DCC-3084, a brain penetrant RAF dimer inhibitor, broadly inhibits BRAF class I, II, and III alterations leading to growth inhibition of intracranially implanted tumors in preclinical models

Gada Al-Ani, Stacie L Bulfer, Jeffery D Zwicker, Chase K Crawley, Kristin M Elliott, Salim Javed, Qi Groer, Molly M Hood, Joshua W Large, Kylie Luther, Yeni K Romero, Forrest A Stanley, Daniel C Tanner, Hanumaiah Telikepalli, Bertrand Le Bourdonnec, Bryan D Smith, and Daniel L Flynn

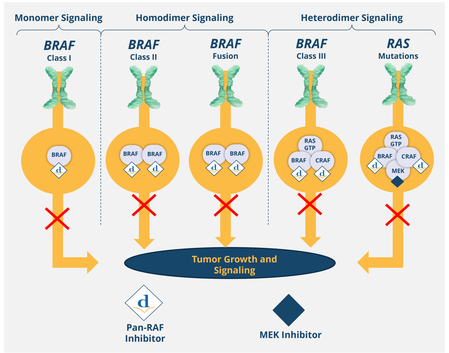
Deciphera Pharmaceuticals, LLC, Waltham, MA, USA

Abstract: 593

Introduction

- Approved BRAF inhibitors benefit patients whose tumors are driven by Class I *BRAF* mutations, including the *BRAF* V600E mutation, but are ineffective for tumors driven by mutations in the RAS/RAF/MAPK pathway signaling through RAF homodimers or RAF heterodimers[1-3]
- Such tumors frequently metastasize to the brain and are associated with poor prognosis[4], and there remains a need for optimized CNS penetrating RAF inhibitors
- DCC-3084 is a novel BRAF/CRAF inhibitor designed to inhibit all relevant MAPK aberrant signaling mechanisms regardless of RAF dimerization[1-3]
- Treatment with DCC-3084 results in potent inhibition of MAPK pathway signaling in a wide range of *BRAF*-, *BRAF* fusion-, and *BRAF/CRAF* heterodimer-driven cell lines and multiple *MAPK*-driven mouse tumor xenograft models; DCC-3084 also has excellent CNS permeability in rats[5]
- The attractive profile of high pan-RAF potency coupled with the ability to access the CNS warrants exploration of DCC-3084 as a candidate in *BRAF*- and *RAS*-driven cancers that metastasize to the brain[4]
- Here, we show treatment with DCC-3084 exhibits dose dependent exposure with robust inhibition of pathway signaling in multiple *MAPK*-driven tumor xenograft models and results in tumor regression or growth inhibition in intracranially implanted *BRAF* Class I and *BRAF* fusion mouse tumor models

Role of RAF kinases in RAS/MAPK pathway signaling



Incidence proportion of brain metastasis at diagnosis of metastatic disease

Cancer type	Incidence proportion (%)[4,a]
Melanoma	28
NSCLC	15–27[b]
Other	~1–23

[a]Represents incidence proportion of brain metastasis in the subset of patients with metastatic disease at diagnosis independent of mutational status.
[b]Variable based on histologic subtype.

Methods

- Inhibition of RAF kinases was measured using recombinant enzymes
- Cellular proliferation was measured using resazurin to monitor cell viability
- Inhibition of ERK or RSK phosphorylation was measured by AlphaLISA or ELISA
- Pharmacokinetics in the plasma, brain, and CSF compartments were measured following oral dosing in Wistar rats
- *RAF*- and *RAS*-mutant mouse xenograft models were used to assess pharmacokinetics, pharmacodynamics, and efficacy

Results

DCC-3084 is a potent and selective inhibitor of BRAF and CRAF

Inhibitor	*BRAF* IC_{50} (nM)	*CRAF* IC_{50} (nM)	*ARAF* IC_{50} (nM)	*BRAF*^{V600E} IC_{50} (nM)
DCC-3084	**71**	**34**	**903**	**2**
Naporafenib	38	29	720	28
Belvarafenib	31	51	276	3
Exarafenib	182	87	2600	31

