THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

**Protocol Abstract Page**

# Phase I/II Trial of MEK Inhibitor MEK162 in Patients with Relapsed and or Refractory Acute Myeloid Leukemia and Patients with Poor Prognosis Acute Myeloid Leukemia Not Suitable for or Unwilling to Receive Standard Therapy.

2013-0116

## Core Protocol Information

| | |
|---|---|
| **Study Chairman:** | Farhad Ravandi-Kashani |
| **Department:** | Leukemia |
| **Phone:** | 713-792-7305 |
| **Unit:** | 428 |
| **Full Title:** | Phase I/II Trial of MEK Inhibitor MEK162 in Patients with Relapsed and or Refractory Acute Myeloid Leukemia and Patients with Poor Prognosis Acute Myeloid Leukemia Not Suitable for or Unwilling to Receive Standard Therapy. |
| **Protocol Phase:** | Phase I/Phase II |
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## Abstract

**Objectives:**

### Primary Objective(s) for Phase I and II

**Phase 1**

-- To determine the MTD/RP2D (recommended phase 2 dose) of MEK 162 in subjects with advanced Leukemias.

**Phase II**

-- To assess the anti-leukemic activity of MEK 162 (overall response including CR and CRi) in older subjects with newly diagnosed KRAS/NRAS mutant poor prognosis AML, who are not candidates for intensive chemotherapy.

### Secondary Objective(s) for Phase I and II

**Phase I**

-- To determine the safety of MEK 162 in patients with relapsed and/or refractory Leukemias.
-- To assess the PK of MEK 162 in patients with Leukemias.
-- To assess anti-leukemic activity (CR and CRi) of MEK 162 in patients with leukemia.

**Phase II**

-- To determine the safety and tolerability of MEK 162 in older subjects with newly diagnosed KRAS/NRAS mutant poor prognosis AML.

## Exploratory Objective(s) for Phase I and II (if necessary)

## Phase I and II

- To explore potential molecular variations in leukemia blasts (e.g. FLT3, K-RAS, N-RAS and other known mutations (IDH1, IDH2, DNMT3A and others) or gene copy number in candidate genes) that may be predictive of differences in response to MEK 162.

The dose finding phase I portion allows for any patient with advanced AML/MDS/ALL/CMML who meets the eligiblity criteria as there is a possibility of activity in partients with those disorders with aberrant signaling along the RAF/RAS/MAPK signaling pathway although the main intention of the phase I is to determine whether the drug is reasonably safe. In the phase II portion of the study Array was only interested in determining the activity in patients with known aberrant pathway (i.e. mutated RAS) as this can also be potentially used as a marker for patient selection. Clearly, if we see significant responses in other patients in the phase I and particularly if it is determined that this activity is related to aberrant RAF/RAS/MAPK signaling, future trials will be conducted in a broader poulation and more dependent of demonstrating aberrant pathway signaling.

**Rationale: (Be as concise as possible)**

Acute myeloid leukemia (AML) is the cause of approximately 1.2% of all cancer deaths in the US with an annual incidence rate of 2.2 per 100,000 and approximately 9,200 new cases per year, representing approximately 90% of all acute leukemias in adults.The most important predictor of outcome after relapse is the length of the initial complete remission.3 For patients whose initial CR lasted greater than 2 years, repeating the initial regimen can result in a 50-60% CR rate, whereas those whose CR was less than 1 year can expect only a 10-20% CR rate with such an approach. Prognosis of patients with refractory disease (i.e. no CR after two courses of induction) is quantitatively similar to those with the short first CR. These patients should be offered investigational therapies. In patients who relapse after an allogeneic transplant, the prognosis also depends on the length of CR.5,6 Donor lymphocyte infusions can produce remissions in some patients. Investigational agents are also indicated in this setting.

A number of risk factors such as white cell count at presentation have been identified that predict the length of remission and the possibility of long-term survival. However, Cytogenetics and molecular features at presentation have been established as the most important factor predicting long-term disease-free survival. Although advancing age has been established as a negative risk factor, it is likely that this relates to other features such as higher incidence of poor risk Cytogenetics, (multi-drug resistance) MDR gene over-expression, and existence of antecedent hematological disorders.

GSK1120212 is a potent and selective allosteric inhibitor of MEK 1 and 2 kinases. In vitro, GSK1120212 inhibited proliferation of myeloid cell lines selectively as compared to lymphoid cell lines. A 2 part study of a single daily oral dosing regimen was conducted to define the recommended Phase 2 dose, evaluate pharmacokinetics, and assess preliminary activity in patients with relapsed or refractory AML, MDS, ALL or CMML. Subjects with WBC< 30,000/uL who met hepatic, renal and cardiac function criteria were eligible for participation. GSK1120212 was given orally, once daily in the following dose cohorts: 3mg loading dose followed by 1mg/day (n=3), 1mg/day without loading dose (n=1), and 2mg/day without loading dose (n=9). The loading dose was discontinued after cohort 1, based on findings in the phase I solid tumor study.

MEK162, previously named ARRY 438162, is a potent and selective allosteric, ATP non-competitive inhibitor of Mek1/2 that is active in inhibiting pERK and growth of BRAF mutant cancer cells in the low nanomolar range. MEK162 is currently being investigated as a single agent and in combination with PI3K or RAF inhibitors in patients with selected advanced or metastatic solid tumors, including biliary cancer, colorectal cancer and melanoma. Four phase I/Ib studies exploring MEK162 in combination with RAF and PI3K inhibitors in patients with advanced RAS/RAF and PIK3CA mutated tumors are ongoing.

The dose of 45 mg BID is considered safe and efficacious and is the dose used in an ongoing Phase 2 study in cancer patients. The maximum tolerated dose (MTD) of MEK162 is 60 mg BID.

**Eligibility: (List All Criteria)**

**Inclusion:**

1) PHASE I -- a. Primary or secondary AML according to WHO classification, with relapsed or refractory disease or newly diagnosed older subjects (greater than or equal to 65 years of age), not candidates for intensive chemotherapy; b. Subjects with MDS, IPSS Int-2 or high risk (RAEB-2 only, i.e. greater than or equal to 10% blast) who are resistant or intolerant to standard treatment and are not candidates for transplantation; c. Subjects with ALL, relapsed, refractory or intolerant to standard treatment and for whom no effective treatment options are available.

2) Age greater or equal to 18 years.

3) Patients should be willing and able to give informed consent.

4) Eastern Cooperative Group (ECOG) PS less than or equal to 2.

5) PHASE II -- Patients aged 60 and older with newly diagnosed primary or secondary AML according to WHO classification, without any prior therapy for AML with the exception of (a) emergency Leukapheresis and (b) emergency treatment for hyperleukocytosis with hydroxyurea that is allowed until 24 hours before start of the trial treatment. Note: Prior therapy for preexisting hematological condition e.g. MDS or MPD, including but not limited to hypomethylating agents is allowed until at least 2 weeks have elapsed from completion of that agent before the first dose of MEK 162. Patients with relapsed AML, and relapsed MDS and CMML, after prior hypomethylating therapy are also eligible to participate

6) Patients with untreated AML must meet at least one of the following conditions: a. Age greater than or equal to 75 years; b. Age greater or equal to 60 and less than 75 years with at least one of the following poor prognostic factors: i. Secondary AML, as determined by known and documented exposure to chemotherapy or radiation therapy; ii. antecedent history of MDS or myeloproliferative disorder according to WHO criteria for at least 3 months prior to trial entry; iii. unfavorable cytogenetic abnormalities including chromosome 5 and 7 as well as complex; iv. ECOG Performance status 2.

7) Patients are willing and able to give informed consent. (Phase II only)

8) Only patients with mutated RAS (KRAS and NRAS) mutations are eligible to participate. (Phase II only)

9) Adequate cardiac function defined as: --left ventricular ejection fraction (LVEF) greater than or equal to 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram; -- QTcF interval less than or equal to 480 ms. (Phase II only)

**Exclusion:**

1) PHASE I and II -- Administration of any antineoplastic therapy within at least 4 weeks (cytotoxic chemotherapy) or 2 weeks (biological and targeted therapy; hypomethylating agents are considered to be biological therapy) of that therapy of the first MEK 162/MEK 162 dose; except the use of hydroxyurea which can be administered up to 5 g/day up to 24 hours before the initiation of the study drug.

2) Patients should not have received an investigational agent for at least 2 weeks prior to the first study drug dose.

3) Clinical evidence of active CNS leukemia requiring active therapy; prior CNS leukemia

well-controlled by ongoing therapy is allowed.

4) Active and uncontrolled infection including but not limited to known infection with HIV, active hepatitis B, or hepatitis C.

5) Major surgery within two weeks prior to trial entry.

6) Liver function tests above the following limits at the screening: total bilirubin > 1.5 x ULN unless related to Gilbert's syndrome or hemolysis, AST and/or ALT > 2.5 X ULN, or for subjects with liver involvement AST and/or ALT > 5 x ULN.

7) Serum creatinine > 1.5 x ULN and/or Creatinine Clearance (CrCl) < 30 mL/min at screening (calculation according to Cockroft & Gault formula).

8) Pregnant or nursing (lactating) women;

9) Female patients of childbearing ptential and male patients with partners of childbearing potential who are not willing ot use highly effective methods of contraception throughout the study and for 1 month after study drug discontinuation. Highly effective contraception methods include: **Total abstinence; or **Male or female sterilization; **Combination of any two of the following (a+b or a+c or b+c); a. Use of oral, injected, or implanted hormonal methods of contraception; b. Placement of an intrauterine device (IUD) or intrauterine system (IUS); c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

10) Female patients with reproductive potential who do not have a negative blood or urine prgenancy test at screening;

11) History of significant difficulty swallowing, malabsorption or other chronic gastro-intestinal disease or conditions that may hamper compliance and/or absorption of the tested product.

12) Has significant cardiac conduction abnormalities and/ or pacemaker or any of the following criteria: -- History of acute coronary syndromes (including myocardial infarction, unstable angina, CABG, coronary angioplasty, or stenting) <6 months prior to screening, --Symptomatic chronic heart failure; evidence of clinically significant cardiac arrhythmias and/or conduction abnormalities < 6 months prior to screening --Uncontrolled arterial hypertension, defined as BP > 140/100 mmHg (average of 3 consecutive readings)

13) History or current evidence of central serous retinopathy (CSR), retinal vein occlusion (RVO).

14) Any ophthalmopathy visible at screening that would be considered a risk factor for CSR or RVO by the ophthalmologist (e.g. uncontrolled glaucoma or ocular hypertension, uncontrolled diabetes mellitus, history of hyperviscosity or hypercoagulability syndromes).

15) Subjects with active other tumors, except early stage squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or cervical intraepithelial neoplasia (CIN).

16) Patients who have neuromuscular disorders that are associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

17) Patients who are planning on embarking on a new strenuous exercise regimen after first dose of study treatment. NB: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CK levels should be avoided while on MEK162 treatment.

18) Impairment of gastrointestinal function or gastrointestinal disease (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection)

**Are patients <18 years of age eligible to participate in this study?** ○ **Yes** ● **No**

**Studies that include children must meet the criteria for inclusion.**
http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc
http://www.hhs.gov/ohrp/policy/populations/children.html

**Studies that exclude children must have appropriate justification. Please select all that apply:**

Other:

Please Specify:
It is felt not justifiable to treat pediatric patients with a non-intensive regimen designed for the elderly AML population as they do reasonably well with standard intensive chemotherapy regimens.

**Are participants >65 years of age eligible to participate in this study?** ● **Yes** ○ **No**

**Are pregnant women eligible to participate in this study?** ○ **Yes** ● **No**

**Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?**
○ **Yes** ● **No**

**Disease Group:**

Leukemia

**Treatment Agents/Devices/Interventions:**

MEK162

**Proposed Treatment/Study Plan:**

Is treatment assignment randomized? ○ **Yes** ● **No**

Is this a blinded or double-blinded study? ○ **Yes** ● **No**

**Table 4-1: Treatment and treatment schedule**

| Study drug | Pharmaceutical form and route of administration | Dose | Frequency |
|---|---|---|---|
| MEK162 | Caplets for oral administration | 30 – 45 mg as recommended by Phase I | BID |

**Table 5-1: Visits**

| | Screening | Cycle 1 | | | | | Cycle 2 and Beyond | | | | | OSA[g] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day (+/- 2 days)** | -14 to -1 | 1 | 4 | 8 | 13-27 | 28 | 1 | 4 | 8 | 13-27 | 28 | |
| MEK162 | | ← | | | | | | | | | → | |
| Written informed consent | X | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | |
| Physical Exam [c f] | X | X | | | | | X | | | | | X |
| ECOG Performance Status [c] | X | X | | | | | X | | | | | X |
| Vital signs [c] | X | X | X | X | | | X | X | X | | | X |
| Adverse events assessment | | X | X | X | X | X | X | X | X | X | X | X |
| Medication history | X | | | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology [c] | X | X | X | X | | | X | | | | | |
| Serum chemistry [c] | X | X | X | X | | | X | | | | | |
| CK and troponin [d] | X | | | | | | | | | | | |
| Serum pregnancy test [e] | X | | | | | | X | | | | | |
| Coagulation profile | X | | | | | | | | | | | |
| Liver Function tests [c] | X | X | X | X | | | X | | | | | X |
| Urinalysis [c] | X | | | | | | X | | | | | |
| 2D Echo or MUGA scan [a] | X | | | | | x | | | | | | |
| | | | | | | | | | | | | |
| Bone marrow examanation | X | | | | | X | | | | | | X[g] |
| Cytogenic and molecular assessment | X | | | | | X | | | | | | X[g] |
| Ophthalmologic exam [b c] | X | | | | | | X | | | | | |
| ECG[h] | X | | | | | X | | | | | | X |

FOOTNOTES:

a: Echo or MUGA may be performed at screening within -28 to -1, after one month of treatment of MEK162 and every two to three months during treatment thereafter.

b: Ophthalmic examination will include slit lamp examination, visual acuity testing, visual field testing, intraocular pressure (IOP) and indirect fundoscopy with attention to retinal abnormalities, especially CSR and RVO. For patients with clinical suspicion of CSR or RVO, additional assessments of fluorescein angiography and/or optical coherence tomography and Electroretinogram (ERG) are recommended.

c: The assessments should be performed monthly.

d: CK and troponin will be performed at the same timepoints as the hematology collections as outlined above. Follow up for total creatine kinase (CK) >/equal to 3 X ULN will include weekly assessment of isoenzymes and myoglobin in blood/or urine, and troponin as applicable.

e: Bone marrow and cytogenic assessment at the end of the study can be waved depending on clinical situation.

f: DLT will be assessed throughout the time the participant remains on study drug.

g: Off study Assessment will be performed within 30 days of the last study drug dose

h: ECG during screening, at day 28, and OSA

Laboratory assessments and vitals recording can be performed at outside facility with the records provided to the study coordinator. However, all outside labs will need to be reviewed, signed and dated by the Principal Investigator (PI) or treating physician (listed on the Delegation of Authority) prior to submission to the electronic medical record. The PI or treating physician should appraise abnormal lab results and determine/document clinical significance.

All visits have a flexibility of +/- 2 days.

## Treating the Patient:

MEK162 will be dispensed by the pharmacist or designee at the Investigator's institution. Patients will receive MEK162 on an outpatient basis unless the patient is inpatient for other reasons. Patients must be instructed to bring any empty study drug bottles and unused study medication with them at the next visit for drug accountability and compliance checks. When returned, unused study medication will be

destroyed in accordance with institutional policy.

## Criteria for dose escalation and determination of MTD (phase I only).

This is a two-part trial to determine dosing and efficacy in leukemia patients of MEK 162. Phase I will determine MEK 162 in dosing subjects with advanced leukemias. The phase I part of the trial has a 3+3 dose escalation design, with 3 subjects in each cohort, using a fixed (15mg) dose escalation scheme, based on the occurrence of DLTs. At the each dose level up to 6 subjects will receive MEK 162 orally twice a day on days 1 to 28 of a 28 day cycle.

## Dose escalation (Phase I only)

-- If 0/3, 0/4, 0/5, or 0/6 evaluable subjects exhibits a DLT after one 28-day cycle, then the next subject will be treated at the next DL.
-- If one subject exhibits a DLT, the cohort will be expanded up to 6 subjects.
-- If one out of six evaluable subjects exhibits a DLT, then the next subject will enroll at the next DL.
-- If more than one out of three to six evaluable subjects exhibit a DLT, then the dose level below it will be determined as MTD.
-- If more than 1 out of 3 to 6 evaluable subjects exhibit a DLT during the first DL then reduced dose level (RDL) will be investigated.

Dose escalations will proceed no sooner than 4 weeks after the last subject in the cohort has begun therapy.

