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-0646 dalotuzumab, IV mCRC	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Phase II/III Study of Dalotuzumab (MK-0646) Treatment in Combination with Cetuximab and Irinotecan for Patients with Metastatic Colorectal Cancer #004

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 (78) Worldwide

PUBLICATION(S): MK-0646-004 Presentation at ASCO [redacted] Abstract for MK-0646-004 at ASCO [redacted].

PRIMARY THERAPY PERIOD: 24-Jan-2008 to 11-Aug-2009 **CLINICAL PHASE:** II/III

DURATION OF TREATMENT: Patients were treated with dalotuzumab (MK-0646) or placebo in combination with cetuximab and irinotecan until one of the following off-study criteria were met: disease progression; pregnancy; unacceptable adverse experiences (AEs); withdrawal of consent; patient noncompliance; or other events that precluded further administration of study drugs in the judgment of the investigator. After Interim Analysis 1, patients continuing on cetuximab and/or irinotecan were treated according to standard of care.

OBJECTIVE(S):

Primary: (1) To determine overall survival of patients with metastatic colorectal cancer expressing the wild type KRAS (wtKRAS) genotype treated with the combination of dalotuzumab, cetuximab, and irinotecan compared to patients treated with cetuximab and irinotecan alone; (2) To evaluate progression-free survival of patients with metastatic colorectal cancer expressing the wtKRAS genotype treated with the combination of dalotuzumab, cetuximab, and irinotecan compared to patients treated with cetuximab and irinotecan alone and (3) To assess the safety profile of dalotuzumab in combination with cetuximab and irinotecan.

Secondary: (1) Evaluate the objective response rate of patients with metastatic colorectal cancer expressing the wtKRAS genotype treated with the combination of dalotuzumab, cetuximab, and irinotecan compared to patients treated with cetuximab and irinotecan alone; (2) Evaluate progression-free survival of patients with metastatic colorectal cancer enrolled prior to Amendment 04 treated with the combination of dalotuzumab, cetuximab, and irinotecan compared to patients treated with cetuximab and irinotecan alone.

Tertiary: (1) Assess the human-anti-humanized-antibody (HAHA) response to dalotuzumab; (2) Characterize the health-related quality of life, health status, and healthcare resource utilization of patients with metastatic colorectal cancer expressing the wtKRAS genotype treated with the combination of dalotuzumab, cetuximab, and irinotecan compared to patients treated with cetuximab and irinotecan alone.

STUDY DESIGN:

This was a multicenter, double-blind, randomized, placebo-controlled, Phase II/III study of dalotuzumab administered to patients with metastatic colorectal cancer who previously failed both oxaliplatin and irinotecan-based chemotherapy regimens. These patients should have progressed upon completion of therapy with objective radiological evidence of progression.

Prior to the start of the blinded study, an open label (OL) assessment of safety for each of the two dalotuzumab dose regimens was performed. DSMB members agreed to continue study to blinded phase.

After Amendment 04, study enrollment was limited to patients with wild-type KRAS (wtKRAS) metastatic colorectal cancer. [redacted]

The enrollment was to be in a 1:1:1 ratio if both dalotuzumab treatment arms had acceptable safety or 1:1 ratio if only one dalotuzumab treatment arm had acceptable safety at the completion of the open label safety run in.

Table 2-1 presents details about different treatment arms used in this study.

Table 2-1

Treatment arms

Open Label (OL) Safety Run in		Blinded Randomized phase		
Q1W	Q2W	Q1W	Q2W	Q1W
MK-0646 10 mg/kg + cetuximab + irinotecan	MK-0646 15 mg/kg / 7.5 mg/kg + cetuximab + irinotecan	MK-0646 10 mg/kg + cetuximab + irinotecan	MK-0646 15 mg/kg / 7.5 mg/kg (placebo given on off weeks) + cetuximab + irinotecan	Placebo + cetuximab + irinotecan
q1w = Every week; q2w = Every two week (every other week)				

