Intra-tumoural treatment with LTX-315, an oncolytic peptide immunotherapy, in patients with advanced metastatic disease induces infiltration of CD8 effectors T-cells and regression in some injected tumors

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Background

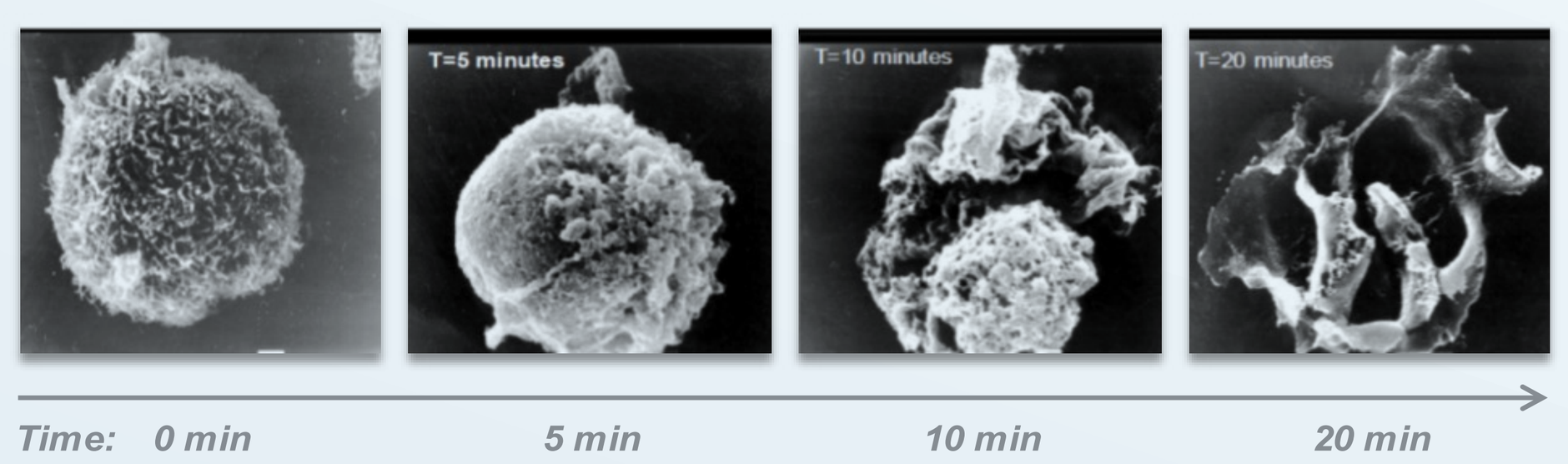
LTX-315, a first in class oncolytic peptide is developed from host defense peptides that have important functions in innate immune responses to microbial pathogens (1).

Pre-clinical studies of LTX-315 demonstrates:

- Induction of immunogenic cell death.
- Release of potent immune stimulating molecules (2).
- Destruction of intracellular organelles resulting in the release of tumour antigens (3).
- Equally activity against drug-resistant and drug-sensitive tumour cells
- Complete regression of injected and non-injected tumours (i.e. abscopal effect) (4).

