Inhibition of oncogenic and drug-resistant PDGFRA and KIT alterations by DCC-2618

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Introduction

Activating mutations and other genetic alterations in KIT and PDGFRA receptor tyrosine kinases (RTKs) have been identified in cancers of mastocytosis, gastrointestinal stromal tumors (GIST), 90% of systemic mastocytosis (SM), and small percentages of gliomas, leukemias, and melanomas. The typical response to imatinib, GIST has been transformed with KIT inhibitors, but heterogeneous drug-resistant mutations arise during therapy, with individual patients often having multiple acquired alterations in different tumor sites. PDGFRA variants in GIST and other cancers also have a significant unmet medical need. DCC-2618 is a kinase switch control inhibitor that potently blocks primary and drug-resistant KIT mutations in exons 9, 11, 13, 14, and 17, as well as primary PDGFRA mutations in exons 12, 13, and 16. DCC-2618 has been designed to bind as a Type II switch control kinase intolerant to imatinib, sunitinib, and regorafenib (ClinicalTrials.gov Identifier: NCT03353753). DCC-2618 is currently in a Phase 1 clinical trial in KIT and PDGFRA-driven cancers (ClinicalTrials.gov Identifier: NCT02571036) and in a Phase 3 clinical trial in GIST patients who have progressed on or are intolerant to imatinib, sunitinib, and regorafenib (ClinicalTrials.gov Identifier: NCT03757373).

DCC-2618 Structure and Type-II Binding Mode

DCC-2618 broadly inhibits KIT and PDGFRA Mutants

DCC-2618 Inhibits KIT and PDGFRA-driven Xenografts

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DCC-2618 Inhibits KIT and PDGFRA-driven Xenografts

Saturation Mutagenesis

- Of relevance to mastocytosis, no secondary KIT mutations were identified in a saturation mutagenesis study starting with Ba/F3 cells expressing KIT exon 17 mutant D816V at a DCC-2618 concentration of 25 nM.
- Of relevance to GIST, no secondary KIT mutations were identified in a saturation mutagenesis study starting with Ba/F3 cells expressing KIT exon 17 mutant D816V at a DCC-2618 concentration of 25 nM.

Broad Decrease of Heterogeneous KIT Mutants in ctDNA from GIST Patients

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Summary

- DCC-2618 is currently in a Phase 1 clinical trial in KIT and PDGFRA-driven cancer patients (ClinicalTrials.gov Identifier: NCT02571036). Data from the Phase 1 clinical trial in GIST patients who have progressed on or are intolerant to imatinib, sunitinib, and regorafenib (ClinicalTrials.gov Identifier: NCT03757373).

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Figure 1. (A) Chemical structures of DCC-2618, active metabolite DP-5439, and analog DP-2976 (gray structure). The compound bind KIT and PDGFRA, including activating kinase mutations, in a Type II or inactive conformation. (B) The phenyl ring of DP-2976 binds in the kinase pocket; the A ring of DCC-2618 interacts with the kinase DCC-2618 pocket nucleated by drug binding. Decoy switch Y823 (green) binds into this nucleated bond network nucleated by drug binding. Decoy switch Y823 (green) binds into this nucleated

Figure 2. Four cellular assays were used to screen for DCC-2618 potency against the listed KIT and PDGFRA-mutant cell lines: ATP-5439: R = H, X = Br

Figure 3. DCC-2618 broadly inhibited KIT or PDGFRA phosphorylation in a panel of GIST cells (x) or Ba/F3 cells expressing KIT exon 11 mutant V560D at DCC-2618 concentrations of x nanomolar. (A) < 1 nM; (B) < 10 nM; (C) < 100 nM; (D) ≥ 100 nM. (E) DCC-2618 was also tested in other cell lines with KIT or PDGFRA alterations.

Figure 4. DCC-2618 broadly inhibited the phosphorylation of KIT in Ba/F3 cells expressing KIT exon 11 mutant V560D. (A) DCC-2618 blocks tumor growth in xenograft models driven by KIT mutants or PDGFRA-activating mutations. Ba/F3 cells expressing KIT exon 11 mutant V560D were implanted subcutaneously into severe combined immunodeficiency (SCID) immunocompromised mice, then treated with DCC-2618 formulated into the diet at 100 mg/kg (red) or 25 mg/kg (blue). Data are represented as mean ± SEM. (B) Treatment in the model was well-tolerated as determined by body weight change. (C) GIST patient-derived xenograft (PDX) KIT exon 11 del. (D) GIST tumor samples across the spectrum of KIT exons 9, 11, 13, 14, and 17. DCC-2618 at 250 mg/kg/day (red) significantly decreases in mutant KIT ctDNA in GIST patients (n=15) across the spectrum of exons 9, 11, 13, 14, 17, and 18, including exon 12/13 insertions and deletions, and difficult to treat mutations such as exon 13 K654E & V656A, exon 14 N825K, exon 17 activation loop mutations C954V, D944E, D952G/Y, N822K, and D842V and D842I.*

Figure 6. Prior presentation of Phase 1 clinical trial data revealed multiple responses in heavily-pretreated GIST patients. A pool of circulating tumor DNA (ctDNA) from the Phase 1 trial has shown decreases in mutant KIT ctDNA in GIST patients (n=15) across the spectrum of exons 9, 11, 13, 14, 17, and 18, including exon 12/13 insertions and deletions, and difficult to treat mutations such as exon 13 K654E & V656A, exon 14 N825K, exon 17 activation loop mutations C954V, D944E, D952G/Y, N822K, and D842V and D842I.*

Figure 5. (A) KIT D816V (B) PDGFRA N655K

Figure 7. Prior presentation of Phase 1 clinical trial data revealed multiple responses in heavily-pretreated GIST patients. A pool of circulating tumor DNA (ctDNA) from the Phase 1 trial has shown decreases in mutant KIT ctDNA in GIST patients (n=15) across the spectrum of exons 9, 11, 13, 14, 17, and 18, including exon 12/13 insertions and deletions, and difficult to treat mutations such as exon 13 K654E & V656A, exon 14 N825K, exon 17 activation loop mutations C954V, D944E, D952G/Y, N822K, and D842V and D842I.*

Figure 8. Patient at first dose cohort Patient in first dose cohort Drug targeted with DCC-2618

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Cell Line Type KIT Mutation(s)

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Bone marrow and other hematopoietic cancers; or imatinib-resistant KIT mutants such as D816V KIT, whereas Type I inhibitors have weaker activity for exon 13/14 mutants. * * * * * * * * * * * *

Exon 11 primary mutations + imatinib-resistance mutations

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