Phase 1 Dose-Escalation Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of DCC-3014 in Advanced Solid Tumors and Tenosynovial Giant Cell Tumor (TGCT) (NCT3069469)

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Disclosures

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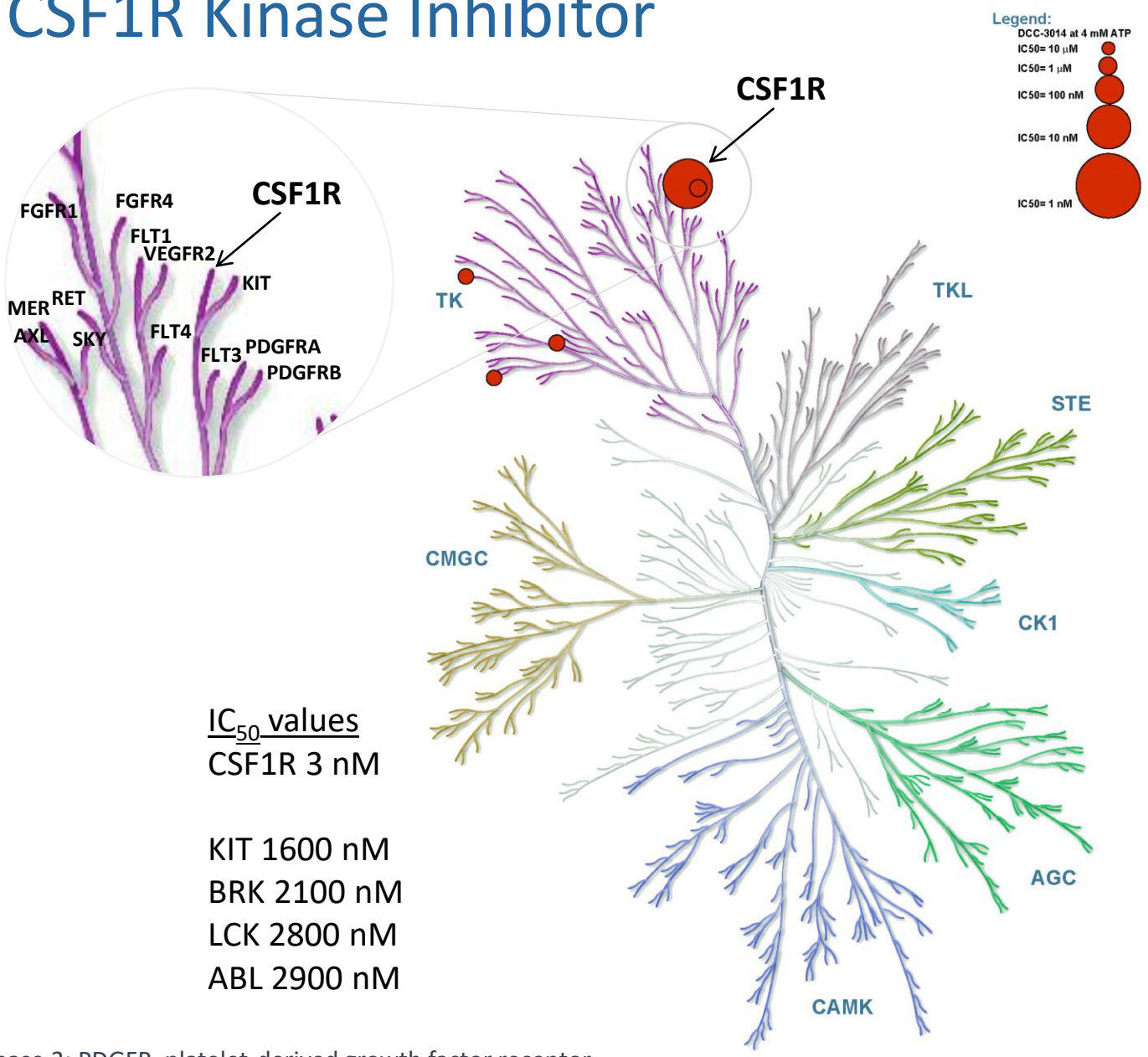
DCC-3014 – Highly Selective CSF1R Kinase Inhibitor

- DCC-3014 is a highly selective, oral, investigational switch control kinase inhibitor that exhibits nanomolar potency for CSF1R with >100-fold selectivity vs closely related kinases (KIT, PDGFRα, PDGFRβ, and FLT3)[1]
- DCC-3014 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



