Presentation # 1006P
Presented at European Society for Medical Oncology
September 13-17, 2024
Barcelona, Spain

Phase I Dose Escalation Study of HFB200603, a Best-in-Class BTLA Antagonist Monoclonal Antibody in Monotherapy and in Combination with the Anti-PD-1 mAb Tislelizumab in Adult Patients with Advanced Solid Tumors

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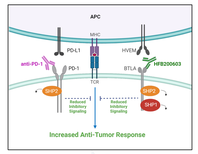
BACKGROUND

- BTLA is a co-inhibitory immune checkpoint molecule primarily expressed on B cells, T cells, and dendritic cells. The binding of HVEM to BTLA induces the recruitment of SHP1 and SHP2, leading to the inhibition of T cell proliferation and cytokine production.
- HFB200603 is a best-in-class, antagonistic monoclonal antibody that inhibits BTLA signaling, thereby enhancing pro-inflammatory responses to promote immune activation[1]. Due to their complementary downstream pathways, the dual blockade of BTLA and PD-1 is expected to result in stronger activation of T effector cells.
- To increase the probability of clinical success, we used our Drug Intelligence Science (DIS®) platform to select tumor types most likely to respond to HFB200603. This selection was based on target biology and single-cell insights from patient tumors, including anti-PD-(L)1 refractory tumors.
- Here, we present data from an ongoing Phase I dose-escalation, multi-center trial evaluating HFB200603 both as a monotherapy and in combination with tislelizumab (TIS) in patients with advanced refractory solid tumors (NCT05789069).



OBJECTIVES and STUDY DESIGN

Primary Objectives
- Safety and tolerability of HFB200603 in monotherapy and in combination with TIS

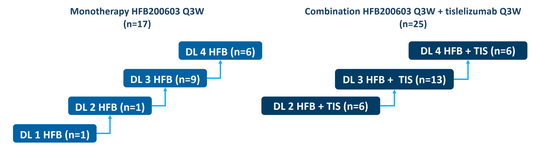
Secondary Objectives
- Assess PK, PD, and immunogenicity of HFB200603
- Establish RDEs and RP2D
- Examine preliminary anti-tumor efficacy, ORR using RECIST 1.1 and iRECIST

Exploratory Objective
- Establish Proof of Mechanism (POM) in paired tumor biopsies and peripheral blood
- Generate biomarker hypothesis for patient enrichment

Key Eligibility Criteria
- Adult patients with advanced or metastatic solid tumors. Tumor types include:
  - clear cell renal cell carcinoma
  - PD-L1+ colorectal cancer
  - PD-L1+ gastric cancer
  - PD-L1+ melanoma
  - PD-L1+ non-small cell lung cancer
- Measurable disease - RECIST 1.1
- ECOG PS 0-1
- Patient must have exhausted standard lines of systemic therapy*

**Other protocol-defined inclusion criteria may apply*

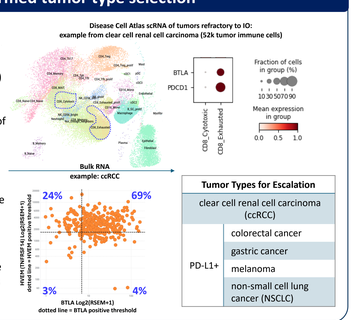
Study design and enrollment status



DL (Dose Level); HFB (HFB200603); Q3W (once every 3 weeks); TIS (tislelizumab)

DIS® informed tumor type selection

- The DIS® platform was used to identify the most promising indications for HFB200603.
- Analysis of our Disease Cell Atlas from tumors refractory to immuno-oncology (IO) therapies revealed RNA co-expression of BTLA and PD-1 in exhausted CD8+ T cells, which is consistent with an inhibitory role of BTLA in these cells.
- To enrich for tumor types likely to respond to HFB200603, the expression of BTLA and its ligand HVEM (TNFRSF14) was assessed using bulk RNA expression databases. These tumors generally also express PD-L1, suggesting a potential benefit from combination treatment.
- Data from the Dose Escalation study will be used to refine the selection of tumor types for Dose Expansion.



Tumor Types for Escalation	
clear cell renal cell carcinoma (ccRCC)	
PD-L1+	colorectal cancer
	gastric cancer
	melanoma
	non-small cell lung cancer (NSCLC)

