RLT ACADEMY

PROJECT RESULT 4

POLICY RECOMMENDATIONS –

TO ENSURE WIDER UPTAKE OF RADIOLIGAND THERAPIES IN EUROPE

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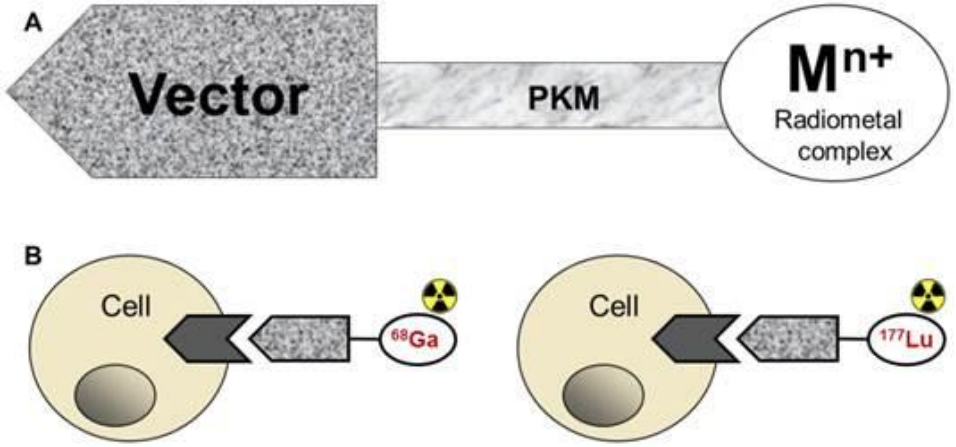
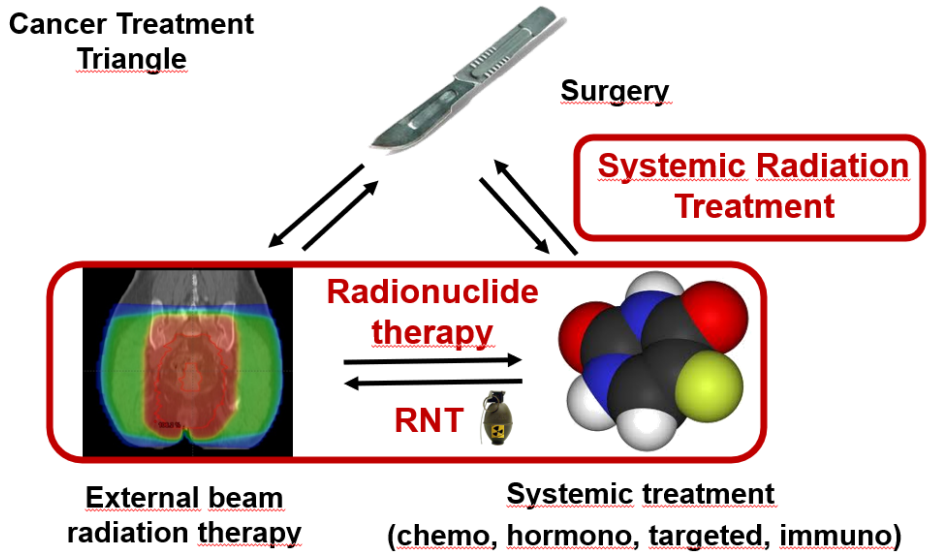
Radionuclide/radioligand therapy

