Study to Evaluate the Safety, Tolerability, Pharmacokinetic and Pharmacodynamic of CC-95775 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin Lymphoma

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT04089527	RECRUITING	SEPTEMBER 13, 2019	FEBRUARY 26, 2020

STUDY DESCRIPTION

Brief Summary

CC-95775-ST-001 is an open-label, Phase 1B, dose escalation and expansion study of CC-95775 in subjects with advanced or unresectable solid tumors, including laBCC, and relapsed/ refractory non-Hodgkin's lymphoma (NHL). The dose escalation part (Part A) of the study will explore escalating oral doses of CC-95775 administered on a 4d on/24d off schedule to estimate the MTD of CC-95775. A mTPI-2 will help guide CC-95775 dose escalation decisions with the final decisions made by an SRC. Approximately 20 subjects will be enrolled. The expansion cohort (Part B) will evaluate the safety, PK, PD safety and preliminary activity of CC-95775 in advanced solid tumors, including laBCC. Approximately 20 subjects will be enrolled.

Condition or Disease: Lymphoma, Non-Hodgkin

Intervention/treatment: Drug: CC-95775

Phase: Phase 1

DETAILED DESCRIPTION

N/A

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 40 participants

Intervention Model : Single Group Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: A Phase 1B Dose Escalation, Multicenter, Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetic and Pharmacodynamic of CC-95775 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-hodgkin's Lymphoma

Actual Study Start Date: October 2019

Estimated Primary Completion Date: June 2023

Estimated Study Completion Date: June 2023

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: CC-95775 Escalating dose finding part A of study and extension Part B of the study. In Part A, subjects will be treated with oral capsules of CC-95775 with a schedule of 4d on/ 24d off (Q4W) and a starting dose of 100 mg/day on a 28-day cycle. Dose increments between cohorts will not exceed 100% of the dose in previous cohort. Patients in Part B will be treated with a schedule of 4d on/24d off (Q4W) at the Maximum tolerated dose (MTD) established from Part A.	Drug: CC-95775 CC-95775

OUTCOME MEASURES

Primary Outcome Measures:
1. Dose Limiting Toxicity (DLT) [Time Frame: C1 Up to approximately 28 days]
is defined as any toxicities occurring within the DLT assessment unless the event can clearly be determined to be unrelated to CC-95775.
2. Maximum Tolerated Dose (MTD) [Time Frame: Part A of the study- estimated 12 months]
dose level that could be given such that the estimated DLT probability is closest to 25%.
3. Non-tolerated Dose (NTD) [Time Frame: Part A of the study-estimated 12 months]
The dose that is higher than MTD
4. Adverse Events (AEs) [Time Frame: From signature of the informed consent until at least 28 days after the last dose of study treatment]
Number of participants with adverse event. An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study

Secondary Outcome Measures:
1. Pharmacokinetics - Cmax of CC-95775 [Time Frame: Part A and part B of the study, estimated 24 months total]
Maximum plasma concentration of drug
2. Pharmacokinetics - AUC of CC-95775 [Time Frame: Part A and part B of the study, estimated 24 months total]
Area under the curve
3. Pharmacokinetics - Tmax of CC-95775 [Time Frame: Part A and part B of the study, estimated 24 months total]
Time to peak plasma concentration
4. Pharmacokinetics - t1/2 of CC-95775 [Time Frame: Part A and part B of the study, estimated 24 months total]
Half-life the time it takes for the concentration of the drug in the plasma to be reduced by 50%

5. Pharmacokinetics - CL/F of CC-95775 [Time Frame: Part A and part B of the study, estimated 24 months]
Measurement of the volume of plasma from which a substance is completely removed per unit time
6. Pharmacokinetics - Vz/F of CC-95775 [Time Frame: Part A and part B of the study, estimated 24 months]
Apparent volume of distribution. It is the volume needed to account for the total amount of drug in the body if the drug was evenly distributed throughout the body and in the same concentration as the site of sample collection such as peripheral venous plasma
7. Evaluate the pharmacodynamic (PD) effects of CC-95775 on gene expression in peripheral blood and in tumor tissue. [Time Frame: Part B of the study, estimated 12 months]
Changes in the expression of genes associated to BET inhibitors in PBMCs and/or other genes, such as GLI1, MYC, in tumor biopsy may provide confirmation that a dose is pharmacologically active and enable identification of dose, which results in optimal target engagement

