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Mélicandré Gomot, Nora Essakhi, Clément Codan, Quentin Pascal, Dmitry Klokov, et al. The inducible KPC:APC mouse model for studying colon carcinogenesis in vivo and ex vivo. EACR 2024 Congress: Innovative Cancer Science, Jun 2024, Rotterdam, Netherlands. irsn-04730239

HAL Id: irsn-04730239

<https://irsn.hal.science/irsn-04730239v1>

Submitted on 10 Oct 2024

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The inducible KPC:APC mouse model for studying colon carcinogenesis *in vivo* and *ex vivo*

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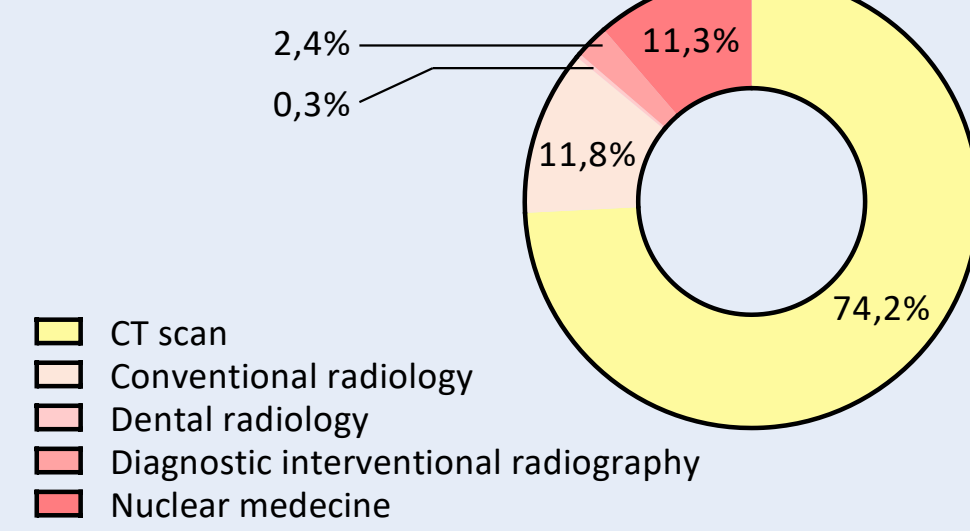
Introduction

Ionizing radiation in medical diagnostic

Origins of the collective effective dose attributable to the diagnostic medical imaging sector

Each day 500 000 CT-scans are performed worldwide, and this number is on the rise¹.

Abdominal and pelvic CT-scans have the highest LAR (Lifetime Attributable Risk) of solid cancer. They deliver 8–31 mGy per scan on average^{2,3}. An increasing number of patients are exposed to doses >100 mSv.¹



Ionizing radiation and colon cancer

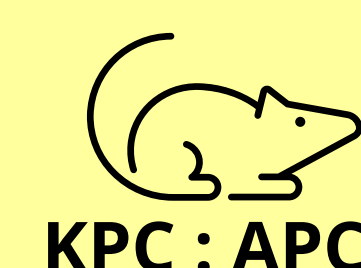
Epidemiological studies show an increased risk of colorectal cancer after low doses X-rays medical exposures but benefits still outweigh the risks.⁴

LDR increase tumor multiplicity and interact with carcinogenesis-related pathways through gene expression modulation, DNA hypomethylation or protein interactions.^{5,6,7}

The *Apc*^{min} mouse strain is one of the most employed model in colon cancer research. However, its limitations make it inadequate for our study. Therefore, more suitable models are needed.

Objectives → To develop and characterize suitable models to study the cellular and molecular effects of low doses of ionizing radiation (in the context of medical diagnostic) on colon carcinogenesis.

