One Mission, Inspired by Patients: Defeat Cancer.™

April 18, 2023

decīphera®

OPENING REMARKS

Steve Hoerter

President and Chief Executive Officer

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DECIPHERA

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Forward-Looking Statements

This presentation may contain forward-looking statements that are based on our current expectations, estimates and projections about our industry, our operations and financial performance, as well as management's beliefs and assumptions. Words such as "anticipates," "expects," "intends," "plans," "believes," "seeks," "estimates," "may," "will," and variations of these words or similar expressions are intended to identify forward-looking statements. Such forward-looking statements are subject to various risks and uncertainties, including important factors that could cause actual outcomes or results to differ materially from those indicated in these statements. These statements include, without limitation, the potential for our pre-clinical and/or clinical stage pipeline assets to be first-in-class and/or best-in-class treatments, plans to continue our geographic expansion of QINLOCK in Key European markets, our planned Phase 3 INSIGHT clinical study of QINLOCK versus sunitinib in second-line GIST patients with mutations in KIT exon 11 and 17/18, our expectations regarding the aggregate potential revenue opportunity for QINLOCK, our ability to expand the market opportunity for QINLOCK in second-line GIST in our INSIGHT Phase 3 study; the vimseltinib enrollment and topline readout for the pivotal Phase 3 MOTION study and phase 1/2 study of vimseltinib, each in TGCT patients; updated data from the dose escalation phase and initial data from the combination dose escalation cohorts of the Phase 1 study of DCC-3116, plans to initiate one or more combination cohorts in the Phase 1/2 study of DCC-3116, plans to initiate new combination studies with ripretinib in patients with GIST and encorafenib and cetuximab in patients with colorectal cancer, plans to present additional preclinical data for DCC-3116, the potential for our autophagy program to be a multi-billion dollar opportunity; submitting an IND for DCC-3084, presenting preclinical data for DCC-3084; nominating additional development candidates from our proprietary discovery engine of novel switch control inhibitors; submitting an IND for DCC-3009 in the second half of 2024; clinical studies including status, progress and results, timing for clinical data readouts, planning efforts for future clinical studies, NDA/MAA (and equivalent) filings and potential additional approvals, research and discovery efforts including the potential of our drug candidates, IND filings, regulatory designations and programs, timing and likelihood of success, plans and objectives of management for future operations, estimated patient populations, the market opportunity for our drug and drug candidates and business guidance, including discovery, clinical and regulatory milestones, cash guidance, expectation regarding our financial performance and business strategy, and the potential impact of the Inflation Reduction Act (the IRA), speak only at the time this presentation was prepared. Such statements are based upon the information available to us now and are subject to change. We will not necessarily inform you of such changes. These statements are not guarantees of future performance and are subject to certain risks, uncertainties and assumptions that are difficult to predict. Therefore, actual results could differ materially and adversely from those expressed in any forward-looking statements as a result of various factors, including, among others, the success of our commercialization efforts with respect to QINLOCK, including our launch in key European markets, our limited experience as a commercial company, our ability to obtain, or any delays in obtaining, required regulatory approvals for our drug and drug candidates, our reliance on sole source third-party suppliers, our exposure to criminal sanctions, civil penalties, contractual damages, reputational harm, and diminished profits and future earnings from our relationships with customers and third-party payors that are subject to applicable anti-kickback, fraud and abuse, and other healthcare laws and regulations, and health information privacy and security laws, our failure to obtain or maintain adequate coverage and reimbursement for new or current products, recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our drug candidates, the potential for QINLOCK or any current drug candidates, such as vimseltinib and DCC-3116, or future drug candidates, if successfully developed and approved, to cause undesirable side effects that limit the commercial profile or result in other significant negative consequences for approved products or delay or prevent further development or regulatory approval with respect to drug candidates or new indications, or cause regulatory authorities to require labeling statements, such as boxed warnings, our competition may discover, develop, or commercialize products before or more successfully than we do, our estimates for market opportunities for our approved drug and drug candidates, market acceptance by physicians, patients, third-party payors, and others in the medical community of QINLOCK, and of any future approved drugs, such as vimseltinib or DCC-3116, if approved, our failure to obtain additional marketing approvals in other foreign jurisdictions, the potential for ongoing enforcement of post-marketing requirements for QINLOCK and any drug candidate for which we obtain marketing approval to subject us to substantial penalties, including withdrawal of QINLOCK or any future approved product from the market, if we fail to comply with all regulatory requirements, our assumptions in connection with the market opportunity for the INSIGHT trial patient population including the aggregate potential revenue opportunity for QINLOCK, our ability to complete, and the costs and timing of completing, the development and commercialization of our drug and drug candidates, our success in enrolling patients in clinical trials, including in our clinical trials of vimseltinib or DCC-3116, the potential for serious adverse events or unacceptable side effects to be identified during the development of our drug or drug candidates, our ability to obtain or, if granted, retain orphan drug exclusivity for our drug or drug candidates; our incurrence of significant operating losses since our inception and our expectation that we will incur continued losses for the foreseeable future and may never achieve or maintain profitability, our ability to raise capital when needed, our reliance on third parties to conduct our clinical trials and preclinical studies, our reliance on third parties for the manufacture of our drug candidates for preclinical testing and clinical trials, and for the manufacture of QINLOCK for commercialization and clinical trials, and our ability to enforce our intellectual property rights throughout the world. New risk factors and uncertainties may emerge from time to time, and it is not possible to predict all risk factors and uncertainties. There can be no assurance that the opportunity will meet your investment objectives, that you will receive a return of all or part of such investment. Investment results may vary significantly over any given time period. The appropriateness of a particular investment or strategy will depend on an investor's individual circumstances and objectives. Investors should independently evaluate specific investments. For further information regarding these risks, uncertainties and other factors, you should read the "Risk Factors" section of Deciphera's Annual Report on Form 10-K for the quarter and year ended December 31, 2022 filed with the Securities and Exchange Commission (the "SEC"), and Deciphera's other SEC filings.

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AACR ANNUAL MEETING 2023 INVESTOR EVENT AGENDA

Opening Remarks	**Steve Hoerter** *President and Chief Executive Officer*
Our Switch-Control Platform	**Dan Flynn, Ph.D.** *Chief Scientific Officer and Founder*
Pan-RAF (DCC-3084)	**Stacie Bulfer, Ph.D.** *Sr. Director, Biological Sciences*
ULK (DCC-3116)	**Madhumita Bogdan, Ph.D.** *Sr. Principal Investigator, Biological Sciences*
Pan-KIT (DCC-3009)	**Bryan Smith, Ph.D.** *Vice President, Biological Sciences*
GCN2 (DP-9149)	**Gada Al-Ani, Ph.D.** *Sr. Principal Investigator, Biological Sciences*
Closing Remarks	**Steve Hoerter** *President and Chief Executive Officer*
Q&A	

Notes: GCN2=general control nonderepressible 2; KIT=KIT proto-oncogene receptor tyrosine kinase; RAF=rapidly accelerated fibrosarcoma; ULK=unc-51-like autophagy-activating kinase.

DECIPHERA

ONE MISSION, INSPIRED BY PATIENTS: DEFEAT CANCER™

Executing on our mission to discover, develop, and commercialize important new medicines to **improve the lives of people with cancer.**

Over $1 Billion	**Peak Worldwide Sales** Potential for QINLOCK® (ripretinib) and Vimseltinib
Two Phase 3 Programs	**MOTION Top-line Data** and INSIGHT Initiation Planned for 2023
Potential First-in-Class Autophagy Program	**Multi-billion Dollar Opportunity** Targeting Autophagy
Proven Discovery Engine	**High-Value Research Pipeline** of Switch-Control Kinase Inhibitors

DECIPHERA

STRATEGIC PRIORITIES FOR 2023

QINLOCK® (ripretinib)

- Initiate INSIGHT Phase 3 study in 2L KIT exon 11+17/18 GIST patients
- Drive continued 4L adoption in US and expansion in key European markets

Vimseltinib

- Announce top-line results from the MOTION Phase 3 study
- Present longer-term follow up from Phase 1/2 study

DCC-3116

- Initiate one or more MEK/G12C expansion cohorts in the Phase 1/2 study
- Initiate new combination study with encorafenib/cetuximab and with ripretinib

DCC-3084

- Submit IND to FDA

Proprietary Drug Discovery Platform

- Nominate development candidate for pan-KIT inhibitor (DCC-3009)

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Notes: 2L=second-line; 4L=fourth-line; FDA=U.S. Food and Drug Administration; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; GIST=gastrointestinal stromal tumor; IND=Investigational New Drug Application; KIT=KIT proto-oncogene receptor tyrosine kinase; MEK=mitogen-activated extracellular signal-regulated kinase.

OUR SWITCH-CONTROL PLATFORM

Dan Flynn, Ph.D.

Chief Scientific Officer and Founder

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DECIPHERA IS A LEADER IN KINASE BIOLOGY

Two Decades of Pioneering Research in Kinase Biology

Novel Library of Switch Control Inhibitors

decīphera®

Proven Track Record of Advancing Novel Drug Candidates from Research to the Clinic and to Patients

Focused Investment in Next Gen Research Programs to Provide First- or Best-in-Class Treatments

SOLVING THE LIMITATIONS OF CLASSICAL KINASE INHIBITORS

High Kinome Selectivity

Ability to Target Broad Spectrum of Kinase Mutations

Hinders Development of Mutational Resistance

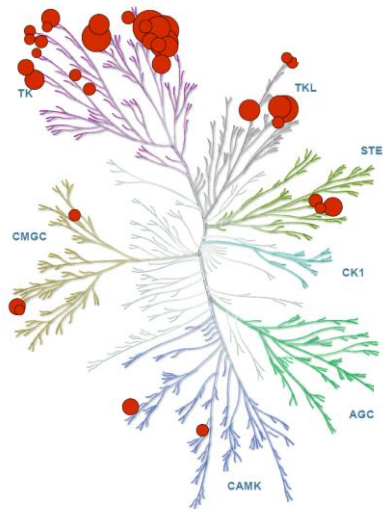
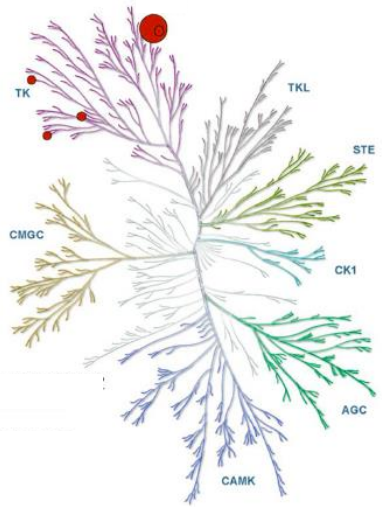
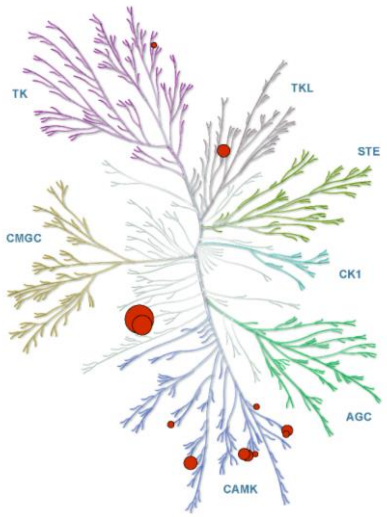
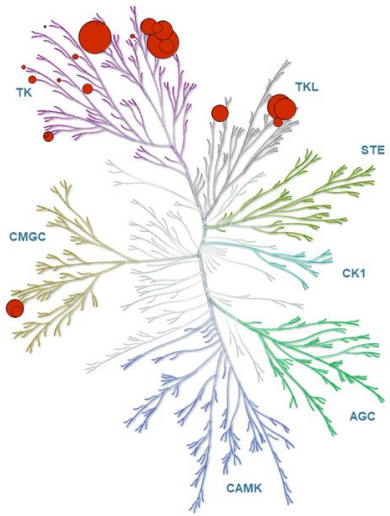
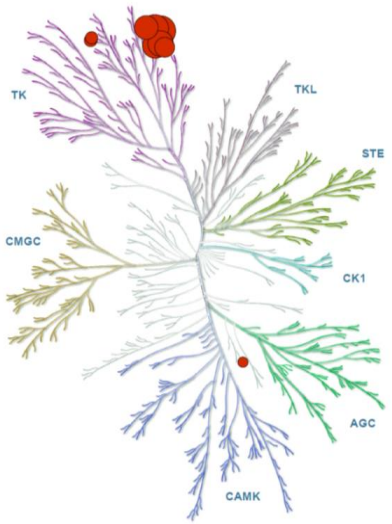
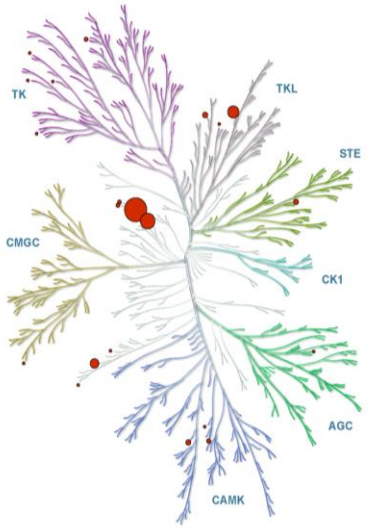
Extended Residency Times (Measured in Hours, Not Minutes)

High Cellular Potency (Cellular ATP Levels do not Compete)

Alternative Manipulation of Switches to Activate Kinases

Notes: ATP=Adenosine Triphosphate.

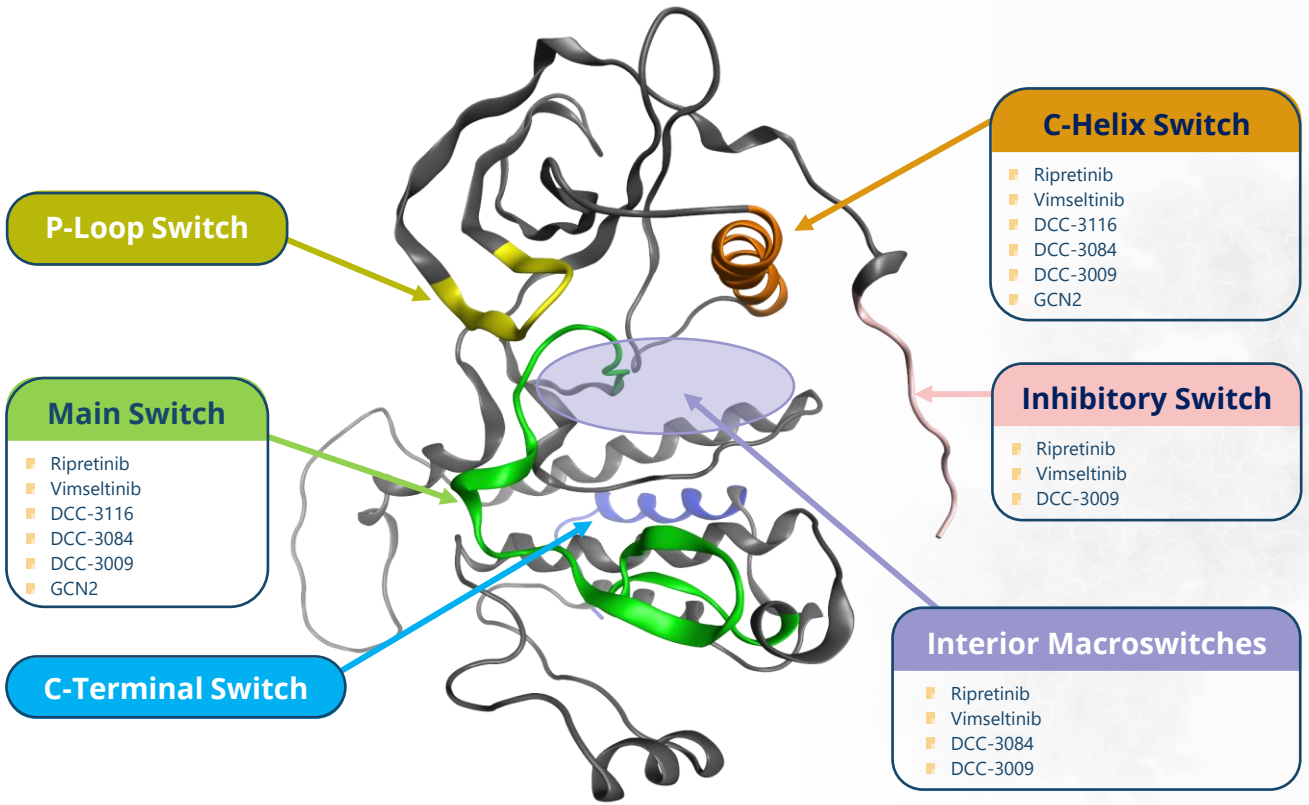
SWITCH CONTROL PLATFORM ALLOWS FOR DESIGN OF HIGHLY SELECTIVE DRUG CANDIDATES

QINLOCK KIT Inhibitor	**VIMSELTINIB** CSF1R Inhibitor	**DCC-3116** ULK Inhibitor	**DCC-3084** Pan-RAF Inhibitor	**DCC-3009** Pan-KIT Inhibitor	**DP-9149** GCN2 Activator
					

Notes: CSF1R=colony-stimulating factor 1 receptor; GCN2=general control nonderepressible 2; KIT=KIT proto-oncogene receptor tyrosine kinase; RAF=rapidly accelerated fibrosarcoma; ULK=unc-51-like autophagy-activating kinase.

DESIGNING MOLECULES TO INTERACT WITH THE KINASE SWITCH REGION

Kinase Switch Regions for Regulation and Activation

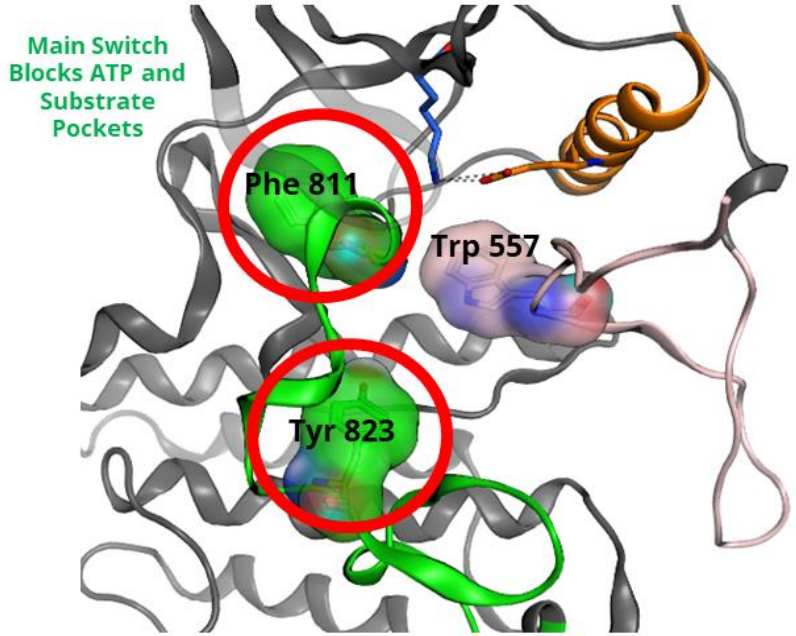


- Kinases are regulated by changes in their shapes controlled by various switch regions
- Unlike classical approaches to kinase inhibition, Deciphera's approach does not focus on binding into a pocket
- Deciphera's candidates bind to Switch Control Amino Acids to prevent kinase activation
- We take advantage of variation in the Switch Control Amino Acid environment to design highly specific molecules

Notes: GCN2=general control nonderepressible 2.

DUAL SWITCH KIT RECEPTOR TYROSINE KINASE ORCHESTRATES SHAPE CHANGES THAT REGULATE KINASE ACTIVITY

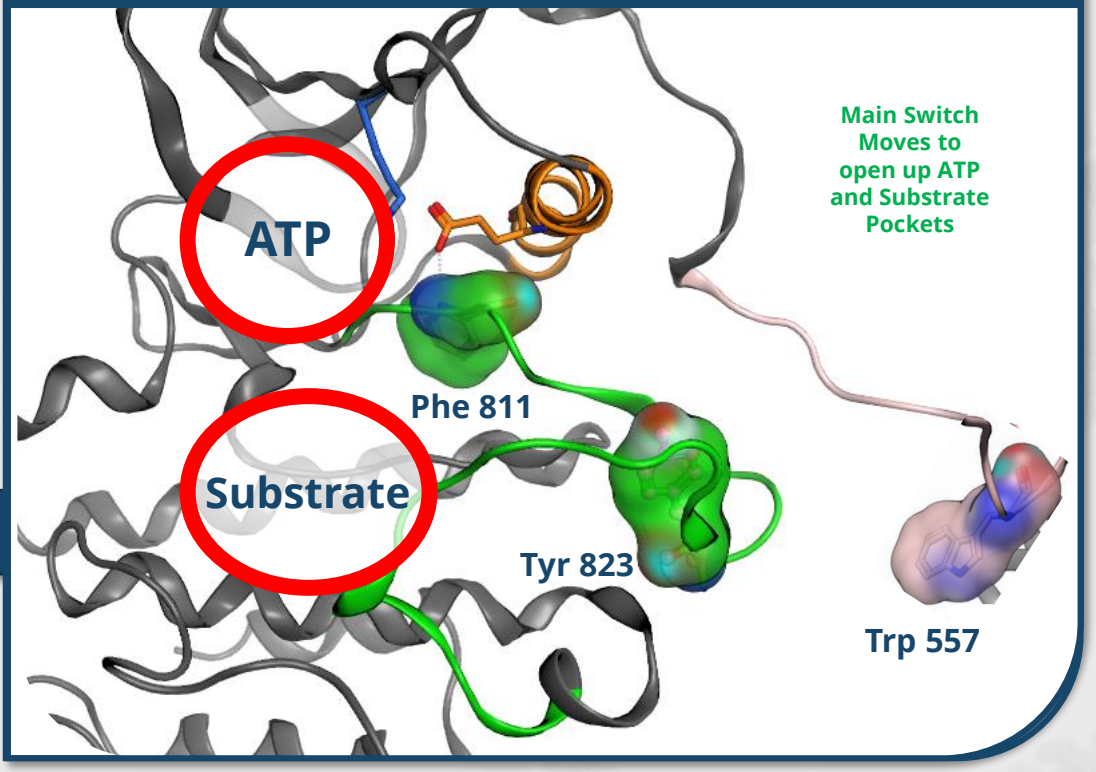
Main Switch in "OFF" State



Turn "ON"

Turn "OFF"

Main Switch in "ON" State



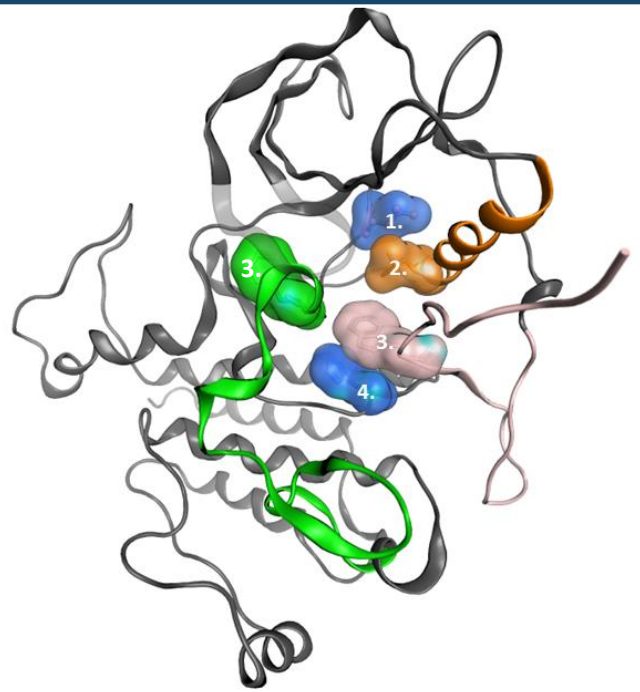
Notes: Chan et al, Mol Cell Biol. (2003) 23(9): 3067-78; ATP=Adenosine Triphosphate; KIT=KIT proto-oncogene receptor tyrosine kinase; Phe=phenylalanine; Trp=tryptophan; Tyr=tyrosine.

