A Multicenter Phase 1, Open-Label Study of DCC-2618 to Assess Safety, Tolerability, Efficacy, and Pharmacokinetics in Patients with Advanced Malignancies

Published: 24-07-2017
Last updated: 04-01-2025

Escalation PhasePrimary ObjectivesThe primary objectives of this study are to:• Determine the safety and tolerability of oral DCC-2618• Determine a maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of oral DCC-261Secondary...

Ethical review	Approved WMO
Status	Completed
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON55457

Source
ToetsingOnline

Brief title
A phase I, open-label study of DCC-2618 in advanced malignancies

Condition

- Leukaemias
- Malignant and unspecified neoplasms gastrointestinal NEC
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced Cancer; advanced malignancies

Research involving

Human

Sponsors and support

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

Intervention

Keyword: advance malignancies, KIT and PDGFRA, open-label

Outcome measures

Primary outcome

Escalation Phase:

The primary objectives are to:

• Determine the safety and tolerability of oral DCC-2618

• Determine a maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D)

of oral DCC-2618

Expansion Phase:

The primary objectives are to:

• Further evaluate the safety and tolerability of oral DCC-2618

• Determine the antitumor activity of DCC-2618 in all diseases under study

Secondary outcome

Escalation Phase:

The secondary objectives are to:

• Determine the pharmacokinetic (PK) profile of oral DCC-2618

• Document preliminary evidence of DCC-2618 antitumor activity

Expansion Phase:

The secondary objectives are to:

• Determine the PK, including population PK, profile of oral DCC-2618

• Evaluate the safety and tolerability of the RP2D of oral DCC-2618 in a cohort

of patients with moderate to severe renal impairment

• Determine allele fraction of KIT and PDGFRA mutations in plasma cfDNA and

compare it with mutation allele fraction in GIST tumor tissue and their

association with prior treatment and study drug response

Study description

Background summary

DCC-2618 is a novel, oral inhibitor of KIT developed by Deciphera Pharmaceuticals, LLC, using its proprietary kinase switch pocket inhibitor technology platform. The discovery and development of DCC-2618 was based on the rationale of potently inhibiting a broad array of mutant forms of KIT and PDGFRα kinases, including mutations that inevitably cause resistance to approved targeted therapies as well as refractory primary mutations in treatment naïve patients. This profile was achieved by optimizing the binding of the inhibitor and forcing these oncogenic kinases into inactive conformations.
While currently approved tyrosine kinase inhibitors have been demonstrated to inhibit certain clinically relevant resistant mutations in KIT and/or PDGFRα, these agents only inhibit a subset of mutant forms of the kinases and do not broadly inhibit the full spectrum of resistance mutations that arise. DCC-2618 comprehensively and potently inhibits a wide range of primary and secondary mutants of KIT and PDGFRα kinases, including activation loop mutations in exons 17 and 18. DCC-2618 has been evaluated in recombinant kinase assays and in cellular assays with gastrointestinal stromal tumor (GIST) cell lines from treatment-resistant patients, mastocytosis and acute myeloid leukemia (AML) cell lines, and cell lines transfected with KIT or PDGFRα mutants.
In vivo, DCC-2618 exhibited robust antitumor effects in GIST models. Oral administration of DCC-2618 in GIST and AML xenograft models demonstrated a significant reduction in tumor volume compared to vehicle treatment, including in exon 17 mutant KIT models. DCC-2618 showed robust inhibition of KIT phosphorylation and signaling for approximately 12 hours after a single oral

dose in the GIST T1 xenograft model. DCC-2618 has pharmaceutical properties amenable to oral administration. DCC-2618 is therefore a promising candidate for the treatment of GIST and mast cell diseases, as well as other cancers driven by KIT or PDGFRα kinases.
A series of in vitro and in vivo non-clinical experiments have been conducted to evaluate the pharmacodynamics (PD), pharmacokinetics (PK), and toxicology profile of DCC-2618. These studies support further development of DCC-2618 based on the efficacy and tolerability observed in these model systems. Additional information can be found in the Investigator Brochure.

The current study is a first-in-human (FIH) study with DCC-2618. The study will consist of an escalation phase assessing increasing doses of single agent DCC-2618 in patients with advanced malignancies, followed by an expansion phase testing for safety and preliminary evidence of antitumor activity in select tumors.

