



HAL
open science

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

Mélessandre Gomot, Nora Essakhi, Clément Codan, Quentin Pascal, Dmitry Klokov, Guillaume Vares

► To cite this version:

Mélessandre 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

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NoDerivatives 4.0 International License

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

Mélanie Gomot^{1*}, Nora Essakhi¹, Clément Codan¹, Quentin Pascal², Dmitry Klokov¹, Guillaume Vares¹

¹ Institut de Radioprotection et de Sûreté Nucléaire (IRSN), PSE-SANTE/SESANE/LRTOX, Fontenay-aux-Roses, France
² Commissariat à l'Energie Atomique et aux Energies Alternatives (CEA), IMVA-HB/IDMIT, Fontenay-aux-Roses, France

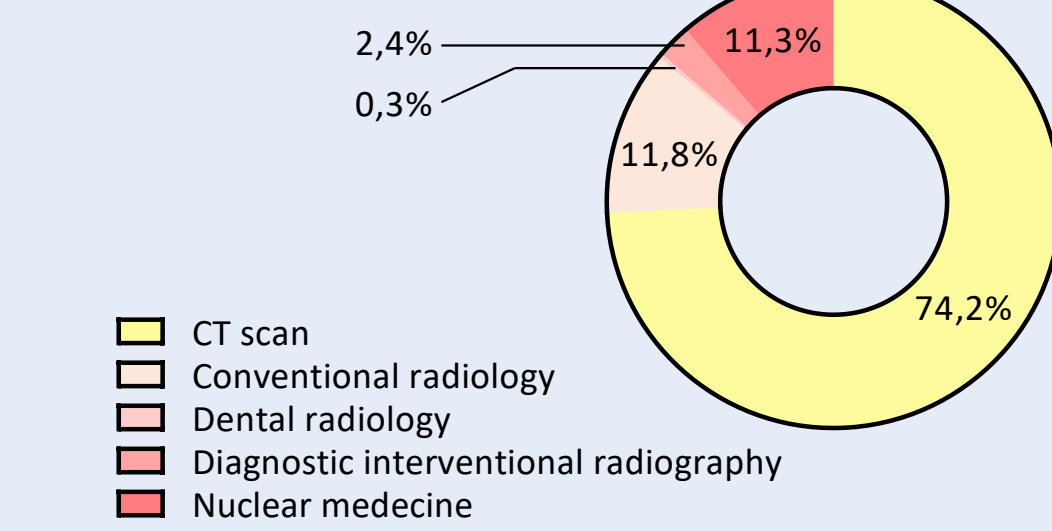
Introduction

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

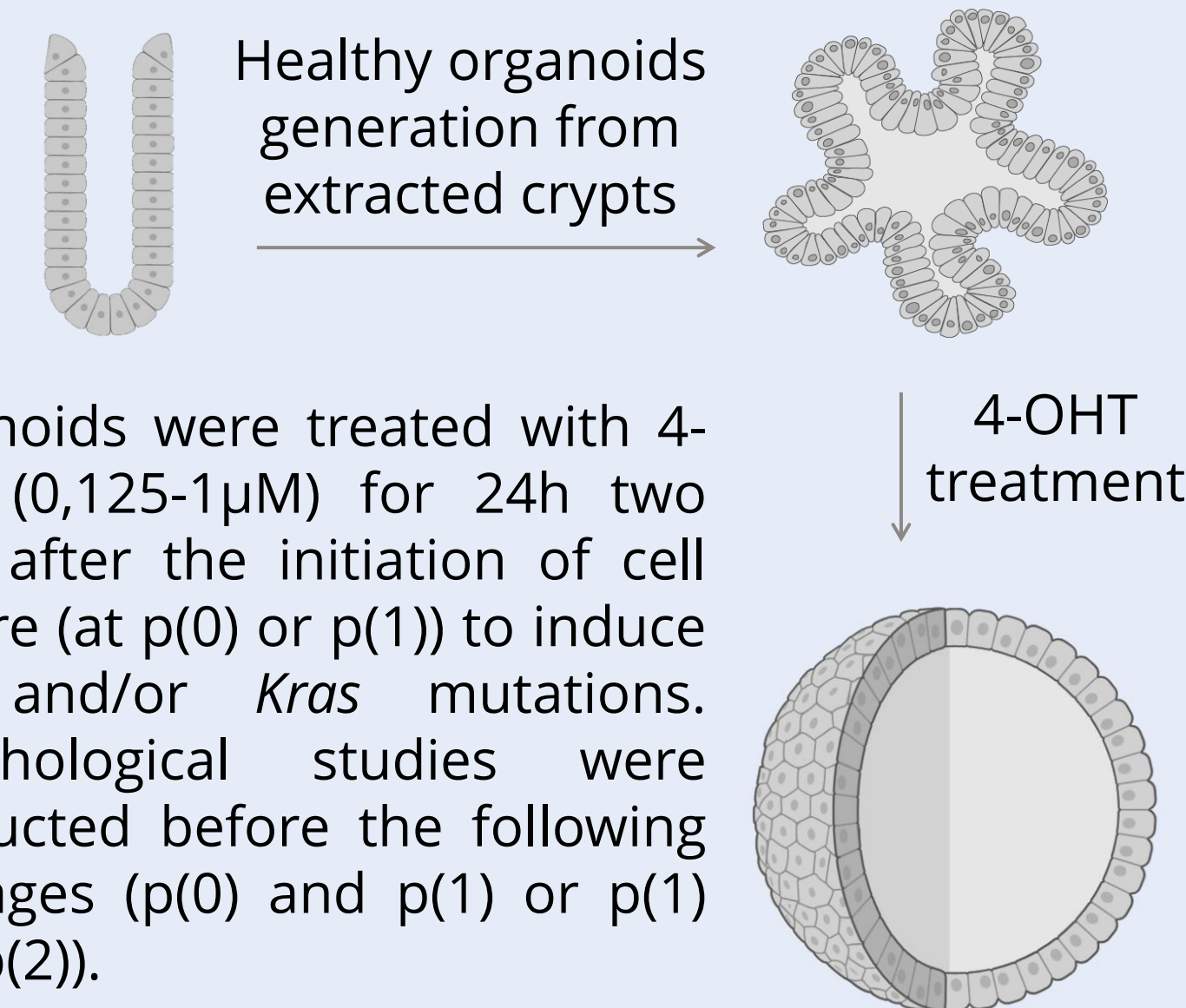
KPC : APC
Inducible colon cancer mouse model

B6.Cg-*Kras^{tm4Tyj} Apc^{tm1Tno} Tg(CD2-cre/ERT2)752Erf/MaraJ⁸*

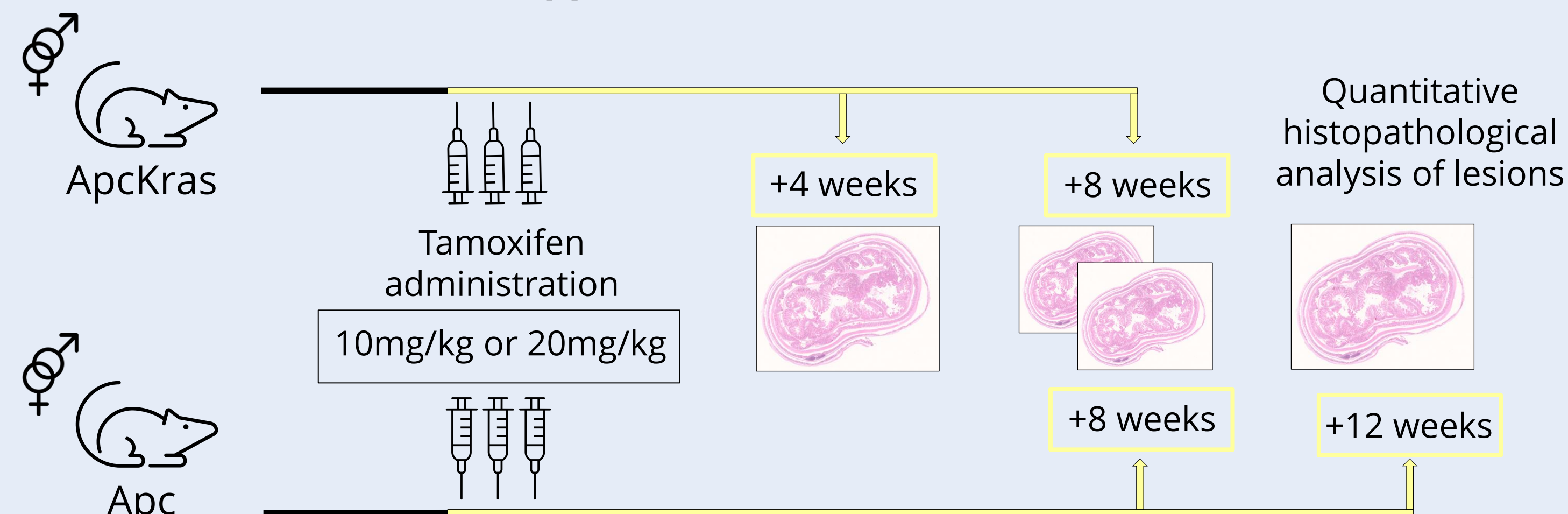
- o CreLox system
- o Control by the CDX2 promoter