**Table 4-2: Phase I Dose Escalation**

| Number of subjects with DLT during the first cycle | Number of subjects in DLT Analysis Set | Action |
|---|---|---|
| 0 | 3 to 6 | Escalate to the next DL |
| 1 | 3 to 6 | If less than 6 subjects, complete the cohort to 6 subjects |
| 1 | 6 | Escalate to the next DL |
| > 1 | 3 to 6 | DL deemed not tolerable, add subjects up to a total of 9 subjects in the DL immediately below this one (which will be the MTD level) |

**Table 4-3: Dose-limiting toxicity (Phase I only)—criteria for determining dose limiting toxicity.**

A toxicity is only considered to be a dose-limiting toxicity, "DLT", when it is determined that the toxicity is related to the study drug, MEK162.

| Toxicity | Any of the following criteria: |
|---|---|
| **TOXICITY** | **DLT CRITERIA** |
| Skipped/ delayed dose | The inability to administer MEK162 on ≥ 75% of scheduled treatment days during cycle 1 due to unresolved adverse event of any grade and considered related to the study drug. |
| Recurrent toxicity | The recurrence of toxicity CTCAE Grade ≥ 2 with the same severity following initial interruption of treatment, resolution and resumption of treatment at the same dose. |
| Cardiac disorders | Asymptomatic decrease of LVEF > 10% compared to baseline and the LVEF is below the institution's LLN<br>Left ventricular systolic dysfunction CTCAE Grade ≥ 3<br>Other cardiac disorders CTCAE Grade ≥ 3 |
| Pulmonary disorders | Interstitial lung disease or pneumonitis ---<br>Discontinue the study drug. |
| Vascular disorders<br>Hypertension | Persistent hypertension CTCAE Grade ≥ 3 requiring more than one drug or more intensive therapy than previously |
| Skin and subcutaneous tissue disorders: a<br>Asymptomatic rash and/or photosensitivity<br>Symptomatic rash and/or photosensitivity | Asymptomatic rash / photosensitivity CTCAE Grade 3 lasting > 48 hrs despite skin toxicity treatment<br><br>Symptomatic rash/photosensitivity CTCAE Grade 3 despite skin toxicity treatment |
| Metabolism and nutrition disorders:<br>Hyperglycemia | Hyperglycemia CTCAE Grade ≥ 3 for > 7 consecutive days despite anti-diabetic treatment<br>Hyperglycemia grade 4<br>Hyperglycemia leading to diabetic keto-acidosis, hospitalization for intravenous insulin infusion, or non-ketotic coma. |
| Metabolism and nutrition disorders:<br>Calcium-phosphate heterostasis tCa x Pi increase | tCa x Pi > 55 mg2/dL2 |
| Gastrointestinal disorders a | Diarrhea CTCAE Grade ≥ 3 ≥ 48 hrs, despite the use of anti-diarrhea therapy |
| | Nausea/ vomiting CTCAE Grade ≥ 3 ≥ 48 hrs, despite the use of anti-emetic therapy |
| Investigations b | Blood bilirubinc CTCAE Grade 2 for > 7 consecutive days |
| | Blood bilirubinc CTCAE Grade ≥ 3 - Discontinue the investigational drug |
| | AST or ALT CTCAE Grade ≥3 in conjunction with blood bilirubinc CTCAE Grade ≥ 2 of any duration |

| | |
|---|---|
| | AST or ALT CTCAE Grade ≥ 2 for > 7 consecutive days AST or ALT CTCAE Grade 3 or higher |
| | Serum alkaline phosphatase CTCAE Grade 4 |
| | Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 3 > 7 consecutive days |
| | Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 4 |
| | Serum creatinine CTCAE Grade ≥ 3 |
| | Serum CK/CPK CTCAE Grade > 3 for > 14 consecutive days if clinically significant (symptomatic)<br>Serum CK/CPK CTCAE Grade 4 for > 14 consecutive days |
| | ECG QTc interval prolonged CTCAE ≥ Grade 3 |
| Eye disorders-Retinopathy CSR and CSR like events | Retinopathy – CSR and CSR-like events CTCAE Grade 3 for > 14 consecutive days confirmed by ophthalmologic examination<br>Retinopathy – CSR and CSR-like events CTCAE Grade 4, confirmed by ophthalmologic examination |
| Eye disorder —Retinal Vein Occlusion | CTCAE Grade ≥ 1 confirmed by ophthalmologic examination |
| Eye disorders - (other specify) | CTCAE Grade 3 > 14 consecutive days<br>CTCAE Grade 4 |
| Other hematologic & non-hematologic toxicities | Any other CTCAE Grade ≥ 3 toxicity **except:**<br>Lymphocyte count decreased (lymphopenia) CTCAE Grade ≥ 3 unless clinically significant |

[a] Patients will initially not receive prophylactic treatment for skin toxicity or nausea/vomiting during cycle 1. However, prophylactic treatment may be initiated in all patients at the dose level where these toxicities have been observed and in all further patients if at least 1 patient has experienced skin toxicity or nausea/ vomiting ≥ CTCAE Grade 3 or if at least 2 patients experienced skin toxicity or nausea/ vomiting ≥ CTCAE Grade 2. However anti-emetics may be applied for treatment if the patient has experienced nausea/vomiting CTCAE Grade ≥ 1, at the discretion of the physician.
[b] For any CTCAE Grade 4 or any CTCAE Grade 2 hepatic toxicity that does not resolve within 7 days to CTCAE Grade ≤ 1 (or CTCAE Grade ≤ 2 if liver infiltration with tumor present), an abdominal CT scan has to be performed to assess if it is related to disease progression.
c Refers to total bilirubin

## Follow-up for dose-limiting toxicities (Phase I only)

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed regularly (as clinically indicated) until resolution or stabilization of the event, whichever comes first.

If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. However, the patient will continue to be followed for toxicity as previously described. All patients will be followed for adverse events and serious adverse events for 30 days following the last dose of MEK162 unless the patient received further cytotoxic chemotherapy. In this case, only those adverse events and serious adverse events believed by the investigatory to have a causal relationship to the study medication will be captured.

## Dosing modifications

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustment to dose level 1 (30 mg bid) is permitted in order to allow the patient to continue the study drug. An individual patient may have one dose reduction to 30 mg bid. This is the lowest dose permitted on the study and doses below 30 mg bid are not permitted. In case of toxicity, the dose should be held until resolution to grade 1 and then restarted at 30 mg bid.

Missed/skipped doses will not be made up (i.e the patient should not double their dose if the previous dose was missed). When the toxicity that resulted in a dose reduction improves to Grade 1 or less, the

dose can be re-escalated a the investigators discretion provided there are no other concomitant toxicities. However, no dose re-escalation is allowed for dose reductions that were due to left ventricular dysfunction.

**Table 4-4: Dose reduction steps for MEK162**

| Dose reduction* | | |
|---|---|---|
| | Starting dose level 1 | Dose level – 1 |
| MEK162 | Ph I: 30 mg bid<br>Ph II: TBA by MTD by Ph I | Ph I: **<br>Ph II: **TBD MTD from phase I |
| *Dose reduction should be based on the worst toxicity demonstrated | | |
| **Dose reduction below 30 mg is not allowed; patients on 30 mg bid who need dose adjustment may have their dose held and then re-introduced at the same dose level | | |

## End of Study Treatment

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Pregnancy
- Non-compliance

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information. Patients may be withdrawn from the study prematurely for one of the following reasons:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- New cancer therapy
- Disease progression
- Treatment duration completed as per protocol

## Study evaluation completion

As a general rule, if a patient discontinues study drug and later is prematurely withdrawn from the study, the reasons for study evaluation completion may include the following:

- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- New cancer therapy
- Clinically significant disease progression

For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

**Study Enrollment:**
The study population for this research will consist of participants from:

Only at MDACC

**Estimated Accrual:**

| | |
|---|---|
| Total Accrual at MDACC: | Phase I 15 + Phase II 42 |
| Estimated monthly accrual at MDACC: | 3 |

**Accrual Comments:**
57

**Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)?** No

**Is this an NCI-Division of Cancer Prevention Protocol (DCP)?** No

**Statistical Considerations:**

The primary endpoint is the overall response (CR+CRi) after one or two cycles of treatment. The historical data suggested the overall response rate is 5%. With the assumption that the improved overall response rate to be 20%, it is estimated that a total of 42 evaluable patients will yield 91% power at a significance level of 5% based on chi-square test.

The overall response (CR+CRi) denoted as OR, and toxicity (DLT definition in phase I), denoted as TOX, will be monitored simultaneously by Bayesian stopping boundaries calculated based on beta-binomial distribution. Independence is assumed between OR and TOX. There are no historical data available. The current regimen will be considered promising if the OR rate is at least 20% and the TOX rate is below 30%. The prior probabilities of OR and TOX for the regimen are modeled by beta distributions (*Beta*(0.4, 1.6) and *Beta*(0.6, 1.4), respectively). Denoting the probabilities of the OR rate and TOX by $\{\theta_{OR}, \theta_{TOX}\}$, the following decision criteria will be applied:

1) stop if $\text{Prob}\{\theta_{OR} < 0.2 \mid \text{data}\} > 0.98$, and
2) stop if $\text{Prob}\{\theta_{TOX} > 0.3 \mid \text{data}\} > 0.85$

Patients will be monitored by a cohort size of 6 according to the following stopping boundaries for OR and toxicity. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M. D. Anderson Cancer Center (MDACC) was used to generate the futility/toxicity stopping boundaries and the OC table.

**Table** 7-2. Stopping boundaries for overall response (OR) and toxicity

| Number of patients evaluated | Stop the trial if there are this many response | Stop the trial if there this many toxiciti |
|---|---|---|
| 6 | Never stop | 4-6 |
| 12 | 0 | 6-12 |
| 18 | 0 | 8-18 |
| 24 | 0-1 | 10-24 |
| 30 | 0-2 | 12-30 |
| 36 | 0-2 | 14-36 |

**Table 7-3.** Operating characteristics of efficacy and safety monitoring

| True Toxicity Rate | True OR Rate | Prob (stop the trial early) |
|---|---|---|
| 0.1 | 0.05 | 0.85 |
| | 0.1 | 0.5 |
| | 0.15 | 0.24 |
| | 0.2 | 0.1 |
| | 0.25 | 0.04 |
| 0.2 | 0.05 | 0.86 |
| | 0.1 | 0.52 |
| | 0.15 | 0.27 |
| | 0.2 | 0.14 |
| | 0.25 | 0.08 |
| 0.3 | 0.05 | 0.89 |
| | 0.1 | 0.65 |
| | 0.15 | 0.46 |
| | 0.2 | 0.37 |
| | 0.25 | 0.32 |
| 0.4 | 0.05 | 0.96 |
| | 0.1 | 0.86 |
| | 0.15 | 0.79 |
| | 0.2 | 0.75 |
| | 0.25 | 0.74 |

## Populations for analysis

**ITT population:** consists of all patients who received at least one dose of study drug.

**Safety population**: consists of all enrolled patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

Please note: the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no

post-treatment safety data of any kind would be excluded from the safety population.

**Per protocol population:** consists of all randomized patients who received at least one dose of the study drug and had no major protocol violations. The per protocol patient population will be identified prior to database lock.

**MTD population:** consists of all patients who either received study drug and had sufficient safety evaluations or discontinued due to unacceptable toxicity and have received at least approximately 75% doses of first cycle of therapy. The MTD patient population will be identified prior to database lock.

**Efficacy population**: consists of all patients treated at MTD who meet the requirements for recruitment into the expansion phase. The primary endpoint is overall response rate (ORR). The ORR will be estimated along with the exact 95% confidence interval.

## Patient demographics/other baseline characteristics

Demographics and other baseline data populations. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

## Treatments (study drug, concomitant therapies, compliance)

Concomitant medications and significant non-drug therapies prior to and after the start of MEK162 will be summarized.

### Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
Not Applicable

Please explain:
This is a Phase I/II study that is not randomized or blinded.

### Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? Yes

Provide a summary or schedule of interim analysis.

Please refer to the designed described in the statistical considerations

### Protocol Monitoring Plan:

This study will be monitored by the MD Anderson IND Office and a protocol-specific monitoring plan will be followed.

### Intellectual Property:

1. Does this study include any agents, devices, or radioactive compound (or drug) manufactured at MD Anderson Cancer Center or by a contract — No

manufacturer?

**Investigational New Drugs (IND):**

Does this protocol require an IND? Yes

Who is the IND Holder/Regulatory Sponsor?
MDACC
IND Number: 121255

Please "Compose" an Investigator's Brochure Cover Letter. For technical assistance, contact the PDOL Help Desk, 713-745-7365.

**Investigational Device (IDE):**

Does this study utilize an Investigational Device? No

**Sponsorship and Support Information:**

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: Array
Support Type: Industry Funding

This Sponsor/Supporter/Granting Agency will receive data.

**Radioactive Material:**

| | |
|---|---|
| Does this study involve the administration of radioisotopes or a radioisotope labeled agent?<br>Click here for help | No |

**Biosafety:**

Does this study involve the use of Recombinant DNA Technology? No

Does this study involve the use of organisms that are infectious to humans? No

Does this study involve human/animal tissue other than blood derived hematopoietic stem cells? No

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

**Laboratory Tests:**

Is there any biomarker testing in this study being used to determine patient/participant eligibility,

treatment assignment, or management of patient/participant care?

● Yes

○ No

○ Not Applicable For This Protocol

Please provide the name of the test(s), the purpose of the test, the performing laboratory identification and contact information, and confirm that the testing lab is CLIA certified (may attach a certificate or provide a certificate number).

Mutated RAS

**Manufacturing:**

| | |
|---|---|
| Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study? | No |

**Student/Trainee Information:**

| | |
|---|---|
| Is this research being conducted as a partial fulfillment for completion of a degree? | No |

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

**Protocol Page**

# Phase I/II Trial of MEK Inhibitor MEK162 in Patients with Relapsed and or Refractory Acute Myeloid Leukemia and Patients with Poor Prognosis Acute Myeloid Leukemia Not Suitable for or Unwilling to Receive Standard Therapy. 2013-0116

## Core Protocol Information

| | |
|---|---|
| **Short Title** | Phase I/II MEK162 relapsed and/or refractory AML and Poor prognosis, not suitable for or unwilling to receive standard therapy |
| **Study Chair:** | Farhad Ravandi-Kashani |
| **Additional Contact:** | Amiben B. Patel<br>Andrea L. Booker<br>Leukemia Protocol Review Group |
| **Department:** | Leukemia |
| **Phone:** | 713-792-7305 |
| **Unit:** | 428 |
| **Full Title:** | Phase I/II Trial of MEK Inhibitor MEK162 in Patients with Relapsed and or Refractory Acute Myeloid Leukemia and Patients with Poor Prognosis Acute Myeloid Leukemia Not Suitable for or Unwilling to Receive Standard Therapy. |
| **Protocol Type:** | Standard Protocol |
| **Protocol Phase:** | Phase I/Phase II |
| **Version Status:** | Terminated 06/06/2019 |
| **Version:** | 15 |
| **Submitted by:** | Andrea L. Booker--12/29/2017 10:56:16 AM |
| **OPR Action:** | Accepted by: Julie Arevalo -- 1/4/2018 3:24:51 PM |

**Which Committee will review this protocol?**

(•) The Clinical Research Committee - (CRC)

## Protocol Body

Array MEK 162 Ravandi Revised - final 11-24-2015- LB.doc

# MEK162 Investigator-initiated Protocol Template
# Phase I/II Trial of MEK Inhibitor MEK162 in Patients with Relapsed and or Refractory Acute Myeloid Leukemia and Patients with Poor Prognosis Acute Myeloid Leukemia Not Suitable for or Unwilling to Receive Standard Therapy.

Study Title: Phase I/II MEK162 relapsed and/or refractory AML and Poor prognosis, not suitable for or unwilling to receive standard therapy.

Array BioPharma Inc. Study #: CMEK162XUS02T

Institutional Study #: 2013-0116

Investigator Name: Farhad Ravandi, MD

Version #: 8

# Contents

# LIST OF TABLES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase/glutamic pyruvic transaminase/GPT |
| AST | aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT |
| b.i.d. | *bis in diem*/twice a day |
| CRD | Clinical Research and Development |
| CRF | Case Report/Record Form |
| CRO | Contract Research Organization |
| ECG | electrocardiogram |
| i.v. | intravenous(lV) |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IMS | Integrated Medical Safety |
| IRB | Institutional Review Board |
| IVRS/IWRS | Interactive Voice Response System/Interactive Web Response System |
| o.d. | *omnia die*/once a day |
| p.o. | *per os*/by mouth/orally |
| REB | Research Ethics Board |
| SAE | serious adverse event |
| SOP | Standard Operating Procedure |
| OSA | End of Study Assessment |
| ORR | Overall response rate |

# 1 INTRODUCTION

## 1.1 Background

### 1.1.1 Overview of acute myeloid leukemia (AML)

Acute myeloid leukemia (AML) is the cause of approximately 1.2% of all cancer deaths in the US with an annual incidence rate of 2.2 per 100,000 and approximately 9,200 new cases per year, representing approximately 90% of all acute leukemias in adults.1 The incidence rises with age; genetic predisposition, drug and environmental exposures and occupational factors may have a role in its genesis.2 Standard therapy of AML includes remission induction with regimens consisting of ara-C and an anthracycline followed by consolidation with similar regimens.1 The most important predictor of outcome after relapse is the length of the initial complete remission.[3] For patients whose initial CR lasted greater than 2 years, repeating the initial regimen can result in a 50-60% CR rate, whereas those whose CR was less than 1 year can expect only a 10-20% CR rate with such an approach.[1] Prognosis of patients with refractory disease (i.e. no CR after two courses of induction) is quantitatively similar to those with the short first CR.[1] These patients should be offered investigational therapies.[1,4] In patients who relapse after an allogeneic transplant, the prognosis also depends on the length of CR.[5,6] Donor lymphocyte infusions can produce remissions in some patients.[7] Investigational agents are also indicated in this setting.[4]

A number of risk factors such as white cell count at presentation have been identified that predict the length of remission and the possibility of long-term survival. However, cytogenetics and molecular features at presentation have been established as the most important factor predicting long-term disease-free survival.[8,9] Although advancing age has been established as a negative risk factor, it is likely that this relates to other features such as higher incidence of poor risk cytogenetics, (multi-drug resistance) MDR gene over-expression, and existence of antecedent hematological disorders.[10-12]

### 1.1.2 MEK inhibitors in AML and other hematological malignancies

GSK1120212 is a potent and selective allosteric inhibitor of MEK 1 and 2 kinases. In vitro, GSK1120212 inhibited proliferation of myeloid cell lines selectively as compared to lymphoid cell lines. A 2 part study of a single daily oral dosing regimen was conducted to define the recommended Phase 2 dose, evaluate pharmacokinetics, and assess preliminary activity in patients with relapsed or refractory AML, MDS, ALL or CMML. Subjects with WBC< 30,000/uL who met hepatic, renal and cardiac function criteria were eligible for participation. GSK1120212 was given orally, once daily in the following dose cohorts: 3mg loading dose followed by 1mg/day (n=3), 1mg/day without loading dose (n=1), and 2mg/day without loading dose (n=9). The loading dose was discontinued after cohort 1, based on findings in the phase I solid tumor study.

Fourteen subjects (10 with AML, 2 MDS transformed to AML, 1 MDS, 1 ALL) entered the trial. Eight were male, and median age was 65 years (range 33 to 85). Pharmacokinetic analysis showed that, upon repeat dosing, GSK1120212 exposure increased in a dose-proportional manner, had a small peak:trough ratio of approximately 4 and an effective half-life of approximately 7.7 days. Steady state concentrations were reached by day 15. Both single and repeat dose pharmacokinetics of GSK1120212 appeared to be similar to a phase I study in patients with solid tumors. Systemic exposure exceeded concentrations that inhibited in vitro leukemic cell proliferation. At the 2mg/day dose level (n=9), drug-related adverse events were diarrhea (7 overall; 6-Grade 1/2, 1-Grade 3), rash (3-Grade 1/2), fatigue (4-Grade 1/2), visual changes (3 Grade 1/2). One subject experienced a Grade 2 reversible serous retinopathy associated visual changes which resolved after drug discontinuation. One dose limiting toxicity was seen in a subject with disease-related Grade 4 thrombocytopenia and pneumonia who experienced a Grade 5 cerebrovascular accident possibly related to drug. One subject in the 2mg/day cohort achieved a CR; peripheral blast count was reduced from 30% at baseline to 0% and bone marrow blast count was reduced from 50% at baseline to 3%. During this time, platelet count increased from 48K to a maximum of 276K. Initial salutary effect was seen after 2 weeks on therapy and duration of CR was 4 weeks bone marrow blast count was 3% and 5%, respectively, at the beginning and end of the 4 week CR duration.

