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Novel strategy for RAS-pathway targeting: Initial results from a phase 1b/2 clinical trial of the oral HDAC inhibitor bocodepsin (OKI-179) combined with binimetinib in patients with RAS-pathway mutated solid tumors and NRAS-mutated melanoma

Rodabe N. Amaria[1], Herbert Duvivier[2], Katy K. Tsai[3], Robert Galamaga[4], Parisa Momtaz[5], Evan Pisick[6], Natalie Langr[7], Harish Dave[8], Duncan Walker[7], Jennifer R. Diamond[9], Kevin Litwiler[7], Ryan Sullivan[10]

[1] MD Anderson Cancer Center, Houston, TX; [2]City of Hope, Atlanta, Newnan, GA; [3]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [4]City of Hope, Phoenix, Goodyear, AZ; [5]Memorial Sloan Kettering Cancer Center, West Harrison, NJ; [6]City of Hope, Chicago, Zion, IL; [7]OnKure, Inc., Boulder, CO; [8]OncoBay Clinical, Raleigh, NC; [9]University of Colorado Anschutz Medical Campus, Aurora, CO; [10]Mass General Cancer Center, Boston, MA.

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Rodabe N. Amaria, MD

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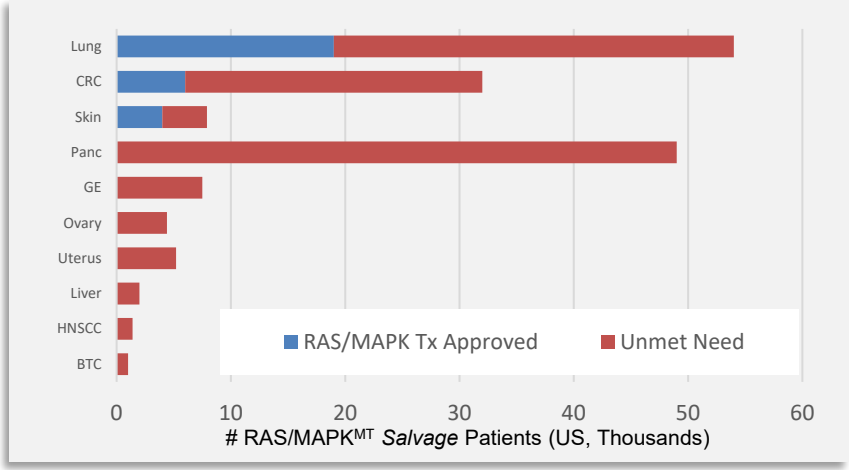
Bocodepsin (OKI-179) + Binimetinib: Targeting the RAS-Pathway with a Novel Mechanism

Cancers with RAS-Pathway Alterations: Large Patient Populations Still Have a Significant Unmet Need[1]



RAS-Pathway Targeting Alone is Often Inadequate

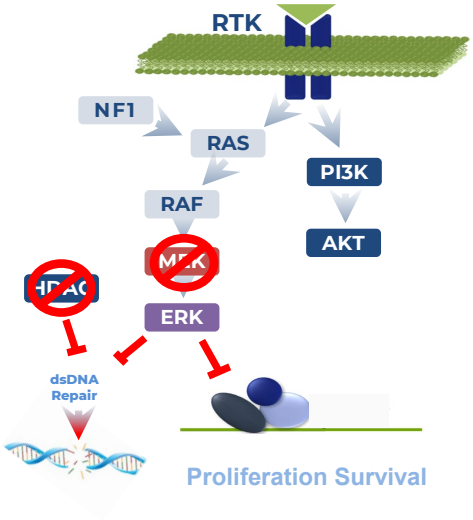
Drug	Indication	ORR	mPFS (mos)
Binimetinib	NRAS Melanoma[2]	15%	2.8
	BRAF CRC[3]	0%	1.4
Sotorasib	$KRAS^{G12C}$ NSCLC[4]	28%	5.6
	$KRAS^{G12C}$ CRC[4]	10%	4