Methods



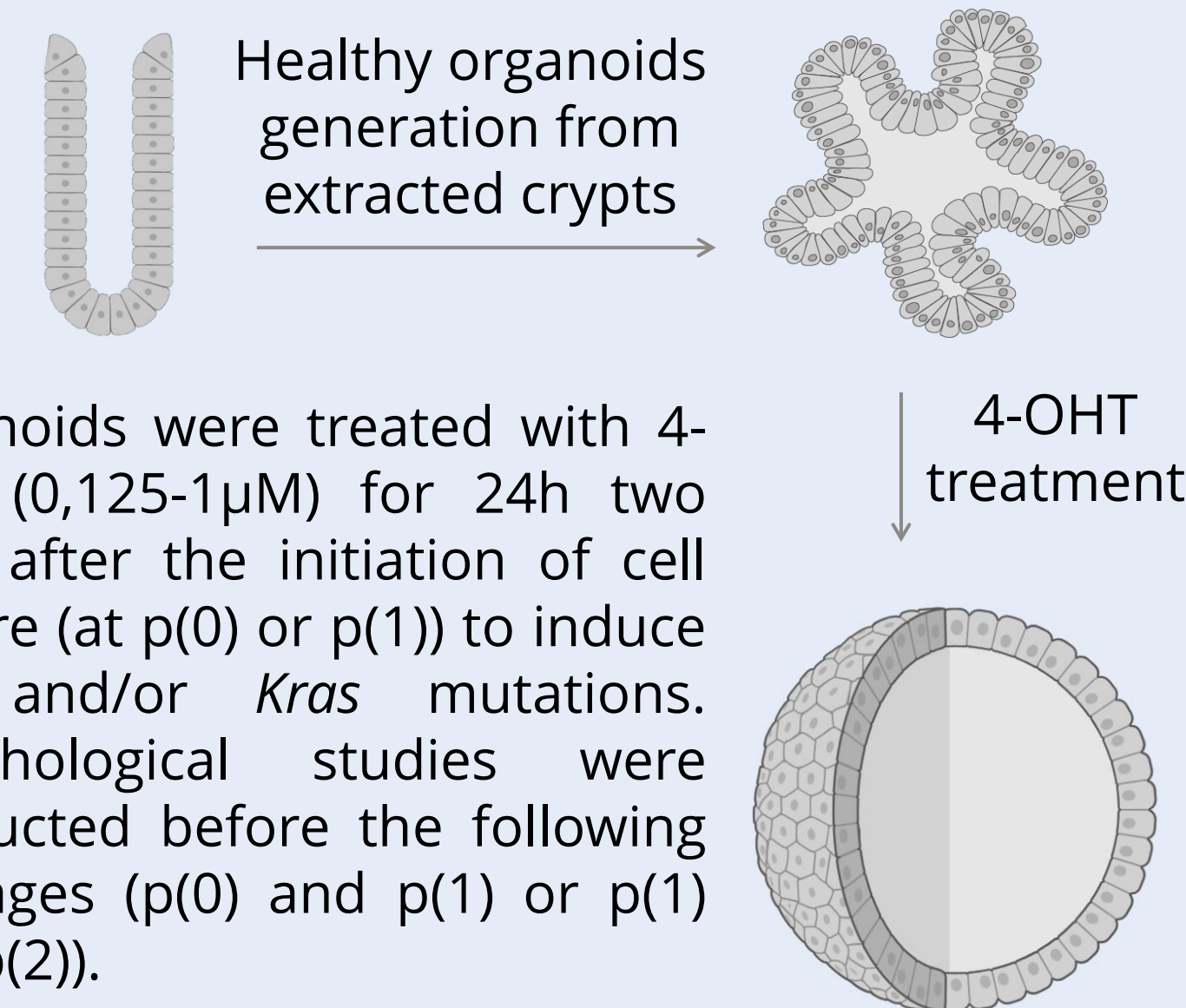
Inducible colon cancer mouse model

B6.Cg-*Kras*^{tm4Tyj} *Apc*^{tm1Tno} Tg(CD2-cre/ERT2)752Erf/Marj⁸

- o CreLox system
- o Control by the CD2 promoter

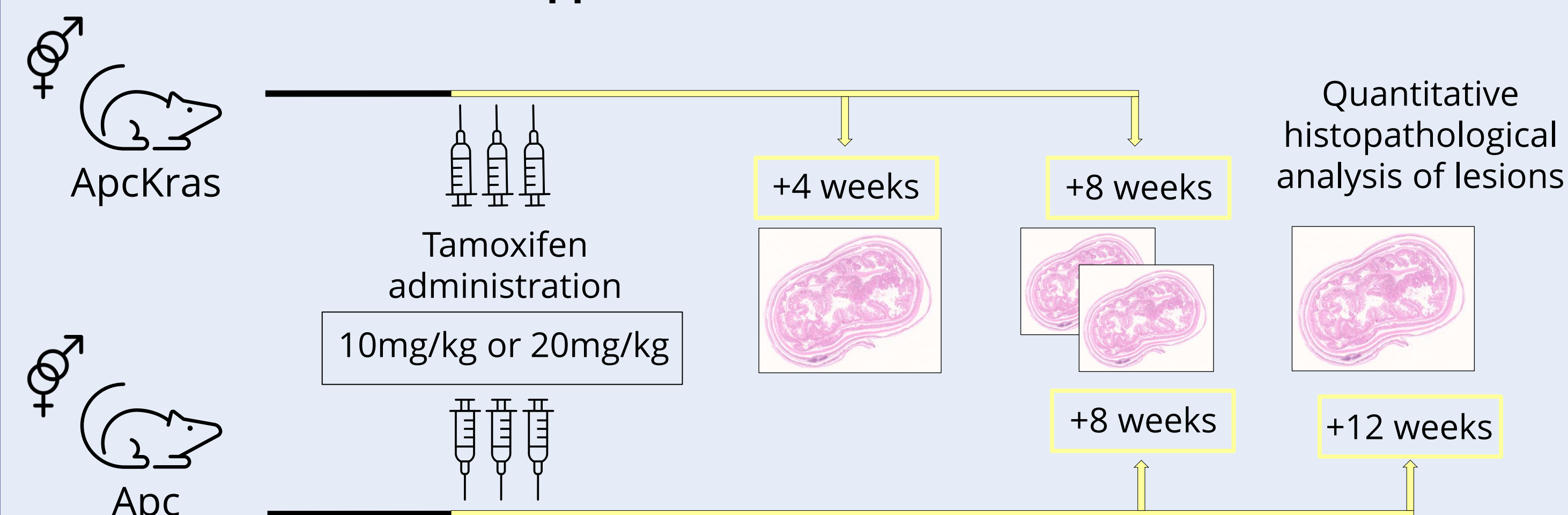
Kras^{+/f} *Apc*^{f/f} *Cre*^{ERT2+} (*ApcKras*)
Kras^{+/+} *Apc*^{f/f} *Cre*^{ERT2+} (*Apc*)
Kras^{+/f} *Apc*^{f/f} (*Control*)

