DRUGGING AUTOPHAGY SUMMIT

Discovery of ULK1/2 inhibitor DCC-3116 for treatment of RAS-driven cancers

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Deciphera Pharmaceuticals

November 19-20, 2020

Disclosures

- I am a full-time employee and own stock/options in Deciphera Pharmaceuticals

Rationale for treatment of RAS mutant cancers with an ULK inhibitor

RAS mutant cancers depend on MEK/ERK signaling and autophagy for survival

- Treatment of *RAS* mutant cancer cells with MAPK pathway inhibitors leads to increased autophagy

ULK1 and ULK2 kinases are initiating factors for activation of autophagy

- First-in-class target opportunity for new therapeutic in *RAS* mutant cancers

DCC-3116 is a selective and potent ULK kinase inhibitor

- Properties designed for combination approach

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RAS Mutant Cancers Represent Significant Unmet Medical Need

RAS mutations are the most common activating mutations of all cancers

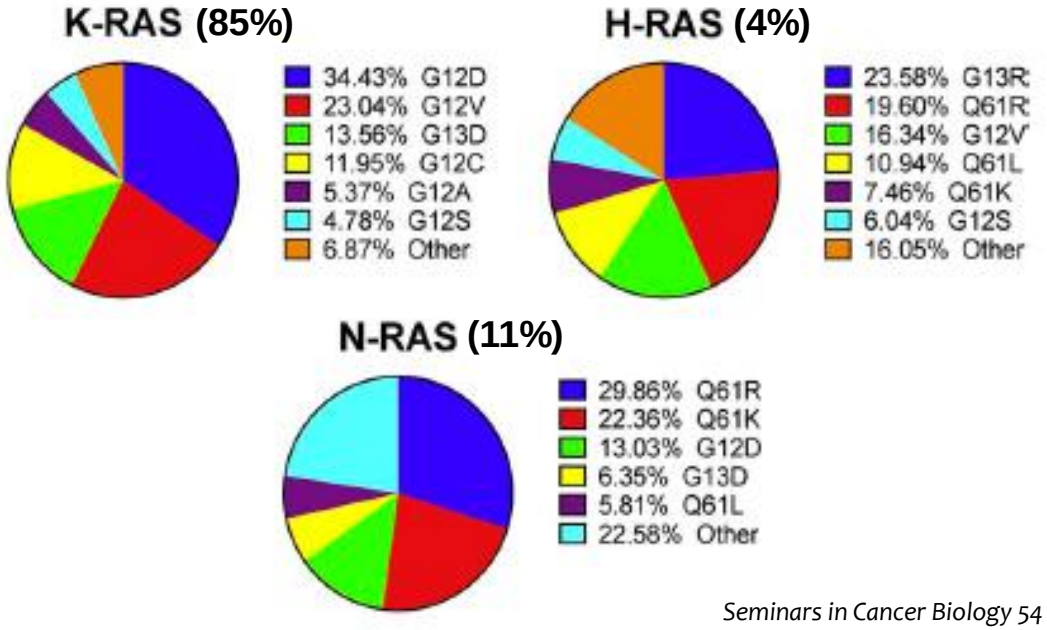
- Pancreatic: ~98%
- Colon: ~ 45%
- Lung: ~ 30%

RAS activates signaling through the MAPK (RAF-MEK-ERK) pathway and the Autophagy pathway

- Addressable by DCC-3116

Mutant BRAF cancers are also addressable by DCC-3116

MAPK inhibitors have not been successful thus far as single agents in RAS mutant cancers



Seminars in Cancer Biology 54 (2019) 138–148

RAS mutant cancers are addicted to autophagy

GENES & DEVELOPMENT 25:460–470

Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis

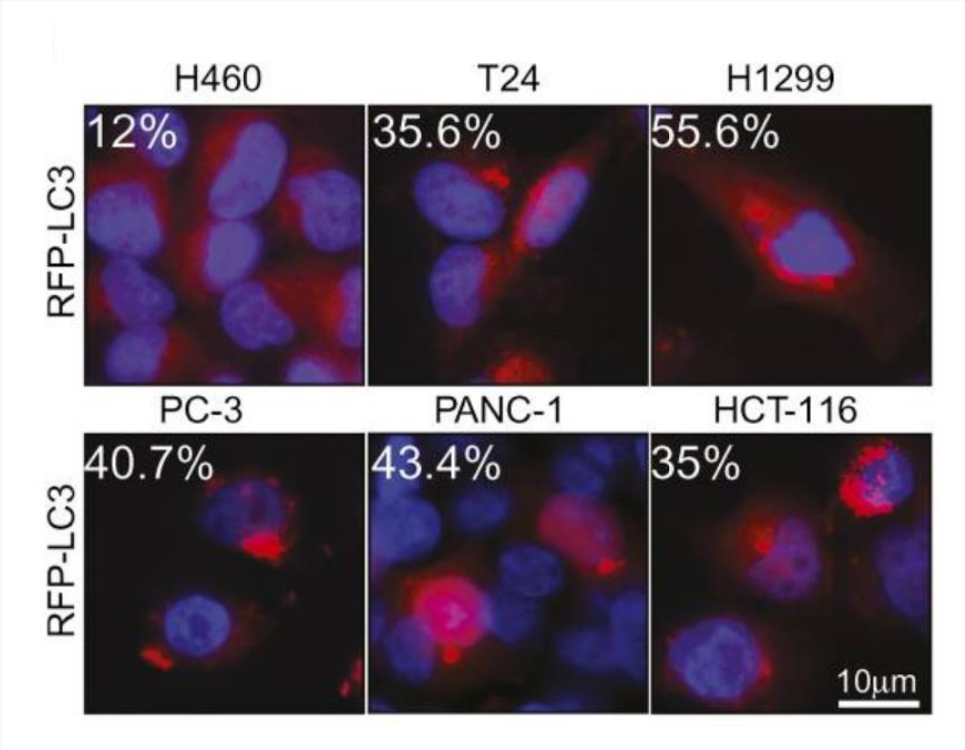
Jessie Yanxiang Guo,[1,2,3,8] Hsin-Yi Chen,[1,2,8] Robin Mathew,[1,4,8] Jing Fan,[5,8] Anne M. Strohecker,[1,4] Gizem Karsli-Uzunbas,[1,2] Jurre J. Kamphorst,[5] Guanghua Chen,[1,2] Johanna M.S. Lemons,[5] Vassiliki Karantza,[1,6] Hilary A. Coller,[1,7] Robert S. DiPaola,[1,6] Celine Gelinas,[1,3,4] Joshua D. Rabinowitz,[1,5] and Eileen White[1,2,4,9]

GENES & DEVELOPMENT 25:717–729

Pancreatic cancers require autophagy for tumor growth

Shenghong Yang,[1] Xiaoxu Wang,[1,11] Gianmarco Contino,[2,3,11] Marc Liesa,[4] Ergun Sahin,[5] Haoqiang Ying,[5] Alexandra Bause,[6,7] Yinghua Li,[1] Jayne M. Stommel,[5] Giacomo Dell'Antonio,[8] Josef Mautner,[9] Giovanni Tonon,[10] Marcia Haigis,[6,7] Orian S. Shirihai,[4] Claudio Doglioni,[8] Nabeel Bardeesy,[2] and Alec C. Kimmelman[1,12]

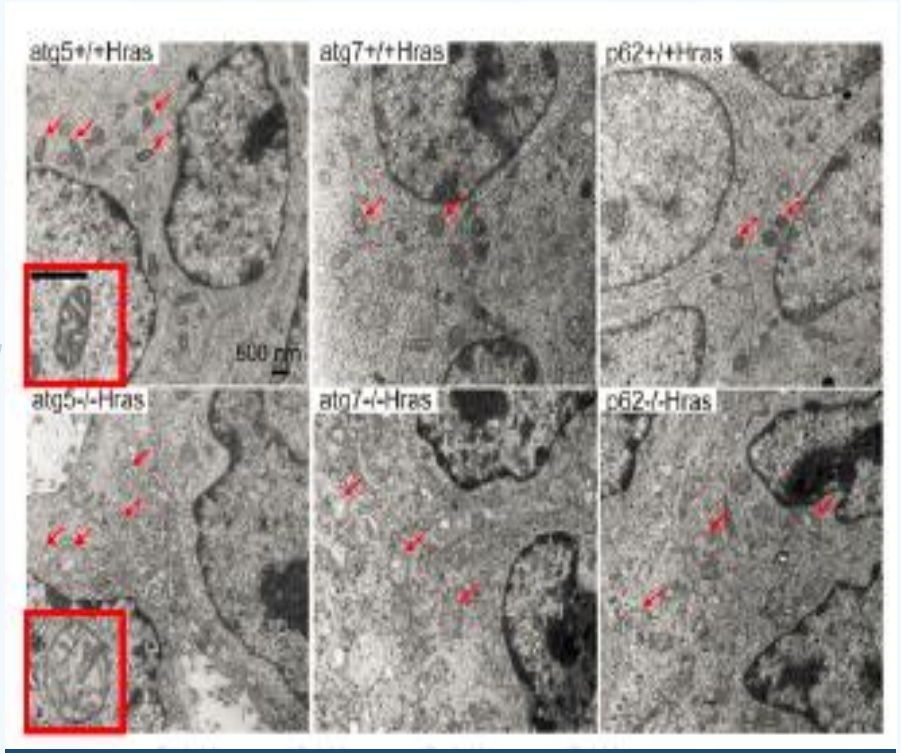
RAS Cancers Exhibit High Levels of Basal Autophagy