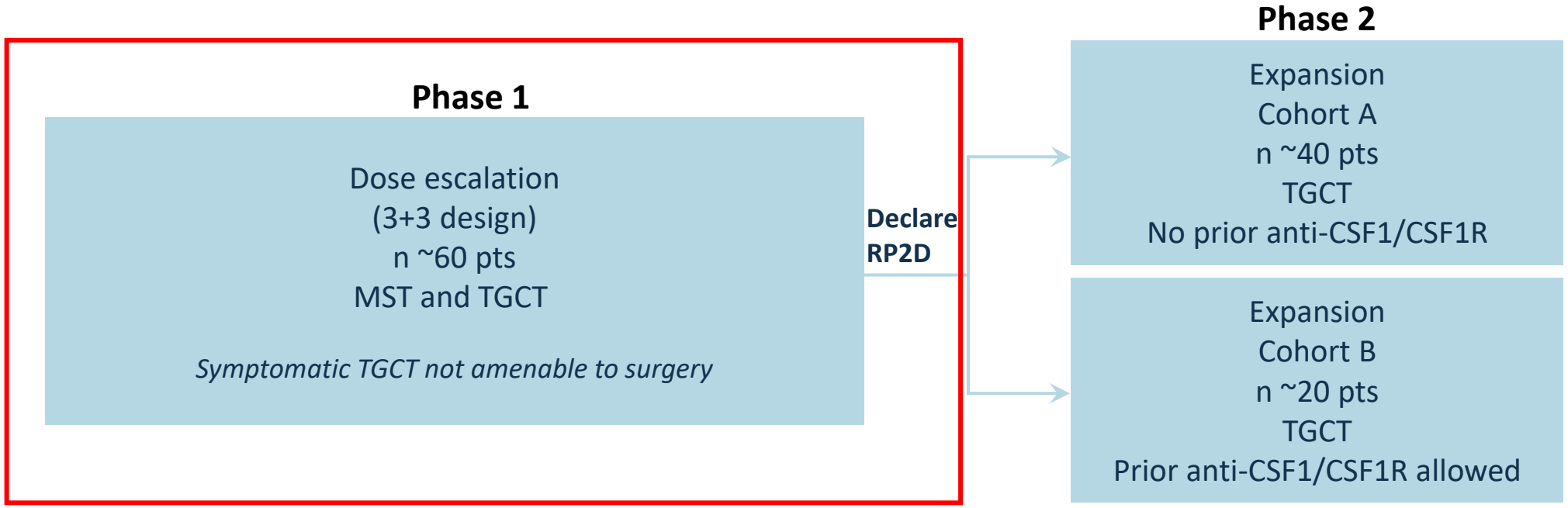
IC_{50} values
CSF1R 3 nM

KIT 1600 nM
BRK 2100 nM
LCK 2800 nM
ABL 2900 nM

CSF1R, colony-stimulating factor 1 receptor; FLT3, fms-like tyrosine kinase 3; PDGFR, platelet-derived growth factor receptor.

1. Smith BD, et al. AACR Annual Meeting; April 16–20, 2016; New Orleans, LA. Abstract 4889.

Study Design



Phase 1 primary objectives

- Assess safety and tolerability of DCC-3014 (including occurrence of DLTs and incidence of TEAEs)
- Characterize the pharmacokinetic profile
- Determine RP2D/MTD

Phase 1 relevant exploratory objectives

- Evaluate preliminary antitumor activity (RECIST v1.1)
  - Read by independent central imaging vendor
- Evaluate pharmacodynamics (CSF1/IL-34 and circulating non-classical monocytes)

