appropriate anti-emetics in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e. 2 pieces of toast or biscuits).				

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.2). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity. Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Once dose is reduced, escalation is not permitted

Table 1. Dose Level Reductions of Trabectedin and Olaparib

Dose Levels	Trabectedin	Olaparib
1 (starting)	1.1 mg/m^2	150 mg BID
-1	0.94 mg/m^2	100 mg BID
-2	0.8 mg/m^2	

Criteria for start of new cycle:

- Platelet $\geq$ 100,000/microliter
- Absolute neutrophil count ≥1000/microliter
- Hemoglobin $\geq$ 9g/dl
- Total bilirubin ≤ 1.5 upper limit of normal (ULN)
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
- Alkaline phosphatase (ALP) ≤ 2.5 x ULN
- Creatine phosphokinase (CK) ≤ 2.5 x ULN
- All non-hematologic toxicities considered related to study treatment must be ≤ grade 2
- Absence of any subjectively intolerable grade 2 adverse event not controlled by supportive therapy

If a patient does not meet criteria to initiate a new cycle of treatment within 28 days of initial medication hold, or requires more than two dose reductions of trabectedin or one dose reduction of olaparib, they should be removed from study treatment.

For hematologic toxicities which meet parameters for dose hold, medication should be held per guidance below. Medication should be resumed at the reduced dose designated below. If AE is recurrent/persistent despite dose reduction as specified below, drug should be discontinued.

Table 2. Criteria for Dose modification of Thrombocytopenia, Neutropenia and Leukopenia

Laboratory Result	Dose Adjustments
Grade 2 Thrombocytopenia	• If does not cause clinically significant symptoms or require a platelet transfusion, continue treatment at current dose and monitor blood counts weekly. • If clinically significant symptoms, hold olaparib. When symptoms resolve and platelets recover to grade 1 (for a maximum of 4 weeks), may resume treatment at any time during the cycle at current dose.
Grade 3 Thrombocytopenia	• Interrupt dosing of olaparib for up to 4 weeks and perform at least weekly blood counts. • If platelet count recovers to grade 1 or better within one week and does not cause clinically significant symptoms or require a transfusion, resume olaparib at reduced dose upon recovery or at start of next cycle, and trabectedin at current dose at start of next cycle. • If platelet recovery to CTCAE grade 1 or better occurs within > 1 week-4 weeks, or causes clinically significant symptoms or requires a transfusion, hold olaparib for the remainder of the cycle and reduce olaparib and trabectedin by one dose level at first occurrence at the start of the next cycle. At second recurrence of recovery within >1 week-4 weeks, clinically significant symptoms or transfusion, hold olaparib for the remainder of the cycle and reduce trabectedin by one dose level at the start of the next cycle.
Grade 4 Thrombocytopenia	• Interrupt dosing of olaparib for up to 4 weeks and perform at least twice weekly blood counts until platelets improve to grade 3 and then at least weekly. • At first occurrence, if platelet count recovers to grade 1 or better within one week and does not cause clinically significant symptoms or require a transfusion, resume olaparib at reduced dose upon recovery or at start of next cycle. If recovery occurs within >1week-4weeks, hold olaparib for the remainder of the cycle. Reduce olaparib and trabectedin by one dose level at the start of next cycle. • At second recurrence of any length, hold olaparib for the remainder of the cycle and reduce trabectedin by one dose level at the start of the next cycle.
Grade 4 Neutropenia	• Interrupt dosing of olaparib for up to 4 weeks and perform at least weekly blood counts. • If neutrophil counts increase to ≥1000/microliter within one week and is not associated with fever or infection, resume olaparib at reduce dose upon recovery or at next cycle, and trabectedin at current dose level at start of next cycle. • If neutrophil count recovery to CTCAE grade 2 or

Laboratory Result	Dose Adjustments
	better occurs within > 1 week-4 weeks, or is associated with fever or infection, hold olaparib for the remainder of cycle and reduce Olaparib and trabectedin by one dose level at first occurrence at the start of the next cycle. At second recurrence of recovery to grade 2 within >1week-4 weeks, or is associated with fever or infection, hold olaparib for the remainder of cycle and reduce trabectedin by one dose level at the start of the next cycle.

Management of hematologic toxicities while on study treatment

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and potential interruption of study drug if CTC grade 3 or worse neutropenia occurs as above. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended for first cycle, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines if felt to be clinically appropriate and in subsequent cycles.

Platelet transfusions, if indicated, should be done according to local hospital guidelines. Appropriate supportive treatment and causality investigation should be performed as indicated clinically.

Management of anemia

Table 3. Management of anemia

Hemoglobin	Action to be taken
Hb < 10 *but* ≥ 8 g/dl (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue study treatment with supportive treatment (e.g. transfusion) or interrupt olaparib for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to ≥ 9g/dl. **Subsequent occurrences:** If Hb< 10 but ≥ 9 g/dl investigator judgement to continue olaparib with supportive treatment (e.g. transfusion) or dose interrupt (for max of 4 weeks) and upon recovery dose reduction of olaparib may be considered (to 100 mg twice daily). If Hb< 9 but ≥ 8 g/dl, interrupt olaparib (for max of 4 weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction of olaparib may be considered (to 100 mg twice daily).
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 9 g/dl. Upon recovery dose reduce olaparib to 100 mg twice daily.

Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2-week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)

- ≥2-week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If blood parameter abnormalities remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to a hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Study treatment should be discontinued if blood counts do not recover to CTC grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Study treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥2-week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence, refer to guidance earlier in this section for the management of this.

Table 4. Criteria for Dose Modification of Non-Hematologic Laboratory Adverse Events

Laboratory Result	**Dose Adjustments**
Total bilirubin >1.5x ULN*	• Hold trabectedin and olaparib • Monitor weekly total bilirubin until recovery to ≤ 1.5x ULN, and then resume olaparib at current dose upon recovery. • If peak bilirubin ≤ 3x ULN, reduce trabectedin by one dose level at start of next cycle. • At second recurrence, reduce trabectedin by next dose level • If third recurrence or peak bilirubin> 3x ULN, permanently discontinue study treatment
AST or ALT*> 2.5x ULN	• Hold trabectedin and olaparib • Monitor weekly LFTs until recovery ≤ 2.5x ULN and then resume olaparib at current dose upon recovery. • If peak value > 2.5x ULN and ≤ 5x ULN, resume trabectedin at same dose at start of next cycle. • If peak value> 5x ULN, reduce trabectedin by one dose level • At second recurrence of peak value>5x ULN, reduce trabectedin by one dose level.
ALP > 2.5x ULN	• Hold trabectedin • Monitor weekly ALP until recovery to ≤ 2.5x ULN • Reduce trabectedin by one dose level • At second occurrence, reduce trabectedin by one dose level
CK >2.5x ULN	• Hold trabectedin • Monitor weekly CK until recovery • If peak value >2.5x ULN-5x ULN, resume trabectedin at same dose. • If peak value >5x ULN, reduce trabectedin by one dose level • At second occurrence of peak value >5x ULN, reduce trabectedin by one dose level

*In case a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN please refer to Appendix A 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

Table 5. Criteria for Dose modification of Non-Hematologic Adverse events

Adverse Event	Dose Adjustment
Grade 2 toxicity that is subjectively intolerable and not controlled by optimal supportive medication	• Interrupt dosing for up to 4 weeks. May resume olaparib at current dose or reduced dose when toxicity improves to tolerable or grade 1 at first recurrence. • Upon resumption of study treatment, can continue trabectedin at current dose or reduce by one dose level at first occurrence at the start of the next cycle. At second recurrence, reduce trabectedin by one dose level at the start of the next cycle • Patient to be withdrawn from study if unable to resume within 4 weeks
Grade 3 or 4 toxicity not controlled by optimal supportive medication	• Interrupt dosing for up to 4 weeks. Do not resume olaparib until start of next cycle. • Upon resumption of treatment, reduce trabectedin and olaparib by one dose level at first occurrence. At second recurrence, reduce trabectedin by one dose level • Patient to be withdrawn from study if unable to resume within 4 weeks

Guidance on renal impairment:
If subsequent to study entry and while still on study therapy, a patient's estimated creatinine clearance (CrCl) falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24-hour urine test of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 100 mg twice daily.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease it is recommended that olaparib be discontinued.

Management of new or worsening pulmonary symptoms
If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further 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 study treatment can be restarted, if deemed appropriate by the investigator. If

significant pulmonary abnormalities are identified, these need to be discussed with the Study Principal Investigator.

Management of nausea and vomiting
Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of olaparib treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e. 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered (e.g.) dopamine receptor antagonist, antihistamines or dexamethasone.

Interruptions for intercurrent non-toxicity related events
Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Principal Investigator.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the patient's record.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to study treatment may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

Special Considerations:

- For ejection fraction reduction to < LLN or clinical evidence of cardiomyopathy, trabectedin should be held until normalization of EF. For absolute reduction in EF 10% or more from baseline and < LLN, reduce trabectedin to DL-1.

5.3 Concomitant Medications/Treatments

- The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:
    - Reason for use
    - Dates of administration including start and end dates
    - Dosage information including dose and frequency

- **Anti-emetics/Anti-diarrheal medications**
  From screening onwards, should a patient develop nausea, vomiting and/or diarrhea, then these symptoms should be reported as AEs (see section 8) and appropriate treatment of the event given.

Prohibited Concomitant Medications:

Prohibited medication/class of drug:	
Anticancer therapy: Chemotherapy Immunotherapy Hormonal therapy* Radiotherapy (except palliative) Biological therapy Other novel agents	Not permitted while the patient is receiving study medication
Live virus vaccines Live bacterial vaccines	Not permitted while the patient is receiving study medication and during the 30 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.

*Hormone Replacement Therapy (HRT) is acceptable

Restricted Concomitant Medications:

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed):**
Strong CYP3A inhibitors (examples): itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir Moderate CYP3A inhibitors (examples): ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	Strong and moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication, then olaparib should be held for the period of concomitant administration for 3 half live afterwards for a maximum period of up to 4 weeks.

