2. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation **Name of Finished Product**: Lenalidomide **Name of Active Ingredient**: CC-5013	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study: A Phase 2, Open-Label Study to Assess The Efficacy and Safety of Lenalidomide in Combination with Cetuximab in Pretreated Subjects with KRAS Mutant Metastatic Colorectal Cancer

Principal Investigators:

Investigators: A list of investigators in provided in Appendix 16.1.4.

Study center(s): Sixteen centers in Australia, Belgium, Italy and Sweden were activated. Thirteen of these sites enrolled subjects.

Publications (reference): None

Studied period (years): 1.14 years **Date first patient enrolled**: 07 Dec 2009 **Date last patient completed**: 25 Jan 2011	**Phase of development**: 2

Objectives:

Primary:

Phase 2a: to determine the maximum tolerated dose (MTD) of lenalidomide in combination with cetuximab in subjects with KRAS mutant metastatic colorectal cancer (CRC)

Phase 2b: to determine the response rate per RECIST in subjects with KRAS mutant metastatic CRC.

Secondary:

To evaluate the safety and tolerability of lenalidomide in combination with cetuximab and to assess the clinical efficacy in subjects with KRAS mutant metastatic CRC.

Exploratory:

To analyze biomarkers as measures for validation of clinical efficacy and toxicity

Methodology:

This was a phase 2, multicenter, open-label study of lenalidomide in combination with cetuximab to determine the efficacy and safety of lenalidomide in combination with cetuximab in subjects with KRAS mutant metastatic colorectal cancer. The study consisted of a safety lead-in phase – Phase 2a, in which the MTD of lenalidomide in combination with cetuximab was determined, and was used as the starting dose for the proof of concept (POC) phase – Phase 2b, in which the response rate per RECIST was to be determined. All subjects who discontinued from the study for any reason other than withdrawal of consent were to enter a Follow-up period that included one follow-up visit 28 days after last dose and subsequent telephone contacts every 90 days until death or 5 years post-discontinuation.

Phase 2a – Safety Lead-in

Subjects meeting all eligibility criteria were enrolled by IVRS into the Phase 2a – Safety Lead-in part to

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receive treatment with lenalidomide in combination with cetuximab to establish the MTD with the combination. The MTD of lenalidomide was defined as the highest dose level at which no more than 1 out of 6 subjects experience a dose-limiting toxicity (DLT) during Cycle 1 of lenalidomide in combination with cetuximab. Initially 6 subjects were enrolled and treated with a daily oral dose of lenalidomide at 25 mg administered on Days 1-28 of each 28-day cycle and intravenous (IV) infusions of cetuximab (400 mg/m^2 first infusion only, then 250 mg/m^2 subsequently) administered on Days 1, 8, 15, and 22 of each 28-day cycle. No dose escalation or intra-patient dose escalation were allowed during the safety lead-in part of the study. All subjects were to continue on investigational product(s) until documented tumor progression, unacceptable toxicity, death, or treatment discontinuation for any other reason. The definition of DLT is provided in Appendix 16.1.1 Section 8.1.2. Subjects who experienced a DLT were allowed to continue on treatment at the Investigator's discretion at a lower dose of lenalidomide in accordance with the dose modification guidelines in Appendix 16.1.1 Section 10.3.1. Following Cycle 1, all subjects were allowed to continue on assigned treatment until documented tumor progression, unacceptable toxicity, death, or treatment discontinuation for any other reason and be followed for toxicity and secondary endpoints.

Phase 2b – Proof of Concept

Subjects meeting all eligibility criteria were to be enrolled and randomized by IVRS at a 1:1 ratio to receive either oral lenalidomide at the MTD (determined during the Safety Lead-in part) on Days 1-28 plus IV infusions of cetuximab (400 mg/m^2 initial infusion only, then 250 mg/m^2 subsequently) administered on Days 1, 8, 15, and 22 of each 28-day cycle or daily oral lenalidomide at 25 mg on Days 1-28 of each 28-day cycle.

