Significant anti-tumor activity of HBI-8000, a class I histone deacetylase inhibitor (HDACi) in combination with nivolumab (NIVO) in anti-PD1 therapy-naïve advanced melanoma (TN-Mel)

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INTRODUCTION & RATIONALE

HBI-8000 (tucidinostat, chidamide) is a member of the benzamide class of histone deacetylase (HDAC) inhibitors designed to block the catalytic pocket of cancer-associated Class I HDACs and one Class IIb HDAC in the nanomolar range and stimulates accumulation of acetylated histones H3 and H4 in tumor cells [*Ning 2012*]. Emerging data suggest two distinct mechanisms of action, a direct antitumor mechanism and immunomodulatory mechanism both of which occur as a consequence of epigenetic regulation. HDAC inhibition has been shown to upregulate PD-1 ligand (PD-L1) in melanoma, potentially augmenting immunotherapy with PD-1 blockade. Furthermore, a recent publication demonstrated the newly discovered role of HDAC2 in the nuclear translocation of PD-L1 that regulates the immune-response gene expression [*Gao 2020*]. This observation is consistent with the notion that inhibition of HDAC2 dependent acetylation of intracellular transport system could enhance the therapeutic effect of immune checkpoint inhibitors commonly used in clinical practice.

A Phase 1b/2 study was initiated in 2016 to investigate the safety and efficacy of HBI-8000 in combination of nivolumab in melanoma (MEL), non-small cell lung cancer NSCLC) and renal cell carcinoma (RCC). HBI-8000 30 mg twice weekly was the recommended phase 2 dose to combine with standard nivolumab regimen for further efficacy and safety assessment in 2017. We present the safety profile and efficacy from 36 anti-PD1-naive advanced melanoma patients receiving nivolumab plus HBI-8000 with data cut-off date of 16 Oct 2020 for this analysis. **(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 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) v 4.03 and association with study treatment. Routine safety labs (CBC, serum chemistries) were assessed every 2 weeks.
- 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

