A Multicenter Phase 1/2, Open-Label Study of DCC-3014 to Assess the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics in Patients with Advanced Tumors and Tenosynovial Giant Cell Tumor

Published: 16-10-2019
Last updated: 21-09-2024

This study has been transitioned to CTIS with ID 2024-514933-39-00 check the CTIS register for the current data. Primary Objectives:• To assess the safety and tolerability of DCC 3014.• To characterize the pharmacokinetic (PK) profile of DCC 3014.•...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54590

Source
ToetsingOnline

Brief title
Advanced Tumors and Tenosynovial Giant Cell Tumor

Condition

- Other condition

Synonym
Cell Tumor

Health condition

Tenosynovial giant cell tumor (TGCT)

Research involving
Human

Sponsors and support

Primary sponsor: Deciphera Pharmaceuticals LLC
Source(s) of monetary or material Support: Deciphera Pharmaceuticals LLC

Intervention

Keyword: Advanced, DCC-3014, in, Tumors and Tenosynovial Giant Cell Tumor

Outcome measures

Primary outcome

Primary Endpoints:

Safety:

DLTs, treatment emergent adverse events (TEAEs), serious adverse events (SAEs),

dose reduction or discontinuation of study drug due to toxicity, physical

examination findings, ECOG PS, changes from baseline in laboratory parameters,

electrocardiograms (ECGs), LVEF, and vital signs.

Pharmacokinetics:

The following PK endpoints, including but not limited to, will be evaluated for

both DCC-3014 parent and its metabolite, DP 7005, if detected:

• Time to maximum observed concentration (Tmax).

• Maximum observed concentration (Cmax).

• Trough observed concentration (Cmin).

• Area under the concentration time curve (AUC).

• t1/2.

Efficacy (TGCT Expansion Cohort A only):

• Objective response rate (ORR=complete response [CR]+partial response [PR]) assessed by independent radiological review using RECIST Version 1.1 at Week 25 (Cycle 7 Day 1).

• Duration of Response (DOR; time from PR or CR to disease progression or death).

Secondary outcome

Secondary Endpoints (TGCT Expansion Cohort A only):

• ORR assessed by independent radiological review using TVS and mRECIST.

Functional Assessments:

• ROM: change from baseline to Week 25 (Cycle 7 Day 1).

• Response based on BPI worst pain NRS and narcotic analgesic use by Brief Pain Inventory-30 (BPI-30) at Week 25 (Cycle 7 Day 1).

• PRO based upon the PROMIS physical function questionnaire and worst stiffness NRS:

* Change from starting value to Week 25 (Cycle 7 Day 1).

Exploratory Endpoints:

Preliminary Evidence of Antitumor Activity:

The following endpoints documenting preliminary evidence of DCC 3014 will be evaluated:

• ORR=CR+PR

• Clinical Benefit=CR+PR+stable disease) at Weeks 9 (Cycle 3 Day 1), 25 (Cycle 7 Day 1), and 49 (Cycle 13 Day 1)

• Time to best response (defined as time from Cycle 1 Day 1 to PR or CR)

• Progression-free-survival (defined as time from Cycle 1 Day 1 to disease

progression or death), except for TGCT patients

• DOR (defined as time from PR or CR to disease progression or death; Dose Escalation and Expansion Cohort B)

Tumor response will be assessed by tumor type using the following criteria:

• MST and TGCT: RECIST, Version 1.1

• TGCT: mRECIST

• TGCT: TVS

• For bone-only disease: a new lesion(s) identified by bone scan will be considered as disease progression (see Section 6.9.2)

• TGCT: ROM mean changes from baseline

PROs (TGCT only and not covered above in secondary endpoints):

Note: Where Cycle 7 Day 1 is mentioned below, the PRO estimate will be calculated by taking the average of the PRO scores from Weeks 2 and 3 of Cycle 6.

