ARGX-110, a novel monoclonal antibody targeting CD70, is a promising immunotherapeutic for T-cell lymphoma

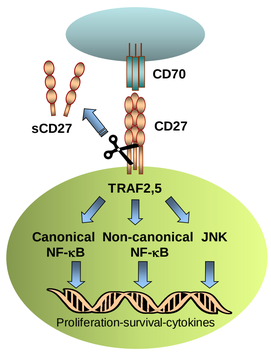
M. Maerevoet[1], J-M Michot [2]P. Aftimos[1], S. Rottey[3], L. Ysebrant de Lendonck[1], W. Schroyens[4], C. Rolfo[4], P. Pauwels[4], K. Zwaenepoel[4], F. Offner[3], K. Silence[5], H. De Haard[5], M. Moshir[5], T. Dreier[5], D. Schaap[5], T. Van Hauwermeiren[5], L. Van Rompaey[5], A. Thibault[5], A. Awada[1], V Ribrag[2], D. Bron[1].

[1]*Institut Jules Bordet, Belgium;* [2]*Institut Gustave Roussy, France;* [3]*Ghent University Hospital, Belgium;* [4]*Universitair Ziekenhuis Antwerpen, Belgium;* [5]*arGEN-X BVBA, Belgium.*

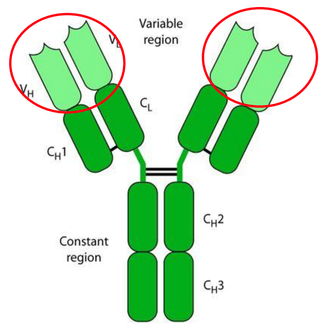
ABSTRACT

CD70/TNFSF7 is a member of the TNF family, signalling through its receptor CD27/TNFRSF7. CD70 is selectively expressed by hematopoietic cell types including T-cells. Next to a pathological role in autoimmune diseases, it is found up regulated in many cancer types. ARGX-110 is a human, afucosylated IgG1 monoclonal antibody that in addition to blocking CD70/CD27 signalling, kills CD70-expressing cancer cells through various mechanisms including enhanced Antibody-Dependent Cell-mediated Cytotoxicity (ADCC). In view of the restricted expression profile and absence of serious adverse events in Phase Ib trials, ARGX-110 has an excellent safety profile. Based on CD70 expression profiling across a spectrum of T-cell lymphomas (TCL) (cutaneous (CTCL), peripheral (PTCL); N=41), *in vitro* and *ex vivo* activity studies, and responses obtained for ARGX-110 in dose escalation and safety expansion Phase Ib studies, a clear rationale is presented to further the development of ARGX-110 in a focused T-cell malignancy trial.

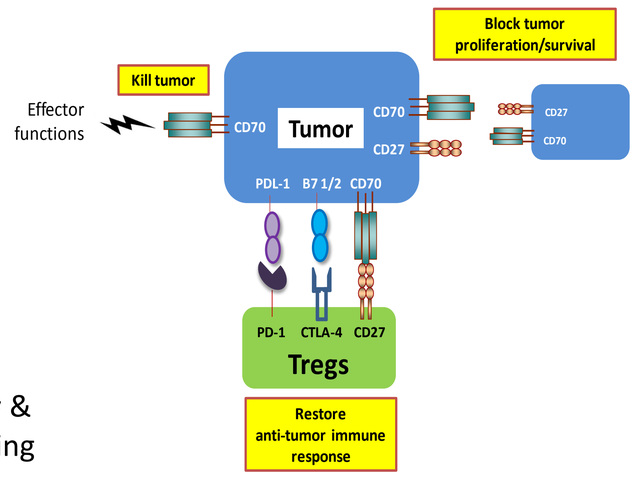
BACKGROUND



- CD27 signaling: proliferation, survival, CD27 shedding



- Fully human IgG1, high CD70 affinity & CD27 blocking, ADCC/CDC/ADCP killing



❖ ARGX-110: 3 modes of action:

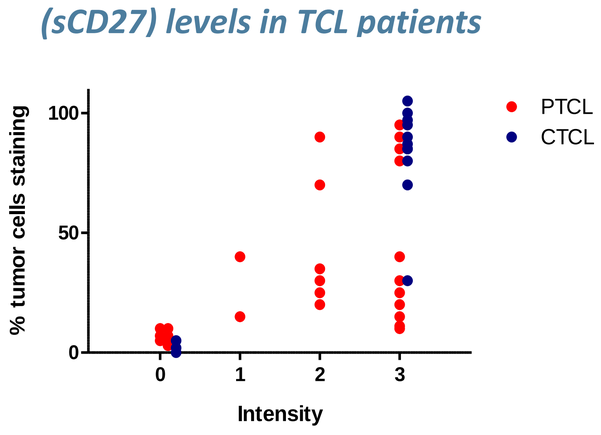
- Tumor killing functions: CDC/ADCP/*enhanced ADCC*
- Block tumor proliferation/survival
- Restore anti-tumor immune response

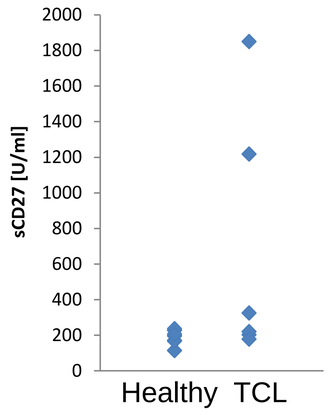
❖ T-, NK-cell neoplasms:

- Heterogeneous group of NHL (~12%), divided over 4 subtypes, comprising 23 diseases
- Aggressive clinical course, high unmet need
- Multi-agent chemo + stem cell transplantation improved survival but patients eventually relapse

CD70 is expressed by many T-cell neoplasms

❖ *Determination of CD70 expression on TCL biopsies and of soluble CD27 (sCD27) levels in TCL patients*





- 71% & 22% of CTCL & PTCL biopsies (N=41) show >50% CD70-positive tumor cells
- Increased levels of sCD27 observed for Phase Ib TCL patients vs. healthy controls

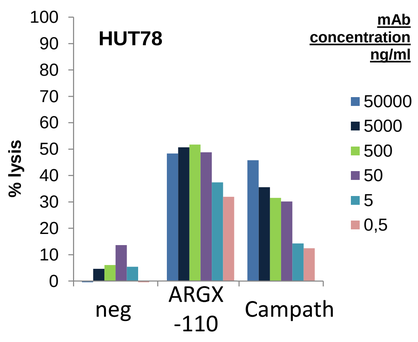
❖ *Literature data:*

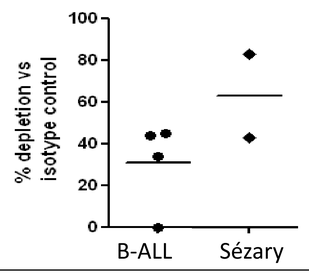
T-, NK-neoplasm subtype	Patients expressing CD70 (methodology)	Reference
lymphoproliferative disease of granular lymphocytes (T and NK cells)	20/21 (FACS)	Zambello, Blood, 2000
Adult T cell leukemia (ATLL)	6/6 (FACS, RNA (cell lines))	Baba, J Virol, 2008
EBV+ T cell lymphoma	1/1 (FACS)	Shaffer, Ped Blood Cancer 2012
Peripheral T cell lymphoma	3/3 (IHC)	Terret et al., 2007
Sézary syndrome	7/10 (RNA – pos. for CD27)	Van Doorn, Cancer Res, 2004
Nasal NK/T lymphoma	7/21 (IHC) – increased sCD27 4/6 (NK, NK/T lines, RNA = FACS)	Yoshino, Br J Haem, 2013

ARGX-110 binds and kills CD70-positive T-cells

❖ *In vitro*: high affinity binding, depletion of CTCL, PTCL cells

TCL	Cell line	Disease	FACS: binding	
			MFI	EC_{50} [ng/ml]
CTCL	HUT78	Sézary Syndrome	+++	66
	HUT102	Mycosis fungoidis	+++	46
	MJ (G11)	Mycosis fungoidis	+++	56
	HH	cutaneous T cell lymphoma	+++	21
PTCL	KARPAS299	CD30+ anaplastic large CL	++	24
	SUPT1	T-lymphoblastic lymphoma	-	
	DERL-2	hepatosplenic gamma-delta TCL	++	32
	DERL-7	hepatosplenic gamma-delta TCL	++	33
T-ALL	MOLT-4	acute lymphoblastic leukemia	-	
	Jurkatt		-	
	CCRF-CEM		-	