At three prespecified intervals during the blinded portion of the study, the interim data obtained were to have been analyzed. These data were to have been reviewed by an independent external Data Safety Monitoring Board (DSMB) to decide whether to continue or stop the study. [redacted]

After Interim Analysis 1, the SPONSOR followed DSMB guidance to discontinue dosing of dalotuzumab or Placebo in all patients with wild-type KRAS cancer. [redacted] Patients with mutant KRAS tumors could continue on the assigned dosing schedule of dalotuzumab or Placebo. Based on this action, no further interim analyses were planned for this study. Patients were followed for AEs related to dalotuzumab or placebo until the earlier of study discontinuation or 30-days after dalotuzumab or placebo discontinuation.

[redacted]

SUBJECT/PATIENT DISPOSITION:

Table 2-2

Disposition of Patients
(all patients as treated)

	MK-0646 10 mg/kg weekly		MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks (OL)		MK-0646 10 mg/kg weekly (OL)		MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks		Placebo + cetuximab + irinotecan		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	180		8		10		180		178		556	
Study Disposition												
Discontinued	176	(97.8)	8	(100.0)	10	(100.0)	176	(97.8)	176	(98.9)	546	(98.2)
Adverse Event	20	(11.1)	2	(25.0)	3	(30.0)	13	(7 2)	21	(11.8)	59	(10.6)
Lost To Follow-Up	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	2	(1.1)	3	(0.5)
Physician Decision	17	(9.4)	0	(0.0)	1	(10.0)	8	(4.4)	9	(5.1)	35	(6.3)
Progressive Disease	118	(65.6)	5	(62 5)	5	(50.0)	138	(76.7)	130	(73.0)	396	(71.2)
Protocol Violation	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Study Terminated By Sponsor	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.2)
Withdrawal By Subject	20	(11.1)	1	(12 5)	1	(10.0)	16	(8 9)	13	(7.3)	51	(9.2)
Unknown	4	(2.2)	0	(0.0)	0	(0.0)	4	(2 2)	2	(1.1)	10	(1.8)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record.
Unknown: A disposition record did not exist at the time of reporting.

Data Source: [redacted]

[redacted]

DOSAGE/FORMULATION NOS.:

Cetuximab was given at an initial dose of 400 mg/m^2 over 120 minutes followed by weekly infusions of 250 mg/m^2 over 60 minutes. Patients were premedicated with a histamine-receptor antagonist prior to the first cetuximab dose. Premedication for subsequent cetuximab doses were at the discretion of the investigator.

Irinotecan was infused over 30 to 90 minutes at the same dose and schedule as that given during the patient's most recent pre-study therapy.

Patients assigned to a dalotuzumab-containing regimen received dalotuzumab as per one of the two specified regimens. In Arm A, dalotuzumab was infused once weekly at 10 mg/kg over 60 or 120 minutes. In Arm B, patients were infused with an initial (loading) of 15 mg/kg dalotuzumab over 60 or 120 minutes followed by infusions at 7.5 mg/kg (maintenance) dose over 60 or 120 minutes beginning every alternate week. Dalotuzumab infusions were started one week after the first dose of cetuximab infusion to distinguish between toxicities due to either drug. Dalotuzumab was formulated as 20 mg/ml solution in a total volume of 12.7 ml.

Table 2-3 presents study medication supply. Irrinotican was locally sources.

Table 2-3

Study Medication Supply

Clinical Material	Potency / Fill Volume	Dosage Form	Batch #
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	[redacted]
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Cetuximab	5mg/mL 20mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Dalotuzumab (MK-0646)	20mg/mL 12mL	Solution for IV Infusion	
Above Information was provided by Merck Global Clinical Supply Operations.			

