HRA00130-C004, a novel anti-DLL3 ADC with bystander effect, high DAR and favorable safety profiles

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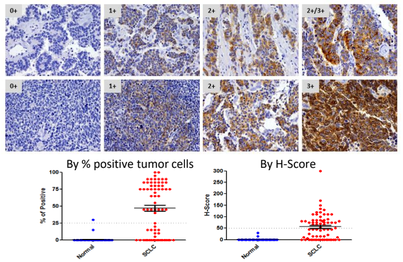
INTRODUCTION

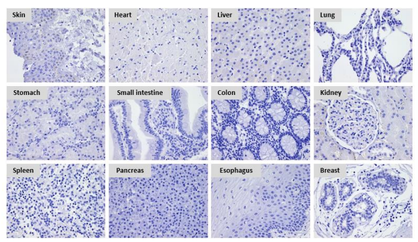
- SCLC is an aggressive disease with limited treatment options beyond first-line therapy[1].
- DLL3 is highly upregulated and aberrantly expressed on the cell surface in SCLC and other high-grade neuroendocrine tumors but is minimally expressed in normal tissues[2]. The DLL3-targeted ADC, rovalpituzumab tesirine, showed clinical antitumor activity in patients with SCLC. Unfortunately, the side effects of the pyrrolobenzodiazepine payload limited its efficacy and OS benefit[3] .
- This study describes a novel anti-DLL3 ADC, HRA00130-C004, consisting of a humanized anti-DLL3 monoclonal antibody coupled to exatecan derivative drug via a cleavable linker.

DLL3 EXPRESSION BY IHC

◆ IHC Results of DLL3 on SCLC



◆ IHC Results of DLL3 on Normal Tissues

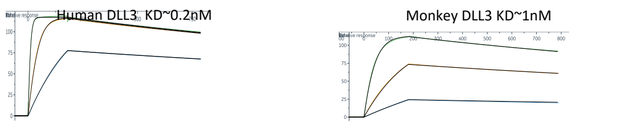


HRA00130-C004 STRUCTURE

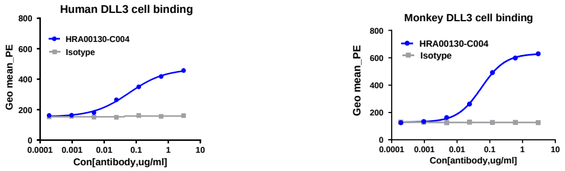
- ◆ A humanized anti-DLL3 IgG1 monoclonal antibody with high binding affinity.
- ◆ A well-selected exatecan derivative drug with better cell permeability and good water solubility [4].
- ◆ High drug to antibody ratio.
- ◆ A selective tetrapeptide-based cleavable linker with high stability.

Binding

◆ Binding Affinity to DLL3 Protein



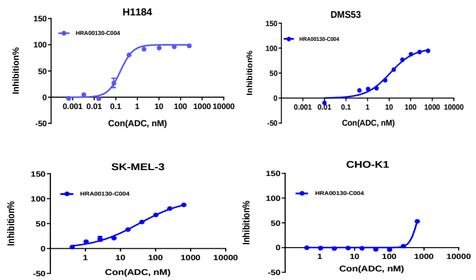
◆ Cell Binding to DLL3 Stable Cell



✓ HRA00130-C004 binds to human and monkey DLL3 at both protein and cellular levels.

