List of Changes

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This amendment is in response to an RA dated 10Dec2018 due to a revision in the CAEPR V 2.5 (18Apr2018). It did not result in any changes to the protocol.

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A8 / 11Jun2018
A9 / 03Jan2019

TITLE: A Randomized Placebo-Controlled Phase II Trial Comparing Gemcitabine Monotherapy to Gemcitabine in Combination with AZD 1775 (MK 1775) in Women with Recurrent, Platinum Resistant Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancers

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NCI-Supplied Agent: *AZD 1775 (MK 1775), NSC#751084;*
Commercially Available Agent: *Gemcitabine*

SCHEMA

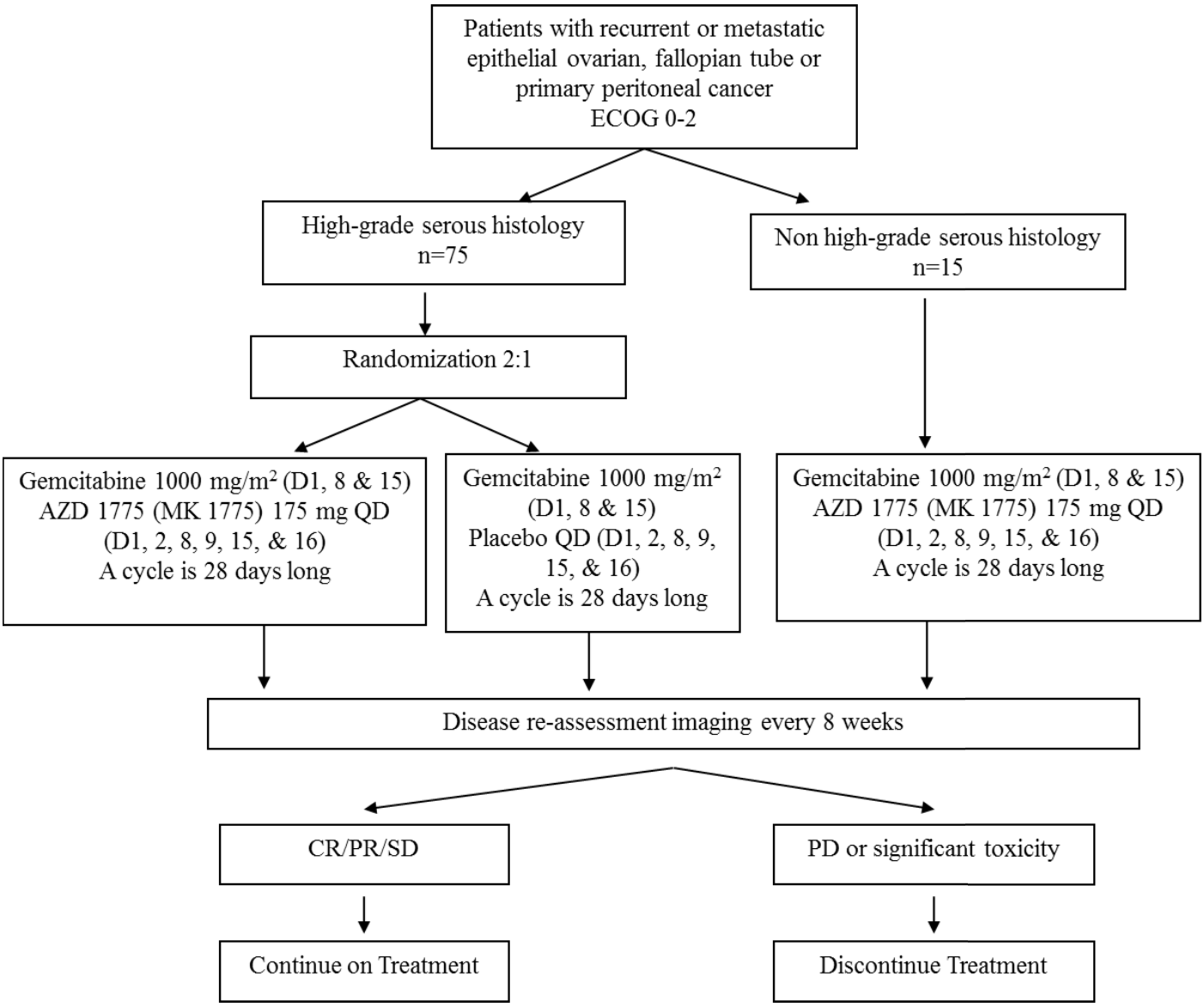
Patients with recurrent or metastatic epithelial ovarian, fallopian tube or primary peritoneal cancer
ECOG 0-2
High-grade serous histology
n=75
Non high-grade serous histology
n=15
Randomization 2:1
Gemcitabine 1000 mg/m2 (D1, 8 & 15)
AZD 1775 (MK 1775) 175 mg QD
(D1, 2, 8, 9, 15, & 16)
A cycle is 28 days long
Gemcitabine 1000 mg/m2
(D1, 8 & 15)
Placebo QD (D1, 2, 8, 9, 15, & 16)
A cycle is 28 days long
Gemcitabine 1000 mg/m2 (D1, 8 & 15)
AZD 1775 (MK 1775) 175 mg QD
(D1, 2, 8, 9, 15, & 16)
A cycle is 28 days long
Disease re-assessment imaging every 8 weeks
CR/PR/SD
PD or significant toxicity
Continue on Treatment
Discontinue Treatment

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

To evaluate the progression free survival (PFS) of subjects with recurrent platinum-resistant ovarian, fallopian tube or primary peritoneal cancer receiving gemcitabine in combination with AZD 1775 (MK 1775) compared to subjects receiving gemcitabine in combination with placebo.

1.2 Secondary Objectives

1. To evaluate the objective response by RECIST 1.1 of patients receiving gemcitabine combined with AZD 1775 (MK 1775) compared to patients receiving gemcitabine in combination with placebo.
2. To evaluate the GCIG CA125 response rate of patients receiving gemcitabine combined with AZD 1775 (MK 1775) compared to patients receiving gemcitabine in combination with placebo.
3. To evaluate the overall survival of patients (max 1-yr follow-up) receiving gemcitabine combined with AZD 1775 (MK 1775) compared to patients receiving gemcitabine in combination with placebo.
4. To evaluate the safety and tolerability of the combination of gemcitabine combined with AZD 1775 (MK 1775) in patients with recurrent, platinum-resistant ovarian, fallopian tube or primary peritoneal cancer.
5. To evaluate *TP53* mutations (presence of mutation and type of mutation) as potential predictive factors of benefit (defined as response or PFS prolongation) to AZD 1775 (MK 1775) and gemcitabine treatment.
6. To evaluate p53 protein expression by immunohistochemistry as potential predictive factors of benefit (defined as response or PFS prolongation) to AZD 1775 (MK 1775) and gemcitabine treatment.

1.3 Exploratory Objectives

1. To evaluate patient reported outcomes using PRO-CTCAE
2. To evaluate the concordance of *TP53* mutations in the tumor specimen and *TP53* mutations determined by tagged-amplicon deep sequencing (TAm-Seq) in circulating tumor DNA.
3. To correlate the levels circulating DNA *TP53* mutations by TAm-Seq with response
4. Validation of pCDC2 and gamma-H2AX in skin and tumour tissue as a pharmacodynamic marker of therapy
5. To correlate changes in pCDC2 and gamma-H2AX with survival outcomes and response rate.

2. BACKGROUND

2.1 Epithelial Ovarian, Primary Peritoneal and Fallopian Tube Carcinoma (10033159, 10026669, and 10016180)

Ovarian cancer is the second most common gynecological malignancy and the leading cause of death from gynecologic malignancy in Canada [1] and US [2], with approximately 20,000 deaths per year. The majority of these cases are (70%) are high-grade serous subtype. Based on their similar histological features and behavior, high grade serous ovarian cancer is closely related to fallopian tube and peritoneal serous carcinoma.

Current initial treatment consists of debulking surgery followed by combination platinum/taxane chemotherapy. In spite of initial response rates as high as 80%, most women relapse. Treatment of recurrent epithelial ovarian cancer depends on the treatment-free interval after primary chemotherapy with a platinum-taxane combination, with evidence of clinical or radiologic disease recurrence. Patients are classified as platinum-sensitive if the disease has recurred at least 6 months after the last platinum containing treatment. Platinum-resistant patients are characterized by a platinum-free interval of less than 6 months; platinum refractory as patients who progress during primary therapy. Platinum-sensitive patients may be re-challenged with platinum based therapy; these patients will ultimately become platinum resistant. For women with platinum resistant disease, preferred therapy is generally single non-platinum agent therapy, such as liposomal doxorubicin, topotecan, taxanes or gemcitabine. The activity of these agents is similar and modest, with an approximate 6 month progression free survival of about 15-25%.[3,4] Novel therapies which act synergistically with conventional chemotherapies are needed to improve response rates and outcomes.

2.2 AZD 1775 (MK 1775)

AZD 1775 (MK 1775) is a selective, small molecule inhibitor of Wee1-Like Protein Kinase. In vitro kinase assays have identified this molecule as a potent inhibitor of Wee1-Like Protein Kinase demonstrating an IC50 value of 5.2nmol/L.[5] Cell-based assays measuring the levels of phosphorylation of CDC2 at tyrosine residue 15 (Tyr 15) confirmed that Wee1-Like Protein Kinase inhibition correlated with inhibited phosphorylation of CDC2.

Cell-based assays in colorectal cell lines demonstrated inhibitory effects of AZD 1775 (MK 1775) in cells pre-treated with several chemotherapy agents namely; gemcitabine, carboplatin and cisplatin, strengthening the hypothesis that Wee1-Like Protein Kinase inhibition abrogates the G2 checkpoint more effectively in combination with chemotherapy.

In the clinical setting, AZD 1775 (MK 1775) has been evaluated in a phase I as single agent and in combination with carboplatin, cisplatin and gemcitabine[6]. In the first 156 patients treated, AZD 1775 (MK 1775) demonstrated acceptable adverse effects to both monotherapy and combination therapy. The most common adverse events were cytopenias, nausea/vomiting, and fatigue. When used in combination with gemcitabine, the maximum tolerated dose (MTD) was 175 mg once daily on days 1, 2, 8, 9, 15, and 16.

2.3 Gemcitabine as Treatment for Platinum-resistant or Platinum-refractory Epithelial Ovarian, Primary Peritoneal and Fallopian Tube Carcinoma

Gemcitabine is a pyrimidine antimetabolite which is phosphorylated into two active drug forms both of which contribute to its antiproliferative effects via the inhibition of ribonucleotide reductase and the incorporation of pyrimidine analogues into DNA thereby causing chain termination[7]. In the platinum-resistant setting, the response rate of gemcitabine (1,000 mg/m2 on days 1, 8, and 15 every 28 days) in phase II and III studies ranges from 12% to 29% .[3,4,8-10] Gemcitabine is one of the recommended treatments in patients with platinum-resistant or refractory epithelial ovarian, primary peritoneal or fallopian tube carcinoma according to the NCCN guidelines. This recommendation is based on the results of two phase III clinical trial in which gemcitabine achieved similar overall survival, progression-free survival and response rate than pegylated-lyposomal doxorubicin.[3,4]

2.4 Rationale

The checkpoint kinases, which include ATR, CHK1 and Wee1-Like Protein Kinase, are important regulators of DNA damage surveillance pathways. Their roles at the various transition points (G1/S, G2/M) of the cell cycle are critical in order for proliferating cells to repair DNA damage accumulated from either endogenous or exogenous sources [11]. Wee1-Like Protein Kinase exerts inhibitory phosphorylation of CDC2 at Tyr14 and Tyr15 which in turn stalls cells at G2/M preventing entry into mitosis. Inhibition of Wee1-Like Protein Kinase releases the inhibition and the decreased levels of pCDC2 allow cells to proceed through mitosis. Cells previously exposed to DNA damaging agents and now under the pressure of Wee1-Like Protein Kinase inhibition would be expected to undergo mitotic catastrophe and apoptosis as a consequence of the accumulation of cytotoxic-induced DNA damage. Malignant cells with ineffective regulation of G1/S transition are therefore heavily reliant on the G2/M checkpoint to allow for repair of critical DNA damage which would otherwise promote mitotic catastrophe, triggering cells to undergo apoptosis. Given this mechanism of action, inhibition of checkpoint kinases active at G2/M (such as Wee1-Like Protein Kinase) are theorized to have synergistic activity with DNA damaging cytotoxics. Preclinical work in a variety of tumor models has been consistent with this hypothesis although the true relevance of functional p53 status is unclear [5,12,13].