[redacted]

DIAGNOSIS/INCLUSION CRITERIA: Patients ≥18 years of age with histologically or cytologically confirmed metastatic colorectal cancer who had previously failed both irinotecan and oxaliplatin and had progressed on or within 3 months of their last therapy. Patients were randomized to receive either MK-0646 10 mg/kg weekly (q1w) or 15 mg/kg loading followed by 7.5 mg/kg every 2 weeks (q2w) or placebo (pbo) combined with cetuximab and irinotecan at standard dose/schedule. Patients continued on treatment until disease progression with radiological response assessments every 6 weeks. Patient has an Eastern Cooperative Oncology Group (ECOG) Performance status of 0 to 1 and adequate organ function. After Amendment 04, patient has wild-type KRAS (wtKRAS) metastatic colorectal cancer.

EVALUATION CRITERIA:

Efficacy Measurements

Radiological evaluation of tumor growth using imaging techniques such as CT or MRI, assessment of overall disease status by categorizing radiological evaluations using Response Evaluation Criteria in Solid Tumors (RECIST), and determination of progression-free and overall survival using statistical analysis. A patient-reported outcome measurement tool, EQ-5D questionnaire, was utilized after Interim Analysis 1 to assess patient quality of life on the respective treatment arms. Paraffin-embedded tumor specimens (from core needle biopsies or fine needle aspirates) were obtained on an optional basis at baseline and Week 6 of study drug administration to determine responsiveness of biomarkers within the tumor to dalotuzumab combination therapy. Both immunohistochemistry (IHC) and expression profiling methods were used for these studies as appropriate. Serum concentrations of dalotuzumab were also measured.

Safety Measurements

The safety endpoints included physical examinations, vital signs, ECOG performance status, laboratory studies, and assessment of AEs. Any toxicity to study drug or comparators was graded and recorded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

[redacted]

STATISTICAL PLANNING AND ANALYSIS:

Efficacy Analyses

The primary and key secondary endpoints, primary analysis population, and the statistical methods that were to be employed for the efficacy analyses are presented in Table 2-1 [redacted]

Comparisons between dalotuzumab and placebo with respect to the dual primary endpoints, progression-free survival (PFS) and overall survival (OS) in the wtKRAS population, were be performed overall at α=0.0250 (one-sided). To limit the probability of a false claim, a Bonferroni style approach was used to divide alpha between overall survival (0.02) and progression-free survival (0.005). [redacted]

Since the trial was terminated early due to lack of efficacy, many of the pre-specified analyses were not performed, including:

- Patient health-related quality of life (EuroQOL, EQ-5D)
- PK parameters
- Genetic polymorphism typing results in human FcγRII and FcγRIII.

Although not pre-specified, additional ITT analyses for all patients, regardless of KRAS evaluation or status were performed for PFS and OS.

Safety Analyses

The All-Patients-as-Treated population was employed for safety analyses. Grade 3-5 AEs, drug related Grade 3-5 AEs, study therapy discontinuations due to an AE, dose modifications due to an AE, and infusion reactions were pre-specified as events of special interest (Tier 1 events). P-values and 95% confidence intervals (CIs) were to be calculated using the Miettinen and Nurminen method [redacted] for between-treatment differences in the percentage of patients with events.

Power and Sample Size

The purpose of the first two interim analyses was to test proof-of-concept for dalotuzumab in metastatic colorectal cancer. The combined tests (Interim Analyses 1 and 2) for POC had approximately 80% probability to detect a clinically meaningful improvement in progression-free survival (true HR=0.63) in at least one of the dalotuzumab arms in comparison to placebo with a 5% chance of a false positive (i.e. true HR=1.00 for both dalotuzumab arms). This study was event-driven, and was to be completed when approximately 700 combined deaths in wtKRAS patients enrolled after Amendment 04 occurred in the continuing dalotuzumab and the control arm in the blinded portion of the trial, presuming that the study was not stopped earlier for futility, efficacy or safety considerations. It was expected that up to 1156 wtKRAS patients would be randomized with an expected follow-up of 14 months to achieve 700 deaths in wtKRAS patients enrolled after Amendment 04. With 700 events in any arm-wise comparison between placebo and dalotuzumab arm, the study had 77% power to detect a 20% reduction in hazard rate (in the efficacious experimental arm versus the control arm) when controlling the overall Type-I error rate at 0.02 (one-sided) for overall survival. It was expected that 1168 patients would enroll in the overall study.