MSC1936369 is a selective non-competitive inhibitor of MEK1/2 with anti-proliferative activity in leukemia cell lines and in human tumor xenograft models with activation of mitogen-activated protein kinase (MAPK) signaling. The preliminary data of the safety run-in part of the phase II trial, in which the primary objective was to determine the maximum tolerated dose

(MTD) for different dosing schedules (S) has been presented. Methods: MSC1936369 was administered orally twice per day (BID), either on days 1–5, 8–12, 15–19 and 22–26 (S1) or on days 1–21 (S2) of a 28-day cycle. Dose escalation within each S followed a modified Fibonacci scheme with 3+3 cohorts. PK samples and peripheral blood leukemia blasts for the measurement of phosphorylated extracellular signal-regulated kinase (pERK) were collected for all pts. Results: 48 pts have been treated, 25 in S1 (8–42 mg BID) and 23 in S2 (8–60 mg BID). Pt characteristics, treatment exposure, and safety signals were similar in both Ss. The median age was 67 years (range 22–80), 66% were male and the Eastern Cooperative Oncology Group Performance Status was 0/1/2 in 25%/58%/17% of pts, respectively. Underlying HMs were: acute myeloid leukemia (AML, n=41), myelodysplastic syndrome (MDS, n=3) and other (n=4). Cytogenetics were known for 42/44 pts with MDS (n=3) and AML (n=39): 3 were favorable, 21 intermediate and 18 unfavorable. RAS mutation was present in 5 pts (not reported in others), of whom 2 also carried a FLT3 mutation. Six additional pts had a FLT3 mutation. The median duration of treatment was 3.7 weeks (range 0.1–77). The MTD has not been reached in either S. One dose-limiting toxicity (DLT) of grade 2 angioedema was seen in S1 at 42 mg BID. The most common non-hematological adverse events (AEs): infections (56%), diarrhea (46%), skin rash (38%), nausea (27%), pyrexia (25%), peripheral edema (21%), dizziness (21%), aspartate aminotransferase increase (21%) and transient visual disorders (with underlying serous retinal detachment in most cases) (21%). Plasma concentrations increased proportionally with dose. Sustained pERK inhibition during the dosing period was observed in blasts and lymphocytes starting at 23 mg BID. Transient clearance or 50% decrease of blasts in bone marrow and peripheral blood have been detected in 6 pts (MDS n=2, AML n=4), 2 RAS mutated.

### 1.1.3 Overview of MEK162

MEK162, previously named ARRY 438162, is a potent and selective allosteric, ATP non-competitive inhibitor of Mek1/2 that is active in inhibiting pERK and growth of BRAF mutant cancer cells in the low nanomolar range. MEK162 is currently being investigated as a single agent and in combination with PI3K or RAF inhibitors in patients with selected advanced or metastatic solid tumors, including biliary cancer, colorectal cancer and melanoma. Four phase I/Ib studies exploring MEK162 in combination with RAF and PI3K inhibitors in patients with advanced RAS/RAF and PIK3CA mutated tumors are ongoing.

The dose of 45 mg BID is considered safe and efficacious and is the dose used in an ongoing Phase 2 study in cancer patients. The maximum tolerated dose (MTD) of MEK162 is 60 mg BID.

## Non-clinical experience

The biological activity of MEK162 has been evaluated *in vitro* (both enzymatic and cell culture assays) and *in vivo* in mouse xenograft studies. MEK162 potently inhibits Mek1/2 in both biochemical assays using purified protein, and in cells. MEK162 has demonstrated robust, but selective, growth inhibitory activity in a wide variety of cancer cell lines. In a collection of ~500 genetically annotated cell lines, MEK162 showed anti-proliferative activity preferentially in cells harboring activating mutations of the MAP kinase pathway (e.g. BRAF, NRAS and KRAS), and in particular, activating mutations in BRAF and NRAS. *In vivo*, MEK162 has demonstrated dose dependent tumor growth inhibition in various subcutaneous tumor transplants harboring $BRAF^{V600E}$ mutations (HT29, COLO205, A-375) as well as activating mutations in both NRAS (Hs. 944T) and KRAS (MiaPaCa2, A549, LoVo, Calu6). These data suggest that MEK162 may provide a potential therapeutic benefit in cancer indications, harboring these mutations, including melanoma.

In animals, exposure (AUC) and $C_{max}$ generally increased in a dose proportional manner. The plasma clearance is low (range: ~2 to 8 mL/min/kg) and the mean plasma half-life values ranges from 2 to 9 hours. MEK162 has moderate membrane permeability and is a substrate of P-gP and BCRP. MEK162 exhibited high plasma protein binding *in vitro* (> 96%, except dog 84%) and is predicted to have good stability with respect to hepatic metabolism. Nonclinical *in vitro* and *in vivo* data indicated that MEK162 is metabolized by multiple routes but primarily by glucuronidation pathways (mainly via UGT1A1, 1A3 and 1A9) and to a lesser extent by oxidation pathways (mainly via CYP1A2 and 2C19). The formation of active metabolite AR00426032 is mediated primarily by CYP1A2 with minor contributions from other cytochrome P450 enzymes (CYPs). MEK162 potently inhibits CYP2B6 and weakly inhibits CYP1A2 and 2C9. It is not considered a time dependent inhibitor of CYP1A2, CYP2C9, CYP2D6 and CYP3A. *In vitro* evidence also suggests that MEK162 could induce CYP3A.

Acute, subchronic, chronic, reproductive toxicity, genotoxicity and phototoxicity studies were completed to support the chronic administration of MEK162 to adult cancer patients. The clinical toxicity of MEK inhibitors has been more similar to that of monkeys than rats and include gastro-intestinal intolerance and diarrhea, rash, central serous retinopathy (only seen in humans) and retinal vein occlusion (rarely seen in humans). *In vitro* and *in vivo* phototoxicity studies conducted in mice indicate that MEK162 has a very low risk of weak phototoxic potential at therapeutic doses. Furthermore, there has been no

evidence of phototoxicity or photosensitivity in humans being treated with MEK162 for cancer or for rheumatoid arthritis. This includes 450 patients who have received at least one dose of MEK162 and is based on data as of 29 February 2012. Given the embryo-lethal effects seen in rats and rabbits and the teratogenic effects seen in rabbits, MEK162 should not be used in pregnant women and women of child-bearing potential must be advised to use highly effective contraception methods.

A detailed summary of available preclinical data is provided in the Investigator's Brochure.

## Clinical experience

As of the data-cutoff date of February 29, 2012, a total of 450 patients and healthy volunteers have received at least 1 dose of MEK162 and been evaluated for safety, including 70 healthy volunteers, 164 patients with rheumatoid arthritis and 216 patients with advanced cancer. A total of 175 and 41patients with advanced solid tumors have been treated with MEK162 as single agent and in combination with PI3K or RAF inhibitors, respectively. Patients with advanced cancer have received or are currently receiving MEK162 (either as a single agent or in combination with PI3K or RAF inhibitors) at doses of 30 to 80 mg BID in the following studies: [ARRAY-162-111] (90 patients with advanced biliary or colorectal cancer), [CMEK162X2201] (81 patients with NRAS or BRAF metastatic melanoma), [CMEK162X1101] (4 Japanese patients with advanced solid tumors), [CMEK162X2101] and [CMEK162X2102] (11 and 21 patients, respectively with advanced solid tumors who have BRAF or RAS mutations) and [CMEK162X2103] (9 patients with advanced solid tumors).

The most frequent treatment-related AEs in patients receiving MEK162 for advanced cancer were rash, dermatitis acneiform, nausea, diarrhea, peripheral edema, vomiting, fatigue and increase in blood creatine phosphokinase.

Seventy-two out of 90 (87%) patients treated with MEK162 as a single agent in the ARRAY-162-111 study and 58/81 (72%) patients in the CMEK162X2201 study developed rash. Across both trials, 78% were assessed as related to MEK162. Most were Grade 1/2 (mild/moderate) and improved or resolved with treatment (topical or oral antibiotics, topical or oral steroids). In most cases, MEK162 was continued during the treatment of the rash, however, a dose interruption and/or dose reduction was required in some patients. Grade 3/4 events of rash occurred in eight patients, one of which was a dose limiting toxicity (DLT) at the 80 mg BID dose level in the ARRAY-162-111 study. In the combination studies of MEK162 with other PI3K or RAF inhibitors, rash was also one of the most commonly reported AEs.

Retinal events have occurred in 17 out of 90 (19%) patients treated in ARRAY-162-111 study. At dose levels of 45 mg BID (2 patients with Grade 1 and 2 patients with Grade 2 events), 60 mg BID (2 patients with Grade 1 and 9 patients with Grade 2 events) and 80 mg BID MEK162 (1 patient with Grade 1 and 1 patient with G3 events). Approximately 71% of these patients reported visual symptoms associated with the retinal abnormalities. Symptoms have included flashing lights/floaters, color variations, blurred vision, and seeing shapes upon opening the eye. Retinal events have been described as "leaky" type detachment with collections of subneurosensory fluid which is best visualized on optical coherence tomography. No "tear" type detachments have been reported. The retinal events have included central serous retinopathy (CSR), retinal deposits, retinopathy, chorioretinopathy and venous stasis retinopathy. To date, these retinal events have been reversible in all patients upon discontinuation or dose reduction of MEK162. In most patients, MEK162 was held until resolution of all signs and symptoms. In two patients in the 45 mg BID cohort, the dose was reduced without holding treatment and there was no reoccurrence of the event. Low grade (Grade 1/2) CSR-like events were also reported by 17/81 patients in the single agent CMEK162X2201 study and 3/3 patients in the Japanese single agent CMEK162X1101 study. Low grade (Grade 1/2) CSR-like events were also reported in all combination studies of MEK162 with PI3K or RAF inhibitors.

Adverse events of reversible elevations of creatine kinase (CK) were reported in 12/90 (13%) patients in the ARRAY-162-111 study. Additionally, clinical laboratory results have shown that 64/90 (71%) patients had an elevated CK after starting study therapy. Most elevations were Grade 1/2. Eight patients had Grade 3 elevations and one patient had a Grade 4 elevation. Most of the CK elevations were asymptomatic and reversible. In the CMEK162X2201 study, increase of the blood CK has been reported in 24/81 (30%) patients, including Grade 3/4 events reported by 16/81 patients. Of those, the event was reported as related to MEK162 treatment in 28% of patients. Reversible elevations of CK have also been reported in the combination studies of MEK162 with PI3K or RAF inhibitors.

As of the data-cutoff date, 32 (15%) out of 216 patients with advanced cancer treated with MEK162 (as a single agent or in combination with PI3K or RAF inhibitors) experienced liver related adverse events (19 patients Grade 1 or 2, 12 patients Grade 3, 1 patient Grade 4). Twenty three of 32 patients had liver metastases at baseline. The reported adverse events included elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (AP), bilirubin, hepatic pain, ascites, cytolytic hepatitis, bile duct obstruction, cholangitis,

jaundice and cholestatic jaundice. Of Note, one case of acute liver failure with fatal outcome, possibly related to MEK162 has been reported.

In study CMEK162X2201, one case of cardiac failure, possibly related to MEK162, has been reported at a starting dose of 60 mg BID. In addition, a non-serious decrease in cardiac ejection fraction Grade 3 (baseline 50% to 24%) was also reported in the same cohort. While a relationship to MEK162 could not be ruled out, this patient had a number of confounding factors, including significant hypothyroidism and hypertension. Additional review of the MUGA/Echo EF values (as of February 28, 2012) revealed an additional patient treated at 45 mg BID experienced a Grade 3 drop in ejection fraction (baseline 58% to 39%). In addition, there were two instances of emerging Grade 2 decrease (one at 45 mg BID and one at 60 mg BID cohort). Of note, while these two patients had decreases from baseline in EF, their EF remained above the lower limit of normal.

In study [CMEK162X2102] (a phase Ib open-label dose escalation study of MEK162 plus RAF265) two serious and one non serious case of decrease left ventricular ejection fraction were reported. All cases improved after interruption or discontinuation of study drug. RAF265 is a potent inhibitor of RAF, VEGFR-2, and platelet-derived growth factor receptor-beta (PDGFR-β), although speculative, it is possible that the combination with RAF265 is increasing the risk of reduced LVEF by its anti-angiogenic activity.

Elevated CK was associated with the administration of MEK162, as described above. It cannot be excluded that in a small percentage of patients with advanced cancer, MEK162 is associated with liver transaminase elevations. No other apparent trends in clinical laboratory parameters, vital signs or electrocardiograms (ECGs) were associated with the administration of MEK162.

For further information regarding clinical experience with MEK162, refer to the Investigator's Brochure.

## Pharmacokinetics

In healthy subjects, MEK162 exposure (as quantified by $C_{max}$ and AUC) tended to increase in a dose-proportional manner following single and multiple doses over a dose range of 5 to 80 mg QD for single dose and 5 to 60 mg QD for multiple doses. One additional cohort received 20 mg BID for 14 consecutive days. The mean apparent half-life was 7 to 8 hours, and the mean apparent time of maximum plasma drug concentration ($T_{max}$) was 1.18 hrs. Plasma drug concentrations by 12 hours post-dose approached the LLOQ of 5 ng/mL in many subjects. These initial PK data supported a BID dosing regimen of MEK162 as appropriate for maintaining sufficient plasma concentrations over the dosing interval at steady state in order to consistently inhibit the primary target. The AR00426032 metabolite represented < 13% of the parent drug in plasma and < 5% of the parent drug was excreted renally. Accumulation of MEK162 was < 40% following QD dosing and < 75% following BID dosing.

Pre-clinical studies in mice support that >50% inhibition in pERK in HT-29 tumors for 24 hours is optimal for significant tumor growth inhibition. This degree of sustained pERK inhibition was best achieved with BID dosing at lower doses ($\leq$ 10 mg/kg/dose) or QD dosing at higher doses ($\geq$ 30 mg/kg/dose). Given that little to no drug was apparent in plasma at 24 hours post-dose (at low doses) in the pre-clinical xenograft studies, a BID dosing regimen was considered to be the most reliable murine schedule to maintain plasma concentrations for optimal efficacy. Therefore, a BID dosing regimen (e.g., 45 mg) should provide sufficient exposure with acceptable safety and adequate continuous pharmacological inhibition of the primary target.

The initial evaluation of the PK of MEK162 in patients with advanced cancer (ARRAY-162-111 and CMEK162X2201) at the doses evaluated to date (30 to 80 mg BID) indicated that both the plasma concentration-time profiles and PK parameters were similar to those in healthy subjects, as well as in patients with rheumatoid arthritis. The inter-subject variability for AUC and $C_{max}$ was ~40%. The mean active metabolite-to-parent ratio was less than 25% across all study days and dose levels tested. Steady-state is reached by Day 15 and accumulation of MEK162, as estimated using non-compartmental methods, is around 50% (or 1.5 fold).

To integrate all the available PK information, a preliminary population PK model describing the PK of MEK162 was built using data from 68 subjects from the Array and Novartis studies. The model suggests that the PK can be adequately described using linear kinetics (2 compartmental open model with first order absorption and a lag time). There was extensive tissue distribution and clearance of MEK162 estimated as 17 L/h. For the typical individual, steady-state is reached by Day 15 and accumulation of MEK162 is around 70% (or 1.7 fold).
For further information refer to the Investigator's Brochure.

### 1.1.4 Overview of comparator/combination drugs

GSK1120212 is a potent and selective allosteric inhibitor of MEK 1 and 2 kinases. In vitro, GSK1120212 inhibited proliferation of myeloid cell lines selectively as compared to lymphoid cell lines. A 2 part study of a single daily oral dosing regimen was conducted to define the recommended Phase 2 dose, evaluate pharmacokinetics, and assess preliminary activity in patients with relapsed or refractory AML, MDS, ALL or CMML. Subjects with WBC< 30,000/uL who met hepatic, renal and cardiac function criteria were eligible for participation. GSK1120212 was given orally, once daily in the following dose cohorts: 3mg loading dose followed by 1mg/day (n=3), 1mg/day without loading dose (n=1), and 2mg/day without loading dose (n=9). The loading dose was discontinued after cohort 1, based on findings in the phase I solid tumor study.

Fourteen subjects (10 with AML, 2 MDS transformed to AML, 1 MDS, 1 ALL) entered the trial. Eight were male, and median age was 65 years (range 33 to 85). Pharmacokinetic analysis showed that, upon repeat dosing, GSK1120212 exposure increased in a dose-proportional manner, had a small peak:trough ratio of approximately 4 and an effective half-life of approximately 7.7 days. Steady state concentrations were reached by day 15. Both single and repeat dose pharmacokinetics of GSK1120212 appeared to be similar to a phase I study in patients with solid tumors. Systemic exposure exceeded concentrations that inhibited in vitro leukemic cell proliferation. At the 2mg/day dose level (n=9), drug-related adverse events were diarrhea (7 overall; 6-Grade 1/2, 1-Grade 3), rash (3-Grade 1/2), fatigue (4-Grade 1/2), visual changes (3 Grade 1/2). One subject experienced a Grade 2 reversible serous retinopathy associated visual changes which resolved after drug discontinuation. One dose limiting toxicity was seen in a subject with disease-related Grade 4 thrombocytopenia and pneumonia who experienced a Grade 5 cerebrovascular accident possibly related to drug. One subject in the 2mg/day cohort achieved a CR; peripheral blast count was reduced from 30% at baseline to 0% and bone marrow blast count was reduced from 50% at baseline to 3%. During this time, platelet count increased from 48K to a maximum of 276K. Initial salutary effect was seen after 2 weeks on therapy and duration of CR was 4 weeks bone marrow blast count was 3% and 5%, respectively, at the beginning and end of the 4 week CR duration.

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## 1.2 Study rationale/purpose

Cellular proliferation, differentiation, and death are regulated by a number of extracellular molecules such as cytokines and hormones, as well as intercellular interactions mediated by neighboring cell surface antigens. These effectors mediate gene transcription either directly or indirectly by activating intracellular signaling pathways, which in turn activate appropriate cellular machinery. Cell-surface receptors that convert external stimuli into intracellular signals are pivotal in this signaling process. They activate intracellular pathways either through their inherent enzymatic function or as a result of their

association with other catalytic proteins. Indeed, most growth factors and cytokines bind these receptors and exert their function through their activation, commonly by phosphorylation.

