Phase 1 study of DCC-3014, an oral inhibitor of CSF1R, to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with advanced solid tumors, including diffuse-type tenosynovial giant cell tumor

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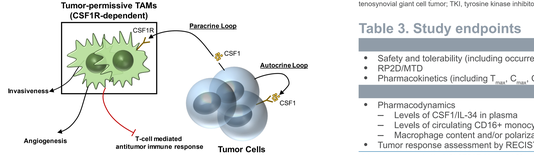
Abstract: C087

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 (**Figure 1**)[1-3]
  - CSF1R has 2 known ligands; CSF1 (also known as macrophage-CSF) and interleukin 34 (IL-34)[4]
- CSF1/CSF1R expression in tumors may also contribute to tumor invasiveness through autocrine signaling pathways (**Figure 1**)[1]

Figure 1. Role of CSF1R receptor in the tumor invasiveness and growth



CSF1, colony stimulating factor 1; CSF1R, CSF1 receptor; TAMs, tumor-associated macrophages.

- DCC-3014 is an orally administered, potent, and selective inhibitor of CSF1R that was engineered to bind into the CSF1R switch pocket and inhibit kinase activity[5]
  - DCC-3014 potently inhibits CSF1R signaling in cellular assays, as well as functionally blocks macrophage-mediated tumor cell migration, osteoclast differentiation, and proliferation of a CSF1R-dependent cell line
  - DCC-3014 is designed for the inhibition of macrophages that contribute to or are the source of tumor development and dissemination
- DCC-3014 has >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]
- Tenosynovial giant cell tumor (TGCT) is a rare disease arising from the joint synovia, 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
- 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
  - Here, we report the results from the dose escalation phase of this trial in patients with malignant solid tumors

METHODS

- This is a phase 1 multicenter, open-label, single arm study of DCC-3014 in advanced solid tumors
- The study consists of 2 parts
  - Part 1 (dose escalation) is designed to 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 from Cohort 2 based on PK profiles observed in Cohort 1
  - Part 2 (dose expansion) will evaluate the safety, tolerability, preliminary antitumor activity, PK, and RD in 2 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
- Solid tumors[a] that have progressed after treatment with all available therapies known to confer clinical benefit
- 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 anticancer therapy, excluding alopecia
- Known active CNS metastases
- NYHA class III or IV heart disease, active ischemia, or any other uncontrolled cardiac condition
- History or presence of clinically relevant cardiovascular abnormalities
- Major surgery within 2 weeks of first dose

[a]Including, but not limited to, metastatic breast or prostate cancer with bone disease, gastric cancer, ovarian cancer, or NSCLC that frequently have malignant associated ascites or effusion.
CNS, central nervous system; NCI-CTCAE, National Cancer Institute common terminology criteria for adverse events; NYHA, New York Heart Association; TGCT, tenosynovial giant cell tumor; TKI, tyrosine kinase inhibitor.

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
  - Levels of CSF1/IL-34 in plasma
  - Levels of circulating CD16+ monocytes in blood by flow cytometry
  - 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}.

RESULTS

Patient demographics and disposition

- As of September 10, 2019, 36 patients with advanced solid tumors (not including diffuse-type TGCT patients) were enrolled and treated, of which 97.2% patients discontinued study treatment (**Table 4**); mainly due to disease progression (60.0%), withdrawal of patient from treatment (17.1%), or adverse events (11.4%)

