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DCC-2618, a pan-KIT and PDGFRA switch control inhibitor, achieves proof-of-concept in a first-in-human study

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DISCLOSURES

- **F. Janku:** Research funding from Deciphera, SAB Deciphera
- **S. George:** Research funding from Deciphera, Blueprint Medicine, Pfizer, Bayer, Novartis
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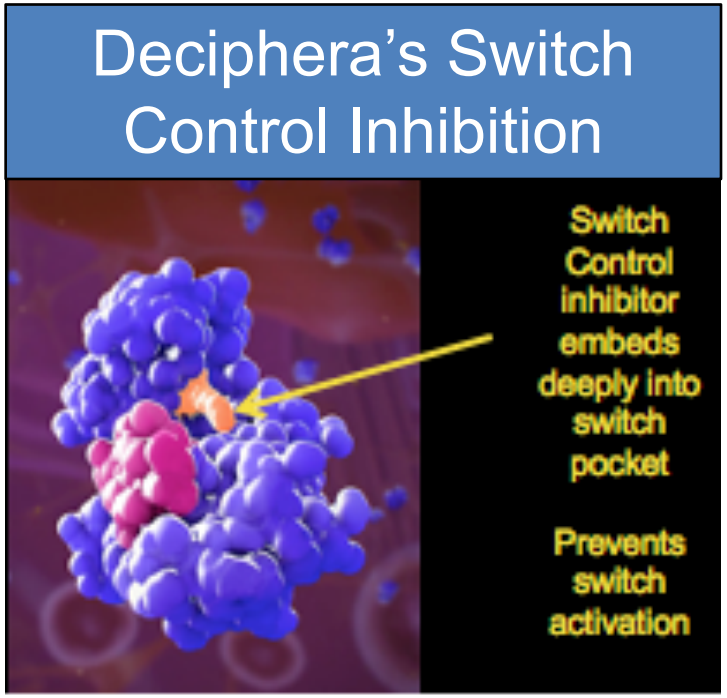
- **D.G. Brooks**, **D. Flynn**, **M. Kaufman**, **J. Pitman**, **O. Rosen**, **B. Smith**, **D. Westwood**: Deciphera employees

- Ongoing study: Presentation contains preliminary data that are partially monitored and validated

BACKGROUND

- DCC-2618 is a *KIT* and *PDGFRA* inhibitor resilient to gain-of-function and drug resistance mutations mutations
  - Potency independent of ATP concentration

