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

Abstract LB 37488

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Introduction

- Many preclinical translational studies have demonstrated that combined inhibition of HDAC3 and RAS-pathway in RAS-pathway-mutated cancers leads to a novel mechanism of cell death by inducing unrepaired dsDNA breaks[1]
- This mechanism is active in RAS-pathway-mutated tumors, regardless of cell type or RAS-pathway mutation, representing an opportunity to treat RAS-mutated cancers, where no adequate therapy exists
- Bocodepsin (OKI-179) is a best-in-class novel orally bioavailable, Class 1-selective HDAC inhibitor with a promising safety profile in Phase 1 studies
- Here, we disclose the activity and safety of bocodepsin in combination with the MEK inhibitor binimetinib in a Phase 1b dose escalation and ongoing Phase 2 study in NRAS-mutated melanomas

Study Design

Phase 1b Dose Escalation — Phase 2 Single-arm Simon Optimal 2-stage Study

Primary Endpoint
- MTD and RP2D

Primary Endpoint
- ORR

RP2D

Phase 1b (n=13) → Phase 2 Stage 1 (n=23) → Phase 2 Stage 2 (n=32)

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

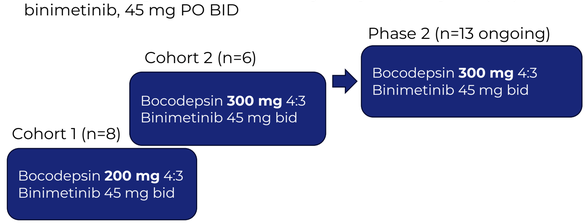
Patients with advanced (unresectable stage III/IV) NRAS-mutated melanoma previously treated with/ineligible for immune checkpoint inhibition (ICI)

Binimetinib has shown a 16% ORR in NRAS^{MT} melanoma patients previously treated with ICI in the NEMO trial[3].
- An ORR ≥ 30% would be considered clinically meaningful

Interim Study Results

As of the Safety Data Cutoff of July 6, 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



Patient Baseline Characteristics[2]

Demographic	Phase 1b Cohort 1 (Boco 200 mg/Bini 45 mg) n=8	Phase 1b Cohort 2 (Boco 300 mg/Bini 45 mg) n=6	Phase 2 (Boco 300 mg/Bini 45 mg) n=13
Age (Years)			
Median (Range)	65 (41 – 75)	70 (42 – 76)	66 (53 – 82)
Sex			
F	5 (63%)	3 (50%)	7 (54%)
M	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%)	–

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

Preferred Term	Phase 1b Cohort 1 (Boco 200 mg/Bini 45 mg) n=8 Grade 1/2	Grade 3	All Grades	Phase 1b Cohort 2 (Boco 300 mg/Bini 45 mg) n=6 Grade 1/2	Grade 3	All Grades	Phase 2 (Boco 300 mg/Bini 45 mg) n=13 Grade 1/2	Grade 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%)

Most common TRAE were as expected based on side-effect profile of binimetinib and bocodepsin alone
No Grade 4/5 TRAEs were reported

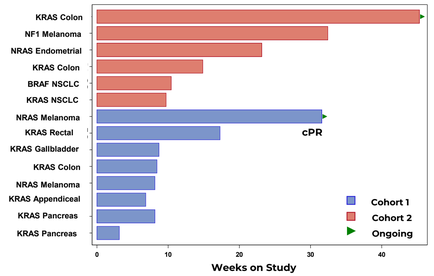
Patients with Dose Holds & Reductions for AEs [2]

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

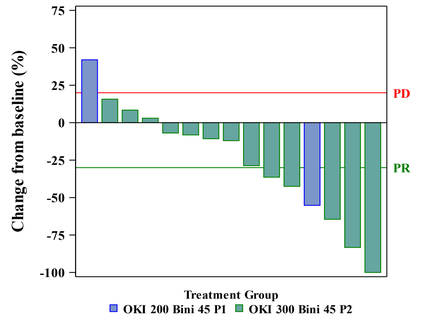
AEs are generally manageable with supportive care or dose interruptions/reductions

Clinical Activity

Phase 1b Time on Treatment



Phase 1b/2 Best change in tumor volume: NRAS-mutated melanoma



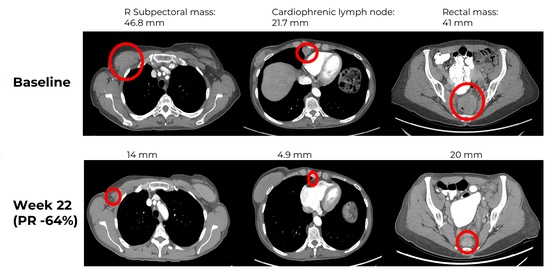
Phase 1b/2 Best Response by RECIST 1.1: NRAS-mutated Melanoma

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

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



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=16) 6 PR were observed (ORR 38%)
  - Binimetinib alone had an ORR of 16% in patients who received prior ICI therapy 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**

[1] Maertens et al. Cancer Discovery (2019), 9, 526-45 [2] Safety data cutoff of July 6, 2023. Clinical activity data cutoff for patients with tumor assessment scan is Sept 26, 2023. [3] Dummer et al Lancet Oncol. 2017 Apr;18(4):435-445

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