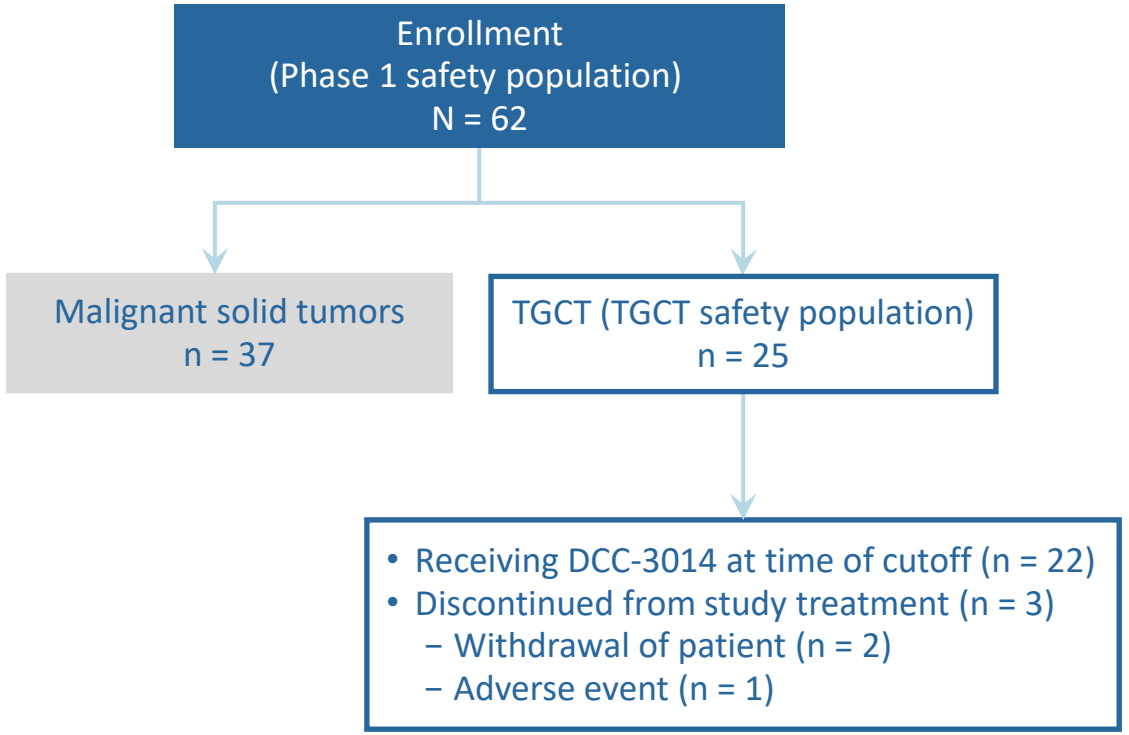
CSF1, colony-stimulating factor 1; CSF1R, colony-stimulating factor 1 receptor; DLT, dose-limiting toxicity; IL, interleukin; MST, malignant solid tumor; pts, patients; MTD, maximum tolerated dose; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event; TGCT, tenosynovial giant cell tumor.

(NCT03069469)

Phase 1 Enrollment and Patient Disposition

- Study initially enrolled patients with malignant solid tumors in the first 7 cohorts
- TGCT patients initially enrolled to escalation cohort 5, then TGCT-specific escalation cohorts 8 and 9 were enrolled

	Loading doses	Dose	MST patients, n	TGCT patients, n
Cohort 1	None	10 mg QD	7	
Cohort 2	10 mg QD x 5 days	10 mg BIW	3	
Cohort 3	20 mg QD x 5 days	20 mg QW	4	
Cohort 4	20 mg QD x 5 days	20 mg BIW	4	
Cohort 5	30 mg QD x 5 days	30 mg BIW	6	7
Cohort 6	40 mg QD x 5 days	40 mg BIW	5	
Cohort 7	50 mg QD x 3 days	20 mg QD	8	
Cohort 8	30 mg QD x 3 days	10 mg QD		12
Cohort 9	20 mg QD x 3 days	6 mg QD		6



Data cutoffs: Safety, September 23, 2020; Efficacy, October 5, 2020.
BIW; twice weekly; MST, malignant solid tumor; QD, daily; QW, weekly; TGCT, tenosynovial giant cell tumor.

TGCT Patient Demographics and Prior Therapies

	Total (N = 25)
Age, years, median (min, max)	52 (23, 73)
Gender	
Female	14 (56)
Male	11 (44)
Race	
White	24 (96)
Asian	1 (4)
Disease location	
Knee	16 (64)
Ankle	5 (20)
Hip	2 (8)
Foot	1 (4)
Wrist	1 (4)
Patients with at least one prior surgery	7 (28)
Patients with at least one prior systemic therapy	4 (16)
Tyrosine kinase inhibitor (imatinib)	3 (12)
Anti-CSF1R monoclonal antibody	1 (4)

Data are presented as No. (%) unless otherwise noted.
CSF1R, colony-stimulating factor 1 receptor; TGCT, tenosynovial giant cell tumor.

