DCC-3116, a first-in-class selective ULK1/2 inhibitor of autophagy, in combination with the KIT inhibitor ripretinib induces complete regressions in GIST preclinical models

Madhumita Bogdan, Mary J Timson, Hikmat Al-Hashimi, Bryan D Smith, and Daniel L Flynn

Deciphera Pharmaceuticals, LLC, Waltham, MA, USA

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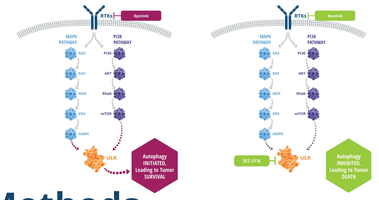
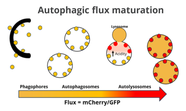
Introduction

- Cancer cells activate autophagy as an adaptive stress response (ASR) escape mechanism to therapies targeting the RTK/RAS/MAPK/PI3K pathways, limiting antitumor response[1,2]
- ULK1/2 kinases are key regulators that initiate autophagy in response to stress, such as RTK pathway inhibition[1,2]
- Most gastrointestinal stromal tumors (GISTs) are driven by mutations in KIT kinase[3]
- KIT signals through MAPK/PI3K pathways, suppressing ULK1/2 kinases and autophagy[3-5]
  - Inhibitors targeting KIT reverse this suppression, activating autophagy and cancer cell survival[3]
- Approved therapies for mutant *KIT*–driven GIST include imatinib, sunitinib, regorafenib, and ripretinib[6]
  - Avapritinib is approved for *PDGFRA* exon 18 mutation–driven GIST[6]
  - Treatment with these inhibitors is initially successful; however, drug resistance can develop[6] through *KIT* secondary mutations or activation of ASR pathways, including autophagy
- DCC-3116 is a selective, potent, first-in-class, investigational inhibitor of ULK1/2 in clinical development in combination with targeted therapies that activate the autophagic ASR escape pathway[1,2]
- Here, we demonstrate ULK1/2 and autophagy activation upon treatment with ripretinib in *KIT*-mutant GIST models and synergy of the ULK1/2 inhibitor DCC-3116 with ripretinib in the GIST-T1 xenograft model resulting in complete regressions



Methods

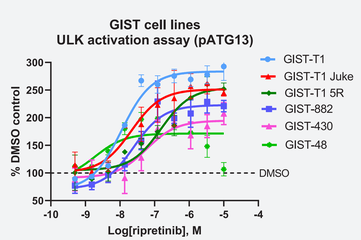
- Inhibition of ULK1/2 in cell assays was measured using an ELISA for the ULK substrate pATG13
- Autophagic flux was measured by monitoring mCherry/GFP-tagged LC3 protein in GIST cells
- Xenograft studies were performed at a CRO with the approval of Animal Care and Use committees

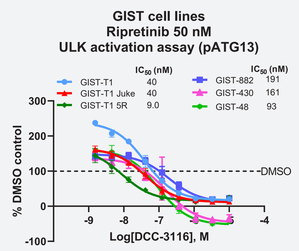


Results

DCC-3116 synergizes with ripretinib to inhibit autophagy and block tumor growth in GIST preclinical models

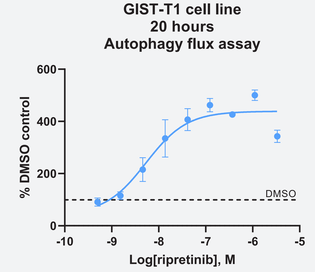
DCC-3116 reverses ripretinib-induced ULK activation in multiple GIST cell lines

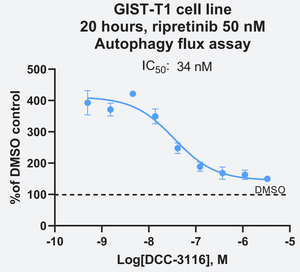


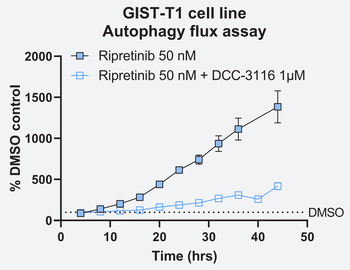


Cell line	*KIT* mutation
GIST-T1	Exon 11^{del}
GIST-T1 Juke	Exon 11^{del}/exon 17^{D816E}
GIST-T1 5R	Exon 11^{del}/exon 14^{T670I}
GIST-882	Exon 13^{K642E}
GIST-430	Exon 11^{del}/exon 13^{V654A}
GIST-48	Exon 11^{V560D}/exon 17^{D820A}