- Majority of RAS-pathway-mutated cancers still have no adequate therapy
- Potential backbone therapy for all RAS^{MT} Cancers (25-35% of cancers)

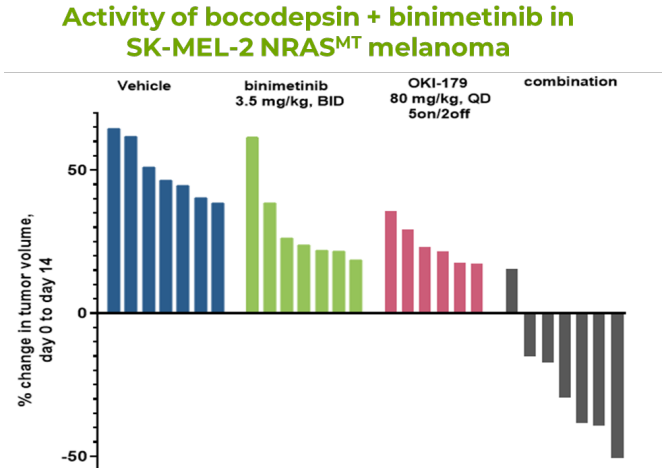
[1] Data from ACS Cancer facts and figures, 2023. CbioPortal (www.cbioportal.org) [2] Dummer et al Lancet Oncol. 2017 Apr;18(4):435-445 [3] Bendell et al Br J Cancer. 2017 Feb 28; 116(5): 575–583 [4] Hong et al *NEJM*. 2020;383(13):1207–1217 Johnson et al *ESMO Congress*. 2022;401(10378):733–746

HDACi is Synergistic with MEKi in RAS Pathway Altered Tumors

- Strong translational data supports novel role for HDACi in potentiating the activity of MEK-targeted therapy[1]



- HDACi + MAPK inhibition induces dsDNA breaks and cell death[1] preferentially in RAS-pathway mutated cancers

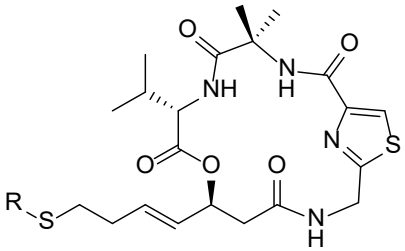


- The HDACi bocodepsin + binimetinib is active in multiple RAS/MAPK-mutated cancer types
- Bocodepsin + binimetinib active with multiple RAS pathway inhibitors (KRASi, RAFi, MEKi, ERKi)

[1] Maertens et al. Cancer Discovery (2019), 9, 526-45; Feiao-Flores and Smalley Melanoma Manag. 2019 Dec 16;6(4):MMT2; Wang et al Cell. 2018 May 31;173(6):1413-1425.e14; Bahr et al Oncotarget. 2016 Oct 25;7(43):69804-69815. Yamada et al Mol Cancer Ther. 2018 Jan;17(1):17-25
A091: The class I selective, oral HDAC inhibitor bocodepsin enhances the response to MAPK pathway inhibitors in multiple tumor types with mutations in MAPK pathway signaling proteins. Rich Woessner, OnKure Therapeutics, Boulder, CO United States.

Bocodepsin (OKI-179): Best-In-Class HDACi For Solid Tumor Combinations

Bocodepsin is Class I-targeting HDACi with potency, safety and oral dosing allowing combination with targeted therapies in solid tumors



R = octanoate thioester (OKI-005)
R = H (OKI-006)
R = l-valine thioester benzenesulfonic acid salt (bocodepsin)

- Oral prodrug, rapidly converts to the active metabolite, OKI-006 *in vivo*
- Low nM activity on Class I, Class IIa HDACs; no significant Class IIb inhibition
- Completed Phase 1 clinical trial in patients with advanced solid tumors with RP2D bocodepsin 300 mg oral daily with intermittent dosing 4 days on 3 days off[1]
- DLTs thrombocytopenia and nausea at high dose and with continuous dosing
- Well tolerated at biologically-relevant exposures
- Favorable PK/PD profile

