2. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation **Name of Finished Product**: Pomalidomide **Name of Active Ingredient**: CC-4047	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study:

A Phase 2, Multicenter, Open-Label, Single Arm, Two-Stage Study to Evaluate the Efficacy and Safety of CC-4047 (Pomalidomide) in Patients with Advanced Soft Tissue Sarcomas Who Have Relapsed or Are Refractory to Systemic Anticancer Therapy

Principal Investigator: [redacted]

Investigators: [redacted]

Study center(s): 6 sites in the US were activated and ready for enrollment [redacted]. 3 of these sites [redacted] enrolled subjects.

Publications (reference):

None

Studied period (years):	**Phase of development**:
Date first patient enrolled: 28 Aug 2008 Date last patient completed: 11 Jan 2009	2

Objectives:

Primary:

Safety [type, frequency, and severity of adverse events (AEs) and relationship of AEs to pomalidomide]

Secondary:

Tumor response (Response Evaluation Criteria in Solid Tumors [RECIST])

[redacted]

Methodology:

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This was a phase 2, multicenter, open-label, single arm, two-stage study to evaluate the safety of CC-4047 (pomalidomide) in the treatment of patients with advanced soft tissue sarcomas who had relapsed or were refractory to systemic anticancer therapy.

Screening

Screening assessments for protocol eligibility were to be performed within 28 days of treatment initiation, as outlined in the Schedule of Assessments within the protocol. All scheduled laboratory studies were to be performed at a central laboratory.

[redacted]

Overall tumor burden and measurable disease were to be evaluated using the following techniques:

For all study subjects:

- Computed Tomography (CT) of the neck, chest, abdomen and pelvis;
- Bone scans

For some study subjects, when appropriate:

- Magnetic Resonance Imaging (MRI) of involved extremities, if appropriate (CT of extremities was allowed, but MRI was the recommended method);
- CT scan of the head may have been performed to rule out active central nervous system (CNS) metastases, if applicable.

All CT scans, MRIs and bone scans were to be sent to a central imaging facility for storage.

If no prior tissue specimen was available, or if tissue specimen was insufficient for the central laboratory to confirm the local histological diagnosis, or if deemed necessary by the investigator, a tissue biopsy was to be performed.

Measurement of pain intensity was to be performed using a numerical rating scale (NRS) and sarcoma-related pain medication intake was to be recorded.

The enrollment procedure was to be accomplished by a validated interactive voice response system (IVRS)/interactive web response system (IWRS).

Treatment Phase

Treatment initiation must have occurred no less than 3 weeks (21 days) from completion of prior approved therapy or procedure, or no less than 3 months (90 days) from completion of prior experimental/investigational drug therapy (non-approved, non-marketed compounds in development). The treatment consisted of 7 mg pomalidomide taken orally once daily (QD) on days 1 through 21 of each 28-day cycle and continued until documented disease progression, unacceptable toxicity, or voluntary withdrawal or at the discretion of the study physician. Hematopoietic growth factors could be used for prevention and for treatment as recommended per the American Society of Clinical Oncology (ASCO) guidelines. All study subjects should have received prophylactic anti-thrombotic therapy (e.g. low-dose aspirin, low-molecular weight heparin, warfarin, etc.).

A guideline for the reduction of the dose of pomalidomide based on National Cancer Institute Common

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Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 is provided in the protocol (Section 16.1.01).

Tumor response was to be assessed using the RECIST guidelines. Stable Disease (SD) must have been maintained for ≥ 16 weeks.

Adverse events were graded using the NCI CTCAE version 3.0.

CT scans and MRIs

Serial measurements of tumor response were to be performed every 8 weeks (C3D1, C5D1, C7D1, and C9D1) for the first 8 months and then every 12 weeks (C12D1, C15D1, etc.) for the remainder of the study treatment phase, at the complete response/partial response (CR/PR) confirmation visit (no less than 4 weeks but no more than 5 weeks after the criteria for response were first met) and at the treatment discontinuation visit with the following techniques:

- CT scan of the neck, chest, abdomen and pelvis
- MRI of involved extremities, only if it was performed and positive at screening (CT of extremities is allowed, but MRI is recommended)

Bone Scans

- If the bone scan was positive for tumor at screening, it was to be repeated at the CR / PR confirmation visit. It was also to be repeated to confirm SD at weeks 16 and 24.
- If the bone scan was negative at screening, it was only to be repeated if a study subject complained of bone pain, suggesting a possible bone metastasis.
- If the bone scan was equivocal for bone lesion(s), the presence of the lesion was to be confirmed with an X-ray, CT or MRI.

