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

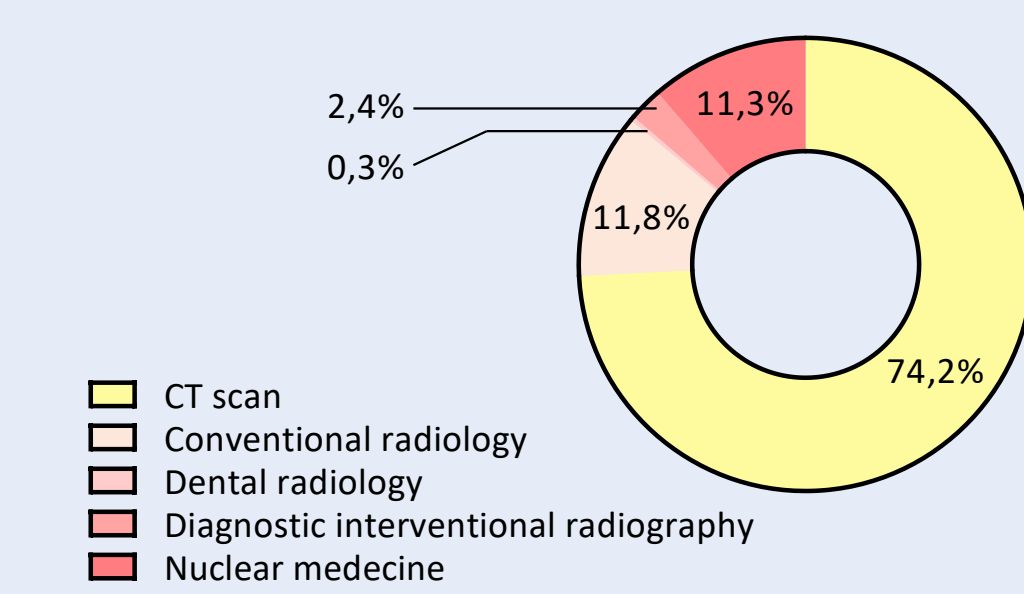
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## Introduction

### 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 rise<sup>1</sup>.

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

### Ionizing radiation and colon cancer

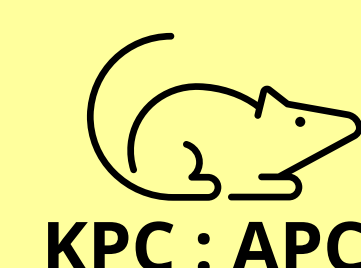
Epidemiological studies show an increased risk of colorectal cancer after low doses X-rays medical exposures but benefits still outweigh the risks.<sup>4</sup>

LDR increase tumor multiplicity and interact with carcinogenesis-related pathways through gene expression modulation, DNA hypomethylation or protein interactions.<sup>5,6,7</sup>

