The oncolytic peptide LTX-315 enhances tumor-specific immune responses and tumor regression in murine 4T1 breast cancer when combined with doxorubicin

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Introduction

There is an increased focus on the combination of different treatment modalities to achieve an enhanced antitumor efficacy.

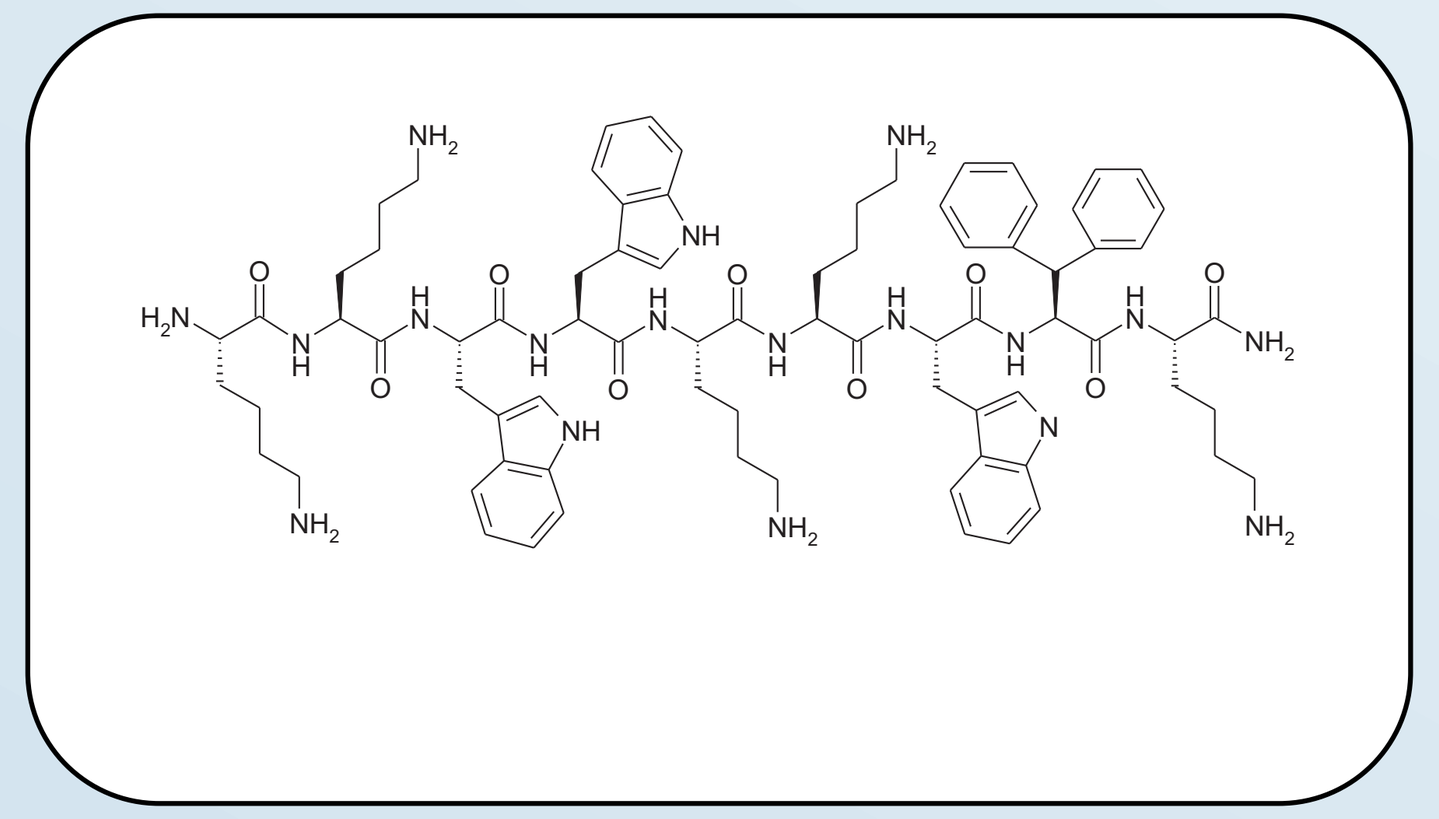
LTX-315 is a novel **oncolytic peptide** derived from the naturally occurring host defense peptide, bovine lactoferricin [1]. LTX-315 interacts electrostatically with anionic components of negatively charged cancer cell membranes as well as intracellular targets such as mitochondria, causing cellular lysis and a subsequent release of endogenous cellular content such as danger signals and tumor antigens [2-7].