CT Scan of the Head:

- Head CT scan was to be done if a subject developed CNS symptoms suggesting metastases.

The development of pleural effusions or ascites were considered as indications of progressive disease (malignant ascites or malignant pleural effusions), unless documented to be non-malignant via a thoracentesis or paracentesis by the investigator.

A subject requiring a sarcoma lesion resection was to be discontinued from the study.

Pain intensity measurement (an average of pain intensity within the 7 days prior to office visit) was to be performed using a NRS every 28 days and at treatment discontinuation visit. Sarcoma-related pain medication intake was to be recorded every 28 days and at treatment discontinuation visit.

Laboratory evaluations (complete blood count [CBC]), differential and serum chemistries were to be obtained weekly for the first 28 days of treatment (Study Days 1, 8, 15 and 22), every two weeks during the following 56 days (Study Days 29, 43, 57 and 71), and every 4 weeks thereafter and at the treatment discontinuation visit. All blood samples were to be collected prior to the administration of pomalidomide.

ECOG performance status was to be evaluated every 28 days and at the treatment discontinuation visit.

Thyroid function tests (thyroid-stimulating hormone [TSH], T3 and T4 levels) were to be performed

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every 3 months and at the treatment discontinuation visit.

An electrocardiogram (ECG) was to be performed weekly for the first cycle (C1D8, C1D15, C1D22); on Day 1 of Cycles 2, 3 and 4, every 8 weeks thereafter (C6D1, C8D1, etc.), and at the treatment discontinuation visit.

Treatment discontinuation assessments were to be obtained if they were not completed in the last 7 days, or in the last 14 days for tumor assessments/imaging tests (± 3 days).

A central laboratory was responsible for performing all laboratory tests and the storing of all imaging studies. Local hematology, chemistry, and imaging tests were to be used for treatment decisions.

[redacted]

Number of patients (planned and analyzed):

Planned: up to 10

Analyzed: 7

Diagnosis and main criteria for inclusion:

- Histological diagnosis of locally recurrent, unresectable, or metastatic soft tissue sarcoma prior to entry into the study.
- Failed or relapsed after systemic chemotherapy which must have contained both doxorubicin and ifosfamide; and have had no prior treatment with any anti-angiogenic therapy.
- Received a minimum of one and a maximum of three prior systemic anticancer therapy regimens.
- Documented disease progression determined as per RECIST criteria within 3 months prior to study enrollment.

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

Celgene Corporation supplied pomalidomide as 1.0, 2.0 and 5.0 mg capsules for oral administration.

Study drug was packaged in bottles containing study capsules for 21 days. Study subjects were to receive 7 mg once daily for 21 days of each 28-day cycle.

The following batches were used:

1 mg: [redacted]

2 mg: [redacted]

5 mg: [redacted]

Duration of treatment:

Study duration was to be a maximum of 5 years. Study subjects could continue study treatment up to disease progression, unacceptable toxicity, or voluntary withdrawal.

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

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Not applicable

Criteria for evaluation:

Efficacy:

Not applicable (see "Summary – Conclusions" section for further detail).

