# Publishable Summary for 22HLT03 AlphaMet
# Metrology for emerging targeted alpha therapies

## Overview

Targeted alpha therapy (TAT) is a rapidly growing cancer treatment modality, whereby alpha-emitting radiopharmaceuticals selectively target tumours whilst minimising the radiation to healthy tissues. Presently only $^{223}RaCl_2$ has regulatory approval, but its success resulted in unprecedented levels of interest and investment in TAT for a variety of cancers. It is showing promising efficacy and increased survival in clinical trials; however, several unmet and unique measurement challenges remain a barrier to enable the safe and optimised implementation of emerging targeted alpha therapies. This project will provide the metrology needed to support end-to-end traceability before wide routine adoption.

## Need

Global cancer incidence is projected to increase 47 % by 2040 with 28.4 million new cases each year. Europe's Beating Cancer Plan recognises the need for personalised cancer treatments and encourages the development of novel radiation therapies like TAT. The success of $^{223}RaCl_2$, the first and only with marketing authorisation for advanced prostate cancer, resulted in unprecedented levels of interest and investment in this promising treatment modality with new treatments based on $^{227}Th$, $^{225}Ac$, $^{212}Pb$, or $^{211}At$ undergoing clinical trials.

The short range and high energy of alpha particles is showing promising treatment efficacies even in patients not responding to its beta-emitting analogue therapy. However, these advantages bring new measurement challenges including the lack of validated primary (secondary) activity standards, the in-growth of the decay progeny, the separation of the decay products, or the quantification of the microscopic distribution of activities and absorbed dose *in-vivo*. The best approach to deliver TAT is under debate and good practice guides are not available, with treatments currently administered with fixed radiopharmaceutical activity levels and not guided by dosimetry. This is in contrast to external beam radiotherapy, where treatments are traceable to primary standards and accuracy in dose delivery to patients is below 5%. The accuracy, reproducibility, and uncertainties in the delivery of TAT are presently unknown, with a recent ICRU Report 96 highlighting the need to address the lack of traceability and standardisation/harmonisation.

An estimated 6 million annual therapies are already delivered across more than 1,500 nuclear medicine centres in the EU, and unprecedented levels of demand for TAT are expected in coming years (100-fold). It is therefore of vital importance to facilitate accurate measurements with minimal uncertainties to improve confidence and evidence in the safe routine implementation of personalised TAT, required to support 2013/59/EURATOM and other regulations.

## Objectives

The overall objective of the project is to address the unique and unmet metrological challenges of targeted alpha therapies. The specific objectives of the project are:

1. To develop and validate **primary and secondary radioactivity standards** with traceability to national standards and low uncertainties that consider decay chain progeny in-growth and the separation of

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decay products for alpha-emitters radionuclides such as $^{211}$At, $^{212}$Pb/$^{212}$Bi, $^{224}$Ra, $^{225}$Ac, and $^{227}$Th. In addition, clinical therapy requirements and achievable clinical measurement accuracies will be assessed by an inter-comparison exercise.

2. To provide guidance for clinical stakeholders on organ **activity quantification methods** using external monitoring systems and nuclear medicine imaging. This will be achieved by: (i) the development of methods to quantify the separation of the decay products during imaging at the required levels of therapy activity; and (ii) the performance of a comparison exercise to assess the accuracy, reproducibility, and the quantification of uncertainties of the developed methods in a clinical setting.

3. To establish **accurate alpha-emitter dosimetry calculations** that enable compliance with 2013/59/Euratom and the assessment of the true dose response relationships. This will be achieved by: (i) the validation of dosimetry pharmacokinetics models for TAT; (ii) the determination of the uncertainties from measured activity to absorbed dose, including the identification of major factors affecting accuracy and precision for alpha emitting therapies; and (iii) the determination at the tissue level of the significance of mean dosimetry for highly heterogeneous distributions of alpha emitters.

4. To determine a **multi-modality imaging protocol that considers differences in bone density and marrow cellularity between individual patients based on**: (i) **a test object** manufactured by 3D printing technology that incorporates relevant tissue-equivalent materials and geometric complexity for the assessment of treatment toxicity and (ii) bone marrow dosimetry.

5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain and end-users (e.g., pharmaceutical as well as medical and healthcare products manufacturers, clinical QA laboratories and clinical stakeholders) and the relevant organisations in the context of the regulation (e. g. EANM, EFOMP, IAEA, EURADOS).

**Progress beyond the state of the art and results**

*Realisation, validation, and dissemination of radioactivity standards – objective 1*

Revision of secondary standards for $^{223}$Ra in 2015 showed a 9% discrepancy with previous data and highlighted the importance of traceability to primary standards and international comparison exercises. Primary and secondary standards will be developed for emerging alpha emitters $^{225}$Ac, $^{212}$Pb and $^{211}$At to enable traceable activity measurements for TAT in (pre)clinical centres, hospitals, and production sites. The robustness of activity standards will be assessed through inter-laboratory comparison and submission to the BIPM-SIR. To meet the needs of end-users, the time-dependence of calibration factors will be investigated when parent-progeny equilibrium conditions are not reached. The metrological traceability and accuracy of radionuclide activities administered to patients and used by (pre)clinical research centres, will be improved via a multi-centre intercomparison using radionuclide calibrators and gamma counters.