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed):**
Strong CYP3A inducers (examples): phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort Moderate CYP3A inducers (examples): bosentan, efavirenz and modafinil	Strong or moderate CYP3A inducers should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer, then they must be monitored carefully for any change in efficacy of Olaparib
• CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • CYP2B6 substrates: bupropion, efavirenz • OATP1B1substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	Effect of olaparib on other drugs Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.
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 study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Administration of other anti-cancer agents	Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

5.4 Other Modalities or Procedures

Palliative radiation therapy may be permitted to a non-target lesion while on study treatment upon discussion with the principal investigator.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for up to 18 months on study until one of the following criteria apply:

- Disease progression as defined in Section 7.0
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient voluntarily withdraws from treatment
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.6 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.5 apply. Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.7. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.7 Duration of Follow-Up

Patients will be followed every 3 months for a minimum of 2 years from registration or until study closure or until death, whichever occurs first. As long as the study remains open with patients on treatment, patients will be followed for survival follow up for at least 2 years from the time of registration. If all patients have completed treatment, the study may be terminated for further follow up before the 2 years from registration for survival follow up for the last patients. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.8 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

- Patient withdraws consent (termination of treatment and follow-up);
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
- Patient is unable to comply with protocol requirements;
- Treating physician judges continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment which would interfere with this study;
- Lost to Follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented
- Termination of the study by The University of Michigan;
- Patient completes protocol treatment and follow-up criteria.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

6.2 Time and Events Table

All screening labs must be performed within 14 days prior to registration unless otherwise stated. Baseline imaging must be obtained within 28 days prior to registration.

	Screening*	Cycle 1 Day 1	Day 1 All Cycles[n]	Day 8, Cycles 1 and 2**[n]	Day 15 All Cycles[n]	Off Treatment[n]	Follow -Up[m]
Olaparib[a]		X	X----------X				
Trabectedin		X	X				
Informed Consent	X						
History, vitals and PE Height & Weight[b]	X	X	X			X	
ECOG Performance Status	X	X	X			X	
ECG	X						

Concomitant medication review	X	X	X				
Toxicity Evaluations		X	X----------X				
Tumor Measurements[c]	X		X[c]			X	
CBC w/diff, PLT[d]	X	X	X	X	X	X	
Serum Chemistry[e]	X	X	X	X	X	X	
APTT, INR[f]	X						
Creatine phosphokinase	X	X	X			X	
Urinalysis[g]	X						
B-HCG[h]	X	X	X			X	
Transthoracic echocardiogram[i]	X		X[i] (every 3 cycles)				
Cardiovascular Biomarkers[j]	X		X[j] (C3D1 only)				
Archival Tissue [k]	X						
Bone marrow or blood cytogenetic samples[l]							

a. Olaparib is administered with continuous twice daily dosing
b. Vitals = temperature, pulse, respirations, blood pressure.
c. CT and/or MRI scans to cover bodily areas in which there is disease or suspected disease. Baseline scans to be obtained within 28 days of registration. Restaging scans will be repeated at C3D1 (±7 days) then every 3 cycles (±7 days) until disease progression. If clinical concerns for progression or significant delays in cycle length, imaging assessment may be obtained early at the discretion of the treating physician and continued at an interval of every 3 cycles at minimum. Scans should be obtained at the end of treatment visit if there is no prior radiographic confirmation of disease progression. The same method of assessment (i.e. CT, MRI) and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. RECIST 1.1 guidelines will be used.
d. Hematology: CBC with differential to include WBC, hemoglobin, platelet count, absolute neutrophil count, absolute lymphocyte count and mean cell volume
e. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT (AST), SGPT (ALT), sodium
f. Activated partial thromboplastin time (APTT) and International normalized ratio (INR) will be performed at screening and if clinically indicated. For patients on warfarin it is recommended that INR monitored at least weekly for the first cycle and then on day 1 of each cycle thereafter, if stable. Each coagulation test result will be recorded in CRF.
g. Urinalysis to include measurement of hemoglobin/red blood cells/ or blood, protein or albumin, and glucose
h. Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment and at start of each cycle and at the 30 day follow up visit. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

i. Transthoracic echocardiogram (TTE) will be obtained at baseline to ensure adequate LVEF. Repeat TTE will be obtained every 3 cycles (±1 cycles) while on trabectedin or if clinical concern of decline in ejection fraction. MUGA can be performed if inadequate assessment by TTE per standard practice.
j. Assessment of cardiovascular biomarkers including suPAR, BNP, high-sensitive troponin-I and high-sensitivity CRP will be obtained at baseline and after 2 doses of trabectedin on cycle 3 day 1.
k. Results of NGS (if available) and archival tumor tissue to test for the presence of alterations in DNA repair pathways. Patients will not be asked to undergo an additional biopsy to obtain tumor sample. Full reports must be provided by the investigator for documentation on the Patient Safety database. These data are not required to be entered into CRF.
l. Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities at any timepoint as clinically indicated as defined in Section 5.2. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample.
m. Patients will be followed every 3 months via phone for documentation of progression and survival status for a minimum of 2 years from registration. If patient is unavailable, then survival status will be determined if possible, by public available information.
n. Visits on day 1 of each cycle, lab measurements at days 1, 8 and 15 of each cycle, and the end of treatment visit, can be completed +/-3 days.

