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-8669 ridaforolimus (formerly deforolimus), Oral Tablet NSCLC	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Randomized Discontinuation Phase II Trial of Ridaforolimus in Non-Small Cell Lung Cancer (NSCLC) Patients with KRAS Mutations #021

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. [redacted]

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter: 54 centers in Brazil, Denmark, France, Germany, Italy, Peru, Poland, Spain, Turkey, and the United States.

PUBLICATION(S):

Abstract: A randomized discontinuation phase II trial of ridaforolimus in non-small cell lung cancer (NSCLC) patients with KRAS mutations. G. Riely, J. Brahmer, D. Planchard, L. Crino, R. Doebele, L. Lopez, S. Gettinger, C. Schumann, X. Li, B. Atkins, S. Ebbinghaus, and R. Rosell. ASCO MEETING ABSTRACTS May 30, 2012:7531 [redacted]

PRIMARY THERAPY PERIOD: 28-Apr-2009 until 22-Jun-2011 **CLINICAL PHASE:** IIb

DURATION OF TREATMENT: Patients continued on study until disease progression, intolerable toxicity, or withdrawal of consent.

OBJECTIVE(S): **Primary:** To determine the efficacy of ridaforolimus in patients with KRAS mutant NSCLC who have progressed after at least one (1) but no more than three (3) prior chemotherapy regimens compared to placebo by progression free survival (PFS) analysis of randomized patients who have stable disease after an 8-week lead-in treatment with ridaforolimus. **Secondary:** In patients with KRAS-mutant NSCLC who receive ridaforolimus after failing at least one (1) but no more than three (3) prior chemotherapy regimens to: evaluate the safety profile of ridaforolimus, evaluate the best overall response rate, evaluate the overall duration of PFS, estimate OS (overall survival), estimate whether continuing therapy with ridaforolimus improves survival in patients who have experienced stable disease after 8 weeks of therapy with ridaforolimus.

STUDY STATUS: Study was terminated early due to failure to satisfy predefined futility analysis..

STUDY DESIGN: This was a Phase II multi-center, randomized discontinuation trial of ridaforolimus in patients with advanced NSCLC progressing after at least one (1) but no more than three (3) prior chemotherapy regimens, measurable disease, and a documented mutation of the KRAS oncogene in their tumor tissue [redacted] All eligible patients received an 8 week unblinded, open-label lead-in treatment with ridaforolimus, and underwent disease re-assessment during the 8th week of lead-in treatment. At that assessment:

- Patients who had evidence of an unconfirmed partial response or better as assessed by the investigator continued on open-label ridaforolimus treatment.
- Patients with stable disease as assessed by the investigator underwent double-blinded randomization assignment to ridaforolimus or placebo.
- At the time of investigator assessed disease progression while on randomized treatment, the patient's treatment assignment was unblinded, and patients who were receiving placebo were permitted to cross-over to open-label treatment with ridaforolimus at the discretion of the investigator.
- Patients who had investigator assessed disease progression at Week 8 discontinued study treatment.

SUBJECT/PATIENT DISPOSITION:

	Total
SCREENING FAILURES	238
ENROLLED AND TREATED	79
RANDOMIZED[†]	28
Male	39
(age range)	43 to 77
Female	40
(age range)	28 to 85
DISCONTINUED	79
Lack Of Efficacy	47
Adverse Event	19
Withdrawal By Subject	6
Study Terminated By Sponsor	3
Physician Decision	2
Lost To Follow-Up	2

[†] randomization occurred only for eligible patients after lead-in treatment

Data Source: [redacted]

DOSAGE/FORMULATION NOS.:

Clinical Material	Potency Concentration	Dosage Form	Batch Number	Catalent Lot Number
MK-8669	10 mg	Enteric coated Tablet	[redacted]	
MK-8669	Placebo 10 mg	Enteric coated Tablet		
MK-8669	10 mg	Enteric coated Tablet		
MK-8669	Placebo 10 mg	Enteric coated Tablet		
MK-8669	10 mg	Enteric coated Tablet		
MK-8669	10 mg	Enteric coated Tablet		

DIAGNOSIS/INCLUSION CRITERIA: This study included patients ≥18 years of age with histologically confirmed stage IIIB/IV non-small cell lung cancer and a documented mutation of the KRAS gene in tumor tissue. In addition, patients also had measurable disease by protocol-specific RECIST criteria (see the IIOM) and evidence of disease progression following at least one (1) but no more than three (3) prior chemotherapy regimens for the treatment of locally advanced or metastatic disease.

