Preclinical Characterization of PRO1160, a Novel Exatecan-based CD70-directed Antibody-drug Conjugate

Lei Wang[1], Haidong Liu[1], Xiao Shang[1,2], Tae Han[2], Zhu Chen[1,2], Baiteng Zhao[1,2]

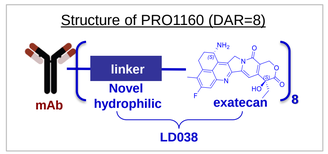
[1]ProfoundBio (Suzhou) Co., Ltd.; [2]ProfoundBio US Co.

AACR2022
Abstract#4344

ProfoundBio

Introduction

- The cell surface antigen CD70 (along with its receptor CD27) facilitates immune evasion and is aberrantly expressed in many hematological and solid malignancies. Studies on the tumor-promoting effects and the downstream signaling of the CD70-CD27 axis suggest CD70 is a promising target in cancer.[1]
- Multiple clinical trials in hematological malignancies or solid tumors have offered clinical proof-of-concept for developing CD70-directed anti-cancer therapeutic modalities including antibody-drug conjugates (ADCs)[2,3,4]
- PRO1160 is a novel CD70-directed ADC designed with three components:
  - A proprietary human IgG1 monoclonal antibody (mAb) targeting CD70
  - exatecan, a topoisomerase I inhibitor with established antitumor activity and pharmacological attributes[5]
  - A novel hydrophilic and protease-cleavable linker (linker along with the drug, exatecan, is collectively dubbed as LD038)[6,7]



Benchmarking ADC (DAR)	Linker-drug
mAb-deruxtecan(8)	mc-GGFG-DXd
mAb-vedotin(4)	mc-vc-PAB-MMAE

Cell line	Tumor type	CD70 Copy number ($X10^3$ per cell)
786-O	renal	149
Caki-1	renal	119
Raji	lymphoma	62
MCF-7	breast	3.8

Binding Affinity and Specificity

A

Antigen	Sample	KD(M)	ka (1/Ms)	kdis (1/s)
Hu CD70	mAb	8.0E-10	3.1E05	2.5E-04
	PRO1160	1.1E-10	4.5E05	5.4E-05
Cyno CD70	mAb	3.9E-10	6.1E05	2.4E-04
	PRO1160	1.4E-10	6.5E05	9.4E-05
Rat CD70	mAb	NA	NA	NA
	PRO1160	NA	NA	NA
Mouse CD70	mAb	NA	NA	NA
	PRO1160	NA	NA	NA

B

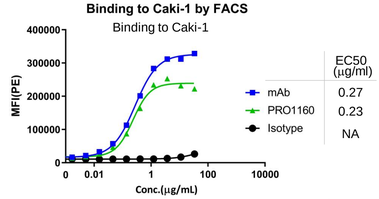


Fig. 1. A. Affinity of mAb or PRO1160 to recombinant CD70 species (human, cyno, rat, mouse) orthologs was measured by Octet RED (Fortbio). B. Binding of mAb or PRO1160 to the target cell line, Caki-1, was evaluated on flow cytometry. No binding was observed with the MCF-7 tumor cells (not shown). NA: response below range of quantitation.

In vitro Internalization Studies

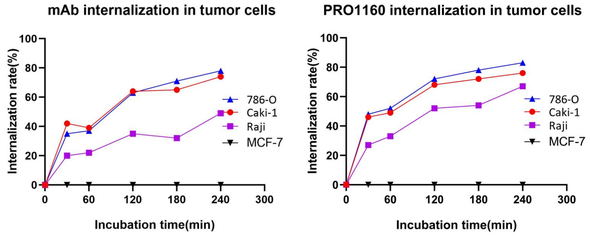
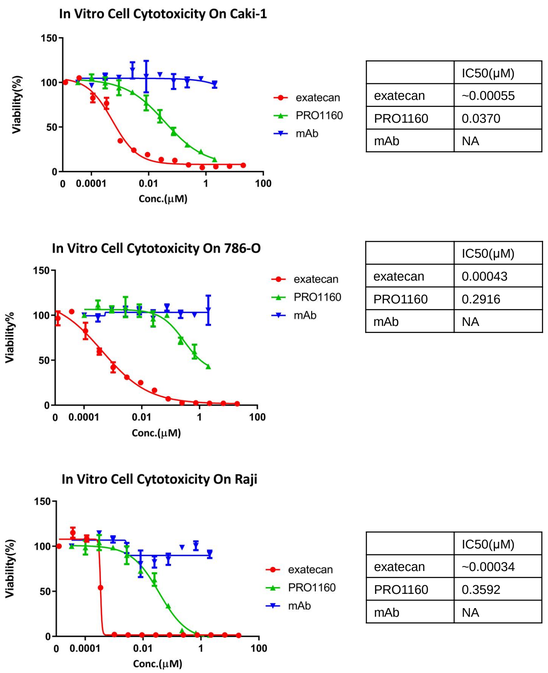


Fig. 2. Internalization of mAb and PRO1160 in tumor cells were determined in a time course manner. Internalization rate was calculated by subtracting the mean fluorescence intensity (MFI) of cell surface-bound antibody at 37°C at each timepoint from the MFI of cell surface-bound antibody at 4°C at time 0, then divided by the MFI of cell surface-bound antibody at 4°C at time 0.

