European Commission

JRC CONFERENCE AND WORKSHOP REPORT

# Translating radiotheranostic cancer research into clinical practice in Europe

*Workshop report with conclusions and recommendations*

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Joint Research Centre

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# Contents

## Abstract

The Joint Research Centre of the European Commission launched in 2023 a series of stakeholder consultation workshops on the difficulties in bringing medical radionuclide innovations to routine use. In this context, JRC held a workshop on 27 April 2023 at its Ispra site on "Translating radiotheranostic cancer research into clinical practice in Europe" in order to look into obstacles blocking patients' access to the best state-of-the-art radiopharmaceutical cancer treatments. Since there are recent market authorisations for radiopharmaceuticals for neuroendocrine tumours and metastatic castration resistant prostate cancer, the workshop looked into these medical indications where the step from research into clinical practice has been made. Several gaps, needs and challenges slowing down research and its translation into clinical practice were discussed at the workshop. In order to enable and maintain patient access to radiotheranostic technologies, a continuous and resilient supply of radionuclides, an adequately trained medical workforce, and properly equipped hospitals were found to be essential. In addition, these procedures need an assessment by the national health systems to be considered for reimbursement. Further research is required to better understand and overcome the limitations of these new therapies, especially understanding and predicting the differences in treatment outcome and the possible benefits of an earlier treatment. Moreover, several aspects of training, logistics, health economy and regulatory issues have to be tackled to continue with the successful development of this approach, possibly expanding radiotheranostics to further types of cancer. To achieve this, a better coordination of actions is required at EU level.

The participants discussed issues around the development, improvement and clinical application of radiopharmaceuticals and came up with the following recommendations:

1. Encourage a coordinated approach between programmes and initiatives (including Euratom, Horizon Europe, EU4Health and Europe's Beating Cancer Plan among others), with solutions for scaling up to market demand and clinical use.
2. Strive for EU autonomy for a continuous, stable and uninterrupted supply of medical radionuclides, considering an increasing demand and use of several radionuclides including alpha-emitters.
3. Harmonise the requirements for clinical trials with radiopharmaceuticals at EU Member States level, in order to enable multicentre European studies, and agilise timelines for approval.
4. Address regulatory issues concerning radiation protection, including harmonisation of guidelines for hospitalisation length after radiopharmaceutical routine treatments.
5. Joining forces on education and training for radiopharmaceutical use to health care providers, radiation protection experts, regulators, decision makers, patients and respective care takers.
6. Encourage the integration of radionuclide technologies in multidisciplinary clinical boards, addressing also pooling of data for harmonisation of clinical practice.
7. Support health technology assessments and cost-effectiveness analysis of radiopharmaceutical diagnosis and treatments in support of reimbursement decisions.

## Acknowledgements

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- Konrade Von Bremen, Vice-President of Nuclear Medicine Europe.
- Barbara Picutti, Member of NET ITALY ETS, Italian association of neuroendocrine tumour patients

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# 1 Introduction

This workshop was the first of a series of discussions with stakeholders from academia, industry, policy makers, research and health experts, clinical end users and public interest groups, to discuss and identify the challenges and roadblocks in the translation of research on nuclear sciences in medical applications into clinical practice. The access to new technologies by patients will define the demand for such therapies in the future and will require innovation, technical solutions, and specialised staff with various medical, nuclear, technical, and scientific profiles. EU Commissioner Mariya Gabriel has chaired a High-level European Nuclear Roundtable on 13 February 2023, which focused on medical applications of nuclear. Several EU initiatives reflect the political commitment to mobilise the collective power of the EU to enable patients' access to the latest state of the art technologies for diagnosis and treatment. The roundtable aimed at launching concrete effort, in the remit of the research programmes, to explore the challenges that hinder the translation of technological advances into adequate and equally accessible radionuclide procedures for European patients.

## **Summary of Commissioner's** introduction at the workshop

Commissioner Gabriel highlighted that Europe has been holding a leadership position in the technological development of radiotheranostics over the past decades. It is essential that we mobilise resources at EU level to continue research and innovation in this area and facilitate a more widespread translation of new technologies for cancer treatment into clinical practices. There are already several EU initiatives underway like the Europe's Beating Cancer Plan, the Cancer Mission, the Strategic Agenda for Medical Ionizing Radiation Applications (SAMIRA) and related nuclear research under the Euratom programme, and other programmes which reflect a strong political commitment at EU level. Synergies between these initiatives, and enhanced cooperation between all stakeholders involved, should be further encouraged in order to make the most of the EU's collective power. Our overarching goal is to guarantee EU patient's access to adequate options for cancer diagnosis and treatment, which can make a great difference in improving their quality of life.

# 2 Summary of Presentations

## 2.1 Session 1 – Radiotheranostics: radionuclide-based therapy and companion diagnostics

Theranostics makes use of specific surface molecules on cancer cells which can be targeted by an appropriate ligand. The ligand is linked with a radionuclide which allows to image and to quantify these surface receptors. Based on these findings, patients are selected for therapy which uses the same ligand but labelled with a beta or alpha particle emitting radionuclide to kill the targeted cancer cells.