Green: Main Switch
Gold: C-Helix Switch
Salmon: Inhibitory Switch

RIPRETINIB SOLVES FOR LOSS OF KIT INHIBITORY SWITCH IN GIST

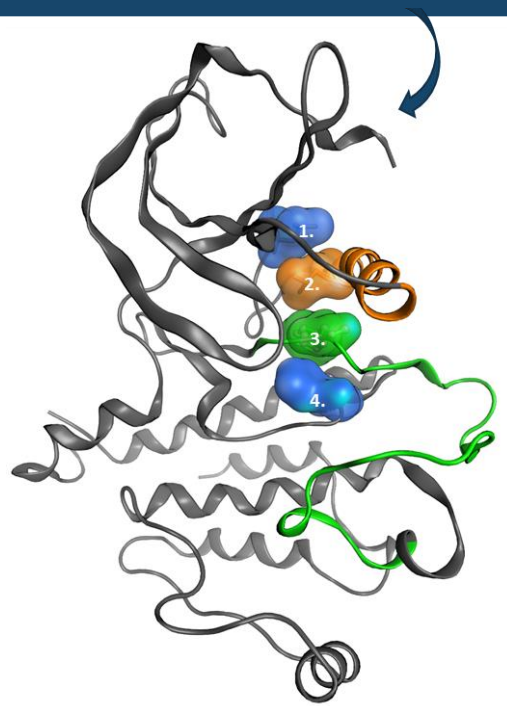
Restoration of the Inhibitory Spine

OFF State Inhibitory Spine



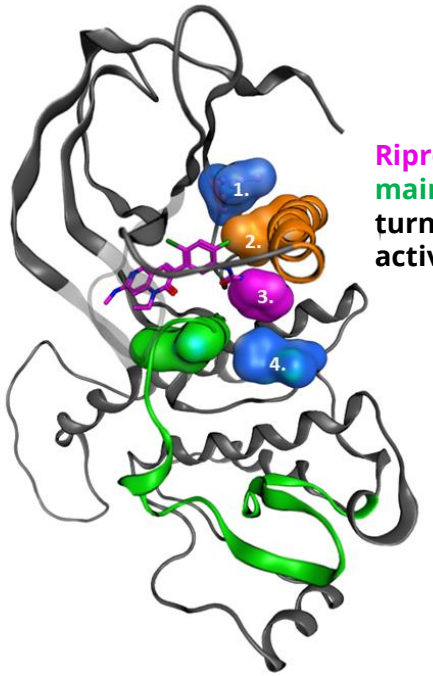
Normal wild type KIT with intact inhibitory switch

ON State Dysregulated Active Spine



Loss of exon 11 inhibitory switch

OFF State Restored Inhibitory Spine



Ripretinib ejects main switch to turn OFF kinase activity

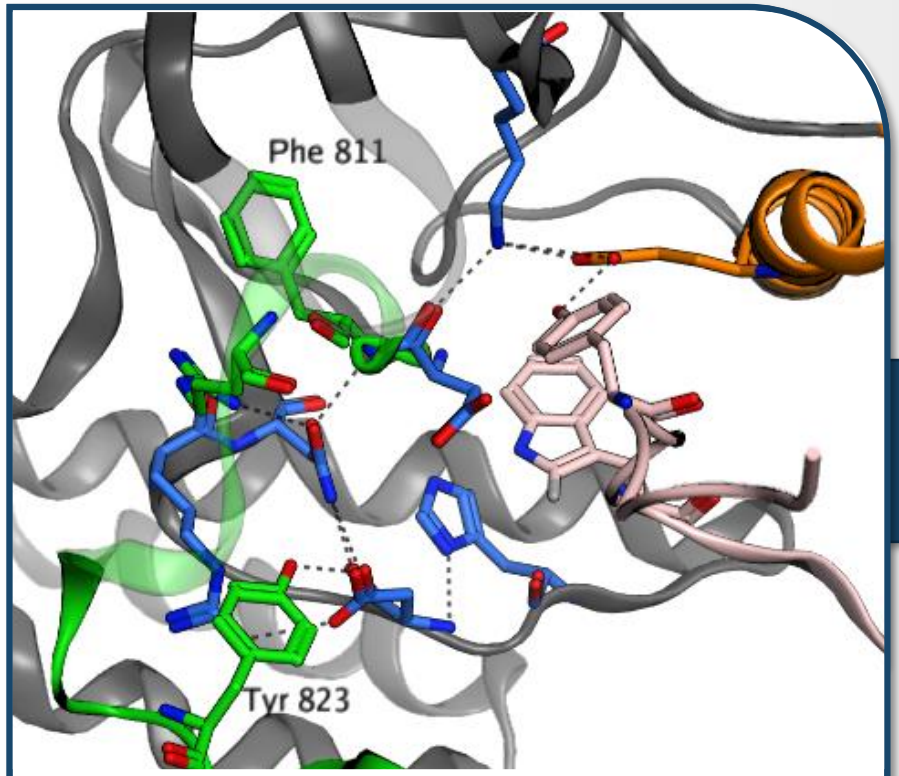
Ripretinib is surrogate for deleted inhibitory switch

Notes: Kornev et al. PNAS 2006;103(47);17783-17788; Smith et al, Cancer Cell (2019) 35: 738-51; GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase.

Green:	Main Switch
Gold:	C-Helix Switch
Blue:	Sacrosanct Switch

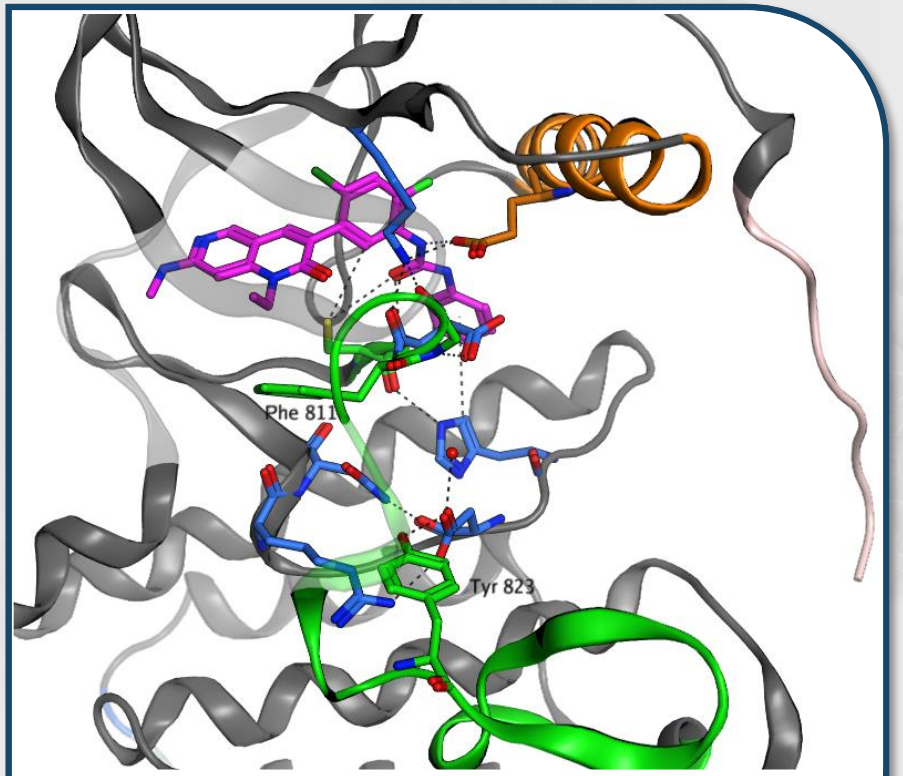
RIPRETINIB STABILIZES THE INHIBITORY HYDROGEN BOND MACROSWITCH

Binding to Sacrosanct Amino Acids



In the KIT OFF state, sacrosanct amino acids form an inhibitory network of 11 hydrogen bonds to maintain the inactive conformation

Ripretinib stabilizes main switch in the OFF state to block ATP and substrate pockets



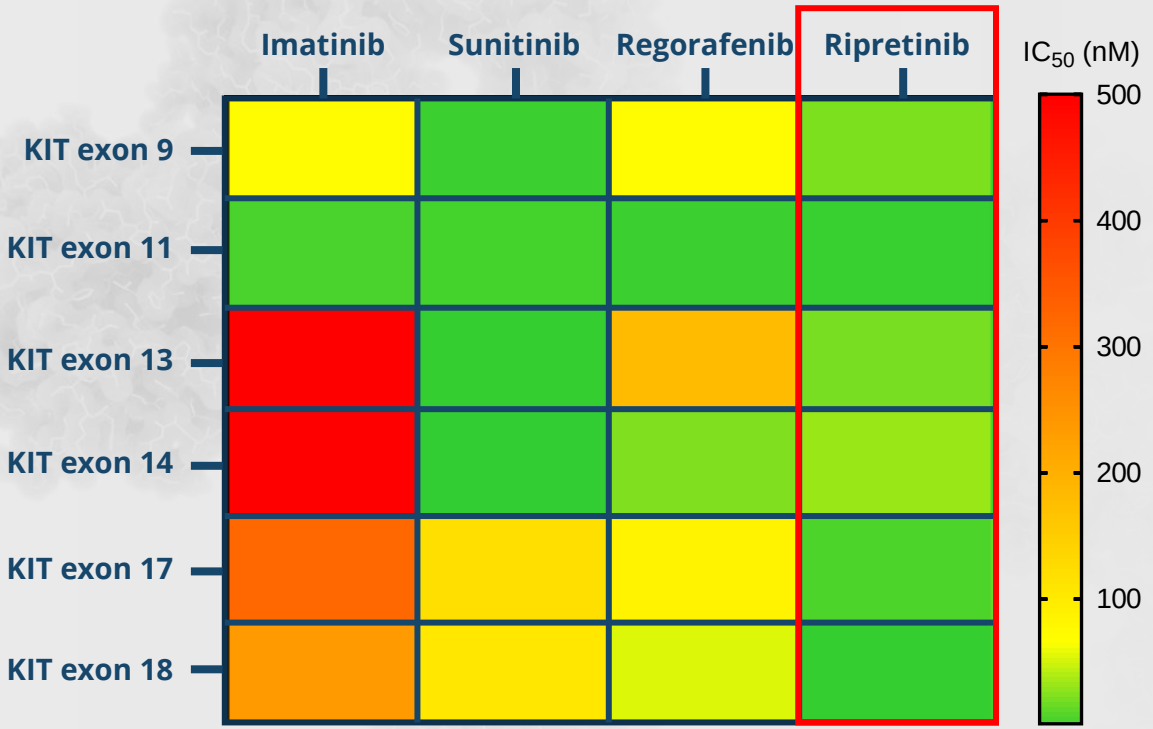
Ripretinib forms 4 direct hydrogen bonds to nucleate and further stabilize the inhibitory hydrogen bond macroswitch network

Notes: ATP=Adenosine Triphosphate; KIT=KIT proto-oncogene receptor tyrosine kinase; Phe=phenylalanine; Tyr=tyrosine.

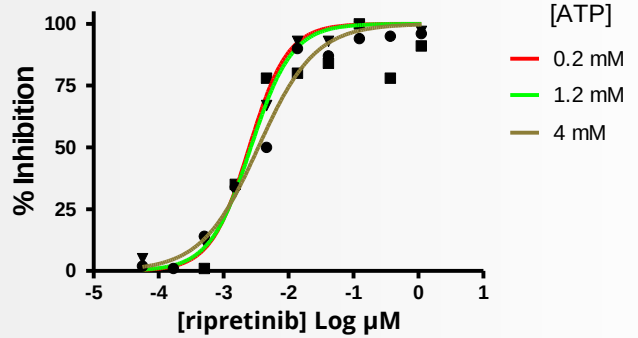
Green:	Main Switch
Gold:	C-Helix Switch
Salmon:	Inhibitory Switch
Blue:	Sacrosanct Switch

DIFFERENTIATION FROM CLASSICAL INHIBITORS

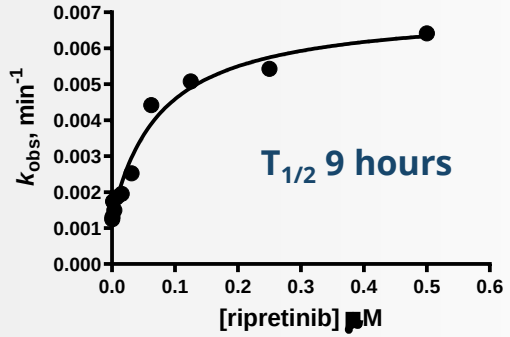
Ripretinib Inhibits KIT Mutations Across Exons 9, 11, 13, 14, 17, and 18



Ripretinib KIT Inhibition is Resilient to 4 mM ATP Concentration



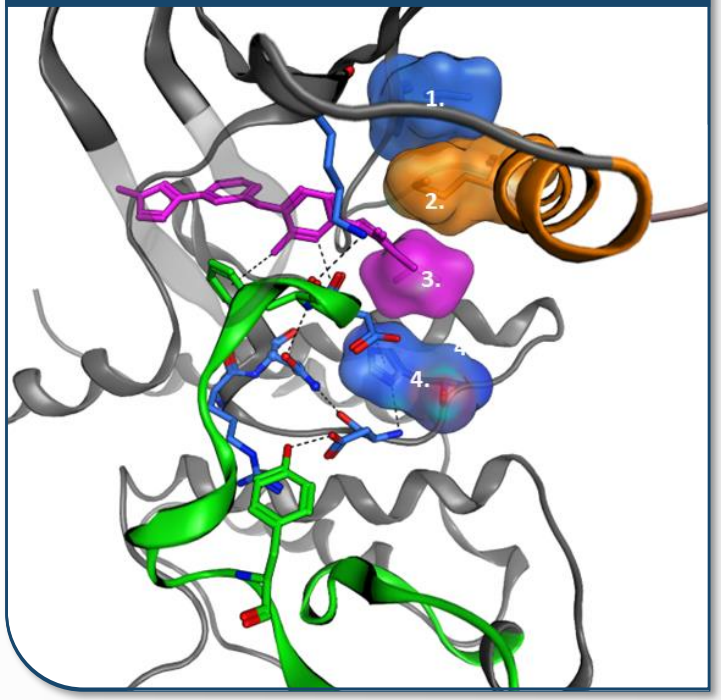
Ripretinib Off-rate Analysis



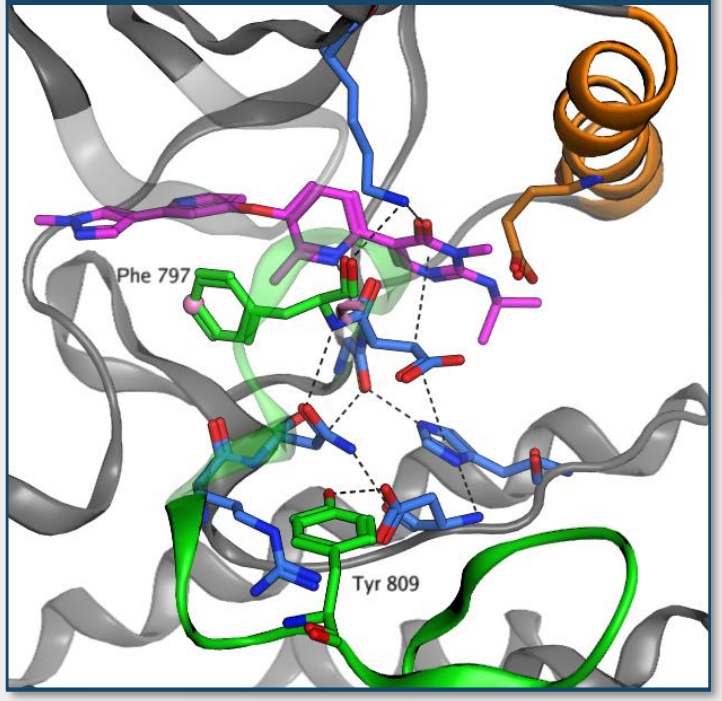
Notes: ATP=Adenosine Triphosphate; KIT=KIT proto-oncogene receptor tyrosine kinase; $T_{1/2}$=half-life.

CSF1R TYROSINE KINASE SWITCHES ARE SIMILAR TO KIT

Vimseltinib Stabilizes Inhibitory Spine Macroswitch, Ejecting Main Switch to the OFF State

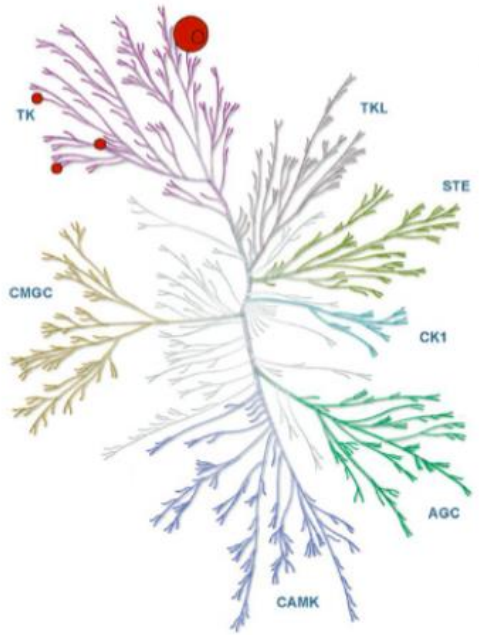


Vimseltinib Nucleates Hydrogen Bond Macroswitch and Stabilizes Main Switch to the OFF State



Vimseltinib

- High Target Selectivity
- Noncompetitive with ATP Concentrations
- Long Residency Time. $T_{1/2}$ 3 hours

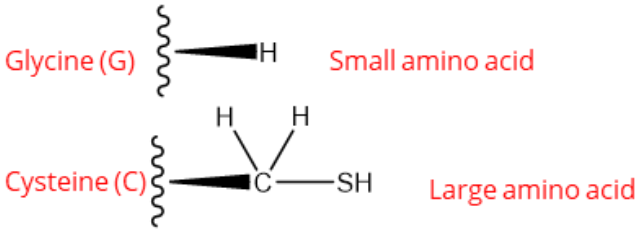


Notes: ATP=Adenosine Triphosphate; CSF1R=colony-stimulating factor 1 receptor; Phe=phenylalanine; $T_{1/2}$=half-life; Tyr=tyrosine.

Green: Main Switch
Gold: C-Helix Switch

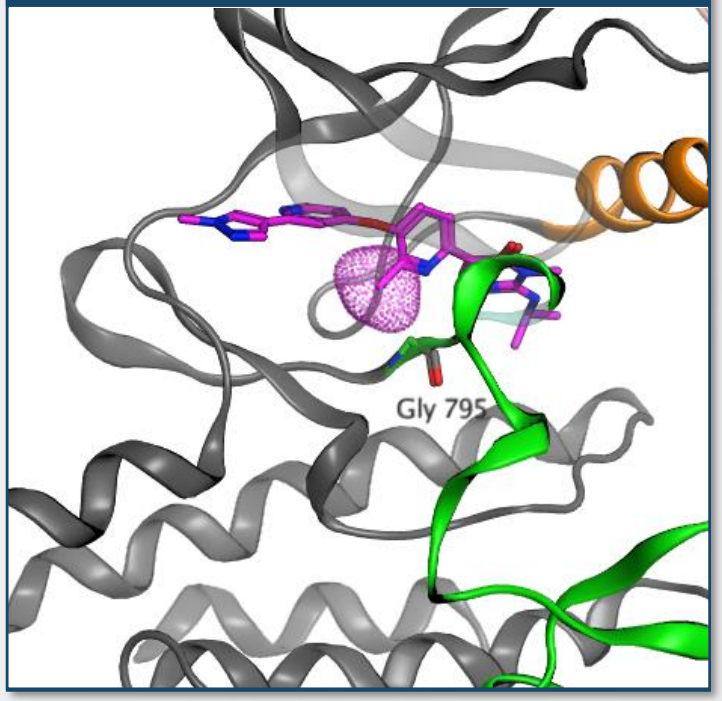
UNIQUE RESIDUES IN CSF1R SWITCH ENABLE HIGH INHIBITOR SELECTIVITY

CSF1R has an Unusual Amino Acid Sequence in the Switch that was Mined for Selectivity

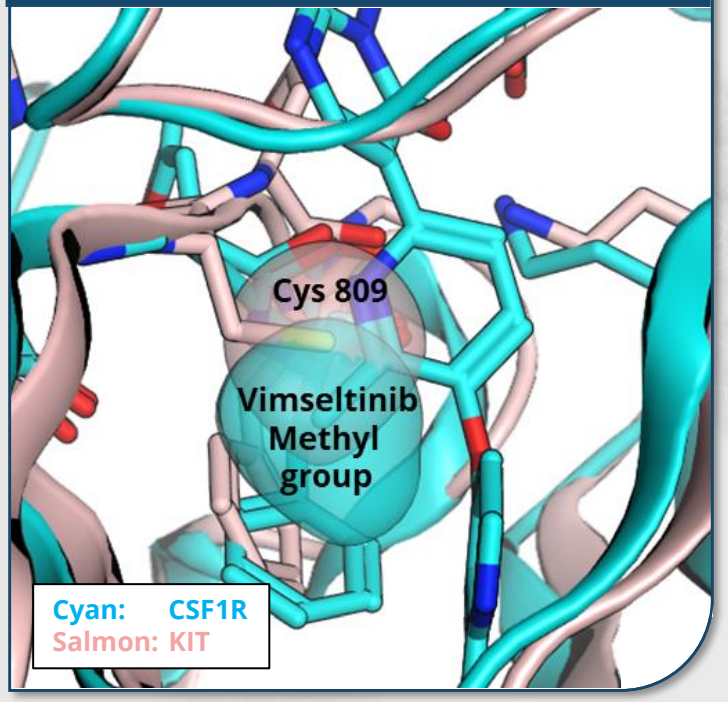


Kinase	Main Switch Region	IC_{50} (nM)
CSF1R	-**G**-D-F-G-	3.0
KIT	-**C**-D-F-G-	1,600
FLT3	-**C**-D-F-G-	>3300
PDGFRA	-**C**-D-F-G-	>3300
PDGFRB	--**C**-D-F-G-	>3300

2-methyl Group of Vimseltinib Occupies Switch "Glycine 795 Hole" Not Available in other RTK Family Members



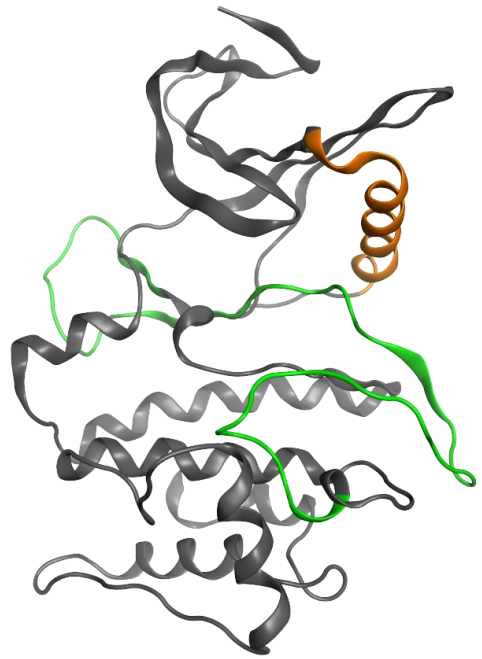
CSF1R Accommodates Vimseltinib at the Switch "Glycine 795 Hole" Whereas KIT does not Accommodate Due to Large Cys 809



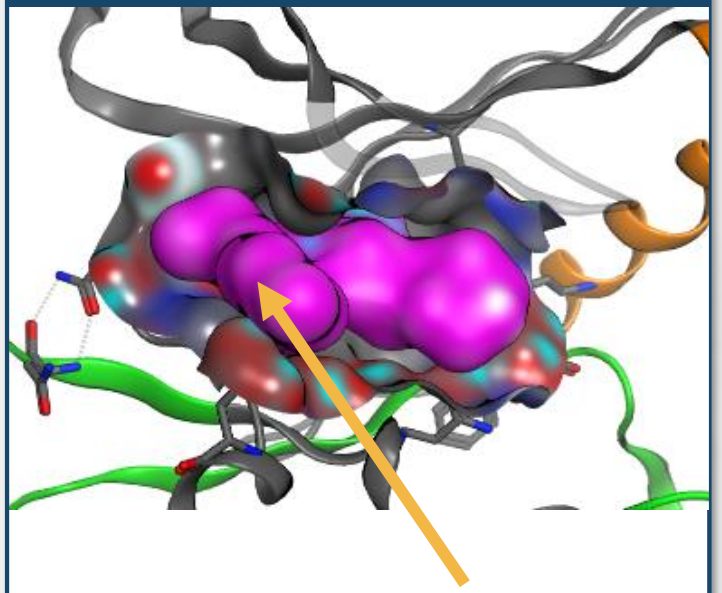
Notes: CSF1R=colony-stimulating factor 1 receptor; Cys=cysteine; FLT3=fetal liver kinase-2; Gly=glycine; KIT=KIT proto-oncogene receptor tyrosine kinase; PDGFRA=platelet-derived growth factor receptor α; PDGFRB= platelet-derived growth factor receptor b; RTK=receptor tyrosine kinase.

ULK SERINE KINASE TYPE I SWITCH CONTROL INHIBITOR

ULK has Unusual Main Switch

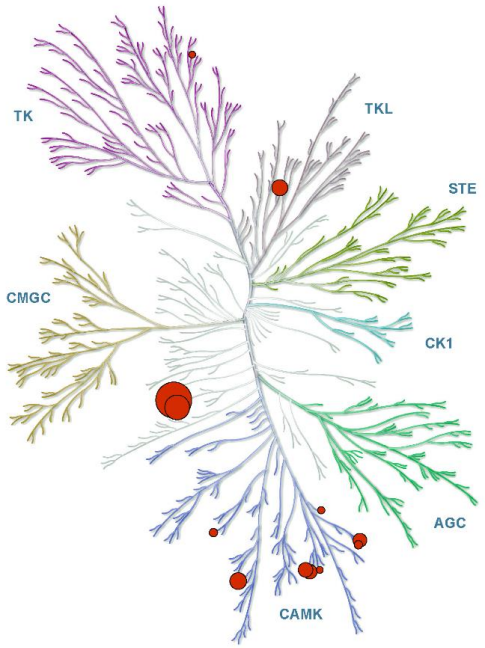


Unique Selectivity Region Created by ULK Switch



DCC-3116

- Highly Potent
- Highly Selective
- Extended Residency Time. $T_{1/2}$ 5 hours



Notes: $T_{1/2}$=half-life; ULK=unc-51-like kinase.

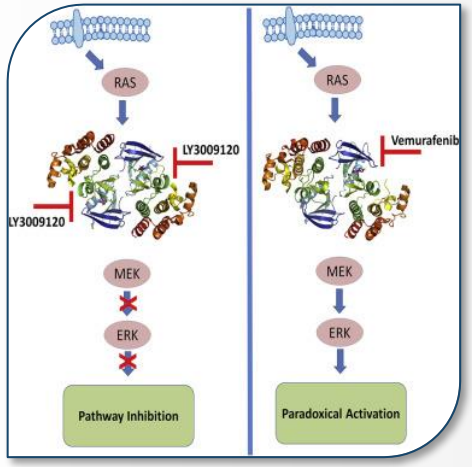
DECIPHERA'S PIONEERING RESEARCH IDENTIFIED THE FIRST PAN-RAF DIMER INHIBITOR

Cancer Cell

Inhibition of RAF Isoforms and Active Dimers by LY3009120 Leads to Anti-tumor Activities in RAS or BRAF Mutant Cancers

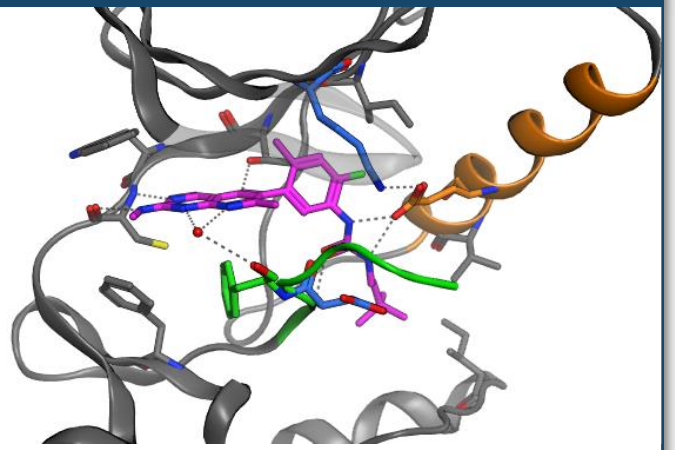
Authors: Sheng-Bin Peng, James R. Henry, Michael D. Kaufman, ..., Gregory D. Plowman, James J. Starling, and Daniel L. Flynn

Graphical Abstract:



In Brief:
Peng et al. show that LY3009120 inhibits all RAF isoforms and inhibits BRAF and CRAF homodimers and heterodimer. Moreover, LY3009120 induces minimal paradoxical activation in BRAF wild type cells. Importantly, LY3009120 exhibits anti-tumor activities in models carrying oncogenic KRAS, NRAS, or BRAF mutations.

