Protocol Title: A Phase 2, Multicenter, International, Single Arm Study To Assess The Safety And Efficacy Of Single Agent CC-486 (Oral Azacitidine) In Previously Treated Subjects With Locally Advanced Or Metastatic Nasopharyngeal Carcinoma

NCT Number: NCT02269943

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DISCLOSURE

REDACTED ORIGINAL PROTOCOL

CC-486-NPC-001

A PHASE 2, MULTICENTER, INTERNATIONAL, SINGLE ARM STUDY TO ASSESS THE SAFETY AND EFFICACY OF SINGLE AGENT CC-486 (ORAL AZACITIDINE) IN PREVIOUSLY TREATED SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC NASOPHARYNGEAL CARCINOMA

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PROTOCOL SUMMARY

Study Title

A Phase 2, Multicenter, International, Single Arm Study to Assess the Safety and Efficacy of Single Agent CC-486 (Oral Azacitidine) in Previously Treated Subjects With Locally Advanced or Metastatic Nasopharyngeal Carcinoma

Indication

Subjects with locally advanced or metastatic nasopharyngeal carcinoma (NPC) with an undifferentiated or poorly differentiated carcinoma, who have previously progressed clinically or radiographically on 1 to 2 previous regimens including platinum-based chemotherapy.

Objectives

Primary Objectives:

To evaluate the efficacy of CC-486 in subjects with NPC

Secondary Objectives:

To evaluate safety in all subjects and pharmacokinetics (PK) of CC-486 in a subset of subjects of Asian-Pacific Island ethnicity at experienced selected sites

Exploratory Objective:

Study Design

This is a Phase 2, single arm, multicenter, international study to assess the safety and efficacy of single agent CC-486 in previously treated subjects with locally advanced or metastatic NPC, having previously failed one to two previous regimens, including a platinum-based chemotherapy.

Approximately 51 to 55 subjects will be enrolled according to a Simon two-stage design; if the predefined activity is met (> 4 responses [complete response/partial response {CR/PR}] out of the first 17 evaluable subjects based on independent radiological assessment), then the study will continue to enroll an additional 34 subjects. If ≤ 4 responses out of 17 are observed, then the study enrollment will be stopped.

Study Population

The study will be conducted in subjects with locally advanced or metastatic undifferentiated or poorly differentiated nasopharyngeal carcinoma who have failed at least one, but not more than two prior regimens, including a platinum-based chemotherapy.

Length of Study

The median duration of study treatment is expected to be 6 months with an estimated median survival for the entire enrolled population of approximately 8 to 10 months.

All subjects will be followed for safety and monitoring of adverse events (AEs) for 28 days after the last dose of investigational product (IP), for response until progression (if applicable), and for new anticancer therapies and for survival until the study is mature for analysis, or the End of Trial, whichever occurs earlier.

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as prespecified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

Study Treatments

Subjects will receive the investigational product (IP) CC-486, administered orally every day (QD) on Days 1-14 of a 21-day cycle at a dose of 300 mg. However, for the first 6 evaluable for safety subjects of Asian-Pacific Island ethnicity, a starting dose of 200 mg will be tested. If there are no safety concerns, eg, unexpected AEs or serious adverse events (SAEs), AEs leading to discontinuation, or death, the 300 mg dose will be administered to all subsequent subjects of Asian-Pacific ethnicity.

Subjects may remain on treatment until radiologic disease progression, unacceptable toxicity, a new anticancer therapy is begun, withdrawal of consent, subject refusal, physician decision, or death.

Overview of Efficacy Assessments

All subjects will be evaluated for tumor response and progression according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 guidelines at screening and every 6 weeks (± 5 days) for the first three tumor evaluations and then every 9 weeks until documented disease progression, start of new anticancer therapy, or withdrawal of consent.

Response assessments will include computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head and neck with supraclavicular node imaging, the chest and abdomen/pelvis, neurological examination with facial nerve evaluation, and bone scans at baseline for all subjects. Bone scans will be repeated only if the subject is symptomatic or with known bone metastasis.

In the follow-up phase, anticancer treatment administered following the last dose of IP and survival will be followed every 8 weeks (± 5 days) until death, withdrawal of consent, or lost-to-follow up, whichever occurs first.

Overview of Safety Assessments

All subjects will be monitored for adverse events, starting from the time the subject signs the Informed Consent Form (ICF) until 28 days after the last dose of IP. A thorough evaluation of medical conditions will be conducted during screening for eligibility. Documented physical examination, vital signs, laboratory assessments, (eg, serum chemistry, hematology, including Epstein-Barr virus [EBV] – deoxyribonucleic acid [DNA]), and Eastern Cooperative Oncology Group (ECOG) performance status will be monitored regularly (Oken, 1982) see Appendix A. Preventative measure will be taken to avoid pregnancy in study subjects or their partners, and females of child-bearing potential will have regular pregnancy testing performed. The full schedule of assessments is described in Table 1 and Section 6.

Overview of Statistical Methods

This Phase 2 multicenter, single-arm study is designed to evaluate the overall response rate (ORR) and progression-free survival (PFS) of CC-486 in previously treated subjects with locally advanced or metastatic nasopharyngeal carcinoma, having received one to two previous regimens. A Simon's optimal two-stage design will be used (Simon, 1989).

Analysis Population

All safety analyses will be based on the population of all enrolled subjects who received at least one dose of IP. All primary and secondary efficacy analyses will be based on the Efficacy Evaluable population, which consists of all subjects who meet all eligibility criteria, and EITHER received at least two cycles of IP at any dose intensity and discontinued treatment for progressive disease; OR received at least four cycles of IP at any dose intensity and have baseline and at least two post-screening tumor assessments.

Sample Size

The sample size estimation is based on having sufficient sample in the Efficacy Evaluable population to show that the ORR is higher than 20% or median PFS is > 5 months. Simon's optimal two-stage design will be used. In the first stage, 17 subjects will be accrued. If there are 4 or fewer responders within these 17 subjects, enrollment will be stopped. Otherwise 34 additional subjects will be accrued for a total of 51 subjects. This Phase 2 study will be considered positive if more than 14 responders are observed in 51 subjects or the hypothesis of median PFS equal to 5 months is rejected. This design yields a marginal one-sided type I error rate of 5% and power of 85% when the true ORR is 40%. After the second stage (n = 51), the power for showing median PFS is > 5 months is 80% (60%) when the true median PFS is about 8 (7) months.

Efficacy Analysis

Efficacy analyses will be performed on the efficacy evaluable population.

The hypothesis testing for the ORR will be based on the exact binomial distribution. Point estimate and two-sided 90% confidence interval (CI) of ORR will be provided. The hypothesis testing for the PFS will be based on the exponential distribution. Median PFS, OS, and their two-sided 90% CIs will be provided.

Safety Analysis

Safety and tolerability will be monitored through continuous reporting of AEs and serious adverse events (SAEs), laboratory abnormalities, and incidence of subjects experiencing dose modifications, dose interruptions, and/or premature discontinuation of IP. Data from all subjects who receive one or more doses of IP will be included in the safety analyses. Adverse events, physical examinations (including vital sign measurements), clinical laboratory information, and concomitant medications/procedures will be tabulated.

All adverse events will be summarized by frequency, severity grade based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 4.0) and relationship to treatment. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class and

preferred term. Serious adverse events, events of interest, and events leading to discontinuation or death will be listed separately.

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1. INTRODUCTION

1.1. Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma, or NPC, is a rare type of head and neck cancer, but it is the most common cancer originating in the nasopharynx, which is composed of the upper part of the throat (pharynx) behind the nose. The pharynx is composed of three sections: the hypopharynx, the oropharynx, and the nasopharynx.

The nasopharynx lies just above the soft palate of the mouth and just in the back of the nasal passages, serving as a passageway for air from the nose to the throat and eventually to the lungs. Anatomically, it has a cuboidal shape that extends from the base of the skull to the upper surface of the soft palate. The lateral walls are formed by the Eustachian tube and the fossa of Rosenmuller (a deep recess, aka the pharyngeal recess). Anteriorly, the nasopharynx abuts the posterior choana and nasal cavity, and the posterior boundary is formed by the muscles of the posterior pharyngeal wall and the mass of lymphoid tissue known as the pharyngeal tonsil. Above the pharyngeal tonsil, in the midline is the pharyngeal bursa, an irregular flask-shaped depression of the mucus membrane.