RESULTS

Baseline demographics and clinical characteristics

Characteristic	Monotherapy (n=17)	Combination (n=25)
Median age, years (range)	62 (39-77)	60 (44-80)
Sex, n (%)		
Women	6 (35)	7 (28)
Men	11 (65)	18 (72)
ECOG PS, n (%)		
0	13 (76)	17 (68)
1	4 (24)	8 (32)
Median time since initial diagnosis (range), years	2.5 (0.9-13.7)	3.5 (0.8-24.3)
Number of prior systemic cancer therapy regimens, n (%)		
Median (range)	3 (1-4)	4 (1-7)
1	2 (12)	1 (4)
2	4 (24)	2 (8)
≥3	11 (65)	22 (88)
Received prior anti-PD-(L)1 therapy, n (%)		
Yes	8 (47)	7 (28)
No	9 (53)	18 (72)
Median follow-up time, months (range)	2.7 (0.9-6.3+)	2.3 (0.5+ - 6.6+)
Tumor types, n (%)		
PD-L1+ Colorectal cancer	7 (41)	12 (48)
PD-L1+ Gastric cancer	3 (18)	6 (24)
Clear cell renal cell carcinoma	3 (18)	4 (16)
PD-L1+ Melanoma	1 (6)	2 (8)
PD-L1+ Non-small cell lung cancer	3 (18)	1 (4)

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-(L)1, programmed cell death protein (ligand) 1.

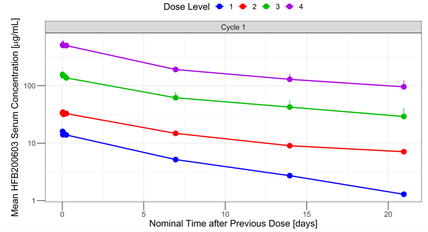
Safety profile of HFB200603 ± tislelizumab

Treatment Related Adverse Events (N=42)								
Adverse Event	HFB200603 Monotherapy (N=17)				HFB200603 + tislelizumab (N=25)			
	All grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	All grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Asthenia	**4 (24)**	4 (24)	-	-	**1 (4)**	1 (4)	-	-
ALT/AST increased	-	-	-	-	**2 (8)**	1 (4)	1 (4)	-
Amylase increased	-	-	-	-	**1 (4)**	1 (4)	-	-
Arthralgia	-	-	-	-	**2 (8)**	1 (4)	-	1 (4)
Arthritis	-	-	-	-	**1 (4)**	1 (4)	-	-
Colitis	-	-	-	-	**1 (4)**	-	1 (4)	-
Diarrhea	**1 (6)**	1 (6)	-	-	**2 (8)**	1 (4)	1 (4)	-
Edema, peripheral	-	-	-	-	**1 (4)**	1 (4)	-	-
Fatigue	-	-	-	-	**3 (12)**	3 (12)	-	-
Hypercalcemia	-	-	-	-	**1 (4)**	1 (4)	-	-
Lipase increased	-	-	-	-	**1 (4)**	1 (4)	-	-
Myalgia	**1 (6)**	1 (6)	-	-	**1 (4)**	-	-	1 (4)
Nausea	**1 (6)**	1 (6)	-	-	-	-	-	-
Oral dryness	-	-	-	-	**1 (4)**	1 (4)	-	-
Palmar erythema	-	-	-	-	**1 (4)**	1 (4)	-	-
Platelet count decreased	-	-	-	-	**3 (12)**	3 (12)	-	-
Pruritus	-	-	-	-	**3 (12)**	1 (4)	2 (8)	-
Rash	-	-	-	-	**2 (8)**	2 (8)	-	-

HFB200603 was well tolerated in monotherapy and in combination with tislelizumab with no DLTs and no TRAEs leading to dose modification or drug discontinuation

HFB200603 PK is favorable for immune antagonism

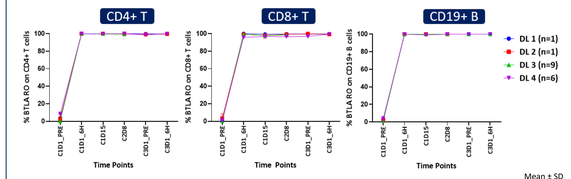
HFB200603 exposures are linear, dose-dependent, and similar to those projected from preclinical studies.



PHARMACODYNAMICS

Peripheral BTLA receptor occupancy (RO) measured in whole blood

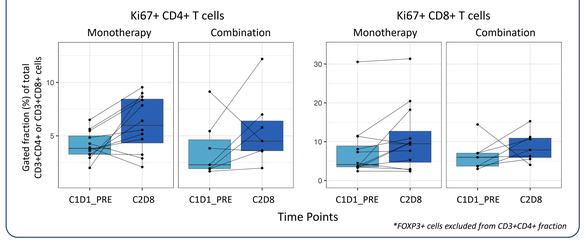
Full BTLA RO in CD4+ T, CD8+ T and CD19+ B cells observed in peripheral blood, across all doses



Mean ± SD

Immune activation in the periphery

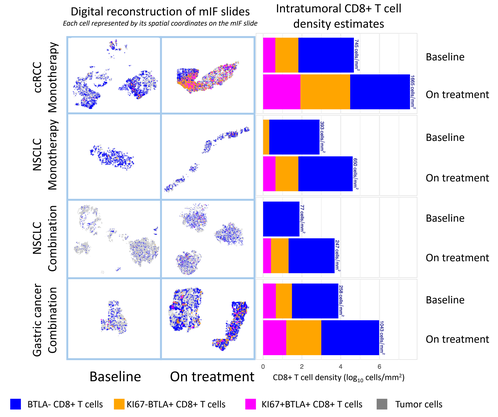
Peripheral flow cytometry analysis revealed that the proliferating (Ki67+) cell fractions of CD4+ and CD8+ T cells* showed moderate expansion following HFB200603 treatment, both as monotherapy and in combination with tislelizumab (Wilcoxon test p<0.05).