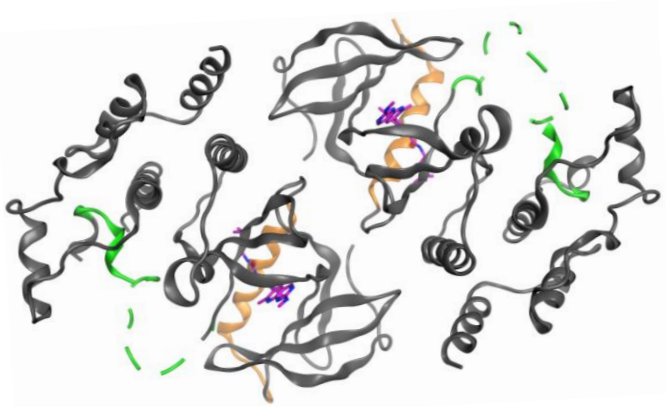
Switch-Control Mechanism for Engineering a pan-RAF Dimer Inhibitor



C-Helix Switch must be in the IN state

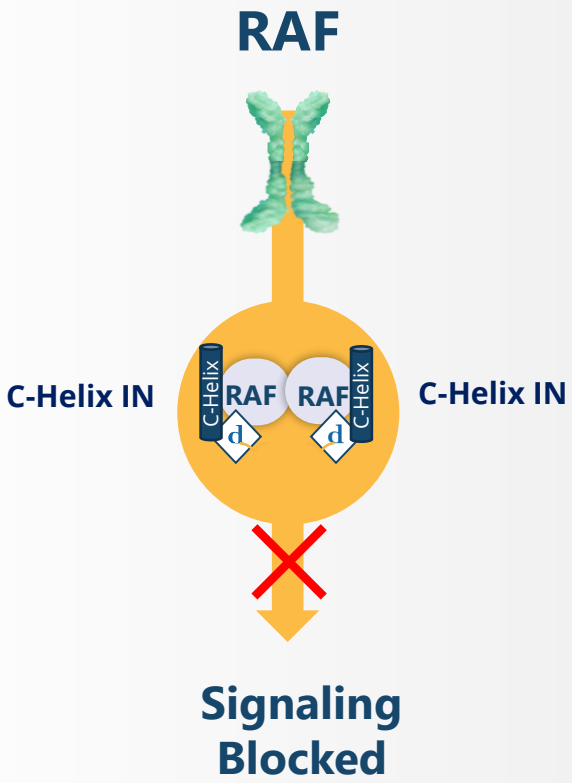
Main Switch must be in the DFG OUT state

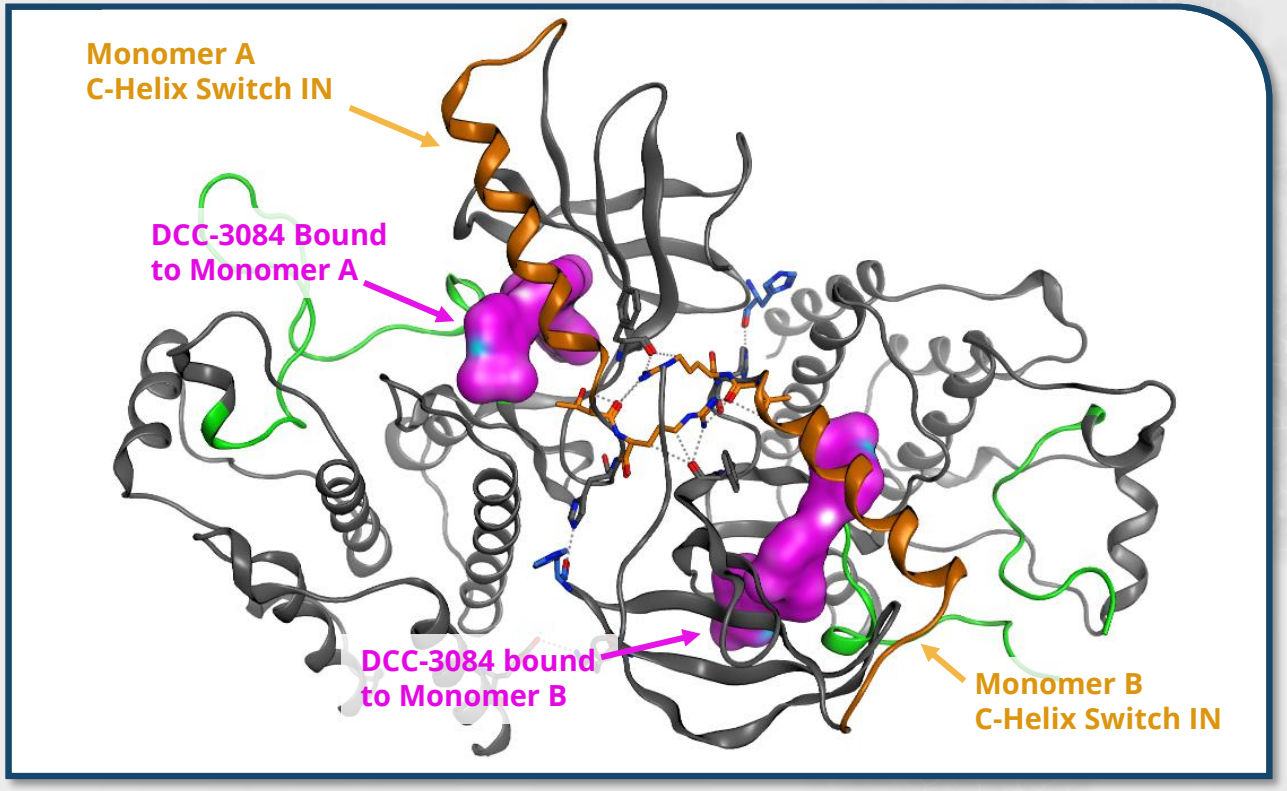
Note pan-RAF Inhibitor LY3009120 Bound into Both RAF Protomers



Notes: BRAF=proto-oncogene b-RAF; CRAF=proto-oncogene c-RAF; DFG=DFG activation loop motif; KRAS=Kirsten rat sarcoma virus; NRAS=neuroblastoma RAS viral oncogene homolog; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.

OUR NEXT GENERATION PAN-RAF INHIBITOR DCC-3084 BINDS TO BOTH MONOMERS OF THE RAF DIMER





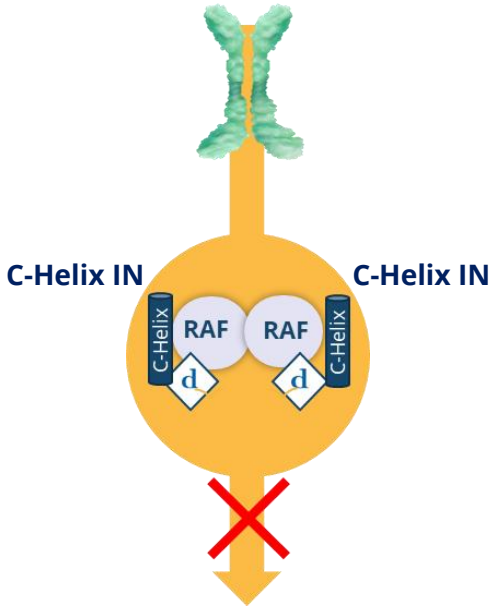
Notes: RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.

GCN2 ACTIVATOR DP-9149 ENGINEERED BY FORCING C-HELIX SWITCH TO ADOPT THE OUT STATE

For **RAF inhibition**, DCC-3084 designed to induce a **C-Helix IN state** to facilitate **binding to BOTH monomers** and **block** dimer signaling….

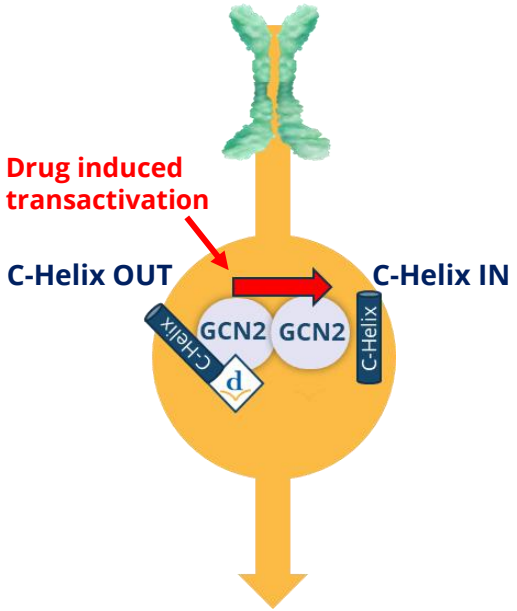
For **GCN2 activation**, DP-9149 designed to induce a **C-Helix OUT state** to facilitate **binding to ONE monomer**, **transactivating** unoccupied monomer to signal.

DCC-3084 Pan-RAF Inhibitor



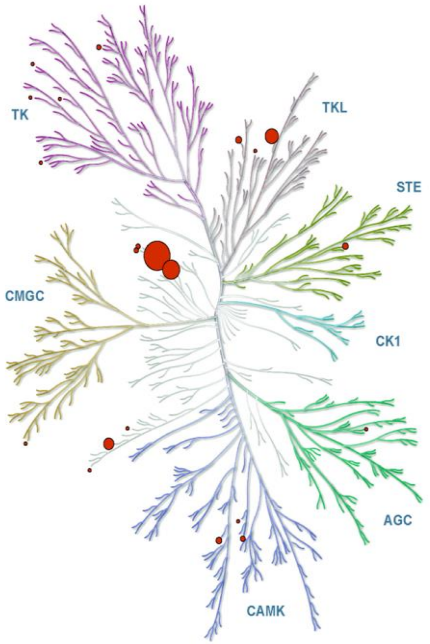
Signaling Blocked

DP-9149 GCN2 Activator



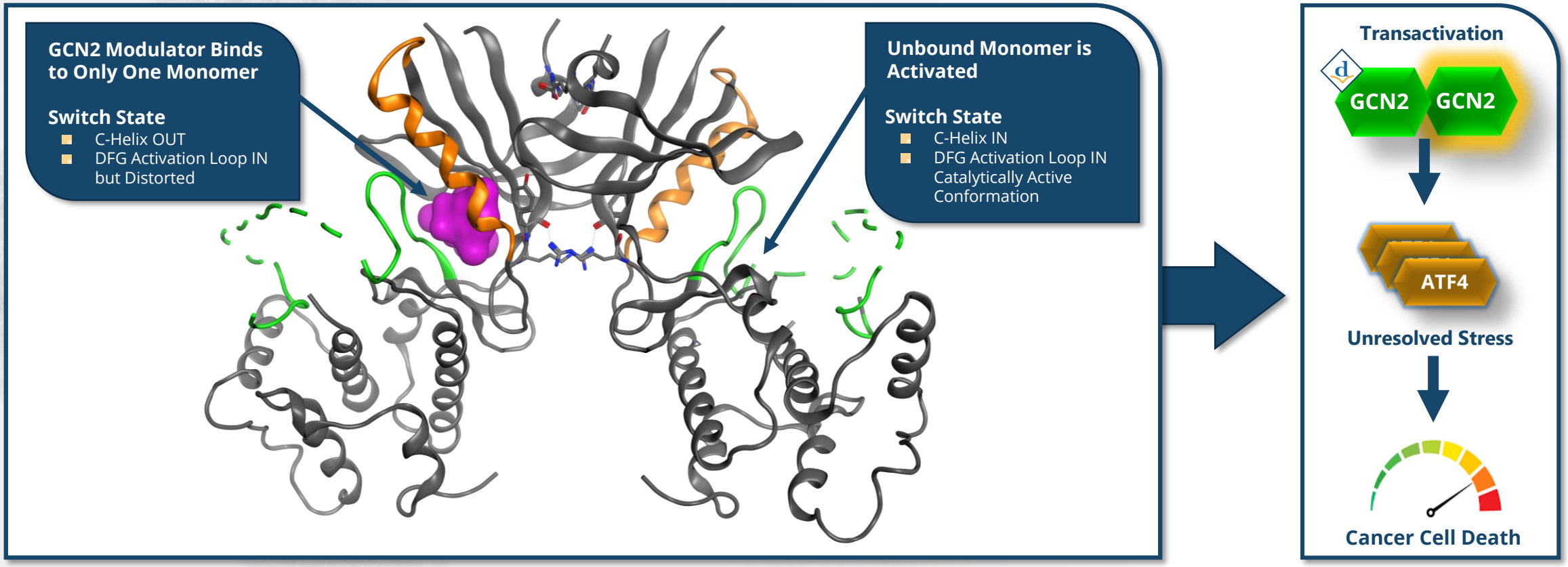
Signaling Activated

DP-9149 is Highly Selective



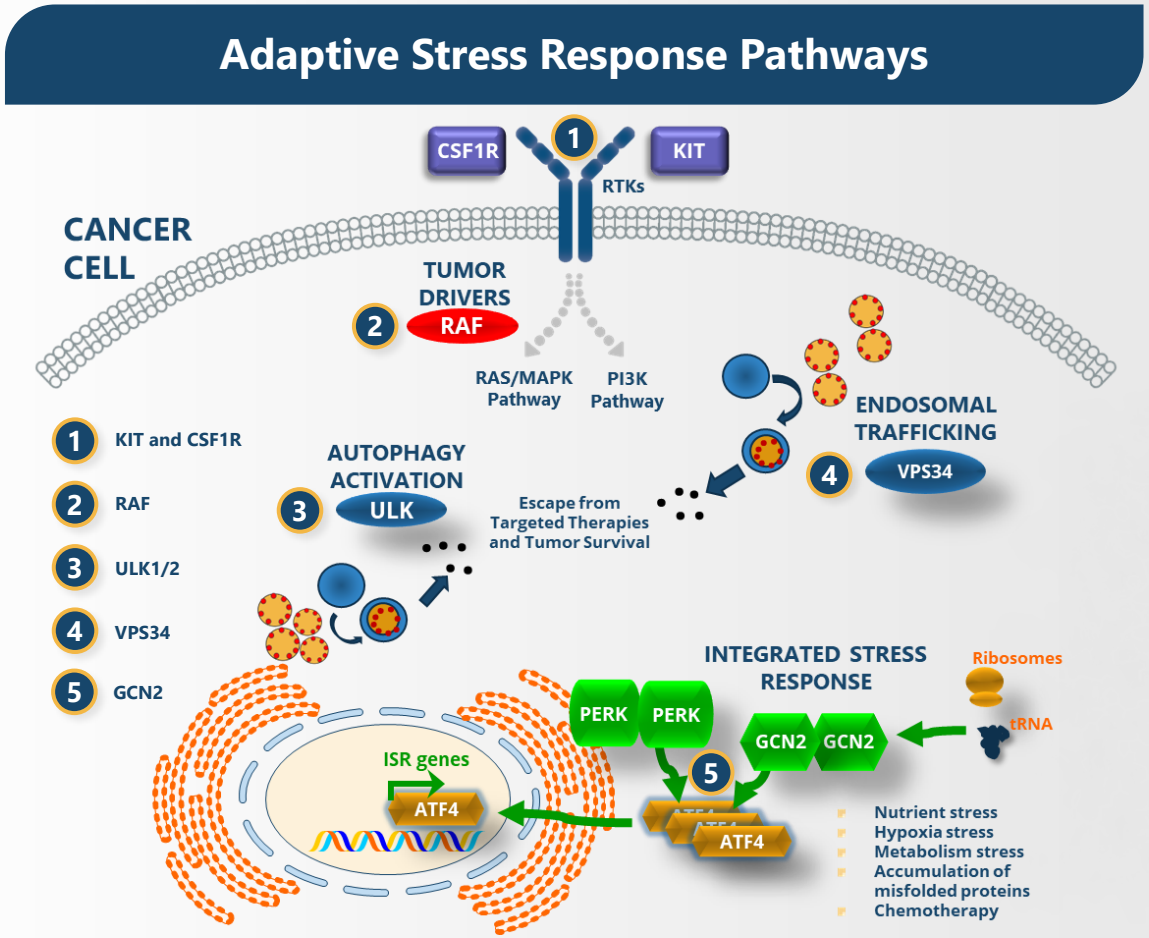
Notes: GCN2=general control nonderepressible 2; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.

SWITCH-CONTROL TRANSACTIVATION MECHANISM FOR GCN2



Notes: DFG=aspartic acid–phenylalanine–glycine; GCN2=general control nonderepressible 2.

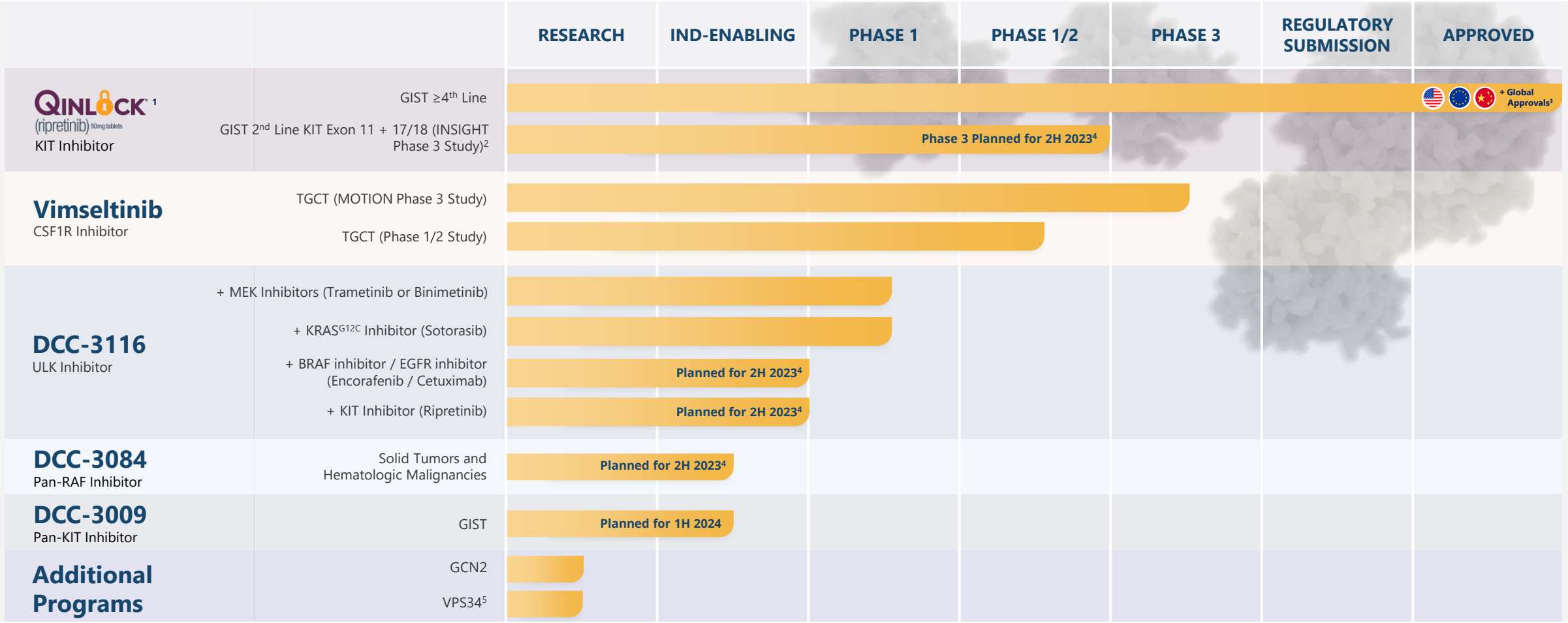
TUMOR DRIVER STRESS CONDITIONS ACTIVATE CANCER ADAPTIVE STRESS RESPONSE PATHWAY SIGNALING



- **Cancer cells activate Adaptive Stress Response pathways** in order to enable their survival and continued proliferation under stressful conditions
- Kinases involved in Adaptive Stress Responses **resolve the stressors caused by tumor drivers**
- **Cancers can become addicted** to both tumor driver pathway and Adaptive Stress Response pathway signaling
- **Modulation of cancer Adaptive Stress Response pathways** are an important emerging field in targeted therapy

Notes: ATF4=activating transcription factor 4; CSF1R=colony-stimulating factor 1 receptor; GCN2=general control nonderepressible 2; ISR=Integrated Stress Response; KIT=KIT proto-oncogene receptor tyrosine kinase; MAPK=mitogen-activated protein kinase; PERK=protein kinase R–like endoplasmic reticulum kinase; PI3K=phosphatidylinositol-3 kinase; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.

ROBUST PIPELINE OF SWITCH-CONTROL KINASE INHIBITORS



Notes: BRAF=proto-oncogene b-RAF; CSF1R=colony-stimulating factor 1 receptor; EGFR=epidermal growth factor receptor; GCN2=general control nonderepressible 2; GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase; MAPK=mitogen-activated protein kinase; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma gene; TGCT=tenosynovial giant cell tumor; ULK=unc-51-like autophagy-activating kinase; (1) Exclusive development and commercialization license with Zai Lab in Greater China for QINLOCK; (2) The patient population for the planned INSIGHT study consists of second-line GIST patients with mutations in KIT exon 11 and 17 and/or 18 and the absence of mutations in KIT exon 9, 13, and/or 14 (also referred to as KIT exon 11 + 17/18 patients); (3) QINLOCK is approved for 4th line GIST in the United States, Australia, Canada, China, the European Union, Hong Kong, Israel, Macau, New Zealand, Switzerland, Taiwan, and the United Kingdom; (4) 2023 Corporate Goal; (5) Agreement with Sprint Bioscience for exclusive in-license worldwide rights to a research-stage program targeting VPS34.

DCC-3084 (PAN-RAF INHIBITOR)

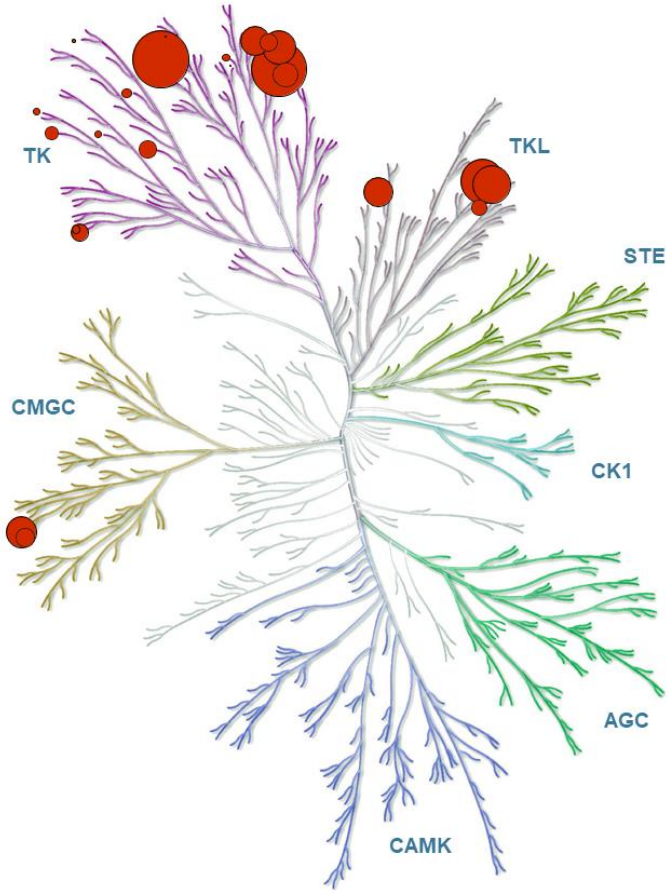
Stacie Bulfer, Ph.D.

Sr. Director, Biological Sciences

decīphera®

Notes: RAF=rapidly accelerated fibrosarcoma.

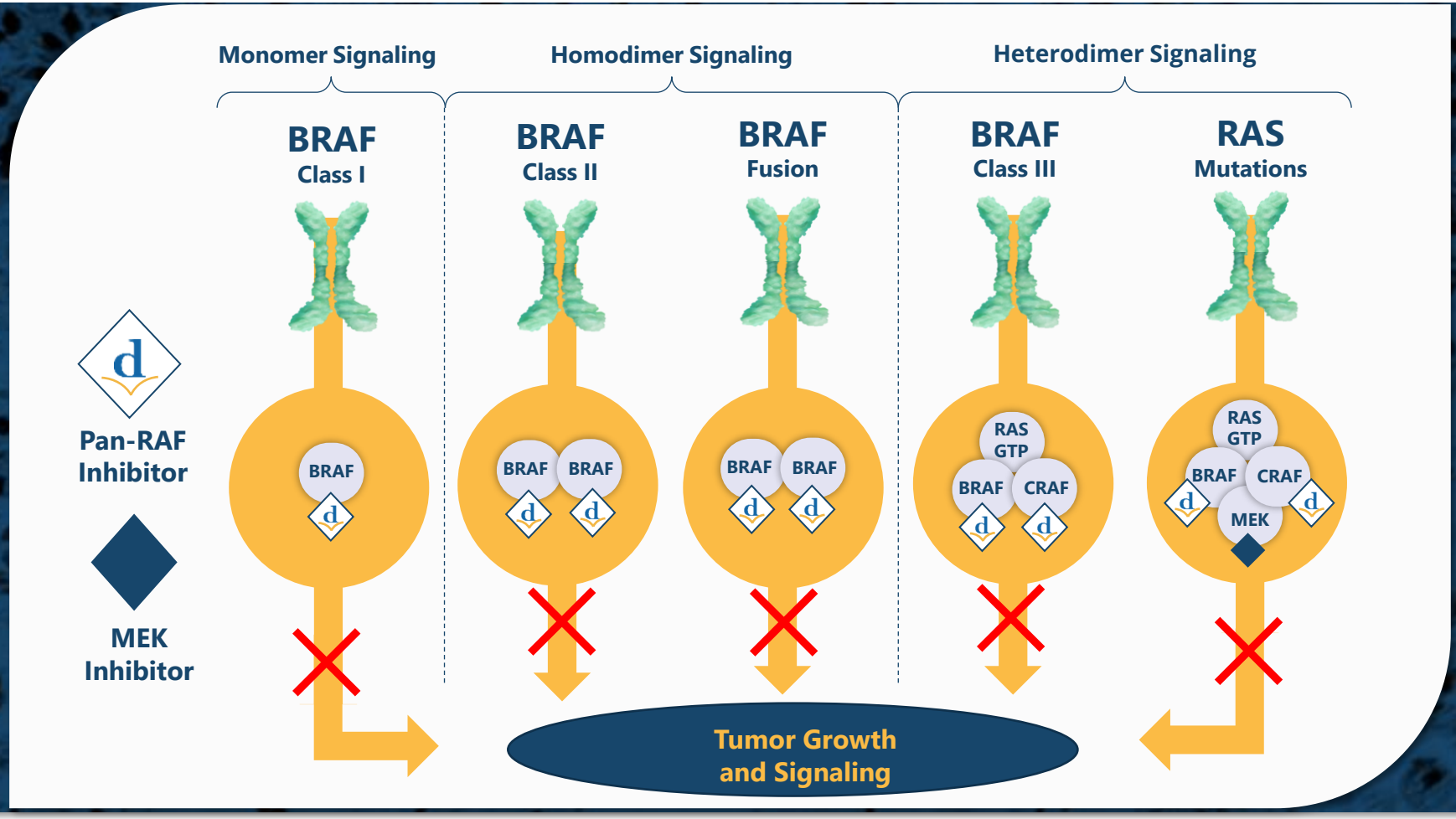
DCC-3084 IS A POTENT AND SELECTIVE PAN-RAF INHIBITOR



- DCC-3084 is a **potential best-in-class pan-RAF inhibitor** engineered using Deciphera's proprietary switch-control platform
- **Potent and selective inhibitor of BRAF and CRAF kinases**, shown preclinically to target all relevant aberrant signaling mechanisms (monomers, homodimers, heterodimers)
- **High permeability**, **CNS penetrance**, and **solubility** at gastric pH to facilitate tumor access
- **Long residency time**, **low efflux,** and **transporter inhibition** to enable durable efficacy
- **Strong pre-clinical data** supports single agent use in RAF and RAS mutant cancers, and deeper responses in combination with MEK inhibitors

Notes: BRAF=proto-oncogene b-RAF; CNS=central nervous system; CRAF=proto-oncogene c-RAF; MEK=mitogen-activated extracellular signal-regulated kinase; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase; RAS=rat sarcoma gene.

