A phase 1/2 study of inlexisertib (DCC-3116) in combination with ripretinib for patients with advanced gastrointestinal stromal tumors: Expansion cohort design

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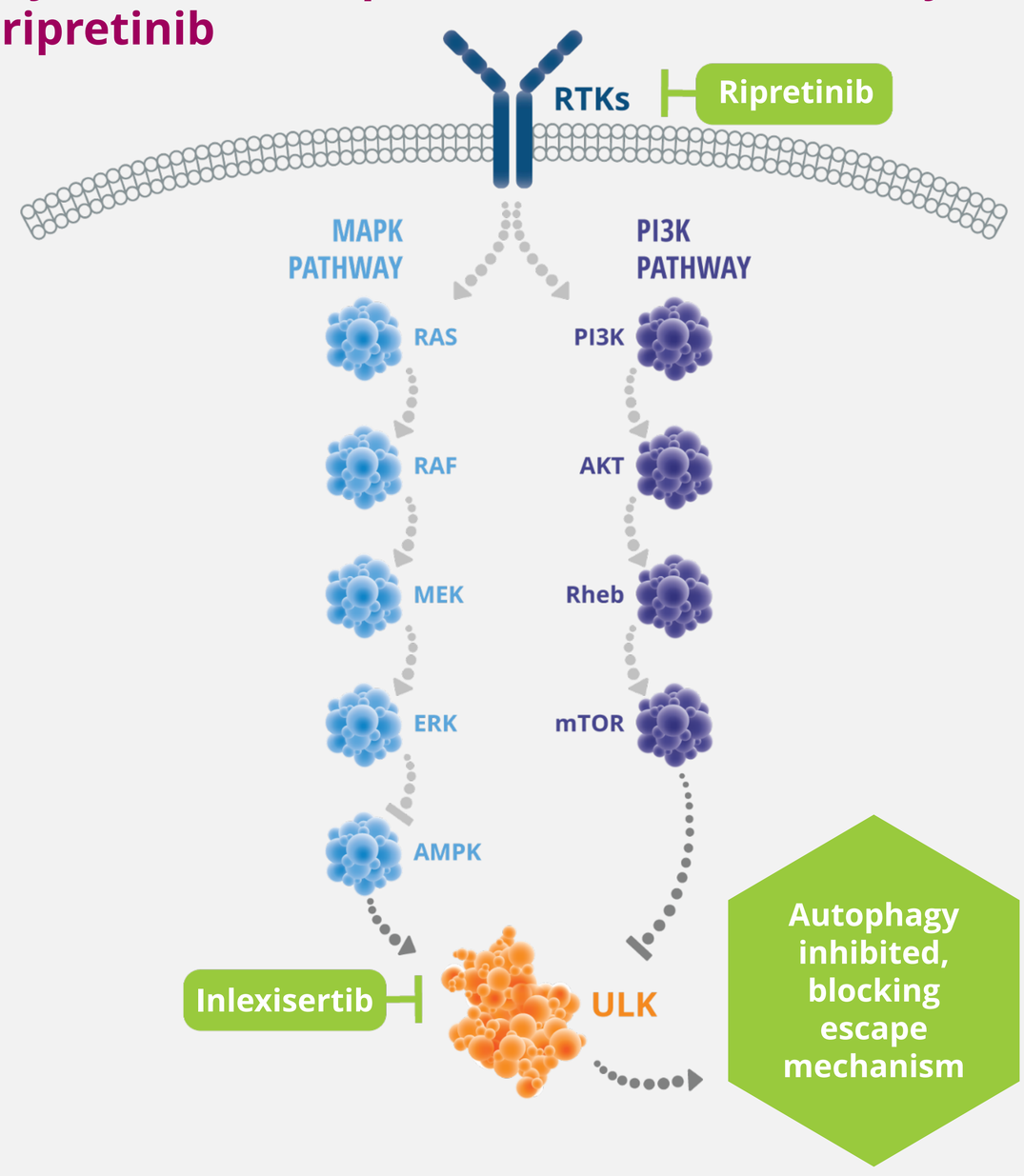
Ping Chi[1], Sreenivasa R Chandana[2], Arun S Singh[3], Jonathan Trent[4], Michael Heinrich[5], Dale R Shepard[6], Syma Iqbal[7], Mia Weiss[8], Attila Kollár[9], Charles M Psoinos[10], Julia Jennings[10], Matthew L Sherman[10], Frederic J Reu[10], Margaret von Mehren[11]

