Novel Folate Receptor α-directed Antibody-drug Conjugate PRO1184 Demonstrates Broad Antitumor Activity with a Promising Safety Profile in Preclinical Models

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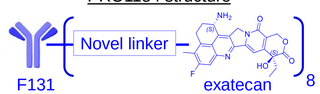
ProfoundBio

Introduction

- Folate receptor α (FRα) is an attractive target for an antibody-drug conjugate (ADC)[1].
  - ❖ FRα is overexpressed in a wide range of solid tumors with limited expression in normal tissues
  - ❖ Clinically validated with an approved therapeutic for FRα-positive platinum-resistant ovarian cancer[2]
- PRO1184 is comprised of a human monoclonal antibody (F131) that selectively binds FRα, a novel cleavable hydrophilic linker, and a topoisomerase 1 inhibitor payload, exatecan[3], with:
  - ❖ Potent antitumor activity in cell-derived xenograft (CDX) models representing ovarian, non-small cell lung, and breast cancer
  - ❖ Pharmacokinetics (PK) akin to that of the unconjugated parent antibody in rats
  - ❖ A preliminary safety profile more favorable than a deruxtecan-based comparator in cynomolgus monkeys
- Further characterization of preclinical activity and safety of PRO1184 along with DM4-based benchmarking ADCs is reported here. A first in human phase 1/2 study in patients with advanced solid tumors is currently recruiting (NCT05579366).

PRO1184 structure

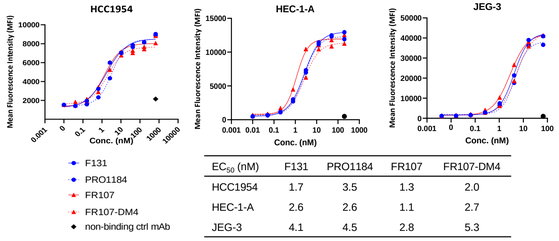


Cell Line	Tumor Type	FRα copy # (X10³/cell)
HCC1954	breast	19
HEC-1-A	endometrial	41
JEG-3	choriocarcinoma	231

Benchmarking ADC (DAR)	Linker-drug
FR107-DM4 (4) (analog of Elahere)	Sulfo-SPDB-DM4
F131-DM4 (4)	SPDB-DM4

In Vitro Binding

F131, FR107, and their respective conjugates demonstrated robust and comparable binding to tumor cells.



EC_{50} (nM)	F131	PRO1184	FR107	FR107-DM4
HCC1954	1.7	3.5	1.3	2.0
HEC-1-A	2.6	2.6	1.1	2.7
JEG-3	4.1	4.5	2.8	5.3

Figure 1. Binding of mAb or ADC to FRα-expressing tumor cell lines were evaluated by flow cytometry (EC_{50} shown in the table).

Internalization and Cytotoxicity

F131 and PRO1184 displayed similar to superior internalization compared to FR107 and FR107-DM4; both ADCs were highly potent in cytotoxicity studies in vitro.

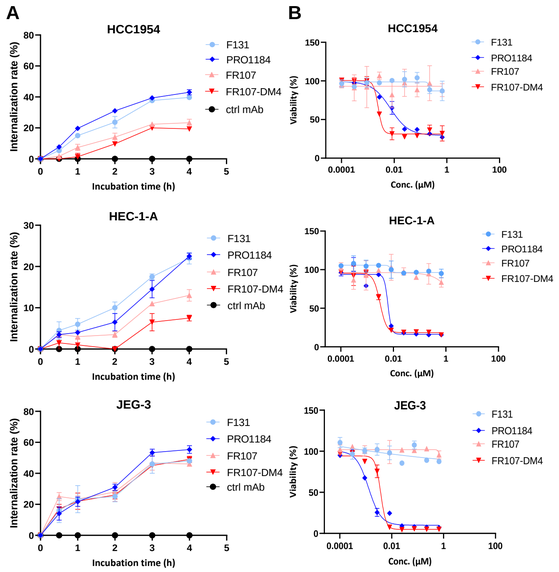


Figure 2. **A**. Internalization of mAb, ADC, or non-binding control mAb in the tumor cells was assessed using a standard indirect fluorescent method. **B**. Cytotoxicity of mAb and ADC was evaluated using the Cell Titer-Glo assay after a 4-day incubation.

Anti-tumor Activity in CDX Models

PRO1184 was more potent in inhibiting tumor growth than FR107-DM4 in all models tested; sustained near complete remission (CR) was observed with PRO1184 in the JEG-3 model.

