A phase 1b trial of a combination of mFOLFIRI with MEK162 in patients with advanced *KRAS* positive metastatic colorectal cancers

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-hCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CK	Creatine Kinase
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events

Abbreviation or Term[1]	Definition/Explanation
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eg	Exempli gratia (for example)
EGFR	Epithelial Growth Factor Receptor
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously

Abbreviation or Term[1]	Definition/Explanation
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MedRA	Medical Dictionary for Drug Regulatory Activities
mCRC	Metastatic colorectal cancer
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Frederichia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

Abbreviation or Term[1]	Definition/Explanation
ULQ	Upper limit of quantitation
UV	Ultraviolet
VEGF	Vascular Endothelial Growth Factor
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

[1] All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

Instructions to multi-site Principal Investigators at locations other than Huntsman Cancer Institute: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office. Retain a copy in the regulatory binder.

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Signature of Principal Investigator **Date**

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Principal Investigator Name (Print)

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Name of Institution

STUDY SUMMARY

Title	A phase 1b trial of a combination of mFOLFIRI with MEK162 in patients with advanced *KRAS* positive metastatic colorectal cancers
Short Title	MEK162 plus mFOLFIRI in *KRAS* positive mCRC
Protocol Number	IRB # 87144
IND	128679
Phase	Phase 1b
Design	Dose escalation, standard 3+3 design followed by dose expansion at the MTD
Study Duration	3 1/2 years
Study Center(s)	Huntsman Cancer Institute and the Huntsman-Intermountain Cancer Care Program (HICCP) centers
Objectives	**Primary:** • To determine the maximum tolerated dose (MTD) of MEK162 when given in combination with mFOLFIRI **Secondary:** • To evaluate response rate • To evaluate clinical benefit rate • Additional Safety **Exploratory:** • To characterize the Pharmacokinetic profile of MEK162 in combination with mFOLFIRI. • To evaluate preliminary antitumor activity • To evaluate the tumor dynamics using plasma samples as surrogate tissue • To assess the sensitivity and specificity of the growth factor receptor network genomic profiles, including MEK, to predict response to mFOLFIRI plus MEK162 in mCRC
Number of Subjects	Dose escalation: up to 18 (3-6 patients per cohort) Dose expansion: 12 patients
Diagnosis and Main Eligibility Criteria	Dose escalation: *KRAS* positive mCRC in both irinotecan naïve and irinotecan refractory patients.

	Dose expansion: *KRAS* positive irinotecan refractory patients
Study Product, Dose, Route, Regimen	MEK162: 30 mg and 45 mg BID PO mFOLFIRI: standard doses every 2 weeks (no bolus 5-FU or leucovorin)
Duration of administration	Until disease progression or unacceptable toxicity
Statistical Methodology	Dose escalation: A traditional 3+3 study design to investigate the safety of escalating doses of MEK162 in combination with mFOLFIRI. Dose expansion: 12 patients will be included for preliminary assessment of efficacy. If the response rate is at least 20% (3 pts) then there is a 84% probability of having 3 or more responses if the true response rate is 35%.

1 OBJECTIVES

1.1 Primary Objectives and Endpoints

Primary Objectives:

To determine the MTD of the combination of mFOLFIRI and MEK162.

Primary Endpoints:

Incidence of dose-limiting toxicities (DLTs)

1.2 Secondary Objectives and Endpoints

Secondary Objectives:

- To evaluate response rate
- To evaluate clinical benefit rate (PR/CR/SD at 4 months)
- Additional safety

Secondary Endpoints:

- Changes in size of target lesions according to RECIST 1.1 to assess PR/CR
- Changes in size of target lesions according to RECIST 1.1 to assess PR/CR/SD at 4months
- Incidence of adverse events (all grades)

1.3 Exploratory Objectives and Endpoints

Exploratory Objectives:

- To evaluate the pharmacokinetic profile of MEK162 in combination with mFOLFIRI.

- To evaluate preliminary anti-tumor activity
- To evaluate tumor dynamics using plasma samples as surrogate tissue
- To assess the sensitivity and specificity of the growth factor receptor network genomic profiles, including MEK, to predict response to mFOLFIRI plus MEK162 in mCRC

Exploratory Endpoints:

- MEK162 serum time-concentration profile and estimated PK parameters: C_{max}, T_{max}, T_{last}, $AUC_{0\text{-}tlast}$, Cl, V and $t_{1/2}$
- Changes in size of target lesions according to RECIST 1.1, Carcinoembryonic antigen (CEA) variation over the course of the treatment and PFS time from study entrance until patient has deceased or progressed.
- Quantification of *KRAS* from circulating cell free DNA (cfDNA) from plasma at baseline, C1D1, C2D1 and at every restaging visit thereafter
- Compare genomics-based measurements of pathway activity in responders (CR/PR) versus non-responders and patients who progress or do not progress using a non-parametric Mann–Whitney U test.

2 BACKGROUND

Colorectal cancer (CRC) is the third most common cancer in US. It is also the second leading cause of death by cancer in this country.[1] Treatment for patients with unresectable metastatic CRC (mCRC) is mainly palliative chemotherapy. 5-fluorouracil or derivatives has been the standard treatment for unresectable mCRC for nearly 50 years.[2] 5-fluorouracil led to improvements in response rate without substantial benefit in survival. In the last decade the addition of new cytotoxics (oxaliplatin, irinotecan) and more recently targeted therapies such as antiangiogenics (bevacizumab, aflibercept) or monoclonal antibodies against epithelial growth factor receptor (cetuximab or panitumumab) has led to a statistically significant improvement in survival for these patients. We will summarize the evidence for the treatment of unresectable mCRC in the next lines.

More than 10 years ago, a randomized phase 3 trial in the first line setting showed an improvement in progression free survival (PFS) when oxaliplatin was added to infusional 5FU/LV (9 vs. 6 months, p=0.0003).[3] However this benefit in PFS did not result in improved overall survival (OS).

At the same time the results of a randomized phase 3 trial in chemo-naïve mCRC combining irinotecan with infusional 5-FU were reported. The addition of irinotecan increased both response rate (49 vs. 31%, $p < 0.001$) as well as time to progression and overall survival (17.4 vs. 14 months, p=0.031).[4] Similarly, EORTC 40896 also found that the addition of irinotecan to 5-FU increased response rate (RR) and PFS although in the EORTC trial there was no difference in survival with the addition of irinotecan.[5]

The next step was to compare the efficacy of oxaliplatin versus irinotecan schedules. Two randomized phase III trials (GOIM9901 and GERCOR) compared infusional 5-

fluorouracil in combination with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) in the first line setting. There was no difference in RR, PFS or OS.[6,7] Therefore either regimen was adopted worldwide as the backbone for the treatment of mCRC.

In an effort to improve the survival of patients with mCRC novel targeted therapies have been tested in combination with either FOLFOX or FOLFIRI. Overall, the addition of some of these targeted therapies has led to statistically significant improvement in survival although often of limited clinical relevance (a few weeks).

Angiogenesis inhibitors have been extensively exploited in this context. A randomized phase III trial showed that adding bevacizumab (a monoclonal antibody against vascular endothelial growth factor) to FOLFOX in the first-line setting increased PFS by 5 weeks (9.4 vs. 8 months, p=0.0023) although no difference was noted in median overall survival.[8] In the second line setting ECOG 3200 showed an 8-week improvement in survival when bevacizumab was added to FOLFOX (12.9 vs. 10.8 months, p=0.001). More recently the TML study showed that maintenance of bevacizumab beyond progression led to statistically significant improvement in survival (11.2 vs. 9.8 months, p=0.0062).[9] Although the hazard ratio in this trial indicated a 20% reduction in the risk of death in the experimental arm, this only translated to an absolute gain in survival of around 5 weeks.

The addition of bevacizumab to irinotecan based schedules has also lead to improvements in survival. Indeed that largest benefit in survival with bevacizumab was evidenced in a randomized phase III trial which tested a suboptimal chemotherapy schedule, bolus 5FU plus irinotecan (IFL), in combination with bevacizumab.[10] Survival in the experimental arm was improved by 5 months. Overall, a recent retrospective SEER review evidenced an improvement in OS when bevacizumab was added to irinotecan regimens. A benefit in OS was not found with oxaliplatin-based regimens.[11] Similar findings have been evidenced with novel monoclonal antibodies against VEGF such as aflibercept. A randomized phase 3 trial in the second line setting in patients with mCRC also evidenced a 6-week improvement in median survival when aflibercept was added to FOLFIRI (13.5 vs. 12.1, HR 0.81, p=0.0032).[12]

A different strategy consisting of blocking the epithelial growth factor receptor (EGFR) using different monoclonal antibodies (mAb) have also been evaluated in several clinical trials. The CRYSTAL trial was a randomized phase 3 trial that tested cetuximab in combination with FOLFIRI in patients with mCRC in the first line setting. A posthoc subgroup analysis in *KRAS* wild-type patients showed a 3 months increase in median survival in the experimental arm (23.5 vs. 20 months, HR 0.696, p=0.0012). However this survival advantage could not be extrapolated to schedules with FOLFOX. In this regard, two randomized trials failed to show any survival benefit with the addition of cetuximab to FOLFOX in the first line even for *KRAS* wild-type patients. Median survival for *KRAS*-wt patients in the experimental versus control arm in MRC COIN was 17.9 vs. 17 months (HR 1.04, p=0.67).[13] Similarly, a posthoc analysis of *KRAS*-wt patients included in the OPUS trial found no improvement in survival after adding cetuximab to FOLFOX (22.8 vs. 18.5, HR 0.85, p=0.39).[14] It remains unknown why the efficacy of cetuximab is in part

related to the chemotherapy backbone used. This is further complicated by the fact that a different EGFR mAb (panitumumab) seems to be synergistic with both FOLFOX and FOLFIRI. A randomized phase 3 trial in the first line tested the benefit of adding panitumumab to FOLFOX (PRIME study). The trial included a prospective analysis by *KRAS* status. The experimental arm showed a statistically significant improvement in PFS and a trend to increased survival (23.9 vs. 19.7 months, HR 0.83, p=0.07). Similarly, a randomized phase 3 study in the second line setting found that in the *KRAS*-wt subset, the addition of panitumumab to FOLFIRI resulted in a 2 months increase in PFS (5.9 vs. 3.9 months, HR 0.73, p=0.004) with a non-significant trend to increased OS (14.5 vs. 12.5, HR 0.85, p=0.12). In this trial, the response rate in patients with *KRAS*-mutant treated with FOLFIRI in the second line setting was 15%.[15]

The next step was to combine chemotherapy with simultaneous inhibition of VEGF and EGFR. Several randomized trials, including PACCE and CAIRO trial, tested this strategy. Surprisingly dual inhibition not only failed to improve outcome but was indeed detrimental.[16, 17]

According to the evidence presented above, first line therapy for unresectable mCRC most often include infusional 5-fluorouracil in combination with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) plus a monoclonal antibody against vascular endothelial growth factor (VEGF) or epithelial growth factor receptor (EGFR). In the US FOLFOX is often the preferred first line treatment option due to a better toxicity profile including absence of alopecia. FOLFIRI is therefore most commonly used in the second line setting in US.