Interim Analyses

Three interim analyses were planned in the Phase II/III portion of this study. The endpoint(s), the timing, and the purpose of the interim analyses are summarized in Table 2-2 below. [redacted]

RESULTS:

Efficacy:

Primary Analysis Results at Interim Analysis 1.

Since the trial was stopped after evaluation of efficacy at the first interim analysis, the first interim analysis is also the final analysis for the trial. These analyses included patients enrolled both before and after Amendment 4 classified as having wild-type KRAS disease as specified in the interim analysis plan. Table 2-4 shows the primary analysis of progression free survival (PFS) at that time; corresponding Kaplan-Meier plots [redacted] Median PFS was longer in the control (placebo+ cetuximab+ irinotecan) group (5.5 months) than in either the q2 weekly MK-0646 group (5.3 months) or weekly MK-0646 group (4.0 months). P-values computed for these analyses were one-sided as the direction of the treatment effect was not anticipated. These are easily converted to 2-sided p-values for comparing the hazard ratios in the MK-0646 groups to control. Compared to control, the weekly MK-0646 group had an elevated hazard ratio of 1.25 (2-sided p-value=0.144) and the q2 weekly MK-0646 group had a hazard ratio of 1.16 (2-sided p-value=0.318).

Table 2-4

Summary of Progression-Free Survival with stratified Cox proportional hazards model (Intention-To-Treat, wild-type KRAS)

Treatment	N	Death or Progression (%)	Median Survival (Months)	12 Months Survival Rate‡	Treatment vs. Control	
					Hazard Ratio (95% CI)†	p-Value†
MK-0646 10 mg/kg weekly	119	83 (69.7)	4.0	0.15	1.25 (0.93,1.69)	0.928
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks	119	89 (74.8)	5.3	0.08	1.16 (0.87,1.56)	0.841
Placebo + cetuximab + irinotecan	116	91 (78.4)	5.5	0.11		

Pairwise Comparison	Hazard Ratio (95% CI)†	p-Value†
MK-0646 10 mg/kg weekly Versus Placebo + cetuximab + irinotecan	1.25 (0.93,1.69)	0.928
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks Versus Placebo + cetuximab + irinotecan	1.16 (0.87,1.56)	0.841
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks Versus MK-0646 10 mg/kg weekly	0.95 (0.70,1.28)	0.359

† Based on score test from a Cox proportional hazards model, stratified for baseline ECOG score (levels: 0, 1). Hazard ratio is based on the hazard of the first treatment listed divided by the second treatment. 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]

Overall survival was also compared between treatment groups in Table 2-5 [redacted] for the same patient population. Median survival was longer in the control (placebo+ cetuximab+ irinotecan) group (14.0 months) than in either the q2 weekly MK-0646 (12.4 months) or weekly MK-0646 (11.0 months) group. Again converting p-values to 2-sided, compared to control the hazard ratio for the q2 weekly MK-0646 was 1.21 (2-sided p=0.272) and for the weekly MK-0646 group was 1.38 (2-sided p=0.072).

Table 2-5

Summary of Overall Survival with stratified log-rank
(Intention-To-Treat, wild-type KRAS)

Treatment	N	Death (%)	Median Survival (Months)	12 Months Survival Rate‡	Treatment vs. Control	
					Hazard Ratio (95% CI)†	p-Value†
MK-0646 10 mg/kg weekly	119	70 (58.8)	11.0	0.46	1.38 (0.97,1.96)	0.964
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks	119	75 (63.0)	12.4	0.51	1.21 (0.86,1.72)	0.864
Placebo + cetuximab + irinotecan	116	59 (50.9)	14.0	0.55		