Common (≥15%) TEAEs, Regardless of Relatedness – TGCT Safety Population

TGCT patients (N = 25)								
Preferred term, No. (%)	Cohort 5 30 mg BIW[a] (N = 7)		Cohort 8 10 mg QD[b] (N = 12)		Cohort 9 6 mg QD[c] (N = 6)		Total TGCT (N = 25)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Blood CPK increased	3 (43)	1 (14)	7 (58)	4 (33)[d]	3 (50)	0	13 (52)	5 (20)
AST increased	4 (57)	1 (14)	6 (50)	2 (17)	1 (17)	0	11 (44)	3 (12)
Periorbital edema	3 (43)	0	7 (58)	0	1 (17)	0	11 (44)	0
Fatigue	3 (43)	0	4 (33)	0	3 (50)	0	10 (40)	0
Lipase increased	1 (14)	0	5 (42)	3 (25)	2 (33)	0	8 (32)	3 (12)
ALT increased	1 (14)	0	5 (42)	0	1 (17)	0	7 (28)	0
Amylase increased	0	0	6 (50)	1 (8)	0	0	6 (24)	1 (4)
Face edema	0	0	5 (42)	0	1 (17)	0	6 (24)	0
Headache	3 (43)	0	3 (25)	0	0	0	6 (24)	0
Pruritis	1 (14)	0	4 (33)	0	1 (17)	0	6 (24)	0
Nausea	2 (29)	0	3 (25)	0	0	0	5 (20)	0
Rash maculo-papular	0	0	4 (33)	0	1 (17)	0	5 (20)	0
Arthralgia	1 (14)	0	2 (17)	0	1(17)	0	4 (16)	0
Diarrhea	1 (14)	1 (14)	3 (25)	0	0	0	4 (16)	1 (4)
Myalgia	0	0	4 (33)	1 (8)	0	0	4 (16)	1 (4)
Peripheral edema	0	0	3 (25)	0	1 (17)	0	4 (16)	0

- Observed transaminase and pancreatic enzyme elevations are consistent with the mechanism of action of CSF1R inhibitors
  - Asymptomatic, not clinically significant
- All bilirubin levels were within the normal limit
- No related SAEs reported
- 2 DLTs reported
  - 1 patient each in cohort 5 and 8
  - Both patients had asymptomatic grade 3 AST elevation
  - Both patients had grade 1 AST elevation at baseline

[a]After 5-day 30 mg QD loading dose; [b]After 3-day 30 mg QD loading dose; [c]After 3-day 20 mg QD loading dose; [d]Only grade 4 AE reported in TGCT patients is grade 4 CPK increased (cohort 8).

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIW, twice weekly; CPK, creatine phosphokinase; DLT, dose-limiting toxicity; Gr, grade; MST, malignant solid tumor; QD, daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TGCT, tenosynovial giant cell tumor.

Dose Modifications Due to Adverse Events

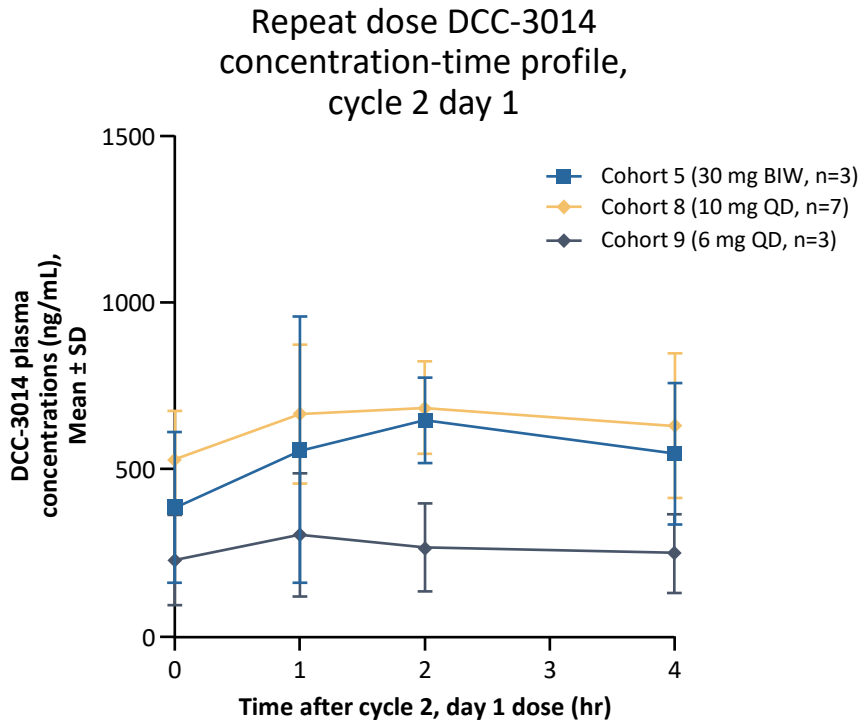
	Cohort 5 30 mg BIW[a] (N = 7)	Cohort 8 10 mg QD[b] (N = 12)	Cohort 9 6 mg QD[c] (N = 6)	Total (N = 25)
Patients with TEAE leading to dose modification, No. (%)	3 (43)	5 (42)	1 (16.7)	9 (36)
Dose interruption	3 (43)	5 (42)	1 (16.7)	9 (36)
Dose reduction	2 (29)	2 (17)	0	4 (16)[d]
Treatment discontinuation	0	1 (8)	0	1 (4)[e]