Doxorubicin is a widely used chemotherapy and works by intercalating DNA. Previous studies have shown that LTX-315 in combination with low-dose cyclophosphamide demonstrated greater antitumor efficacy compared to either treatment alone in an A20 B-cell lymphoma model. Thus, we hypothesized that an enhanced antitumor effect and augmented tumor-specific immune responses could be achieved in the highly aggressive 4T1 breast cancer model when combining LTX-315 with doxorubicin.

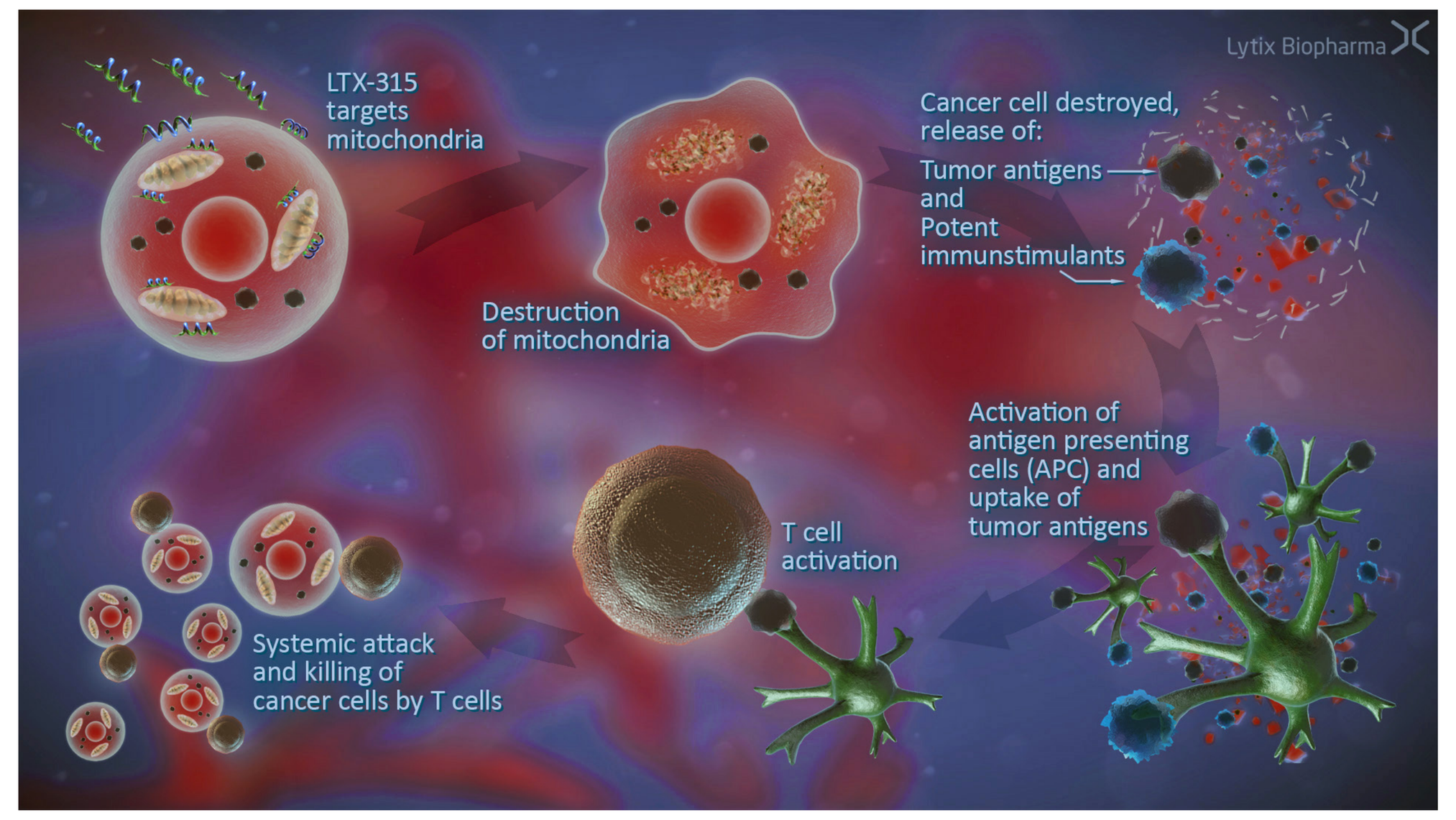
Aim

To investigate the antitumor efficacy of LTX-315 alone or in combination with doxorubicin in the murine 4T1 breast carcinoma model.