For more than 80 years this principle has been applied to image and treat thyroid disease with iodine radionuclides. In the last three decades, progress has been made in using specific molecules to target neuroendocrine tumours (somatostatin receptors) and prostate cancer – through the Prostate Specific Membrane Antigen (PSMA). This has led to the market authorisation of new medications which allow precision oncology treatments of advanced neuroendocrine tumours and prostate cancers with limited therapy options with the beta-emitter $^{177}$Lu. With the discovery of further potential target molecules, radiotheranostic research is now rapidly expanding, promising new treatments for various types of cancer.

The combination of diagnosis and treatment targeting the same molecular structures on the cancer cells, is appealing since one can see what is treated in severely metastasized disease. In spite of sometimes spectacular success, further improvements are needed concerning dosage schemes, the proper timing for treatment in the course of the disease and investigating the reason behind non-responders (patients who exhibit high target density but do not respond to therapy as expected). It can be assumed that dosage schemes still allow for optimisation. It has been reported that reducing dose to account for elevated patient age and comorbidities may further reduce side effects, without significantly compromising treatment success[1]. Also, the use of other radionuclides – especially alpha-particle emitters – may be promising, as shown in small studies so far[2].

The concept of using the alpha emitters $^{225}$Ac and $^{213}$Bi was born in JRC Karlsruhe (ex-Institute for Transuranium Elements or ITU) in the early 1990's. The advantage of using alpha emitting radionuclides is that alpha particles have a high energy (4–9 MeV) and a short range in human tissue (< 0,1 mm), therefore they provide very effective and selective cell killing for oncological treatment purposes. Alpha emitters can overcome resistance of cancer cells to beta-, gamma-radiation and chemotherapy. Work continues on methods for production of $^{225}$Ac to secure its supply, standardized protocols for synthesis and quality control of radiopharmaceuticals based on $^{225}$Ac, preclinical studies in vitro and in vivo, clinical testing, knowledge transfer through provision of training to hospitals in EU and worldwide, and organization of international symposia on Targeted Alpha Therapy.

Oncologists recognise the potential of radiotheranostics in cancer treatment, however, they would like to have a broader statistical basis to understand the differences between responders and non-responders and the best way to monitor the progress of the treatment. Moreover, research is required into biological markers that could predict these differences in treatment response. In view of treating patients in earlier stages of disease, the questions of achieving the best dosage regime as well as quantifying the risk of late radiation-induced secondary malignancies also become more urgent. Depending on disease, further clinical trials are needed, especially looking into combination treatments with established and other emerging new therapy approaches, such as mRNA and immunotherapies.

Since cancer per se is a complex disease, and treatment options become more and more elaborate, the role of centres of excellence and of multidisciplinary tumour boards including pathologists, oncologists, radiologists, and nuclear medicine specialists has been emphasized, to provide the best possible option to the patient at the right time, knowing that this will be a challenge for the already high workload of all medical specialists involved.

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[1] Ugo De Giorgi et al.; Circulating androgen receptor gene amplification and resistance to 177Lu-PSMA-617 in castration-resistant prostate cancer: results of a phase 2 trial. Brit. J. Canc. https://doi.org/10.1038/s41416-021-01508-5
G. Paganelli et al., Dosimetry and safety of 177Lu-PSMA-617 along with polyglutamate parotide gland protector: preliminary results in metastatic castration-resistant prostate cancer patients. EJNMMI https://doi.org/10.1007/s00259-020-04856-1

[2] Larger phase 3 registration studies are under way, e.g. for somatostatin-receptor-positive well-differentiated gatstroenteropancreatic neuroendocrine tumours (e.g. Action-1; NCT05477576).

## 2.2 Session 2 – **The cancer patients' view**

Several cancer patients and care takers shared their experiences relating to pathways from diagnosis to treatment and experience with the radiotheranostic technologies.

Difficulties were reported when seeking radiotheranostic therapy at national level and abroad. Health systems are not harmonised and may differ concerning the standard sequence of therapies as well as their timing, and the implementation of reimbursement decisions for new therapies and diagnostic procedures. Seeking access to such new medical treatments abroad due to lack of access in the country of residence is likely to create reimbursement problems in the country of residence. This points to a general problem when trying to establish a common market for health services.

Two cancer patients treated for neuroendocrine tumours with $^{177}$Lu-DOTATATE, after having undergone several therapies before, reported on their experience and essentially confirmed that the therapy is generally well tolerated. Both patients reported that they could follow their normal daily activities without problems. The same was reported from a prostate cancer patient who had considerable improvement after the first two cycles of $^{177}$Lu-PSMA-617 therapy.