The *Apc*<sup>min</sup> 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



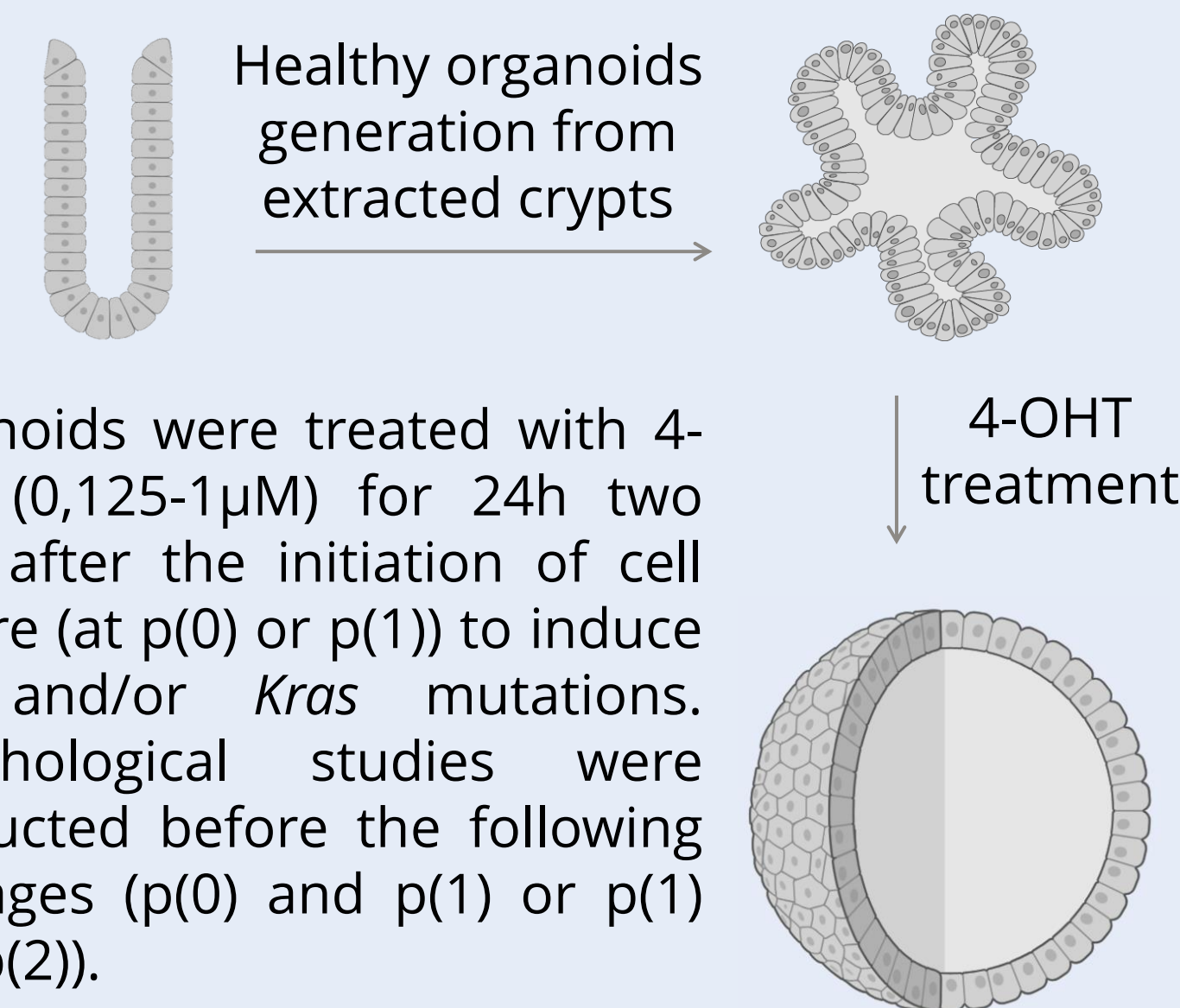
### Inducible colon cancer mouse model

B6.Cg-*Kras*<sup>tm4Tyj</sup> *Apc*<sup>tm1Tno</sup> Tg(CD2-cre/ERT2)752Erf/Maraj<sup>8</sup>

