Pan-exon mutant KIT inhibitor DCC-3009 demonstrates tumor regressions in preclinical gastrointestinal stromal tumor models

Bryan D Smith, Subha Vogeti, Timothy M Caldwell, Hanumaiah Telikepalli, Yu Mi Ahn, Gada Al-Ani, Stacie L Bulfer, Andrew Greenwood, Cale L Heiniger, Joshua W Large, Cynthia B Leary, Wei-Ping Lu, Kylie Luther, William C Patt, Max D Petty, Yeni K Romero, Forrest A Stanley, Kristen L Stoltz, Daniel C Tanner, Sihyung Yang, Yu Zhan, Bertrand Le Bourdonnec, and Daniel L Flynn

Deciphera Pharmaceuticals, LLC, Waltham, MA, USA

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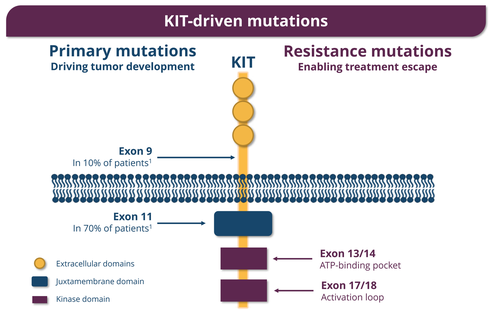
Introduction

- GISTs are predominantly driven by primary mutations in *KIT* exons 9 or 11[1,2]
- Heterogeneous drug-resistant secondary mutations arise in patients treated with FDA-approved KIT inhibitors, including imatinib and sunitinib[3]
  - Drug-resistant secondary mutations are found at multiple regions in the KIT ATP-binding pocket (encoded by exons 13/14) or activation loop (encoded by exons 17/18)
  - Multiple drug-resistant clones can also arise within a tumor or in metastatic tumor sites in individual patients



- An inhibitor that can potently inhibit the spectrum of *KIT* mutations is highly sought
- DCC-3009 was designed using a proprietary switch-control platform[4] as a next-generation KIT inhibitor intended to potently inhibit primary *KIT* mutations in exons 9 and 11 and secondary drug-resistant mutations across exons 13, 14, 17, and 18
- Here, we evaluate the pharmacologic profile and activity of DCC-3009

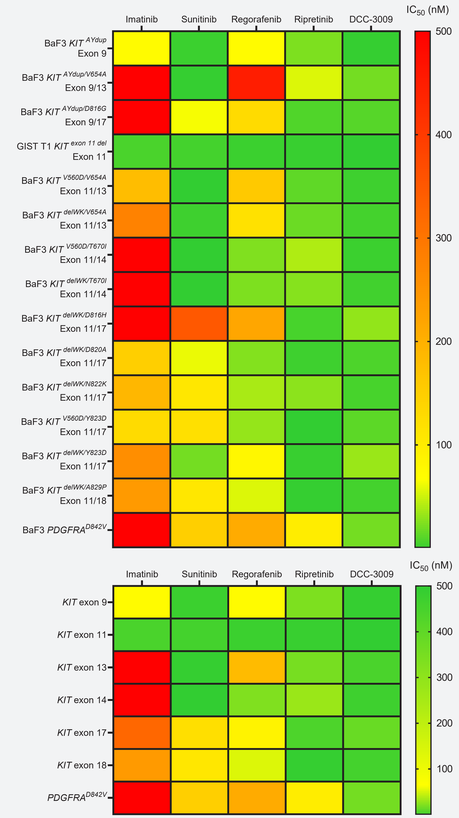
Methods

- Inhibition of *KIT* mutants was assessed using standard enzyme- and cell-based assays
- Levels of phosphorylated KIT were determined by Western blot or ELISA
- Proliferation was measured using the fluorescent dye resazurin
- *KIT*-mutant xenograft or patient-derived xenograft models were developed at AAALAC-accredited facilities, with the approval of Animal Care and Use Committees

Results

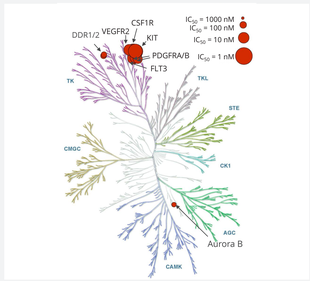
- In GIST cells or BaF3 cells transfected with *KIT* mutants, DCC-3009 potently inhibited the spectrum of known primary and secondary drug-resistant mutations in GIST
- DCC-3009 was superior to second-, third-, and fourth-line standard-of-care therapies *in vitro*
- The high free drug levels attained in mice allow for suppression of all tested *KIT* mutants, which was confirmed in xenograft studies

DCC-3009 inhibits the spectrum of *KIT* mutations in GIST



Top panel: individual cell lines; bottom panel: summary of data by exon.

