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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Abstract #2515

BACKGROUND

- DCC-2618 is a pan-KIT and PDGFRα kinase switch control inhibitor resilient to de-novo and drug resistance mutations and potency independent of ATP concentration.
- DCC-2618 was designed to potently inhibit the broadest 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 pocket (exon 13/14) and activation loop (exon 17/18) 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 (NCT# 02571036)

- Pharmacologically-guided 3+3 escalation Phase I study of oral DCC-2618 administered in 28-days cycles

Study Objectives

- Primary: Safety, tolerability, maximum tolerated dose (MTD), dose-limiting toxicities (DLT)
- Secondary: Pharmacokinetic profile, antitumor efficacy
- Exploratory: In plasma cell-free DNA (cfDNA), mutations were detected by next generation sequencing and quantitated by Guardant 360 v2.9 or v2.10 and described as mutation allele frequency (MAF)

Patients (Major Eligibility Criteria)

- Patients with advanced refractory cancers and molecular rationale for activity
- ECOG 0-1
- Adequate organ function
- Prior KIT/PDGFRα inhibitors were allowed

RESULTS

(cutoff date – 08 May 2017)

Table 1: DCC-2618 Dose Levels & Patient Characteristics (N=48)

Dose (mg)	Range of Cycles	# of Pts	Tumor Types and Tissue and/or Plasma cfDNA Mutations
20 BID	0-19 cycles	4	**GIST**: *KIT* Exon 11 (1x), *KIT* Exon 17 (1x), *PDGFRα* (1x) **GBM**: *PDGFRα / KIT / KDR* co-amplified (1x)
30 BID	0-13 cycles*	4	**GIST**: *KIT* Exon 11 (1x), *KIT* Exon 11 & 17 (1x) **Thymic Carcinoma**: *KIT* Exon 11 (1x) **Desmoid tumor** (1x)
50 BID	0-13 cycles	6	**GIST**: *KIT* Exon 9 (1x), *KIT* Exon 11 (3x) **Astrocytoma**: *PDGFRα / KIT / KDR* co-amplified (1x) **GBM**: *PDGFRα / KIT / VEGFR2* co-amplified (1x)
100 BID	0-12 cycles*	7	**GIST**: *KIT* Exon 9 (3x), *KIT* Exon 11 (1x), *PDGFRα* (1x), *SDHA* (1x) **Gyn SSC**: *PDGFRα / KIT / KDR* co-amplified (1x)
150 BID	0-8 cycles	6	**GIST**: *KIT* Exon 9 (2x), *KIT* Exon 11 (3x), *KIT* Exon 17 (1x)
200 BID	0-3 cycles	7	**GIST**: *KIT* Exon 9 (4x), *KIT* Exon 11 (3x)
100 QD	0-7 cycles	6	**GIST**: *KIT* Exon 11 (1x), *KIT* Exon 11 & 13 (1x) **Adenoid Cystic Carcinoma:** *PDGFRα / KIT / VEGFR2* amplified (1x) **GBM:** *PDGFRα* (2x) **SM:** *KIT* Exon 17 (1x)
150 QD	0-6 cycles	8	**GIST**: *KIT* Exon 9 (1x), *KIT* Exon 11 (2x), *KIT* Ex 9 & 17 (1x), *KIT* Exon 11 & 13 (1x), *KIT* Exon 11 & 17(1x), *PDGFRα* (2x)
		48	mean of **4.7 prior therapies**

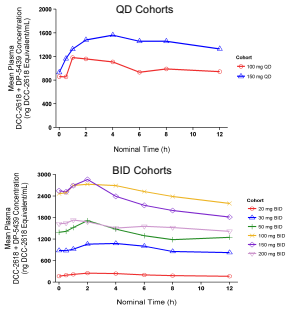
*Patient stayed on study following PD due to clinical benefit

Table 2: Treatment-emergent Adverse Events (TEAEs) (N=48)

Adverse Event	Total	G1/2	G3/4
Fatigue	22	21	1
Alopecia	13	13	0
Anaemia	13	6	7
Lipase increased	12	6	6
Decreased appetite	11	10	1
Abdominal pain	9	8	1
Dyspnoea	9	9	0
Weight decreased	9	9	0
Amylase increased	8	7	1
Nausea	8	8	0
Arthralgia	7	7	0
Constipation	7	7	0
Diarrhoea	7	7	0
Hypertension	7	4	3
Myalgia	7	7	0
Vomiting	7	6	1
Blood bilirubin increased	6	5	1
Cough	6	6	0
Blood creatine phosphokinase increased	5	3	2
Hypokalaemia	5	4	1
Urinary tract infection	5	4	1

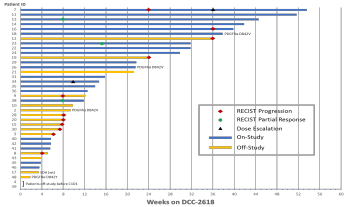
- Summary of TEAE with an incidence of ≥5 (≥10%) by severity.
- All lipase and creatine phosphokinase elevations were not clinically significant.
- Two G3 lipase elevations and a G4 creatine phosphokinase elevation were DLTs and occurred at 100 mg & 200 mg BID and 150 mg QD, respectively.