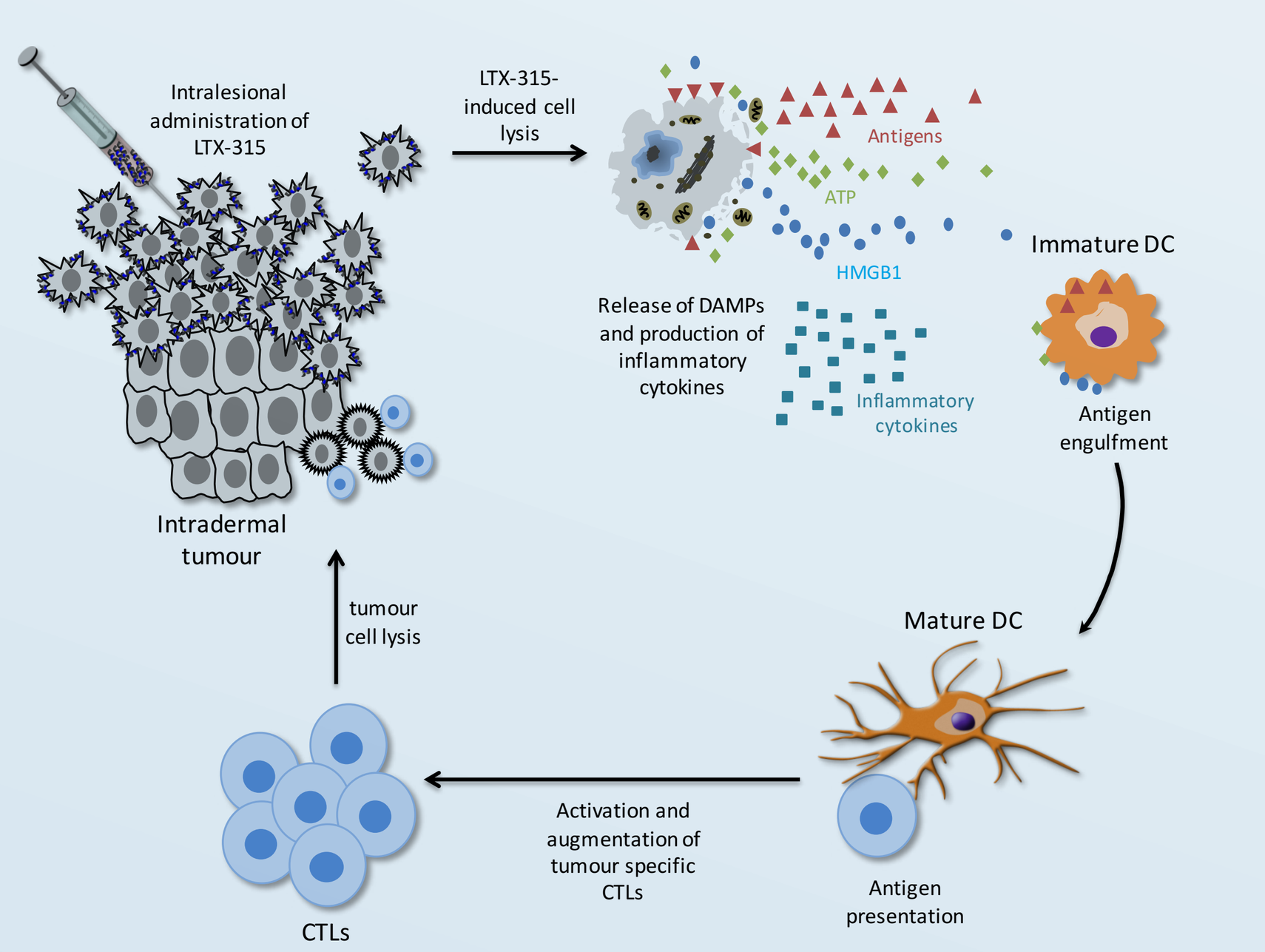
A Phase I clinical trial was initiated to evaluate the potential benefit of the oncolytic peptide LTX-315 as a novel intra-tumoural therapeutic strategy (5).

Rapid disruption of the cell membrane – Effect on Meth A sarcoma cell



LTX-315 targets both the cell membrane and intracellular membranes

Mechanism of Action of LTX-315



Aim

The aim of this study is to further evaluate safety and tolerability of intra-tumoural doses of LTX-135 and the inflammatory responses in order to determine the recommended phase II dose.

