LTX-315, a first in class oncolytic peptide reshapes the tumor microenvironment in the majority of patients with advanced metastatic tumors: Results from an ongoing clinical phase I study

ØYSTEIN REKDAL[1], JEAN-FRANCOIS BAURAIN[2], AHMED AWADA[3], PAAL F. BRUNSVIG[4], REBECCA SOPHIE KRISTELEIT[5], DAG ERIK JØSSANG[6], NINA LOUISE JEBSEN[7], AURELIEN MARABELLE[8], DELPHINE LOIRAT[9], JEROME GALON[10], FABIENNE HERMITTE[11], ANDREW SAUNDERS[12], BALDUR SVEINBJØRNSSON[13], BERIT NICOLAISEN[1], VIBEKE SUNDVOLD GJERSTAD[1], JAMES SPICER[12]

[1]LYTIX BIOPHARMA, NORWAY, [2]CLINICQUE UNIVERSITÉ, UCL, ST. LUC, BELGIUM, [3]INSTITUT JULES BORDET, UNIVERSITÉ LIBRE DE BRUXELLES, BELGIUM, [4]OSLO UNIVERSITY HOSPITAL, NORWAY, [5]UNIVERSITY COLLEGE LONDON HOSPITAL, UK, [6]HAUKELAND UNIVERSITY HOSPITAL, NORWAY, [7]CENTRE FOR CANCER BIOMARKERS (CCBIO), UNIVERSITY OF BERGEN, [8]INSTITUT GUSTAVE ROUSSY, PARIS, FRANCE, [9]INSTITUT CURIE, PARIS, [10]FRANCE LABORATORY OF INTEGRATIVE CANCER IMMUNOLOGY, INSERM, PARIS, FRANCE, [11]HALIODX, MARSEILLE, FRANCE, [12]KINGS COLLEGE, GUY'S HOSPITAL, UK

Background

LTX-315 is a first in class oncolytic peptide with unique "release and reshape" properties[1,2]

Pre-clinical studies of LTX-315 demonstrate:

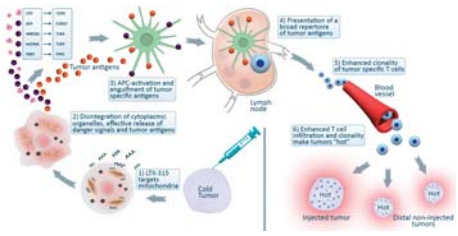
- Unique immunogenic cell death mode of action by targeting the mitochondria[3,4]
- Disintegration of cytoplasmic organelles resulting in effective release of chemokines, danger signals and a broad repertoire of tumor antigens[3-6]
- Reduced number of immunesuppressive cells[7]
- Enhanced infiltration of T cells and T cell clonality
- Complete regression of injected and non-injected tumors (i.e. Abscopal effect)[8,9]

A Phase I clinical trial was initiated to evaluate the potential benefit of the oncolytic peptide LTX-315 as a novel intralesional therapeutic strategy.

Aim

The aim of this study is to evaluate the safety and tolerability of intra-tumoural LTX-315 monotherapy and determine the recommended phase II dose and schedule.

LTX-315's "Release and Reshape" MoA



Study Design

Primary Endpoints

- Safety (including DLTs, AEs, SAEs, lab assessments) of LTX-315
- Inflammatory markers in injected tumor tissue, such as tumor infiltrating lymphocytes

Secondary Endpoints

- Local effects of LTX-315 by assessment of:
  - Necrosis in index lesions determined by ultrasound and resection/biopsy
- Systemic immunological response with LTX-315 in peripheral blood
- Anti-tumor activity of LTX-315 by CT scan assessment (immune-related response criteria (irRC))

Cohort	LTX-315 dose (20mg/ml)	No. of patients	Tumor type
	Single/sequential lesion injection		
1	2mg BD	3	Chordoma; pancreas; breast
2	3mg BD	3	Myo-epithelioma; breast; melanoma
3	4mg BD	3	Breast; melanoma; leiomyosarcoma
4	5mg QD	3	Desmoid; melanoma; breast
5	6mg QD	3	Breast (2); ocular melanoma
6	7mg QD	4	Head & neck (2); melanoma (2)
7	6mg QD (10mg/ml)	4	Head & neck; adrenal; melanoma; urethral
	Multiple concurrent lesion injection		
8	3mg QD in each lesion (20mg/ml)	3	Head & neck; breast; vaginal SCC
9	4mg QD in each lesion (20mg/ml)	2	Head & neck (2)

Safety Summary

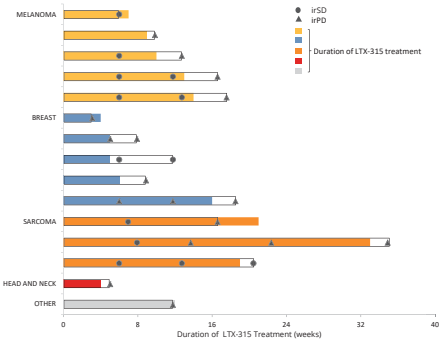
- Doses of between 2-7mg per injection have been evaluated; no MTD was observed
- LTX-315-related adverse events (any grade) have been observed in 21 of 28 patients who received > 1 LTX-315 injection
- 7 of 28 patients (25%) had CTC AE > grade 3 related AEs including allergic reaction/anaphylaxis (4), pain on injection (2) and sepsis (1)
- 3 of 4 episodes of > grade 3 LTX-315 related allergic reaction/ anaphylaxis occurred; 3 occurred after > 10 weeks of treatment; one was a DLT and occurred in week 2