POTENTIAL BEST-IN-CLASS BRAF/BRAF HOMODIMER AND BRAF/CRAF HETERODIMER INHIBITOR



Notes: BRAF=proto-oncogene b-RAF; CRAF=proto-oncogene c-RAF; GTP=guanosine triphosphate; MEK=mitogen-activated extracellular signal-regulated kinase; RAS=rat sarcoma gene.

KEY PROPERTIES FOR A BEST-IN-CLASS PAN-RAF INHIBITOR

Potency & Selectivity

- BRAF/CRAF inhibition of signaling via monomers, homodimers, and heterodimers
- Long on-target residency time
- Limited inhibition of off-target kinases

Pharmaceutical Properties

- High permeability, low efflux and inhibition of resistance transporters to maximize efficacy
- Improved solubility to enhance target inhibition

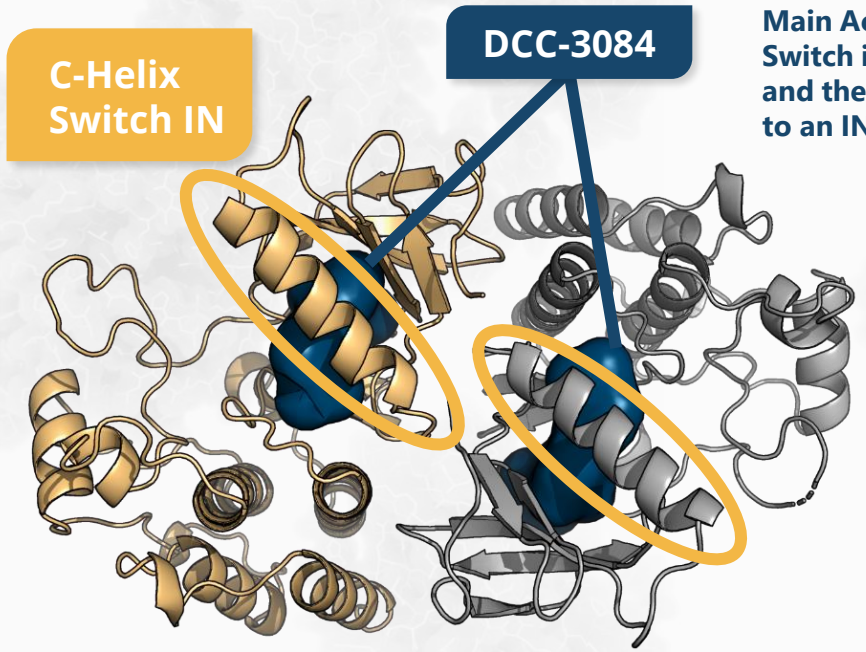
Tissue Distribution

- High accumulation in tumor cells
- CNS penetration for primary and secondary brain tumors

Notes: BRAF=proto-oncogene b-RAF; CNS=central nervous system; CRAF=proto-oncogene c-RAF; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.

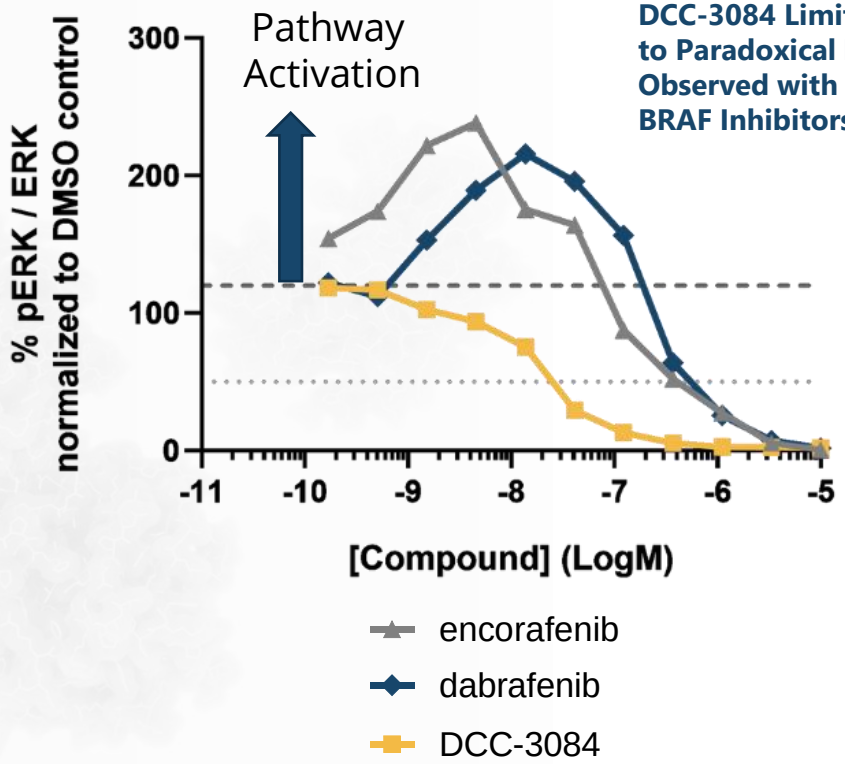
DCC-3084 LIMITS PARADOXICAL STIMULATION BY BINDING INTO BOTH MONOMERS USING SWITCH CONTROL APPROACH

DCC-3084 Binds Both Monomers of a RAF Dimer



DCC-3084 Forces the Main Activation DFG Switch in an OUT State and the C-Helix Switch to an IN State

HCT-116: KRAS G13D Colorectal Cell Lines



DCC-3084 Limits Perk Activity Due to Paradoxical Pathway Activation Observed with First Generation BRAF Inhibitors

Notes: Data presented at the AACR Annual Meeting 2023; BRAF=proto-oncogene b-RAF; DFG=aspartic acid–phenylalanine–glycine; KRAS=Kirsten rat sarcoma virus.

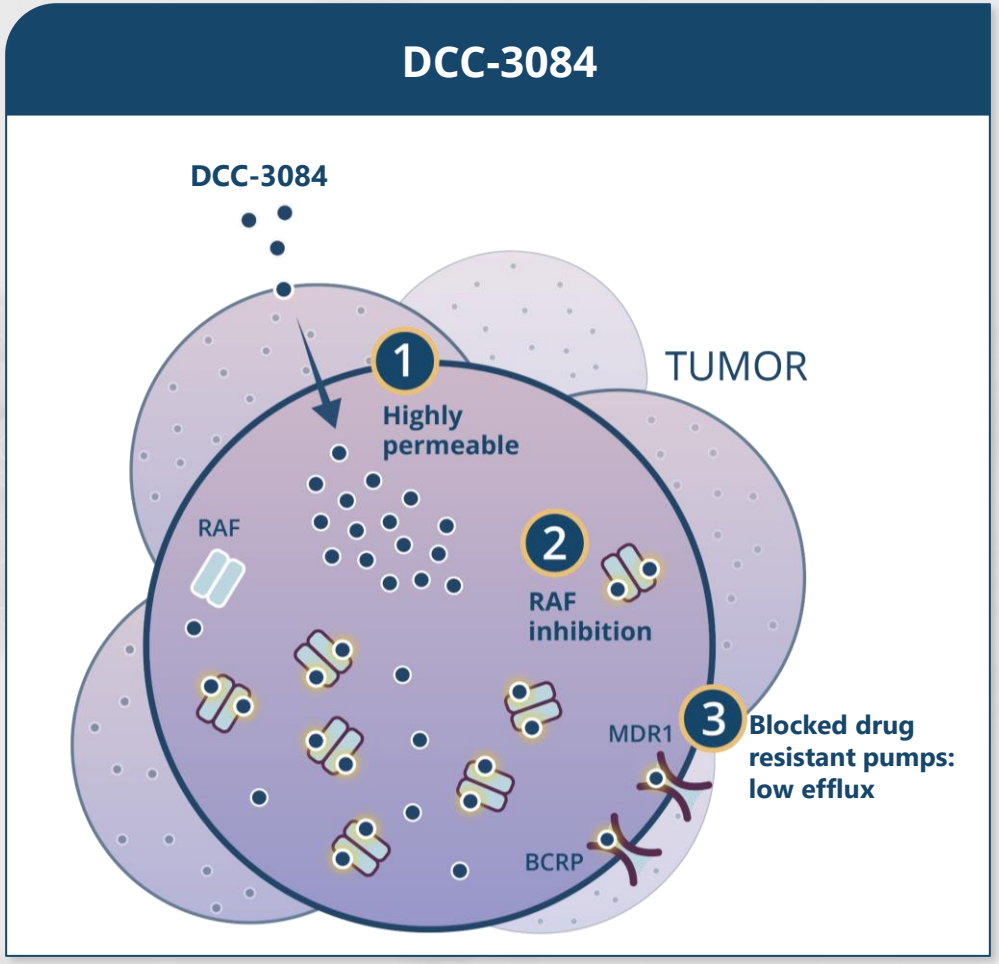
DCC-3084 EXHIBITS OVERALL BEST-IN-CLASS INHIBITION OF CLASS I, II, AND III BRAF-MUTANTS AND RAF FUSION CELL LINES

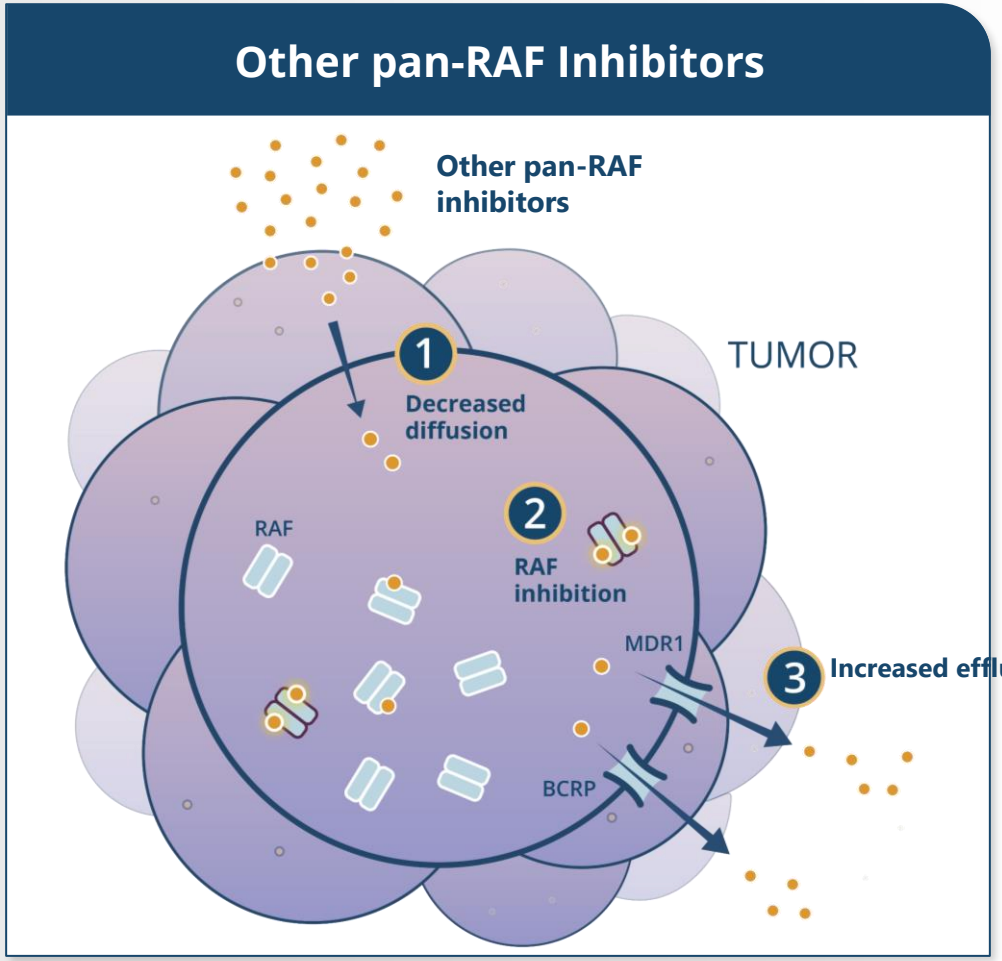
	Class I		Class II		Fusion	Class III + NRAS
Inhibitor	**A375**	**HT-29**	**BxPC-3**	**H2405**	**WM3928**	**WM3629**
DCC-3084	**54**	**13**	**61**	**74**	**42**	**3**
tovorafenib	3,000	5,270	1,100	603	669	305
naporafenib	438	228	19	465	90	3
belvarafenib	144	128	59	149	14	2
exarafenib	170	101	254	549	98	17
JZP815	141	47	200	47	133	2

IC_{50} (nM)

Notes: Data presented at the AACR Annual Meeting 2023; BRAF=proto-oncogene b-RAF; NRAS=neuroblastoma RAS viral oncogene homolog; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.

DCC-3084 HAS EXCELLENT PERMEABILITY, LOW EFFLUX AND IS A STRONG INHIBITOR OF THE MDR1 AND BCRP DRUG RESISTANCE TRANSPORTERS





Notes: BCRP=breast cancer resistance protein transporter; MDR1=multidrug resistance mutation transporter; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.

DCC-3084 SHOWED OPTIMIZED PHARMACEUTICAL PROPERTIES FOR ORAL ADMINISTRATION

- DCC-3084 has good solubility at gastric pH to allow for oral absorption
- DCC-3084 has high cellular permeability and low efflux to aid accumulation in tumor tissue
- Inhibition of drug resistant transporters enables durable efficacy
- DCC-3084 does not inhibit human liver cytochrome P450 isoforms (CYPs).

Pharmaceutical Property	Result
Solubility, pH 1.6	408 µM
Caco2 Cell Permeability	$10x10^{-6}$cm/s
Caco2 Efflux Ratio	0.9
MDCK1-MDR1 Permeability	$21x10^{-6}$cm/s
MDCK1-MDR1 Efflux Ratio	0.9
MDCKII - BCRP Permeability	$33x10^{-6}$cm/s
MDCKII - BCRP Efflux Ratio	0.8
MDR1 Inhibition	IC_{50} = 79 nM
BCRP Inhibition	IC_{50} = 74 nM
CYP inhibition (1A2, 2D6, 3A4-M)	>50,000 nM
CYP inhibition (3A4-T, 2B6)	>9,000 nM
CYP inhibition (2C19)	>5,000 nM
CYP inhibition (2C8, 2C9)	>2,000 nM

Notes: Data presented at the AACR Annual Meeting 2023; BCRP=breast cancer resistance protein transporter; MDR1=multidrug resistance mutation transporter.

DCC-3084 EXHIBITS STRONG ACCUMULATION IN TUMORS AND SUPERIOR CNS PENETRATION

- DCC-3084 accumulated in tumor tissue at a ratio between 1.7x and 1.9x (tumor/plasma)
- DCC-3084 had higher CNS penetration enabled by inhibition of efflux transporters
- Enables potential for use in brain metastases (i.e. lung and melanoma) or primary brain cancer, areas with high unmet medical needs

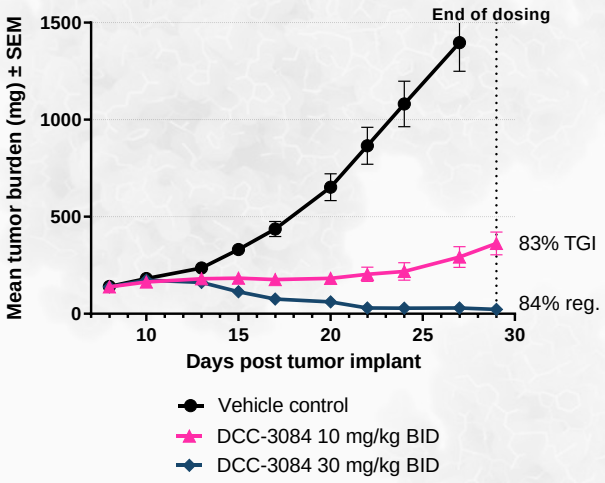
Inhibitor	AUC [brain] / AUC [plasma]	$Kp_{u/u}$	Classification
DCC-3084	**0.49**	**0.30**	**Moderate**
tovorafenib	0.33	0.05	Low
naporafenib	0.11	0.05	Low
belvarafenib	1.74	0.87	High
exarafenib	0.02	0.01	Low

Notes: Data presented at the AACR Annual Meeting 2023; AUC=area under the concentration time curve; CNS=central nervous system; $Kp_{u/u}$=unbound partition coefficient (free brain concentration/free plasma concentration).

DCC-3084 PRODUCES TUMOR REGRESSIONS IN BRAF MUTANT CANCER MODELS AS A SINGLE AGENT

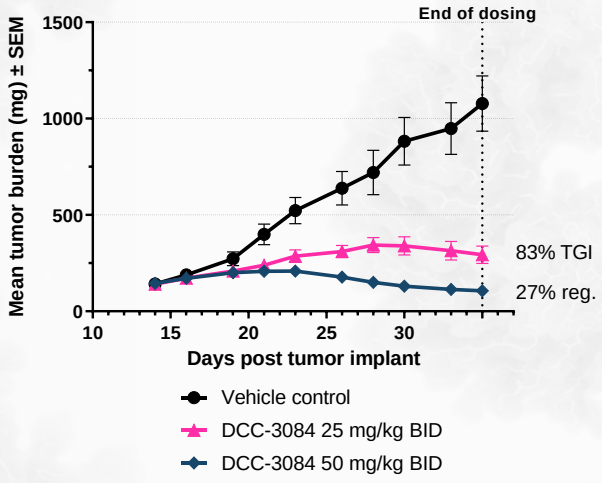
BRAF Class I

A375: BRAF Mutant Melanoma Model



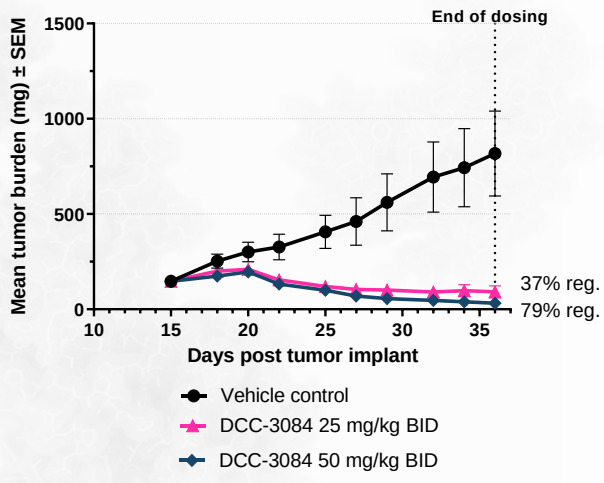
BRAF Class II

BxPC-3: BRAF Mutant Pancreatic Model



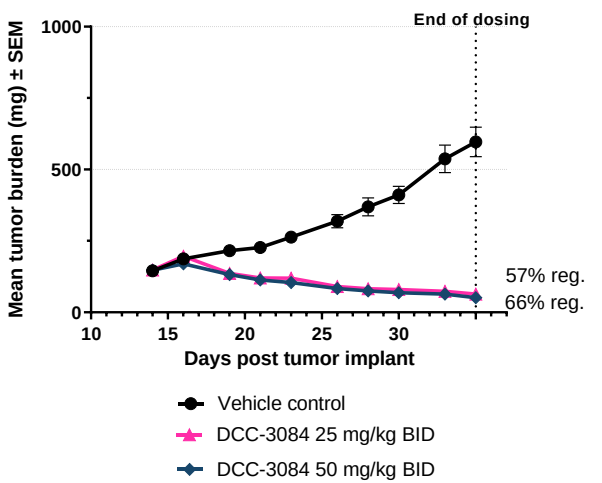
BRAF Fusion

WM3928: SKAP2-BRAF Fusion Melanoma Model



BRAF Class III

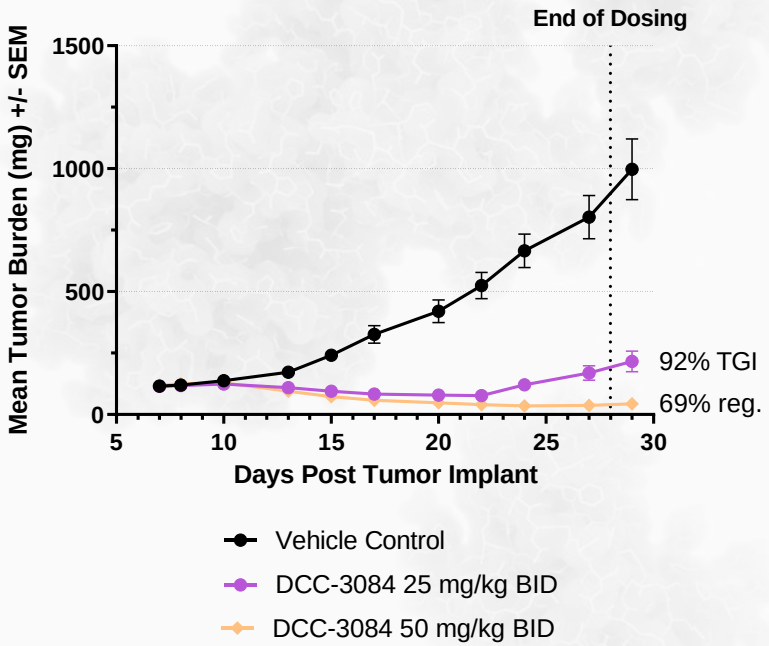
WM3629: BRAF plus NRAS G12D Melanoma Model



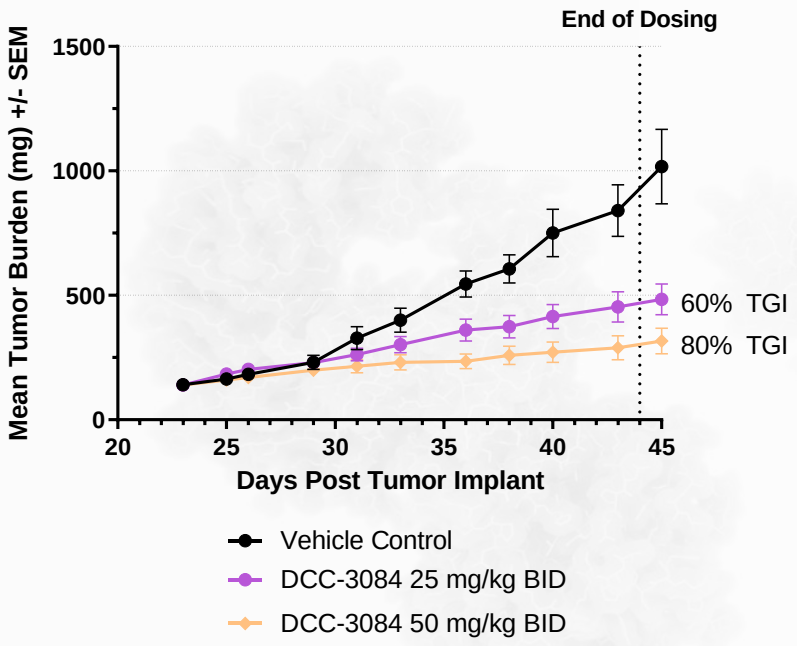
Notes: Data presented at the AACR Annual Meeting 2023; BID=twice daily; BRAF=proto-oncogene b-RAF; NRAS=neuroblastoma RAS viral oncogene homolog.

