PARIS 2022 ESMO congress

Initial monotherapy results of a phase 1 first-in-human study of ULK1/2 inhibitor DCC-3116 alone and in combination with MAPK pathway inhibition

Anthony Tolcher, David S Hong, Andrae Vandross, Ravi Amaravadi, Charles Psoinos, Denise Brennan, Matthew L Sherman, Rodrigo Ruiz-Soto, Madhumita Bogdan, Cynthia Leary, Lakshmi Viswanathan, Kam Sprott, Frederic J Reu, Colin Weekes

Presented by Anthony Tolcher, MD, FRCPC

FPN: 450O
Paris, France. September 10, 2022

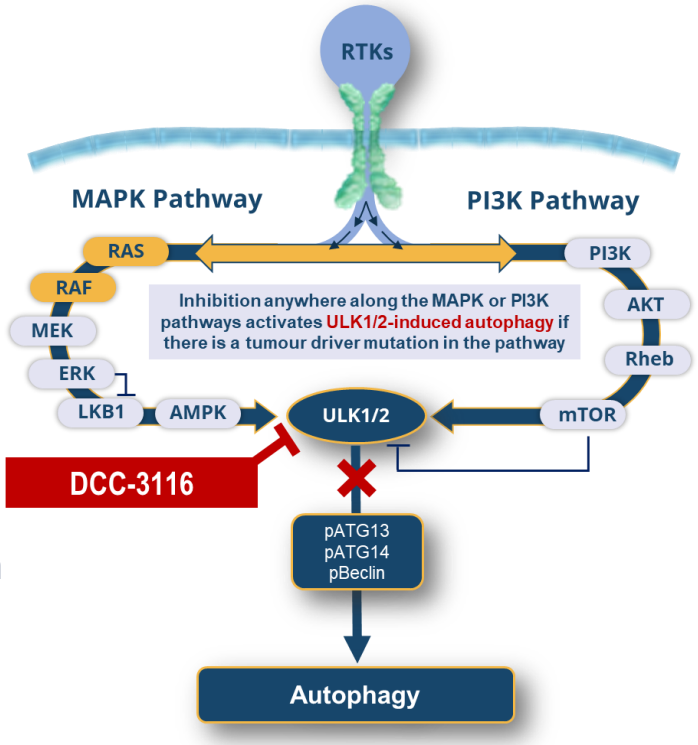
Declaration of Interests

Anthony Tolcher, MD, FRCPC

- Consultant for AbbVie, Inc.; Aclaris Therapeutics; Agenus, Inc.; Asana BioSciences, LLC; Ascentage; Axlmmune; Bayer; BluPrint Oncology; Daiichi Sankyo, Inc.; Gilde Healthcare Partners; HBM Partners; IDEA Pharma; Immuneering; Immunomet Therapeutics, Inc.; Impact Therapeutics US, Inc.; Karma Oncology B.V.; Kirilys Therapeutics, Inc.; Lengo Therapeutics, Inc.; Link Immunotherapeutics; Mekanistic Therapeutics; Menarini Ricerche; Mersana; Nanobiotix; Nurix Therapeutics; Ocellaris Pharma, Inc. & Eli Lilly; Partner Therapeutics; Pfizer, Inc.; Qualigen Therapeutics; Pierre Fabre; Ryvu Therapeutics; Seattle Genetics; SK Life Science; SOTIO Biotechnology Co.; Spirea Limited Inc.; Sunshine Guojian Pharmaceutical (Shanghai) Co., Ltd; Transcenta Therapeutics Inc.; Transgene; Trillium Therapeutics Inc.; Verastem Oncology; VRise Therapeutics, Inc.; and Zentails
- Advisory board member for Adagene, Inc.; Aro Biotherapeutics; BioInvent; Boeringer Ingelheim International GmbH; Deka Biosciences; Eleven Bio; Elucida; EMD Serono/MERCK KGaA, Hiber Cell, Inc.; Ikena Oncology; Immunome, Inc.; Janssen Global Services, LLC; JAZZ; NBE Therapeutics; Mirati Therapeutics Inc. Pelican; Pieris Pharma; PYXIS Oncology; Senti Biosciences; Vincerx; ZielBio, Inc.; and Zymeworks Biopharmaceuticals Inc.
- Fees for consulting and advisory board memberships for Dr. Anthony Tolcher are paid to New Experimental Therapeutics, LLC d/b/a NEXT Oncology, of which Dr. Tolcher is President and Founder