The *RAS/RAF/MEK/ERK* pathway plays a major role in cell growth and survival. The *RAS* oncogenes are the most frequently mutated class of oncogenes in human cancers.[18] This family of oncogenes includes: *KRAS*, *NRAS* and *HRAS*. *KRAS* is mutated in 40% of patients with colorectal cancer. *KRAS* is considered undruggable therefore efforts at silencing the pathway have focused at actionable mutations downstream *KRAS* such as *BRAF*, *MEK* or *ERK*. *MEK* mutations have been found in 2% of CRC (Sanger, COSMIC).

MEK inhibitors have shown activity in RAS activated preclinical models. Abrogation of MEK led to tumor growth inhibition in cell line derived colorectal cancer xenografts (HT-29, COLO205, LoVo and CRC13B02).[19,20] MEK162 also showed dose and time-dependent inhibition of phosphorylation of ERK in HT-29 colorectal xenografts. (Unpublished data from MEK162 IB). Preclinical evidence suggests that the combination of cytotoxics (irinotecan) and MEK inhibition (AZD6244) is indeed synergistic in colorectal cancer cell lines (HCT-116). Indeed recent clinical evidence suggests that this combination may be also synergistic in patients (Hochster et al ASCO 2013 abst. 3587). This early dose finding study tested irinotecan in combination with AZD6244 in the second line setting in patients with *KRAS* or *BRAF* positive mCRC. The RR was 10% and median PFS was 3.4 months. These figures compare favorably with historical controls when FOLFIRI was used in the second line after progression to FOLFOX and suggest that this strategy should be further explored.[7]

A recent phase 1 trial tested the safety of FOLFIRI in combination with a different MEK inhibitor (pimasertib) as second line treatment in *KRAS* mutant mCRC. Unfortunately effective doses of pimasertib could not be reached due to toxicity.[21]

The schedule of administration of MEK inhibitors is critical for the efficacy of the treatment when they are given in combination with cytotoxics. The MAPK pathway plays a key role in cell-cycle progression. Pathway inhibitors could decrease cell population in S-phase and potentially antagonize the activity of cytotoxics that are S-phase specific such as irinotecan or 5-fluorouracil. Indeed in vivo data from patient derived xenografts from biliary cancers have shown that gemcitabine activity is increased with a sequential schedule of AZD6244 (MEK inhibitor). In this work AZD6244 was given after gemcitabine administration and held 48h prior to next dose of gemcitabine. MEK inhibition led to cell-cycle arrest and this could decrease tumor repopulation following chemotherapy administration. On the other hand, holding pathway inhibitor for 48 hours prior to the administration of gemcitabine allowed reentry into S-phase which likely explains higher tumor growth inhibition seen with this schedule.[22] Accordingly, patients in this protocol will hold MEK162 for 48h prior to the administration of mFOLFIRI.

Here we propose a dose finding study with the combination of mFOLFIRI + MEK162 in patients with *KRAS* positive mCRC. mFOLFIRI (irinotecan and 5-fluorouracil continuous infusion without 5-fluorouracil bolus and leucovorin) was chosen over FOLFIRI per our standard local practice of dropping the 5-FU bolus when using FOLFOX or FOLFIRI in the palliative care setting. This is based on the observation that removal of the 5-FU bolus does not decrease the efficacy of the treatment but reduces the risk of hematologic toxicities (as shown in the OPTIMOX1 study[27] where FOLFOX-7 without 5-FU bolus was found to be equivalent to FOLFOX-4). The study will include a lead in period of MEK162 single agent for 6 days to evaluate early changes in tumor dynamics by cfDNA. During the dose escalation phase we will evaluate toxicity and MTD of the combination in irinotecan naïve and irinotecan-refractory mCRC patients. During the dose expansion phase, we will plan to enroll approximately 12 patients with irinotecan-refractory mCRC.

We hypothesize that MEK162 + mFOLFIRI can be given safely in patients with *KRAS* positive advanced colorectal cancer, and that adding a MEK inhibitor improves the activity of mFOLFIRI.

The correlative studies in the dose expansion cohort will include assessment of *KRAS* mutations in circulating free DNA (cfDNA) at baseline, C1D1, C2D1 and at each restaging visit thereafter. We will evaluate tumor dynamics by changes in plasma cfDNA and correlate with changes in CEA as well as target lesions by RECIST 1.1

2.1 Importance of a pathway-based genomic approach

Understanding the aberrant signaling events that occur in a patient's tumor is an important challenge facing researchers attempting to predict drug sensitivity. While linking single mutations to drug sensitivity has been successful in some settings, in practice drug response and genetic aberrations do not necessarily follow a linear pattern due to complex pathway

interactions. As an example, subsets of lung cancer patients without EGFR mutations still respond to drugs that target this pathway, perhaps due to alternative mechanisms of pathway activation. Additionally, *KRAS* mutations confer resistance to EGFR targeted therapy in colon cancer, and approximately one-third of breast cancer patients with amplified HER2 do not respond to trastuzumab in part due to deregulation of downstream or parallel pathway components such as PTEN or PI3K. These findings highlight the importance of simultaneous and comprehensive mapping of pathway activity and crosstalk of GFRN to predict tumor responses to targeted therapies.

Our previous work has used oncogenic signature profiles to predict pathway activity and drug sensitivity. Briefly, we generate these genomic pathway signatures by expressing an active protein in a quiescent normal human epithelial cell, thereby specifically isolating the subsequent events as defined by the activation/deregulation of that single pathway. We are currently extending this approach to profile more than one pathway at a time so that we can study pathway crosstalk and interaction. We capture the acute downstream consequences of gene deregulation by isolating RNA directly after pathway activation and performing gene expression analysis. We are using RNA to measure the acute transcriptional activation of genes following a pathway's activation, as the alteration of transcription integrates signaling pathway activation and generation of new molecular species (mRNA and miRNA) that is dynamic and transient in nature but readily evaluated. To build a signature, we isolate the specific genes deregulated by the induction of a particular pathway component and together use these genes to model pathway status in human tumors. As an example, if a human tumor has a pathway specific gene expression pattern that correlates more with the quiescent control gene pattern, this tumor is predicted to have low pathway activity, and vice-versa. By identifying genes whose transcriptional deregulation best reflects a pathway's activation, we can more accurately model that pathway's status in a human tumor.

Our approach can accurately measure a pathway's activation status in individual tumors. Strikingly, we have previously published the ability of our PI3K genomic signature to predict smokers at high-risk for lung cancer, and those who have dysplastic lesions that respond to a PI3K inhibitor, myoinositol [Ref 2 in comments].[23] Additionally, other studies highlight the ability of our RAS and SRC signatures to predict RAS mutation or SRC pathway deregulation status, respectively, in tumors as well as response to drugs that target these pathways.[24] Further, this approach has been able to identify subsets of more aggressive tumors that have unique patterns of pathway deregulation, highlighting the clinical relevance of our pathway profiles.[23-26] Thus, these studies show a significant relationship between pathway predictions in human tumors and drug sensitivity, and are the basis for our correlative genomic studies in this trial.

Our genomic biomarkers focus on the core GFR pathway components currently targeted in many cancers, including the GFR receptors EGFR, HER2, IGFR and their downstream partners PI3K, AKT, MEK, RAS, and PLC-γ. We will use our multi-pathway genomic biomarkers to map GFR-MEK signaling in colon cancer, and characterize tumors that are MEK-pathway "active" and "inactive". To model pathway activity in tumors, we will use

a Bayesian factor analysis approach to pathway modeling, which uses the pathway signatures and correlation structure as prior information to inform the factor analysis as to the underlying pathway structure in the patient samples. This approach also enables us to effectively predict multi-pathway status using discrete 'omic' data types, such as gene expression and mutation data. These models will be correlated to drug responsiveness to test whether "active" tumors are more likely to respond to the MEK inhibitor/mFOLFIRI treatment than "inactive" tumors, using the methods described below.

Briefly, in order to model GFR/MEK network activity for gene expression profiles, we generate pathway signatures by expressing an active protein in quiescent normal human primary epithelial cells, thereby isolating the specific events as defined by the activation/deregulation of that single pathway. We capture the acute downstream consequences of gene deregulation by isolating RNA after pathway activation and performing gene expression analysis. These pathway signatures often contain a subset of genes known to be relevant for a particular pathway's activation—but importantly also involve many genes not previously discovered. As tumor tissue amounts are often limiting, this approach enables us to examine pathway activity or many signaling networks concurrently, and more comprehensively than measurement of a single protein or gene. In this study we will use established gene expression signatures of key signaling pathways in the growth factor receptor network, such as EGFR and MEK, to study how these signaling network's activity correlates to drug treatment in patients.

Following isolation of RNA from patient biopsies in this trial, we will perform RNA-sequencing to generate expression data. High-throughput sequencing will be performed using an Illumina HiSEQ instrument as previously described. We will multiplex 4 samples per lane to generate approximately 30-50 million ~100bp single-end reads per sample. Image analysis and base quality scoring will be performed using the Genomic Analyzer Pipeline. We will map reads to the reference human genome assembly using the Burrows-Wheeler Aligner69, and process data using TPM.

Following data processing, gene-level data is filtered to exclude probesets with signals present at background noise levels, and for probesets that do not vary significantly across samples. A binary probit regression model is then estimated using Bayesian methods to select genes that best distinguish the quiescent and pathway-activated states. When this model is then applied to an individual patient tumor sample, the expression of the selected geneset for each tumor sample is summarized as a single value, called the metagene score, which corresponds to the value from the first principal component as determined by a singular-value decomposition. The metagene score is scaled to range from 0: "no pathway activity"; to 1 "full pathway activity". This metagene score, which is the output of the pathway signature, gives a measure of the activation of that pathway in that individual sample.

In order to assess the relationship between pathway prediction and response to drug in patients, we will compare the metagene scores from each patient to their response as determined by RECIST 1.1 criteria. Specifically, we will obtain the correlation between

predicted and actual response rate. As our previous signatures for drugs have exceeded 0.5, we are expecting a correlation of 0.5 or higher in this study.

3 MEK162 DRUG INFORMATION

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 paclitaxel, PI3K or RAF or IGF-1R inhibitors in patients with selected advanced or metastatic solid tumors, including melanoma, biliary, colorectal, and ovarian cancers. MEK162 is also being investigated in Noonan syndrome in patients with hypertrophic cardiomyopathy, based on the role of the RAS/RAF/MEK/ERK pathway in cardiomyocyte growth and presence of mutations in the MAPK pathway in this disease.

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.

