Enhanced antitumor activity achieved by combining the oncolytic peptide LTX-315 with anti-PD-L1 antibody

K. A. Camilio[1,2], B. Sveinbjørnsson[1,2], S. Maubant[3], G. Serin[3], J.-F. Mirjolet[3], F. Bichat[3], Ø. Rekdal[1,2]

[1] Lytix Biopharma AS, Norway; [2] Department of Medical Biology, Faculty of Health Sciences, University of Tromso, Norway; [3] Oncodesign, Dijon, France

For more information: contact@oncodesign.com / oystein.rekdal@lytixbiopharma.com

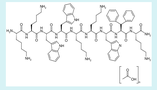
INTRODUCTION

Background

The need for new and improved **anticancer therapies** is imperative, with an increased focus on immunotherapy and the combination of different treatments to achieve an additive anticancer effect and maximize the following immune engagement and activation.

LTX-315 (Oncopore™) is a novel **oncolytic peptide** derived from the naturally occurring host defense peptide, bovine lactoferricin [1]. LTX-315 interacts electrostatically with anionic components of negatively charged cancer cell membranes as well as intracellular targets such as mitochondria, causing cellular lysis and a subsequent release of endogenous cellular content including danger signals and tumor antigens [2-7].

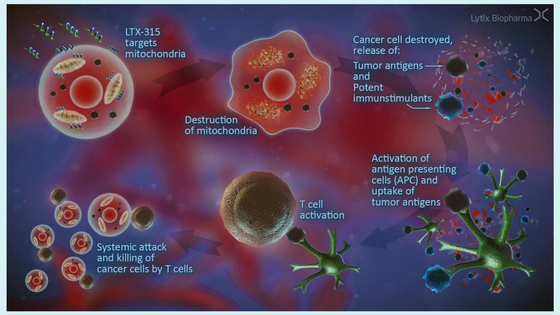
Chemical structure of LTX-315



Targeting immune checkpoints such as programmed cell death protein 1 (PD1), programmed cell death 1 ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen 4 (CTLA4) has achieved noteworthy benefit in multiple cancers by blocking immuno-inhibitory signals and enabling patients to produce an effective antitumor immune response. **Programmed cell death ligand 1 (PD-L1)** is an immune checkpoint ligand expressed on immune cells, some normal tissues and many tumors. PD-L1 binds to PD-1 on lymphocytes to inhibit T cell receptor signaling and activation.

Aim

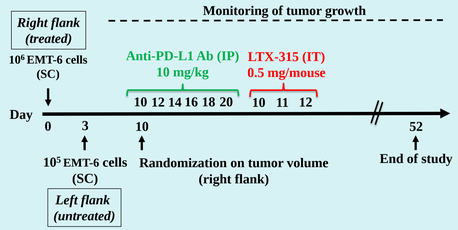
To investigate the anticancer effects of LTX-315 in combination with anti-PD-L1 Ab in the EMT-6 mouse breast carcinoma model.

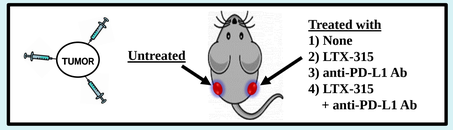


Mode of action

RESULTS

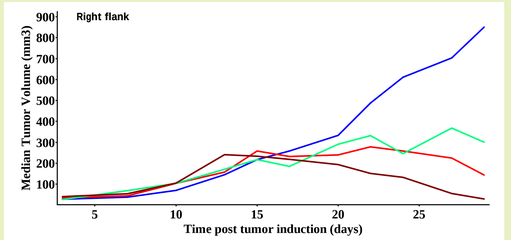
Study design



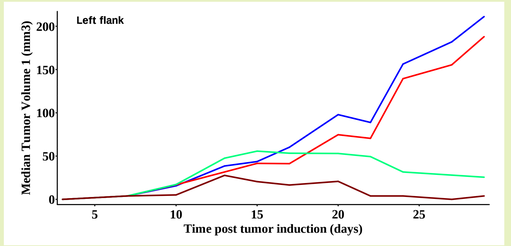


Mice were injected subcutaneously (SC) with EMT-6 tumor cells on D0 and then on D3.
Animals were randomized on D10 and treated during the D10-D20 period with LTX-315 and/or anti-PD-L1 antibody (Ab: antibody; IT: intratumoral; IP: intraperitoneal).

Growth of EMT-6 tumors



	T/C % (D29)
Untreated	100
LTX-315	17
Anti-PD-L1 Ab	35
LTX-315 + anti-PD-L1 Ab	4



Untreated
LTX-315 (IT – right flank)
Anti-PD-L1 Ab (IP)
LTX-315 (IT – right flank) + anti-PD-L1 Ab (IP)

	T/C % (D29)
Untreated	100
LTX-315	89
Anti-PD-L1	12
LTX-315 + anti-PD-L1 Ab	2

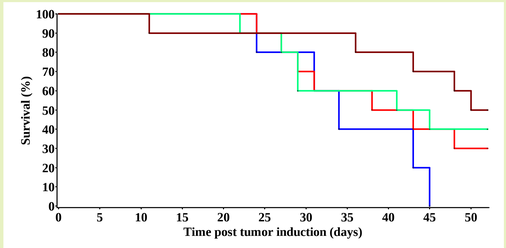
Each point represents the median of the recorded tumor volume *per* group.

Tumor growth inhibition (T/C %) defined as the ratio of the median tumor volumes of treated groups *versus* untreated group was calculated.

D29: last time point at which at least **80 % of mice from all analyzed groups were still alive.**

- Enhanced growth inhibition of tumor size following treatment with LTX-315 in combination with anti-PD-L1 Ab demonstrating the **advantage of the combination therapy in treatment of EMT-6 tumors.**

Survival



Untreated
LTX-315 (IT – right flank)
Anti-PD-L1 Ab (IP)
LTX-315 (IT – right flank) + anti-PD-L1 Ab (IP)

- Treatment with **LTX-315 in combination with anti-PD-L1 Ab resulted in an increase of overall survival** compared to either treatment alone.

	Median survival time (days)
Untreated	34
LTX-315	40.5
Anti-PD-L1 Ab	43
LTX-315 + anti-PD-L1 Ab	51

Tumor free animals

	% tumor free animals on day of sacrifice	
	right flank	left flank
Untreated	0	0
LTX-315	30	10
Anti-PD-L1 Ab	20	30
LTX-315 + anti-PD-L1 Ab	30	50

- **The combination therapy resulted in more tumor free animals** compared to either monotherapy, indicating an augmentation of the systemic antitumor response.

Conclusions

- **LTX-315 shows an enhanced anticancer effect** when combined with anti-PD-L1 Ab compared to either of the compounds alone,
- **LTX-315 in combination with anti-PD-L1 Ab induced enhanced effect** against non-treated tumors compared to anti-PD-L1 Ab alone,
- **The oncolytic peptide LTX-315 is a promising candidate for combination therapy** with immune checkpoint inhibitors,
- **LTX-315 is currently in clinical phase I/2a studies.**

References:
1. Haug *et al.* Med Chem. 2016
2. Camilio *et al.* Cancer Immunol Immunother. 2014
3. Camilio *et al.* Oncoimmunology. 2014
4. Zhou *et al.* Oncotarget. 2015
5. Eike *et al.* Oncotarget. 2015
6. Forveille *et al.* Cell Cycle. 2015
7. Zhou *et al.* Cell Death Dis. 2016