MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2015-0503
Protocol Title	OLAPARIB FOR BRCANESS PHENOTYPE IN PANCREATIC CANCER: PHASE II STUDY
Phase	II
Protocol Version	4
Version Date	10/10/2018
Protocol PI	Milind Javle, MD
Department	GI Medical Oncology
IND Sponsor	MD Anderson Cancer Center
IND #	129,049

	Clinical Study Protocol 2015-0503	
	Drug Substance:	Olaparib
	Study Code:	ISS22810097
	Version Number:	4
	Date:	October 10, 2018

OLAPARIB FOR BRCANESS PHENOTYPE IN PANCREATIC CANCER: PHASE II STUDY

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
Baseline	Refers to the most recent assessment of any variable prior to dosing with study treatment
bid	Bis in die (twice daily)
BoR	Best Overall RECIST Response
BP	Blood pressure
gBRCA	germline Breast Cancer susceptibility gene
BRCA mutation or *BRCAm*	Breast Cancer susceptibility gene mutation (see *gBRCA* mutation or *gBRCAm*)
BRCAness	Clinical features similar to BRCA mutation
BUN	Blood urea nitrogen
CHO	Chinese hamster ovary
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DCO	Data Cut Off
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DSB	Double strand break
ECG	Electrocardiogram

EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
E-code	Enrollment code (allocated by IVRS/IWRS)
ECOG	Eastern Cooperative Oncology Group: A performance status using scales and criteria to assess how a patient's disease is progressing
eCRF	Electronic Case Report form
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FSH	Follicle stimulating hormone
GA	Genetic Aberration
gBRCA mutation or *gBRCAm*	The term "*gBRCA* mutation" is used to refer to a germline *BRCA1* or *BRCA2* mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants
gBRCA wt	gBRCA wildtype (patients without evidence of *BRCA1* or *BRCA2* deleterious or suspected deleterious mutations)
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRD	Homologous recombination repair deficiencies
HRQoL	Health-related Quality of Life
IATA	International Air Transport Association
IB	Investigator's brochure
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IDMC	Independent Data Monitoring Committee
INR	International Normalised Ratio
IPCW	Inverse Probability of Censoring Weighting

IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan Meier
LDH	Lactic dehydrogenase
LH	Luteinizing hormone
LIMS	Laboratory Information Management System
m	Metre
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MDS	Myelodysplastic syndrome
mg	Milligram
MRI	Magnetic resonance imaging
nab	nanoparticle albumen bound
NCI	National Cancer Institute
NE	Not evaluable
NTL	Non-target lesions
OAE	Other Significant Adverse Event
ORR	Objective response rates
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation
PARPi	PARP inhibitors
PD	Progressive disease
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression Free Survival
p.o.	Per os (by mouth, orally)
PR	Partial response
RECIST	Response Evaluation Criteria In Solid Tumors. This study will use RECIST version 1.1
RPSFT	Rank Preserving Structural Failure Time
SAE	Serious adverse event (see definition in Section 6.3).
SAP	Statistical Analysis Plan
SD	Stable disease

SSB	Single strand break
SUSARs	Suspected Unexpected Serious Adverse Reactions
Study treatment	Olaparib or control arm chemotherapy
tBRCA mutation or *tBRCAm*	The term "*tBRCA* mutation" is used to refer to a somatic tumor *BRCA1* or *BRCA2* mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants
TL	Target lesions
US	United States
WBC	White blood cells
WBDC	Web Based Data Capture
wt	Wildtype (patients without evidence of *BRCA1* or *BRCA2* deleterious or suspected deleterious mutations)

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Advanced Pancreas Cancer

Pancreas cancer is a life-threatening disease and is the fourth leading cause of cancer death in the western world. In 2013, it is estimated that there were 45,220 newly diagnosed pancreas cancer cases in the US, and approximately 38,460 people deaths from pancreas cancer. Worldwide, it was estimated that 266,000 people died of pancreas cancer in 2008.[1] Pancreatic adenocarcinoma (PDAC) has a 5-year survival less than 5%. Only 10-20% of patients have surgically resectable disease at time of diagnosis, and even then approximately 80-85% die within 5 years.[2] The poor prognosis of PDAC is a function of late presentation of the disease typically at an inoperable/ locally advanced or metastatic stage.

The development of active and safe regimens for the treatment of advanced pancreatic cancer is an important unmet need.

1.1.2 Chemotherapy for advanced pancreas cancer

Recently, a large phase III study demonstrated that the addition of nanoparticle albumin-bound (nab)-paclitaxel to gemcitabine significantly improved overall survival in treatment-naive patients with metastatic pancreatic cancer, compared with gemcitabine alone.[3] Specifically, in the phase 3 Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) of 861 patients, overall survival was about 2 months better with the chemotherapy combination than with gemcitabine alone (median, 8.5 vs. 6.7 months; hazard ratio [HR], 0.72; P = .000015). In a prior phase I/II study with this combination (n=67), the PR rate was 42% and disease control rate (defined as PR plus SD >16 weeks) was 64%. The median OS for all cases was 10.2 months and PFS 7.1 months.[4] Conroy et al, assigned 342 patients with an ECOG PS of 0 or 1 to receive FOLFIRINOX or gemcitabine.[5] Six months of chemotherapy were recommended in both groups in patients who had a response. The primary end point was overall survival. The median overall survival was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group (HR for death, 0.57; P<0.001). Median progression-free survival was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (HR for disease progression, 0.47; P<0.001). The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (P<0.001). More adverse events were noted in the FOLFIRINOX group; 5.4% of patients in this group had febrile neutropenia. The treatment of metastatic pancreas cancer is associated with modest survival results, even with the most “active” regimens such as FOLFIRINOX or gemcitabine + nab paclitaxel.[3,5]

Unfortunately, these two commonly prescribed regimens also have dose-limiting toxicities. The neurotoxicity and hematologic toxicities of both FOLFIRINOX and gemcitabine + nab paclitaxel and the gastrointestinal toxicities of the former are a significant limitation for this frail population. Second line regimens have a limited impact in this disease, with survival benefit limited to few months only.[6] FOLFOX, gemcitabine, capecitabine or XELOX are the commonly used regimens in this setting.[7,8] Rahma et al, evaluated 44 clinical trials of second

line therapy for pancreatic cancer which enrolled an aggregate total of 1503 patients and showed that second-line chemotherapy was superior to best supportive care in this setting.[8]

1.1.3 Pancreatic Cancer with Family History of Cancer or Germline BRCA Mutation

About 5% of PDAC occurs in cases with germline *BRCA* mutation. Conversely, PDAC is notably over-represented in families with a clustering of breast and ovarian cancers [9-12]. Recently, Princess Margaret Hospital investigators demonstrated pathogenic germline *BRCA1* and *BRCA2* mutations in 13/271 (4.8%) consecutive, ethnically diverse, incident PDAC patients at over about 18 months. *BRCA1* mutations accounted for 1.1% (3/271) and *BRCA2* mutations accounted for 3.7% (10/271) of the cases.[13] However, familial clustering occurs in 10% of PDAC cases often with an autosomal dominant pattern of genetic transmission, suggestive of an inherited cancer syndrome.[14] It seems plausible that there are other genetic aberrations (GAs) other than *BRCA* in these cases with familial clustering. We hypothesize that the latter cases also share the clinical phenotype of BRCA mutation.

BRCA1 and *BRCA2* deficient tumors, particularly in *BRCA1/BRCA2* germline mutation carriers, have a distinct clinical outcome and responsiveness to cisplatin-based therapy. The largest study to date demonstrated superior overall survival data of *BRCA*-associated pancreatic cancer as compared with historic controls.[15,16] Median all–stage OS for all stages of pancreatic cancer (n=58) was 14 months (95% CI 10-23 months). Median OS for patients with stage 1-2 disease has not been reached at 60 months. Median OS for stage 3-4 was 12 months (95% CI 6-15). Superior OS was observed for patients with stage III and IV *BRCA*- associated PDAC treated with platinum versus those treated with non-platinum chemotherapies (22 vs 9 months; p=0.039).

1.1.4 BRCA and PARP inhibition

The BRCA1 and BRCA2 proteins are involved in the regulation of cell cycle checkpoints in response to DNA damage, including the repair of DNA double-strand breaks via homologous recombination (HR).[17] BRCA1/2-deficient cells with HR deficiency (HRD) accumulate DNA double-strand breaks, resulting in genomic instability and increased predisposition to malignant transformation and progression.[18] Somatic, biallelic inactivation of the *BRCA1/2* genes confers sensitivity to inhibition of poly(ADP-ribose)-polymerase (PARP), an enzyme involved in base excision repair [19] as the loss of both HR and PARP1 pathways leads to synthetic lethality during DNA replication. PARP inhibitors (PARPi) increase the sensitivity to chemoradiotherapy treatment in BRCA-2-deficient pancreatic cancer cells.[20] BRCA-defective cells are also more sensitive to platinums, anthracyclines and radiation, as these treatments are selectively lethal in HR-defective cells.[21-23]

To date, the published clinical data supporting the use of individualized therapeutics for *BRCA* associated PDAC is limited. Fogelman et al, described a patient with *BRCA2* associated PDAC who attained a complete pathologic response after treatment with a PARP inhibitor (PARPi) in combination with gemcitabine.[24] In a retrospective study of 15 subjects with *BRCA1/2* associated PDAC, of four patients treated with a PARPi alone or in combination with chemotherapy, three

demonstrated an initial radiographic partial response whereas one had stable disease for 6 months. Furthermore, five of the six patients treated with first line platinum-based chemotherapy also had a radiographic partial response.[25] Single agent PARPi therapy has demonstrated clinical responses in *BRCA* associated PC and additional clinical trials evaluating PARPi in combination with platinum based chemotherapy are currently underway.[26] Study D0810C00042 is the largest study of PARPi in advanced PDAC. A single-arm phase II study of olaparib (capsules) 400mg po bid was conducted in patients with germline *BRCA* mutant malignancies across multiple tumor types. Twenty-three patients with germline *BRCA* mutation-associated advanced pancreas cancer after therapy with gemcitabine were treated with olaparib capsules 400mg po bid. All patients had received a prior gemcitabine regimen and over 50% received a prior platinum containing regimen. The ORR was 22%, DCR 57%, PFS 4.6 mos. and OS 9.8 mos. (Kaufman et al ASCO poster discussion 2013).

To summarize, patients with germline *BRCA* associated PDAC have a more favorable, stage - independent outcome and PARPi may offer therapeutic promise in these cases.