It is well established that inhibition of receptor tyrosine kinases and/or their downstream targets results in therapeutic effects in a variety of tumor types. However, despite recent progress and the availability of targeted kinase inhibitors for certain tumor types, ultimate drug resistance and disease relapse develop in most tumors, underscoring the need to develop more effective kinase inhibitors with favorable benefit-risk profiles.

DCC-2618 inhibits a broad range of primary and secondary mutants of KIT and PDGFRα kinases, including activation loop mutations in exons 17 and 18. DCC-2618 has been evaluated in recombinant kinase assays and in cellular assays with GIST cell lines from treatment-resistant patients, mastocytosis and AML cell lines, and cell lines transfected with KIT or PDGFRα mutants.

Gastrointestinal Stromal Tumors
Gastrointestinal stromal tumors are driven by activating mutations in KIT (approximately 80%) or the related PDGFRα (approximately 10%) receptor tyrosine kinases. In GIST patients at presentation, primary mutations in KIT gene are usually found in exon 9 or 11. Primary mutations in exon 11 disrupt the auto-inhibited form of the kinase, and those in exon 9 increase receptor dimerization. Both of these mechanisms cause ligand-independent receptor activation, which leads to uncontrolled cell growth and transformation.
Multiple KIT targeted therapies have been approved for the treatment of GIST, but there are limitations to their therapeutic success.

Advanced Systemic Mastocytosis and Hypereosinophilic Syndromes
Aggressive SM and MCL are 2 subcategories of SM that in most adults (>80%) are characterized by primary KIT mutations in exon 17.
Currently, imatinib is the only approved therapy for patients with ASM wt-KIT or with unknown KIT mutational status.
None of the currently available KIT inhibitors, including imatinib, sunitinib, and regorafenib, are able to meaningfully inhibit KIT D816V and no curative

therapy for ASM and MCL has become available to date. Treatment of advanced SM remains one of the most challenging areas in clinical hematology. Therefore, a therapeutic agent able to inhibit KIT D816V in these patients would address this high unmet medical need.
Hypereosinophilic syndromes are myeloproliferative neoplasms with significant unmet need.
While some of these disorders are quite sensitive to imatinib and it should be prescribed for patients with fusions or mutations known to be associated with sensitivity to this agent there are cases of resistance that still have unmet need. In addition, rare patients who are intolerant of imatinib may benefit from investigational PDGFR inhibitors such as DCC-2618.

Malignant Gliomas
Gliomas depend on PDGF-PDGFR pathway signaling. Starting early in brain development, the genesis of oligodendroglial precursors is dependent on PDGF-PDGFRA signaling.
This normal embryonic signaling is co-opted by tumors including malignant gliomas. Most GBMs have high expression of PDGFRA. A subset of GBMs exhibit high amplification of the PDGFRA locus, sometimes including the adjacent KIT gene. One such co-amplified GBM has shown an excellent response that is ongoing at 14 months in a patient on the starting dose of DCC-2618. Hence additional patients with malignant gliomas with genomic alterations including amplification and/or mutation of PDGFRA and KIT will be recruited.

Other Solid Tumors
Activating mutations in the receptor tyrosine kinase KIT have been identified in multiple cancer types such as melanoma and testicular seminomas. In addition, aberrant wild-type KIT overexpression is found in melanoma, gliomas, and neuroendocrine tumors . Thus, rare KIT genomic alterations are found in a variety of solid tumors in addition to GIST and malignant gliomas and may benefit from DCC-2618.

In summary, DCC-2618, a novel tyrosine kinase switch pocket inhibitor, could be of high therapeutic value in the treatment of patients with advanced malignancies harboring activated KIT/PDGFRα mutations and those refractory to existing treatments.

Study objective

Escalation Phase

Primary Objectives
The primary objectives of this study are to:
• Determine the safety and tolerability of oral DCC-2618
• Determine a maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of oral DCC-261

Secondary Objectives
The secondary objectives of this study are to:
• Determine the PK profile of oral DCC-2618
• Document preliminary evidence of DCC-2618 antitumor activity in patients with advanced malignancies
• Assess the effect of food on the PK profile of oral DCC-2618

Exploratory Objectives
The exploratory objectives of this study are to:
• Investigate the effects of DCC-2618 on selected PD parameters
•To assess polymorphic variations in genes encoding drug metabolic enzymes and/or transporters involved in metabolism and disposition of DCC-2618 and DP-5439 and/or genes that may potentially be associated with clinical response and/or study drug-related toxicity
• Determine allele fraction of KIT and PDGFRA mutations in plasma cell-free DNA (cfDNA) and compare it with mutation allele fraction in GIST tumor tissue and their association with prior treatment and study drug response
• Assess metabolic tumor response by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) by European Organisation for Research and Treatment of Cancer (EORTC) criteria in selected GIST patients.

Expansion Phase

The primary objectives are to:
• Further evaluate the safety and tolerability of oral DCC-2618
• Determine the antitumor activity of DCC-2618 in all diseases under study
The secondary objectives are to:
• Determine the PK, including population PK, profile of oral DCC-2618
• Evaluate the safety and tolerability of the RP2D of oral DCC-2618 in a cohort of patients with moderate to severe renal impairment
• Determine allele fraction of KIT and PDGFRA mutations in plasma cfDNA and compare it with mutation allele fraction in GIST tumor tissue and their association with prior treatment and study drug response
The exploratory objectives are to:
• To characterize the PK of parent drug DCC-2618 and its metabolite, DP-5439
• To explore the relationship between total drug (DCC-2618 + DP-5439) exposure and potential safety, PD (PK/PD relationships), and total drug exposure and clinical endpoints, analyzed separately for each cohort and in all patients receiving at least RP2D
• To assess polymorphic variations in genes encoding drug metabolic enzymes and/or transporters involved in metabolism and disposition of DCC 2618 and DP 5439 and/or in genes that may potentially be associated with clinical response and/or study drug-related toxicity
• Investigate the effects of DCC-2618 on selected PD parameters
• Assess the effects of DCC-2618 using patient reported outcome (PRO) measures to support the selection of future dosing regimen(s).

Study design

This is an open-label Phase 1 study. The study will start with an Escalation Phase evaluating increasing doses of single agent DCC-2618 administered in repeated 28-day cycles in patients with advanced malignancies with a molecular rationale for activity. The Escalation Phase will be followed by an Expansion Phase testing for further safety, PK PD and evidence of antitumor activity across a variety of tumors with evidence of alterations in genes that are targets of DCC-2618.

Escalation Phase:
Sequentially increasing dose levels of oral DCC-2618 dosed once daily (QD) or twice daily (BID) in repeated 28-day cycles will be evaluated for safety based on pharmacologically guided 3+3 escalation rules until an MTD has been identified or a recommended expansion dose/regimen(s) is declared (ie, RP2D). During the Escalation Phase of the study, the effect of food on DCC-2618 PK and safety was assessed at the baseline visit (Day -7).
As of Amendment 3, the food effect objective was discontinued because sufficient information is available on the effect of a high-fat meal on PK. The food effect objective will not apply to the Expansion Phase of the study.

Dose escalation will follow a pharmacologically guided 3+3 design outlined in Table 5. A minimum of 3 patients will be enrolled in each dose level cohort. The occurrence of 1 DLT during Cycle 1 will trigger a cohort to expand to 6 patients, for additional safety testing if further dose escalation is planned. If 1 or more additional DLT(s) occur in the expanded cohort, the DLT dose level will be declared, dose escalation will end, and an MTD will be determined. Once a dose level has been declared safe, the dose level of the next cohort will be determined in consultation with the investigators based on:
1.) safety data from all enrolled patients, and
2.) supplemental PK data from at least 3 patients in the current cohort who have completed the Cycle 1 Day 15 visit.
If a dose level is declared safe (ie, 0 DLTs in 3 patients or 1 DLT in 6 patients), then the cohort may be expanded to an additional 6 patients to further investigate PK, PD, tolerability, and antitumor activity. AEs occurring in such additional patients that meet the definition of a DLT will not count as DLT but will be considered for the overall safety assessment of a given dose level.
Once the DLT dose level is reached, an MTD may be determined to be a previously confirmed safe dose level (assessed in >=6 patients) or it may result from assessment of additional lower, intermediate dose levels above the last previous safe dose level. An MTD will be defined as the highest dose level immediately below the DLT dose level.
Patients may escalate, after the completion of Cycle 2, to a higher daily dose that has subsequently been found to be safe and tolerable (eg, intra-patient dose escalate).

Expansion Phase:
In the Expansion Phase, additional patients will be enrolled in disease specific cohorts for KIT or PDGFRA mutant GIST, SM and other hematologic malignancies, malignant gliomas, and other solid tumors (See Section 3.4.2 for further details).
Patients with GIST and other solid tumors will start DCC-2618 at the RP2D (150 mg QD) in the Expansion Phase to further evaluate the safety, tolerability, and preliminary evidence of antitumor response. Preliminary PK analysis from three SM patients showed apparently lower exposure than GIST patients. To ensure sufficient drug exposure, 150 mg BID was selected for patients with SM and other hematologic malignancies. A dose of 150 mg BID has been administered to 66 patients to date with acceptable safety. Patients with SM or other hematologic malignancies who are currently receiving DCC-2618 at a dose of 150 mg QD may be dose escalated to 150 mg BID at any time.
In addition to antitumor activity, population PK, PD analysis, and PRO measures may be used to support RP2D confirmation.
Patients with GIST or other solid tumors enrolled in the Expansion Phase who have disease progression by the appropriate indication response criteria (see Appendices 10.2, 10.3, 10.7) may escalate to 150 mg BID after the completion of Cycle 2. See Section 5.2.6.1 for further details on intra patient dose escalation in the Expansion Phase. SM patients who were originally enrolled and dosed at 150 mg QD may be dose escalated to 150 mg BID at any time. Patients with SM and other hematologic malignancies receiving doses of DCC-2618 at a dose of 150 mg BID will not be dose escalated following PD.
The safety and tolerability of DCC-2618 will be evaluated in Cohort 10 - patients with renal impairment (Section 4.2.1). Patients will be dosed at the RP2D, a total of up to 10 patients will be enrolled and evaluated. PK samples will be collected for all patients in this cohort (Section 6.3). Patients who do not have sufficient PK data, may be replaced. Patients with severe renal impairment who do not complete cycle 1 of treatment due to reasons that are not study-drug related such as early disease progression may be replaced. Patients with severe renal impairment who discontinue due to AEs related to DCC-2618 will not be replaced in the study.

Escalation and Expansion Phases:
In addition to safety and assessment of antitumor activity, the PK profile and PD effects of DCC-2618 will be assessed. PD biomarkers from plasma and whole blood will be assessed throughout the study. PD and evidence of treatment response may be investigated in a biopsy containing tumor or mastocytosis cells when available. A single blood sample will be obtained for pharmacogenomics research. FDG-PET scans will be used to assess metabolic activity by EORTC criteria in subsets of patients whose disease can be appropriately assessed with this testing (eg, GIST). As of Amendment 3, the Sponsor no longer requests PET scans in the Escalation Phase because sufficient data are available to estimate the metabolic response rate in KIT mutant GIST. In the Expansion Phase, PET scans will be performed for GIST patients that progress and dose

escalate (ie, intra-patient dose escalation).

The study will be conducted from the third quarter of 2015 to approximately the second quarter of 2019.

Intervention

The current study is a first-in-human (FIH) study with DCC-2618. The study will consist of an Escalation Phase assessing increasing doses of single agent DCC-2618 in patients with advanced malignancies, followed by an Expansion Phase testing for safety and preliminary evidence of antitumor activity in select tumors. Patients in Netherlands will only be enrolled in the Expansion Phase of the study.

Expansion Phase only:
In the Expansion Phase, additional patients will be enrolled in disease specific cohorts for KIT or PDGFRA mutant GIST, SM and other hematologic malignancies, malignant gliomas, and other solid tumors.
Patients will start DCC-2618 at the preliminary RP2D in the Expansion Phase to further evaluate the safety, tolerability, and preliminary evidence of antitumor response. In addition to antitumor activity, population PK, PD analysis, and PRO measures may be used to support RP2D confirmation.
Patients who have disease progression by the appropriate indication response criteria in the Expansion Phase may escalate to a higher daily dose after the completion of Cycle 2. See Section 5.2.6.1 for further details on intra patient dose escalation in the Expansion Phase.

In the Expansion Phase, Patients with GIST and other solid tumors will start DCC-2618 at the RP2D (150 mg QD) in the Expansion Phase to further evaluate the safety, tolerability, and preliminary evidence of antitumor response.
Preliminary PK analysis from three SM patients showed apparently lower exposure than GIST patients. To ensure sufficient drug exposure, 150 mg BID was selected for patients with SM and other hematologic malignancies. A dose of 150 mg BID has been administered to 66 patients to date with acceptable safety. Patients with SM or other hematologic malignancies who are currently receiving DCC-2618 at a dose of 150 mg QD may be dose escalated to 150 mg BID at any time.
In addition to antitumor activity, population PK, PD analysis, and PRO measures may be used to support RP2D confirmation.
Patients with GIST or other solid tumors enrolled in the Expansion Phase who have disease progression by the appropriate indication response criteria (see Appendices 10.2, 10.3, 10.7) may escalate to 150 mg BID after the completion of Cycle 2. See Section 5.2.6.1 for further details on intra patient dose escalation in the Expansion Phase. SM patients who were originally enrolled and dosed at 150 mg QD may be dose escalated to 150 mg BID at any time. Patients with SM and other hematologic malignancies receiving doses of DCC-2618 at a dose of 150 mg BID will not be dose escalated following PD.
The safety and tolerability of DCC-2618 will be evaluated in Cohort 10 -

patients with renal impairment (Section 4.2.1). Patients will be dosed at the RP2D, a total of up to 10 patients will be enrolled and evaluated. PK samples will be collected for all patients in this cohort (Section 6.3). Patients who do not have sufficient PK data, may be replaced. Patients with severe renal impairment who do not complete cycle 1 of treatment due to reasons that are not study-drug related such as early disease progression may be replaced. Patients with severe renal impairment who discontinue due to AEs related to DCC-2618 will not be replaced in the study.

The Expansion Phase will consist of a screening period that will be conducted within 28 days prior to first dose of study drug, a baseline visit, a treatment period of 28-day cycles, an intra-patient dose escalation (if applicable for some patients), a final study visit, and a follow-up safety visit within 30 days after the last dose of study drug.

Patients will be eligible to receive study drug for as long as the patient is showing clinical benefit as evidenced by disease response for as long as DCC-2618 is being developed to support the indication and continuation of treatment does not conflict with the Sponsor*s right to terminate the study as detailed in Section 3.5. The study will end following the last patient last visit.

Study burden and risks

Your disease may not improve or may worsen during your participation in this study. While you are taking the study drug, you may have side effects. You may experience all, some, or no side effects, and the side effects may vary in severity. The side effects may be mild, moderate, severe, long-lasting, permanent or fatal. Many side effects may go away shortly after the drug is stopped, but in some cases, side effects can last longer. Sometimes they can be permanent or serious. DCC-2618 is still being studies in humans and not all the side effects are known. There is a risk of a rare or previously unknown side effect occurring. You must tell your study doctor if you experience any side effects as soon as they occur, even if you think they are not caused by the study drug. The study doctor may give you other drugs to ease any discomfort you experience.
As of August 2018, 227 patients with different types of cancer have received DCC-2618 in the Phase 1 study. The following side-effects have been reported. These side effects may or may not be related to DCC-2618. Some may have been considered serious.
Common side effects reported in more than 20% of patients:
• Fatigue (40%)
• Hair loss (39%)

• Pain or ache in the muscle (34%)
• Constipation (29%)
• Hand-Foot-Syndrome (blisters, redness, swelling, and pain on the palms of hands and/or the soles of the feet, 26%)
• Nausea (25%)
• Loss of appetite (23%)
• High blood levels of an enzyme that breaks down fat (22%)
Occasional side effects reported in 20% or less of patients:
• Weight loss (20%)
• Abdominal pain (18%)
• Diarrhea (17%)
• Vomiting (16%)
• Decreased iron in the blood, which may make you feel tired or short of breath (15%)
• Joint pain (15%)
• High blood pressure (15%)
• Shortness of breath (15%)
• Rash (14%)
• Headache (13%)
• Dry skin (12%)
• Increased levels of blood bilirubin, which is a pigment produced by the liver. Increased levels can cause possible yellowing of the skin and/or eyes and may indicate liver injury (12%)
• Pain in extremity (12%)
• Cough (11%)
• Muscle spasms (11%)
Some reported side-effects were considered serious (e.g., required hospitalization or the doctor felt they were medically important). The following is a list of serious side effects reported in 2 or more patients. They may or may not be related to DCC-2618.
• In 8 patients (4%): abdominal pain
• In 6 patients (3%): shortness of breath
• In 4 patients (2%): fever
• The following side effects were reported in 3 patients (1%) each: intestinal blockage, life-threatening blood infection, urinary tract infection, decreased iron in the blood, increased bilirubin, confusion
• The following side effects were reported in 2 patients (1%) each: fluid accumulation in the belly, trouble swallowing, intestinal bleeding, pneumonia, inflammation of the pancreas, vomiting, fatigue, increased levels of an enzyme that breaks down fat, mental status changes, chest pain, heart failure, blood clots, low blood pressure, kidney failure, falls

One patient treated with DCC-2618 was diagnosed with Stevens-Johnson Syndrome and recovered once the drug was stopped. It is a rare, serious disorder of the skin and mucous membranes. It begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters. Then, the top layer of the affected skin dies, sheds and then heals. This is a serious condition and

may be life-threatening.

One patient treated with DCC-2618 was diagnosed with diastolic dysfunction, which is a condition where the heart has trouble relaxing between beats.

As of August 2018, 27 patients died during the study with most (22 patients) having died due to disease progression. One patient died due to an infection of the bile duct and one died due to heart attack; neither event was considered related to study treatment. Three patients died due to unknown reasons. Although no deaths were considered related to study treatment prior to August 2018, one patient was reported to have died of a heart attack in December 2018 that was possibly related to study treatment.

Skin Side Effects Observed in the Phase 1 study that May be Related to DCC-2618 Some patients treated with DCC-2618 to date have reported changes in the skin. As of August 2018, eleven (11) patients have had a curable form of skin cancer (squamous cell carcinoma) was found. This was treated by removing the tumors using an outpatient surgical procedure. This common cancer tends to occur in sun exposed skin and can be seen with the naked eye as often, dry, flaky, raised or depressed, slow-growing bumps in the skin. Other reported skin changes that are not listed above were non-cancerous skin lesions (actinic keratosis and keratoacanthoma) reported in 13 patients.

Possible Drug Interactions: DCC-2618 may interfere with, other drugs that you are taking, and other drugs may interfere with DCC-2618.

Blood Draws: Blood draws may cause pain, bleeding, and/or bruising. Patients 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), which may create a need for blood transfusions.

Tumor Biopsy, Bone Marrow Biopsy and Bone Marrow Aspirate: Risks associated with biopsy of tumor or bone marrow biopsy and aspirate include bleeding, pain, and infection. Patients will receive anesthesia to numb the area where the biopsy will be taken. Once anesthesia wears off, they 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.

Magnetic Resonance Imaging (MRI): An MRI scan is painless and will not expose patients to any radiation. Some patient may feel frightened of enclosed spaces when they have an MRI scan, as the space inside the machine is cramped. Some people are also frightened by the noise the machines can make.

Radiation Risks Associated with FDG-PET Scans (GIST Patients Who Dose Escalate

Only): GIST patients who escalate to a higher dose will be exposed to radiation from two FDG-PET scans. The total amount of radiation exposed to in this study is [XX] mSv (to compare: the background radiation in the Netherlands is ~2.5 mSv per year). From participating in this study, the maximum amount of additional radiation your body will be exposed to in one year is less than what a person performing imaging scans can receive in one year. There is thought to be an increased long term risk of cancer associated with radiation. However, this risk is small. The patient will be advised not to participate in another scientific study involving exposure to radiation in the near future. Previous studies have shown the more common side effects associated with FDG-PET scanning to be: mild and brief discomfort with placement of the intravenous line in your forearm; slight risk of infection; possible bruising, bleeding or swelling; claustrophobia and anxiety.

Reproductive risks: The effects of DCC-2618 on the unborn child or nursing children are unknown, It is not known if DCC-2618 could affect male sperm.

There is a potential risk of photoirritation/phototoxicity.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria
Patients must meet the following criteria to be eligible to enroll in the study:
1. Patients must have histologically confirmed solid tumors or hematologic malignancies. Eligible patients include the following:
a. GIST patients must have a KIT or PDGFRA mutation and must have progressed on or had an intolerability to at least 1 line of systemic anticancer therapy:
i. Patients with a pre-existing resistance mutation to an approved line of therapy are eligible. For example, imatinib resistant mutations including KIT Exon 17 and PDGFRA D842V.
b. Systemic mastocytosis (SM) patients must have a confirmed diagnosis (confirmed by a central independent pathologist) of advanced SM according to 2016 World Health Organization (WHO) criteria for SM (15) and must have documented KIT mutant disease. Patients with imatinib-sensitive KIT mutations must have progressed on or were intolerant to a tyrosine kinase inhibitor. Patients with advanced SM must present with at least 1 eligible C Finding (organ damage) as outlined in Table 3 of the 2013 International Working Group Myeloproliferative Neoplasms Research and Treatment (IWG MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria (Appendix 10.5); please see below for MCL exception.
Advanced SM includes:
i. Aggressive SM (ASM),
ii. SM-AHN, wherein the AHN does not require immediate alternative therapy, such as acute myeloid leukemia. AHNs that are eligible include: low grade myelodysplastic syndrome (MDS) with a high SM burden who require treatment for SM only, myeloproliferative neoplasms (MPNs), MDS/MPN, unclassifiable MDS, and HES/CEL.
iii. MCL
• Patients with histopathologically-confirmed MCL without a C finding are eligible.
iv. Symptomatic SSM
By definition, SSM patients must have at least 2 B-findings, and clinically significant symptom burden (eg, flushing, diarrhea, etc.) despite maximal treatment with approved agents to treat mediator symptoms, such as antihistamines and cromolyn sodium.
v. Patients with hematologic malignancies featuring clonal expansion of eosinophils driven by genomic alterations of KIT or PDGFR (eg, HES or CEL) must have a diagnosis confirmed by a central independent pathologist and are

eligible if they have progressed on or are intolerant of imatinib therapy. Patients with de novo imatinib resistant mutations, such as but not limited to KIT D816V or PDGFRA D842V, are eligible without prior imatinib therapy.

c. Malignant glioma patients with genomic alterations potentially conferring sensitivity to DCC 2618 including, but not limited to, amplification and/or mutations of PDGFRA and/or KIT.
i. Patients must not require use of enzyme-inducing antiepileptic drugs
ii. Patients that require steroids must be on a stable dose for 2 weeks prior to the first dose of study drug.
d. Other solid tumor patients that have alterations in genes encoding kinases that are targets of DCC-2618. This includes KIT, PDGFR (A or B), TIE2, CSF1R, and VEGFR2. Patients must have received approved treatments known to provide clinical benefit prior to study entry.
e. Melanoma patients with mutations and/or amplification potentially conferring sensitivity to DCC-2618 including KIT, PDGFR (A or B), TIE2, CSF1R, and VEGFR2 (KDR).
i. Patients must have a histologically documented diagnosis of melanoma
ii. Patients must have received approved treatments known to provide clinical benefit prior to study entry
f. Soft tissue sarcoma patients (including but not limited to: malignant peripheral nerve sheath tumors [MPNST], desmoplastic small round cell tumors [DSRCT], and dermatofibrosarcoma protuberans tumors [DFSP] with mutations and/or amplification potentially conferring sensitivity to DCC-2618, this includes KIT, PDGFR (A or B), TIE2, CSF1R, and VEGFR2.
i. Patients must have a histologically documented diagnosis of soft tissue sarcoma
ii. Patients must have received approved treatments known to provide clinical benefit prior to study entry
g. Other solid tumor patients (non-melanoma, non-STS; specifically, germ-cell, penile, and non-small cell lung carcinoma) that have mutations and/or amplification in genes encoding kinases that are targets of DCC-2618. This includes KIT, PDGFR (A or B), TIE2, CSF1R, and VEGFR2. Patients must have received approved treatments known to provide clinical benefit prior to study entry.
2. If signs or symptoms suggest suspected CNS metastases, a brain MRI must be performed to confirm absence of CNS disease prior to receiving study drug.
3. A renal impairment cohort will be formed, comprised of advanced GIST patients as well as other solid tumor patients with at least one prior therapy and with genomic alterations in KIT or PDGFRA/B and creatinine clearance between 20 and 50 mL/min, not requiring dialysis.
4. Patients with known CNS metastases may participate provided that:
a. they are stable (ie, without evidence of progression by magnetic resonance imaging [MRI]) for at least 4 weeks prior to the first dose study drug (patients with active disease may be eligible following discussion between the Investigator and the Sponsor),
b. all neurologic symptoms have been stable for 2 weeks prior to the first dose