Background

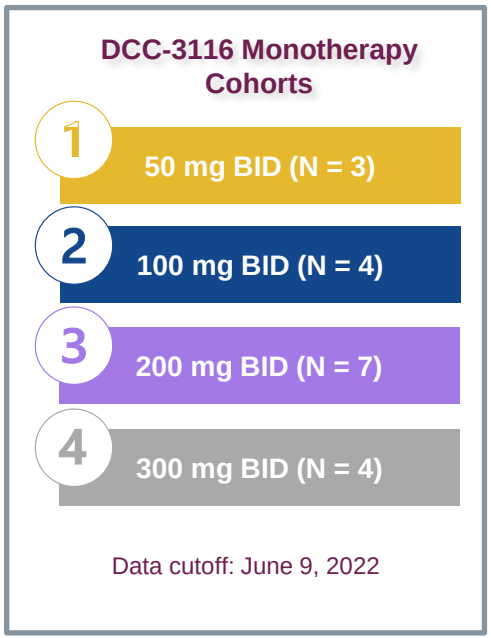
- RTK-, RAS-, and RAF-mutant cancer cells activate autophagy via ULK1/2 as a resistance mechanism to MAPK and PI3K pathway inhibitors[1–3]
- DCC-3116 is a first-in-class, potent, and selective small molecule switch-control kinase inhibitor of ULK1/2[4]
- DCC-3116 potently inhibits phosphorylation of ULK1/2 substrates ATG13 and ATG14 to block autophagy[4,5]
- DCC-3116 produced additive or synergistic antitumour activity when combined with a broad array of MAPK pathway inhibitors in preclinical studies[4,6]
- Here, we describe initial DCC-3116 monotherapy results from an ongoing phase 1/2 study in participants with RAS/RAF mutant advanced or metastatic solid tumours (NCT04892017)



AKT, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; ATG13, autophagy-related protein 13; ATG14, autophagy-related protein 14; ERK, extracellular signal-regulated kinase; LKB1, liver kinase B1; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; mTOR, mammalian target of rapamycin; p, phosphorylated; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma small GTPase protein; Rheb, Ras homolog enriched in brain; RTK, receptor tyrosine kinase; ULK, Unc-51–like autophagy activating kinase.

1. Guo JY, et al. *Genes Dev.* 2011;25:460–70. 2. Kondapuram SK, et al. *J Cancer Metastasis Treat.* 2019;5:32. 3. Kinsey CG, et al. *Nat Med.* 2019;25:620–7. 4. Smith BD, et al. AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics 2019. Poster for Abstract B129. 5. Data on File. Deciphera Pharmaceuticals, LLC. 6. McMahon M, et al. AACR Annual Meeting 2022. Session MS.ET06.01.

Methods and Study Design



- Key eligibility: RAS or RAF mutation, locally advanced or metastatic cancer, progression despite standard therapies
- Monotherapy 3+3 dose escalation
- DCC-3116 orally BID in 28-day cycles
- Primary objectives
  - Safety and tolerability
  - Select DCC-3116 starting dose for combination with trametinib, binimetinib, and sotorasib escalation cohorts
- Additional objectives
  - Antitumour activity per RECIST v1.1
  - Pharmacokinetics
  - Pharmacodynamics

BID, twice daily; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma small GTPase protein; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1 .