1.1.5 PARPi Beyond Germline *BRCA* Mutations

Homologous recombination repair deficient (HRD) PDAC may involve other genotypes beyond germline *BRCA* mutations. There exists a subtype of cancer patients who display remarkable clinical response to DNA damaging agents [27], thus suggesting that the potential therapeutic effects of PARPi extend beyond germline *BRCA 1/2* mutation carriers.[28] In the pre-clinical setting, PARPi are synthetically lethal in pancreatic sporadic cancers with somatic or epigenetic silencing in the presence of HRD.[29] Molecular profiling of tumors indicate that approximately 10% of pancreatic tumors display a *BRCA*–like signature .[30] These tumors are enriched with unstable genomes with widespread structural variation and have genetic mutations in various DNA repair pathways leading to genomic instability (for instance, *PALB2, Rad51, ATM, RPA1, FANCM, REV1L, XRCC* and *HUWE1*). Recently, deleterious *ATM* mutations have been recognized in the germ-line of families with familial PDAC, suggesting that *ATM* is a susceptibility gene in hereditary PDAC.[31] Somatic *ATM* loss by IHC was observed in 50 out of 396 (12.8%) PDACs. When the sporadic (n = 347) and familial (n = 49) pancreatic cancers were analyzed separately, *ATM* loss occurred significantly more frequently in familial cases as compared with sporadic cases (24% vs. 11%, p=0.019). *ATM* loss occurred in 11% of surgically-resected PDAC and was significantly associated with worse OS than those PDAC cases with preserved *ATM* (p=0.005). [32] *ATM* deficiency is associated with responsiveness to PARPi, including olaparib.[33-35]

1.1.6 PDAC with 'BRCA-ness' Phenotype

Our group (MD Anderson and Johns Hopkins) recently conducted a large retrospective analysis of 549 cases with metastatic PDAC to investigate its familial clustering with *BRCA*-associated cancers but who did not meet the MEDICARE guidelines for *BRCA* testing. In this study, patients with 2 or more family members with breast, ovarian or pancreatic cancers constituted 16% of the population of pancreatic cancer; these cases had superior OS than the sporadic PDAC population. This was especially true in patients with 3 or more relatives with either breast, ovarian, or pancreatic cancers (HR=0.41, P=0.004). Patients with 2 or more

relatives having the above cancers experienced improved survival with platinum-based therapy as compared with their sporadic counterparts (Table 1).

No platinum therapy					
Number of relatives with breast, ovarian, or pancreatic cancer	Number of patients	Number of Deaths	Overall Survival (CI)	Hazard ratio	Adjusted P value
0	151	140	7.5 (6.4, 8.8)	1 (Reference)	
1	45	40	6.9 (5.5, 9.6)	1.13 (0.78 to 1.63)	0.50
2	22	21	5.3 (4.0, 11.0)	1.12 (0.70 to 1.78)	0.64
3 or more	6	5	12.0 (5.7, Inf)	0.65 (0.26 to 1.60)	0.35
Platinum therapy					
Number of relatives with breast, ovarian, or pancreatic cancer					
0	190	163	8.3 (7.3, 10.1)	1 (Reference)	
1	83	73	8.0 (6.5, 11.5)	0.97 (0.73 to 1.30)	0.87
2	36	33	10.6 (9.0, 17.0)	0.82 (0.56 to 1.20)	0.30
3 or more	16	13	21.7 (12.3, 47.2)	0.41 (0.22 to 0.76)	0.004

Table 1: Effect of family history on OS associated with platinum-based therapy

These findings suggest that familial clustering of cancers may serve as a positive predictive marker for platinum therapy in patients with metastatic PDAC, even in the absence of BRCA mutation. This clinical phenotype bears close resemblance to *BRCA*- positive PDAC and deserves further exploration for presence of HRD as a target for PARPi.

1.1.7 Exploiting HR Deficiency in PDAC

HRD in PDAC represents a potential target for PARPi as mentioned above. *PALB2, Rad51, ATM, RPA1, FANCM, REV1L, XRCC* and *HUWE1* GAs lead to DNA repair defects and may represent potential targets for PARPi. Unfortunately, targeting of these genotypes in the clinical setting is complicated by lack of validated assays. Next generation sequencing (NGS) may identify many of these genetic aberrations, but the low incidence of these genetic aberrations and high costs of testing makes NGS impractical as a screening tool at the present time. Therefore, it is critical that we identify novel functional and cost-effective tools to identify high-risk HRD cases without the necessarily interrogating each of these genetic aberrations individually. Recently, our group performed genome-wide transcriptome profiling to identify a HRD signature that can accurately predict response to PARPi. Peng et al evaluated gene expression in several breast cancer cell lines with mutations in either *BRCA1 or RAD51* or *BRIT1*.[36] These genes are known to be associated with HRD. There was a set of 230 genes that were consistently altered in all the cell lines. This set was referred to as the HRD gene signature. The same signature was found in BRCA-wt cell lines after knockdown of different DNA-repair genes, including *ATM.* The signature was also tested in ovarian, prostate, lung and kidney cell lines and was found to be a predictor of PARP-1 inhibitor sensitivity regardless of *BRCA* status. We believe that patients with ATM loss/abnormal p53 express the same HRD gene signature as BRCA-mut patients.

In the proposed study, we plan to utilize this novel tool to interrogate cases with PDAC that are BRCA-negative but have a familial profile suggestive of HRD.

1.1.8 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib IB.

1.1.9 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies eg, dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised dog or any behavioural, autonomic or motor effects in the rat at the doses studied.

Rodent and dog toxicology studies have indicated that the primary target organ of toxicity is the bone marrow with recovery seen following withdrawal of olaparib. *Ex vivo* studies have confirmed that olaparib is cytotoxic to human bone marrow cells.

Olaparib was not mutagenic in the Ames test but was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test *in vitro*. When dosed orally, olaparib also induced micronuclei in the bone marrow of rats. This profile is consistent with the potential for genotoxicity in man.

Reproductive toxicology data indicate that olaparib can have adverse effects on embryofoetal survival and development at dose levels that do not induce significant maternal toxicity.

Further information can be found in the current version of the olaparib IB.

1.1.10 Clinical experience with olaparib

Below is an outline of the monotherapy olaparib studies conducted in pancreas cancer patients.

1.1.10.1 Olaparib monotherapy studies in pancreas cancer patients

Study D0810C00042 (Study 42): This was a single arm phase II study of olaparib (capsules) 400mg po bid in patients with germline *BRCA*m malignancies across multiple tumor types. Twenty-three patients with germline *BRCA*m-associated advanced pancreas cancer after therapy with gemcitabine were treated with olaparib capsules 400mg po bid. All patients had received a prior gemcitabine regimen and over half a prior platinum-containing regimen. The ORR was 22%, DCR 57%, PFS 4.6 mos. and OS 9.8 mos. This level of activity compares favourably with that reported for other therapies reported in advanced previously treated pancreas cancer. A retrospective analysis of the patient data from study 42 suggested greatest benefit from olaparib in those patients whose tumors had not progressed on a prior platinum treatment (ORR 33%, DCR 66%, PFS 6.4 mos., OS 13.1 mos.).

1.1.10.2 Olaparib monotherapy in metastatic pancreatic adenocarcinoma

Thus far, 23 metastatic PDAC patients have been enrolled in a single arm, phase II trial to determine the efficacy of olaparib in advanced PDAC with BRCA*ness (protocol 2015-0503)*. Patients who received ≥ 1 prior systemic therapy for metastatic PDAC, ECOG 0-1, patients known to have DDR genetic aberrations (DDR-GA), or have a family history of BRCA-associated cancers in ≥2 first-degree relatives (without DDR-GA) are eligible. Olaparib was well tolerated with grade 1-2 anemia, fatigue and nausea were the commonly reported toxicities. The median PFS was 24.7 weeks (range 3.9 – 41.1). The median treatment duration was 20 weeks and the disease control rate was 72.7% including 2 patients achieved PR and 6 patients had stable disease. This PFS is higher than historically reported in PDAC (3 months) and therefore we wish to expand this study. The trial included optional biopsies to examine the DNA repair aberrations, particularly in patients with family history alone but without detectable genetic aberrations. We wish to expand the study cohort by 10 patients so as to obtain more correlative information that will increase our understanding about potential eligibility for this targeted therapy.

1.2 Research hypothesis

a) PDAC cases with BRCAness have HRD and b) these tumors can be targeted effectively with PARPi. We hypothesize that olaparib will be efficacious and safe in PDAC patients with BRCAness. These cases can be identified by family history, *ATM* loss and HRD signature. The efficacy in this study will be assessed by objective response rate using the RECIST1.1

1.3 Rationale for study design and doses

We hypothesize that PARPi have broader clinical applications than initially proposed. Assessment of HR function examining markers of HR function is feasible.[30,36] Transcriptome profiling to determine PARPi-sensitive, HRD in PDAC maybe a promising avenue for personalized therapy in this otherwise chemo-refractory disease and a HRD signature was proposed recently by Peng et al, from MD Anderson Cancer Center (MDACC) as described above.[36]

We will focus on the following subsets in this study of stage IV PDAC patients negative for *BRCA 1/2* testing with: a) ATM loss as identified by IHC, b) PDAC cases with 2 or more immediate family members having the above cancers, and c) previously identified GAs known to be associated with HRD.

All treated patients have the option to undergo pre-treatment biopsy. Correlative studies will be performed on all treated patients. These studies will include transcriptome profiling for HRD signature and IHC for *ATM* IHC using validated assays. No prospective NGS is planned for this study. As mentioned above, cases previously identified to have HR genetic aberrations on NGS will be offered the opportunity to participate in this PARPi trial. A second research biopsy will be performed at progression. Based on the available data on efficacy and safety of PARPi in germline *BRCA1/2* mutations, we anticipate that olaparib will have a positive benefit risk profile for the treatment of this sub population of PDAC patients with HRD repair.

1.4 Benefit/risk and ethical assessment

As of 2 October 2013, an estimated 2103 patients with ovarian, breast, gastric, pancreas, and a variety of other solid tumors are estimated to have received treatment with olaparib across the dose range 10 mg qd to 600 mg bid in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies. Olaparib has been given as either monotherapy (18 studies, an estimated 1214 patients) or in combination with other chemotherapy/anticancer agents (25 studies, an estimated 889 patients). Many of these combinations studies are ongoing. The majority of patients to date have received the capsule formulation of olaparib (an estimated 1635 patients). Approximately 468 patients have received the tablet formulation to date. Approximately 304 patients have received comparator or placebo across the olaparib development programme.