[1] Diamond et al ASCO, 2021

Nautilus Study Design

Nautilus (OKI-179-230) is a Phase 1b/2 study designed to seek an initial proof of concept for combining bocodepsin with binimetinib in NRAS-mutated Melanoma

Phase 1b Dose Escalation

Primary Endpoint

- MTD and RP2D

Phase 2 Single-Arm Simon Optimal 2-stage Study

Primary Endpoint

- Overall response rate

Advanced solid tumors with any activating RAS pathway mutation:
e.g. RAS, BRAF, NF1

Patients with advanced (unresectable stage III/IV) NRAS-mutated melanoma previously treated with/ineligible for immune checkpoint inhibition (ICI)

Binimetinib has shown a ~15% ORR in $NRAS^{MT}$ melanoma in 2 independent studies.

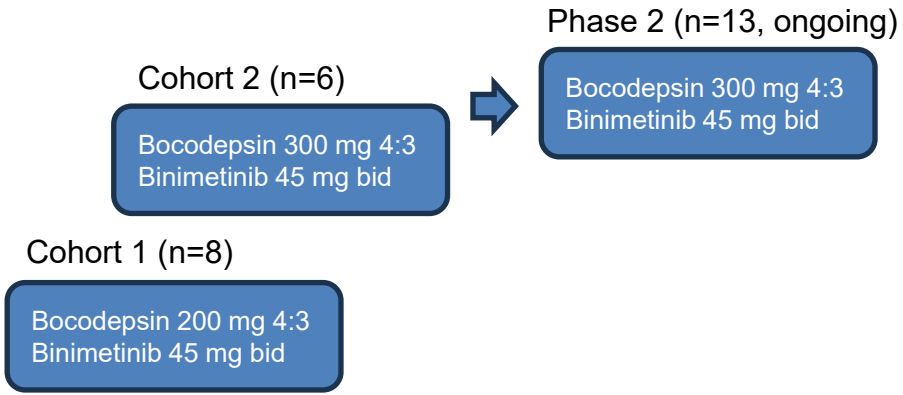
- An ORR ≥ 30% would be considered clinically meaningful

Interim Study Results

At the safety data cutoff[1], 27 patients were enrolled across both Phase 1b and Phase 2

Phase 1b dose ranging:

- No DLT observed in either Cohort 1 or Cohort 2
- RP2D is 300 mg bocodepsin PO daily 4 days on/3 days off (4:3) + binimetinib, 45 mg PO BID



Demographic	Phase 1b		Phase 2
	Cohort 1 (Boco 200 mg / Bini 45 mg) n=8	Cohort 2 (Boco 300 mg / Bini 45 mg) n=6	Boco 300 mg/ Bini 45 mg n=13
Age (Years)			
Median (Range)	65 (41-75)	70 (42-76)	66 (53-82)
Sex			
Female	5 (63%)	3 (50%)	7 (54%)
Male	3 (38%)	3 (50%)	6 (46%)
Race			
Caucasian	6 (75%)	5 (83%)	13 (100%)
Unknown	2 (25%)	1 (17%)	0 (0%)
ECOG PS			
0	4 (50%)	3 (50%)	3 (23%)
1	4 (50%)	3 (50%)	10 (77%)
Prior Lines of Therapy			
Median (Range)	4 (1-6)	2 (1-3)	3 (1-6)
Tumor Types			
Melanoma	2 (25%)	1 (17%)	13 (100%)
Colorectal	2 (25%)	2 (33%)	-
Other	4 (50%)	3 (50%)	-

[1]Safety data cutoff of July 6, 2023. Clinical activity data cutoff for patients with tumor assessment scan is Sept 26, 2023

Treatment-Related AEs >15% Phase 1b/2

Most common TRAE were as expected based on side-effect profile of binimetinib and bocodepsin alone

