This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC MK-1775 Oral capsule solidtumor	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Two Part, Phase I-IIA Study Evaluating MK-1775 in Combination With Topotecan/Cisplatin In Adult Patients With Cervical Cancer. #008

PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: 29-Jun-2010 to 13-Jun-2011

CLINICAL PHASE: I/IIa

DURATION OF TREATMENT: Patients received MK-1775 + topotecan + cisplatin in 21-day cycles until disease progression, unacceptable adverse experiences (AEs), intercurrent illness that prevented further administration of treatment, or withdrawal of consent. Patients were followed for at least 30 days following their last dose of study therapy or until death.

OBJECTIVE(S):

Primary Objectives

1) To determine the safety and tolerability of MK-1775 in combination with topotecan and cisplatin in patients with metastatic and recurrent cervical cancer.
2) To establish a recommended Phase II dose (RP2D)/maximum tolerated dose (MTD) for MK 1775 in combination with topotecan + cisplatin.
   Hypothesis: The side effects observed in patients with metastatic and recurrent cervical cancer after administration of MK 1775 in combination with topotecan + cisplatin will allow for the definition of a combination RP2D/MTD.
3) To determine the preliminary efficacy of MK-1775 in combination with topotecan and cisplatin in patients with metastatic and recurrent cervical cancer.
   Hypothesis: The combination of MK-1775, topotecan and cisplatin causes objective radiological responses (assessed per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) in ≥30% of patients enrolled at the MTD/RP2D or across all dose levels at or below the MTD.

Secondary Objectives

1) To assess the pharmacokinetic (PK) profile of MK-1775 in combination with topotecan and cisplatin in patients with metastatic and recurrent cervical cancer.
2) To determine pharmacodynamic (PD) changes in skin induced by MK-1775 in combination with topotecan and cisplatin in patients with metastatic or recurrent cervical cancer.

[redacted]

STUDY STATUS: The sponsor decided to permanently suspend new enrollment into the trial and discontinue the study. The decision to discontinue this protocol was not related to any concerns over the safety of the product. Patients who were enrolled in the study and had not yet met protocol-defined discontinuation criteria could continue to receive study therapy per protocol and be seen by the principal investigator per usual standard of care providing the investigator felt that such treatment was in the patient's best interest.

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STUDY DESIGN: This was a two part, multicenter, worldwide Phase I/IIa study of MK-1775 in combination with topotecan plus cisplatin administered as first line therapy in patients with metastatic and recurrent cervical cancer who had received previous treatment with chemotherapy plus radiation. Part I of this study was an open-label, nonrandomized, dose-escalation, Phase I study to evaluate the safety, tolerability, and preliminary efficacy of MK-1775 administered in combination with topotecan and cisplatin. The primary purpose of the study was to characterize the dose-limiting toxicities (DLTs) and define the MTD and RP2D for the combination.

In Part I, study therapy was administered in 21-day cycles, as follows:

- topotecan at a dose of 0.75 mg/m^2/day by intravenous infusion over 30 minutes on Days 1-3 of each cycle,
- cisplatin at a dose of 50 mg/m^2 by intravenous infusion over up to 4 hours on Day 1 of each cycle, and
- MK-1775 oral capsules at sequentially rising dose levels (following a modified Fibonacci design) starting at 50 mg twice a day (BID) at intervals of approximately 12 hours on Days 1-4 and once on Day 5 for a total of nine doses per cycle. MK-1775 was administered concomitantly with topotecan plus cisplatin on Day 1 of each treatment cycle, with the morning dose of MK-1775 given prior to topotecan on Days 1-3.

Patients were to be enrolled in cohorts of at least 3 patients each and treated at sequentially rising dose levels. The first cycle of treatment was used to assess the safety and tolerability (DLTs) of the triplet therapy as well as the PK and PD. In order to be declared a DLT (protocol-defined, hematologic and non-hematologic AEs), an AE must be related (i.e. definitely, probably, or possibly related) to the study therapy. All regimens were administered until disease progression, unacceptable AEs, intercurrent illness that prevented further administration of treatment, or withdrawal of consent. Laboratory safety assessments, serious adverse events (SAEs), and pregnancies were monitored throughout the study.

