DCC-2618, a novel pan-KIT and PDGFRα kinase switch control inhibitor, shows encouraging signal in a patient with glioblastoma (GBM)

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Abstract #XX

BACKGROUND

- DCC-2618 is a pan-KIT and PDGFRα kinase switch control inhibitor resilient to de-novo and drug resistance mutations and its potency is independent of ATP concentration.
- Non-clinical data suggest that PDGFRα plays an important role in the development and progression of human gliomas.
- DCC-2618 was designed to potently inhibit the broadest range of mutations in KIT and PDGFRα kinases that emerge during tumor progression or on treatment.
- The dose of 150 mg QD was selected as the Recommended Phase 2 Dose (RP2D).
- To date, few PDGFRα inhibitors with CNS activity have been available.

METHODS

Study Design (NCT# 02571036)

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

Study Objectives

- Primary: Safety, tolerability, maximum tolerated dose (MTD), dose-limiting toxicities (DLT).
- Secondary: Pharmacokinetic profile, antitumor efficacy.

Patients (Major Eligibility Criteria)

- Molecular rationale for activity in glioma patients determined per local standards.
- ECOG 0-1 & adequate organ function.
- Prior KIT or PDGFRα inhibitors were allowed.

Tumor Assessments in Glioma Patients (RANO)

- MRI scans were performed initially every 2 cycles then every 3 cycles.

PDGFRA and KIT analyses in archival tumor tissue were done by NeoGenomics Laboratories, Inc., Aliso Viejo, CA.

RESULTS

(cutoff date – 28 July 2017)

Table 1: DCC-2618 Safety Population - Summary of TEAEs
(Treatment-Emergent AE / Regardless of Causality) ≥10% (n=70)

Event Term	Total Events	< 100 mg/d (N = 8)		≥ 100 mg/d (N = 62)		150 mg QD (N = 21)	
		G1/2	G3/4	G1/2	G3/4	G1/2	G3/4
Lipase increased	33	5	1	15	12	3	2
Fatigue	32	6	0	25	1	5	0
Anaemia	29	1	1	9	18	0	1
Decreased appetite[$]	20	1	0	17	1	3	0
Diarrhoea	16	1	0	15	0	0	0
Alopecia	15	1	0	14	0	4	0
Hypertension	15	0	1	9	5	0	0
Amylase increased	14	3	0	10	1	1	0
Myalgia	14	2	0	12	0	2	0
Weight decreased	14	1	0	13	0	1	0
Dyspnoea[#]	13	4	0	8	1	1	0
Abdominal pain	11	3	0	7	1	0	0
Constipation	11	4	0	7	0	2	0
Nausea	11	2	0	9	0	1	0
Palmar-plantar erythrodysaesthesia	11	0	0	11	0	2	0
Arthralgia	10	2	0	8	0	0	0
Blood bilirubin increased	10	1	0	7	2*	0	1*
Rash	8	2	0	6	0	1	0

All DLT events were not clinically significant: 2 G3 lipase ↑ at 100 mg & 200 mg BID and a G4 CPK ↑ at 150 mg QD

[$]One subject has a "Decreased appetite" AE with no severity grade. This is included in the total events column but nowhere else
[#]One subject has a "Dyspnoea" AE that resulted in death (G5). This is included in the G3/4 column for the ≥ 100 mg/d group
*Unconjugated bilirubin, both patients are homozygous for 28 *(TA)7/(TA)7 UGT1A1 polymorphism per local lab

Table 2: Summary of Malignant Glioma Patients Enrolled (n=8)