3.1 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.
Nonclinical in vitro and in vivo data indicate that MEK162 is metabolized mainly by glucuronidation pathways (mainly via UDP-glucuronosyl transferase [UGT]1A1, 1A3 and 1A9) and to a lesser extent by oxidation pathways (mainly via cytochrome P450 [CYP] 1A2 and 2C19). UGT1A1 was shown to be the major contributor (90%) to the formation of the direct glucuronide in human liver microsomes. UGT1A3 and UGT1A9 contributed 3% and 7%, respectively, to the glucuronidation activity. MEK162 is a reversible inhibitor of CYP2B6 (inhibition constant [Ki] ~ 1.67 μM) and a weak inhibitor of CYP1A2 and

CYP2C9 in vitro. MEK162 is not considered an in vitro time-dependent inhibitor of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5.

Acute, subchronic, chronic and reproductive toxicity, genotoxicity and phototoxicity studies were completed to support the chronic administration of MEK162 to adult cancer patients. The toxic effects of MEK inhibitors in humans are similar to the toxic effects observed in monkeys. The toxic effects 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 686 patients and healthy volunteers who have received at least one dose of MEK162 and is based on data as of January 7, 2013. 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. Women of child-bearing potential must be advised to use highly effective contraception methods.

3.2 Clinical Experience

As of 07-January-2015, a total of 2430 healthy subjects and patients have been enrolled in MEK162 studies and 1945 of whom received at least one dose of MEK162, and have been evaluated for safety, including 204 healthy subjects, 6 liver dysfunction patients, 164 patients with rheumatoid arthritis and 1571 patients with advanced cancer. The study [CMEK162Y2201-NCT01556568] is an open label, phase II, single-agent study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of MEK162 in Noonan syndrome patients with hypertrophic cardiomyopathy opened in February-2012. This study has been voluntarily delayed pending more comprehensive evaluation of AEs observed in other studies with MEK162, as detailed in this IB. As of 07-January-2015, two patients have been screened, but no patient has been treated with MEK162.

The experience of MEK162 in healthy subjects includes 204 subjects in 10 phase I clinical studies. Nine of these 10 studies are completed and 1 study [CMEK162A2104-NCT02050815] (hepatic impairment) is ongoing.

The experience of MEK162 in patients with advanced cancer either as a single agent or in combination with targeted or standard chemotherapy agents includes 20 clinical studies.

As of the data-cutoff MEK162 experience as a single agent in 705 cancer patients includes 6 studies. [ARRAY-162-111-NCT00959127]: phase I, dose-escalation study in patients with advanced solid tumors followed by expansion cohorts in patients with advanced or metastatic biliary cancer or *KRAS*- or BRAF-mutant metastatic colorectal cancer (CCR). [CMEK162X2201-NCT01556568]: phase II study in patients with locally advanced and unresectable or

metastatic malignant cutaneous melanoma, harboring BRAFV600 or NRAS mutations. [CMEK162X1101-NCT01469130]: phase I, dose escalation study in Japanese patients with advanced
solid tumors with the expansion part in patients whose tumors harbor RAS or BRAF mutations. [CMEK162A2301-NCT01763167]: phase III, two-arm, randomized study in patients with advanced unresectable or metastatic NRAS Q61 mutation-positive melanoma.[ARRAY-162-311-NCT01849874]: phase III, two-arm, randomized study in patients with recurrent or
persistent low-grade serous carcinomas of the ovary, fallopian tube or primary peritoneum. [CMEK162AUS11-NCT01885195]: phase II study in patients with RAS/RAF/MEK activated tumors. MEK162 as a single agent at 45 mg BID has been explored in two phase I studies [ARRAY-162-111-NCT00959127], [CMEK162X1101], conducted in patients with advanced solid tumors, advanced or metastatic biliary cancer and *KRAS*- or BRAF-mutant metastatic colorectal cancer (CRC) and in Japanese patients with advanced solid tumors, respectively; in two phase II studies [CMEK162X2201-NCT01320085], [CMEK162AUS11-NCT01885195], conducted in BRAFV600 or NRAS-mutant melanoma patients and advanced solid tumors, respectively; and two phase III studies [CMEK162A2301-NCT01763164], [ARRAY-162-311-NCT01849874] in patients with NRAS-mutant melanoma and low-grade serous carcinomas of the ovary, fallopian tube or primary peritoneum, respectively. The two phase I studies ([ARRAY-162-111-NCT00959127], [CMEK162X1101-NCT01469130]) are completed. The study [ARRAY-162-111-NCT00959127] was a phase I, open-label, dose-escalation of oral MEK162 in patients with advanced solid tumors followed by expansion cohorts in patients with advanced or metastatic biliary cancer or *KRAS*- or BRAF-mutant metastatic CRC. A total of 93 patients received at least 1 dose of MEK162. Four dose levels were evaluated: 30 mg BID, 45 mg BID, 60 mg BID and 80 mg BID. Two of 4 patients receiving 80 mg BID experienced dose limiting toxicities (DLTs), thus the 80 mg BID dose was declared non-tolerable. Seven patients were enrolled at 60 mg BID and no DLTs were observed, therefore, 60 mg BID was declared the MTD. Following completion of the Dose-escalation Phase, a total of 74 patients were enrolled in the Expansion Phase. The dose of 45 mg BID was determined as the recommended phase II dose (RP2D) mainly due to the frequency of ocular AEs in patients at the 60 mg dose level. The study [CMEK162X1101-NCT01469130] is an ongoing, phase I, open label, dose escalation study of MEK162 in Japanese patients with advanced solid tumors with an expansion part in patients whose tumors harbor RAS or BRAF mutations. A total of 21 patients received at least 1 dose of MEK162: 6 patients received 30 mg BID and 15 patients received 45 mg BID. Eighteen patients (as of 10-February-2014) were discontinued from the study and 3 patients were still ongoing. Two patients in the 45 mg BID dose level cohort (dose escalation part) reported 2 DLTs, both were recurrent Grade 2 detachment of retinal pigment epithelium. Therefore, 45 mg BID was declared the MTD in Japanese patients. No DLT was reported in patients enrolled in the expansion part. The most frequently reported AEs suspected to be related to MEK162, regardless of grade and MEK162 dose were dermatological events (rash, dermatitis acneiform), gastrointestinal (GI) events (nausea, vomiting, diarrhea), edema peripheral, fatigue and CPK increased. The majority of these AEs were Grade 1 or 2 with less than 5% of cases Grade 3 or 4, with the exception of elevation of blood CPK,

reported as 24% (44/183 patients) Grade 3 or 4 in [CMEK162X2201-NCT01320085] and 17.2% (10/58 patients) in dose escalation and 16.6% (11/66 patients) in dose expansion [CMEK162X1101-NCT01469130] studies.

MEK162 in combinations:

MEK162 experience in combination with others agents include 866 patients in 13 studies: Five studies with RAF inhibitors encorafenib or RAF265:
[CMEK162X2102-NCT01352273]: phase II study of sequential, single-agent encorafenib followed by a rational combination with targeted agents (including MEK162) after progression, to
overcome resistance in adult patients with locally advanced or metastatic BRAFV600 melanoma. [CMEK162X2110-NCT01543698]: phase Ib dose finding, dose escalation study of MEK162 in combination with encorafenib, in selected advanced solid tumors. [CLGX818X2102-NCT01820364]: phase II study of MEK162 in combination with encorafenib in patients with locally advanced or metastatic BRAFV600 mutant melanoma. [CMEK162B2301-NCT01909453]: phase III, randomized, 2-part study in patients with BRAFV600- mutant locally advanced unresectable or metastatic melanoma. [CLGX818X2109-NCT02159066]: phase II, open-label study of encorafenib and MEK162, followed by a rational combination with targeted agents after progression on encorafenib and MEK162, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma.
Three studies with PI3KC/AKT pathway inhibitors BEZ235 (pan-PI3K/mTOR) buparlisib (pan-PI3K) or BYL719 (PI3Kα) [CMEK162X2103-NCT01337765], [CMEK162X2101-NCT01363232] and [CMEK162X2109-NCT01449058]: all three are phase Ib, dose escalation and expansion studies in selected advanced solid tumors. One study with PKC-selective inhibitor sotrastaurin [CMEK162X2203-NCT01801358]: phase Ib/II study in patients with metastatic uveal melanoma.
One study with CDK4/6 inhibitor LEE011. [CMEK162X2114-NCT01781572]: phase Ib/II study, in patients with NRAS mutant melanoma. One study with IGF-1R monoclonal inhibitor ganitumab. [CMEK162X2111-NCT01562899]: phase Ib/II dose-escalation and expansion study in patients with selected advanced solid tumors. One study with EGFR inhibitor panitumumab [CMEK162X2116-NCT01927341]: phase Ib/II, dose-escalation study in patients with mutant RAS or wild-type RAS metastatic CRC. One study with standard chemotherapy agent paclitaxel [ARRAY-162-112-NCT01649336] phase Ib, dose-escalation and expansion study in women with platinum-resistant or refractory epithelial ovarian, fallopian tube or primary peritoneal cancer. The target RP2D of MEK162 for combination studies with targeted agents is 45 mg BID. In combination with paclitaxel, two dosing schedules of MEK162 plus weekly paclitaxel 80 mg/m^2 were evaluated in the ongoing [ARRAY-162-112-NCT01649336] study: a continuous dose schedule, in which MEK162 was administered at 30 or 45 mg BID continuously and an intermittent dose schedule, in which MEK162 was administered at 45 mg BID on Days 1-5 of each week for 3 weeks out of 4. On the continuous dose schedule, the RP2D was declared as MEK162 30 mg BID with weekly paclitaxel and on the intermittent dose schedule, the RP2D was confirmed as MEK162 45 mg BID with weekly paclitaxel. Currently one phase III study of MEK162 at 45 mg BID is being conducted in patients with

unresectable or metastatic BRAFV600-mutant melanoma in combination with encorafenib [CMEK162B2301-NCT01909453]. The exposure of MEK162 when combined with encorafenib described by Cmax and AUC has the same ranges of values founded in the single agent studies. In the phase Ib study [CMEK162X2102-NCT01352273], Sponsor concluded that the safety available data of the combination of MEK162 with RAF265 no longer supported the enrollment of additional patients into the study. The enrollment was closed on 17-September-2012 and the study was terminated (study information provided in Section 5.2).

Overall, the frequently reported AEs suspected to be related to MEK162 in combination studies were found to be similar to those found in single-agent studies, which include GI events (diarrhea, nausea, vomiting), dermatological events (dermatitis acneiform, rash) CPK elevation and retinal events, described in (Section 5.2.3).