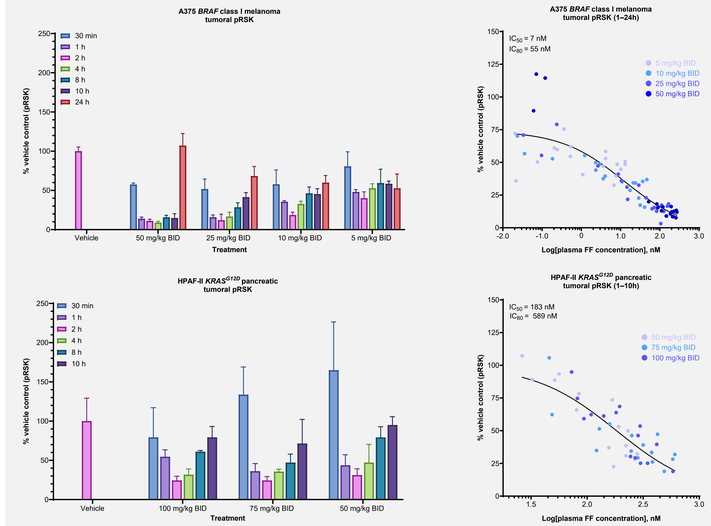
Twelve-point dose with 3-fold dilutions starting at 10 µM. [ATP] = 1 mM.
Recombinant ARAF assay designed to more accurately reflect inhibition of ARAF in cells.

DCC-3084 exhibits overall best-in-class inhibition of cellular proliferation in *BRAF* class I, II, and III mutant and *BRAF* fusion human cancer cell lines

Inhibitor	A375 IC_{50} (nM)	Colo-205 IC_{50} (nM)	HT-29 IC_{50} (nM)	BxPC-3[a] IC_{50} (nM)	H2405 IC_{50} (nM)	WM3928 IC_{50} (nM)	WM3629 IC_{50} (nM)
Mutation class	I	I	I	II	II	Fusion	III + *NRAS*
DCC-3084	**54**	**174**	**13**	**61**	**74**	**42**	**3**
Naporafenib	438	2142	228	19	465	90	3
Belvarafenib	144	486	128	59	149	14	2
Exarafenib	170	624	101	254	549	98	17

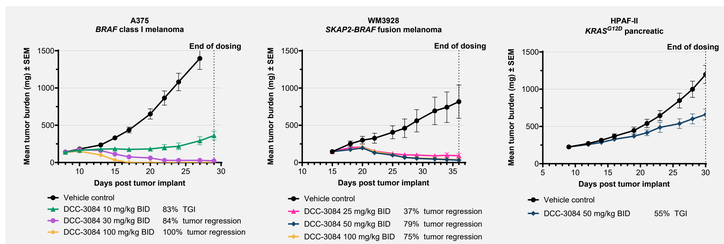
Inhibition of cell proliferation of 12-point dose with 3-fold dilutions starting at 10 µM.
[a]BxPC-3 data are IC_{50}(nM) for inhibition of pERK measured by AlphaLISA after 4-hour treatment.

DCC-3084 inhibits tumoral pRSK in *BRAF* monomer- and *BRAF/CRAF*-driven *KRAS*-mutant cancer models



PK/PD determined at steady state after 5 days of repeat oral dosing. Tumoral pRSK levels were measured by ELISA.

DCC-3084 produces tumor regression in *BRAF* monomer- and *BRAF* homodimer-mutant cancer models and tumor growth inhibition in *BRAF/CRAF*-driven *KRAS*-mutant cancer models



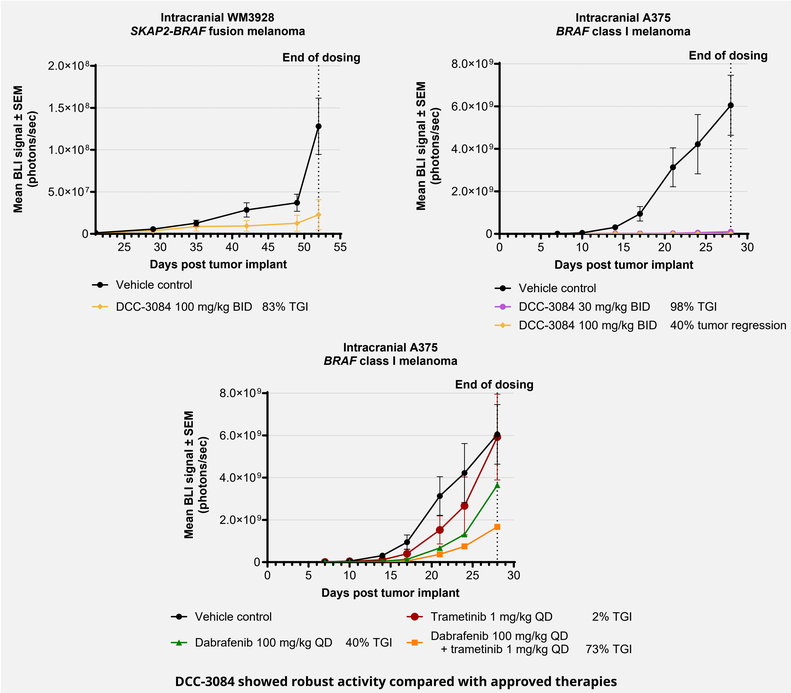
Data represent mean ± SEM. Tumor models were established to 100–300 mm^3 prior to dosing.

