LTX-315, a first in class oncolytic peptide reshapes the tumor microenvironment inducing a local and systemic effect in metastatic tumors: Results from an ongoing study

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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:

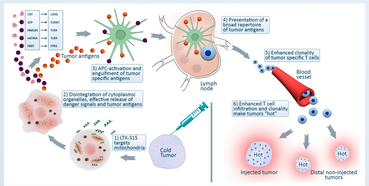
- Unique immunogenic cell death mode of action by targeting the mitochondria. [3,4]
- Disintegration of cytoplasmic organelles resulting in effective release of chemokines, danger signals and a broad repertoire of tumor antigens. [3-6]
- Reduced number of immunesuppressive cells. [7]
- Enhanced infiltration 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-tumoral 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.
- PK profile of LTX-315.
- Anti-tumor activity of LTX-315 by CT scan assessment (immune-related response criteria (irRC)).

Inclusion Criteria

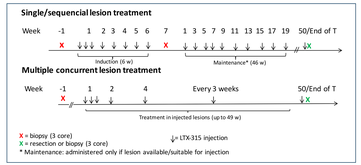
- Histologically confirmed advanced/metastatic disease (all tumors).
- At least one transdermally accessible lesion (in/close to the skin) of ≤ 10 cm in diameter.
- ECOG Performance status (PS): 0 - 1.
- No expectation of other anti-tumor therapy during the treatment period.

Exclusion Criteria

- Investigational drug therapy within 4 weeks prior to study.
- Immunotherapy or vaccine therapy within 6 weeks prior to study.
- External radiotherapy or cytotoxic chemotherapy within the last 4 weeks prior to study.

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 (20 mg/ml)	3	Head & Neck; Breast; Vaginal SCC
9	4mg QD in each lesion (20 mg/ml)	2	Head & Neck (2)

Treatment schedules – LTX-315



Treatment and patient characteristics (n=28)

	Number
Median number of prior treatments for advanced/metastatic disease	3 (0-20)
Median number of LTX-315 injections	14 (4-54)
Median number of injected lesions per patient	1 (1-6)
Median numbers of treatment weeks	9 (3-33)
Median age (range)	60 (26-80)
Male: Female	11:17
ECOG PS	No. of patients
0-1	8-20
Tumor type	No. of patients
Breast	7
Melanoma	7
Head & Neck	6
Sarcoma	3
Other	5

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.
- 14 of 28 patients (50%) had transient (seconds/minutes duration) CTC AE ≤ grade 2 LTX-315 AEs including hypotension (asymptomatic), flushing and pruritis/itching/tingling.
- 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; 3 occurred after ≥ 10 weeks of LTX-315 treatment; one was a DLT and occurred in week 2.
- Protocol has been amended to administer 3-5mg LTX-315 for 3 weeks (6 injections only).

LTX-315 safety (N=28 patients)

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

LTX-315 monotherapy efficacy (Evaluable patients)

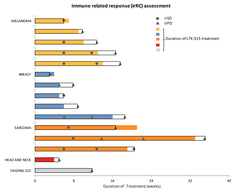
- 15 evaluable patients (irRC criteria).
- SD (best response) was observed in 53% (8/15) patients: melanoma (4), sarcoma (3) and breast (1); median duration of SD (range) was 11 weeks (range 7-21).
- Histological confirmation of an abscopal effect (no tumor visible in biopsy after LTX-315 Tx in a distant non-injected lesion) has been observed.
- Regression (complete or partial) was confirmed in several injected lesions in some patients (ultrasound assessment).

LTX-315 monotherapy efficacy (evaluable# patients (irRC))

Response	2mg bd N=3	3mg bd N=2	4mg bd N=3	5mg OD N=2	6mg OD(20mg/ml) N=1	7mg OD N=2	3mg OD (multiple lesions) N=2	Evaluable patients N=15
CR					0			0
PR					0			0
SD	2	1	2	2	1	0	0	8 (50%)
PD	1	1	1	0	0	2	2	8 (50%)

*N denotes No. of evaluable patients per LTX-315 dose cohort.
#Evaluable patients: patients with a screening and > 1 on study CT scan assessment.

Immune related RECIST response assessment



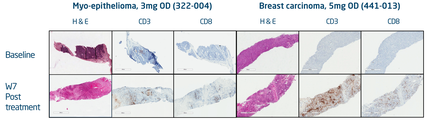
Patients with sustained stable disease

Tumour type	Last Prior Tx (met disease) /response	No. of injected lesions	No of LTX-315 injections	LTX-315 dose
Chordoma	-	2 (subcutaneous)	54	2mg bd
Myo-eithelioma	-	2 (cutaneous)	48	3mg bd
Leiomyosarcoma	-	1 (subcutaneous)	32	4mg bd
Breast	-	1 (cutaneous)	16	2mg bd
Melanoma	Ipilimumab/PD*	2 (lymph nodes)	36	3mg bd
Melanoma	Nivolumab/PD*	2 (cutaneous)	30	4mg bd
Melanoma	Ipilimumab /PD*	2 (cutaneous)	18	4mg bd
Melanoma	Pembro/PD*	2 (cutaneous)	17	6mg od

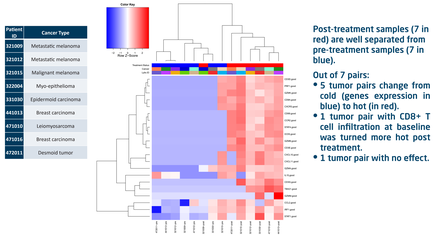
* **PD:** Progressive Disease
- 4/6 patients (all melanoma) who were treated with immune checkpoint inhibitor (ICI) as immediate prior treatment (all had PD as best response to ICI) achieved SD with LTX-315 treatment.

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 14 of 19 patients (74%).



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

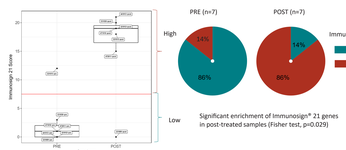


Post-treatment samples (7 in red) are well separated from pre-treatment samples (7 in blue).

Out of 7 pairs:
- **5 tumor pairs change from cold (genes 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.

Immunosign 21 score visualizes LTX-315s ability to convert cold tumors to hot



Significant enrichment of Immunosign® 21 genes in post-treated samples (Fisher test, p=0.029)

Immune Gene Expression Signuature Immunosign® 21 score Infiltration calculated with specified bioinformatics algorithm.

Conclusion

- LTX-315 is generally safe and tolerable; the majority of toxicities are transient grade 1-2, and include hypotension (asymptomatic), flushing, parasthesia and rash.
- No MTD has been reached.
- Regression in injected and non-injected lesions observed:
  - Stable disease ((SD) median duration 11 weeks) in non-injected tumors lesions (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 14 of 19 (75%) 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 evidenced by immune phenotyping using gene expression analysis.
- Results support the rationale and potential benefit of LTX-315 as a novel intratumoural immuno-therapy.
- Combination testing of LTX-315 with immune checkpoint inhibitors is ongoing in melanoma and breast cancer.

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