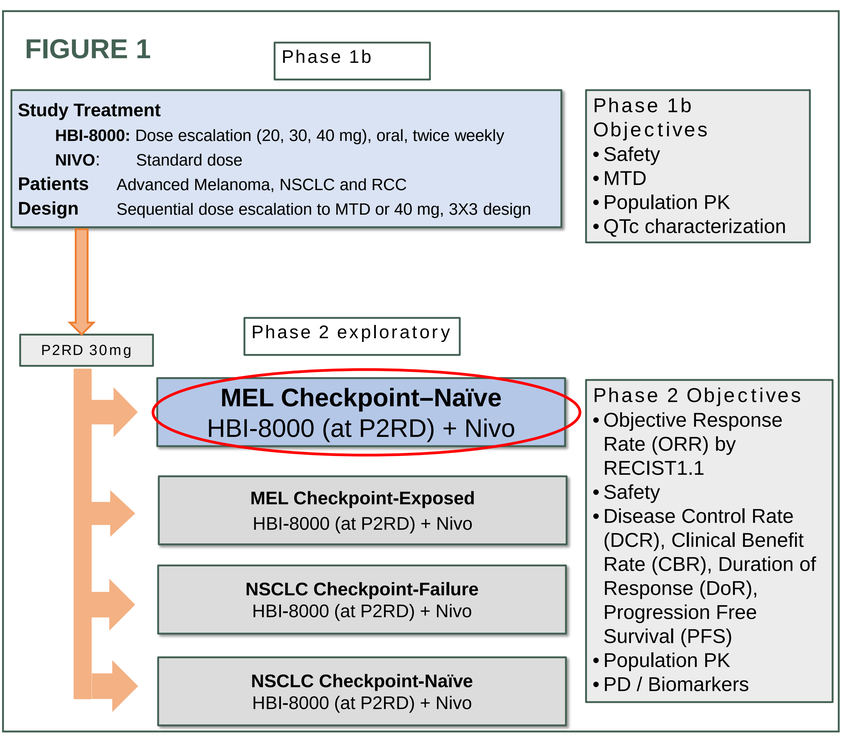


Table 1. Anti-PD1 Therapy-naïve Melanoma Patients and Disease Characteristics

N=36	n (%)
Age (years)	
<65	19 (52.8)
65-75	11 (30.6)
>75	6 (16.7)
ECOG	
0	20 (55.6)
1	16 (44.4)
Gender	
M	21 (58.3)
F	15 (41.7)
BRAF	
Positive	15 (41.7)
Negative	19 (52.8)
unknown	2 (5.6)
Time since initial diagnosis (yrs)	
Mean (Std Dev)	3.0 (4.7)
Median (min, max)	2.8 (0.1, 26.9)
Metastatic Stage	
M1a, M1b, M1	15 (41.7)
M1c	12 (33.3)
Not reported	9 (25.0)
LDH	
>ULN	2 (5.6)
≤ULN	34 (94.4)
unknown	0
Prior Melanoma therapy	
Anti-CTLA-4	3 (8.3)
BRAF targeted therapy	3 (8.3)
other	11 (30.6)

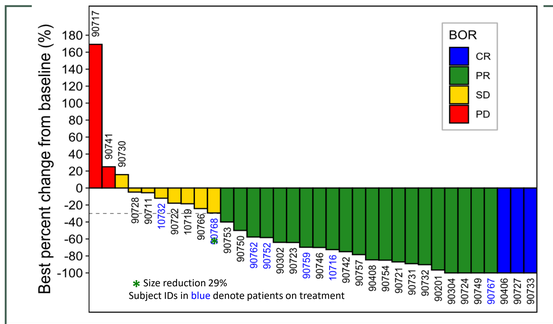
SAFETY

The safety of 36 melanoma patients (without prior anti-PD1 therapy) treated with HBI-8000 (34 patients at 30 mg BIW; 2 patients at 40mg BIW in Phase 1b) in combination with nivolumab was analyzed as of July 2020. The most common all grade treatment related adverse events (AEs) included fatigue (n=30), diarrhea (n=26), nausea (n=21), abdominal pain (n=16), and lymphopenia (n=14). Although HBI-8000 related (in combination with nivolumab or alone) thrombocytopenia (n=28) and neutropenia (n=21) were common, **clinically significant bleeding or febrile neutropenia were not observed**. The most frequent G ≥3 AEs related to HBI-8000 were hypophosphatemia (n=9), neutropenia (n=6), thrombocytopenia (n=2) and lymphopenia (n=3). Sixteen patients discontinued treatment for AEs, while 7 discontinued due to AEs related to HBI-8000 with or without nivolumab.

Table 2 Treatment Related AEs (No. Patients Experienced ≥ 10%)

Relationship	HBI-8000 + Nivolumab		HBI-8000 alone		Nivolumab alone	
Severity	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3
Blood and Lymphatic	10	2	10	0	1	1
Anemia	10	2	10	0	1	1
GI disorders	24	8	19	2	9	1
Diarrhea	19	3	5	1	2	0
Nausea	8	2	12	0	1	0
Abdominal pain	14	2	2	0	0	0
Flatulence	5	0	1	0	1	0
Abdominal distention	6	0	0	0	0	0
Dyspepsia	6	0	1	0	0	0
Dry mouth	4	0	0	0	0	0
General disorders	28	4	6	2	6	1
Fatigue	26	3	3	1	1	0
Peripheral edema	4	0	2	0	1	0
Investigation	22	5	21	7	19	6
Platelet count ↓	8	0	20	2	1	0
Neutrophil count ↓	8	2	13	4	0	0
Lymphocyte count ↓	8	1	5	2	1	0
ALT ↑	8	1	1	1	2	0
Alk phosphatase ↑	7	0	1	0	3	0
AST ↑	6	0	1	0	1	0
Metabolism/nutrition	20	3	17	9	7	1
Hypophosphatemia	4	2	16	7	0	0
Decreased appetite	9	2	4	0	0	0
Hyperkalemia	7	0	4	0	3	0
Hypocalcemia	4	0	5	0	0	0
Hyperglycemia	3	0	0	0	3	0
Musculoskeletal/connective tissue disorder	8	0	3	0	15	1
Muscular weakness	3	0	1	0	3	1
Nervous system disorder	13	2	6	1	5	0
Headache	4	2	2	1	1	0
Dizziness	5	0	2	0	1	0
Respiratory disorder	7	1	2	0	11	1
Dyspnea	4	0	0	0	5	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 -30% definition of partial response. (Data Cut-off Date: 16 Oct 2020)