World Health Organization (WHO) histopathological grading system describes three subtypes of nasopharyngeal carcinoma:

1. Keratinizing squamous cell carcinoma
2. Non-keratinizing differentiated carcinoma
3. Undifferentiated carcinoma (most common subtype)

Each of these subtypes appear more often in some areas of the world than in others. Only about 1 in seven million people in North America are diagnosed with NPC, and of those diagnosed, about 1 in 4 cases are of the keratinizing type (American Cancer Society, 2013). In China, it is mostly of the undifferentiated subtype.

NPC is most common in southeast China (American Cancer Society, 2013), and is much more common in other parts of Asia, North Africa, the Inuit populations of Alaska and Canada, and the Chinese and Hmong immigrant groups in the United States (US), than in the general population.

Although it is not exactly understood what causes NPC, factors thought to predispose patients to this tumor include the presence of the Epstein-Barr virus (EBV), heavy alcohol and tobacco intake, a diet rich in salt-cured meats and fish, and a family history of NPC. The EBV appears in most NPC cells and is thought to be linked although not completely elucidated. Patients with NPC have high levels of antibodies to EBV viral capsid antigen (VCA) and viral nuclear antigens. The presence of these antibodies is thought to precede the development of NPC by several years. The EBV infection has been shown to decrease expression of tumor suppressor genes, which may help understand the carcinogenesis of NPC. In the clinical setting, EBV antibody or circulating viral deoxyribonucleic acid (DNA) titers may be useful as a prognostic tool at diagnosis, and as a measure of tumor burden during treatment.

Heavy alcohol and tobacco intake are mostly associated with the keratinizing squamous cell carcinoma subtype. NPC also appears to be more common in males than in females, and in patients younger than 55 years of age (American Cancer Society, 2013).

Thus, the multifactorial etiology implicates genetic, viral, and environmental factors.

However, studies have shown that all subtypes derive from the epithelial cells that line the surface of the nasopharynx, and many NPCs also contain a high concentration of lymphocytes among the cancer cells. The presence of keratin has been associated with reduced local control and survival.

1.2. Diagnosis and Treatment

Nasopharyngeal carcinoma can be asymptomatic for long periods of time, which precludes early diagnosis. In most cases, the diagnosis is made based on locoregional advanced disease symptoms, with cranial nerve involvement or cervical node metastases (Sham, 1993; Sham, 1990). Most patients present with stages III and IV with cervical node involvement at first clinical presentation. The most frequently reported location of metastasis is to bone (70% to 80%), followed by viscera (liver, 30%; lung, 18%) and, at a decreased rate in axillary, mediastinal, pelvic, and inguinal nodes (Ahmad, 1986).

Standard treatments for patients with NPC include radiation therapy alone, concurrent chemoradiation followed by adjuvant chemotherapy, surgery for residual nodal disease, and chemotherapy alone for metastatic disease. High-dose radiation therapy with chemotherapy is the primary treatment of nasopharyngeal cancer, both for the primary tumor site and the neck (Sham, 1993).

Selected patients with local recurrence may be retreated with moderate-dose external-beam radiation therapy using intensity-modulated radiation therapy, stereotactic radiation therapy, or intracavitary or interstitial radiation to the site of recurrence (Baujat, 2006; Mendenhall, 2011; Vikram, 1985).

If a patient has metastatic disease or local recurrence that is no longer amenable to surgery or radiation therapy, chemotherapy should be considered (Koutcher, 2010; Al-Sarraf, 1988; Jacobs, 1992).

Therefore, chemotherapy remains an important treatment modality for palliative treatment and for metastatic NPC, especially those with a good performance status. Prognosis, especially for locally advanced stages (IIB – IVB) and metastatic NPC remains poor: more than a third of cases will present with local and/or metastatic recurrence. In the recurrent metastatic disease setting, the median survival and progression-free survival (PFS) are even shorter, at approximately 8 to 14 months and 4 to 6 months, respectively. Response rates (RR) range from approximately 14% to 38%. Isolated bone metastasis may be associated with long survival (Ong, 2003). Overall, 5-year survival for all NPC stages ranges from 50% to 70%. In first-line treatment of metastasis, platinum-based doublets, especially that of 5-fluorouracil (5-FU) and cisplatin, is generally recommended. In second line treatment of metastasis, the choice of chemotherapy depends on the previous treatment. In patients pretreated with platins, there is no established standard; reintroduction of platins depending on toxicity and the interval to recurrence: for an interval greater than 6 to 12 months, a second platin-based doublet associating taxanes or gemcitabine seems to be the most effective, with Overall Response (OR) 22% to 75%, but with associated

Grade 3 to 4 hematologic toxicity, which may limit its use. Second line capecitabine, gemcitabine or docetaxel monochemotherapy is recommended in cases of platin resistance (early [<6 months] recurrence) or in fragile subjects in whom toxicity could be threatening (Foo, 2002).

However, a review of the literature on clinical trials for the treatment of metastatic NPC show that there is no consensus in second-line therapy or beyond and after progression with platins. Monotherapy with gemcitabine, capecitabine or taxanes has been the most widely tested, with acceptable results (Chan, 2010). In older studies, the most often used chemotherapy agents for monotherapy were methotrexate, bleomycin, 5-FU, cisplatin and carboplatin, with response rates of 15% to 31% (Bensouda, 2011). There were two Phase 2 studies that focused on metastatic NPC with two other drugs: 4-epidoxorubicine (an anthracycline) and mitoxantrone, and the observed OR rates were about 20% (Shiu, 1989; Dugan, 1993). In more recent clinical studies, other molecules such as gemcitabine, capecitabine, paclitaxel, docetaxel and irinotecan have been studies in patients pretreated with cisplatin (Bensouda, 2011); gemcitabine and capecitabine had OR rates in the range of 23-48% and median survival between 7.2 and 14 months (Foo, 2002; Shiu, 1989; Ma, 2005; Chua, 2003; Chua, 2008; Ciuleanu, 2008; Zhang, 2008). The first study of weekly docetaxel in monotherapy for NPC was conducted in 2008 and reported similar results with an overall response rate (ORR) of 37% and median survival of 12.8 months (Ngeow, 2011). All of the above-mentioned studies have been Phase 2 studies, mostly for pretreated patients, and for metastatic and recurrent NPC.

1.3. CC-486

5-Azacitidine (AZA), an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, and DNA synthesis and metabolism, and causes cytotoxicity (Azacitidine Investigator's Brochure [IB]).

Vidaza® (azacitidine injection) is approved by the US Food and Drug Administration (FDA) for 5 subtypes of the French-American British (FAB) classification system of myelodysplastic syndrome (MDS). Vidaza is also approved by the European Commission for the treatment of adult MDS, acute myeloid leukemia (AML) and chronic myeolomonocytic leukemia (CMMoL) patients who are not eligible for hematopoietic stem cell transplantation. Vidaza can be administered by intravenous (IV) or subcutaneous (SC) routes as designated by country approval.

CC-486 is an orally bioavailable formulation of AZA.

After its incorporation into a cell's DNA during the S-phase of the cell cycle, AZA forms covalent adducts with DNA Methyltransferase 1 (DNMT1) and depletes this enzyme required for the maintenance of DNA methylation patterns, thereby altering the epigenetic status of the cell. Epigenetic changes are covalent modifications of chromatin (DNA and histone proteins) that mediate the stable transmission of a gene's transcriptional status through cell division. One of the first recognized epigenetic alterations in cancer was DNA methylation. The addition of a methyl group to cytosine in the dinucleotide (CpG) is catalyzed by DNA methyltransferases (DNMTs) and is associated with transcriptional repression of genes with high density of CpGs (CpG islands) in the vicinity of their promoters (Miranda, 2007). Genomic methylation patterns are precisely regulated during normal embryonic development and differentiation and have been found to be altered in specific ways in cancer. Specifically, cancer cell genomes are typified by reduced methylation globally with focal areas of aberrant hypermethylation in the CpG islands of

genes encoding known tumor suppressors such as PTEN and BRCA1 as well as genes encoding proteins required for apoptosis, including caspase 8, DAPK and Apaf-1. DNA methylation-based silencing can thus contribute to the establishment and maintenance of the transformed state and limit the effectiveness of anticancer therapies.