An analysis of monotherapy data across 12 AstraZeneca sponsored monotherapy studies in 975 patients who have been given olaparib capsule estimated that 16.1% (157/975) of patients had been exposed to olaparib capsule for ≥12 months at the time of database closure for the 12 studies. Furthermore, 41/ 975 patients received treatment for >24 months (longest duration was 44 months). From the available data to date, there is no evidence of any unexpected toxicity following long-term olaparib (capsule) monotherapy exposure.

Olaparib as monotherapy at doses up to 400 mg bid capsule is generally well tolerated, with most common AEs including nausea, fatigue, vomiting, anaemia mainly mild-to-moderate (CTCAE Grade ≤ 2) in severity. In addition, in a small number of patients MDS/AML or pneumonitis have been observed and identified as important risks.

1.4.1 Important potential risks

1.4.1.1 Myelodysplastic syndrome/acute myeloid leukaemia

There have been 16 reports of myelodysplastic syndrome (MDS) and/or acute myeloid leukaemia (AML) in patients treated with olaparib as of 02 Oct 2013; 11 cases in olaparib monotherapy trials and 5 cases in olaparib combination studies with carboplatin and paclitaxel (n=4) or cediranib (n=1). A total of 2103 patients are estimated to have received olaparib, giving a cumulative incidence of 0.76% for MDS/AML, similar to the cumulative incidence reported from control arms of olaparib randomised studies 0.7% (2/304 patients). All 16 patients had primary ovarian or peritoneal cancer and 12 of them were g*BRCA1/2* positive (3 cases g*BRCA* status unknown; 1 case negative). It has been hypothesised that a deficiency in the expression of *BRCA* genes may leave patients more vulnerable to the adverse effects of chemotherapy, and therefore, at an increased risk of MDS/AML as a result of cancer treatment. Most patients had been treated with extensive previous chemotherapy ranging from 6 to 95 cycles over periods of 3.5 months to 15 years, including platinum agents, topoisomerase II inhibitors, alkylating agents and taxanes. The median time from diagnosis of cancer to onset of MDS was 5.3 yrs (range 2.9 -12.7). The median time from start of olaparib treatment to onset of MDS was 0.9 years (0.1 to 4.8 years). The reported events of MDS/AML occurred post discontinuation of olaparib treatment in 8 of the 16 patients following a median of 0.1 years post treatment discontinuation (range: 0.1 to 1 years). Half of the patients (n=8) had received olaparib for ≤ 12 months (5 patients had ≤ 6 months exposure) and the other 8 cases occurred following longer than 12 month olaparib exposure (3 patients following 12-18 months exposure and 5 patients following >2 years exposure to olaparib).

Since bone marrow is known to be a target organ for olaparib toxicity, a risk of MDS/AML with long-term exposure to olaparib cannot be excluded, but there is insufficient data at present to evaluate the strength, if any, of this relationship. Moreover, while non-clinical data suggest bone marrow progenitor cell populations are reduced temporarily following olaparib treatment, there is no evidence to date linking olaparib treatment to the generation of abnormal bone marrow precursors. Furthermore, all patients who developed MDS/AML had extensive prior chemotherapy and while it is not possible to exclude the contribution of olaparib, it is also considered that there were other potential contributing factors in all cases. Preclinical data also suggest potential benefit with PARP inhibitors in MDS/AML and clinical trials are now underway to assess this effect

To ensure robust safety monitoring, patients in this clinical trial will have weekly safety assessments during the first cycle and then safety assessments every 2 weeks for the first 4 weeks and every 4 weeks thereafter during the rest of the treatment period. Clinical guideline of managing bone marrow toxicity and use of G-CSF is implemented as the safety management plan.

1.4.1.2 Pneumonitis

As of 2nd of Oct 2013, 10 patients out of a total of 2103 patients estimated to have received olaparib have reported pneumonitis, giving a cumulative incidence of 0.5% for pneumonitis. Pneumonitis was also reported for 2 patients (0.7%) of 304 patients that received placebo or

comparator in the olaparib trial programme (1 patient on placebo in Study 19 and 1 patient on paclitaxel in Study 39). The patients were treated with olaparib for breast cancer (n=2), ovarian cancer (n=2), non-small cell lung cancer (n=2), small cell lung cancer (n=1), pancreas cancer (n=1), gastric cancer (n=1) and thymic cancer (n=1). Five of the 10 patients had a history of tobacco smoking. The majority of patients had received prior radiotherapy and/or chemotherapy. The majority of patients had relevant medical histories including pneumonitis, interstitial lung fibrosis, dyspnoea, haemoptysis, chest infection, allergic asthma, pleural effusion, and pleural metastases.

Investigation of any new or worsening pulmonary symptoms has been implemented as a safety management plan (section 6.6.2).

1.4.1.3 New Primary Malignancies

Overall, the number of reports of new primary malignancies is low, with 21 events (in 19 patients) being reported in 02 Oct 2103 olaparib treated patients (0.9%) and one event (bladder cancer) reported in the placebo arm of the double-blind Study 19. In randomised controlled studies, 5 events of new primary malignancies have been reported in four olaparib treated patients and one event in a placebo treated patient:

In the double blind maintenance Study 19, two events of new primary malignancies have been reported in olaparib treated patients and one event in a placebo treated patient. In the open label ovarian monotherapy dose-finding Study 12, three events were reported in two olaparib treated patients.

Of the 21 reported events in olaparib treated patients, in ten the events were non-melanoma skin cancers. There was one report of malignant melanoma. The other 10 events of new primary malignancies were breast cancer (n=2), breast cancer *in situ*, gastric cancer, lung neoplasm (plus event of recurrence of the lung carcinoma), plasma cell myeloma, colon cancer, malignant muscle neoplasm (lesion present pre-olaparib treatment) and one fatal event of T-lymphoblastic lymphoma/leukaemia.

Of the 19 olaparib treated patients subsequently diagnosed with a new primary malignancy, the majority were reported whilst receiving olaparib treatment (16 patients). In 3 patients the event was reported after olaparib discontinuation

The duration of olaparib treatment for the 19 patients was:

- <6 months for 3 patients
- 6 to 12 months for 6 patients
- 12 to 18 months for 2 patients
- 18 to 24 months for 2 patients
- >2 years for 6 patients.

The type of new primary cancers reported were generally in line with secondary cancers observed in ovarian and breast cancer populations reported in the literature [37] or were cancers such as skin cancer, known to be the most common cancer in the general population and associated with high cure rates. Ovarian cancer patients have been reported to have an increased risk of developing second primary malignancies. Patients with *BRCA* mutations are at risk of developing other primary cancers notably breast cancer and skin cancer.[38]

There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all 19 olaparib treated patients. All patients had previously received various chemotherapy agents including multiple cycles of DNA damaging platinum containing chemotherapies, taxanes, anthracyclines and other alkylating and DNA damaging agents. Four patients were reported to have had prior radiotherapy. Seven of the 19 patients had previous medical histories of cancer (ovarian, cervix, breast, peritoneal) and 3 patients with skin cancers had either had previous basal cell carcinoma reported or had skin lesions evident prior to study treatment) prior to the cancer under investigation in the olaparib studies.

There is insufficient evidence for an association between olaparib treatment and the development of new primary malignancies in the clinical trial programme to date.

1.4.2 Potential benefit

Homologous recombination repair deficient (HRD) PDAC may involve other genotypes beyond germline *BRCA* mutations. There exists a subtype of cancer patients who display remarkable clinical response to DNA damaging agents [27], thus suggesting that the potential therapeutic effects of PARPi extend beyond germline *BRCA 1/2* mutation carriers. [28] In the pre-clinical setting, PARPi are synthetically lethal in pancreatic sporadic cancers with somatic or epigenetic silencing in the presence of HRD.[29] Molecular profiling of tumors indicate that approximately 10% of pancreatic tumors display a *BRCA*–like signature.[30] Familial clustering of cancers in PDAC patients may serve as a positive predictive marker for platinum therapy in patients with metastatic PDAC, even in the absence of BRCA mutation. This clinical phenotype bears close resemblance to *BRCA*- positive PDAC and deserves further exploration for presence of HRD as a target for PARPi. We hypothesize that PARPi have broader clinical applications than initially proposed.

Based on the available data on efficacy and safety, we anticipate that in the metastatic disease setting, olaparib will have a positive benefit risk profile for the treatment of this sub population of PDAC patients with HRD repair.

1.5 Study design

This is a phase II, open-label, non-randomised, study of olaparib monotherapy in advanced PDAC patients with:

a) Clinical phenotype of HRD in the absence of *BRCA* mutation: PDAC cases with 2 or more immediate family members having breast, ovarian, pancreatic, gastric or prostate cancers

b) Previously identified GAs known to be associated with HRD.

All patients will be retrospectively investigated for HRD signature using transcriptome profiling and *ATM* expression and the results correlated with PARPi response rates.

Eligible patients will receive treatment with olaparib tablets p.o. 300mg twice daily until progression. Each treatment cycle is described as 28 days long. Patients will have tumor assessments according to RECIST 1.1 at baseline. Patients will then be followed for the final analysis of OS.

Eligible patients will be those patients with stage IV pancreas cancer previously treated for metastatic disease. Patients must have received one prior therapy for the treatment of metastatic disease or refused chemotherapy.

Following study entry, patients will attend clinic visits every two weeks for the first 4 weeks of treatment (Days 1 and 15,). Patients will then attend clinic visits every 4 weeks whilst on study treatment.

Patients should continue to receive study treatment until objective radiological disease progression as per RECIST as assessed by the investigator and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 3.6.

Following discontinuation of study treatment, patients should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule. Patients will be contacted in the 7 days following a specified date (data cut-off date) to capture survival status at that point for each survival analysis. Assessments will be performed as described in Table 2.

Patients will have tumor assessments according to RECIST at baseline and every 8 weeks (±1week) up to 40 weeks and then every 12 weeks (±1 week) until objective radiological disease progression according to modified RECIST criteria. Ongoing collection of site review tumor assessment is required and must be recorded in the electronic case report form (eCRF).

Any patient who discontinues study treatment for reasons other than objective radiological progression should continue to undergo scheduled objective tumor assessments according to the study schedule (see Table 2) in order to assess objective radiological progression of disease. Failure to do so may result in bias to the study results.

