NCI Protocol #: 10264
Version Date: December 11, 2024

To: Cancer Therapy Evaluation Program

From: Rory Shallis, M.D.

Date: December 11, 2024

Re: **Response to Request for Amendment from Melissa M. McKay-Daily, Ph.D. dated 10/1/2024:** Amendment 6, Revision 11: "The PRIME Trial: PARP Inhibition in IDH Mutant Effectiveness Trial. A Phase II Study of Olaparib in Isocitrate Dehydrogenase (IDH) Mutant Relapsed/Refractory Acute Myeloid Leukemia andMyelodysplastic Syndrome."

SUMMARY OF CHANGES – Protocol

I. CTEP Request for Amendment dated 10/1/2024 from Melissa M. McKay-Daily, Ph.D.

#	Section	Comments
1.	All	Updated Version Date in Header
2.	Protocol Type/Version Date	Updated Protocol Type / Version Date
3.	TOC 5.1 5.2.2 5.4.3 5.5 5.5.2 5.10.2.1	ETCTN Biorepository updated to EET Biobank
4.	5.5.2 5.5.3	Address and contact information updated for EET Biobank.

II. Additional Changes by Principal Investigator

#	Section	Comments
5.	Title Page	Added Jan Bewersdorf as Co-Principal Investigator
6.	Study Coordinator	Removed Laura Leary and replaced with Anne Caldwell.
7.	Data Manager	Removed GraceAnne Valentin and replaced with Anne Caldwell.

Protocol #: 10264

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ClinicalTrials.gov Identifier: NCT03953898

TITLE: The PRIME Trial: PARP Inhibition in IDH Mutant Effectiveness Trial. A Phase II Study of Olaparib in Isocitrate Dehydrogenase (IDH) Mutant Relapsed/Refractory Acute Myeloid Leukemia and Myelodysplastic Syndrom

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Amendment 1/ Revision 6 / September 8, 2020
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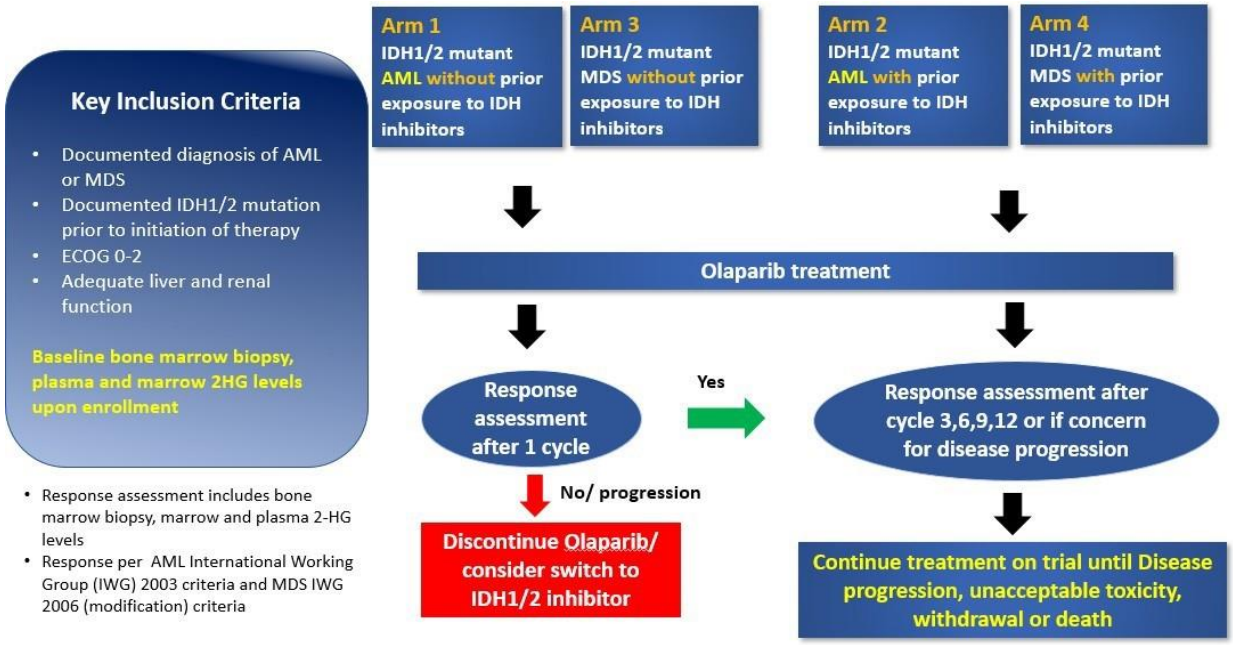
Amendment 4/Revision 9/November 16, 2022
Amendment 5/Revision 10/July 27, 2023
Amendment 6/Revision 11/December 11, 2024

SCHEMA



AML = Acute myeloid leukemia; MDS = Myelodysplastic syndrome; IDH = Isocitrate dehydrogenase; ECOG = Eastern Cooperative Oncology Group

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1. OBJECTIVES

1.1 Primary Objective

1.1.1 To determine the rate of complete response (CR) to olaparib using a composite CR endpoint (CR + CR with incomplete hematologic response [CRi] + CR with partial hematologic response [CRh]) in subjects with Isocitrate Dehydrogenase (IDH)1/2 mutant myelodysplastic syndrome (MDS) or IDH1/2-mutant Acute Myeloid Leukemia (AML).

1.2 Secondary Objectives

1.2.1 To determine the overall response rate (ORR) to olaparib using a composite ORR endpoint (CR + morphologic leukemia-free state [MLFS] + partial response [PR]) in patients with IDH mutant AML or MDS treated with olaparib.

1.2.2 To establish the progression free survival (PFS) of patients with IDH mutant AML or MDS treated with olaparib.

1.2.3 To determine the overall survival (OS) of patients with IDH mutant AML or MDS treated with olaparib.

1.2.4 To establish the duration of response (DOR) to treatment with olaparib.

1.2.5 To evaluate the safety and tolerability of olaparib in AML or MDS patients.

1.3 Exploratory Objectives

1.3.1 To establish a relationship between treatment response and correlative studies such as plasma and bone marrow 2-Hydroxyglutarate (2HG) levels, and IDH variant allele frequency.

1.3.2 To evaluate persistence of double strand breaks in IDH 1/2 mutant AML or MDS.

1.3.3 To evaluate response to therapy in the different IDH mutant genotypes.

1.3.4 To perform molecular profiling assays on malignant and normal tissues, including, but not limited to, whole exome sequencing (WES), RNA sequencing (RNAseq) order to:

1.3.4.1 identify potential predictive and prognostic biomarkers beyond any genomic alteration by which treatment may be assigned.

1.3.4.2 identify resistance mechanisms using genomic DNA- and RNA-based assessment platforms.

1.3.5 To contribute genetic analysis data from de-identified biospecimens to Genomic Data

Commons (GDC), a well annotated cancer molecular and clinical data repository, for current and future research; specimens will be annotated with key clinical data, including presentation, diagnosis, staging, summary treatment, and if possible, outcome.

1.3.6 To bank blood and bone marrow aspirate obtained from patients at the EET Biobank at Nationwide Children's Hospital.

2. BACKGROUND

2.1 Study Diseases

Acute myeloid leukemia (AML) is a heterogenous clonal disorder that is characterized by uncontrolled clonal expansion of myeloid progenitor cells (blasts) that leads to bone marrow failure. Myelodysplastic syndrome (MDS) is a distinct heterogenous clonal disorder characterized by bone marrow dysplasia and ineffective hematopoiesis that leads to peripheral cytopenias and a variable clinical course. The pathogeneses of both these disorders includes recurrent genomic alterations that help define biologically distinct clinical subtypes (Döhner *et al.,* 2017; Papaemmanuil *et al.,* 2016). Despite the significant advancement in our understanding of genetic abnormalities that drive AML pathogenesis, the overall therapeutic algorithm has remained relatively static for several decades. Improved understanding at the genomic level has led to the emergence of some promising targeted therapies in the past year, however, at present prognosis of patients with relapsed or refractory disease remains poor. Thirty percent of MDS patients will progress to AML, and survival for AML arising from MDS is dismal.

Recurring heterozygous *IDH1* mutations were identified as one of the most frequently occurring mutations in the AML cancer genome sequencing project (Mardis *et al.,* 2009; Cancer Genome Atlas Research 2013). Mutations in *IDH2*, the mitochondrial homolog of *IDH1*, are present in approximately 10% of patients with AML (Clark *et al.,* 2016). *IDH 1/2* mutations are also present in 5-12% of patients with MDS (DiNardo *et al.,* 2015a). The normal function of isocitrate dehydrogenase (IDH) enzymes is to catalyze the conversion of isocitrate to α-ketoglutarate (αKG) in the citric acid cycle. In AML there are three recurring pathogenic single allele missense *IDH* mutations (*IDH1-R132*, *IDH2-R140*, *IDH2-R172*) that occur within the conserved active site and lead to loss of the expected Krebs Cycle reaction (Ward *et al.,* 2010). These mutations confer a neomorphic activity on the encoded enzymes, such that they convert α-KG to (R)-2-Hydroxyglutarate (2HG) (Dang *et al.,* 2010). Emerging research indicates that (R)-2HG is an oncometabolite, with pleiotropic effects on cell biology, including chromatin methylation and cellular differentiation, although many questions remain about its impact on tumorigenesis and therapy response (Losman and Kaelin, 2013; Molenaar *et al.,* 2014). In AML, increased cellular 2HG levels contribute to epigenetic mechanisms of pathogenesis by inhibiting αKG-dependent enzymes that are important for normal deoxyribonucleic acid (DNA) methylation (Conway O'Brien *et al.,* 2014; Dang *et al.,* 2016). The prognostic significance of IDH mutations in AML is controversial due to the influence of co-occurring mutations as well as the specific point mutation involved (DiNardo *et al.*, 2015b; Green *et al.*, 2011; Paschka *et al*., 2010), however IDH1/2 mutations have a more consistently negative prognostic impact in MDS with shorter overall survival and greater risk for leukemic progression (Bejar *et al.*, 2015; Jin *et al.*, 2014; Medeiros *et al.*, 2017; Thol *et al.*, 2010).

2.1.1 Evidence supporting PARP inhibitor testing in IDH1/2-mutant tumors with a focus on IDH 1/2 mutant AML and MDS

Therapies for AML and MDS remain very limited, despite advancement in our understanding of disease biology, particularly in the setting of chemotherapy and hypomethylating agent refractory disease, respectively. Approximately 20% of AML patients and up to 12% of MDS patients harbor *IDH1/2* mutations (Papaemmanuil *et al.*, 2016). While a Food and Drug Administration (FDA) approved IDH-1 and -2 inhibitors are available for *IDH*-mutant AML, mutant IDH1/2 inhibitors simply block the neomorphic function of the mutant proteins, without evidence of impact on the mutant IDH clone. There is no clear biomarker to predict response to mutant IDH inhibitors and of the responders, a clear majority will eventually relapse. Recent publications have determined that patients who relapse almost uniformly develop either resistance mutations that impede IDH inhibitor binding or isoform switch from one IDH enzyme to the other (Harding *et al.*, 2018; Intlekofer *et al.*, 2018). In either case, at the time of relapse from mutant IDH inhibitors there is an increase in production of the oncometabolite 2HG, that was suppressed by the inhibitors.

2HG exists as two enantiomers, (R)-2HG and (S)-2HG, and both are implicated in tumor progression via their inhibitory effects on αKG-dependent dioxygenases (Xu et al., 2011). The former is an oncometabolite that is induced by the neomorphic activity conferred by IDH1/2 mutations, while the latter is produced under pathologic process such as hypoxia. Our collaborators at Yale University (Drs. Bindra and Halene) made the novel discovery that IDH1/2 mutations induce a homologous recombination (HR) defect which renders tumor cells exquisitely sensitive to Poly (ADP-Ribose) polymerase (PARP) inhibitors (Sulkowski *et al.*, 2017). As 2HG accumulates in IDH1/2-mutant cells, HR disruption causes cells to rely on alternate low fidelity DNA repair pathways, thus hastening genomic instability and cell death. Remarkably, this “BRCAness” phenotype can be completely reversed by treatment with small molecule inhibitors of mutant IDH1, and, conversely, it can be entirely recapitulated by treatment with 2HG alone in cells with wild-type (WT) IDH1/2. IDH1-dependent PARP inhibitor sensitivity in a range of clinically relevant models, including primary patient-derived glioma cells in culture, genetically-matched tumor xenografts *in vivo* and patient derived AML cells. Similar synthetic lethal interaction between IDH1/2 mutations and PARP inhibitors were also reported by other laboratories, which further strengthens the validity of this discovery (Molenaar *et al.*, 2018). Collectively, these findings directly challenge the current therapeutic strategy to block IDH1/2-mutant function, and they instead provide a novel approach to treat IDH1/2-mutant tumors with PARP inhibitors. Furthermore, these results uncover an unexpected link between oncometabolites, altered DNA repair, and genetic instability.

Thus, PARP inhibitor therapy could potentially eradicate the mutant hematopoietic stem cell by exploiting intrinsic cellular defects in *IDH* mutant cells, which will lead to durable remission. For patients previously treated with mutant IDH inhibitors, at the time of progression/treatment failure 2HG production is restored, also “restoring” their HR defect and PARP sensitivity.

2.1.1.1 Overview

IDH1/2 mutations induce an HR defect that renders tumor cells sensitive to PARP inhibition; the mechanism of action for this interaction is summarized in Figure 1 (Sulkowski *et al.,* 2017). This novel and unexpected phenotype was validated across five unique and genetically diverse cell line pairs that were engineered to express either the WT or the mutant IDH1/2 proteins, and the Bindra lab confirmed the observed double strand break (DSB) repair defect using multiple orthogonal functional assays. This interaction was also demonstrated in a number of clinically relevant models, including *IDH*1/2-mutant primary patient-derived cell lines and genetically-matched tumor xenografts.

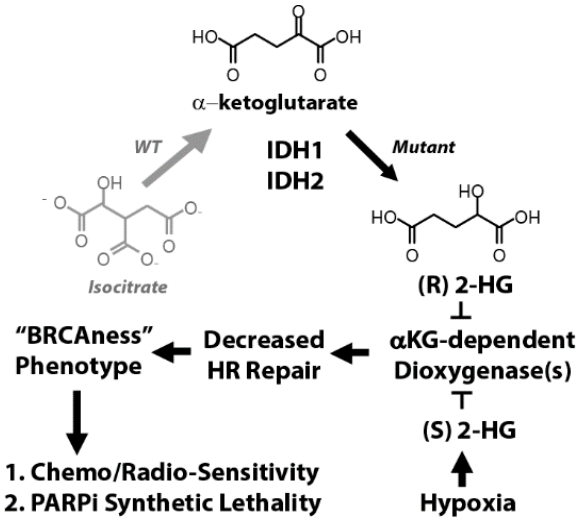


Fig. 1. Proposed mechanism of action of mutant *IDH1/2*-induced BRCAness and consequent PARP inhibitor synthetic lethality.

2.1.1.2 Mutant *IDH1/2*-induced 2HG suppresses HR and confers exquisite PARP inhibitor sensitivity.

The Bindra Laboratory created a clustered regularly interspaced short palindromic repeats-associated (CRISPR/Cas)-engineered R132H model cell line, and subsequently utilized it in a focused, unbiased screen for synthetic lethal interactions with a large collection of DNA damaging agents and DNA repair inhibitors (Sulkowski *et al.,* 2017). This screen revealed an unexpected interaction between mutant *IDH1* and PARP inhibitor sensitivity (Table 1). This novel finding was then validated in a comprehensive series of clonogenic survival assays, to quantify the magnitude of differential sensitivity. The mutant *IDH1*-dependent PARP inhibitor sensitivities were profound and approached a 50-fold difference compared to *IDH1*-WT cells, with the FDA-approved PARP inhibitor, olaparib (Figure 2). This interaction was confirmed with a number of PARP inhibitors, suggesting a class-effect. In addition, a similar phenotype in *IDH2*-mutant cells was confirmed (Sulkowski *et al.,* 2017). These results were reproducible in several cell lines, including a doxycycline (dox)-inducible *R132H*-mutant *IDH1* ORF (Turcan *et*

Table 1 Summary of Initial Sensitivity Screen

Small Molecule Inhibitor		IC50 (uM)		WT/Mut Ratio
Name	Target(s)	IDH1-WT	IDH1-Mut	
BMN-673	PARP	0.27	0.03	9.0
VE822	ATR	0.16	0.06	2.6
TH287	MTH1	0.73	0.75	1.0
TCS2312	CHK1	0.23	0.22	1.0
BEZ-235	PI3K/mTOR*	0.07	0.06	1.3
KU55933	ATM	8.65	6.01	1.4
AZD7762	CHK1	0.08	0.07	1.2
NU7441	DNA-PK	6.03	6.71	0.9
KU0060648	DNA-PK	0.03	0.03	1.0
MK1775	Wee1	0.27	0.21	1.3

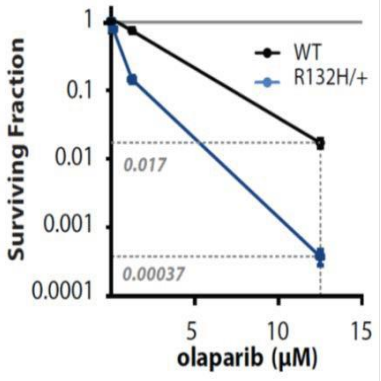


Fig. 2. Synthetic lethal interaction between the IDH1-mutation and PARP inhibition in HCT116 cells.