Phase 2b – Expansion

There was an option to proceed to Phase 2b – Expansion part if the response rate from either arm in the Phase 2b – POC part was deemed significantly higher than 10%.

Subjects meeting all eligibility criteria were to be enrolled by IVRS to take oral lenalidomide (dose determined from Safety Lead-in part) on Days 1-28 plus IV infusions of cetuximab (400 mg/m^2 initial infusion, then 250 mg/m^2 subsequently) administered on Days 1, 8, 15, and 22 of each 28-day cycle. Celgene Corporation was to reassess the feasibility of adding a single agent lenalidomide arm to the Phase 2b – Expansion part of the study depending on results from the Phase 2b – POC part.

Throughout the study adverse events were graded using the CTCAEAE Version 4.0. If cetuximab was discontinued, lenalidomide could be continued until documented tumor progression, unacceptable toxicity, death, or treatment discontinuation for any other reason. Safety measurements and analysis were to be performed at each visit as outlined in Table 2 (Table of Assessments). Tumor assessments were performed using conventional (or spiral) CT/MRI imaging.

For all phase study treatment was to continue until documented tumor progression per RECIST 1.1, unacceptable toxicity, death, or treatment discontinuation for any other reason.

Follow-up Period

All study subjects who discontinued from the study for any reason other than withdrawal of consent were to enter the Follow-up period that includes one follow-up visit 28 days after last dose and subsequent telephone contacts every 90 days until death or 5 years post-discontinuation.

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Enrollment was stopped due to lack of efficacy in any of the treatment arms and failure to achieve the planned response objective. The study was terminated prior to the Expansion Phase and efficacy and survival information were not collected.

Number of patients (planned and analyzed):

Phase 2a: planned: 6 to 18; analyzed: 8

Phase 2b: planned: 82; analyzed: 42 (43 subjects were enrolled but 1 subject never received study drug).

Diagnosis and main criteria for inclusion:

Adult subjects with histologically or cytologically confirmed metastatic colorectal adenocarcinoma with documented KRAS mutant tumor. Subjects must have progressed on oxaliplatin- and irinotecan-containing regimens in the metastatic setting, with at least one of these regimens containing bevacizumab.

Test product, dose and mode of administration, batch number:

Lenalidomide was taken orally at 25 mg/day.

Lot number	Expiration date	Pack type
09F0415	31-Oct-11	Lenalidomide 25mg
09F0414	31-Aug-11	Lenalidomide 20mg
09F0413	31-Mar-12	Lenalidomide 15mg
09F0412	30-Apr-11	Lenalidomide 10mg
09F0411	30-Apr-11	Lenalidomide 5mg

Cetuximab was administered IV (400 mg/m^2 initial infusion only, then 250 mg/m^2 subsequently) on Days 1, 8, 15, and 22 of each 28-day cycle.

Lot number	Expiration date	Pack type
09F0416	31-Aug-11	Cetuximab 100 mg/20 ml vial
09F0421	30-Sep-11	Cetuximab 100 mg/20 ml vial

Duration of treatment:

For both phases treatment was to continue until documented tumor progression, unacceptable toxicity, death, or treatment discontinuation for any other reason.

Reference therapy, dose and mode of administration, batch number:

Not applicable

Criteria for evaluation:

Efficacy: tumor assessment, tumor response rate according to RECIST 1.1, ECOG performance status, overall survival.

Safety: adverse event reporting, concomitant medications, physical examination, vital signs, hematology laboratory evaluations, chemistry laboratory evaluations, pregnancy testing, thyroid function test.

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Exploratory: biomarker analysis.

Statistical methods:

All analyses were performed by study phase and treatment group. The baseline characteristics of treated subjects are summarized. An accounting is made of all subjects who received study drugs and, in particular, the number of subjects who died or withdrew during treatment is specified.

Efficacy Analysis: This report is presented in the abbreviated clinical study report format and therefore does not include a discussion of the analysis of efficacy.