The percentage of patients that discontinued study drug due to AEs regardless of relationship to MEK162 ranged from 2.6% [CMEK162X2203-NCT01801358] to 36% [CMEK162X2101-NCT01363232]. A total of 52 DLTs were observed in the dose-escalation part of combination studies, as following: 10 DLTs in [CMEK162X2102-NCT01352273], 6 DLTs in [CMEK162X2110-NCT01543698], 7 DLTs in [CMEK162X2111-NCT01562899], 6 DLTs in [CMEK162X2103-NCT01337765], 13DLTs in [CMEK162X2101-NCT01363232] and 10 DLTs in [CMEK162X2201-NCT01320085] study. Of these 52 DLTs, 13 were reported in the [CMEK162X2101-NCT01363232] study combining MEK162 with the PI3K inhibitor buparlisib. The most frequents DLTs reported were gastrointestinal events, followed by ocular and dermatological events. A total of 128 deaths were reported during the study or within 30 days of last dose of study drug in cancer patients, either in single-agent or combination studies (45 and 46 respectively). The most frequent cause of treatment discontinuation was disease progression and other events not related to study drug. Based on the experience from the 13 completed phase I studies (9 in healthy subjects , 3 in cancer patients, 1 in rheumatoid arthritis patients) and 1 completed phase II study (in rheumatoid arthritis patients), MEK162 has demonstrated an acceptable and manageable safety profile with the majority of AEs Grades 1 or 2 of intensity and reversible. In order to appropriately describe the incidence of clinically notable AEs (CNAEs)/AEs of special interest observed in patients receiving MEK162, when applicable, terms were pooled into combined categories (regardless of the assessment on relationship with study drug) such as gastrointestinal events, ocular events, cardiac events, dermatological events, liver events, muscular events, edema events, hemorrhage events, thrombotic and embolic events, hypertension events, pneumonitis events, and fatigue/asthenia events. These categories will be described for each study and the pooled data in Section 5.2.3. See Appendix 1 for CNAE/AEs of special interest groupings and the constituent preferred terms. For further information regarding clinical experience with MEK162, refer to the Investigator's Brochure.

3.3 Pharmacokinetics

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 of (i.e., 45 mg) should provide sufficient exposure with acceptable safety and adequate continuous pharmacological inhibition of the primary target.
The PK of MEK162 is characterized by moderate to high variability, approximate dose proportionality and 1.5-fold accumulation at steady state (~15 days). The median t1/2 ranged from ~ 4 – 13 hours across human studies (patient and healthy volunteer).
A human ADME study showed the primary metabolic pathways include glucuronidation (up to 61.2% via UGT1A1), N-dealkylation, amide hydrolysis (up to 17.8% via CYP1A1 and CYP2C19). In urine, 6.5% of the radioactive dose was excreted as unchanged MEK162.

Food-effect clinical studies have shown the influence of food on PK of MEK162 is mild and not clinically relevant; therefore, MEK162 can be taken without regard to food. A drug interaction study with MEK162 and midazolam was conducted; the results suggest that continuous intake of MEK162 produces no relevant CYP3A4 induction. In vitro studies also demonstrated that MEK162 is a P-gp and BCRP substrate, but the effects of inhibitors of these substrates on the PK of MEK162 *in vivo* is unknown. The impact of UGT1A1 inhibitors or inducers has not been clinically assessed. In the cases where the extent of a drug interaction is unknown, it is recommended to co-administer drugs with caution.

For further information refer to the current MEK162 Investigator's Brochure.

3.4 Rationale for dose and regimen selection of MEK162

The 45 mg BID dose of MEK162 was selected as the recommended phase II dose based on safety, antitumor activity and pharmacodynamics considerations.

A Phase I study of MEK162 in patients with advanced or metastatic solid tumors is ongoing (ARRAY-162-111). Enrollment of the dose-escalation phase is completed and the maximum tolerated dose (MTD) of MEK162 has been identified as 60 mg twice daily (BID). Enrollment of an expansion cohort in patients with advanced or metastatic biliary cancer has also been completed and an additional expansion cohort in patients with *KRAS*- and BRAF-mutated metastatic colorectal cancer is currently ongoing. After enrollment of 6 patients at 60 mg BID the starting dose of MEK in the colorectal cancer cohort was reduced to 45 mg BID due to the frequency of reversible visual/retinal events observed at the 60 mg BID dose level. The 45 mg dose was generally well tolerated. Additionally, in CMEK162X2201 single agent study, the 60 mg dose was also explored in a cohort of 25 patients. Two patients presented unexpected suspected SAEs (one case of acute liver failure with a fatal outcome and another case of decreased ejection fraction, heart failure, myocarditis, and tachycardia) that led to Investigator Notification letters and provided further support for the selection of 45 mg as the recommended phase II dose.

It is assumed a BID dosing regimen should provide sufficient exposure and adequate continuous pharmacological inhibition of the primary target.

The 45 mg dose was generally well tolerated. The most frequently reported AEs in patients treated at 45 mg BID were dermatitis acneiform (44%) peripheral edema (36%), diarrhea (33%) and CPK increase (27%). The incidence of visual events at the recommended dose was 20%, most of them grade 1-2.

Importantly, MEK162 showed consistent antitumor activity in patients with NRAS or BRAF mutations. The CMEK162X2201 study reported a response rate of 23% in both cohorts and a PFS of 3.65 months and 3.58 months, in NRAS and BRAF mutant patients, respectively.

Healthy volunteers have previously received a single dose of MEK162 up to 80 mg. Treatment-related adverse events were reported in 20% of subjects who received MEK162, compared with 80% who received placebo. All events were classified as mild symptoms in intensity. In the multiple dose study, healthy volunteers received up to 60 mg QD or 20 mg BID MEK162 for 14 days. Adverse events were reported in 97% of subjects who received MEK162, compared to 75% who received placebo. All events were mild or moderate in intensity.

4 STUDY DESIGN

4.1 Description

This is a Phase 1b, open label, dose-finding study to determine the Maximum Tolerated Dose (MTD) of MEK162 in combination with mFOLFIRI, and to evaluate the response rate, clinical benefit rate and additional safety parameters of the treatment combination:

Dose Escalation Phase:

Prior to starting the combination MEK162 and mFOLFIRI treatment, all patients will undergo a 6-day lead in period with single agent MEK162. Patients will then have 2-days off MEK162 prior to beginning the combination therapy.

MEK162 will be given on days 1-12 of a 14 day cycle PO in combination with mFOLFIRI given every 2 weeks to evaluate the incidence of toxicities and determine the MTD in patients with *KRAS* positive mCRC.

The standard 3+3 design will be used for the dose escalation phase. Patients will be accrued to each dose level as shown in Table 4.1 in cohorts of up to 3-6 patients. Escalation will continue to a second dose level, or until a dose limiting toxicity (DLT) is observed. This study will test 30 mg BID or 45 mg BID dose levels of MEK162 in combination with mFOLFIRI.

Initially 3 patients will be enrolled at dose level 1. If 2/3 patients at dose level 1 experience a dose limiting toxicity (DLT) during the first two cycles of combined treatment, then the next 3 patients will be enrolled at dose level -1. If 1/3 patients at dose level 1 experiences a DLT, three more patients will be added. If 2/6 patients at dose level 1 experience a DLT, then dose level -1 will be used for the next 3 patients. If 0/3 or 1/6 patients at dose level 1 complete two cycles of the study combination experience a DLT, the study will proceed to enroll 3 patients at dose level 2. If ≤ 1/6 patients at the highest dose level experience a DLT, then the dose expansion portion will be open for enrollment. If ≥ 2/6 patients experience a DLT at the highest dose level, then the dose expansion portion will be open and patients will be treated at the next lower dose level. At least 6 patients must be treated at the MTD before proceeding to the dose expansion phase.

Table 4.1

Dose Level	Treatment	MEK Dose
-1	mFOLFIRI at 80% + MEK162	30 mg BID 1 week on 1 week off *
1	mFOLFIRI + MEK162	30 mg BID
2	mFOLFIRI + MEK162	45 mg BID

* 30 mg BID dosing for one week starting after FOLFIRI administration on day 1 of a cycle followed by one week of dose hold.

Dose expansion phase:

After determination of the MTD, an additional 12 patients will be enrolled in the study at that dose to accumulate additional information about response rate, clinical benefit rate and drug safety.

Patients will be treated with the dose of MEK162 as determined in the dose escalation phase. The schedule will be identical to the dose escalation phase schedule, including the MEK162 lead-in which will allow evaluation of early changes in tumor dynamics by cfDNA as well correlation with tumor response by imaging or CEA at 8 weeks. Patients with *KRAS* positive mCRC will be evaluated for response. Patients must complete the first set of scans at cycle 4 to be considered evaluable for response. After the response evaluation period, patients are allowed to continue on MEK162 in combination with mFOLFIRI for as long as the patient receives clinical benefit. Patients will be removed from treatment for disease progression, unacceptable toxicities, patient withdrawal, death or if deemed appropriate by the investigator.

4.2 Dose Limiting Toxicity

Toxicity will be assessed using the NCI CTCAE, version 4.03 unless otherwise specified. A DLT is defined as an AE or abnormal laboratory value (assessed as possibly, probably or definitely related to the study medication) which occurs ≤ 28 days following the first dose of mFOLFIRI + MEK162 (or 2 cycles of therapy, each cycle = 14 days), and meets

any of the criteria listed in Table 4.2.1. The DLT assessment will begin at Cycle 1 Day 1 at the beginning of the combination treatment and after the 6 day lead in period with MEK162. Patients who experience unacceptable toxicities during the 6 day lead-in period will be taken off study, considered non-evaluable for DLT and will be replaced. If a patient experiences toxicity that fulfills the criteria for a DLT during the DLT observation window (cycle 1 day 1 through cycle 3 day 1, treatment with the study drug will be interrupted and the toxicity will be followed up. Patients will be allowed to remain on study if the DLT is resolved within 4 weeks at the discretion of the investigator. Patients will continue on study at the next lowest dose level. If treatment is reduced during the DLT period, or is held for > 2 weeks for any reason, this will be considered a DLT.

Table 4.2.1

TOXICITY	DLT CRITERIA
Hematology	CTCAE grade 4 neutropenia lasting more than 7 consecutive days
	CTCAE grade 4 thrombocytopenia
	CTCAE Grade 3 or 4 neutropenia with fever (temperature ≥ 38.5°C)
Skin and subcutaneous tissue disorders	Rash, hand-foot skin reaction or photosensitivity CTCAE Grade 3 lasting more than 14 consecutive days despite maximal skin toxicity treatment (as per local practice)
	Rash, hand-foot skin reaction or photosensitivity CTCAE Grade 4
Eye disorders	Retinal events CTCAE Grade 2 lasting more than14 consecutive days confirmed by ophthalmologic examination
	Retinal events CTCAE Grade ≥ 3, confirmed by ophthalmologic examination
Gastro-intestinal	CTCAE grade ≥ 3 nausea or vomiting lasting more than or equal to 48 hrs despite optimal anti-emetic therapy
	CTCAE grade ≥ 3 diarrhea lasting more than or equal to 48 hrs despite optimal anti-diarrhea treatment
Hepato-biliary	CTCAE grade ≥ 3 total bilirubin
	CTCAE grade ≥ 3 ALT (isolated increases in AST without concomitant increases in ALT will not be considered dose-limiting, because of the non-specific nature of AST)
	Serum alkaline phosphatase CTCAE Grade 4 lasting more than 7 consecutive days
Respiratory	CTCAE grade ≥ 2 interstitial lung disease and pneumonitis

ECG QTc Interval	QTc interval ≥ 501 ms on at least two separate consecutive ECGs taken 5 min apart
Renal	Serum creatinine > 2x ULN
Cardiac disorders	Absolute decrease of LVEF >10% compared to Baseline and the LVEF is below the LLN
	Symptomatic left ventricular systolic dysfunction grade ≥ 3
	Other cardiac disorders Grade ≥ 3
Non-hematologic events	Any non-hematological CTCAE grade ≥ 3, except for the exclusions noted below
Exceptions to DLT criteria	CTCAE grade 3 fatigue lasting fewer than 5 days
	CTCAE grade 3 edema lasting fewer than 5 days
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be not clinically significant
CTCAE version 4.03 will be used for all grading. Optimal therapy for vomiting or diarrhea will be based on institutional guidelines, with consideration of the prohibited medications listed in this protocol.	