Some patient representatives presented their concerns on a stable, uninterrupted and sustainable supply of therapeutic radionuclides in view of the increasing demand and the current age of the European (and global) nuclear reactor fleet used for their production. While there are several projects to construct new nuclear research facilities, which have the intention to engage in medical radionuclide supply, the market will rely for several years on the existing infrastructures before new facilities can take over. In addition, clinicians pointed out that current supply shortages with $^{177}$Lu-PSMA-617 seem to be rather related with delays in getting new GMP (Good Manufacturing Practices) production sites approved than with radionuclide production. It is however a major concern for patients to face a situation where a sequence of radiotheranostic treatments cannot be continued as planned due to supply shortages of the radiopharmaceutical. In the context of availability the pricing and the reimbursement rules are also a major concern. For patient representatives, issues which limit the availability of a new pharmaceutical, especially when it is perceived to be a more tolerable therapy and/or the best option after standard of care treatment, have an ethical dimension.

## 2.3 Session 3 – Radiotheranostics: innovations and challenges

The first half of this session looked into radiobiological studies on the effects of radiopharmaceuticals. Recent findings pave the way to possible improvements by combinatorial approaches such as those involving immunostimulatory effects of the interaction of cells with radionuclides. They may be exploited in the future in combination of radiopharmaceutical treatments with immune checkpoint inhibitors, including anti-PD-L1 therapy, in patients who are less likely to respond to peptide receptor radiotherapy (PRRT) alone and in patients with heterogeneous disease. This therapy blocks the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) and allows the T cells to continue killing tumor cells, which they otherwise would stop. Therefore, the communication between cells hit by alpha-, beta-particles or Auger electrons and immune cells deserves more attention.

The second half of this session continued to deal with the challenges to bring progress in radiotheranostics to the patients. Promising clinical trial results prospect increasing demand, various new molecular targets and new therapeutic applications are further increasing expectations, but the challenges are growing, especially in Europe. The lack of a start-up culture and the difficulty to get access to venture capital in Europe leads to reduced investment, hampers innovation and drains brain from Europe towards the global players. In the US for example, much higher investments are currently mobilised for radiotheranostic developments and clinical trials, as well as for radionuclide production, especially for alpha-particle emitters.

In the European Union only the market authorisation for medicinal products is centralised by the European Medicines Agency and the European Commission. The regulatory landscape for clinical trials, especially with radiopharmaceuticals, as well as for reimbursement decisions for approved medicines is heterogeneous, scattered and the decision process is slow. The same holds for investments in critical infrastructure. As a

consequence, Europe is losing the technological leadership in nuclear health innovation it held for decades. Treatment capacities in terms of hospital beds are shrinking, and there is a lack of professionals in nuclear medicine. The understanding of biomarker concepts and of radiobiology is poor and regulators have little experience with radiopharmaceuticals. The different national application of the Council Directive 2013/59/EURATOM related to radiation protection raises doubts on their scientific basis and stakeholders call for harmonised European guidelines (cf. Figures 2 and 3). These remarks led to an intense discussion on how to help translation of radiotheranostics into clinical practice.

# 3 Discussion

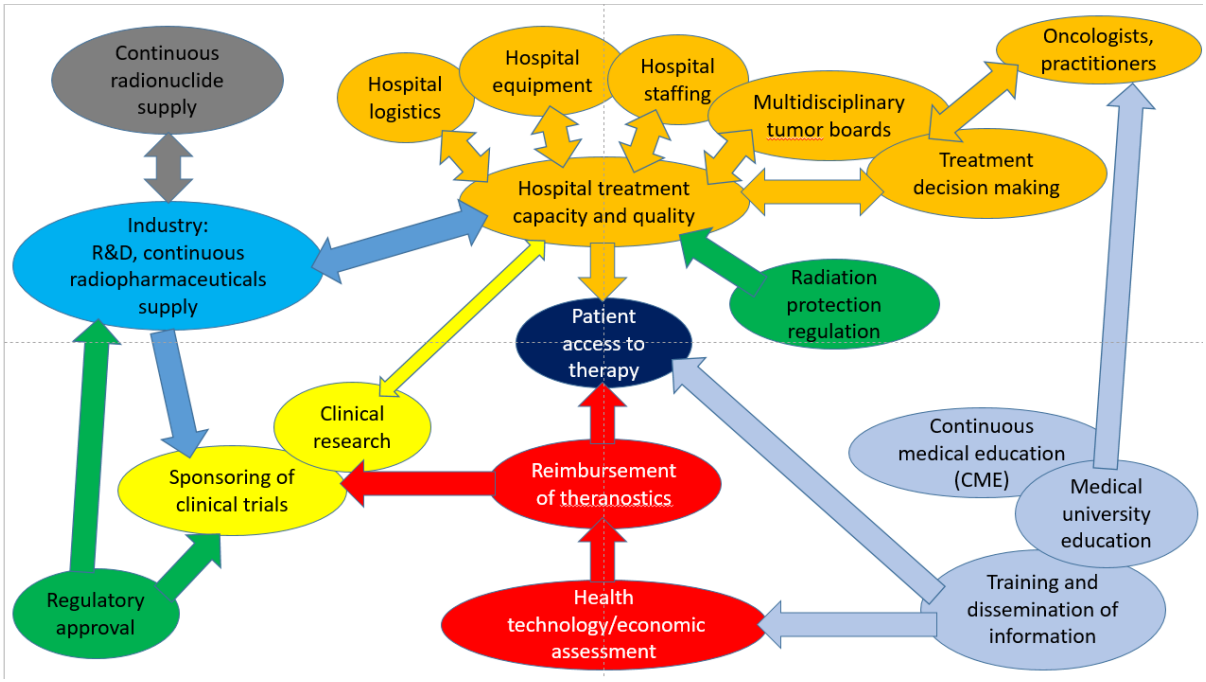
## 3.1 Session 4 – Translating radiotheranostics into clinical practice