Evaluation of Cellular LC-3 Puncta

Competent Autophagy

Incompetent Autophagy



Swollen Mitochondria Accumulate in Cells where Autophagy is Blocked

Genes and Development 2011;25:460-70

RAS Cancers Exhibit Addiction to Autophagy as a resistance mechanism to MAPK inhibitor therapy

THREE 2019 PUBLICATIONS INDEPENDENTLY VALIDATE COMBINED INHIBITION OF MAPK & AUTOPHAGY PATHWAYS AS NEW TARGETED APPROACH FOR POTENTIAL IN RAS CANCERS

nature medicine

Letters

https://doi.org/10.1038/s41591-019-0367-9

Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers

Conan G. Kinsey[1,2], Soledad A. Camolotto[1], Amelie M. Boespflug[1,3,4], Katrin P. Gullien[1], Mona Foth[1], Amanda Truong[1], Sophia S. Schuman[1], Jill E. Shea[5], Michael T. Seipp[5], Jeffrey T. Yap[1,6], Lance D. Burrell[1], David H. Lum[1], Jonathan R. Whisenant[1,2], G. Weldon Gilcrease III[1,2], Courtney C. Cavalieri[1,7], Kaitrin M. Rehbein[1], Stephanie L. Cutler[1], Kajsa E. Affolter[1,8], Alana L. Welm[1,9], Bryan E. Welm[1,5], Courtney L. Scaife[1,5], Eric L. Snyder[1,8] and Martin McMahon[1,10]*

Articles

https://doi.org/10.1038/s41591-019-0368-8

Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer

Kirsten L. Bryant[1], Clint A. Stalnecker[1], Daniel Zeitouni[1], Jennifer E. Klomp[1], Sen Peng[2], Andrey P. Tikunov[3], Venugopal Gunda[4], Mariaelena Pierobon[5], Andrew M. Waters[1], Samuel D. George[1], Garima Tomar[1], Björn Papke[1], G. Aaron Hobbs[1], Liang Yan[6], Tikvah K. Hayes[7], J. Nathaniel Diehl[7], Gennifer D. Goode[4], Nina V. Chaika[4], Yingxue Wang[8], Guo-Fang Zhang[8], Agnieszka K. Witkiewicz[9], Erik S. Knudsen[10], Emanuel F. Petricoin III[5], Pankaj K. Singh[4], Jeffrey M. Macdonald[3], Nhan L. Tran[11], Costas A. Lyssiotis[12], Haoqiang Ying[6], Alec C. Kimmelman[13], Adrienne D. Cox[1,14,15] and Channing J. Der[1,7,15]*

PNAS

MAP kinase and autophagy pathways cooperate to maintain RAS mutant cancer cell survival

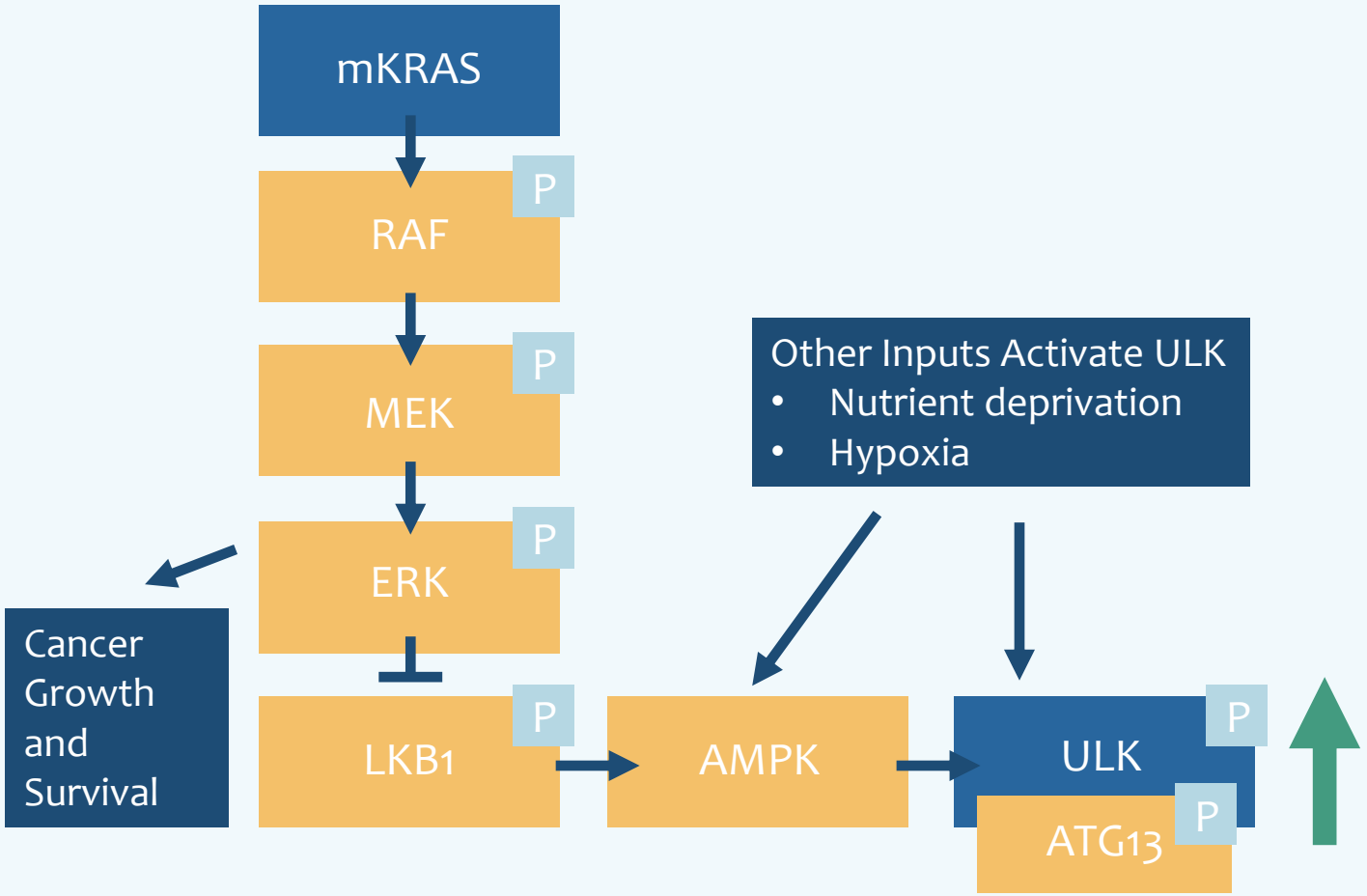
Chih-Shia Lee[a], Liam C. Lee[a,1], Tina L. Yuan[b,2], Sirisha Chakka[c,3], Christof Fellmann[d,4], Scott W. Lowe[d,e,f], Natasha J. Caplen[c], Frank McCormick[b,g,5], and Ji Luo[a,5]

[a] Laboratory of Cancer Biology and Genetics, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892; [b] Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA 94158; [c] Genetics Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892; [d] Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724; [e] Howard Hughes Medical Institute, Memorial Sloan Kettering Cancer Center, New York, NY 10065; f Department of Cancer Biology & Genetics, Memorial Sloan Kettering Cancer Center, New York, NY 10065; and Cancer Research Technology Program, Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Frederick, MD 21702

Edited by Ronald A. DePinho, University of Texas MD Anderson Cancer Center, Houston, TX, and approved December 17, 2018 (received October 18, 2018)