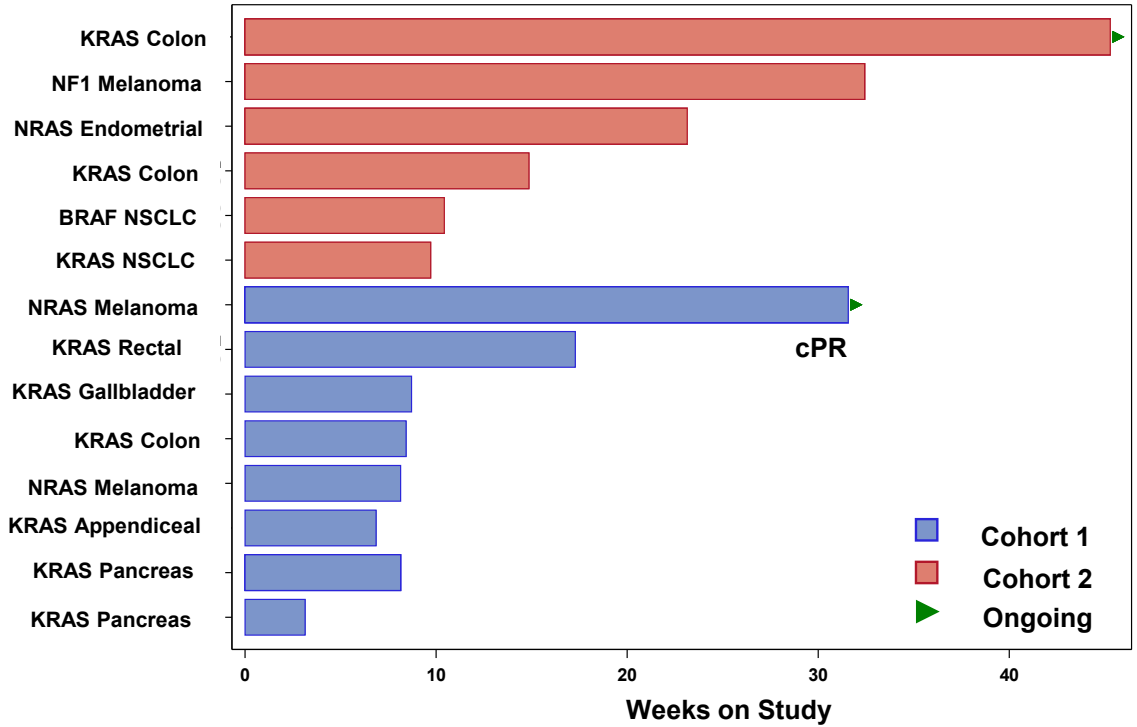
	Phase 1b						Phase 2		
	Cohort 1 (Boco 200 mg / Bini 45 mg) n=8			Cohort 2 (Boco 300 mg / Bini 45 mg) n=6			(Boco 300 mg / Bini 45 mg) n=13		
Preferred Term	Gr 1/2	Gr 3	All Grades	Gr 1/2	Gr 3	All Grades	Gr 1/2	Gr 3	All Grades
Diarrhea	7	–	7 (88%)	4	–	4 (67%)	5	–	5 (38%)
Vision blurred	–	–	–	–	–	–	5	–	5 (38%)
Fatigue	1	1	2 (25%)	4	–	4 (67%)	4	1	5 (38%)
Platelet count decreased	3	–	3 (38%)	1	1	2 (33%)	4	1	5 (38%)
Nausea	4	–	4 (50%)	5	–	5 (83%)	4	1	5 (38%)
Anemia	1	1	2 (25%)	3	2	5 (83%)	4	–	4 (31%)
Vomiting	3	–	3 (38%)	2	–	2 (33%)	2	2	4 (31%)
Blood CPK increased	4	–	4 (50%)	1	1	2 (33%)	2	1	3 (23%)
Dermatitis	3	1	4 (50%)	4	–	4 (67%)	–	3	3 (23%)
Blood LDH increased	2	–	2 (25%)	1	–	1 (17%)	3	–	3 (23%)
Stomatitis	2	–	2 (25%)	1	–	1 (17%)	1	–	1 (8%)
Edema	2	–	2 (25%)	3	–	3 (50%)	1	–	1 (8%)