4.3 Number of Patients

During the dose escalation phase, a minimum of 9 patients and up to 18 patients total are anticipated to be treated. At least 6 patients must be treated at the MTD level before proceeding to the dose expansion phase.

During dose expansion phase, up to 12 additional irinotecan-refractory patients will be treated at the MTD.

4.3.1 Number of Study Centers

The study will be conducted primarily at the Huntsman Cancer Institute at the University of Utah but may also enroll patients through the Huntsman-Intermountain Cancer Care Program (HICCP) for the dose expansion portion of the study.

4.4 Duration

Study patients may remain on treatment with mFOLFIRI in combination with MEK162 until confirmed RECIST 1.1 disease progression, or as long as they are receiving clinical benefit and have not experienced intolerable toxicities at the discretion of the investigator. After a response but with intolerable toxicity from mFOLFIRI patients will be allowed to continue on MEK162 alone if deemed appropriate by the investigator.

The estimated duration for accrual in the dose escalation phase is anticipated to be 12 months. Accrual for the dose expansion phase is anticipated to take 12 months. Estimated duration of total accrual and patient participation is approximately three and a half years.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with signature in the patient research chart.

Patient No. _____
Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria
Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Age ≥ 18 years old

5.1.2 _____ Patients with histologically confirmed *KRAS* positive metastatic colorectal cancer.

5.1.3 _____Patients must have progressed during or after first-line treatment for metastatic disease with oxaliplatin and fluoropyrimidines based chemotherapy (with failure within six months) or not be a candidate for oxaliplatin (i.e. neuropathy).

5.1.4 _____ ECOG Performance Status 0-1

5.1.5 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.1.6 _____ Women of childbearing potential must have a negative blood pregnancy test at the screening visit

5.1.7 _____ Adequate bone marrow, organ function and laboratory parameters as defined by the following:

- ☐ Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L,
- ☐ Hemoglobin (Hgb) ≥ 9 g/dL without transfusions,
- ☐ Platelets (PLT) ≥ 75 x 10^9/L without transfusions,
- ☐ AST or ALT ≤ 2.5 × upper limit of normal (ULN); patient with liver metastases ≤ 5 ×ULN,
- ☐ Total bilirubin ≤ 1.5 × ULN and <2mg/dl,
  Note: Patients who have a total bilirubin level >1.5 × ULN will be allowed if their indirect bilirubin level is ≤1.5 × ULN
- ☐ Creatinine ≤ 1.5 mg/dL × ULN, or calculated creatinine clearance (determined as per Cockcroft-Gault)

5.1.8 _____ Adequate cardiac function as defined by the following:

- ☐ Left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram,
- ☐ QTc interval ≤ 480 ms (preferably the mean from triplicate ECG's)

5.1.9 _____ Must have recovered from adverse effects of any prior surgery, radiotherapy or other antineoplastic therapy. CTCAE adverse events less than or equal to grade 1 are acceptable. CTCAE adverse events grade 2 or greater may be acceptable as determined by the Principal Investigator

5.1.10 _____ Willingness and ability to comply with all study procedures and able to take oral medications

Dose Expansion Phase Additional Inclusion Criteria

5.1.11 _____Patients must be willing and able to undergo biopsy according to the institute's own guidelines and requirements for such procedures

5.1.12 _____ Patients must have measurable disease as defined by RECIST v1.1 (at least one lesion ≥ 10mm in at least one dimension when assessed by CT or MRI, or a cutaneous lesion with clearly defined margins that measures ≥ 10 mm in at least one dimension)

5.1.13 _____Patients must be irinotecan refractory. Patients must have progressed on prior irinotecan therapy but must be able to tolerate standard irinotecan doses.

5.2 Exclusion Criteria
Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ UGT1A1 *28 homozygous patients

5.2.2 _____ Previous treatment with any MEK inhibitor

5.2.3 _____ Treatment with systemic antineoplastic therapy (including unconjugated therapeutic antibodies and toxin immunoconjugates) or any investigational therapy within 4 weeks (< 6 weeks for nitrosurea or mitomycin-C, antibodies except for trastuzumab) or within 5 half-lives of the investigational therapy prior to starting study treatment, whichever is longer

5.2.4 _____ Patient received radiotherapy within 2 weeks prior to the first dose of study treatment except localized radiation therapy for symptomatic bone metastasis.

5.2.5 _____ Have had a diagnosis of another malignancy, unless the patient has been disease-free for at least 3 years following the completion of curative intent therapy, with the following exceptions:

- Patients with treated non-melanoma skin cancer, in situ carcinoma, or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed.
- Patients with organ-confined prostate cancer with no evidence of recurrent or progressive disease based on prostate-specific antigen (PSA) values are also eligible for this study if hormonal therapy has been initiated or a radical prostatectomy has been performed.

5.2.6 _____ History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes.

5.2.7 _____ Personal history of Gilbert's syndrome.

5.2.8 _____ Uncontrolled arterial hypertension defined by blood pressure > 140 (systolic) or100 (diastolic) mm Hg at rest (average 3 consecutive readings at least 5 minutes apart) despite appropriate medical therapy.

5.2.9 _____ Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:

- History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, 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 except atrial fibrillation and paroxysmal supraventricular tachycardia.

5.2.10 _____ Known positive serology for HIV, active Hepatitis B, and/or active Hepatitis C infection (Note: if not suspected, testing is not required at baseline).

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

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

5.2.13 _____ Impairment of gastrointestinal function or gastrointestinal disease (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection that under the judgment of the PI may impair absorption of study drugs).

5.2.14 _____ Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection/inflammation, intestinal obstruction, unable to swallow

medication.(patients may not receive drug through a feeding tube), social/ psychological issues, etc.

5.2.15 _____ Patients who have undergone major surgery ≤ 3 weeks prior to starting study drug or who have not recovered from side effects of such procedure.

5.2.16 _____ Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive β-hCG laboratory test.

5.2.17 _____ Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception throughout the study and for 15 days after study drug discontinuation. Highly effective contraception methods include:

- Total abstinence
- Female sterilization-bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks before starting study treatment. 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.
- Male sterilization of subject partner- vasectomy at least 6 months prior to screening.
- 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

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 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [for US only: and estradiol < 20 pg/mL].

5.2.18 _____ Sexually active males unless they use a condom during intercourse while taking the drug and for 15 days 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.

5.2.19 _____ Medical, psychiatric, cognitive or other conditions that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol or complete the study.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____	_____	_____
Investigator Signature	**Date**	**Time**

6 STRATIFICATION FACTORS

Does not apply.

7 TREATMENT PLAN

7.1 Administration Schedule

mFOLFIRI Treatment

mFOLFIRI treatment will be carried out in accordance with standard of care guidelines with omission of the 5-fluorouracil bolus (400 mg/m^2 slow IV push over 5 minutes on day 1) and leucovorin (400 mg/m^2 IV over 2 hours on day 1). Doses are based on screening or cycle 1 day 1 Body Surface Area (BSA) determined from actual body weight. Doses will be recalculated for > 10% weight loss. Dose may be recalculated for > 10% weight gain at the investigator's discretion.

Irinotecan 180 mg/m^2 IV over 90 minutes on day 1.

5-fluorouracil 1200 mg/m^2 continuous infusion for 48 hours (2400 mg/m^2 in 48 hours).

MEK162 Treatment

MEK162 doses will be 30 mg or 45 mg BID PO daily starting on day 1. When in combination with mFOLFIRI (on day 1 of each cycle), MEK162 will be taken AFTER irinotecan infusion. MEK162 will be taken BID PO daily on days 1 through 12. MEK162 should be held for 48 hours prior to the next dose of mFOLFIRI on days 13 and 14 . If a cycle lengthened or shortened in accordance with the protocol-specified windows, MEK162 should be held for 48 hours prior to the next dose of mFOLFIRI
Prior to beginning the combination, all patients will receive MEK162 single agent 6 day lead in. The subject will discontinue MEK162 for 2 days prior to receiving the MEK162 mFOLFIRI combination on C1D1.

7.2 MEK162 Treatment

7.2.1 How Supplied, Stored, Packaged and Labeled

MEK162 will be provided by Array as film-coated tablets for oral use of dosage strength 15 mg. The study drug will be administered as a flat-fixed dose, and not by body weight or body surface area.

Upon receipt, MEK162 will be stored at the Huntsman Cancer Institute Investigational Pharmacy. MEK162 will be stored according to the instructions specified on the drug labels. Study medication will be provided by Array by an authorized person at the investigator's site.

7.2.2 Preparation and Administration

Patients will be provided with adequate supply of MEK162 for self-administration at home until at least their next scheduled study visit.

MEK162 will be administered with water, irrespective of food. Prescribed BID doses should be taken 12 ± 2 hours 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 crush MEK162 tablets. Patients should not take extra doses of MEK162 to compensate for doses missed for AEs or any other reason. If a patient vomits at any time after dosing, the dose of MEK162 should not be re-administered

7.2.3 Accountability and Compliance

Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

Patients will be asked to complete and return a pill calendar each cycle to verify drug compliance.

At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Array.

7.3 mFOLFIRI Treatment

7.3.1 How Supplied, Stored, Packaged and Labeled

Agents contained in the mFOLFIRI regimen are commercially available and approved by the United States FDA and other regulatory agencies for use in treating patients with multiple types of cancer.

5-Fluorouracil and irinotecan will be supplied by the study site and billed to patients and/or their third-party payer (insurance, a healthcare provider, or applicable government program). 5-Fluorouracil and irinotecan should be stored, handled, and labeled per institutional guidelines.

7.3.2 Preparation and Administration

5-Fluorouracil and irinotecan should be prepared and administered per institutional guidelines.

7.3.3 Accountability and Compliance

Accountability and compliance should be handled per institutional policies for commercially available medications.