LTX-315

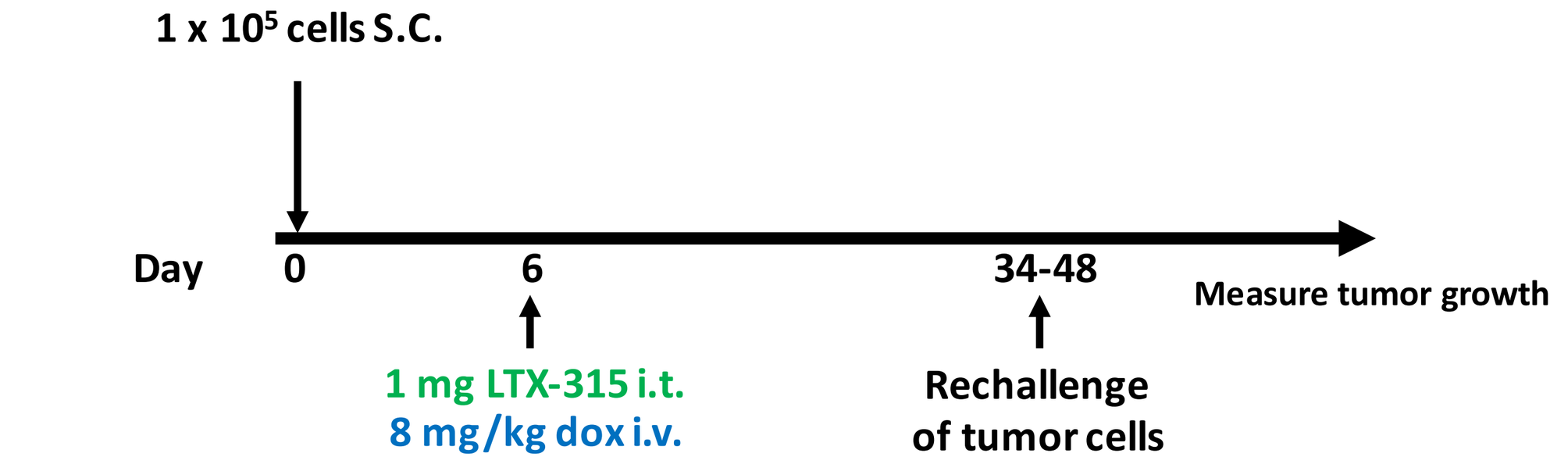


Mode of action

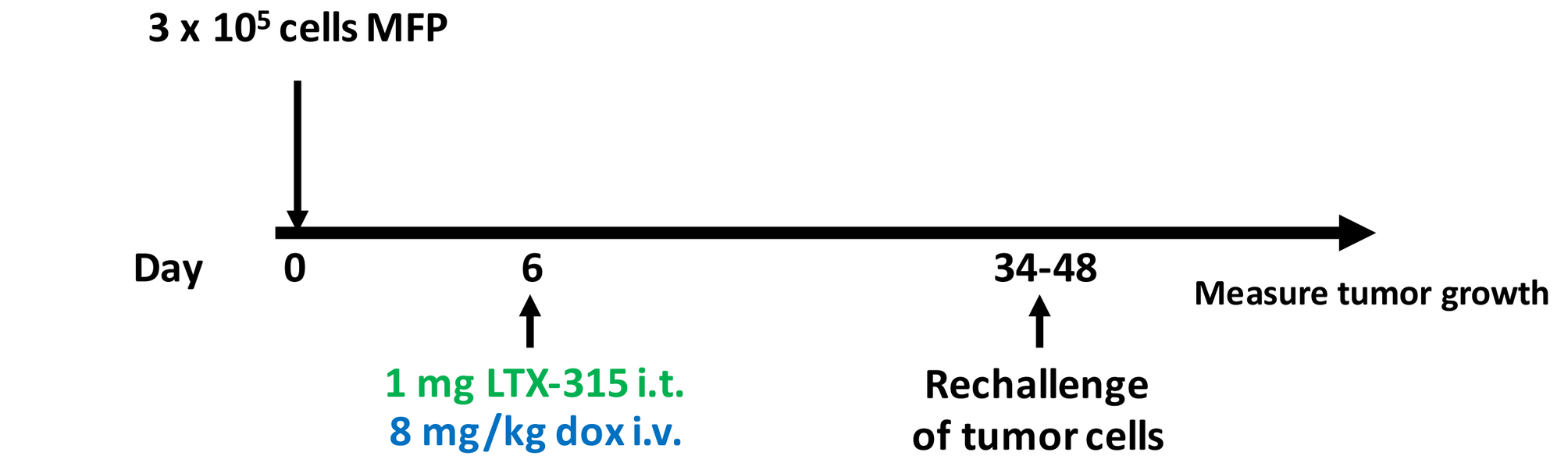

LTX-315 targets mitochondria
Destruction of mitochondria
Cancer cell destroyed, release of:
Tumor antigens and Potent immunstimulants
Activation of antigen presenting cells (APC) and uptake of tumor antigens
T cell activation
Systemic attack and killing of cancer cells by T cells