*In-vivo activity quantification with SPECT in TAT – objective 2*

Quantitative SPECT imaging is not established for alpha emitters, with a range of protocols used for acquisition and post-processing analysis. This project will use in-silico models of clinical SPECT scanners validated via experimental phantom measurements to optimise 3D imaging acquisition parameters and activity quantification methods, with traceability to the newly developed standards. The generated ground-truth data will be used to optimise methods to quantify long-lived decay progeny that may redistribute to other tissues, image reconstruction and correction methods to improve image quality and accuracy of activity quantification with known uncertainties. A standard protocol will be developed and used to perform the first multi-centre comparison of SPECT nuclear imaging for alpha emitters, providing knowledge on the levels of accuracy, reproducibility, and uncertainties achievable for harmonisation. This will provide recommendations for the harmonisation of quantitative imaging following TAT and will identify the major factors that impact accuracy and need further improvements.

*Quantification of absorbed doses in TAT – objective 3*

The ability to quantify the distribution of alpha emitters *in-vivo*, enables the possibility to incorporate dosimetry to optimise the treatment instead of using a ‘one size fits all’ approach with fixed administered activities. Accurate dosimetry relies on accurate knowledge of the spatial and temporal activity distribution and dose conversion factors. Commonly used clinical (macro)dosimetry methods assume a uniform uptake and no redistribution of daughters from the parent radionuclide. A framework will be established in this project to

assess the impact and errors associated with these assumptions through autoradiography, pharmacokinetic modelling and microdosimetry for TAT, including methods to assess the uncertainties in the activity to absorbed dose measurement chain.

*Towards personalised bone marrow dosimetry through quantitative morphological imaging – objective 4*

The red marrow is considered a dose-limiting organ at risk that can limit the administered activity, making marrow dosimetry essential for safety. Reference models for marrow dosimetry are based on relatively simple skeletal models. Variations in bone density, and red and yellow marrow contents can introduce errors of up 200 % on red marrow dosimetry for alpha emitters depending on bone site and age, making it highly patient-specific. This project will evaluate the potential to incorporate patient-specific bone marrow morphology measures into dosimetry calculations through the development of bespoke phantom and morphological imaging protocols based on MR and dual-energy CT imaging.

**Outcomes and impact**

*Outcomes for industrial and other user communities*

This project will be the first international effort to provide metrology support for the determination of end-to-end measurement uncertainties and for improving methods to quantify activity and absorbed doses for alpha-emitting radiopharmaceuticals. The provision of validated radioactivity standards for currently unavailable alpha-emitting radiopharmaceuticals will enable the dissemination of traceability from NMI/DIs and will provide access to improved capabilities for national and accredited laboratories in Europe, supporting consistency in activity measurement capabilities. New standards with recommendations for improving measurements will benefit the end-users that rely on such calibration services, including manufacturers of ionising radiation measurement instruments (radionuclide calibrators, gamma counters, imaging scanners), radionuclide production facilities, and pharmaceutical companies.

Hospitals delivering TAT will be able to administer treatments with traceable activities, with accuracies within the limits recommended by the IAEA. The recommendations for good practice will be of benefit to end-users like healthcare professionals in hospitals and the pharmaceutical industry, providing them with methods to standardise and harmonise imaging and dosimetry methods with robust uncertainty budgets. This will improve reproducibility in multi-centre studies and enable comparison of results, providing greater statistical power to study correlations between absorbed dose and response/outcome measures which are still lacking for TAT. This will provide the basis for evidence-based treatments, facilitating regulatory compliance and marketing authorisation of upcoming alpha radiopharmaceuticals for the pharmaceutical industry, and potentially reducing the development costs by introducing metrology early before routine implementation of TAT.

*Outcomes for the metrology and scientific communities*

Standardisations and improved decay data for alpha emitters will be validated through inter-laboratory comparisons organised by the participating NMIs and linked to the BIPM International Reference System (SIR) to provide a route to demonstrate their accuracy, consistency, and independence, which in turn will support regulatory compliance. Some of the participating members are new to a EURAMET project, which will promote knowledge transfer between the scientific community and metrologists, building networks that will lead to opportunities for further research. Knowledge of activity standardisation techniques will be shared amongst NMIs.

A recent report by the European Commission identified the need for investment towards a sustainable and resilient supply of medical radionuclides in the EU as key to meeting future demands, in particular for alpha emitters. These challenges are presently being addressed by other ongoing initiatives such as Horizon 2020 PRISMAP or the NOAR COST Action project. The outcomes of this project will complement and expand on these initiatives by addressing the measurement challenges of establishing traceable and harmonised measurements to guide the use of upcoming TAT in a clinical setting.