Table 4. Patient disposition

	Cohort 1 (n = 7)	Cohort 2 (n = 3)	Cohort 3 (n = 4)	Cohort 4 (n = 4)	Cohort 5 (n = 6)	Cohort 6 (n = 5)	Cohort 7 (n = 7)	Total (n = 36)
On treatment	0	0	0	0	0	0	1 (14.3)	1 (2.8)
Discontinued from treatment	7 (100)	3 (100)	4 (100)	4 (100)	6 (100)	5 (100)	6 (85.7)	35 (97.2)
Adverse event	1 (14.3)	0	0	1 (25.0)	2 (33.3)	0	0	4 (11.4)[a]
Physician decision	0	0	0	0	1 (16.7)	0	0	1 (2.9)
Progressive disease	3 (42.9)	3 (100.0)	3 (75.0)	3 (75.0)	3 (50.0)	3 (60.0)	3 (50.0)	21 (60.0)
Withdrawal by patient	2 (28.6)	0	0	0	0	1 (20.0)	3 (50.0)	6 (17.1)
Other	1 (14.3)	0	1 (25.0)	0	0	1 (20.0)	0	3 (8.6)[b]

All value n (%). [a]Lipase increased (grade 4), fatigue (grade 3), intestinal obstruction (grade 3), hemorrhage intracranial (grade 4). [b]Other: clinical progression/decline, hospice (2).

- The most frequent diagnoses (≥10%) were colorectal cancer, pancreatic cancer; and ovarian cancer and most patients were heavily pretreated (median of 4 lines of prior treatments) (**Tables 5** and **6**)

Table 5. Baseline demographics and clinical characteristics

	Cohort 1 (n = 7)	Cohort 2 (n = 3)	Cohort 3 (n = 4)	Cohort 4 (n = 4)	Cohort 5 (n = 6)	Cohort 6 (n = 5)	Cohort 7 (n = 7)	Total (n = 36)
Age (years), median (min, max)	64.0 (39, 91)	48.0 (27, 77)	64.0 (55, 74)	70.0 (50, 77)	63.5 (51, 71)	59.0 (55 ,63)	67.0 (46, 74)	62.0 (27, 91)
Female	4 (57.1)	2 (66.7)	3 (75.0)	3 (75.0)	4 (66.7)	4 (80.0)	3 (42.9)	23 (63.9)
Race								
White	6 (85.7)	3 (100)	4 (100)	3 (75.0)	4 (66.7)	5 (100)	6 (85.7)	31 (86.1)
Black or African American	0	0	0	0	1 (16.7)	0	0	1 (2.8)
Other	1 (14.3)	0	0	1 (25.0)	1 (16.7)	0	1 (14.3)	4 (11.1)
Previous regimens, median (min, max)	7.0 (2, 8)	2.0 (1, 7)	3.5 (3, 7)	5.5 (2, 6)	3.5 (2, 5)	5.0 (3, 8)	3.5 (1, 7)	4.0 (1, 8)

Except where indicated, values are n (%).
Max, maximum; min; minimum.

Table 6. Types of cancers

	Total (n = 36)
Colorectal cancer	8 (22)
Pancreatic cancer	5 (14)
Ovarian cancer	4 (11)
Prostate	3 (8)
Leiomyosarcoma	2 (6)
Liver cancer	2 (6)
Uterine cancer	2 (6)
Other[a]	10 (28)

All values n (%).
[a]Anal cancer, breast cancer, chondrosarcoma, endometrial, gastroesophageal junction, melanoma, uveal melanoma, synovial sarcoma, non-small cell lung cancer, thymus.