Organoid generation and carcinogenesis induction



Organoids were treated with 4-OHT (0,125-1µM) for 24h two days after the initiation of cell culture (at p(0) or p(1)) to induce *Apc* and/or *Kras* mutations. Morphological studies were conducted before the following passages (p(0) and p(1) or p(1) and p(2)).

Induction of tumor development



Results

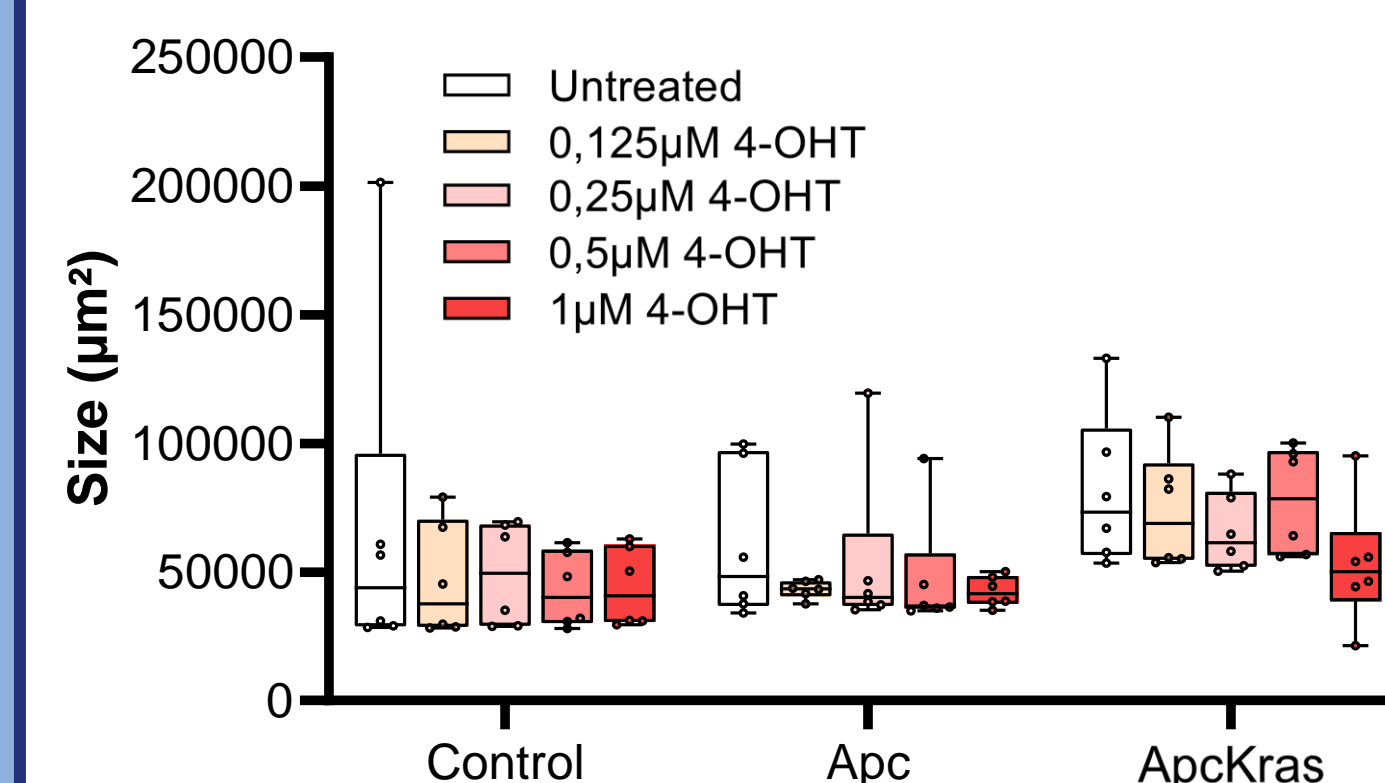
Ex vivo model: carcinogenesis induction

Treatment on the second week of culture p(1)