- Median age: 47.5 years (range 34 - 62)
- ECOG PS: 0: 3 (37.5%); 1: 5 (62.5%)
- Baseline genomic alterations (archival tissue, N=8)
  - GBM 4q12 amplified: 3 (#1: 12 copies, #44: 3-5 copies, #58: not provided)
  - Astrocytoma 4q12 amplified: 1 (#32: high copy number gain)
  - GBM PDGFRA mutated: 4
- Mean prior number of agents: 3.1 (median 3; range 1 - 6)
  - 1: 1/8 (12%)
  - 2: 2/8 (25%)
  - 3: 3/8 (38%)
  - 4+: 2/8 (25%)
- DCC-2618 treatment doses:
  - 20 mg BID: 1 (12.5%)
  - 50 mg BID: 3 (37.5%)
  - 100 mg QD: 2 (25.0%)
  - 100 mg BID: 1 (12.5%)
  - 150 mg QD: 1 (12.5%)

Table 3: Summary Molecular Analyses of Malignant Glioma Patients

ID	Diagnosis	Cohort	Target Kinase[1]	PDGFRA Amp[2] (FISH)	KIT Expression[3] (IHC)	Other Alterations[1]	Response
1	GBM WHO Grade 4	20 mg BID	PDGFRA/KIT/KDR Amplification (12 copies)	9.1	5% at 1+, 2+ and 3+, respectively	NF1 N2387_F2388del/MYCN amp/TP53 P190*	Partial Response 93.60% Decrease
32	Anaplastic Astrocytoma WHO Grade 3	50 mg BID	KIT/PDGFRA Amplification (high gain) PDGFRA Indel exon 7	6.7	0	H3K27M mutated/IDH1 WT/pMGMT methylated/ Deletion or gain in Chr. 1p, 1q, 5q, 9p, 10q, 11q, 17q	Progressive Disease New Target Lesions after 2 Cycles (Recurrence of Pediatric Glioma)
58	GBM WHO Grade 4	50 mg BID	PDGFRA/KIT (partial) Amplification	N.A.[4]	N.A.[4]	Polysomy 7/Single copy PTEN,FGFR2 and RB1 losses /Gains in EGFR, CDK6, MET, BRAF	On Study, Prior to 1st Assessment
44	GBM WHO Grade 4	50 mg BID	PDGFRA/KIT/KDR Amplification (3-5 copies) KIT T847M	9.3	15% at 3+, 10% at 1+ and 2+, respectively	MDM2 amp/CDK4 amp/MET amp/NF-1 del/ERG P439L//REL L156P/TERT promoter variation/EGFR deletion	Progressive Disease after Cycle 2
27	GBM WHO Grade 4	100 mg QD	PDGFRA Y849Y N659K-subclonal	N.A.[4]	N.A[4]	CD274 amp/PDCD1LG2 amp/SOX2 amp/CDKN2A/B loss/PTPN11 G60V	Progressive Disease within 6 Weeks
33	Diffuse Astrocytoma, GBM WHO Grade 4	100 mg QD	PDGFRA I843del	0.9 Chr 4 polysomy	0	PTEN C136*/IDH1 R132H/TP53 V272M/RB1 R787*/SETD2 splice site 71_71+3del	Intratumoral Hemorrhage Surgery Required (Received ~9 Doses) Progressive Disease
53	GBM WHO Grade 4	100 mg BID	PDGFRA D842Y	1	1% at 1+	CDKN2A exon 2 deletion/PTEN E256*/APC exon 14 insertion/NOTCH1 Q2368R/NOTCH2 A2471V/SMARCA4 T1264A Deletion or gain in Chr. 1p, 7, 9p, 13q, 14q, 17	On Study, Prior to 1st Assessment
60	GBM WHO Grade 4	150 mg QD	PDGFRA V658A	1	0	ATM A2274V/ATM S1362N/BRCA1 T710I/NF-1 S2826N/PTEN del/RB1 R445*/TIAF1 S3F/TP53 R248Q/C176R/TSC2 T70I/WT1 G147S	Progressive Disease after 2 Cycles

[1]Reported using various methods per institutional standards
[2]PDGFRA/CEN4 (Chr 4 Centromere) signal ratio
[3]KIT IHC is captured as percentage of cells with different staining intensity 0 (negative), 1+ (weak), 2+ (moderate) and 3+ (strong)
[4]No tumor tissue is available for analysis