EVALUATION CRITERIA: Efficacy assessed by RECIST 1.1 from CT scans of the chest and abdomen in all patients every 8 weeks, with additional tumor imaging for measurable tumor sites if applicable. Patients were assessed clinically with physician visits every 4 weeks. The safety measurements include physical examination, assessment of vital signs, weight, ECOG performance status, complete blood counts, serum chemistry, and serum lipids, and assessment and recording of clinical and laboratory adverse experiences.

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: The primary efficacy endpoint was PFS in the randomized population. The randomized population was defined as all patients who were randomized after 8-week open-label lead-in treatment with ridaforolimus. PFS in the randomized population was defined as the time from randomization to progressive disease or death, whichever comes first. Secondary efficacy endpoints included OS in the randomized population, ORR in the FAS population, which was defined as all patients who entered the study with baseline tumor assessment by CT scan and had at least one dose of study treatment. For PFS and OS analyses, patients who were randomized to the placebo arm at Week 8 were to be censored at Week 8 [redacted]

Safety: Safety analyses were to be performed in the All-Patients-as-Treated (APaT) population. For the purpose of safety analyses, the APaT was considered as a single arm analysis population consisting of all patients who received at least one dose of ridaforolimus.

The estimated sample size was calculated based on the need for 76 randomized patients and the assumption that median PFS for the target study population was 8 weeks, so that the enrollment of 150 patients should yield approximately 76 patients that would have stable disease at 8-weeks and be randomized to ridaforolimus or placebo. The study was event driven. The primary analysis time was to be triggered when 58 PFS events (progression or death, whichever occurred earlier) were observed in the randomized patients, which would provide 80% power, at a 1-sided 10% alpha level to detect a 75% improvement in median progression free survival time (8 weeks vs 14 weeks) or a hazard ratio (treatment vs. control) of 0.57. The Cox model with right-point approximation with Efron tie-handling for treatment comparison was to be used for evaluation of PFS in the randomized population.

One interim analysis (IA) for futility was planned when 75 patients in the FAS population enrolled and had either completed the planned tumor assessment after 8 weeks of open-label lead-in treatment or had discontinued study treatment for any reason. The study was later amended that the futility IA would be conducted after 20 months from the first patient enrolled.

The study was stopped for futility because of the following prespecified criteria:

- ORR at 8 weeks < 2%.
- A point estimate of < 50% PFS rate at 8 weeks. The PFS rate was estimated by the Kaplan-Meier method. This futility bound represents the lower bound of the 70% confidence interval for the reported 8 week disease control rate of a reference agent (sorafenib) in KRAS mutant NSCLC [redacted]

At the time of the IA, the results of the study in patients who were randomized to ridaforolimus or placebo after 8-weeks of lead-in treatment were not known and not taken into consideration in the decision to stop enrollment in the study.

RESULTS:

INTERIM ANALYSIS:

A planned IA for futility was conducted after 20 months with the 69 enrolled patients who either completed the planned tumor assessment after 8 weeks of open-label lead-in treatment or discontinued study treatment for any reason. The IA was conducted on 01Dec 2010 after 20 months of patient enrollment.

The IA specified that the study would be stopped for futility if one of the following 2 scenarios occurred:

- Overall response rate (ORR) at 8 weeks < 2%.
- Progression-free survival rate at 8 weeks < 50% in point estimate.

The results of this analysis revealed that the study met both pre-specified criteria for futility. The overall response rate at 8 weeks was 1.6% (1/61) failing to demonstrate that ridaforolimus treatment results in a best overall response rate at 8 weeks of at least 2% . The Kaplan-Meier estimate of PFS rate for the 8 week analysis was 43%, failing to demonstrate that ridaforolimus treatment results in a PFS rate at 8 weeks of at least 50% in patients with advanced KRAS mutant NSCLC. The adverse event profile of ridaforolimus in this study was consistent with the known adverse event profile of ridaforolimus. Therefore, the study stopped enrollment after the IA for futility. Patients who were still on study were allowed to continue study treatment.