• Response based on BPI average pain NRS and narcotic analgesic use by BPI-30 at Week 25 (Cycle 7 Day 1)

• 36-item short form survey (SF 36; Dose Escalation only), EQ-5D-5L, and NRS about *swelling* and *instability* on a scale of 0 to 10 as:

* Change from mean starting value to the Week 25 (Cycle 7 Day 1) endpoint

• GP5 *burden-of-side-effects* question from the FACT-G

* Proportion of responders that answer with 3 ("quite a bit") or 4 ("very much") at Week 25 (Cycle 7 Day 1)

• Other PRO

* PGIC, PGIS, CGIC, and CGIS summarized by time point and treatment group

Pharmacodynamics:

• Assess changes in monocyte population in peripheral blood.

• Assess changes in plasma cytokines.

• Evaluate changes in macrophage content and/or polarization in tumor biopsies

(MST patients only).

Exploratory PK:

* Correlation of PK with efficacy and/or safety

Pharmacogenomic:

• Germline polymorphisms in genes involved in the metabolism or disposition of

DCC-3014 or related to safety or efficacy

Serum Chemistry Exploratory

• Changes in isoenzymes of alkaline phosphatase, CK, and lactate dehydrogenase

from baseline.

Study description

Background summary

A new compound named DCC 3014 is being developed by Deciphera Pharmaceuticals, LLC, as an oral study drug for the treatment of advanced tumors and DTGCT. This compound is a small molecule that blocks the activity of changes in specific genes, specifically, CSF1R. Genes are the instructions that tell cells what to do. In advanced tumor diseases and DTGCT there are change in the genes so that the instructions are no longer correct. In laboratory studies DCC-3014 has been shown to block genes that are giving incorrect instructions to the cell. Subjects are being invited to take part in a research study of DCC 3014.

Study objective

This study has been transitioned to CTIS with ID 2024-514933-39-00 check the CTIS register for the current data.

Primary Objectives:
• To assess the safety and tolerability of DCC 3014.
• To characterize the pharmacokinetic (PK) profile of DCC 3014.
• To determine the maximum tolerated dose (MTD) of DCC 3014.
• To determine the recommended Phase 2 dose (RP2D) of DCC 3014.
• To evaluate anti-tumorantitumor activity of DCC-3014 using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 in DTGCT (tenosynovial giant cell tumor (TGCT; formerly known as pigmented villonodular synovitis [PVNS] or giant cell tumor of the tendon sheath [GCT-TS]) (Expansion Cohort B A only).
Secondary Objectives (DTGCTTGCT Expansion Cohort BA only):
• To evaluate antitumor activity of DCC-3014 using tumor volume score (TVS) and modified RECIST (mRECIST).
• To assess the effects of DCC-3014 on range of motion (ROM) in DTGCT.).
• To assess the effects of DCC-3014 on physical function, worst pain, and worst stiffness using patient reported outcome (PRO) measures.
Exploratory Objectives:
• To evaluate the preliminary evidence of DCC 3014 antitumor activity (in malignant solid tumor (MST) patients enrolled in (Dose Escalation and Expansion Cohort A)
• To evaluate the preliminary evidence of DCC-3014 antitumor activity in TGCT patients (Dose Escalation and Expansion Cohort B)
• To assess the relationship between efficacy or safety and PK
• To assess the effects of DCC-3014 on ROM in DTGCT (patients enrolled in TGCT (Dose Escalation and Expansion Cohort B)
• To assess the effects of DCC-3014 on symptomatic relief and functional assessments using patient reported outcome (PRO) measures (DTGCT patients only and those not covered as secondary endpoint above).Dose Escalation and Expansion Cohorts A and B)
• To investigate the effects of DCC-3014 on select biomarkers in the tumor microenvironment, and peripheral blood, and skin.
• To investigate the mechanism of serum enzyme level increases.
• To assess germline polymorphic variations in genes involved in the metabolism or disposition of DCC-3014 or in relation to safety or efficacy.

