Cover Page

TITLE: A Phase I/Ib Study of MEK162, a MEK inhibitor, in combination with carboplatin and pemetrexed in patients with non-squamous carcinoma of the lung.

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Commercial Agents: Carboplatin and Pemetrexed

Coordinating Centre: Princess Margaret Cancer Centre Drug Development Program

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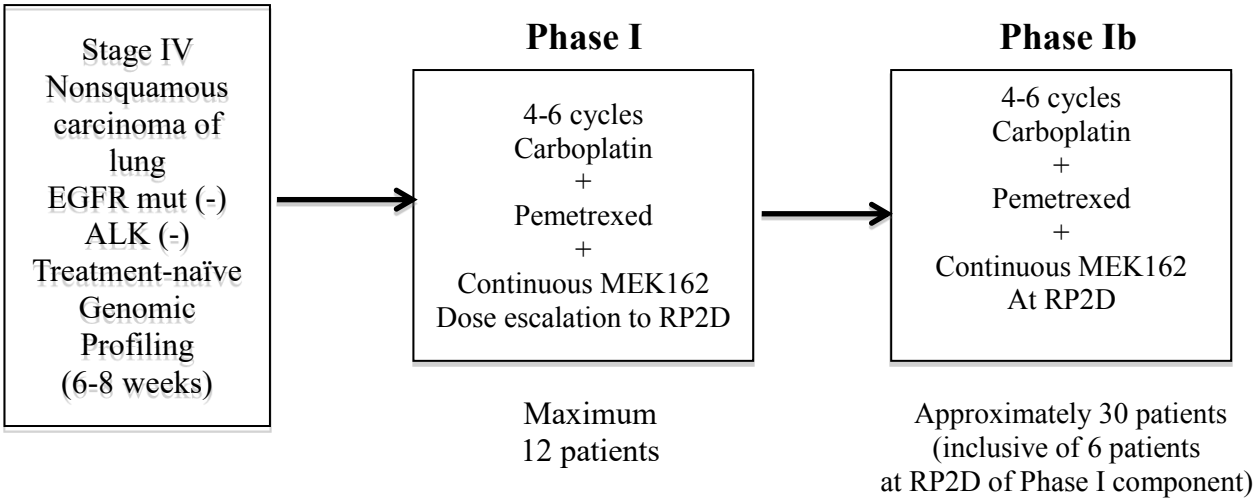
SCHEMA



SYNOPSIS

Title of study: A Phase I/Ib Study of MEK162, a MEK inhibitor, in combination with carboplatin and pemetrexed in patients with non-squamous carcinoma of the lung
Objectives: **Primary** • To assess the safety of MEK162 administered in combination with carboplatin and pemetrexed as first line chemotherapy treatment in advanced non-small cell lung cancer (NSCLC). • To determine the recommended phase II dose (RP2D) of MEK162 to be used when given in a continuous dosing schedule together with pemetrexed and carboplatin administered on a 3-weekly schedule in advanced NSCLC. • To explore the efficacy (as measured by tumor response in the Phase Ib portion) of the combination of MEK162 in addition to pemetrexed and carboplatin in chemotherapy-naïve patients with EGFR wild-type, ALK-rearrangement negative NSCLC of the lung. **Secondary** • To characterize the population pharmacokinetics of MEK162 administered in combination with carboplatin and pemetrexed (Phase I). • To explore relationships between KRAS mutation (and sub-types) and additional genomic mutations and objective clinical response.
Study Design: This is a Phase I/Ib, open-label, dose-escalation, multi-center, non randomized study designed to evaluate the safety and tolerability of oral MEK162 administered as BID dosing in combination with carboplatin and pemetrexed.
Number of patients: Phase I: Standard 3+3 dose-escalation design consisting of up to two independent dose-escalation treatment groups and one dose de-escalation group Phase Ib: 30 patients (including those treated at the same dose combination in the dose-

escalation phase of the study who are eligible for the safety set)

Main criteria for Inclusion/Exclusion:

Inclusion Criteria:

- histologically confirmed stage IV non-squamous lung carcinoma (dose escalation), EGFR/ALK wild type (dose expansion)
- tissue available for KRAS genotyping (unless known)
- presence of measurable disease (RECIST version 1.1)
- no prior chemotherapy treatment for advanced NSCLC
- Eastern Cooperative Oncology Group performance status 0 or 1
- Life expectancy > 3 months
- Treated stable CNS metastases permitted

Exclusion Criteria:

- History of significant ocular disease including retinal vein occlusion, central serous retinopathy, uncontrolled glaucoma, uncontrolled diabetes or hypertension
- History of clinically significant interstitial lung disease or pneumonitis
- QTc prolongation or clinically significant risk for prolonged QT interval
- Active viral infection (hepatitis B, C or HIV)
- Uncontrolled hypertension, recent acute coronary syndromes, other uncontrolled medical illness

Intervention:

- Cycle 1 (28 days): MEK162 days 1-5, then pemetrexed plus carboplatin IV on day 8, resume MEK162 days 8-26
- Cycles 2 – 6 (21 days): pemetrexed plus carboplatin IV day 1, MEK162 days 1-19
- Subjects may receive up to 6 cycles of treatment

Correlatives:

- archival tissue will be analyzed for KRAS mutation status
- for the dose escalation phase, this will be initiated at study enrolment
- for the Phase Ib cohort expansion, this will initiated at study enrolment until one exploratory cohort is full (10 patients each in *KRAS* WT*, G12C* mutant, non-*G12C* mutant cohorts); thereafter it will be required prior to study enrolment

Statistics:

After determination of RP2D, summary statistics will be used to report response rate, toxicity, progression-free survival (Kaplan-Meier), disease control rate. Analysis of outcome and toxicity by KRAS mutation subtype will be explored.

Table outlining dose escalation schedule for study

Dose Escalation Schedule			
Dose Level	**Dose***		
	MEK162 (mg)**	**Carboplatin (AUC)**	**Pemetrexed (mg/m^2)**
Level -1	30 BID***	5	500
Level 1	30 BID	5	500
Level 2	45 BID	5	500

**Doses are stated as exact dose in units (*e.g.*, mg/m², mcg/kg, etc.) rather than as a percentage.*
***Cycle 1: continuous dosing until day 5. Omit doses for 2 days prior to chemotherapy administration (cycle 1 days 6 and 7 and days 27 and 28; for additional cycles omit doses day 20 and 21). Chemotherapy is to be administered cycle 1 day 8 and day 1 of every cycle thereafter. Cycle 1 has 28-day duration with subsequent cycles having 21-day duration.*
****Dose Level -1: MEK162 will be given in Cycle 1 as continuous dosing days 1-5, then days 8-21 in the 28 day cycle; subsequent cycles will include MEK162 continuous dosing days 1-14 in each 21 day cycle.*

In addition to dose levels noted above, intermediate dose levels or non-daily dosing of MEK 162 (e.g. alternate dosing schedule of 2 weeks on/1 week off) may be implemented dependent on toxicity or emergent findings from this and other trials.

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1. OBJECTIVES

1.1 Primary Objectives

- To assess the safety of MEK162 administered in combination with carboplatin and pemetrexed as initial chemotherapy in advanced non-small cell lung cancer (NSCLC).
- To determine the recommended phase II dose (RP2D) of MEK162 to be used when given in a continuous dosing schedule together with pemetrexed and carboplatin administered on a 3-week schedule as initial chemotherapy in advanced NSCLC.
- To explore the efficacy (as measured by tumor response in the Phase Ib portion) of the combination of MEK162 in addition to pemetrexed and carboplatin in chemotherapy-naïve patients with EGFR wild-type, ALK-rearrangement negative NSCLC of the lung.

1.2 Secondary Objectives

- To characterize the population pharmacokinetics of MEK162 administered in combination with carboplatin and pemetrexed (Phase I).
- To explore relationships between KRAS mutation sub-types and objective clinical response.

1.3 Exploratory Objectives

- A limited sampling strategy pharmacokinetic model will be used to ensure that the clearance of MEK162 is not influenced by the concurrent administration of pemetrexed-based chemotherapy.

2. BACKGROUND

2.1 Study Disease

Non-small cell lung cancer (NSCLC) remains the most common and lethal malignancy in the world for both men and women (Canadian Cancer Society, 2013). Over 1 million cases are diagnosed each year (Juergens, 2006) and there are more than 900,000 NSCLC-related deaths annually (Jemal, 2011). The majority of patients are diagnosed with advanced disease at presentation or experience disease recurrence after initial curative approach. In spite of a wealth of translational and clinical research in recent years, there has been little change in overall survival (OS) with five-year survival rates of 18% for all stages combined (Canadian Cancer Society, 2013). Although lung cancer rates have decreased in developed countries in the last decade, the incidence of lung adenocarcinoma continues to rise both in men and women worldwide for reasons that are not fully understood (Charloux 1997, Devesa, 2005, Jemal 2011). Thus, emerging new therapeutic modalities relying on distinct molecular and genetic changes within the lung cancer genome are being extensively studied as targets for new drugs for their potential to improve the outcome for patients with NSCLC (Maione, 2006).

First-line therapy for advanced NSCLC consists of platinum-based doublet chemotherapy (Schiller, 2002). The combination of cisplatin and pemetrexed has yielded greater benefits in the adenocarcinoma subgroup (40-60% of NSCLC). In a trial investigating first-line treatment with this combination compared with cisplatin and gemcitabine, a 2.5-month improvement in overall survival was seen for this group (12.6 *v* 10.9 months) with the pemetrexed-based regimen with a response rate of 30.6% in patients treated in this arm (Scagliotti 2008). The observation of improved efficacy of pemetrexed plus platinum in the adenocarcinoma population and inferior efficacy in squamous cell carcinoma led to the label change in pemetrexed to treat only those patients with non-squamous histology lung cancers. Subsequently, the combination of pemetrexed and carboplatin has been assessed in a number of phase II and III trials (Gervais, 2013; Schuette, 2013; Zukin, 2013; Okamoto, 2013). Response rates have been favorable (20-35.8%) with this combination and toxicity was manageable with many of the populations for these trials being elderly or having reduced performance status.

Subsequently, there has been a paradigm shift in the management of NSCLC with targeted therapy demonstrating proven benefit in patients with activating mutations of the tyrosine kinase domain of the epidermal growth factor receptor (*EGFR*) (Mok, 2009) and translocations in the *ALK* gene (Kwak, 2010). These drugs are now routinely utilized in the front-line setting to treat biomarker positive tumors. Somatic abnormalities in the *EGFR* and *ALK* genes are found in less than 20% of adenocarcinomas. Classification of lung cancer is becoming increasingly focused on genomic abnormalities. This renders the term non-small cell lung cancer less clinically useful and highlights the true molecular and genetic diversity of this disease allowing personalised and patient-centered care.

Within the adenocarcinoma subtype, up to 30% of tumors will harbor activating mutations in *KRAS* (Bos 1989). Because the *RAS-RAF-MEK-ERK* signaling pathway is activated as a consequence of *KRAS* or *BRAF* mutations in human cancer (Davies, 2002), it is an attractive target for small molecule intervention (Ding, 2008). Given the critical location of *MEK* in this signaling pathway, it has been recognized as an important target for anti-cancer therapy. Drug development efforts to inhibit MEK demonstrated clinical benefit, although with limited overall success. For example, PD-0325901, CI-1040, and AZD6244, have achieved objective responses in melanoma, pancreatic cancer, and non-small cell lung cancer (Tzekova, 2008), but none have demonstrated significant single-agent activity in these tumor types.

Recently published data confirm clinical efficacy with the combination of *MEK* inhibition (selumetinib) and docetaxel chemotherapy in the treatment of patients with *KRAS*-mutant NSCLC with improved response rate, progression-free survival and quality of life compared with docetaxel alone (Jänne, 2012). In this study, median progression-free survival was 5·3 months (95% CI 4·6–6·4) in the selumetinib group and 2·1 months (1·4–3·7) in the placebo group (HR for progression with selumetinib 0·58, 80% CI 0·42–0·79; one-sided p=0·014). There was a 37% response rate in the selumetinib arm and no response in the docetaxel arm (two-sided p<0·0001). Grade 3–4 neutropenia, febrile neutropenia, and asthenia were more common in the selumetinib group than in the placebo group; by contrast, grade 3–4 dyspnea was more common in the placebo group than the selumetinib group.

MEK inhibition with trametinib has also been combined with pemetrexed in a second-line phase I/Ib trial with patients stratified by *KRAS* status (Kelly, 2013). In this study, 42 patients were

treated with the combination. While no difference in response rate was seen between these groups (16% vs. 17%), these response rates compare favourably with historical data for pemetrexed treatment (Hanna, 2004) and support the absence of any negative interaction between these agents. In addition, the most common grade 3/4 toxicites were neutropenia (21%), anaemia (14%), asthenia (10%), nausea (7%) and dyspnea (7%). Diarrhoea is a known side effect of *MEK* inhibition and was present at grade 3/4 in 5% of cases. On review of all MEK-inhibitor trials, there is an increased incidence of neutropenia and febrile neutropenia when *MEK* inhibitors are added to chemotherapy. In the phase I/Ib trial combining docetaxel and trametinib supportive granulocyte colony-stimulating factor (GCSF) was used and the regimen was tolerable with disease control rate of 61% (Gandara, 2013).

MEK162 (binimetinib), previously named ARRY-438162, is an oral, ATP non-competitive, highly selective inhibitor of *MEK*1/2 that has nanomolar activity against purified MEK enzyme (IC50 = 12 nM) and inhibits both basal and induced levels of *ERK* phosphorylation in numerous cancer cell lines with IC50s as low as 5 nM. MEK162 is especially potent at inhibiting the cell proliferation of mutant *BRAF* and *RAS* human cancer cell lines in vitro. In vivo, MEK162 has demonstrated dose-dependent tumor growth inhibition in various subcutaneous tumor transplants harboring BRAFV600E or RAS mutations, including HT29, MIA PaCa2, A549, LoVo, Calu6, DU145 and COLO 205. MEK162 has also shown significant inhibition of tumor growth as a single agent in NSCLC xenograft models in mice (*KRAS* mutant A549, *EGFR* mutant Calu-6, H1975) (Winski, 2010). These data suggest that MEK162 may provide a potential therapeutic benefit in cancer indications, harboring these mutations. MEK162 is currently investigated in phase I clinical testing and has been well tolerated up to a MTD of 45mg bid in cancer patients (Bendell, 2011). Studies in advanced or metastatic solid tumors are ongoing in combination with *RAF* and *PI3K* inhibitors (www.clinicaltrials.gov). In ongoing Phase I trials, in combination with other agents, MEK162 has been escalated to MTD of 45mg BID and appears tolerable at this dose. However, due to prior incidence of neutropenia and febrile neutropenia with continuous dosing of MEK-inhibitors in combination with chemotherapy, intermittent dosing schedules are being explored in this setting.

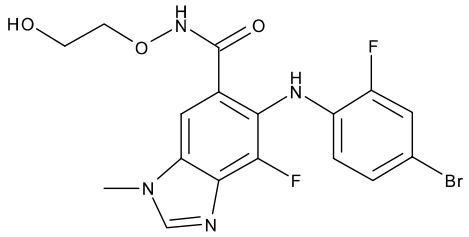
Standard of care in NSCLC at present involves all lung adenocarcinoma samples having immunohistochemical staining for *ALK* rearrangement and *EGFR* mutation testing (both results return in <10 days) to guide treatment decisions. These patients will be commenced on appropriate targeted therapies. The remainder of patients with adenocarcinoma will have platinum-based chemotherapy as their initial therapy or enroll in a clinical trial.

We plan to offer the combination of carboplatin, pemetrexed and MEK162 to patients with lung adenocarcinoma as initial chemotherapy, where no *ALK* translocation or *EGFR* mutation are identified (after dose escalation phase). We will review the outcomes of the treatment combination with a planned review of *KRAS* mutation status, with particular interest in subtypes thereof.

The following factors including the relative frequency of *KRAS* mutant NSCLC adenocarcinoma, along with an overall poorer prognosis and the lack of an established treatment option makes this an attractive option for these patients. This will be the first study combining MEK162 with carboplatin and pemetrexed for patients with advanced lung adenocarcinoma.

2.2 Investigational Agent

2.2.1 MEK162 (binimetinib)



Chemical name
5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-n-(2-hydroxyethoxy)-1-methyl-1h-benzimidazole-6-carboxamide.

Molecular formula
C17H15BrF2N4O3

Relative molecular mass

441.23

Mechanism of action
MEK162, previously named ARRY-438162, is an oral, ATP non-competitive, highly selective inhibitor of MEK1/2 that has nanomolar activity against purified MEK enzyme (IC50 = 12 nM) and inhibits both basal and induced levels of ERK phosphorylation in numerous cancer cell lines with IC50s as low as 5 nM.

