Presentation # 949P
Presented at European Society for Medical Oncology
October 17 - 21, 2025
Berlin, Germany

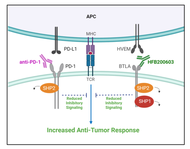
Evaluation of HVEM and PD-L1 Expression Profile in Tumors as Potential Predictive Biomarkers for HFB200603, a BTLA antagonist, as Monotherapy and in Combination with Tislelizumab

María de Miguel[1], Eladio Marquez[2], Germain Margall-Ducos[2], Victor Moreno[3], Valentina Gambardella[4], Gennaro Daniele[5], Jessica Menis[6], Ana Landa Magdalena[7], Anthony B. El-Khoueiry[8], Emiliano Calvo[1], Alice Rossi[6], Francesca Zacchi[6], Olja Rapaic[2], Melissa Harney[2], Juying Li[2], Hombline Poullain[2], Alexander Chung[2], Francisco Adrian[2], Jinping Gan[2*]
START Madrid-CIOCC, Centro Integral Oncológico Clara Campal[1], HiFiBiO Therapeutics Inc.[2], START Madrid - Hospital Fundación Jiménez Díaz[3], Hospital Clinico Universitario de Valencia[4], Fondazione Policlinico Universitario Agostino Gemelli IRCCS – Università Cattolica del Sacro Cuore[5], Azienda Ospedaliera Universitaria Integrata di Verona[6], Clinica Universidad de Navarra[7], University of Southern California Norris Comprehensive Cancer Center[8] , Corresponding author*

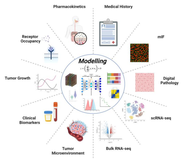
BACKGROUND

- 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.
- Previously we reported Phase 1 results that demonstrated tolerable safety profile and clinically meaningful efficacy with HFB200603 as monotherapy and in combination with tislelizumab (TIS) in advanced refractory solid tumors.[1]
- Here, we report updated safety and efficacy results with longer follow-up time.
- In addition, we report potential biomarkers predictive of response to HFB200603 monotherapy and in combination with TIS.

Schematic of HFB200603 and anti-PD-1 blockade of BTLA-HVEM and PD-1-PD-L1 interaction, respectively

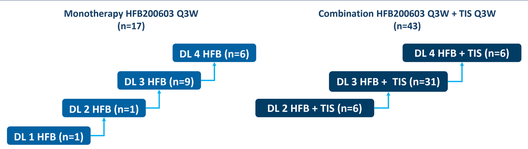


Integrated analysis of potential response predictive biomarkers



STUDY DESIGN and PATIENT DEMOGRAPHICS

Study Design



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

Demographics and Clinical Characteristics

Characteristic	Monotherapy (n=17)	Combination (n=43)
Median age, years (range)	62 (39-77)	63 (44-82)
Sex, n (%)		
Female	6 (35)	15 (35)
Male	11 (65)	28 (65)
ECOG PS, n (%)		
0	13 (76)	27 (63)
1	4 (24)	16 (37)
Median time since initial diagnosis (range), years	2.5 (0.9-13.7)	3.5 (0.4-24.3)
Number of prior systemic cancer therapy regimens, n (%)		
Median (range)	3 (1-4)	3 (1-7)
1	2 (12)	3 (7)
2	4 (24)	11 (26)
≥3	11 (65)	29 (67)
Received prior anti-PD-(L)1 therapy, n (%)		
Yes	8 (47)	22 (51)
No	9 (53)	21 (49)
Median follow-up time, months (range)	2.7 (0.9-12.0)	3.5 (0.5 - 18.2)
Tumor types, n (%)		
PD-L1+ Colorectal cancer	7 (41)	14 (33)
Clear cell renal cell carcinoma	3 (18)	9 (21)
PD-L1+ Non-small cell lung cancer	3 (18)	8 (19)
PD-L1+ Gastric cancer	3 (18)	7 (16)
PD-L1+ Melanoma	1 (6)	5 (11)

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

SAFETY PROFILE

Safety Summary of HFB200603 ± TIS Q3W

HFB200603 ± TIS demonstrated tolerable safety profile

- **HFB200603 monotherapy was well tolerated with treatment-related adverse events (TRAEs) limited to Grade 1 and no Grade 3.**
- **HFB200603 + TIS was also well tolerated with TRAEs mostly Grade 1-2 and few incidence of Grade 3 (12%)**
- **Grade 3 TRAEs in 3 of 5 subjects were lab abnormalities (AST/ALT, lipase increase) which quickly resolved without medication**