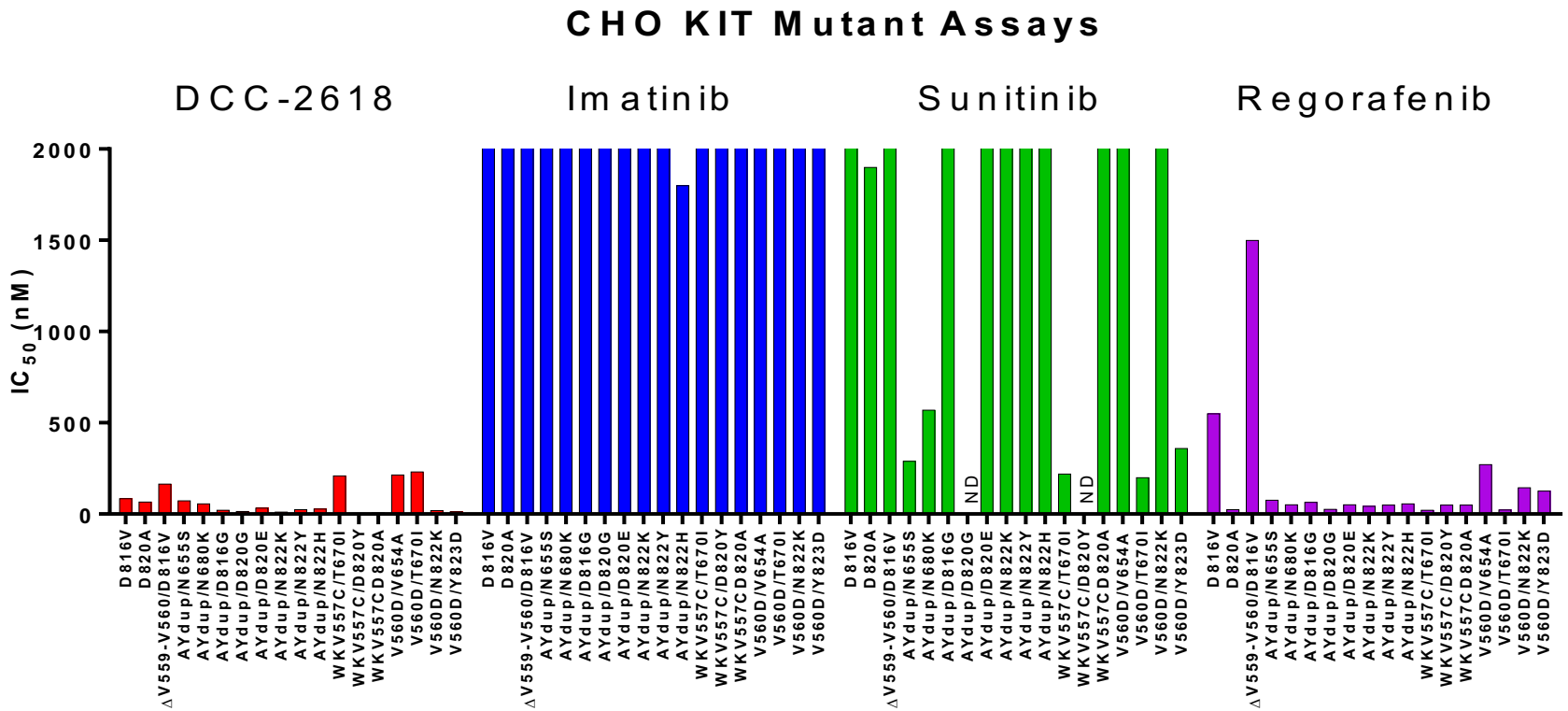


- DCC-2618 was designed to potently inhibit a broad range of mutations in *KIT* and *PDGFRA* kinases

- Gastrointestinal stromal tumor (GIST) is an important disease to achieve proof-of-concept in the FIH study due to the multiplicity and heterogeneity of resistance mutations within *KIT*

RATIONALE FOR DCC-2618 STUDY

- Activity regardless whether primary mutation is in *KIT* Exon 9, Exon 11, or Exon 17
  - IC_{50} for *KIT* Exon 11 deletion 3 nM, IC_{50} *PDGFRA* D842V 60 nM
- Broad activity in secondary *KIT* mutations across Exons 13, 14, 17, and 18
  - Active metabolite DP-5439 possesses comparable activity across all mutations
- *KIT* T670I and V654A secondary mutations are the least sensitive to DCC-2618
  - IC_{50} for *KIT* T670I 221 nM , IC_{50} for 189 nM for *KIT* V654A



DCC-2618-01-001: DESIGN AND OBJECTIVES

- **Design (NCT02571036)**
  - Pharmacologically-guided 3+3 escalation phase I study of oral DCC-2618 administered BID every 28 days
- **Objectives**
  - **Primary**: Safety, tolerability, maximum tolerated dose (MTD), dose-limiting toxicities (DLT)
  - **Secondary**: Pharmacokinetic profile, antitumor efficacy
  - **Exploratory**: Determination of *KIT* and/or *PDGFRA* mutations in plasma cell-free DNA (NGS) and serum tryptase
- **Major eligibility criteria**
  - Patients with advanced refractory cancers and molecular rationale for activity
  - ECOG 0-1
  - Adequate organ function
  - Prior KIT/PDGFRA inhibitors were allowed

DCC-2618: DOSE LEVELS & PATIENTS CHARACTERISTICS

Enrolled: 24 patients with mean of **4.7 prior therapies**

Dose Level (mg) (Time on Study)	Number of Patients	Tumor Types: Tissue and/or Plasma cfDNA Mutations
20 BID (1x > 1year)	**4**	**GIST**: *KIT* Exon 11 (1x), *KIT* Exon 17 (1x), *PDGFRA* (1x) **GBM**: *PDGFRA*/*KIT*/*KDR* co-amplified (1x)
30 BID (1x 6 months*)	**4**	**GIST**: *KIT* Exon 11 (1x), *KIT* Exon 11 & 17 (1x) **Thymic Carcinoma**: *KIT* Exon 11 (1x) **Desmoid tumor** (1x)
50 BID (2x > 6 months)	**4**	**GIST**: *KIT* Exon 9 (1x), *KIT* Exon 11 (3x)
100 BID	**6**	**GIST**: *KIT* Exon 9 (x3), *KIT* Exon 11 (1x), *PDGFRA* Exon 18 (1x), SDHA (1x)
150 BID	**6**	**GIST**: *KIT* Exon 9 (x2), *KIT* Exon 11 (x3), *KIT* Exon 17 (1x)
200 BID	Enrolling	

