

Who are we?

As the MCCA preclinical intervention unit we can take care of the whole trajectory of preclinical trial design and execution, including support in the design/setup of the study, design suitable drug formulations, planning and execution of treatments, follow-up of tumor growth and/or metastasis formation, assessment of therapy response and collection of tissues and reporting of data. We can also set up new techniques that are needed for your animal study.

We are facilitating the treatment and longitudinal follow-up of tumors with our fully trained and dedicated team of technicians that perform the animal work/handling such as surgeries and caliper measurements.

Our team will help researchers design high quality animal experiments. The well trained and dedicated team of animal technicians are treating the animals blindly and therefore increases reproducibility of the preclinical animal experiments. This, together with the correct experimental design and the high health and welfare standards in our animal facility, will decrease the total amount of animals used.

We collaborate with different facilities in our institute the Pharmacology unit to perform pre-clinical pharmacology-pharmacokinetics (PK/PD) studies to study if a compound reaches its target in pharmacologically meaningful quantities.

Models that are made in the Animal model facility of the MCCA can be used for intervention studies. Next to that this facility can perform analyses on collected tissues coming from experiments performed by the preclinical intervention unit .

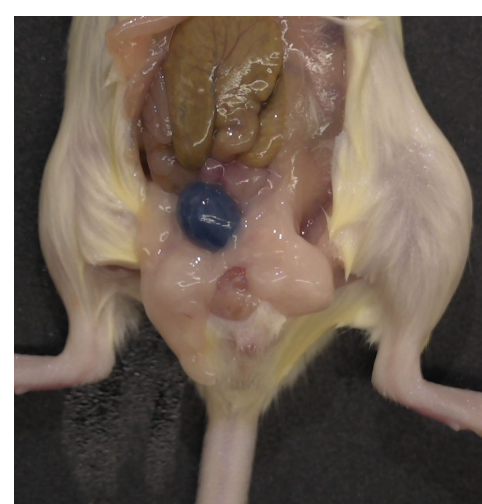
For histo- and immunohistochemical analysis we have a close collaboration with Animal pathology department and the bio-imaging facility of the NKI.



Outgrowth studies

To find and test anti-cancer treatment we have established advanced cancer models, such as transgenic (spontaneous) models, orthotopic transplantation models, human xenografts (PDX) models and Subcutaneous models. With these models we can study almost all kind of cancers. But before we can test anti-cancer treatments we have to determine the outgrowth and treatment window in these advanced cancer models .

Examples of different available models are, mammary gland injections, intraductal injections, intracranial injections, intra tracheal injections, intra thoracic injections, intrahepatic injections, mesenteric vein injections, ceecal wall injections, splenic injections, intravesical injections, prostate injections, ovary injections....



