Presentation # 994P
Presented at European Society for Medical Oncology
October 17 - 21, 2025
Berlin, Germany

Potential Predictive Biomarkers of Clinical Benefit from Emunkitug (HFB200301) in Combination with Tislelizumab: Integrated Analysis of Tumor, Peripheral Blood, and Patient Treatment History

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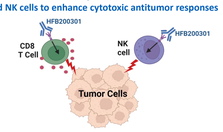
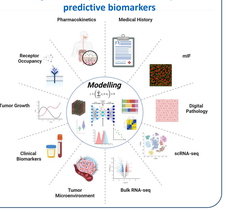
BACKGROUND

- Agonism of tumor necrosis factor receptor-2 (TNFR2) enhances anti-tumor immunity by stimulating T- and NK-cells in the tumor microenvironment.
- Emunkitug (HFB200301), an anti-TNFR2 agonistic monoclonal antibody, triggers both innate and adaptive immune responses.
- Previously we reported Phase 1 results that demonstrated tolerable safety profile and clinically meaningful efficacy with emunkitug as monotherapy and in combination with tislelizumab (TIS) in advanced refractory solid tumors.[1]
- Model-informed optimization of dosing led to Q2W regimen in addition to Q4W.[2]
- Here, we report updated safety and efficacy results with longer follow-up time.
- In addition, we report potential biomarkers predictive of response to emunkitug combined with TIS.

Schematic of emunkitug-mediated activation of CD8 T and NK cells to enhance cytotoxic antitumor responses

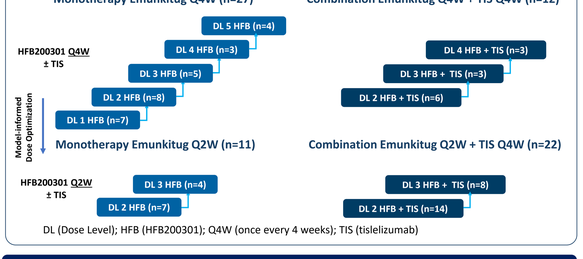


Integrated analysis of potential response predictive biomarkers



STUDY DESIGN and PATIENT DEMOGRAPHICS

Study Design



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

Demographics and Clinical Characteristics

Characteristic	Monotherapy (n=38)	Combination (n=34)
Median age, years (range)	61 (21-77)	62.5 (18-81)
Sex, n (%)		
Female	18 (47)	12 (35)
Male	20 (53)	22 (65)
ECOG PS, n (%)		
0	14 (37)	13 (38)
1	24 (63)	21 (62)
Median time since initial diagnosis (range), years	2.0 (0.3-22.0)	3.2 (0.5-15.9)
Number of prior systemic cancer therapy regimens, n (%)		
Median (range)	2 (1-4)	2 (1-4)
1	9 (24)	4 (12)
2	13 (34)	15 (44)
≥3	16 (42)	15 (44)
Received prior anti-PD-(L)1 therapy, n (%)		
Yes	25 (66)	30 (88)
No	13 (34)	4 (12)
Median follow-up time, months (range)	2.0 (0.5 – 7.3)	2.3 (0.6 – 13.9+)
Tumor types, n (%)		
Clear cell renal cell carcinoma	3 (8)	8 (23)
Cervical cancer	2 (5)	5 (15)
Gastric cancer, EBV+	0 (0)	1 (3)
Head and neck squamous cell carcinoma	5 (13)	3 (9)
Melanoma	3 (8)	5 (15)
Non-small cell lung cancer	7 (19)	7 (20)
Pleural mesothelioma	5 (13)	3 (9)
Sarcoma	11 (29)	1 (3)
Testicular germ cell tumor	2 (5)	1 (3)

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

SAFETY PROFILE

Safety Summary of HFB200301 Q2W/Q4W ± TIS Q4W

Emunkitug Q4W/Q2W ± TIS demonstrated tolerable safety profile

- **TRAEs mostly limited to Grade 1-2, including TRAEs of interest (inflammatory and cutaneous toxicity)**
- **No grade 4 or 5 TRAE and no TRAE leading to discontinuation or dose reduction**