Safety Analysis: Data from all subjects who received at least 1 dose of study drug were included in the safety analyses. Study drug exposure is summarized. Adverse events, vital sign measurements, clinical laboratory information, and concomitant medications are tabulated and summarized by study phase, dose cohort or treatment group. All toxicities are summarized by relative and absolute frequency, severity grade based on the NCI CTCAE version 4.0 and relationship to treatment. Serious adverse events (SAE) are listed separately.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The best response observed was stable disease in a total of 9 subjects from both phases of the study (1 subject from Phase 2a and 8 subjects from the Phase 2b –POC). Five of these subjects were treated with the combination regimen and 3 with lenalidomide monotherapy. Based on these results, enrollment to the study was stopped prematurely and additional efficacy information for enrolled subjects was not collected.

SAFETY RESULTS:

During the Phase 2a portion of the study subjects were treated with lenalidomide for a median duration of 8.1 weeks (range: 4 to 16.4 weeks) and to cetuximab for a median of 7.1 weeks (range: 2.1 to 16.0 weeks). The median dose intensity for lenalidomide (i.e., the median dose of lenalidomide taken per unit time) was 175 mg/week (range: 168.8 to 175.0 mg/week) or 25 mg/day (range: 24.1 to 25 mg/day) suggesting that the majority of subjects tolerated continuous dosing of 25 mg/day lenalidomide for a median of 8.1 weeks. The median dose intensity of cetuximab was 287.9 mg/m^2/week (range: 268.1 to 420.0 mg/m^2/week). Median treatment duration with lenalidomide during the Phase 2b POC portion was 8 weeks for both treatment arms (range: 0.7 to 33 weeks for the lenalidomide treatment arm and 2.3 to 24.1 weeks for lenalidomide+cetuximab treatment arm). Median treatment duration with cetuximab of subjects in the lenalidomide treatment arm was 7.1 weeks (range: 1.3, to 23.1 weeks). The median dose intensity for lenalidomide was 175 mg/week or 25 mg/day for both treatment arms (range: 107.5 to 175 mg/week for the lenalidomide treatment arm and 130.7 to 175 mg/week for the lenalidomide+cetuximab treatment arm). Median dose intensity for cetuximab in the lenalidomide treatment arm was 301 mg/m^2/week (range: 202.7 to 505.6 mg/m^2/week).

One subject experienced a DLT during Cycle 1 of the Phase 2a safety lead-in portion of the study. Subject [redacted] developed grade 3 hypersensitivity reaction to cetuximab. Cetuximab treatment was permanently withdrawn. Since no other DLTs occurred during Cycle 1 of the Phase 2a portion of the study (per Appendix 16.1.1 Section 8.1.1), 25 mg/day lenalidomide daily was declared the MTD and

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was used as the starting dose for the Phase 2b POC portion of the study.

All 8 subjects in Phase 2a experienced at least 1 TEAE. The most commonly occurring TEAEs were gastrointestinal disorders (reported by 7 of 8 subjects [87.5%]) of which diarrhoea was the most common (occurring in 5 of 8 subjects [62.5%]). Rash was the only other TEAE that was reported by 5 of 8 subjects (62.5%). All other TEAEs occurred in no greater than 3 of 8 subjects. In Phase 2b, 20 (95.2%) of the 21 subjects in the lenalidomide treatment arm and all 21 subjects in the lenalidomide + cetuximab treatment arm experienced at least 1 TEAE. As in the Phase 2a portion, the majority (95.2%) of TEAEs reported by subjects in the lenalidomide + cetuximab arm were gastrointestinal disorders of which the most common was diarrhoea. Conversely, only 11 of 21 (52.4%) subjects in the single agent lenalidomide treatment arm reported TEAEs of gastrointestinal disorders and diarrhoea was the least common, occurring in only 1 subject (4.8%). Other common TEAEs occurring in ≥ 20% subjects in the lenalidomide treatment arm include abdominal pain and asthenia in 7 (33.3%) subjects, and fatigue and rash in 6 (28.6%) subjects. In the lenalidomide + cetuximab treatment arm, TEAEs occurring in ≥ 20% subjects include rash in 15 (71.4%) subjects, fatigue in 8 (38.1%) subjects, nausea and asthenia in 7 (33.3%) subjects, abdominal pain in 6 (28.6%) subjects, and constipation, pyrexia and dry skin in 5 (23.8%) subjects. In the single agent lenalidomide arm, nausea, constipation, pyrexia and dry skin occurred in 4 (19%), 4 (19%), 4 (19%) and 0 subjects, respectively.