Table 7. Common (≥10%) TEAEs regardless of relatedness

	Cohort 1 (n = 7)		Cohort 2 (n = 3)		Cohort 3 (n = 4)		Cohort 4 (n = 4)		Cohort 5 (n = 6)		Cohort 6 (n = 5)		Cohort 7 (n = 7)		Total (n = 36)	
	Any	*Grade ≥3*	*Any*	*Grade ≥3*	*Any*	*Grade ≥3*	*Any*	*Grade ≥3*	*Any*	*Grade ≥3*	*Any*	*Grade ≥3*	*Any*	*Grade ≥3*	*Any*	*Grade ≥3*
Constipation	3 (42.9)	0	2 (66.7)	0	2 (50.0)	0	1 (25.0)	0	2 (33.3)	0	1 (20.0)	0	2 (28.6)	0	13 (36.1)	0
Vomiting	3 (42.9)	0	0	0	1 (25.0)	0	1 (25.0)	0	3 (50.0)	1 (16.7)	3 (60.0)	1 (20.0)	1 (14.3)	0	12 (33.3)	2 (5.6)
Diarrhea	3 (42.9)	0	0	0	2 (50.0)	0	0	0	4 (66.7)	0	1 (20.0)	0	0	0	10 (27.8)	0
Nausea	1 (14.3)	0	0	0	3 (75.0)	0	1 (25.0)	0	3 (50.0)	0	2 (40.0)	0	0	0	10 (27.8)	0
Decreased appetite	3 (42.9)	0	0	0	1 (25.0)	0	1 (25.0)	0	1 (16.7)	0	2 (40.0)	1 (20.0)	1 (14.3)	0	9 (25.0)	1 (2.8)
Dyspnea	4 (57.1)	0	0	0	0	0	2 (50.0)	0	1 (16.7)	0	0	0	1 (14.3)	0	8 (22.2)	0
Fatigue	0	0	1 (33.3)	0	1 (25.0)	0	1 (25.0)	1 (25.0)	2 (33.3)	0	2 (40.0)	1 (20.0)	1 (14.3)	0	8 (22.2)	2 (5.6)
Abdominal pain	2 (28.6)	1 (14.3)	2 (66.7)	1 (33.3)	0	0	1 (25.0)	1 (25.0)	1 (16.7)	0	1 (20.0)	0	0	0	7 (19.4)	3 (8.3)
Dehydration	1 (14.3)	0	0	0	1 (25.0)	0	1 (25.0)	0	1 (16.7)	0	2 (40.0)	0	1 (14.3)	0	7 (19.4)	0
Pyrexia	1 (14.3)	0	1 (33.3)	0	1 (25.0)	0	1 (25.0)	0	1 (16.7)	0	1 (20.0)	0	0	0	6 (16.7)	0
Anemia	1 (14.3)	0	0	0	0	0	1 (25.0)	1 (25.0)	1 (16.7)	0	2 (40.0)	0	0	0	5 (13.9)	1 (2.8)
Arthralgia	1 (14.3)	0	1 (33.3)	0	0	0	0	0	2 (33.3)	0	0	0	1 (14.3)	1 (14.3)	5 (13.9)	1 (2.8)
AST increased	3 (42.9)	1 (14.3)	0	0	0	0	0	0	0	0	1 (20.0)	0	1 (14.3)	0	5 (13.9)	1 (2.8)
Asthenia	2 (28.6)	0	0	0	0	0	0	0	1 (16.7)	0	2 (40.0)	0	0	0	5 (13.9)	0
Back pain	2 (28.6)	0	0	0	0	0	0	0	1 (16.7)	0	1 (20.0)	0	1 (14.3)	0	5 (13.9)	0
Pain in extremity	1 (14.3)	0	0	0	0	0	0	0	2 (33.3)	0	0	0	2 (28.6)	0	5 (13.9)	0
Abdominal distension	1 (14.3)	0	0	0	0	0	0	0	2 (33.3)	0	1 (20.0)	0	0	0	4 (11.1)	0
Blood CPK increase	1 (14.3)	0	0	0	0	0	0	0	0	0	1 (20.0)	0	2 (28.6)	0	4 (11.1)	0
Cough	3 (42.9)	0	0	0	0	0	0	0	0	0	0	0	1 (14.3)	0	4 (11.1)	0
Depression	2 (28.6)	0	1 (33.3)	0	0	0	0	0	0	0	1 (20.0)	0	0	0	4 (11.1)	0
Dyspepsia	0	0	0	0	0	0	1 (25.0)	0	1 (16.7)	0	1 (20.0)	0	1 (14.3)	0	4 (11.1)	0
Hypokalemia	2 (28.6)	0	0	0	0	0	0	0	0	0	1 (20.0)	1 (20.0)	1 (14.3)	0	4 (11.1)	1 (2.8)
Insomnia	2 (28.6)	0	0	0	0	0	0	0	1 (16.7)	0	0	0	1 (14.3)	0	4 (11.1)	0
Edema peripheral	0	0	1 (33.3)	0	0	0	1 (25.0)	0	0	0	1 (20.0)	0	1 (14.3)	0	4 (11.1)	0
Periorbital edema	0	0	0	0	1 (25)	0	0	0	2 (33.3)	0	0	0	1 (14.3)	0	4 (11.1)	0
Urinary tract infection	2 (28.6)	0	0	0	0	0	1 (25)	0	1 (16.7)	0	0	0	0	0	4 (11.1)	0

