HBI-8000, a Class I Histone Deacetylase (HDAC) Inhibitor, in Combination with Nivolumab for Treatment of Anti-PD(L)1-Naive Advanced Melanoma: Final Analysis of Study HBI-8000-302

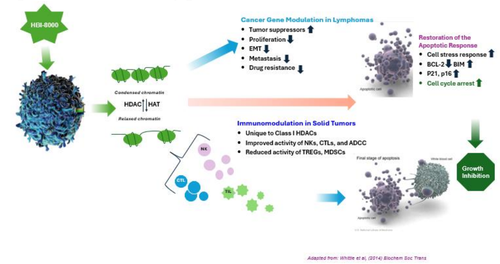
Nikhil I. Khushalani[1], Andrew Brohl[1], Joseph Markowitz[1], Heather Yeckes-Rodin[2], Lori McCormick[1], Charlie Liu[3], Mireille Gillings[3], Gloria Lee[3], and Zeynep Eroglu[1]

[1]H. Lee Moffitt Cancer Center, Tampa FL, [2]Hematology-Oncology Associates of the Treasure Coast, Port. St. Lucie, FL, [3]HUYABIO International, San Diego, CA, USA

INTRODUCTION and RATIONALE

- HBI-8000, an oral selective histone deacetylase (HDAC) inhibitor, has demonstrated extensive effects on immune cell function [*Ning et al. 2012*].
- HDAC inhibition has been shown to upregulate PD-L1 in melanoma, potentially augmenting immunotherapy with PD-1 blockade [*Woods et al. 2015*]
- The role of HDAC2 in the nuclear translocation of PD-L1 that regulates immune-response gene expression has been ascertained [*Gao2020*].
- HBI-8000 preclinically augmented anti-tumor immunity in tumor microenvironment with anti-PD1 agents synergistically. [*Bissonnette et al. 2021*]

Figure 1: HBI-8000 is an Epigenetic Immuno-Modulator



Adapted from: Whittle et al, (2014) Biochem Soc Trans

STUDY OVERVIEW

Study HBI-8000-302

- A Phase 1b/2 trial with a basket design, evaluating the combination of HBI-8000 with standard dose of nivolumab (an anti-PD1 immune checkpoint inhibitor) in melanoma, renal cell carcinoma and non-small cell lung cancer. HBI-8000 30 mg twice a week (BIW) continuous dosing was selected for Phase 2.
- Enrollment period: Aug 2016 to Feb 2021.
- Final data cut-off: March 2023.
- The results of 39 patients with advanced unresectable melanoma not previously treated with immune checkpoint inhibition from Phase 1/2 study are presented.

(ClinicalTrials.gov ID NCT02718066)

PATIENTS and STUDY DESIGN

Primary Objective

To evaluate the safety and tolerability of HBI-8000 30 mg orally twice a week (BIW) continuous dose when combined with a standard dose and regimen of nivolumab in patients with advanced melanoma

Secondary Objective

To explore the efficacy of study treatment as measured by Objective Response Rate (ORR), Disease Control Rate (DCR), Clinical Benefit Rate (CBR), at RP2D

Key Enrollment Criteria

Patients ≥18 years of age, with advanced or metastatic melanoma where treatment with nivolumab is indicated

- ECOG performance status 0 or 1
- Adequate hematopoietic, electrolyte, hepatic, and renal organ functions as measured by clinical laboratory parameters
- No serious uncontrolled autoimmune disease or active viral infection
- No major organ dysfunction or active uncontrolled CNS metastasis

Safety Assessment

- Adverse events (AE) were recorded by frequency and severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 and association with study treatment. Routine safety labs (CBC, serum chemistries) were assessed every 2 weeks.

Tumor Response

- Imaging studies were performed at baseline and every 8 weeks after treatment initiation to assess tumor response according to RECIST v1.1.

Statistical Methods

- Demographic, baseline characteristics and safety data were summarized for treated subjects (N=39),
- Anti-tumor activity (efficacy) data were summarized for treated subjects who have at least one post-baseline tumor assessment (N=38).
- Continuous variables were summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).
- Categorical variables were summarized showing the number and percentage (n, %).
- Time to event variables (i.e., PFS, DoR) were analyzed using Kaplan-Meier methods.

PATIENT DEMOGRAPHICS and DISEASE CHARACTERISTICS

Table 1:

Parameter		N=39
Age (years)	Median (Range)	63 (28 - 83)
ECOG (n, %)	0	23 (59.0)
	1	16 (41.0)
Sex (n, %)	F	16 (41.0)
	M	23 (59.0)
Race (n, %)	White	37 (94.9)
	Other	2 (5.1)
BRAF (n, %)	Negative (wild type)	21 (53.8)
	Positive - V600E	10 (25.6)
	Positive - V600K	4 (10.3)
	Positive - Other/Unknown	2 (5.1)
	NA	2 (5.1)
Metastatic stage (n, %)	M0 or M1a or M1b or M1	20 (51.0)
	M1c	17 (43.6)
	Mx	2 (5.1)
LDH (n, %)	<= ULN	34 (87.2)
	> ULN	5 (12.8)

