Poster #2531
Presented at ASCO®
May 31- June 4, 2024
Chicago, IL

A Phase I monotherapy dose escalation study of HFB301001, a novel next-generation OX40 agonist monoclonal antibody, in adult patients with advanced solid tumors

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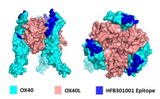
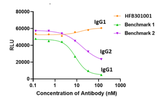
BACKGROUND

- Next-generation OX40 agonist antibodies demonstrated promising preclinical activity but had limited clinical impact, likely due to their pharmacological properties. These properties include:
  - competitive blocking of natural OX40-OX40L interactions
  - decreased surface expression of OX40 on CD4+ T cells
- HFB301001 overcomes these limitations by binding to a unique, non-competing epitope, thus preserving the OX40/OX40L interaction. Moreover, HFB301001 does not decrease OX40 surface levels upon co-stimulation.
- In preclinical studies, HFB301001 demonstrated superior *in vivo* anti-tumor activity compared to benchmark first generation OX40 agonists.
- To enhance the probability of clinical success, we used our Drug Intelligence Science (DIS®) platform to select tumor types most likely to respond, based on target biology and single-cell insights from patient-derived refractory tumors.
- Here, we present the initial data of the ongoing dose-escalation Phase I trial of HFB301001 in patients with advanced solid tumors (NCT05229601).

HFB301001 epitope

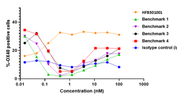


OX40L signaling*



* CHO-BL 130 nM signaling in the presence of non-crosslinked CHO agonistic mAbs

OX40 levels on CD4 T cells upon Ab treatment



OBJECTIVES and STUDY DESIGN

Primary objectives
- Safety and tolerability of monotherapy HFB301001

Secondary objectives
- Assess PK, PD, and immunogenicity of HFB301001
- Determine biologically active dose(s) and preliminary anti-tumor efficacy of HFB301001
- Establish RDE and RP2D
- Examine preliminary anti-tumor efficacy, ORR using RECIST 1.1 and iRECIST

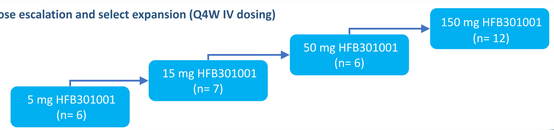
Exploratory objectives
- Establish Proof of Mechanism (POM) in paired tumor biopsies and peripheral blood
- Generate biomarker hypothesis for patient enrichment

Key eligibility criteria
- Adult patients with advanced or metastatic solid tumors. Tumor types included:
  - soft tissue sarcoma (STS)
  - renal cell carcinoma (RCC)
  - hepatocellular carcinoma (HCC)
  - cutaneous melanoma
  - head and neck squamous cell carcinoma (HNSCC)
  - uterine carcinosarcoma (UCS)
- Measurable disease based on RECIST 1.1
- ECOG PS 0-1
- Patient must have exhausted standard lines of systemic therapy*

**Other protocol-defined inclusion criteria may apply*

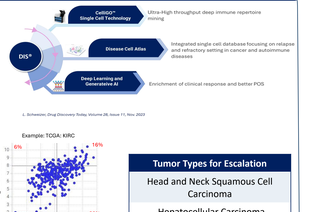
Study design and enrollment

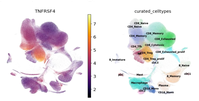
Dose escalation and select expansion (Q4W IV dosing)



DIS® informed tumor type selection

- DIS® was used to identify the most promising indications for HFB301001
- Immune single-cell profiling and analysis of primary and relapse refractory tumors in the Disease Cell Atlas revealed a signature of high OX40-expression in effector T cells (Teff) and regulatory T cells (Treg)





- To enrich for tumor types likely to respond to HFB301001, the prevalence and prognostic value of this high OX40 signature in T_{eff} and T_{reg} cells was assessed in expression databases
- Real time data from the Escalation study will be used to refine the Tumor Types for Expansion

Tumor Types for Escalation
Head and Neck Squamous Cell Carcinoma
Hepatocellular Carcinoma
Melanoma
Renal Cell Carcinoma (KIRC)
Soft Tissue Sarcoma
Uterine Carcinosarcoma