Study design

This is a multicenter, open-label Phase 1/2 study of DCC-3014 (vimseltinib) in patients with advanced tumors and TGCT. There will be 2 distinct parts in this study; Dose Escalation will enroll both MST and TGCT patients (Phase 1) and Expansion will only enroll TGCT patients (Phase 2).
This study will enroll patients with solid tumors or manifestations of cancer with known contribution of macrophages or phagocytes, ie, tumors known to have expression of the receptor colony-stimulating factor 1 receptor (CSF1R) or its ligands, colony-stimulating factor 1 (CSF1) or interleukin (IL)-34, confirmed by the literature or prior testing. The prime example of such diseases is TGCT, where aberrant over-production of CSF1 drives recruitment of macrophages

leading to local destruction of joints and anti-CSF1R therapy has demonstrated clinical efficacy. Patients with any common carcinomas that have high tumor-infiltrating macrophage content will be eligible for the study. In addition, tumor-associated manifestations featuring macrophage pathophysiology including bone metastases and ascites or effusions that typically contain high levels of macrophages will be enrolled.
DCC-3014 will be administered to patients orally in 28-day cycles according to assigned dose and regimen. Patients may remain on treatment until tumor progression, occurrence of unacceptable toxicity, withdrawal of consent, physician*s decision, or commercialization. Patients may continue receiving treatment after tumor progression if agreed upon by the Investigator and Sponsor, if there are no other treatments available. Additionally, treatment may be extended by agreement between the Sponsor and Investigator for patients who exhibit evidence of clinical benefit and tolerability to the drug, and who adhere to the study procedures. Dose Escalation Phase:
Patients with solid tumors will receive the study drug, DCC-3014, at an assigned dose level upon registration. The starting dose is 10 mg once daily (QD), based on data from nonclinical toxicology and PK studies. Based on clinical experience from Cohort 1 (10 mg QD), subsequent cohorts (Cohort 2 and above) will include loading doses followed by maintenance doses.
Additional dosing schemes (eg, loading dosing period of 3 to 7 days or modifications to maintenance dosing schedules) including QD dosing may be explored based on PK, pharmacodynamic, and safety data as well as discussion and agreement between the Sponsor and Investigators following safety and PK/pharmacodynamic readouts.
Dose escalation of study drug will be based on a pharmacologically guided 3+3 study design in patients with MST and TGCT. A minimum of 3 patients will be initially enrolled in each dose level cohort. If a patient experiences a dose-limiting toxicity (DLT) during Cycle 1, then the cohort will be expanded to 6 patients. If <=1 out of 6 patients (fewer than 33%) experience a DLT the dose level may be escalated. If >=2 patients out of 3 to 6 patients (>=33%) experience a DLT(s) during Cycle 1, Dose Escalation will end, and a lower dose level cohort will be expanded for determination of the MTD. Decisions of dose escalation and the dose level of the next cohort will be determined based on evaluation of at least 3 patients completing Cycle 1 and in consultation between the Sponsor and Investigators. A patient will be evaluable in the Dose Escalation phase if the patient either experienced a DLT during Cycle 1 or received >=80% of planned doses of study drug in Cycle 1, following review of available safety, PK and pharmacodynamic. As of Cohort 4, no more than a 50% increase in a total dose given in the first cycle will be allowed from the previous cohort.
The MTD will be defined as the highest dose level at which no more than 1 of 6 DLT-evaluable patients (< 33%) experiences a DLT(s) in Cycle 1 during Dose Escalation. The RP2D may be the MTD or a biologically active or maximally feasible dose that is lower than the MTD. Different RP2Ds may be determined for MST and TGCT patients. The determination of MTD will require treatment of at least 6 patients at the same dose level whereas determination of RP2D will