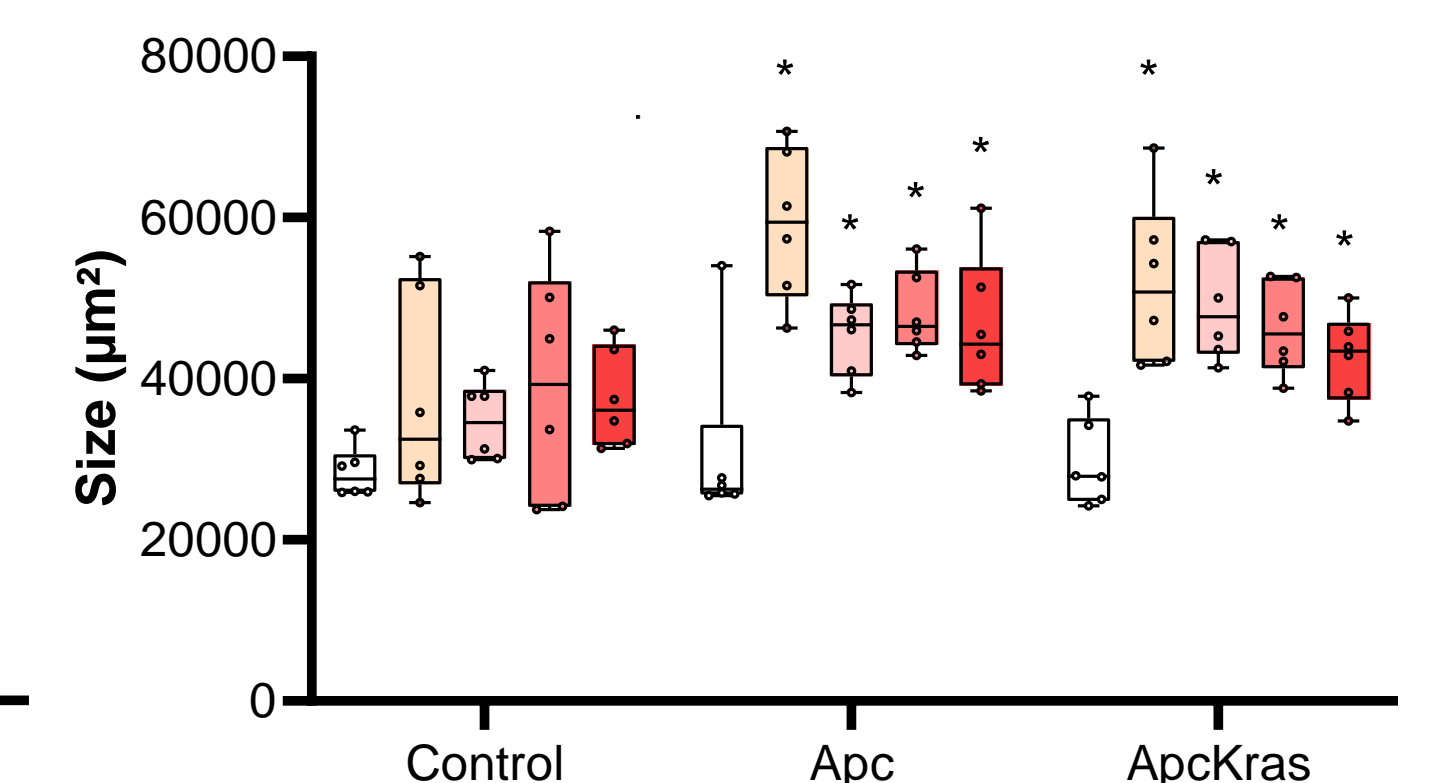
Irrespective of the dose, there were no significant alterations to organoid morphology 12 days following the 4-OHT treatment at p(1). The absence of a statistically significant increase in size after treatment was largely attributable to the high degree of heterogeneity observed between the organoids.