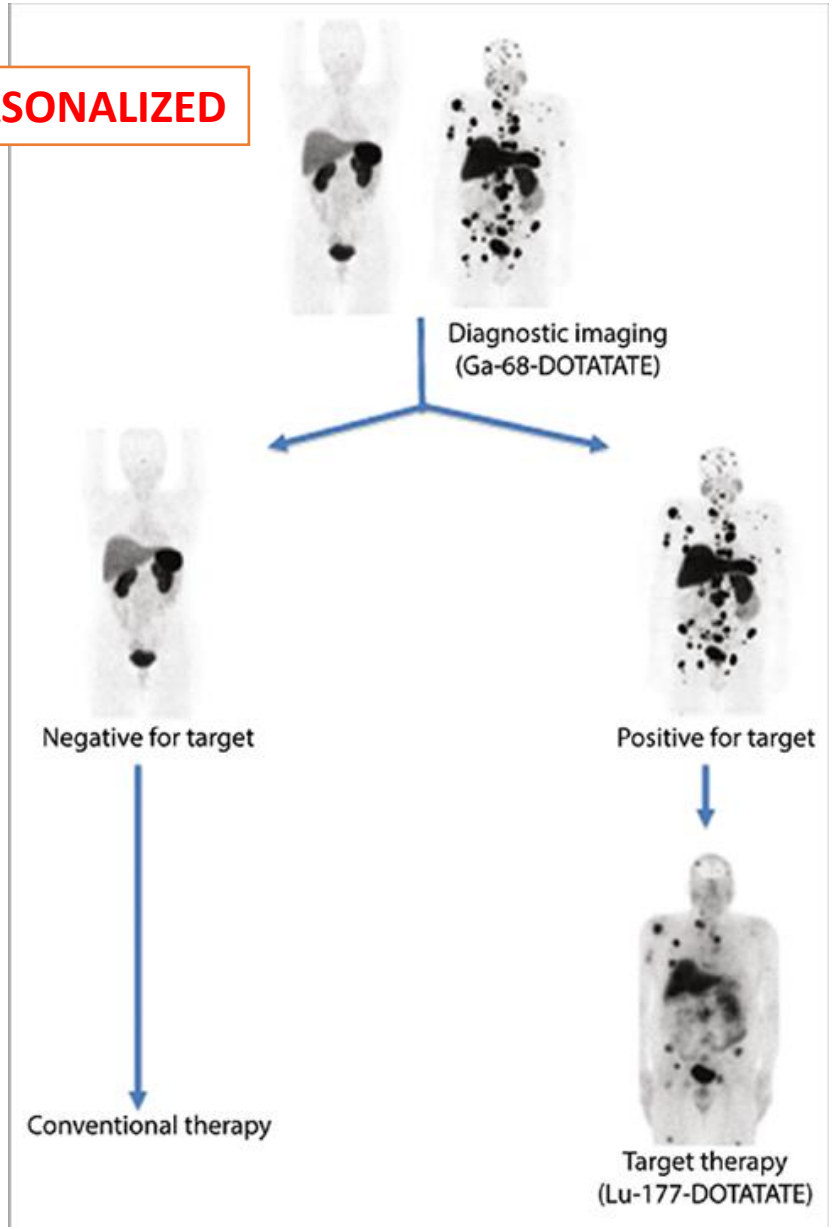
RLT Academy

TARGETED





PERSONALIZED



Radionuclide/radioligand therapy

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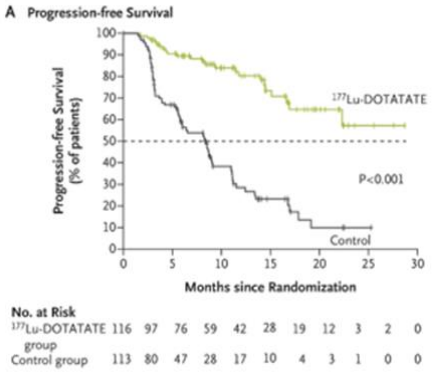
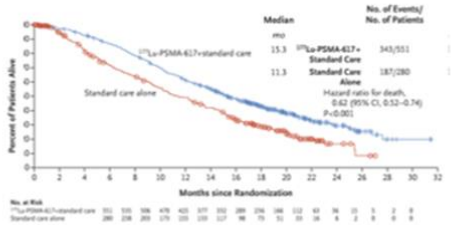
Progression-Free Survival