Adverse Event	Treatment Related Adverse Events (TRAE), ≥2 Incidence or Grade 3							
	HFB200603 Monotherapy (n=17)				HFB200603 + TIS (n=43)			
	Any, n (%)	Gr 1, n (%)	Gr 2, n (%)	Gr 3, n (%)	Any, n (%)	Gr 1, n (%)	Gr 2, n (%)	Gr 3, n (%)
Overall	**6 (35)**	**6 (35)**	**1 (6)**	**-**	**30 (70)**	**13 (30)**	**13 (30)**	**5 (12)**
ALT / AST increased	1 (6)	1 (6)	-	-	3 (7)	1 (2)	-	2 (5)
Anemia	-	-	-	-	2 (5)	-	2 (5)	-
Amylase increased	-	-	-	-	2 (5)	-	2 (5)	-
Arthralgia	-	-	-	-	3 (7)	1 (2)	1 (2)	1 (2)
Diarrhea	1 (6)	1 (6)	-	-	4 (9)	3 (7)	1 (2)	-
Fatigue / Asthenia	5 (29)	5 (29)	-	-	7 (16)	5 (12)	2 (5)	-
Lipase increased	-	-	-	-	2 (5)	-	1 (2)	1 (2)
Myalgia	1 (6)	1 (6)	-	-	3 (7)	2 (5)	-	1 (2)
Nausea	1 (6)	1 (6)	-	-	3 (7)	3 (7)	-	-
Pneumonitis	-	-	-	-	3 (7)	1 (2)	2 (5)	-
Pruritus	1 (6)	1 (6)	-	-	7 (16)	4 (9)	3 (7)	-
Rash / dermatitis acneiform / psoriasis	-	-	-	-	3 (7)	2 (5)	-	1 (2)
Thrombocytopenia	-	-	-	-	2 (5)	2 (5)	-	-

Cutoff: 26-Sep-2025

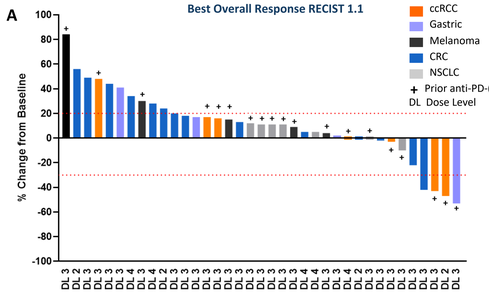
PRELIMINARY ANTI-TUMOR RESPONSE

HFB200603 + TIS Combination Efficacy

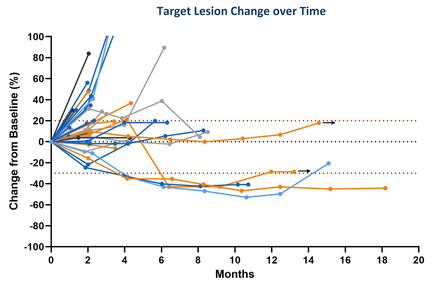
Clinically meaningful responses demonstrated by HFB200603 + TIS

- **Figure A: Partial responses in multiple indications – gastric, clear cell renal cell carcinoma, MSS-CRC**
  - **Responses in subjects with prior immunotherapy and heavily pretreated**
  - **MSS-CRC responder had 7 prior lines of therapy**
- **Figure B: Durable clinical benefit (partial responses and stable disease per RECIST 1.1) observed**

A



B



Note: 6 subjects not shown in Fig A and B had clinical progressions and did not have radiographic assessment of their target lesions