Disease response was assessed by anatomic imaging (computerized tomography of the chest, abdomen, and pelvis and optional magnetic resonance imaging of the pelvis) and physical examinations every six weeks. Plasma samples for MK-1775 PK evaluation were drawn on Cycle 1, Day 1 (pre-dose) and Cycle 1, Day 3 (pre-dose and 3 and 8 hours post-dose). Cisplatin PK plasma samples were collected on Cycle 1, Day 1 (pre-dose; post-dose immediately after the end of the infusion; and 2, 4, and 24 hours after the end of the infusion). Skin biopsies were obtained at Screening and 0-2 hours after the morning dose of MK-1775 on Cycle 1, Day 3.

Part II of the study was a randomized, double-blinded, Phase IIa study to evaluate the effect of the combination of MK-1775 with topotecan plus cisplatin versus topotecan plus cisplatin alone on progression-free survival (PFS), objective response rate (ORR), and overall survival (OS) in the study population, as well as the safety and tolerability of the combination.

As enrollment into the study was stopped before completion of Part I, Part II was not initiated. Patients who were enrolled in the study and had not yet met protocol–defined discontinuation criteria could continue to receive study therapy under a continuous dosing schedule and be seen by the investigator per usual standard of care as long as the investigator felt that such treatment was in the patient's best interest. These patients continued to be monitored by the investigator for SAEs and pregnancy. All other study related procedures and measurements were terminated upon cessation of enrolment.

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PATIENT DISPOSITION: A total of seven patients participated in Part I of this study. The patient baseline characteristics and overall disposition of patients are provided in Table 1 and Table 2 below.

Table 1

Patient Characteristics (Study P008)

	MK-1775 + Topotecan + Cisplatin	
	n	(%)
Patients in population	7	
Gender		
Female	7	(100.0)
Age (Years)		
Less than 65 years	7	(100.0)
65 years or older	0	(0.0)
Mean	50.3	
SD	3.5	
Median	50.0	
Range	46 to 56	
Race		
White	7	(100.0)
Ethnicity		
Not Hispanic Or Latino	7	(100.0)
SD = standard deviation		

Table 2

Disposition of Patients (Study P008)

	MK-1775 + Topotecan + Cisplatin	
	n	(%)
Patients in population	7	
Study Disposition		
Discontinued	7	(100.0)
Adverse Event	2	(28.6)
Progressive Disease	5	(71.4)
Each patient is counted once for Study Disposition based on the latest corresponding disposition record.		

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DOSAGE/FORMULATION NOS.:

MK-1775, topotecan, and cisplatin were administered in 21-day cycles. MK-1775 was administered orally BID for a total of 9 doses per cycle; topotecan and cisplatin were administered intravenously (see full description of dosing regimens in section Study Design above). MK-1775 was supplied by the Sponsor; topotecan and cisplatin were supplied by the investigator or the site as needed. All investigational materials were supplied in an open-label manner. Details of Sponsor-supplied MK-1775 capsules are provided below.

Clinical Material	Potency (concentration)	Dosage Form/Packaging	Batch Number (Formulation Number)
MK-1775	10 mg	Capsule	[redacted]
MK-1775	25 mg	Capsule	[redacted]
MK-1775	100 mg	Capsule	[redacted]

DIAGNOSIS/INCLUSION CRITERIA: Female patients at least 18 years of age with a histologically or cytologically confirmed metastatic and recurrent squamous cell, adenosquamous, or adenocarcinoma of the uterine cervix (Stage II – IVb) that was not amenable to curative treatment with surgery and/or radiation therapy. Patients were required to have received cisplatin in combination with radiation for their cervical cancer and no other treatment for their cancer following the cisplatin-based chemo-radiation or targeted therapy with the exception of non-cytotoxic targeted therapy (monoclonal antibodies and other targeted agents). Recurrence had to have occurred at least 6 months after the cisplatin-based chemotherapy. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤1 and measurable disease based on RECIST 1.1 criteria.