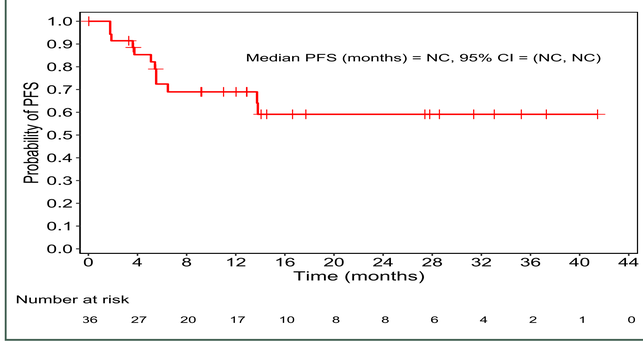


N=36
No post-treatment scan N=2

Evaluable for objective response N=34

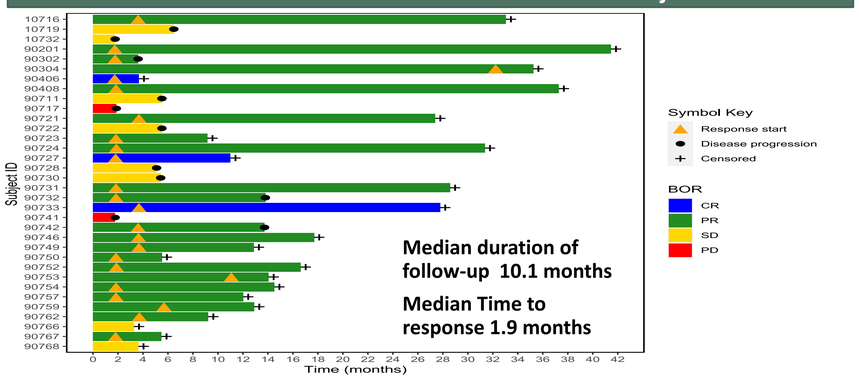
ORR: 71%, DCR: 94%
CR 3 (9%)
PR 21 (62%)
SD 8 (24%)
PD 2 (6%)

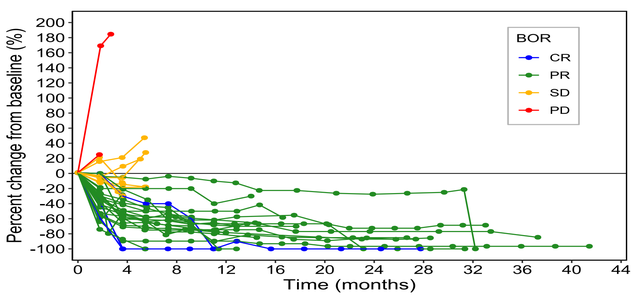
FIGURE 3: Kaplan-Meier Plot of PFS in Melanoma CPI-Naïve Subjects



PFS N=36

FIGURE 4: Swimmer Plot of Melanoma CPI-Naïve Subjects





Summary and Conclusions

The combination of HBI-8000 30mg BIW and nivolumab is well tolerated and demonstrates encouraging efficacy and safety in patients with anti-PD1-naïve advanced melanoma.

- **Efficacy:** ORR was 71% (24/34) and DCR was 94% (32/34).The median onset of objective response was 1.9 months. At median follow-up of 10.1 months, the estimated median PFS or duration of response was not reached.
- **Safety:** Most common AEs related to the treatment were fatigue, diarrhea, nausea, abdominal pain and hypophosphatemia.

Further investigation of this promising combination regimen in the Phase 3 setting is currently being activated comparing Nivolumab alone to Nivolumab plus HBI-8000.