Study design

Primary Endpoints

- Safety: Dose limiting toxicities (DLT), adverse events, optimal dose and schedule
- Inflammatory markers in tumour tissue (i.e. tumour infiltrating lymphocytes)

Secondary Endpoints

- Local effects of LTX-315 in injected lesions (i.e. necrosis, inflammation)
- Immunological response of LTX-315 in peripheral blood (T lymphocytes, cytokines, CRP)
- Pharmacokinetic (PK) profile of LTX-315
- Anti-tumour activity of LTX-315 by immune-related response criteria (irRC) for measureable lesions

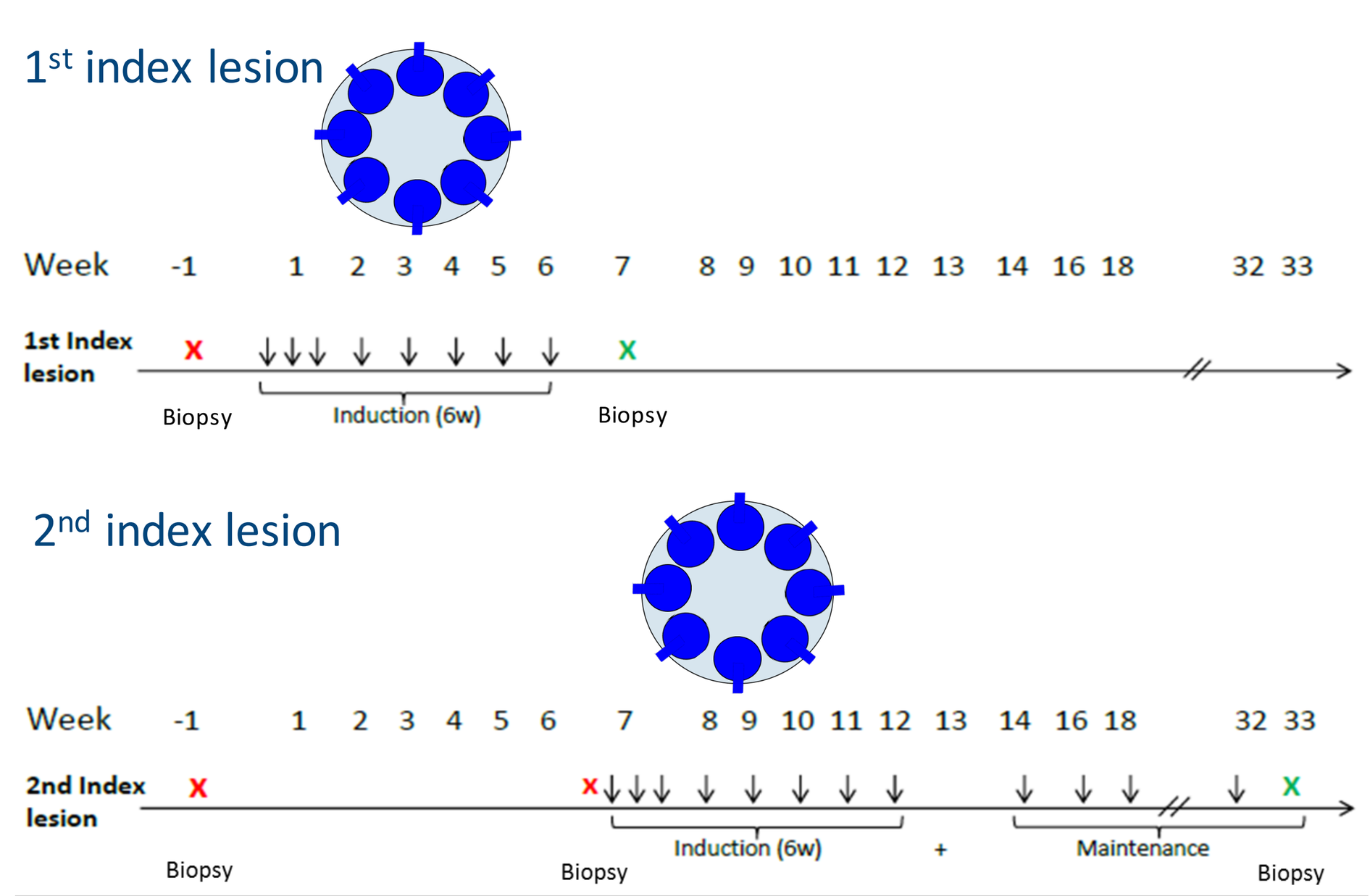
Inclusion Criteria

- Histologically confirmed advanced/metastatic disease (all tumour types)
- At least one transdermally accessible lesion of ≤ 10 cm in diameter
- ECOG Performance status (PS): 0 - 1

