Phase 2 Trial of Olaparib in Patients with Metastatic Urothelial Cancer Harboring DNA Damage Response Gene Alterations

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PROTOCOL SIGNATURE PAGE

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VERSION DATE: 15MAY2019

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

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Signature of Site Investigator Date

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Site Investigator Name (printed)

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Site Investigator Title

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Name of Facility

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Location of Facility (City and State)

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SYNOPSIS

TITLE	Phase 2 Trial of Olaparib in Patients with Metastatic Urothelial Cancer Harboring DNA Damage Response Gene Alterations
SHORT TITLE	Phase 2 Trial of Olaparib in Metastatic UC Patients
PHASE	2
OBJECTIVES	**Primary Objective** • Estimate the objective response rate (per RECIST 1.1 in patients with measurable disease and MD Anderson criteria in patients with bone-only metastases) to treatment with olaparib in subjects with metastatic urothelial cancer harboring somatic DDR alterations. **Secondary Objectives** • Describe the safety of olaparib in subjects with DDR mutant metastatic urothelial cancer. • Describe the progression-free survival of subjects with DDR mutant metastatic urothelial cancer treated with olaparib. • Describe the overall survival of subjects with DDR mutant metastatic urothelial cancer treated with olaparib. **Exploratory Objectives** • Explore the relationship between specific genomic alterations with response to olaparib. • Explore the relationship between prior platinum-based chemotherapy treatment (response, duration of treatment, and time since treatment) with response to olaparib. • Explore the relationship between tumor mutational profile, circulating DNA mutational profile, and response to olaparib. • Determine the feasibility of establishing patient-derived xenografts from circulating tumor cells collected from enrolled subjects at baseline and progression to better explore mechanisms of response and resistance.

STUDY DESIGN	This is a single arm open label multi-institutional phase II trial of olaparib monotherapy in subjects with metastatic urothelial cancer harboring DDR alterations. The primary objective of the study is to estimate the objective response rate (per RECIST 1.1) to treatment with olaparib.
ELIGIBILITY CRITERIA (See Section 3 for full eligibility criteria)	**Inclusion Criteria** 1. Written informed consent and HIPAA authorization for release of personal health information prior to registration. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately. 2. Age ≥ 18 years at the time of consent. 3. ECOG Performance Status of ≤ 1 within 14 days prior to registration. Cisplatin-ineligible chemotherapy-naïve subjects (see inclusion criteria #9) may have an ECOG Performance Status of ≤ 2. 4. Histological or cytological evidence/confirmation of urothelial cancer. 5. Metastatic and/or unresectable (cT4b) urothelial cancer. 6. Metastatic disease evaluable on imaging studies. Subjects may have measurable disease according to RECIST 1.1 or bone-only disease within 30 days prior to registration. **NOTE**: Bone-only subjects are eligible if their disease can be documented/ evaluated by bone scans, CT or MRI. Their disease will be assessed using MD Anderson criteria.[34] **NOTE**: Previously irradiated lesions are eligible as a target lesion only if there is documented progression of the lesion after irradiation. 7. Somatic alteration considered pathogenic/likely pathogenic in one of the following DDR genes as determined by genomic sequencing performed in a Clinical Laboratory Improvement Amendments (CLIA) laboratory. Somatic alterations will include nonsense, frameshift, splice-site or missense mutations or homozygous deletions. Subjects with alterations in DDR genes not included in the list below will be considered on a case by case basis after discussion with the sponsor-investigator. Subjects with germline alterations in DDR genes will be considered on a case by case basis and will be reviewed by the sponsor-investigator. At least 6

subjects will have BRCA or ATM alterations.

Nucleotide Excision Repair	Homologous Recombination		Base Excision Repair	Other
ERCC2	BRCA1	RAD52	XRCC2	MUTYH
ERCC3	BRCA2	RAD54L	XRCC3	RECQL4
ERCC4	RAD50	NBN	XRCC4	POLQ
ERCC5	RAD51	MRE11A	XRCC5	POLE
ERCC6	RAD51B	RAD51D	XRCC6	WRN
	RAD51C	CTIP		

DNA Sensor	Fanconi Anemia Pathway	
ATM	PALB2	FANCE
ATR	BRIP1	FANCF
MDC1	FANCA	FANCG
ATRX	FANCB	BLM
CHEK1	FANCC	
CHEK2	FANCD2	

8. A subject with prior brain metastasis may be considered if they have completed their treatment for brain metastasis at least 4 weeks prior to study registration, have been off of corticosteroids for ≥ 2 weeks, and are asymptomatic.

9. Subjects must have progressed despite at least 1 prior line of treatment for metastatic and/or unresectable urothelial cancer. However, cisplatin-ineligible (defined by a calculated creatinine clearance of > 30 but < 60 mL/min OR CTCAE v4 Grade ≥ 2 audiometric hearing loss OR CTCAE v4 Grade ≥ 2 peripheral neuropathy OR ECOG PS = 2), chemotherapy-naïve subjects are also eligible.

10. Prior cancer treatment (systemic therapy or radiation therapy) must be completed at least 3 weeks prior to registration and the subject must have recovered from all reversible acute toxic effects of the regimen (other than alopecia) to Grade ≤ 1 or baseline.

11. Demonstrate adequate organ function. All screening labs to be obtained within 28 days prior to registration.
    - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
    - Hemoglobin (Hgb) ≥ 9 g/dL
    - Platelets ≥ 100 x 109/L
    - Calculated creatinine clearance[1] > 30 mL/min
    - Bilirubin ≤ 1.5 × upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) ≤ 2.5 × ULN (or ≤ 5 × ULN if liver metastases)

	12. Female subjects must be postmenopausal or there must be evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on day 1. Postmenopausal is defined as: • Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments • Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50 • radiation-induced oophorectomy with last menses >1 year ago • chemotherapy-induced menopause with >1 year interval since last menses • surgical sterilization (bilateral oophorectomy or hysterectomy) 13. Females of childbearing potential must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 90 days after treatment discontinuation. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method. Males must be willing to abstain from heterosexual activity or to use 2 forms of effective contraception from the time of informed consent until 90 days after treatment discontinuation. 14. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study 15. All subjects must have adequate archival tissue available prior to registration (i.e., at least 15 unstained slides or paraffin block). Archival tissue should represent invasive or metastatic urothelial cancer with a preference for metastatic tissue if available. Archival tissue should be identified at screening and shipped by C1D1. Subjects without adequate tissue may be considered on a case by case basis after discussion with the sponsor-investigator. **Exclusion Criteria** 1. Active infection requiring systemic therapy. 2. Pregnant or breastfeeding

	3. Known additional malignancy that is active and/or progressive requiring treatment; subjects with other malignancies that have been definitively treated and who have been rendered disease free will be eligible. 4. Prior treatment with a PARP inhibitor, including olaparib. 5. Treatment with any investigational drug within 30 days prior to registration. 6. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). 7. Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome. 8. Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks. 9. Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents. 10. Subjects with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML. 11. Major surgery within 2 weeks of starting study treatment and subjects must have recovered from any effects of any major surgery. 12. Subjects considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular

	arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan, history of pneumonitis, or any psychiatric disorder that prohibits obtaining informed consent. 13. Subjects unable to swallow orally administered medication and subjects with gastrointestinal disorders likely to interfere with absorption of the study medication. 14. Immunocompromised subjects, e.g., subjects who are known to be serologically positive for human immunodeficiency virus (HIV). 15. Subjects with a known hypersensitivity to olaparib or any of the excipients of the product. 16. Subjects with known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids. 17. Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
TOTAL NUMBER OF SUBJECTS/ SITES	N = 30 Utilizing sites within Hoosier Cancer Research Network
ESTIMATED ENROLLMENT PERIOD	Estimated 36 months
ESTIMATED STUDY DURATION	Estimated 48 months

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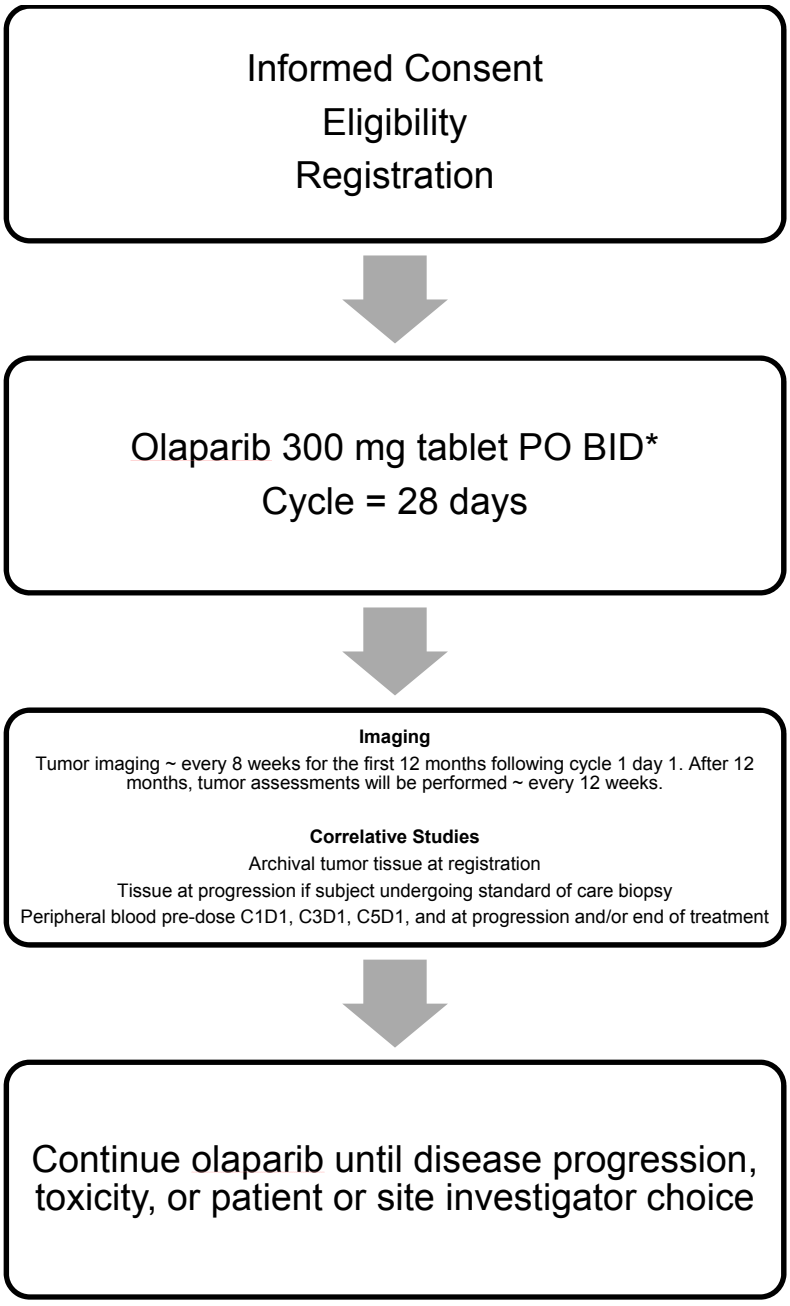
SCHEMA



*The starting dose of olaparib will be 300 mg PO BID. Subjects with a calculated creatinine clearance of > 30 to < 40 mL/min will start at a dose of olaparib tablets 200 mg twice a day.