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



Induction of tumor development



Results

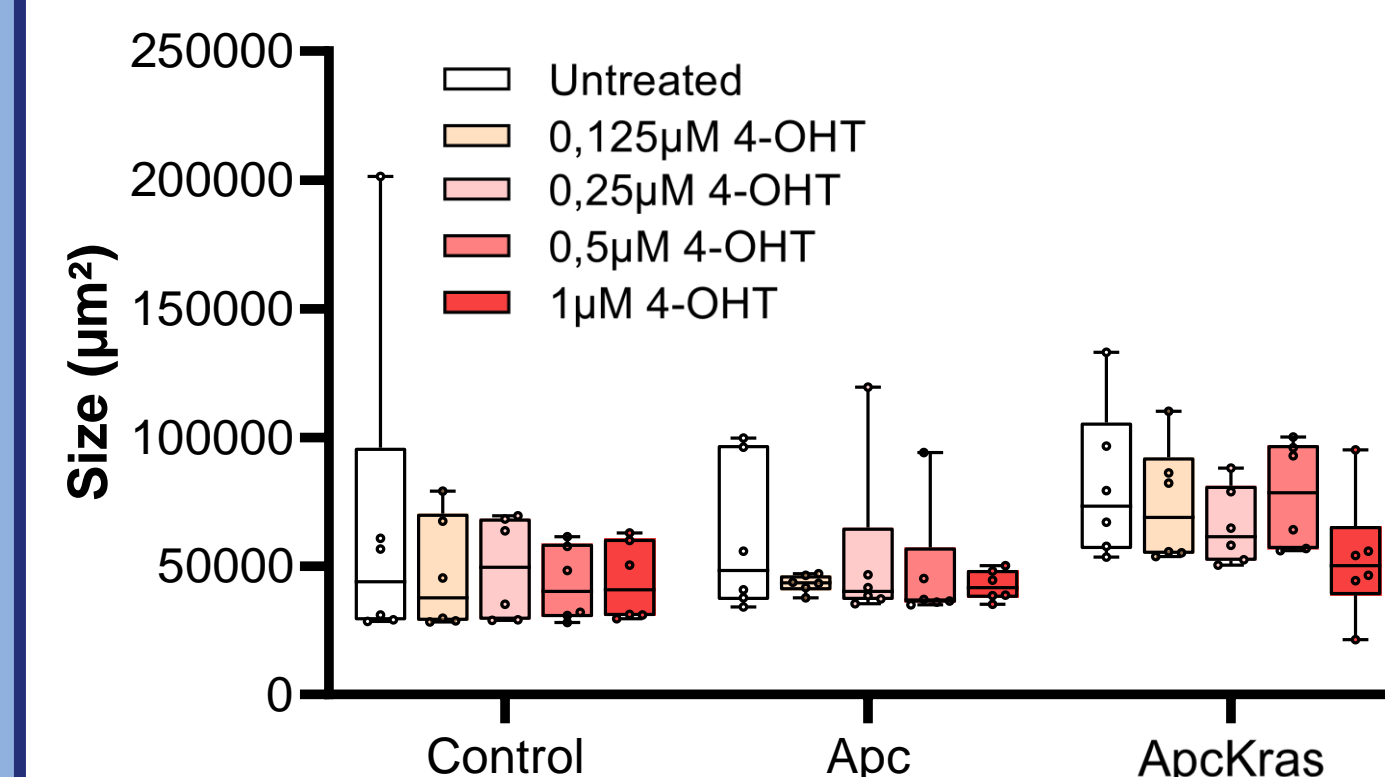
Ex vivo model: carcinogenesis induction

Treatment on the second week of culture p(1)