[a]After 5-day 30-mg QD loading dose; [b]After 3-day 30-mg QD loading dose; [c]After 3-day 20-mg QD loading dose; [d]Grade 3 urticaria, grade 3 diarrhea, grade 1 pyrexia (SAE, not related), grade 2 myalgia, and grade 3 CPK increase; [e]Grade 3 AST increase (DLT).

AST, aspartate aminotransferase; BIW, twice weekly; CPK, creatine phosphokinase; DLT, dose-limiting toxicity; QD, daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

DCC-3014 Pharmacokinetics and Pharmacodynamics

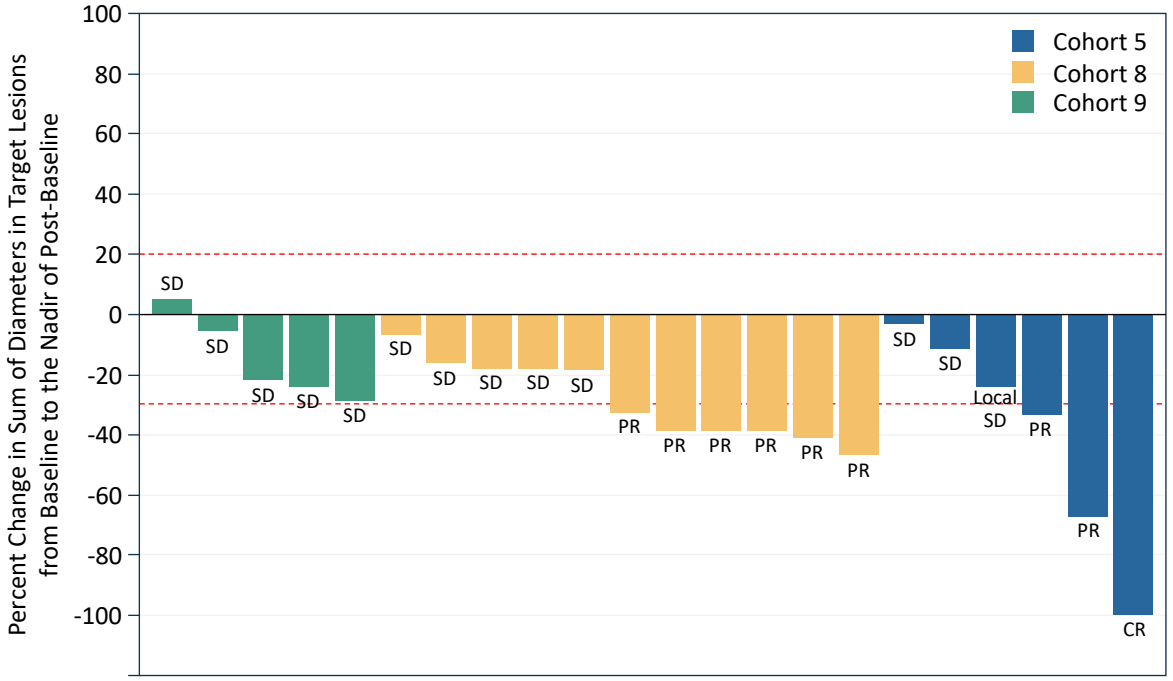
- Steady state DCC-3014 exposure in TGCT patients at cohorts 5, 8, and 9 was characterized
  - Cohorts 5 and 8 had similar PK at cycle 2, day 1
- Across all cohorts, DCC-3014 treatment led to:
  - Increased CSF1 (2.8–41-fold) and IL-34 levels (1.4–13-fold) in plasma
  - Decreased non-classical subtype of monocytes CD14dim/CD16+ (59–87%) in the peripheral blood