2. STUDY OBJECTIVES

2.1) Primary Objective:	Outcome Measure:
• To determine the efficacy of olaparib monotherapy in stage IV pancreatic ductal adenocarcinoma (PDAC) with BRCAness	• Objective Response Rate by using RECIST 1.1

2.2) Secondary Objectives:	Outcome Measure:
• To further determine the efficacy of olaparib in the study population	• Overall Survival (OS) • Progression Free Survival (PFS) • CA 19-9 response

2.3) Safety Objective:	Outcome Measure:
• To assess the safety and tolerability of olaparib	• Safety: Type, frequency, and severity of AEs and SAEs; • Tolerability: dose interruptions, reductions and dose intensity

2.4) Exploratory Objective:	Outcome Measure:
To identify tissue-based biomarkers of defective homologous recombination repair (HRD)	• Retrospective analysis of HRD signature developed by our group • *ATM* expression (IHC)

3. PATIENT SELECTION, ENROLLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study prior to allocation. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

- Patients with histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas.

- Family history: one or more close blood relative with ovarian carcinoma at any age or breast cancer age 50 or younger or two relatives with breast, pancreatic or prostate cancer (Gleason

7 or higher) at any age, or patients with Ashkenazi Jewish ancestry. However, patients with previously identified genetic aberrations that are associated with HRD will be eligible even in the absence of family history [e.g. somatic *BRCA* mutation, *Fanconi Anemia* gene, ATM or *RAD51* mutations].

- Patients must be germline *BRCA* 1 or 2 negative. (Note: If BRCA status was previously determined, that result is acceptable but documentation of status must be available; subjects with unknown status will be referred to genetic counselling for BRCA testing as per standard of care.)

- Patients must have received at least one prior therapy for metastatic disease to be eligible.

- Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan.

- All treated patients have the option to undergo pre-treatment biopsy (liver, omentum, lung or lymph node) to be eligible.

- Patients with prior malignancy and treated with no evidence of active disease, and more than 2 years from initial diagnosis are eligible.

- ECOG Performance Status 0-1 (Karnofsky >70).

- Patients must have adequate organ and marrow function as defined below:

-	leukocytes	≥3,000 cells/mm^3
-	absolute neutrophil count	≥1,500 cells/mm^3
-	platelets	≥75,000 cells/mm^3
-	hemoglobin	≥9 g/dl (no blood transfusions within 4 weeks prior to enrollment)
-	total bilirubin	<1.5 X institutional upper limit of normal (IULN)
-	AST(SGOT)/ALT(SGPT)	≤2.5 X IULN without liver metastasis ≤5 X IULN for patients with liver metastasis
-	creatinine	Not greater than Upper Institutional limits

OR

-	creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

- INR <1.5.
- Patients must be ≥ 18 years of age.
- Women of childbearing potential (defined as not post-menopausal for 12 months or no previous surgical sterilization) and fertile men must agree to use two highly effective forms of contraception while they are receiving study treatment and for one month for female patients and for 3 months for male patients after last dose of study drug. Male subjects must agree to refrain from sperm donation during the study and for 90 days after the last dose of study drugs.
- Ability to understand and the willingness to sign a written informed consent document. Signed informed consent form must be obtained prior to initiation of study evaluations and/or activities.

3.2 Exclusion Criteria

- Uncontrolled intercurrent illness including symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia and myocardial infarction (MI) within 3 months of initiation of therapy.
- Patients whose tumors are deemed to be platinum-refractory will be excluded from the trial.
- Pregnancy or lactation.
- Patient has active and uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy.
- Patient has undergone major surgical resection within 4 weeks prior to enrollment.
- Patient received radiotherapy, surgery, chemotherapy, or an investigational therapy within 2 weeks prior to study entry.
- Patient has serious medical risk factors involving any of the major organ systems such that the investigator considers it unsafe for the patient to receive an experimental research drug.
- Serious psychiatric or medical conditions that could interfere with treatment.
- Major bleeding in the last 4 weeks prior to study entry.
- Concomitant use of CYP3A4 inhibitors.
- Resting ECG with QTc >470msec (**Fredericia's scale)**.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient Enrollment Allocation

Investigator(s) should keep a record, the patient-screening log, of patients who entered pre-study screening.

The Principal Investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Determine patient eligibility. See Sections 3.1 and 3.2.

The Study Coordinator will enter eligible patients on study. The Core System administered by the Office of Protocol Research at UT MD Anderson Cancer Center will be used to register patients.

3.4 Procedures for handling incorrectly enrolled patients

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be allocated or receive study medication. There can be no exceptions to this rule.

Where patients that do not meet the selection criteria are incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the MD Anderson IND Medical Monitor and the investigator regarding whether to continue or discontinue the patient from treatment. Once a decision is made, Investigators need to ensure they comply with all applicable requirements for human patient protection and ethical review.

3.5 Restrictions

3.5.1 Contraception

Women of childbearing potential (defined as not post-menopausal for 12 months or no previous surgical sterilization) and fertile men must agree to use two highly effective forms of contraception while they are receiving study treatment and for one month for female patients and for 3 months for male patients after last dose of study drug. Male subjects must agree to refrain from sperm donation during the study and for 90 days after the last dose of study drugs.

3.5.2 Olaparib and CYP3A4/5

Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4/5 enzyme activity (see Section 7.7.2) starting 5 days before study enrollment until 30 days after the last dose of study medication.

3.6 Discontinuation of investigational product

Patients may discontinue study treatment in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Objective radiological disease progression
- Intolerable toxicity as defined in Section 6.3 Severe Adverse Event if related to study drug.
- Severe non-compliance to study protocol
- Death

3.6.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.2 and6.3); all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 3.7.

Any patient discontinuing study treatment should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule. The patient's tumor status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of study treatment, the principal investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the eCRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

After discontinuation of the study treatment at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Sections 6.2 and 6.3). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.3) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing study treatment to collect and / or complete AE information. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study treatment should also be reported as an AE.

Patients who discontinue treatment prior to disease progression should continue to have RECIST assessments as per the study schedule. All patients must be followed for objective progression (as per RECIST 1.1) and survival, up to the final analysis.

3.7 Criteria for withdrawal

Patients are at any time free to withdraw from study (study treatment and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.2 and 6.3). All study tools and drug supply should be returned by the patient.

Withdrawn patients will not be replaced.

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment*
- Incorrectly enrolled patients ie, the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Death

*If a patient decides at any point in the trial that they do not wish to continue with the full study schedule of assessments but are still willing to provide important study information (eg disease recurrence information and/or survival status information) then the patient should continue in the study and information should continue to be collected on the clinical database. However if a patient does not wish to have any further data collected, only then should they be considered as withdrawing consent from the study. To minimise the number of cases of early withdrawal the investigator should discuss the options with the patient in case they would still be willing to undergo reduced assessments and/or reduced data collection, in which case they would remain in the study.

*If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- to further participation in the study including any further follow up (eg, survival calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples (see Section 5.4.5)

Data obtained prior to withdrawal of consent will be maintained in the clinical database and used in the study reporting.

The status of ongoing, withdrawn (from the study) and 'lost to follow up' patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to collection of further data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

3.7.1 Screen failures

Screen failures are patients who do not fulfil the eligibility criteria for the study. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrollment' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures. To reach the planned 34 patients, up to 51 patients may need to be screened (consented). Those patients who do not meet eligibility will be considered screen failures and will be replaced.

3.7.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrollment code cannot be reused. Withdrawn patients will not be replaced.

3.8 Discontinuation of the study

The study may be stopped if, in the judgment of the investigators, trial patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant,
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

A study initiation visit must be conducted at the centre prior to the commencement of any study activities requiring informed consent. A schedule for the tests and evaluations to be conducted in this study is contained in this section and in Table 2.

Table 2 Study Schedule – Screening, On Study Treatment, Discontinuation and Follow-up

	Pre-Screening	Screening	Treatment Duration				Study treatment discontinued	30-Day follow-up	Survival Follow-up
Cycle/ Visit			**1 (28 days)**		**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**15**	**29**	**57+**			**Every 8 weeks**
Visit window				**±2d**	**±2d**	**±2d**	**±7d**	**±7d**	**±7d**
Informed consent		X							
Demographics		X							
Medical and surgical history, including previous cancer and radiotherapy		X							
Inclusion/exclusion criteria	X	X							
BRCA testing/ Genetic counselling	X								
Archival tumor tissue (FFPE) if available[a]		X							
Research Core Needle Biopsy (CNB)		X[P]					X		
Concomitant medications		X	X	X	X	X	X	X	
ECOG performance status		X	X		X	X	X	X	
Vital signs		X [b]	X [b]	X	X	X	X	X	

	Pre-Screening	Screening	Treatment Duration				Study treatment discontinued	30-Day follow-up	Survival Follow-up
Cycle/ Visit			**1 (28 days)**		**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**15**	**29**	**57+**			**Every 8 weeks**
Visit window				**±2d**	**±2d**	**±2d**	**±7d**	**±7d**	**±7d**
Physical examination [c]		X	X	X	X	X	X	X	
ECG [d]		X	As clinically indicated						
Imaging studies: CT scan or MRI Tumor assessment (RECIST 1.1) [e]		X[e] (no more than 28 days before start of treatment)	Every 8 weeks (± 1 week) for the first 40 weeks then every 12 weeks (±1 week) [e]				If patient does not have disease progression at the time of treatment discontinua-tion, tumor assessments should be continued if they stay on study protocol.[f]		
Haematology/clinical chemistry		X	X [g]	X	X	X	X	X	
Coagulation [h]		X	As clinically indicated						
Urinalysis [i]		X	As clinically indicated						
Pregnancy test [j]		X	X						

	Pre-Screening	Screening	Treatment Duration				Study treatment discontinued	30-Day follow-up	Survival Follow-up
Cycle/ Visit			**1 (28 days)**		**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**15**	**29**	**57+**			**Every 8 weeks**
Visit window				**±2d**	**±2d**	**±2d**	**±7d**	**±7d**	**±7d**
Biomarker blood sample [k]			X			X (only at progres-sion)			
Adverse event [l]		X	X	X	X	X	X	X	
Study drug dispensing [m]			X		X	X			
Study drug return					X	X	X		
Subsequent cancer treatment [n]								X	X
Survival status [o]									X[o]

a Collection of an archival tumor sample is requested in screening period.
b Vital signs performed at screening, cycle 1 days 1 and 15, and on day 1 of every cycle. If vital signs assessed within 7 days before starting study treatment, it does not need to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.
c Physical examination should be performed according to the schedule. After the baseline assessment it is not necessary to record the details on the eCRF. Any clinically significant changes not unequivocally related to disease progression should be reported as adverse events.
d ECG assessments to be completed within 7 days before starting treatment if patient is eligible following completion of all other assessments. After screening, ECGs will only be required if clinically indicated.
e Baseline RECIST assessments will be performed using CT scans of the chest, abdomen and pelvis (or MRI where CT is contraindicated) and should be performed no more than 28 days before start of study treatment. RECIST follow-up assessments will be performed every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week) irrespective of treatment decisions. Follow-up assessment will include CT assessments of chest, abdomen and pelvis (or MRI where CT is contraindicated) for all patients. Any other sites at which new disease is suspected should also be appropriately imaged.