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

LTX-315 dosing schedule



Patient characteristics	
Median age (range)	60 (30-80)
Male: Female	4:11
tumour type (No.)	No. of patients
Breast /Melanoma/other (Chordoma; STS; Pancreas; Myo-epithelioma; Desmoid)	6/4/5
ECOG PS	No. of patients
0/1	5/10
No. of prior treatments for advanced/metastatic disease	No. of patients
Median (range)	4(0-16)
0	2
1-2	4
2-4	4
≥ 5	5
Median number of LTX-315 injections	15 (5-54)
Median number of injected lesions per patient	2(1-3)

LTX-315: Dose cohorts

Cohort	LTX-315 dose	No. of patients	LTX-315 related ≥ Grade 3 or 4	Dose-Limiting Toxicity (DLT)
1	2mg BD	3	0	0
2	3mg BD	3	0	0
3	4mg BD	3	0	0
4	4mg→5mg* QD	3	1#	0
5	4mg→6mg* QD	3¥	0	0

*4mg on day 1 only
#Grade 3 laryngeal oedema (wk 14); discontinued study treatment
¥2 patients ongoing

LTX-315 related Gr 1-2 AEs (in > 2 patients)

Adverse events (preferred term)	2mg BD (N=3)	3mg BD (N=3)	4mg BD (N=3)	4→5mg OD (N=3)	4→6mg OD (N=3)	No of patients N=15
Hypotension	1	3	3	3	1	**11**
Parasthesia	0	2	1	1	1	**5**
Flushing (or similar)	0	1	1	3	2	**7**
Rash (any)	0	3	1	1	0	**5**
Pruritis/itching	0	2	0	1	1	**4**
Sinus Tachycardia/ palpitations	0	0	0	2	0	**2**
Nausea	0	0	0	2	0	**2**
Dizziness	0	1	1	1	0	**3**
Diarrhoea	0	1	0	0	1	**2**

Preliminary efficacy in LTX-315 injected lesions

- Injected lesion SPD (sum of product of longest diameters) by ultrasound in 10 of 15 evaluable patients;18 lesions were injected in 10 pts: 2mg (4); 3mg (8); 4mg (3); 4→5mg (3)
- Complete regression: disappearance of injected lesion on U/S; Partial regression: >50% reduction in SPD on U/S; Stable size/no change: <50% decrease or <25% increase in SPD

Regression in LTX-513 injected lesions					
Response	2mg N*=4	3mg N=8	4mg N=3	4→5mg N=3	All lesions N=18
Complete Regression§	0	2	0	0	2(11%)
Partial Regression¥	0	3	1	0	4(22%)
Stable/No change	2	2	1	3	8(44%)
Progression	2	1	1	0	4(22%)