be based on safety and tolerability of at least 3 patients if no more than 1 of 6 DLT-evaluable patients experiences a DLT(s) in Cycle 1 at a higher dose level.
Each Dose Escalation cohort may enroll up to 6 additional patients for evaluation of safety, efficacy, PK, and pharmacodynamic (up to 12 patients).
As of initiation of Dose Escalation Cohort 8, only TGCT patients will be enrolled into the Escalation phase.
Expansion Phase (Cohorts A and B for TGCT patients):
The Expansion phase will be opened upon determination of RP2D from Dose Escalation and may opened prior to the determination of MTD if further exploration at higher doses is ongoing. Expansion consists of 2 cohorts to further evaluate the safety, PK, pharmacodynamics, and preliminary efficacy of DCC-3014 in patients with TGCT. Patients with MST will not be enrolled into the Expansion phase.
Expansion Cohort A will enroll approximately 40 TGCT patients without prior anti-CSF1 or anti-CSF1R treatment (with the exception of imatinib or nilotinib) who will be treated at the RP2D. Intra-patient dose escalation will be allowed following discussion between the Sponsor and the Investigator; the dose level may be increased by 1 dose level at a time. If no clinical benefit is observed in first 10 patients having completed at least one post-dose scan, Expansion Cohort A will close.
Expansion Cohort B will enroll approximately 20 TGCT patients with prior anti-CSF1 or anti-CSF1R therapy who will be treated at the RP2D; intra-patient dose escalation will be allowed as described for Cohort A. If no clinical benefit is observed in the first 10 patients having completed at least 1 post-dose scan, Expansion Cohort B will close.
If >=33% of patients experience an adverse event (AE) that meets the definition of DLT during Cycle 1 in a given cohort, all patients will be reduced to a lower dose determined by the Sponsor and Investigators. Patients subsequently enrolled will be treated at the lower dose level.

Intervention

N/A

Study burden and risks

Side Effects of DCC-3014
The study drug to be investigated may have side effects. You may experience all, some, or no side effects, and the side effects may vary in severity. The severity may be mild, moderate, severe, life threatening or fatal. Many side effects may go away shortly after the drug is stopped, but in some cases, side effects can last longer or be permanent. Also, there is always the risk of a rare or previously unknown side effect occurring. If any of these side effects occur, you must tell your study doctor who may give you other drugs to ease any discomfort you experience.

This is the first study of DCC-3014 in humans, so the side effects are not well established.

As of August 28, 2020, 60 patients including 37 patients with different types of cancers and 23 patients with tenosynovial giant cell tumors have received DCC-3014 in the Phase 1 escalation (part 1) study at various doses and dosing schedules.

Very common side effects reported in at least 6 patients (10%) are listed below. These side effects were reported as related to DCC-3014:
• Periorbital oedema (Swelling around the eyes due to accumulation of fluid) (28%)
• Increased levels of an enzyme produced by the liver in blood, which in rare cases, may indicate liver injury (23%)
• Fatigue (23%)
• Increased levels of an enzyme produced by the heart or muscle in blood, which may indicate muscle injury/inflammation, rarely heart injury (22%)
• An increase in enzymes produced by the pancreas in the blood which may indicate pancreatic injury or inflammation (17%)
• Diarrhea (12%)
• Nausea (12%)
• Face edema (Swelling of the face due to accumulation of fluid) (12%)
• Itching (12%)

Side effects reported in more than 3 patients (5%) but less than 6 patients (10%):
• Peripheral Edema (swelling of the arms and/or legs due to accumulation of fluid) (8%)
• Rash (8%)
• Muscle pain or muscle aches (7%)
• Abdominal pain (5%)
• Headache (5%)
• Vomiting (5%)

As of August 28, 2020, 14 patients (23%) died during the study. All deaths were considered not related to DCC-3014. Most of the deaths were a result of progressive disease in patients with disease progression. There were no deaths reported in patients with tenosynovial giant cell tumor.
Possible Drug Interactions: DCC-3014 may interfere with other drugs that you are taking. Likewise, other drugs may interfere with DCC-3014. Allergic reactions may occur. For this reason, it is important that you tell your study doctor about any other medications that you are taking, prior to and during the study. Your study doctor may monitor certain medications you take more closely. Your study doctor will tell you about medications that you should avoid taking during this study.
Phototoxicity Precaution: You should avoid strong sunlight, sunlamps, and other sources of ultraviolet radiation (a type of light) for the duration of the

study. For prevention of phototoxicity, use of the following are recommended: sunscreen with sun protection factor of 30 or higher, hypoallergenic moisturizing creams or ointments for dry skin, and gentle skincare with fragrance-free soaps and detergents.