1. BACKGROUND AND RATIONALE

1.1 Disease Background

Each year in the United States, an estimated 77,000 adults are diagnosed with urothelial cancer of the bladder and approximately 16,400 patients succumb to the disease.[1] Urothelial cancer of the bladder is the fourth most common cancer diagnosed in men in the United States. While the majority of patients with urothelial cancer of the bladder present with clinically localized disease, approximately 30% of patients present with muscle-invasive disease which has a high propensity for metastatic spread despite local therapy with curative intent. Furthermore, approximately 5% of patients harbor metastatic disease at the time of diagnosis.

1.2 Current Standard of Care

While metastatic urothelial cancer is a relatively chemotherapy sensitive neoplasm with response rates to first-line platinum-based chemotherapy of approximately 40-60%, responses are generally short-lived and the median progression free survival is only 8-9 months.[2] In 2016, the PD-L1 inhibitor atezolizumab became the first treatment approved by the United States Food and Drug Administration for patients with platinum-resistant metastatic urothelial cancer.[3] However, durable responses to single-agent PD-1/PD-L1 blockade are only achieved in a small minority of patients with metastatic urothelial cancer (approximately 15-20% of patients) highlighting the critical need for the development of additional novel therapeutic strategies.[3–6]

1.3 DNA Damage Response Gene Alterations in Urothelial Cancer

High throughput comprehensive genomic analyses of solid tumors, including urothelial cancer, have uncovered recurrent somatic alterations providing clues to disease pathogenesis and identifying potential therapeutic targets. Indeed, analysis of data from 389 urothelial cancer specimens from The Cancer Genome Atlas[7] reveals deleterious (nonsense, frameshift, splice site, or hotspot point mutations) alterations in DNA damage response genes (DDR) in ~28% of specimens (Figure 1). At least four studies have now demonstrated the potential clinical relevance of DDR alterations in urothelial cancer.[8–11] In an analysis of a cohort of 50 patients with muscle-invasive bladder cancer (25 patients achieving a pathologic complete response and 25 patients not achieving a pathologic complete response with neoadjuvant cisplatin-based chemotherapy), Van Allen and colleagues performed whole exome sequencing on the initial transurethral resection of bladder tumor (TURBT) specimens and demonstrated that the presence of mutations in *ERCC2* were found exclusively in the patients achieving a pathologic complete response.[9] *ERCC2* encodes a nucleotide excision repair protein which is critical for repair of DNA damage resulting from platinum-based chemotherapy. The correlation between *ERCC2* mutations and pathologic complete response to platinum-based chemotherapy was subsequently validated in an independent cohort.[10] Plimack et al performed targeted exome sequencing on a cohort of patients with muscle-invasive bladder cancer treated with dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) chemotherapy.[11] These investigators demonstrated that alterations in one or more of three DDR genes (ATM, RB1, and FANCC) predicted pathologic complete response ($p<0.001$, 87% sensitivity, 100% specificity) and better overall survival ($p=0.007$). Iyer and colleagues performed targeted exome sequencing on a cohort of patients with muscle-invasive bladder cancer treated on a phase 2 trial of neoadjuvant dose-dense gemcitabine plus cisplatin.[8] Mutations in a set of 29 DDR genes were correlated with a higher probability of achieving pathologic complete response. Deleterious DDR gene

mutations were associated with achieving a pathologic complete response with 92% specificity and a positive predictive value of 88%. Such mutations were present in 26% of patients and included mutations in *ERCC2, ERCC5, BRCA2, RAD51C, ATR, CHEK2, and RECQL4*. Together, these data indicate that (a) deleterious DDR alterations are common in urothelial cancer and (b) DDR alterations may be relevant to selection of therapies in the clinic. Additional approaches to exploit these vulnerabilities in a "targeted" fashion are needed.

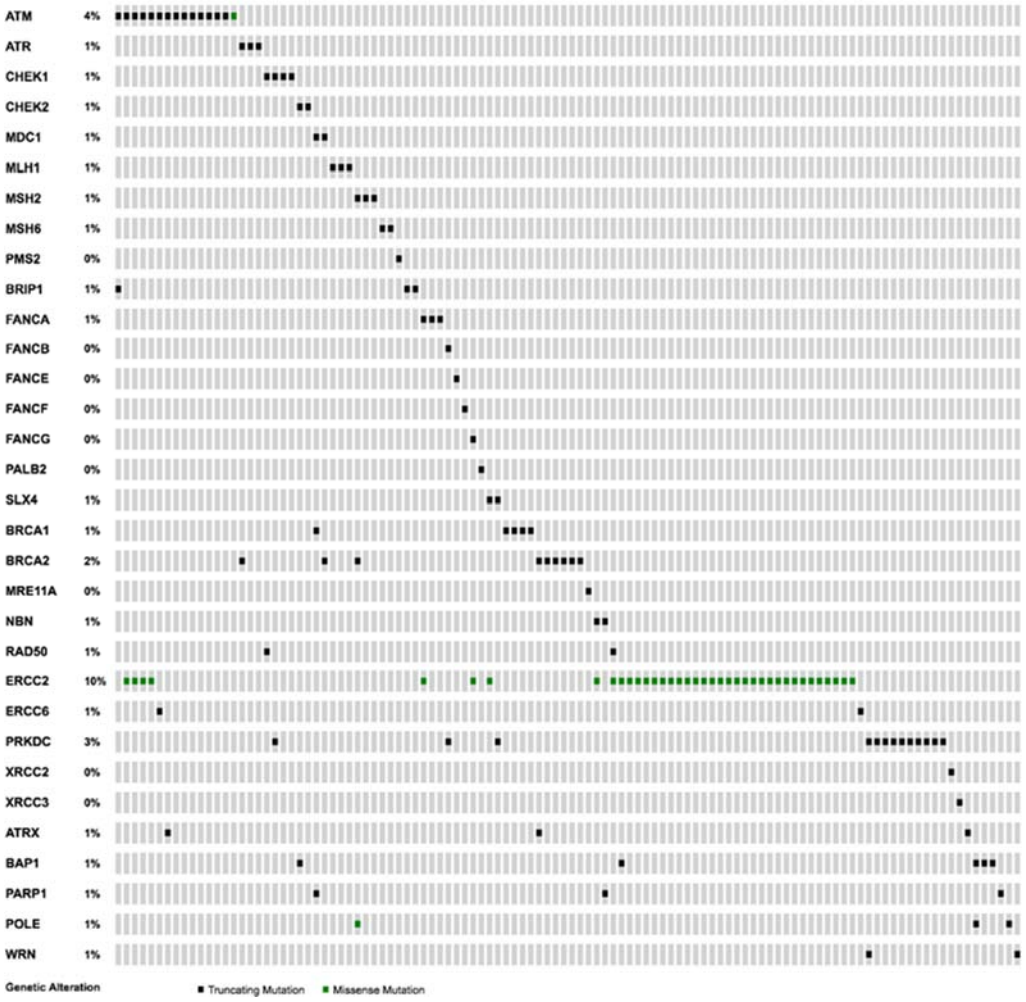


Figure 1. Deleterious DNA Damage Response Gene Alterations in TCGA Urothelial Cancer Dataset

1.4 Targeting Poly ADP Ribose Polymerase (PARP) in DDR mutant Tumors

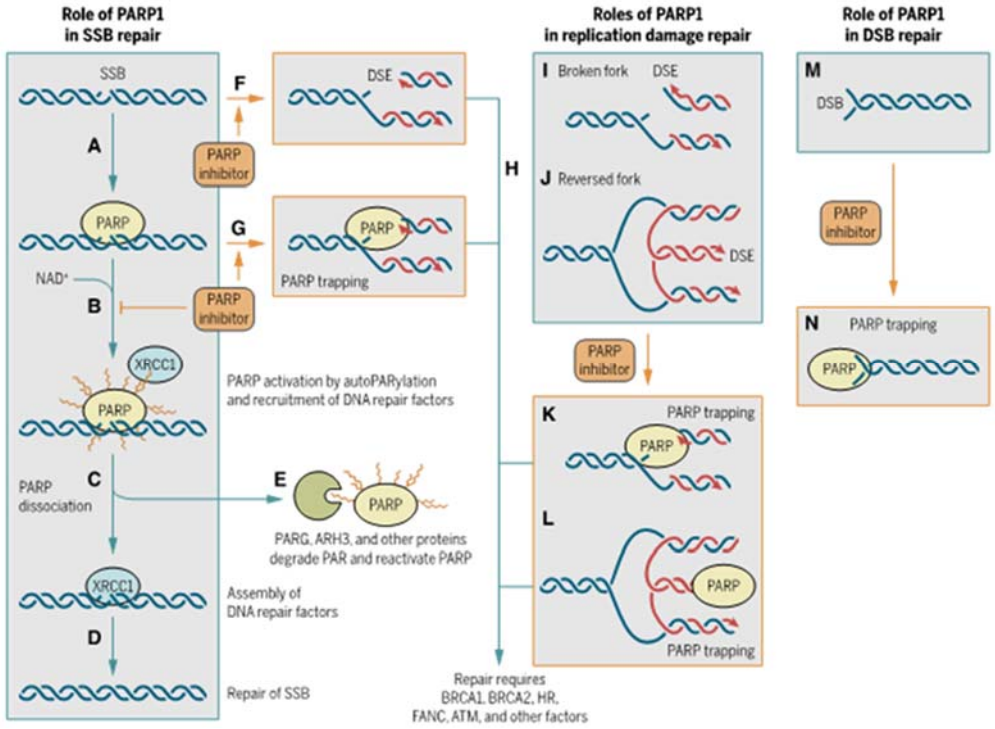


Figure 2. DNA repair by PARP1 and the effects of PARP inhibitors (from Pommier et al, Science Translational Medicine, 2016)

PARP1 plays multiple key roles in the repair of DNA damage including single strand breaks (SSB), double strand breaks (DSB), and replication fork damage.[12] The role for PARP inhibition as monotherapy is based on the concept of synthetic lethality where neither PARP inhibition alone nor DDR mutations alone are lethal but the combination results in lethal cellular damage. This concept was initially based on the hypothesis that unrepaired SSBs resulting from PARP inhibition would be converted into more genotoxic single-ended DSBs (DSEs) in replicating cells. These DSEs could theoretically be repaired effectively in normal cells with functional homologous recombination repair. However, cells with DDR mutations, such as homologous recombination repair deficiencies, would only have low-fidelity repair pathways intact leading to increase in genomic instability and tumor-specific cell death.