FINAL ANALYSIS -

Final analysis was conducted on Sep 27, 2012, with a smaller sample size than planned in the protocol specified statistical analysis plan due to the early termination of the study at interim futility analysis.

EFFICACY RESULTS:

(1) PFS in the randomized population: Patient responses were initially assessed by the investigators. At the end of the study, a blinded central review of scans was performed in order to verify the investigators assessments. For patients who did not have any independent radiologist review assessments at the final analysis and were still alive, PFS was imputed using the investigator evaluation. Based on investigator evaluation, the median PFS was 16.7 weeks in the experimental arm and 7.3 weeks in the control arm. (Table 2-1 and Figure 2-1). Based on independent radiologist review, per RECIST criteria, the median PFS was 21.6 weeks in the experimental arm and 7.3 weeks in the control arm (Table 2-2 and Figure 2-2). Based on independent radiologist review, the hazard ratio of the experimental arm over the control arm was 0.53, and the one-sided p-value was 0.06, favoring the experimental arm (Table 2-2). The primary analysis based on independent radiologist review suggested that ridaforolimus in patients with NSCLC with KRAS mutations improved PFS compared with that in patients treated with placebo in the randomized population. The one-sided p-values in both analyses were less than 0.1, the pre-specified bar for a positive study. The observations were consistent between the investigator evaluation and independent radiologist review using RECIST, though the treatment effect in terms of hazard ratio is smaller based on independent radiologist review.

(2) OS in the randomized population: The median OS was 18.1 months in the experimental arm, and 5.2 months in the control arm (Table 2-3 and Figure 2-3) in the randomized population. The hazard ratio of the experimental arm over the control arm was 0.59. The one-sided p-value was 0.111, favoring the experimental arm (Table 2-3). In the randomized population where patients had stable disease after treating with ridaforolimus for 8 weeks, patients who continued to receive ridaforolimus appear to have an improved OS compared to patients who were randomized to placebo.

(3) PFS in the FAS (full analysis set) population: Based on the investigator evaluation, the median PFS in the FAS population is 10.6 weeks (Table 2-4 and Figure 2-4). Based on independent radiologist review per RECIST criteria, the median PFS in the FAS population was 18.9 weeks (Table 2-5 and Figure 2-5).

(4) OS in the FAS population: The median OS in the FAS population was 7.3 months (Table 2-6 and Figure 2-6).

(5) ORR (overall response rate) in the FAS population: The ORR based on investigator evaluation was 1/79 (1.3%; Table 2-7).

Table 2-1

Summary of Progression-Free Survival Based on Investigator Evaluation
Randomized Population

	Ridaforolimus (N=14)	Placebo (N=14)	Ridaforolimus Versus Placebo		
			Hazard Ratio[‡]	95% CI for Hazard Ratio[‡]	p-Value[‡]
Number (%) of PFS Events	13 (92.9)	12 (85.7)	--	--	--
Person-Weeks	409	126	--	--	--
Event Rate/100 Person-Weeks (%)	3.2	9.6	--	--	--
Median PFS (Weeks)[§]	16.7	7.3	0.30	(0.11,0.77)	0.004
95% CI for Median PFS[§]	(7.7,42.7)	(6.0,8.3)	--	--	--

[†] Progression-free survival is defined as disease progression, or death, whichever occurs first.
[‡] From Cox model test case, as treatment effect is tested. P-Value is one-sided for testing H_0: HR $\geq$ 1 versus H_1: HR < 1.
[§] From product-limit (Kaplan-Meier) method for censored data

Data Source: [redacted]

Figure 2-1

[redacted]

Table 2-2

Summary of Progression-Free Survival Based on Independent Radiology Review
Randomized Population

	Ridaforolimus (N=14)	Placebo (N=14)	Ridaforolimus Versus Placebo		
			Hazard Ratio‡	95% CI for Hazard Ratio‡	p-Value‡
Number (%) of PFS Events	14 (100.0)	12 (85.7)	--	--	--
Person-Weeks	612	211	--	--	--
Event Rate/100 Person-Weeks (%)	2.3	5.7	--	--	--
Median PFS (Weeks)§	21.6	7.3	0.53	(0.24,1.19)	0.060
95% CI for Median PFS§	(9.6,79.7)	(5.0,17.0)	--	--	--

† Progression-free survival is defined as disease progression, or death, whichever occurs first.