CC-486 entered clinical testing in 2006 in subjects with MDS, CMMoL, and AML. The AZA PH US 2007 CL 005 study has shown that CC-486 is bioavailable and a maximal tolerated dose (MTD) of 480 mg daily for 7 days was defined based on dose-limiting diarrhea at 600 mg (Garcia-Manero, 2011). As expected, reversible and manageable myelosuppression was observed. Pharmacodynamic activity (DNA hypomethylation) and clinical responses were observed with CC-486, although the cross-over design (with SC Vidaza administered during Cycle 1) confounded the interpretation of these responses in Part 1 of the study.

The second part of the AZA PH US 2007 CL 005 study went on to explore both daily and twice daily extended dosing schedules of 14 and 21 out of 28 days in a non-crossover fashion. CC-486 administered 300 mg QD for 14 and 21 days of a 28-day cycle produces cumulative exposures (area under the concentration curve [AUC] per cycle) that are approximately 40% and 60% of the exposure achieved with the labeled dose and schedule of Vidaza, respectively. Daily doses of 300 mg have proven to be tolerated on both the 14 and 21 out of 28-day schedules with myelosuppression, gastrointestinal (GI) symptoms, and fatigue being the most common toxicities (Garcia-Manero, 2011).

In the AZA PH US 2007 CL 005 study, DNA methylation levels in blood were measured as a pharmacodynamic (PD) endpoint, to determine DNA hypomethylating activity of CC-486. In summary, it was confirmed that CC-486 is biologically active, reducing DNA methylation when administered at low doses on extended schedules.

1.3.1. CC-486 Experience in Solid Tumors

A Phase 1 study of CC-486 in combination with carboplatin and *nab*-paclitaxel, or as a single agent in subjects with relapsed or refractory solid tumors (AZA-ST-001) was initiated on 30 Nov 2011. In Part 1 of this two-part study, CC-486 at escalating doses of 200 or 300 mg was administered on Days 1 to 14 of a 21-day cycle in three separate arms of the study (Arm A, Arm B, Arm C).

In Arm A of AZA-ST-001, subjects received carboplatin (AUC = 4) on Day 8 of each cycle and in Arm B, subjects received *nab*-paclitaxel 100 mg/m^2 beginning on Day 8. For Arm A, both 200 mg and 300 mg were well tolerated with carboplatin AUC = 4. For Arm B, initially, *nab*-paclitaxel was administered weekly starting on Cycle 1 Day 8 but dose-limiting neutropenia was encountered on this schedule at the first dose level of CC-486. The protocol was amended to give *nab*-paclitaxel on Days 8 and 15 of each cycle (ie, 2 out of 3 weeks) and this was well tolerated in combination with CC-486 at 200 mg. When the CC-486 dose was escalated to 300 mg, dose-limiting neutropenia was again encountered, making the 200 mg the MTD of CC-486 in combination with *nab*-paclitaxel 100 mg/m^2 on a 2- out of 3-week schedule. Arm C of Study AZA-ST-001 assessed the safety of continuous administration of CC-486 on a 21- out of 21-day

schedule. This schedule proved not to be tolerable, with profound granulocytopenia manifesting in 2 out of 6 subjects at the 300 mg dose level during Cycle 2. Single agent CC-486 was better tolerated in subjects when used at the dose of 300 mg daily for 2- out of 3-week cycle with a manageable safety profile, and the recommended Phase 2 dose for Arm C was determined to be 300 mg on Days 1 to 14 of each 21-day cycle.

The most promising hints of activity in AZA-ST-001 were observed on Arm B. Of 8 evaluable subjects with relapsed pancreatic carcinoma, one had a partial response (PR) and 3 others had stable disease (SD) > 16 weeks. Dramatic objective responses were also observed in subjects with relapsed cervical and endometrial cancer. These observations, although provocative, do not provide conclusive evidence of an epigenetic modifying effect by CC-486.

1.3.2. CC-486 in Nasopharyngeal Carcinoma (NPC)

Limited data exists with CC-486 in NPC. In Part 1 Arm C of the AZA-ST-001 study, subjects with NPC were enrolled and received CC-486 as monotherapy. The ongoing Part 2 of the trial included an NPC expansion cohort of up to 11 subjects, of which 5 are enrolled. Two subjects have shown a partial response (PR) [1 not yet confirmed], and 3 subjects are ongoing and too early to be evaluated for tumor response. Although the subject reportedly progressed quickly after showing the initial confirmed PR, the results are encouraging as the subject had received 2 prior anticancer regimens and remained on CC-486 treatment for 370 days.

Please refer to the Azacitidine IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of azacitidine/CC-486.

1.4. Rationale

CC-486 as a single agent has shown promising activity in NPC subjects in a Phase 1 clinical trial with durable responses. CC-486 was tolerated in subjects when used at the dose of 300 mg daily for 14 days out of 21-day cycle with a manageable safety profile.

As an epigenetic modifying agent, it is hypothesized that CC-486 will lead to immune-mediated antitumor effects in subjects with NPC. The use of epigenetic modifying therapy in the treatment of NPC is supported in the scientific literature:

- Frequent wide-spread methylation of cancer-related genes in NPC (Lo, 2013).
- Genetic abnormalities and EBV play major role in pathogenesis of NPC.
- NPC is strongly associated with EBV infection (Thompson, 2007), with DNA methylation playing an important role in the maintenance of specific EBV latency programmers and regulating EBV lifecycle and latency in NPC cells (Paulson, 1999; Tierney, 2000; Salamon, 2001; Zhang, 2012a).

- Promoter hypermethylation is a major mechanism for inactivation of critical tumor suppressor genes (*p16,*RASSF1A) (Lo, 2013).
- DNA CpG methylation is associated with silencing of EBV immunodominant antigens and tumor suppressor genes (Robertson, 1997; Okada, 2013).
  - May inhibit the tumorgenicity of EBV-infected cells

In addition, epigenetic therapy may reactivate the host immune response through demethylation of silenced genes (Kenney, 2014).

- Viral lytic reactivation via demethylation may provide a path to targeting EBV-associated tumors.
- Azacitidine induces demethylation of the EBV genome in tumors (Chan, 2004).
- DNA methylation inhibitors can reverse chemoresistance and prevent the development of acquired drug resistance (Zhang, 2012b).

No standard of care options exist for patients with NPC in second and third line settings.

In a Phase 1 study of Japanese subjects treated at a dose of 300 mg QD for 21 days of 28-day cycle, all evaluable subjects (4 out of 5) experienced Grade 3-4 neutropenia. Although the numbers were small, the 300 mg starting dose and 21 of a 28-day schedule may be difficult to tolerate in Asian-Pacific Island ethnicity. Thus, the current proposal is designed to allow the first 6 subjects of this ethnicity to begin at a reduced dose of 200 mg daily for 14 days of a 21-day schedule to preserve safety and tolerability, before increasing the dose to 300 mg daily for 14 days of a 21-day schedule. Careful monitoring will be followed for all subjects.

The high unmet medical need in patients with NPC who received one or two prior chemotherapy treatments, the lack of standard of care, and the encouraging yet immature data in the Phase 1 study warrant further evaluation of CC-486 as a single agent to confirm the activity of the drug in subjects with NPC.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objective of this study is to evaluate the efficacy of CC-486 in subjects with NPC.

2.2. Secondary Objectives

The secondary objectives of this study are to evaluate safety in all subjects and pharmacokinetics (PK) of CC-486 in a subset of subjects of Asian-Pacific Island ethnicity at experienced selected sites.

2.3. Exploratory Objectives

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The primary endpoints are:

- Overall response rate (ORR) defined as the combined incidence of complete response (CR) and PR, confirmed no less than 4 weeks after the criteria for response are first met, based on independent radiology assessment using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, AND
- Progression-free survival (PFS) measured as time from the start of the study treatment to progression based on an independent radiology assessment of response using RECIST v1.1.