Participant Demographics and Clinical Characteristics

	DCC-3116				All participants N = 18
	50 mg BID n = 3	100 mg BID n = 4	200 mg BID n = 7	300 mg BID n = 4	
Age, mean (SD), years	51.7 (12.66)	58.3 (8.10)	67.4 (5.53)	62.5 (10.28)	61.7 (9.70)
Sex, male	2 (67)	4 (100)	4 (57)	3 (75)	13 (72)
Race					
White	2 (67)	2 (50)	5 (71)	4 (100)	13 (72)
Nonwhite[a]	1 (33)	1 (25)	1 (14)	0	3 (17)
Not reported	0	1 (25)	1 (14)	0	2 (11)
Cancer type					
Colorectal	1 (33)	2 (50)	3 (43)	4 (100)	10 (56)
Pancreas	1 (33)	1 (25)	3 (43)	0	5 (28)
Other[b]	1 (33)	1 (25)	1 (14)	0	3 (17)
Mutation type					
KRAS	2 (67)	3 (75)	6 (86)	4 (100)	15 (83)
BRAF	1 (33)	1 (25)	1 (14)	0	3 (17)
Number of prior anticancer regimens					
Median (range)	2 (2–2)	3 (2–4)	3 (1–10)	3 (2–4)	3 (1–10)
1	0	0	1 (14)	0	1 (6)
2	3 (100)	2 (50)	1 (14)	1 (25)	7 (39)
3	0	0	3 (43)	2 (50)	5 (28)
≥4	0	2 (50)	2 (29)	1 (25)	5 (28)

- Mean age 61.7 years
- Male 72%; White 72%
- Colorectal and pancreatic cancers 83% combined
- KRAS mutation 83%
- Median number of prior anticancer regimens 3 (range 1–10)

Data cutoff: June 9, 2022. Data presented as n (%) unless otherwise indicated. [a]Includes Asian and Native Hawaiian or Other Pacific Islander. [b]Includes parathyroid, intrahepatic bile duct cancer, and thyroid cancer. BID, twice daily; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; KRAS, Kirsten rat sarcoma small GTPase protein; SD, standard deviation.

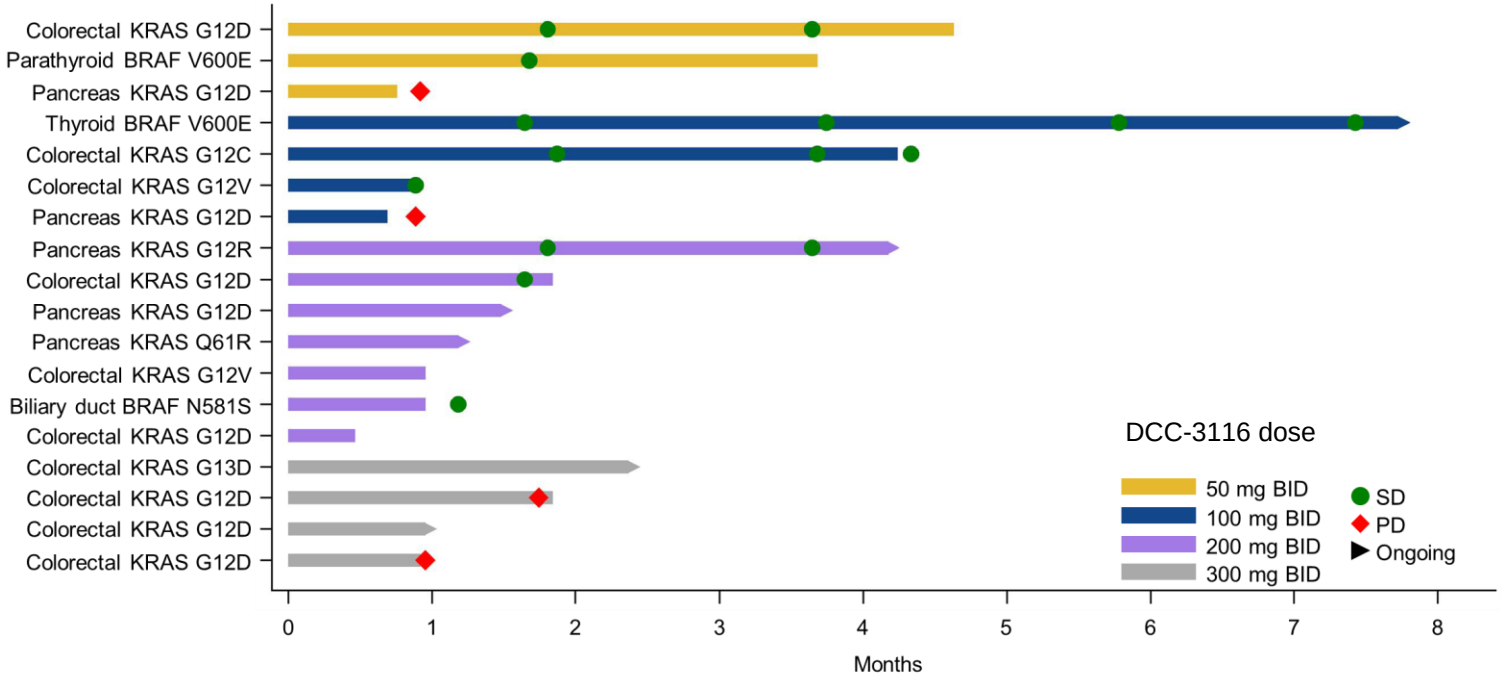
TEAEs Regardless of Relatedness (≥15% of Participants)