Treatment-related AE (TRAE)	Emunkitug Q4W (N=27)	Emunkitug Q2W (N=11)	Emunkitug Q4W + TIS (N=12)	Emunkitug Q2W + TIS (N=22)
Overall TRAE, %	**13 (48)**	**6 (55)**	**8 (67)**	**17 (77)**
Grade 3	*0*	*0*	*0*	*2 (9)*
Inflammatory AE, %	**4 (15)**	**3 (27)**	**4 (33)**	**11 (50)**
Grade 3	*0*	*0*	*0*	*0*
Cutaneous Tox, %	**4 (15)**	**0**	**2 (17)**	**6 (27)**
Grade 3	*0*	*0*	*0*	*1 (5)*
TRAE leading to discontinuation	0	0	0	0
TRAE leading to death	0	0	0	0

Inflammatory AEs: AST/ALT, chills/fever, CRS, erythema, IRR, myositis, stomatitis, tremor

Cutaneous AEs: Dry skin, hives, pruritus, rash,

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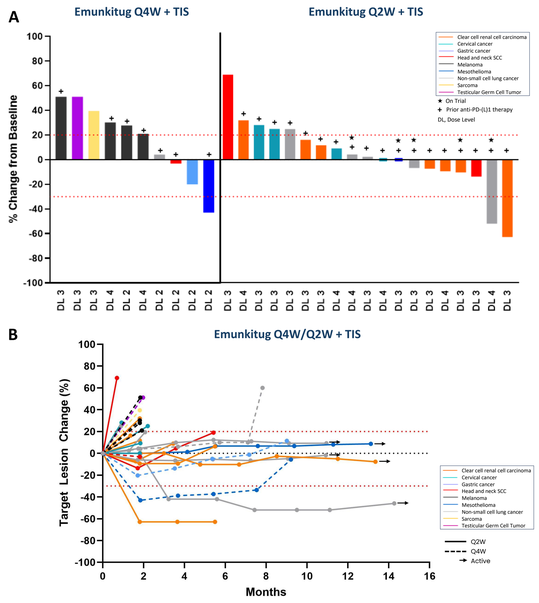
PRELIMINARY ANTI-TUMOR RESPONSE

Emunkitug + TIS Combination Efficacy

Clinically meaningful responses demonstrated by emunkitug + TIS

- **Figure A: Partial responses in multiple indications – mesothelioma, non small cell lung cancer, and clear cell renal cell carcinoma**
  - **All responders had prior immunotherapy and were heavily pretreated**
  - **Disease control rate (DCR) per RECIST 1.1 of 50% in Q2W and 36% in Q4W combination**
- **Figure B: Durable clinical benefit (partial responses and stable disease per RECIST 1.1) observed**



Note: 5 subjects not shown in Fig A and B had clinical progressions and did not have radiographic assessment of their target lesions

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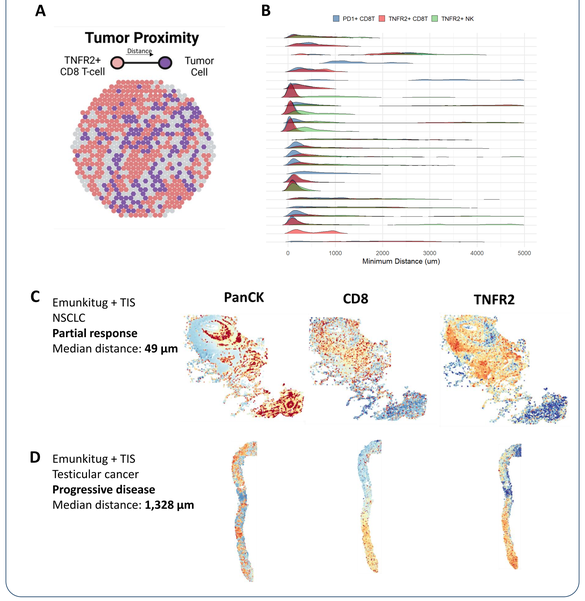
Spatial Proximity Analysis – Tumor mIF