Control the growth of the disease

Strosberg et al., N Engl J Med 2017

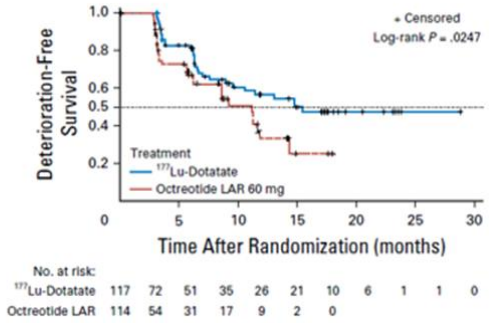
Overall Survival



Make patient **live longer**

Sartor et al., N Engl J Med 2021

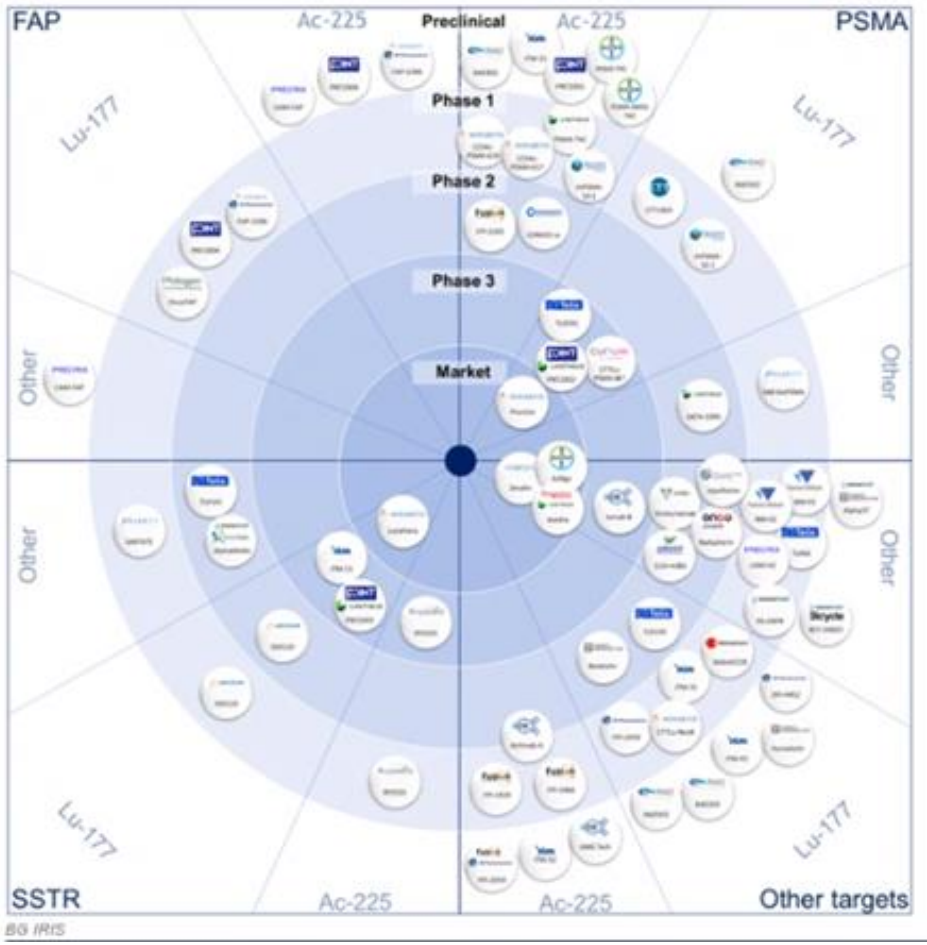
Quality of life: e.g. pain



Make patient **live better**

Strosberg et al., J Clin Oncol 2018

A fast evolving field



RLT policies

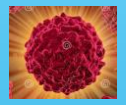
Methodology

Methodology

- 1) Scientific literature review (JUN 2023 – SEP 2023; CMD)
- 2) Landscape consultation round (FEB 2021 – APR 2024; All)
  - Scientific congresses, meetings, work shops, patient advocacy, healthcare policy
  - Focusses on oncology or RLT
- 3) SWOT/PESTEL analysis (Q1 2024: ALG)
- 4) Draft Recommendations (MAY 2024; CMD)
- 5) Discussion draft recommendations (MAY 2024; All)
- 6) Finalization recommendations (JUN 2024; CMD, ALG & JYB)
- 7) Presentation recommendations (JUL 2024; All) – Leuven, Belgium
- 8) Submission to peer-reviewed publication

RLT
SWOT & PESTEL Analysis

RLT SWOT



STRENGHTS

- Targeted treatment
- Effective for specific cancers
- Minimally invasive
- Diagnostic and therapeutic applications
- Personalized medicine

WEAKNESS

- Limited availability
- High cost
- Potential side effects
- Complex production and handling

RLT SWOT

OPPORTUNITIES

- Technological advancements
- Expansion to other cancers
- Combination therapies
- Increasing awareness and education
- Regulatory approvals

THREATS

- Regulatory hurdles
- Competition from other therapies
- Radiation safety concerns
- Supply chain issues
- Reimbursement challenges

RLT PESTEL

RLT Academy

Political Factors:

- Affect the **Deployment** of radioligand therapy.
- National and international **Guidelines** are crucial.
- **Political Stability is crucial** in regions where production and research facilities are located.