Normal hematopoiesis is dependent on intricately regulated signaling cascades that are mediated by cytokines and their receptors. Orderly function of these pathways leads to the generation of appropriate constellation of hematopoietic cells, and their abnormal activation results in neoplastic transformation, impaired apoptosis, and uncontrolled proliferation. Cytokines function in a redundant and pleiotropic manner; different cytokines can exert similar effects on the same cell type, and any particular cytokine can have several differing biological functions . This complexity of function is a result of shared receptor subunits as well as overlapping downstream pathways culminating in activation of common transcription factors.

The serine/threonine MAPKs, which include the Ras-Raf-MEK-ERK pathway, the p38 family of kinases, and the JNK (SAPK) family, are activated by upstream signals and mediate effects on inflammation, cell growth, cell cycle progression, cell differentiation, and apoptosis. The Ras family of proteins belongs to the large superfamily of GTPases that localize to the inner surface of the plasma membrane. Ras proteins play a pivotal role in a number of signaling pathways mediated by RTKs and other receptors. Ligand binding to these receptors initiates the autophosphorylation of specific tyrosine residues in their cytoplasmic domain and creates phosphotyrosyl-binding sites for adapter proteins such as Shc and Grb2, which in turn recruit guanine nucleotide exchange factors and thereby initiate Ras activation.

Once induced, Ras activates Raf serine/threonine kinase, which then phosphorylates MAPK kinases (otherwise known as MEKs). These in turn activate MAPKs or ERKs. which in turn move to the nucleus where they phosphorylate and activate nuclear transcription factors such as Elk-1. ERKs were initially described as a novel family of protein kinases that, when activated, produced proliferative stimuli ERKs that can also activate other kinases such as RSKs (also known as MAPK-activated protein kinases), which are involved in cell-cycle regulation and apoptosis. ERK-activated RSK kinase catalyzes the proapoptotic protein Bad and suppresses Bad-mediated apoptosis. Similarly, the Ras-Raf-MEK-ERK cascade modulates cellular proliferation by regulating the activity of several proteins, including cell-cycle regulators (*e.g.* cyclin D1, $p21^{waf1/cip1}$, $p27^{kip1}$, and cdc25A) and transcription factors (*e.g.*, c-Myc; Ref.)

Constitutive activation of the ERK pathway is frequently seen in human cancers and is often due to over-expression or mutation of upstream receptor tyrosine kinases, increased expression of growth factor ligands, or mutational activation of Ras and its downstream effectors. In human malignancies, activating Ras mutations are common, having been identified in about 30% of cancers. These mutations are found with high incidence in several solid tumor types including pancreatic (90%), colon (45%), thyroid (60%), non-small-cell lung cancer (NSCLC) (35%) as well as AML (30%). MEKs on the other hand, have not been identified as oncogene products in human malignancies. They are, however, present at a crucial point of convergence that integrates signal inputs from a variety of protein kinases through Ras. In addition, MEKs are very restricted in their substrate specificity, with ERK being the sole known substrate.

Sustained MAPK activation plays an important role in a number of hematological malignancies. Activation of MEK resulting in overexpression of p44/42MAPK results in constitutive MAPK activation in the most AML cases. Internal tandem duplication of the Flt3 receptor is observed in up to one third of AML samples and also results in constitutive MAPK activation and the autonomous growth of myeloid cell lines. Direct evidence for a leukemogenic role of the MAPK pathway is derived from the observation that a conditionally active form of MEK1 confers cytokine independence to hematopoietic cells. It has been also demonstrated that small molecule inhibitors as well as interfering RNAs disrupting the signal transduction in MEK/MAPK pathway cause antiproliferative and proapoptotic consequences in AML cell lines and primary AML blasts, while relatively sparing normal hematopoietic progenitors, thus providing the preclinical rationale for the development of MEK/MAPK-targeted therapeutic strategies in AML.

Based on the above data, MEKs are important targets for the development of drugs for patients with hematological malignancies. The phase I dose escalation part will be performed in subjects with refractory hematological malignancies and no effective standard therapies available. The MEK/ERK/MAPK pathway is deregulated in all of those malignancies but the level of activation that render a tumor “dependent” is unknown. Therefore, the MEK inhibitor has a potential to be active in these diseases but no predictive models exist.

GSK1120212 is a potent and selective allosteric inhibitor of MEK 1 and 2 kinases. In vitro, GSK1120212 inhibited proliferation of myeloid cell lines selectively as compared to lymphoid cell lines. A 2 part study of a single daily oral dosing regimen was conducted to define the recommended Phase 2 dose, evaluate pharmacokinetics, and assess preliminary activity in patients with relapsed or refractory AML, MDS, ALL or CMML. Subjects with WBC< 30,000/uL who met hepatic, renal

and cardiac function criteria were eligible for participation. GSK1120212 was given orally, once daily in the following dose cohorts: 3mg loading dose followed by 1mg/day (n=3), 1mg/day without loading dose (n=1), and 2mg/day without loading dose (n=9). The loading dose was discontinued after cohort 1, based on findings in the phase I solid tumor study.

# 2 STUDY OBJECTIVES

**Primary Trial Objective(s) for Phase I and II**

**Phase 1.**

-To determine the MTD/RP2D (recommended phase 2 dose) of MEK162 in subjects with advanced leukemias.

**Phase II**

-To assess the anti-leukemic activity of MEK 162 (overall response including CR and CRi) in older subjects with newly diagnosed KRAS/NRAS mutant poor prognosis AML, who are not candidates for intensive chemotherapy.

**Secondary Trial Objective(s) for Phase I and II**

**Phase I**

-To determine the safety of MEK 162 in patients with relapsed and/or refractory leukemias.
-To assess the PK of MEK 162 in patients with leukemias.
-To assess anti-leukemic activity (CR and CRi) of MEK 162 in patients with leukemia.

**Phase II**

-To determine the safety and tolerability of MEK 162 in older subjects with newly diagnosed KRAS/NRAS mutant poor prognosis AML.

**Exploratory Objective(s) for Phase I and II (if necessary)**

**Phase I and Phase II**

-To explore potential molecular variations in leukemia blasts (e.g.FLT3, K-RAS, N-RAS and other known mutations (IDH1, IDH2, DNMT3A and others) or gene copy number in candidate genes) that may be predictive of differences in response to MEK 162.

The dose finding Phase I portion allows for any patient with advanced AML/MDS/ALL/CMML who meets the eligibility criteria as there is a possibility of activity in patients with those disorders with aberrant signaling along the RAF/RAS/MAPK signaling pathway although the main intention of the phase I is to determine whether the drug is reasonably safe. In the phase II portion of the study Array was only interested in determining the activity in patients with known aberrant pathway (i.e. mutated RAS) as this can also be potentially used as a marker for patient selection. Clearly, if we see significant responses in other patients in the phase I and particularly if it is determined that this activity is related to aberrant RAF/RAS/MAPK signaling, future trials will be conducted in a broader population and more dependent of demonstrating aberrant pathway signaling.

# 3 STUDY DESIGN

This is a two-part trial to determine dosing and efficacy in leukemia patients with MEK 162. Phase I will determine MEK 162 dosing in subjects with advanced leukemias. The phase I part of the trial has a 3+3 dose escalation design, with 3 subjects in each cohort, using the 50% dose escalation scheme, based on the occurrence of DLTs.
At the each dose level subjects will receive MEK 162 orally twice a day on

- Days 1 to 28 of a 28-day cycle

Prior to advancing dose levels, a cohort summary will be completed and submitted to the Clinical Research Monitor (IND Office)

Patients will continue therapy as long as they are receiving clinical benefit.

The MTD/RP2D determined by Phase I will be used in an open label, Phase II part of MEK 162 in older subjects with newly diagnosed KRAS/NRAS mutant poor prognosis AML, who are not candidates for intensive chemotherapy.

**Table 3-1: Dose level**

| Dose level | Dose of MEK 162 |
|---|---|
| 1 | 30 mg po bid |
| 2 | 45 mg po bid |

## 3.1 Study Population

### 3.1.1 Inclusion criteria

**Phase I**

1. a. Primary or secondary AML according to WHO classification, with relapsed or refractory disease or newly diagnosed older subjects (≥ 65 years of age), not candidates for intensive chemotherapy

   b. Subjects with MDS, IPSS Int-2 or high risk (RAEB-2 only, i.e. ≥ 10% blast) who are resistant or intolerant to standard treatment and are not candidates for transplantation,

   c. Subjects with ALL, relapsed, refractory or intolerant to standard treatment and for whom no effective treatment options are available,

2. Age ≥ 18 years,

3. Patients should be willing and able to give informed consent.

4. Eastern Cooperative Group (ECOG) PS ≤ 2

**Phase II**

1. Patients aged 60 and older with newly diagnosed primary or secondary AML according to WHO classification, without any prior therapy for AML with the exception of (a) emergency leukapheresis and (b) emergency treatment for hyperleukocytosis with hydroxyurea that is allowed until 24 hours before the start of the trial treatment. Note: Prior therapy for preexisting hematological condition e.g. MDS or MPD, including but not limited to hypomethylating agents is allowed until at least 2 weeks have elapsed from completion of that agent before the first dose of MEK 162. Patients with relapsed AML, and relapsed MDS and CMML, after prior hypomethylating therapy are also eligible to participate

2. Patients with untreated AML must meet at least one of the following conditions:
   a. Age ≥75 years
   b. Age ≥60 and < 75 years with at least one of the following poor prognostic factors:
      i. Secondary AML, as determined by known and documented exposure to chemotherapy or radiation therapy
      ii. antecedent history of MDS or myeloproliferative disorder according to WHO criteria for at least 3 months prior to trial entry
      iii. unfavorable cytogenetic abnormalities including chromosome 5 and 7 as well as complex:
      iv. ECOG Performance status 2.

3. (Phase II only) Patients are willing and able to give informed consent.

4. (Phase II only) Only patients with mutated *RAS (KRAS* and *NRAS*) mutations are eligible to participate

5. (Phase II only) Adequate cardiac function defined as:
   - left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram,
   - QTcF interval ≤ 480 ms;

### 3.1.2 Exclusion criteria

**Phase I and Phase II Parts**

1. Administration of any antineoplastic therapy within at least 4 weeks (cytotoxic chemotherapy) or 2 weeks (biological and targeted therapy; hypomethylating agents are considered to be biological therapy) of that therapy of the first MEK 162/MEK 162 dose; except the use of hydroxyurea which can be administered up to 5 g/day up to 24 hours before the initiation of the study drug.

2. Participation in other clinical trials within at least 2 weeks of the first study drug dose,

3. Clinical evidence of active CNS leukemia requiring active therapy; prior CNS leukemia well-controlled by ongoing therapy is allowed.

4. Active and uncontrolled infection including but not limited to known infection with HIV, active hepatitis B, or hepatitis C.

5. Major surgery within two weeks prior to trial entry,

6. Liver function tests above the following limits at the screening: total bilirubin > 1.5 x ULN unless related to Gilbert's syndrome or hemolysis, AST and/or ALT > 2.5 X ULN, or for subjects with liver involvement AST and/or ALT > 5 x ULN,

7. Serum creatinine > 1.5 x ULN and/or Creatinine Clearance (CrCl) < 30 mL/min at screening (calculation according to Cockroft & Gault formula),

8. Pregnant or nursing (lactating) women;

9. Female patients of childbearing potential and male patients with partners of childbearing potential who are not willing to use highly, effective methods of contraception throughout the study and for 1 month after study drug discontinuation. Highly effective contraception methods include:

- Total abstinence or
- Male or female sterilization
- Combination of any two of the following (a+b or a+c or b+c)
    a. Use of oral, injected, or implanted hormonal methods of contraception
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

10. Female patients with reproductive potential who do not have a negative blood or urine pregnancy test at Screening;

11. History of significant difficulty swallowing, malabsorption or other chronic gastro-intestinal disease or conditions that may hamper compliance and/or absorption of the tested product,

12. Has significant cardiac conduction abnormalities and/ or pacemaker or any of the following criteria:
    - History of acute coronary syndromes (including myocardial infarction, unstable angina, CABG, coronary angioplasty, or stenting) <6 months prior to screening,
    - Symptomatic chronic heart failure; evidence of clinically significant cardiac arrhythmias and/or conduction abnormalities < 6 months prior to screening
    - Uncontrolled arterial hypertension, defined as BP > 140/100 mmHg (average of 3 consecutive readings);

13. History or current evidence of central serous retinopathy (CSR), retinal vein occlusion (RVO);

14. Any ophthalmopathy visible at screening that would be considered a risk factor for CSR or RVO by the ophthalmologist (e.g. uncontrolled glaucoma or ocular hypertension, uncontrolled diabetes mellitus, history of hyperviscosity or hypercoagulability syndromes)

15. Subjects with active other tumors, except early stage squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or cervical intraepithelial neoplasia (CIN)

16. Patients who have neuromuscular disorders that are associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy)

17. Patients who are planning on embarking on a new strenuous exercise regimen after first dose of study treatment. NB: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CK levels should be avoided while on MEK162 treatment

18. Impairment of gastrointestinal function or gastrointestinal disease (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection)

### 3.1.3 Pregnancy

Subjects and their partners must be willing to avoid pregnancy during the trial and until 3 months after the last trial drug administration. Males with female partners of childbearing potential and female subjects of childbearing potential must therefore be willing to use highly effective methods of contraception throughout the study and for 1 month after study drug discontinuation.

Highly effective contraception methods include:

- Total abstinence or
- Male or female sterilization
- Combination of any two of the following (a+b or a+c or b+c)
  a. Use of oral, injected, or implanted hormonal methods of contraception
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

For the purposes of this trial, childbearing potential is defined as “All female subjects after puberty unless they are post-menopausal for at least two years, surgically sterile or sexually inactive”.

Pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, are not allowed to participate in this study UNLESS they are using highly effective methods of contraception throughout the study and for 1 month after study drug discontinuation. Highly effective contraception methods include:

- Total abstinence or
- Male or female sterilization
- Combination of any two of the following (a+b or a+c or b+c)

d. Use of oral, injected, or implanted hormonal methods of contraception
e. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
f. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Post-menopausal women are allowed to participate in this study. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum Follicle-Stimulating

Hormone (FSH) levels > 40 mIU/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Sexually active males must use a condom during intercourse while taking the drug and for 1month after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

# 4 STUDY TREATMENT

Study drug will be administered as a flat-fixed dose, and not by body weight or body surface area, with a glass of water and irrespective of food. Prescribed bid doses should be taken 12 ± 2 hrs apart. Complete dosing instructions will be provided to study patients and will include the minimum times between doses and instructions for missed doses. Patients will also be instructed not to chew or crush caplets of study drug. Patients will be instructed to return unused study drug to the site at each visit.

If a patient vomits at any time after dosing, the dose of study drug should not be re-administered. Doses of study drug omitted for AEs or any other reason should not be replaced or made up later in the day, or at the end of the dosing period.

The site personnel will train the patient and/or his/her caregiver on dosing procedures for the drug. Patients will be supplied with a sufficient number of caplets for the number of doses to be taken prior to the next scheduled visit.

## 4.1 Investigational (and control) drugs

MEK162 caplets will be provided as investigational study drug.

**Table 4-1: Treatment and treatment schedule**

| Study drug | Pharmaceutical form and route of administration | Dose | Frequency |
|---|---|---|---|
| MEK162 | Caplets for oral administration | 30 – 45 mg<br>as recommended by Phase I | BID |

### 4.1.1 How supplied

Array will supply investigational study drug MEK162.

### 4.1.2 Packaging and labeling

Medication labels will be in the local language and comply with the legal requirements of each country.

### 4.1.3 Supply, receipt and storage

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, MEK162 should be stored according to the instructions specified on the drug labels.

Study drug will be provided as film-coated oval shaped tablets (caplets) and packaged into high-density polyethylene bottles.

### 4.1.4 Disposal and Destruction

The drug supply will be destroyed at an Array facility or Array will provide approval for destruction by the investigational site if they have an appropriate drug destruction policy,

## 4.2 Treatment assignment

The assignment of a patient to a particular dose level will be coordinated by the investigator.

## 4.3 Treating the patient

### 4.3.1 Study drug/study treatment/active control administration

MEK162 will be dispensed by the pharmacist or designee at the Investigator's institution. Patients will receive MEK162 on an outpatient basis unless the patient is inpatient for other reasons. Patients must be instructed to bring any empty study drug bottles and unused study medication with them at the next visit for drug accountability and compliance checks. When returned, unused study medication will be destroyed in accordance with institutional policy.

Records of drug formulation, batch number, bottles dispensed, received and returned must be recorded in the pharmacy study file.

### 4.3.2 Criteria for dose escalation and determination of MTD *(Phase I only).*

This is a two-part trial to determine dosing and efficacy in leukemia patients of MEK 162. Phase I will determine MEK 162 in dosing subjects with advanced leukemias. The phase I part of the trial has a 3+3 dose escalation design, with 3 subjects in each cohort, using a fixed (15 mg) dose escalation scheme, based on the occurrence of DLTs.
At the each dose level up to 6 subjects will receive MEK 162 orally twice a day on days 1 to 28 of a 28-day cycle.

### 4.3.3 Dose escalation (Phase I only).

- If 0/3, 0/4, 0/5, or 0/6 evaluable subjects exhibits a DLT after one 28-day cycle, then the next subject will be treated at the next DL.
- If one subject exhibits a DLT, the cohort will be expanded up to 6 subjects.
- If one out of six evaluable subjects exhibits a DLT, then the next subject will enroll at the next DL.
- If more than one out of three to six evaluable subjects exhibit a DLT, then the dose level below it will be determined as MTD.
- If more than 1 out of 3 to 6 evaluable subjects exhibit a DLT during the first DL then reduced dose level (RDL) will be investigated.

Dose escalations will proceed no sooner than 4 weeks after the last subject in the cohort has begun therapy.