Allergic Reactions

As with taking any drug, there is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions include an itchy rash (hives) or swelling of the throat making it difficult to breathe.

Please seek treatment immediately and tell the study doctor and study staff if you have any of these symptoms, or any other side effects, during the study.

Tests

Blood Sampling

Blood collections may cause injection site swelling and/or pain, dizziness, lightheadedness, bleeding or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count). Fasting may cause your blood sugar to drop. You may feel tired, hungry, and/or nauseous. If you have diabetes, it is important to talk to your doctor about managing your blood sugar while fasting.

The total volume to be collected will depend on how long you will participate in the study. Cycle 1 should be 80 mL and approximatively 60ml during Cycle 2 and cycle 3 and then approximatively 56 mL for the subsequent visits (once a month for 2 years). This may be more if you are required to attend any unscheduled visits. However, this amount should not cause any problems in adults. In comparison: at the blood bank, 500 mL of blood is collected at one time.

Electrocardiogram

Skin irritation from the ECG electrode pads or pain when removing the pads are possible side effects.

Skin punch Biopsy (removing a tiny sample of skin tissue close to the affected joint)

You will receive anesthesia to numb the area where the biopsy will be taken. Once anesthesia wears off, you may feel pain that can last for several days. Risks associated with localized anesthesia include pain during administration, prolonged numbness, infection, or a reaction to the anesthesia.

Tumor Biopsy:

Risks associated with biopsy of your tumor may include bleeding, pain, and infection. You will receive anesthesia to numb the area where the biopsy will be taken. Once anesthesia wears off, you may feel pain that can last for several days. Risks associated with localized anesthesia include pain during administration, prolonged numbness, infection, or a reaction to the anesthesia.

MRI Scan

MRI scanners use a large magnet and radio waves to take pictures of your body. The scanning takes about 30 to 60 minutes. The effects of the magnetic fields in an MRI scanner have been widely studied. There are no known risks from

being exposed to the magnetic fields. Before an MRI scan, you will be asked a series of questions by the MRI staff to be sure that you do not have any medical reasons that stop you from having an MRI. You should not have an MRI if you have a pacemaker, metallic cardiac valve(s), or certain types of metallic aneurysm clips. You should not have an MRI if you have implanted electronic infusion pumps or other metallic pieces in your body.
You will lie flat on a table that will move into a horizontal tube that is within a large magnet. You may feel *closed in* from being in the small space and you will hear loud banging sounds while having the MRI scan. For some MRI scans, you may get an MRI contrast material. This contrast material is injected into your vein. You will not get the MRI contrast material if you have abnormal kidney function. It is uncommon, but you may feel warmth or pain in the area where the needle was inserted. You may also experience nausea, vomiting, or a headache. Serious allergic reactions that may be life threatening are very rare.
The study drug may also cause adverse effects that are unknown and unexpected.