* Screening labs to be obtained within 14 days of initiation of therapy. Baseline imaging to be obtained within 28 days of initiation of therapy.
** Laboratory assessment will be done on day 8 for first 2 cycles to monitor for cytopenias. Continued day 8 laboratory assessment beyond cycle 2 is at the discretion of the treating physician.

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*Eur J Cancer* 45(2): 228-47, 2009]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1.

7.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least 1 cycle(s) of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

7.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) for studies with a slice thickness of ≤5mm or twice the slice thickness or MRI
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered nonpathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should

be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

7.1.3 Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions (with a minimum absolute increase of 5 mm), taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

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.

7.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

7.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/SD	No	PR	≥4 wks. Confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

7.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Patients without disease progression should be censored at the last time point for which their disease was known to not have progressed.

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

7.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

7.2 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 5.0 for reporting of adverse events (http://ctep.cancer.gov/reporting/ctc.html).

8.0 ADVERSE EVENTS

8.1 Adverse Event Report Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of informed consent through 30 days after the last dose of study treatment. Any serious adverse event that occurs more than 30 days after the last study treatment and is considered related to the study treatment must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.2, occurring from informed consent through 30 days following the last dose of the study treatment must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event.

Adverse events after the 30 day follow up period
For Pharmacovigilance purposes and characterization, any SAE of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to the Coordinating Center who in turn will report to AstraZeneca Patient Safety regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

At any time after a patient has completed the study, if an Investigator learns of any SAE including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify the Coordinating Center who in turn will notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and/or post study completion, then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

Otherwise, after study treatment completion (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days).

8.2 Definitions

8.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.
- Diagnostic and therapeutic non-invasive and invasive (i.e. surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.

- Symptoms of the original or targeted disease are not to be considered adverse events for this study. The following symptoms are indicative of underlying disease and will not be reported as adverse events (unless the event is considered serious):
    - Cancer-related pain
- Abnormal laboratory values or test results constitute adverse events if they induce clinical signs or symptoms or require therapy. They are to be captured under the signs, symptoms or diagnoses associated with them.

8.2.2 Adverse Event of Special Interest

Adverse events of special interest (AESI) are events of scientific and medical interest resulting from a previously identified signal (even if non-serious) or are specific to the further understanding of a drug's safety profile. AESIs require close monitoring and rapid communication by the Coordinating Center to AstraZeneca and Janssen.

There are currently no Adverse Events of Special Interest for Yondelis (trabectedin) that will be reported to the Company.

Additional safety events of interest for trabectedin that require expedited reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

<u>Olaparib</u>
Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study there may be other events identified as AESIs that require the use of a questionnaire to help characterize the event and gain a better understanding regarding the relationship between the event and study treatment.

AESIs should not be reported as SAEs unless they meet the SAE reporting criteria per section 8.2.4.

Any AESI that is to be reported to Janssen and AstraZeneca by the Coordinating Center should be recorded on a Serious Adverse Event Report Form and be reported to Janssen and AstraZeneca **within 24 hours of knowledge of the event.**

8.2.3 **Product Quality Complaint (PQC) (for trabectedin only)**

A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

8.2.4 **Serious Adverse Event**

An adverse event is considered “serious” if, in the view of the Sponsor-Investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

  The cause of death of a subject in a study within 30-days of the last dose of study treatment, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

  NOTE: DEATHS FOR ANY REASON SHOULD BE REPORTED WITHIN THE PROTOCOL SPECIFIED SAE REPORTING PERIOD AS OUTLINED IN SECTION 8.4

- A life-threatening adverse event
  An adverse event is considered ‘life-threatening’ if, in the view of the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

- Important medical event

Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of “Serious Adverse Event”. Examples of such medical events include allergic

bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse; or suspected transmission of any infectious agent via a medicinal product.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

Hospitalization
For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

Life-Threatening Conditions
Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

8.2.5 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 and 9.2 for the list of expected adverse events related to the drugs under study.

8.2.6 Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

8.2.7 **Pregnancy**

Any subject who becomes pregnant during the study must promptly discontinue further study treatment.

All study subject pregnancies occurring during the study participation or within 5 months of last dose must be reported to the Coordinating Center within the same time lines as for an SAE even if the patient was discontinued from the study. All pregnancies should be followed through to outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) whenever possible. The Coordinating Center should be notified once the outcome of the pregnancy is known. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects, spontaneous miscarriages and abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

Paternal exposure
Male patients should refrain from fathering a child or donating sperm during the study and for 5 months following the last dose.

All pregnancies in partners of male subjects occurring during the study participation or within 5 months of last dose must be reported to the Coordinating Center within the same time lines as for an SAE even if the patient was discontinued from the study.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) occurring from the date of the first dose until 5 months after the last dose should, if possible, be followed up and documented.

The Coordinating Center will be responsible for reporting to Janssen Scientific Affairs, LLC and AstraZeneca within 24 hours of becoming aware of any patient or patient partner pregnancy using the Serious Adverse Event Form.

8.2.8 **Overdose - Olaparib**

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established.

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 150 mg twice daily (tablet).

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF.

If an overdose on olaparib occurs in the course of the study, then the Investigator or other site personnel inform the Coordinating Center and appropriate AstraZeneca representatives immediately, or no later than 24 hours of when he or she becomes aware of it. The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply. For other overdoses, reporting must occur within 30 days.