‡ From Cox model test case, as treatment effect is tested. P-Value is one-sided for testing H_0: HR ≥ 1 versus H_1: HR < 1.

§ From product-limit (Kaplan-Meier) method for censored data

Data Source: [redacted]

Figure 2-2

[redacted]

Table 2-3

Summary of Overall Survival
Randomized Population

	Ridaforolimus (N=14)	Placebo (N=14)	Ridaforolimus Versus Placebo		
			Hazard Ratio†	95% CI for Hazard Ratio†	p-Value†
Death (%)	11 (78.6)	11 (78.6)	--	--	--
Median Survival (Months)‡	18.1	5.2	0.59	(0.25,1.39)	0.111
95% CI for Median Survival‡	(6.3,24.4)	(1.4,24.1)	--	--	--

† From Cox model test case, as treatment effect is tested. P-Value is one-sided for testing H_0: HR $\geq$ 1 versus H_1: HR < 1.

‡ From product-limit (Kaplan-Meier) method for censored data

Data Source: [redacted]

Figure 2-3

[redacted]

Table 2-4

Summary of Progression-Free Survival Based on Investigator Evaluation
FAS Population

	MK-8669 (N=79)
Number (%) of PFS Events	60 (75.9)
Person-Weeks	1193
Event Rate/100 Person-Weeks (%)	5.0
Median PFS (Weeks)[‡]	10.6
95% CI for Median PFS[‡]	(8.0,16.0)

[†] Progression-free survival is defined as disease progression, or death, whichever occurs first.
[‡] From product-limit (Kaplan-Meier) method for censored data.

Data Source: [redacted]

Figure 2-4

[redacted]

Table 2-5

Summary of Progression-Free Survival Based on Independent Radiology Review
FAS Population

	MK-8669 (N=79)
Number (%) of PFS Events	29 (36.7)
Person-Weeks	901
Event Rate/100 Person-Weeks (%)	3.2
Median PFS (Weeks)‡	18.9
95% CI for Median PFS‡	[redacted]

† Progression-free survival is defined as disease progression, or death, whichever occurs first.
‡ From product-limit (Kaplan-Meier) method for censored data.

Data Source: [redacted]