Based on the first intervention of the panellists and the key messages made, we can summarise that patient access to radiotheranostic procedures depends essentially on the following points:

1. The availability of sufficient radionuclides and radioligand molecules.
2. Agile and comparable clinical trials with valid endpoints on innovative treatments
3. Implementation of harmonised and science-based radiation protection measures for radiopharmaceutical treatments[3].
4. Streamlining of the process to grant marketing authorisation to radiopharmaceuticals.
5. Adequate hospital capacities - hospital beds in nuclear medicine wards with adequate facilities that can handle radioactive waste.
6. The availability of qualified medical and other technical staff to handle and administer the radiopharmaceuticals.
7. The reimbursement of the radiopharmaceuticals by the health system.

These points have to be seen and analysed together as they are interconnected as can be seen in the following figure.

Figure 1. Visualisation of the interdependences to be considered when bringing new radiopharmaceuticals from clinical research to the patient (explanation see text below).




*Source: Uwe Holzwarth*

[3] Limiting the hospitalisation to a safe and reasonable minimum especially when hospitalisation is a burden for advanced stage cancer patients.

The patients' access to therapy is at the centre of the consideration. Patients want the best option for their specific situation to be available and reimbursed by their insurance or health care system. They also need to find a hospital which can perform this treatment with high quality of care.

To be reimbursed the treatment needs to prove clinical efficacy and cost-effectiveness. Reimbursement approval signals to industry that the development of similar therapies has a prospect of revenue and that the economic risk is limited. Missing reimbursement (without a scientific reason) and delay in the approval of clinical trials and market authorisation will discourage sponsors, hamper clinical research and slow down medical innovation. However, looking at differences from country to country, pricing of new products in the absence of competitors is frequently an issue when limited resources enforce prioritizations. Moreover, lack of reimbursement and restricted market in one country may lead to excessive prices in countries where reimbursement is granted.

The production of radiopharmaceuticals requires a continuous just-in-time production and distribution of medical radionuclides, and administration to the patient requires adherence to sophisticated logistics and regulation also at hospital level.

Hospitals must be equipped with special administration rooms, radioactive waste management facilities including for excretions, and they need adequate diagnostics and medical imaging equipment. For each individual case discussion, all relevant medical specialities must be available in multidisciplinary tumour boards, to decide what option(s) to propose to the patient.

All professionals involved in decision making and patient care must be adequately educated and trained. Training and information are also indispensable for a general understanding and awareness for regulatory staff. Ideally, patients and their general practitioners should find unbiased, complete and up-to-date information in public and reliable sources.

### 3.1.1 Hospital capacity and radiation protection

Clinicians see one main limitation for patient access to radiotheranostic therapies in the treatment capacity of the hospitals, i.e., in the available number of beds in specially equipped nuclear medicine wards.

Improving this situation would require investments to upgrade or establish radiotheranostic treatment centres. However, an optimisation of the use of already available hospital resources can also increase the treatment capacity, e.g., by reducing the duration of hospitalisation. Currently, in some countries (e.g. in Germany and Austria) 48 hours of hospitalisation after PRRT (peptide receptor radiotherapy) or RLT (Radioligand Therapy) is a legal requirement, whereas in Italy it is no longer a legal requirement but still remains standard practice in most places[4], and in other countries (e.g. in the Netherlands or France) these therapies can be applied in outpatient schemes. Figures 2 and 3 present a partial synopsis of hospitalisation requirements in various countries for approved treatments with $^{177}$Lu.

[4] A change in Italian legislation in 2020 has eliminated a fixed requirement for hospitalisation for therapeutic radiopharmaceuticals other than $^{131}$I. (https://www.gazzettaufficiale.it/eli/gu/2020/08/12/201/so/29/sg/pdf) The specialised MD after having asked the opinion of the medical physicists and the radiation protection expert can decide flexibly on how to meet the legal dose limits for the patient's environment (Annex XXV). However, the old practice has de facto not been changed, and in most hospitals the 48h hospitalisation has been kept.

