An open label, multicenter, phase II trial testing single agent decitabine in *TP53* mutated relapsed/refractory acute myeloid leukemia

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Protocol Revision History

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Principal Investigator Signature Page

Principal Investigator (printed):

Name of Institution:

PI Signature *Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AML	Acute myeloid leukemia
t-AML	Therapy-related Acute myeloid leukemia
s-AML	Secondary Acute myeloid leukemia
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
BMT	Bone marrow transplant
BM	Bone marrow
CBC	Complete blood count
CNS	Central nervous system
CR	Complete response
CRc	Cytogenetic complete remission
CRi	Complete remission incomplete hematologic recovery
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
DSMC	Data Safety Monitoring Committee
ECG (or EKG)	Electrocardiogram
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
GCP	Good Clinical Practice
HB	Hemoglobin
HHS	Department of Health and Human Services
HI	Hematologic improvement
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IRB	Institutional Review Board
ITT	Intention to Treat
MDS	Myelodysplastic syndrome
mLFS	Morphologic leukemia free state
MM	Multiple myeloma
MPN	Myeloproliferative neoplasm
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
ORR	Overall response rate

OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PB	Peripheral blood
PD	Progressive disease
PI	Principal investigator
PR	Partial remission
QASMC	Quality Assurance and Safety Monitoring Committee
RFS	Relapse free survival
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCC	Siteman Cancer Center
SCT	Stem cell transplant
SD	Stable disease
TSH	Thyroid stimulating hormone
TTLR	Time to leukemia relapse
UPN	Unique patient number
WBC	White blood cell count

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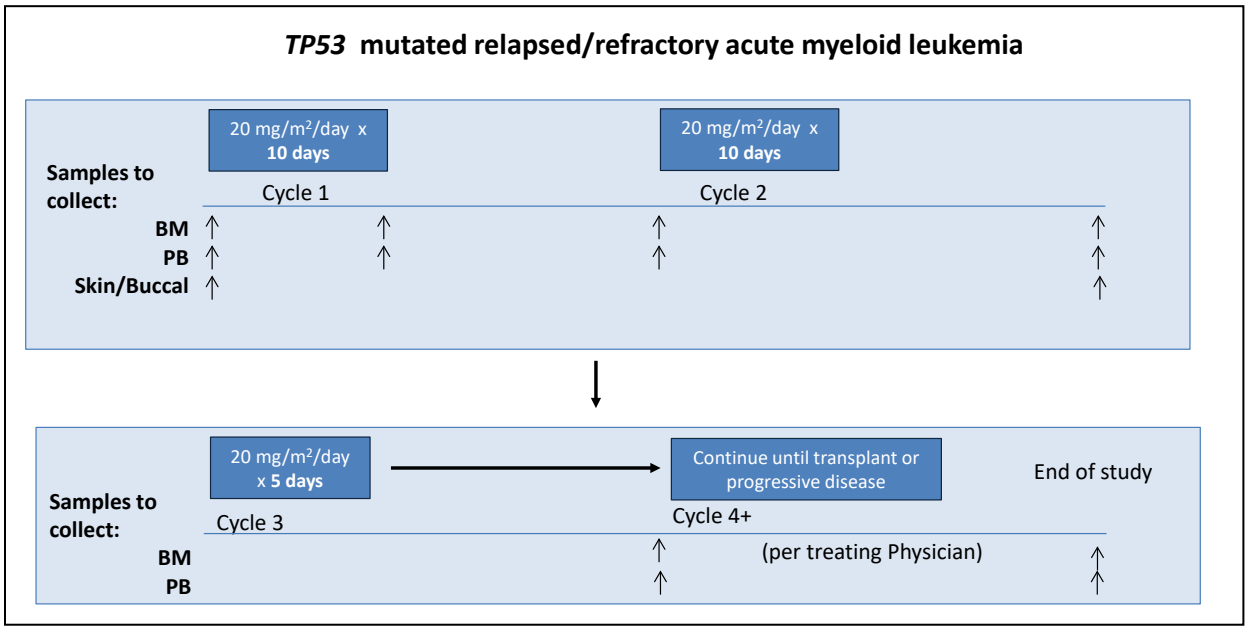
SCHEMA



A bone marrow biopsy may be performed at any time after Cycle 2 if there is clinical concern for progression.

Patients with progressive disease after 2 cycles of decitabine (10 days each) may be removed from study.

After Cycle 2, decitabine dose will be reduced FOR ALL PATIENTS from 20 mg/m^2/day **x 10 days** to 20 mg/m^2/day **x 5 days**. After Cycle 1, patients with blast counts <5% may reduce decitabine dose from 20 mg/m^2/day x 10 days to 20 mg/m^2/day x 5 days. Each cycle is 28 days.

Notes for transplant eligible patients
Anytime after 3 cycles, transplant eligible patients in **CR, CRc, CRi**, or **mLFS*** should **proceed to stem cell transplant** according to institutional protocols.
After 3 cycles, transplant eligible patients in **PR*** may be removed from study and proceed to salvage according to institutional protocols.

Notes for transplant ineligible patients
Transplant ineligible patients **will continue on study with decitabine (x 5 days)** until relapse or progression, with the exception of patients with **SD*** after 4 cycles who may continue on therapy or be removed from study per treating physician preference.

Antimicrobial prophylaxis during therapy is strongly recommended due to anticipated neutropenia. Common agents include acyclovir, ciprofloxacin, and fluconazole. Alternative agents may be used at the discretion of the treating physician.

Correlative samples:
BM and PB should be collected on Cycle 1 Day 0 (C1D0), Cycle 1 Day 10 (C1D10)**, Cycle 1 Day 28 (C1D28), Cycle 2 Day 28 (C2D28)*** and Cycle 3 Day 28 (C3D28). A skin biopsy should be done on C1D0 (buccal swab may be substituted for skin if patient declines skin biopsy). A buccal swab should be done on C2D28. BM and PB should be collected at the time of progression (if possible).

*For definition of responses see Section 12

** Bone marrow aspirate and biopsies on cycle 1 day 10 will only be performed in patients enrolled at Washington University.
*** At the discretion of the treating physician.

1.0 BACKGROUND AND RATIONALE

1.1 Introduction

Acute myeloid leukemia (AML) is an aggressive, relapsing blood cancer characterized by ineffective hematopoiesis and malignant expansion of clonal myeloid cells and a broad variety of genetically distinct sub-types[1].

Through next generation sequencing techniques, we have identified patterns of somatic mutations commonly associated with AML and found that these mutations organize into founding clones and subclones[2].

Treatment options for AML remain limited, and personalized strategies are needed[1]. The 5-year overall survival among patients with AML age 25-64 is 40%[3]. Both clinical and genomic prognostic markers have been identified, including age, performance status, type of AML (de novo, AML with antecedent hematopoietic malignancy, or therapy-related AML), response to induction treatment and, most importantly, genetics[4-7].

Cytogenetic abnormalities have been one of the most important prognostic markers for risk stratification[2]. Specifically, patients with complex karyotype or monosomy karyotype are associated with adverse risk, and often carry mutations in *TP53*[8]. In this population, standard cytotoxic chemotherapy and allogeneic stem cell transplantation result in 5-year survival of less than 10% and a median survival of only few months, and many patients even fail to achieve complete remission after induction chemotherapy[5-7].

We recently observed that AML and myelodysplastic syndrome (MDS) patients with *TP53* mutations have high response rates to decitabine[8]. In this study we will determine whether decitabine leads to an increase in overall survival in patients with *TP53* mutated AML, who have detectable disease after initial induction chemotherapy. These patients represent the group with the poorest prognosis, and alternative therapy is desperately needed.

1.2 Study Rationale

Among patients with complex or monosomy karyotypes, nearly 60% carry *TP53* mutations; whereas nearly all patients with *TP53* mutations have complex or monosomy karyotypes, and these karyotypes almost always involve deletion of chromosome 5q, chromosome 7, chromosome 12, or chromosome 17p[2,4,7,9]. Patients with *TP53* mutations tend to be older (median age 61 vs 54 years), have worse response to conventional chemotherapy (complete remission rate: 28% vs 50%), shorter event free survival (3-year EFS: 1% vs 13%), and overall survival (3-year OS: 3% vs 28%)[7,9].

We correlated response to decitabine with mutation status in 99 patients with AML or MDS. We observed response (complete remission (CR), complete remission with incomplete blood count recovery (CRi), or marrow complete remission (mCR) in 21/21 patients with *TP53* mutations. ($p < 0.0001$). No other gene mutation was associated with

response in the 99 patients sequenced[8] (Figure 1A).

Consistent with this, we observed mutation clearance in all 16 cases with TP53 mutations evaluated at serial time points, and that TP53 mutations were cleared more quickly and consistently than other variants[8] (Figure 2).