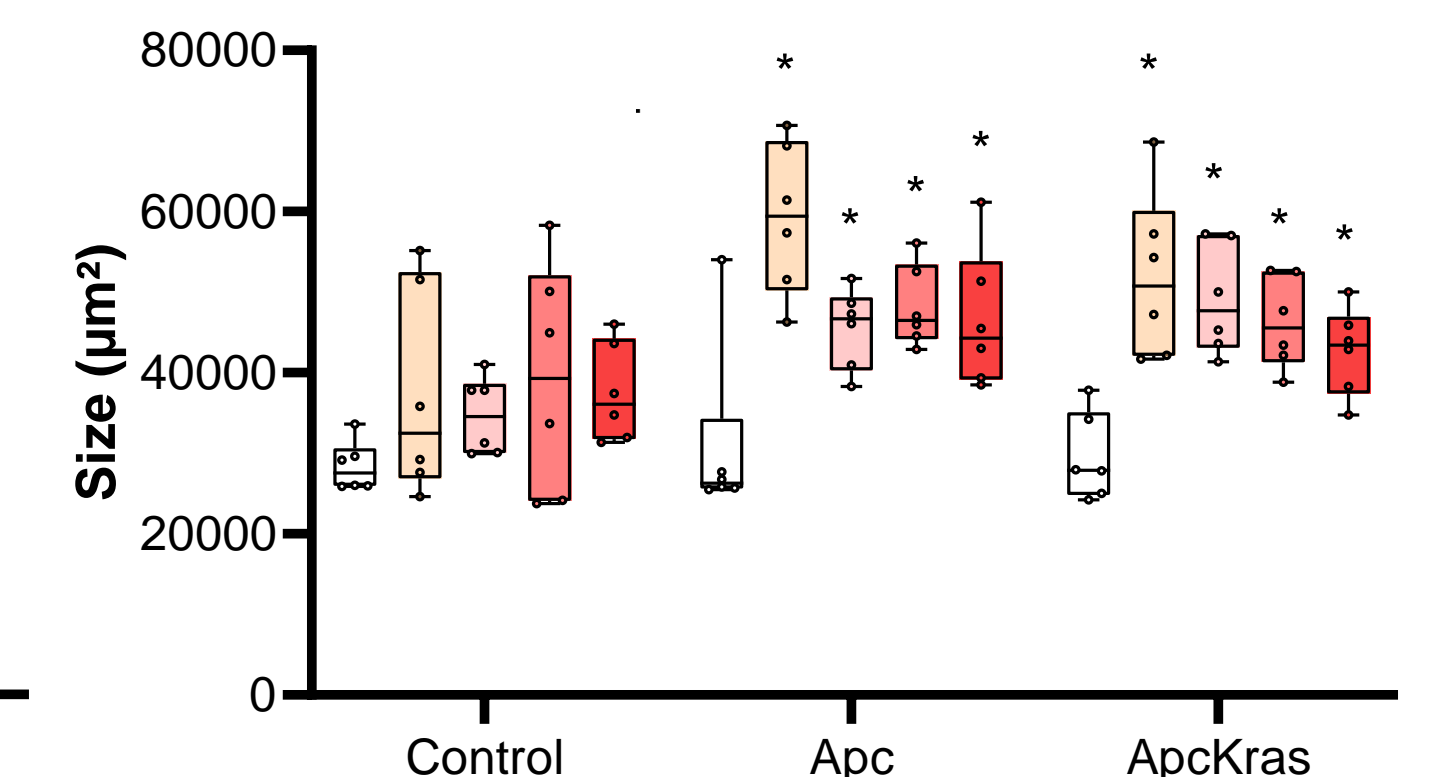
Irrespective of the dose, there were no significant alterations to organoid morphology 12 days following the 4-OHT treatment at p(1). The absence of a statistically significant increase in size after treatment was largely attributable to the high degree of heterogeneity observed between the organoids.

Treatment on the first week of culture p(0)