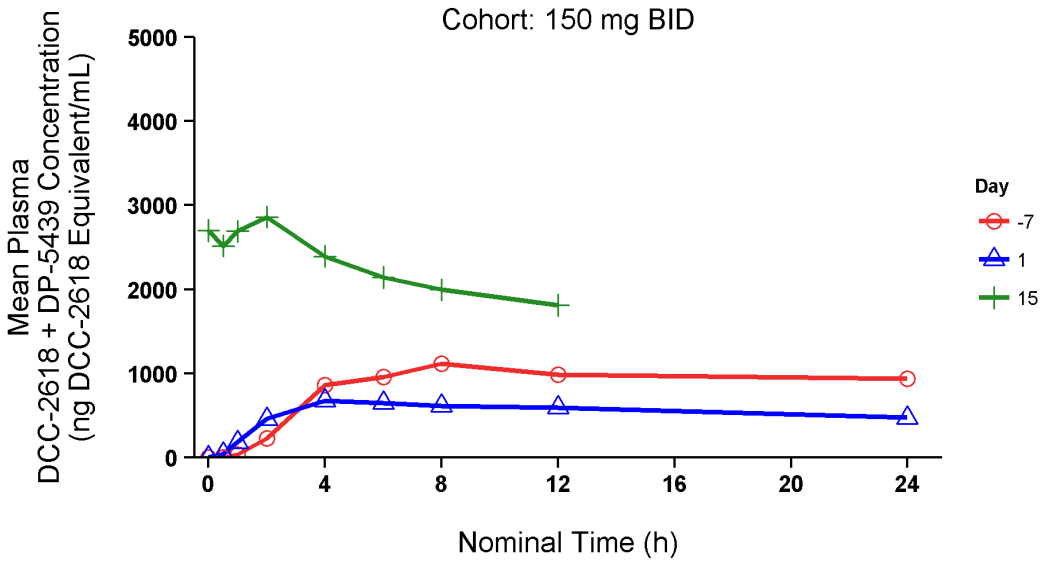
***Patient stayed on study following PD due to clinical benefit**

TREATMENT EMERGENT ADVERSE EVENTS (N=24, cut-off 4 NOV 2016)

Adverse Event	Total	G1/2	G3/4	Adverse Event	Total	G1/2	G3/4
Fatigue	10	9	1	**Blood CPK increase**	**3**	**2**	**1[3]**
Anaemia	9	4	5	Hyperglycemia	3	3	0
Lipase increased	**8**	**6**	**2[1]**	Hypoalbuminaemia	3	3	0
Dyspnoea	7	7	0	Dizziness	3	3	0
Abdominal pain	6	5	1	Cough	3	3	0
Decreased appetite	6	6	0	Rash	3	3	0
Amylase increased	6	6	0	Hot flush	3	3	0
Vomiting	5	5	0	Thrombocytopenia	2	2	0
Myalgia	5	5	0	Hypothyroidism	2	2	0
Alopecia	5	5	0	Dry mouth	2	2	0
Diarrhoea	4	4	0	Hypoalbuminemia	2	2	0
Weight decreased	4	4	0	AST increased	2	2	0
Hypokalemia	4	3	1	Bilirubin increased	2	2	0
Arthralgia	4	4	0	Hypomagnesaemia	2	2	0
Hand foot syndrome	4	3	0	Hypophosphataemia	2	1	1
Hypertension	**4**	**3**	**1[2]**	Muscle Spasms	2	2	0
Constipation	3	3	0	Headache	2	2	0
Nausea	3	3	0	Anxiety	2	2	0
Edema peripheral	3	3	0	Insomnia	2	2	0
Pyrexia	3	3	0	Dry skin	2	2	0
Increased alk. phosphatase	3	3	0	Melena	2	1	1