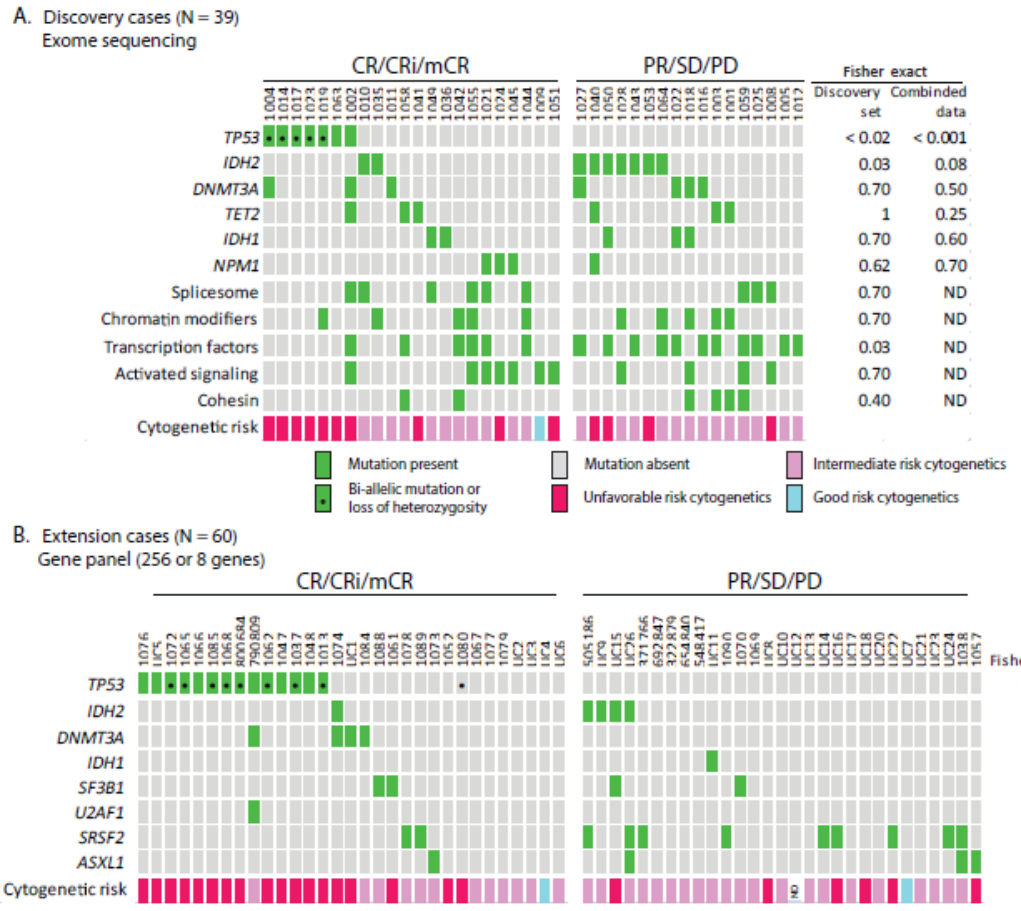


Figure 1. Correlation of mutation status and response in 99 patients with AML or MDS treated with decitabine.

Decitabine alone does not lead to a cure in the majority of responding patients. Mutation clearance is nearly always incomplete, and we could detect low levels of mutations (0.2 - 5%) in 20 of 20 patients analyzed during remission with enhanced exome sequencing. Furthermore, in all 9 patients analyzed at relapse, the relapse occurred via subclonal evolution (expansion of a subclone that carries the founding clone mutations and additional mutations, suggesting that the founding clone mutations persisted during morphologic remission)[8].

Several clinical variables correlated with survival in this cohort: age, performance status (2 vs 0-1), and whether the patient underwent stem cell transplantation (Figure 3A). Thus, additional consolidation (e.g. hematopoietic cell transplantation) appears necessary to

achieve prolonged remissions. Importantly, in this cohort of patients who undergo decitabine induction, the presence of *TP53* mutations no longer adversely affected survival following transplantation[8].

These data suggest that decitabine may have unique efficacy in patients with *TP53* mutations. In this study, we seek to determine whether decitabine therapy can improve outcomes, specifically overall survival, of this selected subset of AML patients with the poorest prognosis based on refractoriness to induction treatment and high-risk genetic mutations.

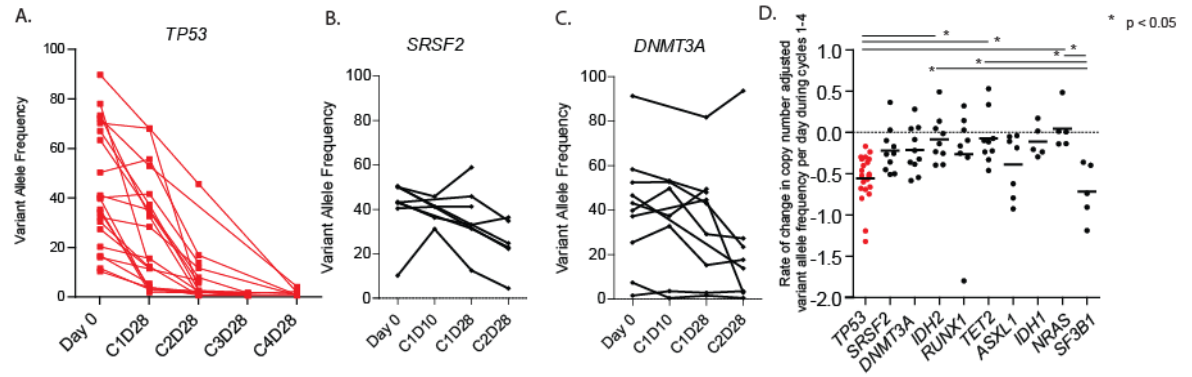


Figure 2. Consistent clearance of *TP53* mutations. A. The variant allele frequency of *TP53* mutations was consistently reduced during decitabine treatment. Twenty-one *TP53* mutations were evaluated at multiple time points in 16 patients, (e.g. cycle 2 day 28, C2D28). Variant allele frequency indicates the proportion of variant reads vs. the total number of reads at that nucleotide, and is proportional to the tumor burden. B and C. Mutation clearance of *SRSF2* and *DNMT3A* mutations. D. Summary of rate of mutation clearance. Note that during decitabine therapy, *TP53* mutations were consistently, and rapidly, cleared when compared with mutations in other genes. P value calculated with ANOVA using Tukey's post-test correction.

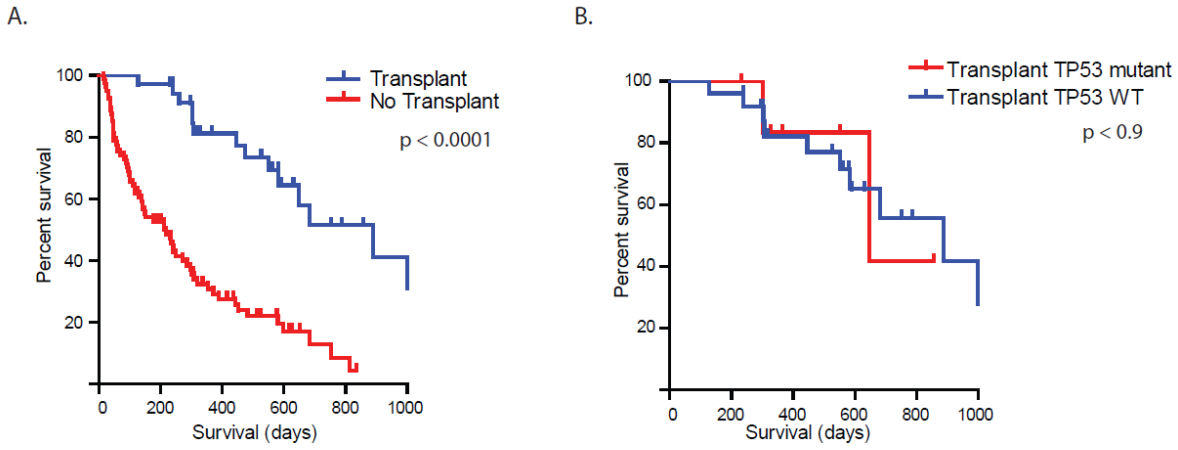


Figure 3. Overall survival subgroup analysis. A. Overall survival was increased in patients treated with 10 day decitabine who underwent stem cell transplantation vs. those who did not. B. Among patients who underwent stem cell transplantation, survival was not impacted by the presence or absence of *TP53* mutations. P value calculated as Log-rank.

1.3 Investigational Agent

Decitabine (5-aza-2'-deoxycitidine) is a DNA hypomethylating agent. Decitabine is an antimetabolite that can replace cytosine in DNA but, unlike cytosine, it cannot be methylated. The exact mechanism of decitabine activity has not been determined and may involve multiple pathways[10-11]. Decitabine is thought primarily to act by altering DNA methylation, a major mechanism for gene expression. Methylation of cytosine in the CpG dinucleotide by DNA methyltransferase leads to transcriptional silencing of genes during normal development and has emerged as a significant mechanism for the loss of tumor suppressor gene expression in human cancer, including AML[12]. Decitabine regulates DNA methylation (specifically targets the methyltransferase, *DNMT1*)[13], effectively demethylating and reactivating different tumor suppressor genes. Other possible mechanisms for decitabine activity include cytotoxicity due to incorporation into DNA during S phase and formation of covalent adducts with DNA methyltransferase[11-12]. The irreversible inhibition and degradation of DNA methyltransferase 1 results in methylation-independent induction of gene expression and it is associated with differentiation[10]. In addition to its differentiation inducing activity at low doses, decitabine has a direct cytotoxic effect at higher doses (1-2 μM)[11-12].

Decitabine has been investigated in hematologic malignancies using a range of doses and schedules. Two dosing regimens are approved in the US compendium. A dose of 15 mg/m^2 every 8 hours for 3 days, based on a Phase III study in adults with MDS that demonstrated improved outcomes in the treatment arm compared to the supportive care arm[14]. And the dose of 20 mg/m^2 daily for 5 days in 28-day cycles is also approved.

In general, decitabine is well tolerated. Unlike conventional cytotoxic chemotherapy, decitabine can be administered in the outpatient setting. Cytopenias commonly result from AML/MDS inhibition of normal hematopoiesis, and often do not resolve until a complete response is achieved. Thus, neutropenic sepsis and thrombocytopenic bleeding remain significant problems regardless of therapy, especially during the first 4-8 weeks. In our experience treating elderly AML patients, neutropenia occurred in 24%, sepsis in 9%, and bacteremia in 7%. Similar results have been observed in MDS patients[14-16]. As a result, death is not uncommon in the first 8 weeks of therapy, occurring in 15-17% of patients, and most commonly resulting from infection and cytopenias related to disease and therapy. While unsettling, these numbers are better than many historical patients treated with cytotoxic chemotherapy, and suggest a need for continued improvements in therapy.

A. Pharmacokinetics and Metabolism of Decitabine

In human subjects, after IV administration, decitabine displayed a distribution phase with a half-life of 7 minutes and a terminal phase elimination half-life of 10-35 minutes as measured by bioassay[17-20]. The short plasma half-life is due to rapid inactivation of decitabine by deamination by liver cytidine deaminase[17]. Total body clearance (Cl_p) in humans was high with a mean value of 126 mL/min/kg[19].