3.2. Secondary Endpoints

The secondary endpoints include:

- Overall survival (OS) defined as the time from first treatment to death by any cause
- Safety to include the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), Grade 3-4 AEs, Grade 3 and higher AEs, adverse events of special interest, and laboratory abnormalities and other safety parameters
- Pharmacokinetics (PK) of CC-486 in a subset of subjects of Asian-Pacific Island ethnicity at experienced selected sites

3.3. Exploratory Endpoints

4. OVERALL STUDY DESIGN

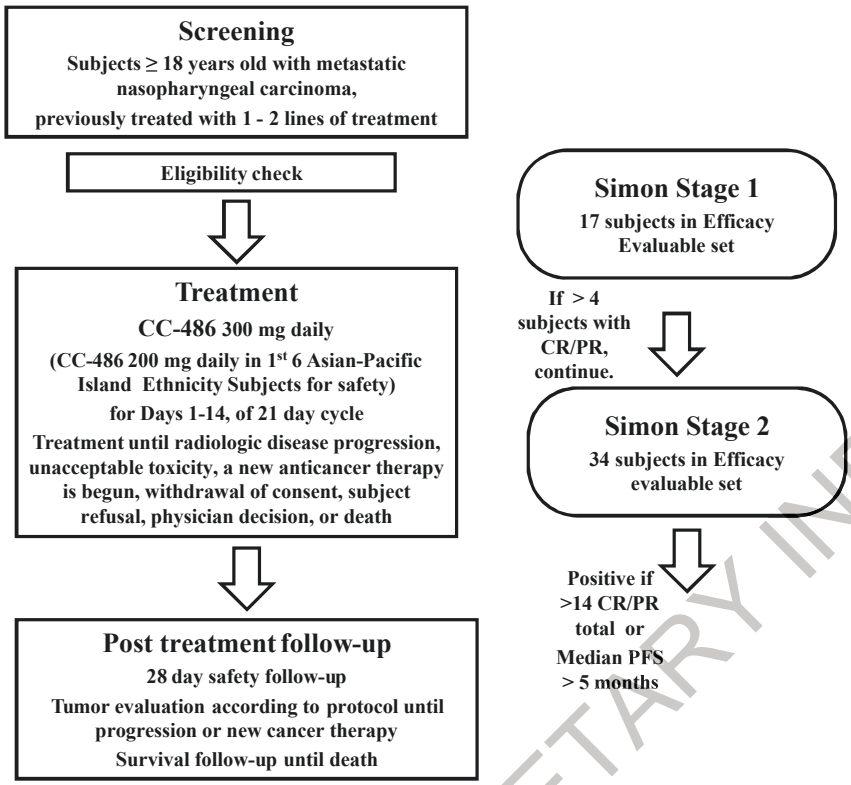
4.1. Study Design

This is a Phase 2, single arm, multicenter, international study to assess the safety and efficacy of single agent CC-486 (oral azacitidine) in previously treated subjects with locally advanced or metastatic nasopharyngeal carcinoma, who have progressed (clinically or radiographically) after having received 1 to 2 previous regimens, including a platinum agent. The co-primary endpoints are ORR and PFS.

Approximately 51 to 55 efficacy evaluable subjects will be enrolled according to Simon's optimal two-stage design; if the predefined activity is met (> 4 responses [CR/PR] out of the first 17 efficacy evaluable subjects based on independent radiological assessment), then the study will continue to enroll an additional 34 efficacy evaluable subjects. If ≤ 4 responses out of 17 are observed, then the study enrollment will be stopped. The Stage 1 decision will be based on ORR only, and the Stage 2 decision will be based on both ORR and PFS. Subjects who are not evaluable for efficacy will be replaced at the discretion of the sponsor. Subjects who are discontinued from study prior to the first tumor assessment for any reason other than for progressive disease are not evaluable and will be replaced. Subjects who progress prior to the end of Cycle 1 are not evaluable and will be replaced.

Subjects will be treated until radiologic disease progression, or as described in Section 6.3. Tumor response will be assessed according to RECIST **v1**.1 **in**itially every 6 weeks (± 5 days) and then according to Section 6.2 until documented disease progression, start of new anticancer therapy, withdrawal of consent, or lost to follow-up. All subjects will also be followed for survival and subsequent anticancer therapies.

Figure 1: Study Design



4.2. Study Duration

The median duration of study treatment is expected to be 6 months with an estimated median survival for the entire enrolled population of approximately 8 to 10 months. All subjects will be followed for safety and monitoring of adverse events (AEs) for 28 days after the last dose of IP, for response until progression (if applicable), and for new anticancer therapies and survival until the study is mature for analysis, or the End of Trial (as defined in Section 4.3), whichever occurs earlier.

4.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date. If ≤ 4 responses out of 17 efficacy evaluable subjects are observed in Stage 1, then the study enrollment will be stopped.

5. TABLE OF EVENTS

Table 1: Table of Events

	Screening Period	Treatment Period[a]					Follow-up Period
Events	**Screening**	**Cycle 1**		**Cycle 2**	**Subsequent cycles**		
Day	**-21 to -1**	**1[b]**	**14**	**1**	**1**	**EOT**	**Disease Progression/ Survival**
STUDY ENTRY							
Informed consent	X	---	---	---	---	---	---
Prior cancer history	X	---	---	---	---	---	---
Prior cancer therapies	X	---	---	---	---	---	---
Complete medical history	X	---	---	---	---	---	---
Demographics	X	---	---	---	---	---	---
IRT [registration/IP accountability only]	X	As needed					
Prior/ concomitant medication evaluation[c]	X(≤28d from screening)	Continuous, until 28 days after treatment discontinuation					
Prior/ concomitant procedures evaluation[d]	X(≤28d from screening)	Continuous, until 28 days after treatment discontinuation					
Inclusion/exclusion criteria	X	---	---	---	---	---	---
SAFETY ASSESSMENTS							
Adverse event evaluation	Continuous starting after informed consent signature, until 28 days after treatment discontinuation						

Table 1: Table of Events (Continued)

	Screening Period	Treatment Period[a]					Follow-up Period
Events	**Screening**	**Cycle 1**		**Cycle 2**	**Subsequent cycles**		
Day	**-21 to -1**	**1[b]**	**14**	**1**	**1**	**EOT**	**Disease Progression/ Survival**
Physical examination (source documented only)	X	X	---	X	X	X	---
Weight	X	X	---	X	X	X	---
Height	X	---	---	---	---	---	---
Vital signs[e]	X	X	---	X	X	X	---
Hematology laboratory	X	X	X	X	X	X	---
Chemistry laboratory	X	X	---	X	X	X	---
Epstein-Barr Virus-DNA [by RT-PCR] in All Subjects	X	X	---	X	X	---	---
Coagulation (Baseline only)	X	---	---	---	---	---	---
Urinalysis[f]	X	X	---	X	X	X	---
12-lead electrocardiogram	X	---	---	---	---	X	---
Serum β-hCG (for all FCBP)[g]	X	---	---	---	---	X	---
Urine β-hCG (for all FCBP)[g]	X(w/in72 hours)	X	---	X	X	X	---

Table 1: Table of Events (Continued)

	Screening Period	Treatment Period[a]					Follow-up Period
Events	**Screening**	**Cycle 1**		**Cycle 2**	**Subsequent cycles**		
Day	**-21 to -1**	**1[b]**	**14**	**1**	**1**	**EOT**	**Disease Progression/ Survival**
EFFICACY ASSESSMENTS							
Tumor evaluation (CT/MRI)	X(≤28d to -1)	Every 6 weeks (± 5 days) from Cycle 1 Day 1, for the first three tumor evaluations and then every 9 weeks until disease progression or start of a new anticancer treatment, or withdrawal of consent					
ECOG performance status	X	X	---	X	X	X	---
BIOMARKER AND PK ASSESSMENTS							
Plasma for Epstein-Barr Virus-DNA	X[h]	X[h]	---	X	(X[i]), C3, 5, and 7 only	---	
HBV and HCV titers (for subjects of A-P ethnicity only)	X	---	---	---	---	X	---
Tumor biopsy* (for Biomarkers)	X[h,j]	X[h,j]	---	X		---	---
PK blood draws sampling	---	X**	X**	---	---	---	---
INVESTIGATIONAL PRODUCT (IP)							
Administer CC-486		Daily on Days 1-14		Daily on Days 1-14	Daily on Days 1-14		
IP accountability	---	X	---	---	X	---	---

Table 1: Table of Events (Continued)

	Screening Period	Treatment Period[a]					Follow-up Period
Events	**Screening**	**Cycle 1**		**Cycle 2**	**Subsequent cycles**		
Day	**-21 to -1**	**1[b]**	**14**	**1**	**1**	**EOT**	**Disease Progression/ Survival**
FOLLOW-UP							
Survival follow-up	---	---	---	---	---	---	Every 8 weeks (+/- 5 days)
Anticancer therapy since IP discontinuation	---	---	---	---	---	---	At every survival follow-up visit

A-P = Asia-Pacific; β-hCG = beta subunit of human chorionic gonadotropin; CT = computed tomography; d = day; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FCBP = female of childbearing potential; FFPE = formalin-fixed, paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; IP = investigational product; IRT = interactive response technology; MRI = magnetic resonance imaging; PK = pharmacokinetics; RT-PCR = real time polymerase chain reaction; w/in = within.