Intravesical injection



Tumor piece transplantation, into the mammary gland



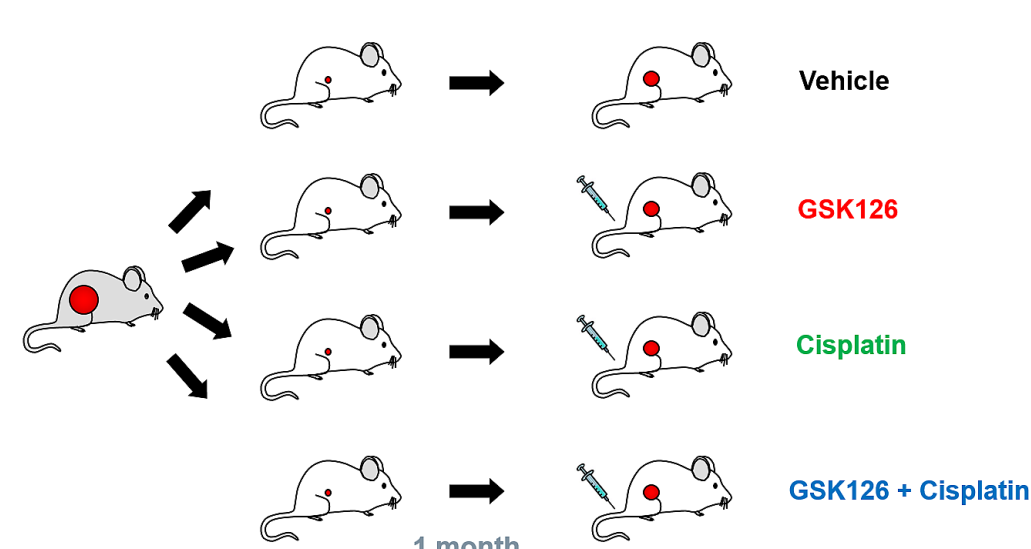
Mesenteric vein injection



Caliper measurement

Intervention studies

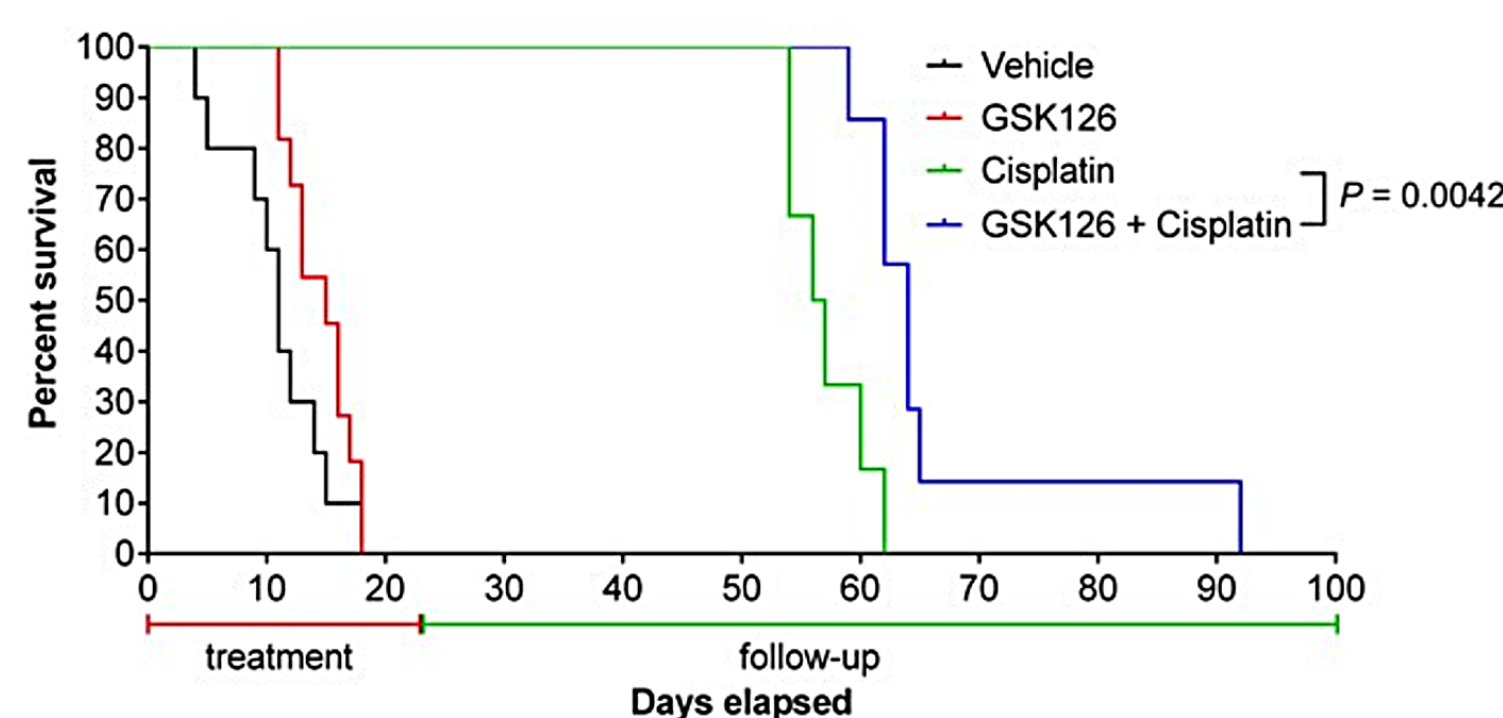
To test the efficacy of a single compound or a combination of compounds, pre-clinical interventions studies can be performed. Tumor growth and hereby the effect of the compounds can be followed. By caliper measurement and/or imaging. Outgrowth and survival curves can be made out of the collected data. We can perform experiments with different treatment routes (i.v., i.p., p.o., s.c., ect.) and schedules (daily, twice daily, weekly ect.)