Preferred term	DCC-3116								All participants n (%) N = 18
	50 mg BID n = 3		100 mg BID n = 4		200 mg BID n = 7		300 mg BID n = 4		
	Grade 1/2	Grade 3	Grade 1/2	Grade 3	Grade 1/2	Grade 3	Grade 1/2	Grade 3	All grades
Fatigue	2	0	1	0	3	0	1	0	7 (39)
Dehydration	0	0	0	0	2	0	2	0	4 (22)
ALT increased	0	0	0	0	0	1	1	1	3 (17)
Anaemia	0	2	0	1	0	0	0	0	3 (17)
AST increased	0	0	0	0	2	0	1	0	3 (17)
Decreased appetite	1	0	1	0	0	0	1	0	3 (17)
Hyponatraemia	1	0	0	0	1	0	1	0	3 (17)
Nausea	0	0	1	0	0	0	2	0	3 (17)
Vomiting	1	0	1	0	1	0	0	0	3 (17)

- No DLTs or treatment-related serious TEAEs were observed
- Most treatment-related TEAEs were Grade 1/2; no treatment-related Grade 4 TEAEs
- Two related asymptomatic, reversible Grade 3 ALT increased TEAEs led to dose interruption and reduction
- No treatment-related TEAEs leading to death

Data cutoff: June 9, 2022.
ALT, alanine transaminase; AST, aspartate transaminase; BID, twice daily; DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event.

Treatment Duration and RECIST v1.1 Response Assessments

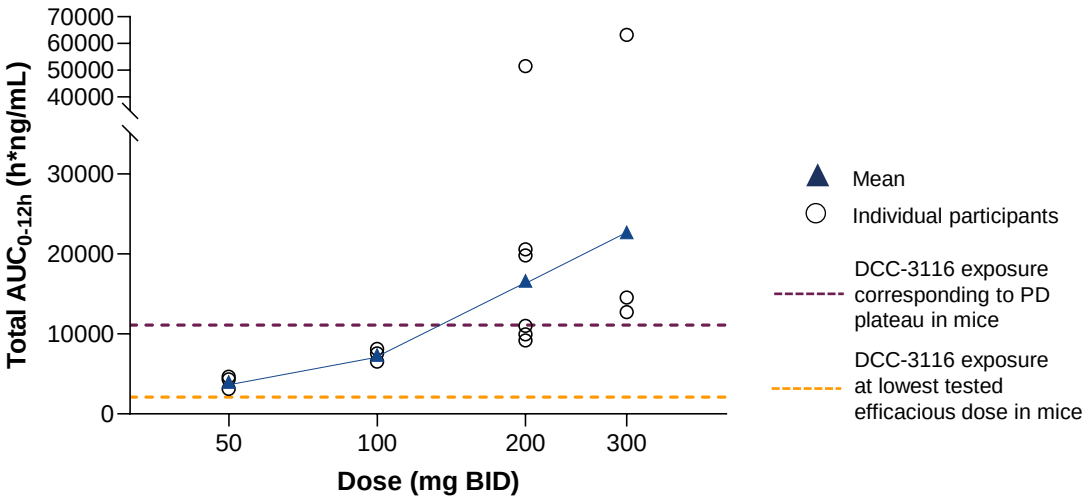


- Best overall response was stable disease
- Disease control rate at week 16 was 29% (4 of 14 response-evaluable participants)