Emerging evidence suggests that the mechanistic basis for synthetic lethality with PARP inhibition is likely more complex and PARP trapping may play a critical role.[13] The concept of PARP trapping was invoked to explain why the cytotoxicity of PARP inhibition was greater than that of genetic loss of PARP1 in model systems and why the cytotoxic activity of PARP inhibitors was abrogated by genetically removing PARP1. PARP trapping was demonstrating by detecting PARP-DNA complexes in cells treated with PARP inhibitors. PARP1 and PARP2 are effectively trapped on DNA until the inhibitor dissociates from the active site. PARP trapping is markedly more deleterious than persistent SSBs. While the basis for the cytotoxicity of PARP inhibition is not fully elucidated, one possibility is that ongoing replication forks collide with

trapped PARP-DNA complexes leading to stalled replication forks which generate DSEs also known as “replication fork collapse”.

1.5 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

Tumors with HR deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens. Indeed, BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models *in vivo* and in the clinic.[14–16] The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair as described in Section 1.4.[13,17] Olaparib has been shown to inhibit selected tumor cell lines *in vitro* and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

The capsule formulation of olaparib was approved in December 2014 by the European Commission (EC) and United States (US) Food and Drug Administration (FDA), as follows:

EU indication: Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

US indication: Lynparza is indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

1.5.1 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib Investigator’s Brochure (IB).

1.5.2 Toxicology and safety pharmacology summary

The toxicology and safety pharmacology is fully described in the current version of the olaparib Investigator’s Brochure (IB).

1.5.3 Clinical experience

The olaparib capsule formulation was registered for use in the EU and US in December 2014. The recommended olaparib monotherapy capsule dose is 400 mg bid. As of 15 June 2016, >5670 patients with ovarian, breast, pancreatic, gastric and a variety of other solid tumors are estimated to have received treatment with olaparib in clinical studies as either monotherapy or in combination with other chemotherapy/anti-cancer agents. The Phase III registration studies and

most new clinical studies are investigating the tablet formulation which delivers the therapeutic dose of olaparib in fewer dose units than the capsule.

The clinical experience with olaparib is fully described in the current version of the olaparib Investigator's Brochure. A large number of clinical studies with olaparib to date have explored the efficacy of olaparib in patients with germline mutations in BRCA. Particularly relevant to the current study is the experience with olaparib in patients with prostate cancer harboring germline and/or somatic DDR alterations. The TOPARP study enrolled 50 patients with castration-resistant metastatic prostate cancer.[18] Targeted next-generation sequencing, exome and transcriptome analysis, and digital polymerase-chain-reaction testing were performed on samples from mandated tumor biopsies. Sixteen of 49 patients who could be evaluated achieved a response (33%; 95% CI 20-48). Next-generation sequencing identified homozygous deletions, deleterious mutations, or both, in DDR genes (including *BRCA1/2*, *ATM*, Fanconi's anemia genes, and *CHEK2*) in 16 of 49 patients who could be evaluated (33%). Of these 16 patients, 14 (88%) achieved a response to olaparib, including all 7 patients with *BRCA2* loss (4 with biallelic somatic loss, and 3 with germline mutations) and 4 of 5 with *ATM* aberrations.

1.5.4 Safety

This section lists those adverse events and laboratory abnormalities that are currently regarded as expected. A full description of the emerging safety profile for olaparib, with guidance for investigators, is provided in Section 6.

Administration of olaparib monotherapy has been associated with reports of the following laboratory findings and/or clinical diagnoses, generally of mild or moderate severity (CTCAE Grade 1 or 2) and generally not requiring treatment discontinuation.

Adverse Drug Reactions reported in Clinical Trials

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE Grade 3 and above
Blood and lymphatic system disorders	Anemia[a]	Very common	Very common
	Neutropenia[a]	Common	Common
	Thrombocytopenia[a]	Common	Common
	Leukopenia[a]	Common	Common
	Lymphopenia[a]	Uncommon	Uncommon
Immune system disorders	Rash[a]	Common	-
	Hypersensitivity[a]	Uncommon	-
	Dermatitis[a]	Uncommon	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon

Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia	Very common	-
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhea	Very common	Common
	Nausea	Very common	Common
	Dyspepsia	Very common	-
	Stomatitis	Common	Uncommon
	Upper abdominal pain	Common	Uncommon
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Increase in creatinine	Common	Uncommon
	Mean corpuscular volume elevation	Uncommon	-

[a] Anemia includes PTs of anemia, hemoglobin decreased, red blood cell count decreased, and hematocrit decreased; Neutropenia includes PTs of neutropenia, granulocytopenia, granulocyte count decreased and neutrophil count decreased, febrile neutropenia and neutropenic sepsis; Thrombocytopenia includes PTs of thrombocytopenia, platelet count decreased and plateletcrit decreased; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Rash includes PTs of rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, exfoliative rash and generalized erythema; Hypersensitivity includes PTs of hypersensitivity and drug hypersensitivity; Dermatitis includes PTs of dermatitis, dermatitis allergic and dermatitis

CIOMS Council for International Organizations of Medical Sciences; CTCAE Common Terminology Criteria for Adverse Events v.3.0; MedDRA Medical Dictionary for Regulatory Activities; SOC System organ class.

The safety profile of olaparib is further highlighted by the SOLO-2 trial which randomized patients with platinum-sensitive ovarian cancer received olaparib 300 mg tablets BID versus placebo.

Adverse Reactions in SOLO-2 trial (≥20% of Patients who received Olaparib)

Adverse Reactions	Olaparib tablets (n=195)		Placebo (n=99)	
	Grade 1-4 %	Grade 3-4 %	Grades 1-4 %	Grades 2-4 %
Blood and lymphatic disorders				
Anemia	44	20	9	2
Gastrointestinal disorders				
Nausea	76	3	33	0
Vomiting	37	3	19	1
Diarrhea	33	2	22	0

Stomatitis	20	1	16	0
Infections and Infestations				
Nasopharyngitis/URI/sinusitis/ rhinitis/influenza	36	0	29	0
General disorders and administration site conditions				
Fatigue including asthenia	66	4	39	2
Metabolism and nutrition disorders	22	0	11	0
Musculoskeletal and connective tissue disorder	30	0	28	0
Nervous system disorders				
Dysgeusia	27	0	7	0
Headache	26	1	14	0

Laboratory abnormalities in SOLO-2 trial (≥25% of Patients who received Olaparib)

Adverse Reactions	Olaparib tablets (n=195)		Placebo (n=99)	
	Grade 1-4 %	Grade 3-4 %	Grades 1-4 %	Grades 2-4 %
Increase in mean corpuscular volume	89	-	52	-
Decrease in hemoglobin	83	17	69	0
Decrease in leukocytes	69	5	48	1
Decrease in lymphocytes	67	11	37	1
Decrease in absolute neutrophil count	51	7	34	1
Increase in serum creatinine	44	0	29	0
Decrease in platelets	42	2	22	1

1.5.5 Summary of Risks

As of 15 June 2016, approximately 5670 patients with ovarian, breast, pancreatic, gastric and a variety of other solid tumors are estimated to have received treatment with olaparib in AstraZeneca-sponsored, investigator-sponsored, collaborative group studies and a Managed Access Program. Olaparib has been given as either monotherapy (an estimated 3624 patients) or in combination with other chemotherapy/anti-cancer agents (an estimated 2046 patients). An estimated 2343 patients to date have received the capsule formulation of olaparib. Since 2012/2013, most new clinical studies have utilized the tablet formulation which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. An estimated 3300 patients to date have received the tablet formulation and 27 patients have received both formulations of olaparib. Approximately 1500 patients have received comparator or placebo across the olaparib development program.

From the available data to date, there is no evidence of any unexpected toxicity following long-term olaparib (capsule) monotherapy exposure. An analysis of data from 12 AstraZeneca-sponsored capsule monotherapy studies (D0810C00001, D0810C00002, D0810C00007, D0810C00008, D0810C00009, D0810C00012, D0810C00019, D0810C00020, D0810C00024 [capsule data], D0810C00042, D9010C0008 and D081AC00001) in 766 patients with ovarian cancer (398/766 [52%]) and other non-ovarian solid tumors (368/766 [48%]) who received

olaparib capsule at a range of doses, estimated that 18.3% (140/766) of patients had been exposed to olaparib (capsule) for >12 months, 9.4% (72/766) for >18 months, 5.4% for >24 months, 3.3% for >36 months and 2.6% for >48 months (as of 08 August 2016). Eighteen patients (2.3%) had received ≥60 months of olaparib exposure.

An estimated 360 patients (all on tablet) have also received olaparib from 11 investigator-sponsored monotherapy studies/collaborative group studies.

1.5.6 Serious adverse events

A review of the AstraZeneca Patient Safety database (which includes AstraZeneca-sponsored, investigator-sponsored/collaborative group monotherapy studies and Managed Access Program reports) as of 15 June 2016 identified a total of 1413 SAEs (1093 unblinded, 320 blinded) received from 752 patients in olaparib monotherapy studies. SAE reports of ≥1% (≥36 patients treated with olaparib/placebo monotherapy) were anemia (n=143), abdominal pain (n=40), vomiting (n=47), nausea (n=42) and dyspnea (n=41). The most commonly reported SAEs from these monotherapy studies were similar for the tablet and capsule formulation.

1.5.7 Other adverse events of interest

Myelodysplastic syndrome/acute myeloid leukemia events

As of 15 June 2016, 23 reports of MDS and/or AML have been received out of a total of 5670 patients estimated to have received olaparib in the clinical study program, giving an estimated cumulative incidence of 0.41% for MDS/AML. Six additional reports of MDS/AML from 6 patients have been received from 2 blinded studies (D0816C00002 and D0818C00001) in which the treatment of the 6 patients (olaparib or placebo) is unknown. If these patients are considered to have been on olaparib treatment, the estimated incidence would be 0.51%.

MDS was also reported for 2 patients who were known to have received placebo or comparator in the olaparib trial program (1 patient received placebo in Study D0810C00019 and 1 patient received liposomal doxorubicin in Study D0810C00012). Of the 23 olaparib-treated patients and 6 patients on blinded treatment, the MDS/AML events have been reported in patients receiving a range of doses from both monotherapy and combination studies and for a variety of tumor types; ovarian, peritoneal or fallopian tube cancer (n= 26), breast cancer (n=1) and pancreatic cancer (n=2). Twenty-one of the 29 patients died: in 12 of these patients, MDS/AML or myelodysplasia was recorded as either a primary or secondary cause of death. The other 9 deaths were reported as follows: 1 due to cerebral hemorrhage and disseminated intravascular coagulation, 1 due to complication of bone marrow transplant, 1 due to hemothorax and 6 due to disease progression (4 ovarian cancer, 1 breast cancer [patient had a prior history of ovarian cancer treated with platinum-based chemotherapy] and 1 pancreatic cancer). In 16 patients, the event of MDS/AML is reported as not recovered (including patients that died of other causes). In 1 patient, the outcome was unknown.