Figure 2: Hospitalisation requirements for $^{177}$Lu-DOTA-TATE treatment of neuroendocrine tumors in different countries

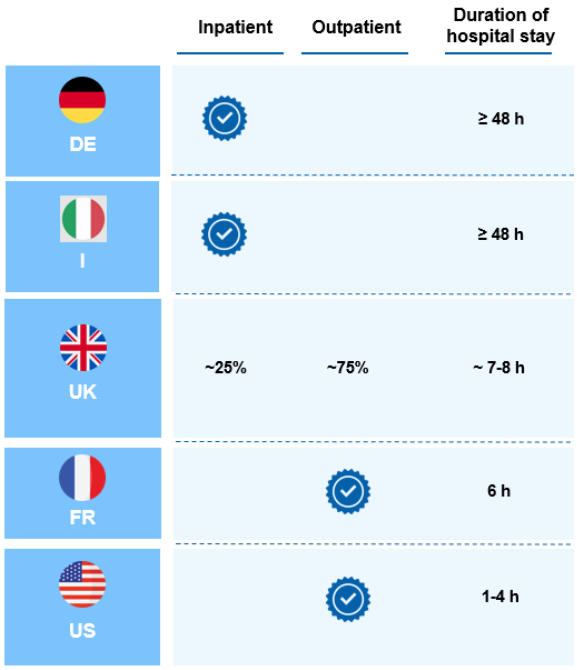
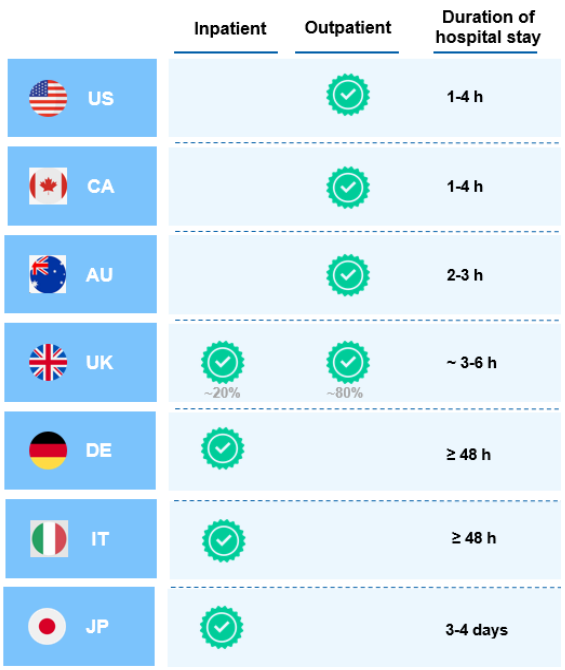



Figure 3: Hospitalisation requirements for $^{177}$Lu-PSMA treatment of prostate cancer in different countries




*Source: Professor Stefano Fanti.*

There was agreement that a common line should be established, based on a sound scientific assessment of existing data including excreted activity during hospitalisation, dose rate measurements of patients at the time of release, and dosimetry data retrieved from the surveillance of family members. The assessment should include treatments with alpha-particle emitters, which are expected to expand appreciably in the near future. If the legal requirements for the radiation protection of the public and the patients' care takers could be fulfilled with shorter hospital stays, many countries could increase the treatment capacities without increasing the number of beds in nuclear medicine wards.

Radiation protection in the EU is legally based on Directive 2013/59/Euratom, which gives member states flexibility in its implementation in national law. It was argued by participants that the national legislation usually goes beyond the EU requirements and that local authorities additionally introduce generous safety margins.

### 3.1.2 Health Technology Assessments and reimbursement

The importance of Health Technology Assessments (HTA) was emphasised, pointing out that a full HTA groups all aspects of clinical, economic and societal impact.

The evidence for clinical efficacy of radiotheranostic treatments must be backed by studies comparing competitiveness, side effects, loss of productivity, etc. with respect to established treatment pathways. Moreover, radiotheranostics selects the patients on the basis of imaging and quantifying their target density profile and avoids treatments without chance of success. Thus, HTA studies should include these particularities and look into the societal cost of disease when comparing different treatment options. Positive signals from HTA would motivate decision-making bodies to integrate radiotheranostic treatments in health care systems.

Proven cost-effectiveness is the key input for positive reimbursement decisions. This will in turn increase the demand for radiotheranostic therapies and will possibly lower the unit price for therapy. The EU programmes could come together to launch specific calls for HTAs of radiotheranostic therapies.

### 3.1.3 Joining efforts for training in nuclear medicine and multidisciplinary training

With the recent developments in radiotheranostics, the number of cancer treatments in nuclear medicine is expected to multiply over the next few years, which will challenge hospital infrastructure but will also lead to a shortage of medical workforce administrating these therapies.

There is an urgent necessity to join forces on education and training. Several activities have been started by different actors which should be integrated, harmonised and amplified, as there is a large workforce to be trained.

The ICPO (International Centres of Precision Oncology) has established the ICPO Academy[5] over the past three years. The academy uses an e-learning platform that provides structured training programmes for nuclear medicine physicians, health physicists, radiochemists/radiopharmacists as well as for nursing staff, in response to the needs of patients. The e-learning training consists of video modules (currently over 50 hours of educational material presented by world-renowned experts) which can be complemented by hands-on training to be conducted at participating clinical centers for physicians, radiochemists/radiopharmacists, health physicists, and nursing staff.