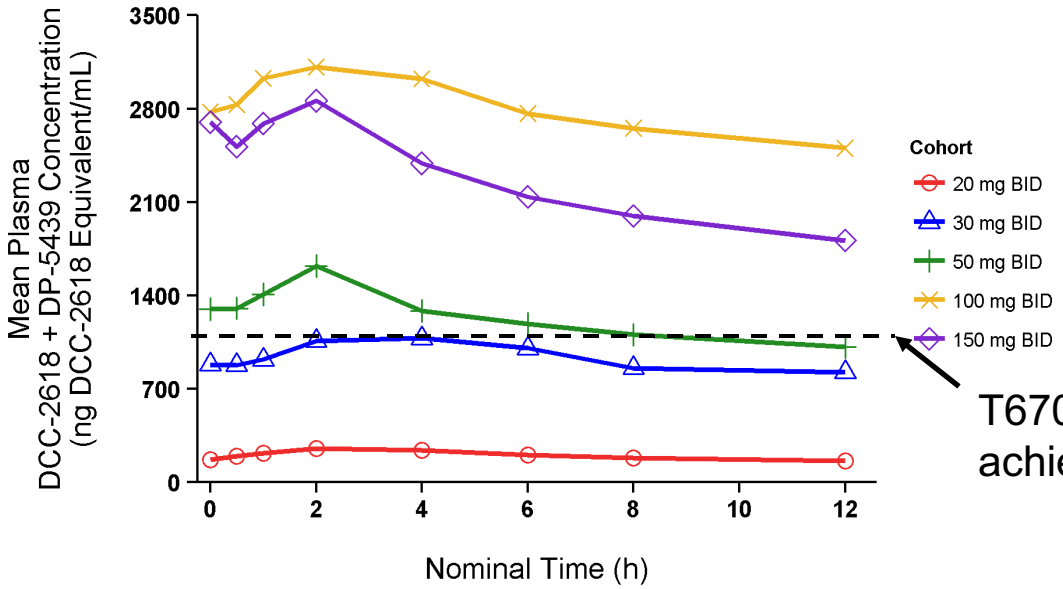
[1]Grade 3 Lipase Elevation (asymptomatic) was a **DLT** in 100 mg BID Cohort
[2]150 mg BID Cohort
[3]30 mg BID Cohort (event considered likely to be exercise-induced)

DCC-2618* Cycle 1 Pharmacokinetics: 150 mg BID Cohort and Across All Dosing Cohorts