Contacts

Public
Deciphera Pharmaceuticals LLC

Smith Street 200
Waltham 02451
US
Scientific
Deciphera Pharmaceuticals LLC

Smith Street 200
Waltham 02451
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria (Dose Escalation Phase)
Patients must meet all of the following criteria to be eligible to enroll in the Dose Escalation phase of the study:
1) Male or female patients >=18 years of age
2) Any of the following solid tumors:
a) Advanced MST that has progressed after treatment with all available therapies known to confer clinical benefit or for which conventional therapy is not considered effective as judged by the Investigator:
i) Solid tumors, including but not limited to, metastatic breast or prostate cancer with bone disease
ii) Solid tumors including, but not limited to, gastric, ovarian or non-small cell lung cancer (NSCLC) that frequently have malignant associated ascites or effusion(s)
iii) Tumors with known contribution of macrophages or phagocytes such as but not limited to:
(1) Tumors with high tumor-infiltrating macrophage content
(2) Tumor types with high expression of the receptor CSF1R or its ligands, CSF1 or IL-34, in the tumor by previous testing
(3) Prostate or breast cancer with bone-only disease
iv) NSCLC patients with:
(1) Histologically or cytologically confirmed metastatic, or unresectable locally advanced, recurrent NSCLC with a known epidermal growth factor receptor (EGFR) mutation(s)
(2) Documented disease progression while on a previous treatment with an EGFR tyrosine kinase inhibitor
b) TGCT patients: Histologically confirmed diagnosis of TGCT (formerly known as pigmented villonodular synovitis or giant cell tumor of the tendon sheath). Tumor biopsy to confirm TGCT diagnosis will be required if no histology/pathology is available at the time of screening
i) Disease for which surgical resection will potentially cause worsening functional limitation or severe morbidity as judged by the Investigator
ii) Symptomatic disease with at least moderate pain or stiffness (a score of 4 or more with 10 describing the worst condition) within 1 month of the first dose documented in the medical record
iii) Prior treatment with anti-CSF1 or anti-CSF1R therapy is allowed
(1) Exception 1: discontinuation of anti-CSF1 or anti-CSF1R due to drug-induced liver injury
3) MST patients only: Able to provide a tumor tissue sample; if an

archival tumor tissue sample is unavailable, patients must be willing to undergo a tumor biopsy prior to the first dose of study drug, if the tumor is accessible to biopsy and, in the judgment of
the Investigator, the tumor biopsy will be done safely
4) Patients must have at least 1 measurable lesion according to RECIST Version 1.1 (non-nodal lesions must be >=1.0 cm in the long axis or >=double the slice thickness in the long axis; nodal lesions must be >=1.5 cm in the short axis) except for prostate or breast cancer patients with bone-only disease
a) A lesion in a previously irradiated area is eligible to be considered as measurable disease as long as there is objective evidence of progression of the lesion before study enrollment
b) Prostate or breast cancer patients with bone-only disease are eligible without a measurable lesion by RECIST Version 1.1
5) MST patients only: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1
6) Adequate organ function and bone marrow reserve as indicated by the following laboratory assessments performed within 14 days prior to the first dose of study drug:
a) Bone marrow function: ANC >=1500/µL; hemoglobin >=9 g/dL; platelet count >=75,000/µL
b) Hepatic function:
i. MST patients: Total serum bilirubin <=1.5 times the ULN except for patients with Gilbert*s syndrome, in which case up to 2 × ULN; serum AST/ALT, <=2.5×ULN (<=5×ULN in the presence of hepatic metastases)
ii. TGCT patients: Total serum bilirubin <=ULN; serum AST/ALT <=ULN
c) Renal function: Serum creatinine <=1.5×ULN or creatinine clearance >=50 mL/min based either on urine collection or Cockcroft-Gault estimation
d) Coagulation Profile: Prothrombin time international normalized ratio and partial thromboplastin time <=1.5×ULN.
Patients on a stable, maintenance regimen of anticoagulant therapy for at least 30 days prior to study drug administration may have prothrombin time adjusted for the international normalized ratio measurements >1.5×ULN if, in the opinion of the Investigator, the patient is suitable for the study. An adequate rationale must be provided to the Sponsor prior to enrollment
7) Must be able to take oral medication
8) Patients of reproductive potential must
a) Have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening for female patients, and
b) Agree to follow the contraception requirements
9) The patient is capable of understanding and complying with the protocol and has signed the informed consent form (ICF). A signed ICF must be obtained before any study-specific procedures are performed

Inclusion Criteria (Expansion Phase, TGCT Patients)
Patients must meet all of the following criteria to be eligible to enroll in Expansion Cohorts A or B:

1) Male or female patients >=18 years of age
2) Histologically confirmed diagnosis of TGCT (formerly known as pigmented villonodular synovitis or giant cell tumor of the tendon sheath). Tumor biopsy to confirm TGCT diagnosis will be required if no histology/pathology is available at the time of screening
3) Disease for which surgical resection will potentially cause worsening functional limitation or severe morbidity as determined by surgical consultation or a multidisciplinary tumor board
4) Symptomatic disease with at least moderate pain per BPI Worst Pain or at least moderate stiffness per Worst Stiffness numeric rating scale (NRS) item (defined as a score of 4 or more, with 10 describing the worst condition) within 30 days of the first dose documented in the medical record
5) Patient should complete 14 consecutive days of questionnaires during the screening period and must meet minimum requirements outlined in Table 7
6) An analgesic regimen, if used, needs to be stable as judged by the Investigator for at least 2 weeks prior to Cycle 1 Day 1
7) Expansion Cohort B: prior systemic treatment with anti-CSF1 or anti-CSF1R therapy, with the exception of imatinib or nilotinib
8) Patients must have at least 1 measurable lesion according to RECIST Version 1.1 (non-nodal lesions must be >=1.0 cm in the
long axis or >=double the slice thickness in the long axis; nodal lesions must be >=1.5 cm in the short axis). A lesion in a previously irradiated area is eligible to be considered as measurable disease as long as there is objective evidence of progression of the lesion before study enrollment
9) Adequate organ function and bone marrow reserve as indicated by the following laboratory assessments performed within 21 days prior to the first dose of study drug:
a. Bone marrow function: ANC >=1500/µL; hemoglobin
>=10 g/dL; platelet count >=lower level of normal
b. Hepatic function: Total serum bilirubin <=ULN; serum AST/ALT <=ULN
c. Renal function: Serum creatinine <=1.5×ULN or creatinine clearance >=50 mL/min based either on urine collection or Cockcroft-Gault estimation
10) Must be able to take oral medication
11) Patients of reproductive potential must:
a. Have a negative serum β-hCG pregnancy test at screening for female patients, and
b. Agree to follow the contraception requirements
12) The patient is capable of understanding and complying with the protocol and has signed the ICF. A signed ICF must be obtained
before any study-specific procedures are performed
13) Must be willing and able to complete PRO assessments on an electronic device

Exclusion criteria

Exclusion Criteria (Dose Escalation Phase)
Patients meeting any of the following criteria will be excluded from the Dose Escalation phase of the study:
1. Treatment with anticancer therapy, therapy for TGCT, including investigational therapy, within 2 weeks prior to the administration of study drug. For immediately prior therapies with a half-life (t1/2) longer than 3 days, or if the t1/2 is not available, the interval must be >=28 days prior to the first administration of study drug
2. Unresolved toxicity according to NCI-CTCAE, Version 4.03 (ie, Grade >1 or baseline) from previous anticancer or TGCT therapy, excluding alopecia
3. The patient has known active central nervous system (CNS) metastases. Patients with previously treated brain metastases may participate provided that:
a. They are stable (ie, no evidence of progression by magnetic resonance imaging [MRI]) for at least 4 weeks prior to the first dose of study drug),
b. All neurologic symptoms have returned to baseline, and
c. Patients do not require continued steroid therapy or use of enzyme-inducing antiepileptic drugs. Patients can be switched to a non-enzyme inducing antiepileptic drug. If signs or symptoms suggest CNS metastases, a brain MRI/computed tomography (CT) scan must be performed to confirm absence of detectable CNS disease within 2 weeks prior to receiving study drug.
4. New York Heart Association class III or IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure
5. Systemic arterial thrombotic or embolic events, such as cerebrovascular accident (including ischemic attacks) or hemoptysis within 6 months prior to the start of study drug
6. Systemic venous thrombotic events (eg, deep vein thrombosis) or pulmonary arterial events (eg, pulmonary embolism) within the 1 month prior to the start of study drug
7. Baseline prolongation of the QTcF based on repeated demonstration of QTcF >450 ms in males or >470 ms in females or history of long QT syndrome
8. LVEF <50%
9. Concurrent treatment with prohibited medications
10. Major surgery within 2 weeks of the first dose of study drug; following major surgeries >2 weeks prior to the first dose of study drug, all surgical wounds must be healed and free of infection or dehiscence
11. Any other clinically significant comorbidities, such as significant concomitant arthropathy in the affected joint, or any other serious medical or psychiatric condition(s), known current alcohol abuse, which in the judgment of the Investigator, could compromise compliance with the protocol, interfere with the interpretation of study results, or predispose the patient to safety risks
12. Malabsorption syndrome or other illness that could affect oral absorption as judged by the Investigator
13. Known human immunodeficiency virus, active hepatitis B, active hepatitis C, or active mycobacterium tuberculosis infection