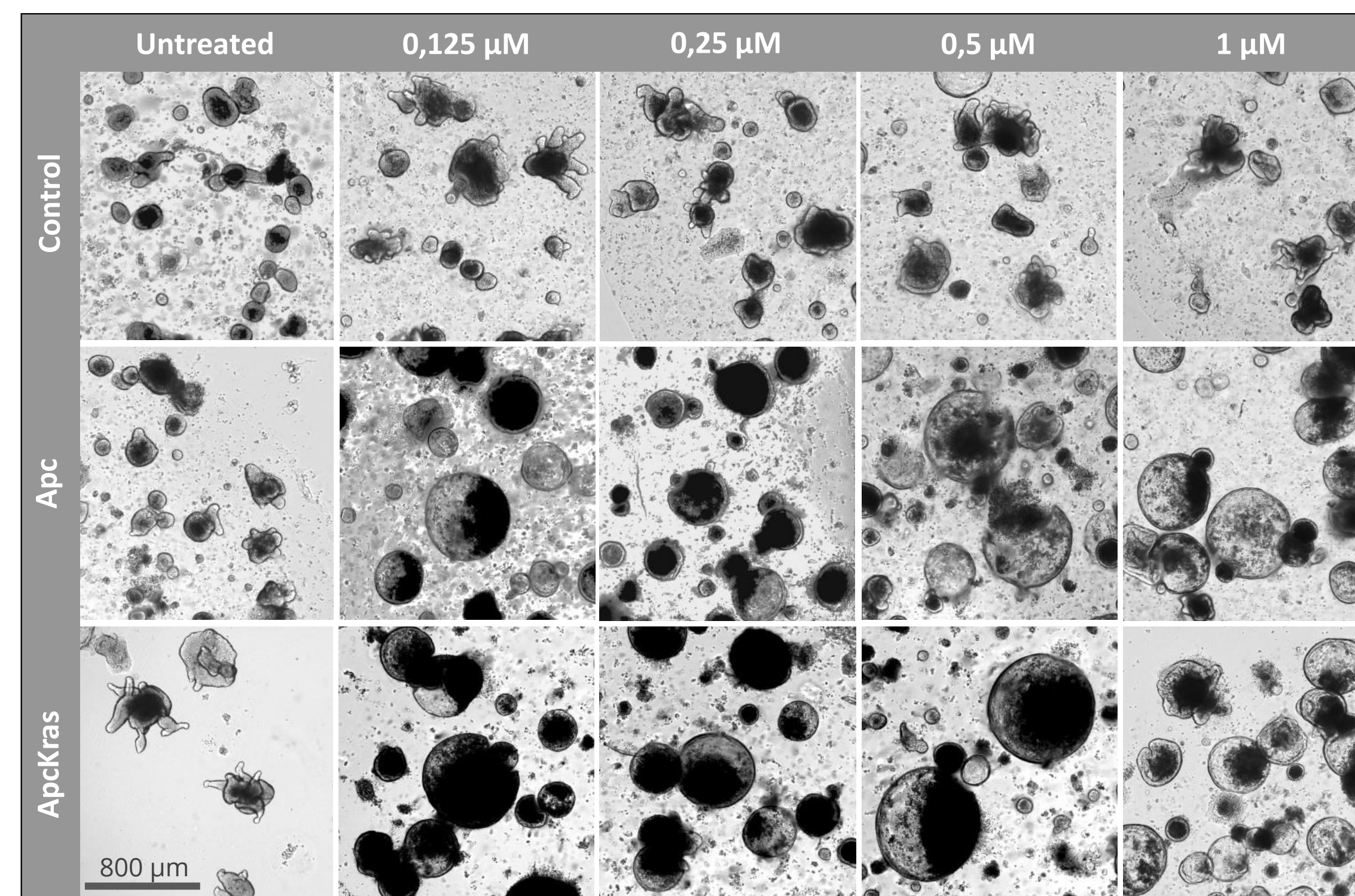
- o CreLox system
- o Control by the CD2 promoter

*Kras*<sup>+/f</sup> *Apc*<sup>f/f</sup> *Cre*<sup>ERT2+</sup> (*ApcKras*)  
*Kras*<sup>+/+</sup> *Apc*<sup>f/f</sup> *Cre*<sup>ERT2+</sup> (*Apc*)  
*Kras*<sup>+/f</sup> *Apc*<sup>f/f</sup> (*Control*)

### Organoid generation and carcinogenesis induction



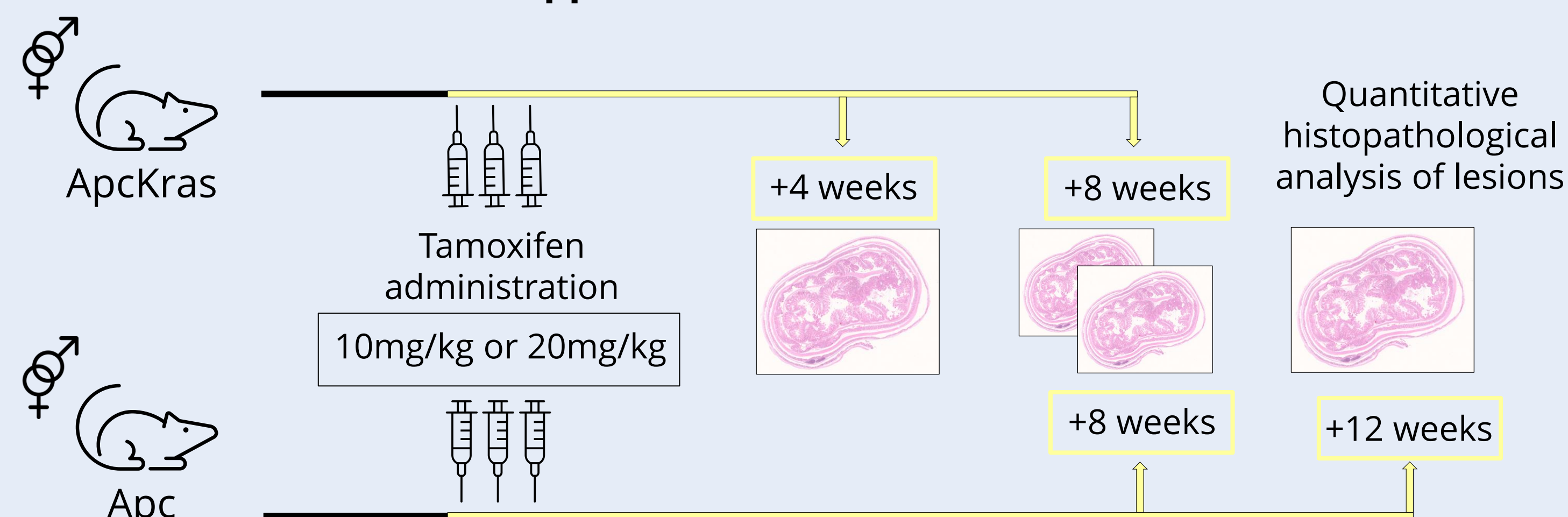
Organoids were treated with 4-OHT (0,125-1µM) for 24h two days after the initiation of cell culture (at p(0) or p(1)) to induce *Apc* and/or *Kras* mutations. Morphological studies were conducted before the following passages (p(0) and p(1) or p(1) and p(2)).



