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Fred Hutchinson Cancer Research Center
University of Washington
Seattle Cancer Care Alliance
Seattle Children's

Current Version: 07/14/2020, v 9.0
Previous Version: 04/27/2020

Individualized Treatment for Relapsed/Refractory Acute Leukemia Based on Chemosensitivity and Genomics/Gene Expression Data

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1. STUDY OBJECTIVE

This study will utilize an in vitro high throughput chemosensitivity assay, mRNA expression microarray data, and patient mutational analysis, as available, to choose specific drugs or drug combinations for the treatment of patients with relapsed (2nd salvage or greater) or refractory (to at least 2 inductions) acute leukemias.

1.1. The primary objective is to test patient cells in a high throughput assay against individual drugs and drug combinations within 21 days to enable optimal choice of drug combinations for therapy. In addition, gene expression that reveals activation of druggable pathways or mutations in genes that confer susceptibility to specific agents may also be considered in choice of treatment.

1.2. The secondary objective is to evaluate the response to the chosen therapy.

2. BACKGROUND

Current approaches to acute leukemia result in complete remission for most children and the majority of adults. Approximately 50% to 70% of patients can achieve long-term disease control when undergoing transplantation in early phases of the disease (De Lima et al. 2004). However, despite a high rate of complete remission to induction chemotherapy, the majority of patients with acute leukemia will relapse. Even in acute lymphocytic leukemia (ALL), which is generally responsive to chemotherapy, nearly 10% to 30% of children are at risk for relapse (Tzortzatou-Stathopoulou et al. 2001). It is generally believed that patients who undergo allogeneic hematopoietic cell transplant have a high likelihood of cure. However, those transplanted with detectable minimal residual disease (MRD) have a high risk of relapse after transplant. MRD tends to be proportional to risk of relapse (Campana, 2009). In fact, most adults and some children will relapse with acute leukemia within 6 to 24 months. For patients diagnosed with acute myeloid leukemia (AML), the projected 5-year survival is only 25% (American Cancer Society, 2015). For patients who have failed multiple attempts at induction, or those who have failed 2 salvage regimens for relapsed AML, or those with initial remission duration of less than six months, the results of treatment are very poor (Estey et al. 1996). For patients with a first complete remission duration of less than 12 months or no initial CR, there was a 0% chance of achieving CR with second salvage induction. Consequently, for patients unable to achieve an initial remission, the 4-year survival rate is 23% (Othus et al. 2015). Even for patients being treated with a first salvage regimen, a poor risk group can be identified by criteria including relapse free interval, age at relapse, cytogenetics, and whether they had a prior stem cell transplant. These patients had a 12 month survival of only 16%, and a 5 year survival of 4% (Breems et al. 2005). There are numerous conventional and experimental chemotherapy regimens available for such patients, but with few exceptions, we cannot predict response. Furthermore, traditional regimens are known to fail in patients who have had two or more salvage regimens.

This, in combination with the morbidity and mortality associated with side effects of chemotherapeutic agents, is why we pursued a prior feasibility trial utilizing a high throughput

chemosensitivity assay to guide individual drug selection for relapsed/refractory acute myeloid leukemia. Entitled "Treatment for Relapsed AML Based on a High Throughput Drug Sensitivity Assay" (NCT # 01872819), this trial finished patient accrual in October 2015.

The in vitro high throughput drug sensitivity assay used in this initial trial was comprised of both investigational drugs and FDA approved drugs. This assay is CLIA-certified for patient diagnostic purposes and testing was performed in the Quellos High Throughput Core Facility, University of Washington Medicine, Seattle WA. Thus far, we have tested a total of 46 AML patient blood samples (30 preclinical and 16 on the prior trial) enriched for blasts to exceed 80-90%, using magnetic bead isolation methods when needed. Two 384-well plates accommodate testing of 80 drugs at 8 concentrations each plus controls. Cells were added to matrix protein coated non-tissue culture-treated 384-well plates at a density of 5,000 cells per well in 50µL of complete media (containing pen/strep and 10mM HEPES buffer) using a Thermo Scientific Matrix WellMate, and incubated overnight to allow adhesion. Compounds (50nL) were added (ranging from 5 pM to 100 µM) to patient samples using the CyBio CyBi-Well Vario and incubated at 37°C, 5% CO_2 for 96 hours. The final solvent concentration, (DMSO) in the assay was 0.1%. CellTiter-Glo (Promega) was dispensed into the individual wells with the WellMate following the manufacturer's recommended procedures and, following 20 minutes incubation on an orbital shaker, luminescence was measured on a Perkin Elmer EnVision Multi-label plate reader to assess viable cells. Measurements were corrected for background luminescence and percentage cell viability is reported as relative to the DMSO solvent control. IC_{50} values were calculated by fitting data using least squares method to the standard four-parameter logistic model where:

"Y" = ("Y_{min}"+("Y_{max}"/(1+(("X"/"IC_{50}")^{Slope}), and Y = % viability, Y_{min} = minimal % viability, Y_{max} = maximal % viability, X = compound concentration, IC_{50} = concentration of compound exhibiting 50% inhibition of cellular viability, Slope = the slope of the resultant curve. Curve fitting was performed using idbs XLFit software (Microsoft Excel).

The novel aspect of the assay is that the cell survival is measured on a substratum to which the cells are adherent, a property which confers drug resistance for all hematologic malignancies. Recent studies (McMillin et al. 2010 and Straussman et al. 2012) demonstrate the importance of the microenvironment in drug sensitivity testing. Our adherence strategy, although it does not substitute for microenvironment, is a component previously demonstrated sufficient to reproduce drug resistance in AML (Becker et al. 2009).

Preliminary testing of 46 patients' leukemic blasts confirmed that each patient's cancer has unique in vitro chemotherapeutic susceptibility (Figure 1). By comparing the EC50 of each drug across all 46 patients, we are able to discern an individual patient's relative in vitro susceptibility to any given drug.

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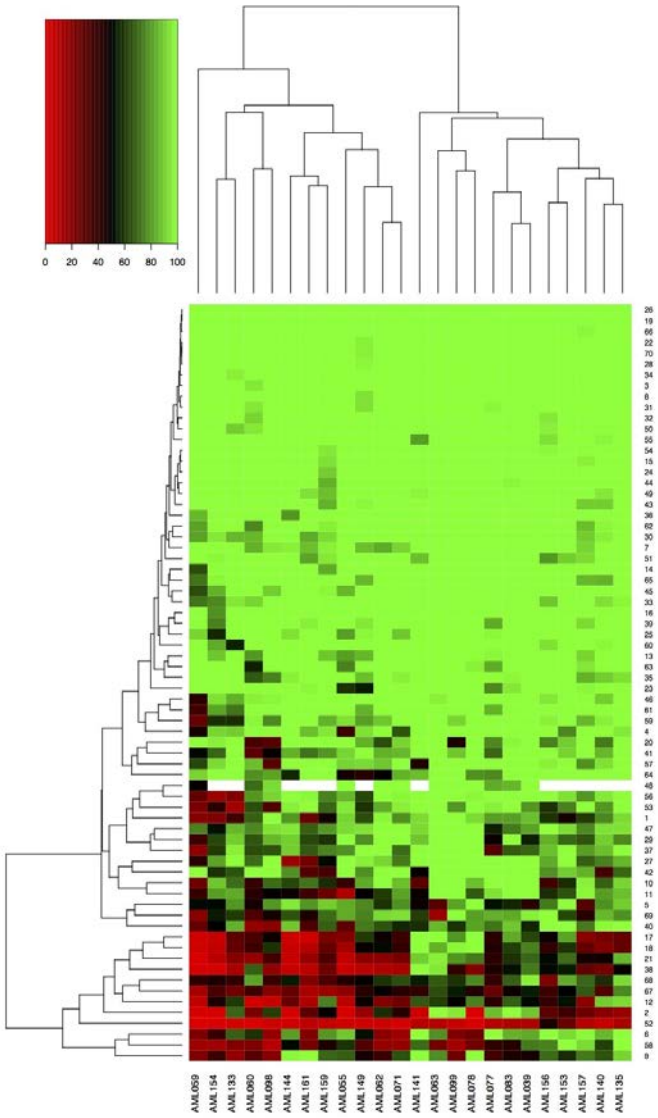

Figure 1. In-vitro high throughput sensitivity data for 0.3 micromolar drug concentration for 24 patients and 160 drugs. Red = cell death, Green = cell survival. Hierarchical clustering is shown for patients and drugs. Note that each patient exhibits a unique pattern of drug susceptibility.

Fifteen patients were enrolled in the initial feasibility study. Individual drugs were chosen on the basis of EC50 and drug availability, and patients received the single agents at the accepted maximal tolerated dose. Within an average of 11.6 (median 9, range 4-28) days, 13 patients received single drugs to which their cells appeared to be sensitive with an EC50 range of 0.026-0.175umol/L, including cladrabine, mitoxantrone, bortezomib or vinblastine. All patients exhibited a decline in blast number after receipt of the indicated drug, on average, by 92.6% (range 80.5-99.8%) (Figure 2). One patient achieved CR and 2 patients achieved partial complete remission (Becker et al. 2014).