DCC-3084 PRODUCES SINGLE AGENT TUMOR REGRESSION OR TUMOR GROWTH INHIBITION IN MUTANT RAS MODELS DRIVEN BY BRAF/CRAF

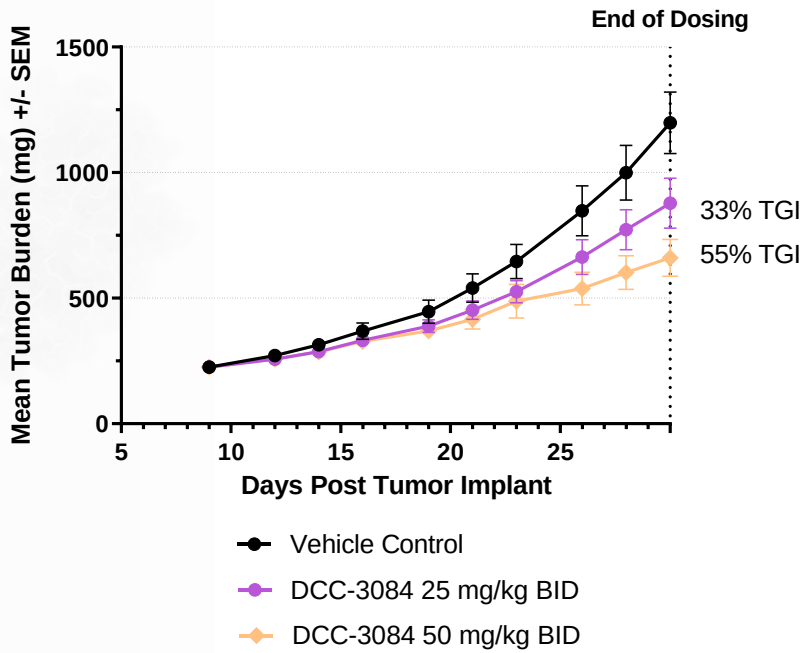
Calu-6: KRAS Q61K Lung Cancer



H358: KRAS G12C Lung Cancer



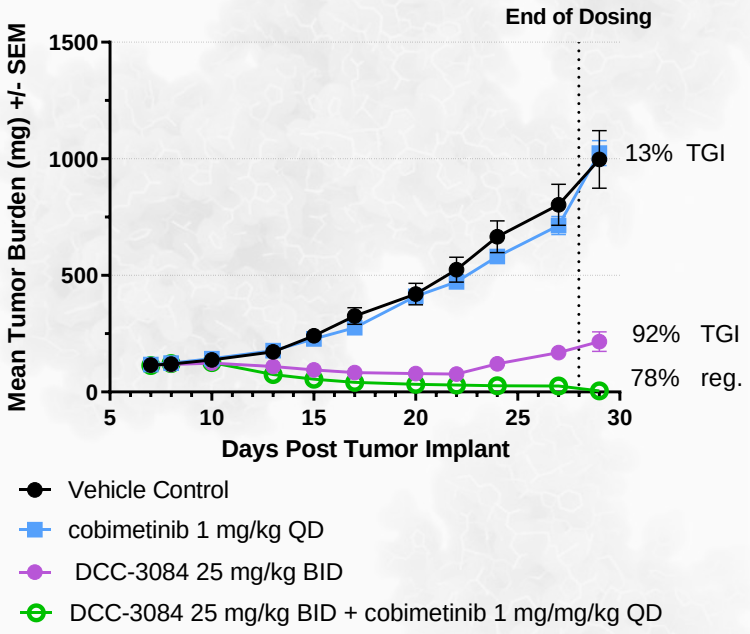
HPAF-II: KRAS G12D Pancreatic Cancer



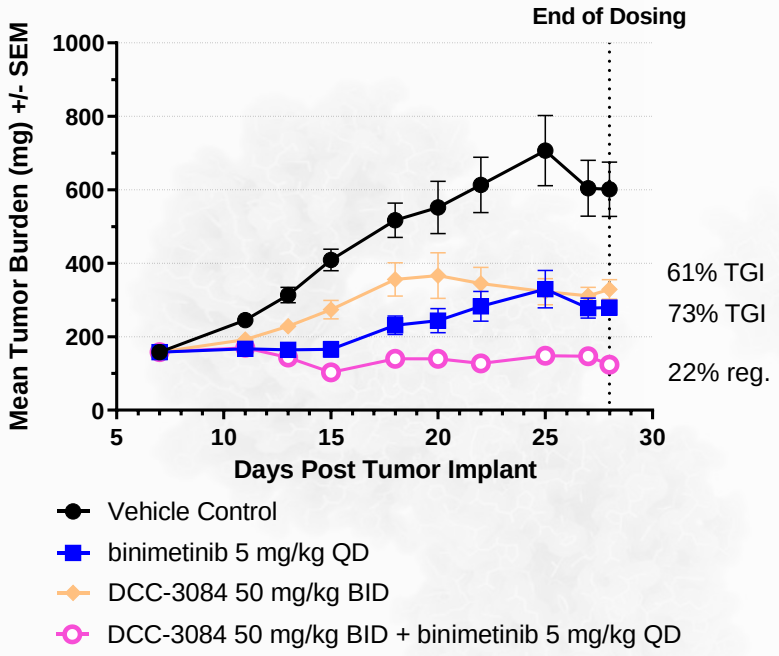
Notes: Data presented at the AACR Annual Meeting 2023; BID=twice daily; BRAF=proto-oncogene b-RAF; CRAF=proto-oncogene c-RAF; KRAS=Kirsten rat sarcoma virus; RAS=rat sarcoma gene; Reg.=regression; TGI=tumor growth inhibition.

DCC-3084 PRODUCES DEEPER TUMOR REGRESSION IN KRAS MUTANT CANCER MODELS IN COMBINATION WITH MEK INHIBITORS

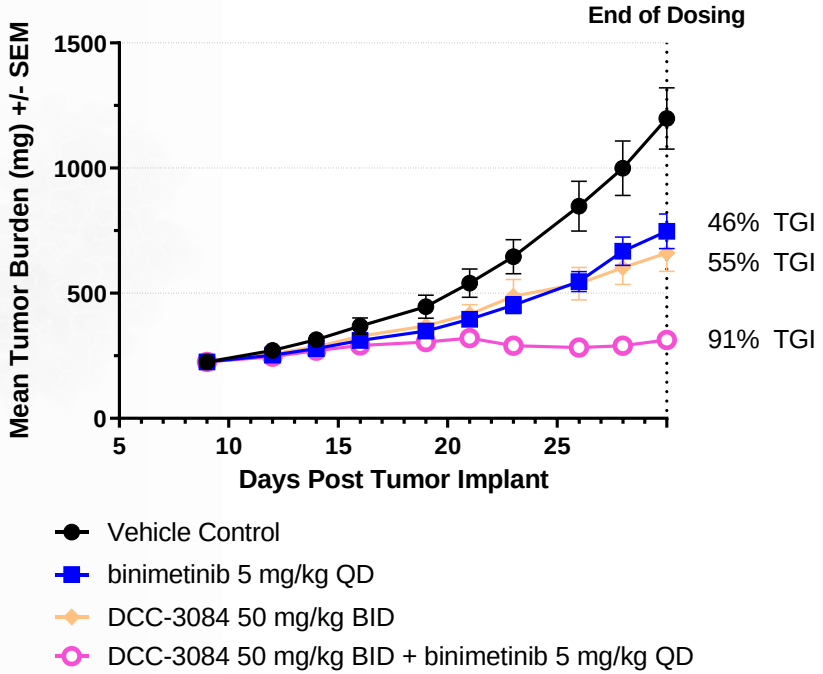
Calu-6: KRAS Q61K Lung Cancer



H358: KRAS G12C Lung Cancer



HPAF-II: KRAS G12D Pancreatic Cancer



Notes: Data presented at the AACR Annual Meeting 2023; BID=twice daily; KRAS=Kirsten rat sarcoma virus; MEK=mitogen-activated extracellular signal-regulated kinase; QD=once daily; Reg.=regression; TGI=tumor growth inhibition.

DCC-3084 IS A POTENTIAL BEST-IN-CLASS PAN-RAF INHIBITOR

- DCC-3084 is a potent and selective inhibitor of BRAF and CRAF kinases, shown preclinically to target all relevant aberrant signaling mechanisms (monomers, homodimers, heterodimers)
- DCC-3084 exhibits high permeability, good central nervous system penetrance, and tumor tissue accumulation
- DCC-3084 exhibits long residency time, low efflux, and transporter inhibition to enable durable efficacy
- Strong pre-clinical data in cancers driven by RAF or RAS mutations supports exploration of single agent and combination opportunities

IND Submission Expected in 2H 2023

Notes: Data presented at the AACR Annual Meeting 2023; BRAF=proto-oncogene b-RAF; CRAF=proto-oncogene c-RAF; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase; RAS=rat sarcoma gene.

DCC-3116 (ULK INHIBITOR)

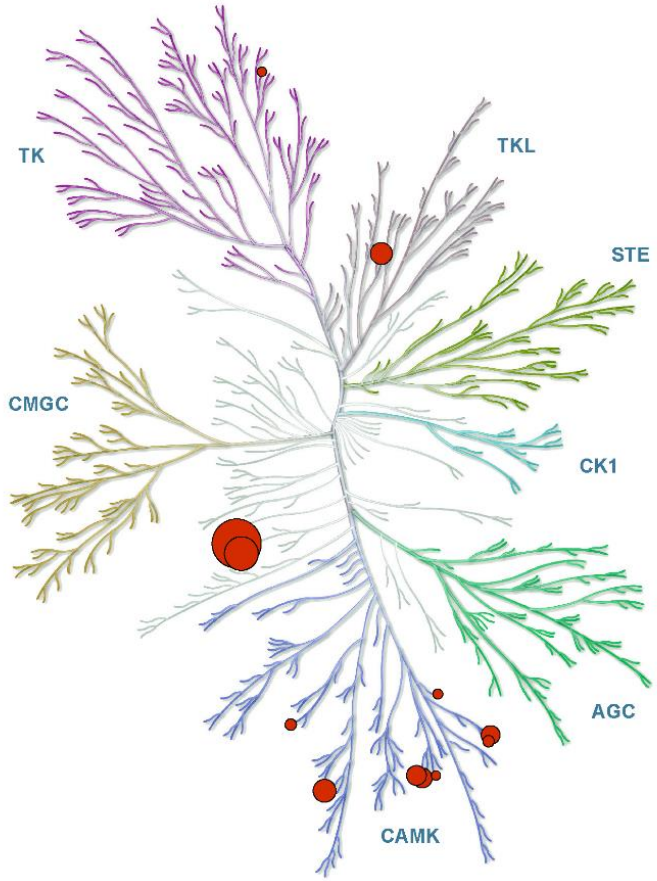
Madhumita Bogdan

Sr. Principal Investigator, Biological Sciences

decīphera®

Notes: ULK=unc-51-like autophagy-activating kinase.

POTENT AND SELECTIVE ULK INHIBITOR DESIGNED TO INHIBIT AUTOPHAGY



First-in-Class Switch-Control ULK Kinase Inhibitor

- Potent and selective inhibitor of ULK, the initiating factor in autophagy
- Strong preclinical data in combination with RTK/RAS/MAPK inhibitors
- Potential backbone combination agent across >70% of cancers

Highly Potent (Cellular IC_{50} values for ULK inhibition)

- ULK1 6 nM
- ULK2 9 nM

Highly Selective

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

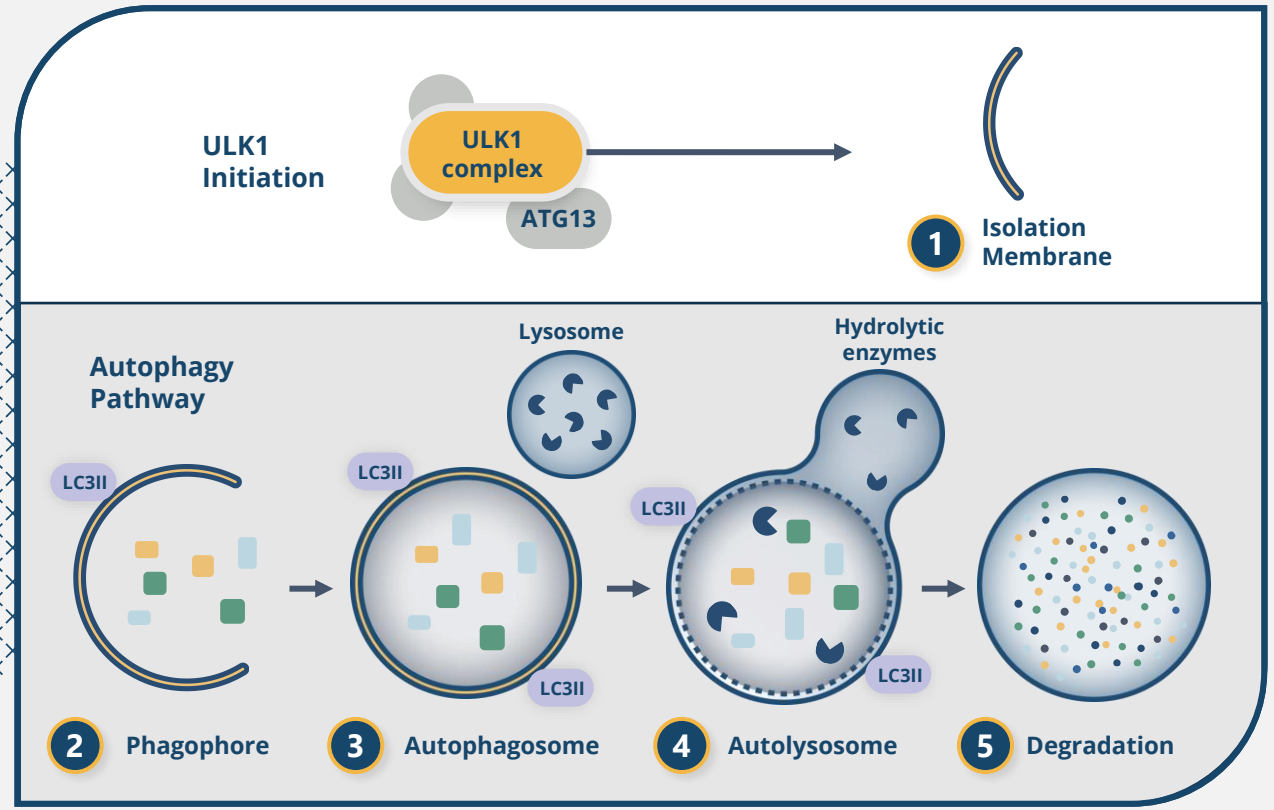
Designed to Avoid CNS Exposure

- Low brain/plasma ratio (4.3%) to avoid CNS autophagy

Notes: MAPK=mitogen-activated protein kinase; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.

AUTOPHAGY: A BROAD RESISTANCE MECHANISM IN CANCER

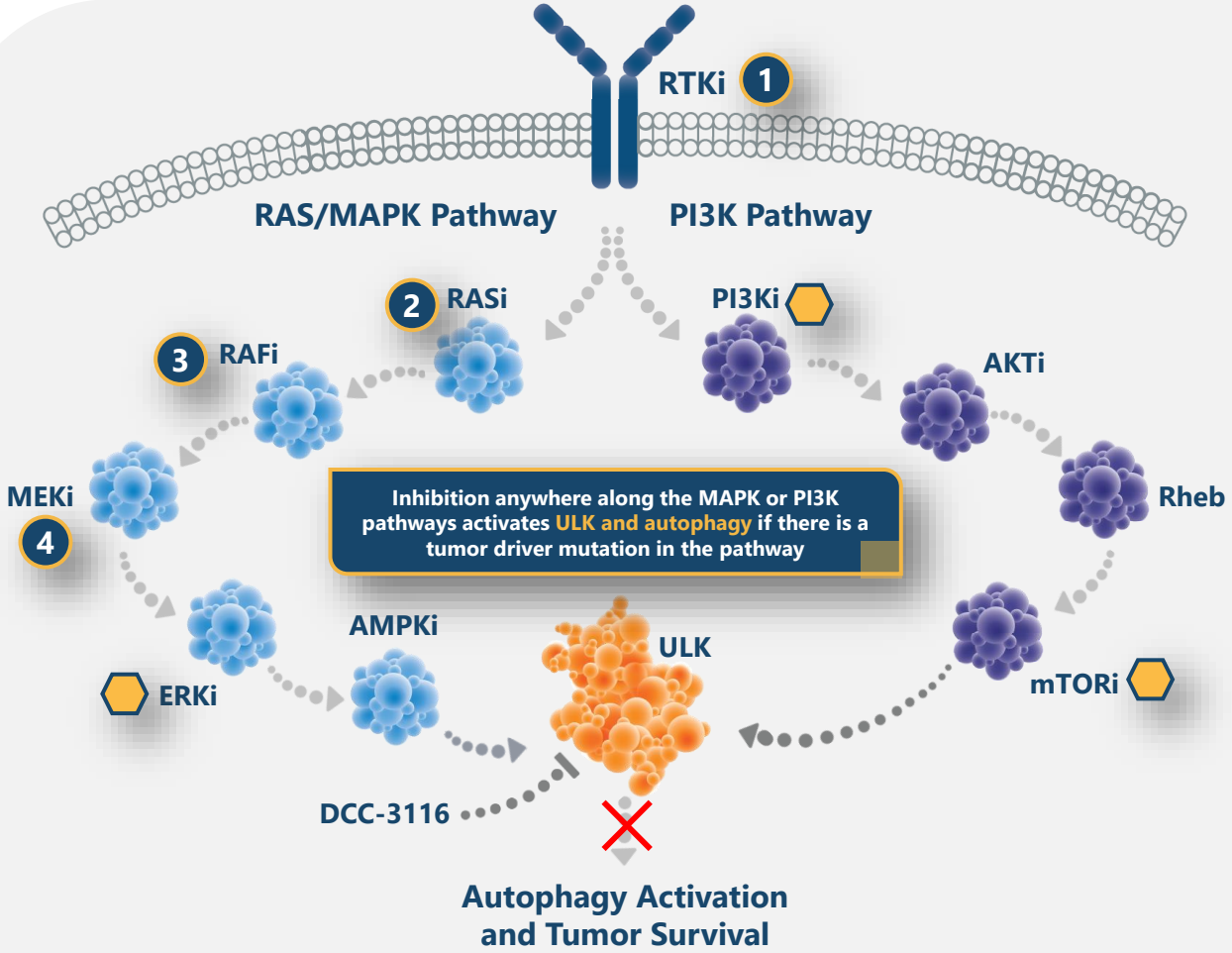
ULK: Initiating Factor for Autophagy



- Autophagy is a catabolic process in which cells recycle components to generate energy
- RTK-, RAS-, and RAF-mutant cancer cells activate autophagy in order to survive stresses or damage **due to anti-cancer therapeutic intervention** with MAPK and PI3K pathway inhibitors
- The **ULK kinase initiates the autophagy pathway** and provides a potential targeted approach to selectively inhibit autophagy in these cancers

Notes: G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; MAPK=mitogen-activated protein kinase; PI3K=phosphatidylinositol-3 kinase; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase; ATG13= Autophagy-related protein 13.

CENTRAL ROLE FOR AUTOPHAGY IN THE RAS/MAPK AND PI3K PATHWAYS



GROWING PRECLINICAL VALIDATION FOR ROLE OF AUTOPHAGY IN CANCER

1 DCC-3116 In Combination with RTK Inhibition

- DCC-3116 exhibits synergy with ripretinib, osimertinib, and afatinib, resulting in tumor regression in EGFR-mutant NSCLC and GIST *in vivo*

2 DCC-3116 In Combination with KRAS^{G12C} Inhibition

- DCC-3116 exhibits synergy with sotorasib and adagrasib resulting in tumor regression in KRAS^{G12C}-mutant NSCLC *in vivo*

3 DCC-3116 In Combination with RAF Inhibition

- DCC-3116 exhibits synergy in combination with encorafenib in BRAFm CRC *in vivo*

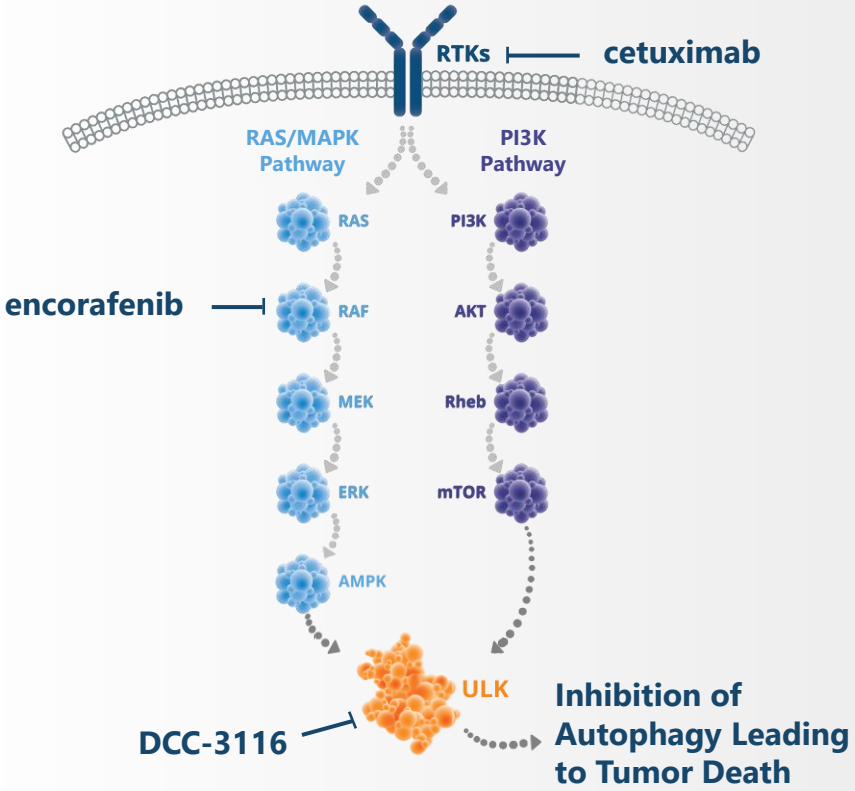
4 DCC-3116 In Combination with MEK Inhibition

- DCC-3116 exhibits synergy in combination with trametinib and inhibited pancreatic, lung, and melanoma xenograft tumor growth

Other targets where therapeutic intervention activates ULK and autophagy

Notes: AKT=protein kinase B; AMPK=AMP-activated protein kinase; EGFR=epidermal growth factor receptor; ERK=extracellular signal-regulated kinase; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; GIST=gastrointestinal stromal tumor; KRAS=Kirsten rat sarcoma virus; LKB1=liver kinase B1; MAPK=mitogen-activated protein kinase; MEK=mitogen-activated extracellular signal-regulated kinase; mTOR=mammalian target of rapamycin; NSCLC=non–small-cell lung cancer; PI3K=phosphatidylinositol-3 kinase; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma gene; Rheb=ras homolog enriched in brain; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.

DCC-3116 SYNERGIZES WITH ENCORAFENIB AND CETUXIMAB IN BRAF^{V600E} MUTANT COLORECTAL CANCER MODELS

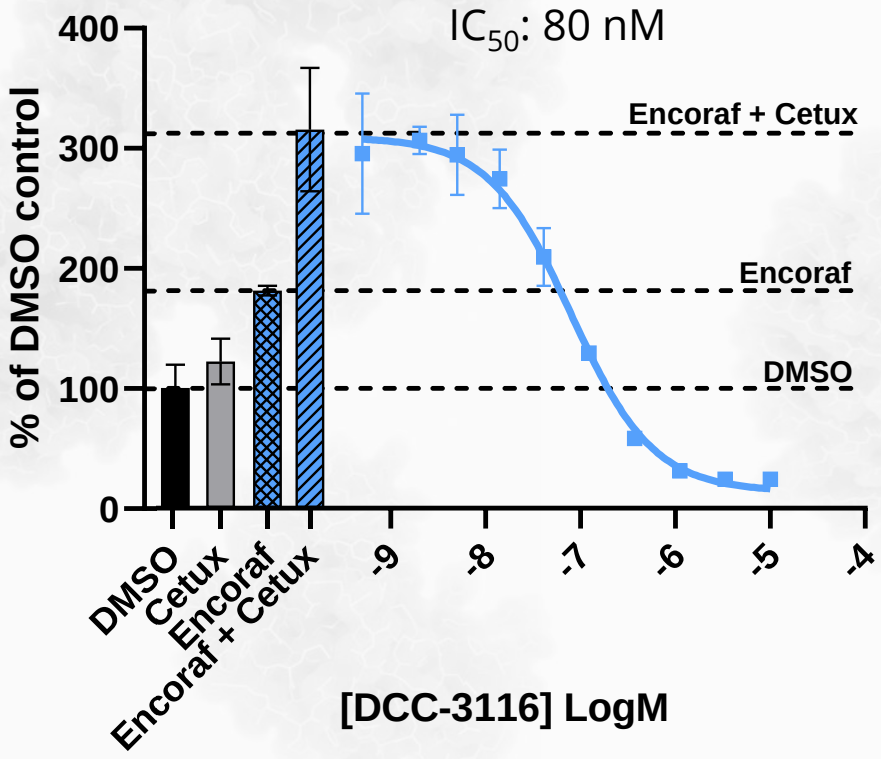


- BRAF^{V600E} mutation occurs in ~10% of colorectal cancer patients and approved treatments include encorafenib (BRAFi) and cetuximab (EGFRi)
- Inhibition of mutant BRAF and EGFR activates autophagy and promotes cancer cell survival
- Drug resistance develops through RTK/MAPK resistant mutations and/or adaptive stress response pathways including autophagy
- Preclinically, DCC-3116 synergizes with encorafenib and cetuximab to increase tumor growth inhibition or tumor regressions by reducing autophagy through inhibition of the ULK kinase

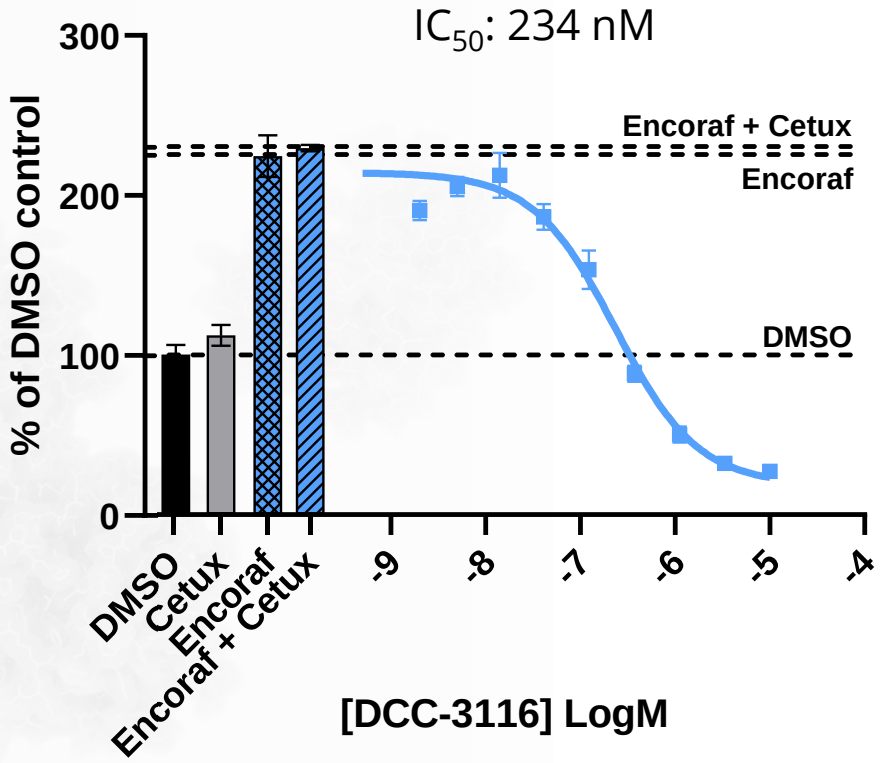
Notes: AKT=protein kinase B; AMPK=AMP-activated protein kinase; BRAF=proto-oncogene b-RAF; BRAFi=BRAF inhibitor; EGFR=epidermal growth factor receptor; EGFRi=EGFR inhibitor; ERK=extracellular signal-regulated kinase; LKB1=liver kinase B1; MAPK=mitogen-activated protein kinase; mTOR=mammalian target of rapamycin; PI3K=phosphatidylinositol-3 kinase; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma gene; Rheb=ras homolog enriched in brain; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.