Of the 23 olaparib-treated and 6 blinded treatment patients subsequently diagnosed with MDS/AML, the diagnosis occurred while receiving study treatment or within 60 days after study treatment discontinuation in 12 patients, more than 60 days and <120 days after study treatment discontinuation in 2 patients, more than 120 days and <240 days after study treatment discontinuation in 2 patients, and more than 240 days after study treatment discontinuation in 4

patients. Time to onset of MDS/AML was not reported in 9 patients. The duration of therapy with olaparib/blinded treatment in patients with MDS/AML reported was <6 months in 16 patients, 6 to 12 months in 4 patients, 12 to 18 months in 1 patient, 18 to 24 months in 1 patient, and >2 years in 5 patients. Duration of therapy with olaparib/blinded treatment was not reported in 2 patients. All patients had other potential features that may be contributing factors for the development of MDS/AML. All patients had received previous chemotherapy with DNA damaging agents including platinum, with many patients having extensive previous chemotherapy with multiple treatment regimens over multiple years including carboplatin, taxanes, anthracyclines, other alkylating and DNA damaging agents and radiotherapy. Twenty-four patients had a documented gBRCA mutation of whom 2 patients were known to be gBRCA wild type. In 5 patients, the BRCA mutation status was unknown. While information from bone marrow examination is not available for all reports, in 12 cases cytogenetic abnormalities typical of therapy–related MDS (abnormalities of chromosomes 5 and 7 and complex karyotypes) were reported.

Therapy-related AML (t-AML) is a rare and fatal complication of cytotoxic chemotherapy, which is often preceded by the development of secondary MDS. MDS is poorly captured in cancer registration, as it is not always considered to be a cancer so it is difficult to quantify background incidence rates from large, population based registries, including Surveillance, Epidemiology, and End Results (SEER).[19–22] Furthermore, changing International Classification of Diseases coding conventions and definitions of primary and secondary MDS, under-diagnosis and under reporting to registries are likely an underestimation of the true incidence as incidence rates based on cancer registries may be 2 to 3 times lower than the actual incidence rate.[21]

A recent study investigated the incidence and risk of developing t-AML in 426,068 adults initially treated with chemotherapy for a first primary malignancy between 1975 and 2008. The study identified 801 tAML cases; this was 4.70-times more than expected in the general population ($p<0.001$).[23] In an earlier study, using the US SEER database, 109 AML cases were identified among 63,359 epithelial ovarian cancer cases, with an overall incidence of 0.17%.[24] The median time to onset of t-AML from ovarian cancer diagnosis is reported as approximately 5.5 years.[24] The overall standardized incidence ratio (8.68 overall) varies over time - 12.07 within 1 to 5 years, 10.81 within 5 to 10 years and 2.30 after 10 years.[23]

There is some evidence that the risk of MDS/AML may be increased in patients with BRCA mutation[25,26], but published data are not available to quantify this risk in BRCA mutated ovarian cancer due to the rarity of the event coupled with the small population of interest, and lack of routine BRCA mutation screening. The development of t-AML in recurrent ovarian cancer has been linked with the use of DNA-damaging therapies, specifically pelvic radiation, alkylating agents and platinum chemotherapies. [23,27–29] The risk of developing t-AML (and secondary MDS) is associated with the cumulative dose and duration of treatment. Travis et al reported an increasing relative risk after platinum therapy rising from 1.9 to 7.6 with doses <500 g to >1000 mg, and from 1.2 to 7.0 with treatment duration rising from <6 months to >12 months.[29] Morton et al reported a reduction of risk in the period 1975 to 1983, due to a shift in treatment from pelvic irradiation and melphalan to platinums, while in the period 1983 to 2008, over which time treatments shifted from cisplatin to carboplatin and taxanes were introduced, the excess risk has remained approximately stable.[23] In order to minimize the potential risk for MDS/AML,

additional safety measures have been incorporated into the Phase III program: specified hematological values are required before inclusion into the studies and regular monitoring is continued while on treatment to detect hematological abnormalities early. In case of prolonged cytopenias, patients are to be referred to a hematologist and bone marrow analysis should be considered. If a diagnosis of MDS/AML is confirmed, study treatment must be discontinued and the event, treatment, course and outcome must be reported as an SAE.

Evidence from across the development program for olaparib does not support a conclusion that there is a causal relationship between olaparib and MDS/AML. All patients had other potential features that may be contributing factors for the development of MDS/AML. This important potential risk for olaparib is being kept under close surveillance.

New primary malignancies
As of 15 June 2016, 23 patients (reporting 25 events) out of a total of 5670 patients estimated to have received olaparib in the clinical program have reported a new primary malignancy (other than MDS/AML), giving a cumulative incidence of 0.41% for new primary malignancies. Eleven additional reports of New Primary Malignancies (NPM) have been received from 4 blinded studies in which the treatment of the patient (olaparib or placebo) is unknown. If these patients were considered to have been on olaparib treatment, the estimated incidence would be 0.60%.

One event (bladder cancer) has been reported in the placebo arm of the double-blind Study D0810C00019 (1/128 [0.78%]).

The new primary malignancies were reported in patients receiving a range of doses from both monotherapy and combination studies and for a variety of tumor types, ovarian (n=24), breast (n=3), and one each of the following: pancreas, chronic lymphocytic leukemia, biliary tract, colorectal cancer, gastric cancer, lung cancer and prostate cancer.

The types of new primary malignancies reported in these 34 patients (36 events) were breast cancer (11), basal cell carcinoma (6), squamous cell carcinoma (2), skin cancers (2), gastric cancer (2), lung cancer (2) and one each of: colon cancer, plasma cell myeloma, malignant melanoma, malignant muscle neoplasm, precursor T lymphoblastic lymphoma/leukemia, tongue cancer, papillary thyroid carcinoma, rectal cancer, ovarian cancer, chronic myelomonocyctic leukemia and bladder transitional cell carcinoma.

Four spontaneous events of new primary malignancy have been received from 3 patients in the post marketing setting. The patients concerned were reported to have developed: peritoneal neoplasm in 1 patient, pancreatic cancer in 1 patient and 1 patient with gastric and renal cancers.

Eleven of the 25 events of new primary malignancies reported by 10 olaparib-treated patients were skin cancers (2 SAEs, 9 AEs). Ten of these were the most common forms of non-melanoma skin cancer; basal cell carcinoma (n=6), squamous cell carcinoma (n=2), skin cancer (n=1) and skin neoplasm (n=1). One event of malignant melanoma was reported for a patient treated for chronic lymphocytic leukemia in an investigator-sponsored study. This patient had previously presented with a pigmented skin lesion 12 months prior to starting olaparib treatment. The lesion increased in size while on study treatment but the investigator did not consider it causally related

to olaparib treatment. Following surgery, the melanoma was removed and the event was reported as recovered by the investigator. The skin cancers recovered in the majority of patients.

Of the 34 patients (23 on olaparib, 11 on blinded treatment) subsequently diagnosed with a new primary malignancy, the majority of events were reported whilst on olaparib treatment. In 4 patients, the new primary malignancy was reported after the follow-up period of the study (>1 year, 68 days, 49 days and 34 days and respectively from stopping olaparib treatment). The time from start of olaparib treatment to the onset of the 36 events was <6 months for 7 patients, 6 to 12 months for 12 patients, 12 to 18 months for 2 patients, 18 to 24 months for 6 patients and >2 years for 9 patients.

There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all of the 23 olaparib-treated patients and the 11 on blinded treatment. All patients had already 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. Twenty-five patients had a documented breast cancer gene mutation (BRCA 1 or 2). Seven patients had previous medical histories of cancer (ovarian, cervix, breast, peritoneal) prior to the cancer under investigation in the olaparib studies, and 3 patients with skin cancers had either had previous basal cell carcinoma reported or had skin lesions evident prior to study treatment.

There is insufficient evidence for an association between olaparib treatment and the development of new primary malignancies in the clinical study program to date. The types of new primary cancers reported were generally in line with secondary cancers observed in ovarian and breast cancer populations reported in the literature or were cancers such as, skin cancers known to be the most common cancer in the general population and associated with high cure rates.[30,31] Patients with gBRCA mutations are at risk of developing other primary cancers notably breast cancer. Ginsburg et al 2010 reported higher rates of skin cancers in patients with BRCA1 (1.6%) and BRCA2 (3.0%) mutations.[32] All patients had other contributory factors that offer alternative explanations for the development of the secondary primary tumor including documented BRCA mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. This safety topic is an important potential risk for olaparib and is being kept under close surveillance. The ongoing placebo-controlled Phase III studies will be important in providing additional information.

Pneumonitis events
As of 15 June 2016, pneumonitis has been reported in 22 olaparib-treated patients out of a total of 5670 patients estimated to have received olaparib in the clinical study program, giving an estimated cumulative incidence of 0.39%. Eleven additional reports of pneumonitis have been received from 4 blinded studies, where the treatment of the patients is unknown (7 either olaparib or placebo [D0816C00002 or D0818C00001]; 2 either olaparib + paclitaxel or placebo + paclitaxel [D081BC00004] and 2 olaparib + abiraterone or placebo + abiraterone [D081DC00008]). If these patients were considered to have been on olaparib treatment, the estimated cumulative incidence would be 0.58% (33/5670).

Pneumonitis has also been reported for 1/128 (0.78%) patient randomized to placebo in Study D0180C00019, 1/62 (1.61%) patient randomized to placebo + paclitaxel in a double-blind study in recurrent or metastatic gastric cancer (Study D0810C00039) and 1/262 (0.38%) patient randomized to placebo + paclitaxel in a double-blind, phase III study in advanced gastric cancer (Study D081BC00004).

The reports of pneumonitis were from patients receiving olaparib at a range of doses, given either as monotherapy or in combination with the other chemotherapy treatments. The diagnosis of pneumonitis was made while on treatment or within a 60-day follow-up period for all patients. The patients were treated with olaparib for ovarian cancer (n=14), breast cancer (n=4), NSCLC or small cell lung cancer (SCLC; n=7), pancreatic cancer (n=1), gastric cancer (n=4), prostate cancer (n=2) and thymic cancer (n=1).

Four of the 33 patients died due to pneumonitis (2 of these patients who were receiving olaparib in combination with liposomal doxorubicin [Study D0810L00001] and the cause of death also included pulmonary insufficiency); in 1 patient receiving olaparib and radiotherapy, the cause of death included bronchopulmonary hemorrhage. An additional 7 patients subsequently died. In 5 patients, the pneumonitis was ongoing at the time of death due to disease progression (n=4) and at the time of euthanasia (n=1). Two patients had recovered from the pneumonitis but then subsequently died due to disease progression (1 patient with gastric cancer and 1 patient with ovarian cancer).