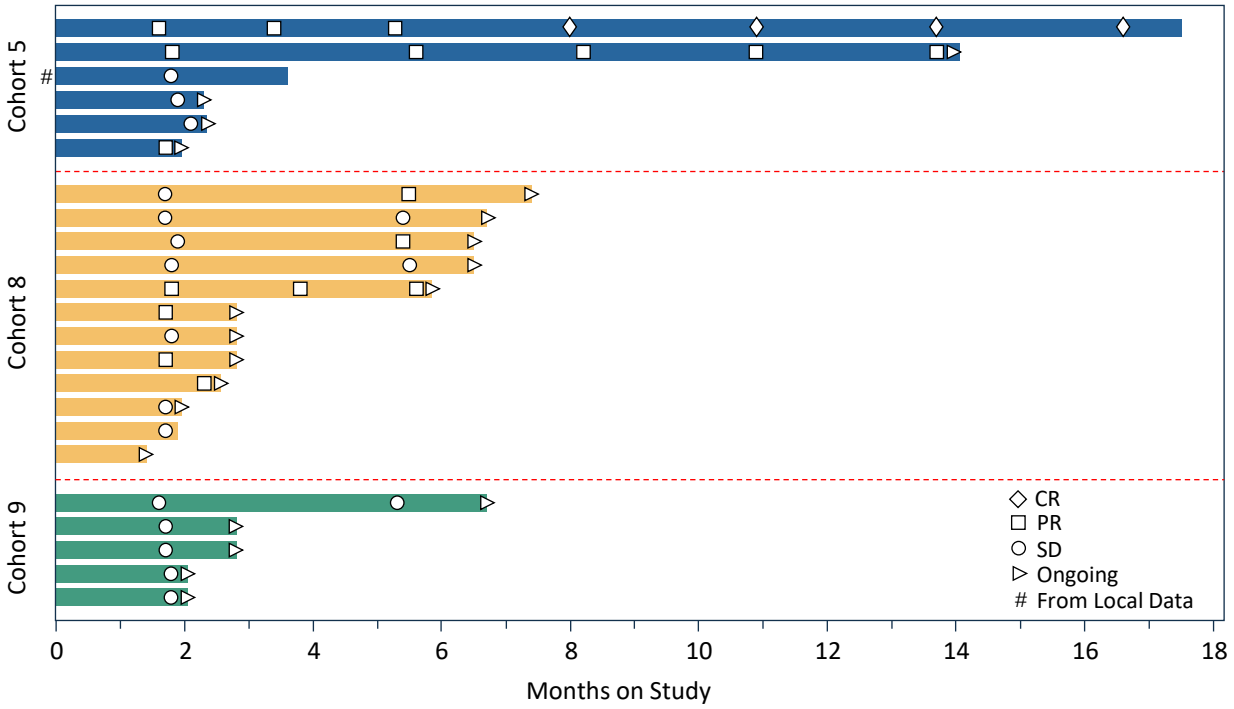


CD, cluster of differentiation; CSF1, colony-stimulating factor 1; IL, interleukin; PK, pharmacokinetics; QD, daily; SD, standard deviation; TGCT, tenosynovial giant cell tumor.

Antitumor Activity in TGCT Patients

- Of the 25 TGCT patients enrolled into the study, 22 patients were evaluable for efficacy by RECIST v1.1 at the data cut off
  - 21 patients had central assessment for efficacy
  - 1 patient had local assessment for efficacy but no central assessment performed
  - 3 patients have not yet reached first efficacy assessment timepoint in the study
- 9 (41%) patients across all TGCT cohorts achieved an objective response (1 complete response and 8 partial responses)
- 7 of the 9 (78%) responders had a partial response at their first restaging scan evaluation