Treatment on the first week of culture p(0)

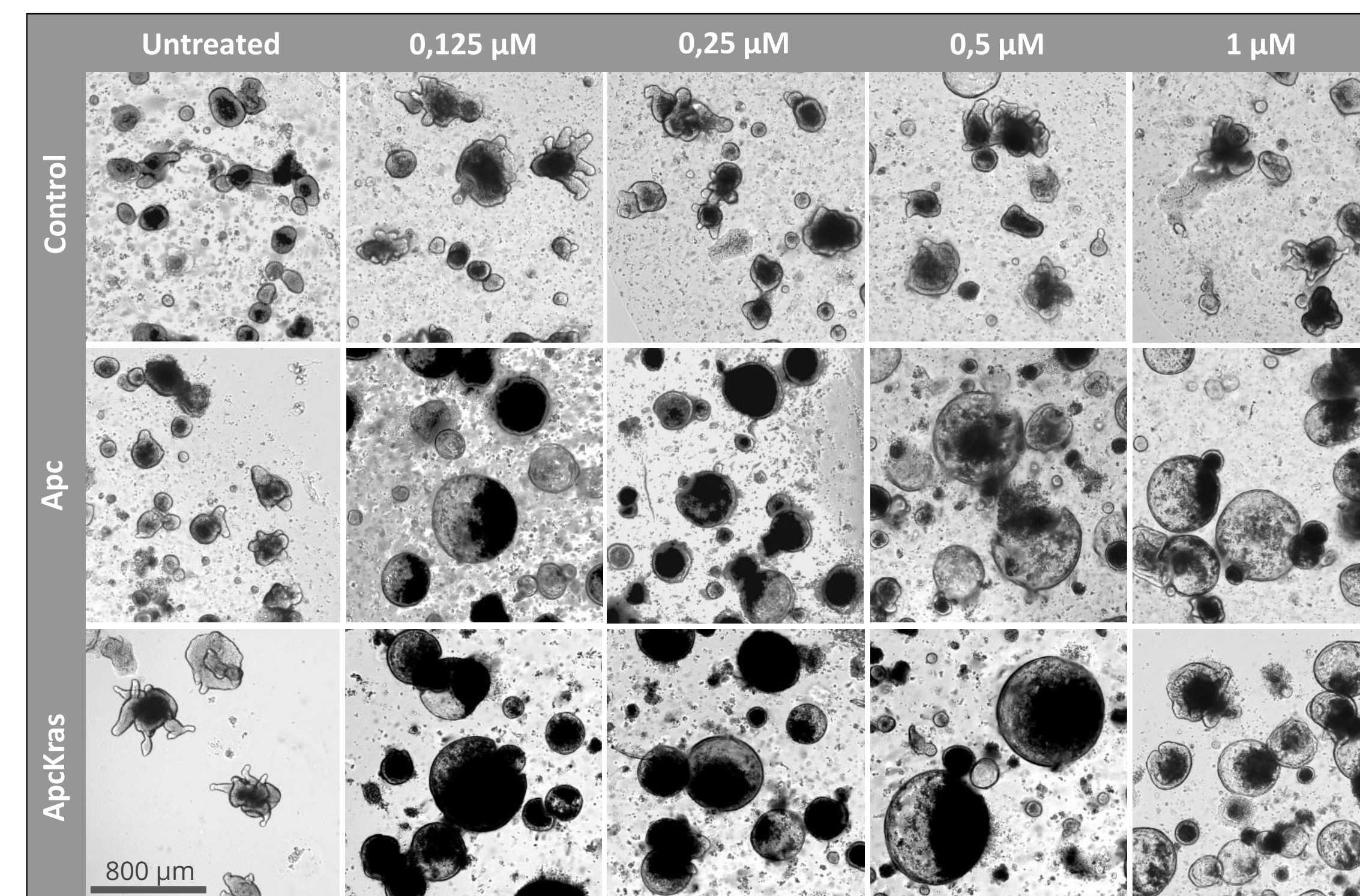
Organoid area 5 days post-treatment Treatment at p(0)



Organoid area 12 days after treatment Treatment at p(0)



N=2 ; n=3 – Dunnett's multiple comparison test, each treated group was compared to the corresponding untreated genotype. Organoids passage was performed 5 days after treatment.