In vitro efficacy studies

The biological activity of MEK162 has been evaluated *in vitro* (enzymatic and cell culture) and *in vivo* mouse xenograft studies.

In biochemical studies, MEK162 has been shown to be a potent and highly selective inhibitor of MEK. In cellular assays, MEK162 has been shown to markedly inhibit the phosphorylation of ERK in human cell lines as well as human whole blood. In human MALME-3M melanoma cells and in HT29 colorectal cancer cells, MEK162 significantly inhibited proliferation and viability, respectively. The ability of MEK162 to inhibit cancer cell growth in culture was evaluated using a standard 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay. In the human HT-29 colorectal cell viability assay, the IC50 of cell growth was observed at a concentration of 163 nM MEK162. In the human melanoma Malme-3M cell proliferation assay, the IC50 of cell growth was observed at a concentration of 30 nM MEK162.

In vivo efficacy studies

In vivo studies were performed to evaluate the activity of MEK162 with respect to inhibiting tumor growth and tumor ERK phosphorylation. In the HT29 and in the COLO 205 colon carcinoma models, dose-dependent inhibition of tumor growth (up to 75% tumor growth inhibition [TGI]) was observed at doses ranging from 3 to 30 mg/kg, qd, by mouth (PO) for 21 days. In the sensitive COLO 205 colon carcinoma model, MEK162 treatment resulted in 84% TGI with significant tumor regressions at a dose of 30 mg/kg. In the BxPC3 pancreatic carcinoma model (which does not harbor either RAS or RAF mutations, but harbors MAP2K4 mutation), significant tumor regressions (59%) were seen at doses of 30 mg/kg. In the BxPC3 pancreatic carcinoma model (which does not harbor either RAS or RAF mutations, but harbors MAP2K4mutation), ~70% TGI and 13% PRs were seen at doses of 30 mg/kg, qd, PO for 21 days. Consistent with the mechanism of action for MEK162, TGI correlates with decreased phospho-ERK levels in tumor xenografts. Overall, MEK162 has demonstrated potent activity against MEK1/2 and broad anti-proliferative activity *in vitro* and *in vivo*.

Non-clinical pharmacokinetics and metabolism of MEK162

PK studies were conducted with MEK162 in rats, dogs and monkeys. After oral administration, the AUC and Cmax values for MEK162 increased in a nearly dose-proportional manner in rats and monkeys. The mean bioavailability was lowest in monkeys, higher in dogs, and highest in rats at equivalent doses (range across species: 13% to 72%). Following intravenous (IV) administration, the plasma clearance (CL) values were low-to-moderate (range: ~2 to 8 mL/min/kg) and tended to increase across species such that monkey > dog > rat. Mean plasma t1/2 values showed a similar trend where monkey > dog > rat (range: ~2 to 9 hrs.). The volume of distribution at steady state (Vss) values ranged from 0.189 to 1.57 L/kg.

In vitro experiments in Caco-2 and LLC-PK1 cells indicated that MEK162 had moderate membrane permeability and is a substrate for P-gp. MEK162 exhibited high plasma protein binding in vitro (> 96%, except dog 84%) and is predicted to have good stability with respect to hepatic metabolism. Nonclinical in vitro and in vivo data indicate that there are multiple pathways of metabolism for MEK162 including oxidation and glucuronidation. MEK162 is metabolized by CYP3A and CYP1A2 with some involvement of CYP2C isoforms. In human plasma, major entities include glucuronides of MEK162, as well as the primary active metabolite, AR00426032, which is equipotent to MEK162. Formation of AR00426032 that has been monitored in clinical studies was found to be mediated primarily by CYP1A2 with minor contributions from other cytochrome P450 enzymes. MEK162 did not significantly inhibit (IC50> 25μM) the major CYP isoforms. MEK162 was not a time-dependent inhibitor of CYP3A.

Following single- and repeat-dose administration of MEK162 to Sprague-Dawley rats for up to 6 months, females were found to have approximately 2-fold higher exposure than males at equivalent doses. The values for Cmax and area under the plasma concentration-time curve for a dosing interval from time 0 extrapolated to infinity (AUCinf) increased with dose, although the increase in exposure was less than dose proportional. Cynomolgus monkeys receiving MEK162 for 28 days or 9 months showed no consistent differences in exposure between females and males. There were no significant changes in exposure versus day.

Toxicity and safety studies with MEK162

The toxicological evaluations of MEK162 include single-dose, and 28-day and 6-month repeat-dose studies in Sprague Dawley rats and 28-day and 9-month repeat-dose studies in cynomolgus monkeys, all of which were conducted in accordance with international regulatory guidelines for nonclinical toxicity studies and in adherence to current GLP guidelines. These studies were supplemented with 3 genotoxicity assays (bacterial mutagenicity, mouse lymphoma assay and mouse micronucleus assay), local tolerance, 9 safety pharmacology studies (hERG channel assay and behavioral, cardiovascular, renal, pulmonary and 2 gastrointestinal function/tolerability studies as well as 2 non-GLP studies evaluating wound healing and immune function) and 3 developmental toxicity studies in the rat and the rabbit.

In all of the GLP toxicology studies conducted, there was no significant effect of MEK162 on vital signs, coagulation parameters, complement, organ weights or urinalysis parameters in doses up to 100 mg/kg in rats and 10 mg/kg in monkeys. Administration of MEK162 to rats by oral gavage was associated with skin lesions (inflammation/scabbing), microscopic findings of soft tissue mineralization (which did not occur with the 26-week dosing regimen) and reversible minimal to mild clinical pathology changes.

Safety pharmacology studies were conducted to assess the effects of MEK162 on key organ systems (cardiovascular, respiratory, neurobehavioral, renal and gastrointestinal function). Rats received single oral doses of 10, 30 or 100 mg/kg and monkeys were given single oral doses of 1, 3 and 10 mg/kg. There were no significant in vivo safety findings at doses up to 100 mg/kg in rats and 10 mg/kg in monkeys in any of these studies.

Clinical experience with MEK162

MEK162 has been previously tested in a single-dose, first-in-human study in healthy subjects [ARRY-162-0601], a multiple ascending dose (MAD) study for 14 days in healthy subjects [ARRY-162-0602], a single-dose relative bioavailability and food effect study in healthy subjects [ARRAY-162-104], a study in patients with rheumatoid arthritis with dosing up to 4 weeks [ARRY-162-0603] and a phase 2 study evaluating 12 weeks of MEK162 in combination with methotrexate in patients with rheumatoid arthritis [ARRAY-162-201]. A Phase 1 dose-escalation study in patients with advanced solid tumors, followed by an expansion phase with cohorts in patients with advanced or metastatic biliary cancer and in patients with *KRAS*- or *BRAF*-mutant metastatic colorectal cancer [ARRAY-162-111], was initiated in August 2009.

Clinical safety

Safety data have been evaluated from 5 completed clinical studies in which MEK162 was administered qd or bid for up to 12 weeks at total daily doses ranging from 5 mg to 80 mg. In the completed studies, 235 subjects/patients received at least 1 dose of MEK162 and have been evaluated for safety, including 70 healthy subjects and 165 patients with rheumatoid arthritis.

In the ongoing clinical study [ARRAY-162-111], a total of 64 cancer patients have received at least 1 dose of MEK162 (as of 23rd November 2010). In the dose-escalation phase, 4 dose levels were explored: 30 mg bid, 45 mg bid, 60 mg bid, and 80 mg bid. 2 out of 3 evaluable patients receiving 80 mg bid experienced DLTs. One patient had CTCAE Grade 3 rash despite maximal

treatment measures and one patient had CTCAE Grade 3 central serous retinopathy (CSR). Thus, 80 mg bid was declared a non-tolerated dose. Six evaluable patients were enrolled at 60 mg bid and no DLTs were observed; therefore 60 mg bid was declared the MTD for the dose-escalation phase and the dose moved forward to the expansion phase. Subsequently, the MTD has been reduced to 45mg BID.

The most commonly reported AEs reported to date have been rash, diarrhea, nausea, peripheral edema, fatigue, and vomiting. Of the patients who developed rash, most occurred within 5-8 days of initiation of study drug, were mild-to-moderate in severity, and responded to treatment (topical antibiotics, topical or oral steroids) or dose reduction. As noted above, 1 patient developed a CTCAE Grade 3 rash which required dose reduction of MEK162. The rash initially presented as CTCAE Grade 1 on Study Day 3 and progressed to CTCAE Grade 3 by Study Day 10. However, in the majority of cases, study drug was continued throughout treatment of the rash.

Elevations in creatine kinase (CK) have been observed, but no other apparent trends in clinical laboratory parameters, vital signs, or electrocardiograms (ECGs) were associated with administration of MEK162.

Of 41 patients in [ARRAY-162-111] dosed at 60mg bid (as of 13-Oct 2010), a total of 10 patients (1 patient in dose escalation, 6 patients in biliary expansion and 3 patients in the CRC expansion) have developed ocular findings, consistent with CSR, such as retinal edema and retinal detachment during the treatment phase of the study. CSR is a known adverse effect of allosteric MEK-inhibitors. All reported events of retinopathy have been CTCAE Grade 1 or 2, and consistently resolved with holding study drug. Two patients have had a recurrence of retinopathy with re-challenge of 45 mg bid. One of the patients was in the dose escalation portion of the study and discontinued the study due to retinopathy, while the other is being re- challenged with 30 mg bid. No retinal events have been reported for 4 patients treated at 45 mg bid during dose escalation. The CSR has been reversible following a drug holiday in all affected patients. To establish the safety profile of MEK162 at 45mg bid, future patients in the CRC expansion phase of study [ARRAY-162-111] are currently enrolled at this dose level.

Clinical pharmacokinetics

In healthy subjects, MEK162 exposure (as quantified by Cmax and AUC) tended to increase in a dose-proportional manner following single and multiple doses over a dose range of 5 to 80 mg for single dose and 60 mg for multiple doses (80 mg was not evaluated in the multiple dose study). The single-dose and multiple-dose studies yielded comparable mean values for MEK162 apparent terminal elimination half-life (t1/2; 8.40 hrs and 7.35 hrs, respectively; all doses included), and each study had a mean apparent time of Tmax of 1.18 hrs. The metabolite- to-parent exposure ratios for AR00426032 and urinary excretion profiles were consistent in the single-dose and multiple-dose studies in healthy subjects with the metabolite representing ~ 7 to 10% of the parent in plasma and < 10% of the parent drug being excreted renally. Accumulation in healthy subjects during 14 days of dosing was < 2-fold for all regimens. Administration of MEK162 with a high-fat meal increased AUC and Cmax by 18% and 26%, respectively.

Interpretation of PK data collected from the multiple-dose study in patients with rheumatoid arthritis was difficult, as the number of patients in each group was small and patients were not

pooled for calculation of overall mean PK values. Over a dose range of 10 to 40 mg, MEK162 plasma exposure when MEK162 was administered concomitantly with methotrexate (MTX; 7.5 to 22 mg weekly) appeared to be comparable to exposure observed when MEK162 was administered as monotherapy. Therefore, it was concluded that no clinically significant drug- drug interaction occurred.

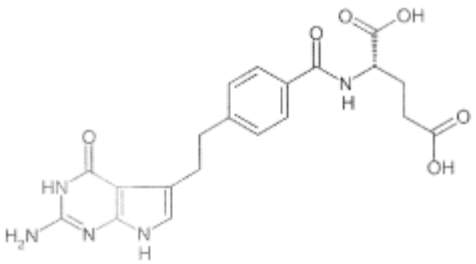
Initial evaluation of the PK of MEK162 in the cancer patient population indicated that there was a slight (1 to 2 hrs) delay in Tmax with the remainder of the plasma concentration-time profile appearing very similar to healthy subjects. Observed exposure has been approximately dose proportional in the doses evaluated to date (30 to 80 mg bid) and comparable to healthy subjects at equivalent doses. The inter-subject variability for AUC and Cmax as measured by coefficient of variation (CV) was ~40%. The active metabolite-to-parent ratio was consistent across the dose range studied, but slightly higher (~10 to 15%) than in the healthy subject population (~7 to 10%).

As this is the first-in-human combination of MEK162 with carboplatin and pemetrexed, the dose will commence at 30mg BID. There will be an initial treatment phase for 5 days of continuous dosing and then a wash-out phase for 2 days prior to chemotherapy administration on day 8 for the first cycle. This is to minimize toxicity by allowing a washout period prior to chemotherapy administration with the aim of not compromising benefit from standard chemotherapy.

Pharmacokinetic data will be collected by obtaining samples on cycle 1 day 5, and cycle 1 day 15 to capture steady-state data.

2.3 Other Agents

2.3.1 **Pemetrexed**



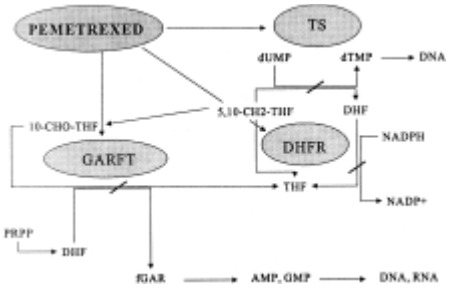
Chemical name
N-[4-[2-(2-amino-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid

Molecular formula
$C_{20}H_{19}N_5Na_2O_6\ 7H_2O$

Mechanism of action
Pemetrexed is an antifolate antimetabolite that targets multiple enzymes in the synthesis of pyrimidines and purines. It is a structural analog of lometroxol, an inhibitor of glycinamide ribonucleotide formyl transferase (GARFT). Its primary mechanism of action is via inhibition of thymidilate synthetase (TS), thereby decreasing the thymidine available for DNA synthesis. It

also inhibits dihydrofolate reductase (DHFR), blocking the synthesis of tetrahydrofolate. In addition, it blocks GARFT activity as well as other enzymes involved in biosynthesis of purines.

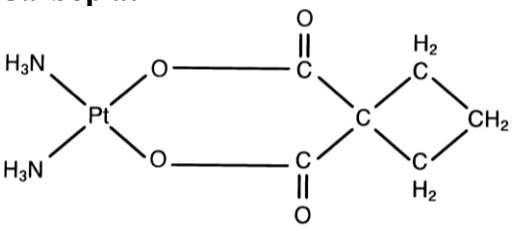
The drug is transported into cells via the reduced folate carrier, and is subsequently polyglutamated (folylpolyglutamate synthase), with potent inhibitory ability of TS. This process of glutamation enhances both the exposure time and intracellular concentrations of the drug (Paz Ares, 2003). Pemetrexed induces G1/S cell cycle arrest and cell death, independent of P53. Preclinical activity has been demonstrated against multiple tumour types. In dog toxicology studies, predominant toxicities included gastrointestinal and hematologic adverse events. The most favourable toxicity profile was determined to be with weekly dosing compared to daily dosing.



In phase I studies in humans, daily, weekly and 3-weekly schedules were explored (McDonald, 1998; Rinaldi 1996; Rinaldi, 1999). Dose-limiting toxicities included neutropenia, thrombocytopenia and fatigue. Recommended doses were 4 mg/m^2/day, 40 mg/m^2/week and 600 mg/m^2 every 3 weeks. Other toxicities included diarrhea, mucositis, rash, and transaminitis. Plasma concentration-time functions followed a two-compartment model, with a mean half-life of 3.1 hours (range, 2.2–7.2 hours), and pemetrexed is highly protein bound (81% in plasma). Clearance is via renal excretion, with 78% of drug excreted unchanged in the urine within 24 hours after administration.

Subsequent development in lung cancer used the dose of 500 mg/m^2 every 3 weeks, which is now standard of care second-line as a single agent or in combination with cisplatin or carboplatin first-line in advanced non-squamous NSCLC (Hanna 2004, Scagliotti 2008).

Carboplatin



Chemical name
cis-diammine [1,1-cyclobutane-dicarboxylato(2-)platinum(II)]

Molecular formula

$C_6H_{12}N_2O_4Pt^{-2}$

Mechanism of action
Carboplatin, an analogue of cisplatin, is a platinum salt that complexes with DNA, yielding interstrand cross-links and intrastrand DNA adducts (Go, 1999). It differs from cisplatin with respect to toxicity profile, but has a similar structure and mechanism of action. While cisplatin has two chloride groups, carboplatin has a cyclobutane group, and requires an approximately ten-fold higher concentration of drug and over seven-fold increase in exposure time to yield similar DNA effects as cisplatin.

Platinum clearance is triphasic; the distribution, elimination and terminal half-lives are 22 minutes, 116 minutes and 5.8 days respectively for carboplatin. Primary excretion of carboplatin is through the urine, with 90% clearance 24 hours after administration; renal clearance of carboplatin is similar to the glomerular filtration rate (GFR), and accounts for almost all elimination of the drug. Given the linear relationship between carboplatin clearance and GFR, the Calvert formula has been derived to calculate the dose of carboplatin required for a specific area under the curve of the drug. Carboplatin efficacy appears optimal between 5 and 7.5 mg/mL/min. Recommended dosing in lung cancer as part of combination therapy ranges from an AUC of 5 to 6 mg/mL/min.