Synergy between gemcitabine chemotherapy and AZD 1775 (MK 1775) has been demonstrated in vivo by the sequential treatment of tumour cells with gemcitabine followed by AZD 1775 (MK 1775). The antigrowth effects of gemcitabine, as demonstrated by the IC50 value in cell viability assays and induced cell death were significantly augmented by the sequential administration of AZD 1775 (MK 1775).[14]

Preclinically, the addition of AZD 1775 (MK 1775) to gemcitabine has shown increased activity in platinum resistant ovarian cancer cell lines, as well as in xenografts derived from those cell lines. Considerable synergy between AZD 1775 (MK 1775) and gemcitabine was also seen in gemcitabine resistant and sensitive cell lines [Internal data provided by Merck - Shumway].

In the clinical setting, confirmed partial responses to AZD 1775 (MK 1775) in combination with chemotherapy have been demonstrated in a number of different disease entities in the phase I setting[6]. AZD 1775 (MK 1775) is currently being investigated in patients with relapsed platinum-sensitive ovarian cancer in combination with carboplatin and paclitaxel [NCT01357161]. In the phase I portion of the study with 15 patients, a response rate of 79% has been observed. In an investigator-initiated study investigating AZD 1775 (MK 1775) in combination with carboplatin in patients with refractory or platinum-resistant ovarian cancer, 6 among the 17 evaluable patients achieved a partial response.

2.4.1 *Rationale for the exploratory cohort*

In the current study, only patients with high grade serous ovarian cancer will be considered for the statistical analysis in order to evaluate a more homogenous population in which *TP53* alterations are common. However, there is little preclinical and clinical information available regarding activity of AZD 1775 (MK1775) in combination with chemotherapy in other ovarian cancer histologies. AZD 1775 (MK1775) may sensitize other non-high grade serous ovarian cancer to gemcitabine as these tumors may have TP53 mutations or other alterations in the cell cycle regulation. Patients with non-high grade serous histologies could be enrolled in an exploratory cohort which would not be included in the statistical analysis of the study. Patients enrolled in the exploratory cohort will receive open-label AZD 1775 (MK-1775).

2.5 Correlative Studies Background

2.5.1 *Determination of TP53 mutations on archival tissue*

TP53 mutations appear to be present in early stage tumours suggesting that they are a critical early event in the tumourigenesis of high-grade serous ovarian cancer.[15] *TP53* is mutated in approximately 97% of high-grade serous ovarian cancer (HGSOC) based on the sequencing of DNA from 145 patients with pathologically confirmed cases. [16] This has recently been confirmed by the results from the Cancer Genome Atlas researchers (TCGA) who found *TP53* mutations in 96% of 489 HGSOC samples tested. [17] The high frequency of *TP53* mutations makes HGSOC an ideal target for strategic therapies that selectively enhance chemotherapy effects in p53-deficient cells.

Preclinical evidence suggests that the activity of AZD 1775 (MK 1775) in combination with a DNA damaging agent, such us chemotherapy or radiotherapy, is enhanced in cells with deficient G1. One of the most common alterations inducing G1 checkpoint deficiency is the loss of p53 function. In pancreatic cancer xenografts, a synergistic effect was observed when combining gemcitibine and AZD 1775 (MK 1775). This effect was limited to p53 deficient models.[13]

In the ovarian cancer cell line TOV21G, which has wild-type *TP53*, abolishing *TP53* function by introducing siRNA sensitizes the cell lines to the combination of AZD 1775 (MK 1775) and chemotherapy (internal data from Merck).

This study will evaluate the presence of *TP53* mutations in archival tissue by two techniques: Sanger Sequencing, which would be considered as our reference "gold" standard, and TAm-Seq. The functional implications of these mutations will be assessed case-by-case in the IARC *TP53* database: http://p53.iarc.fr/

Missense, substitution mutations in *TP53* are curated by the IARC according to median level of transcriptional activity derived from 8 independent promoter-specific assays. These assays were conducted by using endogenous mutants, or by transfecting/over-expressing mutant proteins in human or yeast cell systems. Classifiers the IARC database uses include:

- Nonfunctional (< 20% wild-type transcriptional activity)
- Partially functional (20-75% wild-type transcriptional activity)
- Functional (75-140% wild-type transcriptional activity)
- Gain-of-function ("supertrans") (> 140% wild-type transcriptional activity)

	Transcriptional Activity Data
"Nonfunctional" mutations	Nonfunctional
Partially functional mutations	Partially functional
No change in function mutations	Functional
"Gain-of-function" mutations	Supertrans

For statistical purposes, tumors with "*TP53* null" status will be defined as those tumors with *TP53* mutations classified as "Nonfunctional" based on the "Transcriptional Activity Data" according to the IARC *TP53* database.

2.5.2 *Determination of* p53 *protein expression by immunohistochemistry*

The most common type of *TP53* mutation found in HGSO are missense mutations, occurring in about 50% of cases, with null mutations (including nonsense, frame-shift and splice site mutations) accounting for about 30%. [16] The presence of a null mutation, suggested by negative immunostaining, may be a poor prognostic factor with increased risk of recurrence (HR 0.71, 95% CI 0.51–0.99). [18,19] Null mutations might cause loss of p53 function and might be associated to increased activity of AZD 1775 (MK 1775) in combination with gemcitabine. Some missense mutations induce loss of p53 function (complete or partial), while others cause gain of function. As part of the integrated biomarkers in this study, we will evaluate p53 protein expression by immunohistochemistry to correlate with the mutational status of *TP53* and the clinical activity of AZD 1775 (MK 1775) in combination with gemcitabine. Previously described methodology will be used to determine p53 protein expression [20].

2.5.3 *Determination of TP53 mutations in circulating tumor DNA (ctDNA)*

In a recent publication, *TP53* mutations have been identified in both circulating tumor DNA and tumor specimens from group of patients with ovarian cancers by using TAm-Seq. Prospectively, the variation of the levels of *TP53* mutations in circulating tumor DNA in two patients with ovarian cancer reflected the clinical course of the disease. In the current study, we have established collaboration with Dr. James Brenton to perform the determination of *TP53* mutations in circulating tumor DNA. As part of the research biomarker studies, the

mutational status of *TP53* found in circulating DNA will be correlated with the *TP53* mutational status in archival tissue. This correlation would provide evidence whether the determination of circulating tumor DNA would be a feasible non-invasive technique to evaluate the tumor mutational status in the future.

2.5.4 *Pharmacodynamic assessment of AZD 1775 (MK 1775) activity in tumor tissue: pCDC2, Antigen KI-67, gamma-H2AX, phospho-Histone H3, and cleaved-Caspase-3*

From a molecular standpoint, effective Wee1-Like Protein Kinase inhibition with decreased pCDC2 levels would be expected to result in increased phospho-Histone H3, (demonstrating entry into mitosis) and cleaved-Caspase-3 (indicative of apoptosis). In preclinical models, Wee1-Like Protein Kinase inhibition is associated with decreased pCDC2 levels, increased gamma-H2AX (DNA damage marker), phospho-Histone H3 and cleaved-Caspase-3.[21] Tumors treated with AZD 1775 (MK 1775) or AZD 1775 (MK 1775) combined with gemcitabine expressed higher levels of Antigen KI-67 (proliferation marker) in comparison to the gemcitabine arm.
In the clinical setting, AZD 1775 (MK 1775)-induced pCDC2 inhibition in skin has been described. Paired tumor biopsies have been collected in some ongoing clinical trials for pharmacodynamic evaluation in other tumor types, and preliminary results showed target modulation in paired tumor biopsies.[24]

2.5.5 *Other potential baseline predictors of response to AZD 1775 (MK 1775):* Wee1-Like Protein Kinase*, p21, p16, and Rb*

According to the data from The Cancer Genome Atlas, 10% of the analyzed serous ovarian cancers had up-regulation of the WEE1 mRNA. It is still unknown whether the baseline expression of Wee1-Like Protein Kinase influences the activity of AZD 1775 (MK 1775); hence, there is a rationale to evaluate the role of Wee1-Like Protein Kinase expression in a large prospective cohort of patients treated with AZD 1775 (MK 1775) in combination with a DNA damaging agent.

Some partial loss-of-function *TP53* mutations are able to induce p21 expression, which could be detected by immunohistochemistry. We hypothesize that p21 expression might be a sign of G1 checkpoint activity and in tumors expressing p21 might be less effective in comparison to those tumors lacking p21 expression.

According to The Cancer Genome Atlas analysis, 67% of the high grade ovarian cancers had an alteration in the Rb pathway[17]. This could be another mechanism impairing the activity of the G1 checkpoint. Rb and p16 protein expression will be assessed to evaluate the activity of the Rb pathway.

2.5.6 *BRCA mutation status*

There is substantial evidence that high grade serous ovarian cancer patients with *BRCA1* or *BRCA2* germline mutations have better short term survival than non-carriers[25]. This is now a well described prognostic factor. Given the implications for clinical care, identifying genetic

mutations in *BRCA1/2* is now a priority. Data on patient BRCA mutation status will be collected from patients for whom it is known in order to see if there is any difference in response based on BRCA status.

2.6 Patient Reported Outcomes

This protocol will evaluate patient reported outcomes using methodology that has been developed in conjunction with NCI CTEP, with direct patient assessment of toxicity using paper forms or electronic forms through an internet based application.

2.6.1 Exploratory Study Aims:

- Characterize the profile of symptomatic adverse effects associated with treatment with Gemcitabine+MK-1775 vs. Gemcitabine+ placebo across the first three cycles of treatment, using PRO-CTCAE
- Explore the psychometric properties of PRO-CTCAE, with particular attention to its responsiveness to change and interpretations of the minimally important clinical difference in change over time
- Using a shadow design, simulate the effects on clinical decision making at the patient and trial level as a consequence of one or more provisional/proposed schemas for mapping PRO-CTCAE responses into CTCAE clinical grades

Study Design:
Participating sites (Princess Margaret Cancer Centre, Juravinski Cancer Centre, London Regional Cancer Centre) will approach patients who are also able to read and write in English to complete PRO-CTCAE measures (see symptoms for inclusion below) at time points specified on the study calendar (D1 and D15 of each cycle).

Patients who discontinue treatment for toxicity or at their own request will be asked to complete PRO-CTCAE at discontinuation.