Among five adult patients with advanced solid tumors administered seven courses of 100 mg/m^2 of decitabine by 1-hour infusions[21], maximum plasma concentration ranged from 1 to 4 μM. Disappearance from plasma was biphasic with a rapid initial decline to less than 0.1 μM during the first hour post infusion and a slower decline over the next two hours to 6 nM, the level of detectability. Plasma half-life (mean±SE) was estimated to be approximately 7±1 minutes in the initial phase ($t_{½\alpha}$) and 35±5 minutes in the second phase ($t_{½\beta}$). The area under the plasma concentration-time curve was 408±88 ng.hour/mL for these patients, with a peak plasma concentration of 2.01±0.44 μM (0.44±0.1 μg/mL), while mean volume of distribution (Vd_{ss}) and CLp was 4.59±1.42 L/kg and 126±21 mL/min/kg, respectively. The time course of DAC concentrations was similar in 1 of 2 patients administered 75 mg/m^2, while DAC was usually undetectable in the plasma of patients administered 25 to 60 mg/m^2.

Using a longer infusion time (up to 40 hours), Rivard *et al.*[18] reported a plasma concentration of 0.1 to 0.4 μg/mL. With infusion times of 40-60 hours, at an infusion rate of 1 mg/kg/h, plasma concentrations of 0.43-0.76 μg/mL were achieved. The steady-state plasma concentration at an infusion rate of 1 mg/kg/h was estimated to be 0.2-0.5 μg/mL. The half-life after discontinuing the infusion was 12-20 min[17].

Urinary excretion of unchanged decitabine was low, ranging from less than 0.01% to 0.9% of the total dose, and there was no relationship between excretion and dose or plasma drug levels. High clearance values and a total urinary excretion of <1% of the administered dose suggest that decitabine is eliminated rapidly and largely by metabolic processes, including extrahepatic metabolism[22].

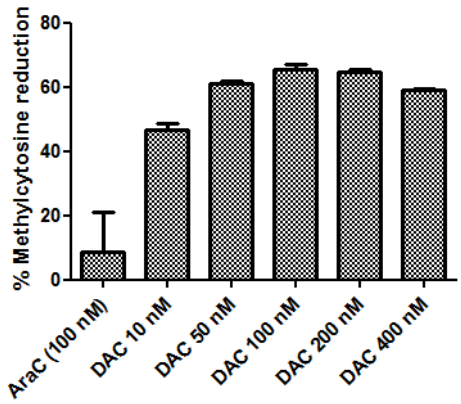
The steady state plasma concentrations (C_{ss}) ranged from 0.31 to 0.39 μg/mL (1.27 to 1.60 μM) during the infusion of 100 mg/m² decitabine over a 6-hour period. The range of concentrations during a 600 mg/m^2 infusion over an 8-hour period was 0.41-16 μg/mL(1.68 to 4.76 μM)[22]. These plasma concentrations are in the same range as the in vitro concentrations that activated the expression of tumor suppressor gene p16 in three human non-small-cell lung cancer (NSCLC) cell lines[21].

Steady state decitabine levels of 0.1 to 0.2 μM were achieved in solid tumor patients dosed with 30 mg/m²/day and 40 mg/m²/day by continuous intravenous infusion over 72 hours[22].

Summary of published steady state serum levels are below and are in proportion to infusion rate ($R^2 = 0.98$, $p < 0.0001$)[23].

Rate	Serum Concentration	
mg/m2/hr	ng/ml	nM
5	55	241
7.5	80	351
15	180	789
21	182.4	800
22.5	350	1535
42	456	2000
84	1140	5000

In our experience treating primary patient blasts *in vitro*, concentrations of 100 – 500 nM are required to maximize methylcytosine reduction without causing cellular toxicity. Because decitabine incorporation into DNA is S-phase dependent, exposure of cells during cell division is necessary for efficacy.



B. Experience with extended dosing schedules

Decitabine does not act quickly and the median time to response is 3 months. Several doses have been tested and reported in the literature with doses ranging from 5 mg/m^2/day for 5-10 days to doses of 135 mg/m^2/day for 3 days[23].

From our experience[8] and from another report[24] there is data to support that lower doses over longer periods of time results in significant improvement in response rate and have lower toxicity.

The mechanism underlying this observation is unclear, however there are some reports that suggest that at lower doses (e.g. 20 mg/m^2), decitabine might promote cell differentiation through effective methylcytosine reduction and gene expression derepression, as opposed to induction of apoptosis via DNA damage that is seen at

higher doses (e.g. 100 mg/m^2) and it is more typical of conventional chemotherapeutic agents[25].

Lower dose schedule (20 mg/m^2/day) on days 1-5 became the standard strategy based on a series of studies.[14,15,16] However, subsequent studies using longer dose schedules (days 1-10) found that this led to improved response rates.[8,24]

Therefore, we will use a dose of 20 mg/m^2/day as a 1-hour intravenous infusion on consecutive Days 1-10 in 28-day cycles, dose reductions for subsequent cycles will be allowed as described in Sections 5.1 and 6.3.

2.0 OBJECTIVES

2.1 Primary Endpoint

To determine the 1-year OS in patients with *TP53* mutations treated with at least one dose of decitabine compared to historic controls (OS = 25%)[5,26].

2.2 Secondary Endpoints

1. To determine the proportion of responding *TP53* mutated patients (CR, CRi) compared to historical controls (10%-15%)[26]

2. To determine the time to stem cell transplant among subjects who are suitable candidates for transplant and have an identified donor.

3. To correlate response and survival with clinical parameters:
   - morphologically evident disease (>5% blasts by cytomorphology) versus molecularly detected disease at the time of enrollment (disease detected with flow cytometry, cytogenetic, or mutational analysis if $\leq$ 5% blasts by cytomorphology);
   - *de novo AML versus* secondary AML *versus* treatment-related AML,
   - presence *versus* absence of cytogenetic abnormalities in addition to *TP53* mutations.

4. To determine the median time to leukemia relapse (TTLR) in non-transplant patients treated with decitabine compared to historical control (6-8 months)[27].

5. To determine the 2-year event free survival after transplant in patients treated with decitabine compared to historical control (18-22%)[28].

6. To determine the median and average number of hospital days during Cycles 1 and 2.

2.3 Exploratory Molecular Endpoints

1. To determine the proportion of patients who achieve mutation clearance to <0.1%, after 3 cycles of decitabine.

2. To determine whether PB or BM has the greater sensitivity for detecting residual mutation burden using a sensitive sequencing technology such as Haloplex.

3. To determine *TP53* clonal burden reduction after consolidation with stem cell transplantation using a sensitive sequencing technology such as Haloplex.

4. To determine whether decitabine induces consistent methylation signatures using whole genome bisulfite sequencing.

5. To determine whether decitabine induces consistent expression signatures using RNA sequencing, and whether these correlate with methylation signatures.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. *TP53* mutant AML. The presence of a *TP53* mutation should be determined by Genoptix (or institutional preferred equivalent assay). Detection of a *TP53* mutation at the time of initial diagnosis is sufficient for enrollment at the time of relapsed/refractory disease. Detection of a *TP53* mutation in either the peripheral blood or bone marrow is adequate for enrollment. (Refer to Appendix B for definition of TP53 mutant AML.) Alternatively, patients who have not had *TP53* mutation analysis performed, but who have > 20% TP53 positive cells by immunohistochemistry detected on a bone marrow aspirate may also be enrolled,[29] provided that mutation analysis is requested at the time of enrollment.

2. Relapsed/refractory AML following 7+3 (or similar cytarabine containing induction chemotherapy for AML) disease detected by one of the following methods:
    - Bone marrow blasts > 5%, or
    - Hematologics flow cytometry assay (threshold > 0.5%) (alternative equivalent assay may be substituted), or
    - Persistent cytogenetic abnormality (e.g. del5, del17p, etc) by FISH or conventional karyotyping, or
    - Persistent *TP53* mutation (at least 5 variant reads with at least 50x coverage) determined by Genoptix (or institutional preferred equivalent assay).

Patients with > 10% blasts on a Day +14 bone marrow biopsy following 7+3 may either be enrolled or may be treated with a course of standard re-induction (e.g. 5+2 or similar) and then re-evaluated for response. Eligible patients will meet any of the above criteria on a subsequent biopsy.

3. Bone marrow and organ function as defined below:
   - Peripheral white blood cell count < 50,000/mcl (patients may receive hydroxyurea as necessary for cytoreduction),
   - Total bilirubin < 1.5 x upper limit of normal,
   - AST and ALT < 2.5 x upper limit of normal,
   - Serum creatinine < 2.0 x upper limit of normal, and,

4. At least 18 years of age.

5. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately

6. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable

7. Performance status ≤ 3

3.2 Exclusion Criteria

1. Prior treatment with either decitabine or azacitidine, or an investigational agent.

2. Acute promyelocytic leukemia with *PML-RARA* or t(15;17).

3. History of HIV, Hepatitis B, or Hepatitis C infection.

4. Concurrent illness including, but not limited to, ongoing uncontrolled infection**,** symptomatic NYHA class 3 or 4 congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

5. Radiation therapy within 14 days of enrollment.

6. Chemotherapy administration in the 7 days preceding enrollment with the exception of hydroxyurea, which can be continued until through Cycle 2. A washout period for oral tyrosine kinase inhibitors (e.g. Jakafi, etc) is not required, although tyrosine kinase inhibitors therapy must be discontinued prior to enrollment.

7. Malignancies (other than AML) requiring active therapy or diagnosed within the last year, with the exception of non-melanoma skin cancer which can be treated or in situ malignancies (such as cervical, breast, prostate, etc.).

8. Currently receiving any other investigational agents.

9. Known CNS leukemia or testicular involvement of leukemia.

10. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to decitabine or other agents used in the study.

11. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative urine pregnancy test within 7 days of study entry.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any treatment on protocol prior to registration through the Siteman Cancer Center. Pre-study assessments, such as blood testing, bone marrow biopsy or others as listed under baseline evaluation (Section 5.1.2) are allowed.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date

6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. The research coordinator or his/her delegate will confirm registration by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.0 INVESTIGATION PLAN

5.1 Summary

See Section 10 for synoptic table.