EVALUATION CRITERIA:

Efficacy: The primary efficacy endpoint for Part I was the ORR, defined as the proportion of patients whose best confirmed response was Partial Response (PR) or Complete Response (CR) per RECIST 1.1. Overall tumor response was to be assessed using RECIST 1.1. Enhanced RECIST 1.1 was to be used in an exploratory manner to assess treatment response.

Pharmacokinetics: The following PK parameters of MK-1775 were to be assessed: C_{8hr}, C_{trough}, and the estimation of steady-state AUC and C_{max}. [redacted]

Pharmacodynamics: Skin biopsies were to be analyzed by immunohistochemistry for PD analysis of biomarkers (cell division control protein 2 [CDC2] and phosphorylated CDC2 [pCDC2]).

Safety: Safety endpoints included all types of AEs including DLTs, in addition to laboratory safety assessments, physical examinations, ECOG performance status, electrocardiograms, and vital signs.

STATISTICAL PLANNING AND ANALYSIS: The study planned to enroll approximately 32 patients for MTD finding and confirmation.

Efficacy: Efficacy analyses were to be performed on the Full Analysis Set (FAS) population, which consisted of all randomized patients who received at least one dose of study treatment and had baseline data for required for analysis. Patients were to be included in the treatment group to which they were randomized for the analysis of efficacy data using the FAS population.

Response rates were to be calculated based on full follow-up. ORR was to be estimated by the proportion of patients who achieved confirmed PR or CR per RECIST 1.1. The 95% confidence interval (CI) for the ORR was to be calculated based on exact binomial distribution. As an exploratory analysis, tumor response could be analyzed based on Volumetric Imaging data. Enhanced RECIST 1.1 was to be used to assess treatment response. Tumor volume changes of -30% for PR and +20% for PD

were to be used to be consistent with RECIST 1.1. These thresholds were expected to be comfortably higher than two times the total variance in the measures of volume for target lesions.

Pharmacokinetics: Pharmacokinetic variables were summarized. [redacted]

Pharmacodynamics: Skin biopsies were analyzed for CDC2 and pCDC2 by immunohistochemistry. The percentages of total CDC2-positive cells that were positive for pCDC2 at baseline and post-baseline were compared to determine the PD changes in skin induced by MK-1775 in combination with topotecan and cisplatin. Data were log-transformed. A mixed effects model including Patient (random) and Time (fixed) was fitted. At each time point, the geometric mean and 90% CI for the pCDC2 measure were calculated. The fold ratio of post-baseline to baseline, the corresponding 90% CI, and p-value were derived.

Safety: Safety data analyses were to be performed on the All Patients as Treated (APaT) population, which consisted of all randomized patients who received at least one dose of study treatment. For the analysis of safety data, patients were included in the treatment group corresponding to the study treatment they received. To assess change from baseline and for inclusion in the analysis of each specific parameter in addition to the baseline measurement, at least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment was required.

Safety analyses related to DLT rate was to be performed on the DLT evaluable population, which consisted of all patients who completed the first cycle of combination therapy or discontinued from the study due to a DLT attributable to study therapy.

Safety and tolerability were assessed by clinical review of all relevant parameters including AEs, ECOG performance status, laboratory tests, vital signs, and electrocardiogram measurements. Descriptive tables summarizing the number and percentage of patients who experienced AEs as categorized in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 were to be generated for the overall population, by dose level and for selected patient subsets. P-values and 95% confidence intervals were planned to be calculated using the Miettinen and Nurminemn method for between-treatment differences in the percentage of patients with events. Laboratory assessments, vital signs, and other safety endpoints were to be summarized as appropriate.

DLTs were to be listed, and summary statistics (median and range) for time to onset of first drug-related toxicity in each dose level were also planned to be provided. Eighty percent credible intervals, based on a Beta (1,1) prior, of DLT and drug-related toxicity rates for the dose levels that were selected for cohort expansion were to be provided.

