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Extending trastuzumab-coated immunoliposome to HER2 negative breast cancer models: a proof of concept study

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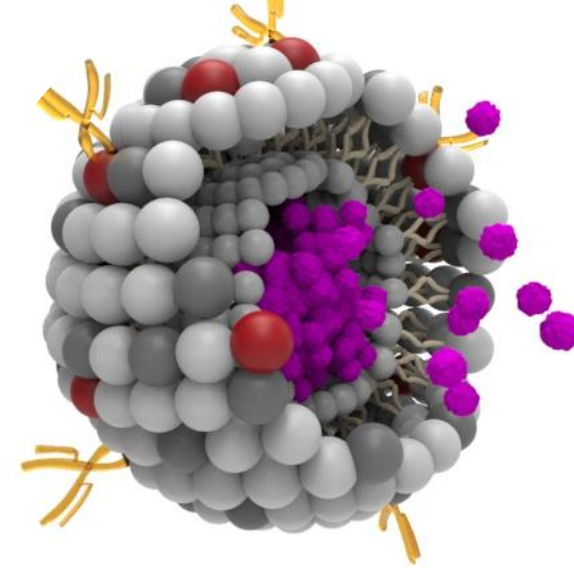
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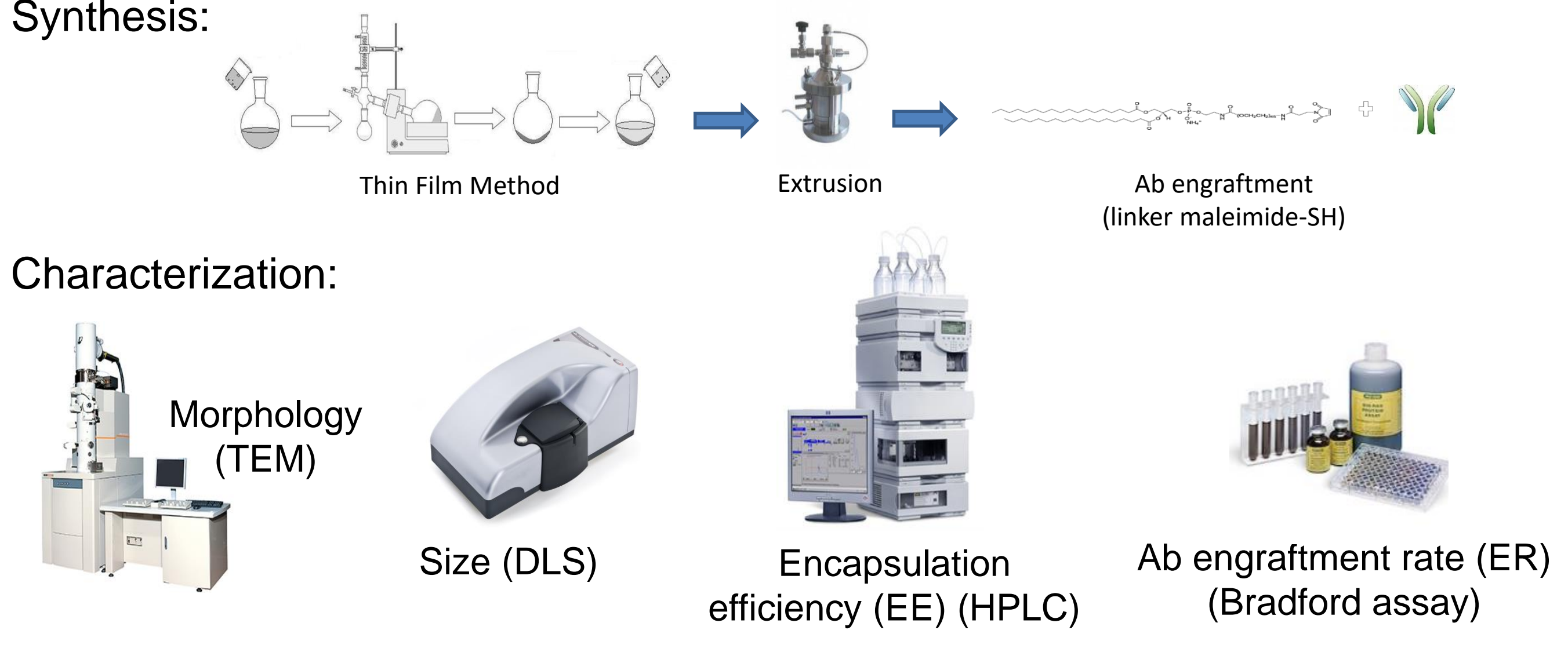
BACKGROUND