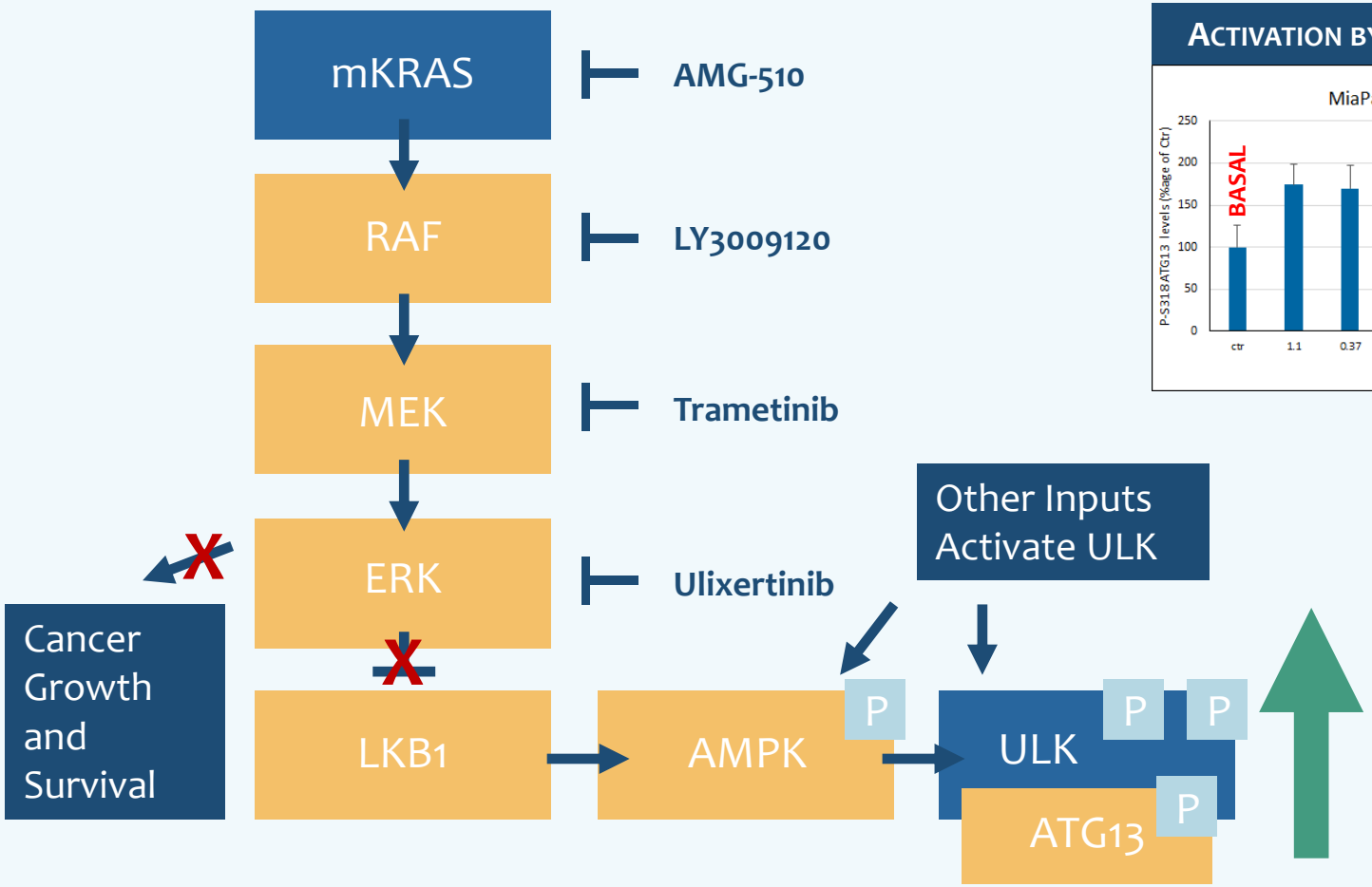
KRAS Activation Drives Tumor Growth and Tonic Regulation of ULK

ULK IS ACTIVE IN RAS MUTANT CELLS, YET SIGNALING THROUGH KRAS MEDIATES A GOVERNOR ON ULK

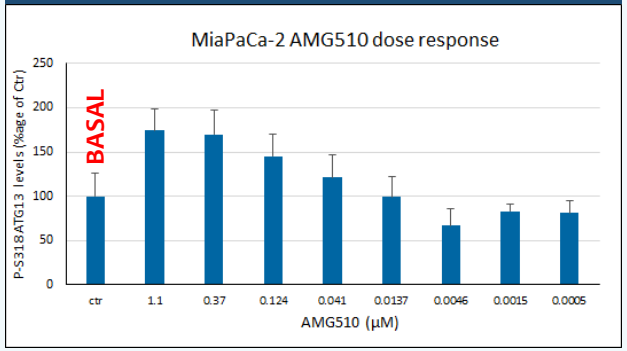


MAPK Pathway Inhibition Leads to Release of Tonic Inhibition of ULK

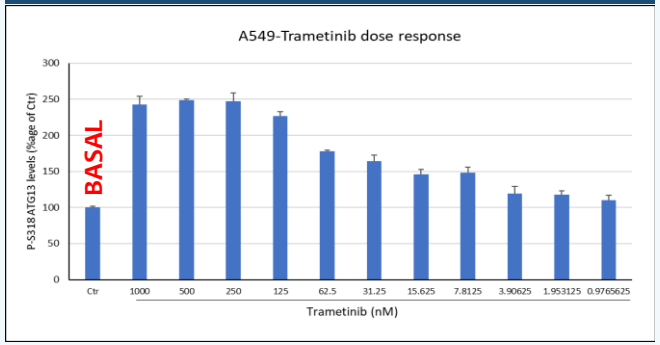
AUTOPHAGY IS A COMPENSATORY SURVIVAL MECHANISM IN MAPK PATHWAY INHIBITOR-TREATED RAS MUTANT CANCERS



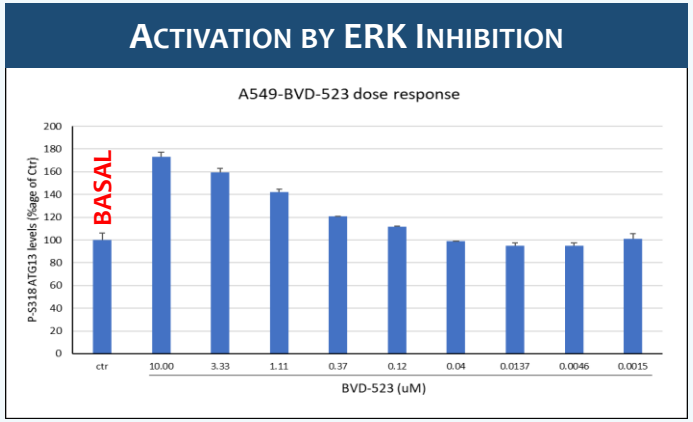
ACTIVATION BY KRAS G12C INHIBITION



ACTIVATION BY MEK INHIBITION



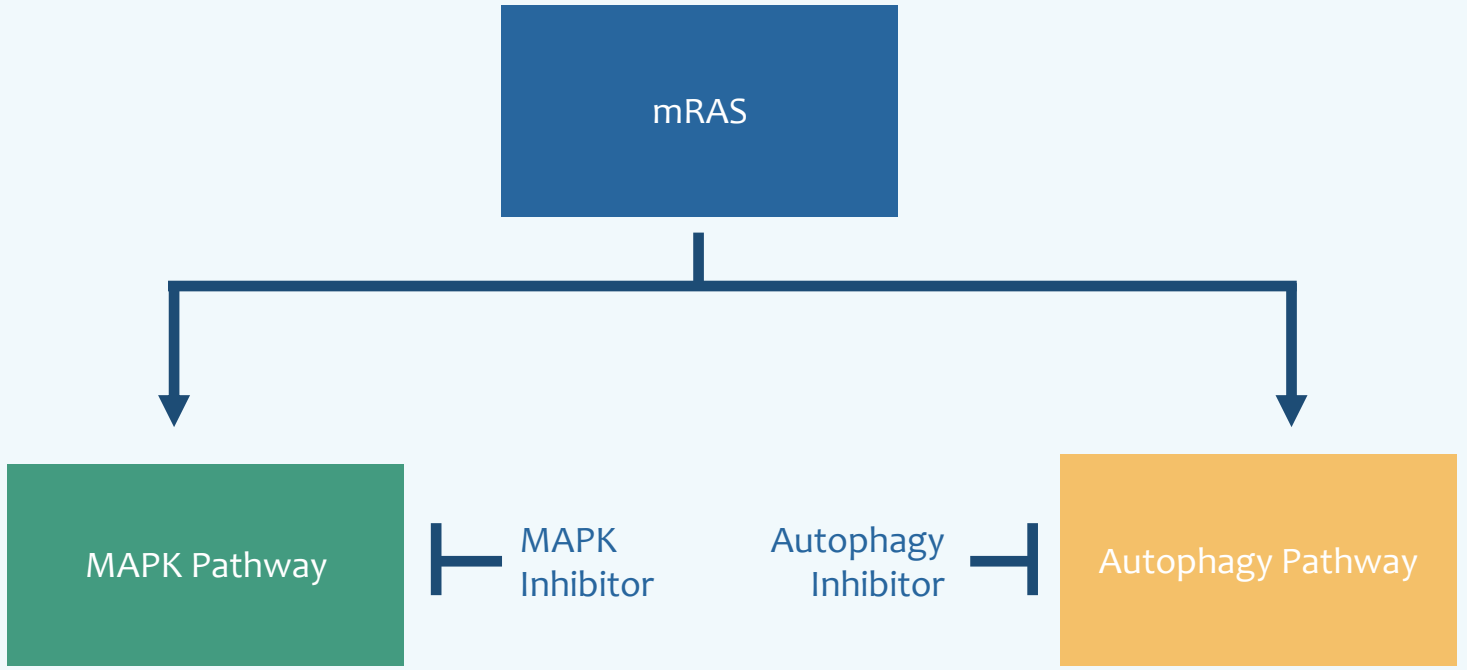
ACTIVATION BY ERK INHIBITION



A New Potential Approach to Potentially Treat RAS Cancers

INHIBITORS TARGETING BOTH EFFECTOR PATHWAYS DOWNSTREAM OF RAS SIGNALING

- mRAS cancers signal through the MAPK signaling pathway
- mRAS cancers are addicted to autophagy for survival
- A drug combination of a MAPK pathway inhibitor and an autophagy pathway inhibitor potentially targets all mRAS cancers (KRAS, NRAS, HRAS)