7.4 Concomitant Medications

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted. Refer to section 7.5 for permitted concomitant medications to be used with caution. Medications required to treat AEs, manage cancer symptoms, concurrent stable diseases and supportive care agents, such as PRBCs, pain medications, anti-emetics, short courses of steroids, and anti-diarrheals are allowed. Oral contraceptive pills are permitted.

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

The investigator should instruct the patient to notify the study site about any new medications including vitamins, supplements and herbal supplements he/she takes after the start of the study drug and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be noted.

Palliative radiation therapy for a single site of bone or brain metastasis is allowed on the study as long as these are the only site of disease progression. The radiation field must not affect any of the target lesions designated for disease assessment. Protocol treatment (MEK and mFOLFIRI) will be held during radiation therapy and will be re-started 2 weeks following the conclusion of therapy.

7.5 Permitted Concomitant Medications to use with caution

- MEK162 has been identified to be primarily metabolized by UGT1A1. 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 AEs. Please refer to Table below for a list of these known drugs; however, this list may not be exhaustive.

List of inhibitors/inducers of UGT1A1 to be used with caution

Inhibitors of UGT1A1	atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib
Inducers of UGT1A1	carbamazepine, nicotine, rifampicin, testosterone propionate

Abbreviations: UGT1A1 = UDP-glucuronosyl transferase 1A1

- *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 (IC_{50} ~ 6 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*. Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of this enzyme.

- CYP3A4 induction by MEK162 has been clinically evaluated and co-administration should not impact the exposure of MEK162 with CYP3A4 substrates.

CYP3A5 and 7 and CYP2B6 substrates to be used with caution

The following therapies should be used with caution unless otherwise specified:

- Strong inducers or inhibitors of CYP3A4 (Refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/)
- Substrates of CYP3A4 with narrow therapeutic windows (Refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/)
- Medications that carry a strong risk for QT prolongation
- Grapefruit, grapefruit juice, and Seville orange juice
- Concurrent anti-neoplastic therapy other than those antineoplastic treatments specified as a part of this protocol are prohibited
- 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.

7.6 Duration of Therapy

Patients will continue treatment until there is any of the following:

1. Evidence of disease progression, unless receiving clinical benefit as determined by the investigator
2. Unacceptable toxicities and/or SAEs that under the investigator judgment warrants treatment discontinuation
3. Patient withdraws from participation on the study

8 TOXICITIES AND DOSAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.03 for adverse event and serious adverse event reporting. A copy of the CTCAE Version 4.03 can be downloaded: (**http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx**).

8.1 Dose Modifications for MEK162

For patients who do not tolerate MEK162, dose adjustments are permitted as described in the table below in order to allow the patient to continue on study drug in both the escalation and expansion phases of the trial. Two dose reductions are permitted from dose level 2 according to the table below. If patients at dose level 1 need a dose reduction an intermittent schedule of MEK162 will be used. Patients requiring additional reductions below dose level -1 must be discontinued from study treatment. Dose interruptions of more than 21 days are not allowed unless approved by the study Medical Monitor.

Missed/skipped doses will not be made up (i.e. the patient should not double their dose if the previous dose was missed).

No dose re-escalation is allowed.

If MEK162 dosing is interrupted for toxicity reasons, patients will be allowed to continue treatment with mFOLFIRI at the discretion of the treating physician and principal investigator.

Dose reduction*				
MEK162	45 mg BID	→	30 mg BID →	30 mg BID**
* Dose reduction should be based on the highest AE grade ** Dose reduction below 30 mg is not allowed. Dose reduction from the standard 30 mg BID includes an intermittent schedule 1 week on 1 week off: 30 mg BID dosing for one week starting after FOLFIRI administration on day 1 of a cycle followed by one week of dose hold.				

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the toxicity and the guidelines provided below. In general, doses should not be reduced or interrupted for Grade 1 toxicities, but treatment to control symptoms should be provided as appropriate. All adverse events (AE) should be followed weekly or as clinically appropriate until stabilization or resolution.

Skin toxicity (such as macular popular rash, acne, rash, dermatitis acneiform, etc.), visual changes (related to Retinal Pigment Epithelial Dystrophy (RPED)), nausea, diarrhea and asymptomatic reversible elevation of CK have been associated with MEK162 administration. Please refer to the tables below for the study drug dose adjustment recommendations for MEK162 induced toxicities.

Table 8.1.1: Guidelines for Skin Rash Management

Step	Grade	Severity	Management	MEK162 Dose Adjustment
1	Mild (Grade 1)	• Localized • Minimally symptomatic • No impact on activities of daily living (ADL) • No sign of superinfection	• Initiate regimen if not already started. Consider using moderate strength topical steroids (e.g. hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) • Reassess after 2 weeks ; if rash worsens or does not improve, proceed to step 2.	• Continue current dose. • Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 2.
2	Moderate (Grade 2)	• Generalized • Mild symptoms	• Initiate regimen if not already started, but using moderate strength topical	• Consider holding treatment

		(e.g., pruritus, tenderness) • Minimal impact on ADL • No sign of superinfection	steroids (e.g. hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) • Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 3	until rash improves • Maintain at current dose • Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 3
3	Severe (≥ Grade 3)	• Generalized • Severe symptoms (e.g. pruritus, tenderness) • Significant impact on ADL • Sign of or potential for superinfection	• Initiate regimen if not already started, but using moderate strength topical steroids PLUS methylprednisolone dose pack • Consider obtaining dermatology consultation • Manage rash per dermatologist's recommendations	• Hold treatment until rash improves (moderate or mild) or resolves • Reduce dose by 1 level • Reassess after 3 weeks; if rash worsens or does not improve, discontinue treatment with MEK162

Table 8.1.2: 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 - Central Serous Retinopathy (CSR) like events	
Grade 1	Maintain dose level of MEK162 and increase frequency of ophthalmic monitoring to at least every 14 days.

Worst toxicity **CTCAE v4.03 Grade (unless otherwise specified*)**	**Dose Adjustment for Study Drug MEK162**
Grade 2	Maintain dose level of MEK162 and refer the patient to ophthalmologist within one week: - If resolved to Grade ≤ 1 in ≤ 21 days, maintain dose of MEK162. - 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: - If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level*** of MEK162 - If not resolved to Grade ≤ 1 in ≤ 21 days, discontinue patient from study drug treatment.
Grade 4	Permanently discontinue MEK162 and close follow up of ophthalmic monitoring.
Eye disorders – Retinal Vein Occlusion (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: -If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level*** of MEK162 - If not resolved to Grade ≤ 1 in ≤ 21 days, discontinue patient from study drug treatment.
Grade 4	Permanently discontinue MEK162
Liver related Adverse Events	
Grade 1 AST or ALT (> ULN - 3 x ULN)	Maintain dose level of MEK162
Grade 2 AST or ALT (> 3.0 – 5.0 x ULN or 3 X baseline value*****) AND **bilirubin elevation[a] ≤ 2.0 x ULN**	Interrupt dose of MEK162 until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: - If resolved in ≤ 14 days, maintain dose level of MEK162. - 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 or baseline, then: - If resolved in ≤ 7 days, reduce dose level** of MEK162. - If resolved in > 7 days, discontinue patient from study drug treatment.

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified*)	**Dose Adjustment for Study Drug MEK162**
Grade 3 AST or ALT (> 5.0 - 8.0 x ULN) **AND blood bilirubin[a]** ≤ 2.0 x ULN	Interrupt dose of MEK162 until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: - If resolved in ≤ 14 days, maintain dose level of MEK162. - If resolved in > 14 days, reduce dose level** of MEK162.
AST or ALT (> 8.0 x ULN)	Permanently discontinue MEK162
AST or ALT > 5.0 x ULN AND **blood bilirubin[a] > 2.0 x ULN**	Permanently discontinue MEK162
AST or ALT Grade 4 (> 20.0 x ULN)	Permanently discontinue MEK162

Cardiac*

Asymptomatic, absolute decrease in LVEF of greater than 10% from baseline that is below the LLN	Withhold MEK162 and evaluate LVEF every 2 weeks. If the LVEF recovers (define as LVEF> 50% or >LLN and absolute decrease <10% compared to baseline) within 21 days, resume treatment with a dose reduction. Monitor LVEF 2 weeks after resuming MEK162, every 4 weeks for 12 weeks and subsequently as per protocol. If the LVEF does not recover within ≤ days permanently discontinue MEK162.
Symptomatic congestive heart	Permanently discontinue MEK162
QTCF > 480 ms (confirmed with repeat ECG) during treatment and change from pre-pretreatment value remains ≤ 60 ms	1st occurrence: • Temporarily interrupt dosing of MEK162 until QTcF < 480 ms. then resume treatment at reduced dose. 2nd occurrence: • Permanently discontinue MEK162
QTcF increase (confirmed with repeat ECG) during treatment is both > 480 ms and > 60 ms change from pre-treatment values	Permanently discontinue MEK162
Creatine Kinase (CK) elevation	
Grade 1-2	Continue treatment on same dose level (If total CK ≥ 3 ULN, measure isoenzymes and myoglobin in blood or urine)
Grade 3 (> 5.0 ULN- 10.0 ULN)	If asymptomatic: Maintain dose of MEK162 and monitor closely If symptomatic (muscle pain/spasms): Interrupt dose of MEK162 until resolved to CTCAE Grade ≤ 1 and monitor closely (then:

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified*)	**Dose Adjustment for Study Drug MEK162**
	- If resolved to grade 1 or baseline in ≤ 21 days, reduce 1 dose level** of MEK162 - If resolved to grade 1 or baseline in > 21 days, then discontinue patient from study drug treatment
Grade 4	If asymptomatic: interrupt and monitor closely - If resolved in ≤ 21 days, reduce 1 dose level** of MEK162 - If resolved in > 21 days, then discontinue patient from study drug treatment If symptomatic : permanently discontinue treatment
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
Interstitial lung disease / pneumonitis	
Grade 1	Maintain dose level of MEK162
Grade 2	Withhold MEK162 for up to 3 weeks If improved to Grade 0 or 1, resume treatment at 1 reduced dose level of MEK162 If not resolved within 3 weeks, permanently discontinue MEK162
Grade 3-4	Permanently discontinue MEK162
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 interruption or 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 30 mg BID is not allowed (intermittent dosing at Dose level -1 should be used when applicable)

*** 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 discontinuing drug and, if in the opinion of the Investigator and DSMC Medical Monitor , 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

8.2 Dose Modifications for mFOLFIRI

For patients who do not tolerate mFOLFIRI, dose adjustments are permitted as described in the table below. There will be no more than 2 dose level reductions in mFOLFIRI. No dose re-escalation is allowed.