Patients must be followed until disease progression assessed using RECIST 1.1 criteria. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

f For patients who discontinue study treatment prior to disease progression, RECIST assessments will continue until objective disease progression (every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week), until objective disease progression as defined by RECIST 1.1.) as long as they stay on study.

g Haematology and clinical chemistry should be performed at screening, cycle 1 days 1 and 15, and day 1 of every cycle (± 2 days) .

h Coagulation test should be performed at screening and if clinically indicated

i Urinalysis should be performed at screening. After screening, urinalysis will only be required if clinically indicated.

j In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

k Mandatory blood samples for biomarker analysis to be taken prior to dosing on Cycle 1 Day 1 and at disease progression.

l Adverse events must be captured from time of first protocol intervention (start of study medication). During Screening: baseline sign and symptoms will be captured. SAEs will be recorded from first protocol specific intervention (start of study medication).

m Continuous olaparib 300mg twice daily dosing. Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice.

n All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigator's opinion of response to them, plus the date of progression post discontinuation of study treatment, need to be recorded.

o The status of ongoing, withdrawn (from the study) and 'lost to follow-up' patients at the time of an OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section3.7). In addition to their regular 8 weekly contacts, patients will be contacted in the 7 days following a specified date (data cut-off date) for each survival analysis.

p. Research Core Needle Biopsy (CNB) from metastatic site will be optional during the screening period.

4.1 Enrollment/screening period

4.1.1 Pre-screening period

The pre-screening period may be utilized to identify potential subjects (pancreatic cancer patients who have advanced disease and are receiving or going to receive first-line treatment). Potential patients with family history of breast, ovarian, pancreatic, gastric or prostate cancer will be identified. These cases will be referred to genetic counselling for *BRCA* testing as per standard of care. If patients have already been screened and are *BRCA* mutation negative, they are potentially eligible (as long as other inclusions are met). If somatic mutation testing has identified mutations in other DNA repair genes, they will also be potentially eligible (as long as other inclusions are met).

4.1.2 Screening period

The following assessments and procedures should be performed during screening.

For details of the schedule and nature of assessments see below:

- Month/ year of birth, sex, race and ethnicity
- Medical and surgical history including previous cancer and radiotherapy
- Previous chemotherapy
  - If patient received a prior platinum drug, describe the setting (adjuvant or advanced), time on treatment (dates), and reason for discontinuation (progression on therapy, discontinuation of therapy for reason other than progression, completion of planned program without progression). Patients who progressed on platinum-based therapy will not be excluded from this current study.
- Current and concomitant medications including previous cancer therapies
- ECOG Performance Status
- Vital signs (blood pressure and pulse; body temperature), body weight, height
- Haematology /Clinical chemistry/Urinalysis
- Coagulation test
  - activated partial thromboblastin time (APTT) will be performed at baseline and if clinically indicated
  - international normalized ratio (INR) will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking

warfarin may participate in this study; however, it is recommended that prothrombin time (INRand APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable

- Physical examination
- CT (or MRI if CT is contraindicated) of chest, abdomen and pelvis
- Research Core Needle Biopsy (CNB) from metastatic site will be optional during the screening period.
- ECG (within 7 days prior to the start of the study treatment)
- Menopausal status; serum or urine pregnancy test for women of childbearing potential. The pregnancy test should be performed within 28 days prior to the start of study treatment and confirmed on day 1 prior to dosing.
- Baseline sign and symptoms will be captured during screening period.
- Archival paraffin embedded tumor tissue sample will be requested

The Principal Investigator/Sub-Investigator should adhere to the study plan, procedures and perform tests/observations in accordance with the protocol.

4.2 Treatment period

The visit schedule is based on 28-day cycles.

Patients will attend the clinic every two weeks on days 1 (1st day of treatment) and 15 following the commencement of study treatment and then every 4 weeks (day 1 of every cycle) until discontinuation of treatment. The following assessments will be performed at time points specified in the study schedule (see Table 2):

- Vital signs: These will include weight, temperature, pulse rate, BP.
- ECOG Performance Status: Day 1 of every cycle and until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose
- Haematology and clinical chemistry: Cycle 1 Days 1 and 15 and then Day 1 of every cycle.
- Physical examination: Cycle 1 Days 1 and 15 and then Day 1 of each cycle. Further assessments after day 1 are not required to be captured on an eCRF, however any significant changes from baseline must be reported as an AE.

- CT of chest, abdomen and pelvis (or MRI if CT is contraindicated) performed until objective disease progression. RECIST assessments to be scheduled every 8 weeks (±1 week) for the first 40 weeks and then every 12 weeks (±1 week).
- ECG at baseline and any time if clinically indicated
- Urinalysis at baseline and any time if clinically indicated
- Serum or urine pregnancy test for women of childbearing potential (prior to treatment on day 1 of 1st day of study treatment). If the test is positive then a confirmatory test should be performed
- AE and concomitant medications (including any blood transfusions) at every visit
- Mandatory blood sample for biomarker analysis at cycle 1 day 1 (pre-dose) and disease progression (Section 5.3.1)

Once patients have discontinued study treatment, other treatment options will be at the discretion of the investigator.

4.3 Follow-up period

4.3.1 Treatment discontinuation visit due to objective radiological disease progression

Patients should be discontinued from study treatment if they have objective radiological disease progression according to RECIST 1.1 criteria. A follow-up visit should be conducted 30 days after the last dose of study treatment. Any serious and/or non-serious AEs ongoing at the time of the Discontinuation Visit or which have occurred during the defined 30-day follow-up period must be followed-up (in accordance with Section 6.2). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF. The assessments to be carried out at the 30-day follow up visit are detailed in the study schedule (Table 2).

Following radiological disease progression patients will be followed for OS.

4.3.2 Treatment discontinuation visit due to any other discontinuation criteria

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled (see Section 3.6). A follow up visit should be scheduled as indicated above. The assessments to be carried out at the 30-day follow up visit are detailed in the study schedule (Table 2).

4.3.3 Survival

Assessments for survival should be made every 8 weeks following objective radiological disease progression. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. Survival data will be collected up to the time of the final overall survival (OS) analysis. In addition, patients should be contacted in the week following the data cut-off for the primary PFS and final survival analyses to provide complete survival data.

Patients will be followed up as per Table 2 to the point of the final analysis. At this point investigators will be notified that no further data collection for the study is required. Monitoring and recording of SAEs will continue as per Section 6.4.

The status of patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section 3.7).

4.3.4 Subsequent Treatment

Following objective progression patients will be assessed every 8 weeks for survival (see Section 4.3.3). Outcome from subsequent therapy is not an objective of this trial.

4.4 Patient management post final analysis

At this time point, the clinical study database will close to new data. Patients who are receiving treatment can either choose to discontinue from the study or where the investigator believes patients are gaining clinical benefit; patients may continue to receive study treatment. All patients will receive follow up care in accordance with standard local clinical practice.

SAEs will continue to be reported to AstraZeneca Patient Safety Department, for any patients who continue on olaparib until 30 days after study treatment is discontinued, in accordance with Section 6.4. Additionally as stated any SAE or non-serious adverse event, that is ongoing at the end of the study, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety.

Drug accountability should continue to be performed until the patient stops study treatment completely

5. STUDY ASSESSMENTS

Electronic Case Report Forms will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.
The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

5.1.1 CT and MRI scans tumor assessments (RECIST 1.1)

Following the baseline assessment, subsequent tumor assessments according to RECIST 1.1 should be performed every 8 weeks (±1 week) for the first 40 weeks and then every 12 weeks (± 1 week) thereafter, up to objective disease progression by RECIST.

For those patients with no evidence of disease at baseline, following a clinical complete response to chemotherapy, progression is defined by the detection of new lesions on follow up radiological assessments (RECIST 1.1).

The imaging modalities used for RECIST assessment will be CT (MRI where CT is contraindicated) scans of the chest, abdomen and pelvis with other regions as clinically indicated. The same imaging modality should preferably be used for each restaging visit. Radiological examinations performed in the conduct of this study should be retained at site as source data.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of scheduled visit ± 1 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients will be evaluated until objective radiological disease progression by RECIST 1.1 as per the study schedule (seeTable 2), and then followed for second progression and survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

5.1.2 Tumor Evaluation

RECIST 1.1 criteria will be used to assess patient response to treatment by determining progression free survival (PFS) times. (The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumor response criteria (complete response, partial response, stable disease, no evidence of disease or progression of disease).

The methods of assessment of tumor burden used at baseline - CT or MRI scans of chest, abdomen and pelvis, with other regions as clinically indicated for the assessment of disease must be used at each subsequent follow-up assessment, see Section 4.3.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumor assessments every 8 weeks (±1 week) for the first 40 weeks then every 12 weeks (±1 week), according to the planned study scheduleTable 2 until objective radiological disease progression as defined by RECIST. If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective radiological disease progression as defined by RECIST 1.1.

Categorization of objective tumor response assessment will be based on the RECIST criteria of response: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), no evidence of disease (NED) and not evaluable (NE). Target lesion (TL) progression will be calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of a best response of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before allocation.

For patients with non-measurable disease only at baseline, categorization of objective tumor response assessment will be based on the RECIST criteria of response: CR (complete response), PD (progression of disease) and Non CR/Non PD. Patients with no disease at baseline will be assessed according to RECIST 1.1 criteria for new lesions with responses of No Evidence of Disease (NED) or progression of disease.

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

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

Following progression, patients should continue to be followed up for survival every 8 weeks as outlined in the study plan. It is important to follow the assessment schedule as closely as possible. Please refer to the study plan and CT/MRI scans in section 5.1.1.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Schedule (see Table 2).