RESULTS: Seven patients participated in Part I of this study. No patients were enrolled into Part II. All patients received at least one dose of MK-1775 at 50 mg BID in Part I. No further dose levels were evaluated because of permanent suspension of enrollment and protocol discontinuation. Patients who were enrolled in the study and had not yet met protocol-defined discontinuation criteria when enrolment was stopped could continue to receive study therapy under a continuous dosing schedule and be seen by the investigator per usual standard of care as long as the investigator felt that such treatment was in the patient's best interest. In addition, the principal investigator continued to monitor for and report any SAE, Event of Clinical Interest (ECI), and pregnancy data. All other study-related procedures and measurements were terminated.

Disposition and Demographics: A total of seven female patients participated in this study. All patients were white and less than 65 years old. Overall patient characteristics and disposition are provided in Table 1 and Table 2, respectively.

Efficacy: Five patients were evaluable for efficacy. Because the study was terminated early, no efficacy analyses were performed. A by-patient listing of best overall response and PFS time assessment per RECIST 1.1 is provided in Table 3 below.

Table 3

Listing of Best Overall Response and Progression-free Survival Time (Study P008)

Patients	Treatment	Best Overall Response	Progression-free Survival Time (days)
[redacted]			

Pharmacokinetics: Preliminary PK data were available for 7 patients who received the first dose (50 mg BID for 4.5 days) of MK-1775 in the dose escalation schedule (Part I). PK measurements were made predose on Day 1 and Day 3, and at the 3 and 8 hours postdose timepoints on Day 3 to assess whether the PK target of 240 nM was achieved 8 hours post-dose on Day 3. These results are presented in Table 4. Individual and mean plasma concentrations are shown in Figure 1.

Table 4

Preliminary Mean (±Standard Deviation) Pharmacokinetic Parameters Following Administration of Multiple Oral Doses of MK-1775 50 mg (Twice a Day for 4.5 Days) in Combination with Topotecan and Cisplatin (Study P008)

	Patient	C_{trough} (nM) (Based on Day 3 predose concentration)	C_{max} *(nM) (at 3 hr)	C_{8hr} (nM) (Based on Day 3, 8 hr timepoint)
	[redacted]			
Mean		199.4	404.3	262.3
Standard Deviation		115.2	179.4	116.2
n		7	7	7

C_{trough} = plasma trough (pre-dose) concentration on Day 3; C_{max} = maximum concentration; C_{8hr} = plasma drug concentration at 8 hours post-dose
* C_{max} estimates were made based on sparse sampling scheme at 3 hour time point on day 3

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Based on the PK data available on Day 3 for the 7 patients (sparse sampling scheme), the mean C_{max} value was 404.3 nM at 3 hours post dose. The mean trough concentration (Day 3 predose) for MK-1775 was 199.4 nM. The mean C_{8hr} on Day 3 at 8 hours postdose was 262.3 nM. Because only 3 points were available on Day 3, AUC values could not be calculated with confidence and are hence not listed. The PK target of a C_{8h} of 240 nM was achieved at 50 mg MK-1775 in combination with topotecan/cisplatin in adult patients with cervical cancer. Because of the limited data available, time to reach steady-state was not assessed, and the relationship of various PK parameters to the PD endpoints was not assessed.

Pharmacodynamics: Data were available for 7 patients in Part I. A statistically significant decrease in pCDC2 from baseline (44.0%) to post-baseline (27.6%) was observed. The geometric ratio of post-baseline to baseline was 0.63 (90% CI 0.42, 0.95) (Table 5).

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Table 5

Pharmacodynamic Changes in Skin Induced by MK-1775 in Combination with Topotecan and Cisplatin (Study P008)

Time	n	Geometric Mean (%) or Ratio[†]	90% CI	p-value[‡]	GSD[§]
Total CDC2-positive cells that were pCDC2 positive					
Baseline	7	44.0	(34.9, 55.6)		1.44
Day 3, 0-2 hrs post morning dose of MK-1775	7	27.6	(21.9, 34.9)		1.38
Day 3 post MK-1775 / Baseline		0.63	(0.42, 0.95)	0.035	1.48

CDC2 = Cell division control protein 2; CI = confidence interval; GSD = geometric standard deviation
[†] Back-transformed least squares mean from log scale: Geometric mean for individual time points and mean ratio between two time points
[‡] 1-sided p-value
[§] Between-patient GSD for individual time points and within-patient GSD for mean ratio

Safety:

Exposure: [redacted] One treatment cycle in this study was 21 days. Mean exposure to MK-1775 in combination with topotecan plus cisplatin was approximately 5 cycles (quartile range 3 to 6 cycles). All patients were included in the assessment of safety and tolerability. As a result of the Sponsor's decision to permanently suspend enrollment into the study, a MTD and RP2D for MK 1775 in combination with topotecan plus cisplatin was not determined and the safety and tolerability analyses planned were not performed.