Economic Factors:

- High costs limit **RLT Accessibility**, especially in low and middle-income countries.
- Impact the availability of **Funding for Research**.
- **Insurance and Reimbursement** influence patient access to RLT.

Social Factors:

- **Awareness and Acceptance** of the public and professional.
- **Aging Population** more prone to cancers.
- **Patient Preferences** for less invasive treatments.

Technological Factors:

- **Advancements in Technology and R&D** enhance effectiveness and safety.
- **Continuous updates in Educational Curricula.**
- **Integration of Advanced Diagnostic Tools** improves patient selection and treatment monitoring, making therapy more precise.

Environmental Factors:

- **Disposal of Radioactive Waste.**
- **Sustainable Practices of Production.**
- **Regulations on Emissions**.

Legal Factors:

Intellectual Property Rights.
Liability and Safety Standards.
Approval Processes.

Policy Recommendations

Research results and draft recommendations

1. Radionuclide/radioligand therapy(RLT)

Radionuclide/radioligand Therapy

- 1) Systemic radiation treatment
- 2) Delivered to all cancer sites through radiopharmaceutical
- 3) Limited healty organ irradiation
- 4) Exploits targets present ↑↑↑ in cancer cells, ↓↓↓ in healthy cells. No need for mechanistic function, can be negative regulator, limited resistance pressure.
- 5) Radiation itself: cornerstone of cancer treatment > 100 years
- 6) Target expression and targeting by radiopharmaceutical: documented by theranostic imaging in ALL lesions: ↑ efficacy, improved patient selection, spares patients from toxicity and cost (€)
- 7) Last 5 years: EBM demonstration of power (Netter-1 & -2, Oclurandom, Vision, PSMAfore, TheraP, ENZA-p,…)
- 7) Potential to become fourth pillar of cancer treatment (next to surgery, external beam radiation treatment (EBRT) and systemic therapy).
- 8) Dynamic landscape:
  - Novel targets -> novel cancer types / novel vectormolecules / novel radionuclides
  - Most potent radionuclides widely unexplored: α-emitters, β^-/Auger electrons, …

RLT Barriers

1) Limited awareness
   - Practitioners
   - Patients
   - Healthcare system
2) Limited availability radionuclides
3) Limited availabity radiopharmaceuticals
4) Limited infrastructure and material for safe administration
5) Lack of trained medical and paramedical staff for administration
6) Waste collection bottlenecks
7) Limited market access and reimbursement
8) Patient impact & perception

Healthcare Policies

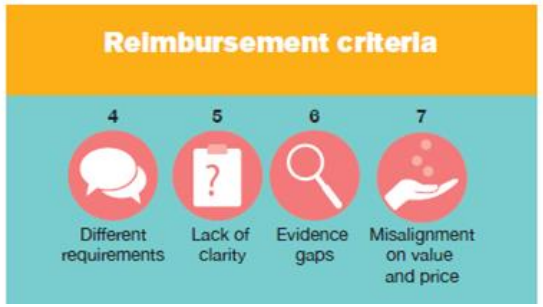
Sustainable isotopes production

Treatment cost

Environmental issues

Lack of trained staff

Lack of guidelines



2. Policy Recommendation – BASIC & CLINICAL RESEARCH

Basic & Clinical Research recommendation

1) ↑ Radiobiology research:
   - ≠ EBRT:
     - RLT: Low dose rate (hours, days) ↔ EBRT: high dose rate (seconds, minutes)
     - RLT: Inhomogenous dose (target expression, perfusion, wash out …) ↔ EBRT: homogenous dose
     - RLT: Limited & indirect control (Inj. Activity; IA) ↔ EBRT: high spatiotemporal control; 3D conformal
   - Cellular level: effect intracellular dose deposition (α, β^-, Auger) – cytoplasmatic membrane, mitochondria, Golgi, ER, Nucleus
   - Histological level: effect dose deposition different organ comparements, e.g. kidney, liver, bone marrow
   - Organ level
- 2) Every new radiopharmaceutical (change in vector molecule, linker, chelator and/or radionuclide):
   - Empirical assessment of maximal tolerated injected activity (IA)
   - Empirical assessment of maximal tolerated absorbed dose to organs
   - No blind extrapolation from EBRT or other radiopharmaceuticals

Basic & Clinical Research recommendation

3) ↑ Research radionuclide production:

- Industrial upscaling
- Strategic autonomy: starting material & infrastructure in EU
- Innovative radionuclides that broaden therapeutic landscape, with variation in: emission type / energy (~range) / $T_{1/2}$ / chemical properties (metal, halogen, …)
- e.g. PRISMAP.