8.3 Adverse Event Characteristics

8.3.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

8.3.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.
Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

8.4 Serious Adverse Event Reporting Guidelines

8.4.1 Reporting procedures for multi-site trials

All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study drug, will be reported to the Principal Investigator and also to the Coordinating Center. All SAEs and UPs must be reported to the Coordinating Center within 24 hours of first awareness of the event. Events should be reported using the Coordinating Center SAE form as available in the study database. A copy of the SAE form should be sent to the Coordinating Center via fax at 734-232-0744 or via email to CTSU-Oncology-Multisite@med.umich.edu within 24 hours of the site's knowledge of the event.

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

All SAEs and UPs will be reported to the IRB per current institutional standards.

The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within 5 days of review of the information by the Coordinating Center's Principal Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study drug. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

8.5 Reporting procedures to Janssen Scientific Affairs, LLC

Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen Scientific Affairs, LLC

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

SAEs, Adverse Events of Special Interest and Special Reporting Situations
All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The Sponsor-Investigator, or designee will transmit all SAEs, Adverse Events of Special Interest and special situations following exposure to a Janssen product under study **within 24-hours of the site becoming aware of the event(s).**

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the Sponsor-Investigator or designee, **within 24 hours of the site becoming aware**, to Janssen Scientific Affairs.

All available clinical information relevant to the evaluation of a related SAE, Adverse Events of Special Interest, serious ADR or special situation is required.

- The Sponsor-Investigator or designee is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC within 24 hours of such report or correspondence being sent to applicable health authorities.

Non-Serious AEs
All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Agreement section entitled Reporting of Data.

PQC Reporting
A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the Sponsor-Investigator, or designee within 24 hours after being made aware of the event. The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the Sponsor-Investigator, or designee must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products
For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the Sponsor-Investigator, or designee should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

Transmission Methods

- The following methods are acceptable for transmission of safety information to the Janssen Scientific Affairs LLC: Electronically via Janssen SECURE Email service (preferred) IIS-BIO-VIRO-GCO@its.jnj.com
- For business continuity purposes, if SECURE Email is non-functional: to 1-866-451-0371
- Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

8.6 Reporting procedures to AstraZeneca

All Serious Adverse Events (SAEs) occurring from the informed consent through 30 days following the last dose of the study treatment will be reported by the Coordinating Center to AstraZeneca. Any SAEs occurring after 30 days following the last dose of the study treatment that are believed to be related to study drug will also be reported to AstraZeneca.

The Coordinating Center will send the initial completed SAE Form within 24 hours of receipt via email to AEMailboxClinicalTrialTCS@astrazeneca.com.

If only limited information is initially available or an ongoing SAE changes in its intensity or relationship to the study drug, or if new information becomes available, a follow-up report will be generated and sent to AstraZeneca within 24 hours of receipt.

If any SAE occurs in the course of the study, then the Coordinating Center will inform the appropriate AstraZeneca representatives within one day i.e., immediately but no later than 24 hours of awareness.

The designated AstraZeneca representative works with the Coordinating Center to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site within 1 calendar day of initial receipt for fatal and life threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. The Coordinating Center informs AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

8.7 Routine Reporting

All other adverse events – such as those that are expected or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

All non-serious adverse events should be reported by the Coordinating Center to Janssen and AstraZeneca as outlined in the Research Agreements.

8.8 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Another example of a UAP would be a product quality compliant (PQCs). A PQC is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB within 14 calendar days of the study team becoming aware of the problem.

9.0 DRUG INFORMATION

9.1 Trabectedin

- Other names for the drug: Yondelis®
- Description: 1 mg sterile lyophilized powder in a single-dose vial.
- Classification - type of agent: alkylating agent
- Mode of action: Trabectedin is an alkylating drug that binds guanine residues in the minor groove of DNA, forming adducts and resulting in a bending of the DNA helix towards the major groove. Adduct formation triggers a cascade of events that can affect the subsequent activity of DNA binding proteins, including some transcription factors, and DNA repair pathways, resulting in perturbation of the cell cycle and eventual cell death.
- Pharmacokinetics: The pharmacokinetics is characterized by a rapid decline phase at the end of the infusion and slower exponential phases. Population pharmacokinetic analyses suggest that the pharmacokinetics of trabectedin is dose-proportional and exposure is time-independent. No accumulation in plasma is observed upon repeated administrations every 3 weeks.

  Binding of trabectedin to human plasma proteins was approximately 97%. Steady state volume of distribution exceeds 5000 L. The estimated mean clearance of trabectedin is 31.5 L/hr (50%) and the terminal elimination half-life is approximately 175 hours.

  CYP3A is the predominant CYP enzyme responsible for the hepatic metabolism of trabectedin. Trabectedin was extensively metabolized with negligible unchanged drug in urine and feces.