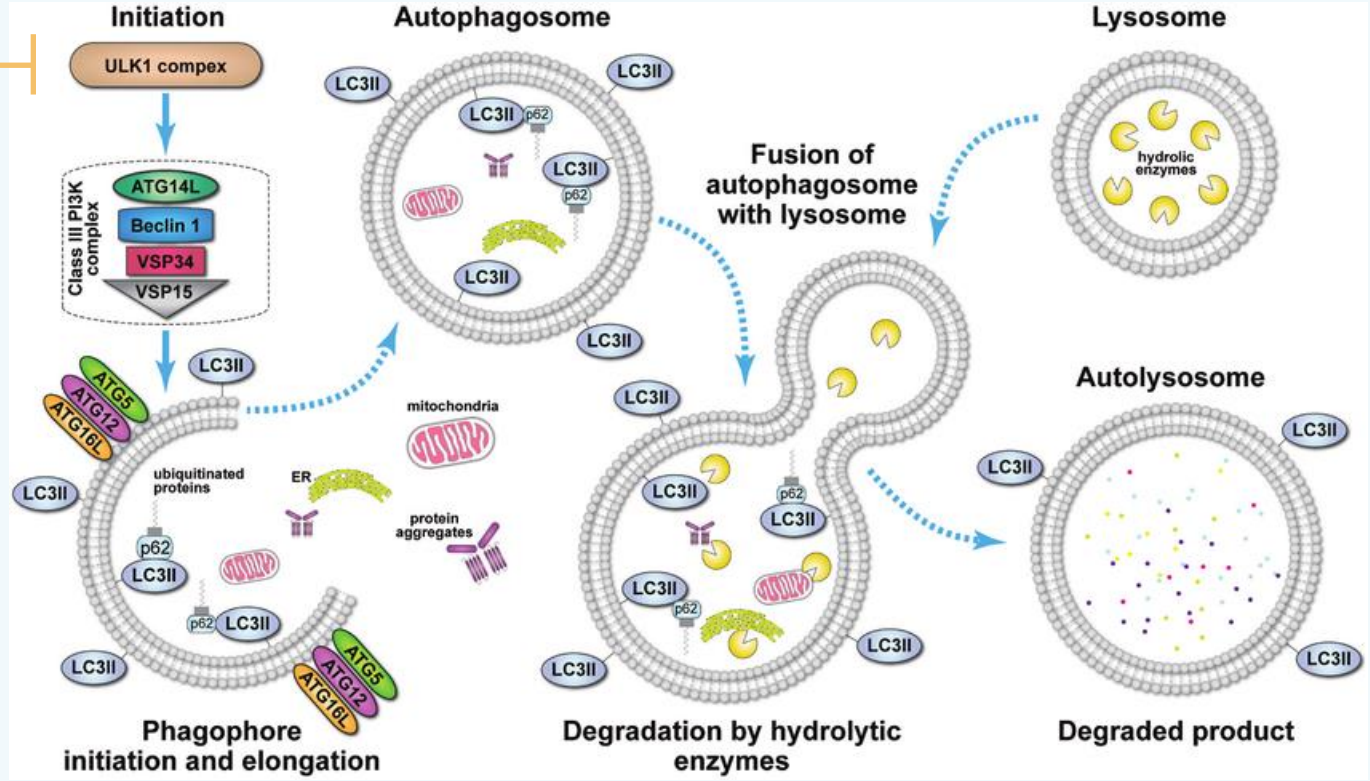


Strategies for Blocking Autophagy in Cancer

ULK Inhibition

- ULK is initiating factor of autophagy
- Druggable serine/threonine kinase
- Receives and processes key input from nutrient and stress sensors

DCC-3116



Adapted from: Ndoye A and Weeraratna AT. Autophagy- An emerging target for melanoma therapy [version 1]. F1000Research 2016, 5:1888. (doi: 10.12688/f1000research.8347.1)

DCC-3116 is a Potent & Selective ULK Inhibitor Designed to Inhibit Autophagy

Summary

Highly Potent (IC_{50} at 1 mM ATP)

- ULK1 4.7 nM
- ULK2 35 nM

Highly Selective

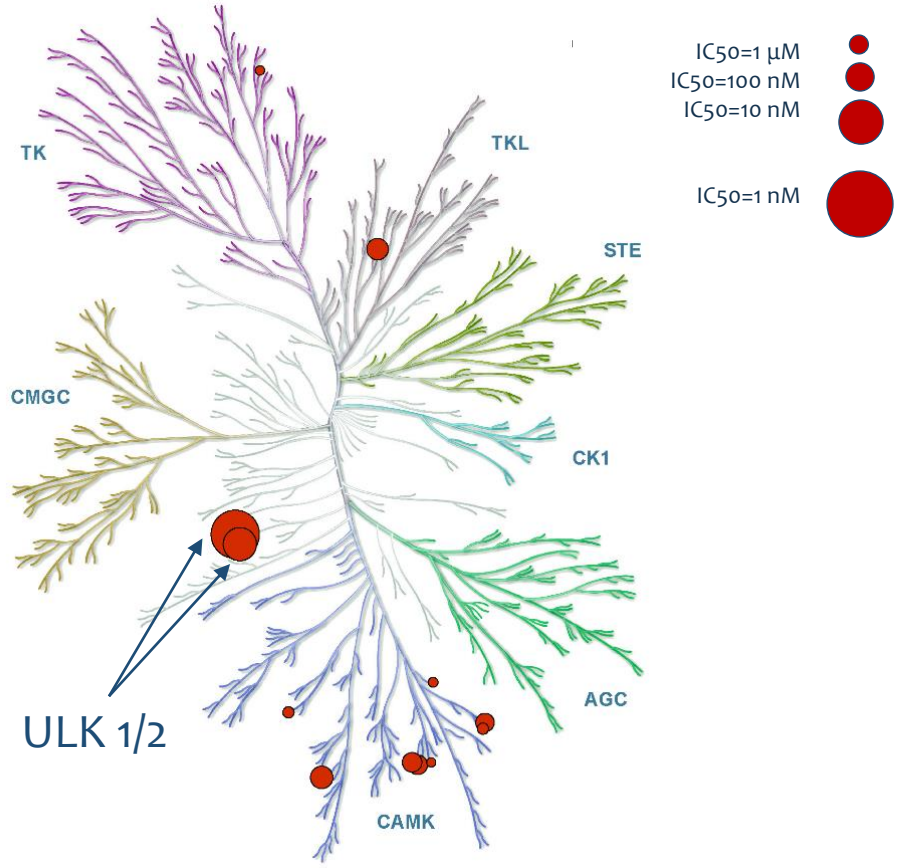
- No off-target kinases within 30-fold of ULK1
- Only 5 kinases within 100-fold of ULK1