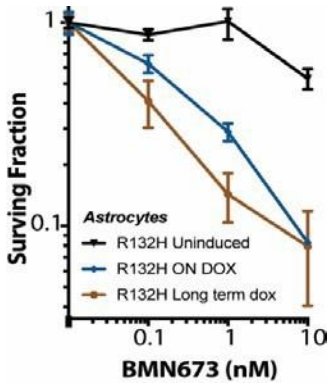


Fig. 3. PARP inhibitor sensitivity in an immortalized astrocyte cell line with dox-inducible mutant IDH1 ORF.

al., 2012) astrocyte cell line, where both transient and long-term induction of mutant IDH1 protein expression conferred marked levels are BMN-673 sensitivity, as detected by clonogenic survival analysis (Figure 3), as well as several additional human glioma cell lines.

In addition, the Bindra lab demonstrated the *IDH1/2*-induced BRCAness phenotype in a range of AML/MDS-related and clinically relevant, primary models *in vitro*, including patient-derived glioma cell lines and primary AML bone marrow cultures (Sulkowski *et al.,* 2017). For example, in primary bone marrow cultures derived from AML patients with known *IDH1* or

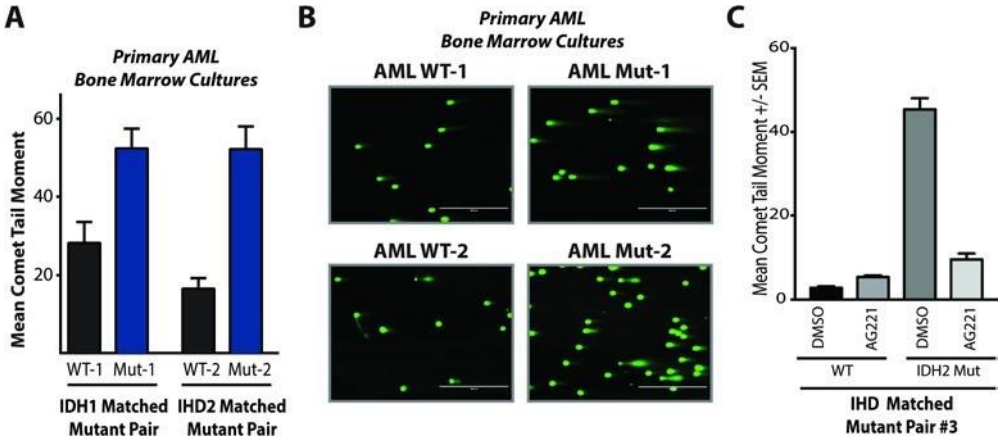


Fig. 4. (A) Evidence of a DNA repair defect in IDH1/2-mutant primary bone marrow cultures, as detected by comet assays, **(B)** representative comet assay images, and **(C)**, reversal of the observed DNA repair defect using small molecule mutant IDH2 inhibitors.

IDH2 mutations, increased baseline persistence of DSBs by comet assay, which is a classic approach to assess functional DSB repair activity, were detected compared to their WT counterparts (Figure 4a,b). Furthermore, this phenotype was completed reversed by treatment with small molecule mutant IDH2 inhibitors (Figure 4c).

2.1.1.3 Mechanism of action studies and effects of small molecule mutant IDH1 inhibitors

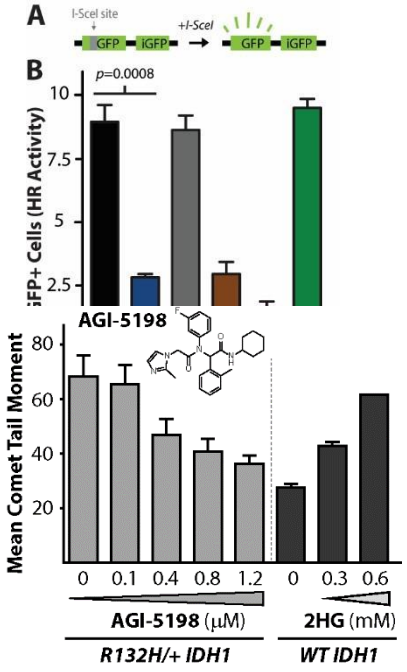


Fig. 6. Reversal of the IDH-associated DSB repair defect with a small molecule inhibitor of mutant IDH1, which can me recapitulated in IDH WT cells by treatment with 2HG alone.

Functional DSB repair assays confirmed a profound HR defect in *IDH1/2*-mutant cells (Sulkowski *et al.,* 2017). Remarkably, our collaborators in the Bindra lab found that 2HG alone was sufficient to down-regulate HR repair activity in cells with WT *IDH1/2* genes. Suppression of HR by 2HG was significant and was observed after the attenuation of two key HR genes, *BRCA2* and *Rad51*, using the well-established DR-GFP assay to measure the activity of this pathway (Figure 5). Mechanistically, this phenotype can be entirely recapitulated by exposure to either 2HG enantiomers, and it cannot be explained by the alterations in nicotinamide adenine dinucleotide (NAD)+ levels that have been seen in IDH1/2-mutant cancers (Tateishi *et al.,* 2015). These data suggest that 2HG-induced HR suppression is mediated via direct inhibition of αKG-dependent dioxygenases, in particular KDM4A. We can recapitulate the *IDH1/2*-associated HR-defective phenotype by treatment of WT cells with small molecule KDM4A inhibitors, and can reverse the effect in mutant cells by overexpression of KDM4A. Importantly, it was noted that treatment with a mutant IDH1-specific small molecule inhibitor known to potently suppress 2HG production (and similar to drugs that are currently in clinical trials) <u>*reversed*</u> the observed HR defect and eliminated the associated PARP inhibitor sensitivity. This reversal was demonstrated in both mutant *IDH1/2* cell lines, and also in a cell line harboring an endogenous *IDH1* mutation. Reversal of the mutant *IDH1*-associated DSB repair defect was confirmed using three unique small molecule inhibitors of the mutant protein, and also with siRNAs targeting the *IDH1* gene, thus ruling out potential off-target effects of the inhibitors. These data strongly suggest that inhibition of mutant IDH1 activity with small molecule inhibitors, as is currently being pursued in multiple clinical studies, is <u>not</u> the most efficacious approach to treat these tumors. This is also the rationale for inclusion of IDH inhibitor naive patients despite the availability of IDH2 inhibitors as part of standard of care (further described in Section 2.3). Representative data from our group that supports these findings is presented in Figure 6, and extensive data supporting these findings is provided in our manuscript. In addition, this work showed that 2HG exposure induced elevated rates of DSBs in a range of cell lines with diverse genetic backgrounds, including immortalized astrocytes, primary melanoma cultures, breast cancer cell lines, and U2OS cells, suggesting that this is a fundamental effect of this metabolite. Of note, treatment of plasmid DNA with 2HG *in vitro* for 8 hours did not induce any DNA cleavage, which ruled out any possible direct effect of this molecule on DNA. Representative data supporting these findings is presented in Figure 7 (from

our group) for reference.

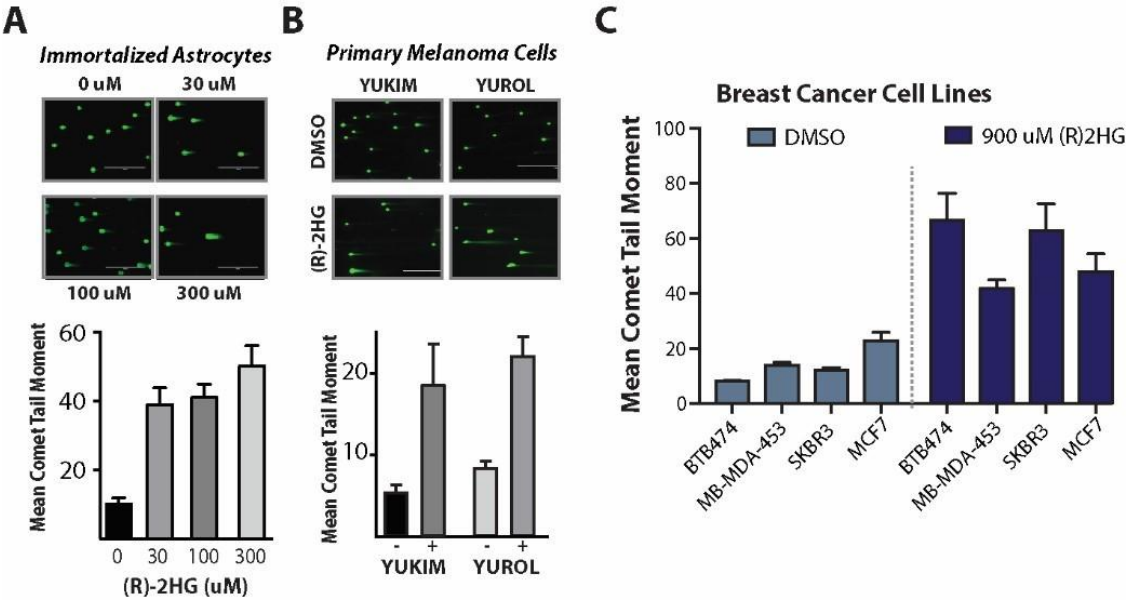


Fig. 7. 2HG exposure induces a DSB repair defect in cell lines with diverse genetic backgrounds.

2.1.1.4 *In vivo* synthetic lethal interaction between mutant *IDH1* tumors and PARP inhibition

IDH1-mutant mouse xenografts treated with PARP inhibitors showed a statistically significant growth delay when compared to vehicle control. In contrast, no statistically significant differences between PARP inhibitors and vehicle in *IDH1*-WT tumor xenografts were detected. This effect was confirmed with two isogenic pairs of *IDH1*-mutant versus –WT cell lines grown as xenografts (HCT116 and HeLa), as well as cell lines with endogenous *IDH1* mutations (*e.g.,* HT1080 fibrosarcoma cell lines, which harbor an R132C *IDH1* mutation). Representative data from out group for HCT116 tumor xenografts is shown in Figure 8 for reference.

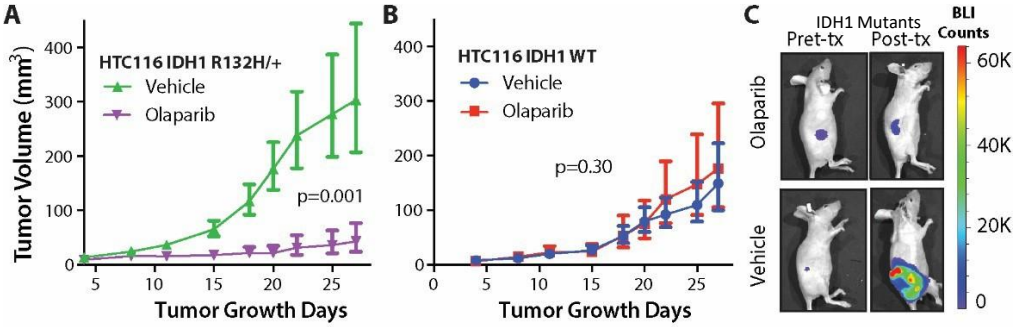


Fig. 8. (A) PARP inhibitors selectively kill HCT116 IDH1-mutant tumor xenografts with **(B)** minimal effects on IDH1-WT cells; **(C)** BLI monitoring of treatment responses.

2.1.1.5 Mutant *IDH1/2* synthetic lethality correlates with PARP trapping activity of PARP

inhibitors.

Recent studies from the Bindra group indicate that PARP inhibitors which specifically "trap" PARP protein at sites of DNA damage, are most effective against IDH1/2-mutant cells. Examples of PARP-trapping PARP inhibitors include: BMN-673, niriparib, ruciparib BGB-290, and olaparib (Murai *et al.,* 2012). In contrast, veliparib, while very effective as a catalytic inhibitor of PARP function, is an extremely poor PARP-trapper (Murai *et al.,* 2012). These PARP inhibitors were profiled for synthetic lethality with *IDH1*-mutant vs. WT cells, which confirmed activity with these PARP-trapping PARP inhibitors, and also that veliparib was not effective under these conditions. Representative data for BGB-290 is presented below in Figure 9, and data for olaparib and BMN-673 was presented above.

2.1.2 Clinical efficacy of Synthetic Lethal Targeting of HR defects with PARP inhibitors

Olaparib is an orally bioavailable PARP inhibitor that has been approved by the FDA as the first monotherapy to treat *BRCA*-mutant advanced ovarian cancer (Kim *et al.,* 2015). PARP is involved in surveillance and maintenance of genome integrity and functions as a key molecule in the repair of DNA single-stranded breaks (SSBs) (Pommier *et al.*, 2016). PARP-inhibited cells accumulate unrepaired SSBs leading to double strand breaks when encountered by the replication machinery.

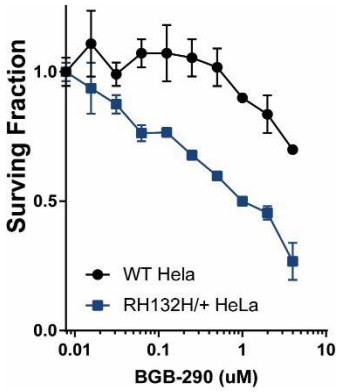


Fig. 9. Confirmation of PARP-trapping PARP inhibitor sensitivity with BGB-290 in IDH1-mutant versus – WT cells.

Based on the principle of synthetic lethality, treatment with single-agent PARP inhibitor has a dramatic therapeutic impact in a proportion of patients with germ-line or tumor-based (somatic) mutations in *BRCA1* or *BRCA2*. Favorable response data have also been observed in a subset of patients without evidence of *BRCA1/2* mutations, and there is emerging consensus that other molecular alterations in DNA repair pathways, including HR deficiency, can increase the likelihood of response to PARP inhibitors (Bryant *et al.,* 2005; Farmer *et al.,* 2005). There are now three FDA-approved PARP inhibitors for the treatment of HR-deficient ovarian cancer, and it is likely that several more will be approved in the next 2-3 years. Robust response rates have been observed with these agents, often with PFS improvements in the range of 2-5 fold compared to control groups (Curtin and Szabo, 2013).

The use of DNA repair inhibitors in IDH1/2-mutant malignancies is analogous to the rationale used for treating BRCA-deficient cells with a PARP inhibitor. As 2HG accumulates in IDH1-mutant cells, HR is disrupted which causes cells to rely on alternative low fidelity DNA repair pathways, thus hastening genomic instability and cell death. This creates a "BRCAness" phenotype which renders them increasingly susceptible to agents that impair the DNA damage response.

2.1.3 Targeted therapy for *IDH* mutant Acute Myeloid Leukemia/Myelodysplastic Syndrome Clinical trials and use of PARP inhibitors

Ongoing trials of targeted therapy for *IDH1/2*-mutant AML and MDS thus far have primarily focused on the impact of new allosteric inhibitors of mutant IDH. The first in class IDH inhibitor is the IDH2 inhibitor AG-221, or enasidenib, and was approved by the FDA for relapsed or refractory AML demonstrated clinical efficacy in AML as a single agent with responses in approximately 40% of patients with *IDH2* mutations (Stein *et al.,* 2017). However, response was relatively short lived, with median DOR of less than 6 months, with persistence of mutant *IDH2* clones. More recently, ivosidenib, an IDH1 inhibitor was also approved by the FDA based on similar response rates (DiNardo *et al.,* 2018) in the *IDH1* mutant population. Several other IDH1, IDH2, and dual IDH1/2 inhibitors are currently investigated in early phase trials as single agent therapies, as well as in combination with hypomethylating agents or intensive chemotherapy. At the present time there are no approved targeted therapies for IDH1 mutant leukemia and IDH 1/2 mutant MDS.

There is very limited data assessing the PARP inhibitor therapy in AML or MDS. Molecular and pre-clinical data previously demonstrated PARP inhibitor sensitivity in leukemic cells driven by AML1 protein-eight Twenty One (AML1-ETO) and promyelocytic leukemia protein-retinoic acid receptor-alpha (PML-RARα), which suppress DNA damage repair (Esposito *et al.,* 2015), and anti-leukemic activity when combining PARP inhibitors with DNA damaging agents. Applying this concept, a recent Phase 1 trial assessed the safety of the combination of temozolomide, a DNA damaging agent with veliparib, a PARP inhibitor (Gojo *et al.,* 2017). This combination was well tolerated. In addition, there is one ongoing Phase 1 trial of the PARP inhibitor talazoparib in an unselected population combining several hematologic malignancies (NCT01399840) that has completed accrual (results are not yet available). This is encouraging with regard to tolerability for our proposed olaparib monotherapy Phase 2 trial.

