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An open-label phase 1/2 study of DCC-3009 monotherapy in patients with advanced gastrointestinal stromal tumor

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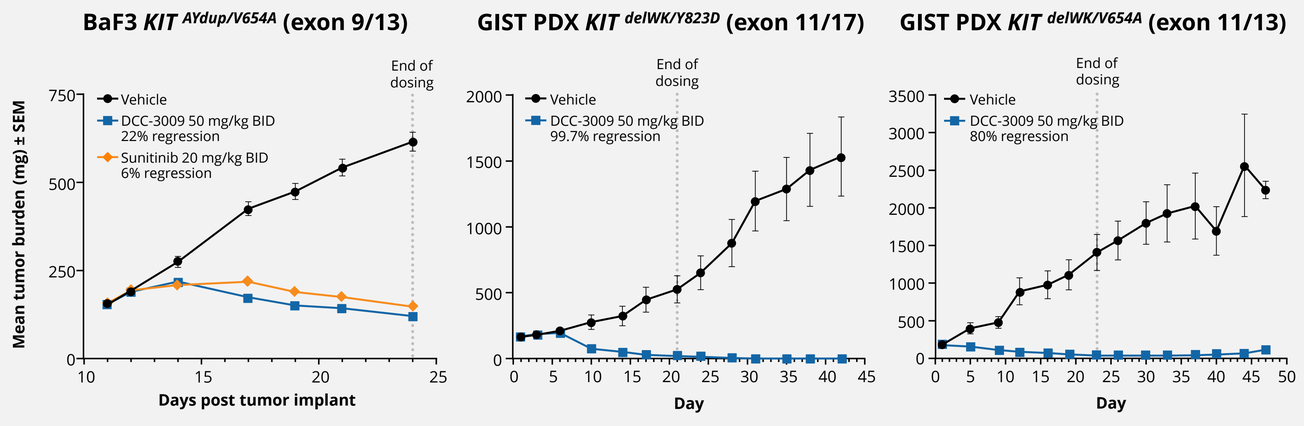
Introduction

- *KIT* and platelet-derived growth factor receptor α (*PDGFRA*) mutations remain the key oncogenic drivers in the majority of patients with advanced gastrointestinal stromal tumor (GIST)[1-5], with acquired secondary drug-resistant mutations contributing to the heterogeneity and complexity of the disease[1,5-9]
- The diversity of these resistance mutations allows escape from standard-of-care tyrosine kinase inhibitor (TKI) therapy,[10-13] creating an unmet need for novel therapies that inhibit all clinically relevant GIST-driving mutations[9]
- DCC-3009 is an investigational, highly potent, and selective switch-control KIT and PDGFRA inhibitor designed to act against known clinically relevant primary and secondary GIST-driving mutations while limiting off-target effects
- In preclinical studies, DCC-3009 demonstrated strong antitumor effects in xenograft models driven by resistant *KIT* mutations (**Figure 1**), and showed optimized properties for oral administration with low risk of cytochrome P450 inhibition[14]
- Here, we describe an ongoing phase 1/2 study evaluating DCC-3009 as a monotherapy in patients with advanced GIST

Figure 1. Robust antitumor activity of DCC-3009 in preclinical GIST models[14]