Measures:
The following 9 PRO-CTCAE symptomatic toxicities will be evaluated:

Bloating [S]	Anorexia [S,I]
Abdominal pain [S,I]	Diarrhea [S]
Difficulty Swallowing [S]	Mucositis [S,I]
Nausea [S]	Vomiting [F]
Fatigue [S,I]	
PRO-CTCAE Symptom Dimensions: Present/Absent (P); Frequency (F); Severity (S); Interference (I)	

In addition, patients will be asked to list any other symptoms that they may be experiencing. Completion of the 12 PRO-CTCAE items should take approximately 2-3 minutes.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed epithelial ovarian, primary peritoneal or fallopian tube carcinoma. All histologic subtypes of epithelial ovarian cancer are eligible, but only patients with high grade serous ovarian cancer will be considered for the statistical analysis. Non-High Grade Serous Cancers will be allowed in an exploratory cohort.

3.1.2 Patients must be platinum-resistant (platinum-free interval < 6 months) or have platinum-refractory disease as per GCIC criteria. Disease progression has to be radiologic or clinical. Biomarker progression with CA125 after a platinum based regimen would not be sufficient evidence of disease progression; the patients must have had radiological progression to that regimen.

3.1.3 Patients must have 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.

3.1.4 There is no limitation in the number of prior lines of therapy

3.1.5 Patients must have completed any prior chemotherapy, radiotherapy or major surgery at least 4 weeks before receiving study treatment. Ongoing toxicities related to treatment must be ≤ grade 1 and patients with grade 2 alopecia or peripheral neuropathy can also be included. Palliative radiation to <10% of bone marrow is permissible if completed within one week of commencing study treatment as long as the toxicities secondary to palliative radiotherapy are limited to grade 1. The lesions that have received radiation treatment immediately before will be excluded as target lesions. Previously irradiated lesions can be considered as targeted lesions, as long as there is prove of radiological progression.

3.1.6 Age ≥18 years on day of consent. Because no dosing or adverse event data are currently available on the use of AZD 1775 (MK 1775) in combination with gemcitabine in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.7 ECOG performance status ≤ 2 (Karnofsky ≥60%, see Appendix A).

3.1.8 Life expectancy of greater than 3 months

3.1.9 Patients must have normal organ and marrow function as defined below:

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL

- hemoglobin ≥ 90 g/L[2]
- PT, PTT & INR ≤ 1.5 ULN
- total bilirubin ≤ 1.5 × institutional upper limit of normal; unless due to Gilbert's syndrome
- AST(SGOT) & ALT(SGPT) ≤ 3 × institutional upper limit of normal (5x if liver metastases)
- creatinine ≤ 1.5 × institutional upper limit of normal
  OR
- creatinine clearance ≥40 mL/min/1.73 m^2 for patients with creatinine levels above 1.5 x institutional limit of normal.

3.1.10 Patients must be able to tolerate oral medication and not have evidence of active bowel obstruction
Note: patients can have a history of prior bowel obstruction, provided the patient is not having symptoms of bowel obstruction at the time of enrolment and the bowel obstruction is not anticipated to recur during the participation in the study.

3.1.11 Patients must have disease amenable to biopsy and must be willing to undergo a paired biopsy for correlative analyses (the first biopsy within 28 days prior to start of treatment and the second biopsy while on treatment).

3.1.12 The effects of AZD 1775 (MK 1775) on the developing human fetus are unknown. For this reason and because gemcitabine is known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

Women of childbearing potential include women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not post-menopausal. Postmenopause is defined as amenorrhea ≥12 consecutive months. Note: women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, ovarian suppression or any other reversible reason.

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who previously received gemcitabine for the treatment of recurrent disease.

3.2.2 Patients who are receiving any other investigational agents.

[2] Blood transfusions are allowed at any time during the screening, treatment or follow-up period, according to the center recommendations.

3.2.3 Patients with clinically or radiologically unstable brain metastases are excluded from this clinical trial.
Note: Patients with stable brain metastases after treatment, for at least 3 months prior to enrolling on this trial, could participate in the study. Patients should be off, or on a stable dose of steroids.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to AZD 1775 (MK 1775) or gemcitabine.

3.2.5 Patients taking the following prescription or non-prescription drugs or other products (i.e. grapefruit juice) are ineligible: sensitive CYP3A4 substrates, CYP3A4 substrates with a narrow therapeutic index, moderate to potent inhibitors / inducers of CYP3A4. Patients would be eligible if the medications can be discontinued two weeks prior to Day 1 of dosing and withheld throughout the study until 2 weeks after the last dose of study medication. Specifically excluded substances may be listed in the Appendix C.

3.2.6 Pregnant and breastfeeding women are excluded from this study.

3.2.7 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with AZD 1775 (MK 1775). 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.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, myocardial infarction within 6 months, congestive heart failure, symptomatic congestive heart failure, unstable angina pectoris, active cardiomyopathy, unstable ventricular arrhythmia, uncontrolled hypertension, uncontrolled psychotic disorders, serious infections, active peptic ulcer disease, active liver disease or cerebrovascular disease with previous stroke, or psychiatric illness/social situations that would limit compliance with study requirements.

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial. This study is designed to include minorities as appropriate. However, the trial is not designed to measure differences in intervention effects. The population of Southern Ontario is ethnically diverse and 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 race or gender (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 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 Princess Margaret Consortium Central Office will enter eligible patients on study centrally. All sites should call the Study Coordinator (listed on cover page) to verify dose level availabilities. The required forms (Eligibility Checklist) will be provided upon site activation.

Following registration, patients should begin protocol treatment within 7-10 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.

There will be no starter supplies for this study. Patient-specific supplies will be sent at the time of registration and follow-up orders will be placed by the institution PI or Ordering Designee through the on-line ordering system (described in the pharmaceutical section provided).

4.2 Registration Process

Prior to registering a patient, each institution must have submitted all necessary regulatory documentation to the PMH Phase II Consortium Central Office. The eligibility 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
- Eligibility Checklist CRF 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

This is a randomized, placebo-controlled, phase II clinical trial evaluating AZD 1775 (MK-1775)/Placebo in combination with gemcitabine. The study is powered to evaluate efficacy in patients with high grade serous ovarian cancer, as outlined in the statistical section.

An exploratory cohort of patients (maximum of 15) with non-high grade serous histology (including but not limited to clear cell, endometrioid, or adenocarcinoma NOS) will be accrued. Response assessment will be by RECIST and > 4/10 objective responses (if available depending on accrual) will be considered a signal of activity.

Simultaneously, 75 patients with high-grade serous histology will be randomized to Gemcitabine with/without AZD1775 (MK-1775).

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 – Open Arm					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
AZD 1775 (MK 1775)	No premedication required before AZD 1775 (MK 1775)	175 mg (7x25mg capsules)	Oral	Days: 1, 2, 8, 9, 15, 16	28 days
Gemcitabine	Dexamethasone 8 mg PO Prochlorperazine maleate 10 mg orally	1000 mg/m^2 in 250 mL Normal Saline	IV in 30 min	Days 1, 8, 15	

Regimen Description – Blind Arms					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
AZD 1775 (MK 1775) or Placebo	No premedication required before AZD 1775 (MK 1775)/Placebo	175 mg (7x25mg capsules)	Oral	Days: 1, 2, 8, 9, 15, 16	28 days
Gemcitabine	Dexamethasone 8 mg PO Prochlorperazine maleate 10 mg orally	1000 mg/m^2 in 250 mL Normal Saline	IV in 30 min	Days 1, 8, 15	

5.1.1 *AZD 1775 (MK 1775)/Placebo*

AZD 1775 (MK 1775)/Placebo is an oral drug that should be ingested 1 hour before a meal or 2 hours after a meal. The first dose will be taken with the gemcitabine infusion (may be taken before, during or immediately after). The second dose should be taken 24 +/- 3 hours after first dose.

Capsules should not be broken, crushed or chewed. Missed doses should not be made up, resume dosing with the next scheduled dose. If vomiting occurs shortly after dosing, the dose should not be repeated. Patients will be instructed to bring all unused capsules and their medication diary (refer to Appendix D) to each study visit for assessment of compliance

5.1.2 *Gemcitabine*

Gemcitabine will be administered as a 30 minute (+/- 5 minutes) intravenous infusion at a dose of 1000 mg/m^2 on days 1, 8, and 15 of each 28 day cycle. Gemcitabine dose will be recalculated

if the weight on day 1 (all cycles) has changed by >10% from baseline or the last time the gemcitabine dose has been adjusted for weight loss. Patients will receive dexamethasone 8 mg orally and prochlorperazine maleate 10 mg orally prior to the gemcitabine administration. In case of nausea after treatment, the patients will receive prochlorperazine maleate 10 mg every 8 hours if needed. Additional anti-nausea medication, such as 5HT3 inhibitors (ondansetron, granisetron) is allowed.

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of AZD 1775 (MK 1775) with other concomitantly administered drugs through the CYP3A4, 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 the CYP3A4.

The following medications are prohibited: sensitive CYP3A4 substrates, CYP3A4 substrates with a narrow therapeutic index, or moderate to potent inhibitors / inducers of CYP3A4. Aprepitant is also prohibited due to interaction with AZD 1775 (MK 1775). Appendix C presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
  - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation
  - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

5.4 Duration of Follow Up

	Follow-Up Period		
	Survival Follow-Up every 12 weeks (±2	Follow-up for progression every 6-8 weeks (after the 30-37 day	Adverse Event Follow Up**

		weeks), up to 1 year	safety visit), until disease progression* or death (whichever occurs first), up to 1year	
Reason Patients removed from study:	Disease progression	X		X
	Unacceptable adverse events (grade 3 or 4 serious adverse event, related to study drug)	X	X	X
	All other patients	X	X	X

* Can be documented clinically or radiologically
** Follow for AEs until all other follow-up requirements are met. Refer to section 7.5 for guidance in the following of ongoing or new AEs or SAEs

Once the AEs are resolved the patients will undergo telephonic follow-up, or health records search every three months during one year to evaluate overall survival, unless the patients are being seen by the study team for other reasons such as receiving conventional treatment. Patients discontinued due to unacceptable adverse events or patients discontinued due to other reasons different to disease progression would not need telephonic follow-up if they are still being assessed every 6-8 weeks until clinical or radiological evidence of disease progression is observed. Once disease progression is observed, the patients will have telephonic follow-up or health records search every three months, up to one year after the patient's 30-37 day safety visit.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the following criteria apply:

- Death
- Withdrawal from study
- Completion of one year follow-up
- Termination of the study by sponsor 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

6.1 General Guidelines

In addition to the recommendations from the guidelines below, more conservative dose reductions will be allowed upon discussion with the sponsor, if there are concerns of toxicity or if it is believed to be in the best interest of a subject´s safety.

Table 6.1-1: AZD 1775 (MK 1775)/Placebo Dose modifications

Dose Level	AZD 1775 (MK 1775)/Placebo Dose
1	*175 mg, once daily (on days 1, 2, 8, 9, 15, and 16)*
-1	*150 mg, once daily (on days 1, 2, 8, 9, 15, and 16)*

-2	*100 mg, once daily (on days 1,2, 8, 9, 15, and 16)*

Table 6.1-2: Gemcitabine Dose Modifications for Non-Hematological Toxicities and Febrile Neutropenia (in any dosing day) and for Neutropenia and Thrombocytopenia Occurring on Day 1 of any Cycle.