4) EU Funding comparitive effectiveness trial:

- Funding calls dedicated to comparitive effectiveness trials with RLT.
- Trial managament: EU funded
- Therapies in arms: funded by healthcare system

5) Evaluate clinical benefit of novel RLT radiopharmaceuticals:

- E.g. “ESMO Magnitude of clinical benefit” scale
- Framework to be adapted for RLT, e.g. long term toxicity element

3. Policy Recommendation – **LEGISLATION**

Legislation

- 1) Difference between RLT/RNT and EBRT to be acknowledged:
  - RLT: Low dose rate (hours, days) ↔ EBRT: high dose rate (seconds, minutes)
  - RLT: Inhomogenous dose ↔ EBRT: homogenous dose
  - RLT: Limited & indirect control (Inj. Activity; IA), dependent on physiological processes (target expression, perfusion, wash out, plasma clearance, …) ↔ EBRT: high spatiotemporal control; 3D conformal.

  - => RLT/RNT: IA prescribed in (k/M/G)Bq ↔ EBRT: defined volume with target absorbed dose (Gy)
  - => RLT/RNT: infusion (IV >> IA > intracavitary) of Radiopharmaceutical, typically in solution ↔ EBRT: external irradiation by ionizing radiation (photons, protons) from particle accelerator (or sealed radioactive source)

  - Lumping together 2 ≠ frameworks results in impediment for:
    - Adoptation
    - Dissemination
    - Optimisation

Legislation

- 2) Radioprotection Legislation
  - Key component of legislative framework encountered in RNT/RLT
  - EURATOM Legislation – for successor of EC Directive 2013/59/Euratom:
    - In definitions: create separate category for Radionuclide therapy, defined as therapy carried out by administration of open source radiopharmaceuticals. Units of administration: Bequerel (and multiples).
    - In definition 81 [“(81) "radiotherapeutic" means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes;”], remove “…, including nuclear medicine for therapeutic purposes;”
    - The following content of Article 56 should <u>not</u> be applied to RLT/RNT:

    [“For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.”]

Legislation

- 3) Create radioprotection framework based on balance of benefits and risks:

  - Encourage research on life cycles of radionuclides trough production routes onto waste disposal
  - Provide specific hospital and RNT/RLT facility discharge limits, differentiated from other nuclear site
  - Harmonize EU regulation on radioprotection measures with emphasis on substantial benefit of RLT (ALARA principle).
    - No mathematical union of all current measures in place!
    - Patient rights and autonomy.

Legislation

- 4) (Radio)pharmaceutical legislation:
  - **Diagnostic agents:** specific legal status of radiopharmaceuticals, recognizing:
    - Specific mode of action: trace amount of externally detectable radiation
    - Low mass amount (pico- to microgram range), below pharmacological threshold in vast majority of cases; single or oligorepeated use over time.
    - Short to ultrashort shelf life (minutes to days) => no stock of active radiopharmaceutical => on time preparation
    - Dependency on radionuclide availability (generator/cyclotron/external provider)
  - **Therapeutic agents:**
    - Similar specificity as diagnostic agents
    - Biological effect due to ↑↑ dose:
      - Tumor: beneficial
      - Healthy cells and organs: potential side effects
  - Provide regulatory framework in clinical trial directive for **development** of:
    - RLT/RNT radiopharmaceuticals
    - Theranostic pairs, either with similar vector molecule (e.g. [^{68}Ga]Ga-DOTATATE and [^{177}Lu]Lu-DOTATATE) or matching diagnostic/therapeutic pair (e.g. [^{68}Ga]Ga-PSMA-11 and [^{177}Lu]Lu-PSMA-617).
  - **Magistral preparations:** proper framework. Important back-up in case problem at centralized industrial production.

