Abstract # 11511

Mutation Profile of Drug Resistant GIST Patients Enrolled in the Phase 1 Study of DCC-2618

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BACKGROUND

- Identifying KIT/PDGFRα driver mutations in GIST patients (pts) has traditionally required tumor biopsies, with limited success.
- DCC-2618, a broad spectrum KIT/PDGFRα kinase switch control inhibitor, has demonstrated durable disease control in heavily pre-treated GIST pts enrolled in the ongoing Phase 1 trial (NCT02571036).
- In the Phase 1 trial doses of DCC-2618 up to 400 mg per day did not result in a DLT or MTD dose level and 150 mg QD was selected as the RP2D.
- The safety profile of DCC-2618 in 100 pts at 150 mg QD was recently presented (Janku et al, AACR 2018).
- At baseline, KIT/PDGFRA mutations were evaluated using both circulating tumor DNA (ctDNA) and fresh tumor biopsy.
- ctDNA was measured in the Phase 1 trial providing an opportunity to assess disease status and response to therapy without the need for biopsies.
- DCC-2618 is being studied in a pivotal, randomized phase 3 trial, INVICTUS (NCT03353753), in the ≥4th line GIST pts.

METHODS

- Phase 1 dose-escalation study of oral DCC-2618 in 28-day cycles (daily doses of 20 to 200 mg BID and 100 to 250 mg QD) followed by expansion into 6 cohorts.
- Tumor assessment: CT scans every 2 month cycles per local assessment.
- ctDNA analysis: 10 ml blood samples were collected in Streck cell-free DNA BCT® tubes and processed to plasma per manufacturing instructions. DNA extracted from plasma was analyzed using Guardant360 (Guardant Health, Inc.).
- Tumor biopsy analysis: Tumor DNA extracted from formalin-fixed paraffin-embedded (FFPE) baseline biopsies and sequenced using Archer's VariantPlex® NGS assay (Cancer Genetics, Inc.).

Patients (Major Eligibility Criteria)

- Pts with advanced refractory cancers (KIT/PDGFRA mutated) with a focus on GIST.
- ECOG 0-2; adequate end organ function.
- Prior treatment with KIT/PDGFRα inhibitors was allowed.

RESULTS

Table 1: Baseline Demographics of GIST Patients Receiving ≥100 mg/d

	2nd Line (n=25)	3rd Line (n=29)	≥4th Line (n=96)^	Total (n=150)
Age Median (yr)	60	64	61	62
Age Min, Max	32, 80	48, 82	27, 87	27, 87
Male n (%)	11 (44%)	16 (55%)	63 (66%)	90 (60%)
Female n (%)	14 (56%)	13 (45%)	33 (34%)	60 (40%)
ECOG PS 0	12 (48%)	10 (35%)	37 (39%)	59 (39%)
ECOG PS 1	13 (52%)	19 (66%)	58 (60%)	90 (60%)
ECOG PS 2	0	0	1 (1%)	1 (1%)

Pts with C1D1 on or before Feb 2, 2018 are included with an efficacy cutoff of April 18, 2018.
^ Efficacy assessments were available in 91 of 96 ≥4th line pts.

Table 2: Mutation Detection by ctDNA (n=136) and Tumor Biopsy (n=97)

	2nd Line		3rd Line		4th Line		Total
	KIT	PDGFRA	KIT	PDGFRA	KIT	PDGFRA	
Tumor Biopsy % (n/N)	81% (13/16)	100% (2/2)	91% (19/21)	NA	91% (49/54)	100% (4/4)	90% (87/97)
ctDNA % (n/N)	71% (15/21)	50% (1/2)	62% (18/29)	NA	80% (62/78)	17% (1/6)	71% (97/136)

n = # of pts in each category determined by respective testing method, tumor biopsy or ctDNA.
N = # of pts in each category by EDC.

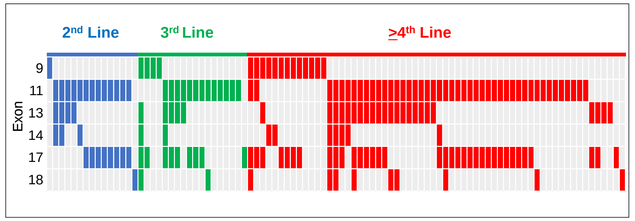
Table 3: KIT Mutations in Baseline Biopsy (n=81) and ctDNA (n=95) in 131 GIST Patients

	Exon 13 %(n)	Exon 14 %(n)	Exon 17 %(n)	Exon 18 %(n)	Total* %(n)
Biopsy (n=81)	31% (25)	5% (4)	57% (46)	7% (6)	84% (68)
ctDNA (n=95)	34% (32)	13% (12)	55% (52)	13% (12)	79% (75)

*Patients with at least KIT mutation detected in exon 13, 14, 17 or 18.

- KIT mutations in Exons 13,14,17,18 were detected by tumor biopsy or ctDNA at baseline and counted by each exon. Some patients had multiple mutations within one exon.
- No correlation was observed between the sum of the longest diameter of the target lesions with the yield of ctDNA at baseline.
- Location of metastatic sites and tumor volume were not collected and may influence ctDNA shedding.