Adverse Experiences: AEs were listed and summarized by body system and preferred term. The incidences of specific AEs were presented for patients as a whole. A summary of adverse events is provided in Table 6 below. Adverse event listings and summaries are available from Table 7 through Table 20.

Table 6

Adverse Event Summary (Study P008)

	MK-1775+Topotecan+Cisplatin	
	n	(%)
Patients in population	7	
with one or more adverse events	7	(100.0)
with no adverse event	0	(0.0)
with drug-related[†] adverse events	7	(100.0)
with serious adverse events	5	(71.4)
with serious drug-related adverse events	3	(42.9)
who died	0	(0.0)
discontinued[‡] due to an adverse event	2	(28.6)
discontinued due to a drug-related adverse event	2	(28.6)
discontinued due to a serious adverse event	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.

All patients reported at least one AE. The most frequent AEs reported were anemia (6/7), neutropenia (6/7), and thrombocytopenia (6/7) in the Blood and Lymphatic System Disorders organ class; headache (5/7) (Nervous System Disorders); constipation (4/7), diarrhea (4/7), and nausea (4/7) in the Gastrointestinal Disorders organ class, and asthenia (4/7) in the General Disorders organ class. All of the anemia, neutropenia, and thrombocytopenia AEs were considered at least possibly related to the study drug by the investigator. Neutropenia was reported to be CTCAE Grade 3 or higher in 6/7 patients, while anemia and thrombocytopenia were Grade 3 or higher in 3/7 and 4/7 patients, respectively. Headache was considered to be drug related in 2/7 patients, but none were Grade 3 or higher. The AEs of constipation, diarrhea, and nausea were considered drug related in 1/7, 4/7, and 4/7 patients, respectively. Of these drug-related gastrointestinal AEs, one event of diarrhea and one event of nausea were Grade 3 or higher in severity. Asthenia was assessed as drug related in 4/7 patients but none was Grade 3 or higher in severity.

Serious Adverse Experiences: Five patients reported at least one SAE. [redacted] None of these events resulted in death or study discontinuation, and all the events resolved. [redacted] No deaths occurred during the study.

Dose Limiting Toxicities: An initial cohort of 3 patients was enrolled at dose of MK-1775 at 50 mg BID. [redacted]

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[redacted] No other DLTs were observed during cycle 1.

CONCLUSIONS:

Efficacy: Because of the small number of patients enrolled, no efficacy analyses were done.

Pharmacokinetics: The PK target of a MK-1775 C_{8hr} of 240 nM was achieved on Day 3 when MK-1775 was administered at 50 mg BID for 4.5 days in combination with topotecan plus cisplatin in adult patients with cervical cancer.

Pharmacodynamics: A statistically significant decrease in pCDC2 from baseline (44.0%) to post-baseline (27.6%) was observed when MK-1775 was administered at 50 mg BID for 4.5 days in combination with topotecan plus cisplatin in adult patients with cervical cancer.

Safety: A MTD and RP2D were not established for MK-1775 in combination with topotecan and cisplatin. The DLTs and most frequently reported AEs were consistent with the safety profile of MK-1775.

[1] Per protocol, "Any Grade 4-5 hematological toxicity using the NCI-CTCAE version 4.0 with the exception of Grade 4 anemia, Grade 4 thrombocytopenia without bleeding or platelet transfusion lasting for <7 days in duration , Grade 4 neutropenia lasting for <7 days in duration. Grade 3 or Grade 4 neutropenia with fever >38.°C and/or infection requiring antibiotic or anti-fungal treatment"