A Phase 1/2 clinical trial in an unselected relapsed/ refractory AML population combining PARP inhibitors with decitabine, a hypomethylating agent, (NCT02878785) is currently underway. The additive benefit of a PARP inhibitor in an unselected population of patients may be limited, with an underwhelming response rate overall, but with robust response in the *IDH* mutant population. Given the frequency of *IDH* mutations in an unselected AML population, this may lead to a negative trial, despite efficacy in a selected population. By limiting our trial to patient's with *IDH* mutations that are known to intrinsic cellular defects sensitizing them to PARP inhibitor therapy, we will maximize our chance of success.

Phase 1/2 trials combining other DNA damaging agents, such as topotecan/ carboplatin, with veliparib (a PARP inhibitor with poor PARP trapping function) in an unselected population of hematologic malignancies are also currently underway (NCT00588991, NCT03289910), however we postulate that combination therapy may prove be too toxic for many patients with relapsed or refractory acute leukemia, particularly due to hematologic toxicity in an already vulnerable population. Additionally, the benefits of PARP inhibition may not be as robust given the use of veliparib in these trials. Finally, we are cognizant of the fact that PARP inhibitors have been implicated in the development of MDS/AMLwhich raised some concern and warrants judicious use of the therapy (development of MDS/AML was noted in less than 1.5% of patients, or 21/1680 patients, with olaparib monotherapy in clinical trials, including long term follow up per FDA review) (Highlights of Prescribing Information: Lynparza, 2018). Rationale for the use of olaparib in this setting would include the fact that all the patients who developed these

secondary hematologic malignancies were heavily pre-treated with DNA damaging agents such as platinum agents and ionizing radiation, which are not part of the treatment algorithm for management of MDS or AML, and more importantly, we strongly believe that in this select subset of AML and MDS patients the benefit of olaparib will greatly outweigh any potential risk. Similar to anthracyclines, which are known to cause secondary hematologic malignancies, but remain part of the backbone of induction therapy, we believe PARP inhibitor therapy will become a key component of management of IDH mutant hematologic malignancies in the near future.

By targeting the IDH mutant leukemia/ MDS population with olaparib, a PARP-trapping PARP inhibitor, we expect a robust response; synthetic lethality without the additive toxicity of chemotherapy. Our proposed trial is the first study that will test the efficacy of a PARP inhibitor-based therapeutic regimen specifically targeting IDH1/2-mutant relapsed or refractory AML and MDS.

2.2 Olaparib (AZD2281)

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (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.

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA SSBs. Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA DSBs during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by HR. Tumors with HR deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models *in vivo* (Rottenberg *et al.,* 2008, Hay *et al.,* 2009) and in the clinic (Fong *et al.,* 2009). The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday 2011; Murai *et al.,* 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumor cell lines *in vitro* and in xenograft and primary explant models as well as in genetic *BRCA* knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

2.2.1 Mechanism of Action

The mechanism of action for olaparib activity as a single agent has been proposed to involve the trapping of inactivated PARP onto the single-strand breaks preventing their repair and generating

a potential block for cellular DNA replication (Helleday, 2011; Murai *et al.,* 2012). An important consequence of this is that processing of trapped PARP-DNA complexes and/or the stalling of replication forks, or collapsing of replication forks, is predicted to lead to the generation of the more serious DNA DSBs. These DSBs would normally be repaired by a process that involves Ataxia Telangiectasia Mutated (ATM) (a major DNA DSB signaling kinase, the 'MRN' nuclease protein complex; made up of Meiotic Recombination 11 Homolog A [MRE11A], human RAD50 homolog [RAD50] and Nijmegen breakage syndrome1 [NBS1]) and additional homologous recombination DNA repair (HRR) proteins such as *E. coli* DNA repair protein RAD51 homolog (RAD51), BRCA1, and BRCA2.

In some instances where DNA repair defects may not result in the same level of sensitivity as *BRCA* mutations, and therefore single agent olaparib treatment may not be sufficient to induce cell kill through synthetic lethality, it may still be possible to induce tumor cell death through combinations with ionizing radiation or chemotherapies that either increase DNA damage accumulation or mitotic stress. The latter is relevant since it is often during mitosis that unrepaired DNA damage leads to cell death through a process known as mitotic catastrophe (Castedo *et al.,* 2004).

2.2.2 Clinical Pharmacokinetics and Metabolism

As of December 15, 2017, there is pharmacokinetic (PK) data from 11 clinical studies. Olaparib is orally available and the tablet formulation is rapidly absorbed, reaching peak plasma concentration (t_{max}) in 1.5 hours (Investigator's Brochure, 2018). The plasma concentrations decline in a biphasic manner with an average terminal elimination half-life ($t_{1/2}$) of 14.9 hours (standard deviation [S_d] 8.2 hours). The mean apparent oral clearance rate was approximately 7.4 L/hour (S_d 3.9 L/hour). The mean volume of distribution (V_d) of olaparib following a single administration of 300 mg oral tablet dose was 158 L (S_d 136 L) indicating olaparib is distributed into the tissues.

The metabolism of olaparib was assessed in a study of six female patients ranging in age from 34-72 years (Investigator's Brochure, 2018). Upon the administration of a single 100 mg dose of olaparib containing 1x50 mg capsule of radiolabeled [^{14}C]-olaparib and 1x50 mg capsule of unlabeled olaparib, 70% of the radioactivity in the blood was olaparib. Three metabolites each comprised around 10% of the material: M12 (9.3%, ring-open piperazin-3-ol), M15 (10.3%, 4-fluorophenol (hydroxy)methyl), and M18 (13.7%, piperazin 3-ol).

Olaparib is eliminated in both the urine (44% of the dose) and feces (42% of the dose) (Investigator's Brochure, 2018). In the urine, olaparib was the most abundant component, accounting for between 10% and 19% of the dosed material. Up to 37 further drug-related components were observed, 18 of which were quantifiable by high performance liquid chromatography with mass spectrometric detection (HPLC/MS) with radioactivity detection. At least 20 components were observed in the pooled fecal samples with 6 components accounting for >1% of the dose and the remaining metabolites detectable only by HPLC/MS. The major components present were unchanged olaparib (0.6 to 14% of the dose) and M15 (0.9 to 8% of the dose). Four further metabolites (M9, M12, M23 and M25) were also prominent each accounting for ≤6% of the dose.

The PK parameters for multiple dosing of olaparib are well predicted from the single dose studies. There is not extensive accumulation with multiple dosing. At 300 mg oral dose bis in die (BID), the temporal change parameter (area under the curve [AUC] at steady state/AUC following a single dose) was approximately 1.5 (S_d 0.6) (Investigator's Brochure, 2018).

At capsule doses ≥40 mg, the inhibition of PARP-1 measured in peripheral blood mononuclear cells (PBMC) reached its maximum of 50% to 60% of the baseline, and this level of inhibition was achieved by 6 hours after the first dose of olaparib and was maintained with repeated dosing (Investigator's Brochure, 2018). In tumor biopsies from 60 breast cancer patients who received doses of olaparib between 10 mg BID and 400 mg BID, PARP inhibition ranged from 20% to 80% and did not relate to the dose.

2.2.3 Clinical Safety Summary

Olaparib monotherapy has been associated with adverse reactions generally of mild or moderate severity (Common Terminology Criteria for Adverse Events v.5.0 [CTCAE] Grade 1 or 2) and generally not requiring treatment discontinuation (Investigator's Brochure, 2018). In a pool of 1248 patients, the most frequently observed adverse reactions across clinical trials in patients receiving olaparib monotherapy (≥10%) were nausea, vomiting, diarrhea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, and anemia. Anemia and other hematologic toxicities were generally low grade (Grade 1 or 2). However, anemia was the most commonly reported Grade ≥3 adverse event (AE) reported in clinical trials. The median time to first report of anemia was approximately 4 weeks (approximately 7 weeks for Grade ≥3). Anemia can be managed with dose interruptions, dose reductions, and blood transfusions where appropriate. In one Phase 3 trial in ovarian cancer patients, the incidence of anemia was 43.6% of patients, with Grade ≥3 in 19.5% of patients, leading to dose interruptions (16.9%), dose reductions (8.2%), discontinuation of treatment (3.1%). In addition, 17.9% of patients treated with olaparib required one or more blood transfusions during treatment.

In clinical studies with olaparib the incidence of Grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 15% (Investigator's Brochure, 2018). Data from a double-blind placebo-controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae; 90% of patients had creatinine values of Grade 0 at baseline and 10% were Grade 1 at baseline.

Nausea was generally reported very early, with first onset within the first month of olaparib treatment in the majority of patients (Investigator's Brochure, 2018). Vomiting was reported early, with first onset within the first 2 months of olaparib treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients and can be managed by dose interruption, dose reduction and/or antiemetic therapy. Antiemetic prophylaxis was not required.

Studies of olaparib in combination with various chemotherapy agents indicate an increase in bone marrow toxicity (anemia, neutropenia, thrombocytopenia) greater than expected if the

agents had been administered alone (Investigator's Brochure, 2018). The effects are generally transient, but treatment delays are common and alternative administration schedules/toxicity management processes have been evaluated within some of these studies. When this type of toxicity has occurred, it has been managed by routine clinical practice including dose delays, dose reductions, intermittent dosing, and/or the use of supportive care measures, including granulocyte colony stimulating factor (G-CSF).

The incidence of developing MDS/AML in patients treated in clinical trials with olaparib monotherapy, including long-term survival follow-up, was <1.5% and the majority of events had a fatal outcome (Investigator's Brochure, 2018).

Pneumonitis has been reported in <1.0% patients treated with olaparib monotherapy in clinical studies (Investigator's Brochure, 2018). When olaparib was used in clinical studies in combination with other therapies there have been events with a fatal outcome. If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or an abnormal chest radiologic finding is observed, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately.

2.3 Rationale

As shown in the study schema the proposed study is a 4-arm Phase 2, open-label study of PARP inhibition (olaparib) in advanced relapsed or refractory *IDH1/2*-mutant AML and MDS. At present, an IDH2 and IDH1 inhibitor, enasidinib and ivosidenib respectively, are FDA approved for the management of patients with IDH2 mutant leukemia (Stein *et al.,* 2015; DiNardo *et al.,* 2018). Based on the scientific rationale described (synthetic lethality of the mutant clone due to accumulation of toxic metabolites), we hypothesize that inhibition of mutant IDH1/2 with small molecule inhibitors is not the most efficacious approach to treat IDH mutant leukemia. Indeed, the synthetic lethality of olaparib is likely most robust in the setting of IDH mutant activity (due to oncometabolite accumulation), and possibly blunted to some degree with the use of an IDH inhibitor. Therefore, we propose a separate arm for evaluation of patients pretreated with IDH inhibitor therapy. In addition, we propose the inclusion of IDH inhibitor -naïve AML patients who present within a "window of opportunity" in this trial (IDH inhibitors are yet to be approved in the MDS setting. AML and MDS have been separated as they are distinct diagnoses, and within each disease group patients have been separated by their exposure to IDH inhibitors; IDH inhibitor naïve and IDH inhibitor exposed. Recognizing that other FDA approved therapeutic options are available, but also that these patients may have a dramatic response to olaparib monotherapy, IDH inhibitor naïve patients will be monitored very closely, including frequent bloodwork and bone marrow evaluation 4 week (or earlier as needed) to safeguard against progression and allow for transition to standard of care therapy within the 12-week period prior to response assessment in the case of progression.

Relapsed/ refractory patients may also have co-occurring targetable mutations, such as FLT3 ITD. At the present time there is no consensus in the AML community on the ideal sequencing of targeted therapies when multiple options are applicable. This is reflected in the current NCCN AML recommendations. In these situations, we will need to rely on the judgement of the local

investigator/ provider to choose the optimal therapeutic option.

In this study, we propose to directly translate our laboratory findings into a proof of concept, biomarker-driven Phase 2 clinical trial. Our study will specifically target IDH1/2-mutant AML and MDS. Phase 1 data combining other PARP inhibitors (*e.g*., veliparib) and DNA damaging agents have demonstrated that this therapeutic strategy is well tolerated, with activity in an unselected advanced AML population. These results are likely to be amplified in a mutant *IDH1/2*- selected population, and with the use of a more potent PARP inhibitor, olaparib. There is concern regarding the risk of development of MDS and AML associated with PARP inhibitors. We believe that by selecting IDH mutated patients, we will significantly increase the therapeutic index and the benefit will greatly outweigh the risk. We will determine the safety of olaparib in *IDH* mutant relapsed or refractory AML and MDS, and subsequently evaluate the overall response rate of this population. In addition, we will employ several unique biomarkers, including 2HG detection in both plasma and bone marrow biopsy samples to refine our understanding of disease response. This Phase 2 trial that will utilize a Simon 2-stage design. This study will be open at all ETCTN sites, which supports our ability to accrue patients for this study in a reasonable time-frame.

This study has the potential to establish a completely novel treatment approach for IDH1/2-mutant tumors, and they will lay the groundwork for future studies aimed at exploiting, rather than suppressing, 2HG-induced BRCAness in AML and MDS.

2.4 Correlative Studies Background

The molecular landscape of cancer is just beginning to be defined. However, we do not know enough about the genomic and molecular landscape of tumors from patients who enter early phase clinical trials. With this study, we will attempt to learn more about specific molecular features of cancers from this patient subgroup. It is particularly important to learn, as early as possible, if there are molecular features within a particular malignant histology or across malignant histologies that can inform about potential response or resistance to treatments in early phase clinical trials. Such knowledge will be used to design more efficient later stage clinical trials for more efficient and more effective drug development.

2.4.1 Integral Biomarker

2.4.1.1 *IDH1* or *IDH2* mutation

This approach to select patients is commonly used in several recent and ongoing clinical trials focused on *IDH1/2*-mutant tumors (*e.g.*, NCT02454634, NCT02771301, NCT02381886, NCT02826642, NCT02074839, NCT02746081, NCT01915498, NCT02481154).

2.4.2 Integrated Biomarkers

2.4.2.1 Peripheral blood and bone marrow 2HG levels

The main objectives of this assay are to: 1) correlate the chances of response to olaparib with baseline 2HG levels and 2) evaluate the longitudinal variations of 2HG levels as a marker of response to treatment and progression.

Based on our experience, as detailed in the background section, the "BRCAness" of IDH mutated patients is related to the exposure of the cell to 2HG. We hypothesize that patients with elevated levels of 2HG may have a better response to olaparib. We also want to confirm that olaparib is able to reduce the levels 2HG and maintain low levels of 2HG in treated patients.

2.4.3 Exploratory Biomarkers

2.4.3.1 Genomic profiling

Objectives:

- The molecular landscape of *IDH1/2*-mutant AML and MDS predictably determines 2HG level.
- The features on this molecular landscape serve as candidate predictive biomarkers of treatment response.
- To evaluate the impact of olaparib on clonal architecture and clonal evolution.

We hypothesize that 1) the molecular landscape of *IDH1/2*-mutant AML and MDS predictably determines 2HG level, and 2) the features on this molecular landscape serve as candidate predictive biomarkers of treatment response. We will test these hypotheses by comprehensive genomic profiling to elucidate co-occurring mutations, DNA methylation patterns, and gene expression profiles, in all patients enrolled on this study. We will study baseline and on-treatment bone marrow aspirate samples, and also at progression when possible, which also will allow us to assess changes in mutant IDH1/2 variant allele fractions, and also to probe for the emergence of molecular resistance markers over time.

For the WES studies, we will search for tumor-specific mutations in known oncogenes and tumor suppressors, as well as additional gene mutations. We are particularly interested in mutations known to co-occur with *IDH1/2* mutations: *NPM1*, *FLT3*, *SRSF2*, *DNMT3A*, *NRAS*, *KRAS*, *RUNX1*, *KMT2A*, *PTEN*, *PHF6*, *TP53*, *BCOR*, *STAG2*, *etc*. (see Figure 10 where 79% of 375 AML cases show genetic alterations from this list). For single cell DNA Seq studies we will base the sequencing panel on mutations identified by the clinical targeted exome and the research WES. We will perform single cell DNA seq on baseline, best response and progression samples. For the RNAseq studies, we will use previously published and publicly available data sets to test whether our cases can be categorized within gene expression clusters found in *IDH1/2*-mutant cancers, using a k-nearest neighbor classification procedure. In addition, we will use RNAseq data to identify recurrent translocations. For the methylation studies, we will use previously published and publicly available data sets (Huang *et al.,* 2018; Benetatos and Vartholomatos, 2018; Wang *et al.,* 2018) to test whether our cases fall within unique methylation clusters found in *IDH1/2*-mutant cancers.