Dose Level	Gemcitabine
1	*1000 mg/m^2*
DL-1	*800 mg/m^2*
DL-2	*600 mg/m^2*

6.1.1 Dose Modifications for Hematological Toxicities

Table 6.1.1-1: Dose Modification for Neutropenia

Neutropenia	Management/Next Dose for AZD 1775 (MK 1775)/Placebo	Management/Next Dose for Gemcitabine
Dose Modification for Neutropenia on day 1 of any cycle – Permanent dose modification		
≤ Grade 1 (<LLN-1.5x 10^9/L)	No change in dose	No change in dose
Grade 2 (<1.5-1.0x10^9 /L)	No change in dose	No change in dose
Grade 3 (<1.0-0.5x10^9/L)	First and second occurrences	
	Hold* until ≤ Grade 2. Resume at one dose level lower	Hold* until ≤ Grade 2 Resume at one dose level lower, if indicated.**
Grade 4 (<0.5x10^9/L)	First and second occurrences	
	Hold* until ≤ Grade 2. Resume at one dose level lower	Hold* until ≤ Grade 2 Resume at one dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should be discussed with PI. Patients may continue therapy if receiving benefit otherwise, patient should discontinue the study. **Patients requiring more than two dose reductions of AZD 1775 (MK 1775)/Placebo or gemcitabine should be discussed with PI. Patients may continue therapy if receiving benefit; otherwise, patient should discontinue the study. The use of GCSF is allowed in patients according to institutional guidelines		
Dose Modification for Neutropenia on day 8 and 15 of any cycle - Temporary dose modification		
≤ Grade 1 (<LLN-1.5x 10^9/L)	No change in dose	No change in dose
Grade 2 (<1.5-1.0x10^9/L)	No change in dose	No change in dose
Grade 3 (<1.0-0.5x10^9/L)	No change in dose	Administer 75% of the dose administered on day 1 of that cycle
Grade 4 (<0.5x10^9/L)	Omit dose for both day 8 and 9, or day 15 and 16 as applicable	Omit dose
Gemcitabine dose reductions due to neutropenia on day 8 or 15 of each cycle are temporary dose reductions. The use of GCSF is allowed in patients according to institutional guidelines.		

Table 6.1.1-2: Dose Modifications for Febrile Neutropenia

Febrile Neutropenia	Management/Next Dose for AZD 1775 (MK 1775)/Placebo	Management/Next Dose for Gemcitabine
Febrile Neutropenia	First and second occurrences	
	Hold* until fever is resolved and neutropenia < Grade2 Resume at one dose level lower, if indicated.**	Hold* until fever is resolved and neutropenia < Grade2 Resume at one dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should be discussed with PI. Patients may continue therapy if receiving benefit otherwise, patient should discontinue the study. **Patients requiring more than two dose reductions of AZD 1775 (MK 1775)/Placebo or gemcitabine should be discussed with PI. Patients may continue therapy if receiving benefit; otherwise, patient should discontinue the study. The use of GCSF is allowed in patients according to institutional guidelines		

Table 6.1.1-3: Dose Modification for Thrombocytopenia

Thrombocytopenia	Management/Next Dose for AZD 1775 (MK 1775)/Placebo	Management/Next Dose for Gemcitabine
Dose Modification for Thrombocytopenia on day 1 of any cycle – Permanent dose modification		
<LLN-100x 10^9/L	No change in dose	No change in dose
<100x 10^9/L-50 x 10^9/L	First and second occurrences	
	Hold* until platelets ≥100 x10^9/L Resume at one dose level lower, if indicated.**	Hold* until platelets ≥100 x10^9/L Resume at one dose level lower, if indicated.**
<50 x 10^9/L	First and second occurrences	
	Hold until platelets ≥100 x10^9/L Resume at one dose level lower, if indicated.**	Hold* until platelets ≥100 x10^9/L Resume at one dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should be discussed with PI. Patients may continue therapy if receiving benefit otherwise, patient should discontinue the study. **Patients requiring more than two dose reductions of AZD 1775 (MK 1775)/Placebo or gemcitabine should be discussed with PI. Patients may continue therapy if receiving benefit; otherwise, patient should discontinue the study.		
Dose Modification for Thrombocytopenia on day 8 or 15 of any cycle – Temporary dose modification		
<LLN-100x 10^9/L	No change in dose	No change in dose
<100x 10^9/L-50 x 10^9/L	No change in dose	Administer 75% of the dose administered on day 1 of that cycle
<50 x 10^9/L	Omit dose for both day 8 and 9, or day 15 and 16 as applicable	Omit dose
Gemcitabine dose reductions due to thrombocytopenia on day 8 or 15 of each cycle are temporary dose reductions.		

Note: no dose modifications were required for leukopenia, lymphopenia or anemia.

6.1.2 Dose Modifications for Non-Hematological Toxicities

Table 6.1.2-1: Dose Modification for Nausea (despite optimal treatment)

Nausea	Management/Next Dose for AZD 1775 (MK 1775)/Placebo	Management/Next Dose for Gemcitabine
Grade 1 or 2 (after optimal management)	No change in dose	No change in dose
Grade 3 (after optimal management)	First and second occurrences	
	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**	Hold* until ≤ Grade 2 Resume at one dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should be discussed with PI. Patients may continue therapy if receiving benefit otherwise, patient should discontinue the study. **Patients requiring more than two dose reductions of AZD 1775 (MK 1775)/Placebo or gemcitabine should be discussed with PI. Patients may continue therapy if receiving benefit; otherwise, patient should discontinue the study Recommended management: antiemetics and intravenous hydration if required Note: Optimal treatment include: ondansetron, granisetron or similar agent, dexamethasone and metoclopramide or olanzapine (The use of Aprepitant is prohibited due to its interaction with AZD 1775 (MK 1775))		

Table 6.1.2-2: Dose Modification for Vomiting

Vomiting	Management/Next Dose for AZD 1775 (MK 1775)/Placebo	Management/Next Dose for Gemcitabine
≤ Grade 1 (1-2 episodes in 24 h)	No change in dose	No change in dose
Grade 2 (3-5 episodes in 24 h) despite optimal treatment	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at same dose level
Grade 3 (≥6 episodes in 24 hrs; tube feeding, TPN or Hospitalization indicated) despite optimal treatment	First and second occurrences	
	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**
Grade 4 despite optimal treatment	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should be discussed with PI. Patients may continue therapy if receiving benefit otherwise, patient should discontinue the study. **Patients requiring more than two dose reductions of AZD 1775 (MK 1775)/Placebo or gemcitabine should be discussed with PI. Patients may continue therapy if receiving benefit; otherwise, patient should discontinue the study. Recommended management: antiemetics and intravenous hydration if required Note: Optimal treatment include: ondansetron, granisetron or similar agent, dexamethasone and metoclopramide or olanzapine (The use of Aprepitant is prohibited due to its interaction with AZD 1775 (MK 1775))		

Table 6.1.2-3: Dose Modification for Diarrhea

Diarrhea	Management/Next Dose for	Management/Next Dose for

	AZD 1775 (MK 1775)/Placebo	Gemcitabine
Grade 1 or 2 (after optimal management)	No change in dose	No change in dose
Grade 3 (after optimal management)	First and second occurrences	
	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**	Hold* until ≤ Grade 2 Resume at one dose level lower, if indicated.**
Grade 4 (after optimal management)	Off protocol therapy	Off protocol therapy

*Patients requiring a delay of >2 weeks should be discussed with PI. Patients may continue therapy if receiving benefit otherwise, patient should discontinue the study.
**Patients requiring more than two dose reductions of AZD 1775 (MK 1775)/Placebo or gemcitabine should be discussed with PI. Patients may continue therapy if receiving benefit; otherwise, patient should discontinue the study.

Recommended management: Loperamide antidiarrheal therapy
Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours)
Adjunct anti-diarrheal therapy is permitted and should be recorded when used.

Table 6.1.2-4: Other Non-Hematological Toxicities:

Event	Management/Next Dose for AZD 1775 (MK 1775)/Placebo	Management/Next Dose for Gemcitabine
Grade 1 or 2	No change in dose	No change in dose
Grade 3	First and second occurrences	
	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**	Hold* until ≤ Grade 2 Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy

*Patients requiring a delay of >2 weeks should be discussed with PI. Patients may continue therapy if receiving benefit otherwise, patient should discontinue the study.
**Patients requiring more than two dose reductions of AZD 1775 (MK 1775)/Placebo or gemcitabine should be discussed with PI. Patients may continue therapy if receiving benefit; otherwise, patient should discontinue the study.

This table only applies to non-hematological adverse events considered related to the study medication and considered clinically significant as per investigator judgment. Clinically non-significant, treatable or reversible lab abnormalities including, but not limited to alkaline phosphatase or gamma-glutamyl transferase, uric acid, or electrolytes abnormalities does not require dose modifications.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

NOTE: Many adverse events on this CAEPR are treatment-emergent events that have been observed in trials of AZD1775 in combination with chemotherapy including carboplatin, cisplatin, gemcitabine, 5-fluorouracil, paclitaxel, or topotecan. There are limited adverse event data reported with monotherapy of AZD1775 at this time.

7.1.1 CAEPRs for CTEP IND Agent

7.1.1.1 CAEPR for AZD 1775 (MK 1775)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 213 patients.* Below is the CAEPR for AZD1775 (MK-1775).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple

investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, April 18, 2018[1]

Adverse Events with Possible Relationship to AZD1775 (MK-1775) (CTCAE 5.0 Term) [n= 213]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Atrial fibrillation	
		Supraventricular tachycardia	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (hepatitis)	
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection[2] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Lymphocyte count decreased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		***Back pain (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		
	Headache		***Headache (Gr 2)***
		Intracranial hemorrhage	
PSYCHIATRIC DISORDERS			

Adverse Events with Possible Relationship to AZD1775 (MK-1775) (CTCAE 5.0 Term) [n= 213]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Hypoxia	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash[3]		***Rash[3] (Gr 2)***
VASCULAR DISORDERS			
		Phlebitis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[3]Rash may include rash, erythema, eczema, and rash maculo-papular.

[4]Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy.

[5]Acute kidney injury includes renal impairment and acute renal insufficiency.

Adverse events reported on AZD1775 (MK-1775) trials but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD1775 (MK-1775) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Blood and lymphatic system disorders - Other (thrombocytosis); Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Myocardial infarction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Ear pain; Hearing impaired; Tinnitus
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (eye swelling); Eye pain; Keratitis; Photophobia; Scleral disorder; Vision decreased; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Belching; Bloating; Cheilitis; Colitis; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Flatulence; Gastric ulcer; Gastritis; Hemorrhoids; Lower gastrointestinal hemorrhage; Oral pain; Rectal hemorrhage; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema trunk; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (catheter site pain); Infusion site extravasation; Malaise; Non-cardiac chest pain; Pain
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (excoriation); Injury, poisoning and procedural complications - Other (ligament sprain)
INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (blood urea increased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Alkalosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Bone pain; Flank

pain; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (groin pain); Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (carcinoid tumor); Tumor pain
NERVOUS SYSTEM DISORDERS - Central nervous system necrosis; Cognitive disturbance; Dysesthesia; Encephalopathy; Lethargy; Nervous system disorders - Other (hemiparesis); Paresthesia; Peripheral neuropathy[4]; Presyncope; Somnolence; Syncope
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression
RENAL AND URINARY DISORDERS - Acute kidney injury[5]; Hematuria; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema; Reproductive system and breast disorders - Other (female genital tract fistula)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Bronchopulmonary hemorrhage; Epistaxis; Hiccups; Nasal congestion; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory, thoracic and mediastinal disorders - Other (diaphragmalgia); Voice alteration; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Bullous dermatitis; Dry skin; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin ulceration; Urticaria
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: AZD1775 (MK-1775) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2 Adverse Event List for Gemcitabine

ORGAN SITE	SIDE EFFECT	(%)	ONSET		
Cardiovascular	Arrhythmia	(rare)		E	
	Arterial thromboembolism	(rare)		E	
	Heart failure	(rare)		E	
	Hypertension	(<2%)		E	
Dermatological	Alopecia	(14%)		E	
	Rash	(25%) (may be severe)		E	
Gastrointestinal	Constipation	(8%)		E	
	Diarrhea	(12%)		E	
	Mucositis	(8%)		E	
	Nausea, vomiting	(64%)	I		
General	Edema	(20%)		E	
	Fatigue		I		
	Flulike symptoms	(37%)	I		
	Other (radiosensitizer)			E	
Hematological	Hemolytic uremic syndrome	(<1%)		E	
	Myelosuppression ± infection, bleeding	(25%) (severe)		E	
Hepatobiliary	↑ LFTs	(68%)		E	

		(10% severe)			
Hypersensitivity	Hypersensitivity	(rare)	I		
	Infection Infection	(9%) (severe 1%)		E	
	Injection site Injection site reaction	(4%)	I		
Musculoskeletal	Musculoskeletal pain	(16%)	I		
Nervous System	Headache			E	
	Peripheral neuropathy	(3%)		E	
	Somnolence	(9%)		E	
Renal	Creatinine increased	(7%)		E	
	Proteinuria	(36%)		E	
Respiratory	Adult respiratory distress syndrome (ARDS)	(rare)		E	
	Dyspnea	(8%)	I		
	Pneumonitis	(rare)		E	
Vascular	Capillary leak syndrome	(rare)		E	D
	Gangrene	(rare)		E	
	Vasculitis	(rare)		E	

"Rare" may refer to events with < 1% incidence
I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months)

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 until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm .

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **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.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients. Once the electronic version of the CTEP-AERS report is submitted to the PMH Phase II Consortium Central Office it will be reviewed prior to being forwarded to NCI.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

In order to ensure the timely fulfillment of both US and Canadian IND regulatory reporting requirements, all CTEP-AERS reports must be sent to the PMH Phase II Consortium Central Office within 3 working days from the date the event was known to the investigator.

- In the unlikely event that an adverse event occurs that does not meet the reporting requirements for CTEP-AERS, but does meet the definition of a Serious Adverse Event, a CTEP-AERS report must still be completed and sent to the Central Office

within 3 working days of the event being known to the investigator. The event must be telephoned or e-mailed to Central Office within 1 working day.

- The PMH Phase II Consortium Central Office will be responsible for reporting to Canadian regulatory authorities all Serious Adverse Events that are both unexpected and related to study drug. The Central Office will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities in Canada from this trial or from other clinical trials as reported to the Central Office by the NCI U.S.

Investigators must notify their local Research Ethics Boards (REB/IRBs), according to their guidelines, of all SAE reports from their centre and file the report in their regulatory study binder. In addition, all reports sent out to centres by the PMH Phase II Consortium Central Office must be sent to local REB/IRBs, according to their guidelines. Documentation from the REB/IRB of receipt of these reportable events must be kept on file in each institution's regulatory binder.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days

Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.5 Follow Up of AEs and SAEs

Ongoing SAEs and AEs should be followed until they are resolved (return to normal or baseline values), stabilized, improve to < Grade 2, the patient is lost to follow-up and cannot be contacted, or the patient has withdrawn consent. 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.

The following table describes the frequency of AE follow up after the 30-37 day safety follow-up visit:

End of Treatment Reason	AE Follow-up Frequency
Disease progression (radiological or clinical)	Every 3 months for: – any ongoing or new Grade 3+ SAEs

	thought to be related to study treatment – any ongoing or new Grade 2 AEs that are related to study treatment AND result in hospitalization
Unacceptable adverse event(s)	Every month for: – any ongoing or new Grade 3+ SAEs thought to be related to study treatment – any ongoing or new Grade 2 AEs that are related to study treatment AND result in hospitalization
All other reasons	Every 3 months for: – any ongoing or new Grade 3+ SAEs thought to be related to study treatment – any ongoing or new Grade 2 AEs that are related to study treatment AND result in hospitalization

7.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

8.1 AZD 1775 (MK 1775) (NSC 751084)

Chemical Name: 2-allyl-1-[6-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]-6-[4-(4-methylpiperazin-1-

yl)anilino]pyrazolo[3,4-d]pyrimidin-3-one hemihydrate

Other Names: AZD-1775 (MK 1775)

Classification: inhibitor of Wee1-kinase

CAS: 1277170-60-1

Molecular Formula: $C_{27}H_{32}N_8O_2 \cdot 0.5H_2O$ **M.W.:** 500.6

Approximate Solubility: Aqueous solubility is 0.02 mg/mL

Mode of Action: AZD 1775 (MK 1775) is an inhibitor of the Wee1-kinase. Wee1 is a tyrosine kinase upstream of CDC2 thereby involved in regulation of cell cycle checkpoints, particularly the G2 checkpoint. As the majority of human cancers harbor abnormalities in the p53 pathway they become more dependent on S- and G2-phase checkpoints. In preclinical models, AZD 1775 (MK 1775) selectively enhanced chemotherapy-induced death of cells deficient in p53 signaling.

Description: AZD 1775 (MK 1775) is a crystalline, non-hygroscopic, hemihydrate of the neutral drug. It dehydrates upon heating leading to formation of a crystalline anhydrate.

How Supplied: AZD 1775 (MK 1775) (NSC 751084) and matching Placebo will be provided free of charge by Merck or Astra Zeneca and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

The capsule consists of a roller compacted granule of AZD 1775 (MK 1775), lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate. The granule is lubricated with a further quantity of magnesium stearate prior to encapsulation of the granule. The placebo capsule is identical with the omission of AZD 1775 (MK 1775).

Open label AZD1775 (MK-1775) will be in high density polypropylene (HDPE) bottles of 20 – 25 mg capsules with a child-resistant cap and tamper evident seal.

Blinded AZD 1775 (MK 1775) and matching Placebo will be supplied in bottles containing 45 – 25 mg capsules of AZD 1775 (MK 1775) or 45 – 0 mg capsules (Placebo for AZD 1775 (MK 1775)) with a child-resistant cap and tamper evident seal.

Storage: Store bottles at 2 to 30˚C (36 to 86˚F). Do not freeze.

Stability: Shelf life studies of AZD 1775 (MK 1775) are on-going.

Administration: Take AZD 1775 (MK 1775) /placebo on an empty stomach, 1 hour prior or 2 hours after a meal.

Potential Drug Interactions: In human liver microsomes, AZD 1775 (MK 1775) is primarily

metabolized by CYP450 3A4, so exercise caution in patients taking 3A4 inhibitors and inducers. It is also a weak reversible inhibitor of CYP2C8, 2C9, 2C19 and 3A4. Avoid concomitant medications with a narrow therapeutic window that are substrates for these isoforms. AZD 1775 (MK 1775) is a p-glycoprotein substrate.

In vitro transporter studies have shown that AZD1775 (MK-1775) was an inhibitor of OATP1B1, OATP1B3, MATE1, MATE2K, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and a substrate for P-gp and BCRP. The PK parameters of AZD1775 (MK-1775) could be altered if AZD1775 (MK-1775) is coadministered with P-gp and BCRP inhibitors/inducers, and there is potential for drug-drug interactions when coadministered with OATP1B1, OATP1B3, MATE1, MATE2K, P-gp and BCRP substrates. This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins. Modelling has predicted a substantial increase in the exposure of atorvastatin when coadministered with AZD1775 (MK-1775) and the use of atorvastatin is therefore prohibited.

Contraindications: Treatment with AZD 1775 (MK 1775) is contraindicated in subjects with hypersensitivity to any component of the drug. Developmental and reproductive toxicity studies of AZD 1775 (MK 1775) have not been performed. AZD 1775 (MK 1775) is not to be given to women who are pregnant or breast feeding. Women of child-bearing potential participating in clinical studies of AZD 1775 (MK 1775) must use appropriate contraception throughout the study including abstinence and double barrier methods throughout treatment. Refer to Section 3.1.12 for more details about appropriate contraceptive methods and duration of use.

8.1.1 *Agent Ordering:*

No blinded or open label starter supplies will be available for this study. Blinded patient-specific clinical supplies will be sent to the registering investigator at the time of registration and should arrive within approximately 7 to 10 days. Patients will be registered by the PMH Phase II Consortium Central Office. The assigned patient ID number must be recorded by the registering institution at the time of registration for proper clinical supply dispersion. Once a patient has been registered, the PMH Phase II Consortium Central Office will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the PMH Phase II Consortium Central Office the day the patient is registered and will be processed by PMB the next business day and shipped the following business day. Shipments within United States will be sent by FedEx Ground (up to five day delivery) and shipments to Canada will be sent by FedEx (generally one to two day delivery). Thus, if a patient is registered on Monday, PMH Phase II Consortium Central Office would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. United States clinical sites could expect to receive their order approximately Monday or Tuesday (depending on the FedEx Ground service) and Canadian clinical sites could expect to receive their order either Thursday or Friday. NOTE: An account number is not needed for regular (FedEx Ground) shipments.

Blinded Clinical Supplies
The initial request will be for 2 bottles of AZD 1775 (MK 1775) or matching placebo, a quantity

sufficient for 2 cycles of therapy. Six (6) weeks after the initial electronic request [i.e., two (2) weeks before needed], sites may reorder an additional 2 bottles of AZD 1775 (MK 1775) or matching placebo by placing an order through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. The assigned patient ID number and the patient initials must be entered in the "Patient or Special Code" field. A separate order is required for each patient ID being ordered. All drug orders will be shipped directly to the physician responsible for treating the patient.

Blinded Patient-Specific Bottle Labeling
Each patient-specific bottle will be labeled with:

- the protocol number (i.e., "9568")
- the bottle number (i.e., "Bottle 1 of 2" and "Bottle 2 of 2")
- the number of capsules (i.e., "45 capsules")
- the patient ID number (e.g.,"093-XXX", where "XXX" represents a unique patient identifier assigned at registration)
- the patient initials (i.e., Last Initial, First initial, Middle initial [e.g., "LFM"])
- the agent identification (i.e., "AZD 1775 (MK 1775) 25 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take __ capsules daily.")
- storage instructions (i.e., "Store at controlled room temperature, not to exceed 30 ºC)."
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2014 = 14, 2015 = 15) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2014 would have a Julian date of '14001' and a bottle labeled and shipped on December 31, 2014 would have a Julian date of '14365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both AZD 1775 (MK 1775) and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind. The Julian Date / order number should be recorded in the "Lot No." field on the NCI Agent Accountability Form (DARF).

Open Label Clinical Supplies
The initial request will be for 6 bottles of AZD1775 (MK-1775), which provides enough study drug for 2 cycles. Six (6) weeks after the initial electronic request [i.e., two (2) weeks before needed], sites may reorder an additional 6 bottles of AZD1775 (MK-1775) by placing an order through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. The assigned patient ID number and the patient initials must be entered in the "Patient or Special Code" field. A separate order is required for each patient ID number being ordered. All drug orders will be shipped

directly to the physician responsible for treating the patient.

Open-label Patient-Specific Bottle Labeling
Each patient-specific bottle will be labeled with:

- the protocol number (i.e., "9568")
- the bottle number (i.e., "Bottle 1 of 6" and "Bottle 2 of 6", etc.)
- the number of capsules (i.e., "20 capsules")
- the patient ID number (e.g.,"093-xxx", where "xxx" represents a unique patient identifier assigned at registration)
- the patient initials (i.e., Last initial, First initial, Middle initial [e.g., "LFM"])
- the agent identification (i.e., "AZD1775 (MK-1775) 25 mg")
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take __ capsules daily.")
- storage instructions (i.e., "Store at 2° - 30°C (36° - 86°F). DO NOT FREEZE.)."
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2014 = 14, 2015 = 15) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2015 would have a Julian date of '15001' and a bottle labeled and shipped on December 31, 2015 would have a Julian date of '15365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both AZD1775 (MK-1775) and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind. The Julian Date should be recorded in the "Lot No." field on the Oral NCI Agent Accountability Form (DARF).