Calvert Formula: Dose (mg) = Target AUC (mg/mLxmin) x [GFR (ml/min) + 25]

2.4 Rationale

Today, the most common type of lung cancer is adenocarcinoma or non-squamous NSCLC, with most patients presenting with advanced incurable disease. For those patients without EGFR mutations or ALK rearrangements in their tumour, the optimal first-line chemotherapy treatment for non-squamous NSCLC is pemetrexed/platinum combination chemotherapy (Scagliotti 2008). Despite this, median survival times remain less than 12 months, with response rates of only 30% and median progression-free survival of 5 months. Approximately 30% of lung adenocarcinomas harbour *KRAS* mutations. Despite being the largest molecular subgroup of lung cancer patients, there is no available targeted therapy that improves outcome beyond chemotherapy.

Recently, studies of MEK inhibitors suggest the potential to improve outcomes in *KRAS* mutant NSCLC when added to second-line chemotherapy (Janne 2013). However the value of MEK inhibition combined with first-line chemotherapy remains undefined. Furthermore, our understanding of the effects of MEK inhibition in *KRAS* wild type NSCLC as well as in different *KRAS* mutant genotypes is limited.

The current study proposes to combine MEK162, a highly potent MEK inhibitor with optimal first-line chemotherapy in advanced non-squamous NSCLC, pemetrexed and carboplatin, a recognized standard in North America (NCCN, 2015). This study is an initial step towards improving current therapy of advanced non-squamous NSCLC and to increasing our current understanding of the role of MEK inhibition in differing molecular subgroups of lung cancer.

2.5 Correlative Studies Background

It is postulated that mutations in the *RAS-RAF-MEK-ERK* pathway, particularly in *KRAS*, may increase sensitivity to MEK inhibition in combination with chemotherapy (see section 2.1). For this reason, we will be conducting *KRAS* genotyping in addition to standard diagnostic molecular and pathologic assessment of NSCLC tissue of participating subjects.

KRAS mutations are seen in approximately 30% of all lung adenocarcinoma cases. The prognostic impact of these mutations remains unclear, but may be associated with less benefit from EGFR TKI therapy (Martin, 2013). While there is no approved targeted therapy for *KRAS* mutant adenocarcinoma of the lung, the combination of a MEK inhibitor, selumetinib, and second-line chemotherapy with docetaxel in advanced KRAS mutant lung cancer may improve response and progression-free survival (Janne, 2013). In a small randomized phase II trial, there was even a signal of improved survival with the addition of the MEK inhibitor. Early phase trials of other MEK inhibitors in lung cancer suggest that there may be higher response rates in selected *KRAS* mutations, such as codon 12 mutations G12C and G12V. There may also be incremental activity in *KRAS* wild type tumours compared to chemotherapy alone (Gandara, 2014).

We hypothesize that the response rate of MEK162 plus pemetrexed/carboplatin will be highest in the cohort with G12C mutation, and that the response rate in the wild type and other *KRAS* mutant populations will be similar.

Following macro-dissection of formalin-fixed archival tumor tissue, all genotyping assays will be performed in the CAP/CLIA-certified Advanced Molecular Diagnostics Laboratory (AMDL) by licensed technologists. This facility routinely performs Sanger sequencing and PCR-based analysis (ABI 7900, ABI 3100/3130) on targeted DNA regions to detect specific mutations that may predict outcome or response to therapy (Kamel-Reid, 2012). This will be the method used for *KRAS* genotyping in this study.

The results of this assessment will not be used prospectively in the phase I part of the study but will be utilized for stratification for the phase Ib component.

Any correlations with response will be determined at the end of the trial.

3. PATIENT SELECTION

3.1 Eligibility Criteria

Subjects eligible for enrolment on the study must meet all of the following criteria:

3.1.1 For dose escalation, patients with histologically confirmed non-squamous carcinoma of lung. This includes patients with EGFR or ALK positive lung carcinoma previously treated with standard TKIs. For dose expansion, patients must have histologically confirmed *EGFR* wild-type, *ALK*-rearrangement negative non-squamous lung carcinoma. Patients with neuroendocrine carcinoma, mixed small and non-small cell carcinoma or squamous carcinoma are not eligible in dose escalation or expansion.

3.1.2 Tissue available for KRAS mutation status analysis, unless *KRAS* genotype is already known.

3.1.3 Patients must have metastatic disease (incurable stage IIIB/stage IV).

3.1.4 Patients must have clinically and/or radiographically documented measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as >10 mm with CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease. Patients must have radiographic evidence of disease progression following the most recent line of treatment. Areas of previous radiation may not serve as measurable disease unless there is evidence of progression post radiation.

3.1.5 At time of registration, if the patient has had previous treatment it must have been at least 4 weeks since major surgery or radiation therapy (two weeks from small field short course palliative RT e.g. to bone), and the patient must have recovered from side effects; four weeks from any other previous anti-cancer therapy including biologics, and 7 days from TKIs (permitted in dose escalation only).

3.1.6 Patients with treated stable CNS metastases are permitted if stability of disease is documented with imaging ≥28 days after treatment completion, and if patients are off corticosteroids for at least 7 days prior to starting study treatment.

3.1.7 Patients may have had prior malignancy if definitively treated and/or, in the opinion of the investigator, the only active malignancy is NSCLC. Patients with mixed small cell lung cancer histology are excluded. Patients who have received radiotherapy to >30% bone marrow are excluded. Consult PI if unsure whether second malignancies meet requirements specified above.

3.1.8 Patients treated for another malignancy, must have recovered from all prior treatment-related toxicities (CTCAE v4.0 ≤ grade 1) at the time of registration (with the exception of alopecia or skin depigmentation).

3.1.9 Able to swallow and retain oral medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels. This includes ulcerative disease, uncontrolled nausea, vomiting, diarrhea, small bowel resection or other malabsorptive syndrome.

3.1.10 Patients receiving medications or substances that are inhibitors or inducers of CYP1A2,

CYP2C19, CYP2B6, CYP3A4 and/or UGT1A1 and UGT1A9 are eligible but these drugs must be used with caution *(Appendix E)*. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.1.11 Age ≥18 years. As no dosing or adverse event data are currently available on the use of MEK162 in combination with pemetrexed and carboplatin in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.12 Eastern Cooperative Group (ECOG) performance status ≤1 (Karnofsky >60%, see Appendix A).

3.1.13 Within 7 days of the proposed start date of treatment, patients must have normal organ and marrow function as defined below:

Absolute granulocytes	$\geq 1.5 \times 10^9$/L
Hemoglobin	≥100 g/L without transfusion support
Platelets	$\geq 100 \times 10^9$/L without transfusion support
Bilirubin	≤1.25 × institutional upper limit of normal
AST(SGOT) / ALT(SGPT)	≤2.5 × institutional upper limit of normal **or** ≤5 × institutional upper limit of normal in the presence of liver metastases
Creatinine clearance	≥50 mL/min/1.73 m^2
Cardiac function	Left Ventricular Ejection Fraction (LVEF) ≥50% determined by multi-gated acquisition scan (MUGA) or echocardiogram

3.1.14 Ability to understand and willing to sign a written informed consent document. Patients must be able to provide Informed Consent based on the details below:

- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
- Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.

3.1.15 Life expectancy of greater than 3 months.

3.1.16 No evidence of active uncontrolled infection (patients on antibiotics are eligible).

3.1.17 Female patients of child bearing potential must have a negative serum or urine pregnancy test within 72 hours prior to the first dose of study drug and four weeks following the last dose of MEK162.

- Women of child-producing potential must agree to use effective contraceptive methods prior to study entry, during study participation, and for at least 120 days after the last administration of study medication. These methods include:
    - Total abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - 2 barrier methods: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
    - A barrier method plus hormonal method from visit 1 to 120 days after the last dose of treatment. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Men treated or enrolled on this trial must agree to use adequate contraception prior to and for 120 days after completion of treatment (see above for adequate contraception methods).

Note: Female patients of childbearing age are defined as follows:
• Patients with regular menses
• Patients, after menarche with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
• Women who have had tubal ligation

Female patients may be considered to NOT be of childbearing potential for the following reasons:
• The patient has undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy or bilateral oophorectomy
• The patient is medically confirmed to be menopausal (no menstrual period) for 24 consecutive months
• Pre-pubertal females. The parent or guardian of young female patients who have not yet started menstruation should verify that menstruation has not begun. If a young female patient reaches menarche during the study, then she is to be considered as a woman of childbearing potential from that time forward.

3.2 Exclusion Criteria

3.2.1 History or current evidence/risk of retinal vein occlusion (RVO) or predisposing factors to RVO (e.g. uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease such as hypertension, diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes). Patients with prior deep venous thrombosis or pulmonary embolism are permitted.

3.2.2 History of retinal degenerative disease.

3.2.3 History of Gilbert's syndrome.

3.2.4 Any serious and/or unstable pre-existing medical (aside from malignancy exception), psychiatric disorder, or other conditions that could interfere with subjects' safety, obtaining informed consent or compliance to the study procedures, in the opinion of the PI.

3.2.5 History of interstitial lung disease or pneumonitis.

3.2.6 Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal metabolic or cardiac disease).

3.2.7 Any factors that increase the risk of QTc prolongation or risk of arrhythmic events (e.g. congenital long QT syndrome, family history of long QT syndrome, hypokalemia) or baseline QTcB interval >480 msec (calculated using Bazett's formula).

3.2.8 History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary artery bypass grafting, angioplasty, or stenting within the past 6 months prior to screening or cardiac metastases.

3.2.9 History or evidence of current clinically significant uncontrolled arrhythmias.

3.2.10 History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).

3.2.11 History of neuromuscular disorders associated with elevated creatine phosphokinase (CK), such as inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy.

3.2.12 Patients planning to embark on a new strenuous exercise regimen after the first dose of study treatment, (muscular activities such as strenuous exercise, that can results in significant increases in plasma CK levels should be avoided while on MEK162 treatment).

3.2.13 Known positivity for Hepatitis B surface antigen or Hepatitis C antibody.

3.2.14 Known Human Immunodeficiency Virus (HIV) positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with MEK162. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.15 Treatment refractory hypertension defined as a blood pressure systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy.

3.2.16 Subjects with intra-cardiac defibrillators or permanent pacemakers.

3.2.17 Pregnant or nursing (lactating) women are excluded from this study because MEK162 is a small molecule kinase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with MEK162, breastfeeding should be discontinued if the mother is treated with MEK162. These potential risks may also apply

to other agents used in this study.

3.2.18 Patients who have had chemotherapy or radiotherapy within 4 weeks of registration (2 weeks for small field short course palliative RT), and patients who have received radiotherapy to >30% of their bone marrow for malignancy.

3.2.19 Patients who have received any prior chemotherapy for metastatic NSCLC. Patients who have received adjuvant treatment or chemoradiation therapy for stage III disease should have completed this ≥12 months prior to study enrollment.

3.2.20 Patients who have had prior treatment with a MEK inhibitor.

3.2.21 Patients who are receiving any other investigational agents.

3.2.22 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MEK162, Pemetrexed or Carboplatin.

3.2.23 Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.24 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, social/psychological issues, 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.

3.3 Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this trial. The intent is to recruit subjects from racial/ethnic/gender groups in close approximation to the incidence of the disease in these groups. We anticipate the study population will be reflective of the population treated at Canadian tertiary cancer centres with advanced NSCLC with respect to gender and ethnic mix. However, the trial is not designed to measure differences in intervention effects. The population of Southern Ontario is ethnically diverse. The proportion of different ethnic groups in the community is provided in the table below. Universal access to health care will ensure that there is no discrimination on the basis of gender or race (Guide to Canadian Human Rights Act: www.chrc-ccdp.ca/public/guidechra.pdf). Individual hospital registries and databases do not routinely collect racial data, under the direction of the Canadian Human Rights Code. The population demographics and distribution of minorities in Southern Ontario is included in the following table.

The population demographics and distribution of minorities in Canada is included in the following table:

Table: Visible minority population by Consortium Provinces (2001 Census)

	British Columbia		Alberta		Ontario		Nova Scotia		Total	
Total population of province	3,868,870		2,941,150		11,285,550		897,570		**18,993,140**	
Visible Minorities	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**
Black	25,465	1%	31,390	1%	411,095	4%	19,670	2%	487,620	**3%**
Asian	768,435	20%	268,660	9%	1,513,825	13%	12,630	1%	2,563,550	**13%**
Latin American (Hispanic)	23,880	1%	18,745	1%	106,835	1%	520	0%	149,980	**1%**
Visible minority, not included elsewhere	4,195	0%	4,220	0%	78,915	1%	1,170	0%	88,500	**0%**
Multiple visible minority	14,465	0%	6,910	0%	42,375	0%	535	0%	64,285	**0%**
Total Visible minority population	836,440	22%	329,925	11%	2,153,045	19%	34,525	4%	3,353,936	**18%**

Source: Statistics Canada, Census of Population.

Data from our consortium has been compiled regarding the representation of minorities on previous clinical trials, and the distribution is as follows:

Population Percentage of Minority and Gender of entering PMHC Trials			
	2010	2011	2012
Visible Minorities			
Black	0.9	2.3	1.2
Asian	10.1	10.9	11.6
Hispanic	10.1	2.3	3.5
Total	**21.1**	**15.5**	**16.3**
Women	**59.6**	**56.6**	**44.2**

4. REGISTRATION PROCEDURES

4.1 General Guidelines

The Study Coordinator at the Drug Development Program office will enter eligible patients on study centrally. All sites should call the Study Coordinator to verify dose level availabilities. The required forms (Registration Checklist) will be provided upon site activation.

Following registration, patients should begin protocol treatment within 3 calendar days. Issues that would cause treatment delays should be discussed with the Principal Investigator (cc the central office study coordinator). If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

Prior to registering a patient, each institution must have submitted all necessary regulatory documentation to the Drug Development Program Central Office. The registration checklist will only be sent once this has been received.

No patient can receive protocol treatment until registration with the Central Office has taken place. All eligibility criteria must be met at the time of registration. There will be no exceptions. Any questions should be addressed with the Central Office prior to registration.

To register a patient, the following documents are to be completed by the research nurse or data manager and sent / faxed to the Central Office Study Coordinator:

- Signed patient consent form
- Registration Checklist signed by the investigator

To complete the registration process, central office will review the checklist and once eligibility has been confirmed:

- Assign a patient study number
- Assign the patient a dose
- Register the patient on the study
- Fax or e-mail the confirmation worksheet with the patient study number and dose to the participating site

To ensure immediate attention is given to the faxed checklist, each site is advised to also call the study coordinator listed on the front sheet. Patient registration will be accepted between the hours of 9am to 5pm Monday to Friday, excluding Canadian statutory holidays when the central office will be closed.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
MEK162	Take with water not later than 30mins after breakfast in morning	15mg tablet**	PO in the a.m. and p.m. Doses should be 12±2 hrs apart.	Daily, continuous dosing. Omit dosing for 2 days prior to chemotherapy administration: cycle 1 day 6 & 7, cycle 1 day 27 & 28, cycle 2+ day 20 & 21 (see section 5.1.3).	*28 days (4 weeks) for cycle 1 only* *21 days (3 weeks) for cycle 2 onward*
Pemetrexed	Pre-medicate with dexamethasone before and after dosing. Ensure vitamin B12 and folic acid supplementation ongoing.	**In 100ml NS	IV over 10 minutes	For cycle 1, day 8, and day 1 of each subsequent cycle.	
Carboplatin	Take 8 glasses water for 2 days prior to dosing.	**In 250 ml 5% glucose	IV over 30 mins	For cycle 1, day 8, and day 1 of each subsequent cycle.	
***Doses as appropriate for assigned dose level.*					

5.1.1 **MEK162**

MEK162 tablets will be taken orally, twice daily, with a glass of water. An intermittent dosing schedule will be employed as outlined in section 5.1. Doses will be administered for 5 days followed by a 2-day omission prior to commencing chemotherapy: for cycle 1, continuous dosing until day 5; omit doses for 2 days prior to chemotherapy administration (cycle 1 days 6 and 7, and cycle 1 days 27 and 28). For cycles 2+, omit doses on day 20 and 21.

The prescribed bid doses for MEK162 should be taken 12 ± 2 hours apart. Each morning daily dose of MEK162 should be taken at approximately the same time each day, and must be taken no later than 30 minutes after the start of the patients' normal breakfast. The second dose of MEK162 should be taken together with a glass of water and irrespective of food, 12 ± 2 hours after the morning dose (except for the pharmacokinetic sampling days on cycle 1 day 5 and cycle 1 day 15 when the patients should take their morning dose at the clinic, and skip the evening dose of MEK162).