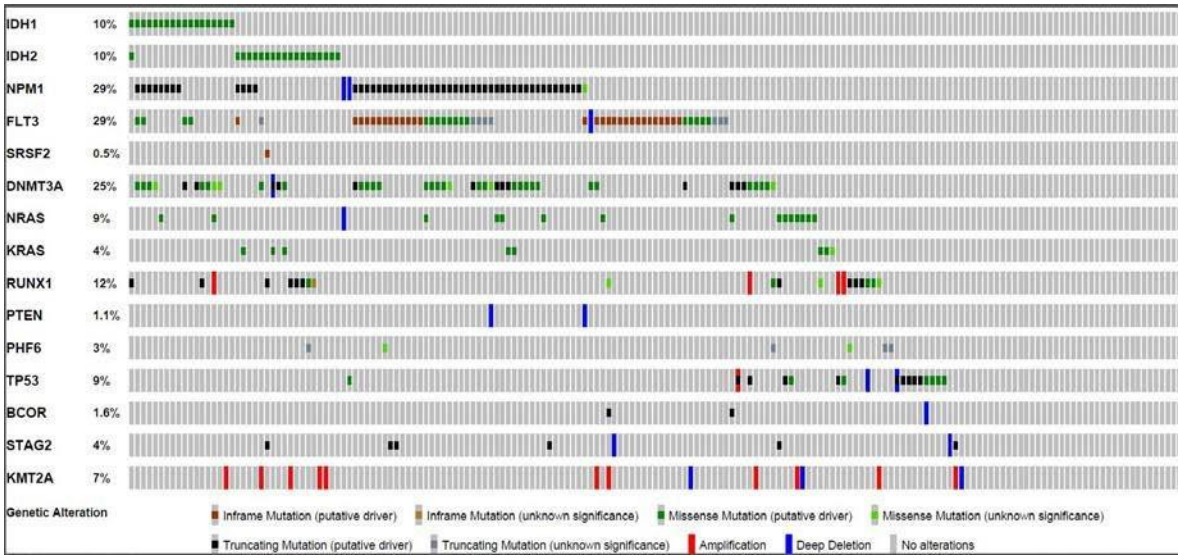


Figure 10: Oncoprint analysis of selected oncogenes and tumor suppressor genes and other reported co-occurring genes in 375 AML cases from TCGA, NEJM 2013 and AML TCGA Provisional).

2.4.3.2 Phamacometabolomic profiling

Objective:

- Olaparib may induce a specific metabolic signature that may correlate with clinical response.

Novel metabolomics technologies allow high-throughput assessment of a large number of endogenous metabolites, which provide powerful tools for mapping biochemical pathways implicated in disease and in response to drug treatment. Pharmacometabolomics is an emerging field that applies metabolomics to define metabolic signature of drug exposure, thereby enabling identification of biochemical pathways implicated in drug efficacy and adverse drug reactions.

We hypothesize that by defining metabolite profiles both at baseline (prior to) and post drug exposure, pharmacometabolomics profile modifications will provide early insights into

mechanism of drug action and molecular basis for variation in drug response.

We will also explore the feasibility of comparing this signature with similar signatures from patients treated with olaparib in the context of solid tumor with or without IDH mutations.

We will identify the circulating metabolites that are significantly altered by olaparib exposure, which may provide insights into the mechanism of drug action. In addition, if the sample size allows, we will examine the associations between the metabolite changes and PK parameters, pharmacodynamic response, toxicity, or clinical response. This may help identify potential circulating biomarkers for the early prediction of clinical outcome.

2.4.3.3 Avatar studies

Objectives:

- Test the extent to which Avatar models can recapitulate treatment responses (or failures) in parallel to patients on study
- Test other DNA repair inhibitors for improved efficacy
- Determine if combinations strategies (*i.e.,* DNA damaging agents, DNA repair inhibitors, epigenetic targeted agents [hypomethylating agents, HDAC inhibitors], immunotherapies) will enhance treatment response.

In subsets of patients where baseline bone marrow aspirates yield sufficient cells (>1x10^7), we will create patient-derived xenograft (PDX) models. We will use these to test the efficacy of olaparib and other DNA repair inhibitors, either alone or in combination, with or without DNA damaging agents, against IDH1/2-mutant AML/MDS. Such studies will be informative for future AML/MDS trials that seek to maximally exploit the observed mutant IDH1/2-induced DNA repair defect.

We will utilize a cutting-edge mouse model for human AML/MDS xenotransplantation recently developed by the Halene laboratory in collaboration with the laboratory of Dr. Richard Flavell using cytokine-humanized immunodeficient M-CSFh/h IL-3/GM-CSFh/h SIRPAh/m TPOh/h Rag2−/− Il2rg−/− (MISTRG) mice (Rongvaux *et al.,* 2014; Rathinam *et al.,* 2011; Strowig *et al.,* 2011). While *Nod Scid* γ-/- (NSG) mice have become the gold standard for transplantation of human hematopoietic cells, engraftment remains low, with predominance of CD3+ human T-cells or CD19+ B-cells with only minimal myeloid engraftment (Martin *et al.,* 2010), or limited to the injected tibial bone, when aided by co-injection of human mesenchymal stem cells (Muguruma *et al.,* 2011). To circumvent the limitations of current xenotransplant models, MISTRG were engineered via knock-in technology to express human cytokines in place of their murine counterparts (Rongvaux *et al.,* 2011). The MISTRG mice carry humanized alleles for M-CSFh/h, IL-3/GM-CSFh/h, hSIRPαh/m, and hTPOh/h on the RAG2-/- γc-/- background, and are viable, healthy and fertile. Each of these gene-humanizations significantly improves the engraftment, differentiation and maintenance of human hematopoietic stem and progenitor cells (published characterization of multiple strains of knock-in mice on the RAG2−/−γc−/− background [Rathinam *et al.,* 2011; Rongvaux *et al.,* 2011]). Importantly, MISTRG mice lack the DNA repair defect inherent to the severe combined immunodeficiency (scid) genotype of NSG mice that is due to loss of DNA protein kinase (DNA-PK) (Biederman *et al.,* 1991; Fulop and Phillips, 1990; Komatsu *et al.,* 1995; Jeggo *et al.,* 1995). DNA-PK is a critical mediator of non-homologous end joining (NHEJ), which is the other main DSB repair pathway that competes

with HR. As such, the use of MISTRG mice is critical for our proposed studies, since we will be testing combinations of DNA repair (*e.g.* PARP) inhibitors and DNA damaging agents for activity against AML cells transplanted in mice.

MISTRG mice support improved engraftment of both normal CD34+ cells as well as CD34+ cells from all subtypes of MDS and of AML that otherwise do not engraft in NSG. MISTRG mice engraft hematopoietic stem cells and support multi-lineage development (Rongvaux *et al.,* 2014). Importantly, MISTRG show improved support of secondary engraftment, essential for the successful propagation of the PDX xenografts. Secondary MDS/AML MISTRG recipients successfully allow engraftment of primary MDS/AML from NSG or MISTRG mice, while NSG mice as secondary recipients support engraftment only for a subset of AML (data not shown). Secondary engraftment serves two purposes: 1) only true leukemia stem cells will give rise to secondary engraftment and leukemia stem cells are at the origin of disease relapse; 2) while primary engrafted mice can show considerable heterogeneity, secondary engrafted mice tend to exhibit more homogeneous engraftment levels; 3) secondary engrafted mice tend to represent uniform clonal distribution.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Age ≥18 years. Because no dosing or AE data are currently available on the use of olaparib in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.2 Diagnosis of MDS or AML per World Health Organization 2016 classification. AML may be *de novo*, or following a prior hematologic disorder, including MDS or Philadelphia chromosome-negative myeloproliferative neoplasm, and/or therapy-related. Please refer to Appendix G.

3.1.3 Patients must have a documented *IDH1* or *IDH2* mutation within 30 days of inclusion based on mutational testing. Only specific mutations that lead to a neomorphic phenotype will be eligible for enrollment, and include those listed below (Mondesir *et al.,* 2016)
IDH1: *R132V*, *R132G*, *R132S*, *R132L*, *R132C* and *R132H*
IDH2: *R140W*, *R140L*, *R140Q*, *R172W*, *R172G*, *R172S*, *R172M*, *R172K*

3.1.4 Patients with AML or MDS should have disease that has relapsed after, or is refractory to, first-line therapy, with or without subsequent additional therapy.

3.1.5 Patients with MDS should have at least a MDS-EB1 at the inclusion and have a revised International Prognostic Symptom Score risk stratification of intermediate, high, or very high risk.

3.1.6 For patients with a known history of human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral

therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.7 For patients with a known history of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.8 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.9 Patients may or may not have been previously treated with IDH targeted therapies.

3.1.10 Patients who have undergone allogeneic stem cell transplant (alloSCT) are eligible if they are ≥180 days from stem cell infusion, have no evidence of graft versus host disease (GVHD) > Grade 1, and are ≥2 weeks off all immunosuppressive therapy.

3.1.11 Previous cytotoxic chemotherapy must have been completed at least 3 weeks and radiotherapy at least 2 weeks prior to Day 1 of treatment on the study, and all AEs (excluding alopecia) due to agents administered more than 4 weeks earlier should have recovered to < Grade 1. Patients with hematologic malignancies are expected to have hematologic abnormalities at study entry. Hematologic abnormalities that are thought to be primarily related to leukemia are not considered to be toxicities (AEs) and do not need to resolve to < Grade 1.

3.1.12 ECOG performance status 0-2 (Karnofsky ≥60%, see Appendix A).

3.1.13 Patient must have recovered from toxicities of any prior treatment regimen (no CTCAE grading over 1 for non-hematological toxicities, return to baseline for hematological values).

3.1.14 Ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making capacity may have a close relative, guardian, caregiver, or Legally Authorized Representative consent on their behalf

3.1.15 Patients must have adequate organ function measured within 28 days prior to administration of study treatment as defined below:

- Total bilirubin ≤ 1.5x institutional upper limit of normal (ULN) unless considered due to Gilbert's syndrome

- Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase [SGOT]) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase [SGPT]) ≤ 2.5 x institutional upper limit of normal unless considered due to organ leukemic involvement. If liver metastases are present in which case they must be ≤ 5x ULN

- Creatinine clearance of > 30 ml/min

- Patients are eligible for this study if low blood count and transfusion support are due to the MDS/AML.

3.1.16 Patients must have, in the best estimate of the treating physician, a life expectance of at least 12-16 weeks.

3.1.17 Postmenopausal or 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 sterilisation (bilateral oophorectomy or hysterectomy)

Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (see appendix D for acceptable methods) if they are of childbearing potential.

3.2 Exclusion Criteria

3.2.1 Patients with acute promyelocytic leukemia.

3.2.2 Patients with active central nervous system (CNS) leukemia or requiring maintenance intrathecal chemotherapy.

3.2.3 Patients receiving concurrent chemotherapy, radiation therapy, or immunotherapy for AML/MDS.

3.2.4 Patients actively receiving any other investigational agents.

3.2.5 Management of treatment for patients with co-occurring mutations, like FLT3, will be prioritized by the treating physician after discussion of treatment options with the patient

3.2.6 Hyperleukocytosis with >50,000 WBC/mcl. Hydroxyurea for WBC count control is permitted before starting treatment and may be continued until Day 28 of Cycle 1. The

maximum dose of hydrea will be 6 grams per day. Patients will be withdrawn from the study if >50,000 WBC/mcl occur or recur >14 days after starting treatment on the study.

3.2.7 Active, uncontrolled infection. Patients with infection controlled with antibiotics are eligible.

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

3.2.9 Patients who are pregnant or nursing. Pregnant women are excluded from this study because olaparib is a PARP inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with olaparib, breastfeeding should be discontinued if the mother is treated with olaparib. These potential risks may also apply to other agents used in this study.

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

3.2.11 Patients with symptomatic uncontrolled CNS disease. Imaging to confirm the absence of brain metastases is not required. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.

3.2.12 The patient can receive a stable dose of corticosteroids, up to 20 mg by mouth (PO) prednisone daily, before and during the study as long as these were started at least 4 weeks prior to treatment.

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

3.2.14 Any previous treatment with PARP inhibitor, including olaparib.

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

for other agents.

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

3.2.17 Patients with a known hypersensitivity to olaparib or any of the excipients of the product.

3.2.18 Patient with active malignancies requiring active treatment that interferes with protocol therapy and/or with significant risk of clinical relapse within 12 months that would require treatment interfering with protocol therapy are excluded.

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

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

3.2.21 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. Patients without reasonable alternative may be included in the trial after discussion with the medical monitor.

3.2.22 Previous double umbilical cord blood transplantation (dUCBT).

3.2.23 Breast feeding women.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

The epidemiology of AML and MDS shows a relatively even gender distribution with a slight male predominance. In therapy related myeloid neoplasms, there is an over-representation of women related to the high number of breast cancer survivors. There is no difference of incidence of AML, MDS, or presence of IDH mutation based on ethnicity or race.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications (*e.g.*, Roster Update Management System [RUMS], OPEN, Rave,),
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval,
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (*i.e.*, Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRB Manager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,

- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select LAO CT018, and protocol number 10264,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Protocol Specific Requirements For NCI Protocol #10264 Site Registration

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.

- ETCTN Specimen Tracking Training
    - All data entry users (Clinical Research Associate Role) at each participating site will need to complete the Theradex-led training.
    - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
    - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
    - This training will need to be completed before first/further patient enrollment at a given site.
    - Peter Clark and Diana Vulih are the main points of contact at Theradex for the training (PClark@theradex.com and Dvulih@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.
To access the Regulatory Submission Portal, log on to the CTSU members' website ➔ Regulatory ➔ Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.4 Checking Site Registration Status

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website
- Click on *Regulatory* at the top of your screen
- Click on *Site Registration*
- Enter your 5-character CTEP Institution Code and click on Go

  Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN/IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and

with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3.2 Special Instructions for Patient Enrollment

For the ETCTN Biobanking and Molecular Characterization Initiative, the following information will be requested:

- Protocol Number
- Investigator Identification
    - Institution and affiliate name
    - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements

listed in Section 3.

- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the ETCTN Biobanking and Molecular Characterization portion of this protocol. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID) and the IWRS-assigned UPID for this trial. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, and patient ID# for this treatment trial, from the institutional pathology report prior to submission.**

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 28 days. For AML patients, treatment should be started as rapidly as possible. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Enrollment/Baseline		
	• Bone marrow (2-3 mL, EDTA tube)	Local CLIA Laboratory
	• Peripheral blood (25 mL, EDTA) • Bone marrow (2-3 mL, EDTA tube)	Pharmacology Core, Karmanos Cancer Institute, Wayne State University School of Medicine
	• Buccal Swab • Peripheral blood (25 mL, EDTA, fresh) • Bone marrow (4-6 mL, EDTA tube, fresh)	EET Biobank
	• Bone marrow (4-6 mL, EDTA tube, fresh)	Halene Lab, Yale School of Medicine
End of Cycle 1		
	• Peripheral blood (25 mL, EDTA) • Bone marrow (2-3 mL, EDTA tube)*	Pharmacology Core, Karmanos Cancer Institute, Wayne State University School of Medicine
	IDHi-naïve cohort only: • Peripheral blood (25 mL, EDTA, fresh) • Bone marrow (4-6 mL, EDTA tube, fresh)	EET Biobank
End of Cycle 3		
	• Peripheral blood (25 mL, EDTA) • Bone marrow (2-3 mL, EDTA tube)*	Pharmacology Core, Karmanos Cancer Institute, Wayne State University School of Medicine
	• Peripheral blood (25 mL, EDTA, fresh) • Bone marrow (4-6 mL, EDTA tube, fresh)	EET Biobank
End of Cycle 6		
	• Peripheral blood (25 mL, EDTA) • Bone marrow (2-3 mL, EDTA tube)*	Pharmacology Core, Karmanos Cancer Institute, Wayne State University School of Medicine
	• Bone marrow (4-6 mL, EDTA tube, fresh)	EET Biobank
End of Cycle 9		
	• Peripheral blood (25 mL, EDTA) • Bone marrow (2-3 mL, EDTA tube)*	Pharmacology Core, Karmanos Cancer Institute, Wayne State University School of Medicine
	• Bone marrow (4-6 mL, EDTA tube, fresh)	EET Biobank
End of Cycle 12		
	• Peripheral blood (25 mL, EDTA) • Bone marrow (2-3 mL, EDTA tube)*	Pharmacology Core, Karmanos Cancer Institute, Wayne State University School of Medicine
	• Bone marrow (4-6 mL, EDTA tube, fresh)	EET Biobank
End of Treatment		
	• Peripheral blood (25 mL, EDTA) • Bone marrow (2-3 mL, EDTA tube)*	Pharmacology Core, Karmanos Cancer Institute, Wayne State University School of Medicine
	• Peripheral blood (25 mL, EDTA, fresh)* • Bone marrow (4-6 mL, EDTA tube, fresh)*	EET Biobank

	• Bone marrow (4-6 mL, EDTA tube, fresh)	Halene Lab, Yale School of Medicine

*Optional collection

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Shipping Kits

Kits are not provided for this study. Sites must use institutional supplies for the collection and shipment of specimens.

5.2.2 Scheduling of Specimen Collections

Fresh blood and bone marrow shipped to the EET Biobank can be collected Mondaythrough Friday, and shipped overnight for receipt Tuesday through Saturday.