Treatment of BRCA1-like breast tumors¹

Typical set up of a preclinical intervention study. In this study a spontaneous breast cancer tumor is re-transplanted in recipient mice and the efficacy of the two single compounds and a combination of these compounds is tested,

Survival curve on the effect of Cisplatin, GSK126 and the combination of both compounds.



MTD + PK/PD studies

Pharmacokinetic studies using plasma and tissues

Many intervention studies use experimental agents that are not (yet) tested for pre-clinical use. To be (potentially) efficacious, an agent should at least reach its target in pharmacologically meaningful quantities. In order to address this issue, we conduct pharmacokinetic studies using plasma and tissues.

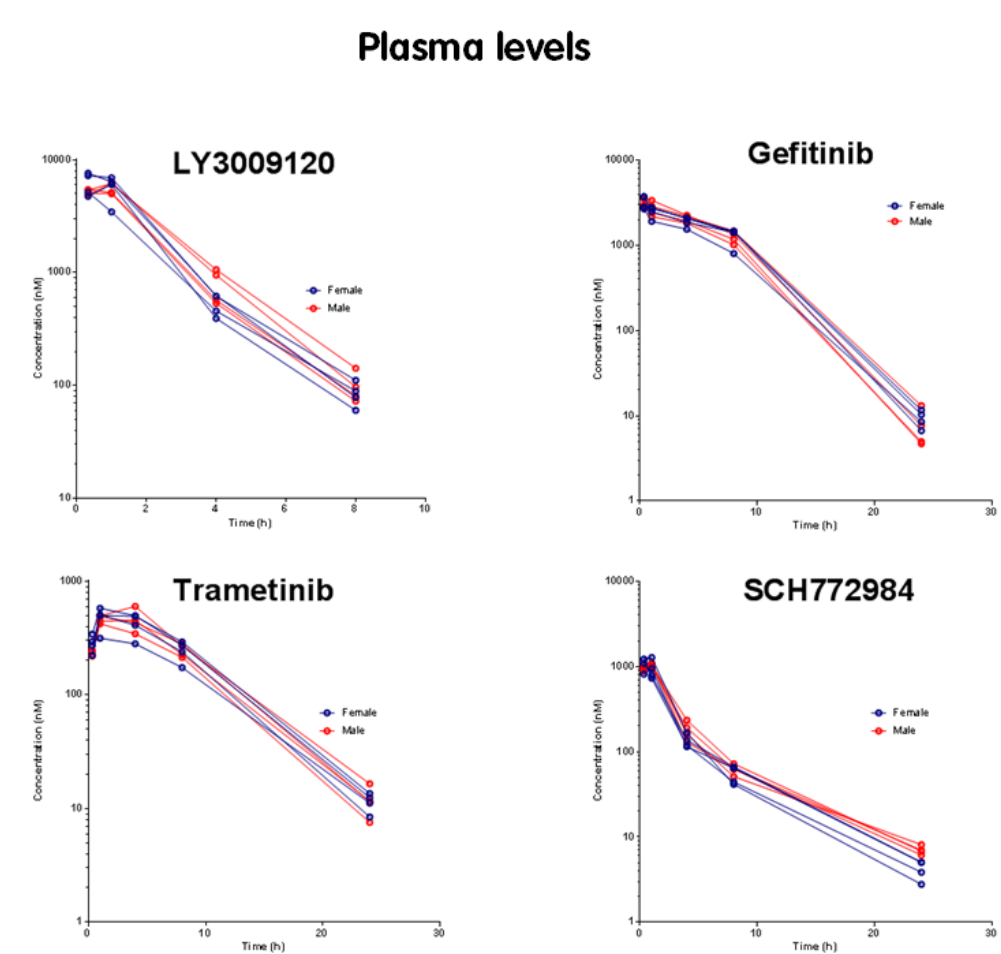
The sensitivity and selectivity of our LC-MS/MS systems usually allows the use of small samples volumes (5-10 µl) and minimal sample pretreatment, while still providing accurate data. This enables us to setup and validate assays for novel compounds in a relative short time frame.