*combined plasma concentration of DCC-2618 and its active metabolite DP-5439

DAY -7, DAY 1, DAY 15



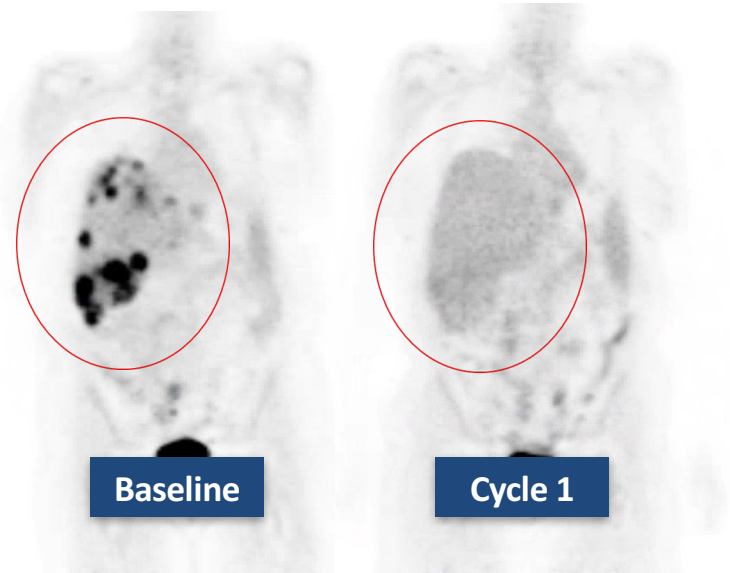
DAY 15

T670I IC_{90} level: 1016 ng/ml (1989 nM) achieved at Cmin of 50 mg BID

DCC-2618: CYCLE 1 PET IN GIST PATIENTS

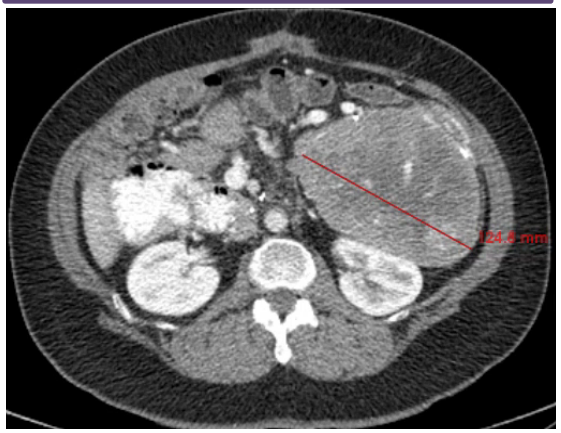
Dose Level mg BID	Mutant Gene	Patient ID	Investigator Review	CT Scan C3D1
30	KIT	01.001	PMR	SD
50	KIT	01.003	PMR	PD
50	KIT	03.003	PMR	SD
50	KIT	03.004	PMR	SD
50	KIT	04.008	PMR	SD
100	**KIT**	**04.009**	**PMR**	**PR**
100	KIT	01.004	PMR	SD
100	KIT	04.010	PMR	SD
100	KIT	01.005	PMR	SD
150	KIT	01.007	PMR	SD
150	KIT	02.002	PMR	SD
150	KIT	03.005	PMR	SD
150	KIT	01.006	PMR	PD
150	KIT	04.012	PMR	Too early
150	KIT	03.007	PMD	SD
100	PDGFRA	04.011	SMD	SD
100	SDHA	03.006	SMD	PD

- 14 of 15 patients with *KIT*-mutant GIST had PMR
- 13 of 15 patients with *KIT*-mutant GIST had PMR confirmed by central review, using EORTC PET response criteria