Designed to avoid CNS exposure

- Low Ratio $Brain_{ff}/Plasma_{ff}$ (4.3%) to avoid CNS autophagy inhibition

IND Filing Expected Q4 2020/early Q1 2021

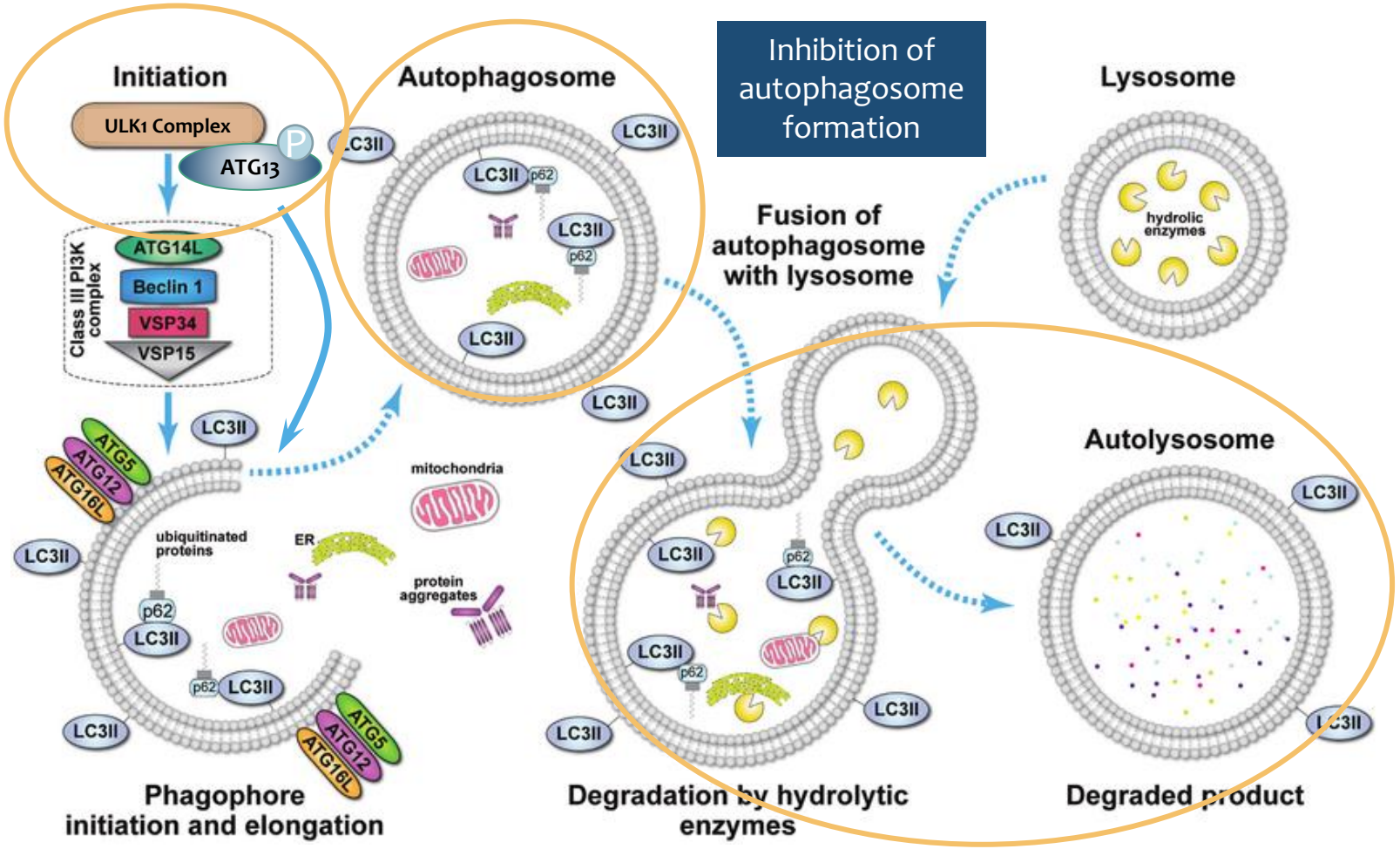
DCC-3116: A Selective ULK1/2 Inhibitor



Source and Notes: Composite of enzyme and cellular kinase phosphorylation data was used. The size of the red circle corresponds to the IC_{50} value obtained. No circles are plotted for kinases with IC_{50} > 1 µM; Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

DCC-3116 Inhibits Autophagy in Cellular Assays

Inhibition of ULK phosphorylation of substrate ATG13 in the presence of MAPKi

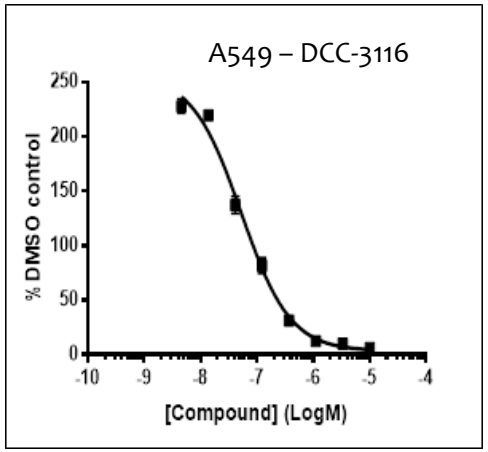


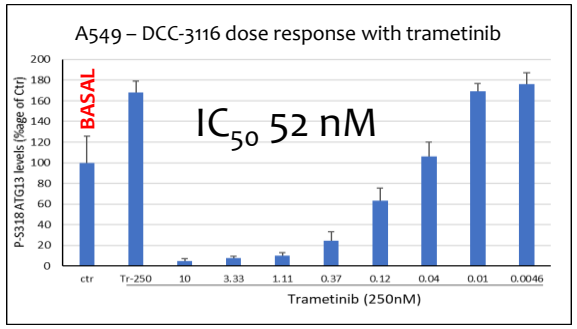
Inhibition of LC3 degradation

Ndoye A and Weeraratna AT. Autophagy- An emerging target for melanoma therapy [version 1]. F1000Research 2016, 5:1888. (doi: 10.12688/f1000research.8347.1)

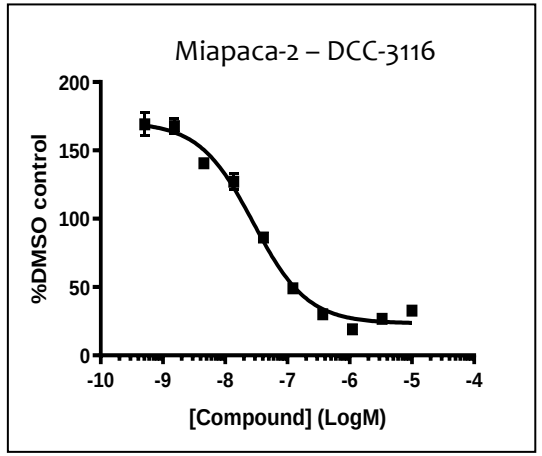
DCC-3116 Potently Inhibits ULK in Multiple RAS Mutant Cancer Cell Lines