[1]Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, Sarcoma Translational Research, New York, NY, USA; [2]START Midwest, The Cancer & Hematology Centers, Grand Rapids, MI, USA; [3]University of California, Los Angeles, Sarcoma and Connective Tissues Medical Oncology, Santa Monica, CA, USA; [4]Sylvester Comprehensive Cancer Center, University of Miami Health System, Medical Oncology, Miami, FL, USA; [5]Portland VA Health Care System and OHSU Knight Cancer Institute, Medical Oncology, Portland, OR, USA; [6]Taussig Cancer Center, Cleveland Clinic, Medical Oncology, Cleveland, OH, USA; [7]University of Southern California Norris Comprehensive Cancer Center, Medical Oncology, Pasadena, CA, USA; [8]Washington University in St. Louis, Medicine, Saint Louis, MO, USA; [9]Inselspital Bern, University of Bern, Medical Oncology, Bern, Switzerland; [10]Deciphera Pharmaceuticals, LLC, Clinical Development, Waltham, MA, USA; [11]Fox Chase Cancer Center, Hematology/Oncology, Philadelphia, PA, USA

Introduction

- Advanced cancers driven by mutations at or downstream of receptor tyrosine kinases (RTKs) can activate autophagy to promote cell survival in response to RTK pathway inhibitors[1]
- Unc-51–like autophagy activating kinases 1/2 (ULK1/2) are key regulators of autophagy initiation
  - ULK1/2 initiates autophagy in response to RTK pathway inhibition, including with KIT inhibitors in *KIT*-mutant gastrointestinal stromal tumor (GIST)[2]
- Targeting ULK1/2 in combination with RTK pathway inhibitors is one strategy for overcoming this adaptive resistance mechanism
- Ripretinib (150 mg once daily [QD]) is a switch-control KIT/PDGFRA tyrosine kinase inhibitor (TKI) approved for patients with advanced GIST who received prior treatment with 3 or more kinase inhibitors, including imatinib[3,4]
  - In the INTRIGUE trial, the primary endpoint of superior progression-free survival (PFS) with ripretinib vs sunitinib in second-line advanced GIST was not met; in patients with mutations in *KIT* exon 11, median PFS with ripretinib vs sunitinib was 8.3 vs 7.0 months and objective response rate was 23.9% vs 14.6%[3]
  - However, ripretinib showed comparable efficacy in the all-patient population (median PFS: 8.0 vs 8.3 months) and favorable safety with fewer grade 3/4 treatment-emergent adverse events (41.3% vs 65.6%) vs sunitinib[3]
  - The National Comprehensive Cancer Network (NCCN) guidelines include ripretinib as an option for patients with advanced GIST intolerant of second-line sunitinib based on the results from the INTRIGUE trial[5]
- Inlexisertib (DCC-3116) is an investigational, selective, and potent switch-control ULK1/2 inhibitor designed to work with therapies that activate autophagy, such as ripretinib (**Figure 1**)

Figure 1. Inlexisertib inhibits autophagy driven by ULK1/2 in response to RTK inhibition by ripretinib



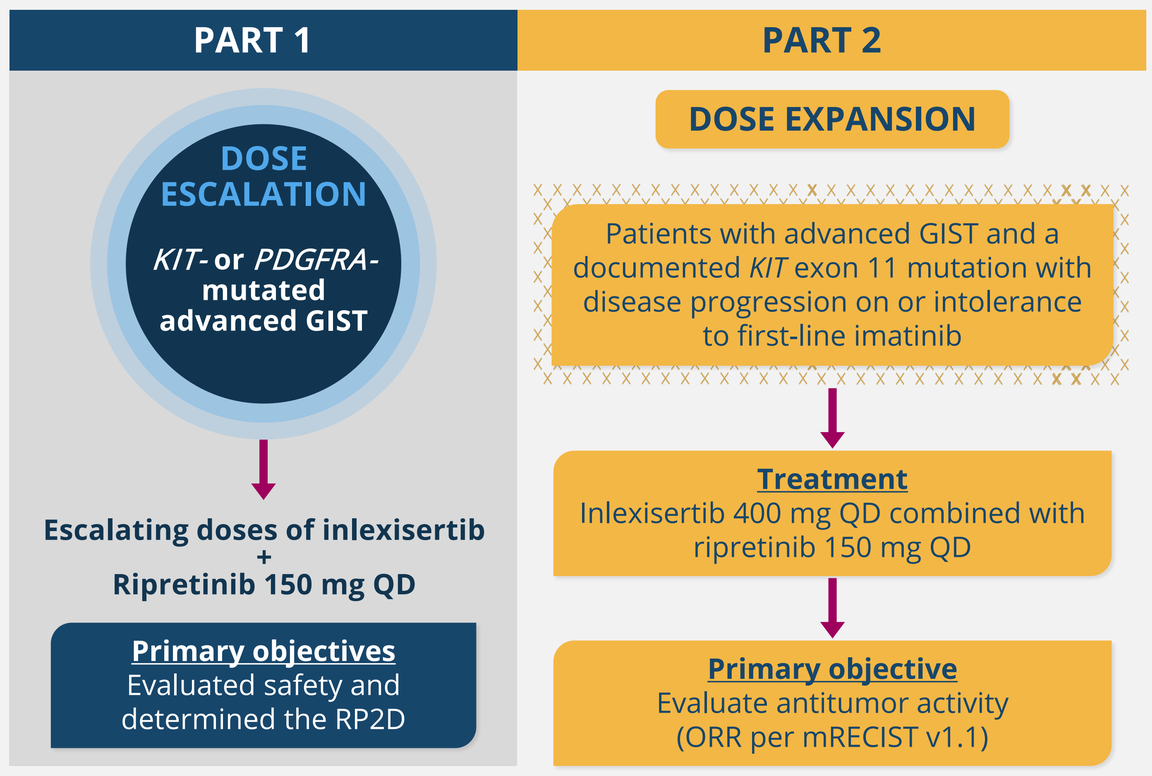
Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; ERK, extracellular signal–regulated kinase; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma small GTPase protein; Rheb, RAS homolog enriched in brain; RTK, receptor tyrosine kinase; ULK, Unc-51–like autophagy activating kinase.