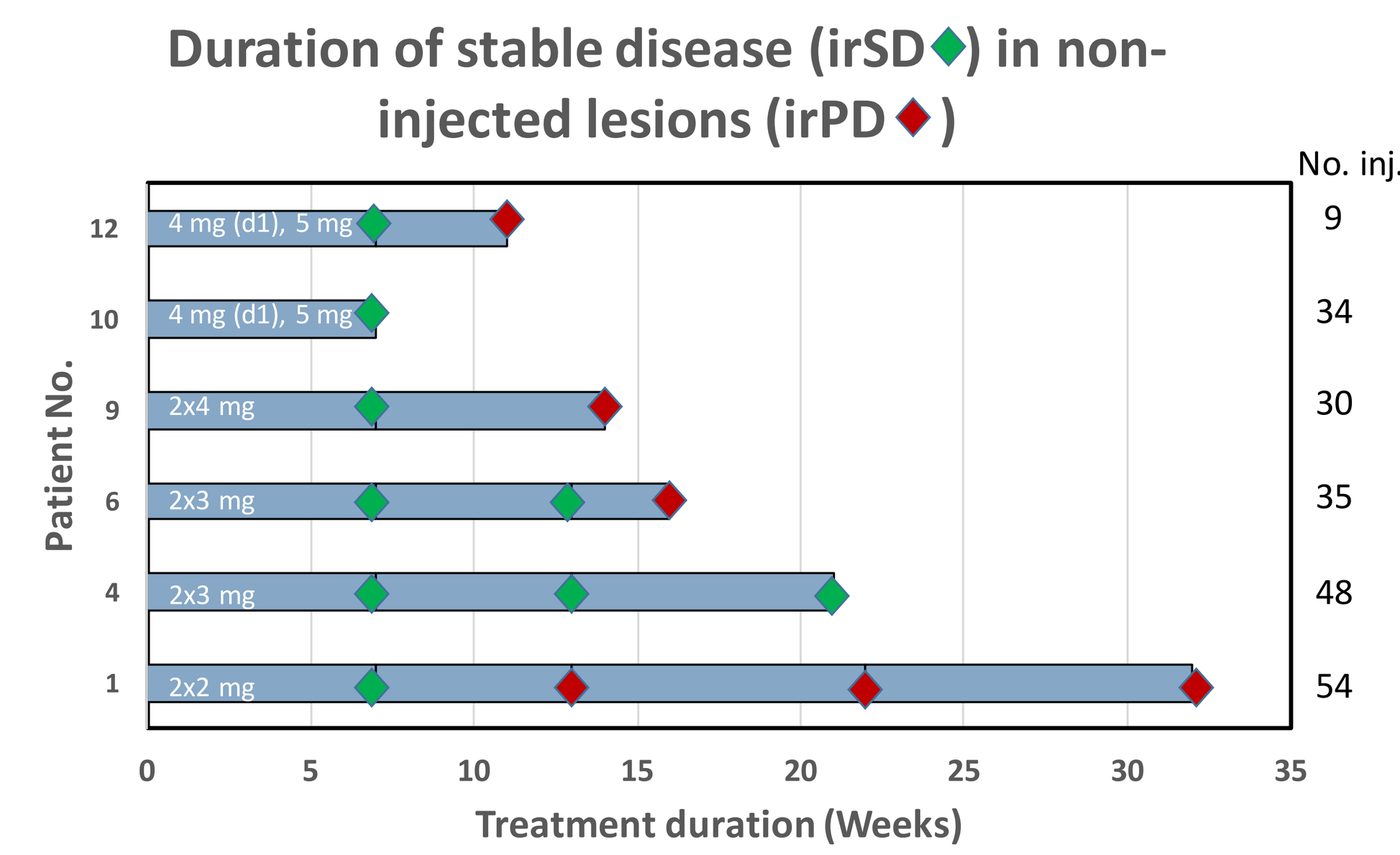
*N denotes No. of injected lesions at a given LTX-315 dose; § CR was observed in 2 of 3 lesions in a breast cancer patient; ¥ PR was observed in 4 lesions in 3 patients (Myoepithelioma, melanoma(2))

Preliminary efficacy in LTX-315 non-injected lesions

- Non-Injected lesions irRC response assessed by CTscan/MRI every 7-10 weeks (9 of 15 evaluable patients): 2mg (2pts); 3mg (3pts); 4mg (3 pts); 4→5mg (1 pt)
- No irRC response were observed to date
- SD in non-injected lesions was observed in melanoma (3), Chordoma (1), Myo-epithelioma (1) and Leiomyosarcoma (1) at any time on study
- Median duration of SD (range) was 13.5 weeks(range 7-21)