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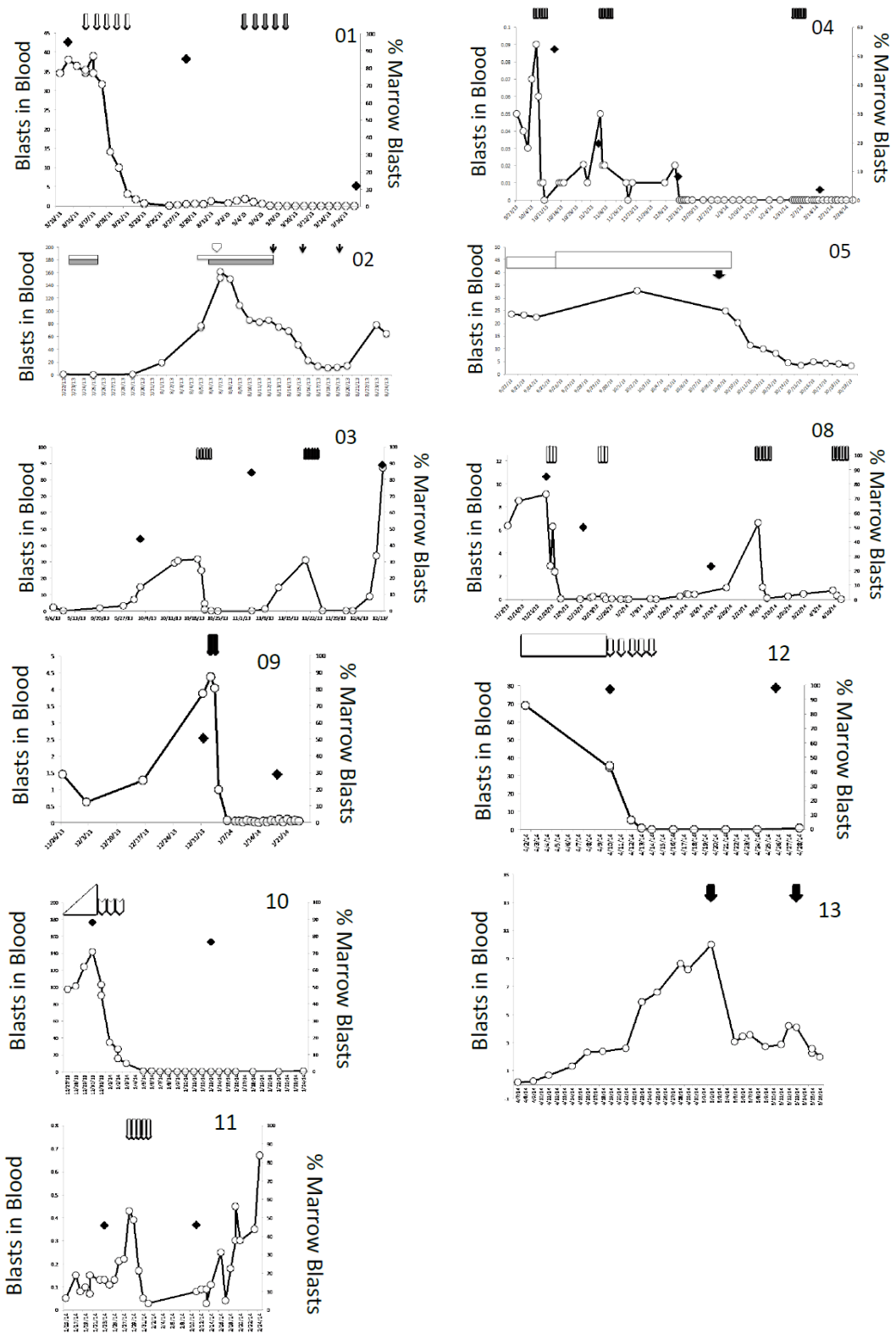

Figure 2. Peripheral blast counts following drug sensitivity guided therapy in 11 of our initial 13 AML patients who had circulating blasts. Patients received a single drug at time points indicated by arrows.

Other groups have used similar assay based approaches to profile in vitro chemosensitivity of an individual patient's AML blasts to traditional chemotherapy (Bennett et al. 2014). In vitro chemosensitivity assays may also be useful for estimating a novel agent's utility in AML. Pemovska et al (2013) identified targeted agents both investigational and approved for other indications that exhibited significant cytotoxicity in an in-vitro assay. Several of these agents (ex dasatinib, sunitinib and temsirolimus) were employed in assay-guided treatment resulting in brief but marked reduction in leukemic burden. Recognizing the inherent limitations of in vitro testing, two separate groups have developed systems to perform sensitivity testing of several chemotherapeutic agents simultaneously within living solid tumors (Klinghoffer et al. 2015; Jonas et al. 2015).

The incorporation of mutational analysis and gene expression data in the choice of chemotherapy has the potential to further refine the approach. Specific mutations in genes implicated in AML can determine responsiveness to certain therapeutic agents. For example, prior studies demonstrated that tyrosine kinase domain (TKD) mutations found in the *FLT3* gene confer chemotherapy resistance to some FLT-3 inhibitors such as sorafenib, but not to others such as crenolanib (Zimmerman et al. 2013; Zhang et al 2014).

Our group is currently analyzing our own in vitro assay data for correlations between gene expression and in vitro drug sensitivity. To this end, we developed a novel computational method, named SPARROW, to reduce the dimensionality of gene expression data by identifying genes that represent important molecular events in publicly available AML expression data (Logsdon et al. 2015). In particular, it aims to identify *hub regulators* whose expression levels are predictive of many downstream gene expression levels. We have found that high expression of several hub regulators correlates well with increased sensitivity to certain classes of drugs. As would be expected, high expression of *FLT3* was associated with increased sensitivity to *FLT3* inhibitors sunitinib, AP24534 and tandutinib. High expression of *SMARCA4* and *TRF2* were both associated with increased sensitivity to topoisomerase inhibitors daunorubicin, mitaxantrone, etopsoside and topotecan. (Lee et al. 2014).

We now propose a second assay-directed therapy trial in adult and pediatric refractory acute leukemia that will utilize drug combinations and incorporate genetic information in the choice of drugs.

3. PATIENT ELIGIBILITY

3.1. Inclusion Criteria

(1) Diagnosis of acute leukemia by WHO criteria (e.g.-acute myeloid leukemia, acute lymphoblastic leukemia, acute leukemia of ambiguous origin).

(2) Either:

a) relapsed after or refractory to prior treatment with at least two regimens or lines of treatment;.

b) prior failure of at least one regimen or line of treatment, with poor cytogenetic or other risk factors, and ineligible for other clinical trials.

(3) Age ≥ 3 years old

(4) ECOG Performance Status 0 – 3.

(5) Expectation that we can obtain about 10 million blasts from blood and/or marrow (e.g., circulating blast count of 5,000 or greater or cellular marrow with greater than or equal to 20% blasts).

(6) Adequate renal and hepatic function as defined below (or more stringent, depending on the individual drugs).

- Bilirubin ⩽ 1 .5 x Upper Limit of Normal (ULN) unless elevation is thought to be due to Gilbert's syndrome, hemolysis, or hepatic infiltration by the hematologic malignancy.
- SGOT (AST) and SPGT (ALT) ⩽ 2.5 x ULN, unless elevation is thought to be due to hepatic infiltration by the hematologic malignancy,
- Alkaline Phosphatase ⩽ 2.5 X ULN, unless elevation is thought to be due to hepatic infiltration by the hematologic malignancy
- Serum creatinine ⩽ 2.0 mg/dL

(7) Informed consent.

(8) Willing to use contraception when appropriate.

(9) Expected survival is greater than 100 days.

3.2. Exclusion Criteria

(1) No other active cancer that requires systemic chemotherapy or radiation.

(2) Active systemic fungal, bacterial, viral or other infection, unless disease is under treatment with antimicrobials and considered controlled in the opinion of the investigator.

(3) Significant organ compromise that will increase risk of toxicity or mortality.

(4) Pregnancy or lactation.

4. STUDY DRUG INFORMATION

Our original drug sensitivity assay included 115 investigational drugs and 45 FDA approved drugs. Approximately 60 of these exhibited activity against at least half the 46 patient samples tested to date. The second-generation assay includes 77 investigational drugs and 70 FDA approved drugs. The latter FDA approved drugs are approved for oncologic indications though not necessarily acute leukemia. Several of these drugs are tested in combination mirroring frequently used anti-leukemic regimens. Table 1 is a list of the drugs included in the 147-drug panel and their mechanisms of action. If mutational analysis reveals an aberrant pathway for which there is an available targeted inhibitor, such a drug will be added to the assay if it can be obtained.

Table 1. The 70 FDA approved and 77 investigational agents and their mechanisms of action comprising the second generation drug sensitivity assay.