LTX-315 safety (n=28)

LTX-315 related adverse event	Grade* 1-2 (No. of pts (%))	Grade* 3-4 (No. of pts (%))
Hypotension	10 (36%)	-
Parasthesia	8 (29%)	-
Rash	8 (29%)	-
Flushing	5 (18%)	-
Pruritis	3 (11%)	-
Tumor pain	2	2
Allergic reaction	-	4 (14%)
Pain (injection site)	-	2 (7%)
Sepsis	-	1 (4%)

* CTC Version 4.0

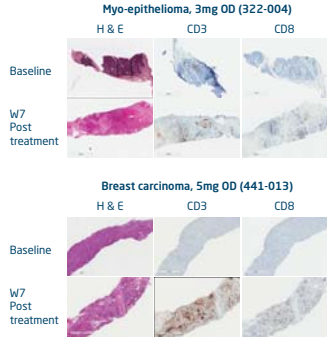
Immune related response (irRC) assessment



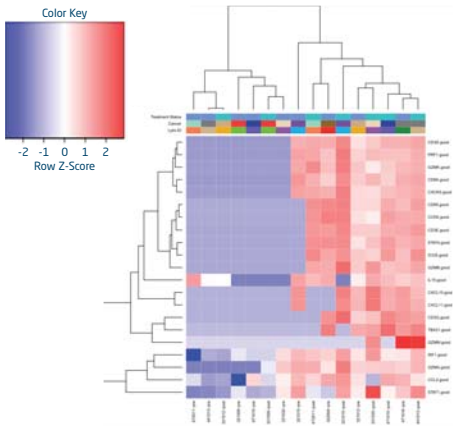
Stable disease ((SD) median duration 11 weeks) by irRC was observed in 8 of 15 evaluable patients (53%).

LTX-315 converts cold tumors to hot

- Biopsies of injected tumors taken at baseline and after treatment have been obtained in 19 patients. All biopsies were taken in up to 3 planes of orientation.
- Enhanced infiltration of CD8+ T-cells in injected lesions in 15 of 17 patients (88%).



Effect of LTX-315 on key genes involved in immune-mediated tumor regression



Post-treatment samples (7 in red) are well separated from pre-treatment samples (7 in blue)

Out of 7 pairs:
- 5 tumor pairs change from cold (gene expression in blue) to hot (in red)
- 1 tumor pair with CD8+ T cell infiltration at baseline was turned more hot post treatment
- 1 tumor pair with no effect

Hierarchical Clustering of Immunosign® 21 Immune Gene Signature (HalioDx) which profiles expressions of a pre-defined set of effector T cell, Th1, chemokine, and cytokine genes

Conclusion

- LTX-315 is generally safe and tolerable, the majority of toxicities are transient grade 1-2, and include hypotension (asymptomatic) flushing, paresthesia and rash
- No MTD has been reached
- Regression in injected and non-injected lesions observed:
  - Stable disease ((SD) median duration 11 weeks) by irRC was observed in 8 of 15 evaluable patients (53%)
  - Abscopal effect observed
- Elevation of tumor infiltrating lymphocytes in injected lesions was observed in 15 of 17 (88%) evaluable patients
- The HalioDx Immune Gene Expression Signature, Immunosign® 21 analysis of LTX-315 treated tumors shows:
  - Clear effect on key genes (effector T cell, Th1 orientation, chemokines and cytokines) involved in immune-mediated tumor regression
  - LTX-315 converts cold tumors to hot, as evident by immune phenotyping using gene expression analysis
- Results support the rationale and potential benefit of LTX-315 as a novel intratumoral immunotherapy
- Combination testing of LTX-315 with immune checkpoint inhibitors is ongoing in melanoma and breast cancer

References

1. Haug, B.E. et al; J. Med. Chem. (2016)
2. Sveinbjørnsson, B. et al.; Future Medicinal Chemistry (2017)
3. Zhou, H. et al.; Oncotarget (2015)
4. Eike, L-M. et al.; Oncotarget (2015)
5. Forveille, S. et al.; Cell Cycle (2015)
6. Zhou, H. et al.; Cell Death Disease (2016)
7. Yamazaki, T. et al.; Cell Death and Differentiation (2016)
8. Camilio et al.; Cancer Immunol Immunother. (2014)
9. Nestvold, J. et al. Onco Immunology (2017)

Lytix Biopharma AS | Gaustadalléen 21, NO-0349 Oslo, Norway | E-mail: post@lytixbiopharma.com | Phone: +47 77 67 55 00 | Fax: +47 77 67 55 01