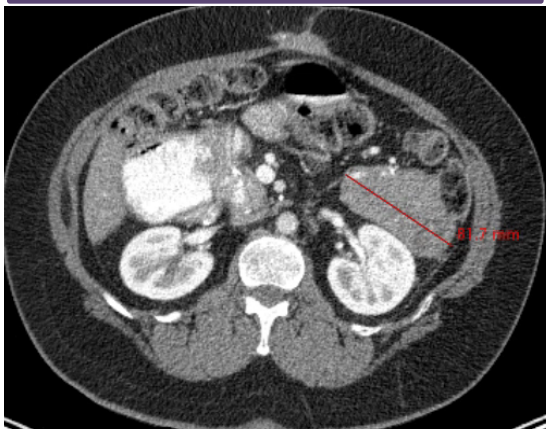


DCC-2618: RECIST RESPONSES

Baseline CT

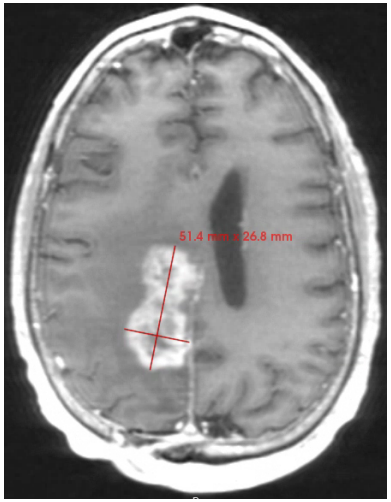


CT after cycle 2

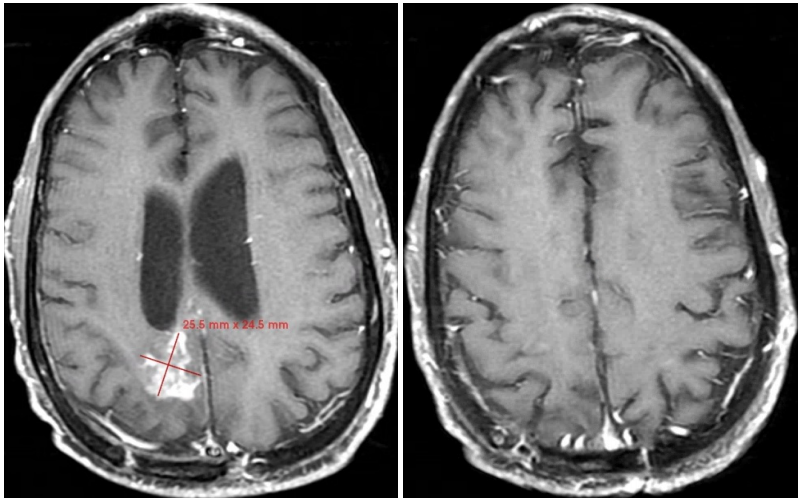


- Widely metastatic **GIST** with *KIT* Exon 11 deletion, who received 6 different prior KIT inhibitors
- **RECIST:** partial response (**-37%**) maintained for 5+ cycles on DL4 100mg BID

Baseline MRI



MRI after cycle 12



- **Glioblastoma multiforme** with *PDGFRA* / *KIT* / *KDR* co-amplification, who received prior XRT and temozolomide and progressed after 3 months
- **RECIST**: partial response (**-49%**), on study for 12+ cycles on DL1 20mg BID
- **RANO:** PR after cycle 12

SUMMARY OF EFFICACY (n=24)

- **RECIST**
  - PR in heavily pretreated patient with GIST KIT exon 11/17 mutation
  - PR in pretreated patient with GBM with *PDGFRA/KIT/KDR* co-amplification (confirmed by RANO)

- **PET metabolic responses**
  - PMR in 14 of 15 patients with heavily pretreated GIST and *KIT* mutation(s), 13 of these responses have been confirmed by central review (analysis ongoing)

- **Time on therapy**
  - A patient with GBM with *PDGFRA*/*KIT*/*KDR* co-amplification on therapy for 12+ months
  - Three patients with heavily pretreated GIST on therapy for $\geq$ 6 months