Patients will receive decitabine 20 mg/m^2/day as a 1-hour infusion on consecutive days 1-10 of each 28-day cycle. Decitabine dose will be calculated on baseline weight (obtained within a week of the start of cycle 1). Decitabine dose should be recalculated for weight changes above or below 10% from baseline weight

Patients with clinical evidence of progressive disease or relapse (see Section 12 for definitions) should undergo a bone marrow biopsy to evaluate for progression.

After 2 cycles, patients with progressive disease or relapse (a clear progression with at least >20% bone marrow blasts and an increase of at least 50% from prior biopsy) should be removed from protocol and proceed to salvage treatment according to center preference.

Transplant eligible patients with PR after 3 cycles, may be removed from protocol and proceed to salvage treatment or transplant according to center preference.

Transplant eligible patients with a suitable donor who achieve mLFS, CR, CRc, or CRi, may proceed to transplant after at 3 cycles (Section 5.5).

Transplant ineligible patients with CR, CRc or CRi, PR will continue on maintenance doses (see below and Section 6.3) until progression or death, whichever occur first.

Transplant ineligible patient with SD after cycle 4 may be removed from protocol and proceed to alternative treatment or continue on protocol according to treating physician's preference.

After Cycle 1, patients with blast counts < 5% may reduce decitabine dose from 20 mg/m^2/day x 10 days to 20 mg/m^2/day x 5 days.

For all other patients, after Cycle 2, decitabine administration dose will be decreased to 20 mg/m^2/day for 5 consecutive days (Days 1-5) every 28 days (unless otherwise specified) to limit myelosuppressive toxicity.

Peripheral blood sampling and bone marrow biopsies with aspirate will be performed pre-study, on Cycle 1 Day 10 ± 2, Cycle 1 Day 28 ± 4, on Cycle 2 Day 28 ± 4, on Cycle 3 Day 28 ± 4, and at progression or relapse. Patients will provide a skin biopsy sample pre-study; a buccal swab can be performed for patients who decline skin biopsy. A buccal swab will be collected on Cycle 2 Day 28 ± 4.

Following Cycle 3, bone marrow biopsies should be performed at the discretion of the treating physician to assess for response and for relapse or progression.

If at any bone marrow collection the aspirate is a "dry tap", two additional tubes of blood (10 mL each) will be collected and banked.

A. Pre-study Procedures

Pre-study procedures must take place no more than 28 days prior to the first dose of decitabine except where noted below.

- Bone marrow aspirate and biopsy. Standard bone marrow procurement procedures will be followed for collection of the tissue. Assessments performed on bone marrow will include correlative studies, morphologic assessment, flow cytometry, cytogenetics, and FISH.
- Bone marrow or peripheral blood for flow cytometry.
- Collection and banking of bone marrow aspirate and peripheral blood.
- Skin biopsy sample: Patients who decline to undergo a skin biopsy can provide a buccal swab as alternative. There is no required time frame for this sample; it may have been collected months or even years prior to the first dose of decitabine. If WBC at enrollment is > 30,000/µl, the skin biopsy should be collected at C1D28.

B. Baseline Evaluation

Baseline evaluations must take place no more than 7 days prior to the first dose of decitabine.

- Medical history
- Physical exam including height, and weight.
- CBC with differential and platelets
- Serum chemistries, including, albumin, creatinine, total bilirubin, AST, ALT, LDH
- Urine βHCG pregnancy test in women of childbearing age

C. Day 1 of Each Cycle

- Physical exam, including weight
- CBC with differential and platelets
- Serum chemistries, including albumin, creatinine, total bilirubin, AST, ALT, LDH

D. All Cycles Days 1-10

Decitabine administration, 20 mg/m^2/day will be given as a 1-hour continuous intravenous infusion. Decitabine dose will be calculated on baseline weight (obtained within a week of the start of Cycle 1). Decitabine dose only should be recalculated for weight changes at the beginning of each cycle that are above or below 10% from baseline weight.

Decitabine may be reduced to Days 1-5 after Cycle 2 or Days 1-3 after Cycle 4. See Section 6 for details.

E. Cycle 1 Day 10 ± 2

Bone marrow aspirate and biopsy. Standard bone marrow procurement procedures will be followed for collection of the tissue. Assessments performed on bone marrow will include correlative studies and morphologic assessment. Bone marrow aspirate and biopsies at this time point will only be performed in patients enrolled at Washington University.

F. Weekly

CBC with differential and platelets. After the first cycle, this may be changed to every other week at the discretion of the treating physician.

G. At the Discretion of the Treating Physician

Serum chemistries, such as bicarbonate, calcium, glucose, total protein, albumin, BUN, potassium, chloride, sodium, creatinine, total bilirubin, AST, ALT, alkaline phosphatase, LDH.

Transfusions should be performed at the discretion of the treating physician and are permitted at any time during the protocol.

H. Cycles 1, 2, and 3 Day 28 ± 4

- Bone marrow aspirate and biopsy. Standard bone marrow procurement procedures will be followed for collection of the tissue. Assessments performed on bone marrow will include: correlative studies, morphologic assessment, cytogenetics, and FISH.
- CBC with differential and platelets

I. End-of-Study Procedures

- Physical exam.
- CBC with differential and platelets.
- Serum chemistries albumin, creatinine, total bilirubin, AST, ALT, and LDH.
- Bone marrow aspirate and biopsy. Standard bone marrow procurement procedures will be followed for collection of the tissue. Assessments performed on bone marrow will include morphologic assessment, cytogenetics, and FISH.

J. Post-study Follow-up

Patients are to be followed according to standard patient care procedures for 30 days following the date of the last decitabine dose to monitor for toxicity, survival, and response. Thereafter, the investigator or designee will record information on subsequent therapy, disease progression, and/or death every 6 months for 2 years after last dose of study drug or until the patient is lost to follow-up or dies.

5.2 Premedication Administration

Patients may be premedicated with lorazepam, prochlorperazine, palonosetron, granisetron, or ondansetron at the treating physician's discretion before decitabine infusion.

5.3 Agent Administration

Cycle 1: All patients will receive decitabine 20 mg/m^2 IV infusion per day over one hour on Days 1-10 of a 28-day cycle.

Cycle 2: Patients with bone marrow blast counts < 5% may receive decitabine 20 mg/m^2 IV infusion per day over one hour on Days 1-5 of a 28-day cycle. All other patients will receive decitabine 20 mg/m^2 IV infusion per day over one hour on Days 1-10 of a 28-day cycle.

Cycle 3 and subsequent cycles: All patients will receive 20 mg/m^2 IV infusion per day over one hour on Days 1-5 of the 28-day cycle

Patients will continue on therapy until time of transplantation or progression as detailed in Sections 5.1 and 6.3. Delays in therapy are permitted due to infection and other complications.

5.4 Relapsed or Progressive Disease

Patients who relapse or who have progressive disease (PD) after 2 cycles of decitabine, may proceed to alternative salvage regimen or to stem cell transplant according to treating physician and to center preference. (Please refer to Section 12 for the definition of PD.)

5.5 Transplantation

Patients in mLFS, CR, CRc, or CRi who are considered fit for stem cell transplantation and who have an appropriate donor will undergo stem cell transplantation per treating physician recommendations. Haploidentical and allogenic transplantation may be utilized. Myeloablative and non-myeloablative protocols may be utilized per institutional protocols. Patients will be considered on study through day of transplant and will be followed for overall survival.

5.6 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum/urine pregnancy test within 7 days prior to the first dose of the study agent.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 6 months following the last dose of the study agent.

If a patient is suspected to be pregnant, the study agent should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 6 months after the last dose of the study agent, the investigator must be notified in order to facilitate outcome follow-up.

5.7 Concomitant Therapy and Supportive Care Guidelines

A. Chemotherapy

Patients may be receiving hydroxyurea at enrollment and may continue on hydroxyurea through Cycle 2 of decitabine. An indication for hydroxyurea following 2 cycles of decitabine is evidence that the patient is not responding and decitabine should be discontinued. Other than decitabine, patients cannot receive chemotherapy during this trial.

B. Growth Factors

Erythroid growth factors should not be routinely administered to patients during the study.

Thrombopoietin receptor agonists should not be routinely administered to patients during the study.

Filgrastim (G-CSF) or sargramostim (GM-CSF) may be administered to patients with septic shock or febrile neutropenia at the discretion of the treating physician.

C. Transfusions

RBC transfusions and platelet transfusions will be administered at the discretion of the treating physician.

D. Prophylactic Antimicrobial Agents

Antimicrobial agents will be administered at the discretion of the treating physician. Common antimicrobial prophylaxis includes acyclovir, ciprofloxacin, and fluconazole. Alternative antibacterial and antifungal agents (e.g. voriconazole or posaconazole) may be used at the discretion of the treating physician.

Administration of live or attenuated vaccination is not permitted.

E. Radiotherapy

Patients cannot receive radiotherapy within 14 days prior to study enrollment or while on study.

F. Plasmapheresis or other anti-cancer therapy

The use of plasmapheresis, other anti-cancer therapies, or other investigational agents is not permitted.

5.8 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue until the start of conditioning therapy for transplant or, in transplant ineligible patients, treatment may continue indefinitely or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.9 Duration of Follow-up

Patients will be followed with regular office visits for at least 2 years since enrollment or until death, whichever occurs first.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

A criterion for discontinuation of the study is a delay of > 12 weeks between any two cycles. Dose delays and modifications are allowed as specified below.

6.1 Delay for Cytopenia or Infection

As cytopenias are a defining feature of AML, their presence alone does not warrant dose modifications or delays. Patients will receive two cycles of therapy without adjustment for any cytopenia. Following Cycle 2, dose delays for cytopenias will be made at the discretion of the investigator in patients who have had significant infection complications.

In patients with febrile neutropenia (temperature ≥ 38.5° with ANC < 1,000/μl) or systemic infections, treatment will be held at discretion of treating physician.

In patients who experience significant infection complications during Cycle 1, Cycle 2 may be reintroduced with a 50% dose reduction (10 mg/m^2/day for 10 consecutive days), or at full dose at the discretion of the investigator.

