A Phase I study with LTX-315 – an immunogenic cell death inducer - in patients with transdermally accessible tumours

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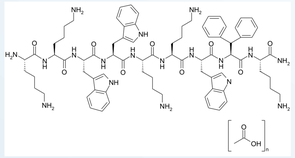
Background

Host defense peptides are naturally occurring cationic peptides that have an important function in innate immune responses to microbial pathogens (1). Through structure-activity relationship studies we have *de novo* designed LTX-315, a short oncolytic peptide derived from a host defense peptide.

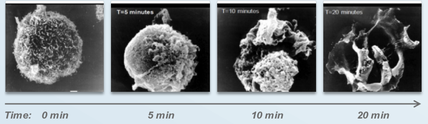
Chemical structure of LTX-315



In nonclinical studies LTX-315 has demonstrated:

- Equally active against drug-resistant and drug-sensitive tumour cells (2)
- Complete regression in several different tumour models (3)
- Release of a number of danger signal molecules (DAMPs) (4)
- Protection against re-challenge, i.e. "memory" response (3)
- Complete and specific regression of disseminated tumours in a rat mesenchymal sarcoma three tumour model (4)

Rapid disruption of the cell membrane



Aim

A phase I dose escalating open label, single centre study was designed to evaluate safety profile and determine recommended dose. Immunological responses to the injections were exploratory endpoints (5).

Study design

Primary Endpoints

- Safety profile
- Recommended dose

Secondary Endpoints

- Anti-tumour activity
- Immunological response
- Pharmacokinetic assessment
- Duration of response

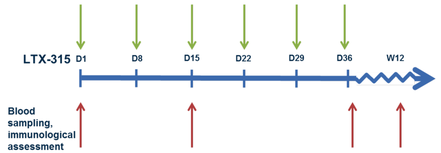
Inclusion Criteria

- Histologically confirmed lymphoma or other malignant tumour, e.g. melanoma or metastasis
- Transdermally accessible lesion in or close to the skin of ≤ 4 cm in diameter
- ECOG Performance status (PS): 0 - 2
- Life expectancy: At least 3 months

Exclusion Criteria

- Investigational drug therapy within 4 weeks prior to study
- Target lesion located in the head and neck region
- Immunotherapy or vaccine therapy within 12 weeks prior to study
- External radiotherapy or cytotoxic chemotherapy within the last 4 weeks prior to study

Patients received weekly ultrasound guided injections of LTX-315 into one transdermally accessible tumour for a maximum of 6 injections



Cohort	Conc. (mg/mL)	Dose
1	10	10% of tumour volume
2	20	10% of tumour volume
3	20	2 mg 1st injection 4 mg next injections

Tumor	Cohort 1	2	3	Total
Melanoma*	3	1	5	9
Lymphoma		4		4
Breast cancer			1	1
Total	3	5	6	14

*1 Ocular melanoma

Safety results

All related Treatment-Emergent Adverse Events

Adverse Event	Cohort 1	2	3	Total
Flushing	1	1	3	5
Hypersensitivity	1	3	0	4
Injection site swelling	0	3	0	3
Hypotension	0	2	1	3
Headache	0	1	1	2
Fatigue	0	1	0	1
Influenza like illness	0	0	1	1
Injection site oedema	0	1	0	1
Trans Ischemic Attack	0	1	0	1
Dyspnoea	0	1	0	1
Influenza	0	1	0	1
Overdose	0	0	1	1

Patients with treatment-emergent adverse events by common toxicity criteria (CTC)

Adverse Event	Cohort 1	2	3	Total
CTC grade				
1	0	3	1	4
2	1	0	3	4
3	1	1	0	2
4	0	1	0	1
Relationship to LTX-315				
Not related	0	1	1	2
Related	2	4	3	9

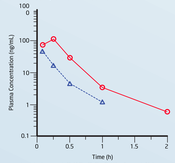
Dose Limiting Toxicity (DLT) related to LTX-315

Cohort 2	Dose	Acute hypotension*	Reversible	Further outcome
Lymphoma patient	8.2 mg	Grade 3	Yes	Continued treatment
Lymphoma patient	9 mg	Grade 4	Yes	Discontinued treatment

*Primarily a transient effect on peripheral circulation due to increased microcirculation/efflux to extracellular tissue. Vital cardiac functions are maintained.

Pharmacokinetic profile at Day 1 and 8

Breast cancer patient – Cohort 3



PK samples taken at 0.25, 0.5, 1, 2, 4 and 6 hours post injection at day 1(Δ) and 8 (○)
T1/2 observed following dosing on Day 8 was 0.28 h

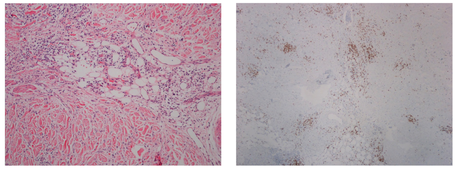
Efficacy results

Cohort 3

In Cohort 3 there were signs of treatment related effects of LTX-315 at doses of 4 mg. One patient, breast cancer, demonstrated treatment related necrosis, tumour infiltrating lymphocytes and tumour regression (50%). Reduction of tumour volume (65%) was also observed in the treated lesion of the ocular melanoma patient.

Tumor-infiltrating lymphocytes (TILs)

Breast cancer patient – Cohort 3



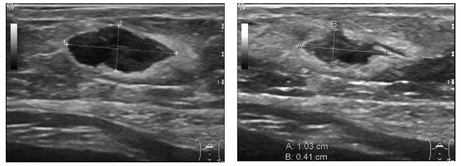
Haematoxilin/Eosin staining

CD8+ cytotoxic T-cells

Presence of treatment-associated necrosis (left panel) and infiltration of immune cells (TILs) (right panel)

Reduction of tumour volume 65%

Ocular melanoma patient – Cohort 3

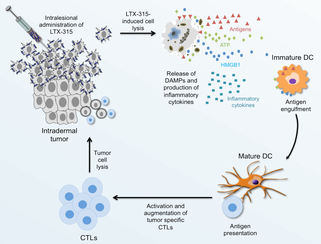


Baseline (14 x 6 mm)

After 6 injections (10 x 4 mm)

A reduction of tumour volume of 50% was also observed in the breast cancer patient

MoA of LTX-315



Intralesional administration of LTX-315 induces cellular lysis (necrosis), leading to release of intracellular content consisting of danger signals such as ATP and HMGB1, together with tumor antigens. These events will initiate the maturation and recruitment of DCs into the tumor bed. Activated DCs are then primed for antigen engulfment and antigen presentation to T cells, creating tumor-specific cytotoxic CD8 that are capable of eradicating residual cancer cells.

Overall conclusion

- The main safety issues were primarily dose-related flushing and transient hypotension
- Tumour infiltrating lymphocytes and tumour regression were observed in some patients
- The findings confirms the rationale and potential benefit of LTX-315 as a novel intralesional immunotherapy
- A Phase I/IIa study with LTX-315 is ongoing at four sites in Europe (ClinicalTrials.gov NCT01986426)

References

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2. R315-11
3. Camilio et al. Cancer Immunol Immunother, 63: 601. (2014)
4. Rekdal et al. The AACR Annual Meeting. Abstract no. 2583, 2014
5. ClinicalTrials.gov NCT01058616

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