**Table 4-2: Phase I Dose Escalation**

| Number of subjects with DLT during the first cycle | Number of subjects in DLT Analysis Set | Action |
|---|---|---|
| 0 | 3 to 6 | Escalate to the next DL |
| 1 | 3 to 6 | If less than 6 subjects, complete the cohort to 6 subjects |
| 1 | 6 | Escalate to the next DL |
| > 1 | 3 to 6 | DL deemed not tolerable, add subjects up to a total of 9 subjects in the DL immediately below this one (which will be the MTD level) |

**Table 4-3: Dose-limiting toxicity (Phase I only)—criteria for determining dose limiting toxicity.**

The Following are considered to be a dose-limiting toxicity, "DLT", except when they are inconvertibly due to extraneous causes.

| **Toxicity** | **Any of the following criteria:** |
|---|---|
| **TOXICITY** | **DLT CRITERIA** |
| Skipped/ delayed dose | The inability to administer MEK162 on ≥ 75% of scheduled treatment days during cycle 1 due to unresolved adverse event of any grade and considered related to the study drug. |
| Recurrent toxicity | The recurrence of toxicity CTCAE Grade ≥ 2 with the same severity following initial interruption of treatment, resolution and resumption of treatment at the same dose. |
| Cardiac disorders | Asymptomatic decrease of LVEF > 10% compared to baseline and the LVEF is below the institution's LLN .<br>Left ventricular systolic dysfunction CTCAE Grade ≥ 3<br>Other cardiac disorders CTCAE Grade ≥ 3 |
| Pulmonary disorders | Interstitial lung disease or pneumonitis ---<br>Discontinue the study drug. |
| Vascular disorders<br>Hypertension | Persistent hypertension CTCAE Grade ≥ 3 requiring more than one drug or more intensive therapy than previously |
| Skin and subcutaneous tissue disorders: [a]<br>Asymptomatic rash and/or photosensitivity<br>Symptomatic rash and/or photosensitivity | Asymptomatic rash / photosensitivity CTCAE Grade 3 lasting > 48 hrs despite skin toxicity treatment<br><br>Symptomatic rash/photosensitivity CTCAE Grade 3 despite skin toxicity treatment |
| Metabolism and nutrition disorders:<br>Hyperglycemia | Hyperglycemia CTCAE Grade ≥ 3 for > 7 consecutive days despite anti-diabetic treatment<br>Hyperglycemia grade 4<br>Hyperglycemia leading to diabetic keto-acidosis, hospitalization for intravenous insulin infusion, or non-ketotic coma. |
| Metabolism and nutrition disorders:<br>Calcium-phosphate heterostasis tCa x Pi increase | tCa x Pi > 55 $mg^2/dL^2$ |
| Gastrointestinal disorders [a] | Diarrhea CTCAE Grade ≥ 3 ≥ 48 hrs, despite the use of anti-diarrhea therapy |
| | Nausea/ vomiting CTCAE Grade ≥ 3 ≥ 48 hrs, despite the use of anti-emetic therapy |
| Investigations [b] | Blood bilirubin[c] CTCAE Grade 2 for > 7 consecutive days |
| | Blood bilirubin[c] CTCAE Grade ≥ 3 - Discontinue the investigational drug |
| | AST or ALT CTCAE Grade ≥3 in conjunction with blood bilirubin[c] CTCAE Grade ≥ 2 of any duration |
| | AST or ALT CTCAE Grade ≥ 2 for > 7 consecutive days AST or ALT CTCAE Grade 3 or higher |
| | Serum alkaline phosphatase CTCAE Grade 4 |

| | |
|---|---|
| | Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 3 > 7 consecutive days |
| | Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 4 |
| | Serum creatinine CTCAE Grade ≥ 3 |
| | Serum CK/CPK CTCAE Grade > 3 for > 14 consecutive days if clinically significant (symptomatic)<br>Serum CK/CPK CTCAE Grade 4 for > 14 consecutive days |
| | |
| | ECG QTc interval prolonged CTCAE ≥ Grade 3 |
| | |
| | |
| | |
| Eye disorders-Retinopathy<br>CSR and CSR like events | Retinopathy – CSR and CSR-like events CTCAE Grade 3 for > 14 consecutive days confirmed by ophthalmologic examination<br><br>Retinopathy – CSR and CSR-like events CTCAE Grade 4, confirmed by ophthalmologic examination |
| Eye disorder —Retinal Vein Occlusion | CTCAE Grade ≥ 1 confirmed by ophthalmologic examination |
| Eye disorders - (other specify) | CTCAE Grade 3 > 14 consecutive days<br>CTCAE Grade 4 |
| Other hematologic & non-hematologic toxicities | Any other CTCAE Grade ≥ 3 toxicity **except:**<br>Lymphocyte count decreased (lymphopenia) CTCAE Grade ≥ 3 unless clinically significant |

[a] Patients will initially not receive prophylactic treatment for skin toxicity or nausea/vomiting during cycle 1. However, prophylactic treatment may be initiated in all patients at the dose level where these toxicities have been observed and in all further patients if at least 1 patient has experienced skin toxicity or nausea/ vomiting ≥ CTCAE Grade 3 or if at least 2 patients experienced skin toxicity or nausea/ vomiting ≥ CTCAE Grade 2. However anti-emetics may be applied for treatment if the patient has experienced nausea/vomiting CTCAE Grade ≥ 1, at the discretion of the physician.

[b] For any CTCAE Grade 4 or any CTCAE Grade 2 hepatic toxicity that does not resolve within 7 days to CTCAE Grade ≤ 1 (or CTCAE Grade ≤ 2 if liver infiltration with tumor present), an abdominal CT scan has to be performed to assess if it is related to disease progression.

[c] Refers to total bilirubin

### 4.3.4 Follow-up for dose-limiting toxicities (Phase I only).

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed regularly (as clinically indicated) until resolution or stabilization of the event, whichever comes first.

If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. However, the patient will continue to be followed for toxicity as previously described. All patients will be followed for adverse events and serious adverse events for 30 days following the last dose of MEK162 unless

the patient received further cytotoxic chemotherapy. In this case, only those adverse events and serious adverse events believed by the investigatory to have a causal relationship to the study medication will be captured.

### 4.3.5 Dosing modifications

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustment to dose level 1 (30 mg bid)is permitted in order to allow the patient to continue the study drug. An individual patient may have one dose reduction to 30 mg bid (Table 4-4). This is the lowest dose permitted on the study and doses below 30 mg bid are not permitted. In case of toxicity, the dose should be held until resolution to grade 1 and then restarted at 30 mg bid.

Missed/skipped doses will not be made up (i.e. the patient should not double their dose if the previous dose was missed). When the toxicity that resulted in a dose reduction improves to Grade 1 or less, the dose can be re-escalated at the investigators discretion provided there are no other concomitant toxicities. However, no dose re-escalation is allowed for dose reductions that were due to left ventricular dysfunction.

In general, doses should not be reduced or interrupted for Grade 1 AEs unless the AE is a new visual or ocular AE (see Table 4-5), but treatment to control symptoms should be provided as appropriate, if applicable. If visual changes or new ocular findings are assessed as not related to study drug after ophthalmologic evaluation, then study drug can be resumed at the same, previous dose. All adverse events should be followed up weekly or as clinically appropriate until stabilization or resolution.

Skin toxicity (acne, rash, dermatitis acneiform, etc.), visual changes (related to CSR), nausea, diarrhea and asymptomatic, reversible elevation of CPK have been associated with MEK162 administration. For skin toxicity, institutional standard of care treatment should be initiated promptly. Treatment of rash may include, but is not limited to, topical or oral antibiotics, topical or oral anti-inflammatories, topical or oral corticosteroids and oral anti-histamines

Management of diarrhea should be as per institutional standard of care.

Furthermore, please refer to Appendix 3 and Appendix 4 for additional supportive care guidelines for the management of MEK162 induced skin toxicity and diarrhea respectively. Visual changes should be graded according to CTCAE version 4.03 as described below.

**Table 4-4: Dose reduction steps for MEK162**

| **Dose reduction*** | | |
|---|---|---|
| | Starting dose level 1 | Dose level – 1 |
| MEK162 | Ph I: 30 mg bid<br>Ph II: TBA by MTD by Ph I | Ph I: **<br>Ph II: **TBD MTD from phase I |
| *Dose reduction should be based on the worst toxicity demonstrated | | |
| **Dose reduction below 30 mg is not allowed; patients on 30 mg bid who need dose adjustment may have their dose held and then re-introduced at the same dose level | | |

**Table 4-5: Recommended Dose Modifications Associated with Treatment-Related Adverse Events**

A dose reduction below 30 mg BID is not allowed. Patients requiring additional reductions must be discontinued from study treatment.

**CTCAE Grading for Eye Disorders**

| **Grade** | **Description** |
|---|---|
| 1 | Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| 2 | Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL |
| 3 | Severe or medically significant but not immediately sight threatening;<br>Hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL |
| 4 | Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye |

Retinal detachment should be graded according to CTCAE version 4.03 as described below.

| Grade | Description |
|---|---|
| 1 | Asymptomatic |
| 2 | Exudative and visual acuity 20/40 or better |
| 3 | Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200) |
| 4 | Blindness (20/200 or worse) in the affected eye |

Diarrhea should be graded according to CTCAE version 4.03 as described below.

**CTCAE grading of diarrhea**

| Grade | Description |
|---|---|
| 1 | Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline |
| 2 | Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline |
| 1-2 Complicated | Definition as above with the following complicating signs/symptoms:<br>• Moderate to severe cramping<br>• Grade ≥ 2 nausea/vomiting<br>• Decreased performance status<br>• Fever<br>• Sepsis<br>• Neutropenia<br>• Frank bleeding<br>• Dehydration<br>• Unresolved diarrhea after 48 hours of treatment with loperamide (including high dose administration) and initiation of second-line treatment |
| 3 | Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting selfcare ADL |
| 4 | Life threatening consequences; urgent intervention indicated |

**MEK162 – Recommended Dose Modifications Associated with Treatment-Related Adverse Events**

| Worst toxicity CTCAE v4.03 Grade (unless otherwise specified*) | Dose Adjustment for Study Drug MEK162 |
|---|---|
| **Eye disorder - CSR like events** | |
| Grade 1 | Maintain dose level of MEK162 and increase frequency of ophthalmic monitoring to at least every 14 days. |
| Grade 2 | Maintain dose level of MEK162 and refer the patient to ophthalmologist within one week:<br>- If resolved to Grade ≤ 1 in ≤ 21 days, maintain dose of MEK162.<br>- If not resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level** of MEK162 or maintain dose of MEK162 based upon the Investigator's discretion after consultation with the ophthalmologist |
| Grade 3 | Interrupt MEK162 and refer the patient to ophthalmologist within one week:<br>- If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level*** of MEK162<br>- If not resolved to Grade ≤ 1 in ≤ 21 days, discontinue patient from study drug treatment. |

| **Worst toxicity CTCAE v4.03 Grade (unless otherwise specified*)** | **Dose Adjustment for Study Drug MEK162** |
|---|---|
| Grade 4 | Permanently discontinue MEK162 and close follow up of ophthalmic monitoring. |
| **Eye disorders -RVO** | |
| Any grade | Permanently discontinue MEK162 |
| **Other eye disorders** | |
| Grade 1 – 2 | Maintain dose level of MEK162 and increase frequency of ophthalmic monitoring to at least every 14 days. |
| Grade 3 | Interrupt MEK162 and refer patient to ophthalmologist within one week:<br>-If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level*** of MEK162<br>- If not resolved to Grade ≤ 1 in ≤ 21 days, discontinue patient from study drug treatment. |
| Grade 4 | Permanently discontinue MEK162 |
| **Liver related Adverse Events** | |
| AST or ALT<br>Grade 1 (> ULN - 3 x ULN) | Maintain dose level of MEK162 |
| Grade 2<br>AST or ALT (> 3 - 5.0 x ULN or 3 X baseline value*****) AND **bilirubin elevation < 2.0 x ULN** | Interrupt dose of MEK162 until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then:<br>- If resolved in ≤ 14 days, maintain dose level of MEK162.<br>- If resolved in > 14 days, reduce dose level** of MEK162. |
| AST or ALT > 3.0 - 5.0 x ULN and **blood bilirubin[a] > 2.0 x ULN** | Interrupt dose of MEK162 until resolved to Grade ≤ 1, then:<br>- If resolved in ≤ 7 days, reduce dose level** of MEK162.<br>- If resolved in > 7 days, discontinue patient from study drug treatment. |
| Grade 3<br>AST or ALT (> 5.0 - 8.0 x ULN) **AND blood bilirubin** < 2.0 x ULN | Interrupt dose of MEK162 until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then:<br>- If resolved in ≤ 14 days, maintain dose level of MEK162.<br>- If resolved in > 14 days, reduce dose level** of MEK162. |
| AST or ALT (>8 x ULN) **AND blood bilirubin < 2.0 x ULN** | Permanently discontinue MEK162 |
| AST or ALT> 5.0 x ULN<br>AND **blood bilirubin[a] > 2.0 x ULN** | Permanently discontinue MEK162 |
| AST or ALT Grade 4 (> 20.0 x ULN) | Permanently discontinue MEK162 |
| **Cardiac disorders** | |
| Left ventricular systolic dysfunction*<br>Asymptomatic decrease of >10% in LVEF compared to baseline and the LVEF is below the institution's lower limit of normal | Interrupt dose of MEK162 and repeat evaluation of LVEF within 2 weeks<br>If the LVEF recovers (defined as ≥ LLN and decrease ≤ 10% compared to baseline) ≤ 4 weeks, reduce 1 dose level**. Monitor LVEF 2 weeks after restarting on MEK162, every 4 weeks for 12 weeks and subsequently as per protocol.<br>If the LVEF does not recover within 4 weeks, permanently discontinue patient from study treatment. Closely monitor LVEF until resolution (or for 16 weeks). |
| Grade 3 – 4 | Permanently discontinue patient from MEK162. Closely monitor LVEF for 16 weeks or until resolution |

| **Worst toxicity CTCAE v4.03 Grade (unless otherwise specified*)** | **Dose Adjustment for Study Drug MEK162** |
|---|---|
| | Note: Copies of ECHO and/or MUGA scans could be requested for patients with decrease of >10% in LVEF compared to baseline and LVEF < LLN |
| **CK elevation** | |
| Grade 1-2 | Continue treatment on same dose level |
| Grade 3<br>(> 5.0 ULN- 10 ULN) | If asymptomatic: Maintain dose of MEK162 and monitor closely<br>If symptomatic (muscle pain/spasms): Interrupt dose of MEK162 until resolved to CTCAE Grade ≤ 1 and monitor closely (Section 7.2.2.5.4), then:<br>- If resolved in ≤ 21 days, reduce 1 dose level** of MEK162<br>- If resolved in > 21 days, then discontinue patient from study drug treatment |
| Grade 4 | If asymptomatic: interrupt and monitor closely<br>- If resolved in ≤ 21 days, reduce 1 dose level** of MEK162<br>- If resolved in > 21 days, then discontinue patient from study drug treatment<br>If symptomatic : permanently discontinue treatment |
| **Rash** | |
| Grade 1 | Treatment with MEK162 should be maintained at the current dose<br>*Initiate prophylactic regimen if not already started.* |
| Grade 2 | Treatment with MEK162 should be continued and the rash should be closely monitored.<br>If worsened, proceed as Grade 3<br>*Initiate prophylactic regimen if not already started and optimize treatment* |
| Grade 3 | The dose of MEK162 should be interrupted. Reassess the patient weekly.<br>Improvement to Grade 1: reintroduce ttreatment with MEK162 at the same dose level<br><br>Improvement to Grade 2 : reintroduce ttreatment with MEK162 at a reduced dose level<br><br>*Consider obtaining dermatology consultation. Manage rash per dermatologist's recommendation* |
| Grade 4 | Permanently discontinue MEK162 |
| **Diarrhea** | |
| Uncomplicated Grade 1-2 | Consider temporary interruption of MEK162 until resolved to Grade ≤ 1. Treatment may then be resumed at current dose level |
| Complicated Grade 1-2 | Temporarily interrupt MEK162 treatment until resolved to Grade ≤ 1. Restart MEK162 at a reduced dose level |
| Grade 3 | Temporarily interrupt MEK162 treatment until resolved to Grade ≤ 1. Restart MEK162 at a reduced dose level |
| Grade 4 | Temporarily interrupt MEK162 treatment until resolved to Grade ≤ 1. Restart MEK162 at a reduced dose level |
| **All other adverse events (suspected to be related)** | |
| Grade 1-2 | In the event is a persistent Grade 2 AE, not responsive to a specific therapy, consider study drug reduction. |
| Grade 3 | Interrupt study drug until resolution to Grade ≤1 or to pre-treatment/ Baseline level. If the event resolves within 21 days then study drug may be restarted at a lower dose (one level below that previously received) based upon the Investigator's discretion. |
| Grade 4 | Permanently discontinue MEK162**** |

* Not according to CTCAE

** Dose reduction below 30mg BID is not allowed

*** Ophthalmic monitoring recommended: further evaluation with specialized retinal imaging (e.g. ocular coherence tomography, angiography)

**** A patient with a Grade 4 AE may resume treatment at the lower dose level if the AE recovers to Grade ≤1 within 21 days of

| Worst toxicity CTCAE v4.03 Grade (unless otherwise specified*) | Dose Adjustment for Study Drug MEK162 |
|---|---|

discontinuing drug and, if in the opinion of the Investigator , the event is not life-threatening, and the patient can be managed and monitored for recurrence of AE. Any patients requiring a treatment interruption of longer than 21 days must discontinue study drug permanently.

***** For patients enrolled with liver metastases and baseline LFT elevations

[a] Refers to total bilirubin

### 4.3.6 Other concomitant medications

The Investigator should instruct the patient to notify the study site of any new medications he/she takes after the start of the study drug.

All medications and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) taken within 2 weeks prior to first dose of study drug must be recorded in the electronic medical record.

All medications (other than study drug) and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) administered after the patient starts treatment with study drug, and any changes in dosing must be recorded in the electronic medical record.

Patients taking concomitant medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible.

#### Permitted concomitant therapy requiring caution and/or action

The solubility of MEK162 is pH dependent and a 10-fold decrease in solubility is observed between pH 1 and 2. Patients receiving concomitant treatments that could potentially modify the gastric pH (i.e. PPI) should be instructed to take them at least two hours after the administration of MEK162.

MEK162 has been identified to be primarily metabolized by UGT1A1 in vitro. It is advised that inhibitors and inducers of UGT1A1 should be taken with caution when co-administered with MEK162. Patients should be closely monitored for the occurrence of adverse events. Please refer to Table 6-10 for a list of these known drugs but this list may not be exhaustive.

**Table 4-~~2~~10 List of inhibitors and inducers of UGT1A1 to be used with caution**

| Inhibitors of UGT1A1 | Inducers of UGT1A1 |
|---|---|
| Atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib | Carbamazepine, nicotine, rifampicin, testosterone propionate |

*In vitro* data showed that MEK162 is a substrate of P-gP and BCRP and thus the use of drugs that are known to inhibit these transporters should be used with caution. Please refer to Table below for a list of these drugs.