Efficacy (irRC) in LTX-315 non-injected tumour lesions					
Response	2mg N*=2	3mg N=3	4mg N=3	4→5mg N=1	All patients N=9
CR	0	0	0	0	0
PR	0	0	0	0	0
SD	1	2	2	1	6 (67 %)
PD	1	1	1	0	3 (33 %)

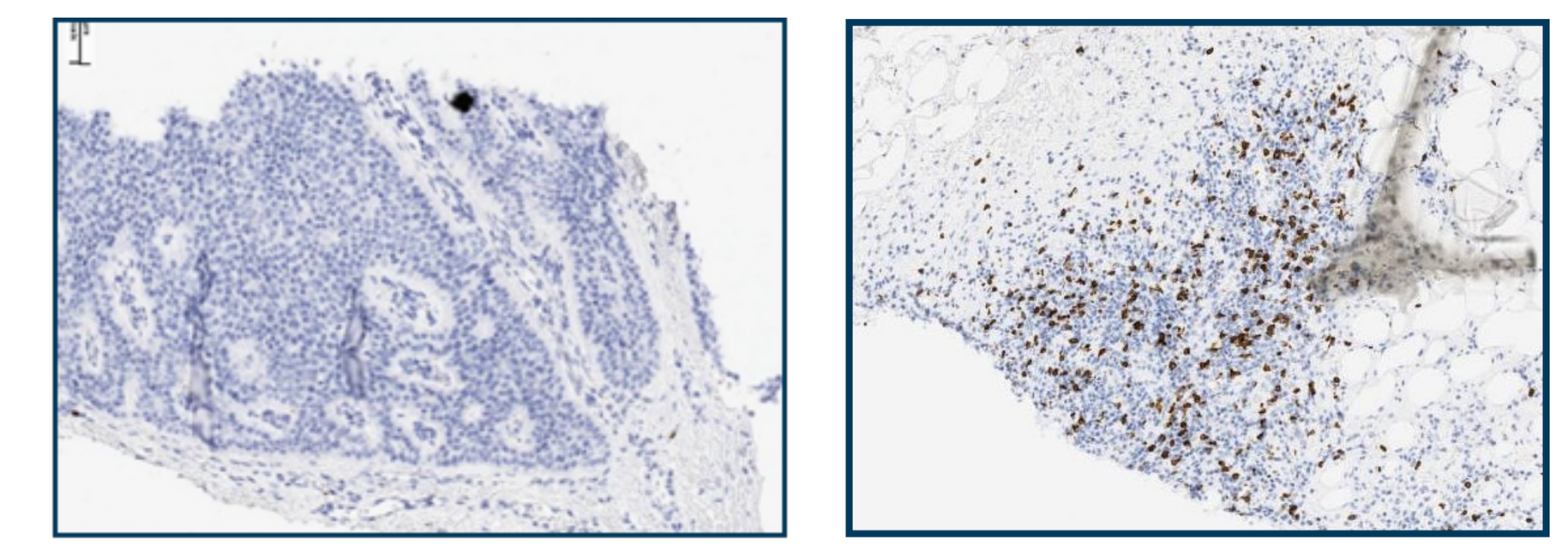
*N denotes No. of patients per LTX-315 dose



