CT010

A PHASE I STUDY OF THE ONCOLYTIC PEPTIDE LTX-315 GENERATES DE NOVO T-CELL RESPONSES AND CLINICAL BENEFITS IN PATIENTS WITH ADVANCED SARCOMA

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Background

LTX-315 is a first in class oncolytic peptide with unique properties to convert "cold" tumors to "hot" (1,2)

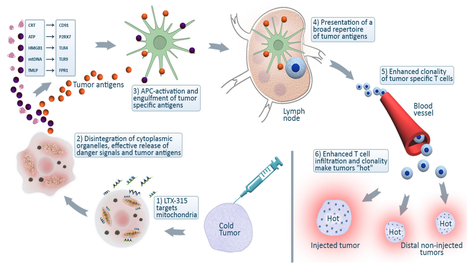
Pre-clinical studies of LTX-315 demonstrate:

- 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 immunosuppressive cells (7).
- Enhanced infiltration of T cells and T cell clonality (8).
- Complete regression of injected and non-injected tumors (i.e. abscopal effect) (8-10).

Aim

- Evaluate the safety and tolerability of intra-tumoral LTX-315 in patients with transdermally accessible tumors
- Evaluate efficacy
- Determine the recommended phase II dose and schedule
- Evaluate immune responses in tumor and peripheral blood samples pre and post treatment

LTX-315's unique mode of action results in effective release of potent immunostimulants and antigens



Study design (NCT01986426)

A phase I/II open label, multi arm, multi centre, multi dose study administering LTX-315 intratumorally to single or multiple transdermally accessible lesions

Primary Endpoint
- Safety (including DLTs, AEs)

Secondary Endpoints
- LTX-315 related immune parameters in tumor and peripheral blood
- Anti-tumor activity of LTX-315 by CT scan assessment (irRC)

Patient Population
- Advanced/metastatic solid tumors
- At least one transdermally accessible lesion

Study Arms

Two monotherapy arms:

Arm A: Single lesions injected sequentially for 7 weeks followed by maintenance
Arm B: Multiple lesions injected concurrently for 3 weeks (no maintenance)

Key inclusion criteria

- Histologically confirmed advanced/metastatic disease (all tumors) not suitable for further conventional therapies.
- At least one transdermally accessible lesion of ≤ 10 cm in diameter.
- ECOG Performance status (PS): 0 - 1
- Meet minimum baseline laboratory criteria

Key exclusion criteria

- Immunotherapy or vaccine therapy within 2 weeks prior to study entry
- External radiotherapy or cytotoxic chemotherapy within the last 4 weeks prior to study entry
- History of autoimmune disease
- Have clinically active or unstable CNS metastases
- Pregnant or lactating
- HIV positive or have active Hepatitis B or C

Safety in Monotherapy; all patients

Arm	Total N	TEAE	Related any grade	Related ≥ gr 3	Related SAE	Discon due to related AE
A	23	22 (97%)	19 (83%)	7 (30%)*	4 (17%)***	5 (22%)
B	16	16 (100%)	4 (25%)	3 (19%)**	0	0

Safety evaluable population = any pt who had at least one dose of LTX-315 (greater denominator than efficacy population)

* Hypotension, dizziness, flushing, general site administration disorders (pain, redness), immune system disorders (hypersensitivity, anaphylaxis)
** Hypotension
*** SAEs- 3 anaphylaxis, 1 hypotension

Acute onset of all related ≥ gr3 TEAEs within 5-10 mins of injection, most resolved with treatment and no sequelae.
Introduction of prophylaxis for anaphylaxis reduced incidence and severity of hypersensitivity in ongoing patients to grade 1/2

Results sarcoma patients

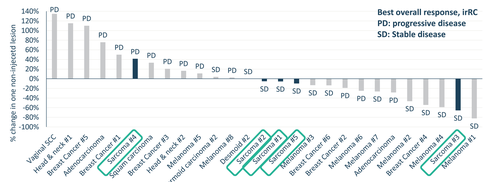
Thirty nine patients were enrolled and had at least one dose of LTX-315 in the monotherapy arms, thereof:

Arm A: 3 STS[1] patients in ITT* population (sarcoma #1-3)
Arm B: 2 STS patients in ITT* population (sarcoma #4, 5)

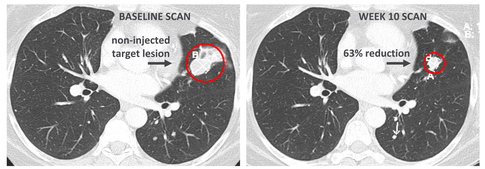
[1] STS = Soft Tissue Sarcoma
* Intention to treat population (ITT)= any pt who had at least one dose of LTX-315 and at least one post dose evaluation.