SAFETY

- The most common adverse events (AEs) related to treatment (HBI-8000 or nivolumab alone or in combination) regardless of severity included: fatigue [29 (74.4%)], diarrhea [26 (66.7%)], nausea [21 (53.8%)], abdominal pain [16 (41.0%)], and hypophosphatemia [23 (59.0%)].
- Thrombocytopenia [28 (71.8%)], neutropenia [24 (61.5%)], leukopenia [24 (61.5%)], and lymphopenia [20 (51.3%)] were common; clinically significant bleeding or febrile neutropenia were not observed.
- The most common treatment-related Grade ≥3 AEs included fatigue, decreased appetite, diarrhea, abdominal pain, and weight loss.
- Treatment emergent serious adverse events (SAE) were reported from 13 subjects; most common were 2 events of anemia (Grade 3), and 2 events of pancreatitis (Grade 3); There were no grade 5 AEs.
- AEs leading to treatment discontinuation were observed in 17 subjects: colitis, pneumonitis, pancreatitis, increased lipase, and fatigue.

Table 2: Adverse Events Related to Both HBI-8000 and Nivolumab reported in ≥15% of Melanoma Patients (N=39)

Adverse Event Term (n=39)		Related to both HBI-8000 and Nivolumab in ≥15% of patients	
		Grade 1-2	Grade 3-4
General disorders	Fatigue	24 (61.5)	2 (5.1)
	Edema peripheral	6 (15.4)	-
Gastrointestinal	Diarrhea	20 (53.9)	2 (5.1)
	Abdominal pain	14 (35.9)	-
	Nausea	9 (23.1)	1 (2.6)
Blood/lymphatic	Anemia	12 (30.7)	1 (2.6)
Investigations	Lymphocyte count decreased	11 (28.2)	3 (7.7)
	Platelet count decreased	8 (20.5)	-
	White blood cell count decreased	8 (20.5)	-
	Alanine aminotransferase increased	8 (20.5)	1 (2.6))
	Aspartate aminotransferase increased	8 (20.5)	-
	Blood alkaline phosphatase increased	7 (17.9)	-
	Weight decreased	6 (15.4)	1 (2.6)
	Neutrophil count decreased	5 (12.8)	2 (5.1)
Metabolism/nutrition	Decreased appetite	7 (17.9)	3 (7.7)
	Hyperkalemia	7 (17.9)	-

Table 3: Investigator-Reported Treatment-Related Adverse Events Reported in ≥15% of Melanoma Patients (N=39)

Adverse Event Term (n=39)	HBI-8000 Alone		Nivolumab Alone		Both HBI-8000 & Nivolumab	
	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3
Anemia	11 (28.2%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	13 (33.3%)	1 (2.6%)
Diarrhea	5 (12.8%)	1 (2.6%)	2 (5.1%)		23 (59.0%)	2 (5.1%)
Nausea	12 (30.8%)		1 (2.6%)		10 (25.6%)	1 (2.6%)
Abdominal pain	3 (7.7%)		1 (2.6%)		14 (35.9%)	
Fatigue	7 (17.9%)	1 (2.6%)	1 (2.6%)		26 (66.7%)	2 (5.1%)
Edema peripheral	3 (7.7%)		1 (2.6%)		6 (15.4%)	
Platelet count decreased	21 (53.8%)	2 (5.1%)	1 (2.6%)		8 (20.5%)	
Neutrophil count decreased	19 (48.7%)	6 (15.4%)			7 (17.9%)	2 (5.1%)
White blood cell count decreased	16 (41.0%)				8 (20.5%)	
Weight decreased	9 (23.1%)	2 (5.1%)	1 (2.6%)		7 (17.9%)	1 (2.6%)
Lymphocyte count decreased	5 (12.8%)	2 (5.1%)	2 (5.1%)		14 (35.9%)	3 (7.7%)
Lipase increased			8 (20.5%)	7 (17.9%)	7 (17.9%)	4 (10.3%)
Alanine aminotransferase increased	2 (5.1%)	1 (2.6%)	3 (7.7%)		9 (23.1%)	1 (2.6%)
Aspartate aminotransferase increased	1 (2.6%)	1 (2.6%)	2 (5.1%)		8 (20.5%)	
Blood alkaline phosphatase increased	2 (5.1%)		3 (7.7%)		7 (17.9%)	
Amylase increased			7 (17.9%)	2 (5.1%)	5 (12.8%)	1 (2.6%)
Hypophosphatemia	19 (48.7%)	7 (17.9%)			4 (10.3%)	2 (5.1%)
Hyperkalemia	4 (10.3%)		3 (7.7%)		7 (17.9%)	
Decreased appetite	8 (20.5%)		1 (2.6%)		10 (25.6%)	3 (7.7%)
Headache	2 (5.1%)	1 (2.6%)	2 (5.1%)		4 (10.3%)	
Dyspnea			9 (23.1%)		5 (12.8%)	
Rash maculo-papular			10 (25.6%)		5 (12.8%)	