Drug	Mechanism of Action	Panel

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Acrichine	Suppresses NF-kB pathway and activates p53 pathway	FDA Approved
Afatinib	Inhibitor of epidermal growth factor receptors 1 (ErbB1; EGFR), 2 (ErbB2; HER2), and 4 (ErbB4; HER4), and certain EGFR mutants	FDA Approved
Arsenic trioxide	Degrades aberrant PML-retinoic acid receptor α fusion protein	FDA Approved
Axitinib	VEGF and PDGF receptor inhibitor	FDA Approved
Azacitidine	Inhibits DNA methyltransferase and tRNA cytosine-5-methyltransferase	FDA Approved
Belinostat	Histone deacetylase inhibitor	FDA Approved
Bexarotene	Activates retinoid X receptors	FDA Approved
Bortezomib	Reversibly inhibits 26S proteosome	FDA Approved
Bosutinib	Dual kinase inhibitor of both Abl and Src kinases	FDA Approved
Busulfan	Cross-links A-G and G-G	FDA Approved
Cabazitaxel	Inhibits microtubule depolymerization	FDA Approved
Cabozantinib	Inhibits MET, RET, VEGF, FLT3, KIT, TRKB and other tyrosine kinase associated receptors	FDA Approved
Carfilzomib	Inhibits 20S proteosome	FDA Approved
Ceritinib	Inhibitor of ALK	FDA Approved
Cladribine	Purine nucleoside antimetabolite	FDA Approved
Clofarabine	Purine nucleoside analog that inhibits ribonucleotide reductase and DNA polymerase	FDA Approved
Crizotinib	Inhibitor of ALK	FDA Approved
Cytarabine HCl	Antimetabolite analog that competes with cytidine for incorporation into DNA and inhibits DNA replication in S phase	FDA Approved
Dabrafenib	inhibitor of BRAF	FDA Approved
Dasatinib	Inhibitor of SRC-family protein-tyrosine kinases	FDA Approved
Daunorubicin HCl	Inhibits DNA replication through topoisomerase-mediated action	FDA Approved
Decitabine	Inhibits DNA methyltransferase	FDA Approved
Erlotinib	Inhibits EGFR	FDA Approved
Etoposide	Inhibits topoisomerase II	FDA Approved
Everolimus	Binds FKBP-12, which binds and inhibits mTOR	FDA Approved
Fludarabine	Inhibits DNA Polymerase alpha, ribonucleotide reductase, and DNA Primase	FDA Approved
Gefitinib	Inhibits EGFR and other TKIs	FDA Approved
Gemcitabine HCl	Converted to dFdCDP, which inhibits ribonucleotide reductase	FDA Approved
Hydroxyurea	Inhibits ribonucleotide diphosphate reductase	FDA Approved
Ibrutinib	Bruton's tyrosine kinase inhibitor	FDA Approved
Idarubicin	Inhibits DNA replication through topoisomerase-mediated action	FDA Approved
Imatinib	Inhibits TKs encoded by bcr-abl, PDGFR, and c-kit genes	FDA Approved
Irinotecan	Inhibits topoisomerase I	FDA Approved
Lapatinib	Blocks phosphorylation of EGFR, Erb82, Erk, and AKT	FDA Approved

Lomustine	Cross-links and carbamoylates DNA	FDA Approved
Lenalidomide	Promotes G0-G1 cell cyle arrest	FDA Approved
Melphalan	Alkylates DNA at N7 of guanine and induces interstrand cross-links	FDA Approved
Mercaptopurine	Inhibits nucleotide interconversion and de novo purine synthesis	FDA Approved
Methotrexate	Inhibits dihydrofolate reductase	FDA Approved
Mitoxantrone	Intercalates into DNA and induces cross-linking	FDA Approved
Nelarabine	Converted to ara-G and inhibits DNA synthesis at S phase	FDA Approved
Nilotinib	Inhibits Bcr-abl, PDGFR, and c-kit	FDA Approved
Olaparib	PARP inhibitor	FDA Approved
Omacetaxine	Binds 80S ribosome and inhibits protein synthesis	FDA Approved
Paclitaxel	inhibits disassembly of microtubules	FDA Approved
Palbociclib	CDK4 and 6 inhibitor	FDA Approved
Panobinostat	HDAC inhibitor	FDA Approved
Pazopanib	Inhibits VEGFR-1,2,3, c-kit, and PDGFR	FDA Approved
Pemetrexed	Inhibits thymidylate synthase	FDA Approved
Pentostatin	Inhibits adenine deaminase	FDA Approved
Pomalidomide	Promotes G0-G1 cell cyle arrest	FDA Approved
Ponatinib	Previously called AP24534: Inhibits Bcr-abl, FLT3, VEGFR, FGFR	FDA Approved
Pralatrexate	Inhibits dihydrofolate reductase	FDA Approved
Rapamycin	Binds FKBP-12, which binds and inhibits mTOR	FDA Approved
Regorafenib	Inhibits VEGFR-2 &3, Ret, Kit, Raf, and PDGFR	FDA Approved
Romidepsin	Inhibits HDAC and depletes Hsp90 dependent oncoproteins	FDA Approved
Ruxolitinib	Inhibits JAK 1 and 2, VEGFR and EGFR	FDA Approved
Selumetinib	Inhibitor of MEK MAPK/ERK Kinase	FDA Approved
Sorafenib	Inhibits Raf kinase, VEGFR, and PDGFR; BRAF and MAP Kinase pathway	FDA Approved
Sunitinib	Inhibits VEGFR, PDGFRb, and c-kit; disrupts microtubules and glutamic acid metabolism	FDA Approved
Temsirolimus	Inhibits mTOR, tubulin polymerization and Hedgehog ligand surface receptors PCTH and SMO	FDA Approved
Thioguanine	Inhibits DNA and RNA synthesis by incorporating into DNA and RNA, HDAC inhibitor	FDA Approved
Topotecan HCl	Inhibits relegation of topoisomerase I mediated single strand DNA breaks	FDA Approved
Trametinib	Inhibitor of MEK MAPK/ERK Kinase	FDA Approved
Tretinoin	Activates retinoid receptors and also inhibits telomerase	FDA Approved
Vandetanib	Inhibits EGFR and VEGFR	FDA Approved
Vinblastine	Causes metaphase cell cycle arrest via microtubule assembly inhibition	FDA Approved
Vincristine	Causes metaphase cell cycle arrest via microtubule assembly inhibition	FDA Approved

Vinorelbine	Causes metaphase cell cycle arrest via microtubule assembly inhibition	FDA Approved
Vorinostat	HDAC inhibitor	FDA Approved
Alisertib	Aurora A kinase inhibitor	Investigational
AMG232	MDM2 inhibitor (p53)	Investigational
AMG900	Pan-aurora kinase inhibitor	Investigational
AT-7519	Inhibits CDK	Investigational
AT9283	Inhibits Aurora kinases A & B, JAK2, and bcr-abl	Investigational
Avagacestat	Gamma secretase inhibitor	Investigational
AZD-7762	Inhibits checkpoint kinases	Investigational
AZD-8055	mTOR inhibitor	Investigational
AZD-8330	MEK1 and 2 inhibitor	Investigational
BAY 11-7082	IKK inhibitor	Investigational
BAY 11-7085	IkBa inhibitor	Investigational
Birinapant	IAP inhibitor	Investigational
Buparlisib	PI3K inhibitor	Investigational
BMS-754807	Inhibits IGF-1R and InsR tyrosine kinases	Investigational
Cediranib	Inhibits VEGFR 1,2,3	Investigational
Crenolanib	PDGFR inhibitor	Investigational
Dactolisib	PI3K and mTOR inhibitor	Investigational
Dinaciclib	CDK inhibitor	Investigational
DMH1	BMP inhibitor	Investigational
Doramapimod	Pan-p38 MAPK inhibtor	Investigational
Dorsomorphin	BMP inhibitor	Investigational
Dovitinib	VEGFR, FGFR inhibitor	Investigational
Entinostat	HDAC inhibitor	Investigational
EPZ-5676	DOT1L inhibitor	Investigational
Flavopiridol	CDK inhibitor	Investigational
Ganetespib	Hsp90 inhibitor	Investigational
GDC-0152	IAP inhibitor	Investigational
Gedatolisib	Dual PI3K/mTOR inhibitor	Investigational
Gliteritinib	Inhibits FLT3, AXL, ALK	Investigational
GSK1210151A	bromodomain BET inhibitor	Investigational
I-BET762	bromodomain BET inhibitor	Investigational
Idelalisib	PI3K inhibitor	Investigational
Iniparib	PARP inhibitor	Investigational
KPT-185	CRM1 inhibitor	Investigational
Lenvantinib	VEFGR2 tyrosine kinase inhibitor	Investigational
Lisitinib	IGF-1R inhibitor	Investigational
Luminespib	Hsp90 inhibitor	Investigational
Masitinib	Inhibits c-Kit, FGFR3, FAK, and PDGFR	Investigational
MG-132	Proteosome inhibitor	Investigational

Midostaurin	PKC inhibitor	Investigational
MK-1775	WEE1 tyrosine kinase inhibitor	Investigational
MK2206	Akt inhibitor	Investigational
Mocetinostat	HDAC inhibitor	Investigational
Nintedanib	Inhibits Src, VEGFR, PDGFR, FGFR	Investigational
NVP-BGJ398	FGFR inhibitor	Investigational
NVP-BYL719	PI3k inhibitor	Investigational
Obatoclax	Bcl-2 inhibitor	Investigational
Otava 7070707035	CDK4 inhibitor	Investigational
OTX015	BRD 2,3,4 inhibitor	Investigational
Pacritinib	Dual jak2/flt3 inhibitor	Investigational
Panobinostat	HDAC inhibitor	Investigational
PD-0325901	MEK inhibitor	Investigational
PF-04691502	PI3K and mTOR inhibitor	Investigational
PFI-1	Bromodomain BET inhibitor	Investigational
Pictilisib	PI3K inhibitor	Investigational
Pimasertib	Inhibits MEK1 and 2 (AS703026)	Investigational
Pexidartinib	KIT, CSF1R, FLT3 inhibitor	Investigational
PLX-4720	BRAF V600E inhibitor	Investigational
Pp242	mTOR/C1/C2 inhibitor	Investigational
Quizartinib	FLT3 inhibitor	Investigational
Rigosertib	Plk-1 inhibitor	Investigational
SB 218078	ATP-competitive inhibitor of Chk1	Investigational
Selinexor	CRM1 inhibitor	Investigational
SGI-1776	PIM kinase inhibitor	Investigational
SNS-032	Multiple CDK, GSK-3 inhibitor	Investigational
Sonidegib	SMO inhibitor	Investigational
Staurosporine	Multiple kinases	Investigational
Tanespimycin	HSP90 inhibitor	Investigational
Tepotinib	MET tyrosine kinase inhibitor	Investigational
Tipifarnib	Farnesyl transferase inhibitor	Investigational
Tivantinib	Inhibits c-Met	Investigational
Tosedostat	Aminopeptidase inhibitor	Investigational
Tozasertib	Aurora A, B, C, Flt3, Abl	Investigational
Vemurafenib	BRAF V600E inhibitor	Investigational
Venetoclax	Bcl-2 inhibitor	Investigational
Vismodegib	PTCH and SMO inhibitor	Investigational
Volasertib	PLK 1, 2, 3 inhibitor	Investigational
YM-155	Survivin inhibitor	Investigational