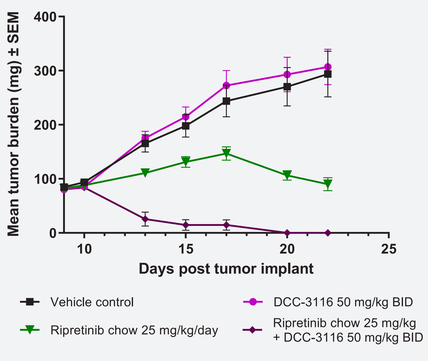
DCC-3116 reverses ripretinib-induced autophagic flux

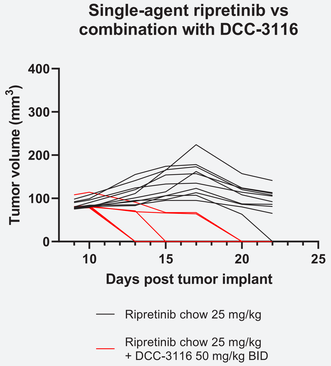






Synergy of DCC-3116 in combination with ripretinib in the GIST-T1 xenograft model





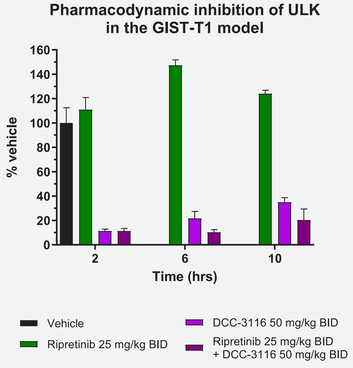


Table 2. Combination treatment resulted in regressions

Treatment	% TGI	% regression	Regressions (n/N)	Complete regressions (n)
Vehicle control	0		0/5	0
Monotherapy				
Ripretinib 25 mg/kg (chow)	96		2/10	1
Ripretinib 100 mg/kg (chow)	-	100	5/5	5
DCC-3116 50 mg/kg	−8		0/10	0
DCC-3116 100 mg/kg	−9		0/10	0
Combination				
Ripretinib 25 mg/kg (chow) + DCC-3116 50 mg/kg	-	100	9/9	9/9
Ripretinib 25 mg/kg (chow) + DCC-3116 100 mg/kg	-	100	10/10	10/10
Ripretinib 100 mg/kg (chow) + DCC-3116 50 mg/kg	-	100	10/10	10/10
Ripretinib 100 mg/kg (chow) + DCC-3116 100 mg/kg	-	100	9/9	9/9

% TGI calculation = 100−{tumor volume last day$_{experimental}$−day 0$_{experimental}$)/tumor volume last day$_{vehicle}$−day 0$_{vehicle}$); % regression = 100- (final tumor vol / initial tumor vol) *100

CONCLUSIONS

- DCC-3116 strongly synergizes with the KIT inhibitor ripretinib, resulting in complete regressions in the GIST-T1 exon 11 deletion xenograft model
- These data demonstrate preclinically that, like other RTK inhibitors[1], ripretinib activates ULK1/2-mediated autophagy as an ASR escape mechanism, which is inhibited by DCC-3116
- This provides the rationale to study DCC-3116 in combination with ripretinib in patients with GIST
- DCC-3116 is currently in a phase 1 clinical trial in patients with advanced solid tumors (NCT04892017), and initiation of a new combination escalation study with ripretinib is expected in the second half of 2023

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CORRESPONDING AUTHOR/DISCLOSURES

Madhumita Bogdan (mbogdan@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

AKT, protein kinase B; AMPK, adenosine monophosphate–activated protein kinase; ASR, adaptive stress response; ATG13, autophagy-related protein 13; BID, twice daily; CRO, clinical research organization; del, deletion; DMSO, dimethyl sulfoxide; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular signal–regulated kinase; GFP, green fluorescent protein; GIST, gastrointestinal stromal tumor; IC_{50}, half maximal inhibitory concentration; LC3, microtubule-associated protein light chain 3; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; mTOR, mammalian target of rapamycin; pATG13, phosphorylated ATG13; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma serine/threonine kinase; RAS, rat sarcoma small GTPase protein; Rheb, Ras homolog enriched in brain; RTK, receptor tyrosine kinase; SEM, standard error of the mean; TGI, tumor growth inhibition; ULK, unc-51-like autophagy-activating kinase.

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