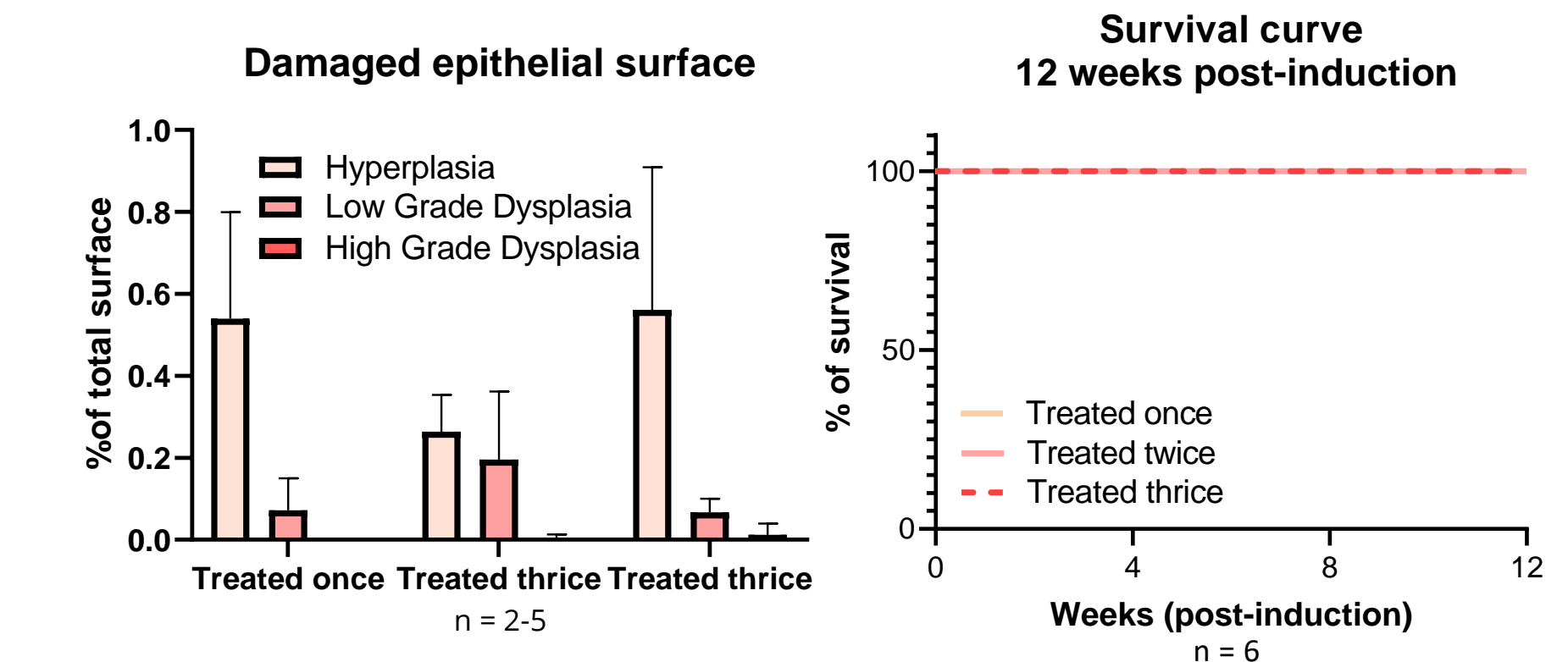
Organoids and tumoroids 12 days after treatment with 4-OHT

Ideal treatment regimen :
0,125µM of 4-OHT for 24h, 2 days after culture initiation