Spatial proximity to tumor with TNFR2+ and PD1+ immune cells

- **Figure A: Graphical representation of mIF-derived analysis of spatial proximity to determine distance between the target cells (e.g. TNFR2+CD8 T cells) and tumor cells**
- **Figure B: Distribution of all target cells' distance from tumor cells (each row represents individual subject)**
- **Figure C and D: Representative images of subjects with close (Fig C) and distant (Fig D) median tumor cell distance to TNFR2+ CD8T**

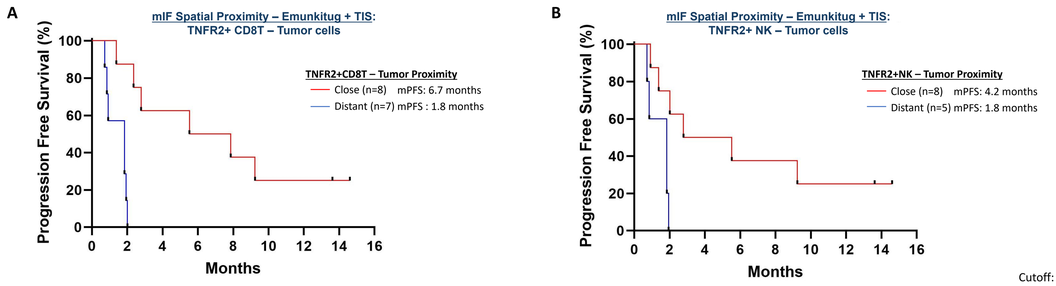


POTENTIAL BASELINE BIOMARKERS PREDICTIVE OF RESPONSE TO EMUNKITUG + TIS

Tumor – mIF: Spatial Proximity of TNFR2+CD8 or TNFR2+NK Cells to Tumor Cells as Potential Response Predictive Biomarker

Closer proximity of tumor cells with TNFR2+ CD8 and TNFR2+ NK cells associated with prolonged progression-free survival (PFS) in response to emunkitug + TIS

- **Figure A: Emunkitug-mediated activation of TNFR2+ CD8 T cells in closer proximity to tumor cells may be predictive of response**
- **Figure B: Emunkitug-mediated activation of TNFR2+ NK cells in closer proximity to tumor cells may be predictive of response**



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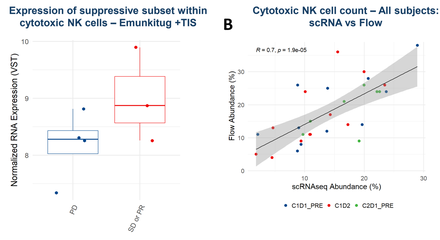
Periphery – Single-cell RNA & Flow Cytometry: NK Abundance as Potential Response Predictive Biomarker

High peripheral levels of suppressive subset of cytotoxic NK cells at baseline may predict clinical benefit to emunkitug + TIS

- **Figure A: scRNA analysis revealed that suppressive subset of cytotoxic NK cells may predict clinical benefit (PR or SD per RECIST 1.1) to emunkitug + TIS**
- **Figure B: Correlation between scRNA versus flow cytometry levels of suppressive subset of NK cells**
- **Figure C and Table 1: Flow cytometry analysis showed that higher peripheral levels of suppressive subset of NK cells may be predictive of prolonged progression-free survival (PFS) and improved DCR (PR+SD)**



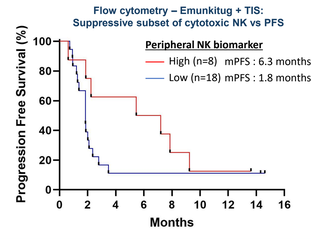


Table 1: RECIST 1.1 BOR vs Suppressive Subset of Cytotoxic NK

HFB200301 Q4W/Q2W + TIS (n=26)		
RECIST 1.1	**NK-Low n=18**	**NK-High n=8**
PR	1	1
SD	4	4
PD	13	3
DCR (PR+SD)	**5 (28)**	**5 (63)**
ORR	1 (6)	1 (13)
Median Prior LOT	2.5 (1-4)	2 (1-4)