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

### Induction of tumor development



## Results

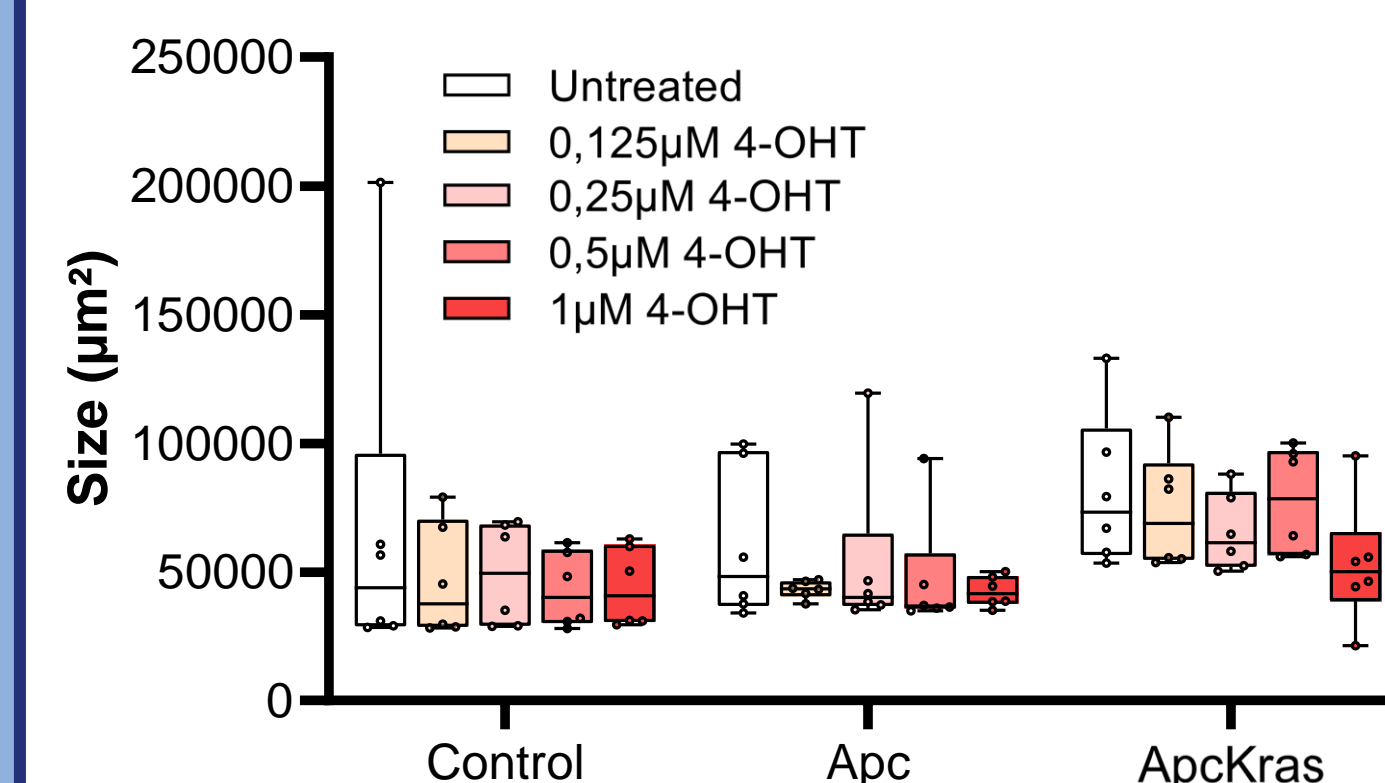
### *Ex vivo* model: carcinogenesis induction