  In patients with solid tumors, following a 3-hour and 24-hour intravenous infusion of ^{14}C-labeled trabectedin, 64% of the total administered radioactive dose was recovered in 24 days with 58% in feces and 6% in urine.
- Side effects: The most common (≥20%) adverse reactions are nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. Please refer to the agent's package insert for a comprehensive list of adverse events.
- Special Warnings and Precautions for Use
  Please refer to the agent's package insert
- Drug Interactions: Co-administration of trabectedin with strong CYP3A inhibitors results in increased trabectedin dose. Co-administration with strong CYP3A inducers results in decreased trabectedin dose.
- Storage and stability: Store trabectedin vials in a refrigerator at 2°C to 8°C (36°F to 46°F). Trabectedin is a cytotoxic drug. Follow applicable special handling and disposable procedures.

  Trabectedin must be stored in a secure, limited access area.
- Preparation and Dispensing:
  - Using aseptic technique, inject 20 mL of Sterile Water for Injection, USP into the

vial. Shake the vial until complete dissolution. The reconstituted solution is clear, colorless to pale brownish-yellow, and contains 0.05 mg/mL trabectedin.
- Inspect for particulate matter and discoloration prior to further dilution. Discard vial if particles or discoloration are observed.
- Immediately following reconstitution, withdraw the calculated volume of trabectedin and further dilute in 500 mL of 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP.
- Do not mix with other drugs.
- Discard any remaining solution within 30 hours of reconstitution the lyophilized powder.
- Trabectedin diluted solution is compatible with Type 1 colorless glass vials, polyvinylchloride (PVC) and polyethylene (PE) bags and tubing, PE and polypropylene (PP) mixture bags, polyethersulfone (PES) in-line filters, titanium, platinum or plastic ports, silicone and polyurethane catheters, and pumps having contact surfaces made of PVC, PE, or PE/PP.

- Administration:
  - Infuse the reconstituted, diluted solution over 24 hours through a central venous line using an infusion set with a 0.2 micron polyethersulfone (PES) in-line filter to reduce the risk of exposure to adventitious pathogens that may be introduced during the solution preparation.
  - Complete infusion within 30 hours of initial reconstitution. Discard any unused portion of the reconstituted product or of the infusion solution.

- Availability**:** Trabectedin is provided by Janssen.

  Under no circumstance will the study medication (Trabectedin®) provided by Janssen be used other than as directed by the protocol.

- Do Not Use Commercially Available Product. Return and Retention of Study Drug: The investigators will be instructed by the Coordinating Center on the return or destruction of unused trabectedin. If any trabectedin is lost or damaged, its disposition should be documented in the source documents. Trabectedin supplies will be retained at the clinical site pending instructions for disposition by the Coordinating Center.

  If instructed to do so, unused supplies of trabectedin should be destroyed according to institutional policies. Destruction will be documented in the drug accountability forms.

- Drug Accountability:
  The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational drug trabectedin. The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

9.2 Olaparib

- Other names for the drug: Lynparza

- Description: Olaparib is available as 100 mg and 150 mg tablets.

- Classification - type of agent: PARP inhibitor

- Mode of action: Olaparib is an inhibitor of PARP enzymes including PARP1, PARP2 and PARP3. PARP enzymes are involved in normal cellular functions such as DNA transcription and repair. Olaparib has been shown to inhibit growth of select tumor cells in vitro and decrease tumor growth in mouse xenograft models of human cancer cells. In vitro studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage and cancer cell death.

- Pharmacokinetics: Olaparib is available as a tablet and capsule formulation. The oral bioavailability of the tablet formulation is higher. Olaparib showed time-dependent PK that the steady state clearance decreased by 15% after multiple doses.

  Following oral administration, absorption is rapid with median peak plasma concentrations typically achieved 1.5 hours after dosing. Systemic exposure (single dose AUC) increases approximately proportionally with doses over the dose range of 25 mg to 450 mg. Co-administration with high-fat meal slowed the rate of absorption but did not significantly alter the extent of absorption (mean AUC increased by approximately 8%).

  Olaparib has a mean apparent volume of distribution of 158 L after a single 300 mg dose. In vitro protein binding is approximately 82%.

  CYP3A4/5 were shown to be enzymes primarily responsible for metabolism of olaparib.

  The mean terminal plasma half-life of olaparib is 14.9 hours. Following a single dose of ^{14}C-labele olaparib, 86% of the dosed radioactivity was recovered within a 7-day collection period, 44% via urine and 42% via feces. The majority of the material was excreted as metabolites.

- Side effects: The most common adverse reactions (≥20%) in clinical trials were anemia, nausea, fatigue (including asthenia), vomiting, neutropenia, leukopenia, nasopharyngitis/upper respiratory tract infection/influenza, respiratory tract infection, diarrhea, arthralgia/myalgia, dysgeusia, headache, dyspepsia, decreased appetite, constipation and stomatitis. Refer the reader to the agent's package insert for a comprehensive list of adverse events.

- Special Warnings and Precautions for Use
  - Myelodysplastic syndrome/Acute myeloid leukemia (AML/MDS): occurred in <1.5% of patients exposed to olaparib monotherapy and the majority of events had a fatal outcome. Monitor patients for hematologic toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed.
  - Pneumonitis: occurred in <1% of patients exposed to olaparib, and in some cases were fatal. Interrupt treatment if pneumonitis is suspected. Discontinue if pneumonitis is confirmed.
  - Embryofetal toxicity: olaparib can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception.

  Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination (as described in Appendix B). This should be started from the signing of the informed

consent and continue throughout the period of taking study treatment and for at least 6 months after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (as described in Appendix B).

Male patients must use a condom during treatment and for 5 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (as described in Appendix B) if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking olaparib and for 5 months following the last dose of olaparib.

For details of acceptable methods of contraception refer to Appendix B Acceptable Birth Control Methods.

- Drug Interactions: Olaparib is increased with co-administration of strong or moderate CYP3A inhibitors. Conversely, olaparib is decreased with co-administration of strong or moderate CYP3A inducers. Olaparib is both an inhibitor and inducer of CYP3A and an inducer of CYP2B6.

- Storage and stability: Store at 20^{o}C to 25^{o}C (68^{o}F to 77^{o}F), excursions permitted to 15^{o}C to 30^{o}C (59^{o}F to 86^{o}F). Store in original bottle to protect from moisture.

  Olaparib must be stored in a secure, limited access area.

- Administration:
  - See Section 5.1

- Availability**:** Provided by AstraZeneca.

  Under no circumstance will the study medication (olaparib) be used other than as directed by the protocol. Do Not Use Commercially Available Product.

- Return and Retention of Study Drug:
  Investigators will be instructed by the Coordinating Center on the return or destruction of unused olaparib. If any olaparib is lost or damaged, its disposition should be documented in the source documents. Olaparib supplies will be retained at the clinical site pending instructions for disposition by the Coordinating Center. Participants will be instructed to return all bottles (empty bottles or unused tablets).

  If instructed to do so, empty bottles and unused supplies of olaparib should be destroyed according to institutional policies. Destruction will be documented in the drug accountability forms.

- Drug Accountability:
  The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational drug olaparib. The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

10.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to evaluate for mutations/alteration in genes responsible for DNA repair and correlate with disease response to therapy. Findings from

any and all correlative studies performed on subject samples will be shared with Janssen and Astra Zeneca for assessment of clinical (safety and efficacy) and/or commercial value.

10.1 Next Generation Sequencing

Results of comprehensive next generation sequencing performed on existing or available tumor samples will be evaluated for genomic alterations to identify predictors of clinical response to therapy. Patients will not be asked to undergo an additional biopsy to obtain tumor sample. Coded data will be stored on a secured server.

10.2 Defects in DNA Damage Repair

In addition to NGS, available tumor samples will be evaluated by changes in DNA damage repair pathways and DNA damage induction by IHC which may include BRCA1, SLFN11, RAD 51/52, PARP1, amongst others. The decrease or increase in expression of DDR genes will be correlated with disease response to therapy.

Specimen Banking
Patient samples retrieved for analysis will be coded and stored in a secure lab for optional unspecified future research. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Specimens being stored long-term for potential use not outlined in the protocol are subject to University Policy Governing Tissue Sample Collection, Ownership, Usage, and Disposition within all UMMS Research Repositories.

10.3 Cardiotoxicity

Serum suPAR, BNP, high sensitivity troponin-I and high sensitivity CRP levels will be obtained at baseline and after 2 doses of trabectedin to determine whether levels change with therapy and whether baseline or changes in levels are predictive of a decline in LVEF.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints

This is a prospective, single-arm, multi-site study evaluating combination trabectedin and olaparib. Eligible patients will be assigned to one of two cohorts. Cohort 1 consists of patients with leiomyosarcoma or liposarcoma. Cohort 2 consists of patients with other bone or soft tissue sarcoma histologies. An independent Simon-minimax two-stage design will be used in each cohort.

The primary objective is to estimate the overall response rate (CR+PR) with an endpoint of objective response as based on RECIST 1.1 criteria anytime within a minimum of 18 months after start of treatment but no more than 2 years from registration. Secondary endpoints include PFS, OS and occurrence of adverse events. Exploratory endpoints include the presence of DNA repair defects by NGS and/or IHC and cardiovascular biomarkers.

11.2 Sample Size and Accrual

In cohort 1, based on currently available phase III data, the ORR for LMS/LPS subgroup to trabectedin monotherapy (including best response of complete or partial response) is 9% with a 43% clinical benefit rate (CBR). Therefore, we will target a RR of 25% with trabectedin plus olaparib to conclude that combination therapy is meaningful. In stage 1,

we will enroll 16 patients. If ≤1 patient had an objective response in the first stage, we will terminate the trial early. If > 1 patients have an objective response in the first stage, then an additional 10 patients will be enrolled in stage 2, for a total of 26 patients. If ≥ 5 out of 26 patients have an objective response, then we will declare that the combination is promising and worthy of further study. The type 1 error rate is 10% and the power is 80%.

In cohort 2, the ORR is approximately 5% to trabectedin monotherapy. Therefore, we will target a RR of 20% for the combination to be meaningful. In stage 1, we will enroll 13 patients; if zero patients had an objective response, we will terminate the study early. Otherwise, if ≥1 patient had an objective response, we will enroll an additional 14 patients in stage 2, for a total of 27 patients. If ≥4 out of 27 patients have an objective response, then we will declare that the combination is promising and worthy of further study. The type 1 error rate is 5% and the power is 80%.