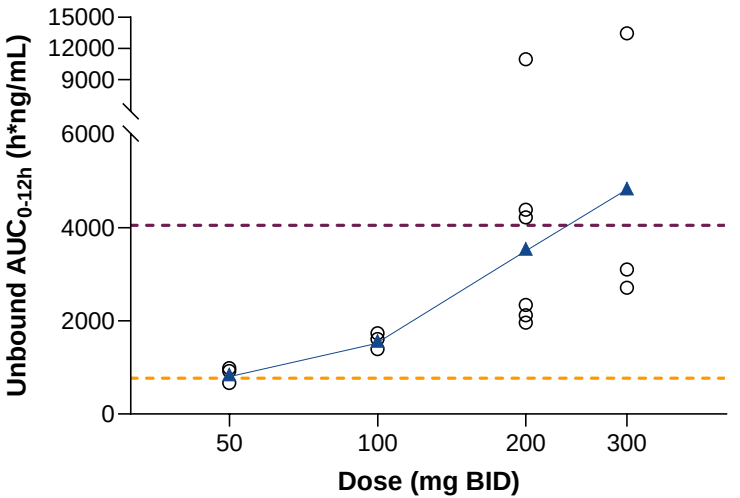
Data cutoff: June 9, 2022. Participants with at least one assessment or who died or discontinued due to clinical PD prior to the first assessment were considered response evaluable.
BID, twice daily; BRAF, v-RAF murine sarcoma viral oncogene homolog B1; KRAS, Kirsten rat sarcoma small GTPase protein; PD, progressive disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Total and Unbound DCC-3116 AUC at Cycle 1 Day 15

Total individual and mean $AUC_{0–12h}$ vs dose[a]



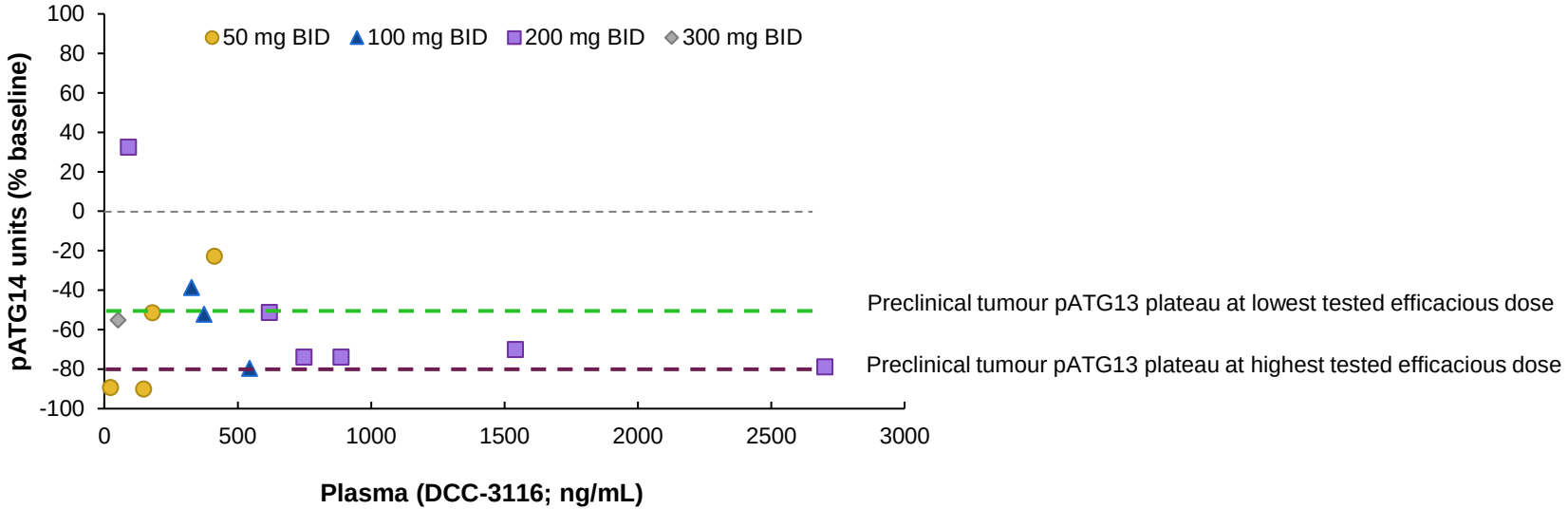
Unbound individual and mean $AUC_{0–12h}$ vs dose[b]