5. PRETREATMENT EVALUATION

5.1. Screening Evaluations/Procedures

1. Signed, written informed consent: Consent must be completed prior to performing any study-related procedures.

2. The following standard of care evaluations, if done, may be reviewed within the electronic medical record to assist with determining eligibility for the study, unless required per the inclusion/exclusion criteria:

a. Medical history: Detailed documentation of disease and treatment history with outcomes

b. ECOG performance status (Appendix A)

c. Concurrent medical conditions.

d. Serum chemistries: Electrolytes (sodium, potassium, chloride, and bicarbonate), blood urea nitrogen (BUN), creatinine, glucose, and liver function tests (aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin

e. Initial standard of care diagnostic bone marrow reports, may include hematopathology, cytogenetics / FISH, flow cytometry and mutation status.

f. MUGA scan may be performed prior to treatment for participants receiving anthracycline therapy

6. PLAN OF TREATMENT

6.1. Chemosensitivity Assay

A blood sample of 25 cc in sodium heparin will be sent to the research laboratory for testing in the high throughput assay, and results will be available in about a week. For patients with less than an absolute blast count in the peripheral blood of 5.0 X 10^9/L, a bone marrow sample of 10 cc will be sent. If this aspirate contains an inadequate number of blasts, another bone marrow aspirate may be obtained with patient approval. Investigator discretion will be used for analyzing the adequacy of the cell counts . Gene expression data will be obtained via methods described elsewhere (Logsdon et al. 2015). Mutational analysis will be performed with the MyAML™, CLIA validated next generation sequencing assay, which screens for mutations in 196 genes associated with AML. (www.genection.com/myaml.html).

1. Treatment with any chemotherapeutic agent necessary to control leukemic burden is permitted during the time of testing and drug procurement. These agents must be stopped prior to initiation of assay-guided therapy.
2. If leukemia is present in a location other than the blood or bone marrow, a sample of fluid or a biopsy from that location (for example, a skin or tumor sample or spinal fluid) may be sent to the research laboratory for testing in the high throughput assay.

6.2. Drug Choice

A drug or combination of 2-3 drugs tested in combination will be chosen from only the FDA approved drugs listed in Table 1 based on availability, insurance clearance, degree of apparent in vitro response (lowest absolute EC50 or lowest EC50 relative to other patients for individual drugs), prior publication of drug or drug combination use in other leukemia patients and difference in class of drug compared to the drugs to which the patient has previously not responded. In addition, gene expression that reveals activation of druggable pathways or mutations in genes that confer susceptibility to specific agents may also be considered in choice of treatment. If an inhibitor is available that has the same target (e.g.-a specific kinase) as the one tested, this drug may be substituted. For combination regimens, we intend to only utilize regimens for which there are clinical data in humans. Additional FDA approved drugs or combinations of drugs may be added to the assay panel in the future if there is evidence to suggest efficacy in leukemia patients. However, the protocol will be amended to include these drugs prior to their use in any assay-guided treatment regimen.

6.3. Drug Dosing

Individual drugs will be used in doses that have been utilized in humans with anti-cancer response, at standard or maximum tolerated dose. Drug combinations will be used at standard doses or doses for which there is published experience. Appendix E contains a list of sample dosages, though they may change if new data emerges showing superior outcomes with alternative dosing strategies.

6.4. Consent for Individual Regimens

In addition to the consent for this study, there will be an individual general clinical consent for treatment that is not considered a research consent and may include printed information that describes the drug or drug combination, mechanisms of drug action in lay terms and applicable side effects, this activity is considered standard practice and is not strictly performed for research, these consents may vary in appearance. Additionally, an alternative clinical trial consent may be used if the patient is found to be eligible for a clinical trial which may contain an assay-guided regimen or agent. These consents will be signed after assignment of the drug or drug combination. These consents will be obtained for the first two treatment regimens directed by the study, and afterward consent will be obtained only as required per institutional policy by treating physicians.

6.5. Duration of Therapy

Subjects may receive up to two distinct assay-guided regimens that will be monitored for response and adverse events for the study. Treating physicians have discretion to continue treatment thereafter based on data from the study and the responses and survival of the patients will be monitored, but not the adverse events.

7. ON STUDY EVALUATIONS

1. The on-study period begins at initiation of study procedures and response data to any study directed therapies will be collected for a period up to 2 years. Adverse events

will be collected from the time of start of assay guided therapy through 14 days after completion of the first or second drug regimen, as applicable.

2. Hematology: CBC with differential and platelet count and peripheral blood smear at frequency per standard of care.

3. Serum chemistries: Electrolytes (sodium, potassium, chloride, and bicarbonate), BUN, creatinine, glucose, and liver function tests (AST, ALT, ALP, total bilirubin, LDH) per standard of care.

4. Bone marrow aspirations by standard practice with measure of cellularity and percent of blasts, bone marrow at blood count recovery to document remission status. Reports for subsequent bone marrow evaluations throughout period of treatment. See Appendix B for the study calendar.

5. Grade 3 and higher adverse events will be recorded using the NCI CTCAE, Version 4.0

8. FOLLOW-UP

1. Response data. All reports for bone marrow evaluations done as standard of care following this treatment, including morphology, flow cytometry, cytogenetics/FISH and mutation studies, will be collected.

2. Subsequent complete blood count, renal function, and liver function tests obtained for clinical reasons for a period of up to one month post the last consolidation chemotherapy cycle, as needed to define toxicity or duration of response.

3. Reports on each patient's course post stem cell transplant, if applicable, will be reviewed to determine response and duration of remission.

4. Disease free and overall survival data will be assessed by contacting the referring MD or the patient every three months for the first two years.

9. CRITERIA FOR RESPONSE

Responses to treatment will be on the basis of 1) standard criteria as well as 2) the degree of cytoreduction.

9.1. Definition of Response by standard criteria

Response will be evaluated using European LeukemiaNet criteria, which are outlined in Appendix C.

9.2. Degree of Cytoreduction

The percent cellularity of the bone marrows obtained within 2-3 weeks of treatment and the percent leukemia by morphology and flow cytometry will be monitored by the study team, and compared to the pre-treatment levels.

9.3. Duration of Response

Time to progression will be noted for patients, regardless of whether they undergo stem cell transplant.

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10. REGISTRATION OF PATIENTS

Patients who fulfill eligibility criteria and who signed consent will be enrolled by the study coordinator. See Appendix D for the registration form.

11. FORMS TO BE KEPT

Case report forms, diagnostic pathology reports, and laboratory test results will be kept in a secure location that protects confidential information or electronically with security access. Follow up information regarding survival and information about time of relapse and subsequent therapy will also be maintained.

12. REGULATORY AND REPORTING REQUIREMENTS

12.1. Adverse Event Monitoring and Reporting

The principal investigator is responsible for monitoring the safety of patients who enroll in the study. The descriptions and grading scales found in the NCI CTCAE version 4.0 will be used for adverse event reporting. Non-hematologic toxicities ≥grade 3 will be recorded from assay-guided therapy administration through 14 days after last administration of study therapy and will be followed until resolution.

12.2. Serious Adverse Events

A serious adverse event (SAE) is any adverse drug experience that occurs at any dose that results in any of the following outcomes:

- Death.
- Life threatening adverse event.
- Hospitalization or prolongation of hospitalization*
- Persistent of significant disability/incapacity.
- A congenital anomaly/birth defect.
- Requires surgical intervention to prevent one of the outcomes listed above.

*For the purposes of this study, hospitalizations or prolongation of hospitalizations for protocol-scheduled procedures, blood product transfusions, or for social reasons (i.e. awaiting transport home) will not be considered a SAE; hospitalization or prolongation of hospitalizations for fever and/or infection will be considered expected, and not be considered a SAE.

12.3. Reporting Serious Adverse Events

In accordance with FHCRC/UW Cancer Consortium IRB policy, all adverse events (AEs; whether occurring on-site or off-site), which in the opinion of the principal investigator are (1) unexpected, and (2) related or possibly related to the research, and (3) serious or suggests that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized, will be submitted to the IRB within 10 calendar days of learning of the problem.

AEs that do not meet the requirement for expedited reporting will be reported to the IRB as part of the annual renewal of the protocol.

13. DATA AND SAFETY MONITORING PLAN

Ongoing trial oversight is carried out by the principal investigator, Dr. Percival and the primary research coordinator. These individuals will meet regularly to review recently acquired data, and adverse events.