---

ELIGIBILITY CRITERIA

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
Subjects must satisfy the criteria below to be enrolled in dose escalation (Part A) and in dose expansion (Part B) of this study.
1. Men and women ≥ 18 years of age, at the time of signing the ICF.
2. Subject must understand and voluntarily sign an ICF prior to any study-specific assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subjects with histological or cytological confirmation of either:
Advanced or unresectable ST, laBCC or R/R NHL.
- Subjects with solid tumors including those who have progressed on (or not been able to tolerate due to medical comorbidities or unacceptable toxicity) standard anticancer therapy or for whom no other approved conventional therapy exists.
- Subjects with laBCC must have unresectable disease which must have progressed after treatment with a smoothened inhibitor (SMOi) or who are intolerant of SMOi on (or not been able to tolerate due to medical comorbidities or unacceptable toxicity).
- For relapsed/ refractory NHL following at least 2 prior lines of therapy (e.g. subjects have failed at least one line of standard therapy and have received at least one prior line of salvage therapy) OR have failed at least one prior line of standard therapy and are not eligible for autologous stem cell transplant (ASCT) OR have declined ASCT; transformed lymphoma following chemotherapy for lower grade lymphoma and at least one standard treatment regimen for DLBCL.
- Subjects with two or more lines of systemic therapy who have been treated with and have lack of response or have responded and relapsed after chimeric antigen receptor T-cell (CAR-T) therapy, if such therapy is available, OR are ineligible for CAR-T therapy at the time of enrollment, OR declined CAR-T therapy.
Subjects must have at least one site of measurable disease according to RECIST 1.1 Previously irradiated lesions are not considered evaluable; for subjects with R/R NHL, bi-dimensionally measurable disease on cross sectional imaging by CT or MRI, with at least one lesion >1.5 cm in its greatest transverse diameter, as defined by the IWG criteria. For subjects with rare malignancies, not falling into the above categories and who might benefit from a treatment with BET inhibitor, evaluable disease can be considered.
5. Subjects consent to tumor archive material analysis. Tumor biopsies to be collected whenever safe and feasible will be collected in Part A. Subjects consents to mandatory tumor biopsies (Screening and on treatment) in Part B.
6. ECOG PS of 0 to 1.
7. Subjects must have the following laboratory values at Screening:
- Absolute neutrophil count (ANC) ≥ 1.5 x 109/L without growth factor support for 7 days (14 days if subject received peg-filgrastim).
- Hemoglobin (HGB ≥10 g/dL (≥ 8g/dL for DLBCL subjects).
- Platelet count (PLT) ≥150 x 109/L (≥100 x 109/L without transfusion for 7 days for DLBCL subjects).
- Serum potassium concentration within normal range, or correctable with supplements
- Serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST) and serum glutamate pyruvic transaminase (SGPT)/alanine aminotransferase (ALT) ≤ 3.0 x Upper Limit of Normal (ULN).
- Serum total bilirubin ≤ 1.5 x ULN.
- Serum creatinine ≤ 1.5 x ULN or measured glomerular filtration rate (GFR) ≥ 50 mL/min/1.73 m2 using an exogenous filtration marker such as iohexol, inulin, 51Cr EDTA or 1125 iothalamate, or creatinine clearance of ≥ 50 mL/min using Cockroft-Gault equation.
- Subjects must have serum albumin > 3.5 g/dL.
- PT (or INR) and APTT within normal range.
8. Subjects must agree not to share study drugs with another person
9. Females of childbearing potential
- A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy or other medical condition does not rule out childbearing potential) for at least 12 consecutive months and verified by an FSH blood test at screening.
- FCBP must either commit to true abstinence from heterosexual intercourse (which must be reviewed monthly and source documented) or to use one highly effective contraceptive method plus one barrier method. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception). Highly effective contraceptive methods are combined (containing estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, intravaginal, patch, or implantable); bilateral tubal ligation; intrauterine device; intrauterine hormone-releasing system; or vasectomized partner sterilization (note that vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the FCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success). Barrier methods are male or female latex or synthetic condom, diaphragm, cervical cap or sponge with spermicide, barrier contraceptive with spermicide. These measures should be used from signing the ICF, throughout the study, and for up to 44 days following the last dose of CC-95775.
- Have two negative pregnancy tests as verified by the investigator prior to starting CC-95775.
- Pregnancy testing:
- A negative serum pregnancy test (or β-subunit of human chorionic gonadotropin (β-hCG pregnancy test) at Screening verified by the Investigator.
- A negative serum or urine pregnancy test (or β-subunit of human chorionic gonadotropin (β-hCG pregnancy test) on Day 1 of dosing verified by the Investigator prior to dosing.
- Agree to ongoing pregnancy testing during the course of the study, and after the end of study treatment. This applies even if the subject practices true abstinence from heterosexual contact.
10. Male subjects must practice true abstinence (which must be reviewed on a monthly basis) or agree to use a condom (a latex or non-latex synthetic condom is required) during sexual contact with a pregnant female or a FCBP and will avoid conceiving from signing the ICF, while participating in the study, during dose interruptions, and for at least 104 days following CC-95775 discontinuation, even if he has undergone a successful vasectomy. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject [female partner's periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].
- Males must agree not to donate semen or sperm for at least 104 days following CC-95775 discontinuation.
- Other than the subject, FCBP and males able to father a child should not handle the study drugs or touch the capsules, unless gloves are worn.
Exclusion Criteria:
The presence of any of the following will exclude a subject from enrollment (in Part A and Part B):
1. Subject has received anti-cancer therapy (either approved or investigational) within ≤ 4 weeks or 5 half-lives, whichever is shorter, prior to starting CC-95775.
• < 42 days for prior nitrosureas or mitomycin C 2. Toxicities resulting from prior systemic cancer therapies must have resolved to ≤ NCI CTCAE Grade 1 prior to starting CC-95775 treatment (with exception of Grade 2 peripheral neuropathy and alopecia). 3. Subject has received autologous hematologic stem cell transplant (HSCT) ≤ 3 months prior to starting CC-95775 treatment. Subjects with allogeneic HSCT will not be allowed on this protocol. 4. Subject has undergone major surgery ≤ 4 weeks or minor surgery ≤ 2 weeks prior to starting CC-95775 or who have not recovered from surgery. 5. Subject has completed any radiation treatment < 4 weeks prior to starting CC-95775 (with exception of palliative bone radiotherapy for which 2-week period is required). 6. Subject has persistent diarrhea due to a malabsorptive syndrome (such as celiac sprue or inflammatory bowel disease) ≥ NCI CTCAE Grade 2, despite medical management, or any other significant GI disorder that could affect the absorption of CC-95775. 7. Subjects with symptomatic or uncontrolled ulcers (gastric or duodenal), particularly those with a history of and/or risk of perforation and GI tract hemorrhages. 8. Subjects with symptomatic or uncontrolled diabetes mellitus. 9. Symptomatic, untreated, or unstable central nervous system (CNS) metastases, (except in case of CNS primary tumors). - Subjects recently treated with whole brain radiation or stereotactic radiosurgery for CNS metastases must have completed therapy at least 4 weeks prior to starting CC-95775 and have a follow-up brain CT or MRI demonstrating either stable or improving metastases 4 or more weeks after completion of radiotherapy (the latter to be obtained as part of the Screening Assessments. - Subjects must be asymptomatic and off steroids or on stable dose of steroids for at least 4 weeks (<4 mg/day dexamethasone or equivalent) or on tapering dose of steroids. 10. Known symptomatic acute or chronic pancreatitis. 11. Impaired cardiac function or clinically significant cardiac diseases, including any of the following: - LVEF CTCAE Grade 2 or hemoptysis > 1 teaspoon within 4 weeks prior to the first dose
19. Subject has any significant medical condition (e.g., active or uncontrolled infection or renal disease), laboratory abnormality, or psychiatric illness that would prevent the subject from participating (or compromise compliance) in the study or would place the subject at unacceptable risk if he/she were to participate in the study.
20. Subject has any condition that confounds the ability to interpret data from the study.
21. Subjects with poor bone marrow reserve as assessed by the Investigator such as in the following conditions:
- Having received extensive bone radiotherapy
- Having experienced several episodes of bone marrow aplasia in previous treatments
- Confirmed histological bone marrow cancer infiltration (with exemption of NHL)
- Requiring regular hematopoietic support (blood transfusion, erythropoietin, G-CSF)
22. Subjects with severely compromised pulmonary function and/or requiring chronic oxygen administration