6.2 Delay for Organ Dysfunction

If renal dysfunction (creatinine ≥ 3 X IULN) or hepatic dysfunction (bilirubin ≥ 2.5 mg/dl or ALT/AST ≥ 3 X IULN) occurs, therapy may not resume until the abnormalities have resolved to below the limits stated above. If renal or hepatic dysfunction occurs during a treatment course, the next dose of decitabine should be held, and serum chemistries should be checked twice per week. Decitabine can be resumed at full dose when creatinine, bilirubin, ALT and AST are below the limits listed above.

For grade 3-4 non-hematologic toxicities related to decitabine, decitabine treatment should be delayed until recovery to baseline or to grade ≤ 1. Decitabine may be reintroduced with a 50% dose reduction (10 mg/m^2/day), or at full dose at the discretion of the investigator.

6.3 Modification in Dose or Schedule

To limit myelosuppressive toxicity, Cycles 3 and beyond will consist of 20 mg/m^2/day for 5 consecutive days (Days 1-5).

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below.

Please refer to Appendix A for definitions and Appendix C for a grid of reporting timelines.
Adverse events will be tracked from the time of consent until 30 days after the last dose of chemotherapy. Adverse events will be tracked from the time of consent until 30 days after the last

dose of chemotherapy. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of baseline adverse events, which shall be recorded on the medical history CRF.

Refer to the data submission schedule in Section 11 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 1.1. Reporting requirements for secondary site study teams participating in Washington University-coordinated research may be found in Section 1.2.

The safety and side effects of decitabine have been well characterized in numerous clinical trials involving patients with AML and MDS. In specific, cytopenias are commonplace in patients with AML and in patients treated with decitabine. These frequently result in infection complications, bleeding complications, and transfusion requirements.

Janssen requires that all events be reported as outlined in Section 7.5.

7.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Washington University Sponsor-Investigator (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent in with the form.

For events that occur at secondary sites, the Washington University Sponsor Investigator (or designee) is required to notify the QASMC within 10 days of Washington University notification via email to qasmc@wustl.edu. Submission to QASMC must include either the myIRB form and supporting documentation or (if not submitted to myIRB) the date of occurrence, description of the event, whether the event is described in the currently IRB approved materials, the event outcome, determination of relatedness, whether currently enrolled participants will be notified, and whether the informed consent document and/or any study procedures will be modified as a result of this event.

7.3 Secondary Sites Reporting Requirements

The research team at each secondary site is required to promptly notify the Washington University Sponsor-Investigator and designee of all serious adverse events (refer to Appendix A, Section D) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report using an FDA Form 3500a (MedWatch form) and Washington University's Cover Sheet (Appendix C). A formal written report must be sent to the Washington University Sponsor-Investigator and designee within **4 calendar days (for fatal or life threatening suspected adverse reactions) or 11 calendar days (for serious unexpected, suspected adverse reaction)** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA, and Janssen.

7.4 Reporting to Secondary Sites

The Washington University Sponsor-Investigator (or designee) will notify the research team at each secondary site of all unanticipated problems involving risks to participants or others that have occurred at other sites within 10 working days of the occurrence of the event or notification of the Sponsor-Investigator (or designee) of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable. Refer to Section 16.0 (Multicenter Management) for more information.

7.5 Reporting to Janssen

A. Overview

As the sponsor of the Study, the principal investigator shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The principal investigator will provide safety information to Janssen Scientific Affairs, LLC on adverse events, special situations including pregnancies and product quality complaints as defined within this section.

B. Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events, special situations including pregnancies and product quality complaints will be reported as described in this Exhibit from the time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last documented use of a product under study within the study. All subsequent AEs and SAEs will be collected after this period if the Principal Investigator considers the AE/SAE to be causally-related to the use of the study drug.

For the purposes of this study, the J&J medicinal product is DACOGEN™ (decitabine).

C. Hospitalization

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

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

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

D. Maintenance of Safety Information and Procedure for Reporting

All safety data should be maintained in a clinical database in a retrievable format. The principal investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs, LLC request.

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

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

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

F. SAEs, Adverse Events of Special Interest and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

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

The principal investigator will transmit all SAEs, Adverse Events of Special Interest, and special situations following exposure to a J&J product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with Section 7.5.L Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

In the event the study is blinded, the principal investigator will submit an unblinded SAE or pregnancy exposure report to Janssen Scientific Affairs, LLC.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the principal investigator, **within 24 hours becoming aware**, to Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs, LLC Serious Adverse Event Report

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

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

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the J&J Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method in Section 7.5.L **within 24 hours of such report or correspondence being sent to applicable health authorities**.

Special Reporting Situations

Safety events of interest for a J&J medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

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

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event**.

G. Non-Serious AEs

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

H. Pregnancy

Initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC by the principal investigator **within 24 hours of becoming aware of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the J&J medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a J&J medicinal product will be reported by the principal investigator within 24 hours of their knowledge of the event using the Serious Adverse Event Form. Depending on local legislation, this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

I. PQC Reporting

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

All initial PQCs involving a J&J medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the principal investigator **within 24 hours after being made aware of the event.** The J&J contact will provide additional information/form to be completed.

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

J. Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-J&J Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-J&J medicinal product under study, the principal investigator should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

K. Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a J&J medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected J&J medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- Gender
- age at AE
- onset
- reporter ID
- adverse event detail (AE verbatim in English)
- onset date
- relatedness
- causality
- action taken
- outcome, (if available)
- J&J protocol ID

L. Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred) to IIS-BIO-VIRO-GCO@its.jnj.com
- For business continuity purposes, if SECURE Email is non-functional: to 1-866-451-0371

- Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC.

7.6 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University principal investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix A for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix A) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix A) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
    - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
    - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman

Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

7.7 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in include:

- planned hospitalizations
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 PHARMACEUTICAL INFORMATION

8.1 Study Drug Preparation

OSHA Guidelines for handling cytotoxic drugs outlined in the American Journal of Hospital Pharmacy must be followed.

Decitabine (5-aza-2'-deoxycytidine) is supplied as a lyophilized powder for injection, 50 mg in 20-ml vials. When reconstituted with 10 ml of sterile water for injection, each ml will contain 5 mg of decitabine and 6.8 mg of KH_2PO_4. The reconstituted solution should be diluted to 0.1-1.0 mg/mL with pre-chilled 0.9% sodium chloride intravenous infusion, which has been cooled to 2-8^{o}C. Reconstitution of the powder results in a rapidly decomposing solution. Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2—8 degrees C) infusion fluids and stored at 2—8 degrees C (36—46 degrees F) for a maximum of 7 hours.

Decitabine will be administered per dosing schedule every 28 ± 4 days.

The site according to institutional drug disposal procedures should discard any partially used vials.

Decitabine may be administered either as an inpatient or as an outpatient.

Recommended safety measures for handling and preparation includes masks, protective clothing, gloves (double glove with nitrile gloves) and vertical laminar airflow safety

cabinets.

A. Supplier

Decitabine is available commercially.

9.0 CORRELATIVE STUDIES

9.1 Correlative Studies Background

A. Methylation Changes

Decitabine causes hypomethylation of DNA by inhibiting DNA methyltransferase (Section 1.3). DNA methylation is an important epigenetic event in modulating development, cellular differentiation, and proliferation[30-32]. DNA methylation, primarily occurring at C5 of the cytosine ring within cytosine–guanine (CpG) dinucleotides, is frequently found clustered at gene regulatory sites such as promoter regions and results in transcriptional silencing of the affiliated gene. Depending on the promoter regions affected, DNA hypermethylation could lead to tumor suppressor gene silencing and ultimately tumorigenesis.

B. Genome-wide decitabine induced DNA methylation signatures

To determine whether decitabine treatment results in hypomethylation at consistent CpGs in AML blasts, we will perform whole genome bisulfite sequencing and assess for DNA methylation patterns in pre-treatment (Day 0), at Day 10 (C1D10), at Day 28 (C1D28), and in samples collected at relapse.

C. Decitabine induced gene expression signatures

To determine if changes in methylation induced by decitabine treatment correlate with gene expression changes, we will perform RNA sequencing on RNA extracted from bone marrow cells pre treatment (Day 0), on Day 10 (C1D10), and on Day 28 (C1D28) post decitabine.

D. DNA Changes

Conventional chemotherapies in AML cause early termination of DNA synthesis (cytarabine) or topoisomerase inhibition (daunorubicin) that ultimately converge onto TP53 that, together with CDKN2A sense irreparable DNA damage and ultimately trigger cell cycle arrest and cell death[33]. Therefore, it is not surprising that AML with defective TP53 are resistant to conventional chemotherapeutic agents. The effectiveness of decitabine that we observed in the cohort of patient with *TP53* mutation suggests that decitabine acts through a different, TP53 independent, mechanism. Interestingly, *Tp53* null mice develop normally[34], thus

suggesting that cell cycle exit via differentiation is intact in these mice. As mentioned in Section 1, treatment with decitabine does not lead to clone eradication. Morphologic blast clearance precedes mutation clearance, with the malignant clone often remaining detectable at low levels over time (Figure 4).

This is consistent with a model in which the proliferating cells of the malignant clone enter terminal differentiation after exposure to the drug, with the remaining quiescent stem cells carrying the mutation remaining dormant and eventually contributing to relapse when challenged to cycle.

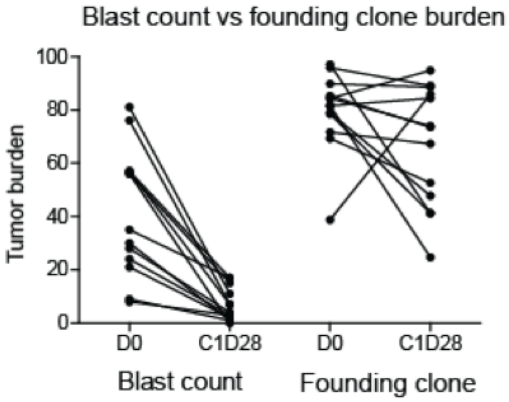


Figure 4: Kinetics of blast clearance versus clonal burden: bone marrow blast reduction detected by morphology at C1D28 does not correlate with founding clone reduction at the same time-point.