Institutional support of trial monitoring is provided in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, Fred Hutch Clinical Research Support (CRS) coordinates data and compliance monitoring by consultants, contract research organizations, or CRS employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits. In addition, protocols are reviewed at least annually by the Fred Hutch/ UW Cancer Consortium Data and Safety Monitoring Committee (DSMC) and the Fred Hutch Institutional Review Board (IRB). The DSMC reviews accrual, adverse events, stopping criteria, and adherence to the data and safety monitoring plan. The Fred Hutch IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of both committees is necessary to continue the study.

14. STATISTICAL CONSIDERATIONS

14.1. Experimental Design

This is a feasibility study with the primary objective of combining drug treatments and initiating therapy based on the results of the drug screen for poor risk patients with any refractory or relapsed acute leukemia. The sample size is determined by funding and time constraints, rather than testing of specific hypotheses. Information from this study will enable us to determine effective combinations of drug treatments based on in vitro response and mutational analyses.

Given the large expenditure of time and funds for each patient, we would like to see the primary objective achieved in at least 40-50% of the patients. We will consider the study successful (feasibility demonstrated) if we are able to choose and initiate a combination drug regimen within 21 days in 9 out of 15 patients. With that outcome, we could say with 90% confidence that the true feasibility rate is at least 40%. Based on our previous study, where 14 of 15 patients were successfully tested and treated within 21 days, we believe that the true feasibility rate in this study could be 70% or more. In that case, we have an 87% chance of observing a 9 out of 15 success rate or better.

Although efficacy is not a primary endpoint, the overall objective of individualized therapy is to increase the rate of CR, and ultimately survival. However, the goal of this study is to establish feasibility, and subsequent trials will be needed to validate the approach and establish superiority over current standard of care.

Patients who sign consent can be screened for eligibility. Part of the definition of eligibility is to be able to obtain ~10 million leukemia blasts for analysis (or per lab ability to assay). Patients for which enough cells are not obtained will be considered screen failures.

Patients who receive assay results and do not receive drug due to other circumstances, such as inability to return to center, patient/doctor decision to not be treated per study recommendation, or patient/doctor preference for palliative care, will be considered discontinuation. Patients who discontinue for this rationale will be replaced in order to complete all objectives of this study; we will continue to follow outcomes of patients who discontinue.

14.2. Stopping Rules

The study will be stopped if we fail to demonstrate feasibility. Operationally, this will be triggered if the 7th patient fails to receive treatment, indicating that the objective of treating 9 of 15 patients will not be met.

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APPENDIX A
PERFORMANCE STATUS CRITERIA

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

APPENDIX B:
STUDY CALENDAR

Assessment	Screening		Treatment Phase	End of Treatment	Long Term Follow-up
Informed Consent	X				
Medical History/Concurrent Conditions	X				
ECOG Performance Status	X			X	
Hematology	X		X[d]	X	X
Serum Chemistries[a]	X	X	X[d]	X	
Bone Marrow Biopsy, Aspirate and Smear Results	X[b]		X[d]	X	X
MUGA[c]	X[c]				
Response Assessment/ Confirmation of Continued Remission Status				X	X
Drug Administration			X		
Adverse Event Assessment	X		X	X	

[a] Electrolytes (sodium, potassium, chloride and bicarbonate), BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, total bilirubin and LDH.

[b] Review of the initial standard of care bone marrow,aspirate and smear results.

[C] For patients receiving anthracycline therapy

[d] According to standard of care

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APPENDIX C
RESPONSE CRITERIA IN AML: FROM DÖHNER ET AL. 2010

Abbreviations: AML acute myelogenous leukemia; EMD, extramedullary disease; CR, complete remission

Response Criterion	Time of Assessment	Neutrophils (μ L)`	Platelets (μ L)	Bone Marrow Blasts (%)	Other
Morphologic leukemia-free state	Varies by protocol	NA	NA	< 5	Absence of blasts w/ Auer rods; Absence of EMD
CR w/ incomplete recovery (CRi)	Varies by protocol	<1,000	<100,00	< 5	Absence of blasts w/ Auer rods; Absence of EMD
Morphologic CR	Varies by protocol	>1,000	> 100,000	< 5	RBC transfusion independence; Absence of EMD
Cytogenetic CR (CRc)	Varies by protocol	>1,000	> 100,000	< 5	Reversion to normal karyotype at time of CR in cases w/ abnormal karyotype at diagnosis; absence of EMD
Molecular CR (CRm)	Varies by protocol	> 1,000	> 100,000	< 5	No standard definition; depends on molecular target
Partial remission (PR)	Varies by protocol	> 1,000	> 100,000	decrease to 5-25	Decrease of pretreatment bone marrow blast percentage by at least 50%

Appendix D

Protocol 9226 Patient Demographics and Eligibility Form

Please Fax this completed form to 206-606.6984 for patient registration.

Questions regarding eligibility should go to Mary-Elizabeth Percival, MD 206-606-1320

Research Subject Registration Form

1.1 UPN#:_____

Patient Name: _____ _____ ___

Last First MI

Date of Birth: ___ ___/___ ___/ ___ ___ ___ ___

Month Day Year

Ethnicity *(choose one)*: instruct the patient to select one of the following:

☐ **Hispanic or Latino** (A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. Term "Spanish Origin" can also be used in addition to "Hispanic" or "Latino"

☐ **Not Hispanic or Latino**

☐ **Declined to Report**

Race *(check all that apply)*: instruct the patient to select one or more of the following:

☐ **American Indian/Alaska Native** (A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment)

☐ **Asian** (A person having origins in any of the original peoples of the Far East, Southeast, Asia, or the Indian subcontinent including, for example, Cambodia, China, India Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam)

☐ **Native Hawaiian/Pacific Islander** (A person having origins in any of the original peoples of Hawaii, Guam, Samoa or other Pacific Islands)

☐ **Black/African American** (A person having origins in any of the black racial groups of Africa.

☐ **White** (A person having origins in any of the original peoples of Europe, the Middle East or North Africa)

☐ **Research Subject does not know race**

☐ **Declined to Report**

Gender:

☐ Male

☐ Female

☐ Unknown

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Appendix E: Drug Dosing and References

Drug or Drug Combination	Dosing	Reference(s)
Afatinib	Adult: 40mg PO qd x14 days Pediatric: not studied	Gordon S, et al. A phase I, open-label, dose-escalation study of continuous once-daily oral treatment with afatinib in patients with advanced solid tumors. Invest New Drugs. 2013 Apr; 31(2):409-416
Arsenic trioxide	Adult: 0.15mg/kg/day IV until bone marrow remission Pediatric: 0.15 mg/kg IV qday for 5days/week x 2 weeks	Powell et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. Blood. 2010 Nov 11;116(19):3751-7 Fox E et al. Phase 1 trial and pharmacokinetic study of arsenic trioxide in children and adolescents with refractory or relapsed acute leukemia, including acute promyelocytic leukemia or lymphoma. Blood 2008 Jan; 111(2): 566-573
Axitinib	Adult: 5 mg PO BID x 14 days Pediatric: not studied	Rugo HS, et al. A Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: pharmacokinetic and clinical results. J Clin Oncol. 2005 Aug 20;23(24):5474-83.
Azacitidine	Adult: 100 mg/m^2 IV or SC daily Days 1-7 Pediatric: not studied	Package Insert
Belinostat	Adult: 1gm/m^2 IV daily on Days 1-5 Pediatric: not studied	Kirschbaum MH et al. A phase 2 study of belinostat (PDX101) in patients with relapsed or refractory acute myeloid leukemia or patients over 60 with newly-diagnosed acute myeloid leukemia: A California Cancer Consortium study. Leuk Lymphoma; 2014 Oct: 55(10): 2301-2304
Bexarotene	Adult: 400mg/m^2 PO qday x 14 days Pediatric: 309mg/m^2 PO qday x 14 days	Tsai DE, Luger SM, Andreadis C, Vogl DT, Kemner A, Potuzak M, et al. A phase I study of bexarotene, a retinoic X receptor agonists, in non-M3 myeloid leukemia. Clin Cancer Res 2008;14:5619–25

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		Mehta N, et al. Bexarotene is active against subcutaneous panniculitis-like T-cell lymphoma in adult and pediatric populations. Clin Lymphoma Myeloma Leuk. 2012 Feb; 12(1):20-25
Bortezomib	Adult: 1.25 mg/m^2 IV twice weekly x 2 weeks Pediatric: not studied	Cortes J, et al. Phase I study of bortezomib in refractory or relapsed acute leukemias.Clin Cancer Res. 2004;10(10):3371-6.
Bosutinib	Adult: 500 mg PO qday x 14 days Pediatric: not studied	Daud AI, et al. Phase I Study of Bosutinib, a Src/Abl Tyrosine Kinase Inhibitor, Administered to Patients with Advanced Solid Tumors. Clin Cancer Res 2012;18(4):1092-1100
Busulfan	Adult: 1.8mg/m^2 PO qday x 14 days Pediatric: same as adult	Product Information: MYLERAN(R) oral tablets, busulfan oral tablets. GlaxoSmithKline, Research Triangle Park, NC, 2005.
Cabazitaxel	Adult: 25mg/m^2 IV q3weeks Pediatric: not studied	Dieras V, et al. Cabazitaxel in patients with advanced solid tumors: results of a Phase I and pharmacokinetic study. Eur J Cancer. 2013 Jan; 49(1):25-34
Cabozantinib	Adult: 175mg PO qday x 14 days Pediatric: not studied	Kurzrock R, Sherman SI, Ball DB, et al. (2011) Activity of XL184 (cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. J Clin Oncol 29:2660–2666
Carfilzomib	Adult: 15mg/m^2 IV on days 1-5 of 14 day cycles Pediatric: not studied	O'Connor, O. A phase 1 dose escalation study of safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. Clin Cancer Res. 2009 Nov 15; 15(22): 7085-91
Ceritinib	Adult: 750mg PO qday x 14 days Pediatric: not studied	Shaw AT, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014 Mar 27; 370(13):1189-97
Cladribine	Adult: 21.5 mg/m^2/day IV over 1 hr Days 1-5 Pediatric: 8.9mg/m^2/d continuous IV for 5 days	Larson RA, et al. Dose-escalation trial of cladribine using five daily intravenous infusions in patients with advanced hematologic malignancies. J Clin Oncol. 1996;14:188-95. Krance RA et al. Experience with 2-chlorodeoxyadenosine in previously untreated children with newly diagnosed acute myeloid leukemia and myelodysplastic diseases. J Clin Oncol. 2001 Jun 1;19(11):2804-11