The reports of pneumonitis presented with no consistent clinical pattern and were heavily confounded by a number of pre-disposing factors (including disease under investigation, underlying pulmonary disease, pre-existing medical conditions, smoking history and/or previous chemotherapy and radiotherapy). The majority of patients had received prior radiotherapy and/or chemotherapy and had other risk factors within the medical histories including pneumonitis, interstitial lung fibrosis, dyspnea, hemoptysis, chest infection, allergic asthma, pleural effusion, pleural metastases, or smoking. Seven patients had current SCLC or NSCLC. An independent review of available chest computed tomography (CT) scans and radiographs associated with the reports of pneumonitis concluded that there appeared to be no clear consistent clinical pattern.

The mechanisms of drug-induced pneumonitis are not well understood. Pre-clinical data do not show any evidence of lung induced toxicity due to a direct effect of olaparib on lung tissues. Patients with lung disorders including cancer (lung and breast), lung metastases, medical history of medications/chemotherapy (including alkylating agents), radiation treatment, occupational and environmental factors are associated with a high risk of development of interstitial lung disease.

Summary of other adverse events of interest
MDS/AML, new primary malignancies and pneumonitis have been identified as important potential risks for olaparib. The cumulative incidences are consistent with that expected for the patient population under study according to the available literature. These events are being closely monitored in ongoing studies.

1.6 Rationale

1.6.1 Rationale for studying olaparib in metastatic urothelial cancer

There are few standard therapies available for patients with metastatic urothelial cancer. While PD-1/PD-L1 blockade represents the first new treatment approved for metastatic urothelial cancer in over 30 years, only ~20% of patients with metastatic urothelial cancer respond such treatment. Novel approaches to treatment are urgently needed.

1.6.2 Rationale for patient selection based on the presence of somatic DDR alterations

Germline and somatic alterations in DDR genes have been associated with response to PARP inhibition across several malignancies establishing proof-of-concept for synthetic lethality. While there are likely a number of mechanisms whereby tumors acquire faulty DDR machinery which may be captured by means other than targeted or whole exome sequencing (e.g., gene expression profiling for evidence of "BRCAness" or assays for "genomic scars"), selection of patients with DDR mutations based on somatic exome sequencing is included in the current study due to (a) the increasing use of exome sequencing in CLIA laboratories as part of routine clinical care, (b) the correlation between DDR mutations and response to PARP inhibition in other solid tumors, and (c) the goal of enriching the population with those most likely to respond in this initial proof-of-concept study (i.e., if sufficient antitumor activity is observed, future studies may enroll patients without DDR mutations in hopes of expanding the biomarker profile associated with response).

1.6.3 Potential limitations of study design and approach to address limitations

There are several potential explanations in the event that anticancer activity is not observed with PARP inhibition in this study. These potential explanations, and our plans to address these limitations, are outlined below:

Specific DDR alterations, as a result of their functional consequences, may not result in synthetic lethality with PARP inhibition. While urothelial cancers harbor a large number of diverse somatic alterations in DDR genes (Figure 1), we will enrich the population with patients harboring somatic alterations in BRCA1, BRCA2, and ATM as alterations in these genes have been associated with sensitivity to PARP inhibition in other studies such as prostate cancer.

There is overlap with mechanisms of sensitivity and resistance to platinum-based chemotherapy such that patients progressing despite prior platinum-based chemotherapy may be uniformly resistant to PARP inhibition. Importantly, in studies in patients with ovarian cancer treated with PARP inhibition, responses have indeed correlated with platinum-sensitivity.[16] However, while patients with platinum-sensitive ovarian cancer achieve the highest response rates with PARP inhibition, response rates in platinum-resistant and platinum-refractory disease are 45% and 23% respectively. Furthermore, cisplatin-ineligible patients will be eligible for the current study.

DDR alterations present in archival primary tumor specimens are not present in metastatic sites relevant to a patient's current disease state. Metastatic lesions may not harbor tumor cells with DDR alterations present in a patient's archival primary tumor specimen due to an elimination of the DDR mutant clones with prior therapy or due to genomic evolution of the disease.[33] While

we will not mandate metastatic biopsies prior to enrollment, we will collect peripheral blood specimens to facilitate retrospective assessment of circulating tumor DNA.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- Estimate the objective response rate (per RECIST 1.1 or MD Anderson criteria for bone only metastases) to treatment with olaparib in subjects with metastatic urothelial cancer harboring somatic DDR alterations

2.1.2 Secondary Objectives

- Describe the safety of olaparib in subjects with DDR mutant metastatic urothelial cancer
- Describe the progression-free survival of subjects with DDR mutant metastatic urothelial cancer treated with olaparib
- Describe the overall survival of subjects with DDR mutant metastatic urothelial cancer treated with olaparib

2.1.3 Correlative/Exploratory Objectives

- Explore the relationship between specific genomic alterations with response to olaparib
- Explore the relationship between prior platinum-based chemotherapy treatment (response, duration of treatment, and time since treatment) with response to olaparib
- Explore the relationship between tumor mutational profile, circulating DNA mutational profile, and response to olaparib
- Determine the feasibility of establishing patient-derived xenografts from circulating tumor cells collected from enrolled subjects at baseline and progression to better explore mechanisms of response and resistance

2.2 Endpoints

2.2.1 Primary Endpoint

- Objective response rate will include confirmed complete response (CR) + confirmed partial response (PR) and will be determined as per RECIST 1.1 or MD Anderson Criteria (for bone-only metastatic disease)

2.2.2 Secondary Endpoints

- Adverse events are defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4
- Progression-free survival is defined as the time from Day 1 of treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death as a result of any cause.
- Overall survival is defined as the time from Day 1 of treatment until death as a result of any cause

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information prior to registration. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status of ≤ 1 within 14 days prior to registration. Cisplatin-ineligible chemotherapy-naïve subjects (see inclusion criteria #9) may have an ECOG Performance Status of ≤ 2.

4. Histological or cytological evidence/confirmation of urothelial cancer.

5. Metastatic and/or unresectable (cT4b) urothelial cancer.

6. Metastatic disease evaluable on imaging studies. Subjects may have measurable disease according to RECIST 1.1 or bone-only disease within 30 days prior to registration.

   NOTE: Bone-only subjects are eligible if their disease can be documented/evaluated by bone scans, CT or MRI. Their disease will be assessed using MD Anderson criteria.[34]

   NOTE: Previously irradiated lesions are eligible as a target lesion only if there is documented progression of the lesion after irradiation.

7. Somatic alteration considered pathogenic/likely pathogenic in one of the following DDR genes as determined by genomic sequencing performed in a Clinical Laboratory Improvement Amendments (CLIA) laboratory. Somatic alterations will include nonsense, frameshift, splice-site or missense mutations or homozygous deletions. Subjects with alterations in DDR genes not included in the list below will be considered on a case by case basis after discussion with the sponsor-investigator(s). Subjects with germline alterations in DDR genes will be considered on a case by case basis and will be reviewed by the sponsor-investigator(s). At least 6 subjects will have BRCA or ATM alterations.

Nucleotide Excision Repair	**Homologous Recombination**		**DNA Sensor**	**Fanconi Anemia Pathway**		**Base Excision Repair**	**Other**
ERCC2	BRCA1	RAD52	ATM	PALB2	FANCE	XRCC2	MUTYH
ERCC3	BRCA2	RAD54L	ATR	BRIP1	FANCF	XRCC3	RECQL4
ERCC4	RAD50	NBN	MDC1	FANCA	FANCG	XRCC4	POLQ
ERCC5	RAD51	MRE11A	ATRX	FANCB	BLM	XRCC5	POLE
ERCC6	RAD51B	RAD51D	CHEK1	FANCC		XRCC6	WRN
	RAD51C	CTIP	CHEK2	FANCD2			

8. A subject with prior brain metastasis may be considered if they have completed their treatment for brain metastasis at least 4 weeks prior to study registration, have been off corticosteroids for ≥ 2 weeks, and are asymptomatic

9. Subjects must have progressed despite at least 1 prior line of treatment for metastatic and/or unresectable urothelial cancer. However, cisplatin-ineligible (defined by a calculated creatinine clearance of >30 but < 60 mL/min **OR** CTCAE v4 Grade ≥ 2 audiometric hearing loss **OR** CTCAE v4 Grade ≥ 2 peripheral neuropathy **OR** ECOG PS = 2) and chemotherapy-naïve subjects are also eligible.

10. Prior cancer treatment (systemic therapy or radiation therapy) must be completed at least 3 weeks prior to registration and the subject must have recovered from all reversible acute toxic effects of the regimen (other than alopecia) to Grade ≤ 1 or baseline.

11. Demonstrate adequate organ function as defined in the table below. All screening labs to be obtained within 28 days prior to registration.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1.5 x 10^9/L
Hemoglobin (Hgb)	≥ 9 g/dL
Platelets	≥ 100 x 10^9/L
Renal	
Calculated creatinine clearance[1]	> 30 mL/min
Hepatic	
Bilirubin	≤ 1.5 × upper limit of normal (ULN)
Aspartate aminotransferase (AST)	≤ 2.5 × ULN (or ≤ 5 × ULN if liver metastases)
Alanine aminotransferase (ALT)	≤ 2.5 × ULN (or ≤ 5 × ULN if liver metastases)

1 Cockcroft-Gault formula will be used to calculate creatinine clearance (See SPM)

12. Female subjects must be postmenopausal or there must be evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on Day 1. Postmenopausal is defined as:
    - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
    - Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50
    - radiation-induced oophorectomy with last menses >1 year ago
    - chemotherapy-induced menopause with >1 year interval since last menses
    - surgical sterilization (bilateral oophorectomy or hysterectomy)

13. Females of childbearing potential must be willing to abstain from heterosexual activity or to use 2 forms of highly effective methods of contraception from the time of informed consent until 90 days after treatment discontinuation. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method. Males must be willing to abstain from heterosexual activity or to use 2 forms of highly effective methods

of contraception from the time of informed consent until 90 days after treatment discontinuation.

Acceptable non-hormonal birth control methods:

- Total sexual abstinence ie, refrain from any form of sexual intercourse in line with the patients' usual and/or preferred lifestyle. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- Intrauterine Device PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon®, Norplant®) PLUS male condom
- Normal and low dose combined oral pills PLUS male condom
- Hormonal shot or injection (eg, Depo-Provera) PLUS male condom
- Intrauterine system device (eg, levonorgestrel-releasing intrauterine system - Mirena®) PLUS male condom

14. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study

15. All subjects must have adequate archival tissue available prior to registration (i.e., at least 15 unstained slides or paraffin block). Archival tissue should represent invasive or metastatic urothelial cancer with a preference for metastatic tissue if available. Archival tissue should be identified at screening and shipped by C1D1. Subjects without adequate tissue may be considered on a case by case basis after discussion with the sponsor-investigator.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Active infection requiring systemic therapy.

2. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).

3. Known additional malignancy that is active and/or progressive requiring treatment; subjects with other malignancies that have been definitively treated and who have been rendered disease free will be eligible.

