

THE MITIGATE CLINICAL STUDY

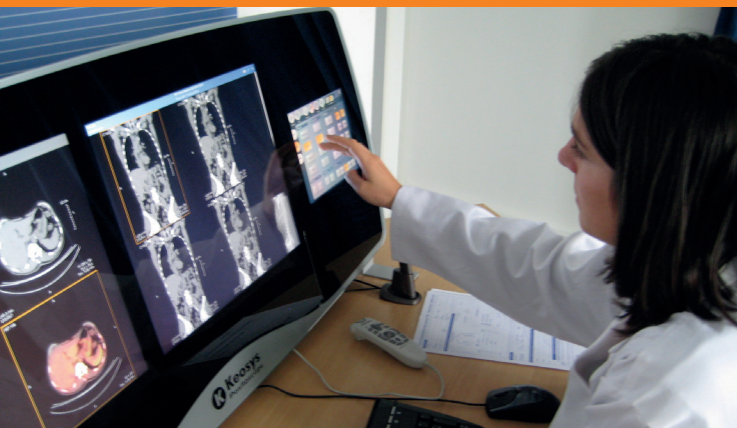
The MITIGATE project runs a first-in-human Phase I/IIa clinical study investigating the safety, tolerability and targeting properties of ⁶⁸Ga-NeoBOMB1 in patients with GIST as a combined phase I/IIa first-in-human study.

The study is carried out at the Medical University Innsbruck in Austria. Patients with advanced GIST – meaning metastatic disease in the liver or other intestinal organs – and predominantly with progressive disease (i.e. failure of established tyrosine-kinase-inhibitor) will be included. This patient group is also the most likely to benefit from future development of theranostic concepts revolving around NeoBOMB1.

The study started in early 2017 and is open to patients from all over Europe. While this study is focused on diagnostics, rather than therapeutic applications, patients may still derive benefit from results of the imaging procedure, such as improved definition of tumour volume and classification of disease.

OUTLOOK

The MITIGATE consortium is continuously exploring funding opportunities to further shape its concept into a comprehensive theranostic approach. MITIGATE partners strive to advance and multiply their results, proving the feasibility of a novel radioactive therapeutic substance in metastatic GIST patients.



MOTIVATION AND OBJECTIVES

Gastrointestinal stromal tumour (GIST) is a rare disease frequently affecting young patients. Its high potential for metastasising often leaves patients with a life expectancy of less than three years. Currently, there is only one class of effective medication – tyrosine-kinase inhibitors – but tumours frequently develop drug resistance after a few years. No molecular imaging technologies indicating drug resistance, early therapeutic response or disease progression are clinically available. Furthermore, effective targeted agents with other mechanisms of action, such as endoradiopharmaceuticals, are not designed for treatment of GIST and alternative minimally invasive treatment options are not well explored. This leaves GIST patients with very limited treatment options.

The MITIGATE project aims to develop new protocols and guidelines to effectively diagnose and treat patients with metastatic GIST resistant to current treatment

EXPECTED OUTCOMES OF MITIGATE

- Optimisation of biopsy and tissue preparation
- Effective targeted agents such as endoradiopharmaceuticals for treatment in patients
- Molecular imaging probes for specific GIST features indicating drug resistance, early therapeutic response or progression
- Minimally-invasive treatment options with fewer side effects for personalised treatment of patients with metastatic disease
- Non-invasive monitoring of treatment effects in clinical routine



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CLOSED-LOOP MOLECULAR ENVIRONMENT FOR MINIMALLY INVASIVE TREATMENT OF PATIENTS WITH METASTATIC GASTROINTESTINAL STROMAL TUMOURS



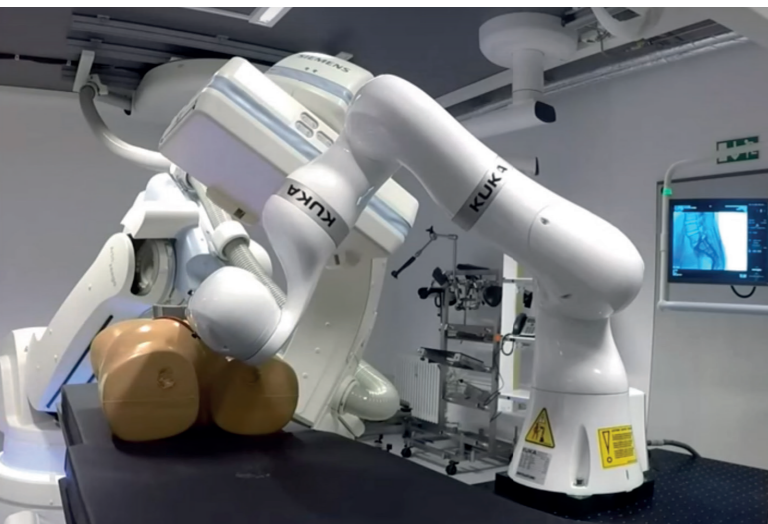
ACHIEVEMENTS OF THE PROJECT

The highly complex research carried out within MITIGATE already lead to a variety of project results and outputs. The achievements will strongly affect GIST patients, improving their personalised diagnosis and treatment. MITIGATE findings may in many cases be transferable to other cancer types.

