A Phase 1b/2 Study of the Safety and Efficacy of HBI-8000-Nivolumab Combination in Melanoma (MEL), Renal Cell Carcinoma (RCC) and Non-Small Cell Lung Cancer (NSCLC)

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INTRODUCTION & RATIONALE

HBI-8000 is an epigenetic immunomodulatory drug inhibiting tumor cell growth accounting for single agent activity vs. lymphoma. The drug also has immune related effects including (i) enhanced immune-cell mediated cytotoxicity in vitro; (ii) enhanced dendritic cell functions, (iii) enhanced tumor infiltration of CD8+ T cells (CTL), and (iv) decreased tumor infiltration and expansion of T-regulatory and myeloid derived suppressor cells, displaying synergistic activity with checkpoint inhibitors (CPIs) in multiple animal models in vivo. HBI-8000 is an oral, benzamide class histone deacetylase inhibitor (HDACi) selective for Class I (HDACs 1, 2, 3) and Class II (HDAC 10). It is approved in China as a treatment for peripheral T-cell lymphoma (PTCL), and is in registration trials for T-cell lymphomas in Japan and Korea.

CPIs such as nivolumab (NIVO) have shown significant therapeutic effects in various cancers by restoring antitumor activities in the tumor microenvironment. Based on preclinical and emerging clinical study data, it is hypothesized that the immune modulatory mechanisms of HBI-8000 could complement and enhance NIVO activity in combination therapy.

In this study, the safety profiles were first evaluated administering escalating doses of HBI-8000 in combination with the standard dose of nivolumab. Once the recommended Phase 2 dose of 30 mg BIW was established, efficacy was explored in a cohort expansion phase in various patient populations. We present the results from the Phase 1b and preliminary efficacy results from the expansion phase in advanced and metastatic melanoma. (ClinicalTrials.gov ID NCT02718066).

PATIENTS AND STUDY DESIGN

- Patients ≥18 years of age, with advanced or metastatic MEL, NSCLC, or RCC where treatment with nivolumab is indicated
- ECOG performance status 0 or 1
- Adequate hematopoietic, electrolyte, hepatic, and renal laboratory functions
- No serious uncontrolled autoimmune disease or active viral infection
- No major organ dysfunction or active uncontrolled CNS metastasis

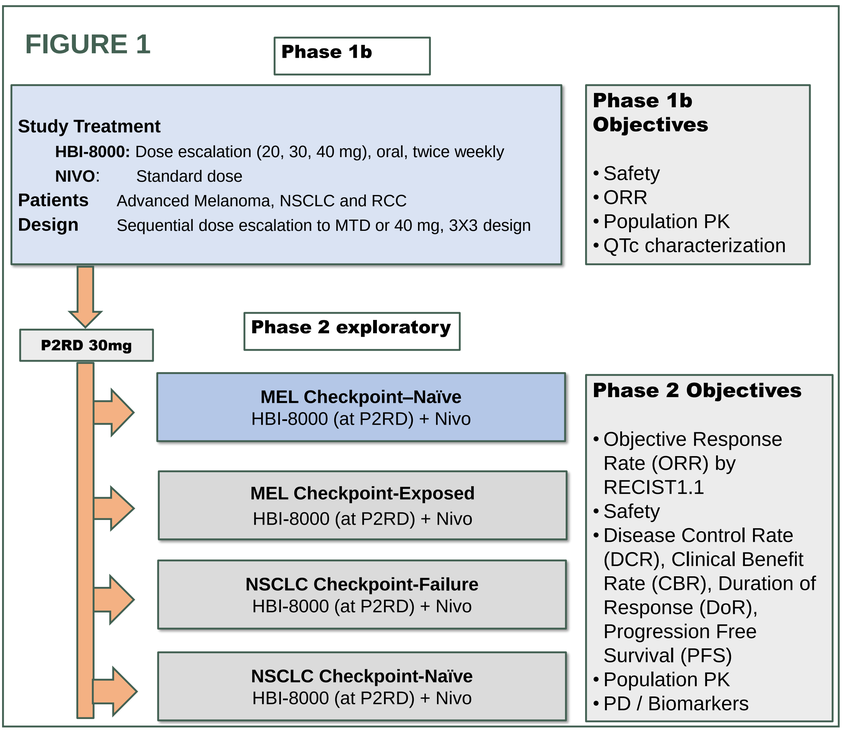
SAFETY ASSESSMENT

- Adverse events (AE) were recorded by frequency and severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 4.03 and association with study treatment. Routine safety labs (CBC, serum chemistries) were also assessed.
- Dose limiting toxicities (DLT) were defined as treatment-related uncomplicated grade 4, complicated hematological toxicity grade ≥3, or non-hematologic toxicities grade ≥3, according to NCI CTCAE v 4.03, observed during the first 28 days of treatment.