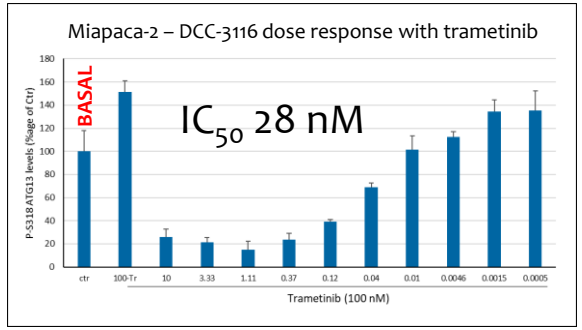
KRAS Lung Cancer



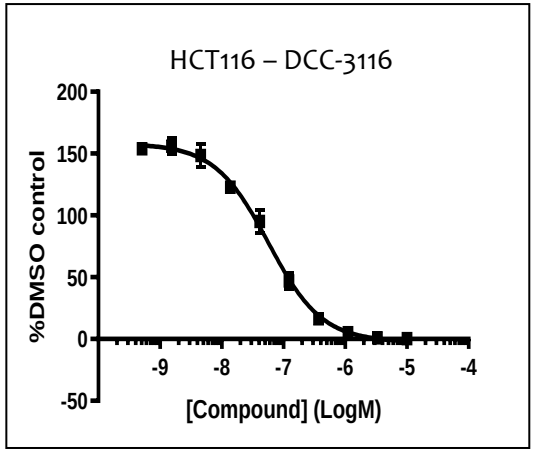


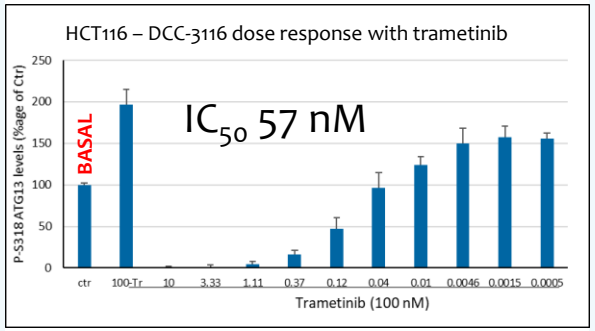
KRAS G12C Pancreatic Cancer



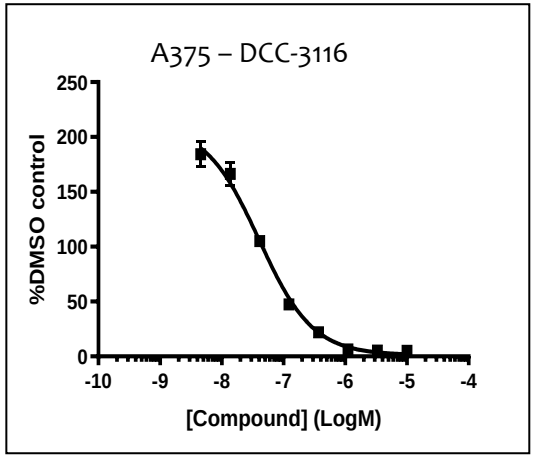


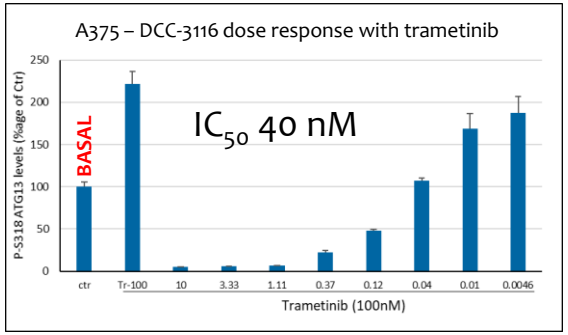
KRAS Colorectal Cancer





BRAF Melanoma Cancer

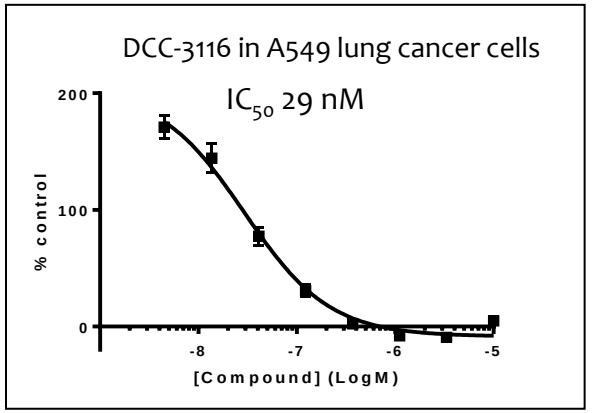


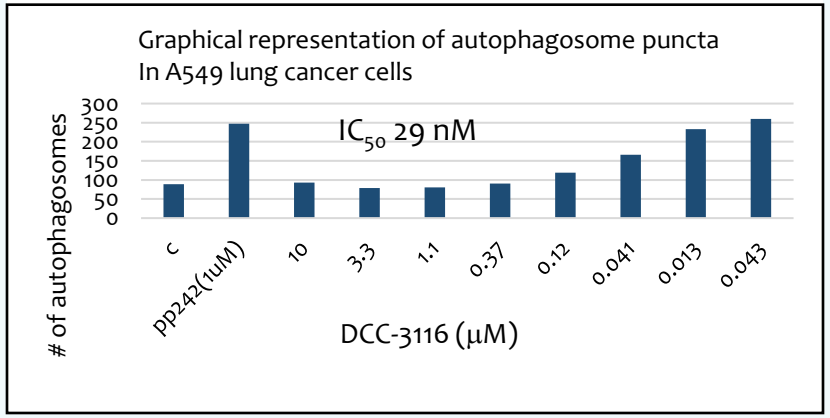


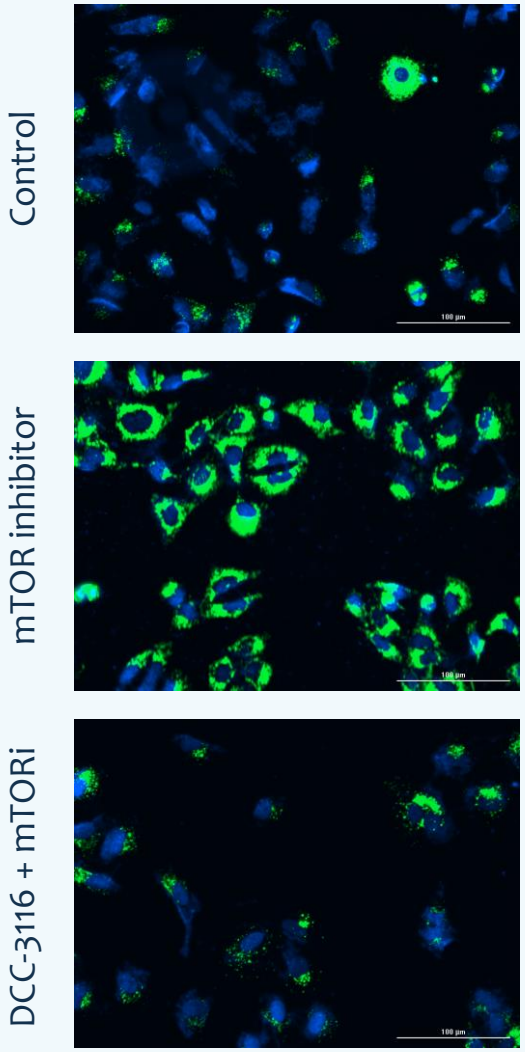
Basal and MAPK inhibitor-mediated compensatory increased autophagy are inhibited

DCC-3116 Inhibits Autophagosome Formation and Lysosomal Degradation in KRAS Mutant Cancer Cells *In Vitro*

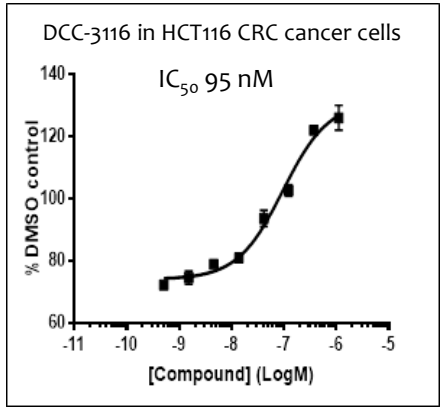
AUTOPHAGOSOME FORMATION INHIBITION

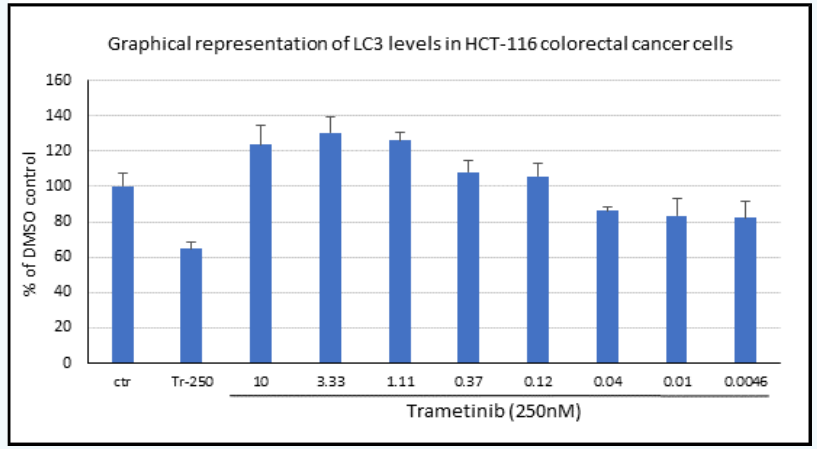






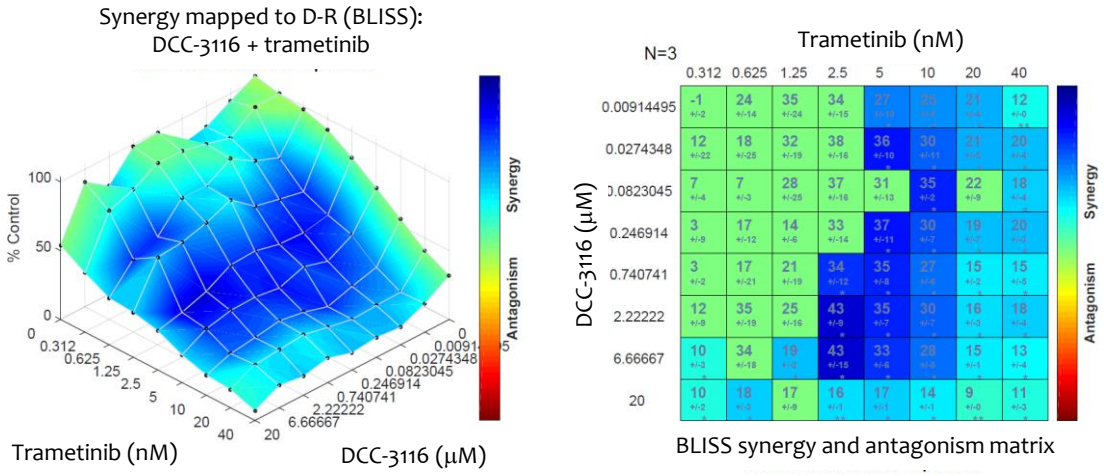
LC3 DEGRADATION INHIBITION





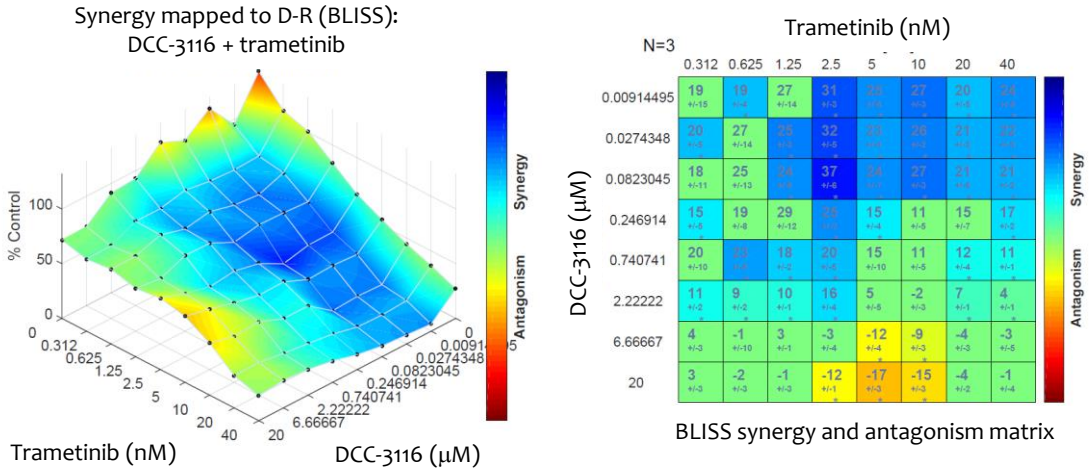
DCC-3116 + Trametinib Synergize to Inhibit Pancreatic Cancer Cell Proliferation *In Vitro*