**List of inhibitors of human transporters to be used with caution**

| Transporters | Category | Substrate |
|---|---|---|
| P-gP | Calcium Channel Blockers | felopidine, verapamil, diltiazem, mibefradil, nifedipine, nitrendipine |
| | Protease inhibitors | indinavir, ritonavir, lopinavir, telaprevir, saquinavir, nelfinavir |
| | Antibiotics | Fexofenadine, clarithromycin, azithromycin, erythromycin, rifampin |
| | Antiarrhythmics | quinidne, dronedarone, amiodarone |
| | Adrenergic Antagonist | carvedilol, talinolol |

| | | |
|---|---|---|
| | Herbal Medications | Schisandra chinensis, St. John's wort, milk thistle (silybum marianum), ginkgo biloba |
| | Others | valspodar (PSC 833), elacridar (GF120918), ranolazine, fluvoxamine, itraconazole, querceptin, captopril, conivaptan, paroxetine, ticagrelor, telmisartan, tolvaptan |
| BCRP | Others | elacridar (GF120918) |

* This table was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" and from the University of Washington's Drug Interaction Database.

For further information, please see the FDA's website:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm081177.htm#PgpTransport

MEK162 potently inhibits CYP2B6 Ki of 1.67 µM Based on these *in vitro* findings, MEK162 may inhibit the metabolic clearance of co-medications metabolized by CYP2B6, if sufficiently high concentrations are achieved *in vivo.* At 45 mg BID, the maximum concentrations achieved in plasma are normally <1.5 µM so the risk of drug interaction is limited. Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of this enzyme.

Please refer to Table below for a list of CYP2B6 substrates.

**List of CYP2B6 substrates to be used with caution**

| Cytochrome | Category | Substrate |
|---|---|---|
| CYP2B6 | Alkylating Agents (anticancer): | cyclophosphamide, ifosfamide, thiotepa |
| | Others | Bupropion[1], efavirenz[1], methadone |

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. The following website may be further useful as a reference to avoid potential drug-drug interactions: http://medicine.iupui.edu/clinpharm/ddis/table.asp.

Drugs with a known, a conditional or a possible risk to induce Torsade de Pointes (TdP) should be used with caution. Patients receiving such medications must be carefully monitored for potentiating of toxicity due to any individual concomitant medication, and may require dose titration of the drug substance. For further information, please visit the website of the QTdrugs.org Advisory Board of the Arizona CERT.

Patients will be advised to contact the study personnel (research nurse or physician) whenever they are to be started on a new medication in order for agents from above list are excluded and alternates are recommended.

### 4.3.7 Prohibited concomitant therapy

- Other investigational therapies must not be used while the patient is on the study with the exception of hydroxyurea, which is allowed during the first cycle of therapy only.
- Anticancer therapies (including chemo- or biologic-therapy or palliative radiation therapy, covering >25% of the red bone marrow reserve, and surgery) other than the study treatments must not be given to patients while the patient is on the study. If such therapeutic measures are required for a patient then the patient must be discontinued from the study.

### 4.3.8 Hormonal contraception

Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to the unknown effect of study drug interactions.

### 4.3.9 Study drug discontinuation

In general, doses should not be reduced or interrupted for Grade 1 AEs unless the AE is a new visual or ocular AE (see Table 4-5), but treatment to control symptoms should be provided as appropriate, if applicable. If visual changes or new ocular

findings are assessed as not related to study drug after ophthalmologic evaluation, then study drug can be resumed at the same, previous dose.

Patients requiring treatment interruptions of >21 days must be discontinued.

All patients must have evaluations for 28 days after the last dose of study treatment. Patients lost to follow up should be recorded. Patients who discontinue study drug before completing the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 28 days following the last dose of study drug.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone

Patients who discontinue study drug should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

## 4.4 End of Study Treatment

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Pregnancy
- Non-compliance

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information. Patients may be withdrawn from the study prematurely for one of the following reasons:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- New cancer therapy
- Disease progression
- Treatment duration completed as per protocol

## 4.5 Study evaluation completion

As a general rule, if a patient discontinues study drug and later is prematurely withdrawn from the study, the reasons for study evaluation completion may include the following:

- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- New cancer therapy
- Clinically significant disease progression

For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

# 5 VISIT SCHEDULE AND ASSESSMENTS

Table 5-1 lists all of the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

**Table 5-1: Visits**

| | Screening | Cycle 1 | | | | | Cycle 2 and Beyond | | | | | OSA[g] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day (+/- 2 days)** | **–14 to -1** | **1** | **4** | **8** | **13-27** | **28** | **1** | **4** | **8** | **13-27** | **28** | |
| MEK162 | | ← | | | | → | ← | | | | → | |
| Written informed consent | X | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | |
| Physical Exam [c f] | X | X | | | | | X | | | | | X |
| ECOG Performance Status [c] | X | X | | | | | X | | | | | X |
| Vital signs [c] | X | X | X | X | | | X | X | X | | | X |
| Adverse events assessment | | X | X | X | X | X | X | X | X | X | X | X |
| Medication history | X | | | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology [c] | X | X | X | X | | | X | | | | | |
| Serum chemistry [c] | X | X | X | X | | | X | | | | | |
| CK and troponin [d] | X | | | | | | | | | | | |
| Serum pregnancy test [c] | X | | | | | | X | | | | | |
| Coagulation profile | X | | | | | | | | | | | |
| Liver Function tests [c] | X | X | X | X | | | X | | | | | X |
| Urinalysis [c] | X | | | | | | X | | | | | |
| 2D Echo or MUGA scan [a] | X | | | | | x | | | | | | |
| Bone marrow examanation | X | | | | | X | | | | | | X[e g] |
| Cytogenic and molecular assessment | X | | | | | X | | | | | | X[e g] |
| Ophthalmologic exam [b c] | X | | | | | | X | | | | | |
| ECG[h] | X | | | | | X | | | | | | X |

FOOTNOTES:

a: Echo or MUGA may be performed at screening within -28 to -1, after one month of treatment of MEK162 and every two to three months during treatment thereafter.

b: Ophthalmic examination will include slit lamp examination, visual acuity testing, visual field testing, intraocular pressure (IOP) and indirect fundoscopy with attention to retinal abnormalities, especially CSR and RVO. For patients with clinical suspicion of CSR or RVO, additional assessments of fluorescein angiography and/or optical coherence tomography and Electroretinogram (ERG) are recommended.

c: The assessments should be performed monthly.

d: CK and troponin will be performed at the same timepoints as the hematology collections as outlined above. Follow up for total creatine kinase (CK) >/equal to 3 X ULN will include weekly assessment of isoenzymes and myoglobin in blood/or urine, and troponin as applicable.

e: Bone marrow and cytogenic assessment at the end of the study can be waved depending on clinical situation.

f: DLT will be assessed throughout the time the participant remains on study drug.

g: Off study Assessment will be performed within 30 days of the last study drug dose

h: ECG during screening, at day 28, and OSALaboratory assessments and vitals recording can be performed at outside facility with the records provided to the study coordinator. However, all outside labs will need to be reviewed, signed and dated by the Principal Investigator (PI) or treating physician (listed on the Delegation of Authority) prior to submission to the electronic medical record. The PI or treating physician should appraise abnormal lab results and determine/document clinical significance.

All visits have a flexibility of +/- 2 days.

## 5.1 Treatments

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the caregiver. This information should be captured in the source document at each visit.

# 6 SAFETY MONITORING

## 6.1 Serious adverse event reporting

### Serious Adverse Event Reporting (SAE) for M. D. Anderson-Sponsored IND Protocols

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

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

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

The following SAEs are not subject to expedited reporting, but would still be included in the annual report via the SAE log.

a) Infection or cytopenias leading to hospitalization or prolongation of hospitalization

b) Disease progression leading to death, life-threating AE, hospitalization or prolongation of hospitalization, or disability.

**Reporting to the FDA:**

- Serious adverse events will be forwarded to FDA by the -IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32
- It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines the sponsor's guidelines, and Institutional Review Board policy.

**Investigator Communication with Supporting Companies:**

Information about all serious adverse events will be collected and recorded on the eSAE form that is used by MDACC for safety reporting to the IND Office and MDACC IRB. Such information will be provided to Array Drug Safety by faxing the information contained in the exemplar Serious Adverse Event Form, which is appended to the Protocol using fax number (303) 386-1516. To ensure patient safety each serious adverse event must also be reported to Array within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Any serious adverse event occurring after the patient has provided informed consent, has started taking the study medication, and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

### 6.1.1 Reporting responsibility

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Array in accordance with institutional guidelines.

### 6.1.2 Reporting procedures

The investigator must complete the eSAE form that is used by MDACC for safety reporting to the IND Office and MDACC IRB and Array SAE coversheet in English, assess the relationship to study treatment and send the initial completed eSAE form and Array SAE coversheet by fax 1-303-386-1516 within 24 hours to the Array Drug Safety Department. The investigator must then ensure that the form and coversheet are accurately and fully completed with follow-up information and fax those to Array Drug Safety within 2 to 3 calendar days for deaths or life-threatening events and 15 calendar days for other serious adverse events. The original and the duplicate copies of the eSAE form, ArraySAE coversheet, and the fax confirmation sheet must be kept with the case report forms at the study site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The eSAE form, Array SAE coversheet, and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

### 6.1.3 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported toArraywithin 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

### 6.1.4 Adverse events of special interest

As a result of signals observed from previous studies, several AEs requiring a close follow-up were identified. For each category, selected AEs similar in nature, will be identified and grouped:

- Ocular/Visual Events
- Retinal Vein Occlusion
- Rash and related events
- Peripheral/generalized edema/anasarca
- Serum CK elevation
- Cardiac failure related events
- Hepatic events

# 7 STATISTICAL METHODS AND DATA ANALYSIS

This is a two-part trial to determine dosing and efficacy in leukemia patients of MEK 162. Phase I will determine MEK 162 dose (MTD) in subjects with advanced leukemias. The phase I part of the trial has a 3+3 dose escalation design, with 3 to 6 subjects in each cohort, using the 50% dose escalation scheme, based on the occurrence of DLTs. Patients will be entered sequentially to each dose level If none of the first 3 patients at a dose level experience dose-limiting toxicity (DLT), new patients may be entered at the next higher dose level. If 1 of 3 patients experience DLT, up to 3 more patients are started at that same dose level. If 1 of 6 experience DLT, then new patients may be entered at the next higher dose level. If 2 or more experience DLT, no further patients are started at that dose. The MTD is the highest dose level in which <2 patients of 6 develop DLT.

The sample size is envisaged to be 15 subjects (assuming no need for replacement of subjects in the MTD analysis set), comprising 2 dose levels (DLs) with a maximum of 6 subjects in each plus 3 additional subjects enrolled at the MTD.

At the each dose level subjects will receive MEK 162 orally twice a day on

- Days 1 to 28 of a 28-day cycle

The MTD determined by Phase I will be used in an open label, Phase II part of MEK 162 in older subjects with newly diagnosed KRAS/NRAS mutant poor prognosis AML who are not candidates for intensive chemotherapy.

**Table 7-1: Dose of MEK 162/MEK 162**

| Provisional Dose levels | Dose of MEK 162/MEK 162 |
|---|---|
| 1 | 30 mg po bid |
| 2 | 45 mg po bid |

## 7.1 Efficacy

The method of Thall, Simon and Estey [1995] will be used for futility and toxicity monitoring for this study. The primary endpoint is the overall response (CR+CRi) after one or two cycles of treatment. The historical data suggested the overall response rate is 5%. With the assumption that the improved overall response rate to be 20%, it is estimated that a total of 42 evaluable patients will yield 91% power at a significance level of 5% based on chi-square test. The overall response (CR+CRi) denoted as OR, and toxicity (DLT definition in phase I), denoted as TOX, will be monitored simultaneously by Bayesian stopping boundaries calculated based on beta-binomial distribution. Independence is assumed between OR and TOX. There are no historical data available. The current regimen will be considered promising if the OR rate is at least 20% and the TOX rate is below 30%. The prior probabilities of OR and TOX for the regimen are modeled by beta distributions (Beta(0.4, 1.6) and Beta(0.6, 1.4), respectively). Denoting the probabilities of the OR rate and TOX by $\{\theta_{OR}, \theta_{TOX}\}$, the following decision criteria will be applied:

1) stop if Prob $\{ \theta_{OR} < 0.2 \mid \text{data}\} > 0.98$, and
2) stop if Prob $\{ \theta_{TOX} > 0.3 \mid \text{data}\} > 0.85$

Patients will be monitored by a cohort size of 6 according to the following stopping boundaries for OR and toxicity. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M. D. Anderson Cancer Center (MDACC) was used to generate the futility/toxicity stopping boundaries and the OC table.

**Table 7-2: Stopping boundaries for overall response (OR) and toxicity**

| Number of patients evaluated | e trial if there are this many response | e trial if there are this many toxicities |
|---|---|---|
| 6 | Never stop | 4-6 |
| 12 | 0 | 6-12 |
| 18 | 0 | 8-18 |
| 24 | 0-1 | 10-24 |
| 30 | 0-2 | 12-30 |
| 36 | 0-2 | 14-36 |

The operating characteristics are summarized in the following table.

**Table 7-3: Operating characteristics of efficacy and safety monitoring**

| True Toxicity Rate | True OR Rate | Prob (stop the trial early) |
|---|---|---|
| 0.1 | 0.05 | 0.85 |
| | 0.1 | 0.5 |
| | 0.15 | 0.24 |
| | 0.2 | 0.1 |
| | 0.25 | 0.04 |
| 0.2 | 0.05 | 0.86 |
| | 0.1 | 0.52 |
| | 0.15 | 0.27 |
| | 0.2 | 0.14 |
| | 0.25 | 0.08 |
| 0.3 | 0.05 | 0.89 |
| | 0.1 | 0.65 |
| | 0.15 | 0.46 |
| | 0.2 | 0.37 |
| | 0.25 | 0.32 |
| 0.4 | 0.05 | 0.96 |
| | 0.1 | 0.86 |
| | 0.15 | 0.79 |
| | 0.2 | 0.75 |
| | 0.25 | 0.74 |

## 7.2 Populations for analysis

**ITT population**: consists of all patients who received at least one dose of study drug..

**Safety population**: consists of all enrolled patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

Please note: the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no post-treatment safety data of any kind would be excluded from the safety population.

**Per protocol population**: consists of all randomized patients who received at least one dose of the study drug and had no major protocol violations. The per protocol patient population will be identified prior to database lock.

**MTD population**: consists of all patients who either received study drug and had sufficient safety evaluations or discontinued due to unacceptable toxicity and have received at least approximately 75% doses of first cycle of therapy. The MTD patient population will be identified prior to database lock.

**Efficacy population**: consists of all patients treated at MTD who meet the requirements for recruitment into the expansion phase. The primary endpoint is overall response rate (ORR). The ORR will be estimated along with the exact 95% confidence interval.

## 7.3 Patient demographics/other baseline characteristics

Demographic and other baseline data *populations)*. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25$^{th}$ and 75$^{th}$ percentiles, minimum, and maximum will be presented.

## 7.4 Treatments (study drug, concomitant therapies, compliance)

Concomitant medications and significant non-drug therapies prior to and after the start of MEK162 will be summarized.

## 7.5 Adverse events (AE)

The investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. Adverse events and protocol specific data will be entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form for this protocol.

## 7.6 Other safety data

Data from other tests (e.g., *electrocardiogram or vital signs*) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

# 8 ADMINISTRATIVE PROCEDURES

## 8.1 Regulatory and ethical compliance

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.

2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.

3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

## 8.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Array before study initiation if in accordance with the institution's policy. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to Array. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

## 8.3 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

## 8.4 Amendments to the protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Array the investigator and IRB prior to implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB. A copy of the written approval of the IRB/IEC/REB, must be sent to Array.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes.

### Discontinuation of the study support

Array reserves the right to discontinue support for any study under the conditions specified in the clinical trial agreement.

## 8.5 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Array and prior to any outside submission.Array must receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Array's responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigator/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Array and, in accord with the trial contract and shall not permit disclosure of Array confidential or proprietary information.

## 8.6 Disclosure and confidentiality

The investigator agrees to keep all information provided by Array in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Array (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Array to the investigator may not be disclosed to others without direct written authorization from Array, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

## 8.7 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

# 9 APPENDIX 1 – CLINICAL RESPONSE CRITERIA FOR ACUTE LEUKEMIA

International Working Group (IWG) consensus criteria for treatment response in AML (modified).

**Morphological Complete Remission (CR):**

- Normalization of the peripheral blood absolute neutrophil count $\geq$ $1.0x10^9$/L, platelets $\geq$ than $100x10^9$/L no residual evidence of extramedullary disease and bone marrow aspirate with $\leq$ 5% blasts, no blasts with Auer rods(AML only).

**Morphological Complete Remission with incomplete blood count recovery (CRi):**

- Same as CR but without normalization of the peripheral blood absolute neutrophil and platelet count

**Partial Remission (PR):**

- Normalization of the peripheral blood absolute neutrophil count $\geq$1.0x109/L, platelets $\geq$ than 100x109/L, and at least a 50% decrease in the percentage of marrow aspirate blasts to 5-25% , or marrow blasts $\leq$5% with Auer rods (AML only).

**Progressive disease (PD):** may be defined as ONE of the following:

- >50% increase in peripheral blood or bone marrow blasts from best assessment with minimum threshold of 20% blasts in the marrow or 1.0x109/L blasts in peripheral blood.

- Development of biopsy proven extramedullary leukemia (if the subject has extramedullary disease at baseline, then PD will be defined by blood and marrow criteria or if new sites of extramedullary disease appear).
- If subject who present with an initial marrow blast percentage sufficiently high to preclude the ability to base disease progression on a>50% increase in marrow blast percentage, disease progression should be based on peripheral blood criteria or development of extramedullary leukemia as above.

**Stable disease:**

- Subjects who fail to achieve CR CRi or PR and who do not have criteria for PD will be defined as having the stable disease. If the subject dies prior to response assessment at the end of Cycle 1, then they will be classified as “indeterminate”.

## 9.1 APPENDIX 2 - CLINICAL RESPONSE CRITERIA FOR ACUTE LEUKEMIA

**Relapse from CR or CRi:**

- Reappearance of leukemic blasts in the peripheral blood; or> 5% blasts in the bone marrow not attributable to another cause (e.g. recovery of normal cells following treatment – induced aplasia or use of growth factors) OR
- Appearance or reappearance of extramedullary disease.
- If there are no circulating blasts and no extramedullary disease and the bone marrow blast percentage is >5% but <20%, then a repeat bone marrow performed at least 7 days after the first marrow examination and documenting bone marrow blast percentage >5% is necessary to establish relapse.