8.1.2 *Agent Inventory Records*

Agent Accountability:
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition and return of all drugs received by the PMB using the Drug Accountability Record Form for Oral Agents (Oral DARF) available on the NCI home page (http://ctep.cancer.gov).

Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI Oral DARF. A separate NCI Drug Accountability Record Form for Oral Agents must be maintained for each patient ID number (e.g., "093-XXX") on this protocol. The combination Julian date / order number in the upper right hand corner of the patient-specific bottle label (e.g., 10365-9999) should be recorded as the lot number.

Agent Returns:
Only undispensed drug supplies (no partial bottles) should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Agent Transfers:
Bottles may **NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the registering investigator for a given patient changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number (240) 276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov).

For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.3 *Emergency Un-blinding Procedures*

Examples of emergencies include which could result in un-blinding the patient:
1) A life threatening unexpected adverse event that is at least possibly related to the investigational agent and for which un-blinding would influence treatment decisions
2) A medication error, such as an accidental overdose.

Contact the Approving Physician (Dr. Amit Oza; 416-946-2818; amit.oza@uhn.ca) outlining the request for the Emergency Un-blinding. If an Executive Officer cannot be reached, contact the PMH Phase II Consortium Central Office and they will contact the Approving Physician or the alternate (Dr. Moore). Note: The Central Office cannot give permission for un-blinding; only a GROUP Approving Physician can authorize emergency un-blinding.

The following information will be required when contacting the Approving Physician:
- Study number (i.e., "PHL-093")
- Patient ID number (e.g., "093-XXX")
- Patient initials
- Institution name
- Name and telephone number of treating physician
- Name and telephone number of person requesting the un-blinding procedure
- Name and telephone number of contact person to inform of treatment assignment
- Reason for emergency un-blinding

After authorization by a designated Approving Physician, the treatment assignment will be provided to the contact person by the PMH Phase II Consortium Central Office.

Note that once a subject is un-blinded, they are permanently removed from the study.

8.2 Gemcitabine

Product description*:* Gemcitabine is a novel deoxycytidine analogue, a pyrimidine antimetabolite related to cytarabine.Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and also blocking the progression of cells through the

G1/Sphase boundary. Gemcitabine is a prodrug and is metabolized intracellularly to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effects of gemcitabine are exerted through dFdCDP inhibition of ribonucleotide reductase and incorporation of dFdCTP into DNA, resulting in inhibition of DNA synthesis and induction of apoptosis.

Please refer to the product monograph for information regarding possible side effects and instructions, formulation, preparation, handling, shelf life and storage.

Route of administration: To be administered as an intravenous infusion, following dilution in 250 mL IV Normal Saline. Care should be taken to avoid contact with the skin or mucous membranes.

Agent Ordering: Gemcitabine is commercially available as 200 mg and 1 gram vials.

9. BIOMARKER, CORRELATIVE AND SPECIAL STUDIES

Table 9-1: Biomarker Summary

Biomarker	Tissue Specimen	Technique	Integral / Integrated / Research	
TP53 mutation	Archival tissue	Sanger sequencing	Integrated	
TP53 mutation	Archival tissue ctDNA	TAm-Seq	Integrated	
p53 protein expression	Archival tissue	IHC	Integrated	
Wee1-Like Protein Kinase expression	Archival tissue Baseline biopsy	IHC	Exploratory	
pCDC2	Paired biopsies: -tumor -skin	Immunofluorescence	Exploratory	
Antigen KI-67	Paired tumor biopsies	Immunofluorescence	Exploratory	
gamma-H2AX	Paired tumor biopsies	Immunofluorescence	Exploratory	
phospho-Histone H3	Paired tumor biopsies	Immunofluorescence	Exploratory	
cleaved-Caspase-3	Paired tumor biopsies	Immunofluorescence	Exploratory	
Intratumoral pharmacokinetics	Biopsy # 2 (on treatment biopsy)	Pharmacokinetics	Exploratory	https://www.ncb

				i.nlm.nih.gov/pmc/articles/PMC6644066/
Plasma pharmacokinetics	Plasma	Pharmacokinetics	Exploratory	

9.1 Biomarker Studies

9.1.1 Biomarker Studies Archival tissue

Paraffin embedded archival blocks are preferred. However if blocks cannot be released, 20 unstained slides 4-5 microns each mounted on positively charged slides are also acceptable. If not tissue is available for this analysis, the baseline biopsy will be used for the evaluation of these biomarkers according to the priority described in Table 9-1.

9.1.1.1 *Determination of TP53 mutations on archival tissue*

Hypothesis: Certain *TP53* mutation might be associated to deficient G1 checkpoint. Tumors with deficient G1 checkpoint might be more sensitive to the combination of gemcitabine + AZD 1775 (MK 1775).

Rationale for this biomarker analysis has been provided in Section 2.5.1

TP53 mutations will be determined by two different techniques: Sanger sequencing (integrated biomarker) and tagged-amplicon deep sequencing methodology (TAm-Seq) (research biomarker), to correlate with the mutations found in circulating tumor DNA. Exons 5 to 8 of *TP53* will be sequence by Sanger direct sequencing; Targeted re-sequencing of exons 2-11 will be performed by TAm-Seq.

Sanger sequencing will be performed at Dr. Suzanne Kamel-Reid's lab (CLIA certified lab) and TAm-Seq re-sequencing will be performed at Dr. James Brenton's lab (Cambridge Research Institute, UK).[22] This biomarker will be ideally analyzed in all patients to evaluate the role of *TP53* mutations as predictors of response to the combination of gemcitabine and AZD 1775 (MK 1775).

9.1.1.2 *Determination of p53 protein expression by immunohistochemistry*

Hypothesis: different p53 staining patterns may correlate with the underlying *TP53* mutations.

In a recent communication, Kobel M., Brenton J. et al.[23] had scored the p53 expression of a collection of 224 ovarian cancer samples using a 4-tier system: complete absence, wild type pattern (nuclear staining of variable intensity from 1-70%), overexpression (>70% strong nuclear staining), and cytoplasmic staining. Aberrant expression combined overexpression, complete absence and cytoplasmic expression patterns. Overexpression was scored to indicate missense mutation while complete absence or cytoplasmic expression was scored as possible indel, nonsense or splicing mutation. Immunohistochemistry for p53 performed on a Leica Bond Max platform using DO-7 DAKO monoclonal antibody, correctly predicted the presence of *TP53* mutation in 92% (sensitivity 96%, specificity 82%, positive predictive value 93%, negative predictive value 88%) and the type of mutation in 94% of cases (sensitivity 98%, specificity 88%, positive predictive value 94%, negative predictive value 94%).

The following evaluations/correlations will be performed as part of the current protocol:

- Retrospectively correlation of the p53 expression by immunohistochemistry and the *TP53* mutational status.
  We will evaluate the compliance of the 3-tier system initially described by Kobel et al[18] and the new 4-tier system described for Kobel, Brenton et al[23].
- Evaluation of p53 protein expression by immunohistochemistry as potential predictive factors of benefit (defined as response or PFS prolongation) to AZD 1775 (MK 1775) and gemcitabine treatment.

Immunohistochemistry will be performed at the Drug Development Program Lab (Dr. Ming S. Tsao). Dr. Tsao and his group have extensive experience on biomarker evaluation by immunohistochemistry. Dr. Tsao has previously evaluated the role of p53 protein expression in non-small cell lung cancers.[20] Additional information on procedures and analysis are described in the standard operating procedures and lab manual.

9.1.1.3 *Other potential baseline predictors of response to AZD 1775 (MK 1775)*

As research biomarkers, the expression of Wee1-Like Protein Kinase, p21, Rb, and p16 will be evaluated. The rationale for this evaluation has been provided in Section 2.5. These exploratory analyses will be performed at the Drug Development Program Laboratory.

Wee1-Like Protein Kinase

- *Hypothesis*: baseline Wee1-Like Protein Kinase expression (in archival tissue and baseline biopsy) might correlate with benefit from the treatment combination.

p21

- *Hypothesis*: p21 expression might be a useful biomarker to identify tumors with *TP53* mutations, but proficient G1 checkpoint.

Rb and p16

- *Hypothesis*: Rb and p16 immuno-staining might identify tumors with deficient G1 checkpoint by dysfunction of the Rb pathway.

9.1.2 Pre- and on-Treatment Fresh Tumor Tissues

Fresh tumor tissues will be collected on 2 occasions only if there is no medical contraindication:

- **Within 28 days prior to day 1 (Biopsy # 1) after having signed the informed consent**
- **On cycle 1 day 2 or 9 post AZD 1775 (MK 1775) (Biopsy # 2); ± 24 hours window is allowed**

**Screening tumor and skin biopsies can be performed on different days, but should be done within 7days of each other. Tumor tissue biopsy to be completed on the same day as skin biopsy for on-treatment timepoint.*

Tru-cut biopsy or 14-gauge (or institutional standard size) core biopsy should be performed using standard surgical techniques in visible lesions or by CT or ultrasound guidance. If possible, 3-4 cores should be obtained at each biopsy. Labeled screw-cap cryovials, a flask of liquid nitrogen, and formalin-filled specimen containers should be brought to the room where the core biopsy is to be performed.

The disposition of the 3-4 core specimens are as follows:

A) One to two core specimens should be immediately immersed in formalin for fixation and then paraffin-embedded. The following evaluations will be performed at the Drug Development Program Lab.
   - Protein expression by immunohistochemistry: formalin fixed paraffin-embedded (FFPE) sections of tumor biopsies will be examined by four-colour immunofluorescence using DAPI to outline individual nuclei for cell by cell analysis. Tissue sections will be scanned using a multilaser scanning platform. Acquired digital images will be analyzed using semi-automated protocols developed in the Definitions Tissue Studio 3.5 semi-automatic

histology image analysis platform which uses a "learn by example" algorithm to delineate and analyze regions of interest (ROI) across a sample set, scoring different parameters to allow for elucidation of co-localization relationships.

- Note: Stability of analytes in FFPE
  Protocols for histological staining of all of the proposed markers (apart from Wee1-Like Protein Kinase and pCDC2) have already been optimized and are in common use at our institution for research purposes; good staining in FFPE samples has been demonstrated.

B) One to two core specimens should be immediately transferred from the core biopsy needle directly into cryovials and embedded in O.C.T. This should then be immediately frozen in liquid nitrogen. Samples should be stored in liquid nitrogen or in a -70°C freezer. If not enough tissue available in the archival specimen, *TP53* determination by sanger sequencing (exons 5 to 8) will be performed in this sample

C) One core from biopsy # 2 will be immediately transferred from the core biopsy needle directly into cryovials and embedded in O.C.T. This should then be immediately frozen in liquid nitrogen. Samples should be stored in liquid nitrogen or in a -70°C freezer. Determination of AZD 1775 (MK1775) levels in the fresh biopsy on treatment will be performed. These levels will be compared with serum levels.

9.1.2.1 *Pharmacodynamic assessment of AZD 1775 (MK 1775) activity in tumor tissue*

Hypothesis: The following exploratory biomarkers are expected to be modulated by the treatment with AZD 1775 (MK 1775) and gemcitabine.