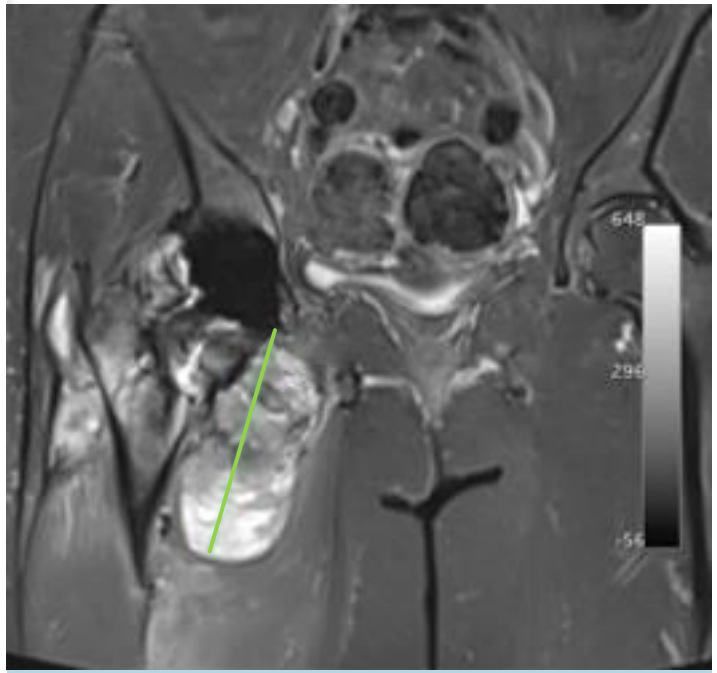
Assessed by independent central review unless otherwise noted (RECIST v1.1). Of the 9 responses, 3 were confirmed and 6 are awaiting confirmation.
Waterfall plot: +20% line is the threshold for disease progression; –30% line is the threshold from baseline to PR.
CR, complete response; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease; TGCT, tenosynovial giant cell tumor.

TGCT Case Studies

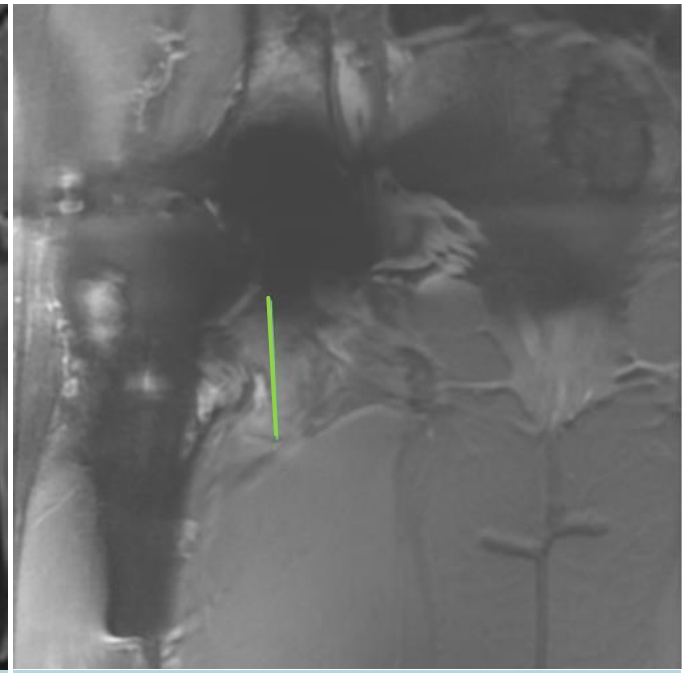
Case Study 1

- 57-year-old female diagnosed with TGCT (hip) in 2014
- Prior surgeries:
  - Resection (May 2014)
  - Synovectomy (August 2015, August 2016)
  - Resection and total hip replacement (August 2018)
  - Cryoablation (May 2019)
- Baseline tumor burden: 101 mm
- Enrolled July 2019 (cohort 5 – DCC-3014 30 mg twice weekly)
  - Dose reduced to 20 mg twice weekly in cycle 6 due to grade 3 urticaria, re-escalated in cycle 10
- Partial response after 2 cycles (33% decrease from baseline)
- Treatment ongoing in cycle 16 (67% decrease at cycle 16, day 1)
  - Durable, deep response