Preliminary Immune responses

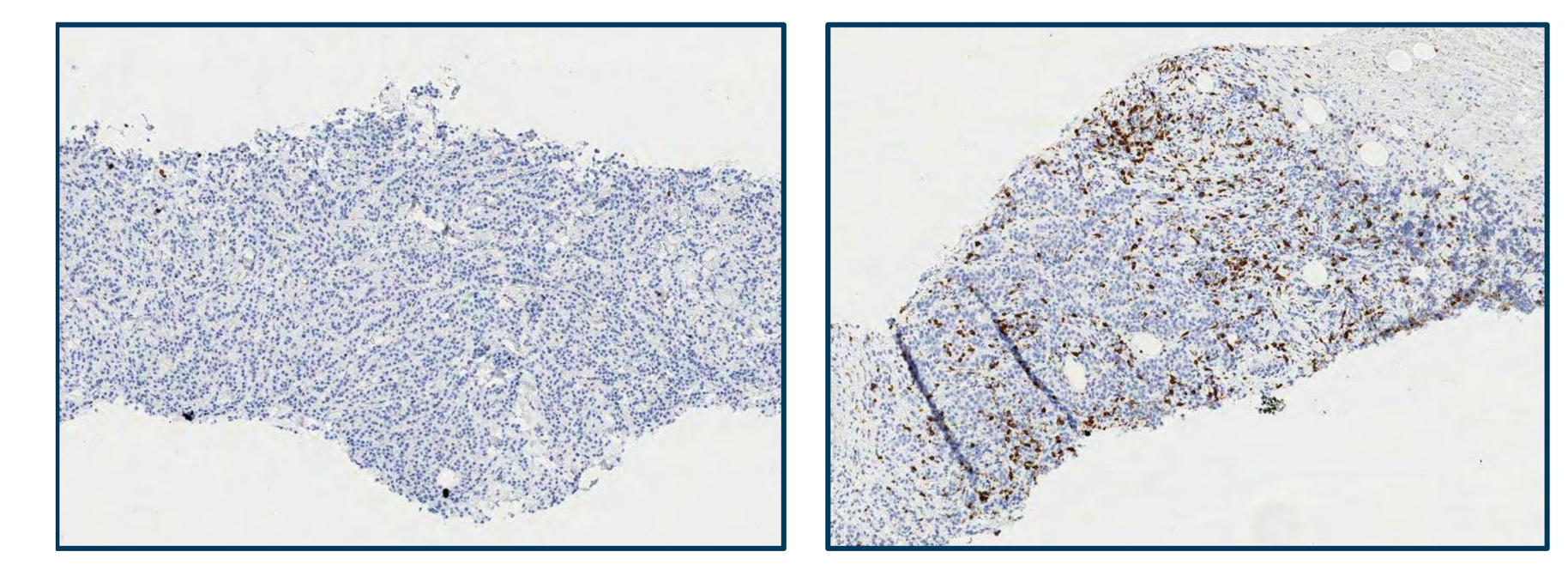
- Biopsies of injected tumours taken at baseline and after treatment (week 7 and/ or End of Treatment) were assessed in 10 patients.
- Up to 10 fold enhanced infiltration of CD8+ T-cells in injected lesions in 5 of 10 patients (50%)
  - Breast cancer (2 mg BID)
  - Myoepithelioma (3 mg BID)
  - Sarcoma (4 mg BID)
  - Desmoid tumour (4→5 mg QD)
  - Breast cancer (4→5 mg OD)

Malignant myoepithelioma patient (3mg)



Before: **Few CD8+ T cells** — **After:** **Plentiful CD8+ T cells**

Breast Cancer patient (5mg)



Before: **Few CD8+ T cells** — **After:** **Plentiful CD8+ T cells**

Overall conclusion

- This phase 1 study with LTX-315, an oncolytic peptide immunotherapy, is ongoing
- The majority of LTX-315 related AEs are transient CTCAE grade 1-2 and include hypotension, flushing, parasthesia and rash
- No Dose Limiting Toxicities (DLTs)
- Tumour necrosis and increased TILs in injected lesions in some patients (50%)
- No irRC responses were observed
- Complete (11%) and partial (22%) regression in 6 of 18 injected lesions; no change (44%) in 8 of 18 injected lesions
- Stable disease (median duration 14 weeks) in non-injected tumour lesions (by irRC) in 6 of 9 evaluable patients (67%)
- The findings support the rationale and potential benefit of LTX-315 as a novel intra-tumoural immunotherapy
- Phase I/II combination studies with LTX-315 in multiple solid tumours are planned for 2016

References

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