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Clofarabine	Adult: 40 mg/m^2/day IV Days 1-5 Pediatric: 52mg/m^2/day IV for 5 days	Kantarjian HM, et al. Phase I clinical and pharmacology study of clofarabine in patients with solid and hematologic cancers. J Clin Oncol. 2003;21(6):1167-73. Jeha S et al. Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemia. Blood. 2004 Feb 1;103(3):784-9
Crizotinib	Adult: 250mg PO BID x 14 days Pediatric: 280mg/m^2 PO BID x 14 days	Kwak E, Bang Y, Camidge R, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010; 363: 1693–703 Mosse YP, et al. Safety and efficacy of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a children's oncology group phase 1 consortium study. Lancet Oncol. 2013 May; 14(6):472-80
Cytarabine HCl	≤ 60 years old: 3gm/m^2 every 12 hr Days 1-6 > 60 years old: 1.5gm/m^2 every 12 hr Days 1-6	Herzig RH, et al. High-dose cytosine arabinoside therapy for refractory leukemia. Blood 1983,62:361-369
Dabrafenib	Adult: 150mg PO q12hrs x 14 days Pediatric: not studied	Falchook GS et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose escalation trial. Lancet. 2012 May 19;379(9829):1893-901
Dasatinib	Adult: 140mg PO qday x 14 days Pediatric: 60 or 80mg/m^2 PO qday x 14 days	Product Information: SPRYCEL(R) oral tablets, dasatinib oral tablets. Bristol-Myers Squibb Company (per FDA), Princeton, NJ, 2013. Zwaan CM, et al. Dasatinib in children and adolsescents with relapsed or refractory leukemia: results of the CA180-018 phase 1 dose-escalation study of the Innovative Therapies for Children with Cancer Consortium. J Clin Oncol 2013 Jul 1;31(19): 2460-8
Daunorubicin HCl	Adult: 90 mg/m^2 IV Days 1-3 Pediatric: not studied	Fernandez, HG, et al. Anthracycline Dose Intensification in Acute Myeloid Leukemia. N Engl J Med 2009;361:1249-59. Lowenberg, B, et al. High-Dose Daunorubicin in Older Patients with Acute Myeloid Leukemia. N Engl J Med 2009;361:1235-48.
Decitabine	Adult: 20mg/m^2 IV qd for 5 days q4weeks	Kantarjian HM, et al: Results of a randomized study of 3 schedules of low-dose decitabine in

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	Pediatric: 10mg/m^2/d IV for 10 days	higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood 2007 January; 109(1): 52-57 Phillips CL et al (2013), Low dose decitabine in very high risk relapsed or refractory acute myeloid leukaemia in children and young adults. British Journal of Haematology, 161: 406–410.
Erlotinib	Pediatric: 125mg/m^2 PO qday x 14 days Adult : 150mg PO qday x 14 days	Geoerger B, et al. Innovative Therapies for Children with Cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors. Neuro Oncol. 2011 January; 13(1):109-118 Hidalgo M et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol. 2001 Jul 1;19(13):3267-79.
Etoposide	Adult: 100mg/m^2 IV on days 1-5 in combination with other approved chemotherapeutic agents Pediatric: same as above	Product Information: TOPOSAR(TM) intravenous injection, etoposide intravenous injection. Teva Parenteral Medicines, Inc. (per DailyMed), Irvine, CA, 2011. Horton, T. M., et al (2014), A Phase 2 study of bortezomib combined with either idarubicin/cytarabine or cytarabine/etoposide in children with relapsed, refractory or secondary acute myeloid leukemia: A report from the Children's Oncology Group. Pediatr. Blood Cancer, 61: 1754–1760.
Everolimus	Adult: 10mg PO qday x 14 days Pediatric: not studied	Tabernero J, et al. Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic study in patients with advanced solid tumors. J Clin Oncol. 2008 Apr 1;26(10):1603-10.
Fludarabine	Adult: 75mg/m^2 IV daily Days 1-5 Pediatric: not studied	Warrell LP JR, et al. Phase I and 2 study of fludarabine phosphate in leukemia: therapeutic efficacy with delayed central nervous system toxicity. J Clin Oncol. 1986 Jan;4(1):74-9.
Gefitinib	Pediatric: 400mg/m^2 PO qday x 14 days Adult: 500mg PO qday x 14 days	Daw NC, et al. Phase I and pharmacokinetic study of gefitinib in children with refractory solid tumors: a Children's Oncology Group Study. J Clin Oncol. 2005 Sep 1; 23(25):6172-80

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		Lorusso PM. Phase I studies of ZD1839 in patients with common solid tumors. Semin Oncol. 2003 Feb; 30(1 suppl 1):21-9
Gemcitabine HCl	Adult: 10 mg/m^2 IV over 12hrs on day 1 Pediatric: not studied	Advani AS, et al. A phase II trial of gemicitabine and mitoxantrone for patients with acute myeloid leukemia in first relapse. Clin Lymphoma Myeloma Leuk. 2010 Dec; 10(6):473-6
Hydroxyurea	Adult: 20 to 30mg/kg PO qday x 14 days Pediatric: not studied	Product Information: HYDREA(R) oral capsules, hydroxyurea oral capsules. Bristol-Myers Squibb Company, Princeton, NJ, 2005
Ibrutinib	Adult: 420mg PO qday x14 days Pediatric: not studied	O'Brien S et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: an open-label, multicenter, phase 1b/2 trial. Lancet Oncol 2014 Jan; 15(1) 48-58
Idarubicin	Adult: 12mg/m^2/day x 3 days (in combination w/ cytarabine) Pediatric: same as adult	Wiernik P.H., et al. (1992) Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. Blood 79: 313–319 Creutzig U et al. Randomized trial comparing liposomal daunorubicin with idarubicin as induction for pediatric acute myeloid leukemia: results from study AML-BFM 2004. Blood. 2013 July; 122(1):37-43
Imatinib	Adult: 600mg PO qday x 14 days Pediatric: 340mg/m^2 PO qday x 14 days	Cohen MH, et al. Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. Clin Cancer Res. 2002 May; 8(5):935-42 Schultz KR, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a Children's Oncology Group Study. J Clin Oncol. J Clin Oncol 2009; 27: 5175–5181
Irinotecan	Adult: 250mg/m^2 IV on days 1 and 15 Pediatric: not studied	Rothenberg ML, et al. Phase I dose-finding and pharmacokinetic trial of irinotecan (CPT-11) administered every two weeks. Ann Oncol. 2001 Nov; 12(11):1631-41
Lapatinib	Pediatric: 900mg/m^2 PO BID x 14 days	Fouladi M, et al. Phase I trial of lapatinib in children with refractory CNS malignancies: a Pediatric Brain Tumor Consortium study. J Clin Oncol. 2010 Sep 20;28(27):4221-7

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	Adult: 1600mg PO qday x 14 days	Burris HA, et al. Phase I safety, pharmacokinetics and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. J Clin Oncol. 2005 Aug 10;23(23):5305-13
Lenalidomide	Adult: 50mg PO qday x14 days Pediatric: 116mg/m^2 PO qday x 14 days	Fehniger TA et al. A phase 2 study of high-dose lenalidomide as initial therapy for older patients with acute myeloid leukemia. Blood 2011 Feb; 117(6): 1828-1833 Warren KE et al. Phase I trial of lenalidomide in pediatric patients with recurrent, refractory or progressive primary CNS tumors: Pediatric Brain Tumor Consortium study PBTC-018. J Clin Oncol. 2011 Jan; 29(3): 324-9
Lomustine	Adult: 130mg/m^2 PO once Pediatric: same as adult	Product Information: Gleostine(TM) oral capsules, lomustine oral capsules. NextSource Biotechnolgy, LLC (per FDA), Miami, FL, 2014.
Melphalan	Adult: 70 mg/m^2 IV once Pediatric: not studied	Sonneveld P, et al. Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON 24 trial. Haematologica 2007 July; 92(7): 928-935
Mercaptopurine	Adult: 75mg/m^2 PO qday x 14 days Pediatric: same as adult	Product Information: PURINETHOL(R) oral tablets, mercaptopurine oral tablets. Gate Pharmaceuticals (per FDA), Sellersville, PA, 2011. Stock W, La M, Sanford B, et al, "What Determines the Outcomes for Adolescents and Young Adults With Acute Lymphoblastic Leukemia Treated on Cooperative Group Protocols? A Comparison of Children's Cancer Group and Cancer and Leukemia Group B Studies," Blood, 2008, 112(5):1646-54.
Methotrexate	Adult: MTX 200 mg/m^2 IV over 2 hours followed by 800 mg/m^2 IV over 24 hours on day 1 Pediatric: not studied	Kantarjian HM, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000; 18(3): 547-61

