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Phase I Dose Escalation Trial of the First-in-class TNFR2 Agonist Monoclonal Antibody, HFB200301, in Monotherapy and in Combination with tislelizumab, an anti-PD-1 Monoclonal Antibody, in Adult Patients with Advanced Solid Tumors

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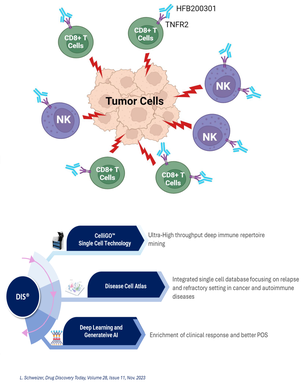
BACKGROUND

- Tumor necrosis factor receptor-2 (TNFR2) is primarily expressed on immune cells, including effector CD8+ and CD4+ T-cells, regulatory T (Treg) cells, natural killer (NK) cells, and myeloid cells. In contrast, TNFR1 is expressed ubiquitously across most cell types.
- HFB200301 is a first-in-class, agonistic monoclonal antibody (mAb) targeting TNFR2. It is designed to stimulate both innate and adaptive immune responses. The stimulation of T-cells and NK-cells within the tumor microenvironment (TME) is expected to enhance anti-tumor immunity effectively.
- To enhance the probability of clinical success, we used our Drug Intelligence Science (DIS®) platform to select tumor types most likely to respond to HFB200301, based on target biology and single-cell insights from patient-derived tumors, including refractory tumors.
- Here, we present the initial data of an ongoing multicenter, dose-escalation, Phase I trial of HFB200301 in monotherapy and in combination with tislelizumab (TIS) in patients with advanced refractory solid tumors (NCT05238883).



L. Schweizer, Drug Discovery Today, Volume 28, Issue 11, Nov. 2023

OBJECTIVES and STUDY DESIGN

Primary Objectives
- Safety and tolerability of HFB200301 in monotherapy and in combination with TIS

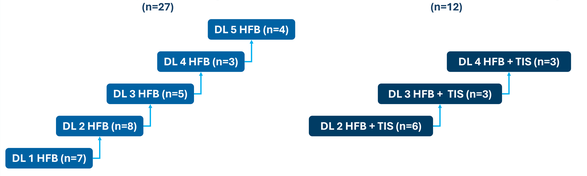
Secondary Objectives
- Assess PK, PD, and immunogenicity of HFB200301
- Establish RDE and RP2D
- Examine preliminary anti-tumor efficacy, ORR using RECIST 1.1, iRECIST, and mRECIST for mesothelioma

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:
  - cervical cancer
  - EBV+ gastric cancer
  - head and neck squamous cell carcinoma
  - melanoma
  - pleural mesothelioma
  - non-small cell lung cancer
  - renal cell carcinoma
  - sarcoma
  - testicular germ cell tumor
- Measurable disease - RECIST 1.1 or mRECIST
- ECOG PS 0-1
- Patient must have exhausted standard lines of systemic therapy*

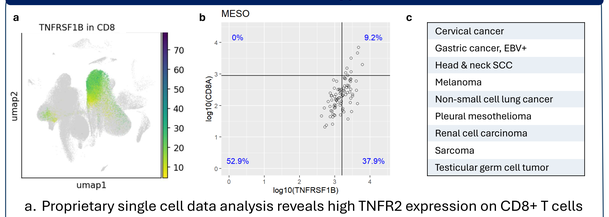
Other protocol-defined inclusion criteria may apply

Study design and enrollment status



DL (Dose Level); HFB (HFB200301); Q4W (once every 4 weeks); TIS (tislelizumab)

DIS® informed tumor type selection



a. Proprietary single cell data analysis reveals high TNFR2 expression on CD8+ T cells in post-PD-1 tumor samples
b. Quadrant analysis in bulk RNAseq database to identify tumor types with TNFR2^{hi} CD8A^{hi} enrichment
c. Tumor types selected by DIS®

RESULTS

Baseline demographics and clinical characteristics

Characteristic	Monotherapy (n=27)	Combination (n=12)
Median age, years (range)	63 (21-77)	60 (18-73)
Sex, n (%)		
Women	13 (48)	3 (25)
Men	14 (52)	9 (75)
ECOG PS, n (%)		
0	9 (33)	5 (42)
1	18 (64)	7 (58)
Median time since initial diagnosis (range), years	1.9 (0.2-15.8)	3.2 (0.8-10.0)
Number of prior systemic cancer therapy regimens, n (%)		
Median (range)	2 (1-4)	2 (1-3)
1	7 (26)	2 (17)
2	9 (33)	6 (50)
≥3	11 (41)	4 (33)
Received prior anti-PD-(L)1 therapy, n (%)		
Yes	17 (63)	8 (67)
No	10 (37)	4 (33)
Median time on treatment, months (range)	1.8 (0.5-7.3)	2.1 (0.8-9.2)
Tumor types, n (%)		
Cervical cancer	2 (7)	0 (0)
Gastric cancer, EBV+	0 (0)	1 (8)
Head and neck squamous cell carcinoma	2 (7)	1 (8)
Melanoma	2 (7)	5 (43)
Non-small cell lung cancer	6 (23)	1 (8)
Pleural mesothelioma	5 (19)	2 (17)
Renal cell carcinoma	0 (0)	0 (0)
Sarcoma	8 (30)	1 (8)
Testicular germ cell tumor	2 (7)	1 (8)