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



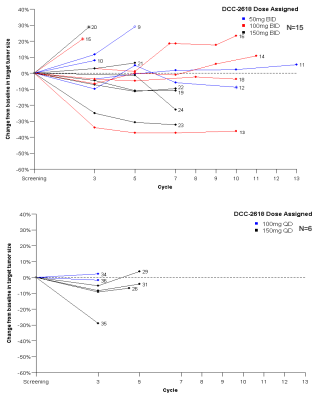
- DP-5439, an active metabolite of DCC-2618, exhibits comparable activity across all KIT mutations and substantially contributes to total drug exposure.
- QD dose cohorts show a dose proportional increase in total exposure from 100 to 150 mg.
- BID dose cohort exposures are dose proportional from 30 to 100 mg BID and then plateau from 100 to 200 mg BID.
- At doses as low as 50 mg BID, reductions in cfDNA were observed across KIT mutations (Fig 6) that include those mutations with the highest in vitro IC_{50} values to DCC-2618 (data not shown)
- Comparison of Day -7 (Fed) to Cycle 1 Day 1 (Fasted) support administration of DCC-2618 with or without food (data not shown).

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



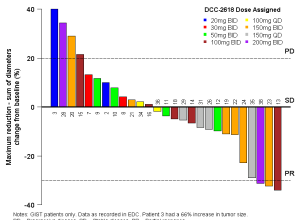
The Disease Control Rate (DCR) for KIT- and PDGFRα GIST cohorts for daily dose equivalents of ≥100 mg at 6 months is 60% (9/15 patients), and at 3 months is 78% (18/23 patients).

Figure 3: DCC-2618: Duration of Disease Control in Heavily Pre-Treated KIT and PDGFRα GIST Patients



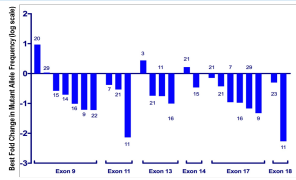
- Spaghetti plots for cohorts for daily dose equivalents of ≥100 mg by cohort.
- Patient IDs are at the end of each plot.
- Closed circles denote that the pt was on DCC-2618 at the time of the scan (open circles for pts off DCC-2618), Stars indicate final visit

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



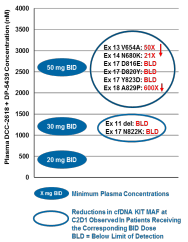
Patient IDs are at the end of each plot.

Figure 5: Use of cfDNA as Pharmacodynamic Biomarker to Demonstrate pan–KIT Activity of DCC-2618 in KIT and PDGFRα GIST Patients (N=12)



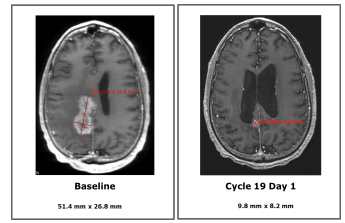
- Waterfall plot of best response for MAF reductions for Exons 9, 11, 13, 14, 17, and 18 (reduction from baseline; log scale for Y axis); only patients with detectable plasma cfDNA and follow up are included.
- Several patients harbored multiple mutations (see patient numbers at each bar).

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



- Comparison of DCC-2618 + DP-5439 plasma concentrations (mean C_{min} on Cycle 1 Day 15) with effect on human cfDNA MAF
- Moderate doses of 30 to 50 mg BID produce robust plasma concentrations (1 to 3 μM)
- At these doses, MAF of all KIT mutations were reduced including Exons 13, 14, 17, and 18 mutations (shown as % reduction in MAF from baseline)

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



Tumor reduction from baseline is 94% on Cycle 19 Day 1 per RANO

CONCLUSIONS

- DCC-2618 is well tolerated up to 200 mg BID.
  - No patient discontinued DCC-2618 due to toxicity.
  - All DLTs were not clinically significant.
- DCC-2618 produced encouraging disease control with objective responses and prolonged stable disease in heavily pre-treated GIST patients.
  - The DCR for KIT- and PDGFRα GIST for cohorts for daily dose equivalents of ≥100 mg at 6 months is 60% (9/15 patients), and at 3 months is 78% (18/23 patients).
- Notable reductions in MAF of imatinib resistance mutations across all relevant exons in KIT suggests activity across a wide range of imatinib resistance mutations in advanced GIST.
- A durable partial response >18 months in a GBM patient (94% tumor reduction to date) at 20 mg BID 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., gliomas.

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