14. If female, the patient is pregnant or lactating
15. Known allergy or hypersensitivity to any component of the study drug
Exclusion Criteria (Expansion Phase, TGCT Patients)
Patients meeting any of the following criteria will be excluded from the Expansion phase:
1. Expansion Cohort A: previous use of systemic therapy targeting CSF1 or CSF1R; previous therapy with imatinib and nilotinib is Allowed
2. Expansion Cohort B: discontinuation of anti-CSF1 or anti CSF1R due to drug-induced liver injury
3. Treatment with therapy for TGCT, including investigational therapy, within 14 days prior to the administration of study drug. For immediately prior therapies with a t1/2 longer than 3 days, or if the t1/2 is not available, the interval must be >=28 days prior to the first administration of study drug
4. Known metastatic TGCT or other active cancer that requires concurrent treatment
5. New York Heart Association class III or IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure
6. Systemic arterial thrombotic or embolic events, such as cerebrovascular accident (including ischemic attacks) or hemoptysis within 6 months prior to the start of study drug
7. Systemic venous thrombotic events (eg, deep vein thrombosis) or pulmonary arterial events (eg, pulmonary embolism) within the 1 month prior to the start of study drug
8. Baseline prolongation of QTcF based on repeated demonstration of QTcF >450 ms in males or >470 ms in females or history of long QT syndrome
9. LVEF <55%
10. Concurrent treatment with prohibited medications
11. Major surgery within 14 days of the first dose of study drug; following major surgeries >14 days prior to the first dose of study drug, all surgical wounds must be healed and free of infection or dehiscence
12. Any clinically significant comorbidities, such as significant concomitant arthropathy in the affected joint, or any other serious medical or psychiatric condition(s), known current alcohol abuse, which in the judgment of the Investigator could compromise compliance with the protocol, interfere with the interpretation of study results, or predispose the patient to safety risks
13. Malabsorption syndrome or other illness that could affect oral absorption as judged by the Investigator
14. Known human immunodeficiency virus (HIV), active or chronic hepatitis B, active or chronic hepatitis C, or active mycobacterium tuberculosis infection
15. If female, the patient is pregnant or lactating
16. Known allergy or hypersensitivity to any component of the study Drug
17. Contraindication to MRI
18. Active liver or biliary disease including evidence of fatty liver, nonalcoholic steatohepatitis (NASH), or cirrhosis

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-06-2020
Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	DCC-3014
Generic name:	N/A

Ethics review

Approved WMO

Date:	16-10-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	12-02-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

	metc-ldd@lumc.nl
Approved WMO Date:	29-06-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	16-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	09-07-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	12-01-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-08-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	07-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

	metc-ldd@lumc.nl
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-06-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-03-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	25-03-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-514933-39-00
EudraCT	EUCTR2019-001856-21-NL
CCMO	NL70948.058.19