- pCDC2 to evaluate target engagement (baseline and on-treatment sample)
- Antigen KI-67 to investigate changes in proliferation (baseline and on-treatment sample)
- gamma-H2AX to evaluate ds DNA damage (baseline and on-treatment sample)
- phospho-Histone H3 to delineate specific activity in S-phase vs at G2/M1 checkpoint (baseline and on-treatment biopsy)
- Cleaved-Caspase-3 to evaluate apoptosis (baseline and on-treatment biopsy)

A comparison between baseline and on treatment and between the two treatment arms will be performed. The rationale for these biomarkers determination has been already defined in section 2.5.

9.1.2.2 *Evaluation of other biomarkers in the baseline biopsy*

- Wee1-Like Protein Kinase expression will be evaluated in the **baseline biopsy** and correlated with the activity of the treatment combination.
- If the available **archival tumor** is not enough for the determination of p53, p21, p16 and Rb, the determination of these biomarkers will be assessed by immunohistochemistry in the baseline biopsy.

9.1.2.3 *Evaluation of intratumoral pharmacokinetics*

- AZD 1775 (MK1775) concentration will be evaluated on biopsy #2. The drug levels achieved in the tumor tissue will be correlated with the plasma pharmacokinetics.

- Rationale: to evaluate the correlation between the drug concentrations achieved in plasma and tissue. Limited drug distribution can potentially be a limitation on drug activity.

9.1.3 Skin Biopsies

Skin biopsies will be performed at each of the two time-points:

- **Within 28 days prior to day 1 (Biopsy # 1)**
- **On cycle 1 day 2 or 9 post AZD 1775 (MK 1775) (Biopsy # 2); ± 24 hours window is allowed**

** Screening tumor and skin biopsies can be performed on different days, but should be done within 7 days of each other. Skin biopsy to be completed on the same day as tumor tissue biopsy for on-treatment timepoint.*

A punch biopsy will be performed using standard surgical techniques from an unexposed skin area. The specimen should be immediately immersed in formalin for fixation and then paraffin-embedded. Protein expression analysis will be performed at the Drug Development Program Laboratory. The protein expression of pCDC2 will be assessed in both biopsies and correlate with the tumor tissue paired biopsies.

9.2 Laboratory Correlative Studies

9.2.1 Determination of *TP53* Mutations in Circulating Tumor DNA (ctDNA)

Blood will be collected in a 9 ml EDTA tube. Sample processing and plasma storage at -80ºC will be performed according to the standard operating procedure (refer to Lab Manual for details). Frozen samples will first be sent to the Princess Margaret Consortium Correlative Studies Laboratory for batching until a patient has completed treatment. At that point, those samples will be sent to the Cambridge Research Institute for analysis. The presence of *TP53* mutation in serial plasma samples will be analyzed and correlated with the radiological response and the CA125 levels.

9.2.2 Pharmacokinetics Study

Plasma pharmacokinetics will be performed in all the patients participating in study. Plasma levels of AZD 1775 (MK 1775) will be correlated with AZD 1775 (MK 1775) in the tumor biopsy.

The following table summarizes the time points for pharmacokinetic sample collection:

Table 9.2.2-1: Pharmacokinetic Samples Collection Schedule

Treatment Day	Timing (from AZD 1775 (MK 1775)/Placebo administration)
Cycle 1 Day 1	**Pre-dose, 1 h, 2 h, 4 h, and 8 h post-dose**
Cycle 1 Day 2	**Pre-dose, 1 h, 2 h, 4 h, and 8 h post-dose**

A 10 minute window pre and post the schedule time is allowed for each sample collection

9.2.2.1 Pharmacokinetic Samples Processing

Five (5) mL of venous blood will be collected by venipuncture, through a heparin lock or through a central line into a heparinized vacutainer at the time points specified above. Samples must be kept in ice bath immediately after collection. Within 30 minutes of collection, each blood sample should be centrifuged at 4°C and 3000 rpm for 10 minutes. The plasma portion will be transferred in equal portions to duplicate properly labeled polypropylene tubes and frozen at -70°C in an upright position within 1 hour of collection. Each tube will be labeled with study number, patient initials, patient's study number, date and time of drug administration, and date and time of sample collection. All labels will be affixed to the test tubes properly and prior to freezing. A PK sample log will be provided by the Princess Margaret Consortium Correlative Studies Laboratory, and completed at the site.

9.2.3 Sample Shipment

9.2.3.1 Archival samples, skin samples, paraffin-embedded samples and fresh frozen biopsy for biomarker and tissue pharmacokinetic analysis

For shipment of samples between facilities, fresh tumor biopsy samples that have been frozen should be sent in dry ice. Frozen samples should be buried in a large quantity of dry ice in a styrofoam container and shipped by overnight FedEx. The person shipping the samples should contact the recipient before the package is sent to ensure that the package will be handled appropriately upon arrival, and provide a FedEx tracking number.

Archival samples, skin samples and paraffin-embedded samples should be sent at ambient temperature. Both kinds of specimens should be shipped to the Princess Margaret Phase II Consortium at the Princess Margaret (see below). Samples should only be shipped on a Monday, Tuesday or Wednesday. Samples and inventory sheet must be shipped by overnight delivery in a Styrofoam container and packaged in dry ice to ensure that they remain frozen. Shipment must be scheduled for a Monday, Tuesday or Wednesday only.

Archival specimens should be shipped to:
Correlative Studies Program
Princess Margaret Cancer Centre
610 University Avenue 9-718
Toronto, Ontario M5G 2M9
Tel: (416) 946-4501 ext 5047
Fax: (416) 946-4431
Email: CCRUcorrelativestudies@uhn.ca

9.2.3.2 Serum Samples for Pharmacokinetic Analysis

Serum for pharmacokinetic analysis will be sent to AstraZeneca or recommended CRO for analysis. Samples will be pack in dry ice in shipping container. The Specimen Shipping Inventory Log (see Lab Manual) should be completed and included in the shipping container.

Please, refer to Lab Manual for additional details on the Notice of Shipment of Biological Specimens and shipping process.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 10 days prior to start of protocol therapy unless otherwise stated. Scans, x-rays and biopsies must be done within 28 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. For subsequent cycles (2+), day 1 and 15 assessments (physical exams, vitals, weight, ECOG, labs, CA125, ctDNA collection) can be completed up to 48hrs prior to day 1 and day 15. A cycle is 28 days long.

	Pre-Study (Screening)		Cycle 1				Cycle 2+			30-37 day Safety Visit (after last dose) + Follow Up[8]
	Within 28 days from start	Within 10 days from start	D1	D8	D15	D22	D1	D8	D15	
AZD 1775 (MK1775)/Placebo[1]			X----------X				X----------X			
Gemcitabine[2]			X----------X				X----------X			
Informed consent[3]	X									
Demographics	X									
Medical History	X									
Physical Examination	X	X	X[4]				X			X
Concurrent medications	X	X	X----------X							
Height	X									
Vital signs (BP, pulse, RR, temp)	X	X	X[4]		X		X		X	X
Weight	X	X	X[4]		X		X		X	X
ECOG Performance Status	X	X	X[4]		X		X		X	X
PT/INR and PTT	X	X								
CBC w/diff plts	X	X	X[4]	X	X	X	X	X	X	X
Serum Chemistry[5]	X	X	X[4]	X	X	X	X	X	X	X
ECG	X		X---------- as indicated ----------X							X[6]
CA125[7]		X	X[4]				X			X
Adverse Event Evaluation			X----------X							
Radiological Evaluation	X		Radiological measurements should be performed every 8 weeks regardless of any delay in treatment. Documentation must be provided for patients removed from study for progressive disease							Must be provided for patients removed from study due to PD
Pregnancy test (B-HCG)[9]	X									
Tumor + Skin Biopsy	X[11]		X[11]							
ctDNA Collection[10]	X		X		X		X		X	X
Pharmacokinetics			X[12]							
PRO-CTCAE[13]	X		X		X		X		X	X
Archival tissue collection	X[14]									

1. AZD 1775 (MK 1775)/Placebo schedule 175 mg once daily on days 1, 2, 8, 9, 15, and 16 of each cycle
2. Gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of each cycle. If any changes are made to dosing schedule for logistical reasons, prior and subsequent doses are to be at least 6 days apart.
3. Completed prior to study related tests
4. If completed within 4 days prior to day 1 it does not need to be completed
5. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Coagulations (aPTT, PT/INR) are required at baseline for eligibility only.
6. To be repeated in the off-study visit in those patients with cardiac history or with clinically significant alterations in the baseline ECG
7. Every 4 weeks for assessment (Day 1) according to GCIG criteria
8. Refer to 5.4 for subsequent follow-up expectations
9. Women of childbearing potential
10. Refer to Section 9.2

11. Refer to section 9.1 for timeline; pre treatment skin and tumor biopsies are to be completed within 7 days of each other; on-treatment skin and tumor biopsies are to be completed on the same day. Pre-treatment biopsy #1 to be performed up to 28 days prior to start of therapy. On treatment biopsy #2 to be performed on D2 or D9, ± 24 hours
12. Refer to table 9.2.2-1 for Day 1 and Day 2 timeline
13. PRO-CTCAE questionnaires will be completed at baseline, on treatment (days 1, and 15 of each cycle), and in the off study assessment at select sites only
14. Archival tissue is to be sent for analysis before the conclusion of the study.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

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 (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Lesions that have been radiated immediately prior to study therapy will be excluded as target lesions. Previously irradiated lesions can be considered as target lesions, as long as there is evidence of radiological progression. The amount of bone marrow radiated during the palliative radiation immediately before participating in the clinical trial will be evaluated by the treating Radiation Oncologist according to the treatment plans and dosimetry on a case-by-case basis. Palliative radiation therapy will be classified as radiating < 10% or ≥ 10% of the bone marrow in order to calculate the required wash out period after the radiation treatment.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with AZD 1775 (MK 1775)/Placebo or gemcitabine.

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 ≥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 may be considered measurable if the lesion has progressed prior to registration.

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), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If 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).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) 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. Response will not change 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	
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	
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.
** 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.

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.

11.2 Other Response Parameters – CA125 Response by GCIG Criteria

Evaluation of Response according to CA-125
Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of normal and within 2 weeks prior to starting treatment.

Definition of response: A response according to CA-125 has occurred if there is at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days.

To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the normal range of CA-125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used and the assay must be tested in a quality-control scheme.

- Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA [1, 2]) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. If assessing therapy that includes two treatment modalities for relapse (e.g., surgery and chemotherapy), any CA-125 response results from both treatments modalities. CA-125 cannot distinguish between the effects of the two treatments.

Patients who have both a CA-125 response and whose CA-125 level falls to within the normal range, can be classified as CA-125 complete responders.

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 Reporting

12.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.1.2 Responsibility for Data Submission

Study participants are responsible for entering their data into the Medidata Rave system and submitting copies of their source notes to the Central Office / Coordinating Centre within 3 weeks of the end of cycle. Please refer to Appendix E, Data Management Guidelines, for further details regarding data submission requirements.

The PMHC is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study

Coordinator) and the procedures for auditing are presented in Appendix B.

The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party

Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Primary Objectives:
To evaluate the progression free survival (PFS) of subjects with recurrent platinum-resistant ovarian, fallopian tube or primary peritoneal cancer receiving gemcitabine in combination with

AZD 1775 (MK 1775) compared to subjects receiving gemcitabine in combination with placebo.