* Refer to Section 6.5, Table 3.

** Refer to Section 6.4, Table 2 for detailed schedule.

[a] All visits have a ± 2-day window, except Cycle 1 Day 1 which must occur within 21 days from Informed Consent Form signature.

[b] Cycle 1 Day 1 evaluations can be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1.

[c] Prior/concomitant medication evaluation ≤ 28 days before first treatment through 28 days after last dose.

[d] Prior/concomitant procedures evaluation ≤ 28 days before first treatment through 28 days after last dose.

[e] Vital sign measurements must be recorded in the database at screening and EOT only, and kept in the source documents at all other visits. However, if an abnormal (out of range) value is reported at a given visit, that parameter should be collected in the case report form (CRF) at every subsequent scheduled visit until it returns to normal.

[f] Urinalysis (a urine dipstick may be used) at screening and D1 of each cycle if abnormal at baseline.

[g] Serum β-hCG (for all FCPB) performed at screening; remaining pregnancy tests may be serum or urine at the Investigator's discretion. Pregnancy testing (for all FCPB) must be done within 72 hours prior to the first administration of IP and prior to dosing on Day 1 of every cycle. If the serum screening pregnancy test is performed > 72 hours before first dose, a urine pregnancy test should be performed. The subject may not receive IP until the Investigator has verified that the result of the pregnancy test is negative.

[h] Sample can be collected during screening or pre-dose Cycle 1 Day 1; being done in Stage 1 subjects only. [STRONGLY encouraged/recommended]

[i] Sample is collected at Cycle 3 Day 1, Cycle 5 Day 1, and Cycle 7 Day 1; being done in Stage 1 subjects only. [STRONGLY encouraged/recommended]

[j] Archival FFPE sample can be submitted for the screening or pre-dose Cycle 1 Day 1 timepoint.

6. PROCEDURES

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 21 days of first dosing unless noted below.

Any questions regarding subject eligibility should be directed to the Celgene medical monitor or designee. Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Safety laboratory analyses and all assessments will be performed locally. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window if necessary.

The following will be performed at screening as specified in the Table of Events (Table 1), after informed consent has been obtained:

- Cancer history (including specific information regarding diagnosis, staging, histology)
- Demographics (initials, date of birth, sex, race, and ethnicity-if allowed by local regulations)
- Interactive response technology (IRT) for subject number registration and IP accountability only
- Prior cancer therapies: includes surgery, radiation, systemic or any other therapy for the subject's cancer
- Complete medical history (all relevant medical conditions occurring ≥ 28 days before screening should also be included)
- Prior and concomitant procedures (including all procedures occurring ≤ 28 days before screening)
- Prior and concomitant medication evaluation (including those taken ≤ 28 days before screening, except for those taken for cancer)
- Physical examination (source documented only), height, weight
- Vital signs (including blood pressure, temperature, and heart rate)
- Eastern Cooperative Oncology Group (ECOG) Performance status (Oken, 1982) see Appendix A
- 12-lead electrocardiogram (ECG)
- Response assessment/ tumor evaluation (see Section 6.3). Subjects with historical tumor scans evaluable per RECIST 1.1 performed ≤ 28 days before the first dose need not repeat scans for the purposes of screening
- Complete blood count (CBC) with differential, including but not limited to red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count, absolute

neutrophil count (ANC), and platelet count. ANC should be measured with automated count where available

- Chemistry panel including, but not limited to, sodium, potassium, calcium, chloride, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase (ALT/SGPT)
- Epstein-Barr Virus-DNA [by real time-polymerase chain reaction (RT-PCR)] in all subjects
- Tumor biopsy: Sample can be collected during screening or pre-dose Cycle 1 Day 1
- HBV and HCV titers (Asian-Pacific ethnicity subjects only)
- Plasma for Epstein-Barr Virus-DNA (Stage 1 subjects only; refer to Section 6.5): Sample can be collected during screening or pre-dose Cycle 1 Day 1
- Coagulation tests including, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
- Urinalysis (a urine dipstick may be used) at screening (and D1 of each cycle if abnormal at baseline)
- Pregnancy test is required for all female subjects of childbearing potential. Serum β-hCG pregnancy test will be performed at screening. Urine (or serum) pregnancy test will be performed to assess subject eligibility within 72 hours prior to the first administration of IP, if the serum pregnancy test did not already occur with 72 hours of dosing (negative results required for IP administration)
- Adverse event assessment begins after the subject signs the informed consent form

Day 1 evaluations for Cycle 1 may be omitted if Screening evaluations are performed within 72 hours of Cycle 1 Day 1.

6.1. Treatment Period

The subject will begin treatment upon confirmation of eligibility. The subject must start treatment within 21 days of signing the informed consent form (ICF). For all subsequent visits, an administrative window of ± 2 days is permitted.

Treatment cycles are 21 days in duration, and will occur as described in Section 8.2.

The following evaluations will be performed at the frequency specified in Table 1, Table of Events. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified:

- Concomitant medications evaluation
- Concomitant procedures evaluation
- Physical examination (source documented only)
- Vital signs: on-treatment vital sign measurements will be source documented only. However, if an abnormal (out of range) value is reported at any given visit, that

parameter should be collected in the case report form (CRF) at every subsequent scheduled visit until it returns to normal, and as an AE if appropriate.

- Weight
- Complete blood count with differential
- Chemistry panel
- Epstein-Barr Virus-DNA [by real time polymerase chain reaction (RT-PCR)] in all subjects
- PK sample (only being done in 6 subjects of Asian-Pacific ethnicity at 200 mg dose initially; then in an additional 6 if dose is escalated to 300 mg dose) (see Section 6.4)
- Tumor biopsy [STRONGLY encouraged/recommended] (Only being done in Stage 1 subjects) (see Section 6.5)
- Plasma for Epstein-Barr Virus-DNA (Stage 1 subjects only)
- ECOG Performance status (Oken, 1982) see Appendix A
- IRT for IP accountability
- Adverse event evaluation (continuously)
- Response assessment/tumor evaluation (see Section 6.3)
- Urine (or serum) β-hCG pregnancy test (prior to dosing on Day 1)
- Urinalysis (at screening and D1 of each cycle if abnormal at baseline)

6.1.1. End of Treatment

An end of treatment (EOT) evaluation should be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made. Subjects should also be discontinued through the IRT system.

The following evaluations will be performed as specified in the Table of Events (Table 1):

- Physical examination (including weight)
- Vital signs
- Concomitant medications evaluation
- Concomitant procedures evaluation
- ECOG performance status (Oken, 1982) see Appendix A
- IRT for IP accountability
- Adverse event evaluation (monitored through 28 days after the last dose of IP)
- Complete blood count (with differential)
- Chemistry panel
- HBV and HCV titers (Asian-Pacific ethnicity subjects only)

- Urine (or serum) β-hCG pregnancy test for females of childbearing potential
- Response assessment/ tumor evaluation will be continued at the schedule defined in the Table of Events, and does not need to be performed specifically for the EOT visit except as specified in Section 6.3.
- 12-lead ECG
- Weight
- Urinalysis

6.2. Follow-up Period

6.2.1. Efficacy Follow-up

All subjects who discontinue treatment for reasons other than disease progression, start of new anticancer therapy, or withdrawal of consent from the entire study will be followed for tumor response assessments and subsequent anticancer therapies as specified in Section 6.3.

6.2.2. Survival Follow-up

After the EOT visit, all subjects will be followed every 8 weeks (± 5 days) for survival until withdrawal of consent, death, or lost-to-follow up, whichever occurs first. Subsequent anticancer therapies should be collected at the same schedule. New anticancer therapy includes (but is not limited to) any systemic or local medication, surgery, radiation, or any other therapy intended to treat the subject's cancer.

Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

6.3. Response Assessments

Response assessments (tumor evaluations) should be performed at screening within 28 days before the start of IP, and every 6 weeks (± 5 days) from Cycle 1 Day 1 for the first 3 tumor evaluations and then every 9 weeks until disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study. Subjects with historical tumor scans evaluable per RECIST v1.1 performed ≤ 28 days before the first dose need not repeat scans for the purposes of screening. Evaluation of response should be performed using RECIST v1.1 guidelines, by Investigator assessment.