Specimens submitted frozen (*e.g.*, bone marrow aspirate and plasma) can be collected on any day but must be stored frozen and shipped to Karmanos Cancer Institute on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained at -80°C.

Specimens shipped to the EET Biobank and shipped to Yale University for single cell sequencing studies (Section 2.4.3.1) and for avatar studies (Section 2.4.3.3) must be fresh and shipped same day of procedure to arrive the following day. All other samples may be frozen.

5.3 Specimen Tracking System Instructions

All biospecimens collected for this trial must be submitted using the ETCTN Rave Specimen Tracking System (STS) unless otherwise noted. The system is accessed through special Rave user roles: “CRA Specimen Tracking” for data entry at the treating institutions and “Biorepository” for users receiving the specimens for processing and storage at reference labs and the Biorepository. Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.

Important: Failure to complete required fields in STS may result in a delay in sample processing. Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact the Theradex Help Desk at CTMSSupport@theradex.com.

A shipping manifest **must** be included with all sample submissions.

5.3.1 Specimen Labeling

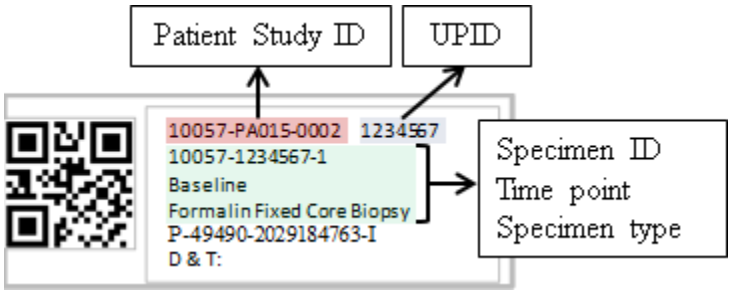
5.3.1.1 Blood and Bone Marrow Aspirate Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma) and bone marrow specimens:

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.,* blood, serum)
- Collection date and time (to be added by hand)

5.3.1.2 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.,* for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

5.3.2 Overview of Process at Treating Site

5.3.2.1 OPEN Registration

All registrations will be performed using the OPEN system. OPEN communicates automatically with the IWRS which handles identifier assignments, any study

randomization and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.3.2.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number (if applicable), Tissue type, Surgical Path ID, number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write collection date and time on each label.
- After collection, store labeled specimens as described in Section 5.4.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Bone Marrow, and/or Molecular Reports (up to 4), Surgical reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have protected health information (PHI) data, like name, mailing address, medical record number or social security number (SSN) redacted. Do not redact the surgical pathology ID (SPID), block number or relevant dates (such as collection date), and include the UPID and patient ID on each document.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter Collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of containers and ship date once for the 1st specimen in a shipment.
- **Copy Shipping** CRF: Select additional specimens to add to an existing shipment

referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.

- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

5.4 Specimen Collection

5.4.1 Collection of Blood in EDTA Tubes for Plasma Processing (shipped to Karmanos Cancer Institute)

1. Label EDTA tubes according to the instructions in Section 5.3.1.
2. Collect 25 mL blood in EDTA tube(s) and gently invert tube to mix.
3. Within 1 h after blood collection, plasma will be separated from the blood sample by centrifugation (1500 x g, 10 minutes, at 4°C)
4. Using a clean transfer pipette, disperse plasma into labeled vials (using the label printed from the ETCTN Specimen Tracking System or following the instructions in Section 5.3.1) creating 4 aliquots of approximately equal volume. Avoid picking up the blood cells when aliquoting by keeping the pipet above the cell layers and leaving a small amount of plasma in the tube.
5. Tightly secure the cap of the vials before storage. Aliquoting and freezing of plasma specimens should be completed within 1 hour of centrifugation.

Store plasma vials upright in a specimen box or rack in a -80°C freezer prior to shipping to the Karmanos Cancer Institute. Do not allow specimens to thaw after freezing.

5.4.2 Collection of Bone Marrow Aspirate for Frozen Samples (shipped to Karmanos Cancer Institute)

1. Label EDTA tubes according to the instructions in Section 5.3.1.
2. Collect 2-3 mL bone marrow aspirate in each EDTA tube and gently invert tube to mix. Bone marrow aspirates will be processed within 1 hour of collection: bone marrow will be layered on Ficoll without dilution, spun at 450g for 20 min with breaks off, and 4 aliquots will be made and frozen in chilled FBS 90%/DMSO 10% at -80°C prior to delivering to laboratory. Do not allow specimens to thaw after freezing.
3. Bone marrow collections for each assay should be collected in separate tubes, with slight adjustment of the aspirate needle for each pull (and visual confirmation of spicules to confirm quality of aspirate).

5.4.3 Collection of Peripheral Blood or Bone Marrow Aspirate for Fresh Samples (shipped to

the EET Biobank or Yale University)

1. Label EDTA tubes according to the instructions in Section 5.3.1.
2. Collect peripheral blood or bone marrow aspirate in each EDTA tube (refer to Section 5.1 for volumes), and gently invert to mix.
3. Samples may be sent in the EDTA tubes at ambient temperature if received within 24 hours (must ship same day).
4. Ship on day of collection (whenever possible) according to instructions in section 5.6.
5. If bone marrow cannot be shipped on the day of collection, they need to be ficolled and viably cryopreserved within 24 hours of procedure (FBS 90%/ DMSO 10% or other freezing medium) on site and shipped at a later time on dry ice.

5.5 Shipping Specimens from the Clinical Site to the EET Biobank

5.5.1 Specimen Shipping Instructions

5.5.1.1 Shipping Fresh Blood or Bone Marrow

The following supplies are needed to ship whole blood or bone marrow: (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen sticker, and (5) a pre-paid FedEx air bill.

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
4. Wrap the biohazard envelope with bubble wrap or other padded material.
5. Put the padded specimens into a Tyvek envelope. Expel as much air as possible and seal securely.
6. Place the Tyvek envelop in a sturdy shipping container (e.g., cardboard FedEx box).
7. Insert a copy of the required forms into a plastic bag and place in the box.
8. Close the outer lid of the shipping box and tape it shut with durable sealing tape.
9. Complete a FedEx air bill and attach to top of shipping container.
10. Attach an Exempt Human Specimen sticker to the side of the shipping container.
11. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.2 Shipping Address for the EET Biobank

Ship to the address below. Ship fresh blood and bone marrow specimens the same day of specimen collection. Do not ship specimens the day before a holiday or weekend.

EET Biobank
2200 International Street
Columbus, OH 43228
PH: (614) 722-3270
FAX: (614) 722-2856
Email: BPCMGLab@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

NOTE: The ETCTN Biorepository FedEx Account will not be provided to submitting institutions.

5.5.3 Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
Phone: (614) 722-3270
E-mail: BPCMGLab@nationwidechildrens.org

5.6 Shipping Specimens from the Clinical Site to Other Laboratories

5.6.1 Shipping of Specimens to Karmanos Cancer Institute

5.6.1.1 Specimen Shipping Instructions

All frozen plasma, blood, and tumor samples should be placed in cardboard tray/box, so samples remain upright. This tray/box is to be placed in a Styrofoam carton with 10-15lbs of dry ice (block with or without pellets) to keep samples frozen during shipping. A copy of PK sheets should be in the shipping box, reflecting the samples that are being sent. Samples should be shipped via FedEx Priority Overnight service. Please notify Jing Li via email (LiJing@wayne.edu) when samples are shipped and include the shipment tracking number.

Samples can be batched and shipped.

5.6.1.2 Shipping Address

Jing Li
Pharmacology Core
Karmanos Cancer Institute
4100 John R, HWCRC – room 523
Detroit, MI 48201

5.6.1.3 Contact Information for Assistance

Dr. Jing Li
Phone: (313) 576-8258
Email: LiJing@wayne.edu

5.6.2 Shipping of Specimens to Yale University

5.6.2.1 Shipping Address

Yale School of Medicine/ Section of Hematology
300 George Street
Room 787A
New Haven, CT 06511

5.6.2.2 Contact Information for Assistance

Dr. Stephanie Halene
Phone: (203)-812-9731
Email: stephanie.halene@yale.edu

5.7 Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Specimen(s) and Time Point(s)	Laboratory Performing Assay
1	IDH1/2 Mutation	DNA sequencing or PCR	• Integral • Eligibility criteria	M	• Bone marrow aspirate • Enrollment	Local CLIA-certified laboratory
2	2HG Levels	LC-MS/MS	• Integrated • Potential biomarker of response	M	• Plasma • Enrollment, after Cycles 1, 3, 6, 9, 12, and end of treatment	Jing Li, Karmanos Cancer Institute LiJing@wayne.edu
3	2HG Levels	LC-MS/MS	• Exploratory • Potential biomarker of response	M/O	• Bone marrow aspirate • Mandatory: enrollment • Optional: after Cycles 1, 3, 6, 9, 12, and end of treatment	Jing Li, Karmanos Cancer Institute LiJing@wayne.edu
4	Genomic Profiling	Whole exome sequencing	• Exploratory • To evaluate clonal evolution and clonal architecture	M/O	• DNA from buccal swab (enrollment only) • DNA from bone marrow aspirate* • DNA from blood • Mandatory: enrollment, after Cycles 1, 3, 6, 9, and 12 • Optional: end of treatment • End of Cycle 1: IDHi-naïve cohorts only	Chris Karlovich – MoCha, National Cancer Institute chris.karlovich@nih.gov
5	Genomic Profiling	RNA sequencing	• Exploratory • To evaluate clonal evolution and clonal architecture	M/O	(Will be assessed using RNA from bone marrow aspirate and blood obtained from WES biomarker.) • Mandatory: enrollment, after Cycles 1, 3, 6, 9, and 12 • Optional: end of treatment • End of Cycle 1: IDHi-naïve cohorts only	Chris Karlovich – MoCha, National Cancer Institute chris.karlovich@nih.gov
6	Genomic Profiling	Single Cell DNA Sequencing	• Exploratory • Evaluation of the clonal heterogeneity/evolution by single cell DNA sequencing	M/O	Samples from the biorepository will be used • bone marrow sample at enrollment, after Cycles 1 (optional), 3 , 6, 12 and end of treatment	Stephanie Halene, Yale University Stephanie.halene@yale.edu Ranjit Bindra, Yale University Ranjit.bindra@yale.edu
7	Avatar Studies	PDX model	• Exploratory • To evaluate disease response	M	• Bone marrow aspirate • Enrollment	Stephanie Halene, Yale University Stephanie.halene@yale.edu Ranjit Bindra, Yale University Ranjit.bindra@yale.edu

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Specimen(s) and Time Point(s)	Laboratory Performing Assay
8	Genomic Profiling	Infinium methylation array	• Exploratory • To evaluate clonal evolution and clonal architecture	M/O	(Will be assessed using DNA from bone marrow aspirate and blood obtained from WES biomarker.) • Mandatory: enrollment, after Cycles 1, 3, 6, 9, and 12 • Optional: end of treatment • End of Cycle 1: IDHi-naïve cohorts only	Michael Berens, Translational Genomics Research Institute mberens@tgen.org
9	Pharmacom-etabolomic Profiling	LC-MS/MS	• Exploratory • To evaluate metabolic signatures	O	(Will be assessed using plasma and bone marrow aspirate collected for 2HG levels.) • Enrollment, after Cycles 1, 3, 6, 9, 12, and end of treatment	Jing Li, Karmanos Cancer Institute LiJing@wayne.edu

*Availability of bone marrow sample: If a bone marrow procedure is not available for any reason, we can consider using a peripheral blood sample (30 mL per time point) for the different studies, provided that a minimum of 1g/L of circulating blasts are present on the differential of the CBC.

Prioritization of analyses for pauci-cellular samples with low cell yield:

- Metabolomic studies can be done on blood only (DiNardo *et al.,* 2013). We will so prioritize the use of bone marrow for the other exploratory objectives. For bone marrow studies, at enrollment and EOT, the priority will be the WES/RNAseq study followed by single-cell DNA sequencing, avatar studies and the methylation studies. During treatment, the priority will be the WES/RNAseq, single-cell DNA sequencing and the avatar study, which take precedent over the methylation studies.
- The viably cryopreserved bone marrow cells can be used as a back-up for the WES, or themethylation analyses.
- Considering time points: For exploratory objectives, if a prioritization needs to be discussed on serial samples, we will keep as a high priority the baseline, end of Cycle 1, and end-of -treatment (EOT) samples. Samples for end of Cycle 3, 6, 9, and 12 are low priority.

5.8 Integral Correlative Study

5.8.1 Detection of IDH1/2 Mutations

5.8.1.1 Site Performing Correlative Study

Mutation-detection for eligibility will be conducted by CLIA-certified laboratories. The WES performed by the Molecular Characterization (MoCha) Laboratory (see Section 5.10.1 for details) will be used as a confirmation method, but will not be used for eligibility.

5.9 Integrated Correlative Studies

5.9.1 Determination of 2HG Levels in Plasma

5.9.1.1 Site Performing Correlative Stud*y*

The determination of 2HG levels will be performed in the laboratory of Dr. Jing Li at the Karmanos Cancer Institute.

5.9.1.2 Specimen(s) Receipt and Processing

The levels of 2HG in plasma samples will be determined using a validated LC-MS/MS method in Karmanos Cancer Institute (KCI) Pharmacology Core. Samples will be shipped to the KCI Pharmacology Core for analysis. The LC-MS/MS analysis will be performed on an AB Sciex QTRAP 6500 LC-MS/MS system, which consists of an enhanced high-performance hybrid triple quadrupole and linear ion trap mass spectrometer, interfaced with a SHIMADZU Nexera ultra-high-performance liquid chromatography system.

The method has been developed and fully validated for the selectivity, sensitivity, linearity, intra- and inter- accuracy and precision, recovery, and stability, based on the US FDA Guidance to Bioanalytical Method Validation. In brief, the chromatographic separation will be achieved on a Phenomenex Synergi^{TM} Polar-RP column (150 × 2 mm,

4 mcm) using a gradient elution consisting of mobile phase A (0.03% formic acid in water) and mobile phase B (0.03% formic acid in acetonitrile), at the flow rate of 0.25 mL/min. 2HG and its stable isotope-labeled internal standard will be monitored under negative electrospray ionization mode at the mass transitions m/z, 147.0 > 128.9 and 150.0 > 131.9, respectively.

2HG levels in plasma will be compared to treatment responses. In addition, we will compare 2HG levels with genomic profiling studies proposed below in order to assess whether correlations can be made with (a) co-occurring mutations, (b) gene expression patterns, and (c) methylation profiles.

5.10 Exploratory/Ancillary Correlative Studies

5.10.1 Determination of 2HG Levels in Bone Marrow Aspirate

5.10.1.1 Site Performing Correlative Study

The determination of 2HG levels will be performed in the laboratory of Dr. Jing Li at the Karmanos Cancer Institute.

5.10.1.2 Specimen Receipt and Processing

The levels of 2HG in bone marrow biopsy samples will be determined using a validated LC-MS/MS method in Karmanos Cancer Institute (KCI) Pharmacology Core. Samples will be shipped to the KCI Pharmacology Core for analysis. The LC-MS/MS analysis will be performed on an AB Sciex QTRAP 6500 LC-MS/MS system, which consists of an enhanced high-performance hybrid triple quadrupole and linear ion trap mass spectrometer, interfaced with a SHIMADZU Nexera ultra-high-performance liquid chromatography system.

The method has been developed and fully validated for the selectivity, sensitivity, linearity, intra- and inter- accuracy and precision, recovery, and stability, based on the US FDA Guidance to Bioanalytical Method Validation. In brief, the chromatographic separation will be achieved on a Phenomenex Synergi^{TM} Polar-RP column (150 × 2 mm, 4 mcm) using a gradient elution consisting of mobile phase A (0.03% formic acid in water) and mobile phase B (0.03% formic acid in acetonitrile), at the flow rate of 0.25 mL/min. 2HG and its stable isotope-labeled internal standard will be monitored under negative electrospray ionization mode at the mass transitions m/z, 147.0 > 128.9 and 150.0 > 131.9, respectively.

2HG levels in bone marrow will be compared to treatment responses. In addition, we will compare 2HG levels with genomic profiling studies proposed below in order to assess whether correlations can be made with (a) co-occurring mutations, (b) gene expression patterns, and (c) methylation profiles.

5.10.2 Genomic Profiling (WES, RNAseq, and Infinium Methylation Array)

5.10.2.1 Specimen Receipt and Processing at the EET Biobank

Upon receipt at the EET Biobank, the bone marrow and blood will be processedfor mononuclear cells using a ficoll-hypaque gradient (baseline and relapse time points) or processed for white blood cells by lysing red blood cells (all other time points). Bone marrow and blood will undergo pathology review to assess the number of blasts. Mononuclear cells and white blood cells will be frozen in a freezing media and stored in a liquid nitrogen vapor phase freezer until distribution for testing. At each time point, DNA and RNA will be co-extracted from bone marrow and blood. Nucleic acids will be stored in a -80°C freezer until distribution for testing.

All samples will be co-extracted for DNA and RNA at each time point.