In cohort 1, we require a minimum of 16 patients and a maximum of 26 patients. Assuming we can enroll 2 LMS/LPS patients per month, we will require a minimum of 9 months and a maximum of 14 months to complete accrual. Assuming we will follow the last patient for an additional 24 months, the expected study duration for cohort 1 is expected to be between 33 and 38 months.

In cohort 2, we require a minimum of 13 patients and a maximum of 27 patients. Assuming we can enroll 2 patients with other sarcoma histologies per month, we will require a minimum of 7 months and a maximum of 14 months to complete accrual. Assuming we will follow the last patient for an additional 24 months, the expected study duration for cohort 2 is expected to be between 31 and 38 months.

The total expected duration to complete accrual and follow-up for cohorts 1 and 2 is 33 and 38 months.

11.3 Data Analyses Plans

To address the primary objective, the overall response rate will be calculated as the proportion (and exact binomial 95% confidence interval) of patients with complete or partial response as defined by RECIST 1.1, within each cohort.

To address the secondary objectives:

a. Progression free survival (PFS) will be calculated by the Kaplan-Meier method with errors according to Peto, within each cohort. Median and 6-month PFS will be estimated along with their 95% confidence intervals.
b. Overall survival (OS) will be calculated by the Kaplan-Meier method with errors according to Peto, within each cohort. Median, 1- and 2-year OS will be estimated along with their 95% confidence intervals.
c. The frequency and rates of adverse events occurring in at least 5% of participants and rates of grade 3-5 adverse events will be tabulated by system organ class and preferred term using Common Terminology Criteria of Adverse Events (CTCAE), within each cohort.

To address the exploratory objectives:

a. The frequency and proportion of alterations in tumor sequencing will be summarized within each cohort.
b. The frequency and proportion of alterations in DNA damage repair pathways will be summarized within each cohort.
c. Changes in levels of novel cardiovascular biomarkers will be summarized and compared to clinical and echocardiographic cardiotoxicity.

12.0 DATA AND SAFETY MONITORING

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan, with oversight by the Rogel Cancer Center Data and Safety Monitoring Committee (DSMC).

The Sponsor-Investigator (S-I)/Study Principal Investigator will provide ongoing monitoring of data and patient safety in this trial and conduct regular data review with participating sites.

The Sponsor-Investigator (S-I)/Study Principal Investigator and/or the Project Manager/Delegate will review data and patient safety issues with participating sites per a defined quarterly meeting cadence. Depending on the protocol activity, the meeting cadence may be more frequent. This data review meeting may be achieved via a teleconference or another similar mechanism to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (SAE reporting, unanticipated problems)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Participating sites are required to ensure all pertinent data for the review period are available in the database at the time of the discussion.

Participating sites unable to participate in the data review meeting are required to provide written confirmation that their site has reviewed the relevant data and patient safety issues for the review period and their site's data are in alignment with the data reported in the database. Written confirmation is to be provided to the Project Manager/Delegate within the timeline requested to retain compliance with monitoring timelines.

Documentation of the teleconference or alternate mechanism utilized to review items above is to be retained in the Trial Master File.

The Project Manager/Delegate is responsible for collating the data from all participating sites and completing the Protocol Specific Data and Safety Monitoring Report (DSMR) form to document the data review meeting discussion.

The DSMR will be signed by the Sponsor-Investigator (S-I)/Study Principal Investigator or designated Co-Investigator and submitted to the DSMC on a quarterly basis for independent review.

13.0 QUALITY ASSURANCE AND AUDITS

The Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

14.0 Data Management

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based electronic data capture (EDC) system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the MSC during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSC. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of registration
    - Subject entry into the EDC
        - Subject Status
        - Demographics
- During study participation
    - All data should be entered online within 10 business days of data acquisition. *[Information on dose limiting toxicity events must be entered within one business day.]* Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 8.4 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

15.0 CLINICAL MONITORING PROCEDURES

Clinical studies coordinated by The University of Michigan Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center of the University of Michigan Rogel Cancer Center. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate Coordinating Center personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes the first treatment cycle**.** The study site will send the redacted source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent redacted source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without

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Appendix A Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 5.2 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.
For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the Company

The Coordinating Center/Study Principal Investigator contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. << For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used>>
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.
No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients << with liver metastases>> who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.
At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Potential Hy's Law Criteria met of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.
The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.
The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, << or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment >>?

  If No: follow the process described in Potential Hy's Law Criteria met of this Appendix
  If Yes:
  Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met
- If there is no significant change no action is required
- If there is a significant change follow the process described above

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix B Acceptable Birth Control Methods

Olaparib is regarded as a compound with medium/high fetal risk.

- Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for at least 6 months after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

- Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for 5 months after last dose of study drug(s) due to the unknown effects of the study drug on the sperm, or they must totally/truly abstain from any form of sexual intercourse (see below). Male patients should not donate sperm throughout the period of taking study treatment and for 5 months following the last dose of study drug(s).

Acceptable Non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must continue for the total duration of study treatment and for at least 6 months after the last dose. <<for 5 months after last dose *for male patients*>>. Periodic abstinence (e.g., calendar ovulation, symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- IUD PLUS male condom. Provided coils are copper-banded

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone-based pill.
- Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
- Norelgestromin / EE transdermal system PLUS male condom
- Intrauterine system [IUS] device (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom