# Phase 1 study of DCC-3014 to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with malignant solid tumors and diffuse-type tenosynovial giant cell tumor

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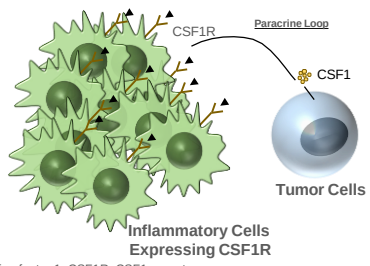
## INTRODUCTION

- Colony stimulating factor 1 receptor (CSF1R) is a receptor tyrosine kinase that is implicated in the recruitment and survival of tumor-associated macrophages (TAMs) through a paracrine interaction with tumor cells in the tumor microenvironment[1-2]
  - CSF1R has 2 known ligands; CSF1 (also known as macrophage-CSF) and interleukin 34 (IL-34)[3]
- Tenosynovial giant cell tumor (TGCT; formerly known as pigmented villonodular synovitis [PVNS] or giant cell tumor of the tendon sheath) is a rare disease arising from the joint synovium, bursa, and tendon sheath caused by translocation in CSF1 gene resulting in overexpression of CSF1 and recruitment of CSF1R-positive inflammatory cells into the lesion (**Figure 1**)[4]
  - TGCT presents either as localized (a single, well-defined nodule) or diffuse-type with multiple nodules that are more aggressive

### Figure 1. Role of CSF1R in development of TGCT




CSF1, colony stimulating factor 1; CSF1R, CSF1 receptor

- DCC-3014 is an orally administered, potent, and selective inhibitor of CSF1R that was engineered to bind as a switch control inhibitor of CSF1R and inhibit kinase activity[5]
  - DCC-3014 potently inhibits CSF1R signaling in cellular assays, as well as blocks macrophage-mediated tumor cell migration, osteoclast differentiation, and proliferation of a CSF1R-dependent cell line
  - DCC-3014 is designed to inhibit macrophages that contribute to, or are the source of, tumor development and dissemination
- DCC-3014 exhibits >100-fold selectivity for CSF1R relative to closely-related kinases, including FLT3, KIT, and PDGFRα/β, and >1,000-fold selectivity vs other kinases[5]
- An ongoing phase 1 study (NCT03069469) was initiated to evaluate the safety, preliminary antitumor activity, pharmacokinetics (PK) and pharmacodynamics (PD) of DCC-3014 in advanced solid tumors, including diffuse-type TGCT

## METHODS

- This is a phase 1 multicenter, open-label, single arm study of DCC-3014 in advanced solid tumors including diffuse-type TGCT
- The study consists of two parts:
  - Part 1 (dose escalation) will determine the recommended phase 2 dose (RP2D) and the maximum tolerated dose (MTD) using a 3+3 dose escalation design with a minimum of 3 patients enrolled at each dose level cohort; starting at a dose of 10 mg once daily (**Tables 1–3**)
    - Loading doses used in Cohort 2 and subsequent cohorts were based on PK profiles observed in Cohort 1
  - Part 2 (dose expansion) will evaluate the safety, tolerability, preliminary antitumor activity, PK, and PD in two expansion cohorts: advanced solid tumors and diffuse-type TGCT

### Table 1. Dose cohorts in Part 1 (3+3 dose escalation)

| | Loading doses | Dose |
|---|---|---|
| **Cohort 1** | None | 10 mg QD |
| **Cohort 2** | 10 mg QD x 5 days | 10 mg twice a week |
| **Cohort 3** | 20 mg QD x 5 days | 20 mg once a week |
| **Cohort 4** | 20 mg QD x 5 days | 20 mg twice a week |
| **Cohort 5** | 30 mg QD x 5 days | 30 mg twice a week |
| **Cohort 6** | 40 mg QD x 5 days | 40 mg twice a week |
| **Cohort 7** | 50 mg QD x 3 days | 20 mg QD |

QD, once daily.

### Table 2. Key inclusion and exclusion criteria for Part 1

| Inclusion criteria |
|---|
| • ≥18 years old |
| • Tumors with known contribution of macrophages or phagocytes |
| • Symptomatic diffuse-type TGCT patients for which surgical resection is not an option |
| **Exclusion criteria** |
| • Prior anticancer therapy or other investigational therapy ≤14 days or <28 days if half-life longer than 3 days |
| • Unresolved toxicity according to NCI-CTCAE, >grade 1 or baseline, from previous therapy |
| • Known active CNS metastases |
| • History or presence of clinically relevant cardiovascular abnormalities |
| • Major surgery within 2 weeks of first dose |

NCI-CTCAE, National Cancer Institute common terminology criteria for adverse events; NYHA, New York Heart Association; TGCT, tenosynovial giant cell tumor.

### Table 3. Study endpoints

| Primary endpoints |
|---|
| • Safety and tolerability (including occurrence of DLTs and incidence of TEAEs[a]) |
| • RP2D/MTD |
| • Pharmacokinetics (including $T_{max}$, $C_{max}$, $C_{trough}$, AUC, $t_{1/2}$) |
| **Relevant exploratory endpoints** |
| • Pharmacodynamics<br>– Levels of CSF1/IL-34 in plasma<br>– Levels of circulating CD16+ monocytes in blood by flow cytometry<br>– Macrophage content and/or polarization in tumor |
| • Tumor response assessment by RECIST version 1.1 |

[a]Adverse events graded by NCI-CTCAE, Version 4.03.

AUC, area under the curve; $C_{max}$, maximum concentration; CSF1, colony stimulating factor; $C_{trough}$, trough concentration; DLT, dose limiting toxicities; IL-34, interleukin 34; MTD, maximum tolerated dose; NCI-CTCAE, National Cancer Institute common terminology criteria for adverse events; RP2D, recommended phase 2 dose; RECIST, response evaluation criteria in solid tumors; TEAE, treatment emergent adverse events; $t_{1/2}$, half-life; $T_{max}$, time of $C_{max}$.

### Types of tumors

- As of September 10, 2019, 39 patients were enrolled (**Table 4**), including 3 patients with diffuse-type TGCT in Cohort 5

### Table 4. Tumor type

| | Total (n = 39) |
|---|---|
| **Colorectal cancer** | 8 (21) |
| **Pancreatic cancer** | 5 (13) |
| **Ovarian cancer** | 4 (10) |
| **Diffuse-type TGCT** | **3 (8)** |
| **Prostate** | 3 (8) |
| **Other[a]** | 16 (41) |

All values n (%).
[a]Leiomyosarcoma (2), liver cancer (2), uterine cancer (2), anal cancer, breast cancer, chondrosarcoma, endometrial, gastroesophageal junction, melanoma, uveal melanoma, synovial sarcoma, non-small cell lung cancer, thymus.
TGCT, tenosynovial giant cell tumor.

## RESULTS

### Safety

- Among treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients (regardless of relatedness), most events were grade 1 or 2 (**Table 5**)
  - Grade ≥3 related TEAEs occurred in 4 patients (grade 3 aspartate aminotransferase [AST] increased, grade 4 lipase increased, grade 3 amylase increased, and grade 3 colitis)
  - No grade ≥3 TEAEs in diffuse-type TGCT patients
- Serious adverse events (SAEs) were reported in 17 malignant solid tumor patients; none of which were related to DCC-3014
  - No SAEs were reported in diffuse-type TGCT patients

### Table 5. Common (≥10%) TEAEs regardless of relatedness

| Preferred term | Advanced solid tumor total n = 36 | | Diffuse-type TGCT n = 3 | | Total (All patients) n = 39 | |
|---|---|---|---|---|---|---|
| | *All* | ≥G3 | *All* | ≥G3 | *All* | ≥G3 |
| **Constipation** | 13 (36.1) | 0 | 1 (33.3) | 0 | 14 (35.9) | 0 |
| **Vomiting** | 12 (33.3) | 2 (5.6) | 1 (33.3) | 0 | 13 (33.3) | 2 (5.1) |
| **Diarrhea** | 10 (27.8) | 0 | 1 (33.3) | 0 | 11 (28.2) | 0 |
| **Nausea** | 10 (27.8) | 0 | 1 (33.3) | 0 | 11 (28.2) | 0 |
| **Fatigue** | 8 (22.2) | 2 (5.6) | 2 (66.7) | 0 | 10 (25.6) | 2 (5.1) |
| **Decreased appetite** | 9 (25) | 1 (2.8) | 0 | 0 | 9 (23.1) | 1 (2.6) |
| **Dyspnea** | 8 (22.2) | 0 | 1 (33.3) | 0 | 9 (23.1) | 0 |
| **Abdominal pain** | 7 (19.4) | 3 (8.3) | 1 (33.3) | 0 | 8 (20.5) | 3 (7.7) |
| **AST increased** | 5 (13.9) | 1 (2.8)[a] | 3 (100) | 0 | 8 (20.5) | 1 (2.6) |
| **Dehydration** | 7 (19.4) | 0 | 0 | 0 | 7 (17.9) | 0 |
| **Pyrexia** | 6 (16.7) | 0 | 1 (33.3) | 0 | 7 (17.9) | 0 |
| **Arthralgia** | 5 (13.9) | 1 (2.8) | 1 (33.3) | 0 | 6 (15.4) | 1 (2.6) |
| **Back pain** | 5 (13.9) | 0 | 1 (33.3) | 0 | 6 (15.4) | 0 |
| **Blood CPK increase** | 4 (11.1) | 0 | 2 (66.7) | 0 | 6 (15.4) | 0 |
| **Anemia** | 5 (13.9) | 1 (2.8) | 0 | 0 | 5 (12.8) | 1 (2.6) |
| **Asthenia** | 5 (13.9) | 0 | 0 | 0 | 5 (12.8) | 0 |
| **Cough** | 4 (11.1) | 0 | 1 (33.3) | 0 | 5 (12.8) | 0 |
| **Headache** | 3 (8.3) | 1 (2.8) | 2 (66.7) | 0 | 5 (12.8) | 1 (2.6) |
| **Pain in extremity** | 5 (13.9) | 0 | 0 | 0 | 5 (12.8) | 0 |
| **Periorbital edema** | 4 (11.1) | 0 | 1 (33.3) | 0 | 5 (12.8) | 0 |
| **Urinary tract infection** | 4 (11.1) | 0 | 1 (33.3) | 0 | 5 (12.8) | 0 |
| **Abdominal distension** | 4 (11.1) | 0 | 0 | 0 | 4 (10.3) | 0 |
| **Depression** | 4 (11.1) | 0 | 0 | 0 | 4 (10.3) | 0 |
| **Dyspepsia** | 4 (11.1) | 0 | 0 | 0 | 4 (10.3) | 0 |
| **Hypokalemia** | 4 (11.1) | 1 (2.8) | 0 | 0 | 4 (10.3) | 1 (2.6) |
| **Insomnia** | 4 (11.1) | 0 | 0 | 0 | 4 (10.3) | 0 |
| **Edema peripheral** | 4 (11.1) | 0 | 0 | 0 | 4 (10.3) | 0 |
| **Pain** | 3 (8.3) | 2 (5.6) | 1 (33.3) | 0 | 4 (10.3) | 2 (5.1) |

[a]Grade 2 by the central laboratory assessment
AST, aspartate aminotransferase; CPK, creatine phosphokinase; G, grade; TGCT, tenosynovial giant cell tumor .

- There were 2 dose-limiting toxicities (DLTs) in the first cohort (10 mg QD): grade 4 lipase increased and grade 3 hypocalcemia
  - Both DLTs could be explained by the mechanism of action of DCC-3014; therefore, any grade of asymptomatic serum enzyme elevation and grade 3 hypocalcemia were excluded from DLTs for evaluation of subsequent cohorts
  - Dose density of Cohort 2 (the total amount of DCC-3014 given in Cycle 1) was lowered from that of Cohort 1 (**Table 1**), and then subsequently increased
- No further DLTs were reported in the other cohorts

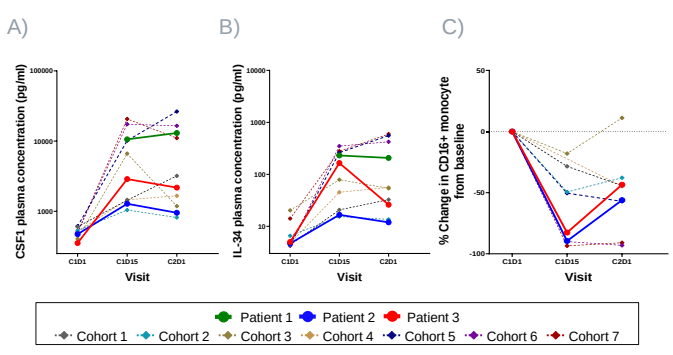
### Laboratory results

- Increases in alanine transaminase (ALT) and AST are considered as an on-target mechanism of action of DCC-3014
  - Grade 1 AST elevations were observed in 84% of patients
  - Grade 2 AST elevations were seen in 8% of patients
  - Grade 1 ALT elevations were seen in 29% of patients
  - Asymptomatic and mostly not reported as AEs
  - Similar increases have been reported with other anti-CSF1R therapies[2]
- No bilirubin elevations were observed by treatment with DCC-3014

### Pharmacokinetics and pharmacodynamics

- DCC-3014 exposure is consistent between diffuse-type TGCT and solid tumor patients
- DCC-3014 treatment caused a dose-related rise in plasma CSF1 and IL-34 and a reduction of CD16+ monocytes in diffuse-type TGCT patients (**Figure 2**)

### Figure 2. Changes in levels of circulating A) CSF1 and B) IL-34 in plasma and C) changes in levels of whole blood CD16+ monocytes



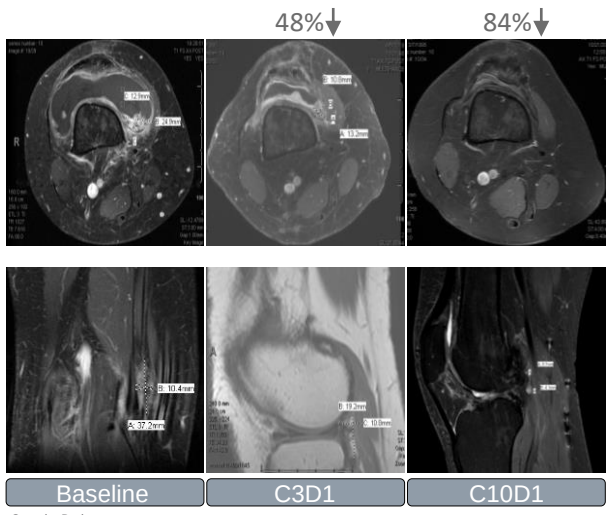

A and B: Levels of CSF1 and IL-34 in plasma were determined by standard ELISA. Plasma samples were collected from patients on Cycle 1 Day 1, Cycle 1 Day 15, and Cycle 2 Day 1. C: Levels of CD16+ monocytes were assessed by flow cytometry. Whole blood samples were collected from patients on Cycle 1 Day 1, Cycle 1 Day 15, and Cycle 2 Day 1.
C, cycle; CSF1, colony stimulating factor 1; D, day; IL-34, interleukin 34.

### Case studies

- Symptomatic improvements are based on descriptive notes obtained from investigators
- Adverse events are summarized in **Table 5**
- Changes in tumor size from baseline by investigator assessment per RECIST version 1.1 are summarized in **Figure 3**

**Patient 1**

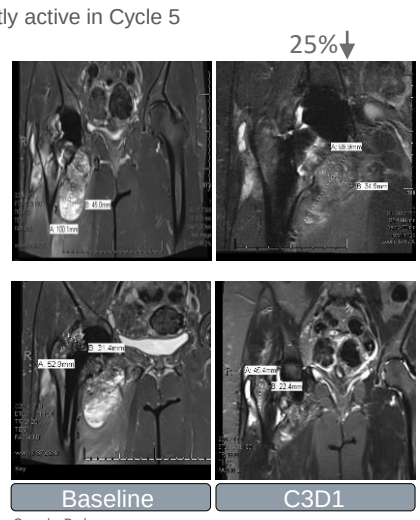
- 24-year-old female patient diagnosed with diffuse-type TGCT (right posterior knee) in Jun 2016
- Prior surgeries: synovectomies/mass resections in Jun 2016, Jul 2016, and Dec 2017
- Recurrence/progression on MRI by Dec 2018
- Enrolled in Feb 2019 in Cohort 5
- Symptom improvement/tumor assessment on the study
  - Taking Mobic and Percocet daily at baseline with inadequate pain control
    - On C10D1, taking Percocet only as needed approximately once a week
  - Improved pain and swelling, effusion nearly resolved in the first cycle
- Change in tumor size: 48%, 61%, 75%, and 84% decreases from baseline (C3D1, C5D1, C7D1, and C10D1 scan, respectively) per RECIST
- Currently active in Cycle 10




C, cycle; D, day.

**Patient 2**

- 57-year-old female patient diagnosed with diffuse-type TGCT (right hip) in 2014
- Prior surgeries: resection (May 2014), synovectomy (Aug 2015 and Aug 2016), total hip replacement (Aug 2016), hip revision and resection (Aug 2018), cryoablation (May 2019)
- Recurrent disease on MRI (Feb 2019)
- Enrolled in July 2019 in Cohort 5
- Symptom improvement/tumor assessment on the study
  - Pain improved, walking 1 mile, increased range of motion, and less stiffness
  - Change in tumor size: 25% decrease from baseline on C3D1 scan per RECIST
- Currently active in Cycle 5

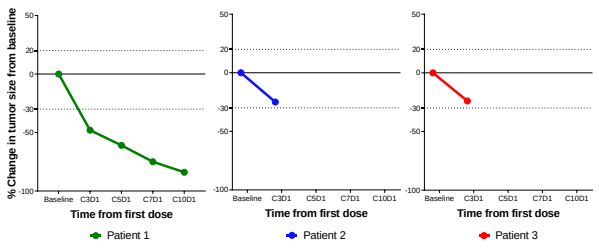



C, cycle; D, day.

**Patient 3**

- 28-year-old male patient diagnosed with diffuse-type TGCT (left knee) in Jan 2016 after several years of pain
- Prior surgery: resection and posterior synovectomy (Jan 2016)
- Pain, swelling, and stiffness recurred due to disease progression not long after surgery
- Enrolled in Mar 2019 in Cohort 5
- Symptom improvement/tumor assessment on the study
  - Rapid symptom improvement, with less pain and swelling and improved range of motion after the first cycle
  - Able to play basketball with no pain
  - Change in tumor size: 24% decrease from baseline on C3D1 scan per RECIST
- Discontinued in Cycle 4 due to relocation to the outside of US
- Patient did not consent for inclusion of MRI images in publication

### Figure 3. Changes from baseline in tumor size assessed per RECIST version 1.1




Dashed lines denote 30% decrease and 20% increase in tumor size threshold for partial response and progressive disease, respectively, per RECIST version 1.1
C, cycle; D, day; RECIST, response evaluation criteria in solid tumors.

## Conclusion

- In this phase 1 study, DCC-3014 was generally well tolerated in patients with malignant solid tumors and diffuse-type TGCT
- All 3 patients with diffuse-type TGCT treated with DCC-3014 to date showed rapid, preliminary anti-tumor activity by cycle 3
  - One patient had a confirmed partial response by cycle 3; sustained for 9 months and ongoing as of last investigator report
- Symptomatic improvements in mobility and reduced pain were observed in all 3 diffuse-type TGCT patients
- Exposure to DCC-3014 was consistent between malignant solid tumor and diffuse-type TGCT patients and associated with an increase in plasma CSF1 and IL-34 in plasma, and a rapid, sustained reduction of CD16+ monocytes in peripheral blood
- Dose-escalation evaluation is ongoing to determine the recommended phase 2 dose for advanced solid tumors and diffuse-type TGCT
- These results are encouraging and support further evaluation of DCC-3014 in diffuse-type TGCT

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### References

**1)** Lin Y, et al. *J Hematol Oncol.* 2019; 12:76; **2)** Cannarile MA, et al. *J Immunother Cancer.* 2017; 5:53; **3)** Droin N, et al. *J Leukoc Biol.* 2010; 87:745-747; **4)** Gouin F, et al. Orthop Traumatol Surg Res. 2017; 103:S91-S97; **5)** Smith BD, et al. AACR Annual Meeting; April 16–20, 2016; New Orleans, LA.