TUMOR RESPONSE

- Imaging studies were performed every 8 weeks to assess tumor response according to RECIST v1.1.

FIGURE 1



CHECKPOINT-NAÏVE MELANOMA PATIENTS (N=20)

Characteristics	
M/F, n (%)	13/7 (65/35)
Median age, years (range)	64.5 (28 – 79)
< 65, n (%)	10 (50)
66 – 75	6 (30)
>75	4 (20)
ECOG Score, n (%)	
0	13 (65)
1	7 (35)
Stage at study entry, n (%)	
M1a	5 (25)
M1b	12 (60)
M1c	3 (15)
Elevated LDH, n (%)	2 (10)
Median tumor burden (target lesions), mm (range)	38 (10 – 167)
Median time since diagnosis, months (range)	13.8 (0.7 – 66.1)
BRAF status, n (%)	
Mutated	4 (20)
Wildtype	1 (5)
Unknown	15 (75)
Prior surgery, n (%)	17 (85)
Prior radiation, n (%)	6 (30)
Prior systemic therapy, n (%) [a]	
Chemotherapy	1 (5)
Immune therapy (excluding PD-(L)1 inhibitor)	3[b] (15)
Other	2[c] (10)

SAFETY

From 30 Aug 2016 to 31 Aug 2017, 17 patients were enrolled in Phase 1b. At 40 mg twice a week, 2 DLTs: 1 G3 headache; 1 G3 fatigue. 30 mg twice a week was recommended for Phase 2 cohort expansion

Cohort-Dose level	Patient N and disease	DLT
1—20 mg	3 RCC n=3	no
2—30mg	4* RCC n=2;NSCLC n=1; Mel n=1	no
3—40mg	7* RCC n=1; NSCLC n=4; Mel n=2	DLT: 1 G3 headache; 1 G3 fatigue
4—30 mg	3 RCC n=1; Mel n=2	no

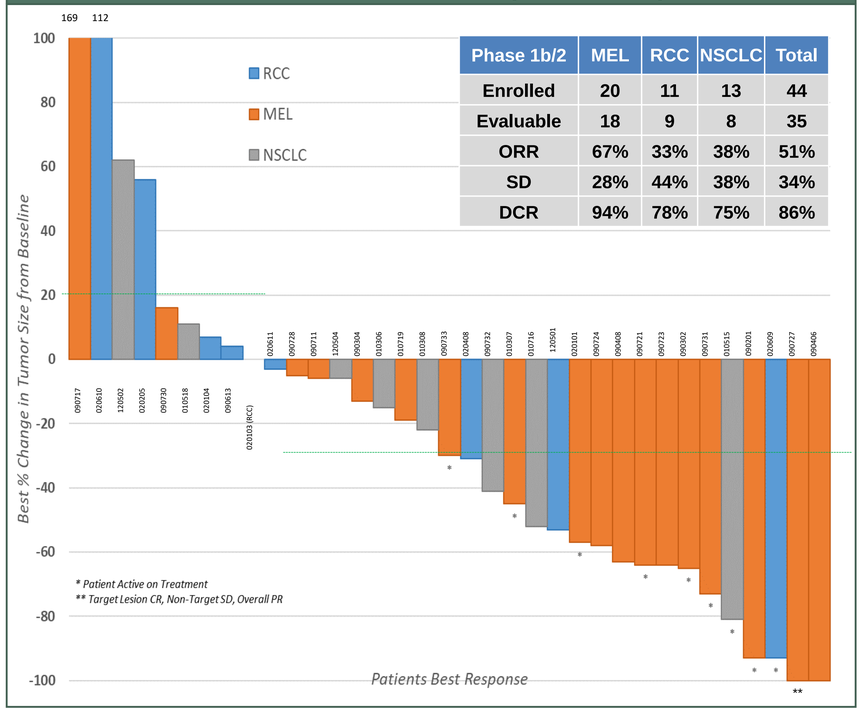
***1 pt non-evaluable**

Phase 2 cohort expansion was initiated Sep 2017. A total of 49 subjects have been enrolled as of 30 Sep 2018. Among total subjects with AE data available (N=63) Treatment Emergent Adverse Event (TEAE), 52% were considered related to treatment (TRAE). Among TRAEs, 47% were associated with HBI-8000 and NIVO, 39% HBI-8000 alone and 14% NIVO alone. Less frequent TRAEs associated with NIVO alone were lipase increase (n=6), rash (n=10), TSH increase (n=5), amylase increase (n=4).

