



CTCL

AACR 2017 | Poster 4589/4 – Preclinical investigation of the novel SGN-CD70A antibody drug conjugate in T-Cell Lymphomas

 Terri Penfold | Apr 12, 2017

At the American Association for Cancer Research (AACR) annual meeting in Washington, DC, USA, on Tuesday 4th April, a poster session titled “Immunoconjugates and Antibodies” took place.


One of the posters on display ([4589 / 4](#)) was titled “Preclinical investigation of SGN-CD70A antibody-drug conjugate in T cell lymphomas” by [Chen-Yen Yang](#) from [University of California San Francisco](#), San Francisco, CA, and colleagues.

SGN-CD70A is a novel antibody drug conjugate; an anti-CD70 monoclonal antibody joined to a pyrrolobenzodiazepine (PBD) dimer (synthetic DNA cross-linking molecule). This group aimed to evaluate the anti-tumor activity of SGN-CD70A in T-Cell Lymphomas (TCLs).

Key Highlights:

- CD70 expression was reported in all subtypes of TCL and all Cutaneous T-Cell Lymphoma (CTCL) cell lines
- CD70 was not expressed in peripheral blood mononuclear cells from healthy subjects
- SGN-CD70A had no significant activity in CD70-negative T-ALL lines, however potently inhibited cell growth in CD70-positive CTCL lines
- SGN-CD70A was more efficient at inducing apoptosis and cell death in CTCL cell lines compared with media and h00d-1910 treated controls
- In a dose-dependent manner, SGN-CD70A inhibited cell proliferation and induced higher caspase 3/7 activity in CD70-positive patient-derived TCL primary cells, while h00d-1910 treated in parallel had no significant effects

In conclusion, this poster stated that CD70 is not expressed by healthy donor cells, but is expressed by nodal and cutaneous TCLs. The antibody drug conjugate SGN-CD70A demonstrated anti-tumor activity in CTCL cell lines as well as in patient derived TCL primary cells. These data indicate that SGN-CD70A is a promising therapeutic option for TCLs.




Preclinical Investigation of SGN-CD70A Antibody-Drug Conjugate in T Cell Lymphomas

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#4589



Abstract

Introduction and Purposes: CD70 is a member of the tumor necrosis factor superfamily and aberrantly expressed in several solid tumors and a variety of hematologic malignancies. The CD70 protein is expressed on highly activated lymphocytes (like in T and B cell lymphomas). Since normal lymphocytes do not express much CD70, it is suggested that anti-CD70 antibodies could be a potential treatment for CD70 positive lymphomas. SGN-CD70A is a novel antibody-drug conjugate (ADC) that combines an anti-CD70 monoclonal antibody with a synthetic DNA cross-linking molecule, pyrrolbenzodiazepine (PBD) dimer. It is currently under phase I clinical trials for renal cell carcinoma, mantle-cell, diffuse large B-cell, and follicular lymphoma. The aim of this study is to investigate the anti-tumor activity of SGN-CD70A in T cell lymphomas.

Experimental Procedures: We first examined CD70 expression in 36 cases of mature T or NK cell lymphomas using immunohistochemical (IHC) staining of patient biopsy specimens. The IHC results were reviewed and scored by 2 independent pathologists. We further investigated CD70 expression in Sezary syndrome (SS), mycosis fungoides (MF), and T cell acute lymphoblastic leukemia (T-ALL) cell lines, along with patient-derived T cell lymphoma primary cells and healthy donors' peripheral blood mononuclear cells (PBMC) by flow cytometry. We next evaluated the anti-tumor activity of SGN-CD70A in cutaneous T cell lymphoma (CTCL) cell lines and patient-derived T cell lymphoma primary cells. Cell lines or primary cells were treated with SGN-CD70A at various concentrations, after which growth inhibition and apoptosis were assessed by CellTiter-Glo Assay, flow cytometry or Caspase-Glo 3/7 Assay, respectively. CD70 negative T-ALL cell lines were treated in parallel as negative controls for CD70 positive CTCL cell lines. Additionally, h00d-1910, an isotype control of the anti-CD70 antibody conjugated to PBD, was used as the negative control for SGN-CD70A.

Results: CD70 expression was observed across all subtypes of T cell lymphomas and all CTCL cell lines. In contrast, CD70 is not expressed in PBMC from healthy subjects. We demonstrated that SGN-CD70A potentially inhibited cell growth in CD70-positive CTCL lines, but had no significant activity in CD70-negative T-ALL lines. In addition, SGN-CD70A induced more apoptosis and cell death in CTCL cell lines compared with media and h00d-1910 treated controls. Furthermore, we showed that SGN-CD70A inhibited cell proliferation and induced higher caspase 3/7 activity in CD70-expressing patient-derived T cell lymphoma primary cells in a dose-dependent manner, while h00d-1910 treated in parallel had no significant effects.