Patients must avoid consumption of grapefruit or grapefruit jucie during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

Patients should be instructed to swallow the tablets as a whole and not to chew or crush them.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

Any doses that are missed should be skipped and should not be replaced or made up during the evening dosing (in the case of MEK162) or on a subsequent day, whichever applies.

If, for any reason, a breakfast was not consumed, then the patient should still take the scheduled morning dose of MEK162 with a glass of water. If this happens on days of PK sampling, it should be documented in source documentation and/or the electronic CRFs.

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

5.1.2 **Pemetrexed**

Intravenous pemetrexed will be administered once every 21 days (1 complete cycle) over a 10-minute (±5min) infusion. Subjects will be pre-medicated with folic acid and vitamin B12 supplements in order to reduce the incidence and severity of hematologic and gastrointestinal toxicities as well as cutaneous hypersensitivity reactions. Recommendations for pre-medication are as follows:

- 350-1000µg folic acid, once daily, by mouth for 5 days preceding the first dose of pemetrexed, during treatment, and for 21 days following the last dose of pemetrexed
- 1000µg vitamin B12 by intramuscular injection in the week preceding the first dose of pemetrexed and every nine weeks thereafter (subsequent vitamin B12 injections may be given on the same day as pemetrexed).
- 4 mg dexamethasone (or equivalent), twice daily, by mouth the day before, the day of, and the day after pemetrexed administration.

Additional information can be found in the prescribing information for pemetrexed
[Alimta Package Insert, 2012].

5.1.3 **Carboplatin**

IV carboplatin will be administered once every 21 days (1 cycle) over a 30-minute (± 10min) infusion.

Carboplatin dosing by BSA is not recommended as it does not take into account the patient's renal function and/or desired platelet nadir, which may result in overdosing (i.e. patients with poor renal function) or underdosing (i.e. with above average renal function). Several methods have been proposed for calculating carboplatin doses, considering the area under the curve (AUC) and its subsequent hematologic toxicity, and also the direct relationship between glomerular filtration and carboplatin clearance.

Calvert Formula (Calvert, 1994): Most commonly used method

Dose (mg) = Target AUC (mg/mL per min) x [CrCl (mL/min) + 25]

To avoid toxicity, FDA recommends capping the carboplatin dose for a desired AUC. The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function:

Maximum Carboplatin Dose (mg) = Target AUC (mg/mL per min) x (125 mL/min + 25)

(See FDA communication on carboplatin dosing)

- Adequate hydration and urinary output should be maintained during the 24 hours following carboplatin dosing.
- Magnesium and potassium supplementation should be given as per institutional guidelines.

Additional information can be found in the prescribing information for carboplatin [Paraplatin] Package Insert, 2010].

5.2 Trial Design

Phase I
A standard 3+3 dose-escalation design consisting of up to two independent dose-escalation treatment groups and one dose de-escalation group will be used to determine the maximum administered dose (MAD) and the RP2D for the combination in subjects with advanced non-squamous lung carcinoma. The cohort will be expanded to 6 patients at the recommended Phase II dose level (RP2D). The MAD is the dose of MEK162 in which ≥2/3 or ≥2/6 patients experience dose-limiting toxicity (Section 5.3). The overall safety and tolerability of each treatment combination will be evaluated independent of the other treatment groups.

Phase Ib
Once RP2D has been identified, an expansion cohort will be opened. The RP2D will be expanded by enrolling additional patients, stratified by *KRAS* genotype, to a total of 30 patients eligible for the safety set (including those treated at the same dose combination in the dose-escalation phase of the study who are eligible for the safety set) to be evaluated for safety, tolerability, pharmacokinetics and biologic activity of MEK162.

Stratification of patients by *KRAS* genotype aims for the targets detailed below:
Wild-type *KRAS:* N=10
KRAS mutant non-G12C: N=10
KRAS mutant G12C: N=10

During the expansion cohort, subjects who do not complete at least one post-baseline disease assessment (clinic or radiologic evaluation) may be replaced. Refer to Section 13 (Statistical Considerations) for specific details.

Dosing for Phase Ib will begin at the RP2D and patients will be stratified by KRAS status as detailed above.

5.2.1 Dose Escalation

The dose of MEK162 will be escalated in fixed increments according to the dose escalation scheme outlined in Section 5.2.1. The starting dose will be 30 mg BID. This dose is based on animal toxicology studies in humans (see Section 2) when given as a single agent and in

combination with other agents. An intermittent dosing schedule of MEK162 is proposed in order to minimize toxicity.

Treatment with MEK162 will commence as a single agent, 1 week prior to administration of cycle 1 of chemotherapy. Doses will be administered for 5 days followed by a 2-day omission prior to commencing chemotherapy. Patients who have completed 4-6 cycles of chemotherapy may continue to receive MEK162 until excess toxicity or disease progression.

Dose Escalation Schedule				
Dose Level	**Dose***			
	MEK162 (total daily dose)	**Carboplatin (every 3 weeks)**	**Pemetrexed (every 3 weeks)**	**Minimum number of patients**
Level -1	30mg bid*+ (60mg total)	AUC 5	500mg/m^2	3
Level 1 (starting)	30mg bid* (60mg total)	AUC 5	500mg/m^2	3
Level 2	45mg bid* (90mg total)	AUC 5	500mg/m^2	3
*For cycle 1, continuous dosing until day 5. Omit doses for 2 days (days 6 and 7, and days 27 and 28) prior to chemotherapy administration. For cycles 2+, omit doses on days 20 and 21. Chemotherapy is to be administered on day 8 of cycle 1, and day 1 of every cycle thereafter. Cycle 1 has 28-day duration with subsequent cycles having 21-day duration. + In the event of MEK162 dose reduction or accrual to Dose Level -1, the schedule of MEK162 will be modified to: cycle 1 daily dosing day 1-5, omit days 6 and 7 (2 days prior to chemotherapy) and then daily dosing days 8-21, omit days 22-28. For cycles 2+, daily dosing days 1-14 and omit days 15-21. Cycle 1 is 28 days, subsequent cycles are 21 days.				

The rate of subject entry and escalation to the next dose level will depend upon assessment of the safety profile of patients entered at the previous dose level. Toxicity will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

A minimum of three patients will be entered on each dose level. All three will be followed for one completed cycle of therapy (28 days in cycle 1) and subsequent enrollment of new cohorts will be based on the toxicity assessment in that first cycle and the documentation of any dose limiting toxicities (for definitions see below).

5.2.2 **Maximum Administered Dose (MAD)**

If 0/3 patients exhibit dose limiting toxicity at <u>this</u> dose level:

- Dose escalation to the <u>next</u> dose level may begin in a <u>new</u> cohort of patients

If 1/3 patients exhibit dose limiting toxicity at <u>this</u> dose level:

- Expand dose level to a total of 6 patients.
- If no further DLT events are seen, dose escalation to the next dose level may begin in a new cohort of patients.
- If further DLT events are seen (2 or more out of 6 patients), this dose level will be considered the maximum administered dose (MAD).

If ≥2/3 patients exhibit dose limiting toxicity:

- This dose level will be considered the maximum administered dose (MAD).
- Before opening the next higher dose level all toxic effects at the preceding dose level will be reviewed and expansion or escalation will be undertaken as appropriate. Conference calls between investigators will be organized as required.

5.2.3 **Recommended Phase II Dose**

As described above the MAD is that dose in which ≥2/3 or ≥2/6 patients experience dose-limiting toxicity.

Normally one dose level below that dose will be considered the recommended phase II dose (RP2D). If the MAD is seen at the starting dose level, then dose level "-1" will be the recommended dose if tolerated. In the event that the MAD (as defined above) is not reached by dose level 2, this will be deemed the RP2D.

If clinically appropriate, intermediate dose levels may be studied to assure that the recommended dose is the highest tolerable.

Up to a total of 6 patients may be treated at the recommended dose to assure information on the safety profile at that dose is complete.

5.2.4 **Patient Replacement During Dose Escalation Phase**

Three patients within a dose level must be observed for the first cycle (28 days) without experiencing a DLT before accrual to the next higher dose level may begin. If a patient is withdrawn from the study prior to completing 15 days of therapy without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level. Patients missing 7 or more doses due to toxicity will not be replaced since these patients will be considered to have experienced a dose limiting toxicity.
The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course and reviewed by the study staff. The subject diary template can be found in Appendix C and Appendix D.

5.3 Definition of Dose-Limiting Toxicity

Toxicity will be graded using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE). Any dose limiting toxicity must be a toxicity that is considered related to study drug in cycle 1 (first 28 days of treatment on study). Dose limiting toxicity is defined as follows:

- The inability to administer MEK162 on ≥75% of scheduled treatment days during cycle 1 due to an unresolved adverse event related to the study drug
- Any ≥ grade 3 non-hematological toxicity (except for abnormalities of AST, electrolyte disturbance responsive to correction within 24 hours, or diarrhea, nausea, vomiting, stomatitis, rash or photosensitivity that respond to standard medical care within 48 hours, or fatigue lasting ≤ 7 days)
- Grade 4 neutropenia persisting for ≥ 7 days, or grade ≥3 febrile neutropenia
- Grade 4 thrombocytopenia
- Retinopathy:
    - Grade 2 central serous retinopathy (CSR) for > 14 consecutive days confirmed by ophthalmologic exam
    - Grade ≥3 central serous retinopathy confirmed by ophthalmologic exam
    - Other retinal disorders grade ≥3 confirmed by ophthalmologic examination
- Treatment delay of ≥ 14 days due to unresolved toxicity
- QTc interval ≥ 501 ms, on at least two separate electrocardiograms (ECGs)
- Serum creatinine > 2X ULN
- Any ≥ grade 2 non-hematological toxicity described in the CTCAE v4.0, which in the judgment of the Principal Investigator, is considered dose-limiting

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional

	patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 **MEK162**

MEK162 is a substrate for many CYP isoforms (CYP3A and 1A2 with some involvement of CYP2C isoforms). Although the risk of metabolic interaction caused by an effect on an individual isoform is minimized for MEK162, caution should be used in patients receiving concomitant treatment with other drugs that are either potent inhibitors or inducers of CYP3A, CYP2B6, 2C8, 2C9, 2C19, and 1A2.

Because there is a potential for interaction of MEK162 with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix F presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

Patients who require agents on the provided list in Appendix F will be excluded from enrolling in the study. Patients who require such an agent during participation in the study may be allowed to continue if the following apply: they have stable or responding disease; no alternative treatment is available; and they have close clinical monitoring while they are enrolled in the clinical trial.

Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator.

No other anti-cancer or investigational agents are permitted during the entire duration of treatment with study drug.

5.4.2 **Pemetrexed**

- 350-1000µg folic acid, once daily, by mouth for 5 days preceding the first dose of pemetrexed, during treatment, and for 21 days following the last dose of pemetrexed
- 1000µg vitamin B12 by intramuscular injection in the week preceding the first dose of pemetrexed and every three cycles thereafter (subsequent vitamin B12 injections may be given on the same day as pemetrexed).
- 4 mg dexamethasone (or equivalent), twice daily, by mouth the day before, the day of, and the day after pemetrexed administration.

5.4.3 **Carboplatin**

Standard antiemetic protocols should be followed for administration of carboplatin (as per institutional anti-emetic guidelines). Note that ondansetron may be used with caution. Zolasetron is excluded because of interaction with cytochrome P450.

5.4.4 **Additional supportive medications**

Supportive and other palliative measures are permitted.

Radiotherapy is permitted after cycle 1 for symptomatic bone metastases which pre-dated study enrollment. MEK162 and chemotherapy should be held for the duration of this treatment. New bone metastases requiring radiotherapy are considered to be indicative of disease progression and patients will have to come off study for this.

Management of diarrhea and skin toxicity is outlined in Appendix G.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), carboplatin and pemetrexed chemotherapy may continue for a maximum of 6 cycles. After the 6th cycle, it is under the Investigator's discretion to continue with pemetrexed alone.

MEK162 treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Clinical progression
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Significant noncompliance with the protocol schedule in the opinion of the investigator

5.6 Duration of Follow Up

Patients will be followed from the end of study drug administration until adverse event stabilization or resolution, disease progression, or until death. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Patients who withdraw consent will no longer be followed.

	Follow-Up Period		
	Safety Follow-Up: 28 days from the End of Study Drug Administration	**120 days after End of Study Drug Administration visit* and then every 120 days until disease**	**Until resolution or stabilization of adverse event(s)*** **

			progression**	
Reason Patients Removed from Study	Objective Disease Progression**	X		X (monthly FU)
	Clinical Progression/ Symptomatic Deterioration	X		X (monthly FU)
	Adverse Events or clinically significant lab value	X	X	X (weekly FU for 4 weeks, then monthly)
	All other patients	X	X	X (monthly FU)

* All study participants are expected to maintain contraceptive practices until 120 days after the end of study drug administration.
** Must be documented radiologically and as per RECIST guidelines.
*** Follow for AEs until all other follow-up requirements are met. Refer to section 7.6 for guidance in the following of ongoing or new AEs or SAEs. Note that disease progression must be demonstrated per RECIST.

5.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed below applies:

- Patient death
- Withdrawal of consent
- Disease progression (radiological or clinical)
- Termination of study by Sponsor-Investigator or Regulatory Authority

The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

Doses will be reduced for haematological and other adverse events. Dose adjustments are to be made according to the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE).

The major adverse effects of MEK162 which limit dose is/are:

- Ocular (retinal) toxicity
- Skin rash
- Persistent fatigue
- Nausea
  Neutropenia (when administered with chemotherapy)

Other frequent treatment-related adverse events in patients receiving MEK 162 (binimetinib) include:

- Vomiting

- Diarrhea
- Peripheral edema
- Creatine phosphokinase (CPK) elevation

Other relevant toxicities include:

- Retinal events
- Blood pressure increase
- Cardiac ejection fraction decrease
- Pneumonitis

The guidelines which follow outline dose adjustments for several of these toxic effects. Carboplatin and pemetrexed dose modifications are based on CCO Regimen Monograph (CCO, 2012 and CCO, 2013).

If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.
Once a dose has been reduced it will not be increased at a later time even if there is no toxicity.

Recommended Dose Modifications for MEK162, Carboplatin and Pemetrexed			
Worst toxicity CTCAE v4.0 Grade (unless otherwise specified*)	**Recommended Dose Modifications any time during a cycle of therapy**		
	MEK162	**Carboplatin**	**Pemetrexed**
Blood and lymphatic system disorder			
Anaemia			
≤Grade 2	Maintain dose levels of all drugs.		
Grade 3	Omit dose until resolved to ≤grade 1.	Hold until ≤grade 1, then dose reduction by 1 AUC.	Hold until ≤grade 1, then reduce dose by 100 mg/m^2
Grade 4	Discontinue all drugs		
Neutrophil count (ANC) decreased (Neutropenia)			
Grade 1	Maintain dose levels of all drugs		
Grade 2	Maintain dose level	Hold carboplatin and pemetrexed for 1 week or until resolved to ≤grade 1 and then administer at same dose as previous.	
Grade 3	Omit dose until ≤grade 1, and then resume at same dose. If resolved in >7 days, then treat with G-CSF. At the second occurrence, reduce dose by 1 dose level**	Hold until ≤grade 1; and then treat with G-CSF. At the second occurrence, dose reduce by 1 AUC.	Hold until ≤grade 1. Then recommence at same dose.
Grade 4	Omit dose until resolved	Hold until ≤grade 1,	Hold until ≤grade 1

	to ≤grade 1, and then maintain dose level. If resolved in >7 days, then treat with G-CSF. At the second occurrence, reduce dose by 1 dose level**	then treat with G-CSF. At the second occurrence, dose reduce by 1 AUC.	and then treat with G-CSF. At the second occurrence, reduce dose by 100 mg/m^2
Febrile Neutropenia			
Grade 3	Omit dose.-If resolved in ≤7 days, treat with G-CSF. At the second occurrence, reduce dose by 1 dose level. If not resolved in ≤7 days, discontinue.	Hold both drugs until ≤grade 2, then treat with G-CSF. At the second occurrence, dose reduce pemetrexed by 100 mg/m^2 and carboplatin by 1 AUC.	
Grade 4	Discontinue all drugs		
Platelet count decreased (Thrombocytopenia)			
Grade 1	Maintain dose level	Maintain doses of both drugs	
Grade 2		Hold both drugs until ≤grade 2 (plt ≥100). Then recommence both drugs at same dose.	
Grade 3	Omit dose until resolved to ≤grade 1, then maintain dose level. If resolved in >7 days, then discontinue.	Hold both drugs until ≤grade 2 (plt ≥100). Then recommence both drugs with pemetrexed dose reduction of 100 mg/m^2 and carboplatin dose reduction of 1 AUC. If bleeding, discontinue both drugs.	
Grade 4	Omit dose until resolved to ≤grade 1, then maintain dose level. If resolved in >7 days, then discontinue.	Hold both drugs until ≤grade 2. Then recommence both drugs with pemetrexed dose reduction of 100 mg/m^2 and carboplatin dose reduction of 1 AUC. If bleeding, discontinue both drugs.	
Investigations			
Serum creatinine			
Grade 1	Maintain dose level	See ***Table for dose modifications of chemotherapy agents based on creatinine clearance	
Grade 2	Omit dose until resolved to ≤grade 1 or baseline, and then maintain dose level.		
Grade 3	Omit dose and discontinue from study treatment.		
Grade 4			
Creatinine phosphokinase (CK/CPK)			
Grade 1 or 2	Maintain dose level of all drugs		
Grade 3	Omit dose until resolved	Hold both drugs until ≤grade 2.	

	to ≤grade 1. If resolved in ≤7 days, reduce dose level by 1 dose level**. If resolved in >7 days discontinue.	Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin, or if bleeding, discontinue both drugs.
Grade 4	Discontinue all drugs	
Bilirubin		
Grade 1	Maintain dose level of all drugs	
Grade 2	Omit dose until resolved to ≤grade 1. If resolved in 7 days, then maintain dose level. If resolved in >7 days, then reduce by 1 dose level**	Hold both drugs until ≤grade 2. Then recommence both drugs at same dose.
Grade 3	Discontinue	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin.
Grade 4	Discontinue all drugs	
AST or ALT		
Grade 1	Maintain dose level of all drugs	
Grade 2	Omit dose until resolved to ≤grade 1 (or ≤grade 2 in case of liver metastases). If resolved in ≤7 days, maintain dose level. If resolved in > 7 days, reduce dose by 1 dose level**	Hold both drugs until ≤grade 2. Then recommence both drugs at same dose.
Grade 3		Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin.
Grade 4	Discontinue all drugs	
Cardiac Disorders		
LV systolic dysfunction*		
Grade 3	Discontinue	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin.
Grade ≥ 4	Discontinue	Discontinue
Other cardiac disorders		
Grade 1 and 2	Maintain dose level	
Grade ≥ 3	Discontinue	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin.