An independent radiological assessment of responses will be conducted using RECIST v1.1.

6.3.1. Assessment of Response According to RECIST Version 1.1

Response will be assessed using RECIST v1.1, according to Investigator assessment. Response assessments include computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head and neck with supraclavicular node imaging, the chest and abdomen/pelvis, neurological examination with facial nerve evaluation, and bone scans at baseline for all subjects. Bone scans will be repeated only if the subject is symptomatic or with known bone metastasis.

The same mode of imaging for lesion evaluation at screening must be used consistently throughout the study. Adherence to the planned imaging schedule is critical regardless of dose delays or unscheduled or missed assessments.

The CT imaging should include contrast unless medically contraindicated. Conventional CT should be performed with contiguous cuts of 5 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm.

All subjects with evidence of objective tumor response (CR or PR) should have the response confirmed with repeat assessments at the next scheduled scan, but after no less than 4 weeks. Response assessments must have occurred ≥ 6 weeks from Cycle 1 Day 1 to be considered as SD for a best response.

6.3.1.1. Other Assessments

Subjects who are symptomatic for brain metastasis at screening must undergo a brain scan to confirm eligibility. All subjects must undergo bone scans at baseline.

6.4. Pharmacokinetics

A subset of enrolled subjects (Asian-Pacific island ethnicity only) at a selected number of experienced sites that have the ability to collect, process, and ship CC-486 PK samples will participate in PK sample collection. Six subjects of Asian-Pacific island ethnicity initially being administered 200 mg CC-486 on Days 1-14 of a 21-day cycle will be asked to participate in the PK sample collection at these selected sites. An additional 6 subjects of Asian-Pacific ethnicity will participate in the PK sampling if the dose is escalated to 300 mg in this population.

On each PK day (ie, Cycle 1 Days 1 and 14), subjects will ingest IP in the clinic after performing the required overnight fasting, if applicable taking antiemetic premedication (eg, odansetron), and completing the required pre-dose assessments (where applicable), with each dose being given at approximately the same time of day. The exact date and time of dosing will be recorded in the source documents and appropriate CRF.

Blood samples for oral azacitidine PK assessment will be collected prior to each dose administration (pre-dose) and over the 8-hour period following each dose administration (0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours post-dose or similar schedule) (see Table 2).

Table 2: Schedule of Pharmacokinetic Blood Sample Collection in the Pharmacokinetics Phase

Nominal Times	Acceptable Deviation Window
Pre-dose	≤ 60 min
0.25 hr	± 3 min
0.5 hr	± 3 min
1 hr	± 3 min
1.5 hr	± 3 min
2 hr	± 3 min
2.5 hr	± 3 min

Table 2: Schedule of Pharmacokinetic Blood Sample Collection in the Pharmacokinetics Phase (Continued)

Nominal Times	Acceptable Deviation Window
3 hr	± 3 min
3.5 hr	± 3 min
4 hr	± 3 min
6 hr	± 20 min
8 hr	± 20 min

6.4.1. Dietary Restrictions in the Pharmacokinetics Phase

Fasted Condition

After an overnight fast of at least 8 hours, all required pre-dose assessments and procedures (including obtaining the pre-dose PK sample) should be performed. Then, if applicable, subjects should ingest antiemetic premedication (eg, odansetron) with 240 mL of water and wait 30 minutes before administration of IP. Subjects will then ingest CC-486 with 240 mL of room temperature water. No food will be allowed for at least 2 hours post-dose. Water can be allowed as desired except for 1 hour before and after CC-486 administration. The only water permitted in the 1-hour period before CC-486 administration is the 240 mL of water for antiemetic and IP ingestion.

6.5. Biomarkers

Biomarkers will be assessed for Stage 1 subjects only.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Approximately 51 to 55 subjects with advanced or metastatic NPC will be enrolled. The study will be conducted at sites globally.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is ≥ 18 years of age at the time of signing the informed consent document.
2. Subject has a histological or cytological diagnosis of undifferentiated or poorly differentiated nasopharyngeal carcinoma that is locally advanced or metastatic.
3. Subject has disease progression either clinically or radiographically after 1 to 2 previous regimens.
4. Subject has received a platinum-containing regimen.
5. Subject has an ECOG performance status 0 to 2. (Oken, 1982) see Appendix A
6. Subject has radiographically-documented measurable disease, as per RECIST 1.1.
7. Subject has adequate organ functions, evidenced by the following:
   a. AST (SGOT), ALT (SGPT) ≤ 2.5 x upper limit of normal range (ULN), or ≤ 5 x ULN range if liver metastasis present
   b. Total bilirubin ≤ 1.5 x ULN
   c. Creatinine ≤ 1.5 x ULN
   d. Potassium within normal range, or correctable with supplements
8. Subject has adequate bone marrow function, evidenced by the following:
   a. Absolute neutrophil count ≥ 1.5 x 10^9 cells/L
   b. Platelets ≥ 100 x 10^9 cells/L
   c. Hemoglobin ≥ 9 g/dL
9. Females of childbearing potential (FCBP) (defined as a sexually mature woman who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or, 2) has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months) must:
   a. Have two negative pregnancy tests as verified by the Investigator prior to starting study therapy: negative serum pregnancy test, sensitivity of at least 25 mIU/mL at screening AND have a negative serum or urine pregnancy test within 72 hours prior to starting study therapy (note that the screening serum pregnancy test can be used as the test prior to starting study therapy in the treatment phase if it is performed within the 72-hour timeframe). She must agree to ongoing pregnancy testing during the

course of the study, and after end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.

b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis) or commit to use, and be able to comply with effective contraception (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) without interruption, 28 days prior to starting IP, during the study therapy (including dose interruptions), and for 3 months after discontinuation of CC-486.

10. Male subjects with a female partner of childbearing potential must commit to true abstinence* from heterosexual contact or commit to the use of an effective contraceptive method throughout the course of the study, and avoid fathering a child during the course of the study (including dose interruptions) and for 3 months following the last dose of CC-486. The ICF will address any country-specific requirements, as needed.
11. Subject understands and voluntarily signs an ICF prior to any study-related assessments/procedures are conducted.
12. Subject is able to adhere to the study visit schedule and other protocol requirements.

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has a history of, or current brain metastasis. In subjects who are symptomatic, a brain scan is required to exclude metastasis. Primary NPC tumors that are touching/penetrating the skull are not considered brain metastasis.
2. Subject has any other malignancy within 5 years prior to randomization, with the exception of adequately treated in situ carcinoma of the cervix, uteri, or non-melanomatous skin cancer (all treatment of which should have been completed 6 months prior to enrollment), in situ squamous cell carcinoma of the breast, or incidental prostate cancer T1a, Gleason < 7, PSA <10 ng/ml.
3. Subject has been previously treated with azacitidine (any formulation), decitabine, or any other hypomethylating agent.
4. Subject has a history of inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis), celiac disease (ie, sprue), prior gastrectomy or upper bowel removal, or any other gastrointestinal disorder or defect that would interfere with the absorption, distribution, metabolism, or excretion of the IP and/or predispose the subject to an increased risk of gastrointestinal toxicity.
5. Subject has an impaired ability to swallow oral medication.
6. Subject has persistent diarrhea or malabsorption ≥ National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 2, despite medical management.

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

7. Subject has significant active cardiac disease within the previous 6 months including unstable angina or angina requiring surgical or medical intervention, significant cardiac arrhythmia, or New York Heart Association (NYHA) class 3 or 4 congestive heart failure.
8. Subject has a known or suspected hypersensitivity to azacitidine, mannitol, or any other ingredient used in the manufacture of CC-486 (see the Azacitidine IB).
9. Subject has a known history or current diagnosis of human immunodeficiency virus (HIV) infection, regardless of treatment status.
10. Subject has any other concurrent severe and/or uncontrolled medical condition that would, in the Investigator's judgment, contraindicate subject participation in the clinical study (eg, chronic pancreatitis, chronic active hepatitis, etc.).
11. Subject has had major surgery within 14 days prior to starting IP or has not recovered from major side effects.
12. Subject has received another investigational therapy within 28 days or 5 half lives of randomization/enrollment, whichever is shorter.
13. Subject has not recovered from the acute toxic effects of prior anticancer therapy, radiation, or major surgery/significant trauma.
14. Subject has had radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting IP, and/or from whom ≥ 30% of the bone marrow was irradiated.
15. Subject is pregnant or breast feeding.
16. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
17. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
18. Subject has any condition that confounds the ability to interpret data from the study.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

Celgene Corporation will supply CC-486 100-, 150-, and/or 200-mg tablets for oral administration. All tablets will be packaged in blister packs. Each tablet is formulated using excipients that are generally regarded as safe and are used in marketed drug products. A list of excipients included in the formulations is provided in the Azacitidine IB.