#### Treatment on the second week of culture p(1)

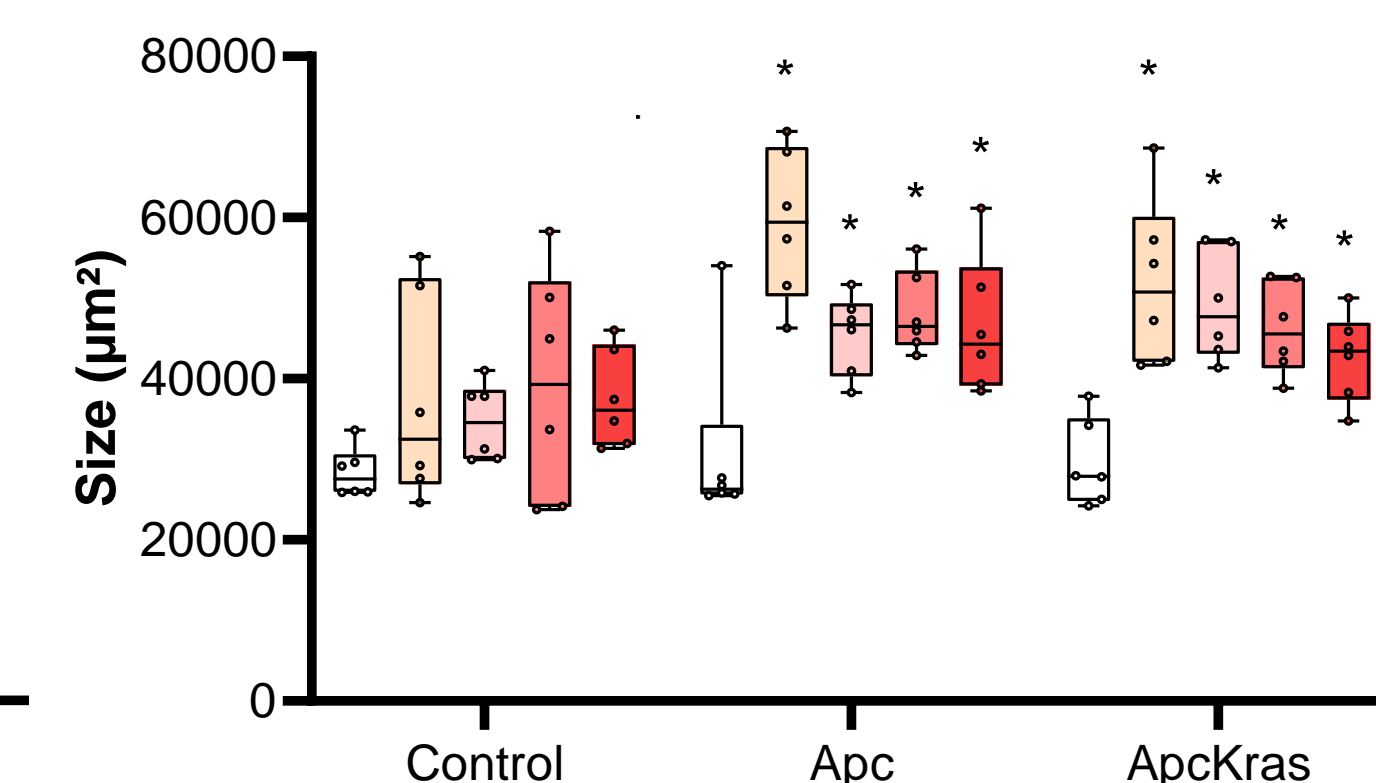
Irrespective of the dose, there were no significant alterations to organoid morphology 12 days following the 4-OHT treatment at p(1). The absence of a statistically significant increase in size after treatment was largely attributable to the high degree of heterogeneity observed between the organoids.