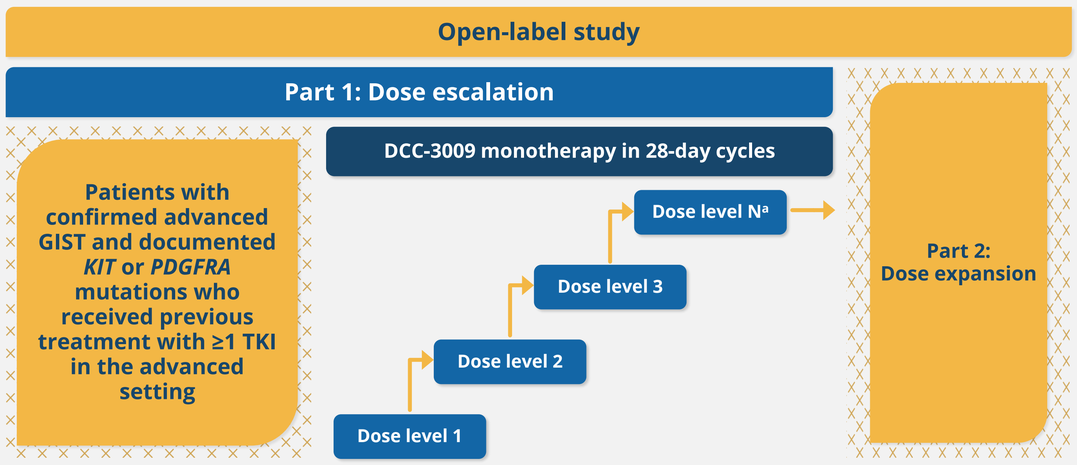


When dosed orally BID, treatment with DCC-3009 led to tumor regression in *KIT* exon 9/13–, 11/13–, and 11/17–mutant models.
BID, twice daily; GIST, gastrointestinal stromal tumor; PDX, patient-derived xenograft; SEM, standard error of the mean.

Study Design

- This is a multicohort, open-label, phase 1/2 trial evaluating the safety, tolerability, and efficacy of DCC-3009 in patients with advanced GIST (NCT06630234)
- This trial uses a modular approach, with each module defined according to the therapy (DCC-3009 alone or in combination with other anticancer agents) and divided into 2 parts (dose escalation and dose expansion)
- Eligible patients for the dose-escalation part of the study will receive DCC-3009 monotherapy orally in 28-day cycles (**Figure 2**)

Figure 2. Dose escalation study design



[a]Escalation will continue until the maximum tolerated dose is reached or until an expansion dose is selected based on the overall safety, PK, and preliminary efficacy profile.
GIST, gastrointestinal stromal tumor; *PDGFRA*, platelet-derived growth factor receptor α; PK, pharmacokinetic; TKI, tyrosine kinase inhibitor.

Key Outcome Measures

Primary outcome measures

- The primary outcome measures for monotherapy dose escalation include safety assessments
  - Dose-limiting toxicities will be assessed for each dose level
  - Safety assessments will include monitoring of treatment-emergent adverse events and serious adverse events

Secondary outcome measures

- Objective response rate, duration of response, and progression-free survival by Modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST v1.1)
- Overall survival
- Pharmacokinetics

Key Eligibility Criteria

KEY INCLUSION CRITERIA (FOR PART 1)

Adults aged ≥18 years
Any participant with histologically or cytologically confirmed advanced/unresectable or metastatic GIST with documented *KIT* or *PDGFRA* mutation, who has progressed on or was intolerant to at least 1 approved TKI regimen in the advanced/metastatic setting
Have at least 1 measurable lesion as defined by mRECIST v1.1
Have ECOG PS of 0 or 1
Adequate organ function, bone marrow function, and electrolytes
Agreement to comply with contraception requirements
Have a life expectancy more than 3 months

ECOG PS, Eastern Cooperative Oncology Group performance status; GIST, gastrointestinal stromal tumor; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; *PDGFRA*, platelet-derived growth factor receptor α; TKI, tyrosine kinase inhibitor.

KEY EXCLUSION CRITERIA

Received systemic anticancer therapy less than 5 half-lives or 14 days (whichever is shorter) prior to first dose of study drug
Prior or concurrent malignancy that requires treatment or is expected to require treatment for active cancer
Known active CNS metastases or an active primary CNS cancer
History or presence of clinically relevant cardiovascular abnormalities
Major surgery within 28 days of the first dose of study drug
Systemic arterial thrombotic or embolic events within 6 months prior to the first dose of study drug
Venous thrombotic events (eg, deep vein thrombosis) or venous thrombotic embolic events (eg, pulmonary embolism) within 1 month prior to the first dose of study drug
Known allergy or hypersensitivity to any component of the study drug
Malabsorption syndrome or other illness that could affect oral absorption
Any other clinically significant comorbidities

CNS, central nervous system.

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