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Mitoxantrone	≤ 60 years old: 15mg/m m^2 Days 1-3 > 60 years old: 12mg/ m^2 Days 1-3	Feldman EJ, et al. Phase I Clinical and Pharmacokinetic Evaluation of High-Dose Mitoxantrone in Combination With Cytarabine in Patients With Acute Leukemia. J Clin Oncol. 1993 Oct;11(10):2002-9.
Nelarabine	Adult: 1500mg/m^2 IV on days 1,3,5 Pediatric: 650mg/m^2 IV qday for 5 consecutive days	Kurtzberg J, Ernst TJ, Keating MJ, et al. Phase I study of 506U78 administered on a consecutive 5-day schedule in children and adults with refractory hematologic malignancies. J Clin Oncol 2005;23:3396-3403
Nilotinib	Adult: 400mg PO BID x 14 days Pediatric: not studied	Tanaka C, et al. (2010), Clinical Pharmacokinetics of the BCR–ABL Tyrosine Kinase Inhibitor Nilotinib. Clin Pharmacol Ther, 87: 197–203
Olaparib	Adult: 400mg PO BID x 14 days Pediatric: not studied	Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet. 2010;376(9737):245-251
Omacetaxine	Adult: 1.25mg/m^2 BID x14 days Pediatric: not studied	Cortes JE, et al. Subcutaneous omacetaxine in chronic or accelerated chronic myeloid leukemia resistant to two or more tyrosine-kinase inhibitors including imatinib. Blood. 2011;118:3761.
Paclitaxel	Pediatric: 430mg/m^2 IV once Adult: 390mg/m^2 IV over 24hrs x 2 doses	Horton, T. M et al. (2008), A Phase 1 and pharmacokinetic clinical trial of paclitaxel for the treatment of refractory leukemia in children: A Children's Oncology Group study. Pediatr. Blood Cancer, 50: 788–792. Rowinsky EK et al. Phase 1 and pharmacodynamic study of taxol in refractory acute leukemias. Cancer Res. 1989 Aug 15;49(16): 4640-7
Palbociclib	Adult: 125mg PO qday x14 days Pediatric: not studied	Flaherty KT et al. Phase I, Dose-Escalation Trial of the Oral Cyclin-Dependent Kinase 4/6 Inhibitor PD 0332991, Administered Using a 21-Day Schedule in Patients with Advanced Cancer. Clin Cancer Res January 15, 2012 18; 568
Panobinostat	Adult: 60mg PO M-W-F x 2 weeks	DeAngelo DJ et al. Phase Ia/II, two-arm, open-label, dose-escalation study of oral panobinostat

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	Pediatric: not studied	administered via two dosing schedules in patients with advanced hematologic malignancies. Leukemia (2013) 27, 1628–1636
Pazopanib	Adult: 800mg PO qday x 14 days Pediatric: not studied	Hurwitz HI, et al. Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res. 2009 Jun 15; 15(12):4220-7
Pemetrexed	Adult: 2700mg IV over 25min once Pediatric: 1910mg/m^2 over 10min once	Abdel-Karim I et al. A phase 1 study of pemetrexed in patients with relapsed or refractory acute leukemia. Invest New Drugs 2011 April;29(2):323-31 Malempati S et al. Phase I trial and pharmacokinetic study of pemetrexed in children with refractory solid tumors: the Children's Oncology Group. J Clin Oncol. 2008 Jan 1;26(1):165
Pentostatin	Adult: 4mg/m^2 IV x 2 doses Pediatric: not studied	Product Information: NIPENT(R) IV injection, pentostatin IV injection. Hospira, Inc, Lake Forest, IL, 2007.
Pomalidomide	Adult: 4mg PO qday x 14 days Pediatric: not studied	Richardson PG et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014;123(12):1826-1832
Ponatinib	Adult: 45mg PO qday x 14 days Pediatric: not studied	Cortes MD et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. N Engl J Med 2012; 367:2075-2088
Pralatrexate	Adult: 15 mg/m² IV qweek Pediatric: not studied	Horwitz SM, et al. Identification of an active, well tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma. Blood 2012;119(18):4115-22
Rapamycin	Adult: 2mg PO qday x 14 days w/ dose adjustment to reach target serum concentration of 10-20pg/ml Pediatric: not studied	Sillaber, C., et al (2008), Evaluation of antileukaemic effects of rapamycin in patients with imatinib-resistant chronic myeloid leukaemia. European Journal of Clinical Investigation, 38: 43–52.
Regorafenib	Adult: 160 mg PO daily x 14 days Pediatric: not studied	Mross K, et al. A phase 1 dose-escalation study of regorafenib (Bay 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res 2012;18(9):2658-67

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Romidepsin	Adult: 7 mg/m² IV over 4 hours on days 1, 3, & 5 Pediatric: not studied	Amiri-Kordestani L, et al. Phase I trial of a new schedule of romidepsin in patients with advanced cancers. Clin Cancer Res 2013;19(16):4499-507(solid tumors)
Ruxolitinib	Adult: 25 mg PO BID x 14 days Pediatric: not studied	Eghtedar A, et al. Phase 2 study of the JAK kinase inhibitor ruxolitinib in patients with refractory leukemias, including postmyeloproliferative neoplasm acute myeloid leukemia. Blood 2012;119(20):4614-8
Selumetinib	Adult: 100mg PO BID x 14 days Pediatric: not studied	Jain N et al. Phase II Study of the Oral MEK Inhibitor Selumetinib in Advanced Acute Myelogenous Leukemia: A University of Chicago Phase II Consortium Trial. Clin Cancer Res Jan 2014 15;20(2): 490-98
Sorafenib	Adult: 400 mg PO BID x 14 days Pediatric: 150mg/m^2 PO BID x 14 days	Borthakur G, et al. Phase 1 study of sorafenib in patients with refractory or relapsed acute leukemias. Haematologica 2011;96(1):62-8 Widemann BC, et al. A phase 1 trial and pharmacokinetic study of sorafenib in children with refractory solid tumors or leukemias: a Children's Oncology Group Phase 1 Consortium report. Clin Cancer Res. 2012 Nov 1; 18(21):6011-22
Sunitinib	Adult: 50 mg PO qd x 14 days Pediatric: 15mg/m^2 PO qday x 14 days	Fiedler W, et al. A phase 1 study of SU11248 in the treatment of patients with refractory or resistant acute myeloid leukemia (AML) or not amenable to conventional therapy for the disease. Blood 2005;105:986–993. Dubois SG, et al. Phase 1 and pharmacokinetic study of sunitinib in pediatric patients with refractory solid tumors: a children's oncology group study. Clin Cancer Res. 2011 Aug 1; 17(15):5113-22
Temsirolimus	Adult: 15 mg/m² IV qweek x 2 doses Pediatric: not studied	Fujisaka Y, et al. A phase 1 clinical study of temsirolimus (CCI-779) in Japanese patients with advanced solid tumors. Jpn J Clin Oncol 2010;40(8):732-8
Thioguanine	Adult: 2 mg/kg PO daily x 14 days Pediatric: not studied	Micromedex

Topotecan HCl	Adult: 6 mg/m² IV daily over 30 mins on days 1, 8, 15 Pediatric: 2.4mg/m^2/d IV for 9 days	Masuda N, et al. Phase 1 and pharmacologic study of weekly bolus topotecan for advanced non-small cell lung cancer. Clin Lung Cancer 2010;11(4):271-9 (NSCLC) FDA approved: 1.5 mg/m² IV daily over 30 mins x 5 days every 21 day cycle (NSCLC) Furman WL et al. Protracted intermittent schedule of topotecan in children with refractory acute leukemia: a pediatric oncology group study. J Clin Oncol. 2002 Mar;20(6):1617-24
Trametinib	Adult: 2 mg PO qd x 14 days Pediatric: not studied	Infante JR, et al. Safety, pharmacokinetic, pharmacodynamics. And efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol 2012 13(8):773-81
Tretinoin	Adult: 150 mg/m² PO qd x 14 days Pediatric: 25mg/m^2 PO BID x 14 days	Lee JS, et al. Phase I evaluation of all-trans-retinoic acid in adults with solid tumors. J Clin Oncol 1993;11(5):959-66 Testi AM et al. GIMEMA-AIEOPAIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. Blood. 2005 Jul 15;106(2):447-53.
Vandetanib	Adult: 300mg PO qday Pediatric: not studied	Caprelsa (vandetanib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; March 2014
Vinblastine	Adult: 6mg/m^2 IV on days 1 and 15 Pediatric: same as adult	Vinblastine (prescribing information). Schaumburg, IL: APP Pharmaceuticals, LLC; October, 2011
Vincristine	Adult: 2mg IV on days 4 and 11 Pediatric: 1.5 to 2mg/m^2 IV once weekly, varies per protocol	Kantarjian, H et al (2004), Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer, 101: 2788–2801. Product Information: vincristine sulfate injection, vincristine sulfate injection. Mayne Pharma (USA) Inc., Paramus, NJ, 2004
Vinorelbine	Adult: 30mg/m^2 IV on days 1 and 8	Vinorelbine (prescribing information). New York, NY: Pfizer; February, 2012.