DCC-3009 is selective for KIT



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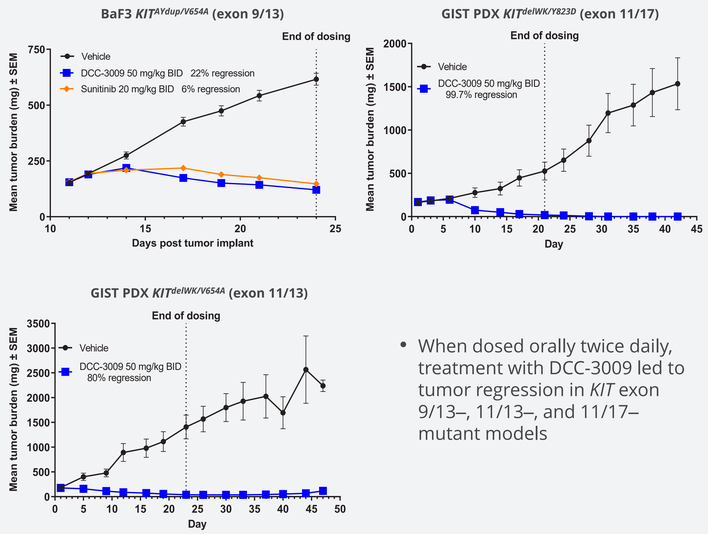
- DCC-3009 was selective for KIT when screened against a large panel of approximately 400 kinases
- This should allow for greater KIT suppression with fewer off-target effects
- DCC-3009 achieved high free drug concentrations in plasma and >80% inhibition of KIT phosphorylation at 2, 6, and 10 hours post dose in a *KIT* exon 11/13–mutant GIST patient-derived xenograft model

DCC-3009 exhibits optimized *in vivo* PK/PD in a *KIT*$^{delWK/V654A}$ (exon 11/13) GIST PDX model

	Time post dose					
	2 h	6 h	10 h	2 h	6 h	10 h
Dose (mg/kg)	Inhibition of KIT phosphorylation (%)			Free drug in plasma (nM)		
25	82	87	94	194	53.6	16.4
50	85	87	92	463	208	102

DCC-3009 demonstrates robust efficacy in preclinical GIST mouse models



- When dosed orally twice daily, treatment with DCC-3009 led to tumor regression in *KIT* exon 9/13–, 11/13–, and 11/17–mutant models

DCC-3009 has optimized properties for oral administration

- Optimized stability in human and mouse microsomes
- Significant free fraction of drug in mouse and human plasma
- Good Caco-2 permeability, with moderate efflux to reduce brain penetration
- No inhibition of major CYP isoforms under 10 μM concentration; no time-dependent inhibition of CYP3A4
- No hERG potassium channel inhibition under 20 μM concentration
- Negative for genotoxicity in an Ames test with 3 strains
- High oral bioavailability in rats and dogs
- Low brain penetration in a rat pharmacokinetic study

Pharmaceutical and ADME profile of DCC-3009

Property	Result
Mouse microsomal stability	$t_{1/2}$ >145 min
Human microsomal stability	$t_{1/2}$ >145 min
Mouse plasma protein binding	98.2% bound
Human plasma protein binding	96.3% bound
Caco-2 permeability	11 × 10^{-6} cm/s
Caco-2 efflux ratio	7.8
CYP inhibition (3A4, 2D6, 2C9, 2C19, 1A2)	IC_{50} >10 μM
CYP3A4 time-dependent inhibition	Negative
hERG inhibition	IC_{50} >20 μM
Ames test (3 strains)	Negative
Rat oral bioavailability	87%
Dog oral bioavailability	100%
Rat brain penetration Kp_{uu}	4%

CONCLUSIONS

- DCC-3009 is a pan-exon switch-control KIT inhibitor exhibiting high potency for *KIT* mutants in preclinical models spanning exons 9, 11, 13, 14, 17, and 18
- *In vivo*, DCC-3009 exhibited tumor regressions in drug-resistant models with *KIT* exon 9/13, 11/13, and 11/17 mutations
- The high free drug fraction enables pharmaceutically active exposures above levels needed to suppress the broad spectrum of *KIT* mutations in GIST
- DCC-3009 has optimized pharmaceutical and ADME properties for oral administration with low brain penetration

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CORRESPONDING AUTHOR/DISCLOSURES

Bryan Smith (BSmith@Deciphera.com)
All authors are/were full time employees of Deciphera Pharmaceuticals, LLC and own/owned Deciphera Pharmaceuticals, LLC stock or options.

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ABBREVIATIONS

AAALAC, Association for Assessment and Accreditation of Laboratory Animal Care; ADME; absorption, distribution, metabolism, and excretion; AGC, protein kinase A, G, and C families; ATP, adenosine triphosphate; AYdup, A502/Y503 duplication; BID, twice daily ; CAMK, Ca2+/calmodulin-dependent protein kinase family; CK1, casein kinase 1 family; CMGC, family of kinases including cyclin-dependent kinases, mitogen-activated protein kinases, glycogen synthase kinases, and cyclin-dependent kinases; CSF1R, colony-stimulating factor 1 receptor; CYP, cytochrome P450; DDR, discoidin domain receptor; del, deletion; delWK, WK557–558 del; ELISA, enzyme-linked immunosorbentassay; FLT3, fms-related tyrosine kinase 3; GIST, gastrointestinal stromal tumor; hERG; human ether-a-go-go–related gene; IC_{50}, half maximal inhibitory concentration; $K_{p,uu}$, unbound partition coefficient (free brain concentration/free plasma concentration); PD, pharmacodynamics; PDGFR, platelet-derived growth receptor; PDX, patient-derived xenograft; PK, pharmacokinetics; SEM, standard error of the mean; STE, homologs of yeast sterile 7, sterile 11, and sterile 20 kinase family; $t_{1/2}$, half-life; TK, tyrosine kinase family; TKL, tyrosine kinase–like kinase family; VEGFR2, vascular endothelial growth factor receptor 2.

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