Conclusions: CD70 is expressed in both nodal and cutaneous T cell lymphomas but not in healthy donors. SGN-CD70A not only shows anti-tumor activity in CTCL cell lines expressing CD70, but also inhibits proliferation and induces apoptosis in patient-derived T cell lymphoma primary cells, indicating it is a promising treatment for T cell lymphomas.

Result II: Flow Cytometry & In Vitro Studies

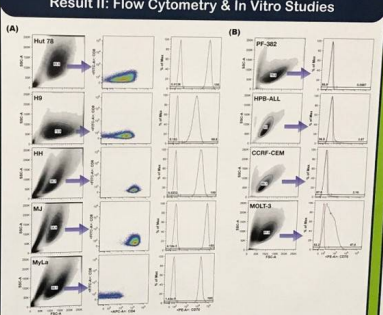


Fig. 1. (A) CD70 is expressed in all CTCL cell lines we examined, including two SS cell lines, Hst 78 and H9, and three MF cell lines, HH, MJ and MyLa. (B) CD70 expression is absent in three out of four T-ALL cell lines, PF-302, HFB-ALL and CORF-CEM. CD70 negative T-ALL cell lines were further treated in parallel as negative controls for CD70 positive CTCL cell lines.

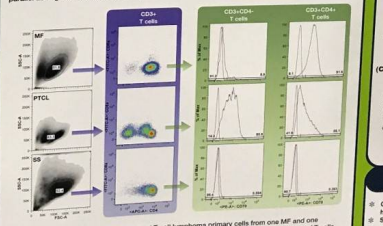


Fig. 2. CD70 is expressed in patient-derived T cell lymphoma primary cells from one MF and one peripheral T cell lymphoma (PTCL) patient. The PTCL patient has two malignant populations of T cells, CD4+ and CD4-, which are both CD70 positive. CD70 expression is absent in patient-derived T cell lymphoma primary cells from one SS subject.

Result I: Immunohistochemistry

Table 1. CD70 expression by IHC in T cell lymphomas

T and NK Cell Lymphoma	N	CD70 expression by IHC	
		Focal Positivity	Diffuse Positivity
Peripheral T cell Lymphoma, not otherwise specified (PTCL NOS)	14	9/14 (64%)	1/14 (7%)
Anaplastic Large Cell Lymphoma (ALCL)	15	1/15 (7%)	8/15 (53%)
Nodal T cell Lymphoma	3	1/3 (33%)	1/3 (33%)
Mycosis Fungoides (MF)	3	1/3 (33%)	1/3 (33%)
Entenopathy-Associated T-cell Lymphoma (EATL)	1	1/1 (100%)	0

Take Home Messages

- CD70 is expressed across all subtypes of T cell neoplasms, but not present in peripheral T cells from healthy subjects.
- SGN-CD70A shows anti-tumor activity and induces apoptosis/cell death in CD70 positive CTCL cell lines and patient-derived T cell lymphoma primary cells, indicating SGN-CD70A is a potent ADC in T cell lymphomas.

There are no relevant conflicts of interest to disclose.

Fig. 3. PBMCs from healthy control (HC) donors, HC1, HC2, HC3 and HC4, are all CD70 negative.

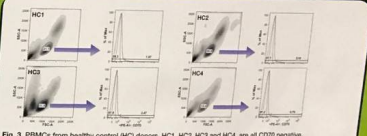


Fig. 4. (A) SGN-CD70A inhibited growth in CD70 positive CTCL cell lines, Hst 78, H9 and MJ, but had no significant effect on CD70 negative T-ALL cell lines, HFB-ALL and CORF-CEM. Growth inhibition was assessed after 72 hr of treatment. (B) SGN-CD70A induced more apoptosis and cell death in CTCL cell lines, Hst 78 and H9, compared with h00d-1910 treated controls. Annexin VPI staining was performed after 48 hr of treatment.

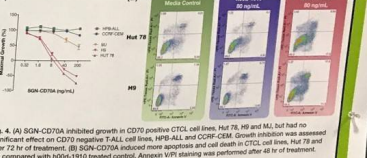
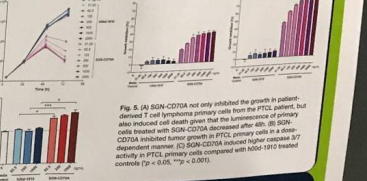


Fig. 5. (A) SGN-CD70A not only inhibited the growth in patient-derived T cell lymphoma primary cells from the PTCL patient, but also induced cell death given that the percentages of primary cells treated with SGN-CD70A decreased after 48h. (B) SGN-CD70A inhibited tumor growth in PTCL primary cells in a dose-dependent manner. (C) SGN-CD70A induced higher caspase 3/7 activity in PTCL primary cells compared with h00d-1910 treated controls. (*p < 0.05, **p < 0.001).



Reference:

- Yang C.Y. et al. Preclinical investigation of SGN-CD70A antibody-drug conjugate in T cell lymphomas [Poster]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2017 Apr 1-5; Washington, DC. Philadelphia (PA): AACR; 2017. Poster nr [4589 / 4].

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