Safety:

- Vital Signs
  - Vital signs including height (at Day 1 of cycle 1[baseline]), weight, blood pressure, pulse, and temperature.
- Hematology
  - Complete Blood Count (CBC), hemoglobin, hematocrit, reticulocyte count, mean corpuscular volume (MCV), white blood cell (WBC) count and differential, ANC, and platelet count. All blood samples were to be collected prior to administration of pomalidomide.
- Serum Chemistries
  - Sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST (SGOT), ALT (SGPT), lactate dehydrogenase (LDH), and uric acid. All blood samples were to be collected prior to administration of pomalidomide.
- Urinalysis
  - Color, clarity, specific gravity, pH, protein, glucose, occult blood and microscopic.
- Thyroid Function Tests
  - TSH, T_3 and T_4 All blood samples were to be collected prior to administration of pomalidomide.
- ECG
  - Twelve lead electrocardiogram.
- Pregnancy Testing for Females of Child Bearing Potential – Beta-Human Chorionic Gonadotropin Hormone (β-HCG)
  - Serum or urine pregnancy testing beta-human chorionic gonadotropin hormone (β-HCG) with a sensitivity of at least 50 mIU/mL was to be done on FCBP only.
- Concomitant Medications/Procedures
- Adverse Events (AEs)

Statistical methods:

Data from all study subjects who received at least one dose of study drug were to be included in the safety analyses.

Adverse events were to be classified using the MedDRA classification system. The severity of the

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toxicities was to be graded according to the NCI CTCAE whenever possible.

Adverse event frequency was to be tabulated by body system organ class and MedDRA term. In the by-subject analysis, a study subject having the same event more than once was to be counted only once. Adverse events were to be summarized by worst NCI CTCAE grade.

Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE grade 3 or higher, study drug-related events, and serious adverse events were to be summarized.

Laboratory data was to be graded according to NCI CTCAE severity grade. Cross tabulations were to be provided to summarize the frequency of abnormalities.

Results of the ECG were to be summarized.

For vital sign and body weight data, means, medians, standard deviations, minimum and maximum values were to be provided.

SUMMARY – CONCLUSIONS

Study enrollment was suspended due to a corporate strategic decision unrelated to patient safety. Subjects already enrolled were allowed to continue on study and receive pomalidomide at 7 mg/day for 21 days of each 28-day cycle for a maximum of 5 years. The protocol was amended to evaluate safety only. Efficacy data was stored but not cleaned or analyzed unless related to safety. This synoptic report summarizes the safety data collected from these subjects.

Study subjects

Seven subjects with advanced soft tissue sarcomas between the ages of 40 and 81 (median age 59 years) were enrolled in the study. All 7 subjects received at least 1 dose of pomalidomide and were included in the safety population. Five subjects discontinued from the study due to disease progression and 1 subject each discontinued due to an AE and death.

EFFICACY RESULTS:

Not applicable.

SAFETY RESULTS:

Median treatment duration was 49 days (range: 3 to 102 days). Six of the 7 subjects received pomalidomide at 7 mg/day for 21 days of a 28-day cycle throughout their participation in the study. Subjects received between 1 and 4 cycles of therapy (median of 2 cycles). One subject [redacted] had a dose interruption for 2 days on Study Day 13 due to an AE, after which pomalidomide was resumed at a reduced dose of 5 mg/day on Study Day 16 for 8 days. Subject started Cycle 2 at 5 mg pomalidomide on Study Day 29 for 4 days after which the dose was reduced to 3 mg/day due to an AE on Study Day 33. Subject continued to receive pomalidomide at 3 mg/day for the subsequent 17 days until discontinuation of study drug on Day 49 due to an AE. This subject discontinued from the study on Day 57 due to disease progression.

All 7 subjects experienced at least 1 AE during the study and 6 subjects had at least 1 AE that was suspected by the investigator to be related to pomalidomide. The most common AEs (that occurred in ≥2 subjects) included:

- Gastrointestinal disorders: nausea (3 of 7 subjects), constipation (2 of 7 subjects), dry mouth (2

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of 7 subjects)

- Blood and lymphatic system disorders: anaemia (4 of 7 subjects), neutropenia (4 of 7 subjects), thrombocytopenia (2 of 7 subjects)
- General disorders and administration site conditions: fatigue (2 of 7 subjects), pain (2 of 7 subjects)
- Respiratory, thoracic and mediastinal disorders: cough (2 of 7 subjects), pleural effusion (2 of 7 subjects)
- Metabolism and nutrition disorders: hypoalbuminaemia (2 of 7 subjects), hypocalcaemia (2 of 7 subjects), hypokalaemia (2 of 7 subjects)

Adverse events that were attributed to pomalidomide by the investigator include neutropenia (4 subjects), nausea (2 subjects each), thrombocytopenia, febrile neutropenia, anaemia, leukopenia, dry mouth, constipation, vomiting, rash, erythema, malaise, fatigue, and hypersensitivity (1 subject each).