Moreover, it allows us to perform analyses on tail vein blood samples that can be drawn serially and thereby obtain full pharmacokinetic plasma concentration – time curves from one animal adhering to the standards of the three R's in animal research.

Next to that we develop and/or provide advise what may be the most suitable formulation of such agents that can be used in animal studies. We perform studies to demonstrate the stability of drug formulations.



Intraperitoneal and oral injection, to deliver the compounds to the system

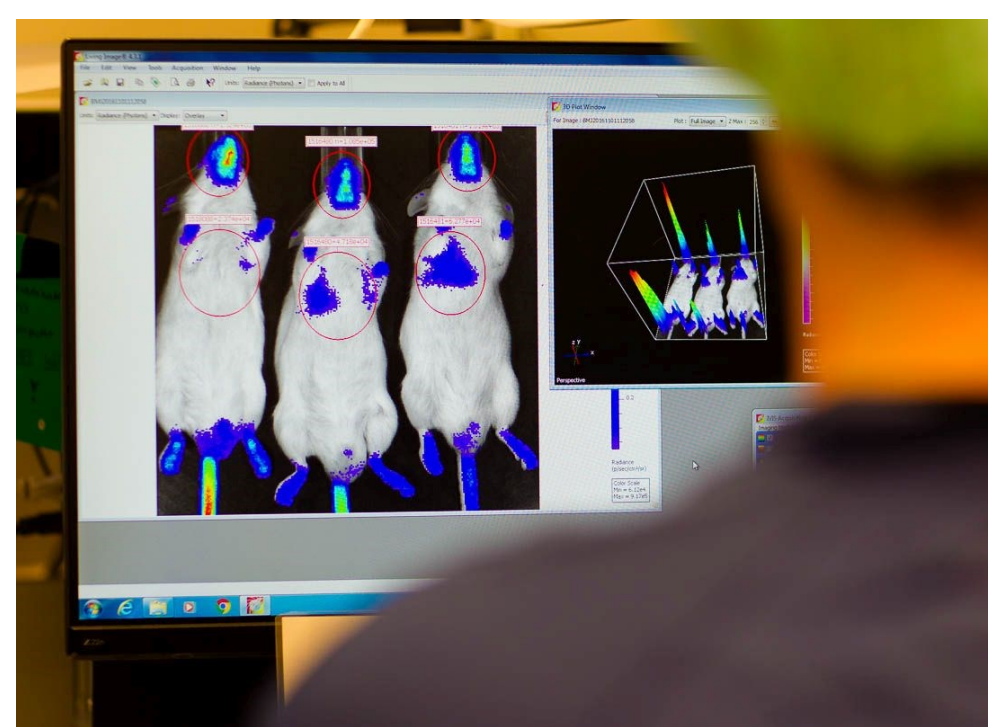


Imaging

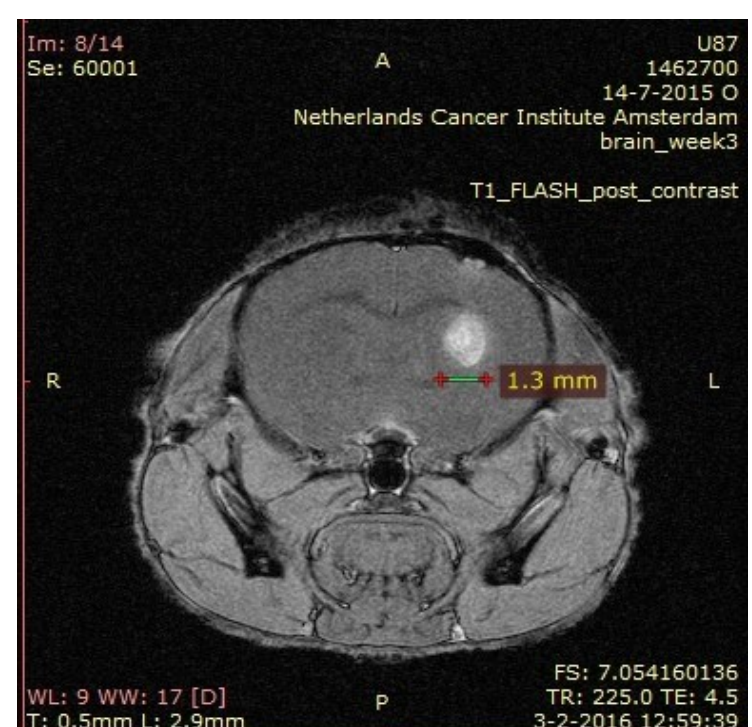
Preclinical imaging systems are essential for accurate measurements of tumor growth, metastasis formation, and therapy