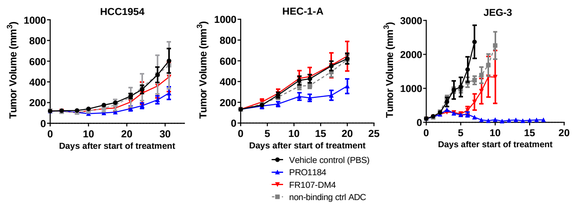


Figure 3. Anti-tumor activity of the ADCs were examined in cell-line derived xenograft (CDX) models in a single-dose (5 mg/kg) regimen (n=6 per group).

Anti-tumor Activity in PDX Models

PRO1184 produced marked tumor growth-inhibition across various tumor types and histologies; PRO1184 was broadly more efficacious than FR131-DM4 or FR107-DM4 in PDX.

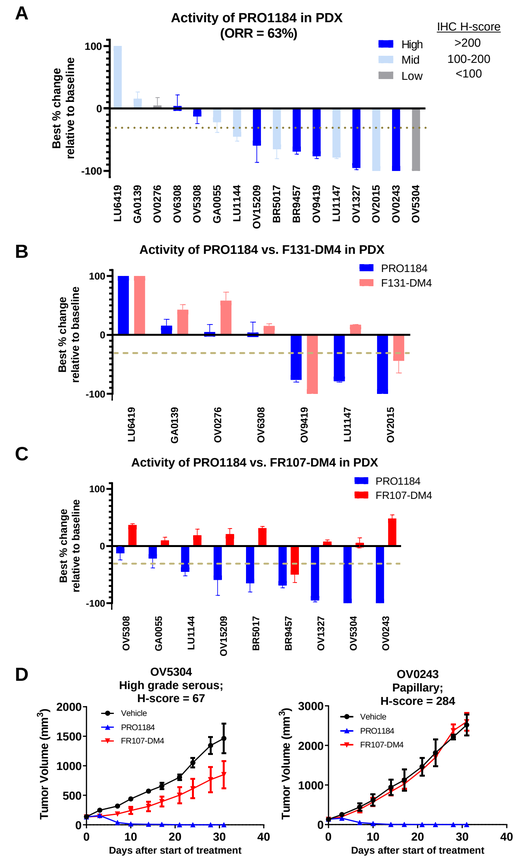


Figure 4. Anti-tumor activity of the ADCs (at a single dose of 5 mg/kg, n=3 per group) was examined using standard methods in patient derived xenograft (PDX) models for lung, gastric, ovarian, and triple-negative breast cancer. **A**. Best response of PRO1184 across 16 models tested, with target expression levels denoted. **B**. F131-DM4 was included in 7/16 models for head-to-head comparison with PRO1184. **C**. FR107-DM4 was included in 9/16 models for head-to-head comparison with PRO1184. **D**. Tumor growth curves in two ovarian models of different histology and target expression levels shown as an example.

Preclinical Toxicity Profile

PRO1184 was well tolerated at the HNSTD with toxicities that were reversible in cynomolgus monkeys and rats.

GLP Study Design	
Test System	Cynomolgus monkeys
Dose Regimen	0, 10, 30, 60 mg/kg, IV, Q3W X 2, 5-week recovery period
N	5/5 M/F per group

- ❖ No histopathological findings in lung
- ❖ Target organs include bone marrow and lymphatic tissues
- ❖ Toxicity profile is consistent with that of exatecan and is reversible
- ❖ Toxicokinetics (TK) are consistent with historical data and support stability of ADC in vivo
- ❖ Toxicity profile and TK in a GLP study in rats are consistent with those in monkeys
- ❖ HNSTD of 30 mg/kg

Conclusions

- PRO1184 demonstrates robust bio-activity in multiple tumor cell lines including HCC1954 (breast cancer), JEG-3 (choriocarcinoma), and HEC-1-A (endometrial cancer), in vitro and in vivo
- PRO1184 elicits marked anti-tumor efficacy that is superior to the benchmarking ADCs in preclinical models of diverse tumor types, histologies, and target expression levels
- PRO1184 displays a well-manageable toxicity profile with no histopathological findings in lung in the cynomolgus monkeys, which may translate to a lower risk of interstitial lung diseases (ILD) compared to deruxtecan-based ADCs in the clinic
- PRO1184 is a promising development candidate for the treatment of FRα-expressing solid tumors. Trial-in-progress for its first in human study is presented concurrently.[4]

References

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