67% ↓



Baseline



Cycle 16, day 1

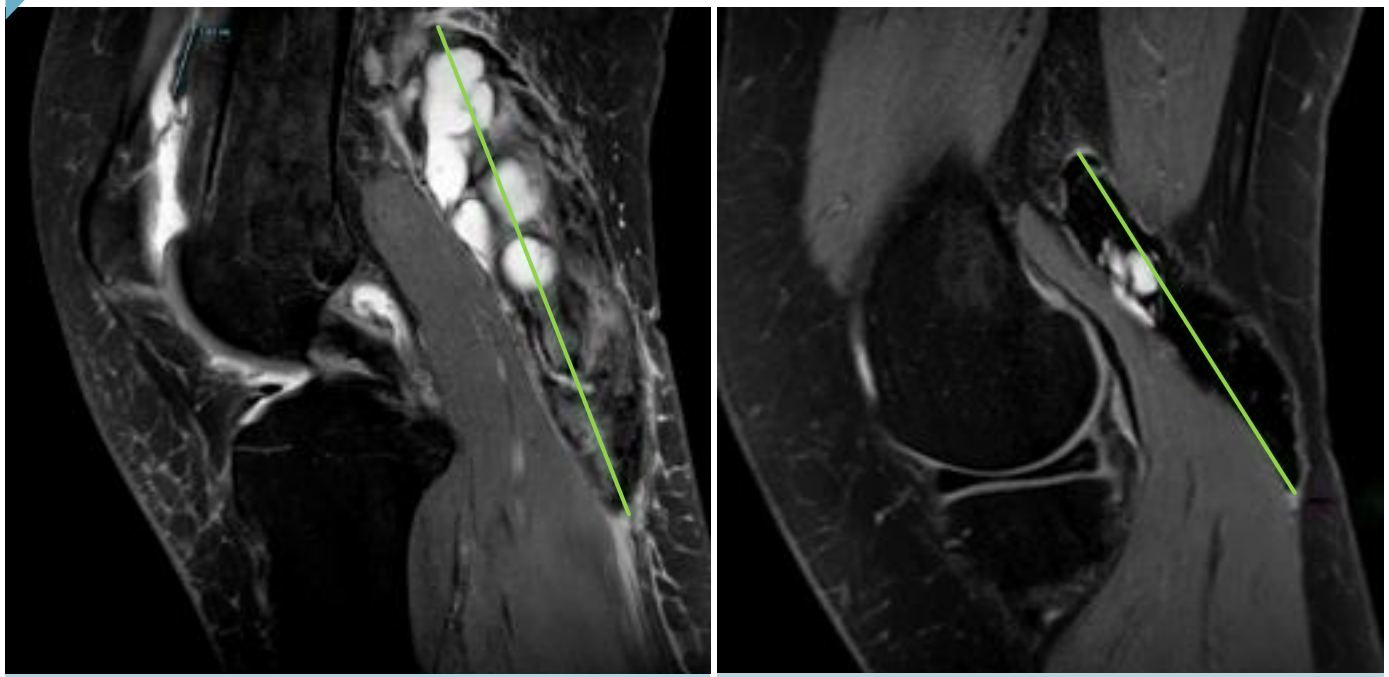
TGCT, tenosynovial giant cell tumor.

Patient provided informed consent for use of these images.

TGCT Case Studies

Case Study 2

- 39-year-old female diagnosed with TGCT (knee) in April 2020
- No prior systemic therapy or surgery
- Baseline tumor burden: 126 mm
- Enrolled in June 2020 (cohort 8 – DCC-3014 10 mg daily)
- Partial response after 2 cycles (41% decrease from baseline)
- Treatment ongoing in cycle 4



Baseline | Cycle 3, day 1

TGCT, tenosynovial giant cell tumor.

Patient provided informed consent for use of these images.

Conclusions

- DCC-3014 is a highly selective, oral, investigational switch control kinase inhibitor of CSF1R and is generally well tolerated in patients with TGCT not amenable to surgery
  - 22 of the 25 TGCT patients remain on the study
- Similar steady state PK profiles were observed between 30 mg twice weekly (cohort 5) and 10 mg daily (cohort 8) dosing regimens; lower exposure was observed in 6 mg daily (cohort 9) dosing regimen
- DCC-3014 treatment resulted in an increase in plasma CSF1/IL-34 and a decrease in non-classical sub-type of monocytes, indicating inhibition of CSF1R
- DCC-3014 showed highly encouraging signs of antitumor activity in TGCT patients (n=22)
  - 9 (41%) patients across all TGCT cohorts achieved an objective response (1 complete response and 8 partial responses)
  - 7 of the 9 (78%) responders had a partial response at their first restaging scan evaluation
  - 2 TGCT patients were on treatment for ≥12 months with responses that deepened over time
- The recommended phase 2 dose for DCC-3014 in TGCT patients was determined to be 30 mg twice weekly (no loading dose)
- These results are encouraging and support further evaluation of DCC-3014 in patients with TGCT not amenable to surgery
  - Study is ongoing and enrolling patients into TGCT expansion cohorts to further evaluate safety and efficacy (NCT03069469)

CSF1, colony-stimulating factor 1; CSF1R, colony-stimulating factor 1 receptor; IL, interleukin; PK, pharmacokinetics; TGCT, tenosynovial giant cell tumor.

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