Results

Experimental setup 1



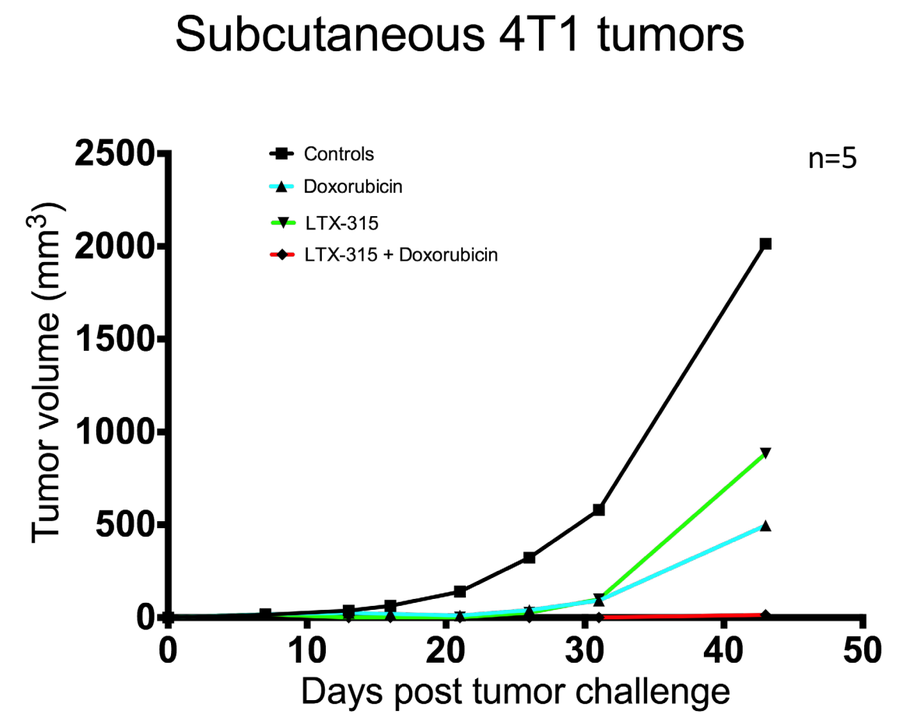
Experimental setup 2



S.C. = subcutaneously
MFP = mammary fat pad

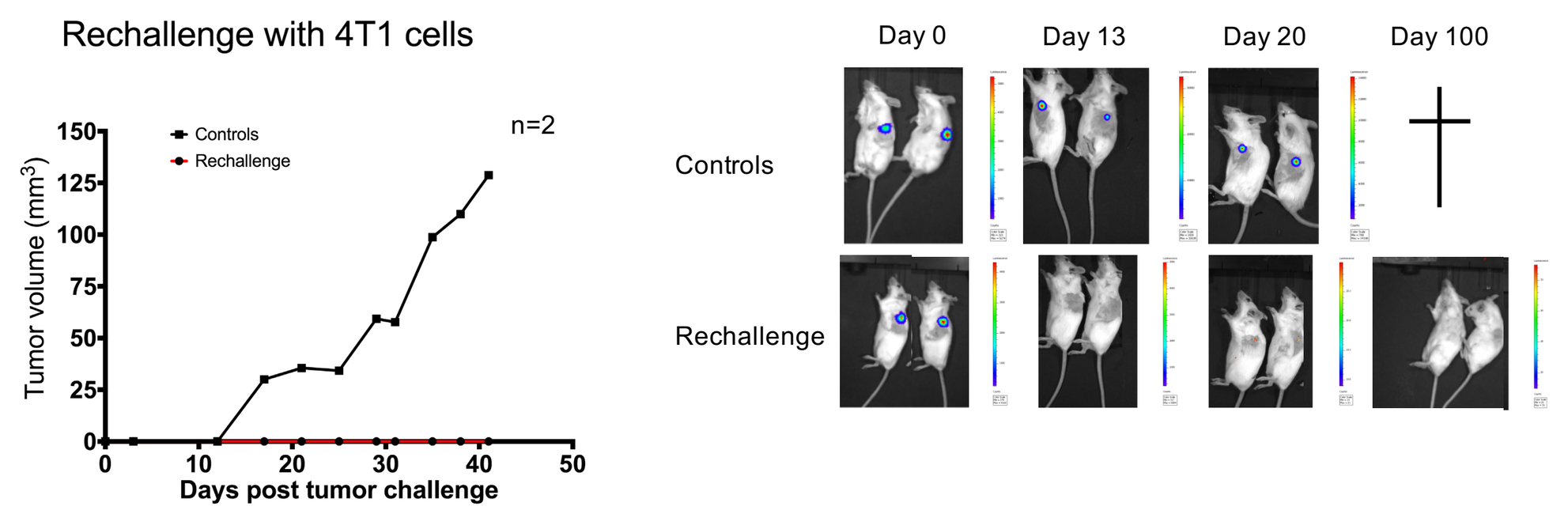
Subcutaneous model

Fig. 1 - LTX-315 induces complete regression of established 4T1 tumors when used in combination with doxorubicin



Tumor growth of subcutaneously established 4T1 tumors injected intratumorally with LTX-315 alone (1 mg/50 µl), intravenously with doxorubicin alone (8mg/kg), or with LTX-315 in combination with doxorubicin.