Pairwise Comparison	Hazard Ratio (95% CI)†	p-Value†
MK-0646 10 mg/kg weekly Versus Placebo + cetuximab + irinotecan	1.38 (0.97,1.96)	0.964
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks Versus Placebo + cetuximab + irinotecan	1.21 (0.86,1.72)	0.864
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks Versus MK-0646 10 mg/kg weekly	0.86 (0.61,1.20)	0.180

† Based on score test from a Cox proportional hazards model, stratified for baseline ECOG score (levels: 0, 1). Hazard ratio is based on the hazard of the first treatment listed divided by the second treatment. P-Value is one-sided for testing H0: HR ≥1 versus H1: HR <1

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

Data Source: [redacted]

Intention-to-treat Analysis

An exploratory analysis was specified in the protocol for all patients randomized. This includes patients with known (wild-type or mutant) or unknown KRAS status. This analysis does not suffer from the potential selection bias of the interim analysis 1. Prior to Amendment 04, patients were not required to have KRAS status evaluated prior to study entry, and some of these patients who were not tested for KRAS prior to enrollment could not be consented for evaluation of KRAS status before they had died. Thus, the analyses above may have under-estimated event rates for wild-type KRAS patients in all treatment groups.

Table 2-6 [redacted] show PFS by treatment group for all randomized patients. With the addition of wild- type and unknown KRAS patients, the median PFS was shorter in each treatment group than in the patients known to have KRAS wild-type disease. Median PFS was longer in the control (placebo+ irinotecan+ cetuximab) group (4.0 months) compared to the q2 weekly MK-0646 (2.9 months) or weekly MK-0646 (3.4 months) group. Compared to control, the hazard ratio was elevated in both the q2 weekly MK-0646 group (hazard ratio=1.14, 2-sided p=0.274) and the weekly MK-0646 group (hazard ratio=1.13, 2-sided p=0.338).

Table 2-6

Summary of Progression-Free Survival with stratified Cox proportional hazards model
(Intention-To-Treat, all patients)

Treatment	N	Death or Progression (%)	Median Survival (Months)	12 Months Survival Rate‡	Treatment vs. Control	
					Hazard Ratio (95% CI)†	p-Value†
MK-0646 10 mg/kg weekly	180	130 (72.2)	3.4	0.11	1.13 (0.88,1.43)	0.831
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks	180	139 (77.2)	2.9	0.05	1.14 (0.90,1.45)	0.863
Placebo + cetuximab + irinotecan	180	137 (76.1)	4.0	0.08		

Pairwise Comparison	Hazard Ratio (95% CI)†	p-Value†
MK-0646 10 mg/kg weekly Versus Placebo + cetuximab + irinotecan	1.13 (0.88,1.43)	0.831
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks Versus Placebo + cetuximab + irinotecan	1.14 (0.90,1.45)	0.863
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks Versus MK-0646 10 mg/kg weekly	1.01 (0.80,1.29)	0.544

† Based on score test from a Cox proportional hazards model, stratified for baseline ECOG score (levels: 0, 1). Hazard ratio is based on the hazard of the first treatment listed divided by the second treatment. P-Value is one-sided for testing H0: HR ≥1 versus H1: HR < 1
‡ From product-limit (Kaplan-Meier) method for censored data

Data Source: [redacted]

Table 2-7 [redacted] show overall survival results in all randomized patients. Median survival was similar in the control (10.1 months) and q2 weekly MK-0646 (10.3 months) and slightly shorter in the weekly MK-0646 group (9.2 months). Hazard ratios for the MK-0646 groups were slightly elevated compared to control (1.04 for the q2 weekly MK-0646 group with 2-sided p=0.760; 1.12 for the weekly MK-0646 group, 2-sided p=0.382).