Grade ≥ 4	Discontinue	If Grade 4, discontinue. Obtain formal cardiology evaluation and discuss with PI.
Persistent Hypertension		
Grade 3 requiring >1 drug or more intensive therapy than previously	Omit dose until resolved to ≤grade 1, then reduce by 1 dose level**	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin.
Grade 4 requiring >1 drug or more intensive therapy than previously	Discontinue	Discontinue both drugs. Medical Management as required. Discuss with PI.
Asymptomatic Amylase and /or Lipase elevation		
≤ Grade 2	Maintain dose level of all drugs	
Grade 3	Omit until resolved to ≤grade 2, then recommence at same dose.	25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin. Perform CT scan/US to assess pancreas, liver and gallbladder within 1 week of 1st occurrence of grade 3 amylase/lipase.
Grade 4	Discontinue all drugs	
Creatine Kinase (CK) elevation		
Grade 1 and 2	Maintain dose level of all drugs. If total CK ≥ 3 x ULN, measure isoenzymes and myoglobin in blood and urine.	
Grade 3 (>5-10 x ULN)	If asymptomatic: Maintain dose. Monitor closely and measure isoenzymes and myoglobin in blood and urine. If symptomatic (muscle pain/spasms): interrupt dose until resolved to ≤grade 1 and monitor closely. Then: - If resolved in ≤ 14 days, reduce 1 dose level** - If resolved in > 28 days, permanently discontinue.	Maintain dose level
Grade 4	If asymptomatic, interrupt dose and monitor closely. - If resolved in ≤ 14 days, reduce 1 dose level** - If resolved in > 28 days, permanently discontinue. If symptomatic,	Maintain dose level

	permanently discontinue.	
Diarrhoea		
Grade 1	Maintain dose but initiate anti-diarrhoea treatment	Maintain dose level of both drugs
Grade 2	Omit dose until resolved to ≤ grade 1, then recommence at same dose. For 2nd occurrence at grade 2, omit dose until resolved to ≤grade 1, then reduce dose by 1 dose level**	Hold both drugs until ≤grade 2. Maintain dose level of both drugs. Follow guidelines in Appendix G for management of diarrhea.
Grade 3	Omit dose until resolved to ≤grade 1, then reduce dose by 1 dose level** For 2nd occurrence at grade 3, discontinue.	Hold both until ≤grade 2. Recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin. Follow guidelines in Appendix G for management of diarrhea.
Grade 4	Discontinue all drugs. Follow guidelines in Appendix G for management of diarrhea.	
ECG QTc-Interval prolonged		
Grade 1 and 2	Maintain dose level of all drugs	
Grade 3	Omit dose until returned to ≤grade 1 or baseline, then reduce 1 dose level** following consultation with PI.	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin.
Grade 4	Discontinue all drugs	
Eye disorders		
Central serous retinopathy		
Grade 1	Maintain dose level. Perform eye examinations every 15 days until resolution.	Maintain dose level of both drugs
Grade 2	Omit dose until resolved to ≤grade 1. If resolved in <14 days, then dose reduce by 1 dose level**. If resolved in >14 days, discontinue patient from study drug treatment.	Hold both drugs until ≤grade 2. Then recommence both drugs at same dose.
Grade 3	Discontinue	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose

		reduction of carboplatin.
Grade 4	Discontinue	Discontinue. Obtain formal ophthalmology evaluation and discuss with PI.
Retinopathy, retinal detachment, tear or retinal vascular disorder (including RVO) – other than CSR		
Grade 1 and 2	Discontinue	
Grade 3	Discontinue	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin.
Grade 4	Discontinue	Discontinue. Obtain formal ophthalmology evaluation and discuss with PI.
Uveitis		
Grade 1	Maintain dose level of all drugs	
Grade 2	Maintain dose level. If unresolved in >14 days, discontinue.	Hold both drugs until ≤grade 2. Then recommence both drugs at same dose.
Grade 3	Discontinue	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin.
Grade 4	Discontinue	Discontinue. Obtain formal ophthalmology evaluation and discuss with PI.
Visual disturbance without retinal changes		
Grade 1	Maintain dose level for all drugs	
Grade 2	Maintain dose level. If unresolved in >14 days, discontinue.	Hold both drugs until ≤grade 2. Then recommence both drugs at same dose.
Grade 3	Discontinue	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin.
Grade 4	Discontinue	Discontinue. Obtain formal ophthalmology evaluation and discuss with PI.
Visual disturbances without retinal changes		
Grade 1 and 2	Maintain dose level for all drugs	
Grade 3	Omit dose until resolved to ≤grade 1. If resolved in <14 days, then dose reduce by 1 dose level**. If resolved in >14 days, discontinue patient from study drug treatment.	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin.
Grade 4	Discontinue	Discontinue. Obtain formal ophthalmology evaluation and discuss with PI.

Eye disorders – other		
Grade 1 and 2	Maintain dose level of all drugs	
Grade 3	Discontinue	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction of pemetrexed, and 1 AUC dose reduction of carboplatin. with PI.
Grade 4	Discontinue	Discontinue. Obtain formal ophthalmology evaluation and discuss with PI.
Skin and subcutaneous disorders		
Rash/Photosensitivity		
Grade 1	Maintain dose level of all drugs but consider initiating skin toxicity therapy according to guidelines (Appendix G).	
Grade 2	Maintain dose of all drugs but initiate skin toxicity therapy according to guidelines (Appendix G).	
Grade 3, despite skin toxicity therapy • Asymptomatic lasting >48 hours • Symptomatic	Omit dose until resolved to ≤grade 1, then if resolved in ≤48 hours, reduce by 1 dose level** If resolved >48 hours, discontinue.	Hold both drugs until ≤grade 2. Then if resolved in ≤48 hours, recommence both drugs at same dose. If resolved >48 hours, recommence both drugs at 25% dose reduction.
Grade 4, despite skin toxicity therapy	Discontinue all drugs	
General disorders		
Fatigue		
Grade 1 or 2	Maintain doses of all drugs	
Grade 3	Omit dose until resolved to ≤grade 1, then if resolved in ≤7 days, reduce by 1 dose level** If resolved >7 days, discontinue.	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction.
Edema		
Grade 1 or 2	Maintain doses of all drugs	
Grade 3	Omit dose until resolved to grade ≤1, then if resolved in ≤14 days, reduce by 1 dose level** If resolved >14 days, discontinue.	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction.
Other adverse events		
Grade 1 or 2	Maintain doses of all drugs	
Grade 3	Omit dose until resolved to grade ≤1, then reduce by 1 dose level**	Hold both drugs until ≤grade 2. Then recommence both drugs at 25% dose reduction.
Grade 4	Discontinue	

*If a patient requires a dose delay of >14 days from the intended day of the next scheduled dose of MEK162, the patient must be discontinued from study treatment. Patients who discontinue from the study for a study-related adverse event or an abnormal laboratory value must be followed at least once a week for 4 weeks and subsequently at 4 week interval, until resolution or stabilization of the event, whichever comes first, except specifically mentioned.
**Patients requiring more than two dose reductions of MEK162 will be discontinued from study drug treatment.
***Table for dose modifications of chemotherapy agents based on creatinine clearance:

Creatinine Clearance	Carboplatin (% previous dose)	Pemetrexed (% previous dose)
61-79	Use Calvert formula	100%, but use NSAIDS with extreme caution
45-60		
30-<45		Discontinue
<30	Discontinue	Discontinue

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

An adverse event is any untoward medical occurrence (including any abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational product) in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment.

7.1 List of Adverse Events and Reporting Requirements

7.1.1 Expected Adverse Events for MEK162

The major adverse effects of MEK162 which limit dose is/are (as referenced in Table 17, MEK162 IB Edition 15):

- Ocular (retinal) toxicity
- Skin rash

Very common treatment-related adverse events in patients receiving binimetinib include:

- Constipation
- Decreased appetite
- Dyspnoea
- Alopecia
- Pruritus
- Abdominal pain
- Fatigue
- Oedema peripheral
- Pyrexia
- Alanine aminotransferase increased
- Myalgia
- Dry skin (Xerosis)
- Rash
- Hypertension

Other relevant toxicities include:

- Other ocular events including raised eye pressure, visual changes

- Blood pressure increase
- Cardiac ejection fraction decrease
- Pneumonitis
- Itching
- Vomiting

Additional risks associated with MEK162

- Among all patients treated with MEK162, a patient experienced acute liver failure (the liver rapidly lost its ability to function normally) leading to death. Due to this case and the observed increase in the value of liver enzymes, your liver function will be evaluated frequently.
- As mentioned above, a decrease of left ventricular ejection fraction has been reported in studies with MEK162. This means the heart may have difficulty pumping enough blood throughout the body. This adverse event has also been described with other similar compounds. Your cardiac function will be evaluated before and during the study. Patients with severe and recent cardiac abnormalities or events should not receive MEK162.
- Bleeding events including bleeding in the stomach, intestines, and brain have been reported in patients treated with MEK162. Please contact your doctor to seek immediate medical attention for any unusual signs or symptoms that might indicate bleeding, e.g. bruising, blood in vomit, black tarry stools, difficulty speaking or walking
- MEK162 has caused mild to moderate visual changes in some patients, which include floaters, swelling and/or inflammation in and around the eyes and changes in the retina. While this type of visual impairment may resolve, there is a risk that the visual changes may continue. Blurred vision and, in some cases, loss of vision might be observed with MEK162. There is the possibility that these changes could affect the activities of your daily life (i.e. driving a car or operating machinery). It is important to tell your doctor about any pre-existing eye problems you have and visual changes that occur while taking the study drug as your doctor may decide to change or stop your treatment with the study drug.
- Hypertensive crisis was described in a single agent study with MEK162. Increase of blood pressure may be a potential risk when receiving MEK162. Patients at risk for high blood pressure will be monitored closely and according to the discretion of the investigator and if necessary these patients will receive specific treatment for hypertension.
- Cases of serious adverse events of inflammation of the lung tissue (Interstitial Lung Disease or Non-Infectious Pneumonitis) have been reported in clinical studies of MEK162. Difficulty breathing, often accompanied by a cough and fever, is the most common symptom of pneumonitis. Please inform your doctor should you experience any of the symptoms described above.
- Blood clots have been reported in patients treated with MEK162 including blood clots in veins in the legs (deep vein thrombosis), in veins of the eyes (retinal vein occlusion) and in arteries of the lungs (pulmonary embolism). Please contact your doctor right away if you have symptoms that may be caused by blood clots such as swelling, increased warmth, redness or pain in your leg, loss of vision, or cough, shortness of breath or chest pain.
- A severe skin reaction including serious illness with blistering of the skin, mouth, eyes

and genitals has been reported in a patient who received Binimetinib (MEK162) in combination with another investigational drug (known as BYL719). It is possible that one of these drugs may have caused this reaction; however, because the patient started both drugs at the same time, it is unknown which of the two drugs may have contributed to the skin reaction. Please contact your physician immediately in case of such symptoms.

- A small number of patients and subjects in clinical trials developed hives and/or swelling in the throat, also known as angioedema, which can be a sign of an allergic reaction. Your doctor should be notified immediately if you experience tightness in your throat which may be associated with difficulty breathing.
- Severe muscle damage with breakdown of muscle tissue (rhabdomyolysis) which may result in organ damage such as kidney failure.

Please refer to the binimetinib investigator's brochure for a comprehensive list of adverse events (Edition 15, 20-Mar-2018, Section 6 Reference Safety Information and Section 7.1 Identified and Potential Risks).

7.1.2 Expected Adverse Events for Carboplatin

The adverse events most likely to occur from carboplatin include:

- myelosuppression
- fatigue
- peripheral neurotoxicity
- audiologic toxicity
- rash

Please refer to the PARAPLATIN package insert for a comprehensive list of adverse events.

7.1.3 Expected Adverse Events for Pemetrexed

The adverse events most likely to occur from pemetrexed in combination with platinum agents include:

- myelosuppression
- stomatitis/pharyngitis
- constipation
- nausea, vomiting

As a single agent, the most likely adverse events of pemetrexed include:

- fatigue
- nausea
- anorexia

Please refer to the ALIMTA package insert for a comprehensive list of adverse events.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found

in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

Associated with the use of the drug: There is a reasonable possibility that the experience may have been caused by the drug/biologic.

Life threatening adverse drug experience: Any adverse drug/biologic experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred.

Serious adverse drug experience: Any event is an AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening AE (The patient was, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not mean that the event, had it occurred in a more severe form, might have caused death).
- Hospitalization or prolongation of existing hospitalization (Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE).
- A persistent or significant disability/incapacity (A substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption).
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization or the development of drug dependency or drug abuse).

Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported as an SAE. A second malignancy is one unrelated to the treatment of a prior malignancy (and is

NOT a metastasis from the initial malignancy).

Events not considered to be serious adverse events are:

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

Any SAE occurring from the start of study medication administration and until 4 weeks after the patient has stopped study participation must be reported. This includes the phase in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during screening phase, change in treatment to a fixed dose of concomitant medication). Serious adverse events occurring more than 4 weeks after the end of study drug administration need only be reported if a relationship to MEK162 is suspected.

Unexpected adverse drug experience: Any adverse drug experience, the nature, frequency, or severity of which is not consistent with the product monographs and investigator brochure, or not consistent with the risk information described above as expected adverse events.

7.3 Serious Adverse Event Reporting

7.3.1 Sponsor Notification

Any serious adverse event must be reported to the Central Office within 24 hours of the Investigator at the site learning of the event by a completed SAE form. The adverse event must be completely described in the case report form.

The Central Office will provide expedited reports of on-study SAEs to Health Canada and Array BioPharma Inc. (Array) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected (as determined by reference to the Investigator Brochure), AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

All adverse signs and symptoms which occur during or following the course of drug administration must be reported in detail on the subject's case report form. This description is to include the nature of the sign or symptom, time of onset in relation to drug application, duration, severity, and possible relationship to drug, required therapy, and outcome. The subject should be followed until the adverse reaction is resolved, or until in the opinion of the Principal Investigator, reversal of the reaction is not likely to occur.

7.3.2 SAE Follow-up

Follow-up SAE reports is subject to the same timelines as the initial report, and is sent to the same parties to whom the original Serious Adverse Event Form was sent. A new serious adverse event form is completed for the follow-up, stating that this is a follow-up to the previously reported serious adverse event and giving the date of the original report. Each re-occurrence, complication or progression of the original event should be reported as a follow-up to that event. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation.

The Sponsor-Investigator and Institution will assist Array in investigating any SAE and will provide any follow-up information reasonably requested by Array.