**Cytogenetic Responses**

Complete cytogenetic response: An abnormal clone is detected in all metaphases prior to treatment and only normal metaphases are observed in all metaphases following treatment.

Partial cytogenetic response: An abnormal clone is detected in all metaphases prior to treatment and the post-treatment sample has 50% or fewer abnormal metaphases compared to the pre-treatment value.

Cytogenetic non-response: An abnormal clone is detected in all metaphases prior to treatment and neither complete nor partial cytogenetic response is observed in post-treatment specimens

Specimens with normal cytogenetic results before treatment will not be evaluated for cytogenetic response. The method used to determine cytogenetic response will be standard metaphase cytogenetics.

**9.2 Appendix 3: Recommended Guidelines for the management of MEK162 induced skin toxicity**

Clinical judgment and experience of the treating physician should guide the management plan of each patient, however, the following options are recommended.
Prophylactic treatment for skin toxicity is recommended. Prophylactic supportive therapy for skin toxicity may be initiated 24 hours prior to the first treatment with MEK162 or as needed. Apply topical agents to the mostly common affected areas such as face, scalp, neck, upper chest, upper back.

- Non oily sunscreen (PABA free, SPF ≥ 15, UVA/UVB protection)Topical steroid, preferably mometasone cream (i.e. Elocon®)
- Topical erythromycin evening (i.e.Eryaknen®)
- Offer doxycycline (100 mg daily) for the first 2-3 weeks of study drug administration.

Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to first treatment, and more often as needed.

Effective medications also include antihistamines, other topical corticosteroids, other topical antibiotics and low-dose systemic corticosteroids

The treatment algorithm based on CTCAE grade is as follows:

**Mild Rash (CTCAE Grade 1)**

- Consider prophylactic rash treatment as described above if not already started
- Topical mometasone cream or other topical corticosteroid and/or topical erythromycin (2%) or other topical antibiotics are recommended.
- The patient should be reassessed after 2 weeks or sooner if rash worsens.

**Moderate Rash (CTCAE Grade 2)**

- Although there has been no evidence of phototoxicity or photosensitivity in patients being treated with MEK162, doxycycline (or minocycline as second option) should be used with careful UV protection (i.e., avoid direct exposure to sunlight, use sunglasses, use sunscreen, etc.).

The treatment recommendation is: topical erythromycin or clindamycin (1%) plus mometasone or pimecrolimus (1% cream) plus oral antibiotics: oxytetracycline (125 mg twice daily) or oral lymecycline (408 mg once daily) or other antibiotics (doxycycline 100 mg BID or minocycline (50 to 100 mg QD).

**Severe Rash (CTCAE Grade 3-4)**

**CTCAE Grade 3**

- Modality 1: In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day to 0).
- Modality 2: In addition to the interventions recommended for moderate rash, consider oral isotretinoin (0.3 to 0.5 mg/kg) (Lacouture et al 2011)

**CTCAE Grade 4**

- Immediately discontinue the patient from study drug and treat the patient with oral and topical medications (see recommendation CTCAE Grade 3).

**In Addition:**

It is strongly recommended that patients who develop rash/skin toxicities receive symptomatic treatment for management of the specific sign or symptom of the toxicity.

- For pruritic lesions, the use of cool compresses and oral antihistamine agents may be helpful.
- For fissuring, the use of Monsel's solution, silver nitrate, or zinc oxide cream is advised.
- For desquamation, emollients that are mild pH 5 neutral are recommended.
- For paronychia, antiseptic bath and local potent corticosteroids in addition to oral antibiotics are recommended and, if no improvement is seen, a dermatologic or surgical consultation is recommended.
- For infected lesions, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated.

**References**

Lacouture ME, Anadkat MJ, Bensadoun RJ, Bryce J, et al (2011) Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer; 19: 1079–95

## Appendix 4: Guidelines for the management of MEK162 induced diarrhea

### Proactively investigate for occurrence of diarrhea

Educate patient

1. Remind patients at each visit to contact the site immediately upon the first sign of loose stool or symptoms of abdominal pain. Additionally, at each study visit, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea-related symptoms. If symptoms were experienced by the patient, then the site should question the patient regarding the actions taken for these symptoms and re-instruct as necessary.
2. In addition to dietary modification, the patients should be instructed on early warning signs (e.g. severe cramping → severe diarrhea, fever with diarrhea → infection).
3. Patients should be instructed on what to report to the investigator if possible (i.e. number of stools, stool composition, stool volume) and how to report symptoms of life-threatening sequelae (e.g. fever or dizziness on standing).

### Anti-diarrhea therapy

In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, patient education as well as proper management of diarrhea is mandatory.

Management of diarrhea should be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. All concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications eCRF. It is recommended that patients be provided loperamide tablets. It is mandatory that patients are instructed on the use of loperamide on the first day of MEK162 dosing in order to manage signs or symptoms of diarrhea at home. In addition to the MEK162 induced diarrhea dosing guidelines in Table 6-6 of the protocol, these instructions should be provided at each visit and the site should ensure that the patient understands the instructions.

Explain the frequency of diarrhea and its relationship to NCI CTCAE grading.

Determine if diarrhea is complicated versus uncomplicated.

### Rule out other or concomitant causes.

These may include:

- Infection by Candida spp, Salmonella spp., Clostridium difficile, Campylobacter spp. Giardia, Entamoeba, Cryptosporidium which can lead to opportunistic infections in mmunosuppressed patients,
- Medications (diarrheogenic agents; laxatives, antacids, etc.)
- Malabsorption/lactose intolerance
- Fecal impaction, partial bowel obstruction

### For uncomplicated Grade 1 to Grade 2 diarrhea

- Stop all lactose-containing products and alcohol and eat frequent small meals that include bananas, rice, applesauce or toast)

- Stop laxatives, bulk fiber (i.e. Metamucil®) and stool softeners (e.g. docusate sodium; Olace®)
- Stop high-osmolar food supplements such as Ensure® Plus and Jevity® Plus (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (e.g. water, Pedialyte®, Gatorade® or broth)
- Consider administration of standard dose of loperamide: initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Discontinue loperamide after 12-hours diarrhea-free (Grade 0) interval.
- If uncomplicated Grade 1 to Grade 2 diarrhea persists for more than 24 hours, escalate to high dose loperamide: 2 mg every 2 hours (max. of 16 mg/day) or after each unformed stool.

**Note:** Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician.

- If uncomplicated Grade 1 to Grade 2 diarrhea persists after 48 hours total treatment with loperamide, discontinue loperamide and begin a second-line agent which can be an opiate (opium tincture or paregoric), or budesonide

**For complicated Grade 1 to Grade 2 diarrhea or Grade 3 to 4 diarrhea**

- The patient must call the investigator immediately
- If loperamide has not been initiated, initiate loperamide immediately. Initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Administer IV fluids and electrolytes as needed. In case of severe dehydration, replace loperamide by octreotide.
- Monitor/Continue IV fluids and antibiotics as needed. Intervention should be continued until the patient is diarrhea free for at least 24 hours.
- Hospitalization may need to be considered.

## Appendix 5: Example eSAE Form

Protocol #: TEST-SAE Incident #: 6933-00

**Protocol #:** TEST-SAE **Incident #:** 6933-00

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

**Internal SAE Report Form for Prompt Reporting**

**Institutional Review Board**

**Submit to: Office of Protocol Research, Unit 1437**

Internal Adverse Events that are Serious, Unexpected and Related will require prompt reporting. MDACC IRB requires SAEs that meet the prompt reporting requirement to be submitted to OPR within 5 working days except Death. Deaths that are unexpected and definitely, probably or possibly related to study intervention that occur during and within 30 days after the last day of active study intervention will need to be reported within 24 hours.

| | |
|---|---|
| **Is adverse event serious?** ☑ Yes ☐ No<br>**Is adverse event unexpected?** ☑ Yes ☐ No<br>**Is adverse event related?** ☑ Yes ☐ No | **Name of PI:** Agueda I. Cohen<br>**Department:** IND Office<br>**Unit:** 1636 |
| **Did the subject die?** ☑ No ☐ Yes<br>If Yes, provide **Date:**<br>**Relation:** | **PI's Phone:** 713/563-5466<br>**Electronically Signed By:** Agueda I. Cohen, ID: acohen on 04/23/2014 15:32:07 |
| **Medical Record:** 9999999<br>**Accession #:** 3<br>**Subject Initials:** TT<br>**Gender:** Male | **Protocol:** TEST-SAE<br>**Protocol Title:**<br>TEST-SAE Please do not update without Maria K Mercado-Cooper's permission ****TEST-5TIMES ****Testing again: error saving checkboxes in CCSG tab |
| **Name of person completing this form:** Agueda I. Cohen<br>**Phone #:** 713/563-5466 | **Status:** Active ☑ Pending Activation ☐<br>Terminated ☐<br>CNPE (Pts on tx) ☐ CNPE (Pts off tx) ☐ |
| **Initial Report** ☑ **Follow Up Report** ☐<br>**Event/Reaction Onset Date:** 2/3/2014<br>**Follow Up Date (if applicable):** | **Date Research Team became aware of SAE:** 2/26/2014<br>**Date IRB notified:** 4/23/2014 |

| **SAE/Reaction (Use term from NCI CTC Terminology)** | **Grade** | **Attribution** |
|---|---|---|
| Hemorrhage, CNS (10022763) | 4 | Definite ☐ Probable ☑ Possible ☐ |

**Provide brief summary:** test
Outcome: Hospitalization.
Attribution: Not Related to Disease; Not Related to Concomitant Meds; Not Related to Imatinib; Not Related to LBH589; Probably Related to Standard Regimen.

**Are these events in the ICD?** ☑ No ☐ Yes **Does the ICD need revision?** ☐ No ☑ Yes

**Should current/previously enrolled subjects be notified of these SAEs?** ☑ No ☐ Yes

**Is current condition being treated with Investigational agent?** ☑ No ☐ Yes

**Other Relevant Medical History:**

**List/Attach Relevant Tests, Notes and Labs Data:**

**List/Attach all Concomitant Meds Subject is taking:**

| | | | |
|---|---|---|---|
| **Name of Agent or Device (list manufacturer and lot)** | Imatinib:<br>LBH589:<br>Standard Regimen: | **Did reaction abate after stopping the drug?** No ☐ Yes ☐ N/A ☑ Date(if yes)<br>**Did reaction reappear after reintroduction?** No ☐ Yes ☐ N/A ☑ Date(if yes) | |
| **Dose (list frequency or schedule)** | Imatinib: test test<br>LBH589: test test<br>Standard Regimen: test test | **Route of administration** | Imatinib: oral<br>LBH589: n/a<br>Standard Regimen: oral |
| | | **Date(s) of administration** | Imatinib: test<br>LBH589: test |

| | | | |
|---|---|---|---|
| | | | Standard Regimen: test |

**Have you also reported this reaction to the manufacturer? No** ☑ **Yes** ☐

**OPR STAFF** **Date return to PI** **for:** ☐ Incomplete form

☐ Signature missing ☐ Incorrect information ☐ Other ☐ Report during Continuing Review

Note: With this new form no need to attach the risk section of the ICD March 2008

# 10 REFERENCES (available upon request)

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

**Informed Consent**

# Please Do Not Use for Patient Consent

**Go to the PDOL Homepage to access the Informed Consent Printer Database**

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

Phase I/II Trial of MEK Inhibitor MEK162 in Patients with Relapsed and or Refractory Acute Myeloid Leukemia and Patients with Poor Prognosis Acute Myeloid Leukemia Not Suitable for or Unwilling to Receive Standard Therapy.
2013-0116

**Subtitle**: CMEK162XUS02T -- Phase 1

Study Chair: Farhad Ravandi-Kashani

Participant's Name _____ Medical Record Number _____

This consent and authorization form explains why this research study is being done and what your role will be if you choose to take part. You may choose not to take part in this study.

## 1. DESCRIPTION OF STUDY

The goal of Phase 1 of this clinical research study is to find the highest tolerable dose of MEK162 that can be given to patients with advanced leukemia.

**This is an investigational study.** MEK162 is not FDA approved or commercially available. It is currently being used for research purposes only. The study doctor can explain how the study drug is designed to work.

The study drug will be provided at no cost to you while you are on study.

Up to 57 patients total will take part in both phases of this study . All will be enrolled

at MD Anderson.

## 2. STUDY PROCEDURES

**Screening Tests**

Signing this consent form does not mean that you will be able to take part in this study. You will have the following screening tests to help the doctor decide if you are eligible:

- You will have a physical exam.
- Blood (about 6 teaspoons) and urine will be collected for routine tests.
- You will have a bone marrow aspiration and/or biopsy to check the status of the disease and for biomarker, pharmacodynamic (PD), and cytogenetic testing. To collect a bone marrow aspirate and biopsy, an area of the hip or other site is numbed with anesthetic, and a small amount of bone marrow and bone is withdrawn through a large needle. Biomarkers are found in the blood and tissue and may be related to your reaction to the study drug. Genetic biomarkers will also be studied. PD testing measures how the level of study drug in your body may affect the disease. Cytogenetic testing looks at how genetic changes to cells may affect how the disease may react to the study drug. If you have already had a bone marrow aspirate and/or biopsy recently and your doctor thinks repeating it is not needed, leftover bone marrow will be used for these tests. If bone marrow cannot be collected, blood (about 1-2 teaspoons) will be drawn for these tests.
- You will have an electrocardiogram (EKG) and either an echocardiogram (ECHO) or a multigated acquisition (MUGA) scan to check your heart function.
- You will have an eye exam by an eye doctor.
- If you can become pregnant, blood (about 1 teaspoon) or urine will be collected for a pregnancy test. To take part in this study, you must not be pregnant.

The study doctor will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

**Study Groups**

If you are found to be eligible to take part in this study, you will be assigned to a study group based on when you join this study. Up to 2 groups of 3-6 participants will be enrolled in Phase 1 of the study.

If you are enrolled in Phase 1, the dose of MEK162 you receive will depend on when you joined this study. The first group of participants will receive the lowest dose level of MEK162. The second group will receive a higher dose of MEK162 than the group before it, if no intolerable side effects were seen. This is designed to find the highest tolerable dose of MEK 162.

Participants in Phase 2 will then receive the highest tolerated dose that was found in Phase 1.

**Study Drug Administration**

You will take MEK162 tablets by mouth 2 times a day (about 12 hours apart) every day with a full cup of water.

There are 4 weeks in each study cycle.

**Study Visits**

On **Day 1 of Cycle 1:**

- You will have a physical exam.
- Blood (about 4 teaspoons) will be drawn for routine tests and blood sugar testing.

On **Days 4 and 8 of Cycle 1**, blood (about 4 teaspoons) will be drawn for routine tests and blood sugar testing.

**Sometime during Days 13-27 of each cycle and again on Day 28 of Cycles 2 and beyond**, the study staff will call you and ask about any drugs you may be taking and any side effects you may be having. The calls should last less than 10 minutes each time.

On **Day 28 of Cycle 1**, you will have a bone marrow aspirate and/or biopsy to check the status of the disease and for biomarker and cytogenetic testing. If bone marrow cannot be collected, blood (about 1-2 teaspoons) will be drawn for these tests. You will have an EKG and either an ECHO or MUGA scan to check your heart function.

On **Day 1 of Cycle 2 and beyond:**

- You will have a physical exam.
- Blood (about 4 teaspoons) will be drawn for routine tests and blood sugar testing.
- Urine will be collected for routine tests.
- You will have an eye exam by an eye doctor.
- If you can become pregnant, blood (about 1 teaspoon) or urine will be collected for a pregnancy test.

On visits when you have blood sugar testing, you should fast for at least 8 hours before the blood draw.

On visits when you have urine collected, you will be given containers to collect your urine over 24 hours if the doctor thinks it is needed.

If it is more convenient to you, you may be able to have some of your blood draws

done away from MD Anderson. The study staff will discuss this with you.

Every two or three months during your treatment, you will have an echocardiogram (ECHO) or a multigated acquisition (MUGA) scan to check your heart function.

**Length of Study**
You may continue taking the study drug for as long as the doctor thinks it is in your best interest. You will no longer be able to take the study drug if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Your participation on the study will be over once you have completed the end-of-treatment visit.

**End-of-Treatment Visit**
After your last dose of study drug:

- You will have a physical exam.
- Blood (about 2 teaspoons) will be drawn for routine tests
- If the doctor thinks it is needed, you will have a bone marrow aspirate and/or biopsy to check the status of the disease and for biomarker, PD, and/or cytogenetic testing. If you have already had a bone marrow aspirate and/or biopsy recently and your doctor thinks repeating it is not needed, leftover bone marrow will be used for these tests. If bone marrow cannot be collected, blood (about 1-2 teaspoons) will be drawn for these tests.
- You will have an EKG.

**Other Instructions**
It is important to tell your doctor about any pre-existing eye problems you have and any vision changes you may have while taking the study drug. Your doctor may decide to change or stop your dose of the study drug. It is important that you do not drive a car or work with machinery if you have any vision changes during the study.

Do not take any new drugs without first checking with your study doctor. This includes prescription drugs, over-the-counter drugs, natural or herbal drugs, and vitamins. You will be given a list of drugs that you should not take while on this study because they may decrease the effect of the study drug.

## 3. POSSIBLE RISKS

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Tell the study staff about any side effects you may have, even if you do not think they are related to the study drug/procedures.

**Binimetinib Side Effects**

**Common (occurring in more than 20% of patients)**

| | | |
|---|---|---|
| ● swelling (arm/leg/abdomen/face)<br>● fatigue<br>● skin irritation/rash<br>● acne | ● skin redness, itchiness, dryness, raised bumps<br>● diarrhea<br>● nausea | ● abnormal liver tests (possible liver damage)<br>● abnormal blood test (possible muscle problems) |

**Occasional (occurring in 3-20% of patients)**

| | | |
|---|---|---|
| ● abnormal blood test (possible heart problems)<br>● severe heart problems<br>● high blood pressure<br>● fever<br>● skin cracking<br>● hair loss (partial or total)<br>● inflammation of the lining of your mouth, stomach, or intestine | ● stomach pain<br>● constipation<br>● vomiting<br>● indigestion<br>● mouth sores/blisters (possible difficulty swallowing)<br>● abnormal digestive blood test (possible inflammation of the pancreas) | ● abnormal taste<br>● loss of appetite<br>● dry mouth<br>● low red blood cell count<br>● dizziness<br>● muscle pain<br>● joint pain<br>● difficulty breathing |

Binimetinib may cause visual changes in some patients which include floaters (spots in your vision), swelling, and/or inflammation in and around the eyes and changes in the retina. Binimetinib may also cause blurred vision and/or a loss of vision.