- Assisting device for minimally invasive treatments
- Novel targeted radiopharmaceutical
- Advances in MRI Imaging
- Innovative endoscopic biopsy system

ASSISTING DEVICE FOR MINIMALLY INVASIVE TREATMENTS

The assisting technology will support physicians performing minimally invasive treatments in planning, execution, and monitoring of the intervention. The manipulator consists of a robotic unit with modifications tailored to the interventional task. To date, the manipulator system show very promising results in terms of intervention precision and time.

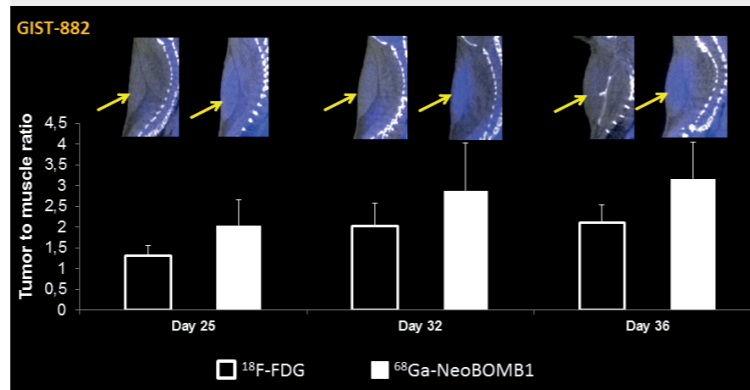


NOVEL TARGETED RADIOPHARMACEUTICAL

MITIGATE partners tested a number of candidate compounds for specific and safe GIST imaging to identify a novel, targeted radiopharmaceutical that provides an effective, non-invasive tool for personalised diagnostic and/or treatment options.

NeoBOMB1 is a new generation bombesin analogue peptide, which binds with high specificity to the gastrin release peptide receptor (GRPR), which is highly overexpressed in GIST.

Performed in vitro studies confirmed a high binding affinity and low internalization of NeoBOMB1. In vivo studies with NeoBOMB1 radiolabelled with ^{68}Ga in mice bearing the GIST tumour xenografts showed



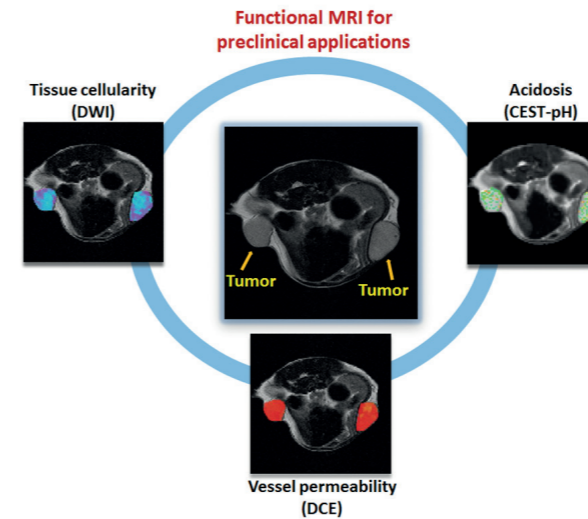
a higher uptake for ^{68}Ga -labelled NeoBOMB1 in comparison with the standard PET tracer ^{18}F -FDG.

No signs of toxicity were observed in rats, indicating that the peptide is well tolerated at a dose several hundred times higher than the intended maximum peptide dose for use in humans.

NeoBOMB1 was therefore chosen as the most suitable radiopharmaceutical compound for the MITIGATE clinical study.

ADVANCES IN MRI IMAGING

Non-invasive, molecular MRI techniques based on physiological ^1H and ^{23}Na MRI in combination with quantitative DWI/DCE/CEST-MRI and DECT will allow earlier detection of vascularisation and



cytotoxicity related to tumour response/progression in clinical routine follow-up procedures.

First results of a new dedicated ^{23}Na -MRI coil show a potential to extend magnetic resonance imaging beyond anatomical imaging by providing physiological information on cellular metabolism at clinical level.

A comprehensive MRI protocol for specific surveillance of drugs response in GIST patients has been established based on MITIGATE's development in MRI techniques.

INNOVATIVE ENDOSCOPIC BIOPSY SYSTEM

MITIGATE partners designed a novel endoscopic biopsy system with a specialized biopsy device taking samples for molecular analysis through a flexible endoscope.

Our solution is similar to a percutaneous biopsy gun and can enter through the mucosal layer and is fast enough to not exhibit a significant deformation of the tissue.

The tissue sample is transported back through a tube inside the endoscope by applying a vacuum.

Experiments have shown the cutting tool to provide uniform cylindrical tissue samples in good overall quality. The designed biopsy-tool has turned out as the valid method for GIST biopsy.