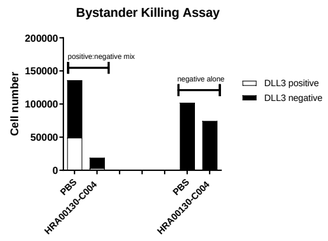
IN VITRO EFFICACY

◆ Killing Effect on Tumor Cells with Different DLL3 Expression levels



Cell Line	H1184 (DLL3++)	DMS53 (DLL3+)	SK-MEL-3 （DLL3+）	CHO-K1 (DLL3-)
IC_{50}(nM)	~0.1	~10	~30	N/A
Imax%	>95	>90	>80	<55

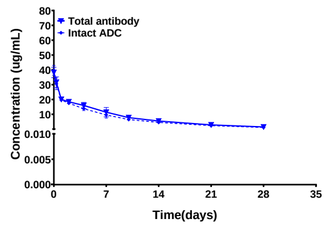
◆ Strong Bystander Effect



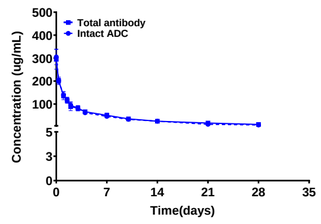
- ✓ HRA00130-C004 strongly inhibited the proliferation of cell lines with different DLL3 expression levels.
- ✓ HRA00130-C004 displayed potent bystander killing effect in the co-culture system of DLL3-positive and negative cells.

PHARMACOKINETICS STUDY

◆ Pharmacokinetics Rat PK Study



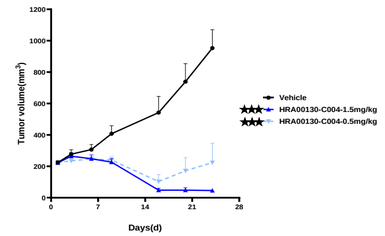
◆ Pharmacokinetics Cynomolgus Monkey PK Study



- ✓ HRA00130-C004 demonstrated a favorable PK profile and satisfactory molecular integrity. Elimination half-life of HRA00130-C004 was >7 days in rats with 3mg/kg dosing, >8 days in cynomolgus monkeys with 10 mg/kg dosing.
- ✓ HRA00130-C004 was well tolerated in rats and cynomolgus monkeys with no drug-related adverse findings.

IN VIVO EFFICACY

◆ DMS53 Cell (low DLL3 expression) - derived Xenograft Model in Mice



Test	Dose mg/kg	Schedule	TGI (%)
Vehicle	/	i.p./D1 D8 qw*2	/
HRA00130-C004	1.5	i.p./D1 D8 qw*2	>100%
HRA00130-C004	0.5	i.p./D1 D8 qw*2	>100%

◆ H1184 Cell (high DLL3 expression) - derived Xenograft Model in Mice

Test	Dose mg/kg	Schedule	TGI (%)
Vehicle	/	i.p./single dose	/
Isotype-ADC	1.5	i.p./single dose	~40%
HRA00130-C004	1.5	i.p./single dose	>100%

- ✓ At the dose of 1.5 mg/kg, HRA00130-C004 exerted strong anti-tumor activities in human SCLC DMS53 and H1184 CDX models. Notably, in HRA00130-C004 1.5 mg/kg group, complete tumor regression was achieved in one mouse. No obvious weight loss was observed during the experiments.
- ✓ Tumor growth inhibition of HRA00130-C004 increased with dose in human SCLC DMS53 CDX model.

CONCLUSIONS AND FUTURE PLAN

- ◆ DLL3 is expressed at relatively low levels in healthy tissues while highly expressed in SCLC.
- ◆ HRA00130-C004 is a novel anti-DLL3-targeted ADC with a highly permeable payload and high DAR, demonstrating great stability and high potency in both *in vitro* and *in vivo* studies.
  - ✓ **High binding affinity** to both human and monkey DLL3
  - ✓ **Potent cell killing effect and bystander killing effect**
  - ✓ **Strong *in vivo* efficacy**
  - ✓ **Favorable pharmacokinetics profiles** in rats and monkeys
  - ✓ **High stability in circulation** improves safety profiles and expands therapeutic window [4].
- ◆ IND-enabling studies are in progress.

REFERENCES

1. Rev Dis Primers. 2021 Jan 14;7(1):3.
2. Oncologist 2022 Nov 3;27(11):940-951.
3. J Thorac Oncol. 2021 Sep;16(9):1547-1558.
4. Cancer Res 2023;83(8_Suppl):Abstract nr LB031.