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

The following laboratory variables will be measured:

Table 3 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin	S-Sodium
B-Red blood cells [RBC]	S-Potassium
B-Platelets	S-Magnesium (baseline only and if clinically indicated)
B-Mean cell volume [MCV]	S-Calcium
B-Mean cell haemoglobin concentration [MCHC]	S-Creatinine
B-Mean cell haemoglobin [MCH]	S-Total bilirubin
B-White blood cells [WBC]	S-Gamma glutamyltransferase [GGT]
B-Absolute differential white cell count – (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available please provide % differentials.	S-Aalkaline phosphatase [ALP] S-Aspartate transaminase [AST] S- alanine transaminase [ALT] S-Urea or blood urea nitrogen [BUN] S-Total protein S-Albumin S-Lactate dehydrogenase (LDH)
Urine Tests	
Urinalysis (Dipstick, baseline only and if clinically indicated)	
U-Hb/Erythrocytes/Blood	
U-Protein/Albumin	
U-Glucose	
Urinalysis (Microscopic analysis, baseline only and if clinically indicated)	

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 5.2.

For blood volume see Section 5.4.1.

5.2.2 Physical examination

For timing of individual measurement refer to study schedule (Table 2).

A physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen and neurologic systems. Additional systems to be examined as clinically indicated.

5.2.3 ECOG

ECOG Performance Status is a widely used, 5-level, clinician reported outcome of the patient's performance status. Below is a description of the clinician's grading system for the ECOG Performance Status. This measure will be applied according to the study schedule (see Table 2).

Table 4 ECOG Performance Status [a]

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

a As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

5.2.4 ECG

5.2.4.1 Resting 12-lead ECG

ECGs are required during screening within 7 days prior to starting study treatment and when clinically indicated afterwards.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

5.2.5 Vital signs

Height will be assessed at screening only.

Weight will be assessed at screening and as clinically indicated at any other time.

Any changes in vital signs should be recorded as an AE, if applicable.

5.2.5.1 Pulse and blood pressure

Blood pressure and pulse rate will be measured preferably using a semi-automatic BP recording device with an appropriate cuff size.

5.2.5.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer.

5.2.6 Other safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Schedule (see Table 2).

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

5.2.6.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential as per the study schedule. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

5.2.7 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected only if clinically indicated for patients with prolonged haematological toxicities as defined in Section 6.6.1.

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. Full reports must be provided by the investigator for documentation on the Patient Safety database.

5.3 Biomarkers

Tumor and blood samples will be collected for the biomarker work as detailed in the Laboratory manual.

For blood volume see Section 5.4.1.

5.3.1 Biomarker samples

The biomarker samples will be collected as described in Table 5**.**

Table 5 Samples for Biomarker Research

Sample Type	Visits
Research biopsy	Screening; after progression
Archival tumor sample (paraffin or cytology) – Requested, if available	Screening
Blood samples for biomarker analysis	Cycle 1 Day 1 and disease progression

The samples and data from this research will be coded and not labelled with any personal details. Each sample will be identified with the study and patient enrollment number. In this way biomarker data may be correlated with clinical data, samples destroyed in the event of withdrawal of consent and regulatory audit enabled. However, only the investigators will be able to link the biomarker sample to the individual patient. The coded samples will be provided to the research laboratories performing the biomarker analyses. Investigators will not provide biomarker results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party unless required to do so by law. The patient's samples will not be used for any other purpose other than those described in the protocol.

5.3.1.1 Guidance for *BRCA* testing of patients with unknown *BRCA* status.

Patients who meet the eligibility criteria of family history will be referred to a genetic counsellor only if their underlying genetic status is unknown. Genetic testing will be ordered as per patient eligibility for testing as per standard of care. If the result shows that the patient has a deleterious/suspected deleterious *BRCA* mutation, the patient will not be eligible to the study. `

5.3.1.2 Collection of blood sample for exploratory assay(s)

All patients will be required to provide a mandatory 12 ml blood sample that will be stored in Dr. Donghui Li's laboratory for subsequent assessment of current and future assay(s).

Residual blood (or its derivatives) may be used to evaluate future HRD companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of pancreas cancer and disease recurrence.

5.3.2 Exploratory Biomarker Research on Archival Tumor Samples (Paraffin block or tissue cytology slides) (Requested, if available)

These samples will be collected from the site pathologist during the screening period. An adequately sized (minimum of 2 mm x 2 mm) archival tumor tissue paraffin block from a core biopsy from the primary tumor or a metastatic site is preferred. Alternatively, 10-20 pre-cut sections mounted on glass slides prepared from the block can be provided. If the only diagnostic test was cytologic, a paraffin block or three unstained slides of tumor tissue should be tested for correlative studies as detailed in the laboratory manual.

Collection of an archival tumor sample is requested if available for all patients. Surplus tissue may be used for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease progression.

Please refer to Investigator Laboratory Manual for further details of archival tissue collection, shipping and storage.

5.3.3 Exploratory Blood samples for biomarker analysis (Mandatory)

All consenting patients will be required to provide a blood sample at Cycle 1 Day 1 and disease progression for exploratory biomarker research.

Patients will be required to provide:

- 1x 6ml blood sample for preparation of serum at cycle 1 day 1 and disease progression.
- 1x 6ml blood sample for preparation of plasma at cycle 1 day 1 and disease progression.

Please refer to Investigator Laboratory Manual for further details of biomarker blood sample collection, shipping and storage.

5.4 Biological sampling procedures

5.4.1 Volume of blood

The volume of blood that will be drawn from each patient will vary, dependent upon the length of time that the patient remains in the trial. The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 6 cycles of treatment, a treatment discontinuation visit and the 30-day follow-up visit, is 255mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore patient to site-specific change. Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments.

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 6 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	5	21	105
	Haematology	5	21	105
	Coagulation	3	1	3
Whole blood sample for genetic testing (retrospective/prospective)		9	1	9
Whole blood sample for assessment of current and future *BRCA* mutation assay(s) (if indicated)		9	1	9
Serum Pregnancy test (site may use urine instead)		Site dependent	Site may use urine instead	
Serum sample for exploratory biomarkers, cycle 1 day 1 (mandatory)		6	1	6
Plasma sample for exploratory biomarkers, cycle 1 day 1 (mandatory)		6	1	6
Serum sample for exploratory biomarkers, disease progression (mandatory)		6	1	6
Plasma sample for exploratory biomarkers, disease progression (mandatory)		6	1	6
Total				255

5.4.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

HR dysfunction expression signature by microarray will be evaluated from fresh RNA extracted from pretreated biopsies performed in the screening period from core needle biopsy from liver, omentum, lung or lymph node (Peng scientific co-PI / MDACC et al). Total RNA will be extracted from the frozen tissues by using a mirVana RNA isolation labeling kit (Ambion, Inc). Five hundred naograms of total RNA will be used for labeling and hybridization using Illumina HumanHT 12v4 (24 rxn) chips according to the manufacturer's protocols (Illumina). All microarray experiments will be conducted in the MDACC Sequencing and Microarray Core Facility, where the protocol for microarray analysis has been standardized to produce robust and reliable microarray data. Microarray data analyses will be consulted with MDACC bioinformatics Shared Resource. Briefly, as described in our previous publication[36], the microarray data will be normalized using the quantile normalization method

in the LIMMA (Linear Models for Microarray Data) package in the R language environment. The expression level of each gene will be transformed into a log2 base before further analysis. Based on cluster analysis of the gene expression array data (Cluster 3.0), we will investigate if the HR-defective gene signature correlates with clinical response to PARPi. We will select the most significant genes in the HR-defective gene signature associated with PARPi response for further study. We will also test if a subset of the gene signature can be identified as predictive markers, which will allow for a more clinically-appropriate PCR-based analysis.

5.4.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria),

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with sponsor and appropriate labelling, shipment and containment provisions are approved.

5.4.4 Chain of custody of biological samples

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

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

If required, sponsor will ensure that remaining biological samples are returned to the site, according to local regulations or at the end of the retention period, whichever is the sooner.

5.4.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, sponsor is not obliged to destroy the results of this research.

Archival tumor sample: If consent to use the sample is withdrawn this will not impact eligibility to study. The patient may continue in the study if the patient is already on study treatment.

Blood samples for biomarker analysis: Although mandatory, the patient may continue in the study if the patient is already on study treatment.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to sponsor
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory (ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and sponsor are informed about the sample disposal.

Sponsor ensures the central laboratory (ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Recording of adverse events

6.2.1 Time period for collection of adverse events

Adverse Events will be collected from first protocol specific intervention (start of study medication) throughout the treatment period up to and including the 30-day follow-up period. All ongoing and any new AEs/SAEs identified during the 30 calendar days follow up period, after the last dose of study medication must be followed to resolution. After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

SAEs will be recorded from first protocol specific intervention (start of study medication).

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The Investigator or designee will be responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial.

6.2.2 Follow-up of unresolved adverse events

Any SAEs or non-serious adverse event that is ongoing at the time of the 30-day follow up, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up.

6.2.3 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.3. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.3.

Severity of AE

For each episode on an adverse event, all changes to the CTCAE grade attained as well as the highest attained CTC grade should be reported.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades the recommendation is that the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version can be downloaded from the NCI website.

6.2.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

6.2.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.2.6 Adverse events based on examinations and tests

The reporting of laboratory/vital signs/ECG abnormality as AE should be avoided unless one of the following is met:

- Any criterion for an SAE is fulfilled
- Causes study treatment discontinuation
- Causes study treatment interruption
- Causes study treatment dose reduction
- The investigator believes that the abnormality should be reported as an AE

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.2.7 Hy's Law

Cases where a patient shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN may need to be reported as SAEs if related to the study medication as per study PI.

6.2.8 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. The development of local regional recurrence or distant metastasis to the primary cancer under study should be

considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

New cancers

The development of a new primary cancer (including skin cancer) should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 6.3). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

Lack of efficacy

When there is deterioration in the cancer, for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless AstraZeneca or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the DEATH eCRF but should not be reported as an SAE

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within 24 hours (see Section 6.3 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.

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

6.3 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or AstraZeneca, it results in any of the following outcomes:

- Death

- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience 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 events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- (**Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last study treatment/intervention, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Reporting to AstraZeneca:

All SAEs must be reported to AstraZeneca (by the investigator or designee) in a timely fashion of study personnel learning of its occurrence.

6.4 Overdose

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

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 and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then Investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

For overdoses associated with SAE, standard reporting timelines apply (see Section 6.4). For other overdoses, reporting should be done within 30 days.

6.5 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.5.1 Maternal exposure

Women of childbearing potential must agree to use adequate contraception. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca.

If a patient becomes pregnant during the course of the study, investigational product should be discontinued immediately.

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 and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **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 within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.5.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days following the last dose. 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) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 30 days after the last dose should be followed up and documented.

To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information.

6.6 Management of toxicity of olaparib

Non-hematological toxicities that are clinically significant and definitely, probably or possible related to olaparib. Note all reductions are final, there will be no re-escalation. Maximal dose reduction allowed is 200 mg bid.