The majority of AEs in the Phase 2a portion of the study were grade 1 or 2. There were no grade 4 AEs in this portion of the study. Grade 3 AEs occurred in 1 subject each and included tachycardia, abdominal pain, fatigue, general physical health deterioration, hypersensitivity, anorexia, hypokalaemia, dyspnoea and hypertension. One subject experienced a grade 5 TEAE of pulmonary embolism. In general, the majority of AEs in both treatment arms of Phase 2b were grade 1 or 2. The most common grade 3 AEs (occurring in ≥ 2 subjects) reported by subjects in the single agent lenalidomide treatment arm included abdominal pain and fatigue in 3 of 21 (14.3%) subjects, and ascites, asthenia, hyperbilirubinaemia and aspartate aminotreansferase (AST) increased in 2 of 21 (9.5%) subjects. Grade 3 TEAEs reported in ≥ 2 subjects in the lenalidomide + cetuximab treatment arm included diarrhoea, fatigue, and hyperbilirubinaemia in 3 of 21 (14.3%) subjects, and rash in 2 of 21 (9.5%) subjects. A total of 3 grade 4 TEAEs were reported by 1 subject each (4.8%) in the lenalidomide treatment arm and included constipation, hyperbilirubinaemia and blood alkaline phosphatase increased. There were no grade 4 AEs reported in the lenalidomide + cetuximab treatment arm. A total of 5 grade 5 AEs were reported in the lenalidomide treatment arm and included general physical health deterioration in 2 of 21 (9.5%) subjects and large intestine perforation, metastases to liver and metastases to lung in 1 subject (4.8%) each. A total of 3 grade 5 AEs were reported by 1 subject each in the lenalidomide + cetuximab treatment arm and included general physical health deterioration, septic shock and respiratory failure.

Five of the 8 subjects in Phase 2a experienced at least 1 TEAE that was suspected by the investigator to be related to lenalidomide. The most common lenalidomide-related TEAE was fatigue, occurring in 3 of 8 (37.5%) subjects followed by diarrhoea, anorexia, pruritus and rash, occurring in 2 (25%) subjects each. All other TEAEs deemed related to lenalidomide occurred in 1 subject each. All 8 subjects in this portion of the study experienced at least 1 TEAE suspected by the investigator to be related to cetuximab. The most common cetuximab-related AEs were rash in 5 of 8 (62.5%) subjects, fatigue, paronychia and dry skin each in 3 of 8 (37.5%) subjects and erythema, stomatitis and pruritus each in 2

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of 8 (25%) subjects. All other cetuximab-related AEs occurred in 1 subject each. In Phase 2b POC, 9 (42.9%) of the 21 subjects in the single agent lenalidomide treatment arm and 13 (61.9%) of the 21 subjects in the lenalidomide + cetuximab treatment arm experienced at least 1 TEAE that was suspected by the investigator to be related to lenalidomide. The most common lenalidomide-related TEAEs experienced by subjects in the lenalidomide treatment arm were rash in 4 (19%) of 21 subjects, fatigue in 3 (14.3%) of 21 subjects and pruritus in 2 (9.5%) of 21 subjects. All other TEAEs deemed related to lenalidomide occurred in 1 subject each. In the lenalidomide + cetuximab treatment arm, the most common lenalidomide-related AEs were fatigue and rash in 7 (33.3%) subjects, diarrhoea and nausea in 3 (14.3%) subjects and mucosal inflammation, headache and dyspnoea in 2 (9.5%) subjects. Nineteen of the 21 subjects in the lenalidomide + cetuximab treatment arm experienced at least 1 TEAE suspected by the investigator to be related to cetuximab. The most common cetuximab-related AEs were rash in 12 (57.1%) of 21 subjects, fatigue in 6 (28.6%) of 21 subjects, dry skin in 5 (23.8%) of 21 subjects, skin fissures in 3 (14.3%) of 21 subjects, and diarrhoea, stomatitis, erythema and pruritus in 2 (9.5%) subjects each. All other cetuximab-related TEAEs occurred in 1 subject each.