CONTACTS AND LOCATIONS

Contacts

Contact:
Contact:

Locations

France	Hopital Saint Louis	Paris
France	Centre Eugene Marquis	Rennes
France	Institut Curie	Paris
Spain	Hospital de Madrid Norte- Sanchinarro	Madrid
Spain	Clinica Universidad de Navarra	Pamplona

Sponsors and Collaborators

Celgene

Investigator

Study Director : Pilar Lardelli, MD PhD Celgene

MORE INFORMATION

Responsible Party :	Celgene
ClinicalTrials.gov Identifier :	NCT04089527
Other Study ID Numbers :	CC-95775-ST-001, U1111-1238-6062, 2019-001092-36
First Posted :	September 13, 2019
Last Update Posted :	February 26, 2020
Last Verified :	February 2020
Individual Participant Data (IPD) Sharing Statement:	
Plan to Share IPD:	Yes
Plan Description:	https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Supporting Materials:	Study Protocol, Statistical Analysis Plan (SAP), Informed Consent Form (ICF), Clinical Study Report (CSR), Analytic Code
Time Frame:	See Plan Description
Access Criteria:	See Plan Description
URL:	https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Studies a U.S. FDA-regulated Drug Product:	Yes
Studies a U.S. FDA-regulated Device Product:	No
Product Manufactured in and Exported from the U.S.:	Yes
Keywords provided by Celgene:	*Lymphoma* *Non-Hodgkin's Lymphoma* *CC-95775 Solid Tumors* *Safety* *Relapsed/Refractory*
Additional relevant MeSH terms :	*Lymphoma* *Lymphoma, Non-Hodgkin*