5.10.2.2 Sites Performing Correlative Study

WES and RNAseq will be performed by the MoCha Laboratory, and Infinium Methylation assays will be performed by the laboratory of Michael Berens at the Translational Genomics Research Institute (TGen).

Genomic profiling will be performed systematically on a separate sample of the bone marrow aspirate, or a “second pull” obtained specifically for biomarker studies. WES study, RNAseq, and methylome will require relatively low amount of nucleic acids with 100 ng of DNA for WES or methylome and 100 ng of RNA for the RNAseq.

5.10.3 Pharmacometabolomic Profiling

5.10.3.1 Specimen(s) Receipt and Processing at the Karmanos Cancer Institute Pharmacology Core

Samples will be processed according to institutional SOPs.

5.10.3.2 Site Performing Correlative Study

Pharmacometabolomic profiling will be performed in the laboratory of Dr. Jing Li at the Karmanos Cancer Institute.

5.10.3.3 Specimen Receipt and Processing

We will apply a LC-MS/MS based targeted metabolomics platform to define the plasma metabolic signature of olaparib exposure in AML patients. Metabolic profiling will be performed in the pre- and post- olaparib treatment plasma samples using a targeted metabolomics platform, which has been established in the KCI Pharmacology Core. This platform can quantitatively measure about 300 metabolites that are involved in major human metabolic pathways (Table 2). All LC-MS/MS analyses were performed on an

AB SCIEX QTRAP 6500 LC-MS/MS system. Analyst 1.6 software was used for system control and data acquisition and MultiQuant 3.0 software was used for data processing and quantitation.

Table 2 Typical endogenous metabolites measured by the LC-MS/MS based targeted metabolomics platform.

Classes or Pathways	Number of Metabolites
Glycolytic, TCA cycle, and pentose phosphate pathway	25
Nucleosides, nucleotides and NAD-related metabolites	40
Amino acid and related metabolites	60
Acyl CoAs	10
Acyl Carnitines	20
Bile acids	15
Ceramides	10
Steroids	10
Short chain fatty acids	8
Phospholipids	15
Gut microbial related metabolites	15
Miscellaneous Metabolites	65
Total	**293**

5.10.4 Creation of Patient-Derived Xenograft (PDX) Models from Baseline Bone Marrow Biopsies.

5.10.4.1 Specimen Receipt and Processing at Yale University

Specimens will be processed according to institutional SOPs.

5.10.4.2 Sites Performing Correlative Study

PDX modeling will be performed in the laboratories of Dr. Stephanie Halene and Dr. Ranjit Bindra at Yale University.

We will stratify MDS/AML PDX mice to treatment arms via pre-treatment determination of engraftment levels in peripheral blood and bone marrow via aspiration. We will determine 2HG levels in plasma before and after treatment. At conclusion of the treatment we will euthanize animals and determine treatment efficacy via comprehensive analysis that includes complete blood count (CBC), flow cytometric analysis for human cell percentage and differentiation, histology, hematopoietic and non-hematopoietic organ infiltration, and spleen size. In addition, to determine the efficiency of the treatment to eliminate the leukemia stem cell we will perform single cell RNAseq and serial transplantation into tertiary recipients to phenotypically and functionally assess possible persistence of leukemic stem cells.

5.10.5 Evaluation of the clonal heterogeneity evolution by single cell DNA sequencing

5.10.5.1 Specimens will be processed according to institutional SOPs

5.10.5.2 Sites performing correlative study

Single cell DNA sequencing will be performed in the laboratories of Dr. Stephanie Halene and Dr. Ranjit Bindra at Yale University

We will use patient's bone marrow samples collected at enrollment and after Cycles 1 [optional], 3, 6, 12 and at end of treatment. Mononuclear cells will be separated using a Ficoll Hypaque purification method and viably cryopreserved in FBS 90%/DMSO10% or other appropriate freezing medium. At time of sequencing batches of 4 samples will be processed at the same time and evaluated using the Mission Bio Tapestri single cell DNA sequencing platform. A minimum of 10^4 living cells are required to proceed for each sample and we will be using the commercially available 45-gene panel. We will compare the evolution of the subclones at the different stages of the treatment, evaluate the proportion of IDH mutated clones persisting after treatment, evaluate the co-mutations as well as the most common mechanisms of resistance (e.g. IDH mutation switch, development of a RAS or FLT3 mutant clone). A subset of the samples (e.g. patients with concomitant IDH and SRSF2 mutations) will be evaluated with a customized panel and another subset of patients will be evaluated using a multi-omic approach using in parallel a barcoded cytometry antibody panel.

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	**Premedications / Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Olaparib	• Do not consume grapefruit juice. • Olaparib tablets can be taken with or without food.	If CrCl = 30 - 50 mL/min: 200 mg (2 x 100 mg tablets)	Tablet PO q12h	Daily	28 days (4 weeks)
		If CrCl > 50 mL/min: 300 mg (2 x 150 mg tablets)			

PO = oral administration, q12h = every 12 hours

- For patients with CrCl between 30 and 50 mL/min, the starting dose will be 200 mg bid.
- For patients with CrCl > 50 mL/min, the starting dose will be 300 mg bid.

6.1.1 Olaparib

Patients will be administered olaparib every 12 hours (q12h). Olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Olaparib tablets can be taken with or without food. It is prohibited to consume grapefruit, grapefruit juice, or Seville oranges while on olaparib therapy.

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

The patient will be requested to maintain a medication diary (see Appendix F) of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

6.1.2 Overdose

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. Per the Olaparib Investigator's Brochure (2019), the Maximum Tolerated Dose is 300 mg twice daily (tablet).

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

6.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of olaparib with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, vitamins, nutritional supplements, or alternative therapies at the time of enrollment and throughout the study. The case report form should capture the dates of administration (including start/end dates if known), dosage (including dosing frequency/schedule), and reason for use. The PI should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

6.2.1 Anti-Emetics/Anti-Diarrheal

From screening part 2 onwards, should a patient develop nausea, vomiting and /or diarrhea, then these symptoms should be reported as AEs and appropriate treatment of the event given. An information sheet for patients regarding management and reporting of diarrhea can be found in Appendix E.

6.2.2 Medications that may NOT be administered:

Prohibited medications

Prohibited medication/class of drug:	
Anticancer therapy: Chemotherapy Immunotherapy	Not permitted while the patient is receiving study medication.
Hormonal therapy* Radiotherapy (except palliative) Biological therapy including growth factors Other novel agents	Hydroxyurea up to 6 g/day in the context of the management of proliferative AML is allowed during screening and until the end of cycle 1. It should be discontinued as soon as possible based on investigator clinical judgement. Note the risk or severity of adverse effects can be increased when hydroxyurea is combined with olaparib.
	Intrathecal chemotherapy for maintenance (but not active treatment of CNS disease) of a controlled CNS disease is allowed.
Live virus vaccines Live bacterial vaccines	Not permitted while the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

*Hormone Replacement Therapy (HRT) is acceptable

6.2.3 Restricted concomitant medications

Restricted concomitant medications

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed):**
Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir Moderate CYP3A inhibitors: ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	Strong or moderate CYP3A inhibitors should be avoided 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 CRF with the reason documented as concomitant CYP3A inhibitor use. • Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg twice daily 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 twice daily 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 inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort Moderate CYP3A inducers: bosentan, efavirenz and modafinil	Strong or moderate CYP3A inducers should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of olaparib.

Restricted concomitant medications

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed):**
• CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • CYP2B6 substrates: bupropion, efavirenz • OATP1B1substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	Effect of olaparib on other drugs: • Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. • Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6. • Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline only after completion of the Cycle 6 response assessment, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Administration of other anti-cancer agents	Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may use hydroxyurea, as outlined in the inclusion criteria, for leukocytosis. While not standard therapy for patients with AML or MDS, Patients may continue the use of bisphosphonates if they are already on these therapies. Low dose corticosteroids may also be used for any chronic condition provided the dose is stable during the study and they were started at least 4 weeks prior to beginning study treatment.

6.3 Duration of Therapy

In the absence of treatment delays due to AE(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AE(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- In patients without prior exposure to IDH inhibitors: the absence of CR/CRh/mCR
- Patient non-compliance
- Pregnancy
    - All women of child-bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.,* missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.4 Duration of Follow-Up

Patients will be seen 90 days after the last dose of the study drug for a follow-up visit and then followed for survival q3 months (+/- 4 weeks) thereafter until death. Patients removed from study for unacceptable AE(s) will be

followed until resolution or stabilization of the AE. Survival data will be followed until death from any cause.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Dose Levels

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 2 weeks of treatment interruption total. If the interruption is any longer, the study team must 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. When dose reduction is necessary patients will take one 150 mg tablet and one 100 mg tablet twice daily or two x 100 mg tablet twice daily, or one 150 mg tablet twice daily or one 100 mg tablet twice daily.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors – see Section 6.2.3).

Olaparib dose reductions to manage adverse events

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily (2 x 150 mg tablets)	250 mg twice daily (1 x 100 mg + 1 x 150 mg tablets)	200 mg twice daily (2 x 100 mg tablets)

7.2 Management of hematological toxicity

Hematologic toxicity will be defined using specific AML/MDS criteria: For patients with documenting response, any CTCAE grade 4 ANC or platelet toxicity lasting >42 days from the initiation of the cycle will be considered a DLT.

In the absence of active disease, study drug should be interrupted until recovery of the hematologic toxicity to ≤ Grade 3 for all subjects regardless of baseline cytopenia. The treatment will then be re-started at the lower dose level as indicated on section 7.1 of the protocol.

The definition and management of hematologic toxicities is complex and we strongly encourage the local investigator to contact the study team to discuss the next steps of management if a hematologic toxicity is suspected.

Note that a complete response with inadequate platelet recovery will not considered a hematologic toxicity.

Olaparib dose reductions to manage hematological toxicities

Initial Dose	Dose reduction 1	Dose reduction 2
300 mg twice daily (2 x 150 mg tablets)	250 mg twice daily (1 x 100 mg + 1 x 150 mg tablets)	200 mg twice daily (2 x 100 mg tablets)

7.3 Management of non-hematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 2 weeks of treatment interruption total. If the interruption is any longer than this the study monitor 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 twice daily as a first step and to 200 mg twice daily as a second step. Treatment must be interrupted if any NCI-CTCAE Grade 3 or 4 AE occurs which the investigator considers to be at least possibly related to administration of study treatment, excluding febrile neutropenias and neutropenic infections.

7.3.1 Management of new or worsening pulmonary symptom

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

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

7.3.2 Management of nausea and vomiting

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

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

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

7.4 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 the study physician.

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

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

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

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

Olaparib dose reductions for non-toxicity related events

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily (2 x 150 mg tablets)	250 mg twice daily (1 x 100 mg + 1 x 150 mg tablets)	200 mg twice daily (2 x 100 mg tablets)

7.5 Renal Impairment

If after study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (>30 ml/min), retesting should be performed promptly.
A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24-hour urine test of between 30 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg twice daily.

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

Olaparib has not been studied in patients with severe renal impairment (CrCl $\leq$ 30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease it is recommended that olaparib be discontinued.

7.6 Dose Reductions when Receiving Strong/Moderate CYP3A4 Inhibitors

As noted in Section 6.2.3, patients should avoid taking strong or moderate CYP3A4 inhibitors while receiving olaparib. The use of any such agent must be discussed with the study monitor. If there is no suitable alternative concomitant medication, the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the case report form (CRF) with the reason documented as concomitant CYP3A inhibitor use.

Olaparib dose reductions if patient must take a strong or moderate CYP3A inhibitor

Initial Dose	Dose if Receiving a Strong CYP3A inhibitor	Dose if Receiving a Moderate CYP3A inhibitor
300 mg twice daily (2 x 150 mg tablets)	100 mg twice daily (1 x 100 mg tablets)	150 mg twice daily (1 x 150 mg tablets)

8. PHARMACEUTICAL INFORMATION

A list of the AEs and potential risks associated with the investigational agent administered in this study can be found in Section 10.1.

8.1 Olaparib (AZD2281) (NSC 747856)

Chemical Name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one

Other Names: AZD2281; KU-0059436; CO-CE 42

Classification: PARP inhibitor

CAS Registry Number: 763113-22-0

Molecular Formula: $C_{24}H_{23}FN_4O_3$ **M.W.:** 434.46

Approximate Solubility: 0.1 mg/mL pH independent solubility across physiologic range

Mode of Action: Olaparib is an inhibitor of subclasses 1, 2, and 3 of polyadenosine 5′ diphosphoribose polymerase (PARP-1, PARP-2, and PARP-3). In tumors that are deficient in the homologous recombination DNA repair pathway (example, BRCA mutants), inhibition of PARP by olaparib causes accumulation of DNA double-strand breaks and genomic instability. Olaparib may also enhance the effects of DNA damage caused by ionizing radiation and chemotherapy.

Description: crystalline solid

How Supplied: AstraZeneca supplies and the Pharmaceutical Management Branch (PMB), CTEP, Division of Cancer Treatment and Diagnosis (DCTD) distributes olaparib as green, film-coated tablets in 100 mg and 150 mg strengths.

- 100 mg tablets are 14.5 mm x 7.25 mmoval-shaped
- 150 mg are 14.5 mm x 7.25 mmoval-shaped

Tablets are packaged in induction-sealed high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle contains 32 tablets with desiccant.

Tablet core components include active drug substance, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. Film coating contains hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black.

Storage: Store in a secure location below 30° C (86° F).

If a storage temperature excursion is identified, promptly return olaparib (AZD2281) to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf-life studies are ongoing. Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the opening date; unused tablets should be discarded. Instruct patients not to open a bottle until they are ready to use it.

Route and Method of Administration: Oral. Take tablets without regard to meals.

Potential Drug Interactions: *In vivo* data indicate that CYP3A4/5 is important for olaparib metabolism and clearance in humans. For this reason, avoid concomitant administration of strong and moderate CYP 3A4/5 inducers and inhibitors. Consult the protocol document or study investigator prior to making any dose adjustments related to potential drug-drug interactions.

In vitro data shows olaparib is a substrate for P-glycoprotein (P-gp), but not for organic anion-transporting polypeptides (OATP1B1 and OATP1B3), organic cation transporter 1 (OCT1), multi-drug resistance protein 2 (MRP-2) efflux transporter or breast cancer resistance protein (BCRP). Administration of strong P-gp inhibitors and inducers should be avoided with concurrent olaparib.

Based on *in vitro* data, olaparib inhibits CYP 3A4 and UGT1A1 enzyme systems and induces CYP 1A2, 2B6, and 3A4. Therefore, avoid concomitant administration of sensitive substrates, particularly those with narrow therapeutic ranges.

Olaparib is also an inhibitor of P-gp, OATP1B1, OCT1, OCT2, OAT3, multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and a weak inhibitor of BRCP, but not an inhibitor of OATP1B3 or MRP-2. *In vitro* studies suggest that olaparib may increase exposure of substrates of these transport systems, although the clinical relevance is not clear. The manufacturer recommends that statins, in particular, should be administered with caution when given concomitantly with olaparib.

Patient Care Implications: Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, women of child-bearing potential and their partners should agree to use two (2) highly effective forms of contraception starting at signing of the informed consent, throughout study participation and for at least one (1) month after the last dose of olaparib. It is not known whether olaparib is found in seminal fluid, so as a precaution, male study participants must use a condom during treatment and for three (3) months after the last dose and should avoid fathering a child or donating sperm during this same time period. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

Lactation is a protocol exclusion criterion and not advised since there is potential for serious adverse reactions in breastfed infants. Advise lactating women to not breastfeed during study treatment and for one (1) month after receiving the last dose of olaparib.

Because the adverse events related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery.

There are no data on the effect of olaparib on wound healing, therefore as a precaution, olaparib treatment should be stopped at least 3 days prior to planned surgery. After surgery olaparib can be restarted when the wound has healed. No stoppage of olaparib is required for any needle biopsy procedure.

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

Availability

Olaparib (AZD2281) is an investigational agent supplied to investigators by the DCTD, NCI.

Olaparib (AZD2281) is provided to NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and DCTD, NCI (see Section 13.5).

- Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual

submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Starter supplies will not be provided. Patients must be registered prior to agent ordering. Sites may request expedited orders Monday-Thursday when they provide courier information.

- Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

- Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

- Useful Links and Contacts

.1 CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
.2 NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
.3 PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
.4 PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
.5 CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
.6 CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
.7 IB Coordinator: IBCoordinator@mail.nih.gov
.8 PMB email: PMBAfterHours@mail.nih.gov
.9 PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

9.1.1 Study Design

This is an open-label study of olaparib in advanced relapsed or refractory IDH1/2-mutant AML and MDS. The study will have 4 arms. Arm 1 will include patients with relapsed or refractory AML with no prior exposure to IDH inhibitors (inhibitor naïve). Arm 2 will be composed of patients with relapsed or refractory AML with prior exposure to IDH inhibitors. Arm 3 will include patients with relapsed or refractory MDS with no prior exposure to IDH inhibitors (inhibitor naïve). Arm 4 will be composed of patients relapsed or refractory MDS with prior exposure to IDH inhibitors.