The EANM (European Association of Nuclear Medicine) is currently involved in setting up the RLT (Radioligand Therapy) Academy. As part of an ERASMUS+ project focused on RLT training, the EANM is a partner of a pan-European consortium coordinated by the University Hospitals Leuven and involving universities, academies, and the industry. The RLT Academy aims to provide an online e-learning platform and opportunities for hands-on training[6].

These international organizations' training initiatives could be coordinated with efforts from other organizations that offer training on a national or local level. This collaboration would help identify additional training gaps and opportunities.

In addition, patient associations could play an important role in the dissemination of knowledge on radiotheranostic treatments in order to increase awareness on their potential and limitations among patients and their general practitioners.

### 3.1.4 Raising awareness and understanding of the benefits of nuclear medicine

Training activities should comprise activities to raise the awareness of the options of radionuclide technologies among other medical disciplines, as well as regulators in the field of pharmaceuticals and radiation protection.

### 3.1.5 Clinical trials – Better design, faster approval and funding

Clinical trials with radiopharmaceuticals are more demanding than those with conventional medicinal products. Treatment with radiotherapeutics requires specialised clinical centres, which limits the number of possible participants (centres and patients). The clinical trials which led to the recent approval radiopharmaceuticals were multinational and even multicontinental, grouping patients from many different countries, different health care systems and different "medical cultures". In such a framework sometimes difficulties may arise due to the comparison with locally different reference treatments. This has been criticised by medical experts of other fields. Oncologists would appreciate to have positive trends in favour of radiopharmaceuticals confirmed by statistically more reliable Kaplan-Meier plots.

Participants suggested to improve the design of future clinical trials by setting them up jointly in a multidisciplinary team with all medical disciplines routinely involved in the treatment of the cancer concerned. Having multidisciplinary cancer boards already available in the participating clinical centres would be

[5] https://www.icpo.foundation/academy/
[6] https://erasmus-plus.ec.europa.eu/projects/search/details/2021-1-BE02-KA220-HED-000032124

beneficial. Trial designs should strive for optimising the comparability especially of international multicentre studies.

Patient representatives and oncologists made the point that narrow inclusion and exclusion criteria for clinical trials may be unrealistic for a real clinical situation where certain cancers go typically along with certain comorbidities. Therefore, the results may not necessarily reflect the clinical situation in a typical group of patients. Patient representatives propose registries gathering all patient and treatment data to better understand side-effects and influences of comorbidities on outcome based on real world data.

It has also been argued that more complex, academic trials are required, which compare more than two or three treatment arms and to extend the duration of trials much beyond the "industrially accepted" time horizon. This is deemed necessary to improve cancer care outcomes especially when looking into combination treatments, defining the best time point for a given treatment in the course of disease and looking into long-term toxicities, especially those that may be caused by radiation effects. However, such trials will require public funding as it will be difficult to find industrial or academic sponsors.

### 3.1.6 Further research challenges

Finding out the difference between super-responders, which live for many years without relapse after radiotheranostic therapy, and non-responders, which have been selected for therapy based on a sufficiently high target density but nevertheless exhibit progressing disease, is one of the most urgent and demanding tasks. The aim is to find predictive markers for non-responding patients and if possible, combination treatments which may overcome this resistance. In this context radiobiological research needs to be intensified, revealing details on the immunological response to radiation emitted by radiopharmaceuticals, which provides information on mechanisms leading to increased radiation resistance of cells and also how this problem could be overcome.

Radiotheranostic therapy is based on patient selection by medical imaging, and therapy monitoring can be performed by imaging the same molecular targets quantified during diagnosis and targeted during therapy. Especially when studying the reason for developing resistance against therapy, oncologists and radiologists consider alternative imaging techniques such as MRI as helpful. Patients with progressive disease may lose receptor expression and progression may be overlooked by the initial radioligand imaging agent, while still being visible in a PET scan aimed at detecting abnormally high glucose metabolism cells. Thus, for most patients conventional imaging is sufficient and PET (which is not standard care for response assessment) is complementary. However, functional imaging should be performed in clinical trials to reveal when it will be necessary in response monitoring and when conventional imaging may be sufficient.

### 3.1.7 Personalised Dosimetry

The topic of personalised dosimetry has been discussed as controversially as it is regulated: while the Basic Safety Standards Directive (Council Directive 2013/59/Euratom) requires a treatment planning based on a personalised patient dosimetry, the regulatory approval of pharmaceuticals requires standardised doses. This regulatory incompatibility is a major problem for radiopharmaceuticals.

From a radiobiological point of view, knowledge of the applied dose is the first parameter needed especially when trying to explain why a therapy failed. However, the distribution of an applied standard activity in severely metastasized cancer depends on the patient specific pharmacokinetics and the target density distribution. To derive radiation doses applied to the primary tumour, and to the metastasis and to the surrounding healthy tissue is practically only possible with automated imaging analysis, giving alert when critical radiation dose values are exceeded in healthy tissue. Without automated image evaluation procedures there is the risk that the high human effort to comply with the dosimetry requirements is further reducing patient access to radiotheranostic therapies.