Since its first approval in 1998, the anti-Her2 monoclonal antibody (Ab) trastuzumab has considerably improved the clinical outcome of women with Her2+ breast cancer. However, only 25 % of breast cancer patients display amplification of Her2 gene and benefit from this therapy. Expanding trastuzumab indication to a wider group of patients with lower levels of Her2 has then largely been studied but was never conclusive. To potentialize trastuzumab tumor uptake and maybe overcome this limitation, we developed a docetaxel immunoliposome coated with trastuzumab.

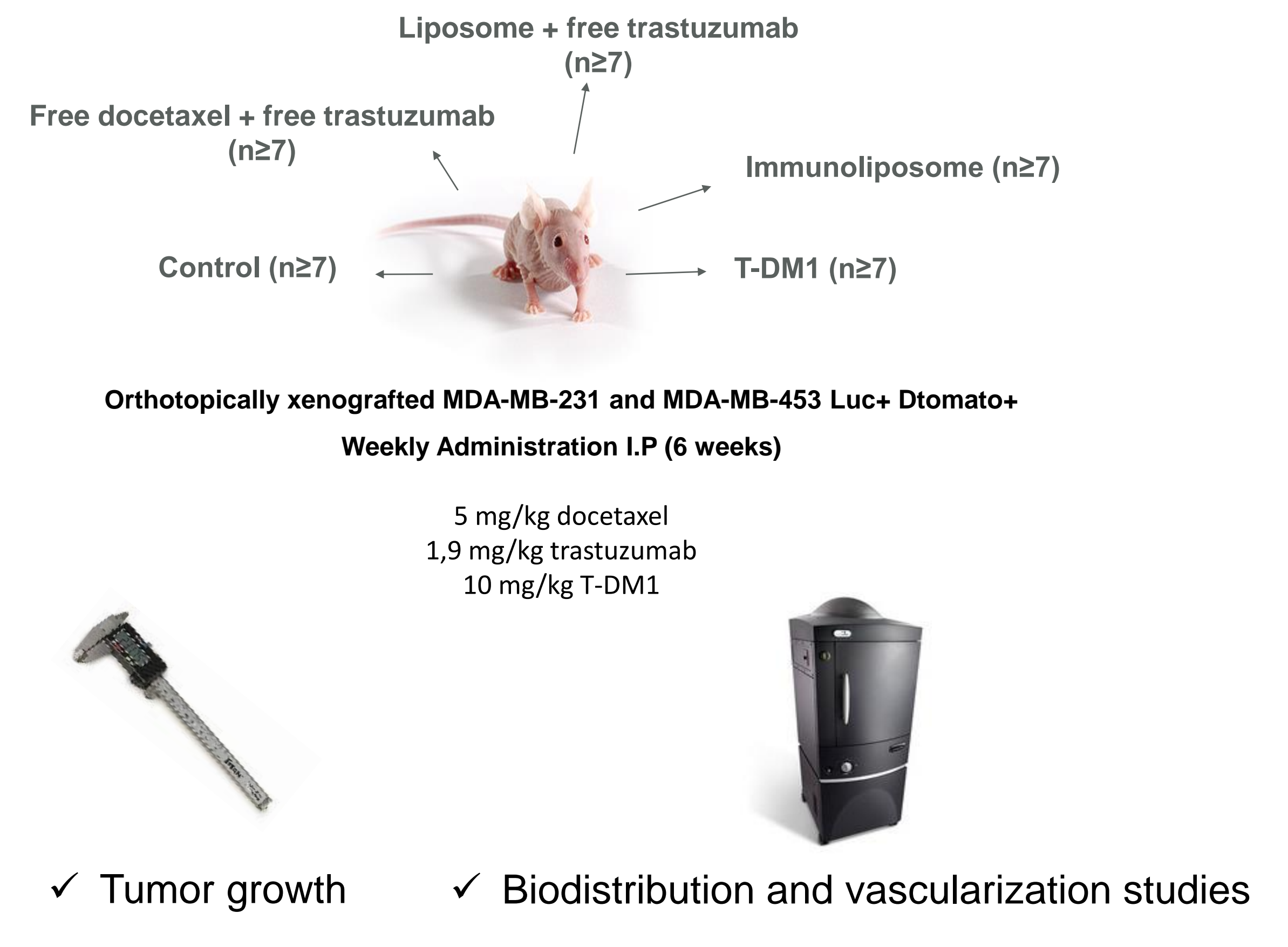


MATERIAL & METHODS

Step 1: Biopharmaceutical development of immunoliposomes