- DCC-3116 AUC appeared to increase proportionally to dose from 50 to 300 mg BID
- DCC-3116 AUC at all dose levels at or above AUC of lowest tested dose that was effective in preclinical studies

Data cutoff: June 9, 2022. Enrollment is ongoing in the 100–300 mg cohorts. One participant each was excluded from the 200 mg BID and 300 mg BID cohorts due to missed doses.
[a]$AUC_{0–12h}$ was calculated by imputing the predose concentration to the 12h timepoint. [b]Unbound AUC was calculated using in vitro Fu of 0.213 in humans.
AUC, area under the curve; $AUC_{0–12h}$, AUC from time 0 to 12h; BID, twice daily; Fu, fraction unbound; h, hour; PD, pharmacodynamic.

Inhibition of Phosphorylation of ULK1/2 Substrate ATG14 in PBMCs According to DCC-3116 Trough Levels



- Decreases in phosphorylation of direct ULK1/2 substrates ATG14 and ATG13 both indicate inhibition of ULK1/2
- At all DCC-3116 dose levels, pATG14 in PBMCs was in range of preclinical pATG13 in tumours at doses that achieved anticancer effects with MEK inhibitor
- pATG14 inhibition in PBMCs reached maximum pATG13 inhibition observed preclinically in tumours

Data cutoff: June 9, 2022. Data points are from matched PD and PK samples at any time at or after cycle 1 day 15.
ATG13, autophagy-related protein 13; ATG14, autophagy-related protein 14; BID, twice daily; MEK, mitogen-activated protein kinase; p, phosphorylated; PBMC, peripheral blood mononuclear cell; PD, pharmacodynamic; PK, pharmacokinetic; ULK1/2, Unc-51–like autophagy activating kinase 1/2.

Conclusions

- DCC-3116 was well tolerated at doses from 50 to 300 mg BID, which achieved exposure and ULK1/2 inhibition associated with anticancer efficacy with MEK inhibitors in preclinical studies
- No DLTs or treatment-related serious TEAEs; treatment-related TEAEs were mainly Grade 1/2 except for related asymptomatic and reversible Grade 3 ALT increases
- Disease control rate at week 16 was 29% with stable disease as best overall response
- DCC-3116 exposure appeared to increase dose proportionally from 50 to 300 mg BID
- Dose cohorts 100 to 300 mg BID are being expanded to further characterise safety, PK, and PD to select the starting dose of DCC-3116 for dose escalation in combination with MEK or KRAS G12C inhibitors

ALT, alanine transaminase; BID, twice daily; DLT, dose limiting toxicity; KRAS, Kristen rat sarcoma small GTPase protein; MEK, mitogen-activated protein kinase kinase; PD, pharmacodynamic; PK, pharmacokinetic; TEAE, treatment-emergent adverse event; ULK1/2, Unc-51–like autophagy activating kinase 1/2.

Acknowledgments

- We thank the participants and their families and caregivers, the investigators, and the investigational site staff of this study
- This study is sponsored by Deciphera Pharmaceuticals, LLC (Waltham, MA, USA)
- Medical writing and editorial support were provided by Lauren Hanlon, PhD, of AlphaBioCom, LLC (King of Prussia, PA, USA) and was funded by Deciphera Pharmaceuticals, LLC (Waltham, MA, USA)