Inhibition of cell proliferation in KRAS mutant MiaPaCa-2 pancreatic cancer cells



Strong synergy observed for various concentrations of DCC-3116 with trametinib combinations across the matrix

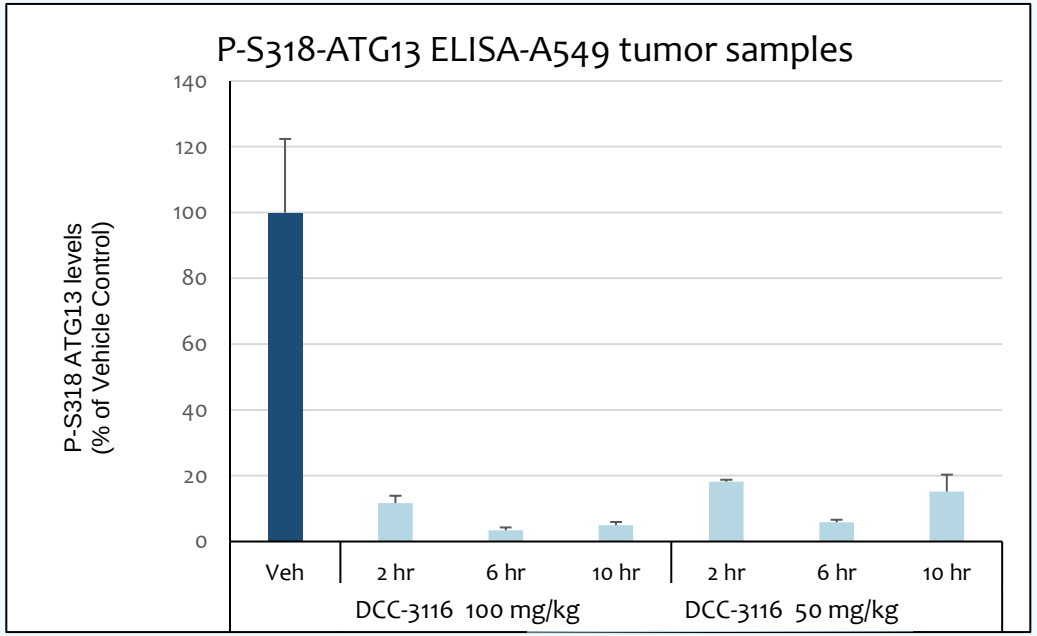
Inhibition of cell proliferation in BRAF mutant BxPC3 pancreatic cancer cells



Synergy at lower concentrations of DCC-3116 and across concentration range of trametinib

DCC-3116 Durably Inhibits ULK *In Vivo* in a KRAS Cancer PK/PD Model

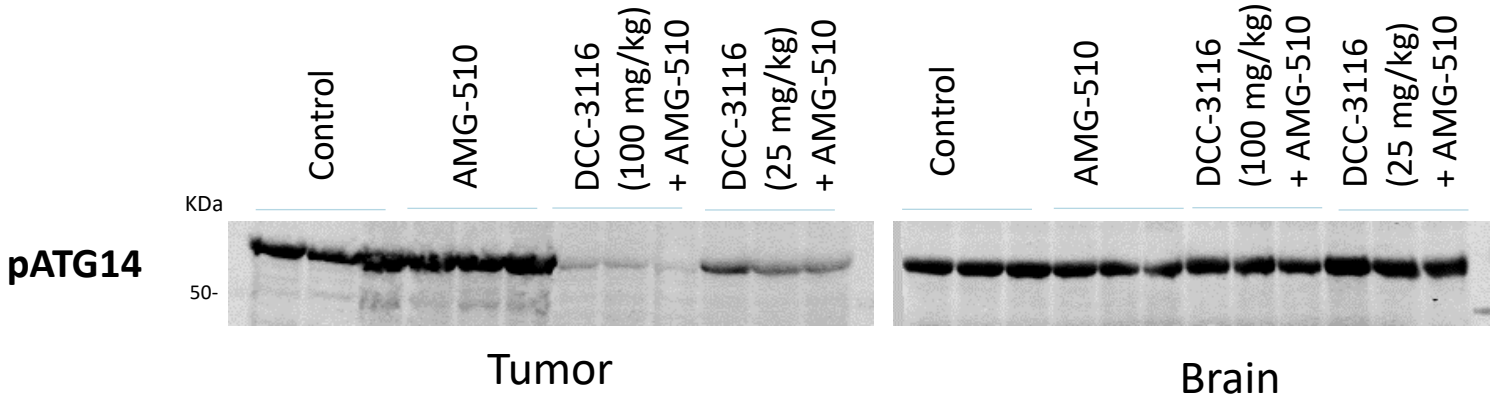
A549 Lung Cancer



	DCC-3116 100 mg/kg			DCC-3116 50 mg/kg		
	2 hr	6 hr	10 hr	2 hr	6 hr	10 hr
Free drug (nM)	9,542	7,058	8,017	7,643	5,140	1,715
% pATG13 inhibition	88	97	95	82	94	85

DCC-3116 spares autophagy signaling in brain tissue

- Phosphorylation of the ULK substrate ATG14 is easily detectable in tumor tissue and brain
- Tumor and brain samples from mouse studies confirm potent inhibition of ULK in peripheral tumors, but the absence of inhibition of ULK in the brain (confirming that DCC-3116 has low brain penetration, as designed).



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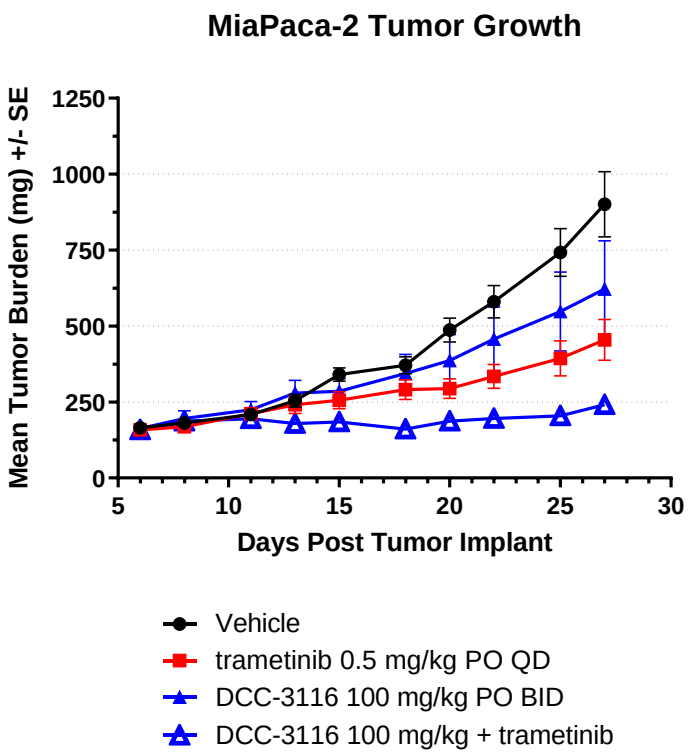
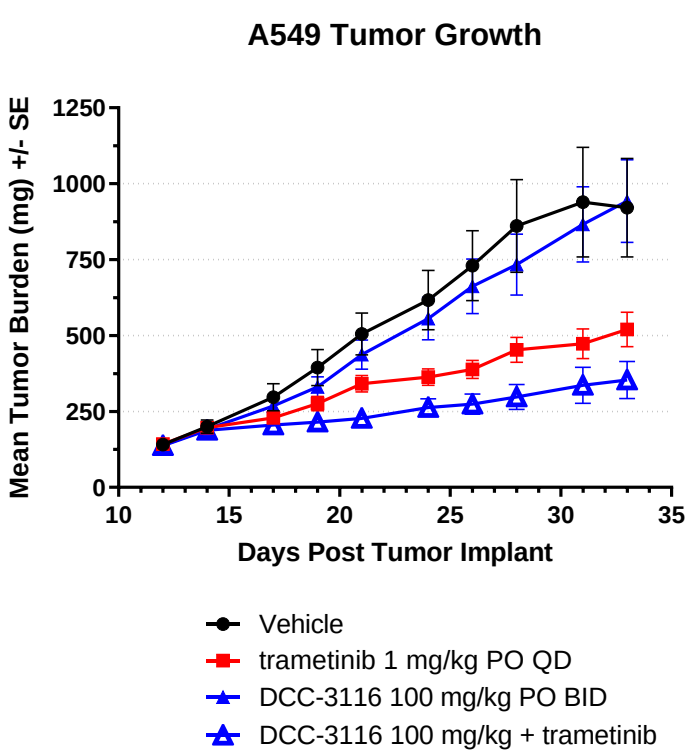
DCC-3116 + MEK inhibitor exhibited reduced tumor growth in vivo