6.6.1 Management of haematological toxicity olaparib

Table 7 Management of Haematological Toxicity from Olaparib

Toxicity	Study treatment dose adjustment
CTCAE[a] gr 1 or 2	Appropriate supportive treatment and causality investigation
Repeat CTCAE gr 2	Dose interruption until recovery to CTCAE gr 1 and resume at same dose. For repeat gr. 2 or higher, dose reduction to 250 mg bid as first step. For repeat toxicities reduce to 200 mg bid
CTCAE gr 3-4	Dose interruption until recovered to CTCAE gr 1 and dose reduction to 250 mg bid as first step. For repeat toxicities reduce to 200 mg bid. Maximal dose interruption allowed is 4 weeks.
Repeat CTCAE gr 3-4	Discontinue study treatment if already at 200 mg bid dosage.

[a] CTCAE Version 4

Note: These dose reductions will not apply to Anemia. Please refer to 6.6.1.1 for the same.

6.6.1.1 Management of anaemia

Adverse events of anaemia CTCAE grade 1 or 2 (Hb $\geq$ 8 g/dl) should be investigated and managed as deemed appropriate by the investigator with or without interruption of study drug or change in dose, taking into account previous history of anaemia. Common treatable causes of anaemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. However, if a patient develops anaemia CTCAE grade 3 (Hb < 8g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks. Study treatment can be restarted at the same dose if Hb has recovered to > 9 g/dl. Any subsequently required anaemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step.

If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependant as judged by investigator, study treatment should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose.

6.6.1.2 Management of neutropenia and leukopenia

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs. 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.

Study treatment can be restarted if an adverse event of neutropenia or leukopenia has been recovered up to CTCAE grade 1 (ANC ≥ 1.5 x 10^9/L).

Dose modifications for neutropenia are described in Table 7 above.

6.6.1.3 Management of thrombocytopenia

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator. In some cases management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

Management of prolonged haematological toxicities while on study treatment.

If a patient develops prolonged haematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia 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 (Platelets < 50 x 10^9/L)

Weekly differential blood counts including reticulocytes and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

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. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

6.6.2 Management of non-haematological toxicity Olaparib

6.6.2.1 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormality occurs, an interruption in study treatment dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If drug-induced pneumonitis is observed, olaparib will be discontinued.

6.6.2.2 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In Study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They 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 study 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. As per international guidance on antiemetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered e.g. dopamine receptor antagonist, antihistamines, dexamethasone.

6.6.2.3 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 AZ study physician.

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

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 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 olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

6.7 Study governance and oversight

6.7.1 Data Monitoring

The MD Anderson IND Office will organize on-site monitoring of this study at MDACC to be conducted as per the Monitoring Plan. The frequency of these visits at the site may depend on accrual or other factors (eg: site issues, etc). A clinical monitor will make regularly scheduled trips to the investigational site to review the progress of the trial. Site monitoring of the study is the responsibility of the Investigator and GI Medical Oncology (GIMO) Department. The

study monitor will advise the Investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP and all applicable regulatory requirements. Before study initiation, at a site initiation visit or at an Investigator's meeting, a GIMO representative will review the protocol and CRFs with the Investigator and his staff. Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the Investigator. This will include telephone calls and on-site visits.

During the on-site visits, the CRFs will be reviewed for completeness with corresponding source documents. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and may periodically request review of the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitor to review CRFs and relevant source documents. The Investigator should be available to answer questions or resolve data clarifications. The Investigator or appointed delegate will receive the study monitor during these on-site visits, cooperate in providing the documents for inspection, and respond to inquiries.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib to the Investigator as film-coated tablets as shown below.

Investigational product	Dosage form and strength
Olaparib[a]	Tablet –100mg and 150 mg

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

7.2 Dose and treatment regimens

Study treatment is available as film-coated tablet containing 150 mg or 100 mg of olaparib.

For all centres, olaparib will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. The study treatment will be dispensed to patients. Each dosing container will contain sufficient medication for at least each treatment period plus overage. The planned dose of 300 mg bid will be made up of two (2) x 150 mg tablets bid with 100 mg tablets used to manage dose reductions. Tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with approximately 240 mL of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved

or divided. Olaparib tablets can be taken with a light meal/snack (eg, two pieces of toast or a couple of biscuits). Multiple bottles of olaparib may be required for dispensing in order to make up the desired dose.

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 (eg, 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.

Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the investigator.

7.3 Labelling

Labels for olaparib will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions and may only be dispensed by investigator or pharmacist qualified designee. The investigational product label on the olaparib bottle and the IB specifies the appropriate storage conditions.

7.5 Compliance

The administration of all study drug should be recorded in the appropriate sections of the eCRF.

Patients should be given clear instructions on how and when to take their olaparib. Patients will self-administer olaparib. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient, but will be discarded by Investigational Pharmacy. All patients must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at the end of the study.

7.6 Accountability

The study treatment provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Study site personnel will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed. Any discrepancies must be accounted for on the appropriate forms.

7.7 Concomitant and other treatments

Any medications (with the detailed exceptions) which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the investigator, providing the medications, the doses, dates and reasons for administration are recorded.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded. This includes any blood transfusions.

The reasons for the use, doses and dates of treatment should be recorded in the patient's medical records

All medications (prescriptions or over the counter medications) continued at the start of study medication or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.

7.7.1 Medications that may NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy, radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication. Hormone replacement therapy (HRT) is acceptable.

Live virus and bacterial vaccines should not be administered whilst 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.

7.7.2 CYP3A4/5 restrictions

The use of any natural/herbal products or other "folk remedies" should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded.

Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. A phase I study to assess the effect of steady state itraconazole (a CYP3A4 Inhibitor) on the pharmacokinetics of olaparib following oral dosing of the tablet formulation has been conducted in patients with advanced solid tumours. Following a single oral administration of olaparib (100 mg tablet), AUC increased by 2.7-fold in combination with itraconazole compared with olaparib administered alone. Cmax also increased by 1.4-fold and

tmax was delayed by about 0.5 hour when olaparib was dosed in combination with itraconazole. (Astrazeneca internal report reference D0816C00007). A phase I study was also conducted in patients to investigate the effect of steady rifampicin, a potent CYP Inducer, on the pharmacokinetics of olaparib following a single oral dose (300 mg) of the tablet formulation. Results showed that olaparib Cmax decreased in the presence of rifampicin by about 71%. There was also an 87% reduction in AUC for olaparib in combination with rifampicin compared with olaparib alone. (Astrazeneca internal report reference D0816C00008).

In vitro data have also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4/5 and consequently, to ensure patient safety, the following potent inhibitors of CYP3A4/5 must not be used during this study for any patient receiving olaparib. While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, idnavir, saquinavir, telithromycin, clarithromycin and nelfinavir

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

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

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

For patients taking any of the above, the required wash-out periods prior to starting olaparib are phenobarbitone 5 weeks, and for any of the others, 3 weeks.

Olaparib can inhibit CYP3A4 and UGT1A1 in vitro. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 substrates or UGT1A1 substrates in the liver or gastrointestinal tract. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (e.g. irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).

7.7.3 **Other concomitant treatment**

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

7.7.4 Anti-emetics/ Anti-diarrheal

Should a patient develop nausea, vomiting and/or diarrhoea, then these symptoms should be reported as AEs (see section 6.2) and appropriate treatment of the event given.

7.7.5 Anticoagulant Therapy

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

7.7.6 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment.

Treatment with bisphosphonates or RANKL inhibitor for the prevention of skeletal related events in patients with bone metastasis is permitted and must be started at least 5 days prior to allocation.

7.7.7 Subsequent therapies for cancer

Details of first and subsequent therapies for cancer after discontinuation of treatment will be collected. Response to subsequent therapies and PFS on those therapies will also be collected.

The choice of subsequent systemic anticancer treatment will be entirely at the discretion of the investigator.

8. STATISTICAL ANALYSIS AND SAMPLE SIZE DETERMINATION

8.1 Statistical considerations

The primary endpoint is the objective response (i.e. CR or PR) achieved during the treatment. Simon's optimal two-stage design [Simon, 1989] will be implemented for the study. With an type I error rate α of 0.058 and a β error rate of 0.19, and assuming P0 (OR rate of standard drug treatment) and P1 (OR rate of new study treatment) are 5% and 20%, respectively, it is estimated that up to 34 patients will be enrolled in the study, with 15 patients in the first stage and 19 patients in the second stage. In the first step, if 0 or 1 response is observed among the first 15 patients treated, the study will be stopped for futility. However, if two or more responses are observed, then 19 additional patients will be enrolled onto the trial. The study drug will be considered of interest if ≥ 4 responders out of the 34 patients are observed. Based on this design, we estimate a 83% probability of early termination under the null hypothesis (i.e. ORR $\leq$ 5%). The expected sample size under the null hypothesis is 18.3. If the alternative hypothesis is true (i.e. ORR $\geq$ 20%), then the probability of early termination is 16.7%.

Further enrollment will continue during the interim analysis unless 0 or 1 responder has been reported by the time of enrollment of the 15th subject being analyzed. In this event, enrollment will be suspended and the first 15 subjects will be followed to further assess their responses. During this follow-up period, as soon as two or more responders among the 15 patients are observed, the enrollment will resume. If 0 or 1responder is observed after the 15 subjects have been fully assessed, the trial will be terminated for futility.

After the first 6 evaluable patients have completed 24 weeks of study treatment, and every 3 patients thereafter, a response/toxicity summary should be submitted to the IND Medical Monitor for review and approval. Enrollment will continue per protocol.

Toxicity monitoring

Unacceptable toxicities will also be monitored closely for the phase II portion of the study using the method of Thall et al. Denote the probability of unacceptable toxicity by T_E, where unacceptable toxicity is defined as treatment related grade 3 or higher toxicities. We assume $T_E \sim$ beta (0.3, 0.7). We will stop the enrollment if at any point $Pr(P_E > 0.30 \mid data) > 0.85$. That is, we will stop the trial if, at any time during the study, we determine that there is more than 85% chance that the unacceptable toxicity rate is more than 30%. This toxicity monitoring rule will be applied after the first 6 patients have been enrolled and evaluated. The corresponding stopping boundaries are to stop the trial if (number of patients with unacceptable toxicities / number of patients) ≥4/(6-8), 5/(9-10), 6/(11-13), 7/(14-16), 8/(17-19), 9/(20-21), 10/(22-24), 11/(25-27), 12/(28-30), 13(31-33). The operating characteristics are listed in table 7.