In vivo model: tumor development

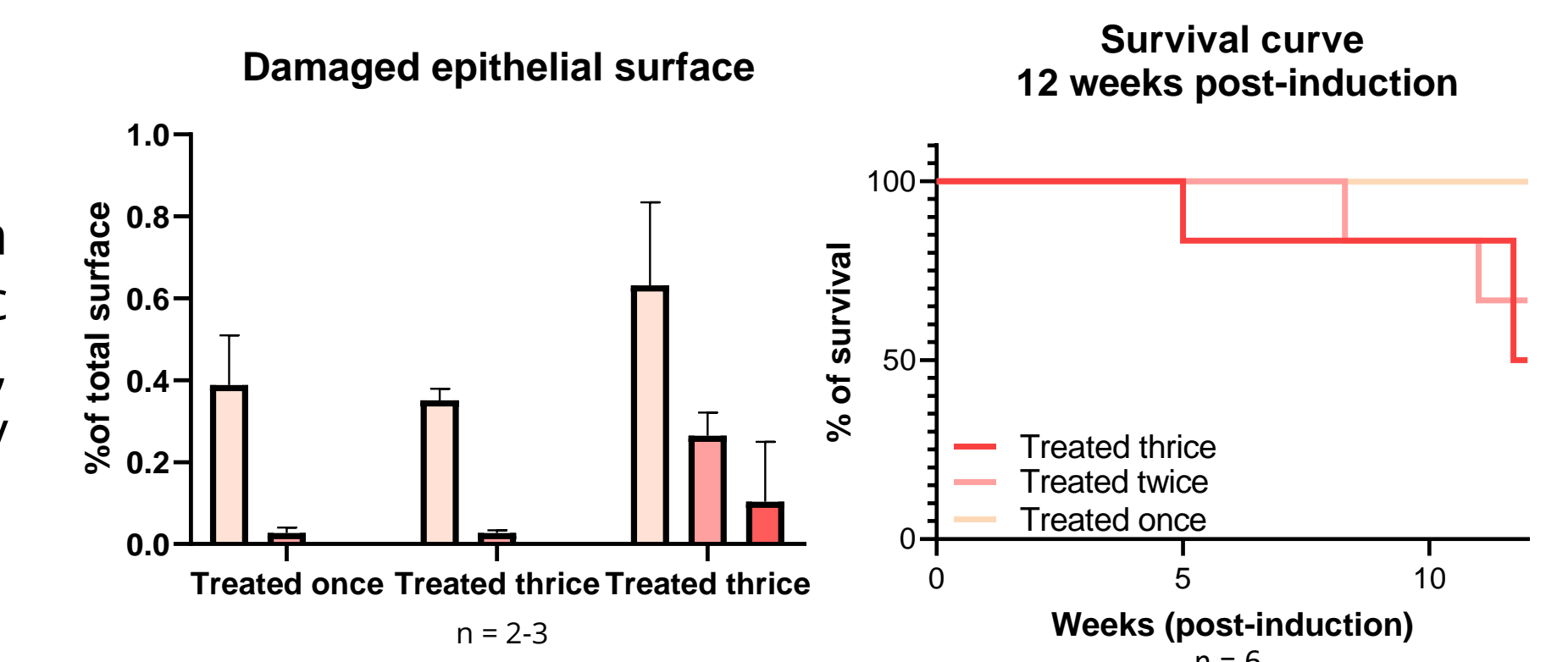
♀ Apc – 10mg/kg

TAM treatment mainly induced hyperplasia, with no differences between repeated treatments. No mortality was observed.



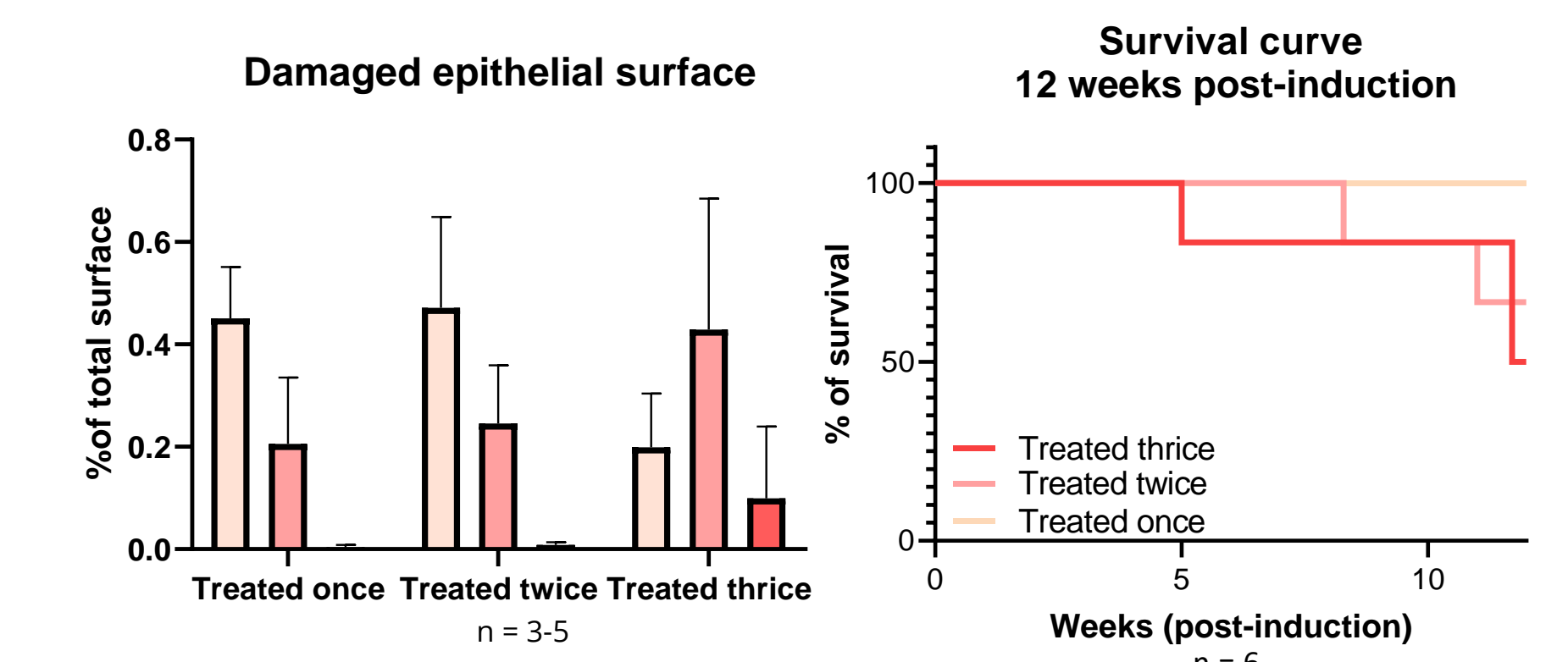
♀ Apc – 20mg/kg

After three tamoxifen administration, dysplastic area significantly increased, but TAM-induced mortality was also observed.



