A PHASE I/II STUDY OF THE ONCOLYTIC PEPTIDE LTX-315 COMBINED WITH CHECKPOINT INHIBITION GENERATES DE NOVO T-CELL RESPONSES AND CLINICAL BENEFIT IN PATIENTS WITH ADVANCED SOLID TUMORS.

3094

JAMES SPICER[1], AURELIEN MARABELLE[2], JEAN-FRANCOIS BAURAIN[3], AHMAD AWADA[4], REBECCA KRISTELEIT[5], DAG ERIK JØSSANG[6], NINA LOUIS JEBSEN[7], DELPHINE LOIRAT[8], PAAL F. BRUNSVIG[9], ANNE ARMSTRONG[10], GIUSEPPE CURIGLIANO[11], BERIT NICOLAISEN[12], HAMINA PATEL[12], ANDREW SAUNDERS[12], BALDUR SVEINBJØRNSSON[12], VIBEKE SUNDVOLD GJERSTAD[12], JÉRÔME GALON[13], FABIENNE HERMITTE[14], AND ØYSTEIN REKDAL[12]

[1]KING'S COLLEGE LONDON, GUY'S HOSPITAL, UK,
[2]GUSTAVE ROUSSY, VILLEJUIF, FRANCE,
[3]S KING ALBERT II INSITUTE, CUSL, UNIVERSITÉ CATHOLIQUE DE LOUVAIN, BELGIUM,
[4]INSTITUT JULES BORDET, UNIVERSITÉ LIBRE DE BRUXELLES, BELGIUM,
[5]UNIVERSITY COLLEGE LONDON HOSPITAL, UK,
[6]HAUKELAND UNIVERSITY HOSPITAL, NORWAY,
[7]CENTRE FOR CANCER BIOMARKERS, UNIVERSITY OF BERGEN, NORWAY,
[8]INSTITUT CURIE, PARIS, FRANCE,
[9]OSLO UNIVERSITY HOSPITAL, NORWAY,
[10]CHRISTIE HOSPITAL, MANCHESTER, UK,
[11]ISTITUTO EUROPEO DI ONCOLOGIA,
[12]LYTIX BIOPHARMA, NORWAY,
[13]LABORATORY OF INTEGRATIVE CANCER IMMUNOLOGY, PARIS, FRANCE
[14]HALIODX, MARSEILLE, FRANCE

Background

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

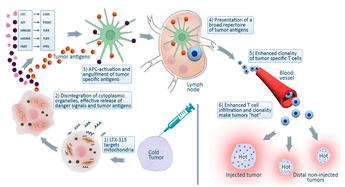
Pre-clinical studies of LTX-315 demonstrate:

- 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 immunesuppressive 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 monotherapy or in combination with either ipilimumab or pembrolizumab in patients with transdermally accessible tumors
- Determine the recommended phase II dose and schedule

LTX-315's Unique Mode of Action Results in Effective Release of Potent Immunostimulants and Antigens



Study Design

Monotherapy with LTX-315 with single and multiple lesion injection (Arm A & B)
Combination of LTX-315 with ipilimumab (melanoma/TNBC) (Arm C) and pembrolizumab (TNBC) (Arm D)

Primary Endpoint

- Safety and tolerability (including DLTs and AEs)

Secondary Endpoints

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

Patient Population

- Advanced/metastatic disease all tumor types)
- At least one transdermally accessible lesion of 1-3 cm in diameter

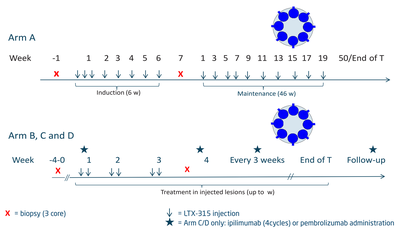
Inclusion Criteria

- Histologically confirmed advanced/metastatic disease (all tumors).
- At least one transdermally accessible lesion (in/close to the skin) which is between 1 and 3 cm in diameter.
- ECOG Performance status (PS): 0 - 1.
- No expectation of other anti-tumor therapy during the treatment period
- Unresectable/metastatic melanoma and have received at least 1 prior line of anti PD-1 treatment (Arm C)
- Unresectable/metastatic triple negative breast cancer who are PD-1 naïve (Arm D)

