Preclinical studies with DCC-3116, a ULK kinase inhibitor designed to inhibit autophagy as a potential strategy to address mutant RAS cancers


Deciphera Pharmaceuticals, LLC, Waltham, MA

INTRODUCTION

• Cancer cells activate autophagy, a catabolic process to resupply nutrients and recycle damaged organelles, in order to survive stresses such as limited nutrients and hypoxia, or chemotherapy treatments.
• RAS mutant cancers, in particular, have been found to require autophagy for tumor growth and survival.1,2 Treating RAS mutant tumors with inhibitors of the downstream MAPK pathway has been largely unsuccessful, as these drugs have been shown to further stimulate autophagy, allowing for tumor cell survival.3-5 Inhibiting autophagy in combination with MAPK pathway inhibition may represent a possible new treatment paradigm for RAS mutant cancers.
• Proof-of-concept for this strategy was obtained in cancer models and in a RAS null pancreatic cancer patient by blocking autophagy with derivatives of chloroquine, in combination with MAPK inhibitors.6,7
• ULK1/2 kinase inhibitors autophagy and provide a potential target for a targeted inhibitory approach in RAS mutant cancers. Herein, we describe preclinical studies with the ULK kinase inhibitor DCC-3116, designed as a potential inhibitor of autophagy in RAS mutant cancers.

METHODS

In vitro kinase assays were performed using cellular levels of ATP (1 mM) and a peptide substrate. In cell assays, ULK activity was assessed using an ELISA for phosphorylated ULK1/2 (a cellular ULK substrate). Autophagosomal formation was measured using the dye Cyto-ID. Autophagic flux was assessed using cells expressing the autophagy protein ATG13 (% of control) in combination with DCC-3116. Xenograft models were used to assess pharmacokinetics (PK) and pharmacodynamics (PD), as well as efficacy in vivo.

ULK KINASE: INITIATING FACTOR FOR AUTOPHAGY

• ULK1/2 kinase inhibitors autophagy by phosphorylating and activating other autophagy pathway proteins (e.g. ATG13, BECN1, and ATG16L1).
• Damaged proteins, organelles, and other cargo are targeted to, and enveloped by, autophagosomes.
• Fusion of autophagosomes and lysosomes allows for breakdown and recycling of metabolic precursors and nutrients.
• Phosphorylation of ATG13 by ULK1/2 triggers autophagosomal formation.

RESULTS

Autophagy is a Compensatory Survival Mechanism in MAPK Pathway Inhibitor-treated RAS Mutant Cancers

• Treatment of a RAS mutant cancer cell line with inhibitors of the MAPK pathway (i.e. RAS, RAF, MEK, or ERK inhibitors) leads to activation of ULK kinase and phosphorylation of downstream autophagy protein substrates.

Figure 2. MAPK inhibition leads to increased ATG13 phosphorylation

DCC-3116 is a Potent Inhibitor of ULK Kinase and Autophagy in Cellular Assays

• DCC-3116 is a potent inhibitor of ULK kinase activity in cellular assays.

Figure 3. DCC-3116 Kinase Tree

• DCC-3116 is a potent inhibitor of ULK kinase and autophagy in cellular assays.
• DCC-3116 Exhibits Synergy with Trametinib in Inhibiting Cell Growth of ULK Substrate ATG13 in RAS- and BRAF-mutant Cell Lines

Figure 4. DCC-3116 Inhibits Both Basal and Trametinib-Induced Phosphorylation of ULK Substrate ATG13 in RAS- and BRAF-mutant Cell Lines

• DCC-3116 is a potent inhibitor of ULK kinase and autophagy in cellular assays in combination with MAPK inhibitors.

Figure 5. DCC-3116 Inhibits Autophagosomal Formation and Autophagic Flux of LC3

• DCC-3116 is a potent inhibitor of ULK kinase and autophagy in cellular assays.

Figure 6. DCC-3116 Exhibits Synergy with Trametinib in Inhibiting Cell Growth of RAS- or RAF-mutant Cancer Cells

• DCC-3116 is a potent inhibitor of ULK kinase and autophagy in cellular assays.

Figure 7. DCC-3116 Inhibited ATG13 Phosphorylation in vivo in a PKPD Model

Conclusions

• RAS cancers have high basal autophagy, and lesser greater autophagy in response to drug treatments.
• ULK kinase inhibitors represent a differentiated approach to autophagy inhibition, and add a new ‘class’ of potential opportunities for therapeutic development.
• DCC-3116 is a potent, selective, and tightly-binding inhibitor of ULK1/2.
• DCC-3116 inhibits ULK1/2-independent autophagic flux in vitro, and combination with MAPK inhibitors in inhibiting cancer cell growth.
• DCC-3116 has potent efficacy in vivo, and in combination with MEK inhibitors, DCC-3116 exhibits enhanced efficacy in vivo.

• Inhibiting autophagosomal autophagy in combination with MAPK pathway inhibitors, in providing a therapeutic approach for RAS mutant cancers.

• DCC-3116 warrants further study as an inhibitor of autophagy, and has been selected as a candidate for potential clinical development in the treatment of RAS mutant cancers.

References


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