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.

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.

Study Design

Phase 1

Dose escalation
(3+3 design)
n ~60 pts
MST and TGCT

Symptomatic TGCT not amenable to surgery

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)

Phase 2

Expansion
Cohort A
n ~40 pts
TGCT
No prior anti-CSF1/CSF1R

Expansion
Cohort B
n ~20 pts
TGCT
Prior anti-CSF1/CSF1R allowed
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

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Loading doses</th>
<th>Dose</th>
<th>MST patients, n</th>
<th>TGCT patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>10 mg QD</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10 mg QD x 5 days</td>
<td>10 mg BIW</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>20 mg QD x 5 days</td>
<td>20 mg QW</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>20 mg QD x 5 days</td>
<td>20 mg BIW</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30 mg QD x 5 days</td>
<td>30 mg BIW</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>40 mg QD x 5 days</td>
<td>40 mg BIW</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>50 mg QD x 3 days</td>
<td>20 mg QD</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>30 mg QD x 3 days</td>
<td>10 mg QD</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>20 mg QD x 3 days</td>
<td>6 mg QD</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

Malignant solid tumors
n = 37

TGCT (TGCT safety population)
n = 25

Enrollment (Phase 1 safety population)
N = 62

- Receiving DCC-3014 at time of cutoff (n = 22)
- Discontinued from study treatment (n = 3)
  - Withdrawal of patient (n = 2)
  - Adverse event (n = 1)

BIW; twice weekly; MST, malignant solid tumor; QD, daily; QW, weekly; TGCT, tenosynovial giant cell tumor.
# TGCT Patient Demographics and Prior Therapies

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

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

- 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

<table>
<thead>
<tr>
<th>Preferred term, No. (%)</th>
<th>TGCT patients (N = 25)</th>
<th>Cohort 5 30 mg BIWa (N = 7)</th>
<th>Cohort 8 10 mg QDb (N = 12)</th>
<th>Cohort 9 6 mg QDb (N = 6)</th>
<th>Total TGCT (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3/4</td>
<td>All grades</td>
<td>Grade 3/4</td>
<td>All grades</td>
</tr>
<tr>
<td>Blood CPK increased</td>
<td>3 (43)</td>
<td>1 (14)</td>
<td>7 (58)</td>
<td>4 (33)d</td>
<td>3 (50)</td>
</tr>
<tr>
<td>AST increased</td>
<td>4 (57)</td>
<td>1 (14)</td>
<td>6 (50)</td>
<td>2 (17)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>3 (43)</td>
<td>0</td>
<td>7 (58)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (43)</td>
<td>0</td>
<td>4 (33)</td>
<td>0</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>1 (14)</td>
<td>0</td>
<td>5 (42)</td>
<td>3 (25)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1 (14)</td>
<td>0</td>
<td>5 (42)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>0</td>
<td>0</td>
<td>6 (50)</td>
<td>1 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Face edema</td>
<td>0</td>
<td>0</td>
<td>5 (42)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (43)</td>
<td>0</td>
<td>3 (25)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritis</td>
<td>1 (14)</td>
<td>0</td>
<td>4 (33)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (29)</td>
<td>0</td>
<td>3 (25)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>0</td>
<td>0</td>
<td>4 (33)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (14)</td>
<td>0</td>
<td>2 (17)</td>
<td>0</td>
<td>1(17)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (14)</td>
<td>1 (14)</td>
<td>3 (25)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
<td>0</td>
<td>4 (33)</td>
<td>1 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0</td>
<td>0</td>
<td>3 (25)</td>
<td>0</td>
<td>1 (17)</td>
</tr>
</tbody>
</table>

aAfter 5-day 30 mg QD loading dose; bAfter 3-day 30 mg QD loading dose; cAfter 3-day 20 mg QD loading dose; dOnly 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

<table>
<thead>
<tr>
<th></th>
<th>Cohort 5 30 mg BIW&lt;sup&gt;a&lt;/sup&gt; (N = 7)</th>
<th>Cohort 8 10 mg QD&lt;sup&gt;b&lt;/sup&gt; (N = 12)</th>
<th>Cohort 9 6 mg QD&lt;sup&gt;c&lt;/sup&gt; (N = 6)</th>
<th>Total (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with TEAE leading to dose modification, No. (%)</td>
<td>3 (43)</td>
<td>5 (42)</td>
<td>1 (16.7)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Dose interruption</td>
<td>3 (43)</td>
<td>5 (42)</td>
<td>1 (16.7)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>2 (29)</td>
<td>2 (17)</td>
<td>0</td>
<td>4 (16)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td>0</td>
<td>1 (8)</td>
<td>0</td>
<td>1 (4)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>After 5-day 30-mg QD loading dose; <sup>b</sup>After 3-day 30-mg QD loading dose; <sup>c</sup>After 3-day 20-mg QD loading dose; <sup>d</sup>Grade 3 urticaria, grade 3 diarrhea, grade 1 pyrexia (SAE, not related), grade 2 myalgia, and grade 3 CPK increase; <sup>e</sup>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.
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
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: 41% ↓
Cycle 3, day 1

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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