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

Dosing Schedule



Patient Characteristics and Disposition

	Monotherapy (N=39)		Combination Therapy (N=26)	
Lines of prior treatments (Patients may have had more than one type of treatment within a single line of regimen)	≤ 3 lines	> 3 lines	≤ 3 lines	> 3 lines
Chemotherapy	20	11	8	11
Immunotherapy	16	1	12	-
Hormonal	-	3	5	-
Other	8	2	7	-
Radiotherapy	30		22	-
Median number of weeks of treatment	3		3	
Median duration of exposure (days)	40		16	
Median total dose exposure (mg)	71		54	
Tumour Type:				
Breast	26			
Melanoma	17			
Head and Neck	6			
Sarcoma and connective tissue	3			
Other	12			

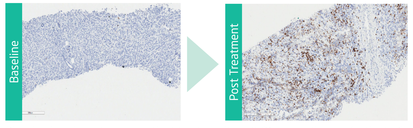
Treatment Emergent LTX-315 Related Adverse Events

- LTX-315 is well tolerated with manageable toxicities
- Total LTX-315 related toxicities: 54% <grade 3; 17.5% ≥ grade 3

	Monotherapy (N=39)		Combination Therapy (N=26)	
LTX-315 related toxicity (≥ 5%)	**Grade 1/2* No. of pts (%)**	**≥Grade 3* No. of pts (%)**	**Grade 1/2* No. of pts (%)**	**≥Grade 3* No. of pts (%)**
Hypotension	16 (43%)	-	3 (12%)	-
Flushing	13 (35%)	-	7 (27%)	-
Anaphylaxis	3 (8%)	3 (8%)	2 (8%)	-
Tachycardia	4 (10%)	-	-	-
Hypersensitivity	3 (8%)	-	5 (19%)	-
Injection site reactions (pain, erythema, rash)	13 (35%)	-	20 (77%)	2 (8%)
Fatigue and influenza like illness	8 (22%)	-	3 (12%)	-
Generalised Rash	14 (38%)	-	5 (19%)	-
Diarrhoea, nausea and vomiting	6 (16%)	-	2 (8%)	-

Response in Injected Lesions

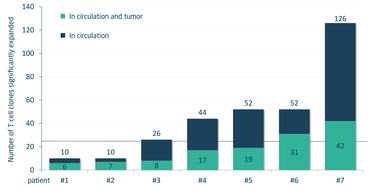
Treatment	No of patients with biopsies evaluable for CD8 IHC to date	No of patients with increased CD8+ TILs in post treatment tumors
LTX-315 monotherapy, arm A + B	22	18 (81%)
LTX-315 + ipilumumab, arm C	2	1 (50%)
LTX-315 + pembrolizumab, arm D	4	4 (100%)



Biopsies from breast cancer patient treated with LTX-315 monotherapy (patient #6)

MONOTHERAPY

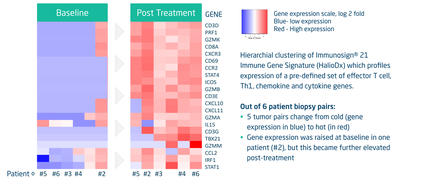
LTX-315 Expands T Cells in Circulation



Significant increase (>25%) in number of expanded T cell clones in the blood in 5 out of 7 patients.