Frequency of Dose Holds & Dose Reductions in Response to TRAEs

AEs are generally manageable with supportive care or dose interruptions/reductions

Drug Name	Dose Modification	Phase 1b		Phase 2
		Cohort 1 (Boco 200 mg / Bini 45 mg BID) n=8	Cohort 2 (Boco 300 mg / Bini 45 mg) n=6	(Boco 300 mg / Bini 45 mg) n=13
Bocodepsin	Dose held	3 (38%)	5 (83%)	5 (38%)
	Dose reduction	–	2 (33%)	3 (23%)
Binimetinib	Dose held	3 (38%)	5 (83%)	7 (54%)
	Dose reduction	2 (25%)	2 (33%)	5 (38%)

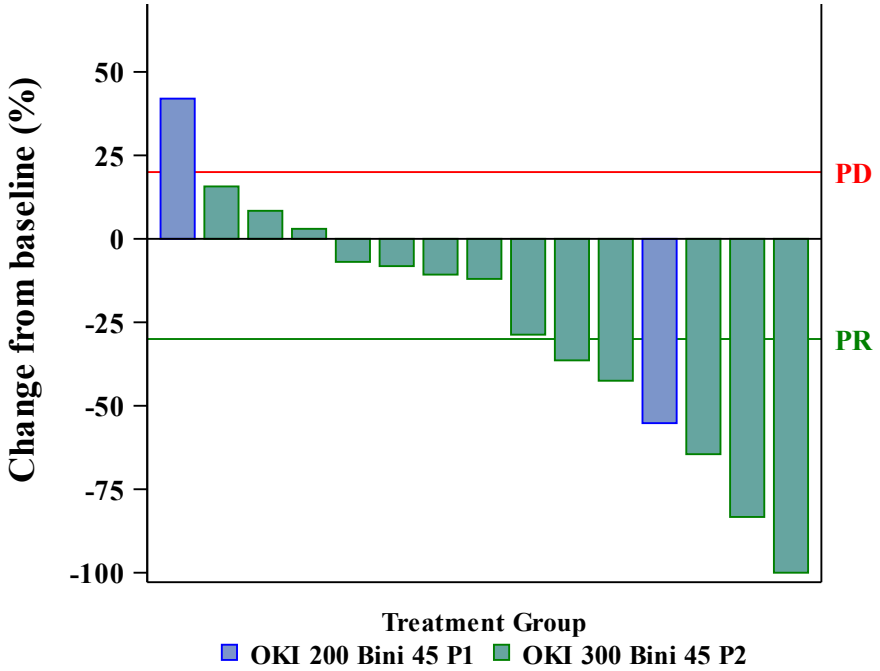
Phase 1b Time on Treatment



- In Phase 1b, 1 PR (NRAS-mutated melanoma in Cohort 1) and 7 SD were observed.
- KRAS CRC patient with stable disease >40 weeks
- Median time on study was 4 months

Best Response by RECIST 1.1 in All Patients with NRAS-Mutated Melanoma in Phase 1b/2

Best change in tumor volume: NRAS-mutated melanoma Phase 1b/2 (N=15)



Phase 1b/2 Best Response by RECIST 1.1 In All NRAS-mutated Melanoma (n=16)

Best Response	Phase 1b n=2[a]	Phase 2 n=14	All NRAS Pts n=16
Complete response	-	-	-
Partial response	1 (50%)	5 (36%)	6 (38%)
Stable disease	–	6 (43%)	6 (38%)
Progressive disease	1 (50%)	3[b] (21%)	4[b] (25%)

[a] both patients were treated at bocodepsin 200mg/binimetinib 45mg BID
[b] 1 patient experienced clinical progression early in Cycle 1 and did not get a scan