The majority of AEs were NCI CTCAE grade 1 and 2. Four of the 7 subjects experienced at least 1 NCI CTCAE grade 3 AE. The majority of these AEs occurred in 2 subjects [redacted]. These AEs included neutropenia, febrile neutropenia, anaemia, dysphagia, hypersensitivity, international normalised ratio increased, hypoalbuminaemia, malnutrition, muscle spasms, muscular weakness, metastatic neoplasm, metastatic pain, syncope pleural effusion and dyspnoea. With the exception of neutropenia, which occurred in 2 subjects, all grade 3 AEs occurred in 1 subject each. Of these grade 3 AEs, neutropenia, febrile neutropenia, anaemia and hypersensitivity were attributed to pomalidomide by the investigator. Only 1 subject experienced a NCI CTCAE grade 4 AE of leukopenia. This AE was suspected to be related to pomalidomide.

Three of the 7 subjects reported at least 1 serious AE (SAE) during the study. These SAEs were reported in 1 subject each and include cancer pain, metastatic neoplasm, metastatic pain, anaemia, febrile neutropenia, leukopenia, neutropenia, tachycardia, dysphagia, malnutrition, muscle spasms, syncope, dyspnea and pleural effusion. The latter 2 SAEs occurred before the subject received the first dose of pomalidomide. Leukopenia (grade 4), neutropenia (grade 3), febrile neutropenia (grade 3) and anaemia (grade 3), all occurring in the same subject [redacted], were attributed to pomalidomide by the investigator.

Four subjects died of disease progression (malignant disease). Only 1 of these deaths [redacted] occurred within 30 days of last dose of pomalidomide.

Two subjects discontinued from the study due to an AE. Adverse events that led to discontinuation were grade 3 hypersensitivity [redacted] and grade 2 malnutrition [redacted]. Hypersensitivity was attributed to pomalidomide.

One subject [redacted] experienced a total of 4 AEs that required a dose reduction and interruption. All 4 AEs were hematological and include grade 4 leukopenia, grade 3 neutropenia, grade 3 febrile neutropenia and grade 3 anaemia. All 4 AEs were attributed to pomalidomide by the investigator.

The majority of subjects did not experience major shifts from normal baseline hematology laboratory parameters to abnormal postbaseline values, and shifts that did occur resolved by last visit (in 6 of 7 subjects).

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Two subjects [redacted] experienced shifts from normal baseline albumin values to low postbaseline values and 3 subjects [redacted] experienced shifts from normal baseline total protein values to low postbaseline values. These abnormal values did not resolve by last visit.

Two of the 7 subjects [redacted] had shifts from normal baseline thyroid stimulating hormone (TSH) to high postbaseline values, 1 subject [redacted] had shifts from normal triiodothyronine (T3) levels to high postbaseline levels and 1 subject [redacted] had shifts from normal baseline T3 levels to low postbaseline levels. No other shifts in thyroid panel were noted.

No notable abnormalities from baseline to postbaseline measurements were observed for urinalysis laboratory tests or vital signs.

CONCLUSION:

The safety profile for pomalidomide in this study is consistent with that documented in other pomalidomide studies (e.g., CDC-407-00-001) and with the underlying disease state of the subjects in this study. Pomalidomide was well tolerated by the majority of subjects in this study. Although all 7 subjects experienced AEs, the majority of these AEs were NCI CTCAE grade 1 and 2 (of a total of 110 AEs 61 (55.4%) were grade 1, 29 (26.4%) were grade 2). Only 1 subject required dose reductions and interruptions due to AEs.

It should be noted, however, that due to the small number of subjects (N=7) and the relatively short duration of exposure to pomalidomide in this study (median treatment duration of 49 days and median of 2 cycles of treatment), further studies are necessary to assess the safety and tolerability of pomalidomide in patients with advanced soft tissue sarcomas.

Date of the report:

09 Mar 2010