Table 7: OCs for unacceptable toxicity monitoring

True Prob(unacceptable tox)	Pr(stop)	mean # Pts (25%, 50%, 75%)
0.1	0.006	33.8 (34, 34, 34)
0.2	0.085	32.0 (34, 34, 34)
0.3	0.367	26.1 (13, 34, 34)
0.4	0.754	17.6 (7, 13, 33)
0.5	0.959	11.1 (6, 7, 13)

Multc Lean V2.1 was used for the toxicity monitoring design.

8.2 Statistical Analysis

8.2.1 Statistical analysis for the primary endpoint

For the primary analysis, patients who are eligible for the trial and receive any dose of olaparib will be included in estimating the response rate. Response outcome in the first 24

weeks will be used for primary analysis. If a patient does not achieve an objective response in the first 24 weeks, the patient will be considered as a non-responder. At any restaging, if there is progression per RECIST or if patient response cannot be assessed for any reason, that patient will be counted as a non-responder. The objective response rate and its corresponding exact 95% confidence interval (CI) will be estimated. If an objective response rate of 20% or more is observed in one cohort with at least 5 patients treated, then treatment is warranted in further study in that cohort.

8.2.2 Statistical analysis for the secondary endpoints

The Progression free survival (PFS) is defined as the time from the date of study entry to the date of progression or to the date of death from any cause, whichever occurred first, or to the last follow-up date if patients are alive without disease progression. If a patient did not have an event, PFS will be censored at the last date of contact. Overall survival (OS) is defined as the time from date of study entry to the date of death from any cause or to the date of last follow-up if patients are alive. If a patient is not known to have died, the OS will be censored at the last date of contact.

The Kaplan-Meier method will be used to estimate the probability of OS and the probability of PFS. The Log rank test and Cox proportional hazards models will be used to determine the association of OS or PFS with patient characteristics.

The CA 19-9 clinical response is defined as the percentage reduction before and after 8 weeks of treatment. The mean, standard deviation, median and range will be summarized for the percentage reduction of CA 19-9.

8.2.3 Statistical analysis for all the other demographic and clinical parameters

For categorical variables, frequencies and percentages will be tabulated. For continuous variables, ranges, medians, means and standard deviations will be calculated. Distributions for categorical variables will be compared by the Chi square test or by Fisher exact test. Test for normality will be done by Shapiro-Wilk normality test. The comparisons of continuous variables will be performed by either t test or Wilcoxon rank sum test, and by ANOVA or Kruskal-Wallis test. All statistical tests will be analyzed to a significance level of 0.05.

8.2.4. Safety analysis

All patients who received at least one dose of olaparib will be included in the safety analysis. Safety and tolerability will be assessed in terms of adverse events (AEs), deaths, laboratory data, vital signs and ECG. AEs and other categorical events will be tabulated using frequencies and percentages. Summaries will be tabulated by severity. Continuous safety outcomes will be summarized using descriptive statistics including mean, standard deviation, median and range.

8.2.5. Statistical analysis for exploratory correlative studies:

To visualize expression patterns of the 230 study HRD signature genes, hierarchical clustering

analysis will be performed based on Pearson correlation (or other distance measures) and will use average linkage algorithms, and the corresponding heat-map and dendrogram will be plotted. ANOVA will be use per gene to identify differentially expressed genes, with Beta-Uniform Mixture (BUM) model to control the false discovery rate (FDR) at 0.05 to adjust for multiple testing. In addition, Fisher's exact test and two sample t test will be used to compare incidence of *ATM* loss and gene expressions between responders and non-responders.

The incidence of *ATM* loss will be examined in the study population. Multivariable logistic regression will be used to evaluate the incidence of *ATM* loss after adjusting for the effects of covariates. Historical data suggest that the incidence of *ATM* loss in the study population is 25%.[32] We will confirm these findings and also use Kaplan Meier method to compare survival between the *ATM* high and loss groups and Cox regression to measure PFS and OS in the study subgroups.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first patient is entered into the study, Principal Investigator will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, monitor representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant

to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

– Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The monitor representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.2 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Q2 2015 & end by Q3 2016.

9.4 Data management

Data management of the trial conducted at MDACC will be performed by Department of Gastrointestinal Medical Oncology.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the **CTCAE v4**.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements at MDACC

10.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

MDACC investigators will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An Institutional Review Board (IRB)/Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to sponsor before enrollment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

Sponsor should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

Sponsor will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, Sponsor and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorised representatives a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements.

11. LIST OF REFERENCES

1. Ma J, Siegel R, Jemal A: Pancreatic cancer death rates by race among US men and women, 1970-2009. J Natl Cancer Inst 105:1694-700, 2013
2. Hidalgo M: Pancreatic cancer. N Engl J Med 362:1605-17, 2010
3. Von Hoff DD, Ervin T, Arena FP, et al: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369:1691-703, 2013
4. Von Hoff DD, Ramanathan RK, Borad MJ, et al: Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol 29:4548-54, 2011
5. Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817-25, 2011
6. Kaddis N, Saif MW: Second-line treatment for pancreatic cancer. JOP 15:344-7, 2014
7. Teo M, McDermott RS: Role of second-line chemotherapy in advanced pancreatic cancer and its influence on phase II/III study results. Ann Oncol 24:2462-3, 2013
8. Rahma OE, Duffy A, Liewehr DJ, et al: Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. Ann Oncol 24:1972-9, 2013
9. Easton DF, Matthews FE, Ford D, et al: Cancer mortality in relatives of women with ovarian cancer: the OPCS Study. Office of Population Censuses and Surveys. Int J Cancer 65:284-94, 1996
10. Lal G, Liu G, Schmocker B, et al: Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations. Cancer Res 60:409-16, 2000
11. Hahn SA, Greenhalf B, Ellis I, et al: BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 95:214-21, 2003
12. Friedenson B: BRCA1 and BRCA2 pathways and the risk of cancers other than breast or ovarian. MedGenMed 7:60, 2005
13. Couch FJ, Johnson MR, Rabe KG, et al: The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev 16:342-6, 2007
14. Shah MA, Kurtz RC: Upper gastrointestinal cancer predisposition syndromes. Hematol Oncol Clin North Am 24:815-35, 2010
15. Poplin E, Feng Y, Berlin J, et al: Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 27:3778-85, 2009
16. Heinemann V, Quietzsch D, Gieseler F, et al: Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 24:3946-52, 2006
17. Venkitaraman AR: Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell 108:171-82, 2002
18. Tutt A, Ashworth A: The relationship between the roles of BRCA genes in DNA repair and cancer predisposition. Trends Mol Med 8:571-6, 2002
19. Bryant HE, Schultz N, Thomas HD, et al: Specific killing of BRCA2-deficient tumors with inhibitors of poly(ADP-ribose) polymerase. Nature 434:913-7, 2005

20. van der Heijden MS, Brody JR, Dezentje DA, et al: In vivo therapeutic responses contingent on Fanconi anemia/BRCA2 status of the tumor. Clin Cancer Res 11:7508-15, 2005
21. Farmer H, McCabe N, Lord CJ, et al: Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434:917-21, 2005
22. Tutt AN, Lord CJ, McCabe N, et al: Exploiting the DNA repair defect in BRCA mutant cells in the design of new therapeutic strategies for cancer. Cold Spring Harb Symp Quant Biol 70:139-48, 2005
23. Cass I, Baldwin RL, Varkey T, et al: Improved survival in women with BRCA-associated ovarian carcinoma. Cancer 97:2187-95, 2003
24. Fogelman DR, Wolff RA, Kopetz S, et al: Evidence for the efficacy of Iniparib, a PARP-1 inhibitor, in BRCA2-associated pancreatic cancer. Anticancer Res 31:1417-20, 2011
25. Lowery MA, Kelsen DP, Stadler ZK, et al: An emerging entity: pancreatic adenocarcinoma associated with a known BRCA mutation: clinical descriptors, treatment implications, and future directions. Oncologist 16:1397-402, 2011
26. Brennan GT, Relias V, Saif MW: BRCA and pancreatic cancer. JOP 14:325-8, 2013
27. Oliver G. R. SE, Laheru D, Diaz L. A.: Family history of cancer and sensitivity to platinum chemotherapy in pancreatic adenocarcinoma. Gastrointestinal Cancers Symposium Abstract no:180, 2010
28. Javle M, Curtin NJ: The role of PARP in DNA repair and its therapeutic exploitation. Br J Cancer 105:1114-22, 2011
29. Drew Y, Mulligan EA, Vong WT, et al: Therapeutic potential of poly(ADP-ribose) polymerase inhibitor AG014699 in human cancers with mutated or methylated BRCA1 or BRCA2. J Natl Cancer Inst 103:334-46, 2011
30. Alexandrov LB, Nik-Zainal S, Wedge DC, et al: Deciphering signatures of mutational processes operative in human cancer. Cell Rep 3:246-59, 2013
31. Kim HS, Kim MA, Hodgson D, et al: Concordance of ATM (ataxia telangiectasia mutated) immunohistochemistry between biopsy or metastatic tumor samples and primary tumors in gastric cancer patients. Pathobiology 80:127-37, 2013
32. Kim H, Saka B, Knight S, et al: Having pancreatic cancer with tumoral loss of ATM and normal TP53 protein expression is associated with a poorer prognosis. Clin Cancer Res 20:1865-72, 2014
33. Weston VJ, Oldreive CE, Skowronska A, et al: The PARP inhibitor olaparib induces significant killing of ATM-deficient lymphoid tumor cells in vitro and in vivo. Blood 116:4578-87, 2010
34. Williamson CT, Kubota E, Hamill JD, et al: Enhanced cytotoxicity of PARP inhibition in mantle cell lymphoma harbouring mutations in both ATM and p53. EMBO Mol Med 4:515-27, 2012
35. Williamson CT, Muzik H, Turhan AG, et al: ATM deficiency sensitizes mantle cell lymphoma cells to poly(ADP-ribose) polymerase-1 inhibitors. Mol Cancer Ther 9:347-57, 2010
36. Peng G, Chun-Jen Lin C, Mo W, et al: Genome-wide transcriptome profiling of homologous recombination DNA repair. Nat Commun 5:3361, 2014
37. Bergfeldt K, Einhorn S, Rosendahl I, et al: Increased risk of second primary malignancies in patients with gynecological cancer. A Swedish record-linkage study. Acta Oncol 34:771-7, 1995

38. Beattie MS, Copeland K, Fehniger J, et al: Genetic counseling, cancer screening, breast cancer characteristics, and general health among a diverse population of BRCA genetic testers. J Health Care Poor Underserved 24:1150-66, 2013