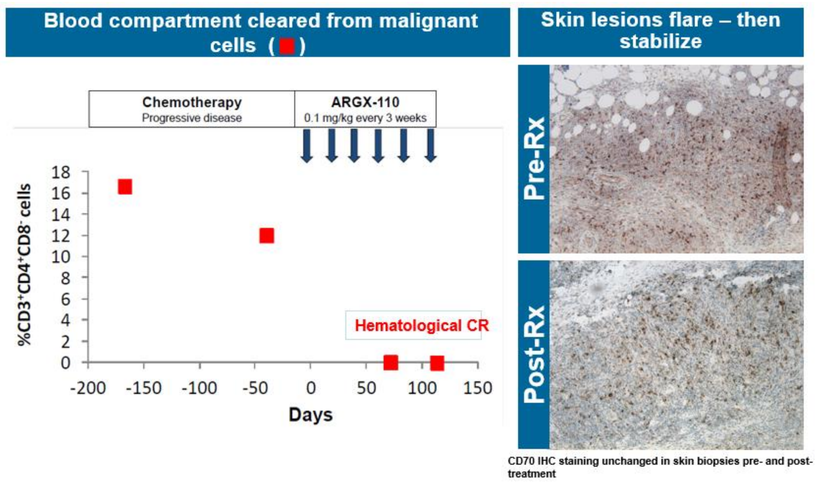




❖ *Ex vivo: ARGX-110 effectively kills malignant cells obtained from Sézary patients*

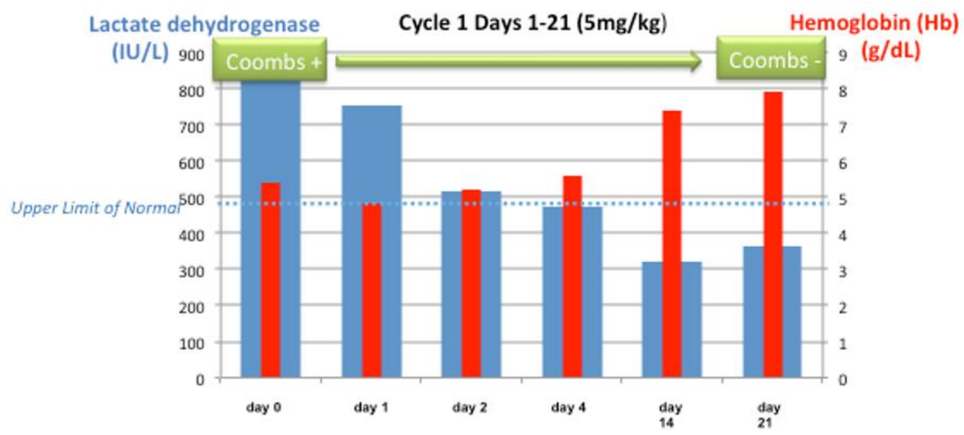
Clinical observations

❖ ARGX-110 induces CR in the blood compartment of a Sézary patient



- 77 year old woman with CTCL-Sézary refractory to multiple lines of chemotherapy
- Elimination of CD70-positive malignant cells in 2nd Sézary patient

❖ ARGX-110: proof of biological activity in angio-immunoblastic TCL (AITL) patient with autoimmune disease



- 61 year-old male AITL patient, elevated LDH and reduced Hb levels
- Refractory to chemotherapy (CHOP + Etoposide /Cyclosporine /Bendamustine - SCT)
- Post-ARGX-110: Hb increase, LDH normalization, 16% reduction in tumor size (CT scan), Coombs-negative

CONCLUSIONS :

- T-cell neoplasms, in particular CTCL, are >70% positive for CD70 expression
- ARGX-110 induces ADCC-mediated killing of malignant T-cells *in vitro, ex vivo*
- ARGX-110 was well-tolerated in solid and heme malignancies Phase Ib trials
- ARGX-110 is associated with clinical activity in T-cell malignancies
- Further clinical investigation in T-cell lymphomas is warranted