DCC-3116 INHIBITS CETUXIMAB- AND ENCORAFENIB-INDUCED pATG13 IN COLORECTAL CANCER CELL LINES

HT-29: pATG13 ELISA



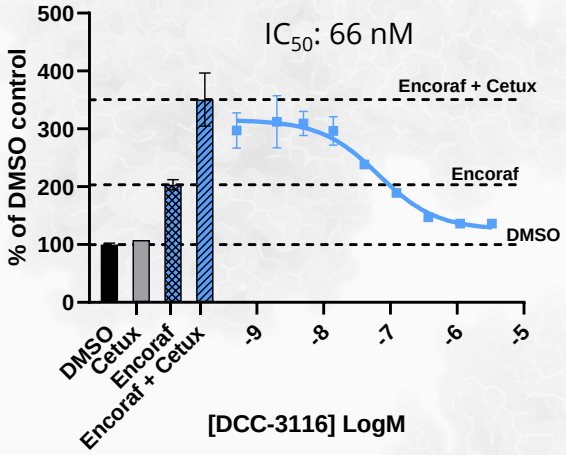
Colo-205: pATG13 ELISA

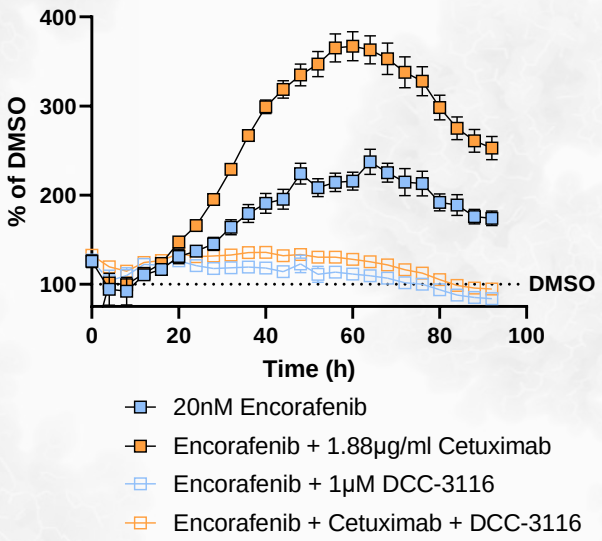


Notes: Data presented at the AACR Annual Meeting 2023; ULK activation is measured by pATG13 by ELISA; DMSO=dimethyl sulfoxide; ELISA=enzyme-linked immunosorbent assay; pATG13=phosphorylated ATG13.

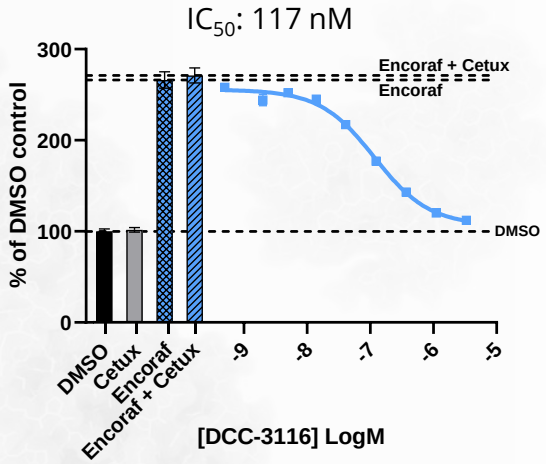
DCC-3116 INHIBITS CETUXIMAB- AND ENCORAFENIB-INDUCED AUTOPHAGIC FLUX IN COLORECTAL CANCER CELL LINES

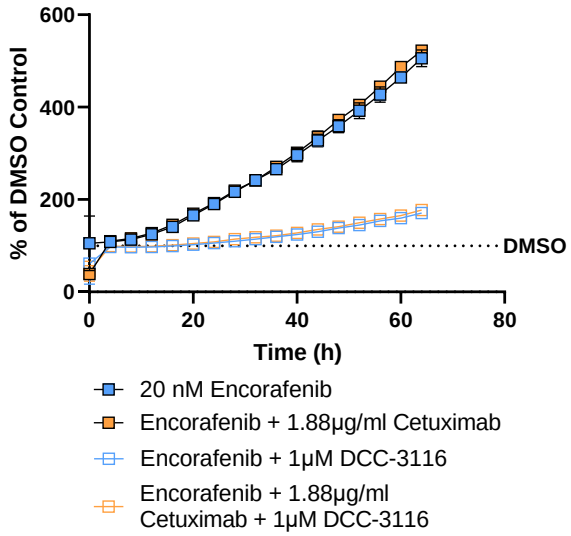
HT-29: BRAF^{V600E} Colorectal Cancer Model





Colo-205: BRAF^{V600E} Colorectal Cancer Model

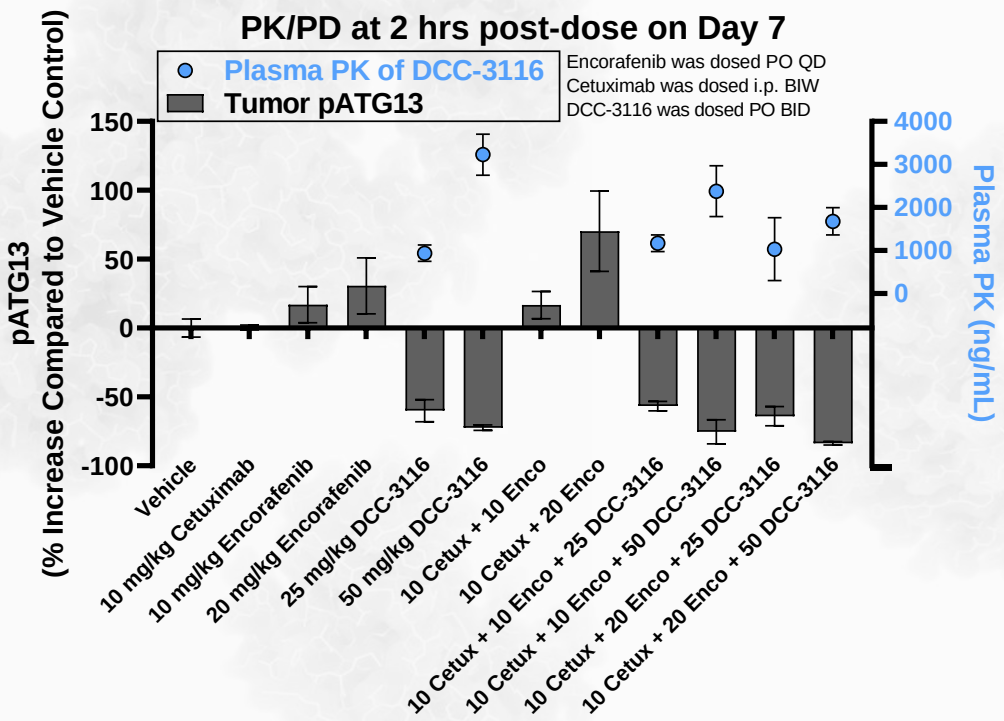




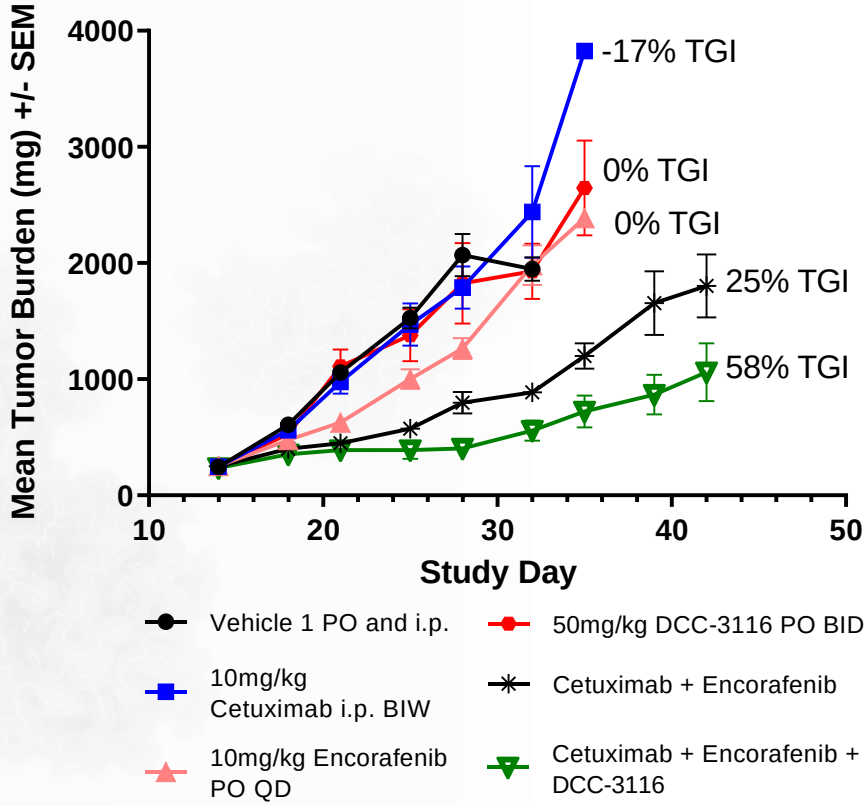
Notes: Data presented at the AACR Annual Meeting 2023; Autophagic flux assay uses cell lines generated by tagging LC3 with mCherry and GFP; Assay measures the loss of GFP fluorescence in the lysosome and normalizes to mCherry signal which is unchanged in the lysosome; BRAF=proto-oncogene b-RAF; DMSO=dimethyl sulfoxide.

DCC-3116 INCREASES TUMOR GROWTH INHIBITION IN COMBINATION WITH ENCORAFENIB AND CETUXIMAB *IN VIVO*

HT-29: DCC-3116 Exposure and Target Engagement



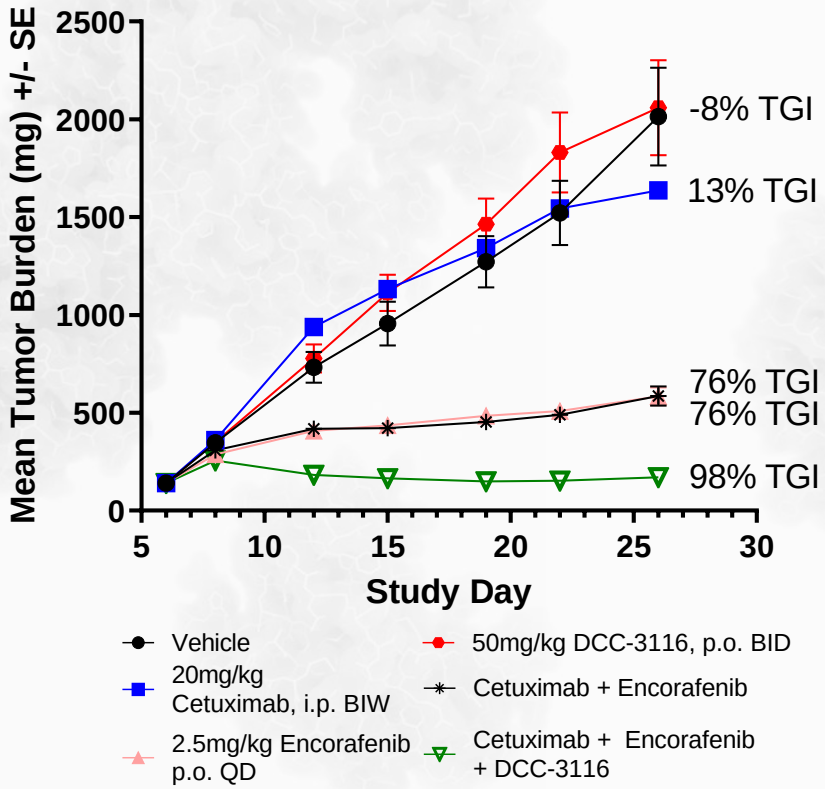
HT-29: BRAF^{V600E} Colorectal Cancer Model



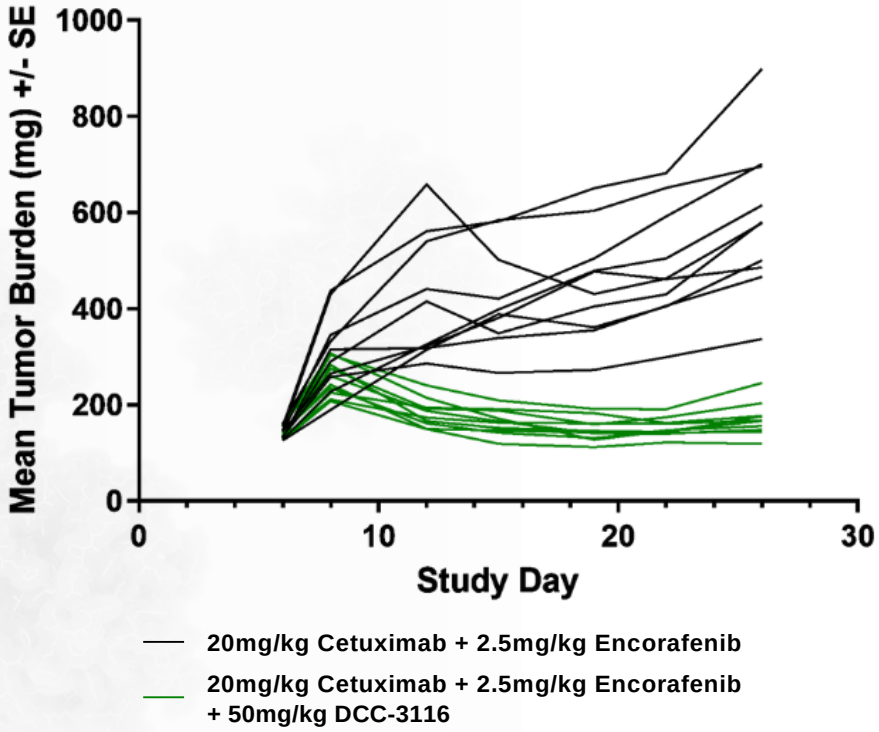
Notes: Data presented at the AACR Annual Meeting 2023; % reg is the percent of mice that had regressions; %TGI and %Reg were calculated at the last day of dosing; BID=twice daily; BIW=2 times a week; BRAF=proto-oncogene b-RAF; pATG13=phosphorylated ATG13; PD=pharmacodynamics; PK=pharmacokinetics; PO=orally; QD=once daily; Reg=regression; TGI=tumor growth inhibition.

DCC-3116 INDUCES TUMOR REGRESSIONS IN COMBINATION WITH ENCORAFENIB AND CETUXIMAB *IN VIVO*

Colo-205: $BRAF^{V600E}$ Colorectal Cancer Model

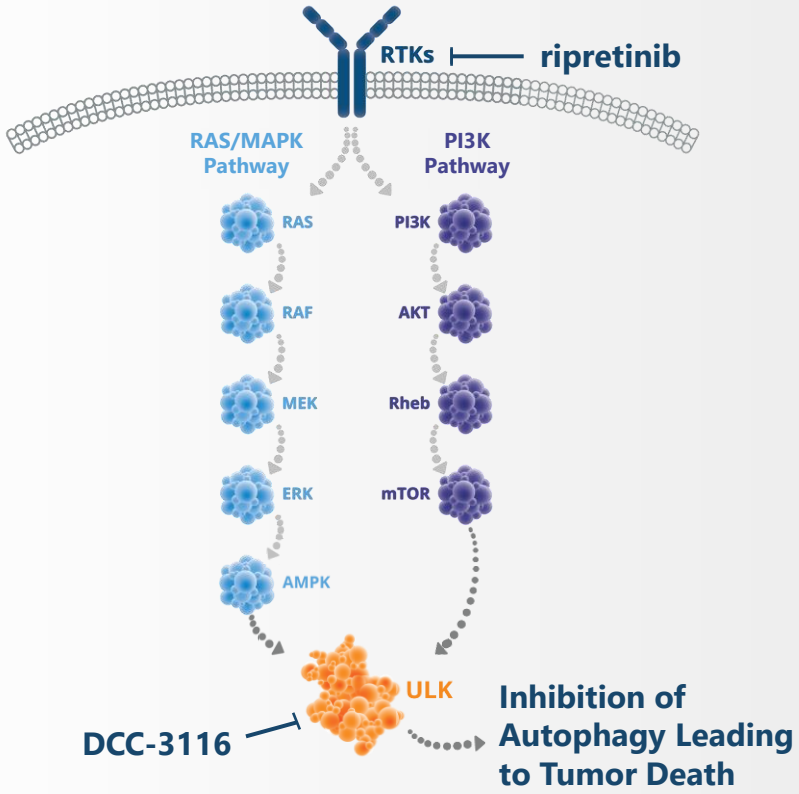


Colo-205: $BRAF^{V600E}$ Colorectal Cancer Model



Notes: Data presented at the AACR Annual Meeting 2023; % reg is the percent of mice that had regressions. %TGI and %Reg were calculated at the last day of dosing; BID=twice daily; BIW=2 times a week; BRAF=proto-oncogene b-RAF; PO=orally; QD=once daily; Reg=regression; TGI=tumor growth inhibition

DCC-3116 SYNERGIZES WITH RIPRETINIB IN GIST CANCER MODELS

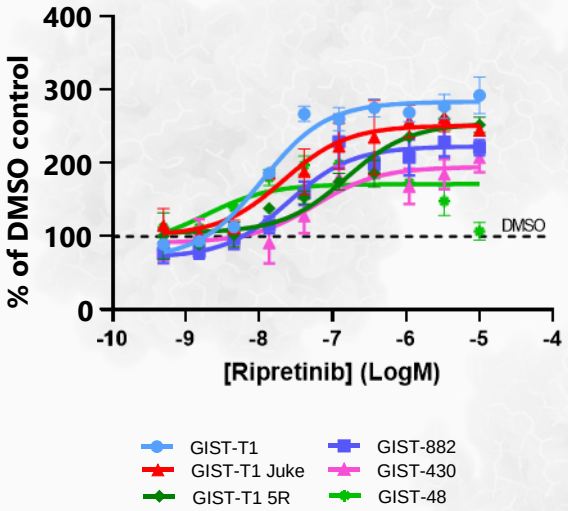


- Most gastrointestinal stromal tumors (GIST) are driven by mutations in KIT kinase and approved treatments include imatinib, sunitinib, regorafenib, and ripretinib
- Inhibition of mutant KIT activates autophagy and promotes cancer cell survival
- Drug resistance generally develops through secondary mutations in KIT as well as through the adaptive stress response pathway, including autophagy
- Preclinically, DCC-3116 synergizes with ripretinib to induce tumor regressions by reducing ULK-mediated autophagy

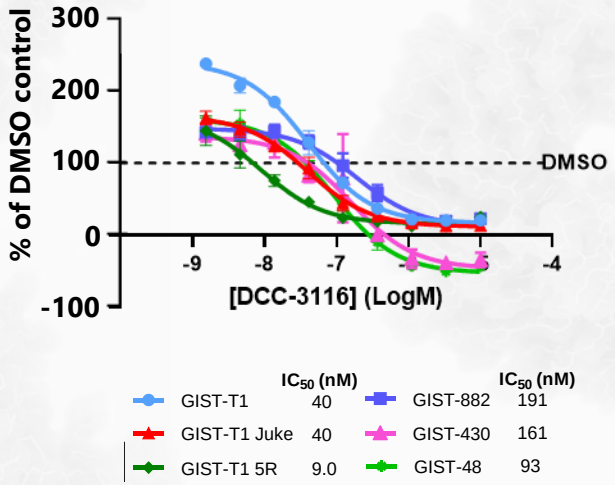
Notes: AKT=protein kinase B; AMPK=AMP-activated protein kinase; EGFR=epidermal growth factor receptor; ERK=extracellular signal-regulated kinase; KIT=KIT proto-oncogene receptor tyrosine kinase; LKB1=liver kinase B1; MAPK=mitogen-activated protein kinase; mTOR=mammalian target of rapamycin; PI3K=phosphatidylinositol-3 kinase; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma gene; Rheb=ras homolog enriched in brain; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.

DCC-3116 INHIBITS RIPRETINIB-INDUCED ULK ACTIVATION AND AUTOPHAGIC FLUX IN KIT-MUTATED GIST CELL LINES

GIST Mutated Cell Lines: Ripretinib

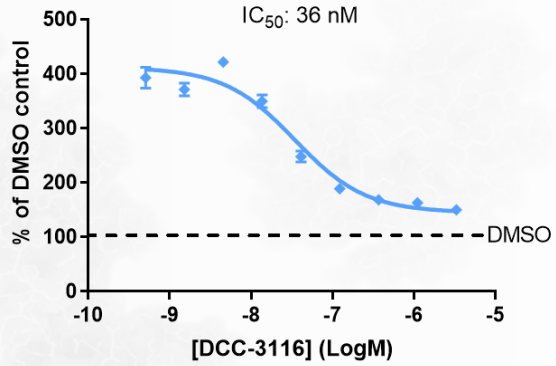


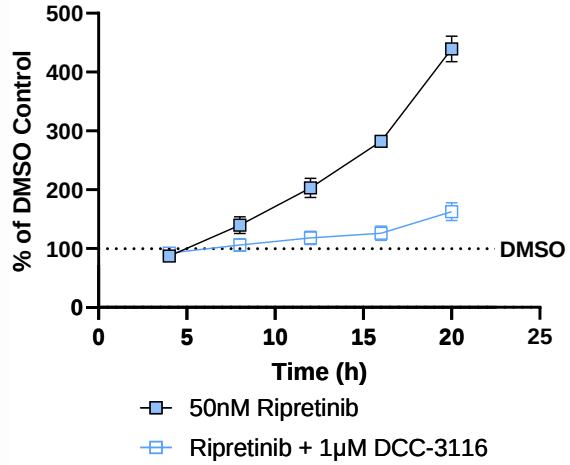
GIST Mutated Cell Lines: 50 nM Ripretinib + DCC-3116



	IC_{50} (nM)		IC_{50} (nM)
GIST-T1	40	GIST-882	191
GIST-T1 Juke	40	GIST-430	161
GIST-T1 5R	9.0	GIST-48	93

GIST-T1: GIST Exon 11 Mutated Cell Line

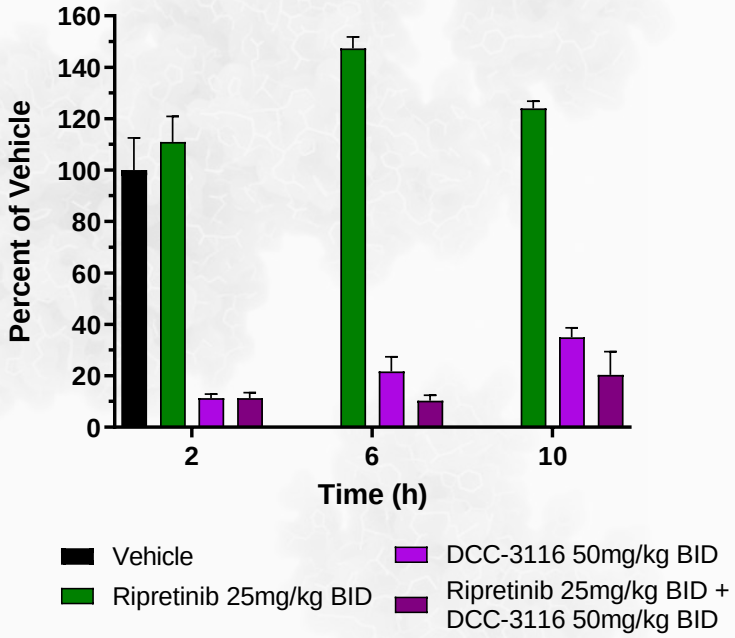




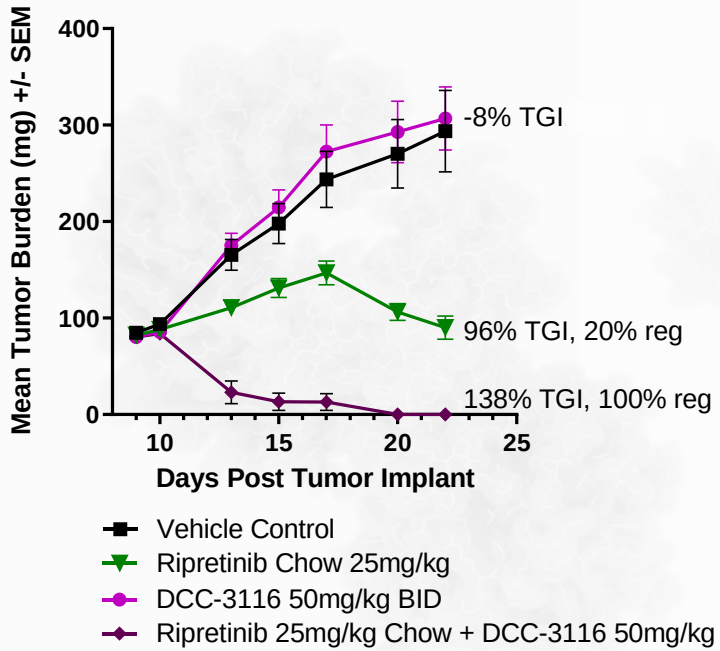
Notes: Data presented at the AACR Annual Meeting 2023; DMSO=dimethyl sulfoxide; GIST=gastrointestinal stromal tumor; GIST-430=Exon 11 del/exon 13 V654A; GIST-882=Exon 13 K642E; GIST-T1=Exon 11 del; GIST-T1 5R=Exon 11 del/exon 14 T670I; GIST-T1 Juke=Exon 11 del/exon 17 D816E; KIT=KIT proto-oncogene receptor tyrosine kinase; ULK=unc-51-like kinase.