RESULTS

Baseline demographics and clinical characteristics

Dose escalation / expansion (Q4W IV dosing, n=31)	
Median age (range), yrs	62 (41-78)
Sex, n (%)	
Women	7 (23)
Men	24 (77)
ECOG PS, n (%)	
0	9 (29)
1	22 (71)
Median time from initial diagnosis to first dose (range), yrs	3.9 (1.2-11.9)
Number of prior systemic cancer therapy regimens, n (%)	
Median (range)	2 (1-4)
1	6 (19)
2	12 (39)
≥3	13 (42)
Received prior anti-PD-(L)1 therapy, n (%)	
Yes	26 (84)
No	5 (16)
Median time on treatment, months (range)	1.9 (0.9-17.0)
Tumor Types, n (%)	
Renal cell carcinoma	11 (35)
Hepatocellular carcinoma	8 (26)
Melanoma	5 (16)
Soft tissue sarcoma	3 (10)
Head and neck squamous cell carcinoma	2 (6)
Uterine carcinosarcoma	2 (6)

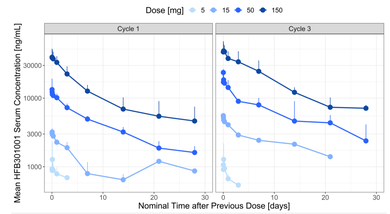
HFB301001 was well-tolerated with no DLTs and no ≥ grade 3 TRAEs

- As of April 2024, Treatment-related adverse events (TRAEs) occurred in 12 patients (39%), none ≥ Grade 3
- The most common TRAEs included rash (16.1%) and amylase increased (9.7%)
- There were no TRAEs leading to treatment discontinuation. No dose-limiting toxicities were observed.

Treatment-related adverse events (TRAE), (n=31)				
Adverse event	**All grades n (%)**	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**
Rash	5 (16.1)	5 (16.1)	-	-
Amylase increased	3 (9.7)	1 (3.2)	2 (6.5)	-
Arthralgia	2 (6.5)	2 (6.5)	-	-
Lipase increased	2 (6.5)	-	2 (6.5)	-
Pruritus	2 (6.5)	1 (3.2)	1 (3.2)	-
Abdominal pain	1 (3.2)	-	1 (3.2)	-
Anemia	1 (3.2)	1 (3.2)	-	-
Angioedema	1 (3.2)	-	1 (3.2)	-
CPK increased	1 (3.2)	1 (3.2)	-	-
Decreased appetite	1 (3.2)	1 (3.2)	-	-
Dysgeusia	1 (3.2)	1 (3.2)	-	-
Edema - facial	1 (3.2)	1 (3.2)	-	-
Edema - peripheral	1 (3.2)	1 (3.2)	-	-
Fatigue	1 (3.2)	1 (3.2)	-	-
Hyperglycemia	1 (3.2)	-	1 (3.2)	-
Infusion related reaction	1 (3.2)	-	1 (3.2)	-
Mucosal inflammation	1 (3.2)	1 (3.2)	-	-
Muscle weakness lower limb	1 (3.2)	1 (3.2)	-	-
Nail ridging	1 (3.2)	1 (3.2)	-	-
Nausea	1 (3.2)	1 (3.2)	-	-
Neutrophil count decreased	1 (3.2)	-	1 (3.2)	-
Sore throat	1 (3.2)	1 (3.2)	-	-
Vomiting	1 (3.2)	1 (3.2)	-	-

Dose-proportional PK

- Small distribution volume, low clearance, and long half-life with mild TMDD effects
- Accumulation observed over multiple Q4W doses of 15 mg and greater



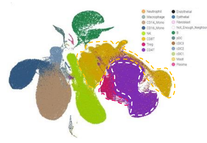
PHARMACODYNAMICS

Key findings
- Multiplex immunofluorescence (mIF) on paired pre- and post-treatment tumor biopsies revealed that unlike first generation agonists which decrease surface expression of OX40 significantly, HFB301001 has little effect on either CD4 Tconv or Treg surface expression
- HFB301001 can increase the infiltration of both CD8+ T cells and NK cells in the TME of the tumor types selected with DIS®.
- Single cell RNA and TCRseq of PBMCs demonstrated that HFB301001 not only increases the CD8/CD4 ratio, but also increases the abundance of CD8 clonotypes found in the tumor. These clonotypes have an expression pattern consistent with an activated, cytotoxic and proliferative phenotype

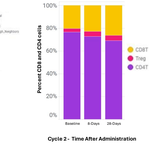
Proof of mechanism in the periphery

UMAP of PBMC scRNA and TCRseq

~205k cells from 5 patients and 7 timepoints

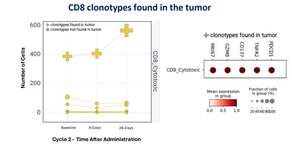


HFB301001 increases the CD8/CD4 ratio



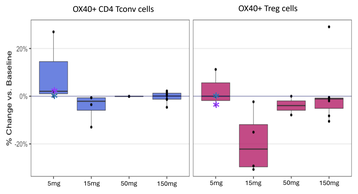
Example RCC patient HFB301001 50mg

HFB301001 increases the abundance of activated, cytotoxic and proliferative CD8 clonotypes found in the tumor



Proof of mechanism in the tumor: OX40 levels

Surface expression of OX40 on CD4 Tconv and Tregs cells is largely unchanged in most patients



Boxplots per dose cohort of change in OX40+ immune cell density (cell/mmsq) from baseline by mIF.
Dose cohort size: 5mg=3pts, 15mg=4pts; 50mg=2 pts; 150mg=7pts

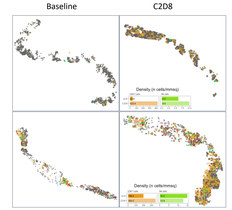
Note that OX40+ cells are much less than 1% of all cells observed.