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Patient Record: Immediate Prior Immunotherapy May be a Surrogate for Tumor and Peripheral Biomarkers

Immediate prior immunotherapy may be predictive of response to emunkitug + TIS combination

- **Figure A and B: Subjects with immediate prior immunotherapy may be linked to closer proximity of TNFR2+CD8/NK to tumor cells and cytotoxic NK cells in the periphery at baseline**
- **Figure C and Table 2: Immediate prior immunotherapy may be predictive of prolonged PFS and increased DCR (PR+SD) amongst patients with indications of interest**

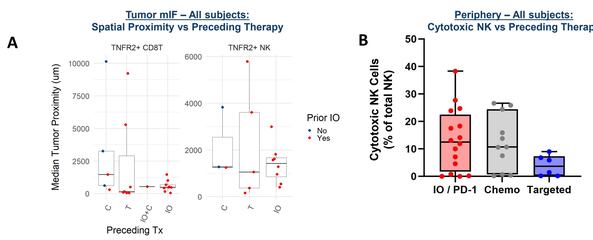

Table 2: RECIST 1.1 BOR vs Preceding Therapy

HFB200301 Q4W/Q2W + TIS (n=22)		
RECIST 1.1	**Others (chemo, targeted) n=12**	**IO (+/- chemo or targeted) n=10**
PR	2	1
SD	4	8
PD	6	1
DCR (PD+SD)	**6 (50)**	**9 (90)**
ORR	2 (17)	1 (10)
Median Prior LOT	3 (1-4)	2.5 (1-4)

NOTE: Included in Figure C and Table 1 are indications of interest (ccRCC, gastric, HNSCC, mesothelioma, NSCLC)

Preceding therapy: C, Chemotherapy; **T**, Targeted; **IO**, Immunotherapy

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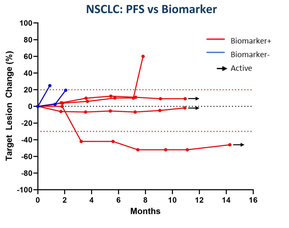
IN DEPTH LOOK AT NSCLC

Clinical and Biomarker Data Support Further Development in NSCLC

Early signs of improvement in PFS with emunkitug + aPD-1 in NSCLC patients, especially in biomarker enriched patients

- **Compared to 2L standard-of-care docetaxel +/- ramucirumab which reported median PFS of 2.7 – 4.5**



RECIST 1.1 Efficacy: Emunkitug + TIS

	3L+ IO-refractory NSCLC*	
	Overall (n=7)	Biomarker+ (n=5)
ORR	14%	20%
DCR	71%	80%
mPFS	7.9 mo	10.5+ mo

*Median prior LOT (3, range: 2-4); all had prior anti-PD-(L)1

Biomarker+: Closer TNFR2+CD8—Tumor proximity and/or higher peripheral cytotoxic NK

Biomarker-: Neither

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CONCLUSIONS

- Longer follow-up continued to show tolerable safety profile and durability of the partial responses and stable diseases in response to emunkitug + TIS.
- Integrative analysis of tumor, peripheral blood, and patient records (treatment history / preceding therapy) identified potential biomarkers predictive of clinical benefit and prolonged PFS in response to emunkitug + TIS.
- Predictive biomarkers in the tumors (TNFR2+CD8T in close proximity to tumor) and periphery (higher levels of suppressive subset of cytotoxic NK cells) align with emunkitug's MOA in activating CD8 T and NK cells
  - Suggests that the combination efficacy is dependent on emunkitug-mediated activation of CD8 T and NK cells in addition to PD-1 blockade
- Patient enrichment for response by NK cell count via flow cytometry may be a practical patient selection strategy for future development
- Early signs of clinically meaningful efficacy in NSCLC warrants 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. Roda, D. et al., (2024) ASCO 2024. Chicago, IL, USA
2. Roda, D. et al., (2024) ESMO 2024. Barcelona, Spain.

Study sponsored by HiFiBiO Inc.

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