Furthermore, difference in DNA methylation may not result in changes in gene expression[34]. For example, AMLs with mutations in *DNMT3A* that result in significant hypomethylation in specific DNA regions, do not display differences in whole transcriptome compared to AML bearing wild type *DNMT3A*[36]. This could be partially explained by the fact that DNA modifications (i.e. methylation status of gene promoters) are not the only determinant of gene transcription. Histones modifications, such as histones methylation, can alter chromatin structure through changes in the chemical moieties on the nucleosome surface and subsequently affect recruitment of the transcription factor machinery to specific DNA regions, silencing or activating gene transcription independently from promoter methylation.

E. Decitabine induced myeloid differentiation

To determine whether decitabine induces multilineage differentiation, or myeloid biased differentiation, we will identify cases where discordant morphologic blast clearance occurs without mutation clearance (Figure 4). We will flow sort differentiated peripheral blood monocytes, neutrophils, T cells, B cells, and NK cells and evaluate each population for the presence of AML-associated mutations. We compare results of samples sorted from Day 0, C1D28, C2D28, and C3D28, as appropriate.

F. Correlation of the rate and depth of mutation clearance with survival

We will assess tumor burden by allele frequency of patient-specific mutations in bone marrow or peripheral blood samples collected pre study, C1D28, C2D28 and C3D28 as well as at regular intervals after transplant. The velocity and depth of tumor response will be correlated to:

- Achievement of clinical CR,
- Time to best response,
- Mutational status,
- Time to disease progression

9.2 Correlative studies sample

Samples should be identified with the patient UPN, the source (e.g. BM: bone marrow, PB: peripheral blood, S: skin; U: buccal), the cycle (e.g. D0: day 0; C1D10: cycle 1 day 10; C1D28; cycle 1 day 28, etc), the month/day/year of collection. Individual tubes or vials may be labeled with a specimen number. Specimen records should be included with each collection.

Peripheral blood and bone marrow samples collected by collaborating institutions should be frozen as viable cells at 5-10^6 cells per ml. For convenience, samples can be stored locally in liquid nitrogen and may be shipped in batches to Washington University for further processing, at the address below:

Washington University
Division of Oncology
SWT621
4940 Parkview Place
St. Louis, MO 63110

Samples to be collected:
Bone Marrow

- Baseline
- C1D10 (± 2)**
- C1D28 (± 4)
- C2D28 (± 4)***
- C3D28 (± 4)
- Progression or relapse

After the necessary samples are obtained for optimal medical care of the patient (if applicable), additional aspiration will be performed to obtain a sample for research purposes. The anticoagulated specimen (10 mL) will be placed in sterile EDTA vacutainer tubes, and then the cellular elements of the collected marrow will be separated and

cryopreserved. If at any bone marrow collection the aspirate is a "dry tap", two additional tubes of blood (10 mL each) will be collected and banked.

** Bone marrow aspirate and biopsies will only be performed in patients enrolled at Washington University.
*** At the discretion of the treating physician

Peripheral Blood

- Baseline
- C1D10 (± 2)
- C1D28 (± 4)
- C2D28 (± 4)
- C3D28 (± 4)
- Progression or relapse

Peripheral blood will be obtained by venipuncture or cannulation of an indwelling venous access device. Ten mL will be placed in sterile EDTA anticoagulated vacutainer tubes which will be processed to cryopreserved cells w/RBC Lyse (up to 15 aliquots at $1x10^7$ cells/aliquot).

Skin Biopsy

- If WBC at time of enrollment is < 30,000/µl, skin biopsy should be collected during enrollment bone marrow biopsy.
- If WBC at time of enrollment is >30,000/µl, skin biopsy should be collected at the time of C1D28 bone marrow biopsy or thereafter.

A single 6 mm punch biopsy of normal skin will be performed using standard techniques and local anesthesia. The skin samples will be placed in a sterile specimen cup and snap frozen following collection.

Buccal Swab

- Baseline (if skin biopsy is declined)
- C2D28 (±4)
- Buccal cells should be spun down and snap frozen as a single pellet at the time of collection.

10.0 STUDY CALENDAR

	Screening	B/l	C1D 1	C1D10	C1D28	C2D1	C2 D28	C3D1	C3 D28	All cycles thereafter		Time of progression	F/U
										D1	D28		
Informed consent	X												
Medical history	X		X			X		X		X			
Physical exam, ht, wt	X	X[4]	X			X		X		X		X	
CBC + diff	X	X[4]	X ---------- X[9]			X[9]	X	X[9]	X	X[9]		X	
Serum chemistry[5]	X	X[4]	X			X		X		X		X	
Pregnancy test[1]	X	X[4]											
HIV, hepatitis tests	X[16]												
BM bx + aspirate[17]				X[13]	X[14]		X[10,14]		X[11,14]		X[12]	X	
Flow cytometry[2]													
PB for research				X[13]	X[14]		X[14]		X[15]			X	
Skin biopsy													
Buccal swab							X						
Decitabine			X ---- X[6]			X[6]		X[7]		X[7]			
AE assessment													
Progression/survival													X[15]

1. Women of childbearing potential only
2. On bone marrow or peripheral blood
3. For BMBX, no more than 28 days prior to the 1st dose of decitabine. For the skin biopsy, if WBC at enrollment is > 30,000/µl, the skin biopsy should be collected during C1D28, or thereafter.
4. No more than 7 days prior to the 1st dose of decitabine
5. Including albumin, creatinine, total bilirubin, AST, ALT, LDH
6. Days 1-10
7. May be reduced to Days 1-5 for Cycles 3 and 4
8. Buccal swab may be performed at baseline in patients who decline skin biopsy
9. Drawn weekly during Cycle 1; may be reduced to Days 1 and 15 of each cycle after Cycle 1
10. Patients who relapse or who have progressive disease (PD) after 2 cycles of decitabine may proceed to alternative salvage regimen or to stem cell transplant per treating physician and center preference.
11. Transplant eligible patients who achieve CR, CRc, CRi, or mLFS after 3 cycles with a suitable donor will proceed to conditioning regimen and transplant; transplant eligible patients who are in PR after 3 cycles will be removed from protocol and proceed to salvage treatment according to center preference; transplant ineligible patients with all responses (CR, CRc or CRi, PR, SD) will continue on maintenance doses until progression or death
12. At the discretion of the treating physician
13. +/- 2 days, only patients enrolled at Washington University
14. Typically 28 +/- 4 days. At the discretion of the treating physician this biopsy may be delayed until the next cycle is initiated. The biopsy at the end of cycle 2 will be collected at the discretion of the treating physician.
15. For 2 years
16. Prior negative screening at any time is sufficient. If no prior screening is available, the patient should be tested during screening.
17. If at any bone marrow collection the aspirate is a “dry tap”, two additional tubes of blood (10 mL each) will be collected and banked.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	**Submission Schedule**
Original Consent Form	Prior to registration
Patient Registration Form Medical and Surgical History Form Treatment History Form On Study Form Correlative Skin Biopsy Form	Prior to starting treatment
Decitabine Form	End of each cycle
CBC Form	Baseline Day 1 Day 10 Day 28 Time of progression
Correlative Bone Marrow Form Correlative Blood Form	Baseline C1D10 End of Cycle 1 End of Cycle 2 End of Cycle 3 Time of progression or relapse
Correlative Buccal Swab Form	Baseline End of Cycle 2
Disease Assessment Form	Baseline End of Cycle 1 End of Cycle 2 End of Cycle 3 Time of progression
Off Treatment Form	Due at the completion of the EOT visit, at the time of death, and/or at the time that the patient is lost to follow-up
Follow Up Form	30 days post date of last decitabine dose. Every 6 months for 2 years after the last dose of study drug.
Hospitalization Form	Time of hospitalization
Death Form	Time of death
Record of Adverse Events	At the time of any AE

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

11.1 Adverse Event Collection in the Case Report Form

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

12.0 MEASUREMENT OF EFFECT

12.1 Response assessment

Bone marrow biopsy will be obtained on Cycle 1 Day 28 ± 4, Cycle 2 Day 28 ± 4, and Cycle 3 Day 28 ± 4. The cycle 2 Day 28 collection may be performed at the discretion of the treating physcian.

All patients will be assessed for response according to the 2017 ELN AML Recommendations[37]:

Complete remission (CR) – Defined as bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count ≥1.0 x 10^9/L (1,000/μL); platelet count ≥100 x 10^9/L (100,000/μL).

Complete remission with incomplete hematologic recovery (CRi): All CR criteria except for residual neutropenia - <1.0 x 10^9/L (1,000/μL) or thrombocytopenia -<100 x 10^9/L (100,000/μL)

Cytogenetic complete remission (CRc) – Defined as morphologic complete remission plus a reversion to a normal karyotype. For this study, reversion of a normal karyotype is defined as no clonal abnormalities detected in a minimum of 20 mitotic cells.

Morphologic leukemia free state (mLFS): Defined as 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 remission (PR) – Defined as all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%.

Stable Disease (SD) – Defined as not meeting the definitions of CR, CRi, PR, PD, or recurrence/morphologic relapse.

Progressive disease (PD) – Defined as a clear increase in bone marrow blast count, typically a greater than 50% increase compared with baseline, or new extramedullary disease. Patients with a > 50% increase in peripheral blast count with an increase of the total peripheral white blood cell count to > 10,000/μl should undergo evaluation by bone marrow biopsy to access for progressive disease. Patients enrolled with a bone marrow blast count < 20% will have > 20% blasts and a > 50% increase compared with baseline.

Recurrence/morphologic relapse **-** Defined as relapse following complete remission is defined as reappearance of blasts in the blood or the finding of ≥ 5% blasts in the bone marrow, not attributable to any other cause. New dysplastic changes is considered relapse. If there are no blasts in the peripheral blood and 5-20% blasts in the bone marrow, bone marrow biopsy should be repeated in > 1 week to confirm relapse.

A. Duration of Response and Stable Disease, Treatment Failure, Overall Survival and Event-free Survival

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented

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

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

Treatment failure is defined as death or failure to achieve a complete or partial remission following 4 cycles of therapy.