The effect of PARP inhibitors is dependent on 2-HG levels, and 2-HG levels are high in both IDH inhibitor naïve patients, as well as in patients who relapse after IDH inhibitors. While 2-HG levels are suppressed in patients actively on IDH inhibitors (independent of response, which discourages concomitant administration), in patients who relapse after IDH inhibitors 2-HG levels are seen to increase despite continued IDH inhibitor therapy. This has been seen in numerous studies (*e.g.*, Intlekofer *et al.*, 2018). Therefore, we expect a rather similar efficacy of PARP inhibitors in both IDH inhibitor naïve and IDH inhibitor pre-treated patients.

For the null hypothesis, the CR rate is 30% in IDH inhibitor naïve AML patient, not for patients with previous IDHi exposure. For the MDS, population, the data for IDHi naïve patients are still limited and we will have a conservative estimate that the rate of response will be similar to AML. The null hypothesis for patients already treated with at least 1 line of therapy and an IDH inhibitor will be set at 5% given the absence of available options for either MDS or AML. Sample sizes and futility rules:

Cohort	H0	H1	Alpha 1 sided	beta	Sample size stage 1	Futility	Sample size total*	Efficacy
AML IDHi naive	30	50	5	20	19	6 or less	39	17 or more
AML IDHi exposed	5	35	5	10	8	0	14	3 or more
MDS IDH I naive	30	50	5	20	19	6 or less	39	17 or more
MDS IDHi	5	35	5	20	6	0	12	3 or more

exposed								

The calculations are based on a Simon 2 Stage Minimax design.
* without the drop-out rate of 15%

The safety and efficacy will be evaluated by an independent data review committee at each critical step of the protocol. Given the patient population, we considered a potential drop-out rate of 15%. Expected monthly accrual is 3-4 patients per month, with a proposed total sample size of 94 patients, over 2 years.

Demographic information such as age and race will be tabulated. Descriptive statistics, including means, standard deviations, and ranges for continuous parameters, as well as percentages and frequencies for categorical parameters, will be presented. Adverse medical events will be tabulated. CTCAE Grade 3 and Grade 4 laboratory abnormalities will be listed.

9.1.2 Primary Endpoints

The primary objective of this stratified Phase 2 study is to determine the CR using a modified CR endpoint (CR+CRi+CRh).

The safety and efficacy will be evaluated by an independent data review committee at each critical step of the protocol.

9.1.2.1 Efficacy Evaluation

Clinical efficacy will be evaluated by MDS International Working Group (IWG) 2006 criteria (Cheson *et al.,* 2006) and AML IWG 2003 criteria (Cheson *et al.,* 2003) after 6 cycles of treatment. The primary endpoint will be cumulative composite CR (CR, CRi, CRh) and we will also record the cumulative ORR will include complete remission (CR), complete remission with incomplete blood count recovery (CRi), partial response (PR), and bone marrow complete remission (marrow CR/MLFS) achieved at least at one point during these 6 cycles.

9.1.3 Stopping Rule for Toxicity

Treatment and study participation may be stopped for excessive toxicity, defined as “any non-hematologic SAE at least possibly related to the drug leading to a treatment interruption of more than 2 weeks or any grade 4 ANC or PLT toxicity for which treatment can’t be restarted within 42 days of the initiation of the cycle and in the absence of active disease. Febrile neutropenias/neutropenic infections are excluded from this definition.”

The maximum toxicity rate allowed in the protocol will be 20% globally and 20% in each individual arm. We will have monthly evaluations of the toxicity rate during the study as well as for study milestones (end of stage 1 of the Simon design for each individual arm). Data will be reviewed by the coordinating team and the local PI. Based on the number of treated patient and the number of patients qualifying for an excessive toxicity, we will have a go/no-go decision for the continuation of the study and/or arm:

Number of patients	Hold inclusions if DLT are seen in
0-10	2 pts or more
11-15	3 pts or more
16-20	4 pts or more
21-25	5 pts or more
26-30	6 pts or more
31-35	7 pts or more

9.2 Sample Size/Accrual Rate

Expected monthly accrual is 3-4 patients per month, with a proposed total sample size of 94 patients, over 2 years.

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	1	1	1	**4**
Asian	2	2	0	0	**4**
Native Hawaiian or Other Pacific Islander	1	1	0	0	**2**
Black or African American	6	6	4	4	**20**
White	20	20	10	10	**60**
More Than One Race	2	0	2	0	**4**
Total	**32**	**30**	**17**	**15**	**94**

9.3 Stratification Factors

Patients will be stratified based on prior exposure to IDH inhibitors. Both untreated and pre-treated cohorts will be evaluated independently from the statistical perspective. AML and MDS patients will also be analyzed separately.

9.4 Analysis of Secondary Endpoints

9.4.1 Toxicity Evaluation and Reporting

All patients will be evaluated for toxicity.

- Non-hematologic toxicity will be evaluated by CTCAE v5 criteria.
- Hematologic toxicity will be defined using specific AML criteria: a hematologic dose limiting toxicity will be defined by the absence of the recovery of a cytopenia (ANC, PLT, Hgb) to baseline levels (Day 1 of the cycle) within 6 weeks of Day 1, in the absence of signs of active disease in blood and bone marrow.

9.4.2 Evaluation of Objective Response Rate

The effectiveness of the drug in patients for each cohort will be independently assessed by composite CR rate (CR+CRi+CRh). Objective Response Rate (ORR) will be included as a secondary endpoint, calculated as a composite CR+MLFS+PR. The exact two-sided 95% confidence intervals for the ORR will be reported. For lifetime data analyses, e.g., overall and progression free survival, the study survival will be estimated using the Kaplan-Meier method with the 95% confidence intervals (CIs). The CI based on the Greenwoods variance will be reported. In addition, the possible risk factors will be compared for survival with log-rank test. For multivariate analysis, the proportional hazards Cox model will be applied to investigate potential prognostic factors, such as age and stage of disease on the survival data. The adjusted p-values of the odds ratios and the adjusted 95% confidence interval will be reported.

9.4.3 Survival Definitions

- OS will be defined by the time interval between the first day of therapy to the time of death or last follow-up, whichever comes first.
- PFS will be defined by the time interval between the first day of therapy to the time of documentation of progression, death of any cause, or last follow-up, whichever comes first.
- DOR will be defined by the time interval between the first documentation of response to the time of documentation of progression, death of any cause, or last follow-up, whichever comes first.
-

9.5 Exploratory Endpoints

We expect to have all patients evaluated for correlatives at least at baseline, and it is reasonable to expect at least 10 patient samples per timepoint/technique to interpret potential trends. In the event that insufficient bone marrow is collected, blood samples may be used (30 mL per collection), provided that a minimum of 1g/L of circulating blasts are present on the differential of the CBC.

9.5.1 Changes in 2HG Levels

The Mann-Whitney U test will be used to test for differences in post-treatment plasma 2HG concentrations between patients with a response to treatment and those without. We will also test for differences in Δ2HG (defined as pre-treatment minus post-treatment plasma concentration) between patients with a response to treatment and those without. Differences with $p \leq 0.05$ will be considered significant. The area under the receiver operating characteristic curve (ROC AUC) will be calculated to determine the cutoff value of the Δ2HG difference. The optimal cutoff value will be determined at the point on the ROC curve at (sensitivity + specificity − 1) is maximized (Youden index).

9.6 Reporting and Exclusions

9.6.1 Evaluation of Toxicity

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

9.6.2 Evaluation of Response

All patients that finish at least 1 cycle of therapy will be considered evaluable for clinical response. Clinical efficacy (Cumulative Overall Response Rate, ORR) will be evaluated by MDS IWG 2006 criteria (Cheson *et al.,* 2006) and AML IWG 2003 criteria (Cheson *et al.,* 2003) after 6 cycles of treatment. Cumulative ORR will include CR, Cri, PR, marrow CR achieved at least at one point during these 6 cycles.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

AE monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the Medidata Rave **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Olaparib (AZD2281, NSC 747856)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3449 patients.* Below is the CAEPR for Olaparib (AZD2281).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, June 5, 2023

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 4)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
Abdominal pain			***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
	Urinary tract infection		
INVESTIGATIONS			
	Creatinine increased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
		Platelet count decreased	
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		
	Myalgia		
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)	
		Skin and subcutaneous tissue disorders - Other (erythema	

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
		nodosum)	
VASCULAR DISORDERS			
		Vascular disorders - Other (venous thromboembolism)	

NOTE: New Primary Malignancies other than MDS/AML
New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented *BRCA* mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. Most are not attributed to olaparib.

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on Olaparib (AZD2281) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Olaparib (AZD2281) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Enterocolitis; Esophageal stenosis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Obstruction gastric; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Fever; Malaise; Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Dermatitis radiation; Fracture; Gastrointestinal anastomotic leak; Injury, poisoning and procedural complications - Other (vena cava injury); Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; Hemoglobin increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypermagnesemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Bone pain; Generalized muscle weakness; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain; Rotator cuff injury; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain
NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Hallucinations; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (decreased glomerular filtration rate); Renal and urinary disorders - Other (hydronephrosis); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Pruritus
VASCULAR DISORDERS - Arterial thromboembolism; Flushing; Hot flashes; Hypertension; Hypotension; Peripheral ischemia; Thromboembolic event

Note: Olaparib (AZD2281) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.5

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.,* those listed in the SPEER column, Section 10.1) should be reported through Medidata Rave only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.5.

- **Attribution** of the AE:

  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the

following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.,* radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** Serious AEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An AE is considered serious if it results in **<u>ANY</u>** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

<u>ALL SERIOUS</u> AEs that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious AEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

<u>Expedited AE reporting timelines are defined as:</u>

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious AEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.3.4 Olaparib Adverse Events of Special Interest

AEs 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 investigators to CTEP. An AESI may be serious or non-serious. The AESI for olaparib are the following Important Potential Risks:

1. MDS/AML
2. New primary malignancy (other than MDS/AML)
3. Pneumonitis
4. Cases of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
    - Treatment-emergent ALT or AST >3×ULN (or >3× baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin >2×ULN (of which ≥35% is direct bilirubin).
    - Treatment-emergent ALT or AST >3×ULN (or >3× baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice.

Any event of MDS/AML, new primary malignancy, pneumonitis, or potential DILI should be reported in an expedited manner to CTEP via Medidata Rave regardless of whether it is considered a non-serious AE (*e.g.,* non-melanoma skin cancer) or SAE, and regardless of the investigator's assessment of causality or knowledge of the treatment arm. For cases of potential DILI, report all relevant laboratory abnormalities and related AEs using the appropriate CTCAE terms.

Events of MDS, AML, or new primary malignancy occurring more than 30 days after the last study treatment must be reported via Medidata Rave regardless of seriousness or causality. Investigators will be asked during the regular follow-up for OS if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

10.3.5 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via Medidata Rave. However, they still must be reported through the routine reporting mechanism (Section 10.4):

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
Investigations	Neutrophil Count Decreased	4	Regardless
Investigations	Platelet Count Decreased	4	Regardless
Blood & Lymphatic System Disorders	Anemia	4	Regardless

[a] Indicates that an AE required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient.

10.4 Routine Adverse Event Reporting

All AEs **must** be reported in routine study data submissions. **AEs reported expeditiously through Medidata Rave must also be reported in routine study data submissions.**

AE data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the AE CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an AE in and of itself, pregnancy as well as its outcome must be documented via **Medidata Rave**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via Medidata Rave. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, AML)
- MDS
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Cycle 1 +/-1	Cycle 2 +/-1	Cycle 3 +/-1	Cycle 4 +/-3	Cycle 5 +/-3	Cycle 6 +/-3	Cycle 7 +/-3	Cycle 8 +/-3	Cycle 9 +/-3	Cycle 10 +/-3	Cycle 11 +/-3	Cycle 12+ +/-3	EOT +/-7	90 day f/u [a] +/-14
Olaparib		A	A	A	A	A	A	A	A	A	A	A	A		
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X	X	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	X		
Physical exam[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X													X	X
Height	X														
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Performance status [b]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
CBC w/diff, plts [f]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Coagulation evaluation [g]	X	X	X		X		X			X			X	X	
Serum chemistry [c, f]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine testing [f]	X	X	X		X		X		X		X		X	X	
EKG (as indicated)	X														
Adverse event evaluation		X	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	X		X
Pregnancy test [d]	X														
Response assessment [e] *without* prior IDH inhibitor exposure		X		X			X			X			X		
Response assessment [e] *with* prior IDH inhibitor exposure				X			X			X			X		
Bone marrow aspiration	X	X		X			X			X			X	X	
Blood collection for biomarker assays [h]	X	X		X			X			X			X	X	
Buccal swab	X														

A:	Olaparib: Dose as assigned; 200 or 300 mg q12h daily PO.
a:	90 day f/u evaluation.
b:	Note: Physical exams and Performance status evaluations are based on a 4-week cycle. At minimum, performance status should be evaluated at the beginning of every cycle.
c:	CBC with differential and platelets assessment to occur twice weekly during Week 1 of Cycle 1, once weekly during Weeks 2-4 of Cycle 1, and then once per cycle thereafter. Assessment to include albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid.
d:	Pregnancy test for women of childbearing potential.
e:	Response Assessment includes bones marrow biopsy, and marrow and plasma 2HG levels. Response per AML IWG (IWG) 2003 criteria and MDS IWG 2006 (modification) criteria.

f: Clinical Safety Laboratory Assessments to occur twice weekly during Week 1 of Cycle 1, once weekly during Weeks 2-4 of Cycle 1, and thenonce per cycle. Assessment to include: Haematology/Haemostasis (whole blood), B-Haemoglobin (Hb), B-Leukocyte count, B-Absolute neutrophil count, B-Absolute lymphocyte count, B-Platelet count, B-Mean cell volume (MCV), Urinalysis (dipstick), U-Hb/Erythrocytes/Blood, U-Protein, U-Glucose, and Clinical Chemistry (serum or plasma): S/P-Creatinine, S/P-Bilirubin, total, S/P- Alkaline phosphatise (ALP), S/P-Aspartate transaminase (AST), S/P-Alanine transaminase (ALT), S/P-Albumin, S/P-Potassium, S/P-Calcium, total, S/P-Sodium, S/P-Urea or Blood Urea Nitrogen (BUN), S/P-Total Protein, S/P lactate dehydrogeneases (LDH), S/P uric acid, & phosphorus

g Coagulation evaluation to occur twice weekly during Week 1 of Cycle 1, once weekly during Weeks 2-4 of Cycle 1, and then once per cycle thereafter. Assessment to include activated partial thromboplastin time (APTT), Prothrombin Time/international normalized ratio (PT/INR), and Fibrinogen as indicated in the calendar, or as clinically indicated (*i.e.*, upon suspicion of DIC). Each coagulation test result will be recorded in CRF. Coagulation evaluation to be conducted pre-study, Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of Cycles 2, 4, 6, 9, 12, *every third cycle after cycle 12, and at End of Treatment.*

H Blood and bone marrow collections to occur after the cycle.

Note: Each Cycle is 28 days.; Visit Windows: Cycle 1 – 3 (+/-1 day); Cycle 4 – 12+ (+/-3 days); EOT +/- 7 days; 90 f/u +/-14 days

EOT= end of treatment, q12h = every 12 hours, PO = by mouth, BUN=blood urea nitrogen; LDH=lactic dehydrogenase; SGOT[AST]=serum glutamic oxaloacetic transaminase [aspartate transaminase]; SGPT[ALT]=serum glutamic pyruvic transaminase [alanine transaminase]. CRF = Case Report Form.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Hematologic Tumors

For patients not previously exposed to IDH inhibitors, response is assessed after cycles 1, 3, 6, 9, and 12 for the first year. For patients *with* prior IDH inhibitor exposure, response is assessed after cycles 3, 6, 9, and 12 for the first year on treatment.