**FOXP3+ cells excluded from CD3+CD4+ fraction*

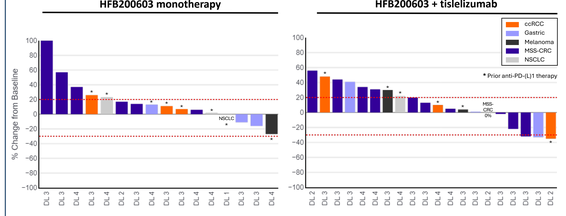
Evidence of mechanism in the tumor

- Multiplexed immunofluorescence (mIF) data from baseline and on-treatment biopsies demonstrates preferential expansion of BTLA+ CD8+ T cells in both monotherapy and in combination therapy with tislelizumab.
- A concomitant enrichment of Ki67+ cells suggests increased proliferation in treated subjects. These findings are consistent with an antagonistic effect of HFB200603 on proliferation through inhibition of the HVEM-BTLA axis.



PRELIMINARY ANTI-TUMOR RESPONSE

Best overall response to HFB200603 ± tislelizumab



Monotherapy (Evaluable patients, n= 17)
- **Disease Control Rate (DCR)* 65%** per RECIST 1.1
  - **75% DCR** in patients with prior **anti-PD-(L)1** therapy (n=8)
  - All **3 gastric** cancer patients had stabilization of disease
- **4 patients** with prolonged **SD > 18 weeks**
  - 1 x MSS-CRC (2 prior LoT), 2 x NSCLC (anti-PD-1 refractory and relapsed), 1 x Melanoma (anti-PD-1 refractory)

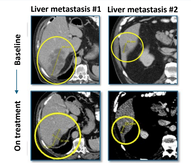
Combination (Evaluable patient, n=23)
- **ORR 13%, DCR* 52%** per RECIST 1.1
  - **1 PR** and **DCR 55%** in heavily pretreated MSS-CRC (n=12; median 4 prior LoT)
  - **1 PR** and **1 SD** in heavily pretreated ccRCC
  - **1 PR** in heavily pretreated Gastric Cancer
- All 3 responders are active on trial and have radiographic evidence of clinical benefit > 4 months

Note: Total of 2 patients in the combination cohort pending their first scan results

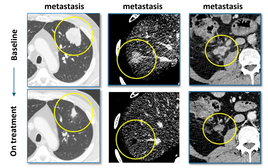
**DCR includes stable disease (SD), partial response (PR) and complete response (CR) in target lesion per RECIST 1.1; LoT, lines of treatment*

Radiographic responses to HFB200603 in combination with tislelizumab

Colorectal Adenocarcinoma (MSS)
Patient & Treatment Information
- 59-year-old male
- Enrolled in HFB200603 DL3 in combination with tislelizumab
- Stage IV, MSS, BRAF wt, KRAS wt, NRAS-PIK3CA (pGlu545Gly)-p53 mutated
- 6 prior lines of therapies in metastatic setting, including chemotherapy and targeted agents
- Current time on treatment HFB200603 trial > 5 mo (ongoing)



Clear Cell Renal Cell Carcinoma
Patient & Treatment Information
- 58-year-old male
- Enrolled in HFB200603 DL2 in combination with tislelizumab
- Stage IV, CPS 3%
- 6 prior lines of therapies in metastatic setting, including anti-PD-L1, targeted, and investigational IO agents
- Current time on treatment HFB200603 trial > 6 mo (ongoing)



SUMMARY and FUTURE DIRECTIONS

- HFB200603 shows a favorable safety profile and demonstrates a dose-dependent PK and PD both as a monotherapy and in combination with TIS in subjects with heavily pre-treated refractory solid tumors.
- Using DIS® guided enrichment of tumor types, we generated compelling proof-of-mechanism data in both the peripheral blood and tumor; reinforcing our confidence in the on-target action of HFB200603, as demonstrated by observed clinical activity and associated predictive biomarkers.
- Preliminary clinical activity in liver metastases across several heavily pre-treated tumor types, including MSS-CRC, ccRCC and gastric cancer, is very encouraging and will be further explored in the Dose Expansion part of the trial.

Acknowledgments and references

We extend our thanks to the patients, their families, and the investigators and staff members who made this trial possible.

1. Li, J. et al., (2022). *HFB200603, a Novel Anti-BTLA Monoclonal Antibody that Provides Therapeutic Potential for Immune Escape and Synergizes with Anti-PD-1 Treatment*. AACR 2022. New Orleans, LA.

Study sponsored by HiFiBiO Inc.

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