In vitro Cytotoxicity Studies



	IC50(μM)
exatecan	~0.00055
PRO1160	0.0370
mAb	NA

	IC50(μM)
exatecan	0.00043
PRO1160	0.2916
mAb	NA

	IC50(μM)
exatecan	~0.00034
PRO1160	0.3592
mAb	NA

Fig. 3. Cell viability was evaluated 4 days after treatment using the Cell Titer-Glo Assay (Promega Corp.) All readings were normalized as percentage of viable cells in the untreated control wells and the IC50 values were calculated. NA: no appreciable activity.

Anti-tumor Activity in CDX Models

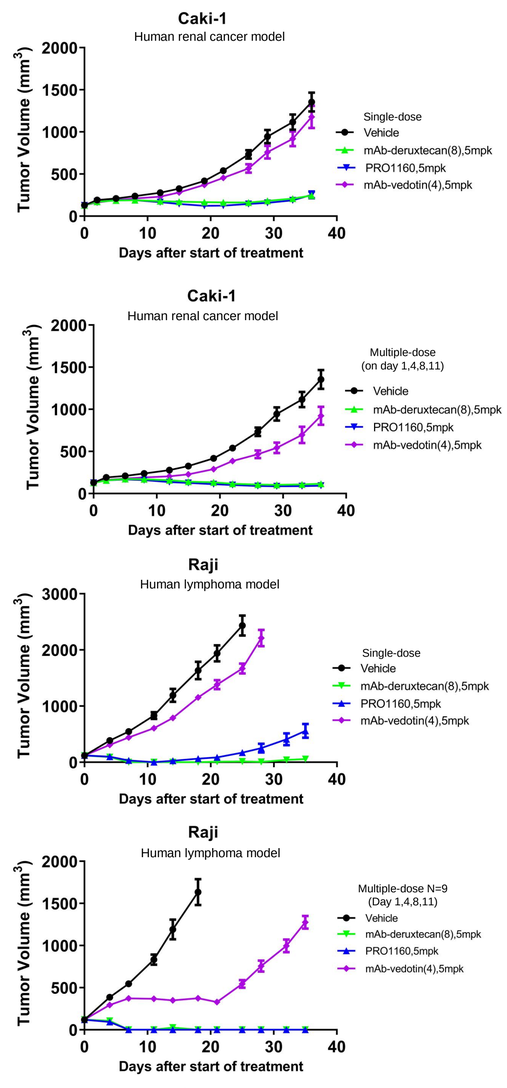


Fig. 4. Anti-tumor activity of the ADCs were examined in various cell-line derived xenograft (CDX) models, in single-dose or multiple-dose regimens as specified in the graphs (n=9~10 per treatment group). None of the ADC-treated animals exhibited appreciable weight loss or apparent distress (not shown).

Plasma PK and Tolerability

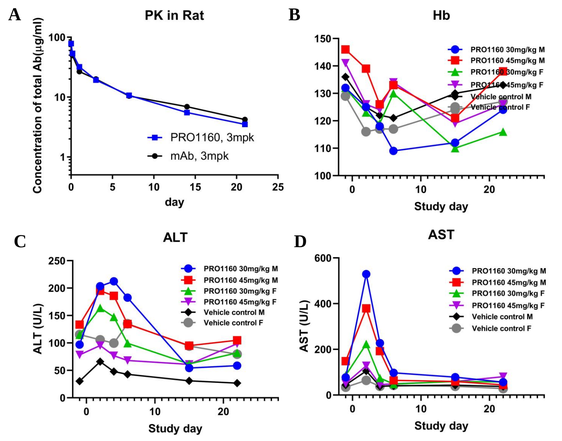


Fig. 5. A. Plasma PK of mAb and PRO1160 in rat (n=3 per group). Concentrations of total antibodies were determined via an ELISA. B, C, D, hemoglobin, ALT, AST levels in a single-dose pilot toxicity study of PRO1160 in cynomolgus monkeys (one male and one female monkey per treatment group). Clinical observations include soft/watery feces and reduced food intake, all reversible by day 22. Additional analyses ongoing.

Conclusions

- PRO1160 displayed strong and specific binding to CD70 and rapid internalization in target cells
- PRO1160 demonstrated robust anti-tumor activity, in vitro and in vivo. In multiple CDX models, anti-tumor activity of PRO1160 was stronger than the vedotin conjugate and at a similar level as the deruxtecan conjugate.
- PRO1160 displayed excellent plasma PK in rat
- Initial analyses demonstrated that PRO1160 was tolerated at the dose of 45mg/kg in non-human primate
- In summary, PRO1160 displays a promising preclinical profile on PK, PD, efficacy, and tolerability. PRO1160 is an attractive candidate for further development in the clinic for various cancers

References

1. Flieswasser T, et al. The CD70-CD27 axis in oncology: the new kids on the block. J Exp Clin Cancer Res, 2022, 41:12
2. Tannir NM, et al. Phase I dose-escalation study of SGN-75 in patients with CD70-positive relapsed/refractory non-Hodgkin lymphoma or metastatic renal cell carcinoma. Invest New Drugs, 2014, 32:1246
3. Aftimos P, et al. Phase I dose-escalation study of the anti-CD70 antibody ARGX-110 in advanced malignancies. Clin Cancer Res, 2017, 23:6411
4. Pal SK, et al. A phase 1 trial of SGN-CD70A in patients with CD70-positive, metastatic renal cell carcinoma. Cancer, 2019, 125:1124
5. Adams VR et al., Camptothecins in Cancer Therapy. 2005, Humana Press
6. Liu H, et al., AACR-NCI-EORTC 2021. Novel hydrophilic drug linkers enable exatecan-based antibody-drug conjugates with promising physiochemical properties and in vivo activity, Poster#P196
7. Liu H, et al. Novel ADC platform delivers promising in vivo activity and safety. AACR 2022, Abstract#4021