A total of 39 subjects died throughout the study. These include 7 of the 8 subjects in the Phase 2a – Safety Lead-in portion and 32 of the 43 subjects enrolled in the Phase 2b – Proof of Concept portion of the study. The majority of deaths (38 of 39) were due to progression of disease. Of these deaths, 34 were coded as "colorectal cancer" under "neoplasms benign, malignant and unspecified" system organ class, 2 were coded as "disease progression" under "general disorders and administration site conditions" system organ class, 1 subject each died of pulmonary embolism and respiratory failure (respiratory, thoracic and mediastinal disorders) associated with progressive disease. One subject died of septic shock (infections and infestations system organ class) that was not associated with disease progression. One subject died without ever taking study drug.

Five (62.5%) of the 8 subjects in Phase 2a experienced at least 1 treatment emergent SAE. All SAEs occurred in 1 subject each with the exception of general physical health deterioration, which occurred in 2 subjects. Of the 21 subjects in each of the treatment arms of Phase 2b POC, 9 (42.9%) subjects per arm experienced at least 1 SAE. In both treatment arms, all SAEs occurred in 1 subject each with the exception of abdominal pain and general physical health deterioration, each of which occurred in 2 subjects in the lenalidomide treatment arm, and diarrhoea, which occurred in 2 subjects in the lenalidomide + cetuximab treatment arm.

Three of the 8 subjects in Phase 2a (and) experienced AEs that resulted in withdrawal of both lenalidomide and/or cetuximab. A total of 4 AEs led to lenalidomide withdrawal. These AEs were general physical health deterioration (NCI CTCAE grade 2) in Subject , bone lesion (grade 2) in Subject , dyspnoea (grade 3) and pulmonary embolism (grade 5) both in Subject . All 4 AEs were classified as SAEs and neither was suspected to be related to either lenalidomide or cetuximab. A total of 6 AEs led to cetuximab withdrawal. These AEs were general physical health deterioration (NCI CTCAE grade 2) in Subject , bone lesion (grade 2) in Subject and tachycardia (grade 3), hypersensitivity (grade 3), dyspnoea (grade 3) and hypertension (grade 3) all in Subject (Listing 16.2.7.4). All 6 AEs were classified as SAEs. The latter 4 (that occurred in Subject) were suspected to be related to cetuximab. Lenalidomide treatment was not changed for this subject due to these AEs. In Phase 2b POC, 7 (33.3%) of the 21 subjects in the

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lenalidomide treatment arm and 5 (23.8%) of the 21 subjects in the lenalidomide + cetuximab treatment arm experienced at least 1 AE that led to permanent withdrawal of lenalidomide treatment. Each of these AEs occurred in 1 subject except for diarrhoea, which occurred in 2 (9.5%) subjects (and) in the lenalidomide + cetuximab treatment arm (and in 0 subjects in the lenalidomide treatment arm) and abdominal pain, which occurred in 4 (19%) subjects (and) in the lenalidomide treatment arm (0 subjects in the lenalidomide + cetuximab treatment arm). Of the AEs that led to discontinuation of lenalidomide, asthenia, back pain, abdominal pain, metastasis to central nervous system, intestinal obstruction, diarrhoea, and general physical health deterioration were classified as SAEs. Metastasis to central nervous system, intestinal obstruction and diahrrhoea (Subject and) also resulted in permanent discontinuation of cetuximab. Six of the 21 subjects in the lenalidomide + cetuximab treatment arm experienced at least 1 TEAE that led to permanent withdrawal of cetuximab. All of these TEAEs occurred in 1 subject each except for diarrhoea, which occurred in 2 subjects (and), and all except hypersensitivity (Subject) were classified as SAEs.