#### 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)

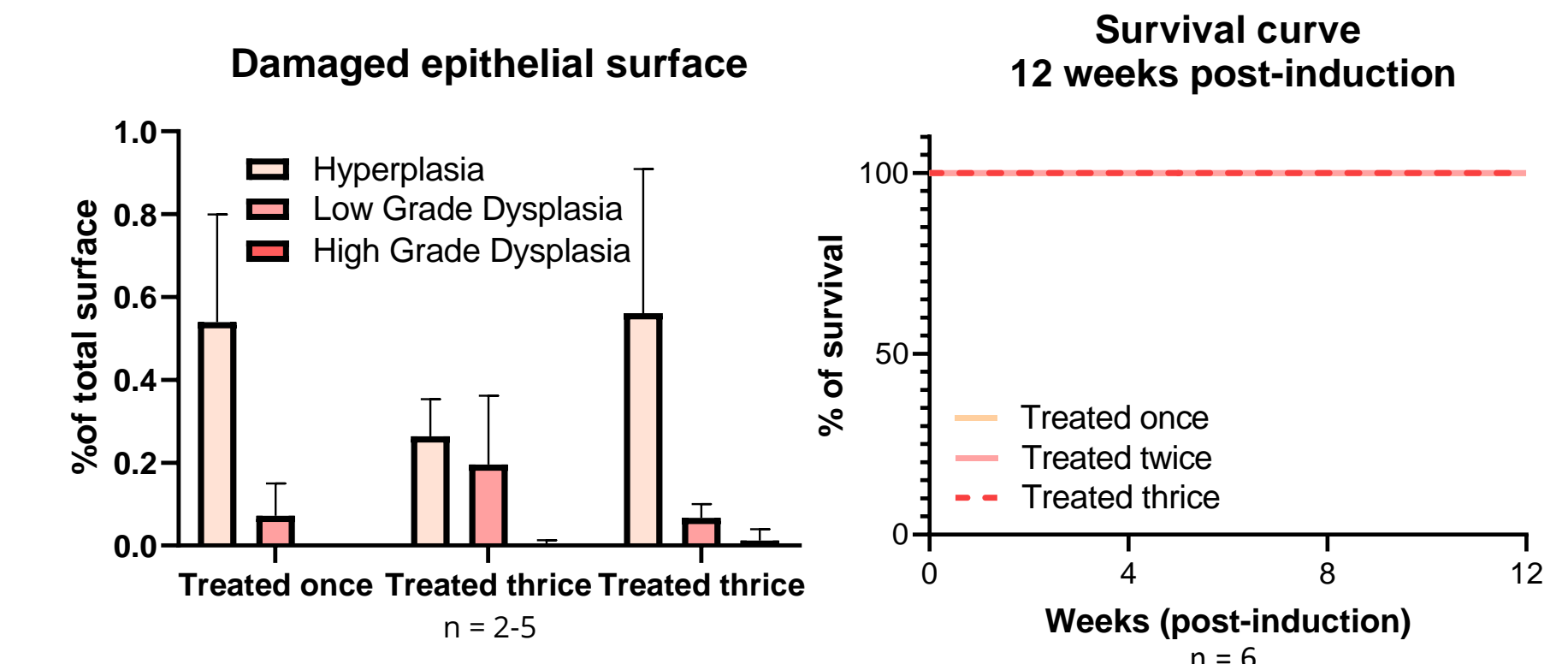


N=2 ; n=3 – Dunnett's multiple comparison test, each treated group was compared to the corresponding untreated genotype. Organoids passage was performed 5 days after treatment.