Step 3: In vivo proof of concept studies



Step 2: In vitro proof of concept studies

- ✓ Her2 expression (flow cytometry)
- ✓ Cellular uptake (confocal microscopy)
- ✓ Cell viability on monolayer cells (MTT assays)
- ✓ Cell viability on 3D spheroids (fluorescent spectrometry)

RESULTS

Step 1: Characterization of immunoliposomes

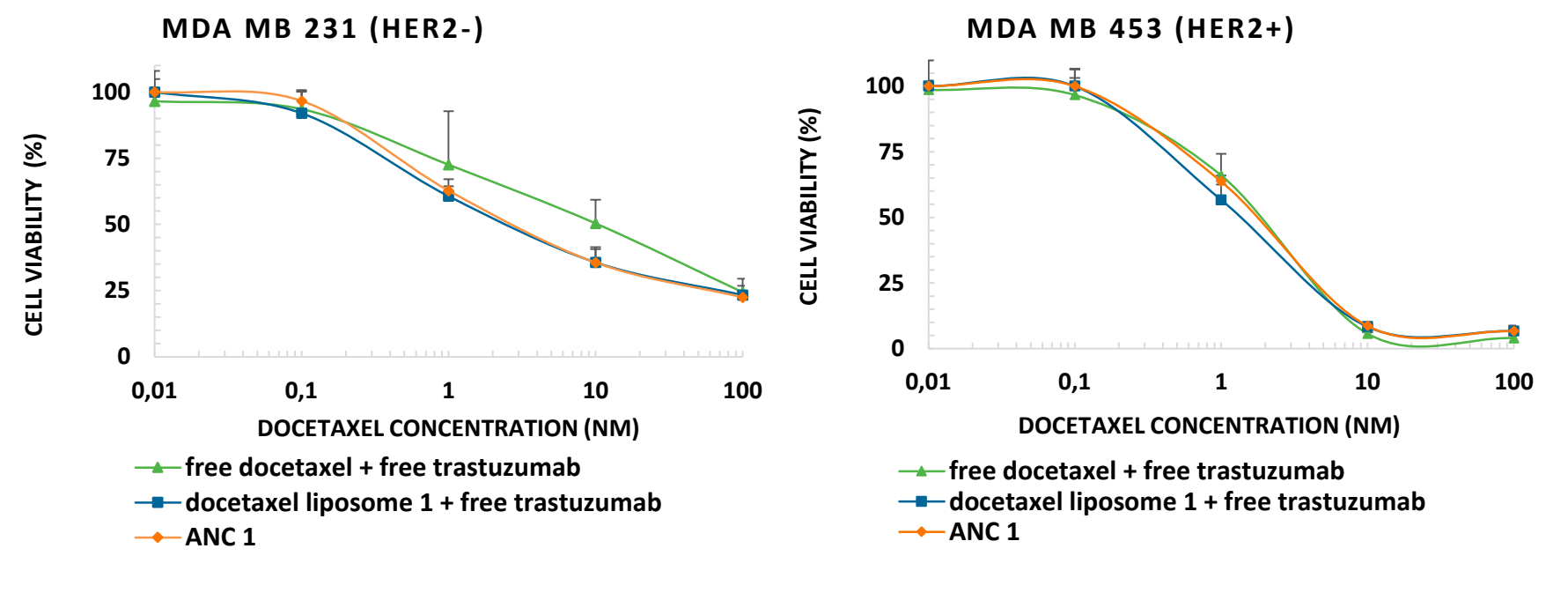
Size (nm)	PDI	Docetaxel EE (%)	Morphology	Ab ER (%)	Stability
140 ± 3	< 0.2	> 90		30 ± 6	One week

Step 2: In vitro proof of concept studies

✓ Her2 expression: MDA-MB-231 (5 300 ± 350 Her2/cell), MDA-MB-453 (215 500 ± 37 900 Her2/cell)

✓ Cellular uptake: Confocal microscopy images showing red fluorescence in MDA-MB-231 and MDA-MB-453 cells.