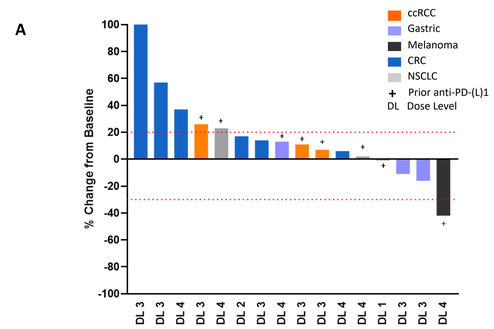
Cutoff: 26-Sep-2025

HFB200603 Monotherapy Efficacy

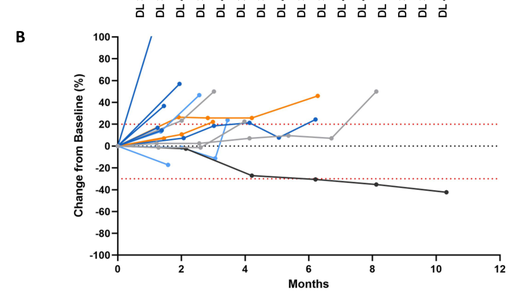
Preliminary clinical activities observed with HFB200603 monotherapy

- **Figure A: Partial response in anti-PD-1 refractory melanoma subject with 3 prior lines of therapy**
- **Figure B: Subjects with durable partial response and prolonged stable diseases observed**

A



B



Note: 1 subject not shown above had clinical progressions and did not have radiographic assessment of target lesions

Cutoff: 26-Sep-2025

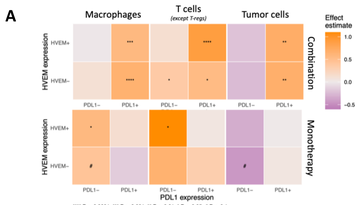
POTENTIAL BASELINE BIOMARKERS PREDICTIVE OF RESPONSE TO HFB200603 ± TIS

Tumor – mIF: HVEM and PD-L1 Expression on Immune Cells as Potential Predictive Biomarker

HVEM on CD8 T and HVEM and PD-L1 on macrophages may be predictive of responses to HFB200603 monotherapy and in combination with TIS, respectively

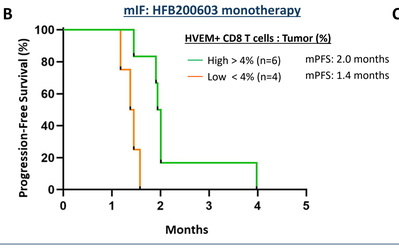
- **Figure A: Density of HVEM+ macrophages and T cells correlates to clinical benefit (PR or SD per RECIST 1.1) in monotherapy and combination; PDL1+ subset densities correlate to benefit only in combination**
- **Figure B: Increased levels of HVEM expressing CD8 T cells may be predictive of prolonged PFS in response to HFB200603 monotherapy**
- **Figure C: Higher expression levels of HVEM and PD-L1 on immune-suppressing macrophages may be predictive of prolonged PFS in response to HFB200603 + TIS combination**

A

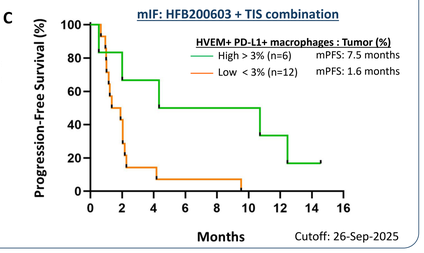


Estimates represent relative contribution of HVEM± and PDL1± subsets to differences in cell density between tumors receiving and not receiving a clinical benefit from HFB200603 as monotherapy and in combination. Estimates are fold differences between marginal means from mixed-effect modeling of baseline cell density as a function of clinical benefit.

B



C



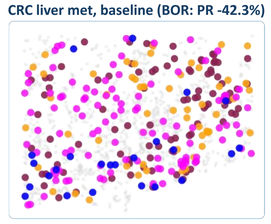
Cutoff: 26-Sep-2025

Tumor – mIF: Further Analysis of HVEM Expression as Response Predictive Biomarker to HFB200603 + TIS Combination

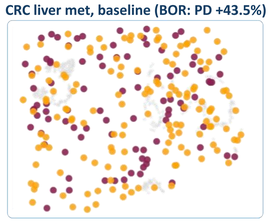
Enhanced clinical benefit in response to HFB200603 + TIS combination may be dependent on HVEM expression

- **Figure A: Digital mIF representation of tumor ROI with higher density of HVEM+ PDL1+ macrophages at baseline in patient deriving clinical benefit from HFB200603 + TIS combination**
- **Figure B: Digital mIF representation of tumor ROI with lower density of HVEM+ PDL1+ macrophages at baseline in patient lacking clinical benefit from HFB200603 + TIS**
- **Figure C: Hazard ratio of PFS in subjects with HVEM+ macrophages compare favorably to those with HVEM-, regardless of PD-L1 expression**