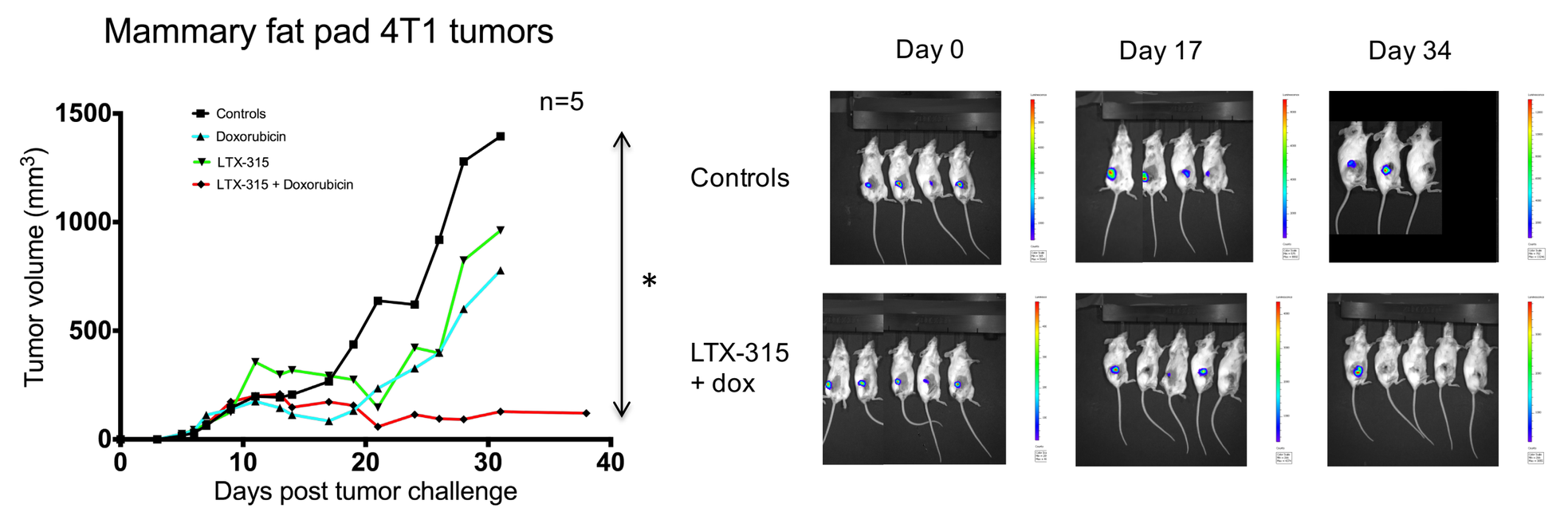
Fig. 2 - Inhibition of tumor growth in animals previously cured with LTX-315 and doxorubicin rechallenged with tumor cells



Tumor growth of rechallenged animals previously cured by LTX-315 in combination with doxorubicin compared to challenged naïve control animals (both 5 x 10^4 4T1 cells). Representative images are shown from an Xenogen IVIS® Spectrum in vivo imaging system from Caliper Life Sciences. Control animals were euthanized due to tumor burden.