Cell viability on monolayer cells



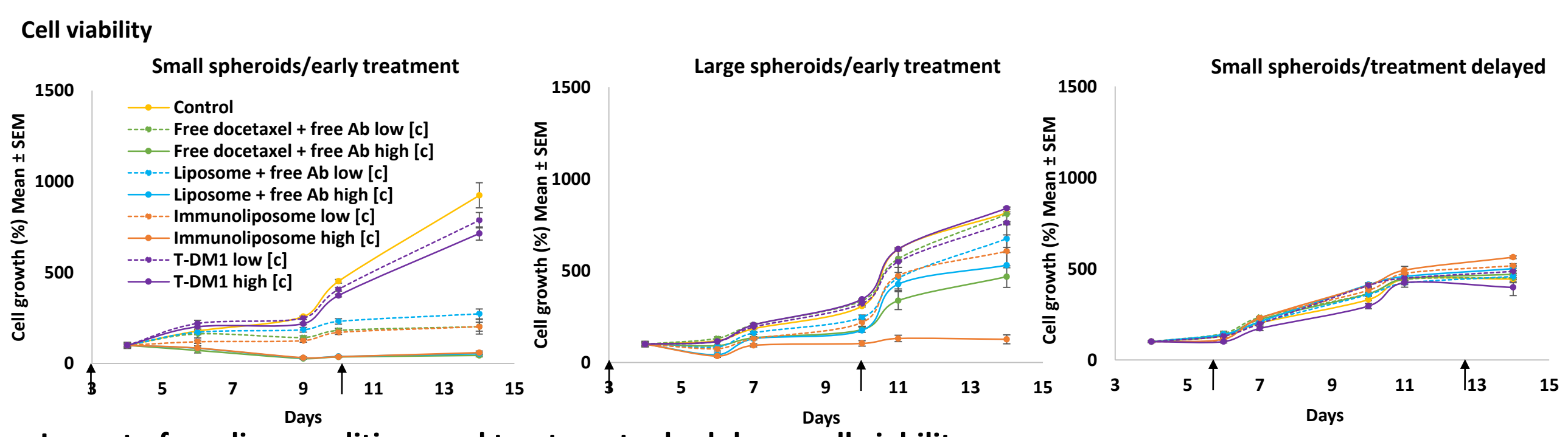
-> Equal or higher *in vitro* efficacy was found for liposomal formulations when compared to standard drugs

Cell viability on 3D spheroids: MDA-MB-453 (similar results on MDA-MB-231)

Spheroids monitoring: Control, Free drugs, Liposome, Immunoliposome, T-DM1

Beginning of study:

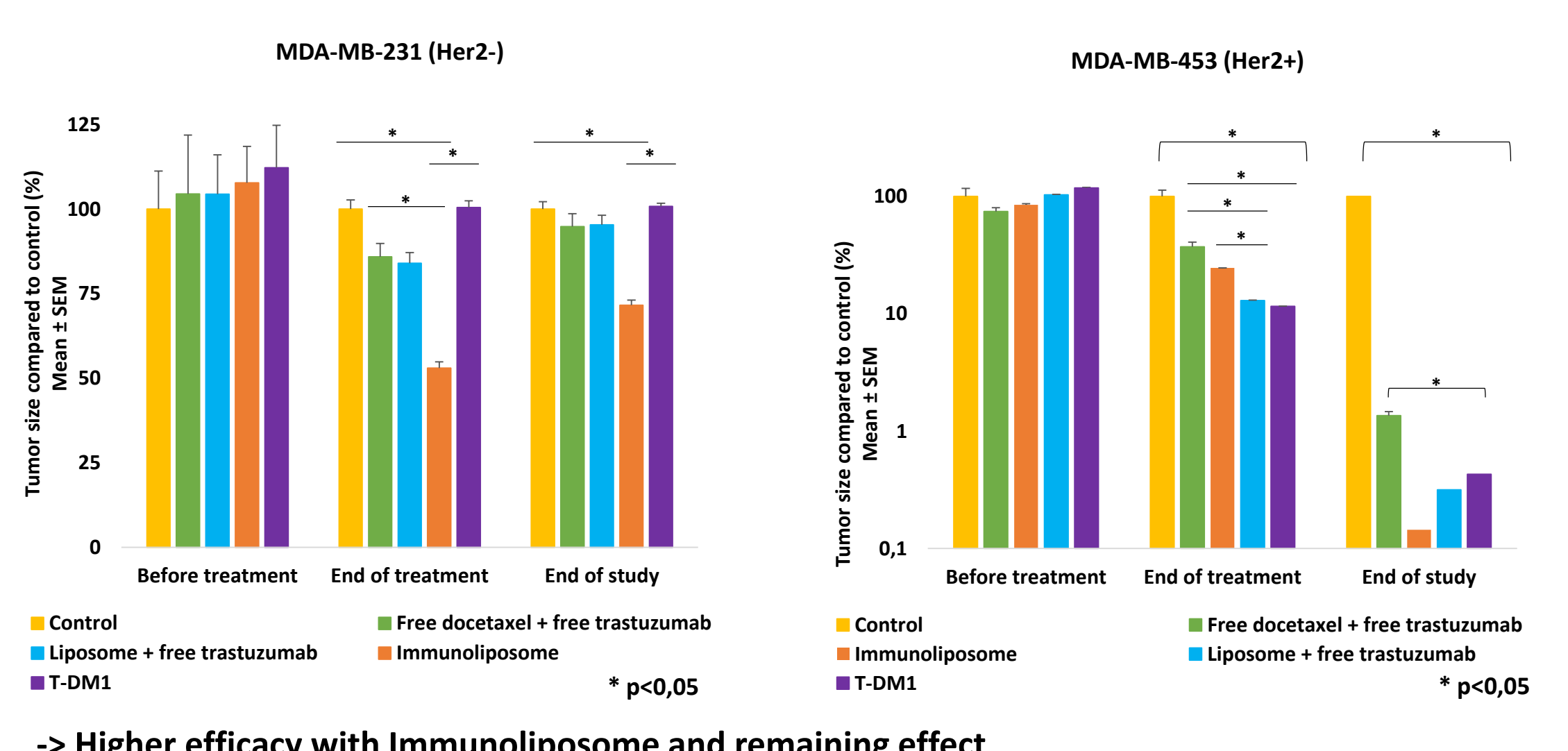
End of study:



-> Impact of seeding conditions and treatment schedule on cell viability
-> No effect of T-DM1
-> Higher antiproliferative effect with Immunoliposome

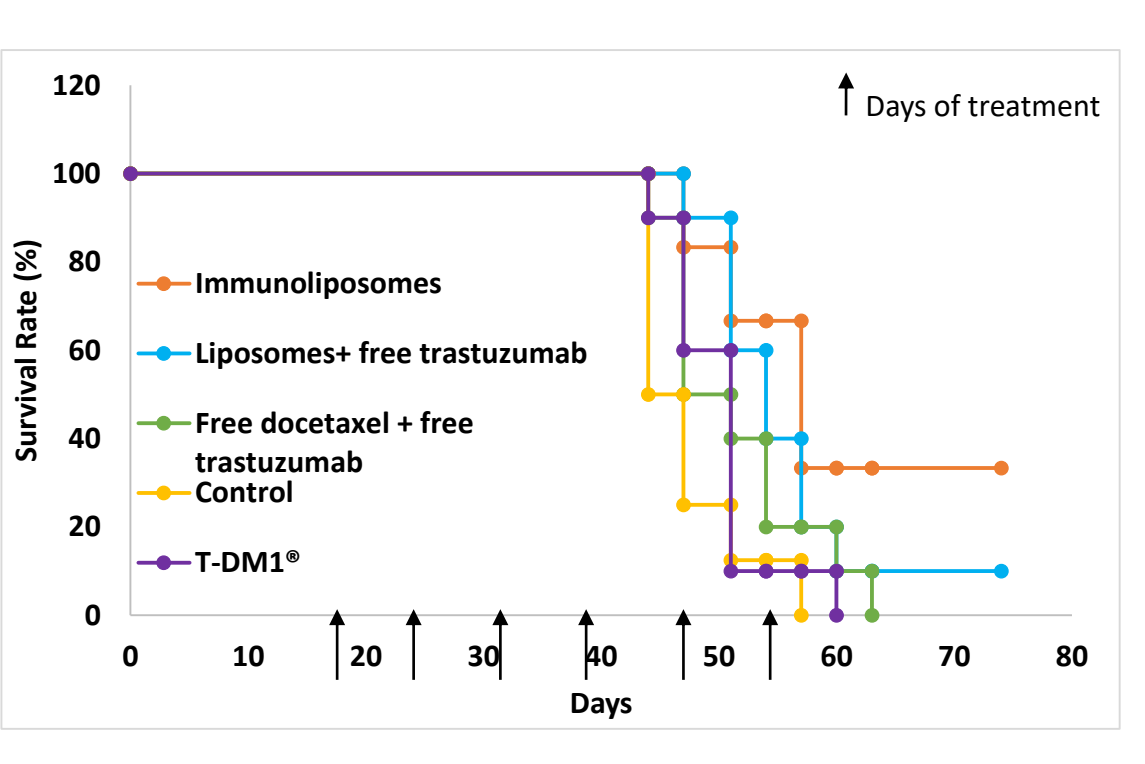
Step 3: In vivo proof of concept studies