These and other initiatives will create and strengthen opportunities and collaborations between metrologists and the scientific community, increasing the competitiveness and international recognition of the European metrology infrastructure. The project outputs will be disseminated to the scientific research community and other stakeholders via reports and recommendations, peer-reviewed publications in high-impact scientific journals, presentations at national and international conferences, and through engagement with the IAEA and international societies such as the EANM, EFOMP and EURADOS.

*Outcomes for relevant standards*

The improved end-to-end measurement traceability provided in this project, from the provision and dissemination of activity primary and secondary standards to the provision of recommendations for accurate imaging and dosimetry with known uncertainties for alpha emitters, will support EU directive 2013/59/EURATOM mandating dosimetry-guided radiopharmaceutical therapies (including TAT), but also 2001/83/EC for medicinal products, and 2001/20/EC for clinical trials.

The experienced consortium will promote the results of the project within the standardisation community and through involvement with international technical committees, including organisations establishing international equivalence for radioactivity measurements (BIPM, EURAMET TC-IR) through the development of radionuclide metrology techniques (ICRM). Good practice guides and recommendations to standardise and harmonise imaging and dosimetry for TAT will be disseminated and promoted within the International Atomic Energy Agency (IAEA), European Association of Nuclear Medicine (EANM), the European Federation of Organisations for Medical Physics (EFOMP), and the European Radiation Dosimetry Group (EURADOS). In particular, the results of a multi-centre comparison exercise of clinical quantitative SPECT imaging for alpha emitters will be of interest to the EANM Forschung GmbH (EARL) initiative establishing accreditation programmes for the harmonisation of nuclear medicine imaging. However, it should be noted that some of these processes can be lengthy and extend beyond the duration of this project.

*Longer-term economic, social, and environmental impacts*

One in 2 people will develop cancer in their lifetimes and as life expectancy increases, the number of patients needing cancer treatment rises. According to an international project by the Lancet Oncology Commission, a comprehensive scale-up of imaging, treatment, and care quality would avert 9.55 million (12.5%) of all cancer deaths, saving 232.30 million life-years. Scale-up of imaging would cost US$6.84 billion in 2020-30 but yield lifetime productivity gains of $1.23 trillion worldwide. Therefore, any advancements towards improving image quantification for emerging novel cancer treatments like TAT will have a major positive economic impact.

The development and translation of new TAT for a variety of cancers is rapidly growing with a global market size of US$ 672 million that is expected to grow 36.7% by 2027. As an example, due to the high incidence of prostate cancer, which is a prime candidate for TAT, an unprecedented level of demand is expected, with 350,000 patients being potentially eligible for $^{225}$Ac-PSMA therapy in coming years if following the same trend as its beta-emitter analogue $^{177}$Lu-PMSA. In the UK, the number of $^{223}RaCl_2$ treatments increased by 100-fold in three years following its approval, further highlighting the potential rate of demand. The traceability for TAT provided by this project is therefore of major importance to support the logistical and scientific challenges that European nuclear medicine departments will face in the imminent future.

The implementation of metrology to support the development and use of alpha-emitting radiopharmaceuticals has a fundamental role in the provision of cost-effective cancer treatments that improve patient outcomes with minimal toxicity. Improved knowledge of the decay data, traceable measurements of activity as well as harmonised imaging and dosimetry protocols for multi-centre studies will provide robust tools and confidence to enable personalised dosimetry-based treatment planning and treatment verification as required by the Basic Safety Standards Directive. The outcomes will also indirectly contribute towards increasing confidence in radiation protection measurements for handling of radioactive material during the delivery of TAT.

On a wider impact scale, the developed innovative approaches and new collaborations established between measurement laboratories and stakeholders will be open to further exploitation and lead to new services and products relating to activity measurements, imaging and dosimetry calculations for TAT that can result in higher employment rates and wealth for society across Europe and worldwide.

**List of publications**

N/A yet

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| Project start date and duration: | 1st September 2023, 36 months | |
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| Internal Beneficiaries:<br>1. CMI, Czech Republic<br>2. CEA, France<br>3. CIEMAT, Spain<br>4. ENEA, Italy<br>5. NCBJ, Poland<br>6. SCK-CEN, Belgium | External Beneficiaries:<br>7. BfS, Germany<br>8. KU Leuven, Belgium<br>9. KUM, Germany<br>10. OSA, Spain<br>11. UGOT, Sweden<br>12. UKW, Germany | Unfunded Beneficiaries:<br>13. ARRONAX, France |
| Associated Partners:<br>14. CHUV, Switzerland<br>15. NPL, United Kingdom<br>16. RSFT, United Kingdom | | |
| Affiliated Entities: 17. BB, Spain (linked to OSA) | | |