All IP must be stored in an area free of environmental extremes and a secured area to prevent unauthorized access, as directed on the package label. A temperature log must be maintained.

8.2. Treatment Administration and Schedule

CC-486 will be administered at a dose of 300 mg orally daily (QD) for 14 days of a 21-day cycle. However, the first 6 Asian-Pacific Island ethnicity subjects evaluable for safety will receive CC-486 at a dose of 200 mg orally daily for 14 of 21 days of Cycle 1; and if well-tolerated, and there are no safety concerns, (see Section 8.2.1) subsequent subjects of Asian-Pacific Island ethnicity will be administered at the 300 mg daily dose for 14 days of a 21-day cycle.

Subjects will ingest IP with approximately 240 mL (8 ounces) of room temperature water. Investigational product may be taken on an empty stomach or with food (a light breakfast or meal of up to approximately 600 calories), except on PK sampling days.

8.2.1. Tolerability Determination in Asian-Pacific Island Ethnicity

The first 6 evaluable for safety subjects of Asian-Pacific island ethnicity receiving 200 mg daily will be assessed for tolerability and determination if dose can be increased to 300 mg daily in subsequent subjects. If ≤ 1 subject of Asian-Pacific Island ethnicity experiences a dose-limiting toxicity (DLT), the initial 200 mg dose will be increased to the 300 mg dose in subsequent subjects. If ≥ 2 subjects of Asian-Pacific Island ethnicity experience a DLT, the dose may be decreased to 150 mg daily, at the discretion of the sponsor.

A DLT is defined as an IP-related AE(s) occurring in Cycle 1 (including predose assessments on Cycle 2 Day 1) that leads to permanent treatment discontinuation or meets one of the following criteria:

- Grade 4 neutropenia lasting > 10 days or accompanied by fever (defined as ≥ 38.5°C requiring hospitalization);
- Grade 3 thrombocytopenia with clinically significant bleeding; and,
- Any Grade ≥ 3 non-hematologic toxicity with the following exceptions:
  - Grade 3 emesis that responds to optimal antiemetic therapy within 72 hours;
  - Grade 3 diarrhea that responds to optimal medical management within 72 hours;
  - Grade 3 fatigue in a subject who had Grade 2 fatigue at study entry and that recovers to baseline grade or less within 72 hours;

– Grade 3 or 4 laboratory abnormalities that are not accompanied by clinical signs or symptoms and are not believed by the Investigator to be medically significant.

An event that starts in Cycle 1 (including Cycle 2 Day 1 predose assessments) that becomes a DLT due to its duration will be considered a DLT.

8.2.2. Dose Adjustment Guidelines

A maximum of 2 dose reductions will be allowed from the original dose. Except for those subjects starting at 200 mg, wherein only one dose reduction is permitted after Cycle 1.

CC-486 may be withheld for up to 7 days between the end of 1 cycle and the start of the next cycle to allow hematologic criteria to recover sufficiently for the next cycle to begin.

The maximum number of days that a dose may be withheld without requiring a dose reduction is 7 days.

The maximum number of days that a dose may be withheld due to unacceptable toxicity before a subject is permanently discontinued from the study is 14 days.

For the purposes of dose adjustments, unacceptable toxicity will be defined as any AE that is deemed by the Investigator to be related to CC-486 that poses a medical risk or substantial discomfort to the subject including, but not limited to, Grade 3 or 4 hematologic or non-hematologic toxicity. Subjects should be discontinued after the 3rd episode.

Please refer to Table 4 for the Dose Adjustment Guidelines due to unacceptable toxicity.

Table 4: Dose Adjustments and Dose Delays for Toxicity

Toxicity	Recommendation
Grade 2 hematologic toxicity causing delay to the planned start of a Cycle Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L Platelets < 75 x 10^9/L	Hold CC-486 until ANC & Platelets ≤ Grade 1 Delay ≤ 7 days, resume CC-486 at same dose Delay 8 – 14 days, reduce CC-486 by 50 mg Delay > 14 days, permanently discontinue from study
Grade 3* neutropenia or thrombocytopenia causing delay to the planned start of a Cycle ANC 0.5-0.99 x 10^9/L Platelets 25-49 x 10^9/L	Hold CC-486 until ANC & Platelets recover to ≤ Grade 1 (ANC ≥ 1.5 x 10^9/L, Platelets ≥ 75 x 10^9/L) Recovery in ≤ 7 days, resume CC-486 at same dose Recovery in 8–14 days, reduce CC-486 by 50 mg No recovery by 14 days, permanently discontinue from study
Grade 4* neutropenia or thrombocytopenia causing delay to the planned start of a Cycle ANC < 0.5 x 10^9/L Platelets < 25 x 10^9/L For ANC < 0.5 x 10^9/L The initiation of G-CSF is left at the Investigator's discretion. If initiated administer G-CSF per institutional practice or package insert and continue until ANC recovers to ≥ 2.0 x 10^9/L	Hold CC-486 until ANC & Platelets recover to ≤ Grade 1 (ANC ≥ 1.5 x 10^9/L, Platelets ≥ 75 x 10^9/L) Recovery in ≤ 7 days, reduce CC-486 by 50 mg No recovery by 7 days, permanently discontinue from study

Table 4: Dose Adjustments and Dose Delays for Toxicity (Continued)

Toxicity	Recommendation
Grade 3 or 4 non-hematologic toxicity or other Investigator defined unacceptable toxicity	Hold CC-486 until recovery to baseline Recovery in ≤ 7 days, resume CC-486 at same dose Recovery in 8-14 days, reduce CC-486 by 50 mg No recovery by 14 days, withdraw from study In case of recurrence of the Grade 3 or 4 toxicity, hold CC-486 until recovery to baseline. Recovery in ≤ 7 days, reduce CC-486 by 50 mg. No recovery by 7 days, withdraw from study

ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; G-CSF = granulocyte colony stimulating factor.
Note: The initiation of G-CSF is left at the Investigator's discretion.
Note: Granulocyte colony stimulating factor (G-CSF) should only be utilized in accordance to ASCO or ESMO recommendations.
Note: If Grade 3 or 4 neutropenia associated with fever or Grade ≥ 3 thrombocytopenia with clinically significant bleeding occurs at any time, the dose adjustment guidelines for Grade 4 hematological toxicity should be enacted.
Note: If neutropenia is associated with fever and severe diarrhea, subject should be managed appropriately according to the local practice. In case of recurrence of the diarrhea with neutropenia and fever, the continuation of the subject in the study should be discussed on a case-by-case basis with the sponsor's study monitor.

8.2.3. Missing Doses

All efforts should be made to administer IP on all of the scheduled days of each 21-day treatment cycle. Any missed doses during that period should not be added after the last scheduled day of administration, but should be returned by the subject for IP accountability.

8.2.4. Overdose

Overdose, as defined for this protocol, refers to CC-486 only.

On a per dose basis, an overdose is defined as any amount over the protocol-specified dose of CC-486 assigned to a given subject, regardless of any associated adverse events or sequelae.

- PO (oral) - any amount over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form (CRF).

8.3. Method of Treatment Assignment

Subjects who enter screening will be assigned the next available subject number. All eligible subjects will receive CC-486.

All IP will be managed by the IRT system as a central subject number assignment and accountability tool only.

8.4. Packaging and Labeling

The labels for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number,

expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

8.5. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for Investigational Product return, disposal, and/or destruction including responsibilities for the site vs. Celgene (or designee).

8.6. Investigational Product Compliance

Accurate recording of all IP administered will be made in the appropriate section of the subject's case report form (CRF) and source documents. The Investigator or designee is accountable for the compliance of all study-specific IP either administered or in their custody during the course of the study.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

In general, the use of any concomitant medication/therapies deemed necessary for the care of the subject is permitted.

All concomitant treatments, including blood and blood products, must be reported on the CRF.