Overall survival is defined as the date of first dose of study drug to the date of death from any cause. Patients still alive at the time of the final analysis will be right-censored.

Event-free survival is defined as the interval from the date of first dose of study drug to date of treatment failure, recurrence, death due to any cause, or loss to follow up.

B. Duration of Remission and Relapse-free Survival for Patients Having Complete Remission

Duration of complete remission is defined as the interval from the date that complete remission is documented to the date of recurrence, death due to any cause, or loss to follow-up.

Relapse-free survival is defined only for those patients achieving a CR or CRi. It is defined as the interval from the date of first documentation of a leukemia-free state to the date of recurrence, death due to any cause, or loss to follow up.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Board (DSMB) will be specifically convened for this trial to review toxicity data. . A DSMB will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. DSMB members must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital. Like investigators, DSMB members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

Until such a time as the first secondary site enrolls its first patient, a semi-annual DSM report to be prepared by the study team will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after study activation at Washington University (if at least one patient has been enrolled) or one year after study activation (if no patients have been enrolled at the six-month mark).

The DSM report for the DSMB will be prepared by the study team with assistance from the statistician, will be reviewed by the DSMB, and will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC). The DSMB must meet at least every six months beginning six months after study activation at Washington University or beginning six months after enrollment of the first patient at a secondary site, no more than one month prior to the due date of the DSM report to QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date and accrual by site
- Objectives of protocol with supporting data and list the number of participants who have met each objective

- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMC responsibilities are described in the DSMC charter.

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 7.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

14.0 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:
- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation

- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

15.0 STATISTICAL CONSIDERATIONS

15.1 Study design and Sample size

This will be an open-label single-arm phase II trial. The primary endpoint of this study is the 1-year overall survival (OS) which will be compared to historical data. *TP53* mutations occur in 10-15% of patients with AML, and tend to occur in older adults[3-6]. Our power analysis suggests that we need at least 60 total patients enrolled. We anticipate that 500-700 total AML patients will need to be available at enrolling institutions in order to reach the patient goal of 60. Time to complete accrual will be 24 months.

15.2 Analysis Populations

Intent-to-Treat - Defined as all patients who receive at least one dose of decitabine.

Efficacy-Evaluable - Defined as all patients who receive at least one cycle of treatment.

Safety - Defined as all patients with at least one dose of decitabine.

15.3 Multicenter studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough patients to warrant an analysis by center

15.4 Statistical Analysis

A. Descriptive Analyses

Patient Disposition: The number of patients discontinued, the reasons for discontinuation, and the number of cycles administered will be summarized.

Demographics and Baseline Characteristics: Descriptive summary statistics will be provided for demographic and important baseline characteristics. For continuous variables, the number of patients, mean, standard deviation, median, minimum and maximum will be provided. For categorical variables, the number and percent of patients in each demographic/characteristic category will be summarized.

B. Primary Endpoint Analysis

The primary end-point of this phase II study is the 1-year survival in primary relapsed/refractory AML patients treated with decitabine.
Overall survival (OS) is defined as the time from enrollment to death due to any cause. For a patient who is not known to be alive at the end of study follow up, observation of OS is censored on the date the patient was last known to be alive (i.e. date of last contact).

C. Overall survival analysis

Kaplan-Meier curves depicting OS in the study population compared to historical control will be generated. Additionally, the median OS and the probability of OS from 1 month to the end of the follow-up period will be reported at pre-specified intervals. The associated 2-sided 90% CIs will be calculated using the complementary log-log transformation method (Collett 1994).

D. Interim Analysis

The estimated duration of the study is approximately 3 years from enrollment of the first patient to the final analysis. An interim analysis for OS will be performed at 1.5-year (where approximately one-fourth of patients will have at least 1-year follow-up if assuming uniform accrual) and the conditional power will be calculated for futility analysis based on the accumulated data. Conditional power is defined as the projected power to reject the null hypothesis (that treatment of *TP53*-mutated AML patients with relapsed/refractory disease is associated with 1-year survival of 25%) at the end of the study given the data accrued up to the interim analysis. Therefore, a small value of conditional power indicates a highly likely, if not inevitable, conclusion of negative finding given the current data. If conditional power of 0.3 or less is obtained at the interim analysis, an early termination due to futility will be recommended.

E. Secondary Clinical Endpoints Analyses

The principal measurement of toxicity will be a measure of the total number hospitalized days during the first 60 days of therapy.

CRc rate will be analyzed based on the ITT population. The remission rate and its 2-sided 90% confidence interval (CI) will be summarized.

Event-free survival: EFS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided using the ITT analysis set. The median EFS and its 2-sided 90% CI using the complementary log-log transformation method (Collett 1994) will be calculated.

Leukemia-free survival: LFS will be analyzed using Kaplan-Meier methodology

and Kaplan-Meier plots will be provided using the ITT analysis set. The median LFS and its 2-sided 90% CI using the complementary log-log transformation method (Collett 1994) will be calculated.

Time to leukemia relapse: TTCR will be summarized using descriptive statistics.

The time to stem cell transplant, the proportion of patients who are able to undergo transplantation, and the average number of hospital days during cycles 1 and 2, will also be documented. The association between response and clinical characteristics (morphologically evident disease -i.e., >5% blasts by cytomorphology- versus molecularly detected disease at the time of enrollment -i.e., disease detected with flow cytometry, cytogenetic, or mutational analysis with ≤ 5% blasts by cytomorphology-, *de novo AML versus* secondary AML *versus* treatment-related AML, presence *versus* absence of cytogenetic abnormalities in addition to *TP53* mutations, etc.) will be described using contingency tables and compared by Chi-square test or Fisher's exact test as appropriate. The association between survival (OS, EFS, LFS) and clinical characteristics will be described using Kaplan-Meier methods and compared by log-rank test.

F. Secondary *Molecular* Endpoints Analyses

Rate of patient specific mutation clearance after 28, and 56 days of therapy will be determined using an Illumina based platform. We will compare the rate of mutation clearance between the patients who achieve a CR/CRi after 4 cycles and those who do not. We anticipate that we will identify between 6 and 25 exonic SNVs per case (the range obtained with >200 AML samples sequenced to date with whole genome or exome sequencing), and that the expected 95% confidence interval of the mean variant allele frequency will be ±2.56% and ±1.25%, respectively, if we assume an anticipated standard deviation of 3.2% within the same clone. The change of tumor burden over time and its association with clinical response will be assessed using 2-way ANOVA for repeated measurement data, followed by the ad-hoc multiple comparisons for between-group differences (e.g., responders vs. non-responders) at given time points as well as the between-time differences within each group. The resultant critical P values will also be corrected using permutation analysis for multiple testing.

The percent decrease in bone marrow methylcytosine will be calculated on day 10±1. We will compare this reduction with previously published data and between the patients who achieve CR/CRi and those who do not. The correlation of peak plasma levels of decitabine with response will be assessed using 2-sample t-test or Mann-Whitney non-parametric rank-sum test as appropriate. The change of total bone marrow DNA methylcytosine from baseline and its association with both steady-state plasma drug levels and response will be assessed using 2-way ANOVA for repeated measurement data, followed by the ad-hoc multiple comparisons for between-group differences (e.g., responders vs. non-responders) and between-time

differences. Similar analyses will be performed for the correlation of expression profiles and SNP analysis with pharmacokinetic data.

The proportion of patients who achieve mutation clearance to <0.1%, after 3 cycles of decitabine, will be calculated and its 2-sided 90% confidence interval (CI) will also be provided. Using a sensitive sequencing technology such as Haloplex, the sensitivity of PB or BM for detecting residual mutation burden, as well as the *TP53* clonal burden reduction after consolidation with stem cell transplantation will be summarized using contingency tables.

G. Statistical Power Justification

Primary endpoint. The primary endpoint of this study is the 1-year overall survival (OS) which will be compared to historical data (1-year OS=25%). Assuming survival times following an exponential distribution and an additional 1-year follow-up period after the accrual period, a total of 60 patients will be enrolled and this allows us 85% power at 1-sided alpha=0.05 to detect 15% difference (40% vs. 25%) in 1-year OS.

Secondary endpoints. A power analysis was performed using two-sample t-test for between-group difference and paired t-test for the change over time. For tumor clearance, this will provide > 99% power to detect a 10% difference in the means at two separate time points for clones with 6 or more variants, and > 98% power to detect a 15% difference if there are 3 or more variants per clone with $\alpha = 0.05$ (power will decrease to 91% and 82%, respectively, in cases where the standard deviation is 4.7%, the maximum we have observed thus far). For pharmacologic correlations, we anticipate 85% power to determine a 25 ng/ml difference between the average Cmax of 45 evaluable responders and 55 evaluable non-responders with an anticipated average Cmax of 70 ng/ml and a standard deviation of 40 ng/ml within the entire cohort, and with $\alpha = 0.05$. We believe a less significant difference would not be sufficient to warrant application in clinical decision making (i.e. whether to continue therapy for more than 1 cycle). We anticipate 99% power to determine a difference of 20% in the reduction of bone marrow methylcytosine between 45 evaluable responders and 55 evaluable non-responders with an expected standard deviation of 15% and $\alpha = 0.05$. The difference in methylcytosine reduction previously observed was 30% between patients achieving CR/PR and those with only hematologic improvement.