If mFOLFIRI dosing is interrupted for toxicity reasons, patients will be allowed to continue treatment with MEK162 at the discretion of the treating physician and principal investigator and if they meet the requirements listed in the protocol. A 48-hours dose hold for MEK162 will be observed prior to restarting treatment with mFOLFIRI

TOXICITY AT THE START OF SUBSEQUENT CYCLES OF THERAPY	Grade or Value	Irinotecan	5-FU Continuous Infusion
ANC*	< 1.2 k/μL	HOLD until resolution	
Platelets	< 75 k/μL		
Diarrhea	≥ 1		
Mucositis	≥ 2		
Bilirubin (total)	≥ 1.5 x ULN		
Hand/foot syndrome	3-4	100%	STOP
PREVIOUS TOXICITY (After resolution)	**First occurrence**		
Neutropenia > 5 days	3-4	100%	100%
Febrile Neutropenia	3-4		
Thrombocytopenia	3-4		
Diarrhea	3	80%	80%
Diarrhea	4	60%	60%
Stomatitis	3	100%	80%
Stomatitis	4	100%	60%
Myocardial Ischemia	—	100%	STOP
PREVIOUS TOXICITY (After resolution)	**Second occurrence**		
Neutropenia > 5 days	3-4	80%	80%
Febrile Neutropenia	3-4		
Thrombocytopenia	3-4		
Diarrhea	3	60%	60%
Diarrhea	4	STOP	STOP
Stomatitis	3	80%	60%
Stomatitis	4	80%	STOP

*For ANC between 1.0 and 1.2 k/μL the patient can be treated if felt safe by the treating physician.

8.3 Supportive Care

8.3.1 All supportive measures consistent with optimal patient care will be given throughout the study.

8.3.2 Refer to Appendix 1 and Appendix 2 for additional supportive care guidelines for the management of MEK162 induced skin toxicity and diarrhea respectively.

9 STUDY CALENDAR

CYCLE Calendar: 1 cycle = 14 days, cycles begin the day of a mFOLFIRI infusion
For all visits, there is a ± 3 day window **if not explicitly specified otherwise**.

Examination	**Screening[1]**	**Single Agent Lead in (6 days)[2]**	**C1[20]**	**C1**	**C2**	**C2**	**C3**	**C4**	**C5**	**C6**	**Subsequent Cycles Until Progression**	**EOT [3, 18]**	**30 day Follow -up[3]**
Day of Cycle:	-28 to -1		**1**	**8**	**1**	**8**	**1**	**1**	**1**	**1**	**1**		
Informed consent	**X**												
Medical history	**X**												
Eligibility criteria	**X**												
Vital signs, weight[16]	**X**		**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	
Physical examination	**X**		**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	
ECOG performance status	**X**		**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	
Ophthalmologic examination[4]	**X**						**X**		**X**		**X**[4]	**X**	
Hematology[5]	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Chemistry[6]	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
LDH, Magnesium, Phosphorus, and uric acid[7]	**X**	**As clinically indicated**											
UGT1A1 Genotyping	**X**												
CK and Troponin[8]	**X**		**X**				**X**		**X**		**X**	**X**	
Thyroid Function Tests[9]	**X**												
Urinalysis	**X**		**X**				**X**		**X**		**X**		
Pregnancy test[10]	**X**											**X**	
ECG[15]	**X**				**X**			**X**		**X**	**X**		
ECHO/ Cardiac MUGA[11]	**X**				**X**		**X**				**X**	**X**	
CT[12]	**X**							**X**			**X**	**X**	
Adverse Event Collection		**X**											
Concomitant Medication Collection	**X**												
MEK162[13]		**X**	**X (BID PO daily, held 48h prior to each dose of mFOLFIRI)**										
mFOLFIRI			**X**		**X**		**X**	**X**	**X**	**X**	**X**		
PK (see 14.1)[14]		**X**	**X**		**X**								
Carcinoembryonic Antigen (CEA)	**X**		**X**		**X**			**X**			**X**	**X**	
Dose expansion only													
cfDNA[19] (see 14.2)	**X**		**X**		**X**				**X**		**X**	**X**	
Biopsy (see 14.2)	**X**							**X**[17]				**X**	

1. ALL Pre-study/Screening procedures should be completed within 4 weeks of study enrollment. Day -1 is the day before the 6 day MEK162 lead in.
2. Physical exam and laboratory assessments do not need to be repeated if performed within 7 days of single agent lead-in. Pregnancy test must be performed within 72hours of single agent lead-in.
3. Evaluation of adverse events, concomitant medication and antineoplastic therapies since discontinuation of study drug only.
4. Ophthalmologic exam to be conducted at baseline and every 4 weeks thereafter; include slit lamp examination, visual acuity testing, visual field testing, intraocular pressure (IOP) and indirect fundoscopy with attention to retinal abnormalities. If there is a clinical suspicion of Retinal detachment or RVO, additional assessments including Ocular Coherence Tomography (OCT) and Fluorescence angiography (FA) , respectively will be done.
5. Hematology includes CBC with differential and platelets. Will be done weekly during the first two cycles.
6. Chemistry includes Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin (if total bilirubin is abnormal, direct and indirect bilirubin will be assessed as clinically indicated), Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, Urea Nitrogen. Will be done weekly during the first two cycles.
7. To be performed at baseline/screening and as clinically indicated while on study.
8. Cardiac/Muscle Enzymes: CK and troponin will be performed on Day 1, every 4 weeks (i.e. Screening/Baseline, C3D1, C5D1, etc.). Follow up for total creatine kinase (CK) ≥ 3 X ULN will include weekly assessment of isoenzymes and myoglobin in blood/or urine, and troponin as applicable.
9. TSH only at screening. If TSH is abnormal, T3 and free T4 to be performed.
10. Pregnancy test must be done at screening, within 72 hours of single agent lead-in, and the EOT for all women of childbearing potential and repeated as clinically indicated.
11. MUGA/ultrasound or ECHO will be performed to determine cardiac ejection fraction at screening, 3 and 6 weeks after beginning single agent treatment and every 9 weeks thereafter.
12. CT scans must be repeated every 8 weeks (± 5 days), until progression.
13. Single dose lead of MEK162 will be given for 6 days followed by 2 days off prior to starting the combination. When in combination with mFOLFIRI, MEK162 will be taken AFTER the mFOLFIRI infusion on Day 1. MEK162 will be taken BID PO daily on days 1 - 12. MEK162 should be held on Days 13 and 14 in order for MEK162 to be held for 48 hours prior to the next dose of mFOLFIRI. For cycles lasting more or less than 14 days, MEK162 will be held for 48 hours prior to the next dose of mFOLFIRI.
14. PK samples must be drawn before MEK162 dosing and 2, 6 and 24 hr post MEK162 dosing on Day 1 of the MEK162 lead in period and before irinotecan, before MEK162 and 2, 6 and 24 hr post MEK162 on C1D1/2 and C2D1/2. 24 hr PK draws must take place before the 3rd dose of MEK 162 is taken. An additional PK should be taken at the time of biopsy. See section 14.1 for more details.
15. If QTc interval is ≥ 501 ms, a second ECG should be obtained within 5 minutes to confirm the QTc interval.
16. At screening, blood pressure measurement to be taken once to determine eligibility. If uncontrolled arterial hypertension (see exclusion criteria 5.2.8).
17. Biopsy at C4D14 (± 3 days) is optional.
18. Within 30 days of last dose.
19. cfDNA should be collected at baseline, C1D1, C2D1 of the combination therapy and at every restaging visit thereafter during the combination therapy.
20. C1D1 is on Day 9 after the start of the MEK162 lead in (6 days MEK162 dosing 2 days off).

9.1 Study Procedures: Recommended Safety Assessments during MEK162 treatment

At every visit, the following assessments should be performed (until drug discontinuation) for safety purposes: physical examination, weight, vital signs, laboratory assessments (hematology, chemistry).

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (total neutrophil count including lymphocyte, monocyte, eosinophil and basophil counts) and platelet count will be measured. Will be done weekly during the first two cycles.
- Clinical Chemistry: BUN/urea (uric acid), serum creatinine, sodium, potassium, magnesium, calcium, glucose (fasting or non-fasting), total protein, albumin, phosphate and LDH will be measured. Additionally liver function test including AST, ALT, alkaline phosphatase, total bilirubin (direct and indirect bilirubin will be measured as clinically indicated). Will be done weekly during the first two cycles.

At every four week visit, the following assessments should be performed cardiac/muscle enzymes), urinalysis, and ophthalmic examination.

Full ophthalmic examination including slit lamp examination, visual acuity testing, visual field testing, intraocular pressure (IOP) and indirect fundoscopy with attention to retinal abnormalities, especially RPED like events and RVO.

- For patients with clinical suspicion of retinal abnormalities (i.e. photopsia, metamorphopsia, impairment of visual acuity, etc.) or RVO, additional assessments of optical coherence tomography (for RPED) and fluorescein angiography (for RVO) are **mandatory**.
- Cardiac/Muscle Enzymes: CK and troponin will be performed on day 1 of every other cycle. Follow up for total creatine kinase (CK) $\geq$ 3 X ULN will include weekly assessment of isoenzymes and myoglobin in blood/or urine, and troponin as applicable.
- Pregnancy and assessments of fertility: All females of childbearing potential (pre-menopausal or less than 1 year after the onset of menopause) will have a serum pregnancy test (β-hCG) at the following time points: Baseline/Screening, C1D1 (not required if Baseline/Screening assessment was done within 72 hours of C1D1), and the End of Treatment visit. Additional serum or urine pregnancy tests are recommended approximately every other cycle for women of child bearing potential. For confirmation of post-menopausal status, serum FSH and estradiol will be determined if amenorrhea is less than 12 months.
- MUGA/ultrasound will be performed to determine cardiac ejection fraction at 3 and 6 weeks after beginning treatment and every 9 weeks thereafter.
- Blood pressure will be measured in the clinic every 14 days. More frequent assessments during the study drug treatment period may also be performed at the discretion of the investigator and if medically indicated.

10 CITERIA FOR EVALUATION AND ENDPOINT

10.1 Safety

The primary endpoint for the dose escalation portion of this study is safety as determined by the incidence of DLT. Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained in the clinic setting. Patients should be sitting for 3-5 minutes prior to obtaining vital signs. Height is required at screening only. Weight is required on day 1 of each cycle.

Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the study calendar.

10.2 Efficacy

The primary endpoint of the dose expansion portion is to evaluate response rate and clinical benefit rate (PR/CR/SD at 4 months). Tumor response will be measured according to RECIST 1.1 criteria. Patients receiving at least 80% of MEK162 are considered evaluable.

The following definitions and criteria (RECIST version 1.1) should be used for the baseline evaluations of existing disease, and for the ongoing evaluation of tumor responses.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter (LD) ≥ 10 mm using CT, MRI, or caliper measurements or ≥ 20 mm with x-ray.

Non-measurable lesions - all other lesions including small lesions (LD < 10 mm with CT, MRI, or caliper measurements or < 20 mm with x-ray).

Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).
- A sum of the LD for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout restaging and follow-up.