### *In vivo* model: tumor development

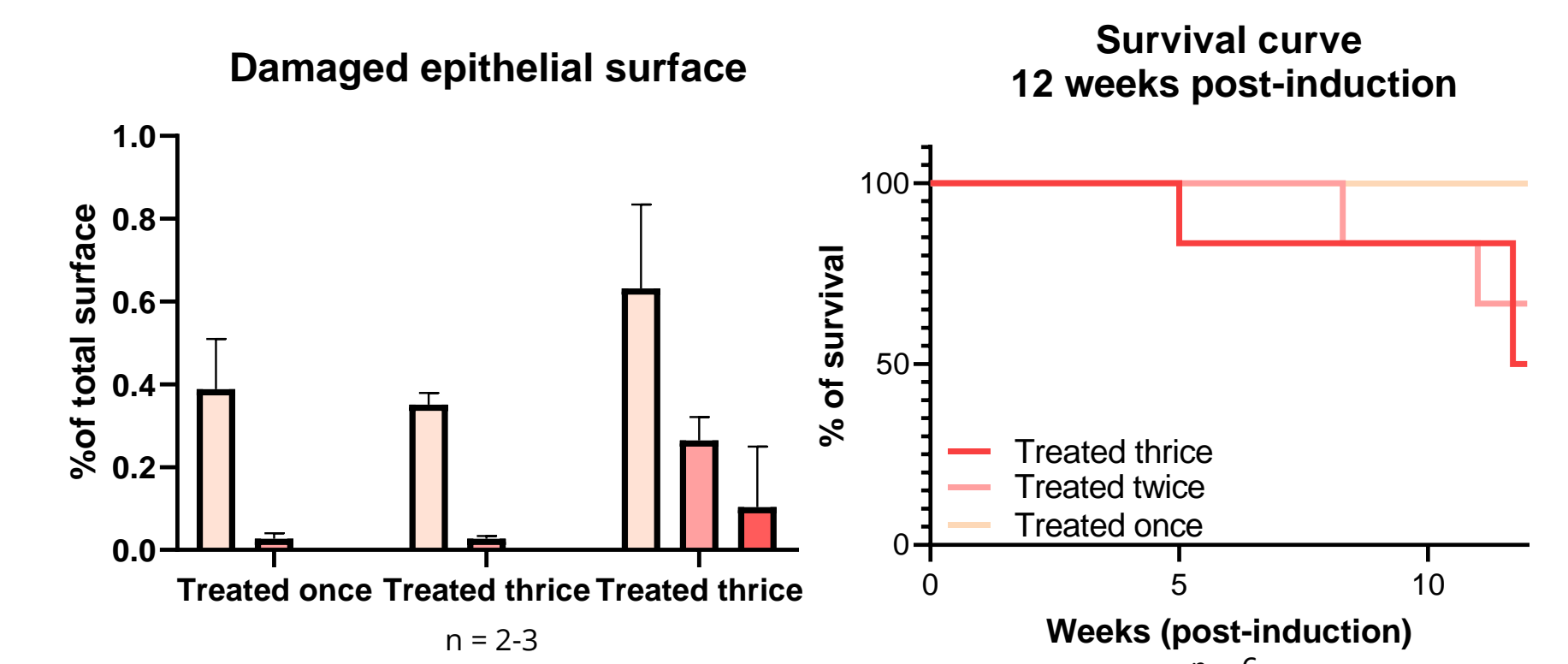
#### ♀ Apc – 10mg/kg

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



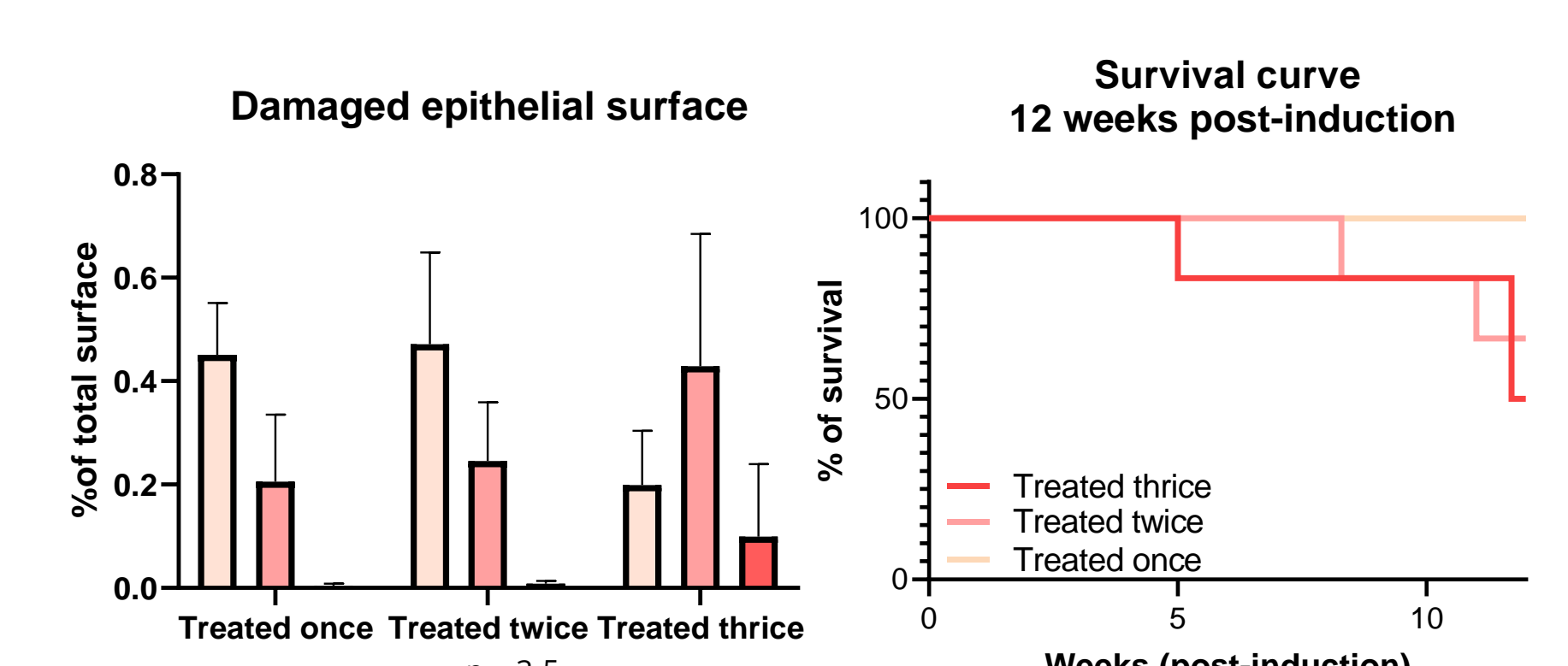
