Pharmacokinetic-driven Phase I study of DCC-2618, a pan-KIT and PDGFRα inhibitor, in patients with Gastrointestinal Stromal Tumor (GIST) and other solid tumors

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BACKGROUND

- DCC-2618 is a pan-KIT and PDGFRα kinase selectivity control inhibitor resistant to disease and drug resistance mutations and potency independent of ATP concentration.
- DCC-2618 was designed to potentially inhibit the broad range of mutations in KIT & PDGFRα kinases.
- Gastrointestinal stromal tumor (GIST) is an important disease to achieve proof-of-concept due to the multiplicity and heterogeneity of resistance mutations within KIT.
- In non-clinical analyses, DCC-2618 showed activity against all available resistant variants covering all secondary ATP-binding site (13 of 14) and activation loop (17 of 18) mutations that have been tested.
- Plasma cfDNA assessment was included to describe and monitor the genomic profile of patients and the impact of treatment with DCC-2618.
- In GIST patients, Next Generation Sequencing (NGS) was applied to cfDNA at baseline and throughout the study to assess whether DCC-2618 is active across a broad range of mutations i.e. a pan KIT inhibitor.

METHODS

Study Design (NCT03571836)

- Pharmacology-guided 3+3 escalation Phase I study of oral DCC-2618 administered in 26-dose cycles
- Study Objectives:
  - Primary Safety: tolerability, maximum tolerated dose (MTD), dose-limiting toxicities (DLT)
  - Secondary Pharmacodynamic profile, antitumor efficacy
- Exploratory: in plasma cell-free DNA (cfDNA), mutations were detected by next generation sequencing and quantified by Quidel 300 or v2 or v3.10 and described as mutation allele frequency (MAF) Patients (Major Eligibility Criteria)
- Patients with advanced refractory cancers and molecular rationale for activity
- Adequate organ function
- Prior KIT/PDGFRα inhibitors were allowed

RESULTS

<table>
<thead>
<tr>
<th>Table 1: DCC-2618 Dose Levels &amp; Patient Characteristics (N=12)</th>
<th>Table 2: Treatment-emergent Adverse Events (TEAEs) (N=48)</th>
<th>Table 3: Duration of Treatment on DCC-2618 in Heavily Pre-Treated KIT and PDGFRα GIST Patients (N=12)</th>
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<tr>
<td>Dose (mg)</td>
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**Patients**

- **Table 1**: Treatment-emergent Adverse Events (TEAEs) (N=48)
- **Table 2**: Duration of Treatment on DCC-2618 – All GIST Patients (N=38)
- **Table 3**: Duration of Disease Control in Heavily Pre-Treated KIT and PDGFRα GIST Patients (N=12)

CONCLUSIONS

- DCC-2618 is well tolerated up to 200 mg BD.
- No patient discontinued DCC-2618 due to toxicity.
- All DLTs were not clinically significant.
- DCC-2618 demonstrated encouraging disease control with objective responses and prolonged stable disease in heavily pre-treated GIST patients.
- Notable reductions in MAF of KIT mutations across all relevant exons in KIT suggests activity across a wide range of intrinsic resistance mutations is maintained.
- Several patients harbored multiple mutations (see patient numbers at each level).
- A durable partial response of 18 months in a GIST patient (94% tumor reduction to date) at 20 mg BD warrants further evaluation in this indication.

Figure 1: DCC-2618 Cycle 1 Plasma Pharmacokinetics Total Exposure Across QD and BID Dosing Cohorts (N=48)

- QT analyses showed a dose proportional increase in total exposure from 100 to 150 mg BD plasma concentrations were measured.
- QTcF change from baseline was not clinically significant.

Figure 2: Duration of Treatment on DCC-2618 – All GIST Patients (N=38)

- The DCR for KIT and PDGFRα GIST cohorts for daily dose equivalents of 150 mg to 6 months in 60% (in 21 patients), at 4 months in 56% (18/33 patients).

Figure 3: DCC-2618 Duration of Disease Control in Heavily Pre-Treated KIT and PDGFRα GIST Patients (N=12)

- Several patients harbored multiple mutations (see patient numbers at each level).
- Moderate doses of 30 to 50 μM DCC-2618 may have an impact on the tyrosine kinase domain, particularly in the ATP-binding domain.

Figure 4: Best Radiographic Response per RECIST in KIT and PDGFRα GIST Patients (N=27)

- Patients 5439, an active metabolite of DCC-2618, is active across a broad range of mutations i.e. a pan KIT inhibitor.
- Several patients harbored multiple mutations (see patient numbers at each level).

Figure 5: Use of cfDNA as Pharmacodynamic Biomarker in Support of Dose Selection

- Plasma cfDNA assessment was included to describe and monitor the genomic profile of patients and the impact of treatment with DCC-2618.
- In GIST patients, Next Generation Sequencing (NGS) was applied to cfDNA at baseline and throughout the study to assess whether DCC-2618 is active across a broad range of mutations i.e. a pan KIT inhibitor.

Figure 6: cDNA as Pharmacodynamic Biomarker in Support of Dose Selection

- Comparisons of TAEs with an incidence of ≥8% are shown.
- All grade and creatine phosphokinase elevations were not clinically significant.

Figure 7: Partial Responses per RANO in Patient with Glioblastoma Multiforme (GBM) after Cycle 18

- The DCR for KIT and PDGFRα GIST cohorts for daily dose equivalents of 150 mg to 6 months in 60% (in 21 patients), at 4 months in 56% (18/33 patients).

CONCLUSIONS

- DCC-2618 is well tolerated up to 200 mg BD.
- No patient discontinued DCC-2618 due to toxicity.
- All DLTs were not clinically significant.
- DCC-2618 demonstrated encouraging disease control with objective responses and prolonged stable disease in heavily pre-treated GIST patients.
- Notable reductions in MAF of KIT mutations across all relevant exons in KIT suggests activity across a wide range of intrinsic resistance mutations is maintained.
- Several patients harbored multiple mutations (see patient numbers at each level).
- A durable partial response of 18 months in a GIST patient (94% tumor reduction to date) at 20 mg BD warrants further evaluation in this indication.
- 150 mg QD is the recommended dose of DCC-2618 for the Phase 1 expansion stage, which includes the following cohorts:
  - Patients with GIST who have progressed on or are intolerant of imatinib.
  - Patients with advanced systemic mastocytosis.
  - Patients with other KIT and PDGFRα driven diseases e.g., glomerulonephritis.