Legislation

- 5) EMA:
  - Create specific committee on radiopharmaceuticals
  - Provide input from:
    - Radiopharmacists
    - Nuclear medicine physicians
    - Radiation physicists
    - Oncologists
  - Add specific radiopharmaceuticals to “Critical Medicines” list, e.g.:
    - Diagnostics: [^{18}F]FDG, SSTR ligands, PSMA ligands, future theranostic agents
    - Therapeutics: Na^{131}I, $RaCl_2$, [^{177}Lu]Lu-DOTATATE, [^{177}Lu]Lu-PSMA-617, …

4. Policy Recommendation – **HEALTH POLICY**

Health Policy

- 1) Tackle 10 most important reasons for delayed patient access to innovative RLT

  - See “Every Day Counts” (https://www.efpia.eu/media/578013/every-day-counts.pdf)
  - Proposed solutions:
    - **Process level:** Allow pre-EMA decision pre-submission and define binding timelines.
    - **Reimbursement criteria:**
      - Homogenize required efficacy criteria, dependent on clinical setting, see e.g. “ESMO Magnitude of clinical benefit” scale
      - Streamline clinical- and cost-effectiveness assessment
      - Avoid evidence gaps by focusing on available evidence of prospective trials (and real worl data if available)
      - Provide price reference range with mix of cost- and value-based pricing, with reference prices per type of RLT/RNT class, e.g. 177Lu-based radiopharmaceutical
    - **Health system readiness:**
      - Include budget for RLT in general oncological drug budget, with anticipation of large influx of new radiopharmaceuticals
      - Implement “Live” online clinical guidelines that can be changed right after EMA approval
      - Increase and optimize existing RNT infrastructure, devices and personnel (see infra)

Health Policy

- 2) Create independent body for reimbursement of radiopharmaceuticals (& radioactive medical devices)
  - At national level
  - E.g. Belgium, Technical Council for Radioisotopes (TCRI), within the national healthcare institute (National Institute for Health and Disability Insurance, aka RIZIV/INAMI)

- 3) Develop country-specific RLT plan (cfr Belgium; “A Radioligand therapy plan for Belgium”; Inovigate):

  - All stakeholders (nuc med physicians, oncologists, radiopharmaceutical manufacturers, patients, hospitals, health care payers, competent and regulatory authorities (drug, radiation), ..)

  - Provide investments in:

    - Infrastructure, including RNT rooms and waste collection

    - Material, including radiopharmacy equipment, isolators, activity calibrators and quantitative cameras (SPECT, PET)

    - Personal

- 4) Set up system to collect long-lived waste from hospitals by radiopharmaceutical manufacturers, with costs carried by manufacturers.

Health Policy

- 5) Set up separate reimbursement body for radiopharmaceuticals and radioactive medical devices:
  - One per member state
  - Recognizing:
    - High production cost
    - High clinical value (↑↑ efficacy; ↓↓ adverse effects)
    - Short shelf life
  - With strict timelines
  - Composition:
    - Representants executive power and society (e.g. medical societies)
    - Scientific experts: radiopharmacists, nuclear medicine physicians, radiation oncologists, representants universities
    - Health care payers: insurers, mutualities
    - Competent authorities: drug regulator, radiation protection.
  - E.g. Belgian TCRI (first EU member state with reimbursement of [^{177}Lu]Lu-PSMA-617 (Pluvicto®); 1 APR 2024)

- 6) Monitor real world use and efficacy of RLT:
  - Set up program for real word usage monitoring
  - Reward data collection
  - Include system for collection of pre-defined late side effects (e.g. end stage renal disease, persistent hematological dysfunction (cytopenia, MDS, leukemia), and other therapy specific toxicities (TBD for each radiopharmaceutical).

Health Policy

- 7) Proper financing of RNT/RLT activities (besides radiopharmaceuticals):
  - Clinical work responsible physician (MDT, consultation, blood draw, clinical examination pre-injection,…)
  - Logistical planning
  - In-patient stay, often in RNT room
  - Post-therapy imaging and dosimetry (radiation physicist, in collaboration with nuc. Med. physician)
  - Radioprotection personal, license handling and waste management
- 8) Define and record Key Performance Indicators for RLT adaption at EU level.
- 9) Increase training levels of staff dealing with RLT procedures in all EU member states:
  - NM physicians, technologists, nurses, radiopharmacists, medical physicists,…
- 10) Pinpointing RLT within the national healthcare systems:
  - Map centers providing RLT currently
  - Determine the current needs of RLT and make population and epidemiology-based projects for next 10 years
- 11) Include RLT in the cancer plan of each member state:
  - Funding for radiopharmaceuticals and process of delivering therapy
  - Implementation trajectory for building sufficient capacity for current and projected care need.