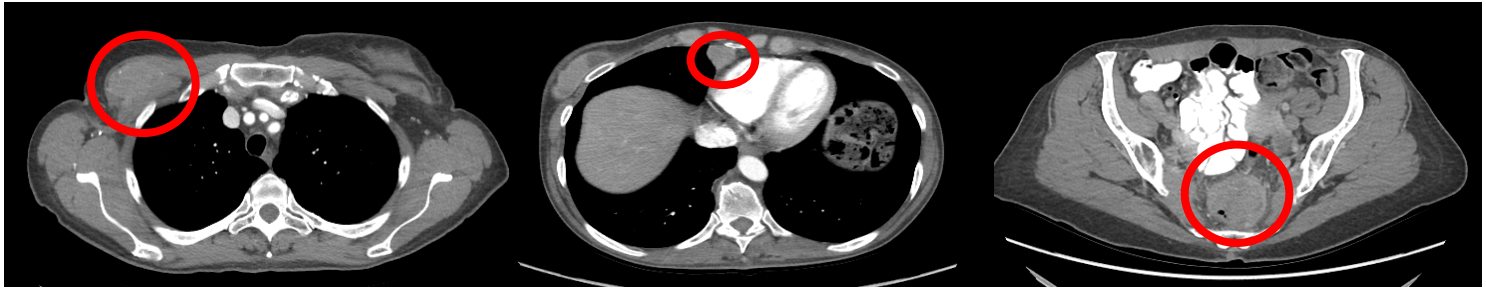
Case Report: NRAS (Q61K) melanoma

59yr. old female / ECOG=0 / 5 prior lines of therapy

R Subpectoral mass:
46.8 mm

Cardiophrenic lymph node:
21.7 mm

Rectal mass:
41 mm

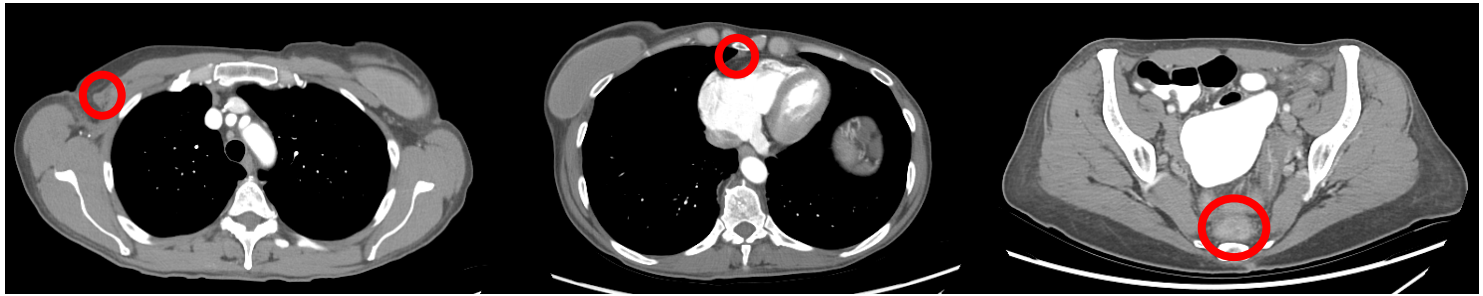


Baseline

14 mm

4.9 mm

20 mm



Week 22
(PR -64%)

Summary

- The combination of the oral HDAC inhibitor bocodepsin plus binimetinib exploits a novel mechanism for targeting RAS-pathway mutated cancers
- Bocodepsin was tolerated in combination with binimetinib in Phase 1 at both dose levels, with no DLT observed
- AEs were consistent with the effect of either bocodepsin or binimetinib alone
- 300 mg bocodepsin (PO, QD, 4 days on/3 off) + binimetinib 45 mg BID PO was the recommended dose to advance to Phase 2
- In all NRAS melanoma patients evaluable for response (n=15) 6 PR were observed (ORR 40%)
  - Binimetinib alone had an ORR of 15% in a similar patient population in the NEMO phase 3 trial.
- **The Nautilus study is continuing to enroll.**
- **These data support continued development of bocodepsin in combination with binimetinib in NRAS melanoma and other indications, such as KRAS-mutated CRC and NSCLC**

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