A

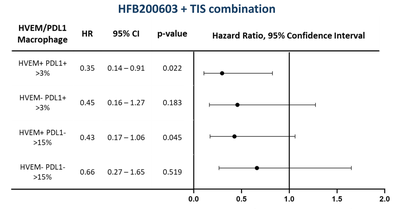


B



Macrophages: HVEM- PDL1- **HVEM+** PDL1- HVEM- **PDL1+** **HVEM+ PDL1+** **Tumor cells**

C



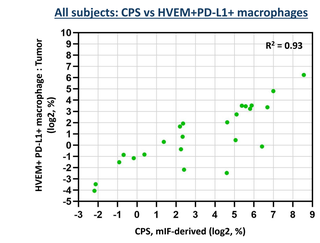
Cutoff: 26-Sep-2025

PD-L1 CPS – HVEM+PDL1+ Macrophage Correlation and its Implication in MSS-CRC

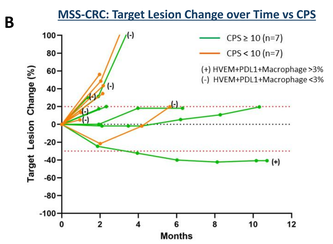
PDL1 CPS score correlates with HVEM+PDL1+ macrophage and may predict response in subjects with MSS-CRC

- **Figure A: Correlation between CPS (mIF derived) and HVEM+ PD-L1+ macrophage observed in all subjects with available biopsy data**
- **Figure B: Higher CPS may be predictive of response and prolonged PFS in subjects with MSS-CRC in response to HFB200603 + TIS combination**

A



B



RECIST 1.1 Efficacy: HFB200603 + TIS

	4L+ aBTLA + aPD-1*	
	Overall (n=14)	CPS >10 (n=7)
ORR	7%	14%
DCR	36%	57%
mPFS	2.1 mo	2.3 mo

*Median prior LOT (4, range: 3-6)

Note: CPS derived from patient record due to data availability

Cutoff: 26-Sep-2025

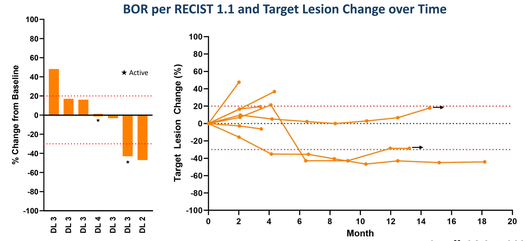
IN DEPTH LOOK AT CLEAR CELL RENAL CARCINOMA

Clinical Data Support Further Development in ccRCC

Durable partial responses and stable disease observed in subjects with clear cell renal cell carcinoma (ccRCC)

- **Partial responder and durable stable disease subjects are still active after progressing on 3 and 5 prior lines of therapy, respectively**
- **Recently discontinued patient with durable PR had 6 prior lines of therapy**

ccRCC – HFB200603 + TIS:
BOR per RECIST 1.1 and Target Lesion Change over Time



Cutoff: 26-Sep-2025

CONCLUSIONS

- Longer follow-up continued to show tolerable safety profile and durability of the partial responses and stable diseases in response to HFB200603 ± TIS.
- Integrative analysis of tumor mIF dataset identified biomarkers potentially predictive of clinical benefit and prolonged PFS in response to HFB200603 as monotherapy and in combination with TIS.
- Potential predictive biomarkers identified (HVEM+CD8T) to HFB200603 monotherapy aligns with HFB200603 MOA in activating BTLA+ CD8 T cells.
- HVEM+ PD-L1+ macrophage as a potential predictive biomarker for the combination treatment suggests that blockade of both BTLA-HVEM and PDL1-PD-1 on immune-suppressing macrophages may be necessary for optimal combination response
- CPS may be a surrogate for selecting patients with higher HVEM+ PDL1+ macrophages as a potential response enrichment strategy.
- Based on clinical and biomarker data, MSS-CRC and ccRCC warrant further evaluation with additional patients.

Acknowledgments and references

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

1. de Miguel. et al., (2024) ESMO 2024. Barcelona, Spain.

Study sponsored by HiFiBiO Inc.

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