Binimetinib may cause low red blood cell counts:

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.

**Rare but serious (occurring in fewer than 3% of patients)**

| | | |
|---|---|---|
| ● fast/slow/irregular heartbeat<br>● severe increase in blood pressure (possible stroke)<br>● low blood pressure (possible dizziness and/or fainting)<br>● blood clots in a vein | ● very severe blistering skin disease (with ulcers of the skin and digestive tract)<br>● hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering) | ● weakness of the neck muscles resulting in difficulty holding the head up (dropped head syndrome)<br>● severe muscle damage and/or muscle breakdown<br>● lung inflammation |

| | | |
|---|---|---|
| (possible pain, swelling, and/or redness)<br>● blood clots in an artery (possible organ damage such as stroke and/or heart attack)<br>● dehydration<br>● nail disorders | ● blockage and/or hole in the intestines (possibly leaking contents into the abdomen)<br>● increased risk of bleeding (possible in the nose, stomach, intestines and/or brain)<br>● liver failure<br>● muscle spasms | (possible difficulty breathing)<br>● breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage) |

The drug may cause an increased risk of infection, such as pneumonia. This infection may occur anywhere (including the skin). It may become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

There is the possibility that these changes could affect the activities of your daily life (such as driving a car or operating machinery) It is important to tell your doctor about any pre-existing eye problems you have and visual changes that occur while taking the study drug as your doctor may decide to change or stop your treatment with the study drug.

**Other Risks**

**Blood draws** may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

**Bone marrow aspirations/biopsies** may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the aspiration/biopsy site of the collection. An allergic reaction to the anesthetic may occur. A scar may form at the aspiration/biopsy site.

**Genetic research** may result in the development of beneficial treatments, devices, new drugs, or patentable procedures. There are no plans to provide you compensation from such developments. The results of any genetic tests may be put in your health records. If this information were released, it could be misused. Such misuse could be distressing, and it could cause you or your family members to have difficulty obtaining insurance coverage and/or a job.

**Fasting** may cause your blood sugar to drop. You may feel tired, hungry, and/or nauseous. If you have diabetes, it is important to talk to your doctor about managing your blood sugar while fasting.

During the **eye exams**, your pupils will be dilated with eye drops to allow a good view of the back of the eye. This will result in some blurred vision lasting for a few

hours. You will not be able to drive during this time.

This study may involve unpredictable risks to the participants.

**Pregnancy Related Risks**
Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while on this study. If you are sexually active, you must use birth control from the screening period until 3 months after the last study drug dose.

Birth Control Specifications: Acceptable forms of birth control for females include using any 2 of the following methods at the same time:

- Hormonal birth control, including injections, implanted birth control, or oral birth control ("the pill")
- Use of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap), combined with a spermicidal foam, gel, cream, or vaginal suppository

Male participants must use a condom plus one of the birth control methods above.

If you have had a vasectomy or tubal ligation surgery, you do not have to use these birth control methods.

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

## 4. POTENTIAL BENEFITS

Taking the study drug may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

## 5. OTHER PROCEDURES OR TREATMENT OPTIONS

You may choose to receive chemotherapy. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

## 6. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson or Array for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-2933 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

## ADDITIONAL INFORMATION

7. You may ask the study chair (Dr. Farhad Ravandi-Kashani, at 713-792-7305) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-2933 with any questions that have to do with this study or your rights as a study participant.

8. Your participation in this research study is strictly voluntary. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson.

9. This study or your participation in it may be changed or stopped at any time by the study chair, Array, the U.S. Food and Drug Administration (FDA), the Office for

Human Research Protections (OHRP), or the IRB of MD Anderson.

10. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

11. MD Anderson may benefit from your participation and/or what is learned in this study.

12. This study is sponsored and/or supported by: Array.

13. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s). If you have any questions about this, you may call the IRB at 713-792-2933.

**Outside Care**

Part of your care may be provided outside of MD Anderson by your home doctor(s).

**Authorization for Use and Disclosure of Protected Health Information (PHI):**

A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:

- Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
- The IRB and officials of MD Anderson
- Array, who is a sponsor or supporter of this study, and/or any future sponsors/supporters of the study
- authorized agents of Array and governmental agencies in other countries where the study drug may be considered for approval
- Study monitors and auditors who verify the accuracy of the information
- Individuals who put all the study information together in report form

Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson's contracts require sponsors/supporters to protect this information and limit how they may use it.

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

   Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer of MD Anderson at 713-745-6636. If you withdraw your authorization, the data collected about you up to that point can be used and included in data analysis, but no further information about you will be collected.

E. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

# Please Do Not Use for Patient Consent

## Go to the PDOL Homepage to access the Informed Consent Printer Database

**CONSENT/AUTHORIZATION**

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS** _____ _____

SIGNATURE OF PARTICIPANT DATE

**LEGALLY AUTHORIZED REPRESENTATIVE (LAR)**

The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS** _____ _____

SIGNATURE OF LAR DATE

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS** _____

RELATIONSHIP TO PARTICIPANT

**WITNESS TO CONSENT**

I was present during the explanation of the research to be performed under Protocol **2013-0116**.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS** _____ _____

SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE

A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

**PERSON OBTAINING CONSENT**

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

SIGNATURE OF STUDY CHAIR
OR PERSON AUTHORIZED TO OBTAIN CONSENT

DATE

**TRANSLATOR**

I have translated the above informed consent as written (without additions or subtractions) into _____ and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

| NAME OF TRANSLATOR | SIGNATURE OF TRANSLATOR | DATE |
|---|---|---|

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

| SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION (OTHER THAN TRANSLATOR, PARENT/GUARDIAN, OR STUDY CHAIR) | DATE |
|---|---|

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

**Informed Consent**

# Please Do Not Use for Patient Consent

**Go to the PDOL Homepage to access the Informed Consent Printer Database**

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

Phase I/II Trial of MEK Inhibitor MEK162 in Patients with Relapsed and or Refractory Acute Myeloid Leukemia and Patients with Poor Prognosis Acute Myeloid Leukemia Not Suitable for or Unwilling to Receive Standard Therapy.
2013-0116

**Subtitle**: CMEK162XUS02T -- Phase 2

Study Chair: Farhad Ravandi-Kashani

Participant's Name _____ Medical Record Number _____

This consent and authorization form explains why this research study is being done and what your role will be if you choose to take part. You may choose not to take part in this study.

## 1. DESCRIPTION OF STUDY

The goal of Phase 2 of this clinical research study is to learn if MEK162 can help to control AML in older patients with advanced leukemia. The safety of this drug will also be studied.

**This is an investigational study.** MEK162 is not FDA approved or commercially available. It is currently being used for research purposes only. The study doctor can explain how the study drug is designed to work.

The study drug will be provided at no cost to you while you are on study.

Up to 57 patients total will take part in both phases of this study. All will be enrolled at MD Anderson.

## 2. STUDY PROCEDURES

**Screening Tests**

Signing this consent form does not mean that you will be able to take part in this study. You will have the following screening tests to help the doctor decide if you are eligible:

- You will have a physical exam.
- Blood (about 6 teaspoons) and urine will be collected for routine tests.
- You will have a bone marrow aspiration and/or biopsy to check the status of the disease and for biomarker, pharmacodynamic (PD), and cytogenetic testing. To collect a bone marrow aspirate and biopsy, an area of the hip or other site is numbed with anesthetic, and a small amount of bone marrow and bone is withdrawn through a large needle. Biomarkers are found in the blood and tissue and may be related to your reaction to the study drug. Genetic biomarkers will also be studied. PD testing measures how the level of study drug in your body may affect the disease. Cytogenetic testing looks at how genetic changes to cells may affect how the disease may react to the study drug. If you have already had a bone marrow aspirate and/or biopsy recently and your doctor thinks repeating it is not needed, leftover bone marrow will be used for these tests. If bone marrow cannot be collected, blood (about 1-2 teaspoons) will be drawn for these tests.
- You will have an electrocardiogram (EKG) and either an echocardiogram (ECHO) or a multigated acquisition (MUGA) scan to check your heart function.
- You will have an eye exam by an eye doctor.
- If you can become pregnant, blood (about 1 teaspoon) or urine will be collected for a pregnancy test. To take part in this study, you must not be pregnant.

The study doctor will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

**Study Groups**

If you are found to be eligible to take part in this study, you will be assigned to a study group based on when you join this study. Up to 42 participants will be enrolled in Phase 2 of the study.

Participants in Phase 1 were given a dose of MEK162 based on when they joined the study. Groups of participants were given different dose levels until the highest tolerable dose of MEK162 was found.

If you are enrolled in Phase 2, you will receive MEK162 at the highest dose that was

tolerated in Phase 1.

**Study Drug Administration**
You will take MEK162 tablets by mouth 2 times a day (about 12 hours apart) every day with a full cup of water.

There are 4 weeks in each study cycle.

**Study Visits**
On **Day 1 of Cycle 1:**
- You will have a physical exam.
- Blood (about 4 teaspoons) will be drawn for routine tests and blood sugar testing.

On **Days 4 and 8 of Cycle 1**, blood (about 4 teaspoons) will be drawn for routine tests and blood sugar testing.

**Sometime during Days 13-27 of each cycle and again on Day 28 of Cycles 2 and beyond**, the study staff will call you and ask about any drugs you may be taking and any side effects you may be having. The calls should last less than 10 minutes each time.

On **Day 28 of Cycle 1**, you will have a bone marrow aspirate and/or biopsy to check the status of the disease and for biomarker and cytogenetic testing. If bone marrow cannot be collected, blood (about 1-2 teaspoons) will be drawn for these tests. You will have an EKG and either an ECHO or MUGA scan to check your heart function.

On **Day 1 of Cycle 2 and beyond:**
- You will have a physical exam.
- Blood (about 4 teaspoons) will be drawn for routine tests and blood sugar testing.
- Urine will be collected for routine tests.
- You will have an eye exam by an eye doctor.
- If you can become pregnant, blood (about 1 teaspoon) or urine will be collected for a pregnancy test.

On visits when you have blood sugar testing, you should fast for at least 8 hours before the blood draw.

On visits when you have urine collected, you will be given containers to collect your urine over 24 hours if the doctor thinks it is needed.

If it is more convenient to you, you may be able to have some of your blood draws done away from MD Anderson. The study staff will discuss this with you.

Every two or three months during your treatment, you will have an echocardiogram (ECHO) or a multigated acquisition (MUGA) scan to check your heart function.

**Length of Study**

You may continue taking the study drug for as long as the doctor thinks it is in your best interest. You will no longer be able to take the study drug if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Your participation on the study will be over once you have completed the end-of-treatment visit.

**End-of-Treatment Visit**

After your last dose of study drug:

- You will have a physical exam.
- Blood (about 2 teaspoons) will be drawn for routine tests
- If the doctor thinks it is needed, you will have a bone marrow aspirate and/or biopsy to check the status of the disease and for biomarker, PD, and/or cytogenetic testing. If you have already had a bone marrow aspirate and/or biopsy recently and your doctor thinks repeating it is not needed, leftover bone marrow will be used for these tests. If bone marrow cannot be collected, blood (about 1-2 teaspoons) will be drawn for these tests.
- You will have an EKG.

**Other Instructions**

It is important to tell your doctor about any pre-existing eye problems you have and any vision changes you may have while taking the study drug. Your doctor may decide to change or stop your dose of the study drug. It is important that you do not drive a car or work with machinery if you have any vision changes during the study.

Do not take any new drugs without first checking with your study doctor. This includes prescription drugs, over-the-counter drugs, natural or herbal drugs, and vitamins. You will be given a list of drugs that you should not take while on this study because they may decrease the effect of the study drug.

## 3. POSSIBLE RISKS

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Tell the study staff about any side effects you may have, even if you do not think

they are related to the study drug/procedures.

**Binimetinib Side Effects**

**Common (occurring in more than 20% of patients)**

| | | |
|---|---|---|
| ● swelling (arm/leg/abdomen/face)<br>● fatigue<br>● skin irritation/rash<br>● acne | ● skin redness, itchiness, dryness, raised bumps<br>● diarrhea<br>● nausea | ● abnormal liver tests (possible liver damage)<br>● abnormal blood test (possible muscle problems) |

**Occasional (occurring in 3-20% of patients)**

| | | |
|---|---|---|
| ● abnormal blood test (possible heart problems)<br>● severe heart problems<br>● high blood pressure<br>● fever<br>● skin cracking<br>● hair loss (partial or total)<br>● inflammation of the lining of your mouth, stomach, or intestine | ● stomach pain<br>● constipation<br>● vomiting<br>● indigestion<br>● mouth sores/blisters (possible difficulty swallowing)<br>● abnormal digestive blood test (possible inflammation of the pancreas) | ● abnormal taste<br>● loss of appetite<br>● dry mouth<br>● low red blood cell count<br>● dizziness<br>● muscle pain<br>● joint pain<br>● difficulty breathing |

Binimetinib may cause visual changes in some patients which include floaters (spots in your vision), swelling, and/or inflammation in and around the eyes and changes in the retina. Binimetinib may also cause blurred vision and/or a loss of vision.

Binimetinib may cause low red blood cell counts:

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.

**Rare but serious (occurring in fewer than 3% of patients)**

| | | |
|---|---|---|
| ● fast/slow/irregular heartbeat<br>● severe increase in blood pressure (possible stroke)<br>● low blood pressure (possible dizziness and/or fainting)<br>● blood clots in a vein (possible pain, swelling, and/or redness) | ● very severe blistering skin disease (with ulcers of the skin and digestive tract)<br>● hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering)<br>● blockage and/or hole in the intestines | ● weakness of the neck muscles resulting in difficulty holding the head up (dropped head syndrome)<br>● severe muscle damage and/or muscle breakdown<br>● lung inflammation (possible difficulty breathing) |

| | | |
|---|---|---|
| ● blood clots in an artery (possible organ damage such as stroke and/or heart attack)<br>● dehydration<br>● nail disorders | (possibly leaking contents into the abdomen)<br>● increased risk of bleeding (possible in the nose, stomach, intestines and/or brain)<br>● liver failure<br>● muscle spasms | ● breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage) |

The drug may cause an increased risk of infection, such as pneumonia. This infection may occur anywhere (including the skin). It may become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

There is the possibility that these changes could affect the activities of your daily life (such as driving a car or operating machinery) It is important to tell your doctor about any pre-existing eye problems you have and visual changes that occur while taking the study drug as your doctor may decide to change or stop your treatment with the study drug.

**Other Risks**

**Blood draws** may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

**Bone marrow aspirations/biopsies** may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the aspiration/biopsy site of the collection. An allergic reaction to the anesthetic may occur. A scar may form at the aspiration/biopsy site.

**Genetic research** may result in the development of beneficial treatments, devices, new drugs, or patentable procedures. There are no plans to provide you compensation from such developments. The results of any genetic tests may be put in your health records. If this information were released, it could be misused. Such misuse could be distressing, and it could cause you or your family members to have difficulty obtaining insurance coverage and/or a job.

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During the **eye exams**, your pupils will be dilated with eye drops to allow a good view of the back of the eye. This will result in some blurred vision lasting for a few hours. You will not be able to drive during this time.

This study may involve unpredictable risks to the participants.

**Pregnancy Related Risks**
Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while on this study. If you are sexually active, you must use birth control from the screening period until 3 months after the last study drug dose.

Birth Control Specifications: Acceptable forms of birth control for females include using any 2 of the following methods at the same time:

- Hormonal birth control, including injections, implanted birth control, or oral birth control ("the pill")
- Use of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap), combined with a spermicidal foam, gel, cream, or vaginal suppository

Male participants must use a condom plus one of the birth control methods above.

If you have had a vasectomy or tubal ligation surgery, you do not have to use these birth control methods.

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

## 4. POTENTIAL BENEFITS

Taking the study drug may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

## 5. OTHER PROCEDURES OR TREATMENT OPTIONS

You may choose to receive chemotherapy. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

## 6. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson or Array for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-2933 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

## ADDITIONAL INFORMATION

7. You may ask the study chair (Dr. Farhad Ravandi-Kashani, at 713-792-7305) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-2933 with any questions that have to do with this study or your rights as a study participant.

8. Your participation in this research study is strictly voluntary. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson.

9. This study or your participation in it may be changed or stopped at any time by the study chair, Array, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson.

10. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

11. MD Anderson may benefit from your participation and/or what is learned in this study.

12. This study is sponsored and/or supported by: Array.

13. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s). If you have any questions about this, you may call the IRB at 713-792-2933.

**Outside Care**

Part of your care may be provided outside of MD Anderson by your home doctor(s).

**Authorization for Use and Disclosure of Protected Health Information (PHI):**

A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:

- Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
- The IRB and officials of MD Anderson
- Array, who is a sponsor or supporter of this study, and/or any future sponsors/supporters of the study
- authorized agents of Array and governmental agencies in other countries where the study drug may be considered for approval
- Study monitors and auditors who verify the accuracy of the information
- Individuals who put all the study information together in report form

Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson's contracts require sponsors/supporters to protect this information and limit how they may use it.

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

   Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer of MD Anderson at 713-745-6636. If you withdraw your authorization, the data collected about you up to that point can be used and included in data analysis, but no further information about you will be collected.

E. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

# Please Do Not Use for Patient Consent

## Go to the PDOL Homepage to access the Informed Consent Printer Database

**CONSENT/AUTHORIZATION**

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS** _____ _____

SIGNATURE OF PARTICIPANT DATE

**LEGALLY AUTHORIZED REPRESENTATIVE (LAR)**

The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS** _____ _____

SIGNATURE OF LAR DATE

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS** _____

RELATIONSHIP TO PARTICIPANT

**WITNESS TO CONSENT**

I was present during the explanation of the research to be performed under Protocol **2013-0116**.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS** _____ _____

SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE

A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

**PERSON OBTAINING CONSENT**

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

SIGNATURE OF STUDY CHAIR
OR PERSON AUTHORIZED TO OBTAIN CONSENT

DATE

**TRANSLATOR**

I have translated the above informed consent as written (without additions or subtractions) into _____ and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

| NAME OF TRANSLATOR | SIGNATURE OF TRANSLATOR | DATE |
|---|---|---|

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

| SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION (OTHER THAN TRANSLATOR, PARENT/GUARDIAN, OR STUDY CHAIR) | DATE |
|---|---|