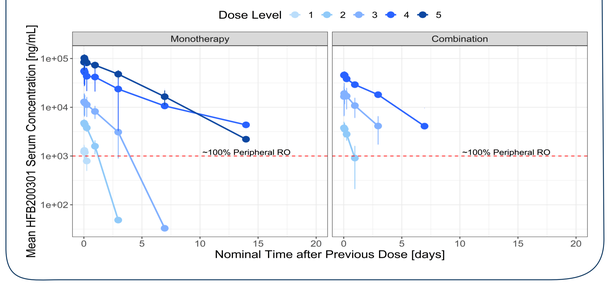
EBV+, Epstein-Barr virus positive; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-(L)1, programmed cell death protein (ligand)1.

HFB200301 was well tolerated in monotherapy and combination with TIS with no DLTs and no ≥ Grade 3 TRAEs

Adverse Event	HFB200301 Monotherapy (n=27)				HFB200301 + Tislelizumab (n=12)			
	All grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	All grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Pruritus	3 (11)	3 (11)	-	-	1 (8)	1 (8)	-	-
Tremor	2 (7)	-	2 (7)	-	-	-	-	-
Fatigue	2 (7)	1 (3)	1 (3)	-	-	-	-	-
Asthenia	2 (7)	2 (7)	-		-	-	-	-
Nausea	2 (7)	2 (7)	-	-	1 (8)	1 (8)	-	-
Fever	1 (3)	-	1 (3)	-	2 (16)	1 (8)	1 (8)	-
Dyspnea	1 (3)	-	1 (3)	-	-	-	-	-
Chills , shivers	1 (3)	1 (3)	-	-	1 (8)	1 (8)	-	-
Dizziness	1 (3)	1 (3)	-	-	-	-	-	-
Emesis	1 (3)	1 (3)	-	-	-	-	-	-
Weakness - hands	1 (3)	1 (3)	-	-	-	-	-	-
Mucositis oral	1 (3)	1 (3)	-	-	-	-	-	-
Muscular Weakness	1 (3)	1 (3)	-	-	-	-	-	-
Myalgia	1 (3)	1 (3)	-	-	-	-	-	-
Weight loss	1 (3)	1 (3)	-	-	-	-	-	-
Xerosis	1 (3)	1 (3)	-	-	-	-	-	-
Rash	1 (3)	1 (3)	-	-	1 (8)	1 (8)	-	-
WBC decreased	-	-	-	-	-	-	-	-
Creatinine increased	-	-	-	-	1 (8)	-	1 (8)	-
ALT increased	-	-	-	-	2 (16)	2 (16)	-	-
AST increased	-	-	-	-	2 (16)	2 (16)	-	-
Diarrhea	-	-	-	-	1 (8)	1 (8)	-	-
Dysgeusia	-	-	-	-	1 (8)	1 (8)	-	-
Hives	-	-	-	-	1 (8)	1 (8)	-	-

HFB200301 PK is favorable for immune agonism

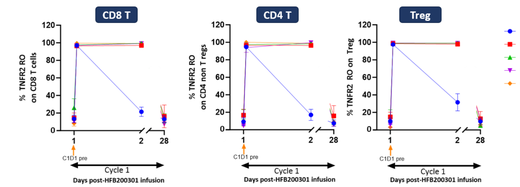
Dose-proportional exposures and rapid clearance which may provide favorable disposition for pulsatile agonism of TNFR2.



PHARMACODYNAMICS

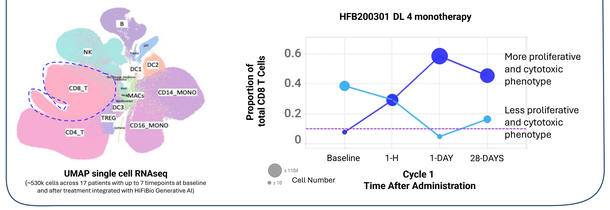
Peripheral TNFR2 receptor occupancy (RO) measured in PBMCs

Full TNFR2 RO in CD8+ T, CD4+ T and Treg cells observed in peripheral blood. At least 24 hours of full RO was observed in DL 2 and above. Peripheral RO is positively associated with soluble TNFR2 levels in serum (data not shown).



Proof of mechanism in the periphery

Peripheral single-cell analysis reveals a majority of TNFR2+ CD8+ T cells are reprogrammed to become proliferative and cytotoxic following HFB200301 treatment. This reprogramming persists for at least 28 days. Expression analysis confirms activation of NFκB pathway. Tregs are unaffected by HFB203001 (data not shown).
Example from a pleural mesothelioma patient is below.