7.3.3 REB Notification of SAEs

Investigators must notify their Research Ethics Boards (according to their local REB policies) and file the report in their study files. Documentation as outlined below must be maintained for reportable SAEs. Documentation that serious adverse events (SAEs) have been reported to REB must be forwarded to the DDP and kept on file at the Centre. Documentation can be any of the following:

- letter or email from the REB acknowledging receipt
- stamp from the REB, signed and dated by REB chair, acknowledging receipt
- letter demonstrating the SAE was sent to the REB
- email submission to REB by site

7.3.4 Health Canada SAE Reporting

All serious, unexpected adverse drug reactions must also be reported by the Princess Margaret Cancer Centre DDP Central Office to Health Canada within 15 days if the reaction is neither fatal nor life threatening, and within 7 days if the reaction is fatal or life threatening.

The Central Office will be responsible for reporting all serious unexpected adverse events to Health Canada. The Central Office will generate SUSAR reports for all SAEs deemed Health Canada reportable.

7.3.5 SAE Reporting to Array BioPharma Inc.

To ensure patient safety, each serious adverse event must also be reported to Array (in English) within 15 calendar days of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported within 15 calendar days of the Investigator-sponsor receiving it. The SAE Report Form must indicate the relationship to study treatment and be signed by the investigator. The Princess Margaret Cancer Centre DDP Central Office will report the SAE to Array:

Attention:
Drug Safety
drugsafety@arraybiopharma.com
Fax: (303)-386-1516

A summary of SUSARs (see Section 7.3.4) from this study will be generated every 6 months, and submitted to Array Biopharma.

7.4 Routine Adverse Event Reporting

For abnormal laboratory values, it is the responsibility of the Principal Investigator or delegate to assess the clinical significance of each abnormality. Only abnormal laboratory values that can be assessed for grade using CTCAE version 4.0 will be documented. The Investigator will determine whether abnormal laboratory values are considered clinically significant and represent AEs based on their medical judgment.

Data on all adverse experiences/toxicities regardless of seriousness must be collected for documentation purposes only.

7.4.1 Clinical Laboratory Abnormalities:

All abnormal laboratory values should be captured on source documentation and assessed for clinical significance by the Investigator at the site. Only abnormal laboratory values deemed clinically significant should be listed as AEs in source and CRFs. All clinically significant abnormal laboratory results will be followed up until the related AE resolves, returns to < grade 2 or baseline value in the follow-up period. Clinically significant laboratory abnormalities will be dictated in the clinic notes. Additionally, laboratory abnormalities resulting in an intervention are considered to be clinically significant.

7.5 Documentation of Adverse Events

All AEs must be captured in the source documents, as well as reported in *electronic document capture (EDC) system*. AEs reported using SAE forms must also be reported in *EDC system*.

All serious and non-serious AEs occurring from the start of study medication administration to the end of study drug administration visit must be recorded as AEs on the CRF. The Investigator should review all documentation (e.g., hospital progress notes, laboratory, or diagnostic reports) relative to the event being reported.

7.6 Follow-Up of AEs and SAEs

SAEs and AEs should be followed for 28 days after the last dosing of study drug or until they are resolved (return to normal or baseline values), stabilized, improve to < Grade 2, or the patient is lost to follow-up and cannot be contacted. Additional investigations (*e.g.*, laboratory tests, diagnostic procedures, or consultation with other healthcare professionals) may be required to completely investigate the nature and/or causality of an AE or SAE. If the patient dies during the study or within 28 days following the last dose of study medication, any postmortem findings (including histopathology) should be provided to the Sponsor. CRF data should be updated with any new information as appropriate.

7.7 Pregnancy

Any pregnancy of a study subject or of a study subject's partner that occurs during study participation should be reported for pregnancies that occur up to 30 days after the last dose of study medication. If the study subject is the father, then two forms should be completed, one for the father and the other for the mother and neonate. To ensure patient safety each pregnancy must also be reported to Array within 15 days of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

7.8 Investigator Notifications

The Sponsor-Investigator will receive Investigator Safety Letters (ISLs) issued by Array for suspected, unexpected serious adverse reactions which have occurred in Array-sponsored studies with the study drug. The Sponsor-Investigator is responsible for forwarding these ISLs to all sub-investigators participating in the study, as well as to the Research Ethics Boards, according to local practice.

7.9 Data Safety and Monitoring Board

A Data Safety and Monitoring Board, an independent group of experts, through the Princess Margaret Cancer Centre Drug Development Program will be reviewing the data from this research throughout the study to see if there are unexpected or more serious side effects than described in the consent.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 Investigational Agent

8.1.1 MEK162

MEK162 is currently supplied as film-coated tablets in dosage strength of 15mg. The film-coated tablets consist of MEK162 drug substance, lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and a commercial film coating.

The tablets are yellow to dark yellow capsule-shaped.

As development continues additional strengths of similar formulation may be developed.

Investigational agent Manufacturing

Array manufactures MEK162 for clinical use.

Investigational Agent Packaging and Labeling

MEK162 will be packaged and labeled by a contract manufacturing organization and stored by Array. Study drug labeling will contain the following information in English and French:

Protocol Code: MEK162

Investigational Drug name and formulation (mg): MEK162

Lot Number: DP-ARR16-118-A

Contents: 15mg tablets

Store at 25°C

Investigational drug: To be used by qualified investigators only.

Sponsor: Princess Margaret Cancer Centre

Investigational Agent Handling and Storage

Investigational agent will be stored under secure (with limited access), temperature-controlled conditions for the duration of the study. Investigational agent bottles will be stored at ambient temperature (i.e.15-25°C) and protected from light, in an area accessible only to authorized staff. Patients will be asked to store their one-month supply of drug at ambient temperature and protected from light. Packaging is in plastic bottles acceptable for pharmaceutical use. The Investigator, or designee will keep study drug inventory forms.

Availability

MEK162 is provided under a Collaborative Agreement between the Sponsor and the agent manufacturer (Novartis/Array).

Investigational Agent Ordering and Shipping

Investigational agents may be ordered only after the initial REB approval and the site has been activated by the Drug Development Program Central Office.

Array will supply MEK162 to the study site. Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. The Principal Investigator, or authorized study personnel, upon receipt of the study medication supplies, will conduct an inventory and acknowledge receipt to Array, or designee. The study drugs should be stored according to the instructions specified on the drug labels.

Study medication should only be dispensed once a patient has (1) signed an informed consent form

(ICF), (2) met all eligibility criteria for entry into the study, (3) completed all screening and continuing eligibility requirements, and (4) been assigned a patient identification number.

Agent Accountability

The Investigator is responsible for study medication accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study personnel must maintain study medication accountability records throughout the study.

The accountability records maintained during the study will be used to support patient dosing data. Site personnel are responsible for reconciling and resolving discrepancies in study medication accountability.

Missing study medication must be recorded along with an explanation of the discrepancy. At the conclusion of the study, all unused study medication and all medication containers will be returned to Array or designee, unless other arrangements have been approved by Array.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received using their site-specific Drug Accountability Record Form (DARF).

8.2 Non-Investigational Agents

8.2.1 Carboplatin

Carboplatin is a cisplatin derivative and shares the same mechanism of action. Highly reactive platinum complexes are formed intracellularly. These complexes inhibit DNA synthesis through covalent binding of DNA molecules to form intrastrand and interstrand DNA crosslinks. Carboplatin is considered to be cell cycle phase-nonspecific, but recent studies have shown complex and variable effects on the cell cycle.

Availability

Paraplatin AQ® (Brand Discontinued), Generic brands available

Reconstituted in 250ml normal saline 0.9% or glucose 5%. Carboplatin is physically incompatible with any IV set, needle or syringe containing aluminum. Carboplatin solutions are stable for 8 hours at room temperature (25°C). Intravenous administration over 30 minutes.

Ordering and Shipping

Carboplatin will be sourced locally by the study site and reimbursed through provincial drug funding mechanisms. The Principal Investigator, or authorized study personnel, upon receipt of the study medication supplies, will conduct an inventory.

Study medication should only be dispensed once a patient has (1) signed an informed consent form (ICF), (2) met all eligibility criteria for entry into the study, (3) completed all screening and continuing eligibility requirements, and (4) been assigned a patient identification number.

Accountability

The Investigator is responsible for study medication accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study personnel must maintain study medication accountability records throughout the study.

The accountability records maintained during the study will be used to support patient dosing data. Site personnel are responsible for reconciling and resolving discrepancies in study medication accountability.

Missing study medication must be recorded along with an explanation of the discrepancy. At the conclusion of the study, all unused study medication and all medication containers will be returned to the clinical trials pharmacy, unless other arrangements have been approved by the sponsor.

8.2.2 Pemetrexed

Pemetrexed is a pyrrolopyrimidine antifolate that exerts its antineoplastic activity by inhibiting thymidylate synthase (TS), glycinamide ribonucleotide formyltransferase (GARFT) and dihydrofolate reductase, which are all folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Inhibition of TS appears to be the primary mechanism of action. Severe toxicity in early clinical studies (6% toxic death rate) led to the introduction of mandatory folate and vitamin B12 supplementation.

Availability

Commercial name Alimta® (Eli Lilly)

Reconstituted in 100ml normal saline 0.9%. Pemetrexed is incompatible with calcium containing solutions and should not be co-administered with other drugs and diluents. Keep unopened vials at room temperature. Pemetrexed is not light sensitive. Intravenous administration over 10 minutes.

Ordering and Shipping

Pemetrexed will be sourced locally by the study site, and reimbursed through provincial funding mechanisms. The Principal Investigator, or authorized study personnel, upon receipt of the study medication supplies, will conduct an inventory.

Study medication should only be dispensed once a patient has (1) signed an informed consent form (ICF), (2) met all eligibility criteria for entry into the study, (3) completed all screening and

continuing eligibility requirements, and (4) been assigned a patient identification number.

Accountability
The Investigator is responsible for study medication accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study personnel must maintain study medication accountability records throughout the study.

The accountability records maintained during the study will be used to support patient dosing data. Site personnel are responsible for reconciling and resolving discrepancies in study medication accountability.

Missing study medication must be recorded along with an explanation of the discrepancy. At the conclusion of the study, all unused study medication and all medication containers will be returned to clinical trials pharmacy, unless other arrangements have been approved by the sponsor.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

All participating sites will provide documentation of IATA training to the Central Office for all study staff delegated to the task of shipping and handling of specimens.

9.1 Pharmacokinetics
The blood sampling regimens for determining the pharmacokinetics of MEK162 and its primary active metabolite AR00426032, are given in Table 9.1. Blood samples for MEK162/AR00426032 plasma concentration measurements will be collected on all patients in the study.

Pharmacokinetic (PK) testing will occur over a 24-hour period on each of cycle 1 day 5 and cycle 1 day 15 (see Table 9.1). This will allow steady-state information to be obtained related directly to the chemotherapy dose and without chemotherapy. PK kits will be provided for this study.

All samples are to be taken as closely as possible to the times specified above in Section 9.1. If samples are taken at times different from this schedule, they are still valuable provided the sample times are accurately recorded.

Exact dates and clock times of drug administration and actual PK blood draw will be recorded on the appropriate CRF. The time of the last meal should be recorded on all post-dose PK sampling days. **If a patient experiences an AE that results in an unscheduled visit or fits the criteria of a SAE as determined by the Investigator, a blood sample (4 mL) should be collected for measurement of plasma drug concentrations**. Additionally, if a patient experiences an ocular event of any grade, a blood sample should be collected.

If vomiting occurs within 4 hours following study-drug administration on the day of PK blood sampling, the time (using the 24 hour clock) of vomiting should be recorded on the transmittal forms, which accompanies the sample. No additional trial medication should be taken that day in an effort to replace the material that has been vomited. If a patient withdraws prematurely from the study, a PK blood sample (4 mL of sample) must be obtained whenever possible. Sample

should be as soon as possible after the last dose of MEK162, and the date and time of last dose recorded.

Intravenous cannulation of an antecubital or forearm vein may be performed prior to drug administration on serial PK sampling days to facilitate collection of blood specimens. The cannula will be kept patent by means of a heparin/saline lock. If a cannula is utilized, an initial 1 mL volume of blood will be collected and wasted prior to collection of each whole blood sample to assure the heparin/saline solution does not dilute the blood sample. Pharmacokinetic sample tubes will be clearly labeled with the drug name, study number, patient serial number, sample date, and sample collection time (relative to dosing). The date and time of sample collection will be captured on Pharmacokinetics Forms (Form PK). If for any reason a sample is not collected, the sample date and time should be recorded as not done (ND) on the Pharmacokinetics Form (Form PK). Complete instructions for sample collection, processing, handling and shipment will be provided in the lab manual.

9.1.1 PK Shipping Instructions

A sample inventory detailing the number and identities of the samples sent must accompany each batch of samples dispatched. Samples should be shipped to avoid arrival at the laboratory during weekends. Please refer to the lab manual for complete instructions.

All samples must be carefully packed in suitable material containing sufficient dry ice to keep them frozen during shipment. A list of samples, including the date, subject number, and the time of sampling should be included in the shipment. Any missing samples should be notified on the list.

Any sampling problems should be noted on the CRF and on appropriate source documentation.

Table 9.1. Pharmacokinetic sampling schedule

Cycle	**Day**	**Scheduled time for pharmacokinetic sampling relative to dosing**
1	5	Pre-dose
1	5	0.5 hr post dose ± 15 min

1	5	1.5 hr post dose ± 15 min
1	5	3 hr post dose ± 30 min
1	5	5 hr post dose ± 1 hr
1	5	8 hr post dose ± 1 hr
1	15	Pre-dose
1	15	0.5 hr post dose ± 15 min
1	15	1.5 hr post dose ± 15 min
1	15	3 hr post dose ± 30 min
1	15	5 hr post dose ± 1 hr
1	15	8 hr post dose ± 1 hr
N/A	Safety follow-up (28 days from the End of Study Drug Administration)	Post-dose, unspecified time point

9.2 Biomarker Studies

The collection of a representative sample of tumor tissue is an important part of this trial and is mandatory for participation in the study for the evaluation of *KRAS* mutations, as well as *KRAS* codon subtypes. Tumor blocks will be the preferred material to collect. These will optimize the amount of tissue available to investigators and permit the preservation of the tumor block submitted. If tissue is obtained from another hospital and, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request. The methodology for KRAS mutation testing is detailed in the lab manual. If *KRAS* analysis is already available, the patient will be eligible for the study.

All patients will be approached for optional consent for tissue samples to be banked for future biomarker exploration.

Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of registration to the trial the surgical/histology number and/or patient initials.

This information will be generated retrospectively in the dose escalation phase, but will also be used for stratification purposes for the phase Ib portion of the study.

9.3 Laboratory Correlative Studies

N/A

10. STUDY CALENDAR

Baseline (pre-study) evaluations are to be conducted within 14 days prior to start of protocol therapy, unless specified differently in the study calendar. Informed consent and scans and x-rays must be done within28 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. The following schedule of assessments applies to all subjects. More frequent assessments should be obtained if clinically indicated. If pre-study physical exam, vital signs, weight, performance status, and blood assessments were done within 3 days prior to treatment initiation, they do not need to be repeated for cycle 1 day 1. For subsequent cycles 2+, day 1 assessments can be completed up to 72 hours prior to day 1. A cycle is 28 days long for cycle 1 only, and 21 days for cycle 2 and onwards.