response in mouse models of human cancer. For this purpose, a dedicated Imaging Unit within the NKI animal facility is available to researchers interested in incorporating imaging into their studies. The imaging unit consists of an imaging suite of both functional and anatomical imaging for the purpose of *in vivo* imaging in mice. The systems available in the imaging unit are small animal versions of similar devices available in the clinic for the purpose of translational research. Available imaging equipment:

Precision Xray SmART+, image-guide radiation therapy system

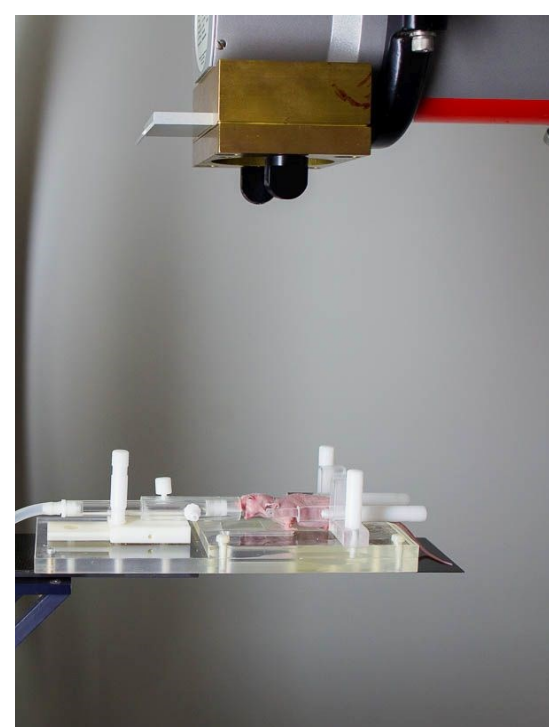
Brüker Biospec 7T MRI,
Albira PET/CT,
MILabs U-SPECT/CT,
PerkinElmer IVIS Spectrum
Faxitron Fullbody irradiation
Brüker ICON1T MRI