DCC-3116 SHOWS 100% TUMOR REGRESSIONS IN COMBINATION WITH RIPRETINIB IN KIT EXON 11 MUTATED GIST XENOGRAFT MODEL

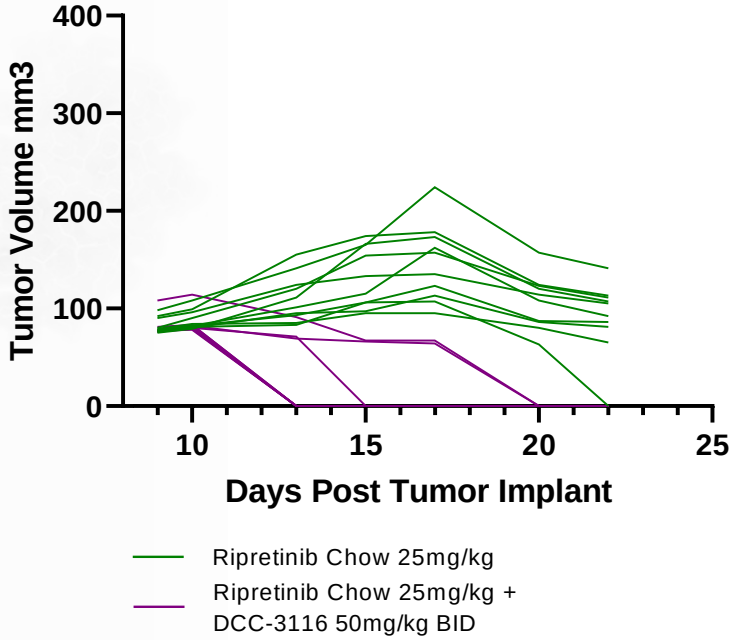
GIST-T1: PK/PD



GIST-T1: Tumor Growth Inhibition



GIST-T1: Tumor Volume



Notes: Data presented at the AACR Annual Meeting 2023; % reg is the percent of mice that had regressions; %TGI and %Reg were calculated at the last day of dosing; BID=twice daily; GIST=gastrointestinal stromal tumor; GIST-T1=Exon 11 del; KIT=KIT proto-oncogene receptor tyrosine kinase; PD=pharmacodynamics; PK=pharmacokinetics; Reg.=regression; TGI=tumor growth inhibition.

STRONG PRECLINICAL DATA SUPPORTS NEW CLINICAL COMBINATIONS

DCC-3116 + Encorafenib + Cetuximab

- DCC-3116 blocked $BRAF^{V600E}$ inhibitor and cetuximab-induced ULK activation and autophagic flux in preclinical models
- DCC-3116 exhibited combination efficacy in preclinical cancer models, leading to superior inhibition of tumor growth or to tumor regression

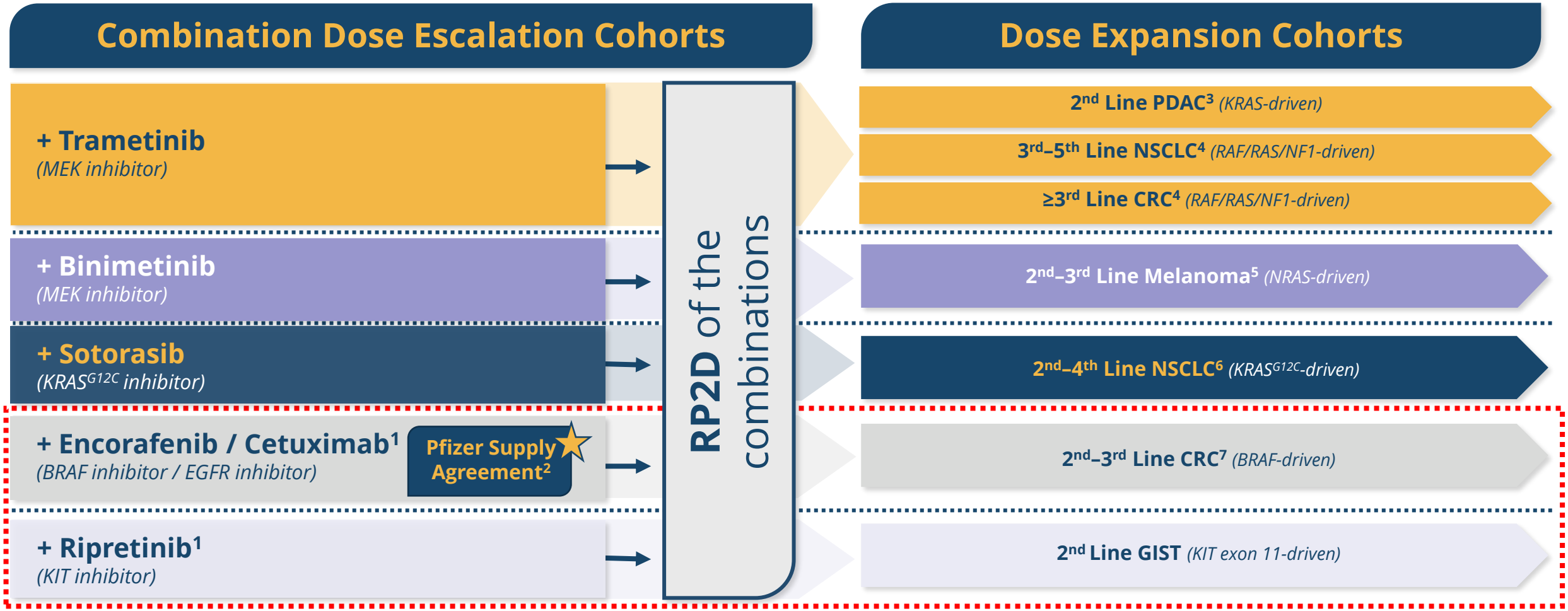
DCC-3116 + Ripretinib

- DCC-3116 blocked ripretinib-induced ULK activation and autophagic flux in preclinical models
- DCC-3116 exhibited combination efficacy in preclinical cancer models, leading to strong tumor regressions

Initiation of DCC-3116 dose escalation cohorts in combination with ripretinib and with encorafenib + cetuximab expected in 2H 2023

Notes: Data presented at the AACR Annual Meeting 2023; BRAF=proto-oncogene b-RAF; ULK=unc-51-like kinase.

PHASE 1 COMBINATION COHORTS EVALUATING MULTIPLE COMBINATIONS



Notes: CRC=colorectal cancer; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; KRAS=Kirsten rat sarcoma virus; MEK=MAPK/ERK kinase; MTD=maximum tolerated dose; NRAS=neuroblastoma RAS viral oncogene homolog; NSCLC=non–small-cell lung cancer; PDAC=pancreatic ductal adenocarcinoma; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase; RAS=rat sarcoma gene; RP2D=recommended Phase 2 dose; (1) Corporate goal planned for 2H 2023; (2) Under the terms of the clinical trial collaboration and supply agreement with Pfizer, Inc., Deciphera will sponsor the trial and Pfizer will supply encorafenib at no cost; (3) with a documented mutation in KRAS; (4) with a documented mutation in KRAS, NRAS, NF1, or BRAF; (5) with a documented mutation in NRAS; (6) with a documented mutation in $KRAS^{G12C}$; (7) with a documented mutation in $BRAF^{V600E}$.

DCC-3009 (PAN-KIT INHIBITOR)

Bryan Smith, Ph.D.

Vice President, Biological Sciences

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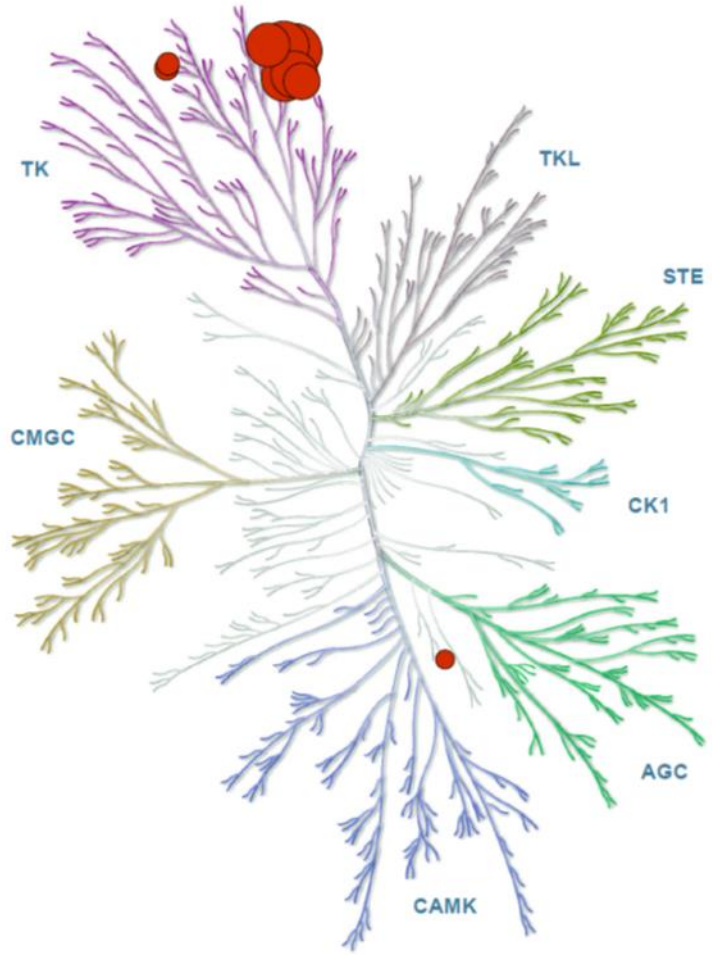
Notes: KIT=KIT proto-oncogene receptor tyrosine kinase.

DCC-3009 IS A POTENT AND SELECTIVE NEXT-GEN KIT INHIBITOR



- DCC-3009 is a **potential best-in-class pan-KIT inhibitor** engineered using Deciphera's proprietary switch-control platform
- Unmet medical need remains for a **pan-KIT inhibitor** that can broadly and potently inhibit the **spectrum of KIT mutations** that drive GIST
- Potent inhibitor of primary KIT mutations in **exons 9 and 11 and secondary mutations across exons 13, 14, 17, and 18**
- Highly selective for KIT with **optimized pharmaceutical and ADME properties**
- **Strong pre-clinical efficacy data** in xenograft models driven by drug resistant KIT mutations

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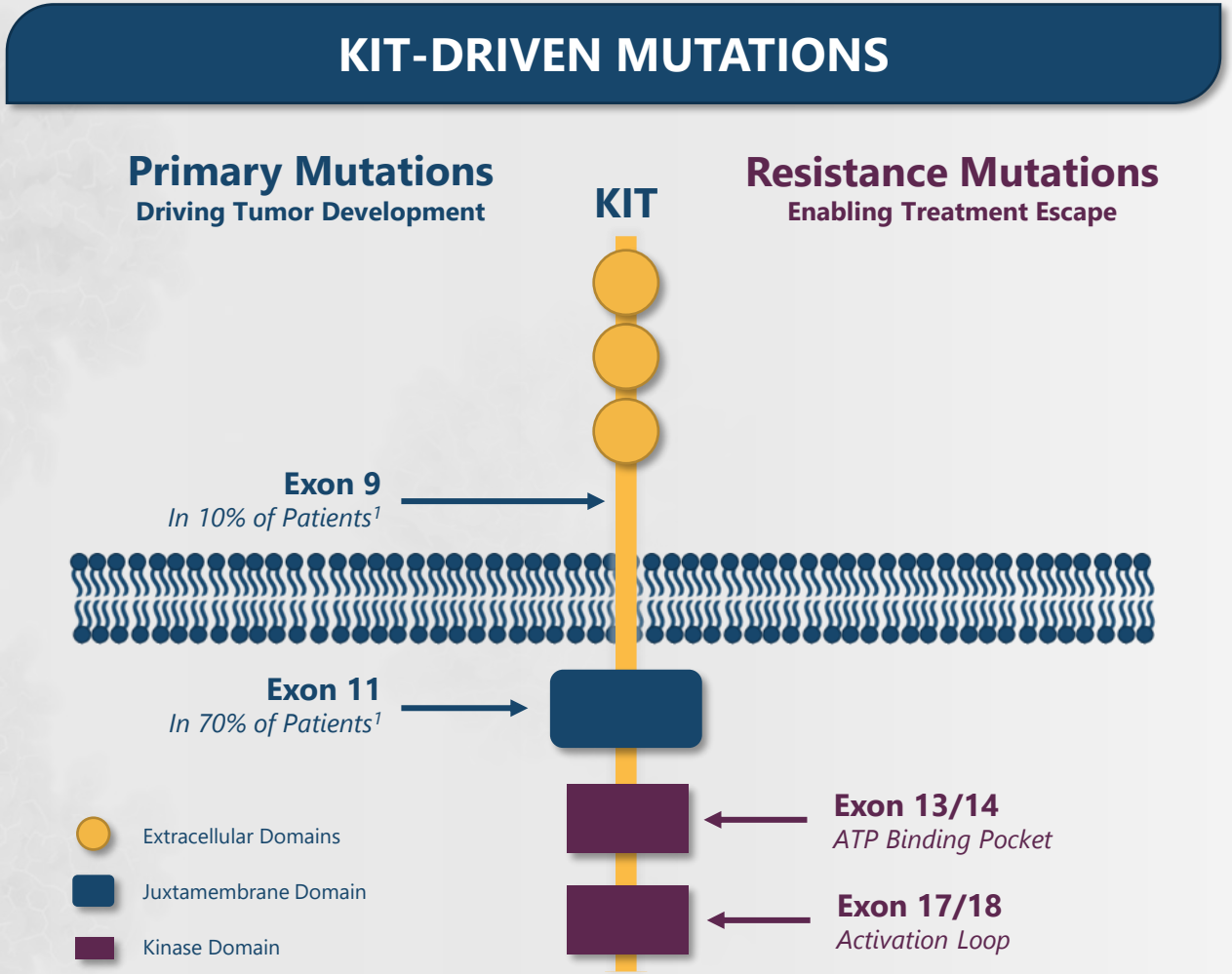
Notes: ADME=absorption, distribution, metabolism, and excretion; GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase.

GIST PROGRESSION DRIVEN BY SECONDARY RESISTANCE MUTATIONS IN KIT



Notes: ATP=Adenosine Triphosphate; GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase; (1) Oppelt et al. J Gastrointest Oncol 2017;8(3):466-473.

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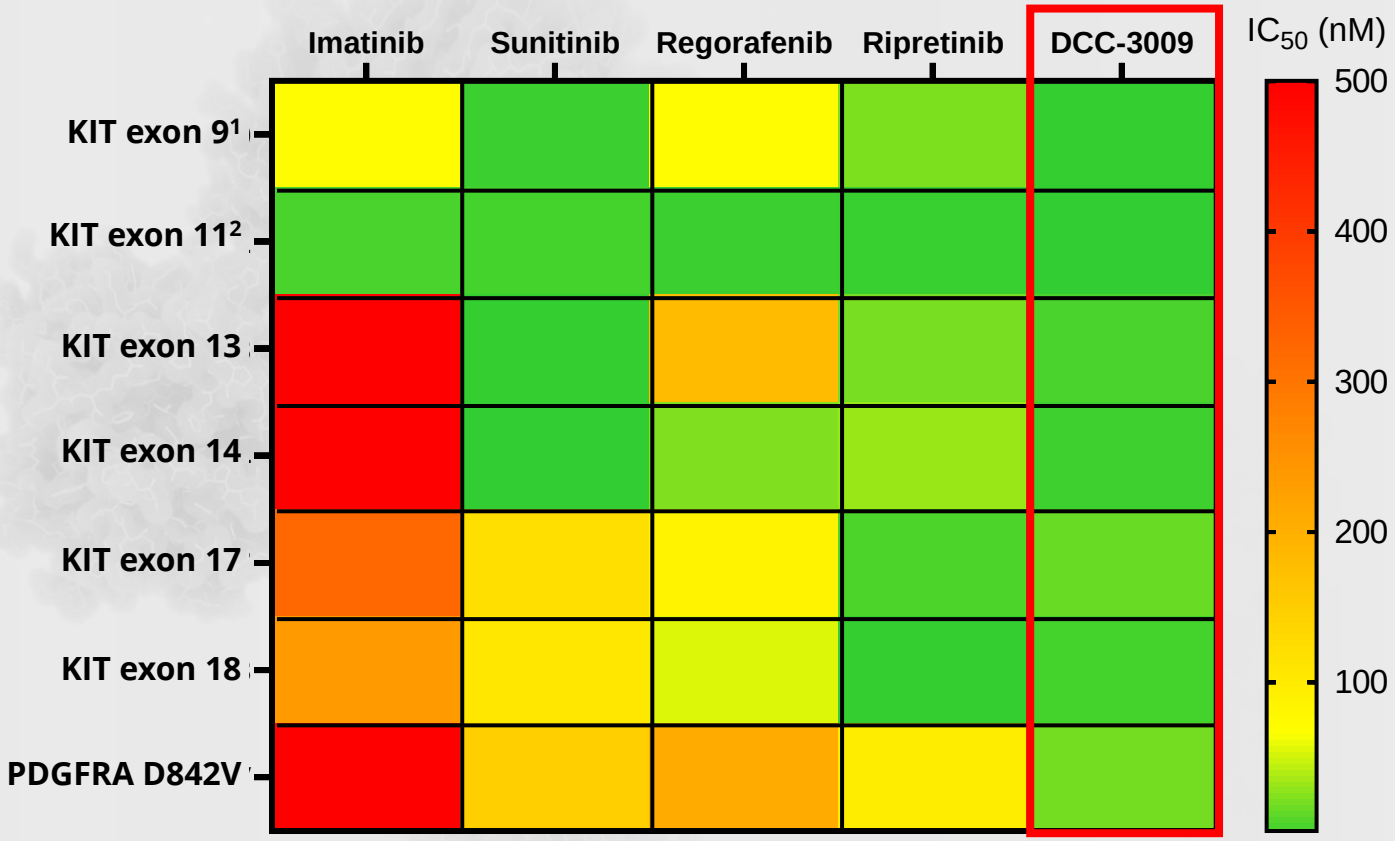
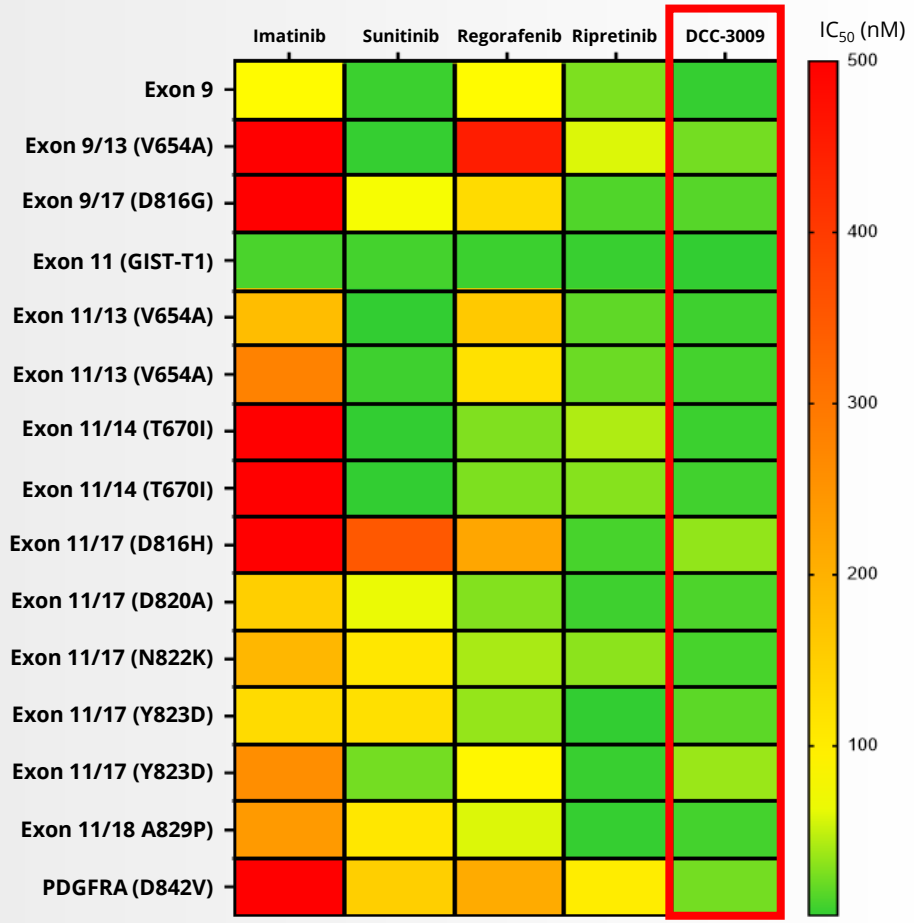
DCC-3009 POTENTLY INHIBITS THE SPECTRUM OF KNOWN PRIMARY AND SECONDARY DRUG-RESISTANT MUTATIONS IN GIST





Notes: GIST=gastrointestinal stromal tumor; GIST-T1=exon 11 del; (1) exon 9 primary is A502/Y503 duplication; (2) exon 11 primary mutations include deletions or the V560D point mutation.

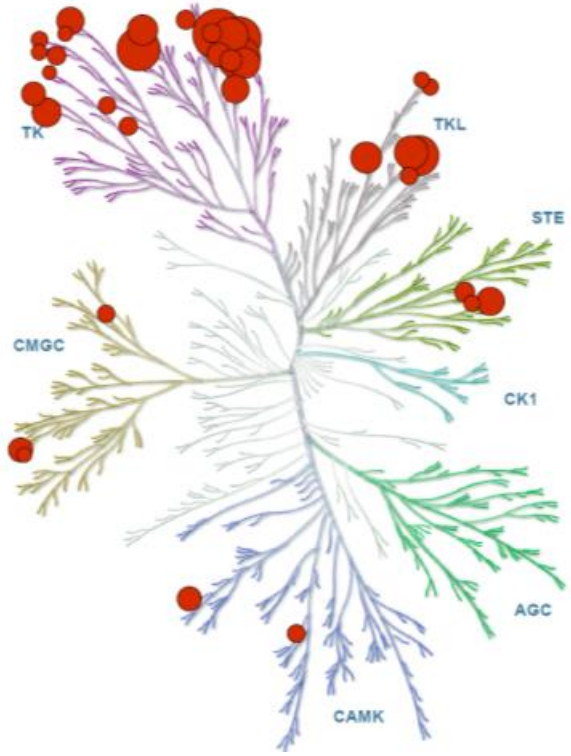
DCC-3009 SHOWED OPTIMIZED PHARMACEUTICAL AND ADME PROPERTIES FOR ORAL ADMINISTRATION

Property	Result
Human Microsomal Stability	$t_{1/2}$ > 145 min
Human Plasma Protein Binding	96.3% bound
Caco2 Permeability	$11x10^{-6}$ cm/s
Caco2 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 $K_{pu/u}$	4%

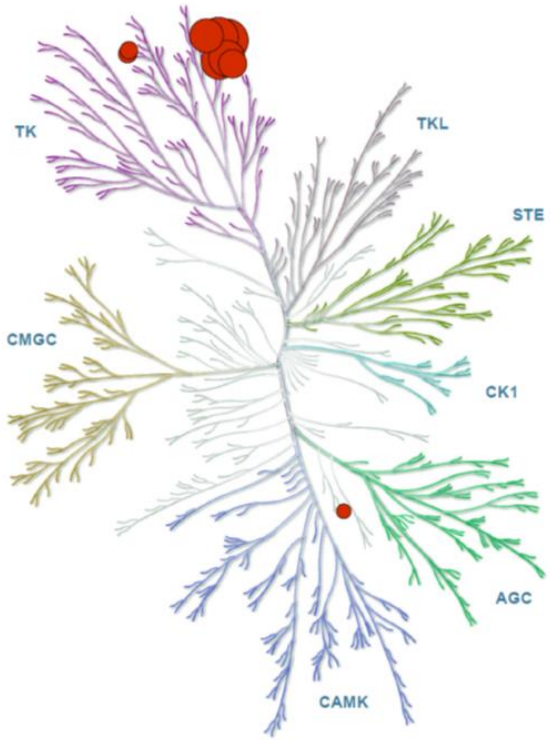
Notes: Data presented at the AACR Annual Meeting 2023; CYP=cytochrome P450; hERG=human ether-a-go-go–related gene; ; $K_{pu/u}$=unbound partition coefficient (free brain concentration/free plasma concentration); $T_{1/2}$=half-life.

DCC-3009 EXHIBITS A FAVORABLE KINOME SELECTIVITY PROFILE

Ripretinib



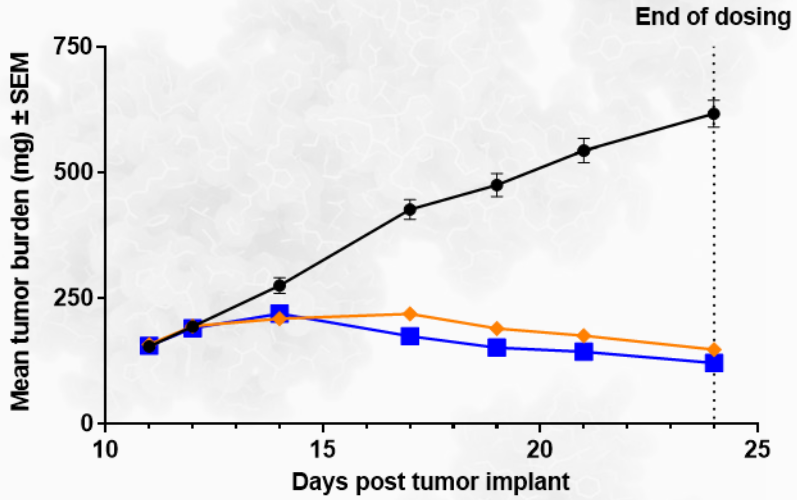
DCC-3009



Notes: Evaluation in a ~400 kinase panel – all IC50 values < 1 µM are shown.