16.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

17.0 REFERENCES

1. Dohner, H., Weisdorf, D.J. & Bloomfield, C.D. Acute Myeloid Leukemia. N Engl J Med 373, 1136-1152 (2015).
2. Cancer Genome Atlas Research, N. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med 368, 2059-2074 (2013).
3. Dohner, H., et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 115, 453-474 (2010).
4. Breems, D.A. & Lowenberg, B. Acute myeloid leukemia with monosomal karyotype at the far end of the unfavorable prognostic spectrum. Haematologica 96, 491-493 (2011).
5. Papaemmanuil, E., et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. N Engl J Med 374, 2209-2221 (2016).
6. Patel, J.P., et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med 366, 1079-1089 (2012).
7. Rucker, F.G., et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood 119, 2114-2121 (2012).
8. Welch, John S., et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. New England Journal of Medicine 375.21 (2016): 2023-2036.
9. Hou, H.A., et al. TP53 mutations in de novo acute myeloid leukemia patients: longitudinal follow-ups show the mutation is stable during disease evolution. Blood Cancer J 5, e331 (2015).
10. Christman, J.K. 5-Azacytidine and 5-aza-2'-deoxycytidine as inhibitors of DNA methylation: mechanistic studies and their implications for cancer therapy. Oncogene 21, 5483-5495 (2002).
11. Lubbert, M. DNA methylation inhibitors in the treatment of leukemias, myelodysplastic syndromes and hemoglobinopathies: clinical results and possible mechanisms of action. Curr Top Microbiol Immunol 249, 135-164 (2000).
12. Issa, J.P., Baylin, S.B. & Herman, J.G. DNA methylation changes in hematologic malignancies: biologic and clinical implications. Leukemia 11 Suppl 1, S7-11 (1997).
13. Link, P.A., Baer, M.R., James, S.R., Jones, D.A. & Karpf, A.R. p53-inducible ribonucleotide reductase (p53R2/RRM2B) is a DNA hypomethylation-independent decitabine gene target that correlates with clinical response in myelodysplastic syndrome/acute myelogenous leukemia. Cancer Res 68, 9358-9366 (2008).
14. Kantarjian, H., et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer 106, 1794-1803 (2006).
15. Jabbour, E., Issa, J.P., Garcia-Manero, G. & Kantarjian, H. Evolution of decitabine development: accomplishments, ongoing investigations, and future strategies. Cancer 112, 2341-2351 (2008).
16. Kantarjian, H., et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood 109, 52-57 (2007).
17. Chabot, G.G., Bouchard, J. & Momparler, R.L. Kinetics of deamination of 5-aza-2'-deoxycytidine and cytosine arabinoside by human liver cytidine deaminase and its inhibition by 3-deazauridine, thymidine or uracil arabinoside. Biochem Pharmacol 32, 1327-1328 (1983).

18. Rivard, G.E., et al. Phase I study on 5-aza-2'-deoxycytidine in children with acute leukemia. Leuk Res 5, 453-462 (1981).
19. Lin, K.T., Momparler, R.L. & Rivard, G.E. Sample preparation for the determination of 5-aza-2'-deoxycytidine in plasma by high-performance liquid chromatography. J Chromatogr 345, 162-167 (1985).
20. Momparler, R.L., Rivard, G.E. & Gyger, M. Clinical trial on 5-aza-2'-deoxycytidine in patients with acute leukemia. Pharmacol Ther 30, 277-286 (1985).
21. Momparler, R.L., et al. Pilot phase I-II study on 5-aza-2'-deoxycytidine (Decitabine) in patients with metastatic lung cancer. Anticancer Drugs 8, 358-368 (1997).
22. Aparicio, A., et al. Phase I trial of continuous infusion 5-aza-2'-deoxycytidine. Cancer Chemother Pharmacol 51, 231-239 (2003).
23. Bryan, J., Kantarjian, H., Garcia-Manero, G. & Jabbour, E. Pharmacokinetic evaluation of decitabine for the treatment of leukemia. Expert Opin Drug Metab Toxicol 7, 661-672 (2011).
24. Blum, W., et al. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. Proc Natl Acad Sci U S A 107, 7473-7478 (2010).
25. Saunthararajah, Y. Key clinical observations after 5-azacytidine and decitabine treatment of myelodysplastic syndromes suggest practical solutions for better outcomes. Hematology Am Soc Hematol Educ Program 2013, 511-521 (2013).
26. Mrozek, K. Cytogenetic, molecular genetic, and clinical characteristics of acute myeloid leukemia with a complex karyotype. Semin Oncol 35, 365-377 (2008).
27. Kadia, T.M., et al. TP53 mutations in newly diagnosed acute myeloid leukemia: Clinicomolecular characteristics, response to therapy, and outcomes. Cancer (2016).
28. Middeke, J.M., et al. Outcome of high-risk acute myeloid leukemia after allogeneic hematopoietic cell transplantation: negative impact of abnl(17p) and -5/5q. Blood 120, 2521-2528 (2012).
29. Fernandez-Pol S, Ma L, Ohgami RS, Arber DA. Immunohistochemistry for p53 is a useful tool to identify cases of acute myeloid leukemia with myelodysplasia-related changes that are TP53 mutated, have complex karyotype, and have poor prognosis. Mod Pathol. 2017;30:382-92.
30. Robertson, K.D. & Wolffe, A.P. DNA methylation in health and disease. Nat Rev Genet 1, 11-19 (2000).
31. Li, E. Chromatin modification and epigenetic reprogramming in mammalian development. Nat Rev Genet 3, 662-673 (2002).
32. Jones, P.A. & Baylin, S.B. The fundamental role of epigenetic events in cancer. Nat Rev Genet 3, 415-428 (2002).
33. Saunthararajah, Y., et al. p53-Independent, normal stem cell sparing epigenetic differentiation therapy for myeloid and other malignancies. Semin Oncol 39, 97-108 (2012).
34. Jacks, T., et al. Tumor spectrum analysis in p53-mutant mice. Curr Biol 4, 1-7 (1994).
35. Tuma, R.S. Epigenetic therapies move into new territory, but how exactly do they work? J Natl Cancer Inst 101, 1300-1301 (2009).
36. Ley, T.J., et al. DNMT3A mutations in acute myeloid leukemia. N Engl J Med 363, 2424-2433 (2010).
37. Döhner, Hartmut, et al. "Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel." Blood (2016): blood-2016.

APPENDIX A: Definitions for Adverse Event Reporting

Definition: An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:

http://www.hhs.gov/ohrp/policy/advevntguid.html

All serious adverse events (SAE) that occur within 30 days of the last dose of therapy will be coded using NCI CTCAE v. 4.0. Grade 3-5 laboratory abnormalities will only be considered if they do not resolve within 7 days. The incidence of treatment-emergent adverse events (number and percent of patients reporting the adverse event at least once during the study) will be summarized. In addition, adverse events will be summarized by investigator attribution of relationship to study medication and by grade.

A. Serious Adverse Event (SAE)

Definition of SAE: any adverse drug experience that results in any of the following outcomes and is unrelated to infection, bleeding, or a transfusion reaction:

- Death
- A life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- A suspected transmission of any infectious agent via a medicinal product
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above
- It is medically important *

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

B. Adverse Events of Special Interest (AESI)

Definition of Adverse Events of Special Interest

Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious).

No adverse events of special interest will be collected for this study.

C. Unexpected Adverse Experience/Reference Safety Information

Definition: an adverse event is considered unlisted if the nature or severity is not consistent with the applicable reference safety information. current investigator brochure (or risk information, if an IB is not required or available). For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable Package Insert..

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=deb4a13c-855b-4372-9778-6e81da598df6

D. Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death. Disease progression should not be recorded as an adverse event or serious adverse event term.

E. Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

F. Product Quality Complaint (PQC)

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

Examples of PQC include but not limited to:

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

G. Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

H. Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

I. Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

APPENDIX B: Definition of TP53 Mutant AML

A patient with *TP53* mutant AML is defined as having a minimum variant allele frequency of 10% identified with at least 50 total reads and 5 variant reads. If a germline sample was sequenced, the variant reads must have a Fisher exact test p value < 0.01 when compared with the leukemia sample. If a germline sample was not available for sequence comparison, the *TP53* variant must be described in Cosmic and not identified in dbGaP as a germline variant in $> 0.1\%$ of the population.

APPENDIX C: Reporting Timelines

Expedited Reporting Timelines					
Event	**HRPO**	**QASMC**	**FDA**	**IBC**	**Janssen**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	N/A	Report within 24-hours of becoming aware of the event(s).
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information		Report within 24-hours of becoming aware of the event(s).
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment			
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.				
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.				
Protocol exception	Approval must be obtained prior to implementing the change				
Clinically important increase in the rate of a serious suspected adverse reaction of			Report no later than 15 calendar days after it is determined that the information qualifies for reporting		

Expedited Reporting Timelines					
Event	**HRPO**	**QASMC**	**FDA**	**IBC**	**Janssen**
that list in the protocol or IB					
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.				
Breach of confidentiality	Within 10 working days.				
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.				
SAEs, and Adverse Events of Special Interest and Special Reporting Situations (See Section 7.5.F)					Report within 24-hours of becoming aware of the event(s).
Pregnancy					Report within 24-hours of becoming aware of the event(s).

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Janssen**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	
Minor deviation	Report summary information at the time of continuing review.			
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

Expedited Reporting Timelines for Secondary Sites				
Event	**WU (Coordinating Center)**	**Local IRB**	**FDA**	**Janssen**
Serious AND unexpected suspected adverse reaction	Report no later than 11 calendar days after it is determined that the information qualifies for reporting.	Report all applicable events to local IRB according to local institutional guidelines.	The research team at Washington University is responsible for reporting all applicable events to the FDA as needed.	The research team at Washington University is responsible for reporting all applicable events to Janssen as needed.
Unexpected fatal or life-threatening suspected adverse reaction	Report no later than 4 calendar days after initial receipt of the information.			
Unanticipated problem involving risk to participants or others	Report no later than 4 calendar days after initial receipt of the information.			

Expedited Reporting Timelines for Secondary Sites				
Event	**WU (Coordinating Center)**	**Local IRB**	**FDA**	**Janssen**
Adverse event or SAE that does not require expedited reporting	As per routine data entry expectations			
Protocol exception	Approval must be obtained prior to implementing the change.			

APPENDIX D: Washington University Serious Adverse Event Reporting Cover Sheet

SAE COVER SHEET- Secondary Site Assessment

Washington University HRPO#:	Sponsor-Investigator:
Subject Initials:	Subject ID:
Treating MD:	Treating Site:
EVENT TERM:	Event Start Date:
EVENT GRADE:	Date of site's first notification:

Treating MD Event Assessment:

Is this event **possibly, probably, or definitely** related study treatment?

☐ yes ☐ no

If yes, please list which drug (if more than one)_____

Explain _____

_____

_____ _____ _____

Physician's Name **Physician's Signature** **Date**