TRAE ≥ 5% frequency and number of subjects n (% of N)

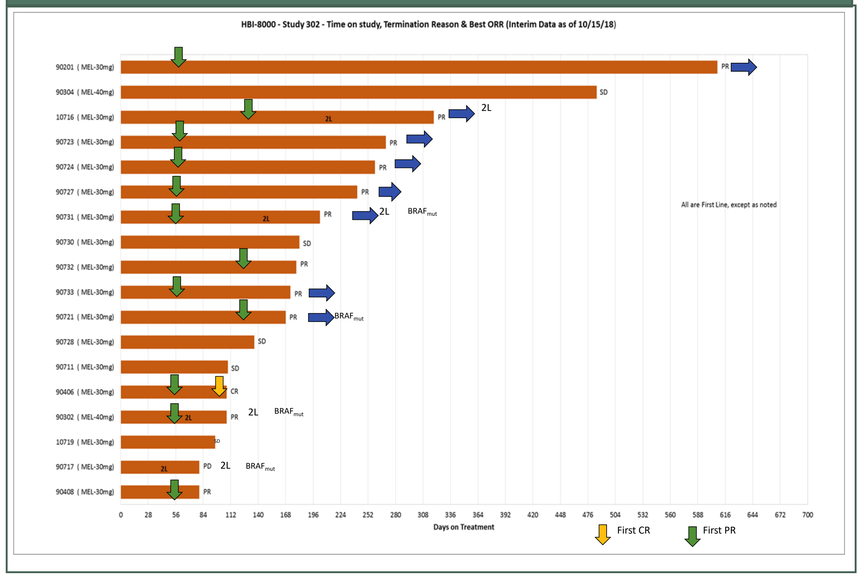
AE Term	Association								
	HBI-8000+ NIVO			HBI-8000			NIVO		
	G1-2	G3	G4	G1-2	G3	G4	G1-2	G3	G4
Fatigue	24 (38)	4 (6)	0	0	0	0	0	0	0
Diarrhea	19 (30)	3 (5)	0	0	0	0	4 (6)	1 (2)	0
Lymphocyte decrease	6 (10)	1 (2)	0	0	0	0	0	0	0
Neutrophil decrease	4 (6)	2 (3)	0	8 (13)	5 (8)	1 (2)	0	0	0
WBC decrease	6 (10)	1 (2)	0	11 (17)	1 (2)	0	0	0	0
Platelet decrease	10 (16)	0	0	23 (37)	3 (5)	0	0	0	0
Anemia	0	0	0	14 (22)	1 (2)	0	0	0	0
Hypophosphatemia	0	0	0	6 (10)	4 (6)	0	0	0	0

FIGURE 2: Waterfall plot of CPI-naïve subjects dosed with HBI-8000 and nivolumab. Each bar represents a single patient's best response as defined by sum of target lesion diameters. Data expressed as change in percent (baseline is 0% change). Green dotted lines represent the +20% definition of progressive disease and the -30% definition of partial response. Bars within the green lines are defined as stable disease. * Patient on treatment (15 Oct 2018)



Phase 1b/2	MEL	RCC	NSCLC	Total
Enrolled	20	11	13	44
Evaluable	18	9	8	35
ORR	67%	33%	38%	51%
SD	28%	44%	38%	34%
DCR	94%	78%	75%	86%

FIGURE 3: Swimmer Plot of Melanoma CPI-Naïve Subjects. Bars represent patient treatment length in days, green and yellow arrows represent first PR and CR, respectively. Blue bars represent patients still on treatment as of Oct 15, 2018. Patients who entered study after previous treatment noted as 2L. BRAF mutation status noted.



Summary and Conclusions

1. HBI-8000 in combination with standard dose of nivolumab was well tolerated; RP2D was selected to be 30 mg twice a week. No evidence of new or increase of known toxicity from either agent.
2. Encouraging efficacy was observed in advanced/metastatic melanoma patients with no prior checkpoint inhibitor therapy. Patient accrual is ongoing in both CPI-naïve and CPI-exposed populations.
3. Further clinical investigation of HBI-8000 in combination with nivolumab is warranted.

Footnotes:
a. 2 subjects received multiple therapies
b. ipilimumab (2); cellular immunotherapy (1)
c. vemurafenib (1); 1 subject received MEK inhibitor & BRAF Inhibitor