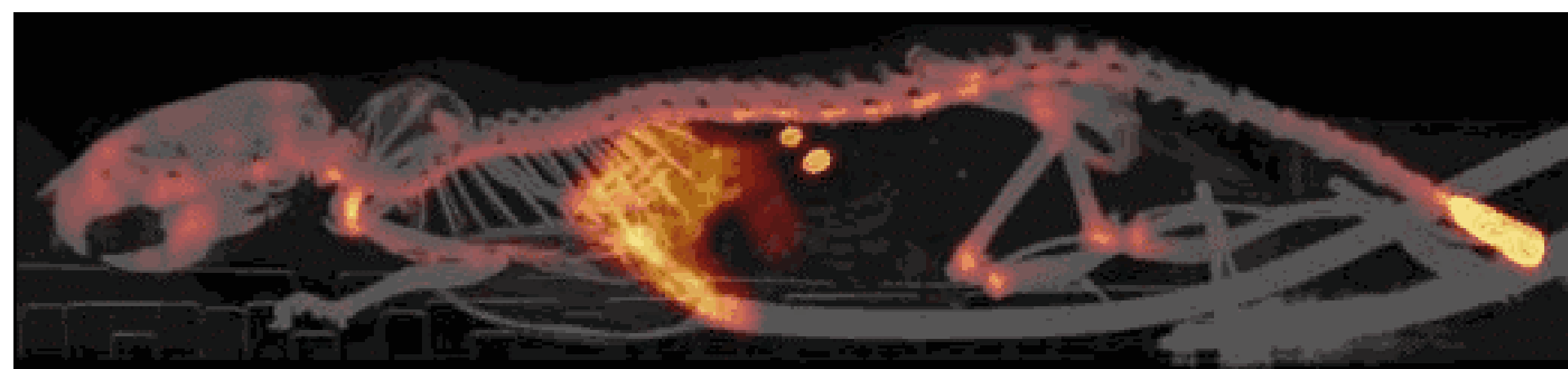
IVIS-imaging of a lung tumor model



MRI image of a brain tumor model



Irradiation of a brain tumor on the precision Xray SmART



SPECT/CT image on the MILabs U-SPECT/CT

Publications

Examples of Publications where animal experiments are performed within the preclinical intervention unit;

Combined inhibition of EZH2 and ATM is synthetic lethal in BRCA1-deficient breast cancer

Leonie Ratz, Chiara Brambillasca, Leandra Bartke, Maxim A. Huetzen, Jonas Goergens, Orsolya Leidecker, Ron D. Jachimowicz, Marieke van de Ven, Natalie Proost, Björn Siteur, Renske de Korte-Grimmerink, Peter Bouwman, Emilia M. Pulver, Roel de Bruijn, Jörg Isensee, Tim Hucho, Gaurav Pandey, Maarten van Lohuizen, Peter Mallmann, Hans Christian Reinhardt, Jos Jonkers and Julian Puppe.

EZH2 Is Overexpressed in BRCA1-like Breast Tumors and Predictive for Sensitivity to High-Dose Platinum-Based Chemotherapy

Julian Puppe; Mark Opdam; Philip C. Schouten; Katarzyna Jóźwiak; Esther Lips; Tessa Severson; Marieke van de Ven; Chiara Brambillasca; Peter Bouwman; Olaf van Tellingen; René Bernards; Jelle Wesseling; Christian Eichler; Fabian Thangarajah; Wolfram Malter; Gaurav Kumar Pandey; Luka Ozretić; Carlos Caldas; Maarten van Lohuizen; Michael Hauptmann; Kerstin Rhiem; Eric Hahnen; H. Christian Reinhardt; Reinhard Büttner; Peter Mallmann; Birgit Schömlig-Markieff; Rita Schmutzler; Sabine Linn; Jos Jonkers

Extensive preclinical validation of combined RMC-4550 and LY3214996 supports clinical investigation for KRAS mutant pancreatic cancer

Katrin J.Frank, Antonio Mulero-Sánchez, Alexandra Berninger, Laura Ruiz-Cañas, Astrid Bosma, Kıvanç Görgülü, Nan Wu, Kalliopi N. Diakopoulos, Ezgi Kaya-Aksoy, Dietrich A. Russ, Derya Kabacoglu, Franz Schmidt, Larissa Kohlmann, Olaf van Tellingen, Bram Thijssen, Marieke van de Ven, Natalie Proost, Susanne Kossatz, Wolfgang A. Weber, Bruno Sainz, Sara Mainardi

Patient-derived organoids model cervical tissue dynamics and viral oncogenesis in cervical cancer

Kadi Löhmussaar, Rurika Oka, Jose Espejo Valle-Inclán, Milou H H Smits, Hila Wardak, Jeroen Korving, Harry Begthel, Natalie Proost, Marieke van de Ven, Onno W Kranenburg, Trudy G N Jonges, Ronald P Zweemer, Sebastiaan Veersema, Ruben van Bortel, Hans Clevers

References

1. EZH2 Is Overexpressed in BRCA1-like Breast Tumors and Predictive for Sensitivity to High-Dose Platinum-Based Chemotherapy; Julian Puppe et al. PRECISION MEDICINE AND IMAGING | JULY 15 2019
2. www.combatcancerandaging.nl and www.nki.nl/research/facilities-platforms/animal-facility-mouse-cancer-clinic/

More
information

Website



Movie