Figure 2-5

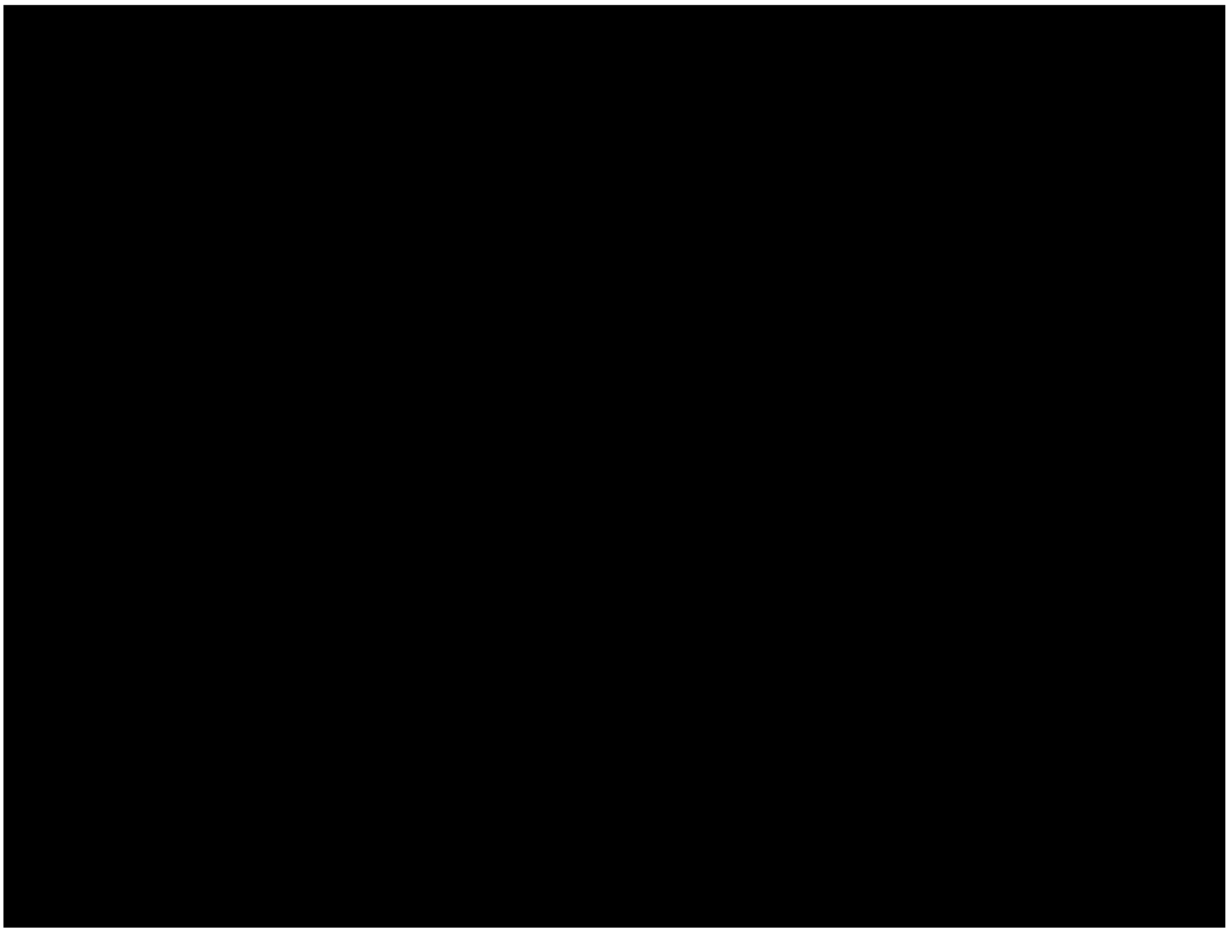

Table 2-6

Summary of Overall Survival
FAS Population

	MK-8669 (N=79)
Death (%)	55 (69.6)
Median Survival (Months)†	7.3
95% CI for Median Survival†	(4.4,10.8)

† From product-limit (Kaplan-Meier) method for censored data

Data Source: [redacted]

Figure 2-6

[redacted]

Table 2-7

Summary of Best Overall Response

	MK-8669	
	n	(%)
Patients in population	79	
COMPLETE RESPONSE	0	(0.0)
PARTIAL RESPONSE	1	(1.3)
STABLE DISEASE	36	(45.6)
PROGRESSIVE DISEASE	25	(31.6)
DISCONTINUED PRIOR TO ASSESSMENT	17	(21.5)

Data [redacted]

SAFETY ANALYSIS:

(1) Table 2-8 presents the overall AE (adverse experience) summary. Of the 79 patients as treated in the study, 68 (86.1%) experienced at least one AE considered by the investigator as related to study treatment. 49 (62%) patients were reported to have a SAE (serious adverse experience), and drug-related SAEs were reported in 12 (15.2%) patients. [redacted] The most common AEs included diarrhea, fatigue, mucosal inflammation (mucositis), nausea and rash. Overall, the AE profile of ridaforolimus reported in this study is consistent with the current AE profile of ridaforolimus in advanced cancer patients from other studies [redacted]

Table 2-8

Adverse Event Summary
APaT

	MK-8669	
	n	(%)
Patients in population	79	
with one or more adverse events	77	(97.5)
with no adverse event	2	(2.5)
with drug-related[†] adverse events	68	(86.1)
with serious adverse events	49	(62.0)
with serious drug-related adverse events	12	(15.2)
who died	22	(27.8)
discontinued[‡] due to an adverse event	20	(25.3)
discontinued due to a drug-related adverse event	3	(3.8)
discontinued due to a serious adverse event	18	(22.8)
discontinued due to a serious drug-related adverse event	2	(2.5)

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

Data Source: [redacted]

CONCLUSIONS: Ridaforolimus showed improved PFS with a favorable OS trend in NSCLC patients with KRAS mutation compared to placebo in the randomized population after 8 weeks ridaforolimus open-label lead-in. However, since the study met the stopping rule for futility at the IA based on the results of the 8-week, open-label lead-in period, enrollment in the study was terminated early. As a result, the sample size in the randomized population was smaller than planned and the actual level of statistical significance cannot be formally established. The AE profile of ridaforolimus reported in this study is consistent with the safety profile of ridaforolimus in advanced cancer patients from other studies.

AUTHORS: [redacted]