In session 1, an example of a clinical trial was reported where the standard dose was reduced to take into account the physical constitution of the patient and comorbidities. The results showed potential for further improvement without compromising treatment results.

There was consensus that dosimetry should be studied carefully during clinical trials phase I and II to derive criteria which can be generalised, while being sufficiently safe in routine administration, where the effort for a complete dosimetry is risking introducing a burden that compromises patient access to the procedure. Moreover, in light of recent findings concerning the immunological responses to radiopharmaceutical therapies, the effect of dose in terms of energy delivered to cells and DNA damage caused by it is only a part of the picture.

### 3.1.8 Artificial Intelligence and efficiency gains in medical practice and research

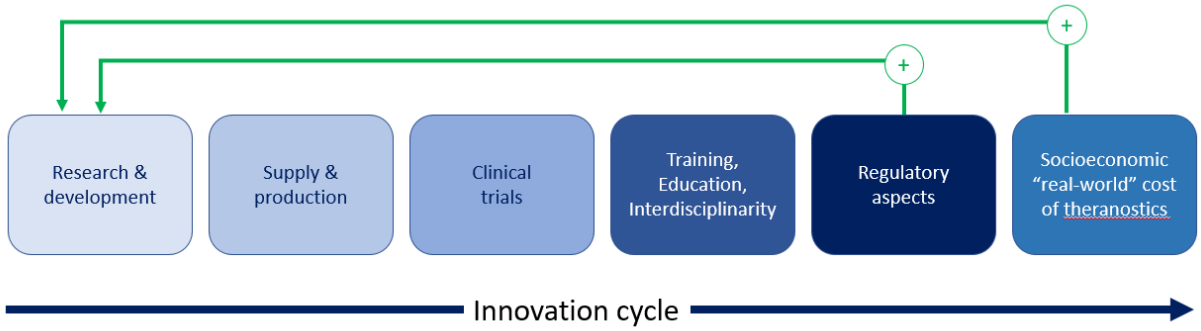
Radiotheranostics is characterised by a high imaging effort. The same holds for radiology. As imaging becomes more and more important in oncology in general, especially in cases of patients that have undergone a long history before receiving a final diagnosis, the capability to compare imaging procedures taken with different imaging equipment and methods and to determine changes over time becomes increasingly important. Therefore, since nuclear medicine and radiology physicians suffer of a high workload with imaging procedures they would benefit from systems capable of analysing historic sequences of imaging procedures. Hence, increasing efficiency by creating and applying new evaluation and comparison software based on artificial intelligence algorithms is a desirable development. This would especially support the work of multidisciplinary tumour boards which adds *per se* an additional workload to physicians, but is nevertheless inevitable when striving for the best possible cancer care.

Benefits of artificial intelligence are also expected for the identification of predictive tumour markers and of new molecular targets for therapy, which would reduce the time and investments required to develop new pharmaceuticals and to improve existing therapies.

# 4 Conclusions and Recommendations

In consideration of the discussion several recommendations can be made, which will affect the whole life cycle of health innovations and is presented in a linear way in Figure 4 below. In view of continuous improvement of therapies it could be presented as a circle as well.

Figure 4: Simplified innovation life cycle diagram




*Source: Claudius Griesinger*

The figure starts with the idea of a preclinically researched radiopharmaceutical, followed by the production and supply of an experimental pharmaceutical to be applied in clinical trials by adequately trained staff, leading to the regulatory approval of a successful product and its application in clinical practice providing "real-world data" including economic impact information. Fast regulatory approvals, clinical efficacy and proven cost-effectiveness have positive feedback on research.

Based on the discussion the following recommendations were made:

1. Encourage a coordinated approach between the research programmes (including Euratom, Horizon Europe, EU4Health and Europe's Beating Cancer Plan among others), with solutions for scaling up to market demand and clinical use.
2. Strive for EU autonomy for a continuous, stable and uninterrupted supply of medical radionuclides, considering an increasing demand and use of several radionuclides including alpha-emitters.
3. Harmonise the requirements for clinical trials with radiopharmaceuticals across EU Member States, in order to enable multicentre European studies, and agilise timelines for approval.
4. Address regulatory issues concerning radiation protection, including harmonisation of guidelines for hospitalisation after radiopharmaceutical routine treatments.
5. Joining forces on education and training for radiopharmaceutical use to health care providers, radiation protection experts, regulators, decision makers, patients and respective care takers.
6. Encourage the integration of radionuclide technologies in multidisciplinary clinical boards, addressing also pooling of data for harmonisation of clinical practice.
7. Support health technology assessments and cost-effectiveness analysis of radiopharmaceutical diagnosis and treatments in support of reimbursement decisions.