	Pre-Study Day -14	**Cycle 1**				**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6**	**Subsequent cycles**	**End of Treatment[d]**	**Safety F/U[i]**	**Disease Progression FU**
		D 1	D 8 m	D 15 m	D 21 m	D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15	D 1				
MEK162		A……..A																				
Pemetrexed			B			B			B			B			B*			B*				
Carboplatin			C			C			C			C			C*			C*				
Informed consent	X																					
Demographics	X																					
Medical history	X																					
Inclusion/ Exclusion criteria	X																					
Concurrent meds	X	X……..X																				
Physical exam	X	X	X	X	X	X			X			X			X			X	X	X	X	
Vital signs **	X	X	X	X	X	X			X			X			X			X	X	X	X	
Height	X																					
Weight	X	X	X	X	X	X			X			X			X			X	X	X	X	
Performance status	X	X	X	X	X	X			X			X			X			X	X	X	X	
CBC w/diff, plts	X	X	X	X	X	X			X			X			X			X	X	X	X	
Coagulation screen	X					X														X	X	
Serum chemistry[a]	X	X[l]	X	X	X	X[l]			X[l]			X[l]			X[l]			X[l]	X	X	X	
ECG[b]	X					X						X						X	X	X		
Echocardiogram / MUGA[c]	X							X									X		X			
Adverse event evaluation		X……..X																		X		
Tumor measurements	X	Tumor measurements are repeated every 6-8 weeks[e]. Documentation (radiologic) must be provided for patients removed from study for progressive disease.																		X[n]		X
Radiologic evaluation	X	Radiologic measurements should be performed every 6-8weeks[e].																		X		X
B-HCG	X	X[f]																		X		
Pharmacokinetic testing		X[g]		X																	X	
Ophthalmologic assessment[h]	X					X						X						X		X		
Audiogram[j]	X					X																
Research blood sample [k]	X					X						X								X		
Consent for genomic profiling	X																					

A: MEK162: Dose as assigned; administration schedule (omit dose for 2 days prior to each administration of chemotherapy).
B: Pemetrexed: Dose as assigned; administration schedule.
C: Carboplatin: Dose as assigned; administration schedule.
*: Optional cycle 5 and 6 of chemotherapy.
**: Vital signs include heart rate, blood pressure, respiratory rate, temperature, oxygen saturation
a) Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, creatine kinase (CK).
b) ECG to be performed at baseline, Cycle 2 day 1 (prior to treatment), then every 6 weeks (± 7 days) irrespective of cycle until MEK162 discontinuation, and at end of treatment visit.
c) LV assessment (echocardiogram or MUGA) to be performed at baseline, prior to cycle 3 (week 6 or 7), then every 9 weeks (± 7 days) irrespective of cycle until MEK162 discontinuation.
d) End of treatment evaluations
e) Tumour measurements to be performed according to RECIST 1.1.
f) Serum pregnancy test (women of childbearing potential)-3 days
g) Pharmacokinetic testing: Cycle 1 day 5 (0-8hr), cycle 1 day 15 (0-8hr) and safety follow-up
h) Ophthalmologic assessment at baseline, then in week 4 or 5 (prior to cycle 2 day 1 treatment), and then every 6 weeks ± 7 days irrespective of cycle. Exam includes slit lamp examination, visual acuity testing, visual field testing, intraocular pressure, and indirect fundoscopy
i) Safety follow-up 28 days from the end of study drug administration (± 2 days). AEs (including concomitant medications taken for ongoing AEs) and ongoing anti-neoplastic treatments will be collected for 28 days (±2 days) after the last dose of study drug. Note that pregnancy follow up is required at 120 days (± 2 days) for all subjects of child bearing potential.
j) Patients with significantly impaired hearing must be made aware of potential ototoxicity and may choose not to participate in the study. If those with hearing impairment are included baseline audiograms are recommended and should be followed by repeat audiograms prior to treatment on cycle 2 day 1.
k) Only for patients who sign optional consent. To be drawn prior to treatment and at specified timepoints.
l) Amylase (to be completed within 72 hours prior to receiving treatment)
m) Day 8, 15, and 21 assessments to be completed ± 1 day
n) Only required when patient is taken off study treatment for reasons other than progressive disease and when a radiological scan was not completed within 3 weeks (± 7 days) of this decision.

10.1 Baseline/Pre-Study Evaluations

The study IRB/IEC/REB approved informed consent must be signed and dated before any screening procedures are performed (procedures which are part of the clinical routine during the initial diagnostic work-up of the patient may be performed before obtaining the ICF). A copy of the ICF must be given to the patient or to the person signing the form. Patients who sign the study informed consent but fail to be started on treatment for any reason will be considered a screen failure.

Baseline (pre-study) evaluations are to be conducted within 14 days prior to start of protocol therapy, unless specified differently in the study calendar. Scans and x-rays must be done <28 days prior to the start of therapy. Patients who sign the study informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log.

10.2 Treatment

Carboplatin and pemetrexed are given intravenously on a 3-weekly schedule. Treatment with chemotherapy will start on cycle 1 day 8 following a week of treatment with MEK162 alone.

MEK162 which will be taken orally bid, with the exception of Cycle 1 Day 5 and Cycle 1 Day 15, when only the morning dose of MEK162 will be taken (to allow for pharmacokinetic assessments). In addition, MEK162 will be omitted for 2 days prior to administration of chemotherapy for every cycle. This is to minimize toxicity by allowing a washout period prior to chemotherapy administration with the aim of not compromising benefit. All patients will receive the study drug on a continuous basis with these exceptions. There is no fixed treatment duration; patients may continue treatment with MEK162 until the development of any unacceptable toxicity that precludes any further treatment, disease progression, and/or treatment is discontinued at the discretion of the Investigator or by patient refusal. For details of assessments, refer to section 10.

Patients with significant impaired hearing at baseline must be made aware of potential

ototoxicity and may choose not to participate in the study. If included, baseline audiograms are recommended and should be followed by repeat audiograms prior to treatment on cycle 2 day 1.

Ophthalmologic examination will occur at baseline and if ophthalmologic symptoms occur.

- 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**.
- Images of the ophthalmic exams (at a minimum, OCT and fluorescein angiography) should be sent to the investigative site along with the results of the exam and be maintained in the patient's source document file.
- 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.

Tumor reassessments and CT Thorax, abdomen and pelvis will be performed every 6-8 weeks.

10.3 Specific guidance related to blood pressure

Risk of hypertension has been highlighted on prior studies involving MEK162. Based on the analysis of current available data with MEK162 it appears this risk may be limited to patients with underlying risk factors for hypertension.

Blood pressure must be carefully monitored during the first 2 cycles (49 days) in patients with known underlying risk factors for hypertension at screening.

- Patients must monitor their blood pressure at home or at medical facility at day 10 and day 30 following drug initiation if they meet the following criteria:
    - Patients with history of hypertension and/or
    - Patients receiving antihypertensive drugs before onset of study treatment and/or
    - Patients with a screening systolic blood pressure (SBP) of ≥140mmHg and/or
    - Patients with a screening diastolic blood pressure (DBP) of ≥90mmHg

- The investigator should educate the patient on the signs and symptoms of hypertension and use of the home blood pressure monitor, if applicable. More frequent assessments during the study may also be performed at the discretion of the investigator and if medically indicated.

- Measurements are to be taken at the same time on days 10 and 30 after taking any hypertensive medications and after being at rest for 5 minutes in a sitting position. If SBP ≥160mmHg, or DBP ≥100mmHg, the patient should contact his/her investigator to have an unscheduled visit. At this unscheduled visit, the patient's blood pressure should be assessed formally for grading and these measurements must be documented in the appropriate section of the case report form (CRF). Clinical decisions will be based on the BP assessment performed in clinic. Early

initiation of treatment and aggressive management of emergent hypertension must be implemented after its diagnosis.

- For patients monitoring their blood pressure at home, it is suggested to develop a patient diary to record their self-assessed blood pressure measurements and present the collected data to the investigator for evaluation and appropriate management. This diary must be maintained with the patient's source documentation.

10.4 End of Study Drug Administration and Follow-Up Evaluations

Patients who discontinue study treatment before completing the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the end of treatment (EOT) visit will be performed. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 28 days (+/- 2 days) following the last administration of study treatment.

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

If a withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the EOT CRF page. EOT or premature patient withdrawal is not considered as the end of the study.

Patients will be followed as per section 5.6 and the study calendar above.

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 6-8 weeks. In addition to a baseline scan, confirmatory scans will also be obtained 8 weeks following initial documentation of an objective response.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6-8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 **Definitions**

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with MEK162.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 **Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 **Methods for Evaluation of Measurable Disease**

All measurements should be taken and recorded in metric notation using a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT & MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. CT should be performed with slice thickness of 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

11.1.4 **Response Criteria**

11.1.4.1 **Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study, including baseline. Overall response will not go from PR to SD.

11.1.4.2 **Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 **Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 **Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

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

11.1.6 **Progression-Free Survival**

Progression free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. If such event is not observed after 6 months of follow up, patients are censored.

11.1.7 **Response Review**

All CR and PR responses will be reviewed by an expert independent of the study at the patient's completion of the study by simultaneous review of patient files and radiologic images.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Collection and Reporting

All data obtained in the clinical trial described in this protocol will be reported on eCRFs in the Medidata Electronic Document Capture system (Medidata). Data reported on eCRFs should be consistent with the source documents and verifiable. All data for the primary and secondary endpoints will source verified prior to publication. The Investigator will review the data and electronically sign the eCRFs to acknowledge agreement with the data entered. Data will be entered into Medidata will be used for developing tables and listings for the final study report.

Prior to the start of the study, the Investigator will complete a Site Participant's Log showing the signatures and handwritten initials of all individuals who are authorized to make or change entries on source documents and eCRFs.

12.2 Source Documents

Source documents refer to the original documents, data, and records where the first recording of a data point occurred. Examples of source documentation include, but are not limited to:

Hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)

Please ensure that source document entries are attributable, legible, contemporaneous, original, and accurate. Note that sign-off of source documents should be attributable to a single record and "bracketing" multiple entries on source document pages for a single signature is not allowed. Corrections to source document entries should only be completed by drawing a single line through the previous entry and then recording the corrected data, initialing the change, and dating the change. Only the individual that initially recorded the data should make any corrections.

12.3 Retention of Patient Records and Study Files

The ICH guidance document, Good Clinical Practice: Consolidated Guidelines (ICH Guidance Document E6) (1997) states that the investigator and sponsor shall retain study records relating to the study until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. In the event of a trial discontinuation, sponsor records should also be kept for a minimum of 2 years. Per Health Canada, all original records should be maintained for 25 years after the above requirements are satisfied and the final report has been issued. Records contained in the Clinical Trial Application should be maintained on file for at least 25 years. We will comply with these regulations. The Sponsor will notify sites when documents are to be destroyed.

12.4 Site and Study Closure

Upon completion of the study, the following activities, when applicable, will be completed by the Central Office in conjunction with the Investigator, as appropriate:

- Collection of study materials (i.e., specimen collection kits, drug shippers, etc.)
- Data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and unused study medication
- Review of site study records for completeness

If the Sponsor or Investigator or appropriate regulatory officials identify conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among the Sponsor and Investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study

- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information to the Sponsor, or appropriate regulatory authority
- Insufficient adherence to protocol requirements
- Refusal of the Investigator to supply source documentation of work performed in this clinical trial

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonisation (ICH) sixth efficacy publication (E6) on Good Clinical Practice, Section 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Primary

Phase I

- Development of dose-limiting toxicity (DLT), (defined in section 4.3) as measured with NCI CTCAE v4.0 in cycle 1.
- Adverse events, serious adverse events, changes in hematology and chemistry values, vital signs, ECGs.

Phase Ib

- Objective response rate (ORR) as per RECIST v1.1. ORR is defined as the percentage of patients that have achieved complete or partial response as the overall response.
- Evaluation progression-free survival (PFS) and disease control rate (DCR) for patients with and without KRAS mutation in tumor tissue. PFS is defined as the time from start of treatment to disease progression or death. DCR is defined as the percentage of patients that have achieved either stable disease, partial or complete response as the overall response.

Secondary

Phase I

- Pharmacokinetic profile of MEK162 when administered with carboplatin and pemetrexed.

Phase Ib

- Exploratory analysis of KRAS mutation sub-type.

Exploratory

- A limited sampling strategy pharmacokinetic model will be used to ensure that the clearance of MEK162 is not influenced by the concurrent administration of pemetrexed-based chemotherapy.

13.2 Sample Size/Accrual Rate

Final sample size will be dependent upon the number of dose levels required to reach the RP2D. Once the RP2D is established, at least 6 patients will be enrolled to further evaluate toxicity, response and translational research of this regimen. It is anticipated that 9 to 12 patients will be enrolled in the phase I part of this study. In phase Ib, a total of 30 patients will be enrolled.

Accrual and Duration of Study
It is expected that accrual for the phase I portion of this study will be completed in 36 weeks. For the phase Ib part, the estimated accrual for this study is 3-4 patients per month. Thus, patient accrual for 30 patients is expected to be completed within another 9 months. Additional time is required to allow the response data to mature.

13.3 Analysis of Primary Endpoints

Baseline patient and tumour characteristics, safety and efficacy outcomes will be summarized by dose level and phase, and combined, using descriptive statistics. Time to progression will be estimated using the Kaplan-Meier method. No statistical testing will be performed, except in an exploratory fashion for tertiary analyses. Plots, tables, and listings will be used to improve understanding of the study results. 95% confidence intervals will be constructed for outcomes of interest.

13.4 Stratification Factors

There are no stratification factors for the dose escalation portion of the study. Once RP2D has been identified, an expansion cohort will enrol additional patients stratified by *KRAS* genotype.

Stratification of patients by *KRAS* genotype aims for the targets detailed below:
Wild-type *KRAS:* N=10
KRAS mutant non-G12C: N=10
KRAS mutant G12C: N=10

13.5 Analysis of Secondary Endpoints

Pharmacokinetic parameters will be summarized by dose level and phase, and combined using descriptive statistics. Exploratory analysis of response rate by KRAS genotype will be summarized using descriptive statistics.

If responses are reported as a secondary objective, the following criteria will be used. Every report should contain all patients included in the study. For the response calculation, the report should contain at least a section with all eligible patients. Another section of the report may detail the response rate for evaluable patients only. However, a response rate analysis based on a

subset of patients must explain which patients were excluded and for which reasons. 95% confidence limits will be given.

13.6 Analysis of Exploratory Endpoints

The pharmacokinetic analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable PK data. The PAS will be used for summaries of PK data (Tables and Figures) as well as for listings of derived parameters.

Note: patients will be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of the analyses.

Demographic and other baseline data including disease characteristics will be summarized for all patients in the PAS.

Genomic analysis will be performed on the submitted tumor specimen for each patient and this will be retrospectively analysed for correlation with response data.

The dose-determining set consists of all patients from the safety set who either meet the following minimum exposure criterion and have scheduled safety evaluations, or discontinue earlier due to DLT. A patient is considered to have met the minimum exposure criterion if having received at least 16 out of the 24 planned daily combination doses of MEK162 (bid) in the first 28 days of dosing.

Patients who do not experience DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

Patients who do not meet these minimum safety evaluation requirements will be regarded as ineligible for the dose-determining set and will need to be replaced.

Time to event will be estimated using the Kaplan Meier approach. Groups of different prognosis, in particular KRAS mutation status will be compared with the log rank test.

All conclusions will be based on all eligible patients. Subgroup analyses may be performed including by *KRAS* genotype. Patients may be excluded for major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, etc.). Subgroup analysis of efficacy will be exploratory only, and the reasons for excluding patients from the analysis will be clearly reported. The 95% confidence intervals will be provided.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B DATA MANAGEMENT GUIDELINES

Data Management Guidelines

Case Report Form Submission Schedule

The Registration Checklist will be a paper CRF that will be provided by the Drug Development Central Office and all other data required for the study will be collected in eCRFs in Medidata. The form submission schedule is outlined below.

Case Report Form	Submission Schedule
Registration Checklist	At the time of registration
Baseline Folder	Within 3 weeks of on study date
Cycle Folder	Within 3 weeks of the end of each cycle of treatment
End of Treatment Folder	Within 3 weeks of the patient coming off treatment
Follow-up Folder(s)	Within 3 weeks of the patient coming to clinic
Final Report Folder	Within 3 weeks of the follow-up period being complete or of the patient's death being known to the investigator unless this constitutes a reportable adverse event when it should be reported according to expedited guidelines in Section 7.

Case Report Form Completion

The paper Registration Checklist CRF must be completed using black or blue ink. Any errors must be crossed out so that the original entry is still visible, the correction clearly indicated and then initialed and dated by the individual making the correction. Medidata Rave eCRFs will be completed according to the schedule noted above.

All patient names or other identifying information will be removed prior to being sent to the Central Office and the documents labeled with patient initials, study number and the protocol number if applicable.

Monitoring

This is an investigator initiated study and study monitoring will be performed by the Drug Development Program Central Office or its designate.

Data in the Medidata Rave eCRFs will be monitored on a regular basis (according to the monitoring plan) and quality assurance measures will be performed. Electronic data queries as well as paper query letters may be issued to the site.

Regulatory Requirements

- Please submit all required documents to the DDP Central Office.

- Canadian Principal Investigators must submit a completed Qualified Investigator Undertaking. The signed originals are to be submitted to the DDP Central Office.
- All investigators must have an up-to-date CV (signed within 2 years) on file with the DDP Central Office.
- Laboratory certification/accreditation and normal ranges are required
- Investigators and site staff are required to complete Medidata eCRF training modules depending on delegated tasks
- Consent forms must be reviewed by the Central Office before submission to the local ethics regulatory board (REB/IRB) and must include a statement that 1) information will be sent to and 2) medical records will be reviewed by the DDP Central Office.
- A Membership list of the local ethics board is required.
- A copy of the initial approval letter from the ethics board must be submitted to the DDP Central Office.
- A completed Site Participant List/Training Log is required and must be submitted to DDP
- Continuing approval will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purposes.

Retention of Patient Records and Study Files

ICH Good Clinical Practice guidelines apply to this study. It is the responsibility of the Drug Development Program Central Office to inform the investigator/institution as to when trial-related records are no longer need to be retained. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

APPENDIX C PATIENT DIARY (CYCLE 1)

Daily Drug Administration Diary: Cycle 1

Today's Date: _____Patient Initials:_____ Patient Study ID: _____

INSTRUCTIONS

1. Complete one form for the first cycle of treatment.
2. You will take ____**mg** MEK162 tablet each day (____ mg total dose), twice a day, 1 hour before or 2 hours after food, continuously, except on days 6, 7, 27, and 28 (no dose on these days).
3. On days 5 and 15, you will take your AM dose in the clinic, so please bring your tablets with you.
4. Record the date and time you took the tablet, try take the tablets at the same time each day.
5. On day 8, take MEK162 after chemotherapy.
6. If you vomit after taking a dose, do not take another tablet.
7. Swallow each tablet whole. Do not crush or chew the tablets.
8. If you have any comments or notice any side effects, please record them in the comments column.
9. Please bring this form and your bottle of MEK162 at the end of each cycle.
10. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.