Figure 1: Duration of Treatment on DCC-2618 of All Glioma Patients

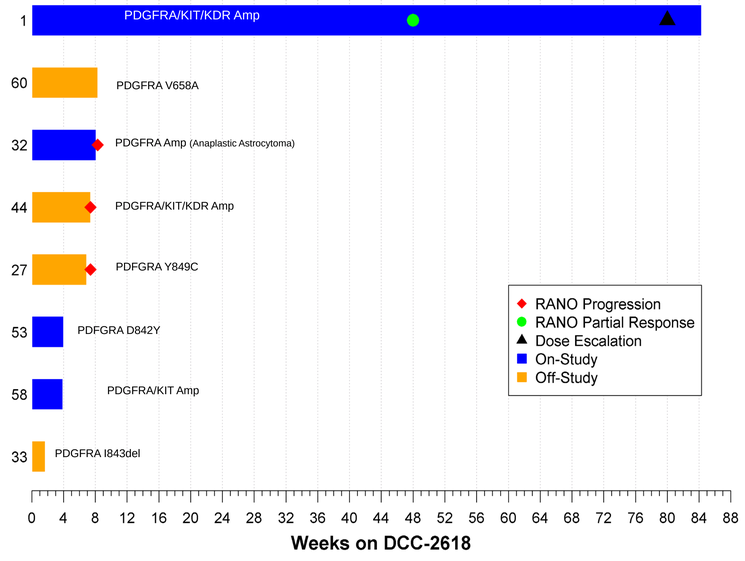
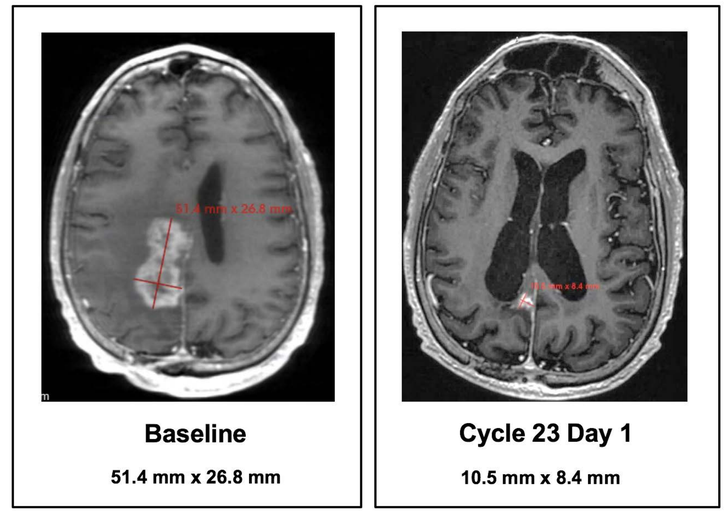


Figure 2: Partial Response per RANO in Patient with Glioblastoma Multiforme (GBM) after Cycle 22



Tumor reduction from baseline is 94% on Cycle 23 Day 1 per RANO

CONCLUSIONS

- DCC-2618 is well tolerated up to 200 mg BID.
  - All DLTs were not clinically significant.
  - At the RP2D of 150 mg QD appears to have a more favorable safety profile compared to the overall cohort of patients treated at ≥100 mg/d
- DCC-2618 produced an encouraging partial response in a GBM patient with triple amplification of PDGFR α, KIT and KDR (4q12 amplicon)
  - The tumor reduction from baseline is 94% on Cycle 23 Day 1 per RANO
- To date, other patients with similar amplifications or PDGFRa alterations did not derive similar benefit from treatment with DCC-2618
  - The population is very heterogeneous i.e. all patients exhibited multiple genetic alterations in addition to PDGFRα alterations
- The single exceptional responder warrants further testing of patients with KIT and PDGFRα driven gliomas in the ongoing expansion phase of the Phase I study. Fresh tumor biopsies and additional analyses are required to better define patients with clinical benefit from DCC-2618.

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