## References

Ugo De Giorgi et al., *Circulating androgen receptor gene amplification and resistance to 177Lu-PSMA-617 in castration-resistant prostate cancer: results of a phase 2 trial*. British. Journal of. Cancer. 2021 Oct;125(9):1226-1232. doi: 10.1038/s41416-021-01508-5

G. Paganelli et al., *Dosimetry and safety of 177Lu-PSMA-617 along with polyglutamate parotide gland protector: preliminary results in metastatic castration-resistant prostate cancer patients*. EJNMMI. 2020 Dec;47(13):3008-3017. doi: 10.1007/s00259-020-04856-1

## List of abbreviations and definitions

| | |
|---|---|
| $^{117}$Lu | Lutetium 177 |
| $^{213}$Bi | Bismuth 213 |
| $^{225}$Ac | Actinium 225 |
| EANM | European Association for Nuclear Medicine |
| Erasmus+ | EU programme to support Education, Training, Youth and Sport in Europe |
| EU4Health | EU's Health funding programme for 2021-2027 |
| EURATOM | European Atomic Energy Community |
| GMP | Good Manufacturing Practices |
| Horizon Europe | EU's Research and Innovation funding programme for 2021-2027 |
| HTA | Health Technology Assessment |
| ICPO | International Centres for Precision Oncology |
| $^{177}$Lu-DOTATATE | Radiopharmaceutical with market authorisation for the peptide receptor radiotherapy of neuroendocrine tumours |
| $^{177}$Lu-PSMA-617 | Radiopharmaceutical with market authorisation for the radio ligand therapy of metastatic castration resistant prostate cancer |
| MeV | Megaelectron volts; frequently used unit to describe the energy of particles emitted in a radioactive decay event |
| MRI | Magnetic Resonance Imaging |
| mRNA | Messenger ribonucleic acid |
| Nuclear Medicine Europe | European Industrial Association for Nuclear Medicine |
| PD-L1 | Programmed death-ligand 1 |
| PET scan | Positron emission tomography scan |
| PRRT | Peptide receptor radiotherapy |
| RLT | Radioligand Therapy |
| SAMIRA | Strategic Agenda for Ionizing Radiation Applications |

# List of figures

# Annexes

## Annex 1. Workshop Agenda

| | |
|---|---|
| 09:30-10:00 | Welcome and Introduction<br>EU Commissioner Mariya Gabriel<br>JRC DDG Bernard Magenhann |
| 10:00-12:35 | Session 1 – Radiotheranostics: radionuclide-based therapy and companion diagnostics |
| 10:05-10:35 | Principles of and clinical experiences with peptide receptor radiotherapy (PRRT) of neuroendocrine tumours and radioligand therapy (RLT) of advanced prostate cancer (Richard P. Baum; Curanosticum Wiesbaden-Frankfurt) |
| 10:35-11:05 | Results of $^{177}$Lu-PSMA-617 phase II prospective trial IRST-185 and role of androgen receptor amplification in PSMA-RLT(Giovanni Paganelli; IRST-IRCCS, Istituto Romagnolo Studio Tumori "Dino Amadori") |
| 11:05-11:20 | mCRPC patients receiving $^{225}$Ac-PSMA-617 therapy in the post–androgen deprivation therapy setting (Alfred Morgenstern; JRC, Directorate Nuclear Safety and Security, Karlsruhe) |
| 11:35-12:05 | The role of Centers of Excellence and multidisciplinary tumor boards for quality treatment of NET (Marianne Pavel; University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany) |
| 12:05-12:35 | Radioligand therapy of metastatic prostate cancer– the oncologists view (Silke Gillessen; Oncology Institute of Southern Switzerland, Department of Medical Oncology, Bellinzona) |
| 12:35-13:15 | Session 2 – **The cancer patients' view**<br>Erik Briers (Europa Uomo), Anna Nilsson (care giver), Luciano Licciardello and Barbara Picutti (Associazione Pazienti con Tumori Neuroendocrini) |
| 14:20-15:20 | Session 3 – Radiotheranostics: innovations and challenges |
| 14:20-14:50 | Exploiting radiobiological effects of targeted radionuclide therapy (Jean-Pierre Pouget; Institut de Recherche Cancerologie de Montpellier, Universite de Montpellier) |
| 14:50-15:20 | New developments and challenges facing clinical translation of radiotheranostics (Ken Herrmann; Department of Nuclear Medicine, University of Duisburg-Essen, Duisburg) |
| 15:20-17:05 | Session 4 – Translating radiotheranostics into clinical practice<br>Panelists: Odile Jaume (ICPO), Heinz-Peter Schlemmer (EACS), Stefano Fanti (University of Bologna), Konrade von Bremen (Nuclear Medicine Europe), Ulla Engelmann (JRC) |
| 15:20-16:05 | Identification of critical factors, potential roadblocks and the relevant stakeholders |
| 16:05-17:05 | How to tackle roadblocks |
| 17:05-17:15 | Wrap-up & recommendations |
| 17:15-17:20 | Concluding remarks |

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