MONOTHERAPY

LTX-315 Upregulates Key Genes Involved in Tumor Regression



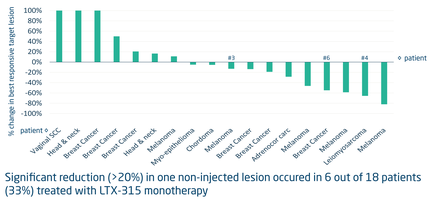
Hierarchial clustering of Immunosign® 21 Immune Gene Signature (HalioDx) which profiles expression of a pre-defined set of effector T cell, Th1, chemokine and cytokine genes.

Out of 6 patient biopsy pairs:

- 5 tumor pairs change from cold (gene expression in blue) to hot (in red)
- Gene expression was raised at baseline in one patient (#2), but this became further elevated post-treatment

MONOTHERAPY

Response in Non-Injected Lesions



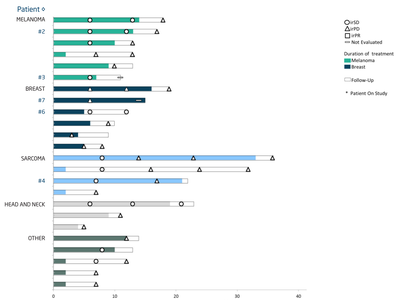
Significant reduction (>20%) in one non-injected lesion occured in 6 out of 18 patients (33%) treated with LTX-315 monotherapy

LTX-315 Efficacy (BOR)

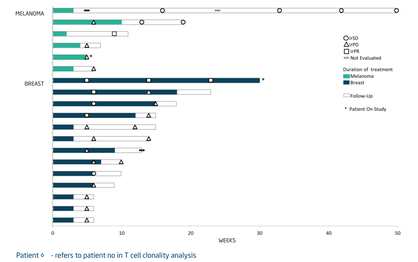
irRC > week 7	Monotherapy, Arm A + B N=24	LTX-315 + ipilimumab N=6	LTX-315 + pembrolizumab N=13
PR	0	1 (17%)	2 (15%)
SD	11 (46%)	2 (33%)	3 (23%)
CR	0	0	0

Time on Treatment, with Immune-Related Response

LTX-315 Monotherapy



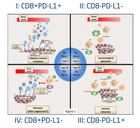
LTX-315 + ipilimumab (Melanoma)/pembrolizumab (TNBC)



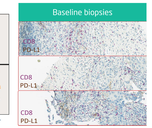
Patient ◇ - refers to patient no in T cell clonality analysis

CASE STUDY ARM D

Breast Cancer Patient Treated with LTX-315 + pembrolizumab



Mechanisms (11)
I: Adaptive resistance
II: Immune ignorance
III: Intrinsic induction
IV: Tolerance (other)



Halioseek® PD-L1/CD8 IHC assay anti-PD-L1 and anti-CD8 dual staining:

- CD8+ cell densities : 621 cells/mm2
- PD-L1+ Tumor Cells: 0%
- PD-L1+ Immune Cells Score: 1
- Proximity index between CD8+ and PD-L1+ cells: Low score at 20µm (Long Distance)

◇ CD8+ « High » Score at baseline Type IV: CD8+/PD-L1-

Post Treatment biopsies: necrotic

Patient was in Partial Response (irPR) 2 months after LTX-315 and pembrolizumab, but progressed after 4 months.

Conclusion

LTX-315:

- converts "cold" tumors to "hot" as demonstrated by gene expression analysis
- promotes infiltration of CD8+ TILs in the majority of patients
- increases the T cell repertoire
- reduces the size of non-injected lesions in several patients, indicating a systemic response
- is generally safe and tolerable; the majority of toxicities are grade 1-2 and transient, including hypotension (asymptomatic), flushing, paresthesia and rash.

These results support the rationale and potential benefit of LTX-315 as a novel intratumoral immunotherapy. A phase II combination trial is planned in 2018.

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, K. et al.; Cancer Immunol Immunother. (2014)
9. Camilio, K. et al.; Oncoimmunology (2014
10. Nestvold, J. et al.; Oncoimmunology (2017)
11. Teng MW, et al. Cancer Research (2015)

NCT 01986426

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