4. Prior treatment with a PARP inhibitor, including olaparib.

5. Treatment with any investigational drug within 30 days prior to registration.

6. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

7. Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome.

8. Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.

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

10. Subjects with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

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

12. Subjects considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan, history of pneumonitis, or any psychiatric disorder that prohibits obtaining informed consent.

13. Subjects unable to swallow orally administered medication and subjects with gastrointestinal disorders likely to interfere with absorption of the study medication.

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

15. Subjects with a known hypersensitivity to olaparib or any of the excipients of the product.

16. Subjects with known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids.

17. Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. Subjects will be considered registered when an "on study" date is entered into the EDC system.

Subjects must be registered prior to starting protocol therapy and begin study treatment **within 7 business days** of registration.

5. TREATMENT PLAN

This is a single-arm open label phase II trial of olaparib in subjects with DDR mutant metastatic urothelial cancer. Subjects will receive olaparib, in the absence of prohibitive adverse events, until the time of disease progression.

5.1 Olaparib

Olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least 28 days plus overage. Olaparib will be dispensed to subjects on Day 1 of each cycle thereafter until the patient completes the study, withdraws from the study or closure of the study.

Study treatment is available as a film-coated tablet containing 150 mg or 100 mg of olaparib. Subjects will be administered olaparib orally twice daily. Olaparib tablets should be taken at the same time each day, approximately 12 hours apart. The starting dose of olaparib tablets will be dependent on the subject's calculated creatinine clearance (CrCl). Subjects with a CrCl of ≥ 40 mL/min will start at a dose of olaparib tablets of 300 mg twice a day (total 600 mg per day). Subjects with a CrCl of > 30 to < 40 mL/min will start at a dose of olaparib tablets 200 mg twice a day (total 400 mg per day).

Olaparib should be taken with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Olaparib tablets can be taken with or without food. It is not recommended to consume grapefruit juice or consume Seville oranges while on olaparib therapy.

5.2 Concomitant Medications

5.2.1 Allowed Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care unless as otherwise indicated below.

5.2.1.1 Anticoagulant Therapy

Subjects who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

5.2.1.2 Anti-emetics/Anti-Diarrheals

If a patient develops nausea, vomiting and/or diarrhea, these symptoms should be reported as AEs and should be treated per institutional guidelines.

5.2.1.3 Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the site investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

5.2.1.4 Contraception

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

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for at least 90 days after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

Male subjects and their partners, who are sexually active and of childbearing potential, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for 90 days after last dose of study drug(s) due to the unknown effects of the study drug on the sperm, or they must totally/truly abstain from any form of sexual intercourse (see below). Male subjects should not donate sperm throughout the period of taking study treatment and for 90 days following the last dose of study drug(s).

Acceptable non-hormonal birth control methods:

- Total sexual abstinence ie, refrain from any form of sexual intercourse in line with the patients' usual and/or preferred lifestyle. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- Intrauterine Device PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon®, Norplant®) PLUS male condom
- Normal and low dose combined oral pills PLUS male condom
- Hormonal shot or injection (eg, Depo-Provera) PLUS male condom
- Intrauterine system device (eg, levonorgestrel-releasing intrauterine system - Mirena®) PLUS male condom

5.2.2 Prohibited Concomitant Medications

The use of any natural/herbal products or other traditional 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 in the case report form (CRF).

5.2.2.1 Medications that may NOT be administered

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

Live virus and live bacterial vaccines should not be administered while the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

5.2.2.2 Restricted concomitant medications

Subjects must not be taking strong or moderate CYP3A inhibitors or strong or moderate CYP3A inducers at the time of study enrollment. Subjects for whom these medications are being considered after subjects have already been enrolled on study should follow the guidance below:

Strong or Moderate CYP3A inhibitors

Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib.

If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the eCRF with the reason documented as concomitant CYP3A inhibitor use.

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg bid for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards.
- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg bid for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards.
- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

Strong or Moderate CYP3A inducers

Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil) of CYP3A should not be taken with olaparib.

If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib.

If a patient requires use of a strong or moderate CYP3A inducer or inhibitor then they must be monitored carefully for any change in efficacy of olaparib.

P-gp inhibitors

It is possible that co-administration of P-gp inhibitors (eg amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.

Effect of olaparib on other drugs
Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp.

The efficacy of hormonal contraceptives may be reduced if co administered with olaparib. Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:
- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP1A2 – duloxetine, melatonin
- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 - serum creatinine
- OAT3 -furosemide, methotrexate

5.2.2.3 Administration of other anti-cancer agents
Subjects must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Subjects may continue the use of bisphosphonates or denosumab for bone disease.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS
The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays/Dose Modifications
For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors or inducers cannot be avoided see section 5.2.2.

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is > 4 weeks, the sponsor-

investigator should be informed. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued. There will be no dose reductions for subjects (with moderate renal insufficiency) starting at a dose of 200 mg twice daily.

6.1.1 Dose Levels for Dose Reductions

Table 1 Dose reductions for olaparib*

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300mg twice daily	250mg twice daily	200mg twice daily

*see section 6.1 for more specific guidance

Once dose is reduced, escalation is not permitted except as indicated in section 5.2.2. for temporary dose reductions association with concomitant use of CYP3A inhibitors or inducers.

6.2 Management of Hematological Toxicity

6.2.1 Management of Anemia

Table 2 Management of anemia

Hemoglobin	Action to be taken
Hb < 10 ***but*** **≥ 8 g/dl (CTCAE Grade 2)**	Give appropriate supportive treatment and investigate causality. Site investigator judgement to continue olaparib with supportive treatment (e.g. transfusion) *or* interrupt dose for a maximum of 4 weeks. If repeat Hb **< 10** ***but*** **≥ 8 g/dl**, dose interrupt (for max of 4 weeks) until Hb ≥ 10 g/dl and upon recovery dose reduction to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step may be considered.
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks. until improved to Hb ≥ 10 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where subjects develop prolonged hematological toxicity (≥ 2 week interruption/delay in study treatment due to CTC Grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 6.2.3 for the management of this.

6.2.2 Management of Neutropenia, Leukopenia and Thrombocytopenia

Table 3 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

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 hours (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary. Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where subjects develop prolonged hematological toxicity (≥ 2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to Section 6.2.3.

6.2.3 Management of Prolonged Hematological Toxicities While on Study Treatment

If a patient develops prolonged hematological toxicity such as:

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

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

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the site investigator to HCRN who will then report to AstraZeneca Patient Safety (See Section 11). Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

6.3 Management of Non-Hematological Toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the sponsor-investigator must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg bid as a first step and to 200 mg bid as a second step. Treatment must be interrupted if any NCI-CTCAE Grade 3 or 4 adverse event occurs which the site investigator considers to be related to administration of study treatment.

6.3.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the site investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the sponsor-investigator. If pneumonitis is confirmed, discontinue olaparib.

6.3.2 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 subjects and 36% in the placebo treated subjects and vomiting was reported in 34% of the olaparib treated subjects and 14% in the placebo treated patients. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

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

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

6.3.3 Renal Impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion, retesting should be performed promptly.

A dose reduction is recommended for subjects who develop a decline in renal function as defined by a calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 39 ml/min for any reason during the course of the study: the dose of olaparib should be reduced to 200mg BID.

Olaparib should be discontinued if the calculated creatinine clearance declines to ≤ 30 ml/min.

6.4 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 sponsor-investigator.

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 needle biopsy procedure.

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

6.5 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF)

- Documented disease progression
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - In a subject decides to prematurely discontinue protocol therapy (“refuses treatment”), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Pneumonitis
- Protocol therapy is interrupted for > 4 weeks.

6.6 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 28 days	Screening	Treatment	Tumor Assessments[8] ± 7 days	Safety Follow Up Visit[13]	Survival Follow Up[14]
	-28 days	Cycle 1 + Day 1 ± 2 days		30 Days Post Treatment (±7 days)	Every 3 Months (±7 days)
REQUIRED ASSESSMENTS					
Informed Consent	X				
Medical History[1]	X				
Physical Exam	X	X		X	
Vital signs and ECOG Performance Status[2]	X	X		X	
Documentation of DDR alteration in CLIA lab assay[3]	X				
ECG[4]	X[4]				
AEs & Concomitant Medications	X	X		X	
LABORATORY ASSESSMENTS					
Complete Blood Cell Count with diff (CBC)[5]	X	X		X	
Comprehensive Metabolic Profile (CMP)[5]	X	X		X	
PT/INR and aPTT[6]	X				
Pregnancy test (serum or urine) (WOCBP)[7]	X	X[7]			
Urinalysis	X				
DISEASE ASSESSMENT					
CT of chest[8]	X		X[8]		
CT or MRI of abdomen and pelvis[8]	X		X[8]		
Bone Scan[8]	X		X[8]		
TREATMENT EXPOSURE					
Olaparib		X			
CORRELATIVE SAMPLES					
Archival Tumor Tissue[9]	X				
Collection of tumor tissue obtained as standard of care[10]				X[10]	
Blood Samples for correlative research[11]		X[11]		X[11]	
BANKING SAMPLES					
Whole Blood[12]		X[12]		X[12]	
FOLLOW-UP					
Survival Status, Subsequent Therapy					X

Key to Footnotes

1: Medical History should include the following information: (1) Diagnosis and staging to include Tumor Node Metastasis (TNM) staging (2) smoking history, (3) trial awareness question (4) prior cancer treatment history and (5) genetic sequencing information.

2: Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status.

3: The laboratory report indicating the presence of a DDR alteration (see eligibility) from a CLIA laboratory is required for registration.

4: ECG is required within 7 days prior to starting study treatment.

5: If screening (baseline) CBC and CMP were performed within 7 days of Day 1 of treatment, these do not need to be repeated. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

6: Subjects taking warfarin may participate in this study; 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.

7: For women of childbearing potential (WOCBP): urine or serum βhCG will be checked at screening and prior to study drug on Cycle 1 Day 1 (only if clinically appropriate). If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

8: Tumor imaging to continue near the end of every 2nd cycle (~every 8 weeks) for the first 12 months following Cycle 1 Day 1. After 12 months, tumor assessments will be performed near the end of every 3rd cycle (~every 12 weeks). Imaging selected for each subject should remain the same throughout the study. Bone scan will be obtained at screening if there is any clinical or laboratory suspicion of metastatic bone involvement. If bone scan is positive at baseline for metastases, it will be included with tumor response assessments as noted above.

9: All subjects must have adequate archival tissue available; identified at screening and shipped by C1D1 (i.e., at least 15 unstained slides or paraffin block). Archival tissue should represent invasive or metastatic urothelial cancer with a preference for metastatic tissue if available. If acceptable archival tissue is not available, this should be discussed with the sponsor-investigator. Subjects will be consented to optional banking of any remaining tumor samples after protocol-specified studies are complete. Banked samples will be reserved for future unspecified cancer-related research. See Correlative Laboratory Manual (CLM) for additional details.