Table 2-7

Summary of Overall Survival with stratified log-rank
(Intention-To-Treat, all patients)

Treatment	N	Death (%)	Median Survival (Months)	12 Months Survival Rate‡	Treatment vs. Control	
					Hazard Ratio (95% CI)†	p-Value†
MK-0646 10 mg/kg weekly	180	117 (65.0)	9.2	0.41	1.12 (0.86,1.46)	0.809
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks	180	121 (67.2)	10.3	0.40	1.04 (0.80,1.35)	0.620
Placebo + cetuximab + irinotecan	180	109 (60.6)	10.1	0.42		

Pairwise Comparison	Hazard Ratio (95% CI)†	p-Value†
MK-0646 10 mg/kg weekly Versus Placebo + cetuximab + irinotecan	1.12 (0.86,1.46)	0.809
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks Versus Placebo + cetuximab + irinotecan	1.04 (0.80,1.35)	0.620
MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks Versus MK-0646 10 mg/kg weekly	0.91 (0.70,1.18)	0.234

† Based on score test from a Cox proportional hazards model, stratified for baseline ECOG score (levels: 0, 1). Hazard ratio is based on the hazard of the first treatment listed divided by the second treatment. P-Value is one-sided for testing H0: HR ≥1 versus H1: HR <1
‡ From product-limit (Kaplan-Meier) method for censored data

Data Source: [redacted]

[redacted]

Safety :
Table 2-8 presents an overall summary of clinical and laboratory AEs reported for the total of 556 patients by arm. Overall, all of the patients experienced one or more AEs. The percentage of patients who experienced drug-related adverse events was comparable among all active and placebo treatment arms. The percentage of patients who experienced SAEs was slightly higher in MK-0646 10 mg/kg weekly arm compared to placebo and combination arms in the blinded part of the study; it was similar between placebo and MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks arm in the blinded part of the study. The percentage of patients who experienced drug-related SAEs was comparable between placebo arm and combination arms in the blinded part of the study. The percentage of patients who discontinued the study due to AE was comparable between placebo arm and combination arms in the blinded part of the study. The percentage of patients who discontinued the study due to drug-related AE was comparable between placebo arm and combination arms in the blinded part of the study. The percentage of patients who had an AE associated with death during the study period was comparable between placebo arm and combination arms in the blinded part of the study.

Table 2-8

Adverse Event Summary
(all patients as treated)

	MK-0646 10 mg/kg weekly		MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks (OL)		MK-0646 10 mg/kg weekly (OL)		MK-0646 15 mg/kg / 7.5 mg/kg q2 weeks		Placebo + cetuximab + irinotecan		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	180		8		10		180		178		556	
with one or more adverse events	180	(100.0)	8	(100.0)	10	(100.0)	180	(100.0)	178	(100.0)	556	(100.0)
with no adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related† adverse events	177	(98.3)	8	(100.0)	10	(100.0)	176	(97.8)	168	(94.4)	539	(96.9)
with serious adverse events	92	(51.1)	5	(62.5)	4	(40.0)	77	(42.8)	75	(42.1)	253	(45.5)
with serious drug-related adverse events	43	(23.9)	2	(25.0)	3	(30.0)	33	(18.3)	24	(13.5)	105	(18.9)
who died	34	(18.9)	0	(0.0)	1	(10.0)	29	(16.1)	32	(18.0)	96	(17.3)
discontinued‡ due to an adverse event	44	(24.4)	3	(37.5)	4	(40.0)	40	(22.2)	45	(25.3)	136	(24.5)
discontinued due to a drug-related adverse event	11	(6.1)	3	(37.5)	3	(30.0)	20	(11.1)	15	(8.4)	52	(9.4)
discontinued due to a serious adverse event	35	(19.4)	1	(12.5)	3	(30.0)	23	(12.8)	37	(20.8)	99	(17.8)
discontinued due to a serious drug-related adverse event	5	(2.8)	0	(0.0)	2	(20.0)	6	(3.3)	9	(5.1)	22	(4.0)

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

Data Source: [redacted]

The AEs for all toxicity grades that were most commonly reported (in at least 20% of patients) [redacted] for all treatment arms including placebo were diarrhea (70.9%), nausea (53.2%), stomatitis (49.5%), decreased appetite (49.3%), dermatitis acneiform (49.1%), neutropenia (42.3%), rash (36.5%), fatigue (36.3%), abdominal pain (34.0%), dry skin (33.5%), vomiting (31.8%), hyperglycemia (29.7%), paronychia (27.9%), skin fissures (27.5%), asthenia (27.3%), alopecia (26.8%), pruritus (25.7%), constipation (25.5%), and hypomagnesaemia (21.8%).