✓ Tumor growth



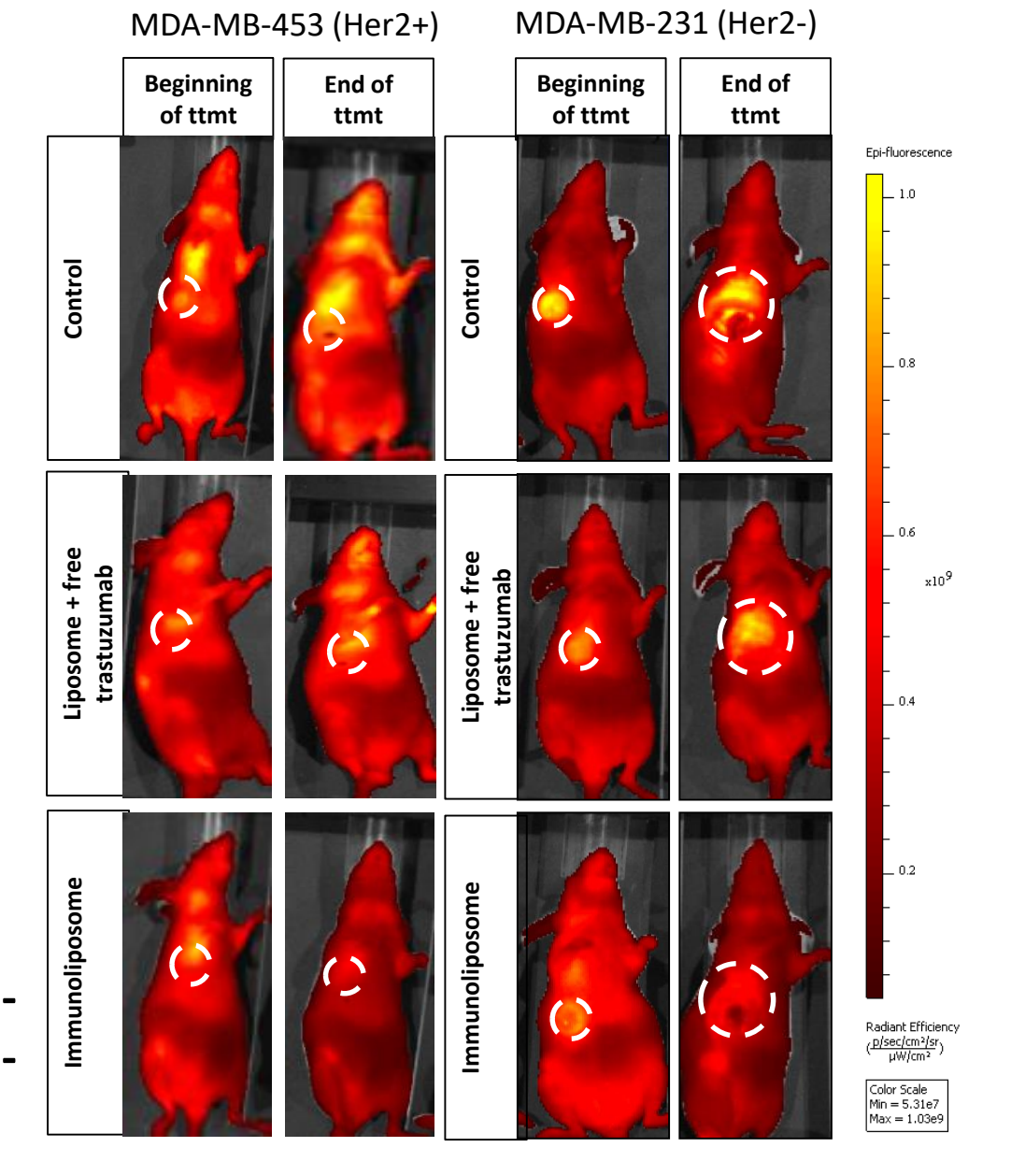
-> Higher efficacy with Immunoliposome and remaining effect
-> No effect of T-DM1 on Her2- cells