10: If a subject has a biopsy at progression or for other clinical reasons as per standard of care, they will be asked permission to store some of this tissue for research directed at mechanisms of resistance. Subjects will also be consented to optional banking of any remaining tumor samples after protocol-specified studies are complete. Banked samples will be reserved for future unspecified cancer-related research. See Correlative Laboratory Manual (CLM) for additional details.

11: Serial blood samples will be collected to support biomarker research; There are 4 time points for blood samples to be obtained: (1) pre-dose C1D1, (2) pre-dose C3D1, (3) pre-dose C5D1 and at (4) Progression. If a subject comes off study due to progression, samples may be obtained at the Safety Follow Up visit. See CLM for additional details.

12: Serial blood samples will be collected for banking; See CLM for additional details. There are 4 time points for blood samples to be obtained: (1) pre-dose C1D1, (2) pre-dose C3D1, (3) pre-dose C5D1 and at (4) Progression. If a subject comes off study due to progression, samples may be obtained at the Safety Follow Up visit.

13: Safety Follow-Up Visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of treatment. Subjects who have an ongoing Grade ≥ 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to Grade ≤ 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

14: Survival Follow Up will occur in all subjects until documented disease progression. Subjects who discontinue treatment for any reason without documented disease progression will be followed for disease progression every 3 months for 2 years from safety follow up visit. Once disease progression is documented, subjects will enter a survival follow up period every 3 months for 2 years from the time of documented progression. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. During this follow up, any radiology imaging results performed should be entered into the EDC system.

8. BIOSPECIMEN STUDIES AND PROCEDURES

See Correlative Laboratory Manual for collection, processing and shipping instructions for all tissue and blood specimens.

8.1 Correlative Analyses

Tissue based and peripheral-blood based correlative analyses will focus on the identification of biomarkers of response and resistance to treatment with olaparib and will include, but not be limited to, DNA, RNA, and protein-based assays. Because all patients enrolled on this study will have been previously identified as having a DDR mutation, we will obtain prior genetic sequencing reports for exploratory analyses of co-alterations and response/resistance to treatment and time-to-event outcomes. Furthermore, whole exome sequencing may be pursued on select archival specimens, or all specimens, to better define the genomic landscape. Circulating DNA will be utilized to correlate genomic alterations in the peripheral blood with alterations present in tumor tissue.

In addition to the analyses described above, we may generate circulating tumor cell-based patient-derived xenograft models and/or organoids using an approach that we have previously described.[35,36] The feasibility of establishing these models will be assessed and if successful, we will evaluate sensitivity and resistance to olaparib in these model systems.

8.2 Archival Tissue

All subjects must have adequate archival tissue available; identified at screening and shipped by C1D1 (i.e., at least 15 unstained slides or paraffin block). Archival tissue should represent invasive or metastatic urothelial cancer with a preference for metastatic tissue if available. If archival tissue is not available, enrollment must be discussed with the sponsor-investigator on a case by case basis.

8.3 Peripheral Blood

All samples to be drawn prior to study drug administration (if applicable). Serial blood samples will be collected to support biomarker research; There are 4 time points for blood samples to be obtained: (1) pre-dose C1D1, (2) pre-dose C3D1, (3) pre-dose C5D1 and at (4) Progression. If a subject comes off study due to progression, samples may be obtained at the Safety Follow Up visit.

8.4 Tumor Specimens Obtained at the Time of Disease Progression or for Other Clinical Purposes

Subjects may have tumor tissue obtained during the course of the study or at the time of disease progression for clinical purposes (e.g., confirmation of disease progression, management of complication of disease progression, etc.). Specimens obtained in these settings may be accessed by the research team to facilitate an understanding of the pharmacodynamic effects of treatment at the level of the tumor and microenvironment including mechanisms of treatment resistance.

8.5 Samples for Future Unspecified Cancer Related Research

Subject consent will be obtained for additional samples collected for future unspecified cancer related research. Hoosier Cancer Research Network will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository.

- Whole Blood will be collected prior to treatment on Cycle 1 Day 1, C3D1, C5D1 and at progression/D30 Safety Follow-up visit.

8.6 Storage of Excess Biospecimens

Excess biospecimens not completely utilized in these experiments will be stored indefinitely at HCRN for future use in research focused on GU malignant diseases that are yet to be determined. All specimens collected will maintain the assigned unique study number of the corresponding patient. Deidentified samples may be shared with other research institutions. We believe that allowing for storage and usage of the remaining samples for future research is ethically justified and a preferred option to discarding these materials given the potential impact on improving clinical outcomes for subjects with bladder cancer. Subjects will be given the option to store excess specimens during the informed consent process.

8.7 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's sequence ID number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's sequence number.

9. CRITERIA FOR DISEASE EVALUATION

9.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.1 Malignant Lymph Nodes

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

9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) **NOTE:** If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.8 Definitions for Response Evaluation – RECIST 1.1

9.8.1 First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR.

9.8.2 Confirmation of Response
To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

9.8.3 Duration of Response
Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

9.8.4 Duration of Overall Complete Response
The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

9.8.5 Objective Response Rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.6 Disease Control Rate
The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.7 Time to Progression:
A measurement from the date of initiation of therapy until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

9.8.8 Progression Free Survival
A measurement from the date of initiation of therapy until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.8.9 Overall Survival
Overall survival is defined by the date of enrollment to date of death from any cause.

9.9 Definitions for Response Criteria for patients with bone-only metastases; MD Anderson (MDA) criteria[34]

Complete Response (CR)	• Complete sclerotic fill-in of lytic lesions on XR or CT • Normalization of bone density on XR or CT • Normalization of signal intensity on MRI • Normalization of tracer uptake on SS
Partial Response (PR)	• Development of a sclerotic rim or partial sclerotic fill-in of lytic lesions on XR or CT • Osteoblastic flare - Interval visualization of lesions with sclerotic rims or new sclerotic lesions in the setting of other signs of PR and absence of progressive bony disease • ≥ 50% decrease in measurable lesions on XR, CT, or MRI • ≥ 50% subjective decrease in the size of ill-defined lesions on XR, CT, or MRI • ≥ 50% subjective decrease in tracer uptake on SS
Progressive Disease (PD)	• > 25% increase in size of measurable lesions on XR, CT, or MRI • > 25% subjective increase in the size of ill-defined lesions on XR, CT, or MRI • > 25% subjective increase in tracer uptake on SS • New bone metastases
Stable Disease (SD)	• No change • < 25% increase or < 50% decrease in size of measurable lesions • < 25% subjective increase or < 50% subjective decrease in size of ill-defined lesions • No new bone metastases
Abbreviations: XR: radiography; CT: computed tomography; SS: skeletal scintigraphy; MRI: magnetic resonance imaging.	

Measurements are based on the sum of a perpendicular, bi-dimensional measurement of the greatest diameters of each individual lesion.

10 DRUG INFORMATION

Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug.

10.1 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP-1, -2 and -3).

10.1.1 Supplier/How Supplied

Astra Zeneca will supply olaparib at no charge to subjects participating in this clinical trial.

The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply olaparib to the investigator as round or oval *film coated tablets*. **NOTE:** The capsule and tablet forms of olaparib should not be substituted as they have different bioavailability and dosing instructions.

Investigational product	Dosage form and strength
Olaparib	*100 mg tablet*
Olaparib	*150 mg tablet*

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

10.1.2 Preparation

When possible, refer to the prescribing information and/or investigator's brochure for details on the preparation of the drug. Dosing and administration should be addressed in the Treatment Plan section.

10.1.3 Storage and Stability

All study drugs should be kept in a secure place under appropriate storage conditions. Olaparib tablets should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture.

10.1.4 Handling and Disposal

Investigational drug should be disposed as per institutional policy.

10.1.5 Dispensing

Olaparib must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Olaparib should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

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

Each bottle of olaparib will have an investigational product label permanently affixed to the outside stating that the material is for clinical trial/investigational use only and should be kept out of reach of children. The label will include the dosing instructions and a space for the enrolment code (E-code) to be completed at the time of dispensing.

The label will include the following information:

blank lines for quantity of tablets to be taken
enrolment code (E-code)
date of dispensing
Instructions stating that the olaparib tablets should be taken at approximately the same time each morning and evening

10.1.6 Potential Adverse Events

See the most current IB or package insert for a comprehensive list of adverse events.

11 ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v4 will be utilized for AE assessment. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the Study Procedure Manual or in the EDC system (Documents and Information Tab).

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Olaparib Adverse Events of Special Interest (AESI)

Adverse events of special interest [AESI] are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and rapid communication by the local investigator to the sponsor-investigator via HCRN. An AESI may be serious or non-serious. Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

ANY event of MDS/AML, new primary malignancy, or pneumonitis should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE [eg non-melanoma skin cancer] or SAE, and regardless of site investigator's assessment of causality.

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

11.1.4 Overdose of Olaparib

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

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol

should be reported as an overdose. 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 eCRF 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, site investigators or other site personnel inform appropriate Hoosier Cancer Research Network (HCRN) **within one business day** and HCRN will report to AstraZeneca **within one business day.**

11.1.5 Reproductive Reporting Information

11.1.5.1 Pregnancy
All outcomes of pregnancy should be reported to HCRN who will then report to AstraZeneca.

11.1.5.2 Maternal Exposure
If a patient becomes pregnant during the course of the study, olaparib should be discontinued immediately. The outcome of any conception occurring from the date of the first dose until 1 month *after the last dose* should be followed up and documented. 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 withdrawn from the study.

If any pregnancy occurs in the course of the study, site investigators or other site personnel must inform HCRN **within one business day** and HCRN will report to AstraZeneca **within one business day.**

11.1.5.3 Paternal Exposure
Male subjects should refrain from fathering a child or donating sperm during the study and for 3 months 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 3 months *after the last dose* should be followed up and documented.

11.1.6 Unexpected Adverse Event
For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the

pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.7 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- AEs considered related to study drug(s) will be followed until resolution to Grade ≤ 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.
- Transient asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 30 days after discontinuation of study drug(s).
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form may be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed in 11.2.2.1), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting Events to AstraZeneca

HCRN will report all SAEs, AESIs, and other reportable events to AstraZeneca **within 1 business day** of knowledge of the event. Follow-up information will be provided to AstraZeneca as reasonably requested.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca, preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com.

11.2.2.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.2.2.4 HCRN Responsibilities to FDA

This protocol was deemed exempt by the FDA 10/27/17. For protocols exempt from the requirements of an IND, the above stated requirements are not applicable. HCRN will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

11.2.2.5 IND Safety Reports Unrelated to this Trial

AstraZeneca will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STATISTICAL METHODS

12.1 Study Design

This is a single arm open label multi-institutional phase II trial of olaparib monotherapy in subjects with metastatic urothelial cancer harboring somatic DDR alterations. The primary objective of the study is to estimate the objective response rate (per RECIST 1.1 or MD Anderson criteria for bone-only metastases) to treatment with olaparib.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

The primary endpoint is objective response rate as determined by RECIST 1.1 (or MD Anderson criteria for bone-only metastases). Objective response rate will include confirmed complete response (CR) + confirmed partial response (PR) and will be determined as outlined in section 9.