9.1. Permitted Concomitant Medications and Procedures

Subjects may be administered supportive and palliative care (eg, pain control) as clinically indicated throughout the study.

The use of myeloid growth factors (granulocyte colony stimulating factor [G-CSF] and granulocyte macrophage colony-stimulating factor [GM-CSF]) may be given per Investigator's discretion and according to American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines only for the treatment of neutropenic infections.

Antiemetics are not required during the study; however, at the Investigator's discretion, subjects may receive prophylactic antiemetics approximately 30 minutes prior to each dose of CC-486.

Treatment with antidiarrheal medications should be prescribed at the first sign of diarrhea. Pre-medication with antidiarrheal medication for subsequent doses of CC-486 may be appropriate at the Investigator's discretion.

9.2. Prohibited Concomitant Medications and Procedures

The following concomitant medications are specifically **prohibited** during the course of the study:

Cytotoxic, chemotherapeutic, targeted, or investigational agents/therapies or any other anticancer treatment.

Vidaza (azacitidine), decitabine, or other demethylating agents.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

10.1. Overview

This is a Phase 2, single arm, multicenter, international study to assess the safety and efficacy of single agent CC-486 in previously treated subjects with locally advanced or metastatic NPC, having failed one to two previous regimens, including a platinum agent. The primary efficacy endpoints are ORR and PFS, based on an independent radiology assessment using RECIST v1.1.

10.2. Study Population Definitions

The following study population will be used for this study:

- Safety Population – All subjects who received at least one dose of IP.
- Efficacy Evaluable Population – All subjects who meet all eligibility criteria, and EITHER
    1. Received at least two cycles of IP at any dose intensity and discontinued treatment for progressive disease, OR
    2. Received at least four cycles of IP at any dose intensity and have baseline and at least two post-screening tumor assessments.

Subjects not eligible for the Efficacy Evaluable population will be replaced at the discretion of the sponsor.

- Pharmacokinetic Population – All subjects who have evaluable pharmacokinetic data from at least one dose of IP.

Subjects receiving the 200 mg dose will be efficacy evaluable for response if they meet the defined criteria.

10.3. Sample Size and Power Considerations

Approximately 51 to 55 efficacy evaluable subjects will be enrolled and administered CC-486 orally.

The sample size estimation is based on having sufficient sample in the Efficacy Evaluable population to show that the ORR is higher than 20% or median PFS is > 5 months. Simon's optimal two-stage design will be used (Simon, 1989). The null hypothesis that the true ORR is at least 20% or median PFS is at least 5 months will be tested against a one-sided alternative. In the first stage, 17 subjects will be accrued. If there are 4 or fewer responders in these 17 subjects, enrollment will be stopped. Otherwise, 34 additional subjects will be accrued for a total of 51 subjects. Subjects who progress to the end of Cycle 1 are not evaluable for efficacy and will be replaced. This Phase 2 study will be considered positive if more than 14 responders are observed in 51 subjects or the hypothesis of median PFS equal to 5 months is rejected. This design yields a marginal one-sided type I error rate of 5% and power of 85% when the true ORR is 40%. After the second stage (n = 51), the power for showing median PFS is > 5 months is 80% (60%) when the true median PFS is about 8(7) months.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

Efficacy analyses will be performed on the Efficacy Evaluable population.

The hypothesis testing for the ORR will be based on the exact binomial distribution. The point estimate and two-sided 90% confidence interval (CI) of ORR will be provided. In addition, if Stage 2 is conducted, the Kaplan-Meier procedure will be used to estimate the median PFS and two-sided 90% CI. The hypothesis testing for the PFS will be based on the exponential distribution.

Subjects who die, regardless of the cause of death, will be considered to have had an event. Subjects who withdraw consent for the study will be considered censored at the time of withdrawal. Subjects who are still alive at the time of the clinical data cut-off date will be censored. All subjects who were lost to follow-up prior to the clinical data cut-off date will also be considered censored at the time of last contact.

The Kaplan-Meier procedure will be used to estimate proportions of event-free intervals for OS. Median OS and two-sided 90% CI will be provided.

10.7. Safety Analysis

The safety population will be included in the safety analyses.

Safety and tolerability will be monitored through continuous reporting of adverse events and serious adverse events, laboratory abnormalities, and incidence of subjects experiencing dose modifications, dose interruptions, and/or premature discontinuation of IP. Data from all subjects who receive one or more doses of IP will be included in the safety analyses. Adverse events, physical examinations (including vital sign measurements), clinical laboratory information, and concomitant medications/procedures will be tabulated and summarized.

Adverse events will be analyzed in terms of TEAE defined to be any event that begins or worsens in grade after the start of IP through 28 days after the last dose of IP. Adverse events will be summarized by severity/grade based on the CTCAE v4.0 and relationship to study treatment. If a subject experiences the same AE multiple times during the treatment, the event will be counted only once and by the greatest severity. All AEs, as well as TEAEs, will be summarized by system organ class and preferred term. Adverse events leading to death or to discontinuation from treatment, events classified as CTCAE Grade 3 or Grade 4, IP related

events, and serious adverse events will be summarized separately. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events of special interest of CC-486 identified in previous trials will be summarized in a similar manner.

10.8. Interim Analysis

Interim analysis will be performed according to Simon's optimal design based on the population evaluable for efficacy as described in Section 10.2.

10.9. Assessment of Pharmacokinetics

Pharmacokinetic measures are incorporated into the study to assess the extent of exposure, and to explore the relationship between CC-486 and PD effects. Blood samples for PK will be collected from a subset of subjects at selected visits. As appropriate, PK parameters, but not limited to the following, will be determined from plasma concentration versus time profile data:

- Area under the plasma concentration time-curve (AUC);
- Peak (maximum) plasma concentration (C_{max});
- Terminal half-life ($t_{1/2}$);
- Time to maximum plasma concentration (T_{max});
- Clearance (apparent, CL/F); and,
- Volume of distribution (apparent, V_z/F).

Descriptive statistics (N, mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, min, and max) will be provided for all data. Results will be presented in tabular and graphic forms as appropriate.

Sample collection kits and detailed instructions for PK sample collection, processing, storage, shipping, and handling will be provided to the Investigator sites upon study initiation.

Plasma azacitidine will be measured using validated liquid chromatography-mass spectrometry methods (LC-MS/MS).

10.10. Other Topics

There is no formal Steering Committee for this Phase 2 study. Safety findings and updates, study conduct and Interim Efficacy results will be discussed with the regional Principal Investigators (PIs) regularly. The interval of these reviews will be defined with the PIs at the Kick-off Meeting.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 11.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 8.2.4 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);

- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

11.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the CTCAE, Version 4.0; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity / intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3. Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	Means a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

11.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

11.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

11.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

11.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

11.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 3 months of the subject's last dose of CC-486, are considered immediately reportable events. IP is to be

discontinued immediately and the subject instructed to return any unused portion of CC-486 to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

If a female partner of a male subject taking CC-486 becomes pregnant, the male subject taking CC-486 should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. The female partner may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation. Male subjects should avoid fathering a child during the course of the study and for 3 months following the last dose of CC-486. The ICF will address any country-specific requirements, as needed.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to CC-486) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of investigational product (IP), and any SAE made known to the Investigator at anytime thereafter that are suspected of being related to IP. SAEs occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug

Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

11.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-486 based on the Azacitidine Investigator's Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Events of disease progression for the disease under study (including deaths due to disease progression for indications that are considered to be fatal) will be assessed as expected adverse events and will not be reported as expedited safety reports to regulatory authorities.

Celgene or its authorized representative shall notify the Investigator of the following information

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity; and,

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

Celgene Drug Safety Contact Information:

- For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

12. DISCONTINUATIONS

12.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product and/or from the study:

- Adverse Event
- Progressive Disease
- Symptomatic deterioration (global deterioration of health status)
- Physician decision
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Other (to be specified on CRF)

The reason for discontinuation should be recorded in the CRF and in the source documents.

The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

12.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study follow-up periods:

- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation
- Other

The reason for discontinuation should be recorded in the CRF and in the source documents.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/Contract Research Organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

13.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

14.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

14.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc...).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;

Failure to adhere to the study protocol.

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

15.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;

- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigator meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

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19. APPENDICES

Appendix A. Eastern Cooperative Oncology Group (ECOG) Performance Status

Table 5: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken, 1982.

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Meaning: Approved, no changes necessary.
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