- In a *KIT* exon 11–mutant GIST xenograft model, ripretinib alone stabilized tumor growth while the combination of ripretinib and inlexisertib led to complete regression[6]
- Part 1 of a phase 1/2, multicenter, open-label study (NCT05957367) established the recommended phase 2 dose of inlexisertib for combination with ripretinib in patients with advanced GIST
- Here, we describe part 2, which evaluates the efficacy, safety, and tolerability of inlexisertib in combination with ripretinib as a second-line treatment after imatinib in patients with advanced GIST and *KIT* exon 11 mutations

Study Design

- This is a phase 1/2, multicenter study designed to evaluate the efficacy, safety, and tolerability of inlexisertib in combination with ripretinib (**Figure 2**)

Figure 2. Study design for dose expansion



GIST, gastrointestinal stromal tumor; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; QD, once daily; RP2D, recommended phase 2 dose.

- In part 1, safety was evaluated and the RP2D of inlexisertib 400 mg QD with ripretinib 150 mg QD was determined
- Part 2 will evaluate antitumor activity of the RP2D as second-line treatment in *KIT* exon 11 mutant-GIST

Part 2: Dose Expansion Outcome Measures

Primary Efficacy Outcome Measure

- Objective response rate based on investigator assessment using modified Response Evaluation Criteria in Solid Tumors version 1.1

Secondary Outcome Measures

- PFS
- Duration of response
- Overall survival
- Pharmacokinetics

Key Eligibility Criteria

INCLUSION
Pathologically confirmed diagnosis of GIST with a documented *KIT* exon 11 mutation
Confirmed progression on or intolerance to imatinib in the locally advanced or metastatic setting
Male or female ≥18 years of age
At least 1 measurable lesion according to mRECIST v1.1
ECOG PS of 0 or 1 at screening
Life expectancy >3 months, as determined by the investigator
Adequate organ function and bone marrow reserve

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.

EXCLUSION
Received anticancer therapies or investigational therapies within 14 days or 5x the half-life (whichever is shorter)
Received anticancer therapies or medications including certain herbal medications that are known strong or moderate inhibitors or inducers of CYP3A4 or P-glycoprotein within ≤14 days or 5x the half-life (whichever is longer)
History or presence of clinically relevant cardiovascular abnormalities ≤6 months prior to the first dose of study drug
Ongoing participation in an interventional study
Active viral infection (including HIV, hepatitis B, or hepatitis C)
Known allergy to ripretinib or inlexisertib and their excipients
Known active metastasis of the central nervous system or presence of leptomeningeal disease
Previous treatment with systemic therapy for GIST other than imatinib

GIST, gastrointestinal stromal tumor.

Trial Enrollment

- This trial (NCT05957367) is currently enrolling in the phase 2 dose expansion; to learn more about enrolling your patient, please contact medicalinformation@Deciphera.com. Recruiting locations can be found at clinicaltrials.gov.

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CORRESPONDING AUTHOR
Attila Kollár
Attila.Kollar@insel.ch

DISCLOSURES

Attila Kollár reports advisory or consulting roles with Deciphera Pharmaceuticals, LLC.

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Please scan to access the clinicaltrials.gov site for this study (NCT05957367).