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	Pediatric: 20mg/m^2 IV on days 1 and 8	Shukla N, Kobos R, Renaud T, et al. Phase II trial of clofarabine with topotecan, vinorelbine and thiotepa for pediatric patients with relapsed or refractory acute leukemia. Pediatr Blood Cancer. 2014;61:431-435
Vorinostat	Adult: 400mg PO qd x 14 days Pediatric: 230mg/m^2 PO qd x 14 days	Kelly WK et al. Phase I study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced cancer. J Clin Oncol. 2005 Jun 10;23(17):3923-31 Fouladi M et al. Pediatric phase I trial and pharmacokinetic study of vorinostat: a Children's Oncology Group phase I consortium report. J Clin Oncol. 2010 Aug 1;28(22):3623-9
Methotrexate + cytarabine	Adult: MTX 200 mg/m^2 IV over 2 hours followed by 800 mg/m^2 IV over 24 hours on day 1; cytarabine 3 g/m^2 over 2 hours every 12 hours × 4 on days 2 and 3 Pediatric: not studied	Kantarjian HM, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000; 18(3): 547-61
Mitoxantrone + etoposide + cytarabine	Adult: (Mitoxantrone 6mg/m^2 IV bolus, etoposide 80mg/m^2 IV over 1hr, cytarabine 1g/m^2 IV over 6hrs) x 6 days Pediatric: mitoxantrone 12mg/m^2 IV D1,3,5; cytarabine 100mg/m^2 IV D1-10, etoposide 100mg/m^2 IV D1-5	Amadori S, et al. Mitoxantrone, etoposide, and intermediate-dose cytarabine: an effective and tolerable regimen for the treatment of refractory acute myeloid leukemia. J Clin Oncol 1991; 9(7):1210-1214 Gibson, B. E. S., et al for the United Kingdom Childhood Leukaemia Working Group and the Dutch Childhood Oncology Group (2011), Results of a randomized trial in children with Acute Myeloid Leukaemia: Medical Research Council AML12 trial. British Journal of Haematology, 155: 366–376.
Cladribine + cytarabine + mitoxantrone + filgrastim	Adult: Cladrabine 5mg/m^2 IV days 1-5, cytarabine 2gm/m^2 IV days 1-5, mitoxantrone 10mg/m^2 IV days 1-3, filgrastim 300 mcg SC days -1 through 5 Pediatric: not studied	Wierzbowska A, et al. Cladribine combined with high doses of arabinoside cytosine, mitoxantrone and G-CSF (CLAG-M) is a highly effective salvage regimen in patients with refractory and relapsed acute myeloid leukemia of the poor risk: a final report of the Polish Adult Leukemia Group.

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Clofarabine + cytarabine	Adult: Clofarabine 40mg/m^2 IV days 2-6, cytarabine 1gm/m^2 IV days 1-5 Pediatric: clofarabine 52mg/m^2 IV days 1-5, cytarabine 1gm/m^2 IV days 1-5	Faderl S, et al. Clofarabine and cytarabine combination as induction therapy for acute myeloid leukemia (AML) in patients 50 years of age or older. Blood, July 2006, 108(1):45-51 Cooper, T. M., et al (2014), AAML0523: A report from the Children's Oncology Group on the efficacy of clofarabine in combination with cytarabine in pediatric patients with recurrent acute myeloid leukemia. Cancer, 120: 2482–2489
Fludarabine + cytarabine + idarubicin + filgrastim	Adult: Fludarbine 30mg/m^2 IV days 1-4, cytarabine 2gm/m^2 IV days 1-4, idarubicin 12mg/m^2 IV days 2-4, filgrastim 200mcg SC starting day -1 through neutrophil recovery Pediatric: same as above	Estey E et al. Randomized Phase II Study of Fludarabine + Cytosine Arabinoside + Idarubicin ± All-Trans Retinoic Acid ± Granulocyte Colony-Stimulating Factor in Poor Prognosis Newly Diagnosed Acute Myeloid Leukemia and Myelodysplastic Syndrome. Blood, Apr 1999, 9(8): 2478-2484 Fleischhack, et al. (1998), IDA-FLAG (idarubicin, fludarabine, cytarabine, G-CSF), an effective remission-induction therapy for poor-prognosis AML of childhood prior to allogeneic or autologous bone marrow transplantation: experiences of a phase II trial. British Journal of Haematology, 102: 647–655.
Fludarabine + cytarabine + filgrastim	Adult: Fludarabine 30mg/m^2 IV days 1-5, cytarabine 2mg/m^2 IV days 1-5, filgrastim 300mcg SC or IV starting day -1 through neutrophil recovery Pediatric: same as above	Virchis, A et al. (2004), Fludarabine, cytosine arabinoside, granulocyte-colony stimulating factor with or without idarubicin in the treatment of high risk acute leukaemia or myelodysplastic syndromes. British Journal of Haematology, 124: 26–32. McCarthy, A.J., Pitcher, L.A., Hann, I.M. and Oakhill, A. (1999), FLAG (fludarabine, high-dose cytarabine, and G-CSF) for refractory and high-risk relapsed acute leukemia in children. Med. Pediatr. Oncol., 32: 411–415.
Azacitidine + sorafenib	Adult: Azacitidine 75mg/m^2 IV qday for 7days, sorafenib 400mg PO BID x 14 days Pediatric: not studied	Ravandi, F et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and *FLT*-3 internal tandem duplication mutation. Blood. 2013 Jun 6; 121(23): 4655-4662
Idarubicin + Bortezomib	Adult: idarubicin 8mg/m^2 IV and bortezomib	Howard DS et al. A phase I study using bortezomib with weekly idarubicin for treatment

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	1.2mg/m^2 IV on days 1,8,15 and 22 Pediatric: not studied	of elderly patients with acute myeloid leukemia. Leuk Res. 2013 Nov; 37(11):1502-8

Protocol 9226 Eligibility

I) Inclusion Criteria:

Each of the following questions (1-9) must be marked "Yes" for the patient to enroll on Protocol 9226

1) Yes ☐ No ☐ Capable of understanding the investigational nature, potential risks and benefits of the study, and able to provide valid informed consent.

Patient signed and dated consent form and HIPAA authorization.

Date: _____

Date of IRB approval of consent form: _____

2) Yes ☐ No ☐ Diagnosis of acute leukemia by WHO criteria (e.g. acute myeloid leukemia, acute lymphoblastic leukemia, acute leukemia of ambiguous origin).

3) Yes ☐ No ☐ Either: relapsed after or refractory to prior treatment with at least two regimens or lines of treatment.

Or: Prior failure of at least one regimen or line of treatment, with poor cytogenetic or other risk factors, and ineligible for other clinical trials.

4) Yes ☐ No ☐ Age ≥ 3

5) Yes ☐ No ☐ ECOG Performance status of 0-3.

6) Yes ☐ No ☐ Expectation that we can obtain about 10 million blasts from blood and/or marrow (e.g., circulating blast count of 5,000 or greater or cellular marrow with greater than or equal to 20% blasts).

7) Yes ☐ No ☐ Adequate renal and hepatic function as defined below (or more stringent depending on the individual drugs) function. Please check **yes** if patient meets all of the following criteria:

Yes ☐ No ☐ Bilirubin ≤ 1 .5 x Institutional Upper Limit of Normal (IULN) unless elevation is thought to be due to Gilbert's syndrome, hemolysis, or hepatic infiltration by the hematologic malignancy,

Yes ☐ No ☐ SGOT (AST) and SPGT (ALT) ≤ 2.5 x IULN, unless elevation is thought to be due to hepatic infiltration by the hematologic malignancy,

Yes ☐ No ☐ Alkaline Phosphatase ≤ 2.5 X ULN, unless elevation is thought to be due to hepatic infiltration by the hematologic malignancy,

Yes ☐ No ☐ Serum creatinine ≤ 2.0 mg/dL

8) Yes ☐ No ☐ Willing to use contraception.

9) Yes ☐ No ☐ Expected survival is greater than 100 days.

II) Exclusion Criteria:

Each of the following questions (10- 13) must be marked "No" for the patient to enroll on

Protocol 9226

10) Yes ☐ No ☐ Active systemic fungal, bacterial, viral or other infection, unless disease is under treatment with antimicrobials and considered controlled in the opinion of the investigator.

11) Yes ☐ No ☐ No other active cancer that requires systemic chemotherapy or radiation therapy

12) Yes ☐ No ☐ Significant organ compromise that will increase risk of toxicity or mortality.

13) Yes ☐ No ☐ Pregnancy or lactation.

Date of eligibility assessment: _____

Name of person completing form:_____Phone number:_____

Signature of person completing form:_____Date:_____

Signature of **FHCRC** Investigator:_____Date:_____

ATTACH SIGNED CONSENT AND HIPAA AUTHORIZATION FORMS, AND SEND TO STUDY COORDINATOR< FHCRC WITHIN 24 HOURS OF CONFIRMED ELIGIBILITY FOR STUDY TREATMENT.

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FAX COVER LETTER

DATE:_____

TO: Cody Hammer, Study Coordinator

FAX: (206) 288-6354

RE: RESEARCH SUBJECT REGISTRATION FORM
PROTOCOL 9226
Total # of pages (including cover): _____

FROM:_____

FAX:_____

PHONE:_____