Figure 1: KIT Mutations in Baseline ctDNA (n=95) in 131 GIST Patients



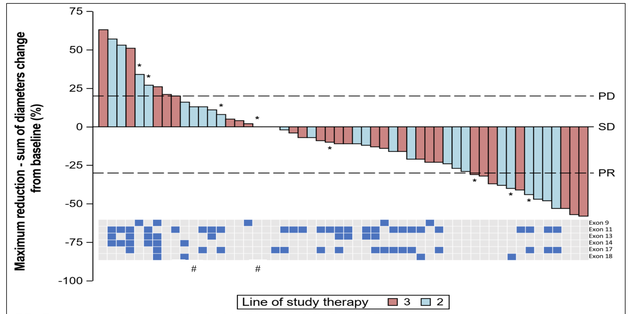
- Each column represents an individual pt.
- In pts where a KIT mutation was detected in baseline ctDNA, secondary KIT mutations in exon 13, 14 17 and 18 were found across 2nd to ≥4thline pts.

Table 4: Objective Response and DCR By Line of Treatment at ≥100 mg/d (n=145)

Line Of Therapy	Patients (n)	DCR @ 3 Months	ORR Rate
2nd Line	25	79%	24%
3rd Line	29	82%	24%
≥4th Line	91	64%	9%
Total	**145**	**70%**	**15%**

Total of 145 pts excludes 5 pts without a RECIST assessment recorded in the data base

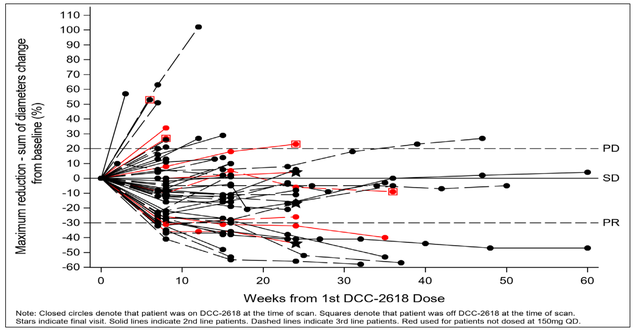
Figure 2: Best Response in 2nd and 3rd Line Pts at ≥100 mg/d (n=54)



PD=Progressive Disease. SD=Stable Disease. PR=Partial Response.
* indicates patients not dosed at 150mg QD # PDGFRA mutation

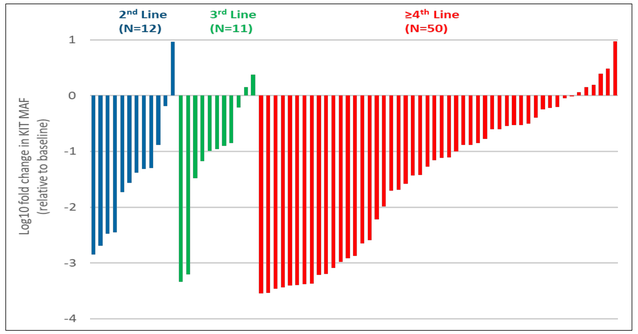
- Baseline ctDNA mutation profile in 2nd line pts previously treated with imatinib and 3rd line pts previously treated with imatinib and sunitinib

Figure 3: Spaghetti Plot of 2nd and 3rd Line Pts at ≥100 mg/d (n=54)



Note: Closed circles denote that patient was on DCC-2618 at the time of scan. Squares denote that patient was off DCC-2618 at the time of scan. Stars indicate final visit. Solid lines indicate 2nd line patients. Dashed lines indicate 3rd line patients. Red used for patients not dosed at 150mg QD.

Figure 4: ctDNA Response After ≥2 Cycles of DCC-2618 (n=73)



- Among 73 pts with detectable KIT mutations by ctDNA at baseline, 35 pts became KIT ctDNA negative (MAF is below detection limit, i.e. MAF <0.05%) on treatment at least at one time point: 8 pts are PRs and 27 are at SD.
- 57 pts (78%) achieved a reduction in KIT MAF of more than 50%.
- ctDNA from pts with a PR as best response was analyzed at baseline (21 pts) and post treatment (20 pts): KIT mutations were detected
  - in 10 pts at baseline and 8 pts became non-detectable after treatment; 1 pt has 1 exon undetectable and one MAF at less than 0.1%
    - one patient (Exon 11 and 13) does not have any post treatment sample.
  - in 1 pt at C5D1 only (follow up until C7D1)
  - In 10 pts, KIT mutations were not detected at any time point.
- Long-term KIT ctDNA negativity on treatment was observed in pts with prolonged stable disease (shown in Figure 3). Clear ctDNA patterns at disease progression were not observed.
- In addition to KIT/PDGFRA, other mutations such as IDH2, RB1,TP53, were detected in baseline and post-treatment ctDNA.

CONCLUSIONS

- The GIST pts in this study are one of the largest prospective cohorts of ctDNA from liquid biopsies to be analyzed by NGS and compared with tumor tissue data.
- The mutational profile of KIT in tumors and plasma at baseline in GIST pts supports the need for a broad spectrum KIT inhibitor in all post-imatinib lines of therapy.
- This data demonstrates for the first time that the distribution of resistance mutations in KIT across exons 13, 14, 17 and 18 or a combination thereof is similar in 2nd, 3rd and 4th line patients.
- ctDNA requires further evaluation as a non-invasive marker for estimating responses and/or predicting clinical benefit in this population.
- Although preliminary, the ORR with DCC-2618 in 2nd line pts appears to be favorable to that reported for sunitinib in 2nd line pts (7.0%) and regorafenib in 3rd line pts (4.5%).
- Preliminary data indicate that in KIT-driven GIST, DCC-2618 provides improved clinical benefit in 2nd line pts compared to ≥4th line pts.
- These efficacy results together with the recently presented safety data at the RP2D of 150mg QD support the pivotal, randomized Phase 3 study, INVICTUS, (NCT03353753) in the ≥4th line GIST and the planned randomized Phase 3 study in 2nd line GIST.

Acknowledgment: *We would like to thank the patients, their families, and the site staff of the DCC-2618-01-001 trial.*