Secondary Objectives:

1. To evaluate the objective response by RECIST 1.1 of patients receiving gemcitabine combined with AZD 1775 (MK 1775) compared to patients receiving gemcitabine in combination with placebo.
2. To evaluate the GCIG CA125 response rate of patients receiving gemcitabine combined with AZD 1775 (MK 1775) compared to patients receiving gemcitabine in combination with placebo.
3. To evaluate the overall survival (max 1-yr follow-up) of patients receiving gemcitabine combined with AZD 1775 (MK 1775) compared to patients receiving gemcitabine in combination with placebo.
4. To evaluate the safety and tolerability of the combination of gemcitabine combined with AZD 1775 (MK 1775) in patients with recurrent, platinum-resistant ovarian, fallopian tube or primary peritoneal cancer.
5. To evaluate *TP53* mutations (presence of mutation and type of mutation) as potential predictive factors of benefit (defined as response or PFS prolongation) to AZD 1775 (MK 1775) and gemcitabine treatment.
6. To evaluate p53 protein expression by immunohistochemistry as potential predictive factors of benefit (defined as response or PFS prolongation) to AZD 1775 (MK 1775) and gemcitabine treatment.

Exploratory Objectives:

1. To evaluate patient reported outcomes using PRO-CTCAE
2. To evaluate the concordance of *TP53* mutations in the tumor specimen and *TP53* mutations determined by TAm-Seq in circulating tumor DNA.
3. To correlate the levels circulating DNA *TP53* mutations by TAm-Seq with response
4. Validation of pCDC2 and gamma-H2AX in skin and tumour tissue as a pharmacodynamic marker of therapy
5. To correlate changes in pCDC2 and gamma-H2AX with survival outcomes and response rate.

Only patients with high-grade serous cancers will be considered for the efficacy endpoint analysis.

13.2 Sample Size/Accrual Rate

A randomized phase 2 design recruiting patients to receive gemcitabine in combination with placebo or AZD 1775 (MK 1775) at a ratio of 1:2 will be used to detect a difference between placebo and AZD 1775 (MK 1775).

All patients with epithelial ovarian cancer are eligible to participate. As *TP53* mutations are most prevalent in high grade serous ovarian cancer, the sample size assessments will be based on this population. If *TP53* mutation/functional mutations seem to be responsible for clinical synergy with AZD 1775 (MK1775), the cohort size will be amended to ensure sufficient statistical power in women with loss of function *TP53* mutations.

An exploratory cohort of patients with non-high grade serous histology (including but not limited to clear cell, endometrioid, or adenocarcinoma NOS) will be accrued. Response assessment will be by RECIST and > 4/10 objective responses (if available depending on accrual) will be considered a signal of activity.

Seventy-five patients with high grade ovarian cancer should be accrued over approximately 15 months, randomized 2:1 in favor of the experimental (AZD1775(MK175)) arm, and followed for PFS for approximately 8 months, until 65 events are observed, yielding 90% power to detect a 100% increase in median PFS (7 vs. 3.5 months), at the 1-sided .10 significance level.

If this comparison is negative, the comparison could be repeated in an expanded *TP53* "non-functional" mutation subpopulation, according to the following design.

Before accrual is re-opened to the *TP53* "non-functional" mutation subpopulation, a restricted (futility analysis) comparison could be made among the patients with *TP53* "non-functional" mutations already accrued, at the .35 significance level. If this comparison is positive, the *TP53* "non-functional" mutation subpopulation could be expanded to a total of 40 patients, with approximately 12 months additional accrual, randomized 2:1 in favor of the experimental arm, and followed for PFS for approximately 6 months, until 36 events are observed, yielding 90% power to detect a 150% increase in median PFS (6.25 vs. 2.5 months), at the 1-sided .10 significance level. (The futility analysis would yield 65% likelihood of termination if there is no true treatment effect in the restricted population, with 94% likelihood of expansion if the true treatment related median PFS increase in the restricted population is the targeted 150%.)

The functional implications of *TP53* mutations will be assessed case-by-case in the IARC *TP53* database:

http://p53.iarc.fr/

Missense, substitution mutations in *TP53* are curated by the IARC according to median level of transcriptional activity derived from 8 independent promoter-specific assays. These assays were conducted by using endogenous mutants, or by transfecting/over-expressing mutant proteins in human or yeast cell systems. Classifiers the IARC database uses include:

- Nonfunctional (< 20% wild-type transcriptional activity)
- Partially functional (20-75% wild-type transcriptional activity)
- Functional (75-140% wild-type transcriptional activity)
- Gain-of-function ("supertrans") (> 140% wild-type transcriptional activity)

	Transcriptional Activity Data
"Nonfunctional" mutations	Nonfunctional
Partially functional mutations	Partially functional
No change in function mutations	Functional
"Gain-of-function" mutations	Supertrans

For statistical purposes, tumors with "*TP53* null" status will be defined as those tumors with *TP53* mutations classified as "Nonfunctional" based on the "Transcriptional Activity Data" according to the IARC *TP53* database.

13.3 Stratification Factors

NA

13.4 Analysis of Secondary Endpoints

Summary statistics, such as mean, median, counts and proportion, will be used to summarize the patients. Survival estimates will be computed using the Kaplan-Meier method. Potential association between variables will be measured using Pearson correlation coefficients, chi-square tests, one- or two-sample t-tests or logistic regression analyses as appropriate. Non-parametric tests such as Spearman correlation coefficients, Fisher's exact tests and Wilcoxon rank sum test may be substituted if necessary. 95% percent confidence intervals will be constructed and selected results will be illustrated using figures and plots.

Frequency and severity of adverse events will be tabulated using counts and proportions detailing frequently occurring, serious and severe events of interest.

All the analysis results are considered hypothesis generating.

13.5 Reporting and Exclusions

13.5.1 **Evaluation of Toxicity:** All patients will be evaluable for toxicity from the time of their first treatment with AZD 1775 (MK 1775)/PLACEBO or gemcitabine.

13.5.2 **Evaluation of Response:** All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 8 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-7 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-7 will be protocol specific.

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation

of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also 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 CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

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

The patient _____ is enrolled on a clinical trial using the experimental agent AZD 1775 (MK 1775). This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

AZD 1775 (MK 1775) 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:

The following medications are specifically prohibited for the duration of the study treatment:

Prohibited CYP3A Inhibitors:		
amprenavir	fluconazole	nelfinavir
aprepitant	fosamprenavir	posaconazole
atazanavir	grapefruit juice	ritonavir
boceprevir	imatinib	saquinavir
ciprofloxacin	indinavir	telaprevir
clarithromycin	itraconazole	telithromycin
conivaptan	ketoconazole	verapamil
darunavir/ritonavir	lopinavir/ritonavir	voriconazole
diltiazem	mibefradil	
erythromycin	nefazodone	

Prohibited CYP3A Inducers:		
avasimibe	glucocorticoids	phenytoin
bosentan	modafinil	rifampin
carbamazepine	nafcillin	St. John's wort
efavirenz	nevirapine	
etravirine	phenobarbital	

Prohibited CYP3A Substrates:		
alfentanil	eletriptan	nisoldipine
aprepitant	eplerenone	pimozide
astemizole	ergotamine	quetiapine

budesonide	everolimus	quinidine
buspirone	felodipine	saquinavir
cisapride	fentanyl	sildenafil
conivaptan	fluticasone	simvastatin
cyclosporine	indinavir	sirolimus
darifenacin	lopinavir	tacrolimus
darunavir	lovastatin	terfenadine
dasatinib	lurasidone	tipranavir
dihydroergotamine	maraviroc	tolvaptan
dronedarone	midazolam	triazolam

- 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 switch any medicines that are considered strong inducers/inhibitors or sensitive substrates of CYP3A4 or CYP3A4 substrates with a narrow therapeutic range.
- 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's usually big and catches your eye. They also have a generic name—it's 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 AZD 1775 (MK 1775)/PLACEBO.

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 **AZD 1775 (MK 1775).** This clinical trial is sponsored by the NCI. **AZD 1775 (MK 1775)** 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, or 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.

AZD 1775 (MK 1775) interacts with a specific liver enzyme called **CYP3A4** and must be used very carefully with other medicines that interact with this enzyme.

- 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 **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 D DIARY CARD

INSTRUCTIONS

1. You will take **7 x 25mg** AZD 1775 (MK 1775)/Placebo capsules once a day on the designated days (1, 2, 8, 9, 15 and 16). Capsules must be taken on an empty stomach 1 hour before or 2 hours after a meal. The day 2 dose should be taken 24 +/- 3 hours after day 1 dose.
2. Swallow each capsule whole. Do not crush or chew the capsules.
3. If you miss any of the doses or you vomit one of the capsules do not repeat or replace the dose. Resume dosing at the next scheduled dose.
4. Record the date and time that the dose was taken.
5. If you have any comments or notice any side effects, please record them in the comments column.
6. Please bring this form at each clinic visit.
7. 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	AZD 1775 (MK 1775) OR Placebo Dose	Comments
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
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28			

Physician's Office will complete this section:
The above information has been reviewed with the patient:
Patient Name: _____
Physician/Nurse Signature _____Date _____

APPENDIX E DATA MANAGEMENT GUIDELINES

Case Report Form Submission Schedule

Data required for the study will be collected in Case Report Forms provided by the PMHC Central Office. The site will be required to complete a paper Eligibility Checklist case report form (CRF) at the time of patient registration. All other data will be collected on electronic case report forms (eCRFs) in the Medidata Rave system. Site staff access to Medidata Rave will be initiated at the time of site activation. The form submission schedule is outlined below.

Case Report Form	Submission Schedule
Eligibility Checklist	At the time of registration
Baseline eCRFs	Within 3 weeks of on study date
On Treatment (Cycle) eCRFs	Within 3 weeks of the end of each cycle of treatment
Off Treatment eCRFs	Within 3 weeks of the patient coming off-study
Short Follow-up eCRFs	Within 3 weeks of the patient coming to clinic.
Final eCRFs	Within 3 weeks from 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 CTEP-AERS guidelines

Case Report Form Completion

The paper Eligibility Checklist CRF must be completed using black 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.

eCRFs will be completed according to the schedule noted above and all relevant supporting documentation such as scans, progress notes, nursing notes, blood work, pathology reports, etc., will be submitted to the PMHC Phase 2 Consortium Central Office for review. 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.

eCRF completion guidelines are available for all sites.

Monitoring

Central data monitoring will take place throughout the trial at the Central Office. On-site monitoring will be performed once a year at participating sites during which a subset of PMHC studies will be picked for on-site monitoring.

Data in the Medidata Rave eCRFs will be monitored on a regular basis and quality assurance measures will be performed. Electronic data queries as well as paper query letters may be issued to the site prior to the quarterly submission of data to CDUS.

Patient Registration

- Refer to Section 4 of the protocol

Data Safety

A Data Safety and Monitoring Board, an independent group of experts, 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.

Regulatory Requirements

- Please submit all required documents to the PMHC Central Office.
- Canadian Principal Investigators must submit a completed Qualified Investigator Undertaking.
- All investigators must have a current NCI investigator number on file with the PMHC Central Office.
- All investigators must have an up-to-date CV (signed within 2 years) on file with the PMH Phase 2 Consortium Central Office.
- Laboratory certification/accreditation and normal ranges are required
- Confirmation of all investigators having undergone training in the Protection of Human Research Subjects is required. It is preferred that other staff involved in the trial also undergoes such training.
- Investigators and site staff are required to complete Medidata eCRF training modules depending on delegated tasks
- OPRR assurance numbers for each institution are required
- 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 PMHC 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 PMHC Central Office.
- A completed Site Participant List/Training Log is required and must be submitted to PMHC
- Continuing approval will be obtained at least yearly until follow-up on patients is completed