Abstract CT029

Pharmacokinetic (PK), Safety, and Tolerability Profile of DCC-2618 in a Phase 1 Trial Supports 150mg QD Selected for Pivotal Phase 3 Trials in Gastrointestinal Stromal Tumor (GIST)

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BACKGROUND

- DCC-2618, a broad spectrum KIT and PDGFRα kinase switch control inhibitor, is being studied in a pivotal, randomized Phase 3 trial, INVICTUS (NCT03353753), following encouraging disease control observed in a Phase 1 trial in heavily pretreated GIST patients (pts).
- In the Phase 1 trial, escalating doses of DCC-2618 up to 400 mg per day did not result in a DLT or MTD dose level. The RP2D of 150 mg QD was selected based on PK, PD, efficacy and safety observed across the dose escalation cohorts and subsequently used to enroll pts into expansion cohorts.
- Across the dose escalation and expansion cohorts more than 100 pts have now received the RP2D of 150 mg QD.
- Based on the practice of intra-patient dose escalation (IPDE) with imatinib in GIST, IPDE was permitted during the expansion phase for GIST pts with tumor progression per RECIST. Fifteen dose expansion pts opted for treatment beyond progression and were escalated from 150 QD to 150 mg BID; 12 pts have had post-IPDE tumor assessments.

METHODS

- Dose-escalation study of oral DCC-2618 in 28-day cycles (daily doses of 20 to 200 mg BID or 100 to 250 mg QD) followed by expansion into 6 cohorts, including 3 GIST cohorts.
- Tumor assessment: CT scans every 2 cycles per local assessment.
- IPDE pts: PET scans were performed while patients received 150 mg QD and repeated after one cycle post dose escalation.
- Population PK/PD: a model was developed to characterize concentration-time profiles of DCC-2618 and DP-5439, and an exploratory analysis was conducted to assess the relationships between exposures and safety endpoints.
- Major Eligibility Criteria included advanced refractory cancers (KIT or PDGFRα mutated) with a focus on GIST, ECOG 0-1 and adequate end organ function; prior KIT/PDGFRα inhibitors were allowed.

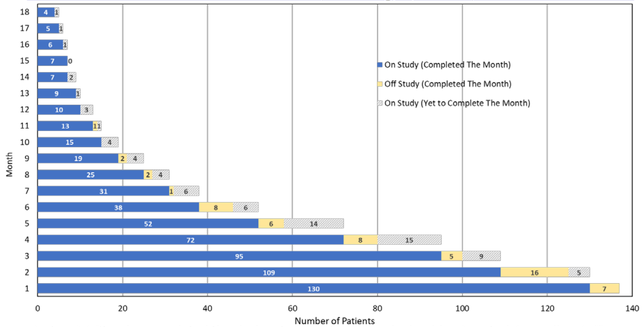
RESULTS

Patient Demographics as of January 18, 2018

- Of the total safety population of 169 patients, 113 were exposed to the dose of 150 mg QD.
- Of 142 GIST patients, 100 received the RP2D of 150 mg QD.
- 131 GIST patients have received ≥1 cycle of treatment.
- 81 GIST patients remain on treatment.

RESULTS

Figure 1: GIST (KIT or PDGFRα) Patient Exposure per Month Intervals (≥100 mg/d, n=137)



Notes: (a) Pts who completed the designated month are marked as blue (on study) or yellow (off study) and pts on study but yet to complete the designated month are marked as grey as of March 19, 2018; (b) includes pts who opted to stay on study following progression per RECIST (n=27); (c) includes 100 pts receiving the RP2D of 150mg QD and 15 pts with IPDE after PD.

- PK profiles of DCC-2618 and its active metabolite DP-5439 were well described using a joint parent-metabolite population PK model. The model was supported by data from 158 pts contributing 4,431 PK samples. Steady state exposures of both DCC-2618 and DP-5439 increased in a manner that was approximately proportional to the increases in DCC-2618 dose (data not shown).

Exposure-Toxicity Analysis (Patients at ≥100 mg/d; n=151)

- AEs were identified based on possible relatedness or uncertainty of relatedness to study medication.
- For each of the safety endpoints, pts were assigned to exposure quartiles based on individual DCC-2618 area under the plasma concentration-time curve for 24 hours (AUC_{0-24}) and the combined DCC-2618 + DP-5439 AUC_{0-24} on the day of the event or censored date based on pt dosing history. The AUC_{0-24} values were determined using the population PK model and pt dosing history.
- Incidence of AEs was plotted as time to first event of Grades 1, 2 or 3 (or censoring date if pt did not have an event).
- If pts had records of both Grade 1 and Grade 2, the time to first event was considered as the time to Grade 2 event.

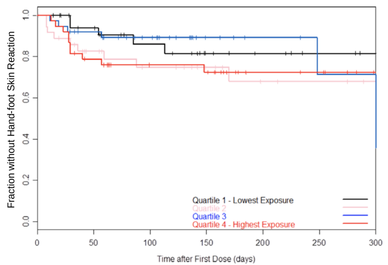
Table 1: Summary of Treatment Emergent Adverse Events (TEAE) That Occurred in >=10% GIST Patients* @ 150 mg QD (n=100)