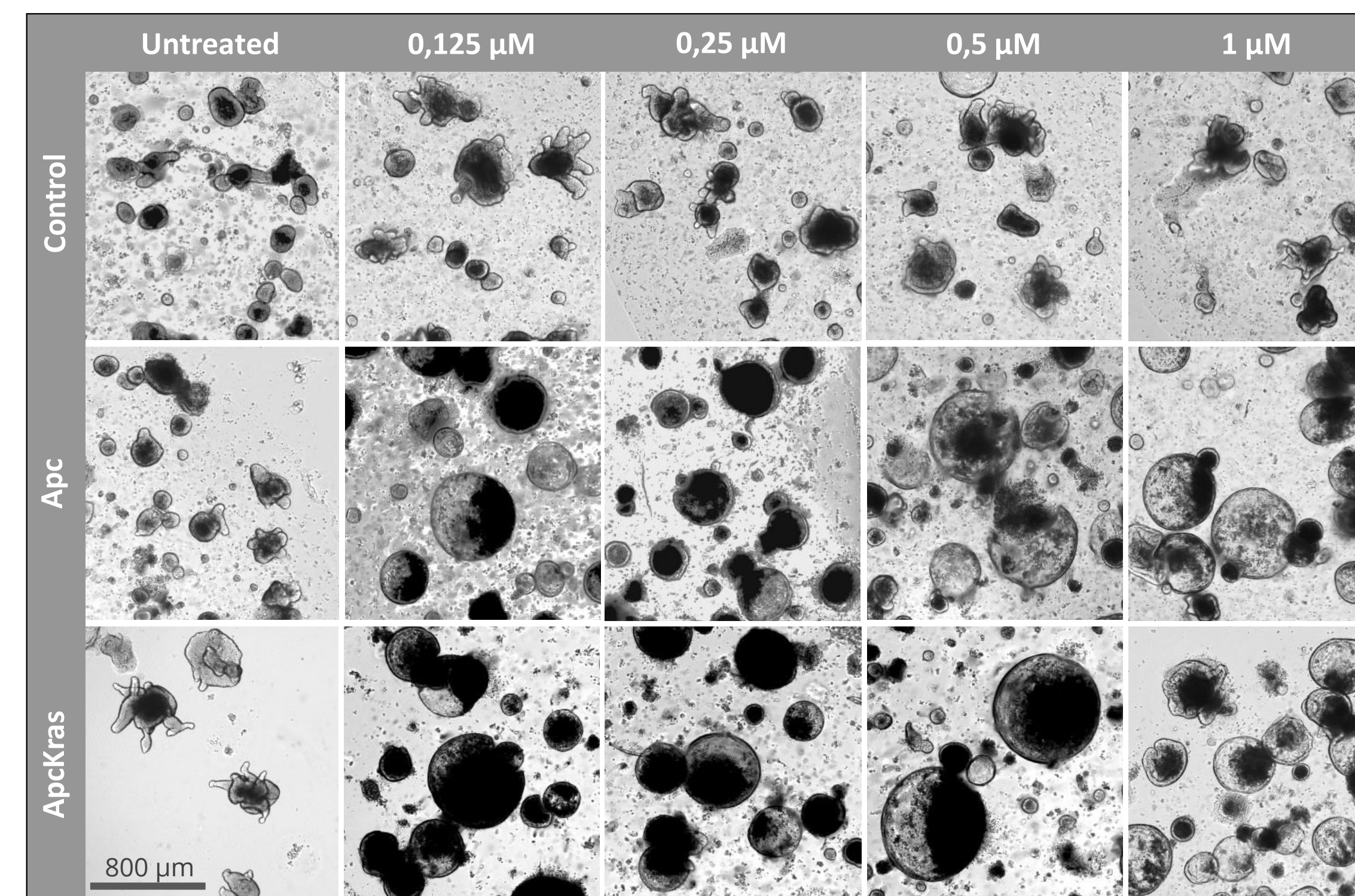
Organoid area 5 days post-treatment Treatment at p(0)



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.