EFFICACY

Table 4: Overall Response Rate

Best Overall Response and Response Status according to RECIST 1.1 (Investigator Overall Assessment)	(N=38*) n (%)
Best Overall Response	
Complete Response (CR)	6 (15.8%)
Partial Response (PR)	19 (50.0%)
Stable Disease (SD)	9 (23.7%)
Progressive Disease (PD)	3 (7.9%)
Not Evaluable (NE)	1 (2.6%)
Objective Response Rate (CR+PR)	25 (65.8%) 95% CI (48.6, 80.4)
Disease Control Rate (CR+PR+SD)	34 (89.5%) 95% CI (75.2, 97.1)
Clinical Benefit Rate (CR, PR, or SD lasting at least 12 weeks)	33 (86.8%) 95% CI (71.9, 95.6)

* 1 subject received only 2 weeks of HBI-8000, not evaluable for efficacy

Figure 2: Waterfall Plot

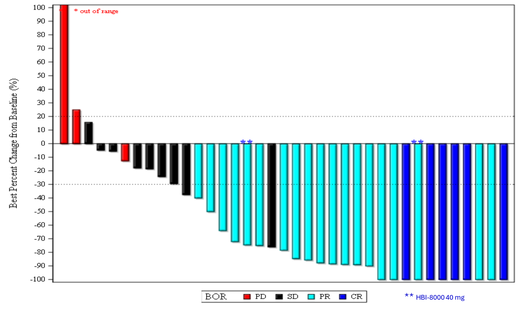
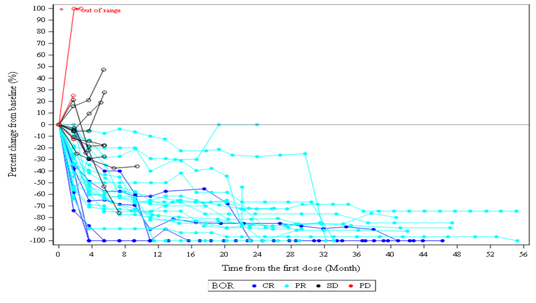


Figure 3: Spider Plot of Tumor Response over TIme



TUMOR RESPONSE OVER TIME

Figure 4: Swimmer Plot

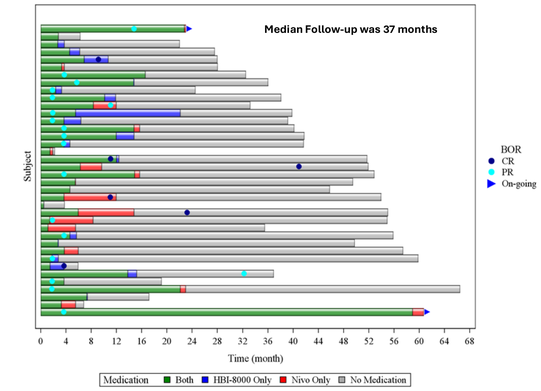


Figure 5: Progression-Free Survival

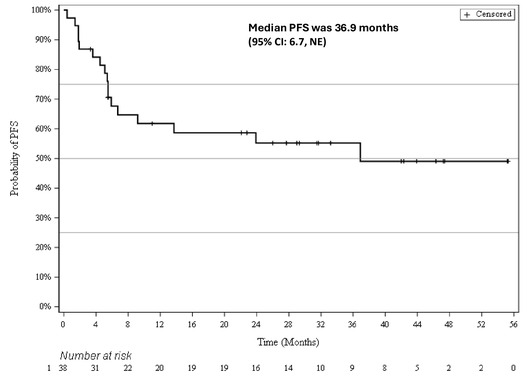


Table 5: Patient Discontinuations

Reason for Discontinuation	Number of Subjects
Clinical PD	3
PD by RECIST 1.1	6
Any Adverse Event(s) related or unrelated to HBI-8000 and/or Nivo	9
Investigator (and patient) decision	9
Subject withdrawal	7
Other	3
On treatment until End of Study	2
Total Subjects	**39**

SUMMARY and CONCLUSIONS

- The combination of HBI-8000 and nivolumab represents a novel dual immunotherapy.
- It has demonstrated promising efficacy and good tolerability in anti-PD(L)-1-treatment naïve advanced melanoma.
  - ❖ The most common treatment-related ≥ grade 3 adverse events (AEs) included fatigue, decreased appetite, diarrhea, abdominal pain and weight loss.
  - ❖ Immune related toxicity does not seem to increase with HBI-8000.
  - ❖ The overall response rate was 65.8% including 6 (15.8%) completes responses (CR) and 19 (50%) partial responses (PR) with a clinical benefit rate (CR, PR or stable disease lasting at least 12 weeks) of 87%.
  - ❖ The median follow-up was 37 months; median progression-free survival was 36.9 months (95% CI: 6.7, NE). Median duration of response was not reached.

Conclusion

Based on these encouraging results, a global Phase 3 study in patients with advanced melanoma has been initiated and was fully accrued in Q2 2024.

.

Acknowledgments: HUYABIO would like to thank the patients, caregivers and many others who contributed to this study. Your participation and support are invaluable to advancing healthcare and improving patient outcomes.

sitc2024 Society for Immunotherapy of Cancer NOV. 6-10 | HOUSTON

HUYABIO INTERNATIONAL