Proof of mechanism in the tumor

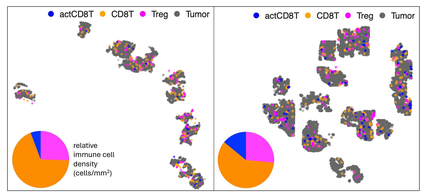
HFB200301 monotherapy activates CD8 T cells in the TME.

HFB200301 DL 1 monotherapy
BOR: Stable Disease

HFB200301 DL1 monotherapy increased the abundance of activated CD8+ T-cells (e.g., PD1+, TNFR2+, or OX40+ represented as blue fraction) in this pleural mesothelioma.

HFB200301 alone was sufficient to induce a BOR of SD in this patient.

Each colored dot is a cell.

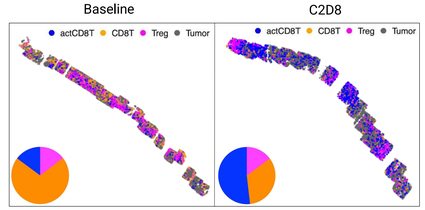


HFB200301 DL 2 + tislelizumab
BOR: Partial Response

Since HFB200301 monotherapy activates CD8 T-cells, a combination with tislelizumab may augment their expansion and enhance clinical activity.

The same pleural mesothelioma patient above that demonstrated radiographic response exemplifies this enhancement with a BOR of PR.

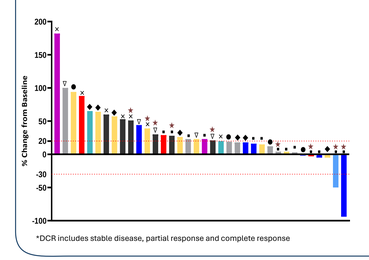
HFB200301 DL2 in combination with tislelizumab markedly increased the abundance of activated CD8+ T-cells (blue fraction).



Digitally rendered multiplex immunofluorescence (mIF) of representative patients.

PRELIMINARY ANTI-TUMOR RESPONSE

Best overall response to HFB200301



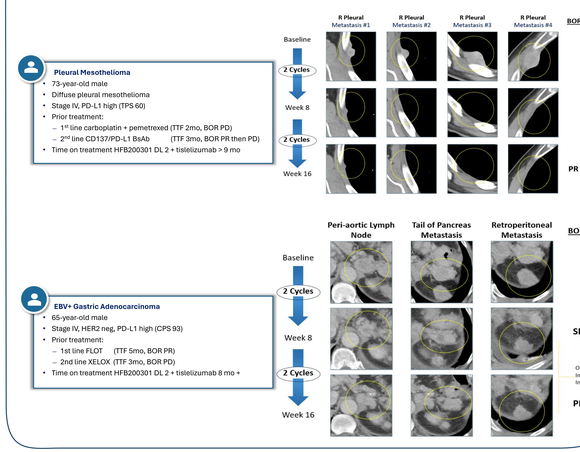
*DCR includes stable disease, partial response and complete response

- **44%** Overall Disease Control Rate (DCR)* in monotherapy and in combination with tislelizumab in heavily pretreated tumors

Monotherapy
- DCR in anti-PD-L1 refractory tumors
  - **67%** in NSCLC as 4th – 5th line therapy
  - **80%** in pleural mesothelioma as 3rd – 4th line therapy

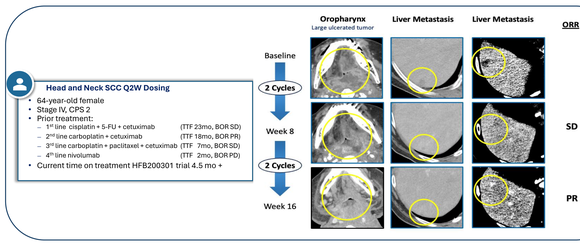
Combination
- **PR** in anti-PD-L1 refractory pleural mesothelioma
- **PR** in EBV+ gastric cancer

Radiographic responses to HFB200301 in combination with tislelizumab



SUMMARY and FUTURE DIRECTIONS

- HFB200301 demonstrates a favorable safety profile and dose-dependent PK with PD and preliminary clinical activity in monotherapy and in combination with TIS in patients with heavily pre-treated refractory solid tumors.
- Using DIS® guided enrichment of tumor types, we generated convincing proof of mechanism data in the periphery and in the tumor; thereby increasing our confidence in the on-mechanism action of HFB200301 as evidenced by the observed clinical activity and associated predictive biomarker.
- The baseline and on-treatment patient and tumor characteristics, along with PK and PD data, and our DIS®-informed predictive modeling, indicated that more frequent Q2W dosing of HFB200301 may be beneficial. Initial monotherapy results in a HNSCC patient are promising.
- With further optimization of dosing schedule and predictive biomarkers for patient selection, we anticipate increased clinical responses in tumor specific expansion cohorts.



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