of study drug,
c. patients do not require use of enzyme-inducing antiepileptic drugs.
d. patients that require steroids must be on a stable dose for 2 weeks prior to the first dose of study drug
5. Patients with solid tumors (with the exception of glial tumors and tumors that are anatomically inaccessible) must have an archival tumor biopsy sample as long as no anticancer therapy was administered since the sample was collected; otherwise, a current biopsy is required. In the case of glial tumors and anatomically inaccessible tumors, the most recent archival tissue is required.
6. Male or female patients >=18 years of age.
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of <=2.
8. Female patients of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-hCG) pregnancy test within 28 days prior to the start of study drug. For clinical sites in the UK and Germany, pregnancy testing must occur within 7 days prior to the start of study drug.
9. Patients of reproductive potential must agree to follow the contraception requirements outlined in Section 6.8.11.
10. The patient is capable of understanding and complying with the protocol and has signed the informed consent document. A signed informed consent form must be obtained before any study specific procedures are performed. Standard procedures performed as part of the practice of medicine prior to consent (eg, imaging, physical exam) can be used to determine eligibility if completed within 28 days prior to the initial dose of study drug.
11. Patients with solid tumors 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) or Response Assessment in Neuro-Oncology Criteria (RANO).
a. A non-brain 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.
12. Adequate organ function and bone marrow function as indicated by the following central laboratory screening assessments performed within 14 days prior to the first dose of study drug. Local laboratory values obtained after screening and prior to Cycle 1 Day 1 dosing that do not meet the criteria below must be discussed with the Sponsor:
a. Solid Tumor Patients: Bone Marrow Function: Absolute neutrophil count (ANC) >=1500/µL; hemoglobin >=9 g/dL; platelet count >=75,000/µL.
b. All Patients:
i. Hepatic Function: Serum direct bilirubin <=1.5 times the upper limit of normal (ULN) (<=3 × ULN if this elev

Exclusion criteria

Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:
1. GIST patients with wild type or unknown KIT or PDGFRA status
2. Patients with SM or other hematologic malignancies will be excluded if the following apply:
a) SM patients with neutropenia accompanied by fever or infection, or thrombocytopenia associated with clinically significant bleeding.
• Patients with an infection that is well controlled with antibiotics are eligible if there is an immediate need for treatment
b) SM-AHN patients diagnosed with:
i. SM with MDS (SM-MDS) who require treatment.
ii. Patients requiring immediate treatment for AHN.
c) Patients with leukemias, with the exception of MCL and CEL, that have progressed after imatinib.
d) Eosinophilic myeloproliferative neoplasm patients:
i. Lacking a mutation that is a known target of DCC-2618. This includes, but is not limited to, fusions/mutations of fibroblast growth factor receptor 1 (FGFR1), Janus kinase 2 (JAK2), and Abelson murine leukemia viral oncogene (ABL).
3. Prior or concurrent malignancy whose natural history or treatment have the potential to interfere with the safety or efficacy assessment of DCC-2618. Patients receiving adjuvant cancer treatment are not eligible if those medications are potentially active against GIST or excluded per protocol.
4. Treatment with anticancer therapy, including investigational therapy, within 2 weeks prior to the administration of study drug, with the exception of hydroxyurea that is allowed to control white blood cell count. For prior therapies with a half-life longer than 3 days, the interval must be at least 28 days prior to the first administration of study drug.
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. Arterial thrombotic or embolic events such as cerebrovascular accident (including ischemic attacks) or hemoptysis within 6 months before start of study drug.
7. Venous thrombotic events (eg, deep vein thrombosis) or pulmonary arterial events (eg, pulmonary embolism) within the 3 months before start of study drug. Patients with venous thrombotic events >=3 months before start of study drug on stable anticoagulation therapy are eligible.
8. Baseline prolongation of the rate-corrected QT interval based on repeated demonstration of QTcF >450 ms in males or >470 ms in females or history of long QT syndrome.
9. LVEF <50% or below the institute lower limit of normal (whichever is higher).
10. Major surgery within 4 weeks of the first dose of study drug; following major surgeries >4 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 uncontrolled pulmonary disease, active infection, or any other condition, 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.
13. Known human immunodeficiency virus or hepatitis C infection only if the patient is taking medications that are described in Section 5.8.2.2, active hepatitis B, or active hepatitis C infection.
14. If female, the patient is pregnant or lactating.
15. Known allergy or hypersensitivity to any component of the investigational drug product. Patients with history of Stevens-Johnson syndrome on a prior TKI are excluded.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	07-05-2018
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DCC-2618
Generic name:	DCC-2618

Ethics review

Approved WMO

Date:	24-07-2017

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

Approved WMO Date:	31-01-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	03-05-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	06-05-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	27-05-2019

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	01-07-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	25-09-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	03-03-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	01-12-2020

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	28-12-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	27-09-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	18-01-2022

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
EudraCT	EUCTR2016-001324-60-NL
CCMO	NL61963.058.17

Study results

Date completed:	15-03-2022
Results posted:	29-04-2023
Actual enrolment:	3

First publication
18-04-2023