Subjects n=100 (%)	All	1	2	3	4
Alopecia	39 (39.0)	29 (29.0)	10 (10.0)		
Fatigue	**39 (39.0)**	**29 (29.0)**	**10 (10.0)**		
Myalgia	35 (35.0)	29 (29.0)	6 (6.0)		
Constipation	**29 (29.0)**	**23 (23.0)**	**6 (6.0)**		
Hand-Foot-Skin Reaction	27 (27.0)	22 (22.0)	4 (4.0)	1 (1.0)	
Rash #	**21 (21.0)**	**20 (20.0)**	**1 (1.0)**		
Lipase increased	20 (20.0)	7 (7.0)	3 (3.0)	8 (8.0)	2 (2.0)
Nausea	**19 (19.0)**	**16 (16.0)**	**3 (3.0)**		
Decreased appetite	18 (18.0)	13 (13.0)	5 (5.0)		
Diarrhoea	**18 (18.0)**	**14 (14.0)**	**2 (2.0)**	**2 (2.0)**	
Hypertension	17 (17.0)	7 (7.0)	8 (8.0)	2 (2.0)	
Abdominal pain	**16 (16.0)**	**11 (11.0)**	**3 (3.0)**	**2 (2.0)**	
Arthralgia	15 (15.0)	14 (14.0)	1 (1.0)		
Weight decreased	**13 (13.0)**	**11 (11.0)**	**2 (2.0)**		
Headache	12 (12.0)	11 (11.0)	1 (1.0)		
Vomiting	**12 (12.0)**	**8 (8.0)**	**4 (4.0)**		
Anaemia	11 (11.0)	5 (5.0)	3 (3.0)	3 (3.0)	
Dyspnoea	11 (11.0)	7 (7.0)	3 (3.0)	1 (1.0)	
Hypomagnesaemia	11 (11.0)	10 (10.0)	1 (1.0)		
Pain in extremity	11 (11.0)	11 (11.0)			
Dry skin	10 (10.0)	9 (9.0)	1 (1.0)		
Muscle spasms	10 (10.0)	9 (9.0)	1 (1.0)		

Notes: *by descending order of occurrence in overall column. #includes reports of Palmar-Plantar Erythrodysesthesia.

The study safety population, n=169, is predominantly determined by the 113 pts treated at the RP2D. The focus on 100 GIST pts is relevant for the INVICTUS study. The study safety population includes dose ranges of 20 - 200 mg BID and 100 - 250 mg QD.

Figure 2: Hand-foot Skin Reaction - Preliminary Association between Exposure and Incidence



- DCC-2618 exposure level in the highest quartile was associated with more events than in lower exposure groups (data not shown). Currently, these trends were less evident when combined exposure with the active metabolite was considered (Fig. 2).
- Other TEAE tested (myalgia, alopecia or anemia) do not appear to be exposure-dependent based on parent or combined parent and metabolite exposure. For fatigue, the lowest DCC-2618 exposure group experienced a higher incidence of fatigue (data not shown).

Table 2: Intra-Patient Dose Escalation Summary (IPDE) (n=12*)

Patient	Time to IPDE	Nature of 1st PD	FDG-PET Result Post-IPDE	Best CT Response Post-IPDE	Status	Total No of Cycles on Treatment
51	2 cycles	NL	SMD	SD	Active (> Cycles 2 post IPDE)	>4 cycles
64	2.1 cycles	NL & NTL	ND	SD	Active (> Cycles 2 post IPDE)	>4 cycles
68	6.2 cycles	NL	PMR	SD	Active (> Cycles 2 post IPDE)	>4 cycles
71	2.4 cycles	NTL	ND (central) SMD (local)	PD	Off study after 16 days post IPDE	4.6 cycles
82	1.3 cycles	TL	ND	SD but CP	Withdrew after 46 due to clinical PD	3 cycles
86	2 cycles	TL	ND	PD	Off study after 54 days post IPDE	5.8 cycles
89	4.2 cycles	TL & NL	PMR	SD	Active (in Cycles 2 post IPDE)	In Cycle 6
102	2 cycles	NL	SMD	PD	Off study after 58 days post IPDE	4 cycles
106	4 cycles	TL	SMD	PD	Off study after 14 days post IPDE	4.2 cycles
120	2 cycles	TL	ND	PD	Off study after 29 days post IPDE	3 Cycles
136	2.1 cycles	NL	SMD	SD	Active (> Cycles 2 post IPDE)	>4 cycles
138	2 cycles	TL & NTL	SMD	SD	Active (> Cycles 2 post IPDE)	>4 cycles

Notes: *Pts participating in IPDE (150 mg QD to BID) following PD per RECIST; (a) FDG-PET scans were conducted before and after 1 cycle of 150 mg BID and assessed per central review; (b) Tumor assessment per CT scans by local review; (c) TL=target lesion, NTL=non-target lesion, NL=new lesion; (d) SMD=stable metabolic disease, PMR= partial metabolic response, ND=not disclosed; (e) SD=stable disease, PD=progressive disease, CP=clinical progression.

CONCLUSIONS

- The 169 pts enrolled in study DCC-2618-01-001 enables a comprehensive assessment of its safety profile.
- Based on 113 pts treated at the RP2D, 150 mg QD is well-tolerated facilitating long-term exposure to DCC-2618 in the pivotal, randomized Phase 3 trial, INVICTUS (NCT03353753).
- Using a joint parent-metabolite population PK model, steady state exposures of DCC-2618 and DP-5439 are predicted to increase in proportion to increases in the daily DCC-2618 dose.
- Preliminary exposure-safety endpoint analyses for TEAE were performed based on either a potential relatedness or the lack thereof:
  - The data is too immature to determine an exposure dependence to DCC-2618 and DP-5439; although there is a trend to suggest a relationship of hand-foot skin reaction with DCC-2618 plasma levels.
- Subsequent time-to-event analyses will further assess the relationship between exposure levels and TEAEs. In addition, analyses to relate efficacy to exposure may provide insights into personalized dosing.
- The IPDE data are too immature to determine whether there is a benefit from IPDE following RECIST progression.

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