Proof of mechanism in the tumor: Immune Infiltration

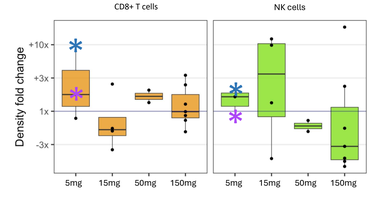
HFB301001 can increase the infiltration of both CD8 T cells and NK cells in the TME of most patients

HFB301001 5mg RCC
- Time on treatment: 17 mo
- Number of prior lines of therapy: 4

HFB301001 5mg HCC
- Time on treatment: 3 mo
- Number of prior lines of therapy: 2

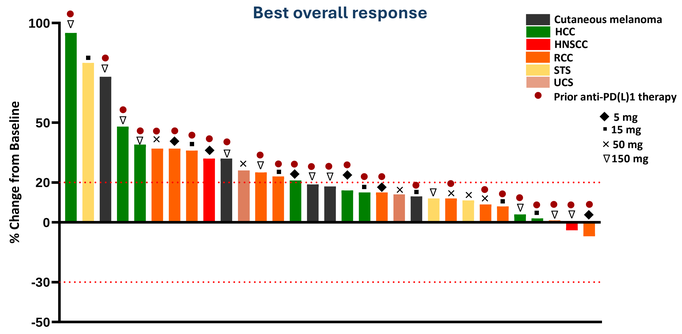


Digitally rendered mIF of representative patients.
Full view of all patients in boxplots to the right. Colored stars track same patient.



Boxplot per dose cohort of change in Immune cells density from baseline (cell/mmsq) by mIF.
Dose cohort size: 5mg=3pts, 15mg=4pts; 50mg=2 pts; 150mg=7pts

PRELIMINARY ANTI-TUMOR RESPONSE



Key findings
- **55%** overall disease control rate (DCR)* observed in advanced solid tumors as assessed by iRECIST
- **55%** DCR in RCC
  - 3 median prior lines of therapy (range 3-4)
  - All were TKI and anti-PD-(L1) refractory tumors
  - Of the 11 evaluable RCC patients, 1 patient had stable disease with tumor shrinkage for 17 months
- **50%** DCR in HCC
  - 2 median prior lines of therapy (range 1-2)
  - All were anti-VEGF and anti-PD-(L)1 refractory tumors
  - Median Time on Treatment 1.8 mo (range 1 – 3.7 mo)
  - The 5 and 15 mg doses, median Time on Treatment 3.2 mo, with 1 subject still on treatment >4 mo

* DCR – Includes stable disease, partial and complete response

SUMMARY and FUTURE DIRECTIONS

- HFB301001 demonstrates a favorable safety profile, dose-dependent PK and PD consistent with OX40 agonism, and preliminary clinical activity in heavily pre-treated solid tumors.
- Unlike first-generation OX40 agonists, HFB301001 does not reduce OX40 receptor levels while modulating intratumor T-cell activity across all tested doses.
- Lower doses of HFB301001 result in increased activation of CD8+ T-cells and NK cells within the TME, suggesting that these doses optimize the biological activity of the drug.
- By using DIS®-guided enrichment of tumor types, we generated convincing proof of mechanism data both peripherally and within tumors. This bolstered our confidence in the mechanism-driven action of HFB301001, which induced the observed clinical activity.
- HFB301001 demonstrated good disease control in heavily pre-treated HCC and RCC tumors that were refractory to anti-VEGF and/or anti-PD-(L)1 therapies. Preclinical studies have indicated potential synergism between anti-VEGF therapy and OX40 agonism. Therefore, combining HFB301001 with anti-VEGF and/or anti-PD-(L)1 therapies may offer clinical benefit in these specific tumors.
- We are actively exploring a combination strategy for HFB301001 targeting specific tumor types, such as HCC and RCC, where its mechanism of action is observed. Potential partners being considered include checkpoint inhibitors and VEGF inhibitors, which have a strong biological rationale for improving clinical outcomes when combined with OX40 agonism.

For additional information, please email: contact@hifibio.com or visit HiFiBio.com