Day	Date	Actual Dose Taken		Time of Dose		Comments
		AM	PM	AM	PM	
1						
2						
3						
4						
5		*		*		* you will take this dose in clinic, please bring tablets with you
6						
7						
8						Take dose AFTER chemotherapy (BID), please bring tablets with you.
9						
10						
11						
12						
13						
14						
15		*		*		*you will take this dose in clinic, please bring tablets with you
16						
17						

18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						

Signature of Reviewer: _____ Date of Review: _____

APPENDIX D PATIENT DIARY CYCLE 2+

Daily Drug Administration Diary: Cycle ___

Today's Date: _____Patient Initials:_____ Patient Study ID: _____

INSTRUCTIONS

1. Complete one form for each cycle of treatment.
2. You will take ____**mg** MEK162 tablet each day (____ mg total dose), twice a day, 1 hour before or 2 hours after food, continuously over a 19 day period.
3. Record the date and time you took the tablet, try take the tablets at the same time each day.
4. On day 1, take MEK162 after chemotherapy.
5. If you vomit after taking a dose, do not take another tablet.
6. Swallow each tablet whole. Do not crush or chew the tablets.
7. If you have any comments or notice any side effects, please record them in the comments column.
8. Please bring this form and your bottle of MEK162 at the end of each cycle.
9. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.

Day	Date	Morning (AM)		Evening (PM)		Comments
		Time	Number of pills	Time	Number of pills	
1						Take dose AFTER chemotherapy (BID), please bring tablets with you.
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						

14						
15						
16						
17						
18						
19						
20						
21						

Signature of Reviewer: _____ Date of Review: _____

APPENDIX E INFORMATION ON POSSIBLE DRUG INTERACTIONS

Permitted Concomitant Therapy requiring Caution and / or Action

MEK162 is a substrate for many CYP isoforms (CYP3A and 1A2 with some involvement of CYP2C isoforms). Although the risk of metabolic interaction caused by an effect on an individual isoform is minimized for MEK162, caution should be used in patients receiving concomitant treatment with other drugs that are either potent inhibitors or inducers of CYP3A, 2C8, 2C9, 2C19, and 1A2.

In vitro data showed that MEK162 is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and thus the use of drugs that are known to inhibit these transporters should be used with caution.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#PgpTransport

MEK162 potentially induces CYP3A4. MEK162 may induce the metabolic clearance of co-medications metabolized by CYP3A4, if sufficiently high concentrations are achieved in vivo. Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with MEK162.
http://medicine.iupui.edu/clinpharm/ddis/table.asp

Drugs with a conditional, possible or known risk to prolong the QT interval and/or induce Torsade de Pointes should be used with caution. See the website from QTdrugs.org Advisory Board of the Arizona CERT.
http://www.crediblemeds.org/everyone/composite-list-all-qtdrugs/

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

[Note to investigators: This appendix includes an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times.]

The patient _____ is enrolled on a clinical trial using the experimental agent **MEK162**. *This form is addressed to the patient, but includes important information for others who care for this patient.*

MEK162 interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

MEK162 interacts with certain specific enzymes in your liver.

- The enzymes in question are ***CYP3A4 and 2C8, 2C9, 2C19, and 1A2.***
- ***MEK162*** potentially inhibits CYP3A4 and may increase clearance of co-medication that is broken down by this enzyme.
- *MEK162* must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.

- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to modify or change any medicines that are considered "strong inducers/inhibitors or substrates of ***CYP3A4 and 2C8, 2C9, 2C19, and 1A2.***
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.

- Please be very careful! Over-the-counter drugs have a brand name on the label—it is usually big and catches your eye. They also have a generic name—it is usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
    - If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
    - If you take herbal medicine regularly: You should not take St. John's wort while you are taking MEK162.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

and he or she can be contacted at

_____

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the experimental agent **MEK162.** MEK162 interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

MEK162 may interact with specific liver enzymes called **CYP1A2, 2C and CYP3A4**, and must be used very carefully with other medicines that interact with these enzymes.

- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP1A2, 2C and CYP3A4**."
- Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____
- and can be contacted at _____**.**

APPENDIX F LISTING OF AGENTS INTERACTING WITH CYTOCRHOME P450

P450 Enzyme	Enzyme Reaction	Substrates			Inhibitors	Inducers
CYP1A2	7-Ethoxyresorufin	Acetaminophen	Caffeine	Imipramine	Furafylline	Charcoal - broiled beef
	0-dealkylation	Acetanilide	Estradiol	Methoxyresofurin	α-Naphthoflavone	Cigarette smoke
		Aromatic amines	Ethoxyresorufin	Phenacetin		Cruciferous vegetables
				Theophylline		Omeprazole
				Warfarin		
CYP2A6	Coumarin	Coumarin			Diethyldithiocarbamate	Barbiturates
	7-hydroxylation	Butadiene			β-Methoxypsoralen	
		Nicotine			Tranylcypromine	
CYP2B6		Cyclophosphamide	Ifosfamide		Orphenadrine	Not known
CYP2C8	Taxol 6-hydroxylalation	Carbamazepine	Taxol		Quercetin	Not known
CYP2C9	Tolbutamide	Diclofenac	Tenoxicam	Tolbutamide	Sulfaphenazole	Rifampin
	Methylhydroxylation	Phenytoin	Tetrahydrocannabinol	Torsemide	Sulfinpyrazone	
		Piroxicam	Tienilic acid	S-Warfarin		
CYP2D19	S-Mephenytoin	Citalopram	Imipramine	Mephobarbital	Tranylcypromine	Rifampin
	4'-hydroxilation	Diazepam	Lansoprazole	Pentamidine		
		Diphenylhydantoin	S-Mephenytoin	Proguanil		
		Hexobarbital	Omeprazole	Propranolol		
CYP2D6	Dextromethorphan	Amiflamine	Encainide	Nortriptyline	Ajmaline	Not known
	O-demethylation	Amitriptyline	Flecainide	Ondansetron	Chinoidine	
		Aprodine	Fluoxetine	Paroxetine	Corynanthe	
		Brofaromine	Flunarizine	Perhexiline	Fluoxetine	
		Bufurolol	Fluphenazine	Perphenazine	Lobelin	
		Captopril	Guanoxan	Propafenone	Propidin	
		Cinnarizine	Haloperidol (reduced)	Propranolol	Quinidine	
		Citalopram	Hydrocodone	N-Propuylajmaline	Trifluperidol	
		Clomipramine	Imipramine	Remoxipride	Yohimbine	
		Clozapine	Indoramin	Sparteine		
		Codeine	Methoxyamphetamine	Thioridazine		
		Debrisoquine	Methoxyphenamine	Timolol		
		Deprenyl	Metoprolol	Tomoxetine		
	Dextromethorphan	Desmethylcitalopram	Mexiletine	Trifluperidol		
	O-demethylation	Desipramine	Mianserin	Tropisetron		
		Dextromethorphan	Miniaprine			

APPENDIX F continued

P450 Enzyme	Enzyme Reaction	Substrates			Inhibitors	Inducers
CYP2E1	Chlorzoxazone 6-hydroxylation	Acetaminophen	Enflurane	Theophylline	3-Amino-1,2,4-triazole	Ethanol
		Alcohols	Halogenated alkanes		Diethyldithiocarbamate	Isoniazid
		Aniline	Isoflurane		Dihydrocapsaicin	
		Benzene	Methylformamide		Dimethylsulfoxide	
		Caffeine	Nitrosamines		Disulfiram	
		Chlorzoxazone	p-Nitrophenol		Phenethyl isothiocyanate	
		Dapsone	Styrene		4-Methylprazole	
CYP3A4	Testosterone 6β-hydroxylation	Acetaminophen	Etoposide	Tacrolimus (FK506)	Clotrimazole	Carbamazepine
		Aldrin	Flutamide	Tamoxifen	Ethinylestradiol	Dexamethasone
		Alfentanil	Hydroxyarginine	Taxol	Gestodene	Phenobarbital
		Amiodarone	Ifosfamide	Teniposide	Itraconazole	Phenytoin
		Astemizole	Imipramine	Teniposide	Ketoconazole	Rifampin
		Benzphetamine	Lansoprazole	Terfenadine	Miconazole	Sulfadimidine
		Budesonide	Lidocaine	Tetrahydrocannabinol	Naringenin	Sulfinpyrazone
		Carbamazepine	Loratadine	Theophylline	Troleandomycin	Troleandomycin
		Cyclophosphamide	Losartan	Toremifene	Activator: α-Naphtoflavone	
		Cyclosporin	Lovastatin	Triazolam	Grapefruit juice	
		Dapsone	Midazolam	Troleandomycin		
		Digitoxin	Nifedipine	Verapamil		
		Diazepam	Quinidine	Zalosetron		
		Erythromycin	Rapamycin	Zonisamide		
		Ethinylestradiol	Retinoic Acid	Diltiazem		
		Omeprazole	Steroids (e.g., cortisol)	Warfarin		

APPENDIX G MANAGEMENT OF DRUG-INDUCED TOXICITY

Patient history of diarrhea

At screening, the patient's history of diarrhea should be reviewed and the patient should be appropriately informed of chemotherapy-induced diarrhea and its' management:

- Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery, abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions;
- Stop all diarrheogenic agents at screening if possible, otherwise exclude from trial;
- Instruct patients regarding risk of developing diarrhea;
- Perform baseline clinical/laboratory studies according to the trial protocol (e.g. one could rule out carrier state of Salmonella spp., Clostridium difficile, Campylobacter spp.,

Proactively investigate for occurrence of diarrhea

Educate patient

1. Remind patients at each visit to contact the site upon signs of loose stool or symptoms of abdominal pain. Additionally, at the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea-related symptoms. If symptoms were experienced by the patient, then the site should question the patient regarding the actions taken for these symptoms and re-instruct as necessary.

2. In addition to dietary modification, the patients should be instructed on early warning signs (e.g. severe cramping → severe diarrhea, fever with diarrhea → infection). Patients should be instructed on what to report to the investigator if possible (i.e. number of stools, stool composition, stool volume) and how to report symptoms of life-threatening sequelae (eg, fever or dizziness on standing).

3. Contact the patient 2 times a week after the start of MEK162 treatment to detect diarrhea early during at least the first 2 cycles. If no problems occur, instruct the patient to call when a problem does arise.

4. Stop all lactose-containing products, alcohol

5. Stop laxatives, bulk fiber (like Metamucil®), and stool softeners (i.e, docusate sodium; (Colace®)

6. Stop high-osmolar food supplements such as i.e, Ensure® Plus and i.e, Jevity® Plus (with fiber)
7. Drink 8 to 10 large glasses of clear liquids per day (like i.e, water, Pedialyte®, Gatorade®, broth)
8. Eat frequent small meals (i.e, bananas, rice, applesauce, toast)

Loperamide supply

It is recommended that patients are provided a sufficient supply of loperamide tablets with the administration of MEK162 at the start of each cycle in case the patient experiences diarrhea. When loperamide is provided to patients, it is mandatory that patients are instructed at each cycle in detail on the use of loperamide in order to manage signs or symptoms of diarrhea at home. The site should ensure that the patient understood the instructions.

Patients should be instructed to start oral loperamide at the first sign of loose stool or symptoms of abdominal pain.

Multiple events of diarrhea may occur throughout the duration of treatment. When each occurrence of diarrhea is first reported, the following steps to manage the event are recommended:

Evaluate condition of patient

- Obtain history of onset and duration of diarrhea including a description of the number of stools and stool composition (e.g. watery, blood or mucus in stool);
- Assess patient for fever, abdominal pain/cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration);
- Obtain medication profile (i.e., to identify any diarrheogenic agents) and dietary profile ((i.e., to identify diarrhea-enhancing foods).
- For study drug dose adjustment see Table 5.3 in the study protocol.
- Analyze the following:
    - Blood from stool;
    - C. difficile toxin;
    - Fecal cultures may be performed if infection is suspected. These may include: Shigella and pathogenic E.coli-enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water).
- Administer intravenous hydration and electrolyte replacement as needed.
- Endoscopic examinations may be considered only if absolutely necessary. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

Loperamide is the recommended first-line treatment of diarrhea (any Grade).

Persistent symptoms may require the administration of high dose loperamide followed by treatment with second-line agents such as opium tincture and octreotide acetate, based on severity and duration of diarrhea and related signs/symptoms.

Upon treatment with any anti- diarrhea agents, the patient's response to treatment should be observed and appropriately documented in the source document and eCRF.

Guidelines for the treatment of study drug combination induced skin toxicity

Skin rash has been observed for MEK162 in the ongoing studies [ARRAY-162-111] and thus is recognized as potential overlapping toxicity associated with the concurrent use of both compounds. The majority of the rash was CTCAE Grade 1 or 2, but also dose-limiting as Grade 3 at the 80mg bid dose for MEK162.

The results of the STEPP study (Mitchell 2009, Piperdi 2009) support the use of pre-emptive skin treatment for patients at risk of treatment induced skin toxicity. In this study, the pre-emptive skin treatment regimen reduced the incidence of specific CTCAE Grade ≥ 2 skin toxicity by more than 50% as compared to the group who received only reactive skin toxicity treatment.

In this study, patients will not initially receive prophylactic treatment for skin toxicity during cycle 1. However, prophylactic treatment for skin toxicity may be introduced in subsequent cycles of treatment and in new patients if at least one patient has experienced CTCAE Grade 3 or greater skin toxicity, or if at least two patients have experienced such toxicities that are CTCAE Grade ≥ 2. Prophylactic supportive therapy for skin toxicity (i.e. initiated 24 hrs prior to study drug combination) including skin moisturizers, sunscreen (PABA free, SPF ≥ 15, UVA/UVB protection), topical steroid (1% hydrocortisone cream), and doxycycline (100 mg BID) may be initiated in all patients at the dose levels where these toxicities have been observed and may be advised to all further patients. Effective medications also include antihistamines, topical corticosteroids and low-dose systemic corticosteroids (the latter should be used with caution due to risk of hyperglycemia).

The treatment algorithm is as follows (See section 5.3):

Mild rash (CTCAE Grade 1)

- Treatment with MEK162 should be maintained at the current dose.
- Topical hydrocortisone (1% or 2.5% cream) for macular rash and/or topical clindamycin ((1%) for pustular rash is recommended.
- The patient should be reassessed after 2 weeks. (

Moderate rash (CTCAE Grade 2)

- Treatment with MEK162 should be maintained at the current dose, and the rash should be closely monitored for change in severity.
- Doxycycline or minocycline are not recommended due to phototoxicity and should be replaced with oxytetracycline or lymecycline. However, if doxycycline or minocycline are used, precaution measurements should be taken (i.e., avoid direct exposure on sun, use of sunglasses, sunscreen, ect.). The recommendation is: topical clindamycin (1%) plus either hydrocortisone (2.5% cream) or pimecrolimus (1% cream) plus

oxytetracycline (500 mg twice daily) or lymecycline (408 mg once daily).

Severe rash (CTCAE Grade 3-4) (CTCAE Grade 3)

Asymptomatic

The dose of MEK162 should be omitted until resolved to CTCAE Grade ≤ 1, in line with protocol recommendations, and the rash should be closely monitored for any change in severity.

In addition to the interventions recommended for moderate rash, prednisolone (25 mg) may be given (with caution due to risk of hyperglycemia).

If asymptomatic skin toxicity CTCAE Grade 3 is not resolved within 48 hrs, discontinue patient from study drug treatment

Symptomatic

If symptomatic skin toxicity CTCAE Grade 3 occurs the dose of MEK162 should be omitted and patients discontinued from study drug treatment.

CTCAE Grade 4

If skin toxicity CTCAE Grade 4 occurs the dose of MEK162 should be omitted and patients discontinued from study drug treatment.

APPENDIX H BLOOD PRESSURE DIARY TEMPLATE

Blood Pressure Diary

Today's Date _____ Patient Initials_____ Patient Study ID _____

INSTRUCTIONS:

1. Complete blood pressure measurements on day 10 and day 30 of treatment and record on this form.
2. Measurements are to be taken at the same time each day, after taking any hypertensive medications.
3. Please bring this form with you at your clinic visits to review with your doctor/nurse.
4. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.

Day	Date	Time	Systolic	Diastolic	Comments
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
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15					
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30					

Physician's Office will complete this section:
Physician/Nurse reviewing diary: _____
Date reviewed: _____