✓ Survival studies



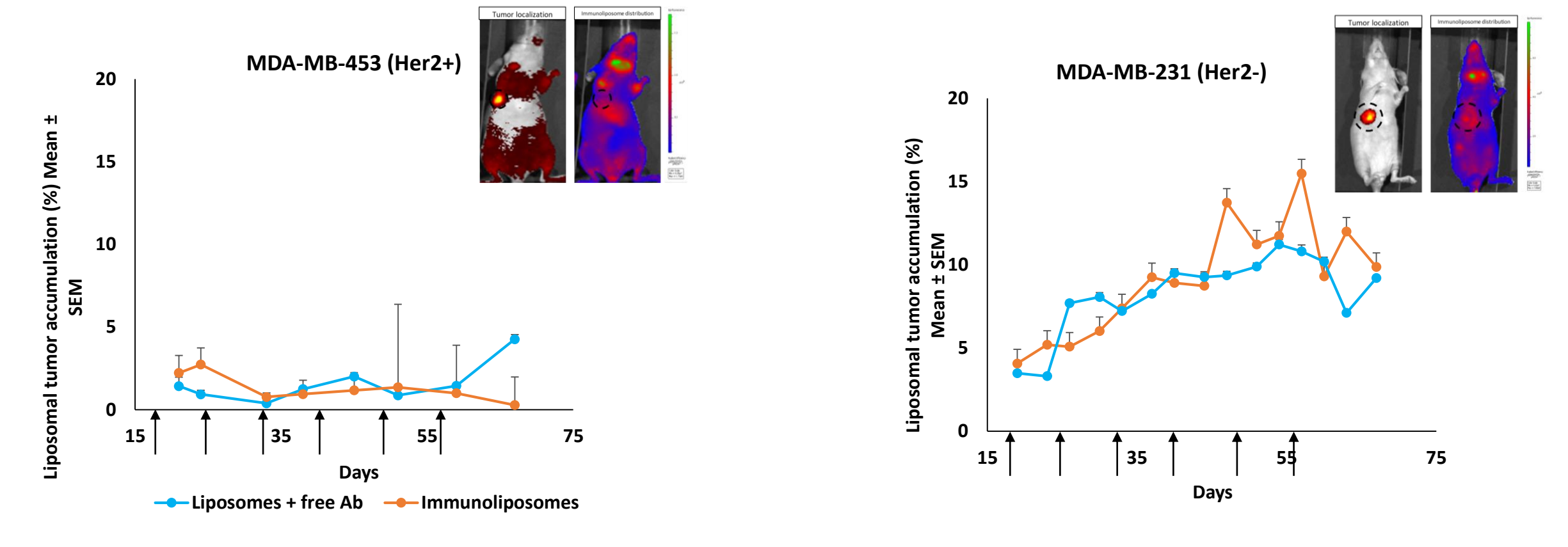
-> Mean survival was not reach for MDA-MB-453 xenografted mice
-> Survival was 22 % longer with Immunoliposome

✓ Vascularization studies



Vascular density increased in time <-
Vascular density/Immunoliposome tumor uptake <-

✓ Biodistribution studies



-> No difference in tumor uptake between Liposome and Immunoliposome
-> Intratumor accumulation was 3 % and 15 %
-> Intratumor accumulation was independent to Her2 expression

CONCLUSION & PERSPECTIVES

- ✓ **Conclusions**
 - Feasibility of making 3rd generation liposomes, fitting optimal characteristics.
 - Immunoliposome achieved higher antiproliferative effect on 2D and 3D cell models.
 - Optimized biodistribution profile, leading to higher *in vivo* efficacy with Immunoliposome.
 - Her2 expression and especially vascular density dependent tumor uptake, demonstrating the interest of such nanoparticle in triple negative breast cancer.

- ✓ **Perspectives**
 - Pharmacokinetic studies: plasmatic and intratumor docetaxel dosing
 - Optimization of *in vitro* models (co-cultured spheroids and organoids)
 - Confirmation of Immunoliposome advantages on a second Her2- model (MCF7)
- ✓ **References**
Rodallec *et al.* Int. J. Nanomedicine, 2018