CT069

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

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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)

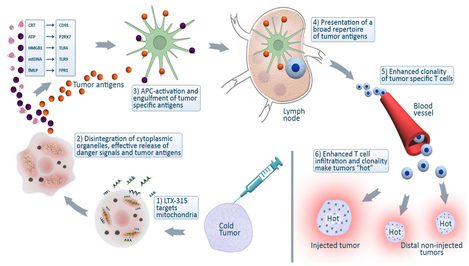
Pre-clinical studies of LTX-315 demonstrate:

- 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 hypersensitivity

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 melanoma patients

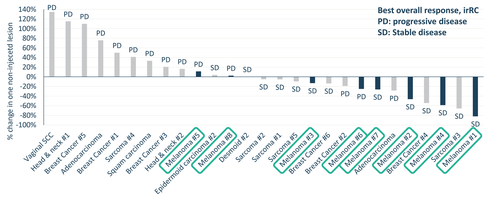
Thirty nine patients were enrolled and had at least one dose of LTX-315 in the monotherapy arms, thereof:

Arm A: 5 melanoma patients in ITT* population (melanoma #1-5)
Arm B: 3 melanoma patients in ITT* population (melanoma #6, 7)

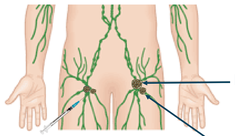
* Intention to treat population (ITT)= any pt who had at least one dose of LTX-315 and at least one post dose evaluation.

ALL PATIENTS TREATED WITH LTX-315 MONOTHERAPY

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



CASE #1: LTX-315 local treatment leads to systemic response

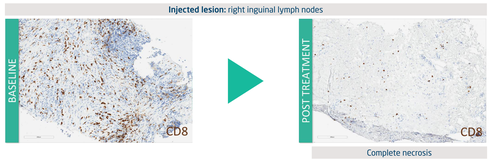


Injected lesions, size (mm²)	
Lesion 1	Lesion 2
32	123

Non-injected lesions, size (mm²)		
	Lesion 1	Lesion 2
Baseline	715	286
Post treatment	438 (-39%, W18)	51 (-82%, W13)

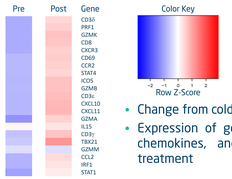
- Patient with metastatic cutaneous melanoma
- Treatment with local intratumoral LTX-315 injections in right inguinal lymph nodes.
- Prior treatments: surgery, dacarbazine, ipilimumab
- Duration of stable disease 10W. Total target lesion reduction by 48%
- No SAEs, Grade 1 injection site irritation, diarrhoea and hypotension- related to LTX-315

CASE #1 (CONTINUED):



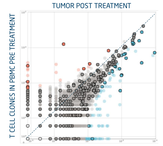
CASE #3

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



T CELL CLONES IN PBMC PRE TREATMENT

Contracted in blood	75
Contracted in blood & detected in tumor	24
Expanded in blood	18
Expanded in blood & detected in tumor	8
No significant change in frequency	37772
Not significant & detected in tumor	381

- 26 significantly expanded T-cell clones in blood post LTX-315 treatment
- 8 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 melanoma patients

Case Number (sex/age)	Subtype	Best response	Total duration of treatment (Weeks)/Arm	IHC TILS pre v post Rx
1 (M/74)	Skin	irSD	15/A	Totally necrotic tissue post treatment
2 (F/80)	Skin	irSD	10/A	Substantial increase of TILs
3 (F/64)	Unk site	irSD	11/A	Substantial increase of TILs Significant expansion of 26 T-cell clones post treatment in blood of which 8 present in the tumor post treatment
4 (F/41)	Ciliary Body	irSD	17/A	Substantial increase of TILs
5 (F/61)	Skin	irPD	9/A	No paired biopsies
6 (F/71)	Skin	irPD	3/B	Substantial increase of TILs Immune score increased from intermediate to high
7 (M/71)	Uveal	irSD	3/B	Increase of TILs
8 (M/64)	Uveal	irPD	3/B	No 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 melanoma 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.

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