10.2.1 Response Criteria

	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions (Must persist for a minimum of four weeks)
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD (Must persist for a minimum of four weeks)
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

	Evaluation of non-target lesions
Complete Response (CR)	Disappearance of all non-target lesions
Stable Disease (SD)	Persistence of one or more non-target lesion(s)
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

10.3 Stopping Rules

Refer to section 4.2 for definition and evaluation of Dose Limiting Toxicities. Refer to Section 7.6 for reasons to discontinue study medication.

11 STATISTICAL CONSIDERATIONS

Dose Escalation Phase

For the Dose escalation phase of the study a 3+3 design will be used, dose levels will be assigned as outlined earlier in Table 4.1. The primary endpoint is safety as summarized by dose limiting toxicity (DLT). All patients who receive any study treatment will be included in the final summaries and listings of safety data. Detailed information collected for each AE will include a description of the event, duration, severity, relatedness to study drugs, action taken, and clinical outcome. Severity of the AEs will be graded according to the CTCAE version 4.03. The statistical analysis of the safety data will be descriptive and tabular in nature.

For the PK analysis we will use WinNonlin

Changes in plasma levels of *KRAS* (at baseline, C1D1, C2D1 and at the time of restaging thereafter) will be correlated with changes in CEA levels measured at similar time points.

Dose Expansion Phase

An expansion cohort of up to 12 patients with *KRAS* positive irinotecan refractory disease will be enrolled at the MTD determined in the dose escalation phase. An exact binomial confidence interval will be used to summarize objective response (OR) and Kaplan-Meier methodology will be used to estimate progression-free survival (PFS) in the expansion cohort. Three or more responses in an expansion cohort of up to 12 patients will be considered preliminary evidence of efficacy. There is an 84% probability of 3 or more responses in 12 patients if the true response rate is 35%. There is an 11% probability of 3 or more responses in 12 patients if the true response rate is 10%.

Genomic Biomarkers will be tested for accuracy by a Mann Whitney U test.

12 REGISTRATION GUIDELINES

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Study related screening procedures can only begin once the patient has signed a consent form. Patients must not begin protocol treatment prior to registration.

Treatment should start within five working days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to: CTORegistrations@hci.utah.edu.

13 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of electronic forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. **Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.** These forms will be completed on an on-going basis during the study. The medical records will be the source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site monitors in their activities.

14 SPECIAL INSTRUCTIONS

14.1 Pharmacokinetic Sample collection

Blood samples will be collected to determine the PK of MEK162 and its primary active metabolite AR00426032 in combination with mFOLFIRI (CPT-11 and SN-38). Blood samples will be collected on all patients (both dose escalation and dose expansion).

Required time points for PK collection

Blood for full PK profiling of MEK162 and CPT-11 (Irinotecan) will be collected at different time points on C1D1 and C2D1 of mFOLFIRI + MEK162.

Schedule of PK sample collections: PK samples will be taken on Day 1 of the MEK162 lead and Cycles 1 and 2 of the MEK mFOLFIRI combination therapy, and at the time of any biopsy.
The 24 hr post MEK162 PK draws must be completed before the patient takes their dose of study medication.

Cycle	Day	Sample	window
MEK162 lead in	1	Pre dose MEK162	Within 15 prior to dosing MEK162
	1	2hr post MEK162 dosing	+/- 15 min

	1	6hr post MEK162 dosing	+/- 15 min
	2	24hr post MEK162 dosing	+/- 30 min
Cycle 1 and 2	1	Pre dose Irinotecan	Within 15 prior to dosing Irinotecan
	1	Pre dose MEK162	Within 15 prior to dosing MEK162
	1	2hr post MEK162 dosing	+/- 15 min
	1	6hr post MEK162 dosing	+/- 15 min
	2	24hr post MEK162 dosing	+/- 30 min

PK sample collection details will be covered in the lab manual.

14.2 Correlative Studies

14.2.1 Tumor specimens

Tumor biopsies will be collected before and, if the patient allows, during treatment with MEK162 and mFOLFIRI.

Fresh pre- and post-treatment tumor biopsies will be obtained, if accessible, from all patients included in the dose expansion cohort only. The pre-treatment tumor biopsy sample is required. However, the post-treatment samples are optional and will be obtained after four cycles of therapy (C4D14 +/- 3 days). If feasible it is recommended that a third biopsy will also be collected at the time of progression.

Pharmacodynamic assessments will be performed in tumor tissues to provide evidence of specific target inhibition by the study drug combination (this will include but is not limited to evaluation of p-MEK, p-ERK, p-AKT)

Collection of Fresh tumor sample details will be covered in the lab manual

14.2.4 Collection of cell-free DNA (cfDNA)

5-30mL of blood will be collected from the patient to quantify *KRAS* mutations in circulating cell-free DNA at baseline, C1D1, C2D1 and at every restaging visit thereafter for all patients included in the dose expansion cohort only. Levels of *KRAS* mutations from circulating cell-free DNA isolated from plasma will be measured and correlated with biochemical response by CEA as well as radiological response by CT scan.

Collection of cfDNA sample details will be covered in the lab manual

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

15.2 Institutional Review

Study will be approved by the Institutional Review Board of University of Utah.

15.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) and approved by the NCI to assure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI approved plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a **Phase I study**. For each phase I study using an agent of potential risk a member of the DSMC will be assigned as the primary medical monitor. The primary medical monitor will be notified immediately of all SAEs. A formal report should be submitted to the primary medical monitor within 10 days. All serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC quarterly. Approval from the primary medical monitor is required for all dose escalations. The full committee will also review all grade 3 or greater toxicities for patients on treatment and within 30 day follow-up window (only if possibly, probably or definitely related).

15.4 Adverse Events / Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0.3 for AE and SAE reporting. An electronic copy of the CTCAE Version 4.0.3 can be downloaded from:
http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx

15.4.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only

considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Adverse event collection will begin after the first dose of study treatment and end 30 days after the last dose of study treatment.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.
The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade based on CTCAE v.4 (grade 1-5)
2. its relationship to the all study drugs (definite, probable, possible, unlikely, not related)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 8 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug is described in the Drug Information (section 3) and the most recent Investigator Brochure. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

15.4.2 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

15.4.3 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- causes congenital anomaly or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition

Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not.

Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

15.5 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB, and Array, according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to compliance@hci.utah.edu as soon as possible, but no later than 10 days of first knowledge or notification of event (5 days for fatal or life threatening event).

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study.
- The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the quarterly DSMC meeting.
- For multisite studies the HCI DSMC will notify all participating sites of all unexpected and related SAEs via the Research Compliance Office. The RCO will also notify all investigators at remote clinical sites participating in a multisite trial of any other safety update, including external safety reports, manufacturer's reports and updates to the investigator's brochure.

FDA Notifications:

- Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:
    - Serious
    - Unexpected
    - Definitely, Probably or Possibly Related to the investigational drug
- Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.
- All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.
- The RCO will review the MedWatch report for completeness, accuracy and applicability to the regulatory reporting requirements.
- The RCO will ensure the complete, accurate and timely reporting of the event to the FDA.
- The Regulatory Coordinator will submit the report as an amendment to the IND application.

- All other adverse events and safety information not requiring expedited reporting that occur or are collected during the course of the study will be summarized and reported to the FDA through the IND Annual Report.

IRB Notification:

- Events meeting the University of Utah IRB reporting requirements (http://www.research.utah.edu/irb/) will be submitted through the IRB's electronic reporting system within 10 working days.

Array Notifications:

- The investigator must complete the FDA MedWatch 3500a form and Array SAE coversheet in English, assess the relationship to study treatment and send the initial completed MedWatch form and Array SAE coversheet by fax 1.303.386.1516 within 24 hours to Array Drug Safety. 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 5 calendar days for other serious adverse events. 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 MedWatch form, Array fax 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.

- **Pregnancies:** To ensure patient safety, each pregnancy occurring while the patient is on study treatment and for up to 3 months after last dose, must be reported to Array within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.
  Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to Array Drug Safety. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Array study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

*Medwatch 3500A form can be found at
http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/ucm082728.pdf

15.6 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to be submitted amendment for FDA review.

15.7 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

15.8 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect (21 CFR 312.33).

15.9 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

15.10 Record Keeping

Per 21 CFR 312.57, Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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17 Appendices

Appendix 1: 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. In general, the following interventions are in addition to the MEK162 induced rash dosing guidelines in Table 8.1.1 of the protocol

Prophylactic treatment for skin toxicity is recommended. Prophylaxis of skin toxicity to be initiated 24 hours prior to the first treatment with MEK162 or later as needed. Apply topical agents to the mostly common affected areas such as face, scalp, neck, upper chest, and 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®)
- Possibly oral 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 antibiotic (erythromycin (2%)) are recommended.
- The patient should be reassessed after 2 weeks or sooner if rash worsens or as per investigator opinion.

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-line) should be used with careful UV protection (i.e., avoid direct exposure to sunlight, use sunglasses, use sunscreen, etc.).
- Use of topical erythromycin or clindamycin (1%) plus mometasone or pimecrolimus (1% cream) plus oral antibiotics such as: oral lymecycline (408 mg once daily), doxycycline (100 mg BID) or minocycline (50 to 100 mg QD).

Use of acitretin is not recommended

Severe Rash (CTCAE Grade 3-4)

CTCAE Grade 3

- 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).
- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low doses, i.e. 0.3 to 0.5 mg/kg) (Lacouture et al 2011)

- Use of acitretin is not recommended

CTCAE Grade 4

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

Symptomatic treatment:

It is strongly recommended that patients who develop rash/skin toxicities receive symptomatic treatment:

- For pruritic lesions, use of cool compresses and oral antihistamine agents
- For fissuring, use of Monsel's solution, silver nitrate, or zinc oxide cream. If not sufficient use mild steroid ointments or combination of steroids and antibiotics such as Fucicort.
- For desquamation, use emollients with mild pH 5 (best containing urea 10%)
- For paronychia, antiseptic bath and local potent corticosteroids, use oral antibiotics and, if no improvement is seen, refer to a dermatologist or surgeon
- For infected lesions, obtain bacterial and fungal cultures and treat with topical or systemic antibiotics based on sensitivity of culture

Appendix 2: 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 asked regarding occurrence of diarrhea or diarrhea-related symptoms. If the patient had symptoms, the patient should be asked regarding the actions taken for these symptoms and re-instruct if indicated.
2. In addition to dietary modification, the patients should be instructed on early warning signs of diarrhea and potentially life-threatening illnesses (e.g. severe cramping → severe diarrhea, fever with diarrhea → infection and dizziness on standing might be a sign for shock).
3. Patients should be instructed on what to report to the investigator if possible (i.e. number of stools, stool composition, stool volume)

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 and are instructed on the use of loperamide on the first day of MEK162 treatment In addition to the MEK162 induced diarrhea dosing guidelines in Table 8.1.2 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 (Table 8.1.2 of the protocol)
Determine if diarrhea is complicated versus uncomplicated (Table 8.1.2 of the protocol)

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 immunosuppressed patients,
- Medication-induced diarrhea
- 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; Colace®)

- 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.

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