#### ♀ Apc – 20mg/kg

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



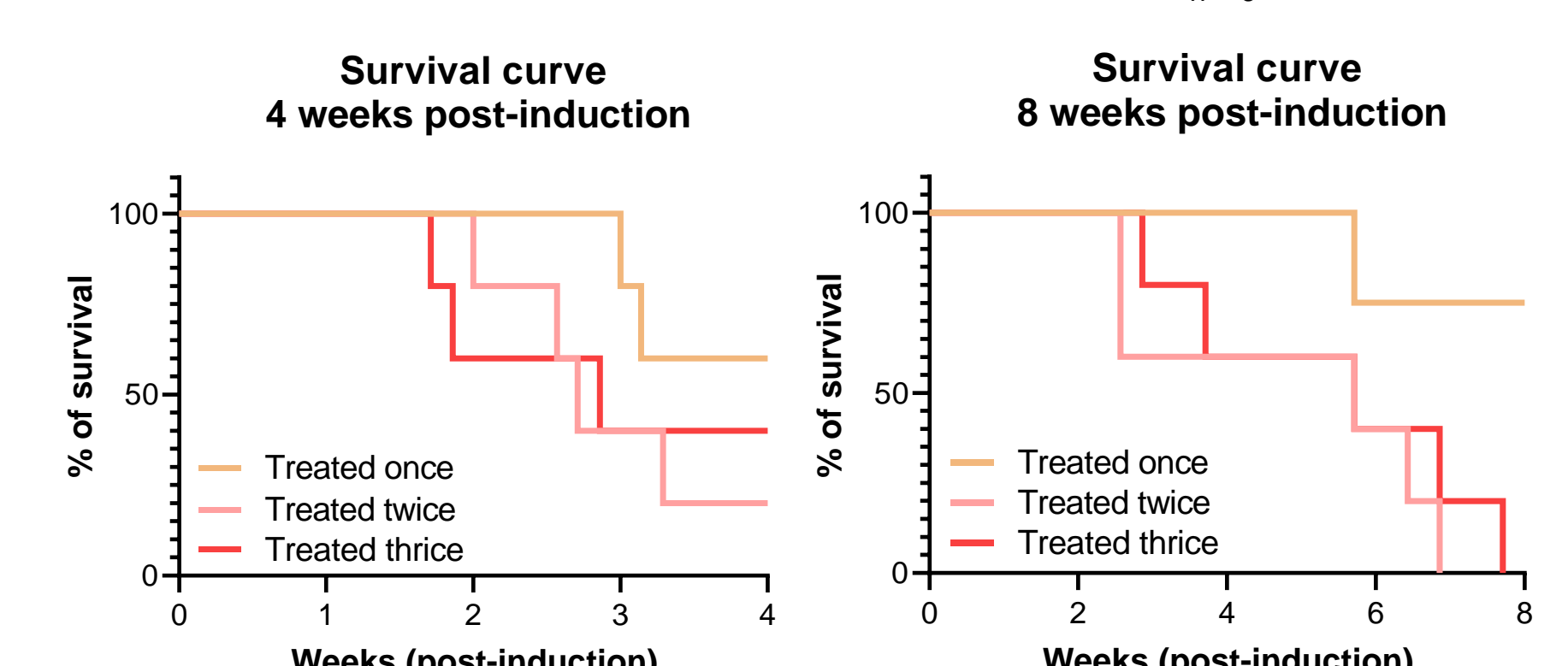
#### ♀ ApcKras – 10mg/kg

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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