Two subjects in Phase 2a experienced at least 1 TEAE that led to reductions and/or interruptions of lenalidomide. These TEAEs were general physical health deterioration, pyrexia and viral infection. The AE of general physical health deterioration was deemed related to both lenalidomide and cetuximab and dosing of both drugs was interrupted. Pyrexia and viral infection were not considered to be drug related. In Phase 2b, 6 (28.6%) of the 21 subjects in the lenalidomide treatment arm and 9 (42.9%) of the 21 subjects in the lenalidomide + cetuximab treatment arm experienced AEs that led to dose reductions and/or interruptions of lenalidomide, and 7 (33.3%) subjects in the lenalidomide + cetuximab treatment arm experienced AEs that led to dose reductions and/or interruptions of cetuximab. Each of these AEs occurred in 1 subject with the exception of fatigue, which caused dose modifications of lenalidomide in 2 subjects in both treatment arms, and rash, which caused dose modifications of cetuximab in 2 subjects.

In Phase 2a, shifts from normal at baseline to low post-baseline values (in ≥ 2 subjects) were observed for absolute neutrophil count (ANC) (in 2 of 7 [28.6%] subjects), absolute lymphocytes (in 3 of 7 [42.9%] subjects) and hemoglobin (in 3 of 8 [37.5%] subjects). Shifts from normal at baseline to high post-baseline values (in ≥ 2 subjects) were observed for absolute monocytes, basophils, eosinophils, neutrophils (each in 2 of 7 [28.6%] subjects), platelets, (in 2 of 8 [25%] subjects) and monocytes (in 5 of 7 [71.4%] subjects). In Phase 2b, shifts from normal at baseline to low post-baseline values (in ≥ 20% subjects) in the lenalidomide treatment arm, were observed for absolute lymphocytes (in 4 of 20 [20%] subjects), hematocrit, RBC (each in 8 of 20 [40%] subjects) and hemoglobin (in 9 of 20 [45%] subjects). In the lenalidomide + cetuximab treatment arm, shifts from normal to low (in ≥ 20% subjects) were observed for absolute lymphocytes (in 7 of 21 [33.3%] subjects) and lymphocytes (in 10 of 21 [47.6%] subjects). Shifts from normal at baseline to high post-baseline values (in ≥ 20% subjects) in the lenalidomide treatment arm were observed for neutrophils (in 4 of 20 [20%] subjects), absolute monocytes (in 5 of 20 [25%] subjects), absolute eosinophils, basophils, eosinophils and monocytes, (each in 7 of 20 [35.0] subjects). In the lenalidomide + cetuximab treatment arm, shifts from normal to high (in ≥ 20% subjects) were observed for WBC (in 5 of 21 [23.8%] subjects), ANC, basophils, eosinophils, platelets (each in 6 of 21 [28.6%] subjects), absolute monocytes, neutrophils (each in 7 [33.3%] subjects) and monocytes (in 10 of 21 [47.6%] subjects).