AST, aspartate aminotransferase; CPK, creatine phosphokinase; TEAE, treatment-emergent adverse events.

- 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 (except for Hy's law cases) and grade 3 hypocalcemia were excluded from DLTs for evaluation of subsequent cohorts
  - Dose density of Cohort 2 (a total dose 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
- Increases in alanine transaminase (ALT) and AST are considered as the mechanism of action of DCC-3014
  - These increases have been reported with other anti-CSF1R therapies[2]
  - Here, primarily AST elevations were observed; as well as slight increases in the levels of ALT, which were mostly under the upper limits of normal
- No bilirubin elevations were observed with treatment with DCC-3014

Preliminary antitumor activity

- The overall median treatment duration was 36 days
- There were 5 patients with a best response of stable disease (2 with colorectal cancer and 1 each with prostate cancer, thymoma, and uveal melanoma)
  - A patient with thymoma maintained stable disease for 6 months

Safety

- Most treatment-emergent adverse events (TEAEs) regardless of relatedness were grade 1 or 2 (**Table 7**)
  - Common (≥10%) related TEAEs were fatigue (16.7%), diarrhea (11.1%), and nausea (11.1%)
  - 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)
- Serious adverse events were reported in 17 patients; none of which were related to DCC-3014

Pharmacokinetics and pharmacodynamics

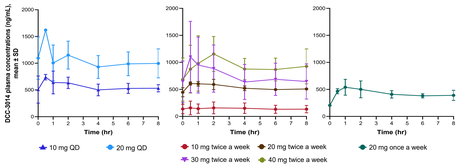
- DCC-3014 exposure appears approximately dose proportional (**Table 8** and **Figure 2**)

Table 8. DCC-3014 geometric mean PK parameters on C2D1 by cohort

	Cohort	n	Dose	C_{max} (ng/mL)	AUC_{0-8} (h*ng/mL)	C_{trough} (ng/mL)
QD	Cohort 1	5	10 mg QD	767[a]	4510[a]	447
QD	Cohort 7	3	20 mg QD	1250	7980	1040
Twice a week	Cohort 2	3	10 mg twice a week	149	1030	122
Twice a week	Cohort 4	3	20 mg twice a week	642	4300	441
Twice a week	Cohort 5	3	30 mg twice a week	953	5420	574
Twice a week	Cohort 6	3	40 mg twice a week	1150	7290	570
Once a week	Cohort 3	2	20 mg once a week	530	3380	205

[a]n = 3.
AUC_{0-8}, area under the concentration curve from 0 to 8 hours postdose; C2D1, cycle 2 day 1; C_{max}, maximum concentration; C_{trough}, trough concentration; PK, pharmacokinetic; QD, once daily.

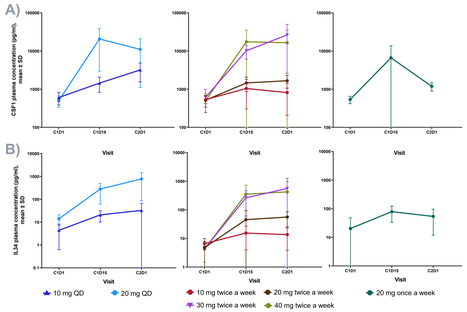
Figure 2. DCC-3014 concentration vs time profiles on C2D1



C2D1, cycle 2 day 1; QD, once daily; SD, standard deviation.