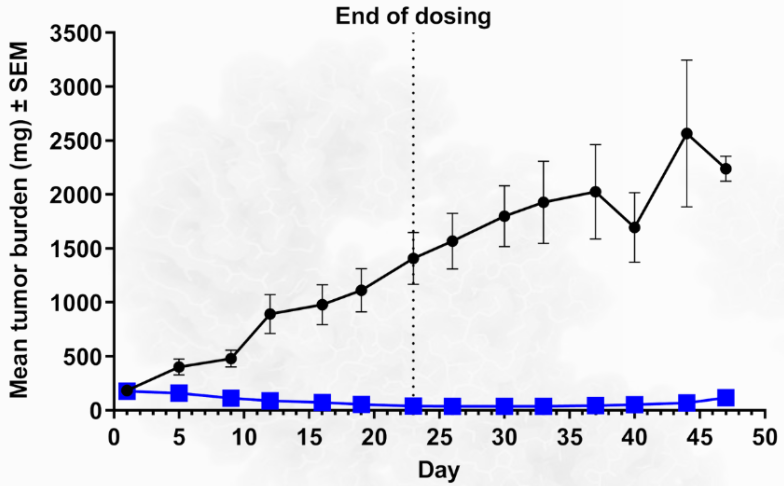
DCC-3009 RESULTED IN TUMOR REGRESSIONS IN GIST XENOGRAFT MODELS, INCLUDING KIT EXONS 9, 11, 13 AND 17 MUTATIONS

V654A: BaF3 KIT Exon 9 AY dup / Exon 13



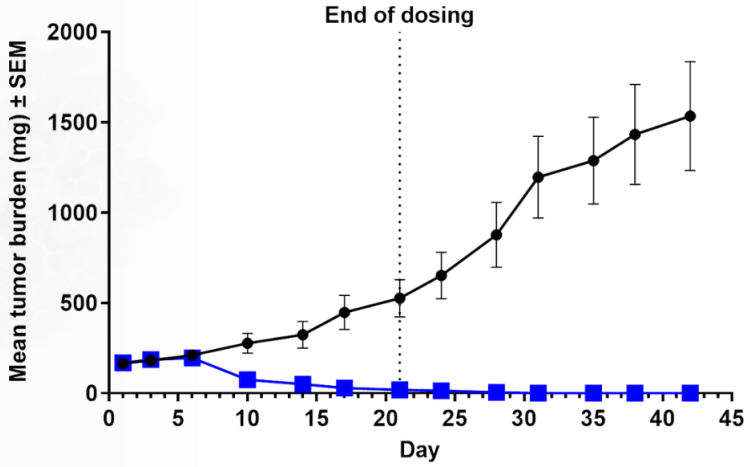
- Vehicle
- DCC-3009 50 mg/kg BID — 22% regression
- Sunitinib 20 mg/kg BID — 6% regression

V654A: GIST PDX KIT Exon 11 delWK / Exon 13



- Vehicle
- DCC-3009 50 mg/kg BID — 80% regression

Y823D: GIST PDX KIT Exon 11 delWK / Exon 17



- Vehicle
- DCC-3009 50 mg/kg BID — 99.7% regression

Notes: Data presented at the AACR Annual Meeting 2023; BID=twice daily; GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase; PDX=patient-derived xenograft.

DCC-3009 IS A POTENTIAL BEST-IN-CLASS PAN-KIT INHIBITOR

- DCC-3009 is a pan-KIT inhibitor exhibiting high potency for KIT mutants in pre-clinical 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
- DCC-3009 is highly selective for KIT and has a high free fraction to enable 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

★ **DCC-3009 IND expected in 1H 2024**

Notes: Data presented at the AACR Annual Meeting 2023; ADME=absorption, distribution, metabolism, and excretion; GIST=gastrointestinal stromal tumor; IND=Investigational New Drug Application; KIT=KIT proto-oncogene receptor tyrosine kinase.

DP-9149 (GCN2 ACTIVATOR)

Gada Al-Ani, Ph.D.

Sr. Principal Investigator, Biological Sciences

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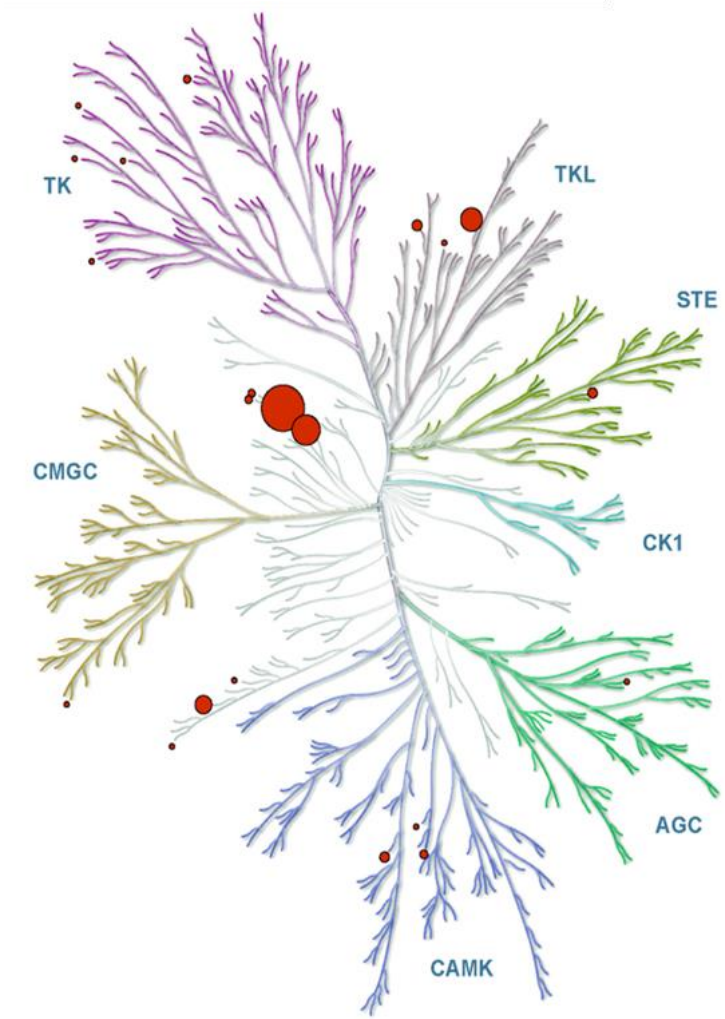
Notes: GCN2=general control nonderepressible 2.

DP-9149 IS A POTENT AND SELECTIVE ACTIVATOR OF THE GCN2 KINASE



Compelling Preclinical Data

- Potent and selective activator of GCN2 kinase
- Strong single agent activity in solid tumor models *in vivo*
- Tumor regressions in combination with standard of care agents *in vivo*

Novel Mechanism of Action

- Leveraging the cytotoxic arm of the Integrated Stress Response pathway enables the engagement of cancer cell death pathways
- GCN2 overexpression in solid tumors provides a favorable therapeutic window as evident by tolerability in preclinical models
- Synergizes with other stress-inducing therapies (anti-angiogenics/tumor driver-targeting agents) and effective in RAS/MAPK driven cancers

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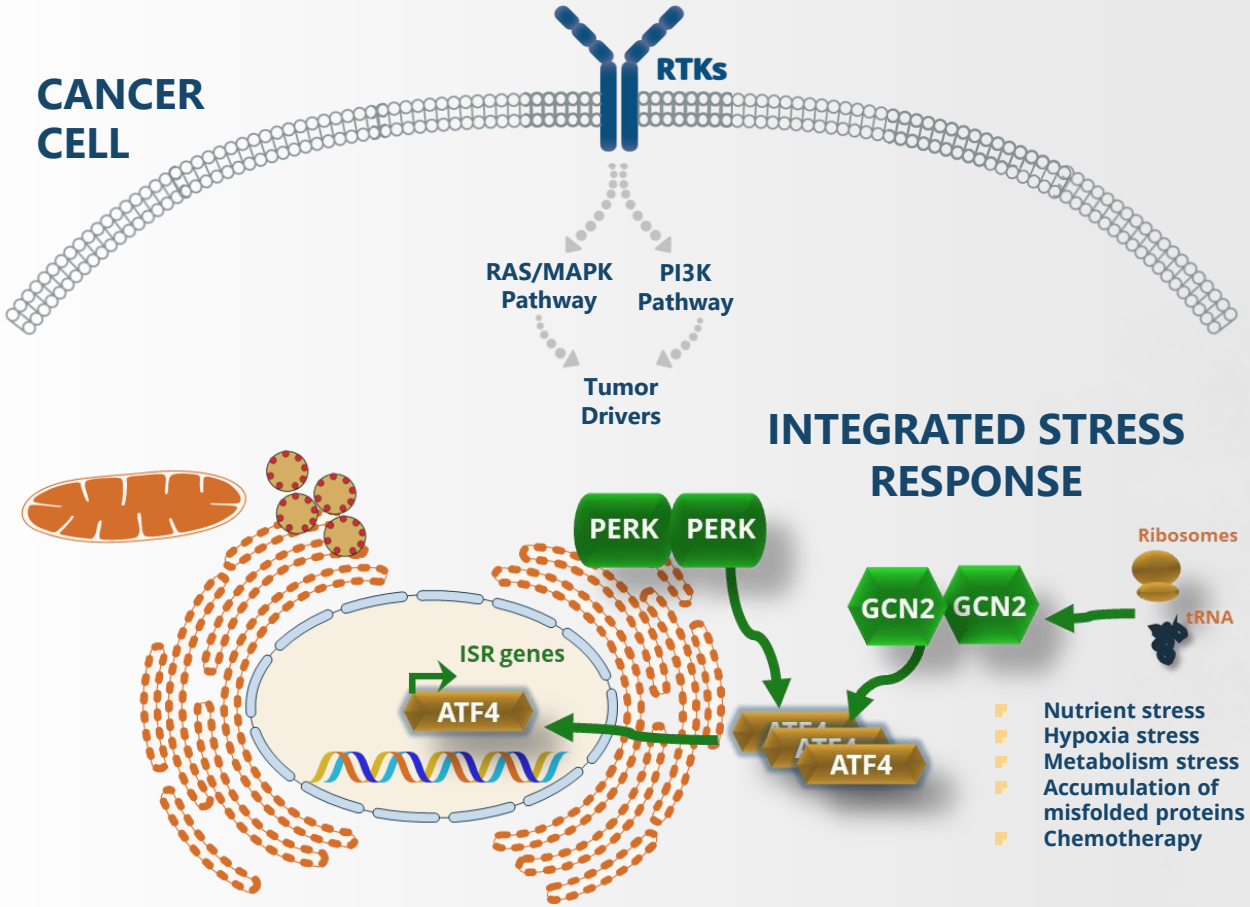
Notes: GCN2=general control nonderepressible 2; MAPK=mitogen-activated protein kinase; RAS=rat sarcoma gene.

THE INTEGRATED STRESS RESPONSE PATHWAY & GCN2 ACTIVATION



- The Integrated Stress Response (ISR) is a **major adaptive stress response pathway in cancer** and plays an important role in cell fate determination
- Oncogene addicted solid tumors are under high stress levels and are **dependent on a well-balanced ISR pathway** for accelerated growth
- Inhibition or stimulation of GCN2 in solid tumors can be pharmacologically leveraged to **induce anti-tumoral effects**
- Deciphera's GCN2 activator (DP-9149) has shown **anti-tumoral effects in solid tumors *in vitro* and *in vivo***

Notes: ATF4=activating transcription factor 4; GCN2=general control nonderepressible 2; ISR=Integrated Stress Response; MAPK=mitogen-activated protein kinase; PERK=protein kinase R–like endoplasmic reticulum kinas; PI3K=phosphatidylinositol-3 kinase; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase.

GCN2 ACTIVATOR UPREGULATES THE ISR TO PROMOTE CANCER CELL DEATH

Binding of GCN2 activator to only one monomer **selectively and potently transactivates** the unbound GCN2 protomer

Robust upregulation of ISR genes: ATF4 upregulation, expression of CHOP, and apoptotic signals

Persistent activation of the cytotoxic arm of the ISR leading to unresolved stress and **cancer cell death**

Notes: ATF4=activating transcription factor 4; GCN2=general control nonderepressible 2; ISR=Integrated Stress Response.

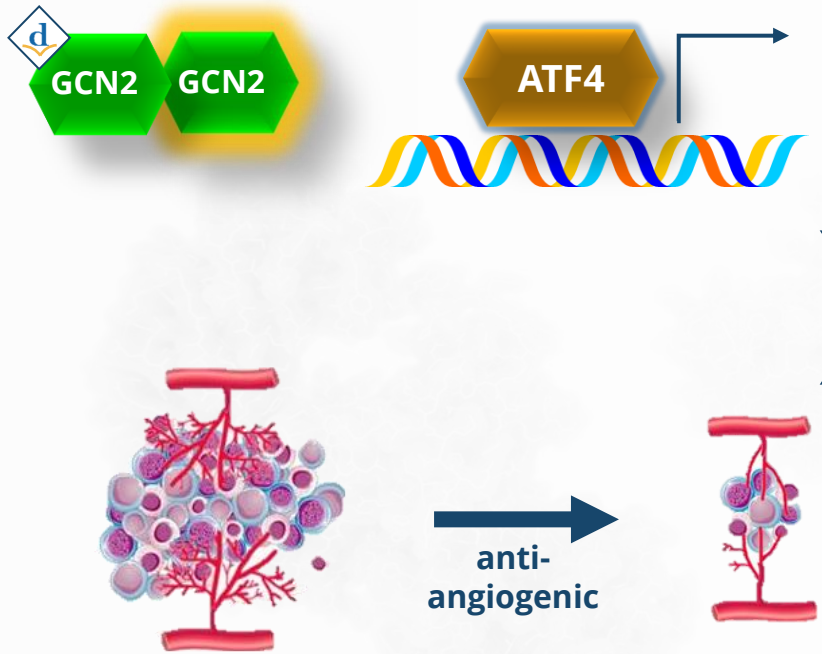
GCN2 ACTIVATOR INDUCES CELL DEATH AS A SINGLE AGENT AND PROMOTES TUMOR REGRESSION IN COMBINATION

Single Agent Activity

Oncogene-driven cancer cells are vulnerable to activation of cytotoxic arm of the ISR

Combination Opportunities

Therapy induced cytotoxicity (e.g. anti-angiogenics, MAPKi) further sensitizes cancer cells to ISR pathway activation



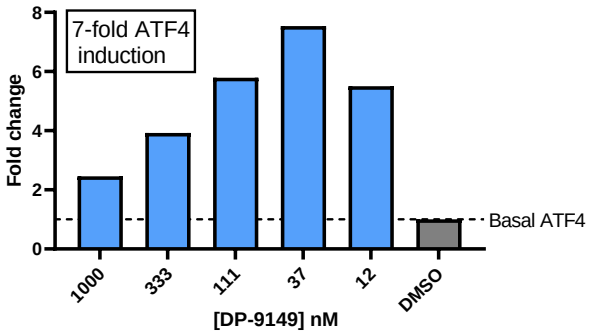
Deeper Response and **Tumor Regression** Induced by Combination Therapy

Notes: ATF4=activating transcription factor; GCN2=general control nonderepressible 2; ISR=Integrated Stress Response; MAPKi=mitogen-activated protein kinase inhibitor.

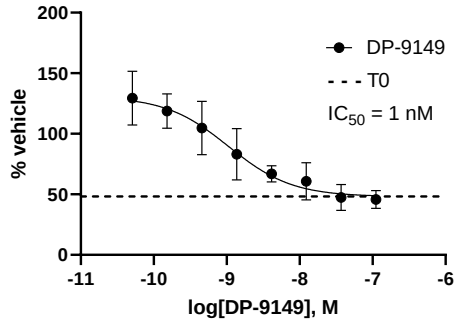
DP-9149 SELECTIVELY AND POTENTLY ACTIVATES GCN2 AND HAS AN OPTIMIZED PHARMACEUTICAL AND SELECTIVITY PROFILE

DP-9149 Upregulates the ISR Pathway and Potently Inhibits Cell Growth as a Single Agent

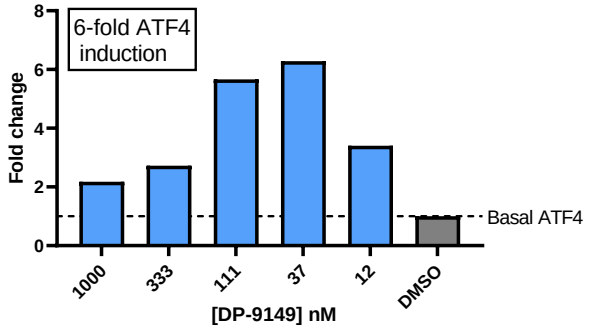
786-O: Renal Cell Carcinoma
ATF4 Upregulation



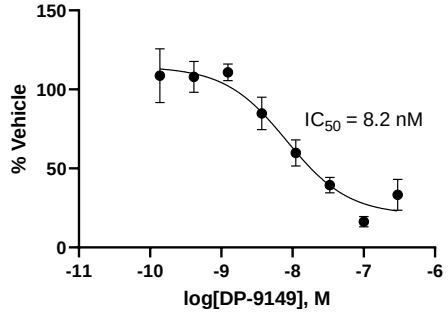
786-O: Renal Cell Carcinoma
Spheroid Growth Inhibition



LoVo: KRAS G13D Colorectal ATF4
Upregulation



LoVo: KRAS G13D Colorectal
Spheroid Growth Inhibition



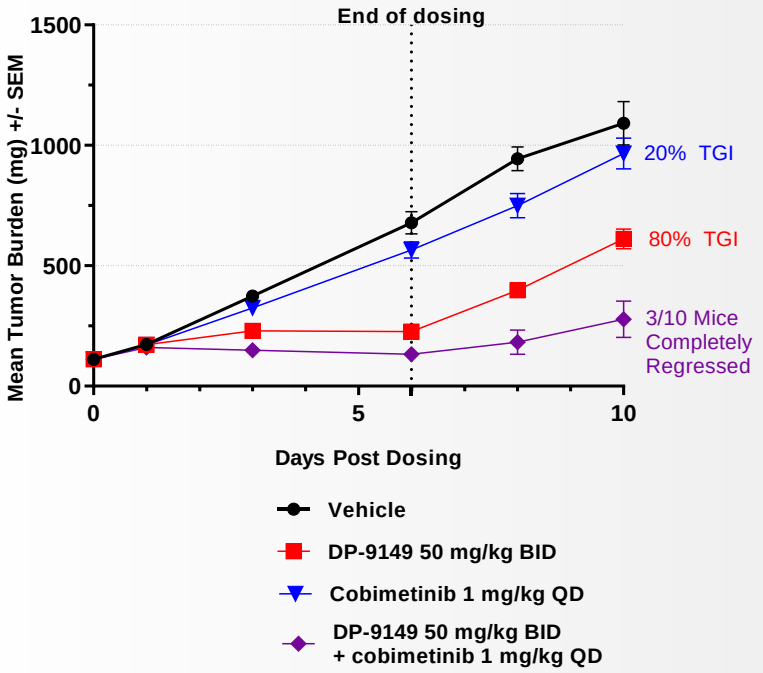
DP-9149 was Designed as a Potent and Selective Activator of GCN2

	Assay	DP-9149
Enzymatic Assays	GCN2 recombinant enzyme activation versus control	**2.5-fold activation**
Cellular Assays	ATF4 stimulation versus control 786-O (Renal; VHL-mut)	**7-fold activation**
	ATF4 Stimulation versus control LoVo (Colorectal; KRAS G13D)	**6-fold activation**
	Spheroid growth inhibition 786-O (Renal; VHL-mut)	**IC_{50} = 1 nM**
	Spheroid growth inhibition LoVo (Colorectal; KRAS G13D)	**IC_{50} = 8.2 nM**
Off-Target Profile	Kinome selectivity and safety (Cerep)	**High selectivity**
In Vivo	PK/PD	**Target engagement achieved**

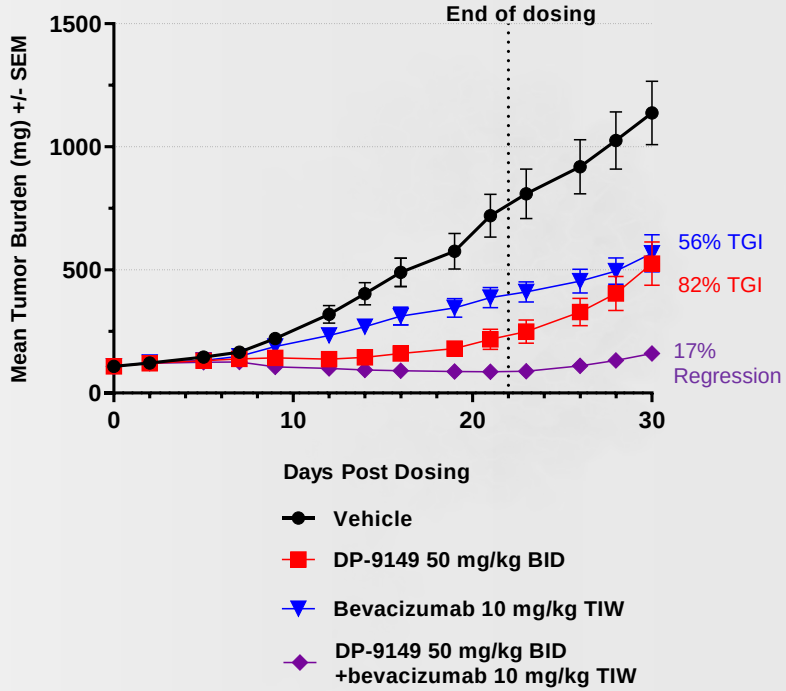
Notes: Data presented at the AACR Annual Meeting 2023; ATF4=activating transcription factor; DMSO=dimethyl sulfoxide; GCN2=general control nonderepressible 2; ISR=Integrated Stress Response; KRAS=Kirsten rat sarcoma virus; PD=pharmacodynamic; PK=pharmacokinetic; VHL=Von Hippel-Lindau.

DP-9149 RESULTS IN TUMOR GROWTH INHIBITION AS A SINGLE AGENT AND TUMOR REGRESSIONS IN COMBINATION *IN VIVO*

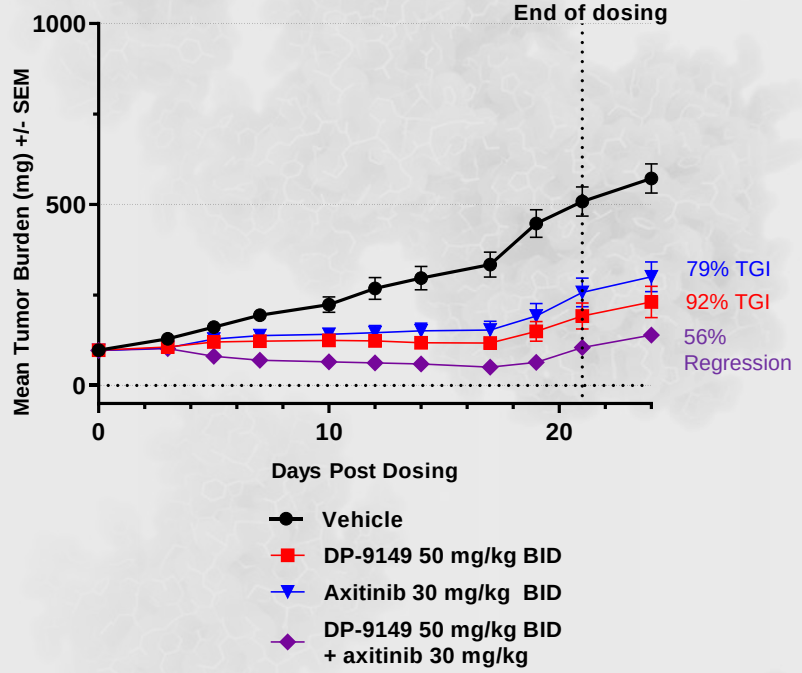
HT-1080: NRAS Fibrosarcoma Model
DP-9149 + Cobimetinib



LoVo: KRAS G13D CRC Model
DP-9149 + Bevacizumab



786-O: VHL Mutant RCC Model
DP-9149 + Axitinib



Notes: Data presented at the AACR Annual Meeting 2023; HT-1080 TGI was calculated on Day 6; LoVo TGI was calculated on Day 21; 786-8 TGI was calculated on Day 19; BID=twice daily; CRC=colorectal cancer; GCN2=general control nonderepressible 2; QD=once a day; BID= twice a day; RCC=renal cell carcinoma; TGI=tumor growth inhibition; TIW=3 times a week.

DP-9149 IS A NOVEL GCN2 ACTIVATOR WITH STRONG PRECLINICAL DATA

- The Integrated Stress Response is a novel Adaptive Stress Response mechanism in oncogene addicted solid tumors targetable through activation of GCN2
- DP-9149 was designed as a potent and selective activator of GCN2 with an optimized pharmaceutical and selectivity profile
- DP-9149 Exhibited Robust Activity in RAS mutant cancers and in VHL-mutant renal cell cancers as a single agent and in combination with standard-of-care agents *in vivo*
- Upregulating the ISR by activation of GCN2 through DP-9149 represents a novel anti-tumor approach in solid tumors *in vitro* and *in vivo* both as a single agent and in combination

DP-9149 is currently undergoing further preclinical studies

Notes: Data presented at the AACR Annual Meeting 2023; GCN2=general control nonderepressible 2; ISR=Integrated Stress Response; RAS=rat sarcoma gene; VHL=Von Hippel-Lindau.

CLOSING REMARKS

Steve Hoerter

President and Chief Executive Officer

decīphera

DECIPHERA

EXPECTED 2023 MILESTONES

QINLOCK®

- ✓ Present additional data from Phase 3 INTRIGUE ctDNA analysis at an ASCO Plenary Session
- Initiate INSIGHT Phase 3 study in 2L KIT exon 11+17/18 GIST patients **(2H 2023)**
- Continue geographic expansion with launches in key European markets **(2023)**

VIMSELTINIB

- ✓ Complete enrollment in the Phase 3 MOTION study
- Announce top-line results from MOTION study **(4Q 2023)**
- Present updated Phase 1/2 data in TGCT patients **(2H 2023)**

DCC-3116

- ✓ Present preclinical data on new combinations
- Present updated Phase 1 single agent and initial combination dose escalation data **(2H 2023)**
- Initiate MEK/G12C expansion cohort(s); initiate escalation cohort for encorafenib/cetuximab **(2H 2023)**

DCC-3084

- ✓ Present data on preclinical profile
- Submit IND to FDA **(2H 2023)**

PROPRIETARY DRUG DISCOVERY PLATFORM

- ✓ Nominate development candidate for pan-KIT inhibitor (DCC-3009 pan-KIT inhibitor)
- ✓ Present new preclinical data from research programs

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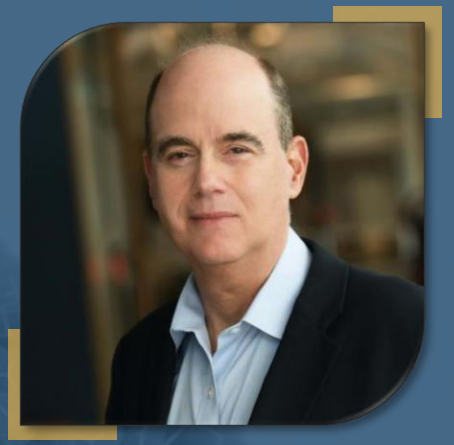
Notes: 2L=second-line; ASCO=American Society of Clinical Oncology; ctDNA=circulating tumor deoxyribonucleic acid; FDA=U.S. Food and Drug Administration; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; GIST=gastrointestinal stromal tumor; IND=Investigational New Drug Application; KIT=KIT proto-oncogene receptor tyrosine kinase; MEK=mitogen-activated extracellular signal-regulated kinase; TGCT=tenosynovial giant cell tumor.

DECIPHERA

Q&A

Steve Hoerter
Chief Executive Officer

Dan Flynn
Chief Scientific Officer



Matt Sherman
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Dan Martin
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Biological Sciences

Madhumita Bogdan
Sr. Principal Investigator,
Biological Sciences

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Vice President,
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THANK YOU