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Shifts from normal at baseline to low post-baseline values (in ≥ 2 subjects) in Phase 2a were observed for chloride, creatinine, phosphate, potassium, sodium (each in 2 of 8 [25%] subjects), albumin, calcium, uric acid (each in 3 of 8 [37.5%] subjects) and urea (blood urea nitrogen [BUN]) (in 4 of 8 [50%] subjects). Shifts from normal at baseline to high post-baseline values (in ≥ 2 subjects) were observed for direct bilirubin (in 2 of 8 [25%] subjects), lactate dehydrogenase (LDH) (in 3 of 8 [37.5%] subjects), aspartate aminotransferase (AST) (in 4 of 8 [50%]) subjects) and alanine aminotransferase (ALT) (in 5 of 8 [62.5%] subjects). In the lenalidomide treatment arm of Phase 2b, shifts from normal at baseline to low post-baseline values (in ≥ 20% subjects) were observed for total protein (in 5 of 20 [25%] subjects), potassium (in 6 of 20 [30%] subjects) and albumin (in 7 of 20 [35%] subjects). In the lenalidomide + cetuximab treatment arm, shifts from normal to low (in ≥ 20% subjects) were observed for bicarbonate, phosphate, uric acid and magnesium (each in 5 of 21 [23.8%] subjects), creatinine and total protein (each in 6 of 21 [28.6%] subjects), calcium (in 7 of 21 [33.3%] subjects), albumin, potassium and urea (BUN) (each in 8 of 21 [38.1%] subjects). Shifts from normal at baseline to high post-baseline values (in ≥ 20% subjects) in the lenalidomide treatment arm were observed for total bilirubin (in 4 of 20 [20%] subjects), ALT (in 5 of 20 [25%] subjects) and direct bilirubin (in 6 of 20 [30%] subjects). In the lenalidomide + cetuximab treatment arm, shifts from normal to high (in ≥ 20% subjects) were observed for alkaline phosphatase, urea (BUN) (each in 5 of 21 [23.8%] subjects), total bilirubin (in 6 of 21 [28.6%] subjects), AST (in 8 of 21 [38.1%] subjects), ALT (in 9 of 21 [42.9%] subjects) and direct bilirubin (in 12 of 21 [57.1%] subjects).

There were few shifts in thyroid function from normal at baseline to abnormal post-baseline. During the Phase 2a portion of the study, 2 of 6 evaluable subjects had shifts from normal baseline thyroid stimulating hormone (TSH) levels to low post-baseline levels. During the Phase 2b POC portion of the study, 2 of 10 evaluable subjects in the lenalidomide treatment arm and 3 of 12 evaluable subjects in the lenalidomide + cetuximab treatment arm had shifts from normal baseline values of free triiodothyronine (T3) to low post-baseline values.

A total of 15 subjects had abnormal laboratory values that were reported as AEs. Most of these parameters were related to liver function and included increases in bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH). All of these subjects entered the study with target lesions in the liver and in some of these subjects there was an increase in the size of these lesions or appearance of new non-target lesions upon subsequent measurements. Changes in electrolyte levels (particularly potassium and calcium) were also frequently reported as AEs.

No notable shifts from normal baseline vital signs to abnormal post-baseline values were observed during the Phase 2a portion of the study. During the Phase 2b portion, 6 of 21 (28.6%) subjects and 8 of 21 (38.1%) subjects in the lenalidomide + cetuximab treatment arm had shifts from normal baseline to abnormal post-baseline diastolic blood pressure and pulse measurements, respectively.

Biomarker analysis of blood samples collected from all enrolled subjects at baseline and at each tumor assessment showed no correlation between OS and ; however, OS was significantly longer in -positive subjects than in -negative subjects.

CONCLUSION:

The AE and lab profile observed in this study is consistent with that observed in this patient population

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with advanced metastatic colorectal cancer. The safety profile for lenalidomide and cetuximab in this study is consistent with that observed for lenalidomide in other non-hematological malignancies (e.g., Studies CC-5013-ST-001, CC-5013-ST-002, CC-5013-ST-003, CC-5013-ST-004) as well as that reported for cetuximab in this subject population (see Erbitux® package insert). While the combination regimen appeared to be well tolerated, the relatively short duration of exposure to both drugs limits drawing a definitive conclusion regarding the safety of this treatment regimen in this subject population.

Date of the report:

13 Jun 2011

Date of Amended Report:

23 May 2012