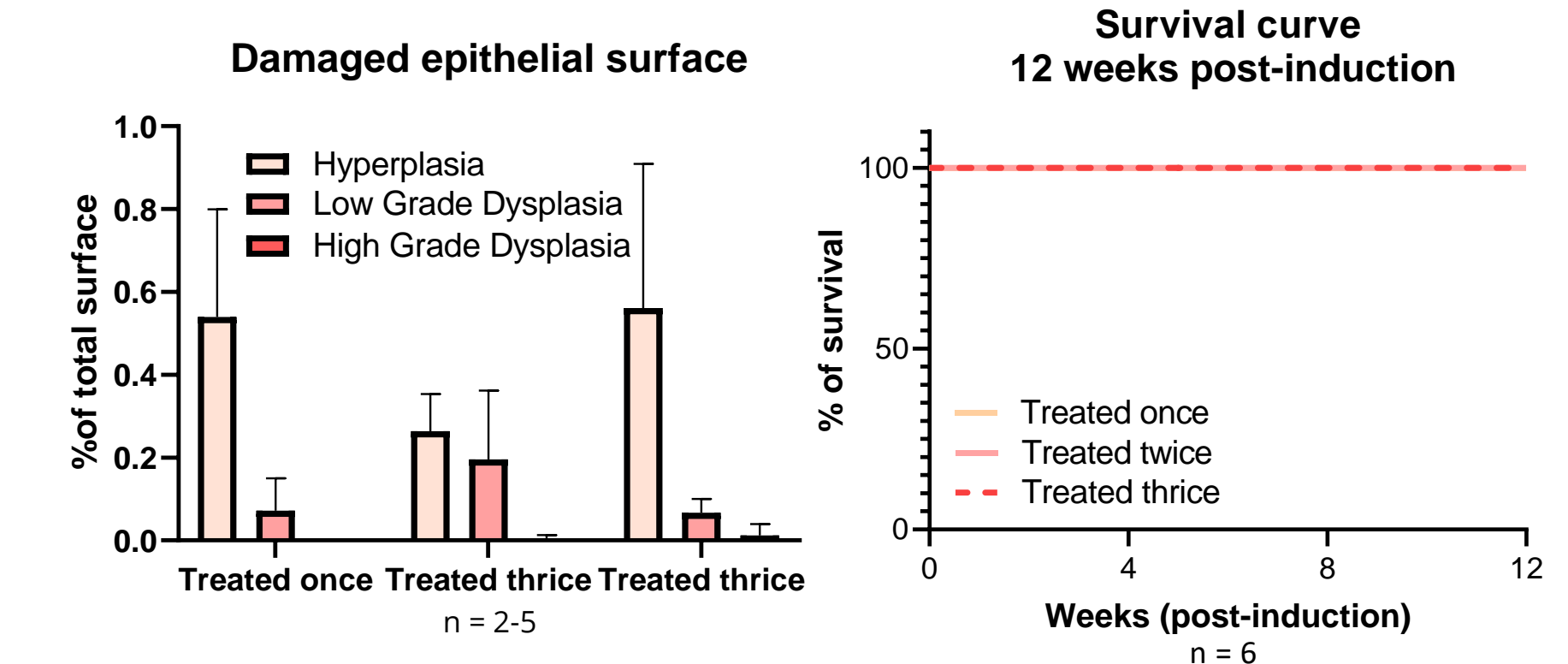
Organoids and tumoroids 12 days after treatment with 4-OHT