Health Policy

- 12) Accrediation of theranostic centers – e.g. EANM:
  - Including EARL (68Ga, 18F, 89Zr, 177Lu)
  - Including personal (physician, radiopharmacist, radiophysicist, …)
  - Tier 1: routine products
  - Tier 2: clinical trials – phase II-IV
  - Tier 3: clinical trials – phase I (including dosimetry and pharmacokinetics).

5. Policy Recommendation – EDUCATION

Education

- 1) Tackle gaps in educational landscape described in mapping of European landscape
  - Reinforce STEM (science, technology, engineering, mathematics) education in secondary school.
  - Include biomedical education and interaction of chemistry, physics and biology, including applications of radioactivity (imaging, theranostics, therapy)
  - Mandatory inclusion of nuclear medicine, including imaging and therapy, in curriculum of medical doctors:
    - Basic principles of radioactivity, its detection and therapeutic applications
    - Current applications
    - Mandatory inclusion in training of oncologist, both medical oncologists and organ specific oncologists (GI, respiratory, hematology, urology, breast, …)
  - Provide optional in depth courses on theranostics in curriculum medical doctors
  - Include diagnostic and therapeutic applications of radioactivity in medical sector in range of different formations, including radioprotection aspects:
    - Chemistry & pharmacy
    - Physics & Engineering
    - Medical imagers – radiographers
    - Nurses and caregivers
- 2) Provide and finance on-site training networks to foster on-site experience
  - Different duration:
    - 1 week: in depth focus on 1 specific procedure
    - 1 month: multiprocedure and general organization
    - 6 month: focus on building up clinical expertise in wide range of clinical scenario's.
  - Financing of applicant and hosting institution
  - In combination with theoretical courses
  - E.g RLT-Academy

Education

- 3) Develop multidisciplinary RLT guidelines:
  - Integration within standard oncological care
  - Multidisciplinary teams
  - Focus on:
    - Methodology: how to administer, SOPs
    - Patients: indications, contra-indications, special situations (e.g. impaired kidney function, high tumor burden, specific organ involvement
    - Setting: which line? Previous therapies necessary
    - Combination therapy: evidence, specific reductions of (radio)pharmaceutical

Education

- 4) Patient education:
  - Provide education for patients confronted with specific disease, to allow informed consent:
    - Concept of RLT
    - Beneficial effects for particular disease
    - Side-effects: acute, subacture, long term
    - Time schedule of treatment, including hospitalization and radioprotection measure periods
  - Provide standardized material for patients undergoing treatment:
    - By manufacturer, medical societies, compent authorities
- 5) General public education:
  - ↑ awareness of beneficial aspect of radioactivity use
  - Stress importance of therapy for metastatic cancer patients
  - Provide framework to understand the – limited or lack of – risks of RLT,
    - E.g. comparison to dose rate in air flight at 10 km

6. Policy Recommendation – WASTE MANAGEMENT

Waste Management

- 1) Facilitate waste management from manufacturers and hospitals
  - Centralised waste facility for mother vials with long-lived contaminants (Lu-177m, Ho-166m, Eu-152,…)
  - Encourage production routes free of long-lived contaminants;
  - Pragmatic discharge limits for hospitals based on real world evidence
  - Investment in centralized waste collections sites in hospitals

RLT KEY RECOMMENDATIONS

RLT Academy

Research and Development

- Fundings for pre-clinical and clinical research
- RPM cancer cells specificity improvment
- Reliable supply of ligands and radioactive isotopes
- Fast track committees approval for early phases trials

Recognition of clinical interest

- Significant increased therapeutic window
- Fast new approvals by regulatory bodies
- Diffusion to health community

Referral Multidisciplinary Networks

- Assure multidisciplinary education
- Peer accreditation (Level of expertise 1 to 3)
- Online Guidelines for safe and high quality RLT from bench to bedside
- Monitor real world use and efficacy

Healthcare policies

- Increase number of accredited RLT centers
- Independent bodies for reimbursement of radiopharmaceuticals
- Financial support for RLT patient pathway
- National and European regulatory Compliance
- Place RLT as a key component of the cancer plans of each member state