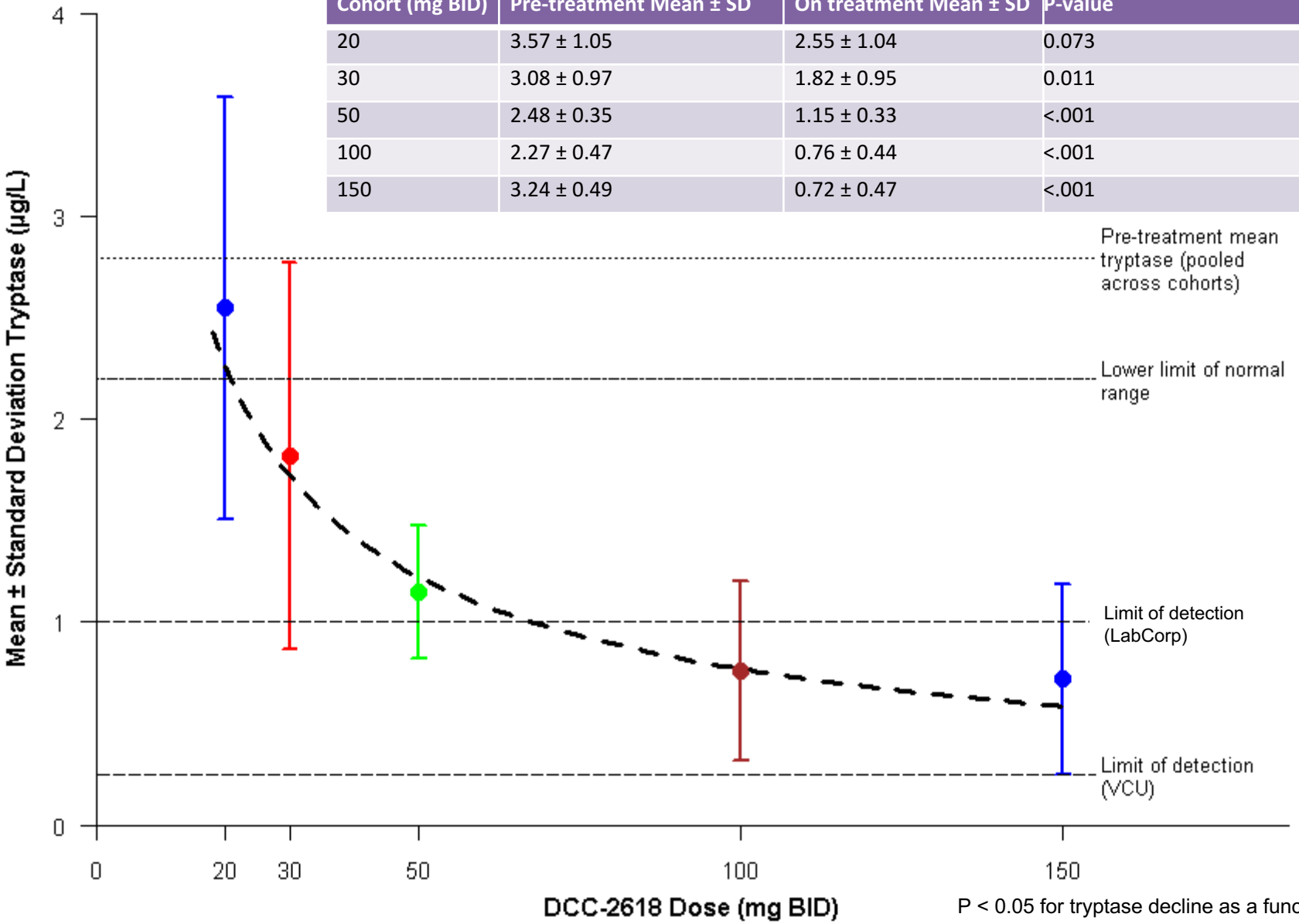
DCC-2618: PLASMA cfDNA *KIT* MUTATIONS

In **13**/15 patients, we detected total of 33 *KIT* mutations in 6 exons (9, 11, 13, 14, 17, 18)

Patient (dose mg)	No. of *KIT* mutations	Change in *KIT* mutation allele fraction (MAF)	Comment
1 (30 BID)	2	Undetectable after C2 - C6	Includes Exon 17 (N822K) resistance mutation
2 (50 BID)	1	Undetectable after C2 & C4	Exon 11 initiating mutation
3 (50 BID)	6	All mutations undetectable after C2	Includes 3 distinct Exon 17 resistance mutations (D816E, D820Y, and Y823D)
4 (50 BID)	2	MAF 16 & 21 x ↓ after C2	Includes Exon 14 (N680K) resistance mutation
5 (50 BID)	3	MAF 50 to >600x ↓after C2; 136 to > 600x ↓ after C4	Resistance mutations in Exons 13 (V654A) & Exon 18 (A829P) undetectable after C2 & 4
6 (100 BID)	1	Undetectable after C2	Exon 9 initiating duplication
7 (100 BID)	3	MAF 9-10x ↓after C2	Includes known Exon 13 (K642E) and Exon 17 (N822K) resistance mutations

DCC-2618: DOSE RESPONSE RELATIONSHIP WITH SERUM TRYPTASE LEVELS

Cohort (mg BID)	Pre-treatment Mean ± SD	On treatment Mean ± SD	P-value
20	3.57 ± 1.05	2.55 ± 1.04	0.073
30	3.08 ± 0.97	1.82 ± 0.95	0.011
50	2.48 ± 0.35	1.15 ± 0.33	<.001
100	2.27 ± 0.47	0.76 ± 0.44	<.001
150	3.24 ± 0.49	0.72 ± 0.47	<.001



P < 0.05 for tryptase decline as a function of dose

CONCLUSIONS

- DCC-2618 is well tolerated to date with an encouraging safety profile and robust exposure following oral doses from 20 to 150 mg BID
  - Starting at 50mg BID, mean trough levels of combined plasma concentration exceed IC_{90} of least sensitive mutations T670I and V654A
  - MTD has not been reached yet and dose escalation is ongoing
  - Asymptomatic grade 3 lipase elevation has been the only DLT to date
- Preliminary signals of activity per RECIST and PET have been observed in pretreated patient GBM with co-amplification of *PDGFRA*/*KIT*/*KDR* and GIST(s) with *KIT* mutations
- DCC-2618 leads to rapid clearance of broad spectrum of *KIT* mutations from plasma cfDNA in patients with heavily pretreated GIST
- Dose-dependent rapid reduction of serum tryptase warrants testing of DCC-2618 in systemic mastocytosis

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