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

In vivo model: tumor development

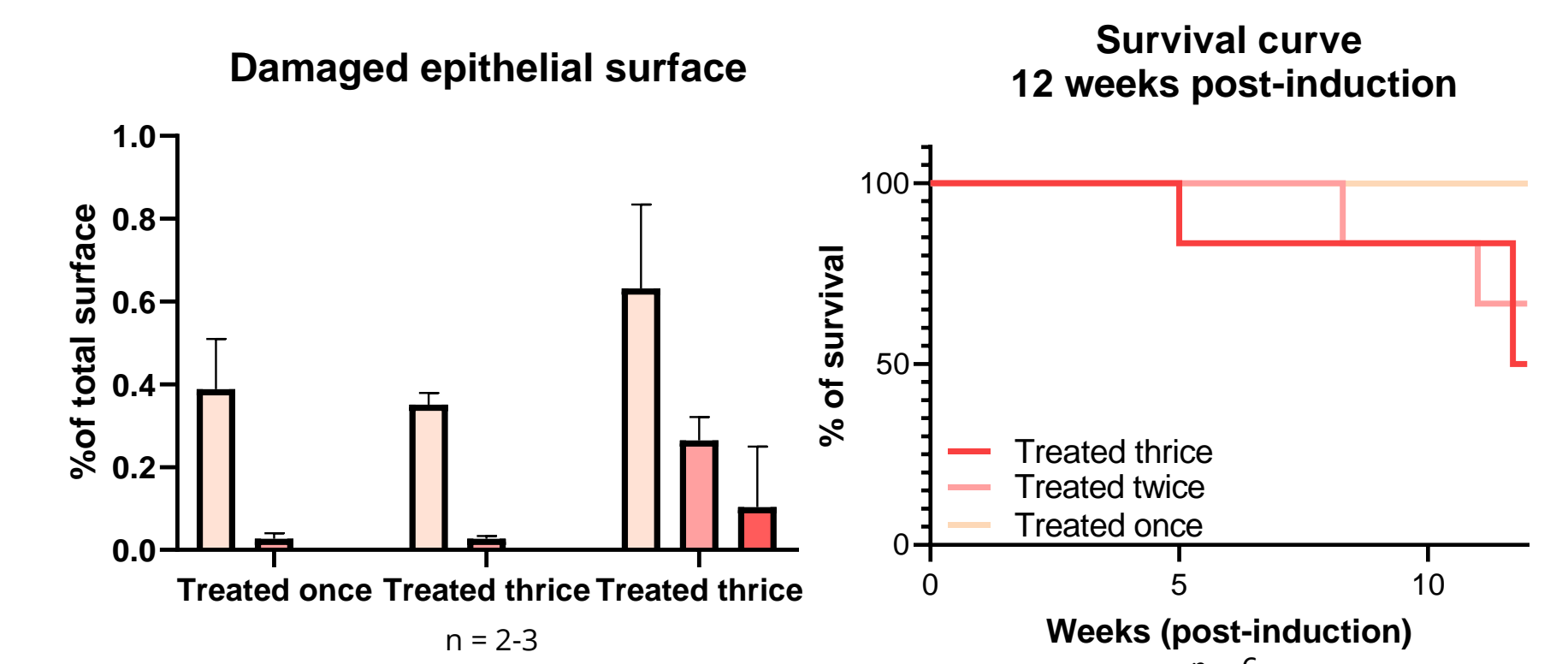
♀ Apc – 10mg/kg

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



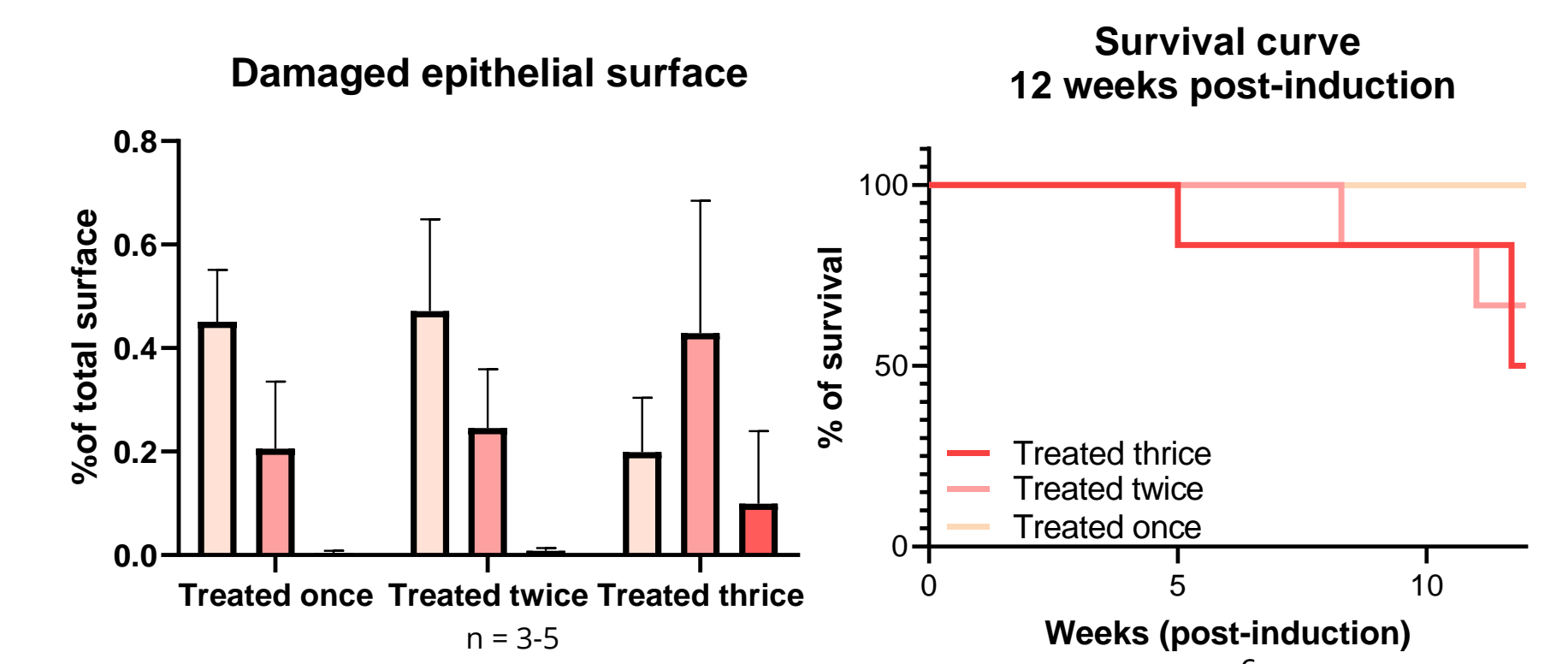
♀ Apc – 20mg/kg

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



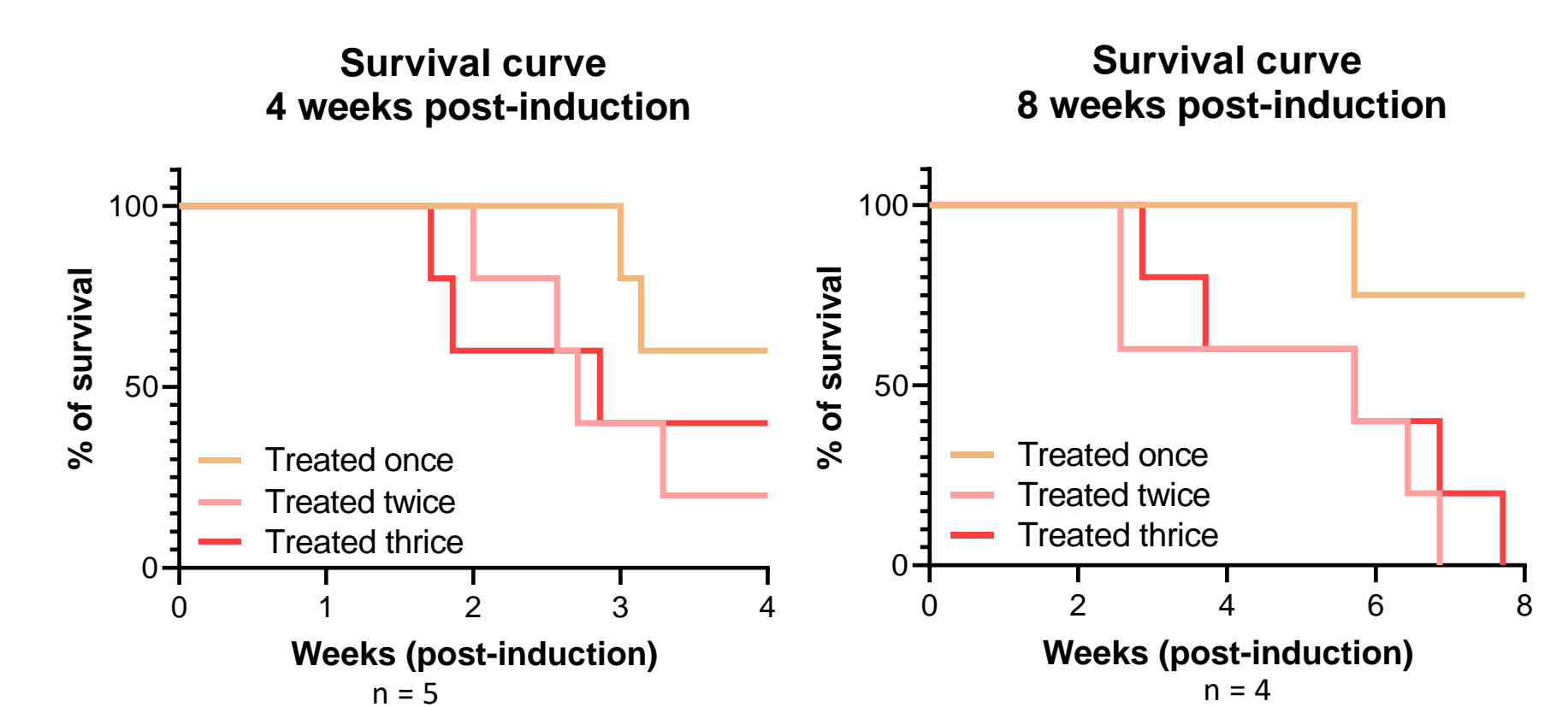
♀ ApcKras – 10mg/kg

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.

References

1. IRSN, Exposition de la population aux rayonnements ionisants - Rapport EXPRI, 2017.
2. S.Bagherzadeh et al., Evaluation of radiation dose and radiation-induced cancer risk associated with routine CT scan examinations, Radiation Physics and Chemistry, 2023.
3. J. Albert, Radiation Risk From CT: Implications for Cancer Screening, American Journal of Roentgenology, 2013.
4. A. Gonzales, Radiation-Related Cancer Risks From CT Colonography Screening: A Risk-Benefit Analysis, American Journal of Roentgenology, 2012.
5. D. Trani, Sex-dependent Differences in Intestinal Tumorigenesis Induced in Apc1638N/+ Mice by Exposure to γ Rays, International Journal of Radiation Biology, 2012.
6. S. Soleymanifard et al., Effects of radiation dose on the stemness-related genes expression in colorectal cancer cell line; International Journal of Radiation Biology, 2021.
7. J.-H. Bae, Identification of radiation-induced aberrant hypomethylation in colon cancer, BMC Genomics, 2015.
8. R. Maitra et al., Development and Characterization of a Genetic Mouse Model of KRAS Mutated Colorectal Cancer, International Journal of Molecular Sciences, 2019.