12.2.2 Definition of Secondary Endpoints

- Safety of olaparib, defined as rates of Grade 1-5 toxicity according to CTCAE v4.03.
- PFS, which is defined as the time from initiation of treatment to death or progression, depending on which occurs first (as defined by RECIST 1.1).
- Overall survival (OS), which is defined as the time from initiation of treatment to death.

12.3 Sample Size and Accrual

Assume the null hypothesis (P0) of 10% as the response rate (the response rate with standard cytotoxic chemotherapy in this setting[37]), a sample size of 27 achieves 81% power to detect a difference (P1-P0) of 18% (that is, P1=28%) using a one-sided exact test with a target significance level of 0.05. The actual significance level achieved by this test is 0.0471. The sample size may be inflated to 30 if replacement of subjects is needed due to early withdrawals or unevaluable subjects.

12.4 Data Analysis Plans

12.4.1 Analysis Plans for Primary Objective

Any subjects who receive at least one dose of treatment on this protocol will be included in the analysis of the objective response rate. Patients who discontinue treatment prior to the first response assessment will be defined as “non-evaluable” but will be included in the denominator. The objective response rate and its associated 95% confidence interval will be constructed based on the exact binomial test due to the small sample size.

12.4.2 Analysis Plans for Secondary Objectives

Any subject who receives at least one dose of treatment on this protocol is evaluable for toxicity, progression free survival and overall survival. Toxicity rates will be summarized using frequency tables. Progression free survival and overall survival curves will be based on the Kaplan-Meier method.

12.4.3 Analysis Plans for Exploratory Objectives

To explore the relationship between specific genomic alterations with response to olaparib, Fisher's exact test will be used. To explore the relationship between prior platinum-based chemotherapy treatment (exposure, response, duration of treatment, and time since treatment) with response to olaparib, Fisher's exact test (for chemo response) and T-test (for duration of treatment and time since treatment) will be used. To explore the relationship between tumor mutational profile, circulating DNA mutational profile, and response to olaparib, both Fisher's exact test and T-test will be used.

12.5 Stopping Study for Excessive Toxicities

A stopping rule will be employed after 10 and 20 subjects finish at least one cycle of treatment. This safety stopping rule will be performed with respect to a) SAEs that are treatment related and b) events of specific interest (that is, MDS/AML, new primary malignancies and pneumonitis). Two-sided 95% exact binomial confidence intervals (CIs) of these event rates will be constructed at 10 and 20 subjects. If their lower bounds exceed pre-defined levels, the study drug will be considered unacceptably toxic for this patient population and the study will be terminated. Therefore, we have the following 2 stopping rules:

1. In a prospective trial of olaparib in subjects with advanced solid tumors and germline BRCA 1 and 2 mutations, among the ovarian, breast, pancreatic, and prostate cancer groups, 10.4%, 9.7%, 17.4%, and 12.5% of subjects, respectively, experienced serious AEs considered causally related to olaparib.[38] We will use 15% as our cutoff and if the lower bounds of the CIs exceed 15%, the study will be halted. This corresponds to ≥ 5+ (5 or more) out of 10 and ≥ 7+ out of 20 subjects.
2. The rate of other events of interest (that is, MDS/AML, new primary malignancies and pneumonitis) varies around 1% (see Section 1.5.6). If the lower bounds of the CIs exceed 1%, the study will be halted. This corresponds to ≥ 2+ (2 or more) out of 10 and ≥ 2+ out of 20 subjects.

Enrollment will not be halted while these safety assessments take place.

There will be no planned interim efficacy assessment.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with the Icahn School of Medicine/Tisch Cancer Institute's DSMP.

HCRN oversight activities include:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution Data Safety Monitoring Committee according to Icahn School of Medicine/Tisch Cancer Institute's DSMP.

13.2 Icahn School of Medicine/Tisch Cancer Institute Data Safety Monitoring Committee

HCRN will provide the following for the Icahn School of Medicine/Tisch Cancer Institute's DSMC to review:

- Adverse event summary report
- Audit results if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The Icahn School of Medicine/Tisch Cancer Institute's DSMC will review study data every quarter. Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with HCRN to address the DSMC's concerns.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

Participating sites may also be subject to quality assurance audits by BMS or its designee as well as inspection by appropriate regulatory agencies.

13.3.1 Onsite Monitoring

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee. The trial site may also be subject to quality assurance audit by AstraZeneca-MedImmune or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform, a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, AstraZeneca, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

16 REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2015;66(1):n/a-n/a.
2. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000;18(17):3068–77.
3. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet (London, England) 2016;
4. Galsky M, Retz M, Siefker-Radtke A, Baron A, Necchi A. Efficacy and Safety of Nivolumab Monotherapy in Patients with Metastatic or Surgically Unresectable Locally Advanced Urothelial Cancer Who Have Received Prior Treatment: Phase II CheckMate 275 Study. In: ESMO. 2016.
5. Apolo AB, Infante JR, Hamid O, et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with metastatic urothelial carcinoma from the JAVELIN solid tumor phase 1b trial: Analysis of safety, clinical activity, and PD-L1 expression. ASCO Meet Abstr 2016;34(15_suppl):4514.
6. Plimack ER, Bellmunt J, Gupta S, et al. Pembrolizumab (MK-3475) for advanced urothelial cancer: Updated results and biomarker analysis from KEYNOTE-012. ASCO Meet Abstr 2015;33(15_suppl):4502.
7. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 2014;
8. Iyer G, Balar AV, Milowsky MI, et al. Correlation of DNA damage response (DDR) gene alterations with response to neoadjuvant (neo) dose-dense gemcitabine and cisplatin (ddGC) in urothelial carcinoma (UC). ASCO Meet Abstr 2016;34(15_suppl):5011.
9. Van Allen EM, Mouw KW, Kim P, et al. Somatic ERCC2 Mutations Correlate with Cisplatin Sensitivity in Muscle-Invasive Urothelial Carcinoma. Cancer Discov 2014;4(10):1140–53.
10. Liu D, Plimack ER, Hoffman-Censits J, et al. Clinical Validation of Chemotherapy Response Biomarker ERCC2 in Muscle-Invasive Urothelial Bladder Carcinoma. JAMA Oncol 2016;
11. Plimack ER, Dunbrack RL, Brennan TA, et al. Defects in DNA Repair Genes Predict Response to Neoadjuvant Cisplatin-based chemotherapy in Muscle-invasive Bladder Cancer. Eur Urol 2015;
12. Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med 2016;8(362).
13. Murai J, Huang SN, Das BB, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. Cancer Res 2012;72(21):5588–99.
14. Rottenberg S, Jaspers JE, Kersbergen A, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with

platinum drugs. Proc Natl Acad Sci U S A 2008;105(44):17079–84.

15. Hay T, Matthews JR, Pietzka L, et al. Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous Brca2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin. Cancer Res 2009;69(9):3850–5.
16. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol 2010;28(15):2512–9.
17. Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. Mol Oncol 2011;5(4):387–93.
18. Mateo J, Carreira S, Sandhu S, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med 2015;373(18):1697–708.
19. Dowsett M, Cuzick J, Howell A, Jackson I, ATAC Trialists' Group. Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the "Arimidex and tamoxifen alone or in combination" (ATAC) trial. Br J Cancer 2001;85(3):317–24.
20. Aul C, Gattermann N, Schneider W. Age-related incidence and other epidemiological aspects of myelodysplastic syndromes. Br J Haematol 1992;82(2):358–67.
21. Cogle CR, Craig BM, Rollison DE, List AF. Incidence of the myelodysplastic syndromes using a novel claims-based algorithm: high number of uncaptured cases by cancer registries. Blood 2011;117(26):7121–5.
22. Rollison DE, Howlader N, Smith MT, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. Blood 2008;112(1):45–52.
23. Morton LM, Dores GM, Tucker MA, et al. Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. Blood 2013;121(15):2996–3004.
24. Vay A, Kumar S, Seward S, et al. Therapy-related myeloid leukemia after treatment for epithelial ovarian carcinoma: An epidemiological analysis. Gynecol Oncol 2011;123(3):456–60.
25. Friedenson B. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer 2007;7(1):152.
26. Cole M, Strair R. Acute Myelogenous Leukemia and Myelodysplasia Secondary to Breast Cancer Treatment: Case Studies and Literature Review. Am J Med Sci 2010;339(1):36–40.
27. YEASMIN S, NAKAYAMA K, ISHIBASHI M, et al. Therapy-related myelodysplasia and acute myeloid leukemia following paclitaxel- and carboplatin-based chemotherapy in an ovarian cancer patient: a case report and literature review. Int J Gynecol Cancer 2008;18(6):1371–6.
28. SEE HT, THOMAS DA, BUESO-RAMOS C, KAVANAGH J. Secondary leukemia after treatment with paclitaxel and carboplatin in a patient with recurrent ovarian cancer. Int J Gynecol Cancer 2006;16(S1):236–40.

29. Travis LB, Holowaty EJ, Bergfeldt K, et al. Risk of Leukemia after Platinum-Based Chemotherapy for Ovarian Cancer. N Engl J Med 1999;340(5):351–7.

30. Bergfeldt K, Einhorn S, Rosendahl I, Hall P. Increased risk of second primary malignancies in patients with gynecological cancer. A Swedish record-linkage study. Acta Oncol 1995;34(6):771–7.

31. Fowble B, Hanlon A, Freedman G, Nicolaou N, Anderson P. Second cancers after conservative surgery and radiation for stages I-II breast cancer: identifying a subset of women at increased risk. Int J Radiat Oncol Biol Phys 2001;51(3):679–90.

32. Ginsburg OM, Kim-Sing C, Foulkes WD, et al. BRCA1 and BRCA2 families and the risk of skin cancer. Fam Cancer 2010;9(4):489–93.

33. Faltas BM, Prandi D, Tagawa ST, et al. Clonal evolution of chemotherapy-resistant urothelial carcinoma. Nat Genet 2016;48(12):1490–9.

34. Hayashi N, Costelloe CM, Hamaoka T, et al. A prospective study of bone tumor response assessment in metastatic breast cancer. Clin Breast Cancer 2013;13(1):24–30.

35. Vidal SJ, Rodriguez-Bravo V, Quinn SA, et al. A targetable GATA2-IGF2 axis confers aggressiveness in lethal prostate cancer. Cancer Cell 2015;27(2):223–39.

36. Williams E, Rodriguez-Bravo V, Chippada-Venkata U, et al. Generation of Prostate Cancer Patient Derived Xenograft Models from Circulating Tumor Cells. [Internet]. J Vis Exp. 2015 [cited 2015 Nov 17];105. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26555435

37. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;NEJMoa1613683.

38. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015;33(3):244–50.