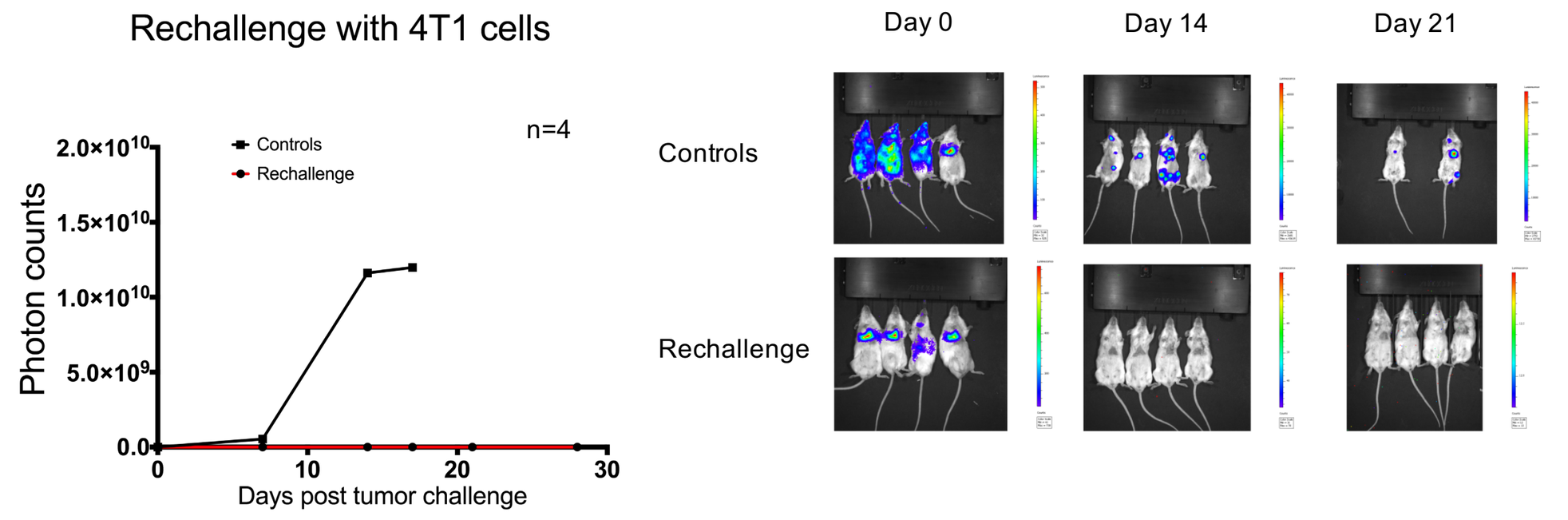
Orthotopic model

Fig. 3 - LTX-315 in combination with doxorubicin induces complete regression of orthotopic 4T1 tumors established in the mammary fat pad



Tumor growth of orthotopically established 4T1 tumors injected intratumorally with LTX-315 alone (1 mg/50 µl), intravenously with doxorubicin alone (8mg/kg), or with LTX-315 in combination with doxorubicin. * p = 0.0119. Representative images are shown from an Xenogen IVIS® Spectrum in vivo imaging system from Caliper Life Sciences. Control animals were euthanized due to tumor burden.

Fig. 4 - Animals previously cured with LTX-315 in combination with doxorubicin showed protection against tumor growth when rechallenged through left ventricular injection (LVI)



Animals with orthotopic 4T1 mammary fat pad tumors were treated with LTX-315 in combination with doxorubicin. Curves demonstrate tumor growth of cured animals rechallenged with 4T1 cells compared to naïve control animals challenged with 4T1 cells (both 1 x 10^5 cells). Representative images are shown from an Xenogen IVIS® Spectrum in vivo imaging system from Caliper Life Sciences. Control animals (50%) were euthanized on day 17 due to tumor burden.

Conclusion

- LTX-315 in combination with doxorubicin induced complete regression of both subcutaneous and orthotopic aggressive 4T1 tumors
- Animals treated with the combination therapy demonstrated protective immune responses when rechallenged with 4T1 tumor cells
- LTX-315 is currently in clinical phase 1/2a studies

References

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