The AEs of all toxicity grades that were most commonly reported as drug-related by investigators [redacted] for all treatment arms including placebo (in at least 20% of patients) included diarrhea (65.3%), dermatitis acneiform (49.1%), nausea (48.6%), stomatitis (46.6%), decreased appetite (42.1%), neutropenia (40.5%), rash (34.9%), fatigue (32.9%), dry skin (32.7%), skin fissures (26.8%), paronychia (26.3%), alopecia (26.3%), hyperglycemia (25.0%), vomiting (24.8%), pruritus (24.6%), asthenia (21.4%), and hypomagnesaemia (20.0%).

The AEs with a toxicity ≥ Grade 3 that were most commonly reported [redacted] for all treatment arms including placebo (in at least 10% of patients) were neutropenia (25.7%), diarrhea (19.6%), and hyperglycemia (15.3%), and neoplasm malignant (15.1%) (*Events of progression of disease are encoded as "Neoplasm Malignant"*).

The AEs with a toxicity ≥ Grade 3 that were most commonly reported as drug-related by investigators [redacted] for all treatment arms including placebo (in at least 5% of patients) included neutropenia (25.2%), diarrhea (18.0%), hyperglycemia (12.4%), dermatitis acneiform (8.1%), asthenia (6.1%), fatigue (5.6%), and rash (5.6%).

The percentage of patients who experienced at least one of investigator-reported clinical AEs of hyperglycemia, increased blood glucose, hypoglycemia, and decreased blood glucose was higher in treatment arms with MK-0646 with the range of 25.0% to 40.0% compared to placebo arm with 19.7%. [redacted]

In addition, data analysis was also performed to evaluate the incidence of increased or decreased serum glucose in the evaluable patients during the treatment and post-study period. These patients should have had both baseline and post-study (the first 16 days post-dose) glucose test results available and the data analysis captured the most severe post baseline grade.

All the patients in MK-0646 10 mg/kg weekly (OL) treatment arm experienced hyperglycemia that was detected by increased serum glucose test; the percentage for remaining treatment arms including placebo was comparable. The percentage of patients with grade 3 and higher hyperglycemia was higher in active treatment group with the range of 22.2% to 37.5% compared to placebo arm with 9.9%. [redacted]

The percentage of patients who experienced at least one clinical AE related to hearing loss was higher in MK-0646 10 mg/kg weekly (OL) treatment arm (10%). None of the patients in treatment arm MK-0646 15 mg/kg /7.5 mg/kg q2 weeks (OL) experienced AR related to hearing loss [redacted].

The most commonly reported SAEs for all toxicity grades [redacted] for all treatment arms including placebo were neoplasm malignant for 86 patients (15.5%) (The event of disease of progression was encoded as "neoplasm malignant"), diarrhea (5.8%) and febrile neutropenia (3.1%).

The most commonly reported drug related SAEs for all toxicity grades [redacted] for all treatment arms including placebo were diarrhea (5.0%) and febrile neutropenia (2.7%).

Four (4) deaths were reported in the study as related to the study drugs [redacted]

[redacted]

CONCLUSIONS:

Based on a prespecified interim analysis and at the recommendation of the Data Safety and Monitoring Board (DSMB), the study was discontinued since the addition of MK-0646 to cetuximab and irinotecan failed to improve PFS or OS in patients with wt KRAS mCRC. Predictive biomarker analysis is ongoing to identify subpopulations that may benefit from treatment with dalotuzumab.

AUTHORS:

[redacted]