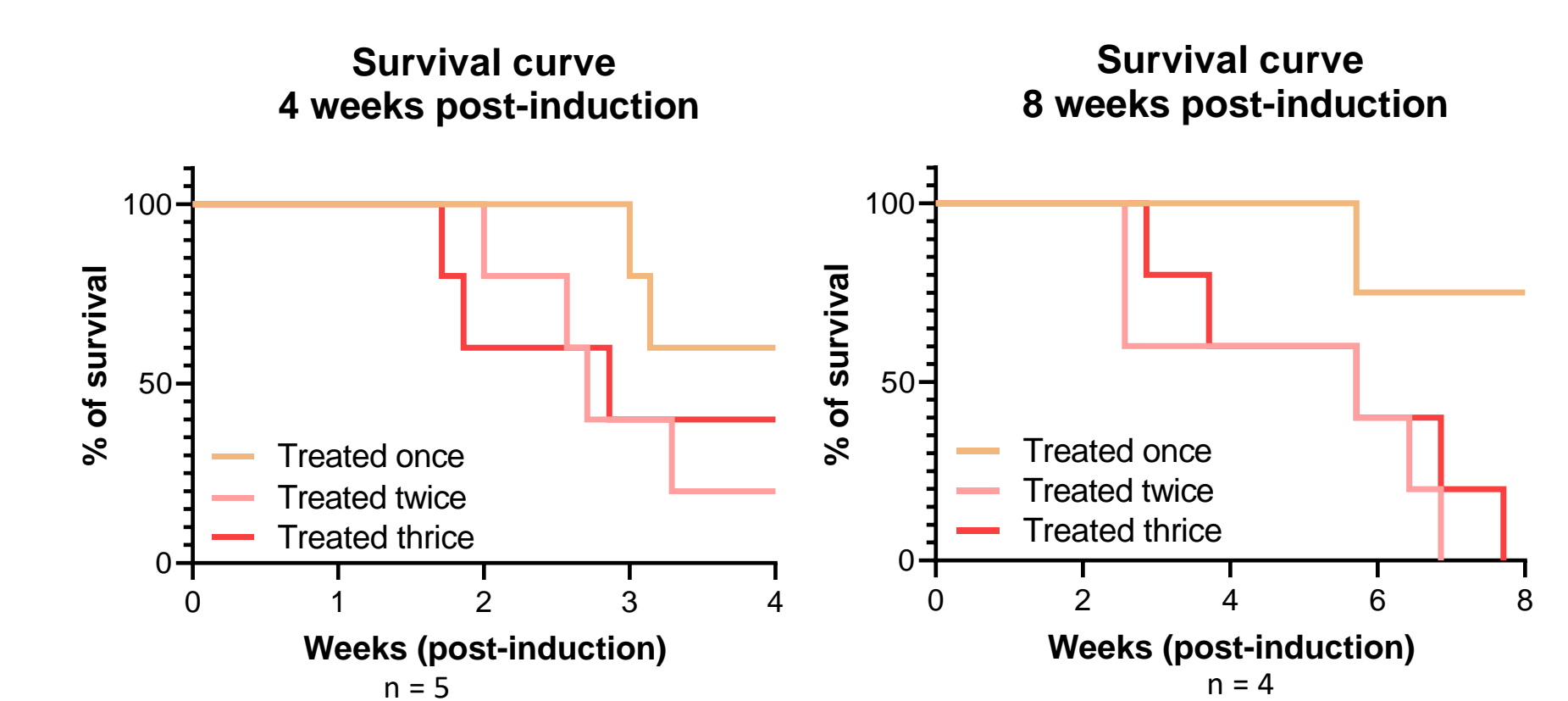
♀ ApcKras – 10mg/kg

Three TAM administration also induced a significant increase in dysplasia and mortality.



♀ ApcKras – 20mg/kg

Independently of the number of tamoxifen administrations, the 20mg/kg dose in *ApcKras* mice triggered high mortality, attributed to tumor development.



Ideal treatment regimen :
1x20mg/kg for Apc and 2x10mg/kg for ApcKras

Conclusions

The KPC/APC mouse model characterization showed a strong dependency of the lesions on the genotype of the mouse. A KPC:APC dynamic organoid model has been established, which allows to induce and study colon carcinogenesis *in vitro*.

The *in vivo* and *ex vivo* models provide the opportunity to perform parallel histopathological and mechanistic studies to advance colon cancer research and to investigate the effects of low-dose radiation exposures.

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