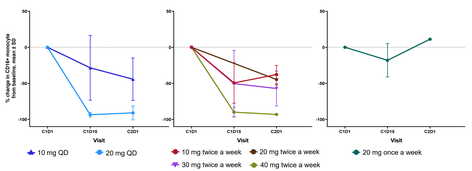
- DCC-3014 treatment caused a rise in plasma CSF1 and IL-34 that was drug concentration dependent, a rapid and sustained reduction of CD16+ monocytes that was dose dependent, as well as a reduction in CD163+ macrophages in tumors (**Figures 3–5**)

Figure 3. Changes in levels of circulating A) CSF1 and B) IL-34 in plasma



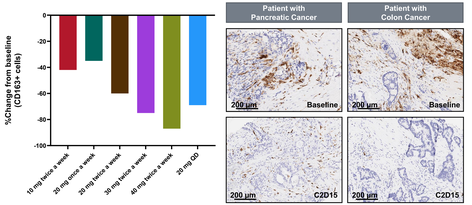
Levels of CSF1 and IL-34 in plasma were determined by standard ELISA. Plasma samples were collected from patients on Cycle 1 Day 1, Cycle 1 Day 15, and Cycle 2 Day 1.
C, cycle; CSF1, colony stimulating factor 1; D, day; IL-34, interleukin 34; QD, once daily; SD, standard deviation.

Figure 4. Changes in levels of whole blood CD16+ monocytes



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; D, day; QD, once daily; SD, standard deviation.

Figure 5. Changes in levels of CD163+ macrophages in tumors



Changes in CD163+ macrophage populations were assessed in paired tumor biopsies taken at screening and at Cycle 2 Day 15 (C2D15). Samples were processed for IHC analysis of CD163 (10D6). Whole tissue image was analyzed by using the Flagship cTA platform to quantify CD163. Pathologist reviewed and approved final analysis results as stratified representation of positivity of a population of cells in the tissue.
C2D15, cycle 2 day 15; QD, once daily.

CONCLUSIONS

- Dose-escalation evaluation is ongoing to determine the recommended phase 2 dose for advanced solid tumors and diffuse-type TGCT
- In this study, DCC-3014 was generally well tolerated in patients with advanced solid tumors
- Exposure to DCC-3014 was dose proportional and was associated with an increase in plasma CSF1 and IL-34 in plasma; and a rapid, sustained reduction of CD16+ monocytes in peripheral blood, and substantial decreases in CD163+ macrophages in tumor
- These results support further evaluation of DCC-3014 in advanced solid tumors as single agent or in combination, as well as in diffuse-type TGCT
  - The preliminary results from initial diffuse-type TGCT patients will be presented at Connective Tissue Oncology Society Annual Meeting (Abstract #3241734, November 13–16, 2019, Tokyo, Japan)

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics; Boston, MA; October 26–30, 2019

Acknowledgments

This study was sponsored by Deciphera, LLC. Medical writing and editorial support were provided by Nicole Seneca, PhD; and Stefan Kolata, PhD, of AlphaBioCom, LLC (King of Prussia, PA).

References

1) Lin Y, et al. *J Hematol Oncol.* 2019; 12:76; **2)** Cannarile MA, et al. *J Immunother Cancer.* 2017; 5:53; **3)** Patsialou A, et al. *Cancer Res.* 2009; 69:9498-506; **4)** Droin N, et al. *J Leukoc Biol.* 2010; 87:745-7; **5)** Smith BD, et al. AACR Annual Meeting; April 16–20, 2016; New Orleans, LA.