ALL PATIENTS TREATED WITH LTX-315 MONOTHERAPY

Best overall response (irRC) and best response in one non-injected lesion

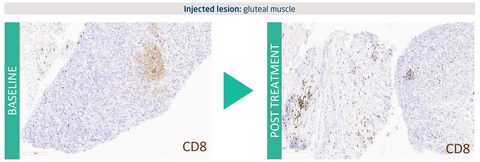


CASE #3: LTX-315 local treatment leads to systemic response

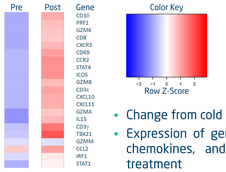


- Patient with recurrent metastatic leiomyosarcoma after primary surgical resection.
- Treatment with local intratumoral LTX-315 injections in the gluteal muscle lesion.
- Prior treatment: Surgery.
- Duration of stable disease 74 days. No SAEs, grade 1 hypotension post dosing.

CASE #3 (CONTINUED):

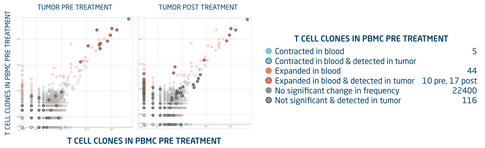


Immunosign® 21 gene signature



- Change from cold (genes expression in blue) to hot (in red)
- Expression of genes related to effector T cells, Th1 cells, chemokines, and cytokine are increased post LTX-315 treatment

T-cell clonality



- 44 significantly expanded T-cell clones in blood post LTX-315 treatment
- 17 of these T-cell clones were also present in tumor post treatment
- Novel T-cell clones significantly expanded in blood and the presence of these clones in tumor post treatment suggests that LTX-315 generates a *de novo* T-cell response

Summary of sarcoma patients

Case Number (sex/age)	Subtype	Best response	Duration of treatment (Weeks)/ Arm	IHC TILS (CD8+) pre v post Rx
#1 (M/48)	Chondroma	irSD	31/A	Increase
#2 (F/32)	Myoepithelioma	irSD	23/A	Substantial increase
#3 (F/62)	Leimyosarcoma	irSD	21/A	Substantial increase
#4 (F/63)	Malignant Nerve Sheath Sarcoma	irPD	3/B	Substantial increase
#5 (F/64)	Uterine Leimyosarcoma	irSD	3/B	Not paired biopsies

Study Conclusion

LTX-315:

- is generally safe and tolerable; following incidents of anaphylaxis and allergy with prolonged exposure, the dosing schedule was adjusted and mandatory prophylaxis introduced. The majority of toxicities seen were grade 1/2 and transient, including hypotension (asymptomatic), flushing, paresthesia and rash
- reduces the size of several non-injected lesion, indicating a systemic response
- promotes TILs in all evaluable sarcoma patients
- converts "cold" tumors to "hot" as demonstrated by gene expression analysis
- promotes significant expansion of T-cell clones in blood, of which several are novel and present in tumor post treatment, suggesting generation of a *de novo* anti-tumor T-cell response

The dosing regimen of LTX-315 will be optimized and assessed to position LTX-315 as a therapeutic agent in combination with other targeted immune therapies such as immune check point inhibitors to address an unmet need in a select group of indications.

References

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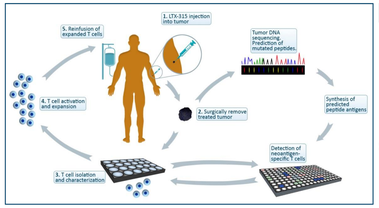
ONGOING TRIAL: LTX-315 in combination with Adoptive T cell therapy for sarcoma patients (NCT03725605)



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