Category	Definition	Comment
Complete Response (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L (1,000/mcL); platelet count ≥100 × 10^9/L (100,000/mcL)*****	
CR with incomplete hematologic recovery (CRi)/CRh	All CR criteria except for residual neutropenia (<1.0 × 10^9/L [1,000/mcL]) or thrombocytopenia (<100 × 10^9/L [100,000/mcL])***** CRh: complete remission with partial hematological recovery (platelets > 50,000 mcL and ANC > 500/mcL)	
Morphologic leukemia-free state (“marrow CR”, MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be aplastic—at least 200 cells should be enumerated, or cellularity should be at least 10%
Partial response (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to between 5% and 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Stable disease (SD)	Absence of CR, CRi, PR, MLFS; and criteria for PD not met	The period of stable disease should last at least 3 months

Category	Definition	Comment
Progressive disease (PD)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (>0.5 × 10^9/L [500/mcL], and/or platelet count to >50 × 10^9/L [50,000/mcL] nontransfused) • >50% increase in peripheral blasts (WBC × % blasts) to >25 × 10^9/L (>25,000/mcL) (in the absence of differentiation syndrome**) • New extramedullary disease	In general, at least two cycles should be administered prior to PD assessment. Patients with PD may remain on study, after discussion with the PI, if it is judged that they are deriving clinical benefit from doing so.
Primary refractory disease	No CR or CRi after two courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	
Death in aplasia	Death occurring ≥7 days following completion of initial treatment while cytopenic; with aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistence leukemia	
Death due to indeterminate cause	Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	
Hematologic relapse (after CR, CRi)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease	

* CBC values for up to 14 days after bone marrow assessment may be used to determine response.
** Certain targeted therapies, *e.g.,* those inhibiting mutant IDH proteins, may cause a differentiation syndrome, *i.e.,* a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts. In the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.
ANC=absolute neutrophil count, IDH=isocitrate dehydrogenase, MFC=multiparameter flow cytometry, RT-qPCR=real-time quantitative polymerase chain reaction, WBC=white blood count. (Döhner *et al.*, 2017)

12.2 Other Response Parameters

Other endpoints can be found in Section 9.4.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

AE lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol PI is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious AEs; reporting of expedited AEs; and accumulation of reported AEs from other trials testing the same drug(s). The Protocol PI and statistician have access to the data at all times through the CTMS web-based reporting portal.

During the Phase 2 portion of the study, the Protocol PI will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol PI and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of AEs for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and

- To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and

Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

13.4 CTEP Multicenter Guidelines

Not Applicable

13.5 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to: Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13.6 Genomic Data Sharing Plan

The investigators and statistician and/or bioinformaticians for a study will have access to all data on mutations and variants stored in the Theradex Data Base and the GDC. This information will be sequestered from access throughout the study until it is analyzed for purposes of reporting and publishing of the study results. As specified in the CRADA for the agents used in the clinical study, the pharmaceutical collaborator will have at least 6 months, longer if needed for a regulatory filing, to review the data and or receive copies of the data once the study is completed and analyzed, or sooner, if specified for purposes of generating Intellectual Property. Once these timeframes have been exceeded, the data will be available through a Data Access Committee (DAC) in the GDC following NCI and Collaborator review of the proposals.

13.7 Incidental/Secondary Findings Disclosure Procedure

Given the potential clinical implications conferred by detecting a germline and/or somatic mutation in one of the proven cancer susceptibility genes, this protocol will use the following disclosure procedure, consistent with the recommendations of the American College of Medical and Genomics (ACMG) (Green *et al*., 2013 and Kalia *et al.,* 2016):

The NCI Molecular Characterization Laboratory will review the mutations/variants once at the time of initial specimen evaluation according to the most recent version of the ACMG guidance on variants. The NCI Molecular Characterization Laboratory will not re-review all specimens received if a new version of the ACMG guidance is published after the initial review.

For each participant with a pathogenic or likely pathogenic germline and/or somatic variant detected in the WES of blood (as defined in the ACMG guidance), the NCI Molecular Characterization Laboratory will report to the Program Director or Scientific Officer the UPID and variant(s) identified. The Program Director or Scientific Officer will contact Theradex to obtain the name of the protocol, investigator treating the patient, and the Principal Investigator of the grant. The treating physician will be contacted by phone and in writing to ask the patient whether he or she is interested in learning more about the finding.

If the patient wants to know more, the physician should contact the Program Director for more information about the mutation/variant. The treating physician and a medical genetics counselor should meet with the patient to discuss the importance and meaning of the finding, but not the finding itself, and notify the patient that this research finding must be confirmed by Sanger sequencing at the patient's/patient insurer's expense in a CLIA-approved laboratory. The treating physician and genetic counselor should inform the patient of the confirmed result and its meaning and significance to the patient. If desired, the patient may elect to undergo genetic counseling and confirmatory CLIA-approved clinical testing on his or her own. Neither the research laboratory nor the National Cancer Institute will be responsible for the costs incurred for any confirmatory genetic testing or counseling.

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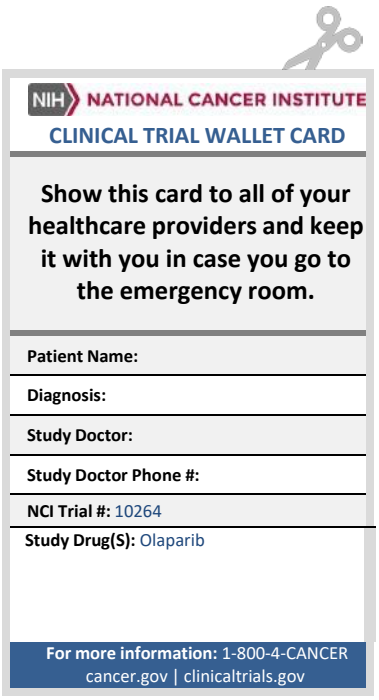
APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.,* light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B PATIENT CLINICAL TRIAL WALLET CARD



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Diagnosis:

Study Doctor:

Study Doctor Phone #:

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Study Drug(S): Olaparib

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APPENDIX C ACTIONS REQUIRED IN CASES OF COMBINED INCREASE OF AMINOTRANSFERASE AND TOTAL BILIRUBIN – HY'S LAW

Briefly, Hy's Law cases have the following three components:

The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo

Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)

No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Finding one Hy's Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe drug induced liver injury (DILI) when given to a larger population.

The following actions are required in cases of combined increase of aminotransferase and total bilirubin:

1. Confirmation

In general, an increase of serum AST/A:T to >3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Serum AT may rise and fall quite rapidly, and waiting a week or two before obtaining confirmation of elevations may lead to a false conclusion that the initially observed abnormality was spurious. Of greater concern, delay in retesting may allow progression to severe worsening if the initial abnormality was the herald of a severe reaction to follow. The need for prompt repeat testing is especially great if AST/ALT is much greater than 3xULN and/or TBL is greater than 2xULN. For outpatient trials, or trials in which subjects are far away from the trial site, it may be difficult for the subjects to return to the trial site promptly. In this case, the subjects should be retested locally, but normal laboratory ranges should be recorded, results should be made available to trial investigators immediately, and the data should be included in the case reports. If symptoms persist or repeat testing shows AST/ALT >3xULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening. If close monitoring is not possible, the drug should be discontinued.

2. Close Observation

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. A threshold of aminotransferase levels greater than 3xULN seems reasonable, as lesser elevations are common and nonspecific. If additional testing, beyond that specified in the trial protocol, is carried out, it is important that the subject's information be added to the case report forms and database. Close observation includes:

Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
Obtaining a more detailed history of symptoms and prior or concurrent diseases.
Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
Obtaining a history of exposure to environmental chemical agents.
Obtaining additional tests to evaluate liver function, as appropriate (*e.g.*, INR, direct bilirubin).
Considering gastroenterology or hepatology consultations.

3. Decision to Stop Drug Administration

It has been observed that de-challenge (stopping drug administration) does not always result in immediate improvement in abnormal lab values. Abnormal test values and symptoms may progress for several days or even weeks after discontinuation of the drug that caused the abnormality. For example, rising TBL usually follows serum AT increases by a few days to weeks. The primary goal of close observation is to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or will progress. For most DILI, no specific antidotes are available (except N-acetylcysteine for acute acetaminophen overdose if given promptly, and, possibly, intravenous carnitine for valproic acid hepatotoxicity).

Promptly stopping the offending drug usually is the only potentially effective therapy.

Because transient fluctuations of ALT or AST are common, and progression to severe DILI or acute liver failure is uncommon, automatic discontinuation of trial drug upon finding a greater than 3xULN elevation of ALT or AST may be unnecessary. For most people, the liver appears capable of adapting to injury by foreign chemical substances, which may render a person tolerant to the drug despite continued exposure. Stopping a drug at the first hint of mild injury does not permit learning whether adaptation will occur, as it does for drugs such as tacrine, which cause liver injury but do not cause severe DILI. On the other hand, continuing drug appears unacceptably dangerous if there is marked serum aminotransferase elevation or evidence of functional impairment, as indicated by rising bilirubin or INR, which represent substantial liver injury. Although there is no published consensus on exactly when to stop a drug in the face of laboratory abnormalities and the decision will be affected by information on related drugs, the accumulating clinical experience, the clinical status of the patient, and many other factors, the

following can be considered a basic guide. Discontinuation of treatment should be considered if:

ALT or AST >8xULN
ALT or AST >5xULN for more than 2 weeks
ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

It should be noted that although these guidelines have not been evaluated systematically in a prospective fashion, they represent an approach that is similar to current practice.

4. Evaluating Data for Alternative Causes

An important purpose of close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following common causes:

Acute viral hepatitis. The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute DILI. The presence of acute viral hepatitis A, B, and C should be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries and in patients in trials conducted in those countries. Also rare are hepatocellular liver injuries caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are seen more typically in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with cytomegalovirus disease.

Alcoholic and autoimmune hepatitis. Acute alcoholic hepatitis usually is recurrent, with a history of binging exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, hepatomegaly, and AST >ALT, that may help distinguish it from other causes of liver injury. Other features of the physical examination may include the presence of stigmata of cirrhosis, such as spider nevi, palmar erythema, estrogenic changes in males, and Dupuytren's contractures. Alcoholic and autoimmune hepatitis should be assessed by history, physical examination, and laboratory testing, including serologic testing (*e.g.*, antinuclear or other antibodies).

Hepatobiliary disorders. Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.

NASH. NASH may be seen in obese, hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels, and hepatic and sometimes splenic

enlargement. It is sometimes associated with cirrhosis and portal hypertension.

Cardiovascular causes. Cardiovascular disease, especially right heart failure and hypotension or any cause of impaired oxygenation of the liver, may cause acute centrilobular hypoxic cell necrosis (ischemic hepatitis) with rapid and sometimes spectacular increases of serum AT (*e.g.*, AT >10,000 U/L). Cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure, should be assessed by physical examination and history.

Concomitant treatments. It is critical to discover concomitant treatments, including exposure to nonprescription and dietary supplement products that might be responsible for injury. Many people take multiple drugs, perhaps less often in controlled clinical trials because of exclusion criteria, but subjects may not report taking disallowed drugs or other agents. The possible exposure to potentially toxic herbal or dietary supplement mixtures (sometimes of unknown composition), nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

5. Follow-Up to Resolution

All trial subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be DILI, indicating that liver injury was related to underlying liver disease.

6. Re-challenge

Whether or not to re-challenge a subject who showed mild DILI is a difficult decision. Re-exposure may initiate a sometimes explosive and more severe reaction, as was observed with halothane several decades ago. Some cases of DILI show indicators of immunological reaction such as eosinophilia, rash, fever, or other symptoms or findings, and it is possible that such cases are more prone to recur with re-exposure. Re-challenge may not be considered negative unless the subject is exposed to and tolerates the same dose and treatment duration that preceded the original reaction. A negative re-challenge does not necessarily allow a conclusion that the drug did not cause the injury. Most people can adapt to xenobiotic substances, including new drugs, and develop tolerance for them. This has been observed even for drugs that can cause severe injury, such as isoniazid. The large majority of people showing hepatocellular injury while taking isoniazid recover fully or recover while continuing to take the drug, and some, but not all, can resume or continue taking the drug without further adverse consequence. If such tolerance has developed, the use of re-challenge to verify drug causation would give a false negative result.

Generally, re-challenge of subjects with significant AT elevations (>5xULN) should not be attempted. If such subjects are re-challenged, they should be followed closely. Re-challenge can be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show a potential for severe injury. The subject should be made aware of the potential risk, and consent to the re-challenge, and the PI consulted.

APPENDIX D ACCEPTABLE BIRTH CONTROLS METHODS

Olaparib is regarded as a compound with medium/high foetal 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]. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception if they are of childbearing potential (as listed below). Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

Acceptable Non-hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month after the last dose of study drug <<for 3 months after last dose *for male patients*>>. (Periodic abstinence [*e.g.*, calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial] and withdrawal are not acceptable methods of contraception).
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- IUD PLUS male condom. Provided coils are copper-banded

Acceptable hormonal methods:

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

APPENDIX E PATIENT INFORMATION SHEET ON DIARRHEA MANAGEMENT

Diarrhea is a common problem experienced by many patients and is a risk with olaparib. If it is not controlled quickly, it can lead to dehydration.

WHEN TO CALL YOUR DOCTOR TO REPORT DIARRHEA

- Fever 100.5° F or higher with diarrhea.
- If you are experiencing diarrhea for the first time after starting therapy. Based on questions answered during that phone call, we will advise starting with 2 milligrams (mg) of loperamide (Imodium) if it seems the symptoms are related to the treatment.
- If you still have diarrhea 24 hours or more than 6 loose bowel movements after starting loperamide (Imodium) (your doctor may advise additional medications or want to evaluate you in person if there is a concern that you are becoming dehydrated).

OVER THE COUNTER MEDICATION MANAGEMENT OF DIARRHEA

- For diarrhea that occurs more than 2 episodes a day, use loperamide (**Imodium**). We recommend that you have loperamide (Imodium) on hand at home before starting therapy.
    - 1st episode of diarrhea: Take 2 caplets (4 mg).
    - During the day: Take 1 caplet (2 mg) after each episode of diarrhea.
    - During the night: Take 2 caplets (4 mg) at bedtime if you are still having diarrhea.
    - Do not take more than 8 tablets (16 mg) of loperamide in 24 hours.

DRINK PLENTY OF FLUIDS

- Drink 8 to 10 large glasses of liquids a day to replace those lost by diarrhea. Drink small quantities at a time slowly.
- **AVOID** caffeinated, very hot, or very cold fluids.
  Examples of acceptable fluids:
    - **Water** (should only be part of the 8 to 10 glasses a day)
    - **Jello/gelatin**
    - **Gatorade**
    - **Clear soup** or **broth**
    - Other non-caffeinated fluids

EAT SMALL MEALS OFTEN

- A good choice of foods for diarrhea is the BRAT diet:
    - **B** - bananas
    - **R** - rice
    - **A** - applesauce
    - **T** - toast
- When these foods are being well tolerated, then you can add other bland low fiber foods such as:
    - Chicken (white meat without the skin), steamed rice, crackers, white bread, pasta noodles without sauce, and canned or cooked fruits without skins.
    - Foods high in potassium: bananas, apricots without skin, peach nectar, potatoes

without skin, broccoli, halibut, mushrooms, asparagus, non-fat milk.

- Foods that can make diarrhea and cramping worse:
  - Fatty, fried, greasy, or spicy foods can cause more problems and discomfort.
  - High-fiber foods: Bran, whole grain cereals, dried fruit, fruit skins, popcorn, nuts, and vegetables.
  - Foods that cause gas: Beer, beans, cabbage, carbonated drinks.

APPENDIX F PATIENT MEDICATION DIARY - OLAPARIB

CTEP-assigned Protocol # 10264

Local Protocol # _____

PATIENT'S MEDICATION DIARY

Today's date_____ **Agent**____Olaparib____

Patient Name_____*(initials acceptable)* **Patient Study ID**_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form every four weeks.
2. You will take 2 tablets twice each day (supplied as either 100mg or 150mg tables),____in the morning and____in the evening.
   - You should take the tablets with 8 oz. water, with or without any moderate fat or low-fat food.
   - Do not consume grapefruit, grapefruit juice, or Seville oranges while on olaparib therapy.
   - Do not chew, dissolve, or crush olaparib tablets.
   - If you miss a dose, you have up to 2 hours to make this dose up. Otherwise, write "missed" where you would normally write the time of your dose. Do not double-up on the next dose.
   - If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted.
3. Record the date, the number of tablets you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return the forms to your physician when you go for your next appointment.

Day	Date	Time of morning dose	# of tablets taken	Time of evening dose	# of tablets taken	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						

22						
23						
24						
25						
26						
27						
28						

Patient's Signature_____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

APPENDIX G WORLD HEALTH ORGANIZATION DIAGNOSTIC CRITERIA FOR ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROMES

Arber D.A., A. Orazi, R. Hasserjian, *et al*., (2016). The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 127(2391-2405).

Acute myeloid leukemia (AML) and related neoplasms

AML with recurrent genetic abnormalities

AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11 APL with PML-RARA
AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A
AML with t(6;9)(p23;q34.1);DEK-NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1 Provisional entity: AML with BCR-ABL1
AML with mutated NPM1
AML with biallelic mutations of CEBPA
Provisional entity: AML with mutated RUNX1

AML with myelodysplasia-related changes

Therapy-related myeloid neoplasms

AML, NOS

AML with minimal differentiation

AML without maturation

AML with maturation

Acute myelomonocytic leukemia

Acute monoblastic/monocytic leukemia

Pure erythroid leukemia

Acute megakaryoblastic leukemia

Acute basophilic leukemia

A cute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome

Transient abnormal myelopoiesis (TAM)

Myeloid leukemia associated with Down syndrome

Myelodysplastic syndromes (MDS)

MDS with single lineage dysplasia

MDS with ring sideroblasts (MDS-RS)

MDS-RS and single lineage dysplasia

MDS-RS and multilineage dysplasia

MDS with multilineage dysplasia

MDS with excess blasts

MDS with isolated del(5q)

MDS, unclassifiable