DCC-3084 exhibits good CNS penetration properties *in vivo*

Inhibitor	AUC [brain]/AUC [plasma]	Kp_{uu}	Classification[6]
DCC-3084[a]	**0.49**	**0.30**	**Moderate**
Naporafenib	0.11	0.05	Low
Belvarafenib	1.74	0.87	High
Exarafenib	0.02	0.01	Low
Dabrafenib[b]	0.02	NA	Low

Free fraction was determined based on percent rat brain and plasma binding.
[a]DCC-3084 brain and plasma concentrations were measured in Wistar rats after 5 days of oral BID dosing at 30-mg/kg. Brain and plasma concentrations for other inhibitors were measured in Wistar rats after a single oral 30-mg/kg dose.
[b]Following IV administration of 2.5 mg/kg dabrafenib in WT FVB mice.[7]

DCC-3084 exhibits robust activity in *BRAF* monomer- and *BRAF* homodimer-mutant intracranial cancer models



DCC-3084 showed robust activity compared with approved therapies

CONCLUSIONS

- DCC-3084 is a potential best-in-class pan-RAF inhibitor engineered using Deciphera's proprietary switch-control platform
- 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 good CNS penetration and produces tumor regressions or tumor growth inhibition in intracranially implanted tumor models driven by aberrant BRAF signaling
- Strong preclinical data in cancers driven by *RAF* or *RAS* mutations support exploration of therapeutic opportunities
- The phase 1 study of DCC-3084 (NCT06287463) is planned to initiate in the first half of 2024 and includes CNS disease eligibility criteria

PRESENTED AT THE AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR) ANNUAL MEETING
SAN DIEGO, CA, APRIL 5–10, 2024

CORRESPONDING AUTHOR/DISCLOSURES
Gada Al-Ani (galani@deciphera.com)
All authors are/were full-time employees of Deciphera Pharmaceuticals, LLC and own/owned Deciphera Pharmaceuticals, LLC stock or options.

ACKNOWLEDGMENTS
We thank Yu Mi Ahn, Randy McCall, Guenaele Raphael, Fred Reu, Cheryl Gradziel, Doug Bevan, Carla Marashio, Alex Thibonnier, Ann Gelormini, and Kevin Roesch for their contributions to this work.
Editorial support was provided by Allison Yankey, PhD, of AlphaBioCom, a Red Nucleus company, and was funded by Deciphera Pharmaceuticals, LLC.

ABBREVIATIONS
ARAF, serine/threonine protein kinase A–rapidly accelerated fibrosarcoma; ATP, adenosine triphosphate; AUC, area under the concentration time curve; BID, twice daily; BLI, bio-layer interferometry; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; CNS, central nervous system; CRAF, serine/threonine-protein kinase C-Raf; CSF, cerebrospinal fluid; DFG, aspartic acid–phenylalanine–glycine; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular signal–regulated kinase; FF, free fraction; FVB, Friend Leukemia Virus B; GTP, guanosine triphosphate; h, hours; IC_{50}, half maximal inhibitory concentration; IV, intravenous; Kp_{uu}, unbound partition coefficient (free brain concentration/free plasma concentration); KRAS, Kirsten RAS; M, molar; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; NRAS, neuroblastoma RAS; NSCLC, non-small cell lung cancer; PD, pharmacodynamics; PDB, Protein Data Bank; pERK, protein kinase R-like endoplasmic reticulum kinase; PK, pharmacokinetics; pRSK, phosphorylated RSK; QD, once daily; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma small GTPase protein; RSK, ribosomal s6 kinase; SEM, standard error of the mean; SKAP2, Src kinase-associated phosphoprotein 2; TGI, tumor growth inhibition; WT, wild-type.

REFERENCES
1. Kortum RL and Morrison DK. *Cancer Cell*. 2015;28(3):279-81.
2. Peng SB, et al. *Cancer Cell*. 2015;28(3):384-98.
3. Yao Z, et al. *Cancer Cell*. 2015;28(3):370-83.
4.Cagney DN, *et al. Neuro Oncol*. 2017; 19(11):1511-21.
5. Bulfer SL, et al. AACR Annual Meeting. 2023;4045.
6. Loryan I, et al. *Pharm Res*. 2022;39(7):1321-41.
7. Mittapalli R, et al. *J Pharmacol Exp Ther*. 2013;344(3):655-64.