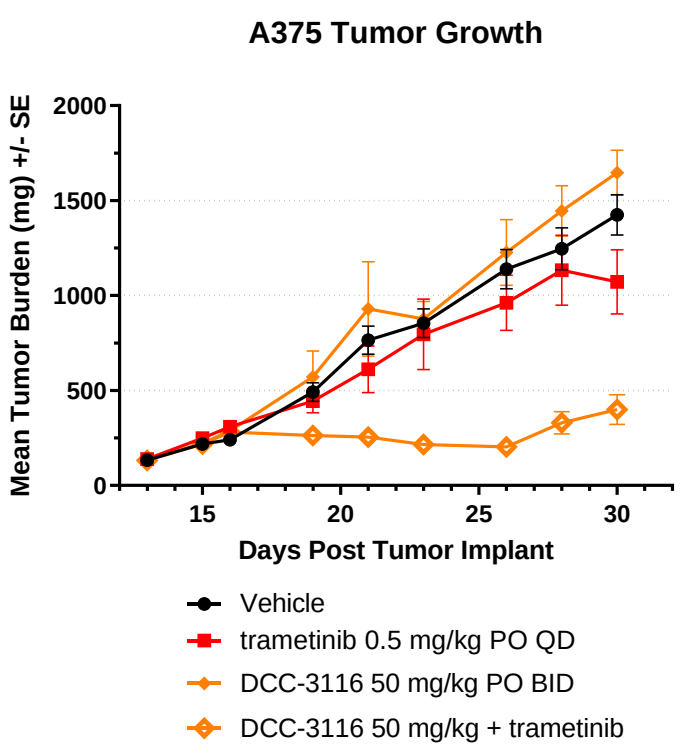
KRAS mutant pancreatic



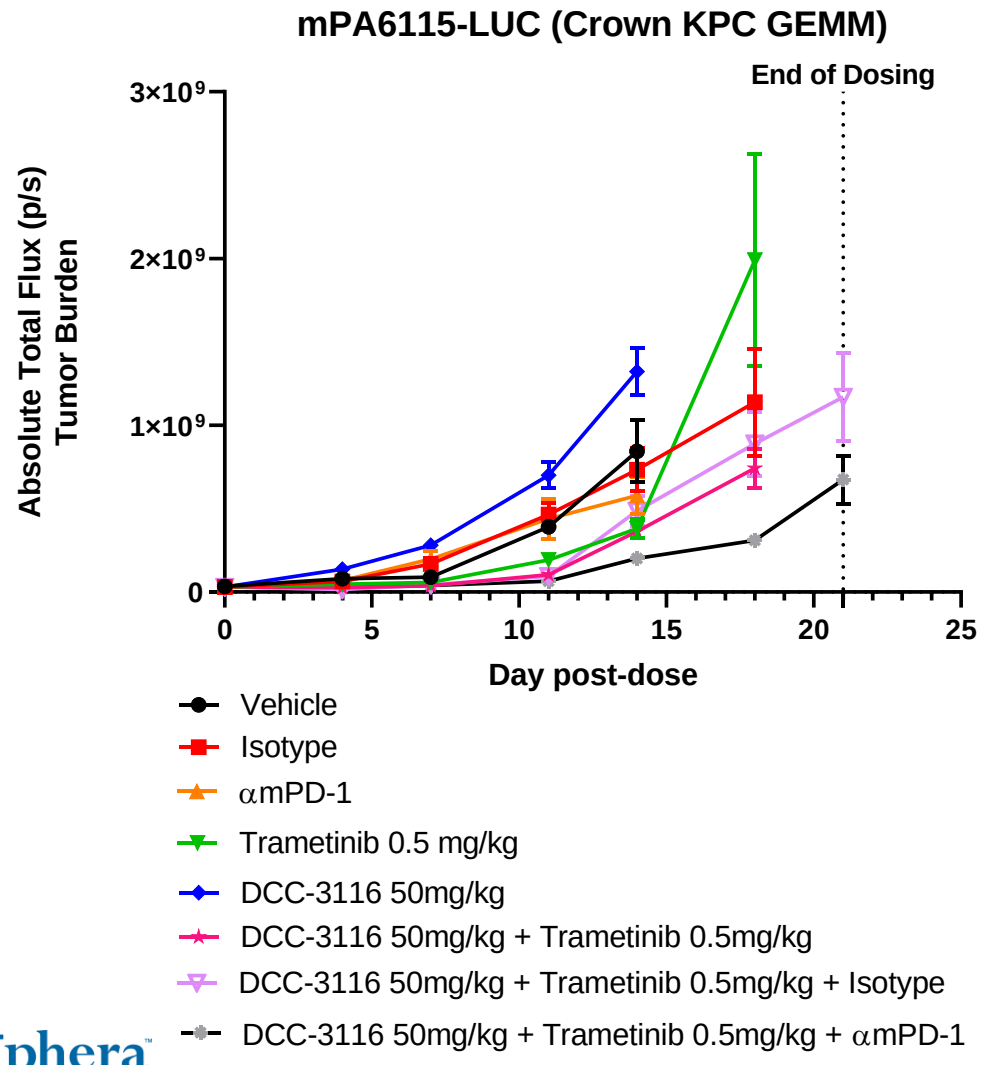
KRAS mutant lung

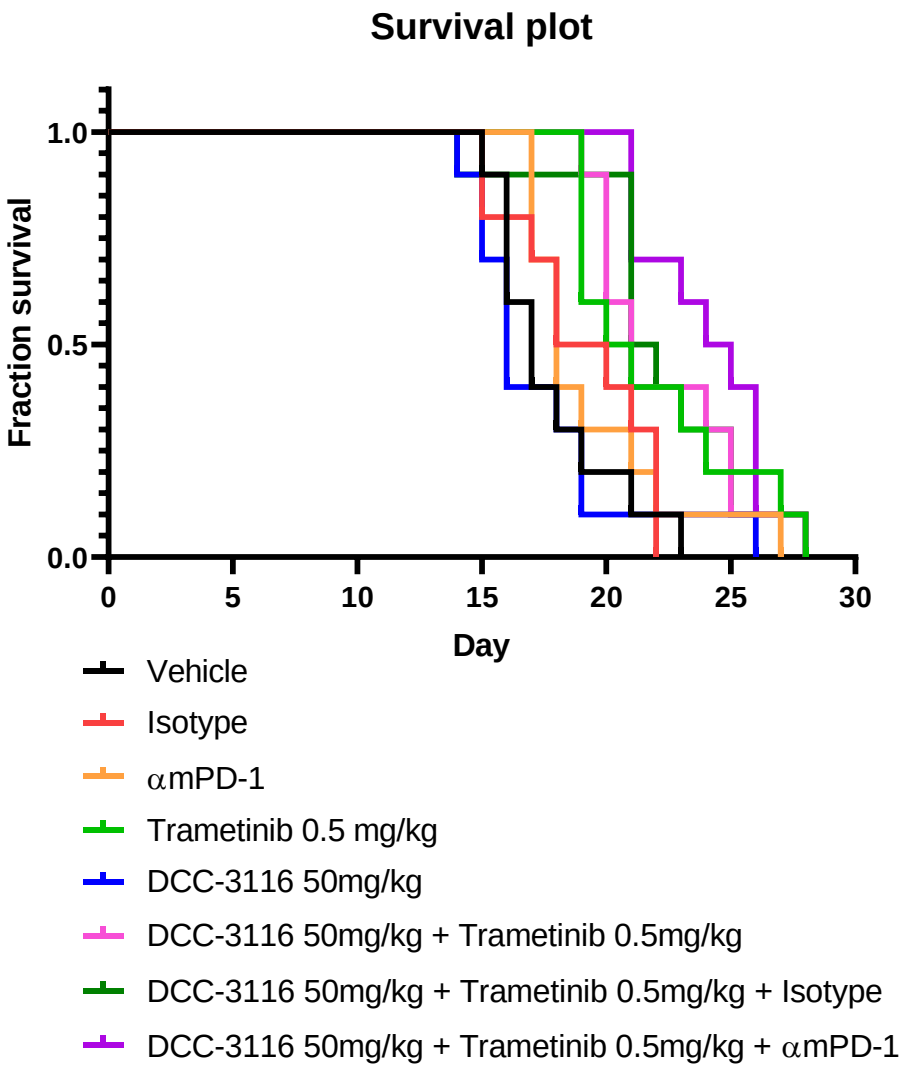


BRAF mutant melanoma



DCC-3116 exhibits efficacy in combination with Trametinib and anti-PD1 in KPC syngeneic pancreatic cancer model





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Rationale for Treatment of Mutant RAS Cancers with DCC-3116

Mutant RAS cancers depend on MEK/ERK signaling and autophagy for survival

- ULK kinase is an initiating factor for activation of autophagy

DCC-3116 is a potential first-in-class ULK kinase inhibitor

- Highly selective and potent inhibitor of ULK kinase
- Designed for combination approach

Strong preliminary preclinical validation

- DCC-3116 inhibits autophagy in RAS mutant cancer cells
- DCC-3116 potently and durably inhibits autophagy *in vivo*
- Combination of DCC-3116 plus MAPK pathway inhibitors block *RAS* mutant cancer growth *in vivo*

Acknowledgements

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Martin McMahon (U. Utah)

Thank You

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